

Benzeneglycols

Starting Materials for the Syntheses of Cyclitols

Minoru NAKAJIMA, Ichiro TOMIDA and Norio KURIHARA*

(Department of Agricultural Chemistry, Faculty of Agriculture, Kyoto University)

Received January 11, 1960

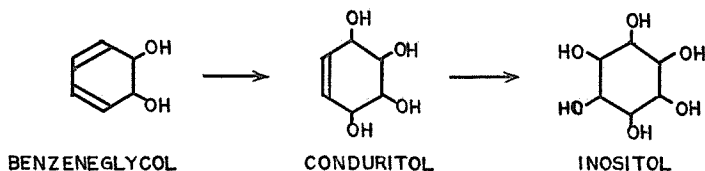
Benzeneglycols (5,6-dihydroxycyclohexadiene-1,3) were prepared from BTC (benzene tetrachloride), and proved to be very useful starting materials for preparing cyclitols. From these key-substances, five conduritols and seven inositols were synthesized. Some other synthetic methods of these compounds were also reviewed.

1. BENZENEGLYCOLS

1.1. Introduction

Polyhydroxycyclohexanes and their related compounds, such as inositols, quercitols and conduritols *etc.*, are generally called cyclitols. They have intimate relations with physiological action of animals, plants and microorganisms; a certain isomer of inositol is believed to have some nutritional actions on animals and yeasts, and some derivatives of inositol (inosamines *etc.*) are constituents of such important antibiotics as streptomycin¹⁾, kanamycin²⁾, and hygromycin³⁾. On the syntheses of these cyclitols, many organic chemists are active at present, and some key-substances have been desired from which cyclitols could be synthesized systematically.

As an example of such compounds, a cyclohexadiene derivative—5,6-dihydroxycyclohexadiene-1,3 is supposed. There are two possible stereoisomers, *cis* and *trans*, for this compound, both of which were synthesized and named "benzeneglycol" by the authors^{4,9)}. Now, benzeneglycols were proved to be very useful starting materials for preparing various cyclitols. On step-wise hydroxylation, in fact, they gave inositols through conduritols. The processes will be described precisely in the following chapters.



Several authors had attempted the synthesis of benzeneglycols without success. For example, Milas⁵⁾ oxidized benzene itself with H_2O_2 using V_2O_5 as catalyst, but obtained only phenol. Booth *et al.*⁶⁾ tried the reduction of *o*-quinone with LiAlH_4 , isolating only catechol.

* 中島 稔, 富田 一郎, 栗原 紀夫

The authors succeeded in synthesizing benzeneglycols from 3,4,5,6-tetrachlorocyclohexene-1 (benzene tetrachloride, BTC) as follows.

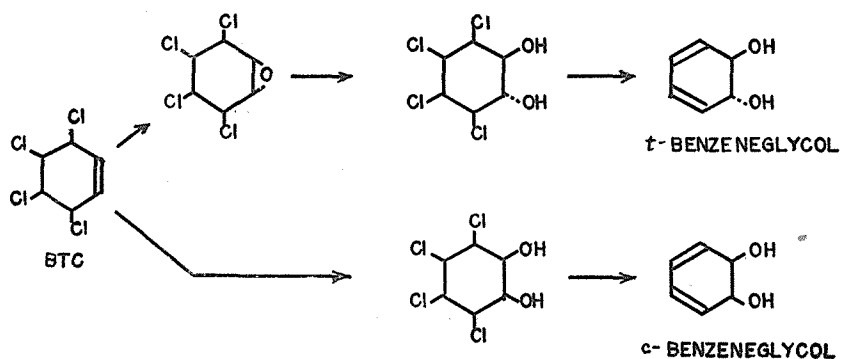
1.2. Syntheses

BTC was prepared by Calingaert *et al.*,⁷⁾ which is assumed to be an intermediate in the production of benzene hexachloride from benzene but cannot be isolated by normal technics. Using iodine (or iron, oxygen, iodine chloride and so on) as negative catalyst of the additive chlorination, they carried out the photochlorination of benzene to obtain the mixture of polychlorinated cyclohexenes from which the substance of m.p. 33.5° was isolated after rectifications and recrystallizations. This is an isomer of BTC and named α -BTC, the conformation of which was determined as $\overline{\text{HHeeaa}}$.

BTC was heated vigorously with CrO_3 in acetic acid for a few minutes to give a product of m.p. 90° which was proved to be α -1,2-epoxy-3,4,5,6-tetrachlorocyclohexane (α -BTC epoxide)⁸⁾. For this compound, two diastereomers epimeric at C-1 and C-2 are possible, but it has not been determined yet which isomer corresponds to the epoxide obtained. This epoxide is so stable against the hydrolytic scission that it must be heated with 50% H_2SO_4 for preparing *trans*-3,4,5,6-tetrachlorocyclohexanediol-1,2 (*trans*-BTC diol), m.p. 138°, and in this case, Walden inversion occurred at C-1 or C-2.

trans-BTC diol was converted to the chlorine-free substance by vigorous stirring with zinc powder in hot water. *trans*-Benzeneglycol was thus obtained as leaflets, melted at 74°⁴⁾.

On permanganate oxidation, BTC gave tetrachloroadipic acid at higher temperature⁷⁾, but with cooling and in the neutral medium a neutral substance of m.p. 140°—*cis*-3,4,5,6-tetrachlorocyclohexanediol-1,2⁹⁾. It melted about at the same point with *trans* isomer, but the mixed m.p. showed clear depression. The diol gave *cis*-benzeneglycol of m.p. 60° on dechlorination with zinc under the similar condition as *trans* isomer⁹⁾.



1.3. Properties

Some physical properties of benzeneglycols are listed in the following table.

Benzeneglycol	M.p.	B.p. of diacetate	λ_{max}	$\log \epsilon$
<i>trans</i>	73-4°	88-9°/1 mmHg	262 $m\mu$	3.49
<i>cis</i>	60°	98°/2 mmHg	262 $m\mu$	3.57

Both isomers of benzeneglycol are easily soluble in water and alcohol, and on hydrogenation, each isomer gave the corresponding stereoisomer of cyclohexanediol. Benzeneglycols suffered dehydration to phenol easily. Especially, *cis*-isomer is so unstable that, on standing in weak acidic medium, it changed rapidly and quantitatively to phenol, though it was rather stable in alkaline solution.

On oxidation of benzeneglycols with lead tetraacetate, one geometrical isomer of muconic dialdehyde was obtained, the configuration of which was proved to be *cis, cis*, since it gave *cis, cis*-muconic acid as the only product when treated with perbenzoic acid. This isomer isomerized very easily to *cis, trans*-isomer of m.p. 59° and furthermore to *trans, trans*-muconic dialdehyde of m.p. 121°.

EXPERIMENTAL

trans-Benzeneglycol

Chromic acid oxidation of BTC. To 120 ml of glacial acetic acid solution containing 15 g of BTC, 12 g of chromic anhydride were added and the solution was heated at 100° with occasional shaking. When small bubbles appeared, the shaking became unnecessary, as the reaction followed smoothly. Constant and violent boiling continued for about 5 minutes and heating was stopped, NaHSO₃ was added to consume excess chromate ion. Green colored solution thus obtained, on steam distillation, gave 10.4 g of colorless crystalline masses. Recrystallization from *n*-hexane gave 1.2 g of BTC epoxide and ca. 8 g of recovered material. The epoxide melted at 90° (prisms).

$C_6H_6OCl_4$ (235.9) Calcd. C 30.54 H 2.56 Cl 60.11

Found C 30.61 H 2.77 Cl 59.96

Hydrolysis of BTC epoxide. Ten grams of BTC epoxide were heated at 100° in 300 ml of 50% H₂SO₄ with continuous stirring for 7 hours. After dilution with water, the slightly turbid solution was extracted continuously with ether. On evaporation of ether, 10 g of crude crystals were obtained (93%). It melted at 133-137°. On recrystallization from chloroform, there were obtained analytically pure substance, m.p. 137.5-138° (plates).

$C_6H_8O_2Cl_4$ (254.0) Calcd. C 28.38 H 3.18 Cl 55.85

Found C 28.66 H 3.16 Cl 55.80

Dechlorination of *trans*-BTC diol (Preparation of *trans*-benzeneglycol). In a mortar, 5 g of *trans*-BTC diol were mixed thoroughly with 10 g of zinc powder. The mixture in 40 ml of water was vigorously stirred for 30 minutes

Benzeneglycols

at 60°. Undissolved materials including zinc powder were filtered off from the hot reaction mixture. The filtrate was extracted continuously with ether. After about 10 hours, 2.0 g (quantitative) of crude *trans*-benzeneglycol were obtained. It melted at 71-73°. Recrystallization from benzene raised the m.p. to 73-74° (leftlets).

$C_6H_8O_2$ (112.1) Calcd. C 64.27 H 7.19

Found C 64.19 H 7.09

Catalytic hydrogenation of *trans*-benzeneglycol.

When 20.3 mg of *trans*-benzeneglycol were hydrogenated at 1 atm. in 3 ml of ethanol using 20 mg of 10% Pd-BaSO₄, they consumed 8.5 ml (2 moles equiv.) of hydrogen in 15 minutes. The filtrate was dried up to give 20 mg (96%) of crystals, m.p. 100-103° (recrystallized from benzene). Admixture of authentic *trans*-cyclohexanediol-1, 2 (m.p. 104°) did not depress the m.p.

$C_6H_{12}O_2$ (116.2) Calcd. C 62.04 H 10.41

Found C 62.16 H 10.39

***trans*-Benzeneglycol diacetate.** One gram of *trans*-benzeneglycol was dissolved in 3 g of pyridine, and to the solution 5 g of acetic anhydride were added with cooling with ice-water. After 24 hours, the solution was poured onto crushed ice and extracted with ether. The ethereal solution was washed with 2*N*-H₂SO₄ and then sat. NaHCO₃ solution, dried and veaporated to give 1.42 g of diacetate as a colorless oil (81%), b.p. 112°/5 mmHg.

Glycol cleavage of *trans*-benzeneglycol with periodic acid. To 2 ml of aqueous solution of 115 mg of *trans*-benzeneglycol, there were added 4.5 ml of periodic acid solution (containing 241 mg of HIO₄) with cooling. Soon the solution colored yellow and 18 mg (16%) of precipitate separated, which after recrystallization from benzene-hexane gave needles of m.p. 99°. They are identical with the product obtained by the oxidation of *trans*-benzeneglycol with lead tetraacetate (see below).

The filtrate, after 1.5 hours standing, was extracted with ether. After evaporation and recrystallization of the residue, 60 mg (53%) of *trans*, *trans*-muconic dialdehyde, m.p. 121°, were obtained.

$C_6H_6O_2$ (110.1) Calcd. C 65.44 H 5.49

Found C 65.17 H 5.46

Glycol cleavage of *trans*-benzeneglycol with lead tetraacetate. Four hundred mg of *trans*-benzeneglycol in 100 ml of absolute benzene were stirred at 35°, to which 1.6 g (1 mole equiv.) of lead tetraacetate were added, resulting yellow solution. After 10 minutes more stirring, the precipitate was filtered off and the filtrate dried up in vacuo. The crude *cis*, *cis*-muconic dialdehyde (0.38 g, 97%) was obtained, which after recrystallization from benzene-hexane gave the m.p. 99° (yellow needles).

$C_6H_6O_2$ (110.1) Calcd. C 65.44 H 5.49

Found C 65.47 H 5.82

cis-Benzeneglycol

Permanganate oxidation of BTC. One hundred and twenty ml of ethanol

solution of 2.20 g of BTC were mixed with 20 ml of aqueous solution of 3.0 g of MgSO_4 , and there were added 3.20 g of potassium permanganate in 200 ml of water drop by drop at 1.5–4.0° with continuous stirring. After about a half volume of the permanganate solution was added, the mixture of 20 ml of aqueous solution of 3.0 g of MgSO_4 and 120 ml of ethanol were added. After standing overnight, MnO_2 was filtered off, washed with ethanol, and the filtrate concentrated and extracted with ether. The ethereal layer on evaporation gave crude crystals which were recrystallized from chloroform giving 1.31 g (62%) of *cis*-BTC diol, m.p. 140° (prisms).

$\text{C}_6\text{H}_8\text{Cl}_4\text{O}_2$ (254.0) Calcd. C 28.38 H 3.18 Cl 55.85
Found C 28.48 H 3.45 Cl 56.11

Dechlorination of *cis*-BTC diol (Preparation of *cis*-benzeneglycol). Five grams of *cis*-BTC diol were mixed with 10 g of zinc powder and 60 ml of water. The mixture was vigorously stirred at 55°. Then the exothermic reaction occurred and the temperature began to rise very quickly. At that time it was necessary to maintain the temperature below 70°, as otherwise the formation of phenol was remarkable. After 5 minutes more heating, the reaction mixture was filtered and 4 *N*-NaOH was added to alkalize the filtrate. Ethereal extract of the filtrate was dried and evaporated. Recrystallization of the residue from *n*-hexane gave 1.72 g (78%) of *cis*-benzeglycol, m.p. 60° (leaflets).

$\text{C}_6\text{H}_8\text{O}_2$ (112.1) Calcd. C 64.27 H 7.19
Found C 64.19 H 7.44

***cis*-Benzeneglycol diacetate.** To the solution of 1.23 g of *cis*-benzeneglycol in 5 g of pyridine, 6 g of acetic anhydride were added in portion with cooling. After standing overnight, the mixture was poured onto crushed ice. The whole solution was extracted with ether, and washed with dilute H_2SO_4 , water, sat. NaHCO_3 and then water. The ethereal layer was dried over Na_2SO_4 and evaporated to give an oily residue. It boiled at 97–93°/2 mm Hg, and weighed 1.78 g (83%).

Catalytic hydrogenation of *cis*-benzeneglycol diacetate. When 96 mg of the diacetate were hydrogenated in 30 ml of ethanol using 50 mg of 10% Pd- BaSO_4 as catalyst, 11.8 ml (1 mole equiv.) of hydrogen were consumed in 2 minutes and 23.6 ml (2 moles equiv.) in 2.5 hours. After distillation of the hydrogenated product, 70 mg of a colorless oil were obtained, b.p. 141–5°/17 mm Hg.

Sixty mg of the oil were boiled with 5 ml of 5% alc. NaOH for an hour on the steam bath. After evaporation of the solvent, the residue was dissolved in water and extracted with ether. Evaporation of ether gave 30 mg (86%) of colorless leaflets m.p. 89–90°. Recrystallizations from benzene-hexane raised the m.p. to 98–99°. The mixed m.p. with authentic *cis*-cyclohexanediol-1,2 did not show any depression.

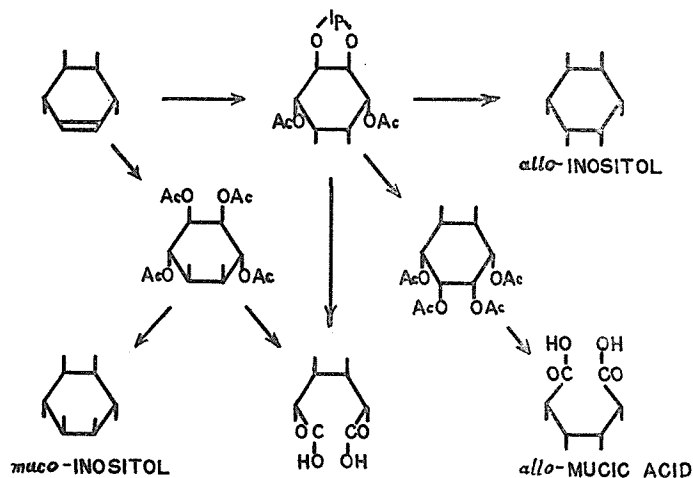
$\text{C}_6\text{H}_{12}\text{O}_2$ (116.2) Calcd. C 62.04 H 10.41
Found C 62.17 H 10.46

Glycol cleavage of *cis*-benzeneglycol with lead tetraacetate. To the solution of 1.00 g of *cis*-benzeneglycol in 100 ml of absol. benzene, 4.0 g of lead tetraacetate were added in portion with stirring at 2-5°. After 10 minutes more stirring the solution was filtered and the filtrate was dried up in vacuo. A crude product (0.94 g) (96%) was obtained, m.p. 95-99°, which on recrystallization from benzene-hexane without warming gave *cis*, *cis*-muconic dialdehyde, m.p. 99° (yellow needles).

2. CONDURITOLS

2.1. Introduction

In 1908, Kubler¹⁰⁾ isolated an isomer of 3, 4, 5, 6-tetrahydroxycyclohexene-1 (m.p. 142-3°) from a wine bark (*Marsdenia condurango*), and named "conduritols". On its nature and structure several researches were carried out, among which the work of Dangschat and Fischer¹¹⁾ was important, *i.e.* they established the conformation of the natural conduritols to be $\overline{H}H\overline{e}eaa^*$ by such a way as shown in the following figure.



On the basis of ring conversion, the ten theoretically possible isomers of 3, 4, 5, 6-tetrahydroxycyclohexene-1 are reduced to six separable forms (Column 4 in the following table). Thanks to works of McCasland^{12) 13)}, Angyal¹⁴⁾ and Criegee¹⁵⁾, and also to the recent researches in Kyoto^{9) 16)}, all those isomers are now synthetically known and called "conduritols" as the generic name. Each isomer is distinguished from others by adding alphabetical suffix; for example the natural conduritols isolated by Kubler is named conduritols-A and the newest one⁹⁾ synthesized by the authors from *cis*-benzeneglycol conduritols-F. Melting points and conformations of the isomers are shown in the following

* Conformations of the substituent groups on cyclohexene rings may be called quasi-equatorial or quasi-axial, as they are somewhat different from the conformations of ones on cyclohexane rings. On the designation of the conformations, see ref. (8).

table*.

3, 4, 5, 6-Tetrahydroxycyclohexene-1 (Conduritol)

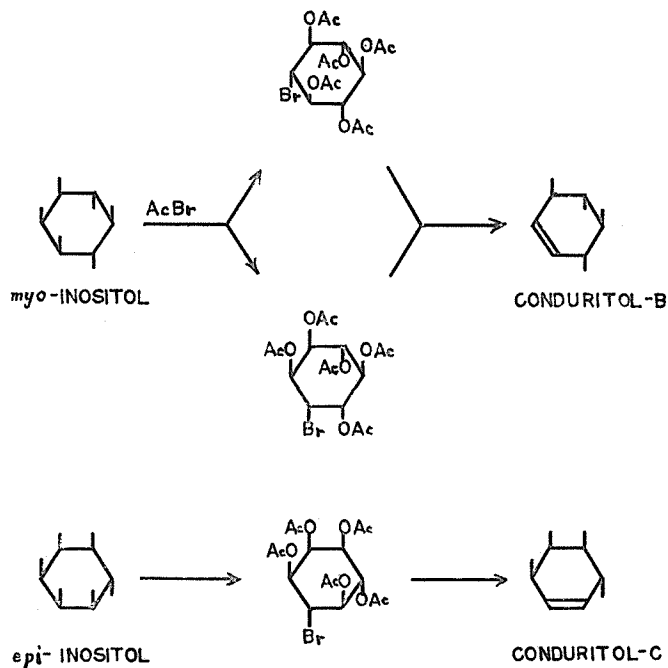
Conduritol	M.p.	M.p. of tetraacetate	Conformation
A	142-143°	163°/0.5 mm Hg	$\overline{\text{HH}}\text{aaee} (\rightleftharpoons \overline{\text{HH}}\text{eaaa, i.e., identity})$
B	204.5-205°	92-93°	$\overline{\text{HH}}\text{eeee} \rightleftharpoons \overline{\text{HH}}\text{aaaa}$
C	151.5-152.2°	90-92°	$\overline{\text{HH}}\text{eae} \rightleftharpoons \overline{\text{HH}}\text{aeaa}$
D	ca. 62°	103-103.5°	$\overline{\text{HH}}\text{eaea} (\rightleftharpoons \overline{\text{HH}}\text{aeae, i.e., identity})$
E	179-180°	152.5-153°	$\overline{\text{HH}}\text{aeaa} \rightleftharpoons \overline{\text{HH}}\text{eaae}$
F	103-104°	92°	$\overline{\text{HH}}\text{ae} \rightleftharpoons \overline{\text{HH}}\text{eaaa}$

2.2. Syntheses

Until now, the following synthetic methods of conduritols are known.

- (1) From bromoquercitols
- (2) From disulfonyl derivatives of inositols
- (3) By a diene synthesis
- (4) From benzeneglycols

2.2.1. From bromoquercitols. McCasland and Horswill¹²⁾ obtained two bromoquercitols by heating *myo*-inositol with acetyl bromide in a sealed tube

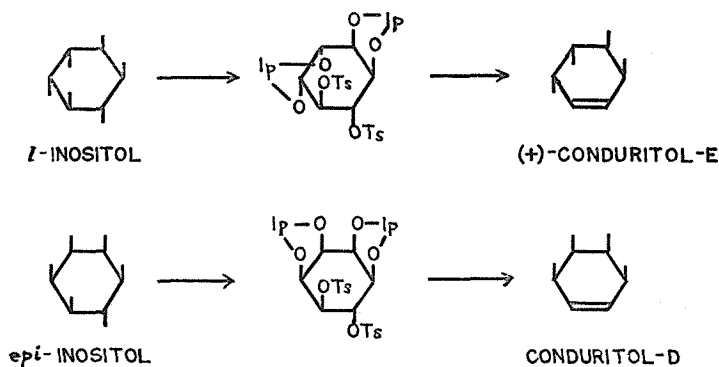


* Conduritols are soluble in water but not in ether, and have a weak sugarlike sweet taste.

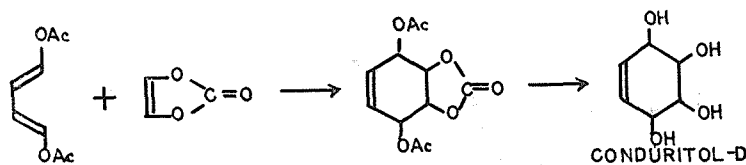
and, by debromination of their pentaacetate with zinc, prepared an acetylated tetrol of m.p. 93° which was hydrolyzed to a new unsaturated tetrol (m.p. 205°) named conduritol-B. The conformation of the unsaturated tetrol was established by hydrogenation to a known cyclohexanetetrol (eeee)¹⁷.

In a similar way, McCasland and Reeves prepared conduritol-C ($\overline{\text{HHe}}\text{aee}$) from *epi*-inositol¹³.

2.2.2. From disulfonyl derivatives of inositols. Angyal and Gilham¹⁴ prepared the disulfonyl derivatives of two inositols, *L*- and *epi*-, and heated these compounds of their di-O-isopropylidene derivatives with sodium iodide in acetone in sealed tubes, obtaining an optical active conduritol (an optical isomer of conduritol-E) and *all-cis* isomer (conduritol-D) from *L*-, and *epi*-inositol respectively.



2.2.3. By a diene synthesis. Recently, Criegee and Becher¹⁵ synthesized conduritol-D using *trans, trans*-diacetoxybutadiene as a diene compound, and vinylenecarbonate as a dienophile. The addition proceeded at 205-210° in a sealed tube. The adduct thus obtained on hydrolysis with Ba(OH)₂ gave conduritol-D as a syrup which crystallized after standing for several months on P₂O₅, but did not show a sharp melting point (about 62°).

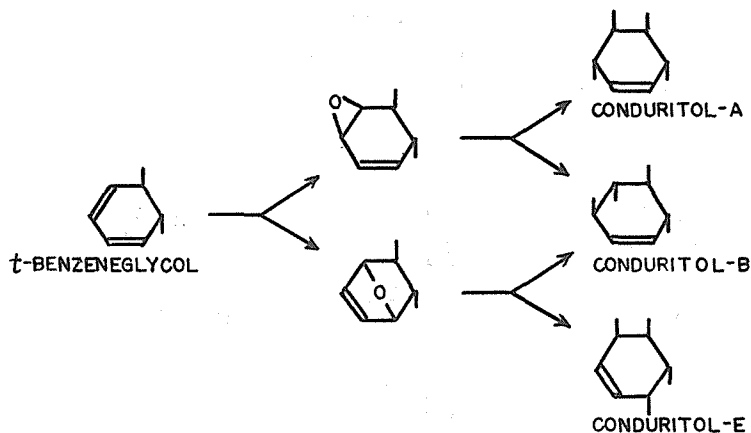


2.2.4. From benzeneglycols. The authors succeeded in preparing all the theoretically possible isomers of the conduritol except conduritol-D by hydroxylation of benzeneglycols⁹⁾¹⁶.

When *trans*-benzeneglycol was treated with perbenzoic acid in aqueous solution, it gave a syrup from which conduritol-A (the natural conduritol) was isolated by cellulose powder chromatography as colorless crystals in 40% yield. Thus the natural conduritol was synthesized for the first time which had been isolated in the beginning of this century. By this procedure, conduritol-E (5

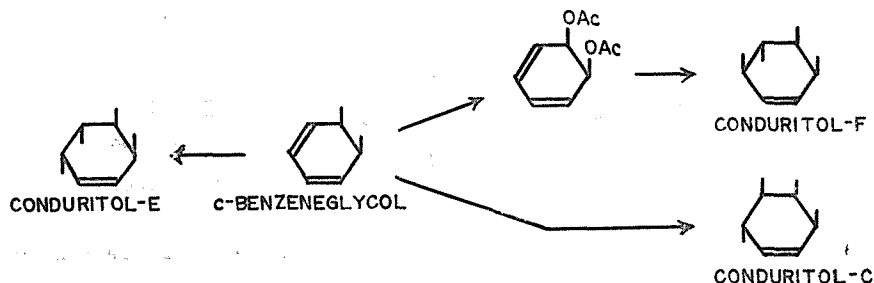
%) and very small amount of conduritol-B were also isolated.

trans-Hydroxylation of diacetate of *trans*-benzeneglycol also gave conduritol-A but in lower yield. It gave conduritol-E in 16.5% and -B in 3.5%. Conduritol-E has the conformation $\overline{\text{HH}}\text{ae}a \rightleftharpoons \overline{\text{HH}}\text{eae}$ which is the racemic compound of the active conduritol prepared from *L*-inositol by Angyal & Gilham¹⁴. The formation of conduritol-E from *trans*-benzeneglycol confirms the existence of 1,4-epoxide as an intermediate¹⁰.



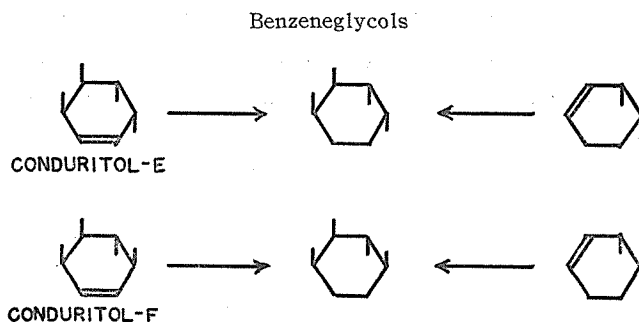
cis-Benzeneglycol diacetate, on permanganate oxidation (*cis*-hydroxylation), gave conduritol-E in a fairly high yield. The *all-cis* conduritol has not been isolated from the resulted syrup although the formation of this isomer is theoretically possible.

On the other hand, *trans*-hydroxylation of *cis*-benzeneglycol gave conduritol-C only but not conduritol-F. When it was allowed to react as diacetyl derivative, conduritol-F tetraacetate was obtained as plates, which was deacetylated to conduritol-F⁹.



Silver chlorate and osmium tetroxide were used for the *cis*-hydroxylation of *trans*-benzeneglycol. From the resulted material, conduritol-C was isolated as its tetraacetate¹⁰.

The structures of conduritol-E and -F were determined by hydrogenation to the known saturated tetrols which had been prepared from 3,4-dihydroxycyclohexene-1 by Posternak and Friedli¹⁷.



The yield of conduritol isomers from benzeneglycols are listed below.

Benzeneglycol isomers	Conduritol isomers (%)					
	<u>A</u> (HH ^{ee} aa)	<u>B</u> (HH ^{ee} ee)	<u>C</u> (HH ^{ee} ae)	<u>D</u> (HH ^{ee} ae)	<u>E</u> (HH ^{ae} ae)	<u>F</u> (HH ^{ae} ee)
<i>cis</i> -B.G.	0(c)	—	34(t)	0(c)	51(c)	22(t)
<i>trans</i> -B.G.	40(t)	6(t)	24(c)	—	25(t)	0(c)

— ...theoretically impossible, (c)...*cis*-, (t)...*trans*-hydroxylation.

EXPERIMENTAL

Perbenzoic acid oxidation of *trans*-benzeneglycol (Preparation of conduritol-A, -B and -E).

(i) In aqueous solution: Five hundred mg of *trans*-benzeneglycol dissolved in 50 ml of water were added with cooling to 100 ml of aqueous perbenzoic acid solution (containing 720 mg; 1.25 moles equiv.). After 3 days standing at room temperature the precipitated benzoic acid was filtered off and the filtrate washed with ether. The aqueous layer was dried up in vacuo to give 740 mg of a syrup which was chromatographed on an alumina column (1.5 cm×21 cm) with methanol or on a cellulose powder column (4.5 cm×40 cm) with acetone-water 4:1. Conduritol-A was the first component to come off the column and conduritol-E and -B followed. The fractions containing conduritol-A (detected by paper chromatography) were collected and dried up to give a colorless syrupy residue. Extracted with boiling dry acetone or ethanol, and cooled in the refrigerator, it crystallized and weighed 265 mg (m.p. 120-130°). Recrystallized from ethanol, conduritol-A melted at 135°.

In a similar way, slower moving fractions gave 10 mg of conduritol-E (m.p. 174-176°).

(ii) In chloroform solution: One gram of *trans*-benzeneglycol diacetate dissolved in 5 ml of chloroform was added to 15 ml of chloroform solution of perbenzoic acid (containing 890 mg; 1.25 moles equiv.). After 3 days standing in the refrigerator, the solution was washed with 2 *N*-Na₂CO₃ and water and dried over Na₂SO₄. On distillation the solution gave 1.03 g of an oil, b.p. 122-127°/1 mm Hg. When 1.54 g of the oil were warmed in 10 ml of water with 1 drop of 2 *N*-H₂SO₄ on the steam bath, the oil was soon dissolved, and after cooled, the

solution neutralized with 1 drop of 2 *N*-Na₂CO₃ and evaporated to dryness. To the syrupy residue, 5 g of pyridine and 7.5 g of acetic anhydride were added. After standing overnight at room temperature, the mixture was poured onto crushed ice. After extraction with ether and washing with 2 *N*-H₂SO₄, water sat.-NaHCO₃ and water in turn, the ethereal layer was dried and the solvent evaporated. Four hundred and ninety mg of conduritol-E tetraacetate (m.p. 152.5-153°) were separated as plates.

C₁₄H₁₈O₈(314.3) Calcd. C 53.50 H 5.77
Found C 53.60 H 5.93

From the filtrate, 1.42 g of an oil (I) (b.p. 157-158°/1 mm Hg) were obtained.

Three hundred and twenty mg of conduritol-E tetraacetate were dissolved in 22 ml of a saturated solution of dry ammonia in absol. methanol. After standing overnight at room temperature and evaporating the solvent, acetamide was sublimed off from the residue at 70°/8 mm Hg. The residue, on recrystallization from absol. ethanol gave 0.10 g (67.5%) of conduritol-E, m.p. 179-180° (colorless plates).

A part (1.19 g) of the oily mixture described above (I), after redistillation, was ammonolysed with 40 ml of a saturated solution of dry ammonia in absol. methanol. After removal of the solvent and acetamide, the syrupy residue was chromatographed on alumina column (1.5 cm×15 cm) with absol. methanol and 90% methanol in turn. From the faster moving fractions, 0.11 g of a syrup, and from the slower moving fractions, 0.09 g of a syrup were obtained respectively. On extraction with hot acetone and recrystallization from absol. ethanol, the former syrup gave 60 mg of conduritol-A (m.p. 140-141°) which did not show any depression when mixed with the natural conduritol.

C₆H₁₀O₄(146.1) Calcd. C 49.31 H 6.90
Found C 49.51 H 7.29

When the slower moving material was treated with absol. acetone, it gave 40 mg of conduritol-B (m.p. 199-200°).

C₆H₁₀O₄(146.1) Calcd. C 49.31 H 6.90
Found C 49.58 H 7.03

Silver chlorate oxidation of *trans*-benzeneglycol (Preparation of conduritol-C). To 0.42 g of *trans*-benzeneglycol in 5 ml of water added 5 ml of aqueous solution containing 0.21 g of silver chlorate and a few mg of osmium tetroxide. The dark brown or black colored solution thus obtained was allowed to stand for 4 days in a dark place at room temperature. Then the precipitated silver chloride was filtered off and the filtrate, after washed with ether, evaporated to dryness. A syrupy residue (0.56 g) resulted to which 1.5 g of pyridine and 3 g of acetic anhydride were added. After standing overnight, the reaction mixture was poured into ice-water, extracted with ether and washed with 2 *N*-H₂SO₄, water, sat.-NaHCO₃ and again water. On evaporation of ether after drying over Na₂SO₄, the extract gave 0.65 g of residue which was recrystallized from methanol to give 0.4 g (34.5%) of conduritol-C tetraacetate, m.p. 92°.

C₁₄H₁₈O₈(314.3) Calcd. C 53.50 H 5.77
Found C 53.58 H 5.92

Benzeneglycols

From 0.31 g of the tetraacetate, 0.1 g (70%) of crystalline conduritol-C were obtained by ammonolysis with 22 ml of a saturated solution of dry ammonia in absol. methanol. A mixed m.p. of the crystals (148-149°) with ones synthesized by McCasland was not depressed.

$C_6H_{10}O_4$ (146.1) Calcd. C 49.31 H 6.90
Found C 49.30 H 7.11

Permanganate oxidation of *cis*-benzeneglycol diacetate (Preparation of conduritol-E). To 65 ml of ethanol solution of 1.38 g of the diacetate, 1.1 of $MgSO_4$ in 10 ml of water were added. There were dropped in portion 110 ml of 1% $KMnO_4$ solution with vigorous stirring at -4 to -5°. When about a half of the permanganate solution was added, there was poured a cooled mixture of 65 ml of ethanol with 1.1 g of $MgSO_4$ in 10 ml of water. After standing overnight, MnO_2 was filtered off and the filtrate evaporated to dryness. The residue was treated with 7 g of pyridine and 7 g of acetic anhydride. Recrystallization from ethanol gave 1.36 g (61%) of conduritol-E tetraacetate, m.p. 149-150°.

$C_{14}H_{18}O_8$ (314.3) Calcd. C 53.50 H 5.77
Found C 53.79 H 6.07

Perbenzoic acid oxidation of *cis*-benzeneglycol (Preparation of conduritol-C and -F). Oxidation was carried out in a similar way as described above.

(i) In aqueous solution: From 0.44 g of *cis*-benzeneglycol and 0.66 g of perbenzoic acid in 100 ml of water, 0.55 g of a syrup were obtained. Four hundred and thirty mg of it gave 0.15 g of conduritol-C (m.p. and mixed m.p. 144-145°) and 0.27 g of a viscous product.

(ii) In chloroform solution: From 2.63 g of *cis*-benzeneglycol diacetate and 2.20 g of perbenzoic acid in 57 ml of chloroform, an oily residue was obtained and hydrolyzed with 2 *N*- H_2SO_4 to give 3 g of an oil. From the oil, 15 g of pyridine and 15 g of acetic anhydride, 2.84 g of a viscous oil were gained. Recrystallized from methanol. Giving 1.27 g of conduritol-F tetraacetate melted at 92° (colorless prisms).

$C_{14}H_{18}O_8$ (314.3) Calcd. C 53.50 H 5.77
Found C 53.35 H 5.74

From the filtrate, 1.38 g of an oily substance were obtained.

From 0.32 g of the tetraacetate and 25 ml of ammonia saturated absol. methanol, 0.11 g of conduritol-F, m.p. 103-104° (plates) were obtained.

$C_6H_{10}O_4$ (146.1) Calcd. C 49.31 H 6.90
Found C 49.17 H 7.06

3. INOSITOLS

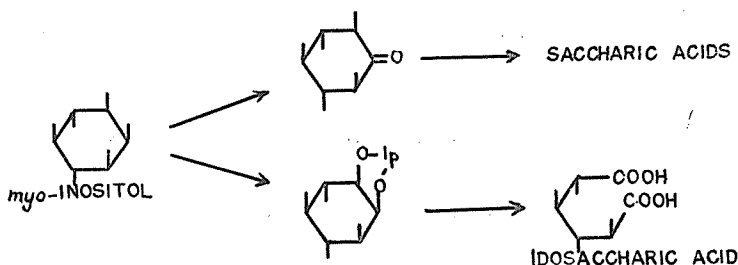
3.1. Introduction

Inositols have a wide distribution in the tissue of plants and animals, and many investigations on them have been carried out from the biochemical standpoint. Organic chemists, also, have had interests in inositols since

inositols have given them many attracting stereochemical problems.

The conformation of *myo*-inositol, the first isolated inositol¹⁸⁾, had not been determined until 1942. In this year, Posternak¹⁹⁾ used an enzymatic dehydrogenation to introduce a keto-group stereospecifically at C-2* in the cyclohexane ring. 2-Ketodeoxyinositol thus obtained was called *myo*-inosose-2 and was oxidized to yield saccharic acids.

Dangschat, on the other hand, prepared the isopropylidene derivative of *myo*-inositol, from which he derived another dicarboxylic acid, idosaccharic acid²⁰⁾. These experimental results established the conformation of *myo*-inositol.



This is an example of the conformational analysis of inositol isomers. Later, such interesting reactions as enzymatic dehydrogenation have been developed into other parts of the cyclitol chemistry. Besides that, many organic chemists began to make attempts to synthesize inositols. On the syntheses of inositols, we will review in the following sections.

The following table shows the melting points of inositols and their hexaacetate⁴⁴⁾.

Inositol	M.p.	M.p. of hexaacetate	Conformation
<i>myo</i>	223°	217°	aeceee $\rightleftharpoons$ eaaaaa
<i>dl</i>	253°	112°	aaeece $\rightleftharpoons$ eeaaaa
<i>epi</i>	304° (dec.)	188°	aeaece $\rightleftharpoons$ eaeaaa
<i>muco</i>	ca 300° (dec.)	178°	aaaaee ($\rightleftharpoons$ eeeaaa, i.e., identity)
<i>allo</i>	ca 320° (dec.)	144°	aaeae ($\rightleftharpoons$ eaeaaa, i.e., <i>d</i> $\rightleftharpoons$ <i>l</i> isomers)
<i>scyllo</i>	355°	301°	eeeece $\rightleftharpoons$ aaaaaa
<i>cis</i>	377° (dec.)	208°	aeaeae ($\rightleftharpoons$ eaeaea, i.e., identity)
<i>neo</i>	315° (dec.)	253°	aeaece $\rightleftharpoons$ eaeaaa

* There is no generally accepted method of numbering the derivatives of inositol. In this paper, we use the following method.

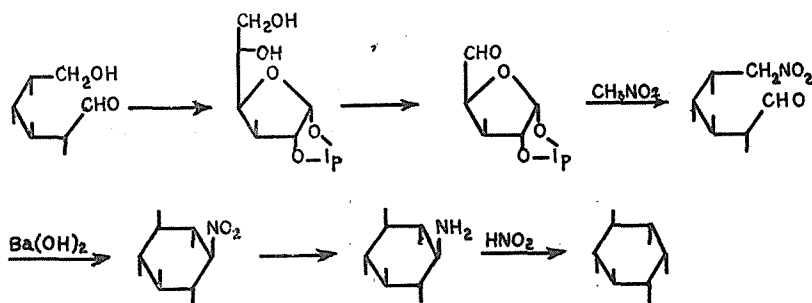
For each of inositols and their derivatives, each carbon atom on the ring is numbered so that the larger number of functional groups on one side of the average cyclohexane plane is described by the lowest possible numbers.

3.2. Syntheses

3.2.1. Hydrogenation of hexahydroxybenzene. In 1914, Wieland and Wishart²¹⁾ achieved the first synthesis of an inositol. The starting material was hexahydroxybenzene, which was catalytically hydrogenated to yield mainly (over 50%) *myo*-inositol—the isomer having the widest distribution in plants and animals out of eight possible isomers of inositol. Since then, similar reactions were carried out by Anderson and Wallis²²⁾, and by Kuhn *et al.*,²³⁾ but they obtained several cyclitols including *myo*-inositol in smaller yield.

Recently, Angyal and McHugh²⁴⁾ reported a precise and energetic work on hydrogenation of hexahydroxybenzene. They used tetrahydrobenzoquinone as starting material, which gave hexahydroxybenzene readily during the hydrogenation. Using chromatography, they could isolate troublesomely fourteen products including seven inositols and three quercitols, among which *myo*-inositol was isolated in 17.2% yield in one experiment, and *cis*-inositol in 20% yield in the other experiment.

3.2.2. Cyclization of sugars. Cyclization of hexose derivatives was carried out by Grosheintz and Fischer²⁵⁾ in 1948. They prepared 6-nitrodeoxyglucose (or -idose) after three operations from glucose (or idose). It was treated with baryte to give nitrodeoxyinositol, which on catalytic hydrogenation gave aminodeoxyinositol (*all trans*). Later, Posternak²⁶⁾ treated this inosamine with nitrous acid to obtain *myo*-inositol. In this reaction, a substitution occurred, and a hydroxyl group entered the position with inversion where the amino-group had been situated. It is the only example that an isomer of the cyclitol was synthesized by cyclization of sugars. This synthetic method of *myo*-inositol is an interesting one from the biogenetic standpoint. In fact, some authors reported the conversion of glucose to *myo*-inositol and vice versa in the rat^{26a) 27) 28)}.



3.2.3. Reduction of inososes. There is another way to prepare inositols, that is the reduction of ketogroup of inososes. Inososes have been obtained by the dehydrogenation of inositols. Consequently, the reduction of inososes does not have the practical meaning for the synthesis of inositols, but rather gives some interesting problems in stereochemistry.

(1) The first inosose was reported by Posternak in 1936²⁹⁾. He oxidized *myo*-inositol with nitric acid and obtained a sugar like substance which showed

reducing power. On catalytic hydrogenation, it gave *epi*-inositol. From this fact and other experimental data, he confirmed that this substance was *myo*-inosose-4.

Later, two kinds of stereospecific dehydrogenation reaction, one of which was cited in the introduction of this chapter, were performed on inositols. The one is dehydrogenation with *Acetobacter suboxydans*, and the other the metal catalytic dehydrogenation with oxygen.

When *myo*-inositol was dehydrogenated with *Acetobacter suboxydans*, it gave only one isomer of inosose—*scyllo*-inosose (= *myo*-inosose-2)³⁰⁾. If the starting inositol was *epi*-inositol, the only product was *epi*-inosose-2 (= *myo*-inosose-4)³¹⁾. Similar results were obtained concerning other cyclitols³²⁾ showing that dehydrogenation occurred favorably at the axial hydroxyl group. Some precise investigations were carried out recently^{33) 34)}, and the following rule was proposed. The hydroxyl group attacked must satisfy the following conditions: (1) being axial, (2) having an equatorial-OH at the *meta* position and (3) having an equatorial-OH at the *para* position. This rule might be revised in the future, but it is no doubt that this dehydrogenation reaction is highly stereospecific.

Another stereospecific dehydrogenation was reported by Heyns *et al.*³⁵⁾ who investigated the catalytic oxidation of sugars. *myo*-Inositol was mixed with Pt-C in neutral medium, and oxygen gas introduced. *myo*-Inosose-2 was the main product which was identical with the inosose obtained by the bacterial dehydrogenation.

Also in other examples^{26) 37)}, this catalytic dehydrogenation attacked only the axial hydroxyl group, but we may say that the catalytic dehydrogenation is less stereospecific than the bacterial one.

(2) Inososes were reduced to the corresponding inositols by catalytic hydrogenation or Na-Hg reduction. Generally speaking, catalytic hydrogenation of cyclic ketone gave the axial hydroxyl group, although sodium amalgam yield the equatorial one. The following Table shows some examples of the preparation of inositols by these methods^{29) 30) 36)}.

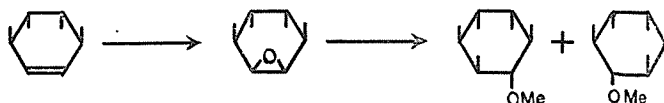
Starting inosose	Method	Product(s) (Inositols)
<i>myo</i> -inosose-2	H ₂ -Pt	<i>myo</i> + <i>scyllo</i> (trace)
	Na-Hg, AcOH	<i>myo</i> + <i>scyllo</i> (almost equal amount)
<i>epi</i> -Inosose-2	H ₂ -Catal.	<i>epi</i> (chiefly)
	Na-Hg, acidic	<i>epi</i> + <i>myo</i> (3:1)
<i>neo</i> -Inosose-2	Na-Hg	<i>myo</i> (40%)

3.2.4. Hydroxylation of conduritols. The authors succeeded in preparing all the inositols except *cis*-inositol by introducing two hydroxyl groups to the double bond of conduritols³⁸⁾.

(1) ***trans*-Hydroxylation.** In 1947, Schöpf³⁹⁾ prepared conduritol-A epoxide

Benzeneglycols

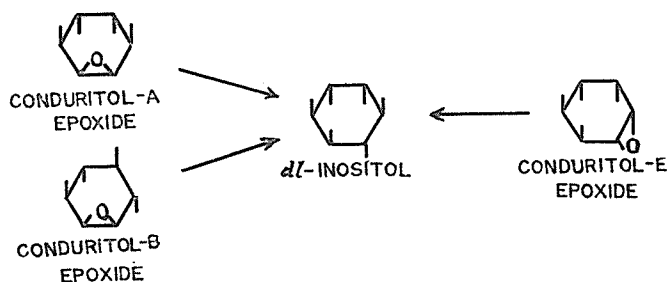
from the natural conduritol by the oxidation with perbenzoic acid in acetic acid and chloroform. The conformation was established by Angyal and Gilham⁴⁰⁾ who treated this epoxide with sodium methoxide and obtained ($\pm$)-pinitol.



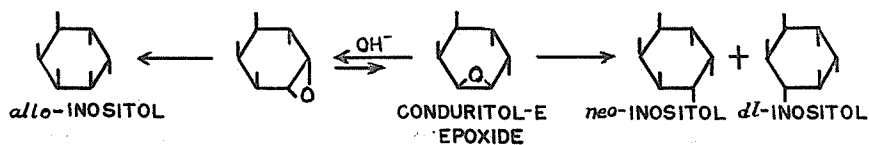
The authors synthesized the other conduritol epoxides in the similar way as Schöpf's and, by hydrolysis of them with dilute sulfuric acid, obtained most isomers of inositol³⁸⁾. Among these epoxides, the conformations of conduritol-C epoxide and conduritol-F epoxide were not determined yet. The investigation on this problem is now going on.

Most conduritol epoxides were hygroscopic and some of them did not show the sharp melting point. The epoxides were hydrolyzed easily to give the corresponding isomers of inositol with dilute acid or alkali. *dl*-Inositol was the only product from conduritol-A epoxide and was obtained also from conduritol-B or -E epoxide. Conduritol-B epoxide gave the other isomer—*scyllo*-inositol—in small yield.

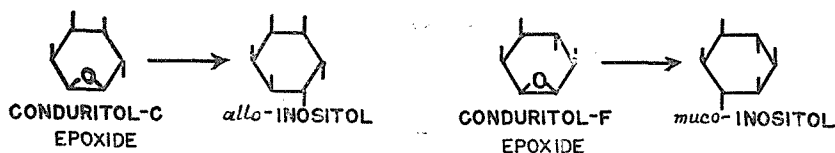
Conduritol epoxide	M.p.
A	112°
B	155°
C	134-146°
E	{176° 186-189°
F	157.5°



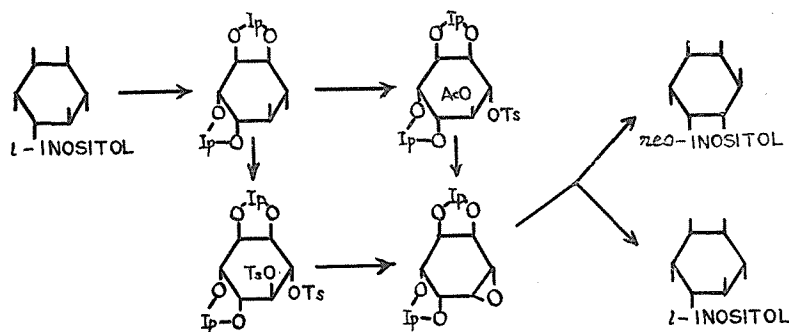
Conduritol-E epoxide gave also *neo*-inositol, the newest isomer of inositol ; but on alkaline hydrolysis, epoxide migration⁴⁰⁾ occurred, and *allo*-inositol also formed.



allo-Inositol was the main product from conduritol-C epoxide and *muco*-inositol from conduritol-F epoxide. Conduritol-C epoxide gave very small amount of *myo*-inositol, which was not yet obtained from conduritol-F epoxide.



Angyal and Matheson⁴¹⁾ prepared some mono- and ditosyl esters of inositols, which were treated with dilute sodium methoxide. They obtained some anhydroinositols (conduritol epoxides) from which they synthesized some inositols. From *l*-inositol, for example, they obtained *neo*- and *l*-inositol in the following way.



Later, Angyal and Gilham⁴⁰⁾ obtained two other anhydroinositols from *epi*-inositol, which correspond conduritol-D epoxides. These epoxides were also hydrolyzed to yield inositols, the formation of which was confirmed only by paper chromatography.

(2) ***cis*-Hydroxylation.** *cis*-Hydroxylation of the natural conduritol (conduritol-A) was carried out by Dangschat and Fischer¹¹⁾ in order to establish its conformation. As described in the section 2.1., they obtained *allo*-inositol and *muco*-inositol, the former of which was obtained only from the isopropylidene derivative of the conduritol. It suggests the existence of the steric effect of isopropylidene group to the approach of the oxidizing agent.

Recently, the extensive work on the *cis*-hydroxylation of conduritol isomers was accomplished in Kyoto³⁸⁾. On hydroxylation with potassium permanganate, each conduritol tetraacetate examined gave one or two inositols, respectively. *myo*-Inositol was the only product from conduritol-B tetraacetate, *allo*-inositol from conduritol-E tetraacetate, and *dl*-inositol from conduritol-F tetraacetate.

Criegee and Becher¹⁵⁾ prepared *allo*-inositol from conduritol-D with silver chlorate and osmium tetroxide, and Angyal and Gilham¹⁴⁾ also oxidized conduritol-D and an optical active conduritol-E to obtain only *allo*-inositol. As shown in these experimental results, *cis*-inositol, which might be formed by

Benzeneglycols

the *cis*-hydroxylation of conduritol-D, cannot be isolated as yet.

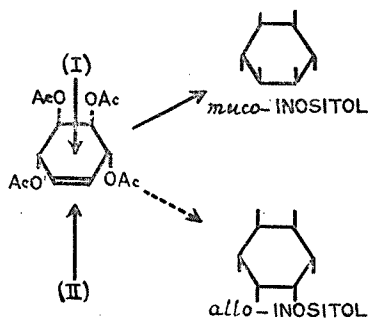
(3) Inositols obtained from conduritols by *cis*- or *trans*-hydroxylation are listed below. The numbers in the table show the yield of each isomer.

Conduritols	Inositol hexaacetates						
	<i>myo</i> - aeeee	<i>dl</i> - aeeee	<i>epi</i> - aeae	<i>muco</i> - aaaa	<i>allo</i> - aaee	<i>scyllo</i> - eeeee	<i>neo</i> - aeae
A ($\overline{\text{HH}}\text{aaee}$)	—	59(t)	—	60(c)	0(c)	—	—
B ($\overline{\text{HH}}\text{eeee}$)	65(c)	44(t)	—	—	—	3(t)	—
C ($\overline{\text{HH}}\text{eae}$)	3(t)	—	4(c)	—	54(t)	—	20(c)
E ($\overline{\text{HH}}\text{aeae}$)	—	27(t)	—	—	45(c)	—	44(t)
F ($\overline{\text{HH}}\text{ae}$)	0(t)	69(c)	0(c)	15(t)	—	—	—

The experimental results mentioned above reveal some interesting stereochemical features in the hydroxylation reaction.

Conduritol epoxides were cleaved in such a way as to give favorably the two hydroxyl groups having the axial orientation. (Fürst and Plattner's rule⁴²⁾ of diaxial opening of steroid epoxides is applied to those cases). For example, conduritol-B gave *dl*-inositol in much higher yield than *scyllo*-inositol. In the cases of conduritol-C and -F, the situation was similar. But, in conduritol-E, the yields of two products were comparable. This suggests that the both conformations of conduritol-E epoxide have a comparable stability and the inter-conversion of the ring occurred easily.

In the cases of *cis*-hydroxylation, the yield ratio of products might be controlled greatly by the easiness of the approach of the reagents and by the steric hindrance between the hydroxyl groups in the products. For example, the *cis*-hydroxylation of conduritol-A tetraacetate gave only *muco*-inositol but not *allo*-inositol. In this case, we can consider that the approaching of the reagent would be easier from the side (I) than the side (II). (See the figure). And, of the products, *muco*-form has smaller non-bonded interactions than *allo*-form according to the Barton's theory⁴³⁾ on non-bonded interactions of the cyclohexane derivatives.



EXPERIMENTAL

trans-Hydroxylation of conduritols

Perbenzoic acid oxidation of conduritol-A. Eighty mg of conduritol-A (m.p. 139-140°) dissolved in 6 ml of glacial acetic acid were mixed with 2.3 ml of chloroform solution of 128 mg of perbenzoic acid. After 3 days standing at room temperature, the solvent was evaporated in vacuo, and the residue washed with absol. ether several times. Then it was dissolved in a few ml of absol. ethanol and rubbed with cooling. Conduritol-A epoxide (m.p. 111-112°) separated as colorless crystals.

$C_8H_{10}O_5$ (162.1) Calcd. C 44.44 H 6.22

Found C 44.26 H 5.90

This epoxide was heated for 2 hours on the steam bath with 4 ml of 0.5 *N*- H_2SO_4 . After cooling and neutralization with 1 *N*- Na_2CO_3 , the solution was evaporated to dryness and the residue heated for 1 hour on the steam bath with 1 g of pyridine and 1 g of acetic anhydride. The reaction mixture was poured into ice-water and extracted with ether. The ethereal layer was washed with 2 *N*- H_2SO_4 , water, sat.- $NaHCO_3$ and then water again. After drying over Na_2SO_4 , it was evaporated to a viscous oil which gave 0.14 g (59%) of crystals when rubbed with aqueous methanol, m.p. 106-108°. It melted at 110-111° after recrystallizations and did not depress the melting point when mixed with authentic *dl*-inositol hexaacetate.

$C_{18}H_{24}O_{12}$ (432.4) Calcd. C 50.00 H 5.60

Found C 49.81 H 5.74

One hundred and fifty mg of *dl*-inositol hexaacetate were dissolved in 5 ml of ethanol and boiled with 5 ml of conc. HCl for 2 hours. Evaporation of the solvent and crystallizations from ethanol gave 60 mg (96%) of *dl*-inositol, m.p. 240-243° (dec.). After recrystallizations, it decomposed at 243°.

$C_6H_{12}O_6$ (180.2) Calcd. C 40.00 H 6.71

Found C 39.75 H 6.86

trans-Hydroxylation of conduritols other than conduritol-A was carried out in a similar way as described above.

Conduritol-B, 0.1 g, acetic acid, 7 ml, and prebenzoic acid, 0.16 g, in chloroform, 3 ml gave conduritol-B epoxide, m.p. 154-155°. After hydrolysis of the epoxide and following acetylation, *dl*-inositol hexaacetate, 0.13 g (44%), was obtained, m.p. 106-107°. *scyllo*-Inositol hexaacetate, 10 mg (3%), were also obtained, m.p. 289-290°.

Conduritol-C, 0.1 g, acetic acid, 5.5 ml, and perbenzoic acid, 159 mg, in chloroform, 2.5 ml, gave conduritol-C epoxide, m.p. 134-146°. After hydrolysis and following acetylation, *myo*-inositol hexaacetate, 10 mg (3%), m.p. 211-213°, and *all*-inositol hexaacetate, 160 mg (54%), m.p. 138-139°, were obtained.

Conduritol-E, 0.28 g, water, 5 ml, acetic acid, 15 ml, and perbenzoic acid, 467 mg, in chloroform, 11 ml, gave conduritol-E epoxide, 0.1 g (32%) (m.p. 186-189°) and 0.18 g (58.7%) (m.p. 175-176°). From the epoxide, 0.1 g, and 0.5 *N*- H_2SO_4 , 4 ml, *neo*-inositol, 50 mg (45%), m.p. 315° (dec.), was obtained. After

acetylation of the uncrystallized part, *dl*-inositol hexaacetate, 80 mg (30%) was obtained, m.p. 104-108°.

Conduritol-E epoxide, 0.12 g, treated with 0.5*N*-Ba(OH)₂, 6 ml, gave 0.14 g of an oil, which after acetylation gave *neo*-inositol hexaacetate, 10 mg (4%), *allo*-inositol hexaacetate, 50 mg (19%), and *dl*-inositol hexaacetate, 20 mg (8%).

Conduritol-F, 0.17 g, acetic acid, 10 ml, perbenzoic acid, 272 mg, in chloroform, 6.2 ml, gave conduritol-F epoxide, m.p. 157-157.5°. After hydrolysis and following acetylation, *muco*-inositol hexaacetate, 75 mg (15%), was obtained, m.p. 173-178°.

cis-Hydroxylation of Conduritols

Permanganate oxidation of conduritol-A tetraacetate. To 8 ml of ethanol solution of 0.28 g of conduritol-A tetraacetate, 0.14 g of MgSO₄ in 1 ml of water were added. There were added drop by drop 14 ml of 1% KMnO₄ solution with vigorous stirring at -4 to -5°. When about a half volume of the permanganate solution was added, there was poured a cooled mixture of 8 ml of ethanol with 0.14 g of MgSO₄ in 1 ml of water. After standing overnight, MnO₂ was filtered off and the filtrate evaporated to dryness. The residue was treated with 1 g of pyridine and 1 g of acetic anhydride. Recrystallization from methanol gave 0.23 g (60%) of crystals, m.p. 171-176°. After several recrystallizations, it melted at 177-178°. When mixed with authentic *muco*-inositol hexaacetate, it did not depress the melting point.

C₁₈H₂₄O₁₂ (432.4) Calcd. C 50.00 H 5.60

Found C 50.02 H 5.61

From 70 mg of the hexaacetate, by the method as described above, 20 mg (69%) of *muco*-inositol were obtained which was recrystallized several times from ethanol, but did not show any sharp melting point. It decomposed between 280-300°.

C₆H₁₂O₆ (180.2) Calcd. C 40.00 H 6.71

Found C 40.09 H 6.70

***cis*-Hydroxylation of conduritols other than conduritol-A** was carried out in a similar way as described above.

From conduritol-B tetraacetate, 0.1 g, ethanol, 6 ml, MgSO₄, 0.1 g, water, 1 ml, and 1% KMnO₄, 5 ml, and then pyridine, 0.5 g, acetic anhydride, 0.5 g; *myo*-inositol hexaacetate, 90 mg (65%), was obtained, m.p. 213°.

From conduritol-C tetraacetate, 0.4 g, dioxane, 6 ml, MgSO₄, 0.4 g, water, 2 ml, and 2% KMnO₄, 10 ml, and then pyridine, 1 g, and acetic anhydride, 2 g; *neo*-inositol hexaacetate, 0.11 g (20%), m.p. 252-253°, and *epi*-inositol hexaacetate, 20 mg (4%), m.p. 186-186.5°, were obtained.

From conduritol-E tetraacetate, 0.2 g, ethanol, 10 ml, MgSO₄, 0.2 g, water, 2 ml, and 1% KMnO₄, 10 ml, and then pyridine, 0.3 g, and acetic anhydride, 0.5 g; *allo*-inositol hexaacetate, 75 mg (45%), was obtained, m.p. 138-139°.

From conduritol-F tetraacetate, 0.2 g, ethanol, 12 ml, MgSO₄, 0.2 g, water, 2 ml, and 1% KMnO₄, 10 ml, and then pyridine, 1 g, and acetic anhydride, 1 g; *dl*-inositol hexaacetate, 0.19 g (69%), was obtained, m.p. 109-110°.

REFERENCES

- (1) R. L. Peck, C. E. Hoffhine Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, *J. Am. Chem. Soc.*, **68**, 776 (1946) ; O. Wintersteiner and A. Klingsberg, *J. Am. Chem. Soc.*, **70**, 885 (1948) ; K. Heyns and H. Paulsen, *Ber.*, **89**, 1152 (1956).
- (2) M. J. Cron, D. J. Johnson, F. L. Palermitt, Y. Perron, H. D. Taylor, D. F. Whitehead and I. R. Hooper, *J. Am. Chem. Soc.*, **80**, 752 (1958).
- (3) R. L. Mann and D. O. Woolf, *J. Am. Chem. Soc.*, **79**, 120 (1957).
- (4) M. Nakajima, I. Tomida, A. Hashizume and S. Takei, *Ber.*, **89**, 2224 (1956) ; M. Nakajima, I. Tomida and A. Hashizume, *Botyu-Kagaku*, **21**, 99 (1956).
- (5) N. A. Milas, *J. Am. Chem. Soc.*, **59**, 2342, 2345 (1937).
- (6) J. Booth, E. Boyland and E. E. Turner, *J. Chem. Soc.*, 1188 (1950).
- (7) G. Calingaert, M. E. Griffing, E. R. Kerr, A. J. Kolka and H. D. Orloff, *J. Am. Chem. Soc.*, **73**, 5224 (1951).
- (8) S. Takei, M. Nakajima, and I. Tomida, *Ber.*, **89**, 263 (1956).
- (9) M. Nakajima, I. Tomida and S. Takei, *Ber.*, **92**, 163 (1959).
- (10) K. Kubler, *Arch. Pharmaz.*, **246**, 620 (1908).
- (11) G. Dangschat and H. O. L. Fischer, *Naturwiss.*, **27**, 756 (1939).
- (12) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **75**, 4020 (1953).
- (13) G. E. McCasland and J. M. Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955).
- (14) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 375 (1958).
- (15) R. Criegee and P. Becher, *Ber.*, **90**, 2516 (1957).
- (16) M. Nakajima, I. Tomida, and S. Takei, *Ber.*, **90**, 246 (1957) ; M. Nakajima and I. Tomida, *Botyu-Kagaku*, **22**, 247 (1957).
- (17) Th. Posternak and H. Friedli, *Helv. Chim. Acta*, **36**, 251 (1953).
- (18) J. Scherer, *Ann.*, **73**, 322 (1850).
- (19) Th. Posternak, *Helv. Chim. Acta*, **25**, 746 (1942).
- (20) G. Dangschat, *Naturwiss.*, **30**, 146 (1942).
- (21) H. Wieland and R. S. Wishart, *Ber.*, **47**, 2082 (1914).
- (22) R. C. Anderson and E. S. Wallis, *J. Am. Chem. Soc.*, **70**, 2931 (1948).
- (23) R. Kuhn, G. Quadbeck and E. Röhm, *Ann.*, **565**, 1 (1949).
- (24) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 3682 (1957).
- (25) J. M. Grosheintz and H. O. L. Fischer, *J. Am. Chem. Soc.*, **70**, 1479 (1948).
- (26) Th. Posternak, *Helv. Chim. Acta*, **33**, 1597 (1950).
- (26a) J. W. Halliday and L. Anderson, *J. Biol. Chem.*, **217**, 797 (1955).
- (27) Th. Posternak, W. H. Schopfer and D. Reymond, *Helv. Chim. Acta*, **38**, 1283 (1955).
- (28) L. Anderson and R. H. Coots, *Biochim. Biophys. Acta*, **28**, 666 (1958).
- (29) Th. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).
- (30) Th. Posternak, *Helv. Chim. Acta*, **24**, 1045 (1941).
- (31) E. Chargaff and B. Magasanik, *J. Biol. Chem.*, **165**, 379 (1946).
- (32) B. Magasanik and E. Chargaff, *J. Biol. Chem.*, **174**, 173 (1948).
- (33) B. Magasanik, R. E. Franzl and E. Chargaff, *J. Am. Chem. Soc.*, **74**, 2618 (1952).
- (34) L. Anderson, R. Takeda, S. J. Angyal and D. J. McHugh, *Arch. Biochem. Biophys.*, **78**, 518 (1958).
- (35) K. Heyns and H. Paulsen, *Angew. Chem.*, **69**, 600 (1957), and references cited there.
- (36) G. R. Allen, *J. Am. Chem. Soc.*, **78**, 5691 (1956).
- (37) L. Anderson, E. S. DeLuca, A. Bieder and G. G. Post, *J. Am. Chem. Soc.*, **79**, 1171 (1957).
- (38) M. Nakajima, I. Tomida, N. Kurihara and S. Takei, *Ber.*, **92**, 173 (1959).
- (39) Cl. Schöpf and W. Arnold, *Ann.*, **558**, 123 (1947).
- (40) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 3691 (1957).
- (41) S. J. Angyal and N. K. Matheson, *J. Am. Chem. Soc.*, **77**, 4343 (1955).
- (42) A. Fürst and Pl. A. Plattner, Abstr. of papers, 12th International Congress of Pure and Applied Chemistry (New York) 1951, p. 405.
- (43) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
- (44) S. J. Angyal and L. Anderson, *Advances in Carbohydrate Chem.*, **14**, 135 (1959).