[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Cyclitols. VIII. Bromination of *epi*-Inositol. Synthesis of Conduritol-C[1a,2]

BY G. E. MCCASLAND AND JOHN M. REEVES

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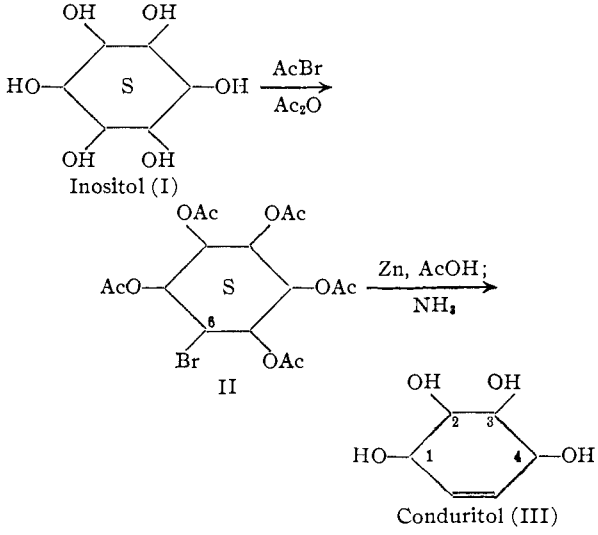
Conduritol-*C*, a new diastereomer of natural conduritol, has been synthesized from *epi*-inositol, and shown to have the configuration DL-XII. When *epi*-inositol is heated with acetyl bromide–acetic anhydride the pentaacetate of a new bromoquercitol is obtained. This pentaacetate on reaction with zinc–acetic acid gives conduritol-*C* tetraacetate, from which the free tetrol can be obtained by ammonolysis. On hydrogenation conduritol-*C* gives the known cyclohexane-1,2,3,4-tetrol (DL-XI), previously prepared by Posternak and Friedli from the cyclohexenediol X.

The conduritols or cyclohexenetetrols (structure III) are of interest because at least one of them occurs in nature, and because they can serve as intermediates for the synthesis of cyclitols which otherwise would be inaccessible.

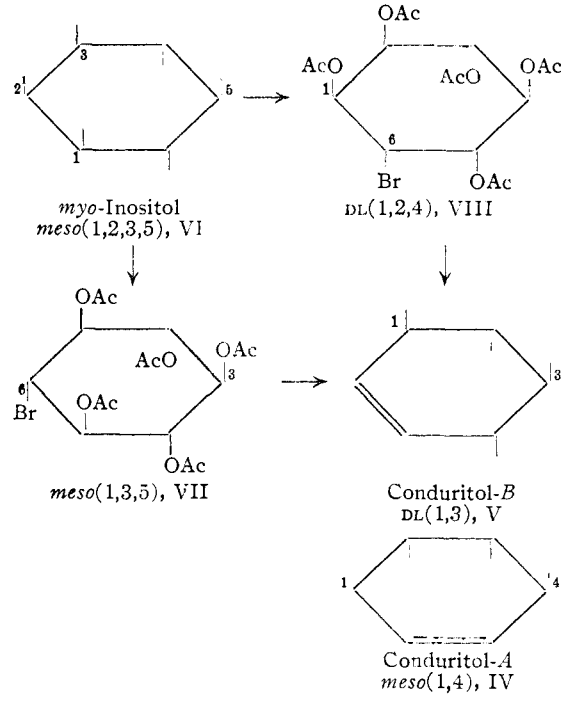
Six diastereomeric conduritols are possible, and of these two have been reported previously. Natural conduritol, which we now call conduritol-*A*, was isolated from condurango bark by Kubler[3] in 1908. It was shown later by Dangschat and Fischer[4a] to have the *meso*(1,4)-configuration, IV. The first synthetic conduritol was prepared in our laboratory[1c] in 1953. It was obtained by treating either of two bromoquercitol pentaacetates (formulas II and VII or VIII), derived from *myo*-inositol, with zinc and acetic acid. This synthetic conduritol was designated conduritol-*B*, and was shown[1c] to have the DL(1,3)-configuration, V.



The success of the reaction sequence (I → II → III) led us to seek other bromoquercitols from which new conduritols might be obtained. Of the twenty possible diastereomeric bromoquercitols only three[5] have been reported previously. Although

CHART I

BROMINATION OF *myo*-INOSITOL AND SYNTHESIS OF CONDURITOL-*B*



myo-inositol on bromination probably forms traces of bromoquercitols other than VII and VIII, there seems little chance of obtaining any of them pure and in a useful yield. The other two natural inositols are unpromising starting materials, since racemic inositol gives the same principal mono and dibromo products[6a] as *myo*-inositol, and Müller[6b] previously reported that *scyllo*-inositol also gives these same products. Of the remaining synthetic inositols, only *epi*-inositol is easily accessible, and it was accordingly chosen for the synthesis now reported.

When *epi*-inositol (IX)[7] was heated with acetyl bromide–acetic anhydride as previously described for *myo*-inositol,[1c] a new bromoquercitol pentaacetate of m.p. 153° was obtained in 35–40% yield. This intermediate, when treated with zinc and acetic acid, gave a new conduritol tetraacetate of m.p. 92°. On ammonolysis of this tetraacetate a free

(1) (a) For preceding paper in this series see G. E. McCasland and E. C. Horswill, THIS JOURNAL, **76**, 2373 (1954); (b) **76**, 1654 (1954); (c) **75**, 4020 (1953).

(2) From an M.A. Thesis submitted by J. M. Reeves to the Graduate School, University of Toronto, 1954.

(3) K. Kubler, *Arch. Pharm.*, **246**, 620 (1908).

(4) (a) G. Dangschat and H. O. L. Fischer, *Naturwissenschaften*, **27**, 756 (1939); (b) D. and F. prepared the tetraacetate of conduritol-*A*, but it was an oil and apparently has never been obtained in crystalline form.

(5) See formulas VII and VIII. The third diastereomer, reported by Kubler (ref. 3), is rather inaccessible, and its pentaacetate is unknown; on treatment wth zinc it might regenerate conduritol-*A*.

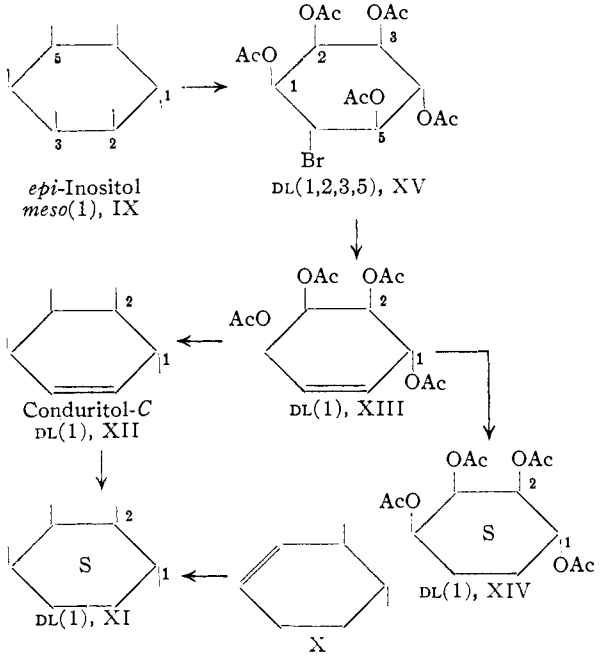
(6) (a) G. E. McCasland and J. M. Reeves, unpublished work; (b) H. Müller, *J. Chem. Soc.*, **101**, 2383 (1912).

(7) *epi*-Inositol was prepared first by Posternak in 1936 (ref. 9b) by hydrogenation of *epi*-inosose with platinum catalyst. We find it is more convenient to use commercial Raney nickel catalyst with water as solvent; an 85% yield of product, m.p. 283–285°, is obtained after two hours of hydrogenation at 3 atm. at 25°.

conduritol of m.p. 152° was obtained. This new diastereomer, which we call conduritol-*C*, clearly differs from conduritol-*A* (m.p. 143°) and conduritol-*B* (m.p. 205°). Although conduritol-*B* tetraacetate also melts at 92°, a mixed m.p. with conduritol-*C* tetraacetate was depressed.[4b]

CHART II

BROMINATION OF *epi*-INOSITOL AND SYNTHESIS OF CONDURITOL-*C*



epi-Inositol *meso*(1), IX

DL(1,2,3,5), XV

Conduritol-*C* DL(1), XII

DL(1), XIII

DL(1), XIV

DL(1), XI

X

In order to establish the configuration of conduritol-*C* a sample was hydrogenated, giving a saturated tetrol of m.p. 157°. This dihydroconduritol was shown by mixed m.p. and fusion analysis[8] to be identical with a cyclohexane-1,2,3,4-tetrol of the same m.p. which Posternak and Friedli[9a] had prepared recently from the cyclohexenediol X. Since Posternak and Friedli proved their tetrol to have the DL(1)-configuration[10] XI, it is apparent that conduritol-*C* must have the equivalent configuration XII.

The previously unreported tetraacetate XIV of Posternak's saturated tetrol was prepared by hydrogenation of conduritol-*C* tetraacetate; it melts at 112°.

Knowing the configurations of *epi*-inositol and of conduritol-*C* tetraacetate, one can draw some conclusions regarding the configuration of the bromoquercitol intermediate II. Since the conduritol double bond presumably is formed by a *trans* elimination, one need consider only the four diastereomers of II which would be produced by *trans* additions of bromine acetate (BrOAc) to conduritol-*C* tetraacetate, *i.e.*, DL(1,2,3,4), DL(1,2,3,5), DL-(1,2,3,6) or *meso*(1,5). Of these four possibilities, we are inclined to favor the DL(1,2,3,5) configuration XV,[10] since it could be formed easily by a single SN2 displacement of acetoxy by bromide[11] at position 3 (or 5) in *epi*-inositol hexaacetate (IX).

The reaction of IX hexaacetate to give mainly the product XV would be plausible from a mechanistic standpoint, since the acetoxy group displaced at position 3 (formula IX) is an *axial group with two neighboring cis equatorial groups*.[12] Any such group on a cyclitol ring must be unusually susceptible to rearward SN2 attack, *e.g.* by bromide ion, because the ring carbon bearing it would be relatively free from steric hindrance. This same mechanism was encountered previously[1c] in the displacement of the axial acetoxy group 2 (formula VI) of *myo*-inositol hexaaacetate to form VII.

While this mechanism may well represent one favored reaction path, it cannot be the exclusive path, since it is known that *myo*-inositol forms at least one other bromoquercitol product (VIII), and *epi*-inositol probably forms additional products not yet isolated. It is probable that simultaneous acetoxy participation mechanisms[1c] also are involved. In the case of *epi*-inositol this "participation" would presumably lead to retention of the "*epi*" configuration and substitution by bromine at position 1 or 2 (formula IX).

Experimental

All melting points (corrected) were taken on Köfler microblock unless otherwise noted; microanalyses are by Micro-Tech Laboratories, Skokie, Ill.; configurational assignments[10] should be regarded as tentative.

Preparation of DL(1,2,3,5)R-6-Bromoquercitol Pentaacetate (M.p. 153°) from *epi*-Inositol.—To 1.5 g. of *epi*-inositol[9b,7] in a Pyrex tube was added 1.32 ml. of acetyl bromide and 3.85 ml. of acetic anhydride. The tube was kept in a bath at 0° until the initial exothermic reaction had subsided, sealed off and the reactants were then mixed as thoroughly as possible by hand-shaking. The tube was then heated in an electric furnace at 130° for six hours.

After cooling, the tube contents were transferred to a flask and vacuum distilled. The oily residue was boiled under reflux with a fresh 3-ml. portion of acetyl bromide for one-half hour, and the mixture again vacuum distilled down to an oily residue. This residue was taken up in 2 ml. of hot absolute ethanol.

After 12 to 24 hours, the colorless crystals which had separated were collected, giving 1.67 g. of crude product. The product was recrystallized from ethanol, giving 1.42 g. (38%) of colorless needles, m.p. 149.5–151.5°. A sample recrystallized twice for analysis melted at 151.5–152.5°.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.37; H, 4.67. Found: C, 42.06; H, 4.92.

(8) W. C. McCrone, *Anal. Chem.*, **21**, 436 (1949).

(9) (a) T. Posternak and H. Friedli, *Helv. Chim. Acta*, **36**, 251 (1953); (b) T. Posternak, *ibid.*, **19**, 1333 (1936).

(10) The parenthesized numbers in each configurational prefix, *e.g.*, "*meso*(1,2,3,5)" (see formula VI) list the groups which are to one side of the plane of the cyclohexane ring; the remaining groups are assumed to be on the other side. Whenever, as in formula VI, the ordinary structural numbering would be ambiguous, the clockwise or counterclockwise direction and, if necessary the starting point, for numbering are so chosen as to yield the smallest numbers in the configurational prefix. "R" stands for relative and "A" for absolute configuration. For further explanation see the pamphlet, "A New General System for the Naming of Stereoisomers," available from *Chemical Abstracts*, c/o Ohio State University, Columbus 10, Ohio.

(11) We assume a preliminary fast acetylation, followed by slow reaction of hexaacetate with liberated hydrobromic acid. The apparent SN2 displacement actually may be a concerted displacement of acetoxy by bromide and hydrogen ions. There also may be internal displacement of an acetoxy group by a neighboring *trans*-acetoxy group; here also, hydrogen ion may simultaneously attack the departing acetoxy group. Because the hydrogen ion is of such small radius and need not penetrate to the ring carbon itself, any effect of steric hindrance on it is presumably negligible.

(12) The following predominant conformations are assumed for the inositols here mentioned: *myo*, AEEEEE; *scyllo*, EEEEEE; racemic, AAEEEE; *epi*, AEAEEE. For a valuable discussion on the role of conformation in determining stability and reactivity in the cyclitol series, see S. J. Angyal and J. A. Mills, *Australian Rev. Pure Appl. Sci.*, **2**, 185 (1952).

Attempts to hydrolyze the pentaacetate of m.p. 153° to the corresponding free bromoquercitol, by means of aqueous ethanolic hydrogen chloride or bromide, and by other methods, failed to yield any pure product.

DL-(1)R-5-Cyclohexene-1,2,3,4-tetrol Tetraacetate ("Conduritol-*C*" Tetraacetate, M.p. 92°).—The above bromoquercitol pentaacetate (0.55 g.) was treated by the procedure[1c] previously described for making conduritol-*B* tetraacetate from bromo*vibo*quercitol-*A* pentaacetate. The crude product melted at 85–91° and weighed 0.37 g. It was recrystallized from methanol–water (1:2), giving 0.20 g. (58%) of pure conduritol-*C* tetraacetate, m.p. 90–92°.

A mixed m.p. with conduritol-*B* tetraacetate,[1c] which has almost the same m.p. was depressed.

A sample recrystallized twice more for analysis melted at 90.5–92°.

Anal. Calcd. for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.61; H, 5.90.

The compound gives a sluggish reaction with bromine in either carbon tetrachloride or water, but gives a definite positive test for unsaturation with potassium permanganate–acetone. The presence of a double bond was confirmed by hydrogenation (see below).

On ammonolysis, the tetraacetate gave conduritol-*C* (see below).

DL(1)R-5-Cyclohexene-1,2,3,4-tetrol ("Conduritol-*C*," M.p. 152°).—The above tetraacetate of m.p. 92° (0.31 g.) was dissolved in 22 ml. of saturated anhydrous methanolic ammonia. After 24 hours at 25° the solution was filtered. Methanol, ammonia and most of the acetamide were removed by vacuum distillation. The oily residue was taken up in 3 ml. of hot absolute ethanol. The crystals which separated on cooling were collected, giving 0.10 g. of product melting at 151.5–152.2°. A second crop of 0.012 g. with the same m.p. was obtained: total yield 83%. A sample recrystallized once more for analysis showed no change in m.p.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.29; H, 6.97.

Conduritol-*C*, unlike its tetraacetate, reacts rapidly with bromine in water. The reaction with bromine in carbon tetrachloride is sluggish. The potassium permanganate test for unsaturation was positive. A negative test with dinitrophenylhydrazine showed that no rearrangement to a carbonyl compound had occurred.

On hydrogenation conduritol-*C* gave a saturated cyclohexanetetrol (see below).

Hydrogenation of Conduritol-*C* to DL(1)R-Cyclohexane-1,2,3,4-tetrol, M.p. 157°.—Conduritol-*C* (0.150 g.) in 5 ml. of water was hydrogenated with Raney nickel catalyst at 3 atm. at 28° for about two hours. After hydrogenation, the filtered mixture was vacuum distilled, giving a colorless crystalline residue of m.p. 110–154°. This was recrystallized from absolute ethanol, giving 0.057 g. (39%) of colorless crystals, m.p. 150–156°. A sample was recrystallized again, raising the m.p. to 155–157°.

The product was shown by mixed m.p. and fusion analysis[8] to be identical with the cyclohexane-1,2,3,4-tetrol (formula XI) of m.p. 157° prepared by Posternak and Friedli in 1953.[9a]

Hydrogenation of Conduritol-*C* Tetraacetate to DL(1)R-Cyclohexane-1,2,3,4-tetrol Tetraacetate, M.p. 112°.—Conduritol-*C* tetraacetate (0.12 g.) in 5 ml. of absolute ethanol was hydrogenated at 1 atm. at 26° for about two hours with Raney nickel catalyst. After hydrogenation the filtered mixture was vacuum distilled, giving 0.06 g. (50%) of a colorless crystalline residue of m.p. 108–115°. A sample of this residue was recrystallized from aqueous methanol, giving crystals of m.p. 110.5–111°. A sample recrystallized again for analysis melted at 111.0–111.5°.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.37; H, 5.98.

We also attempted to prepare the tetrabenzoate of reported[9a] m.p. 154° by benzoylation of the tetrol XI, but have not yet succeeded in purifying the product obtained.

Acknowledgment.—We are indebted to Dr. Théodor Posternak of the Université de Genève, Switzerland, for providing a sample of his cyclohexanetetrol of m.p. 157°; to Mr. Kenneth Irvine for assistance in the preparation of *epi*-inositol; and to the Research Council of Ontario and the Advisory Committee on Scientific Research for generous financial support.

TORONTO 5, CANADA

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Effect of Configuration on the Reactivity of the Chalcone System[1]

BY ROBERT E. LUTZ AND JAMES O. WEISS

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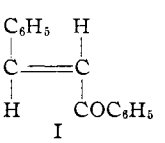
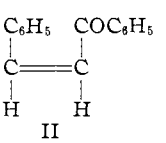
Phenylmagnesium bromide adds largely 1,4 to both *cis*- and *trans*-chalcones. Phenyllithium, which adds largely 1,2 to the *trans* isomer, adds chiefly 1,4 to the *cis*. Both isomers are reduced exclusively 1,2 at the carbonyl groups by aluminum isopropoxide and sodium borohydride, the *trans* isomer more easily than the *cis;* and both isomers are reduced 1,2 by lithium aluminum hydride. *trans*-Benzalacetomesitylene is not reduced by aluminum isopropoxide or sodium borohydride but is reduced 1,4 by lithium aluminum hydride. These results have been interpreted in terms of greater steric interferences in *cis*-chalcone, especially at the carbonyl carbon.

In the light of *cis–trans* differences in ultraviolet absorptivities and chemical reactivities of the α-phenylchalcones,[2] it was important to extend the study of such differences to the parent chalcones themselves (I, II) utilizing the now available *cis* isomer.[3]



I



II

Reaction with Alkaline Hydrogen Peroxide.—It has been pointed out[2a] that *trans*-chalcone (I), which has the more effectively conjugated system, reacts several times more rapidly with this reagent than does the *cis* isomer to give the same epoxide (the possible stereoisomeric epoxide is known[4b]). That this difference in rate of reaction is a true measure of the relative rates of peroxide attack and not of isomerization of the *cis* isomer first to the more reactive *trans* isomer, is now shown by the fact

(1) This investigation (a) was supported by a grant from the National Science Foundation, and (b) is described in a Master's thesis (J.O.W.), University of Virginia, August, 1954. (c) The work on the α-phenylchalcones by Lutz and Rinker (ref. 2c) also was supported by the grant from the National Science Foundation but was erroneously credited only to a grant from the Office of Ordnance Research under which the investigation was initiated.

(2) W. B. Black and R. E. Lutz, THIS JOURNAL, (a) **75**, 5990 (1953); (b) **77**, in press (1955); (c) R. E. Lutz and E. H. Rinker, **77**, 366 (1955).

(3) (a) R. E. Lutz and R. H. Jordan, *ibid.*, **72**, 4090 (1950); (b) L. P. Kuhn, R. E. Lutz and C. R. Bauer, *ibid.*, **72**, 5058 (1950).