point with a specimen of 2α,4α-dibromocholestan-3-one, m.p. 190–192.5° dec., was 184–190° dec., undepressed.

Debromination of the Bromochlorocholestanones.—(a) A solution of 200 mg. (0.40 mmole) of **5** and 63 mg. (0.43 mmole) of freshly recrystallized 2-naphthol in 5 ml. of carbon disulfide was treated with 1 ml. of glacial acetic acid containing 22 mg. of hydrogen bromide. After 3.5 hr. at room temperature, the reaction mixture was diluted with ether and washed successively with water, dilute sodium bicarbonate solution, dilute sodium hydroxide solution, and saturated sodium chloride solution. The dried organic solution was evaporated to leave 157 mg. (93%) of **2α-chlorocholestanone**. One recrystallization from chloroform–methanol gave 117 mg., m.p. 184–185° (cap.) (reported,[9] m.p. 185–186°), whose infrared spectrum in carbon disulfide (20 mg./0.1 ml.) was identical with that of authentic 2α-chlorocholestanone.

Anal. Calcd. for $C_{27}H_{45}OCl$ (421.09): Cl, 8.43. Found[35]: Cl, 8.57; Br, 0.71.[37]

Acidification of the sodium hydroxide washes and extraction with ether gave 82 mg. which was recrystallized from petroleum ether. There was obtained 14 mg. of 1-bromo-2-naphthol, m.p. 81–83.5° (reported,[36] m.p. 84°).

(b) A 200-mg. (0.40 mmole) sample of **4** was treated exactly as in part (a) except the reaction time was 4 hr. Work-up as described in (a) gave 162 mg. (96%) of crystalline **2α-chlorocholestanone**. One recrystallization from chloroform–methanol yielded 128 mg., m.p. 185.5–186.5° (cap.), whose infrared spectrum in carbon disulfide (20 mg./0.1 ml.) was identical with that of authentic 2α-chlorocholestanone.

Anal. Calcd. for $C_{27}H_{45}OCl$ (421.09): Cl, 8.43. Found[35]: Cl, 7.86; Br, 1.29.[37]

Acidification of the sodium hydroxide washes and extraction with ether gave 77 mg. which was recrystallized from petroleum ether. There was obtained 31 mg. of 1-bromo-2-naphthol, m.p. 78–82°.

Relative Rates of Debromination of 4 and 5.—A solution of 90 mg. (0.18 mmole) of **4** or **5** and 27 mg. (0.187 mmole) of freshly recrystallized 2-naphthol in 0.50 ml. of carbon disulfide was pipetted into a solution of 0.35 mg. of hydrogen bromide in 0.10 ml. of carbon disulfide contained in an n.m.r. sample tube. The spectrum of the capped tube (temperature = 37°) was recorded periodically over the region of C-19 methyl absorption (sweep width 250 cycles, sweep time 250 sec., spectrum amplitude 16, filter bandwidth 1, radio frequency 0.16). The 2-naphthol caused a 3 c.p.s. upfield shift of the C-19 methyl peak of both **4** and **5**. The area under the diminishing C-19 methyl peak was determined by the cut-and-weigh technique. The debromination was treated as a pseudo first-order reaction since the hydrogen bromide concentration will remain constant. First-order rate constants were determined graphically from a plot of log weight of C-19 methyl peak *vs.* time elapsed. The ratio k_4/k_5 obtained in this manner was 2.3. As a check the ratio of the rates of appearance of the C-19 methyl peak of 2α-chlorocholestanone was determined in the same way and found to be 2.5.

Acknowledgment.—The author wishes to thank the National Science Foundation for support under grant G15752 and for a generous departmental grant G18795 toward the purchase of the nuclear magnetic resonance spectrometer, without which this work could not have been done. He also wishes to thank Dr. R. J. Highet and Mrs. K. Warren, National Heart Institute, Bethesda, Maryland, for the rotatory dispersion measurements.

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[36] A. J. Smith, *J. Chem. Soc.*, **35**, 789 (1879).

[37] The small amount of bromine is probably from 2α-bromocholestanone present as a contaminant in the starting material **4** or **5**, or formed from **21** (small amount present in **4**) by debromination.

Synthesis of the Five Diastereomeric 1,2,4,5-Cyclohexanetetrols. Nuclear Magnetic Resonance Configurational Proofs[1,2]

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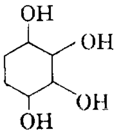
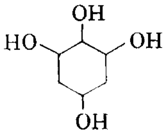
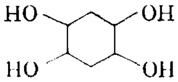
The five predicted diastereomers of 1,2,4,5- or "*para*" cyclohexanetetrol have now all been synthesized, and their configurations established by means of nuclear magnetic resonance spectra. *cis*-Hydroxylation of 1,4-cyclohexadiene gave a mixture of the two *cis/cis* tetrols, m.p. 225 and 241°; *trans*-hydroxylation, the two *trans/-trans* tetrols, m.p. 208 and 285°. N.m.r. spectra revealed that the 241 and 208° diastereomers each have four equivalent methylene protons, and so must have the configurations *meso*(12/45) and DL(14/25), respectively. The 225 and 285° diastereomers must then have the remaining configurations *meso*(1245) and *meso*(15/24), respectively. Successive *trans*- and *cis*-hydroxylation gave a tetrol, m.p. 209°, for which only the *cis/trans* configuration DL(124/5) is possible. Conformations are discussed. Acetate and benzoate derivatives were prepared.

In recent publications[2,5] we have reported the use of nuclear magnetic resonance spectra for establishing the configurations and conformations of newly synthesized stereoisomers of dimercaptocyclohexanetetrol and cyclohexanepentol (quercitol). We have now extended this approach to the cyclohexanetetrols[6] (deoxyquercitols).

A cyclohexanepentol or cyclohexanehexol can have various configurations, but only one *structure*. To characterize a cyclohexanetetrol, however, both structure and configuration must be established. The three possible structures for the tetrols are 1,2,3,4- or *ortho* (A); 1,2,3,5- or *meta* (B); and 1,2,4,5- or *para* (C).[7]


(A)


(B)


(C)

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[1] Presented before the Division of Carbohydrate Chemistry at the 143rd National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

[2] Paper XIV on Cyclitol Stereochemistry by G. E. McCasland and coworkers; for preceding paper see *J. Org. Chem.*, **28**, 456 (1963).

[3] To whom any correspondence should be addressed: Institute of Chemical Biology, University of San Francisco, San Francisco 17, Calif.

[4] Varian Associates.

[5] G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, (a) *J. Am. Chem. Soc.*, **83**, 2335 (1961); (b) **83**, 4243 (1961).

[6] The similar problem of preparing cyclopentanetetrols has recently been undertaken. See H. Sable and T. Posternak, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 6-D; see also Y. Gaoni, *Bull. Soc. Chim.*, 705 (1959), and note error in proposed configuration of tetrol, m.p. 137°.

[7] Disubstituted cyclohexanes can be described by the benzene prefixes *ortho*, *meta*, and *para*, and it is convenient to use these same prefixes to specify location of the methylene groups in tetrasubstituted cyclohexanes.

For the *ortho* structure, six diastereomers (two *meso*, four active) are predicted, and all are known,[8] thanks largely to the work of T. Posternak. For the *meta* structure, one *meso*[9b] and two active[10,11] diastereomers have been reported, and work on the three remaining *meso* diastereomers is in progress.[12] For the *para* structure, five diastereomers (three *meso*, two active) are predicted (formulas I, II, VIII, IX, X, Chart I), and all five have now been prepared and characterized. Although earlier preparations[9,13] of certain of these *para* isomers have been reported (see below), configurations were not established until now.[14–16]

Methods which have been employed for the preparation[17] of cyclohexanetetrols include: The reduction or *hydrogenation* of (1) cyclohexenetetrols,[10] (2) trihydroxycyclohexanones,[10] (3) pentahydroxycyclohexanones (inososes),[18] (4) hydroxylated aromatics,[16] or (5) hydroxylated quinones[16]; the (6) *hydrogenolysis* of dibromocyclohexanetetrols[9b]; the (7) *hydration* of diepoxycyclohexanes[13]; and the *hydroxylation* of (8) cyclohexadienes[13] or (9) cyclohexenediols.[8a] Methods 1 and 3 are suitable only for *ortho* tetrols, and methods 7 and 8 only for *ortho* or *para*.

The most attractive starting material for preparation of para cyclohexanetetrols appeared to be the commercially available[19] 1,4-cyclohexadiene, V. Since structural rearrangement was not expected[20] in the reactions employed, only the *para* structure needed to be considered for the products. By *cis*-addition of two hydroxyl groups at each double bond, this diene should give the two *cis/cis* tetrols, I and II; by *trans*-addition, the two *trans/trans* tetrols, VIII and IX; and by combination of *cis* and *trans*, the *cis/trans* tetrol, X.

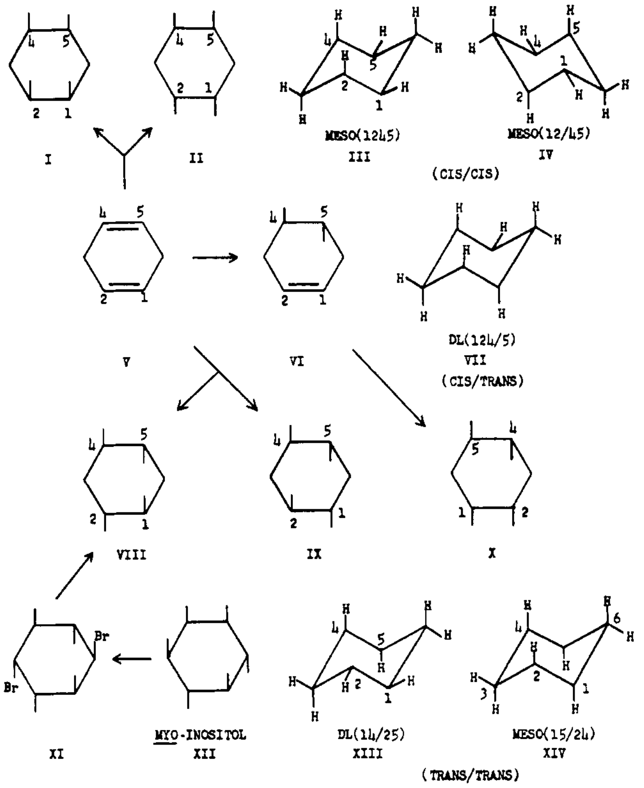

Chart I.—Configurations and conformations of the five diastereomeric 1,2,4,5-cyclohexanetetrols, showing synthetic routes. (Short vertical lines represent —OH or —OCOR groups.)

Table I

The 1,2,4,5 or *para* Cyclohexanetetrols[a]

Configuration	Conformation: Favored	Conformation: Unfavored	Melting points: Tetrol	Melting points: Tetraacetate	Melting points: Tetrabenzoate
		meso Diastereomers			
cis/cis, (1245), I	EAAE	AEEA[b]	225	128	. .
cis/cis, (12/45), II	EAEA	AEAE[b]	241	170	. .
trans/trans, (15/24), IX	EEEE	AAAA	285	. .	267
		Active[c] diastereomers			
cis/trans, (124/5), X	EAEE	AEAA	209	93	173
trans/trans, (14/25), VIII	EEAA	AAEE[b]	208	148	181

[a] Three *meso* and two active diastereomers predicted. [b] Two equally favored and indistinguishable conformations in rapid equilibrium. [c] Known only in racemic form at present.

Experimentally, *cis*-addition with silver chlorate/osmium tetroxide[8a,21] gave a mixture of two tetrols, m.p. 225 and 241° (Table I), richer in the latter. *trans*-Addition with silver benzoate/iodine gave a mixture of two tetrabenzoates, m.p. 181° and 267° (much richer in the former), from which were obtained the corresponding tetrols, m.p. 208 and 285°.

The choice between the two possible *cis/cis* configurations for each of the two isomers, m.p. 225 and 241°, would be very difficult by traditional methods. Since the molecules I and II would each have two *cis* (axial–equatorial) pairs of secondary alcohol groups, and at corresponding locations on the ring, the two diastereomers should respond almost identically[22]

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(8) (a) T. Posternak, *et al.*, *Helv. Chim. Acta*, **36**, 251 (1953); (b) **38**, 208 (1955); (c) **38**, 195 (1955); (d) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957); (e) P. Bedos and A. Ruyer, *Compt. rend.*, **196**, 625 (1933).

(9) (a) G. E. McCasland and E. Horswill, *J. Am. Chem. Soc.*, **76**, 1654 (1954); (b) **76**, 2373 (1954); (c) **75**, 4020 (1953).

(10) G. Dangschat and H. O. L. Fischer, *Naturwiss.*, **27**, 756 (1939).

(11) In a previous publication by G. E. McCasland [*J. Am. Chem. Soc.*, **76**, 2377 (1954)] it was erroneously stated that a *meta* cyclohexanetetrol should have *three* active diastereomers.

(12) G. E. McCasland and S. Furuta, to be published.

(13) N. Zelinski and A. Titova, *Ber.*, **64**, 1399 (1931).

(14) In 1901 E. von Lippmann [*Ber.*, **34**, 1159 (1901)] reportedly isolated from beet sugar molasses a weakly dextrorotatory (exact rotation not measured) cyclohexanetetrol, m.p. 224°. No acetate or benzoate was prepared. Conceivably this natural tetrol could be an active form of one of our two racemic products now reported.

(15) In 1932 F. Micheel [*Ann.*, **496**, 77 (1932)] reportedly prepared an *ortho*-cyclohexanetetrol, m.p. 229°, MD +47.5°, by cyclization of a diiodohexanetetrol derivative. It is now evident that this product could not have the configuration (12/34) which Micheel assigned it [*cf.* S. Angyal, *J. Chem. Soc.*, 376 (1958)]. If Micheel's product was in reality a cyclohexanetetrol, it could conceivably be an active form of one of our racemic para tetrols now reported.

(16) In 1957 S. J. Angyal by hydrogenation of quinonetetrol reportedly obtained a cyclohexanetetrol (m.p. 205–210° dec., tetraacetate 124°) of unknown structure and configuration. This isomer conceivably may correspond to our all-*cis*-*para* tetrol, m.p. 225° (tetraacetate 128°). See *J. Chem. Soc.*, 3682 (1957).

(17) Now that dimercaptotetrols are available (see our preceding publication), reduction should furnish a convenient new route to cyclohexanetetrols, at least those of *ortho* structure; experiments are in progress.

(18) G. Post and L. Anderson, *J. Am. Chem. Soc.*, **84**, 471 (1962).

(19) Aldrich Chemical Co., Milwaukee, Wis.

(20) In 1955 E. Van Tamelen [*J. Am. Chem. Soc.*, **77**, 1704 (1955)] suggested that the *trans*-cyclohexene-4,5-diol which McCasland and Horswill had reported the year before might actually be bicyclo[3.1.0]hexane-2,4-diol, due to unexpected rearrangement. However, experiments which he then performed confirmed the cyclohexenediol structure which McCasland and Horswill had originally assigned.

(21) G. Braun, *ibid.*, **51**, 228 (1929).

(22) Dipole moments no doubt would have served to distinguish the two *cis/cis* tetrols, if a suitable solvent (or derivative) for the dielectric constant measurements could be found.

Fig. 1.—Sixty-megacycle n.m.r. spectra of the five diastereomeric 1,2,4,5-cyclohexanetetrols in deuterium oxide. P.p.m. downfield from tetramethylsilane used as external reference. (A) *cis/cis*, m.p. 225°; (B) *cis/cis*, m.p. 241°; (C) *trans/trans*, m.p. 208°; (D) *trans/trans*, m.p. 285°; (E) *cis/trans*, m.p. 209°.

to nearly all characterizing procedures, chemical or physical. The choice between the two *trans/trans* configurations for each of the isomers, m.p. 208 and 285°, would also have been difficult, although in principle a decision between DL-VIII and *meso*-IX might have been reached by resolving[23] the substance having the former configuration. This was not found necessary, since the elegant and convenient approach of nuclear magnetic resonance has now provided a firm basis for both the *cis/cis* and *trans/trans* configurational decisions.

The 60-Mc. n.m.r. spectrum (Fig. 1-C) of the *trans/trans* tetrol, m.p. 208°, in deuterium oxide solution was first examined. The signals from the four methylene protons (XIII or XIV) appear in a narrow pattern (width less than 22 c.p.s.) at $\delta = 2.33$, where δ = p.p.m. downfield from tetramethylsilane (external) reference. The narrow pattern indicates that in this isomer there is very little if any chemical shift between the four protons of the two methylene groups. This was substantiated by examination of the same sample at 100 Mc., since the 100-Mc. spectrum showed essentially no change in the methylene signal fine structure. At $\delta = 4.26$ in the 60-Mc. spectrum (Fig. 1-C) there is a very similar pattern produced by the four O-C-H ring protons (positions 1,2,4,5, formula XIII or XIV), revealing that there is also very little if any chemical shift between these four protons.

This absence of chemical shifts suggests a rapid conformational interchange which on a time-average basis causes the two protons in each methylene to become equivalent with each other and with the protons of the other methylene; likewise, the four O-C-H protons become all-equivalent. Such a situation would exist in the diaxial–diequatorial chair conformation XIII, which on ring-inversion changes into a second diaxial–diequatorial conformation which is indistinguishable from the original (Table I). It may be concluded that the tetrol m.p. 208° has the *trans/trans* configuration[24] DL(14/25), VIII.

The other *trans/trans* tetrol, m.p. 285°, gave a spectrum (Fig. 1-D) in which the four methylene protons produce two sets of signals centered at about $\delta = 1.85$ and 2.67. The 2.67 pattern is basically a doublet of triplets, with a large doubling of 13 c.p.s. and a small tripling of 4 c.p.s. Such spacings would be expected for an equatorial proton (position 3 or 6, XIV) coupled to the geminal proton and to two neighboring axial ring protons. The pattern at $\delta = 1.85$ is quite wide, approximately 36 c.p.s., as would be expected for an axial proton coupled to two adjacent axial ring protons. Because of the molecular symmetry of XIV, the equatorial proton in one methylene is equivalent to the equatorial proton in the other methylene, likewise for the two axial methylene protons. The four O-C-H protons are all-equivalent.

A detailed assignment of all spectral peaks for the tetrol m.p. 285° would not be easily accomplished, since the eight protons produce a complicated $A_4B_2C_2$ signal pattern.[25] It is sufficient, however, to demonstrate that the two protons in each methylene are non-equivalent. Such non-equivalence would be expected for the conformation XIV, with four equatorial *hydroxyl* groups, since there would be very little tendency for ring-inversion into the highly unfavored tetraaxial[26] conformation. Thus the tetrol, m.p. 285°, can be assigned the corresponding *trans/trans configuration*, *meso*(15/24), IX.

The spectra of the two *cis/cis* tetrols can be interpreted by a similar approach. The m.p. 241° tetrol produces a spectrum (Fig. 1-B) which is basically a pair of triplets at $\delta = 2.33$ and 4.46. Here again the narrow signal pattern, at 2.33, of the four methylene protons indicates little or no chemical shift between them. This equivalence would be anticipated in the conformation IV, which by ring-inversion would change into a second diaxial–diequatorial conformation indistinguishable from the original.

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(23) Very few optical resolutions of racemic polyols or sugars have been reported. The well known methods used for racemic monohydroxy compounds often are unsatisfactory for polyols.

(24) For explanation of the fractional nomenclature used here to designate diastereomeric configurations, see our previous article, *J. Am. Chem. Soc.*, **83**, 2340 (1961). In each perspective formula, Chart I, the starting point and direction of numbering are so chosen that the numerator will have the longest and lowest set of numbers—*e.g.*, diastereomer X is designated (124/5), *not* (125/4) or (1/245).

(25) Terminology of J. Pople, W. Schneider, and H. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p. 98. The four all-equivalent O-C-H protons in the molecule XIV are designated "A".

(26) It is important to note that the *axial* O-C-H ring protons mentioned in the n.m.r. discussions and shown in the chair-type formulas, Chart I, correspond to *equatorial* hydroxyl groups and *vice versa*.

The m.p. 225° tetrol, on the other hand, gives a spectrum (Fig. 1-A) in which there is a 47 c.p.s. spread in the methylene signal pattern, which becomes even wider upon examination at 100 Mc. This corresponds to the situation in conformation III, in which the two protons in each methylene are non-equivalent.[27] It may be concluded that the tetrol diastereomers of m.p. 225 and 241° have the *cis/cis* configurations *meso*(1245), I, and *meso*(12/45), II, respectively.

From the method of preparation (*i.e.*, *cis*-addition to *trans*-cyclohexene-4,5-diol[28] derived from the 1,4-diene) the *cis/trans* tetrol, m.p. 209° (Table I), can have only[29] the configuration DL(124/5), X. Its n.m.r. spectrum (Fig. 1-E) has not been fully interpreted, but the complexity of the spectrum is consistent with the lack of symmetry in a molecule with the configuration and conformation, VII.

The spectrum of the tetraacetate or tetrabenzoate of each of the five diastereomeric tetrols was also recorded, using chloroform-*d* as solvent (see Experimental section), but these spectra were not found to be useful[30] for configurational assignments. In Table I the configurations, conformations and melting points for the five tetrols and their derivatives are given.

The n.m.r. spectra of the *para* cyclohexanetetrols reflect the interesting symmetry characteristics of these molecules. On the basis of chair conformations,[31] *meso*-IV has a center but no plane of symmetry, *meso*-XIV has a center and one plane of symmetry; and *meso*-III has one plane but no center of symmetry. The tetrol DL-VIII, although dissymmetric in all conformations, has a twofold simple axis of symmetry in conformation XIII. The *cis/trans* tetrol, DL-X, apparently has no element of symmetry in any conformation.

Although correlations of symmetry and melting point are not always a reliable guide to configuration, there can be little doubt that the unusually high m.p., and low solubility, of the *trans/trans* tetrol, m.p. 285°, and its tetrabenzoate, m.p. 267°, reflect the high symmetry of configuration *meso*-XIV as compared with DL-XIII. Likewise, the higher m.p. and lower solubility of the tetrol m.p. 241° and its acetate reflect the relatively high symmetry of the *cis/cis* configuration *meso*-IV, as compared with *meso*-III. These properties support the conclusions based on n.m.r. spectra.

In the reaction of cyclohexadiene, V, with aqueous silver chlorate/osmium tetroxide (see Experimental section) the tetrol product *meso*-II predominated over *meso*-I by an apparent ratio of 2 or 3:1. This ratio is estimated from isolated yields of pure products, no precise measurements of formation ratios have yet been made. Although II, being freer of 1,3-diaxial repulsions, would be thermodynamically more stable than I, the product-ratio more likely is kinetically controlled. No advance prediction of the predominant product could safely be made without a more intimate knowledge of the mechanism than was available. The experimentally found predominance of II possibly is due to greater transannular repulsions between cyclic chlorate or osmiate ester groups which presumably are present in the intermediates or transition states leading to I.

An advance prediction of predominant product might have been safer for the reaction of cyclohexadiene with silver benzoate/iodine in hot benzene (see Experimental section), since experimentally the tetrabenzoate product, m.p. 181°, strongly predominates over the tetrabenzoate, m.p. 267°, the apparent ratio being 20 or 30:1. A similar ratio was observed when the isolated enediol dibenzoate VI was allowed to react with a reduced proportion of silver benzoate/iodine. Assuming the usual diaxial addition at the (second) double bond, formation of the tetrabenzoate *meso*-IX would require a highly unfavored 1,2,4,5-tetraxial transition state; thus the alternative reaction course, to DL-VIII, which involves a minimum of 1,3-diaxial repulsions, should be favored. Although the primary product of addition at the second double bond may actually be an iodocyclohexanetriol tribenzoate (not isolated), this could be converted by the usual neighboring group mechanism to the tetrabenzoate DL-VIII, with retention of configuration. The prediction that DL-VIII should predominate over *meso*-IX is confirmed by the n.m.r. results.

The *para* Cyclohexanetetrols of Zelinski and Titova.—In 1931 Zelinski and Titova[13] by reaction of potassium permanganate with cyclohexadiene, V, prepared a cyclohexanetetrol of reported[13] m.p. 241–242°, and from its mother liquors isolated after acetylation a cyclohexanetetrol tetraacetate, m.p. 168°. These products undoubtedly correspond to our *cis/cis* tetrol *meso*-II and its tetraacetate, although direct comparison has not been made. From the same mother liquors two additional tetraacetates, m.p. 52–54° and 101°, reportedly[13] were isolated. These do not correspond to any tetrol derivatives prepared by others, and possibly are polymorphic crystalline forms. Zelinski unfortunately did not establish any relationship between the three tetraacetates and corresponding free tetrols.

From the diene, V, Zelinski also prepared a diepoxide, reported[13] m.p. 110°, which when heated with water reportedly[13] gave a cyclohexanetetrol monohydrate, m.p. 195° dec. This possibly corresponds to our DL-(14/25) tetrol, m.p. 208°; however, under the condi-

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[27] The *cis/cis* molecule III also can exist in two equally favored and indistinguishable conformations. The non-equivalence of two protons within the same methylene is due to the fact that when one proton is axial it is *trans* to the four hydroxyl groups; when the other proton is axial, it is *cis*. However, on a time-average basis the two methylene protons *cis* to the four hydroxyl groups *are* equivalent to each other; likewise, the methylene protons which are *trans* to the four hydroxyl groups are equivalent to each other.

[28] *trans*-Cyclohexene-4,5-diol has also been prepared from the epoxycyclohexene, and converted *via* its acetate–tosylate to the *cis* epimer. The latter, which can also be prepared from vinylene carbonate and butadiene, offers a possible alternative route to the *cis/trans* and *cis/cis* tetrols. See M. D. Ali and L. Owen, *J. Chem. Soc.*, 1066 (1958); M. Newman and R. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

[29] The two modes of *cis*-addition to active *trans*-cyclohexene-4,5-diol would give a single *active* tetrol product; to the racemic enediol, a single *racemic* product.

[30] In the n.m.r. spectrum of a cyclitol acetate, methylene proton signals, if present, usually are obscured by acetate methyl proton signals. Such interference can be avoided by using benzoate or trifluoroacetate derivatives.

[31] It is noteworthy that textbook symmetry decisions often are based on some purely formal representation of a molecule, which makes no significant contribution to the molecular population. For example, on the basis of formulas I and II, the tetrols *meso*(1245) and *meso*(12/45) might be stated to have *two* planes and *one* plane of symmetry, respectively. It is safer and more informative to consider the symmetry of conformations actually abundant in the molecular population. For discussions on the relation of symmetry to activity, see: (a) G. E. McCasland, R. Horvat, and M. Roth, *J. Am. Chem. Soc.*, **81**, 2399 (1959); G. E. McCasland and S. Proskow, *ibid.*, **77**, 4688 (1955); (b) K. Mislow, *Trans. N. Y. Acad. Sci.*, **19**, 298 (1957). See also J. Donohue and D. Dows, *J. Chem. Educ.*, **39**, 480 (1962).

tions of our experiments hydrate formation has not been observed.[32]

The *para* Cyclohexanetetrols of McCasland and Horswill.—In 1954 McCasland and Horswill,[9a] by essentially the procedure now described for the isomer *meso*-IX, obtained a tetrabenzoate, m.p. 181°, and the free tetrol, m.p. 208°. For mechanistic reasons this tetrol was tentatively assigned the configuration DL-VIII, now confirmed by n.m.r. From the same reaction they isolated a crystalline sample, m.p. about 265°, too small for definite identification, but now known to be the other *trans/trans* tetrabenzoate, *meso*-IX.

At about the same time, the tetrol DL-VIII was also prepared[9b] by hydrogenolysis of the dibromotetrol XI, which had been obtained by the action[33] of hot acetyl bromide on *myo*-inositol XII, followed by hydrolysis. At the time, some detailed proposals[9b] were made for the stereochemical course of conversion of inositols to certain bromopentols, dibromotetrols, tetrols, diepoxydiols and diaminotetrols. These proposals now gain support from our definite proof of configuration for the tetrol DL-VIII, although their complete correctness in every detail has not yet been established.

Our experience suggests that *trans*-hydroxylation is best accomplished by the ordinary or "dry" Prevost reaction, using silver benzoate,[34] with subsequent deesterification. On the other hand, attempted use of the "wet" Prevost reaction[35] with the enediol dibenzoate VI gave poor results, and we consider the use of silver chlorate with catalytic amounts of osmium tetroxide[21,8a] superior for such *cis*-hydroxylations. The deesterification of benzoates from the dry Prevost reaction can usually be effected easily with hot aqueous alkali. However, the *meso*(15/24) tetrabenzoate, IX, resisted this process, and it was necessary to employ base-catalyzed ethanolysis (see Experimental section).

We have recently prepared[12] a new cyclohexanetetrol of the *meta* structure B (m.p. 193°, tetraacetate 118°) by hydrolysis and hydrogenolysis of a dibromocyclohexanetetrol tetraacetate, m.p. 173°, which unexpectedly was obtained on reaction of 5,6-anhydro-*allo*-inositol diacetone ketal with hydrogen bromide. This work will be described in a subsequent publication.

Experimental

All melting points have been corrected, and unless noted otherwise, were measured on a Nalge-Axelrod micro hot stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Illinois. Sixty-megacycle nuclear magnetic resonance spectra were measured with Varian Model A-60, and 100-Mc. spectra with Varian HR-100, high resolution n.m.r. spectrometers, using deuterium oxide as the solvent for cyclohexanetetrols, and chloroform-*d* as solvent for tetraacetate or tetrabenzoate derivatives. Chloroform-*d* was used with a tetramethylsilane internal reference, and deuterium oxide with a tetramethylsilane external reference. Infrared spectra were measured on a Perkin-Elmer, Model 137, Infracord recording infrared spectrometer.

Darco G-60 decolorizing charcoal was used. Each solid filtration residue was washed with an appropriate wash-solvent, and the wash-liquid combined with an appropriate filtrate. Each crop of crystals was dried to constant weight *in vacuo,* in some cases with use of heat. Each non-aqueous solution to be evaporated was dried with an appropriate dessicant. Evaporations were performed under reduced pressure.

1,4-Cyclohexadiene, V.—Gas chromatography was used to check the purity of the commercial[19] diene used. A 30-μl. sample was run through a Beckman GC-2 gas chromatograph, using a 162 × 0.63 cm. silicone column, at 70°, with helium carrier gas at 30 lb./in.^{2}. The chromatogram revealed the presence of only a trace of (presumably 1,3-diene) impurity, not exceeding three parts per thousand.

DL-*trans*-Cyclohexene-4,5-diol Dibenzoate, VI.—From 5.85 g. of commercial[19] 1,4-cyclohexadiene (purity checked by gas chromatography, see above) there was obtained by the method of McCasland and Horswill[9a] 5.9 g. (38%, *based on iodine*) of the desired product, m.p. 99–100° (reported[9a] yield 37%, m.p. 99–100°).

DL-*trans*-Cyclohexene-4,5-diol, VI.—The procedure of McCasland and Horswill[9a] was modified as follows. The enediol dibenzoate (3.2 g., m.p. 99–100°) was added to a solution of 1.96 g. of potassium hydroxide in 35 ml. of 95% ethanol. The mixture was boiled for 1 hr. under reflux. After cooling, the mixture was acidified with 12 *M* hydrochloric acid. The liberated benzoic acid and potassium chloride was partly removed by filtration, and the filtrate evaporated to dryness. The residue was washed with 15 ml. of benzene at 25°, and the filtered benzene solution evaporated to dryness. The residue was taken up in water (3 × 15 ml., *filter*), and the combined aqueous extracts passed through a column containing 30 ml. (moist volume) of Amberlite MB-1 mixed bed resin. The column was eluted with 125 ml. of water (chloride test negative). The eluate was evaporated. The residual oil, which soon solidified, was taken up in benzene (10 ml.), and 3.0 ml. of petroleum ether (b.p. 65–110°) added. On standing there was obtained 1.0 g. of product, m.p. 94–96°. This was recrystallized, giving 0.91 g. (80%) of colorless crystals, m.p. 95–96° (reported[9a] yield 66%, m.p. 95–96°).

cis/cis Series

***meso*(12/45) Diastereomer of (*cis/cis*) 1,2,4,5-Cyclohexanetetrol, M.p. 241°, II.**—To a solution of 7.6 g. of silver chlorate and 10 mg. of osmium tetroxide in 60 ml. of water was added 4.0 g. of 1,4-cyclohexadiene. After stirring the mixture in the dark at 25° for 3 days, the pH was adjusted to 1.0 by addition of 12 *M* hydrochloric acid. After stirring 0.5 hr. more, silver chloride was removed by filtration and the filtrate evaporated. The residue was stirred with 25 ml. of water (filter) and the solution passed through an Amberlite MB-1 mixed bed resin column (30 × 1.5 cm.), and the column eluted with 250 ml. of water. The eluate (negative chloride test) was evaporated. The residue was crystallized from 80% ethanol (charcoal), giving 1.0 g. of colorless crystals, m.p. 238–239.5°. This material was recrystallized, giving 0.8 g. (11%) of the desired product, m.p. 240–241°. A portion was recrystallized again for analysis, m.p. unchanged.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.02; H, 8.25.

A second crop of 430 mg., m.p. 233–236°, and a third crop of 70 mg., m.p. 228–234°, were obtained.

The third crop mother liquor was reserved for preparation of the all-*cis* diastereomer (see below).

The n.m.r. spectrum (Fig. 1) was recorded.

***meso*(12/45) Diastereomer of (*cis/cis*) 1,2,4,5-Cyclohexanetetrol Tetraacetate, M.p. 170°, II.**—A 220-mg. portion of the tetrol (m.p. 240–241°) was boiled with a large excess of redistilled acetic anhydride containing fused sodium acetate (120 mg.) for 4 hr. under reflux (anhydrous conditions). The mixture was evaporated. The residue was distributed between 20 ml. each of chloroform and water, and the separated chloroform phase processed in the usual manner, giving a solid residue. This was crystallized from absolute ethanol (charcoal), giving 430 mg. (92%) of colorless crystals, m.p. 169–170°. When a portion was recrystallized again, for analysis, the m.p. was unchanged.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.23; H, 6.42.

The n.m.r. spectrum[30] showed a single peak at δ = 2.07, indicating equivalence of all four acetate methyl groups. At

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[32] Even when an aqueous solution of the tetrol, m.p. 208°, was allowed to evaporate spontaneously at 25° and 1 atm., the crystalline residue did not contain any water of hydration.

[33] According to Dr. B. Franck of the University of Göttingen (personal communication, July, 1962) *myo*-inositol reacts with hot acetyl bromide to give not only the previously reported *meta* and *para* products, but also an *ortho* dibromocyclohexanetetrol, which is a derivative of the DL(13/24) tetrol ("dihydroconduritol-*B*").

[34] Silver benzoate is best prepared by mixing solutions of ammonium benzoate and silver nitrate. The well washed precipitate is repeatedly pulverized to facilitate drying *to constant weight* in a vacuum oven.

[35] F. Brutcher and G. Evans, *J. Org. Chem.*, **23**, 618 (1958).

$\delta = 5.3$ there was a less well defined pattern corresponding to the four O-C-H protons, which presumably also are equivalent.

meso(1245) **or All-*cis*-Diastereomer of 1,2,4,5-Cyclohexanetetrol, M.p. 225°, I.**—The third crop mother liquor from the m.p. 241° diastereomer (see above) was evaporated. The residual sirup was taken up in 5 ml. of absolute ethanol. After 3 days, crystals were collected, giving 1.1 g. of product, m.p. 218–225°. This material was recrystallized, giving 800 mg. of product, m.p. 213–225°, which was again recrystallized, giving 500 mg. (7%) of nearly pure product, m.p. 223–225°. When this material was again recrystallized, for analysis, there were obtained 290 mg. of pure product, m.p. 224–225°.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.45; H, 7.98.

From the mother liquor of the 1.1 g. batch, there was obtained 100 mg. of additional product, m.p. 218–225°.

The n.m.r. spectrum (Fig. 1) was recorded.

meso(1245) **or All-*cis* Diastereomer of 1,2,4,5-Cyclohexanetetrol Tetracetate, M.p. 128°, I.**—A 220-mg. portion of the tetrol (m.p. 223–225°) was acetylated in the manner described above, giving a crude solid product, which when crystallized from absolute ethanol (charcoal) yielded 0.35 g. of product, m.p. 113–117°. This was recrystallized, giving 290 mg. of product, m.p. 123–126°, and again recrystallized, giving 250 mg. (53%) of the desired pure tetraacetate, m.p. 127–128°. The m.p. was not changed by further recrystallization.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.43; H, 6.35.

The n.m.r. spectrum showed a single peak at $\delta = 2.07$ corresponding to the four equivalent acetate methyl groups. The methylene signals were obscured[30] by the acetate methyl signals. At $\delta = 5.1$ there was a not too well defined pattern corresponding to the four presumably equivalent O-C-H protons.

cis/trans Series

DL(124/5) **Diastereomer of (*cis/trans*) 1,2,4,5-Cyclohexanetetrol, M.p. 209°, X. (A). From the *trans*-Enediol.**—To a solution of 900 mg. of the *trans*-enediol (m.p. 95–96°) in 10 ml. of water was added a solution containing 600 mg. of silver chlorate and 2 mg. of osmium tetroxide in 30 ml. of water. The mixture was stirred for 3 days at 25° in the dark, then adjusted to pH 1 by addition of 12 *M* hydrochloric acid, and stirred 0.5 hr. longer. Silver chloride was removed by filtration. The filtrate was passed through a column containing 10 ml. (moist volume) of Amberlite MB-1 mixed bed resin, and the column eluted with 50 ml. of water (test for chloride ion negative). The eluate was evaporated, and the colorless solid residue recrystallized from 85% ethanol (charcoal). After 24 hr. there was obtained 570 mg. of colorless crystals, m.p. 208–209°. Including a 250-mg. second crop (m.p. 207–209°), the yield was 70%. A portion of the first crop was recrystallized for analysis.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.68; H, 8.04.

The n.m.r. spectrum (Fig. 1-E) showed a complicated methylene pattern centered at $\delta = 2.3$ with more than eighteen peaks, and a similarly complicated O-C-H pattern centered at $\delta = 4.2$.

(B) From the Tetrabenzoate.—Since in one run the free tetrol could not be induced to crystallize, it was converted to the crystalline tetrabenzoate from which by hydrolysis the pure tetrol was obtained in crystalline form. To 0.25 g. of the tetrabenzoate (m.p. 171–173°) was added a solution of 2.8 g. of potassium hydroxide in 2.5 ml. of water plus enough absolute ethanol to make 50 ml. The mixture was boiled under reflux for 1 hr. After cooling, the mixture was acidified with 12 *M* hydrochloric acid. The resulting mixture was evaporated, leaving a crystalline residue. Water (15 ml.) was added and the mixture filtered.

The filtrate was passed through a column of 10 ml. of moist Amberlite MB-1 mixed bed resin, and the column eluted with 35 ml. of water. The eluate was evaporated. The crystalline residue was taken up in 3 ml. of 95% ethanol (charcoal) and the filtered solution allowed to stand 24 hr. The crystals which separated were collected, giving 45 mg. (69%) of product, m.p. 203–204° (closed capillary).

(C) Attempted Use of "Wet" Prevost Reaction.—The *trans*-enediol (230 mg., m.p. 95–96°) was treated with iodine and silver acetate in acetic acid containing added water, essentially according to the procedure used by Brutcher and Evans[35] for *cis*-1,2-cyclohexanediol. However, since we omitted the saponification[35] with potassium hydroxide, the colorless crystalline product isolated (120 mg., m.p. 102–108°) consisted presumably of a mixture of the 4-monoacetate and the 5-monoacetate of racemic (124/5)-cyclohexanetetrol (combined yield of mixed acetates 40%). The infrared spectrum on a sample of the mixture showed strong O—H stretching absorption at 3500 cm.$^{-1}$ and a split ester carbonyl peak at 1680, 1710 cm.$^{-1}$, supporting the tetrol monoacetate structure. This material has not been further investigated, since the silver chlorate/osmium tetroxide method now appears more satisfactory.

DL(124/5) **Diastereomer of (*cis/trans*) 1,2,4,5-Cyclohexanetetrol Tetraacetate, M.p. 93°, X.**—A 450-mg. portion of the tetrol, acetylated in essentially the manner described above, gave an oily product, which on recrystallization from absolute ethanol (charcoal), gave 800 mg. of the desired product, colorless crystals, m.p. 90–93°. This material was recrystallized, giving 500 mg. (53%) of the pure tetraacetate, m.p. 91–93°. A sample was again recrystallized for analysis.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.26; H, 6.55.

The n.m.r. spectrum[30] showed a large peak at $\delta = 2.05$, and two peaks about half as large at $\delta = 2.00$ and 2.10, corresponding to two accidentally equivalent acetate methyl groups, and two other methyl groups not equivalent to each other or to the first two groups. A broad pattern centered at $\delta = 4.2$ corresponded to the four O-C-H protons, all presumably non-equivalent.

DL(124/5) **Diastereomer of (*cis/trans*) 1,2,4,5-Cyclohexanetetrol Tetrabenzoate, M.p. 173°, X.**—The crude oily tetrol prepared from 320 mg. of *trans*-enediol (m.p. 95–96°) by the silver chlorate method was dissolved in 4 ml. of anhydrous pyridine, and 1.7 g. of benzoyl chloride was added. After standing 12 hr. the mixture was evaporated, and the residual viscous syrup distributed between 30 ml. each of chloroform and water. The separated chloroform layer was processed in the usual manner, giving a semisolid residue, which was taken up in 25 ml. of boiling (3:1) ethanol–benzene (charcoal). After 12 hr. at 25° there were collected 1.1 g. of colorless crystals, m.p. 169–173°. This material was recrystallized, giving 0.8 g. (51%) of product, m.p. 171–173°. A portion recrystallized again, for analysis, melted at 172–173°.

Anal. Calcd. for $C_{34}H_{28}O_8$: C, 72.33; H, 5.00. Found: C, 72.02; H, 5.46.

trans/trans Series

DL(14/25) **Diastereomer of (*trans/trans*) 1,2,4,5-Cyclohexanetetrol, M.p. 208°, VIII.**—One half gram of a crude sample (1962 m.p. 200–204°) which had been prepared by McCasland and Horswill[9a] in 1954 was recrystallized from 90% ethanol (charcoal), giving 260 mg. of colorless crystals, m.p. 206–208° (reported[9] m.p. 208°). This material was used for the n.m.r. spectrum (Fig. 1-C), which had not previously been observed.

DL(14/25) **Diastereomer of (*trans/trans*) 1,2,4,5-Cyclohexanetetrol Tetraacetate, M.p. 148°, VIII.**—A sample of crude tetraacetate (900 mg., 1962 m.p. 143–147°) which had been prepared by McCasland and Horswill in 1954 was recrystallized from absolute ethanol (charcoal), giving 710 mg. of colorless crystals, m.p. 146–148° (reported[9a] m.p. 148°).

The n.m.r. spectrum[30] showed a single very strong peak at $\delta = 2.1$, corresponding to the four equivalent acetate methyl groups. The widened base of this peak covers up the signals of the four methylene protons; which presumably are all equivalent. At $\delta = 5.1$ there was a narrow pattern corresponding to the four O–C–H ring protons (all four equivalent).

meso(15/24) **Diastereomer of (*trans/trans*) 1,2,4,5-Cyclohexanetetrol, M.p. 285°, IX.**—The tetrabenzoate of this configuration showed an unusual resistance to ammonolysis or (alkaline or acid) hydrolysis, only starting material being recovered after procedures which would successfully deesterify other cyclitol benzoates. Ethanolysis, however, was successful.

To a solution of 70 mg. metallic sodium in 15 ml. of absolute ethanol was added 220 mg. of the tetrabenzoate (m.p. 267°). The mixture was boiled under reflux (anhydrous conditions); a flocculent precipitate separated after 1.5–2 hr. After 3 hr. boiling, 2 ml. of water was added (precipitate dissolved). After 10 min. additional boiling, and cooling, the separated solids were removed by filtration. The filtrate was evaporated to dryness. The residue was washed twice with dry ether. The insoluble residue was taken up in 1 ml. of water, and the solution passed through a 20 × 8 mm. column of Amberlite MB-1 mixed bed resin. The column was eluted with 50 ml. of water, and the eluate evaporated.

The colorless crystalline residue was recrystallized from 70% ethanol, giving 50 mg. (50%) of the desired product, m.p. 283–285° (cap.) with decomposition. For analysis and n.m.r. spectrum (see Fig. 1), the material was again recrystallized, giving 25 mg., m.p. 284–285° dec. (cap.).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.68; H, 8.09.

***meso*(15/24) Diastereomer of (*trans/trans*) 1,2,4,5-Cyclohexanetetrol Tetrabenzoate, M.p. 267°, IX.** (A). **From Diene.**—To a solution of 45.6 g. of iodine in 400 ml. of anhydrous benzene was added a slurry of 82 g. of dry silver benzoate[34] in 250 ml. of benzene. The mixture was stirred 30 min., then 3.6 g. of 1,4-cyclohexadiene[19] was added and the resulting mixture boiled 1 hr. under reflux (anhydrous conditions), then allowed to stand overnight.

The yellow precipitate was removed by filtration, and the filtrate washed successively with water, sodium bicarbonate solution, sodium thiosulfate solution, and again with water. After drying, the benzene solution was evaporated. The oily residue was taken up in 120 ml. of boiling absolute ethanol, and the solution cooled. After 12 hr., the crystals were collected, giving 0.8 g. of crude product, m.p. 236–250°.

This material was taken up in 30 ml. of chloroform (filter), and absolute ethanol (15 ml.) was added. After 12 hr., the colorless needles which separated were collected, giving 420 mg. (3%) of the desired product, m.p. 266–267° (reported[9] m.p. 265°).

Anal.[36] Calcd. for $C_{34}H_{28}O_8$: C, 72.33; H, 5.00. Found: C, 71.14; H, 5.09.

The original ethanolic filtrate was reserved for preparation of the m.p. 208° isomer.

The 100-Mc. n.m.r. spectrum showed well defined strong patterns centered at $\delta = 7.6$ and 8.0 due to the twenty aromatic protons. The *ortho* protons were responsible for the signals at $\delta = 8.0$, while the *meta* and *para* protons produced the signals around $\delta = 7.6$. The four O-C-H proton signals were centered around $\delta = 5.7$ and the symmetrical pattern was 28 c.p.s. wide. Two of the methylene protons produced a doublet of spacing 13 c.p.s., with fine structure indicative of a tripling with a 3 c.p.s. splitting. This pattern was centered around $\delta = 2.9$. The other two methylene protons produced a poorly defined pattern of signals 55 c.p.s. wide around $\delta = 2.0$. Except for the enhanced chemical shifts and a difference in clarity, this tetrabenzoate spectrum (not shown) was very similar to that of the corresponding free tetrol (Fig. 1-D).

(B) **From Enediol Dibenzoate.**—To a mixture of finely pulverized, dry silver benzoate[34] (9.2 g., 0.04 mole) and 5.1 g. of iodine (0.02 mole) in 100 ml. of dry benzene was added a solution of 3.2 g. (0.01 mole) of the enediol dibenzoate (m.p. 99–100°) in 20 ml. of benzene. After stirring 0.5 hr., the mixture was boiled under reflux for 4 hr., then kept at 20° for 65 hr., and filtered. The filtrate was successively washed with water, sodium bicarbonate solution, sodium thiosulfate solution, and again with water. After drying, the benzene solution was evaporated. The residual oil was taken up in 38 ml. of absolute ethanol (charcoal). After 12 hr., the white powdery crystals were collected, giving 40 mg. of crude product, m.p. 253–257°. A second crop of 20 mg. was obtained, m.p. 248–254°.

The product (60 mg.) was taken up in 3.0 ml. of chloroform (charcoal) and 4.0 ml. of absolute ethanol added. After 12 hr. at 20° there was obtained 50 mg. (0.9%) of the desired pure product, m.p. 266–266.5°).

The original ethanolic mother liquors were reserved for preparation of the m.p. 208° isomer.

A mixture m.p. with the tetrabenzoate[9c] (m.p. 259–260°) of racemic (13/24) *ortho* cyclohexanetetrol ("dihyroconduritol-*B*") was depressed, and infrared spectra confirmed non-identity of the two samples. (If the 1,4-diene starting material used contained a large amount of 1,3 impurity or if the unconjugated diene rearranged into conjugated diene during the reaction, the isolated product might conceivably be the *ortho* tetrol tetrabenzoate.)

Infrared Spectra.—The infrared spectrum was recorded for each new compound prepared, using potassium bromide pellets. The cyclohexanetetrols showed the expected strong O—H stretching absorption. The tetraacetates showed strong ester carbonyl absorption, and an absence of O—H absorption. One tetrol monoacetate was examined (see above). The tetrabenzoates, in addition to carbonyl absorption, showed the "C-H rock" characteristic of monosubstituted benzenes at about 710 cm.$^{-1}$.

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(36) The 1.19% low carbon value is possibly due to persistence of some iodocyclohexanetriol tribenzoate in the repeatedly recrystallized product. Any such impurity is eliminated during preparation of the free tetrol, which gave an excellent microanalysis for carbon and hydrogen.

The Absolute Configuration of *threo*-2-Amino-1,2-diphenylethanol. A Correction of the Literature

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The absolute configurations of the *threo*-2-amino-1,2-diphenylethanols have been corrected as D-(+) and L-(−) or by the Cahn, Ingold, Prelog system as *1R:2R*-(+) and *1S:2S*-(−).

The stereochemistry of the epimeric 2-amino-1,2-diphenylethanols (I) was established by Weijlard *et al.*,[1] in 1950, and these authors confirmed the earlier assignment that the *threo*-racemate was the lower-melting and the *erythro*-racemate the higher-melting form. By converting one of the optically active *erythro* isomers of established absolute configuration into one of the *threo* isomers, an absolute configurational assignment was made to the *threo* forms. Since the method of interconversion was shown to involve epimerization of the hydroxyl asymmetric center, the D-*threo* isomer was assigned the levo rotation.

In 1955, Pratesi, *et al.*,[2] supported this configurational assignment but later[3] offered evidence contradicting both their earlier conclusion and that of the Merck group.[1] Watson and Youngson[4] in 1954 gave unequivocal evidence for the absolute configuration of the

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(1) J. Weijlard, K. Pfister, 3rd, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1216 (1951).

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