estra-1,3,5(10)-trien-16-one in 0.4 ml. of 20% sodium hydroxide, and the solution was mixed. When the product crystallized, the solution was diluted with water and filtered, and the product was recrystallized three times from methanol. The 5 mg. of X thus obtained melted at 225.5–229°. Huffman and Lott[4] report m.p. 223.5–224.5°.

16β-Acetoxyestr-4-en-3-one.—Acetylation of 16β-hydroxyestr-4-en-3-one (75 mg.) in 2 ml. of pyridine with 0.5 ml. of acetic anhydride yielded 75 mg. of crude product, m.p. 87.5–89.5°. Two recrystallizations from aqueous acetone yielded 35 mg. of 16β-acetoxyestr-4-en-3-one, m.p. 90–90.5°, $[\alpha]^{25}\text{D}$ +21.5° (CH_3OH), $\lambda_{\max}^{CH_3OH}$ 238 mμ (ε 15,000).

Anal. Calcd. for $C_{20}H_{28}O_3$ (mol. wt. 316.42): C, 75.91; H, 8.92. Found: C, 75.67; H, 9.01.

16α-Acetoxyestr-4-en-3-one.—Acetylation of 16α-hydroxyestr-4-en-3-one (100 mg.) in 5 ml. of pyridine with 1 ml. of acetic anhydride yielded an oil, which showed no optical rotation, $\lambda_{\max}^{CH_3OH}$ 239.5 mμ (ε 15,000). The infrared absorption spectrum showed the presence of an ester group but no hydroxyl group; $\lambda_{\max}^{KBr}$ 5.72, 5.93, 6.12, and 7.99 μ.

Aluminum *t*-Butoxide Reduction of Estr-4-ene-3,16-dione (VII).—A solution of 100 mg. of VII in 10 ml. of benzene and 1 ml. of 2-butanol was slowly distilled until 2.5 ml. of distillate was collected. Then 74 mg. of aluminum *t*-butoxide was added, and the mixture was refluxed for 5 hr. After cooling and dilution with 10 ml. of benzene the mixture was washed once with 30 ml. of 5% sodium hydroxide solution and thrice with 10-ml. portions of water. The organic layer was dried over magnesium sulfate, and the residue obtained on evaporation of solvent was chromatographed on a 25-g. silica gel column by development with 425 ml. of methylene chloride–hexane (1:1), 500 ml. of methylene chloride–hexane (3:1), 1 l. of methylene chloride, and 500 ml. of ether–methylene chloride (1:9).

Examination of the eluate by paper chromatography showed starting material in the 490–970-ml. fraction. The 1480–1820-ml. fraction contained 16β-hydroxyestr-4-en-3-one, and the 2170–2330-ml. fraction contained a smaller amount of the 16α-isomer.

Laboratory Fermentation Studies.—Laboratory-scale fermentations were conducted in the following manner. Inoculum was prepared by transferring an aqueous suspension of the culture to a 500-ml. erlenmeyer flask containing 100 ml. of a medium consisting of lactalbumin hydrolysate[13] (20 g.), glucose (20 g.), corn steep liquor (5 g.), and water to make 1000 ml. The pH was adjusted to 7.0. The culture was incubated on a reciprocating shaker; *B. megaterium* was incubated at 37° for 7 hr.; *C. acremonium* and *S. roseochromogenes* were incubated at 28° for 64 hr. In each instance 5 ml. of the microbial suspension was used to inoculate 100 ml. of fresh medium in 500-ml. erlenmeyer flasks. All cultures were than shaken at 28° for 24 hr. prior to addition of the steroid substrate. Each steroid was added in methanolic solution to provide a concentration of 100 μg./ml. in the flask. Aliquots were removed at intervals and extracted with a three-volume portion of ethyl acetate, and the extract was analyzed by thin layer chromatography.

A mixture of compounds, VI, VII, and VIII, was observed in one or more of the samples removed from the fermentations of V, VI, VII, and VIII with each organism. The mobilities of these compounds on silica gel G developed with benzene–acetone (7:3 v./v.) were as follows: V, R_f 0.68–0.74; VI, R_f 0.42–0.46; VII, R_f 0.55–0.62; and VIII, R_f 0.34–0.38. After spraying with sulfuric acid and heating, the 3,16-dione (VII) shows a distinctive olive green color prior to charring.

Acknowledgment.—We thank Mr. L. Brancone and associates for analytical data, Mr. W. Fulmor and associates for infrared and ultraviolet absorption spectra and rotation data, Dr. J. Schultz and staff for conducting pilot plant fermentations, and Mr. M. Dann and staff for extraction of pilot plant fermentations and concentration of the extracts.

Application of Spin Decoupling and 100-Megacycle Spectra to Characterization of Carbohydrates. Novel Synthesis of a Cyclohexanetetrol[1,2]

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Reaction of 5,6-anhydro-*allo*-inositol diketal with hydrogen bromide–acetic acid unexpectedly gave a dibromocyclohexanetetrol tetraacetate, from which was obtained a new cyclohexanetetrol, m.p. 193°. By use of spin decoupling and 100-Mc. spectra, this tetrol was shown to have the structure 1,2,3,5 and the configuration *meso* (123/5). Another diastereomer, m.p. 180°, prepared in 1954 from *myo*-inositol, was shown by 60- and 100-Mc. spectra to have the configuration *meso* (13/25). Configurational assignments have also been made to two optically active diastereomers, prepared by Dangschat and Fischer in 1939. By means of rotation predictions, it is now shown that their isomers of reported molecular rotations −90 and −12° have the absolute configurations L (12/35) and L (125/3), respectively.

For n.m.r. configurational studies, spin coupling is a generally useful and often indispensable phenomenon, but there are times when it produces such spectral complexity that interpretation becomes impossibly difficult. This has been especially true for carbohydrate spectra,[5] because of the numerous similar functional groups.

It now appears that such difficulties can largely be overcome, owing to two lately reported n.m.r. developments. The first development, spin decoupling,[6,7] permits the simple uncoupled signal of almost any chosen proton, or set of protons, in a molecule to be observed. Although anticipated by Bloch[6] as early as 1954, spin decoupling has only recently become fully practical and convenient for general use. The

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[1] Presented by G. E. M. to the Division of Organic Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

[2] Paper 18 on Cyclitol Stereochemistry by G. E. McCasland and coworkers; for recent papers in this series, see *J. Org. Chem.*, **28**, 2096 (1963); **29**, 724 (1964); *J. Am. Chem. Soc.*, **85**, 2866 (1963).

[3] To whom any requests for reprints should be sent (University of San Francisco).

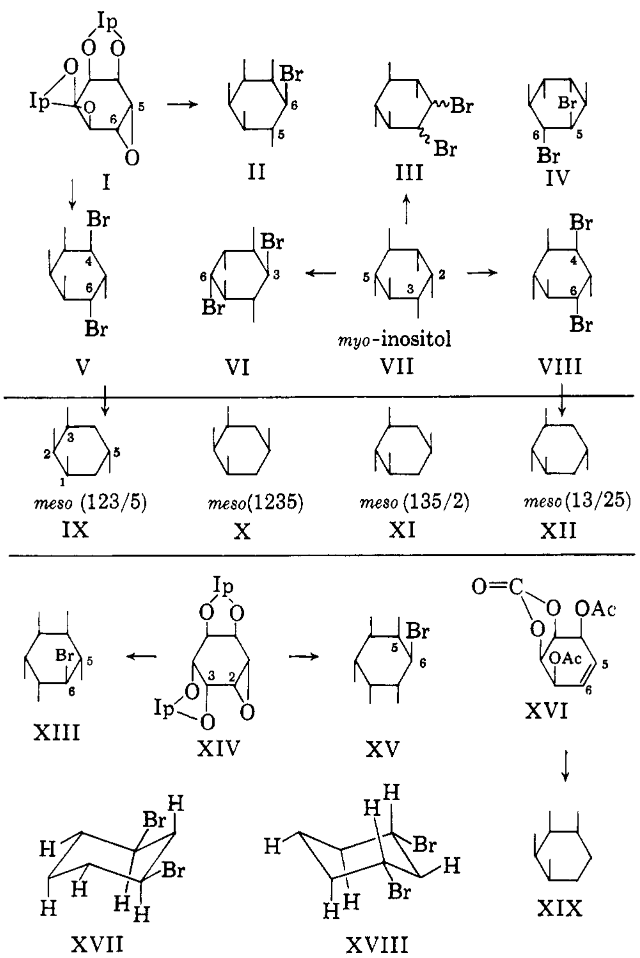
[4] Varian Associates.

[5] For our own previous n.m.r. studies on carbohydrates (cyclitols), see G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery: (a) *J. Org. Chem.*, **28**, 894 (1963); (b) *J. Am. Chem. Soc.*, **83**, 4243 (1961); (c) **83**, 2335 (1961); (d) (with A. Furst), *J. Org. Chem.*, **28**, 456 (1963); (e) G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **29**, 724 (1964).

[6] Double irradiation was originated by F. Bloch [*Phys. Rev.*, **93**, 944 (1954); **94**, 496 (1954)]. The theory was developed by A. Bloom and J. N. Shoolery [*ibid.*, **97**, 1261 (1955)]. The first application to proton-proton spin decoupling was by W. Anderson [*ibid.*, **102**, 151 (1956)], who studied 2,3-dibromopropene and 2,2-dichloroacetaldehyde. For a recent review, see J. Baldeschwieler and E. Randall, *Chem. Rev.*, **63**, 81 (1963).

[7] The spin-decoupling method used here is that described by R. Freeman and D. Whiffen [*Mol. Phys.*, **4**, 321 (1961)]. The instrumentation is described by L. F. Johnson, Varian Associates Technical Information Bulletin, Vol. 3, No. 3, Palo Alto, Calif.. 1963, pp. 5-7, 11-13.

Chart I



second development is the recent use in numerous laboratories of higher frequency apparatus for proton spectra, *i.e.*, 100 Mc. (23.5 kilogauss) in place of 60 Mc. (14.1 kilogauss). With the resultant spreading out of signals, the interpretation of very difficult spectra is often greatly facilitated. It is especially helpful to make successive proton spectral observations on the same sample at 60 Mc. and then at 100 Mc. By well-known principles, spin couplings (field invariant) can then be unequivocally distinguished from chemical shifts. This approach has occasionally been employed in the past with other frequency combinations.

Since few applications of spin decoupling or 100-Mc. spectra to carbohydrates have yet been reported, we now describe the use of these techniques for certain cyclohexanetetrol[8] configurational studies, in order to help demonstrate the power[9] of these new methods.

The occasion for our present research was the preparation of a cyclohexanetetrol, m.p. 193°, by a novel and unexpected synthesis (Chart I). The first step was reaction of 5,6-anhydro-*allo*-inositol diketal[10d,11] (I) with hydrogen bromide in acetic acid at room temperature. In previous work,[5c] the diastereomer XIV with this reagent gave a high yield of monobromo pentaacetate products, XIII and XV. Our new reaction was thus expected to produce the diastereomeric monobromo pentaacetate (II), especially since the monobromopentol (II) is in fact the product with hydrogen bromide *in water*.[5b]

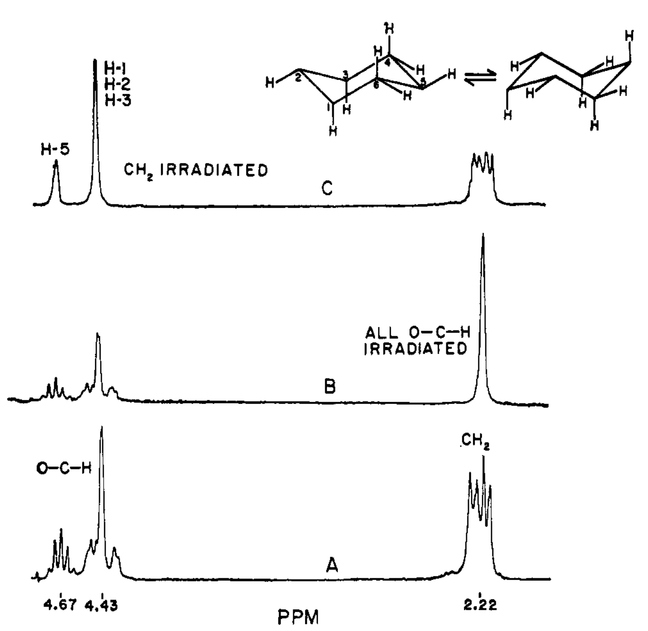
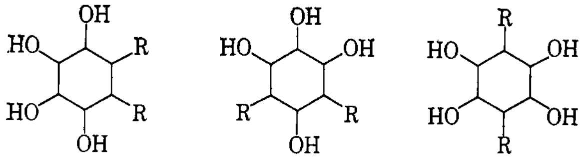


Fig. 1.—(A) 100-Mc. n.m.r. spectrum of 1,2,3,5-cyclohexanetetrol, m.p. 193°, in deuterium oxide; (B) O-C-H protons irradiated; (C) methylene protons irradiated.

To our surprise, the actual HBr-AcOH product, which crystallized in high yield directly from the reaction mixture, contained two atoms of bromine, and turned out to be a dibromocyclohexanetetrol tetraacetate, m.p. 173°. This was hydrolyzed to the dibromotetrol, m.p. 182°, which on hydrogenolysis gave a new cyclohexanetetrol, m.p. 193° dec. For such a tetrasubstituted cyclohexane, three structures (A, B, C), which we call *ortho*, *meta*, and *para*, are possible. To ascertain the actual structure, 100-Mc. spectra and spin decoupling were employed. (In the present instance, decoupling at 60 Mc. would also have been satisfactory.)



A, R = H
D, R = Br

B, R = H
E, R = Br

C, R = H
F, R = Br

N.m.r. Structural Proof for the Cyclohexanetetrol, M.p. 193°.—The spectrum of the new tetrol in deuterium oxide was recorded at 100 Mc. (Fig. 1-A). Values of the chemical shift are taken as positive when downfield from the zero reference signal of a capillary of tetramethylsilane. These values, stated in p.p.m., may differ somewhat from the true δ-values based on a tetramethylsilane internal reference. Spin-coupling con-

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[8] Regarding the possible biological significance of these dideoxy inositols, see (a) H. Eagle and G. E. McCasland, *Biochemistry*, **2**, 1125 (1963); (b) *Chem. Eng. News*, **40**, 51 (1962).

[9] L. Jackman has suggested that spin decoupling and improvements in magnet materials may increase the value of n.m.r. to organic chemists "by an order of magnitude" ("Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 5).

[10] S. J. Angyal, personal communications: (a) April, 1960; (b) June, 1956; (c) S. J. Angyal and P. Gilham, *J. Chem. Soc.*, 3698 (1957); (d) S. J. Angyal and P. Gilham, *ibid.*, 375 (1958).

[11] Each "ketal" or "diketal" mentioned here is a normal acetonation product.

stants are given in c.p.s. In the figures, H, the applied field, increases from left to right.

The four methylene protons produce the quartet at 2.22 p.p.m., and the four O–C–H protons the complex pattern at 4.43 and 4.67. Since the methylene quartet was almost unchanged at 60 Mc. (not shown), the splitting is attributed to spin coupling only.

When integrals of spectra are obtained using the Varian V-3521 integrator in the HR-60 or HR-100 systems, they are the result of 2-Kc. field modulation and audio-phase detection.[7] By using a low modulation index, high radiofrequency power, and proper phasing, one can obtain spectra 2 Kc. below or above the actual radiofrequency. In this mode of operation spin–spin decoupling is easily achieved by field modulating with a larger index using an additional audio frequency which will create a large side-band component of the radiofrequency power elsewhere within the spectrum.[7] This irradiating field is large enough to effectively "stir up" the spin states of the nuclei precessing at the frequency of the irradiating field, thus allowing any nuclei which are normally spin coupled to the irradiated group to see only an average (zero) spin state.

When operating on the lower 2-Kc. side band, the additional audio-frequency modulator must be tuned to a value less than 2 Kc. by an amount approximately equal to the chemical shift of two spin-coupled groups in order to record a spectrum showing a decoupled high field group. Figure 1-B was obtained by using an irradiating modulation frequency, ω_2, which was approximately 233 c.p.s. less than the nominally 2-Kc. detecting side-band frequency, ω_1. By using a sufficiently large modulation index at ω_2 it was possible to produce a component of the radiofrequency power near 4.5 p.p.m. large enough to perturb all of the various O–C–H resonances while observing the CH_2 signals. The methylene quartet is thus collapsed to a singlet, confirming that there is little or no chemical shift between the four methylene protons. These protons are spectroscopically equivalent, although geometrically not strictly equivalent.

An *ortho–meta–para* structural decision can now be achieved by reviewing the methylene proton environments possible in the various configurations and conformations. For an *ortho* structure, none of the six configurations would permit a conformation with all methylene protons equivalent.[12] For a *para* structure, two of the five configurations[5a] permit conformations with equivalent methylene protons; however, these conformations would also require equivalence of the O–C–H protons,[5a] which is not found (Fig. 1-C). The one remaining possibility for the cyclohexanetetrol, m.p. 193°, then is the *meta* structure. This structure in certain configurations can have conformations with the methylene protons equivalent, as explained below.

The *meta* structural assignment is supported by certain other evidence. The reported properties of the six diastereomeric *ortho* tetrols and derivatives were compared with those of the new tetrol and its tetraacetate (m.p. 118°) and tetrabenzoate (m.p. 189°). Four of the six isomers were promptly excluded. It appeared for a time that Criegee's isomer,[13] m.p. 222°, might be identical with our new tetrol,[14] since it has an all-*cis* configuration (XIX) resembling that of the anhydro diketal I. Criegee's isomer was finally excluded on the basis of the tetrabenzoate melting point, and also by synthesis of the previously unreported tetraacetate, m.p. 65°, which was nonidentical with our new tetraacetate, and not a dimorph. The new tetraacetate of m.p. 65° was prepared from the unsaturated carbonate diacetate XVI.[13] The (12/34) tetrol and its tetraacetate have suitable melting points, but this isomer is excluded by the n.m.r. data.

To exclude the *para* structure, we synthesized all five of the possible diastereomers,[5a] none of which were identical with the new cyclohexanetetrol, m.p. 193°.

These results help to confirm the *meta* assignment based on n.m.r. For the *meta* structure, four *meso* and two racemic configurations are predicted (Table I). To ascertain the actual configuration, 100-Mc. spectra and spin decoupling were again employed. Although the tetraacetate spectrum, Fig. 2, is more easily interpreted (see below), evidence from Fig. 1 will first be considered.

TABLE I

THE 1,2,3,5 OR *meta* CYCLOHEXANETETROLS

Configuration and favored conformation	M.p., °C. (molecular rotation)			Ref.
	Tetrol	Tetra-acetate	Tetra-benzoate	
	meso Diastereomers			
(1235), X, EAEE				
(123/5), IX, EAEA ⇌ AEAE	193 dec.	118	189	*a*
(135/2), XI, EEEE				
(13/25), XII, EEEA	180	86	206	*a, b*
	Active or Racemic Diastereomers			
(12/35), XX, AEEE	151 (−90°)			*c, d*
(125/3), XXII, EAAE ⇌ AEEA	208 (−12°) or 200			*c, d*

[a] This article. [b] Ref. 23. [c] Ref. 18. [d] Ref. 29.

N.m.r. Configurational Proof for the Cyclohexanetetrol, M.p. 193°.—As noted, spectroscopic (but not necessarily geometric) equivalence of the methylene protons was demonstrated by irradiation of the O–C–H protons (Fig. 1-B). The next experiment was to irradiate the methylene protons at their resonant frequency while observing the O–C–H signals. When this was done the O–C–H pattern collapsed into two sharp singlets (Fig. 1-C). The smaller singlet (4.67 p.p.m.) must be produced by H-5, which no longer is coupled with any neighboring proton. The larger (4.43 p.p.m.) must be produced by H-1, H-2, and H-3, revealing that there is little if any chemical shift between these three protons. Although H-1 and H-3 might be geometrically equivalent in any of the *meso* configurations (IX–XII), the spectroscopic equivalence of H-2 must be attributed to an accidental degeneracy in the spectrum.

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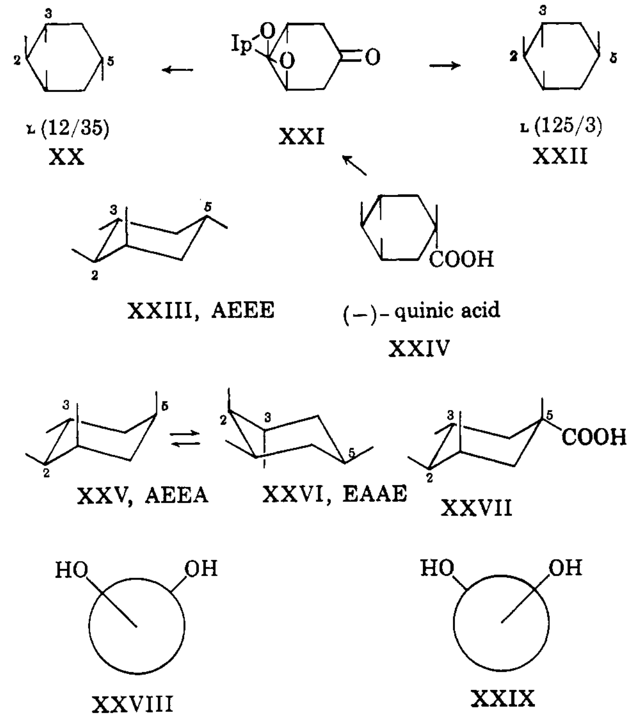
(12) In any of the six *ortho* diastereomers, the two protons *within* a methylene group cannot be equivalent, because one proton has a *cis* neighboring hydroxyl group, the other a *trans*. (The neighbor on the other side in each case is the remaining methylene group.) The two methylene protons "above" the ring plane, or "below" it, are also nonequivalent, except in the two *meso* diastereomers, because of the nonsymmetrical disposition of the hydroxyl groups at positions 1 and 4, or 2 and 3.

(13) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957). We would like to thank Professor Criegee for a generous sample of the carbonate diacetate of conduritol-D.

(14) The new cyclohexanetetrol melts with decomposition at 193° in a sealed capillary, but in an open capillary slowly darkens and decomposes over a wide range near 220°.

Chart II



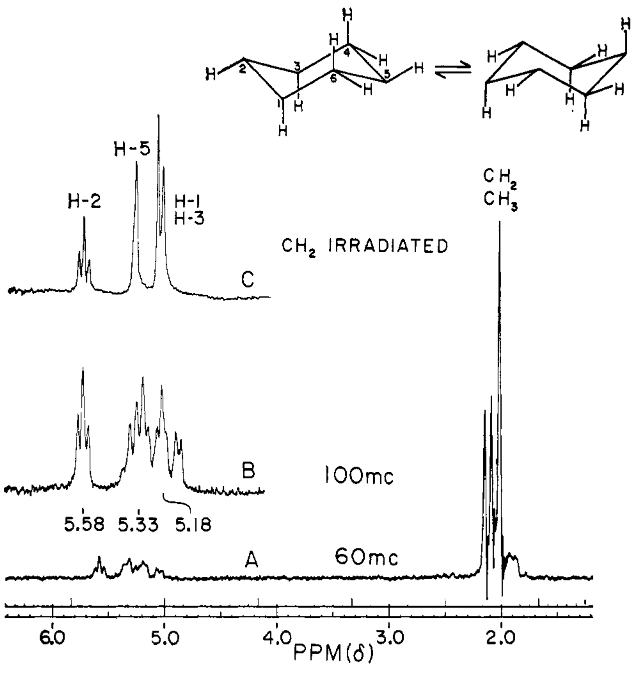


Fig. 2.—N.m.r. spectrum in chloroform-*d* of the tetraacetate, m.p. 118°, from 1,2,3,5-cyclohexanetetrol, m.p. 193°: (A) at 60 Mc., (B) at 100 Mc., (C) at 100 Mc.; methylene protons irradiated.

Since H-1 and H-3 are equivalent, and since the two methylene protons "above" (and also the two "below") the ring are equivalent, the molecule must have a plane of symmetry. This plane, which passes through positions 2 and 5 (see formulas in Fig. 1) is perpendicular to the ring plane. Thus one may exclude the two active (or racemic) configurations[15] (12/35) XX, and (125/3) XXII (Chart II).

In the remaining four (*meso*) configurations, geometric equivalence for two protons *within* the same methylene group is not possible. Nevertheless, the situation of equivalence can be approximated[16,17] if two conditions are met by the methylene protons, *e.g.*, at position 4: (1) the neighboring protons (H-3, H-5) must have a *trans*, not *cis*, configuration; and (2) each methylene proton must be partly axial, partly equatorial in its time-average n.m.r. response.

Condition 2 implies mobile equilibrium between two chair conformations of nearly equal energy, which in the case of a cyclohexanetetrol must be diaxial–diequatorial. Similar requirements apply to the methylene protons at positions 6, and their neighbors (H-1, H-5).

The configurations *meso* (1235) or "all-*cis*", and *meso* (135/2) (formulas X and XI) can be excluded because they violate both conditions 1 and 2. The configuration *meso* (13/25) XII, satisfies condition 1 but violates condition 2.

The one remaining possibility for the new cyclohexanetetrol, m.p. 193°, is the configuration *meso* (123/5) IX, which does meet both of the conditions.

Two additional facts support this assignment.

(1) The stereoisomer *meso* (13/25), m.p. 180°, which is the only other *meso* isomer meeting condition 1, has been shown to be nonidentical with the tetrol, m.p. 193°, by comparison of the n.m.r. spectra, which are very different.

(2) The levorotatory stereoisomer[18] (125/3) XXII, which is the only other isomer meeting condition 2, has also been shown to be nonidentical with our new tetrol, by comparison of n.m.r. spectra. Although the (125/3) isomer was optically active (molecular rotation −12°, m.p. 208°), and our isomer inactive, the nonidentity of the spectra *in solution* shows a difference in diastereomeric configurations.

The remaining features of the spectra (Fig. 1) may now be examined. At 4.67 p.p.m. (Fig. 1-A) the signal for H-5 appears as a quintet, due to spin coupling with the four equivalent methylene protons. The methylene signal (2.22 p.p.m.) appears as a pair of doublets, because of coupling of the methylene protons with H-3 and H-5, or H-1 and H-5.

The observed H-5 splittings (Fig. 1-A) show an average coupling constant of 3.8 c.p.s. between H-5 and the methylene protons. The individual coupling constants in such a system cannot be directly calculated from the observed splittings.[19,20] However, time averaging for both conformations of constants EE, EA, AE, and AA (normal values: 3, 3, 3, and 8 c.p.s.) would give an average coupling constant for H-5 of 4.2 c.p.s., not far from the observed 3.8.

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(15) Following *Chemical Abstracts* practice, we number the *meta* cyclohexanetetrols "1,2,3,5," *not* "1,3,4,5." For specifying configuration by the fractional system, the longest series of smallest numbers is placed in the numerator, *e.g.*, "(125/3)," *not* "(1/235)." For further explanation, see our previous articles.

(16) When a methylene group in a cyclohexane ring has two like neighboring *trans* substituents, the axial methylene proton in one chair conformation will have an immediate environment which is identical with that of the axial methylene proton in the other conformation; likewise for the equatorial methylene protons. If the methylene group has two neighboring *cis* substituents, this will not be true. The "immediate environment" here includes the system -CHY-CH_2-CHY- and the three remaining ring carbon atoms, but not necessarily the substituents on the three remaining ring carbon atoms.

(17) Compare 1,3-cyclohexanediol studies by H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962); also the 2,4-pentanediol studies by J. Pritchard and R. Vollmer, *ibid.*, **28**, 1545 (1963).

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

(19) R. Abraham and H. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

(20) D. Grant and H. Gutowsky, *J. Chem. Phys.*, **34**, 699 (1961).

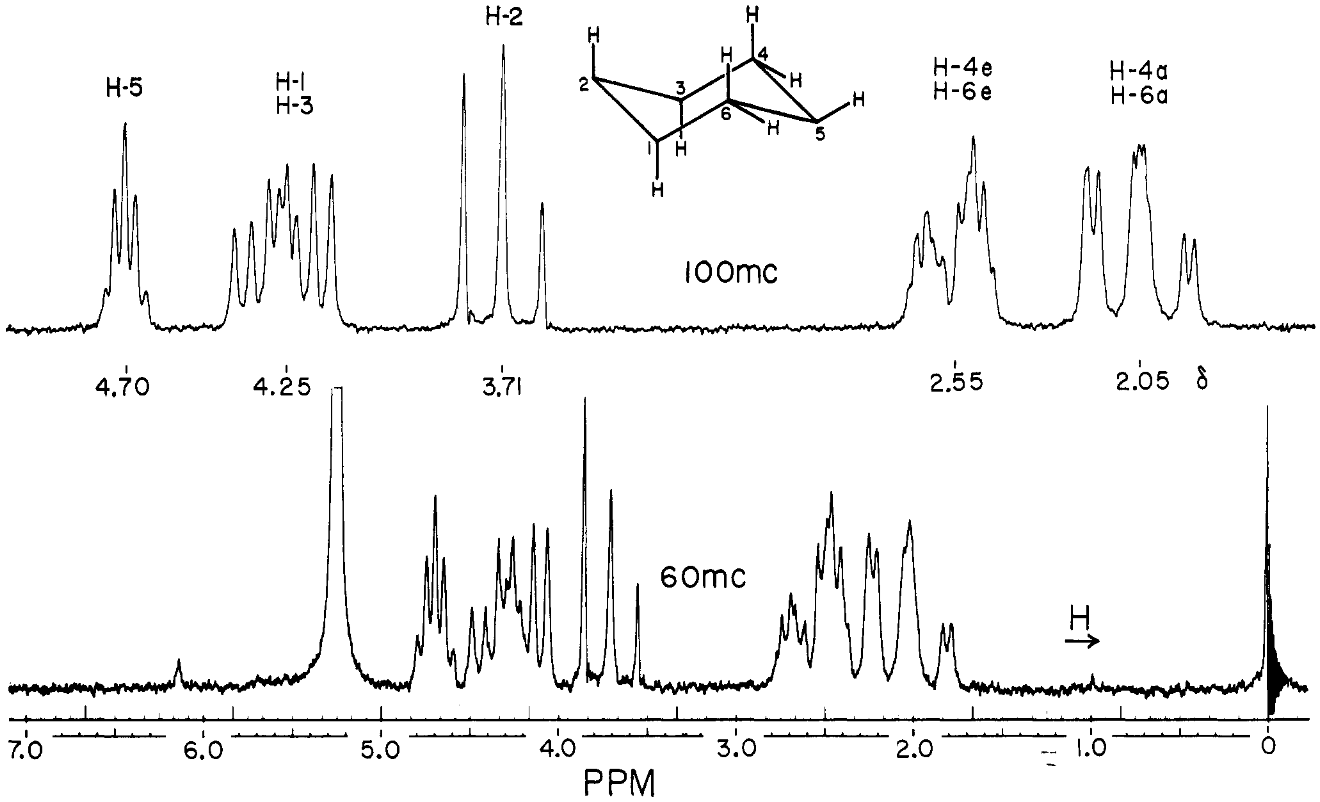

Fig. 3.—N.m.r. spectra of 1,2,3,5-cyclohexanetetrol, m.p. 180°, in deuterium oxide at 60 and 100 Mc.

The pattern at 4.43 p.p.m. in the nondecoupled spectrum (Fig. 1-A) for H-1, H-2, and H-3 is not easily interpreted, owing in part to the fact that H-1 and H-3 are coupled with methylene protons, but H-2 is not.

Spectrum of the Tetraacetate, M.p. 118°.—A sample of the tetraacetate from the new m.p. 193° cyclohexanetetrol was first examined in chloroform-*d* at 60 Mc. (Fig. 2-A). In the region δ 2.00–2.15 (p.p.m. downfield from dissolved tetramethylsilane) there are signals due to four acetate methyl groups, of which only two are equivalent (no doubt at positions 1 and 3). The methylene signals are partly obscured by the methyl signals. The four O–C–H protons produced a poorly resolved pattern in the region δ 5.0–5.7, which was considerably improved at 100 Mc. (Fig. 2-B), but still difficult to interpret. To remove the difficulty, spin decoupling was again employed.

Irradiation of the four methylene protons (which in the tetraacetate are not necessarily equivalent) at their resonant frequency caused the O–C–H pattern to collapse into a singlet, a doublet, and a triplet (Fig. 2-C).

The singlet (δ 5.33) must be due to H-5, which no longer is coupled with any neighboring proton. The doublet (δ 5.18) must be due to the equivalent pair (H-1 and H-3), now coupled only to H-2. The triplet (δ 5.58) must be due to H-2, coupled only to H-1 and H-3, and thus unaffected by the methylene decoupling (Fig. 2-B, 2-C).

The small constant (2.3 c.p.s.) between H-2 and its neighbors is consistent with time averaging of EA and AE couplings. These n.m.r. results support assignment of the configuration *meso* (123/5) IX to the cyclohexanetetrol, m.p. 193°, and its tetraacetate.

Acetylation caused a downfield shift of 0.66 p.p.m. for H-5, and 0.75 p.p.m. for H-1 and H-3. Since the downfield shift for H-2 was 1.15 p.p.m., its degeneracy with H-1 and H-3 was destroyed, and separate signals were obtained (compare Fig. 1-C and 2-C).[21]

N.m.r. Configurational Proof for the Cyclohexanetetrol, M.p. 180°, of Horswill and McCasland.—When *myo*-inositol (VII) is heated with acetyl bromide, one of the products is a dibromocyclohexanetetrol tetraacetate, m.p. 130°.[22–24] This can be hydrolyzed to the dibromotetrol, m.p. 216°, for which a *meta* structure, E, was proposed[25] and is now confirmed.

In 1954 Horswill[23b] converted this dibromotetrol to a cyclohexanetetrol, m.p. 180°, which also appeared to have the *meta* structure; B. McCasland and Horswill[23b] assigned this tetrol the tentative configuration *meso* (13/25) XII, based on assumptions regarding the acetyl bromide reaction mechanism. This structural and configurational assignment has

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[21] The relatively great downfield shift of H-2, compared with H-1 and H-3, on acetylation can possibly be attributed to the fact that H-2 is more equatorial in the tetraacetate than in the tetrol, and H-1 and H-3 more axial. This in turn would result from a relatively large population of that conformation in which the acetate groups at 1 and 3 are equatorial.

[22] (a) H. Müller, *J. Chem. Soc.*, **91**, 1790 (1907); (b) **101**, 2383 (1912); (c) E. Griffin and J. Nelson, *J. Am. Chem. Soc.*, **37**, 1552 (1915); (d) A. Menzel, M. Moore, and O. Wintersteiner, *ibid.*, **71**, 1268 (1949); (e) E. Flynn, Ph.D. Thesis, University of Illinois (with Professor H. E. Carter), 1949; (f) M. L. Wolfrom, J. Radell, R. Husband, and G. E. McCasland, *J. Am. Chem. Soc.*, **79**, 160 (1957).

[23] G. E. McCasland and E. C. Horswill, *ibid.*, (a) **75**, 4020 (1953); (b) **76**, 2373 (1954). In the latter article Kubler's m.p. 176° dibromocyclohexanetetrol was inadvertently omitted from the list of known isomers (see formula IV).

[24] *myo*-Inositol reacts with hot acetyl bromide to give not only the *meta*- and *para*-dibromocyclohexanetetrol tetraacetates reported by previous investigators, but also an *ortho* isomer (B. Franck, personal communication, Aug., 1962); see formula III, Chart I.

[25] The structural proof for the dibromocyclohexanetetrol, m.p. 216°, was based on periodate studies, which seem highly reliable because (after further oxidation) a dibromohydroxyglutaric acid was actually *isolated*, confirming the *meta* structure.[22c] The corresponding tetrol, m.p. 180°, gave an unequivocal 2 moles/mole uptake of periodate, also indicating a *meta* structure (McCasland and Horswill, 1954).

now been fully confirmed. Although the 60-Mc. spectrum might have provided this confirmation, interpretation was greatly facilitated by recording both the 100- and 60-Mc. spectra. (Fig. 3).

At 100 Mc., the spectrum spread out into five well-separated patterns, shown by integration to contain 1, 2, 1, 2, and 2 protons, from left to right. The pattern separations must represent chemical shifts, since they are dependent on the magnetic field strength.

The triplet at 3.71 p.p.m. must result from spin coupling, since the splittings are essentially constant at 14.1 and 23.5 kilogauss. The triplet must correspond to H-2, which is coupled with the equivalent pair (H-1 and H-3). The coupling constant of about 9 c.p.s. demonstrates that H-2, and also H-1 and H-3, must be axial.[26]

The quintet at 4.70 p.p.m. (Fig. 3) must be produced by H-5, which is coupled with about equal constants of 3.0 c.p.s. to the four methylene protons. The coupling must be EE or EA, and establishes H-5 as equatorial. The H-5 pattern appears at lower field than the axial proton signals, as would be expected.

From the demonstrated conformational sequence (AAAE) at positions (1,2,3,5), the configuration *meso* (13/25) is fully established, confirming the 1954 assignment.

The (H-1 and H-3) diaxial assignment is supported by analysis of the octet at 4.25 p.p.m. which shows splittings[27,28] of 11.8, 9.0, and 4.7 c.p.s., due to AA, AA, and AE coupling of H-1 with the three protons at positions 2 and 6, and of H-3 with protons at 2 and 4.

Since this tetrol exists in a single, favored conformation (Table I) axial–equatorial time averaging is not encountered, and the equatorial methylene pattern is located about 0.50 p.p.m. downfield from axial, as might be expected. As in all the *meso* isomers (IX–XII) the two methylene protons "above" the ring are equivalent and likewise the two "below."

The methylene patterns (each presumably of 8 lines) may be attributed to spin couplings (large, small, small) of the equatorial protons (2.55 p.p.m.) with geminal and neighboring protons, and to couplings (large, large, small) of the axial protons (2.05 p.p.m.).

The **tetraacetate,** m.p. 86°, from the tetrol, m.p. 180°, was also examined, in chloroform-*d* at 60 Mc. (not shown). A wide methylene pattern (55 c.p.s.) confirmed nonequivalence of axial and equatorial methylene protons, but detailed interpretation was not accomplished.

Optical Rotatory Configurational Proof for the Two Active Diastereomers of 1,2,3,5-Cyclohexanetetrol.—In 1939, Dangschat and Fischer[18] degraded natural levorotatory quinic acid (XXIV) into a ketal (XXI) of 3,4,5-trihydroxycyclohexanone. From this intermediate by reduction and deacetonation were obtained two epimeric *meta* cyclohexanetetrols, XX and XXII, m.p. 151° (molecular rotation −90°), and m.p. 208°[18] or 200°[29] (molecular rotation −12°). The epimer m.p. 151° was reportedly obtained with aluminum isopropoxide; the epimer 208°, with hydrogen–nickel (reactions probably not stereospecific).[29] There was no basis at the time for deciding which epimer was which, but new methods for optical rotation prediction now permit a decision.[30,31]

According to Whiffen[30] or Brewster,[30] each diol grouping in the "front-left" conformation XXVIII contributes +45° to the molecular rotation; in the "front-right" XXIX, −45°; and in a diaxial conformation, 0°.

The L (12/35) epimer XX, with a single favored (AEEE) conformation XXIII, would then have a predicted rotation: −45° + −45° = −90°. The epimer of reported[18] molecular rotation −90° (m.p. 151°) can be assigned this absolute configuration.

Since the rotational contribution of an isolated dissymmetric center is assumed negligible, it might appear that epimerization at position 5 (formula XX) could not change the molecular rotation. However, such an epimerization can *indirectly* affect the rotation if it causes a shift in ratio of the molecule's two chair conformations.

Since the epimer L (125/3) is diaxial–diequatorial, it would consist of two conformations, XXV and XXVI, of roughly equal energy, in mobile equilibrium. The predicted molecular rotation for conformation XXV is −90°, as before; but for conformation XXVI it is +45° + 0° = + 45°. The epimerized tetrol should then be more dextrorotatory, or less levorotatory, so that the m.p. 208° epimer (molecular rotation −12°) can reasonably be assigned the absolute configuration L (125/3).

From the observed rotation, −12°, the estimated conformational ratio, XXV–XXVI, is about 2:3. The nearly equal molecular populations are perhaps due to competing effects of steric repulsion and hydrogen bonding between 1,3-diaxial hydroxyl groups.

In a similar manner one can predict the rotation of quinic acid itself from its known absolute configuration and assumed favored conformation XXVII. Assuming negligible contribution by the C(OH)(COOH) dissymmetric center, the predicted molecular rotation is −45° + −45° = −90° (found,[32] −84°).

Structure and Formation of the Dibromotetrol Tetraacetate, M.p. 173°.—The crystalline product obtained by reaction of the anhydro diketal (I) with HBr–AcOH was shown by microanalysis and infrared and nuclear magnetic resonance spectra to be a dibromocyclohexanetetrol tetraacetate. The *ortho* structure was excluded by nonreaction with sodium iodide[33,34] (see Experimental).

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(26) Note that the axial O–C–H protons in the n.m.r. discussion correspond to equatorial functional groups, and vice versa.

(27) R. Lemieux, R. Kullnig, H. Bernstein, and W. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(28) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(29) The two Dangschat–Fischer tetrols were recently prepared again by S. J. Angyal and P. A. J. Gorin (personal communication, Aug., 1962). Hydrogenation of the triolone ketal, using platinic oxide (not nickel) followed by deacetonation, reportedly gave a 77:23 ratio of the (125/3) and (12/35) epimers, from which was isolated the pure (125/3) epimer, m.p. 200°. We would like to thank Drs. Angyal and Gorin for a sample of their product, m.p. 200°.

(30) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5483 (1959); D. Whiffen, *Chem. Ind.* (London), 964 (1956).

(31) We would like to thank Professor S. J. Angyal for suggesting the use of rotation predictions in cyclitol studies (personal communication, Feb., 1960). We applied such predictions in 1961 to certain quercitols [*J. Am. Chem. Soc.*, **83**, 2335 (1961)]. According to recent word from Professor Angyal and P. Gorin, they have independently assigned absolute configurations to the Dangschat–Fischer tetrols in agreement with those proposed by us, presumably on the basis of rotation calculations.

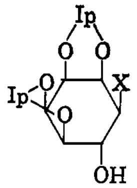
(32) (a) T. Posternak, "Les Cyclitols," Hermann, Paris, 1962 [for review see *J. Am. Chem. Soc.*, **85**, 2189 (1963)]; (b) p. 269.

The *meta* structure was established by successive conversion to the dibromotetrol V and the tetrol IX.

The dibromo tetraacetate, m.p. 173°, has now been shown by n.m.r. spectra to have the *trans*-dibromo configuration V (not XVII or XVIII); details will be given in a subsequent publication.

In early experiments, periodate titrations on the new dibromotetrol V and tetrol IX seemed to favor an *ortho* or *para* structure (see Experimental). Since other anomalous periodate results on cyclitols have been reported,[35] and since the *ortho* and *para* tetrol structures have now been firmly excluded by synthesis and n.m.r. data, the matter has not been pursued further.

No mechanism has yet been established for the remarkable reaction by which the HBr–AcOH reagent [36d] at room temperature converts the epoxide diketal (I) into a dibromo product (V, tetraacetate). An acceptable mechanism would need to explain these facts: (1) the same reagent with other diastereomers (*e.g.*, XIV) gave only monobromo products; (2) the same reagent with *epi*-inositol diketal[37] (XXX) failed to give any bromine-containing product,[38] despite similarity in the configurations; (3) the same reagent with the bromopentol diketal XXXI failed to give any of the dibromo tetraacetate V.



XXX, X = OH
XXXI, X = Br

From this last experiment, it appears that rearward, ring-opening attack by bromide ion on an epoxide ring carbon (position 6, formula I) must take place *after* similar attack on a ketal ring carbon (position 4). (Protonation of oxygen would facilitate each attack.)

Experimental[36]

All melting points have been corrected and, unless noted otherwise, were measured on a Nalge–Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. n.m.r. spectra (100-Mc.) were obtained with Varian HR-100 and 60-Mc. spectra with Varian A-60 high resolution spectrometers. Spin-decoupling experiments were accomplished through the use of a modified Varian V-3521 integrator.[7] Deuterium oxide[36b] with tetramethylsilane[36c] external reference was used as solvent for cyclohexanetetrols and dibromotetrols; chloroform-*d*[36a] with tetramethylsilane internal reference, for tetraacetates and tetrabenzoates.

Infrared spectra were measured on a Perkin-Elmer Model 137 Infracord recording spectrometer.

Darco G-60 decolorizing charcoal[36e] was used. Each solid filtration residue was washed with an appropriate wash solvent, and the wash liquid was combined with an appropriate filtrate. Each crop of crystals was dried to constant weight *in vacuo*, in some cases with the use of heat. Each nonaqueous solution to be evaporated was dried with an appropriate desiccant. All evaporations were performed under reduced pressure.

DL (1234/56) **Diastereomer of 4,6-Dibromo-1,2,3,5-cylcohexanetetrol Tetraacetate (V), M.p. 173°.**—To 240 mg. of 1,2:3,4-di-*O*-isopropylidene-5,6-anhydro-*allo*-inositol[10c] (m.p. 102°) was added 3.0 ml. of commercial[36d] 30% hydrogen bromide in glacial acetic acid, and the solution was stirred 12 hr. at room temperature (anhydrous conditions). Acetic anhydride (2.0 ml.) was added and stirring was continued for 12 hr. more. The powdery crystals were collected and dried over sodium hydroxide.

The crude product was taken up in 3.0 ml. of hot absolute ethanol and the solution was treated with charcoal, and then kept at 0° for 12 hr. or longer. The crystals were collected, giving 350 mg. (74%) of product, m.p. 172–173°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.40; H, 4.67; Br, 17.63. Calcd. for $C_{14}H_{18}Br_2O_8$: C, 35.46; H, 3.83; Br, 33.71. Found: C, 35.56; H, 3.74; Br, 33.46.

The infrared spectrum showed strong carbonyl absorption at 1750 cm.$^{-1}$, and no hydroxyl absorption. It resembled that of other dibromocyclohexanetetrol tetraacetate isomers, and not that of a bromocyclohexanepentol pentaacetate. The n.m.r. spectrum was recorded.

Sodium Iodide Test for Vicinal Dibromides.[33,34]—To 30 mg. of the dibromo tetraacetate (m.p. 173°) in a 200 × 4 mm. Pyrex tube was added a solution of 75 mg. of sodium iodide in 0.5 ml. of acetone. The tube was flushed with nitrogen, cooled with Dry Ice, and sealed off in a flame. The tube was heated at 100° for 15 hr. The tube contents were then slightly yellow (not red-brown), and no (sodium bromide) crystals were visible. A control tube from which the dibromo tetraacetate had been omitted showed no visible difference.

DL (1234/56) **Diastereomer of 4,6-Dibromo-1,2,3,5-cyclohexanetetrol (V), M.p. 182°.**—A solution of 350 mg. of the tetraacetate (m.p. 173°) in 6.0 ml. of a molar solution of hydrogen chloride in 50% (v./v.) ethanol was boiled under reflux for 5 hr., then evaporated. Absolute 2-methyl-1-propanol (3.0 ml.) was added and evaporation was repeated; the addition and evaporation were then again repeated. The residue was taken up in 2.0 ml. of hot 2-propanol (treated with charcoal). After 12 hr. at 0° (small yield of crystals separated), the solution was warmed to room temperature, and petroleum ether (b.p. 65–110°) was added. After an additional 12-hr. period at 0°, the crystals were collected and washed with 2-propanol, giving 200 mg. (88%) of the desired product, m.p. 180–182°.

Anal. Calcd. for $C_6H_{10}Br_2O_4$: C, 23.55; H, 3.29; Br, 52.24. Found: C, 23.57; H, 3.39; Br, 51.96.

The n.m.r. spectrum in deuterium oxide contained signals for two Br–C–H protons and four O–C–H protons crowded together into two narrow patterns centered at 4.8 and 4.9 p.p.m. The area of the latter pattern corresponded to one proton.

meso (123/5) **Diastereomer of 1,2,3,5-Cyclohexanetetrol (IX), M.p. 193°.**—To a solution of 200 mg. of the dibromotetrol (m.p. 182°) in 5.0 ml. of water was added 0.5 g. of moist Raney nickel catalyst and 0.2 g. of moist Amberlite IR-45 ion-exchange resin.[36f] The mixture was hydrogenated at 3 atm. and room temperature for 6 hr., then filtered. The filtrate was freed of nickel ions by treatment with Amberlite IR-120 (H$^+$) resin,[36f] then adjusted to pH 5 by stirring with Amberlite IR-45 resin. The filtrate from the resin treatment was evaporated, giving an oil which was taken up in 3.0 ml. of absolute ethanol (treated with charcoal). After 12 hr. the crystals which had separated were collected, giving 60 mg. (62%) of product, m.p. (in a sealed capillary) 192–193° dec. A sample was recrystallized again from abso-

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[33] R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 159.

[34] The reaction of 1,2-dibromocyclohexane with sodium iodide to give cyclohexene, iodine, and sodium bromide proceeds rapidly only with the *trans* diastereomer. However, the *cis* diastereomer may react slowly, probably because it reacts slowly with iodide to give the *trans* iodobromide, which can then undergo the usual rapid elimination reaction (D. Cram and G. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 401). Little, if any, information is available on the behavior of dibromodideoxy carbohydrates in this reaction. However, the comparable reaction of cyclitol ditosylates with sodium iodide to give cyclohexenetetrols (conduritols) has been carried out (Angyal and Gilham, 1958).

[35] S. J. Angyal and L. Anderson, *Advan. Carbohydrate Chem.*, **14**, 150 (1959); see ref. 22d; J. Green, "The Carbohydrates," W. Pigman, Ed., Academic Press, New York, N. Y., 1957, pp. 350, 351.

[36] Products that were used in experiments were obtained from the following companies: (a) Merck Sharp and Dohme of Canada, Ltd., Montreal; (b) Nichem, Inc., Bethesda, Md.; (c) Anderson Chemical Co., Weston, Mich.; (d) Distillation Products Industries, Rochester, N. Y.; (e) Darco Division, Atlas Powder Co., Wilmington, Del.; (f) Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

[37] The 1,2:3,4 and 1,2:4,5 di-*O*-isopropylidene derivatives of *epi*-inositol have very nearly the same melting point, but can be distinguished by a qualitative periodate test.

[38] The expected bromopentol pentaacetate, m.p. 153°, had previously been prepared by reaction of *epi*-inositol itself with hot acetyl bromide; see G. E. McCasland and J. Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955).

lute ethanol for analysis, melting point unchanged. The infrared spectrum was very similar to that of the m.p. 180° diastereomer.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.44; H, 8.20.

In some earlier runs the product was recrystallized from aqueous ethanol and then appeared to melt with decomposition (slow darkening) at about 220° in an open capillary. Its nonidentity with a 1,2,3,4-cyclohexanetetrol of reported[13] m.p. 222° was shown by comparison of the tetraacetates (see below).

The n.m.r. spectrum in deuterium oxide at 60 and 100 Mc. was examined with the aid of spin decoupling.

Periodate Titrations of the Cyclohexanetetrol, M.p. 193°, and Dibromocyclohexanetetrol, M.p. 182°.—(Figures in parentheses refer to the dibromotetrol.) To a 14.8-mg. (13.0 mg.) sample of the tetrol (dibromotetrol), was added 50 ml. (25 ml.) of 0.200 *M* (0.0196 *M*) sodium metaperiodate and water *q.s.* 100 ml. (50 ml.). Ten-milliliter aliquots of the clear solution were withdrawn at intervals for titration. Each aliquot was immediately mixed with 25 ml. (15 ml.) of 0.0100 *N* sodium arsenite, 10 ml. (5 ml.) of saturated sodium bicarbonate, and 1 ml. (0.5 ml.) of 1.2 *M* potassium iodide. After 15 min., the excess arsenite was determined by iodometric titration. The titration results were as follows.

Time, hr.	0	0.5	1.0	3.0	3.5	5.0	17.5	24.0
Periodate consumed, moles/mole								
Tetrol	0	3.1	3.1	3.2		3.3	3.5	4.0
Dibromotetrol	0	2.4	2.6		3.2	3.4		4.7

A control analysis on a sample of DL-*trans*-1,2-cyclohexanediol showed the expected 1 mole/mole of periodate uptake.

***meso* (123/5) Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetraacetate (IX), M.p. 118°.**—A mixture of 40 mg. of the tetrol (m.p. 193°) with 30 mg. of fused sodium acetate and 3.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. The crude product, isolated in the usual manner, was a sirup. A solution of this sirup in 3.0 ml. of hot 2-propanol was treated with charcoal, and the filtrate was concentrated to 2.0 ml. Petroleum ether (3.0 ml.) was added, and the mixture was kept at 0° for 12 hr. The crystals were collected, giving 60 mg. of colorless needles, m.p. 117–118°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.12.

The infrared spectrum was very similar to that of the m.p. 86° diastereomer except in the region 8.5–12 μ. A 15-mg. second crop, m.p. 116–118°, was obtained, total yield 88%.

The n.m.r. spectrum in chloroform-*d* at 60 and 100 Mc. was examined, with the aid of spin decoupling. The 60-Mc. integral showed 16 protons, with steps of 1, 3, and 12 protons. Only the latter step was sharply defined.

***meso* (123/5) Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetrabenzoate (IX), M.p. 189°.**—To 50 mg. of the tetrol (m.p. 193°) was added 0.31 g. of redistilled benzoyl chloride and 2.0 ml. of anhydrous pyridine. The mixture was stirred at room temperature for 24 hr. The crude product, isolated in the usual manner, was a viscous clear oil. This was taken up in 3.0 ml. of hot absolute ethanol (treated with charcoal), and the solution was kept at 0° for 24 hr. The colorless needles were collected, giving 60 mg. (31%) of product, m.p. 188–189°. A sample was recrystallized again for analysis, melting point unchanged.

Anal. Calcd. for $C_{34}H_{28}O_8$: C, 72.33; H, 5.00. Found: C, 72.32; H, 5.19.

The infrared spectrum was similar to that of the m.p. 206° diastereomer in the region 2.5–7.5 μ.

N.m.r. Spectrum of the M.p. 180° Diastereomer of 1,2,3,5-Cyclohexanetetrol (XII).—A sample of the crude tetrol (2.6 g.), prepared by Horswill[23b] in 1954, was recrystallized from 90% ethanol (treated with charcoal), giving 1.4 g. of colorless crystals, m.p. 179–180° (lit. m.p. 181.5–182.5°). The n.m.r. spectrum in deuterium oxide was recorded at 60 and 100 Mc. The 60-Mc. integral showed 8 protons with steps at 1, 2, 1, and 4 protons. Only the first step was sharply defined.

N.m.r. Spectrum of the M.p. 86° Diastereomer of 1,2,3,5-Cyclohexanetetrol Tetraacetate (XII).—A 450-mg. sample of the tetrol (m.p. 180°) was acetylated in the usual manner, giving 610 mg. of twice-recrystallized (from absolute ethanol)[39] product, m.p. 84–86° (lit.[23b] m.p. 91–92°). The spectrum in chloroform-*d* was recorded at 60 Mc. The acetate methyl signals in the spectrum consisted of sharp 9-proton and 3-proton peaks (δ 2.08 and 2.15). The equivalence of three (instead of two) methyl groups may be due to accidental degeneracy. The O–C–H chemical shifts were compressed into a 19-c.p.s. pattern, compared with 74 c.p.s. in the tetrol, so that interpretation was not possible. The wide methylene pattern was partly obscured by the methyl signals.

N.m.r. Spectrum of (−)-(125/3) Stereoisomer of 1,2,3,5-Cyclohexanetetrol (XXII).—A small sample of the tetrol,[18] which had been prepared by Angyal and Gorin[29] (m.p. 200°) was examined in deuterium oxide at 60 Mc. using a microcell.[40] The spectrum showed a complex methylene pattern centered at 2.3 p.p.m., and complex O–C–H patterns centered at 4.17 and 4.5 p.p.m. The spectrum was decidedly different from that of the (optically inactive) 193° diastereomer.

Nonreaction of DL-1,2:3,4-Di-*O*-isopropylidene-*epi*-inositol (XXX) with Hydrogen Bromide.—To 130 mg. of the *epi*-inositol 1,2:3,4-diketal,[10d,37] m.p. 181°, was added 2.0 ml. of commercial 30% hydrogen bromide in glacial acetic acid. The solution was stirred for 1 day at room temperature. The orange solution was evaporated. To the residual brown oil was added 2.0 ml. of 50% aqueous acetic acid, and the mixture was heated at 90–100° for 1 hr. The solution was evaporated, and the evaporation was repeated after addition of 2.0 ml. of toluene.

Redistilled acetic anhydride (2.0 ml.) and 20 mg. of fused sodium acetate were added, and the mixture was boiled for 4 hr. On evaporation there was obtained an oil, which was taken up in 2.0 ml. of 2-propanol (treated with charcoal), and the solution was kept at 0° for 12 hr. A 160-mg. yield of *epi*-inositol hexaacetate, m.p. 186–188° (lit.[32] m.p. 188°), was obtained. A sodium fusion test for halogen was negative.

DL (12346/5) Stereoisomer of 1,2:3,4-Di-O-isopropylidene-6-bromoquercitol (Bromocyclohexanepentol Diketal) (XXXI).—To 170 mg. of the bromopentol[5b] (m.p. 209°) was added a solution of 290 mg. of fused zinc chloride in 10 ml. of acetone. The mixture was stirred at 25° for 5 days. Since a solid residue was still present, the mixture was boiled for 3 hr., giving a clear solution. To the cooled solution was added 1.38 g. of anhydrous potassium carbonate in 1.9 ml. of water, and the mixture was stirred 0.5 hr., and then filtered. The solid residue was washed with three 5-ml. portions of acetone, and the combined acetone filtrate was dried and evaporated, giving 100 mg. of colorless residue.

This was recrystallized from absolute ethanol (treated with charcoal), giving 70 mg. of colorless crystals, m.p. 206–207° with sublimation (capillary). A second crop of 15 mg. (total yield 38%), m.p. 205–206° (cap.) with sublimation, was obtained.

Anal. Calcd. for $C_{12}H_{19}BrO_5$: C, 44.59; H, 5.93; Br, 24.73. Found: C, 44.75; H, 5.83; Br, 24.75.

When this product was dissolved in a solution of hydrogen bromide in acetic acid and the solution was kept at room temperature for many hours, no crystals separated, and none of the expected dibromocyclohexanetetrol tetraacetate could be isolated from the reaction mixture.

***meso* (1234) or All-*cis* Diastereomer of 1,2,3,4-Cyclohexanetetrol Tetraacetate (XIX), M.p. 65°.**—From 0.84 g. of conduritol-D 2,3-carbonate 1,4-diacetate,[18] there was obtained in the manner previously reported about 300 mg. of dihydroconduritol-D as a sirup (lit.[13] m.p. 222°).

A mixture of the sirup with 0.1 g. of fused sodium acetate and 4.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. The crude product, isolated in the usual manner, was a sirup, which turned crystalline when vacuum-dried over phosphorus pentoxide for 24 hr. The product was recrystallized from a 1:3 mixture of 2-propanol and petroleum ether (b.p. 65–110°), giving 130 mg. (13% based on carbonate diacetate) of the desired tetraacetate, m.p. 65.0–65.5°. A sample was recrystallized for analysis, melting point unchanged.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.85; H, 6.55.

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(39) The spectrum contained a very small triplet at 1.28 p.p.m. probably due to a trace of ethanol impurity. This may have lowered the melting point but did not appreciably affect the remaining n.m.r. signals.

(40) The microcell technique has been described by J. N. Shoolery, in Varian Associates Technical Information Bulletin, Vol. 3, No. 3, Palo Alto, Calif., 1963, pp. 8,9.

The product was not identical with the m.p. 118° diastereomer, and not a dimorph.

Infrared Spectra.—The research spectrum was recorded, using the potassium bromide pellet method, for each new compound. The spectra showed the principal expected peaks, but have not been interpreted in detail.

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Photochemical Reactions of Diketones. II.[1a,b] The 1,2-Addition of Substituted Toluenes to 9,10-Phenanthrenequinone

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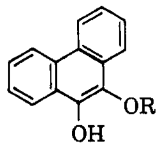
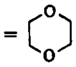
Reversible photochemical addition of substituted toluenes to phenanthrenequinone (PQ) proceeds *via* 1,2-addition to give 9,10-dihydro-9-hydroxy-9-X-benzyl-10-ketophenanthrenes (**6**) contrary to earlier reports that 1,4-addition occurs in these reactions. In addition to physical evidence, this was established by conversion of both phenanthrenequinone and the *p*-xylene–phenanthrenequinone adduct (**6d**) to *trans*-9,10-dihydro-9,10-dihydroxy-9,10-bis(*p*-methylbenzyl)phenanthrene (**7d**). Attempted synthesis of the *cis* isomer of **7d** was not successful. These results contrast with the 1,4-additions of ethers and aldehydes to phenanthrenequinone; the relative rates of addition of benzaldehyde, dioxane, and *p*-xylene to phenanthrenequinone were 48:2.7:1. The mono(*p*-methylbenzyl) ether (**2**) of 9,10-dihydroxyphenanthrene was synthesized by a new and apparently general method; photoirradiation of **2** afforded the 1,2-adduct **6d**.

In connection with the study[1b] of the photochemical addition of ethers to 9,10-phenanthrenequinone (PQ) to give products typified by the dioxane adduct (**1**), we have reinvestigated the photoaddition of *p*-xylene and related compounds to 9,10-phenanthrenequinone. This reaction was first reported in 1914 by Benrath and Von Meyer[2] and was re-examined almost 40 years later by Moore and Waters.[3] The earlier workers proposed that the 1:1 adducts obtained by sunlight irradiation of solutions of phenanthrenequinone in *o*- or *p*-xylene, mesitylene, pesudocumene, or quinaldine were substituted monobenzyl ethers (**2**) of 9,10-dihydroxyphenanthrene (**3**). This assignment was based on analogy with the photoaddition of aldehydes to phenanthrenequinone reported earlier by Klinger[4] to give monoesters (**4**) of **3** and, on degradations to **3**, phenanthrenequinone and phenanthrene quinhydrone. The surprising observation that the infrared spectrum of the *p*-xylene–phenanthrenequinone adduct exhibited both hydroxyl (2.98 μ) and carbonyl (5.96 μ) absorption was rationalized by the later workers on the assumption that appreciable tautomerization of the phenol **2** to the corresponding keto form occurred.[5]



1, R = 

2, R = p-$CH_3C_6H_4CH_2$–

3, R = H

4, R = $C_6H_5\overset{|}{C}=O$

If structure **2** were correct, the *p*-xylene–phenanthrenequinone adduct would be expected to exhibit an ultraviolet spectrum very similar to the spectra of the ether (**1**) and aldehyde (**4**) adducts. Further, the spectrum should be changed markedly in alkaline solution owing to conversion to the corresponding phenoxide ion as was observed with **1** and **4**. In fact, the ultraviolet spectrum of the *p*-xylene–phenanthrenequinone adduct (two maxima) was significantly different from the spectra of compounds of types **1** and **4** (six maxima) and remained unchanged on prolonged standing in alkaline solution. These results as well as the infrared data would be satisfactorily accommodated by the assumption that 1,2-addition of *p*-xylene to phenanthrenequinone had occurred to give 9,10-dihydro-9-hydroxy-9-(*p*-methylbenzyl)-10-ketophenanthrene (**6d**).[7a,b] The n.m.r. spectrum of the adduct exhibited singlets at τ 6.0 (hydroxyl proton, broad), 7.01 (CH_2), and 7.72 (CH_3) (relative intensities 1:2:3), and complex absorption at τ 2–3 (aromatic protons) in agreement with the revised structure.

Chemical evidence confirmed the correctness of this conclusion. Reaction of phenanthrenequinone with an equimolar quantity of *p*-methylbenzyl magnesium bromide led to formation, in low yield, of a substance identical with the photoadduct; the other products isolated were recovered phenanthrenequinone and 1,2-bis-*p*-tolylethane, the product of Grignard coupling.

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[1] (a) Presented in part at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; (b) for the previous paper in this series, see M. B. Rubin, *J. Org. Chem.*, **28**, 1949 (1963).

[2] A. Benrath and A. Von Meyer, *J. prakt. Chem.*, **89**, 258 (1914).

[3] R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 3405 (1953).

[4] H. Klinger, *Ann.*, **249**, 137 (1888).

[5] 9,10-Dihydro-9-ketophenanthrene has been prepared[6] and reported to be unstable in air and to undergo rapid change in solution.

[6] E. J. Moriconi, F. T. Wallenberger, L. P. Kuhn, and W. F. O'Connor, *J. Org. Chem.*, **22**, 1651 (1957).

[7] (a) W. I. Awad and A. R. A. Raouf, *ibid.*, **22**, 881 (1957), have described the related substance, 9,10-dihydro-9-hydroxy-9-phenyl-10-ketophenanthrene [λ_{max} 245, 270 (sh), and 330 mμ in reasonably close agreement with the spectrum of the photoadduct of phenanthrenequinone and *p*-xylene]; (b) Ramart-Lucas, M. J. Matti, and T. Guilmart, *Bull. soc. chim. France*, 1215 (1948), report λ_{max} 278 and 330 mμ for 9,10-dihydro-9,9-dimethyl-10-ketophenanthrene.