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STUDIES ON CYCLITOLS—XV

THE MECHANISM OF *TRANS*-HYDROXYLATION OF CONJUGATED DIENES BY PERMANGANATE*†

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Abstract—When 1,3-cyclohexadiene **1** and cyclopentadiene **12** are treated with neutral or alkaline permanganate, two sets of products are formed in each case. One set of products is formed by normal hydroxylation, and consists of the respective DL-*cis*-1,2-cycloalkenediols **3** or **14**, and the corresponding DL-(1,2/3,4)-cycloalkane-1,2,3,4-tetrols, **6a** and **11**. The other set of products is formed by abnormal hydroxylation, and consists chiefly of the all-*cis*-DL-1,2-anhydro-1,2,3,4 tetrols **2** and **13**, and the DL-(1,2,3/4)-cycloalkane-1,2,3,4-tetrols **4a** and **15**. Small amounts of the DL-(1,2,4/3)-cycloalkane-1,2,3,4-tetrols **5** and **16** are also formed. The abnormal pathway predominates in the cyclopentanoid series, but substantial amounts of both sets of products are always formed. The ratios of (1,2,3/4)-tetrol to (1,2,4/3)-tetrol obtained by the hydroxylation procedure are approximately the same as the ratios of these compounds formed by hydrolysis of the anhydrotetrols in dilute acid. It is proposed (1) that the anhydrotetrols or reactive intermediates related to them are intermediates in the abnormal tetrahydroxylation; and (2) that the *cis*-cycloalkenediols are intermediates in the normal but not the abnormal hydroxylation, nor in the formation of the anhydrotetrols. By treatment with NaN_3 and subsequent acetylation, the anhydrotetrol **2** has been converted into DL-(1,2,3/4)-1,2,3-tri-O-acetyl-4-azidocyclohexane-1,2,3-triol **22b**; catalytic reduction of **22b** followed by acetylation gives DL-(1,2,3/4)-4-acetamido-1,2,3-tri-O-acetylcyclohexane-1,2,3-triol **23b**. Treatment of **2** with HBr produces a DL-bromocyclohexanetriol **20** or **21**, whose structure and configuration have not yet been established.

HYDROXYLATION of alkenes and cycloalkenes by permanganate has generally been considered to give only *cis* glycols, although α-ketoalcohols may also be obtained when the reaction mixture is insufficiently alkaline.[2] A single exception to this rule was known: Zelinskii *et al.*[3] reported that 1,3-cyclohexadiene **1** was convereted into a tetrol by oxidation with permanganate, and nearly 20 years later Posternak and Friedli[4] proved that the product was DL-(1,2,3/4)-cyclohexanetetrol **4a**.

More recently, we observed[5a] that cyclopentadiene **12** was converted into the corresponding (1,2,3/4) tetrol **15**, and also that both *trans*-1,2- and *trans*-1,3-cyclopentenediols could be converted into **15**. On the assumption that the formation of **15** from **12** involved the intermediate formation of a diol such as **10**, we attempted to identify such a substance in the hydroxylation mixture. Instead, we found that the only other major product present was the all-*cis* epoxydiol, DL-1,2-anhydro-(1,2,3,4/0)-cyclopentanetetrol **13**. When the epoxide group of **13a** was opened by dilute aqueous sulfuric acid,[5b] the tetrol product obtained consisted chiefly of **15** (95–99%) with a small amount of the isomeric tetrol **16**. This finding supported the idea that **13**

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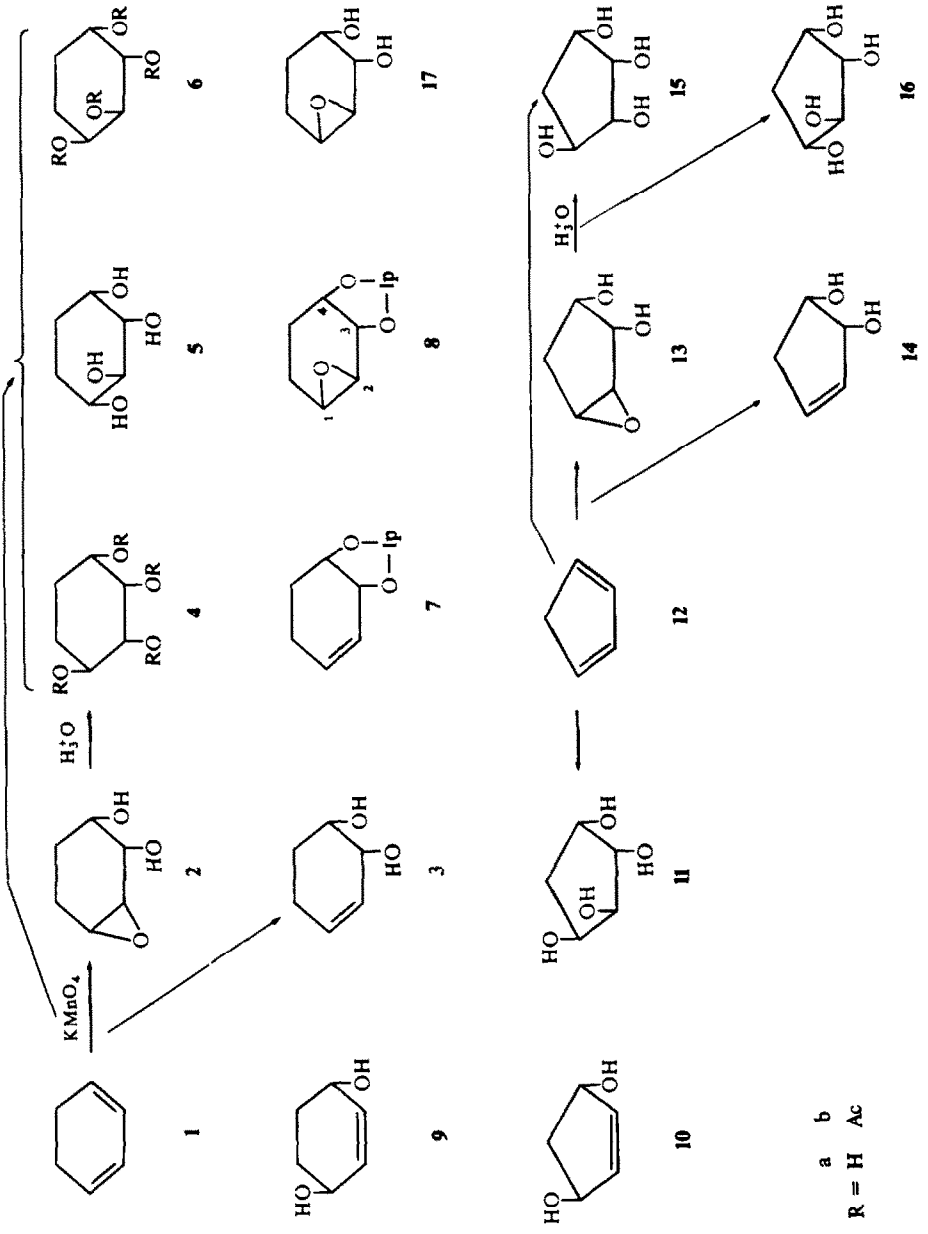
† For part XIV see reference (1).

CHART 1. Hydroxylation of cyclic dienes by permanganate.



might be an intermediate, rather than the product of a side reaction, in the formation of **15** from **12**. The present communication describes the results of a reinvestigation of the hydroxylation of the conjugated dienes **1** and **12** by neutral and alkaline permanganate. The production of tetrols with the (1,2,3/4) configuration is confirmed. The tetrol mixture also contains small amounts of the isomeric (1,2,4/3) tetrols **5** and **16** and the (1,2/3,4) tetrols **6a** and **11**. In addition, the hydroxylated products include varying amounts of the *cis*-1,2-cycloalkenediols **3** and **14** and the corresponding 1,2-epoxydiols **2** and **13**. It is proposed that the products are formed from two competing reactions: normal hydroxylation gives the cycloalkenediols and the (1,2/3,4) tetrols, while abnormal hydroxylation leads to the other products named. In the cyclopentanoid series the abnormal route predominates. No evidence has been obtained to support the suggestion made previously[6] that the first step in the abnormal hydroxylation is a 1,4-addition of permanganate, leading to the *trans*-cycloalkenediols **9** and **10**.

RESULTS

Products of hydroxylation of cyclopentadiene

(a) *Abnormal hydroxylation.* The principal products formed[5] when cyclopentadiene is treated with neutral or alkaline permanganate are the tetrol **15** and the anhydrotetrol **13**. Analysis by paper chromatography showed that some preparations contained traces of a substance with the same mobility and color reactions as the *cis*-diol **14**, but attempts to isolate the diol were unsuccessful. Better separation was achieved[7,8]

TABLE 1. TLC ANALYSIS OF HYDROXYLATED PRODUCTS OBTAINED BY OXIDATION OF CYCLOPENTADIENE

Cyclopentadiene, dissolved in ethanol or acetone, was oxidized with zinc permanganate. The products were separated by partition between water and methylene chloride, and the methylene chloride-soluble was purified by vacuum distillation. Some of the material was hydrolyzed in dilute H_2SO_4, and after exhaustive extraction with methylene chloride the aqueous solution was analyzed. The backing material was Silica gel G; the developing solvent was butanone, glacial acetic acid, 2% boric acid (9 : 1 : 1 by volume); the detecting reagent was a permanganate–periodate spray.[28]

Substance analyzed	R_f of components
Methylene chloride-soluble fraction[a]	0·52–0·56 (major) 0·67–0·69 (minor)
Anhydrotetrol **13**	0·54
Cyclopentenediol **14**	0·69
Hydrolyzate of methylene chloride fraction	0·17–0·19 (major) 0·27–0·30 (minor)
Tetrol **15**	0·18
Tetrol **16**	0·30

[a] Products from five separate experiments and the reference substances were analyzed on the same plate.

by TLC,* and all preparations were then found to contain two minor components with R_f corresponding to diol **14** and tetrol **16**. The amount of **16** was small; by comparison with known amounts of authentic material it was estimated to represent about 1 to 5% of the mixture of tetrols. When the anhydrotetrol **13** was hydrolyzed and the hydrolyzate chromatographed, the chromatogram resembled chromatograms of the mixture of tetrols obtained from the direct hydroxylation of **12**. No evidence was obtained by TLC that there was also a third tetrol component, although such evidence was obtained much later by VPC analysis (see below). Results of typical thin-layer analyses are shown in Table 1. Since epoxide-opening generally occurs with inversion of one of the asymmetric carbon atoms of the oxirane ring, hydrolysis of **13** should give rise only to tetrols **15** and **16**. In view of the occurrence of **13**, **15** and **16** as the principal products of the hydroxylation reaction, it is reasonable to assume either that a single reactive intermediate, formed when **12** reacts with permanganate, can be converted to these three products, or that **13** is formed first and is an obligatory intermediate in the formation of the tetrols (see Discussion).

The presence of the diol **14** in the mixture raised the question whether the sequence **12** → **14** → **13** → **15** might be involved. Authentic diol **14** was therefore treated under the conditions used for the hydroxylation of the diene **12**. In several experiments the product was an intractable tar. In one case TLC evidence was obtained for the formation of a minute amount of tetrol, which was not identical with **15**. The reason for the occurrence of the diol and the proof of its structure are described below.

(b) *Normal hydroxylation.* After most of the experiments described in this paper were complete, the products of the hydroxylation reaction were reinvestigated by VPC (Table 2). In addition to the products listed, another compound was observed, whose retention time suggested that it was a tetrol. The availability[5a,8] of the authentic tetrol **11** made the identification easy. The diol **14** and tetrol **11a** are the expected products of partial and complete hydroxylation of **12**, and they are therefore referred to as the normal products. Most likely they are formed by a mechanism identical with that proposed[2] for the hydroxylation of simple alkenes. Diol **14** or a reactive species related to it is probably the substrate for a second normal hydroxylation, leading to **11**. Table 2 shows that the abnormal pathway is favored. Indeed, in some experiments the yield of tetrols has been almost negligible, and the amount of **14** so small that the distillate of the methylene chloride-soluble fraction (see Experimental) gave correct elemental analysis for pure **13**. In a few cases, in which the abnormal product was mainly tetrol **15**, the methylene chloride-soluble fraction was chiefly diol. One of these products was used to establish the identity of diol **14**. This was accomplished by catalytic reduction of the diol to a product which then gave a *bis-p*-nitrobenzoate **24d**, identical with that obtained from authentic *cis*-1,2-cyclopentanediol **25** (see Chart 2).

Products of hydroxylation of 1,3-*cyclohexadiene*

(a) *Abnormal hydroxylation.* The similarity of the configuration of the tetrol[3,4] obtained from cyclohexadiene **1** to that obtained from **12**, suggested that the related diol **3** and anhydrotetrol **2** should also be formed. These substances have now been identified in the mixture of products obtained when **1** is oxidized with unbuffered

* The following abbreviations are used: DSS, 2,2-dimethyl-2-silapentane-5-sulfonate; nmr, nuclear magnetic resonance; ppm, parts per million; R_t, retention time; TLC, thin-layer chromatography; TMS, tetramethylsilane; VPC, gas–liquid chromatography; W_h, width at half height.

TABLE 2. VPC ANALYSIS OF THE PRODUCTS OF HYDROXYLATION OF CYCLOPENTADIENE AND 1,3-CYCLOHEXADIENE

The material to be analyzed was dissolved in pyridine and treated with chlorotrimethylsilane. The solution was injected on a column of 6% SE30 on ABS 90/100, 6 feet × 1/8 inch; oven temperature 150° (see text and Experimental for details).

Substance or mixture	RT	%	Substance or mixture	RT	%
	min			min	
Experiment 1			Experiment 2		
A. Authentic Cyclopentanoid Compounds			A. Authentic Compounds		
			Diol **14**	1·6	
Tetrol **11**	10·2		Anhydrotetrol **13**	4·0	
Tetrol **16**	12·0		Tetrol **11**	10·9	
Tetrol **15**	12·4		Tetrol **15**	13·4	
B. Hydrolyzate[a] of	10·2	0·003	B. Crude Hydroxylation	1·7	18·2
anhydrotetrol **13**	12·6	>99·9	product[a] from Cyclo-	3·9	57·5
C. Water layer of a hydroxylation mixture[a,b]	10·1	80	pentadiene	10·7	5·5
	12·4	20		13·4	18·8
Experiment 3			Experiment 4		
A. Authentic Cyclohexanoid Compounds			A. Authentic Compounds		
			Diol **3**	2·1	
Tetrol **6a**	13·6		Anhydrotetrol **2**	4·5	
Tetrol **4a**	19·4		Tetrol **6a**	11·2	
Tetrol **5**	21·2		Tetrol **4a**	15·7	
			Tetrol **5**	17·6	
B. Water layer[b] of a	13·7	18	B. Crude Hydroxylation	2·2	53·9
hydroxylation mixture	19·0	79·6	product from Cyclohexadiene	4·6	39·5
	21·3	~2[c]		11·2	2·0
				15·5[d]	4·6
C. Hydrolyzate of	13·6	trace			
anhydrotetrol **2**	18·9	>99			
	21·1	<1			

[a] It was impossible to distinguish the presence of small amounts of tetrol **16** in a large amount of **15**, under the conditions of the experiment. Peaks assigned as **15** in experiments 1B and 2B may actually contain some **16**.

[b] The water layer is obtained as follows: when reaction was complete, the mixture was freed of precipitate, the solution concentrated to remove acetone; and then extracted exhaustively with methylene chloride.

[c] In this case the relative amount of [5] was determined by comparison with a series of known mixtures of **5** and **4a**.

[d] Small amounts of tetrol **5** would not have been detected, and may be present in the peak assigned as **4a**. In another experiment under slightly different conditions the four compounds indicated were present in the ratio 52:28:6:14, showing the same distribution between normal and abnormal hydroxylation.

potassium permanganate, potassium permanganate-potassium carbonate, or buffered permanganate. The work-up of the products is facilitated when the solution obtained contains no salt; consequently most of the studies were carried out with zinc permangate. However similar results were obtained when potassium permanganate-magnesium sulfate mixtures were used. As in the study of cyclopentanoid compounds, the hydroxylated products were usually separated by partition between water and

methylene chloride. Table 3 shows the analysis by TLC* of typical products. The substance with R_f 0·63–0·68 was presumed to be diol **3**, and that with R_f 0·46–0·53 was presumed to be the epoxydiol **2**. TLC analysis of the aqueous solution remaining after extraction with the organic solvent always indicated the presence of only one substance, of R_f 0·23–0·28. Evaporation of water gave tetrol **4a**, m.p. 154·5–155·5°

TABLE 3. TLC ANALYSIS OF HYDROXYLATED PRODUCTS OBTAINED BY OXIDATION OF CYCLOHEXADIENE[a]

1,3-Cyclohexadiene, dissolved in acetone, was oxidized with neutral or alkaline permanganate. In some cases the products were separated by partition between water and methylene chloride, and the methylene chloride-soluble material purified by vacuum distillation. In one case *trans*-3-cyclohexene-1,2-diol was oxidized with OsO_4-$AgClO_3$. In another case the methylene chloride-soluble material was treated with m-chloroperoxybenzoic acid. Analysis was carried out as described in Table 1.

Substance analyzed	R_f of components
A. Mixed oxidation product	0·29, 0·51, 0·67
B. "Aqueous" layer of A	0·29
C. Methylene chloride-soluble material of A	0·50, 0·66
D. Acid Hydrolyzate of C	0·26, 0·64
E. OsO_4-$AgClO_3$ oxidation product[b] (tetrol **5**)	0·29
F. Peracid oxidation product	0·24, 0·50
G. Authentic tetrol **4a**	0·23–0·29

[a] Values are taken from separate but comparable thin-layer analyses.

[b] In this experiment tetrol **4a** was used as a reference compound on the same thin-layer plate and had R_f = 0·29.

(lit.[4] 154–155°). Acetylation of the latter gave a tetraacetate, m.p. 112·5–113·5°, whose nmr spectrum[9] showed the presence of one axial and three equatorial acetoxyl groups. This compound is DL-(1,2,3/4)-*tetra*-O-*acetylcyclohexane*-1,2,3,4-*tetrol* **4b**. As in the cyclopentanoid series, evidence for the tetrol **6a**, produced by normal hydroxylation was obtained later (see below). Spectroscopic analysis of the methylene chloride-soluble material showed the presence of the appropriate functional groups. IR spectra of dilute solutions of the material in carbon disulfide showed bands characteristic of: free (>3600 cm^{-1}), and intramolecularly bonded OH groups (3500, 3560 cm^{-1}); olefinic C—C stretching (1690 cm^{-1}); oxirane[8,10] (840 cm^{-1}) and vinylic C-H bending (730 cm^{-1}) modes. The nmr spectra has signals at δ 3·6–3·75 and δ 5·7–5·9, characteristic of oxirane O—C—H and vinylic protons, respectively. Under hydrolytic conditions (100°, 0·02 N H_2SO_4, 1 hr) the material of R_f 0·46–0·53 disappeared and corresponding amounts of tetrol **4a** were isolated from the hydrolyzate (Table 3). The precursor of the tetrol must have contained a vicinal *cis* glycol function, and must therefore be either the *cis*-anhydrotetrol **2** or the diastereoisomer **17** with the (1,2/3,4)

* The R_f values varied for two reasons: no attempt was made to control the temperature at which the chromatography was performed; and solvent in a chromatographic tank was used several times, thus changes in composition occurred, due to loss of the more volatile components.

configuration. Proof of structure was carried out in the following way: the methylene chloride-soluble material was treated[11] with NaN_3 to produce an azidotriol. The latter compound was acetylated to give a triacetate which proved to be DL-(1,2,3/4)-1,2,3-*tri*-O-*acetyl*-4-*azidocyclohexane*-1,2,3-*triol* **22b**. The structure-proof of **22b** was facilitated by the availability[12] of two of the isomeric tetraacetyl "conduramines" **19b** and **27b**; catalytic reduction of **22b** and subsequent acetylation gave a tetraacetyl derivative identical with DL-(1,2,3/4)-4-*acetamido*-1,2,3-*tri*-O-*acetylcyclohexane*-1,2,3-**23b**, which in turn has been prepared by reduction of "tetraacetyl conduramine C-4" **19b**. The isomeric substance DL-(1,2,4/3)-4-*acetamido*-1,2,3-*tri*-O-*acetylcyclohexane*-1,2,3-*triol* **26b** was similarly produced from "tetraacetyl conduramine F-4" **27b**, and was easily distinguished, by IR spectroscopy and m.p. from **23b**. The configuration of **22** proves that in the parent compound all three oxygen atoms are *cis* to one another, and are attached to adjacent C atoms; thus the parent compound is proved to be DL-(1,2,3,4/0)-1,2-*anhydrocyclohexane*-1,2,3,4-*tetrol* **2**. It is seen that in this case, as in the case of the analogous cyclopentanoid compound **13**, the epoxide opens preferentially at the position farther from a hydroxyl group.[5,8]

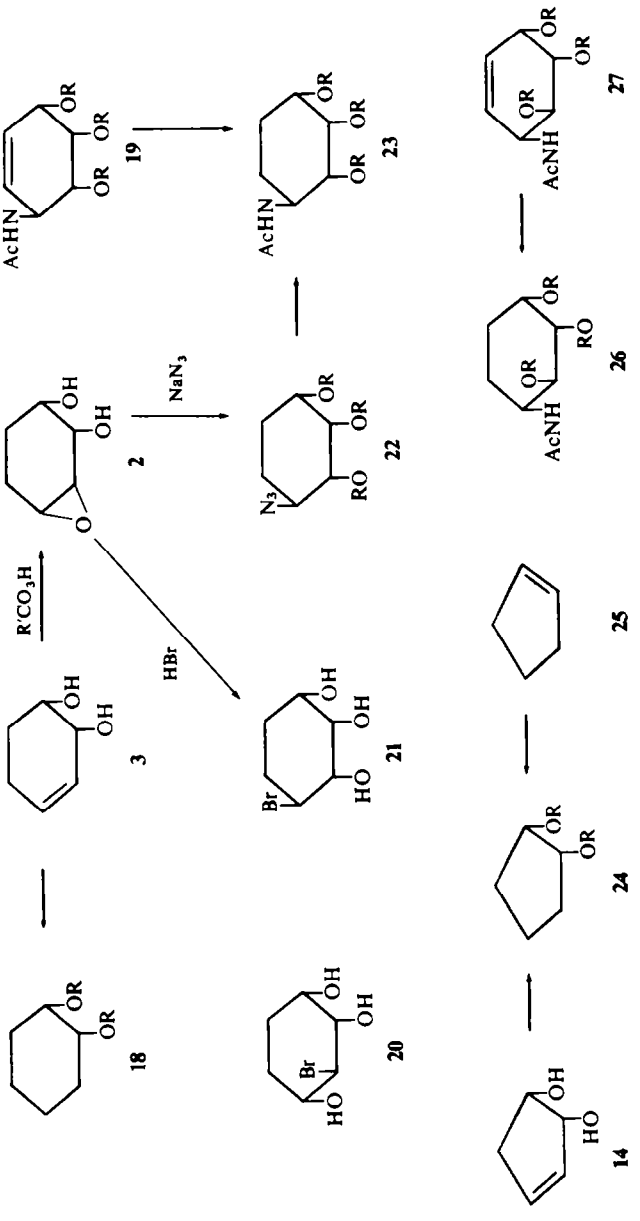
The anhydrotetrol **2** reacts with aqueous HBr to give a bromotriol, which may be either DL-(1,2,3/4)-4-*bromocyclohexane*-1,2,3-*triol* **21** or DL-(1,2,5/6)-6-*bromocyclohexane*-1,2,5-*triol* **20**. These alternatives appeared to be distinguishable by titration with periodate. In the former case two molar equivalents, and in the latter one molar equivalent of periodate should be consumed. Actually 1·4 molar equivalents were consumed, so the analysis is inconclusive.

(b) *Normal hydroxylation.* The principal component of the methylene chloride-soluble fraction, and one of the two major products of hydroxylation of diene **1** is a substance whose R_f (0·63–0·68) suggests that it is a diol. When the crude material is treated with *meta*-chloroperoxybenzoic acid, the substance of R_f 0·63–0·68 disappears, and is replaced by tetrol **4a** and anhydrotetrol **2**. The presumed diol must therefore be unsaturated, and its structure must be **3**. The isomeric *cis*-4-cyclohexene-1,2-diol would not be a suitable precursor for the products actually obtained on treatment with the peroxyacid. Since catalytic hydrogenation of the crude product converted it into *cis*-1,2-cyclohexanediol **18a**, the structure of **3** is proved.

When the products of hydroxylation of **1** were re-examined by VPC, the normal tetrol product **6a** was found to be formed (Table 2). The two cyclic dienes are thus seen to behave similarly under conditions of hydroxylation by permanganate. Experiment 4 in Table 2 shows that the normal route may predominate in the cyclohexanoid series. This experiment is not entirely typical, since so little tetrol product was formed. However, the major product, the diol, is formed by normal hydroxylation. This is different quantitatively from the cyclopentanoid series, in which the major product was either tetrol **15** or anhydrotetrol **13**, both formed by abnormal hydroxylation. Qualitatively, however, both 1,3-dienes give the same result.

O-Isopropylidene derivatives. One sample of tetrol **5** was prepared by a new procedure, in which diol **3** was converted successively into **7** and **8** (Chart 1) and the latter hydrolyzed to produce **5**. The IR and NMR spectra of these compounds were examined (see below) and the hydrolysis of the isopropylidene epoxydiol **8** was investigated. In an earlier study[8] we found that partial hydrolysis of the cyclopentanoid analogue of **8** gave rise to the analogue of **17**, and no isopropylidene tetrol was detected. This indicated that the epoxide was hydrolyzed less readily than the O-isopropylidene

CHART 2. Structure proof of diols and epoxydiols.



group. In the present study a series of replicate solutions of **8** in 4×10^{-4} N H_2SO_4 was heated at 100° for varying lengths of time, and the hydrolyzate analyzed by TLC. Compounds **2**, **3** and **5** were used as the standards, since neither **17** nor the 1,2-O-isopropylidene derivative of **5** is known. TLC plates of the partial hydrolyzates showed two spots, one corresponding to tetrol **5** and the other having a mobility equal to that of **3**. This suggests, but by no means proves, that in this case the epoxide is hydrolyzed more easily than the O-isopropylidene group.

Spectroscopic studies

(a) *Infrared.* The IR spectra of all the cyclopentanoid epoxides we have studied[5b, 8, 10] have bands at 3010–3040 cm^{-1} ascribed to an oxirane C—H stretching vibration,[13] and a medium-to-strong, sharp band at 835–850 cm^{-1} ascribed to an unspecified oxirane vibrational mode. Epoxydiol **2** has a band at 3005 cm^{-1} and the O-isopropylidene epoxydiol **8** has a band at 2990 cm^{-1}. These findings agree with the spectral measurements of Henbest *et al.*[13] on closely related compounds. In the 800–850 cm^{-1} region, the spectrum of **2** has a band at 840 cm^{-1}; that of **8** has a strong band at 800 cm^{-1} and an additional weak band at 850 cm^{-1}. It is uncertain which, if either, of these represents the band normally found at 840 cm^{-1}.

The isopropylidene derivatives we have studied[5b] all show a strong doublet, ascribed to the *gem*-dimethyl function, at 1365–1380 cm^{-1}, $\Delta\nu \cong 10$ cm^{-1}. The spectrum of **8** shows this doublet at 1365 and 1375 cm^{-1}, but that of **7** has a triplet at 1360, 1365 and 1370 cm^{-1}, instead of the usual doublet. Presumably, the appearance of an additional band is due to the fact that **7** can exist in two, nonequivalent, half-chair conformation, and to the presence of significant amounts of both forms in the solution.

In the O—H stretching region, the spectrum of **3** has bands 3603 and 3564 cm^{-1}, ascribed to one free and one intramolecularly H-bonded OH group. The spectrum of **2** has bands at 3557 and 3500 cm^{-1}, due to two intramolecularly H-bonded groups, and no free OH. The values of $\Delta\nu$ are difficult to assess for reasons described elsewhere[5b, 10] but are probably about 60 and 110 cm^{-1}, indicating that the H-bonds are very strong. In this respect **2** closely resembles[5b, 10] its cyclopentanoid analogue **13**.

(b) *Nuclear magnetic resonance.* The NMR spectra were consistent with the proposed structures. Only first-order analyses are reported here.

Diol **3**. (D_2O) CH_2: two multiplets at δ 1·76 (2), width 27 Hz and δ 2·11 (2), width 22 Hz. OCH: δ 3·85 (1) multiplet of at least 7 lines; δ 4·14 (1) multiplet of at least 6 lines. The olefinic protons give a pattern centered at δ 5·83 (2) which resembles the AB portion of an ABX_mY_n spectrum, width 36 Hz.

Epoxydiol **2**. (D_2O) CH_2: two well defined multiplets showing geminal and several vicinal couplings at δ 1·53 (2) and δ 2·08 (2). Oxirane CH: narrow triplet at δ 3·43 (2). OCH: well-defined multiplets at δ 3·70 (1) and δ 4·13 (1).

3,4-*Isopropylidene epoxydiol* **8**. ($CDCl_3$) CH_3: δ 1·37 (3), δ 1·44 (3). CH_2: δ 1·72 (2) multiplet at least 20 Hz wide; δ 1·98 (2) poorly resolved multiplet, at least 20 Hz wide. Oxirane CH: δ 2·98 (1), doublet of triplets. The doubling is due to $J_{12} = 3{\cdot}7$ Hz; the tripling is ascribed to $J_{23} = 2{\cdot}2$ Hz, and virtual coupling[14] of H_2 and H_4($J_{24} = 0$), giving line-separations within the triplet of 1·1 Hz. δ 3·57 (1), broad envelope, $W_h = 8$ Hz. Dioxolane OCH: δ 4·43 (2), narrow band with two small satellite peaks. Maximum width = 9 Hz.

Isopropylidene diol 7. ($CDCl_3$) CH_3: δ 1·38 (3), δ 1·43 (3). CH_2: δ 1·90 (4), multiplet, width 27 Hz. OCH: δ 4·37 (2) multiplet, width 27 Hz. The olefinic protons give a multiplet at δ 5·85, width 35 Hz, which could be the AB portion of an ABX_mY_n system.

(1,2/3,4)-*Tetraacetyl derivative* **6b**. ($CDCl_3$) All signals except those of the acetyl groups are unresolved multiplets. OAc: δ 2·01 (6), δ 2·08 (6). CH_2: δ 1·89 (4). OCH: δ 5·28 (2), δ 5·43 (2). The acetyl signals have the chemical shifts expected[9] from the symmetry of the compound, whose two preferred conformations *aeea* ⇄ *eaae* must be almost identical in conformational energy content.

(1,2,3/4)-*Tetraacetyl derivative* **4b**. ($CDCl_3$). The acetyl resonances were found at δ 2·00 (6), δ 2·03 (3) and δ 2·14 (3), consistent[9] with the proposed structure and the preferred conformation *eaee*.

Tri-O-*acetylazidotriol* **22**. ($CDCl_3$). The acetyl resonances were found at δ 2·01 (3), δ 2·08 (3) and δ (2·17) indicating the presence of one axial and two equatorial acetoxyl groups.[9]

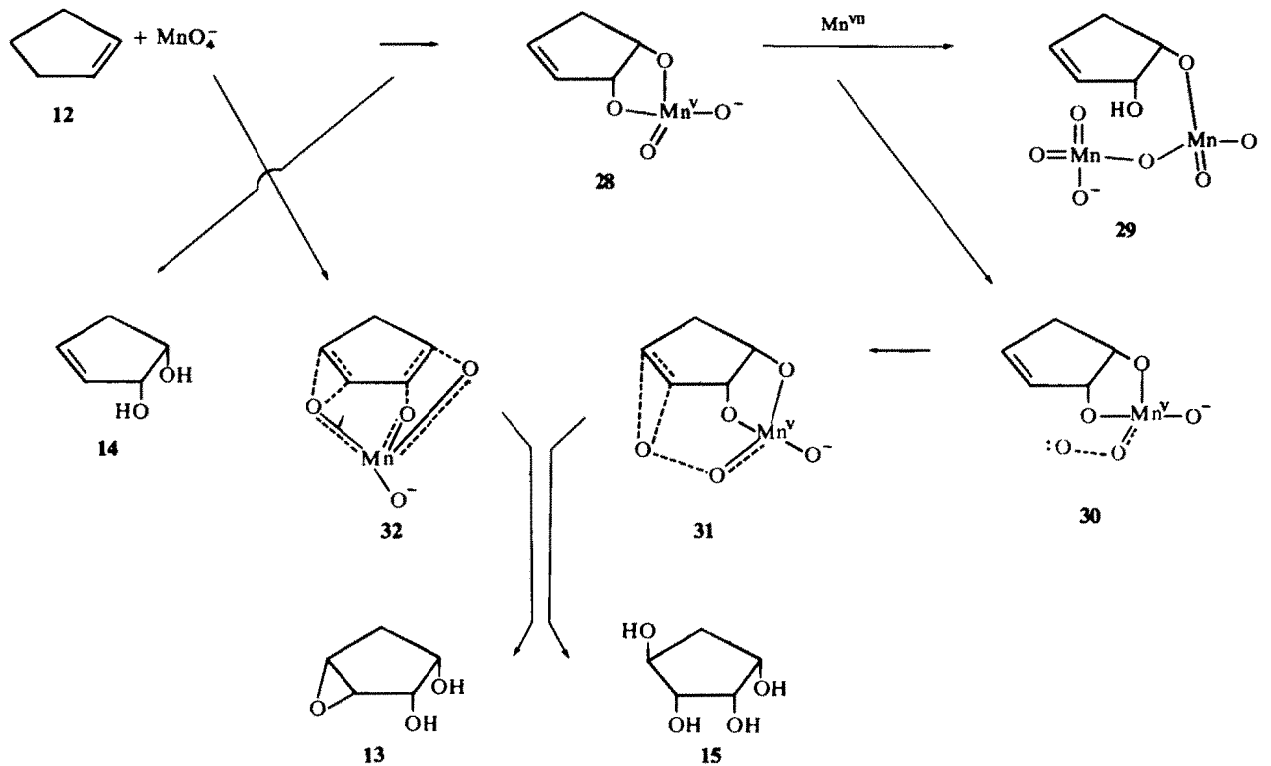
Tri-O-*acetylacetamidotriol* **23b**. ($CDCl_3$). Acetyl resonances were found at δ 1·92 (3), δ 2·00 (6) and δ 2·17 (3), characteristic of an equatorial acetamido, two equatorial and one axial acetoxyl groups.[9]

DISCUSSION

The dihydroxylation of olefins almost certainly proceeds[2] *via* cyclic esters of Mn (V). Such esters have not been isolated, but ^{18}O-tracer experiments[15a] strongly favor such a mechanism, which is analogous to the known formation of cyclic osmate esters from olefins and OsO_4. In a kinetic study, Wiberg and Geer[15b] found evidence that the first step, addition of permanganate to the double bond, was pH-independent, and that the Mn (V) species is then oxidized by MnO_4^-. That part of the tetrahydroxylation which leads to the (1,2/3,4) tetrols **6a** and **11**, can be visualized as occurring by two two successive normal additions, and the *cis*-cycloalkenediols **3** and **14** or reactive intermediates related to them could represent the first step of the reaction. The other *cis,cis*-isomers, i.e. the (1,2,3,4/0) tetrols, might conceivably be formed also, but numerous examples from this and other laboratories[8, 16–18] show that steric hindrance causes the second addition to occur *anti* to the first one. On the other hand neither the (1,2,3/4) and (1,2,4/4) tetrols nor the epoxydiols can be considered to have arisen by two successive dihydroxylations, and a sequential or concerted mechanism must be invoked. Although the free diols **3** and **4** cannot be involved, a reactive intermediate like **28** could be common to both pathways as described below. Other examples of epoxidation of cycloalkenes by permanganate are known,[2c, 19] although the reaction conditions were quite different; e.g. a steroidal 11, 12-alkene, treated with $KMnO_4$ in an acidic medium (95%–80% acetic acid) gave an epoxide rather than a glycol. In view of the markedly different oxyanions of manganese which predominate in acidic, neutral and alkaline media,[2, 20] the last example can hardly be considered analogous to the present case.

As noted above, the nature and proportions of the products formed from the dienes suggest that the epoxydiol or an intermediate related to it must be on the direct route to the tetrols. In order for a diene to be converted into an epoxydiol by permanganate, the latter must behave as a bifunctional or mixed-functional reagent.[21] An "oxenoid" species[21] might be involved. The reaction probably goes in two steps, similarly to

CHART 3. Some possible mechanisms of formation of anhydrotetrols and other products.



the two-step reaction[15b] referred to above in connection with the oxidation of monoolefins. A mono- or diesterified oxymanganese species would somehow donate an atom of oxygen to the nearby double bond, in a manner analogous to the epoxidation of allylic alcohols by pertungstic acid,[22] or a dimeric or complex species (e.g. see Ladbury and Cullis,[20] p. 409) might be involved. The reactions of the various oxyanions of manganese are insufficiently understood to permit a definitive mechanism to be written at this time.[20,23] A purely speculative representation of some of the possibilities is indicated in Chart 3. A reactive intermediate resembling **31** or **32** would satisfy the requirement that both tetrol and epoxydiol arise from the same path: the oxygen-manganese bonds may rupture before the oxirane ring is attacked, in which case **13** is obtained, whereas attack on the oxirane ring before the oxygen-manganese bonds are broken gives **15**. If a species resembling **32** were involved, the manganese would be reduced in one step from VII to III or from VI to II depending on whether MnO_4^- or $MnO_4^=$ is the attacking species. The MnO_2 which forms would then arise from reaction of Mn (II) or Mn (III) cations with one or another of the oxyanions.[20] In connection with Chart 3, it should be noted that although an intermediate like **30** could explain the reaction, such peroxy compounds may actually be destroyed by reaction with oxyanions.

In several experiments, only about one-half of the theoretical amount of permanganate was added, with either of the dienes. In all cases the distribution of products resembled that obtained with larger amounts of oxidant. This finding suggests strongly that the formation of epoxydiols occurs either by a concerted mechanism, or that if it occurs by a stepwise mechanism, the second step is fast. This is in harmony with the proposal that a free cycloalkenediol is not an intermediate in the reaction. It is conceivable that free cycloalkenediol forms a hydrogen-bonded complex with permanganate, analogous to that formed between allylic alcohols and peroxycarboxylic acids.[24] The apparent rapidity of formation of the epoxydiols seems to be opposed to this suggestion.

Two further analogies must be mentioned: (a) cyclic esters have been proposed as intermediates in the oxidation of *cis*-glycols by chromic acid;[25] such esters resemble the intermediate proposed for hydroxylation of alkenes by permanganate; (b) oxidation of certain terpenoid 1,5-dienes does not produce tetrols, but instead[26] high yields of 2,5-*bis*-hydroxymethyltetrahydrofurans are obtained; the authors have proposed mechanisms which resemble those indicated in Chart 3.

An additional factor which must be considered in the writing of a mechanism for the reactions described, is the presence in some of the intermediates (e.g. **28**, **30**) of an allylic ester. Such esters may behave differently from ordinarly alkyl esters.[27] The question of whether or not alkyl-oxygen cleavage occurs will also have to be investigated.

EXPERIMENTAL

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. IR spectra were measured with a Perkin-Elmer 237B spectrophotometer. The samples were examined as Nujol mulls (solids) or thin films or as dilute solns in CS_2 or chlorinated hydrocarbons. NMR spectra were recorded in $CDCl_3$ or D_2O, with a Varian Associates A-60 NMR Spectrometer, with TMS or DSS as internal reference. Values are reported on the δ-scale in ppm. M.p's were determined on a Kofler Micro hot stage, and are corrected. B.p's are uncorrected.

TLC was carried out with silica gel G as backing and the developing solvent was butanone-glacial acetic acid-2% boric acid (9:1:1 by volume). The detecting reagent was a permanganate-periodate spray.[28]

GLC was carried out with a Victoreen Gas Chromatograph, under the following conditions: stainless steel column 6 ft × ⅛ in (O.D.), packed with 6% Silicone SE 30 on ABS 90/100 mesh; oven temp 150°; injection temp 250°; flame ionization detector temp 280°. The sample, 10 mg, was dissolved in 1 ml anhyd pyridine, and 0·2 ml hexamethyldisilazane and 0·1 ml trimethylchlorosilane were added,[29] and allowed to react at least 5 min; samples of 0·4–0·5 μl were injected on the column. Chart speed 1 in per min; per cent of each cpd was measured by tracing the curve on paper and weighing the cut-out pieces. Control samples were run for each expt.

Hydroxylation of cyclopentadiene. Cyclopentadiene **12** was prepared from the dimer by heating the latter and fractionating the vapor in a 50 cm Vigreux column. The receiver was kept in ice and the distillate was used the day it was prepared. In a typical expt 20 g of **12** were dissolved in 1200 ml of acetone, chilled in dry ice-alcohol between −20° and −30°. The oxidant was one of the following: (a) 50 g of $Zn(MnO_4)_2 \cdot 6H_2O$* in 500 ml H_2O; (b) 54·5 g $KMnO_4$ and 4·7 g K_2CO_3 in 1 liter of water; (c) 54·5 g $KMnO_4$ and 48 g $MgSO_4 \cdot 7H_2O$ in 1 liter of water. The soln of oxidant was filtered over glass wool and added dropwise to the soln of **12**, with vigorous stirring. Time for addn varied between 3 and 5 hr. Ocassionally the mixt was stored overnight at −10°. The mixt was centrifuged in an International Centrifuge, model PR-2; the ppt resuspended in 500–800 ml of 70% acetone and recentrif. The supt soln and washings were combined and conc at reduced pressure in a rotary evaporator to 300–400 ml. This soln was then extracted with CH_2Cl_2 under continuous reflux, for 2 to 3 days. The organic soln was evap and dist in vac, b.p. 74–77°, 0·3 torr; yield was usually 6·5–7·5 g, but once 11·6 g were obtained. The aqueous phase was deionized, if necessary, by passage over columns of Duolite A-4 OH^- and Dowex-50 H^+ resins, and evap to dryness, giving 3·5–5·2 g of crude tetrol.[5]

Proof of the production of cis-3-*cyclopentene*-1,2-*diol.* In one product, obtained by treatment with $KMnO_4$-$MgSO_4$, the material of R_f 0·67–0·69 was the major component, and the epoxydiol was the minor component; 2·2 g of this mixture was dissolved in 150 ml of 95% EtOH, 200 mg of PtO_2 were added and H_2 bubbled through the soln with contin. stirring for 2 hr. After filtrn, solven was evap. The yellow oily residue was dissolved in 200 ml of 0·02 N H_2SO_4 and the soln heated at 100° for 1 hr to hydrolyze the epoxydiol. After neut with $BaCO_3$ and filtrn, the soln was extr for 4 days with CH_2Cl_2. Evap left an oily product which was dissolved in 20 ml dry pyridine and treated with 4 g p-NO_2-BzCl. The ester was purified as usual[5] and recryst four times from EtOH; m.p. 117–118°. (Found: C, 57·11; H, 4·16. $C_{19}H_{16}O_8N_2$ requires: C, 57·00; H, 4·03%). The identity of this subst as *di*-O-p-*nitrobenzoyl*-cis-*cyclopentane*-1,2-*diol* **24d** was established by comparing it with an authentic sample prepared as described below.

Freshly dist cyclopentene, b.p. 44° (11·55 g) was diss in 300 ml Me_2CO, and kept at −10° to −20° while a soln of 24 g $Zn(MnO_4)_2 \cdot 6H_2O$ in 750 ml of H_2O was added, over 1½ hr, and stirred for an addl ½. MnO_2 was reduced by a stream of SO_2 gas, and the white ppt remaining was filtered off. The filtrate was conc and the product was extracted with CH_2Cl_2. The cyclopentanediol was dist in vac, and a portion converted into the O-isopropylidene derivative, proving the presence of a vicinal *cis*-glycol. Another portion was converted into the *bis*-p-nitrobenzoate as described, and recryst twice from EtOH. m.p. 115–116·5°; m.m.p. with the analytical sample 114–116°.

Hydroxylation of 1,3-*cyclohexadiene with permanganate.* Freshly dist cyclohexadiene **1** (b.p. 78°) 12·3 g, was diss in 1 liter of Me_2CO and the soln kept at −10° to −20° during addn of 42·6 g $Zn(MnO_4)_2 \cdot 6H_2O$ in 500 ml H_2O (3½ hr). The work-up was carried out exactly as described for cyclopentadiene. The H_2O layer obtained after ext with CH_2Cl_2 was evap, leaving 2·4 g of solid which was recryst twice fron EtOH; m.p. 154·5–155·5° (reported[4] for tetrol **2a**, 154–155°). The identity of this subst as a cyclohexanetetrol was established by its conversion into a tetracetate (see below). Anal by TLC showed one component, R_f 0·29. The CH_2Cl_2 soln was evap, and the oily residue dist in vac: 6 ml distillate, b.p. 92–93°, 0·3 torr. Anal by TLC showed two components, R_f 0·47 and 0·63.

DL-(1,2,3/4)-1,2,3,4-*tetra*-O-*acetylcyclohexanetetrol* **4b**. Tetrol **4a** (250 mg, 1·69 mmole) was diss in 2·4 ml dry pyridine, and Ac_2O 1·5 ml added. The soln was left overnight at room temp in a stoppered tube. Excess reagents were evap, and the solid recryst from EtOH; 363 mg, 1·18 mmole; m.p. 112·5–113·5°. (Found: C, 53·37; H, 6·32. $C_{14}H_{20}O_8$ requires: C, 53·16; H, 6·37%).

Formation of tetrol **4a** *from diol and epoxydiol*

A. *From epoxydiol* **2a**. CH_2Cl_2-sol material (300 mg) obtained by hydroxylation of **1** was diss in 25 ml

* Obtained from Carus Chemical Co., Inc., LaSalle, Illinois.

0·02 N H_2SO_4, the soln was heated at 100° for 1 hr. The acid was neut with $BaCO_3$, and after filt the soln was extr for 24 hr with CH_2Cl_2. TLC anal of the extract showed only the component of R_f 0·66. The H_2O soln contained a major component of R_f 0·24 and a trace of material of R_f 0·68. Evap left a solid m.p. 152·5–154·5°, not depressed on admixture with authentic tetrol **4a**.

From diol **3a**. A sample of CH_2Cl_2-sol material was shown by TLC to consist chiefly of the faster-moving component; 500 mg were diss in 26 ml 75% AcOH and a soln of 1·2 g *m*-Cl-peroxy BzOH in 20 ml $CHCl_3$ added. The soln was left in the dark 3 days. Solvents were evap and H_2O (20 ml) added. The insol material, presumably *m*-Cl-BzOH, was filt off and the filtrate extracted once with Et_2O, and then extracted continuously with CH_2Cl_2. Evap of the equeous phase gave a solid which was cryst once from EtOH; m.p. 148–151°, not depressed on admixture with authentic **4a**. The organic phase contained only the component of R_f 0·50; an nmr spectrum (D_2O) agreed with that described under RESULTS. Hydrolysis of part of this product gave a nearly-quantitative yield of tetrol **4a**.

Proof of identity of the diol **3**. CH_2Cl_2-sol material was obtained by treatment of **1** with $ZnMnO_4$; 826 mg were dissolved in 100 ml 80% EtOH, 200 mg PtO_2 were added, and H_2 bubbled through with stirring 3 hr; after filt the solvent was evap, the oily residue was diss in 50 ml 0·02 N H_2SO_4, and the soln heated at 100° for 1 hr, cooled, neut with $BaCO_3$ and extracted with CH_2Cl_2 for 2 days. Evap of solvent gave 306 mg of cryst product m.p. 81–91°; recryst from toluene, m.p. 95–98°; m.m.p. with authentic *cis*-cyclohexane-1,2-diol (see below) 95–98°.

In one sample of CH_2Cl_2-sol material kept for 3 yr all the epoxydiol had been converted into tetrol. Re-extrn with CH_2Cl_2 and dist gave a product b.p. 73–77° (0·3–0·4 torr), whose nmr spectrum (see RESULTS) was correct for an unsymmetrical cyclohexenediol. (Found: C, 62·89; H, 8·78. $C_6H_{10}O_2$ requires: C, 63·13; H, 8·83%).

cis-Cyclohexane-1,2-diol was prep from cyclohexene b.p. 81°; 21 ml of cyclohexene in 300 ml Me_2CO was treated with a soln of 25 g $KMnO_4$ in 750 ml H_2O under the usual conditions. MnO_2 was dec with SO_2, the soln concd and the diol obtained by continuous extraction with Et_2O for 24 hr; the product was recryst twice from EtOAc, m.p. 97·5–99° (lit.[29] 99–100°). Some was benzoylated as usual,[5] recryst from EtOH; m.p. 62·5–64° (lit.[30] 71·5°). (Found: C, 73·81; H, 6·04. Calc. for $C_{20}H_{20}O_4$: C, 74·05; H, 6·21%). The cyclohexanediol obtained by reduction was benzoylated in the same way; m.p. 68–70°; m.m.p. with authentic sample 69–71°. Probably the products represented polymorphic crystalline forms.

Pure epoxydiol **2**. 5·33 g of crude CH_2Cl_2-sol material from hydroxylation of **1** was diss in 370 ml $CHCl_3$, in an amber bottle, and 16 g of *m*-Cl-peroxy BzOH added. After 2 days the soln was evap to dryness, H_2O added and the ppt filtered; the filtrate was neut with $BaCO_3$ and filtered again. The soln was extracted with CH_2Cl_2 for 3 days, the CH_2Cl_2-sol material dist; b.p. 78° (0·25 torr). The product cryst in the receiver, m.p. 38–40°. (Found: C, 55·5; H, 7·83. $C_6H_{10}O_3$ requires: C, 55·37; H, 7·75%).

Structure proof of epoxydiol **2**

A. *Triacetyl azidotriol* **22b**. CH_2Cl_2-sol material from treatment of **1** with $ZnMnO_4$ (1·1 g) was diss in 15 ml of 2-methoxyethanol. A soln of 202 mg NH_4Cl and 434 mg NaN_3 in 4 ml H_2O was added, the soln heated under reflux for 3 hr, and the solvent evap. To the residue were added 10 ml pyridine and 8 ml Ac_2O and left overnight. The reagents were evap and the residue chromatographed on a column of Al_2O_3 (Merck acid-washed alumina), eluted with $CHCl_3$. Those eluate fractions with a strong absorption at 2120 cm^{-1} (N_3-stretching of an azido group) were combined. Evap gave 0·25 g of oil which cryst after standing for a week; m.p. 75–82°. Two recryst from hot EtOH gave 112 mg, m.p. 84–85·5°. (Found: C, 48·20; H, 5·76; N, 13·90. $C_{12}H_{17}O_6N_3$ requires: C, 48·16; H, 5·73, N, 14·04%).

B. *Triacetyl acetamidotriols* **23b** and **26b**. "Tetraacetylconduramine C-4" **19b**, 40 mg, was diss in 10 ml MeOH sat with NH_3 plus 10 ml of MeOH and left overnight. Solvent and acetamide were removed in-vac and the residue was diss in 20 ml of 50% EtOH. PtO_2 (50 mg) was added and H_2 bubbled through for 3 hr. After filtrn solvent was evap and the residue was acetylated (5 ml pyridine, 1 ml Ac_2O, 3 days). The reagents were evap and the residue was diss in 2 ml Et_2O. Cryst occurred in 3 days at 5°; **23b**, needles 30 mg, m.p. 156–157°.

"Tetraccetylconduramine F-4" **27b** was treated in the same way, giving 30 mg of **26b**, m.p. 144–145°.

Triacetylazidotriol **22b**, 49 mg, was diss in 20 ml 50% EtOH, 50 mg of PtO_2 was added and H_2 bubbled through for 1 hr; 0·1 ml of 2 N HCl was added and hydrogenation continued for 1 hr. After filtrn and evap the residue was acetylated (2 ml pyridine, 1 ml Ac_2O, 2 days). After evap of the reagents the product was chromatographed on alumina with chloroform. Eluted fractions were assayed by infrared, and were combined according to the presence in the spectra of absorption due to N—H stretching and bending

modes. Solvent was evap and the product was recryst from Et_2O; m.p. 154–158°, not depressed by admixture with authentic **23b**.

Unidentified bromocyclopentanetriol. CH_2Cl_2-sol material from oxidation of **1** (1·0 g) was dissolved in 25 ml N HBr. The soln was heated for 15 min at 100°. Water and HBr were evap and the dark brown syrup cryst at room temp in a few days. Recryst twice from EtOAc, m.p. 162–164°; an anal sample melted at 164–165°. (Found: C, 34·27; H, 5·33; Br, 37·64. $C_6H_{11}BrO_3$ requires: C, 34·14; H, 5·25; Br, 37·86%). In a spectrophotometric periodate tiration[30] the ratio: μmoles periodate consumed/μmole of substrate was: 11 hr: 0·73; 21 hr: 0·95; 26 hr: 0·91; 31 hr: 1·16; 44 hr: 1·43; 53 hr: 1·43.

O-*isopropylidenecyclohexenediol* **7**. Diol **3**, 6·4 g, was diss in 120 ml 2,2-dimethoxypropane, 3 drops conc H_2SO_4 added and soln stirred 1 day. Conc NH_4OH was added to pH 6, and solvents were evap. The remaining liquid was diss in Et_2O; the soln was washed with H_2O, dried with Na_2SO_4 and dist; b.p. 87–89° (33 torr). (Found: C, 69·93; H, 9·10. $C_9H_{14}O_2$ requires: C, 70·10; H, 9·15%).

O-*isopropylidenecyclohexanepoxydiol* **8**. A $CHCl_3$ soln of peroxybenzoic acid[32] containing 91 mg/ml ($Na_2S_2O_3$ titration) was prepared; 2·0 g of **7** were diss in 30 ml of the soln, and kept at 5° for 5 days. The soln was washed 4 times with 60 ml portions of 5% Na_2CO_3 and twice with H_2O, dried with Na_2SO_4 and dist. b.p. 106–107° (36 torr). The product solidified at ice temp; m.p. 30–32°. (Found: C, 63·73; H, 8·42. $C_9H_{14}O_3$ requires: C, 63·51; H, 8·29%).

DL-(1,2,4/3)-*Cyclohexanetetrol* **5**. This tetrol was usually prepared by treatment of *trans*-1,2-cyclohexenediol[4] with OsO_4, m.p. 142° (lit.[4] 142°). Alternatively it was prep by hydrol of the isopropylidene epoxydiol **8** (0·8 g) in 0·02 N H_2SO_4 (430 ml), for 2 hr at 100°. m.p. 139–140·5°, not depressed on admixture with authentic tetrol.

DL-(1,2/3,4)-*Cyclohexanetetrol* **6a** and *tetraacetyltetrol* **6b**. The tetrol **6a** was prep by treatment[4] of diol **3** with OsO_4. Recryst from EtOH, m.p. 209–211° (lit[4] 216°). The tetraacetyl cpd **6b** was prep by acetylating the tetrol in the usual way. M.p. of crude product 104–110°. The NMR spectrum (see RESULTS) was correct for the expected structure.

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