Studies on Cyclic Polyols. III. The Configurations and Reactions of Some Epoxydiols of Cyclopentane[1,2]

J. A. FRANKS, JR., BERNADINE TOLBERT, RUTH STEYN, AND HENRY Z. SABLE[3]

The Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland, Ohio 44106

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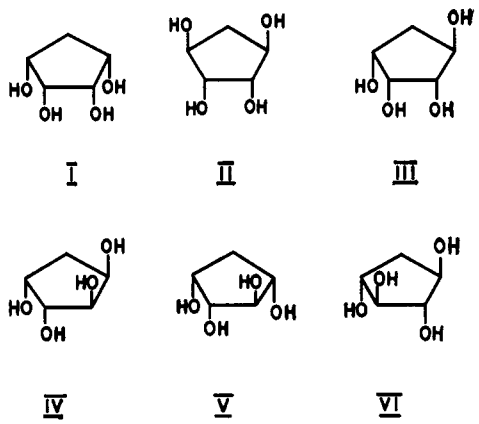
The proposed all-*cis* configuration of the 2,3-anhydrocyclopentanetetrol (XIV) obtained by epoxidation of *cis*-1-cyclopentene-3,5-diol (XIII) has been substantiated as follows. Treatment of XIV with HBr or HCl gives halotriols which are convertible in high yield to O-isopropylidene derivatives. Subsequent treatment of these derivatives with aqueous sodium hydroxide produced the (1,2,3,4/)-1,2-anhydro-3,4-O-isopropylidenecyclopentanetetrol (XI). The latter compound is all-*cis* because the oxygen atoms in the parent halotriols were *cis* and the halogen *trans*, and the formation of the epoxide occurs because of nucleophilic attack by the neighboring hydroxyl group on the C–Br functional group with concomitant inversion as the Br is expelled. The other known 1,2-anhydro-3,4-O-isopropylidenecyclopentanetetrol obtained by epoxidation of 3,4-O-isopropylidenecyclopent-1-ene (X) must therefore be the *trans* isomer, *i.e.*, (1,2/3,4)-1,2-anhydro-3,4-O-isopropylidenecyclopentanetetrol (XII). Epoxidation of *cis*-1-cyclopentene-3,4-diol (VII) yields a 1,2-anhydrotetrol whose infrared spectrum shows two absorption bands characteristic of strongly intramolecularly bonded hydroxyl groups, and no absorption characteristic of unbonded hydroxyl groups. This proves that the anhydrotetrol is (1,2,3,4/)-1,2-anhydrocyclopentanetetrol (VIII). In conformity with the proposed structure, VIII is easily converted to XI. Treatment of VIII with ethanolic HBr yielded predominantly one bromotriol, (1,2,3/4)-4-bromocyclopentanetriol (XX). An explanation is proposed for the preferential attack by nucleophilic reagents at C-1 of epoxydiol VIII. The acid hydrolysis of XI, XII, and four isomeric anhydrotetrols to free tetrols has been studied: in the case of the anhydrotetrols the reaction follows pseudo-first-order kinetics, whereas with XI and XII the reaction follows a more complicated course because the oxirane ring and the O-isopropylidene group are hydrolyzed at different rates. The rate constant for hydrolysis of the anhydrotetrols is directly proportional to acid concentration.

In the preceding paper[4] the following cyclopentane derivatives were described: one of the six possible triols (Chart I) (the 1,3/2-triol[5]), five of the six possible

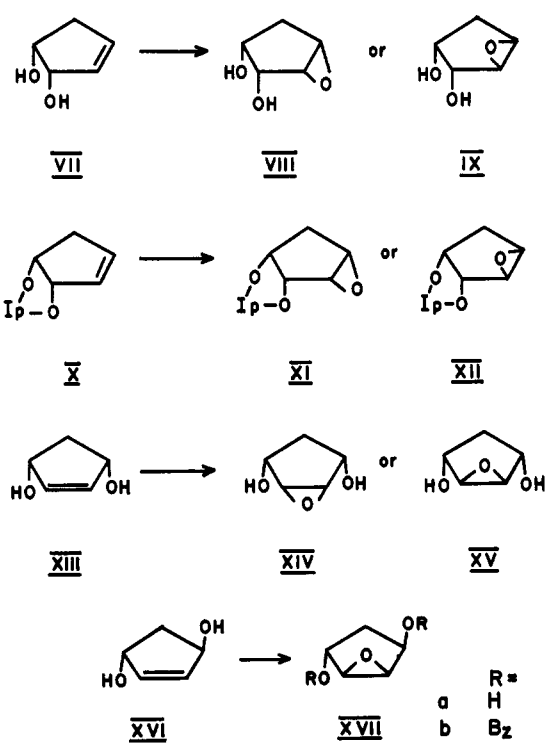
CHART I



tetrols (II, DL-III, DL-IV, DL-V, and DL-VI), and one of the four possible pentols (the 1,2,4/3,5-pentol). In the course of these syntheses a number of epoxydiols and one O-isopropylideneepoxydiol were prepared and then hydrolyzed with aqueous acid. The epoxides were prepared by treatment of the corresponding cycloalkenes with peroxybenzoic acid. Chart II shows the possible structures produced in these reactions. (Structures XIII–XV are *meso* forms while all the other compounds represented in the chart are DL pairs.) Acid hydrolysis of VIII, IX, XI, and XII should proceed with a single inversion involving one or other of the oxirane carbon atoms, as well as removal of the isopropylidene group with no involvement of the asymmetric centers. Unless epoxide migration occurred, each of these four structures could thus give rise to a mixture of varying proportions of III and V. The epoxide obtained from VII gave predominantly DL-III,[4] whereas the product obtained by epoxidation of X

CHART II

EPOXIDATION WITH PEROXYBENZOIC ACID



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(2) We thank Dr. G. E. McCasland, University of San Francisco, for very helpful suggestions and discussions of this work.

(3) To whom any correspondence should be addressed.

(4) H. Z. Sable, T. Adamson, B. Tolbert, and T. Posternak, *Helv. Chim. Acta*, **46**, 1157 (1963).

(5) We have used the nomenclature commonly applied to cyclitols: *cf.* G. E. McCasland, S. Furuta, and V. Bartuska, *J. Org. Chem.*, **28**, 2096 (1963).

and subsequent hydrolysis was almost pure DL-V. Acid hydrolysis of either XIV or XV with a single inversion can give rise only to DL-V. Hydrolysis of XVIIa with a single inversion could give a mixture of IV and VI; actually only DL-VI has been identified in the hydrolysis product,[6] although traces of IV may be present. It seemed interesting, therefore, to determine the configurations of all the epoxides in order to permit further study of the course of epoxide opening reactions.

The following discussion of the stereochemistry of the epoxides depends on incontrovertible structure proof of the parent cycloalkenediols. The configurational assignment of *cis* and *trans* to the two isomeric cyclopentene-3,4-diols is easily made on the basis of reactivity. For example the diol considered to have structure VII was converted to an O-isopropylidene derivative X by Young, *et al.*[7]; catalytic reduction of VII yields a product identical with the cyclopentane-1,2-diol whose infrared spectrum shows a very strong intramolecular hydrogen bond.[8] On the other hand the configurational assignments of the isomeric 3,5-dibromocyclopentenes, and the 3,5-diols derived from them have been the subject of prolonged controversy. Young, *et al.*,[7] resolved the uncertainties, but Gaoni[9a] and Saegerbarth[9b] reopened the question of assignment of *cis* and *trans* to the isomeric cyclopent-1-ene-3,5-diols. Two separate groups of investigators[10] substantiated the assignments of Young, *et al.*, by chemical and infrared data, and since that time these assignments have been confirmed by n.m.r. spectroscopy.[11]

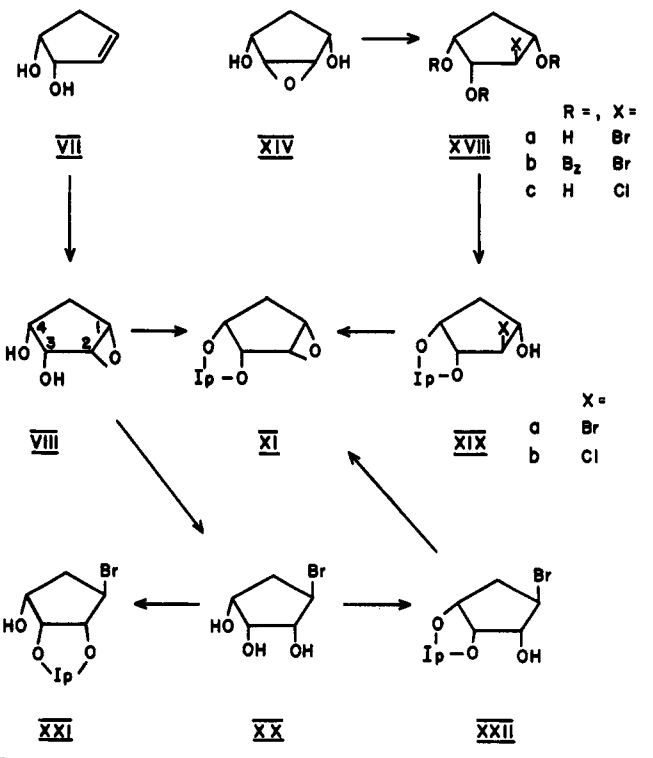
In the earlier publication we assigned structures tentatively on the basis of Henbest's rule[12] for epoxidation of cycloalkenes with allylic substituents. The presence of bulky allylic substituents (except a hydroxyl group) causes the oxirane ring to form on the less hindered side of the ring; an allylic hydroxyl group causes the epoxide to form on the more hindered side, presumably because of hydrogen bonding with the peroxybenzoic acid. On this basis the preferred configurations are VIII, XII, and XIV. The present work substantiates these configurational assignments.

Results

Epoxide Formation. A. N.m.r. Evidence.—On treatment with peroxybenzoic acid in water or in chloroform solution *cis*-1-cyclopentene-3,5-diol (XIII) is converted in high yield to an epoxydiol[4] which does not consume periodate. The absence of a vicinal glycol group restricts the possible structures to XIV, XV, and XVIIa. Configuration XVII which could have arisen if an allylic rearrangement occurred during the epoxidation was eliminated by examination of n.m.r. spectra. A substance presumed to have this configuration had been prepared in the earlier study[4]; its spectrum shows complicated patterns in the methylene, oxirane, and carbinyl O–C–H regions (see Experimental). Although this spectrum has not yet been analyzed in all details, it indicates clearly the presence of six nonequivalent ring protons. On the other hand, the n.m.r. spectrum of the epoxydiol obtained from the symmetrical cycloalkenediol XIII is considerably simpler (see Experimental). The methylene protons and the adjacent O–C–H protons constitute an ABX_2 system.[13] Such a spectrum proves a symmetrical structure in which a plane of symmetry bisects the methylene group and the oxirane ring and is therefore consistent only with structures XIV and XV. In many cases the question of *cis* and *trans* isomerism is settled easily by examination of the appropriate coupling constants in the n.m.r. spectra. In the present case n.m.r. spectroscopy does not give the answer. Coupling of the oxirane protons with adjacent protons in fused rings is associated with small or zero-line splitting.[11,14] The apparent zero coupling of the oxirane protons with the adjacent O–C–H protons is therefore not a reliable indicator of the configuration. Fortunately the structure proofs of all epoxides have been achieved by classical techniques (see next section).

B. Structure Proof of the Anhydrotetrols.—The key reaction in these structure proofs was the formation of *trans* halohydrins when the anhydrotetrols were treated with HBr or HCl[5] (see Chart III). Treatment of the symmetrical anhydrotetrol with aqueous HBr produced a bromotriol XVIIIa which could not be crystallized. The bromotriol consumed 1 mole of periodate, and it was converted under the usual mild

CHART III



(6) Unpublished observations; details of these procedures will be included in later publications.

(7) W. G. Young, H. K. Hall, Jr., and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4338 (1956).

(8) (a) L. P. Kuhn, *ibid.*, **74**, 2492 (1952); (b) *ibid.*, **76**, 4323 (1954); (c) *ibid.*, **80**, 5950 (1958); (d) L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger, Jr., and L. Eberson, *ibid.*, **86**, 650 (1964).

(9) (a) Y. Gaoni, *Bull. soc. chim. France*, 705 (1959); (b) K. A. Saegerbarth, *J. Org. Chem.*, **25**, 2212 (1960).

(10) (a) H. Z. Sable and T. Posternak, *Helv. Chim. Acta*, **45**, 370 (1962); (b) A. C. Darby, H. B. Henbest, and I. McClenaghan, *Chem. Ind.* (London), 462 (1962).

(11) H. Z. Sable, W. M. Ritchey, and J. E. Nordlander, manuscripts in preparation.

(12) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(13) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance Spectroscopy," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 98.

(14) L. D. Hall, *Chem. Ind.* (London), 950 (1963).

conditions and in high yield to an O-isopropylidene derivative XIXa. The periodate oxidation is proof of the existence in the parent compound XVIIIa of a vicinal glycol grouping, and the formation of the acetonide proves that the glycol is *cis*, since the cyclopentane ring cannot assume any conformation which could allow the formation of a 1,2-*trans*-acetonide. The ring opening proceeds by an SN2 mechanism, in which the leaving group is one of the C–O bonds of the oxirane ring and inversion occurs as a result of entrance of the bromide ion. The unbroken C–O bond becomes a hydroxyl group. Since this new hydroxyl group is *cis* to the preexisting hydroxyl groups which were present in the anhydrotetrol, all three oxygens in the anhydrotetrol must be on the same side of the cyclopentane ring, as shown in structure XIV. Although some cases are known of retention of configuration during ring opening,[15] all the examples are of severely hindered epoxides being opened with weak nucleophiles or in nonpolar solvents. That the bromide ion is a much more powerful nucleophile than water is well known, and this is borne out by the high yield of bromotriol in aqueous solution. Rate studies were not carried out, but the reaction must be very rapid. The anhydrotetrol XIV is very easily hydrolyzed by dilute aqueous acid (see kinetic studies below) and, if ring opening by bromide ion did not occur quickly, an appreciable yield of (1,2,4/3)-cyclopentanetetrol (V) would have been obtained.

Young, *et al.*,[7] have discussed the effect of alkali treatment on *cis*- and *trans*-bromohydrins, with particular reference to the cyclopentane series. Their conclusions are based on reactants and products whose configurations have been firmly established by measurements of dipole moments.[10a,16] *cis*-Bromohydrins undergo elimination of HBr and a hydride shift leads to formation of a carbonyl group, whereas in the case of *trans*-bromohydrins the loss of HBr occurs by an intramolecular equivalent of an SN2 reaction leading to epoxide formation. This inversion by a participating neighboring group has been useful in establishing the configurations proposed for the two isomeric 3,4-O-isopropylidene-1,2-anhydrocyclopentanetetrols (XI and XII) and thus also the configuration of the anhydrotetrol VIII. Treatment of the 3,4-O-isopropylidene-1,2-bromohydrin (XIXa) with aqueous alkali at room temperature produced a substance whose elemental analysis was that of an O-isopropylideneanhydrotetrol. The infrared spectrum contained absorption bands reported to be characteristic of *gem*-dimethyldioxolanes and epoxides[17] (Table I). The n.m.r. spectrum was consistent with this structure (see Experimental). The configuration of the precursor and the manner of formation of the product permit only the all-*cis* configuration proposed (XI). The same sequence of reactions XIV → XVIIIc → XIXb → XI was also observed when HCl was used in place of HBr. The infrared and n.m.r. spectra of the isomeric substance XII differed in detail from those of XI, although they still agreed with the requirements of the various functional groups. Only two configurations are possible for these functional groups and, since the all-*cis* structure belongs to the other isomer, the substance produced by epoxidation of X is proved to be (1,2/3,4)-DL-3,4-O-isopropylidene-1,2-anhydrocyclopentanetetrol (XII).

TABLE I

SOME ABSORPTION FREQUENCIES IN INFRARED SPECTRUM OF O-ISOPROPYLIDENEANHYDROTETROL (XI)

ν, cm.$^{-1}$	Intensities[a]	Assignment
3033	w	Oxirane C–H
3014	w	Oxirane C–H
1379	s	*gem*-Dimethyl
1369	s	*gem*-Dimethyl
1259	m	Dioxolane
1230	s	Dioxolane
1210	s	Dioxolane
1157	s	*gem*-Dimethyl
1084	m	Dioxolane
1069	vs	Dioxolane
845	m	Epoxide

[a] vs = very strong, s = strong, m = medium, w = weak.

Treatment of the cycloalkenediol VII with peroxybenzoic acid produced a liquid anhydrotetrol[4] presumed to have configuration VIII. The infrared spectrum shows no absorption bands in the region of 3600 cm.$^{-1}$ which Kuhn[8a,b] has shown to be due to the O–H stretching mode of unbonded hydroxyl groups. There are two bands of medium intensity at 3534 and 3519 cm.$^{-1}$, whose relative intensities are independent of concentration of the sample and which represent two intramolecularly hydrogen-bonded OH groups. In the case of *cis*-cyclopentane-1,2-diol Kuhn[8a,b] reported a frequency shift of 61 cm.$^{-1}$ for the bonded OH group, and Darby, *et al.*,[10b] found shifts of 83 and 63 cm.$^{-1}$ for 1,3-O—H···O bonding in *cis*-1,2-epoxycyclopentan-4-ol and *cis*-cyclopentane-1,3-diol, respectively. This indicates that the hydrogen bonds are of approximately equal strength in all these cases. Based on an average value of 3603 cm.$^{-1}$ for unbonded OH groups in our series, the frequency shifts for the OH groups of VIII are 69 and 84 cm.$^{-1}$, respectively showing, that both OH groups are strongly intramolecularly hydrogen bonded. This can only occur if the substance has the all-*cis* configuration. Further substantiation of this proposed configuration was obtained when treatment of the anhydrotetrol with acetone and anhydrous $CuSO_4$ produced a substance whose infrared spectrum and other physical properties were identical with those of XI. The epoxidations X → XII, VII → VIII, and XIII → XIV are thus proved to have proceeded in accordance with Henbest's rule[12] for allylic epoxidation.

Epoxide Opening.—The stereoselective rupture of one of the C–O bonds of an epoxide by nucleophilic reagents has been stated to be governed by conformational factors,[18,19] electronic effects,[20] and steric effects.[4]

(15) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 102; (b) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); (c) J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956); (d) H. H. Wasserman and N. E. Aubrey, *ibid.*, **78**, 1726 (1956).

(16) W. D. Kumler, A. C. Huitric, and H. K. Hall, Jr., *ibid.*, **78**, 4345 (1956).

(17) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 116–119, and references cited therein; (b) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 58; (c) W. J. Bailey and C. E. Knox, *J. Org. Chem.*, **25**, 511 (1960); (d) J. A. Franks, Jr., and H. Z. Sable, manuscript in preparation.

(18) M. Nakajima, I. Tomida, N. Kurihara, and S. Takei, *Chem. Ber.*, **92**, 173 (1959).

(19) See discussion of this point in T. Posternak, "Les Cyclitols," Hermann, Paris, 1962, p. 38.

(20) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, **80**, 2237 (1958).

In our earlier work the formation of tetrol V from XII and of tetrol VI from XVIIa was considered to be due to steric hindrance at one end of the oxirane ring. In an analogous situation in the cyclohexane series[18,19] an epoxide corresponding to XVIIa opens in the opposite direction, apparently because the preferred half-chair conformation favors a transition state which leads to the configuration corresponding to IV. Neither steric hindrance nor conformational factors can apply to the opening of the unhindered epoxydiols VIII and XIV.

Ring opening of XIV by nucleophilic attack leads only to one pair of enantiomers: DL-V, DL-XVIIIa and DL-XVIIIc. Such is not the case with VIII, from which two diastereoisomers are to be expected. Ring opening of VIII with acidified water produced predominantly one isomer which was proved[4] to be the (1,2,3/4)-tetrol (III). Attack by the bromide ion on C-1 would lead to the formation of bromotriol XX, whereas attack at C-2 would produce the same bromotriol XVIIIa which was obtained from the symmetrical epoxydiol XIV. Neither bromotriol has been crystallized. However, crude bromotriols produced from XIV and VIII consume 1 mole and 2 moles of periodate in accordance with the theoretical values for the structures XVIIIa and XX, respectively. XVIIIa has been converted to a crystalline tribenzoate XVIIIb, whereas the benzoylated derivative of XX has not crystallized. However, on the basis of periodate consumption one may safely conclude that XX is indeed the principal product.

Treatment of XX with acetone yielded a liquid whose elemental analysis and infrared spectrum agreed with the postulated mono-O-isopropylidenebromotriol. When the liquid was hydrolyzed in dilute aqueous acid, the product of hydrolysis consumed 2 moles of periodate, confirming the result obtained with the crude bromotriol. The infrared spectrum of the isopropylidene derivative (see Experimental), though qualitatively similar to the spectra of other compounds in this series,[17d] differed from the spectra of known pure compounds in one important respect. Many of the absorption bands were either considerably broader or showed more complexity than the corresponding bands in the spectra of the pure compounds. This observation suggested that the liquid was really a mixture of isomers. Only two such isomers are possible, *i.e.*, the 2,3-O-isopropylidene- and the 3,4-O-isopropylidenebromohydrins (XXI and XXII). This was substantiated as follows. The presumed mixture was treated with dilute aqueous alkali at room temperature, and the solution was extracted with ether. After drying and removal of the ether the material was distilled. The infrared spectrum of the distillate now showed absorption bands not present before alkali treatment undoubtedly due to the formation of XI from XXII. The liquid distillate was exposed to the laboratory air, since the compound XI has been found to be extremely volatile. In a few days the liquid product had become crystalline. The crystalline residue, purified by sublimation, had the same elemental analysis as that of the original O-isopropylidenebromotriol, but its infrared spectrum differed from that of the original liquid. No new absorption bands had appeared but some had disappeared and a number of the bands had become narrower and less complex. None of the bands characteristic of epoxides was present. Since the alkali treatment transformed isomer XXII to substance XI the crystalline substance must have structure XXI.

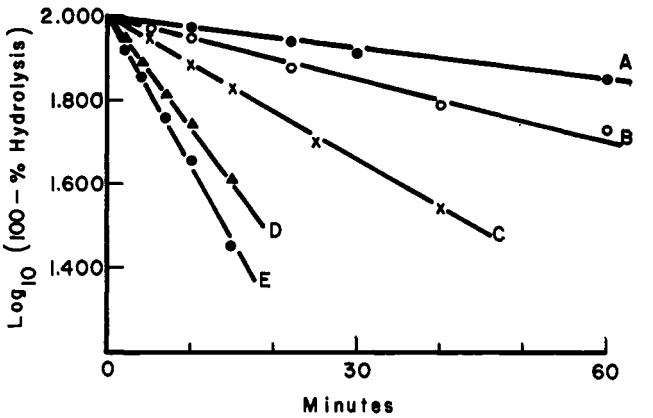


Figure 1.—The hydrolysis of DL-2,3-anhydrocyclopentane-(1,2,3/4)-tetrol (XVIIa) in different concentrations of H_2SO_4 at 100°: A, 0.01 *N*; B, 0.02 *N*; C, 0.04 *N*; D, 0.08 *N*; E, 0.12 *N*. Initial concentration of anhydrotetrol was 8×10^{-3} *M*.

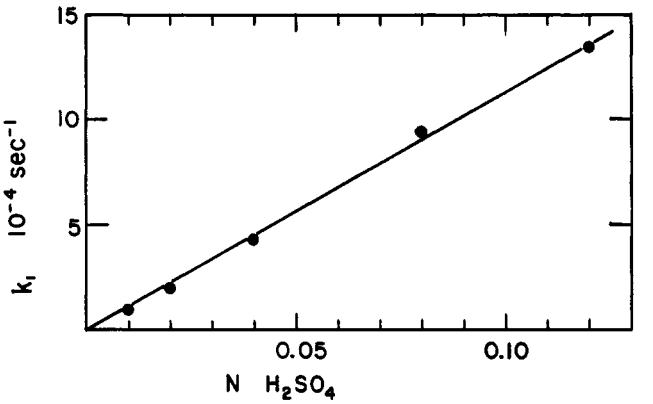
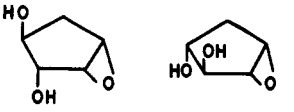


Figure 2.— Dependence of $k_{\text{first order}}$ for hydrolysis of epoxydiol XVIIa on acid concentration. Initial concentration of the epoxydiol was 8×10^{-3} *M* in each case; temperature, 100°.

Kinetics of Epoxide Hydrolysis.—A kinetic study of the acid hydrolysis of anhydrotetrols and O-isopropylideneanhydrotetrols was carried out. In addition to compounds VIII, XI, XII, XIV, and XVIIa, a crystalline anhydrotetrol of structure XXIIIa or XXIIIb was available.[6,21] The rate of epoxide opening was determined by periodate titration. In each case the final hydrolysis product was a tetrol consuming 3 moles of periodate, whereas the starting materials consumed only 1 mole (VIII and XXIII) or none at all. The analytical method can also detect differences in the rates of hydrolysis of the oxirane and isopropylidene residues of XI and XII; if the hydrolytic rates are significantly different there will be rapid formation of a



XXIII a XXIII b

(21) The substance presumed to have structure XXIII is converted by acid hydrolysis to cyclopentane-(1,4/2,3)-tetrol, proving the existence of a vicinal *trans* glycol. The manner of fusion of the oxirane ring (*cis* or *trans* to the adjacent hydroxyl group) is still under investigation. NOTE ADDED IN PROOF.—Treatment of XXIII with HBr leads to the formation of (1,4/2,3)-1-bromocyclopentanetriol, proving that structure XXIIIa is correct.

species consuming 1 mole of periodate and slower conversion of the intermediate species to the free tetrol. Figure 1 shows that at five different concentrations of H_2SO_4 the hydrolysis of XVIIa follows pseudo-monomolecular kinetics. Similar hydrolysis curves were obtained with the other three anhydrotetrols. First-order rate constants were calculated from the hydrolysis curves. Figure 2 shows the direct dependence of the rate constant on the acid concentration. The relative susceptibility to acid hydrolysis of the four anhydrotetrols is shown in Table II. In both cases the presence of one hydroxyl group *trans* to the oxirane ring reduces the rate of hydrolysis to 60–70% of that of the all-*cis* isomer. The 1,2-anhydrotetrols are hydrolyzed approximately 25 times as rapidly as the corresponding 2,3-anhydrotetrols.

TABLE II

RELATIVE LABILITY OF ANHYDROTETROLS IN AQUEOUS ACID AT 100°

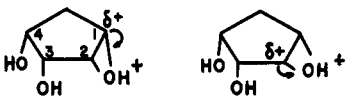
Configuration	H_2SO_4, N	k_{hydrol},[a] M^{-1} sec.$^{-1}$
VIII	5×10^{-3}	0.477
XXIII[b]	5×10^{-3}	0.257
XIV	9×10^{-2}	0.0167
XVIIa	9×10^{-2}	0.0113

[a] k_{hydrol} is the second-order constant obtained by dividing $k_{first\ order}$ by normality of acid. [b] See footnote 21 concerning the proposed structure of XXIII.

In the case of the O-isopropylideneanhydrotetrols the formation of periodate-reactive material did not follow a simple rate law, but occurred rapidly at first and then very much more slowly. This suggested that one of the two possible partial hydrolysis products was accumulating. This was verified in preliminary experiments by thin layer chromatography[6] by which the presence of appreciable amounts of anhydrotetrols was demonstrated in partial hydrolysates. Since monoisopropylidene tetrols were not observed in the chromatograms it is clear that the oxirane ring is much less labile than the O-isopropylidene group under conditions of acid hydrolysis.

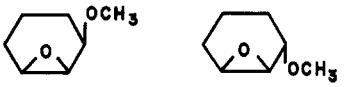
Discussion

The preferential attack on C-1 of VIII both by a strong nucleophile (Br^-) and a weak nucleophile (H_2O) is analogous to an observation by Lemieux, Kullnig, and Moir[20] in the cyclohexane series. The accepted mechanism of epoxide opening involves protonation of the oxirane oxygen, and this is substantiated by our observation of a direct relationship between the rate constant and the normality of the acid. The protonation increases the electrophilic character of C-1 or C-2 (VIIIa and VIIIb). In the presence of an electronegative group on C-3 the developing carbonium ion of



VIII a VIII b

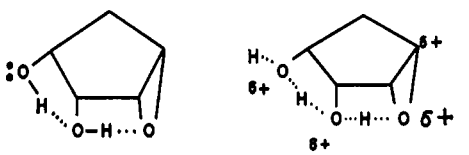
the transition state VIIIb is destabilized more than is that of VIIIa, leading to preferential attack by the nucleophile on C-1. This explanation was proposed by Lemieux, *et al.*,[20] in the case of the *cis*- and *trans*-3-methoxycyclohexene oxides (XXIV and XXV). Alternative explanations may be invoked, however, for the preferential opening at C-1 in both cases. Lemieux, *et al.*,[20] pointed out that in XXV steric hindrance due to the methoxyl group might have some influence,



XXIV XXV

but dismissed this as a major factor because no steric effect seemed possible in XXIV. We believe, on the contrary, that a steric explanation may apply to XXIV. Two skew chair conformations of this substance are possible; in one the methoxyl group on C-3 is involved in 1,3-interaction with the axial hydrogen atom on C-5; in the other conformation no such interaction exists. The latter conformation will certainly be favored. In the transition state for opening this epoxide the developing bond must be *trans*-diaxially oriented with respect to the retained C–O bond. Such a transition state can be achieved without any other conformational change only if the nucleophile attacks C-1 of the favored conformation. This direction of opening is therefore favored by the steric as well as the electronic considerations. Other examples of epoxide opening being directed by a preferred conformation are found in the cyclitol field.[18,19]

An entirely different explanation for the preferred direction of opening of anhydrotetrol VIII concerns the participation of intramolecular hydrogen bonds. Both OH groups are strongly hydrogen bonded, one to the oxygen atom of the adjacent OH group and the other to the adjacent oxirane oxygen as shown in structure



VIII c VIII d

VIIIc. The concerted pull of these bonds might deform the oxirane ring, stretching and weakening the C-1–O bond. One might therefore consider that the deformation of the oxirane ring has initiated the formation of a transition state favorable to the stereoselective opening observed. The required oxirane protonation might occur without prior breaking of the hydrogen bonds, if the protonation first involved the outermost (C-4) oxygen atom, and then led to the form VIIId. Neither the theory nor the nonclassical structure VIIId is easily susceptible to proof, but appear to us to be worthy of some consideration.

The differences in acid stability of the anhydrotetrols are best explained on the basis of the electronic theory of Lemieux, *et al.* In the case of the 2,3-anhydrotetrols, no matter at which end of the oxirane ring the transition state carbonium ion develops, it is destabilized by a vicinal hydroxyl group. The increased stability of the *trans* epoxy alcohols probably has a steric basis. In XVIIa the *trans* hydroxyl group certainly protects the adjacent end of the oxirane ring from the attacking

species, and probably protects the other end to a certain extent also. In the case of XXIII, if structure b were correct, exactly the same argument would hold, but even in structure XXIIIa the *trans* hydroxyl group probably causes a moderate amount of hindrance to the approach of the nucleophile. As a result the *trans* epoxy alcohols have a lower probability of reacting, as shown by the smaller k_{hydrol} observed. The importance of the steric effect is also seen in the nature of the product isolated after acid hydrolysis of XVIIa. The two possible products are the tetrols whose configurations are 1,2/3,4 (IV) and 1,3/2,4 (VI). In the earlier study[4] the hydrolysate was benzoylated, and the derivative was purified. The yield of tetrabenzoate was nearly 60% based on the weight of epoxide, and only the substance of configuration VI was obtained. Since that time the configuration has been verified by n.m.r. studies,[11] and analysis by thin layer chromatography[6] has confirmed that the hydrolysate consists principally of tetrol VI with only small amounts of another tetrol, presumably IV. The preferential formation of VI occurs because the epoxide opens by attack at the less hindered position.

Experimental

Epoxidizing Agents.—Peroxybenzoic acid[22] was used in the earlier stages of this work, and *m*-chloroperoxybenzoic acid[23] in the later stages. The latter reagent was 85% pure and was used without further purification.

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Dr. K. Eder, Ecole de Chimie, Geneva, Switzerland.

Spectra.—Infrared spectra were measured with a Perkin-Elmer Model 237B spectrophotometer. All spectra were determined on solutions of the compounds in carbon disulfide. N.m.r. spectra were measured with a Varian Associates DP60 high-resolution n.m.r. spectrometer.

Physical Constants.—Melting points were determined on a Kofler micro hot stage (Arthur H. Thomas and Co.) and are corrected. Boiling points are uncorrected. Refractive index was measured with an Abbe refractometer.

Rate Constants for the Hydrolytic Reactions.—Rates were measured as follows. Replicate mixtures of substrates and acid were prepared in the cold, placed in a boiling water bath, and incubated for various intervals of time. The hydrolysis was stopped instantaneously by plunging the reaction vessel into an ice bath and adding excess ammonium acetate solution, to make the pH of the solution approximately 5.0 or higher. The extent of hydrolysis was determined by periodate titration[24a]; the results were plotted semilogarithmically.

N.m.r. Spectrum of Anhydrotetrol XIV.—The methylene protons are represented by two six-line multiplets each of which is a doublet of triplets. One multiplet, centered at δ 1.26 has a doubling (J_{gem}) of 12.2 c.p.s. and a tripling of 8.8 c.p.s. The other multiplet is centered at δ 2.08 and shows the 12.2-c.p.s. doubling and a tripling of 7.5 c.p.s. The H–O–C–H ring protons appear as a three-line signal (arising from two doublets with nearly overlapping inner lines) of total width of 16.0 c.p.s. The oxirane protons give a sharp singlet at δ 3.41.

N.m.r. Spectrum of Anhydrotetrol Dibenzoate XVIIb.—The methylene protons appear as an irregular multiplet centered at δ 2.20, with a total width of 56 c.p.s. At least 12 lines are discernible. The ester O–C–H protons appear as an irregular multiplet centered at δ 5.65. The oxirane protons appear as two unequal multiplets centered at δ 3.85. In a double irradiation experiment, irradiation at the frequency of the ester O–C–H signal collapsed the oxirane signal to an AB pattern[24b] of two doublets.

N.m.r. Spectrum of O-Isopropylideneanhydrotetrol (XI).—The methyl groups are seen as two sharp singlets at δ 1.29 and 1.54. The methylene protons form two multiplets at δ 2.07 and 2.52. The oxirane protons form an irregular envelope at δ 3.75 and the dioxolane O–C–H protons form a multiplet at δ 4.95.

(1,2,4/3)-DL-3-Bromo-1,2-*O*-isopropylidenecyclopentanetriol (XIXa).—Hydrogen bromide gas was vigorously bubbled for 1 min. through a solution of (1,2,3,4/)-2,3-anhydrocyclopentanetetrol[4] (XIV, 0.50 g., 4.3 mmoles in 25 ml. of water). The solution became hot, and was then stirred for 17 hr. at room temperature. Water was removed under reduced pressure and an orange sirup was obtained which was dried by repeated addition and vacuum distillation of absolute ethanol. The material could not be crystallized. On analysis by periodate titration 2.0 mg. (10.2 μmoles) consumed 9.3 μmoles of periodate (91% yield for a 1,2-glycol). This sirup was stirred overnight in a stoppered flask with 50 ml. of anhydrous acetone and 2 g. of anhydrous $CuSO_4$. Concentrated NH_4OH was added to make the pH 7, the solid phase was removed by filtration and washed with acetone. The combined filtrates were evaporated under a current of cool air to a green sirup. The sirup was extracted with methylene chloride (100 ml.) and after filtration of the solution the solvent was evaporated in the same manner. The product (1.0 g.), which was still green, solidified, m.p. 44–47°. Sublimation for 2 hr. at 65° and 0.5 torr yielded white crystals (0.83 g., 3.5 mmoles, 81.4%), m.p. 53.5–54.0°.

Anal. Calcd. for $C_8H_{13}BrO_3$: C, 40.53; H, 5.53; Br, 33.70. Found: C, 40.75; H, 5.58; Br, 33.72.

(1,2,4/3)-DL-3-Chloro-1,2-O-isopropylidenecyclopentanetriol (XIXb).—Hydrogen chloride gas was vigorously bubbled for 1 min. through a solution of (1,2,3,4/)-2,3-anhydrocyclopentanetetrol (XIV, 0.50 g., 4.3 mmoles) in 25 ml. of water. The solution became hot and was then stirred for 20 hr. at room temperature. Solvent was removed and the substance was acetonated as described for XIXa.

The crude material obtained after evaporation of the methylene chloride extract (0.8 g.) was sublimed twice (0.5 hr., 45° bath at 0.1 torr, condenser 0°) and gave 0.67 g. (3.48 mmoles, 81%) of white crystals, m.p. 42.5–43.5°.

Anal. Calcd. for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80; Cl, 18.40. Found: C, 50.02; H, 6.80; Cl, 18.18.

(1,2,4/3)-DL-3-Bromotri-O-benzoylcyclopentanetriol (XVIIIb).—Bromotriol XVIIIa prepared as above (0.188 g., 0.9555 mmole) was dissolved in 3 ml. of dry pyridine. The solution was chilled in an ice bath and 1.1 g. (2.88 mmoles) of benzoyl chloride was added with vigorous agitation. The mixture was left overnight at room temperature. Excess benzoyl chloride was decomposed by addition of a small amount of water and stirring for 2 hr. The mixture was dissolved in methylene chloride, and the resulting solution was extracted twice with 1 *N* sulfuric acid, twice with 5% sodium carbonate, and once with water. After removal of the methylene chloride the product was dissolved in hot ethanol, precipitated by addition of water, and then crystallized from ethanol (0.297 g., 0.585 mmole, 61%), m.p. 100–106°. An analytical sample recrystallized twice more from ethanol melted at 107–107.5°.

Anal. Calcd. for $C_{26}H_{21}BrO_6$: C, 61.31; H, 4.15; Br, 15.69. Found: C, 61.49; H, 4.29; Br, 15.81.

(1,2,3,4/)-DL-3,4-Anhydro-1,2-O-isopropylidenecyclopentanetetrol (XI). A. From Anhydrotetrol VIII.—Freshly distilled (1,2,3,4/)-DL-1,2-anhydrocyclopentanetetrol[4] (VIII, 11.47 g., 98.7 mmoles) was stirred 25 hr. at room temperature in a stoppered flask with anhydrous acetone (200 ml.) and anhydrous $CuSO_4$ (5 g.). The reaction mixture was filtered, the residue was washed with dry acetone, and the combined filtrates were concentrated under water pump vacuum. Distillation yielded a clear liquid (2.39 g., 15.3 mmoles, 15.5%), b.p. 80–81.5° (1.5 torr). The nonvolatile residue within the distillation flask solidified into a thick gum upon continued heating. The distilled crude liquid was impure as shown by the presence of absorption bands in the hydroxyl region of the infrared spectrum. The liquid product was therefore dissolved in ether and extracted three times with 10-ml. portions of water, and the ether phase was dried (0.5 hr.) over anhydrous $MgSO_4$. The usual pro-

(22) G. Braun, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 431.

(23) Purchased from FMC Corp, Carteret, N. J.

(24) (a) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944); (b) see ref. 13, p. 119.

cedures then yielded[25] a clear liquid (0.488 g., 3.13 mmoles, 20%), b.p. 65° (2.5 torr), $n^{23}D$ 1.4591.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.72; H, 7.69.

B. From Bromohydrin XIXa.—A solution of 0.95 g. (4.0 mmoles) of XIXa in 50 ml. of 0.3 *N* sodium hydroxide was stirred for 1 hr. at room temperature. The solution was extracted three times with 25-ml. portions of ether, the ether extracts were concentrated under water pump vacuum, and the residue was distilled under the same vacuum. The product (0.056 g., 0.35 mmole, 9%) had the same boiling point, infrared spectrum, and refractive index as compound XI prepared by acetonation of the anhydrotetrol.

C. From Chlorohydrin XIXb.—Similar treatment of (1,2,4/3)-DL-3-chloro-1,2-O-isopropylidenecyclopentanetriol (0.405 g., 2.1 mmoles) with 25 ml. of 0.3 *N* sodium hydroxide (2 hr.) also gave a pure product (0.112 g., 0.58 mmole, 29.1%) having a boiling point, infrared spectrum, and refractive index identical with the product described above.

(1,2/3,4)-DL-3,4-Anhydro-1,2-O-isopropylidenecyclopentanetetrol (XII).—A solution of DL-*cis*-1-cyclopentene-3,4-O-isopropylidene-3,4-diol[7] (2.6 g., 18.5 mmoles) and *m*-chloroperoxybenzoic acid (5.5 g., 28.8 mmoles) in chloroform (100 ml.) in a glass-stoppered brown bottle was stirred 21 hr. in the dark at room temperature. The mixture was then chilled in an acetone–Dry Ice bath, and the precipitate was removed by filtration. The mother liquor was concentrated under reduced pressure almost to dryness. Methylene chloride (50 ml.) was added, and the resulting solution was filtered by gravity, extracted twice with 150-ml. portions of 5% Na_2CO_3, washed once with water, and dried over sodium sulfate. The solvent was removed *in vacuo* leaving a clear liquid (2.33 g., 14.9 mmoles, 80.7%). The entire quantity of crude product was distilled yielding a clear liquid (1.79 g., 11.45 mmoles, 78%), b.p. 84–85° (17 mm.), $n^{23}D$ 1.4500.

Anal. Calcd. for $C_8H_{12}O_3$; C, 61.52; H, 7.74. Found: C, 61.34; H, 7.77.

(1,2,3/4)-DL-4-Bromocyclopentanetriol (XX).—Hydrogen bromide gas was vigorously bubbled for 1 min. through a solution of (1,2,3,4/)-DL-1,2-anhydrocyclopentanetriol (VIII, 1.36 g., 11.7 mmoles) in 50 ml. of absolute ethanol. The solution became very hot and was then stirred for 0.5 hr. The temperature fell during this interval. HBr was removed by repeated addition of ethanol and concentration to small volume under reduced pressure. The orange sirup residue could not be crystallized. On analysis by periodate titration 2.30 mg. (11.7 μmoles) consumed 22.7 μmoles of periodate.

(1,2,3/4)-DL-4-Bromo-1,2-O-isopropylidenecyclopentanetriol (XXII) and (1,2,3/4)-DL-4-Bromo-2,3-O-isopropylidenecyclopentanetriol (XXI).—The crude bromotriol XX obtained from 1.36 g. (11.7 mmoles) of VIII was stirred overnight in a stoppered flask with anhydrous acetone (100 ml.) and 5 g. of anhydrous $CuSO_4$. The green reaction mixture was neutralized with concentrated NH_4OH to pH 7 and filtered. The residue was washed with acetone (20 ml.), and the combined filtrates were evaporated under a current of cool air. The residue was extracted with 50 ml. of methylene chloride. This extract was filtered into a separatory funnel, for separation of occluded water, and then concentrated under a warm current of air. The resulting brown sirup was transferred into a distilling flask with the aid of anhydrous acetone, and the acetone was removed by evaporation at 60 mm. pressure. Distillation of the residue gave a pale brown liquid (1.46 g., 6.16 mmoles, 52.7%), b.p. 117° (1.5 torr). Redistillation of this product (1.19 g., 5.0 mmoles) yielded a faintly yellow liquid (0.786 g., 3.2 mmoles, 66%), b.p. 94.5–96.0° (0.4 torr), $n^{24.8}D$ 1.4962, which turned light brown after standing in a sealed tube for 2 days.

Anal. Calcd. for $C_8H_{13}BrO_3$: C, 40.52; H, 5.53; Br, 33.70. Found: C, 40.46; H, 5.61; Br, 33.52.

The product was analyzed by periodate titration as follows. A solution of 1.31 mg. (5.53 μmoles) in 0.40 ml. of 0.001 *N* H_2SO_4 was heated in a boiling-water bath for 1 hr. to liberate the free bromotriol. The solution was cooled and neutralized with ammonium acetate and then treated with a standardized solution of sodium metaperiodate. The material consumed 12.3 μmoles of periodate (110% yield for a 1,2,3-triol).

(1,2,3/4)-DL-4-Bromo-2,3-O-isopropylidenecyclopentanetriol (XXI).—The mixture of XXI and XXII obtained above (0.439 g., 1.85 mmoles) was added to 35 ml. of 0.4 *N* sodium hydroxide at room temperature. The liquid was initially immiscible with the aqueous phase, but after 5 min. stirring, solution was complete. Stirring was continued for 1.5 hr. and the solution was then extracted three times with 25-ml. portions of ether. The ether was removed at water-pump pressure, leaving two liquid phases. The lower phase was collected with a capillary pipet and distilled *in vacuo*. The product, b.p. 90° at 2.5 torr (0.05 ml.) was analyzed by infrared spectroscopy and showed absorption bands at 3033 and 3011 (oxirane C–H) and at 845 $cm.^{-1}$ (epoxide) which characterize the epoxides of our series,[17d] in addition to strong absorption in the hydroxyl region of the spectrum. The regions of the spectrum characteristic of dioxolane C–O–C stretching (1200–1000 $cm.^{-1}$) and *gem*-dimethyl C–C stretching (1375 $cm.^{-1}$) showed a complicated pattern of many strong absorption bands. The distillate was exposed to the laboratory air for 2 days, and a crystalline product formed, m.p. 58–62.5°. Purification was achieved by removing adhering liquid on a porous plate for 1 hr. The material was sublimed (bath temperature 40° at 0.2 torr, condenser 5°), m.p. 63.0–63.5° (yield 0.0242 g., 0.10 mmole, 5.5%), m.m.p. 30–45° with XIXa. The infrared spectrum showed none of the bands characteristic of epoxides, and simplification of the dioxolane and *gem*-dimethyl regions. The spectrum was also different from that of the mixture of XXI and XXII, which, however, contained all the bands of XXI.

Anal. Calcd. for $C_8H_{13}BrO_3$: C, 40.52; H, 5.52; Br, 33.70. Found: C, 40.53; H, 5.58; Br, 33.65.

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(25) Two factors may have contributed to the over-all yield of XI. The gummy residue obtained during the first distillation probably represents decomposition products of polymers formed by acid catalysis in the reaction mixture. The distillate always contains some unreacted epoxydiol VIII probably due to the formation of an azeotrope. In order to obtain pure XI partition between an organic solvent and water was necessary, and some of the desired product was lost because of its moderate solubility in water.