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Retention of Configuration in Reactions with Opening of an Epoxide Ring

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Information on the opening of an epoxide ring with retention of the initial configuration under conditions of catalytic hydrogenation and under the action of various nucleophilic reagents is examined. It is noted that when an electron-donating *p*- or π-grouping is present in the α position to the epoxide ring the retention of the initial configuration is more probable than its inversion. Bibliography of 182 references.

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I. INTRODUCTION

A large number of reactions of epoxides with various reagents has now been studied. The great mass of results that had accumulated were summarised in several exhaustive reviews[1-6], and the most recent of these also dealt with the stereochemical aspect of the transformations. In 1951 Fürst and Plattner[7] formulated the "rule for the biaxial opening of the expoxide ring", which three years later Cookson[8,9] and Angyal[10] extended its applicability from the position of conformational analysis to cyclic systems. According to these ideas, the opening of the oxide should be accompanied by inversion of the configuration of one of the carbon centres of the three-membered ring. However, at approximately the same time publications appeared showing that in several instances opening of the epoxide ring takes place with retention of the original configuration. An analysis of the constantly increasing number of experimental results shows that the so-called "sterically anomalous (*cis*-)opening of an epoxide ring" is observed among various representatives of the class of oxide compounds when various reagents act on them. The present review considers those instances which have not yet been summarised in the literature and covers information published up to July 1966.

II. SOME GENERAL FEATURES OF THE CHEMISTRY OF EPOXIDES

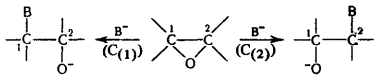
In the reviews mentioned above the correctness of the following general features of the chemistry of epoxides has been demonstrated convincingly.

1. The epoxide group often reacts in two ways, interacting with both electrophilic and nucleophilic agents under definite conditions. However, information on reaction with the latter predominates in the literature. The changes in the presence of electrophilic and radical reagents, and also on irradiation, lead mainly to the formation of products of various rearrangements of the oxide ring.

2. Breaking of the C–O bond of the epoxide takes place under the influence of various agents. Breaking of the C–C bond of the oxide ring is improbable and is observed only in the presence of strongly electronegative substituents, as occurs, for example, for oxides of cyclic trienes[11] and pentaenes[12], tetracyanoethylene oxide[13], etc.

3. The mechanism of the opening of the epoxide under the action of a nucleophilic reagent depends on the electronic and steric properties of the two reagents and on the reaction conditions. The results of the opening of the oxide are usually explained by schemes of the unimolecular and bimolecular substitution type. The direction of

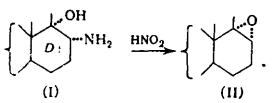
the opening of unsymmetrically substituted epoxides depends on the above factors and in general the formation of two structural isomers is possible:



The ratio of the latter cannot be predicted, although in some particular instances useful empirical relations exist.

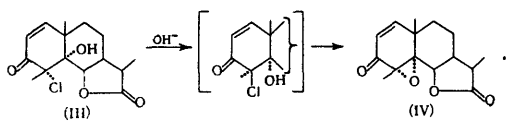
4. The stereochemistry of the opening of epoxy-compounds is determined by the steric rules for the occurrence of S_N1 and S_N2 processes. The stereochemical requirements for an S_N2 mechanism arise in the formation of a *trans*-coplanar transition state as a result of axial attack by the nucleophilic reagent on one of the carbon atoms of the epoxide with subsequent inversion of the configuration of the centre being attacked. In the cleavage of the epoxide ring by an S_N1 type mechanism as a result of the interaction with the nucleophilic reagent formation of products with both retention and inversion of the initial configuration can be expected.

5. A necessary condition for the closing of an epoxide ring is the coplanar antiparallel location of the attacking and leaving substituents. However, some departures from the classical scheme of closing of an epoxide ring are known. Thus Shoppee and coworkers[14] found that on treating the D-homopregnane amino-alcohol (I) with nitrous acid the α-oxide (II) is obtained in good yield. The explanation for this type of closing of the oxide ring is that the OH group of the *cis*-*e*, *a*-amino-alcohol (I) is in a position convenient for the formation of a pyramidal transition state, and consequently the removal of the diazonium group proceeds as a result of a synchronous process of the pinacoline type without formation of an intermediate carbonium ion.



(I) (II)

Moreover, it is known that in the diazotisation of *threo*-1,2-diphenyl-2-aminoethanol the oxide of *trans*-stilbene is produced in low yield[15]. The retention of the initial configuration is also observed in the treatment of the *cis*-chlorohydrin (III) with alkali[16]. However, here it is suggested that the ketol (III) is first isomerised by a retro-aldolisation type of mechanism into an intermediate *trans*-chlorohydrin, which is then converted into the keto-oxide (IV):



(III) (IV)

A similar process evidently takes place in the series of diastereoisomeric esters of α-chloro-β-hydroxy-β-trifluoromethylpropionic acid, which give only one epoxypropionate on treatment with sodium hydride[17].

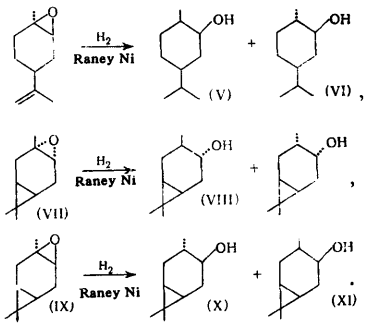
III. STEREOCHEMISTRY OF EPOXIDE RING OPENING PROCEEDING WITH RETENTION OF THE CONFIGURATION

It must be noted that the presence in the literature of isolated information on the "sterically anomalous" opening of an oxide ring, and also the absence, with a few exceptions, of systematic investigations in this field still do not allow a satisfactory classification to be given for all instances of this interesting phenomenon. Nevertheless we can provisionally distinguish two large groups of epoxy-compounds in which this phenomenon is observed.

A. Epoxy-Compounds in which the Effect of Conjugation is Absent

The *cis*-opening of the oxide ring in this group of compounds is encountered extremely rarely and is characteristic for the conformationally rigid secondary-tertiary and ditertiary cyclic epoxy-compounds. It is therefore quite probable that in all the examples considered below the steric factor plays a paramount part.

1. Reductive *cis*-opening of an oxide ring. Examples are known when the catalytic hydrogenation of cyclic epoxides leads to cleavage products with retention of the configuration of the initial oxides. Evidently such conversions were first observed by Brunel[18,19] and Kötz and Hoffman[20] in studying the hydrogenation of methylcyclohexene oxides in the presence of nickel and platinum catalysts. According to their results, for example, 1-methylcyclohexene oxide gives *trans*-2-methylcyclohexanol. This result signifies that the entry of hydrogen and the breaking of the C–O bond probably occur at the same side of the cyclohexane molecule, which also ensures the *cis*-opening of the oxide ring. On the basis of an analysis of the complex mixture of products obtained in the hydrogenation of 1,2-, 2,3-, and 3,4-epoxymethanes in the presence of palladium hydroxide, Pigulevskii and Kozhin[21] assumed the similar possibility of the retention of the configuration of the original oxide as did Kergomard and Geneix[22,23], who studied the catalytic hydrogenation of tetrahydromyrcene oxide, pinene oxide, carbomenthene oxide, and limonene oxide. It was recently shown that the products of the hydrogenation of the sterically homogeneous *trans*-*p*-menthadiene oxide contain not only neoisocarbomenthol (V) but also carbomenthol (VI),[24,25] which arises as a result of the *cis*-opening of the epoxide ring.

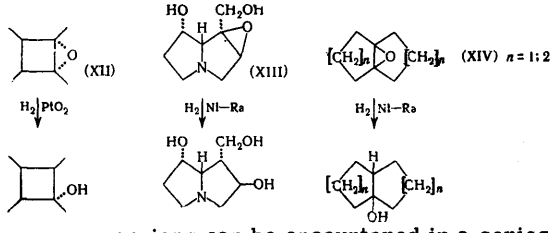


(V) (VI) (VII) (VIII) (IX) (X) (XI)

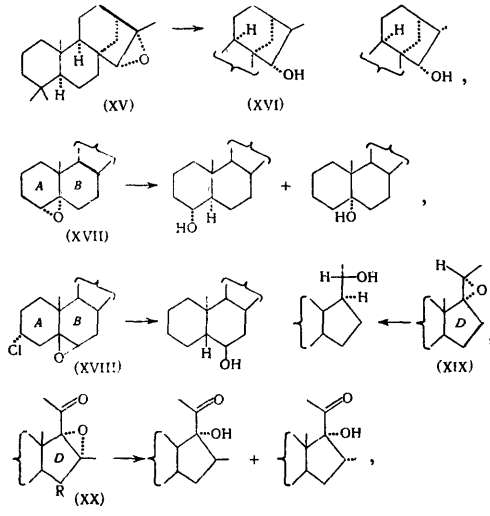
Similar results are obtained in investigating the hydrogenation of isomeric carene oxides (VII) and (IX) over Raney nickel catalyst under pressure[26]. Here with the oxide (VII) there is 82% *cis*-opening of the epoxide ring—formation of product (VIII)—and with oxide (IX) the products of the *cis*- and *trans*-opening, (X) and (XI), are formed in approximately equal amounts.

Retention of the initial configuration is observed in the catalytic hydrogenation of epoxytetramethylcyclobutane

(XII)[27] and of the oxides of the bicyclic alkenes (XIII)[28] and (XIV)[29].

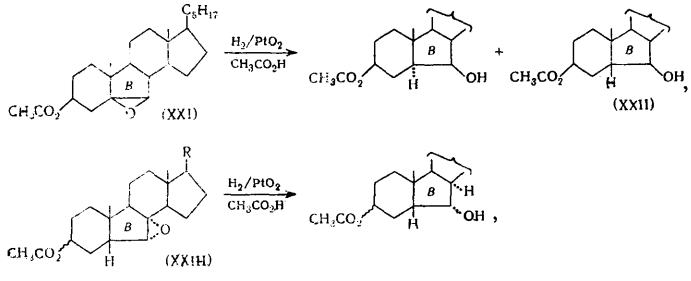


Analogous conversions can be encountered in a series of polycyclic epoxy-compounds. Thus isophyllocladene oxide (XV) in the presence of Adams catalyst gives a mixture of epimeric alcohols with a preponderance of the product of *cis*-cleavage (XVI)[30]. Under the same conditions 4α,5α-epoxycholestane (XVII) is converted into a mixture of approximately equal amounts of the 4α- and 5α-alcohols[31], whereas only the 6β-alcohol is obtained from 3α-chloro-5β,6β-epoxycholestane (XVIII)[32]. Furthermore, exclusively *cis*-opening is observed[33,34] in the catalytic hydrogenation of pregnane 17α,20α-oxides (XIX) over Raney nickel. As regards the ditertiary pregnane keto-acids (XX) in the presence of a palladium catalyst they undergo either partial or complete *cis*-opening, depending on the hydrogenation condition[35,36]:



where R = H or Br.

Recently, Šorm and coworkers[37,38] described the opening of oxides of the B-norcholestane and B-norandrostane series. Here the 5β,6β-oxide (XXI) gave a mixture of alcohols with a considerable preponderance of product (XXII), which exhibits the configuration of the original epoxide. With the 6α,8α-oxide (XXIII) the opening proceeds exclusively with retention of the original configuration

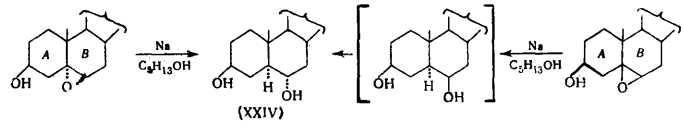


where R = C_8H_{17}, O_2CCH_3.

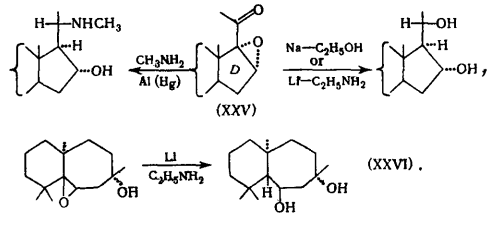
To explain the conversions mentioned it is necessary to assume that the generally accepted ideas about the mechanism of catalytic hydrogenation of steroidal alkenes[39] are also applicable to steroidal epoxides.

It is extremely probable that here also the reaction proceeds by *cis*-addition of a molecule of H_2, adsorbed on the surface of the catalyst, to the sterically most accessible C–O bond of the oxide ring.

cis-Opening is much more rarely encountered for other methods of reducing the oxides. Thus, Urushibara and Chuman[40] observed the reduction of 5α,6α-oxides of cholesterol by sodium in pentyl alcohol to give the 3β,6α-glycol (XXIV):



They obtained the same product in identical conditions from cholesterol 5β,6β-oxide. However, it appeared that initially there is *trans*-opening of the cholesterol β-oxide to the intermediate 3β,6β-glycol, which subsequently isomerises to the more stable 6α-epimer under the conditions of the redox reaction. It is also known that the reductive amination of the steroidal 20-keto-16α,17α-oxides (XXV) is accompanied by their *cis*-opening[41]. The same result is observed in the reduction of oxides (XXV) by sodium in alcohol[42] or by lithium in ethylamine[43]. With the aid of the last reagent Widdrol β-oxide† was converted into the glycol (XXVI) in ~ 40% yield[44].

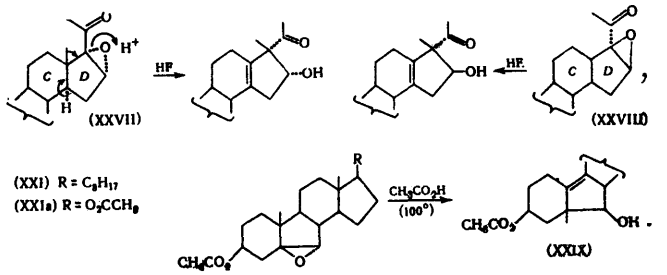


2. Oxides in Wagner–Meerwein type rearrangements. The reaction of cyclic secondary-tertiary and ditertiary oxides with acids, just like the epoxidation of the corresponding alkenes, often leads to the formation of products of various rearrangements[3,6]. It is usual to explain these conversions by the concept of the carbonium-ion intermediate, the manner of the "neutralisation" of which determines the structure of the final products. Sometimes these can be products of a Wagner–Meerwein type rearrangement. It is well known that the latter includes the simultaneous formation of an electron-deficient centre and an antiparallel *cis*-1,2-displacement of the migrating substituent (usually methyl), that for an epoxide will signify its *trans*-opening. Such a situation is preferable, since this process does not result in the formation of a discrete carbonium ion. However, it is possible for there to be a non-simultaneous process including the anticipatory stage of the formation of a stable carbonium ion at the site of the rupture of the C–O bond of the oxide ring[45,46]. The latter implies that with the mutual *cis*-arrangement of the epoxide and migrating groups the configuration of the two carbon centres of the original oxide will be retained. Both these types of mechanism

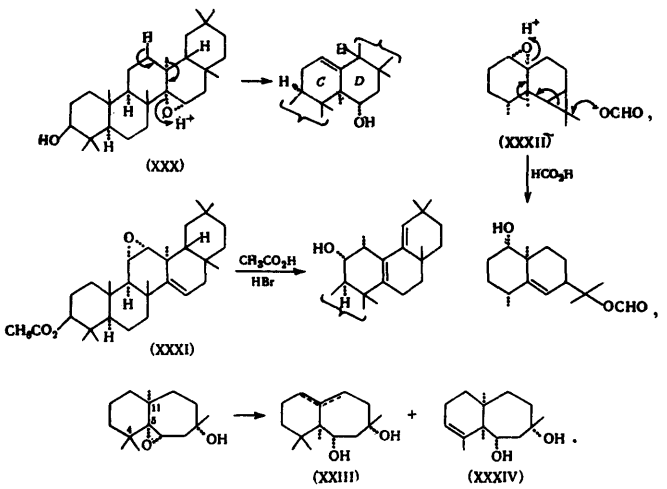
† The symbols α and β in the present review signify, as in steroids, the configuration of the three-membered oxide ring.

are observed experimentally, as is illustrated by the conversion of isomeric keto-oxides of the pregnane series (XXVII) and (XXVIII)[47,48].

On the other hand, on heating the 5β,6β-oxides (XXI) and (XXIa) in acetic acid *cis*-opening takes place exclusively[37], and the formation of 19,B-bis-nor-products (XXIX) does not have an analogy in the normal steroidal series which contains a six-membered ring B.



The literatures also describes the "anomalous" opening of terpene epoxides in the presence of acids, as is shown by the examples of taraxerine oxides (XXX)[49] and (XXXI)[50] and calarene oxide (XXXII)[51]:

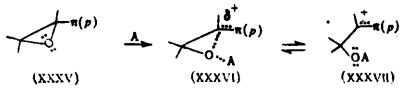


An interesting example is Widdrol α-oxide itself, which on boiling in water gives a mixture of homoallyl alcohols (XXIII) and (XXXIV)[44]. It is suggested that the configuration at $C_{(5)}$ is retained as a result of the formation of an hydrated carbonium-ion intermediate which is subsequently stabilised by a displacement of the methyl group at $C_{(4)}$ or $C_{(11)}$.

B. Epoxy-Compounds in which the Effect of Conjugation Appears

To this group belong the compounds in which the oxide ring is adjacent to an unsaturated bond or to an atom with an unshared *p*-pair of electrons. Like conjugated cyclopropanes and aziridines, the epoxy-compound (XXXV) displays the conjugation, as is shown by the ultraviolet spectra of monoepoxides of conjugated dienes[52], aryl oxides[53] and keto-oxides[54]. However, it must be stated that the investigation of infrared spectra of acyclic keto-oxides[55] and epoxypropionates[56] did not disclose any appreciable conjugation between the oxide ring and the C=O group, although this effect probably occurs to an insignificant extent in several cyclic keto-oxides[57].

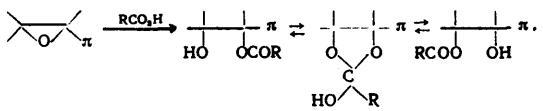
The greatest number of examples of *cis*-opening have been described for epoxides of the type of (XXXV). In all these examples, except for the reaction of indene oxide[58] and phenylcyclohexene oxide[59] with dilute alkali and also the reduction of certain oxides by alkali metal complex hydrides[60-62] or by lithium in ethylamine[63] the reaction takes place under conditions of electrophilic catalysts. According to generally accepted ideas, under such conditions partial or complete rupture of the C–O bond of the epoxide is possible with formation of cationic intermediate transition states (XXXVI) and (XXXVII):



where $\pi(p)$ is aryl or ester; and A is a Lewis acid.

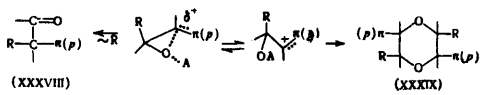
Here it is considered that the existence of this type of transition state is the main reason determining the "sterically anomalous" opening of the oxide ring (XXXV). A similar approach to the solution of the problem under discussion is justified by the following observations.

1. The primary change leading to products of the *cis*-opening of the oxide ring takes place at the carbon atom connected to the electron-donating substituent. This is not always evident for the reactions of oxides with carboxylic acids owing to the frequently observed secondary process of the migration of the acyl residue and the possible formation of a mixture of monoesters[59,64-71]:



To show the direction of attack of the nucleophilic reagent it is convenient to use an acid the acyl residue of which exhibits reduced tendency to migration, for example, mesitylenecarboxylic acid[65,66]. The determination of the direction of acid hydrolysis of the epoxy-compounds (XXXV) is more complex. Definite results in this instance can be obtained with the aid of optically active substances, as was done for styrene oxide[65] and phenylpropene oxide[72].

2. The opening is often accompanied by the formation of carbonyl products (XXXVIII), which arise as a result of the rearrangement of the epoxide under the action of electrophilic catalysts[3,6]. Sometimes such a direction for the reaction predominates, this being especially characteristic for oxides of type (XXXV). Under certain conditions stabilisation of the new electron-deficient centre can be brought about by dimerisation (XXXIX), as for example, with 3-methoxydihydronaphthalene oxide[73,74]:



where R = H, alkyl, aryl, acyl.

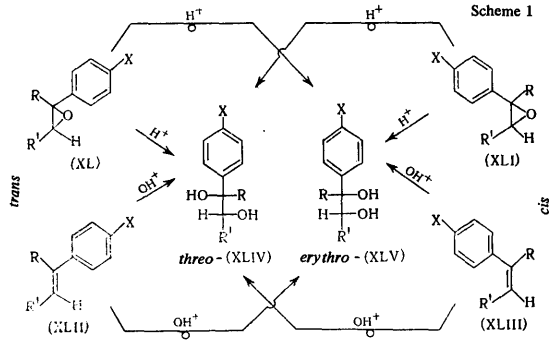
3. Kinetic investigations show that the opening of the oxide (XXXV) can be described by either S_N2 or S_N1 mechanisms with each of these taking part in different proportions in any particular instance[3,6]. In this connection the production of a mixture of products with inversion and retention of the configuration of the reaction centre can be expected. The *cis*-opening of the oxides (XXXV) is usually connected with the possibility of unimolecular substitution, although this viewpoint has been criticised[2,3].

1. *cis*-Opening of Aryloxides. The account of the information on the *cis*-opening of one of the most widely studied groups of epoxides of type (XXXV)—the aryl-

oxides—must begin with consideration of some of the conversions of styrene oxide, although in view of the primary–secondary nature of the latter the stereochemistry of these changes cannot be discussed conclusively. For example, it is found that the attack of carboxylic acids[64,65,67] and hydrogen halides[67,75-78] is directed preferentially at the benzyl carbon atom and the products of the reaction of optically active styrene oxide with weak acids (benzoic and mesitylenecarboxylic) are racemates. On treatment with trichloroacetic (in benzene), acetic, and dilute sulphuric acids, and also with phenylmercaptoborane[79] (in tetrahydrofuran) inversion is observed, equal respectively to 37, 62, 66, and 85%. On this basis it was suggested[65,67,79] that opening of styrene oxide, which is catalysable by weak acid, proceeds preferentially by an S_N1 mechanism with formation of a rather stable intermediate benzyl carbonium ion.

With the appearance in the molecules of styrene oxides a second asymmetric centre it seems possible to consider definitely the stereochemistry of the opening of the epoxide ring as a process depending on the steric and electronic factors of the substituents, the nature of the attacking agent, etc. In the general form, such opening is represented in scheme I by hydrolysis of the isomeric oxides (XL) and (XLI), and also by the equivalent epoxidation of alkenes (XLII) and (XLIII) by some certain per-acids. In this the "sterically anomalous" process in a series of *trans*‡-compounds (XL) and (XLII) should lead to *threo*-glycols (XLIV), but in the *cis*§-systems (XLI) and (XLII), to the *erythro*-glycols (XLV). Böeseken and coworkers[80,81] evidently were the first to observe such changes; they isolated a mixture of monoacetates of racemic and meso hydrobenzoins in the epoxidation of stilbenes (XLII, XLIII; R = X = H; R′ = C_6H_5). Analogous results on the opening of aryl oxides and the epoxidation of the corresponding alkenes obtained by other authors are summarised in Table 1.

Scheme 1



The data in this table show that in a comparatively non-polar medium the predominating direction of the opening of the *trans*-oxides (XL) by acids is, like the addition of the elements of per-acids to *trans*-alkenes (XLII), "sterically anomalous". In the *cis*-series (XLI, XLIII) these reactions are characterised by a lower degree of stereospecificity, and moreover the yield of final products is somewhat less. In almost every instance carbonyl compounds are observed as side-products, their formation depending to a considerable extent on the pH of the medium. For example, the amount of 4-methoxybenzyl phenyl ketone is increased threefold when the reaction of *trans*-4-methoxystilbene with $C_6H_5CO_3H$ takes place in benzene saturated with water (Table 1, Nos. 21 and 22). When a non-polar solvent is used the pH of the medium has little effect on the yield of products with retained configuration (Table 1, Nos. 9–16) but considerably affects the rate of the process. Thus for the opening of *trans*-stilbene oxide chloroacetic acid (p*K* 2.81) requires the reaction mixture to be boiled for several hours, whereas with trichloroacetic acid (p*K* 0.1) the reaction is completed in the cold in a few minutes (in benzene)[86,87]. Probably the increased reaction rate in the presence of a strong acid can also explain the formation of trichloroacetates of hydrobenzoins (instead of benzoates) in the epoxidation of stilbenes by an equimolecular mixture of perbenzoic and trichloroacetic acids (Table 1, Nos. 17, 18, 33).

The data in Table 1 show that *cis*-opening of the oxide ring of the systems being considered is evidently not characteristic in a strongly polar medium. For example, acid hydrolysis and acetolysis of isomeric oxides of methylstyrene (XL, XLI; R = X = H, R′ = CH_3), or the epoxidation of the corresponding alkenes (XLII, XLIII) with performic acid leads predominantly to products with inverted configuration (Table 1, Nos. 1–8). Similarly, the acid hydrolysis of *trans*-anisyltolylethylene (XL; R = H, X = OCH_3, R′ = *p*-$CH_3C_6H_4$) gives a mixture of diastereoisomeric glycols (Table 1, No. 26), whereas treatment with benzoic acid in chloroform (rather low polarity) results in full retention of the configuration (Table 1, Nos. 25).

Instances of the stereospecific opening of aryl oxides irrespective of the polarity of the medium have been described. Thus, it is known that acid hydrolysis of the secondary-tertiary *trans*-α-methylstilbene oxide (XL; R = CH_3, X = H, R′ = C_6H_5) gives *threo*-α-methylhydrobenzoin[90-92]. Complete retention of the initial configuration i observed in the opening of the same oxide under milder con ditions, and also in the epoxidation of the corresponding *trans*-alkene (XLII; R = CH_3, X = H, R′ = C_6H_5) (Table 1, Nos. 29–33).

The effect, mentioned above, of the polarity of the solvent on the nature of the opening of the epoxide ring is illustrated by the celebrated examples of the reaction of hydrogen halides with aryl keto-oxides, β-phenylepoxypropionates, and stilbene oxides. Thus, Jorlander[93] found that, depending on the solvent used (alcohol or acetic acid), 1-anisyl-2,3-epoxy-3-phenylpropan-1-ol forms various chlorohydrins with hydrogen chloride. Later it was shown by other examples that such compounds are not structural isomers. Moreover it was found that in every instance the halogen atom is attached in the β position to the C=O group and that frequently such addition proceeds with retention of the configuration of the original oxide (Table 2).

As Table 2 shows, when hydrogen halides react with disecondary carbonyl-containing phenyl oxides (XLVI) and (XLVII) in non-polar solvents there is a stereospecific *cis*-opening of the epoxide ring, whereas in polar media there is complete inversion of the configuration (Table 2, Nos. 1, 2, 12, 13). With the secondary-tertiary dypnone oxide and *cis*-bromodiphenacyl oxide, irrespective of the polarity of the solvent there is a "sterically anomalous" reaction (Table 2, Nos. 6, 7, 10, and 11). In this respect these epoxides behave completely analogously to the *trans*-α-methylstilbene oxide (XL; R = CH_3, X = H, R′ = C_6H_5) mentioned above.

The stereospecific *cis*-opening of the oxides (XLVI and XLVII) proceeds in the presence of Lewis acids (Table 2, Nos. 3–5, 8, and 9). When using boron trifluoride–diethyl

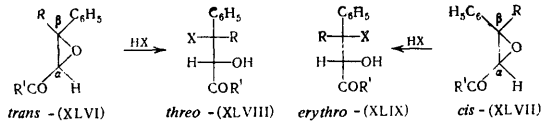
† Relative to the substituents R′ and *p*-C_6H_4X.

‡ Relative to the substituents R′ and *p*-C_6H_4X.

Table 1. Epoxidation of substituted styrenes and cleavage of the corresponding oxides.

Oxide (alkene)	No.	Acid and solvent	Monoester, % *threo-*	Monoester, % *erythro-*	Reference	Notes
Oxide of *trans*-methylstyrene (XL; R = X = H, R′ = CH_3)	1	H_2SO_4—H_2O	~37	63	82, 83	mixture of diols
	2	CH_3CO_2H	—	80	85	
Oxide of *cis*-methylstyrene (XL; R = X = H, R′ = CH_3	3		90	—	84	
	4	H_2SO_4—H_2O	80	~20	82, 83	mixture of diols
(+) and (–) forms of oxide of *trans*-methylstyrene	5			~76	72	mixture of diols; (–)-*erythro*-glycol is a side-product of the hydrolysis (H_2O–$HClO_4$) (+)-*cis*-oxide.[85]
(+) and (–) forms of the oxide of *cis*-methylstyrene	6		75			
trans-Methylstyrene (XLII; R = X = H, R′ = CH_3)	7	HCO_3H	a	b	82, 83	a small quantity b main product
cis-Methylstyrene (XLIII; R = X = H, R′ = CH_3)	8		b	a		
Oxide of *trans*-stilbene (XL; R = X = H, R′ = C_6H_5)	9	$ClCH_2CO_2H$—C_6H_6	62	—	86	
	10	$ClCH_2CO_2H$—CCl_4	68	—		
	11	Cl_2CHCO_2H—C_6H_6	62	—		
	12	Cl_3CCO_2H—C_6H_6	78	—	87	
(+) and (–) forms of the oxide of *trans*-stilbene	13		71	—		
Oxide of *cis*-stilbene (XLI; R = X = H, R′ = C_6H_5)	14	$ClCH_2CO_2H$—C_6H_6	d	45[c]	86	c isolated in the form of the glycol d traces
	15	Cl_2CHCO_2H—C_6H_6		48		
	16	Cl_3CCO_2H—C_6H_6	—	64	87	
trans-Stilbene (XLII; R = X = H, R′ = C_6H_5)	17	$C_6H_5CO_3H$—Cl_3CCO_2H (1:1) — C_6H_6	72[e]	—		e monotrochloroacetate
cis-Stilbene (XLIII; R = X = H, R′ = C_6H_5)	18		—	44[e]		
Oxide of *trans*-4-methoxystilbene (XL; R = H, X = OCH_3, R′ = C_6H_5)	19	$C_6H_5CO_3H$—$CHCl_3$	70	—	88	
	20	$C_6H_5CO_2H$—C_6H_6	60	—		
trans-4-Methoxystilbene (XLII; R = H, X = OCH_3, R′ = C_6H_5)	21	$C_6H_5CO_3H$—C_6H_6	65	—	89	
	22	$C_6H_5CO_3H$—C_6H_6—H_2O	57	—		
cis-4-Methoxystilbene (XLIII; R = H, X = OCH_3, R′ = C_6H_5)	23	$C_6H_5CO_3H$—$CHCl_3$	43[e]	—	88	f isolated in the form of the glycol
	24		20[f]	76		
Oxide of *trans*-4-methoxy-4′-methylstilbene (XL; R = H, X = OCH_3, R′ = *p*-$C_6H_4CH_3$)	25	$C_6H_5CO_2H$—$CHCl_3$	64	—		
	26	H_2SO_4—H_2O	g			g ratio of diols not stated
trans-4-methoxy-4′-methylstilbene (XLII; R = H, X = OCH_3, R′ = *p*-$C_6H_4CH_3$)	27	$C_6H_5CO_3H$—$CHCl_3$	60	—		
cis-4-Methoxy-4′-methylstilbene (XLIII; R = H, X = OCH_3, R′ = *p*-$C_6H_4CH_3$)	28		—	40		
Oxide of *trans*-α-methylstilbene (XL; R = CH_3, X = H, R′ = C_6H_5)	29	CH_3CO_3H	60	—	66	
	30	Cl_3CCO_2H—C_6H_6	62	—		
	31	mesitylenecarboxylic acid (without solvent)	20	—		
trans-α-methylstilbene (XLII; R = CH_3, X = H, R′ = C_6H_5)	32	CH_3CO_3H	55[h]	—		h isolated in the form of the glycol
	33	$C_6H_5CO_3H$—Cl_3CCO_2H (1:1)—$CHCl_3$	79[i]	—		i monotrichloroacetate

ether, House[97] noted the formation of carbonyl side-products, the quantity of which increases rapidly with increase in the concentration of the complex:



trans-(XLVI) *threo*-(XLVIII) *erythro*-(XLIX) *cis*-(XLVII)

Somewhat unexpectedly there is complete inversion of the configuration in the reaction of a *cis*-epoxypropionamide (XLVII; R = H, R′ = NEt_2) with HCl, both in benzene and in methanol (Table 2, Nos. 14 and 15). Here the *erythro*-isomer (XLIX) is formed. The strict stereospecificity of this reaction is evidently due to the thermodynamic stability of the corresponding transition state, and will be discussed in detail below.

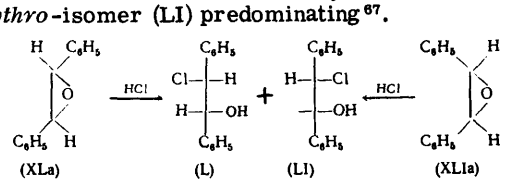
Thermodynamic control probably plays a decisive part in the conversions of some other epoxypropionates. Thus it is well known that acid hydrolysis of *trans*-β-phenylepoxypropionic acid (XLVI; R = H, R′ = OH) proceeds with retention of the configuration and gives *threo*-diol (XLVIII; R = H, R′ = X = OH)[103]. House and Blaker[56] assume the possibility of side reactions for epoxy-β-methyl-β-phenylpropionates (XLVI, XLVII; R = CH_3, R′ = OC_2H_5). However, the available published information on this subject does not permit any general conclusions to be drawn.

Table 2. Halogenohydrins from phenoxides.

Oxide	No.	Reagent and solvent	Yield of halogenohydrin, %		Reference
			threo-	*erythro-*	
Oxide of *trans*-benzal-acetophenone (XLVI; R = H, R′ = C_6H_5)	1	HCl—$(C_2H_5)_2O$	43	—	94
	2	HCl—C_2H_5OH	—	44	94,95
	3	$SnCl_4$—C_6H_6	72	—	94,96
	4	0.5 *M* BF_3 $(C_2H_5)_2O$	59	—	
	5	2*M* BF_3 $(C_2H_5)_2O$	38	—	94,97
Oxide of *trans*-dypnone (XLVI; R = CH_3, R′ = C_6H_5)	6	HCl—CH_3CO_2H(HCl—C_2H_5OH)	76	—	98
Oxide of *cis*-dypnone (XLVII; R = CH_3, R′ = C_6H_5)	7		—	84	
trans-Bromodiphenacyl (XLVI; R = CH_2Br, R′ = C_6H_5)	8	CH_3COBr (sealed ampoule, 100°)	58*	—	99, 100
	9		—	60*	
cis-Bromodiphenacyl (XLVII; R = CH_2Br, R′ = C_6H_5)	10	HBr—$(C_2H_5)_2O$—C_6H_6	—	69	100, 101
	11	HBr—$(C_2H_5)_2O$	—	85	100
trans-*NN*-diethyl-3-phenyl epoxypropionamide (XLVI; R = H, R′ = $N(C_2H_5)_2$)	12	HCl—C_6H_6	97	—	102
	13	HCl—CH_3OH	—	94	
cis-*NN*-diethyl-3-phenyl-epoxypropionamide (XLVII; R = H, R′ = $N(C_2H_5)_2$)	14	HCl—C_6H_6	84	—	
	15	HCl—CH_3OH	76	—	
Oxide of *trans*-stilbene (XLa)	16	HCl—C_6H_6	>90	—	67
	17	HCl—$CHCl_3$	>76	—	
	18	HCl—$(C_2H_5)_2O$	75	10	
	19	HCl—dioxan	70	30	
Oxide of *cis*-stilbene (XLIa)	20	HCl—C_6H_6	80	20	
	21	HCl—$CHCl_3$	~80	<10	
	22	HCl—$(C_2H_5)_2O$	87	4	
	23	HCl—dioxan	70	30	

* Acetate of the bromohydrin.

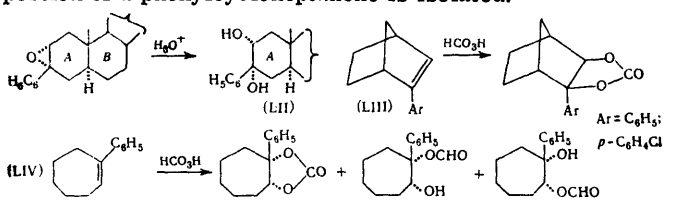
Extremely interesting results were obtained by Berti and coworkers[67] who reexamined previous studies[104-106] of the addition of HCl to isomeric oxides of stilbene (XLa, XLIa). In investigating the effect of solvents of various polarities on the stereochemistry of the reactions, they succeeded in showing (Table 2, Nos. 16–23) that in a comparatively non-polar medium the *trans*-isomer (XLa) undergoes *cis*-opening exclusively, as took place when the same oxide was treated with chloroacetic acids (Table 1, Nos. 9–13). With increase in the polarity of the solvent there is an increase in the yield of the product of the *trans*-opening of the oxide (XLa) and, for example, in the medium of moist ether a mixture of the chlorohydrins is formed with the *erythro*-isomer (LI) predominating[67].



(XLa) (L) (LI) (XLIa)

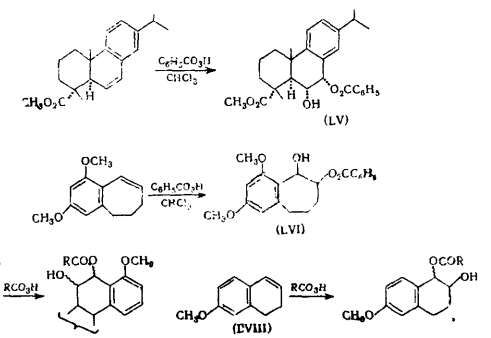
Unlike the *trans*-oxide, the *cis*-isomer (XLIa) in all the solvents used gave mainly the product of *trans*-opening (L) together with small amounts of the diastereoisomer (LI) and carbonyl compounds. These results differe from those in which there is exclusively *cis*-opening of oxide (XLIa) under the action of chloroacetic acids (Table 1, Nos. 14–16), which could be due to the nature of the carboxylate and halide nucleophilic ions, which participate in the realisation of the corresponding transition states[67].

The epoxides of aryl cyclenes stand somewhat apart from the aryl oxides considered above. There is extremely little information on their *cis*-opening, just as for the *cis*-addition of the elements of per-acids to the corresponding alkenes. It is known, for example, that acid hydrolysis of 2α,3α-epoxy-3β-phenylchloestane gives only the 2α,3α-glycol (LII)[107]. A similar result is obtained in the epoxidation with performic acid of the arylnorbornenes (LIII)[108,109] and phenylcycloheptene (LIV).[110] In the latter instances, in addition to the orthocarbonate and a mixture of monoformates (the secondary formate arises as a result of the migration of the formyl group) a considerable proportion of a phenylcycloheptanone is isolated.



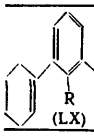
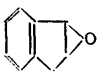
Only keto-products are formed in the epoxidation of Δ⁶-dehydroabietane by perbenzoic acid[111]. For the same reason the yield of the *cis*-benzoate (LV) from methyl Δ⁶-dehydroabietate is only 43%.[111]

On the basis of the spectroscopic results and analogies in the literature, the sole product of the epoxidation of dimethoxybenzocycloheptadiene was ascribed the structure of the *cis*-monobenzoate (LVI).[112] More frequently, however, examples are encountered when arylcyclenes and their oxides give mixtures of substances which are epimeric at a benzyl centre. Thus, the addition of the elements of per-acids to the steroidal fragment (LVII), used by Johnson and coworkers[113,114] in the synthesis of aldosterone proceeds non-selectively and gives a mixture of monoesters of isomeric diols. A similar picture is observed in the epoxidation of methoxydihydronaphthalene (LVIII)[73,74] and in the conversions of the oxides and alkenes (LIX)–(LXII) shown in Table 3.



The data given in Table 3, while not so complete as for the acyclic aryl oxides considered above, nevertheless permits the conclusion that the opening, which is catalysed by acids, of the phenylcyclohexene oxide (LIX) and indene oxide (LXI) in polar media takes place with considerable inversion of the initial configuration. This conclusion is confirmed by the results on the opening of oxide (LIX) by an aqueous solution of sodium nitrite in acetic acid[126] and also by the preliminary results of Berti and coworkers[127] in respect of the influence of polar and ionising strength of the medium on the direction of the opening of phenylcyclohexene oxides. In investigating, in particular, the

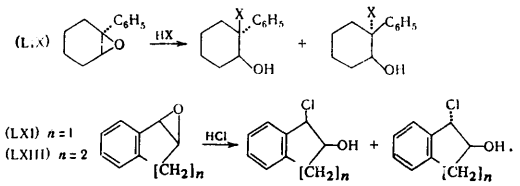
Table 3. Cleavage of cyclic aryl oxides and epoxidation of arylcyclenes.

Oxide (alkene)		No.	Reagent and solvent	Yield of glycol, % cis-	Yield of glycol, % trans-	Reference
	(LIX)	1	H_2O	51	—	115, 116
		2	H_2O—H_2SO_4	42—60	21—50	58, 117—120
		3	HCO_2H—$(C_2H_5)_2O$	90	10	59
		4	Cl_3CCO_2H—C_6H_6	65[a]	—	
	R=R'=H	5	HCO_3H	67—95	0—5	59, 108, 121
(LX)	R=CH_3; R'=H	6	CH_3CO_3H	50	—	121
	R=R'=OCH_3	7	HCO_3H	70	—	122, 123
	(LXI)	8	H_2O	38	19	58
		9	H_2O—$NaHSO_3$	60	20	124
		10	H_2O—H_2SO_4	41	—	58
		11	H_2O—CH_3CO_2H	50	19	
		12	H_2O—$FClO_3$—dioxan	48	48	125
	(LXII)	13	HCO_3H	35[b]	5[b]	68

[a] Secondary trichloroacetate. [b] 2-Formate.

acid hydrolysis in various media, including such strongly ionising solvents as dimethyl sulphoxide (DMSO) and hexamethylphosphoric triamide (HMTA), Italian investigators[127] found that the percentage retention of the configuration of these oxides falls rapidly in the following sequence of solvents: $C_6H_6 > HCO_2H > H_2O >$ dioxan + $H_2O >$ DMSO + $H_2O >$ HMTA + H_2O.

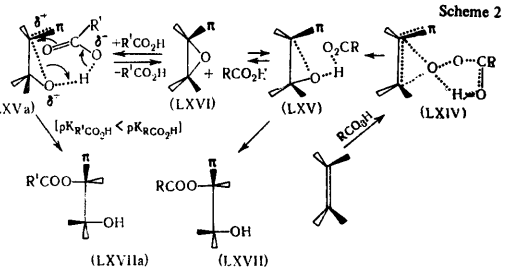
The meagre available information suggests that the above regularity is also observed in the opening of aryl oxides by hydrogen halides[128-130]. Thus, in the treatment of the oxide (LIX) with hydrogen chloride or bromide in the relatively non-polar chloroform, only the product of *cis*-opening is produced, whereas in alcoholic medium a mixture of halogenohydrins epimeric at a benzyl centre is formed[128]. A mixture of *cis*- and *trans*-isomers is also produced in the reaction of hydrogen chloride with indene oxide (LXI) and dihydronaphthalene oxide (LXIII) in dioxan[129]:



The above influence of the polarity of the medium on the direction and stereochemistry of the opening of cyclic aryl oxides should probably appear in the epoxidation of arylcyclenes. The published information confirms this suggestion. In fact, in a comparatively non-polar medium the process proceeds with a high degree of selectivity, giving products of the *cis*-addition of the elements of the per-acids at a double bond (Table 3, Nos. 5–7, 13). Here it must be noted that both in the epoxidation of phenylcyclohexene by performic acid and in the opening of epoxide (LIX) with formic and trichloroacetic acids (Table 3, Nos. 3 and 4) an increase in the yield of the *trans*-compounds on reducing the reaction temperature is observed[59]. As for the influence of conformational factors on the direction and stereochemistry of the opening of cyclic arylepoxides, except for a preliminary report[127] on the opening of the conformationally fixed phenylcyclohexene oxides, there is hardly any published information on this subject at present.

2. Mechanism of the *cis*-opening of aryl oxides. An examination of the material shows that analogous final results are obtained irrespective of whether one is dealing with the addition of per-acids to aromatic alkenes or with the opening of the corresponding oxides under conditions of electrophilic catalysis. In the general form this can be expressed by Scheme 2.

Scheme 2



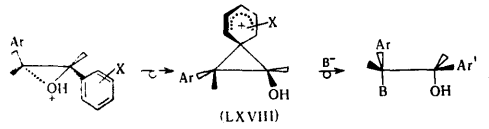
It is well known that the epoxidation of alkenes is an irreversible process, which is evidently not subject to the action of acid catalysis[6,89,131,132] and probably proceeds through the formation of a spiran[133] transition state (LXIV). The geometry of the latter is evidently not symmetrical[134,135] and reflects both the state of the electron density of the double bond being attacked (determined, in turn, by the nature of the substituent) and also by the nature of the attacking electrophilic reagent. Such a view of the nature of the transition state (LXIV) is purely speculative but it finds indirect confirmation in the kinetic results for the oxidation of a series of alkenes by per-acids. For example, whereas, according to Lynch and Pausacker[132] and Campbell and coworkers[89], if the rate of oxidation of *trans*-stilbene (XLII; R = X = H; R' = C_6H_5) by perbenzoic acid (benzene, 25°C) is taken as unity, then the ratios of the oxidation rates of the corresponding 4-Cl-, 4-CH_3O-, and 4-CH_3O-4'CH_3O-substituted compounds under the same conditions is approximately 0.6 : 5 : 20. Similar results were obtained by Ogata and Tabushi[134,135] in the epoxidation of certain α-methylstilbenes. It also follows from the kinetic results that the irreversible decomposition of the transition state (LXIV) should lead to the formation of the protonated oxide (LXV). The latter, in its turn, is in equilibrium with a carboxylic acid produced from the per-acid and with the epoxide (LXVI), which is the final product of the reaction on using per-acids of the monoperphthalic type. The existence of such an equilibrium was convincingly demonstrated by experiments on the oxidation of *trans*-4-methoxystilbene with perbenzoic acid containing labelled benzoic acid[89]. It appeared from this that the formation of the final benzoate is equally probable from both the labelled $C_6H_5CO_2H$ initially present in the substrate and the $C_6H_5CO_2H$ produced from the perbenzoic acid. The oxidation of stilbene by perbenzoic acid in the presence of trichloroacetic acid, as a result of which trichloroacetates (but not benzoates) of hydrobenzoins (Table 1, Nos. 17, 18, 33) are obtained also shows the probability of the existence of an intermediate oxide (LXVI) in view of the impossibility of the exchange reaction[89,136]:

$$RCO_3H + R'CO_2H \rightleftarrows RCO_2H + R'CO_3H.$$

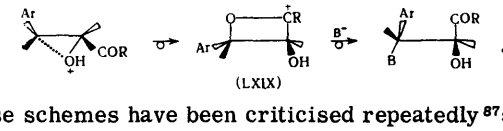
Furthermore, experiments with mixtures of acids clearly demonstrate the well known fact that the opening of an epoxide ring is catalysed by acid; therefore in the presence of two acids of unequal strength the conversion of the oxide (LXVI) into the final products (LXVII, LXVIIa) proceeds more rapidly with the stronger acid.

Consequently, both the addition of the elements of the per-acid to an aromatic alkene, and the acid-catalysable opening of the corresponding oxide proceeds through an intermediate protonated epoxide (LXV, LXVa), the conversion of which is a kinetically controllable stage of both processes[89,132]. Thanks to the appearance of a dynamic effect of conjugation, the protonated oxide, which, like transition state (LXIV), probably cannot be symmetric, is characterised by the presence of a broken C–O bond and consequently a rather stable carbonium ion in the vicinity of the electron-donating substituent[65,128,134,135].

To explain the formation of products of the *cis*-opening of aryl oxides several schemes have been proposed. According to one of these, a double inversion with participation of the "phenonium" ion (LXVIII),[88] or of a four-membered oxide ring (LXIX),[98] is assumed to be possible in systems of the stilbene oxide or dypnone oxide type:

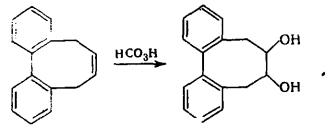


(LXVIII)



(LXIX)

These schemes have been criticised repeatedly[87,92,110], although decisive arguments against them have not been forthcoming. However, such hypotheses can explain only a few particular examples and in several other instances the formation of a "phenonium" ion is improbable (for example, phenylpropene, indene, etc.). Furthermore, it must be noted that the formation of a four-membered transition state, in particular (LXIX), is energetically unfavourable[137]. Nevertheless, the recently described *cis*-addition of the elements of performic acid to dibenzocyclooctatriene (LXX)[138] can be regarded as the result of the stabilisation of the corresponding transition state by a mechanism of the "phenonium" ion type:

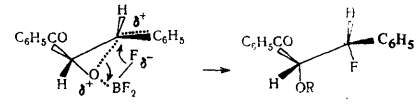


(LXX)

In fact, both reaction centres of the original alkene are homobenzylic and for such systems a transition state of type (XXXVI) cannot be represented.

According to the scheme which seems most probable at present, the *cis*-opening of the oxide ring is described by a "push-pull" process taking place in the "solvent cage".[92] Here the state of the mutual orientation of the C–O bond of the epoxide and the molecule of proton-donating nucleophilic reagent is considered. The molecules of the epoxy-compound and of the proton donor, being included in the "solvent cage", interact with one another in the way typical of hydrogen bond formation[3,6,98]. The "pulling" force here is the progressing protonation of the oxidic oxygen atom. As a result of this protonation there is a removal of the stress in the three-membered ring and the formation of a stabilised carbonium ion, together constituting the driving force of formation of a transition state of type (LXV). Because the elements of the "ion pair"[92,98] are favourably arranged in this way at the side of the nucleophilic reagent, a minimal "push" is required for converting the transition state (LXV) into the final product (LXVII) with the configuration of the initial oxide (LXVI). Here the role of the steric factors, which hinder the approach of the nucleophilic reagent, are probably insignificant.

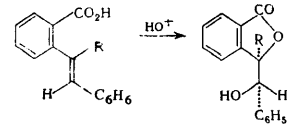
The "phenonium" ion and "ion pair" schemes have been widespread in the literature and there has recently been a worthy attempt to combine them[67]. However, the scheme involving the "ion pair" is preferred more often as it allows a large number of experimental facts to be explained. For example, by starting from these hypotheses the *cis*-opening of epoxides under the action of a Lewis acid can be described by a scheme which House[139] proposed when he obtained the *cis*-fluorohydrin on treating *trans*-benzalacetophenone oxide with boron trifluoride–diethyl ether:



where R = BF_2 or H.

An analogous succession of changes occurs apparently in the reaction of stilbene oxides with phenylmercaptoborane[79] and hexadeuteriodiborane[140].

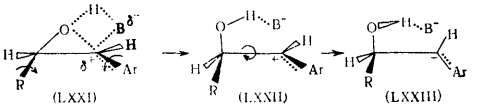
The idea of the orientated complex of the epoxide and the proton-donating nucleophilic reagent allow the influence of the solvent on the occurrence of the "sterically anomalous" opening of the oxide ring to be explained. In fact it is easy to suggest that the formation of this complex, considering the nature of the forces acting, which was discussed above, will be more probable in a non-polar (non-ionising) solvent. On the other hand, in an ionising solvent its destruction will be more probable. Therefore a greater percentage of configuration retention is to be expected in non-polar systems, which agrees with the results shown in Tables 1–3. Furthermore, in a polar (non-ionising) solvent the degree of dissociation of the acidic nucleophilic reagents considered in the tables is increased. This indicates that there is a simultaneous increase in both the number of protonated (and more solvated) epoxide molecules of the (XXXVI; A = H^+) type and the concentration of strongly nucleophilic ions RCO_2^- and X^-. Hence conditions are created for the attack of the oxide ring from any side and the probability of an energetically favourable bimolecular *trans*-opening increases. An analogous situation is observed when a nucleophilic reagent is fixed by the structure of the molecule itself so that attack with formation of inverted products is always possible, as occurs in the opening of the isomeric 2-stilbazole oxides[141] and the epoxidation of stilbene-2-carboxylic acids[142–144]. In these instances, irrespective of the polarity of the medium, *trans*-opening of the epoxide ring is observed exclusively, for example:



where R = H, CH_3.

This scheme explains the reduced stereospecificity observable during the opening of the *cis*-aryl epoxides (Tables

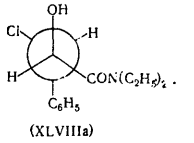
1 and 2), in which the "*cis*-effect"[145] of neighbouring bulky groups appears. This effect should facilitate the conversion of the transition state (LXXI) of the *cis*-aryl oxide into its extreme state (LXXII) with sp^2-hybridised benzyl carbon atom. For the same reason rotation of the plane of this centre around the C–C bond by 90° is possible before attack by the nucleophilic ion B^- takes place.



(LXXI) (LXXII) (LXXIII)

As a result of the isomerisation[67] of cisoid cation (LXXII) into the stable transoid one through intermediate state (LXXIII), a product should arise with inverted configuration of the initial oxide and such an explanation of its formation seems better founded than direct *trans*-addition of the nucleophilic reagent. The probability of the isomerisation should increase on using a polar solvent, just as it should on increasing the steric capacity of the neighbouring substituents (increase in the "*cis*-effect"). Tables 1 and 2 confirm this assumption. We can take as an example the epoxidation of the 4-methoxystilbenes by perbenzoic acid: from the *trans*-isomer only the *threo*-monobenzoate is obtained, whereas the *cis*-isomer gives a mixture of diastereoisomers (Table 1, Nos. 21–24). Analogous results are obtained in the opening of the stilbene oxide by hydrogen chloride (Table 2, Nos. 16–23). The observed preferential formation of reaction products with retention of the configuration of the *cis*-isomer does not agree with the behaviour of the same oxide in relation to chloroacetic acids, where there is *cis*-opening (Table 1, Nos. 14–16). Berti and coworkers[67] explain this difference by the reduced nucleophilic nature of the chloride ion in comparison with carboxylate ions, which attack the cisoid intermediate state of type (LXXII) before its isomerisation takes place. The results of Tung and Speziale on the opening of the *cis*-epoxypropionamide by hydrogen chloride (Table 2, Nos. 14 and 15) can be explained similarly,

Probably the already rather weak protonation of the oxide ring for the interaction between the two hindered bulky groups in the transition state (LXXI; R = $CONEt_2$, Ar = C_6H_5, B = Cl) led to the energetically more favourable state of type (LXXIII), the subsequent neutralisation of which gives the *threo*-chlorohydrin (XLVIIIa):

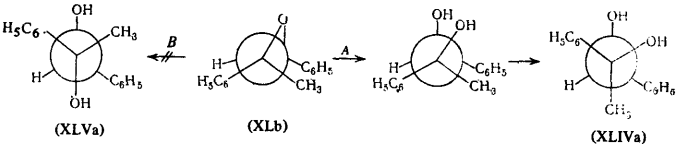


(XLVIIIa)

There is also the noteworthy fact that in the treatment of the *threo*-chlorohydrin (XLVIIIa) with sodium methoxide in addition to the expected *cis*-epoxypropionamide (XLVII; R = H, R′ = NEt_2) the *trans*-isomer (XLVI; R = H, R′ = NEt_2) is obtained, in the ratio 3 : 2. On the other hand, the *erythro*-chlorohydrin (XLIX; R = H, R′ = NEt_2, X = Cl) under these conditions is converted quantitatively into the *trans*-epoxypropionamide[102].

So far we have discussed examples which illustrate the dependence of the *cis*-opening of the oxide ring on the polarity of the solvent, on the nucleophilic nature of the reagent, and also on the steric factors which influence the formation of the transition state, leading to this type of result. It was noted above, however, that the secondary-tertiary α-methylstilbene oxide undergoes *cis*-opening irrespective of the polarity of the solvent (Table 1, Nos. 29–31). An analysis of the results in Table 2 allows a similar steric selectivity to be found for secondary-tertiary bromodiphenacyls and dypnone oxides.

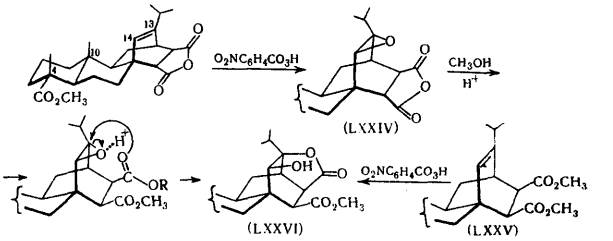
Purely qualitative consideration of the acid hydrolysis of *trans*-α-methylstilbene oxide (XLb) which takes place with breaking of the tertiary C–O bond[66] suggests with a high degree of probability that here also the predominating influence is the steric factor, which determines the formation of the energetically most favourable transition state. In fact, path *B*, as a result of which the *erythro*-diol (XLVa) should be formed, corresponding to the *trans*-opening of the initial oxide, requires the surmounting of a considerable energetic barrier in the transition state, due to the interaction of hindered methyl and phenyl groups.



(XLVa) (XLb) (XLIVa)

On the other hand, for the realisation of the transition state from which the experimentally observable *threo*-diol (XLIVa), with the configuration of the initial oxide, is obtained, the surmounting of a minimal energetic barrier is necessary (path *A*). It is easy to see that analogous considerations can lead to identical conclusions for the secondary-tertiary dypnone oxide and halogenodiphenacyl oxides. Unfortunately, a more rigorous discussion of these energetic factors is impossible owing to lack of quantitative data.

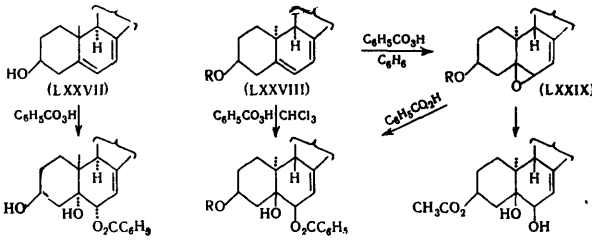
The influence of the steric factor on the direction of the acid-catalysed opening of an epoxide ring can be illustrated by the methanolysis of oxide (LXXIV) obtained from the adduct of methyl laevopimarate with maleic anhydride, and also the epoxidation of the unsaturated diester (LXXV)[146]. The *cis*-hydroxylactone (LXXVI) which is liberated in both instances with a yield of ~ 45% is evidently formed by intramolecular attack on the protonated epoxide by the solvated carboxyl group. Intermolecular attack of the nucleophilic reagent, leading to products of *trans*-opening, is probably hindered by screening of the $C_{(13)}$–$C_{(14)}$ bond by the axial methyl groups at $C_{(4)}$ and $C_{(10)}$. The examples examined show the possibility in principle in some instances of the *cis*-opening of epoxide in systems which differ from oxides of the (XXXV) type.



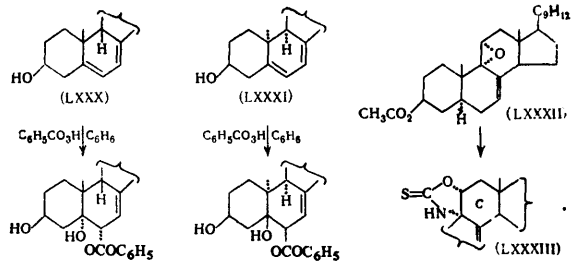
(LXXIV) (LXXVI) (LXXV)

3. *cis*-Opening of mono-oxides of conjugated dienes and of oxides of enol-esters. The *cis*-opening of monoxides of conjugated dienes was observed mainly in the steroid series. In every instance in discussing the reaction mechanism the stable allyl carbonium ion is considered, nucleophilic attack of which should be effected from the sterically least hindered region of the steroidal molecule. In fact, on treating ergosterol (LXXVII) with perbenzoic acid only the 5α,6α-glycol benzoate is formed[147]. On the other hand the conversion of

lumisterol (LXXVIII), which exhibits "unfavourable" combination of rings A, B, and C, leads exclusively to the 5β,6β-diol monobenzoate[148-150]:



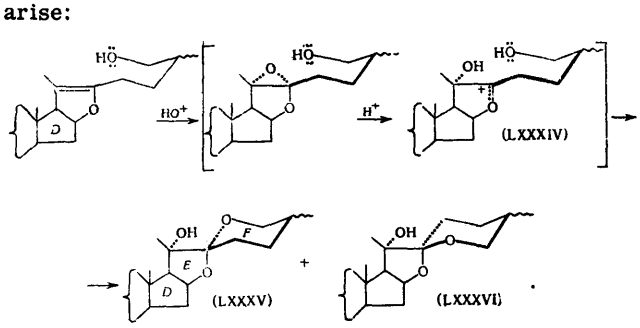
The opening by benzoic acid and water[148-150] of lumisterol β-oxide (LXXIX) obtained by oxidation of the diene (LXXVIII) in benzene[149,150] proceeds in an analogous manner. The epoxidation of 9β-ergosterol (LXXX) and of 9α-lumisterol (LXXXI) by perbenzoic acid in benzene is also accompanied by the formation of considerable quantities of the products of the *cis*-opening of the corresponding unstable allyl epoxides. The authors[151] think that the latter are intermediates in both reactions:



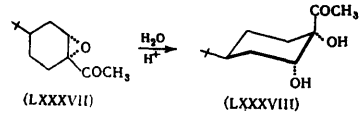
Mention must also be made of the result obtained by Ueda and Mosettig[152], who observed the *cis*-opening of ergostadiene 9α,11α-oxide (LXXXII) into the thio-oxazolidone (LXXXIII) in the presence of hydrogen thiocyanate.

Apart from what has been considered above there is hardly any published information on the "sterically anomalous" opening of other monoxides of conjugated dienes. Reference can only be made to results on the epoxidation of cyclopentadiene by peracetic[153] and performic[154] acids and the hydrolysis of the corresponding monoepoxides[155]. In every instance a complex mixture of products is obtained, among which *cis*-cyclopentene-1,2-diol is observed.

In the steroidal series several instances have been described of the stabilisation of the carbonium ion produced during epoxidation by the unshared pair of *p*-electrons of a neighbouring oxygen atom. Thus, in the treatment of pseudosapogenions with per-acids the kinetically controllable rear attack of the OH group of the side-chain of the stabilised carbonium ion (LXXXIV) can lead to the formation of products of *cis*-opening (LXXXV) of the intermediate oxide[156,157]. In the presence of destabilising thermodynamic factors[157] *trans*-opening products (LXXXVI) also arise:

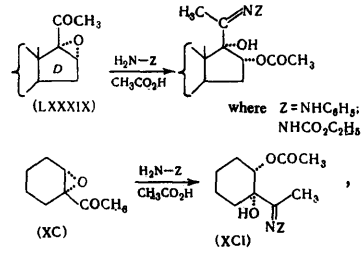


4. *cis*-Opening of oxides of conjugated ketones. Information has recently been published on the *cis*-opening of αβ-epoxyketones of the cyclohexane and steroid series under conditions of acid catalysis. The main distinguishing characteristic of these conversions is evidently the fact that in every instance, as will be shown below, the C–O bond in the α position to the keto-group of the initial epoxide is broken. This signifies the appearance in the corresponding transition state of a deficiency in the electron density adjacent to the carbonyl function. By virtue of the electron-withdrawing nature of the latter such a state should exhibit high energy[158,159]; however, there is the possibility of its being reduced, owing to enolisation of the C=O group[160]. Here the transition state will be represented by the special case of the states of type (XXXVI) considered above, and probably in acid hydrolysis of the keto-oxide (LXXXVII) it is partly realised with formation of the *cis*-diol (LXXXVIII)[161].



This example is still the only one in the keto-oxide series, analysis of the conversions of which is often hindered by the possible formation of secondary products as a result of enolisation, retroaldolisation, epimerisation, etc. taking place. All the remaining known instances of *cis*-opening relate to the reactions of keto-oxides in the presence of reagents at the carbonyl group.

Such a reaction was first described in the patent literature[162] as a method for obtaining substituted 16α,17α-glycols from pregnane 20-keto-16α,17α-epoxides (LXXXIX) in the presence of phenylhydrazine. The latter was soon replaced by ethoxycarbonylhydrazine (ECH)[163]. Subsequently it was shown by the example of acetylcyclohexene oxide (XC) that products with retained configuration (XCI) are also formed in the presence of semicarbazide, 2,4-dinitrophenylhydrazine, and hydroxylamine[164]

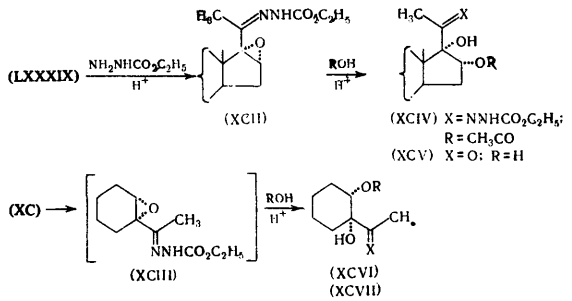


where Z = $NHCO_2C_2H_5$, $NHCONH_2$, $NHC_6H_3(NO_2)_2$, or OH.

As a result of a thorough study of the reactions of steroidal keto-oxides (LXXXIX) with ECH it was found that the opening of the epoxide ring precedes the formation of the corresponding carbonyl derivatives (XCII)[69,165,166], and in some instances the process almost stops at this stage[167,168]. An analogous sequence of changes is also observed in the cyclohexane series, although for the keto-oxide (XC) the intermediate ethoxycarbonylhydrazone (XCIII) could not be isolated[164].

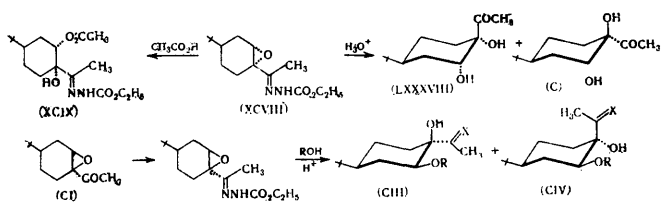
A detailed analysis of the way in which these reactions proceeded showed that the stages of "sterically anomalous" hydrolysis of the hydrazone-oxides (XCII) and (XCIII) and the removal of the hydrazone grouping from compounds of

the type (XCIV) and (XCVI) can coincide, which was verified in practice.



Hence the keto-oxides (LXXXIX) and (XC) could be converted, formally in one stage, into the corresponding *cis*-keto-glycols (XCV) and (XCVII)[169,170] and a synthesis of the latter in the steroidal series by this path is probably the simplest and most reliable[171].

Interesting results were obtained in investigating similar changes of the conformationally fixed stereoisomeric keto-oxides (LXXXVII) and (CI)[172,173]. In the presence of ECH they are also converted into ethoxycarbonylhydrazones (XCVIII) and (CII), the acetolysis of the α-isomer being strictly stereo-directed, leading exclusively to the secondary acetate (XCIX):



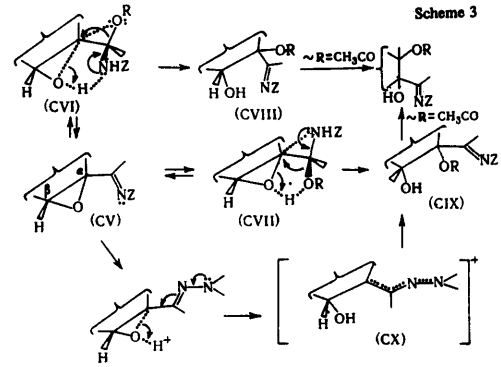
where X = O, $NNHCO_2C_2H_5$; R = H, CH_3CO.

The acid hydrolysis of the α-hydrazono-oxide (XCVIII) proceeds less selectively and gives a mixture of keto-glycols (LXXXVIII) and (C) in the ratio ~ 3 : 2. In acetolysis and hydrolysis of the β-isomer (CII) such selectivity in the opening of the oxide ring is not observed. However, in these instances in the mixture of products (CIII) and (CIV), the *trans*-diequatorial isomer (CIV) predominates. This emphasises the fact that as a result of the acetolysis of the ethoxycarbonylhydrazones of the oxides secondary acetates are isolated in all the examples examined.

The acid hydrolysis of the ditertiary oxide of 1-acetyl-2-methylcyclohex-1-ene in the presence of ECH gives a mixture of diastereoisomeric keto-glycols[168]. In this respect the results obtained are analogous to those given above for the conversion of keto-oxides (LXXXVII) and (CI) under the same conditions. However, with the conformationally labile ditertiary keto-epoxide an analysis of the results is hindered by the observed isomerisation of the product of the *cis*-opening of the oxide into the *trans*-glycol[168].

The available results, in particular those on the opening of the keto-oxides (XCVIII) and (CII) allow us to speak about the structural directionality of the conversions. Namely, in every instance the introduction of a molecule of water or acetic acid takes place at the carbon centre of the epoxide adjacent to the hydrazone group. The formation of secondary acetates of keto-diols is the consequence of the instability of the initially formed tertiary esters, which then undergo intramolecular reesterification[70,71]. These results show the presence of an electron-deficient α carbon atom of the hydrazono-oxide in its opening. The possibility of attack at this centre by molecules of nucleophilic reagents is shown in Scheme 3.

Scheme 3



According to Scheme 3, under the reaction conditions the carbonyl derivative (CV) is in equilibrium with the isomeric carbinolamines (CVI) and (CVII). As a result of the intramolecular attack of the residue OR situated in the immediate vicinity of the reaction centre keto-glycols and their derivatives (CVIII) and (CIX) are formed. Here it is considered[69,166] that the stabilisation of the electron-deficient α carbon centre in the transition states (CVI) and (CVII) is effected by the unshared p-pair of electrons of the oxygen and nitrogen atoms respectively. On the whole this scheme is similar to the "ion pair" scheme considered above.

However, it was shown that the keto-oxides (LXXXVII), (XC), and (CI) do not undergo opening on replacing the reagents for the carbonyl group by primary amines of various basicities[172-174]. This fact suggests the participation in the redistribution of the electron density of the second nitrogen atom of the hydrazine derivatives, or of the oxygen atom of the hydroxylamine derivatives. The protonation of the oxygen atom of the epoxide leads to the formation of transition state (CX) which is characterised by the presence of a positive charge on the α carbon atom, stabilised by $p\pi$-conjugation. Furthermore, it cannot be ruled out that stabilisation is effected by the unshared p-pair of electrons of the imine nitrogen atom of the hydrazonium group. The subsequent attack of this centre by the nucleophilic reagent can lead to products with either retention or inversion of the configuration of the original keto-oxide.

It should be noted that the schemes discussed allow these transformations to be considered as formally similar in mechanism to the reduction of a keto-oxide in the presence of chromium(II) salts[175,176], by the method of Huang-Minlon[177], by the method of Wharton and Bohlen[178], and also to conversions of α-substituted ketones in the presence of hydrazine derivatives[179-182]. At present it is quite difficult to choose between the schemes for the conversion of the carbonyl derivatives of cyclic $\alpha\beta$-epoxy-ketones that we have considered. In these systems, just as in a series of aryl oxides, the decisive role is evidently played by the nucleophilic nature of the reagent, the polarity of the medium, and also the steric and conformational factors.

---oOo---

The material considered on the "sterically anomalous" opening of an epoxide ring allows the conclusion that reactions leading to the formation of products with retention of the configuration of the initial oxide include the act of

interaction of the nucleophilic reagent with the deficit in electron density arising on one of the carbon centres of the epoxide ring in the transition state. The solvated carbonium ion intermediate is usually stabilised by π- or p-electrons adjacent to the epoxide ring grouping. The formation of products with retention of the configuration of the original epoxy-compound depends on the direction of nucleophilic attack, which is determined by the steric effects of the addition of the nucleophilic reagent to the carbon atom carrying a stabilised positive charge. In this discussion the term "sterically anomalous" opening of the oxide ring acquires formal significance.

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