THE LITHIUM ALUMINUM HYDRIDE REDUCTION
OF P-SUBSTITUTED STILBENE OXIDES

by

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INTRODUCTION

INTRODUCTION

The chemistry of the unsymmetrically substituted ethylene oxides is unique in that the reactions of the three-membered rings may theoretically yield isomeric compounds, whose identity depends on which of two carbon-oxygen bonds is cleaved. In the literature, there are recorded numerous attempts to elucidate the factors involved in the determination of the direction of ring opening. This is the important question both from a theoretical and a synthetic approach. It is toward this end that the experimental work and the theoretical discussions are directed.

This thesis sets forth the currently accepted view of the steric and the electronic factors involved in the direction of ring opening which we believe to be valid. The treatment of epoxide reactions from the viewpoint of the Transition State Theory provides a theoretical foundation for some of the electronic theories offered. In addition, it permits the advancement of new correlations between the nature of the reactants and the direction of ring opening.

This thesis further sets forth a study in the chemical reactions of p-substituted stilbene oxides. New information which concerns the electronic factors, evaluated in the absence of the steric effects, indicates that the effect of the substituent on the cleavage of the bond between the oxygen and the carbon atom adjacent to the substituted phenyl group is in the order $p\text{-CH}_3 > p\text{-H} > p\text{-Cl}$.

The effect of the substituent on the direction of ring opening is explained in terms of the interactions of the substituent and the epoxide linkage by means of the "Transition State Theory" and in terms of resonance in the initial state and the transition state which involves the carbon-carbon bond of the epoxide linkage.

It is hoped that the small contributions to the chemistry of the epoxides embodied in this thesis are of some value in the development of science and the progress of mankind.

THE REACTIONS OF EPOXIDES WITH LEWIS BASES

THE REACTIONS OF EPOXIDES WITH LEWIS BASES

Base Catalyzed Reactions of Epoxides

Classification of Epoxide Reactions

A broad survey of the available literature on the reactions of ethylene oxides and its substitution products has indicated the need for a systematic and logical classification of all of the reactions of ethylene oxides in terms of electronic theory. The ethylene oxide ring, in reality, has three reactive centers, two carbon atoms of relatively low electron density and an oxygen atom of relatively high electron density. Advantage may be taken of this fact to classify the reactions of epoxides into two major groups: (A) reactions with Lewis bases and (B) reactions with Lewis acids. The first of these groups, which comprise the chemical reactions of epoxides with Lewis bases may be classified into six categories based upon the relative acid-base strengths of the reactants and arranged in the order of decreasing basic character of the attacking reagent and increasing acidic character of the epoxide carbon atoms. The full significance of the acid-base relationships, hence of the classification, will be brought out in the discussion

of the factors which influence the direction of ring opening of unsymmetrically substituted ethylene oxides and in the application of "transition state theory" to epoxide reactions.

Anion attack.— Many examples are known in which epoxides are attacked by the anion of some salt, as illustrated in equation I, where B^- represents the anion. The reaction may then be completed in one of several important ways: (A) The reaction may be completed by the abstraction of a proton from the solvent or hydrolyzing media, (B) The reaction may be completed by an intramolecular condensation which, in the case illustrated for diethyl malonate, gives rise to a lactone (1), (C) The epoxidic oxygen may be eliminated to form an ethylene sulfide (2,3) and (D) The reaction may be completed by the formation of a new epoxide linkage (4).

Catalysis by the anion of the base.— A commonly used procedure in the reaction of epoxides with alcohols (5) is the addition of a small amount of sodium metal to the alcohol to form the alkoxide, followed by addition of the epoxide. The reaction of the epoxide with the anion and the uncharged molecule proceeds simultaneously, but apparently, the rate of attack of the anion and its regeneration is very much faster than the rate of attack of the uncharged alcohol. It may be noted that the concentration of the attacking anion is smaller here than in the case of I.

From the viewpoint of the mechanism of the reaction there is little difference between attack of an anion as described in the first category and true basic catalysis as described above. Hence, in accordance with current usage, the term, "base catalyzed reaction," will be used in reference to both types of reaction.

Catalysis by a weak base. - The reaction of epoxides with alcohols may be catalyzed by the addition of small amounts of certain amines such as pyridine and sterically hindered secondary and tertiary amines (6,7) as shown in equation III. Presumably, the function of the amine is to increase the nucleophilic character of the attacking Lewis base.

III.

Uncatalyzed reactions. - The reaction of an epoxide with an uncharged Lewis base such as methanol (IVa) usually requires more vigorous conditions in the absence of a basic or acidic catalyst (5). Primary, secondary, and tertiary amines (8) readily react with epoxides in the presence of alcohol or water. Apparently, a source of protons other than the amine is necessary for the completion of the reaction as shown in equation (IVb).

IVa.

IVb.

Catalysis by a strong acid.— The reaction of epoxides with such bases as alcohols (5) or amines (10,11) may be catalyzed by strong acids. The first step, apparently, involves the formation of an oxonium ion. The oxonium, as suggested by King, Berst, and Hayes, (10) is then subject to direct attack at the carbon atom as shown in equation VIa, or as proposed by Kadesch (12) for the case of butadiene monoxide, the oxonium may undergo a unimolecular ring opening followed by attack of the base on the intermediate carbonium ion as shown in equation VIb.

VIa

VIb

Mechanism of Base Catalyzed Reactions of Epoxides

The mechanism of the base catalyzed reactions has been established as a bimolecular nucleophilic attack of the reagent on the ring carbon atom. Kinetic studies and studies of the Walden inversion have aided in the elucidation of the mechanism.

Kinetics.—Hansson (13), Ferrero, Berbe, and Flamme (14), Potter and McLaughlin (15), Smith and Nilsson (16) and Smith, Mattson and Anderson (17) have reported that the rate of reaction of epoxides such as ethylene oxide, propylene oxide, epichlorohydrin and glycidol with ammonia and primary, secondary, and tertiary amines is first order with respect to the attacking reagent. Eastham and Darwent (11) and Eastham, Darwent, and Beaubien (8) also reported second order rate constants for the reaction of ethylene oxide with amines. Barker and Cromwell (18) reported, similarly, that the reaction of epoxybenzylacetophenone with morpholine is also a second reaction. Banerjee and Sen (19), Bronsted, Kilpatrick, and Kilpatrick (20), Porret (21), Ross (22) and Sen, Barat, and Pal (23) have demonstrated bimolecular kinetics for the reactions of ethylene oxide, propylene oxide, cyclohexene oxide, epichlorohydrin and glycidol with reagents such as ammonium and alkali halides, thiocyanates and thiosulfates.

Walden Inversion.- Walden inversion has been demonstrated by Grigsby, Hind, Chanley, and Westheimer (24) in the reaction cyclopentene oxide with ethyl malonate ion. Newman and VanderWerf (25) found that the reaction of cyclohexene oxide with the malonate ion also proceeds with Walden inversion. McCasland, Clarke, and Carter (26) and Winstein and Boschan (27) obtained the trans-amino-alcohol and thus established a Walden inversion in the reaction of cyclohexene oxide with ammonia. Similarly, McCasland and Smith (28) and Fodor and Kiss (29) proved that inversion occurs in the reaction of cyclopentene oxide with ammonia. Heisler (30) recently established a Walden inversion in the reaction of cyclopentene oxide and cyclohexene oxide with sodium azide. Numerous Walden inversions have been reported in the reactions of anhydro sugars (31) with ammonia, water, alcohols, and mercaptans. Boeseken and van Loon (32) established inversion in the alkaline hydrolysis of indene oxide. Godchot, Mousseron, and Richaud (33) recorded an inversion in the uncatalyzed hydrolysis of cyclopentene oxide, and Swern (34) established Walden inversion in the alkaline hydrolysis of 9,10-epoxystearic acid. By means of meso- and D(+)-2,3-epoxybutane, Dickey, Fickett, and Lucas (35) proved an

inversion in the reaction with ammonia. In view of the available evidence, there is little doubt that the base catalyzed reactions of epoxides involves a bimolecular nucleophilic attack on the ring carbon atoms.

It is worth noting that Bartlett and Ross (36), in the sodium methoxide catalyzed reaction of methanol with butadiene monoxide, obtained evidence in favor of a bimolecular nucleophilic attack at both the primary and the secondary carbon atoms. When seven times the normal amount of catalyst was added, the ratio of products remained unchanged. If attack on the primary position involved direct participation of the methoxide ion and the attack on the secondary position did not, a ratio of secondary alcohol-primary ether to primary alcohol-secondary ether seven times greater than previously observed should have resulted.

The Direction of Ring Opening

The striking fact about the base catalyzed reactions of the epoxides is that the reagents exhibit strong preferential attack at the primary carbon atom of propylene oxides, butadiene monoxides, and styrene oxides. As the facts to be presented suggest, reactions of butadiene monoxide are more likely to result in attack at both the primary and the secondary carbon atoms than styrene

oxide, whereas mixtures in the case of propylene oxides are rarely reported. With few exceptions, attack occurs mainly at the primary carbon atom in the three classes of epoxides.

Propylene oxides.~ In the case of the base catalyzed reactions of propylene oxide, an overwhelming number of reports show attack at the primary carbon atom. Thus, none of the product which corresponds to attack at the secondary carbon atom has been reported in the following cases: ammonia (37,38) methylamine (39,40), ethylamine (41), isopropylamine (42), benzylamine (42), ethanolamines (43), dimethylamine (44,45), diethylamine (45-47), piperazine (48,49), morpholine (50,51) anasabine (52), tetrahydroquinoline (53), decahydroquinoline (54), acetoacetic ester (55,56), cyanoacetic ester (57), malonic ester (1), diphenylacetonitrile (51,58,59), sodium phenolate (61-63), thiophenols (64,65), methyl, ethyl, allyl, and other alcohols (5,66,-69), ^{and} sodium azide (30), ~~and lithium aluminum hydride (70).~~ The review of epoxide reactions by Winstein and Henderson contains additional examples of reagents which attack exclusively at the primary position of analogs of propylene oxide.

Only a few authors record the formation of the product which corresponds to attack at the secondary carbon atom of propylene oxide and its analogs. Thus, Chitwood and Freure (5) reported a trace of primary alcohol-secondary ether in the reaction of propylene oxide with ethanol catalyzed by sodium hydroxide. Swern, Billen, and Knight (69) obtained evidence for attack at both carbon atoms, with primary attack predominating in the reaction ^{of glycidol} with allyl alcohol.

Butadiene monoxide.— Ettlinger (2) found that the reaction of butadiene monoxide with ammonia gave attack mainly at the primary carbon atom, but that some of the isomer which corresponds to attack at the secondary carbon atom could be isolated and identified. Bartlett and Ross (36), in the reaction of butadiene monoxide with methanol, reported the formation of secondary alcohol-primary ether, which corresponds to primary attack, together with smaller amounts of the isomer. Adams and VanderWerf (56) also found that acetoacetic ester gave a mixture of isomers. Zuidema, Cook, and Van Zyl (71) reported a mixture in the reaction with cyanoacetic ester, but structures have not as yet been assigned. Trevo and Brown (72) and Fuchs (73) found that lithium aluminum hydride attacked the epoxide

mainly at the primary carbon atom, but some of the isomer which results from attack at the secondary carbon atom was isolated and identified. Swern, Billen, and Knight (69) reported exclusive attack at the secondary carbon atom of butadiene monoxide in the reaction with allyl alcohol. Heisler (30) found that in the reaction of butadiene monoxide with sodium azide, attack occurred exclusively at the secondary carbon atom in preference to primary attack.

A few cases have been reported in which none of the product corresponding to attack at the secondary carbon atom was isolated or identified. Thus, in the reaction of butadiene monoxide with alcohols, catalyzed by alcoholates, Petrov (74-76) and Kadesch (12) reported only the isolation of secondary alcohols. Russel and VanderWerf (1), in the reaction with malonate ion, obtained the product which corresponds to exclusive attack at the primary carbon atom, as did Massie (77) in the reaction with mercaptans.

Styrene oxide.- Reeve and Christoffel (78) found that the methanolysis of styrene oxide yielded the product corresponding mainly to attack at the primary carbon atom. Kaelin (79) also found some evidence for attack at the secondary carbon in the same reaction.

Mannich, Neumann, and Jacobsohn (80) reported a mixture in the reaction of 3,4-dimethoxystyrene oxide with secondary amines. In the reaction of styrene oxide with allyl-alcohol, Swern, Billen, and Knight (69) obtained a mixture containing 90% of a product which they identified as 2-allyloxy-2-phenylethanol and 10% of the isomer. Hayes and Gutberlet, however, re-ran the reaction and concluded that the assigned structures were incorrect and that the base catalyzed reaction with allyl alcohol actually gives mainly primary attack. Kaelin (79) reported that the methoxide ion attacked 3,4-diacetoxystyrene oxide exclusively at the secondary carbon atom. McEwen, Conrad, and VanderWerf (82) also reported exclusive attack at the secondary carbon atom with the azide ion.*

Several reports have appeared in the literature in which the product corresponding to attack at the secondary carbon of styrene oxide**was not isolated or identified, among which are the following: dimethylamine (83), diethylamine (84), secondary amines (85),

* The possibility of isomerization of the primary azido-secondary alcohol, if formed, to the secondary azido-primary alcohol may be considered.

** Cristol and Helmreich (295) recently reported that the ethyl malonate ion attached exclusively at the primary carbon atom of p-nitrostyrene oxide.

mercaptans (77,86), allyl alcohol (69,81), 5-ethyl barbituric acid (87), lithium aluminum hydride (72), acetoacetic ester (56), and malonic ester (1,87).

Contradictory reports.- Several reports have appeared in the literature which give evidence for attack at the secondary carbon atom, but these have not been substantiated. Thus, the work of Emerson (88) was denied by Reeve and Christoffel (32). Swern, Billen and Knight (69) reported that the reaction of styrene oxide with the allyl oxide anion gave attack mainly at the secondary carbon atom. Doubt was cast upon the identity of the products isolated by the work of Hayes and Gutberlet. (81). Haworth and Richardson (89) reported that the reaction of safrole oxide with the acetoacetic ester carbon ion attacked at the secondary carbon atom, but the conclusions drawn were contradicted by the subsequent work of Haworth and Atkinson (90) and Fuchs (73). Carpmael (91) reported that he obtained α -aceto- β -methylbutyrolactone in the condensation of acetoacetic ester and propylene oxide. Buchman and Richardson (55) and Adams and VanderWerf (56), however, established that the acetoacetic ester anion attacks exclusively at the primary carbon atom and not the secondary carbon atom, as indicated by Carpmael.

Theory of the Direction of Ring Opening

The application of modern electronic theory, the reinvestigation of epoxide reactions in doubtful cases, and excellent work on new reactions has thrown new light on the question of the direction of ring opening. Not all of the factors involved in displacement reactions as they apply to epoxide reactions are, however, well understood. Several of the factors which may be considered are:

- (1) Energies of repulsion between the epoxide carbon atoms and the attacking reagents.
- (2) Bond strengths of the oxygen-carbon linkages.
- (3) Base strengths of the attacking reagents.
- (4) Resonance in the initial state.
- (5) Resonance in the transition state.
- (6) Polarizability of the bond between the substituent and epoxide carbon atom.
- (7) Hyperconjugation.
- (8) Polarization of the carbon-carbon epoxide bond.
- (9) Steric effects: primary carbon atoms vs. secondary carbon atom.
- (10) Steric effects: size of substituents on the ring.
- (11) Steric effects: size of the attacking group.
- (12) Steric inhibition of resonance.
- (13) Steric effect of a neighboring group.
- (14) Steric configuration of the epoxide.

Repulsion energies.— Chitwood and Freure (5) suggested that the electron-releasing effect of the methyl group in propylene oxide was responsible for the almost exclusive attack of the methoxide ion on the primary carbon atom. In the absence of other factors, an electron-releasing group should increase the electron density on the adjacent carbon atom which would leave the primary carbon atom with a relatively low electron density. The base would then attack preferentially at the carbon of lower electron density because of the lower repulsion energy, i.e., the primary carbon atom.

It is known, however, that displacement reactions occur more readily at a primary than at a secondary carbon atom (92). In this particular case, then, the two factors, electronic and steric, lead to the same product, and it becomes difficult to determine the relative contributions of the factors which direct the attack at the primary carbon atom.

That the repulsion energies alone are not the decisive factor in determining the direction of ring opening is made clear in the case of epoxides with electron withdrawing groups. Electron-withdrawing groups (93)* such as the chloromethyl, alkoxymethyl, vinyl, and phenyl should decrease the electron density on the secondary carbon atom more than the primary carbon atom. Hence, attack should occur preferentially at the secondary atom due to the lower energy of repulsion. The vast majority of reports in the case of epichlorohydrin and the glycidyl ethers indicate, however, that predominant attack occurs at the primary carbon atom. This points to the importance of the steric factor.

Nevertheless, butadiene monoxide and styrene oxide do give substantial yields of the product which corresponds to attack at the secondary carbon atom. While this has been attributed to the fact that the vinyl and the phenyl

* The assignment of an $-I_E$ (electron-withdrawing) effect is based upon measurements of the ionization constants of substituted acetic acids which appears in International Critical Tables, VI, 264. Also see ref. 94(a).

groups are electron withdrawing groups, it is inconsistent with the fact that the chloromethyl and alkoxy-methyl epoxides do not give attack at the secondary carbon atom. Furthermore, the fact that butadiene monoxide and styrene oxide give products which correspond to secondary attack may be attributed to resonance in the transition state and to polarization of the bond between the secondary carbon atom and the substituent.

As noted, observations of the inductive effect (electron-withdrawing and electron-releasing effects) on the repulsion energies are obviously obscured by the steric effect in monosubstituted ethylene oxides. While the effect of substituent on the direction of ring opening may be evaluated theoretically, experimental verification without elimination or minimization of the steric factors appears to be impossible in the cases cited.

Bond strengths.- Swern, Billen, and Knight (69) suggested that the effect of the substituents on the bond strengths of the ring carbon-oxygen bonds may be important in the determination of the direction of ring opening. An electron-releasing substituent would be expected to weaken the secondary carbon-oxygen bond more than the primary carbon-oxygen bond, since the secondary

carbon is relatively more negative than the primary carbon atom. This will facilitate attack at the secondary carbon atom. An electron-withdrawing substituent should facilitate attack at the primary carbon atom due to the greater strength of the secondary carbon-oxygen bond.

IX.

X.

It may be noted that bond strength considerations and repulsion energy considerations lead to opposite predictions of the direction of ring opening.* The relative contributions of repulsion energies and bond strengths to the direction of ring opening will be treated systematically in the discussion of the transition state theory as applied to epoxide reactions.

Base strengths.— Fournneau and Billeter (95) reported that in the reactions of β -phenylglycidic esters and amides with amines aniline attacked at the α -carbon atom, whereas dimethylamine attacked at

* Remick (94b) discusses the reversal of the substituent effect for simple base displacement reactions.

the β -carbon atom. They attributed this to the fact that the amines differ in base strength. The effect of base strength on the direction of ring opening is intimately connected with repulsion energies and bond energies. Its theoretical foundations will be discussed in the transition state treatment of epoxide reactions where additional evidence will be presented.

Resonance in the initial state.— Tamelen, Van Zyl, and Zuidema (96) suggested the possibility of resonance stabilization in the initial state of the 3, 4-dihydronaphthalene-1,2-epoxide molecule as being responsible, in part, for directing the attack of the diethylmalonate anion at the α -carbon atom.

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As they pointed out, the resonance theory, although useful, is inadequate when applied without consideration of the steric factors, since malonic ester anion attacks styrene oxide at the primary carbon atom, whereas, resonance favors attack at the secondary carbon atom. The attack of the malonate ion on the dihydronaphthalene oxide molecule,* in which the steric factors are minimized, is at the carbon atom favored by resonance stabilization.

Resonance in the transition state.- Bartlett and Ross (36) introduced the concept of resonance stabilization in the transition state to explain the formation of some primary alcohol in the reaction of butadiene monoxide with methanol. Adams and VanderWerf (56) applied the theory to explain the attack of the acetoacetic ester anion on the secondary carbon atom of butadiene monoxide. The theory may, in fact, be applied to all the base catalyzed reactions of styrene oxide and its nuclear substitution products and of butadiene monoxide where products which correspond to attack at

* See ref. 97.
Evidence is cited to the effect that piperidine attacks 3,4-dihydronaphthalene oxide at the β -carbon atom.

the secondary carbon atom were identified.

XII.

It appears, then, that although the effect of resonance stabilization may be observed in the reactions of butadiene monoxides and styrene oxides despite the steric factors, the minimization of the steric factors, as in the dihydronaphthalene oxide reaction, clarifies the resonance effect even further.

Polarizability.— Alexander (98) suggested that in base catalyzed reactions of butadiene monoxide the attack of the base on the secondary carbon atom is facilitated

by the polarizability of the adjacent vinyl group. The demand of the attacking base is an electron deficient center, and since the electron sink, in the form of a vinyl group, is on the secondary carbon atom, this should be the favored point of attack.

The theory may, as in the case of resonance stabilization in the transition state, be applied to those reactions of butadiene monoxides and styrene oxides in which attack at the secondary carbon atom occurs.

Kadesch (12) schematically suggested that in the reaction of butadiene monoxide with methoxide ion, the attack at the primary carbon atom is facilitated by the electron-release effect of the vinyl group which stems from polarization of the double bond.

This cannot be. It would appear that since the demand of the methoxide ion is for an electron deficient center, only an electron withdrawing group may aid the attack, and in this case, the attack at the secondary carbon atom would occur preferentially as suggested by Alexander (98). The attack at the primary carbon atom may, perhaps, best be explained by steric considerations.

Hyperconjugation.- Rogers (99) suggested that the dipole moments of ethylene oxide and propylene oxide are in the direction to be expected for significant contributions from structures of type X.

It may be noted that, in the transition state, hyperconjugation would favor attack at the secondary carbon atom due to resonance stabilization. Since it appears that the steric factors overshadow the electronic factors, it is not possible in the case of propylene oxide to study the inductive effects of the methyl group or of hyperconjugation on the direction of ring opening. The role of

hyperconjugation will be treated more extensively in the discussion of the experimental results.

Polarization of the carbon-carbon epoxide bond.

A number of studies have shown that ethylene oxides behave in many ways like the corresponding ethylene derivatives. The ultraviolet absorption bands of compounds with an epoxide linkage adjacent to a double bond tend to occur at wave lengths between those of the analagous compounds with alkyl groups adjacent to the double bond and those with conjugated double bonds, but whose maxima are usually observed closer to those in the conjugated systems. This is illustrated in Table I (99).

Table I

The Absorption Maxima of Styrene Oxide
and the Corresponding Saturated
and Unsaturated Compounds

	$\lambda_{\text{max.}} \text{ \AA}^\circ$
Ethylbenzene	2060
Styrene Oxide	2120
Styrene	2455

As Rogers (99) pointed out, the electrons of the ring bonds must be more loosely held than those of the usual single bonds and the corresponding orbitals also must have a larger extension in space. It is

possible, then, that the carbon-carbon bond of the epoxide is more easily polarized than the carbon-carbon bond of a straight chain alkyl group, in a manner similar to an ethylene linkage. We should like to suggest that the effect of a substituent group on the direction of ring opening of an epoxide is in accord with its effect on the polarization of the carbon-carbon bond, just as is the case when the two carbon atoms concerned are multiply bonded. Electron withdrawing groups such as the chloromethyl and the alkoxymethyl groups may be expected to aid attack of the base on the primary carbon atom in preference to the secondary carbon.

The observed facts are that primary attack predominates in both the case of an electron-withdrawing group and an electron-releasing group. As previously pointed out, the steric factor is probably more important than the electronic factor which accounts for the observed direction of ring opening. To evaluate

properly the electronic effect of a substituent on the direction of ring opening, it becomes necessary to minimize or eliminate the steric factors. Experimental evidence will be presented in the discussion of the p-substituted stilbene oxides — where the steric factors are minimized — which supports the contention that the effect of a substituent on the polarization of the carbon-carbon bond of the epoxide plays a major role in the determination of the direction of ring opening.

Accessibility of the carbon atoms.— Steric factors have only recently been considered in the reactions of epoxides with Lewis bases. Tamelen, Van Zyl, and Zuidema (96) suggested that the accessibility of the ring carbon atoms may outweigh the electronic factors in determining the direction of ring opening. As evidence, they cited the fact that, in the reaction of styrene oxide with the malonate ion (1), the attack occurred exclusively at the primary carbon atom in preference to the carbon adjacent to the phenyl group, whereas, in the reaction of 3,4-dihydronaphthalene-1,2-oxide (96), the attack occurred exclusively at the carbon adjacent to the phenyl group. In both cases, based on resonance in the initial state and in the transition state, it would be expected that attack

occur mainly at the carbon adjacent to the phenyl group. The difference in the mode of attack was attributed to the fact that the alpha-position in the dihydronaphthalene oxide is less sterically hindered than the secondary carbon atom in styrene oxide. Winstein and Henderson (100) suggested the order of preferential attack of a base on the epoxide carbon atom as primary > secondary > tertiary.

Size of the substituent.- Adams and VanderWerf (56) suggested that the size of the substituent on the ethylene oxide ring, in part, determined the direction of ring opening. It was found that the reaction of styrene oxide with acetoacetic ester anion gave attack at the primary carbon atom exclusively, but that butadiene monoxide with the same anion gave a mixture of isomers. This was attributed by them to the smaller size of the vinyl group, compared to the phenyl group. This is further confirmed by the frequency with which attack at the secondary carbon has been reported in butadiene monoxide compared to styrene oxide.

Steric factors: Size of the attacking group.- Adams and VanderWerf (56) also suggested that the size of the attacking reagent, in part, determined the direction of ring opening. The reaction of butadiene monoxide with the malonate anion was reported by

Russel and VanderWerf (1) to yield the product which corresponds to attack at the primary carbon atom exclusively, while with butadiene monoxide and acetoacetic anion, a mixture was obtained. This was attributed to the fact that the acetoacetic ester anion is less bulky than the malonate ion.

Steric inhibition of resonance.- The possibility of steric inhibition of resonance in the transition state may also be considered. It is possible, for example, to assume that the attack of the diethyl malonate anion on the primary carbon atom, exclusively, is due to steric interference with the coplanarity requirement of the resonance system.

Neighboring group effect.- Furst and Plattner (101) and Pataki, Rosenkrantz, and Djerassi (102) found that in the lithium aluminum hydride reductions of steroid epoxides of the allo series, where the hydrogen at the 5-position is trans to the methyl group at the 10-position, the attack on 2(α), 3(α)-epoxides is at the less hindered 2(β)-position which results in the formation of the 3(α)-hydroxy steroid. This is in contrast to the reduction of the 2(β), 3(β)-epoxides where the attack is at the 3(α)-position and

results in the formation of 2(β)-hydroxy steroids.

The evidence, then, justifies the conclusion that the steric effect of hydrogen in the 5-position affects the direction of ring opening.

Plattner, Heusser, and Feurer (103) reported that reduction of α - and β -cholesterol acetate oxides with lithium aluminum hydride led to attack at the 5-position in the β -cholesterol acetate and at the 6-position in the α -cholesterol acetate.

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The evidence again appears to justify the conclusion that a neighboring group - in this case, the acetoxy group - may affect the direction of ring opening.

Configuration of the epoxide.- Fourné and Benoit (105) reported still another example of steric factors influencing the direction of ring opening. The diastereoisomers—pseudoephedrine, and l-ephedrine—were converted to the respective alpha-phenyl-propylene oxides* by deamination of the cholines, a reaction which involves a single inversion. The d-epoxide obtained from l-ephedrine on reaction with

* The stereospecificity exhibited by these epoxides was brought to our attention by R. Heisler (30) Alexander and Dittmer (106) in the acid catalyzed isomerization of cis- and trans-2,3-epoxybutane, clearly proved the importance of stereochemistry in the reactions of epoxides.

XXII.

methylamine yielded a mixture of l-ephedrine and d-isoephedrine. The racemic epoxide obtained from pseudoephedrine on reaction with methylamine yielded exclusively pseudoephedrine.

Steric hindrance has also been observed in the reactions of the sugar epoxides. Prins (104) reduced methyl 2,3-anhydro-4,6-benzylidene- α -D-mannopyranoside with lithium aluminum hydride and obtained the product corresponding to attack at the 3-position. Apparently, the 2-position is more sterically hindered than the 3-position. In contrast, methyl 2,3-anhydro-4,6-benzylidene- α -D-allopyranoside on reduction gives the product which corresponds to attack at the 2-position.

Transition State Theory

The generalized theory of the transition state* as extended by Hinshelwood, Laidler, and Timm (108) may be applied to the reactions of epoxides in an effort to evaluate the electronic factors affecting the direction of ring opening. Consider a typical displacement reaction:

which can be broken up into four steps involving four energy factors:

E_1 may be taken as the repulsion energy of A for B - C, E_2 as a function of the bond strength of B - C, E_3 as a function of the bond strength of A - B, and E_4 as a function of the repulsion energy of A - B for A - C.

Two assumptions may now be made in order to evaluate the effect of substituents on reaction rates; first,

* Remick (94C) and Waters (107) discuss the application of transition state theory to simple three center reactions.

that changes in reactivity which result from electrostatic displacements caused by substituents are due primarily to changes in the energy of activation and second, that the additional charges on a given atom as a result of the electronic displacements introduce an extra electrostatic term into the energy of the bond between the given atom and its neighbor, and this may be calculated as though it were a classical coulombic term.

Let e_A , e_B , and e_C represent the effective charges on A, B, and C respectively, X , the inter-atomic distances, and W , the resonance contribution. Then,

$$E_1 = W_1 - \int_{\infty}^{r_a} \frac{e_A e_B dx}{x^2} = W_1 + \frac{e_A e_B}{r_a} \quad (\text{XXV})$$

$$E_2 = W_2 - \int_{r_1}^{r_c} \frac{e_B e_C dx}{x^2} = W_2 - \frac{e_B e_C}{r_c} \left(\frac{r_c - 1}{r_1} \right) \quad (\text{XXVI})$$

and $E = E_1 + E_2$.

If an H atom in the group B is substituted by R the effective charge on B is changed. ~~Let this change~~

Let this change be δe_B , hence it follows that

$$\Delta E_1 = \frac{e_A \delta e_B}{r_A} \quad \text{and} \quad \Delta E_2 = \frac{-e_C \delta e_B}{r_C} \left(\frac{r_C}{r_1} - 1 \right)$$

XXVII.

XXVIII.

Note that the two effects are in the opposite direction.

In general it will be found that as a result of introducing a substituent, changes in the energy of repulsion, ΔE_1 , will be far more pronounced than changes in the bond energy, ΔE_2 , assuming that e_A and e_C are of the same order of magnitude. A substituent will, in other words, increase the energy of activation, E , if it increases the repulsion between the attacking reagent and the seat of the reaction in the molecule attacked and vice versa.

Consider the case of ethylene oxide which contains two reactive centers and where the group being expelled is identical for both centers. It follows that the rate of attack at both carbon atoms in ethylene oxide is the same.

Substitution of an electron withdrawing group gives:

Compared to ethylene oxide, δe_B of the β -C atom is greater than the δe_B of the α -C atom. Since δe_B is positive and e_A negative, then ΔE_1 is negative. Since ΔE_2 is assumed to be small, the change in the energy of activation, ΔE , for attack at the β -C atom is more negative than ΔE for attack at the α -C atom. The attack of the group B^- will take place preferentially at the point of lower energy of activation, hence, at the β -C atom. While the rate of attack at both carbon atoms is increased, the rate at the β -C atom is increased more. The conclusion, then may be drawn that, insofar as repulsion energies are critical, introduction of an electron withdrawing group into the ethylene oxide molecule will aid the attack of the Lewis base at the secondary carbon atom, i.e., the β -C atom. Similarly, the introduction of an electron-releasing group will aid attack at the primary carbon atom.

Now consider variations of R in the monosubstituted ethylene oxides. Let R' be more strongly electron withdrawing than R. The effect of changing from R to R' is in the same direction as changing from H to R in ethylene oxide since the e_B on the β -C atom in XXX is more positive than the e_B on the β -C atom in XXX'. The energy of activation, therefore, is less for attack at the β -C atom in XXX than in XXX'. We may conclude,

then, the greater the electron - withdrawing ability of a substituent in ethylene oxide, the more likely the attack at the secondary carbon atom, i.e., the β -C atom and vice versa. $R \leftarrow \overset{\delta^+}{CH} - \overset{\delta^-}{CH_2} \quad \text{xxx} \quad R \leftarrow \overset{\delta^+}{CH} - \overset{\delta^-}{CH} \quad \text{xxx} \quad 1.$

In the treatment so far, we have considered variations in the epoxide substituents assuming that ΔE_2 , the change in the bond energy brought about by the substituent, is small compared to ΔE_1 , the change in the repulsion energies. If, however, e_A were small compared to e_O then ΔE_2 would become the predominant factor. Hence, it may be stated that with the weakening or removal of any well defined charge in the attacking reagent, the effect of the substituent will be determined more by its effect on the bond strength of the bond being broken in the molecule and less by its effect on the repulsion energies.

In the case where R, an electron withdrawing group, is substituted in the ethylene oxide molecule and where the attacking base is A, which has no well defined charge, the rate of attack on the ring carbon atoms will now be determined by the relative bond strengths of $O-\alpha-C$ and $O-\beta-C$ bonds. The effect of an electron withdrawing group is to strengthen the $O-\beta-C$ more than the $O-\alpha-C$ bond. We may conclude, then, that in the case of an electron-withdrawing group,

the weaker the attacking base, the more likely the attack at the primary carbon atom. Similarly, in the case of an electron-releasing group, the weaker the attacking base, the more likely the attack at the secondary carbon atom.

Chitwood and Freure (5) reported that the uncatalyzed reaction of propylene oxide with ethanol led to a mixture of isomers containing 56% of the secondary alcohol corresponding to attack at the primary carbon atom, whereas, the sodium ethoxide catalyzed reaction gave 83% of the secondary alcohol and none of the primary alcohol. They attributed this to the fact that the non-catalytic reaction is less specific in its course because the higher temperatures needed to give a suitable reaction rate lessens the directive effect of electronic density.

An alternative explanation may be offered in terms of the generalization developed by application of the transition state theory; namely, that in the case of an electron-releasing group, i.e., the methyl group, the weaker the base, the more likely the attack at the secondary carbon atom. Thus, in the uncatalyzed reaction of propylene oxide with methyl alcohol, the molecule which attacks is uncharged, whereas, in the base cata-

lyzed reaction, the attacking group is the negatively charged methoxide ion. Based on the generalization, some attack at the secondary carbon atom might be expected in the uncatalyzed reaction. The effect of the catalyst is actually to speed up the reaction at the primary carbon atom much more than at the secondary carbon atom.

Fourneau and Billeter (95), in the reactions of phenylglycidic esters and amides, reported that aniline attacked the glycidic compound at the α -O atom, whereas dimethylamine attacked at the carbon atom adjacent to the phenyl group. They attributed this to the fact that aniline is a weaker base. This is in line with the generalization that base strength may affect the direction of ring opening.

The discussion on changes in base strength, up to this point, assumed that the energy contribution, W , of the reagents to the total energies of activation is constant. This may be true for a given base and its substitution products, i.e., methyl and ethyl alcohol. The assumption may not be true for reagents which differ in functional groups, i.e., alcohols and amines. The effect of a change in functional grouping may be evaluated separately.

The Reactions of Epoxides with Lewis Bases
Acid Catalyzed Reactions of Epoxides

Direction of Ring Opening

The outstanding fact in the acid catalyzed reactions of propylene oxides, butadiene monoxides, and styrene oxides is that mixtures of the isomeric compounds are obtained which usually contain a much higher proportion of the product corresponding to attack at the secondary carbon atom than in the case of the base catalyzed reactions. The effect of the catalyst, then, is to increase the rate of attack at the secondary carbon atom much more than at the primary carbon atom.

Propylene oxides.- Chitwood and Freure (5) found that the reaction of propylene oxide with alcohol gave mainly attack at the primary carbon atom with some attack at the secondary carbon atom. Reeve and Sadle (66) reported, similarly, that the oxide with methanol gave mainly primary with some secondary attack. Sexton and Britton (62) obtained a mixture in the reaction with phenols and Scheutz (65) indicated the same for thiophenols. Petrov (67,68) also reported mixtures in the acid catalyzed reactions of propylene oxide with alcohols. Smith (109), Fosberg and Smith (110) and

Fickett, Garner and Lucas (111) obtained mixtures in which the primary carbon atom of propylene oxide was attacked in preference to the secondary carbon atom. Raimond (112), however, reported the attack occurred mainly at the secondary atom in the same reaction. Levene and Walti (113) obtained more than 50% inversion in the acid catalyzed hydrolysis of optically active propylene oxide which indicates that the attack occurred mainly at the secondary carbon atom. Halperin, Donahoe, Kleinberg, and VanderWerf (114) recently reported similar results in the reaction of 1,2-epoxybutane with the halogen acids. Paul (115) found that a mixture was obtained in the reaction of hydrochloric acid with 5-methoxy-1,2-epoxypentane in which primary attack predominated.

Butadiene monoxides.—Petrov (76), Kadesch (12), Bartlett and Ross (36) and Swern, Billen and Knight (69) reported that the acid catalyzed addition of alcohols to butadiene monoxide gives attack exclusively at the secondary carbon atom. Petrov (116-119), similarly, found that halogen acids added to halogen substituted butadiene monoxides to give primary alcohols.

Styrene oxides.- Reeve and Cristoffel (78)

found that styrene oxide with methanol gave a mixture containing mostly primary alcohol, i.e., attack occurred mostly at the secondary carbon atom. Hayes and Gutberlet (81) reported that allyl alcohol attacked styrene oxide at the secondary carbon atom. King, Berst, and Hayes (10) found that with pyridine catalyzed by pyridine salts of strong acids a high percentage of attack occurred at the secondary carbon atom. Emerson (88) and Columbia and Cottle (120) found that hydriodic acid added to styrene oxide to give exclusively the primary alcohol.

Mechanism of Ring Opening

The mechanism of ring opening may throw some light upon the increase in secondary attack brought about by acid catalysis. The available kinetic data indicate that the acid catalyzed reactions are third order and that the rate is proportional to the concentrations of the oxide, the acid, and the attacking base. Walden inversion usually occurs in the acid catalyzed reactions, although examples are known in which only partial inversion occurs. Any mechanism which is proposed must be consistent with these facts.

Kinetics.- Bronsted, Kilpatrick, and Kilpatrick (20) determined the rate of reaction of glycidol with

hydrobromic acid as a third order reaction where $-dc/dt = k(\text{oxide})(\text{H}_2\text{O})^+(\text{Br})$. Similarly, Smith, Wodhe, and Widhe (121) found that the reaction of epichlorohydrin with strong acids is third order. Eastham and Darwent (11) reported that ethylene oxide in excess pyridine gave a second order reaction where $-dc/dt = k(\text{oxide})(\text{HA})$. Kadesch (12) found that the rate of reaction of butadiene monoxide with methanol in ether catalyzed by sulfuric acid was dependent upon the methanol concentration.

Walden inversion.- Walden inversion has frequently been demonstrated in the acid catalyzed reactions of alicyclic epoxides. Thus, Bartlett (122) and Winstein (123) obtained inversions in the reactions of cyclohexene oxide with hydrochloric and hydrobromic acids. Winstein, Hess and Buckles (124) and Clarke and Owen (125) demonstrated an inversion in the reactions of cyclohexene oxide with sulfonic acids. Winstein and Henderson (126) observed an inversion in the acid catalyzed addition of an alcohol to cyclohexene oxide. Mousseron and coworkers (127-129) demonstrated Walden inversion in the acid catalyzed hydrolyses of cyclopentene, cyclohexene, and cycloheptene oxides and their derivatives.

Theory of Direction of Ring Opening

Bimolecular ring opening.- It is generally agreed that the first step in the acid catalyzed reactions of epoxides with Lewis bases is the addition of a proton to the epoxide with the formation of an oxonium complex. Many reactions appear to involve opening of the oxonium complex by attack of the base from the rear of the epoxide carbon which results in Walden inversion in the rate determining step.

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If the first step is ignored, the mechanism may be looked upon as a typical S_{N}^2 reaction which involves a base displacement on the carbon atom of the oxonium complex analogous to attack of the base on the uncharged epoxide in the base catalyzed reactions.

Cis- and trans-2,3-epoxybutane have been used in several reactions to show Walden inversion. Thus, Lucas and Gould (130) and Lucas and Garner (131)

found an inversion in the reaction with hydrochloric acid. Winstein and Lucas (132) and Helmkamp and Lucas (133) proved inversion in the acid catalyzed reactions with alcohols. Similarly, Wilson and Lucas (134) observed an inversion in the acid catalyzed hydration and alcoholysis of 2,3-epoxybutane. The mechanism of Walden inversion in the reactions of epoxides is discussed by Darzens and Meyer (135).

Reulos and coworkers (136,137) demonstrated Walden inversion in the addition of halogen acids to cis- and trans-stilbene oxide. Kuhn and Ebel (138) obtained 100% inversion in the slightly acid or basic hydrolysis of cis-epoxysuccinic acid, but only a partial inversion in the slightly acid hydrolysis the trans-epoxysuccinic acid. Partial inversion has also been noted by Oldham and Robertson (139) in the acid catalyzed hydrolysis of a sugar and by Boeseken (140) and Boeseken and van Loon (141) in the hydrolysis of some alicyclic epoxide.

Unimolecular ring opening.- Kadesch (12) suggested that the acid catalyzed reaction of butadiene monoxide with methanol may proceed by way of a unimolecular ring opening of the oxonium complex in order to explain attack at the secondary carbon atom.

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He found that the rate of the reaction depends upon the methanol concentration and suggested that this is consistent with the proposed mechanism provided that $k_2 \gg k_3$.

Branch and Calvin (142), however, forcibly point out that the difference between uni- and bimolecular processes does not lie in the relative rates of preliminary and successive reactions. The bimolecular reaction is three centered and the rate of reaction is proportional to the concentration of the attacking base. The most generally accepted theory for the uni-molecular reaction is that it is a slow ionization as shown in step (1) followed by a fast reaction of the carbonium ion with methanol as in step (2), i.e., $k_3 \gg k_2$. The fact that the rate of reaction is dependent upon the methanol concentration cannot be explained away by the assumption that $k_2 \gg k_3$.

Nevertheless, it is probable that the rate determining step is the opening of the ring and the mechanism is of the S_N^1 type. The dependence of the rate of reaction upon the methanol concentration may be explained in terms of Swain's push-pull termolecular mechanism (143) with third order kinetics - since the kinetic measurements of the reaction of butadiene monoxide with methanol in the presence of sulfuric acid were made in dry ether, a non-polar solvent.

In accordance with this scheme, there is formed in the transition state a solvated oxonium complex as shown in step (1). The ionization of the solvated oxonium complex in the rate determining step to form a solvated carbonium ion as shown in step (2) may satisfactorily explain the effect of methanol upon the rate.

The intermediate formation of such a carbonium ion is supported by the fact that epoxides may be isomerized to aldehydes and ketones in acid solution and probably proceeds through the same intermediate. Additional support comes from the acid catalyzed alkylation of the benzene nucleus which also probably proceeds by way of a carbonium ion.

Since an S_N^2 reaction is always accompanied by complete Walden inversion whereas an S_N^1 reaction is usually accompanied by partial Walden inversion, there does exist direct evidence for the unimolecular ring opening, as proposed by Kadesch (12). The best evidence available comes from the work of Boeseken and his co-workers (140,141). They studied the hydrolysis of the seven compounds listed below in both alkaline and acid solution. It was found that compounds $\times \times \times \vee \text{II}$, $\times \times \times \vee \text{III}$, $\times \times \times \text{IX}$, and $\times \text{L}$ on hydrolysis in basic and acidic solution gave trans-glycols exclusively. Compounds $\times \text{LI}$, $\times \text{LII}$, and $\times \text{LIII}$ on hydrolysis in alkaline solution also gave trans-glycols exclusively. They concluded that in basic solution Walden inversion occurs invariably. In acid solution, however, compounds $\times \text{LII}$, $\times \text{LI}$ and $\times \text{LIII}$ gave mixtures of cis- and trans-glycols. They concluded that the phenyl group on

the ethylene oxide ring was the cause of cis-glycol formation. The cis-glycol formation may best be explained by an S_N^1 , unimolecular, ring opening of the oxonium complex at the carbon adjacent to the phenyl group.

Reulos and co-workers (136,137) found that stilbene oxides, to the contrary, added halogen acids with Walden inversion. Thus, cis-stilbene oxide with hydrochloric acid gave the threo-halohydrin and trans-stilbene oxide gave erythro-halohydrin. This would tend to prove that, even under acid conditions, attack at a carbon atom adjacent to a phenyl group may, under certain conditions, proceed with complete Walden inversion.

In the case of propylene oxide, there is proof that attack at the secondary carbon atom may proceed by way of an S_N^2 mechanism. Levene and Walti (113) found that on acid hydrolysis of optically active propylene oxide more than 50% inversion occurred. The attack must have been at the secondary carbon since attack at the primary carbon atom would lead to retention of configuration. This is consistent with the work of Boeseken and co-workers who found the introduction of a methyl group on the ethylene oxide ring did not prevent the occurrence of Walden inversion, in acid hydrolysis.

REACTIONS OF EPOXIDES WITH LEWIS ACIDS

REACTIONS OF EPOXIDES WITH LEWIS ACIDS

Mechanism of Reaction

The reaction of epoxides with Lewis bases has received considerable attention in the current literature. The reaction of epoxides with Lewis acids, however, has been less extensively explored. The reaction apparently involves a bimolecular nucleophilic attack of the basic ring oxygen on the acid center of the reacting molecule to form an oxonium complex (144) as shown below. The displaced base then attacks the carbon atom of the oxonium complex which opens the ring.

Kinetics.— Sjöberg (147) determined that the rate of reaction of epichlorohydrin with acetyl chloride was second order. This supports the postulation of

an S_N^2 mechanism.

Walden inversion.- In further support of the proposed S_N^2 mechanism is the fact that the reaction of cyclohexene oxide with benzoic anhydride, acyl halides and alkyl halides (145, 146) has been shown to proceed with Walden inversion.

Acid catalysis.- The function of the acid catalyst, as in the reaction with Lewis bases, appears to be that of lowering the energy of activation but by an entirely different mechanism. With Lewis bases, the acid catalyst acts by polarization of the carbon-oxygen bonds of the epoxide ring. The positive character of the ring carbon atoms is increased and this results in an increase in the rate of reaction. In the reaction of epoxides with Lewis acids, however, the function of the acid catalyst appears to be that of polarization of the bonds of the attacking reagent rather than the epoxide itself, which thereby, increases the positive character of the acid center in the reagent as shown below.

XLV

Gustus and Stevens (144), however, suggested that the function of the catalyst is "the promotion of the decomposition of the complex."

Analogy with acid catalyzed reactions of Lewis bases.- There is a strong analogy between the reactions of Lewis acids and the acid catalyzed reactions of Lewis bases. In the case of Lewis acids, the first step in the reaction appears to be the formation of oxonium complex which involves the coordination of the epoxide oxygen atom and the reactive carbon center of the Lewis acid, whereas, in the case of the acid catalyzed reaction with Lewis bases, the first step in the reaction appears to be the formation of an oxonium complex which involves the coordination of the epoxide oxygen with a proton. The second step, in both cases, is the attack of a base

on the carbon atom of the oxonium complex. From a mechanistic viewpoint the reactions are very similar.

Reactions with Lewis Acids

Acyl halides.- The reaction of epoxides with acyl halides result in the formation of alpha-haloesters (144,145,147,148,155). The reaction proceeds readily with iodides even at -80 degrees C., in large yield, in the absence of catalysts. Acyl chlorides react more slowly, but may be catalyzed by the addition of a drop of HCl.

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Anhydrides.- The reaction of epoxides with acid anhydrides produces diesters (146,150,156-165). Ferric chloride, zinc chloride and HCl have been used as catalysts. Bedos obtained the trans-dibenzoate in the reaction of cyclohexene oxide with benzoic anhydride at 160 degrees C. for 24 hours.

Aldehydes and ketones.- The reaction of epoxides with aldehydes and ketones is a useful preparative method for cyclic acetals (173-180).

Although stannic chloride has been used successfully as a catalyst, boron trifluoride etherate is the most satisfactory of the catalysts.

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Phosphorus and sulfur compounds.- The reactions of epoxides with Lewis acids are not restricted to those reagents having the positive center on carbon. Thus, bonds may be formed between the epoxide oxygen and sulfur as well as phosphorus.

Epoxides have been reported to react with sulfonyl chloride yielding chloroalkyl esters of chlorosulfonic acids (181,182).

Albertson and Fernilius (183) studied the temperature-composition curve for the sulfur dioxide-ethylene oxide system. They found a maximum at -95 degrees C. which corresponded to an equimolar mixture of sulfur dioxide and ethylene oxide, and assumed that the compound resulted from the formation of a covalent bond between the epoxide oxygen and the sulfur dioxide molecule.

Phosphorous trichlorides and tribromides (184-187) are also known to react with epoxides as shown:

Direction of Ring Opening

Little is known about the direction of ring opening of epoxides with Lewis acids. Epichlorohydrin has been reported to give the product which corresponds to an attack on the primary carbon atom of the oxonium complex with acyl halide (147,154,155), alkyl halides (166), haloethers (168,169) and sulfuryl chloride (181). Glycidol (153) has been reported to give a mixture with acyl halides. Sjöberg (147), however, reported that glycidol gave principally the product which corresponds to primary attack. Hunt and Renshaw (151) found that the primary carbon atom was attacked in the reaction of propylene oxide with acetyl bromide. In contradistinction, Malinovsky (182) reported the product which corresponds to secondary attack was obtained in the reaction of propylene oxide with sulfuryl chloride. It may be that, despite some contrary indications, the primary carbon atom is attacked preferentially in this type of reaction.

DISCUSSION OF EXPERIMENTAL RESULTS

DISCUSSION OF EXPERIMENTAL RESULTS

Direction of Ring Opening of Stilbene
Oxides

Minimization of Steric Factors.

It was pointed out in the discussion of the direction of ring opening of base catalyzed reactions of propylene oxides, that the attack was predominantly at the primary carbon atom, with little or no attack at the secondary carbon atom indicated in the vast majority of reports. The same is true of styrene oxide, but the occurrence of attack at the secondary carbon atom to a small extent was often reported. In the case of butadiene monoxide, attack occurred predominately at the primary carbon, but secondary attack was somewhat more pronounced than in the case of styrene oxide. Attack mainly at the secondary carbon atom was rarely reported. The evidence points to a strong steric factor which operates to obscure the effect of electronic factors on the direction of ring opening.

The problem is clearly posed—to study the electronic effects, it is necessary to minimize or eliminate steric hinderance as a factor which governs the direction of ring opening. It appears that the p-substituted stil-

bene oxides were suited for such a study. In cis- or trans-stilbene oxide, the epoxide carbon atoms are sterically equivalent. The introduction of a p-substituent would not be expected to destroy that equivalence. Ordinarily, the principle of vinylogy would allow a prediction that the placement of a phenyl group between the methyl group and the ring would not hinder the transmission of the electronic effects of the methyl group. It is necessary, however, to take into account whether the p-substituted stilbene oxides^{are}, cis- or trans-, since it is known that a configuration may be imposed in which the directly transmitted effects of the polarities of substituents is at a maximum or minimum. Inhibition of conjugation effects is more likely in the cis- configuration due to the effect of the ortho-hydrogens on the coplanarity of the molecule. Hence, it appears that the trans-p-substituted stilbene oxides may adequately serve to elucidate the electronic effects of the various substituents of interest, and thus, were chosen for study.

p-Methylstilbene oxide, in particular, was synthesized because of the close analogy with propylene oxide. The first prediction was that the product which corresponded to attack at the carbon atom adjacent to

the phenyl group would be obtained predominately. This prediction was based solely on application of the concept of repulsion energies. The p-chlorostilbene oxide was desired because it was thought, on the basis of repulsion energies, that attack would occur predominately at the carbon atom adjacent to the chlorophenyl group. Actually, the predictions in both cases did not coincide with the experimental results.

Aluminum hydride was chosen as the base both because it previously had been established that its reactions were of the S_N^2 type and because it was found to react readily with the relatively unreactive stilbene oxides. Further, the analysis of the mixture of isomeric diaryl alcohols is facilitated by the fact that the individual alcohols can be easily synthesized and characterized.

Lithium aluminum hydride.

Studies in the direction of ring opening have been previously reported in which lithium aluminum hydride was the attacking reagent. Thus, with styrene oxide, Brown (72,70) reported a 75% yield of the product corresponding to attack at the primary carbon atom, whereas, with butadiene monoxide, a mixture was obtained.

These authors further established the mechanism of reduction of epoxides as a bimolecular nucleophilic reaction by proof of Walden inversion in the cyclopentene oxide and cyclohexene oxide series. Prins (104) also obtained a Walden inversion in the reduction of sugar epoxides to desoxysugars. The proof by Leroux and Lucas (188) that optically active 2,3-epoxybutane on reduction with lithium aluminum hydride gave 2-butanol of 99% optical purity further established the S_N^2 character of the reagent. The nucleophilic character of the hydride has been established in reductions of halides (72,189-191) and p-toluene sulfonate (192,193) as well.

The mechanism proposed by Trevoy and Brown (72) as shown below therefore appears to be correct. They note that the attacking group is probably $Al X_n - H_{4-n}$ where n progresses from zero to four as the reaction proceeds.

Lithium aluminum hydride, apparently, acts in the same manner as a Lewis base. Thus, propylene

oxide is known to react with the methoxide ion exclusively at the primary carbon atom. Similarly, lithium aluminum hydride was reported (70) to attack propylene oxide at the primary carbon atom. In other reactions also the hydride attacked the primary carbon atom in preference to a secondary or a tertiary carbon atom. Thus, Foster and Overend (194) found that in 1,2-3,6-dianhydro mannitol, attack occurred exclusively at the 1-position. Brown and his students (70,72) found that butadiene monoxide and styrene oxide were attacked mainly at the primary carbon atom. Similarly, Eliel and Freeman (190) reported that α -methylstyrene oxide was attacked at the primary position. It may be concluded, then, that the lithium aluminum hydride reductions of epoxides have little or none of the characteristics of acid catalyzed reactions since attack at the secondary carbon atom is not observed to any appreciable extent except where sterically favored as in the case of butadiene monoxide.

In the foregoing discussion of lithium aluminum hydride, fairly conclusive evidence was presented that the reactions are of the S_N^2 type. In the discussion of the mechanism of acid catalyzed reactions, it was mentioned that stilbene oxides, even under acid

conditions which favor S_N^1 reactions, react by way of the S_N^2 mechanism. It appears reasonable, then, to assume that the reactions of stilbene oxides with lithium aluminum hydride are of the bimolecular nucleophilic type.

Experimental Results

It is reported in the experimental section of this thesis that the lithium aluminum hydride reduction of p-methylstilbene oxide yielded 59.9% of the product which corresponds to attack at the carbon atom adjacent to the methylphenyl group and 40.1% of its isomer, a ratio of 1.50 to 1.00. It is further reported that the analogous reduction of p-chlorostilbene oxide yielded 39.1% of the product which corresponds to attack at the carbon atom adjacent to the chlorophenyl group and 60.9% of its isomer, a ratio of 0.640 to 1.00. As previously mentioned, these results are not in accord with predictions based on repulsion energies or by analogy with the reaction of propylene oxides. Hence, it becomes necessary to investigate more thoroughly the reasons for the reversed substituent effect.

The Substituent Effect

The stilbene oxides offer a unique method for the study of the effects of a p-substituent on a side chain carbon. Previous methods involved a study of the rates of reactions of the p-substituted and the unsubstituted benzyl halides, benzoic acid esters, amides, halides, etc. In the substituted stilbenes, the ratio of products serves the same purpose. Thus it was found that the p-substituent increased the rate of attack on the adjacent side chain carbon atom in the order, p-methyl- > p-hydrogen- > p-chloro-. The numerical ratio of the p-methyl to the unsubstituted is 1.50 : 1.00 and the p-chloro- to the unsubstituted is 0.640 1.00.

The effect of the substituent on the ratio of products obtained in the p-substituted stilbene oxides corresponds to the order obtained in the hydrolyses of p-substituted benzyl chlorides and fluorides in aqueous acetone or alcohol and the reactions of p-substituted benzyl chlorides with potassium iodide in aqueous acetone. These reactions are known to be of the S_N^1 type.

The exact opposite order has been determined for the effect of p-substituents on the rates of reaction of benzyl chlorides with potassium iodide in acetone, benzyl fluorides with sodium ethoxide in ethyl alcohol, benzoyl chlorides with ethyl alcohol, ethyl benzoates on alkaline hydrolysis, and benzamides on alkaline hydrolysis. The order, p-chloro- > p-hydrogen- > p-methyl- has been correlated with the fact that these reactions are of the S_N^2 type.

It does not seem reasonable to assume, since the effect of the substituents in stilbene oxides is the same as for the S_N^1 reactions and the reverse for the S_N^2 reactions, that the reactions of the stilbene oxides with lithium aluminum hydride are also S_N^1 . Evidence in favor of an S_N^2 interpretation for the stilbene oxide reactions has previously been cited which leaves little doubt as to the mechanism.

Direction of Ring Opening

The reversed effect of the p-methyl and the p-chloro substituent may perhaps be explained in terms of the bond strengths of the carbon-oxygen bonds of the epoxide linkage or resonance involving the carbon-carbon bond of the epoxide linkage.

Bond strengths.- In the discussions of the transition state, it was brought out that the effect of a substituent on the direction of ring opening in base catalyzed reactions may vary depending upon the charge and the nature of the attacking base. Thus, a decrease in the charge of the attacking group increases the importance of bond strengths relative to repulsion energies (94b). If the nature of the attacking reagent is such that the permanent repulsion is high, the importance of bond strengths relative to repulsion energies increases (94e). A third factor involves the bond distances in the transition state compared to the bond distances in the initial state. A transition state in which the distances of the carbon-base bond (r_0) and carbon-oxygen bond (r_a) are large compared to the carbon-oxygen bond (r_1) in the initial state will increase the importance of the bond strengths relative to the repulsion energies, i.e., ΔE_2 compared to ΔE_1 (142b)

$$\begin{aligned}\Delta E_1 &= e_A \int e_B / r_a & \text{xxvii.} \\ \Delta E_2 &= \frac{-e_C \int e_B}{r_0} \left(\frac{r_0}{r_1} - 1 \right) & \text{xxviii.}\end{aligned}$$

It is possible that the direction of ring opening of the stilbene oxides may be attributed to the lithium aluminum hydride reagent. It is conceivable that due to the large size of the attacking hydride, particularly in the latter stages of the reaction,

and due to the bulkiness of the phenyl groups on the epoxide linkage that a distension of the bond between the attacking base and the ring carbon atom occurs which gives rise to a significant increase in the ratio of r_0 to r_1 , hence a diffuse transition state. The importance of ΔE_2 is thereby increased, and it would be predicted that an electron-withdrawing group should hinder the attack of the base relative to hydrogen. Branch and Calvin (142b) have called attention to the fact that the effect of a substituent may be in accord with its effect on the bond strengths rather than the repulsion energies in a reaction which involves a diffuse transition state. It is also possible that due to the interaction of the two phenyl groups there is a shortening of the two carbon bonds (r_1) in the ground state of the molecule. Since this factor would also increase the importance of ΔE_2 relative to ΔE_1 , it is perhaps not surprising that in p-chlorostilbene oxide, the electron withdrawing chlorine group favors attack at the carbon atom adjacent to the phenyl group. Similarly, a methyl group should facilitate attack at the carbon atom adjacent to the methylphenyl group in p-methylstilbene oxide. Apparently, the experimental results are in accord with the results predicted by the theory as outlined.

The bond strength theory may also be applied to a new discovery made recently by Waters (4). He found that in the reaction of 1-methoxy-2,3-epoxybutane with sodium methoxide in methanol, the

attack of the methoxide occurred exclusively at the carbon atom adjacent to the methoxymethyl group. This is the point of attack which would be predicted based on repulsion energies since the methyl group is electron-releasing and the methoxymethyl group is electron-withdrawing.

With lithium aluminum hydride, however, the attack of the base is at the carbon atom adjacent to the methyl group. If we assume a diffuse transition state in the reaction with lithium aluminum hydride, the reversed attack is to be expected since the effect of the substituents is to weaken the bond between the oxygen atom and the carbon atom adjacent to the methyl group more than the other carbon-oxygen bond.

The reaction of p-substituted benzyl bromides with pyridine in dry acetone is often cited (216, 217) as an example of a bimolecular nucleophilic displacement reaction in which the effect of the substituent on the rate of reaction is in accord with its effect on the bond strengths rather than the repulsion energies. Normally, in S_N^2 reactions, the nitro group markedly increases the rate of reaction, but in this particular case, the nitro group slows the reaction. We cite this as supporting evidence of the possibility of a reversal of the substituent in a strictly S_N^2 reaction.

Carbon-carbon bond of epoxide linkage in p-methylstilbene oxide. - In the initial state of the p-methylstilbene oxide molecule, the electron-releasing effect of the methyl substituent on the carbon-carbon bond of the epoxide group is such that attack of the base at the carbon atom adjacent to the methylphenyl group is facilitated.

Consider now the positive charge on the carbon atom adjacent to the methylphenyl group in the transition state. There can be little doubt, from the viewpoint of resonance theory, that the positive charge is stabilized on this carbon atom, which facilitates attack of the base at this point.

LVII

The importance of the resonance structure with the positive charge on the carbon adjacent to the methylphenyl group is due to the stabilizing influence of the methyl group, either through the inductive effect, as postulated by some authors, or through hyperconjugation. In this base hyperconjugation may assume increased importance due to conjugation with the epoxide carbon-carbon bond. It may well be that herein lies the explanation of the predominant attack of the base at the carbon atom adjacent to the methylphenyl group.

Carbon-carbon bond of the epoxide linkage in p-chlorostilbene oxide. - In the initial state, the effect of the electron-withdrawing properties of the chloro group on the carbon-carbon bond of the epoxide linkage is such that attack of the base at the carbon atom adjacent to the phenyl group is to be expected. The reasoning, as previously described, involves an analogy of the epoxide carbon-carbon bond with an ethylenic linkage as shown below.

LVIII.

We may now consider the effect of the chlorine atom on the stabilization of the positive charge in the transition state. Whereas, the methyl group would stabilize the positive charge on the carbon atom adjacent to the methylphenyl group due to its electron-releasing properties, the chloro group on the other hand would destabilize the positive charge on the carbon atom adjacent to the chlorophenyl group due to its electron-withdrawing properties. Thus attack on the carbon atom adjacent to the phenyl group would be facilitated in the case of p-chlorostilbene oxide. Further, it may be expected that the negative charge on the carbon atom adjacent to the chlorophenyl group would be stabilized due to the resonance structure which involves the expanded valence of chlorine as shown below.

Hence, it is proposed that within the concept of resonance involving the carbon-carbon bond of the epoxide and the expanded valence of chlorine lies the explanation of a base attack predominantly at the carbon atom adjacent to the phenyl group in p-chlorostilbene oxide.

Resonance in the Transition state.— In the transition state of propylene oxide, it appears that structures of types I and III are more important than structures of type II. Hence attack at the primary atom would be expected.

$$\left(\text{CH}_3 \overset{+}{\text{CH}} - \text{CH}_2 \right)$$

In the case of butadiene monoxide and styrene oxide, structures of type II assume greater importance than in the former case due to an allylic type resonance, hence, secondary attack may well be expected.

$$\text{CH}_2=\text{CH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_2$$

Let us examine the effect of the methyl substituent in the p-methylphenyl group in ordinary S_N^2 reactions such as the base displacement reactions of chloride in p-methylbenzyl chloride by iodide in dry acetone. The methyl group slows the reaction which may be attributed to a weakening of the forces of attraction between the benzyl carbon atom and the iodide. In the stilbene oxides, in contradistinction, the stabilization of the positive charge in the transition state, as in type II structures, appears to be the important factor. The effect of the methyl group is to speed up the reaction at the carbon

atom adjacent to the methylphenyl group. This may easily be understood since in the transition state the effect of the methyl group is to stabilize the positive charge on the adjacent carbon due either to the inductive effect or to hyperconjugation. Thus in the base attack on p-methylstilbene oxide, the rate is faster at the carbon atom adjacent to the methylphenyl group.

In the case of the chloro group in p-chlorostilbene oxide, the positive charge on the carbon atom adjacent to the chlorophenyl group will be destabilized, thus increasing the importance of structures of type III in the transition state. Structures of type III will be further stabilized due to the expanded valence of chlorine.

The effect of the substituent in the S_N^2 reactions of stilbene oxides is in the same order as S_N^1 reactions of benzyl halides since in the latter case the stabilization of the positive charge on the carbon atom is also the important factor in determining the rate of their reaction.

Deactivation of the Epoxide Ring

Evidence of Deactivation. - Experimental evidence reported in this thesis indicates that the stilbene oxides are less reactive to some degree than other classes of epoxides. In the reduction of p-methylstilbene oxide, the analysis indicates that 31.9% of the oxide did not react even in the presence of a large excess of lithium aluminum hydride. Similarly, in the reduction of p-chlorostilbene oxide, there was recovered 30.7% of the oxide. In the attempted reaction of p-nitrostilbene oxide with sodium methoxide in methanol, almost all of the oxide was recovered. In the hydrolysis of p-nitrostilbene oxide in the presence of an acidic or basic catalyst, 72.0% of the starting material was recovered. This may be compared with the 79% yield of ether-alcohol obtained in the acid catalyzed reaction of 2,3-epoxybutane with methanol (133) and the 80% yield of 2-butanol obtained in the lithium aluminum hydride reduction of 2,3-epoxybutane (188).

The remarkable stability of the stilbene oxides was noticed by Rabe and Hallensleben (195) and commented upon by Read and Campbell (196-198). The oxides were found to be resistant to the action of Fehlings solution, ammoniacal silver nitrate, alcoholic ferric chloride, potassium permanganate, and chromic acid oxidation. Read and Campbell (196) found that 1-trans-stilbene oxide did not react with 1 mole of hydrochloric acid in chloroform solution. They later reported (198) that p,p'-dimethoxy-

stilbene oxide was highly resistant to hydrolysis in 7.5% sulfuric acid and 8% sodium hydroxide. The compound showed no tendency to isomerize or polymerize in contact with concentrated sulfuric acid over a period of six hours. Boeseken and Elsen (199) could not obtain the glycol in the acid catalyzed hydrolysis of stilbene oxide. Steinmetz (200) found that p-methoxystilbene oxide did not react with ammonia gas, aqueous ammonium hydroxide, sodamide in liquid ammonia, ammonium chloride in liquid ammonia, ammonium hydroxide in a bomb at 100°, ammonium chloride in ammonium hydroxide at 100°. Attempts to reduce the epoxide linkage with platinum oxide and hydrogen at 40 lbs./sq. in. or sodium amalgam under different conditions also gave no reaction. Similarly, aluminum isopropoxide failed to reduce the compound. He reported also that p-nitrostilbene oxide resisted the addition of ammonia under various conditions.

Theory of deactivation of the epoxide ring.-

Read and Campbell (196-198) were very much concerned with the lack of reactivity demonstrated by the stilbene oxides. They felt that, "the extraordinary stability of these well defined crystalline oxides is in keeping with the views of Thorpe and Ingold (201) on the effect of substituents in relieving the strain inherent in small rings."

It is possible, also, that the lack of reactivity may be correlated with the ring unsaturation properties. Thus, there may be a high degree of resonance stabilization in the ground state and in the transi-

tion state due to structures of the type shown below which results in a strengthening of the carbon-oxygen bonds.

LXIV

This explanation is analogous in some respects to that offered for the deactivation of the double bond in the reaction of stilbene with bromine as a result of resonance.

Another possible interpretation of the lack of reactivity is that steric hindrance due to the phenyl groups slows the rate of reaction. The possibility may be checked by the comparison of yields or reaction rates in the reactions of stilbene oxide and α,β -dicyclohexyl ethylene oxide. This phase of the problem is now under investigation (202).

Reactions of stilbene oxides. - It may not be inferred from the above that the stilbene oxides are completely devoid of activity. Thus, Lutz, Freek and Murphy (203) obtained excellent yields of the amino-alcohols in the reactions of cis- and trans-stilbene oxide with ammonia in dioxane at 120° for 10 hours. Similarly, they reported the reactions of the same epoxides with many primary and secondary amines at reflux temperature or at 150°, but in lower yields. Lutz and Murphy (204) reported the reactions of p,p'-dichlorostilbene oxide with ammonia, primary

and secondary amines under approximately the same conditions. Read and Campbell (196) reported the reaction of 1-trans-stilbene oxide with absolute ethanol merely on standing for 15 days at room temperature. Kayser (205-207) obtained the products expected in the reactions of cis- and trans-stilbene oxides with Grignard reagents. Tiffeneau and Levy (208-212) found that the p-methyl- and p-methoxystilbene oxides could be isomerized to aldehydes and ketones with heat and acid catalysts. Reulos and co-workers (136, 137, 213) were able to isolate the products of the reactions of cis- and trans-stilbene oxides with the halogen acids. It is possible also to reduce the stilbene oxides to the corresponding stilbenes with Grignard reagents (206-207), thiourea and KCNSe (214).

Weill and Kayser (215) reduced p-methylstilbene oxide with nickel in alcohol solution at 35-40° and obtained p-methylphenylbenzyl carbinol, exclusively. This is in contrast to the mixture obtained on lithium ~~thium~~ aluminum hydride reduction where the isomer was the predominant product. From the viewpoint of the mechanism of the reactions of epoxides with Lewis bases, only the lithium aluminum hydride reaction is of concern since ample evidence is available that its reactions are of the S_N^2 type.

Cleavage Reactions of Stilbene Oxides

It was reported in the experimental section that on alkaline hydrolysis of p-nitrostilbene oxide, benzaldehyde was isolated and identified. In the attempted synthesis of p-chlorostilbene oxide by the Bergmann-Hervey method (218), p-chlorobenzyl chloride was treated with benzaldehyde in methanol solution in the presence of potassium carbonate. p-Chlorobenzaldehyde was isolated and identified. Bergmann and Hervey (218) isolated the methyl ether of p-nitrobenzyl-alcohol from the attempted condensation of p-nitrobenzaldehyde with benzyl chloride. A possible explanation may be given in terms of electron theory:

LXVI

The cleavage reactions may be used to determine the effect of a substituent on the relative rates of attack of the base at the epoxide carbon atoms. Caution, however, must be used in drawing conclusions from the examples cited since no attempt was made to determine all the products and their relative percentages.

Direction of Ring Opening of Styrene Oxide
with Aryl Lithium Reagents

In the preparation of p-methylbenzylphenyl carbinol, difficulty was experienced due to coupling of the p-methylbenzyl magnesium bromide. The work of Cristol, Douglass and Meek (219) suggested the possibility of obtaining the product from the reaction of styrene oxide with p-methylphenyl lithium.

Direction of ring opening with lithium reagents. - The reactions of styrene oxide with lithium reagents appears to fall in the same category as the base catalyzed reactions of epoxides with Lewis bases. Thus, Cristol, Douglass and Meek (219) found that styrene oxide with phenyl lithium gave attack at the primary carbon atom. That this is due to the fact that attack at a primary carbon atom is less hindered than attack at a secondary carbon atom is shown by the work of Cathcart (220), who found that phenyl lithium attacked at the α -carbon atom in 3,4-dihydronaphthalene-1,2-epoxide. The α -carbon atom in 3,4-dihydronaphthalene-1,2-epoxide is less sterically hindered than the carbon atom adjacent to the phenyl group in styrene oxide. The results of the reaction of styrene oxide with p-methylphenyl lithium, as reported in the experimental section, confirm the work of Cristol and co-workers. There is a possibility that a small amount of the isomer may have been produced because the melting-point of the product, even after distillation, was not sharp. No

isomer, however could be isolated or identified. The product obtained was identified as p-methylbenzylphenyl carbinol by a mixed melting-point with an authentic sample synthesized in the reaction of p-methylbenzyl magnesium bromide with benzaldehyde.

Direction of ring opening with Grignard reagents.-

The lithium aryl reagent was chosen instead of the p-methylphenyl magnesium bromide because of the catalytic influence of the magnesium ion which directs the attack of the aryl group to the secondary carbon atom of styrene oxide. Further, the magnesium ion may catalyze the isomerization of styrene oxide to phenylacetaldehyde and the undesired isomer may be obtained.

Kharasch and Glapp (221) reported that phenyl magnesium bromide and anisyl magnesium bromide gave, in addition to the product from the isomerized styrene oxide, the product which corresponds to attack at the secondary carbon atom. Rose and Gale (222) also obtained secondary attack in the reaction of styrene oxide with phenylacetylene magnesium bromide.

The reactions of styrene oxides with Grignard reagents are remarkably like the acid catalyzed reactions of styrene oxide with Lewis bases. From a mechanistic viewpoint, the reactions are almost identical. The Grignard reagent contains the electrophilic, Mg^{++} , and nucleophilic, R^- , elements in the same molecule.

LXVII

Actually the dissociation of RMgX in ether as shown is oversimplified. The usual postulation is in terms of the Schlenk (223) equilibrium,

LXVIII

where the MgX^+ is thought to coordinate with the epoxide oxygen atom. The work of Stewart and Ubbelohde (224) indicates, however, that the alkyl or aryl group may be tied up in a complex anion with free magnesium ions.

E. The Preparation of the Stilbenes.

Dehydration of p-Substituted Diarylethanols.-

A useful route for the synthesis of p-substituted stilbene oxides involves the reaction of p-substituted benzyl magnesium halides with benzaldehyde or the reaction of p-substituted benzaldehydes with benzyl magnesium chloride followed by dehydration of the resultant diarylethanols. The stilbenes may then be oxidized by perbenzoic acid to the corresponding epoxides. The synthesis was particularly convenient because the pure ethanol as well as the olefins were necessary for the determination of the percent-composition of the products from the lithium aluminum hydride reduction of the p-substituted stilbene oxides.

In the specific instance of the use of p-methylbenzyl magnesium bromide, the method failed because of the speed with which the Grignard reagent coupled. The p-methylstilbene, however, was synthesized by dehydration of p-methylphenylbenzyl carbinol. An alternative route to the p-methylbenzylphenyl carbinol was provided by the reaction of styrene oxide with p-methylphenyl lithium as described in the experimental section.

The dehydration of p-methylphenylbenzyl carbinol was reported (212) to proceed smoothly in aqueous sulfuric acid and no difficulty was encountered in the preparation of p-methylstilbene by this method. p-Chlorophenylbenzyl carbinol, however, resisted dehydration with 50% aqueous sulfuric acid. Excellent yields of the p-chlorostilbene were obtained by

acetylation of the alcohol followed by decomposition of the ester under the conditions reported in the experimental section.

Kon and Spickett (225) were able to show that the dehydration of o-methylphenylbenzyl carbinol with phosphorus pentoxide gave the trans-stilbene. The work reported herein has established the fact that the dehydration of p-methylphenylbenzyl and p-chlorophenylbenzyl carbinols also gave trans-stilbenes. This was proven by mixed melting-points with the corresponding stilbenes obtained from the Meerwein synthesis which also afforded the trans-olefins.

In the synthesis of p-methylbenzylphenyl carbinol by the Grignard method, there was isolated some p-methylbenzylphenyl ketone. The side reaction was noted by Sabatier and Murat (226) and studied by Marshall (227). Thus, the reaction of benzaldehyde with methyl magnesium iodide yielded mainly acetophenone.

Meerwein synthesis. - Meerwein, Buchner and Van Emster (223) condensed several β -substituted- α, β -unsaturated aldehydes, esters, and acids with aryl diazonium salts to obtain the corresponding unsaturated derivative with the aryl nucleus attached to the α -carbon atom. In the case of cinnamic acids, the corresponding stilbenes were isolated due to the ease of decarboxylation. Thus they were able to prepare the p-methyl-, p-chloro-, and p-nitrostilbenes, among others, in yields which ranged from 49-69% based on the cinnamic acid consumed.

LXIX

An ionic mechanism has been proposed by Meerwein, Buchner and Van Emster (228) which involves the addition of an aryl cation to the α -carbon atom of cinnamic acid. This view was supported by Bergmann and Shapiro (229). Koelsch, however, proposed a free radical mechanism, where the aryl group adds to the α -carbon atom of cinnamic acid because of resonance stabilization of the odd electron in the β -phenyl ring. Koelsch (230) recognized that steric factors may determine the point of attack, i.e., the aryl group attacks the β -carbon atom of methyl acrylate, where the β -carbon atom is less sterically hindered. Bergmann and Weizmann (231) pointed out the role of the diazonium salt in the reaction; stabilization of the aryl cation, apparently, is important since diazotized p-aminobiphenyl yields 12% of p-phenylstilbene compared to 1.2% of stilbene itself. Further, o-substituted anilines almost invariably result in lower yields of the stilbene than the corresponding p-substituted anilines.

The conditions of the reaction were studied by Meerwein, Buchner and Van Emster (228) who determined that the reaction is catalyzed by cupric salts and that the best yields were obtained in aqueous acetone when the solution was buffered with sodium acetate.

Koelsch (230) ran the reaction at a pH of 6. An extensive study of the reaction appeared in a patent. It was reported that Cu or Cu^{++} was important and that numerous solvents such as alcohol, acetic acid, and methylene chloride were satisfactory. The patent reported various salts of weak acids which were also found to be effective.

In the attempts at increasing the yields as reported in the experimental section, it was found that the use of dioxane, changes in the order of addition of the reagents, the time of reaction, the temperature of the reaction, changes in the molar ratios of the reactants, and the purity of the reagents did not greatly affect the yields under the conditions used. It was found that approximately the same yields were obtained with cupric sulfate and the sulfate of the aniline as with cupric chloride and the hydrochloride of the aniline. ~~Contrary to reports,~~ The method was not satisfactory for large scale runs and in general, the Grignard method may be considered as the preferred method.

Preparation of Stilbene Oxides

Preparative Methods

Decomposition of cholines.- An excellent method for the preparation of stilbene oxides (195-198, 232) which appears to be stereospecific is illustrated in the scheme below. The amino alcohols are exhaustively methylated and the quaternary ammonium halides converted to the base with silver oxide and decomposed. Thus, the erythro-amino-alcohol gives rise to the trans-epoxide and the threo-amino-alcohol, the cis-epoxide. The method is particularly well suited for the synthesis of optically active epoxides.

LXX

Nitrous acid deamination of amino-alcohols.- The synthesis of stilbene oxides by means of the nitrous acid deamination (196, 232, 233) of the amino-alcohols is a poor method. Generally, it gives rise to mixtures of the oxide with the hydrobenzoin and aldehydes.

Dehydration of glycoles. - Another method which does not appear to be general or useful was reported by Mueller and Kraemer (234) and involves the formation of stilbene oxide from the reaction of the glycol with hydrazine. In fact, the recorded melting-point does not agree with the accepted values for either cis- or trans- stilbene oxide, but may be a mixture.

Dehydrohalogenation of halohydrins.- The method of preparation of stilbene oxides from the halohydrins (136, 137, 201, 213) by the use of alkali appears to be stereospecific. Thus starting with the erythro-chlorohydrin, trans-stilbene oxide was synthesized and from the threo-chlorohydrin, the cis-epoxide.

Peracetic acid and monoperphthalic acid.- The oxidation of stilbene with peracetic acid has been reported (235) and the rates of reaction with cis- and trans-stilbene studied. The reaction of trans-p-methylstilbene with peracetic acid reported in the experimental section in chloroform solution failed to

give any isolable epoxide, although exactly the theoretical quantity of peracetic acid was consumed. Monoperphthalic acid was attempted and discontinued as an epoxidizing agent because of contamination with unchanged phthalic anhydride.

Perbenzoic acid.- The most frequently used method for the preparation of stilbene oxides is the perbenzoic acid oxidation of the corresponding stilbenes. The synthesis was relatively easy, quick, and the yields quantitative, at least in the case of p-methyl- and p-chlorostilbene oxides as reported in the experimental section.

Perbenzoic acid gives the epoxide by cis-addition of the oxygen (34,236). Hence, it may be concluded that since the trans-olefins were used, the epoxides were of trans-configuration also.

Taub (237) proposed the following mechanism which agrees with the analysis of epoxide formation made by Swern (238):

Condensation of benzyl chlorides with benzaldehydes.-

The synthesis of epoxides by the condensation of benzyl chlorides and benzaldehydes was classified by Newmann and Magerlain (239) as a Darzens-like condensation and postulated, probably correctly, the following mechanism:

LXXII

Bergmann and Hervey (218) assumed the existence of a methylene radical, $\text{NO}_2\text{-C}_6\text{H}_4\text{-CH}^\bullet$, but this has been refuted by Kleucker (240) and by Hahn (241) who also showed that some structure assignments by the former authors were not correct.

The synthesis was originally developed by Hatzig (242), Barrow (243), and Chrzscinski (244) and later extended by Kleucker (245) and Bergmann and Hervey (218). In the preparation of p-nitrostilbene oxide, two isomers were reported in the experimental section. The melting-points agreed fairly well with those reported by Chrzscinsky. The work of Kleucker (245), Bergmann and Hervey (218) and Bodforss (246) indicated the isomers were the cis and trans forms. The higher melting p-nitro-stilbene oxide was probably the trans-epoxide since Steinmetz (200) reported the same melting-point. The latter oxidized p-nitrostilbene prepared by the dehydration of the diaryl ethanol, a method which usually gives the trans-olefin, with perbenzoic acid.

Bergmann and Hervey (218) tried to extend the synthesis to include benzyl chloride as well as p- and o-nitro-benzyl chlorides which usually gave good yields of the epoxide. The unsubstituted benzyl chloride did not yield an epoxide contrary to the claim of Bergmann and Hervey (218). As described in the experimental section of this thesis, the attempts to condense benzyl chloride and p-chlorobenzyl chloride with benzaldehydes failed to give any isolable epoxide.

If the proposed mechanism is correct, it would be expected that an electron-withdrawing group should facilitate the reaction, and apparently this was proved to be the case. The reaction appears to be of sufficient importance to warrant further study.

In the condensation, the stilbene corresponding to the reaction of two moles of the benzyl halide occasionally was isolated. Kleucker (240) proposed the following mechanism:

LXXIII

Sometimes, the ether which corresponds to the benzyl halide used in condensation was isolated. Kleucker (245) has shown that since the reaction is run in alcohol in the presence of potassium carbonate, the ether probably arises from a simple displacement reaction.

LXXIV

Kleucker (245) noted that in the reaction of benzyl chloride with p-nitro-benzaldehyde Bergmann and Hervey (218) obtained a product which melted at 187-189°. They suggested that this was not the expected epoxide but a chlorohydrin, since Chrzosinski (244) reported that he had isolated the isomeric p-nitro-stilbene oxides, m.p 122° and 74-76°. The suggestion of chlorohydrin formation appears reasonable since we probably isolated a chlorohydrin in the reaction of benzyl chloride with p-chlorobenzaldehyde as reported in the experimental section.

In the reaction of p-nitrobenzaldehyde with benzyl chloride, the methyl ether of p-nitrobenzyl alcohol was obtained as reported by Bergmann and Hervey (218). In the reaction of benzaldehyde with p-chlorobenzyl chloride, as reported in the experimental section, there was isolated some p-chlorobenzaldehyde. It was suggested previously that the products could be accounted for by an attack of the base on the ring carbon atom followed by cleavage of the carbon-carbon bond of the epoxide ring.

Another interesting side reaction is the formation of a carboxylic acid which corresponds to the benzaldehyde

used in the condensation. One possible mechanism may involve a preliminary Tischenko reaction followed by an O-alkylation:

LXXV.

The possibility of a Cannizzaro reaction cannot be excluded since p-chlorobenzyl alcohol, although in small yield, was definitely proved. Special procedures to exclude moisture from the reaction mixture failed to prevent the formation of the acids. The mechanism shown above provides a second possible route to the formation of ethers from the corresponding aldehydes.

Proof of structure of p-methyl- and p-chloro-stilbene oxide

Perbenzoic acid is an effective reagent for conversion of olefins to the corresponding epoxides. It

has been observed, however, that a carbonyl compound may be formed rather than the epoxide. Thus Salzer (247) found that 3,4-dihydro-6-methoxy-naphthalene gave 6-methoxy- β -tetralone on oxidation with perbenzoic acid. Newbold and Spring (248) obtained diphenylacetaldehyde from 1,1-diphenylethylene with the same reagent. Similarly, Zaugg, Freifelder and Horrom (249) reported 1-phenyl-2-tetralone from 1-phenyl-3,4-dihydro-naphthalene. Weisenborn and Taub (250) obtained from 1-(biphenyl)-3,4-dihydronaphthalene, the corresponding 2-tetralone.

Although the epoxide of p-methylstilbene and the two isomeric ketones have been characterized in the literature, the three compounds were synthesized. The physical properties precluded the possibility of confusing the epoxide with either of the ketones. The same may be said for the epoxide obtained by the perbenzoic acid oxidation of p-chlorostilbene.

Analysis of Isomeric Products

Analysis of Reduction Products of p-Chlorostilbene Oxide

Previous analytical applications.- One of the major problems in determining the effect of a substituent on the direction of ring opening of epoxides is the quantitative analysis of the isomeric products obtained in the reactions. Analysis by quantitative separation of isomeric mixtures is usually difficult due to the similarity in the physical properties. Fractional distillation has been used successfully by Chitwood and Freuve (5) in the reaction of propylene oxide with ethanol. Separations have been made based on differences in the rates of esterification of primary and secondary alcohols. Thus, Cox, Nelson and Cretcher (251) were able to separate and identify the isomeric ether-alcohols obtained in the non-catalyzed reaction of propylene oxide with n-propyl alcohol. Guss (252,253), however, indicated that this method may not be quantitative. It is possible, also, to transform the isomeric products to derivatives suitable for fractional crystallization. Ettlinger (2), for example, was enabled to separate the mixture of amino alcohols obtained in the reaction of butadiene monoxide

with ammonia by fractional crystallization of the oxalates. It may even be necessary to subject the isomeric compounds to a series of chemical reactions and to separate and identify the end products. Thus, Adams and Vander Werf (56) successfully converted the products of the reaction of butadiene monoxide with acetoacetic ester to the isomeric alcohols, 3-heptanol and 2-ethyl-1-pentanol, which were separated quantitatively by fractional distillation and identified by oxidation to the known ketones. Separations such as described are limited, however, particularly if one of the isomers is present in small amounts.

The quantitative analysis of isomeric mixtures without actual separation of the components has proved useful. Methods based on differences in the physical properties of the isomers falls in this category. Thus, Reeve and Christoffel (78) found that the isomeric ether-alcohols obtained in the reaction of styrene oxide with methanol could be analyzed by virtue of the differences in the viscosities of the primary alcohol-secondary ether and the secondary alcohol-primary ether. In general, refractive indices and densities are not suitable

for analytical methods because of the small differences between the isomers. It may be possible, also, to make use of the physico-chemical methods in the same manner. Halperin and Vander Werf (254), however, were unable to use infrared data on the isomeric butylene halohydrins obtained in the reaction of the similarity in the spectra. In the special case of halohydrin isomers such as obtained by Smith (109,255,256) and Paul (115) in the reactions of alkylene oxides with hydrochloric acid and by Swern, Billen and Knight (69) in the reaction of epichlorohydrin with allyl alcohol, it was possible to analyze the isomeric mixtures due to differences in the rates of reaction with alkali.

Melting-point composition curves have been used satisfactorily by Guss (252,253,257-260) and his students. Thus, in the reaction of styrene oxide with naphthol which yielded an isomeric mixture of aryl-ether-alcohols, the analysis was made by use of a phase diagram constructed by plotting melting-points against composition of known mixtures prepared from the pure isomers. The melting-points of the mixtures obtained from the epoxide reactions and of the known mixtures were observed under crossed polaroids in a

Beckmann-like apparatus with a calibrated thermometer. Raimond (112) used the Rheinboldt method in the determination of the isomeric 3,5-dinitrobenzoates of the chlorohydrins obtained in the reaction of propylene oxide with hydrochloric acid. Skau and Wakeham(261) advocate caution in the preparation of phase diagrams by the Reinboldt or capillary method as it is called. "In the first place, it does not readily permit the attainment of a true equilibrium between the solid and liquid phases, and secondly, the technique for the preparation of specimens of known composition involves a considerable source of error."

Rheinboldt method.- The capillary method and its modifications were attempted because of the apparent ease of manipulation and the small amounts of material needed. Analytically pure phenyl urethane derivatives of p-chlorobenzylphenyl- and p-chlorophenylbenzyl carbinol were prepared and fifteen samples which ranged in composition from 0-100% were weighed out to the nearest tenth of a milligram on an analytical balance. The samples were weighed by difference from a weighing-tube and transferred directly to the bottom of a test tube without touching the sides. An intimate mixture

was obtained by melting the components. On cooling, the solid was transferred to an agate mortar and pestle and finely ground. The melting points obtained by use of capillary tubes proved to be poorly reproducible. Better results were obtained by the use of a heating stage and observation of the melting-points under a microscope lens. The phase diagram constructed from the data so obtained indicated solid solution formation with a minimum at about 93° C. and a composition of 50-60% of the urethane of p-chlorophenylbenzyl carbinol. The ends of the phase diagram appeared to be satisfactory, but the points in the center of the diagram, between 40-60% did not fit the curve and, in fact, were not easily reproducible. The use of a Kofler heating stage microscope with crossed polaroids indicated that the compositions of the mixtures probably were not uniform. The method was abandoned in favor of thermal measurements since it was apparent that the Rheinboldt method as applied to the analysis of the reduction products of p-chlorostilbene oxide lacked the necessary precision and accuracy.

Thermal analysis.- It was reported in the experimental section that the reduction of p-chloro-

stilbene oxide gave $60.9 \pm 3.0\%$ of the urethane of p-chlorophenylbenzyl carbinol and $39.1 \pm 3.0\%$ of the isomer. The precision, then, is approximately 5-8 parts per hundred. From these data, it was assumed that the carbinols from which the urethanes were derived were present in the same ratio.

To check the assumption and to establish the accuracy of the method, a synthetic mixture of carbinols was prepared with 61.4% of p-chlorophenylbenzyl carbinol and 38.6% of the isomer. The carbinols were converted to the urethanes and analyzed by the phase diagram method as was done for the unknown mixture. The experimental determination showed 64.5% of p-chlorophenylbenzyl carbinol derivative. This involved an error of 3.1% or about 5 parts per hundred. The accuracy of the method may be considered as established since the error involved is no greater than the attainable precision.

The phase diagram indicated solid solution formation with a minimum at 77.5°C. and a composition of 57.5% of the urethane of p-chlorophenylbenzyl carbinol. Apparently the Rheinboldt method was even more inaccurate than at first supposed since the minimum appeared at

93° C. in the latter method. Solid solution formation was to be expected because of the similarity in the molecular structure.

Analysis of Reduction Products of p-Methylstilbene Oxide

Thermal method.- Fifteen accurately weighed mixtures of the analytically pure phenyl urethane derivatives of the isomeric p-methylphenylbenzyl-p-methylbenzylphenyl carbinols were prepared and the melting-points and freezing points determined in the manner described for the thermal analysis of the isomeric p-chloro-alcohols. Only heating curves could be obtained. Once the mixture was melted, it could not be crystallized again even on standing and seeding. The phase diagram indicated solid solution formation from 50-100% of p-methylphenylbenzyl carbinol and a eutectic at 80.5° between 0 and 50%. All mixtures between 0 and 50% showed a flat at approximately 80.5° , but the upper points could not be interpreted. It might have been possible to make use of the area between 50 and 100% for analytical purposes, but because of our inability to bring about crystallization of molten mixtures and because of uncertainties in the phase diagram, the thermal method was abandoned in favor of a cryoscopic method not previously reported for use with solid solutions.

Gryoscopic analysis: non-solid solution formation.- A generalized method, developed by the Bureau of Standards (262) for the determination of the percentage composition of a known component in a mixture of unknown composition consists of the determination of the freezing-point depression with a solvent which is not a component of the mixture and the freezing-point depression with the known component as solvent. Since the freezing-point depression in the latter case will be due only to those components of the mixture which differ from the solvent, it becomes possible to calculate the percentage composition of the known component. The method has been applied to the analyses of D.D.T. isomers (263).

The total number of moles of all components in a one gram sample of the unknown mixture, m_t , is solved for by use of equation 1:

$$(1) \quad m_t = \frac{W_s \cdot \Delta t_s}{1000 \cdot w_m \cdot K_{fs}}$$

W_s = the weight of solvent, s, which is known not to be a component of the unknown mixture, i.e., camphor or triphenylmethane.

Δt_s = freezing-point depression of solvent s.

K_{fs} = cryoscopic constant of solvent s.

w_m = weight of unknown mixture.

In a similar manner, by means of equation 2, the total number of moles of all components exclusive of the known component, m_x , in a one gram sample of the unknown mixture may be solved for with the known component as solvent:

$$(2) \quad m_x = \frac{w_A \cdot \Delta t_A}{1000 \cdot w_m \cdot K_{fA}}$$

w_A = weight of solvent A known to be a component of the mixture.

Δt_A = freezing-point depression of solvent A.

K_{fA} = cryoscopic constant of the solvent A.

w_m = weight of the unknown mixture.

From equation 3, m_A , an approximation of the total number of moles of component A, known to be a component of the mixture, in a one gram sample of the unknown mixture may be obtained:

$$(3) \quad m_t - m_x = m_A$$

The weight of component A in w_m grams of the unknown mixture, W'_A , may be obtained from equation 4:

$$(4) \quad w_m \cdot m_A \cdot M_A = W'_A$$

M_A = molecular weight of component A.

A more precise value of m_x and m_A may be obtained from equations 5 and 6:

$$(5) \quad m'_x = \frac{(W_A + W'_A) \cdot \Delta t_A}{1000 \cdot w_m \cdot K_{fA}}$$

$$(6) \quad m_t - m'_x = m'_A$$

The percentage composition of component A in the unknown mixture may now be evaluated by means of equation 7:

$$(7) \quad \%C_A = m'_A \cdot M_A \cdot 100$$

The equations are based on several assumptions:

(1) that the solutions are ideal and Raoult's law holds in the range of concentrations used.

- (2) that the freezing-point depression is small.
- (3) that the weight of solute is small compared to the weight of solvent.
- (4) that the latent heat of fusion of the solvent is not a function of temperature.
- (5) that on cooling the mixture, pure solvent solid separates, i.e., solid solution formation does not occur.

In dilute solutions, the first four assumptions are usually valid. If, however, solid solution does occur, the method must be modified.

Cryoscopic analysis of solid solutions.- It can be shown that equation 8 is valid for a two component system which forms solid solutions:

$$(8) \quad K'_{fA} = K_{fA} (1 - k) = m_B \Delta t_A$$

K_{fA} = cryoscopic constant of solvent A.

K'_{fA} = apparent cryoscopic constant of solvent A.

m_B = molality of B in A.

k = distribution coefficient of B between the solid and liquid phases of solvent A.

The composition of a given mixture of A and B

may be determined if the apparent cryoscopic constant can be evaluated. One method of obtaining the apparent cryoscopic constant is to determine the freezing-point depression of known mixtures of solute B in solvent A and graphing concentration vs. freezing-point depression for three or four mixtures over a relative short range of concentrations. The apparent cryoscopic constant of solvent A may then be evaluated, not only for the prepared mixtures, but for all concentrations over the range used. A second graph may be constructed by plotting the freezing-point depressions vs. the apparent cryoscopic constant. After determination of the freezing-point depression of the unknown mixture, the apparent cryoscopic constant may be obtained directly from the latter graph.

For a three component system, A, B, and C, which form solid solutions, the generalized method for a cryoscopic analysis previously described may be used, where equation 2 is transformed into equation 9:

$$(9) \quad m_x = \frac{W_A \cdot \Delta t_A}{1000 \cdot w_B \cdot K'_{fA}}$$

The apparent cryoscopic constant, K'_{fA} , is now a function of the distribution of the components exclusive of A, i.e., B and C, between the solid and liquid phases of solvent A.

It may be possible to approximate K'_{fA} by assuming that the distribution coefficient of C in A is the same as B in A. The apparent cryoscopic constant can then be evaluated at the experimentally determined freezing-point depression by means of the graph constructed from mixtures of solute B in solvent A as described above for two component systems.

The procedure for determination of the percentage composition of A in a mixture of A, B, and C is otherwise identical with that previously described for non-solid solution formation.

Discussion of cryoscopic results.- By use of the cryoscopic method for the analysis of solid solutions as described in the preceding paragraphs and reported in the experimental section, it was found that p-methylphenylbenzyl carbinol was present as $28.1 \pm 3.1\%$ of the total mixture and the isomer as $42.0 \pm 3.0\%$. The precision attainable in the determination of the percentage composition was approximately

7-11 parts per hundred. The lack of better precision may be due to the fact that the freezing-point depression is the difference between two large values, or it may be due to the assumption that the apparent cryoscopic constant of the carbinol-solvent is the same for the non-carbinol-solvents as for the carbinol-solute.

The accuracy of the method was checked by the analysis of a synthetic mixture of approximately the same composition as the unknown mixture. Thus, a three component mixture of p-methylphenylbenzyl carbinol (25.6%), p-methylbenzylphenyl carbinol (49.0%) and p-methylstilbene oxide was analyzed in the same manner as the unknown mixture. The determination, as reported in the experimental section, gave 22.7% of p-methylphenylbenzyl carbinol and 44.5% of p-methylbenzylphenyl carbinol, which involves an error of 9-11 parts per hundred. It appears that the error involved in the cryoscopic analysis is not greater than the precision attainable. The accuracy of the method is sufficient for the purposes set forth; namely, the determination of the ratio of isomers formed in the lithium aluminum hydride reduction of p-methylstilbene oxide.

It was assumed prior to the analysis that the reduction products consisted mainly of three components with unchanged p-methylstilbene oxide as the third component. This was verified by calculation of the average molecular weight of the reduction products by means of equation 10 (equation 1 inverted):

$$(10) \quad \text{Mol. Wt.} = 1/m_c$$

The molecular weight was found to be 218. Since the molecular weight of the carbinols is 212 and the molecular weight of the epoxide, 210, it appeared reasonable to assume that the epoxide was the third component.

The time-temperature curves for the mixtures, as illustrated in the experimental section, Diagram III, were typical of solid solution formation. This was to be expected because compounds which have similar structures are recognized as compounds which generally form solid solutions.

It is evident from Diagram IA that the apparent cryoscopic constant is not constant and may change by as much as 15-20% even in solutions as dilute as 0.06

mole fraction. As expected, in very dilute solutions, hence for small freezing-point depressions, the constant for p-methylphenylbenzyl carbinol approaches a constant value of 6.54. The deviation from 6.54 in more concentrated solutions may be due to deviations from Raoult's law. Similarly, it was found that the apparent cryoscopic constant of p-methylbenzylphenyl carbinol approached a constant value of 7.15.

The Bureau of Standards' method was used to determine the percent-composition of D.D.T. isomers. No mention, however, was made of the fact that the isomers probably formed solid solutions. The method as originally described was set up only for the analysis of mixtures in which pure solvent solid separates when the sample is cooled. Attention was called to the fact that the determination of the "cryoscopic constant" of the isomers lacked precision. This was attributed to the use of a Beckmann thermometer instead of thermocouples. It is more likely that the discrepancy arises from the marked change of the apparent cryoscopic constant with changes in concentration even in what may be considered as the range of dilute solutions.

The cryoscopic constant of triphenylmethane was

determined, as reported in the experimental section, with p-methylphenylbenzyl carbinol as the solute. The value of 12.3 closely checks the literature value of 12.45.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION

Thermal Analysis of Reduction Products of p-Chlorostilbene Oxide

Preparation of samples.-- p-Chlorophenylbenzyl and p-chlorobenzylphenyl carbinols were synthesized by the Grignard method and purified by distillation followed by recrystallization from Skelly C. The reference urethanes, used in the preparation of the phase diagram, synthesized from the purified alcohols by treatment with phenyl isocyanate and products purified by solution in carbon tetrachloride, filtration, evaporation and recrystallization from Skelly C. and methanol. Only analytically pure urethanes, which were analyzed for carbon and hydrogen and found within the limits of error of the analysis, were used in the preparation of the phase diagram.

The reduction products were prepared for analysis by solution in methanol to remove unchanged epoxide. The mixture of carbonols was treated with phenyl isocyanate, and the urethanes were purified as described. The unknown mixture so prepared was found to consist solely of the desired urethanes by carbon and hydrogen analysis. A synthetic mixture of pure carbinols was prepared in approximately the ratio

as determined for the unknown mixture. The carbinols were converted to the isomeric urethanes for analysis. The exact methods for the preparation of all samples are carefully described in the section on Synthetic Procedures. Details as to the quantities used, the yields obtained and the analytical data are given.

All samples were weighed by difference directly into the Beckmann cell.

Apparatus.— Time-temperature curves were taken in a modified Beckmann cell with a calibrated copper-constantan thermocouple used in conjunction with a Model S, Leeds and Northrup Micromax automatic recording potentiometer. A typical heating curve and cooling curve is reproduced in Diagram A. The curves were inked in on graph paper which was subdivided in intervals of 2 degrees C. and 10 minutes. The design of the Beckmann cell is shown in Diagram C. Thermal equilibrium was attained by means of a spiral shaped glass stirring rod attached to a soft iron core and operated at 80 cycles per minute in vertical motion by a solenoid attached to a circuit breaker. The "hot" junction of the asbestos covered copper-constantan thermocouple was placed in the narrow glass tube

which was immersed directly in the sample and which contained sufficient nujol to cover the welded junction. Instrumental calibrations were made against the urethanes, benzoic acid, and the ice-point with the reference junction at constant room temperature. A calibrated electrically heated oil bath was used to control the rate of heating from 0.5 to 1.5 C. per minute.

Precision of measurements.-- Both cooling-curves and heating-curves were obtained and automatically recorded as described. The lower freezing-points were more easily read from the cooling-curves and more reliance was placed upon these values which were reproducible to 1.0 C. on any given sample. The upper melting-points were obtained from heating-curves with difficulty. Due to decomposition, only three or four curves were taken on any one sample.

Phase diagram.-- Ten samples of analytically pure urethane derivatives of the isomeric carbinols were prepared with compositions which ranged from 0-100%. The composition of the last mixture to be employed was chosen to check the minimum melting-point of the phase diagram. The data was recorded in Table II. The phase diagram is shown in Diagram B.

Analysis of unknown mixture.— The unknown mixture was added to the urethane of p-chlorophenylbenzyl carbinol, quantitatively, and the melting-point and freezing-point obtained. The new mixture was of such composition to bring the composition into a well calibrated section of the phase diagram. By the appropriate calculations, the percentage-composition of the urethane of p-chlorobenzylphenyl carbinol was determined. A similar procedure was employed for the analysis of the urethane of p-chlorophenylbenzyl carbinol. The data are recorded in Table III.

$$\%C_A = \frac{\%C_A^* \cdot W_t}{W_m}$$

$\%C_A$ = percent-composition of p-chlorobenzylphenyl derivative in the unknown mixture

$\%C_A^*$ = percent-composition of p-chlorobenzylphenyl carbinol derivative in the new mixture

W_t = total weight of unknown mixture and the added p-chlorophenylbenzyl derivative

W_m = weight of unknown mixture

Analysis of synthetic mixture.— The same procedure employed for the analysis of the unknown mixture was used for the analysis of the synthetic mixture. The data are recorded in Table IV.

TABLE II

Phase Diagram: Binary System

Phenylurethane derivatives of
p-Chlorophenylbenzyl Carbinol (A)
and
p-Chlorobenzylphenyl Carbinol (B)

Sample #	Wgt. of A	Wgt. of B	%comp. of A	%Comp. of B	Upper m.p.	Lower m.p.
1	-	-	100	0.0	-	115.5
2	5.87	1.21	83.0	17.0	104.0	98.0
3	3.47	1.49	70.0	30.0	96.0	87.0
4	2.93	2.10	58.2	41.8	-	77.0
5	3.61	3.37	51.7	48.3	96.0	82.0
6	3.24	4.25	42.0	58.0	106.5	92.0
7	1.61	4.95	34.6	65.4	112.0	99.5
8	1.02	4.26	19.3	80.7	124.0	112.0
9	-	-	0.0	100.0	-	130.5

TABLE III

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p-Chlorostilbene Oxide
Analysis of Phenylurethane Derivatives
of Reduction Products

Phenylurethane of p-chlorophenylbenzyl Carbinol (A)

Phenylurethane of p-Chlorobenzylphenyl Carbinol (B)

	<u>Solvent A</u>	<u>Solvent B</u>
Weight of solvent:	1.896	2.810
Weight of solute (unknown mixture)	1.973	1.972
Lower melting-point:	94.0	106.0
Percent-composition of solvent-solute mixture (Phase Diagram)		
A:	78.5%	26.3%
B:	21.5%	73.7%
Percent-composition of unknown mixture (calculated)		
A:	57.8%	63.9%
B:	42.2%	36.1%
<u>Average:</u>	60.9 $\pm$ 3.1% of the phenylurethane of p-Chlorophenylbenzyl Carbinol (A)	
	39.1 $\pm$ 3.1% of the phenylurethane of p-Chlorobenzylphenyl Carbinol (B)	

TABLE IV

Synthetic Mixture of
Phenylurethane Derivatives of
p-Chlorophenylbenzyl Carbinol (A)
and
p-Chlorobenzylphenyl Carbinol (B)

Percent-composition of alcohols:		
p-chlorophenylbenzyl carbinol:		61.4%
p-chlorobenzylphenyl carbinol:		38.6%
Weight of solvent B:		2.787 g.
Weight of solute (phenylurethane derivatives of the synthetic mixture of alcohols):		1.940 g.
Lower melting-point of solvent-solute mixture:		105.3
Percent-composition (by phase diagram) of		
	A:	26.5%
	B:	73.5%
Percent-composition (calculated) of:		
	A:	64.4%
	B:	35.6%
Error: parts per hundred:		5-8

Cryoscopic Analysis of Reduction products
of p-Methylstilbene Oxide

Preparations of samples.- The unknown mixture, an oil, obtained from the reduction of p-methylstilbene oxide was used without further treatment other than washing with water and dilute alkali, drying, and concentrating the product. The reference alcohols were synthesized by the Grignard method in the case of p-methylphenylbenzyl carbinol and by the reaction of styrene oxide with p-methylphenyl lithium in the case of p-methylbenzylphenyl carbinol. The alcohols were purified by fractional distillation through a two-foot column packed with glass beads followed by several recrystallizations from Skellysolve. The alcohols considered pure enough for use when five recrystallizations successively showed no change in melting-point and the carbon and hydrogen content was within experimental error. Details as to the quantities used, the yields obtained and the analytical data are given in the section on Synthetic Procedures.

Apparatus.- All melting-points were taken in a modified Beckmann cell with a platinum resistance thermometer. The design of the Beckmann cell is shown

in Diagram C. Thermal equilibrium was established by means of a spiral-shaped glass stirring rod attached to a soft iron core and operated in vertical motion at 80 cycles per minute by a solenoid wired to a circuit breaker. The dimensions of the stirrer were such that it did not touch the sides of the Beckmann cell or the thermometer so as to avoid mechanical shock and heat effects due to friction. A calibrated electrically heated oil bath was used to control the rate of heating within 0.01 C. per minute by the proper adjustment of the two Variacs connected in series.

The platinum resistor thermometer was manufactured by the Leeds and Northrup Company (Serial No. 683834) and calibrated by the Bureau of Standards (N. B. S. 958). The following constants were used: steam point, $c = 0.00392488$, sulfur point, $= 1.492$. The resistance at 0 C. was found to be approximately 25.447 Absolute Ohms. The change in the resistance was almost exactly 0.100 Ohm per degree C. The thermometer itself had a four lead cable and consisted of a pyrex tube 0.7 cm. in diameter and approximately 46 cm. long. The sensitive portion was about 2 cm. long. All measurements were made with a current of

2.0 milliamperes in conjunction with a Leeds and Northrup No. 2284-d Type HS Galvanometer with a sensitivity of 0.05 uv. and a calibrated Type G-2 Mueller Bridge (Serial No. 740,547). The measurements, in absolute ohms, with the commutator in the N (normal) position, were converted to degrees C. by means of the Callendar equation.

Melting-point procedure and precision of measurements.- The preferred cooling-curves could not be obtained because of the pronounced tendency for supercooling exhibited by the isomeric p-methyldiaryl alcohols. The sample was weighed by difference directly into the Beckmann cell and melted in an oil bath at a temperature only 3 or 4 degrees above the melting-point. When the stirring became labored as the sample crystallized, the voltage control was adjusted so as to raise the temperature at the rate of 0.01 to 0.07 C. per minute. The heating curves, an example of which is given in Diagram D, were constructed by a graph of resistance vs. time.

The melting-points were obtained from the heating-curves at the point of intersection, where the rate of heating markedly changed. The change in the rate of heating indicated the disappearance of the solid

phase. A visual check was made after the break in the curve appeared to be certain. A minimum of two melting-points were taken on any given sample. The average deviation never exceeded ± 0.004 ohm ($\pm 0.04^\circ\text{C.}$) and the maximum deviation never exceeded ± 0.007 ohm ($\pm 0.07^\circ\text{C.}$). Generally, the average deviation was ± 0.002 ohm ($\pm 0.02^\circ\text{C.}$) and the maximum ± 0.002 ohm ($\pm 0.02^\circ\text{C.}$). One sample, in which the melting-point was taken without stirring, showed, for six determinations, an average deviation of ± 0.009 ohm ($\pm 0.09^\circ\text{C.}$) and a maximum of ± 0.018 ohm ($\pm 0.18^\circ\text{C.}$).

Apparent cryoscopic constant as a function of the freezing point depression.--The melting point of pure p-methylphenylbenzyl carbinol and the three mixtures with its isomer as solute was recorded in Table V. From the data, a melting-point vs. composition plot, Diagram E, was constructed. A second graph, Diagram F, was constructed, in which the apparent cryoscopic constant, calculated by means of equation 8 from the data in Diagram V and recorded in Table VI, ^{was plotted} against freezing-point depression. In Table VII were recorded the melting points of pure p-methylbenzylphenyl carbinol and three mixtures with its isomer as solute. Diagram G was constructed from the data in Table VII. Diagram H was constructed

from the data in Diagram G and recorded in Table VIII, as was done for the isomeric compound.

Cryoscopic constant of triphenylmethane. —

The cryoscopic constant of triphenylmethane was determined with p-methylphenylbenzyl carbinol as the solute. Equation 11 was used.

$$(11) \quad K_{fs} = \frac{M_x \cdot W_s \cdot \Delta t_s}{1000 \cdot w_x}$$

K_{fs} = cryoscopic constant of triphenylmethane

W_s = weight of triphenylmethane

Δt_s = freezing point depression of triphenylmethane

w_x = weight of p-methylphenylbenzyl carbinol

M_x = molecular weight of p-methylphenylbenzyl carbinol

The data was recorded in Table IX.

Analysis of the reduction products. — An

accurately weighed sample of the unknown mixture, w_m , was placed in the Beckmann cell and to this was added analytically pure p-methylphenylbenzyl carbinol,

W_A , in large enough quantities to bring the mole fraction of the solute between 0 and 0.06. The freezing-point depression was determined precisely as described above. The apparent cryoscopic constant was taken from Diagram E at the determined freezing point depression. The data thus obtained were substituted in equation 9 to give the total number of moles of all components exclusive of p-methylphenylbenzyl carbinol in a one gram sample of the unknown mixture. To obtain the total number of moles of all components in a one gram sample of the mixture, the freezing point depression of a dilute solution of the mixture in triphenylmethane was determined and the proper values inserted in equation 1. The percent-composition of p-methylphenylbenzyl carbinol was then found by means of equations 3-7. The data for two different samples was summarized in Table X. The same procedure was followed for p-methylbenzylphenyl carbinol and the data recorded in Table XI.

Analysis of the synthetic mixture. ** A synthetic mixture of p-methylphenylbenzyl carbinol, and p-methylbenzylphenyl carbinol, and p-methylstilbene oxide was prepared with approximately the same composition as determined for the unknown mixture. The synthetic mixture was analyzed in the

same manner as the unknown mixture and the data recorded in Tables XII and XIII. The total number of moles of all components, was, however, calculated from the known molecular weights and the weights of sample used and recorded in Table XIV.

TABLE V
Two Component System
Melting-point Composition Data

m.p. 67.31°C.

mol. wgt. 212.3

m.p. 45.64°C.

mol. wgt. 212.3

Sample no.	Weight solvent grams	Weight solute grams	Molality of solution	m.p. of mixture degrees C	m.p. de- pression degrees C
# 1	4.620	0.2270	0.2314	65.70	1.61
# 2	7.301	0.4084	0.2635	65.41	1.90
# 3	7.301	0.4606	0.2971	65.04	2.27

TABLE VI

Apparent Cryoscopic Constant of
p-Methylphenylbenzyl carbinol*

$$K'_f = \Delta t / m$$

<u>Molality</u>	<u>Δt ° C.</u>	<u>K'_f</u>
0.0400	0.26	6.50
0.0800	0.52	6.50
0.0900	0.59	6.55
0.100	0.65	6.50
0.120	0.79	6.58
0.140	0.92	6.57
0.150	0.99	6.60
0.160	1.06	6.62
0.180	1.20	6.67
0.200	1.35	6.75
0.220	1.51	6.85
0.240	1.69	7.03
0.260	1.87	7.20

* Data obtained from Melting-point Composition
Curve, Diagram E.

TABLE VII
Two Component System
Melting-point Composition Data

m.p. 45.64°

mol. wgt. 212.3

m.p. 67.31°

mol. wgt. 212.3

Sample no.	Weight solvent grams	Weight solute grams	Molality solution	m.p. of mixture degrees C	m.p. de- pression degrees C
# 4	7.945	0.2062	0.1222	44.76	0.88
# 5	8.230	0.3154	0.1805	44.26	1.38
# 6	7.543	0.3724	0.2326	43.78	1.86

TABLE VIII

Apparent Cryoscopic Constant of
p-Methylbenzylphenyl Carbinol*

$$K'_f = \Delta t / m$$

<u>Molality</u>	<u>$\Delta t^\circ \text{C.}$</u>	<u>K'_f</u>
0.0200	0.145	7.25
0.0400	0.290	7.25
0.0600	0.435	7.25
0.0800	0.580	7.25
0.100	0.725	7.25
0.120	0.880	7.28
0.140	1.03	7.36
0.160	1.20	7.48
0.180	1.37	7.61
0.200	1.54	7.70
0.230	1.85	8.04

* Data obtained from Melting-point Composition
Curve, Diagram G.

TABLE IX

Cryoscopic Constant of Triphenylmethane

Mol. wgt. 212.3

Weight of triphenylmethane:	8.077 g.
Weight of solute:	0.3471 g.
Melting-point of triphenylmethane:	93.51° C.
Melting-point of triphenylmethane-solute mixture	91.03° C.
Freezing-point depression:	2.48° C.
Cryoscopic constant (calcd):	12.3

TABLE X

Reduction of p-Methylstilbene Oxide
Cryoscopic Data of Unknown Mixtures

M.p. 67.31°C.

Mol. wgt. 212.3

	Sample # 9	Sample # 10
Weight of solvent (grams):	7.637	7.637
Weight of solute (unknown Mixture, grams):	0.3866	0.4991
Melting-point of solvent- solute mixture (deg. C.):	66.18	65.97
Melting-point depression (deg. C.):	1.13	1.34
Molality at freezing-point depression (see figure)::	0.170	0.198
Apparent cryoscopic constant at molality:	6.65	6.76
Percent-composition of solvent in unknown mixture:	25.0	31.1

Average: $28.1 \pm 3.1\%$ of p-Methylphenylbenzyl
carbinol

Precision: 11.0 parts per hundred

TABLE XI

Reduction of p-Methylstilbene Oxide
Cryoscopic Data of Unknown Mixtures

M.p. 45.64°

Mol. wgt. 212.3

	Sample # 7	Sample # 8
Weight of solvent (grams):	8.735	8.076
Weight of solute (unknown mixture, grams)	0.2990	0.4930
Melting-point of solvent- solute mixture (deg.C.):	44.97	44.56
Melting-point depression (deg. C.):	0.67	1.08
Molality at freezing-point depression (see figure):	0.0092	0.0146
Apparent cryoscopic constant at Molality:	7.25	7.40
Percent-composition of solvent in unknown mixture:	39.0	45.0

Average: $42.0 \pm 3.0\%$ of p-Methylbenzylphenyl
carbinol

Precision: 7.1 parts per hundred

TABLE XII
Three Component Mixture

Solvent:

M.p. 67.31° C.

Composition of solute:	Sample # 12
p-Methylphenylbenzyl carbinol	0.0497 g. (25.6%)
p-Methylbenzylphenyl carbinol	0.0964 g. (49.7%)
p-Methylstilbene oxide	0.0480 g. (24.7%)
Weight of solute:	0.1941 g.
Weight of solvent:	4.167 g.
Melting-point of solvent- solute mixture:	66.19° C.
Melting-point depression:	1.12° C.
Molality at m.p.	0.169
Apparent cryoscopic constant at molality:	6.64
Percent-composition of p-methylphenylbenzyl carbinol-experimental:	22.7%
Error: parts per hundred	11.3

TABLE XIII
Three Component Mixture

m.p. 45.64°C.

Composition of solute:	Sample # 11
p-Methylbenzylphenyl carbinol	0.190 g. (49.0%)
p-Methylphenylbenzyl carbinol	0.101 g. (26.0%)
p-Methylstilbene oxide	0.097 g. (25.0%)
Weight of solute:	0.388 g.
Weight of solvent:	7.653 g.
Melting-point of solvent- solute mixture:	44.68°C.
Melting-point depression:	0.96°C.
Molality at m.p.:	0.130
Apparent cryoscopic constant at molality:	7.31
Percent composition of p-Methylbenzylphenyl carbinol-experimental:	44.1%
Error: parts per hundred:	10.0

TABLE XIV

p-Methylstilbene Oxide
Total Number of Moles of All Components
in Reduction Products

Wgt. of triphenylmethane (solvent):	8.34 g.
Wgt. of solute (reduction products)	0.400 g.
M.p. of triphenylmethane (solvent):	93.51° C.
M.p. of solvent-solute mixture	90.81° C.
Melting-point depression:	2.70° C.
 Total no. of moles of all components in one gram sample of reduction products:	 0.00458
Average molecular weight of reduction products:	218

HEATING CURVE: COMP., 34.6 % A

COOLING CURVE COMP., 70.0 % A

TIME - TEMPERATURE CURVES

PHENYLURETHANES OF P-CHLOROPHENYL-
BENZYL CARBINOL (A) AND P-CHLORO-
BENZYLPHENYL CARBINOL (B).

Diagram A

Diagram B

MELTING-POINT APPARATUS

Diagram D

MELTING POINT - COMPOSITION CURVE

SOLVENT: P-METHYLPHENYLBENZYL CARBINOL

SOLUTE: P-METHYLBENZYLPHENYL CARBINOL

P-METHYLPHENYLBENZYL CARBINOL (A)

P-METHYLBENZYLPHENYL CARBINOL (B)

Diagram G

Synthetic Procedures

p-Methylbenzyl Bromide

The compound was prepared by a slight modification of the procedure of Atkinson and Thorpe (264). To 1000 ml. (861 g., 8.12 moles) of p-xylene maintained at 130°, there was added, dropwise, 544 ml. (1710 g., 10.7 moles) of bromine. The reaction mixture was refluxed under vacuum produced by a water pump to remove dissolved hydrobromic acid. Distillation through a 75 cm. column packed with glass beads yielded (1) unchanged p-xylene, b.p. 32°/15 mm., 35°/18 mm. (reported (265): 50°/32 mm.), (2) p-bromoxylene, b.p. 84°/13 mm. (reported (266): 205.5°/755 mm.), (3) p-methylbenzyl bromide, 712 g. (475%), b.p. 97°/13 mm., 99°/15 mm., 111°/24 mm., 114°/28 mm., 121°/41 mm. (reported (264): b.p. 218-20°/740 mm.) which crystallized on standing, m.p. 37-8° (reported (264): m.p. 35°) and (4) the residue which consisted mostly of p-xylylene dibromide.

A yield of 45.5% of p-methylbenzyl bromide was obtained on repetition of the experiment.

Alkaline potassium permanganate oxidation of

p-methylbenzyl bromide yielded terephthalic acid.

861 g.	1710 g.	712 g.
(8.12 moles)	(10.7 moles)	(3.85 moles)

$$\begin{aligned} \% \text{ Yield} &= \frac{\text{Moles of p-methylbenzyl bromide} \cdot 100}{\text{Moles of p-xylene}} \\ &= \frac{3.85 \cdot 100}{8.12} = 47.5\% \end{aligned}$$

Reduction of p-toluic acid

To 67.0 g. (1.77 moles) of finely ground lithium aluminum hydride in 500 ml. of dried ether, 100 g. (0.735 mole) of p-toluic acid was added in small portions. When the addition was completed, the reaction mixture was hydrolyzed with water and dilute hydrochloric acid. The ether layer was separated and the aqueous portion extracted with fresh solvent. The combined ether solutions were washed successively with water, 10% sodium hydroxide solution, and water. The ether was dried over Drierite and concentrated. The residual was distilled to give 30.7 g. of an oil, b.p. 210-4°/731 mm. The oil contained some p-methylbenzaldehyde. The 2,4-dinitrophenylhydrazone derivative, m.p. 239-240.5°, showed no depression in a

mixed melting-point with an authentic sample. A second fraction was obtained, b.p. 171-4°/12 mm., which crystallized. The melting-point, after recrystallization from ethanol, was 63.0-4.0° (reported for di-p-xylyl ether (267): b.p. 310-11°, m.p. 61.5-2.5°).

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02.
Found: C, 85.27; H, 8.41.

p-Methylbenzaldehyde

The compound was prepared by a slight modification of the procedure of Haas and Bender (268). Ninety-two grams (1.04 moles) of 2-nitropropane was added to a solution of 23.0 g. (1.00 mole) of sodium metal dissolved in 1 l. of absolute ethanol. To the warm reaction mixture, there was added at one time 185 g. (1.00 mole) of p-methylbenzyl bromide. The reaction mixture was allowed to stand for 4-5 hours, extended with ether, washed successively with water, 10% sodium hydroxide, and water. The ether solution was dried over Drierite and concentrated. Distillation of the residual oil through a 75 cm. column packed with glass beads ~~which~~ yielded 94.9 g. (79.1%) of p-methylbenzaldehyde, b.p. 88-5°/13 mm., 99-102°/27 mm.; 2,4-dinitrophenylhydrazones, m.p. 239.6-40.0° (reported (269): m.p. 232.5-234.5°):

semicarbazone, m.p. 217.0-217.1° (reported (270):
m.p. 215°, 219-220°).

A yield of 80.0% of p-methylbenzaldehyde was
obtained on repetition of the experiment.

A commercial sample of p-methylbenzaldehyde,
"practical grade", was found to contain a large
amount of the o-isomer. The 2,4-dinitrophenylhydrazone
was recrystallized several times from ethanol, m.p.
185-215° (reported for derivative (271) m.p. 195°;
derivative (271) m.p. 232.5-4.5°, 239.6-240.6°,
239.0-40.5°). The semicarbazone was recrystallized
once from ethanol, m.p. 211-12° (reported for
derivative (271) m.p. 212°; for derivative (270)
m.p. 215°, 219-20°, 217°). Alkaline hydrogen peroxide

oxidation of the aldehyde yielded the toluidic acid, m.p. 85-100° (reported for derivative (272): m.p. 102°; for derivative (273): m.p. 177°).

The commercial p-methylbenzaldehyde, so-called, was condensed with benzylmagnesium chloride as described in the preparation of p-methylphenylbenzyl carbinol by Method A. Dehydration of the carbinol, as described in the preparation of p-methylstilbene by method A, gave a small amount of p-methylstilbene, m.p. 119-20° and a larger amount of a compound melting at 41-5° (reported for methylstilbene (229): m.p. 120°). Preparation of the phenylurethane derivative of the carbinol gave a m.p. of 102.5-103.1° (reported for derivative (215): 114°.).

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73%; H, 6.39%.
Found: C, 79.82%; H, 6.45%.

p-Methylphenylbenzyl carbinol

Method A.- The standard techniques for the preparation of a Grignard reagent were used. Two hundred and thirty ^{ml.} (253 g., 2.00 moles) of redistilled benzyl chloride was added to 48.6 g. (2.00 moles) of magnesium turnings suspended in 2 l. of sodium dried ether. The reaction mixture was allowed to stand for several hours. To the ether solution, there was added drop-

wise 180 g. (1.5 moles) of freshly distilled p-methylbenzaldehyde. After several hours, the reaction mixture was hydrolyzed at 0-10°, with a saturated ammonium chloride solution. The ether solution was separated and the aqueous portion extracted with ether. The combined ether solutions were washed successively with water, 10% sodium hydroxide, and water. The ether was dried over Drierite and concentrated. The residual oil, on distillation through a short vigreux column, yielded a small amount of dibenzyl and 235 g. (74.0%) of p-methylphenylbenzyl-carbinol, b.p. 148°/ 1.5 mm., crude m.p. 66.8-68.2.

A yield of 80.5% of p-methylphenylbenzyl carbinol was obtained on repetition of the experiment.

For the purposes of cryoscopic analysis, the carbinol was redistilled through a 60 cm. column packed with glass beads and was then recrystallized several times from Skelly C and finally from methanol. The changes in melting-point were followed by means of the platinum resistance thermometer. When 5 additional recrystallizations showed no rise in the m.p., 67.06-67.31°, the sample was analyzed

for carbon and hydrogen, (reported (274.215) m.p. 66°; 68°).

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85%; H, 7.60%
Found: C, 84.87%; H, 7.60%.

253 g.	180 g.	235 g.
(2.00 moles)	(1.50 moles)	(1.11 moles)

$$\begin{aligned} \% \text{ Yield} &= \frac{\text{Moles of p-methylphenylbenzyl carbinol}}{\text{Moles of p-methylbenzaldehyde}} \times 100 \\ &= \frac{1.11 \times 100}{1.50} = 74.0\% \end{aligned}$$

Phenylurethane derivative.—A mixture of 34.6 g. (0.163 mole) of p-methylphenylbenzyl carbinol prepared by Method A and 18 ml. (0.165 mole) of redistilled phenyl isocyanate were warmed on a steam bath for 1 hour. The oil crystallized on standing. The solid was triturated under Skelly C to remove the unchanged isocyanate, dissolved in carbon tetrachloride, and filtered to remove any diphenylures. The solvent was removed and 42.0 g. (64.0%) of the urethane recovered. The product was recrystallized from Skelly C and from ethanol, m.p. 114.8-115.8°

(reported (215): m.p. 114°).

A yield of 60.0% was obtained on repetition the experiment with larger quantities of the carbinol.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 79.73; H, 6.39%.
Found: C, 79.92%; H, 6.22%.

Method B.— The usual techniques for the preparation of a Grignard reagent were employed. One hundred and fifty-eight ml. (219 g., 1.28 moles) of p-bromotoluene was added dropwise to 31.6 g. (1.3 moles) of magnesium turnings suspended in 2 l. of sodium dried ether. The reaction mixture was allowed to stand for an hour. To the ether solution, there was added 140 ml. (143 g., 1.19 moles) of freshly distilled phenylacetaldehyde. After several hours, the reaction mixture was worked up as described in Method A.

Distillation of the oil yielded 53.6 g. (21.1%) of p-methylphenylbenzyl carbinol, m.p., after several recrystallizations, 66.5-67.8°. The phenylurethane derivative was prepared, as described in Method A, m.p. after several recrystallizations from Skelly C, 109.6-114.2°. A mixed melting point with the authentic analytically pure phenylurethane showed no depression.

145 g.

219 g.

55.6 g.

(1.19 moles)

(1.28 moles)

(0.252)

% Yield = $\frac{\text{Moles of p-methylbenzyl carbinol} \times 100}{\text{Moles of phenylacetaldehyde}}$

$$= \frac{0.252 \times 100}{1.19} = 21.1\%$$

p-Methylbenzylphenyl carbinol

Method A. The standard techniques for the preparation of Grignard reagent were used with the exception that a tantalum wire Hirschberg stirrer was employed. One hundred and sixty-seven g. (0.905 mole) of p-methylbenzyl bromide dissolved in 500 ml. of sodium dried ether was added rapidly to 22.0 g. (0.906 mole) of magnesium turnings suspended in 1.5 l. of ether cooled in an ice, water, and salt bath. To the reaction mixture, there was added 90.5 ml. (95.0 g, 0.897 moles) of freshly distilled benzaldehyde dissolved in 500 ml. of ether. After several hours, the reaction mixture was worked up as described in the preparation of the isomer.

Addition of methanol to the residual oil, caused the separation of 30.0 g. (35.3%) of symmetrical-p,

p'-dimethyldiphenylethane, which was recrystallized several times from methanol, m.p. 81.4-82.4° (reported (275): m.p.

Anal. Calcd. for $C_{16}H_{18}$ C, 91.37% H, 8.62%.
Found: C, 91.05%; H, 8.32%.

Removal of the methanol and distillation of the residual oil yielded unchanged benzaldehyde, b.p. 52°/2.1 mm., 42.5°/0.9 mm. (reported (271) b.p. 179°) and 27.5 g. of a higher boiling fraction, b.p. 110-113° (0.035 mm.). Addition of Skelly C to the latter fraction caused the separation of p-methylbenzylphenyl ketone which was recrystallized several times from Skelly C, m.p. 95.8-97.5°. The sample thus obtained, when mixed with an authentic specimen of the ketone, showed no depression in the melting point.

Removal of the Skelly C yielded 20.4 g. (10.7%) of p-methylbenzylphenyl carbinol which was recrystallized several times from Skelly A, m.p. 44.6-46.2°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85%; H, 7.60%.
Found: C, 84.69%; H, 7.30%.

A yield of 68.4% of sym.-p,p'-diphenyldiphenylethane, b.p. 106° (0.20 mm.), was obtained

in a similar experiment.

167 g.	95.0 g.	20.4 g.
(0.905 mole)	(0.897 mole)	(0.0962)

$$\begin{aligned} \% \text{ Yield} &= \frac{\text{Moles of p-methylbenzylphenyl carbinol} \times 100}{\text{Moles of Benzaldehyde}} \\ &= \frac{0.0962 \times 100}{0.897} = 10.7\% \end{aligned}$$

Phenylurethane derivative.— The phenylurethane of p-methylbenzylphenyl carbinol was prepared as described in the preparation of its isomer. The melting point, recrystallization from Skelly C, was 98.0-98.6°.

Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_2$: C, 79.73%; H, 6.39%.
Found: C, 79.96%; H, 6.45%.

Method B.—The standard techniques for the preparation of a lithium reagent were used. One hundred and thirty-five ml. (187 g., 1.09 moles) p-bromotoluene in 500 ml. of sodium dried ether was added, dropwise, to 15.3 g. (2.20 moles) of lithium shot suspended in 500 ml. of ether. The reaction mixture was cool-

ed in an ice, water and salt bath and 115 ml. (120 g., 1.00 mole) of freshly distilled styrene oxide, b.p. 76°/10 mm., added dropwise. After several hours, the reaction mixture was hydrolyzed and worked up as previously described for Grignard reactions.

The oil was distilled through a short vigreux column. There was obtained 103.6 g. (48.8%) of p-methylbenzylphenyl carbinol, b.p. 129° (0.023 mm.), crude m.p. 40.0-45.2°; phenylurethane, after recrystallization from methanol, m.p. 98.6-100.2°. A mixed melting-point with an authentic sample of the phenylurethane, prepared as in Method A, showed no depression.

A yield of 66.1% was obtained on preparation of the carbinol starting with 3.0 mole of styrene oxide.

For the purposes of cryoscopic analysis, the carbinol was redistilled through a 60 cm. column packed with glass beads and recrystallized several times from Skelly A. The changes in the melting-point were followed by means of the platinum resistance thermometer. When five additional recrystallizations showed no rise in the melting-point of 45.28.

-45.64°, the sample was analyzed for carbon and hydrogen.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85%; H, 7.60%.
Found: C, 84.80%; H, 7.56%.

120 g.	187 g.	103.6 g.
(1.00 moles)	(1.09 moles)	(0.488 mole)

$$\% \text{ Yield} = \frac{\text{Moles of p-methylbenzylphenyl carbinol} \times 100}{\text{Moles of styrene oxide}}$$

$$= \frac{0.488 \times 100}{1.00} = 48.8\%$$

p-Methylphenylbenzyl ketone.

Method A. From a mixture of 30.0 g. (0.141 mole) of carbinol, 28.8 g. (0.141 mole) of aluminum isopropoxide and 100 ml. of cyclohexanone, warmed in a water bath for 16 hours at 60-80°, there was obtained 23.2 g. (80.0%) of the ketone, crude m.p. 107.2-111.0°. The product, recrystallized four times from methanol, m.p. 109.2-110.8°, on duplicate analysis gave low results for carbon. Five additional recrystallizations gave a product, m.p. 109.7-110.8° which

on duplicate analysis indicated high results for carbon.

The semicarbazone was prepared by the method of Shriner and Fuson, crude m.p. 164.6-165.6°, recrystallized from methanol, m.p. 170-171° (reported for the semicarbazone (276) m.p. 168.9°, for the ketazine (276): m.p. 172-173°).

The oxide was prepared by the method of Shriner and Fuson (269b) crude m.p. 96.0-98.5°, which on standing reverted to a more stable form, m.p. 127.0-131.0°. The oxime was recrystallized once from methanol, m.p. 128.0-130.5° (reported (277,278): m.p. 131°, 130-131°).

30.0 g.

16.9 g.

(0.141 mole)

(0.0805 mole)

$$\% \text{ Yield} = \frac{\text{Moles of p-methylphenylbenzyl ketone} \times 100}{\text{Moles of p-methylphenylbenzyl carbinol}}$$

$$= \frac{0.0805 \times 100}{0.141} = 57.1\%$$

Method B.- A mixture of 30.0 g. (0.141 mole) p-methylphenylbenzyl carbinol and 28.8 g. (0.141 mole)

of aluminum isopropoxide in 150 ml. of methyl ethyl ketone was dried refluxed for 35 hours, hydrolyzed with water and hydrochloric acid, and extracted with ether. The ether was dried over Drierite and concentrated. A yield of 16.9 g. (57.1%) was obtained, m.p., after recrystallization from ethanol, 109.6-111.1° (reported (279,280, 212) m.p. 108-110°, m.p. 110°, m.p. 107.5°).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.66%; H, 6.71%.
Found: C, 85.84%; H, 6.48%.

p-Methylbenzylphenyl ketone. Method A.- A mixture of 19.4 g. (0.0915 mole) of p-methylbenzylphenyl carbinol and 18.6 g. (0.0915 mole) of aluminum isopropoxide in 100 ml. of dried methyl ethyl ketone was refluxed for 35 hours. The reaction mixture was hydrolyzed with water and hydrochloric acid. The aqueous portion was extracted with ether and the ether washed with water. The solution was dried over Drierite and concentrated. The residual oil, 5.6 g. (29.0%), was dissolved in methanol, seeded, and recrystallized from ethanol, m.p. 96.3-97.5° (reported (278): m.p. 94°). When mixed with the ketone obtained in the preparation of p-methylbenzylphenyl carbinol, m.p. 95.8-97.5°, the melting-point

showed no depression.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.66%; H, 6.71%
Found: C, 85.76%; H, 6.86%.

19.4 g.

5.8 g.

(0.0915 mole)

(0.0266)

% Yield = $\frac{\text{Moles of p-methylbenzylphenyl ketone} \times 100}{\text{Moles of p-methylbenzylphenyl carbinol}}$

$$= \frac{.0266}{.0915} \times 100 = 29.1\%$$

Method C.- To 193 g. (1.45 mole) of aluminum chloride suspended in 200 ml. of toluene, there was added 100 g. (0.650 mole) of phenacyl chloride dissolved in 300 ml. of toluene. The reaction mixture was refluxed for 16 hours and then hydrolyzed with cracked ice and concentrated hydrochloric acid. The toluene solution was separated and dried by azeotropic distillation. The residual oil was distilled through a small vigreux column and re-distilled through a 60 cm. column packed with glass beads yielding 16.4 g. (12.0%), of a mixture of products, b.p. 139-140° /33 mm., crude m.p. 78.0-87.0°.

Twelve recrystallizations from methanol raised the melting-point to 96.3-99.0°. This sample, when mixed with an authentic sample of the p-methylbenzylphenyl ketone (m.p. 95.8-97.5°), showed a distinct depression; mixed m.p. 93.6-94.6°. The product is evidently an ~~e~~-isomer of p-methylbenzylphenylketone. By the same procedure, Strzelecka (281) reported a product which melted at 57° and Collet (282) reported a melting-point of 84-5°.

p- Methylstilbene.

Method A.- The usual techniques for the preparation of a diazonium salt were employed. A solution of 150 g. (2.00 moles) of sodium nitrite in 300 ml. of water was added to 214 g. (2.00 moles) of p-toluidine in 400 ml. of water and 600 ml. of conc. hydrochloric acid cooled to 0°. To the diazotized solution, there was added 1 l. of dioxane, 440 g. (3.24 moles) of sodium acetate and 85.0 g. (0.500 mole) of cupric chloride. To the cold solution, there was now added, 148 g. (1.00 mole) of cinnamic acid. The reaction mixture was allowed to stand overnight with stirring at room temperature. The oil which formed was separated and the aqueous portion extracted with ether. The ether and oil were combined and

washed successively with water, dilute hydrochloric acid, saturated sodium bicarbonate solution, 10% sodium hydroxide solution, and finally with saturated sodium chloride solution. The ether was dried over Drierite and concentrated. The residual oil on distillation yielded an oily solid, b.p. 212-228°/38 mm., which on recrystallization from ethanol gave 56.0 g. (28.8%) of p-methylstilbene, m.p. 118-121°. A mixed melting-point with p-methylstilbene obtained by dehydration of p-methylphenylbenzyl carbinol showed no depression.

A yield of 20.0% of p-methylstilbene was obtained on repetition of the experiment under approximately the same conditions. The procedure of Heerwein, Buchner and van Emster (228) (reported: 48.8% yield) and of Bergmann and Shapiro (229) (reported: 40.0% yield, m.p. 120°) gave lower yields than reported. Other variations in the conditions of the experiment such as a change in the molar ratio of the reactants or the solvent, showed slightly lower yields of p-methylstilbene. In several experiments, 30.5-76.5% of the cinnamic acid was recovered from the sodium bicarbonate extracts. In one experiment, 17.5%

of p-chlorotoluene was isolated, b.p. 153-8°/733 mm. The identity was established by oxidation to p-chlorobenzoic acid, m.p. 239-242° (reported (272): m.p. 242°).

In several experiments, an acid, assumed to be a diarylacrylic acid, was isolated from the sodium hydroxide extracts ranging in yields from 23.5 to 56.0%, recrystallized from aqueous methanol, m.p. 173.8-175.0°. Decarboxylation by heat yielded benzaldehyde. The identity of the aldehyde was proved by the preparation of the semicarbazone and a mixed melting point with an authentic specimen of the derivative. Decarboxylation of the acid by means of copper and quinoline yielded a product, probably styrene, b.p. 30°/9.5 mm (reported (272): b.p. 33°/10 mm., which gave a positive test for unsaturation with bromine in carbon tetrachloride. The products of the decarboxylation were not further identified:

$$\% \text{ Yield} = \frac{\text{Moles of p-methylstilbene} \times 100}{\text{Moles of annamic acid}}$$

$$= \frac{0.288 \times 100}{1.00} = 28.8\%$$

Method B.— p-Methylphenylbenzyl carbinol was added to 50% sulfuric acid (by volume) and refluxed for several hours. The reaction mixture was cooled, extended with water and extracted with benzene. The solvent was removed and the p-methylstilbene recrystallized from ethanol, m.p. 119.2-119.5° (reported (274,229 283): m.p. 117°, 120°, 119.5°-120°).

p-Methylstilbene Oxide.

Perbenzoic acid.— The procedure of Tiffeneau and Levy (212) was used with slight modification. To a solution of 10.4 g. (0.452 mole) of freshly cut sodium dissolved in 200 ml. of absolute methanol at -5°, a solution of 100 g. (0.413 mole) of benzoyl peroxide in 400 ml. of dry chloroform at 0° was added slowly and with shaking while the temperature was kept at -5° to 0°. The reaction mixture was quickly extracted twice with a total of 1000 ml. of water and cracked ice. The aqueous extract was washed twice with a total of 400 ml. of ice-cold chloroform. To the aqueous solution, there was added 450 ml. of 1 N

sulfuric acid, cooled to 0° . The oil which precipitated was extracted three times with a total of 600-650 ml. of chloroform. Titration of released iodine with sodium thiosulfate indicated a yield of 41.6 g. (73.1%) in 650 ml. of wet chloroform solution.

The yields in the preparation of perbenzoic acid by the procedure ranged from 73.1% to 85.5%.

Oxidation procedure.— To a cold solution of 38.5 g. (0.279 mole) of perbenzoic acid in 600 ml. of wet chloroform, there was added a cold solution of 40.0 g. (0.206 mole) of p-methylstilbene (m.p. $119-120^{\circ}$) dissolved in 200 ml. of chloroform. The reaction mixture was allowed to stand for 12 hours in a refrigerator (consumption of active oxygen by titration, 96.5%) and an additional 5 hours at room temperature (consumption of active oxygen, 100.0%). The remaining 3.2 g. of perbenzoic acid in 50 ml. of chloroform, used as a blank, showed no loss in active oxygen for the first 12 hours. The chloroform solution was extracted twice with a total of 500 ml. of 10 % sodium hydroxide, washed with water, and concentrated on the steam bath. On cooling, the residual oil crystallized. There was obtained

40.1 g. (92.2%) of p-methylstilbene oxide, m.p. 59.0-60.0° crude, after recrystallization from Skelly A, (reported (212) m.p. 59-60°).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.66%; H, 6.71%.
Found: C, 85.81%; H, 6.54%.

40.0 g.

38.5 g.

40.1 g.

(0.206 mole)

(0.279 mole)

(0.190 mole)

$$\% \text{ Yield} = \frac{\text{Moles of p-methylstilbene oxide} \times 100}{\text{Moles of p-methylstilbene}}$$

$$= \frac{.190 \times 100}{0.206} = 92.2\%$$

Reduction of p-Methylstilbene Oxide To 330 ml.

of an ether solution containing 0.0180 g. per ml. (0.156 mole) of lithium aluminum hydride, analyzed by a modification of the gasometric procedure of Field and Grunwald, there was added, dropwise, a solution of 65.7 g. (0.313 mole) of p-methylstilbene oxide dissolved in 500 ml. of sodium dried ether. The reaction mixture was stirred at room temperature for an additional 12 hours and then hydrolyzed with water and saturated ammonium chloride solution. The

ether layer was separated and the aqueous solution extracted with fresh solvent. The combined ether solutions were washed with saturated sodium bicarbonate solution, dried over Drierite and concentrated on a steam bath under vacuum. The residual oil weighed 59.0 g. The aqueous portion was carefully acidified with dilute hydrochloric acid and extracted with ether. The ether was washed with water, saturated sodium bicarbonate solution, dried and concentrated under vacuum. An additional 2.6 g. of the oil was obtained; total recovery, 61.6 g. (93.9%).

The oil was shown by cryoscopic analysis to contain $28.1 \pm 3.1\%$ of p-methylphenylbenzyl carbinol and $42.0 \pm 3.0\%$ of p-methylbenzylphenyl carbinol. The remainder was assumed to be unchanged p-methylstilbene oxide. A synthetic mixture composed of 25.6% of p-methylphenylbenzyl carbinol, 49.0% of p-methylbenzyl carbinol and 25.4% of p-methylstilbene oxide, analyzed by the cryoscopic method, was shown to contain 22.7% of p-methylphenylbenzyl carbinol and 44.5% of p-methylbenzylphenyl carbinol.

p-Chlorobenzylphenyl carbinol

The usual techniques for the preparation of a Grignard reagent were employed. To 48.6 g. (2.00 moles) of magnesium turnings suspended in 1500 ml. of sodium dried ether, there was added, dropwise, 362 g. (2.00 moles) of p-chlorobenzyl chloride, b.p. 98° (16mm.), 104° (22 mm.). To the Grignard reagent, there was added 203 ml. (212 g., 2.00 moles) of redistilled benzaldehyde, b.p. 174.5° (740 mm.). The reaction mixture was hydrolyzed with a saturated ammonium chloride solution at $0-10^{\circ}$, then with dilute hydrochloric acid, until all salts were dissolved. The two layers were separated and the aqueous portion extracted with ether. The combined ether solutions were washed first with water, then with 10% sodium hydroxide, and dried over Drierite. The ether was concentrated and the residual oil, distilled through a short vigreux column, yielded 310 g. (67.0%) of p-chlorobenzylphenyl carbinol, b.p. $199-203^{\circ}$ (15 mm.) crude m.p. $49.0-51.7^{\circ}$, m.p., after recrystallization from Skelly C, $55.0-56.5^{\circ}$.

Anal. Calcd. for $C_{14}H_{13}ClO$; C, 72.26%; H, 5.63%; Cl, 15.24%. Found C, 72.27%; H, 5.61%; Cl, 14.87%, 14.94%.

362 g.	212 g.	310 g.
(2.00 moles)	(2.00 moles)	(1.34 moles)

$$\% \text{ yield} = \frac{\text{Moles of p-chlorobenzylphenyl carbinol}}{\text{Moles of p-chlorobenzyl chloride}} \times 100$$

$$= \frac{1.33 \times 100}{2.00} = 67.0\%.$$

Phenyl urethane derivative.—A mixture of 50.0 g. (0.215 mole) of p-chlorobenzylphenyl carbinol and 25.0 ml. (27.5 g., 0.231 mole) of phenyl isocyanate was heated on a steam bath for 16 hours. The product was triturated under Skelly A, dissolved in carbon tetrachloride and filtered. The solvent was removed and there was obtained after several recrystallizations from Skelly C, 66.7 g. (88.2%) of the phenyl urethane which corresponds to p-chlorobenzylphenyl carbinol, m.p. 130.4–132.0°.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$; C, 71.69%; H, 5.61%. Found: C, 71.80%; H, 4.99%.

The refractive index of the urethane derivative, taken with a Fischer-Jelly Refractometer at 140°, gave the following bands: red, 1.550-1.555; yellow, 1.555; green, 1.555-1.563; violet, 1.562-1.570.

p-Chlorophenylbenzyl carbinol

The usual techniques for the preparation of a Grignard reagent were employed. To 48.6 g. (2.00 moles) of magnesium turnings suspended in 1000 ml. of sodium dried ether, there was added, dropwise, 230 ml. (254 g., 2.00 moles) of redistilled benzyl chloride. To the Grignard reagent there was added 282 g. (2.00 moles) of freshly redistilled p-chlorobenzaldehyde dissolved in 250 ml. of ether. The reaction mixture was hydrolyzed and worked up as described in the preparation of the isomer. A yield of 285 g. (61.5%) of p-chlorophenylbenzyl carbinol was obtained, b.p. 155°/1.4 mm., 212-13°/20 mm., m.p., after recrystallization from Skelly C, 52.5-3.5°.

Anal. Calcd. for $C_{14}H_{13}ClO$: C, 72.26%; H, 5.63%. Found: C, 72.26%; H, 5.54%.

282 g.

(2.00 moles)

254 g.

(2.00 moles)

285 g.

(1.23 moles)

$$\% \text{ yield} = \frac{\text{Moles of p-chlorophenylbenzyl carbinol}}{\text{Moles of p-chlorobenzaldehyde}} \times 100$$

$$= \frac{1.23 \times 100}{2.00} = 61.5\%$$

Phenylurethane derivative. - A mixture of 50.0 g. (0.215 mole) of p-chlorophenylbenzyl carbinol and 25 ml. (27.5 g., 0.231 mole) of phenyl isocyanate was heated on a steam bath for 16 hours. The product was triturated under Skelly A, dissolved in carbon tetrachloride and filtered. The solvent was removed and there was obtained, after several recrystallizations from Skelly C, 55.0 g. (72.5%) of the phenylurethane corresponding to p-chlorophenylbenzyl carbinol, m.p. 114.6-115.6°.

Anal. Calcd. for $C_{21}H_{15}ClNO_2$: C, 71.69%; H, 5.16%. Found: C, 72.03%, 72.05%; H, 5.20%, 5.35%.

The refractive index of the urethane derivative, taken with a Fischer-Jelly Refractometer at 140°, gave the following bands: red, 1.550-1.555; yellow, 1.555; green, 1.555-1.563; violet, 1.563-1.570.

p-Chlorobenzylphenyl ketone

A mixture of 75.0 g. (0.322 mole) of p-chlorobenzylphenyl carbinol and 66.0 g. (0.322 mole) of aluminum isopropoxide in 300 ml. of dried methyl-ethyl ketone was refluxed for 5 hours. The reaction mixture was hydrolyzed with water and dilute hydrochloric acid. The aqueous portion was extracted with ether and the ether washed with water. The ether solution on evaporation deposited 16.1 g. of p-chlorobenzylphenyl ketone, crude m.p. 128-134°. The residual oil on distillation yielded 51.0 g. of an oil, b.p. 136-146°/0.40-0.60 mm. Addition of ethanol to the oil gave 3.2 g. of the ketone, m.p. 131-134°. The ethanol was removed and 47.8 g. (63.8%)

of the carbinol was recovered, m.p. 45.0-49.0°. The p-chlorobenzylphenyl ketone was recrystallized several times from ethanol, m.p. 136.4-137.4° (reported (284-286) m.p. 133°, 138°).

Anal. Calcd. for $C_{14}H_{11}ClO$: C, 72.88%; H, 4.81%; Cl, 15.37%. Found: C, 73.16%; H, 4.84%; Cl, 15.50%, 15.26%.

75.0 g.
(0.322 mole)

19.3 g.
(0.0836 mole)

$$\begin{aligned} \% \text{ yield} &= \frac{\text{Moles of p-chlorobenzylphenyl ketone}}{\text{Moles of p-chlorobenzylphenyl carbinol}} \times 100 \\ &= \frac{0.0836 \times 100}{0.322} = 26.0\% \end{aligned}$$

p-Chlorophenylbenzyl ketone

A mixture of 75.0 g. (0.322 mole) of p-chlorophenylbenzyl carbinol and 66.0 g. (0.322 mole) of aluminum isopropoxide in 315 ml. of dried methyl-ethyl ketone was refluxed for 22 hours and allowed to stand at room temperature for several days. The reaction mixture was hydrolyzed with water and dilute hydrochloric acid. The aqueous portion was extracted with ether and the ether washed with water. The ether solution was concentrated and the residual oil partially crystallized. Methanol was added and 15.8 g. (21.2%) of p-chlorophenylbenzyl ketone ob-

tained, m.p., after several recrystallizations from methanol, 106.4-107.4° (reported (284) m.p. 107.5°).

Anal. Calcd. for $C_{14}H_{11}ClO$: C, 72.88%; H, 4.81%; Cl, 15.37%. Found: C, 72.94%; H, 5.03%; Cl, 15.26%.

75.0 g.
(0.322 mole)

15.8 g.
(0.0685 mole)

$$\% \text{ yield} = \frac{\text{Moles of p-chlorophenylbenzyl ketone}}{\text{Moles of p-chlorophenylbenzyl carbinol}} \times 100$$

$$= \frac{0.0685 \times 100}{0.322} = 21.2\%$$

Trans-p-chlorostilbene

Method A. - The procedure of Meerwein, Buchner and Van Emster was used. To a solution of 150 g. (1.01 moles) of cinnamic acid dissolved in 1250 ml. of acetone cooled to -2°, there was added a filtered solution of diazotized p-chloroaniline, prepared from 130 g. (1.01 moles), 400 ml. of concentrated hydrochloric acid, 500 ml. of water, and 75.0 g. (1.09 moles) of sodium nitrite in 150 ml. of water. To the reaction mixture there was added 220 g. (1.62 moles) of hydrated sodium acetate and 42.5 g. (0.250 mole) of hydrated cupric chloride in 100 ml. of water. The reaction mixture was allowed to stir for an additional 12 hours. The oil was separated and

steam distilled. The distillate gave 19.8 g. (13.2%) of p-dichlorobenzene, m.p., after recrystallization from methanol, 52.7-53.2°. The identity was verified by a mixed melting-point with an authentic sample of p-dichlorobenzene. The aqueous residue deposited 14.0 g. (9.5%) of cinnamic acid on cooling. The identity was verified by a mixed melting-point with an authentic sample of cinnamic acid. The residual oil was extended with ether and extracted with 10% sodium hydroxide solution. The ether, dried over Drierite and concentrated, yielded 9.3 g. (4.3%) of p-chlorostilbene, crude m.p., 126.0-129.0°; m.p., after recrystallization from methanol, 129.6-130.2° (reported (287-289) m.p. 127°, 129°).

Anal. Calcd. for $C_{14}H_{11}Cl$: C, 78.68%; H, 4.72%. Found: C, 78.08%, 78.30%; H, 5.06%, 5.09%.

The sodium hydroxide extract was neutralized with hydrochloric acid and extracted with ether. The ether was dried and concentrated on a steam bath. The residual oil on distillation yielded 72.3 g. (33.6%) of p-chlorostilbene. A mixed melting point with the analytical sample of p-chlorostilbene showed no depression. The undistilled residue, 36.3 g., consisted of a mixture of acids, crude m.p. 163.0-174.0°. Recrystallization of the mixture from aqueous acetic acid gave a compound, m.p. 182.4-182.9°, sufficient only for a single analysis. The compound may be a p-chloro-diphenylacrylic acid.

Anal. Calcd. for $C_{15}H_{11}ClO_2$: C, 69.64%; H, 4.39%. Found: C, 70.31%; H, 4.27%.

150 g.	130 g.	81.5 g.
(1.01 moles)	(1.01 moles)	(0.381 mole)

$$\begin{aligned} \% \text{ yield} &= \frac{\text{Moles of p-chlorostilbene}}{\text{Moles of cinnamic acid}} \times 100 \\ &= \frac{0.381 \times 100}{1.01} = 37.8\% \end{aligned}$$

Method B. - A solution of 267 g. (1.15 moles) of p-chlorophenylbenzyl carbinol in 250 ml. of acetic anhydride (reagent grade) was refluxed for 19 hours. The reaction mixture was distilled at atmospheric pressure to remove the unchanged acetic anhydride and the acetic acid which formed. On cooling the residual oil crystallized and gave 218 g. (88.7%) of p-chlorostilbene, m.p., after one recrystallization from ethanol, 129.0-130.0°. A mixed melting point with an authentic sample of p-chlorostilbene prepared by the Meerwein reaction showed no depression.

The use of 50% sulfuric acid gave a mixture of carbinol and stilbene.

267 g.	218 g.
(1.15 moles)	(1.02 moles)

$$\begin{aligned}\% \text{ yield} &= \frac{\text{Moles of p-chlorostilbene}}{\text{Moles of p-chlorophenylbenzyl carbinol}} \times 100 \\ &= \frac{1.02 \times 100}{1.15} = 88.7\%\end{aligned}$$

Method G. - The procedure of Wawzonek (290) for the preparation of diaryl acrylonitriles was used. A solution of sodium ethoxide, prepared from 7.0 g. (0.304 mole) of freshly-cut sodium dissolved in 100 ml. of absolute ethanol, was added, dropwise, to a solution of 117 g. (1.00 mole) of benzyl cyanide and 141 g. (1.00 mole) of p-chlorobenzaldehyde in 650 ml. of 95% ethanol. The reaction mixture was allowed to stir overnight. The solid which formed was filtered and triturated under ethanol. There was obtained 217.8 g. (91.5%) of α -phenyl- β -chlorophenyl acrylonitrile, crude m.p. 99-100°, m.p., after recrystallization from methanol, 101.5-102.2° (reported (289): m.p. 108°).

Anal. Calcd. for $C_{15}H_{10}ClN$: C, 75.12%; H, 4.20%. Found: C, 74.95%; H, 3.96%.

The same procedure gave high yields of the corresponding p-methoxy compound, m.p. 94-95° (reported (291-293): m.p. 93°, 95°) and the p-dimethylamino compound, m.p. 136.2-136.5° (reported (294): m.p. 136°).

Hydrolysis experiments on the p-methoxy and the p-dimethylamino compounds with a mixture of sulfuric acid, acetic acid, and water or with potassium hydroxide in cellosolve or butyl cellosolve gave low

yields of the corresponding acids. Hence, attempts to prepare p-chlorostilbene by decarboxylation of the acrylic acid corresponding to α -phenyl- β -p-chlorophenyl acrylonitrile were abandoned in favor of Method B.

p-Chlorostilbene Oxide

Method A. - To a solution of 50.0 g. (0.234 mole) of p-chlorostilbene dissolved in 375 ml. of chloroform, there was added 48.8 g. (0.354 mole) of perbenzoic acid in 700 ml. of wet chloroform, prepared and analyzed as previously described. The reaction mixture was allowed to stand for four hours in a refrigerator and for 14 hours at room temperature. At the end of 16 hours, 99.0% of the theoretical amount of perbenzoic acid was consumed. The chloroform solution was extracted with 10% sodium hydroxide solution, washed with water, dried and concentrated. The residual oil, which crystallized on standing, yielded 52.2 g. (96.5%) of p-chlorostilbene oxide, crude m.p. 95-98.5°; m.p., after recrystallization from Skelly C, 100.4-101.5°.

Anal. Calcd. for $C_{14}H_{11}ClO$: C, 72.88%; H, 4.81%. Found: C, 73.11%; H, 4.79%.

50.0 g.	48.8 g.	52.2 g.
(0.234 mole)	(0.354 mole)	(0.226 mole)

$$\% \text{ yield} = \frac{\text{Moles of p-chlorostilbene oxide}}{\text{Moles of p-chlorostilbene}} \times 100$$

$$= \frac{0.226 \times 100}{0.234} = 96.5\%$$

Method B.- The attempted base catalyzed condensation of p-chlorobenzaldehyde and benzyl chloride failed to give p-chlorestilbene oxide which could be isolated. The procedure of Bergmann and Hervey was used. Several attempts were made in which the catalyst and the solvent were varied. In all cases, p-chlorobenzaldehyde, benzyl chloride, and the catalyst were used in a molar ratio of 1:1:1 in a large excess of solvent and refluxed for several hours. Pure reagents, free of all traces of water, were used.

1. Potassium carbonate-methanol: The reaction mixture was extended with water and extracted with ether. The ether was washed with water, dried and concentrated. After distillation of the lower-boiling fractions, there was isolated from the residue an unidentified compound, m.p. 229-233°

2. Sodium methoxide-methanol: The reaction mixture was extended with water and extracted with ether. The ether was washed, dried and concentrated. After distillation of the lower-boiling fractions, there was isolated from the residue an unidentified compound, m.p. 188-192°.

3. Sodium ethoxide-ethanol: The reaction mixture was extended with water and extracted with ether. The aqueous portion on acidification with dilute nitric acid yielded p-chlorobenzoic acid, m.p.

239-241°. A mixed melting point with an authentic sample of p-chlorobenzoic acid showed no depression. The acidified solution gave a positive test for chloride ion. The ether solution was washed with water, dried and concentrated. After partial distillation of the lower-boiling fractions, the residue deposited p-chlorobenzyl alcohol, m.p., after recrystallization from Skelly C, 71.4-71.6° (reported: m.p. 70.5°, 75°). A sodium fusion gave a positive test for chlorine.

Anal. Calcd. for C_7H_7ClO : C, 58.96%; H, 4.95%. Found: C, 59.13%; H, 4.84%.

4. Sodium methoxide-ether: The reaction mixture was hydrolyzed with water. The aqueous portion yielded on acidification 14.0% of p-chlorobenzoic acid. The ether was dried and concentrated. After distillation of the lower-boiling fractions, there was isolated from the residue a small amount of a compound, probably an unsymmetrical p-chlorophenyl-phenyl-ethylenechlorhydrin, which gave a positive test for chlorine after boiling in aqueous sodium hydroxide solution, m.p., after recrystallization from aqueous methanol, 64.0-64.5°.

Anal. Calcd. for $C_{12}H_{13}Cl_2O$: C, 62.95%; H, 4.53%. Found: C, 62.12%; H, 4.24%.

5. Sodium ethoxide -n-butyl ether: The reaction mixture was hydrolyzed with water. The aqueous portion on acidification with dilute nitric acid yielded 67.0% of p-chlorobenzoic acid. The butyl ether was dried and concentrated. The residual oil yielded an unidentified fraction, b.p. 199-203°/22 mm., which

gave a positive test for unsaturation with potassium permanganate and bromine test solutions.

Method G.— The attempted base catalyzed condensation of p-chlorobenzyl chloride and benzaldehyde also failed to yield isolable p-chlorostilbene oxide. p-Chlorobenzyl chloride, benzaldehyde, and anhydrous potassium carbonate in a 1:1:1 molar ratio were refluxed in a large excess of absolute methanol for 5 days and allowed to stand at room temperature for an additional 2 days. The reaction mixture was treated with dilute hydrochloric acid and extracted with ether. The ether was washed with water and saturated sodium bicarbonate solution, dried and concentrated. The residual oil on distillation yielded: (1) a fraction, b.p. 84-88°/46 mm., which probably contained unreacted benzaldehyde, (2) a fraction, b.p. 104-105°/24-25 mm., in which p-chlorobenzaldehyde was identified by odor and isolated as the 2,4-dinitrophenylhydrazone, crude, m.p. 251-255° (reported (271): m.p. 264°, 265°), and as the semicarbazone, crude m.p. 232-233° (reported (271): m.p. 230°). A mixed melting point with an authentic sample of the semicarbazone showed no depression, and (3) higher-boiling fractions which were not identified.

Reduction of p-Chlorostilbene Oxide

To 46.6 g. (0.202 mole) of p-chlorostilbene oxide in 100 ml. of sodium dried ether, there was added 50.0 ml. of an ether solution containing 0.0419 g. per ml. (2.10 g., 0.554 mole) of lithium aluminum hydride, analyzed by a modification of the procedure of Field and Grunwald. The reaction was mildly exothermic and the ether refluxed mildly within a few minutes after the addition. The reaction mixture was stirred at room temperature for 16 hours and then hydrolyzed with water and dilute acetic acid. The ether was separated and washed with water. The aqueous portions gave a positive test for chloride ion with silver nitrate solution. The ether was extended with chloroform and dried by azeotropic distillation. The residual oil partially crystallized. Methanol was added and the solution filtered yielding 14.3 g. (30.7%) of unchanged p-chlorostilbene oxide. The methanol was removed from the filtrate yielding 30.2 g. (65.0%) of a mixture of p-chlorophenylbenzyl and p-chlorobenzylphenyl carbinols.

Phenylurethane derivatives.- To 6.0 g. (0.026 mole) of the reduction products of p-chlorostilbene oxide, there was added 3.0 ml. (3.3 g., 0.028 mole) of phenyl isocyanate. The reaction mixture was warmed on a steam bath for an hour. The resulting oil was extracted with Skelly A to remove the unchanged phenyl isocyanate. The oil crystallized and was then dissolved in carbon tetrachloride and filtered to remove diphenylurea. The carbon tetrachloride was removed under vacuum and the crystallized product triturated under Skelly A, which yielded 4.6 g. (50.5%) of the urethane derivatives of the isomeric carbinols. The product was analyzed without further treatment.

Anal. Calcd. for $C_{21}H_{15}ClNO_2$: C, 71.69%; H, 5.16%; N, 3.98%; Cl, 10.08%. Found: C, 71.42%, 71.69%; H, 4.92%, 5.03%; N, 4.26%, 4.25%; Cl, 10.06%, 9.82%.

The urethane derivatives of the reduction products of p-chlorostilbene oxide were shown by phase diagram studies to contain $60.9 \pm 3.0\%$ of the urethane corresponding to p-chlorophenylbenzyl carbinol and $39.1 \pm 3.0\%$ of the urethane corresponding to p-chlorobenzylphenyl carbinol.

A synthetic mixture of the isomeric carbinols, containing 61.4% of p-chlorophenylbenzyl carbinol, gave a 56.8% yield of the corresponding urethanes. The synthetic mixture of urethanes was shown by the phase diagram method to contain 64.5% of the urethane corresponding to p-chlorophenylbenzyl carbinol, which is within experimental error.

p-Nitrostilbene Oxide

A solution of 100 g. (0.582 mole) of p-nitrobenzyl chloride, 60.0 ml. (63.0 g., 0.592 mole) of freshly-distilled benzaldehyde and 81.0 g. (0.582 mole) of anhydrous potassium carbonate was refluxed for 24 hours. On cooling, there was obtained, by filtration and trituration under dilute hydrochloric acid, 78.1 g. (55.6%) of p-nitrostilbene oxide, m.p., after recrystallization from ethanol, 126.0-127.0° (reported (218, 240, 244): 125-126°, 122°).

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.71%; H, 4.60%. Found: C, 69.92%; H, 4.57%.

The alcohol, on evaporation, yielded 17.6 g. (12.6%) of an isomeric p-nitrostilbene oxide, m.p., after recrystallization from methanol, 79.6-80.5° (reported (240, 244): m.p. 74-76°).

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.71%; H, 4.60%. Found: C, 70.11%, 70.25%; H, 4.58%, 4.85%.

Methanolysis of p-nitrostilbene oxide

A solution of 10.0 g. (0.0415 mole) of p-nitrostilbene oxide, m.p. 126-127°, and 0.10 g. (0.0015 mole) of sodium methoxide was refluxed in 100 ml. of absolute methanol for 5 days. The reaction mixture was allowed to stand at room temperature for an additional two days. The starting material was recovered.

Hydrolysis of p-nitrostilbene oxide

Hydrolysis of 5.0 g. (0.21 mole) of p-nitrostilbene oxide, m.p. 126-127°, in 100 ml. of 15% aqueous potassium hydroxide for 12 hours gave an

oil which co-distilled with water. The oil was identified as benzaldehyde by the preparation of its 2,4-dinitrophenylhydrazone, m.p. 234-237°. A mixed melting point with an authentic sample of the derivative showed no depression. A second attempt at alkaline hydrolysis gave a small amount of a brick-red compound, m.p. 144-147°, insufficient for purification and identification. The evolution of ammonia was noted. Hydrolysis in 5% (by volume) of aqueous sulfuric acid gave a small amount of compound, m.p. 153-158°, insufficient for purification and identification. In another experiment 72.0% of the starting material was recovered.

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