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RELUCTANT CARBONIUM IONS AS PROBES FOR
CONCERTED DISPLACEMENT REACTIONS

By

Stanley Jay Jasne

1973

A dissertation submitted to the Graduate Faculty in
Chemistry in partial fulfillment of the requirements for
the degree of Doctor of Philosophy, The City University
of New York.

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To

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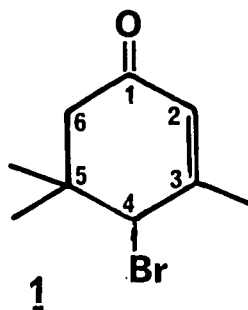
To my mother who provided me with motivation and incentive to continue my studies, I am forever grateful. I wish to also thank her for her assistance in typing this manuscript.

To my wife who helped edit this dissertation, I am indebted. I am grateful for her patience and faith in my ability.

To my friends, Kenneth Marion for his editing, and V.V.K. Prasad for his proofreading ability, I am indebted.

Abstract

The reactions of 4-bromoisophorone (1) (4-bromo-3,5,5-trimethylcyclohex-2-enone) with various solvents and added nucleophiles were studied. The C-4 carbonium ion, a vinylog of a C-2 carbonium ion, should only form reluctantly because of the destabilizing effect of the carbonyl group towards the developing positive charge. This prediction was confirmed by the fact that 1 is inert to solvolytic displacements by water, ethanol and pivalic acid.



In organic carboxylic acids, i.e. acetic acid, 1 decomposes by acid autocatalysis to 3,4,5-trimethylphenol (2), but with added silver perchlorate 2 and its phenyl ester are recovered. The role of silver ion in causing a change in the product distribution is explained by a novel use of Hammond's Principle. Under basic conditions, 1 rearranges to a mixture of 2 and 2,3,5-trimethylphenylphenol (54). The proposed intermediate involves initial carbanion formation by removal of a proton from C-6 and then displacement of the halogen

resulting in a C-4, C-6 cyclopropane intermediate. Methyl migration from C-5 to C-4 or to C-6 yields the phenols.

Under buffered, or mildly basic conditions, nucleophilic attack occurs at C-4, i.e. an S_N2 reaction at a hindered neopentyl site and/or at C-2, i.e. an S_N2' type of reaction. The S_N2' reaction is unusual because, initially, the allylic rearrangement leads to an unconjugated compound. The product distribution depends on the solvent and the nature of the cation. After considering several alternative mechanisms it was concluded that the C-2 substitution is a concerted S_N2' reaction with possible assistance from the cation by complexing with the carbonyl oxygen atom. The absence of displacement by nucleophilic solvents seems to preclude intermediacy of ion-pairs.

In protic solvents such as pivalic acid, the reaction of 1 with pivalate ion gives only the S_N2' product (2-pivoxyisophorone, 58) and with silver pivalate in this solvent, the out of conjugation product (2-pivoxy-3,5,5-trimethylcyclohex-3-enone, 89) was isolated. It appears that S_N2 substitution is enhanced by the presence of unsolvated anions in aprotic solvents. As the size of the cation is increased in going from Li^+ , Na^+ , K^+ to Et_4N^+ the product from the S_N2' substitution decreases in yield and the S_N2 product increases. HMPT,

in general, inhibits the yield of the C-2 substitution product.

Similar reactions were repeated with 6-tosyloxyisophorone (54), a substrate with a leaving group at a neopentyl position but one which is unable to undergo a S_N2' reaction because the leaving group is not on an allylic position. A mixture of C-2 and C-6 substituted isophorones was obtained and believed to arise from a C-3 methyl carbanion giving a cyclopropanone intermediate which is attacked at either the C-2 or C-6 positions. It was demonstrated that under the conditions where 1 undergoes substitution, 44 reacts through a carbanion mechanism.

It was also determined that in C-5 gem-substituted isophorones a C-4 halogen and C-6 oxygen substituent make the geminal groups non-equivalent in nmr analysis. However, the chemical shifts of the gem groups is the same when a C-4 oxygen or C-6 halogen is present.

New compounds synthesized during these investigations include: 2-, 4-, 6- pivoxyisophorone, 5,5-dimethyl-2-hydroxy-3-phenyl- and 5,5-dimethyl-3-phenyl-2-pivoxycyclohex-2-enone, 3,4,5-trimethylphenyl pivalate, 2-bromo-3,4,5-trimethyl-, 2,3-dimethyl-5-phenyl-, 3,4-dimethyl-5-phenylphenol and 4-bromo-5,5-diphenylcyclohex-2-enone.

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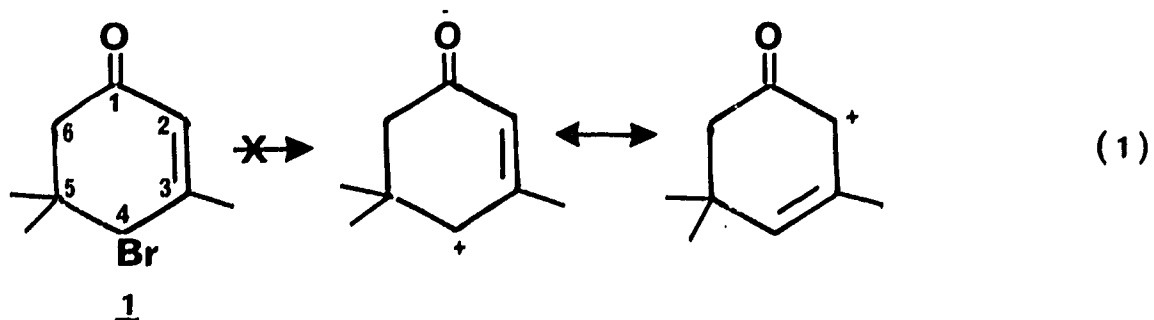
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INTRODUCTION

Introduction

There are still numerous reactions in organic chemistry whose mechanisms are not completely understood. Determination of the mechanisms through which alkyl group migration proceeds is one such problem. The existence of a concerted S_N2' mechanism in the formation of "abnormal" allylic rearrangement products (derived from allylic halides) or whether these "abnormal" allylic rearrangement products can be accounted for by invoking other mechanistic schemes is another such problem.

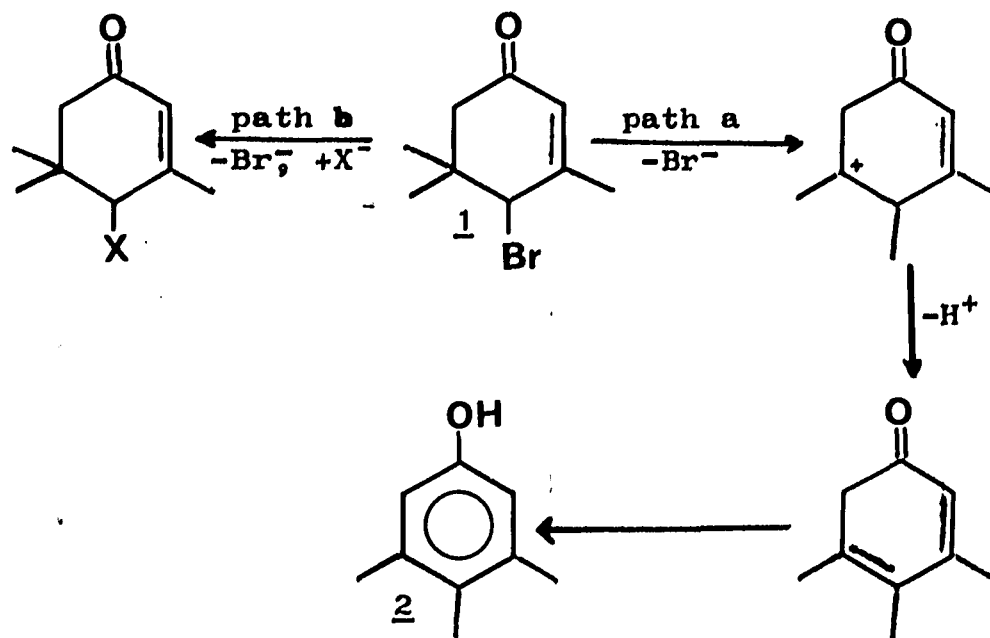
4-Bromoisophorone(1)(3,5,5-trimethylcyclohex-2-enone) is uniquely designed to offer additional information to help clarify these mechanistic dilemmas. Reactions of 1 leading to a C-4 carbonium ion are inhibited. The C-4 carbonium ion is a vinylog of the C-2 cation and placement of a positive charge alpha to a carbonyl group would result in an untenable situation due to the inherent dipole quality of the carbonyl function as shown in Eq 1:



The mechanisms involved in various reactions of 1 can, likely, be elucidated without the interference of mechanisms

involving C-4 or C-2 carbonium ions.

Migration of a methyl group from the neopentyl C-5 to an incipient C-4 carbonium ion should not be inhibited in this cyclic system. In fact, this migration should be favorable because the developing positive charge is removed from C-4. Because no rapid equilibrium can exist (with the methyl group shifting between C-5 and C-4) every molecule which reacts through methyl migration should lead to the formation of 3,4,5-trimethylphenol (2). (See scheme I-path a).

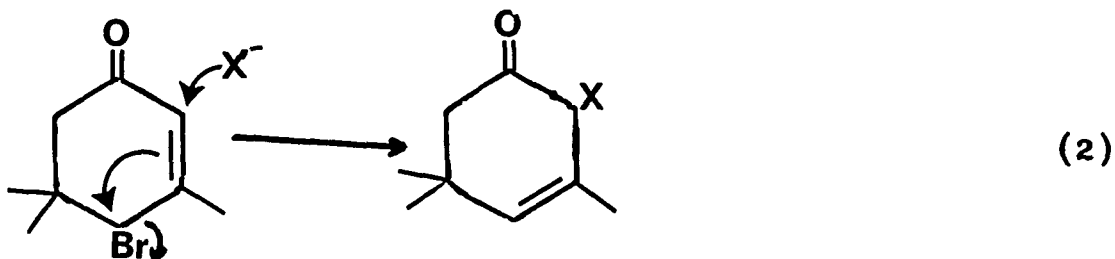


Scheme I

If a methyl group on C-5 does not influence the departure of the leaving group, direct substitution products should be observed as shown in path b. Direct substitution on C-4 is sterically hindered by the methyl groups on C-5 and C-3.

When nucleophilic displacements on an allylic site is sterically hindered by neighboring alkyl groups at C-5,

S_N2' reactions can occur. With 1, S_N2' reactions lead initially to a 2-substituted β,γ -ketone, as shown in Eq 2:



The S_N2' attack on 1 might be inhibited because conjugation is lost. On the other hand, the carbonyl group withdraws electron density from the double bond, thereby making the C=C bond more susceptible to attack by a nucleophile.

If an allylic rearrangement product is observed it would be of interest to determine the mechanism for the formation of this product. It is desirable to elucidate how the type of nucleophile(s) and solvent systems influence the S_N2 compared to the S_N2' pathway. Also, a determination of the relative yields of Meerwin rearrangement products, direct substitution products and allylic rearrangement products might indicate whether the forementioned reactions are concerted.

The C-6 position of isophorone is also a neopentyl position. A substituent in this position, however, is no longer allylic and, therefore, cannot undergo an S_N2' type reaction. Thus, an interesting comparison of products can be made when analogous reactions are attempted with C-4 and C-6 substituted isophorone molecules.

BACKGROUND

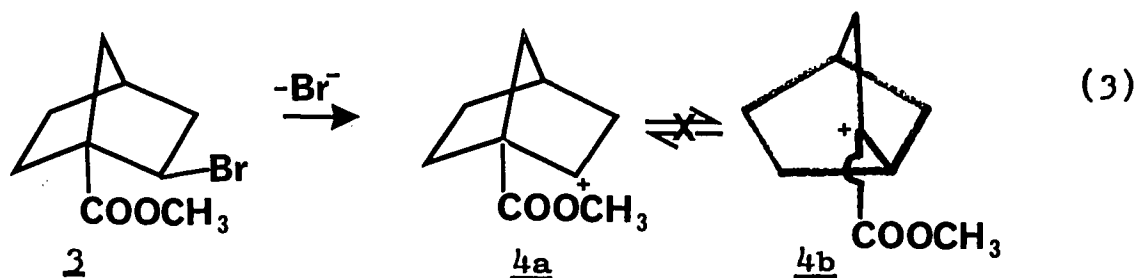
Background

A. The Reluctant Carbonium Ion

As previously mentioned on page 2, the high energy of a carbonium ion on C-4 of 1 would make direct substitution at this position follow a concerted bimolecular mechanistic pathway. If a positive charge developed on the C-4 position it would be analogous to placing a positive charge alpha to the carbonyl function because the C-4 position is a vinylog of C-2 in this system. This is an unfavorable position for a positive charge to be developed.^{1a, b} Eliel² has concluded that α -haloketones react very slowly in ionization-type reactions but quite fast in bimolecular displacement reactions. The slow rate of reaction is explained by the destabilizing effect of the positive end of the $\delta^+C=O\delta^-$ dipole on the developing carbonium ion.

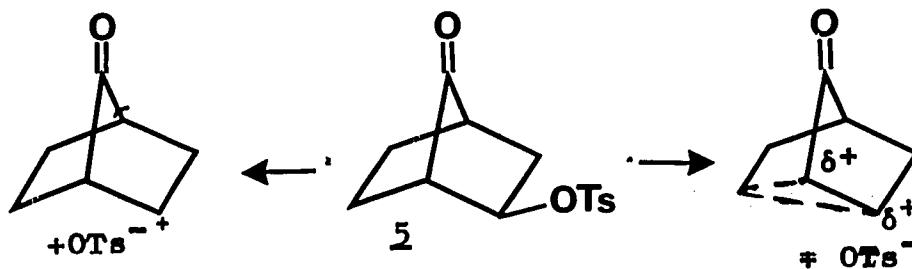
Work has been done recently on norbornyl and norboranone systems in which the effect of having positive charge distributed alpha to a carbonyl group causes significant rate changes and/or alters the product distribution. Wilt and Wagner³ solvolyzed methyl exo-2-bromonorborane-1-carboxylate(3) in an ethanol(80%)-water(20%) mixture. The bridgehead carbomethoxy group retards the loss of bromide ion by a factor of 4.9×10^{-4} . Wilt concluded that only classical ionic intermediates are involved in the

solvolysis of 3. All of the products (substitution by ethanol or water and elimination products) are expected from intermediate 4a without 1,6- σ electron participation as shown in Eq 3:



1,6- σ Electron participation would introduce positive charge alpha to the carbonyl function of the COOMe group. Such a carbonium ion, 4b, has a very high energy and cannot readily form.

Exo-2-(5a) and endo-2-(5b)-hydroxybicyclo(2.2.1.)heptan-7-one tosylates were acetolyzed⁴ to shed some light on the classical versus nonclassical carbonium ion problem. If both the exo- and endo-tosylates solvolyze through a classical carbonium ion then the presence of a carbonyl group at C-7 would not have any effect on the rate of solvolysis because the developing positive charge would be beta to the carbonyl group as shown in scheme II.



Scheme II

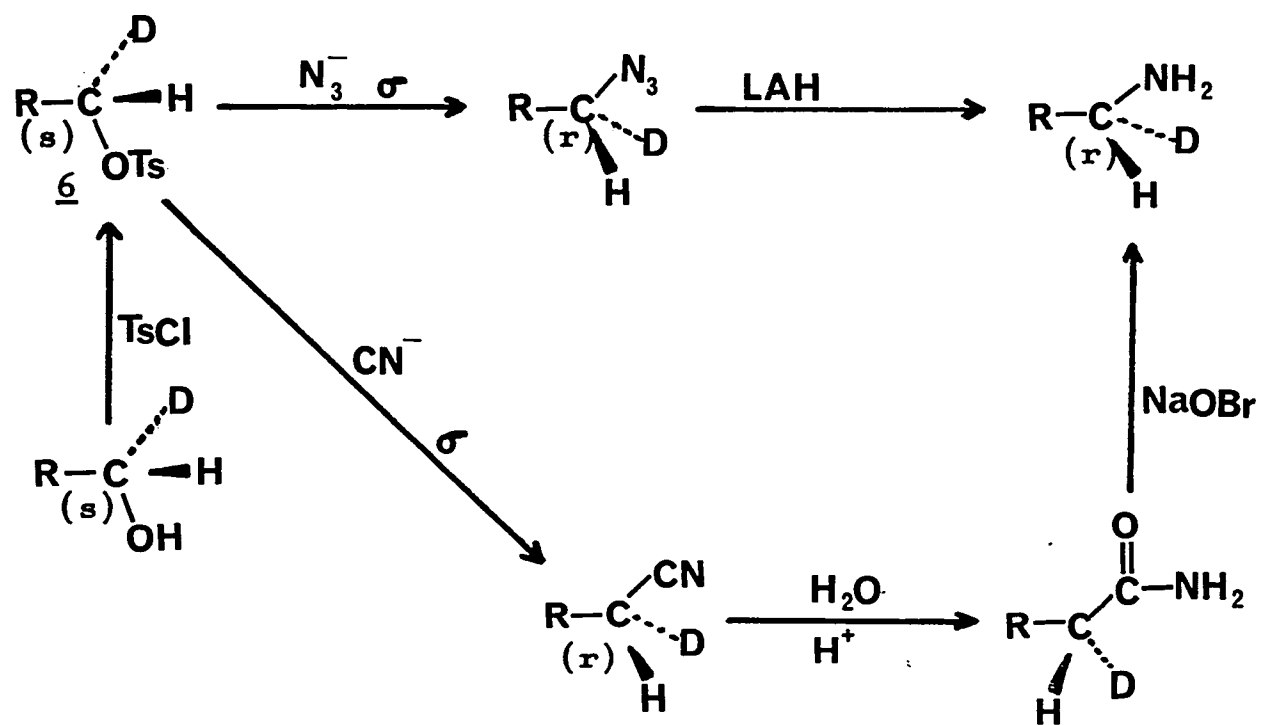
However, if the "norbornyl exo/endo rate ratio is due to anchimeric assistance, the presence of a carbonyl function at C-7 would be expected to have drastic effects."⁴ Thus, if the exo solvolysis proceeded with 1,6- σ participation the carbonyl group at C-7 would inhibit this assistance. This assistance would involve concurrent development of positive charge at a position alpha to a carbonyl group as shown in scheme II. Gassman found that 5a solvolyzed six times slower than 5b (at 25°), whereas, for the parent compounds, exo- and endo-2-hydroxybicyclo(2.2.1)heptane tosylates, the exo/endo rate ratio is 1.7×10^3 . Ethanolysis rates for 5a and 5b were close to the results obtained for acetolysis. These results appear to confirm the fact that the "nonclassical" solvolysis of 5a is inhibited by the "drastic" effect of having a carbonyl function alpha to a developing positive charge.

The reluctance of formation of an electron deficient carbon in a position alpha to a carbonyl group is again demonstrated by the fact that "with any hydrogen halide, the addition to an α,β -unsaturated acid or other carbonyl compound occurs in a way such that the halogen atom becomes joined to the beta carbon atom, regardless of the experimental conditions and regardless of Markovnikov's rule",⁵

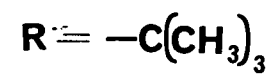
B. Neopentyl Substitution

Direct nucleophilic substitution at a neopentyl position, such as C-4 of 1 is possible. Neopentyl acetate is obtained in a 40% to 70% yield when neopentyl iodide is treated with potassium acetate.⁶ Neopentyl iodide when treated with silver nitrate in water gives a 45% yield of neopentyl alcohol. Neopentyl mercaptan was obtained in a 64% yield (together with neopentyl sulfide) by the reaction of neopentyl p-tosylate with sodium hydrogen sulfide in 2-methoxyethanol (reflux, 2.5 hrs).⁷

Recently Mosher⁸ and co-workers observed neopentyl substitution, without rearrangement, by an S_N2 pathway. Neopentyl tosylate with azide ion in dimethylformamide (DMF) afforded direct substitution product (10% yield). When hexamethylphosphortriamide (HMPT) was employed as the solvent the reported yield of direct substitution product, neopentyl amine was 87% (obtained from lithium aluminum hydride reduction of the initially formed azide). These workers further showed that the displacement by both azide and cyanide ions on (s)-neopentyl-1-d-tosylate(6) in HMPT proceeds with inversion of configuration in a typical S_N2 manner, as shown in scheme III on page 10.



Scheme III



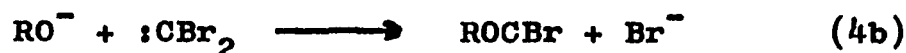
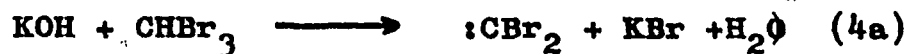
C. Neopentyl Rearrangements

In the neopentyl rearrangement of 1 (migration of a methyl group from C-5 to C-4), the resulting product is 3,4,5-trimethylphenol (2). Rearrangements usually predominate during neopentyl substitution reactions. By the use of isotopic labelling experiments, it has been shown by Skell⁹ and Karabatos¹⁰ that neopentyl rearrangements occur entirely by 1,2 methyl shifts rather than a protonated cyclopropane intermediate.

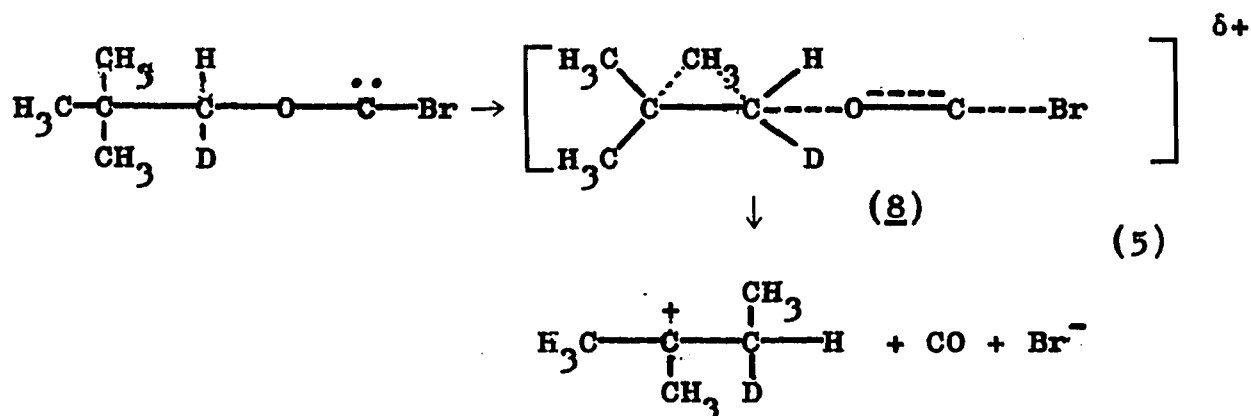
There is still a question as to whether a discrete classical neopentyl ion forms prior to the methyl group migration or whether this rearrangement is concerted, i.e. the migrating methyl group begins to bond to the alpha carbon before the leaving group fully departs. McElrath¹¹ and co-workers used compounds of the type $R(CH_3)_2CCH_2OBs$ (7) (where R was varied from methyl to tert-butyl) to show that the unimolecular rate constant in solvolytic reactions increases slightly as R becomes bulkier. The authors attribute this result to the relief of steric strain through participation of a neighboring carbon. All of the reacting brosylates gave completely rearranged products.

Sanderson and Mosher¹² treated optically active neopentyl-1-d alcohol with bromoform and potassium hydroxide and obtained as one of the products optically active 2-methyl-1-butene-3-d. The general mechanism for this

type of reaction is shown below in Eq 4a-d:



These results were explained by postulating a concerted mechanism as shown in Eq 5:



The authors state that 8 can be considered as "the transition state between the neopentyl bromomethylene and cation during simultaneous ionization and methyl migration."¹² Such a process would be stereospecific and would lead to a product whose configuration is inverted. The fact that a highly stereospecific product was found tends to rule out the formation of a free carbonium ion. It is doubtful though that this reaction can be construed as a general one for all reactions in which neopentyl rearrangements are noted.

Others,¹³ claimed that the small rate enhancement in

the solvolytic reactions of substituted neopentyl systems is not conclusive evidence for a concerted process. They pointed out that the recorded rate enhancements are generally quite small considering the great amount of energy saved when going from a primary to tertiary cation. For example, when R in compound 7 is changed from methyl to tert-butyl the relative rates are shown as follows: methyl (1.0); ethyl (2.4); n-propyl (2.3); n-butyl (2.4); isobutyl (4.1); isopropyl (7.1); sec-butyl (7.9); tert-butyl (34.0).¹¹

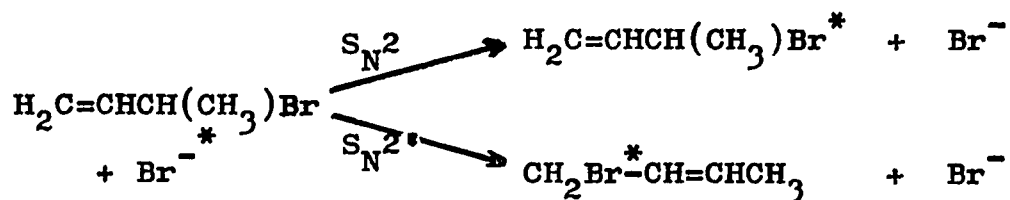
An inductive effect has also been postulated to account for some of the rate enhancement noted.¹³

D. The S_N2' Reaction

Nucleophilic attack on the C=C bond of an allylic halide causing a shift of the double bond and displacement of the halogen atom was first conceived in 1938 by Hughes and other workers.¹⁴ The postulated reaction is shown in Eq 6:



In 1955, England¹⁵ determined the rates and activation energies for the S_N2 and S_N2' reactions of 1-methylallyl bromide (9a) and 3-methylallyl bromide (9b) with radioactive lithium bromide in acetone. The S_N2 rate of 9a can be followed by the incorporation of radioactive bromide because no new product is formed. The S_N2' route can be discerned by determining the yield of "abnormal" rearranged product, as shown in scheme IV.

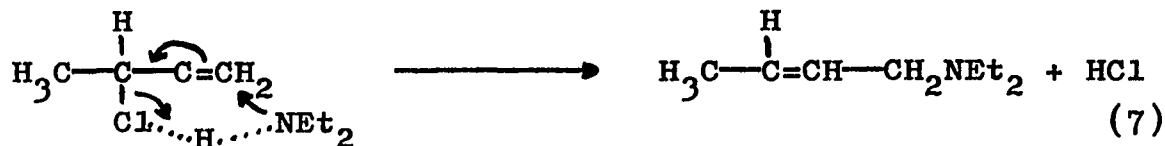


Scheme IV

England determined that the S_N2 substitution of 9a is sixty times faster than the corresponding S_N2' reaction. The corresponding ratio for 9b is 2.8×10^4 . This larger difference for 9b than 9a is undoubtedly due to the greater steric inhibition of the S_N2' reaction and lesser steric

inhibition of the S_N2 reaction. DeWolfe and Young¹⁶ have pointed out that England did not eliminate thermal or lithium ion catalyzed isomerization by an S_N1 or S_Ni mechanism. These mechanisms could have been discarded if the rate of rearrangement had been shown to be independent of the cation of the bromide salt and the products stable to heat.

There have been various reports of S_N2 products from the reaction of allylic halides with amines. Young¹⁷ and co-workers allowed 3-methylallyl chloride (10) ($\text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl}$) and 1-methylallyl chloride (11) ($\text{CH}_3\text{CHClCH}=\text{CH}_2$) to react with diethylamine. In both cases the product was shown to be N,N-diethyl-3-methylallylamine (12) ($\text{CH}_3\text{CH}=\text{CH}-\text{CH}_2\text{NEt}_2$). Similar results were obtained when the secondary amine is replaced by triethylamine (in benzene). The authors state that when the secondary amine is the nucleophile, a hydrogen bond between the amine hydrogen and the leaving chloride, as shown in Eq 7, may exist.

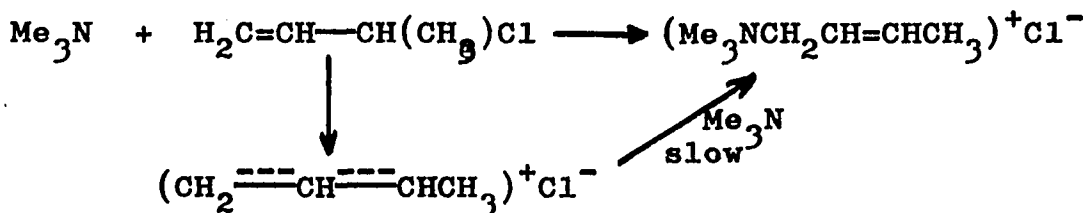


Ingold¹⁸ has classified these reactions as following an S_Ni' mechanism rather than an S_N2' pathway. DeWolfe and Young,¹⁹ though, have stated that hydrogen bonding of this type is rather a weak interaction compared to the covalent bonding in the intermediate complexes of an S_Ni' reaction.

It would seem to be a matter of personal choice as to whether this cyclic type process is a modification of an S_N2' reaction or a borderline case of an S_Ni' .

Young et al.,²⁰ have shown that preliminary hydrogen bonding is not a necessary condition for S_N2' product formation. When 11 was treated with trimethylamine in acetone the second order reaction yielded 70% of the "abnormal" rearranged product (trimethyl-3-methylallylammonium chloride) and 30% of the direct substitution product. Neither the starting material nor the products rearrange under the reaction conditions.

However, attack of the nucleophile on an ion-pair is not eliminated. Bordwell²¹ has pointed out that an S_Ni' - S_N2 mechanistic pathway is also not eliminated. The rapid rearrangement of 11 to 10 has been ruled out by the data. But rapid formation of an ion-pair which reacts with trimethylamine is not. However, a limitation of this postulate, as Bordwell pointed out is that on internal return only the secondary chloride must be formed as shown in scheme V.



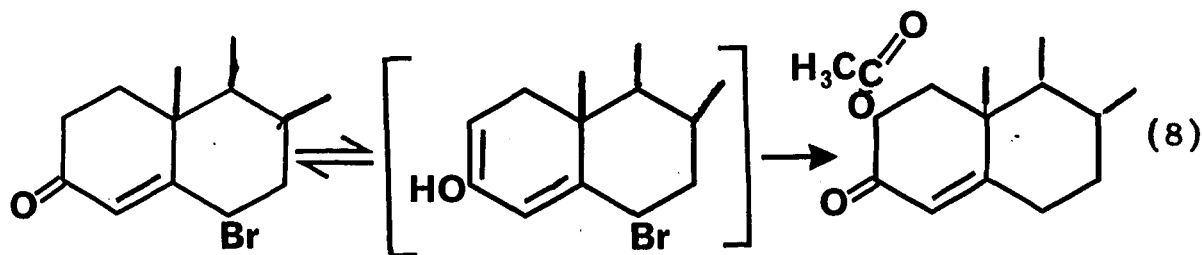
Scheme V

Fry²² suggested that an isotope effect should be expected for each of the carbon atoms (exclusive of the

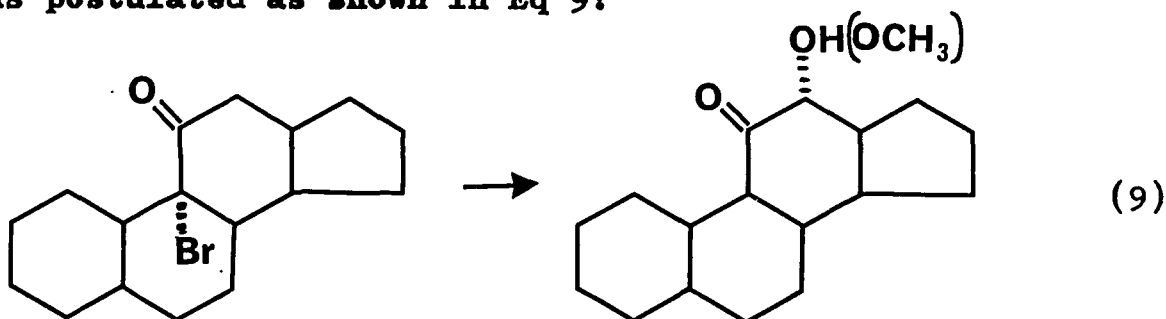
methyl group) in the reaction of 11 with diethylamine. A C^{14} isotope effect was noted for each of the expected carbon atoms. A chlorine isotope effect was noted as well. It was thus demonstrated that bond changes in all positions were occurring in the activated complex.

Dittmar and Marcantonio²³ have treated 11 with N-deuteriodiethylamine (13). If the hydrogen of the secondary amine was stretched significantly in going from its initial state to the transition state as depicted by Ingold, a primary isotope effect should be observed when a N-deutero amine is substituted for a nondeuterated species. No isotope effect was noted when either 13 or N-deutero-N-methylaniline was employed as the nucleophile. This result argues against significant hydrogen participation in the transition state.

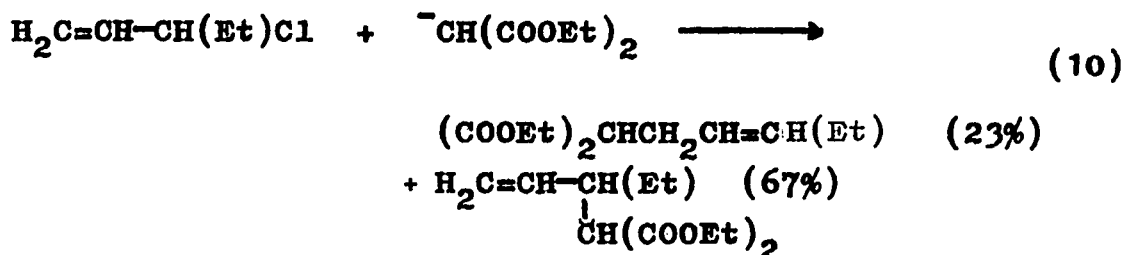
Others^{24, 25} reported the formation of 2- α -acetoxy- Δ^4 -cholesten-3-one (17%) from the reaction of 6- β -bromo- Δ^4 -cholesten-3-one with potassium acetate in acetic acid. A possible mechanism for this transformation, as pointed out by DeWolfe and Young²⁶ involves a S_N2' attack on the enol form of the starting material as shown in Eq 8:



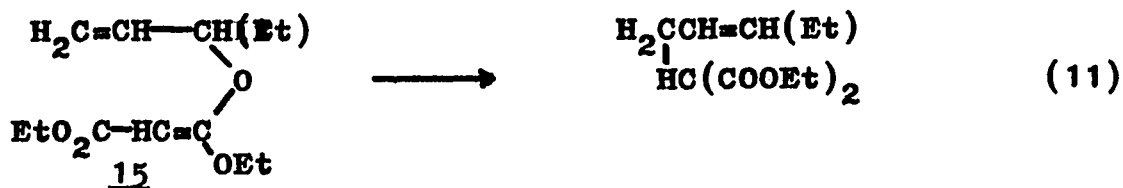
Similarly²⁷ when 9- α -bromo-11-keto steroids(14a) were treated with either methoxide or hydroxide ions, an S_N2' type reaction giving a 12-methoxy or 12-hydroxy-11-keto steroid(14b), respectively, was obtained. Again, an S_N2' reaction through the enol form of the starting material was postulated as shown in Eq 9:



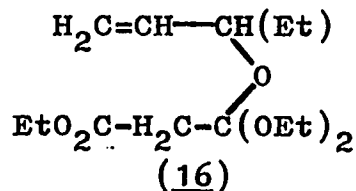
When the sodium salt of diethylmalonate was allowed to react with either α -methyl or α -ethylallyl chloride the "abnormal" S_N2' substitution product was observed in 10% and 23% yields respectively.²⁸ The authors believed that this was a true case of an S_N2' reaction (see Eq 10):



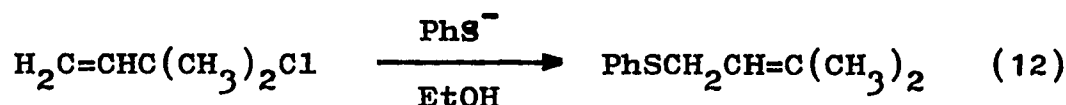
De la Mare, not completely satisfied with the postulated mechanism, proposed a possible attack by oxygen followed by a (3,3) sigmatropic rearrangement as shown in Eq 11:



Others¹⁶ pointed out that the suggested intermediate 15, a ketene acetal, would be expected to add ethanol (the solvent of the reaction) to give an ortho ester(16) rather than rearrange. Also, the type of rearrangement postulated by de la Mare usually occurs under pyrolytic conditions rather than at the employed temperature of refluxing ethanol. Some "abnormal" product was obtained when this reaction was run at room temperature.

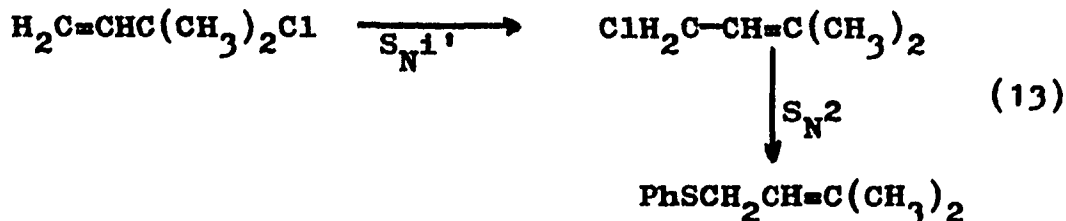


1,1-Dimethylallyl chloride undergoes bimolecular substitution, in the presence of sodium thiophenoxide, to yield almost quantitatively the $\text{S}_{\text{N}}2'$ product 3-methylbutenyl-phenyl sulphide³⁰ as shown in Eq 12:

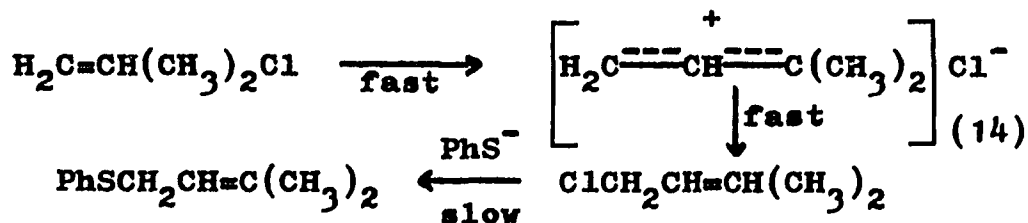


The possibility of the rearrangement of the initially formed $\text{S}_{\text{N}}2$ product was negated by showing that this reaction proceeded at a faster rate than the bimolecular displacement of thiophenoxide on 1-methylallyl chloride (11). If the $\text{S}_{\text{N}}2$ product was formed first the rate of reaction should certainly not be increased by the addition of a second methyl group at the alpha position. Bordwell states, however, that an $\text{S}_{\text{N}}1'-\text{S}_{\text{N}}2$ pathway, which would also lead to the

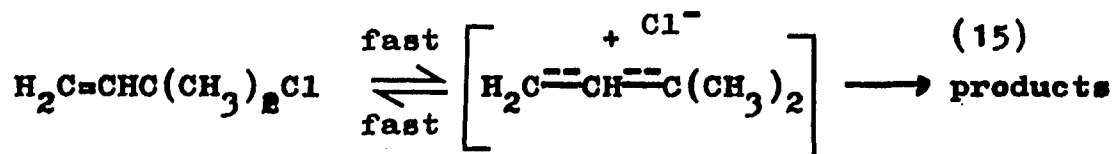
allylic rearrangement product, has not been eliminated based on the data presented.³¹ This pathway is shown in Eq 13:



De la Mare recently countered this criticism.^{32a} In order for the $\text{S}_{\text{N}}1'$ - $\text{S}_{\text{N}}2$ mechanism to be valid the rate of rearrangement to 3,3-dimethylallyl chloride would have to be faster than the allylic substitution reaction, as shown below in Eq 14: Such is not the case.



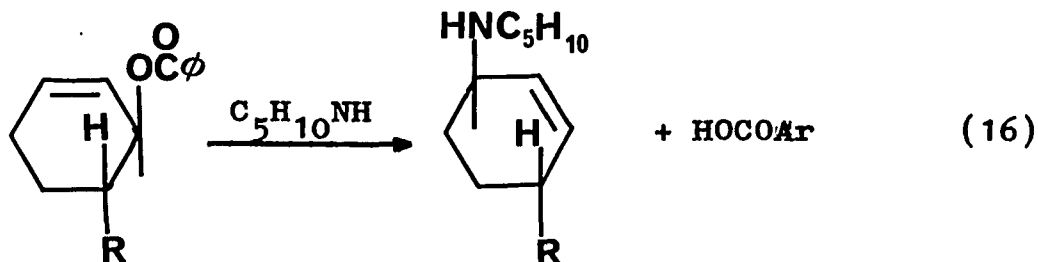
Bordwell³¹ also speculates that fast formation of an ion-pair followed by a slow reaction with the incoming nucleophile would account for the observed product, as shown in Eq 15:



De la Mare discounts this possibility, based on the result that no rearranged chloride was observed after partial reaction. If this argument is not accepted, then as the author points out, the reaction would have to proceed by

a pathway which involves complete ionization of the starting material to give a rapidly formed ion-pair in a pre-equilibrium which gives no significant rearrangement and then is followed by a nucleophilic attack on the ion-pair to give the observed S_N2' product.

Various other researchers have determined the presence of allylic rearrangement products. The reaction of 3,3,3-trichloro-2-methylpropene with sodium thiophenoxide gives mainly the S_N2' product.^{32b,c} The reaction of piperidine with trans-6-alkylcyclohex-2-en-1-yl-2,6-dichlorobenzoate leads to formation of an S_N2' product with the entering group cis to the leaving group as shown in Eq 16:³³

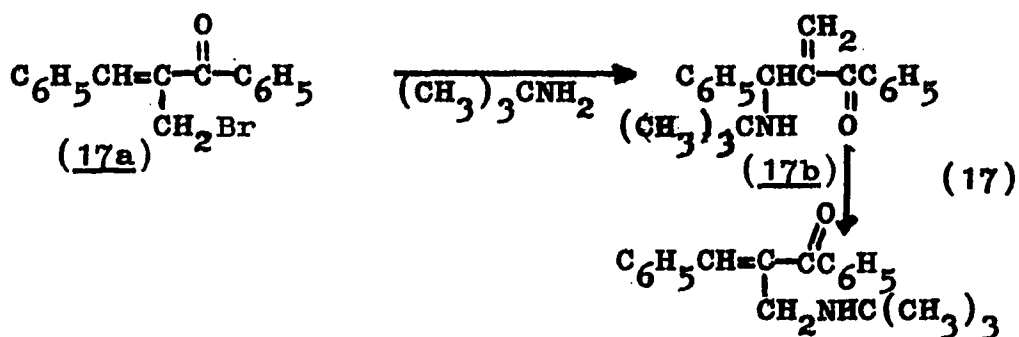


Bordwell has set forth in a series of papers his doubts concerning the existence of a concerted S_N2' mechanism. He states that there appears to be no unambiguous case of an S_N2' concerted mechanism. He suggests that all of the reactions previously reported as following an S_N2' mechanistic pathway can be explained by substituting one of the following mechanistic pathways (a) S_N2-S_N1' ; (b) S_N1 ; (c) $S_N1'-S_N2$; (d) rate limiting attack on an ion-pair; and (e) a type of S_N1' invoking hydrogen bonding (used to explain the reaction involving primary or secondary

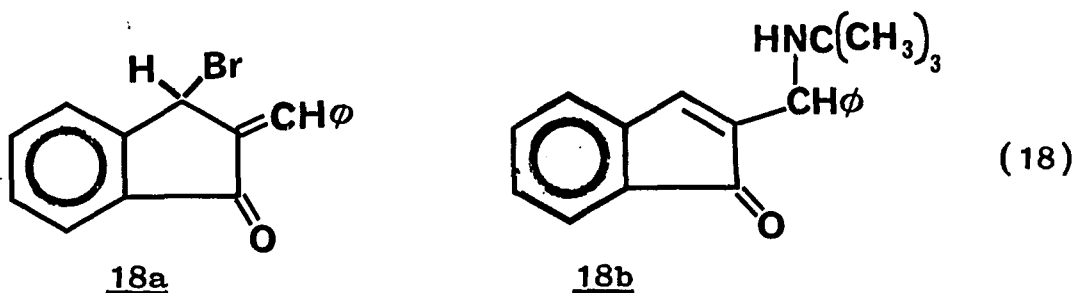
amines).³¹ Bordwell bases his analysis on examination of mechanistic possibilities which were not accounted for in previous work and on the reaction of various systems which he developed. These systems were designed to enhance the formation of the S_N2' product, but actually did not yield any of the rearranged substitution product.

Bordwell incorporated a sulfonyl group in his compounds because this electron withdrawing group would make the C=C bond more susceptible to attack by the nucleophile.³⁴ The sulfonyl group also "serves to eliminate competition from S_N1 or S_Ni' type processes by greatly retarding formation of an allylic carbonium ion."³⁴ Bordwell also notes that a carbonyl group can serve a similar function.

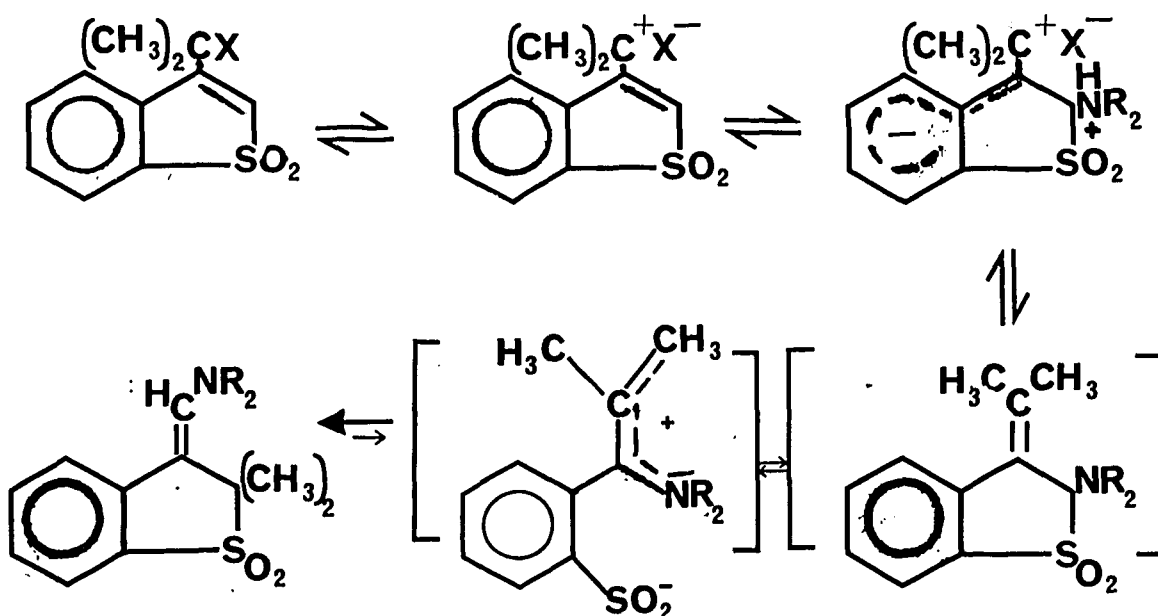
Cromwell, for example, determined that trans- α -(bromoethyl)-chalcone(17a) reacts with tert-butyl amine in either pentane^{35a} or hexane^{35b} to give initially the allylic rearrangement product, α - α (-(N-t-butylamino)-benzyl)-acrylophenone (17b) as shown in Eq 17:



Cromwell demonstrated that the reaction of 3-bromo-2-benzyl-1-indanone(18a) with two equivalents of tert-butylamine in benzene at 25° gave initially 3-(t-butylamino)-2-benzyl-1-indanone(18b),^{36a, b} as shown in Eq 18:



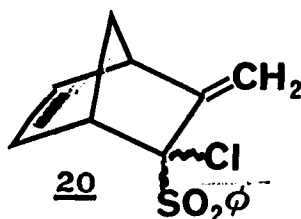
Bordwell³⁷ treated 3-(α -halo- α -methylethylbenzo(b))thiophene-1,1-dioxide(19a) with various nucleophiles and observed allylic rearrangement products. He favors a mechanism in which the initial addition-elimination product rearranges through an ion-pair(19b) as shown in scheme VI.



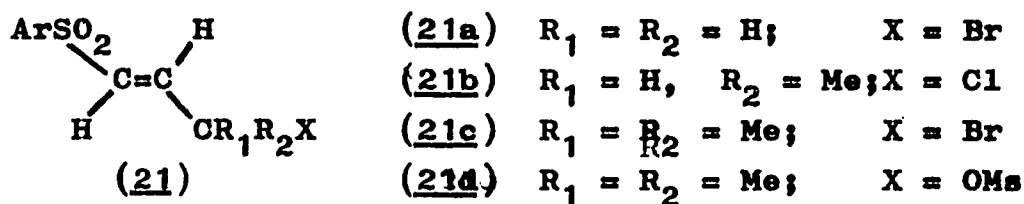
Scheme VI

The $k^{\text{Br}}/k^{\text{Cl}}$ leaving group ratios for the reaction of 19a are 25/1 for piperidine in DMF, 26/1 for piperidine in methanol and 41/1 for lithium azide in DMF. Although a concerted S_N2' mechanism can explain the product formation, Bordwell favors the formation of an intermediate ion-pair. The addition of a nucleophile to give a carbanion intermediate is possible, but it is difficult to explain the leaving group effect if a carbanion intermediate is invoked. Direct carbanion attack on 19a is eliminated by these data.

Exo- and endo-2-chloro-2-phenylsulfonyl-3-methylene-bicyclo(2.2.1)hept-5-ene (20) were shown to be inert in the presence of lithium azide in DMF, sodium methoxide in refluxing methanol, piperidine in refluxing methanol and triethylammonium thiophenoxide in refluxing benzene.³⁸ The sulfonyl group is predicted to enhance S_N2' attack by virtue of its inductive effect and also "strongly discourage" the formation of carbonium ion reactions. Because only starting material is recovered from the aforementioned reactions, in a system which is supposedly designed to enhance S_N2' reactions, Bordwell concludes that carbonium ion intermediates are involved in previously designated S_N2' reactions.



Bordwell also uses compounds 21a-d to demonstrate the absence of concerted S_N2' reactions. Only S_N2 products were isolated when the primary halide 21a was treated with methanol in DMF, sodium benzene sulfinate in DMF or potassium thiocyanate in acetone.



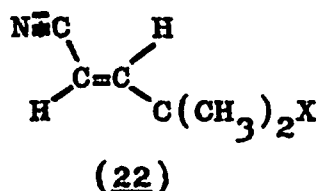
When the more basic nucleophile lithium azide (in methanol or DMF) was employed the product was the tautomer ($\text{PhSO}_2\text{CH}_2\text{CH}=\text{CHN}_3$) of the initially formed product ($\text{PhSO}_2\text{CH}=\text{CHCH}_2\text{N}_3$) (see page 27).

Reaction of the secondary chloride, 21b with either sodium methoxide, triethylamine, piperidine, or lithium bromide in methanol gave the direct substitution products. The product of the reaction in which lithium azide was employed was about 80% tautomerized.

Reactions of either 21c or 21d with methanol, lithium azide in methanol, 70%(v/v) dioxane:water, acetic acid, and 60% aqueous methanol yielded only the S_N2 product. It should be noted that because reactions were obtained under solvolytic conditions, carbonium ion type reactions are not completely eliminated from this system.

It is possible that the sterically large aryl sulfonyl group could inhibit S_N2' attack. However, when

this group was replaced by the small linear cyano function and the resulting compound, 22, treated with methanol, lithium azide in methanol or benzene sulfinic acid in DMF substitution at the tertiary center was found. Because 21c and 22 behaved similarly, it was argued that steric effects were inconsequential. No kinetic data, however, was given for these reactions. It appears possible to us that the initially formed S_N2' product (at least in the case where lithium azide is the nucleophile) could rearrange to yield the resulting product of the reaction.



Bordwell,³⁹ in earlier work, has shown that the sulfonyl group is capable of a steric inhibition of reactivity. Rates of reaction for the following compounds, 23a-d were determined and are shown below.

	<u>rate</u>
(<u>23a</u>) $\text{C}_7\text{H}_7\text{SO}_2\text{CH}_2\text{Cl}$	.2
(<u>23b</u>) $\text{N}\equiv\text{CCH}_2\text{Cl}$	3000
(<u>23c</u>) $\text{N}\equiv\text{CCH}=\text{CHCH}_2\text{Cl}$	1400
(<u>23d</u>) $\text{C}_7\text{H}_7\text{SO}_2\text{CH}=\text{CHCH}_2\text{Cl}$	1100

When the sulfonyl group and the cyano group are directly attached to the reaction center, the reaction rate of the cyano substituted methyl chloride (23b) is greater than that of the sulfonyl compound (23a) by a

factor of 10^4 . However, when these functional groups are separated from the reaction center by a C=C group (i.e. vinyls of 23a and 23b) the sulfonyl group and the cyano group act in a similar fashion in enhancing the rate of reaction as shown by the reactivities of 23c and 23d. This series of reactions have demonstrated that the large, bulky sulfonyl group is capable of inhibiting the rate of reaction.

Another objection to Bordwell's work can be raised. An S_N2' reaction on 22 would give a β,γ -unsaturated nitrile which is unconjugated and therefore less stable than the α,β -unsaturated isomer. The substrate would resist loss of conjugation, thereby retarding the S_N2' reaction and favoring the S_N2 reaction. This fact cannot be used to rationalize the absence of S_N2' reactions with the sulfones 21c and 21d because a β,γ -unconjugated is more stable than a α,β -conjugated sulfone.⁴⁰ Hence, the work with the nitrile, 22, does not negate the fact that the arylsulfonyl group may have sterically hindered the S_N2' reaction. Again, because reaction occurred under solvolytic conditions carbonium ion mechanisms, although inhibited, are not completely eliminated.

Bordwell, comparing the results obtained from the reactions of 21a and 21c, has concluded that 21c reacts through an ion-pair S_N2 mechanism at a tertiary center,⁴¹ based his conclusion on the following results: (a) that

the rate of reaction in 60% aqueous methanol compared to pure methanol is four times greater in 21c than 21a. This demonstrates that a more polar solvent system enhances the rate of reaction as would be expected in the formation of an ion-pair intermediate; (b) there was a negative salt effect upon addition of lithium perchlorate in methanol or 60% aqueous methanol for the reactions of 21a but a positive salt effect on the reactions of 21c; (c) a beta deuterium isotope effect was observed for 21c in the reaction of lithium azide in 60% aqueous methanol (1.22 rate retardation per CD₃ group) as well as the reaction of lithium azide in methanol (1.10 rate retardation per CD₃ group). A negligible isotope effect (as would be expected) was found for similar reactions of 21a; (d) in the reaction of 21a with potassium thiocyanate in methanol or acetone greater than 98% of the substitution occurred at the sulfur end of the nucleophile as would be expected for a typical S_N2 type reaction. However, in the presence of this nucleophile 21c gave a ratio of RSCN:RNCS products of 1.3:1.0 respectively, as expected for reactions involving carbonium ions. The rate of the reaction comparing 21a to 21d was shown to be 11:1.26 x 10⁴.

Bordwell claimed that an ion-pair mechanism at a tertiary center with 21c and 21d is due to: (a) the electron withdrawing effect of the aryl sulfonyl group

"which is sufficient to inhibit ion-pair dissociation, but not ion-pair formation;"^{4f} (b) the delocalizing effect of the vinyl group, which decreases the positive charge on the methyl groups and thus decreases the tendency towards elimination reactions; and (c) "the smaller steric effect resulting from the displacement of an alkyl group by a vinyl group which facilitates nucleophilic attack on the cation and may inhibit elimination."^{4d}

E. Ion-Pair Formation

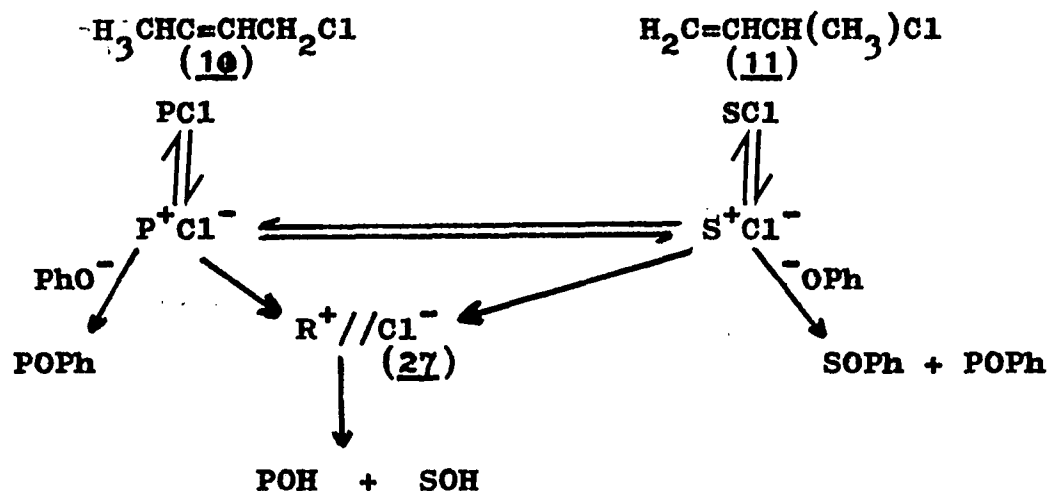
It has recently been postulated by Snee that all reactions occurring at a saturated carbon center react through an ion-pair intermediate. The unifying species in this theory is a configurationally stable ion-pair whose formation is rate determining at the S_N1 end of the mechanistic spectrum and whose destruction by nucleophilic attack is rate determining at the S_N2 end. "Borderline" behavior is exhibited when the rates of formation and destruction of this intermediate are competitive.^{42a, b, c, 43, 44}

Schleyer^{45a, b} and co-workers treated 2-adamantyl tosylate (24), 1-adamantyl bromide (25), and 2-propyl bromide (26) with azide ion, in an attempt to document results which would confirm or deny the existence of ion-pair intermediates in these systems. It was shown that in the reactions of 24 and 25 little rate enhancement was obtained upon addition of azide ion.

Kurz and Harris⁴⁶ have reported on the nucleophilic displacement reactions of α -halo acetic acids, which establish that "a full positive charge cannot be present on the central carbon atom of activated complexes for nucleophilic displacements: such a charge is required by an ion-pair mechanism."⁴⁶

Recent work with α - and γ -substituted allylic chlorides led to the contention that all substitution

reactions occur via preformed ion-pairs. For example, for the reactions of α -methylallyl chloride (11) and γ -methylallyl chloride (10) initial discrete primary and secondary ion-pairs are postulated, respectively, which are in equilibrium with each other and with a solvent separated ion-pair (27). Each of these ion-pairs may go on further to give product. The ratio of primary and secondary solvolysis products of 10 and 11 was invariant when the concentration of the nucleophile was changed. This is consistent with a mechanistic scheme which assumes that both primary and secondary solvolysis products arise from a single intermediate as shown in scheme VII.^{47a,b,c}



Scheme VII

When 10 and 11 were treated with phenoxide ion a variation in the ratio of primary versus secondary substitution compounds was noted. As the concentration of phenoxide was increased, a constant ratio of rearranged

primary γ -methylallyl phenyl ether to the unrearranged secondary ether is found (17:83). The decreasing value of this ratio at lower phenoxide concentrations is ascribed to the rearrangement of 11 to 10 competitive with the bimolecular attack of phenoxide. The residual 17% of rearranged γ -methylallyl phenyl ether, formed bimolecularly, is stated to be an authentic example of an S_N2' reaction.

The authors conclude that the postulated intimate ion-pair mechanism can best account for the observed product spread in addition to the fact that allylic rearrangement and solvolysis occur competitively. Also consistent with an ion-pair mechanism is the established fact that the rates of bimolecular attack by azide ion on α,γ - and γ,γ -dimethylallyl chloride take place at "virtually identical rates, independent of the extent of substitution at the reaction center".

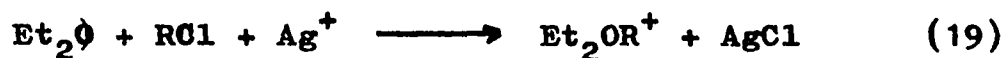
F. Reactions of Alkyl Halides with Silver Salts

It is the view of Kornblum⁴⁸ and other workers that the reaction of silver salts with alkyl halides proceeds via a concerted S_N1 - S_N2 process in which "the relative importance of the electrophilic pull of the silver and the nucleophilic push of the anion in the transition state varies as a function of the alkyl halide, the silver salt, and the solvent."⁴⁸

When optically active 2-bromobutane or 2-iodooctane were treated with silver nitrate in diethyl ether, petroleum ether (bp 30-60°) or acetonitrile the resulting nitrates ($RONO_2$) and nitro compounds were obtained with net inversion.⁴⁹ Kornblum suggested that the reacting alkyl halide is being adsorbed and desorbed on the silver salt crystal surface. Although the silver ion may pull on the halogen, a 2-octyl carbonium ion is difficult to form. The adsorption-desorption process of the alkyl halide takes place until a nitrate (or nitrite) ion is situated on the crystal surface in a position behind the carbon-bromine bond and is able to give the needed push to allow the reaction to proceed.

Kornblum observed retention of configuration when treating optically active α -phenylethyl chloride with silver nitrate and silver nitrite. Under these conditions this substrate should give a relatively stable benzylic

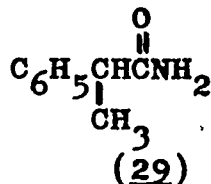
type carbonium ion which should lead to inversion and racemization. In diethyl ether this carbonium ion can also be stabilized by the solvent in a manner suggested by Kornblum as shown in Eq 19: To explain retention he assumes that diethyl ether attacks the incipient carbonium ion with inversion. Now the attacking nucleophile dislodges the bound solvent molecule from the oxonium ion (28) with a second inversion.



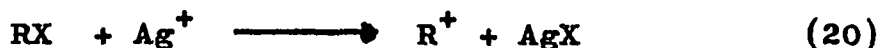
In non-nucleophilic solvents in which silver salts are insoluble (e.g. petroleum ether, bp 30-60°), when the silver salt pulls off the halogen the developing carbonium ion can only react with the nucleophilic anion. Furthermore, the carbonium ion is constrained to react on the surface of the silver salt and, therefore, the anion will enter from the same side which the silver pulls off the halogen giving net retention.

Silver nitrate and silver nitrite are soluble in acetonitrile. The anions present are not constrained to react on the surface of the silver salt and are available to aid the reaction by a rearward pushing to remove the halide. As expected, a product with ~~net~~ inversion is obtained. α -Phenylethyl nitrate was isolated in a 82% yield from this reaction and thereby showed that the reaction with solvent is minimal. However, when a

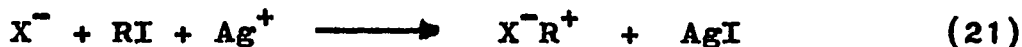
non-nucleophilic anion is used (e.g. silver fluoreborate) the solvent (acetonitrile) substituted product, after hydrolysis, N- α -phenylethyl acetamide (29) is obtained in a 60% yield.



Further indication that this type of reaction takes advantage of the push of the anion is shown by Hammond⁵⁰ who determined that the reaction of silver nitrate with alkyl iodides is much faster than that of the weakly nucleophilic anion of silver perchlorate. If the only effect is to regulate the silver activity, as shown in Eq 20:



then the perchlorate salt would be more reactive because the more nucleophilic nitrate should bind to the silver better than the perchlorate ion. Hammond,⁵⁰ however, also points out that the inverted configuration products of the 2-octyl series of reactions could come about from nucleophilic attack on a tight ion-pair as shown in Eq 21:



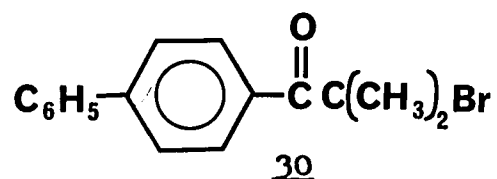
When the push of the anion is prevented by steric factors, the rate of reaction is decreased. Thus, when ethyl iodide and neopentyl iodide are treated with silver nitrate in acetonitrile at 25°, the rates of reaction are 18 and $0.064 \times 10^2 \text{ l}^2/\text{mole}^2\text{sec}$, respectively.

Kornblum⁵¹ has shown that when silver nitrate is allowed to react with 4-substituted benzyl bromides, at 0°, the graded S_N1-S_N2 mechanism gives way to a simple carbonium ion mechanism. He accomplished this by showing the increased life-time of the developed carbonium ion in the reaction series of p-nitro, p-methyl, and p-methoxy benzyl bromide.

When the leaving halogen atom is alpha to a carbonyl function a decrease in reaction rate is observed. Kornblum has shown that whereas primary bromides react completely with silver nitrate in sixty to 80 hours, the ethyl ester of bromoacetic acid reacts to an extent of only 12% in 156 hours. The author attributes this result to the fact that when silver pulls on the halogen the carbon-bromine bond becomes more polarized, thereby increasing the electron deficiency of the carbon alpha to the carbonyl group. "But the carbonyl carbon itself has an electron deficiency and, hence, the transition state for the reaction is of higher energy than it would be in the absence of the carbonyl group."⁵¹

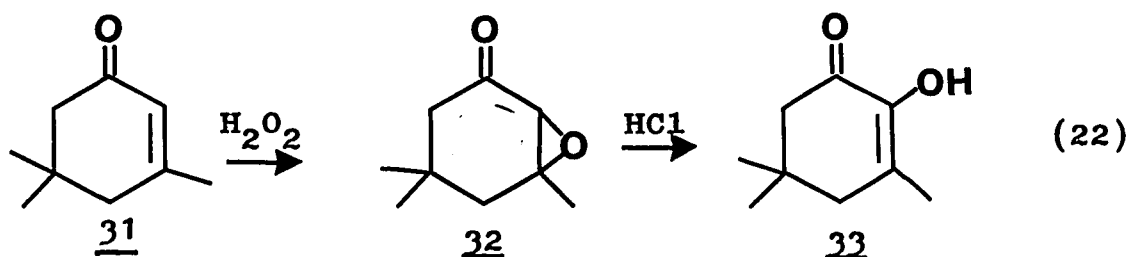
Cromwell and Kevill⁵² have treated α-bromo-p-phenylisobutyrophenone (30) with silver nitrate and silver perchlorate and have shown that the initial rate ratio of these two silver salts is 130:1, respectively.

This data are consistent with Kornblums results which indicate that reactions with halogens alpha to a carbonyl group have to take place with greater S_N2 character in their transition states. The authors suggest that electrophilic assistance by the silver and nucleophilic aid by the nitrate ion and lack of it by the perchlorate anion account for the initial rate differences.



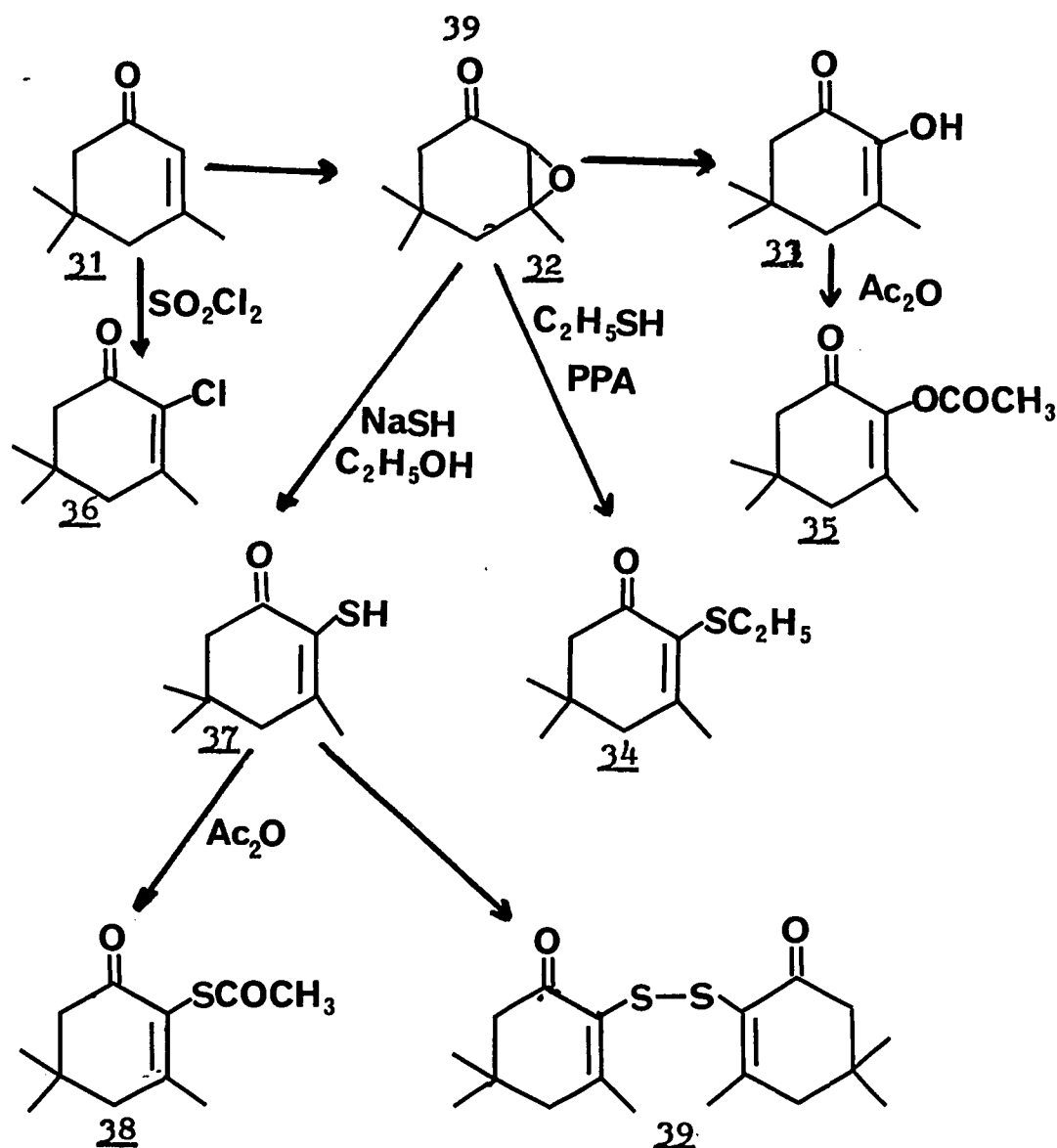
G. Reactions Employing Derivatives of Isophorone (31)

2-Hydroxyisophorone (33)(3,5,5-trimethyl-1,2-cyclohexandione) has been prepared by the epoxidation of isophorone (31)(3,5,5-trimethylcyclohex-2-enone) followed by acidic rearrangement of the resulting epoxide as shown in Eq 22.^{53a, b}



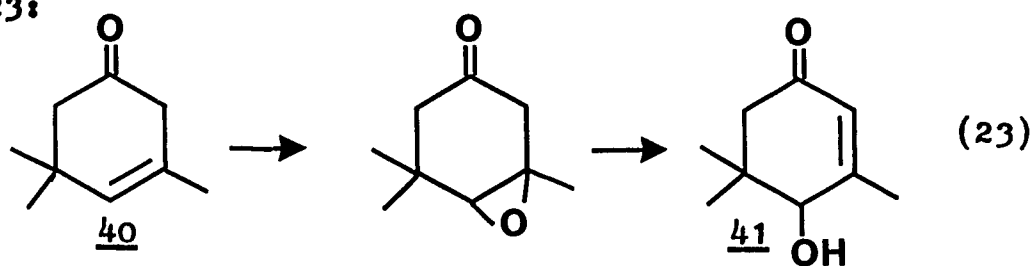
Tomoeda,⁵⁴ et al., conducted nmr studies of 2-substituted isophorone molecules including 2-ethylthio- (34), 2-hydroxy- (33), 2-acetoxy- (35), 2-chloro- (36), 2-mercapto- (37), and 2-acetylthio- (38)-3,5,5-trimethylcyclohex-2-enones, as well as bis-(3,5,5-trimethylcyclohex-2-enon-2-yl) disulphide (39). The synthetic routes followed to obtain these compounds are shown in scheme VIII.

3,5,5-Trimethylcyclohex-3-enone (40) was first prepared by Kharasch and Tawney⁵⁵ by the action of methyl magnesium bromide on 31 in the presence of a trace of ferric chloride. A clarification of the experimental details involved in this reaction was recently published.⁵⁶



Scheme VIII

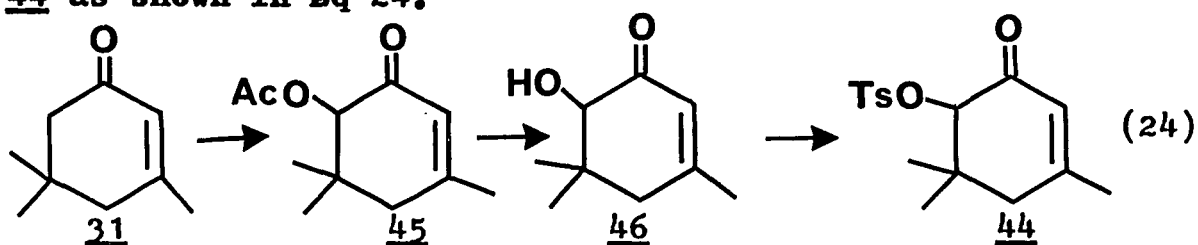
4-Hydroxyisophorone (41) was prepared by Marx and Sondheimer⁵⁷ by the reaction of *m*-perchlorobenzoic acid with 40 followed by a base catalyzed reaction as shown in Eq 23:



Edgar⁵⁸ and co-workers reported the synthesis of 4-bromoisophorone (1), obtained from the reaction of 31 with N-bromosuccinimide. The reaction of 1 with aqueous sodium carbonate reportedly gave 41. They also prepared 4-acetoxyisophorone (42) by the reaction of 1 with silver acetate (3 hr, 90°, 31% yield).

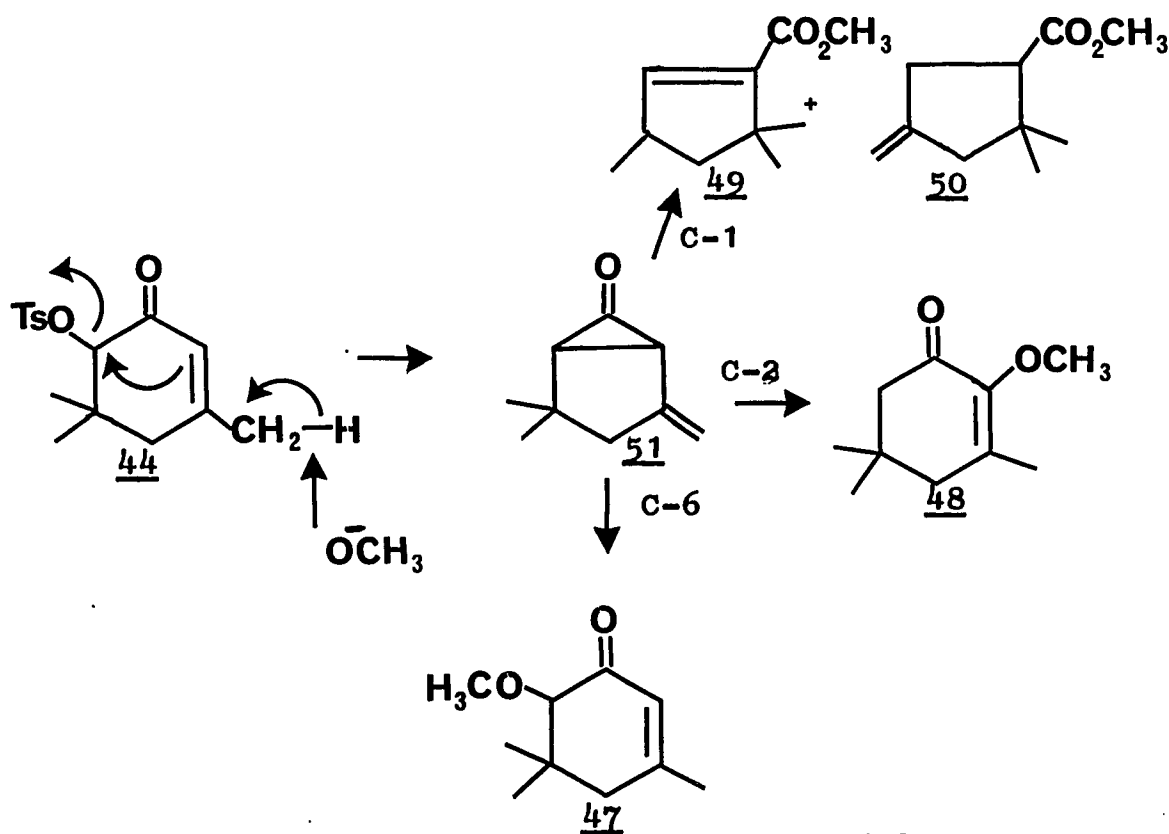
Meislich⁵⁹ and co-workers allowed 1 to react with silver perchlorate in benzene and obtained a mixture of 3,4,5-trimethylphenol(2) and bis(3,4,5-trimethylphenyl) ether(43).

Fort^{60a, b} prepared 6-tosyloxyisophorone (44) in three steps from 31. Acetoxylation of 31 with lead tetraacetate yielded 6-acetoxyisophorone (45) which was then hydrolyzed with concentrated hydrochloric acid to yield 6-hydroxyisophorone (46) and then treated with p-toluenesulfonyl chloride to yield the desired 44 as shown in Eq 24:



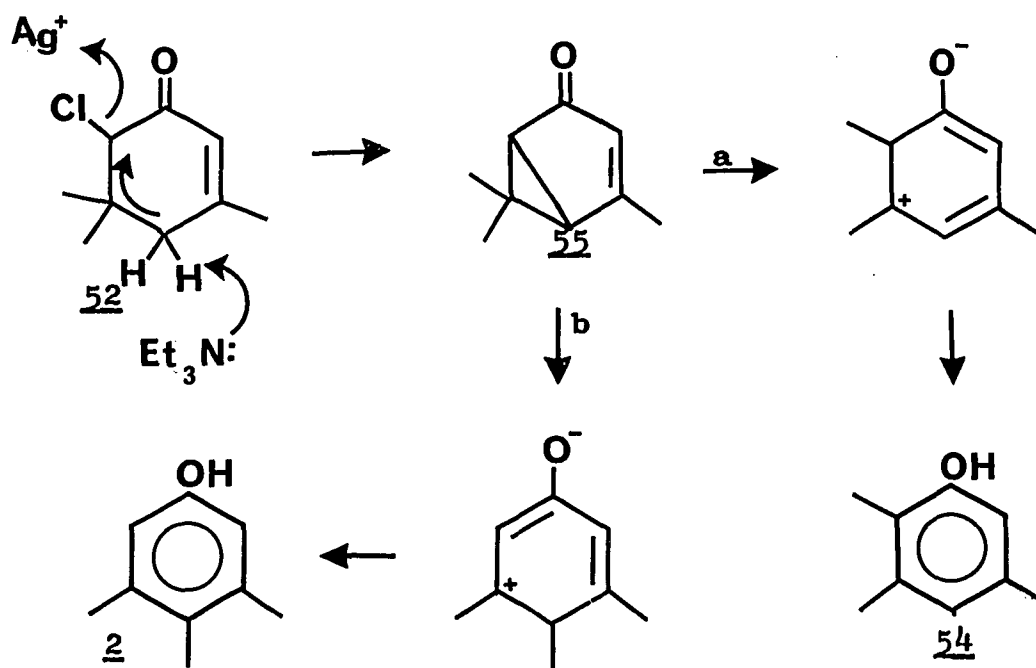
When 44-was treated with a dioxane-hydrochloric acid solution at reflux for 30 minutes, the only acidic product obtained was 2.^{60b} The proposed mechanism for this reaction involves enol formation of the starting

material followed by solvolysis of the tosyl group and then rearrangement of a methyl on C-5 to C-4. Under basic conditions (sodium methoxide in methanol) 44 gave a mixture of 2-methoxyisophorone (47), 6-methoxyisophorone (48) and a mixture of methyl esters of 3,5,5-trimethylcyclopent-2-encarboxylic acid (49) and 2,2-dimethyl-4-methylenecyclopentane carboxylic acid (50). Fort⁶¹ proposed a mechanism for this reaction in which a proton from the C-3 methyl group is removed by the base resulting in a cyclopropanone type intermediate (51). Attack on the C-1, C-2 or C-6 positions of the intermediate (51) by either the solvent or base present will give the observed products as shown in scheme IX.



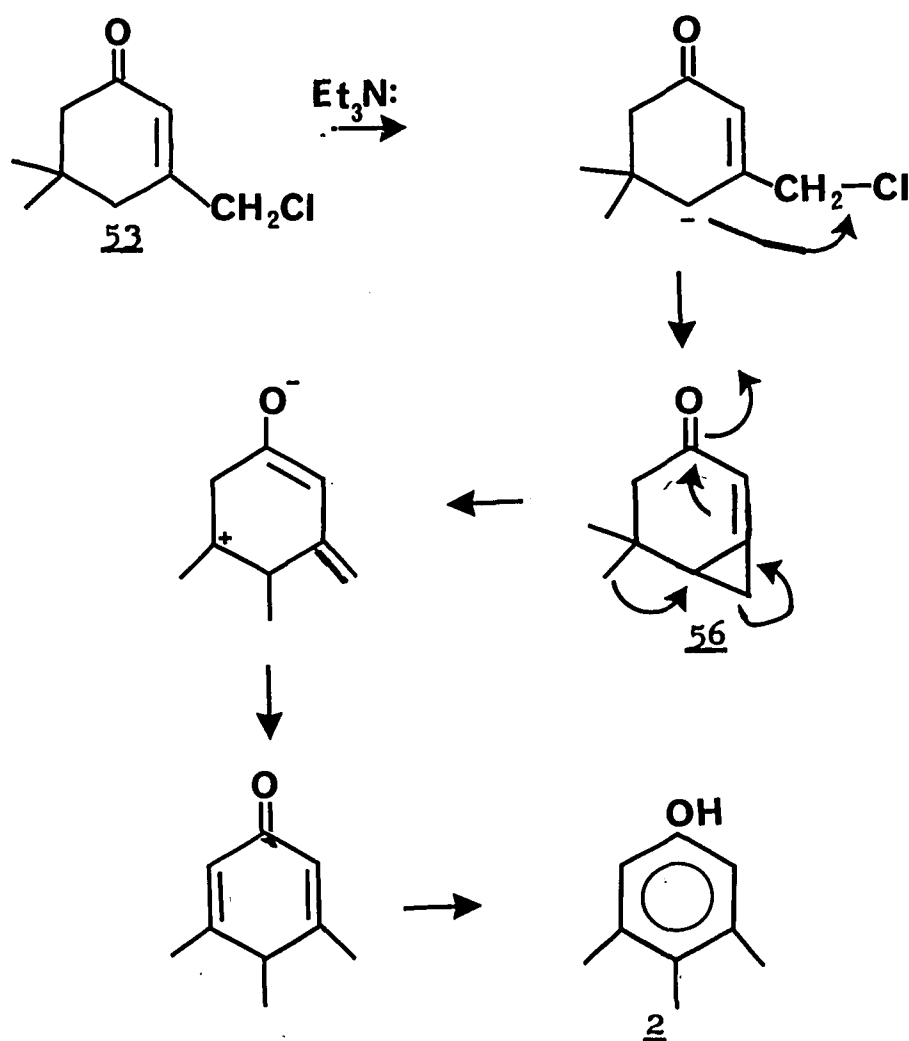
Scheme IX

Kosower⁶² reported that the reaction of copper (II) chloride and lithium chloride in DMF with 31 yielded a mixture of 6-chloroisophorone (52) and 3-chloromethyl-5,5-dimethyl-2-cyclohexanone (53) as well as some phenolic material. When 52 was treated with silver nitrate in triethylamine, a slow reaction (50 hr, 80°) took place which resulted in a 40% yield of phenols (2,3,5-trimethylphenol, 54) (60%) and 2 (40%). Kosover suggested that this reaction proceeded via a cyclopropane intermediate (55) followed by methyl migration to C-6 or C-4 to give 54 and 2 respectively as shown in scheme X.



Scheme X

Kosower⁶² also treated 53 with triethylamine (38 hr, reflux) and obtained 2 in a 50% yield. The suggested mechanism requires formation of a cyclopropane intermediate (56) derived from an anion on C-4 which internally displaces the the chloride ion on the C-3 methyl group as shown in scheme XI.



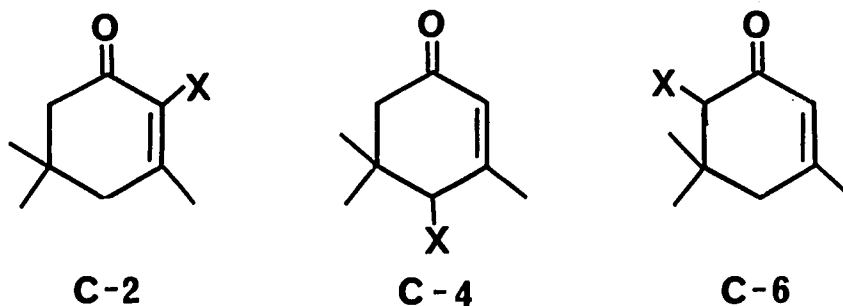
Scheme XI

RESULTS AND DISCUSSION

Results and Discussion

Section A: Method of Analysis of Product Distribution

Generally, the relative yields of each product in the reaction mixture were determined by nmr analysis. Commonly, the reactions of 4- or 6- substituted isophorones (4- or 6- 3,5,5-trimethylcyclohex-2-enones) resulted in either substitution at the C-2, C-4 or C-6 positions or in phenol formation. All chemical shifts are reported in δ units downfield of the internal standard tetramethylsilane.



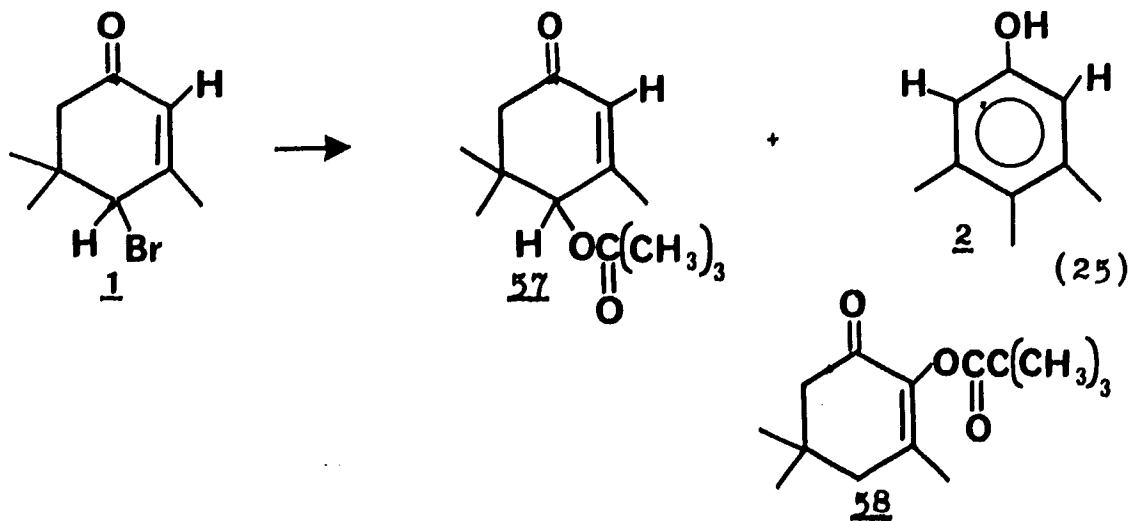
The aromatic protons in the phenols 2,3,5-trimethylphenol (54) or 3,4,5-trimethylphenol (2), all of which are ortho or para to the shielding hydroxy group, appear at about $\delta 6.4$ to $\delta 6.6$. The methyl group protons of these compounds occur between $\delta 2.0$ and $\delta 2.4$.

The vinylic protons in either C-4 or C-6 substituted isophorones absorb at ca. $\delta 5.8$. The C-4 allylic hydrogens of C-4 substituted isophorone atoms are observed from $\delta 4.0$ to $\delta 5.5$ depending on the C-4 substituent.

The position of the proton on the six position of C-6 oxygen substituted isophorones is commonly between $\delta 5.0$ and $\delta 5.6$ for the compounds studied. C-2 Substituted isophorones contain no vinylic protons or any other protons downfield of $\delta 2.7$.

The methylene protons and the hydrogens of the C-3 vinylic methyl group appear between $\delta 1.8$ and $\delta 3.0$ in the so-called "alkyl" region. The nine equivalent tert-butyl hydrogens, of the pivalate group and the C-5 gem-dimethyl group protons usually appear between $\delta 0.90$ and $\delta 1.3$, in the so-called "gem" region.

For most of the C-4 and C-6 substituted isophorones and aromatic compounds obtained in this study, the chemical shift of peaks downfield of $\delta 3.0$ are unique. To illustrate, the following product mixture is assumed; 4-bromoisophorone (1), 3,4,5-trimethylphenol (2), 4-pivoxylisophorone (57) and 2-pivoxylisophorone (58). This hypothetical mixture is shown in Eq 25:



The proton on C-4 of 1 occurs at $\delta 4.3$ while the vinylic C-2 proton of 1 absorbs at $\delta 5.8$. The C-4 allylic proton of 57 appears at $\delta 5.4$, while the vinylic hydrogen of this compound is present at $\delta 5.8$. The two equivalent aromatic protons of 2 are observed at $\delta 6.5$. By determining the relative areas of these peaks, and by knowing how many protons each peak is supposed to represent, the approximate relative yield for each of the aforementioned compounds can be obtained. A typical calculation is shown in Chart 1.

A C-2 substituted isophorone, e.g. 58, contains no peaks downfield of $\delta 3.0$. The compound 58 contains fifteen hydrogens in the gem region of the nmr (nine tert-butyl protons and six protons from the C-5 methyl groups), in addition to seven protons in the alkyl region (four protons from the C-4 and C-6 methylene groups and three protons from the C-3 methyl group).

The expected integration, of the alkyl and gem regions, is calculated based on the other compounds present which contain peaks downfield of $\delta 3.0$. The difference between the observed value and the calculated expected value is attributed to the C-2 substituted compound. The expected number of protons in each region is known. Therefore, the relative area per proton for each proton of 58 can be calculated. From this information, the relative yields of each of the reaction

CALCULATION OF PRODUCT YIELDS

CHART 1

Compound	Chemical Shift (PPM)	Area (# of boxes)	boxes/proton (A)	# of protons in gem region	x (A)
<u>1</u>	δ 4.37	5	5	6	30
	δ 5.82 (a)	5	5		
<u>2</u>	δ 6.51	8	4	0	0
<u>57</u>	δ 5.57	5	5	15	75
	δ 5.88 (a)	5	5		
					<u>105</u> (total) (calculated)

(a) not separable in nmr

Total observed area (# of boxes) 195
Total calculated area 105

Observed area - calculated area 90 (B)

Number of protons expected for 58 in gem region 15 (C)

Number of boxes/proton for 58 = B/C 90/15= 6

CHART 1 (continued)

Compound	Area/proton (in boxes) (D)	relative yield D/E
<u>1</u>	5	25%
<u>2</u>	4	20%
<u>57</u>	5	25%
<u>58</u>	$\frac{6}{20}$ (E)	30%

(E) = Total area/proton (in number of boxes)

products can be determined.

Because of the sensitivity limitations in the nmr technique, as used for quantitative analysis, the reported yields of products have a deviation of about $\pm 5\%$ of the actual yields. Also, for C-2 substituted isophorones, the yields reported are the maximum because there is the possibility of unidentified minor products contributing to the total area of this region. These semiquantitative yields are more than adequate to elucidate qualitative trends with assurance.

Even if the peaks in the gem or alkyl region are not separable for integration purposes, they do have distinctive chemical shifts. For example, the peaks of both the tert-butyl hydrogens and gem methyl protons in compounds as closely related as 57 and 58 can be distinguished so that the presence of both compounds, and even a rough approximation of their relative yields can be ascertained.

The nmr spectra for all of the compounds employed during the course of these investigations are recorded in the experimental section.

Section B: Solvolytic Reactions of 4-Bromoisophorone (1)

In order to study the reactions of 1 in the presence of added nucleophiles, it is first necessary to observe the reactions of 1 under solvolytic conditions (Table 1).

Solvents which are non-nucleophilic, but in which reactions with added nucleophiles were investigated, are also included in Table 1).

As can be seen from entries 1-7, 11, 13, and 15-19 of Table 1, 1 is inert under a wide variety of solvolytic conditions. Solvolysis of 1 has to occur through a solvated carbonium ion mechanism. However, this type of reaction mechanism is inhibited because of the relatively high energy of the delocalized C-4 carbonium ion.

Under acetolysis (entry 8) and ethanolysis (entry 9) conditions, solvent substitution products are not obtained. Instead, the only isolatable product is 3,4,5-trimethylphenol (2). This almost quantitative formation of phenol can be explained as follows. A microscopic amount of dissociation of 1 gives a carbonium ion which could react with protic solvents or rearrange to phenol. In either case hydrogen bromide is a by-product. This strong acid is capable of catalyzing the formation of phenol and not the solvolytic product as shown in Eq 26:

Table 1

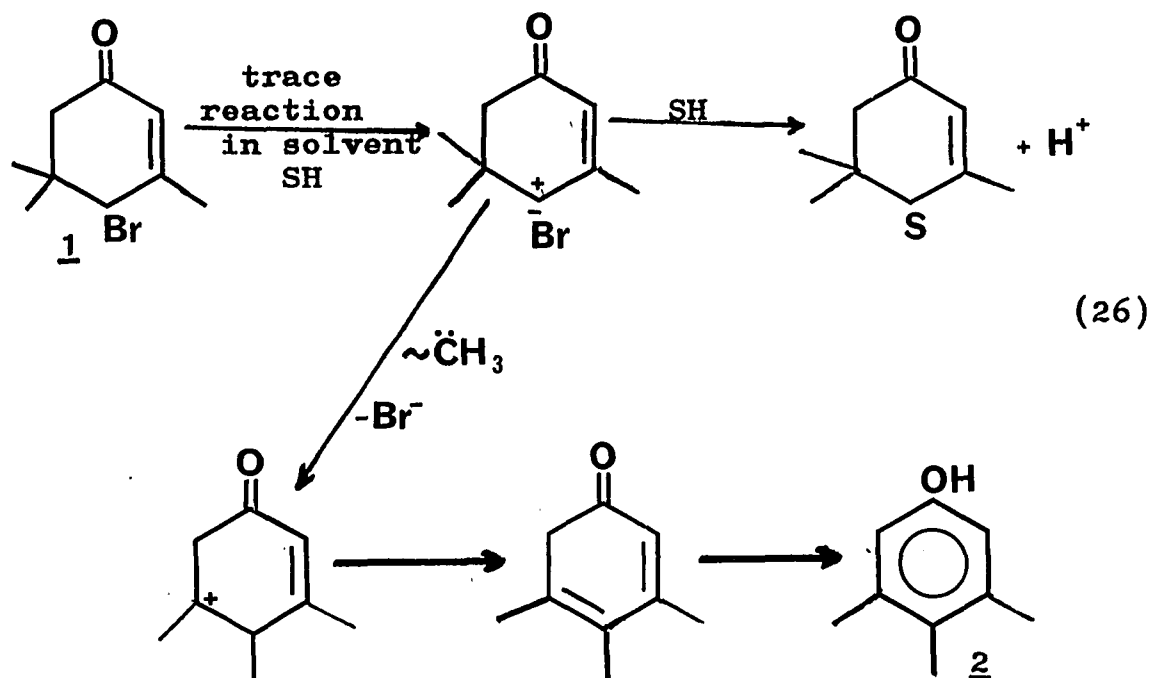
Reactions of 4-Bromoisophorone(1) in Various Solvents

Entry	Solvent	Volume (ml)	Products(yield)
1	pivalic acid	2	No Reaction (NR)
2	pyridine	2	NR
3	dioxane:water (1:1 v/v)	5	NR
4	DMF ^f	5	NR
5	DMF:water (9:1 v/v)	5	NR
6	DMF: $\text{pH } 4$ buffer ^h (1:1 v/v)	5	NR
7	benzene	5	NR
8	acetic acid	2	<u>2</u> (95%)
9	ethanol ^b	5	<u>2</u> (90%)
10	ethanol:water (9:1 v/v) ^b	5	<u>2</u> (90%)
11	ethanol: 2,6-lutidine ^{b,d}	5	NR
12	DMF, pivalic acid ^c	5	<u>2</u> (45%); <u>1</u> (45%)
13	dioxane: $\text{pH } 8$ buffer ⁱ (1:1 v/v)	5	NR
14	nitromethane	5	NR
15	DMF: $\text{pH } 4$ buffer ^h (1:1 v/v) pivalic acid ^c	5	NR

Table 1 (continued)

Entry	Solvent	Volume (ml)	Products(yield)
16	DMF, methanol ^e	5	NR
17	HMPT ^g	5	NR
18	DMF:water(1:1 v/v), pivalic acid ^c	5	NR
19	nitromethane, pivalic acid ^c	5	<u>2</u> (62%); <u>1</u> (32%)
20	DMF, acetic acid ^c	5	NR
21	dioxane, pivalic acid ^c	5	NR
22	chloroform, pivalic acid ^c	5	NR
23	methylene chloride, pivalic acid ^c	5	NR
24	dioxane, acetic acid ^c	5	NR
25	chloroform, acetic acid ^c	5	NR
26	methylene chloride, acetic acid ^c	5	NR

(a) 0.434 g (0.002 mol) of 4-bromoisophorone (1); reaction conditions: 40.5 hrs; reaction temperature $45 \pm 2^\circ$ unless otherwise noted. (b) length of reaction- two weeks. (c) one equivalent. (d) two drops. (e) 0.5 equivalents. (f) di- methylformamide. (g) hexamethylphosphoramide. (h) Potassium Bipthalate Buffer, 0.05 molar, mole inhibitor .05% formalin. (i) 50 ml 0.1 M NH_4OH - 950 ml 0.1 M NH_4Cl .



The initial formation of a few molecules of hydrogen bromide leads to a "snowballing" effect in the non-buffered solvent media causing conversion of 1 to 2. The catalytic effect of hydrogen bromide was substantiated by showing that the rate of conversion of 1 to phenol was increased by adding this gas to glacial acetic acid.

This explanation is further confirmed by run 11, which is identical to run 10 except for the addition of 2 drops of 2,6-lutidine. This small amount of added base is capable of neutralizing any initially formed acid under the solvolytic conditions and thereby preventing the "snowballing" effect. However, had any significant reaction occurred, the acid build up would have overwhelmed the small amount of base present and phenol formation should be observed.

The absence of any product other than 1 in reaction 11, which is run for approximately ten times the length of the "usual" reactions indicates that solvolytic reaction of 1 are exceedingly and imperceptibly slow. The absence of solvolysis reactions of 1 leads to an important conclusion. Compound 1 is indeed reluctant to form carbonium ions. Compound 1 may form a tight ion-pair (R^+X^-), but cannot proceed to give a solvent separated ion-pair ($R^+//X^-$). It is clear that if a tight ion-pair is formed it can only revert to starting material.

All reactions in this section and following sections were run for 40.5 hours at $45 \pm 2^\circ$ in order to standardize reaction conditions. The choice of reaction temperatures was dictated by the use of pivalic acid as the solvent for ensuing reaction. Pivalic acid melts at 33° .

It is of interest to compare reaction 1 and 8 of Table 1. Pivalysis (reaction 1) gave only recovered starting material, whereas, acetolysis (reaction 8) yielded only 2. This diverse result cannot be ascribed to the small difference in the K_A values or to the dipole moment of the monomeric and dimeric forms of the acid. See Table 2.

The K_A values of the acids differ by a factor of only five. Dipole moments of the dimeric and monomeric forms of these organic acids are also similar.

The dielectric constant of acetic acid is 6.15. Organic acids which have the same empirical formula as

Table 2. Physical Constants of Acetic Acid and Pivalic Acid.

<u>Physical Constant</u>	<u>Acetic Acid</u>	<u>Pivalic Acid</u>
melting point	16.6° ^{63a}	33°
K _A (10 ⁴)	3.2 ^{63c}	0.60 ^{63c}
dipole moment (monomer)	1.63 ^{63c} 1.64- 1.77 ^{64a}	1.9 ^{63c} 1.77- 1.81 ^{64b}
dipole moment (dimer)	0.91 ^{63c}	0.98 ^{63c}
dielectric constant	6.15 ^{63b}	

pivalic acid (e.g. valeric and isovaleric acid) also have a low dielectric constant of about 2.6. This difference of ca. 4 in dielectric constants may be significant because in media of dielectric constant less than 10 small differences are more important.⁶⁵

The organic acid may catalyze enol formation or hemiacetal formation (page 69) and/or aid in the removal of the leaving group by hydrogen bonding. Under the reaction conditions acetic acid may exist in the monomeric and dimeric forms. Pivalic acid may exist either as monomer or as a dimer, both of which are large and sterically hindered and thus be incapable of reacting. To test this suggestion, 1 was treated in an inert solvent with one equivalent of pivalic acid. Under these conditions, pivalic acid should exist in its monomeric form. In reaction 12 of Table 1 using DMF as the solvent, with one equivalent of pivalic acid, 45% of 2 as well as 45% of starting material plus minor amounts of other products were observed. No reaction was noted in DMF (dielectric constant (D) = 37).⁶⁶ Similar results were obtained with nitromethane as the solvent (entries 14 and 19) (D=35.9)⁶⁶ When 1 equivalent of acetic acid was stirred with 1 in DMF (entry 20) only 2 (62%) and 1 (32%) were obtained. These results are similar to those obtained with pivalic acid.

The dielectric constant of the solvent may be important for the initial formation of strong acid. The reaction of 1 with one equivalent of pivalic acid in dioxane ($D=2.20$), ^{63b} chloroform ($D=4.80$) ^{63b} and methylene chloride ($D=9.08$) ^{63b} as well as one equivalent of acetic acid in these solvents (entries 21-26) resulted in the recovery of only starting material. It is apparent that the dielectric constant of the medium may be important when considering the decomposition of 1 in monomeric acids. However, the slightly greater dielectric constant of acetic acid compared to pivalic acid is not enough to account for the difference in reactivity. The different steric requirements of the monomeric and dimeric forms of the acids could be a factor in the observed results. Entry 16 (DMF, methanol) shows that without acid, hydrogen bonding capability of the solvent is insufficient to induce a reaction.

Water and DMF (entry 5) cause no solvolysis reaction. As shown by reaction 6, buffered solutions at $pH=4$ are not strong enough to initiate the acid catalyzed reactions of 1 leading to phenol formation. When the solvent is DMF: $pH=4$ buffer, in the presence of one equivalent pivalic acid (entry 15) no reaction is observed. When DMF:water is the solvent with one equivalent of pivalic acid present (entry 18), no reaction is noted.

It is reasonable to assume that the water solvates the pivalic acid attenuating its catalytic behavior. Because strong acid, if formed, could easily accumulate in reaction 18, it is clear that the added water completely inhibits any reaction.

Section C. The Reaction of 4-Bromoisophorone (1) with DMSO

When 1 is allowed to react with DMSO at ca. 45° for 40.5 hrs an interesting product distribution is observed. The nmr spectrum of the total recovered crude product showed an almost total absence of peaks in the gem region, indicating the absence of cyclohexenone compounds.

Extraction of the total crude products with 10% sodium hydroxide left only approximately 10% (by weight) of the crude reaction product as non-acidic products. An nmr spectrum of this neutral material showed the presence of a significant amount of starting material, 1, and other compounds. No attempt was made to isolate and identify these minor neutral products.

The acidic products were separated by preparative thick layer chromatography. Table 3 indicates the results of this separation.

Table 3

Results of Thick Layer Chromatography on Acidic Reaction Products of the Reaction of 1 with DMSO

Cut	R _f	Weight(in mg)	Comments ^b	Yield ^a
A	0.59	37	white solid- mp 133°	10.7%
B	0.48	154	white solid-mp 42-43°	61.5%
C	0.29 to 0	44		27.8%

(a) based on acidic products recovered. (b) thick layer plates from Brickmann Chem. Co.-Silcia gel (250 microns thick) plates developed in benzene.

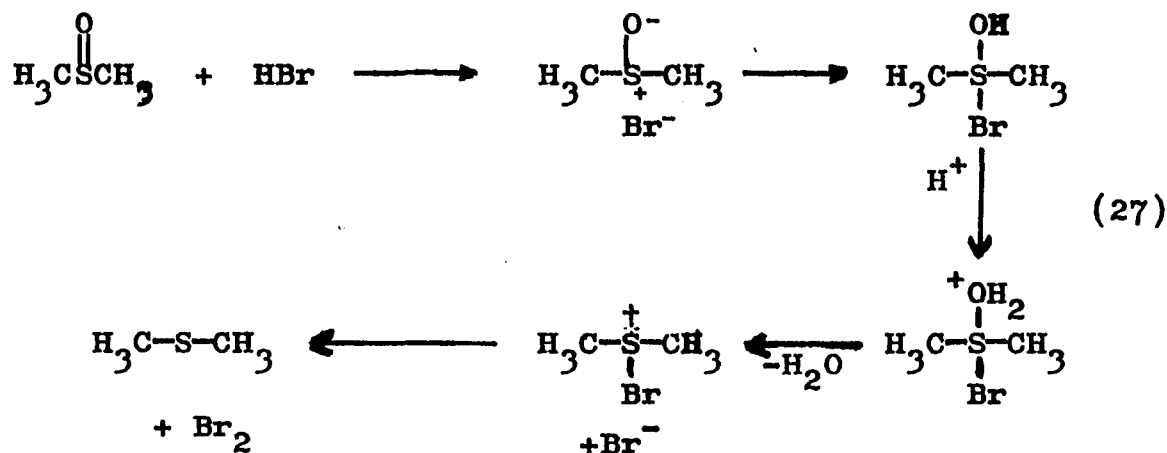
The nmr spectrum of cut C, as well as tlc comparisons proved that this product is 3,4,5-trimethylphenol (2).

The nmr spectrum of cut B indicated the presence of three distinct aromatic methyl groups, as well as one aromatic hydrogen. The existence of an acidic hydrogen, exchangeable in deuterium oxide, was also noted. Mass spectroscopy analysis demonstrated the presence of a bromine atom. The parent peaks of this compound are at m/e 214 and 216. A reasonable structure consistent with these data is 2-bromo-3,4,5-trimethylphenol (59).

Monobromination of 2 was attempted with bromine in carbon disulfide. The recrystallized product (mp 45.2-46°) showed no melting point depression upon comixture with cut B. Identical results were also observed in tlc, ir, nmr and elemental analysis.

The nmr spectrum of cut A shows at least four peaks in the alkyl region and no aromatic protons. The mass spectrum of this cut showed the presence of parent peaks at m/e 292, 294 and 296, in a ratio of approximately 1:2:1, which is indicative of the presence of two bromine atoms. The crude mp of this material is 133-4°. We suggest that a likely structure for this compound is the known 2,6-dibromo-3,4,5-trimethylphenol (lit. mp 145-154.5°)⁶⁷ (60).

Products A and B could likely come from the mono and dibromination of initially formed 2. Bromine could be formed from the reaction of DMSO with hydrogen bromide^{68a, b} as shown in Eq. 27:



The initial molecule of hydrogen bromide could arise from aromatization of 1 in this solvent.

As can be seen from the data in Table 4, the addition of either solid (calcium carbonate) or liquid (triethylamine) base inhibits the reaction of 1 with DMSO. Compound 1 does not react in an aqueous solution of DMSO, probably because of hydration of the DMSO. This inhibiting effect of water was also observed in entry 18, Table 1 when the reaction of pivalic acid with 1 was prevented.

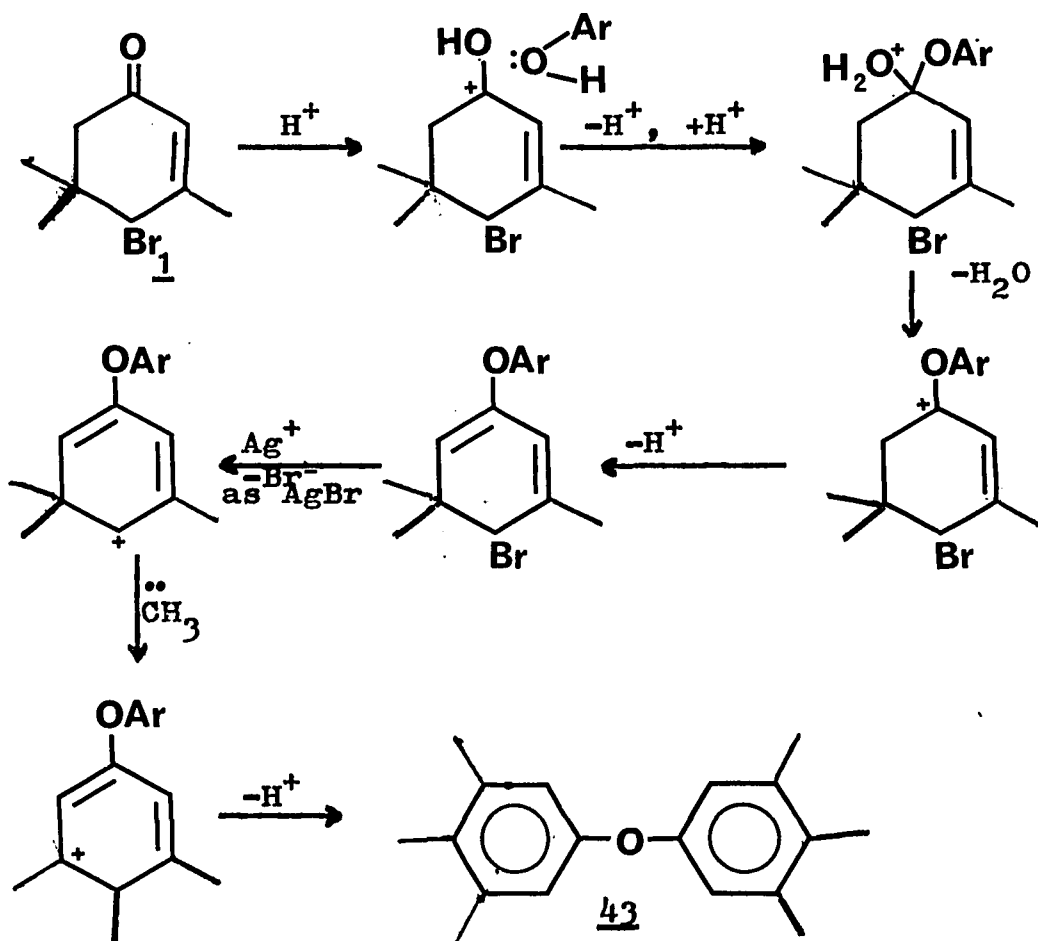
Table 4

Reactions of 1 in DMSO

<u>Entry</u>	<u>Reactants</u>	<u>Products (yield)</u>
1	DMSO(5 ml) + 1.3 equiv. CaCO_3	No Reaction
2	DMSO(5 ml) + 1.3 equiv. Et_3N	No Reaction
3	DMSO(2.5 ml) + water(2.5 ml)	No Reaction
4	DMSO(5 ml)	<u>1</u> (trace), <u>2</u> (27.8%) <u>59</u> (61.5%), <u>60</u> (10.7%)

Section D. The Reactions of 4-Bromoisophorone (1) in the Presence of Silver Perchlorate

Recently,⁵⁹ 4-bromoisophorone (1) was allowed to react with silver perchlorate in benzene to yield 3,4,5-trimethylphenol (2) (45%) and bis-(3,4,5-trimethylphenyl)-ether (43) (45%). The proposed mechanism for the formation of 43 involves the acid-catalyzed attack by 2 on the carbonyl carbon atom of 1 as shown in scheme XII. The acid is generated during the formation of 2.



Ar = 3,4,5-trimethylphenyl

Scheme XII

The attack of 2 on protonated 1, loss of water, and then loss of a proton, gives the enol ether. Silver ion now removes the bromine from C-4 of the enol ether as silver bromide. Methyl migration and loss of a second proton gives the symmetrical ether 43.

The generality of this reaction was studied using carboxylic acids, such as pivalic and acetic acid as solvents in order to see whether phenyl carboxylates would be formed. The reaction products of 1 with these acids, in the presence of silver perchlorate, are noted in Table 5. Perchlorate, having negligible nucleophilicity, was chosen to avoid reactions of 1 with the anion. As a useful comparison the reactions of 1 with the different organic acids alone are listed. The differences in reactivity of acetic acid (entry 1) and pivalic acid (entry 2) have already been analyzed in section B, page 51.

Table 5^a

Reactions of 4-Bromoisophorone (1) in the Presence of Silver Perchlorate

Entry	Solvent	Amt.	Products (yield)
1	acetic acid	2 ml	<u>2</u> - 95%
2	pivalic acid	2 g	No Reaction
3	acetic acid ^b	2 ml	<u>2</u> - 66%(92%); 3,4,5-trimethyl-phenyl acetate(<u>61</u>)- 34%(8%)
4	pivalic acid ^b	2 g	<u>2</u> - 56%(86%); 3,4,5-trimethyl-phenyl pivalate(<u>62</u>)- 44%(14%)

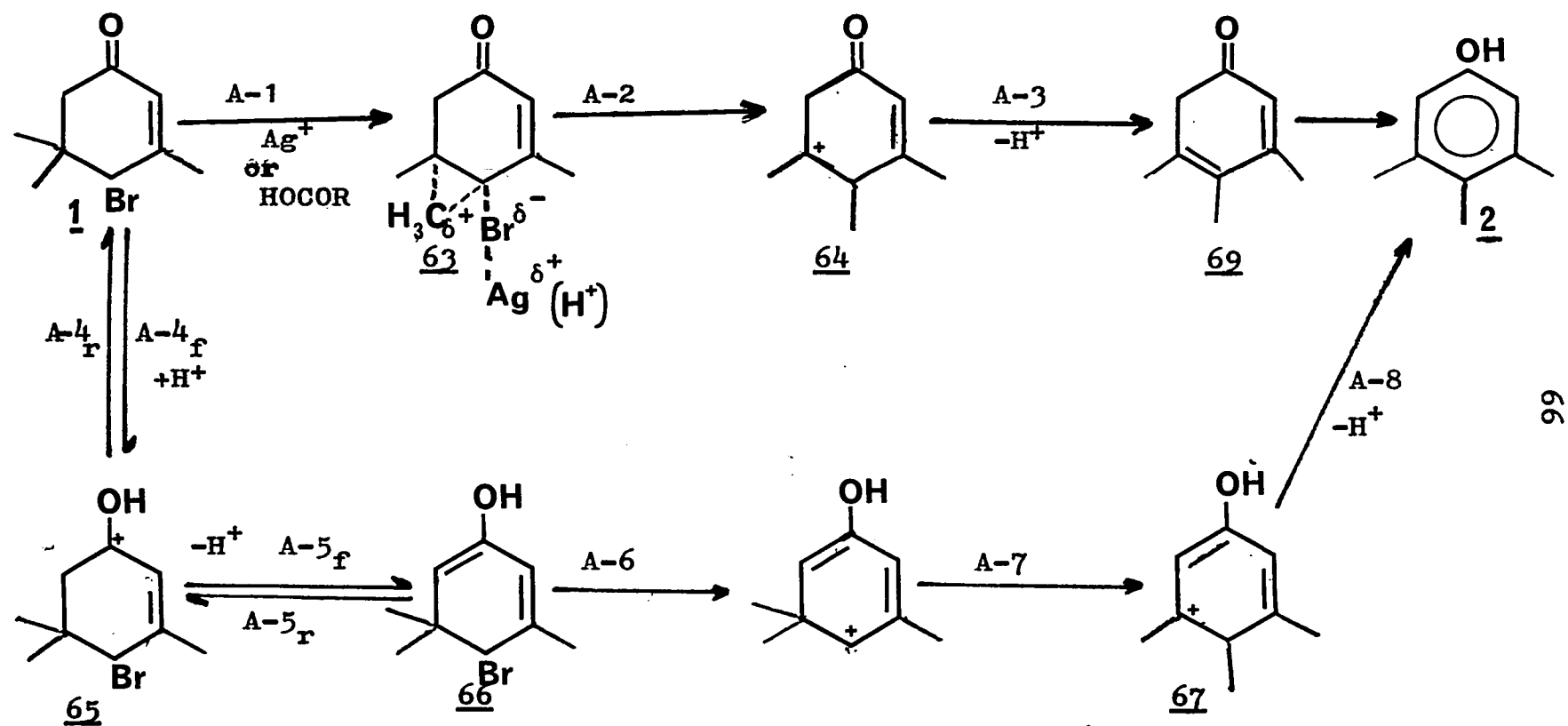
(a) Reactions were run for 40.5 hrs at ca. 45° using 0.434 g (0.002 m) of 1. (b) 1.3 equivalents of silver perchlorate added.

For reactions 3 and 4 of Table 5, two different series of yields are given. The first is for reactions with more than two year old silver perchlorate. The second series (in parenthesis) is for identical reactions, except that fresh silver perchlorate (less than two months old) was employed. In both cases, the very hygroscopic silver perchlorate was stored in the dark, in a desiccator, over drying agent.

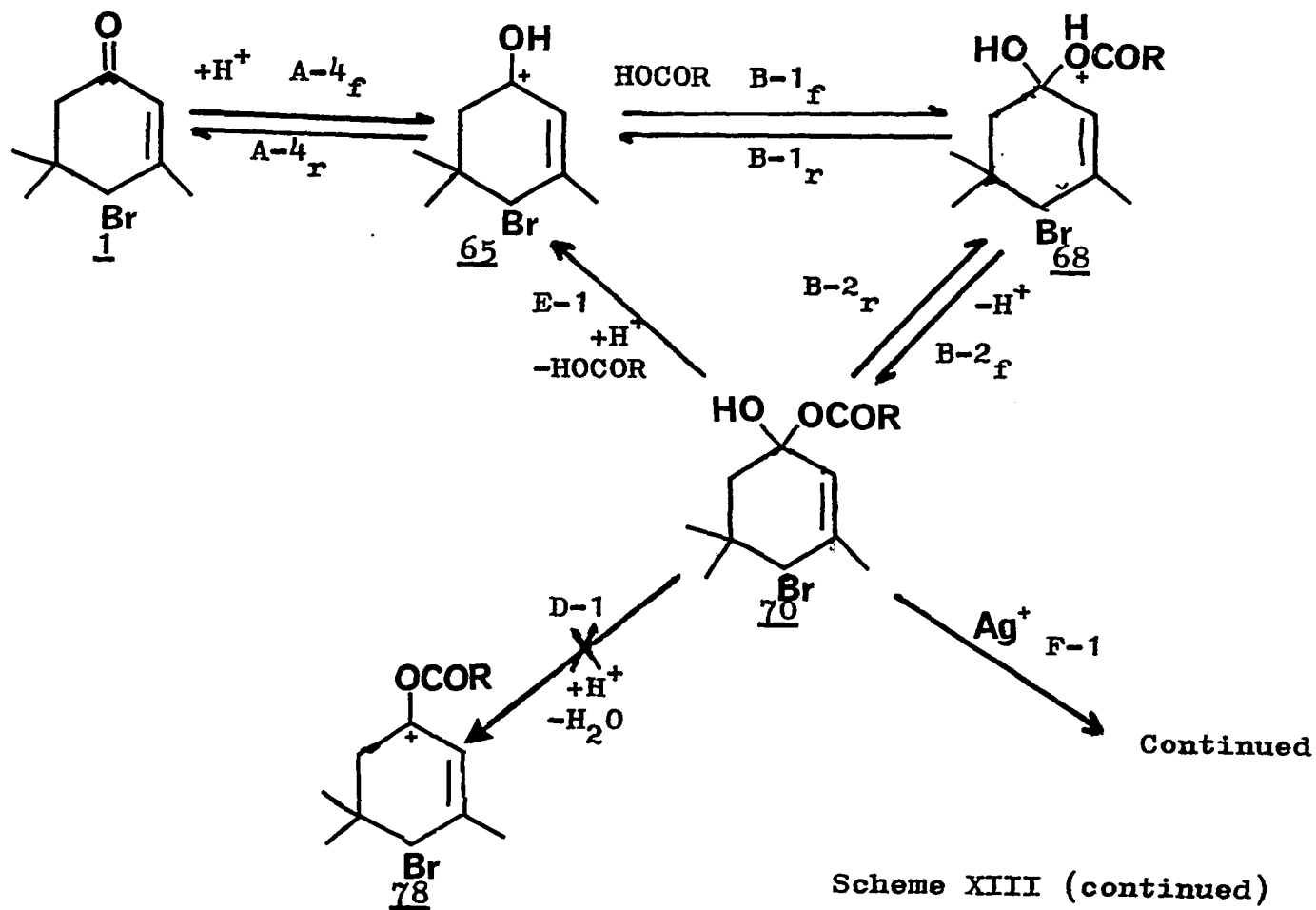
Clearly, the products are different with and without added silver perchlorate. In the absence of silver ion only phenolic material (entry 1) is isolated. In the presence of silver ion some phenyl derivatives are formed (entries 3 and 4 of Table 5 and reference 59).

A comprehensive mechanism for the formation of 2 and its ester derivatives is given in scheme XIII. Based on these observations the following features must be incorporated into this scheme: 1) acid catalysis; 2) a common intermediate for the formation of 2 and the phenyl esters; and 3) a rationalization for the different product distribution in the presence and absence of silver ion.

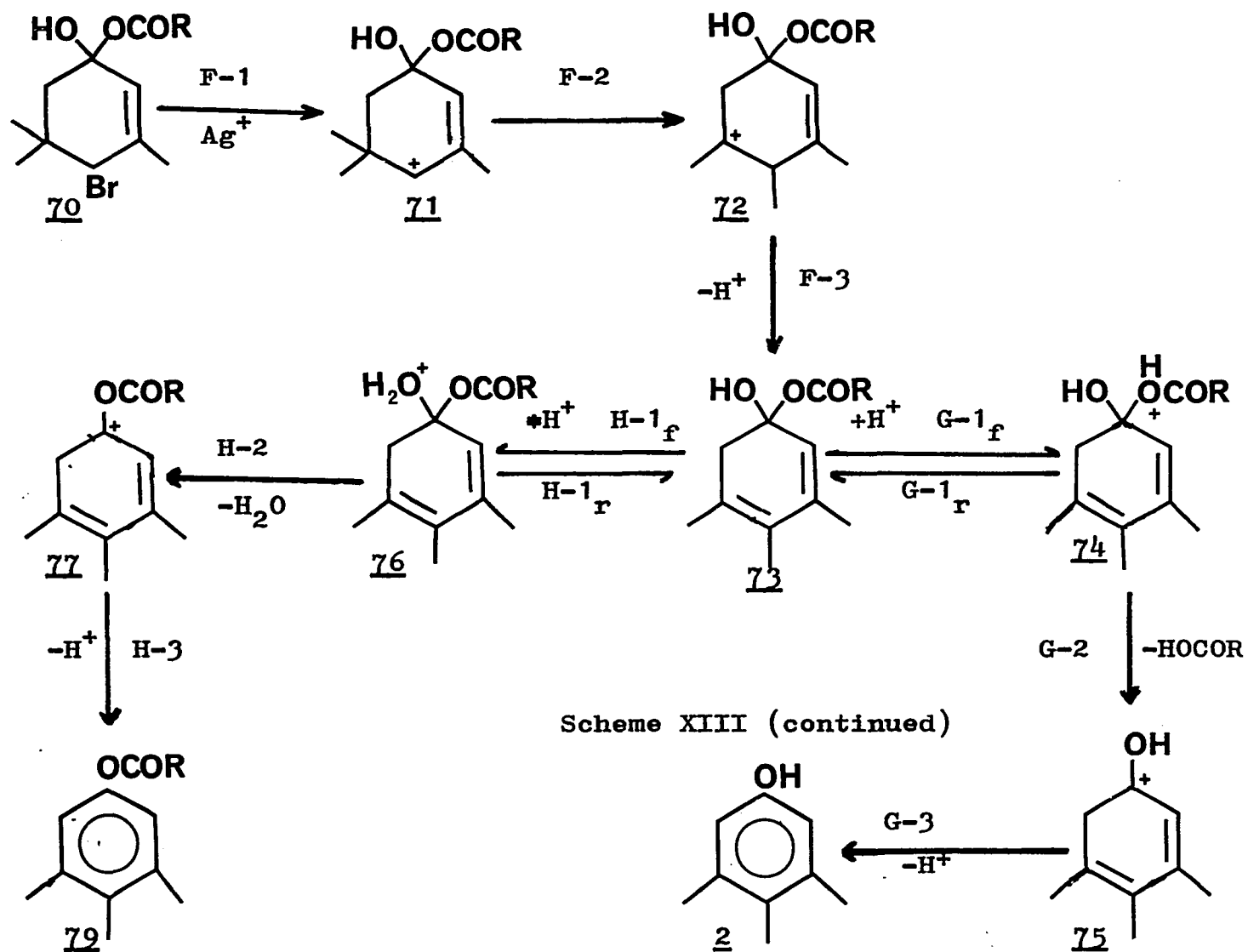
Initial strong acid may arise by a microscopic amount of silver ion aided or self-aromatization; steps A-1, A-2 and A-3. Note that a molecule of 2 and a molecule of strong acid are generated coincidentally. In this avenue, the methyl group may or may not migrate in a



Scheme XIII



Scheme XIII (continued)



Scheme XIII (continued)

synchronous manner (structures 63 and 64) as the C-4 halogen is removed by silver ion or by hydrogen bonding with the solvent. If it is assumed that a C-4 carbonium ion is indeed "reluctant", formation of 2 from 1 without enol intervention may proceed by a concerted methyl migration. Hence, 63 could be considered a transition state rather than an intermediate. This structure, 63, goes on to 2 by loss of a proton in step A-3. This pathway must be considered whenever 2 is obtained without acid or base catalysis.

The somewhat similar acid-catalyzed route is shown in steps A-4_f, A-5_f, etc. Step A-6 should go more easily than step A-2 because the constraint of having a positive charge next to a carbonyl group is removed. Therefore, more acid and product(s) arise from the route A-4_f through A-7 than from the pathway A-1 through A-3.

A carboxylic acid could add reversibly to 65 (step B-1_f) as the phenol did in scheme XII. The hemiacetal (70) is the common intermediate for the formation of both 2 and its carboxylate derivatives. In the absence of silver ion, intermediate 70 reverts back to intermediate 65 which goes on to 2.

When silver ion is present, extraction of bromine, as silver bromide, from 70 (step F-1), is now competitive with reformation of the intermediate 65. The resulting carbonium ion (71) rapidly undergoes methyl migration

(structure 72, step F-2) and deprotonation (step F-3) to give a key species, the neutral diene 73.

Under acidic conditions, 73 can be protonated and undergo an E_1 elimination of either H_2O or $HOCOR$. Pathway G-1_f etc shows the protonation of the carboxylate group (structure 74) followed by loss of $HOCOR$ to give the carbonium ion 75 which goes on to 2. Pathway H-1_f shows the protonation of the hydroxyl group (structure 76) followed by loss of H_2O to give the carbonium ion 77 which goes on to the phenyl ester.

To account for the role of silver ion in giving phenol derivatives rather than only 2, an important assumption is made: If intermediate 70 undergoes an acid-catalyzed E_1 elimination only $RCOOH$ is lost to give 2, whereas, if intermediate 73, whose formation requires silver ion, undergoes an acid-catalyzed E_1 elimination either $RCOOH$ or H_2O can be eliminated to give the phenol or the phenyl ester respectively. The argument for this assumption makes use of the "Hammond Principle."⁶⁹

The first step in the E_1 elimination of 70 gives either the hydroxy stabilized carbonium ion 65 or a carboxylate stabilized carbonium ion 78. The hydroxy group can better stabilize the carbonium ion than can the carboxylate group ($-OCOR$). Therefore, because 65 is more stable, it is formed at the exclusion of 78.

In the E_1 elimination of 73, the corresponding

carbonium ions 75 and 77 are formed from loss of RCOOH and H_2O respectively. The carbonium ions are conjugated with two double bonds and are more stable than 65 and 78 which are conjugated with only one double bond.

We now assume that the difference in ground state energies of protonated 70 and 73 is insignificant when compared to the difference in energies of the carbonium ions. Then according to transition state theory the enthalpy of activation for the formation of carbonium ions 75 and 77 is less than for formation of 65 and 78. Furthermore, the transition states for formation of 75 and 77 lies more towards the reactants and has less carbonium ion character. Consequently, the relative stabilization effect of the hydroxy and carboxylate groups is less important when comparing 75 and 77 than it is when comparing 65 and 78, making the $\Delta\Delta H^*$ for the former less than that of the latter case. Based on the decrease in the $\Delta\Delta H^*$ for the reactions of 73, the formation of 2 and the phenyl esters becomes competitive as shown in fig 1:

When a few drops of water are added during reactions 3 and 4 of Table 5, with fresh silver perchlorate, the yield of aromatic ester was decreased. It appears that either step B-1_f or F-1 is eliminated. Were water to compete with acid in step B-1_f a hemiacetal (80) would result. This compound could react further by any of the postulated pathways to give only 2. The water could

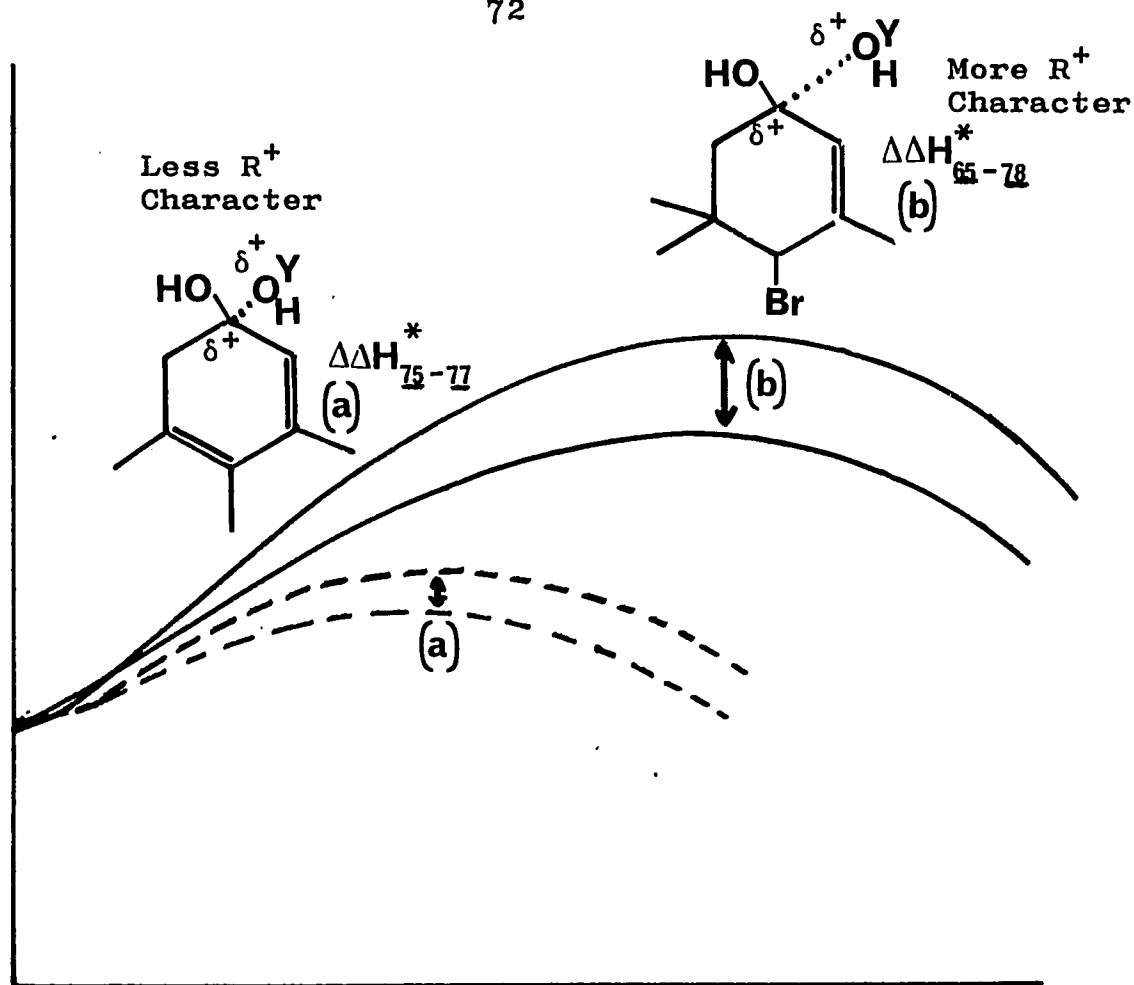
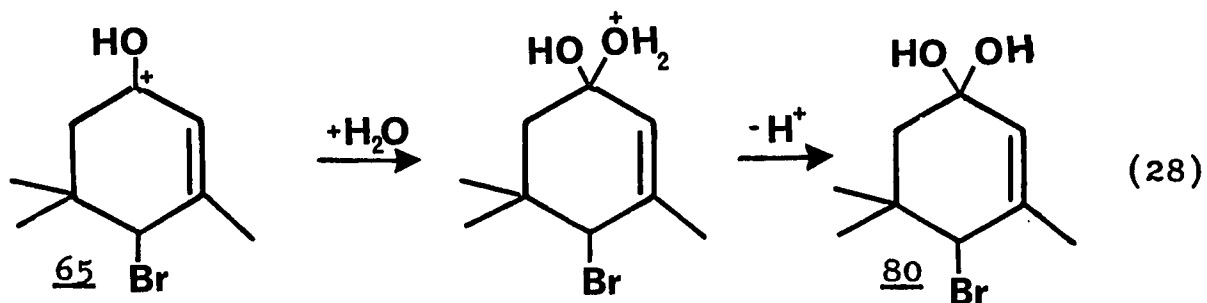


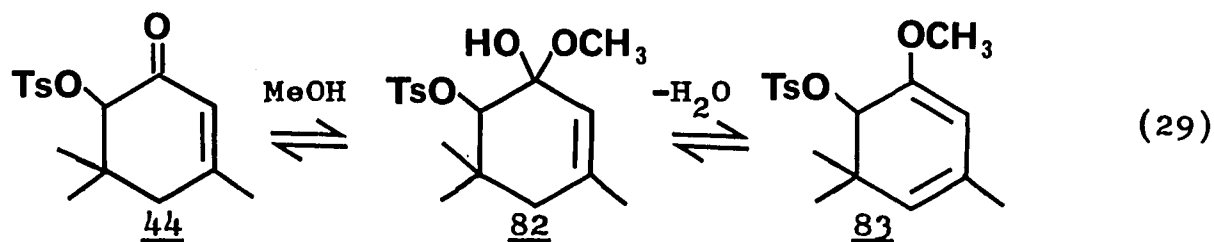
Fig 1:

Relative Energy Levels for Reactions of 70 and 73 also decreases the reactivity of the silver cation by solvation, thereby retarding step F-1. The competing reversal to intermediate 65 takes over to give only 2 as shown in Eq 28:



It is noteworthy that solvent cannot add directly to 1 as demonstrated by the inertness of 1 to dioxane:water (1:1 v/v) and ethanol (with a trace of 2,6-lutidine added to prevent accumulation of acid).

A confirmation of this reaction scheme is demonstrated by the methanolysis of 6-tosyloxyisophorone (44) in the presence of hydrogen chloride to give only 3,4,5-trimethyl anisole (81).^{60b} It is postulated that methanol, with acid catalysis, adds to the carbonyl group of 44 to give the equilibrium condition shown below in Eq 29:



Note the similarity between 82 and intermediate 70 of scheme XIII. Protonation of the methoxy or hydroxy group of 82 and loss of water or methanol leads to enol and enol ether formation respectively. However, in this compound water is preferentially lost because the electron donating properties of the methyl group make the methoxy stabilized carbonium ion more favorable than the hydroxy stabilized one. Therefore, without the aid of silver ion the enol ether 83 rather than the enol is formed. Solvolysis of the tosyl group from 83 and migration of a methyl group from C-5 to C-4 leads to the observed product 81.

3,4,5-Trimethylphenyl acetate (61) was synthesized by the reaction of 2 with acetic anhydride in pyridine. 3,4,5-Trimethylphenyl pivalate (62) was prepared by the reaction of 2 with pivalic acid in trifluoroacetic anhydride. Spectral data confirms these results.

Section E. The Reactions of 4-Bromoisophorone (1) with Base

In the previous section, we have examined the reaction of 4-bromoisophorone (1) under acidic conditions. As an interesting comparison we decided to investigate the reaction products when 1 is treated with base.

As previously stated, 1 did not react with dioxane: water (1:1 v/v) under the "usual" reaction conditions. However, when 1.3 equivalents of triethylamine are added phenolic products are isolated exclusively. (Table 6, entry 2). These products are 3,4,5-trimethylphenol (2) and 2,3,5-trimethylphenol (54). No reaction is observed when triethylammonium bromide replaces the base (entry 9). This tends to indicate that the observed phenol formation requires base and may follow from initial formation of a carbanion.

We suggest that this reaction proceeds via the identical intermediate, 55, which Kosower⁶² postulates as occurring during the reaction of 6-chloroisophorone (52) with silver nitrate and triethylamine, as shown in scheme XIV.

It appears that after carbanion formation some assistance is needed to remove the bromine as indicated by reactions 3, 5, 6, and 7 of Table 6, in which benzene, dioxane, pyridine, and DMF are the reaction solvents respectively. No reaction is observed in any of these four systems. This is attributed to the inability of

Table 6
The Reactions of 4-Bromoisophorone (1) with Base^a

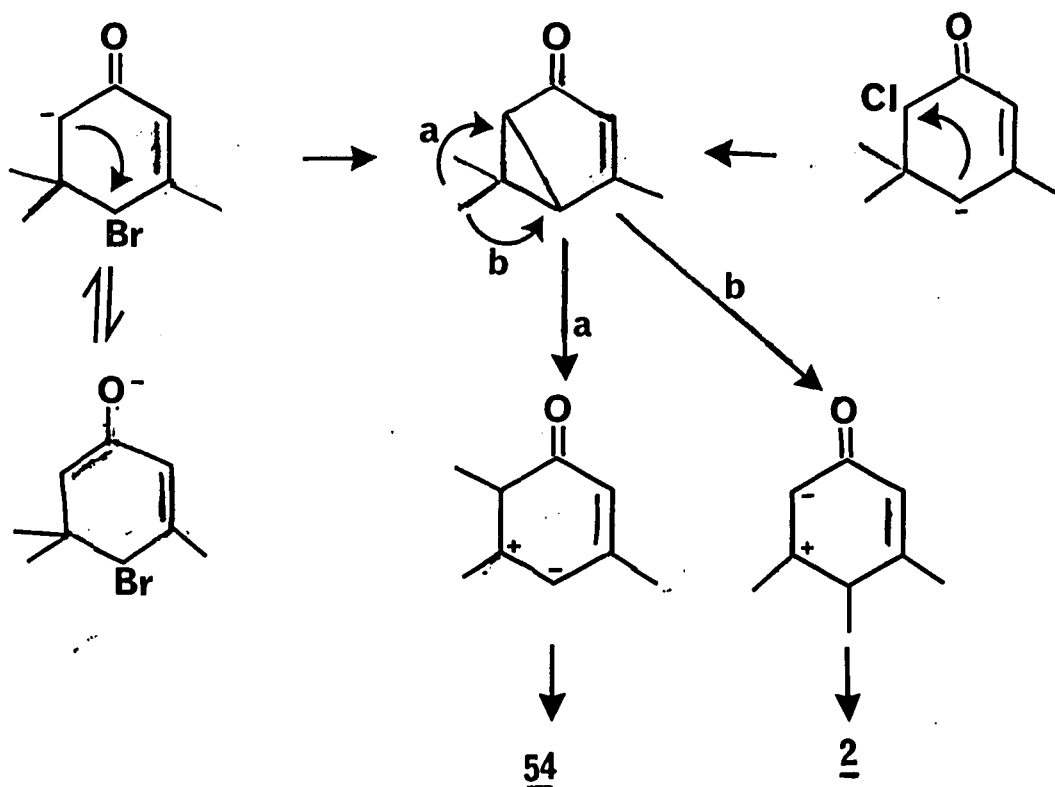
Entry	Reactant	Base	Equiv	Solvent ^b	Products (yield)	
1	<u>1</u>	-	-	dioxane:H ₂ O	No Reaction (NR)	
2	<u>1</u>	Et ₃ N	1.3	dioxane:H ₂ O	<u>2</u> ^c (45%),	<u>54</u> ^d (45%)
3	<u>1</u>	Et ₃ N	1.3	benzene	NR	
4	<u>1</u>	Et ₃ N	1.3	dioxane: H _p 7 buffer	<u>2</u> (45%),	<u>54</u> (45%)
5	<u>1</u>	Et ₃ N	1.3	dioxane	NR	
6	<u>1</u>	-	-	pyridine	NR	
7	<u>1</u>	Et ₃ N	1.3	DMF	NR	
8	<u>84</u> ^e	Et ₃ N	1.3	dioxane:H ₂ O	<u>85</u> ^f	<u>86</u> ^g
9	<u>1</u>	Et ₃ NHBr	1.3	dioxane:H ₂ O	NR	

(a) reactions run with 0.002 mol of substrate for 40.5 hrs at 45 ± 2°.

(b) 5 ml of solvent used; when dioxane:H₂O is employed 2.5 ml of each solvent is used. (c) 3,4,5-trimethylphenol; (d) 2,3,5-trimethylphenol;

(e) 4-bromo-5,5-dimethyl-3-phenylcyclohex-2-enone;

(f) 4,5-dimethyl-3-phenylphenol; (g) 2,3-dimethyl-5-phenylphenol



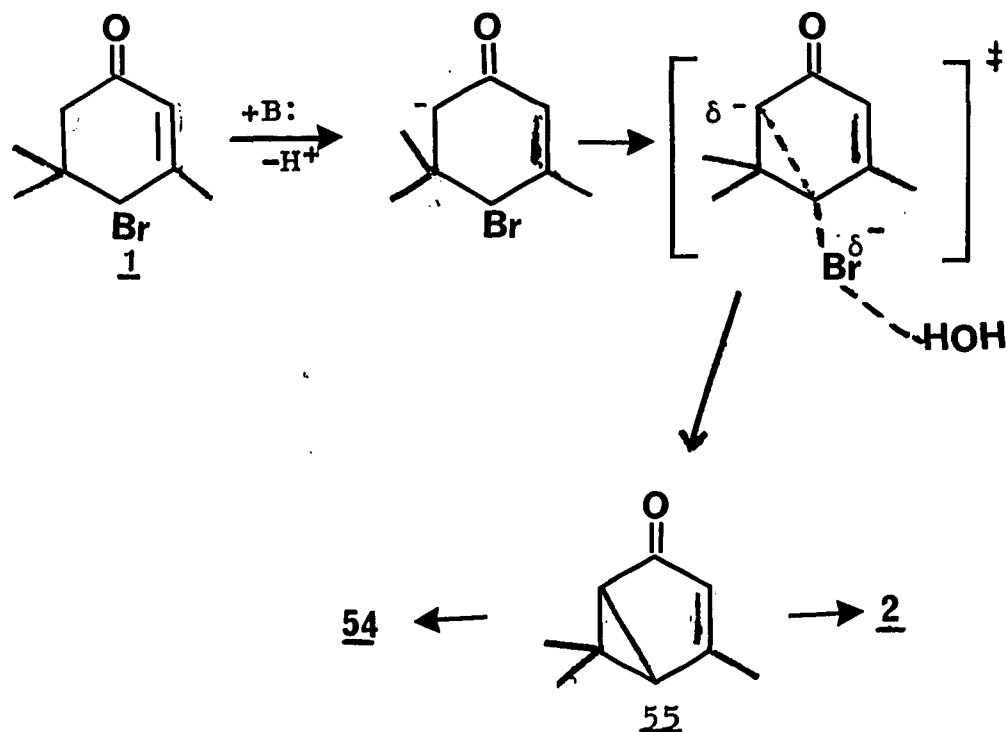
Scheme XIV

these non-protic solvents to aid in the removal of the C-4 halogen from the previously formed carbanion. In absolute ethanol, another protic solvent, a reaction of 1 with triethylamine was observed to give mainly a mixture of 2 and 54 in addition to a minor amount of starting material and unidentified products. Similar results were obtained in 90% aqueous ethanol.

The argument can be made that an initial attack by water on the carbonyl group of 1 preceeds the attack by base. However, it is doubtful that the C-6 protons would then be acidic enough to be removed by triethylamine. It would also be difficult to conceive of the enolate anion, which is the resulting species of the initial attack of

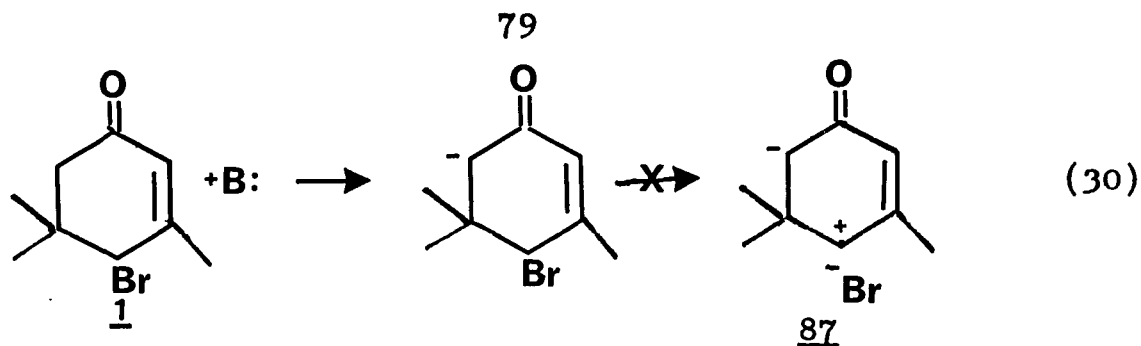
base on C-6, undergoing nucleophilic attack by water.

The suggested mechanism involving some assistance for the removal of bromide ion is shown in scheme XV.

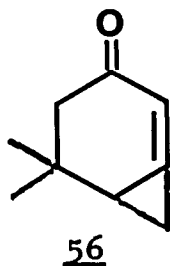


Scheme XV

Parenthetically, it appears that in DMF, a solvent of fairly high dielectric constant, the C-6 carbanion of 1 does not exist as an ion-pair. One would expect that an ion-pair (structure 87 in Eq 30:) should have the needed separation of bromide ion to allow formation of intermediate 55.

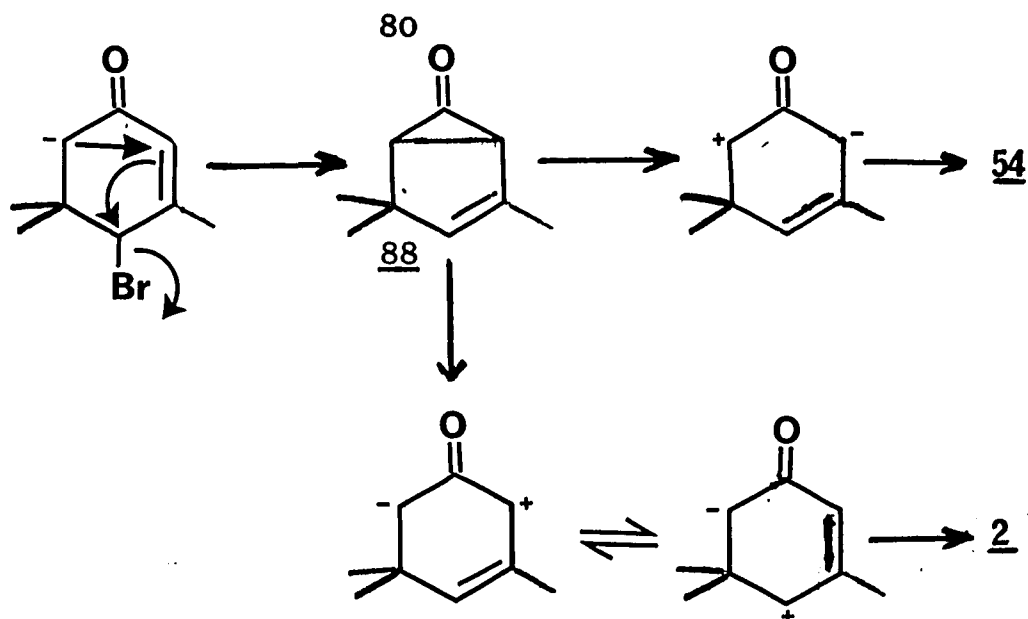


It is plausible that the resulting phenols, 54 and 24 are derived from more than one cyclopropyl intermediate. Structure 56 has been postulated by Kosower⁶² as an intermediate in the formation of 2 in the reaction of 3-chloro-5,5-dimethylcyclohex-2-enone (53) with triethylamine.



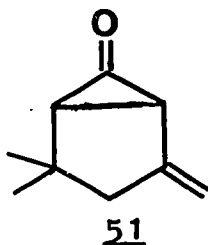
Intermediate 88 could arise by a vinylogous Favorskii-type reaction, also conceived as an intramolecular S_N2' reaction. Methyl migration from C-5 to C-6 forms 54. Migration of a methyl group from C-5 to C-4 leads to 2 as shown in scheme XVI.

Fort⁶¹ treated 6-tosyloxyisophorone (44) with methoxide ion in methanol and, significantly, obtained no phenolic products. He suggested the existence of an intermediate (51) similar to 88 except for the exo position of the double bond. In addition, we have reacted



Scheme XVI

6-tosyloxyisophorone(44) under identical conditions to those in which 1 yielded 2,3,5-trimethylphenol (54) and 2. It seems unlikely that 88 would yield phenolic products while 51 does not.



To test the viability of 56 as an intermediate, a reaction identical to run 2, Table 6, was performed with 4-bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) instead of 1. This compound is identical to 1 except for the substitution of a phenyl group on C-3 for a methyl group. Therefore, a structure similar to 56 cannot form.

If this intermediate is involved in phenol formation from 1 then no phenol should be found in the reaction of 84 with base.

From this reaction (run 8, Table 6) two isomeric phenols, 4,5-dimethyl-3-phenylphenol (85) and 2,3-dimethyl-5-phenylphenol (86) are found. This suggests a single intermediate, 55, which undergoes methyl migration from C-5 to either C-4 or C-6.

When 1 is refluxed for thirty minutes with dioxane and concentrated hydrochloric acid the only product recovered is 2. When 84 is treated under similar conditions, a single acidic product is observed. After purification, a white solid (mp 107.9-108.2°), with the empirical formula $C_{14}H_{14}O$ is recovered. Spectral analysis confirmed the molecular weight of this compound and its phenolic character. Because 84 should not react differently than 1 under the above conditions, structure 85 was assigned to this phenol.

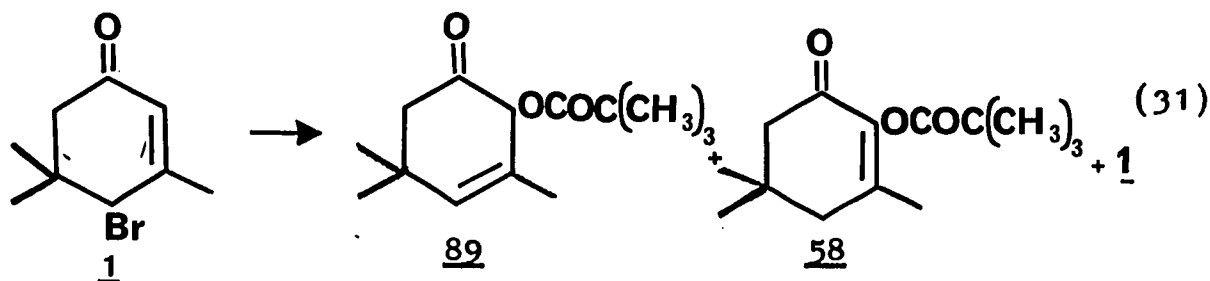
The isomeric phenol, 86, was isolated from the reaction mixture from a large scale analog of reaction 8. Thin layer chromatography indicated the presence of two major and two minor components. The reaction products were separated by preparative thick layer chromatography on silica gel plates, developed in benzene. The product which had an R_f of 0.54 to 0.63 was eluted from the silica gel to yield a crude solid (mp 58-65°). This

product was thrice recrystallized from hexane to yield a white solid (mp 68.5-68.9°) which had the empirical formula $C_{14}H_{14}O$. Spectral analysis confirmed the molecular weight of this compound and its phenolic structure. This compound was assigned the structure 86.

Section F: The Reactions of 4-Bromoisophorone (1) with
Added Nucleophiles

The comparison of reaction products and product distribution when 1 is allowed to react with various nucleophiles shows how changes in the solvent, cation, and/or the nucleophile lead to a variety of interesting results and trends. The work reported in this section will involve mainly the reactions of various pivalate and acetate salts with 1.

In pivalic acid(2g), sodium pivalate and potassium pivalate (1.3 equivalents) react similarly with 1 (0.002m) (40.5hr, at $45 \pm 2^\circ$) to give about 28% 2-pivoxysisophorone (58). The remainder, ca. 72%, is starting material. (Table 7, entries 2 and 3). When silver pivalate is used, 65% of 1 is recovered, 2-pivox-3,5,5-trimethylcyclohex-2-enone (89) is isolated in about 25% yield, and the conjugated isomer of 89, 58 accounts for the remaining 10% of the reaction mixture as shown in Eq 31:



When the salt was changed to lithium pivalate, no reaction was noted (entry 1). When it was tetraethylammonium

pivalate, starting material (54%) and 58 (46%) are recovered (entry 5, Table 7).

The products indicate a novel allylic rearrangement resulting in loss of conjugation between the C=C and C=O groups. The bulky pivalate anion, additionally solvated by pivalic acid cannot undergo a typical S_N2 reaction at the neopentyl C-4 position. Hence, an alternate reaction path prevails.

Table 7^a

Reactions of 1 in Pivalic Acid with $M^+ \overset{O}{\parallel} \text{OC}(\text{CH}_3)_3^-$

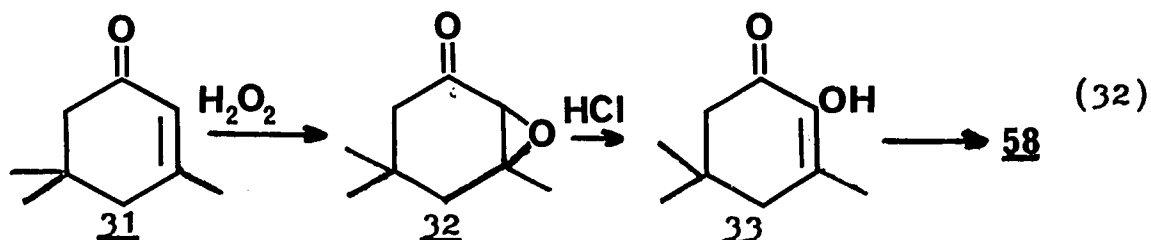
Entry	M^+	Products (Yield)
1	Li	<u>1</u> (100%)
2	Na	<u>1</u> (71%); <u>58</u> (29%)
3	K	<u>1</u> (75%); <u>58</u> (25%)
4	Ag	<u>1</u> (65%); <u>58</u> (10%); <u>89</u> (25%)
5	Et_4N	<u>1</u> (54%); <u>58</u> (46%)

(a) all reactions run for 40.5 hrs, at $45 \pm 2^\circ$, using 0.002 mol of 1 in 2 g of acid with 1.3 equivalents of pivalate salt.

Although 89 was not isolated as an analytically pure sample, the spectral data of this compound were consistent with the assigned structure: nmr(CDCl_3); δ 5.56 (broad, 2H, C=C-H, HCO), 2.41 (AB pattern, 2H, CH_2), 1.67 (t, J=1Hz, 3H, C=C- CH_3), 1.23 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.11 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ir(neet film): 1750cm^{-1} (s, ester), 1740cm^{-1} (s, shoulder of 1750, ketone); mass spec: m/e = 238 (parent peak). In the presence of base, 89 reverts exclusively to 58.

Compound 58 was isolated from the reaction mixture by subjecting the entire crude reaction mixture to an acidic hydrolysis (dioxane:water: concentrated hydrochloric acid (1:1:1 v/v/v), reflux for 30 min). Under these conditions, 58 is inert, whereas, 1 converts exclusively to 3,4,5-trimethylphenol (2), which is extracted by strong base. The possibility exists that minor amounts of some compound(s) containing no nmr peaks downfield of $\delta 3.0$ and yielding an acidic compound under the above hydrolysis conditions could be present in the initial reaction mixture.

Compound 58 was independently synthesized from isophorone (31). 2-Hydroxyisophorone (33) was prepared^{53a,b} and esterified with trifluoroacetic anhydride and pivalic acid⁷⁰ to give 58 as shown in Eq32:



Since the reaction of 1 with silver pivalate shows little rate enhancement in terms of amount of recovered starting material compared to the sodium, potassium and tetraethylammonium salts, apparently there is little of the expected catalysis by silver cation. Again, this lack of catalysis may be due to steric hinderance to approach at the neopentyl C-4 position by Ag^+ which is most

likely tightly ion-paired to the pivalate anion. The isolation of 89 rather than the conjugated isomer 58 when silver pivalate is employed needs explanation. When present with Na^+ or K^+ , the pivalate anion is "free" enough to furnish the basic catalysis needed for conjugation. With Ag^+ , the pivalate exists as a tight ion-pair with considerable covalent character and hence lacks sufficient basicity.

When lithium pivalate is present (entry 1, Table 7) only starting material is recovered. Oxygen is more covalently bound to lithium than to sodium or potassium.^{71a,b} From these results it would appear that the lithium-oxygen bond may be more covalent than the silver-oxygen bond. Carboxylate is designated as a "hard" base and, therefore, more likely to be tightly bound to lithium, a "hard" acid rather than to the "soft" silver.^{71c} This greater covalency may diminish the nucleophilicity or basicity of the pivalate anion so that no reaction is observed.

The "freeness", or quantity of negative charge residing on the anion is an important factor in the determination of reaction products. An aprotic solvent such as DMSO or DMF is capable of solvating cations, but not anions. The pivalate anion of a salt such as sodium or potassium pivalate should now bear a "full" negative charge and be highly reactive. Table 8 compares the distribution of reaction products of 1 with several pivalate

Table 8Reactions of 1 with Pivalate Salts^a

Entry	Solvent	M1	M ⁺	Products(yield)		
1	DMSO	5	Li	<u>58</u> (90%)		<u>1</u> (trace)
2	DMSO	5	Na	<u>58</u> (47%)	<u>57</u> (36%)	<u>1</u> (17%)
3	DMSO	5	K	<u>58</u> (34%)	<u>57</u> (66%)	
4	DMF	5	Li	<u>58</u> (90%)		<u>1</u> (trace)
5	DMF	5	Na	<u>58</u> (46%)	<u>57</u> (18%)	<u>1</u> (36%)
6	DMF	5	K	<u>58</u> (29%)	<u>57</u> (71%)	
7	CH ₃ NO ₂	17	Na			<u>1</u> (95%)
8	CH ₃ CN	17	Na			<u>1</u> (95%)
9	HMPT	8, 5	K		<u>57</u> (90%)	
10	HMPT	8	Li	<u>58</u> (54%)	<u>57</u> (46%)	
11	dioxane:H ₂ O (9:1v/v) ²	5	Na	<u>58</u> (trace)		<u>1</u> (90%)
12	DMF:H ₂ O (9:1 ² v/v)	5	K	<u>58</u> (45%)	<u>57</u> (13%)	<u>1</u> (35%)
13	DMSO:H ₂ O (9:1v ² /v)	5	K	<u>58</u> (50%)	<u>57</u> (37%)	<u>1</u> (9.0%)
14	DMSO	5	Et ₄ N	<u>58</u> (17%)	<u>57</u> (58%)	<u>1</u> (25%)
15	DMF	5	Et ₄ N	<u>58</u> (17%)	<u>57</u> (59%)	<u>1</u> (24%)
16	HMPT	5	Et ₄ N	<u>58</u> (16%)	<u>57</u> (61%)	<u>1</u> (23%)

(a) reactions run for 40.5 hrs at 45 ± 2°; 0.002 mol of 1 employed. (58) 2-pivoxylsophorone; (57) 4-pivoxylsophorone

salts in various solvents.

Table 9 lists various important physical constants of the aprotic solvents employed in the course of these investigations. Of the three aprotic solvents analysed, HMPT has the lowest dielectric constant and DMSO has the greatest. The basicities of these solvents listed in order of increasing basicity is DMF, DMSO, HMPT.

No reaction occurs in relatively polar aprotic solvents in which the pivalate salt is insoluble (entries 7, and 8, Table 8). Direct substitution and/or allylic rearrangement products are noted in solvents which dissolve the sodium, potassium, lithium, or tetraethylammonium salts and which effectively solvate the cation but not the anion (reactions 1-6, 9, 10, 14-16). Under similar conditions more of the starting material reacts in these aprotic solvents than in pivalic acid, probably because of the greater reactivity of the unsolvated anion. The more reactive unsolvated anion is less susceptible to steric effects of the C-3 and C-5 methyl groups of 1 than is a solvated anion. Some direct substitution is, therefore, observed.

In DMF as in DMSO, potassium pivalate reacts to yield (within 5%) the same relative amount of direct and allylic rearrangement substitution products. In these solvents, the change to sodium pivalate retards the reaction because some 1 remains unchanged. In DMSO as well

Table 9

Physical Properties of Some Aprotic Solvents

<u>Solvent</u>	<u>Dipole Moment</u>	<u>Dielectric Constant</u>
DMSO ⁷²	4.3	48.9
DMF ⁷²	3.82	37.6
HMPT ⁷³	4.31 - 5.37	30.0

as DMF (entries 2 and 5, Table 8), sodium pivalate gives more C-2 substitution than direct substitution product. The reverse is true for the potassium and tetraethylammonium salts in which the direct substitution product predominates (entries 3, 6, 14, 15). When lithium pivalate reacts with 1 in either DMSO or DMF, only the C-2 substitution product, 58 is isolated (entries 1 and 4) in a significant quantity.

In entries 12 and 13 of Table 8 we note that the presence of 10% water by volume decreases the rate of reaction. (Compare entries 6 to 12, and 5 to 13). In addition, the ratio of C-2 to C-4 substitution products increases slightly.

The reaction of 1, in the highly polar solvent dioxane:water (1:1 v/v) with sodium pivalate yields mainly starting material and a small amount of 58 (entry 11, Table 8). It appears that even in a highly polar solvent, if the anion is significantly solvated, the rate of reaction is less than the reaction of 1 in polar aprotic solvents.

As indicated previously, the more covalent the metal oxygen bond, the more the pivalate anion can be inactivated. The lithium-oxygen bond would be expected to have the greatest amount of covalency, while the potassium - or tetraethylammonium-oxygen bond the least. It appears that the larger and more deactivated the attacking species the greater is the extent of the reaction directed towards the C-2 position of 1.

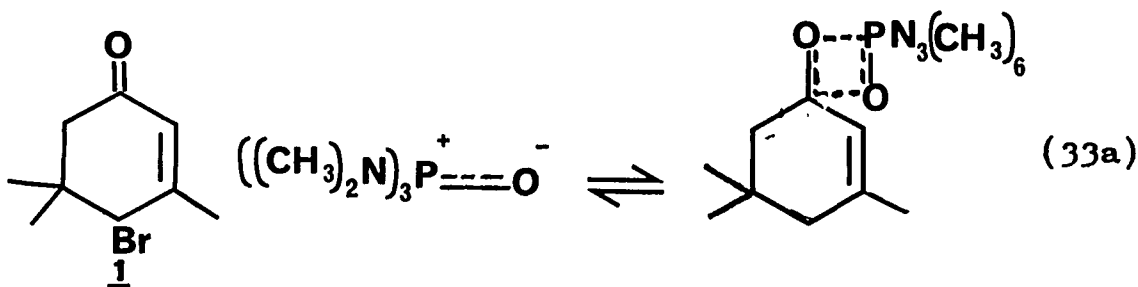
Also, there is the possibility that coordination of the carbonyl group by the cation aids in the formation of the C-2 substitution product. The tetraethylammonium salt has its positive center surrounded by bulky ethyl groups which should make coordination with the carbonyl group more difficult than if the positive charge was distributed on the outside surface of the cation. As a result, we note (entries 14, 15) that the yield of the C-2 substitution product decreases significantly while the yield of the C-4 substitution product remains approximately the same (e.g. entries 3 and 6). The remainder is starting material.

Special attention must be given to the reactions of 1 in HMPT. When 1 reacts with potassium pivalate in HMPT, only the C-4 substitution product is isolated. Others have observed enhancement of the yield of the direct substitution product in HMPT, e.g. the reactions of neopentyl-1-d-tosylate⁸ and 20-tosyl- α , and β -steroids.^{74a,b} An increase in reaction rate compared with DMSO and DMF was noted when 1-butyl bromide was treated with azide ion.

Other researchers have shown that when HMPT is employed in the reaction of alkyl halides with various salts of ethyl acetoacetate, the greatest O/C alkylation ratio is obtained. This result is attributed to the greater

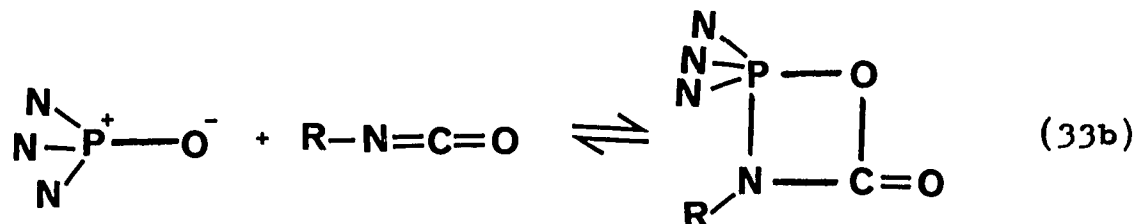
basicity of HMPT versus DMSO or DMF. These authors conclude that "the use of more highly basic aprotic solvents will tend to solvate the counterion and hence leave the oxygen atom of the anion exposed to approach by the alkylating agent"; and that the "freer the anion, the larger the O/C ratio".^{71a}

Even the reaction of lithium pivalate with 1 in HMPT gave an almost 50/50 mixture (Table 8, entry 10) of the C-2 and C-4 substitution products, whereas, in DMF it was almost all C-2 substitution. Clearly, the HMPT may hinder reaction at C-2 by some direct effect or merely modify the reactivity of the anion. We suggest that the basicity of HMPT might account for this result. It is also possible that HMPT interacts with the carbonyl function as shown below in Eq 33a:



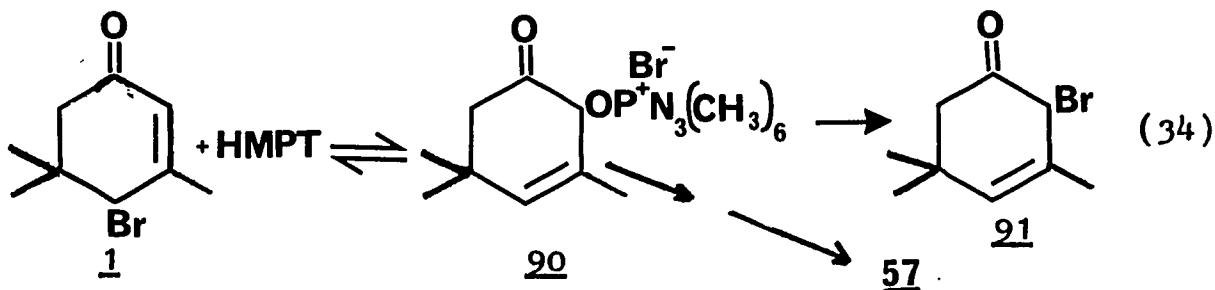
This bulky complex sterically hinders nucleophilic attack at C-2 favoring attack at C-4. In support of this contention, HMPT has been shown to complex with isothiocyanate to form an intermediate carbodiimide as shown

in Eq 33b:⁷³



However, the ir spectrum of 1 in HMPT shows a strong carbonyl band at about 1665cm^{-1} , about where it appears in other solvents. Unfortunately, the uv spectrum of the starting material, 1, absorbs in the same region as HMPT. Therefore, possible modification of the absorption of the carbonyl group's double bond character cannot be observed. If the postulated intermediate exists, the interaction between the carbonyl group and the P^+-O^- bond must be weak.

The possibility of HMPT acting as a nucleophile by replacing the C-4 halogen as shown below in Eq 34: is eliminated because of the demonstrated inertness of 1 in HMPT.



When 1 is allowed to react with lithium pivalate, in HMPT, both direct and allylic substitution products are

obtained (Table 8, entry 10). Again, HMPT inhibits allylic substitution but not completely. This result can be explained by a coexisting competition between the solvent and the lithium salt for coordination with the carbonyl function of 1. If the lithium salt coordinates with the carbonyl group then the C-2 substituted product is obtained. If HMPT coordinates, C-4 substitution is obtained.

When 1 is treated with tetraethylammonium pivalate in either DMSO, DMF, or HMPT the relative product distribution is similar (Table 8, entries 14, 15 and 16). This salt probably exists in such a highly ionic state that the role of HMPT in directing C-4 substitution is no longer the controlling factor. Therefore, these three high dielectric aprotic solvents behave similarly in directing the course of the reaction.

Silver acetate or pivalate react only in organic acids or pyridine. No reaction was obtained when 1 was treated with silver acetate in cyclohexane, benzene, glyme, chloroform, acetonitrile (96.5 hrs at room temperature) and nitrobenzene, and benzene (40.5 hrs, 45°).

When silver acetate (entry 1, Table 10) and silver pivalate (run 3, Table 10) are reacted with 1 in their respective acids, starting material (ca. 66%) is recovered

in each case. As stated earlier, the other reaction products when 1 reacts with silver pivalate in pivalic acid are 2-pivoxy-3,5,5-trimethylcyclohex-2-enone (89) (25%) and 2-pivoxyisophorone(58) (10%). In run 1, however, besides recovered starting material 21% 3,4,5-trimethylphenol (2) and 10% of the direct substitution product 4-acetoxyisophorone (42) were noted. This latter result is based on nmr peaks downfield of $\delta 3.0$. The integration of the alkyl and gem regions were slightly greater than calculated, and the possibility of a small amount (ca.10%) of 2-acetoxyisophorone (35) cannot be excluded.

Table 10^a
Reactions of 1 with Ag⁺X⁻

Entry	X ⁻	Solvent	Products (Yield %)
1	acetate	acetic acid	<u>1</u> (68); <u>2</u> (21); <u>42</u> (10); other(s)
2	acetate	pyridine	<u>1</u> (32); <u>2</u> (18); <u>42</u> (50).
3	pivalate	pivalic acid	<u>1</u> (65); <u>89</u> (25) <u>58</u> (10).
4	pivalate	pyridine	<u>57</u> (45); <u>58</u> (55).

(a) all reactions run with 1.3 equivalents of X⁻. Reactions run for 40.5 hrs, at ca. 45°.

The phenol formed in reaction 1 can arise from a concerted methyl migration. The silver cation may aid in the removal of the halogen concurrent with methyl migration from C-5 to C-4. Because strong acid cannot build up in

the presence of basic pivalate anion, acidic aromatization of 1 is not possible. However, enol formation, ultimately leading to phenol formation cannot be excluded. The sterically smaller silver acetate salt may be capable of aiding in the removal of the halogen from C-4 and thus allow the anion to attack directly at C-4.

In pyridine, both silver pivalate and silver acetate readily dissolve to give a red solution resulting from a silver-pyridine complex.⁷⁵ Precipitated silver bromide is present at the completion of the reaction. In either reaction 2 or 4, the direct substitution product is obtained in about 50% yield. However, when silver pivalate is present (run 4, Table 10) the only other isolable product is 58 (45%). It should be noted that no reaction was obtained when 1 was stirred with pyridine, or with pyridinium hydrobromide under the reaction conditions employed. Nor were any pyridinium cyclohexenone salts isolated from either the concentrated aqueous or organic layers of these reactions. The reaction of silver acetate in pyridine with 1 gives in addition to the direct substitution product, starting material (1) (32%) and 2 (18%).

Unlike the reaction of silver acetate in pyridine, silver pivalate reacts completely with 1. The fact that pivalate is more reactive than acetate may be attributed to the greater nucleophilicity of pivalate than acetate,

$K_A = 0.60$ and 3.2×10^4 , respectively.

As stated earlier, when the silver salt is insoluble in the solvent employed, only unchanged starting material is recovered. Even though reactions of alkyl halides and silver salts can take place on the surface of undissolved silver salts, it appears that the highly sterically hindered halogen on C-4 of 1 is incapable of positioning itself properly in order to have the silver aid in its removal.

At this time we cannot explain the formation of the C-2 substitution product in reaction 4 but not reaction 2. It can only be suggested that the bulkier pivalate cannot attack C-4 as easily as the smaller acetate.

The reaction of sodium acetate in acetic acid with 1 results in the recovery of starting material (69%), 2 (15-20%) and possibly 35 (10-15%). Again, the formation of 2 can be explained by either a synchronous methyl migration mechanism, or reaction of 1 through a preformed enol. Only starting material (71%) and 58 (29%) were recovered when sodium pivalate was stirred with 1 in pivalic acid.

Compound 1 was reacted in an organic acid with a silver salt with a non-nucleophilic anion. Compound 1 with silver perchlorate in pivalic acid gave only 2 and 3,4,5-trimethylphenyl pivalate (62). Evidently, this reaction permits accumulation of acid, giving the acid

catalyzed aromatization (Page 63).

We have seen in this section how sensitive reactions of 1 are to changes in the solvent and/or the nucleophile employed. Conditions have been obtained in which 1 will undergo only direct substitution or only S_N2' type reaction. It will be of value at this point to attempt to elucidate the mechanism for the formation of the allylic rearrangement products.

Section G: Mechanism of Allylic Rearrangement Products

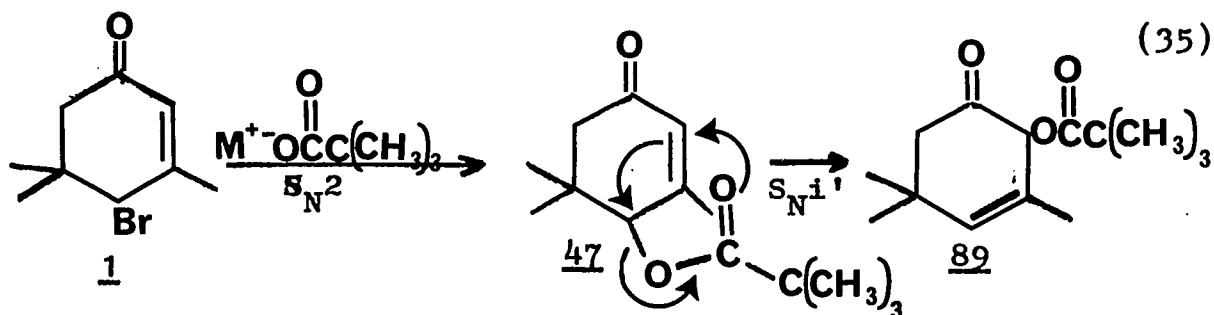
The generality of the formation of an allylic rearrangement substitution product when 4-bromoisophorone (1) was allowed to react with pivalate salts in various aprotic and protic solvents prompted us to investigate the mechanism of this transformation. In addition, unpublished work by Meislich⁷⁶ demonstrates that in the reaction of 1 with sodium methoxide in methanol, the major product of this reaction is 2-methoxyisophorone (47). A small amount of 2-(3,4,5-trimethylphenyl ether)-3,5,5-trimethylcyclohex-2-enone (92) is also recovered. This product probably arises by attack of the pre-formed anion of 3,4,5-trimethylphenol and C-2 of 1.

Various alternative mechanisms have been postulated to account for the formation of an S_N2' product other than by concerted attack on the carbon-carbon double bond with loss of the allylic halogen. These mechanisms include: 1) S_N1 ; 2) S_N2-S_N1' ; 3) $S_N1'-S_N2$; and 4) attack on an ion-pair.³¹ A summary of the arguments for and against these mechanisms, as they pertain to other allylic rearrangements have been previously surveyed beginning on page 14.

S_N1 type reactions have been previously eliminated in section B, page 51 because 1 is generally inert towards solvolysis. No reaction was noted when 1 was

stirred in: dioxane; dioxane:water(1: 1 v/v); ethanol (with a trace of 2,6-lutidine), pivalic acid, DMF, HMPT; DMSO:water(1:1 v/v). A more complete discussion of the solvolytic reaction of 1 is found in section B.

The S_N2-S_N1' pathway of obtaining 2-substituted isophorones involves initial formation of the C-4 direct substitution product followed by an internal allylic rearrangement as shown in Eq 35:



A concerted mechanism to yield 2-pivoxy-3,5,5-trimethylcyclohex-3-enone (89) would force the initially formed 4-pivoxyisophorone (47) out of conjugation. The re-conjugated, C-2 substitution product would then be rapidly obtained.

The above pathway is eliminated easily by demonstrating that 47 is stable under the reaction conditions (40.5hrs, ca. 45°). Only starting material was recovered when 47 was treated with silver pivalate, and silver bromide in pivalic acid, or potassium pivalate and potassium bromide in DMF.

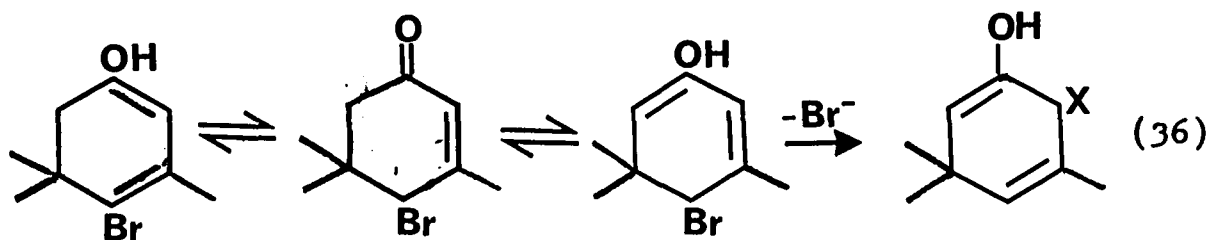
The $S_N1'-S_N2$ route involves an initial rearrangement of 1 to 2-bromo-3,5,5-trimethylcyclohex-3-enone (91).

Any type of self-ionization mechanism of 1 to form 91 would have to involve a solvent separated ion-pair reaction which is precluded. In addition, no 2-bromo-isophorone (93) has been recovered from any of the reactions, and one would expect that the return to conjugation of 91 should be competitive with substitution.

It is also possible that some bromide salt present could attack 1 to give 91. However, because of the previously discussed difficulty in formation of a carbonium ion in this system, attack by bromide ion (e.g. potassium bromide) would have to involve a non-carbonium ion mechanism. Under the reaction conditions employed, no rearrangement was observed when 1 was treated with: 1) sodium bromide in pivalic acid or 2) potassium bromide in DMF (with a trace of 2,6-lutidine).

The rate limiting attack of a nucleophile on an ion-pair leading to the formation of an allylic rearrangement product, will be discussed later.

Enol formation of 1 is possible under acidic conditions. Attack, specifically at the C-2 position of enol 1a allows formation of the observed C-2 substitution product, as shown in Eq 36:



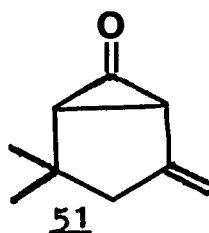
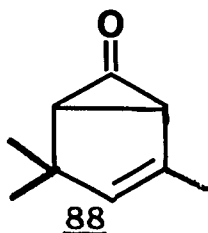
Attack at C-6 of 1a would yield a 6-substituted isophorone but is much more sterically hindered. The reaction of 1 with sodium pivalate in pivalic acid o-d₁ gave the S_N2' product at a rate faster than substitution of deuterium at C-6. This result is based on mass spectroscopy and nmr analysis of the recovered starting material and thus precludes the S_N2' type reaction from occurring via the enol form of 1.

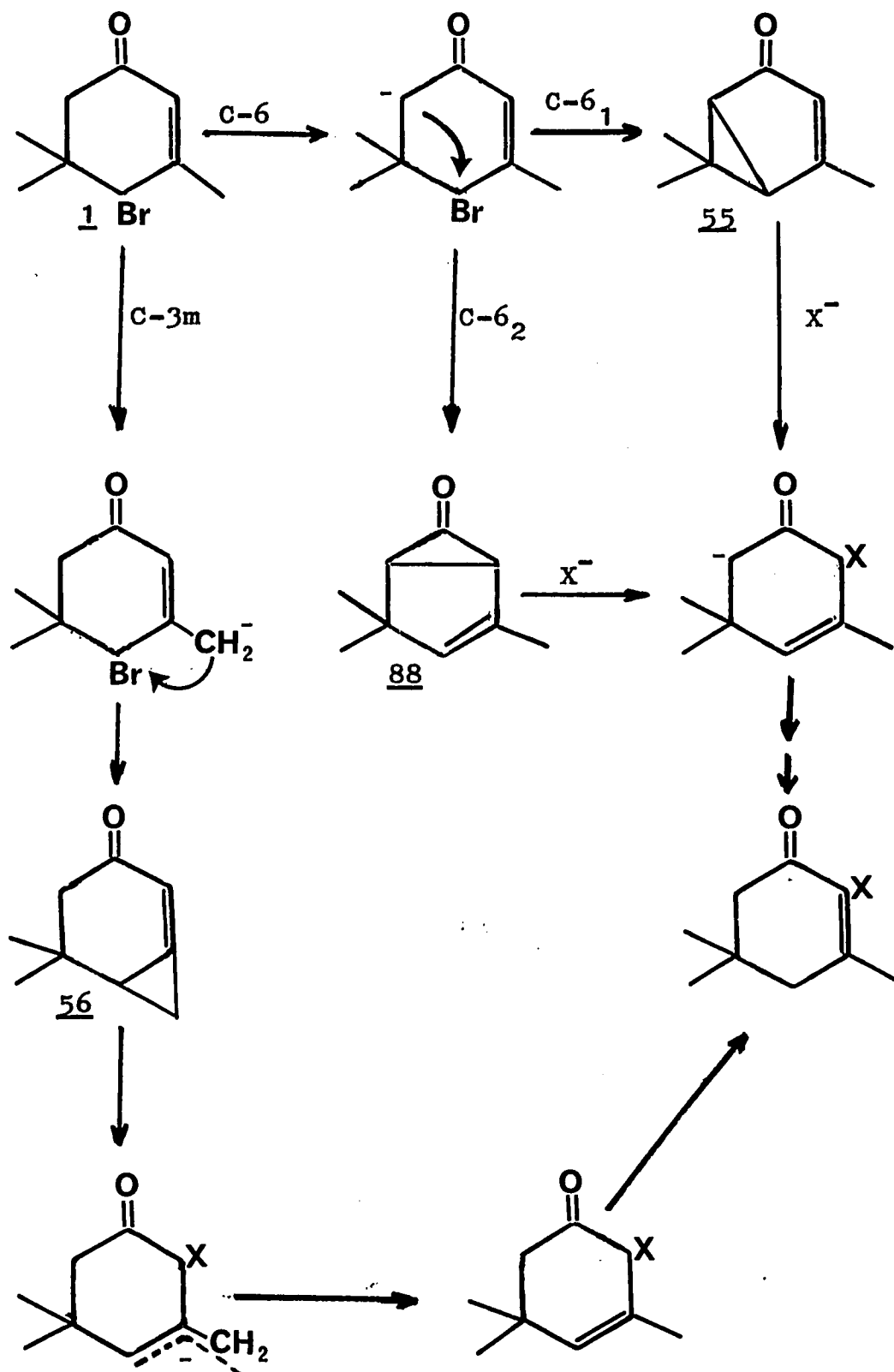
Deuterium substitution at C-6 of 1 has to be at least equal to the rate of formation of the S_N2' product. Otherwise the initial formation of the C-6 carbanion could not be explained. The nmr spectrum of the reaction of 1 (mw 216, 218) with sodium pivalate in pivalic acid o-d₁ still shows the existence of protons on C-6, C-4 and the C-3 methyl group of recovered 1. The ratio of the parent peak to the parent plus one peak in the mass spectrum of 1 is 8.85 (m/e 216/217) and 8.35 (m/e 218/219). The recovered starting material had ratios of 1.89 and 1.80 for the relative intensities of the m/e 216/217 and 218/219 peaks respectively. Also, in the reaction of pivalic acid o-d₁ with 1, some exchange is noted in the recovered starting material. These results demonstrate that some exchange of deuterium for hydrogen occurs at C-6 and other acidic positions. However, the exchange on C-6 is less than would be expected if 58 is formed from 1a.

It is possible that the pivalate anion is basic enough to remove a proton from 1. Therefore, intermediates originating from carbanions which react further to yield the C-2 substitution product must be considered. Three intermediates are immediately suggested. Two arise from removal of a proton from C-6, while the third originates from removal of a proton from the C-3 methyl group. The mechanistic scheme citing these possibilities is shown in scheme XVII.

Intermediate 55 was suggested previously for the reaction of 6-chloroisophorone (58) with silver nitrate and triethylamine.⁶² Nucleophilic attack on C-2 of 55 results in migration of the double bond, as well as the opening of the cyclopropane ring to give, ultimately, the C-2 substituted isophorone.

The cyclopropanone intermediate 88 arises when a C-6 carbanion (pathway C-6₂) attacks the carbon-carbon double bond at C-2 instead of directly displacing the C-4 halogen. Intermediate 88 is the endo analog of the one proposed by Fort,^{60a, b} 51, in the reaction of 6-tosyloxyisophorone (44) with sodium methoxide. Attack at C-2 of 88 or 51 would open the cyclopropane ring rendering the allylic rearrangement product.



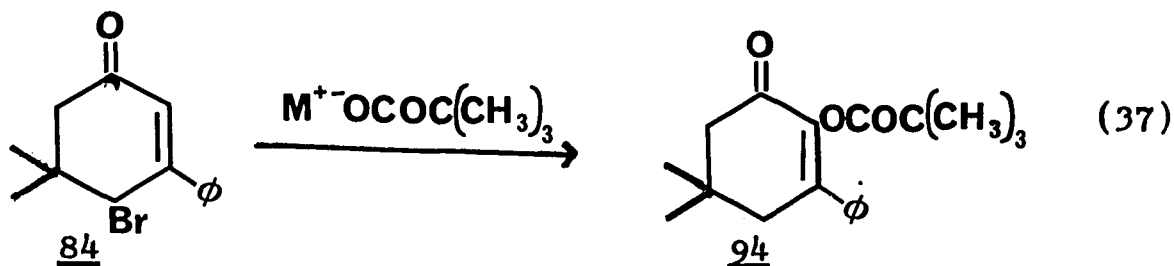


Scheme XVII

The third, three membered ring intermediate 56 arises from the removal of a proton from the C-3 methyl group of 1 (pathway C-3m), followed by intramolecular displacement of bromide. Kosower⁶² reported this intermediate from the reaction of 3-chloromethyl-5,5-dimethylcyclohex-2-enone (53) with base. Attack by the nucleophile on C-2 of 56 gives an allylic carbanion which readily converts in two steps to a C-2 substituted isophorone.

4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) has been synthesized by Kaminsky.⁷⁷ This compound has a C-3 phenyl group instead of a C-3 methyl group and hence cannot react by a 56 type intermediate.

When 84 is treated with potassium pivalate in either pivalic acid (13 days, ca. 45°) or DMF (40.5 hrs, ca. 45°), the only product recovered is 5,5-dimethyl-3-phenyl-2-pivoxycyclohex-2-enone (94) as shown in Eq 37:



Only S_N2' type reactions are noted with 84 probably because: 1) the phenyl group, at C-2, is bulkier than a methyl group making nucleophilic attack at C-4 more difficult and/or 2) attack at C-2, while causing loss of

conjugation of the double bond with the carbonyl group, still allows the double bond to remain in conjugation with the phenyl group. Thus, ensuing attack on C-2 is not as energetically poor as attack on C-2 of 1. We, therefore, conclude that S_N2' -type products from 1 can occur without initial formation of a carbanion derived from the C-3 methyl group. Identification of this new compound, 94, was confirmed by elemental and spectral analysis.

Elimination of mechanisms initiated by C-6 carbanion formation is slightly more circuitous. The reaction of 1 with potassium pivalate in DMF gave both 57 and 58. The rate of any reaction proceeding via a carbanion should be enhanced by the addition of a base, other than the reacting nucleophile. The added base must be one like triethylamine which is sterically hindered from behaving as a nucleophile. If carbanion formation in the ensuing step is rate-determining, increasing the concentration of the base should increase the rate of such reactions. Reactions not proceeding through a carbanion, should be negligibly affected by changing the concentration of added bases. The reaction of 1 with potassium pivalate in DMF which gave 57 and 58 was chosen to test this hypothesis. Compound 57 should arise by direct S_N2 displacement at C-4 and, therefore, not be affected by added triethylamine. If 58 arose via a carbanion, its

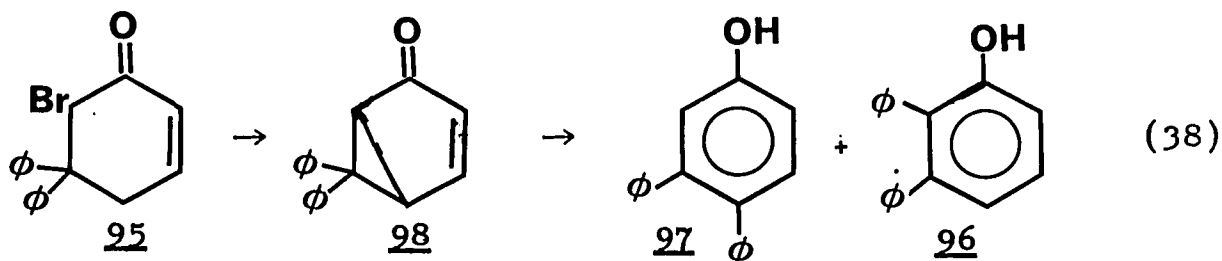
rate of formation should be influenced by added base. If the foregoing situation prevails, the addition of triethylamine should alter the product distribution of 57 and 58.

Identical reactions were run, treating 1 with potassium pivalate, in DMF, except that 1.3 equivalents of triethylamine was added to one of the reactions. Aliquots were taken from the reaction mixture periodically. Analysis by nmr of the crude mixtures demonstrated that added base had no effect on either the product distribution or the rate of formation of these products. It is concluded, therefore, that formation of 58 does not proceed through a C-6 carbanion.

This conclusion is reinforced by the observation that the reaction of potassium pivalate with 1, in HMPT, which results only in the formation of the direct substitution compound (reaction 1, Table 11) showed no product change when triethylamine was added (entry 15, Table 11). When this base was added to the reaction of lithium pivalate with 1 in DMF (reactions 9 and 19, Table 11) only the allylic rearrangement product is isolated. This is the same result as in the absence of base.

The intermediate 55 has been demonstrated to give a mixture of 2,3,5-trimethylphenol (54) and 3,4,5-trimethylphenol (2).⁶² In addition, Zimmerman⁷⁸ treated 6-bromo-5,5-diphenylcyclohex-2-enone (95) with potassium tert-butoxide in tert-butanol and obtained a

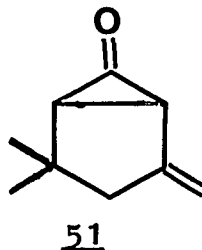
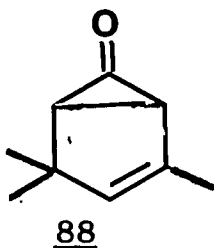
mixture of 2,3-diphenylphenol (96) and 3,4-diphenylphenol (97). The author proposes an intermediate similar to the one postulated by Kosower. Again, a 4,6-cyclopropane intermediate has been demonstrated to yield a mixture of phenols as shown in Eq 38:



Compound 1 with triethylamine in dioxane:water (1:1 v/v) (Table 6, reaction 2) gave 2 and 54. However, no phenol was isolated when 1 was treated with $M^+ \text{ } ^-\text{O}^{\text{O}}\text{C}(\text{CH}_3)_3$ in DMF, DMSO, HMPT or pivalic acid.

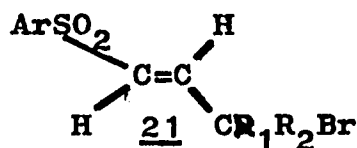
Of additional significance, was the isolation of C-2 and C-6 substitution products when 6-tosyloxyisophorone (44) was treated with potassium pivalate in DMF. These products are presumed to arise through intermediate 51 (formed from an initially developed carbanion). This intermediate is the exo analog of 88. It is unlikely that the reactivity of these similar cyclopropane intermediates would be so different, under identical reaction conditions, as to give different substitution products. Based on all of the above evidence, we conclude that

carbanion formation is not involved in the formation of allylic rearrangement products obtained from reactions of 1. (A discussion of the reactions of 44 can be found in section I, page 121).



It is difficult to determine whether ion-pair formation precedes nucleophilic attack on C-2 because its formation cannot be observed directly. The presence or lack of an ion-pair can only be inferred from various solvent and salt effects. The nature of an ion-pair is a semantic question. Some researchers (page 30) suggest that an ion-pair is similar to a full carbonium ion with a negatively charged anion in close proximity. Others have concluded that a significant degree of covalent bonding exists between the cation and anion.

Bordwell³⁸ suggested that in compounds similar to 21c ($R_1 = R_2 = \text{CH}_3$) ion-pair formation is possible, but that the strong electron withdrawing effect of the sulfonyl group does not allow the dissociation of the ion-pair. He theorizes that 21c initially forms an



ion-pair because of the difference in reactivity between this compound and the similar primary bromide 21a ($R_1 = R_2 = H$). Bordwell also predicts that positive charge, on the ion-pair, is distributed to a position alpha to the sulfonyl group. An increase in the ionizing power of the solvent (methanol compared to 60% aqueous methanol) causes a greater rate increase in the tertiary system, 21c, than in the primary bromide 21a, when these compounds are treated with lithium azide. A positive salt effect (lithium perchlorate in methanol and 60% aqueous methanol) is noted for 21c and a negative one for 21a.

It is quite significant than even in the S_N1 inhibiting systems, reactions occur under solvolytic conditions, e.g. methanol, 60% aqueous methanol, acetic acid, 70% (v/v) dioxane:water and 60% dioxane water.³⁸ Thus, solvolysis reactions which probably occur through a solvent separated ion-pair are observed.

We have noted that no reaction of 1 occurs under a wide variety of solvolysis conditions (section B). We suggest that with a substrate like 1 which would have to form a "reluctant" carbonium ion, reactions occurring through a pre-formed ion-pair are much more difficult to envision than in the substrate employed by Bordwell.

Solvent and salt effects have been used to attempt to elucidate the role of ion-pairing in the formation of 57 and 58. When 1 is treated with potassium pivalate

in HMPT (Table 11, reaction 1) only 57 is isolated. When 1.3 equivalents of potassium perchlorate (reaction 2) is added to this mixture, 20% 58 is obtained in addition to 80% 57. Aliquots, analyzed by nmr shows the presence of starting material and, therefore, added salt slows the rate of formation of the C-4 substitution product. It is not possible to conclude from these data whether the rate of formation of 58 increased, remained the same, or was lowered but to a lesser extent than the retardation of direct substitution. Any of these possibilities can account for the formation of some 58. This negative salt effect for the rate of formation of 57 is expected for an S_N2 reaction.

When 1.3 equivalents of potassium perchlorate are added to the reaction of 1 with potassium pivalate in DMF (Table 11, entries 3 and 4) a significant amount of starting material is recovered. The reaction appears to be slowed because only 25% of 57 is obtained. The slowing down of the direct substitution reaction is consistent with the results obtained in entries 1 and 2. The yield of 58 is increased slightly by the addition of the second salt. Unfortunately, this reaction is not homogeneous, and it is possible that the addition of potassium perchlorate causes some potassium pivalate to precipitate, which results in the observed product distribution. The same reactions repeated in DMSO (entries 5 and 6) remained homogeneous. The product distribution,

Table 11^aAdditional Reactions of 1 with Pivalate Salts

Entry	Solvent	Pivalate Salt	Base or ^b Salt-2	Products (yield)		
1	HMPT	K		<u>57</u> (90%)		
2	HMPT	K	KClO ₄	<u>57</u> (80%)	<u>58</u> (20%)	
3	DMF	K		<u>57</u> (71%)	<u>58</u> (29%)	
4	DMF	K	KClO ₄	<u>57</u> (25%)	<u>58</u> (40%)	<u>1</u> (30%)
5	DMSO	K		<u>57</u> (66%)	<u>58</u> (34%)	
6	DMSO	K	KClO ₄	<u>57</u> (62%)	<u>58</u> (38%)	
7	DMF:H ₂ O(9:1)	K		<u>57</u> (13%)	<u>58</u> (45%)	<u>1</u> (35%)
8	DMSO:H ₂ O(9:1)	K		<u>57</u> (37%)	<u>58</u> (50%)	<u>1</u> (9%)
9	DMF	Li			<u>58</u> (95%)	
10	DMSO	Li			<u>58</u> (95%)	
11	DMSO	Li	LiClO ₄		<u>58</u> (95%)	
12	DMF	Li	LiClO ₄		<u>58</u> (95%)	
13	DMSO	Et ₄ N		<u>57</u> (58%)	<u>58</u> (17%)	<u>1</u> (25%)
14	DMF	Et ₄ N		<u>57</u> (59%)	<u>58</u> (17%)	<u>1</u> (24%)
15	HMPT	K	Et ₃ N	<u>57</u> (90%)		
16	DMF	Li	Et ₃ N		<u>58</u> (95%)	

(a) Reactions conditions: 0.434 g (0.002 mol) of 4-bromoisophorone(1), for 40.5 hrs at ca. 45°; 1.3 equivalents of pivalate salt used in each reaction.

(b) 1.3 equivalents

(57) 4-pivoxylisophorone

(58) 2-pivoxylisophorone

with and without the added perchlorate salt, show no significant difference.

To test for solvent effects, ten percent aqueous DMF and DMSO (reactions 7 and 8) were employed as the solvent from the reactions of 1 with potassium pivalate. In 90% aqueous DMF, the yield of 57 dropped to 13%. Starting material (36%) and 58 (45%) were also recovered. The homogeneous reaction of 1 with potassium pivalate in 10% aqueous DMSO yields 9% 1, 37% 57, and about 50% 58. In both cases, the presence of water decreases the yield of the direct substitution product, whereas, the yield of the allylic rearrangement product is slightly raised. The increase in yield of the S_N2' product can be accounted for by the solvation of the anion. Water solvates the anion, making it larger and less reactive. As demonstrated, the rate of the S_N2 reaction is decreased significantly while that of the S_N2' varies slightly in an unpredictable manner. The increased ionizing power of the reaction medium is also expected to stabilize ion-pair formation, but it is unclear which of these factors causes an increase in the yield of the allylic rearrangement product.

As noted earlier, the reaction of 1 with lithium pivalate in DMSO and DMF gives only 58 (entries 9 and 10). The addition of lithium perchlorate to these reactions can demonstrate whether a change in the rate of

formation in the S_N2' product with an increase in the ionizing power of the reaction media is possible. Aliquots from reaction 12 show that the rate of the reaction and rate of disappearance of starting material are unchanged. Both reactions were homogeneous after five hours of stirring. No change in the reaction product(s) was noted when DMSO was substituted for DMF in the above reactions. These results are shown in reactions 10 and 11 of Table 11.

Sneen has postulated that allylic rearrangement reactions occur through pre-formed ion-pairs. He suggests that each allylic ion-pair is a discrete species in equilibrium with a solvent separated ion-pair. According to Sneen,⁷⁹ ion-pairs have very high energy and should be indiscriminate in their behavior. Therefore, they would be expected to react with solvent as well as with anionic nucleophiles.

It is significant that no solvolysis products are obtained in the reactions of 1. If ion-pair formation¹ occurs, this ion-pair never becomes a solvent separated ion-pair within experimental error. Therefore, the formation of a solvent separated ion-pair leading to substitution or methyl migration does not seem possible. We question whether it is necessary to invoke the formation of an ion-pair.

There are other mechanisms that involve initial

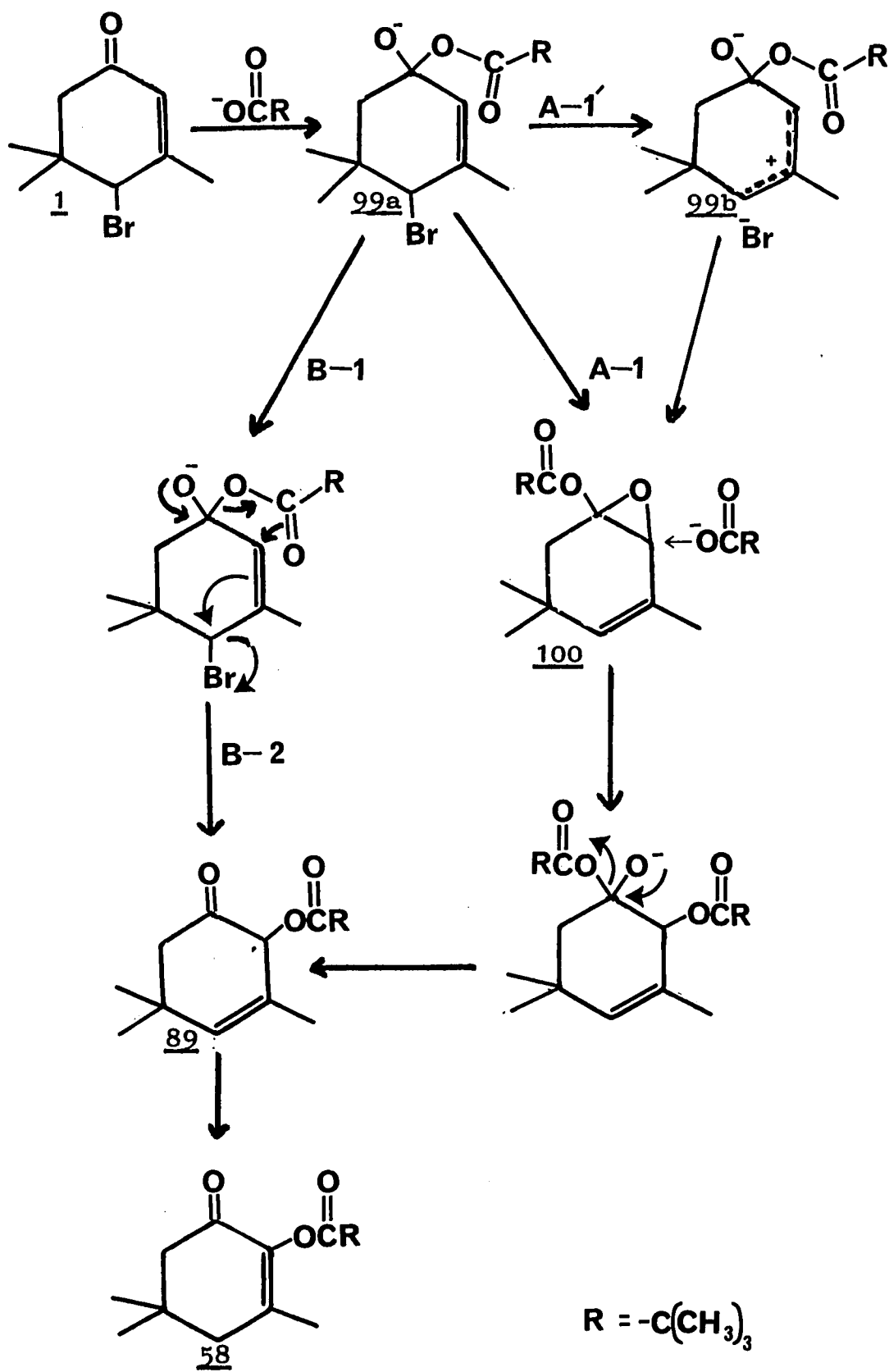
attack of the anion on the carbonyl group, which cannot be readily eliminated by the data, as shown in scheme XVIII.

Pathway B-1 involves an internal attack of the pivalate carbonyl group on the C-2 position (or on an ion-pair). Ion-pair formation is not eliminated because the constraint of having a carbonyl group alpha to a positive charge is eliminated. Either in a concerted or non-concerted manner; 1) the free electrons on the C-1 oxygen cation reforms a carbonyl group; 2) the C=O of the ester attacks at C-2; 3) the pi bond migrates; and 4) the halogen is lost from C-4. This sequence results in the formation of 89, which then reconjugates to give 58. This mechanism is obviously specific for an ester type nucleophile.

The possibility of a second nucleophile attacking the initially formed intermediate 99 (a or b) is not likely because it requires the collision of two negatively charged species.

Pathway A-1 involves epoxide formation of the initial intermediate 99a or its ion-pair 99b (step A-1). Attack specifically on the C-2 position of 100 opens the epoxide ring, followed by reformation of the carbonyl group (A-3) and loss of a pivalate anion leads to 89. Formation of 58 follows. Both of these above reactions can be considered to be intramolecular S_N2' reactions.

The constraint on formation of an ion-pair on compound 99a (i.e. 99b) is now eliminated because of the

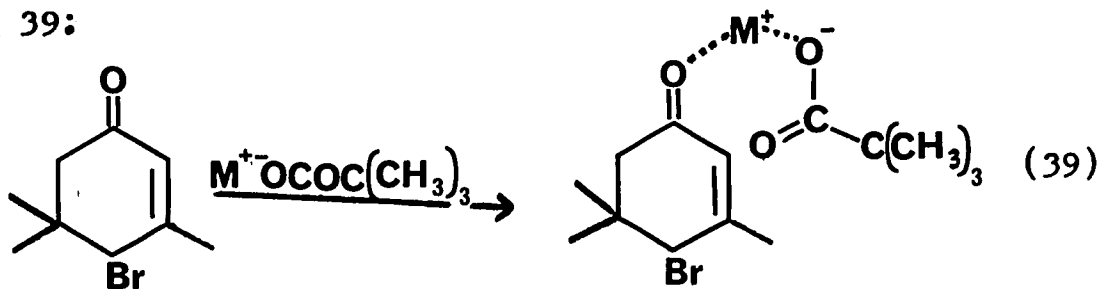


Scheme XVIII

removal of the carbonyl group. If an ion-pair was now formed, one would expect to find a significant solvolysis reaction in 90% aqueous DMSO of DMF (Table 11, entries 7 and 8). A direct S_N1 solvolysis reaction is now likewise allowed.

In fact, only products of nucleophilic addition, not solvent addition, are noted. We can, therefore, conclude that either reactions through pathway A-1 and B-1 are much faster than formation of a solvent separated ion-pair, or an S_N1 type reaction, which would lead directly to a significant amount of 4-hydroxyisophorone (41) or that this intermediate (99a) does not form.

It is also possible that initial coordination of the cation with the carbonyl oxygen atom on 1 is necessary for formation of the allylic rearrangement product. This type of reaction could be considered to be an S_N2' reaction through a cyclic transition state, as shown in Eq 39:



In reactions 13 and 14 of Table 11 the quaternary ammonium salt was employed as the nucleophile and a decrease in the yield of C-2 substitution product was

observed. The positively charged nitrogen atom is buried within a sphere of bulky ethyl groups. Therefore, coordination by this center with the carbonyl oxygen atom is difficult. Experimentally, a decrease in the yield of C-2 substitution product is observed. This supports the contention that initial complexation between the cation and the carbonyl oxygen may aid in this product formation. The proposed cyclic intermediate is applicable for ester type functions and may not apply when most other nucleophiles are present (e.g. alkoxides).

All of the results in this section have not eliminated from consideration the possibility that formation of the allylic rearrangement product occurs through a concerted S_N2' mechanism.

Section: H: The Direct Substitution Reaction

At this point it is valuable to review the mechanism involved, as well as the conditions employed in the formation of the direct substitution product.

When silver acetate or silver pivalate reacts with 4-bromoisophorone (1), in pyridine, about fifty percent of the recovered product is the ester from direct substitution. Silver salts are known to form silver-pyridine complexes which leaves a more reactive anion capable of reacting at C-4 of 1.

In general, a non-solvated anion, being more reactive is effected less by the steric factors of the substrate, allowing an enhanced displacement at C-4. Thus, except for the lithium salt, pivalate in DMSO or DMF, give mainly 57; in HMPT, the only product is 57.

Initial formation of a carbanion is not involved in the formation of 57 as demonstrated by the reaction of 1 with pivalate salts in DMSO and DMF. Added base causes no change in the rate of formation of the C-4 substitution product. When 1 was treated with lithium pivalate in DMF only 2-pivoxisophorone (58) was isolated. Added triethylamine did not result in the formation of any direct substitution products. Potassium perchlorate was added to 1 with potassium pivalate in HMPT. The addition of the second salt caused a decrease in the

yield and rate of formation 57 with concurrent formation of 58.

The possibility that 2-pivoxo-3,5,5-trimethylcyclohex-2-enone (89) rearranges to the direct substitution product was eliminated by demonstrating that 89 converts only to 58 under the reaction conditions (i.e. potassium pivalate in pivalic acid or DMF).

These results are consistent with the conclusion that the direct substitution product is a true case of an S_N² reaction at a neopentyl position.

Section I: Reactions of 6-Tosyloxyisophorone (44)

Unlike 4-bromoisophorone (1), 6-tosyloxyisophorone (44) is incapable of giving a S_N2' reaction. However, like that of 1 the leaving group of 44 is at a neopentyl position and it is difficult for it to undergo S_N2 reactions. Because the leaving group is alpha to the carbonyl group, S_N1 reactions of this compound should also be difficult. It was of interest, therefore, to compare the reactivity of 44 and 1. In this section the reactions of 44 are reported. In the following section comparisons between the reactions of 1 and 44 are made.

As can be seen from Table 12, 44 is inert to solvolytic conditions. The reactions of 44 were generally run in more dilute systems than the reactions of 1 because of the difficulty of dissolving 44.

Table 12^a
Solvolytic Reactions of 44

Entry	Solvent	Volume	Products
1	dioxane:H ₂ O (1:1 v/v)	19 ml	No Reaction (NR)
2	methanol	15 ml	NR
3	dioxane: H ₉ P buffer (1:1 v/v)	19 ml	NR
4	acetic acid	8 ml	NR
5	pivalic acid	8 ml	NR ^b
6	DMF	10 or 5 ml	NR
7	DMSO	10 or 5 ml	NR

(a) Reactions run with 0.001 mol of 44 for 40.5 hrs at ca. 45° (b) not homogeneous

No reaction was noted when 44 was treated with sodium acetate trihydrate in acetic acid (Table 13, entry 1) or with sodium pivalate in pivalic acid (entry 2) for 40.5 hrs at 45°. The lack of reaction in the latter case could be due to the insolubility of 44 in the solvent employed. When 44 is treated with sodium pivalate and triethylamine in dioxane:water (1:1 v/v) (entry 3) only 6-hydroxyisophorone (46) is recovered. The formation of 46 can be accounted for in four ways: 1) hydrolysis of the starting material; 2) direct substitution at C-6 by water; 3) hydrolysis of initially formed 6-pivoxyisophorone (101); or 4) attack by water specifically at C-6 on an intermediate similar to that obtained by Fort⁶¹ in the reaction of 44 with sodium methoxide (page 41).

Mechanisms 1 and 2 are immediately eliminated because 44 is inert to dioxane:water (1:1 v/v) (Table 12, entry 1). Both these reactions would be expected to occur under solvolytic conditions. Reactions 4 and 5 of Table 13 confirm that 46 can be obtained without sodium pivalate. In addition, 101 has been shown to be inert under the reaction conditions and, therefore, could not be a precursor of 46.

Entries 4 and 5 also reveal that the rate of formation of 46 is dependent on the concentration of base. This result is consistent with initial carbanion formation

Table 13^a

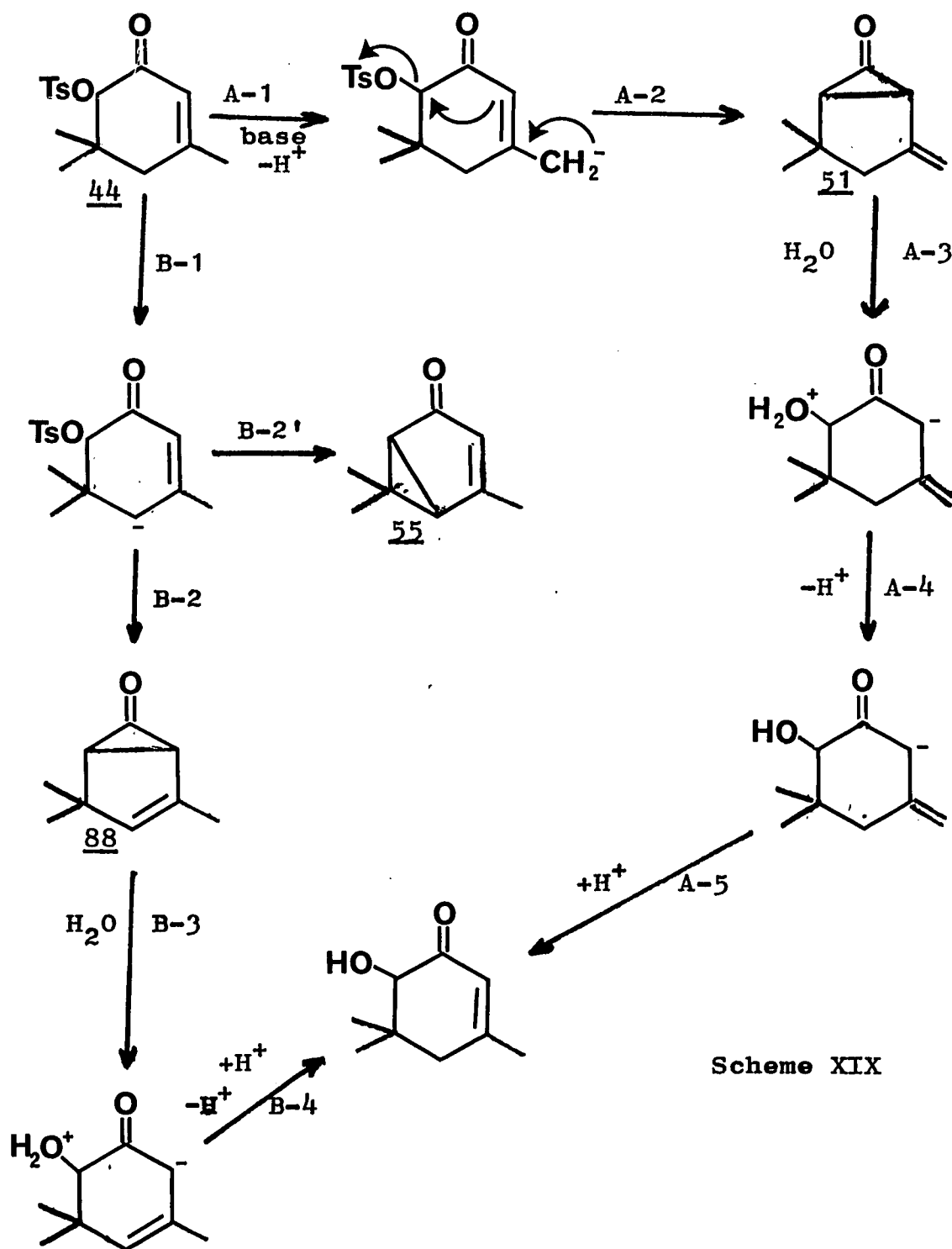
Reactions of 6-Tosyloxyisophorone (44)

Entry	Solvent	Salt^b	Added Base (Equiv)	Products(Yield)
1	acetic acid (8ml)	NaOAc·3H ₂ O		No Reaction
2	pivalic acid (8ml)	NaOCOC(CH ₃) ₃		No Reaction
3	dioxane:H ₂ O (1:1v/v)(19ml)	NaOCOC(CH ₃) ₃	Et ₃ N (2.0)	<u>46</u> (95%)
4	dioxane:H ₂ O (1:1v/v)(19ml)		Et ₃ N (1.0)	<u>46</u> (40%) <u>44</u> (60%)
5	dioxane:H ₂ O (1:1v/v)(19ml)		Et ₃ N (4.0)	<u>46</u> (95%)
6	dioxane (19ml)		Et ₃ N (1.0)	No Reaction
7	dioxane:H ₂ O (1:1v/v)(19ml)	KClO ₄	Et ₃ N (1.0)	<u>46</u> (32%) <u>44</u> (68%)
8	DMF (5ml)	KOCOC(CH ₃) ₃		<u>101</u> (56%) <u>58</u> (44%)
9	DMF (5ml)	KOCOC(CH ₃) ₃	Et ₃ N (1.0)	<u>101</u> (56%) <u>58</u> (44%)
10	DMF (5ml)	LiOCOC(CH ₃) ₃		<u>101</u> (55%) <u>58</u> (45%)
11	HMPT (5ml)	KOCOC(CH ₃) ₃		<u>101</u> (55%) <u>58</u> (45%)
12	DMF (5ml)		Et ₃ N (1.3)	No Reaction

(a) Reactions employed 0.001 mol of 6-tosyloxyisophorone (44) for 40.5 hrs at 45 ± 2°. (b) 1.3 Equivalents. (46) 6-Hydroxyisophorone

(58) 2-Pivoxoisophorone (101) 6-Pivoxoisophorone

leading to a cyclopropanone intermediate, as shown below in scheme XIX followed by attack of water at C-6. See pathway A-1, etc.



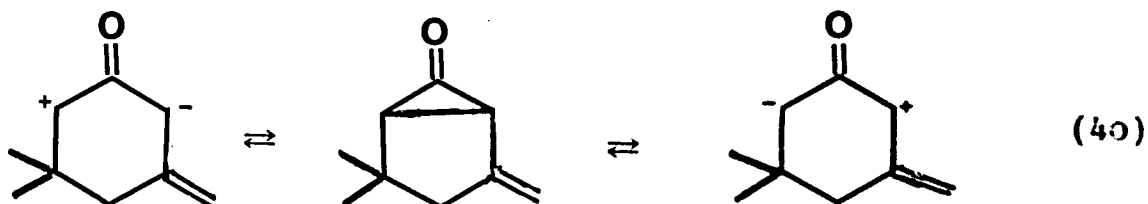
Scheme XIX

Step B-1 involves the removal of a proton from C-4 of 44. The resulting carbanion could attack C-6 directly giving 55 (step B-2'). This intermediate has previously been postulated as occurring during the reaction of 6-chloroisophorone (52) with triethylamine⁶² and in the reaction of 1 with this base in dioxane:water (1:1 v/v). In both these reactions 2,3,5-triethylphenol (54) and 3,4,5-trimethylphenol (2) were recovered. However, no phenolic products were recovered from the reactions of 44 under these basic conditions. Therefore, intermediate 55 can be excluded. The intermediate that gives the cyclopropanone intermediate is a proton from the C-3 methyl group. The intermediate that goes on to 51 (steps A+...) intermediates differ by the placement of the methyl group.

It is in the suggested intermediate for the reaction of 44 to a mixture of phenols 54 and 2 is unclear why the bulky base, triethylamine prefers to remove a proton from C-4 rather from the more acidic and less hindered C-3 methyl group.

A cyclopropanone intermediate may be in equilibrium with dipolar forms as shown in Eq 40: The positive charge on 51b can be stabilized by delocalization through the allylic system. The positive charge on 51a is not stabilized at all. Therefore, it may react much faster

than 51b when nucleophilic water molecules are present. This could account for the formation of the C-6 substitution product.



Unless the leaving group from 44 is solvated, e.g. by water, the initially formed carbanion does not form intermediate 51 (Table 13, entries 6 and 12). It is also possible that 51 forms but is specifically attacked at C-6 by the tosyl group, thereby regenerating the starting material. No reaction was noted when 44 was treated with triethylamine in DMF (entry 12). There is no evidence in this system to suggest that a cyclopropanone intermediate does not form, but as in entry 6, the tosyl group probably attacks this intermediate specifically at C-6 to regenerate the starting material.

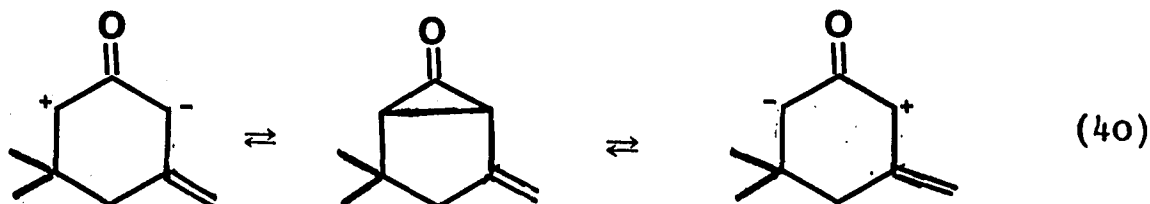
When 44 was treated with potassium pivalate in DMF, 56% 101 and 44% 58 were isolated (entry 8). As explained in earlier sections, an anion in DMF is unsolvated and, therefore it is a stronger base than in a protic solvent system. The pivalate anion is capable of removing a proton from the C-3 methyl group or the C-4 methylene group, ultimately leading to intermediate 51 and/or 88. The pivalate

Step B-1 involves the removal of a proton from C-4 of 44. The resulting carbanion could attack C-6 directly giving 55 (step B-2'). This intermediate has previously been postulated as occurring during the reaction of 6-chloroisophorone (52) with triethylamine⁶² and in the reaction of 1 with this base in dioxane:water (1:1 v/v). In both these reactions 2,3,5-triethylphenol (54) and 3,4,5-trimethylphenol (2) were recovered. However, no phenolic products were recovered from the reactions of 44 under these basic conditions and therefore, intermediate 55 can be excluded. The carbanion could react to give the cyclopropanone intermediate 88. Removal of a proton from the C-3 methyl group could give a carbanion that goes on to 51 (steps A-1 and A-2). These intermediates differ by the placement of the double bond.

It is interesting that the suggested intermediate for the reaction of 52 which leads to a mixture of phenols 54 and 2 is 55. It is unclear why the bulky base, triethylamine prefers to remove a proton from C-4 rather from the more acidic and less hindered C-3 methyl group.

A cyclopropanone intermediate may be in equilibrium with dipolar forms as shown in Eq. 40: The positive charge on 51b can be stabilized by delocalization through the allylic system. The positive charge on 51a is not stabilized at all. Therefore, it may react much faster

than 51b when nucleophilic water molecules are present. This could account for the formation of the C-6 substitution product.



Unless the leaving group from 44 is solvated, e.g. by water, the initially formed carbanion does not form intermediate 51 (Table 13, entries 6 and 12). It is also possible that 51 forms but is specifically attacked at C-6 by the tosyl group, thereby regenerating the starting material. No reaction was noted when 44 was treated with triethylamine in DMF (entry 12). There is no evidence in this system to suggest that a cyclopropanone intermediate does not form, but as in entry 6, the tosyl group probably attacks this intermediate specifically at C-6 to regenerate the starting material.

When 44 was treated with potassium pivalate in DMF, 56% 101 and 44% 58 were isolated (entry 8). As explained in earlier sections, an anion in DMF is unsolvated and, therefore it is a stronger base than in a protic solvent system. The pivalate anion is capable of removing a proton from the C-3 methyl group or the C-4 methylene group, ultimately leading to intermediate 51 and/or 88. The pivalate

anion present is highly reactive, and less discriminating. Nucleophilic attack occurs at either C-2 or C-6 of these cyclopropanone intermediates leading to 58 and 101, respectively. Added base, 1.3 equivalents of triethylamine (entry 9), causes no change in the product distribution. This result suggests that the formation of both products involves initial carbanion formation. The possibility that neither product requires a carbanion intermediate is untenable. When treated with either lithium pivalate in DMF or potassium pivalate in HMPT, compound 44 yields ca. 55% 101 and 45% 58 (entries 10 and 11). Added inert salt, potassium perchlorate (run 7) shows no significant change in the product distribution.

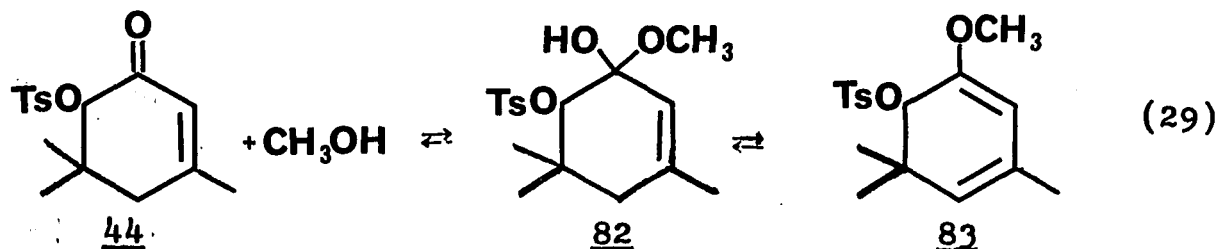
On reviewing our observations and those of Fort⁶¹ an interesting trend is observed. As the basicity and/or the nucleophilicity of the attacking species increases, a greater amount of product arises from reaction at C-2 or the carbonyl carbon of the cyclopropanone intermediate. Thus, when 44 reacts with methoxide ion in methanol both 6-methoxyisophorone (48), 2-methoxyisophorone (47) and Favorskii type products (derived from methoxide attack on the carbonyl group of 51) are obtained. Only attack at C-6 is found when 44 reacts with pivalate ion in DMF. When neutral weak nucleophiles are present, e.g. water or methanol, attack on 51 or 88 is directed solely (or almost so) at the C-6 position.

Section J. Comparison of the Reactions of 6-Tosyloxy-
isophorone (44) with 4-Bromoisophorone(1)

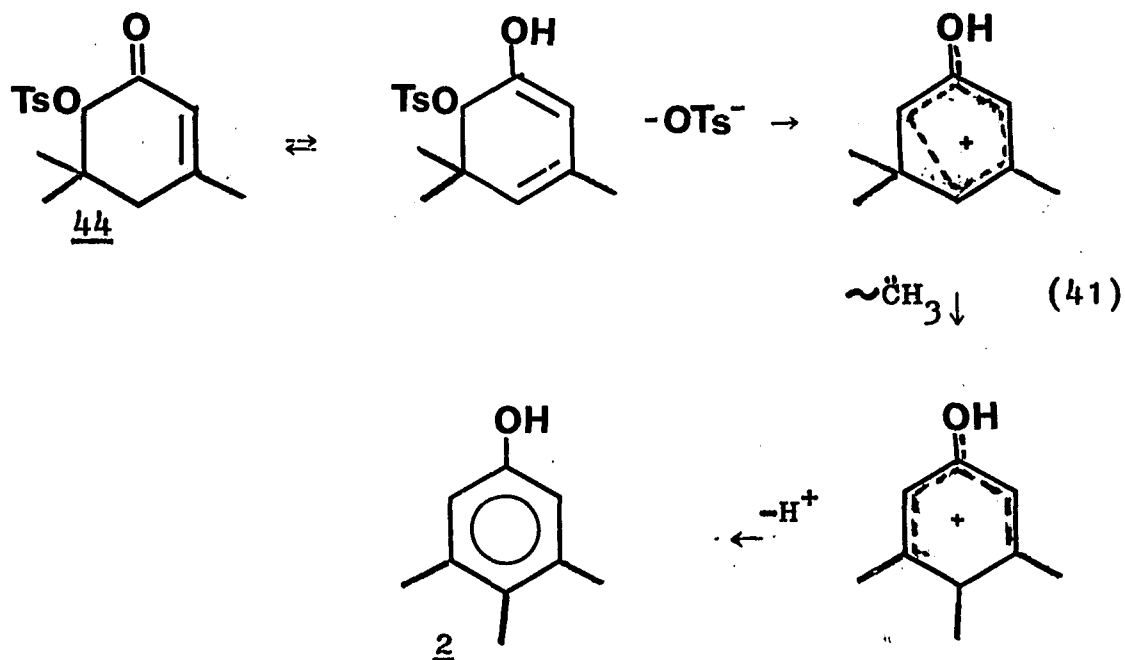
In this section we will compare the product distribution and reaction mechanisms involved in the reactions of 44 and 1.

Neither 1 nor 44 undergo solvolysis. They are inert towards hydrolysis, methanolysis, ethanolysis, and pivalolysis. However, 1 is aromatized to 3,4,5-trimethylphenol (2) under acetolysis conditions, whereas, 44 is inert.

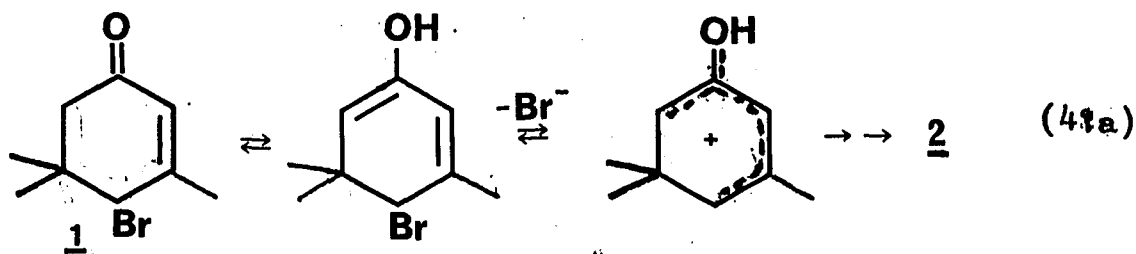
With methanol and dry hydrogen chloride, 44 affords 3,4,5-trimethylanisole^{60a} (81); no phenols were obtained. Fort^{60a} explains the formation of the anisole by a pre-equilibrium of 44 with methanol to give an enol ether which then ionizes and undergoes aromatization. Loss of water from 82 gives the enol ether as shown in Eq 29:



In strong aqueous acid (refluxing dioxane with concentrated hydrochloric acid) both 44 and 1 rearrange to 2. Fort^{60a} postulates that this reaction occurs by initial enol formation followed by the loss of the tosylate group as shown in Eq 41:



A similar ionization mechanism can be conceived for the hydrolysis of 1, as shown in Eq 41a: It appears that methyl migration occurs exclusively from C-5 to C-4.



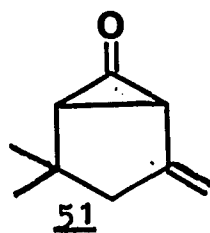
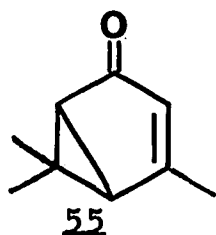
We previously demonstrated that when treated with dioxane:water and triethylamine, 1 affords phenolic products; 44 gives only 6-hydroxyisophorone (46) (Table 14, entries 1 and 2). We showed that conversion of 44 to 46 probably proceeds by attack of water at C-6 of intermediate 51. The reaction of 1 with base is

Table 14^aReactions of 1 and 44

Entry	Substrate	Solvent (ml)	Base or Salt (Equiv)	Products(yield)	
1	<u>44</u>	dioxane:H ₂ O (1:1 v/v) ² (19)	Et ₃ N (1.0)	6-tosyloxyisophorone (<u>44</u>) (60%) 6-hydroxyisophorone (<u>46</u>) (40%)	
2	<u>1</u>	dioxane:H ₂ O (1:1 v/v) ² (5)	Et ₃ N (1.0)	3,4,5-trimethylphenol (<u>2</u>) (45%) 2,3,5-trimethylphenol (<u>54</u>) (45%)	
3	<u>44</u>	DMF (5)	KOCOC(CH ₃) ₃ (1.3)	2-pivoxisophorone (<u>58</u>) (44%) 6-pivoxisophorone (<u>101</u>) (56%)	
4	<u>1</u>	DMF (5)	KOCOC(CH ₃) ₃ (1.3)	4-pivoxisophorone (<u>57</u>) (71%) <u>58</u> (29%)	
5	<u>44</u>	HMPT (5)	KOCOC(CH ₃) ₃ (1.3)	<u>58</u> (44%)	<u>101</u> (56%)
6	<u>1</u>	HMPT (5)	KOCOC(CH ₃) ₃ (1.3)	<u>57</u> (90%)	
7	<u>44</u>	DMF (5)	LiOCOC(CH ₃) ₃ (1.3)	<u>58</u> (44%)	<u>101</u> (56%)
8	<u>1</u>	DMF (5)	LiOCOC(CH ₃) ₃ (1.3)	<u>58</u> (90%)	
9	<u>44</u>	DMSO (5)		No Reaction	
10	<u>1</u>	DMSO (5)		2,6-dibromo-3,4,5-trimethylphenol (<u>60</u>) (11%); 2-bromo-3,4,5-trimethylphenol (<u>59</u>) (61%); <u>2</u> (28%)	

(a) All reactions run for 40.5 hrs at 45 ± 2°
using .001 mol of 44 and .002 mol of 1.

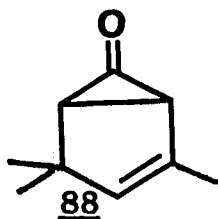
suggested to proceed through 55 followed by methyl migration to C-4 and C-6 to give 3,4,5-trimethylphenol (2) and 2,3,5-trimethylphenol (54), respectively. Formation of both 51 and 55 involve initial carbanion formation but, clearly, no methyl migration occurs from structure 51. Both 51 and 55 are independent species and not in equilibrium with each other.



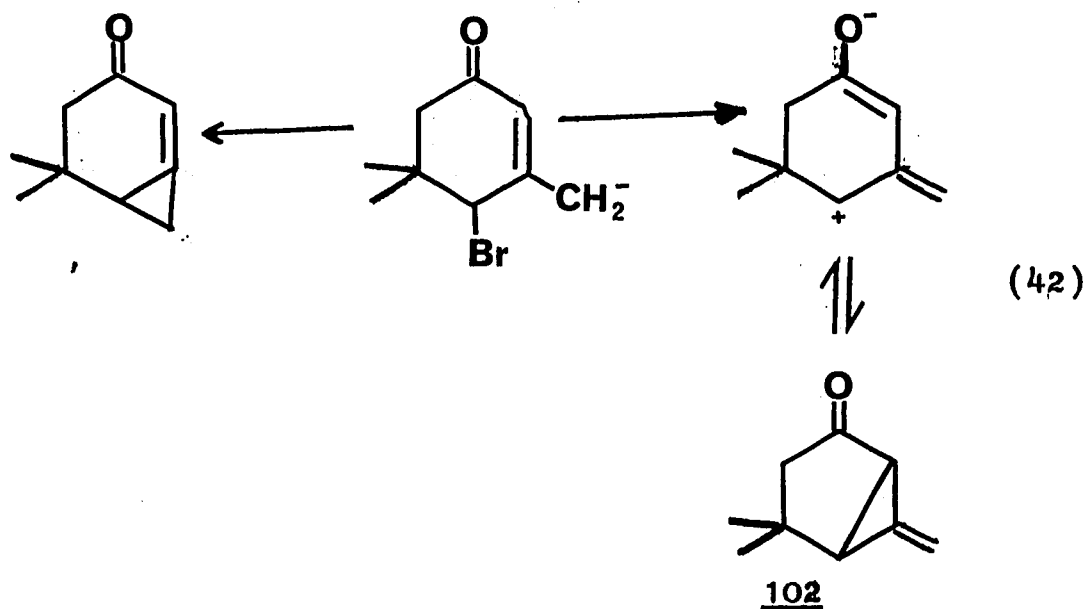
Upon reaction with potassium pivalate in DMF compound 1 yields the direct substitution (S_N2) and allylic rearrangement (S_N2') products. Neither of these products comes from a pre-formed carbanion (section G). When 44 is treated under these conditions, products derived from nucleophilic attack on the C-2 and C-6 positions of 51 are observed (entries 3 and 4). Thus, we have demonstrated that under identical conditions 44 reacts via a carbanion mechanism while 1 does not. When HMPT replaces DMF as the solvent for the reaction of 1 with potassium pivalate, only the direct substitution product is obtained. However, with 44 the change from DMF to HMPT causes no change in the product distribution (entries 5 and 6). When lithium pivalate replaces

potassium in the pivalate salt, in DMF, 1 gives only the S_N2' product, 58; the S_N2 product, 57, was absent. With 44, under these conditions, no difference in the product distribution was observed. It is noteworthy in this reaction that there was no enhancement of C-2 product as there was with 1. Clearly, reaction of 1 with pivalate salt is very sensitive to change in the cation and solvent, whereas, the reaction of 44 is not. Compound 44 is also inert to treatment with DMSO, while 1 yields a mixture of phenolic products. Nucleophilic attack of DMSO, which leads to the formation of strong acid, may be allowed with 1, but not with 44 (entries 9 and 10).

In accounting for the variation in behavior of 1 and 44, it is first assumed that the differences in the leaving groups, tosylate and bromide, are minimal. Apparently, unlike 1, 44 reacts with pivalate faster to give a carbanion than to give direct displacement. This, notwithstanding the fact that a carbonyl group enhances the S_N2 reaction rate of α -carbonyl displacements.² This may be due to the fact that the C-3 methyl hydrogen, whose removal is required to give 51, is more acidic and more readily accessible than is the C-6 hydrogen of 1 whose removal is required to give intermediate 55 or 88.



If a proton is removed from the C-3 methyl group of 1, the three membered ring intermediates that could be formed from this carbanion are shown below in Eq 42:



The formation of these intermediates may be very slow (slower than the S_N2 or S_N2' reactions of 1) so that carbanion formation is fast and reversible but is not involved in product formation.

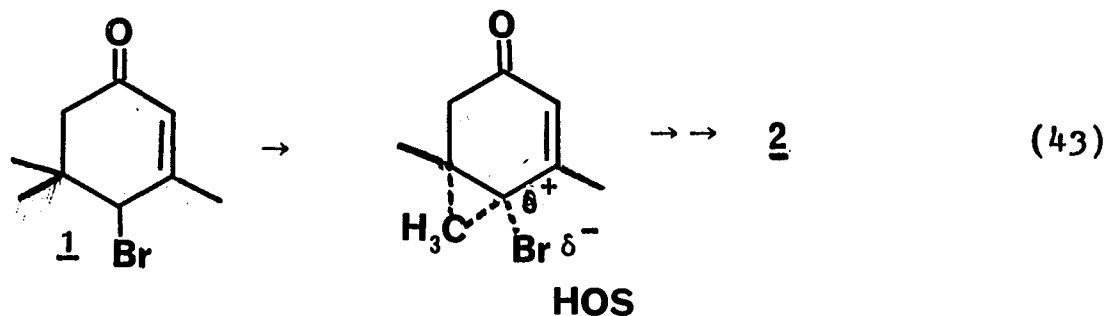
Section K. Methyl Migration

As suggested in the introduction (page 3) migration of a methyl group from C-5 of 4-bromoisophorone (1) to a developing positive charge center on C-4 should lead to the formation of 3,4,5-trimethylphenol (2). At this point it is instructive to address ourselves to the question of the concertedness of methyl migration to a carbonium ion, i.e. whether the migrating C-5 methyl group aids in the removal of the C-4 halogen.

In previous sections we have noted the formation of 2 and 2,3,5-trimethylphenol (54). The mechanisms for the formation of these products have been discussed. Under acetolysis conditions, 1 is converted to 2 via a hemiacetal (page 69) and/or through the enol of 1. Under basic conditions, the formation of both phenols has been suggested as proceeding through the cyclopropane intermediate 55 (page 75) followed by migration of a C-5 methyl group to C-4 and C-6. These schemes, however, are not informative as to the concerted nature of the reaction because they do not directly involve the bromo-ketone 1.

A major tenet of this thesis has been the difficult or "reluctant" formation of a C-4 carbonium ion in systems similar to 1. A way of stabilizing developing positive charge is to have the C-5 methyl group begin to bond to C-4 as the halogen is removed from C-4. Thus,

the positive charge could be distributed and stabilized by the methyl group. If migration of this group continues, compound 2 would result as shown in Eq 43:



With this concerted migration it is not required that a large amount of positive charge be developed on C-4. If this "push" by the neopentyl methyl group was important under solvolytic conditions (i.e. hydrolysis and ethanolysis, page 51) a reaction should be observed. However, as noted earlier, only starting material is recovered from these reactions. These results suggest that concerted methyl group migration and stabilization of developing positive charge on C-4 in a "non-classical" manner is not important in the systems investigated.

Section L. NMR Conformational Analysis

A compilation of the nmr spectra of C-4 and C-6 substituted cyclohex-2-enones used in our investigations, as well as those of other workers leads to an interesting observation concerning the equivalency of the C-5 groups as shown in Table 15.

When a halogen is present on C-4 (entries 1, 5, and 6) the C-5 groups are non-equivalent. When there is an oxygen substituent on C-4 there is little difference in the chemical shifts of the two C-5 groups. Conversely, when a halogen is present on C-6 (entries 10 and 12) the C-5 groups are equivalent. However, with a C-6 oxygen substituent (entries 7, 8, 9, and 11), clearly, the C-5 groups are no longer equivalent. See fig 2: below.

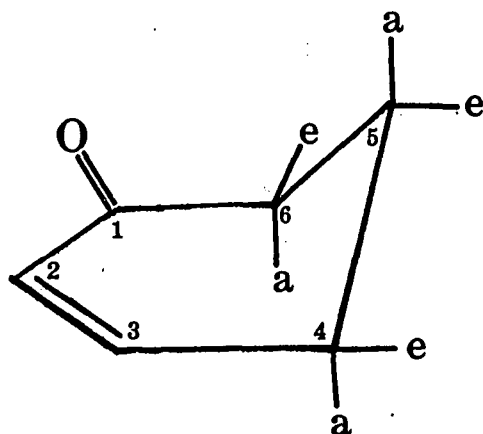


fig 2

The conformation of a cyclohex-2-enone ring requires that the C-1, C-2, C-3, C-4 and C-6 positions be planar while the C-5 carbon is above the plane. The C-4e and C-6e positions bisect the R, C-5, R angle causing the C-5

Table 15

NMR Gem Group Analysis of C-4 and C-6 Substituted Cyclohex-2-enones

<u>Entry Compound</u>		<u>C-5 Chemical Shifts^a</u> <u>(δ Units)</u>
1	4-bromoisophorone (<u>1</u>)	1.30(3H); 1.22(3H)
2	4-hydroxyisophorone (<u>41</u>)	1.08(3H); 1.03(3H)
3	4-acetoxyisophorone (<u>42</u>)	1.03(3H); 1.02(3H)
4	4-pivoxyisophorone (<u>57</u>)	1.02(6H)
5	4-bromo-5,5-dimethyl-3-phenyl- cyclohex-2-enone (<u>84</u>)	1.33(3H); 1.22(3H)
6	4-bromo-5,5-diphenylcyclohex-2-enone ^b (<u>103</u>)	7.25(5H); 7.38(5H)
7	6-hydroxyisophorone (<u>46</u>)	1.20(3H); 0.83(3H)
8	6-acetoxyisophorone (<u>45</u>)	1.10(3H); 0.98(3H)
9	6-tosyloxyisophorone (<u>44</u>)	1.08(3H); 0.97(3H)
10	6-chloroisophorone (<u>52</u>)	320 (benzene = 0) (6H)
11	6-pivoxyisophorone (<u>101</u>)	1.09(3H); 0.99(3H)
12	6-bromo-5,5-diphenylcyclohex-2-enone (<u>95</u>)	7.35 (partially resolved singlets) (10H)

(a) All peaks are singlets & are given in δ units downfield of tetramethylsilane ($\delta = 0$) except as noted. (b) See section N for synthesis of this compound.

substituent to be equivalent with respect to these substitutions.

A C-4 substituent can occupy either the axial or equatorial position. The equatorial position is almost eclipsed with the C-3 group, a hydrogen, or as in isophorone (31), a methyl group, whereas, the axial position has a single 1,3 interaction with the C-6 axial hydrogen. It appears that when a halogen is present on C-4 the former occupies the axial position. Oxygen substituents have a larger A-value⁸⁰ than bromine making the 1,3 interaction more severe. Therefore, the oxygen occupies an equatorial position.

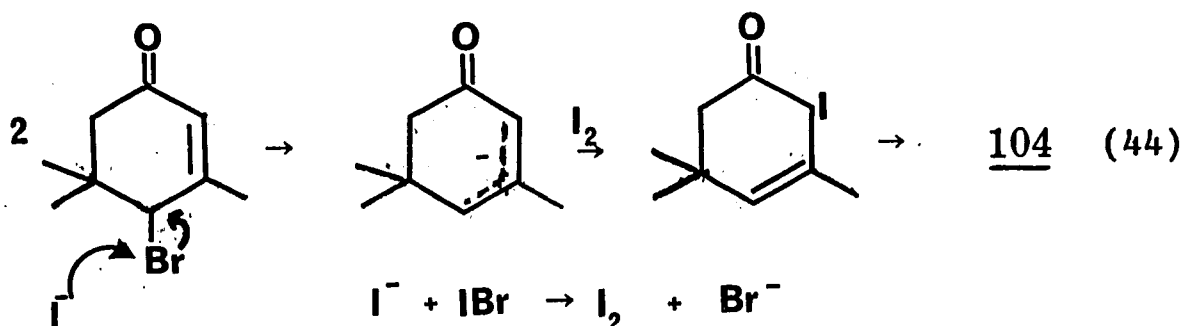
A C-6 electron withdrawing group in the equatorial position has a repulsive dipole-dipole interaction with the carbonyl group. The C-6 axial position has a single 1,3 interaction with the C-4 axial hydrogen atom. From the data, it appears that with a C-6 halogen substituent, the 1,3 interaction is worse than the dipole-dipole interaction. Therefore, this group occupies the equatorial position. The reason for the axial preference of a C-6 oxygen substituent is still unclear.

It should be noted that in 6-hydroxyisophorone (46) the greatest degree of non-equivalency is noted (22 Hz). We suggest that internal hydrogen bonding, from the more favorable C-6 axial position to the carbonyl function, makes the ring less flexible.

Section M. Miscellaneous Reactions and Results

Some of the experiments which were performed are tangential to the work discussed, but are worthy of reporting here.

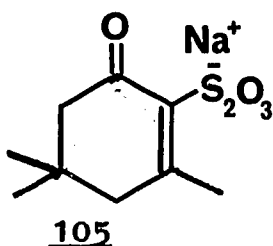
The reaction of 4-bromoisophorone (1) under standard S_N2 conditions, i.e. sodium iodide in acetone (1.3 equivalents of salt, at 45° for 40.5 hrs) yielded four products based on tlc analysis. Nmr analysis demonstrates that very little C-4 or C-6 substitution products are present due to the almost total lack of peaks between $\delta 3.0$ and $\delta 6.0$. There are numerous peaks in the alkyl and gem region. However, the possible presence of 2-iodoisophorone (104) cannot be overlooked. Besides an S_N2' type attack, 104 can result from an initial attack of the iodide anion on the C-4 bromide as shown in Eq 44:



Thus, there appears to be still another mechanism which is possible with certain nucleophiles to account for the formation of the C-2 substitution product.

The reaction of 1 with sodium thiosulfate pentahydrate in dioxane:water was attempted. After workup,

the organic layer contained only starting material. From the aqueous layer a white solid which was also soluble in chloroform was obtained. Nmr analysis of this product showed the presence of a singlet in the gem region, as well as three singlets in the alkyl region. No peaks were observed downfield of $\delta 3.0$. This spectrum is consistent with the C-2 Bunte salt 105.

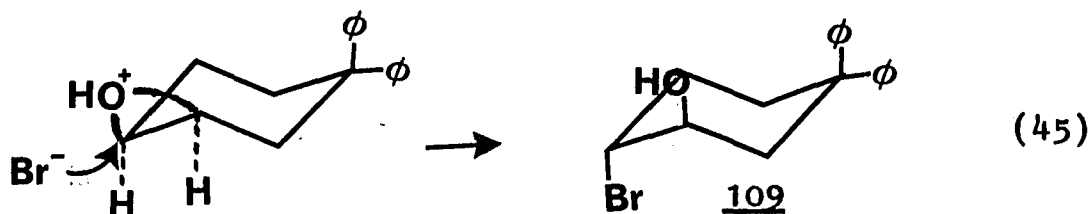


A reaction was observed when 1 was treated with thiourea in DMF, DMSO, or dioxane:water and with thiocyanate salts in DMSO. However, the products of these reactions were not fully analysed.

The reaction of 1 with triphenylphosphine, after workup yields a triphenylphosphonium salt. In addition, nmr analysis of the recovered product(s) closely resembles the spectrum of isophorone (31). It appears that reduction of 1 occurs. This reaction is probably a vinylog of the reduction of alpha-halo ketones with triphenylphosphine.⁸¹

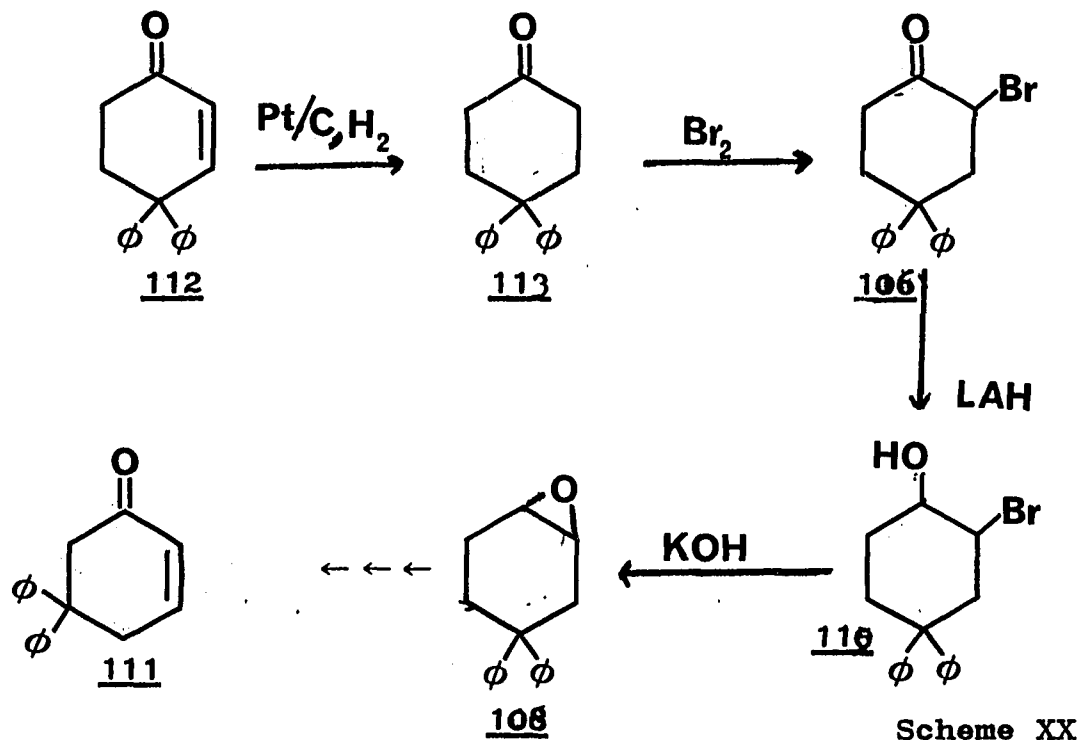
Section N. Synthesis of 4-Bromo-5,5-diphenylcyclohex-2-enone (102)

Bordwell⁸² worked on the transposition of a ketone in a 6-membered cyclic system. He converted 2-bromo-4,4-diphenylcyclohexanone (106) to 2-bromo-5,5-diphenylcyclohexanone (107) by the diaxial ring opening of 1,2-oxido-4,4-diphenylcyclohexanone (108)^{83a, b} as shown in Eq 45:



The bromide ion attacks from below the ring in the C-1 position for diaxial opening. Diaxial opening would also occur if the bromide ion attacks the C-2 position from above the ring to regenerate 2-bromo-4,4-diphenylcyclohexanol (110). However, this attack is precluded because of the 1,3 interaction between the bulky phenyl group and the entering bromide. Therefore, the bromide enters at C-1, and the net result, after oxidation is migration of the carbonyl function. This method would leave a bromide in the C-2 position, and elimination of hydrogen bromide would yield 5,5-diphenylcyclohex-2-enone (111). Scheme XX shows the synthesis

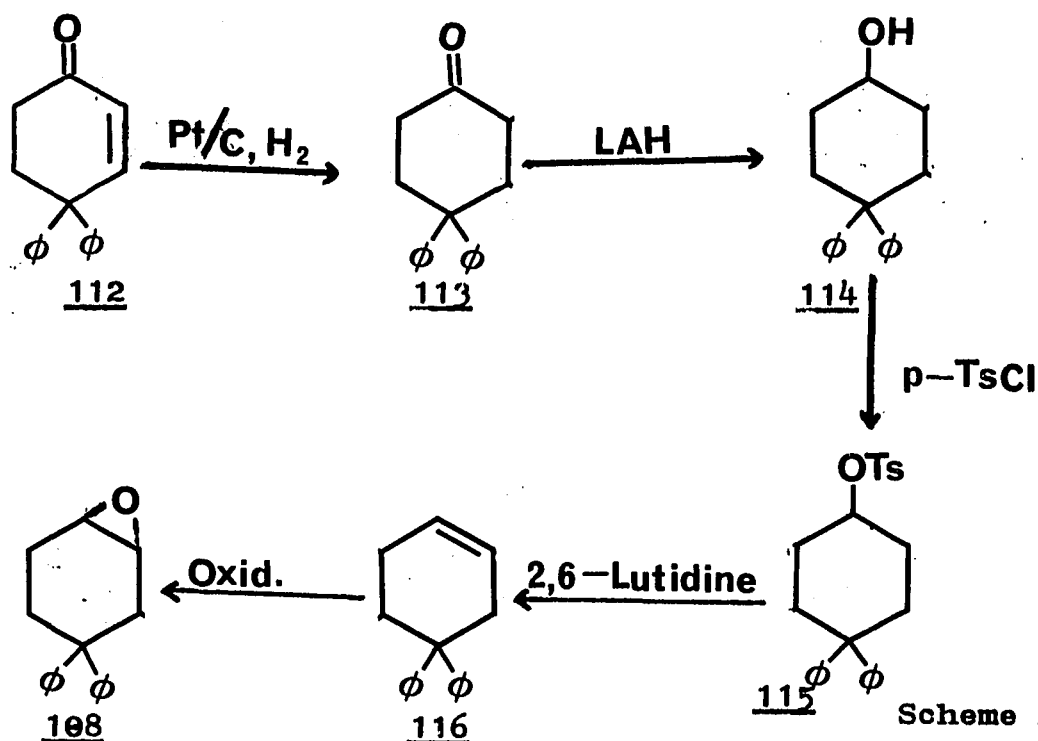
of 108 from 4,4-diphenylcyclohex-2-enone (112).



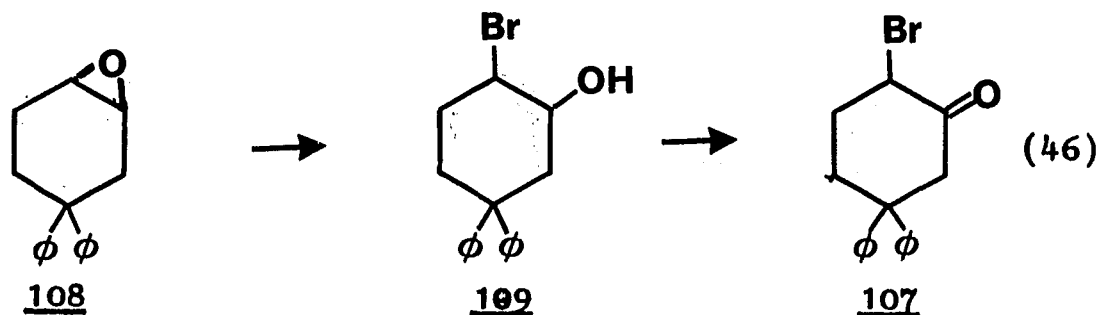
This synthesis suffers in that extreme care must be taken to prevent hydrogenolysis of the bromine at step 3. In fact, when this procedure was attempted, a mixture of products was obtained from this step. The following procedure (shown in scheme XXI) was designed to circumvent this problem.

An attempt to convert 112 to 4,4-diphenylcyclohexanol (114) using sodium borohydride in pyridine was made.^{84a, b} However, the ir spectrum of the resulting compound(s) showed the presence of both a carbonyl band and a hydroxy group.

Hydrogenation of 112 to give 4,4-diphenylcyclohexanone (113), was followed by reduction with lithium



aluminum hydride to give 114. The tosylate of this alcohol (115) was prepared by the reaction of 114 with p-toluene sulfonyl chloride in pyridine. The tosylate 115 was refluxed in 2,6-lutidine to yield 4,4-diphenylcyclohexene (116), which was then oxidized with m-perchlorobenzoic acid to give 108. The epoxide was then opened following Bordwell's procedure using concentrated hydrobromic acid. The resulting bromohydrin was oxidized using Jones' reagent to give 107 as shown in Eq 46:



The above synthesis was accomplished without much difficulty.

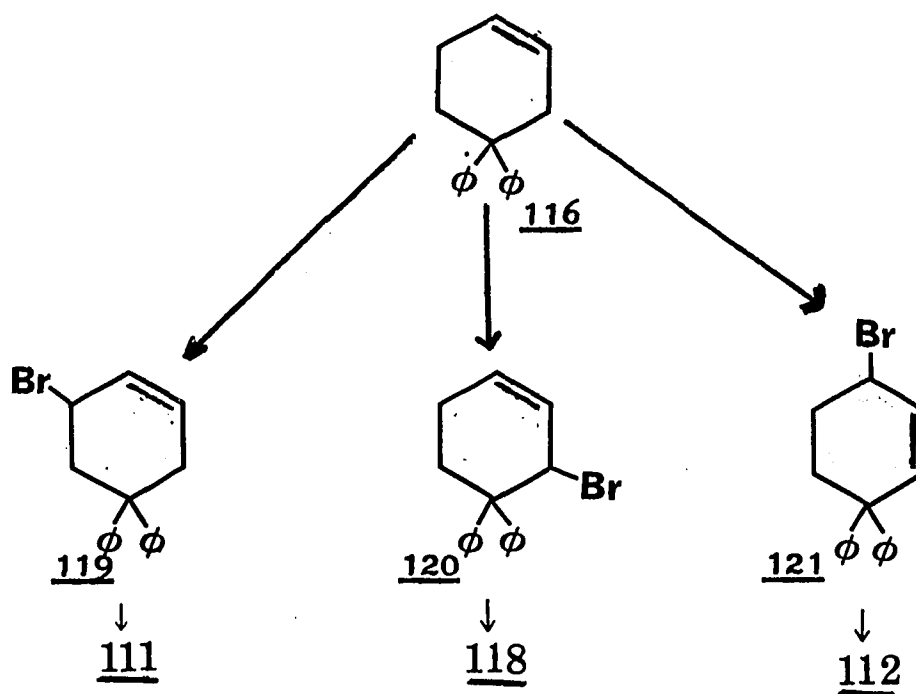
Seven methods were attempted for the conversion of 107 to 111: 1) By refluxing in 2,6-lutidine; it was hoped that the elimination would occur in the same manner that the tosylate 115 was converted to 116. 2) The compound 107 was converted to the α -tosyl ketone, 5,5-diphenyl-2-tosyloxycyclohexanone (117) with silver tosylate in acetonitrile. This tosylate was then refluxed in 2,6-lutidine as in method 1. 3) Compound 107 was refluxed in DMF in the presence of lithium bromide.⁸⁵ 4) Compound 107 was heated in HMPT for 19 hrs at 125-146°.⁸⁶ 5) Compound 107 was stirred with one equivalent of 1,5-diazobicyclo(5.4.0)-undec-5-ene (DBU) in DMF for 29 hrs at room temperature. 6) Compound 107 was treated with potassium t-butoxide in DMSO for 2 days at room temperature and then 45-50° for one day. 7) Compound 107 was refluxed in absolute ethanol with one equivalent of potassium hydroxide. All these methods were abortive.

The absence of any α,β -unsaturated ketone was shown by the fact that the ir spectrum of the resulting products contained a carbonyl band only above 1715 cm^{-1} . An α,β -unsaturated ketone would be expected to give a band between 1660 and 1690 cm^{-1} . The nmr spectra showed only minor peaks in the vinyl region. It is obvious that a simple elimination does not take place to a significant degree.

At this time it was learned that Dauben⁸⁷ reported the allylic oxidation of 116 with a chromium trioxide-pyridine complex to yield 67% 112 as well as 13% of the desired α,β -unsaturated ketone 111. It was reported only that the recovered oil had a mass of 248, an ir $\nu_{\max}$ of 1665 and 1559 cm^{-1} , and the following nmr spectrum: δ 7.15(10H, s), 6.75(1H, m), 5.9(1H, doublet of triplets), 3.1(4H, m). This procedure was not followed because the reported yield was low and it was felt that the product which Dauben isolated may have been contaminated with other products, i.e. 112 and/or 6,6-diphenyl-2-cyclohexenone (118).

Dauben's work, however, suggested the possibility that if 116 was treated with N-bromosuccinimide, allylic Bromination would occur in the C-6 position without migration of the double bond to give 3-bromo-5,5-diphenylcyclohexene (119). This mode of attack would probably be preferred to the unrearranged allylic attack of the bromine radical alpha to the gem-diphenyl groups to give 3-bromo-4,4-diphenylcyclohexene (120). Migration of the double bond followed by attack of the bromine radical would yield 6-bromo-3,3-diphenylcyclohexene (121) as shown in scheme XXII.

These bromo compounds could then be converted to α,β -unsaturated ketones by treatment with silver tosylate and then oxidation with DMSO in the presence of sodium bicarbonate.^{88a, b} The allylic oxidation of 116 resulted



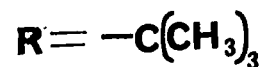
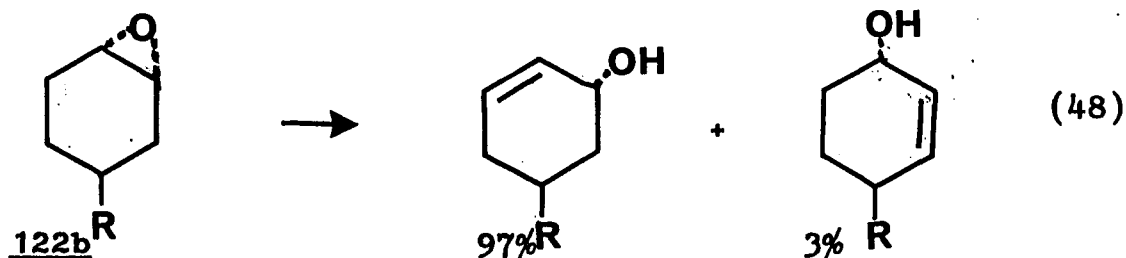
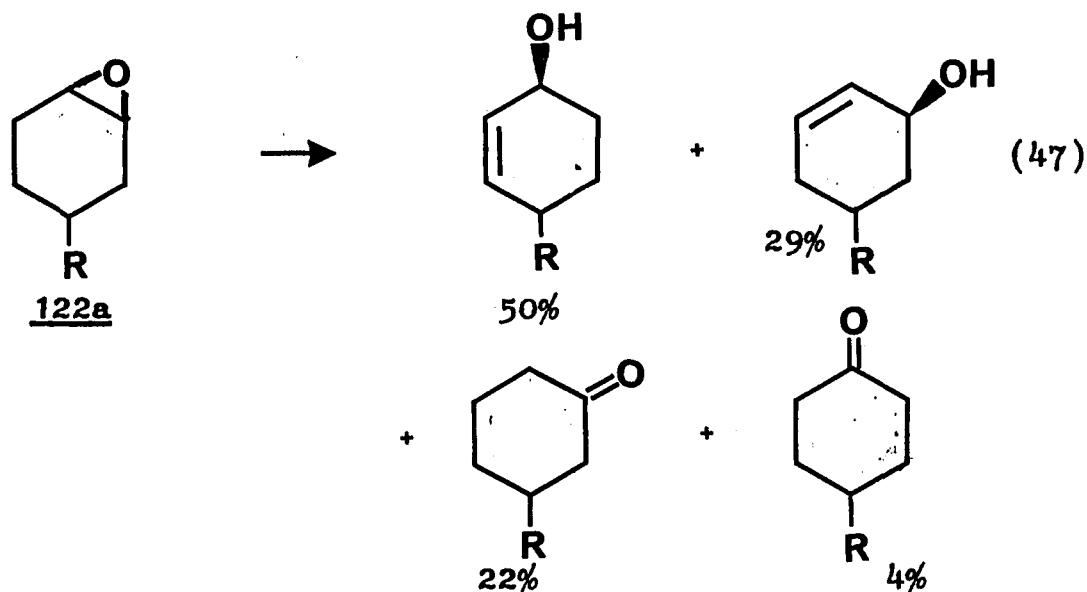
Scheme XXII

in the recovery of a brown oil, which contained new peaks in the nmr spectrum between $\delta 4.0$ and 5.0 the position expected for the allylic hydrogen on the carbon containing the halogen in 119, 120 and 121. Treatment of the crude oil by tlc analysis suggested that at least four compounds were present.

The ir spectrum showed that a carbonyl band was present at 1675 cm^{-1} suggesting the presence of an α,β -unsaturated ketone. A DNPH spray indicated that the only ketonic material present had an R_f similar to 112. This result indicates that rearrangement of the allylic radical is favored over initial attack of the bromine radical. Other methods of allylic oxidation of 116 were considered, i.e. lead tetraacetate, mercuric diacetate and selenium dioxide, but because of the numerous side

reactions and/or low yields reported these methods were rejected.

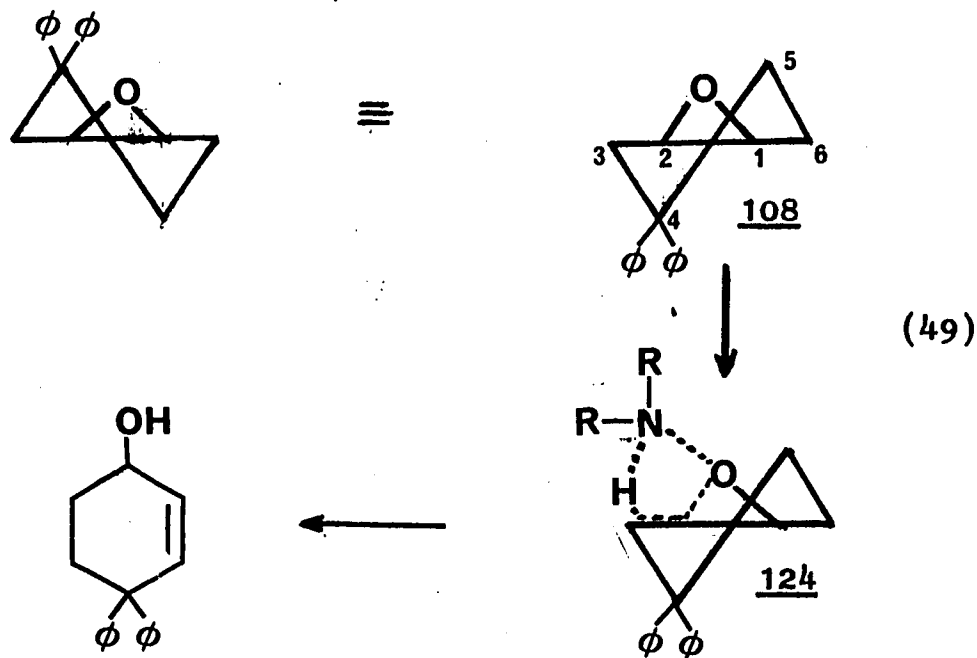
Thummel and Rickborn⁸⁹ reported the rearrangements of cis-(122a) and trans-(122b)-4-tertbutylcyclohexane epoxide to allylic alcohols using diethylamine as shown in Eqs 47 and 48:



It was felt that the treatment of 108 with this base could result in the formation of 5,5-diphenylcyclohex-2-en-1-ol (123) which could be easily oxidized

to give 111. However, when this reaction was attempted, the only product recovered, after a Jones oxidation was 112. This is exactly opposite to what Thummel and Rickborn observed with 122b.

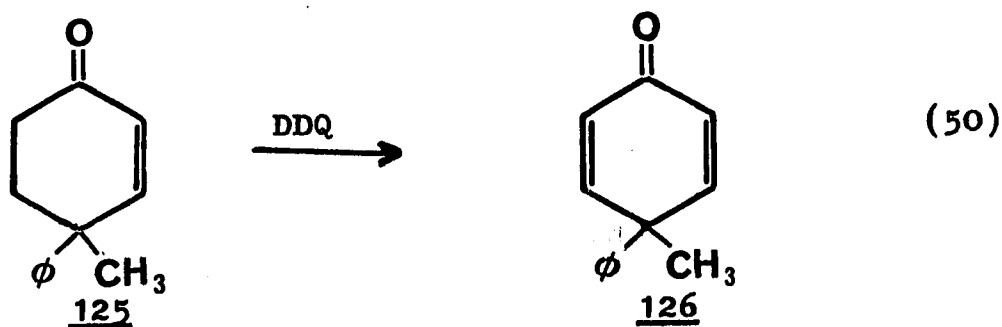
These results can be accounted for by considering the steric and inductive effects of the gem-diphenyl groups. A syn elimination is proved by the authors for this reaction. The transition state (124) for the reaction of 108 is the best one which can be postulated for this reaction because: 1) the most acidic hydrogen, in this case, the one alpha to the gem-diphenyl group, is being picked off by base and 2) the steric interaction between the base and the phenyl groups is minimized as shown in Eq 49:



When the phenyl groups are replaced by alkyl groups which have an electron donating effect, the C-6 protons are now the most acidic ones, and discounting steric effects, the 5-cyclohexanol isomer should be obtained, as Thummel demonstrated in the reaction of 122b. However, when steric factors become important, a greater mixture of products is expected because of the competing steric and inductive factors, as shown in the reaction of 122a. The cis isomer was also noted to react more slowly than the trans isomer.

An attempt was made to rearrange 108 to 123 using a potassium salt in the hope than an anti-elimination would give the desired compound because there would be much more complexing using a lithium salt rather than a potassium salt. However, the reaction of 108 with one equivalent of potassium ~~tert~~butoxide in DMSO yielded only starting material.

Zimmerman⁹⁰ reported the elimination of hydrogen in 4-methyl-4-phenylcyclohex-2-enone (125) in a 76% yield to give 4-methyl-4-phenylcyclohex-2,5-diene (126) using dichlorodicyanobenzoquinone (DDQ) as shown in Eq 50:



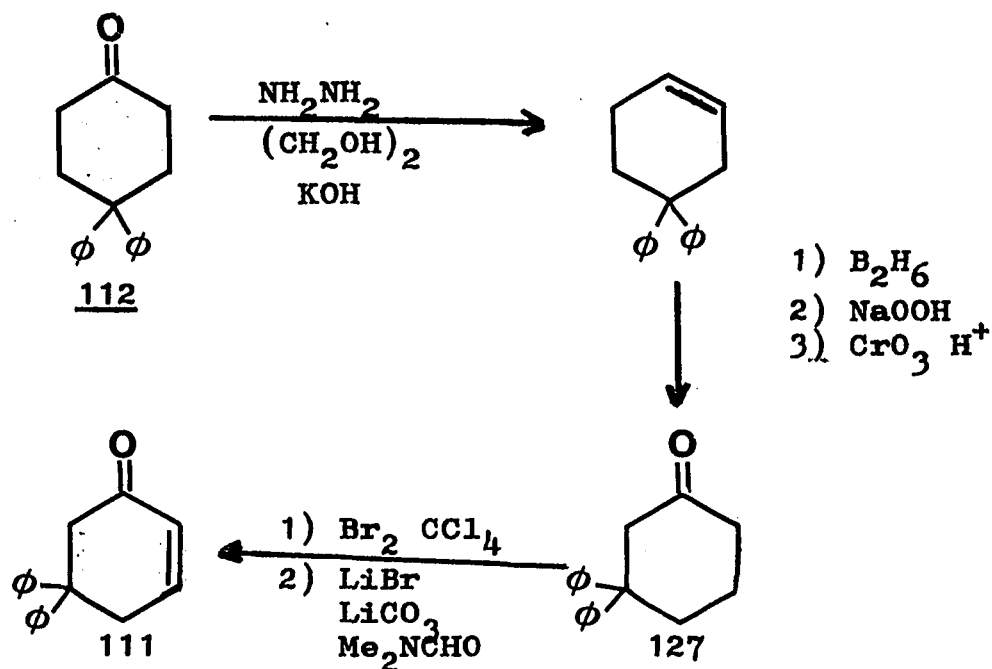
It was thought that 3,3-diphenylcyclohexanone (127) could undergo this type of reaction to give 111. The synthesis of 127 was accomplished by the reduction of 107 with zinc in acetic acid.^{97a, b}

The resulting ketone was treated with DDQ in dioxane. It was noted that the reaction did not give the desired product until the hydroquinone precipitates. Furthermore, the time required for the hydroquinone to precipitate is directly related to the concentration of the reactants. The more concentrated the mixture, the shorter amount of time it takes for the precipitation to occur. Only approximately 30% of the expected mass is recovered. The ir spectrum of the crude material shows the presence of an α, β -unsaturated ketone at approximately 1675 cm^{-1} with no indication of any other carbonyl compound.

The product was isolated using dry column chromatography. The first cut from the column resulted in the isolation of a colorless oil which solidified upon standing. Sublimation of this material resulted in the recovery of a white solid (mp $89-91^{\circ}$). Spectral analysis was consistent with 111. This solid was used as is for the final bromination.

Bromination of 111 was accomplished with N-bromosuccinimide in carbon tetrachloride to yield 4-bromo-5,5-diphenylcyclohex-2-enone (103) (mp $125.5-126^{\circ}$).

Well after the conclusion of the previously described investigations, Zimmerman reported the synthesis of 111 from 112 as shown in scheme XXIII.⁷⁸



Scheme XXIII

A Huang-Minlon Wolff-Kishner reduction of 112 yielded 116 in a 57% yield. Hydroboration of 116 and oxidation of the resulting mixture of compounds gave a 34% yield of 127 (mp 114-115°). Bromination of 127, followed by dehydrobromination, after chromatography, gave a 34% yield of 111 (mp 110.5-112°).

EXPERIMENTAL

Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York, N.Y. 11377. Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 Mass Spectrometer at 70 ev under direct sample inlet conditions and linear mass scan. Infrared spectra were determined using a Perkin-Elmer 137 spectrophotometer and a Beckman IR 20A spectrophotometer. Absorption maxima are expressed in reciprocal centimeters. Proton magnetic resonance spectra were determined using a Varian A-60 spectrometer and a Jeolco C-60HL spectrometer. Chemical shifts are expressed in ppm (δ) downfield from internal tetramethylsilane ($\delta = 0$).

ExperimentalSection A. PreparationsPreparation of 4-Bromoisophorone (1)⁵⁸

Freshly distilled isophorone (31)(56.0g, 0.406 mol), N-bromosuccinimide (80.0g, 0.45 mol) and 300 ml of methylene chloride were added to a 1-l 3-necked flask, equipped with a reflux condenser, drying tube and magnetic stirrer. This mixture was heated at reflux, while being irradiated by a long wave length uv light, until the solution became homogenous. An additional 15 min of heating resulted in the precipitation of succinimide. At this point, the reaction flask was rapidly cooled in an ice bath and the precipitated succinimide suction filtered. The resulting solution was concentrated to one-half the volume, under reduced pressure, at room temperature. The resulting precipitate was suction filtered and added to the previously recovered succinimide. The remaining solvent was evaporated under reduced pressure, leaving a viscous red oil which was diluted with 100 ml of petroleum ether (bp 30-60°) and stored in a freezer (4°) for 18 hrs. The resulting solid was suction filtered and recrystallized three times from petroleum ether (bp 30-60°) to yield 38.7g (44.1%) of a white solid (mp 49.5-50.2°) (lit⁵⁸ mp 48-49.5°); nmr(CDCl₃): δ 5.66(t, J=1 Hz, 1H, C=CH),

4.40(d, $J=1$ Hz, 1H, CHBr), 2.37(AB pattern, 2H, CH_2) 2.13 (d, $J=1$ Hz, 3H, $\text{C}=\text{C}-\text{CH}_3$), 1.30(s, 3H, CH_3), 1.22(s, 3H, CH_3); ir(CHCl_3 solution): 1675(s, ketone).

Preparation of 3,4,5-Trimethylphenol (2)

4-Bromoisophorone (1)(0.434g, 0.002 mol) was placed in a 10 ml flask fitted with a condenser and magnetic stirrer, along with 2 ml of 1,4-dioxane and 2 ml 6N hydrochloric acid. The reaction mixture was heated at reflux for 15 min. After the solution was cooled to room temperature, diethyl ether (30 ml) was added and the organic layer washed with 3-30 ml portions of water, 1-30 ml portion of 10% sodium bicarbonate, dried over MgSO_4 , concentrated at room temperature under reduced pressure to give 0.25g (92%) of a white solid which was identical in all respects to a known sample of 2. nmr(CDCl_3): δ 6.52 (broad, 2H, $\text{C}=\text{CH}$), 4.55(broad, 1H, OH), 2.22(s, 6H, 2 m- CH_3), 2.08(s, 3H, p- CH_3).

Preparation of 3,5,5-Trimethylcyclohex-3-enone (40)

4-Bromoisophorone (1)(32.5g, 0.15 mol) was added to 300 ml of 95% ethanol in a 500 ml flask fitted with a reflux condenser, drying tube and mechanical stirrer. Zinc dust (65g, 1 mol) was added and the reaction mixture was stirred rapidly for 14.5 hrs at $41-45^\circ$. The reaction mixture was suction filtered, and the solid washed with

100 ml of diethyl ether which was combined with the filtrate and concentrated under reduced pressure, at room temperature. The resulting solution was placed under a nitrogen atmosphere and stored in the freezer (4°). Fractional vacuum distillation gave: cut 1) bp $34-37^{\circ}$ (1.8 Torr), cut 2) bp $>40^{\circ}$ (2 Torr). A rough nmr analysis indicated that cut 1 contained the desired product contaminated with isophorone (31). There appeared to be a significant amount of liquid collected in the dry ice-acetone vacuum trap. Analysis of this material by nmr showed it to be mainly 40, contaminated with ethanol. Diethyl ether (200 ml) was added to the material collected from the trap and this solution was extracted with 3-200 ml portions of water, dried over MgSO_4 and concentrated at reduced pressure, at room temperature. The resulting liquid was added to the material from cut 1 to yield a total of 4.78g (23.1%) of 40 (lit bp⁵⁶ ca 70° at 10 Torr). nmr (CDCl_3): δ 5.42(broad, 1H, C=CH), 2.65(s, 2H, C=C-CH₂), 2.23(s, 2H, CH₂), 1.68(d, J=1 Hz, 3H, C=C-CH₃), 1.00(s, 6H, 2-CH₃); ir(neet): 1735(s, ketone).

Preparation of 3-Oxido-3,5,5-trimethylcyclohexanone (128)

3.5.5-Trimethylcyclohex-3-enone (40) (0.50g, 3.56 mmol) was dissolved in chloroform (10 ml) and placed in a 3-neck 25 ml flask fitted with a condenser, drying tube and magnetic stirrer. Solid m-perchlorobenzoic

acid (0.77g, 3.8 mmol) was added in small portions to the stirred solution over an eight min period. Chloroform (2 ml) was used to wash some solid from the side of the flask into the solution. The reaction mixture was stirred for 15 min and then allowed to stand for 70 min. The white solid, m-chlorobenzoic acid, which resulted was suction filtered. The filtrate was concentrated, under reduced pressure, at room temperature, yielding a white solid which was partially dissolved upon the addition of 10 ml petroleum ether (bp 30-60°). The resulting solid was suction filtered and a second crop of crystals was suction filtered from the solution. The solution was concentrated, under reduced pressure, at room temperature, to yield a colorless liquid which was used as is, immediately, for the following reaction. nmr (CDCl₃): δ 2.88(s, 1H, HC $\overset{\text{O}}{\parallel}$ C), 2.67(s, 1H, C $\overset{\text{O}}{\parallel}$ C-CH), 2.60(s, 1H, C $\overset{\text{O}}{\parallel}$ C-CH), 2.13(AB pattern, 2H, H₂C-C=O), 1.38(s, 3H, C $\overset{\text{O}}{\parallel}$ C-CH₃), 1.17(s, 3H, CH₃), 1.03(s, 3H, CH₃); ir (neet): 1740(s, ketone).

Preparation of 4-Hydroxyisopherone (41)

The 3-oxido-3,5,5-trimethylcyclohexanone (128) obtained from the above reaction was dissolved in 2 ml diethyl ether and 2 ml distilled water in a 10 ml flask fitted with a condenser, magnetic stirrer and drying tube. The pH of the solution was brought to between 11 and 12

by the dropwise addition of 10% sodium hydroxide. The mixture was stirred at this p_H , at room temperature, for 5.73 hrs and diethyl ether was added when necessary to maintain a constant volume. The layers were separated and the ethereal solution washed with 2-10 ml portions of a saturated sodium chloride solution, and dried over $MgSO_4$. The aqueous sodium hydroxide layer was extracted with 2-15 ml portions of a saturated NaCl solution, dried over $MgSO_4$ and added to the previously recovered ethereal solution. The combined ethereal solutions were concentrated, under reduced pressure at room temperature to yield 0.272g (48%) of 41. nmr ($CDCl_3$): δ 5.87(broad, 1H, C=CH), 4.37(broad, 1H, OH), 4.03(broad, 1H, HC-O), 2.32(AB pattern, 2H, H_2C-), 2.06(broad s, 3H, C=C- CH_3), 1.08(s, 3H, CH_3), 1.03(s, 3H, CH_3); ir(neet): 3400(m, hydroxy group), 1670(s, conjugated ketone).

Preparation of 4-Pivoxvisophorone (57) (Method A)

Crude 4-hydroxyisophorone (41)(1.0g, 6.6mmol) and 10 ml trifluoroacetic anhydride were placed in a 25 ml flask fitted with a condenser and magnetic stirrer. Pivalic acid (0.663g, 6.6 mmol) was added and the reaction flask stoppered lightly. After being stirred for 4 hrs at room temperature the reaction mixture was diluted with 20 ml of benzene. The organic layer was then extracted with 3-20ml portions of 10% sodium hydroxide,

2-20 ml portions of a saturated NaCl solution, dried over MgSO_4 , concentrated under reduced pressure, at room temperature to yield 0.928g of a yellow oil. This oil was divided into two parts and placed on two 20 x 20 cm thick layer silica gel chromatography plates, activated for ca. 15 min at 100° . After development in 1,2-dichloroethane three bands were observed. The silica gel between R_f 0.28-0.31 were scraped from the plates and the organic material extracted from the adsorbent by addition of 2-50 ml portions of acetone. The combined acetone solutions were concentrated under reduced pressure at room temperature to yield 0.472g (27.8%) of 57;

nmr (CDCl_3): δ 5.75(broad, 1H, C=CH), 5.48(broad, 1H, HCO), 2.33(s, 2H, CH_2), 1.87(t, $J=1$ Hz, 3H, C=C- CH_3), 1.27(s, 9H, $\text{C}(\text{CH}_3)_3$), 1.02(s, 6H, 2- CH_3); ir (neet): 1740(s, ester), 1680(s, conjugated ketone); mass spec: $m/e = 239(.074)$, 238(.47), 192(.15), 164(.56), 149(.15), 147(.16), 146(.16), 122(.14), 118(.12), 108(.73), 103(.24), 94(.95), 91(.16), 88(.11), 76(.14), 67(.14), 66(1.00, base peak), 64(.12), 50(.78), 48(.22).

A DNPH derivative of this liquid was prepared (mp $146-147^\circ$). Anal Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_6$: C, 57.40; H, 6.26; N, 13.38. Found: C, 57.81; H, 6.30; N, 13.19.

Preparation of 4-Pivoxylsophorone (57) (Method B)

4-Bromoisophorone (1)(15.19g, 0.07 mol), silver

pivalate (14.56g, 0.07 mol) and 56 ml of pivalic acid were placed in a 250 ml flask fitted with a condenser, magnetic stirrer and drying tube. The entire apparatus was covered with aluminum foil to prevent light-catalyzed decomposition of the silver salt. The reactants were heated at ca. 90-95° for 5 hrs-55 min. The precipitated silver bromide was suction filtered and triturated with 350 ml of diethyl ether. The ethereal layer was washed with 10% sodium bicarbonate until the washings were no longer acidic (1800 ml) and then dried over MgSO_4 , concentrated under reduced pressure at room temperature to yield 11.89g of an orange oil.

The crude product was prepared for wet column chromatography. A column, 3.4 cm diameter, using Davidson Silica Gel (ca. 900g), Activity Grade III, 100-200 mesh was used. A slurry of silica gel to a height of 114 cm, in benzene, including 1 cm of glass wool packing and 2 cm of sand below the absorbant was used. The entire quantity of orange oil was placed on the column using a minimal amount of benzene. Cuts of 100 ml were generally taken. The solvent system for cuts 1-15, benzene; cuts 16-20 2% ethyl acetate, 98% benzene; cuts 21-27, 5% ethyl acetate, 95% benzene; cuts 28-35, 8% ethyl acetate, 92% benzene; cuts 36-40, 10% ethyl acetate, 90% benzene; cuts 41-46, 33% ethyl acetate, 67% benzene; cuts 47-53, ethyl acetate. Cuts 1-33 were combined based on tlc analysis but were not

fully analyzed because they contained less than 10% of the weight of the material placed on the column. Based on rough nmr analysis cuts 34-40 were combined to yield 6.39g of an orange oil which appears to contain mainly, based on spectral analysis, 2-pivoxo-3,5,5-trimethyl-3-cyclohexenone (89). Cuts 43-50 were combined based on rough nmr analysis and were proved to be 57 by comparison with a sample obtained using method A. A light yellow oil was recovered (3.6g, 30.9%).

Isolation of 2-Pivoxo-3,5,5-trimethylcyclohex-3-enone (89)

From the above reaction of 4-bromoisophorone (1) with silver pivalate in pivalic acid one of the recovered products was 2-pivoxo-3,5,5-trimethylcyclohex-3-enone (89) as shown above. The spectral data for this compound are; nmr (CDCl_3): δ 5.56(broad, 2H, $\text{C}=\text{CH}$, HCO), 2.41(AB pattern, 2H, CH_2), 1.67(t, $J=1$ Hz, 3H, $\text{C}=\text{C}-\text{CH}_3$), 1.23(s, 9H, $\text{C}(\text{CH}_3)_3$), 1.15(s, 3H, CH_3), 0.99(s, 3H, CH_3); ir (neet): 1750(s, ester), 1740(s, shoulder of 1740, unconjugated ketone); mass spec: $m/e = 239(.02)$, $238(.15)$, $154(.051)$, $153(.38)$, $138(.34)$, $137(.065)$, $136(.30)$, $125(.080)$, $121(.073)$, $112(.25)$, $111(.076)$, $109(.15)$, $98(.14)$, $91(.053)$, $85(.46)$, $79(.094)$, $77(.69)$, $69(.60)$, $67(.12)$, $58(.16)$, $57(1.00, \text{base peak})$, $56(.065)$, $55(.16)$, $53(.087)$, $43(.13)$, $42(.062)$, $41(.41)$.

Preparation of 4-Acetoxyisophorone (42)⁵⁸

4-Bromoisophorone (1)(15.7g, .072 mol) and silver acetate (16.0g, 0.096 mol) were heated with 64 ml of glacial acetic acid in a 250 ml flask covered with aluminum foil and fitted with a magnetic stirrer, condenser, and drying tube, at 90° for 4.5 hrs. The cooled suspension was suction filtered and concentrated at reduced pressure with external heating (ca. 85°). The resulting oil was taken up in 150 ml of diethyl ether, washed with water (100 ml), 2-100 ml portions of 10% sodium bicarbonate, dried over MgSO₄, and concentrated under reduced pressure, at room temperature. This resulting oil was subjected to a vacuum fractional distillation. A yellow liquid (4.4g, 31.8%) was collected at 110-112° (1.8 Torr)(lit⁵⁸ bp 92-95°, 0.5 Torr).

Dry column chromatography was employed using 4.0g of this material for further purification. A 3.75 cm flat diameter nylon column was packed in the usual fashion with 400g of Woelm Alumina, Activity III, giving a column height of 42 cm. The crude product was placed on the column using 16g of alumina. The column was fully developed with benzene in a period of 25 min. Five cuts were taken, based on uv analysis: cut 1, 0-3 cm; cut 2, 3-8 cm; cut 3, 8-17.5 cm; cut 4, 17.5-30.5; cut 5, 30.5-42. The organic products were eluted from the alumina with 200 ml of acetone for each cut.

Concentration of the acetone solutions and then rough nmr analysis showed that cut 3 contained the purest sample of 42 (1.14g). Gas chromatography on a 10 ft, 20% OV-1 column, at 160° column temperature, retention time 1450-1913 sec, resulted in the recovery of a pure sample of 42. nmr (CDCl₃): δ5.92(t, J=1 Hz, 1H, C=CH), 5.52(d, J=1 Hz, 1H, HCO), 2.35(s, 2H, CH₂), 2.17(s, 3H, H₃C-C=O), 1.88(t, J=1 Hz, 3H, C=C-CH₃), 1.03(s, 3H, CH₃), 1.02(s, 3H, CH₃); ir (neet): 1748(s, ester), 1675(s, ketone).

Preparation of 2-Hydroxyisophorone (33)^{53b}

Isophorone (31)(27.6g, 0.2 mol) and 260 ml of 95% ethanol were placed in a 3-necked 1-l flask fitted with a magnetic stirrer, thermometer, dropping funnel, adapter, reflux condenser, and drying tube. Sodium hydroxide (3.0g) was added in 30 ml of water to the above stirred solution while the temperature of the reaction mixture was kept between 30-35°. Over a 20 min period, 30% hydrogen peroxide (33g, 0.3 mol) was added and after an additional hour of stirring, water (400 ml was added and the product was extracted with 3-100 ml portions of chloroform. The combined chloroform layers were washed with 200 ml water, dried over MgSO₄ and concentrated, under reduced pressure, at room temperature. The recovered isophorone oxide (32) was used without further purification for the next reaction (lit^{53b} bp 68-69°

(5 Torr), n_D^{20} 1.4539).

The previously synthesized isophorone oxide (32) was added to a cold (0-5°) stirred solution of concentrated hydrochloric acid in a 500 ml flask. Stirring was continued at this temperature for 3 hrs after which the reaction mixture was allowed to come to room temperature during an additional 3 hrs. After dilution with 200 ml of water, the product was suction filtered. Recrystallization from petroleum ether(bp 30-60°) yielded white solid needles mp 90-91° (10.1g, 38.2% yield for two steps) (lit^{53b} mp 91-92°); nmr (CDCl₃): δ6.25(s, 1H, OH), 2.32(s, 2H, H₂C-C=O), 2.23(broad, 2H, CH₂), 1.85(t, J=1 Hz, 3H, C=C-CH₃), 1.03(s, 6H, 2-CH₃); ir (KBr disc): 3400(s, hydroxy group), 1650(s, conjugated ketone).

Preparation of 2-Acetoxyisophorone (35)⁵⁴

In a 25 ml flask, 2-hydroxyisophorone (33)(2g, 0.013 mol) was added to 10 ml pyridine which had been dried over sodium hydroxide. After being cooled to 0-5°, 10 ml of acetic anhydride was added slowly and the solution placed in the freezer (4°) for 44 hrs. The cold solution was poured into 50g of ice and water and after acidification with 10% H₂SO₄, the product was extracted with 3-25 ml portions of 10% sodium bicarbonate, once with 50 ml of water and dried over MgSO₄. The ethereal layer was concentrated at reduced pressure at room

temperature to yield after recrystallization from petroleum ether (bp 30-60°) 1.74g (68.4%) of a white solid, mp 59-60° (lit⁵⁴ mp 60-62°). nmr (CDCl₃): δ2.30(broad, 4H, 2-CH₂), 2.18(s, 3H, O=C-CH₃), 1.80(s, 3H, C=C-CH₃), 0.90(s, 6H, 2-CH₃); ir (KBr disc): 1760(s, ester), 1685(s, conjugated ketone).

Preparation of 2-Pivoxylsophorone (58)

A general method for the esterification of hindered acids was employed.⁷⁰ 2-Hydroxylsophorone (33) (1.0g, 65 mmol) and pivalic acid (0.663g, 65 mmol) were added to 5 ml of trifluoroacetic anhydride in a 25 ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at room temperature for 3.5 hrs. Benzene (20 ml) was added and the benzene solution was washed with 3-15 ml portions of 10% sodium hydroxide, once with a 20 ml portion of water, dried over MgSO₄ and concentrated under reduced pressure at room temperature. The resulting solution was distilled under reduced pressure to give 0.527g (34.1%) of a colorless liquid 58, bp 113-115° (2.5 Torr); nmr (CDCl₃): δ2.33(s, 2H, CH₂), 2.27(s, 2H, CH₂), 1.78(s, 3H, C=C-CH₃), 1.30(s, 9H, C(CH₃)₃), 1.08(s, 6H, 2-CH₃); ir (neet): 1748(s, ester), 1685(s, conjugated ketone); mass spec: m/e = 239(.012), 238(.055) 154(.41), 153(1.00, base peak), 138(.47), 125(.20), 124(.17), 111(.36), 110(.13), 107(.055), 97(.42), 84(.13),

82(.19), 69(.38), 68(.24), 66(.088), 58(.083). mp
 DNPH deriv. 181-182.5°. Anal Calcd for $C_{20}H_{24}N_4O_6$:
 C, 57.40; H, 6.26; N, 13.38. Found: C, 57.68; H, 6.37;
 N, 13.29.

Isomerization of 2-Pivox-3,5,5-trimethylcyclohex-3-enone
(89) to 2-Pivoxisophorone (58). (Method A)

In a 25 ml flask fitted with a magnetic stirrer, condenser and drying tube, potassium hydroxide (0.149g, 2.1 mmol), 0.275g (1.17 mmol) 89 and 10 ml of 95% ethanol were stirred at room temperature for 50 min. The reaction mixture was then diluted with diethyl ether (100 ml) and the ethereal layer washed with 3-100 ml portions of water. The aqueous layer was back extracted with 1-75 ml portion of diethyl ether. The combined ethereal layers were washed with 1-50 ml portion of a saturated NaCl solution, dried over $MgSO_4$, and concentrated at room temperature under reduced pressure to yield 0.185g of a slightly yellow oil which was identical in all respects to 58.

Isomerization of 2-Pivox-3,5,5-trimethylcyclohex-3-enone
(89) to 2-Pivoxisophorone (58) (Method B)

Compound 89 (0.191g, 0.8 mmol), potassium pivalate (0.157g, 1.2 mmol) and 2 ml DMF were placed in a 20 ml flask fitted with a magnetic stirrer. The flask was lightly stoppered and the reaction mixture stirred for

40.5 hrs at ca. 45° . Diethyl ether (15 ml) was added to the reaction mixture and the organic layer was washed with 2-25 ml portions of water, 1 portion (20 ml) of 10% sodium bicarbonate solution, once (20 ml) with water, dried over MgSO_4 and concentrated at room temperature under reduced pressure to give 0.143g of a slightly yellow oil whose spectral properties matched those of 58.

Isomerization of 2-Pivoxo-3,5,5-trimethylcyclohex-3-enone (89) to 2-Pivoxoisophorone (58) (Method C)

Into a 20 ml flask fitted with a magnetic stirrer, 89 (0.157g, 0.65 mmol), potassium pivalate (0.118g, 0.845 mmol) and 1g of pivalic acid were added. The reaction mixture was stirred in the corked flask for 40.5 hrs at $45 \pm 2^{\circ}$. Diethyl ether (20 ml) was added and the ethereal layer was washed with 1-20 ml portion of water, 2-20 ml portions of 10% sodium bicarbonate, 1-20 ml portion of a saturated sodium chloride solution, dried over MgSO_4 and concentrated under reduced pressure at room temperature to yield 0.108g of a slightly yellow oil whose spectral properties showed it to be 58.

Preparation of 6-Acetoxoisophorone (45)^{60a}

Freshly distilled isophorone (31) (138g, 1 mol), 600 ml glacial acetic acid, and 400 ml acetic anhydride were added to a 2-l 3-necked flask fitted with a magnetic

stirrer, condenser, drying tube and thermometer. The reaction flask was heated to 60° and lead dioxide (700g, 1.2 mol) was added in small portions over a 190 min period maintaining the reaction temperature at $75 \pm 3^{\circ}$. The stirred reaction mixture was heated and maintained at ca. 75° for an additional 4 hrs. The solvent was concentrated, under reduced pressure, with external heating (ca. 85°) until a solid remained. Warm water (1.2l) was added followed by 1.2l of diethyl ether. The aqueous layer was extracted again with 1.3l of diethyl ether. The combined ethereal layers were washed with 1l water, 1l 10% sodium bicarbonate, 1l water, dried over MgSO_4 , and concentrated, under reduced pressure at room temperature. The resulting oil was diluted with petroleum ether (350 ml, bp $30-60^{\circ}$) and placed in the freezer (4°) for ca. 40 hrs. The resulting precipitate was suction filtered and recrystallized from petroleum ether (bp $30-60^{\circ}$) to give 29.8g (mp $75-76.5^{\circ}$, yield 15.2%) of a white solid (lit^{60a} mp $77-77.5^{\circ}$); nmr (CDCl_3): δ 5.83(broad, 1H, C=CH), 5.17(s, 1H, HCO), 2.37(AB pattern, 2H, CH_2), 2.17(s, 3H, C=C- CH_3), 1.97(s, 3H, $\text{H}_3\text{C}-\text{C}=\text{O}$), 1.10(s, 3H, CH_3), 0.98(s, 3H, CH_3).

Preparation of 6-Hydroxyisophorone (46)^{60a}

6-Acetoxyisophorone (45) (22g, 0.112 mol) was placed in a 100 ml flask along with 90 ml 6N hydrochloric

acid and stirred at room temperature for 18 hrs. The acidic solution was neutralized with 10% sodium bicarbonate and then extracted with 1l of diethyl ether. The organic layer was dried over MgSO_4 and concentrated under reduced pressure, at room temperature. Hexane was added and the solution placed in the freezer (4°). The precipitate was suction filtered to yield 14.31g (93%) of a slightly yellow solid, mp $43-45^\circ$ (lit^{60a} mp $45-46^\circ$); nmr (CDCl_3): δ 5.92(broad, 1H, C=CH), 3.97(s, 1H, HCO), 3.72(broad, 1H, OH), 2.30(AB pattern, 2H, CH_2), 1.97(s, 3H, C=C- CH_3), 1.20(s, 3H, CH_3), 0.83(s, 3H, CH_3).

Preparation of 6-Tosyloxyisophorone (44)^{60a}

6-Hydroxyisophorone (46)(12.3g, 0.063 mol) was dissolved in 10 ml of cold pyridine and placed in a 125 ml flask. p-Toluenesulfonyl chloride (11.5g, 0.060 mol) in 25 ml cold pyridine was added. The reaction mixture was stoppered in the freezer (4°) for 72 hrs. Water (200 ml) was added and then the aqueous solution was extracted with 3-100 ml portions of diethyl ether. The combined ethereal layers were washed with 2-75 ml portions of 6N hydrochloric acid, 3-100 ml portions of water, dried over MgSO_4 and concentrated, at reduced pressure at room temperature. The resulting solid was recrystallized from acetone to yield 13.5g (75%) of a white solid, mp $133-135^\circ$ (lit^{60a} mp 133dec.); nmr (CDCl_3): δ 7.53(AB

pattern, 4H, ArH), 5.75(broad, 1H, C=CH), 4.02(s, 1H, HCO), 2.40(s, 3H, ArCH₃), 2.40(s, 1H, CH of CH₂), 2.30(s, 1H, CH of CH₂), 1.92(s, 3H, C=C-CH₃), 1.08(s, 3H, CH₃), 0.97(s, 3H, CH₃).

Preparation of 6-Pivoxvisophorone (101)

To a 100 ml flask fitted with a magnetic stirrer, condenser and drying tube were added 1.54g (0.01 mol) of 6-hydroxyisophorone (46) and 3.60g (0.03 mol) pivaloyl chloride. Pyridine (5 drops) was added and this mixture was then stirred and heated in a pre-heated oil bath at 125° for 2.5 hrs. The cooled solution was slowly poured unto 100g of ice-water. The organic products were extracted with 3-100 ml portions of diethyl ether. The ethereal layer was washed with 2-150 ml portions of 10% sodium bicarbonate, 2-100 ml portions of a saturated salt solution, dried over MgSO₄ and concentrated under reduced pressure, at room temperature, to yield 2.13g of a brown oil. The oil was vacuum distilled and the product collected between 123-132° (3.0 to 3.2 Torr) was shown to be mainly the desired 101. This material was diluted with 20 ml of diethyl ether and washed with 3-15 ml portions of 10% sodium hydroxide, 2-20 ml portions of water, dried over MgSO₄ and concentrated at room temperature, under reduced pressure to yield 1.80g (76.2%) of a colorless liquid; nmr (CDCl₃): δ5.86(broad, 1H,

$\text{C}=\text{CH}$), 5.17(s, 1H, HCO), 2.35(AB pattern, 2H, CH_2),
 1.97(s, 3H, $\text{C}=\text{C}-\text{CH}_3$), 1.28(s, 9H, $\text{C}(\text{CH}_3)_3$), 1.08(s,
 3H, CH_3), 1.00(s, 3H, CH_3); ir (neet): 1740(s, ester),
 1670(s, conjugated ketone); mass spec: $m/e = 239(.051)$
 238(.20), 220(.20), 156(.24), 154(.14), 153(.24), 137(.29),
 136(1.00, base peak), 135(.15), 125(.43), 123(.13),
 121(.53), 109(.18), 107(.23), 90(.30), 85(.91), 83(.19),
 82(.61), 79(.20), 77(.21), 72(.39), 71(.26), 69(.47),
 67(.21), 65(.11), 58(.16), 57(.94), 56(.17), 55(.41),
 53(.24), 44(.21), 43(.24), 41(.57), 39(.25). A DNPH
 derivative of this liquid was prepared (mp 158-160°d);
Anal Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_6$: C, 57.40; H, 6.26.
 Found: C, 57.11; H, 6.26.

Preparation of 3,4,5-Trimethylphenyl Acetate (61)

3,4,5-Trimethylphenol (2)(0.2 g, 1.47 mmol), 1 ml
 pyridine and 1 ml acetic anhydride were placed in a 25 ml
 flask. The stoppered flask was placed in the freezer (4°)
 for about four days. The solution was poured onto 20 ml
 of ice and water. The organic product was extracted
 with 2-25 ml portions of diethyl ether. The ethereal
 solution was washed with 2-25 ml portions of 4N hydro-
 chloric acid, 1-20 ml portion of a saturated sodium chloride
 solution, dried over MgSO_4 , and concentrated at room
 temperature to yield 0.19g (72%) of a slightly brown
 solid which was recrystallized from hexane to yield a

white solid mp 56.5-57.5°; nmr (CDCl₃): δ6.70(s, 2H, ArH), 2.20(s, 6H, 2-m CH₃), 2.17(s, 3H, H₃C-C=O), 2.07(s, 3H, p-CH₃).

Preparation of 3,4,5-Trimethylphenyl Pivalate (62)

3,4,5-Trimethylphenol (2)(2.72g, 0.02 mol) was placed in a 50 ml flask, fitted with a magnetic stirrer, along with pivalic acid (2.04g, 0.02 mol) and trifluoroacetic anhydride (15 ml). After the solution was stirred at room temperature for 3.5 hrs, benzene (40 ml) was added and the organic layer washed with 3x50 ml portions of 10% sodium hydroxide, 1-50 ml portion of water, dried over MgSO₄, and concentrated at room temperature under reduced pressure. The resulting viscous oil solidified after standing at room temperature for ca. two weeks. After recrystallization twice from ethanol 2.5g (53%) of a white solid, mp 41.5-42°, was recovered. nmr (CDCl₃): δ6.58(s, 2H, ArH), 2.13(s, 6H, 2m-CH₃), 2.00(s, 3H, p-CH₃), 1.27(s, 9H, C(CH₃)₃); ir (KBr disc): 1745(s, ester); mass spec: m/e = 221(.03), 220(.17), 137(.26), 136(.92), 135(.50), 120(.79), 118(.10), 107(.16), 105(.27), 103(.19), 93(.29), 92(.84), 86(.22), 80(.42), 79(.15), 78(.41), 77(.13), 68(.21), 67(.10), 66(.39), 64(.16), 59(.17), 58(1.00, base peak), 57(.14), 56(.27), 54(.26); Anal Calcd for C₁₄H₂₀O₂: C, 76.32; H, 9.15; Found: C, 76.75; H, 8.82.

Preparation of 2-Bromo-3,4,5-trimethylphenylphenol (59)

3,4,5-Trimethylphenol (2)(0.95g, 7.5 mmol) was dissolved in carbon disulfide (15 ml) and introduced into a 50 ml flask fitted with a magnetic stirrer, thermometer, dropping funnel, condenser and drying tube. The reaction mixture was cooled to below 3° by means of an external ice-salt bath. Bromine (1.2g, 7.5 mmol) was dissolved in 12 ml of carbon disulfide and added dropwise, to the reaction mixture over a 55 min period. Stirring was continued at 0° for 60 min at which time the solution was allowed to come to room temperature. After being stirred for a period of 3.5 hrs, the light brown solution was concentrated at room temperature, under reduced pressure to yield a brownish solid (1.48g, 92%), mp 40-41°. A sample of this material was sublimed and then recrystallized from pentane twice at -78° to yield a white solid, mp 45.2-46.0°; nmr (CDCl₃): δ6.70(s, 1H, ArH), 5.38(broad, 1H, OH), 2.32(s, 3H, CH₃), 2.17(s, 3H, CH₃), 2.10(s, 3H, CH₃); ir (KBr disc): 3370(s, hydroxy group); mass spec: m/e = 217(.11), 216(.87), 215(.38), 214(.86), 213(.25), 201(.60), 199(.60), 136(.18), 135(1.00, base peak), 115(.11), 107(.11), 106(.15), 105(.22), 103(.13), 92(.16), 91(.59), 79(.32), 78(.16), 77(.45), 67(.20), 66(.20), 65(.43), 63(.27), 53(.21), 52(.18), 51(.47), 50(.17). Anal Calcd for C₉H₁₁BrO: C, 50.26; H, 5.16; Found: C, 50.17; H, 5.17

Preparation of 3-Ethoxy-5,5-dimethylcyclohex-2-enone (129)⁹²

Into a 1-l flask fitted with a Dean-Stark trap, condenser, drying tube and magnetic stirrer, were placed dimedone (154g, 1.1 mol), absolute ethanol (100 ml), p-toluenesulfonic acid monohydrate (2g) and benzene (600 ml). The reaction mixture was stirred at reflux until no more water separated (20 hrs). The solvent was evaporated at atmospheric pressure. The resulting oil was distilled, bp 84-90° (1.2 Torr). The distillate solidified in the collection flask affording 165.5g (89.7%) of a white solid, mp 57-61° which was used as is for the following reaction. nmr (CDCl₃): δ 5.22(s, 1H, C=CH), 3.83(q, J=7 Hz, 2H, OCH₂), 2.23(s, 2H, CH₂), 2.12(s, 2H, CH₂), 1.33(t, J=7 Hz, 3H, CH₂CH₃), 1.05(s, 6H, 2-CH₃).

Preparation of 5,5-Dimethyl-3-phenylcyclohex-2-enone (130)⁷⁷

Bromobenzene (157g, 1.0 mol) was dissolved in 500 ml of anhydrous diethyl ether and added dropwise, over a 100 min period, to magnesium turnings (24g, 1.0 mol) in 100 ml of anhydrous diethyl ether contained in a 2-l flask fitted with a reflux condenser, drying tube, dropping funnel and magnetic stirrer. The reaction mixture was stirred at reflux for an additional 40 min. 3-Ethoxy-5,5-dimethylcyclohex-2-enone (129) (84g, 0.5 mol) was dissolved in diethyl ether (400 ml) and added dropwise to

the reaction mixture over a 200 min period. The reaction mixture was stirred at room temperature for an additional 120 min. 6N Hydrochloric acid was then added dropwise to the cooled solution. The layers were separated and the aqueous layer extracted with 2-150 ml portions of diethyl ether. The combined ethereal layers were washed with 300 ml of 10% sodium bicarbonate, 300 ml of water, dried over MgSO_4 and concentrated at reduced pressure, at room temperature. The resulting solid was recrystallized from petroleum ether (bp 30-60°) to yield 45.79g (45.7%) of a white solid; mp 51-53.4° (lit⁹³ mp 53.8-54.8°); nmr (CDCl_3): δ 7.32(m, 5H, ArH), 6.32(t, J=1 Hz, 1H, C=CH), 2.55(d, J=1 Hz, 2H, C=C-CH₂), 2.25(s, 2H, H₂C-C=O), 1.07(s, 6H, 2-CH₃); ir (KBr disc): 1660(s, conjugated ketone).

Preparation of 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84)⁷⁷

5,5-Dimethyl-3-phenylcyclohex-2-enone (130)(1.34g, 6.7 mmol), N-bromosuccinimide (1.2g, 6.7 mmol), a trace of benzoyl peroxide, and 20 ml of carbon tetrachloride were introduced into a 50 ml flask fitted with a magnetic stirrer, condenser and drying tube. The reaction mixture irradiated with a long wave length uv lamp was stirred at reflux for a total of 21.75 hrs. The reaction flask was cooled in an ice-bath and the solid present suction

filtered. The mother liquor was concentrated, at room temperature, under reduced pressure. The resulting solid was recrystallized from pentane to give 1.04g (56%) of a white solid, mp 83-85^o; nmr (CDCl₃): δ7.50(m, 5H, ArH), 6.32(s, 1H, C=CH), 4.92(d, J=1 Hz, HCB₂), 2.50 (AB pattern, 2H, CH₂), 1.33(s, 3H, CH₃), 1.22(s, 3H, CH₃); ir (KBr disc): 1655(s, conjugated ketone); Anal Calcd for C₁₄H₁₅BrO: C, 56.98; H, 5.12; Br, 28.67; Found: C, 56.15; H, 5.22; Br, 28.11.

Preparation of 3,4-Dimethyl-5-phenylphenol (97)

4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) (2.0g, 7.15 mmol) was added to 15 ml dioxane and 15 ml 6N hydrochloric acid in a 50 ml flask fitted with a condenser and magnetic stirrer. The reaction mixture was heated at reflux for 30 min and then cooled to room temperature and diluted with 20 ml of diethyl ether. The organic layer was then washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate, 1-20 ml portion of water, dried over MgSO₄ and concentrated with external heating (ca. 85^o) at reduced pressure to yield 1.24g(81.3%) of a slightly brownish solid. The recovered solid was recrystallized twice from petroleum ether (bp 30-60^o) and then twice from hexane to yield a white solid, mp 107.9-108.2^o; nmr (CDCl₃): δ7.30(s, 5H, Ph), 6.60(m, 2H, ArH), 4.92(s,

1H, OH), 2.28(s, 3H, CH₃), 2.07(s, 3H, CH₃); ir (CHCl₃ solution): 3420(s, sharp, hydroxy group), 3320(s, broad, hydroxy group); mass spec: m/e = 199(.13), 198(.89), 197(.32), 191(.06), 198(.09), 183(.33), 165(.09), 153(.09), 100(.14), 99(.09), 98(.20), 92(.24), 90(.12), 81(.27), 69(.12), 68(.14), 57(.50), 36(.21), 44(.14), 43(1.00, base peak). Anal Calcd for C₁₄H₁₄O: C, 84.81; H, 7.12; Found: C, 84.12; H, 7.05.

Isolation of 2,3-Dimethyl-5-phenylphenol (96)

In a stoppered 100 ml flask fitted with a magnetic stirrer, 4-bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) (2.76g, 0.01 mol), triethylamine (1.31g, 0.013 mol), and 50 ml of dioxane:water (1:1 v/v) were stirred at 45 to 47° for 40.5 hrs. The resulting solution was diluted with 150 ml of diethyl ether and the ethereal layer was extracted with 3-100 ml portions of water, dried over MgSO₄, and concentrated at room temperature under reduced pressure. A brown oil (1.26g) was recovered. Preparative thick layer chromatography was performed on this oil using three silica gel plates 250 microns thick, developed in benzene. The sample with R_f 0.65 to 0.43 was eluted from the adsorbant with acetone. After concentration, under reduced pressure at room temperature, a white solid, mp 58-65° was recovered (0.312g, 16%). This solid was thrice recrystallized from hexane to yield a white solid, mp

68.5-69.2[°]; nmr (CDCl₃): δ 7.32(m, 5H, Ph), 7.00(broad, 1H, ArH), 6.85(broad, 1H, ArH), 6.20(broad, 1H, OH), 2.28(s, 9H, CH₃), 2.18(s, 3H, CH₃); ir (CHCl₃ solution): 3400(s, hydroxy group); mass spec: m/e = 199(.17), 198(1.00, base peak), 197(.18), 184(.05), 183(.33), 181(.05), 165(.10), 155(.07), 153(.07), 152(.08), 128(.06), 115(.089), 99(.06), 91(.08), 79(.068), 77(0.78), 76(.069), 51(.073), 39(.066); Anal Calcd for C₁₄H₁₄O: C, 84.81; H, 7.12; Found: C, 84.99; H, 7.18.

Preparation of 5,5-Dimethyl-2-hydroxy-3-phenylcyclohex-2-enone (131)

To a solution of 5,5-dimethyl-3-phenylcyclohex-2-enone (130)(7.5g, 0.0375 mol) in 45.5 ml of 95% alcohol in a 250 ml 3 necked flask fitted with a condenser, drying tube, thermometer, magnetic stirrer and dropping funnel, sodium hydroxide (0.561g, 0.014 mol) in 5.6 ml water was added dropwise over a 10 min period. Hydrogen peroxide (30%)(6.25g, 0.056 mol) was added dropwise over a 20 min period, to the stirred solution. Stirring was continued for an additional 120 min while maintaining the temperature below 35[°]. The reaction mixture was diluted with water (150 ml) and extracted with three 100 ml portions of chloroform. The organic layer was dried over MgSO₄ and concentrated at room temperature under reduced pressure.

Analysis by nmr showed only approximately 42% reaction had taken place. Therefore, this resulting oil was redissolved in 35 ml 95% alcohol and placed in the same apparatus. Sodium hydroxide (0.4g, 0.001 mol) in 4 ml water was added as before and hydrogen peroxide (30%) (4.7g, 0.0415 mol) was added dropwise over a 20 min period. An additional 3g portion of 30% hydrogen peroxide was added, over a 10 min period after an additional 1 hr of stirring. The reaction mixture was stirred for an additional 26.5 hrs at which time it was diluted with 100 ml of water and extracted with three 75 ml portions of methylene chloride. The combined organic layers were washed with 2-75 ml portions of water, dried over MgSO_4 , and concentrated at room temperature to yield a white solid (5.9g) which was shown by rough nmr analysis to be crude 5,5-dimethyl-2-oxido-3-phenylcyclohexanone, mp 49-55° (73% if pure) which was used as is, immediately, for the following reaction.

The entire crude sample of epoxide from above was added to a solution of 100 ml of concentrated hydrochloric acid, cooled to 0° which was contained in a 150 ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at 0° for 3 hrs and then was allowed to warm to room temperature over an additional 3 hr period. The resulting solid was suction filtered to yield 2g (25.8%) of 131. The recovered solid was recrystallized four times

from petroleum ether (bp 30-60°) to yield a white solid, mp 92-92.5°; nmr (CDCl₃): δ7.62(m, 5H, Ph), 6.72(s, 1H, OH), 2.68(s, 2H, CH₂), 2.48(s, 2H, CH₂), 1.17(s, 6H, 2-CH₃); ir (CHCl₃ solution): 3400(s, hydroxy), 1660(s, conjugated ketone); mass spec: m/e = 217(.20), 216(.64), 215(.29), 188(.25), 173(.24), 170(.22), 145(.24), 144(.32), 143(.13), 141(.14), 133(.14), 132(.47), 131(.30), 104(.88), 103(.60), 102(.18), 91(.40), 78(.46), 77(1.00, base peak), 51(.42), 43(.50), 41(.58), 39(.50).

Anal Calcd for C₁₄H₁₈O₂: C, 77.75; H, 7.55; Found: C, 77.73; H, 7.49.

Preparation of 5,5-Dimethyl-3-phenyl-2-pivoxycyclohex-2-enone (94)

4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone(84) (0.556g, 2.0 mmol), potassium pivalate (0.364g, 2.6 mmol) and DMF (5 ml) were added to a 25 ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at 45° for approximately 13 days. The reaction mixture was then dissolved in diethyl ether (20 ml) and washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate solution, 1-20 ml portion of water, dried over MgSO₄ and concentrated under reduced pressure at room temperature to yield a slightly yellow solid (0.450g, 75%) of crude 94. The solid was recrystallized four times from petroleum ether (bp 30-60°) to yield a

white solid, mp 112-113°; nmr (CDCl₃): δ 7.34(s, 5H, Ph), 2.69(s, 2H, CH₂), 2.44(s, 2H, CH₂), 1.18(s, 3H, CH₃), 1.13(s, 9H, C(CH₃)₃), 1.11(s, 3H, CH₃); ir (CCl₄ solution): 1755(s, ester), 1690(s, conjugated ketone); mass spec: m/e = 301(.18), 300(.76), 286(.10), 285(.05), 232(.052), 218(.061), 217(.49), 216(1.00, base peak), 215(.30), 188(.14), 160(.12), 145(.05), 132(.07), 103(.05); Anal Calcd for C₁₉H₂₄O₃: C, 75.97; H, 8.05; Found: C, 76.26; H, 8.33.

Preparation of Sodium Pivalate

Pivalic acid (21.0g, 0.26 mol) was added to 20 ml of water in a 250 ml flask fitted with a magnetic stirrer. The stirred mixture was made basic to a phenolphthalein end point using a 10% sodium hydroxide solution. After gravity filtration of the solution, the solvent was evaporated, under reduced pressure using external heating (ca. 85°) until a white solid remained. The solid was washed with 200 ml of acetone, and 100 ml of diethyl ether, air dried for 4 hrs and then placed under high vacuum (1 Torr) at room temperature for 18 hrs. A white solid (27.4g, 87.5%) was recovered.

Preparation of Potassium Pivalate

This compound was prepared from potassium hydroxide in a similar manner to that of the sodium salt.

Preparation of Lithium Pivalate

This compound was prepared from lithium hydroxide in a similar manner to that of the sodium salt.

Preparation of Tetraethylammonium Pivalate

This compound was prepared from tetraethylammonium hydroxide in a similar manner to that of the sodium salt.

Preparation of Silver Pivalate⁹⁴

Pivalic acid (40.8g, 0.4 mol) and 600 ml of water were placed in a 2-l flask fitted with a magnetic stirrer. Sodium hydroxide (10%) was added dropwise until the solution was just basic to a phenophtalein indicator (163.8 ml). The reaction flask was covered with aluminum foil and one equivalent of silver nitrate (68g, 0.4 mol), in 50 ml of water was added. The resulting precipitate was suction filtered, in the dark, washed with 800 ml of water, 463 ml of methanol, and 463 ml of diethyl ether, dried under high vacuum (1 Torr) for 4 hrs to yield 60.2g (75%) of a slightly grey solid.

Preparation of Silver Acetate

Silver acetate was prepared from acetic acid in a similar manner as described above for silver pivalate.

Section B. Reactions

Reactions were generally run in a stoppered flask fitted with a magnetic stirrer at $45 \pm 2^\circ$ for 40.5 hrs unless otherwise noted. Reactions involving silver salts had the reaction flask covered with aluminum foil in order to eliminate light.

When silver salts were used as one of the reactants, the resulting silver bromide was suction filtered and washed with diethyl ether. When lithium, sodium, potassium, or tetraethylammonium salts were employed, the reaction mixture was diluted directly with diethyl ether except when 6-tosyloxyisophorone (44) was a reactant, in which case, because of solubility difficulties in diethyl ether, ethyl acetate was used. These organic solutions were then washed with water, then with 10% sodium bicarbonate if acetic acid or pivalic acid was present; dilute hydrochloric acid if pyridine or another base (e.g. triethylamine) was present; or water if water soluble solvents, such as DMSO, dioxane, DMF, HMPT, etc. were used. The organic layer would then be washed with water, or a sodium chloride solution if the layers did not separate readily, dried over MgSO_4 and concentrated at room temperature under reduced pressure.

Analysis of the product distribution was usually performed by nmr. The technique for the determination of relative product yields has been explained on page 45.

A few specific examples of reactions performed under these criterion are given below.

Reaction of 4-Bromoisophorone (1) with Sodium Pivalate in Pivalic Acid

In a stoppered 20 ml flask fitted with a magnetic stirrer, 4-bromoisophorone (0.434g, 0.002 mol) and pivalic acid (2g) were stirred at $45 \pm 2^\circ$ for 40.5 hrs. The reaction mixture was diluted with 20 ml of diethyl ether and the ethereal layer was then washed with 20 ml of water, 2-20 ml portions of 10% sodium bicarbonate, 1-20 ml portion of a saturated sodium chloride solution, dried over MgSO_4 and concentrated at room temperature under reduced pressure to give 0.439g of a viscous oil. Analysis by nmr showed the presence of 71% 1 and 29% 2-pivoxysisophorone (58).

Reaction of 6-Tosyloxyisophorone (44) with Triethylamine in Dioxane:Water

6-Tosyloxyisophorone (44) (0.308g, 1.0mmol), triethylamine (0.101g, 1.0 mmol) and 19 ml of 1,4-dioxane:water (1:1 v/v) were placed in a 35 ml flask fitted with a magnetic stirrer. The flask was stoppered and the reaction mixture was stirred at ca. 45° for 40.5 hrs. The reaction mixture was diluted with ethyl acetate (15 ml) and the organic layer separated. The organic layer was

then washed with 3-15 ml portions of water, 1-15 ml portion of dilute hydrochloric acid, 1-15 ml portion of a saturated salt solution, dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield 0.121g of a white solid. Nmr analysis showed that this mixture contained 60% 44 and 40% 6-hydroxyisophorone (46).

Reaction of 4-Bromoisophorone (1) with Lithium Pivalate in DMF

4-Bromoisophorone (1)(0.434g, 2.0 mmol), lithium pivalate (0.281g, 2.6 mmol) and DMF (5 ml) were added to a 20 ml flask fitted with a magnetic stirrer. The reaction mixture was stoppered and stirred at ca. 45° for 40.5 hrs. Diethyl ether (20 ml) was added to the reaction mixture and the organic layer washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate solution, 1-20 ml portion of water, dried over MgSO_4 , and concentrated at room temperature under reduced pressure to yield a yellow oil (0.370g). Analysis by nmr showed the reaction mixture to contain greater than 90% 2-pivoxisophorone (58). A trace of other compounds are noted due to the unaccountable peaks in the gem and alkyl region.

Reaction of 4-Bromoisophorone (1) with Tetraethylammonium Pivalate in HMPT

4-Bromoisophorone (1)(0.434g, 2 mmol), tetraethylammonium pivalate (0.60g, 2.6 mmol) and HMPT (5 ml) were added to a 20 ml flask fitted with a magnetic stirrer. The reaction mixture was stoppered and stirred at ca. 45° for 40.5 hrs. Diethyl ether (20 ml) was added to the reaction mixture and the organic layer was washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate solution, 1-20 ml portion of water, dried over MgSO_4 and concentrated at room temperature, under reduced pressure to yield a pale yellow oil (0.353g). Analysis by nmr of the reaction mixture showed the presence of 1(23%), 4-pivoxysisophorone (57)(61%), and 2-pivoxysisophorone (58)(16%).

Reaction of 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) with Potassium Pivalate in DMF

4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (84) (0.279g, 1.0 mmol), potassium pivalate (0.182g, 1.3 mmol) and 5 ml DMF were added to a 20 ml flask fitted with a magnetic stirrer. The reaction mixture was stoppered and stirred at 45 $\pm$ 2° for 40.5 hrs. Diethyl ether (20 ml) was added to the reaction mixture and the organic layer was then washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate solution, 1-20 ml

portion of water, dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield a yellow solid (0.25g). Analysis by nmr showed that the reaction mixture contained only 5,5-dimethyl-3-phenyl-2-pivoxycyclohex-2-enone (94).

Reaction of 4-Bromoisophorone (1) with Silver Pivalate in Pyridine

4-Bromoisophorone (1) (0.434g, 2.0 mmol), silver pivalate (0.540g, 2.6 mmol) and 2g of dry pyridine (dried by refluxing over barium oxide and then distilling into a flask containing sodium hydroxide pellets) were added to a 20 ml flask, which was completely covered with aluminum foil to eliminate light. The reaction mixture was stoppered and stirred at ca. 45° for 40.5 hrs. The resulting silver bromide was suction filtered and washed with 2-35 ml portions of water, 1-30 ml portion of dilute hydrochloric acid, 1-30 ml portion of water, dried over MgSO_4 , and concentrated at room temperature under reduced pressure to yield a viscous brown oil. Analysis by nmr showed that this reaction mixture contained 45% 4-pivoxisophorone (57) and 55% 2-pivoxisophorone (58).

Reaction of 4-Pivoxysophorone (57) with Potassium Bromide, Potassium Pivalate in DMF

4-Pivoxysophorone (57)(0.238g, 1.0 mmol), potassium bromide (0.165g, 1.3 mmol), potassium pivalate (0.182g, 1.3 mmol) in 2.5 ml DMF were added to a 20 ml flask. The flask was stoppered and the reaction mixture stirred at ca. 45° for 40.5 hrs. Diethyl ether (20 ml) was added. The organic layer was washed with 2-20 ml portions of water, 1-18 ml portion of 10% sodium bicarbonate solution, 1-20 ml portion of water, dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield 0.166g of a slightly yellow oil. Analysis by nmr of this oil showed only the presence of starting material.

Reaction of 4-Bromoisophorone (1) with Sodium Pivalate in DMSO

4-Bromoisophorone (1)(0.434g, 2.0 mmol), sodium pivalate (0.328g, 2.6 mmol) and DMSO (5 ml)(stored over molecular sieves) were added to a 20 ml flask fitted with a magnetic stirrer. The reaction mixture was stoppered and stirred at ca. 45° for 40.5 hrs. Diethyl ether (20 ml) was added to the mixture and the organic products washed with 2-20 ml portions of water, 1-20 ml portion of 10% sodium bicarbonate solution, 1-20 ml portion of water, dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield 0.357g of a yellow oil.

Analysis of this oil by nmr showed the composition of products to be 17% 1, 36% 4-pivoxylsophorone and 47% 2-pivoxylsophorone.

Reaction of 4-Bromoisophorone (1) with DMSO

4-Bromoisophorone (1)(0.434g, 2.0 mmol) was dissolved in 5 ml of DMSO (dried over molecular sieves). The reaction mixture was stirred in a stoppered 25 ml flask, fitted with a magnetic stirrer at $45 \pm 2^{\circ}$ for 40.5 hrs. The reaction mixture was diluted with 20 ml of diethyl ether. The ethereal layer was washed with 4-20 ml portions of water, dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield a pale yellow oil (0.364g).

A rough nmr analysis indicated the presence of only traces of non-aromatic products. Therefore, the entire crude product was dissolved in diethyl ether (20 ml) and extracted with 4-15 ml portions of sodium hydroxide (2.5N). The combined aqueous extracts were then acidified carefully with cold concentrated hydrochloric acid, and then the acidic solutions was extracted with 3-15 ml portions of chloroform. The chloroform layer was dried over MgSO_4 , and concentrated at room temperature under reduced pressure to yield 0.290g of an oil. The original ethereal solution containing the neutral and basic products from the initial reaction mixture was dried over MgSO_4 and concentrated at room temperature under reduced

pressure to yield 30 mg of a brown oil. Rough nmr analysis of this material showed a trace of starting material, as well as some unextracted aromatic products. Because this material accounted for only 10% of the organic products (by weight), no further work was done on this material.

Thin layer chromatography indicated the presence of 3,4,5-trimethylphenol (2) in the acidic products extract. Based on this work, thick layer chromatography (Eastman silica gel chromatography plates) was performed. The plates were activated for 15 min at 100°. Benzene was used as the developing solvent. Three cuts were taken: cut A, R_f 0.69-0.59 (37 mg); cut B, R_f 0.58-0.46 (154 mg); cut C, 0.29-0 (44 mg).

Cut A was a white solid, mp 133-134°. Nmr analysis showed the absence of peaks downfield of δ 3.0. Mass spec: m/e = 297(0.38), 296(.50), 294(1.00), 292(.53), 281(.13), 279(.27), 277(.13), 210(.51), 208(.53).

Cut B was a white solid, mp 45-46°. A mixed mp with known 2-bromo-3,4,5-trimethylphenol (59) showed no depression. Spectral analysis (see page 172) also confirmed the identification of cut B.

Cut C based on spectral analysis and mixed mp showed this material to be 3,4,5-trimethylphenol (2).

Section C. Synthesis of 4-Bromo-5,5-diphenylcyclohex-2-enone (103)

Preparation of 4,4-Diphenylcyclohex-2-enone (112)

The general procedure of Zimmerman⁹⁵ was followed for the synthesis of 112.

Preparation of 4,4-Diphenylcyclohexanone (113)⁹⁶

4,4-Diphenylcyclohex-2-enone (112) (50g, .205 mol) was dissolved in 300 ml of glacial acetic acid. Palladium on charcoal (5%, 4g) was added and a hydrogenation was performed in a Parr apparatus until hydrogen uptake ceased. The resulting solution was filtered through diatomaceous earth and then washed with hot acetic acid. After the addition of water the acidic layer was extracted with diethyl ether (750 ml). The combined ethereal layers were washed with a 10% sodium bicarbonate solution until effervescence ceased, and then once with water. The organic layer was dried over MgSO_4 , and concentrated at 30° to yield 46.85g (93.5%) of a white solid, mp $136-138^\circ$ (lit⁹⁶ mp $142-143^\circ$); nmr (CDCl_3): $\delta 7.45$ (m, 10H, ArH), 2.53 (m, 8H, 4-CH_2); ir (CHCl_3 solution) 1710 (s, ketone).

Preparation of 4,4-Diphenylcyclohexanol (114)

Into a 3 necked flask fitted with a magnetic stirrer,

addition funnel, condenser, and drying tube, 4,4-diphenylcyclohexanone (113) (46.85g, 0.187 mol) in 1500 ml of dry diethyl ether was added over a 45 min period to 5.7g (0.15 mol) of lithium aluminum hydride in 100 ml of diethyl ether. The reaction mixture was refluxed for 3 hrs at which time it was cooled to 0° and the calculated amount of sodium potassium tartrate solution was added in order to destroy the hydride (note that 241g of sodium potassium tartrate in 275 ml of water will destroy 1 mole of lithium aluminum hydride). After being stirred for 30 min the solid present was suction filtered and washed with diethyl ether. The organic solution was concentrated under reduced pressure at room temperature to yield a white solid (114) (44.95g, 95.5%), mp 131-133°; nmr (CDCl₃): δ 7.24(m, 10H, ArH), 275(septet, J=4 Hz, 1H, HCO), 1.37-2.80(m, 8H, 4-CH₂), 1.62(s, 1H, OH); ir (CHCl₃ solution): 3550(m, sharp OH), 3350(m, broad, OH), no carbonyl present.

Preparation of 4,4-Diphenylcyclohexyl Tosylate (115)

4,4-Diphenylcyclohexanol (114) (50.25g, 0.2 mol) and 476 ml of pyridine were added to a 1 l flask. The mixture was cooled to 0° and p-toluenesulfonyl chloride (103.2g, 0.6 mol) was added in small portions. After solution was attained the stoppered flask was placed in the freezer (4°) for 48 hrs. The reaction mixture was poured unto 2 l

of ice and water and was then extracted with 3l of diethyl ether. The combined ethereal layers were washed with 750 ml of 6N hydrochloric acid, water and dried over MgSO_4 and concentrated at room temperature under reduced pressure to yield 70g (88%) of a white solid, mp $117-119.5^\circ$; nmr (CDCl_3): $\delta 7.45$ (AB pattern, 4H, tosyl ArH), 7.34 (s, 10H, Ph), 4.58 (m, 1H, HCO), 2.40 (s, 3H, CH_3), $1.56-2.82$ (m, 8H, 4- CH_2).

Preparation of 4,4-Diphenylcyclohexene (116)

The tosylate (115) prepared from the above reaction was added to 180 ml of 2,6-lutidine in a 500 ml flask fitted with a condenser, drying tube and magnetic stirrer. The solution was refluxed for 7.75 hrs at which time the reaction mixture, after cooling to room temperature, was diluted with water and extracted with diethyl ether. The combined ethereal layers were washed with 6N hydrochloric acid, water and then dried over MgSO_4 and concentrated at reduced pressure, at room temperature to give a white, pungent smelling solid (36.15g) which was recrystallized from hexane to give 27.4g of 116, mp $62.5-63.5^\circ$ (lit⁷⁸ mp $65-66.5^\circ$) The yield of the last 2 steps is 66%. nmr (CDCl_3): $\delta 7.14$ (s, 10H, Ph), 5.72 (m, 2H, $\text{C}=\text{CH}$), $2.68-2.10$ (m, 4H, 2- CH_2), $1.95-1.50$ (m, 2H, CH_2); ir (KBr disc): 1486 (s), 1433 (s).

Preparation of 1,2-Oxido-4,4-diphenylcyclohexane (108)

4,4-Diphenylcyclohexene (116)(14g, 0.06 mol) and 200 ml of methylene chloride were added to a 3 necked 11 flask fitted with a condenser, thermometer, drying tube and magnetic stirrer. After cooling the solution to 5°, m-perchlorobenzoic acid (24.4g, 0.12 mol)(100% excess assuming 85% purity) in 150 ml of methylene chloride was added dropwise in 90 min while maintaining the temperature below 10°. The solution was then refluxed for 150 min. After being cooled to room temperature the reaction mixture was washed with 4 portions of a 10% sodium sulfite solution (until a negative potassium iodide test) and then with a 10% sodium bicarbonate solution (until basic). The organic layer was dried over MgSO₄ and concentrated at room temperature to give 14.8g (98.5%) of a slightly yellow solid, mp 92-93.5° (lit⁸² mp 98-99°); nmr (CDCl₃): δ7.16(m, 10H, Ph), .98-3.45(m, 8H, 2-  and 3-CH₂); ir (KBr disc): 1504(s), 1458(s), 804(s).

Preparation of 2-Bromo-5,5-diphenylcyclohexanol (109) and
Oxidation of 109 to 2-Bromo-5,5-diphenylcyclohexanone (107).

The procedure of Bordwell⁸² was followed for these reactions.

Preparation of 3,3-Diphenylcyclohexanone (127)

2-Bromo-5,5-diphenylcyclohexanone (26.5g, 0.08 mol)

and 575 ml of glacial acetic acid were added to a 3 necked 11 flask fitted with a condenser, mechanical stirrer, stopper and drying tube. The reaction mixture was brought to reflux and zinc dust (100g) was added rapidly. Stirring and refluxing were continued for 3.25 hrs. After cooling the solution, the solid present was filtered and the filtrate diluted with 750 ml of diethyl ether and 500 ml of water. The aqueous layer was extracted with an additional 650 ml of diethyl ether. The combined ethereal layers were washed with a 10% sodium bicarbonate solution until the washings were basic, 1 portion of water, dried over MgSO_4 and concentrated at room temperature to give 19.6g (97%) of a white solid, mp $93.5-96^\circ$ (lit⁸² mp $114.5-115^\circ$); nmr (CDCl_3): $\delta 7.17(\text{s}, 10\text{H}, \text{Ph})$, $2.91(\text{s}, 2\text{H}, \text{Ph}_2\text{C}-\underline{\text{CH}_2}-\text{C}=\text{O})$, $2.71-2.00(\text{m}, 4\text{H}, 2-\text{CH}_2)$, $1.85-1.28(\text{m}, 2\text{H}, \text{CH}_2)$; ir (KBr disc): $1709(\text{s}, \text{ketone})$.

Preparation of 5,5-Diphenylcyclohex-2-enone (111)

3,3-Diphenylcyclohexanone (127)(2.0g, 0.008 mol) and 25 ml of 1,4-dioxane were added to a 3 necked flask fitted with a magnetic stirrer, condenser, and drying tube. Refluxing was commenced and 2.4g of dichlorodicyanobenzoquinone (DDQ)(1.3 equivalents) was added. The solution was refluxed until 2,3-dichloro-5,6-dicyano-hydroquinone precipitated, a total of 7 hrs. The total reflux time when 2.5g of 127 was used is 2.75 hrs(20 ml

of solvent), and 30 min (5 ml of solvent). The resulting solid was suction filtered and diethyl ether (160 ml) was added and the mixture suction filtered again. The ethereal layer was washed 3 times with 10% sodium hydroxide and then a saturated sodium chloride solution until neutral, dried over MgSO_4 and concentrated at room temperature under reduced pressure. A brown oil (0.9g) was recovered. This product was chromatographed using 81g of Woelm dry column alumina in a column 10 cm diameter (flat). Developing time in benzene was 5 min. The material from 1 cm to 9 mm was eluted from the alumina by washing with chloroform. After concentration at reduced pressure, at room temperature, a pale yellow oil was recovered. This oil solidified after remaining in the freezer (4°) for 3 days. Sublimation of this solid (0.30g) gave a white solid, mp $89-91^\circ$ (lit⁷⁸ mp $110.5-112^\circ$); nmr (CDCl_3): δ 7.25(s, 10H, Ph), 6.90(m, 1H, C=CH), 6.03(d, J=10 Hz, 1H, C=CH), 3.20-3.08(m, 4H, 2- CH_2); ir (KBr disc): 1668 (s, conjugated ketone).

Preparation of 4-Bromo-5,5-diphenylcyclohex-2-enone(103)

5,5-Diphenylcyclohex-2-enone (111)(0.217g, 0.008 mol), N-bromosuccinimide (0.156g, 0.008 mol), benzoyl peroxide (0.008g) and 3 ml of carbon tetrachloride were added to a 25 ml flask fitted with a magnetic stirrer, condenser and drying tube. This solution was refluxed for 90 min and

after being cooled to room temperature the resulting solid was suction filtered. The organic filtrate was concentrated at room temperature and the resulting solid was suction filtered and added to the previously recovered succinimide. Further concentration of the organic solution resulted in the formation of a pale yellow solid. This solid was recrystallized from hexane to yield a white solid, mp 125.5-126°; nmr (CDCl₃): δ 7.20(m, 11H, Ph, C=CH), 5.91 (d, J=1 Hz, 1H, C=CH), 5.66(doublet of doublets, J=8 Hz, J=1 Hz, 1H, HCB_r), 3.52(m, 2H, CH₂); ir (CHCl₃ soln); 1675(s, conjugated ketone); Anal: Calcd for C₁₈H₁₅BrO: C, 66.07; H, 4.59. Found: C, 65.94; H, 4.66. This product decomposes if left at room temperature.

Isomerization of 1,2-Oxido-4,4-diphenylcyclohexane (108)
to 4,4-Diphenylcyclohex-2-en-1-ol (123)

Diethylamine (2.5 ml, 0.025 mol, 2.5 equiv) in 25 ml of diethyl ether was placed under N₂ in a 3 necked flask fitted with a dropping funnel, gas adapters, magnetic stirrer and condenser and then cooled to 0°. N-Butyl lithium in hexane (2.25M, 0.025 mol, 2.5 equiv) was then added rapidly at this temperature to the solution stirred under N₂. After stirring for 10 min 1,2-oxido-4,4-diphenylcyclohexanol (108)(2.5g, 0.01 mol, 1 equiv) in 25 ml of diethyl ether was added rapidly and the mixture refluxed for 8.5 hrs under a slow stream of nitrogen. Water (50 ml) was added to the cooled solution

and the layers separated. The aqueous layer was extracted with diethyl ether and the combined ethereal layers were washed with 2-50 ml portions of 1N hydrochloric acid, 5% sodium bicarbonate solution till neutral, dried over MgSO_4 and concentrated at 50° under reduced pressure. A slightly tan solid (1.95g, 78%), mp $96-98^\circ$ was recovered.

Oxidation of 4,4-Diphenylcyclohex-2-en-1-ol to 4,4-Diphenylcyclohex-2-enone (112)

A standard Jones oxidation was performed on 4,4-diphenylcyclohex-2-en-1-ol (123) yielding only 4,4-diphenylcyclohex-2-enone (112) as proved by comparison with a known sample.

Appendix A: Compounds Commonly Mentioned

<u>Compound</u>	<u>Number</u>
4-Bromoisophorone	<u>1</u>
3,4,5-Trimethylphenol	<u>2</u>
Isophorone	<u>31</u>
6-Tosyloxyisophorone	<u>44</u>
6-Hydroxyisophorone	<u>46</u>
2,3,5-Trimethylphenol	<u>54</u>
4-Pivoxylisophorone	<u>57</u>
2-Pivoxylisophorone	<u>58</u>
2-Pivoxyl-3,5,5-trimethylcyclohex-3-enone	<u>89</u>
6-Pivoxylisophorone	<u>101</u>

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