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# DEHYDROBROMINATION REACTIONS OF 2-BROMO-2-(p-SUBSTITUTED-BENZYL)-1-INDANONES AND 2-BROMO-2-(p-SUBSTITUTED-BENZYL)-3,3-DIMETHYL-1-INDANONES

by

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# TITLE

DEHYDROBROMINATION REACTIONS OF 2-BROMO-2-(p-SUBSTITUTEDBENZYL)-1-INDANONES and 2-BROMO-2-(p-SUBSTITUTEDBENZYL)-3,3-diethyl-1-INDANONES

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# INTRODUCTION

The purpose of this study was to obtain further evidence for the mechanism of dehydrohalogenation of bromoindanones and to substantiate a "nonclassical" elimination mechanism proposed by Cromwell and coworkers.

The first portion of this study was to synthesize various 2-bromo-2(p-substituted-benzyl)-1-indanones as well as intermediates and related compounds, study their chemical and physical properties and relate these to previously investigated compounds in this laboratory.

The second part of this investigation was to concern itself with the kinetic data of the dehydrohalogenation reaction in acetonitrile from various bromoindanones and relate these findings to available data.

## A. Review of the Chemistry of Indanones and Tetralones.

The chemistry, stereostructure and absorption spectra of both the tetralones as well as indanones were adequately reviewed by Ayer.[1]

## B. Elimination and Substitution Reactions.

### (1) General

The area of elimination and substitution reactions has been the subject of extensive reviews and the indicated references are suggested for detailed discussions.[2,3,4,5]

(2) Merged Elimination-Substitution Mechanisms.

Ingold[6] in 1927 suggested the following base induced reaction for quaternary ammonium salts.

$$BASE + H\text{-}CR_2\text{-}CR_2\text{-}X \longrightarrow BH^+ + CR_2{=}CR_2 + X^-$$

The reaction is second order, first in each component, and the basic reagent removes the $\beta$ proton in a synchronous manner as the electron attracting group leaves. This mechanism was defined as an $E_2$ mechanism. It should be pointed out that no intermediates are involved but rather a transition state between reactants and products.

Another elimination mechanism, termed an $E_{cb1}$ mechanism, involves the removal of the $\beta$-hydrogen by a base to form a carbanion which in a second step loses the leaving group to form the olefin.

$$BASE + H\text{-}\overset{|}{\underset{|}{C}}\text{-}\overset{|}{\underset{|}{C}}\text{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} :\overset{|}{\underset{|}{C}}\text{-}\overset{|}{\underset{|}{C}}\text{-}X \xrightarrow{k_2} \diagdown C{=}C \diagup + X^-$$

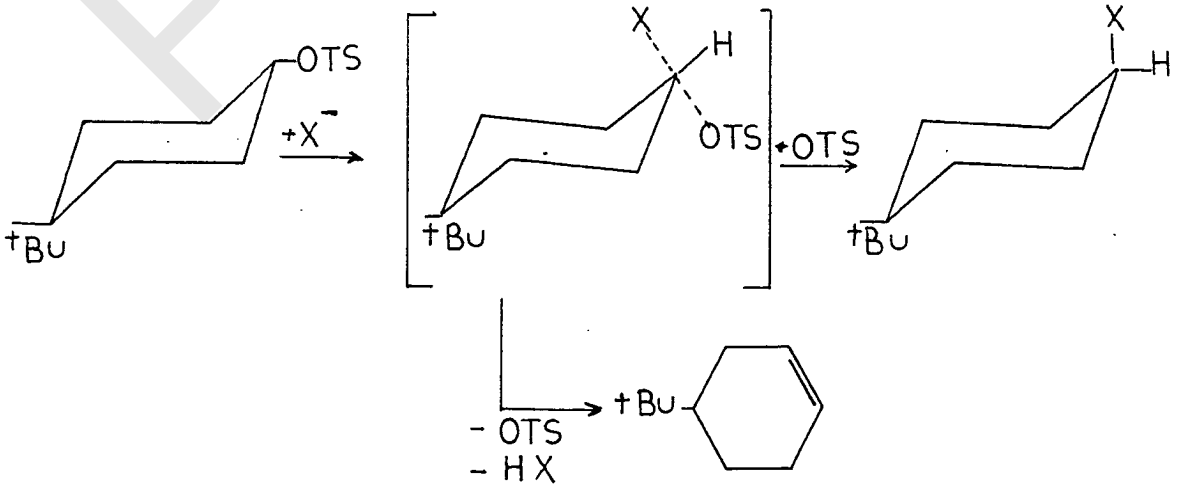
Carbanion mechanisms of this general type are rare and hard to realize experimentally.

Hughes and Ingold[7] realized that two distinctly different paths may exist for nucleophilic substitution reactions. The first was called an $S_{N2}$ mechanism which involved a bimolecular nucleophilic attack at the carbon atom attached to the leaving group forming a half bonded intermediate. The second termed

an $S_{N1}$ mechanism involved a dissociation into carbonium ion intermediate followed by rapid nucleophilic attack.

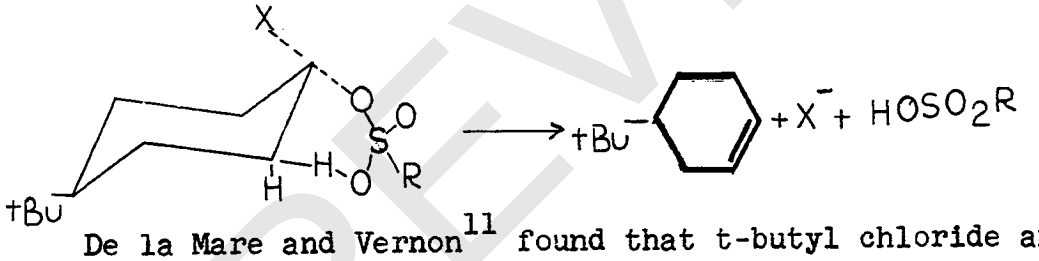
Weinstock and Pearson[8] found that p-toluene sulfonates of cis and trans-2-p-toluenesulfonylcyclohexanol undergo base induced elimination to yield 1-p-toluenesulfonylcyclohexene exclusively. No 3-p-toluenesulfonylcyclohexene was formed by anti elimination. The 1-olefin formation is due to a loosening of the proton at the ring carbon adjacent to the sulfone function and thus exposing it to direct basic attack.

Winstein and Darwish[9] found that trans-4-t-butylcyclohexyl-p-toluenesulfonate undergoes a bimolecular elimination in the presence of bromide and thiophenolate ions but not with a strong base such as ethoxide ion. A direct diaxial elimination is not possible. To account for these findings, he suggested a direct bimolecular attack of the carbon holding the equitorial tosylate group by a highly nucleophilic bromide or thiophenolate ion to give a transition state as shown which may lead to either a substitution or elimination product.

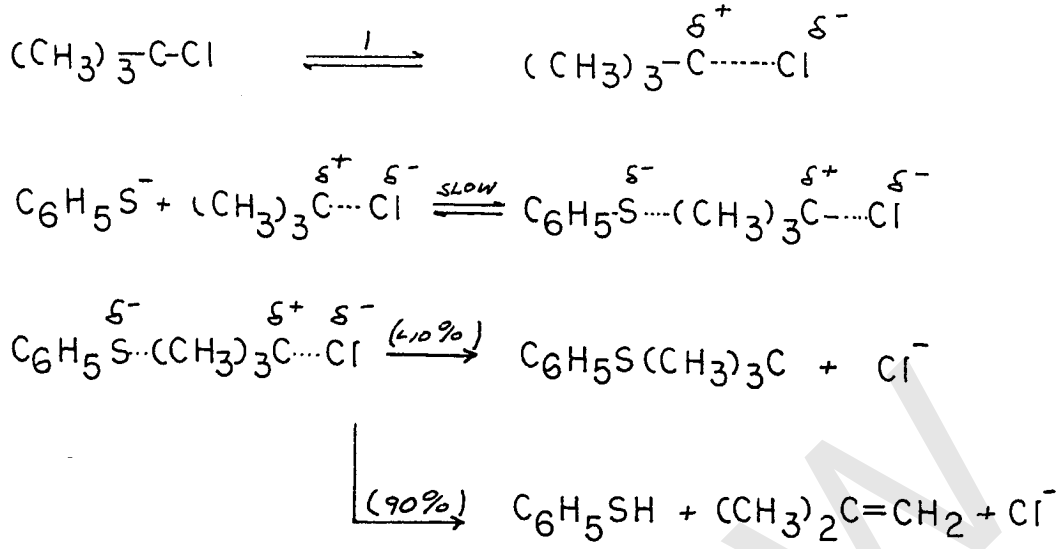


He termed reactions of this general type as merged substitution-elimination reactions.

Banthrope[10] pointed out that generally anions have less basic character toward acyclic compounds and that the relative orientation of the hydrogen and leaving group is different from the classical straight chain compound which follow the normal elimination mechanism. Acyclic tosylates are somewhat unreactive in either an $E_1$ or $E_2$ process, which is not true for an $S_{N1}$ or $S_{N2}$ process. He pointed out that most merged mechanisms proposed involve acyclic tosylates and suggested a six membered transition state of the following type to explain the olefin formation.



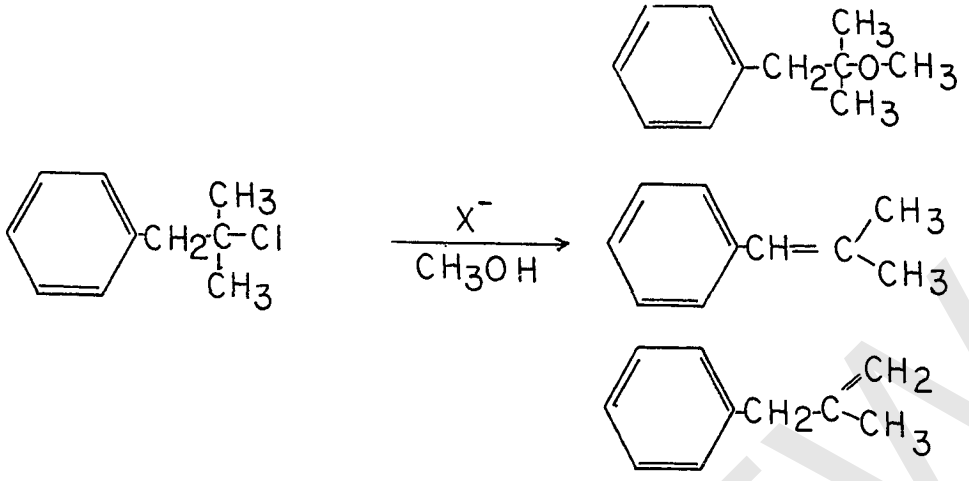

De la Mare and Vernon[11] found that t-butyl chloride and thiophenoxide ion in ethanol gave 90% olefin and a small amount of substitution product t-butylphenylsulfide. It was suggested that this reaction would involve an $E_2$ mechanism. Cromwell and Kevill[12] pointed out that the rate is abnormally large for an $E_2$ attack by a weakly basic and strongly nucleophilic thiophenoxide ion at the carbon atom center. It was suggested tha t the mechanism followed would be that proposed by Winstein and Darwish.[9]



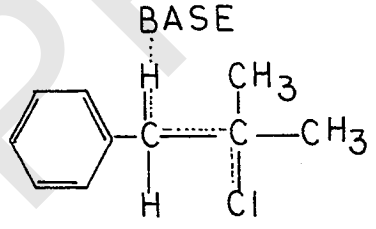
Eliel and Ro[13] pointed out that the merged mechanism proposed by Winstein can be responsible for the high elimination rates which are observed in the reaction of cyclohexyltosylate, cis-4-t-butyl-cyclohexyltosylate and t-butyl chloride with sodium thiophenolate.

Eliel[14] found that 4,4-dimethylcyclohexyltosylate in the presence of thiophenolate ion gives almost exclusively a substitution product, whereas cyclohexyltosylate gives half substitution and half elimination products.

Bunnett[15] investigated the elimination reaction of benzyldimethylcarbonyl chloride with anions in the presence of alcohol and obtained the following reaction products.



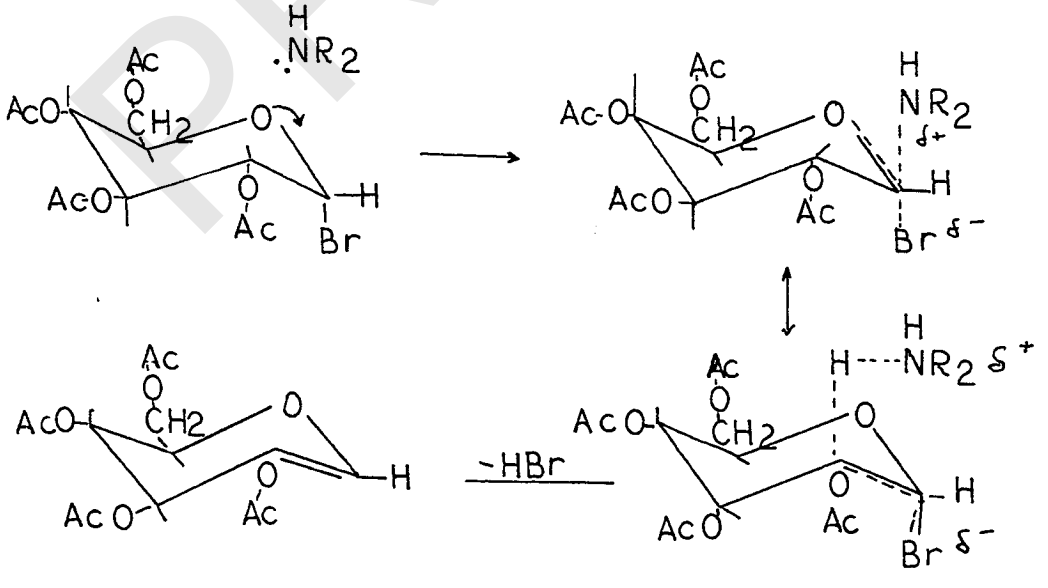
Bunnett showed through product studies and kinetic investigation that this reaction shows unusual $E_2$ character. He observed an isotope effect of 2.5 at 25°, which he interpreted to indicate that the carbon hydrogen bond breaking is running behind the carbon chloride bond breaking. This interpretation is consistent with the fact that a tertiary halide is involved and the isotope effect follows Westheimer's[35] explanation. Bunnett proposed the transition state of the following type:



He pointed out that a small effect due to substitution on the $\beta$ phenyl group may be expected in a transition state of this type, as the conjugative interaction with the developing

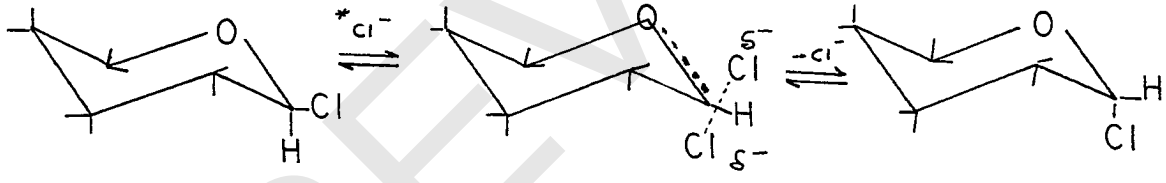
double bond would be small and mesomeric stabilization of a negative charge on the β carbon atom should have no importance in the transition state of this type. Bunnett in attacking the merged substitution elimination mechanism finds that no substitution product is found in the case of the thiophenoxide anion.

Lemieux and Lineback[16] in studying the dehydrobromination of tetra-O-acetyl-α-D-glucopyranosyl bromide in the presence of amines obtained evidence that the glycosyloxocarbonium bromide resulting from the dissociation of glycosyl bromide is stabilized by amine. The author suggests that the first stages of the reaction involve a nucleophilic attack at the anomeric center rather than attack at the β carbon hydrogen as is the case in a classical $E_2$ mechanism. Kinetic data and solvent effects give strong evidence for a charge separation in the transition state. The following reaction mechanism has been suggested to account for these findings:



Lemieux found that the amine must be important in the breaking of the carbon-bromine bond by solvating the cation through electrostatic nondirective bonding. This mechanism is similar to that suggested by Winstein and Darwish[9] and by Hassner, Cromwell and Davis.[31]

Lemieux and Hayami[17] investigated the anomerization of tetra-O-acetyl-α-glucopyranosyl chloride with labeled tetraethylammonium chloride ($Cl^{*36}$) in acetonitrile and found the reaction to be first order in chloride ion and second order overall. He suggested that the following transition state be involved, which is similar to the merged substitution-elimination mechanism proposed by Winstein and by Cromwell.



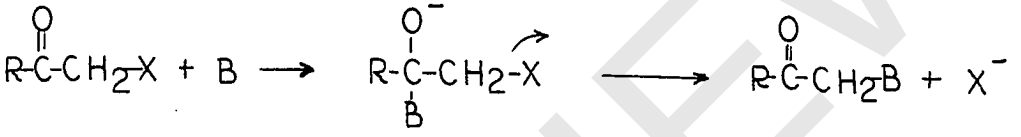

(3) Elimination Reactions of α-Haloketones

It has been realized for a long time that α-haloketones possess unusual reactivity. Hughes and Ingold[19] attributed this reactivity of α-haloketones to a polar effect in which the electron attracting carbonyl function induces a positive charge on the carbon holding the halogen.

Pearson[18] also attributes the reactivity to proximity of the positively charged center which electrostatically would facilitate the approach of the nucleophile along the normal path to the adjacent carbon atom. Larger and polarizable

nucleophiles should enhance the rate of reaction. This was found to be true as the second order rate constants were considerable higher using weakly basic charged nucleophilic reagents than with nucleophiles possessing a lone electron pair which were stronger bases.

Baker[20] proposed a mechanism which involved the addition of the nucleophile to the carbonyl carbon atom, followed by a rapid intramolecular displacement.

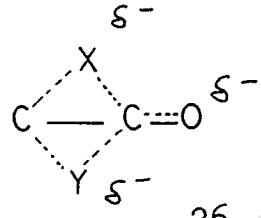


Clark[21] had found that phenacyl bromide was 54 times as reactive as phenacyl chloride toward pyridine in ethanol at 55.6°. This would indicate that the rate determining step must involve a displacement of the halogen, where bromine is more reactive than chlorine, in direct contrast to the Baker mechanism.

Stevens[22] found that α-chloropropiophenone reacts with sodium methoxide to give 1-phenyl-1-methoxy-1,2-epoxypropane. He states that isolation of the epoxyether and its rapid reaction with alcohol to give an α-hydroxyketal confirms the mechanism proposed by Ward and Kohler[23] for the formation of hydroxyketals from certain α-haloketones. These are postulated to proceed in alcoholic sodium alkoxide via epoxy-ether intermediates. McPhee and Klingsberg[24] also postulated the

rearrangements of α-haloketones to acids or esters in the presence of base to go through epoxyether intermediates.

Dewar and Winstein[25] proposed a mechanism in which there is neighboring group orbital overlap with the adjoining electron deficient carbon atom. The transition state of α-haloketones includes partial bonding of the reagent with the p-orbital of the carbonyl group.




Bartlett and Trachtenberg[26] pointed out that the mechanism proposed by Dewar and Winstein must meet strict stereochemical requirements. Their results substantiate Winstein's mechanism in preference to Pearson's and they attributed the rate enhancement with various nucleophiles as being due to additional covalent bonding in the transition state with the electron deficient carbonyl carbon atom.

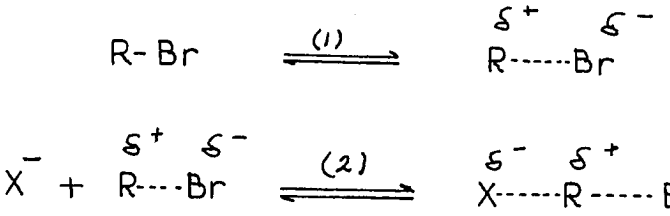
Sisty and Lowell[27] in order to differentiate between Pearson's and the Winstein-Dewar proposed mechanism, investigated the kinetics of the reaction of charged nucleophiles having relatively small bonding orbitals and an uncharged nucleophile with a large bonding orbital with some α-halocarbonyl compounds. His evidence seemed to favor a Winstein type of mechanism.

Newman[28] suggested the idea that the α-haloketones would

react extremely slowly in an ionizing solvent and that they should fail to give an alcoholic silver nitrate test. Cromwell[29] found this not to be true for $\alpha$-keto tertiary halides and suggested the idea that silver ion promoted dehydrobromination reactions which are $E_1$ in character. Metal assistance is conceivable and enhancement may be received from nucleophiles in the solution and the electron pair of the $C_\beta$ - H bond.

Kevill and Cromwell[30] found that 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone in the presence of piperidine in acetonitrile undergoes a facile elimination reaction yielding mainly 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene and a small amount of 2-benzal-4,4-dimethyl-1-tetralone. The elimination was first order in reference to the bromotetralone while of indefinite order in piperidine. A first and zero order component were realized. It had been found that the first order rate coefficient for bromotetralone in acetonitrile at $60^\circ$ was $3.2 \times 10^{-7}$ $sec^{-1}$. The first order rate coefficient of the ketone under identical conditions in the presence of piperidine was $7.1 \times 10^{-6}$ $sec^{-1}$. Kevill and Cromwell suggested that the first order component (zero order in piperidine) indicates an axial bromine carbon bond elongation which may also occur in bimolecular reactions. A nucleophilic attack upon the activated intermediate is the second step of the reaction path. The ion pair which is produced may have a fair amount

of covalent bonding associated with it. The order of the mechanism is determined by the relative rates of the different stages of the mechanism.



Kevill and Cromwell[30] investigated the kinetics of bromide ion promoted elimination reaction of 2-benzyl-2-bromo-4,4-dimethyl-1-tetralone in acetonitrile. It was shown by comparing the kinetic order in salts, the reaction rates and temperatures for tetraethylammonium bromide and for piperidinehydrobromide, only sufficiently dissociated bromide ions can promote elimination reactions. This is consistent with the proposal that the negatively charged bromide ion attacks at the positively charged carbon center of the activated intermediate. Piperidine, uncharged, would be less favored than bromide ion to attack at the positive dipole. Kevill and Cromwell, however, believe "piperidine to promote reactions of activated intermediates as an alternative to deactivation." They suggested the following type of transition state in which coordination with the carbonyl group is expected.