In presenting the dissertation as a partial fulfillment of
the requirements for an advanced degree from the Georgia
Institute of Technology, I agree that the Library of the
Institute shall make it available for inspection and
circulation in accordance with its regulations governing
materials of this type. I agree that permission to copy
from, or to publish from, this dissertation may be granted
by the professor under whose direction it was written, or,
in his absence, by the Dean of the Graduate Division when
such copying or publication is solely for scholarly purposes
and does not involve potential financial gain. It is under-
stood that any copying from, or publication of, this dis-
sertation which involves potential financial gain will not
be allowed without written permission.

(  _____

7/25/68

PART ONE

OXYMERCURATION-DEMERCURATION OF

2-ENDO-CARBETHOXYBICYCLO[2.2.2]OCT-5-ENE

PART TWO

THE MODE OF TRANSMISSION OF SUBSTITUENT

EFFECTS THROUGH THE BICYCLOOCTANE MOLECULE

A THESIS

Presented to

The Faculty of the Graduate Division

by

Ernest Lawrence Slightom

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

Georgia Institute of Technology

June, 1970

PART ONE

OXYMERCURATION-DEMERCURATION OF

2-ENDO-CARBETHOXYBICYCLO[2.2.2]OCT-5-ENE

PART TWO

THE MODE OF TRANSMISSION OF SUBSTITUENT

EFFECTS THROUGH THE BICYCLOOCTANE MOLECULE

Approved:

_____

Chairman

Date approved by Chairman: 5/6/71

## ACKNOWLEDGEMENTS

I am indebted to Dr. Charles L. Liotta for suggesting the problem and his continuous assistance during the course of the research. I also wish to thank Dr. James Stanfield and Dr. Leon Zalkow for reading the final manuscript.

Thanks go to my parents for their love and understanding and to Georgia Institute of Technology for financial assistance.

In order that this thesis might be finally typed under restricted conditions, special permission was received from the Graduate Division to use a spacing slightly less than the required double spacing.

PART ONE

OXYMERCURATION-DEMERCURATION OF

2-ENDO-CARBETHOXYBICYCLO[2.2.2]OCT-5-ENE

TABLE OF CONTENTS

v

LIST OF TABLES

PART TWO

THE MODE OF TRANSMISSION OF SUBSTITUENT

EFFECTS THROUGH THE BICYCLOOCTANE MOLECULE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF CHARTS

SUMMARY

2-<u>endo</u>-Carbethoxybicyclo⎣2.2.2⎦oct-5-ene was oxymercurated
and then demercurated. The product distribution was viewed in light
of mechanisms put forth in the current literature. The hydroxy esters
produced were separated from the reaction mixture using column chroma-
tography. The rate of ester hydrolysis and the pKa's of the corres-
ponding acids of the separated hydroxy esters were determined. The
reactivities of these compounds were analyzed using the σ-inductive
and electrostatic models for transmission of substituent effects.
Although both predict qualitatively the reactivities, they lack
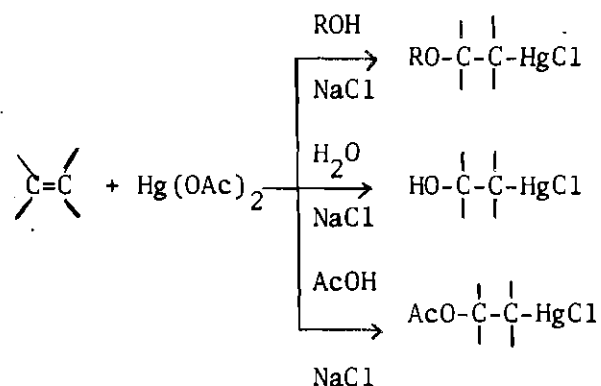quantitive accuracy in the systems studied here.

PART ONE

OXYMERCURATION-DEMERCURATION OF

2-ENDO-CARBETHOXYBICYCLO [2.2.2.] OCT-5-ENE

CHAPTER I

INTRODUCTION

The addition of mercuric salts across a carbon-carbon double
bond has been known for quite some time. Kucherov[1] in 1892 was the
first to observe this reaction. In 1900 Hofman and Sand[2] further
studied this reaction and, in subsequent investigations, showed that
the reaction of mercury (II) salts forms hydroxyalkylmercury com-
pounds and their derivatives.[1]

$$
\begin{array}{c}
\ce{>C=C<} + \ce{Hg(OAc)_2}
\end{array}
\quad
\begin{array}{ll}
\xrightarrow[\text{NaCl}]{\text{ROH}} & \ce{RO-C-C-HgCl} \\[2em]
\xrightarrow[\text{NaCl}]{\text{H_2O}} & \ce{HO-C-C-HgCl} \\[2em]
\xrightarrow{\text{AcOH}} & \ce{AcO-C-C-HgCl} \\
\text{NaCl}
\end{array}
$$

Before Hofman and Sand discovered the conditions for the formation
and isolation of the simple addition products of olefins it was
impossible to study this reaction because of the unknown reactions,
thought to be other substitution and oxidation reactions,[3] that
would also take place.

Since Hofman's and Sand's initial work there has been consider-
able interest in this reaction. In 1913 Schoeller, Schrauth, and
Essers[4] showed that the solvent played an essential role in the
addition, for example, in alcoholic solution the alkyl ethers were
produced. Later[3] it was found that in glacial acetic acid, mercuric
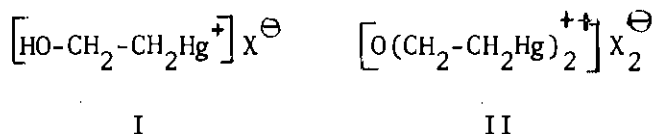acetate yields the acetyl derivative,

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-Hg-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$
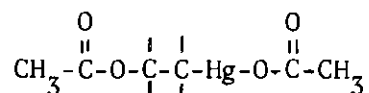
and that N-B(chloromercuricethylpiperdine)[3] was formed when piperidine was used as a solvent.

In 1920 Monchot and Klug,[5,6] believing there was evidence for complex formation, brought out a controversy concerning whether or not the mercury formed a complex with the double bond or whether a saturated compound was formed. It is now accepted that the product of addition of mercury (II) salts to olefins is a saturated addition compound.[1,3]

Early[7,8,9] kinetic studies of the formation of the mercury compounds indicated that the reaction was complex and came closest to following second order kinetics, the rate depending on the concentration of the mercuric salt and the olefin. Although the reaction is thought to be reversible, attempts[10,11] to approach the equilibrium by decomposition of the methoxy mercurials in methyl alcohol by acetic acid have indicated very little if any, reversal. Lucas, Hepner, and Winstein[8] suggested that there may be other, less stable, reversibly-formed coordination complexes present as intermediates before the final addition product is formed, similar to the complexes of Ag with ethylenic compounds. As an example, the resonating forms of the cyclohexenemercurinium ion can be represented as follows:
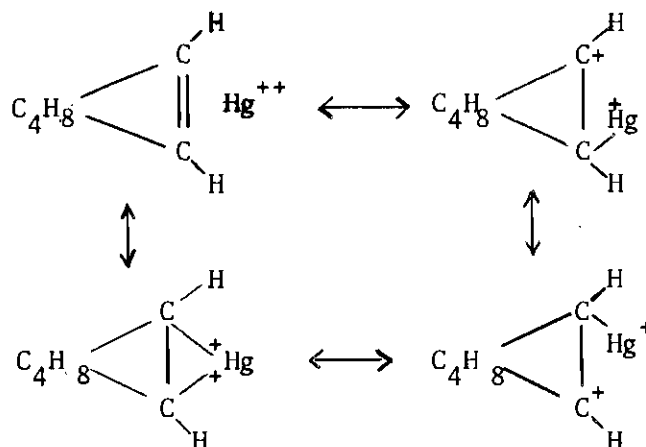
Evidence for four series of simple mercuric complexes has been found.
Structures I and II are true addition compounds while evidence for

$$\left[\text{HO-CH}_2\text{-CH}_2\text{Hg}^+\right]X^{\ominus} \qquad \left[\text{O(CH}_2\text{-CH}_2\text{Hg)}_2^{++}\right]X_2^{\ominus}$$

I                                       II

structures III and IV were found by Lucas, Hepner, and Winstein.[8]



III                                      IV
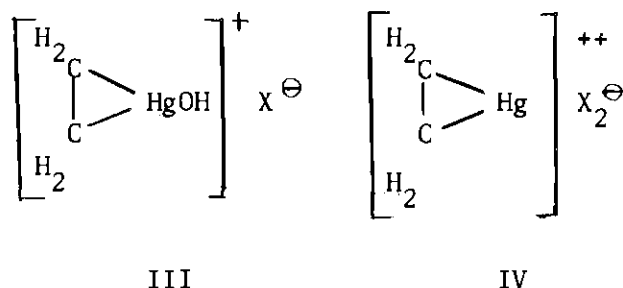
The evidence was based upon a two-phase system the two phases being
carbon tetrachloride and an aqueous solution of $Hg(NO_3)_2$ and $HNO_3$.
The pH of the aqueous solution was changed and the equilibrium of
cyclohexene between the two phases was measured. Ploting the equi-
librium values thus obtained versus $\frac{1}{[H+]}$ and finding an equation
consistent with the data resulted in an equation involving the
equilibrium of both structures III and IV.

The addition of mercury (II) salts to olefins proceeds stereo-
specifically[1]--from the cis and trans-isomers of alkenes different
diastereomers are obtained free from the second isomer. The rate
of hydroxymercuration of the cis-alkenes is greater than that of the
trans-alkenes, which allows this reaction to be used to determine the
configuration of the alkenes.

Two mechanisms have been proposed[1] for oxymercuration. A non-
ionic mechanism proposed by Wright in which there is first alcoholysis
(hydrolysis) of the mercury (II) acetate with formation of a hydrox-
acetomercury (II) or an acetatoalkoxymercury (II) complex,

$$CH_3OH + Hg(CH_3CO)_2 \rightleftharpoons CH_3OHgOCCH_3 + CH_3COH$$
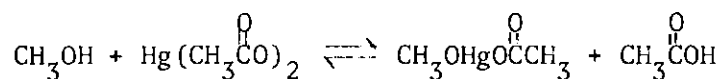
(1)

which then reacts with the alkene in the slow step of the reaction.
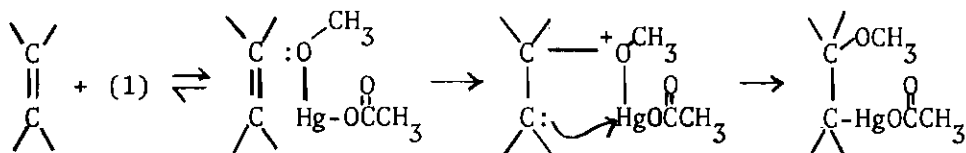


This mechanism is presumed not to be correct since it indicates
nucleophilic attack on the unactivated double bond by oxygen. A
four-centered transition state will overcome the presumption of
nucleophilic attack.
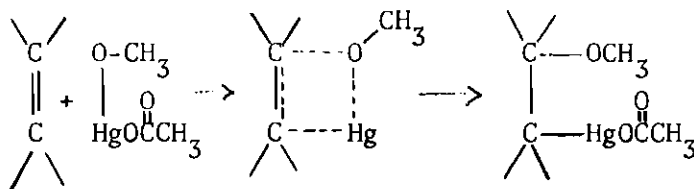


To explain instances of trans-addition, the "coordinative
dipole" mechanism was introduced by Wright.
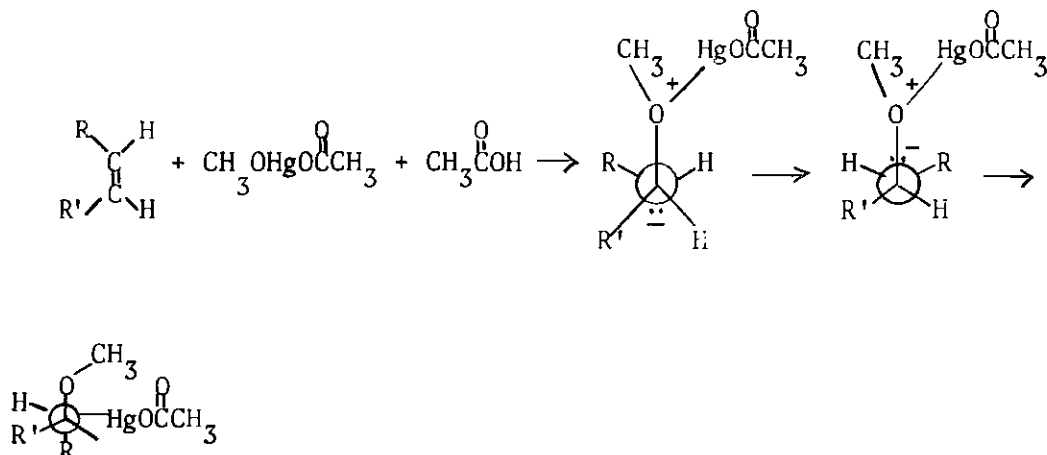


Oxygen first attacks one of the carbons of the double bond shifting
the electrons of the double bond to the other carbon and trans to the

attacking oxygen. The positive and negative centers are then coordinated to each other because of mutual attraction by rotation about the carbon-carbon single bond. This mechanism also indicates nucleophilic attack of oxygen on an unactivated double bond and is thought to not be valid.

Winstein and co-workers[8] have proposed an ionic mechanism as a result of a study of the distribution of cyclohexene between carbon tetrachloride and an aqueous solution of mercury (II) nitrate. It was found, as stated before, that cyclohexene forms two types of complexes with the mercury ions,
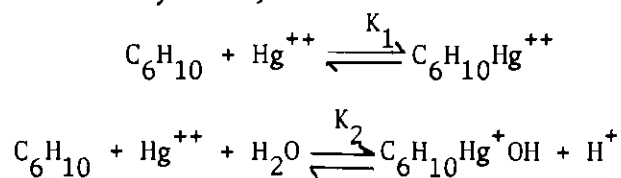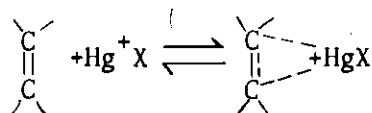
$$C_6H_{10} + Hg^{++} \underset{\longleftarrow}{\overset{K_1}{\rightleftharpoons}} C_6H_{10}Hg^{++}$$

$$C_6H_{10} + Hg^{++} + H_2O \underset{\longleftarrow}{\overset{K_2}{\rightleftharpoons}} C_6H_{10}Hg^+OH + H^+$$

where $K_1 = 2.2 \times 10^4$. $K_2 = 5.0 \times 10^4$.

By analogy to the "bronomium" cation Winstein proposed the mercurium ion to be an intermediate in the oxymercuration reaction,



which can then be attacked by solvent to form the addition product.
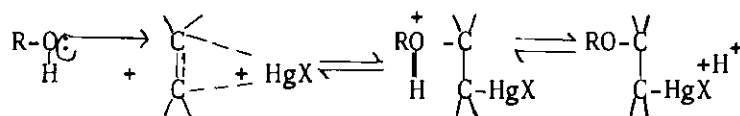


By analogy with the "bromonium cation, hydroxymercuration should take place as a trans-addition.

The oxymercuration of butadiene occurs with only 1,2-addition,

$$CH_2 = CH-CH = CH_2 + Hg(OAc)_2 \qquad \overset{OAc}{AcOHgCH_2-CH-CH = CH_2}$$

and the oxymercuration of bicycloheptenes does not lead to the usual rearrangements[12] of the bicyclic skeleton.

$$\text{(norbornene)} + Hg(ClO_4)_2 \xrightarrow{H_2O} \xrightarrow{NaCl} \text{(product)} \begin{array}{c} OH \\ HgCl \end{array}$$

The organomercury compounds are isolated as their chloride salts rather than their acetate salts due to the greater stability of the chlorides.[1,2] These two results indicate very little carbonium ion character in the intermediate. Reaction with bicycloheptene gives exclusively cis products. The trans-addition can be explained easily by an attack from t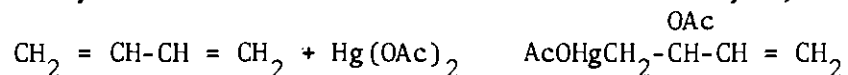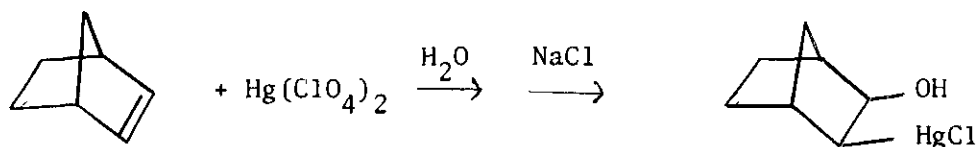he rear by the solvent, but the cis-addition of mercury (II) salts to bicycloheptene needs a further explanation. Traylor[12] has studied the oxymercuration of bicyclo-[2.2.2] oct-2-ene to determine what structural features in the olefin lead to cis or to trans oxymercuration. The effect of solvent and of reagents on stereochemistry of addition are listed in Table 1.

There is a striking difference in product distribution in different solvents and a very noticable product redistribution when NaOAc was added in run four. Another interesting fact is that in run four the trans acetate was not obtained. Generally it is observed that in aqueous solution cis-oxymercuration with mercuric acetate yields some acetate product, but no acetate product is observed in trans-oxymercuration; however, in a solvent that is a poor nucleophile, trans-acetate is obtained.[12]

$$\text{(cyclohexene)} + Hg(OAc)_2 \xrightarrow{t\text{-}BuOH} \begin{array}{c} OC_4H_9 \\ HgOAc \end{array} + \begin{array}{c} OAc \\ HgOAc \end{array}$$
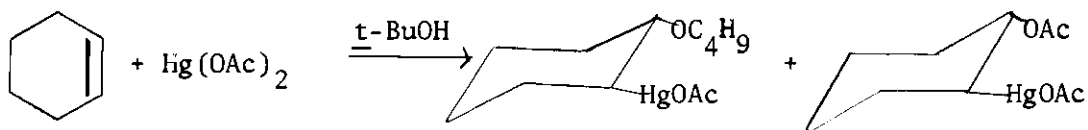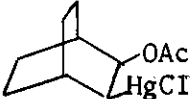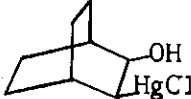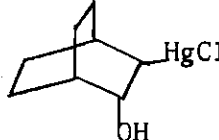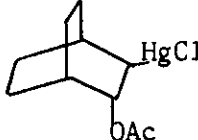
Table 1. Products of Oxymercuration of Bicyclo[2.2.2]oct-2-ene

| Condition | Solvent | Conc. $Hg(OAc)_2$ mol/1 | Conc. NaOAc mol/1 |  |  |  |  |
|---|---|---|---|---|---|---|---|
| 1 | $H_2O$ | 0.1 | | 0 | 50 | 50 | 0 |
| 2 | $H_2O$ Acetone | 0.067 | | 0 | 60 | 40 | 0 |
| 3 | $H_2O$ Acetone | 0.09 | | Trace | 60 | 40 | 0 |
| 4 | $H_2O$ Acetone | 0.1 | 0.139 | 75 | 0 | 25 | 0 |
| 5 | HOAc | 0.37 | | 100 | 0 | 0 | 0 |

Traylor[12] has proposed a general mechanism to explain the
data above.
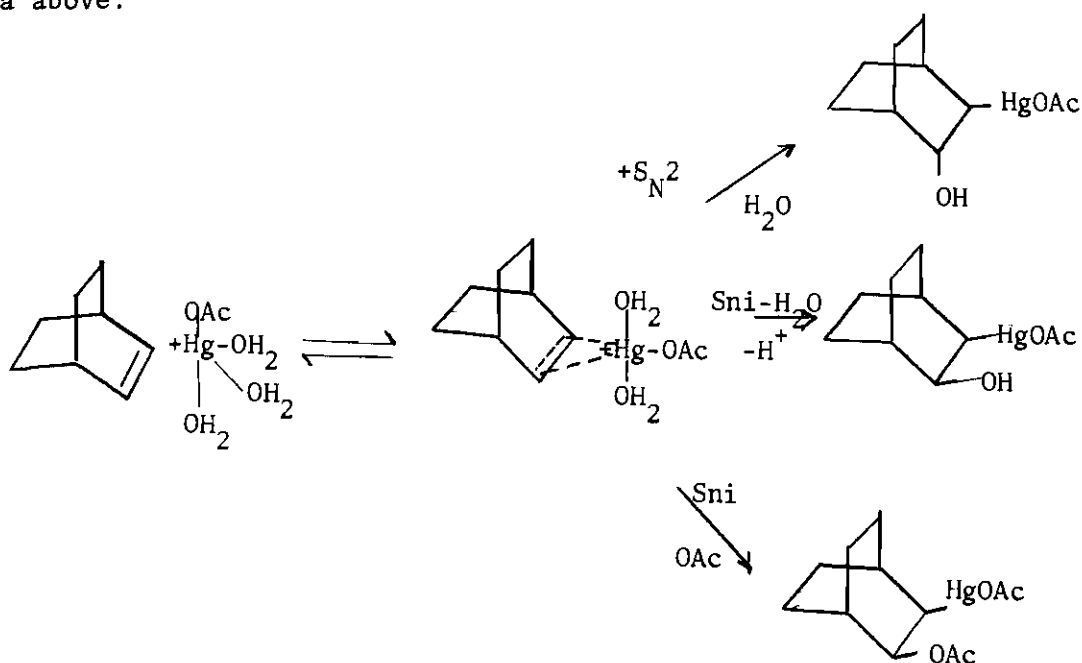


Although the mercurinium ion does not occur in high concen-
tration in aqueous solution, Traylor believes that the kinetics
and stereochemistry of addition are good evidence to include it in
a mechanism. After the intermediate mercurinium ion is formed,
there are two methods of ring opening and in aqueous solution two
nucleophiles to do the opening.

In the $S_N2$ opening, water or acetate ion can enter from
the back side of the mercurinium ion to either one of the two
equivalent carbon atoms. Because acetate ion is a weaker nucleo-
phile than $H_2O$ and because the concentration of $H_2O$ is greater,
the trans-acetate was not observed. The cis-acetate and alcohol
could arise through 6- and 4-centered transition states,[12]
respectively:
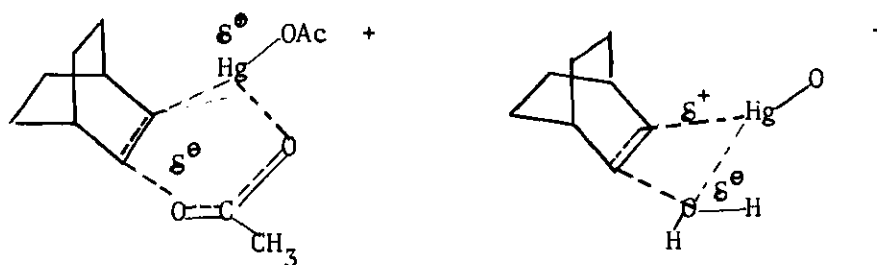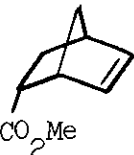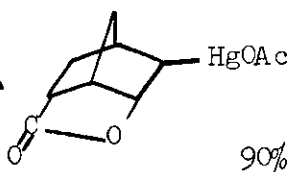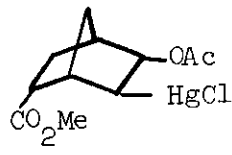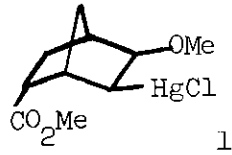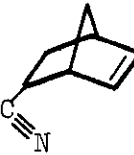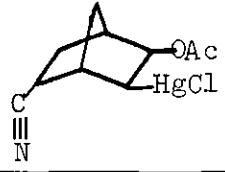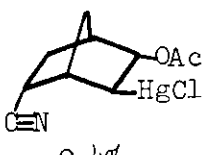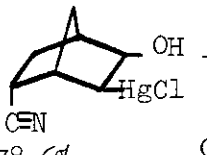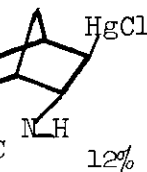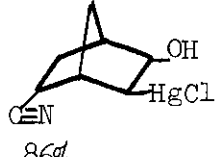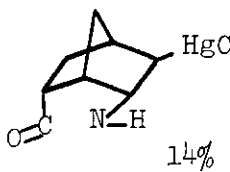
It would be expected that the 6-membered transition, because of less bond angle distortion, would be of lower energy than the 4-membered transition state. Although very little if any acetate was observed when the only acetate source was $Hg(OAc)_2$, the addition of only 0.139 moles/l of NaOAc in condition four of Table 1 shows that three times as much cis-acetate was formed as trans-alcohol. That no cis-alcohol was found can be explained if the transition states are truly 6 and 4 centered.

Traylor[13] has published some results of the effects of neighboring groups on the oxymercuration of norbornene, shown in Table 2.

In Table 2 are the results of oxymercuration of endo-5-carbomethoxy-2-norbornene and endo-5-cyano-2-norbornene. As can be seen, the nature of the solvent is very influential to the product distribution, 5 substituted norbornenes give only cis products, except when the cyano and carbomethoxy group participates. The lactones and lactames are always formed when water is present, but the lactames are not formed as readily.

With a substituent on one of the other bridges the mercurinium ion is unsymmetrical and the problem arises as to which side of the 3-membered ring is attacked. Traylor [13] feels the cyano and ester group decrease the positive charge on nearest carbon. In effect this is strengthening the closest Hg-C bond over the other one. The 3-membered ring then opens leaving the Hg attached to the carbon nearest the cyano or ester group.

## Table 2.  Products of Oxymercuration of Norbornene

| Substrate | Reagent | Conditions | Products |
|---|---|---|---|
| (norbornene-CO$_2$Me) | + Hg(OAc)$_2$ | $\dfrac{25\% \text{ acetone}}{\text{H}_2\text{O}}$ | (bicyclic-HgOAc, lactone) 90% |
| " | + " | (1)HOAc / (2)NaCl | (OAc, HgCl, CO$_2$Me) |
| " | + " | (1)MeOH / (2)NaCl | (OMe, HgCl, CO$_2$Me) 100% |
| (norbornene-C≡N) | + Hg(OAc)$_2$ | (1)HOAc / (2)NaCl | (OAc, HgCl, C≡N) |
| " | + " | (1)25 acetone-H$_2$O / (2)NaCl | (OAc, HgCl, C≡N) 9.4% + (OH, HgCl, C≡N) 78.6% + (HgCl, O=C, N–H) 12% |
| " | + " | (1)25%acetone-H$_2$O .1M NaOAc (0.1M) / (2)NaCl | " 59.7% + " 27.5% + " 12.8% |
| " | + Hg(NO$_3$)$_2$ | (1)25%acetone-H$_2$O / (2)NaCl | (OH, HgCl, C≡N) 86% + (HgCl, O=C, N–H) 14% |
| " | + HgCl$_2$ | (1)25%acetone-H$_2$O / (2)NaCl | " 97% + " 3% |

Bordwell and Douglas[14] have reported on the reduction of alkyl organo-mercurials using $NaBH_4$ in aqueous alkaline medium.

$$RHgX + NaBH_4 \xrightarrow{\ OH^{\ominus}\ } RH + Hg + XB^{\ominus}H_3 + Na^{+}$$
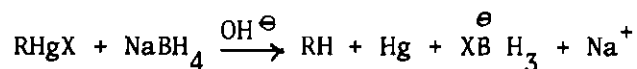
The reaction proceeds very rapidly at room temperature.

H. C. Brown[15] has combined the stereoselectivity of oxymercuration with the mild conditions of $NaBH_4$ reduction as a means for the Markovnikov hydration of the carbon-carbon double bond.

Using the procedure outlined in Brown's communication the object of this research will be to add the elements of water to the double bond in endo-2-carboxybicyclo[2.2.2]oct-5-ene and to analyze the reaction products using prior knowledge of the mechanisms. The hydroxyesters obtained in this reaction will be used in the second part of this project. Traylor[13] has done the oxymercuration reaction on endo-5-carbomethoxy-2-norbornene, but not on its bicyclooctene counterpart. It will be interesting to compare the products obtained in both cases. If the oxymercuration-demercuration reaction is a very selective reaction, and if the mechanisms and assumptions put forth are valid, then two products would be expected.
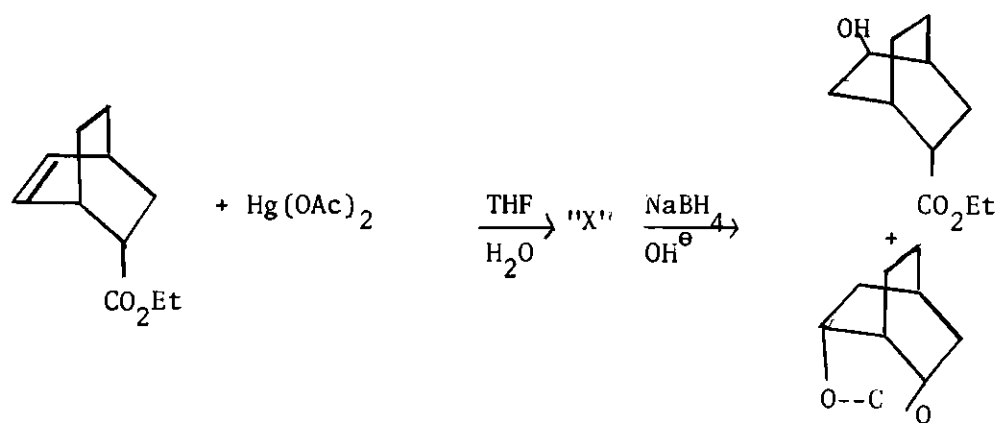
Traylor's[13] reaction of endo-5-carbomethoxy-2-norbornene with Hg(OAc)$_2$ in H$_2$O/ acetone produced 90 per cent lactone.

CHAPTER II

REAGENTS AND EQUIPMENT

## Reagents

Ethylene glycol was Fisher Certified and was not distilled.

Sodium hydroxide was Baker Analyzed Reagent-pellets and was used as obtained.

Ethyl acrylate was Eastman-Practical and was not distilled before use.

Cyclohexene was Fisher (stabilized with NaOH) highest purity and was not distilled before use.

Mercuric acetate was Baker Analyzed Reagent and Fisher-Certified ACS and was not purified before use.

Bromine was obtained from Dow Chemical Company and was not purified before use.

Tetrahydrofuran was Baker Analyzed Reagent and was distilled before use.

$NaBH_4$ was obtained from Metal Hydrides Incorporated and was used as obtained.

NaCl was Fisher-USP and was used as obtained.

Silica Gel was Fisher Certified (100-200 mesh) and was used as obtained.

Benzene was Fisher Certified and was distilled over Na before use.

Chloroform was Fisher USP and Mallinckrodt Technical and was dried over $CaCl_2$ before use.

Ether was Fisher anhydrous and was not distilled before use.

## Equipment

The Nuclear Magnetic Resonance Spectrophotometer was a Varian model A-60.

The gas liquid chromatograph was an F and M model 700 dual column with an SE-30 and a three per cent Carbowax column.

The infrared spectrophotometer was a Perkin-Elmer 457-Grating Infrared Spectrophotometer.

The mass spectrometer was a Varian model M66.

The melting point apparatus was from Mel-Temp.

The evaporator was a Roto-Vac-Flash Evaporator from Buchler Instruments.

Chromatography columns included a 1" by 48" and a 1.5" by 40" and a 50 ml burette using a ratio of absorbent to material separation of 50:1.

The spinning band column was a Nester/Faust model 332 with a 1.5" by 28" column.

CHAPTER III

EXPERIMENTAL

### Preparation of 1,2-Dibromocyclohexane from Cyclohexene

A two liter three-necked flask containing 502g of cyclohexene was cooled to -60°C using a dry ice-acetone bath. A $CaCl_2$ drying tube was put into the center neck and a thermometer into one of the side necks. Nine Hundred seventy-eight grams of $Br_2$ was slowly added from a separatory funnel through the remaining neck so as to keep the temperature of the flask below 0°C. The mixture was stirred by a magnetic stirrer, during the addition of bromine. The mixture was then distilled, the desired product distilling at 100-101°C at 13mmHg. (604g, 40.8 per cent).

### Preparation of Cyclohexadiene from 1,2-Dibromocyclohexane

In a three-necked two liter flask, fitted with a condenser and a stirring rod, 604g of 1,2-dibromocyclohexane was added from a separatory funnel to a solution of 500g of NaOH in 1000g of ethylene glycol at such a rate so as to keep the temperature of the distilling vapors below 100°C. After the 1,2-dibromocyclohexane was added, the mixture was heated to distill off the cyclohexadiene. The crude distillate, which contained cyclohexadiene and cyclohexane plus some other impurities, was distilled and the fraction boiling at 85-87°C (72.9g, 36.5 per cent) collected.

### Preparation of Endo- and Exo-2-Carbethoxybicyclo [2.2.2] oct-5-ene from Cyclohexadiene and Ethyl Acrylate

Thirty-three grams of cyclohexadiene and 52.8g of ethyl acrylate were placed into 100ml glass tube and cooled in dry ice and sealed. The sealed tube was placed into a bomb and heated for 12 hours at 175°C. The tube was then cooled in dry ice-acetone and broken open. The mixture was then distilled on a spinning band column at atmospheric pressure to take off low boiling material.

The distillation was then continued at 3mm of Hg and the Diels-Alder product was collected at 114.5 to 116°C. (31g, 41.8 per cent). GLC taken using SE-30 column at 105°C showed the octene to be 15 per cent exo and 85 per cent endo.

### Separation of Endo and Exo-2-Carbethoxybicyclo[2.2.2]oct-5-ene

Seventeen and two-tenths grams of 15 per cent exo and 85 per cent endo octene was eluted through a column containing 250g of silica gel. The column was 1.5" in diameter and 40" in length. The elutant was 15 per cent benzene and 85 per cent cyclohexane by volume. Eight and two-tenths grams of pure endo, as determined by GLC, was obtained. No attempt was made to obtain pure exo. The exo was eluted first along with increasing amounts of endo. When all of the exo had been eluted, pure benzene was used to remove the remaining endo. Approximately 1000ml of 15 per cent benzene 85 per cent cyclohexane was used to remove the exo and 1000ml of pure benzene to elute the remaining endo. Fractions were checked on five per cent Carbowax GLC column at a temperature of 105°C.

### The Oxymercuration-Demercuration of 2-Carbethoxybicyclo[2.2.2]oct-5-ene Using the Method Described by Brown

Using the method described by Brown[15] 35.6g of mercuric acetate was placed in a 500ml Erlenmeyer flask. One hundred ten milliliters of $H_2O$ and 110 ml of distilled THF were added. Upon adding the THF, the solution turned a bright yellow. Then 20g of the octene ester was added and the solution was stirred by a magnetic stirrer. After approximately two hours the yellow color disappeared. Generally, the mixture was stirred for five to ten times the length of time that it remained yellow. In this case it was allowed to stir over night. Then 110 ml of 3M NaOH and 110 ml of a solution of 0.5M $NaBH_4$ in 3M NaOH were added separately to the reaction flask while the flask was cooled in ice because of the exothermic reaction. Immediately the solution turned gray, indicating the presence of metallic mercury. The mercury was allowed to settle and the solution

was saturated with NaCl to separate the THF and $H_2O$ into separate layers. The THF layer was dried with $MgSO_4$, evaporated, and an IR and a GLC taken of the remaining liquid. The $H_2O$ layer was extracted with $HCCl_3$, dried with $MgSO_4$, and evaporated. (16.5g from THF layer, 75 per cent; and 5.15g extracted from the $H_2O$ layer. This reaction was repeated nine times using various amounts of olefin.
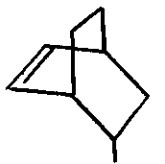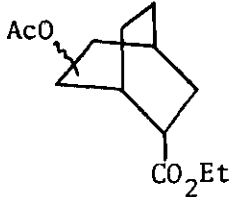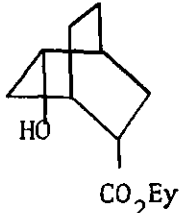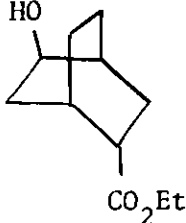
### Separation of Oxymercuration-Demercuration Reaction Products

Separation of reaction products was best achieved by using column chromatography. Silica gel was used as the absorbent and $CHCl_3$ as the eluting solvent. Various column sizes were used, but the ratio of absorbent to substance being separated was always kept at 50 to one. In one case five grams of oxymercuration-demercuration product was separated using 250g of silica gel. If complete separation was not achieved after putting the substance through the column once, various fractions were put through a column again. This procedure was repeated until enough pure material was obtained. To check the purity, the solvent would be evaporated and if any liquid remained it would be checked by GLC. Because of the complex nature of the mixture, the following procedure was used.

By use of NMR and IR it was found that the major peaks observed on the SE-30 column were acetates and alcohols, with the acetates appearing as later peaks; however, when the Carbowax column was used, the acetate and alcohol peaks merged. The SE-30 column would be excellent to indicate if there was separation of the acetates and alcohols by column chromatography. The peak that represented the alcohol, however, was found not to be that of a single compound. Upon putting a sample of the pure alcohol peak (that appeared on SE-30) through a Carbowax column, at least two distinct peaks appeared and there was an indication of another. So the procedure consisted of first analyzing the fractions using SE-30 column, then the Carbowax column, since the acetates came off the silica gel column first.

Using a 1" by 48" silica gel column with 250g of silica gel and five grams of oxymercuration-demercuration product, the following

amounts of chloroform were used to bring out the different components.

| Compound | Ml at Appearance of Peak | Ml at Disappearance of Peak |
|---|---|---|
|  CO$_2$Et | 300 | 500 |
| AcO  CO$_2$Et | 400 | 700 |
|  HO CO$_2$Ey | 600 | 1100 |
| HO  CO$_2$Et | 1100 | 1600 |

### Reaction of Oxymercuration Mixture with CH$_3$COCl in Pyridine

Approximately one gram of oxymercuration-demercuration mixture was poured into 25ml of dry pyridine and two milliliters of acetyl chloride was slowly added. The reaction was carried out in dry pyridine, dried by distillation from CaO. The reaction was allowed to sit for a few minutes and then was filtered to remove solids. Most of the pyridine was evaporated off and the mixture was put onto a GLC SE-30 column.

# CHAPTER IV

## RESULTS AND DISCUSSION

The mixture of products obtained from oxymercuration-



demercuration was found to contain 18.5 per cent starting material, 7.31 per cent of a 2,6 lactone, 46.1 per cent isomeric alcohols and 28.1 per cent of isomeric acetates. It was found when the mixture was put through a silica-gel column, with a 50:1 weight ratio of absorbent to reaction product, $CHCl_3$ brought through the starting material first, then the acetates, and finally the alcohols. With the size columns used, the alcohols could not be separated in one pass through the column. The alcohol fractions were put through a six foot five per cent Carbowax GLC column and were found to contain three compounds. It was found that two of these compounds, I and II, could be separated by using silica gel and $CHCl_3$. The two compounds that were separated were assigned the following structures.
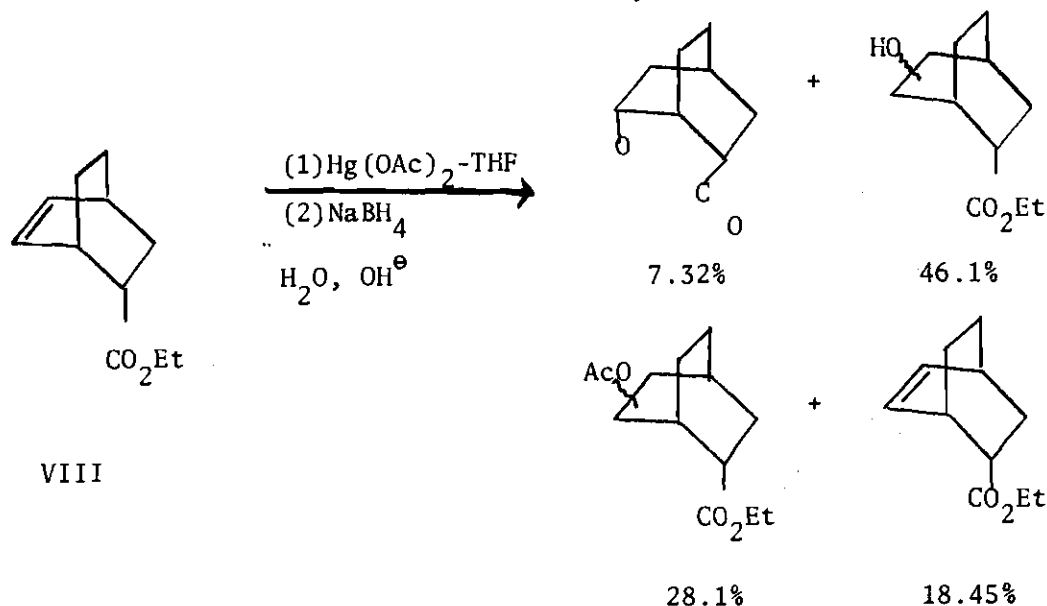
HO

CO$_2$Et
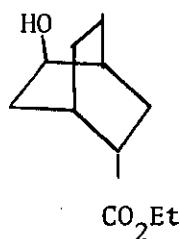
(I)

58.8 per cent of total
acetate mixture

HO

CO$_2$Et
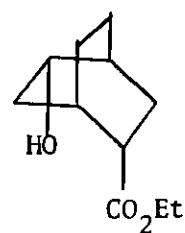
(II)

28 per cent of total
acetate mixture

The percentages of the alcohols (I), (II), and (III) were
determined from ratios of acetates after the oxymercuration-demer-
curation product was acetylated with acetyl chloride in dry pyridine.
The ratios were determined from the area under peaks of a GLC taken
of the reaction mixture after the pyridine was removed.

Compound II came off the silica gel column first, possibly
because there is intramolecular hydrogen bonding and it is, therefore,
absorbed to a lesser extent; however, the carbonyl stretching fre-
quency was very similar for compounds I and II, so hydrogen bonding
cannot be very great.

The spectral data for compounds I and II are as follows:

Compound I

NMR

    8.75    (triplet)   (3H)

    5.87    (quartet)   (2H)

    6.82    (singlet)   (1H)   (sharp)

    5.84-6.2   (multiplet)   (2H)

    7.2-9.0   (multiplet)   (10 H)

IR

    3420 cm$^{-1}$, 2940 cm$^{-1}$, 2870 cm$^{-1}$, 1728 cm$^{-1}$

Mass spec.

    M$^+$ = 198

Compound <u>II</u>

NMR

       8.76    (triplet)   (3H)

       5.85    (quartet)   (2H)

       6.74    (singlet)   (1H)   (broad)

       5.95-6.35   (multiplet)   (2H)

       7.25-8.9   (multiplet)   (6H)

       8.5    (singlet)   (4H)

IR

       3430 $cm^{-1}$, 2950 $cm^{-1}$, 2875 $cm^{-1}$, 1730 $cm^{-1}$

Mass spec.

       $M^+$ = 198

The singlet at 8.5 for compound II was thought to be due to the bridge with no substituent, because the substituents on the other bridges were far enough away not to cause splitting.[17] The broad singlet at 6.74 for compound II indicates that the hydroxyl hydrogen is being affected by the carbethoxy group on carbon 2. These two facts indicate that structure assigned to compound II is correct.

The third compound that was not separated from the mixture of alcohols was assigned the following structure.



CO$_2$Et
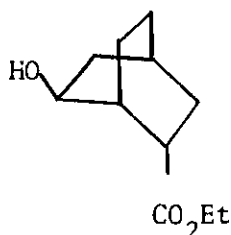
13.3 per cent of total acetate mixture

(III)

This structure was assigned because III had a retention time similar to a compound made by another route by Fisher[18]:

$$\xrightarrow[\text{(2)}H_2O_2, \ OH^{\ominus}]{\text{(1)}B_2H_6, \ THF}$$

CO$_2$Et       CO$_2$Et    +    CO$_2$Et
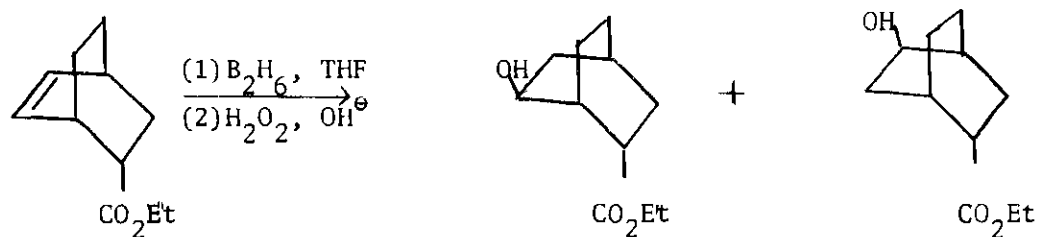
The acetates from the oxymercuration reaction could be separated on an SE-30 glc column, but they were not able to be separated by solid-liquid column chromatography using silica-gel and chloroform. On SE-30, three peaks were obtained and they were thought to correspond to the three isomeric acetates. Samples of the two pure alcohols I and II were acetylated and it was found that compounds were formed corresponding to the acetates of the original mixture, thus confirming they were acetates and relating each alcohol to its acetate.

The lactone was assigned the following structure:
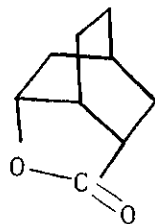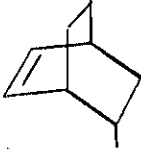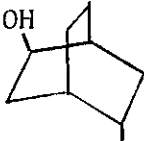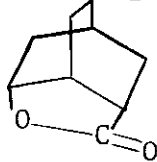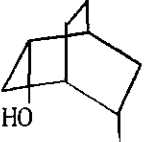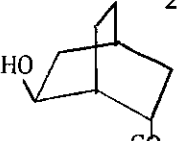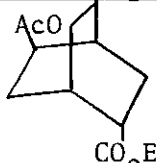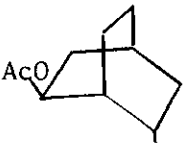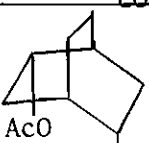


(IV)

Compound IV has a similar retention time to a lactone of known structure.[18]

The retention times for the products in the oxymercuration-demercuration of endo-2-carbethoxybicyclo[2.2.2]oct-5-ene are listed below in Table 3.

Table 3. Retention Times for Products of Oxymercuration-
Demercuration of Endo-2-Carbethoxybicyclo[2.2.2]oct-5-ene

Retention Time in Minutes; Temp=160°C; Flow rate= 30-60 ml/min

| Compound | SE-30 Retention Time | 5 per cent Carbowax Retention Time |
|---|---|---|
| (structure) CO$_2$Et | 2.5 | .5 |
| (structure) OH ... CO$_2$Et | 7.25 | 4.20 |
| (structure) O—C=O | 4.5 | 1.25 |
| (structure) HO ... CO$_2$Et | 7.25 | 3.00 |
| (structure) HO ... CO$_2$Et | 7.25 | (4.0) |
| (structure) AcO ... CO$_2$Et | 12.75 | |
| (structure) AcO ... CO$_2$Et | 10.10 | |
| (structure) AcO ... CO$_2$Et | 11.40 | |

It is interesting to compare oxymercuration of compounds of similar structure. Traylor's results of oxymercuration of compounds V and VI in $H_2O$/acetone are as follows[13,12]:

(V) + Hg(OAc)$_2$ $\xrightarrow[\text{(2)NaCl}]{\text{Acetone/H}_2\text{O}}$  HgCl ... HO (40%)  +  HO ... Hg—Cl (60%)

(V)

(VI) + Hg(OAc)$_2$ $\xrightarrow[\text{(2)NaCl}]{\text{Acetone/H}_2\text{O}}$  Hg—Cl ... O—C=O lactone (90%)

$CO_2Me$

(VI)

90%
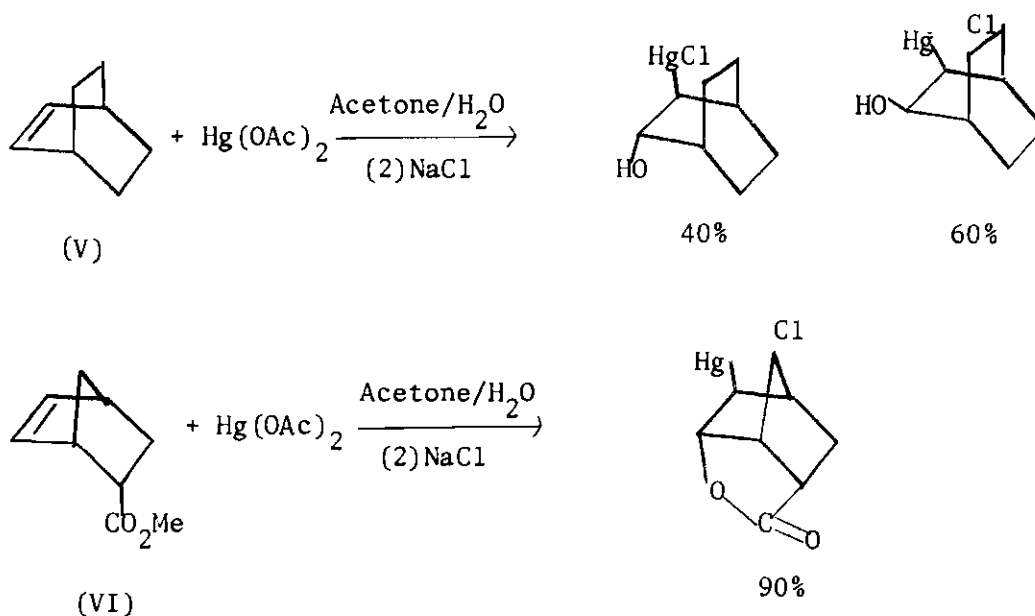
The oxymercuration-demercuration of compound VII in 50 per cent THF/$H_2O$ produced only 7.32 per cent lactone, compared to 90 per cent for the oxymercuration of compound VI. Traylor's[13] oxymercuration of compound VI in carefully dried methanol gave no lactone. Compound VII is less rigid than VI because of the two carbon bridges of VII and compound VII is an ethyl ester, while compound VI is a methyl ester. It is not easy to understand the difference in lactone formation in view of these structural differences.

If the mercurium[8] ion is the initial step in the oxymercuration reaction, the formation of the final products can be rationalized by the following mechanisms:
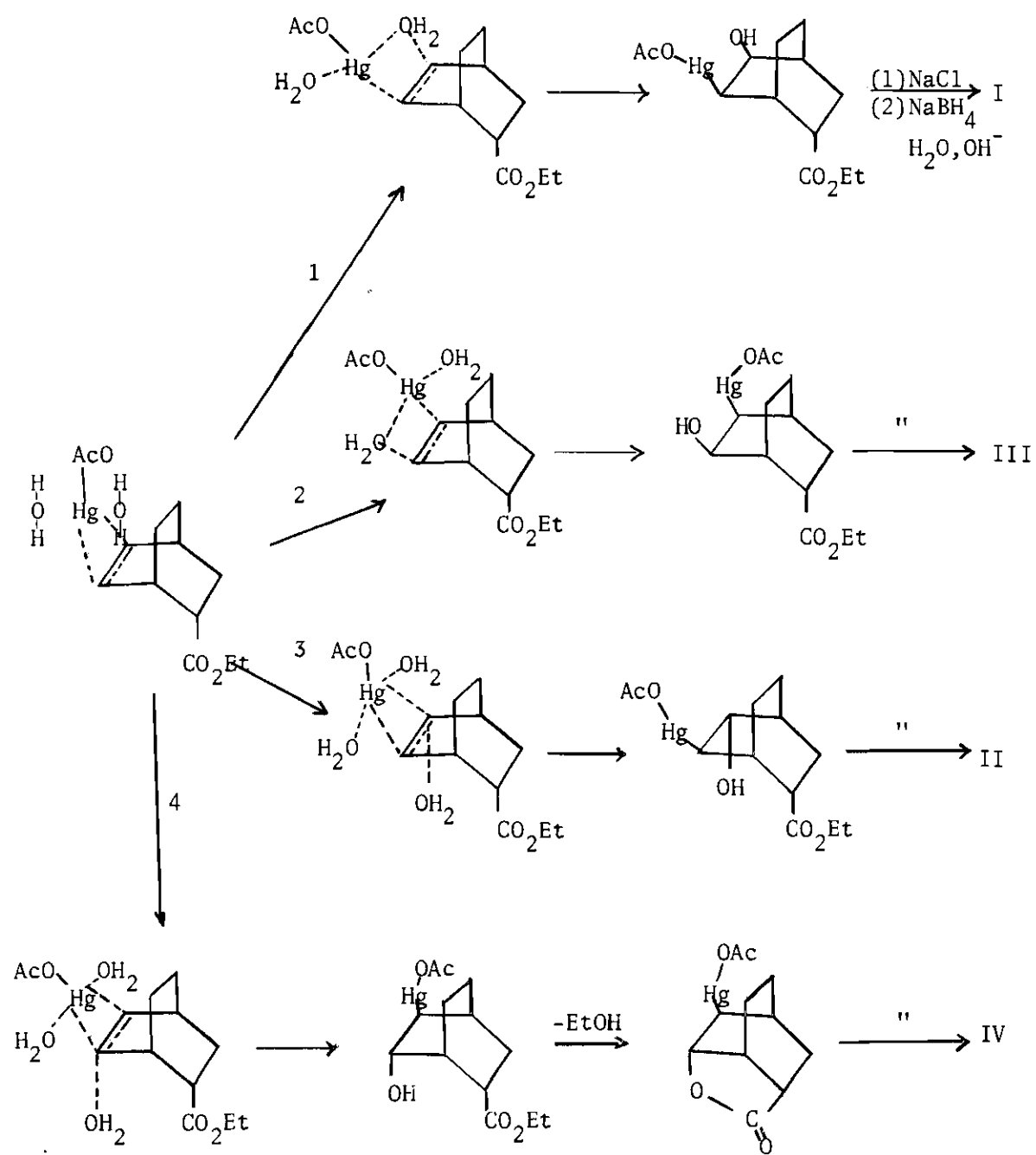
If the mercurium ion is present, then mechanisms 1 and 3 must be of lower energy since the majority of the alcohol products of oxymercuration are the ones ascribed to these two pathways. The formation of the acetates could follow similar pathways. If the mercurium ion VIII were symmetrical, we would expect there to be equal amounts of compounds I and III, not the 58.8 per cent and 13.3 per cent as reported. The unsymmetrical nature of the mercurium ion could be accounted for in several ways.
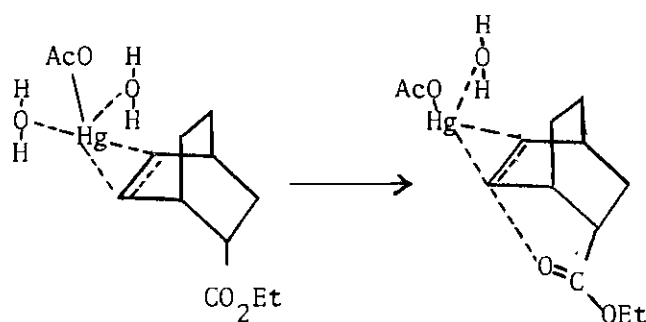


The source of electron density from the carbonyl oxygen in the 2 position could increase the electron density at the 6 position by electrostatic interaction, thereby strengthening any bonds in which the carbon at position 6 is participating. Increasing the electron density between the mercury and the carbon in position 6 would create an unsymmetrical mercurium ion. The weaker bond between the mercury and the carbon in the 5 position would be the more easily broken in a nucleophilic attack.

The preferred attack at the 5 position could also be explained in terms of the stability of a developing positive charge at the 5 and 6 positions. The carbon at position 5, being further away from the positive carbonyl carbon, would be more stable causing the transition state to be of lower energy and, therefore, the preferred pathway. As noted earlier, oxymercuration does not lead to the usual rearrangements[12] characteristic of carbonium ions; thus there is nothing to indicate that a carbonium ion is formed upon opening of the mercurium ion.

Still another possible mechanism involves a comples formed between the mercury and the carbonyl oxygen.[16]
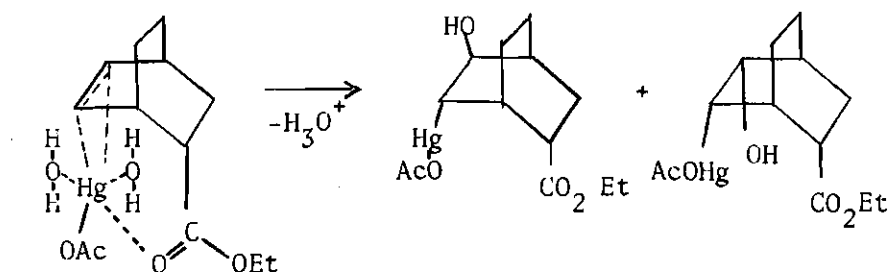
Again the mercurium ion is unsymmetrical and the bond be-
tween the mercury and the carbon in position 5 would be weaker
because of the lengthening of the bond by the attraction between
the carbonyl oxygen and the mercury.

Traylor's[12] oxymercuration of bicyclo[2.2.2] oct-5-ene
in $H_2O$/acetone produced no acetates while in this study 28.1 per
cent of the three isomeric acetates were formed. In view of the
fact that the reduction was done in 3N NaOH solution, more acetates
may have been produced than is evident from the final products.

The oxymercuration-demercuration procedure of Brown[15]
was originally carried out to prepare compound I; however, the
addition to the double bond of endo-2-carbethoxybicyclo[2.2.2] -
oct-5-ene is not selective enough to exclude formation of other
possible isomers.

It must be said that the structural proof for compounds I,
II, and III is not absolutely conclusive since it is based upon
NMR spectral data and mechanisms discussed earlier. In part
II of this study, further evidence will be brought forward in the
form of rate of alkaline hydrolysis and pKa's of the corresponding
acids to see if the difference in reactivities can be explained
by the assumed structures.

CHAPTER V

CONCLUSIONS

Oxymercuration-demercuration provides a relatively easy procedure to the hydration of an olefin.

The oxymercuration-demercuration of 2-endo-carbethoxybicyclo- [2.2.2] oct-5-ene is not a steroselective reaction to the exclusion of other products. Addition to the double bond of 2-endo-carbethoxy- bicyclo[2.2.2] oct-5-ene occurs more at the 5 position than the 6 position.

All products obtained can be explained by mechanisms put forth in current literature.

CHAPTER VI

RECOMMENDATIONS

2-carbethoxybicyclo[2.2.2.]hept-5-ene should be oxymercurated-demercurated by Brown's[15] procedure to compare products.

Brown's procedure should be modified by the addition of sodium acetate to see if product distribution changes.

2-exo-carbethoxybicyclo[2.2.2.]oct-5-ene should be oxymercurated-demercurated.

The oxymercuration-demercuration of 2-carbethoxybicyclo-[2.2.2.]oct-5-ene should be oxymercurated-demercurated.

The oxymercuration-demercuration of 2-carbethoxybicyclo-[2.2.2.]oct-5-ene should be studied in anhydrous acetic acid and anhydrous methanol.

BIBLIOGRAPHY

1. N. S. Zefirov, Russ. Chem. Rev., 34, 527 (1965).

2. K. Hofman and Sand, J., Ber., 33, 1340, 2692 (1900).

3. J. Chatt, Chem. Rev., 48, 7 (1951).

4. W. Schoeller, Schrauth, W., and Esser, W., Ber., 46, 2864 (1913).

5. W. Manchot, Ber., 53B, 984 (1920).

6. W. Manchot, and Klug, A., Ann., 420, 170 (1920).

7. J. Sand and Breest, F., Z. Physik. Chem., 59, 424 (1907).

8. H. J. Lucas, Hepner, F. R., and Winstein, S., J. Am. Chem. Soc., 61, 3102 (1939).

9. G. F. Wright, J. Am. Chem. Soc., 57, 1993 (1935).

10. W. H. Brown and Wright, G. F., J. Am. Chem. Soc., 62, 1991 (1940).

11. J. Romeyn and Wright, G. F., J. Am. Chem. Soc., 69, 697 (1947).

12. T. G. Traylor, J. Am. Chem. Soc., 86, 244 (1964).

13. T. G. Traylor and Factor, A., J. Org. Chem., 33, 2607 (1968).

14. F. G. Bordwell and Douglass, M. L., J. Am. Chem. Soc., 88, 993 (1966).

15. H. C. Brown and Geoghegan, F., Jr., J. Am. Chem. Soc., 89, 1522 (1967).

16. M. Abercrombie, Rodgman, A., Bharucha, K., and Wright, G., Canad. J. Chem., 37, 1328 (1959).

17. Private Communication, C. L. Liotta and W. F. Fisher.

18. Private Communication, W. F. Fisher.

PART TWO

THE MODE OF TRANSMISSION OF SUBSTITUENT

EFFECTS THROUGH THE BICYCLOOCTANE MOLECULE

CHAPTER I

INTRODUCTION

The influence of substituents upon a reaction center has
been looked at with much interest, but to date no satisfactory
theory has been proposed that can relate quantitatively substituent
parameters (charge, dipole moment, distance, angle, etc.) to
reaction center reactivity. In 1962 Dewar and Grisdale[1] published
a series of articles in which they made an analysis of substituents
effects. The substituents' modes of transmission were grouped
into five different processes listed below.

Field effect is the transmission of the influence of a charge
or a dipole, upon the reaction center, through space.

$\sigma$-Inductive effect is the transmission of the substituent
effect through the molecular frame work by successive polarization
of the intervening $\sigma$-bonds.

$\pi$-Inductive effect is similar to the $\sigma$-inductive except that
any $\pi$-bonds located between the substituent and the reaction center
are polarized by neighboring $\sigma$ or $\pi$-bonds which can then transmit
the original effect to the reaction center directly, or indirectly
by polarization of intervening $\sigma$-bonds.

Mesomeric effect is the polarization of the $\pi$-electron system
by resonance interaction with the substituent.

Electromeric effect is the direct resonance interaction
of the $\pi$-electron system between the substituent and reaction center.

The systems to be studied in this work are semi-rigid
bicyclo $[2.2.2]$ octane isomers and therefore the field and $\sigma$-inductive
effects are the only ones to be considered.

Among the earliest to attack the problem of substituent effects
in saturated systems was Bjerrum.[2] Using a simple electrostatic
model, Bjerrum tried to predict the ratio of dissociation constants

of various symmetrical substituted dibasic acids. His reasoning
was that the negative charge on the dibasic acid, after the first
hydrogen pulled off, caused the dissociation of the next hydrogen
to be of much higher energy. Euchen[3] then extended this theory to
include dipolar substituents. Both theories gave poor quantitative
results largely because of neglecting the molecular framework by
assuming the dielectric between substituent and reaction center to
be that of the solvent. Smallwood[4] took the molecular framework
into account by giving it a dielectric of unity and by suggesting
the substituent effects are transmitted through the molecular frame
rather than the solvent. The results were qualitatively good for
dipolar substituents, but left much to be desired for charged
substituents.

Kirkwood and Westheimer[5] took both the molecular framework
and the solvent into account in developing an expression for the
influence of substituent. A dielectric of two was proposed for
the molecular framework equating the framework to that of liquid
paraffin hydrocarbons and this was used to evaluate the effective
dielectric, $D_E$. The expression for dipolar substituent is as follows:

$$\log \frac{K_x}{K_H} = \frac{e \mu \cos \Theta}{2.3 KTR^2 D_E}$$

where $e$ is the electronic charge, $\mu$ the difference in group or bond
moment between the substituent and hydrogen, R the distance from
the center of the dipole to the ionizable proton, $\Theta$ is the angle R
makes with the direction of the bond moment, $D_E$ is the effective
dielectric and KT has its usual meaning.

Roberts and Moreland[6] synthesized a series of 4-substituted
bicyclo[2.2.2]octane-1-carboxylic acids and analyzed their experi-
mental reactivities to that calculated by the Kirkwood-Westheimer
electrostatic equation. However, the discrepancies were found in
the $\Delta$pKa values calculated and found. Tanford,[7] noting these
discrepancies, modified the Kirkwood-Westheimer equation by introducing

the concept of placing the dipole or charge at certain depth within the cavity. By calculating the depth that gave the best results for amino acids and for halogenated carboxylic acids, Tanford chose a depth of 1 $\overset{o}{A}$ for the dipole.

Siegel and Kormarmy[8] determined the pKa values of some trans-4-substituted cyclohexane carboxylic acids in several solvent systems but it was not possible to correlate experimental data quantitatively to calculated values. Stock and Holtz[9] determined the pKa values of some 4-substituted bicyclo[2.2.2]octane acids in 50 per cent aqueous ethanol with an accuracy of $\pm$ 0.03 pKa units. However, dispite the improved data, the correlation between theory and experiment was not good.

Dewar and Grisdale[1] proposed a model in which both the field and resonance effects were taken into account. It was suggested that because the negative end of the dipole would be solvated away from the molecule to a certain extent, treating the interaction as single charges interacting with one another, would be more in line with reality. Thus the effect of the substituent upon the reaction center with distance would vary somewhere between the first and second power of that distance. Using meta-substituted benzoic acids as standards the following expression was proposed:

$$F = (\sigma_x)_M r_{1,3}$$

where F is a measure of the field effect, $(\sigma_x)_M$ is a parameter for the meta substituent and $r_{1,3}$ is the distance between the first and third carbons of the aromatic ring. The carbon-carbon distances used in all calculations of aromatic systems is that of benzene. The general expression for the field effect when the $\pi$-inductive and mesomeric effect is taken into account is as follows:

$$F = \sigma_{ij} r_{ij} - M_{qij} r_{ij}$$

(m=M for meta substituents) =0

Here, M is the measure of the combined $\pi$-inductive-mesomeric effect of the substituent and $q_{ij}$ is the formal charge at position j produced by attacking the group $-CH_2$ at position i. Using the above equation they generated $\sigma$-values for various systems of molecules that agreed well with experiment. The reactions used to generate the $\sigma$-values were ionization of carboxyl group and ester formation.

Holtz and Stock[9] analyzed by several methods, including Dewar's, the dissociation of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. It was found that for saturated systems Dewar's method was inadequate, possibly because the mode of transmission of substituent effects in Dewar's standard acid was not analyzed correctly, since the standard is aromatic and the method is best applied to similar systems.

In opposition to the field effect model is the $\sigma$-inductive model as proposed by Branch and Calvin.[10] According to this model the substituent effect $\lambda_s$, is transmitted through the $\sigma$-bonds to the reaction center, not through space, but by the successive polarization of the intervening $\sigma$-bonds. The substituent effect is diminished by a constant factor $\epsilon$, which is less than one and is called the attenuation factor. The resultant effect $\lambda_{s\pm n}$ is summed over all pathways as illustrated in the following equation:[11]

$$\lambda_{s\pm n} = \lambda_s \sum_p (\epsilon_{s\pm n})_p$$

Taft[12] has observed that for each methylene group placed between a substituent and the reaction center the reactivity changes by a factor of 2.3 to 3.2 based upon $\sigma^+$ values. Ritchie[13] has observed that Taft's $\sigma^*$ values for alkyl groups do not fall in line with other substituents. Others [14,15,16] have estimated fall-off factors to be from two to three.

Taft[12] has proposed that there is a relationship between $\sigma^+$ values and electronegativities. Chang and Tai[17] have published the results of the calculation of a constant for the inductive effect

of a group, called the inductive index which can relate systematically and quantitatively the inductive effect exerted upon a chemical bond in a molecule by a group from the electronegativity and atomic radii of the group elements involved in the chemical bond. It was also observed that where steric or conjugative effects predominate, the relationship between chemical reactivity and the inductive index remains no longer linear. Hinze, Whitehead, and Jaffe[18] have found a correlation between calculated group electronegativities and Taft's $\sigma$-values.

Dewar[1,19] suggested that the $\sigma$-inductive effect diminishes to nothingness when the reaction center is separated from the substituent by one or two bonds. Ehrenson[20] feels that both the $\sigma$-inductive and field effects are likely factors contributing to substituent effects on reaction centers.

Because of their measure of the susceptibility of a reaction to polar effects, Bowden[21] has made use of Hammett reaction constants (p and p'), in order to relate molecular features, such as geometry of the molecular cavity and solvent environment around substituent and reaction center to reactivity by calculating reactivities of a system with reference to various modes of transmission. Comparing these values, Bowden hoped to evaluate the importance or nonimportance of each theory.

The Kirkwood-Westheimer model was used by Bowen for the electrostatic field, 4-substituted cyclohexane carboxylic acids used as a standard for the aliphatic and alicyclic systems and the para-substituted benzoic acids as the standard for the aromatic systems. The molecules were considered to be in a cavity with a dielectric of two and the reaction center was considered to be 0.89Å beyond the carbonyl carbon on a line passing through the bond between the carbonyl carbon and the ring carbon attached to it. The calculated ratios of $\cos \theta / R^2$ of the various systems used were compared to the ratio which was experimentally determined using Hammett reaction constants.

The Branch and Calvin approach to the inductive model was used by Bowden. However the value of the transmission factor was

found to vary greatly from 0.1 to 0.6. Bowden used calculated trans-
mission factors based upon data for the change in Hammett constants
for the following system:
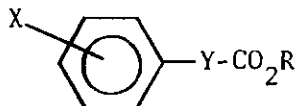


By using groups for y that contained carbons of various hybridiza-
tion, Bowden assigned the following values of $\epsilon$ to different carbons:

$$C(sp^3) = 0.48+ \pm 0.04, \quad C(sp^2 \text{ ethylenic}) = 0.67 \pm 0.02,$$
$$C(sp^2 \text{aromatic}) = 0.06 \pm 0.02, \quad C(sp) = 0.57 \pm 0.01,$$
$$C(sp^2 \text{carbonyl}) = 0.43, \quad O = 0.61 \pm 0.01.$$

Using the appropriate transmission factor and the same standard
systems as for the field effect model, ratios of calculated reactivities
were compared to corresponding ratios of Hammett constants.

Bowden believed that the field effect is important in the
transmission of polar effects and that the inductive effect is less
important; however, for aromatic and conjugated systems he considered
that the -inductive effects were significant.

Bowden[22] has also noted the effect of the solvent upon the
ionization of ortho-substituted benzoic acids compared to the meta
and para isomers. The results indicated that substituents dloser
to the reaction center are more medium independent than substituents
farther away. Bowden believed that this observation fits the
electrostatic model for transmission of substituent effects.

Baker, Parish, and Stock[23] showed that the transmission of
substituent effects was independent of the number of pathways and
independent of the hybridization of the intervening carbon atoms when
comparing the dissociation constants of the series of bicyclo[2.2.2]-
oct-2-ene-1-carboxylic acids, dibenzo[2.2.2]oct-2,5-diene-1-carboxylic
acids and cubane carboxylic acids. Wilcox and Leung[24] have compared
the dissociation constants of some bicyclo[2.2.2]octane and bicyclo-
[2.2.1]heptane-1-carboxylic acids. They have concluded from this

data that the field effects model was more in agreement with experimental results than was the classical inductive model.

Golden and Stock[25] have demonstrated in the case of 8-substituted ethano-bridged anthracene-1-carboxylic acids a reverse substitutent effect. Adcock and Dewar[26] observed an angular dependence ob substituents in 1- and 2-fluoronapthalenes as did Grubbs and Fitzgerald[27] in geometrically isomeric 11, 12-dichloro-9,10-ethano-anthracenes. However, Grubbs and Fitzgerald did not find a reversal in normal substituent effects as had Golden and Stock. Bowden and Parkin[28] reported a reverse substituent effect for 8-substituted-1-naphthoic acids and for cis and trans-$\alpha$-phenylsuccinic acids with substituents in the ring B-to the carboxyl group; however, Dewar[29] feels that Bowden and Parkin's interpretation is not valid due to the evidence for hydrogen bonding between substituent and reaction center in the above systems.

The following study will be taken hopefully to put more light on an already greatly studied area of research. Two isomeric alcohol esters will be hydrolyzed in 50 per cent $EtOH/H_2O$ (w/w) under alkaline conditions and the pKa's of the corresponding acids determined.

The two compounds,
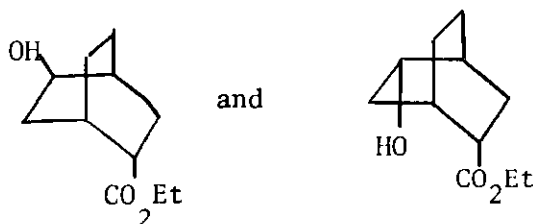


differ only in distance and angle of the substituent to reaction center. The results of the experimental studies will be discussed to see which mode of transmission of substituent effects best fits the experimental data.

CHAPTER II

REAGENTS AND EQUIPMENT

## Reagents

The ethanol qas 95 per cent and was distilled using a $CaCl_2$ solution to prevent $CO_2$ adsorption and stored in ground glass bottles.

The $H_2O$ was distilled from basic potassium permanganate using a $CaCl_2$ solution to prevent $CO_2$ adsorption and stored in ground glass bottles.

The NaOH was Baker Analyzed Reagent pellets.

The HCl was Fisher Reagent.


## Equipment

The Hickman Stills which were used to distill small quantities of liquid were made by the glass blowing shop.

The pH meter was a Beckman Research pH meter model no. 1019 with platinum electrode.

The gas liquid chromatograph was F and M model 700 dual column with an SE-30 and a Carbowax column.

The mass spectrometer was a Varian model M66.

The melting point apparatus was a Mel-Temp unit.

CHAPTER III

EXPERIMENTAL

### Preparation of NaOH and HCl Solutions

To 500 ml of 50 per cent EtOH/$H_2O$ (w/w) solution 0.8g of
sodium hydroxide was added to give approximately a 0.04$\underline{N}$ solution.
Two hundred-fifty milliliters of this solution was diluted to
500 ml with 250 ml of 50 per cent EtOH/$H_2O$. These solutions were
titrated against potassium acid phthalate that had been dried by
heating under a vacuum. The HCl solution was made from a concen-
trated solution that was diluted with water to approximately
0.04$\underline{N}$ and titrated against the standardized sodium hydroxide
solution.

### Purification of Compounds for Kinetic Runs

After the alcohol esters were purified by column chroma-
tography, as explained earlier, they were placed in a special
Hickman still used to distill small quantities of material.
From 0.2g to 0.6g of material was distilled by placing the bulb
of the still into an oil bath to insure even heating.

Boiling point for compound I was 125-130°C at 3mmHg.
Boiling point for compound II was 120-125°C at 3 mmHg.
Boiling point for compound III was 89-94°C at 3 mmHg.

### Method of Measuring the Alkaline Rates of Hydrolysis

For the hydrolysis of                                    the following



I    $CO_2Et$
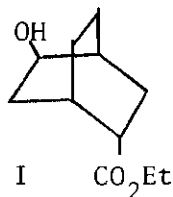
procedure was used. The alcohol ester (0.0767g) was placed in a
vial and ten milliliters of 50 per cent EtOH/$H_2O$ was added. The
solution was allowed to equilibrate at 25°C for 30 minutes and then

ten milliliters of 0.0389N sodium hydroxide in 50 per cent EtOH/H$_2$O
was added. After approximately 20 minutes one milliliter of this
solution was added to one milliliter of 0.0387N HCl. One drop of
one per cent phenolphthalein solution in 50 per cent EtOH/H$_2$O was
added to the acidified portion and the whole was titrated to the
phenolphthalein end point with 0.0194N sodium hydroxide and the data
was recorded. This procedure was repeated 17 times over a period of
21 hours. Three runs were made. For                the

HO          CO$_2$Et

II
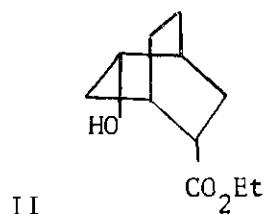
same procedure was used, except that 0.0557g of the alcohol ester
was dissolved in seven milliliters of 50 per cent EtOH/H$_2$O and
seven milliliters of 0.042N sodium hydroxide as added. In this
case ten points were taken over a period of five hours. For

HO

III          CO$_2$Et
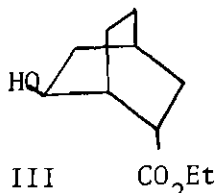
0.0444g of the alcohol ester was dissolved in six milliliters
of 50 per cent EtOH/H$_2$O (w/w) and six milliliters of 0.0374N
sodium hydroxide was added. In this case ten points were taken
over a period of nine hours. From this data the rate of dis-
appearance of base was calculated and the reciprocal of the base
concentration was plotted against the time. A straight line was
fitted to the points. The data was put through a least squares
program by a computer and values for the slopes with the best fit
were obtained.

Preparation and Purification of Compounds I and II for pKa Study

Compounds I and II were allowed to stand for several days
in a slightly alkaline solution, then continuously extracted with
ether. The extracts were discarded. The aqueous solutions were
made acid with HCl to about a pH of three and extracted continuously

with ether. After drying these ether extracts over $MgSO_4$, the ether was taken off. The solid remaining was sublimed under vacuum and yielded 0.258g of the acid of compound I having a melting point of $147^{\circ}$-$152^{\circ}$ uncorrected. Similarly, 0.216g of the acid of compound II having a melting point of $126^{\circ}$-$128^{\circ}C$, uncorrected, was obtained.

## Measurement of pKa's

Each acid (0.1701g) was placed into 100ml of 50 per cent $EtOH/H_2O$. Thirty milliliters and 20ml samples were titrated with 0.01$\underline{N}$-NaOH solution and between each addition of base the pH was recorded. The pH was determined initially and four or five points recorded around the midpoint and 0.1 ml portions of base were added around the endpoint. The pH meter had been standardized at pH of 5.738 with a half-neutralized solution of benzoic acid.

## Preparation of Compound III from Its Acetate

Compound III was not able to be separated as its alcohol, but could be as an acetate. A fraction (0.6391g) containing approximately 90 per cent acetate of compound III and ten per cent of the alcohol of III and I was added to 25ml of dry EtOH to which 0.066g of sodium had been added. This mixture was allowed to stand for eight hours and was then added to 50ml of de-ionized water containing 0.282ml of concentrated HCl. This mixture was extracted continuously with ether. The solution was dried over $MgSO_4$ and the ether taken off. No acetate was present as evidenced by glc analysis. This compound was prepared for alkaline hydrolysis as described before.
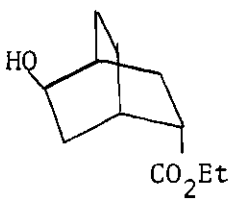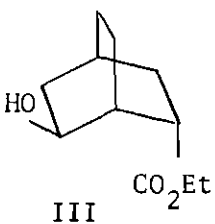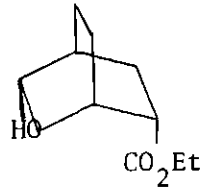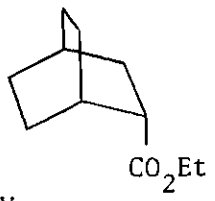
CHAPTER IV


DISCUSSION AND RESULTS


The rates of alkaline hydrolysis of compounds I through
IV and the pKa's of the corresponding acids are listed in Table 1.

In order to use the Kirkwood-Westheimer electrostatic model,
it is necessary to know the angle between substituent dipole
and reaction center and the distance from the center of the dipoles
of the substituent to the reaction center. The reaction center for
the rate alkaline hydrolysis was chosen as the carbonyl carbon.
The reaction center for the pKa's was chosen 1.45$\overset{o}{A}$ from the carbonyl
carbon, on a line joining the carbonyl carbon to the carbon
adjacent to it. Table 2 contains the angles and distances for the
systems concerned herein as calculated using known bond angles
and distances.

The analysis of the rates of alkaline hydrolysis and pKa's
of compounds I through IV by the use of the Kirkwood-Westheimer
electrostatic model are tabulated in Table 3.

The log Kx/Kh values calculated for the rates of alkaline
hydrolysis and pKa's of compounds I, II and III differ slightly
from experimental log Kx/Kh values. The calculated log Kx/Kh
values for compounds I and III are smaller than experimental, where-
as for compound II the calculated log Kx/Kh is still smaller than
experimental. This smaller value for the calculated log Kx/Kh
of compound II, as compared to experimental log Kx/Kh, can be
explained by participation of the hydroxyl group in the transition
state as shown.

Table 1. Reactivities of Some Bicyclic Hydroxy Esters

| Compound | Rate of Alkaline Hydrolysis $X \ 10^2$ | pKa of Acid |
|---|---|---|
|  I | 7.565 ± 0.037 | 6.416 ± 0.023 |
|  III | 9.856 ± 0.083 | 6.261 ± 0.002[*] |
|  II | 20.49 ± 0.285 | 6.045 ± 0.016 |
|  IV | 2.16 ± 0.003[*] | 6.722 ± 0.006 |

[*]Private communication, W. F. Fisher

Table 2. Angles and Distances
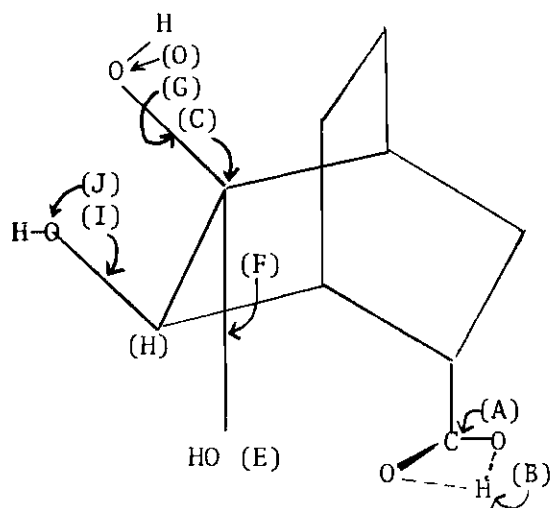


Bond Lengths, Å

C-O = 1.42

C-C = 1.536

C-$\overset{\,/\!/}{C}$ = 1.516

$\overset{O}{\underset{O}{C}}$---H = 1.45

| Distance | Value of Distance Å | Angle | Value of Angle |
|---|---|---|---|
| A-C | 3.56 | AGC | $76^{\circ}\ 23'$ |
| B-C | 4.51 | BGC | $79^{\circ}\ 44'$ |
| A-B | 1.45 | CFA | $94^{\circ}\ 27'$ |
| A-E | 3.54 | CFB | $96^{\circ}\ 35'$ |
| A-F | 3.55 | BIH | $80^{\circ}\ 7'$ |
| A-G | 4.24 | AIH | $76^{\circ}\ 42'$ |
| A-D | 4.92 | | |
| B-E | 4.16 | | |
| B-F | 4.34 | | |
| B-G | 5.20 | | |
| B-D | 5.88 | | |
| A-H | 2.91 | | |
| A-J | 3.63 | | |
| B-H | 3.84 | | |
| B-J | 4.45 | | |
| A-I | 3.27 | | |
| B-I | 4.15 | | |
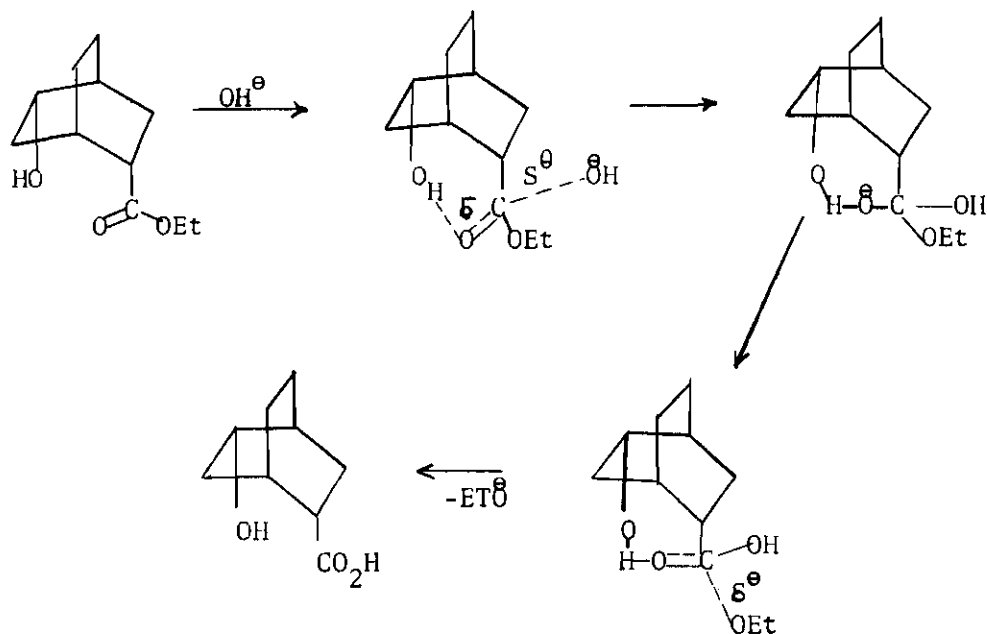
In Table IV the $\sigma$-inductive analysis of the rates of the 5- and 6-substituted bicyclooctane compounds are tabulated.

The $\sigma$-inductive model, using a fall off factor of 2.7, predicts very closely the ratio of the 5- and 6-reactivities. The reactivity of compound II, because of direct interaction of the hydroxyl, does not follow the $\sigma$-inductive model.

In order to see how the Kirkwood-Westheimer electrostatic model relates the reactivities of the 5- and 6-substituted compounds, the ratios of the calc. and exp. reactivities of the 5- and 6-substituted alcohol esters and acids are listed in Table 5.

The Kirkwood-Westheimer electrostatic equation does not predict absolute reactivities in a quantitative manner, but it ' is still qualitatively good considering its basic theoretical assumptions. The $\sigma$-inductive equation does not start from such a basic background and can work for any system when the right attenuation factor is used. In this case an attenuation factor of 2.7 for both the pKa's and kinetics of hydrolysis give a 5-6 ratio of 0.721, which is between both experimental values. If two different attenuation factors were used for the pKa's and kinetics, the 5-6 ratios calc. and 5-6 ratios exp. could be made to coincide. For the Kirkwood-Westheimer electrostatic model
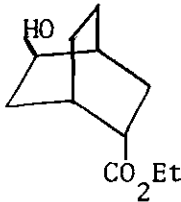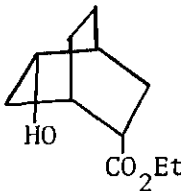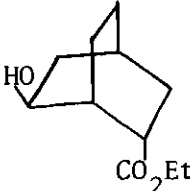
Table 3. Calculated and Experimental Values
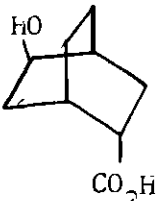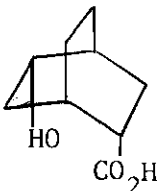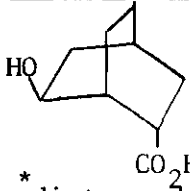
| Compound | $r_1 \overset{O}{A}$ * | DE** | log Kx/Kh calc. (numerical value) | log Kx/Kh exp. (numerical value) |
|---|---|---|---|---|
| (structure) I | 4.24 | 3.58 | 0.130 (1.35) | 0.542 (3.48) |
| (structure) II | 3.55 | 3.242 | 0.079 (1.20) | 0.9764 (9.46) |
| (structure) III | 3.27 | 3.06 | 0.294 (1.775) | 0.659 (4.56) |
| (structure) | 5.195 | 4.115 | 0.057 (1.14) | 0.305 (2.02) |
| (structure) | 4.34 | 3.59 | 0.0684 (1.17) | 0.677 (4.75) |
| (structure) | 4.15 | 3.54 | 0.10 (1.26) | 0.459 (2.88) |

* distance between substituent and reaction center
** dielectric constant calculated between substituent and reaction center

Table 4. $\sigma$-inductive Model Results



$$2 X \left(\frac{1}{F}\right)^3 + \left(\frac{1}{F}\right)^5 + \left(\frac{1}{F}\right)^7 = X$$

fall off factor for position 5

for (F = 2), X = 0.28906

for (F = 3), X = 0.07968

for (F = 2.7), X = 0.109335



$$\left(\frac{1}{F}\right)^2 + \left(\frac{1}{F}\right)^4 + \left(\frac{1}{F}\right)^6 = X$$

fall off factor for position 6

for (F = 2), X = 0.35938

for (F = 3), X = 0.12562

for (F = 2.7, X = 0.16535

| F | ratio 5-6(calc.) | ratio 5-6 kinetics(exp.) | ratio 5-6 pKa(exp.) |
|---|---|---|---|
| 2. | 0.805 | 0.768 | 0.701 |
| 2.7 | 0.721 | | |
| 3 | 0.635 | | |

Table 5. Ratios of Reactivities of Compounds I and III

| | kinetics esters calc. | kinetics esters exp. | pKa acids calc. | pKa acids exp. |
|---|---|---|---|---|
| $\dfrac{K_I}{K_{III}}$ | 0.761 | 0.768 | 0.905 | 0.071 |

the 5-6 ratio calc. for alkaline hydrolysis, 0.761, is very close to the experimental ratio of 0.768. The 5-6 ratio calc. for pKa's is 0.905 compared to the value of 0.701 found experimentally. Both the $\sigma$-inductive and the electrostatic equation of Kirkwood-Westheimer predict within the same order of magnitude, but both lack quantitative accuracy in the systems studied here.

The Kirkwood-Westheimer equation must have the knowledge of angles and distances to a very high degree of accuracy. The bicyclo $\overline{2.2.2}$ octane molecule substituted in the 2 and 5 positions is a flexible structure. A small change in distance and angle can easily be visualized. Even these small changes can change the calculated reactivities greatly because the Kirkwood-Westheimer equation involves the ratio of log terms. To insure exact knowledge of angles and distances a more rigid system such as 2- and 5-substituted bicyclo $\overline{2.2.1}$ heptane would be better; however, this system has the disadvantage of having isomers with the substituents in different environments.

Another source of error in applying the electrostatic model in this study is when using the hydroxyl group as a substituent to neglect the H-O dipole in determination of where the center of the group dipole is. In this study the center of the hydroxyl dipole was taken at the center of the carbon-oxygen bond. The electro-negativity of hydrogen is 2.1 and carbon is 2.5. The dipole of the hydrogen-oxygen bond would be expected to be of a greater magnitude than the carbon-oxygen dipole of the hydroxyl group. When taking the hydrogen-oxygen dipole into account there would be the problem of determining exactly where to place the dipole, since it is free to rotate around the carbon oxygen bond. This could be very important in compound II where, because of the closeness of the substituent and reaction center, the hydrogen-oxygen bond of the hydroxyl group could be coordinated to the carbonyl oxygen. As shown below the dipole due to the vector summation of the carbon-oxygen dipole and the hydrogen-oxygen dipole would place the dipole closer to the reaction center and would increase the angles used in the Kirkwood-Westheimer equation.

If we let log Kx/Kh = 1 for an angle of 75°, a change in
this angle to 80° gives a log Kx/Kh value of 0.67. This would
mean that a substituent with a dipole angle of 75° with respect
to the reaction center would be 2.14 times as reactive as the same
substituent with an angle of 80°. If we let log Kx/Kh = 1
for a distance of 4.0Å, a change in distance to 4.1Å would give
a log Kx/Kh = 0.952. A substituent 4.0Å from a reaction center
would be 1.12 times as reactive as a substituent 4.1Å away.
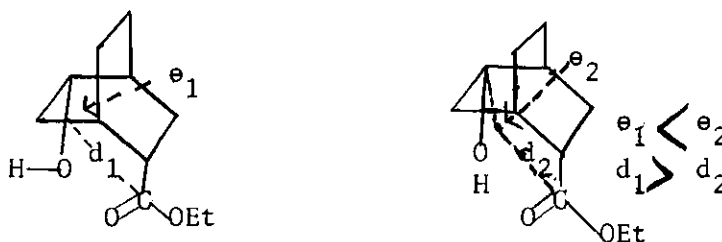


Both of these factors, greater angle and shorter
distance, would cause the log Kx/Kh value calc. to be greater
than that previously calculated and, therefore, closer to the
experimental values. The question arises as to what extent the
hydrogen-oxygen bond is coordinated to the carbonyl oxygen.
Since in a rate process the transition state is the important step,
we should be more concerned with what is happening at that
moment. It would be expected that even greater coordination
would be associated with the transition state because of the
increased negative charge on the reaction center. But whether
or not this coordination is partial or total is not known.

Another question arises in the field effect model when
treating compounds such as II. Where does the field effect stop
and direct interaction or, in this case, hydrogen bonding start?
There is no reason why the field effect should stop totally at any
distance, but hydrogen bonding should fall off greatly beyond a
certain distance where the probability of electron overlap becomes
small. It would appear that dipolar electrostatic interactions
should be important in hydrogen bonding, but in what way such

interactions could be evaluated is not evident.

A plot of the pKa's versus the log K of alkaline hydrolysis of the ethyl esters of various bicyclooctane molecules is shown in Chart I.

It can be seen from this chart that the steric and electronic environment for both the pKa's of the acids and the rates of alkaline hydrolysis of their esters are similar.
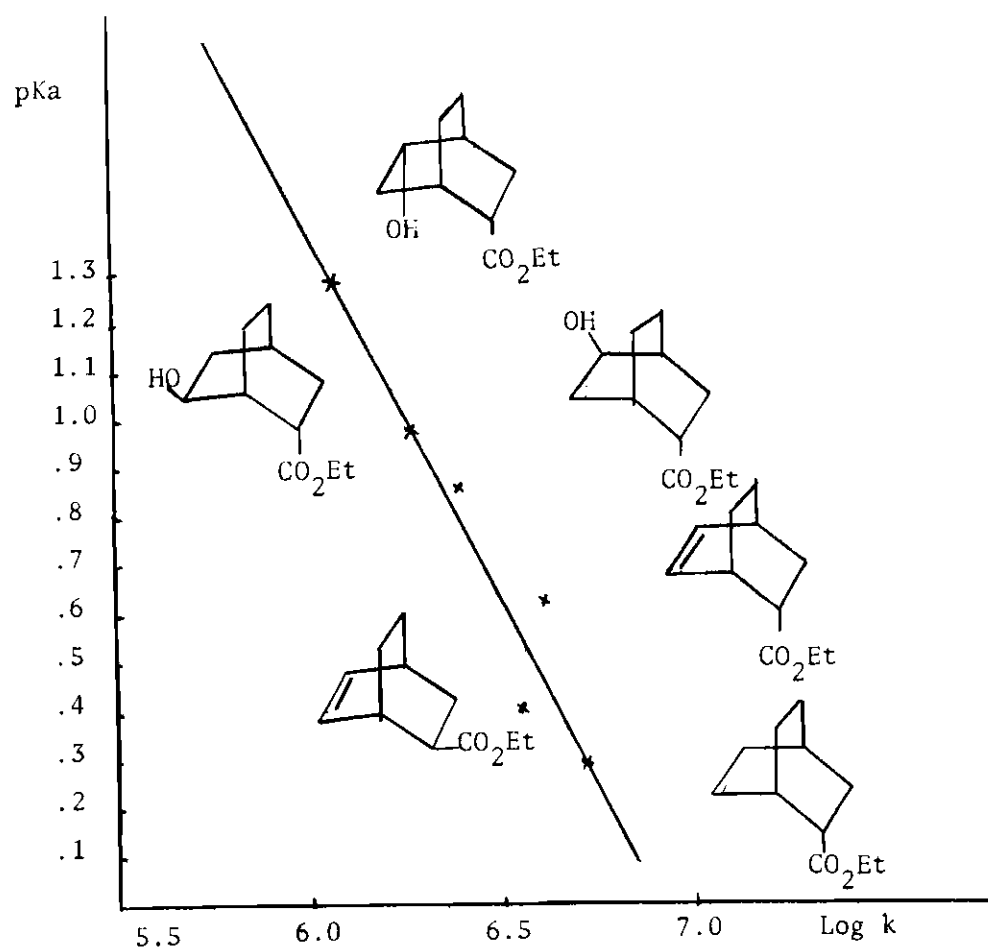
Chart I. pKa's vs Log K of Alkaline Hydrolysis of Ethyl Ester of Various Bicyclooctanes

CHAPTER V

CONCLUSION

The analysis of the reactivities of the compounds studied
here by the $\sigma$-inductive and the electrostatic model of Kirkwood-
Westheimer shows that neither model is superior to the other.
Both models predict reactivities qualitatively, but both lack
quantitative accuracy.

CHAPTER VI

RECOMMENDATIONS

The more rigid bicyclo [2.2.1] heptane counterparts of the
system studied here should be made and studied so that the distance
and angles of substituent to reaction center can be more firmly
fixed.

The halogen substituents should be studied to lessen the
chances of direct participation as found for compound II.

When the hydroxyl group is used as a substituent in the
Kirkwood-Westheimer the hydrogen-oxygen dipole should be taken
into account as well as the carbon oxygen dipole.

BIBLIOGRAPHY

1. M. J. S. Dewar and Grisdale, J., J. Am. Chem. Soc., 84, 3539, 3548 (1962).

2. N. Bjerrum, Z. Physik. Chem., 106, 219 (1923).

3. A. Eucken, Angew. Chem., 45, 203 (1932).

4. H. M. Smallwood, J. Am. Chem. Soc., 54, 3048 (1932).

5. J. G. Kirkwood and Westheimer, F. H., J. Chem. Phys., 6, 500 (1938). F. H. Westheimer and Shookhoff, M. W., J. Am. Chem. Soc., 61, 555 (1939). F. H. Westheimer and Kirkwood, J. G., ibid., 6, 513 (1938).

6. J. D. Roberts and Moreland, W. T., ibid., 75, 2167 (1953).

7. C. Tanford, ibid., 79, 5348 (1957).

8. S. Siegel and Kormarmy, J. M., ibid., 82, 2547 (1960).

9. H. D. Holtz and Stock, L. M., ibid., 86, 5288 (1964).

10. G. E. K. Branch and Calvin, M., The Theory of Organic Chemistry, Prentice Hall, New York, 1941.

11. M. J. S. Dewar and Marchand, A. P., ibid., 88, 354 (1966).

12. R. W. Taft, Jr., Steric Effects in Organic Chemistry, M. S. Newman, ed., Wiley, Inc., New York, 1965, Chapter 13.

13. C. D. Ritchie, J. Phys. Chem., 65, 2091 (1961).

14. J. C. McGowan, J. Appl. Chem., 10, 312 (1960).

15. B. M. Wepster, Rec. Trav. Chem., 71, 1171 (1952).

16. G. W. Stevenson and Williamson, D., J. Am. Chem. Soc., 80, 5943 (1958).

17. M. Chang and Tai, T., Sic Sinica, (Peking), 12, 785 (1963).

18. H. Hinze, Whitehead, M. A., and Jaffe, H. H., J. Am. Chem. Soc., 85, 148 (1963).

19. M. J. S. Dewar and Marchand, A. P., ibid., 88, 354 (1966). ibid., 88, 3318 (1966).

20. S. Ehrenson, Progress in Physical Organic Chemistry, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, eds., Interscience

Publishers, New York, 1964, pp. 195-251.

21. K. Bowden Can. J. Chem., 41, 2781 (1963).

22. K. Bowden and Janser, G. E., Can. J. Chem., 46, 2941 (1968).

23. F. W. Baker, Parish, R. C., and Stock, L. M., J. Am. Chem. Soc., 89, 5677 (1967).

24. C. F. Wilcox and Leung, C., ibid., 90, 336 (1968).

25. R. Golden and Stock, L. M., ibid., 88, 5928 (1966).

26. W. Adcock and Dewar, M. J. S., J. Am. Chem. Soc., 89, 379 (1967).

27. E. J. Grubbs and Fitzgerald, R., Tetrahedron Letters, 4901 (1968).

28. K.Bowden and Parkin, D. C., Chem. Comm. 75 (1968).

29. M. J. S. Dewar, ibid., 547 (1968).