The potassium salts of 6-vinyl-7, 8, 9, 10-tetrahydro-6(5H)benzo and 3-methoxybenzocyclooctenols were found to undergo ring expansion by 1, 3 sigmatropic shifts at 25°C when dissolved in hexamethyl phosphoric triamide (HMPT). The rate constants were measured and compared. Hammet's linear free energy equation was used to estimate a $f$ value. From the sign and magnitude of the $f$ value mechanistic conclusions were drawn.
Ring Expansion 3-Methoxy-6-Vinyl-7, 8, 9, 10-tetrahydro-6(5H)-benzocyclooctenol

by

Mehdi Meshgini

A THESIS

submitted to

Oregon State University

in partial fulfillment of the requirements for the degree of

Master of Science

Completed March 1978

Commencement March 1978
APPROVED:

Redacted for Privacy

Associate Professor of Chemistry
in charge of major

Redacted for Privacy

Chairman of the Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented March 9, 1978

Typed by Margie Wolski for Mehdi Meshgini
ACKNOWLEDGEMENTS

I would like to thank Dr. Richard Thies for his guidance and giving generously of his time. I would also like to thank Dr. Phil Seitz and other members of our group. Special thanks go to Mr. Karl Swenson and Ms. Susan Randall. Last, but certainly not least, I thank my wife, Roshanak, for her love, patience and moral support.
TO

Roshanak and Rod
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL</td>
<td>2</td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION</td>
<td>19</td>
</tr>
<tr>
<td>SYNTHETIC METHODS</td>
<td>32</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>36</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>54</td>
</tr>
</tbody>
</table>
RING EXPANSIONS OF AIKOXIDES AS POSSIBLE SYNTHETIC METHODS OF HORMONE ANALOGUES

INTRODUCTION

The ring expansion experiments used here are part of an exploration of possible methods to prepare certain hormone model systems such as an 8:9, 13:14 disecosteriod and its derivatives with the ultimate goal of investigating its birth control activities.

\[
\text{diseconorestrone} \quad \begin{array}{c}
\text{HO} \\

\text{estrone} \quad \begin{array}{c}
\text{HO}
\end{array}
\end{array}
\]

That this disecosteriod is analogous to a female sex hormone (estrogen) is obvious from the structure of estrone, though it should be borne in mind that it does not possess the rigidity of the hormone skeleton.
HISTORICAL

The migration of a sigma (\(\sigma\)) bond flanked by one or more pi (\(\pi\)) electron systems to a new position within the molecular skeleton is known as a sigmatropic rearrangement. The common examples may be generalized as shown in Scheme 1.

\[
\text{Scheme 1} \quad \text{G} \quad \text{C} \quad \text{G} \\
\text{c} \quad (\text{c} = \text{c})_n \quad (\text{c} = \text{c})_n \quad \text{c}
\]

where a \(\text{C}\) bond at the end of a conjugated \(\pi\) bond system migrates to the other end of the \(\pi\) system with a simultaneous shift of the \(\pi\) bonds (Schemes 2 and 3).

\[
\text{Scheme 2} \quad \text{G} \quad \text{C} \quad \text{C} \quad \text{G} \quad \text{C} \\
\text{C} \quad \text{C} \quad \text{1, 3} \quad \text{C} \quad \text{C} \quad \text{C}
\]

\[
\text{Scheme 3} \quad \text{G} \quad \text{C} \quad \text{C} \quad \text{1, 5} \quad \text{C} \quad \text{C} \\
\text{C} \quad \text{C} \quad \text{G} \quad \text{C} \quad \text{C} \quad \text{C}
\]

The \(\text{C}\) bond may also be located between two \(\pi\) bond systems (Schemes 4 and 5).
A rearrangement is designated with two numbers, $i$ and $j$, where $i$ and $j$ refer to the number of atoms to which each end of the migrating bond goes, starting from the original two atoms forming the original bonds, e.g., $i, j$ are 1, 3 in Scheme 4.

In 1940 A. C. Cope reported \((1, 2)\) the thermal rearrangement of certain diallyls to isomeric diallyl compounds (Scheme 6).

\[ \text{X and Y = CN or CO}_2\text{Et} \]
This Cope 3,3 sigmatropic shift of a bis-allylic system is the best known of these transformations and differs from Claisen rearrangement essentially in the substitution of oxygen for carbon.

Low temperature rearrangement can be observed when $E_a$ is low and rearranged product has a more favorable energy than reactant. An example is that of cis-divinyl cyclopropane where a diallyl $\rightarrow$ diallyl rearrangement is accompanied by release of angle strain in opening the cyclopropane ring (Scheme 7).

![Scheme 7 Diagram](image)

The thermal rearrangement of 3-hydroxy-1,5-hexadiene systems have been well studied and are known to take place in a number of different ways: (1) a 3,3 sigmatropic shift leading to an enol (Scheme 8).

![Scheme 8 Diagram](image)
(2) a 1,3 sigmatropic shift leading to another enol (Scheme 9)

Scheme 9

(3) a 1,3 sigmatropic shift resulting in a non-enolic compound (Scheme 10)

Scheme 10

(4) finally, a 1,3 sigmatropic shift leading to β hydroxy olefin cleavage (Scheme 11).

Scheme 11

The first two rearrangements which lead to formation of enol have been designated (3) as oxy-Cope rearrangements. The tendency of oxygen to enter into conjugation with the double bond in the product is apparently an important driving force in the enol formation rearrangements.
R. W. Thies has used the oxy-Cope rearrangement as a possible synthetic pathway to a two carbon ring expansion (4) where a 1,3 sigmatropic shift occurs as shown below (Schemes 12 and 13).

The yields are low, however, because of effective competition from \( \beta \)-hydroxy olefin cleavage.

In an attempt to increase the yields of two carbon expansion, in 1972, Thies (5) introduced the method of siloxy-Cope rearrangement. A trimethyl silyl blocking group was used in systems like 1 and 3 above to eliminate the undesirable \( \beta \)-hydroxy olefin cleavage. The pyrolysis of 1-trimethyl siloxy-1-vinyl cyclonon-3-ene gave both 1,3 and 3,3 shift products as shown below (Scheme 14).
The author noted a substantial improvement in the yield with the siloxy-Cope variation relative to the oxy-Cope method. Serious $\beta$-hydroxy olefin cleavage and elimination side reactions were successfully prevented and a further advantage appeared, it could be run in the liquid phase rather than the gas phase.

Subsequent work by Thies and co-workers further established the advantages and limitations of the new method. Some of the results are summerized below (Scheme 15).

Scheme 14

Scheme 15

+ Ring Contracted Products

55%
Products formed from 12 and 13 upon thermolysis at 300-310° followed by hydrolysis are shown below with their relative percentages (Scheme 16).

Scheme 16

Thies and Bolesta further showed (6) that the same type of two carbon ring expansion is feasible for large systems; even though such systems have less ring strain to be released and thus higher $E_a$. The 3, 3 shift reaction competes effectively as shown below (Scheme 17).
As part of an exploration at a possible method to prepare hormone model systems, recently Thies and Shih reported (7) another thermolytic siloxy-Cope two carbon ring expansion (Scheme 18).

All of the rearrangements discussed so far are conducted under rather severe temperature conditions. Lower temperatures are possible for certain anionic rearrangements. Franzus et al. (8) conducted a base catalyzed rearrangement of 7-norborndienol and
discussed the low rearrangement enthalpy of 7-norbornadienol in terms of rearrangement via a 1,3 sigmatropic shift (Scheme 19).

Scheme 19

Dramatic rate enhancements are observed for the anionic rearrangements relative to the thermolytic rearrangements. For example a 3 M solution of 23 in 0.08 M NaOH in methanol completely rearranges to the tropyl skeleton 24 within 5 min. at ambient temperatures in sharp contrast to temperatures of over 170°C for analogous systems where the -O\(^-\) group is replaced by OCH\(_3\).

Pentadienal anions are used in terpene synthesis by Wilson et al. (9). A variety of electrophiles (E) were used to react at 0°C with lithium pentadienylide (Scheme 20).

Scheme 20
In a recent publication (10) Wilson et al. reported solvent and cation effects on a 1, 3 sigmatropic rearrangement of 29 and 30 (Scheme 21).

\[
\begin{align*}
\text{Scheme 21} & \\
\begin{array}{c}
\text{H}_3\text{C-} \\
\text{OM}
\end{array} & \xrightarrow{\text{CH}_3} \\
\begin{array}{c}
\text{OM}
\end{array}
\end{align*}
\]

They found the reaction is accelerated in going from less polar to highly ionized salts $K > Na > Li$ and also accelerated in highly ionized solvents $\text{HMPA} > \text{THF} > \text{ether}$ and by complexing agents $\text{18-crown-6}$ or $\text{15-crown-5}$. For example when $M = Li$ and solvent is THF the half-life is 4 hours at $65^\circ C$ while for $M = K$ and the same solvent the half-life is only 10 min. at $0^\circ C$. The solvent effect is also pronounced. When $M = Na$ and solvent is THF $t_{1/2} = 2$ hrs at $65^\circ C$ while for $M = Na$ and HMPA as solvent $t_{1/2} = 30$ min at $0^\circ C$. Another interesting result is that rearrangement for $M = K$ has a $t_{1/2}$ at $-7^\circ$ of 40 min and in the presence of one equivalent of $\text{18-crown-6}$ the reaction was complete in only 5 min.

The exceptionally facile rearrangement of a 1,5-hexadiene alkoxide compared to its alcohol counterpart was reported by Evans and Golob (11). The simple modification on oxy-Cope substrates resulted in observed rate accelerations in the range of $10^{10} - 10^{17}$. 
The systems chosen for study were the dienol 31 and 31b as shown below (Scheme 22).

Scheme 22

31

\[ \text{Scheme 22} \]

\[ \begin{align*}
\text{31} & \quad \text{32} \\
\text{H} & \quad \text{OM} \\
\text{34} & \quad \text{33}
\end{align*} \]

\[ \begin{align*}
a, \ R = \text{OCH}_3 & \quad b, \ R = \text{H}
\end{align*} \]

The nature of the metal ion was shown to play a significant role in the rate of rearrangement. Counterion effects were tested in the rearrangement of diene alkoxide 32a in refluxing (66\(^\circ\)) anhydrous tetrahydrofuran (THF) with the following results:

alkoxide 32a, M = Li, MgBr, showed no evidence of rearrangement over 24 hour period; the sodium alkoxide, 32a (M = Na), rearranged to the enolates 33a with a half-life \( (t_{1/2}) \) of 1.2 hr; the potassium alkoxide rearranged giving over 98% methoxy ketone 34a with a half-life of only 1.4 min. Further acceleration was achieved with 18-Crown-6 and hexamethyl phosphoric triamide (HMPT). For
example for 32a (M = K) in THF at 0°C containing between one and three equivalence of 18-Crown-6, a limited 180-fold rearrangement rate acceleration was observed. The authors concluded that ion pair dissociation results in maximal rate acceleration and that the rate dependence upon solvent dielectric is negligible. These startling rate enhancements at lower reaction temperatures coupled with higher yields for these anionic oxy-Cope processes implied significant improvement in the synthetic utility of these rearrangements.

In a related work Evans (12) discovered a novel method of synthesizing biologically important prenylated quinones, using anion-accelerated sigmatropic shifts to regiospecific quinon-isoprene coupling (Scheme 23).

Scheme 23

\[
\begin{array}{c}
\text{X} \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{O} \\
\text{R}
\end{array}
\]

\[
\begin{array}{c}
\text{X} = \text{HALOGEN}
\end{array}
\]

Addition of masked quinone, to allylic magnesium bromide 39 gave 40. Treatment of the masked quinol 40 with aq NaF-THF (25°C, 3 hrs) under neutral conditions resulted in deprotection followed by facil rearrangement to 2-isopentenyl hydroquinine 42 in 70% yield.
Oxidation results in 2-isopentenyl-p-benzoquinone (Scheme 24).

Scheme 24

Isopreny cation methodology was used in a similar reaction in synthesis of naturally occurring naphthoquinones. Addition of 39 to 43a gave 44a. Deprotonation of 44a with aq AgF - THF (25°C, 3 hr) afforded deoxylapachol (46a) with an average yield of 67-71% based upon 43a, which is a substantial yield increase over earlier methods of arylprenyl couplings. Formation of 46b from 43b resulted in 62% yield under identical conditions (Scheme 25).
Scheme 25

An even more striking result was addition of 39 to 43c at a low temperature of only -22°C. The addition proceeded via 1,2-carbonyl addition and followed by Cope rearrangement of the magnesium alkoxide which upon deblocking with AgF gave vitamin K_2(5) in 71% overall yield, further supporting low temperature facile 3,3 sigmatropic anionic rearrangement.

Thies and Seitz reported recently the first enhanced 1,3 shift of oxy-Cope systems occurring at room temperature under the influence of potassium hydroxide and HMPT (13 and 14). The
potassium alkoxide of 47a-d in highly dissociating media, viz, HMPT or 18-crown-6 with either dimethoxy-ethane (DME) or tetrahydrofuran (THF) were rearranged to 48a-d, 49a-d and 50a-d (Scheme 26). Comparing the half-life estimates for the alkoxides 47a-c in HMPT with earlier thermal rates for trimethyl siloxy derivatives, the authors gave approximate rate enhancements for the alkoxide process in the range of $10^{15}$ - $10^{17}$.

Scheme 26

For the medium-sized rings 47a-c the predominant rearrangement is a 1,3 shift ring expansion giving 48 and/or 49, while the large ring system 47 led to mainly 3,3 shift and product 50. Based on the large rate enhancements the authors proposed that the
process is not homolytic and the tremendous rate increases are partly due to the naked anion becoming delocalized in the transition state leading to the resonance stabilized enolate and partly due to the better donor properties of the anion moiety relative to the neutral compounds.

The authors also reported the rearrangement of the previously unstudied benzo eight-membered ring cases 51a-d shown below (Scheme 27).

**Scheme 27**

![Scheme 27](image)

a. \( R = \text{SiMe}_3 \) \( R' = \text{H} \)
b. \( R = \text{H} \) \( R' = \text{H} \)
c. \( R = \text{H} \) \( R' = \text{CH} = \text{CH}_2 \)
d. \( R = \text{H} \) \( R' = \text{CH} = \text{CHCH}_3 \)

While thermal rearrangement of 51a at 350°C and 11 hrs gave 47% yield of 52, treatment of 51b with potassium hydride in HMPT at 25°C and 5.5 hrs produced 57% 52. Four carbon ring expansion of 51c and 51d was also investigated. However, they only observed
1, 3 shift products 52c and 52d upon treatment with potassium hydride in HMPT.
RESULTS AND DISCUSSION

The kinetics of rearrangement of 7, 8, 9, 10-tetrahydro-6-vinyl-6(5H)-benzoctenol 53a and 3-methoxy-6-vinyl-7, 8, 9, 10-tetrahydro-6(5H)-benzocyclooctenol 53b when treated with potassium hydride in highly dissociating medium of hexamethylphosphoric triamide (HMPT) at a temperature of 30.0°C were studied as shown in Scheme 28.

Scheme 28

\[
\begin{align*}
\text{a} & \quad R = H \\
\text{b} & \quad R = \text{OCH}_3
\end{align*}
\]

The structural assignment for 54a is based largely on the NMR spectrum as well as the IR spectrum, oxidative cleavage reaction of 54a and comparison of 54a to the thermal 1, 3 shift product that was previously worked out by Thies and Seitz (14). The identity of 54a here was assigned by comparing GLC retention times to the times of such a previously characterized sample, and by coinjection with such an authentic sample, and by spectral comparison. The compound 53b was assumed to undergo the comparable rearrangement. The conversion results determined in duplicate by GLC are
summarized in Tables 1-4. A trial run had shown that the 53b rearrangement was much faster than 53a and appropriate time intervals for sample-taking were based on results obtained from the trial run. The ratio of peak areas were calculated by the peak-height times half-width method. The percent reactant left does not take into account the disappearance of starting material or product by other pathways.

For a first order reaction a plot of the logarithm of reactant concentration vs. time must give a straight line. From such plots, all four cases gave, within experimental errors, fairly straight lines from which the magnitude of the rate constants were determined. Alternatively, the rate constants were calculated using first order rate equation \[ \log \frac{x_o}{x} = \frac{k(t-t_0)}{2.3} \]. Finally, the computer results of correlation and simple progression were used to get the magnitude of the rate constants. The results are summarized below.

<table>
<thead>
<tr>
<th>Method</th>
<th>Run one min(^{-1})</th>
<th>Run two min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated (ave.)</td>
<td>0.0296</td>
<td>0.0294</td>
</tr>
<tr>
<td>Graphical</td>
<td>0.0250</td>
<td>0.028</td>
</tr>
<tr>
<td>Corr. and Simple Prog.</td>
<td>0.0227</td>
<td>0.0277</td>
</tr>
</tbody>
</table>
Rate Constants, $k_{OCH_3}$, for 59b

<table>
<thead>
<tr>
<th>Method</th>
<th>Run one min$^{-1}$</th>
<th>Run two min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated (ave.)</td>
<td>0.0876</td>
<td>0.0753</td>
</tr>
<tr>
<td>Graphical</td>
<td>0.075</td>
<td>0.071</td>
</tr>
<tr>
<td>Corr. and Simple Prog.</td>
<td>0.0782</td>
<td>0.0728</td>
</tr>
</tbody>
</table>

Using these rate constants, and Hammet's linear free-energy relationship, $\log \frac{k}{k_0} = \sigma \rho$, and the given value of $\sigma$ for methoxy group of +0.12 (20), the reaction constant $\rho$ which is a measure of susceptibility of the reaction to electrical effects is calculated. The results are given below.

$$\log \frac{k_{OCH_3}}{k_H}$$

<table>
<thead>
<tr>
<th>Method</th>
<th>Run one</th>
<th>Run two</th>
</tr>
</thead>
<tbody>
<tr>
<td>K calculated</td>
<td>3.93</td>
<td>3.40</td>
</tr>
<tr>
<td>K Graphical</td>
<td>3.97</td>
<td>3.37</td>
</tr>
<tr>
<td>K linear prog.</td>
<td>4.48</td>
<td>3.50</td>
</tr>
</tbody>
</table>

The fact that $\rho$ is positive of course, indicates the need of this reaction for an electron withdrawing group. Putting it another way the transition state has a reaction center which is electron rich. Even in the absence of a good model system for comparison,
the rather large size of $f$ is a further indication of the high sensitivity of the reaction rate to substituent change, and supports high negative charge development at the reaction center. This suggests that the mechanism goes through a carbanion, even though it does not rule out concerted 1,3-shift with fair amount of charge in the transition-state.

If the mechanism is actually concerted then the carbanion 56 is merely a contributing resonance form concentrating significant negative charge on the migrating carbon.

The large $\delta f$ value argues against a diradical intermediate.
These $\sigma_f$ values should be used with some caution, however, because of treating only two points and the fact that $\sigma_f$ values are not normally obtained in HMPT.
Table 1. Kinetics run for 59a.

<table>
<thead>
<tr>
<th>t(min)</th>
<th>peak heights (cm)</th>
<th>1/2 height baseline ratios</th>
<th>corrected peak area ratios</th>
<th>% R left</th>
<th>k, min⁻¹ = (2.3 \log \frac{A_0}{A} / t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t₁ - tᵢ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>17.50</td>
<td>5.50</td>
<td>0.26/0.30</td>
<td>15.17</td>
<td>5.50</td>
</tr>
<tr>
<td>15</td>
<td>20.3</td>
<td>10.0</td>
<td>0.25/0.28</td>
<td>18.12</td>
<td>10.0</td>
</tr>
<tr>
<td>20</td>
<td>17.6</td>
<td>15.0</td>
<td>0.26/0.29</td>
<td>15.78</td>
<td>15.0</td>
</tr>
<tr>
<td>30</td>
<td>8.5</td>
<td>12.9</td>
<td>0.26/0.29</td>
<td>7.62</td>
<td>12.9</td>
</tr>
<tr>
<td>40</td>
<td>6.7</td>
<td>16.1</td>
<td>0.26/0.28</td>
<td>6.22</td>
<td>16.1</td>
</tr>
<tr>
<td>50</td>
<td>4.6</td>
<td>14.5</td>
<td>0.40/0.40</td>
<td>4.6</td>
<td>14.5</td>
</tr>
<tr>
<td>80</td>
<td>1.3</td>
<td>9.7</td>
<td>0.47/0.35</td>
<td>1.75</td>
<td>9.7</td>
</tr>
</tbody>
</table>

ave = 0.0296
Table 2. Kinetics run one for 59b.

<table>
<thead>
<tr>
<th>t(min)</th>
<th>peak heights (cm)</th>
<th>1/2 height baseline ratios</th>
<th>corrected peak area ratios</th>
<th>% R left</th>
<th>$k$, min$^{-1}$</th>
<th>$\frac{A_0}{A}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_f-t_i$</td>
<td>R/P</td>
<td>R/P</td>
<td></td>
<td></td>
<td>t</td>
</tr>
<tr>
<td>2</td>
<td>23.4</td>
<td>4.9</td>
<td>0.30/0.37</td>
<td>18.97</td>
<td>4.9</td>
<td>79.41</td>
</tr>
<tr>
<td>4</td>
<td>21.9</td>
<td>9.1</td>
<td>0.37/0.45</td>
<td>18.0</td>
<td>9.1</td>
<td>66.4</td>
</tr>
<tr>
<td>6</td>
<td>18.1</td>
<td>13.2</td>
<td>0.31/0.37</td>
<td>15.2</td>
<td>13.2</td>
<td>53.52</td>
</tr>
<tr>
<td>7</td>
<td>13.9</td>
<td>12.3</td>
<td>0.31/0.36</td>
<td>11.97</td>
<td>12.3</td>
<td>49.32</td>
</tr>
<tr>
<td>8</td>
<td>9.65</td>
<td>10.0</td>
<td>0.37/0.40</td>
<td>9.0</td>
<td>10.0</td>
<td>47.00</td>
</tr>
<tr>
<td>9</td>
<td>9.9</td>
<td>11.8</td>
<td>0.40/0.45</td>
<td>8.8</td>
<td>11.8</td>
<td>42.70</td>
</tr>
<tr>
<td>10</td>
<td>6.9</td>
<td>9.1</td>
<td>0.37/0.40</td>
<td>6.4</td>
<td>9.1</td>
<td>41.30</td>
</tr>
<tr>
<td>12</td>
<td>7.8</td>
<td>12.9</td>
<td>0.37/0.40</td>
<td>7.2</td>
<td>12.9</td>
<td>35.80</td>
</tr>
<tr>
<td>14</td>
<td>11.6</td>
<td>25.4</td>
<td>0.32/0.35</td>
<td>10.6</td>
<td>25.4</td>
<td>29.40</td>
</tr>
</tbody>
</table>

ave = 0.0876
Table 3. Kinetics run two for 59a.

<table>
<thead>
<tr>
<th>t</th>
<th>R</th>
<th>P</th>
<th>P/R</th>
<th>corrected peaks</th>
<th>corrected peaks</th>
<th>% left</th>
<th>k, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12.8</td>
<td>4.1</td>
<td>.37/.30</td>
<td>12.8</td>
<td>5.06</td>
<td>75.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.2</td>
<td>5.9</td>
<td>.44/.35</td>
<td>18.2</td>
<td>7.42</td>
<td>71.04</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>22.4</td>
<td>12.2</td>
<td>.35/.32</td>
<td>22.4</td>
<td>13.34</td>
<td>62.84</td>
<td>.031</td>
</tr>
<tr>
<td></td>
<td>12.4</td>
<td>7.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>18.5</td>
<td>13.6</td>
<td>0.40/0.38</td>
<td>18.5</td>
<td>14.32</td>
<td>56.37</td>
<td>.0333</td>
</tr>
<tr>
<td></td>
<td>17.2</td>
<td>12.8</td>
<td>.37/.30</td>
<td>17.2</td>
<td>15.79</td>
<td>52.14</td>
<td>52.555</td>
</tr>
<tr>
<td>30</td>
<td>6.3</td>
<td>7.5</td>
<td>0.43/0.40</td>
<td>11.1</td>
<td>14.41</td>
<td>43.51</td>
<td>.0277</td>
</tr>
<tr>
<td></td>
<td>11.1</td>
<td>13.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>7.1</td>
<td>15.3</td>
<td>0.37/0.37</td>
<td>7.1</td>
<td>15.3</td>
<td>31.7</td>
<td>.0285</td>
</tr>
<tr>
<td></td>
<td>9.4</td>
<td>19.4</td>
<td>.38/.35</td>
<td>9.4</td>
<td>21.06</td>
<td>30.86</td>
<td>31.18</td>
</tr>
<tr>
<td>50</td>
<td>4.5</td>
<td>14.4</td>
<td>.40/.40</td>
<td>4.5</td>
<td>14.4</td>
<td>23.8</td>
<td>.0282</td>
</tr>
</tbody>
</table>

ave = 0.0294
Table 4. Kinetics run two for 59b.

<table>
<thead>
<tr>
<th>t</th>
<th>R</th>
<th>P</th>
<th>P/R</th>
<th>corrected</th>
<th>corrected</th>
<th>% left</th>
<th>$k, \text{ min}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>peaks</td>
<td>peaks</td>
<td></td>
<td>(\text{min}^{-1})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>P</td>
<td></td>
<td>(2.3 \log \frac{A_0}{A/t})</td>
</tr>
<tr>
<td>2</td>
<td>14.2</td>
<td>1.0</td>
<td>0.80/52</td>
<td>14.2</td>
<td>1.54</td>
<td>90</td>
<td>0.0754</td>
</tr>
<tr>
<td>4</td>
<td>12.2</td>
<td>2.8</td>
<td>.80/63</td>
<td>12.2</td>
<td>3.56</td>
<td>77.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12.3</td>
<td>5.1</td>
<td>.65/54</td>
<td>12.3</td>
<td>6.14</td>
<td>66.7</td>
<td>66.0 0.0776</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>6.4</td>
<td>.62/50</td>
<td>15</td>
<td>7.94</td>
<td>65.3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20.1</td>
<td>12.9</td>
<td>.67/57</td>
<td>20.1</td>
<td>15.16</td>
<td>57</td>
<td>56.7 56.85 0.0766</td>
</tr>
<tr>
<td></td>
<td>18.2</td>
<td>11.5</td>
<td>.58/48</td>
<td>18.2</td>
<td>13.90</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10.2</td>
<td>8.4</td>
<td>.57/50</td>
<td>10.6</td>
<td>10.31</td>
<td>50.7</td>
<td>0.0717</td>
</tr>
<tr>
<td></td>
<td>10.6</td>
<td>8.8</td>
<td>.75/64</td>
<td>10.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ave = 0.0753
Run one for conversion of non-methoxy

<table>
<thead>
<tr>
<th>$2,3 \log % A$ left</th>
<th>$t$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.296</td>
<td>10</td>
</tr>
<tr>
<td>4.166</td>
<td>15</td>
</tr>
<tr>
<td>3.937</td>
<td>20</td>
</tr>
<tr>
<td>3.614</td>
<td>30</td>
</tr>
<tr>
<td>3.363</td>
<td>40</td>
</tr>
<tr>
<td>3.178</td>
<td>50</td>
</tr>
<tr>
<td>2.725</td>
<td>80</td>
</tr>
</tbody>
</table>
Run one for conversion of methoxy

<table>
<thead>
<tr>
<th>2.3 log % A left</th>
<th>t (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.375</td>
<td>2</td>
</tr>
<tr>
<td>4.196</td>
<td>4</td>
</tr>
<tr>
<td>3.980</td>
<td>6</td>
</tr>
<tr>
<td>3.898</td>
<td>7</td>
</tr>
<tr>
<td>3.850</td>
<td>8</td>
</tr>
<tr>
<td>3.754</td>
<td>9</td>
</tr>
<tr>
<td>3.721</td>
<td>10</td>
</tr>
<tr>
<td>3.578</td>
<td>12</td>
</tr>
<tr>
<td>3.381</td>
<td>14</td>
</tr>
</tbody>
</table>

time in min.
Run two for conversion of non-methoxy

<table>
<thead>
<tr>
<th>2.3 log % A left</th>
<th>t (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2958</td>
<td>10</td>
</tr>
<tr>
<td>4.1400</td>
<td>15</td>
</tr>
<tr>
<td>3.9619</td>
<td>20</td>
</tr>
<tr>
<td>3.7730</td>
<td>30</td>
</tr>
<tr>
<td>3.4398</td>
<td>40</td>
</tr>
<tr>
<td>3.1697</td>
<td>50</td>
</tr>
</tbody>
</table>

2.3 log % A left over vs. time in min.
Run two for conversion of methoxy

<table>
<thead>
<tr>
<th>2.3 log % A left</th>
<th>t (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4998</td>
<td>2</td>
</tr>
<tr>
<td>4.3490</td>
<td>4</td>
</tr>
<tr>
<td>4.1897</td>
<td>6</td>
</tr>
<tr>
<td>4.0404</td>
<td>8</td>
</tr>
<tr>
<td>3.9359</td>
<td>10</td>
</tr>
</tbody>
</table>

2.3 log % A left over time in min.
SYNTHETIC METHODS

The preparation of 53b started with freshly vacuum transferred commercially available (Aldrich) benzosuberone 59. A considerable number of steps were involved which are outlined below in Scheme 29.

![Diagram of chemical reactions and structures](image-url)
Nitration of benzosuberone and consequent catalytic reduction of the nitro product with hydrogen gas in a Parr apparatus essentially followed the method of the Smith and Berry (15). The aminoketone 61 was then diazotized and hydrolyzed to obtain the phenolic ketone 62. Methylation of 62 followed a general method of methylation as described in Hilgetage and Martin (16). A second method of methylation using methyl iodide was also tried (17) with comparable results. Synthesis of 65 employed trimethyl silyl cyanide as a reagent for the direct formation of trimethyl silyl cyanohydrin ethers from ketones as reported by Evans, Carrol and Truesdale (18) and modified by Thies and Seitz. The reaction was quite sensitive to moisture which required that special drying precautions be used. The trimethyl silyl cyanohydrin ether was immediately reduced with LAH/ether. The ring expanded ketone was then reacted with freshly prepared Grignard reagent to give 53b.

The preparation of 68 followed essentially that of Evans and Truesdale (18). Diazotization of 68 and Grignard addition to 69 are similar to the methods of Thies and Seitz (14) as discussed before. The overall synthetic plan is given in Scheme 30 below.
The overall yield for the first two steps was only 47% (compared to 84% reported by Thies and Seitz). Two other tries failed to produce higher yields. However, almost complete conversion in the last two steps made the overall yield of 53a somewhat respectable.

Formation of 3-hydroxy-7, 8, 9, 10-tetrahydro-6-vinyl-6(5H)-benzocyclooctanol 70 was attempted following demethylation method of Fentrill and Mirrington (19) using thio alkoxide ion in DMF as shown below in Scheme 31.
Compound 53b was synthesized as discussed previously starting with benzosuberone. From comparison of peak areas of three benzene hydrogens to methoxy hydrogens it was estimated that there was two-thirds conversion of 53b to 70. Compound 70 did not rearrange when treated with potassium hydride in HMPT (unpublished results of R. H. Chiarello).
EXPERIMENTAL

General Information

The infrared spectra were measured on a Perkin-Elmer 727B infrared spectrometer. NMR spectra were measured on an HA-100 (100 Mhz) nuclear magnetic resonance spectrometer. Low resolution mass spectra were obtained from an Atlas CH 7. High resolution mass spectra were obtained with a CEC 110B instrument at the University of Oregon. Gas-liquid chromatography (GLC) analyses were carried out on a Varian Aerograph Series 1200 gas chromatograph fitted with flame ionization detector and on a Varian Aerograph series 920 gas chromatograph with thermal conductivity detector. The column used for most of the work was a 5 ft x 1/4 in. 6.5% OV 101 on chromosorb G 80-100. The flow through the column was Ca. 19.8 ml/min.

Preparative Details

Preparation of 3-Nitrobenzosuberan-5-one (60)

Following the procedure used by Smith and Berry (15) 6.0 g of benzosuberan-5-one 59 was slowly dripped into 17.5 ml of yellow fuming nitric acid (d = 1.49) at 14°C over a 10 min. period and the mixture was kept between -10 and -5°C for 25 min. It was then
poured on ice, precipitating 7.0 g of impure product with m.p. 65-80°C range. The fourth and final recrystallization from 95% ethanol gave 4.40 g (yield 57.0%) of 3-nitrobenzosuberan-5-one with m.p. 90-92°C: IR (1.5% KBr pellet) 3340, 3080, 2930, 2860, 2760, 1970, 1820, 1675, 1620, 1410, 1345, 1260, 1220, 1180, 1150, 1095, 970, 920, 860, 820, 770, 750, 630; NMR (CCl₄/CDC₁₃) δ 8.52 (d, J = 2 Hz, 1H), 8.24 (dd, J = 2, 8 Hz, 1H) 7.32 (d, J = 8 Hz, 1H) 3.1 (t, J = Hz, 2H) 2.8 (t, J = Hz, 2H, 2.05-1.8 (m 4H).

Preparation of 3-aminobenzosuberan-5-one (61)

A suspension of 20.0 g of 3-nitrobenzosuberan-5-one in 200 ml of 95% alcohol was hydrogenated in a Parr apparatus at 50 psi and 28°C over 0.10 g of Adams catalyst. After 20 min. the resulting yellow solution was filtered from catalyst and solvent was removed with a rotary evaporator, leaving light orange needles m.p. 98-103. Recrystallization from 95% alcohol gave 11.2 g of crystals: m.p. 101.5-103°C, yield 66%: IR (2% KBr pellet) 3430, 3340, 3230, 3020, 2930, 2850, 1890, 1740, 1660, 1600, 1580, 1500, 1440, 1420, 1320, 1280, 1200, 1180, 1160; NMR (CDCl₃) δ 7.1 (d, J = 2Hz, 1H) 7.0 (d, J = 8 Hz, 1H) 6.75 (dd, J = 2, 8 Hz, 1H) 3.57 (Broad 5, 2H) 2.9-2.6 (m, 4H) 2.0-1.74 (m 4H).
Preparation of 3-Hydroxybenzosuberan-5-one (62)

An 11.1 g sample of 3-aminobenzosuberan 61 was dissolved in 300 ml of 10% H$_2$SO$_4$ (v/v) and cooled to 8°C and diazotized at that temperature by 4.55 g of sodium nitrite dissolved in a small amount of water (ca. 40 ml distilled H$_2$O). The reaction mixture was allowed to stir at 8°C for about 20 min. and then the excess nitrous acid was destroyed by adding enough sulfamic acid. The mixture was then filtered and poured into 800 ml of 10% sulfuric acid, overlaid with 300 ml of benzene, and kept for 72 hours at room temperature. The initially colorless benzene layer slowly turned to dark yellow then to orange over this time period. The layers were then separated and the aqueous phase was extracted with 500 ml (5x) of benzene. The combined extracts were dried with a rotary evaporator to give 8.8 g of crude crystals (80% yield). Two sublimations at 1 mm and 160-190°C gave 6.4 g of pure pale yellow analytical sample, m.p. 99-100°C, yield 58%: IR (neat) 3200 (Broad H-bonded OH), 2930, 1640, 1610, 1560, 1495, 1460, 1350, 1300, 1220, 1200, 980, 880, 830, 710; NMR (CDCl$_3$), $^\delta$ 7.4 (d, J = 2 Hz 1H) 7.03 (c, J = 8 Hz 1H) 6.95 (dd, J = 2, 8 Hz 1H) 6.7 (1H), 3.0-2.68 (m, 4H), 2.0-1.74 (m 4H).
3-Methoxybenzosuberan-5-one (63)

Following the methylation of phenol procedure described in Hilgetag and Martin (16), 3.10 g (0.018 mole) of hydroxybenzosuberone 62 and 0.7 g of NaOH was dissolved in 14 ml of water in a 100 ml, 3 neck flask fitted with a reflux condenser, a dropping funnel and a thermometer. The mixture was cooled with stirring to slightly below 10°C and 2.38 g = 1.7 ml (0.018 mole) of dimethylsulfate were run slowly into the stirred mixture from the dropping funnel. The whole mixture was then heated up to 40°C and then a second portion of 3.10 g of hydroxybenzosuberone and 0.7 g NaOH water solution mixture was added to the 3-neck flask and the whole mixture was refluxed for two hours. The reaction was worked up by separating the two layers, extracting the aqueous solution with benzene and then removing the benzene with a rotary evaporator to give 4.24 g of 63 (yield 63%): IR (neat) 2930, 2860, 1670, 1600, 1570, 1495, 1460, 1410, 1320, 1280, 1260, 1240, 1205, 1180, 1170, 1150, 1100, 1080, 1040, 970, 860, 840, 740, 700; NMR (CDCl3) 6 7.17 (d, 2 Hz, 1H), 7.04 (d, 8 Hz, 1H), 6.85 (dd, J = 2, 8 Hz, 1H), 3.8 (s, 3H) 2.85, (t, J = 6 Hz, 2H), 2.65 (t, J = 6 Hz, 2H), 1.94-1.7 (m, 4H).
Preparation of 3-Methoxy-5-aminomethyl-6, 7, 8, 9-tetrahydro-5-
benzocycloheptanol (65)

An 8.88 g sample of methoxybenzosuberone 63, purified by
vacuum transfer, was put into a dry 100 ml round bottom flask,
equipped with a magnetic stirrer and nitrogen head. A wide mantle,
short (10 x 3 cm) test tube was charged with 0.8 g of ZnI₂, evacu-
ated (1 mm), flushed with dry nitrogen, evacuated again and
ZnI₂ then sublimed using a Bunsen burner. The ZnI₂ was tapped
down from the sides to the bottom of the test tube into a powder, and
a microstirring bar was added, and the tube was put under nitrogen.
Then 4.0 ml of freshly TMSCN was syringed into the ZnI₂ test
tube and the mixture was stirred for 5 min. While this mixture was
stirring, the methoxy benzosuberone was cooled to 0°C in an ice
bath. The ZnI₂-TMSCN mixture was syringed into cool methoxy-
benzosuberone and the solution was stirred for one-half hour at ice
bath temperature. A 2.0 g sample of LiAlH₄ was weighed into a
beaker and then 50 ml of dry ether was added. The slurry was
mixed for a few minutes and then let settle. It was then added drop-
wise to the cyanohydrin ether prepared in previous step over 45 min.
The mixture was stirred for another 15 min. at 0°C and for 30 min.
at room temperature. After cooling 20 ml of water was added to
the reaction mixture followed by addition of 20 ml of 15% solution
of NaOH and finally 60 ml of distilled water. The reaction mixture
was then stirred for 3 hours, during which time the gray mixture turns almost white. The precipitate was filtered off and washed well with 200 ml of ether (5X). The amino alcohol was extracted from ether by 200 ml of 10% $\text{H}_2\text{SO}_4$ (5X). The free amine was recovered by neutralizing the $\text{H}_2\text{SO}_4$ extract with enough 15% NaOH solution to get a pH of about 10 and then extracting with ether (200 ml - 5X). A more polar solvent, chloroform, was tried to remove more of the amino alcohol from the aqueous layer as well as solid precipitate on the container walls (assumed to be the amino alcohol) with no success. The ether layer was dried over anhydrous MgSO$_4$, filtered, and the solvent was removed with a rotary evaporator. The white crystalline solid obtained melted between 109-112.5; (yield 16%). IR, 3350, 3150 (NH stretch buried in broad OH peak) 2920, 2900, 2840, 1600, 1570, 1480, 1450, 1280, 1240, 1220, 1195, 1160, 1095, 1040, 920, 890, 840, 820, 740, 700; NMR (CDCl$_3$) $\delta$

7.37 (d, J = 2 Hz, 1H) 7.02 (d, J = 8 Hz, 1H) 6.68 (dd, J = 2, 8 Hz 1H) 3.82 (s, 3H) 3.08 (dd, J = 12, 2 Hz, 2H), 2.98-2.74 (m 2H), 2.30-1.74 (Broad m, 8H); exact mass m/e 221.143 (calculated for $\text{C}_{13}\text{H}_{19}\text{O}_2\text{N}$, 221.143).

**Preparation of 3-Methoxy-7, 8, 9, 10-tetrahydro-6(5H)-benzocycloctenone, (66)**

A 1.50 g sample of amino alcohol from the previous step was
put into a 100 ml one neck flask and 45 ml of 10% solution of acetic acid was added to it. The mixture was stirred until most of the amino alcohol was dissolved. The mixture was then cooled in an ice bath and then 30 mls of 1.25 M NaNO₂ solution was added to it. The mixture was stirred for 0.5 hr in an ice bath and then overnight (ca. 10 hours) at room temperature. After cooling the mixture to 0°C, a drop of phenolphthalein was added followed by enough 15% NaOH solution to get a pH of about 9. The solution was then extracted with 200 ml of ether (5X). The ether layer was dried over anhydrous MgSO₄, filtered and the solvent was removed with a rotary evaporator, which gave 1.00 (yield 72%) of ketone:

IR (neat) 2930, 2850, 1700, 1610, 1580, 1500, 1460, 1320, 1250, 1160, 1105, 1040, 950, 810, 760, 700 cm⁻¹; NMR (CCl₄) δ 7.03 (d, J = 8 Hz, 1H) 6.80-6.56 (m 2H) 3.77 (s, 3H) 3.66 (s, 2H), 2.86-2.68 (distorted t, 2H) 2.4-2.16 (dist t 2H) 2.1-1.6 (Broad m, 4H); exact mass m/z 204.115 (calculated for C₁₃H₁₆O₂, 204.116).

Preparation of 3-Methoxy-7,8,9,10-tetrahydro-6-vinyl-6(5H)-benzocyclo-octenol, (53b)

A 100 ml 3-neck round-bottom flask was charged with 1.00 g of 66 in 5 ml THF and equipped with a magnetic stirrer, a condenser, nitrogen head and a dropping funnel. The dropping funnel was charged with 25 ml of vinyl magnesium bromide solution.
(9.6 \times 10^{-4} \text{ mole/m}) freshly prepared for this purpose. The 8 ml of vinyl magnesium bromide was then run dropwise into the THF solution of 58 with stirring as the oil bath temperature raised to 65°C. The mixture was stirred for 1.25 hr, then cooled and 0.25 ml of methanol was added to the reaction mixture which was stirred for 5 min and then another 8 ml of vinyl bromide was added drop by drop while raising the temperature back to 65°C. The reaction mixture was then stirred for another 1.25 hr. At this time a small (ca., 0.15 ml) sample of reaction mixture was taken, treated first with 0.5 ml of saturated NH$_4$Cl solution and then 0.5 ml of H$_2$O, shaken well and then extracted with 1 ml of ether, and ca. 0.3 ml was injected into the G.C. which indicated 70% completion. Another 0.25 ml of MeOH was added to the original reaction mixture in the round bottom flask, which was stirred for 5 min. and the rest of the vinyl magnesium bromide solution was then added drop by drop while raising the temperature to 65°C. Again the reaction mixture was stirred for another hour. The reaction mixture was then quenched with 3.5 ml of saturated NH$_4$Cl solution and then 20 ml of H$_2$O. The aqueous layer was extracted with 100 ml of ether (5X), dried over anhydrous magnesium sulfate and solvent was removed with a rotary evaporator to give 1.305 g of a dark brown oil. Vacuum transfer gave 0.673 g (59% yield) of a pale yellow oil: IR (neat) 3300 (Broad) 2920, 2850, 1600, 1580, 1500, 1460, 1320, 1295, 1260, 1200, 1160,
1040, 1000, 920, 810, 760, 780 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 7.14-7.04 (m, 1H) 6.96-6.70 (m, 2H) 6.14 (dd, \(J = 10, 17\) Hz, 1H), 5.34 (dd, \(J = 1, 17\) Hz, 1H), 5.14 (dd, \(J = 1, 10\) Hz, 1H) 3.8 (s, 5H) 3.0-2.6 (m, 4H) 1.9-1.35 (Broad m, 4H).

Preparation of 3-methoxy-5, 6, 9, 10, 11, 12-hexahydro-8(7H)-benzocyclodecenone 54a by rearrangement of the potassium salt of (53b)

A 25 ml conical flask was charged with 0.4 g of 25% potassium hydride in oil (ventron) and placed in a nitrogen atmosphere. The oil was rinsed from the potassium hydride with five 4.0 ml portions of hexane by adding hexane, stirring for a few minutes (magnetic stirrer, and allowing the hydride to settle. The hexane-oil layer was then carefully removed with a pipette from the top. Meanwhile 0.10 g of the vinyl alcohol 53b prepared in the previous step was weighed into a small vial and 2 ml of HMPA were added to it. Another 8 ml of HMPA were added to the washed KH. The HMPA solution of vinyl alcohol was added to KH-HMPA in 25 ml pear-shaped flask. The mixture was stirred for 25 minutes and the first sample (0.15 ml) was then taken. The sample treatment procedure is as follows: each 0.15 ml sample taken was put into 5 ml of ether, washed 5 times with 2 ml of distilled water (total 10 ml of distilled water) dried over anhydrous magnesium sulfate and then concentrated to about 0.5 ml and this concentrated ether solution was
used for G. C. injection.

The original reaction mixture was then further stirred for 15 min. The reaction was worked up by first adding 1 ml of water dropwise while stirring and then adding more water slowly until eventually 100 ml of water was added. The acidified aqueous solution was extracted with 100 ml of ether (5X). A base soluble by-product was extracted with 50 ml of 5% NaOH solution (5X) and saved for further investigation. The ether layer was washed with 50 ml of saturated NH₄Cl (2X) and once with 25 ml of saturated NaCl solution, dried over anhydrous MgSO₄ and concentrated to give 0.073 g of 53b: IR (neat) 2920, 2850, 1698, 1605, 1570, 1500, 1480, 1450, 1365, 1295, 1245, 1230, 1212, 1180, 1140, 1100, 1040, 1000, 995, 970, 930, 910, 880, 860, 850, 800, 750, 700 cm⁻¹; NMR (CCl₄) 7.02 (d, J = Hz, 1H) 6.6 (m, 2H) 3.72 (s, 3H) 2.7-1.5 (Broad m 14H). Exact mass m/e232.146 (calculated for C₁₅H₂₀O₂, 232.146).

Preparation of 5-aminomethyl-6, 7, 8, 9-tetrahydro-5-benzocycloheptenol (68)

A dry 100 ml r. b. flask was charged with 6.0 g of benzosuberone, a magnetic stirrer and kept under nitrogen atmosphere while cooling to 0°C in ice-water bath. A short wide mouth test tube (10 cm x 3 cm) was dried in oven, cooled under nitrogen and
charged with 1.0 g of ZnI$_2$. The ZnI$_2$ was sublimed using a bunsen burner while pumping to 1 mm Hg using a vacuum pump. The tube was then equipped with a magnetic stirrer and nitrogen head. A 3.5 ml* amount of TMSCN was syringed into the ZnI$_2$ test tube and stirred for 5 minutes. The TMSCN-ZnI$_2$ mixture was syringed into cold benzosuberone and stirred for 20 minutes.

A 4.0 g sample of LiAlH$_4$ was weighed into a large test tube and 199 ml of dry ether were added to it. The mixture was stirred for a few minutes and then let set until cyanohydrin ether from above was ready to be reduced.

The LiAlH$_4$ ether was pipetted dropwise into cold (0°C) cyanohydrin ether mixture in about one hour time and let sit and stir for another half-hour at room temperature. The reaction mixture was then quenched by cautious addition of 20 mls of water, 20 mls of 15% NaOH solution, and 60 mls of water. The whole mixture was then stirred for 2 hr, at room temperature. The precipitate was then filtered off and well washed with ether to make about 150 ml of ether solution. The ether layer was then extracted with 150 ml of 10% V/V H$_2$SO$_4$ (5X). The H$_2$SO$_4$ layer (aqueous layer) was made basic.

* Actually 6.0 ml of TMSCN was calculated to be needed. However, there were only 3.5 ml of distilled TMSCN available to be used. The product yield will be calculated on the basis of this limiting (TMSCN) factor.
by adding enough 15% solution of NaOH to get a pink solution with phenolphthalein as indicator (pH 9). The solution was cooled and then extracted with about 150 ml (5X) of ether. The ether layer was dried with anhydrous MgSO$_4$, filtered and concentrated to yield 3.4 g (47.5%) of 68: IR (solid KBr pellet) 3350, 3290, 3050, 2910, 2850, 2750, 1705, 1600, 1480, 1450, 1360, 1340, 1280, 1230, 1160, 1110, 1040, 1000, 950, 740 cm$^{-1}$; NMR (CDCl$_3$) $^\delta$ 7.6-7.8 (m, 1H), 7.1-7.3 (m, 3H), 2.8-3.35 (m, 4H), 1.7-2.2 (broad m, 6H) cm$^{-1}$.

Preparation of 7, 8, 9, 10-tetrahydro-6(5H)-benzo cyclooctenone (69)

All of the amino alcohol from the previous step (3.4 g) was put in 100 ml of 10% HOAC (V/V) and stirred vigorously to help dissolve and then cooled to 0°C. Then 60 ml of 1.25 M NaNO$_2$ were added to it and then mixture was stirred for 0.5 hr. in an ice bath and then further stirred for 4 hours at room temperature. The mixture was then cooled in an ice bath and a drop of phenolphthalein was added and the solution was made basic by adding enough 15% NaOH to give a pink solution of pH 9. The solution was then extracted with 150 ml of ether (6X) and the ether layer was washed with 10 ml of saturated Na$_4$Cl solution, dried over anhydrous MgSO$_4$, concentrated and further dried with vacuum pump which yielded 2.98 g of 69 (96%): IR (neat) 3050, 3010, 2920, 2850, 1700, 1600, 1580, 1495, 1451, 1350, 1320, 1280, 1260, 1240, 1195, 1160,
1120, 1040, 995, 960, 760, 720 cm\(^{-1}\); NMR (CCl\(_4\)) \(\delta\) 7.05-7.2 (m, 4H) 3.7 (s, 2H) 2.7-2.9 (m, 2H) 2.18-2.35 (m, 2H) 1.55-2.05 (broad m, 4H).

Preparation of 7,8,9,10-tetrahydro-6-vinyl-6(5H)-benzocyclooctenol, (53a)

A 100 ml round bottom 3-neck flask was charged with 1.96 g of benzooctanone and equipped with a magnetic stirrer, a reflux condenser, a 25 ml dropping funnel and a nitrogen head. A 6 ml portion of THF was added and stirring was started. The dropping funnel was charged with 25 ml of freshly prepared vinyl magnesium bromide in THF (9.6 x 10\(^{-4}\) mole \text{ml}^{-1}).

About 10 ml of vinyl magnesium bromide solution were run slowly (over ~ 10 min.) into benzooctanone and the temperature increased from room temperature to 65°C and the mixture stirred for 2 hours. At this time a small sample (0.15 ml) of reaction mixture was taken and this sample was treated with saturated NH\(_4\)Cl (0.5 ml) and then 0.5 ml H\(_2\)O and shaken well. This solution was then extracted with 0.5 ml of ether and injected (0.3 ml) into G.C.

At this time 0.28 ml of CH\(_3\)OH were syringed into the round bottom flask containing the reaction mixture near room temperature, stirred for a few minutes and then another 10 ml of vinyl magnesium
bromide solution was run into the round bottom flask drop by drop and the temperature raised to 65°C and stirred for another 2 hours. Then another small sample (0.15 ml) of the reaction was taken and treated as before (NH₄Cl saturated, H₂O ether extraction G.C. injection).

Again 0.28 ml of methanol was syringed into cooled (room temperature) reaction mixture in the round bottom flask and stirred for a few minutes and then 8 ml more of vinyl magnesium bromide solution were run into the round bottom flask drop by drop and the temperature raised to 65°C and stirred for 2 more hours. The reaction mixture was then quenched by addition of 4 ml of saturated NH₄Cl and then by about 30 ml of water. The aqueous layer was extracted with 100 ml ether (5X), dried over anhydrous magnesium sulfate and the solvent was removed with a rotary evaporator which yielded 1.39 g (100%) of 53a: IR (neat) 3400 (Broad) 3060, 3010, 2920, 2850, 1495, 1470, 1450, 1420, 1160, 1140, 1120, 1040, 1000, 920, 750, 710 cm⁻¹; NMR (CDCl₃) δ 7.1 (s, 4H) 6.1 (d of d, J = 11, 18 Hz, 1H), 5.35 (d of d, J = 2, 18 Hz, 1H) 5.15 (d of d, J = 2, 10 Hz, 1H) 3.05-2.6 (broad m, 4H), 1.9-1.2 (broad m, 7H); mass spectrum m/ (rel %) 202 (8.3), 184 (100), 55 (100); Anal. Calc for C₁₄H₁₈O: C, 83.12, H, 8.97. Found: C, 82.93; H, 8.75.
Preparation of 5, 6, 9, 10, 11, 12-hexahydro-8(7H)-benzocyclodecenone by rearrangement of the potassium salt of 6-vinyl-7, 8, 9, 10-tetrahydro-6(5H)-benzocyclooctenol in HMPA

A 25 ml, conical flask was charged with 0.4 g of 25% potassium hydride in oil (Ventron) and placed in a nitrogen atmosphere. The oil was rinsed from the potassium hydride with five 4.0 ml portions of hexane (20 ml) by adding hexane, stirring (magnetic stirrer) for a few minutes, and allowing the potassium hydride to settle. The hexane-oil layer was then carefully removed with pipette from the top. To the washed potassium hydride is then added 8 ml of HMPA. In a small vial 0.10 g of 7, 8, 9, 10-tetrahydro-6-vinyl-6(5H)-benzocyclooctenol was weighed and 2 ml of HMPA was added to it. This solution of alcohol was then added to KH-HMPA in 25 ml conical flask. The mixture was stirred for 25 minutes and then a sample (0.15 ml) was taken. This sample was put into 5 ml of ether, washed 5 times with 2 ml of distilled water each time, dried over anhydrous magnesium sulfate and concentrated to about 1/2 ml and used for G. C. injection. The original reaction mixture was further stirred for another 25 min. and the reaction was then worked up by dropwise addition of 1 ml of $\text{H}_2\text{O}$ with stirring and then slow addition of more water until eventually 100 ml of water was added. The acidified aqueous solution was extracted by 100 ml of ether (5X). The ether layer was washed with 50 ml of saturated $\text{NH}_4\text{Cl}$ (2X) and
once with 25 ml of saturated NaCl solution, dried over anhydrous MgSO₄ and the solvent was evaporated with a rotary evaporator.

**Preparation of 3-hydroxy-7,8,9,10-tetrahydro-6-vinyl-6(5H)-benzocyclooctanol**

Following the method of G. I. Fentrill and R. N. Mirrington (19) for demethylation of arylmethyl ethers with thioethoxide ion in dimethyl formamide, a 100 ml 3-neck flask was charged with 0.65 g of 9 and 25 ml of DMF and equipped with a magnetic stirrer, a condenser, a nitrogen head and a dropping funnel. The mixture was brought up to refluxing temperature and then a freshly prepared solution of thio-t-butoxide (made by reacting t-butyl mercaptan with elemental sodium) in DMF was added to the flask through the funnel. The whole mixture was refluxed for 3 hours. The reaction mixture was then worked up by acidifying the cooled mixture with 3 N HCl and extracting 20 with 150 ml ether (5X). The product was recovered from 1.2 N NaOH solution washing of the total extract. It was purified by acidification, ether extraction of phenol and again washing of the ether with 1.2 N NaOH solution. After final acidification and ether extraction, the solvent was removed and 0.30 g of oily product recovered: IR (neat) 3300 (Broad), 2920, 1660, 1600, 1580, 1500, 1450, 1410, 1380, 1300, 1250, 1190, 1160, 1100, 1040, 1000, 920, 870, 820, 770, 660 cm⁻¹.
A well insulated constant temperature oil bath was set up equipped with a powerful mechanical stirrer, a Bailey temperature control and an thermometer. Three holes were also drilled in the oil bath cover to just accommodate three test tubes which would suspend in the oil sitting on the cover supported by their top edges. Each test tube was equipped with a magnetic stirrer and a nitrogen head. The temperature of the oil bath was calibrated with a platinum resistance thermometer and maintained at 30.0°C.

In one kinetic run 0.10 g of each reactant (53a and 53b) were put in each of the two test tubes and the third test tube was charged with 0.70 g of hexane washed potassium hydride and 8 ml of HMPA. The three test tubes were allowed to sit and equilibrate to the bath oil temperature for half an hour. Two 4 ml portions of the KH-HMPA mixture were then quickly syringed out and injected into each of the two vinyl alcohols in the other two test tubes (53a and 53b) and allowed to react. From trial runs it was established that the methoxy alcohol (53a) had a faster rearrangement time and that 1 and 2 minute intervals were appropriate for sample taking. The slower reaching non-methoxy alcohol (53a) samples were taken at 5 and 10 minute intervals. All samples were immediately quenched
upon removal by addition of a few ml of water and acidified with 10% H$_2$SO$_4$. The work up procedure is as described before (page 50). Two later runs were made as above but not concurrently. The kinetics results are summerized on Tables 1-4.


