The effect of alkyl substitution on the oxidative cleavage of alkylphenylmethanols by ceric ammonium nitrate

Neil Stewart Fox

Iowa State University

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The effect of alkyl substitution on the oxidative cleavage of alkylphenylmethanols by ceric ammonium nitrate

by

Neil Stewart Fox

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of The Requirements for the Degree of DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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For the Major Department

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For the Graduate College

Iowa State University
Ames, Iowa
1974
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DEDICATION

To my parents
QUOTATIONS

Read not to contradict and confute; nor to believe and take for granted; nor to find talk and discourse; but to weigh and consider.

Francis Bacon
Of Studies

There is a time in every man's education when he arrives at the conviction that envy is ignorance; that imitation is suicide; that he must take himself for better, for worse, as his portion; ... The power which resides in him is new in nature, and none but he knows what that is which he can do, nor does he know until he has tried.

Ralph Waldo Emerson
Self Reliance
NOMENCLATURE

The nomenclature used throughout this thesis was chosen to emphasize the alkyl portions of alkylphenylmethanols studied. For example, 1-phenylpropanol is described in this thesis as ethylphenylmethanol.
INTRODUCTION

Metal-ion oxidation of alcohols is an important process in organic chemistry (1-5). The three major modes of alcohol oxidation are characterized by specific products:

1. Carbonyl Formation.

\[
\begin{align*}
R-C-R' & \rightarrow R-C=O \\
\end{align*}
\]

2. Oxidative Cleavage.

\[
\begin{align*}
R-C-R' & \rightarrow RCHO + R' \\
\end{align*}
\]

3. Cyclic Ether Formation.

\[
\begin{align*}
R-C-CH_2CH_2CH_2R' & \rightarrow R-O-R' \\
\end{align*}
\]

Carbonyl formation and oxidative cleavage are more common modes of alcohol oxidation than cyclic ether formation. Intramolecular oxidative cyclization of alcohols with lead tetraacetate has recently been reviewed (6,7). It is an important reaction only when a five-membered ring can form.

Metal-ion oxidative cleavage of alcohols has been recently reviewed (8). The mechanism involves the rapid formation of a one to one complex of the metal-ion and the alcohol. This complex decomposes in a rate determining step to products. The C-C bond cleavage appears to be a one-
electron process which forms a radical through a polar transition state.

If a radical as stable as isopropyl can form, oxidative cleavage will be the main pathway for oxidation of an alcohol by a one-electron oxidant. Cerium(IV) appears to be the most effective oxidant used to bring about oxidative cleavage of alcohols.

The major goal of this work is to show how the nature of the alkyl group influences the oxidative cleavage of alkylphenylmethanols by ceric ammonium nitrate (CAN). The alkylphenylmethanols are excellent model compounds since phenyl radical is slow to form. This means that only the alkyl radical is expected to form from cleavage, otherwise ketone formation will occur. The benzaldehyde to ketone ratio, determined from the product mixtures, is a sensitive probe indicative of the relative rates of oxidative cleavage to ketone formation. Cerium(IV) was used as the metal ion oxidant since it readily facilitates oxidative cleavage and is easily available from ceric ammonium nitrate.
HISTORICAL
Oxidative Cleavage of Alcohols

Although oxidative cleavage of monohydric alcohols by metal-ion oxidants has been known since 1944 (9), there have been only a few systematic studies on the effect of the departing alkyl group on the reaction. It has been reported that the \( t \)-butyl and benzyl groups are readily cleaved from \( t \)-butylphenylmethanol and benzylmethanol with oxidation by vanadium(V) (10). Hoare and Waters have measured the relative rates of cobalt(III) consumption by a series of tertiary alcohols (11). They found that the ease of oxidation of the alcohols is related to the ease of fission of the alkyl groups. The relative rates of elimination of alkyl groups were reported as: \( \text{MeOCH}_2 \), 6300; \( \text{i-Pr} \), 2300; \( \text{Et} \), 100; \( \text{n-Pr} \), 40; \( \text{Me} \), 1.0. Hoare and Waters also found that C-C bond cleavage occurs concomitant with ketone formation when secondary alcohols are oxidized with cobalt(III) (12). The major products from the cleavage reaction of the secondary alcohols are aldehydes.

Trahanovsky and Cramer found only products from ketone formation or cleavage of the alkyl group when a series of alkylphenylmethanols were oxidized with cerium(IV) (13).

\[
\text{Ph-C-R} \quad \overset{\text{Ce(IV)}}{\text{Ce(IV)}} \quad \overset{\text{k_{C-C fission}}}{\text{PhCHO + R}^*} \quad \overset{\text{k_{C-H fission}}}{\text{PhCR}} \quad (1)
\]
The relative rates of oxidative cleavage to ketone formation were expressed as the ratios of benzaldehyde to alkyl phenyl ketone found in the product mixtures. The ratios for the various alkyl groups are: t-Bu, 195; i-Pr, 184; Et, 3.30; Me, 0.04. The relative rates of alkyl group elimination are: t-Bu and i-Pr, 4500; Et, 80; Me, 1. Trahanovsky and Cramer pointed out that these values agree quite well with those reported by Hoare and Waters (11) and with the relative rates of elimination of alkyl groups from tert-alkoxy radicals which are: i-Pr, 3600; Et, 100; Me, 1 (14).

Trahanovsky and Macaulay have determined the relative rates of formation of allyl, benzyl, and tert-butyl radicals by oxidative cleavage of tertiary alcohols with cerium(IV) (15). Three tertiary alcohols, allylbenzylphenylmethanol, allyl-tert-butylphenylmethanol, and benzyl-tert-butylphenylmethanol underwent oxidative cleavage to produce ketones. From the yields of the ketones, the relative rates of formation of the allyl:benzyl:tert-butyl radicals by oxidative cleavage were calculated to be 1:4.4:19.9-62.9.

Nave and Trahanovsky have shown that the oxidative cleavage of alcohols by cerium(IV) and chromic acid, generating substituted benzyl radicals, follows the Hammett relationship (16,17). They found negative $\rho$ values and better correlations by $\sigma^+$ than with $\sigma$ values.

There have been no other systematic studies on the
effect of the departing group on the oxidative cleavage reaction of alcohols by metal-ion oxidants.

Cerium(IV) in Organic Chemistry

Most of the early uses of cerium(IV) in organic chemistry were for analytical purposes (18). It is a powerful one-electron oxidant and reacts with a wide variety of organic compounds. Although there has been a steady growth in the interest of the organic reactions of cerium(IV) (19), the synthetic potentiality of cerium(IV) with various functional groups has only recently been seriously studied (20). Cerium(IV) readily brings about oxidative cleavage of alcohols (8).

Ceric ammonium nitrate (CAN) is a convenient source of cerium(IV). CAN is an easily handled, nontoxic, nonhygroscopic solid which is readily available in pure form. Solid CAN consists of a cerium atom surrounded by six bidentate nitrates (21). It forms a homogeneous solution in aqueous acetonitrile.
RESULTS

A series of alkylphenylmethanols were oxidized by 2 equiv of ceric ammonium nitrate (CAN) in 50% aqueous acetonitrile at an oil bath temperature of ca. 80°. Mixture of CAN and the alcohols resulted in appearance of a red color attributed to complex formation. The red color faded to colorless or faint yellow as the oxidations took place. The oxidations took 1.5-20 min. The absolute yields of the recovered starting materials and products were determined by glpc and nmr analysis using internal standards. These yields are reported in Table 1. From the ratios of benzaldehyde to ketone that were obtained from the alkylphenylmethanols it is seen that oxidative cleavage is the main pathway when the R group is a secondary alkyl group. Oxidative cleavage and ketone formation are both important when R is a primary alkyl group. The material balance is good in all cases except for the 2-chloroethylphenylmethanol where it is 129%. The work up in this case resulted in an emulsion. This may have caused some error in the determination of the absolute yields. The ratio of benzaldehyde to ketone is probably less sensitive to error than the material balance since the recovered starting material is not a parameter in its determination.
Table 1. Absolute Yields of Recovered Starting Materials and Products from the CAN Oxidation of Alkylphenylmethanols, PhCHOHR.\textsuperscript{a}

<table>
<thead>
<tr>
<th>R</th>
<th>PhCHOHR</th>
<th>PhCOR</th>
<th>PhCHO</th>
<th>Yield of PhCHO</th>
<th>Yield of PhCOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethyl\textsuperscript{b}</td>
<td>20.9 ± 0.3</td>
<td>14.8 ± 0.3</td>
<td>61.1 ± 0.7</td>
<td>4.13 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>isobutyl\textsuperscript{b}</td>
<td>15.4 ± 1.6</td>
<td>15.1 ± 0.0</td>
<td>55.6 ± 0.0</td>
<td>3.69 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>cyclopropylmethyl</td>
<td>14.7 ± 0.4</td>
<td>3.15 ± 0.46</td>
<td>75.5 ± 1.4</td>
<td>24.4 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>5-hexenyl</td>
<td>36.5 ± 1.6</td>
<td>13.8 ± 0.4</td>
<td>44.0 ± 0.6</td>
<td>3.19 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>4-methoxybutyl</td>
<td>30.8 ± 0.6</td>
<td>21.8 ± 0.7</td>
<td>47.0 ± 0.7</td>
<td>2.16 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>3-methoxypropyl</td>
<td>45.5 ± 3.2</td>
<td>24.7 ± 1.7</td>
<td>26.9 ± 2.7</td>
<td>1.10 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>2-methoxyethyl</td>
<td>42.1 ± 1.7</td>
<td>39.8 ± 0.9</td>
<td>19.4 ± 0.4</td>
<td>0.487 ± 0.004</td>
<td></td>
</tr>
<tr>
<td>4-bromobutyl\textsuperscript{b,c}</td>
<td>26.0 ± 1.0</td>
<td>44.0 ± 0.0</td>
<td>25.0 ± 2.0</td>
<td>0.58 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>2-bromoethyl\textsuperscript{c}</td>
<td>32.0 ± 10.0</td>
<td>62.0 ± 18.0</td>
<td>6.4 ± 1.5</td>
<td>0.096 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>2-chloroethyl\textsuperscript{b,c}</td>
<td>61.0 ± 4.0</td>
<td>46.0 ± 4.0</td>
<td>22.0 ± 2.0</td>
<td>0.48 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>2-fluoroethyl\textsuperscript{c,d}</td>
<td>47.0</td>
<td>45.0</td>
<td>10.0</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}In 50% aqueous acetonitrile in 80° oil bath; yields were determined by glpc using an internal standard and are based on at least 3 runs unless otherwise noted.

\textsuperscript{b}Results based on 2 runs; average instead of standard deviations are presented.

\textsuperscript{c}Yields were determined by nmr using an internal standard.

\textsuperscript{d}Results based on 1 run.
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield of PhCHOHR</th>
<th>PhCOR</th>
<th>PhCHO</th>
<th>Yield of PhCOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexyl</td>
<td>4.46± 0.62</td>
<td>0.753± 0.027</td>
<td>89.6±0.9</td>
<td>119.0 ±2.9</td>
</tr>
<tr>
<td>cyclopentyl</td>
<td>23.4 ± 4.0</td>
<td>1.16 ± 0.26</td>
<td>74.4±1.2</td>
<td>66.1 ±14.8</td>
</tr>
<tr>
<td>cyclobutyl</td>
<td>23.0 ± 4.1</td>
<td>4.79 ± 0.54</td>
<td>61.4±3.9</td>
<td>12.9 ±1.7</td>
</tr>
<tr>
<td>cyclopropyl</td>
<td></td>
<td></td>
<td>22.0</td>
<td>&gt;8</td>
</tr>
<tr>
<td>7-norbornyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Starting material was found unstable to the acid conditions of the reaction media.

*Based on a crude estimate from the nmr of the product mixture from reaction of 7-norbornylphenylmethanol with 6 equiv of CAN ca. 80°C in 50% aqueous acetonitrile. One run and no standard added.
The difference between the benzaldehyde to ketone ratio found in this work for ethylphenylmethanol, 4.13, and that reported by Trahanovsky and Cramer (13), 3.30, is small but real. They used commercial grade ethylphenylmethanol without further purification for their study. The commercial grade ethylphenylmethanol obtained for this study was found to contain a small amount of the corresponding ketone as impurity. This ketone was removed by treating the commercial material with sodium borohydride. The value of 4.13 was obtained from ketone free alcohol. A slight amount of alkyl phenyl ketone explains the lower value for the benzaldehyde to ketone ratio reported by Trahanovsky and Cramer.

The cyclopropylphenylmethanol was unstable to reaction conditions. In a control run using a cerium(III) solution (prepared from CAN and pinacol) and cyclopropylphenylmethanol, little starting material was found after work up. The major product was isolated and its nmr found consistent with that of 4-phenylbut-3-en-1-ol. Since aqueous CAN solutions are acidic, an acid catalyzed rearrangement is possible. The nmr of the product mixture from the CAN oxidation of 1-cyclopropylethanol showed no cyclopropyl hydrogens. The CAN oxidation of cyclopropylmethanol has been reported to produce a 64% yield of cyclopropanecarbaldehyde (22). The postulate that additional substitution on the methanol carbon leads to acid catalyzed rearrangement as a major reaction is supported by the finding that 1'-methylcyclopropylmethylen-
3,5-dinitrobenzoate undergoes solvolysis 1000 times faster than cyclopropylmethyl-3,5-dinitrobenzoate (23).

The cyclopropylmethylphenylmethanol when oxidized by CAN gives a benzaldehyde to ketone ratio significantly greater than found from the other alcohols with primary alkyl groups. A mixture of allylphenylmethanol and cyclopropylmethylphenylmethanol in the ratio of 1:1.12 was oxidized by 1 equiv of CAN. The ratio of the recovered starting materials was 1:1.19 respectively. These ratios were determined by glpc and the nmr of the reaction mixture indicated a 20% yield of benzaldehyde.

The relative rates of ketone formation for all of the alkylphenylmethanols listed in Table 1 must be approximately the same if the benzaldehyde to ketone ratios for these alcohols can be used as a measure of their relative rates of oxidative cleavage. In order to partially establish the validity of this approximation, a tertiary alkylphenylmethanol, ethyl(2-methoxyethyl)phenylmethanol, was oxidized with CAN (equation 2). The yields of products were determined by

\[
\begin{align*}
\text{CH}_3\text{OCH}_2\text{CH}_2\text{C}-\text{CH}_2\text{CH}_3 + \text{Ce}^{IV} & \rightarrow \text{CH}_3\text{OCH}_2\text{CH}_2\text{CPh} + \cdot\text{CH}_2\text{CH}_3 \\
\text{CH}_3\text{OCH}_2\text{CH}_2\text{C}-\text{CH}_2\text{CH}_3 + \cdot\text{PhCCH}_2\text{CH}_3 & \rightarrow \text{CH}_3\text{OCH}_2\text{CH}_2\cdot + \cdot\text{PhCCH}_2\text{CH}_3
\end{align*}
\]
glpc analysis using an internal standard. These yields are reported in Table 2. The oxidation was well behaved and

Table 2. Absolute Yields of Recovered Starting Material and Products from the CAN Oxidation of ethyl(2-methoxyethyl)phenylmethanol.\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethyl(2-methoxyethyl)phenylmethanol</td>
<td>30.6 ± 0.6</td>
</tr>
<tr>
<td>ethyl phenyl ketone</td>
<td>7.82 ± 0.35</td>
</tr>
<tr>
<td>2-methoxyethyl phenyl ketone</td>
<td>60.3 ± 0.4</td>
</tr>
<tr>
<td>Yield of 2-methoxyethyl phenyl ketone</td>
<td>7.73 ± 0.39</td>
</tr>
<tr>
<td>Yield of ethyl phenyl ketone</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)In 50% aqueous acetonitrile in 80° oil bath; yields were determined from 3 glpc runs.

the material balance high, 99%. The CAN oxidation of this tertiary alcohol resulted in two phenyl ketones since either the ethyl or 2-methoxyethyl group was cleaved off. If the relative rates of ketone formation for ethylphenylmethanol and 2-methoxyethylphenylmethanol are the same, the ratio of 2-methoxyethyl phenyl ketone to ethyl phenyl ketone obtained from CAN oxidation of 1 should be ca. 8.48 since

$$\frac{[\text{CH}_3\text{OCH}_2\text{CH}_2\text{COPh}]}{[\text{CH}_2\text{CH}_2\text{COPh}]} = \frac{k_{\text{Et}}}{k_{2-\text{MeO}}} \approx \frac{k'_{\text{Et}}}{k'_{2-\text{MeO}} k_{\text{ketone}}} = \frac{4.13}{0.487} = 8.48$$

where \(k_{\text{Et}}\) and \(k_{2-\text{MeO}}\) are defined in Equation 2, \(k'_{\text{Et}}/k'_{\text{ketone}}\)
is the benzaldehyde to ketone ratio obtained from ethylphenylmethanol and \( k'_{2-MeO}/k_{ketone} \) is the benzaldehyde to ketone ratio obtained from 2-methoxyethylphenylmethanol. The 2-methoxyethyl phenyl ketone to ethyl phenyl ketone ratio was found to be \( 7.73 \pm 0.39 \) which is in excellent agreement with the predicted value. Evidence for the preferential loss of the ethyl group over the 2-methoxyethyl group is also found in the mass spectrum of 1. This is presented in Table 3.

Table 3. Partial Mass Spectrum of \( \text{CH}_3\text{CH}_2-C(\text{CH}_2\text{CH}_2\text{OCH}_3)\text{Ph} \).

<table>
<thead>
<tr>
<th>Ion</th>
<th>70-eV, %</th>
<th>16-eV, %</th>
<th>Loss of</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>100.0</td>
<td>100.0</td>
<td>( \text{CH}_2\text{CH}_3 )</td>
</tr>
<tr>
<td>135</td>
<td>47.5</td>
<td>24.0</td>
<td>( \text{CH}_2\text{CH}_2\text{OCH}_3 )</td>
</tr>
</tbody>
</table>

The effect of reaction temperature on the benzaldehyde to ketone ratio is presented in Table 4. The effect is relatively small. For ethylphenylmethanol, a decrease in the reaction temperature of \( 50^\circ \) decreases the benzaldehyde to ketone ratio by a factor of only 2. The respective decrease for cyclohexylphenylmethanol is only a factor of 2.5. The slopes were determined from graphs of the logarithms of the benzaldehyde to ketone ratios versus \( 1/T \). From these slopes the \( \Delta\Delta E_a \) were calculated. They are for the CAN
Table 4. Effect of Temperature on the Benzaldehyde to Ketone Ratio.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Oil Bath Temp.</th>
<th>Reaction Time, Min.</th>
<th>Material Balance</th>
<th>Benzaldehyde to Ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylphenylmethanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80°</td>
<td>10.5</td>
<td>96.7</td>
<td>4.13</td>
</tr>
<tr>
<td>50°</td>
<td>138</td>
<td>93.5</td>
<td>2.87</td>
</tr>
<tr>
<td>30°</td>
<td>1320</td>
<td>93</td>
<td>2.00</td>
</tr>
<tr>
<td>Cyclohexylphenylmethanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80°</td>
<td>3.5</td>
<td>95</td>
<td>119</td>
</tr>
<tr>
<td>50°</td>
<td>30</td>
<td>103</td>
<td>79.6</td>
</tr>
<tr>
<td>30°</td>
<td>270</td>
<td>94</td>
<td>47.5</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction with CAN in 50% aqueous acetonitrile; Yields were determined by glpc using an internal standard.

The oxidation of ethylphenylmethanol and cyclohexylphenylmethanol is 3.0 kcal/mol and 4.0 kcal/mol respectively.

The detection and identification of the products arising from the radical moiety in the cleavage reaction is somewhat difficult since many of these compounds are unstable, volatile, or very water soluble. Thus in most of the cases studied no great effort was made to determine all the products from the cleaved radical. Trahanovsky and Cramer found that alkyl nitrates account for a large portion of the cleaved radical (13). The distinctive nitrate bands at 1660-1625 cm\textsuperscript{-1} and at 1300-1255 cm\textsuperscript{-1} were observed in the ir spectra of the product mixtures from the CAN oxidation of many of the alkylphenylmethanols in this study. The fate of the radical...
moiety was studied in greater detail for the oxidative cleavage of cyclopentylphenylmethanol and cyclohexylphenylmethanol. The products found from the radical moiety are reported in Table 5. The roughly equal distribution of olefin

Table 5. Products Arising from the Radical Moiety from the Oxidative Cleavage by CAN of Alkylphenylmethanols.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Radical</th>
<th>Olefin</th>
<th>Nitrate</th>
<th>Solvent Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}<em>5\text{H}</em>{12}$</td>
<td>$\text{C}<em>5\text{H}</em>{10}$</td>
<td>$\text{C}<em>5\text{H}</em>{10}\text{NO}_2$</td>
<td>\textbf{(not determined)}</td>
</tr>
<tr>
<td>$\text{C}<em>6\text{H}</em>{12}$</td>
<td>$\text{C}<em>6\text{H}</em>{10}$</td>
<td>$\text{C}<em>6\text{H}</em>{10}\text{NO}_2$</td>
<td>15-20\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yields are relative to benzaldehyde and were determined by nmr unless otherwise noted.

\textsuperscript{b}Yield determined by glpc.

and nitrate products from oxidative cleavage of bicyclic alcohols by CAN has been reported (24). This equal distribution is also noted in this study. Cyclohexylphenylmethanol was oxidized by CAN under a variety of conditions to determine what factors might influence the distribution of olefin and
nitrate products. Using temperatures of 120° (sealed tube experiment), 80°, and 30°, no significant change in the distribution was found. The presence of a small amount of cupric nitrate in the reaction mixture did not change the roughly equal distribution of nitrate and olefin. Little effect on this distribution was found when the reaction media was varied: 20%, 50%, and 90% aqueous acetonitrile.

Bicycloalkylphenylmethanols

A series of bicycloalkylphenylmethanols was prepared and their oxidation by CAN studied. The reaction rates were determined by following the disappearance of the absorption at 448 nm and are reported in Table 6. The temperature was maintained by circulating water at 20.00±0.05° around the uv cell compartment. The measurements were taken on a mixed solution that was 80% aqueous acetonitrile, 0.6 M nitric acid, 0.05 M in alcohol, and 0.0025 M in CAN. These conditions were used because the addition of nitric acid retarded the rate of oxidation enough so that all the rates could be measured at the same temperature.

The rate of oxidation of anti-7-norbornenylphenylmethanol (2) was too fast for determination of the complexation constant with CAN. Complexation constants were determined
Table 6. Pseudo First Order Rate Constants for Disappearance of the 448 nm Absorption of Solutions of CAN and Indicated Substrates.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$k \times 10^{-4}$ sec(^{-1})</th>
<th>$t_{1/2}$ sec</th>
<th>Relative Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOPh</td>
<td>56.3 ±4.7\textsuperscript{b}</td>
<td>121±14</td>
<td>16.2 425</td>
</tr>
<tr>
<td>CHOPh</td>
<td>3.46 ±0.49</td>
<td>2,040±285</td>
<td>1.0 26</td>
</tr>
<tr>
<td>CHOPh</td>
<td>0.133±0.0005</td>
<td>52,250±250</td>
<td>0.038 1.0</td>
</tr>
<tr>
<td>CHOPh</td>
<td>3.29 ±0.05</td>
<td>2,106±31</td>
<td>0.95 24.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All measurements were obtained under the same conditions; 20.00°, $\lambda$=448 nm, 80% acetonitrile-20% aqueous nitric acid, 0.6 M nitric acid, 0.0025 M CAN, and 0.05 M substrate.

\textsuperscript{b}These are all average deviations.
for syn-7-norbornenylphenylmethanol (3) and 7-norbornylphenylmethanol (4) and are shown in Table 7. The constants for

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Keq</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopentanol</td>
<td>3.19±0.20</td>
</tr>
<tr>
<td></td>
<td>3.1±0.10</td>
</tr>
<tr>
<td>n-hexanol</td>
<td>2.16±0.08</td>
</tr>
<tr>
<td></td>
<td>1.59±0.03</td>
</tr>
<tr>
<td>3</td>
<td>5.18±0.60</td>
</tr>
<tr>
<td>4</td>
<td>4.52±0.53</td>
</tr>
</tbody>
</table>

\(^a\) Determined in 70% aqueous acetonitrile and 0.49 M nitric acid at 20\(^\circ\).

\(^b\) Calculated from RAWDAT program (25, 26).

\(^c\) Data from L. B. Young and W. S. Trahanovsky (27).

cyclopentanol and n-hexanol were determined and compared to previously reported values in order to check experimental technique. It appears that the equilibrium constants for 3 and 4 are experimentally close and that the double bond has little effect on the degree of complexation. The assumption can be made that the equilibrium constant for 2 and CAN is probably close to 5.0 also. There is no correlation established here between reaction rates and degree of complexation with CAN.

The rate data presented in Table 6 do not represent
relative rates of oxidative cleavage. Comparison of the rates from Table 6 indicate the CAN reacts with the double bond at least as fast as it does with the hydroxyl group in these bicyclic compounds. The product mixtures from oxidation of 2 and 3 with 2 equiv of CAN contain almost no g LPC detectable benzaldehyde. The IR spectra show strong nitrate absorptions at 1290 and 1640 cm\(^{-1}\). Oxidative cleavage cannot be an important reaction for CAN oxidation of 2 and 3. Reaction of 2 equiv of CAN with 2 and 4 resulted in recovery of about 50% of the starting material. A similar reaction with 2 resulted in recovery of only a small amount of starting material. Reaction of 4 with 6 equiv of CAN in 50% aqueous acetonitrile was stopped after 20 min at 80°. The NMR of the product mixture indicated the major components were benzaldehyde and recovered starting material. The benzaldehyde to ketone ratio was estimated as greater than 8 from the NMR spectrum. If 4 is allowed to react in a solution of 80% aqueous acetonitrile and CAN a side reaction produces significant amounts of N-(7-norbornylphenylmethyl)acetamide (6).

To further elucidate the reactivity of CAN with double bonds versus the hydroxyl group, the following experiments were run.
A mixture of 1 equiv each of 1-methylcyclohexene and isobutylphenylmethanol was oxidized by 2 equiv of CAN. The red color faded to colorless in 2 min at 80°. Only a small amount of benzaldehyde was observed in the product mixture by nmr. Isobutylphenylmethanol required 19 min to react with CAN alone. The 1-methylcyclohexene alone reduces CAN to a colorless state rapidly (4 min) at room temperature to give nitrate products. It is clear that highly substituted or strained double bonds react rapidly with CAN. Phenyl-substituted olefins have been shown to yield nitrates as major products (28) in agreement with the results of this study.

A mixture of commercial exo- and endo-5-benzoyl-2-norbornenes was reduced to the corresponding mixture of alcohols with sodium borohydride. The nmr of the mixture contained a multiplet at 3.78 δ and at 4.1 δ. These were attributed to the hydrogens on the methanol carbons for the two compounds. The reaction of 1 equiv of CAN and the mixture of alcohols at 80° was over in 2 min. The nmr of the product mixture contained the multiplet at 4.1 δ but the one at 3.78 δ was undetectable. The CAN selectively oxidized one isomer.

Synthesis

The cyclohexyl-, cyclopentyl-, cyclobutyl-, 2-methylpropyl, 2-bromoethyl, and 2-chloroethylphenylmethanols were
prepared by sodium borohydride reduction of the corresponding ketones. The synthetic routes of the other alkylphenylmethanols and related compounds are described in Chart 1.

\[
\begin{align*}
CH_2=CHCH_2Br & \xrightarrow{1. \text{ Mg, ether}} CH_2=CHCH_2CHOHPh \\
& \xrightarrow{2. \text{ PhCHO}} CH_2=CHCH_2CHOHPh \\
& \xrightarrow{3. \text{ NH}_4^+ / H_2O} 37\%
\end{align*}
\]

\[
\begin{align*}
\text{Zn-Cu} & \xrightarrow{\text{CH}_2=\text{CH}_2} CH_2CH_2CHOHPh \\
& \xrightarrow{\text{CrO}_3-\text{Pyridine}} CH_2CH_2CHOHPh \\
& \xrightarrow{\text{Zn-Cu}} 37\% \quad 100\%
\end{align*}
\]

\[
\begin{align*}
CH_2=CH(CH_2)_4OH & \xrightarrow{1. \text{ Mg, ether}} CH_2=CH(CH_2)_4CHOHPh \\
& \xrightarrow{2. \text{ PhCHO}} CH_2=CH(CH_2)_4CHOHPh \\
& \xrightarrow{3. \text{ NH}_4^+ / H_2O} 76\% \quad 61\%
\end{align*}
\]

\[
\begin{align*}
\text{Br(CH}_2)_4\text{Br} & \xrightarrow{\text{NaOH}} CH_3O(CH_2)_4\text{Br} \\
& \xrightarrow{1. \text{ Mg, ether}} CH_3O(CH_2)_3CH(CH(OH)Ph \\
& \xrightarrow{2. \text{ PhCHO}} CH_3O(CH_2)_3CH(CH(OH)Ph \\
& \xrightarrow{3. \text{ NH}_4^+ / H_2O} 42\% \quad 52\%
\end{align*}
\]

\[
\begin{align*}
\text{CrO}_3-H_2\text{SO}_4 & \xrightarrow{\text{Acetone}} CH_3O(CH_2)_4\text{COCH}_3 \\
& \xrightarrow{75\%} \\
& \xrightarrow{\text{H}_2\text{SO}_4} CH_3O(CH_2)_3\text{COCH}_3 \\
& \xrightarrow{\text{H}_2\text{SO}_4} CH_3O(CH_2)_3\text{COCH}_3 \\
& \xrightarrow{\text{NaBH}_4} CH_3O(CH_2)_3\text{COCH}_3 \\
& \xrightarrow{\text{CH}_3\text{OH}} 62\% \quad 86\%
\end{align*}
\]

Chart 1. Synthetic Routes for Alkylphenylmethanols and Related Compounds.
PhCH=CH₂ + ClCH₂OCH₃ → PhCHClCH₂CH₂OCH₃

KOH, H₂O → PhCHOHCH₂CH₂OCH₃ → PhCOCH₂CH₂OCH₃

1. CH₃CH₂MgBr
2. H⁺NH₄+/H₂O

PhCOCH₂CO₂CH₃ + Br(CH₂)₃Br → NaOCH₂CH₃

HBr → PhCO(CH₂)₄Br → NaBH₄ → PhCHOH(CH₂)₄Br

PhCHOHCH₂CH₂Cl → PhCHOHCH₂CH₂K⁺

a Prepared for this study by Myong-Gi Park.

Chart 1. (Continued)
The preparation of cyclopropylmethylphenylmethanol involved the Simmons-Smith reaction. This involved the preparation of a zinc-copper couple. The procedures of Schank and Schecter (29) and of Le Goff (30) required the isolation of the couple before use. In this work the method of Rawson and Harrison (31) was found to be simpler and resulted in higher yields of product. The couple is prepared in-situ by refluxing zinc dust and cuprous chloride together in dry ether and then adding a mixture of olefin and methylene diiodide. In all the Grignard reactions leading to secondary alkylphenylmethanols a small amount of the corresponding alkyl phenyl ketone was produced. This was removed by treatment with sodium borohydride.

The synthetic pathways leading to the bicycloalkylphenylmethanols are shown in Chart 2.

The yield of alcohol mixture 2 and 3 was not affected by the preparation of the Grignard reagent. Whether the syn-7-bromonorbornene was added to magnesium turnings over 2 hours or over 28 hours, the yields of alcohol mixture were similar. The use of "activated magnesium" (32) for preparation of the Grignard reagent also did not improve the yield of the alcohol mixture.

Column chromatography on silica gel or alumina failed to separate the mixture of alcohols 2 and 3. The initial fractions were slightly richer in the anti isomer 2 but not enough to consider this a practical method for separation. The
Chart 2. Preparation of Bicycloalkylphenylmethanols.
isomers sublimed together and distillation lead to polymerization. The syn isomer 3 could be obtained by the selective destruction of the anti isomer by oxidation with CAN. The isomers were separated by preparative glpc using a 100 X 2 cm column of copper tubing packed with 20% carbowax 20 M on chromosorb P. This very tedious technique was unsatisfactory since only 40% of injected material was collected.

The alcohol mixture was converted to a mixture of the corresponding acetates. This acetate mixture was even less separable by glpc. It was found, however, that silver ion selectively complexes with the syn isomer 3. The two epimeric alcohols were separated by simply washing the ether solution of the mixture with aqueous silver nitrate solution. The anti isomer 2 remained in the ether layer and the syn isomer 3 was extracted into the aqueous layer. Addition of ammonium to this aqueous layer released the syn-alcohol from solution. The alcohol mixture was found to contain a 2 to 1 ratio of syn to anti alcohol.

The alcohols 2 and 3 exist in a preferred conformation with the OH and phenyl groups pointed away from the 2-3 and 5-6 bonds as shown below. The nmr of the anti isomer 2 has two broad singlets of 3.03 and 2.2 6. Also in the nmr for the syn alcohol 3 there are two broad singlets at 2.92 and 2.08. These are the bridgehead protons. In each case one hydrogen signal is shifted upfield due to the magnetic anisotropy of the phenyl ring. There is direct evidence that
the H is forced over the double bond in the preferred conformation of 2. For the **anti** alcohol 2 a doublet occurs at 4.38 δ while in the **syn** alcohol 3 the doublet is at 3.98, the anisotropy of the double bond causing the upfield shift. Finally, there is no evidence of intramolecular hydrogen bonding from the hydroxyl H to the double bond in 3 from the ir spectrum.
DISCUSSION

Benzaldehyde to Ketone Ratio

The determination of the relative rates of oxidative cleavage by CAN of a series of alkylphenylmethanols and the resulting quantitative analysis of the relative formation tendencies for the corresponding radicals is the major contribution of this study. The validity of using the benzaldehyde to ketone ratio determined from the product mixtures of the CAN oxidations of alkylphenylmethanols as a measure of the relative rates of oxidative cleavage is essential for this thesis. The verisimilitude of this postulate is well supported.

Although cerium(IV) is known to oxidize benzaldehyde to benzoic acid, the reaction is severely retarded by nitrate ion (33). In fact, CAN oxidation of benzyl and related alcohols to the corresponding aldehydes is synthetically useful (34). The recovery of the phenyl ring is high for the oxidations presented in Table 1. The phenyl ring is accounted for as benzaldehyde, alkyl phenyl ketone, and starting material. This suggests that there is little loss of the phenyl ring by further CAN oxidation and supports the reliability of the benzaldehyde to ketone ratio as a measure of the relative rate of oxidative cleavage to ketone formation.

Assuming that the rate of oxidation of the alkylphenylmethanol to the corresponding ketone is not greatly affected
by changing the alkyl group, Trahanovsky and Cramer used the benzaldehyde to ketone ratio to determine the relative rates of radical formation by oxidative cleavage. The rates agree quite well with those determined by other means. This agreement is good evidence for the validity of their assumption. The assumption is supported also by the argument that the site for oxidation to ketone is more removed from the effects of an alkyl group than the site for oxidative cleavage. This assumption was directly tested by the CAN oxidation of a tertiary alkylphenylmethanol and the results are presented in Table 2. The relative rate of cleavage generating an ethyl radical is 8.48 times the rate of cleavage generating a 2-methoxyethyl radical. Comparing benzaldehyde to ketone ratios obtained from oxidation of the corresponding secondary alkylphenylmethanols reported in Table 1, the ratio is 7.73. These values are in close agreement and this strongly supports the assumption that the relative rates of ketone formation are approximately the same.

The benzaldehyde to ketone ratios have been determined for ethylphenylmethanol and cyclohexylphenylmethanol for several temperatures. These data are presented in Table 4. Using these values, the ratio of the rate of formation of cyclohexyl radical to that of ethyl radical is 28.8 at 80°;

\[ ^{1}\text{Their results are presented on pages 4-5.} \]
27.7 at $50^\circ$; and 23.8 at $30^\circ$. Temperature changes by $50^\circ$ have only a small effect. It is interesting to note that the relative rates of ejection of cyclohexyl vs ethyl radical from $t$-alkoxy radicals is reported as 23 at $80^\circ$ (35). This agreement is excellent.

It seems clear that the benzaldehyde to ketone ratio is a good measure of the relative rate of oxidative cleavage and hence a good measure of relative rates of radical formation.

Transition State

The "polar effect" in free radical reactions is the terminology for a charge separation in the transition state of a homolytic reaction. This theory was developed to explain the dependence of the reactivity on the attacking radical in hydrogen atom transfer reactions (36). This idea is well established and has recently been reviewed (37). For example, if a C-H bond is attacked by an electronegative radical $\cdot X$, the transition state is polarized. The electrons are drawn toward the attacking radical. This charge separation in

$$\text{C-H + } \cdot X \rightarrow \text{C}^+ \cdot H \cdots \cdot X \rightarrow \text{C}^+ + H-X$$

the transition state is stabilized or destabilized by substituents adjacent to the C-H bond. Quantitative relationships with reactivity have been described by Hammett style correlations (37).

Recently Zavitsas has challenged the polar effect concept
(38-40). He has claimed that the charge separation in the transition state is not a factor in controlling reaction rates for hydrogen abstractions by radicals. He has reported that the polar effect argument would predict $\varphi \approx 0$ for hydrogen abstractions from substituted toluenes by the methyl radical and $\varphi$ should be zero or positive for the t-butyl radical. His postulation requires that all $\varphi$ values be negative and he has predicted that $\varphi \approx -1.4$ for abstractions by t-butyl radical (39). The validity of Zavitsas' postulation has been seriously questioned (41). Pryor and his coworkers have reported a Hammett $\rho$ correlation for the reaction of t-butyl radicals with substituted toluenes. They reported $\varphi = 0.99 \pm 0.04$, the first reported positive $\varphi$ value for radical abstractions from toluenes. Pryor's work supports the theory of polar effects and greatly damages the arguments of Zavitsas.

Polar effects are thought to be important factors in many free radical forming reactions. Rüchardt and coworkers have reviewed the relations between structure and reactivity in free radical chemistry (42,43). They pointed out that polar effects have a strong influence on the rate of fragmentation of peroxy esters. Kochi has attributed the high degree of selectivity found in the fragmentation of alkoxy radicals to polar contributions in the transition state (44). A polar effect has been reported for the oxidative cleavage of 1,2-diarylethanols with CAN (16). The $\varphi$ value of $-2.0$ was ob-
tained for the cleavage based on $\sigma^+$ substituent parameters. A Hammett plot of the relative rates of CAN oxidation of meta- and para-substituted phenylacetic acids with $\sigma^+$ values gave a $\rho$ of -3 (45). The negative $\rho$ is considered good evidence that a significant amount of positive character develops on the benzylic carbon atom during the transition state. This is consistent with the electronegative metal ion polarizing the transition state.

Ring Size Effects

One of the first useful correlations of ring size with reactivity was made by Brown and coworkers (46). He introduced the $I$-strain concept. The changes in hybridization of a carbon atom in a cyclic system may change the $I$-strain ("internal strain"). For example, changing a tetravalent carbon to a trivalent carbon relieves strain for a five-membered ring while the strain is increased for a six-membered ring (47,48). Solvolysis of 1-methylcyclopentyl chloride is 100 times faster than for 1-methylcyclohexyl chloride (42,43,47). This conformational effect does not influence the formation of carbanions (42,43). In fact, the rates of formation of carbonium ions and carbanions depend characteristically and differently on ring size (42,43).

The effect of ring size upon the rates of formation of cyclic radicals varies with the mode of radical generation. The thermolysis of various cycloalkyl azo compounds always
show more rapid rates for the five-membered ring than the six. The decomposition of azo-1-methylcyclopentane is ca. 10 times faster than the azo-1-methylcyclohexane (42). The rate of homolytic fragmentation of cycloalkyl peroxy esters decreases roughly as the size of the ring decreases (42,43). The rate of decomposition does not pass through a minimum for the six-membered ring as observed for thermolysis of azo compounds or for carbonium ion formation. Rüchardt's interpretation is that ring strain effects have no appreciable influence on the decomposition of peroxy esters and that the C-CO bond is only weakly stretched in the transition state with essentially tetrahedral geometry (42,43). He points out that polar effects are less important in the thermolysis of symmetrical azo alkanes than for the fragmentation of peroxy esters. He concludes that polar effects are important on radical formation reactions in which the transition state occurs early on the reaction coordinate as with fragmentation of peroxy esters (43).

From Rüchardt's arguments it appears the relative rates of reactivity of the five- and six-membered rings should be very informative about determining the position of the transition state for any reaction in question and about the relative importance of polar effects. The relative rates of oxidative cleavage from the benzaldehyde to ketone ratios presented in Table 1 (pages 8-9) for the cyclobutyl, cyclopentyl and cyclohexyl systems are 1.0, 5.1, and 9.2 respectively. The
relative rates of decomposition of the cyclic diacyl peroxides is respectively 1.0, 4.3, and 8.3 (49). This agreement is excellent. A direct comparison of the rate of formation of the cyclohexyl versus the cyclopentyl radical reveals excellent agreement among reactions influenced by polar effects: From the internal competition during decomposition of 1-cyclopentyl-1-cyclohexyl-ethylhypochlorite, 2.56 (42); From comparison of the relative rates of cyclohexyl versus ethyl and cyclopentyl versus ethyl ejection from t-alkoxy radicals, 2.56 (35); From diacyl peroxide decomposition, 1.9 (49); From CAN oxidative cleavage, 1.8, Table 1 (pages 8-9). From these comparisons it is clear that the transition state of the oxidative cleavage reaction of an alkylphenylmethanol with CAN lies early on the reaction coordinate and is polar. This description leads to the prediction that electronegative alkyl groups present in alkylphenylmethanols should retard the relative rate of oxidative cleavage by CAN. That this is the case is evident from the data in Table 1 (pages 8-9).

Oxidative Cleavage of a Primary Alkyl Group

The benzaldehyde to ketone ratios for ethyl-, 2-methylpropyl-, and 5-hexenylphenylmethanols are respectively 4.13, 3.69, and 3.19 (Table 1, pages 8-9). The ratio for 2-tert-butylethylphenylmethanol has been determined by Trahanovsky and Himstedt and is 3.27 (50). The ratio of ca. 4 is general for the several alkylphenylmethanols studied
that produce primary radicals. These results indicate that
the size of the primary radical which is being formed during
the oxidative cleavage does not significantly affect its rate
of formation. Furthermore the formation of ethyl radical
is fastest among the primary alkyl radicals, roughly according
to hyperconjugative order. Kochi has reported a similar con­
clusion for the fragmentation of alkoxy radicals (44,51).

The 5-hexenyl radical normally picks up a hydrogen
atom or cyclizes to a five-membered ring. This cyclization
has been intensely studied and reviewed (52-54). Kinetics
and products of the thermal decomposition of 6-heptenoyl
peroxide indicate that its initial cleavage occurs without
a neighboring group effect from the double bond (52).
Reaction of 6-bromo-l-hexene with tributylstannane
yields no evidence for participation of the double bond during
radical generation (53). Our results with the CAN oxidation
of 5-hexexylphenylmethanol also indicate no participation
of the double bond during oxidative cleavage.

Slow Rates of Oxidative Cleavage

A methoxy substituent on the alkyl radical which is
being formed during the oxidative cleavage significantly
retards its rate of formation. In Table 1 (pages 8-9)
are presented the benzaldehyde to ketone ratios obtained
from the CAN oxidation of a series of methoxy-substituted
alkylphenylmethanols. It is seen that the relative rate of
oxidative cleavage for even the 4-methoxybutyl alcohol is slower than that of ethylphenylmethanol. The relative rates of oxidative cleavage decrease regularly from the 4-methoxybutyl to the 2-methoxyethyl alcohol. The methoxymethylphenylmethanol is a mono-methyl ether of a 1,2-glycol and is expected (55) and was found (56) to undergo oxidative cleavage exclusively. The effect of the methoxy groups on the relative rates of oxidative cleavage is most readily explained by their inductive effect. The stability of the polar transition state for the cleavage reaction is decreased by the electron withdrawing methoxy groups. The good material balance rules out any attack at the methoxy group which leads to products other than those expected from attack at the hydroxy group.

Although the 2- and 3-methoxy groups retard the rates of solvolysis of ω-methoxyalkyl-1 p-bromobenzenesulfonates, the 4-methoxy group leads to a rate increase (57). This rate increase is ascribed to neighboring group participation which involves the formation of a 5-membered ring. In the CAN oxidative cleavage reaction, the low rate of cleavage for the 4-methoxybutylphenylmethanol indicates that neighboring group participation by methoxy groups is unimportant.

A halogen substituent on the alkyl radical which is being formed during the oxidative cleavage significantly retards the cleavage. In Table 1 (pages 8-9) the benzaldehyde to ketone ratios from the CAN oxidation of several halogen substituted alkylphenylmethanols show this retardation. Even
if the halogen is four methylene groups removed from the radical center, as is the case of the 4-bromobutyl, there is a marked reduction in cleavage versus ketone formation. In fact in all the halogen compounds studied oxidative cleavage is the minor reaction in favor of formation of ketone. This is in contrast with all other compounds studied except for the 2-methoxyethyl alcohol. The yields for the halogen substituted alcohols were determined by nmr and the material balances are high. Even if the benzaldehyde to ketone ratios determined by nmr are less accurate than those determined by glpc, it is clear that a greater amount of ketone formation than cleavage has occurred. Although the CAN oxidation of chloromethylphenylmethanol resulted in several complications (56), the major oxidation product was the chloromethyl phenyl ketone. As with the methoxy groups the relative rates of oxidative cleavage is most readily explained by the inductive effect. The observed order of cleavage for the 2-bromoethyl, 2-chloroethyl, and the 2-fluoroethyl is not explained by the inductive effect. The possibility of some direct interaction of the halogens and CAN exists since the formation constants for the 1:1 cerium(IV)-alcohol complexes for ethanol and 2-chloroethanol are respectively 0.74±0.05 and 0.13±0.2 (27). The nature of this interaction is not known but it does not change the expected cleavage retardation by the electronegative halogens.

Taft used the differences in rates of hydrolysis of
esters in acid and base as a measure of the polar effect of various groups (58). He expressed this inductive effect of a group by the symbol σ*, known now as the Taft polar substituent constant. Taft demonstrated that an excellent correlation exists between σ* and electronegativity of groups. Some σ* values pertinent to this discussion are presented in Table 8. Other substituent constants have been determined. For our purposes the most useful are probably the σ_I values determined from the ionization of substituted acetic acids (59). Some of these are presented in Table 9.

Table 8. Some polar Substituent Constants.\(^a\)

<table>
<thead>
<tr>
<th>Group</th>
<th>σ*</th>
<th>Group</th>
<th>σ*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH(_2)</td>
<td>1.10</td>
<td>CH(_3)OCH(_2)</td>
<td>0.52</td>
</tr>
<tr>
<td>ClCH(_2)</td>
<td>1.05</td>
<td>CH(_3)</td>
<td>0.00</td>
</tr>
<tr>
<td>BrCH(_2)</td>
<td>1.00</td>
<td>C(_2)H(_5)</td>
<td>-0.10</td>
</tr>
<tr>
<td>CF(_3)CH(_2)</td>
<td>0.92</td>
<td>(CH(_3))(_3)SiCH(_2)</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

\(^a\)Values obtained from reference (58).

Table 9. Some Inductive Effect Substituent Constants.\(^a\)

<table>
<thead>
<tr>
<th>Group</th>
<th>σ_I</th>
<th>Group</th>
<th>σ_I</th>
<th>Group</th>
<th>σ_I</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)OCH(_2)</td>
<td>-0.07</td>
<td>CH(_3)</td>
<td>-0.05</td>
<td>CH(_3)O</td>
<td>0.25</td>
</tr>
<tr>
<td>ClCH(_2)</td>
<td>0.15</td>
<td>NO(_2)</td>
<td>0.76</td>
<td>H(_2)C=CH(_2)</td>
<td>0.13</td>
</tr>
<tr>
<td>CF(_3)CH(_2)</td>
<td>0.14</td>
<td>F</td>
<td>0.52</td>
<td>(CH(_3))(_3)SiCH(_2)</td>
<td>-0.05</td>
</tr>
<tr>
<td>BrCH(_2)</td>
<td>0.18</td>
<td>Cl</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>0.00</td>
<td>Br</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Values obtained from reference (59).
In order to facilitate our discussion, some benzaldehyde to ketone ratios and the corresponding alkyl groups from Table 1 (pages 8-9) are repeated in Table 10.

Table 10. Relative Rates for Radical Formation From Oxidative Cleavage by GA-i-J of alkylphenylmethanols.a

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Rate</th>
<th>Group</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)CH(_2)</td>
<td>4.13</td>
<td>CH(_2)=CH(CH(_2))(_4)</td>
<td>3.19</td>
</tr>
<tr>
<td>CH(_3)OCH(_2)CH(_2)</td>
<td>0.49</td>
<td>CH(_3)O(CH(_2))(_4)</td>
<td>2.16</td>
</tr>
<tr>
<td>BrCH(_2)CH(_2)</td>
<td>0.10</td>
<td>Br(CH(_2))(_4)</td>
<td>0.58</td>
</tr>
<tr>
<td>ClCH(_2)CH(_2)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCH(_2)CH(_2)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data obtained from Table 1 (pages 8-9).

From Tables 8 and 9 it is clear the inductive effects of the three halogens are expected to be about the same. In Table 10 it is seen that the differences in the relative rates of formation for the 2-haloethyl radicals are small when compared to the differences from the other radicals. The inductive order shown in Table 9 of halogen>methoxy>double bond is nicely manifested by the relative rates of formation of the respective 4-substituted butyl radicals presented in Table 10. It is clear that the relative rates of radical formation, i.e. oxidative cleavage, can be predicted on the basis of the inductive effect predicted by "polar" or
"inductive" substituent constants.

Rapid Rates of Oxidative Cleavage

The polar nature of the transition state of the CAN oxidative cleavage of alcohols suggests that neighboring groups which stabilize cations may accelerate the corresponding oxidative cleavages. The ratio of cleavage versus ketone formation for the CAN oxidation of cyclopropylmethylphenylmethanol is 24.4 whereas the corresponding ratio for the model compound, isobutylphenylmethanol, is 3.69 which is very close to the ratio of 4.13 obtained for ethylphenylmethanol (Table 1, pages 8-9). It is clear that cleavage leading to the cyclopropylmethyl radical is more rapid than that of a normal primary carbon radical. The relative rates of formation for the cyclopropylmethyl radical from various sources are summarized in Table 11 (60-67). The radical attack by chlorine and bromine on methylcyclopropane also qualitatively indicates rate enhancement (68). These studies and others (68-72) illustrate the intense interest in the cyclopropylmethyl radical. The esr spectrum of the cyclopropylmethyl radical indicates it exists in a preferred bisected conformation (73-74). The data certainly indicate that cyclopropyl bonds are able to interact with an adjacent incipient radical and stabilize it. This is consistent with the theory of bonding in cyclopropanes (75). The enhancement is remarkable since the cyclopropane group is known to be in-
Table 11. Relative Rates of Formation for Cyclopropylmethyl Radicals, $\overset{\text{3}}{\text{CH}}^2/\overset{\text{4}}{\text{R}}-\text{CH}^2$

<table>
<thead>
<tr>
<th>Reaction</th>
<th>R</th>
<th>Relative Rate</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative cleavage by CAN</td>
<td>isopropyl</td>
<td>6.61</td>
<td>a</td>
</tr>
<tr>
<td>Decomposition of azo compounds</td>
<td>isopropyl</td>
<td>8.9</td>
<td>(60)</td>
</tr>
<tr>
<td>Decomposition of bis-α-cyano-alkyl azo compounds</td>
<td>cyclohexyl</td>
<td>14.5</td>
<td>(61)</td>
</tr>
<tr>
<td>Decomposition of peroxides</td>
<td>cyclohexyl</td>
<td>55</td>
<td>(62)</td>
</tr>
<tr>
<td>Hydrogen atom addition to carbonyls</td>
<td>isopropyl</td>
<td>36.0</td>
<td>(63,64)</td>
</tr>
<tr>
<td>Radical addition to olefins</td>
<td>isopropyl</td>
<td>5</td>
<td>(65)</td>
</tr>
<tr>
<td>Fragmentation of dialk-oxyalkyl radicals</td>
<td>n-butyl</td>
<td>4</td>
<td>(66)</td>
</tr>
<tr>
<td>NBS bromination of hydrocarbons</td>
<td>isopropyl</td>
<td>3.3</td>
<td>(67)</td>
</tr>
</tbody>
</table>

*aBased on data from Table 1 (pages 8-9 of this thesis).

ductively electron withdrawing (76) and this would tend to retard the cleavage reaction. Its participation in the oxidative cleavage reaction is most likely $\sigma-\pi$ conjugative overlap. This type of interaction has been discussed by Traylor and coworkers and termed "vertical stabilization" (77). This $\sigma-\pi$ conjugation can be used to also rationalize the only other case of neighboring group participation known for oxidative cleavage at this time. The benzaldehyde to ketone ratio for the 2-(trimethylsilyl)ethylphenylmethanol is 166±26 (50).
Neighboring Group Participation

Neighboring group participation is the behavior of some substituents to influence a reaction by stabilizing the transition state and becoming bonded or partially bonded to the reaction center (78). If an increased reaction rate results, the neighboring group is said to provide anchimeric assistance. It has been shown that the cyclopropyl and the trimethylsilyl groups provide anchimeric assistance in the oxidative cleavage reaction.

Neighboring group participation is expected to be more important in carbonium ion reactions than in free radical reactions since there is a much greater electron deficiency at the reaction center of a carbonium ion. Solvolysis reactions are commonly enhanced by neighboring groups four methylenes from the reaction center (78). The resulting five-membered rings are readily formed. From Table 10 (pages 8-9), however, it is clear that there is not enough neighboring group participation to overcome the inductive effects of the 4-methoxy, 4-ethenyl, and 4-bromo groups during oxidative cleavage.

Neighboring group participation by certain substituents adjacent to a leaving group is well known in carbonium ion chemistry (78). Recently there has been a great deal of interest in the possibility of the existence and effects of bridged free radicals. Most recent reviews in free radical
chemistry deal with the question to some extent. Interest has been aroused in two specific areas because of the entertaining controversies.

One major controversy is concerned with bridging in free radicals by a β bromine. This bridging is strongly advocated by Thaler (79) and Skell and Shea (80). The major evidence for neighboring group participation by a β-bromine is from the observed stereospecific products and rate enhancements for reactions that pass through a β-bromine free radical (80). Recently β-haloalkyl radicals have been examined by ESR (81-83). The β-chloroethyl radicals were found to exist in a preferred conformation with the C-Cl bond parallel with the axis of the unpaired electron orbital. The β-fluoroethyl radical was found to have a lower barrier to rotation about the C-C bond than the β-chloroethyl radical. The β-bromoethyl was too unstable to be examined in detail by ESR (81).

The rate enhancements observed for reactions that pass through a β-bromine free radical have been considered as evidence for anchimeric assistance by a β bromine (80). The reactions studied were bimolecular. For example, anchimeric assistance by bromine has been postulated for hydrogen abstraction reactions (84). Tanner and coworkers have announced a serious objection to this interpretation (85,86). They suggested that the apparently high rate of bromination at the β-position in alkyl bromides in solution is attributable to the importance of the reverse reaction occurring in the solvent cage at
all other positions. The objection has been vigorously contested by Skell and Shea (87) and Trayham and coworkers (88). Tanner's idea has recently received support, however, from gas-phase bromination of halogen substituted cyclohexane and cyclopentane (89).

It is important to note that most of the reactions studied to determine the role of a bridging halogen free radical have been bimolecular. It has been pointed out by the proponents of bridging bromine radicals that high selectivity by the attacking radical depends on substantial bond breaking and radical character development in the transition state (79,88). This selectivity is essential for neighboring bromine participation.

There appears to be no information regarding the formation of the β-bromoethyl radical by a unimolecular cleavage (80). The results from the CAN oxidation of 2-bromoethylphenylmethanol presented in Tables 1 (pages 8-9) and 10 (page 38) indicate there is no participation by the β-bromine during oxidative cleavage. The simplest way to interpret the low benzaldehyde to ketone ratio when compared to that for ethylphenylmethanol is that the transition state is relatively destabilized by the inductive effect of the halogen. It is also argued that the predicted pyramidal transition state in the oxidative cleavage reaction does not allow for a favorable interaction of the bromine with the developing electron deficient center. It cannot be argued that cerium(IV) is not a selective enough oxidant to cause the necessary
polarity for bromine bridging since the \( \beta \)-cyclopropyl group enhances the oxidative cleavage by an amount close to the enhancement observed during NBS brominations of hydrocarbons as shown in Table 11 (page 40) (67) and anchimeric assistance by bromine has been reported and strongly postulated in photobromination of alkyl bromides with NBS (84). Thus the cyclopropyl group is able to participate to ca. the same amount in two different reactions whereas the bromine does not. It is of high importance to emphasize that almost all of the "evidence" for bromine assistance comes from reactions with bimolecular transition states.

The second controversy deals with the question of participation of the double bond during the formation of a radical at the 7 position in norbornene. There is compelling evidence for participation of the double bond during the formation of a cation at the 7 position (90-93). Story was first to postulate anchimerically assisted hydrogen abstraction at the C-7 position of norbornadiene (94). Wilt and Levin suggested in 1962 that the facile decarbonylation of norbor-2-ene-anti-7-carboxaldehyde was anchimerically assisted by the double bond (95). Wilt and coworkers suggested stabilization of the radical by the double bond (96). Recently, he has reported that there is no good evidence supporting his earlier suggestion of \( \pi \) electron assistance in the bicyclic systems he studied (97). Other claims that the 7-norbonenyl radical is "nonclassical" (98-100) have provoked strong counterclaims
(101-104). In fact, the suggestion of a nonclassical free radical was based on incorrect analysis of the nmr of a product mixture (101)! The esr of the 7-norbornenyl free radical has been reported and interpreted as evidence for little or no stabilization by double bond participation (104). Theoretical calculations on this system have described it as having tremendous electron delocalization by the double bond (99,100) and as having very little such delocalization (104-106). There has been a recent claim for a transannular interaction of a cyclopropyl bond with a radical center (107). The evidence so far indicates that the 7-norbornenyl free radical undergoes little or no stabilizing interaction with a transannular double bond. It was thought that the reaction of CAN with the bicycloalkylphenylmethanols 2-4 would allow us to elucidate the role of this uniquely situated double bond during oxidative cleavage. It is clear from Table 6 (page 17) that the double bond position in the bicyclic systems 2 and 3 is responsible for a significant difference in rate of reaction with CAN. The product mixtures, however, lack any significant amount of benzaldehyde. The search for neighboring group participation during the oxidative cleavage by an anti double bond in this bicyclic system has been frustrated by the lack of cleavage products in the product mixtures. The significant rate differences are probably due to direct oxidation of the double bonds by CAN. These rate
differences however have not been explained and may be the basis of further research. The greatest difficulty in the study, the separation of the anti- and syn-7-norbornenylphenylmethanols, has been overcome.

Synthesis and Separation of syn- and anti-7-Norbornenylphenylmethanols (2 and 2)

The action of magnesium on syn-7-bromonorbornene has been investigated. Carbonation of the organometallic reagent led to a 2:1 mixture of the corresponding anti and syn carboxylic acids (108,109). Production of the 7-norbornenyl anion by basic oxidative cleavage of anti- and syn-7-norbornenylhydrazines in deuterium oxide afforded the anti- and syn-7-deuterionorbornenes, in approximately a 94:6 ratio, as the sole products of deuteron capture (110). The preference for anti capture was explained in terms of an equilibrated mixture of the anti- and syn-7-norbornenyl anions which contains predominantly anti anion. This anti-

\[
\begin{array}{c}
\text{anti} \\
\end{array}
\]

anion is also calculated to be the more stable conformation (105,106). In contrast to these findings the synthesis of 2 and 2 by the Grignard reaction of syn-7-bromonorbornene with benzaldehyde resulted in a 2:1 ratio of the syn alcohol (2) to
the anti alcohol (2). The size of the substrate being attacked by the "anion" may be an important factor in determining the stereochemistry of the products. This should be an interesting area for further study.

The separation of 2 and 3 by silver ion from their mixture is remarkable since separation by other methods is very difficult. Separation of olefinic mixtures using silver ion is not new. Silver ion chromatography is a vast topic and recently has been reviewed (111). Olefin retention times on silver nitrate columns have been examined by glpc (112). Substituent effects on silver-olefin complexation have been examined for various bicyclic olefins (113-116). The oxo-syn-7-norborenyl system forms good chelate complexes with metals (116-117). It has been pointed out that silver ion forms especially good complexes with olefin alcohols, probably by chelation (118-119). Our observation that the syn alcohol 3 is readily removed from the ether solution of a mixture of 3 and 2 by selective complexation with silver ion in an aqueous layer is consistent with these known facts for silver-olefin complexes.
Fate of the Radical from Cleavage

In aqueous acetonitrile a secondary radical produced by oxidative cleavage by CAN is further oxidized by CAN and forms roughly equal amounts of olefin and nitrate products (see Table 5, page 15). These results are consistent with those of previous workers (13). It seems clear that CAN oxidations carried out in aqueous acetonitrile at a variety of temperatures should result in the cleaved radical going to mostly nitrate and olefin products. The olefin and acetonitrile products probably both arise from the cation probably produced from the radical and Ce(IV). Kochi has reviewed the oxidation reactions of free radicals by metal ions (120). It has been found the ceric perchlorate readily cleaves bicyclic alcohols (26). Olefins were the only observed products consistent with the poor ability of perchlorate to act as a ligand.
CONCLUSIONS

The benzaldehyde to ketone ratios obtained from the CAN oxidation of alkylphenylmethanols are good measures of the relative rates of oxidative cleavage. The transition state of the oxidative cleavage reaction probably occurs early on the reaction coordinate and the geometry of the incipient radical is close to pyramidal. The transition state is polar and influenced in a regular way by the inductive effect of the alkyl substituent. The relative rates of oxidative cleavage vary directly with the electronegativity of the alkyl substituents as measured by polar substituent constants.

Neighboring groups which are known to greatly stabilize cations by \( \sigma-\pi \) conjugation ("vertical stabilization") can accelerate oxidative cleavage. Neighboring groups which cause anchimeric assistance by lone pair participation, i.e. \( \text{Br} \) and \( \text{CH}_3\text{O} \), do not enhance the oxidative cleavage reaction.

Bridging bromine radicals have been postulated for a number of reactions. They all are bimolecular with transition states late on the reaction coordinate. There is no evidence of an activating effect by a neighboring bromine in the unimolecular oxidative cleavage reaction.
EXPERIMENTAL

Equipment and Methods

The nuclear magnetic resonance (nmr) spectra were recorded with a Varian A-60, Varian HA 100, or Perkin Elmer R20-B spectrometer. Chemical shifts are reported as δ values in ppm from tetramethylsilane (TMS), the internal standard. The infrared (ir) spectra were recorded with a Beckman IR-12 or IR-18A spectrometer. Mass spectra were measured on an Atlas CH-4 spectrometer. High resolution mass spectra were recorded with an Associated Electronics Industries MS-902 instrument. Melting points were determined with a Thomas Hoover Melting Point Apparatus in open capillary tubes and are uncorrected. Gas liquid partition chromatography (glpc) was performed on a Varian Aerograph 1700 with dual thermal conductivity detectors. Absorbance measurements were taken on a Beckman Model DU spectrophotometer fitted with a water cooled cell compartment. A Haake Model F Constant temperature circulator was used to maintain the temperature.

Analysis for C and H was performed by Spang Microanalytical Laboratory or Galbraith Laboratories, Inc.

Computer calculations for determination of equilibrium constants were done at the Iowa State University Computation Center using a slightly modified version of the RAWDAT program.
used by Young (25) and Flash (26). The procedures for measuring absorbance are modified forms of the procedures used by P. Flash (26).

Chemicals

Many of the commercial chemicals used in this study are listed in Table 12. Most were found to be pure enough as received for the respective application.

Table 12. Commercial Chemicals

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopropyl phenyl ketone</td>
<td>Aldrich Chemical Co.</td>
</tr>
<tr>
<td>Cyclohexyl phenyl ketone</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Cyclopentyl phenyl ketone</td>
<td>Peninsular Chemresearch</td>
</tr>
<tr>
<td>Cyclobutyl phenyl ketone</td>
<td>Peninsular</td>
</tr>
<tr>
<td>Isobutyl phenyl ketone</td>
<td>Eastman Kodak Co.</td>
</tr>
<tr>
<td>Ethyl phenyl ketone</td>
<td>Aldrich</td>
</tr>
<tr>
<td>2-Bromoethyl phenyl ketone</td>
<td>Frinton Laboratories</td>
</tr>
<tr>
<td>(recryst., pentane)</td>
<td></td>
</tr>
<tr>
<td>2-Chloroethyl phenyl ketone</td>
<td>Aldrich</td>
</tr>
<tr>
<td>5-Norbornenyl phenyl ketone</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Cyclopropylphenylmethanol</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Ethylphenylmethanol</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Cyclohexanol</td>
<td>J. T. Baker Chemical Co.</td>
</tr>
<tr>
<td>Cyclopentanol</td>
<td>Aldrich</td>
</tr>
<tr>
<td>t-Butyl alcohol</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td>1,1,2,2-Tetrachloroethane</td>
<td>Mallinckrodt Chemical Works</td>
</tr>
<tr>
<td>Methyl benzoate</td>
<td>J. T. Baker</td>
</tr>
</tbody>
</table>
Table 12. (Continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde (dist.)</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td>5-Hexenol</td>
<td>Columbia Organic Chemicals</td>
</tr>
<tr>
<td>Ethyl bromide</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td>Styrene</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Chloromethyl methyl ether</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Ethyl benzoylelactate</td>
<td>Aldrich</td>
</tr>
<tr>
<td>1,3-Dibromopropane</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Norbornene</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Pinacol</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Diiodomethane</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>J. T. Baker</td>
</tr>
<tr>
<td>Ceric ammonium nitrate</td>
<td>G. F. Smith Chemical Co.</td>
</tr>
<tr>
<td>Sodium Methoxide</td>
<td>Mallinckrodt</td>
</tr>
</tbody>
</table>

Prepared Materials

The following columns were prepared and used for g LPC analysis: column A, 1m x 6.35mm aluminum column, 20% carbo-wax 20M on chromosorb W; column B, ½m x 6.35mm aluminum column, 20% carbowax 20M on chromosorb W; column C, 1m x 6.35mm alu-minum column, 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on chromosorb P; column D, 1.2m x 6.35mm aluminum column, 20% TCEP on chromosorb P; column E, 1m x 6.35mm aluminum column, 20% SE 30 on chromosorb W.
Ethylphenylmethanol

The commercial ethylphenylmethanol was found to contain about 6% of the corresponding ketone as an impurity based on glpc analysis [column A, 60 ml/min, 155°, Tr=10 min, Tr (impurity)=6 min]. This commercial material, 11.4 g, was treated with sodium borohydride, 1.5 g, in aqueous ethanol. The recovered ethylphenylmethanol was ketone free by glpc and nmr: nmr (CCl₄) δ 7.22 (s,5H), 4.37 (t,1H,J=6.5 Hz), 3.5 (bs,1H,OH), 1.58 (m,2H), 0.80 (m,3H).

Isobutylphenylmethanol

Isobutyl phenyl ketone, 16.2 g (0.1 mol) was reduced with 1.89 g (0.05 mol) of sodium borohydride in 60 ml of 95% ethanol. The yield was 12.7 g (78%) of a colorless oil: bp 114°/9 Torr [lit. (121) bp 98°/4 Torr]; nmr (CCl₄) δ 7.03 (s,5H), 4.40 (m,1H), 3.63 (d,1H,J=3.5 Hz), 1.4 (m,3H), 0.84 (d,6H,J=6.0 Hz).

 Allylphenylmethanol

From 24.3 g (1.0 mol) of magnesium turnings and 92.8 g (0.77 mol) of allyl bromide the Grignard reagent was prepared. To this, 74 g (0.7 mol) of benzaldehyde was added. After addition was complete the mixture was refluxed for an hour. The mixture was worked up with saturated aqueous ammonium chloride. The crude product was distilled and a colorless oil was collected which weighed 38.5 g, 37% yield: bp 108°/11
Torr [lit. (122) bp 106-108°/10 Torr]; nmr (CCl₄) δ 7.03 (s,5H), 5.50 (m,1H), 4.84 (m,2H), 4.37 (t,1H,J=6.5 Hz), 3.55 (s,1H), 2.26 (t,2H,J=6.5 Hz).

Cyclopropymethylphenylmethanol

This alcohol was prepared according to the procedure of Lansbury and Pattison (122). The only modification was the use of the zinc-copper couple described by Rawson and Harrison (31). From 7.4 g (0.05 mol) of allylphenylmethanol and 10.5 ml (0.13 mol) of diiodomethane there was obtained 3 g, 37% yield, of a colorless oil which slowly darkened on standing at room temperature. It was distilled and stored in the refrigerator: bp 109-111°/5.5 Torr [lit. (122) bp 125-130°/12 Torr]; nmr (CCl₄) δ 7.16 (s,5H), 4.49 (t,1H,J=6.5 Hz), 3.75 (s,1H), 1.44 (m,2H), 0.32 (m,3H), -0.02 (m,2H).

Cyclopropymethyl phenyl ketone

This ketone was prepared from the corresponding alcohol using the oxidation procedure developed for the Collins reagent (123). The cyclopropymethylphenylmethanol, 0.405 g (0.0025 mol), was treated with 4.16 g (0.015 mol) of chromium trioxide-pyridine complex. After work up a brown oil was obtained. This was purified by filtration through a 18 x 1.5 cm silica gel column using hexane as eluent. The ketone was obtained in quantitative yield, 0.424 g, and was a sweet
smelling colorless oil: nmr (CCl₄) δ 7.85-7.60 (m, 2H), 7.4-7.2 (m, 3H), 2.65 (d, 2H, J=7.0 Hz), 1.5-0.0 (m, 5H); ir (CCl₄) 3080 (w), 1696 (s), 1211 (m), 1020 (m) cm⁻¹.


6-Bromohexene

This procedure is a modification of a method using triphenyl phosphite (124). Bromine, 16.0 g (0.1 mol), was dropped into a stirring mixture of 28.0 g (0.107 mole) of triphenyl phosphine and 100 ml of ether at 0°. To the resulting mixture was added 10.0 g (0.1 mol) of 5-hexenol in 7.9 ml (0.10 mol) of pyridine. After work up and distillation, 7.9 g, 48% yield, of the product, a colorless oil, was obtained: bp 44-47°/14 Torr [lit. (125) bp 47-51°/16 Torr, 66% yield using phosphorous tribromide.]; nmr (CCl₄) δ 6.1-4.8 (m, 3H), 3.35 (t, 2H, J=6.5 Hz), 2.3-1.3 (overlapping multiplets, 6H).

5-Hexenylphenylmethanol

The Grignard reagent was prepared by dropping a solution of 5.0 g (0.03 mol) of 6-bromohexene in 25 ml of ether into 25 ml of ether containing 1.0 g (0.041 mol) of magnesium turnings. Benzaldehyde, 2.9 g (0.027 mol), in 25 ml of ether, was added and the mixture stirred for three hours at room temperature. After work up, 4.3 g of a yellow oil
was obtained. This was distilled and 3.88 g, 76% yield, of
a colorless oil was collected, bp 114-116°/2 Torr. This
product alcohol was contaminated by a small amount of
5-hexenyl phenyl ketone. An additional distillation did not
remove the ketone. Treatment of 1.8 g (0.010 mol) of the
material with 0.2 g (0.005 mol) of sodium borohydride in
ethanol resulted after work up in 0.96 g of a colorless oil
which was free by nmr, ir, and glpc of any carbonyl compounds:
nmr (CCl₄) δ 7.16 (s,5H), 6.1-4.7 (overlapping multiplets,
3H, vinyl), 4.4 (m,1H), 4.0 (s,1H,OH), 2.1-1.05 (overlapping
multiplets, 8H); ir (CCl₄) 3620 (m), 2940 (s), 2860 (s),
1650 (m), 1500 (m), 1460 (s) cm⁻¹; Tr (column A, 60 ml/min,
195°)=16.2 mm.

Anal. (Spang) calcd for C₁₃H₁₈O: C, 82.06; H, 9.53.
Found: C, 82.00; H, 9.42.

6-Hexenyl phenyl ketone

This compound was prepared according to the Jones oxi­
dation as described by Meinwald and coworkers (126). From
0.38 g (2 mmol) of 5-hexenylphenylmethanol and 0.14 g (1.4
mmol) of chromium trioxide was obtained 0.233 g of ketone,
a colorless oil, 61% yield: nmr (CCl₄) δ 8.0-7.7 (m,2H),
7.5-7.2 (m,3H), 6.0-4.8 (m,3H, vinyl), 2.85 (t,2H, J=7.0 Hz),
2.2-1.2 (overlapping multiplets, 6H); ir (CCl₄) 2950 (s),
1700 (s), 1600 (m), 1450 (m) cm⁻¹; Tr (column A, 60 ml/min,
195°)=10.5 min; mass spectrum (70 eV) 188 (m+), 120, 105,
57

83, 82, 77.


4-Methoxybutyl bromide

This preparation was based on published procedures (127,128). Commercial sodium methoxide, 8 g (0.15 mol), was spooned into a stirring solution of 30 g (0.14 mol) of 1,4-dibromobutane in 50 methanol. After work up and distillation, the product was obtained as a colorless oil, 9.8 g, 42% yield: bp 60°/15 Torr [lit. (127) 60°/15 Torr]; nmr (CCl₄) δ 3.35-3.15 (overlapping signals, 7H, s at 3.25, OCH₃), 2.2-1.4 (m, 4H).

4-Methoxybutylphenylmethanol

The Grignard reagent was prepared from 9.8 g (0.059 mol) of 4-methoxybutyl bromide and 1.6 g (0.065 mol) of magnesium turnings. Benzaldehyde, 5.3 g (0.05 mol), was added and the mixture worked up with saturated aqueous ammonium chloride. The resulting colorless oil weighed 5 g, 52% yield. This product contained a small amount of the alkyl phenyl ketone as impurity which was not removed by distillation. The product, 3 g, was treated with 0.2 g of sodium borohydride and the recovered material was free of ketone: bp 119-122°/2 Torr [lit. (129) bp 122°/2 Torr]; nmr (CCl₄) δ 7.16 (s, 5H), 4.4 (m, 1H), 3.5 (s, 1H, OH), 3.1-3.3
(overlapping signals, 5H, s at 3.12, OCH₃), 1.0-1.8 (m, 6H); ir (neat) 3450 (broad peak), 2950, 2880, 1460, 1125 cm⁻¹; Tr (column A, 60 ml/min, 200°) = 11.5 min.

4-Methoxybutyl phenyl ketone

This ketone was prepared according to the Jones oxidation as described by Meinwald and coworkers (126). From 0.5 g (5 mmol) of chromium trioxide and 1.4 g (7 mmol) of 4-methoxybutylphenylmethanol was obtained 1.03 g of ketone, a colorless oil, in 75% yield: nmr (CCl₄) δ 8.0-7.75 (m, 2H), 7.5-7.2 (m, 3H), 3.45-3.15 (overlapping signals, 5H, s at 3.21, OCH₃), 2.88 (m, 2H), 2.0-1.2 (m, 4H); ir (neat) 2950, 2880, 1695, 1455, 1125 cm⁻¹. This compound has been prepared by another route with only the boiling point reported (130).

3-Methoxypropyl phenyl ketone

Cyclopropyl phenyl ketone, 10 g (0.0685 mol), was dissolved in 50 ml of absolute methanol. The mixture was stirred, 3 ml of concentrated sulfuric acid added, and heated to reflux for nine days. The mixture was poured into 100 ml of ether and 300 ml of water. The ether layer was removed and the aqueous phase extracted two times with 100 ml of ether. The organic portions were combined and washed with 100 ml of 1 M aqueous sodium bicarbonate. The organic liquid was dried with magnesium sulfate, filtered, and rotary evaporated. The crude product was a yellow oil, 10.7 g. It was distilled to give a
colorless oil, 7.6 g, 66% yield: bp 136°/10 Torr; nmr (CCl₄) δ 7.9 (m,2H), 7.4 (m,3H), 3.38 (t,2H,J=6.0 Hz), 3.25 (s,3H), 2.98 (t,2H,J=7.0 Hz) 1.92 (overlapping triplets,2H,J=6.0, J=7.0); ir (CCl₄) 2930 (m), 2875 (m), 1690 (s), 1555 (m), 1450 (m), 1215 (m), 1121 (s), 1000 (m), 830 (s) cm⁻¹; mass spectrum (80 eV) m/e (rel intensity) 178 (M⁺), 163, 146, 133, 121 (88), 120 (100), 106 (83), 105 (100), 77 (100), 59 (90), 45 (95); Tr (column A, 60 ml/min, 195°)=7.3 min.

A small amount of ketone was collected by glpc for analysis.

Anal. (Galbraith) calcd for C₁₁H₁₄O₂: C, 74.13; H, 7.92; mass spec, 178.0994. Found: C, 73.78; H, 7.80; mass spec, 178.0996.

This compound has been reported once but no experimental was given other than bp 103-104°/1 Torr (131).

3-Methoxypropylphenylmethanol

3-Methoxypropyl phenyl ketone, 5.35 g (0.03 mol), was reduced with 0.58 g (0.015 mol) of sodium borohydride in ethanol. After work up there was obtained 4.62 g of a colorless oil, 85.5% yield: bp 121-122°/5 Torr; nmr (CCl₄) δ 7.18 (s,5H), 4.44 (m,1H), 3.68 (s,1H,OH), 3.20 (t,2H,J= 6.0 Hz), 3.14 (s,3H), 1.7-1.3 (overlapping multiplets,4H); ir (CCl₄) 3620 (m), 3430 (m), 2930 (s), 2875 (s), 1452 (m), 1121 (s) cm⁻¹; mass spectrum (16 eV) m/e (rel intensity) 180 (2.6,P⁺), 179 (16), 162 (6.3), 148 (12.5), 120 (31), 117 (25), 107 (100), 105 (32), 91 (13.5), 79 (43), 77 (31);
The compound was collected by g LPC for analysis.

Anal. (Spang) calcd for C_{11}H_{16}O_{2}: C, 73.30; H, 8.95. Found: C, 73.17; H, 8.95.

2-Methoxyethylphenylmethylchloride

This compound was prepared according to the procedure of Mamedov and Kydyrov (132). To a mixture of 80.5 g (1.0 mol) of chloromethyl methyl ether and 1.21 g of anhydrous zinc chloride (133) in carbon tetrachloride was added 104 g (1.0 mol) of styrene. After work up an orange oil was obtained which weighed 103 g, 94% yield: nmr (CCl_{4}) δ 7.25 (m,5H), 5.04 (t,1H,J=7.5 Hz), 3.6-3.0 (m,2H), 3.20 (s,3H), 2.16 (m,2H).

2-Methoxyethylphenylmethanol

This alcohol was prepared using the reported procedure of Mamedov and coworkers (134). The 2-methoxyethylphenylmethylchloride, 80 g (0.43 mol), was stirred in refluxing 20% aqueous potassium hydroxide for 60 hours. Following work up, 49 g of product was obtained as a colorless oil, 69% yield: bp 111-115°/5 Torr [lit. (134) bp 112-113°/5 Torr]; nmr (CCl_{4}) δ 7.18 (s,5H), 4.64 (t,1H,J=6.5 Hz), 3.8 (s,1H,OH), 3.28 (m,2H), 3.12 (s,3H), 1.77 (q,2H,J=6.0); ir (CCl_{4}) 3615 (m), 3520 (s), 2920 (m), 1460 (m), 1390 (m), 1123 (m) cm^{-1}; Tr (column A, 60 ml/min, 175°)=16.5 min.
2-Methoxyethyl phenyl ketone

This ketone was prepared by the Jones procedure as described by Meinwald and coworkers (126). The 2-methoxyethylphenylmethanol, 17 g (0.1 mol), was oxidized with 7.0 g (0.07 mol) of chromium trioxide and after work up there was obtained 9.5 g, 60% yield, of product, a colorless oil: bp 121-123°/10 Torr [lit. (135) bp 125-126°/16 Torr]; nmr (CCl₄) δ 7.8 (m, 2H), 7.3 (m, 3H), 3.64 (t, 2H, J=6.2 Hz), 3.24 (s, 3H), 3.04 (t, 2H, J=6.2 Hz); ir (CCl₄) 2930 (m), 2900 (m), 1695 (m), 1460 (m), 1230 (m), 1190 (m), 1128 (s) cm⁻¹.

Ethyl(2-methoxyethyl)phenylmethanol

The Grignard reagent was readily formed from 2.43 g (0.1 mol) of magnesium turnings in 30 ml of ether and the dropwise addition of 10.9 g (0.1 mol) of ethyl bromide in 70 ml of ether. Next, 6.6 g (.04 mol) of 2-methoxyethyl phenyl ketone in 50 ml of ether was dropped into the stirring black Grignard mixture. This mixture was allowed to stir overnight. Saturated aqueous ammonium chloride was added until a clear two-phase mixture was obtained. This mixture was extracted with ether and the extracts combined and washed with saturated aqueous sodium chloride. The ether solution was dried with magnesium sulfate, filtered, and concentrated under vacuum. There was obtained a faintly yellow oil, 7.0 g (90% yield). The material was distilled through a 9 cm Vigreux column to yield a colorless oil: bp 117-118°/9 Torr; nmr (CCl₄) δ 7.25
(m,5H), 3.65 (s,1H), 3.5-3.1 (overlapping signals,5H, s at 3.12 is OCH₃), 2.2-1.5 (overlapping signals,4H, q at 1.85, \( J=7.0 \) Hz), 0.7 (t,3H, \( J=7.0 \) Hz); ir (CCl₄) 3510 (s), 2930 (s), 1440 (m), 1580 (m), 1110 (s) cm⁻¹; mass spectrum (70 eV) \( m/e \) (rel intensity) 176 (10.5), 165 (100), 135 (47.5), 133 (58), 105 (79), 77 (29). This material was collected by glpc to obtain a pure sample.

Anal. (Galbraith) calcd for \( \text{C}_{12}\text{H}_{18}\text{O}_2 \): C, 74.19; H, 9.34. Found: C, 73.83; H, 9.25.

4-Bromobutyl phenyl ketone

This ketone was prepared according to the procedure of Bieber and Eisman (136). The product was recrystallized from pentane to give 8.2 g of colorless crystals in 20% yield: mp 57.5-58.0° [lit. (136) mp 52-54, (137) mp 61°]; nmr (CCl₄) \( \delta \) 7.8 (m,2H), 7.4 (m,3H), 3.4 (m,2H), 2.9 (m,2H), 1.9 (m,4H); ir (CCl₄) 1704 (s), 1608, 1458, 1228 cm⁻¹.

4-Bromobutylphenylmethanol

The 4-bromobutyl phenyl ketone, 3.6 g (0.015 mol), was reduced with 0.38 g (0.01 mol) of sodium borohydride in aqueous ethanol. The crude product weighed 3.36 g, 93% yield and was an amber oil. This material was distilled and then recrystallized from pentane at -20°: bp 129°/1 Torr; nmr (CCl₄) \( \delta \) 7.28 (s,5H), 4.49 (t,1H, \( J=5.8 \) Hz), 3.28 (t,2H, \( J=6.0 \) Hz), 3.26 (s,1H, OH), 2.0-1.0 (overlapping signals,
6H); ir (CCl$_4$) 3622, 2945, 1461, 1060 cm$^{-1}$; mass spectrum (70 eV) m/e 244, 242, 226, 224, 162 (100%), 107, 105, 91, 77.

**Anal. Calcd for C$_{11}$H$_{15}$BrO: mass spec, 242.0307.**
**Found: mass spec, 242.0302.**

**2-Bromoethylphenylmethanol**

Commercial 2-bromoethyl phenyl ketone, 11.2 g (0.05 mol), was reduced with 1.9 g (0.05 mol) sodium borohydride at low temperature following the procedure of Campaigne and coworkers (138). After work up 9 g of a red oil was obtained. This was distilled to give 2 g of the product, a colorless oil; 115-117$^\circ$/2 Torr; nmr (CCl$_4$) $\delta$ 7.12 (s,5H), 4.61 (t,1H,$J=8.0$ Hz), 3.4-3.1 (m,3H), 2.2-1.8 (m,2H) [lit. (139) bp 98$^\circ$/1 Torr; nmr $\delta$ 7.2 (s,5H), 4.7 (t,1H,$J=9.5$ Hz), 3.5-3.15 (m,2H), 2.2-1.9 (m,2H).]

**2-Chloroethylphenylmethanol**

2-Chloroethyl phenyl ketone, 8.4 g (0.05 mol), was reduced with 1.9 g (0.05 mol) of sodium borohydride at low temperature following the procedure of Campagne and coworkers (138). After work up an amber oil was obtained that weighed 7.9 g. This was distilled to give 4.88 g of product, a colorless oil: bp 125-130$^\circ$/6-8 Torr [lit. (140) 130-132$^\circ$/8 Torr]; nmr (CCl$_4$) $\delta$ 7.10 (s,5H), 4.62 (m,1H), 3.6-3.0 (m,3H), 2.1-1.7 (m,2H).
2-Fluoroethylphenylmethanol

This alcohol was synthesized from 2-chloroethylphenylmethanol, potassium fluoride, and potassium hydrogen fluoride in glycerol at 155°. This synthesis was carried out by Myong-Gi Park following the procedure of Shirokov and coworkers (141). From 3.4 g of starting chloride, he obtained 0.68 g of colorless oil, the fluoroalcohol: bp 121-122°/12 Torr [lit. (141) 96°/4 Torr]; nmr (CCl₄) δ 7.24 (s,5H), 5.0-4.5 (m,2H), 4.2-3.9 (m,1H), 2.3-2.0 (m,1H), 1.9-1.7 (m,2H); ir (CCl₄) 3620, 2960, 1550, 1250, 1030 cm⁻¹; mass spectrum (70 eV) m/e 154, 135, 107, 105, 91, 79, 77.

Cyclohexylphenylmethanol

Cyclohexyl phenyl ketone, 25 g (0.133 mol) was reduced with 1.89 g (0.07 mol) of sodium borohydride in 120 ml of 95% ethanol. The product was distilled and the 21.73 g (87% yield) of colorless oil obtained crystallized after standing for three days: bp 106°/1 Torr; mp 49-50° [lit. (142) mp 49-50°]; nmr (CCl₄) δ 7.15 (s,5H), 4.12 (d,1H,J= 6.0 Hz), 3.1 (s,1H), 2.0-0.8 (overlapping signals, 11H).

Cyclopentylphenylmethanol

Cyclopentyl phenyl ketone, 10 g (0.057 mol), was reduced with 1.0 g (0.026 mol) of sodium borohydride in 50 ml of 95% ethanol. The crude product was distilled to give 8.6 g of a colorless oil, 85% yield: bp 119°/2 Torr [lit. (143)
Cyclopentene

Cyclopentene was distilled from a mixture of 10 ml cyclopentanol and 1 ml of sulfuric acid: bp 42-43° [lit. (144) bp 45-46°]; nmr (CCl₄) δ 5.65 (s, 2H), 2.28 (m, 4H), 1.80 (m, 2H).

Cyclopentyl nitrate

Cyclopentyl nitrate was prepared from cyclopentyl alcohol and a mixture of concentrated nitric and sulfuric acids at -20° according to the procedure of Kornblum and Teitelbaum: bp 86°/60 Torr [lit. (145) bp 74°/30 Torr]; nmr (CCl₄) δ 5.3 (m, 1H), 1.8 (m, 8H).

Cyclohexyl nitrate

The method of synthesis was based on a patent procedure. The large quantities were dangerous to handle and the reaction went wild. I do not recommend this procedure (146). The method of Kornblum and Teitelbaum is probably better (145). The cyclohexyl alcohol, 62 ml, in 60 ml of carbon tetrachloride was dropped into a stirring mixture of 120 ml concentrated nitric acid and 208 ml of concentrated sulfuric acid at -10°. After addition the mixture was gradually warmed to 20° at which time it went out of control! Ice water was
poured on it to stop it. The ice water mixture was extracted with carbon tetrachloride. The solvent was removed by rotary evaporation and the residue distilled. There was obtained 9 g of a colorless oil: bp 45\(^0\)/4 Torr; ir (CCl\(_4\)) 2940 (m), 1630 (vs), 1455 (w), 1280 (vs), 1011 (w), 947 (w), 902 (w), 870 (s), 845 (w) \[lit. (147) bp 70\(^0\)/4 Torr; ir 1626 (vs), 1464 (m), 1280 (vs), 1007 (m), 942 (m), 902 (m), 870 (vs), 843 (m) cm\(^{-1}\).]

**Cyclobutylphenylmethanol**

Cyclobutyl phenyl ketone, 10 g (0.0625 mol), was reduced with 1.2 g (0.03 mol) of sodium borohydride in aqueous ethanol. The crude product was distilled to give a 67\% yield of the alcohol, a colorless oil: bp 97\(^0\)/1 Torr \[lit. (122) bp 121-122\(^0\)/5 Torr]; nmr (CCl\(_4\)) \(\delta\) 7.10 (s,5H), 4.25 (d,1H, J=7.5 Hz), 3.78 (s,1H), 2.35 (m,1H), 1.71 (m,6H).

**exo-2-syn-7-Dibromonorbornane**

Norbornene, 163.0 g (1.73 mol), was brominated with 285 g (1.78 mol) of bromine using a modification of the published procedure (148) described by Holland (149). There was obtained after fractionation through a six inch column, 135 g of product, a colorless oil (31\% yield): bp 100-102\(^0\)/3.5 Torr \[lit. (149) 103-107\(^0\)/4 Torr]; nmr (CCl\(_4\)) \(\delta\) 4.0 (m,2H), 2.8-2.1 (m,4H), 1.8-1.1 (m,4H).
Syn-7-bromonorbonene

This was prepared following the procedure of Holland (149). The exo-2-syn-dibromonorbonane, 157 g (0.65 mol) was dissolved in 250 ml of dry dimethyl sulfoxide (distilled from calcium hydride). This solution was added as rapidly as possible to a warm solution of 26 g (0.669 mol) of potassium metal in 500 ml of sodium dried t-butyl alcohol. (The potassium metal was easily dissolved in hot t-butyl alcohol under a positive pressure of nitrogen with vigorous mechanical stirring.) The mixture was stirred at gentle reflux for 36 hours under a positive nitrogen pressure. The dark reaction mixture was poured into 2500 ml of water. The aqueous mixture was extracted with ether and ether portions combined and dried with magnesium sulfate. The ether was removed by rotary evaporation and the residual oil fractionated through a 6 inch column. The yield was 77.3 g, 73%, of colorless, foul smelling, oil. The nmr compared perfectly with the reported spectrum (149): bp 67-68°/14 Torr [lit. (149) bp 85-90°/30 Torr]; nmr (CCl₄) δ 6.0 (m,2H), 3.8 (m,1H), 3.0 (m,2H), 2.0-0.9 (overlapping multiplets,4H).

anti- and syn-7-Norbornenylphenylmethanol (2 and 3)

A solution of 17.3 g (0.1 mol) of syn-7-bromonorbornene in dry ether was dropped into a stirring mixture of 5 g (0.205 mol) magnesium turnings and 150 ml of dry ether under
a nitrogen atmosphere. After a short time the mixture became grey-black. After addition was complete, ca. 2 hours, the mixture was heated at reflux for a few minutes. Benzaldehyde, 9.6 g (0.09 mol), in 50 ml of ether was added dropwise with cooling. The mixture was allowed to stand overnight. Saturated aqueous ammonium chloride was added until all the precipitate dissolved. The mixture was extracted with ether and the extracts combined, dried with magnesium sulfate, filtered, and concentrated under vacuum to give 17.8 g of an orange oil. The oil crystallized on standing. Recrystallization from hexane resulted in two crops of product crystals which totaled 5 g, 28% yield. The colorless needles had mp 91-101°. The two isomers in the mixture could be separated by glpc. The retention times were 19.3 and 25.0 min on column A at 200°, 60 ml/min. The ratios were 1:2 respectively for the two peaks. The nmr of the mixture contained two doublets, δ 4.38 and 3.98 which are attributed to CHOH in the two isomers. They were in a ratio of 1:2 respectively. The δ 4.38 doublet is normal and attributed to the anti isomer 2, while the doublet at δ 3.98 is shifted upfield due to interaction of the π bond in the syn isomer 3. This preparation was repeated several times with the same result; 2:1 ratio of syn to anti isomer. The isomers were separated and collected by glpc for characterization.
syn-7-Norbornenylphenylmethanol (3) mp 104.5-106°;
nmr (CCl₄) δ 7.19 (2,5H), 5.96 (m,2H), 3.98 (d,1H,J=10.5 Hz, CHOH), 2.92 (broad singlet,1H,bridgehead), 2.26 (s,1H,OH), 2.08 (broad singlet,1H,bridgehead), 1.85-0.85 (overlapping multiplets,5H); ir (CCl₄) 3630 (m), 3070 (m), 2970 (s), 1501 (m), 1460 (m), 1330 (m) cm⁻¹ (No evidence for intramolecular hydrogen bonding);
Anal. (Spang) calcd for C₁₄H₁₈O: C, 83.96; H, 8.05.
Found: C, 83.69; H, 8.05.

anti-7-Norbornenylphenylmethanol (2) mp 85-86.5°;
nmr (CCl₄)δ 7.18 (s,5H), 5.95 (broad singlet,2H), 4.38 (d,1H, J=8.5 Hz,CHOH), 3.03 (broad singlet,1H,bridgehead), 2.2 (broad singlet,1H,bridgehead), 1.9 (s,1H,OH), 1.8-0.8 (overlapping multiplets,5H); ir (CCl₄) 3624 (m), 3070 (m), 2970 (s), 2880 (m), 1500 (m), 1460 (m), 1340 (s), 1025 (m) cm⁻¹;
mass spectrum (17 eV) m/e 200 (P⁺), 182, 123, 122, 121, 107;
Anal. (Spang) calcd for C₁₄H₁₆O: C, 83.96; H, 8.05.
Found: C, 83.62; H, 8.06.

Silver ion separation of syn and anti alcohols 3 and 2

An ether solution, 100 ml, of 3.4 g of the alcohol mixture (4:1,syn:anti) was prepared. The 0.17 M alcohol solution was washed four times with 25 ml of saturated aqueous silver nitrate. After each wash the ether portion was examined by glpc. After the fourth wash no more syn alcohol 3 was detected in the ether layer. The ether was
next washed with saturated sodium chloride and a large precipitate formed. The ether solution was dried with magnesium sulfate and rotary evaporated. The colorless residue was 0.68 g, 91% yield, of the pure anti alcohol 2, mp 87-88°. The total aqueous washings were combined and treated with concentrated ammonia until the first formed brown precipitate dissolved. The mixture was cooled in an ice-water bath during the addition of the ammonia. A total of 250 ml of concentrated ammonia was added (the complex, conceivably, could be destroyed by addition of sodium chloride). This aqueous mixture was extracted three times with 100 ml of ether. The ether portions were combined and washed once with 100 ml of water followed by 100 ml of saturated aqueous sodium chloride. The ether was dried over magnesium sulfate, filtered, and rotary evaporated to give a colorless residue of crystals, 2.5 g, 93% yield of syn alcohol 2, mp 109-110°.

Acetates of the mixture of alcohols 2 and 3

Acetates of the mixture of alcohols 2 and 3 were prepared by a modification of a procedure used by Howell (150). The mixture of alcohols 2 and 3, 0.5 g (2.5 mmol) was dissolved in 40 ml of dry pyridine. To this stirring mixture was added 0.8 g (8 mmol) of acetic anhydride. This was allowed to stir overnight with a Drierite tube in the flask neck. The contents of the flask were poured into 300 ml of water. The mixture was extracted once with 100 ml of ether and twice
more with 75 ml of ether. The ether portions were combined and washed twice with 50 ml 20% aqueous hydrochloric acid, twice with 50 ml of saturated aqueous sodium chloride. The ether extracts were dried over magnesium sulfate, filtered, and rotary evaporated. The slightly yellow oil of 0.47 g was an 80% yield. Only one peak was seen on a carbowax 20 M or an SE 30 column. (Both columns were 1 m x 6.35 mm aluminum.). The nmr indicated it was a mixture of the acetates in about the same ratio as the mixture of starting alcohols: nmr (CCl₄) δ 7.4 (s, 5H), 6.13 (m, 2H), 5.76 and 5.48 (1H, d, J=10.5 Hz, and d, J=11 Hz, CHOAc), 2.81 (broad singlet, 1H), 1.94 (s, 3H), 1.0 (m, 2H), 2.3-0.7 (m).

7-Norbornylphenylmethanol (4)

To 110 mg of Adams's catalyst (platinum oxide) covered by 50 ml of ethyl acetate in a 250 ml Parr pressure bottle, was added 2.0 g (0.01 mol) of the mixture of alcohols 2 and 3. The bottle and contents were placed in a Parr Pressure Reaction Apparatus and a pressure of 45 psi of hydrogen gas was passed into the bottle. The shaker was started and shut off two hours later. The catalyst was filtered off and the solvent evaporated from the filtrate. The residue was recrystallized from hexane to give 1.6 g of colorless cubic crystals, 80% yield: mp 117-118°; nmr (CCl₄) δ 7.21 (s, 5H), 4.29 (d, 1H, J=10.0 Hz, CHO₃), 2.3 (broad singlet, 2H), 2.0-
0.9 (overlapping multiplets, 10H); ir (CCl₄) 3625 (m), 2970 (s), 2890 (m), 1468 (m), 1320 (m), 1070 (m), 1005 (m) cm⁻¹; mass spectrum (16 eV) m/e 202 (P⁺), 184, 125, 124, 123 (base), 107, 79, 78, 77.

Anal. (Spang) calcd for C₁₄H₁₈O: C, 83.12; H, 8.97. Found: C, 83.02; H, 8.96.

7-Norbornyl phenyl ketone

The 7-norbornylphenylmethanol, 0.2 g (1 mmol), was oxidized with 0.07 g (0.7 mmol) of chromium trioxide following the Jones procedure described by Meinwald and coworkers (126). The product was 1.2 g (60% yield) of a colorless oil: nmr (CCl₄) δ 7.68 (m, 2H), 7.20 (m, 3H), 3.06 (broad singlet, 1H), 2.44 (broad singlet, 1H), 1.8-1.0 (overlapping signals, 8H).


CAN oxidations

General considerations

The alkylphenylmethanols were oxidized by 2 equiv of CAN in 50% or 56% aqueous acetonitrile. The flask, fitted with a reflux condenser, containing the reactants stirring magnetically, was placed in an oil bath maintained at 80-85°. After a few minutes gentle reflux was observed. A thermometer placed in the stirring, refluxing reaction mixture registered ca. 78°. It is known that acetonitrile
and water form an azeotrope which boils at \( 77^\circ \) (151). The mixture in the flask was allowed to stir at reflux until the red color of the complex had faded to colorless or faint yellow. This usually took only a few minutes. The mixture was worked up and the absolute yields of starting material and products were determined by glpc or nmr analysis using internal standards. The products were determined by glpc peak enhancement or collection and spectral analysis. Methyl benzoate was used as the internal standard for glpc analysis for the oxidation mixtures from the alkylphenylmethanols. The order of elution in all cases was the same; benzaldehyde, methyl benzoate alkyl phenyl ketone, and alkylphenylmethanol. The glpc scans were xeroxed and the copies cut and weighed. The yields determined relative to standard were corrected by factors obtained from control experiments. In this way the yields of products and the benzaldehyde to ketone ratio for each run were obtained. The mean and standard or average deviation were calculated and are presented in Table 1, (pages 8-9). For the glpc analysis of the oxidation of the tertiary alkylphenylmethanol, cyclopentyl phenyl ketone was used as the internal standard.

Some of the oxidation mixtures were analyzed on 1 m x 6.35 mm aluminum column of 20% \( 1,2,3\text{-tris(2-cyanoethoxy)} \)-propane (TCEP) on chromosorb P. It was found during the course of this study that a 20% carbowax 20 M on chromosorb W was a more useful column material for the typical analysis.
For nmr analysis 1,1,2,2-tetrachloroethane was used as an internal standard. The aldehyde proton of benzaldehyde was compared directly to the standard. The other yields were determined by comparison of the total aromatic region and the ortho protons with standard. The typical oxidation mixture had a characteristic nmr: δ 9.95 (s, CHO), 8.1-7.7 (m, ortho H), 7.6-7.4 (m, meta and para H), ~7.2 (s, 5H), 6.0 (s, standard). Since benzaldehyde was known by direct comparison with standard the yields of the ketone and alcohol could be determined by simple calculations.

Correction factors were determined in every case with the exception of the 2-fluoroalcohol and were found to be quite similar. The usual control experiment consisted of the preparation of a pseudo reaction mixture. Typically 1 equiv each of alcohol, ketone, and benzaldehyde and 2 equiv of Ce(III) (prepared in situ from CAN reduced with pinacol) were mixed together and subjected to same reaction conditions, work up, and analysis as the actual oxidation mixtures. In this way the correction factors were determined and the stability of the products to the reaction conditions ascertained.

Alkynitrates

The ir spectra from many of the oxidations with CAN contained two prominent peaks around 1630 and 1280 cm\(^{-1}\). These are the intense characteristic peaks for alkyl nitrates.
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(147). Also it was noticed in the glpc scans of the product mixtures that there was a curious peak which caused the base line to lower as a result of its elution. This was found to be characteristic of the cyclohexyl and cyclopentyl nitrates.

Ethylphenylmethanol

Procedure A

Into a 10 ml round bottom flask containing a stirring bar was placed 2 ml acetonitrile, 1 ml water, and 1 ml of a 1 M solution of ethylphenylmethanol in acetonitrile. Then 2 ml of 1 M aqueous CAN was added resulting in 0.167 M alcohol and 0.33 M CAN. The flask was fitted with a condenser and placed in an oil bath at 80-85° and stirring of the 56% aqueous acetonitrile solution was started. After 10.5 min the red color had faded to colorless and the heating was stopped. After the mixture had cooled to room temperature 0.5 ml of a 1 M solution of methylbenzoate in acetonitrile was added. About 3 ml of saturated aqueous sodium chloride was added and the mixture extracted twice with 3 ml of ether. The extracts were washed with 3 ml saturated sodium chloride, twice with 3 ml 1 M aqueous sodium bicarbonate, and once with 3 ml of saturated aqueous sodium chloride. It was dried over magnesium sulfate, filtered, and analyzed on a 1 m x 6.35 mm aluminum column of 20% carbowax 20 M on chromosorb W at 130°, 60 ml/min, and temperature programing 1°/min. The benzaldehyde to ketone ratios obtained from two runs were 4.09 and 4.17.
Procedure B  This was essentially the same as that outlined by Trahanovsky and Cramer (13) except that an 80-85° oil bath was used as the heat source instead of a steam bath. The reaction took 15 min. The solution was 50% aqueous acetonitrile and 0.25 M in alcohol and 0.5 M in CAN. The benzaldehyde to ketone ratio from one run was 4.05.

Procedure A was used for two runs in a 50° oil bath and two runs in a 30° oil bath.

The following compounds were oxidized with CAN and are presented with the respective oxidation procedure, reaction time, and analysis conditions.

2-Methylpropylphenylmethanol  Procedure B; 19 min; column A, 95°, 1°/min to 165°.

Cyclopropylmethylphenylmethanol  Procedure B; 4 min; column C, 75°, 1°/min to 165°.

5-Hexenylphenylmethanol  Procedure B using 1/5 scale; 12 min; column A, 145°, temperature increased to 212° immediately after elution of standard peak.

4-Methoxybutylphenylmethanol  Procedure A; 11 min; column A, 130°, temperature increased to 210° immediately after elution of standard peak.

3-Methoxypropylphenylmethanol  Procedure A; 10 min; column A, 130°, temperature increased to 220° immediately after elution of standard peak.

2-Methoxyethylphenylmethanol  Procedure A; 9 min; column B, 100°, temperature increased to 165° immediately
after elution of standard.

**Cyclohexylphenylmethanol.** Procedure A; 3.5 min; column A, 130°, temperature increased to 205° immediately after elution of standard. Cyclohexyl acetamide was collected by glpc from reaction mixtures and recrystallized from hexane: mp 104-105° [lit. (152) 103-104]; nmr (CCl₄) δ 7.1 (broad peak, H), 3.5 (broad peak, 1H), 2.0-1.0 (overlapping multiplets, 13H, singlet at 1.88, CH₃). A trace of cyclohexanol was identified by peak enhancement. Yields of cyclohexyl nitrate and cyclohexene relative to benzaldehyde were determined by nmr analysis of the reaction mixtures using the signals at 4.9, 5.6, and 9.95 δ respectively. Procedure A was also used for reactions run at 50° and 30°.

**Cyclopentylphenylmethanol** Procedure B; 2 min; column D, 95°, temperature increased to 160° immediately after elution of standard peak. Yields of cyclopentyl nitrate and cyclopentene relative to benzaldehyde were determined by nmr using the signals at 5.3, 5.65, and 9.95 δ respectively.

**Cyclobutylphenylmethanol** Procedure B; 4 min; column D, 80°, 1°/min to 150°.

**Cyclopropylphenylmethanol** This alcohol was not stable to the reaction conditions. When it was mixed with Ce(III), generated *in situ* from CAN and pinacol, glpc analysis on column D revealed almost no starting alcohol left. A new peak was observed with a longer retention time. Using a silica gel column, a colorless oil corresponding to the
glpc peak was isolated. The nmr is similar to the reported
nmr of 4-phenylbut-3-en-l-ol (153); nmr (CCl₄) δ 7.0 (m,5H),
6.4-5.6 (m,2H), 3.5 (t,2H,J=7.0 Hz), 3.13 (s,1H), 2.25
(q,2H,J=7.0 Hz).

Haloalkylphenylmethanols Haloalkylphenylmethanols
were oxidized using Procedure A. The only modification was
use of the nmr standard instead of the glpc standard and
distillation of the ether solvent. The nmr of the remaining
oil was taken and the region between 10.0-5.0 δ integrated.
The times for reaction follow: 4-bromobutyl-, 9 min; 2-
bromoethyl-, 8 min; 2-chloroethyl-, 20 min; 2-fluoroethyl-, 8 min.

The best results were obtained when the standard was
added just after reaction and before work up.

7-Norborylphenylmethanol (4) After 1 hour at
80°, the mixture of CAN (6 mmol) and 4 (1 mmol) in 10 ml
80% aqueous acetonitrile was still orange in color. It was
worked up by Procedure B and only one major peak was
detectable by glpc. It was collected from column E and
recrystallized from ether to form colorless cubes. This
material was characterized as N-(7-norborylphenylmethyl)l-
acetamide (6): mp 159-161°; Tr (column E, 210°, 60 ml/min)=
12 min; nmr (DCCl₃) δ 7.22 (s,5H), 6.0 (d,1H,J=8.0 Hz,NH),
4.78 (d of d,1H,J=8.0 Hz,J=12.0 Hz), 2.15 (broad singlet,2H),
1.91 (s,3H), 1.85-1.10 (overlapping multiplets,9H); ir
(HCCl₃) 3460 (m), 2970 (s), 2890 (m), 1680 (vs), 1510 (s),
1380 \text{(m) cm}^{-1}; \text{mass spectrum (70 eV, m/e) 243 (P+), 185 (loss of CH}_3\text{CONH), 148 (loss C}_7\text{H}_6\text{NO), 106 (base peak).}

\text{Anal. Calcd for C}_{16}^\text{H}_{21}^\text{NO: mass spec, 243.16230. Found: mass spec., 243.16227.}

By changing the solvent to 50\% aqueous acetonitrile and allowing a shorter reaction time, 20 min, the production of acetamide 6 was reduced dramatically and oxidative cleavage products detected. The glpc benzaldehyde peak was overlapped by some other peak so nmr was used to estimate that the benzaldehyde to ketone ratio was greater than 8. There was a large amount of remaining starting material.

\text{anti-7-Norbornenylphenylnethanol (2)} The alcohol 2, 0.10 g (0.5 mmol), was allowed to react with 0.548 g (1.0 mmole) of CAN in 80\% aqueous acetonitrile. The red color faded to colorless in 2 min at room temperature. After work up no benzaldehyde was detected by nmr or glpc. The ir had two prominent peaks at 1290 and 1640 cm}^{-1}.

\text{syn-7-Norbornenylphenylnethanol (3)} When 1 mmol of alcohol 3 was allowed to react with 2 mmol of CAN at 80^\circ, the red color faded to colorless after 11 min. The nmr of the product mixture indicated that a trace of benzaldehyde and a large amount of starting material was present.

\textbf{Kinetic procedure}

A stock solution of 3.0 M nitric acid was prepared for use in the kinetic runs. 189.0 ml of concentrated nitric
acid (70.4% nitric acid, specific gravity 1.42 g/ml) was mixed with enough distilled water in a volumetric flask to make a 1.0 liter solution. A typical run started with the preparation of "bench" solution by adding the 3.0 M nitric acid (4 ml) to acetonitrile (16 ml). The resulting solution reaction is endothermic and forms a homogeneous mixture which is 20% aqueous nitric acid-80% acetonitrile and has a concentration of nitric acid of 0.6 M. This liquid was used to make a solution of substrate 0.075 M in a 5 ml volumetric flask. Enough "bench" solution was used to make 10 ml of solution of 0.0412 g CAN in a volumetric flask. This is a 0.0075 M CAN solution. The substrate solution (2.0 ml) was syringed into one leg of a U-tube and 1.0 ml of the CAN solution was syringed into the other leg. The U-tube was stoppered with a rubber septum and placed in a water cooled aluminum storage block. The cuvetts were placed into the water cooled cell compartment of a Beckman DU Spectrophotometer. Water thermostated at 20.00±0.05° was circulated through the system by a Haake Kodel F constant temperature circulator. The solutions were allowed to stand for about an hour in the apparatus. The U-tube was fitted into the cuvette opening and the two conjugated tubes shaken until all the solution was transferred into the cuvette. The stoppered cuvette was placed into the cell compartment and absorbance followed with time. After the mixing, the resultant solution is calculated to be 0.6 M nitric acid, 0.0025 M CAN, and 0.05
M in substrate. The rate constants were calculated by a graphical method.

**Spectrophotometric equilibrium constants**

A 0.18 M solution of the alcohol was made up in acetonitrile. Aliquots of the solution were transferred to one arm of a U-tube as follows: 0.0 ml, 0.35 ml, 0.6 ml, 0.9 ml, 1.2 ml, and 1.5 ml. Acetonitrile was then added to each tube to make a total volume of 2.1 ml. The second arm of the U-tube was filled with 0.9 ml of a 0.0333 M ceric ammonium nitrate in 1.654 M nitric acid solution. The U-tubes were then cooled in an aluminum block at 20° for at least 30 minutes. The tubes were removed just before use, shaken thoroughly, and the contents poured into cooled uv cells. The initial absorption was noted as a wavelength of 520 nm. If the absorbance fell with time, an extrapolation to time zero was made by plotting log absorbance versus time for about 10-15% reaction. The equilibrium constants were calculated from the absorption data using the linear least squares program, RAWDAT.
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ACKNOWLEDGMENTS

I am thankful to Professor Walter S. Trahanovsky for allowing me to work on this problem and for his many excellent suggestions and ideas. I am deeply grateful for the many discussions with him that resulted in my increased motivation.

This work would never have been started without the motivation and encouragement from my parents. Their support helped me through the most difficult time of my life. This work is rightfully dedicated to them.

I am especially thankful to Barbara Abraham and Kristen Olson. They have been my best friends and brought beauty and warmth into my life.

Dr. Bobby Howell enriched my life with his willingness to discuss almost anything. His deep understanding of organic chemistry has been very helpful to me. Everyone in 230 Chem Hall has contributed in some way to my enjoyment at Iowa State. To Mike, Dr. Mike, and all the rest, Thanks.

I am indebted to Marilyn Saul for typing this manuscript and at the same time maintaining her cheerfulness!

I also acknowledge P. C. Heaton.