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PART I: THE THERMAL REARRANGEMENT OF ALLYLHYDRAZONES

PART II: STUDIES ON THE SYNTHESIS OF ASPIDOSPERMA ALKALOIDS

by

Edward E. McEntire

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy

Thesis Director's signature

Robert [Signature]

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March, 1972
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To Joyce
ACKNOWLEDGMENTS

I would like to express my sincerest appreciation for the continuing instruction and capable guidance of Dr. R. V. Stevens, who has made this work a source of continuing excitement.

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PART I

THE THERMAL REARRANGEMENT
OF ALLYLHYDRAZONES
INTRODUCTION

Numerous examples of [3+3] sigmatropic rearrangements\(^1\) are found within the chemical literature, dating back at least to 1912.\(^2\) The reaction may be generalized as below, where A through F represent atoms of valence greater than one.

\[
\begin{array}{cccc}
\text{I} & \rightarrow & \text{II} & \leftrightarrow \\
\text{III} & \rightarrow & \text{IV}
\end{array}
\]

The most widely studied rearrangements of this class include the Claisen rearrangement (C=oxygen; A, B, D=F=carbon) and the Cope rearrangement (A=F=carbon). The scope and mechanism of these reactions have been studied in great detail. Both are known to proceed in a concerted fashion\(^3\) to yield products as shown above.

Other examples of this rearrangement have been discovered (i.e., C=nitrogen, sulfur, or phosphorus and A, B, D=F=carbon) and each has been shown to proceed as above.\(^4\) There are fewer examples of this reaction involving reactants containing more than one hetero atom, but these are also thought to be concerted.\(^5\) Due to the specific nature of the above rearrangements, many have been found to be of great synthetic importance.\(^4\)

From the number of successful reactions cited above, the reaction I \(\leftrightarrow\) II appears to be quite general and most useful. It was for this and other reasons that it was decided to attempt a somewhat different elemental substitution pattern from those previously explored.
Thus, it appeared to us that if an allylic hydrazine was condensed with an aldehyde or ketone to form an allylhydrazone, Ia (B, C = nitrogen; A, D-F = carbon), thermolysis might proceed in the manner indicated to IIa (B, C = nitrogen; A, D-F = carbon). This is illustrated more clearly below. The diazene IIa (R = H or alkyl) thus formed might then decompose under the reaction conditions in the manner illustrated to yield an olefinic hydrocarbon, V, and nitrogen.\(^6\)

The synthetic potential of this reaction lies in the facile formation of the allylic hydrazones from readily available materials and their subsequent thermolysis to form a carbon-carbon bond, a sometimes difficult yet desirable task. Included in this work are the results of our synthesis and pyrolytic study of allylhydrazones, and of our probes into the pyrolysis reaction mechanism.
RESULTS AND DISCUSSION

For the reactions described above to be of significant synthetic value, a prerequisite is that the allylhydrazones must be easily derived. Perhaps the most convenient synthesis of allylhydrazones is from the condensation of aldehydes or ketones with the required allylhydrazine.

The most direct approach to allylhydrazines lies in the alkylation of hydrazine with allylic halides.\textsuperscript{7} Monoallylhydrazine and unsym\textsuperscript{diallylhydrazine were synthesized accordingly.}\textsuperscript{7c} Then acetone allylhydrazone \([1]\) was made by reacting acetone with allylhydrazine with external cooling.\textsuperscript{8} Several sealed tube pyrolyses of neat \([1]\) were attempted, using the potential catalysts ammonium chloride and potassium carbonate and varying the temperature above 190\(^\circ\). Each time a low yield of the desired olefin \([3]\) was produced, as well as two other materials presumed to be \([4]\) and \([5]\) by comparison of their glpc retention times on several columns with those of the authentic materials. No catalytic effect was observed.

\[
\begin{align*}
(CH_3)_2C=NMNNH & \quad \longrightarrow \quad \text{H}_3\text{CNC}_3\text{H}_2\text{NNH} \quad \longrightarrow \quad \text{H}_3\text{CNC}_3\text{H}_2\text{NNH} & \quad \text{CH}_3 & + & \text{CH} = \text{CH} & + & \text{CH} = \text{CH} \\
\end{align*}
\]

Upon collection of this somewhat encouraging data, benzophenone allylhydrazone \([6]\) was prepared with some difficulty (see experimental section). Pyrolysis of the neat compound at 190\(^\circ\) for 40 hours in a sealed tube gave a moderate yield of 4,4-diphenyl-1-butene \([8]\) and diphenylmethane \([9]\). A proposed explanation of this data is shown in
Scheme 1. These products were purified by preparative chromatography and identified by comparison of their pmr and mass spectra and glpc retention times with those of the authentic materials (see experimental and spectral sections). Compound [8] was shown to be stable under the reaction conditions.

At this time in our study it seemed apparent that the reactions studied were not entirely concerted, if concerted at all, in nature as evidenced by the appearance of products [4], [5], and [9]. These by-products indicated that radical dissociations were occurring at some stage in the reaction, perhaps via [10] or [11]. Even the product [8] may be formed via [10] or [11]. The pyrolysis of [6] was repeated varying the catalyst as before, but no significant catalytic effect was found (see experimental section).
During these investigations we became aware of unpublished work by Wenkert and Barnett on the pyrolysis of allylhydrazone. By coincidence none of the compounds studied by either group were identical, thus the studies complimented one another.

Using the simplified procedure of Wenkert and Barnett several other allylhydrazone were pyrolyzed. Although our pyrolysis of neat benzaldehyde allylhydrazone [13] yielded volatile products as evidenced by glpc, the pyrolysis was repeated using triethylene glycol (TEG) as solvent. Only two major volatile products were present. These were isolated and identified as cis-1-methyl-2-phenylcyclonpropane and 4-phenyl-1-butene, the expected rearrangement product. Next, acetophenone allylhydrazone [14] was prepared and pyrolyzed as above, but the reaction yielded only a trace of two non-basic compounds, neither of which was the desired 4-phenyl-1-pentene. However, the pyrolysis of trimethylacetaldehyde diallylhydrazone [15] yielded the expected 4-t-butyl-1,6-heptadiene as the only isolable product. Data from the experiments mentioned above as well as that of Wenkert and Barnett are recorded in Tables 1 and 2.

It is apparent from Table 1 that product yields are the highest when \( R_1 \) and \( R_2 \) are aromatic groups. The yields decline somewhat when one of the groups is replaced by hydrogen and decline still further when \( R_1 = R_2 = \text{methyl} \). This decrease in yield may be due to competing intermolecular condensation reactions because of less hindered electrophilic centers and the relatively more acidic protons of the methyl groups. Since in all of the above pyrolyses appreciable amounts of yellow to brown residue (part of which was water soluble) remained when the starting material had disappeared, it is not unreasonable to assume
TABLE 1. PYROLYSIS OF ALLYLHYDRAZONES (R₁R₂C=NNR₃R₄)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Solvent</th>
<th>Pyrolysis Temperature</th>
<th>Reaction Time (hr)</th>
<th>Products (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>CH₃</td>
<td>CH₃</td>
<td>allyl</td>
<td>H</td>
<td>TEG</td>
<td>300°</td>
<td>3.0</td>
<td>4-methyl-1-pentene (6.1)</td>
</tr>
<tr>
<td>[6]</td>
<td>Ph</td>
<td>Ph</td>
<td>allyl</td>
<td>H</td>
<td>TEG</td>
<td>300°</td>
<td>8.0</td>
<td>4, 4-diphenyl-1-butene (20) (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-diphenylmethane (22) (30)</td>
</tr>
<tr>
<td>[13]</td>
<td>Ph</td>
<td>H</td>
<td>allyl</td>
<td>H</td>
<td>TEG</td>
<td>300°</td>
<td>1.5</td>
<td>4-phenyl-1-butene (11) (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cis-1-methyl-2-phenylcyclopropane (8) (8)</td>
</tr>
<tr>
<td>[14]</td>
<td>Ph</td>
<td>CH₃</td>
<td>allyl</td>
<td>H</td>
<td>TEG</td>
<td>270-280°</td>
<td>1.0</td>
<td>--e</td>
</tr>
<tr>
<td>[15]</td>
<td>t-Bu</td>
<td>H</td>
<td>allyl</td>
<td>allyl</td>
<td>TEG</td>
<td>260°</td>
<td>10.5</td>
<td>4-t-butyl-1, 6-heptadiene (3.2)</td>
</tr>
<tr>
<td>[16]b</td>
<td>Ph</td>
<td>H</td>
<td>allyl</td>
<td>allyl</td>
<td>TEG</td>
<td>274-280°</td>
<td>0.5</td>
<td>4-phenyl-1, 6-heptadiene (2.9)</td>
</tr>
<tr>
<td>[17]b</td>
<td>fluorenyl</td>
<td>allyl</td>
<td>allyl</td>
<td>TEG</td>
<td>205-210°</td>
<td>0.5</td>
<td>9, 9-diallylfluorene</td>
<td></td>
</tr>
<tr>
<td>[18]b</td>
<td>Fluorenyl</td>
<td>allyl</td>
<td>allyl</td>
<td>H</td>
<td>DEG</td>
<td>205-210°</td>
<td>0.5</td>
<td>9-allylfluorene (32) bifuoure (13)</td>
</tr>
</tbody>
</table>

a Yields are percent isolated unless noted. Little attempt was made to improve the yields.
b Work with these compounds was performed by Wenkert and Barnett.
c Analytical glpc yield using an internal standard.
d No yield given.
e See experimental section.
# TABLE 2. SYNTHESIS AND PROPERTIES OF ALLYLHYDRAZONES

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Solvent</th>
<th>Catalyst</th>
<th>Yield</th>
<th>bp (mm of Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>none</td>
<td>none</td>
<td>36%</td>
<td>66.0° (30)</td>
</tr>
<tr>
<td>[6]</td>
<td>CH₃OH</td>
<td>TsOH</td>
<td>89%</td>
<td>138.0° (0.5)</td>
</tr>
<tr>
<td>[13]</td>
<td>Et₂O</td>
<td>none</td>
<td>79%</td>
<td>89.0° (0.4)</td>
</tr>
<tr>
<td>[14]</td>
<td>Et₂O</td>
<td>HOAc</td>
<td>84%</td>
<td>115.0° (1.2)</td>
</tr>
<tr>
<td>[15]</td>
<td>Et₂O</td>
<td>HOAc</td>
<td>42%</td>
<td>95.5° (30)</td>
</tr>
<tr>
<td>[16]</td>
<td>CH₃OH</td>
<td>HOAc</td>
<td>50%</td>
<td>90-110.0° (0.024)</td>
</tr>
<tr>
<td>[17]</td>
<td>CH₃OH</td>
<td>HOAc</td>
<td>74%</td>
<td>--</td>
</tr>
<tr>
<td>[18]</td>
<td>CH₃OH</td>
<td>HOAc</td>
<td>90%</td>
<td>--*</td>
</tr>
</tbody>
</table>

* mp 67-68° (EtOH). \( \nu_{\text{max}} \) 2.96 (NH) and 6.05μ (C=C).
aldol-like condensations produced some of this material. Another side reaction which probably occurs is nitrogen-nitrogen bond cleavage to form nitriles and amines. This reaction was discovered by Crow and Solly in their pyrolysis of benzaldehyde phenylhydrazone at 400° to produce benzonitrile and aniline.\textsuperscript{11}

Substitution of an allyl group at R\textsubscript{4} also decreases the yield, but this may have been expected from differences in the intermediate diazene. Monodiazenes have been isolated and are found to decompose by a bimolecular pathway, usually quite cleanly in the absence of oxygen.\textsuperscript{6} Azo compounds, however, are known to decompose thermally via a radical mechanism which allows scrambling of radicals as shown below. If an active

$$R-N=N-R' \xrightarrow{-N_2} R^* + R'^* \xrightarrow{\text{SH}} R-R + R-R' + R'-R'$$

hydrogen source is available (i.e., solvent), the radicals may also be trapped before coupling products are formed.

At this point, the isolable products had been those predicted in every case studied but one. However, the by-products in the pyrolysis of [1], [6], and [18] indicated that the reaction of the allylhydrazones may not be concerted, since the predicted products may also be explained by the radical processes shown in Scheme 1. It was thus decided to test the reaction with a labeling experiment to determine its degree of specificity.

The plan was devised to pyrolyze a specifically deuterated allylhydrazone. A hydrazone was selected which would yield maximum new information about the reaction mechanism, namely labeled benzaldehyde
methallylhdyrazone [19]. The study of its reaction was selected because of its expected facile synthesis, because it was of the type (i.e., [13]) which had previously produced a cyclopropane by-product, and it was itself a new example of the rearrangement in question.

The unlabeled compound [19] was synthesized from benzaldehyde and methallylhdyrazine, prepared from methallyl chloride and hydrazine. Pyrolysis of [19] yielded the expected 2-methyl-4-phenyl-1-butene and a by-product, 1,1-dimethyl-2-phenylcyclopropane, which was identified by comparison of its pmr spectra with that of the reaction product of 3,3-dimethylcyclopropene and phenyllithium.

The addition of phenyllithium to 3,3-disubstituted cyclopropanes to yield phenyl substituted cyclopropanes seems to be a somewhat general reaction. The cis addition of phenyllithium to cyclopropene to give phenylcyclopropane has been demonstrated by Magid and Welch,12 and the addition to 3,3-dimethyl- and 3,3-diethylcyclopropene was demonstrated by this author in work performed under the direction of R. M. Magid. This is evidence contrary to that reported by Welch who reported no addition of phenyllithium to 3,3-dimethylcyclopropene.13

Since the above synthesis and pyrolysis of [19] were successful, the major task remaining in the labeling study was the synthesis of a specifically labeled allylhydrazone. The synthesis of a deuterated allylhydrazone from a deuterated allylic chloride14 and hydrazine again seemed the best method, provided the specific labeling was maintained during this reaction.

Since no data was available concerning the mode of reaction (normal or abnormal) of hydrazine with allylic halides, it was decided to run several preliminary reactions to determine the feasibility of the
deuterium labeling sequence. Limited data concerning the reaction of allyl halides with amines\textsuperscript{15} led us to expect some abnormal attack on reaction of hydrazine with \( \alpha \)-methylallyl chloride. The reaction of allyl chloride-\( ^{14}\)C with trimethylamine gave 7% abnormal attack, and reactions of secondary amines with \( \alpha \)-methylallyl chloride gave exclusively abnormal products. The abnormal attack by secondary amines has been proposed to be due to hydrogen bonding between the amine hydrogen and the leaving chloride [20].\textsuperscript{15} So, with hydrazine also capable of hydrogen bonding in the transition state, some abnormal product was predicted in its bimolecular reaction with allylic chlorides.

Table 3 summarizes the results of addition of substituted allylic chlorides to excess hydrazine hydrate (reaction conditions were similar to those in the preparation of monoallylhydrazine; see experimental section). It may be seen from this data that hydrazine preferentially attacks in a normal fashion. Primary chlorides [21] and [23] show exclusively normal attack (presumably bimolecular). Normal attack still predominates in the secondary [22] and tertiary [24] chlorides, whereas, reaction of [23] with diethyl- or dimethylamine gives entirely abnormal attack.\textsuperscript{15}

These results may be explained by a change in mechanism for reaction of the more highly substituted chlorides. Since hydrazine hydrate is probably a strongly ionizing medium (\( \varepsilon_{N_2H_4} = 53, \varepsilon_{H_2O} = 78 \)), heterolytic
### Table 3. Reaction of Allyl Chlorides with Hydrazine Hydrate

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chloride</th>
<th>Reaction Temperature</th>
<th>Normal Addition</th>
<th>Abnormal Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>[21]</td>
<td>trans-crotyl (≥97% trans)</td>
<td>40-55°</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>[22]</td>
<td>α-methylallyl</td>
<td>40°</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>[23]</td>
<td>γ,γ-dimethylallyl</td>
<td>20°</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>[24]</td>
<td>α,α-dimethylallylb</td>
<td>0°</td>
<td>67%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*a Product ratios were determined by pmr integration (±2% error as specified by the instrument manufacturer).

*b This compound was reacted at a lower temperature to prevent its rearrangement to [23] which occurs at elevated temperatures.
cleavage of the carbon-chlorine bond may occur in preference to bimolecular abnormal attack or normal attack of hydrazine at the secondary or tertiary center. Then the hydrazine may preferentially capture the site with the greatest positive character \((3^\circ > 2^\circ > 1^\circ)\) in the allylic cation. As the site of higher positive character in the intermediate cation becomes more hindered (i.e., compare [22] and [24]), the reaction mode shifts to favor more of the abnormal product.

The primary allylic chlorides, however, probably experience rapid, preferential bimolecular attack at the primary center due to the relatively higher nucleophilicity of hydrazine \((\equiv\text{-effect})^{16}\) compared to secondary amines. Thus, in changing from primary to secondary and tertiary allylic chlorides, reaction mechanism appears to change from \(S_N^{2}\) to \(S_N^{1}\) (or a combination of \(S_N^{1}\) and ionization-recombination/\(S_N^{2}\)).\(^{17}\) Certainly kinetic data on the hydrazine/allylic chloride system would be interesting and informative.

The results above demonstrating preferential normal attack of hydrazine on allylic chlorides led us to believe, that, contrary to our previous thoughts, a specific deuterium label in \(\beta\)-methylallyl chloride might be retained in its reaction with hydrazine. To test this proposal, 3-chloro-3,3-dideuterio-2-methyl-1-propene [25] was prepared from the reaction of 1,1-dideuterio-2-propen-1-ol [26]\(^{18}\) with thionyl chloride.\(^{13}\) Reaction of [25] with hydrazine hydrate gave (1,1-dideuterio-2-methyl-2-propenyl) hydrazine [27], the product of normal substitution. This product was shown to be 98% dideuterated in the one-position by pmr analysis of its benzaldehyde condensation product [28]. Therefore the reaction between hydrazine and [25] proceeded by at least 98% normal attack.
With the labeled methylallylhydrazone in hand, the mechanism of its rearrangement could be studied. As an added bonus, quantities of methyl substituted allylhydrazines were available for further studies.

The labeled hydrazone [28] was pyrolyzed at 300° in TEG and two products were isolated and purified by preparative glpc. One compound was 2-methyl-4-phenyl-1-butene which was 91% diduteated in the 1-position [29a] and 9% diduteated in the 3-position [29b] as shown by pmr analysis. The other compound was shown to be 1,1-dimethyl-2-phenylcyclopropane [30], diduteated entirely on the methyl cis to the phenyl group.

The cis stereochemistry of the dideuteriomethyl group was assigned by its chemical shift of δ 0.80 compared to δ 1.19 for the trans methyl group. For comparison, the methyl absorption for cis-1-methyl-2-phenylcyclopropane lies at δ 0.80, and at δ 1.20 for trans-1-methyl-2-phenylcyclopropane.13

Compound [29a] corresponds to the expected product from a concerted, six-center rearrangement (Path A in Scheme 2). Compound [29b] corresponds to products very likely derived via a higher energy, nonconcerted mechanism, possibly via Path B or C. Hydrazone [28] may dissociate directly into radicals20 (Path B) which may recombine to give diazenes [31] and [32], in equal amounts (A statistical mixture of isotopic compounds was isolated from recombination of allylic radicals produced in the
pyrolysis of 3,3'-azo-1-propene-3,3-d$_2$.). These diazenes could then decompose to yield olefins [29a] and [29b] respectively. Isomerization of [28] may also occur$^{22}$ to yield azo compound [33] (Path C), and thermal decomposition of this intermediate would be predicted to yield equal parts of [29a] and [29b]$^{21}$ Thus, at least 82% of the reaction which produced [29] was via a synchronous pathway (Path A), and a maximum of 18% was by another label scrambling pathway (probably C since [30] is labeled only in the cis-methyl and not on the cyclopropane ring).

An alternate explanation may involve [33]. If cis-[33] were produced, a concerted decomposition can be imagined to give [29a] exclusively. Whereas this mechanism cannot be ruled out with the data at hand, this
author prefers the monodiazen intermediate for the reaction, since it has been found to yield both olefin and cyclopropane in separate experiments. It is also difficult to imagine a pathway by which the cyclopropane [30] may be formed from [33]. Although some precedent for the

![Chemical Structure]

[33]-cis

above extrusion rearrangement is known, no example of the synchronous rearrangement of an acyclic cis-allylic azo compound such as [33]-cis was found in the literature, and no synchronous rearrangement of a trans-diazen as above has been demonstrated.

Again, in the pyrolysis of [28] a cyclopropane was formed with unexpected stereoselectivity. In each case of benzaldehyde hydrazone pyrolysis, the cyclopropane was formed with the 1-carbon of the hydrazone in a methyl group cis to the phenyl group in the resulting cyclopropane.

![Chemical Structure]

[34] R = H or CH₃

[35]

[36]

Since formation of [35] from the hydrazone [34] requires that two bonds must be broken from the benzylic carbon, and two bonds must be formed between it and C₂ and C₃, a complex series of reactions is probably occurring.
At this point, the possibility occurred to us that cyclopropane products [35] and olefinic products [36] may arise from the same intermediate. With [37] as a precursor to [35], a more attractive situation exists than above. To form [35], only one bond from the benzylic carbon of [37] must be broken and reformed to carbon 2.

To determine if the olefin and cyclopropane products were actually derived from the same intermediate diazene, the decision was made to prepare the proposed intermediate by another route. Several methods are known for the synthesis of monodiazenes. The method selected was the thermal or base catalyzed elimination of p-toluenesulfonic acid (TsH) from the appropriately substituted p-toluenesulfonhydrazine (tosylhydrazine).

The following reactions were used to prepare 1-[(1-phenyl-3-buteny1)-2-p-toluenesulfonhydrazine [38] (see experimental section):

Upon pyrolysis of [38] in ethylene glycol at 100° until evolution of nitrogen ceased, only two volatile compounds were produced: 4-phenyl-1-butene and cis-1-methyl-2-phenylcyclopropane of unexpected stereoselectivity. Pyrolysis of [38] in benzene or acetic acid produced similar results. These products are identical to those produced during the
pyrolysis of benzaldehyde allylhydrazone, thus presenting convincing evidence that both olefinic and cyclopropane products arise from the same intermediate monodiazene [37a].

A mixture of cis- and trans-cyclopropanes was expected in the pyrolysis of [38] since no means of influence of the configuration of the intermediate diazene was apparent by this method of synthesis. Pyrolysis of the corresponding hydrazone could possibly produce the diazene intermediate in a stereospecific manner, obvious if compared to the specific chair-like transition state proposed for the Cope rearrangement. The stereospecifically produced conformer could then eliminate nitrogen in a specific fashion yielding only cis-cyclopropane.

Since in earlier examples (i.e., pyrolysis of [6] and [18]), doubt had been cast on the degree of concertedness of the rearrangement by the observance of radical coupling and abstraction products, further proof of concertedness was deemed necessary. In order to confirm the generality of the rearrangement, and to possibly secure additional mechanistic information, another system was selected, this time to study the transfer of an isoprene unit.

Benzophenone 1,1-dimethyl-2-propenylhydrazone [39] was formed by condensing benzophenone with the corresponding hydrazine previously prepared. When [39] was pyrolyzed at 250°, three products were isolated. These were identified as diphenylmethane, 5,5-diphenyl-2-methyl-2-pentene [40] and 1,1-dimethyl-2,2-diphenylcyclobutane [41] from their pmr and mass spectra. Product [40], isolated in 22% yield, is the expected product from concerted rearrangement of [39] through diazene [42]. Compound [41], isolated in 18% yield, may also arise via [42]. The diphenylmethane may be produced via a radical cleavage as shown in Scheme 1. Compound [43] might be
expected to form$^{26}$ in a radical reaction analogous to those proposed in Scheme 1, but none was observed by glpc or pmr analysis of the product mixture. Postulated intermediate [42] defied preparation by a route similar to that used to synthesize [37a]. The attempted preparation of 4-methyl-1,1-diphenyl-3-penten-1-ol was not possible by the addition of the allyl Grignard reagent to the ketone as before. Instead, 2,2-dimethyl-1,1-diphenyl-3-buten-1-ol was produced, which when treated with phosphorous tribromide, provided 1-bromo-2,2-dimethyl-3,3-diphenylcyclobutane. Attempts to secure the desired alkyl hydrazine from the bromocyclobutane proved fruitless (see experimental section).

The appearance of cyclobutane [41] was unexpected. In view of earlier results, the trisubstituted cyclopropane above might have been expected. The production of this unusual product led us to consider in detail several mechanistic possibilities for formation of the cyclic products.
SCHEME 3
An interesting mechanism for diazene decomposition which will account for all of the cyclic products is an intramolecular one, expelling nitrogen, transferring hydrogen, and forming the carbon-carbon bond either simultaneously or by intramolecular radical processes as illustrated in Scheme 3. The reaction may be viewed as the intramolecular addition of a diazene to a double bond. Analogy for the synchronous process is found in the intermolecular addition of hydrogen from diazene (diimide) itself to an olefin. This reaction is thought to be synchronous and to occur only with cis-diazene\(^{27}\) as illustrated below. Instead of transferring two hydrogen atoms, one hydrogen atom and a carbon radical could be transferred as shown in Scheme 3, also via six-center transition states. Inspection of models shows that the cis-diazene would probably be a requirement for the synchronous mechanism to operate.

Intermediates [45] and [50] may also intervene, resulting from the transfer of a hydrogen atom from the respective diazenes [37] and [42]. These intermediates could then eliminate nitrogen to form diradicals [46] and [51] which could then couple intramolecularly to form products [35] and [41], or collapse to form cyclic diazenes [48] and [52] which could eliminate nitrogen to give the diradicals [46] and [51].

The pathways involving [46] or [48] are unlikely since bond rotation would very likely occur at these high reaction temperatures in the diradical species or previously, allowing cyclopropane [47] to form as well as
Compound [47] was not an observed product, but this does not rigorously rule out [46] as an intermediate, since closure of the diradical may compete with bond rotation* resulting in formation of only [35] if [46] were formed in a stereospecific manner, and since [48] itself has not been prepared and pyrolyzed to determine if its reaction is stereospecific. This evidence coupled with the results of others strongly suggests, however, that the reaction does not proceed via intermediates [48] or [46]. The corresponding intermediates [51] and [52] cannot be excluded upon similar grounds, since the cyclobutane product [41] can exhibit no stereoisomerism.

Two more detailed proposals, one intramolecular, the other bimolecular in nature, may be considered to give the cis-cyclopropane [35]. From the inspection of models, the intramolecular mechanism would probably involve a cis-diazene. It involves the transfer of a hydrogen from nitrogen to the double bond, and must involve quite a specific transition state.

The hydrogen transfer must occur only while the molecule is in the certain conformation (i.e., [37x]). This conformation may be favored due to steric interactions of the phenyl and allyl groups. Once the transfer has occurred, then specific bond rotation must occur (solid arrow and

*Trans-3,5-diphenyl-Δ¹-pyrazoline was found to yield more cis-1,2-diphenylcyclopropane as the pyrolysis temperature was increased, from 50° to 85°, providing evidence for increased bond rotation vs. coupling at higher temperatures. The decomposition of cis- or trans-3,4-dimethyl-Δ¹-pyrazoline also produces mixtures of stereoisomeric 1,2-dimethylcyclopropanes.
not dotted arrow) in order for backside displacement of nitrogen by the carbon radical to occur. However, reactions in which backside radical displacement of nitrogen is proposed to occur have never been shown to yield only one specific cyclopropane product, as does the reaction of [37].

Another possible mechanism involves a bimolecular collision between two diazene molecules as postulated by Kosower for the decomposition of monodiazenes. This collision between the hindered molecules may require a specific conformation of [37] as shown below [37y]. (This required conformation may occur without the above mentioned collision, if this conformation is required for the specific transition above. Studies with Dreiding models do not, however, indicate a large difference in steric hindrance between conformations [37x] and [37y].)
From conformation [37y], either a concerted or stepwise process can occur as shown, neither of which requires bond rotation. This bond rotation is likely, in diradical intermediates such as [45c] as mentioned previously, and therefore the concerted pathway is more reasonable. However, a proton transfer instead of a hydrogen transfer from the diazenes may not be ruled out on the grounds presented above. These proposed reaction pathways are similar to those shown in Scheme 3 except for the initial orienting of the diazene.

Any of the explanations above could also explain the formation of the cyclobutane [41]. The differences in cyclic product from that above may be explained by the differences in stability of the carbon radicals produced upon hydrogen transfer, or by preferential charge stabilization at differently substituted sites in the transition state.

A reaction mechanism proceeding via a triplet diazene\(^{24}\) (Scheme 4) may be excluded since a primary radical must be created in preference to a secondary or tertiary one and since cyclic diazene [48] would not be expected to decompose stereoselectively to yield only [35].\(^{28}\)

\[
\begin{align*}
[37] & \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N-H}
\end{array} & \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{CH}_2
\end{array} & \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{R}
\end{array} & \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{CH}_3
\end{array} & [35] \\
\text{[48]}
\end{align*}
\]

**SCHEME 4**

Still another reaction which may account for the formation of the cyclic products is the known reaction of monodiazenes with base to form a carbanion.\(^{30}\) If the diazene intermediate [37] (the same argument holds also for [42]) were deprotonated, anion [53] should be formed which may be trapped by a proton donor in olefinic or cyclic form.

This anionic mechanism is very unlikely, however, since cis- and trans-cyclopropane should be observed, and only cis is found. Further
evidence that an anionic mechanism is not operative was found when
tosylhydrazine [38] was decomposed in ethanol/potassium ethoxide. A

\[
[37] \xrightarrow{[53]} \begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{v} \quad \text{v} \\
\end{array} \rightleftharpoons \begin{array}{c}
\text{Ph} \\
\text{v} \\
\end{array} \rightarrow [35]
\]

quantitative yield of 4-phenyl-1-butene was observed. No methylphenyl-
cyclopropane was detected by glpc analysis (amounts <1% could have been
detected). This result indicates that [35] is not formed by any such
base catalyzed reaction, but that the olefinic product may be formed in
this manner.

A radical mechanism very similar to the above anionic mechanism can
be proposed to explain the cyclic products. Evidence of the occurrence
of phenyl radicals upon oxidation of phenyl diazene has been presented. 31
Diazene [37] could decompose via hydrogen abstraction to provide a diazenyl
radical which would be predicted to loose nitrogen 31 to give radical

\[
[37] \xrightarrow{[54]} \begin{array}{c}
\text{Ph} \\
\text{a} \\
\text{b} \\
\end{array} \rightleftharpoons \begin{array}{c}
\text{Ph} \\
\text{b} \\
\end{array} \rightarrow [35]
\]

[54], which may be trapped by a hydrogen donar to give olefin or the
cyclopropane 32 as above. Again, this mechanism may be disputed because
only cis-cyclopropane [35] and no trans-cyclopropane [47] was formed as
expected via this mechanism. Also, the benzyl radical [54a] would be
expected to be much more stable than the methyl radical [54b], and should
be trapped by hydrogen donars in preference to [54b]. 33, 34 A reaction
was conducted to further dispute the participation of [54] in the formation of cyclopropane [35]. A molar equivalent of tributyltin hydride was added slowly to 4-bromo-4-phenyl-1-butene [55] in refluxing benzene to generate radical [54]. Tin hydride reagents are known to propagate radical chain

\[ \text{Ph} \quad \text{Bu}_3\text{SnH} \rightarrow [54] \rightarrow \text{Ph} \quad \]

[55]

reactions upon reaction with alkyl halides. If [54] were an intermediate in the decomposition of diazene [37], then some cyclopropane should be observed in the tin hydride reduction above, since the intermediate radical [54] was created under similar conditions (refluxing benzene). The reaction of tributyltin hydride with bromide [55] gave only olefin as product with no detectable [35]. Thus it is very likely that [54] does not participate in the decomposition of diazene [37].

Since the decomposition of diazene [42] may also proceed via a radical intermediate, [56], to give radical [57] which might be trapped by

\[ [42] \rightarrow \quad \text{Ph} \quad \text{Ph} \quad \quad \rightarrow \quad \text{Ph} \quad \text{Ph} \quad \quad \rightarrow \quad \text{SH} \quad \text{Ph} \quad \text{Ph} \quad \]

[56] SCHEME 5 [57] [41]

radical donors (i.e., solvent), it was decided to test for the existence of [57] in this proposed reaction pathway (Scheme 5) by creating it by another route. To accomplish this, 3-bromo-2,2-dimethyl-1,1-diphenylcyclo-
butane [58] (prepared from 2,2-dimethyl-1,1-diphenyl-3-buten-1-ol, see
experimental section) was added to an excess of tributyltin hydride. Tin hydrides when employed in excess are known to trap radicals, sometimes even before facile rearrangement can occur,\(^{35}\) so cyclobutane [41] was the expected product of the reaction, possibly with some 4,4-diphenyl-1,1-dimethyl-1-butene (the observed product from rearrangement of hydrazone [39]). The only product detected, however, was 3,3-dimethyl-4,4-diphenyl-1-butene [43]. Thus radical [57] cannot be an intermediate in the reaction of hydrazone [39], since no [43] was observed in the products of its reaction.

To attempt to gain additional information of the ring-forming, diazene decomposition, the effects of increased reaction temperature were studied. Thus a solution of tosylhydrazine [38] in diethylcarbitol (DEC) was added dropwise to refluxing DEC, bp 188°. A 76% yield of 4-phenyl-1-butene [59] and cis-1-methyl-2-phenylcyclopropane [60] was detected by glpc analysis in the ratio of 28 : 72 respectively. This greatly increased quantity of cyclopropane was somewhat unexpected in view of pyrolytic reactions of allylhydrazine [13] which produced more olefin than cyclopropane at 300°. Pyrolysis in DMSO (190°) produced similar results.

However, a similar pyrolysis of [38] in refluxing quinoline, bp 237°, produced [59] and [60] in the ratio of 88 : 12 respectively. The increase in olefin content of the reaction mixture appears to be due to the fast decomposition of the diazene anion produced by bases present. This predominance of olefinic products was also demonstrated by reacting [38] with potassium ethoxide (see experimental section). These results explain the greater ratio of olefin vs. cyclopropane in the high temperature pyrolysis of hydrazone [13]. Since basic materials are present in the reaction
mixture and probably catalyze diazene decomposition by an anionic mechanism, the product is predominantly olefin.

These results suggested that allylhydrazone pyrolysis in acidic solvents may produce greater portions of cyclic products, and that perhaps even the acidic or neutral pyrolysis of tosylhydrazines might be a useful synthetic method for the synthesis of small ring compounds, especially in view of the stereoselective nature of the reaction.

It was this belief which led us to attempt the synthesis of several unsaturated tosylhydrazines. These attempts are summarized below. None

\[ \text{Ph}_2\text{CO} + \text{H}_3\text{CCH}_3 \rightarrow \text{PhHCH}_3 \rightarrow \text{PhOH} \rightarrow \text{PBr}_3 \rightarrow \text{PhN}_2\text{H}_3 \]

\[ \text{PhCH} \rightarrow \text{H}_2\text{CO} \rightarrow \text{PhOH} \rightarrow \text{PhCl} \rightarrow \text{PhN}_2\text{H}_3 \]

\[ \text{CHO} \rightarrow \text{CHOH} \rightarrow \text{OTs} \rightarrow \text{N}_2\text{H}_3 \]

\[ \text{or} \left[ \text{N}_2\text{H}_3 \right]_2 \]
of these methods were found to produce the desired tosylhydrazines in acceptable amounts.

The possibility of substituting an acetylene linkage for the olefin linkage in tosylhydrazine [38] occurred to us, and accordingly 1-(1-phenyl-1-butyn-3-yl)-2-p-toluenesulfonylhydrazine [61] was synthesized by a route similar for that of [38]. When [61] was pyrolyzed at 100° in diethylene glycol in an attempt to produce 1,1-methylene-2-phenylcyclopropane [62], a 93% yield of 4-phenyl-1-butyne [63] was isolated. It

\[ \text{Ph} \quad \text{NHTs} \quad \text{HN} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \]

\[ \text{[61]} \quad \text{[62]} \quad \text{[63]} \]

was therefore concluded that although the pyrolysis worked well to produce cyclopropanes, the method was not readily adaptable to the synthesis of cyclopropylidenes.

An additional experiment was carried out to broaden the scope of the reaction somewhat. Hydrazone [6] was photolyzed at 15° in pentane to yield diphenylmethane [9] and 4,4-diphenyl-1-butene [8] in yields of ca. 10% each, plus other unidentified volatile products. Compounds [8] and [9] are the same two products resulting from the pyrolysis of [6], however, no mechanistic correlation can be made without further experimentation. It is likely, however, that these yields may be improved substantially with appropriate changes in the photolysis conditions.

In view of the known catalytic effect of palladium complexes on at least one [3+3] sigmatropic rearrangement, an attempt at catalysis was made in the rearrangement of benzaldehyde allylhydrazone [13]. When a
small amount of a triphenylphosphine/palladium catalyst\textsuperscript{37} was heated with [13], colorful reactions occurred, but neither expected product [59] or [60] was detected by glpc analysis.

\textbf{SUMMARY}

Thus several allylhydrazones have been synthesized from readily available starting materials and pyrolyzed to yield olefins and cyclopropanes or cyclobutanes, depending on the substitution in the allylic portion of the starting material. Two examples of the rearrangement have been shown to proceed mostly or entirely with inversion at the allylic site, indicative of a concerted mechanism in competition with a higher energy radical dissociation.

Both the olefin and cyclopropane (and probably cyclobutane) products very likely arise \textit{via} a monodiazene, as evidenced by preparation of this intermediate by another route. The cyclopropane products are formed stereoselectively from the diazene intermediate by a mechanism that is not entirely clear, but many formerly reasonable mechanisms have been experimentally excluded. The favored mechanism at present is the stereoselective intramolecular addition of the diazene portion of the molecule to the olefinic portion as shown in Scheme 3. The ratio of cyclopropane products to olefin was found to increase with pyrolysis temperature. Therefore, the pyrolysis of the tosylhydrazines necessary to generate the diazene intermediate may in itself prove to be a synthetically useful method for the production of cyclic products.
In the synthesis of the above allylic hydrazones, it was discovered that hydrazine preferentially attacks allylic chlorides at the site of chlorine substitution, a result different than that predicted. In addition, the scope of the rearrangement reaction was broadened somewhat by the photolysis of one allylhydrazone which produced products similar to those found in its pyrolysis.
PART II

STUDIES ON THE SYNTHESIS OF

ASPIDOSPERMA ALKALOIDS
INTRODUCTION

Alkaloids containing the ring system [64] have been isolated from plants of the genera *Amsonia*, *Aspidosperma*, *Kopsia*, *Pleiocarpa*, *Stemmadenia*, and *Vinca* of the family Apocynaceae. Remarkable progress in the identification, synthesis, and biosynthesis of these bases has occurred within the past decade. In fact, no structure was known before 1960. Now the structures of over one hundred are known and a few have been synthesized. 38

It shall not be the purpose of this introduction to exhaustively review the chemistry of the *Aspidosperma* and related alkaloids, since this has been adequately accomplished in several recent reviews. 38 However, an attempt will be made to summarize certain important aspects of the chemistry of these alkaloids and to provide an extensive review of all previous synthetic approaches to these pentacyclic alkaloids, including some mention of biosynthetic information where appropriate.

The structure of (-)-aspidospermine [65] was nearly solved by chemical degradation, but the final solution was provided by a single crystal X-ray analysis of its methiodide 39 by optical rotary dispersion data, 40a and from infrared spectra. 40b Later another important structure, that of
vinblastine [66], a dimeric Vinca alkaloid, was solved directly by X-ray analysis. Dimeric alkaloids of this type have been found to have potent antileukemic properties, which accounts partially for the rapid advances in the chemistry of these substances.

Mass spectrometry has been relied upon heavily for structure determination of these alkaloids since the elegant work of Biemann and others. These workers found that high resolution spectra could be used to determine
the exact mass and therefore the empirical formula of the alkaloid, as well as the exact mass of each fragment ion. This data, plotted on an "element map," coupled with a knowledge of fragmentation patterns of the known pentacyclic alkaloids have led to structural identification of several of these bases, as well as to the position of substituents.

Characteristic mass spectral fragmentation of the aspidospermine-type alkaloids is shown below for deacetyl aspidospermine. However, recently a related alkaloid, vallesamidine, has also shown the characteristic P-28 and m/e 124 peaks in its mass spectrum, thus warning that caution should be exercised in assigning structures to these alkaloids.

Since the powerful physical tools mentioned above have become available, structure determination has become much less of a challenge to the organic chemist, and is now done almost routinely. Therefore, perhaps the greatest challenge lies in the development of efficient syntheses of complex compounds, especially natural products. This enables the chemist
to define new chemical methods while providing routes to materials obtainable often only in minute amounts from natural sources. The remainder of this introduction will deal primarily with the synthetic approaches to aspidospermine-like alkaloids.

Soon after the structure of aspidospermine was revealed, Stork and Dolfini completed the first synthesis. In a four step sequence from buteraldehyde, 4-ethyl-4-(2-carbomethoxy)-2-cyclohexenone [67] was obtained. Ketalization of [67] and then reaction with ammonia gave an amide which was treated with lithium aluminum hydride, acid, then base to give the bicyclic 10-ethyl-7-ketodecahydroquinoline [68]. The next ring was introduced by exposing [68] to chloroacetyl chloride followed by potassium t-butoxide. This provided ketoamide [69]. Ketalization
of this substance, followed by lithium aluminum hydride reduction and hydrolysis gave aminoketone [70]. Formation of its o-methoxyphenylhydrazone and heating it in acetic acid gave [71, \( R = OCH_3 \)], which was reduced with lithium aluminum hydride and acetylated to give (\( \pm \))-aspidospermine [65], in a minimum of 15 steps. Also, reduction of similarly prepared pentacycle [71, \( R = H \)] with potassium borohydride gave the closely related alkaloid (\( \pm \))-quebrachamine [72].

In a closely related synthesis, Ban and co-workers\(^{45}\) also synthesized [65]. Bicyclic lactam [73] was prepared by heating dinitrile [74] (from 2-butanone) with acid. Then [73] was converted into aminoketone [75] by hydrogenation, treatment with lithium aluminum hydride, and Oppenauer oxidation. This intermediate was not, however, identical to [68] prepared by Stork.
Treatment of [75] with chloroacetyl chloride and potassium t-butoxide as in Stork's synthesis yielded tricyclic material [76], also not identical with its analog [70]. However, conversion of Ban's tricyclic material into (±)-aspidospermine [65] was accomplished as before. So even though isomeric aminoketones were used, both gave the identical pentacyclic alkaloid by epimerization of at least one asymmetric center at some stage of the cyclization.

It was determined later by Ban\textsuperscript{46} that Stork's intermediate [70] possessed structure [77] and Ban's intermediate [76] had structure [78]. Both intermediates had previously been assigned incorrect stereochemistry.\textsuperscript{44,45} Thus Stork's intermediate [77] may proceed directly to

\begin{align*}
\text{[77]} & \quad \text{[78]}
\end{align*}

(±)-aspidospermine without epimerization, since it contains the required A/B cis ring fusion. Ban's intermediate [78] must undergo epimerization at the central carbon, possibly via a mechanism proposed by Stork,\textsuperscript{46} during its reaction to give (±)-aspidospermine. Ban\textsuperscript{47} has also synthesized (±)-pseudo-(C/D:trans)-aspidospermine\textsuperscript{48} from intermediate [78] by changing his acid cataylist from acetic acid to formic acid.
A unique and efficient synthesis of the pentacyclic ring system was discovered by Barton and Harley-Mason. Recognizing the similarities in the "non-tryptophan" moieties of *Aspidosperma* and *Hunteria* alkaloids, these workers devised a plan to approach both types of alkaloids from a common intermediate. Alkylation of 4-formylhexanoate [79] with allyl bromide gave methyl-4-ethyl-4-formylhept-6-enoate [80].

![Chemical Structures]

Reaction of [80] with tryptamine gave tetracyclic lactam [81]. Then treatment of [81] with boron trifluoride etherate catalyzed its rearrangement to indolenine-lactam [82] which was reduced with lithium aluminum hydride to give (±)-3-methyllaspidospermidine [83]. Thus, in six steps the pentacyclic ring system was achieved with remarkable stereoselectivity (the structure of [83] was identified by X-ray
analysis\textsuperscript{50}). In addition, these workers found that [81] could be converted in three steps to (±)-eburnamine [84].

The formation of [82] from [81] was thought to parallel somewhat the biogenetic formation of these pentacyclic bases. It has been found by feeding isotopically labeled compounds to plants that tryptamine and a C\textsubscript{9} or C\textsubscript{10} monoterpenic unit are incorporated into the alkaloids during their biogenesis.\textsuperscript{51} This proposal was made in 1961 by Thomas\textsuperscript{52} and Wenkert\textsuperscript{53} upon realizing that a monoterpenic unit was present in a variety of related alkaloids isolated from, in some cases, the same plant.

By an enormous amount of work only recently completed, it has been found, mostly by isotopic labeling experiments, that the biosynthesis of the indole alkaloids proceeds by the route shown below.\textsuperscript{51b} It was further discovered, that vincoside [85] was transformed \textit{in vivo} into the pentacyclic \textit{Aspidosperma} bases via [86] \rightarrow [88].\textsuperscript{51b}

The rearrangement of stemmadenine [87] to alkaloids of \textit{Iboga} and \textit{Aspidosperma} has been accomplished \textit{in vitro}\textsuperscript{54} by acid catalysis, although others could not repeat this work.\textsuperscript{55} Tabersonine [89], however, gave allocatharanthine [90] under similar conditions.\textsuperscript{54,55} These experiments provide analogy for the \textit{in vivo} rearrangement at the full alkaloid stage.

It was demonstrated by Kutney and Piers\textsuperscript{56} that dihydrocleavamine [91], upon mercuric acetate oxidation and subsequent reduction was converted stereospecifically into pentacyclic [92]. It was later shown that (−)-quebrachamine (−)-[72] could be converted stereospecifically to (+)-dehydroaspidospermidine [93] by oxidation with potassium permanganate\textsuperscript{57} or mercuric acetate,\textsuperscript{58} then into (+)-aspidospermidine [94].
by reduction. This cyclization has also been demonstrated for the 3-carbomethoxydihydrocleavamine.\textsuperscript{59} Thus rearrangements or reaction at the full alkaloid stage may be a useful step in alkaloid synthesis.

\[ \text{[91]} \quad \text{[92]} \]

\[ \text{[72]} \quad \text{[93]} \quad \text{[94]} \]

Kuehne and Bayha\textsuperscript{60} presented a synthesis of the tricyclic intermediate hydrolulolidine [70] of Stork's synthesis. These workers alkylated proline ethyl ester [95] with \( \gamma \)-bromoethylbutyrate to give [96] which was cyclized with sodium hydride, then hydrolyzed and decarboxylated to yield aminoketone [97]. Compound [97] was reacted with triphenylphosphine-ethylene, and the resulting amino olefin reduced, then oxidized with mercuric acetate to yield enamine [98]. This enamine was condensed with methyl acrylate to give vinylogous amide [99]. This was hydrogenated under acidic conditions to give an amino alcohol which was
oxidized to ketoamine [100]. In addition, reduction of [99] with lithium aluminum hydride gave the isomeric aminoketone [101]. Neither [100] or

[95]  [96]  [97]  [98]

[99]  [100]  [101]

[101] were the isomers used previously in the synthesis of aspidospermine, and no attempt to convert these intermediates into the full alkaloid was reported.

Soon after the conversion of quebrachamine to aspidospermidine, Kutney provided a somewhat general synthesis of the pentacyclic skeleton by preparing (±)-quebrachamine. Alkylation of ethyl γ-benzylxoxypromylmalonate with ethyl iodide, then alkaline hydrolysis gave diacid [102]. Decarb-oxylation followed by esterification gave a monoester, which when treated with triphenylmethylsodium and ethyl bromoacetate gave [103]. When succinate [103] was reacted with tryptamine, a succinimide resulted
which was reduced to pyrrolidine [104] with lithium aluminum hydride. When [104] was treated with mercuric acetate and the product treated immediately with sodium borohydride, the tetracyclic amine [105] resulted. Exposure of this amine to boron tribromide removed the benzyl group leaving an alcohol function. Treatment of the resulting amino alcohol with methanesulfonyl chloride in pyridine gave the quaternary mesylate [106] which was reduced with sodium and liquid ammonia to give (±)-quebrachamine [72]. This synthesis coupled with the previous conversion completes a 13 step synthesis of (±)-aspidospermidine. A full account of this work with some refinements has been recently published.61a

An improved synthesis using [107] instead of [103] was also communicated.61b Condensation of [107] with tryptamine gave lactam [108]
in one step. Reduction of [108] with lithium aluminum hydride gave [105]. Thus this synthesis is slightly more efficient.

In a series of reactions similar to those used to synthesize (±)-3-methyldapidospermidine [83], Harley-Mason and Kaplan [62] also synthesized (±)-aspidospermidine [94]. Conversion of their formylester [79] to its acetal and ozonolysis followed by borohydride reduction gave the hydroxyester [109]. This was reacted with tryptamine as before to


Ziegler [63] has also synthetically constructed the quebrachamine skeleton. Enamine [112], prepared in seven steps from buteraldehyde,
was alkylated with methyl bromoacetate followed by reduction to give aminoester [113]. Treatment of [113] with 3-indoyl acetyl chloride yielded amide [114]. Hydrolysis of the methyl ester and exposure of the resulting acid to polyphosphoric acid gave ketolactam [115]. This completed the quebrachamine ring system. Then [115] was reduced with lithium aluminum hydride to give 6% of (±)-quebrachamine [72] and 57% of 3,4-dehydroquebrachamine [116], which could not be reduced further to [72].63b

An entry to the Vinca bases was provided by Kutney61b by utilizing an intermediate from a previous synthesis. These workers found when salt [106] was reacted with potassium cyanide in dimethylformamide, a nitrile [117a] was produced. This product was hydrolyzed and esterified
yielding the corresponding ester, a mixture of (±)-vincadine and (±)-
epivincadine [117b]. Oxidation of [117b] gave (±)-vincadifformine [118],

\[ R = \text{CN} \quad \text{a)} \]
\[ R = \text{CO}_2\text{Me} \quad \text{b)} \]

which had properties identical to those of a natural sample. The
N-methyl analogs of [117] and [118] were also prepared.

An attempt at the synthesis of the Vinca series was made by Wenkert,
et al.\textsuperscript{64} Their reaction of chloroester [119] with methyl nicotinate
gave a salt which was hydrogenated to give the tetrahydropyridine [120].

\[ \text{[119]} \]
\[ \text{[120]} \]
\[ \text{[121]} \]

Treatment of [120] with methanolic hydrogen chloride yielded [121],
containing a vinlylogous urethane group which undoubtably stabilizes the
compound from further reaction. This species was not cyclized further to the pentacyclic ring system.

Further efforts by Wenkert and co-workers\textsuperscript{65} provided hydrolulolidine [122] of undefined stereochemistry. Alkylation of nicotinaldehyde with 5-bromo-2-pentanone ethylene ketal provided a salt which was hydrogenated to give vinylogous amide [123]. Exposure of [123] to acidic ethylene glycol provided bicyclic aldehyde [124]. Hydrolysis and aldolization gave the unsaturated ketone [125] which was hydrogenated to provide [122]. This hydrolulolidine [122], however, lacks the ethyl substitution necessary to proceed to the aspidospermidine ring system.

Following this work, a significant improvement in the synthesis of hydroquinoline [126a], an intermediate in Stork's synthesis, was reported from these laboratories.\textsuperscript{66} Piperidone [127] was benzylated and reduced
with di-isobutyl-aluminum hydride (DIBAL-H) to provide enamine [112]. Reaction of [112] with methyl vinyl ketone then gave [126b] which yielded the desired [126a] upon reductive debenzylolation. This sample was identical with that prepared by Stork. A similar hydroquinoline [128], potentially useful in the synthesis of C-21 oxygenated Aspidosperma alkaloids, was also prepared by a similar method.

Soon afterward, Harley-Mason presented a synthesis of (±)-8-oxovincatine [129], included here because of its obvious similarity to the pentacyclic alkaloids. This alkaloid was prepared by the acetate buffered reaction of 1-methyl-3-oxindolyl-ethylamine [130] with dimethyl 4-ethyl-4-formylpimelate [131] to give separable racemates. Reduction
of the lower melting racemate [129] gave a diol [132], identical with that obtained from the reduction of natural vincatine.

More recently, Ziegler and Spitzer\textsuperscript{68} prepared a \textit{Vinca} alkaloid following a pathway related closely to the proposed biogenetic pathway.\textsuperscript{51} Their reaction of 2-lithio-N-methylindole with ethyl oxalate and saponification of the product led to the acid [133]. Esterification with diazomethane, then exposure of the ester to methylenetriphenylphosphine gave acrylate [134]. Refluxing this compound with 1-benzyl-3-ethyl-

\[
\begin{align*}
\text{[133]} & \quad \text{[134]} \\
\text{[135]: a) } R &= \text{PhCH}_2 \\
\text{b) } R &= \text{H} \\
\text{[136]} & \quad 
\end{align*}
\]

1,4,5,6-tetrahydropyridine gave isomeric mixture [135a], which was converted to [135b] by reductive debenzylation. Alkylation with ethylene dibromide gave the previously synthesized\textsuperscript{61b} (±)-minovine [136] in reasonable yield.
An attempted construction of the pentacyclic skeleton was thwarted when photolysis of [137] gave only a 5 percent yield of unreactive [138]

\[
\text{[137]} \quad \text{[138]} \quad \text{[139]}
\]

instead of the desired [139]. The conjugated pyridine was unreactive toward alkylation, thus the introduction of ring E could not be effected.

A portion of these efforts were reclaimed, however, when these same workers reduced acrylonitrile [137] with sodium borohydride and hydrolyzed this nitrile to give amide [140]. Acidic hydrogenation of

\[
\text{[140]} \quad \text{[141]} \quad \text{[142]}
\]

[140] gave tetracyclic amide [141], which was treated with bromoacetyl bromide to give an intermediate bromo-diamide which cyclized in low yield to [142] upon heating in dimethylformamide/sodium bicarbonate, thus completing the pentacyclic skeleton. The authors feel that a trans-C/D ring junction is responsible for the low yield in the last step. The reductive cyclization above is quite noteworthy although this method of ring formation precludes any substitution at C-5 which is common in the natural products.
A synthesis of (±)-6,7-dehydroquebrachamine was recently completed by Ziegler and Bennett. Enol ether [143], formed from the diketone and diazomethane, was exposed to ethyl magnesium bromide and the product treated with sodium borohydride to provide the allylic alcohol [144]. This alcohol was converted into amide [145] by treatment with dimethylacetamide dimethylacetal and then reductive cleavage of the benzyl group. Reaction of [145] with β-indolylacetyl chloride as before gave [146] which was cyclized with polyphosphoric acid to [147]. This ketoamide was reacted with lithium aluminum hydride in dioxane to give dehydro derivative [148] (and some [149]) which was hydrogenated to produce (±)-quebrachamine [149].

Very recently from these laboratories, a quite different approach to the synthesis of hydrolulolidine [150] has evolved. Cyclopropane-carboxaldehyde [151] was reacted with 6-amino-3-ethyl-2-hexanone.
ethylene ketal to give cyclopropyl imine [152]. Then acid catalyzed thermolysis of [152] gave endocyclic enamine [153], which cyclized on treatment with acid, and gave keto-ester [154] on workup. Reaction of [154] with sodium methoxide caused cyclization to a diketone which was trapped with acidic methanol as a mixture of tricyclic enol-ethers, [155] and [156]. Reduction of the major isomer [156] with lithium aluminum hydride, then hydrolysis and dehydration provided enone [157]. Catalytic reduction of [157] gave the hydrolulolidine [150] which was found identical to [76], previously prepared by Ban. 46 This formally completed the synthesis of aspidospermine.

More recently, an elegant preparation of an important 41a _Vinca_ alkaloid has appeared. 73 Reaction of 1-chloro-3-ketobutene and 1-methyltryptamine gave the cis-vinylogous amide [158]. Acetylation of [158]
to eliminate internal hydrogen bonding, then heating with boron trifluoride etherate provided tetracyclic ketoamide [159]. Hydrolysis of

\[ \text{[158]} \quad \text{[159]} \quad \text{[160]} \]

[159] gave a secondary amine which condensed with acrolein to give a mixture of epimeric ketols which were dehydrated to yield the pentacyclic ketone [160]. Exposure of [160] to ethyl iodide and base led to the \( \beta,\gamma \)-unsaturated ketone [161], thus completing the desired ring system, but lacking the necessary substituents on ring C.

\[ \text{[161]} \quad \text{[162]} \]

\[ \text{[163]} \quad \text{[164]} \]
Reaction of [161] with dimethyl carbonate and sodium methoxide produced [162] which was reacted with alkaline hydrogen peroxide to give [163]. Reduction of the ketone [163] with lithium aluminum hydride and acetylation provided (±)-vindrosine [164]. This unique preparation creates the basic ring system in seven steps, and the complex alkaloid [164] in eleven, completing the first synthesis of the Vinca system with the full substitution on ring C.

(±)-Tabersonine [89] was synthesized by Ziegler using modifications of his previous syntheses. The preparation of 3-α-hydroxyethyl-5-methoxylpyridine [165] from 5-bromonicotinamide was accomplished in good yield in four steps. Reaction of [165] with benzyl chloride to form a quarternary salt, and its reductive elimination with lithium aluminum hydride gave a mixture of enol ethers [166]. Hydrolysis and reduction of the resulting enone gave allylic alcohols [157], which, upon heating with ethyl orthoacetate gave ester [168]. Debenzylation followed by reaction with 3-indoleacetyl chloride, saponification, and polyphosphoric acid treatment as before gave keto lactam [169]. Reduction of [169] with lithium aluminum hydride gave a mixture of diastereomeric amino alcohols which gave quarternary salt [170] on exposure to methane sulfonyl chloride. Treatment of this salt with
potassium cyanide in dimethylformamide gave a nitrile which was
saponified and esterified with diazomethane to provide α and β esters

[169] [170] [171]

[171]. Oxidation of the major isomer, α-ester [171], with platinum-
oxygen produced (±)tabersonine [89].
RESULTS AND DISCUSSION

In view of these many diversified syntheses of the pentacyclic alkaloids, it may at first seem presumptuous to undertake yet another synthesis. However, it was our intention to develop synthetic routes to three different alkaloid types utilizing a common intermediate, and at the same time broaden the scope of the acid catalyzed cyclopropyl imine rearrangement and annelation sequences developed in these laboratories.

The initially proposed scheme involved common intermediate, nitroenamine [172], synthesized from the rearrangement of the corresponding cyclopropyl imine. Methylation of this enamine \( R = \text{CH}_3 \) with various alkylating agents, if substitution occurred on carbon, should produce imine salt [173] which when reduced should produce an analine intermediate which should cyclize spontaneously to give [174] which contains the physostigmine skeleton. Akylation\(^{75}\) with methyl iodide would then be expected to produce deoxyseroline [175], an effective model for alkaloids of the Calabar bean.\(^{76}\)

Alternatively, acylation of enamine [172] (with \( R = \text{CH}_2\text{Ph} \) for later removal via catalytic hydrogenolysis) with methyl chloroformate would be expected to produce iminium salt [176], which upon reduction and further reaction should yield oxindole alkaloid [177]. In the event of a specific nitrogen substituent on [176], \( \text{i.e.}, R = 4\text{-oxo-3-ethyl-hexanyl (ethylene ketal)}, \) an acid catalyzed cyclization of the iminium salt should occur\(^{65}\) to give [178], a potential precursor to alkaloids of \textit{Aspidosperma}.\)
With this scheme in mind, synthesis of the required enamine [172] was undertaken. To obtain this enamine, nitroaldehyde [179] was needed.

Synthesis of 1-arylcyclopropane-1-carboxaldehydes has been accomplished by alkylating aryl acetonitriles with ethylene dibromide and various strong bases, and the product reduced with di-isobutylaluminum hydride to give the aldehydes in generally high yield.\textsuperscript{77} Thus, [180] was prepared in two steps from o-nitrotoluene by a known procedure,\textsuperscript{78} and its alkylation attempted with ethylene dibromide, using ammonia as the base,\textsuperscript{79,80} since attempts at this reaction using stronger bases have failed.\textsuperscript{81} Formation of the benzyl anion was evidenced by the formation of a deep purple color, but after stirring the reaction mixture for six hours, the starting material [180] was recovered quantitatively. Attempted reaction of [180] with ethylene glycol dimesylate in ammonia gave only recovered starting material, even at 50° in a sealed tube. Reaction of [180] with ethylene dibromide and 1,5-diazabicyclo[5.4.0]undec-5-ene in toluene at 120° gave tar formation with no starting material remaining.

After these disappointing attempts at synthesis of [179], it was decided to attempt the direct nitration of 1-phenylcyclopropanecarbonitrile [181] or 1-phenylcyclopropanecarboxaldehyde [182] in view of the known
directed ortho nitrations of phenylcyclopropane.\textsuperscript{83} Nitration of [181] with acetyl nitrate\textsuperscript{83a} at -22° gave an 85% yield of nitrated material which was composed of 1-α-nitrophenylcyclopropanecarbonitrile [183] (17%) and 1-β-nitrophenylcyclopropanecarbonitrile [184] (83%). The mixture was crystalline, and upon crystallization from methanol/water, the pure para isomer (mp 159.5-160°) was isolated. Evaporation of the filtrate yielded the impure ortho isomer (ca. 90% pure).

Since the desired isomer [183] was formed only in low yield, an alternate method was attempted. Reduction of [181] with di-isobutyl-aluminum hydride gave aldehyde [182] in high yield. Nitration of this aldehyde with acetyl nitrate again provided mostly para nitro substitution and some by-products. However, nitration of the ethylene acetal of [182] gave 68.5% ortho nitration. On workup, [179] could be obtained in a nearly pure yellow oil (see experimental section). The predominance of the ortho nitration is quite remarkable in this example, due to the highly hindered ortho positions. For comparison, nitration of t-butylbenzene provides a 1 : 8 ratio of ortho- and para-nitro-t-butylbenzenes, respectively.\textsuperscript{84a}

To account for this greatly increased ortho/para nitration ratio, steering mechanisms have been proposed.\textsuperscript{84} Hetero atoms or olefinic

\[
\begin{align*}
\text{[185]}
\end{align*}
\]
bonds may donate electrons to an incoming nitrating species forming a nitrating complex such as [185], thus directing attack at the ortho position. Methyl phenethyl ether, when nitrated with acetyl nitrate, provides the o-nitropheneethyl ether in yields of 62-66%. Thus, even though the ortho position of the cyclopropyl acetal is more hindered than in methyl phenethyl ether, a greater portion of the attack is directed to the ortho position by the two ether oxygens in the acetal.

With a sufficient quantity of the desired nitroaldehyde [179] in hand, the proposed scheme of synthesis was continued with the preparation of methyl imine [186]. This was accomplished by stirring a benzene solution of [179], methyl amine, and magnesium sulfate. The rearrangement of [186] proceeded smoothly catalyzed with ammonium iodide to give nitroenamine [187], identified by its mass spectrum and comparison of its pmr and ir spectra with other endocyclic enamines. Enamine [187] has a strong ir band at 1595 cm\(^{-1}\) compared with a band at 1613 cm\(^{-1}\) for the non-nitrated enamine. The pmr signals of these enamines differ slightly in chemical shift, the olefinic and methyl proton absorptions being shifted 0.24 ppm and 0.21 ppm downfield respectively for the nitroenamine.\(^8\)
Before proceeding with acylation or alkylation of the somewhat more precious nitroenamine, acylation was attempted using an available sample of 1-benzyl-3-phenyl-2-pyrroline [188]. Reaction of [188] with methyl chloroformate gave the N-acylation product, 1-carbomethoxy-3-phenyl-2-pyrroline, identified by its spectral characteristics (see experimental section). While this result was somewhat discouraging, the enamine [188] represents a special case, since other benzyl amines are known to debenzylate upon treatment with ethyl chloroformate. This debenzylation did, however, preclude further acylations of the nitrobenzyl pyrrole.

Acylation was then attempted with previously prepared methyl enamine [187]. Reaction of [187] with methyl chloroformate in refluxing benzene or acetonitrile, then reduction with sodium borohydride gave complex mixtures of non-basic products, indicating that N-acylation had occurred again. Only traces of an unidentified basic product were present.

Alkylation of [187] with methyl fluorosulfonate followed by sodium borohydride reduction provided 4-dimethylamino-2-(o-nitrophenyl)-1-

![Chemical structures]

[190], identified from its spectral data. The production of [189] may be explained by initial N-alkylation to give salt [190], followed by reduction and elimination.
This predominance of N- over C-alkylation in the pyrroline [187] may be explained by simply a greater electron density at nitrogen as evidenced in many cases with acyclic enamines\textsuperscript{87} or increased steric hindrance at the nucleophilic carbon, or both. Acylation of enamines, however, is normally found to result in C-acylated products, since the N-acylated products either are not stable and rearrange or react as acylating agents themselves to give C-acylated products, or C-acylation occurs directly.\textsuperscript{87} In view of the above results, the pyrrolidine enamines acylate first at nitrogen, since the N-acylated benzyl pyrroline was trapped by debenzylation before the C-acylated material could be formed. Another competing reaction of the nitroenamine [187] may be its oxidation-reduction as described by Danishefsky.\textsuperscript{88} These reactions may also explain the moderate yields in which the nitroenamines were prepared.

Since pursuit of the physostigmine and oxindole series seemed futile by these approaches in view of the N-alkylation and acylation, respectively, the approach to the \textit{Aspidosperma} series was attempted. While dealkylation may have been a problem in the acylation of [187] and [188], probably occurring by attack of chloride ion on the leaving group,

\[
\begin{align*}
\text{Cl}^- & \quad \text{R} \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{NO}_2 \\
\text{R} & = \text{CH}_2\text{Ph} \text{ or } \text{CH}_3
\end{align*}
\]

it was decided that a less activated, more hindered nitrogen substituent might prevent this dealkylation. In addition, increased hindrance about the enamine nitrogen might be predicted to shift the acylation to give C-acylated products.\textsuperscript{87} In accordance with these characteristics the
3-ethyl-2-keto(ethylene ketal)-1-hexyl imine of 1-o-nitrophenylcyclo-
propanecarboxaldehyde was prepared and rearranged to provide enamine
[191] (see experimental section). This enamine was identified by its

![Chemical Structures]

[191] [192] [193]

IR absorption at 1595 cm$^{-1}$ and its pmr olefinic proton absorption at
$\delta$ 6.67, as well as by mass spectral data.

At this point, a second possible pathway to the pentacyclic material
was envisaged. Acid catalyzed ring closure was predicted$^{65,73}$ to occur
to [191], and in fact when [191] was treated with ethereal hydrogen
chloride and a special aqueous workup$^{65}$ was employed, bicyclic compound
[192] was isolated in low yield. This compound was identified by its
pmr and mass spectrum, and by its characteristic Bohlmann bands in the
infra red at 2793 and 2732 cm$^{-1}$. The cyclization was also catalyzed
by toluenesulfonic acid in refluxing benzene, but ketal [193] was iso-
lated, in greatly improved yield however. It could be hydrolyzed in
high yield to [192] with aqueous hydrogen chloride.

Since [192] contains two carbons bearing potentially acidic hydro-
gens, the methyl carbon and the benzylic carbon, insertion of a carbonyl
fragment (see [194]) between these two carbon sites with the use of an
appropriate base and acylating agent seemed to be a facile route to the tricyclic diketone. By using this method to introduce the third ring, one does not have to rely upon the difficult C-acylation [172]-[178] as shown previously. Thus [192] was treated with dimethyl carbonate and sodium methoxide in refluxing methanol for four days. No change

\[ \text{[194]} \]

in the tlc was observed, and upon workup, 79% of the starting material was recovered. Reaction of [192] with dimethyl carbonate and sodium methoxide in dimethylformamide, or reaction with sodium methoxide in refluxing dimethyl carbonate gave mostly recovered starting material. A further experiment was performed, reacting [192] first with sodium hydride in dimethylformamide, then with methyl chloroformate. Starting material was again recovered in 63 to 85% yield, even after heating at 50° overnight.

Since numerous base/solvent systems had been utilized with no encouraging results, this method of approach was abandoned, and the aforementioned acylation was attempted. Enamine [191] was subjected overnight to methyl chloroformate in refluxing ether or tetrahydrofuran, with some disappearance of starting material as noted by the fading of the dark solution. Then hydrogen chloride was passed into the solution and this
solution was either stirred or refluxed overnight. In these reactions again, coupled with a special, mild workup procedure, the major component isolated was bicyclic material [192], indicating that no acylation had occurred, or that it was reversible. A further reaction of [191] with phosgene in tetrahydrofuran also produced some [192] as well as a small amount (2%) of a material which had an IR absorption at 1730 cm⁻¹, which is comparable to that expected for tricyclic material [194]. However, due to the frustratingly low yields and recovered bicyclic material, and due to the conception of a different route to the pentacyclic alkaloids using similar starting materials, this approach was abandoned.

The reason for the lack of reactivity of [191] and [192] towards acylating agents can very likely be summarized as hindrance at the benzylic carbon. This carbon is tertiary and has the added hindrance of an ortho nitro group on the aromatic ring. If acylation of enamine [191] occurs, it probably does so at the enamine nitrogen (although the possibility of nitro group acylation should not be overlooked). The acyl group is then very likely lost during workup or during reaction with acid to eventually yield the bicyclic ketone [192]. The same acylation/deacylation probably occurs with enamine [187], since some starting material was recovered after its reaction with methyl chloroformate.

The final scheme of proposed synthesis of the pentacyclic ring system required 1-benzyl-3-o-nitrophenyl-2-pyrrole [195] which was prepared from aldehyde [179] and benzyl amine without isolation of the intermediate benzyl imine (see experimental section). In view of the successful reaction of methyl vinyl ketone with [195] to give [196a] (work performed in these laboratories by R. Zimmerman), reaction of [195]
with propyl vinyl ketone was predicted to yield the analogous product [196b]. This bicyclic material was expected to possess a cis ring fusion

\[ \text{[195]} \]

\[ \text{[196]} \]

\[ a) \text{R} = H \\
b) \text{R} = \text{Et} \]

in view of the related reactions of methyl vinyl ketone with endocyclic enamines,\(^9\) this cis fusion being a requirement of the proposed synthesis since the pentacyclic natural products contain this same ring fusion. Reductive debenzylation of this bicyclic material should produce another bicyclic species [197] with nucleophilic centers at positions 1 and 7, ideal for introducing (stereospecifically, because of the cis ring fusion) a 3-carbon fragment to form a third ring. Bromination and dehydrohalogenation of this tricyclic ketone should give an unsaturated ketone [198] (if the nitro group remains unreduced, it may be reduced chemically at this stage.) to which the aniline nitrogen may add via an intramolecular
Michael reaction to give pentacyclic alkaloid [199] possibly in a stereospecific fashion.

The reaction of [195] with propyl vinyl ketone in refluxing acetonitrile produced a moderate yield of a yellow oil identified as [196b] by its spectral data. The ir spectrum showed a carbonyl absorption at 1710 cm\(^{-1}\) and indolizidine Bohlmann bands at 2740 and 2800 cm\(^{-1}\). The pmr spectrum shows a triplet corresponding to the terminal ethyl protons. The ir and pmr spectra are comparable to those of [133a].

**SUMMARY**

Although approaches to two of the alkaloid systems sought starting from a common intermediate have failed, the third approach to the *Aspidosperma* alkaloids seems to hold promise. By using a directed ortho nitration, the desired intermediate nitroaldehyde [179] was produced. Imine formation and rearrangement proceeded smoothly to provide the required enamines which refused to acylate as expected. However, reaction of the benzyl enamine [195] with propyl vinyl ketone has provided bicyclic intermediate [196b], which should undergo facile conversion to alkaloids of the *Aspidosperma*.
EXPERIMENTAL

Proton magnetic resonance (pmr) spectra were recorded using a Varian Associates A-60 or A-56/60 spectrometer, or a Perkin-Elmer R-12B spectrometer, using tetramethylsilane as an internal standard. All pmr absorptions are reported in the form: \( a(x, y, z) \), where \( a \) = chemical shift in parts per million downfield from tetramethylsilane, \( x \) = multiplicity, \( y \) = relative peak area, \( z \) = proton assignment. Infrared spectra were obtained on a Beckmann IR-8 spectrophotometer and ultraviolet spectra were recorded in 95% ethanol using a Bausch and Lomb Spectronic 505 instrument. Mass spectra were recorded using a Consolidated Electro-dynamics Corp. 21-110 high resolution mass spectrometer.

Analytical gas-liquid partition chromatographic (glpc) work was performed using a Perkin-Elmer Model 800 gas chromatograph equipped with a flame ionization detector and a disc integrator. Preparative glpc was performed with a Varian Areograph Model 202-1B gas chromatograph equipped with a thermal conductivity detector. Boiling and melting points are uncorrected and are recorded in degrees Centigrade. All solvents used in this work were reagent grade unless otherwise specified. Preparative layer chromatography operations employed Brinkmann precoated 20 x 20 cm plates of aluminum oxide F-254, type-T, 1.5 mm thick.

Acetone allylhydrazone [1]. According to the method of Ioffe, et al., \(^8\) acetone (7.5 g, 0.13 mole) was added dropwise under nitrogen to 8.0 g (0.11 mole) allylhydrazine with stirring, maintaining a temperature of less than 50° with external cooling. After the addition, anhyd. potassium carbonate (18 g) was added and the slurry allowed to stand
overnight. Ether was added, the slurry filtered, and the solution distilled to yield 9 g (73%) of pure [1]: b$_{30}$ 66°; [lit.$^{90}$ b$_{20}$ 56.3-56.5°]; mass spectrum (70eV) m/e 112 (parent ion), pmr (CCl$_4$) δ 5.6-6.3 (m, 1, CH), 4.85-5.3 (m, 2, =CH$_2$), 4.15 (s, 1, NH), 3.67 (m, 2, CH$_2$), 1.86 (s, 3, CH$_3$), 1.68 (s, 3, CH$_3$); ir (film) 1638 cm$^{-1}$ (C=N).

Pyrolysis of acetone allylhydrazone [1]. A 0.162 g sample of [1] and 0.153 g cyclooctane (internal standard) were added to 1.937 g triethylene glycol (TEG), Fisher-purified, and the solution sealed in a pyrex tube (0. D. 10 mm, I. D. 6 mm). The tube was then heated 3 hr at 300°±2°; cooled slowly to -80°, and opened. Noticeable pressure was released. The dark solution was poured into ca. 50 ml water and the resulting emulsion extracted with n-dodecane. Glpc analysis (Carbowax 20M (10%) on 60/80 Mesh Chromosorb P, 1/8 in x 20 ft) showed that 4-methyl-1-pentene [3] was formed in 6.1% yield, and 1,5-hexadiene [4] was formed in 5.0% yield. Trace amounts of a compound with the same retention time as 2,3-dimethylbutane were also present. No attempt at isolation of these products was made. Identification of these products was made solely on the basis of comparison of glpc retention times with those of authentic samples.

Benzophenone allylhydrazone [6]. Benzophenone (6.03 g, 0.033 mole), allylhydrazone (5.06 g, 0.082 mole), anhyd. methanol (6.2 g), and a small crystal of toluenesulfonic acid were combined and refluxed under nitrogen four days. Glpc analysis (SE-30 (20%) on Chromosorb P, 1/8 in x 3 ft) showed only ca. 75% product. One gram anhyd. sodium sulfate was added and reflux continued for 21 days, during which time the amount of product gradually
increased to 98%. The solution was filtered and distilled, yielding 6.94 g (89%) of [6]: b$_0$.5 138°; mass spectrum (70eV) m/e 236 (parent ion); pmr (CCl$_4$) δ 7.80-6.95 (m, 10, PhH), 6.23-5.55 (m, 1, CH), 5.18 (s, 1, NH), 5.2-4.82 (m, 2, =CH$_2$), 3.78 (m, 2, CH$_2$). A higher boiling solvent or a larger amount of catalyst should shorten the reaction time.

Pyrolysis of benzophenone allylhydrazone [6]. A 2.40 g (0.0102 mole) sample of [6] was added to 70 ml TEG and the mixture was heated under nitrogen for 8 hr at 300°. The resulting dark solution was poured into 500 ml water, and the emulsion was extracted with petroleum ether. The extracts were dried over calcium sulfate and the solvent removed to yield a yellow oil. The oil was chromatographed on silica gel eluting with 25% ether in petroleum ether (b 30-60°) yielding 1.32 g of a light yellow oil. Pmr analysis of the oil showed that it consisted of the following materials: 4,4-diphenyl-1-butene [8] - 0.428 g (20%), diphenylmethane [9] - 0.395 g (22%), and benzophenone - 0.536 g (20%). [The benzophenone present is probably due to hydrolysis of the starting material during the reaction (due to wet TEG) or during workup.] The oil was then subjected to preparative glpc (SE-30 (20%) on Chromosorb W-DMCS, AW, 60/80 Mesh, 1/4 in x 5 ft) at 200°. Two peaks were collected, the first was identified as diphenylmethane by comparison of its pmr spectrum and glpc retention times with those of authentic diphenylmethane (Aldrich); the second was a mixture of benzophenone and 4,4-diphenyl-1-butene [8]: pmr (CCl$_4$) δ 7.10 (s, 10, PhH), 6.0-5.3 (m, 1, =CH), 5.15-4.7 (m, 2, =CH$_2$), 3.92 (t, 1, J = 7.8 Hz, CH), 2.73 (m, 2, CH$_2$). Compound [8] was identified by comparison of its pmr spectrum with that of an authentic sample prepared from the reaction of allyl chloride with diphenylmethyl lithium,
formed by addition of n-butyllithium (Foote Mineral Company) in hexane to a molar amount of diphenylmethane in tetramethylethlenediamine (TMEDA).

**Attempted catalysis of the benzophenone allylhydrazone rearrangement.**

To determine if the pyrolysis reaction was catalyzed by acids or bases, the following experiment was conducted. Ca. 0.2 ml freshly distilled [6] containing triphenylmethane as an internal standard was added to each of four thick walled pyrex tubes, treated individually as below:

1. Washed in chromic acid, water, and ethanol, dried at 100°.
2. Washed in alcoholic potassium hydroxide, water, acetone, ethanol, dried at 100°.
3. Prepared as 1; also contained 0.1 g ammonium chloride.
4. Prepared as 2; also contained 0.1 g anhyd. potassium carbonate.

The tubes were sealed and heated at 210° for 14.5 hr, then cooled to -80° and opened and analyzed by gcpc (SE-30 (30%) Chromosorb W, 80/100 Mesh, 1/8 in x 10 ft) at 210°. Tubes 1 - 4 gave about the same results as shown below, except for 4, which gave a higher ratio of [8]/[9], and

<table>
<thead>
<tr>
<th>Tube</th>
<th>Relative Areas of Glpc Curves</th>
<th>Percent Conversion</th>
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<tr>
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<td>[8]</td>
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<tr>
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gave other unidentified volatile products. The relative glpc peak areas are approximately proportional to compound weights [see W. A. Dietz, J. Gas Chromatogr., 5, 68 (1967)].

Pyrolysis of 4,4-diphenyl-1-butene [8]. Control Experiment. A mixture of [8] and diphenylmethane [9] in a ratio of 13 : 1 was added to an excess of TEG and the solution was sealed in a pyrex tube and heated to 340° for 36 hr. The contents of the tube were analyzed after cooling by glpc. The ratio of the starting materials was unchanged.

Benzaldehyde allylhydrazone [13]. Benzaldehyde (15.9 g, 0.15 mole) was added dropwise under nitrogen to 10.5 g (0.17 mole) allylhydrazone in ca. 50 ml anhyd. ether at such a rate as to maintain a gentle reflux. During the addition, an aqueous phase separated. After the addition, the ether layer was decanted and dried over calcium sulfate, filtered, and distilled giving 19.1 g (79.5%) of [13]: \( \beta \) 0.4 89°; mass spectrum (70eV) m/e 160 (parent); pmr (CCl₄) δ 7.45-6.87 (m, 6, PhH and N=CH), 6.08-5.43 (m, 1, =CH), 5.28 (s, 1, NH), 5.23-4.82 (m, 2, =CH₂), 3.66 (m, 2, CH₂). Glpc analysis (Carbowax 20M (10%) on Chromosorb P, 1/8 in x 6 ft) indicated the liquid was comprised of two compounds, the minor compound (ca. 10%) having the shorter retention time. Presumably the mixture consists of syn and anti isomers about the C=N bond. The isomers could not be distinguished from the pmr spectrum of the mixture, since the hydrazone proton (N=CH) signals were buried in the aromatic multiplet. By analogy to other alkyldiazones, the major isomer is expected to have the phenyl and the NH-allyl group in an anti configuration.
Pyrolysis of benzaldehyde allylhydrazone [13]. A 2.3 g sample of [13] in 30 ml TEG was heated with stirring under nitrogen for 1.5 hr at 300°. The yellow solution was cooled and poured into 300 ml water, and the resulting emulsion extracted with four 70 ml portions of pentane. The combined extracts were washed once with water and dried over magnesium sulfate. The solvent was removed. Chromatography of the yellow residue on silica gel (200 g Baker activated, 60-200 mesh) and eluting with pentane gave 0.48 g of a clear hydrocarbon oil. Preparative g1pc (SE-30 (25%) on 60/80 mesh Chromosorb P, 3/8 in x 3 ft) at 145° gave 0.214 g (11%) analytically pure 4-phenyl-1-butene: mass spectrum (70eV) m/e (rel intensity) 132 (100, parent), 91 (81); pmr (CCl₄) δ 7.22 (s, 5, PhH), 6.15-5.55 (m, 1, =CH), 5.25-4.80 (m, 2, =CH₂), 2.9-2.1 (m, 4, CH₂); and 0.156 g (8.2%) analytically pure cis-1-methyl-2-phenylcyclopropane: mass spectrum (70eV) m/e (rel intensity) 132 (100, parent), 117 (94); pmr (DCCl₃) δ 7.37 (s, 5, PhH), 2.10 (m, 1, PhCH), 1.42-0.23 (m, 6, CH). The pmr spectrum of this material was identical to that of an authentic sample of cis-1-methyl-2-phenylcyclopropane.¹⁰

In an attempt to determine the maximum possible yield of the reaction under the usual conditions, 0.4122 g (0.00257 mole) of [13] and 0.1648 g (0.00103 mole) phenylcyclohexane (as an internal standard) were combined. TEG (20 ml) was added and the reaction mixture stirred under nitrogen while heating. The reaction was followed by analytical g1pc (Carbowax 20M (20%) on Chromosorb P, 1/8 in x 5 ft). After 0.5 hr, temperature had reached 280° and products had begun to form as well as a yellow color. After 3.3 hr. at a temperature of 310°, no starting material was left. The yields of products are as follows: 4-phenyl-1-butene - 28.4%, cis-1-methyl-2-phenylcyclopropane - 8.26%, and unknown material (same retention
time as toluene) - 0.97%. The solution contained less than 2\% other unidentified volatile materials, leaving ca. 60\% of the material unaccounted for, presumably in the form of high molecular weight, nitrogenous materials.

**Acetophenone allylhydrazone** [14]. A mixture of 18 g (0.15 mole) acetophenone, 9.3 g (0.15 mole) allylhydrazone, and 2 drops acetic acid in ca. 50 ml ether were refluxed in a nitrogen atmosphere with 7 g of calcium sulfate for 3.5 hr. Glpc analysis (Carbowax 20M (10\%) on Chromosorb P, 1/8 in x 6 ft) showed only 75\% acetophenone had reacted, so 5 ml excess allylhydrazone was added and the solution refluxed 13 hr. The resulting mixture was filtered, concentrated, and distilled giving 22 g (84\%) of [14]: \( b_1.2 \) 114.5-115°; mass spectrum (70eV) m/e 174 (parent ion); pmr (CCl₄) \( \delta \) 7.58-6.87 (m, 5, PhH), 6.18-5.50 (m, 1, =CH), 5.21-4.80 (m, 2, =CH₂), 4.63 (s, 1, NH), 3.76 (m, 2, CH₂), 2.07 (s, 0.27 syn-CH₃), 1.88 (s, 2.73, anti-CH₃). Again glpc analysis showed two components in the solution, the smaller fraction having the lower retention time. The pmr spectrum of the solution showed singlets at \( \delta \) 1.88 and \( \delta \) 2.07 for the methyl group in the integrated ratio of 91 : 9 respectively. These were probably due to isomers about the C-N bond, the larger signal due to the more stable isomer with the methyl and the NH-allyl group in a syn configuration. Upon heating the mixture of isomers under nitrogen at 140° for 8 hrs, the ratio of syn to anti changed from 91 : 9 to 97 : 3, indicating that isomerization had occurred about the C-N double bond to give a larger portion of the more stable isomer. No nitrogen elimination products were detected.
Pyrolysis of acetophenone allylhydrazone [14]. A 3.5384 g sample of [14] and 0.0307 g hydroquinone were combined in a flask equipped with an air cooled reflux condensor and a nitrogen atmosphere. TEG (76.9 g) was added and the solution stirred and heated with increasing temperature over 2 hr (maximum temperature ca. 340°). After cooling, the system had lost 0.2323 g which corresponds to 41% of the available nitrogen. Glpc (Carbowax 20M (20%) on Chromosorb P, 1/8 in x 5 ft) showed 2 peaks and a trace of starting hydrazone as the only volatile materials. The dark reaction mixture was added to 400 ml water and the resulting emulsion was extracted with pentane. The pentane extracts were washed with 15% sodium hydroxide solution, then dried over magnesium sulfate and the solvent removed to give 0.285 g of a yellow oil. The oil was subjected to preparative glpc (SE-30 (25%) on Chromosorb P, 3/8 in x 3 ft) at 150°. The two peaks that had retention times close to that expected for 4-phenyl-1-pentene were collected, and pmr and mass spectra were recorded of each. Neither sample was the desired 4-phenyl-1-pentene. One had a molecular weight of 132, the other 181. No vinyl proton absorptions were present in the pmr spectrum of either compound.

Trimethylacetaldehyde diallylhydrazone [15]. To 100 ml saturated sodium carbonate solution was added 25 g (0.16 mole) of the sodium bisulfite addition compound of trimethylacetaldehyde (Aldrich). The mixture was stirred 0.5 hr and extracted three times with ether. The extracts were combined and dried over calcium sulfate. Then 2 drops glacial acetic acid were added, followed by dropwise addition 15.5 g (0.14 mole) unsym-diallylhydrazine with stirring under nitrogen. The reaction mixture was allowed to stand one hr over calcium sulfate, then filtered and
distilled to yield 10.5 g (37%) of [15]: b$_{30}$ 95.5°; mass spectrum (70eV) m/e 180 (parent ion); pmr (CCl$_4$) δ 6.42 (s, 1, NCH), 6.04-5.38 (m, 2, =CH), 5.18-4.78 (m, 4, =CH$_2$), 3.56 (m, 4, CH$_2$), 1.04 (s, 9, CH$_3$).

Pyrolysis of trimethylacetaldehyde diallylhydrazone [15]. A 1.60 g sample of [15] was mixed with 70 ml TEG and heated under nitrogen in a flask equipped with a reflux condensor at 260° for 10.5 hr. The resulting dark solution was poured into ca. 500 ml water and the emulsion extracted three times with petroleum ether (b 20-40°). The extracts were dried and the solvent removed yielding a yellow oil. Column chromatography on silica gel eluting with petroleum ether gave a colorless mixture of hydrocarbons. Preparative glpc (TCEP (15%) on 60/80 Mesh Chromosorb P, 3/8 in x 9 ft) at 115° yielded 0.044 g (3.25%) of 4-tert-butyl-1,6-heptadiene: mass spectrum (703V) m/e (rel intensity) 152 (2, parent), 95 (100), 57 (93), 41 (93); pmr (CCl$_4$) δ 0.93 (s, 9, CH$_3$), 1.23 (m, 1, CH), 2.06 (m, 4, CH$_2$), 4.65-5.06 (m, 4, =CH$_2$), 5.37-6.07 (m, 2, =CH-).

Reaction of phenyllithium with 3,3-dimethylcyclopropene. A 3 g sample of 3,3-dimethylcyclopropene (prepared according to Closs, et al., 91) was added dropwise to 95 ml 0.74 N phenyllithium (from bromobenzene) in ether under nitrogen at 0°. The reaction mixture was stirred 3 hr and warmed to room temperature, then hydrolyzed cautiously by the addition of water. The resulting ether layer was separated and dried over magnesium sulfate. The solvent was removed and the resulting oil subjected to preparative glpc to yield 1,1-dimethyl-2-phenylcyclopropane: micro bp 196°, pmr (CCl$_4$) δ 0.75 (s, 3, CH$_3$-cis to phenyl), 0.5-1.0 (m, 2, CH$_2$), 1.17 (s, 3, CH$_3$-trans to phenyl), 1.80 (m, 1, CH), 6.85 (s, 5, PhH).
Pyrolysis of benzaldehyde β-methylallylhydrazone [19]. A 3.0 g sample of [19] and 13 ml TEG were combined and heated with stirring under nitrogen at 300° for 45 min in a flask equipped with a reflux condensor. After cooling, a light brown, two-phase mixture resulted. Glpc analysis (Carbowax 20M (10%) on Chromosorb P-AW, 80/100 Mesh, 1/8 in x 5 ft) showed that no starting material remained, and that two materials were present which had retention times between ethylbenzene and phenylcyclohexane. No other volatile materials were present in significant amount. The reaction mixture was poured into 300 ml water, and the resulting emulsion extracted three times with 75 ml portions of pentane. The solvent was removed and the material was chromatographed on silica gel (Baker 60/200 Mesh) eluting with petroleum ether (b 34-59°). The two materials were only partially separated. The solvent was removed and the resulting solution was subjected to preparative glpc (Carbowax 20M (30%) on Chromosorb P, 60/80 Mesh, 3/8 in x 10 ft) at 210°. The two compounds were collected. The compound of lower retention time was identified as 1,1-dimethyl-2-phenylcyclopropane by comparison of its pmr spectrum with that of a sample prepared from 3,3-dimethylcyclopropene, and by its mass spectrum (70eV) m/e (rel intensity) 146 (52, parent), 131 (100). The compound of greater retention time was identified by its pmr spectrum as 2-methyl-4-phenyl-1-butene: (CCl₄) δ 1.67 (m, 3, CH₃), 2.0-2.3 (m, 2, -C=CH₂), 2.5-2.8 (m, 2, PhCH₂); 4.54 (m, 2, -CH₂), 6.87 (s, 5, PhH).

α,ω-Dimethylallylhydrazone [24]. Water (9 g, 0.5 mole) and 16 g (0.5 mole) hydrazine (Matheson, Coleman, and Bell; Ahydrous, 97%+) were combined in a 100 ml flask equipped with a nitrogen atmosphere, and
mechanical stirrer, and cooled with an ice bath. Then 7.1 g (0.068 mole) \(\alpha,\alpha\)-dimethylallylchloride\(^{92}\) was added dropwise over 0.5 hr with vigorous stirring, maintaining a temperature of ca. 0°. The reaction mixture was stirred for 2 hr at 0°. Two phases resulted. The heterogeneous mixture was then stirred 0.5 hr at 50°, cooled, and extracted with ether. The ether extract was distilled yielding 2.4 g (35%) \(\alpha,\alpha\)-dimethylallylhydrazine: \(b\)\(_{30} 57-58^\circ\); \(\text{p}M\) \((\text{CCl}_4) \delta 1.2 (s, 6, \text{CH}_3), 2.85 (s, 3, \text{NH}), 4.8-5.2 (m, 2, \text{CH}_2), 5.4-5.9 (m, 1, \text{CH}), \text{ir} \) (see spectral section), and 1.45 g (21%) \(\gamma,\gamma\)-dimethylallylhydrazine: \(b\)\(_{30} 84-85.5^\circ\); \(\text{p}M\) \((\text{CCl}_4) \delta 1.69 (d, 3, \text{CH}_3, J < 1 \text{ Hz}), 1.75 (d, 3, \text{CH}_3, J = 1 \text{ Hz}), 3.03 (s, 3, \text{NH}), 3.26 (m, 2, \text{CH}_2), 5.19 (m, 1, \text{CH}).

3-Chloro-3,3-dideuterio-2-methyl-1-propene [25]. According to the procedure of Welch,\(^{13}\) freshly distilled thionyl chloride (14.3 g, 0.12 mole) was added dropwise over 2.5 hr to a solution of 7.9 g (0.11 mole) 1,1-dideuterio-2-methyl-2-propen-1-ol\(^{18}\) in 24 g (0.13 mole) tri-n-butylamine and 24 ml di-n-butylether. During the addition and for 45 min after addition, a temperature of -20 to -30° was maintained. Upon warming the mixture to room temperature, the yellow mixture turned to dark green. The mixture was vacuum distilled through a short path column for 3 hr at 12 mm, using a receiver cooled in liquid nitrogen. The thawed distillate was then washed with 100 ml of cold 3% sodium carbonate solution, then dried over calcium sulfate. Distillation yielded 6 g (60%) of [25]: \(b\) 72-76°; \(\text{p}M\) (neat) \(\delta 4.7 (m, 2, =\text{CH}_2), 1.7 (m, 3, \text{CH}_3).\)

\((1,1\text{-Dideuterio-2-methyl-2-propenyl})\) hydrazine [27]. To a solution of 18 g (1 mole) water and 32 g (1 mole) hydrazine (Matheson, Coleman,
and Bell; Anhydrous, 97%+) maintained at 40° was added 6.0 g (0.065 mole) of [25] with vigorous stirring over 1.5 hr. Then the solution was stirred 1 hr at 80°. The resulting solution was extracted with ether continuously overnight. The ether extract was distilled giving 4.2 g (74%) of [27]: b 141-144°; pmr (neat) δ 4.70 (m, 2, =CH₂), 3.20 (s, 3, NH), 1.66 (t, 3, J = 1 Hz, CH₃).

Benzaldehyde (1,1-dideuterio-2-methyl-2-propenyl) hydrazone [28].
Benzaldehyde (2.75 g, 0.025 mole) was added dropwise over 45 min to 2.00 g (0.023 mole) [27] in 25 ml anhyd. ether. The ether phase was then decanted from the aqueous phase and dried over 4.5 g barium oxide. The solution was filtered and distilled giving 2.9 g (73%) of [28]: b 0.15 86°; pmr (neat) δ 7.42-6.80 (m, 6, PhH and N=CH), 5.50 (s, 1, NH), 4.70 (m, 2, =CH₂), 3.52 (m, 0.04, NCHD), 1.60 (m, 3, CH₃). The pmr spectrum showed the compound to be 98% dideuterated at the 1-position. A sample of non-deuterated material was prepared via the same route.

Pyrolysis of benzaldehyde 1,1-dideuterio-2-methyl-2-propenyl hydrazone [28]. The pyrolysis was conducted in a similar fashion to that of benzaldehyde β-methylallylhydrazone [19]. The materials isolated were as follows: ca. 0.1 g (4%) 1-cis-dideuteriromethyl-1-trans-methyl-2-phenyl-cyclopropane [30]: pmr (CCl₄) δ 6.88 (s, 5, PhH), 1.82 (m, 1, PhCH, J = 6 and 8 Hz), 1.19 (s, 3, CH₃), 0.80 (s, 1, CD₂H), 0.86-0.68 (m, 2, CH₂), and ca. 0.1 g (4%) 1,1-dideuterio-2-methyl-4-phenyl-1-butene [29a]: pmr (CCl₄) δ 6.9 (s, 5, PhH), 4.56 (m, 0.21, =CHD), 2.05-2.30 (m, 1.84, =C-CH₂), 2.50-2.84 (m, 2.00, PhCH₂), 1.68 (s, 3, CH₃). The amount of deuterium (1.79) at the vinyl position corresponds to 1.79/1.96 x 100 = 91.4% of that possible (1.96 is the maximum amount of deuterium possible
at the vinyl position (98% x 2 = 1.96), since the starting material was 98% deuterated. The amount of deuterium (0.16) at the allylic position corresponds to 8.16% of the maximum. This accounts for 99.6% of the starting deuterium. The accuracy of the integration for the spectrometer is specified at 2%.

1-Phenyl-3-buten-1-ol. Allylmagnesium bromide was prepared\textsuperscript{93} from 75 g (0.57 mole) allylbromide and 35 g (1.45 mole) magnesium turnings. Then 50 g (0.47 mole) benzaldehyde was added with stirring and cooling over 0.5 hr. Then the mixture was refluxed 0.5 hr, cooled, and 100 ml saturated ammonium chloride solution was added with cooling and stirring. This mixture was stirred overnight. The ether solution was decanted, the solvent removed, and the residue distilled yielding 58.4 g (84%) of analytically pure 1-phenyl-3-buten-1-ol: b$_1$ 80.5-81.0°; pmr (CCl$_4$) δ 7.17 (s, 5, PhH), 6.02-5.34 (m, 1, =CH), 5.14-4.74 (m, 2, =CH$_2$), 4.47 (m, 1, OCH), 3.51 (s, 1, OH), 2.32 (m, 2, CH$_2$).

4-Bromo-4-phenyl-1-butene. In a procedure similar to that of Hwa and Sims,\textsuperscript{94} 58.4 g (0.394 mole) 1-phenyl-3-buten-1-ol was added dropwise over 2 hr to a stirred solution of 45 g (0.165 mole) phosphorous tribromide and 1 drop of 48% HBr at 10 to 15°. The mixture was then stirred overnight at room temperature. The upper phase was separated and washed 3 times each with 40 ml portions each of ice water, cold 5% sodium bicarbonate solution, ice water. The solution was then dried over calcium chloride, filtered through Celite to remove cloudiness, yielding 75.9 g (91.5%) of 4-bromo-4-phenyl-1-butene which was nearly pure according to its pmr spectrum. The bromide was distilled to yield
analytically pure material: \( b_{2.1} 84-85^\circ; \text{pnmr (CCl}_4\) \( \delta 7.25 \) (m, 5, PhH), 6.05-5.41 (m, 1, =CH), 5.27-4.85 (m, 2, =CH\_2), 4.86 (t, 1, BrCH, \( J = 7.5 \) Hz), 2.92 (m, 2, CH\_2).

1-Phenyl-3-butynylhydrazine. Hydrazine (36.5 g, 1.14 mole) and water 20.5 g (1.14 mole) were stirred vigorously at 38\(^\circ\) under nitrogen while 30 g (0.142 mole) 4-bromo-4-phenyl-1-butene was added dropwise over 1.25 hr, maintaining the temperature at 38\(^\circ\). After the addition, the stirred reaction mixture was heated at 80\(^\circ\) for 0.5 hr, then stirred overnight at room temperature. The two-phase mixture was then extracted 3 times with 50 ml ether after 40 ml of 40\% sodium hydroxide was added. The solvent was then removed and the residue distilled yielding 13.7 g (60\%) of 1-phenyl-3-butynylhydrazine: \( b_{1.2} 86-89^\circ; \text{pnmr (CCl}_4\) \( \delta 7.21 \) (s, 5, PhH), 6.05-5.38 (m, 1, =CH), 5.16-4.74 (m, 2, =CH\_2), 3.55 (t, 1, NCH, \( J = 6.8 \) Hz), 3.05 (s, 3, NH), 2.33 (m, 2, CH\_2).

Oxidation of 1-phenyl-3-butynylhydrazine with mercuric oxide. To a stirred slurry of 1.51 g (0.007 mole) red mercuric oxide and 2 g sodium sulfate and 25 ml dry benzene at 0\(^\circ\) under nitrogen was added dropwise 0.250 g (0.00154 mole) of 1-phenyl-3-butynylhydrazine in 10 ml dry benzene, according to the procedure of Al-Sader and Crawford.\(^{21}\) After the addition, the slurry was stirred at room temperature overnight. A dull orange powder resulted in the solution. GLpc (Carbowax 20M (10\%) on 60/80 Mesh Chromosorb P, 1/8 in x 20 ft) showed that both 4-phenyl-1-butene and cis-1-methyl-2-phenylcyclopropane were formed in a ratio of ca. 4 : 1 in small amounts, as well as other compounds of higher retention time. Isolation of the compounds was not attempted, and they were identified only by
comparison of their glpc retention times with those of the authentic materials.

1-(1-Phenyl-3-butenyl)-2-p-toluenesulfonylhydrazine \([38]\). In a procedure similar to that used by Cram and Bradshaw,\(^{30}\) 4.0 g (0.0247 mole) of 1-phenyl-3-butenylhydrazine in 80 ml dry pyridine was stirred at 0° under nitrogen while 4.7 g (0.0247 mole) \(p\)-toluenesulfonylchloride (recrystallized from chloroform/petroleum ether) in 40 ml dry pyridine was added dropwise over 1.25 hr. The reaction mixture was then allowed to warm to room temperature and poured into 870 ml cold 3 N hydrochloric acid. An orange solid precipitated which was collected by suction filtration. The solid was dissolved immediately in 300 ml ether, and the solution washed with saturated sodium bicarbonate solution. The ether solution was decolorized with Norite, then dried overnight over sodium sulfate. The solution was then filtered and solvent removed until crystals began to form. Then 200 ml pentane was added and the crystals were collected by filtration and washed with pentane, yielding 3.67 g (47%) of cream-colored crystals. Recrystallization from ether/pentane yielded needles of \([38]\): mp 119-119.5° (with bubbling), pmr (DCC\(_3\)) \& 7.52 (m, 4, ArH), 7.20 (m, 5, PhH), 5.83 (s, 1, SO\(_2\)NH), 5.3-6.0 (m, 1, =CH), 4.8-5.2 (m, 2, =CH\(_2\)), 3.77 (t, 1, NCH, \(\delta = 7\) Hz), 3.33 (s, 1, CNH), 2.43 (s, 3, CH\(_3\)), 2.33 (m, 2, CH\(_2\)). The two separate absorptions at different chemical shifts due to protons attached to nitrogen indicate that the protons are bonded to different nitrogen atoms.\(^{30}\)

Pyrolysis of 1-(1-phenyl-3-butenyl)-2-p-toluenesulfonhydrazine \([38]\).

A. In ethylene glycol. Dry nitrogen was bubbled through 50 ml ethylene glycol overnight to remove oxygen, then 1.00 g (0.00316 mole) of \([38]\) was
added and stirring begun. The solid did not dissolve until the flask was partially immersed in a bath of boiling water whereupon within 3 min, all of the solid has dissolved. The dissolving of the solid was accompanied by frothing due to evolving gas. After 5 min, bubbling had slowed and 67 ml gas had been collected in an inverted cylinder filled with water. After 2 hr of heating, 70 ml (99% of theory) of gas had been collected, and a light yellow solution resulted. The cooled solution was poured into 400 ml water, and the resulting emulsion extracted three times with 75 ml pentane. The pentane solution was dried, the solvent removed, and the resulting oil was chromatographed on a 20 x 1.5 cm column of silica gel, eluting with hexane. The hexane was removed yielding 0.228 g of a colorless oil. Pmr and glpc analysis showed that the oil was a mixture of 0.187 g (45%) 4-phenyl-1-butene [59] and 0.041 g (9.8%) cis-1-methyl-2-phenylcyclopropane [60].

B. In benzene. A 0.200 g (0.00633 mole) sample of [38] was dissolved in 10 ml dry benzene, and 0.043 g phenyl-n-propyl ether and 0.038 g mesitylene were added as internal standards. The reaction mixture was heated to reflux in a nitrogen atmosphere, collecting the evolving gas. After 1.2 hr 13 ml of nitrogen had evolved. Reflux overnight produced a total of 13.2 ml of nitrogen (93%). Glpc analysis (Carbowax 20M (10%) on 60/80 Mesh Chromosorb P, 1/8 in x 20 ft) showed the reaction had formed 0.044 g (52%) of 4-phenyl-1-butene [59] and 0.0041 g (5%) of cis-1-methyl-2-phenylcyclopropane [60].

C. In acetic acid. A 0.057 g (0.00018 mole) sample of [38] was dissolved in 8 ml glacial acetic acid and stirred in a flask under nitrogen. The flask was immersed in a water bath (80-100°) and stirred 1 hr as nitrogen slowly evolved. The reaction mixture was then poured into cold
3 N sodium hydroxide solution and extracted with ether. Gopc analysis of
this ether solution showed [59] and [60] as the only products in a
ratio of 91 : 9 respectively.

D. In ethanol/potassium ethoxide. To 10 ml absolute ethanol and
0.0437 g phenyl-n-propyl ether as an internal standard under nitrogen
was added 0.032 g (0.00088 mole) potassium. A 0.23 g (0.00073 mole)
sample of [38] was added and the stirred solution was heated to reflux
until no more nitrogen evolved (1.25 hr). Then the cooled reaction mix-
ture was poured into 400 ml water and extracted with pentane. Gopc analy-
ysis of the pentane solution showed that 0.099 g (103%) 4-phenyl-1-butene
was the only product.

Benzophenone 1,1-dimethyl-2-propenylhydrazone [39]. A 2.0 g (0.02
mole) sample of ß,ß-dimethylallylhydrazone [24] and 3.5 g (0.019 mole)
benzophenone were combined and 10 ml anhyd. methanol and 4 drops glacial
acetic acid were added. The solution was refluxed under nitrogen. After
19 hr, gopc analysis showed only 50% reaction. The solvent was replaced
with n-propanol, then the solution refluxed for 24 hr. The solvent was
removed and the residue chromatographed on a silica gel column eluting
with 25% ether/petroleum ether. A fraction was obtained containing 0.57 g
benzophenone and 3.26 g (62%) of [39]: pmr (CDCl₃) δ 7.47-6.90 (m, 11, PhH
and N=CH), 6.12-5.65 (m, 1, =CH), 5.10-4.70 (m, 2, =CH₂), 1.24 (s, 6, CH₃).

Pyrolysis of benzophenone 1,1-dimethyl-2-propenylhydrazone [39].
A 1.7 g sample of [39] containing 0.25 g benzophenone was added to 25 ml
TEG (dried and freshly distilled) and the solution heated under nitrogen
to 250°. The reaction was monitored by analytical gopc (SE-30 (30%) on
Chromosorb P, 80/100 Mesh, 1/8 in x 10 ft). After 7 hr, over half of the starting hydrazone had disappeared. After 46 hr, no detectable hydrazone remained. The reaction mixture was then poured into 300 ml water and the resulting emulsion was extracted with pentane. Removal of the solvent gave 1.38 g of a yellow oil which was chromatographed on 400 g silica gel eluting with petroleum ether (b 30-60°). Three compounds were separated. The compound first off the column had the same retention time (glpc) and the same R_f on the tlc (silica gel) as diphenylmethane and also showed the characteristic pmr absorption of δ 3.78. The next compound 0.239 g (18%) was identified as 1,1-dimethyl-2,2-diphenylcyclobutane [41]: mass spectrum (70eV) m/e (rel intensity) 236 (35, parent), 193 (100), 180 (91); pmr (CCl_4) δ 7.13 (m, 10, PhH), 0.7-1.7 (m, 4, CH_2), 0.96 (s, 6, CH_3). The third compound isolated was 0.288 g (22%) of 5,5-diphenyl-2-methyl-2-pentene [40]: pmr (CCl_4) δ 1.49 (m, 3, CH_3), 1.55 (m, 3, CH_3), 2.71 (m, 2, CH_2), 3.90 (t, 1, CH, J = 7.5 Hz), 5.08 (m, 1, =CH), 7.10 (s, 10, PhH).

**Reaction of 4-bromo-4-phenyl-1-butene [55] with tri-n-butyltin hydride.** A 1.34 g (0.0064 mole) sample of freshly distilled [55] and 8 ml benzene (freshly distilled from lithium aluminum hydride) were stirred under nitrogen while 1.94 g (0.0067 mole) tri-n-butyltin hydride in 5 ml dry benzene was added at room temperature over 20 min. The solution was then stirred at room temperature for 4.5 hr, then 0.01 g benzoyl peroxide was added and the solution was refluxed overnight.

The benzene was removed by distillation and the residue was subjected to preparative glpc (Carbowax 20M (30%) on Chromosorb W, 60/80 Mesh,
3/8 in x 10 ft). An analytically pure 0.56 g (66%) sample of 4-phenyl-1-butene was obtained. This was the only detectable volatile product by prn and glpc analysis.

The experiment was repeated as above, but at benzene reflux initially. Again only 4-phenyl-1-butene was detected, comprising >99% of the products.

**Pyrolysis of 1-(1-phenyl-3-butenyl)-2-tosylhydrazine [38] at increased temperatures.** Since injection of ether solutions of [38] into the heated injector port (200°) of the gas chromatograph produced 4-phenyl-1-butene [59] and cis-1-methyl-2-phenylcyclopropane [60] in a lower ratio than in previous experiments, an attempt was made to duplicate these results on a useful scale. The following experiments were conducted:

A. **In ether.** To 50 ml of dry TEG at 200° was added dropwise a solution of 0.25 g of [38] in 25 ml ether. Nitrogen was passed over the reaction mixture during the reaction, and ether was allowed to escape through a water cooled condensor. As the concentration of [38] built up in the hot solution, small explosions occurred after a few seconds, so the addition rate was controlled to avoid a large accumulation of [38]. After the addition and cooling, the solution was poured into 300 ml water and extracted with pentane. Glpc analysis (Carbowax 20M (10%) on Chromosorb P, 60/80 Mesh, 1/8 in x 20 ft) showed only two products, [59] and [60] in the ratio of 1 : 2, respectively.

B. **In diethylcarbitol (DEC).** A solution of 0.1346 g of [38] in 10 ml dry DEC (distilled from and stored over sodium) was added dropwise under nitrogen with stirring to 15 ml refluxing DEC (188°) over 0.5 hr. After the addition, the solution was cooled and 0.0587 g of durene was added as an internal standard. The only two products present by glpc analysis
were [59], 21% and [60], 55% of the theoretical yield. Two other products of lower retention time than the above compounds were present, but no attempt was made at isolation.

C. In dimethylsulfoxide (DMSO). 0.291 g (0.00092 mole) of [38] was dissolved in 10 ml anhyd. DMSO and the solution added dropwise over 15 min through a reflux condensor to ca. 50 ml refluxing DMSO (190°). Durene was added as an internal standard after the solution was cooled. Glpc analysis revealed that [59] and [60] were produced in a 1:3 ratio respectively in a combined yield of 63%. In a similar experiment starting with 2 g of [38], [60] was isolated after the pyrolysis by pouring the cooled DMSO solution into a large excess of water and extracting with pentane. The pentane was removed and the residue subjected to preparative glpc at 145° (30% Carbowax 20M on 60/80 Mesh Chromosorb W, 3/8 in x 10 ft). Pmr analysis of the purified cyclopropane indicated that it was >97% cis-1-methyl-2-phenylcyclopropane.

D. In quinoline. A 0.0958 g sample of [38] was dissolved in 10 ml of quinoline and the solution was added dropwise with stirring under nitrogen to refluxing quinoline (237°). Durene was employed as an internal standard. Only two materials were present by glpc analysis: [59] in 55% and [60] in 7.8%.

2,2-Dimethyl-1,1-diphenyl-3-buten-1-ol. γ,γ-dimethylallyl chloride (12.6 g, 0.12 mole) in 50 ml dry ether was added dropwise under nitrogen with stirring to 24.3 g (1.0 mole) magnesium turnings in 100 ml dry ether with a crystal of iodine to initiate the reaction. The reaction bath was maintained in a 0° cooling bath over the addition period of 7 hr. Then the reaction mixture was stirred overnight at 0°, then heated to reflux
for 0.5 hr. Benzophenone (16.5 g, 0.091 mole) in 25 ml dry ether was added over 1.25 hr with ice bath cooling. After the addition the reaction mixture turned yellow on refluxing for 30 min. After cooling, ca. 20 ml saturated ammonium chloride solution was added with stirring and cooling. The ether solution was decanted and the solvent removed to yield a colorless oil identified by pmr as mostly 2,2-dimethyl-1,1-diphenyl-3-buten-1-ol. Tlc on silica gel eluting with benzene showed three spots: one minor spot with the same Rf as benzophenone, another with a much higher Rf which was likely comprised of C5H9 dimers, and the third, the desired product. A 4 g sample of the mixture was chromatographed on 400 g silica gel eluting with benzene to obtain 2.7 g of the alcohol: pmr (CCl4) δ 7.65-7.0 (m, 10, PhH), 6.48-6.02 (m, 1, CH), 5.32-4.94 (m, 2, CH2), 2.32 (s, 1, OH), 1.15 (s, 6, CH3).

3-Bromo-2,2-dimethyl-1,1-diphenylcyclobutane. To a solution of 1.22 g (0.0045 mole) phosphorus tribromide and 1 drop 48% HBr cooled to 10-15° was added dropwise with stirring 2.7 g (0.0106 mole) 2,2-dimethyl-1,1-diphenyl-3-buten-1-ol over 0.5 hr. Then the mixture was stirred at room temperature overnight. The resulting crystalline mass was dissolved in ether, and the solution washed with ice water, 5% sodium bicarbonate, and water. The solvent was removed to yield 3.5 g crude material which solidified on standing at -10°, and remained solid on warming. Preparative tlc on silica gel was attempted, eluting with benzene. Two compounds were extracted from the plate support with refluxing ether, but each gave the same two spots on tlc. Apparently the compound isomerizes on silica gel or on heating. Vacuum sublimation of the crude material was attempted to give a white crystalline material, but tlc produced results similar to
those above. A reasonably pure sample of the sublimed material showed
the following data: mp 76.5-79°; pmr (CCl₄) δ 7.2 (m, 10, PhH), 3.63
(m, 1, CH₂, J = 10, 7 Hz), 3.23 (m, 1, CH₂, J = 10, 8 Hz), 1.85 (m, 1,
CHBr, J = 7, 8 Hz), 1.20 (s, 3, CH₃), 1.01 (s, 3, CH₃). From its pmr
spectrum and reactions, the structure was assigned as 3-bromo-2,2-dimethyl-
1,1-diphenylocyclobutane.

Attempted reaction of hydrazine with 1-bromo-2,2-dimethyl-3,3-diphenyl-
cyclobutane. A 0.26 g sample of the bromocyclobutane was found to be
insoluble in 0.1 mole hydrazine hydrate, and no apparent change occurred
on stirring overnight. Then 1 ml pyridine was added to dissolve the
cyclobutane and the reaction mixture was stirred two days at room tempera-
ture. After adding the reaction mixture to 50 ml 10% potassium hydroxide
solution, the resulting mixture was extracted with ether. The ether
extracts were washed with water (100 ml), saturated sodium chloride solu-
tion, and dried over sodium sulfate. When the solvent was removed, only
starting material was present by pmr analysis.

Reaction of 3-bromo-2,2-dimethyl-1,1-diphenylocyclobutane with tri-n-
butyltin hydride. A 0.298 g (0.00095 mole) sample of 3-bromo-2,2-dimethyl-
1,1-diphenylocyclobutane was dissolved in 15 ml dry benzene. Then 0.338 g
(0.00116 mole) tri-n-butyltin hydride in 5 ml benzene was added dropwise
with stirring under nitrogen. The reaction mixture was stirred at room
temperature overnight. Then 0.01 g benzoyl peroxide was added and the
solution was refluxed 4 hr. The solvent was removed and the colorless
oil was chromatographed on a 20 x 2 cm column of silica gel eluting with
hexane. A pmr spectrum of the 0.488 g recovered showed a 1:1 mixture
of tri-n-butyltin bromide and 3,3-dimethyl-4,4-diphenyl-1-butene [43]:

$$^{1}$$H NMR (CCl₄) δ 7.47 (m, 10, PhH), 6.31-5.84 (m, 1, -CH), 5.15-4.74 (m, 2, =CH₂), 3.76 (s, 1, CH), 1.06 (s, 6, CH₃), 2.45-0.5 (m, 27, Bu₃SnBr).

The mixture was not conveniently separable using chromatographic methods. The amounts of material recovered corresponds to an 85% yield of each.

The experiment was repeated in a similar fashion except a solution of the bromocyclobutane in benzene was added dropwise over 15 min under nitrogen to a three-fold molar excess of tri-n-butyltin hydride heated by a boiling water bath with no added benzoyl peroxide. The reaction mixture was then cooled to room temperature and allowed to stand for three days. The solvent was removed, and the pmr spectrum of the reaction mixture revealed that the only products were again [43] and tri-n-butyltin bromide.

**1-Phenyl-3-butyne-1-ol.** According to a slight modification of the procedure of Gaudemar,⁹⁶ 50 g (2 mole) of magnesium turnings were placed in a flask under nitrogen and covered with dry ether. About 0.1 g mercuric chloride and 1 g propargyl bromide were added, and the reaction mixture stirred until the reaction had begun. Then 59 g (0.50 mole) propargyl bromide (dried over calcium chloride) in 150 ml dry ether was added dropwise over 5 hr. Then the reaction mixture was stirred overnight, cooling with an ice bath. Then 53 g (0.5 mole) benzaldehyde was added dropwise with cooling over 1 hr. The mixture was refluxed 15 min, cooled, and 50 ml saturated ammonium chloride solution was added. The solvent was removed and the residue distilled to give 31 g (42%) of analytically pure 1-phenyl-3-butyne-1-ol: b₅₀ 67.5-71°; pmr (CCl₄) δ 7.19 (s, 5, PhH), 4.63 (m, 1, OCH, J = 6.5 and 4 Hz), 3.60 (d, 1, OH, J = 4), 2.42 (m, 2, CH₂, J = 2.7 and 6.5 Hz), 1.86 (t, 1, =CH, J = 2.7).
4-Bromo-4-phenyl-1-butyne. Phosphorous tribromide (20 g, 0.074 mole) and 1 drop 48% HBr. were cooled to 10-15° and 25.8 g (0.1765 mole) 1-phenyl-3-butyn-1-ol was added dropwise with stirring over 2 hr, then the mixture was stirred at room temperature overnight. The red lower phase was discarded and 100 ml ice water was added to the upper phase causing it to solidify. The solid was then dissolved in ether, washed with water, then with 5% sodium bicarbonate which caused extreme cloudiness. The aqueous phase was acidified with dilute hydrochloric acid causing an emulsion which separated on addition of more ether and water. The ether phase was dried over calcium chloride, filtered through Celite, and the solvent removed to give 19.6 g of an oil which solidified on storage at -10°. The solid was recrystallized twice from methanol/water to give 19.9 g (54%) of 4-bromo-4-phenyl-1-butyne as white needles: mp 36.0-36.2°; pmr (CCl₄) δ 7.30 (m, 5, PhH), 4.98 (t, 1, BrCH, J = 7.2 Hz), 3.05 (m, 2, CH₂, J = 7.2 and 2.6 Hz), 1.92 (t, 1, ≡CH, J = 2.6 Hz).

1-Phenyl-3-butynylhydrazine. A 6.35 g (0.030 mole) sample of 4-bromo-4-phenyl-1-butyne was added dropwise (heated addition funnel) with vigorous stirring over 1 hr to a solution of 18 g water and 32 g of hydrazine maintained at 40 to 50°. After the addition, the reaction mixture was heated at 70° for 0.5 hr. The cooled, yellow reaction mixture was extracted with ether and the extracts distilled yielding 0.96 g (25%) trans-1-phenyl-1-butene-3-yne: b₁₀ 47-49°; pmr (neat) δ 7.13 (s, 5, PhH), 6.80 (d, 1, PhCH, J = 16 Hz), 6.02 (m, 1, CHC≡, J = 16 and 2.2 Hz), 3.09 (d, 1, ≡CH, J = 2.2); and 1.7 g (35%) of 1-phenyl-3-butynylhydrazine: b₁₀ 97-97.5°; pmr (CCl₄) δ 7.25 (s, 5, PhH), 3.72 (t, 1, CHN, J = 6.5 Hz), 3.26 (s, 3, NH), 2.44 (m, 2, CH₂), 1.93 (t, 1, ≡CH, J = 2.3 Hz).
1-(1-Phenyl-3-butynyl)-2-p-toluenesulfonylhydrazine [61]. According to Cram and Bradshaw, a solution of 1.435 g (0.00897 mole) 1-phenyl-3-butynylhydrazine in 30 ml dry pyridine at 0° was made and 1.71 g (0.00897 mole) p-toluenesulfonylchloride in 15 ml dry pyridine was added slowly with stirring. The reaction mixture was allowed to stand at 0° overnight, then poured into 325 ml 3 N hydrochloric acid. An orange material oiled out. The mixture was extracted with ether and the extracts were washed with water, dried over sodium sulfate, and decolorized with charcoal. The solvent was removed and the resulting oil was crystallized from ether/pentane, cooling the crystallizing mixture with dry ice to induce crystallization. A recrystallization produced 1.237 g (44%) of white crystals of [61]: mp 107.5-108° with bubbling; pmr (DDCl₃) δ 7.9-7.1 (m, 9, ArH), 5.76 (s, 1, SO₂NH), 4.4-3.7 (m, 2, NH and NCH), 2.53 (m, 2, CH₂C≡, J = 2.5 and 6.5 Hz), 2.45 (s, 3, CH₃), 1.96 (t, 1, ≡CH, J = 2.5 Hz).

Pyrolysis of 1-(1-phenyl-3-butynyl)-2-p-toluenesulfonylhydrazine [61]. A solution of 0.334 g (0.0011 mole) of [61] in 50 ml diethylene glycol was heated in a boiling water bath. Nitrogen evolved for 25 min. Heating was continued an additional hour, then the solution was poured into 400 ml water and extracted with pentane. During the extraction, the walls of the funnel became coated with a white, apparently crystalline material insoluble in water and pentane, which was assumed to be polymer. The pentane extracts were combined, dried, and the solvent was removed on a rotary evaporator with no external heating, yielding 0.13 g (93%) of 4-phenyl-1-butyne: pmr (CCl₄) δ 7.05 (s, 5, PhH), 2.9-2.6 (m, 2, PhCH₂), 2.1-2.5 (m, 2, ≡CCH₂), 1.72 (t, 1, ≡CH, J = 2.2 Hz).
Photolysis of benzophenone allylhydrazone [6]. A 1.038 g sample of [6] was added to 220 ml sodium dried pentane and the solution degassed by bubbling nitrogen through it for 1.75 hr. The solution was then exposed to irradiation at 15° for 5 hr from a 450 watt Hanovia medium pressure mercury lamp with a Corex filter. The reaction was followed by analytical glpc (SE-30 (30%) on Chromosorb P, 60/80 Mesh, 1/8 in x 10 ft, column temperature 211°). After 0.5 hr, two compounds had appeared in the solution which had the same retention time as diphenylmethane and 4,4-diphenyl-1-butene. Their amounts increased to ca. 10% yield each when the starting material had disappeared after 5 hr. Other volatile compounds were present in the reaction as evidenced by glpc, but their identification was not attempted.

**Attempted catalysis of the benzaldehyde allylhydrazone [13] rearrangement with a soluble palladium catalyst.** Nitrogen was bubbled for 1 hr through 15 ml dry triethylamine (distilled from lithium aluminum hydride) in a 50 ml flask equipped with a reflux condensor and a magnetic stirrer. Then 0.108 g (0.000356 mole) palladium acetylacetonate and 0.187 g (0.000714 mole) triphenylphosphine were added, and nitrogen was bubbled through the mixture 1 hr. Then 1.028 g of [13] was added by syringe, whereby the yellow mixture turned green. Upon heating, all of the material dissolved forming a deep purple solution. The solution was refluxed under nitrogen. After 40 min, no 4-phenyl-1-butene [59] was detectable by analytical glpc. After 7 hr reflux, the solution was cooled, dumped into 200 ml cold 3 N hydrochloric acid, and extracted with ether. Glpc showed no [59] present in the ether solution.
l-Phenylcyclopropane-l-carboxaldehyde [182]. A 5.31 g (0.037 mole) sample of l-cyano-l-phenylcyclopropane [181] was dissolved in 150 ml benzene (freshly distilled from lithium aluminum hydride). Then 24.4 ml of a benzene solution containing 5.8 g (0.041 mole) di-isobutylaluminum hydride was added dropwise under nitrogen with stirring during 20 min. Ice bath cooling was used to maintain a temperature of 5-10°. After the addition was complete, the solution was stirred 0.5 hr while warming to room temperature, then poured cautiously into 150 ml of a 5% sulfuric acid solution. This mixture was then stirred 0.5 hr. The benzene layer was separated and combined with ether washings of the aqueous phase. After drying over potassium carbonate, the solvent was removed to yield 5.1 g (94%) of a clear liquid identified as [182]: pmr (DCl₃) δ 9.27 (s, 1, CHO), 7.30 (s, 5, ArH), 1.44 (m, 4, CH₂); ir (film) 1710 cm⁻¹ (C=O).

l-Phenylcyclopropane carboxaldehyde ethylene acetal. l-phenylcyclopropane carboxaldehyde, 67.5 g, 0.46 mole and 31 g (0.5 mole) ethylene glycol and a crystal of toluene sulfonic acid were added to 250 ml benzene. The stirred mixture was refluxed removing water with a Dean-Stark trap. After the theoretical amount of water was collected, the benzene solution was extracted two times with 100 ml 5% sodium bicarbonate solution one time with saturated sodium chloride solution, and dried over calcium sulfate. The benzene was removed and the residue distilled to yield 83.4 g (95%) of the clear liquid acetal, which solidified on cooling: b₁₀ 98-99°, mp 17.5°, pmr (DCl₃) δ 7.45 (m, 5, ArH), 4.95 (s, 1, CH), 3.78 (s, 4, OCH₂), 0.92 (m, 4, CH₂).
1-(p-Nitrophenyl) cyclopropane carboxaldehyde [179]. According to a modification of a known procedure, \(^{183a}\) fuming (90%) nitric acid (100 ml) was added dropwise with stirring and cooling to 325 ml acetic anhydride in a 1-liter 3-necked flask over ca. one-half hour. The solution was then cooled to -30° with a dry ice acetone bath at which point the solution slurried with crystals.

The mixture was allowed to warm until the slurry could be easily stirred. Then 59.7 g (0.314 mole) of 1-phenylcyclopropane carboxaldehyde ethylene acetal was added dropwise over ca. one-half hour, maintaining the temperature of the reaction at -18 to -10° during the addition. The solution was then stirred at -18° for 1.5 hours.

The solution was then allowed to warm gradually, over two hours, to 20°. The entire solution was then poured with caution into 2 liters of boiling water while stirring in a 5-liter flask. The mixture was stirred without further heating for 0.7 hr. Then ice was added to cool the solution and a yellow solid precipitated, which then liquified. The mixture was extracted with chloroform, washed with water, dilute sodium carbonate solution, saturated sodium chloride solution, and dried over calcium sulfate. Evaporation of the solvent gave 71.3 g (120%) of a crude yellow oil. Pmr analysis showed by the aldehyde proton absorbances that this oil contained 68.5% of the ortho isomer and 31.5% of the para isomer, and no starting material.

This oil on standing at room temperature for three hours became partially crystalline. The mixture was cooled 1.5 hr in a refrigerator, then filtered to yield light yellow crystals and an orangish-yellow filtrate. The crystals were dissolved in a minimum amount of hot methanol and water added to the point of saturation, allowing crystallization.
Light yellow crystals (13.7 g, 22.8%) were collected and found by pmr analysis to be the pure para nitro isomer: pmr (DCl)$_3$ δ 9.07 (s, 1, CHO), 7.85 (m, 4, ArH), 1.59 (m, 4, CH$_2$); ir (HCl) 1712 cm$^{-1}$.

The filtrate was found to be the ortho nitro aldehyde contaminated with the para isomer. The isomers could be separated also by a short path distillation, but much material was lost through decomposition. A sample was purified by distillation to yield a light yellow liquid, b$_{0.7}$ 146-150°, which was identified as pure [179]: mass spectrum (70eV) m/e 191 (Parent), 190 (P-H), 160 (P-CHO), 145 (P-NO$_2$); ir (film) 1711 cm$^{-1}$ (C=O); pmr (DCl$_3$) δ 9.08 (s, 1, CHO), 7.25-8.30 (m, 4, ArH), 1.54 (m, 4, CH$_2$). The para isomer was higher boiling, b$_{0.7}$ 155-160°. A lower boiling, b$_{0.7}$ 54-60°, material also distilled which amounted to roughly 15% of the mixture. This fraction was subjected to pmr analysis which showed no absorptions in the aromatic region.

Methyl imine [186]. A solution of methyl amine (95 ml of 0.41 N) in benzene was added to 3.03 g (0.0159 mole) of the crude nitro aldehyde mixture and 8 g magnesium sulfate and stirred at room temperature under nitrogen for two days. The solution was filtered and the solvent removed to yield [186] as an orangish oil: ir (film) 1650 cm$^{-1}$ (C=N); pmr (DCl$_3$) δ 7.4-8.5 (m, 5, ArH and N=CH), 3.25 (d, 3, J = 1.5 Hz, CH$_3$), 1.32 (m, 4, CH$_2$). The pmr spectrum showed no remaining aldehyde. Kugelrohr distillation was attempted, but extensive decomposition occurred.

1-Methyl-3-(p-nitrophenyl)-2-pyrroline [187]. Ammonium iodide (0.0864 g, 0.61 mmole) and 3.509 g (17.2 mmole) of cyclopropyl imine [186] were dissolved in 20 ml
dry acetonitrile. The solution was refluxed under nitrogen for 46 hours. Then the acetonitrile was removed and 20 ml ethanol was added to dissolve the dark material. This solution was acidified with a 20% hydrogen chloride solution to pH 1, then poured into 500 ml water and washed with chloroform. The aqueous portion was bacisified with 12 N sodium hydroxide to pH 13 and extracted with chloroform to yield a deep red solution which was dried overnight. The solvent was removed to give 1.12 g (32%) of [187] as a red oil which became semisolid upon standing overnight: ir (DCCl₃) 1595 cm⁻¹ (C=CN; pmr (DCCl₃) δ 7.8-7.1 (m, 4, ArH), 6.56 (t, 1, J = 1.5, NCH=), 3.05 (m, 4, CH₂), 2.78 (s, 3, CH₃).

Alkylation of 1-methyl-3-(o-nitrophenyl)-2-pyrroline [187]. A 0.24 g (0.00118 mole) sample of freshly distilled methyl fluorosulfonate (Aldrich Magic Methyl) in 10 ml benzene (freshly distilled from lithium aluminum hydride) was added dropwise over 0.5 hour at room temperature under nitrogen to 0.157 g (0.0012 mole) of [187] in 5 ml benzene. After the addition, a light orange solution resulted, with a semisolid mixture in the bottom of the flask. After stirring the reaction mixture for 4 hours, 15 ml dry dimethylformamide and 0.046 g (0.0012 mole) sodium borohydride was added slowly with stirring. All solid material dissolved resulting in a clear red solution.

After stirring 17 hr, 5 ml methanol was added and the solution stirred an additional 24 hr. Then ca. 5 ml 20% hydrogen chloride solution was added slowly, producing a yellowish solution. The solution was poured into 300 ml water and washed with chloroform. Then the solution was bacisified with 12 N sodium hydroxide solution and extracted with chloroform. The solvent was removed and the residue dissolved in
ether. This solution was washed with water to remove dimethylformamide, then dried over sodium carbonate. When the ether was removed, 0.11 g (42%) of a yellow oil resulted which was tentatively identified as 4-dimethylamino-2-(o-nitrophenyl)-1-butene [189]: \[ \text{pmr (DCCl}_3\text{) } \delta 7.55 \text{ (m, 4, ArH), 5.32 (m, 1, } \text{=CH), 5.10 (m, 1, } \text{=CH), 2.54 (m, 4, CH}_2\text{), 2.24 (s, 6, CH}_3\text{)}; \] \[ \text{ir (HCCl}_3\text{) } 3087 \text{ cm}^{-1} \text{ (=CH), 1638 (C=C), 1350 and 1520 (NO}_2\text{).} \]

**Acylation of 1-benzyl-3-phenyl-2-pyrroline [188].** A 0.389 g (1.65 mmole) sample of sublimed [188] was dissolved in 12 ml dry acetonitrile and 0.24 g (2.5 mmole) freshly distilled methyl chloroformate was added. An immediate reaction occurred as evidenced by tlc analysis. The solution was allowed to stir overnight. The addition of more methyl chloroformate produced no further reaction. The solvent and excess methyl chloroformate were removed by vacuum. Sodium borohydride reduction at this stage showed no change in the tlc analysis.

By extracting an ethanol water solution of the residue with ether, drying, and evaporating the ether, 0.135 g (40%) of a crystalline compound was isolated and identified as 1-carbomethoxy-3-phenyl-2-pyrroline [188]. Recrystallization from cyclohexane gave white crystals: \[ \text{ir (HCCl}_3\text{) } 1690 \text{ cm}^{-1} \text{ (HCO}_2\text{); mass spectrum (70eV) m/e (rel intensity, assignment) 203 (100, parent), 144 (54, p-CO}_2\text{Me); pmr (DCCl}_3\text{) } \delta 7.41 \text{ (s, 5, PhH), 7.20 (m, 1, NCH=), 4.00 (m, 2, NCH}_2\text{), 3.84 (s, 3, CH}_3\text{), 2.98 (m, 2, CH}_2\text{).} \]

**3-Ethyl-2-keto-(ethylene ketal)-1-hexyl imine [191].** A 2.65 g (0.0142 mole) sample of 6-amino-3-ethyl-2-hexanone ethylene ketal and 2.71 g (0.0147 mole) of distilled aldehyde [179] were dissolved in ca.
50 ml benzene. The solution was refluxed removing water with a Dean-Stark trap for three hours; then the benzene was distilled off. After the solvent was removed by high vacuum, 5.06 g (99%) of an orangish oil [191] was isolated: ir (film) 1645 (C=N); pmr (DCCl₃) δ 7.3-8.3 (m, 5, ArH and N=CH), 3.92 (s, 4, OCH₂), 3.35 (m, 2, NCH₂), 1.25 (s, 3, CH₃), 0.7-2.1 (m, 17, alkyl). Pmr analysis showed that the resulting mixture contained no starting aldehyde.

Rearrangement of [191]. Ammonium iodide (0.005 g, 0.035 mmole) and 0.205 g (0.57 mmole) of cyclopropyl imine [191] were combined and the mixture degassed. Then 9 ml benzene was added and the solution refluxed 5 hr, at which time tlc showed no starting material remained. The solvent was removed by vacuum. The reaction mixture was placed on Activity III alumina and rapidly chromatographed, eluting with benzene. Three bands were formed. A brown band eluted first, followed by an intense purple band which had a bright yellow leading edge. The brown band yielded an orange solution which was evaporated to give 0.129 g (63%) of the desired 1-(4-ethyl-5-oxo ethylene ketal)-3-(o-nitrophenyl)-2-pyrrole [191] as a deep red oil: ir (HCCl₃) 1595 (NC=C), 1520 and 1350 cm⁻¹ (NO₂); mass spectrum (70eV) m/e 360 (parent); uv max (95% C₂H₅OH) 268 mμ (ε 5.29 x 10⁴) and 332 mμ (ε 1.43 x 10⁴); pmr (DCCl₃) δ 7.44 (m, 4, ArH), 6.67 (t, 1, J = 1.5, NCH=), 4.00 (s, 4, OCH₂), 2.5-3.6 (m, 6, pyrrole CH₂'s and NCH₂), 1.28 (s, 3, CH₃), 0.7-1.9 (m, 13, alkyl).

The yellow band was collected as a greenish flourescent solution, and the solvent removed to give an orangish oil tentatively identified as 1-(4-ethyl-5-oxo ethylene ketal)-3-(p-nitrophenyl) pyrrole: pmr (DCCl₃)
δ 7.9 ([AA'BB'], 4, ArH), 7.14, 6.77, & 6.53 (m, 3, pyrrole H's), 3.93 (m, 6, CH₂O, NCH₂), 1.24 (s, 3, CH₃); mass spectrum (70eV) m/e 358 (parent), IR (DCCl₃) 1525 and 1323 cm⁻¹ (NO₂). The undecomposed purple band was isolated as an orange solution which was evaporated to yield 1-(4-ethyl-5-oxo ethylene ketal)-3-(p-nitrophenyl)-2-pyrroline as a dark oil: pmr (DCCl₃) δ 7.7 (AA'BB', ArH), 6.9 (m, NCH=), 4.0 (s, CH₂O), 3.2 (m, pyrrole CH₂'s), 1.27 (s, CH₃), IR (HCCl₃) 1573 cm⁻¹ (NC=C), 1515 and 1325 cm⁻¹ (NO₂).

**Acid catalyzed cyclization of [192].**

**Hydrogen chloride/ether.** Following a procedure similar to that of Wenkert,⁶⁵ a 0.497 g (1.38 mmole) sample of enamine [192] was dissolved in 20 ml dry ether (freshly distilled from lithium aluminum hydride) in a flask under nitrogen. Then dry hydrogen chloride was passed through the deep red solution with ice bath cooling. This caused a light yellow solution and yellow oil. Excess hydrogen chloride was bubbled through the solution until most of the oil had dissolved. The mixture was then stirred 17 hrs; then a rapid stream of nitrogen was passed over the stirred mixture to remove the acid and solvent. The residue was dissolved in chloroform and stirred with 15 g Fisher Basic Alumina, Brockman Activity I, 80-200 mesh. As the slurry stirred, it turned red-brown. After stirring ca. 2 hr exposed to atmospheric moisture, the solvent was removed from the slurry and the resulting alumina mixture added to the top of a small (ca. 15 g) basic alumina column and chromatographed, eluting with chloroform. The material eluting was separated into four fractions which were analyzed by tlc. Preparative scale tlc (alumina, eluting with methylene chloride) of the third fraction gave 0.044 g
(9%) of yellow crystals. The material was recrystallized from hexane and sublimed to yield nearly white crystals of [194]: mp 145-145°; mass spectrum (70eV) m/e 316 (parent); ir (HCl) 1693 cm⁻¹ (C=O), 1524 and 1352 (NO₂), 2793 and 2732 (indolizidine Bohlmann bands); nmr (DCCl₃) δ 7.49 (m, 4, ArH), 1.63 (s, 3, COCH₃), 0.76 (t, 3, J = 7.5 Hz, CH₃), 1.4-4.0 (m, 17, alkyl).

p-Toluensulfonic acid/benzene. In a procedure similar to that of Wenkert,⁶⁵ a 0.137 g (0.38 mmole) sample of enamine [192] was added to 0.206 g (1.2 mmole) of anhydrous toluenesulfonic acid in 50 ml dry benzene. The resulting yellow solution was refluxed 16 hr, and the cooled, dark solution was added slowly into a stirred mixture of excess sodium bicarbonate in methylene chloride, not excluding atmospheric moisture. After two hours stirring, the solution was filtered and the solvent removed. The residue was dissolved in ether and the solution washed with cold 5% sodium hydroxide solution, then dried over potassium carbonate. The solvent was removed to yield 0.103 g of a brown oil. Tlc (alumina eluting with methylene chloride) ir, and nmr analysis indicated the bicyclic material was still mostly in the ketal form. Stirring with hydrogen chloride/methylene chloride and work-up as before did not cleave the ketal.

The dark oil was dissolved in 5 ml methanol and 50 ml 5% aqueous hydrogen chloride was added and the solution stirred overnight. The aqueous solution was then washed with ether, then basified with 12 N sodium hydroxide solution and extracted with ether. The basic ether extracts were dried over calcium sulfate, and the solvent removed to yield 0.071 g (52%) of a light yellow solid, [194], identified as before.
1-Benzyl-3-(o-nitrophenyl)-2-pyrroline [196]. Benzyl amine (2.105 g, 0.02 mole) and 3.554 g (0.019 mole) nitro aldehyde [179] were dissolved in 50 ml benzene and the solution refluxed for 1.2 hours under nitrogen with a Dean-Stark trap for water removal. After the water was removed, 15 ml benzene was added and distilled from the reaction mixture to insure dryness (the benzyl imine: ir (film) 1660 cm\(^{-1}\); pmr (DCCl\(_3\)) \(\delta\) 7.2-8.3 (m, 5, ArH and N=CH), 7.3 (s, 5, PhH), 4.54 (m, 2, PhCH\(_2\)), 1.25 (m, 4, CH\(_2\)), can be isolated at this stage). Then 0.27 g (0.0019 mole) of ammonium iodide was added and reflux continued for 19 hours, following the reaction by tlc (alumina/ether). The reaction mixture had turned a deep red-brown.

The solvent was removed with a rotary evaporator and the dark oily residue was chromatographed rapidly on 200 g of Activity III alumina eluting with benzene/hexane (40:60, v/v). Two prominent bands formed, a brown band which was faster moving and a deep purple band which moved slower. As the bands moved down the column, the purple band began to turn bright yellow at its leading edge. (If the purple band was allowed to remain undisturbed on the column for several hours, it faded entirely to yellow.)

The brown band was collected and found to be the desired product [196], isolated by removing the solvent and subjecting to high vacuum to give 2.61 g (50%) of a deep red oil: ir (HCCCl\(_3\)), 1587 cm\(^{-1}\) (C=C-N); pmr (DCCl\(_3\)) \(\delta\) 7.0-7.8 (m, 9, ArH), 6.73 (t, 1, J = 1.5, N=CH=), 4.21 (s, 2, PhCH\(_2\)), 3.07 (m, 4, (CH\(_2\))\(_2\)). The material slowly crystallized on standing and was found to be air sensitive. It could be stored under nitrogen at <0° for several days without noticeable decomposition. The
yellow band preceding the purple band was tentatively identified as 1-benzyl-3-(p-nitrophenyl) pyrrole, and the purple band as 1-benzyl-3-(p-nitrophenyl)-2-pyrroline.

Propyl vinyl ketone. According to the procedure of Bowden, et al., a solution of cromic oxide (10.3 g, 0.103 mole) in 30 ml water and 8.7 ml sulfuric acid was added over 2 hr to a stirred solution of 12 g (0.12 mole) 1-hexene-3-ol in 30 ml acetone with ice bath cooling. After stirring an additional 30 min at 25°, the slurry was poured into 250 ml water and extracted with ether. The ether extracts were washed once with water and dried over calcium sulfate. The solution was distilled to yield 6.13 g (51%) of the lacrymatory propyl vinyl ketone, \( b_{100} 68^\circ \text{(lit.,} 68^\circ \text{)} \); \( b_{150} 88-90^\circ \); ir (film) 1679 cm\(^{-1}\) (C=O); pmr (DCCl\(_3\)) \( \delta 6.8-5.6 \) (m, 3, CH=CH\(_2\)), 2.56 (t, 2, COCH\(_2\), \( \downarrow = 7 \) Hz), 1.57 (m, 2, CH\(_2\)Me, \( \downarrow = 7 \) Hz), 0.93 (t, 3, CH\(_3\), \( \downarrow = 7 \) Hz).

Annulation of enamine [195]. 0.967 g (0.00345 mole) of pyrroline [195] was dissolved in 40 ml dry benzene and hydrogen chloride passed over the solution with stirring. A yellow salt oiled out. When the solution was completely yellow, the benzene was removed by vacuum until a crystalline yellow-white salt remained. Then 50 ml freshly distilled acetonitrile and 1.4 ml propyl vinyl ketone were added. The solution was refluxed under nitrogen, following the reaction by tlc analysis. After refluxing 16 hrs, most of the solvent was removed and the residue dissolved in 400 ml 0.5 N hydrochloric acid. The resulting emulsion was washed three times with ether (100 ml), basified with sodium hydroxide, and extracted again with ether. The basic extracts were dried over calcium sulfate.
The solvent was then removed and the residue (0.789 g) was chromatographed on 200 g of activity III aluminum oxide eluting with ether (the residue was not preabsorbed on alumina but placed directly on the column in a minimum of solvent). The first band eluting from the column was 0.23 g (18%) of the desired bicyclic product [196b]:

\[ \text{pmr (DCCl}_3) \delta 7.26 (m, 9, ArII), 3.58 (s, 2, PhCH}_2), 0.83 (t, 3, CH}_3, J = 7 \text{ Hz), (see spectral section); ir (HCCl}_3) 1710 \text{ cm}^{-1} (\text{C=O}), 2740, 2800 (\text{indolizidine Bohlmann bands}), 1527, 1365 (\text{NO}_2). \]

The remaining fractions collected from the column consisted of mixtures of [196b] and other unidentified compounds.
LITERATURE CITED


3. This is correct except in rare cases, and these cases have been found to proceed at least partially in a concerted fashion. 2

4. Several examples of the synthetic use of the sigmatropic rearrangements may be found in the following review: A. Jefferson, and F. Scheinmann, Quart. Rev., 22, 391 (1968).


   b) O. Diels, ibid., 56, 133 (1923).


9. E. Wenkert, private communication.

10. The pmr spectrum of a sample of >99% isomeric purity was supplied by R. M. Magid in a private communication.


15. Reference 5, p 691.


36. W. E. Billups, unpublished data.


42. a) K. Biemann, Lloydia, 27, 397 (1964).


65. E. Wenkert, K. G. Dave, and R. V. Stevens, ibid., 90, 6177 (1968).


74. F. E. Ziegler and G. B. Bennett, ibid., 93, 5931 (1971).


80. M. Fitzpatrick has formed 1,1-dicyanocyclopropane from the reaction of malononitrile, ethylene dibromide, and liquid ammonia in these laboratories.

81. Bases such as sodium ethoxide, sodium hydride, butyllithium, sodium amide, and lithium amide have been used in these laboratories in this reaction. These experiments, performed by R. Zimmerman, resulted in either isolated starting material, or tar formation.


   b) D. E. Pearson and C. A. Buehler, Synthesis, 455 (1971), and references therein.


   c) S. L. Keely, Jr. and F. C. Takh, ibid., 99, 5584 (1968).


