Summer 1974

THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF N-ALKOXYCARBONYL-7-AZABENZNORBORNENOLS AND -NORBORNENONES

LEO LEMUEL LAUGHLIN JR.

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THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF
N-ALKOXYCARBONYL-7-AZABENZNORBORNENOLS AND
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University of New Hampshire, Ph.D., 1974
Chemistry, organic

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THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF
N-ALKOXYCARBONYL-7-AZABENZNORBORNENOLS
AND -NORBORNENONES

by

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B.S., GEORGETOWN UNIVERSITY, 1959
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A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
The Requirements for the Degree of
Doctor of Philosophy

Graduate School
Department of Chemistry
August 1973
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ACKNOWLEDGEMENTS

The work described in this thesis was carried out under a Fulltime Outservice Training Program sponsored by the Bureau of Medicine and Surgery, United States Navy.

The author wishes to express his profound gratitude to Dr. Gloria G. Lyle under whose guidance this research was completed. Her patient and understanding direction was a constant source of encouragement.
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF FIGURES</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL BACKGROUND</td>
<td>3</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>9</td>
</tr>
<tr>
<td>Considerations in the selection of a synthetic approach</td>
<td>9</td>
</tr>
<tr>
<td>Synthesis of 7-azabenznorbornadiene</td>
<td>15</td>
</tr>
<tr>
<td>Attempts at synthesis of benztropinone</td>
<td>26</td>
</tr>
<tr>
<td>Hydroboration of N-alkoxycarbonyl-7-azabenznorbornadiene</td>
<td>28</td>
</tr>
<tr>
<td>Asymmetric hydroboration</td>
<td>36</td>
</tr>
<tr>
<td>Optical activity</td>
<td>46</td>
</tr>
<tr>
<td>Absolute configuration of (+)- and (-)-N-alkoxycarbonyl-7-azabenznorbornenols</td>
<td>57</td>
</tr>
<tr>
<td>Transition state considerations</td>
<td>59</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>67</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>68</td>
</tr>
<tr>
<td>General</td>
<td>68</td>
</tr>
<tr>
<td>Synthetic procedures</td>
<td>70</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>92</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Infrared Spectrum of $\text{N-}^{\text{t}}\text{-Butoxycarbonyl-7-}$</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornadiene.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NMR of $\text{N-}^{\text{t}}\text{-Butoxycarbonyl-7-}$</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornadiene.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Infrared Spectrum of $\text{N-Ethoxycarbonyl}$ Pyrrole.</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>NMR of $\text{N-Ethoxycarbonyl}$ Pyrrole.</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>Infrared Spectrum of $\text{N-Ethoxycarbonyl-7-}$</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornadiene.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NMR of $\text{N-Ethoxycarbonyl-7-}$ azabenznorbornadiene.</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>Infrared Spectrum of $(\pm)$-exo-$\text{N-Ethoxycarbonyl-7-}$</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornenol.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NMR of $(\pm)$-exo-$\text{N-Ethoxycarbonyl-7-}$ azabenznorbornenol.</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Spectrum II is after the addition of $\text{D}_2\text{O}$.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Infrared Spectrum of $(\pm)$-N-Ethoxycarbonyl-7-</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornenone.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ultraviolet Spectrum of $(\pm)$-N-Ethoxycarbonyl-7-</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornenone.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Infrared Spectrum of $(-)$-exo-$\text{N-Ethoxycarbonyl-7-}$</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornenol (neat).</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Infrared Spectrum of $(+)\text{-exo-}$-$\text{N-Methoxycarbonyl-7-}$</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>azabenznorbornenol Acetate.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>NMR of $(+)\text{-exo-}$-$\text{N-Methoxycarbonyl-7-}$ azabenznorbornenol</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Acetate.</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>14</td>
<td>Infrared Spectrum of (+)-exo-N-Methoxycarbonyl-7-azabenznorbornenol (CHCl₃).</td>
<td>43</td>
</tr>
<tr>
<td>15</td>
<td>Infrared Spectrum of (+)-exo-N-Methoxycarbonyl-7-azabenznorbornenol (CHCl₃).</td>
<td>44</td>
</tr>
<tr>
<td>16</td>
<td>ORD of (+)- and (-)-N-Alkoxycarbonyl-7-azabenznorbornenol.</td>
<td>47</td>
</tr>
<tr>
<td>17</td>
<td>CD of (+)- and (-)-N-Alkoxycarbonyl-7-azabenznorbornenol.</td>
<td>49</td>
</tr>
<tr>
<td>18</td>
<td>Ultraviolet Spectrum of (-)-exo-N-Ethoxycarbonyl-7-azabenznorbornenol.</td>
<td>50</td>
</tr>
<tr>
<td>19</td>
<td>Orbital Geometries for pi-pi Overlap in exo-N-Alkoxycarbonyl-7-azabenznorbornenol.</td>
<td>53</td>
</tr>
<tr>
<td>20</td>
<td>Third Sphere Contribution to Cotton Effect (Snatzke).</td>
<td>55</td>
</tr>
<tr>
<td>21</td>
<td>Absolute Configuration.</td>
<td>58</td>
</tr>
<tr>
<td>22</td>
<td>Postulated Transition State for Asymmetric Hydroboration (After McKenna).</td>
<td>61</td>
</tr>
<tr>
<td>23</td>
<td>CD of (+)-N-Methoxycarbonyl-7-azabenznorbornenone.</td>
<td>63</td>
</tr>
<tr>
<td>24</td>
<td>CD of (+)-2-Benzonorbornenone.</td>
<td>64</td>
</tr>
<tr>
<td>25</td>
<td>Application of β,γ-Unsaturated Ketone Rule (Mislow).</td>
<td>66</td>
</tr>
</tbody>
</table>
ABSTRACT

THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF N-ALKOXYCARBONYL-7-AZABENZNORBORNENOLS AND -NORBORNENONES

by

LEO L. LAUGHLIN, JR.

1R, 2S-(+)-Exo-N-methoxycarbonyl-7-azabenznorbornenol and 1S, 2R-(-)-exo-N-ethoxycarbonyl-7-azabenznorbornenol were prepared by asymmetric hydroboration of their corresponding N-alkoxycarbonyl-7-azabenznorbornadienes; oxidation to the ketone I followed. The Optical Rotatory Dispersion and Circular Dichroism were measured and their absolute configurations were assigned by comparison of the CD of the asymmetrically perturbed benzene chromophore in these molecules with the CD of asymmetrically perturbed benzene chromophores in carbocyclic homologues of known absolute configuration. This was further confirmed by application of the $\beta,\gamma$-unsaturated ketone rule to the CD of the ketones prepared.

$$\text{NCOOR}$$

$$I, R = \text{CH}_3, \text{CH}_2\text{CH}_3$$

vii
INTRODUCTION

The synthesis of new ring systems in organic chemistry has led to a variety of carbocyclic and heterocyclic structures which have been useful in both theoretical and practical applications. A number of new ring systems have been synthesized in order to investigate the theoretical spectral aspects of interactions of certain functional groups. Further, the synthetic methods which have been developed are frequently applicable to all fields of synthetic chemistry.

The purpose of the research described below was the synthesis of a new ring system which would permit examination of the long-range electronic interactions of nitrogen and carbonyl chromophores with an aryl system and to prepare a known ring system in optically active form to determine the stereochemistry and chiroptical properties of the system. The two main synthetic objectives were:

a) the preparation of the unknown ring system benztropinone, I,

b) the conversion of the known heterocyclic ring system 7-azabenzenorbornadiene, II, to the optically active alcohol 7-azabenzenorbornenol, III, and ketone 7-azabenzenorbornenone, IV.

The exploration of the synthetic routes to these compounds and an examination of their chemical and optical properties constitute the subject of this thesis.
HISTORICAL BACKGROUND

The 7-azabenzonorbornadiene ring system, II, represents a rigid ring system in which the rate of inversion on the nitrogen substituent can be determined. Gribble\textsuperscript{1} has calculated the barrier to inversion to be $\Delta G^\ddagger = 14$ kilocalories/mole with a methyl substituent on nitrogen. Using the N-chloro compound, Rautenstrauch\textsuperscript{2} has calculated a barrier of $\Delta G^\ddagger = 23.5$ kilocalories/mole. Both agree that the anti-invertomer is favored.

\[
\begin{array}{c}
\text{Cl} \quad \text{N} \\
\text{syn-}
\end{array}
\quad \leftrightarrow \quad
\begin{array}{c}
\text{N} \quad \text{Cl} \\
\text{anti-}
\end{array}
\]

The possibility exists that this ring system may be an entry into the unknown benztropane system, I, after appropriate manipulation. Tropane alkaloids are present in a variety of plants\textsuperscript{3} and include atropine, scopolamine and cocaine, all of which are physiologically active compounds. Modification of the basic tropane ring system by fusing a benzene ring to it may also lead to physiologically active compounds having different properties from those of the known tropanes.

Synthesis of the parent ring compound, tropinone, under physiological conditions, was carried out by Robinson\textsuperscript{4} by condensing succinic
SYNTHESSES OF 3-TROPINONES

\[
\begin{align*}
\text{CH}_2\text{-CHO} + \text{CH}_3\text{NH}_2 + \text{CH}_2\text{COOH} & \rightarrow \text{CH}_3\text{N} \\
\text{CH}_2\text{-CHO} + \text{CH}_2\text{COOH} & \rightarrow \text{Y. Kashman and S. Cherkez,}
\end{align*}
\]

R. Robinson

\[
\begin{align*}
\text{C}_6\text{H}_5\text{-CH}-\text{NH}_2 + \text{N} & \rightarrow \text{Y. Kashman and S. Cherkez,}
\end{align*}
\]


SCHEME 1
dialdehyde with methylamine and acetone dicarboxylic acid as shown in Scheme 1. However, attempts to prepare a benztropanone via o-phthalaldehyde were unsuccessful. More recently, tropinone has been synthesized by the Michael addition of methylamine to cycloheptadienone, and a variety of amines was used in similar reactions to prepare some optically active N-substituted nortropinones (Scheme 1).

Benztropinones could be prepared from the 7-azabenzonorbornadiene II modeled on an analogous reaction in the carbocyclic series. It has been shown that dichlorocarbene addition to norbornene is followed by spontaneous rearrangement, as shown in Scheme 2. Lithium aluminum hydride reduction and then acid hydrolysis of the vinylic chloride gave the ketone biocyclo[3.2.1]octan-3-one as shown.

An optically active benznorbornenone has been prepared by asymmetric hydroboration of benznorbornadiene (Scheme 3), and its absolute configuration has been assigned. This conformationally rigid, disymmetric β,γ-benzoketone exhibits a Cotton effect for the n → π* transition whose rotational strength and sign is that predicted for a β,γ-unsaturated ketone chromophore by the generalized octant rule.

The research described in this Dissertation includes the extension of the reactions described above to attempt (1) the preparation
Scheme 2
(+)-α-Pinene

\[ \text{P}_2^*\text{BH} \]

\[ \text{OH} \]

+ 16°

\[ \text{0} \]

+ 262°


SCHEME 3
of benztropinone and (2) the hydroboration of the azabenznorbornadiene II to yield chiral alcohols and ketones.

The preparation of optically active alcohols and ketones from the 7-azabenznorbornadiene system would provide a rigid ring system on which optical rotatory dispersion (ORD) and circular dichroism (CD) measurements could be made. These data may then be compared to the ORD and CD data obtained from analogous carbocyclic system\(^8\) whose stereochemistry is known and the stereochemistry of the heterocyclic system may be determined on the basis of these comparisons.
CONSIDERATIONS IN THE SELECTION OF A SYNTHETIC APPROACH

The desired parent ring system, 7-azabenznorbornadiene, II, can be synthesized by two general methods, both of which involve a Diels-Alder reaction. In one method an isoindole, usually substituted to stabilize the isoindole, reacts as the diene with some reactive dienophile to give the desired product. Wittig has used maleic anhydride as the dienophile with a variety of substituted and unsubstituted isoindoles to obtain 7-aryl- and 7-alkyl-7-azabenzonorbornenes (Scheme 4).

Emmett has used the much more reactive dienophile dimethylacetylene dicarboxylate to prepare 7-azabenzonorbornenes in reasonable yields (Scheme 5).

A more general method, however, is the one in which an appropriately substituted pyrrole is the diene. Although pyrrole has been considered unsuitable as a diene, substituted pyrroles will undergo Diels-Alder reactions. Mandell and Blanchard, using acetylene dicarboxylic acid as the dienophile, as shown in Scheme 6, reported recovering products resulting from Diels-Alder addition to the pyrrole nucleus. In attempting to explain the diene behavior of pyrrole, citing N-benzyl pyrrole, Mandell and Blanchard considered the energy required to achieve co-planarity between the nitrogen atom...
SCHEME 4

SCHEME 5

SCHEME 6
and its substituents; the group bulk has an effect on this energy. As the size increases, the energy required to achieve a coplanar system also increases. The increase is reflected in a lessening of the aromatic character of the pyrrole nucleus or as an increase in the diene character of the pyrrole.

However, when the bulk of the group on nitrogen was increased to triphenyl methyl, no adduct was formed, but α-naphthylmethyl pyrrole reacted to give the Diels-Alder adduct under the same reaction conditions. Mandell\textsuperscript{13} revised his earlier proposal to suggest that the insolubility of the zwitterion formed shifts the equilibrium of the reaction to favor adduct formation.

A more acceptable explanation, supported by experimental work, is the one proposed by Acheson and Vernon\textsuperscript{14}. Although they failed to isolate the adduct, the products obtained were proposed to have come from a retro Diels-Alder rearrangement of the adduct (Scheme 7). The electron-withdrawing nature of the group on the nitrogen of the pyrrole nucleus inhibits the conjugation of the π electrons on nitrogen with the π electrons of the ring system, thus effectively causing an increase in the diene character of the ring system by decreasing the extent of delocalization of the ring electrons.
**Scheme 7**

\[
\text{Pyridine} + \text{Acryloyl chloride} \rightarrow \text{Pyridine derivative}
\]

**Scheme 8**

\[
\text{Pyridine} + \text{Benzene} \rightarrow \text{Benzene derivative}
\]

**Scheme 9**

\[
\text{Pyridine derivative} + \text{Benzene} \rightarrow \text{Benzene derivative}
\]
This is supported by hydrogenation data. Adkins\textsuperscript{15} showed that N-carbethoxypyrrole is easier to reduce catalytically than pyrrole itself. Further support is found in the work of Prinzbach\textsuperscript{16} and his associates, in which they successfully reacted N-methoxycarbonyl pyrrole with dimethylacetylene dicarboxylate to obtain the intermediate postulated in Scheme 7. Stability studies\textsuperscript{16}, using various \(p\)-substituted N-phenyl pyrroles indicate that maximum stability for the ring system formed comes with that substituent having the greatest electron-withdrawing capability (i.e., \(p\)-NO\(_2\)).

The use of an electron-withdrawing group on the nitrogen of the pyrrole nucleus is therefore essential. The resultant increase in the diene character of the pyrrole enables it to more readily undergo Diels-Alder reactions to give stable products in reasonable yields. Although Carpino\textsuperscript{17} does not discuss the electron-withdrawing effect of the \(t\)-butoxy carbonyl group used to block the pyrrole nitrogen, this choice of \(N\)-substituents enabled him to obtain the Diels-Alder adduct with benzyne generated from \(o\)-fluorobromobenzene in 40\% yield (Scheme 8).

The previous preparation by Wittig and Behnisch\textsuperscript{18} of 7-azabenzonorbornadienes with other substituents on nitrogen gave low yields. Wolthius\textsuperscript{19} has reported, however, the preparation of
N-substituted 7-azabenznorbornadienes from completely substituted pyrroles in 50% yields (Scheme 9).

Curiously, Wolthius' use of 2,5-disubstituted pyrroles gave only substituted 2-aminonaphthalenes\(^\text{20}\) and no trace of the expected 7-azabenznorbornadiene. Since Wolthius has reported this general reaction sequence as a successful synthesis several times, the failure to isolate any substituted 7-azabenznorbornadiene should not be attributed to any experimental shortcoming. Substitution in the 3,4-positions of the pyrrole nucleus resulted in the formation of the expected 7-azabenznorbornadiene\(^\text{21}\).
SYNTHESIS OF 7-AZABENZNORBORNADIENE

From a synthetic viewpoint, the simplest route to the azabenznorbornadiene ring system is the condensation of an appropriately substituted pyrrole, i.e., one with an electron-withdrawing group on the nitrogen, with benzyne from any one of several precursors.

Following Carpino's procedure in which the N-t-butoxycarbonyl pyrrole is condensed with benzyne generated from o-fluorobromobenzene, N-t-butoxycarbonyl-7-azabenznorbornadiene, II, was prepared in the expected yield. The infrared spectrum (Fig. 1) shows a carbonyl absorption at 1705 cm⁻¹ for the urethane group in the bridged ring. The nmr spectrum (Fig. 2) agrees with that obtained by Carpino, except that the aromatic and olefinic multiplet which is centered at 7.20 ppm is reported to be centered at 7.60 ppm.

Because of the severe headaches caused by t-butyl azidoformate which was used to prepare the N-t-butoxycarbonyl pyrrole, it was decided to investigate other electron-withdrawing groups for use in this synthesis. N-Ethoxycarbonyl- and N-methoxycarbonyl pyrrole were prepared from their alkyl chloroformates in slightly better yields than the corresponding N-t-butoxycarbonyl pyrrole, following the same procedures (Scheme 10). The alkyl chloroformate was added to a cooled suspension
Fig. 1. Infrared Spectrum of N-t-Butoxycarbonyl-7-azabenznorbornadiene.
Fig 2. NMR of N-t-Butoxycarbonyl-7-azabenznorbornadiene.
SCHEME 10
of potassium pyrrole and stirred for several hours before being allowed to warm to room temperature. After workup, the alkoxy carbonyl compounds obtained by distillation showed an infrared absorption (Fig. 3) at 1750 cm$^{-1}$ for the urethane carbonyl absorption, indicating N-carboxylation$^{14}$. The nmr spectra contain the four protons on the pyrrole nucleus in their expected $A'_{2}B'_{2}$ pattern (Fig. 4).

The reaction of N-ethoxycarbonyl- or N-methoxycarbonyl pyrrole with o-fluorobromobenzene, carried out like a Grignard synthesis, proceeded smoothly. The magnesium shavings were dried in an oven and all glassware was flamed. Occasionally, methyl iodide or ethylene dibromide was used to initiate the reaction. Yields of the N-alkoxycarbonyl-7-azabenzonorbornadiene were comparable to those previously$^{17}$ obtained, i.e., 35-45%. The infrared spectra of these compounds showed a carbonyl absorption at 1705 cm$^{-1}$ for the N-alkoxycarbonyl group (Fig. 5). The nmr spectra obtained were similar to those obtained from the t-butoxycarbonyl derivative except that the alkyl protons of the ethoxycarbonyl group (Fig. 6) showed the quartet and triplet pattern of an ethyl group.

The selection of a benzyne precursor is a matter of preference. Comparable yields are achieved in the reaction with o-fluorobromobenzene.
Fig 3. Infrared Spectrum of N-Ethoxycarbonyl Pyrrole.
Fig 4. NMR of N-Ethoxycarbonyl Pyrrole.
Fig 5. Infrared Spectrum of N-Ethoxycarbonyl-7-azabenzonorbornadiene.
Fig 6. NMR of N-Ethoxycarbonyl-7-azabenznorbornadiene.
as a source of benzyne and with benzenediazonium carboxylate as the source. The latter compound is readily available\textsuperscript{22} from o-anthranilic acid, and, by its use, one avoids those problems usually associated with Grignard-type reactions in which the magnesium salts obtained during workup are difficult to separate. Following the recommended procedure\textsuperscript{22} and keeping the diazonium salts wet with solvent eliminates most of the explosion hazards associated with diazonium salts. But even with plastic funnels and rubber or teflon spatulas, detonation can and has still occurred\textsuperscript{23}. Small amounts dry very rapidly, particularly in a hood and the dry diazonium salt is very sensitive to the slightest shock.

Keeping in mind these precautions, benzyne is very conveniently generated thermally in the presence of the appropriate N-alkoxycarbonyl pyrrole. The course of the reaction can be followed by observing the evolution of nitrogen and carbon dioxide. Running the reaction in refluxing tetrahydrofuran shortens the reaction time from 40 to 50 hours needed by Prinzbach\textsuperscript{21} to 1 or 2 hours with comparable yields. The desired N-alkoxycarbonyl-7-azabenzenorbornadiene was prepared as shown on the following page:
The selection of a particular alkoxy carbonyl group to use with the pyrrole is a matter of preference, expense and health. Any of the three used here gave comparable yields, but the disadvantages of handling the \( \text{-} \text{t-Butylazidoformate} \) make its use a serious hazard. Further, the results obtained with the two different benzyne precursors were the same; benzyne, regardless of the method of generation, reacts in the same way. 

\[ R = \text{-COO-t-Butyl, -COOC}_2\text{H}_5, \text{-COOCH}_3 \]
ATTEMPTS AT SYNTHESIS OF BENZTROPINONE (I)

With sufficient quantities of the azabenznorbornadiene available, a potential route to benztropinone was the next objective via the route suggested by the carbocyclic analog\textsuperscript{25}. Addition of dichlorocarbene, from any convenient precursor, to the norbornene ring system has been shown to give spontaneous rearrangement\textsuperscript{25} to the ring enlargement product:

\[
\begin{align*}
\text{norbornene} + : \text{CCl}_2 & \rightarrow \text{norbornene with Cl} \\
\text{Lithium aluminum hydride reduction of the alkyl chloride, followed by acid hydrolysis of the vinyl halide, has been shown}^\text{26,27} \text{ to produce the ketone, bicyclo(3.2.1)octanone-3 (V).}
\end{align*}
\]

Dichlorocarbene addition to the double bond in N-\text{t}-butoxycarbonyl-7-azabenznorbornadiene (II, R = COO-\text{t}-Bu) was attempted in order to give ultimately N-\text{t}-butoxycarbonyl-7-azabenztropinone (I).
Initially dichlorocarbene was generated from chloroform, using potassium t-butoxide as the base, but no adduct could be isolated, although the reaction was repeated several times. Ethyl trichloroacetate was used as the carbene precursor with potassium t-butoxide as the base. Again, no adduct was isolated. The base was changed to sodium methoxide since it was reported\textsuperscript{28} that traces of t-butyl alcohol in the potassium t-butoxide can interfere with the reaction. Both chloroform and ethyl trichloroacetate were used as carbene precursors, and still, after workup, no product was isolated. Other workers\textsuperscript{29} have reported a similar lack of success in the 1-benzazapine ring system using dibromocarbene generated with potassium t-butoxide, although when phenyl(tribromomethyl)mercury was used, the reaction was reported to give the expected dibromocarbene adduct.

On the other hand, in the nitrogen heterocyclic series, no evidence for the expected adduct was ever obtained; usually starting material was the only identifiable, recovered product. After a series of futile attempts, including carrying out the lithium aluminum hydride reduction and acid hydrolysis without isolating any intermediates, this route was abandoned.
HYDROBORATION OF
N-ALKOXYCARBONYL-7-AZABENZNORBORNADIENE

Following reactions successfully carried out in the analogous\textsuperscript{8,30} carbocyclic systems, N-\textit{t}-butoxycarbonyl-7-azabenzonorbornadiene, \textit{I}la, was hydroborated, using diborane, to give the alcohol \textit{Il}la, after oxidative workup. The procedure developed by Brown and Zweifel\textsuperscript{31} was used with N-ethoxycarbonyl-7-azabenzonorbornadiene which was also treated with diborane in tetrahydrofuran. Oxidation of the resulting alkylborane was carried out with alkaline hydrogen peroxide to give the racemic alcohol, \textit{Il}lb, as a pale rose oil. The infrared absorption spectrum (Fig. 7) showed the hydroxyl absorption at 3450 cm\textsuperscript{-1} and the carbonyl absorption at 1705 cm\textsuperscript{-1}. The nmr spectrum (Fig. 8) showed the hydroxyl proton at 3.35 ppm; addition of D\textsubscript{2}O caused disappearance of this peak. The bridgehead protons appear at 5.05 ppm, an upfield shift of 0.5 ppm from the unsaturated compound. The methyl and methylene protons of the ethoxycarbonyl group appear at 1.25 ppm and 4.15 ppm, respectively, with J = 14 Hz. The C-2 endo proton, which is expected to be deshielded by the adjacent oxygen, is buried in the methylene quartet at 4.15 ppm. If one dissects the quartet, using the coupling constants obtained above, the peak at 3.95 ppm is seen to be extraneous to the methylene group.
Fig. 7. Infrared Spectrum of (+)-exo-N-Ethoxycarbonyl-7-azabenznorbornenol.
Fig. 8. NMR of (+)-exo-N-Ethoxycarbonyl-7-azabenzonorbornenol. Spectrum II is after the addition of D_2O.
The multiplet at 1.85 ppm is assigned to the C-3 protons.

Oxidation of the alcohol, IIa and b, to the ketone, IV, was attempted with several oxidizing agents (Scheme 11). Oppenauer oxidation with aluminum isopropoxide was not successful in this system, although the reaction gave good yields of ketones in analogous carbocyclic systems which had no alkyl groups in the bridgehead position.

Since the bulky t-butoxycarbonyl group on the nitrogen could be inhibiting the oxidation reaction through a steric effect, the corresponding N-ethoxycarbonyl alcohol was prepared (IIIb, R = COOC₂H₅) as described above.

Dimethyl sulfoxide/acetic anhydride oxidation was carried out on the N-ethoxycarbonyl alcohol IIIb, and the product, IV, showed two carbonyl absorption bands, one at 1750 cm⁻¹ and one at 1705 cm⁻¹ which is for the N-ethoxycarbonyl group. However, the yield was very low, so this approach was not pursued.

Direct oxidation of the trialkyl borane formed by diborane addition to the unsaturated compound II, using chromic acid as the oxidizing agent, produced the desired ketone IV. The infrared spectrum (Fig. 9) showed no OH absorption and two carbonyl
SCHEME II
Fig. 9. Infrared Spectrum of (+)-N-Ethoxycarbonyl-7-azabenznorbornenone.
absorptions, the N-ethoxycarbonyl group at 1705 cm\(^{-1}\) and the ketone carbonyl at 1750 cm\(^{-1}\). The UV spectrum (Fig. 10) shows a carbonyl absorption pattern \([327 \text{ nm (687); 317 nm (606); 300 nm (920); 287 nm (625)}]\) which Mislow\(^{35}\) has described as characteristic for the strengthened \(n \rightarrow \pi^*\) carbonyl transition in \(\beta,\gamma\)-unsaturated ketones.

Based on these results, it appeared that chromic acid oxidation of the alcohol would give the desired ketone. Because the ring system II is sensitive to acid\(^{17}\) and does rearrange in acid solution to substituted naphthalenes, chromium trioxide in pyridine was used.\(^{36}\) The reaction was successful and is described in a subsequent section.
Fig 10. Ultraviolet Spectrum of (±)-N-Ethoxycarbonyl-7-azabenzonorborneno
ASYMMETRIC HYDROBORATION

Once it had been shown that hydroboration would take place in this system and that the resulting N-alkoxycarbonyl-7-azabenzonorbornenol could be oxidized to the ketone, attention was turned to the use of optically active hydroborating agents\textsuperscript{37,38} to give the previously prepared alcohols in optically active form. (\(-\))\-\(\alpha\)-Pinene was used with diborane obtained commercially as a 1 M solution in tetrahydrofuran to give the (\(\varphi\))\-di-3-pinanylborane\textsuperscript{39}. (\(\varphi\))\-\(\alpha\)-Pinene was reacted with diborane generated \textit{in situ} from sodium borohydride and boron trifluoride etherate in diglyme to give the (\(-\))\-di-3-pinanylborane\textsuperscript{38}. Both N-ethoxycarbonyl- and N-methoxycarbonyl-7-azabenzonorbornadiene were used as the symmetrical substrates. The former was reacted with the adduct formed from (\(-\))\-\(\alpha\)-pinene and the latter with the adduct from (\(\varphi\))\-\(\alpha\)-pinene.

The reaction of \(\alpha\)-pinene with diborane proceeded smoothly at 0\(^{\circ}\) yielding the partially insoluble di-3-pinanyl borane. After addition of the N-alkoxycarbonyl-7-azabenzonorbornadiene, the reaction was maintained at 0\(^{\circ}\) for three hours before being allowed to come to room temperature. Both the temperature and the time factors were controlled as closely as possible in order to prevent the possibility of the same sort of stereo-chemical reversal which Mislow reported\textsuperscript{8}. 
Since the alcohols obtained differed essentially only in their optical activity (see below), the general discussion which follows refers to both chiral alcohols interchangeably.

After oxidation with alkaline hydrogen peroxide and workup, the crude reaction product containing isopinocampheol and the alcohol III was purified in one of two ways. It was distilled to remove most of the isopinocampheol and the distillation residue was chromatographed repeatedly on Florisil to obtain the alcohol as an orange oil which solidified on standing. The infrared spectrum (Fig. 11) showed a hydroxyl peak at 3450 cm\(^{-1}\) and a carbonyl absorption peak at 1705 cm\(^{-1}\).

Alternatively, the crude reaction product was acetylated with acetic anhydride in pyridine\(^8\). Fractionation of the acetates was done on Florisil to give the N-alkoxy-7-azabenznorbornenol acetate as an oil. The infrared spectrum (Fig. 12) showed no hydroxyl absorption and a broad carbonyl absorption from 1750 cm\(^{-1}\) to 1700 cm\(^{-1}\). The acetate carbonyl absorption is reported to be at 1740 cm\(^{-1}\) for the analogous homocyclic system\(^8\). The carbonyl absorption for the N-alkoxycarbonyl occurs at 1705 cm\(^{-1}\). The nmr for IIIc acetate (Fig. 13) shows, in addition to the aromatic proton multiplet at
Fig 11. Infrared Spectrum of (+)-exo-N-Ethoxycarbonyl-7-azabenzonorbornenol (neat).
Fig 12. Infrared Spectrum of (+)-exo-N-Methoxycarbonyl-7-azabenzonorbornenol -Acetate.
Fig. 13. NMR of (+)-exo-N-Methoxycarbonyl-7-azabenznorbornenol Acetate.
7.3 ppm and the bridgehead protons' singlet at 5.25 ppm, a doublet of doublets at 4.85 ppm, which integrates for one proton and is assigned to the endo C-2 proton which is further deshielded than in the alcohol, by the adjacent acetate group. The doublet has $J = 8$ Hz, which results from coupling with the cis endo proton at C-3. The doublet of doublets results from further coupling of the C-2 proton with the trans exo-proton at C-3, $J = 14$ Hz. The acetate methyl protons appear as a singlet at 3.80 ppm. The urethane methyl singlet at 2.15 ppm stands out of the C-3 proton multiplet at 2.10 ppm, which cannot be further analyzed because of the overlap of the two signals.

Repeated attempts to obtain a sample of the acetate which would show two carbonyl absorptions in the infrared were unsuccessful. Successive elutions from alumina and Florisil gave the acetate as an oil which showed only the broad carbonyl absorption described. Since there was no sharp doublet at 1385 and 1365 cm$^{-1}$ which is characteristic of a gem-dimethyl group$^{40}$, the sample was judged to be free of any isopinocampheol acetate.

Reduction of the acetate IX with lithium aluminum hydride and subsequent workup gave the desired alcohol. The infrared spectra of
the alcohols obtained by either method were identical.

The spectrum taken in chloroform (Fig. 14) showed two hydroxyl absorptions typical of an alcohol, the band at lower wavenumber indicating some type of hydrogen bonding and that at higher wavenumber the nonbonded hydroxyl. The fact that hydrogen bonding to an aromatic ring is very weak and that amides are possible but as yet unproved hydrogen bond acceptors even at the carbonyl group eliminates these functional groups from hydrogen bonding as shown in this IR spectrum. Further evidence for the absence of intramolecular hydrogen bonding was obtained from dilution study. In the solution spectrum of III (c, 0.2 mol/liter CHCl₃, Fig. 14), there is a sharp band at 3600 cm⁻¹ and a broad band at 3450 cm⁻¹ of much greater intensity. Dilution with chloroform (c, 0.008 mol/liter, Fig. 15) causes an intensification of the band at 3600 cm⁻¹ while the absorption at 3450 cm⁻¹ diminishes so that the relative intensities are reversed (Fig. 15). This is indicative of intermolecular, rather than intramolecular hydrogen bonding. In order for intermolecular hydrogen bonding to occur in this bridged system, the alcohol group at C-2 must have the exo-configuration. This is in agreement with Brown's work in norbornene systems in which hydroboration of the double bond
Fig. 14. Infrared Spectrum of (+)-exo-N-Methoxycarbonyl-7-azabenzenorborneol·(CHCl₃).
Fig. 15. Infrared Spectrum of (+)-exo-N-Methoxycarbonyl-7-azabenznorbornenol (CHCl₃).
For difference in concentration and comparison with Fig. 14, see text.
results in formation of the exo-alcohol. Further, in Mislow's preparation of 2-benzenorbornenone the exo-acetate obtained from hydroboration of benzenorbornadiene and subsequent reaction with acetic anhydride/pyridine accounted for 99% of the reaction product.

It is concluded, then, that in the azabenzenorbornenol system the alcohol formed by hydroboration of azabenzenorbornadiene is the exo-alcohol, which is the one formed in carbocyclic systems used as models (Scheme 3).
OPTICAL ACTIVITY

Once the alcohols were obtained and their configurations determined to be exo-, their chiroptical properties were measured. The optical rotatory dispersion curves (ORD) (Fig. 16) and the circular dichroism (CD) curves (Fig. 17) show that exo-N-ethoxycarbonyl-7-azabenznorbornenol and exo-N-methoxycarbonyl-7-azabenznorbornenol are optically active and mirror images at the chiral center. The exo-N-methoxycarbonyl-7-azabenznorbornenol, prepared from (α)-α-pinene, has a positive Cotton effect \( [\alpha]_{\text{max}} = 9 \times 10^3 \), 222 nm, while the exo-N-ethoxycarbonyl-7-azabenznorbornenol, prepared from (-)-α-pinene, has a negative Cotton effect \( [\alpha]_{\text{max}} = -12 \times 10^3 \), 222 nm. *

The ultraviolet absorption spectrum of the alcohols (Fig. 18) shows a maximum absorption at 210 nm. In Fig. 16 the point of zero rotation of the major Cotton effect occurs at 212 nm. This uv band at 210 nm, then, is the optically active absorption band.  

In the carbocyclic system, (α) exo-2-benzenorbornenol, VII, has a moderate Cotton effect \( [\alpha]_{\text{max}} = 4400 \) at 226 nm which is attributed to the primary benzenoid transition. Further, * The ellipticities are given for the products of unknown optical purity.
Fig 16. ORD of (+)- and (-)-N-Alkoxycarbonyl-7-azabenzonorbornenol.
(\(\Phi\))-2-methylenebenzonorbornene VIII also shows a Cotton effect at 224 nm, but the intensity (\([\theta]_{\text{max}} < 12 \times 10^4\)) is much greater. The increased intensity is the result of the transition arising from a mixing of the ethylenic states with the states of the primary benzenoid transition.

Based on this, consideration of the CD for (\(\Phi\)) III, in which the principal Cotton effect is at 222 nm, suggests that the intensity of this Cotton effect is the result of a transition involving the primary benzenoid transition mixed with the n-\(\pi^*\) transition of the -NCOOR (carbamate) group. The intensity is at least twice that of the corresponding carbocyclic compound VII. The only chromophore present in the molecule, in addition to benzene, which absorbs in this region and which is not present in VII, is the N-methoxycarbonyl group.

This type of enhancement had been considered as a charge-transfer type interaction, but more recently, the interaction has been described as a through-space or transannular one.

In order for this sort of transannular interaction to occur, the geometrical conformation of the molecule must be such that the benzene ring and the -NCOOR group are coplanar or nearly so.
Fig 17. CD of (+)- and (-)-$	ext{N}$-Alkoxy carbonyl-7-azabenzonorbornenol.
Fig 13. Ultraviolet Spectrum of (-)-exo-x-Ethoxycarbonyl-7-azabenzonorbornanol.
VII

(+)-exo-2-benzonorbornenol

VIII

(+)-2-methylenebenznorbornene
Examination of Dreiding models and Fig. 19, which is an edge-on view of exo-N-alkoxycarbonyl-7-azabenzenorbomenol, shows that the plane of the -NCOOR group is almost parallel to that of the benzene ring and the pi orbitals of the carbamate group are nearly parallel to the pi orbitals of the benzene ring. Although the exact geometry of amide and urethan functions is not yet resolved, the planar N-C=O for the peptide bond argues for a planar rather than a tetrahedral nitrogen. The overlap of the orbitals of the free pair of electrons on nitrogen and the carbonyl pi electrons will decrease the bond length of the N-C bond and increase its double bond character. The alkoxy group of the urethan will thus lie over one of the bridgehead carbons and the carbonyl over the other with interchange of position rapid at room temperature. The nmr (Fig. 8) of the alcohol (-)-IIb suggests that the rate of interconversion of these structures might be slow enough to measure on the nmr time scale. One finds, therefore, that the Cotton effect at 222 nm, which corresponds to the optically active ultraviolet absorption band at 210 nm, is the result of a mixing of the n→π* excited state of the -NCOOR group with those of the primary benzenoid π→π*transition.

This Cotton effect, seen at 222 nm, is basically that of an asymmetrically perturbed benzene chromophore, enhanced by some through-space contribution from the carbamate group.
FIG 19. Orbital geometries for $\pi-\pi$ overlap in exo-N-alkoxycarbonyl-7-azabenzenorbornenol.
Since the 260 nm transition is a forbidden one for benzene\textsuperscript{53},
the low intensity or even absence of any absorption in this region is
to be expected. Mislow reported\textsuperscript{43} the absence of any Cotton effect
for this secondary benzene transition in exo-2-benznorbornenol (VII)
in which the primary benzenoid transition was the optically active
absorption band.

Benzene as an optically active chromophore has been described
by Verbit\textsuperscript{54,55} and other workers\textsuperscript{56,57,58}. More recently,
Snatzke\textsuperscript{59,60} has proposed sector rules for correlation of the sign of
the Cotton effect in the CD with the absolute configuration of benzenoid
compounds. Using the chiral sphere concept\textsuperscript{61} in a compound such as
III requires that the chiral third sphere be the determining factor in the
prediction of the sign of the Cotton effect. Local symmetry in the
second sphere, i.e., a lack of helicity, precludes its use in the pro-
posed sector rules. As Fig. 20 shows, however, there are two ways
in which (\textpm)-III can be fitted to the chiral third sphere sector rules:
(a) the nitrogen bridge can be down, below the plane, or (b) up, out
of the plane. This, of course, allows one to predict the sign of the
Cotton effect arising from the primary benzene transition to be negative
for the 1R:2S or positive for the 1S:2R configuration. Since
FIG 20. Third Sphere Contribution to Cotton Effect (Snatzke). The model is applied to (+)-1R,2S-IIIc. Note that the back sectors (i.e., below the plane of the benzene ring) reverse the predicted sign of the Cotton effect.
exo-N-methoxycarbonyl-7-azabenzenorbornenol (IIIc) shows a positive Cotton effect at 220 nm, it may be assigned the 1S:2R configuration on the basis of Snatzke's rule. Unfortunately, this is incompatible with a prediction based on Mislow's model compound and fails to fit the final result of the ketone. Consequently, it seems unlikely that Snatzke's hypothesis applies in this instance.

A better predictive model for correlating the sign of the Cotton effect with the absolute configuration is the \( \beta,\gamma \)-unsaturated ketone rule which is described in detail in the section dealing with the ketones resulting from oxidation of (+)- and (-)-III.
ABSOLUTE CONFIGURATION

The optically active transition in the enantiomers of both \( \text{exo-\textsubscript{N}-alkoxycarbonyl-7-azabenznorbornenols (III)} \) is then the result of the asymmetrically perturbed benzene chromophore, intensified by some transannular interaction with the \(-\text{NCOOR}\) group. Mislow has shown\(^8\) for the carbocyclic system that the \( \text{(+)-exo-2-benznorbornenol (VII)} \) has the \( (2S)\)- configuration and that this compound has a positive Cotton effect at 226 nm arising from the asymmetrically perturbed benzene chromophore. Therefore, in order for its nitrogen analog, \( \text{(+)-exo-\textsubscript{N}-methoxycarbonyl-7-azabenznorbornenol (IIIc)} \) to have a positive Cotton effect at 222 nm from the same chromophore, it also must have the \( (2S)\)- configuration. Correspondingly, its enantiomeric type homolog, \( \text{(-)-exo-\textsubscript{N}-ethoxycarbonyl-7-azabenznorbornenol (IIlb)} \) must have the \( (2R)\)- configuration (Fig. 21).
Fig 21. Absolute Configuration
TRANSITION STATE CONSIDERATIONS

The absolute configurations of (+) IIIc and (-) IIIb have been assigned, based on their Cotton effects, resulting from the comparison with a compound of known configuration (VII). It now becomes of interest to examine the stereochemical outcome of the asymmetric induction in terms of some model in order to correlate empirical observations and conclusions drawn from them with the predictive capabilities of the model. One such model which has been suggested for asymmetric hydroboration of cis alkenes is that of McKenna.

Using the McKenna model for prediction of the stereochemistry of the products requires the assumption that the cyclic N-alkoxycarbonyl-7-azabenznorbornadiene will undergo the same sort of transition intermediate as an acyclic cis alkene. Peroxide oxidation of the carbon-boron bond has been shown to proceed with retention of configuration. Further, it has been shown that hydroboration in this bridged system, as well as in other bicyclic systems, produces the alcohol having the exo-configuration. Therefore, the transition state leading to the optically active alcohol product will be the one in which an exo-boron-carbon bond is formed. In the McKenna model, the steric
interactions between the angular methyl group in the tetra-3-pinanyldiborane and the nitrogen bridge of the azabenznorbornadiene are such that the favored transition state is the one in which the nitrogen bridge is on the side away from the angular methyl group (Fig. 22).

The product from asymmetric hydroboration and oxidation of N-alkoxycarbonyl-7-azabenznorbornadiene with (-)-di-3-pinanylborane is the exo-alcohol with the S configuration at C-2.

The McKenna^ model thus predicts the same configuration as has been assigned by consideration of the CD and by the use of the modified octant rules^ for the ketone resulting from oxidation of the alcohol which will be discussed below.

Oxidation of (±) III to (±) IV was carried out smoothly, using a modified Sarett procedure in which the chromium trioxide-pyridine complex is prepared and used in methylene chloride. The infrared spectrum (Fig. 9) of the ketone obtained after purification by elution from alumina showed no hydroxyl absorption and two carbonyl absorptions. The keto-carbonyl absorption is at 1750 cm\(^{-1}\), while the urethane carbonyl absorption is at 1705 cm\(^{-1}\). The ultraviolet spectrum (Fig. 10) shows the quadruplet between 280 nanometers and 325 nanometers,
FIG 22. McKenna model for reaction of (-)-tetra-3-pinanyl-diborane with (+)-IIIc in the bond forming step of the reaction. The product is predicted to have the 1R,2S-configuration.
which Mislow\textsuperscript{35} has described as characteristic for the strengthened \( n \rightarrow \pi^* \) transition in \( \beta, \gamma \)-unsaturated ketones.

The CD spectrum of (\( \dagger \))-IVc (Fig. 23) shows a strong positive Cotton effect at 304 nm for the optically active carbonyl transition, and a second, more intense, positive Cotton effect at 231 nm, which is attributed to the asymmetrically perturbed benzene \( \pi \rightarrow \pi^* \) transition intermixed with the \( n \rightarrow \pi^* \) transition of the urethane group. This transition is shifted approximately 10 nm toward longer wavelengths than the same transition in the alcohol, (\( \dagger \)) IIIc. This same red shift is also apparent in the CD spectra of the corresponding carbocyclic ketone (VIIa) and alcohol (VIIb) obtained by Mislow (Fig. 24). It is attributed\textsuperscript{35} to the interaction which occurs between the benzene \( \pi \) electrons and the non-bonding \( \pi \) electrons of the carbonyl oxygen.

Since the configuration of the ketone (\( \dagger \)) IVc has not been changed by oxidation of the 1R,2S(\( \dagger \))-IIIc alcohol, the sign of the short wavelength Cotton effect, resulting from the asymmetrically perturbed benzene chromophore, will not change. As Fig. 17 shows, it is positive. The absolute configuration of the ketone (\( \dagger \)) IVc, then, is the same as the alcohol (\( \dagger \)) III from which it was prepared. Both have the 1R configuration.
Fig 23. CD of (+)-N-Methoxycarbonyl-7-azabenzonorbornone.
Fig. 24. CD of (+)-2-Benznorbornenone.
Further support for the assignment of the 1R configuration for (+) IVc is found in the use of the modified octant rule for $\beta, \gamma$-unsaturated ketones$^{62}$. In order to satisfy the geometrical requirements of the octant rule that the angle of intersection between the two planes be about 120° for rigid systems, the nitrogen bridge must be down. The result is shown in Fig. 25; 1R-(+)-IVc is predicted to have a positive Cotton effect at 300 nm, while its enantiomeric homolog 1S-IVb is predicted to have a negative Cotton effect for the same carbonyl transition.
Fig. 25. Application of $\beta,\gamma$-Unsaturated Ketone Rule$^6$ to the ketone (+)-IVc leads to prediction of positive Cotton effect at 300 nm.
SUMMARY

N-alkoxycarbonyl-7-azabenznorbornadienes II were prepared by Diels Alder reaction of benzyne with an appropriately substituted pyrrole. N-alkoxycarbonyl-7-azabenznorbornenols, III, enantiomeric at C-2, were obtained by asymmetric hydroboration with (+)- and (-)-α-pinene. The _exo_- configuration for the hydroxyl group was confirmed by observation of peak intensity changes in the infrared for successive dilutions of chloroform solutions of the alcohols, III. The ORD and CD were measured and the absolute configurations of (+)-IIIc and (-)-IIlb were assigned as 1R,2S and 1S,2R, respectively, based on consideration of the ORD and CD of the homologous carbocyclic compounds. An attempt to apply Snatzke's predictive model for benzene chromophores gave contradictory results.

Using McKenna's transition state model for predicting the stereochemistry of the products from asymmetric hydroboration, the configurations predicted were in agreement with those assigned on the basis of the ORD and CD.

The alcohols III were oxidized to the ketones IV and their ORD and CD were measured. Using the modified octant rule for β,γ-unsaturated ketones supports the 1S and 1R assignments made for (-)-IVb and (+)-IVc, respectively, and therefore the absolute configurations assigned for the alcohols IIlb and Ilic.
EXPERIMENTAL

GENERAL

Melting Points. Melting points were determined in capillaries using a Thomas-Hoover melting point apparatus and are corrected.

Infrared Absorption Spectra. Infrared spectra were obtained on one or more of the following instruments: Perkin-Elmer model 337 spectrophotometer, Perkin-Elmer model 700 spectrophotometer, Perkin-Elmer model 221 spectrophotometer, Beckmann model IR5 spectrophotometer. All of these instruments were equipped with sodium chloride optics. Samples were run as thin films between sodium chloride plates or in chloroform solution in 0.1 mm matched sodium chloride liquid sampling cells. The frequency of absorption maxima are given in units of reciprocal centimeters (cm⁻¹).

Ultraviolet Absorption Spectra. Ultraviolet absorption spectra were measured with a Cary model 14 spectrophotometer in absolute methanol, unless otherwise indicated, from 360 to 200 nm using cells with a pathlength of 1 cm. Positions of absorption maxima (λ_{max}) are reported in units of nanometers (nm) in the form λ (ε) where ε is the extinction coefficient at wavelength λ.
Optical Rotatory Dispersion Curves. Optical rotatory dispersion curves were determined with a Cary model 60 recording spectrophotometer in methanol, in 1.0 cm or 0.1 cm pathlength cells.

Circular Dichroism Curves. Circular dichroism curves were determined with a Cary model 60 recording spectrophotometer equipped with a CD attachment. Samples were run as solutions in methanol unless otherwise indicated in cells of 1 cm or 0.1 cm pathlengths. Points for maxima, minima and zero rotation are reported at wavelength $\lambda$ in the form $\lambda [\theta]_{\text{max}}$ where $[\theta]_{\text{max}}$ is the molecular ellipticity.

Nuclear Magnetic Resonance Spectra. Nuclear magnetic resonance spectra were obtained in chloroform-d solution, using a Varian Associates model A-60 nmr spectrometer or a Japan Electron Optics Laboratory model HA-100 nmr spectrometer. Chemical shifts are reported in parts per million (‰) downfield from an internal tetramethyilsilane (TMS) reference. Coupling constants (J) are given in units of cycles per second (Hz).
REACTION SCHEME

\[
\begin{align*}
&\text{Ncoor} \quad \text{V} \\
&\text{Ncoor} \quad \text{V} \\
&\text{Ncoor} \quad \text{V} \\
&\text{Ncoor} \quad \text{V} \\
&\text{Ncoor} \quad \text{V}
\end{align*}
\]
t-Butyl Pyrrole-1-carboxylate (VIa). A solution of 35 g (0.51 mol) of commercial pyrrole (Aldrich) in 250 ml of tetrahydrofuran which had been dried over sodium was heated to reflux with stirring under nitrogen. Small pieces of potassium metal (19.5 g, 0.05 mol) were added with stirring over a 2-hr period. The reaction mixture was heated at reflux until there was no metal visible (about 2 hr) and then cooled to 0°C in an ice-salt bath. t-Butyl azidoformate (Aldrich, 50 g, 0.35 mol) in 50 ml of dry tetrahydrofuran was added dropwise with stirring and cooling over a 2-hr period. Stirring with cooling was continued for an additional 2 hr, after which the reaction mixture was allowed to come to room temperature; 100 ml of water and 100 ml of ether were added. The organic layer was separated and the aqueous layer was extracted twice with 50 ml of ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give a dark red oil. The product VI obtained by distillation was a colorless oil, 35.2 g (60%), bp 66-67°C (6 mm) (lit17 91-92°C, 20 mm), ir (neat) 1750 cm⁻¹ (C = O); nmr (CDCl₃): δ 1.50 (s, 9H, t-butyl), 6.12 (t, 2H, 3,4-H), 7.20 (t, 2H, 2,5-H).
**Ethyl Pyrrole-1-carboxylate, (Vlb).** Potassium pyrrole was prepared as above and the reaction mixture was cooled to 0° in an ice-salt bath. Ethyl chloroformate (Eastman) (54 g, 0.50 mol) was added dropwise over 1.5 hr with stirring which was continued for an additional 1 hr, after which the reaction mixture was allowed to come to room temperature. Water (100 ml) and ether (100 ml) were added and the aqueous layer was separated and washed twice with ether. The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was distilled to give 50.75 g (72%) of a pale yellow oil, Vlb, bp 76-78° (18 mm) (lit^1^ 179-181°, 760 mm); ir (neat): 1750 cm⁻¹ (C = O); nmr (CDCl₃): δ 0.83 (t, 3H - OCH₂CH₃), 3.90 (2H - OCH₂CH₃), 5.82 (t, 2H, 3,4-H), 6.90 (t, 2H, 2,5-H).

**Methyl Pyrrole-1-carboxylate (Vlc).** This compound was prepared as above, using methyl chloroformate (Eastman) in place of ethyl chloroformate. After distillation, the product was a clear liquid (32 g, 52%), bp 68-69.5° (22 mm) (lit^1^ 168-170°, 760 mm); ir (neat): 1750 cm⁻¹ (C = O).

**N-t-Butoxycarbonyl-7-azabenzonorbornadiene (IIa).** t-Butylpyrrole-1-carboxylate (Vla) (3.2 g, 0.02 mol) and 0.45 g magnesium turnings in 500 ml dry tetrahydrofuran were heated to reflux under nitrogen for 0.25 hr. Approximately 25% of a solution of o-fluorobromobenzene in
50 ml tetrahydrofuran was added. After the reaction began, as shown by the darkening color, the remainder of this solution was added over 0.5 hr and heating at reflux was continued for 1.5 hr. The reaction mixture was cooled to 5° in an ice-salt bath and poured into a solution of 30 g of ammonium chloride and 1 ml of concentrated ammonia in 100 ml of water. The layers were separated; the aqueous layer was extracted with tetrahydrofuran and the organic layer was washed with water. The combined organic layers were dried over potassium carbonate, filtered and the solvent removed under reduced pressure. The crude red oil was taken up in ligroin and filtered. After solvent removal under reduced pressure, the oily product was cooled and triturated with cold petroleum ether (bp 30-60°). The light tan crystals obtained were air-dried to a constant weight (1 g) and sublimed at 65° (3 mm) yielding white crystals, 0.35 g (35%), mp 70-71° (lit17 72-73°); ir (KBr): 1705 cm⁻¹ (C = O), 760 cm⁻¹ (aromatic); nmr (CDCl₃): δ 1.39 (s, 9H, t-Butyl), 5.48 (t, 2H, bridgehead H), 7.2 (m, 6H, 4 aromatic, 2 olefinic).

7-Azabenznorbornadiene Hydrochloride (X)¹⁷. A stirred solution of 11a (30 g) in 100 ml of nitromethane was cooled to 0° in an ice-salt bath. Hydrogen chloride gas was bubbled through slowly, with
stirring, for 5 min. After stirring for an additional hour, 100 ml of dry ether was added. The crude product was collected by filtration; air drying gave 2.0 g (90%) of pale purple crystals, mp 200-204° (dec) (lit 17 198-200°).

7-Azabenzonorbornadiene (XI)17. To 3.5 g (0.02 mol) of the amine hydrochloride X in 30 ml water was added 30 ml of 5 N sodium hydroxide solution. After four extractions with ether, the organic layers were combined, dried over potassium carbonate and filtered. The amine was obtained as a red oil by solvent removal under reduced pressure; ir (neat): 3200 cm⁻¹ (N-H), 760 cm⁻¹ (aromatic); nmr (CDCl₃): δ 3.30 (s, 1H, N-H), 4.85 (s, 2H, bridgehead H), 7.1 (m, 6H, 4 aromatic, 2 olefinic).

N-Ethoxycarbonyl-7-azabenzonorbornadiene (IIb). A. Ethyl pyrrole-1-carboxylate (Vlb) (35.3 g, 0.25 mol) was stirred in 100 ml dry tetrahydrofuran, under nitrogen, with magnesium turnings (6.0 g, 0.25 g-atoms) and heated at reflux for 0.25 hr. o-Fluorobromobenzene (44 g, 0.25 mol) (Aldrich) in 50 ml dry tetrahydrofuran was added slowly until the reaction started. Heating was discontinued and the remainder of the o-fluorobromobenzene was added slowly with cooling
as necessary to control the reaction. When addition was complete, heating at reflux was resumed for 0.5 hr. The reaction mixture was cooled to room temperature and poured into 100 ml of a saturated aqueous solution of ammonium chloride containing 5 ml of concentrated ammonium hydroxide. The organic layer was separated, washed with water and dried over potassium carbonate. Filtration and solvent removal under reduced pressure gave a tacky, red oil which was taken up in petroleum ether (bp 30-60°). The mixture was filtered to remove semisolid material; concentration of the filtrate gave a red oil which was chromatographed on Florisil with petroleum ether/benzene (3/1). Trituration of the resulting orange oil with cold petroleum ether gave 13.2 g (25%) of a yellow solid, mp 50-57°. Sublimation of I lb at 50° (1 mm) for 1 hr gave white crystals, mp 51-3°; ir (CHCl₃): 1705 cm⁻¹ (C = O); nmr (CDCl₃): δ 1.18 (t, 3H, CH₃CH₂-), 4.08 (quart, 2H, CH₃CH₂-), 5.58 (t, 2H, bridgehead H), 7.1 (m, 6H, 4 aromatic, 2 olefinic). Anal. Calcd for C₁₃H₁₃NO₂: C, 72.50; H, 6.03, N, 6.50. Found: C, 71.69, H, 5.72, N, 6.56.

B. Alternatively, N-ethoxycarbonylpyrrole (VIb) (32.5 g, 0.23 mol) was heated at reflux with stirring for 2 hr with 50 g of wet benzenediazonium
carboxylate prepared according to Friedman\textsuperscript{22}. The reaction mixture was poured into water and the organic layer was separated, washed with water and dried over potassium carbonate. After filtration and solvent removal under reduced pressure, the tacky, red oil was taken up in ligroin and filtered to remove semisolid material. The filtrate was concentrated to an orange oil which solidified upon cooling and scratching to give 18 g (35\%) of a yellow-white material, mp 37-52\degree; ir (neat) : 1705 cm\(^{-1}\) (C = O); the nmr was identical with that obtained above.

\begin{center}
\textbf{N-Methoxycarbonyl-7-azabenznorbornadiene (IIc).} N-Methoxycarbonylpyrrole (V\textit{lc}) (12.5 g, 0.1 mol) in 100 ml tetrahydrofuran was heated and stirred at reflux for 2 hr with benzenediazonium carboxylate prepared from 13.7 g (0.1 mol) of anthranilic acid. The reaction mixture was cooled, poured into water and the organic layer separated. The aqueous layer was extracted with ether, and the combined organic layers were dried over potassium carbonate. After filtration, the solvent was removed under reduced pressure; petroleum ether was added to the oily yellow residue and the solution was filtered. The filtrate was concentrated to a yellow oil which was cooled and scratched to yield 8 g (40\%) of a pale yellow solid, mp 50-53\degree; ir (neat) : 1705 cm\(^{-1}\) (C = O).
N-Aminocarbonylpyrrole (XII). N-Ethoxycarbonylpyrrole (VIb) was heated with 15 ml of concentrated ammonium hydroxide on a steam bath for 4 hr. After cooling to room temperature, the reaction mixture was extracted with ether and the organic layer was dried over potassium carbonate. Filtration and solvent removal gave beige crystals, mp 156-61° (lit\textsuperscript{14} 163°); ir (KBr) : 3400 cm\textsuperscript{-1} (NH); 1670 cm\textsuperscript{-1} (C = O).

\((\pm)\)-N-Ethoxycarbonyl-7-azabenznorbornol (IIIb). N-Ethoxycarbonyl-7-azabenznorbornadiene (IIb) (6.0 g, 0.028 mol) was stirred in 50 ml tetrahydrofuran at room temperature. Diborane (15 ml, 0.015 mol) in tetrahydrofuran was added slowly while the temperature was held between 25° and 40°. After stirring for 1 hr, water was added to destroy excess diborane. Sodium hydroxide (3 ml, 3N) was added, followed by hydrogen peroxide (3 ml, 30%). Stirring was continued for 2 hr at 40-50°. The reaction mixture was extracted with ether and the organic layer was dried over potassium carbonate. After filtration and solvent removal under reduced pressure, the pale rose oil obtained was chromatographed on Florisil with petroleum ether/benzene (1/1) to give racemic IIIb as a clear viscous oil; uv (meOH) : \(\lambda_{\text{max}} (\varepsilon) : 278 (280), 263 (380), 242 (550),\)
210 (8000); Ir (neat): 3450 cm⁻¹ (OH), 1705 cm⁻¹ (C = O);

nmr (CDCl₃): δ 1.25 (t, 3H, -CH₂CH₃), 1.35 (t, 2H, C-3 H),
3.35 (s, 1H, OH) 4.15 (m, 3H, -CH₂CH₃, C-2 endo-H), 5.05
d, 2H, bridgehead H), 7.2 (m, 4H, aromatic).

(±)-N-Ethoxycarbonyl-7-azabenznorbomene-2-one (IVb).

(±)-N-Ethoxycarbonyl-7-azabenznorbornenol (IIIb) (0.20 g, 0.9 mmol)
was taken up in 5 ml of dimethyl sulfoxide and 2 ml of acetic anhydride
was added. The solution was stirred at room temperature for 20 hr and
poured into 100 ml water. Ammonium hydroxide (25 ml, 28%) was
added and the reaction mixture was extracted with ether. After washing
with water, the ether layer was dried over potassium carbonate. The
red oil obtained from filtration and solvent removal under reduced pressure
was distilled to give 0.13 g (65%) of a dark oil, bp 184° (14 mm);
ir (neat) 1760 cm⁻¹ (C = O), 1710 cm⁻¹ (carbamate C = O); the OH
absorption region was clear; uv (EtOH): λ max (ε) 343 (790), 327
(700), 300 (920), 287 (1000), 278 (750), 275 (910), 268
(845), and 263 (845).

(-)-exo-N-Ethoxycarbonyl-7-azabenznorbornenol-2 [(-)-IIIb].

Diborane (50 ml, 1 M) in tetrahydrofuran was stirred at 0° under
nitrogen and 20.4 g (0.15 mol) (-)-α-pinene was added over 0.75 hr.
Stirring was continued for 3.5 hr as the white alkylborane formed. N-Ethoxycarbonyl-7-azabenzonorbornadiene (IIb) (2.15 g, 0.01 mol) was added at 0° over a 0.75-hr period. Stirring was continued for 4 hr, after which the reaction mixture was allowed to come to room temperature. Sodium hydroxide (15 ml, 3N) and 15 ml of hydrogen peroxide (30%) were added with ice as necessary to keep the temperature at 35-50° and stirring was continued for 4 hr. The reaction mixture was extracted 3 times with ether; the ether layers were washed with water and dried over potassium carbonate. The crude product obtained after filtration and solvent removal under reduced pressure was distilled to remove isopinocampheol. The distillation residue was chromatographed on alumina and the petroleum ether/chloroform eluate was rechromatographed on Florisil with benzene/ether to give a clear yellow oil; ir (neat): 3450 cm$^{-1}$ (OH), 1705 cm$^{-1}$ (C = 0); nmr (CDCl$_3$): $^6$ 1.30 (t, 3H, -CH$_2$CH$_3$), 2.0 (m, 2H, C-3 H), 3.65 (s, 1H, OH), 4.25 (m, 3H, -CH$_2$CH$_3$, endo-C-2 H), 5.35 (d, 2H, bridgehead H), 7.4 (M, 4H, aromatic H); uv (MeOH): identical to the racemic IIIb; CD (MeOH): 280 (0), 273 (-324), 271 (-243), 267 (-143), 264 (-197), 255 (0), 222 (-11,700), 212 (0), 208 (-6300). Anal. Calcd. for (C$_{13}$H$_{15}$N$_3$O$_3$) • (H$_2$O)$_2$: C,63.66; H, 6.71; N, 5.71. Found: C,63.44; H, 6.55; N, 5.60.
(α)-exo-N-Methoxycarbonyl-7-azabenzonorbornenol-2 [(+)-IIIc].

Boron trifluoride etherate (14.2 g, 0.10 mol) was added to a solution of (α)-α-pinene (27.2 g, 0.2 mol) and sodium borohydride (2.85 g, 0.75 mol) in diglyme at 0° and stirring under nitrogen was continued for 4 hr. A solution of N-methoxycarbonyl-7-azabenzonorbornadiene (IIc) (8.0 g, 0.04 mol) in 50 ml of diglyme was added. Stirring at 0° was continued for 4 hr, after which the reaction mixture was allowed to come to room temperature. Water was added to destroy excess diborane and the reaction mixture was warmed to 35°. Sodium hydroxide (35 ml, 3N) was added, followed by 35 ml of hydrogen peroxide (30%), while maintaining the temperature between 35 and 50°. The reaction mixture was stirred for 3 hr at 45°, cooled to room temperature and extracted with ether. The extract was washed with ice water, then with saturated sodium chloride solution and dried over potassium carbonate. After filtration and solvent removal under reduced pressure, the dark red oil obtained was distilled at reduced pressure to remove most of the isopinocampheol. The distillation residue was chromatographed on alumina with benzene/chloroform to give the alcohol (+)-IIIc, as a pale orange oil; ir (neat): 3410 cm⁻¹ (OH), 1705 cm⁻¹ (C = O); ir (CHCl₃): 3600 cm⁻¹ (OH, unbonded), 3450 cm⁻¹ (OH, bonded), 1705 cm⁻¹ (C = O);
CD (MeOH) : λ [°] , 235 (0), 223 (±9000), 212 (0), 205 (-10,300), 200 (-96,000). The compound was homogeneous on thin layer plates in two solvent systems. Combustion analyses were inconclusive due to small sample size and instrument malfunctions.

(+)–N–Methoxycarbonyl-7–azabenznorbornenol–2–Acetate [(+)–IXc] .

A solution of crude (+)–N–methoxycarbonyl-7–azabenznorbornenol [(+)–IIlc, 0.50 g] in 10 ml of dry pyridine and 10 ml of acetic anhydride was stirred at room temperature for 16 hr. The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, saturated sodium bicarbonate and saturated sodium chloride solutions, and dried over potassium carbonate. After filtration and solvent removal under reduced pressure, the orange oil was chromatographed on Florisil with petroleum ether/benzene which eluted isopinocampheol acetate. The desired product was eluted with 5% absolute methanol in benzene as an orange oil which was rechromatographed on Florisil with hexane. The acetate was obtained as a yellow oil by elution with 5% absolute methanol in chloroform; ir (neat) : 1750, 1700 cm⁻¹ (C = O, acetate and urethane); the OH absorption region was clear; nmr (CDCl₃) :

$^6$2.10 (m, 2H, –C–3–CH₂) ; 2.15 (s, 3H, –NCOOCH₃) ; 3.80 (s, 3H, CH₃C = 0) ; 4.85 (m, 1H, endo C–2H) ; 5.25 (s, 2H, bridgehead H) ; 7.35 (m, 4H, aromatic H).
The acetate was converted to the alcohol by refluxing a solution of the acetate in ether with lithium aluminum hydride for 4 hr. Sodium hydroxide (3N) was added to decompose the complex and the reaction mixture was filtered and extracted with ether. The extracts were dried over potassium carbonate, filtered and the solvent removed under reduced pressure. The oil obtained was chromatographed on Florisil to give the alcohol as a pale orange oil whose IR was identical to that of the alcohol IIIc.

\((\pm)-N\text{-methoxycarbonyl-7-azabenzonorbornenone-2-[(+)-IVc]}\).

Chromic trioxide (6.0 g, 0.06 mol) was added with stirring to 10 ml (9.42 g) of dry pyridine in 150 ml of methylene chloride; after stirring for 0.25 hr, \((\pm)-\text{exo-N-methoxycarbonyl-7-azabenzonorbornenol-2 (IIIc)}\) (2.1 g, 0.01 mol) in 10 ml of methylene chloride was added. Stirring was continued for 0.5 hr, and the supernatant was decanted from the residual tar which was washed with ether. The combined organic layers were filtered, washed with 5% aqueous sodium hydroxide, 5% aqueous sodium bicarbonate and saturated sodium chloride. The organic layer was dried over potassium carbonate, filtered and concentrated under reduced pressure. The dark oil obtained was chromatographed on silicic acid with benzene/chloroform (1:1) to give the ketone IV as a pale yellow
oil: ir (CHCl₃): 1750 cm⁻¹ (C = O, ketone), 1705 cm⁻¹ (C = O) urethane; the OH absorption region was clear; uv (MeOH): λ max (ε):
343 (793), 327 (687), 317 (606), 300 (918), 287 (1012), 278 (818), 275 (912), 269 (837), 263 (837); CD (MeOH): λ max ([η]): 338 (0), 325 (+415), 314 (+172), 304 (+1515), 295 (+1226), 275.6 (0), 273 (-108), 265 (-162), 260-250 (0), 236.8 (+2272), 235.6 (+2055), 231.8 (+2921). Thin layer chromatography in two solvent systems showed a single compound. Combustion analysis gave poor results because of the small sample size.

2,4-Dimethyl-3,5-dicarbethoxy pyrrole (XII). Ethyl acetoacetate (Fisher) (130 g, 1 mol) in 300 cc glacial acetic acid was stirred at 5°; sodium nitrite (35.7 g, 0.48 mol) in 50 ml water was added slowly with cooling and stirring. When addition was complete, stirring at 5° was continued for 1 hr and the reaction mixture was then allowed to come to room temperature. Zinc dust (65.4 g-atom) was added cautiously until refluxing began and then added at a rate to maintain reflux. Stirring and heating was continued for an additional hour after which the reaction mixture was poured into 3 liters of water which was being stirred vigorously. Washing with water and air drying gave 127 g (53%) of a white solid, mp, 124-129°. Recrystallization
from aqueous ethanol gave a pale yellow solid, mp 132-134° (lit 136-137°). Ir (CHCl₃): 3250 cm⁻¹ (N-H), 1700 cm⁻¹ (C = O); nmr (CDCl₃): δ 1.35 (t, 6H, CH₃CH₂C00); 2.51 (s, 3H, CH₃); 2.54 (s, 3H, CH₃); 4.25 (quart, 2H, CH₃CH₂C00); 4.29 (quart, 2H, CH₃CH₂C00).

N-Benzyl 2,4-dimethyl-3,5-dicarbethoxy pyrrole (XIII).

2,4-Dimethyl-3,5-dicarbethoxy pyrrole (XII) (60 g, 0.25 mol) was heated at reflux under nitrogen in toluene; sodium metal (5.5 g, 0.25 mol) was added in small pieces and stirring with heating was continued until all the sodium had dissolved. The reaction mixture was cooled to room temperature and benzyl chloride (31.6 g, 0.25 mol) was added over 0.25 hr. The reaction was heated at reflux for 6 hr, cooled and filtered. The solid obtained was washed with petroleum ether; the resulting white solid, mp 128-132°, was identified as starting material by its nmr. The filtrate was concentrated and cooled in ice to give an orange granular solid, mp 117-121°, which was washed with petroleum ether. The white solid obtained, mp 133-135°, was identified as starting material by its nmr. The petroleum ether washings were also examined and only starting material was found.
**N-Acetyl imidazole (XIV).** Imidazole (35 g, 0.5 mol) was dissolved in acetic anhydride (0.51 mol, 55 g) and heated on a steam bath for 0.25 hr. The pressure was reduced and the crude product was obtained as a white solid which was recrystallized from ethyl acetate to give white crystals, mp 101-105° (lit\(^6\) 101-102°), \text{nmr (CDCl}_3\text{)}: 2.65 (s, 3H, \text{-CH}_3\text{); 7.1 (m, 1 H, C-4H); 7.47 (t, 1H, C-5H); 8.14 (s, 1H, C-2H}).

**N-Acetyl pyrrole (XV).** Pyrrole (Aldrich) (13.6 g, 0.2 mol) was heated at reflux with N-acetyl imidazole (XIV) for 1 hr. The reaction was cooled and distilled at reduced pressure to give the product as a clear oil, bp 56-57° (20 mm), lit\(^6\) 181-182°, 760 mm); ir (neat): 1705 cm\(^{-1}\) (C = 0); \text{nmr (CDCl}_3\text{)}: 1.70 (s, 3H); 5.28 (t, 2H); 6.35 (t, 2H).

**N-Acetyl-7-azabenzonorbornadiene (XVI).** N-Acetyl pyrrole (XV) (10 g, 0.1 mol) was heated at reflux under N\(_2\) in 50 ml dry tetrahydrofuran. Magnesium turnings (5 g) were added, followed by small portions of o-fluorobromobenzene (8.7 g, 0.05 mol) in 100 ml dry tetrahydrofuran. Although the reaction foamed and the magnesium metal was used up, indicating formation of the benzyne intermediate, no color change occurred as it had in previous benzyne reactions to indicate product
formation. After heating at reflux for 4 hr, the reaction was cooled and filtered. Extraction with petroleum ether and solvent removal gave a colorless oil whose infrared spectrum was identical with that of N-acetyl pyrrole. This reaction was repeated twice more with the same results.

**t-Butylazidoformate (XVII).** Phenyl chloroformate (100 g, 0.66 mol) was added over 2 hr with stirring and cooling to a solution of t-butyl alcohol (64 ml, 0.66 mol) and quinoline (80 ml, 0.66 mol) in 200 ml methylene chloride. After addition was complete, the reaction mixture was poured into a separatory funnel and 150 ml water was added. The organic layer was separated, washed twice with water, twice with 5% hydrochloric acid, then dried over anhydrous magnesium sulfate. The orange oil obtained after filtration and solvent removal was distilled under vacuum to give 50 gm (40%) of colorless t-butyl phenyl carbonate. Hydrazine (15 g, 0.30 mol) was added to t-butyl phenyl carbonate and the mixture was stirred and heated for 0.25 hr. After cooling, 100 ml ether and 250 ml 4N NaOH was added. The entire reaction mixture was continuously extracted with 250 ml ether for 48 hr. The ether layer was separated, dried over magnesium sulfate and filtered. Solvent removal and vacuum distillation of the residual oil gave 30.7 g (90%) of t-butyl carbazate.
To this material (30.7 g, 0.23 mol) was added glacial acetic acid (0.4 M) and 75 ml water. The mixture was cooled to 10° and a concentrated aqueous solution of sodium nitrite (18 g, 0.25 mol) was added slowly while maintaining the temperature at 10-15°.

After addition was completed, the reaction mixture was maintained at 10° for 0.5 hr, then diluted with 100 ml water. The reaction mixture was extracted with four 100-ml portions of ether. The ether extracts were washed with water and then neutralized with 1 M sodium bicarbonate. After drying over magnesium sulfate, the solvent was removed after filtration to yield a dark red oil. t-Butylazidoformate (27 g, 43%) was obtained as a yellow oil by vacuum distillation (bp 69-71°, 55 mm).

N-methylphthalimide (XVIII). Phthalimide (20 g, 0.135 mol) was stirred in 400 ml hot methanol. Potassium hydroxide (7.29, 0.13 mol) in 30 ml of 75% methanol was added. The mixture was stirred and cooled for 0.5 hr. After filtration, the mother liquor was heated and an additional 20 g of phthalimide was added, followed by 7.2 g potassium hydroxide in 30 ml of 75% methanol. Stirring and cooling, followed by filtration and washing with acetone gave 39.0 g (80%) of potassium phthalimide. This (9.5 g, 0.05 mol) was heated
at reflux with methyl iodide (24 g, 0.2 mol) in diethylether for 8 hr. After cooling, the reaction mixture was poured into water and the ether layer was separated, washed with water and dried over potassium carbonate. After filtration and solvent removal, the white solid obtained was recrystallized from methanol to give white crystals, mp 128-132° (lit 69 132°).

**N-Ethoxycarbonyl-8-aza-2,3-dichloro-6,7-benz-hept-3-ene (XIX).** 1lb (5.0 g, 0.22 mol) was stirred at reflux in 50 ml diglyme while sodium trichloroacetate (9.0 g, 0.05 mol) in 10 ml diglyme was added. Stirring with heating was continued for 12 hr, then allowed to cool overnight. The reaction mixture was poured into 100 ml water and extracted into ether. The organic layer was separated and washed with two 50-ml portions of ice water, then dried over potassium carbonate. The dark oil obtained after filtration and solvent removal was distilled under reduced pressure to give only starting material identified by its nmr.

**N-t-Butoxycarbonyl-8-aza-2,3-dichloro-6,7-benz-hept-3-ene (XX).** To a cooled solution of N-t-butoxycarbonyl-7-azabenznorbornadiene (2.3 g, 0.01 mol) in 50 ml dry pentane under nitrogen was added (2.7 g, 0.02 mol) potassium t-butoxide. After stirring for 0.25 hr,
ethyl trichloroacetate (2.0 g, 0.01 mol) in 10 ml pentane was added slowly. Stirring was continued for 6 hr, then the reaction mixture was allowed to warm to room temperature. After addition of 100 ml water, the organic layer was separated, filtered and dried over magnesium sulfate. Filtration and solvent removal gave a red oil which was identified as starting material by its nmr.

N-p-toluenesulfonamide isoindolidine (XXI)\textsuperscript{70}. p-Toluene sulfonamide (12.0 g, 0.07 mol) in a solution of 5 g sodium metal in 220 ml methanol was added over 0.75 hr to \(\alpha\)-xylene dibromide in 100 ml of methanol being heated and stirred at reflux. After addition was complete, the reaction mixture was cooled and poured into 100 ml water. Acetic acid was added to neutralize the solution and the suspension was refrigerated overnight. White crystals (12.5 g, 65%), mp 172-176\(^\circ\) (lit\textsuperscript{70} 175-176\(^\circ\) were obtained by filtration and air drying, nmr (CDCl\textsubscript{3}): \(\delta\) 2.40 (s,3H,\(p\)-CH\(_3\)); 4.65 (s,4H,-CH\(_2\)); (m, 8H aromatic).

Isoindolidine (XXII).\textsuperscript{71} XXI (6.0 g, 0.022 mol) was heated at reflux under nitrogen in a mixture of 65 ml of 48% hydrobromic acid, 7 ml propionic acid and phenol (60 g, 0.65 mol) for 2 hr. The reaction mixture was cooled and washed with ether. The aqueous layer
was slowly poured into concentrated aqueous sodium hydroxide with cooling and stirring. The aqueous reaction mixture was extracted with four 50-ml portions of ether, which were combined and dried over potassium carbonate. After filtration and solvent removal, the isoindolidine was obtained as a dark oil, which was used without further purification, \text{nmr (CDCl}_3): \delta 2.2 \text{ (s, 1H, N-H), 3.58 (s, 4H, -CH}_2\text{), 6.4 (s, 4H, aromatic.)}

\textit{N-Methyl isoindolidine methyliodide (XXIII). XXII (.24 g, 0.002 mol) was taken up in 10 ml dry ether. Potassium hydroxide was added, followed by methyl iodide (1.2 g, 0.1 mol). Filtration gave a tan solid which was recrystallized from ethanol to give grey crystals, mp 247-249\degree C (dec), \text{nmr (D}_2\text{O): \delta 2.9 (s, 6H, N^+-(CH}_3\text{)_2), 4.4 (s, 4H, -CH}_2\text{), 7.05 (s, 4H, aromatic.)}}

Alternatively, to N-methylisoindolidine in dry ether was added methyl iodide. The grey crystals (mp 235-237\degree dec) collected by filtration and air drying had an nmr identical to the salt obtained above.

\textit{N-Methyl isoindolidine (XXIV). The methiodide salt obtained above was taken up in 5 ml water. Solid sodium hydroxide was added and the resulting oil was extracted with three 20-ml portions of ether. The combined extracts were dried over potassium carbonate, filtered}
and the solvent was removed under reduced pressure. The product was obtained as a rose colored oil which was not further purified, nmr (CDCl₃): δ 2.45 (s, 3H, N-CH₃); 3.75 (s, 4H, -CH₂-); 7.1 (s, 4H, aromatic H).

Alternatively, N-methylphthalimide (XVIII) was heated at reflux with lithium aluminum hydride in tetrahydrofuran for 18 hr. The reaction mixture was cooled and 0.3 ml water, 0.3 ml of 15% sodium hydroxide and 0.9 ml water were added successively. The reaction mixture was filtered, washed with water and dried over potassium carbonate. Filtration and solvent removal gave a dark oil whose nmr was identical to that obtained above.
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