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π-ROUTE SYNTHESIS OF AZABICYCLICS.

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π-ROUTE SYNTHESIS OF AZABICYCLICS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

John Henry Dygos, B.S.

The Ohio State University
1970

Approved by

[Signature]
Adviser
Department of Chemistry
ACKNOWLEDGMENTS

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VITA

John Henry Dygos, the son of John and Sophia Dygos, was born in Watervliet, New York on October 18, 1943. He attended Maplewood Grammar School and Watervliet High School in Watervliet, New York. In September of 1961 he entered St. Lawrence University, Canton, New York and received his Bachelors Degree in June, 1965. In September of 1965 he entered The Ohio State University as a pre-doctoral student. He and his wife Dorothy were married on September 7, 1968.
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HISTORICAL

Part 1: Nitrenium Ions

Until recently, the role of nitrenium ions as reaction intermediates had not been extensively studied. The first report of a reaction in which a nitrenium ion was postulated was the reaction of medium sized ring N-chloramines and N-chloramides with silver salts in aqueous dioxane which gave transannular insertion products. When N-chloroazacyclononane (1) was treated with silver tetrafluoroborate in aqueous dioxane, indolizidine (2) was obtained in 68\% yield.

\[ \text{AgBF}_4 \quad \rightarrow \quad \text{2} \]

Similarly, N-chloro-N-methylcyclooctylamine (3) gave 9-methyl-9-azabicyclo[3.3.1]nonane (4) in low yield.

\[ \text{3} \quad \xrightarrow{\text{AgBF}_4} \quad \text{4} \]

1. The term "nitrenium ion" will be used to designate a divalent, positively charged nitrogen species. The singlet state in which the free electrons are paired will be represented by R-N-R. The triplet state in which the free electrons are unpaired will be represented by R-N-R.
The authors proposed that 1 ionized to give the nitrenium ion 4, which can abstract a hydride ion intramolecularly to give 5, which can collapse to give the protonated form of 2. They also stated that a concerted dehalogenation-hydride abstraction mechanism cannot be excluded on the basis of their results.

Recently, it has been shown that the same reaction occurs thermally in the absence of silver ion. Trent reported that 2 was obtained in good yield when a solution of 1 in aqueous dioxane was heated on a steam bath until the solution gave a negative test for active chlorine.

On the basis of results to be discussed later, a third possible mechanism for the formation of 2 may be postulated. In theory, the singlet nitrenium ion, 4, could undergo a spin inversion to the triplet state, 6, in which the non-bonded electrons are unpaired. The triplet ion could then abstract a hydrogen atom intramolecularly to give the diradical, 7, which could collapse to give the protonated form of 2.


Although these cyclizations can be explained on the basis of a nitrenium ion mechanism, they do not necessitate the existence of a divalent, positively charged nitrogen atom.

Gassman and Fox, in an attempt to demonstrate the existence of nitrenium ions, observed Wagner-Meerwein type rearrangement products in the methanolysis of N-chloro-2-azabicyclo[2.2.2]octane (8) and N-chloro-6-azabicyclo[3.2.1]octane (2) using silver ion as catalyst. It is highly unlikely that these products could result from

either a radical or triplet nitrenium ion mechanism since both of these mechanisms would involve a 1,2-alkyl migration to a radical-like center, a process which has not been observed with carbon radicals.

Since the early work of Gassman and Fox, there have been several reports of reactions which can be adequately explained on the basis of nitrenium ion intermediates.

Gassman and Dygos reported that the solvolyses of several methyl and phenyl N-chloroaziridines gave products and rates which were consistent with a concerted ring opening of the aziridine as illustrated for 10. An ionic mechanism is indicated by the fact that 1-chloro-

\[ \text{cis,trans-2,3-dimethylaziridine (10b) solvolyzed 76 times faster in water than in the poorer ionizing solvent methanol. Further support for an ionic mechanism was the fact that there was a predictable increase in the rates of solvolysis of various mono- and disubstituted} \]

aziridines, indicative of a developing positive charge in the transition state. An attempt to prepare the N-chloro derivatives of the diphenylaziridines led only to the recovery of benzaldehyde indicating that the phenyl groups accelerated the ring opening process to such an extent that isolation of the N-chloroaziridines was impossible.

Horwell and Rees extended the solvolysis of N-chloroaziridines to the synthesis of isoquinoline from the aziridine, 11.

\[
\begin{align*}
\text{NH} & \xrightarrow{\text{NaOCl}_2} \quad [\text{N-Cl} \rightarrow \text{N}^+\text{Cl}^-] \\
& \rightarrow \text{N}\text{N}
\end{align*}
\]

Two additional examples of nitrenium ion reactions involve the solvolyses of appropriately substituted N-chloroanilines. Treatment of N-chloro-N-\text{t}-butylaniline (12) with a methanolic solution of silver ion gave a mixture of the ortho- and para-methoxy-N-\text{t}-butylanilines along with the corresponding ortho- and para-chloro derivatives. The

\[
\begin{align*}
\text{Cl} & \text{N} \rightarrow \text{HN} \quad \text{Cl} \text{C}_\text{H}_\text{3}O \\
& \text{HN} \quad \text{OCH}_\text{3}(\text{Cl})
\end{align*}
\]


formation of methoxy derivatives is not consistent with either a radical or anionic process and indicates that even the chlorination products may be arising via a nitrenium ion mechanism. Furthermore, when $N$-chloro-$N$-(t-butyl)-p-toluidine (13) was treated with a methanolic solution of silver ion, $^{14}$ was obtained in 70% yield and 15 was obtained in 17% yield. Similarly, 16 gave 17 which was hydrolyzed without purification to give 18 in 62% yield.

These results are best rationalized on the basis of initial formation of a nitrenium ion with subsequent delocalization of the positive charge by the benzene ring followed by solvent incorporation.

The products of the solvolysis of the substituted $N$-chlorocyclopropylamine, 12, were also explained on the basis of a nitrenium ion mechanism.

Conclusive evidence for the discrete existence of nitrenium ions, both the singlet and triplet states, has recently been presented by Gassman and Cryberg. The solvolysis of N-chloro-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (20) in methanol was reported to give 56% of 21, 20% of 22 and 7% of 23. The reaction scheme proposed by Gassman to explain the formation of the products is outlined in Chart 1.

The formation of 23 requires that a discrete intermediate 24 be formed which has a finite lifetime and which can spin flip to give the triplet state 26. The triplet nitrenium ion can then abstract a hydrogen atom from the solvent to give the protonated cation radical 27. Hydrogen atom abstraction by 27, a process which has analogy in the Hofmann-Loeffler-Freytag reaction, produces the protonated form of 23.

It was postulated that if the nitrenium ion generated by the heterolysis of the N-Cl bond was a discrete intermediate having a unit positive charge, it might be possible to choose reaction conditions which would lead to a spin inversion of the initially produced singlet nitrenium ion to its triplet state resulting in a greater yield of 23. The results of such a study are listed in Table 1.

The fact that the ratio of products in the least polar medium studied, methanol-hexane, is approximately the same as in the most polar medium, methanol, rules out the possibility of a solvent polarity effect in the results of the solvolysis in the other solvents studied. The fact that heavy atom solvents can catalyze spin inversion of nitrenes from singlet to triplet states has been reported in at least two instances.14,15 The formation of greater amounts of 23 at the expense of 21 and 22 when halogenated solvents were used in the solvolysis of 20 is in excellent agreement with the results predicted on the basis of the reaction scheme in Chart 1. This last set of experiments firmly establishes the presence of both singlet and triplet nitrenium ions in the solvolysis of 20 and suggests a method of determining the multiplicity of nitrenium ions in other reactions.

Table 1

Products from the Solvolysis of \( \theta \)

<table>
<thead>
<tr>
<th>Solvents (^{a},^{b})</th>
<th>% Yield</th>
<th>Total % Yield</th>
<th>% Yield of Singlet Products</th>
<th>Singlet Prod.</th>
<th>Triplet Prod.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_3\text{OH-hexane} )</td>
<td>56</td>
<td>10</td>
<td>8</td>
<td>74</td>
<td>66</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH-p-Br}_2\text{C}_6\text{H}_4 )</td>
<td>33</td>
<td>10</td>
<td>25</td>
<td>68</td>
<td>43</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH-CCl}_4 )</td>
<td>13</td>
<td>&lt; 1</td>
<td>59</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH-CHCl}_3 )</td>
<td>4</td>
<td>&lt; 1</td>
<td>63</td>
<td>67</td>
<td>4</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH-CHBr}_3 )</td>
<td>ca. 1</td>
<td>&lt;&lt; 1</td>
<td>45</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>( \text{CH}_3\text{OH-CH}_3\text{OH} )</td>
<td>59</td>
<td>20</td>
<td>7</td>
<td>86</td>
<td>79</td>
</tr>
</tbody>
</table>

\(^{a}\) With the exception of the \( \text{CH}_3\text{OH-p-Br}_2\text{C}_6\text{H}_4 \) solvent mixture, which was made up on a 1 ml of \( \text{CH}_3\text{OH} \) to 1 gm of \( \text{p-Br}_2\text{C}_6\text{H}_4 \) basis, all of the solvent mixtures were 1:1 by volume.

\(^{b}\) To a first approximation the table is arranged in order of increasing solvent polarity.
Part 2: Nitrogen Radicals

The chemistry of nitrogen radicals has been extensively studied by two groups of researchers. Of particular interest are the reports of the addition of nitrogen radicals, generated from dialkyl N-chloramines, to various substituted olefins and diene systems. Before discussing specific examples, however, the methods of generating nitrogen radicals will be briefly outlined.

Minisci reported the generation of nitrogen radicals from N-chloramines utilizing a redox system such as Fe²⁺-Fe³⁺ or Cu⁺-Cu²⁺ according to the following equation. The use of solvents such as methanol or acetone supposedly leads to free nitrogen radicals (29) as opposed to the protonated nitrogen radicals (30) obtained when sulfuric acid-acetic acid is used as solvent.

\[
R_2NC\text{Cl} + Fe^{++} \rightarrow R_2N^* + FeCl^{++}
\]

29

Neale, on the other hand, prefers the solvent system 4 M sulfuric acid in acetic acid which leads to protonated nitrogen radicals (aminium radicals). The major disadvantage of aminium

---

radicals is that they can also act as electrophilic chlorinating agents under certain conditions which will be discussed later.

$$\text{R}_2\text{NHCl} \rightarrow \text{R}_2\text{NH} + \text{Cl}^+$$

The intermediacy of a radical species in these systems has been conclusively demonstrated in several cases. Minisci reported that the addition of N-chlorodiethylamine to a methanol solution of butadiene in the presence of both Cu$^+$ and Fe$^{++}$ salts gave 1-diethylamino-4-chloro-trans-2-butene in 54% yield. \(^{17}\)

$$\text{Et}_2\text{NCl} + \text{CH}_2=\text{CHCH}=\text{CH}_2 \xrightarrow{\text{CH}_3\text{OH} \quad \text{Cu}^+/\text{Fe}^{++}} \text{Et}_2\text{NCH}_2\text{CH}=\text{CHCH}_2\text{Cl}$$

Neale likewise observed that aminium radicals also gave a 1,4-addition product with butadiene in good yield along with a small amount of a 1,2-addition product which incorporated the acetate group.

$$\text{Bu}_2\text{NCl} + \text{CH}_2=\text{CHCH}=\text{CH}_2 \xrightarrow{\text{HOAc}} \text{Bu}_2\text{NCH}_2\text{CH}=\text{CHCH}_2\text{Cl} + \text{CH}_2=\text{CHCHCH}_2\text{Cl} \text{OAc}$$

The fact that the minor product is a 1,2-adduct and that it has incorporated solvent is indicative of an ionic mechanism analogous to that observed in the reaction of butadiene with N,N-dibromobenzene-sulfonamide in methanol reported by DeGraw. \(^{18}\)

---


When the reaction of N-chlorodibutylamine with butadiene was carried out in the presence of oxygen, no 1,4-adduct was found. However, 72% of dibutylamine along with 20% of the 1,2-adduct was obtained indicating that the radical mechanism had been eliminated in favor of electrophilic chlorination.

In a competitive experiment to determine whether aminium radicals would add to butadiene if another mode of reaction was possible, N-chloro-(methyl-1-phenylbutyl)amine (31) gave a 53% yield of 32 and a 26% yield of the Hofmann-Loeffler-Freytag product 33 after treatment of the reaction mixture with lithium aluminum hydride.

Thus, the addition of N-chloramines to butadiene must be preferred to chloremine rearrangement.

Minisci further reported that the addition of N-chloropiperidine to styrene in the presence of Fe^{++} under nitrogen gave the
radical addition product $\mathbf{34}$ in good yield. When the reaction was

$$
N\text{-Cl} + \phi\text{-CH=CH}_2 \xrightarrow{\text{Fe}^{++}/N_2} \phi\text{-CHCH}_2\text{-N}
$$

$\mathbf{34}$

carried out in the presence of oxygen, the major product was $\mathbf{35}$ indicating that the initially formed benzyl radical was trapped by oxygen.

$$
\phi\text{-CHCH}_2\text{-N} + O_2 \rightarrow \phi\text{-CHCH}_2\text{-N}
$$

$\mathbf{35}$

The use of nitric oxide as a trapping agent led to the formation of $\mathbf{36}$ and $\mathbf{37}$ in respectable yields.

$$
N\text{-Cl} + \phi\text{CH=CH}_2 \xrightarrow{\text{CH}_3\text{OH/Fe}^{++}} N\text{-NO} + \phi\text{CCH}_2\text{-N}
$$

$\mathbf{36}$ $\mathbf{37}$

Neale reported that aminium radicals added to olefins in yields ranging from 0-42% The major side reaction appeared to be electrophilic chlorination. In an attempt to increase the yield of radical

addition products, Neale reacted a series of N-chloramines with various olefins substituted with groups such as -Cl and -Br which would be expected to stabilize a radical center to a greater extent than a carbonium ion center. Thus, 1-chlorocyclohexene gave a 60% yield of the adduct when treated with N-chlorodiethylamine which was attributed to stabilization of the radical intermediate by the chlorine atom.

\[
\begin{align*}
\text{Et}_2\text{NCl} + \text{ClHCl} \rightarrow \text{Et}_2\text{N}^+\text{HCl} + \text{Fe}^{++} & \rightarrow \text{Et}_2\text{NH}^+ + \text{FeCl}^{++}
\end{align*}
\]

Minisci refuted Neale's hypothesis of radical stabilization by conducting a competitive experiment involving the reaction of N-chloropiperidine with an equimolar mixture of cyclohexene and 1-chlorohexene. In order to avoid the electrophilic chlorination reaction, a solution of the N-chloramine in sulfuric acid was added to a solution of ferrous sulfate and the olefins in sulfuric acid. The high concentration of ferrous ion is reported to effect the reduction of the protonated N-chloramine to prevail over electrophilic chlorination of the olefin.

The competitive reaction gave 39 and 40 in a ratio of 4 to 1 respectively.

\[
\begin{align*}
\text{N-Cl} + \text{cyclohexene} + \text{cyclohexene} \xrightarrow{\text{H}_2\text{SO}_4/\text{FeSO}_4} & \text{39} + \text{40} \\
\end{align*}
\]

When the reaction was run in methanol with ferrous sulfate to generate the unprotonated nitrogen radical, 39 was obtained in greater than 95% yield. These results were interpreted as evidence against the stabilization of an intermediate carbon radical by chlorine. The author suggests that the "polar features of protonated or unprotonated nitrogen radicals prevail over the resonance stabilization of the incipient alkyl radical and that the contribution of polar forms to the transition state must determine the reactivity." \(^{21}\)

The reaction of cyclohexene with N-chloropiperidine in acid gave a mixture of the cis and trans adducts whereas the reaction in methanol \(^{17}\) with ferrous ion gave only the cis adduct. Minisci explained these results by postulating that the unprotonated nitrogen radical was coordinated with the species FeCl\(^{++}\) which directed the addition of chlorine in a cis manner. In the case of the protonated
nitrogen radical, no such coordination is possible and the transfer of chlorine must occur in a nonspecific manner such as a radical chain reaction.

\[
\text{Et}_2\text{NCl} + \text{CH}_2=\text{CHCH}_3 + \text{CH}==\text{CCH}_3 \xrightarrow{\text{Cl}} \text{Et}_2\text{NCH}_2\text{CHCH}_3 + \text{Et}_2\text{NCH}_2\text{CCH}_3
\]

\[42\]

\[41\]

This result is in direct contrast with Minisci's competitive experiment and Neale warns that the "conclusions derived from one amino radical system cannot be safely extended to others without the support of experimental evidence." Neale also suggests that free,
neutral amino radicals cannot be the reactive species in any of the redox systems because of "implications in the literature that free, neutral amino radicals possess a strong tendency to abstract hydrogen from olefins," a process which was not observed in either his own or Minisci's studies. Neale feels that a metal ion-amino radical complex, such as that proposed by Minisci to explain the cis addition of N-chloropiperidine to cyclohexene, is probably the reactive species in all the metal salt catalyzed reactions in methanol. The similarities in the reactions of aminium radicals and radicals generated in a redox system could then be explained by viewing both intermediates as radicals in which the free electron pair is similarly coordinated.

\[ \text{FeCl}^{++} \xrightarrow{\text{R}_2\text{NH vs } \text{R}_2\text{N}^-} \]

This explanation is unique in that it could "bestow similar reactivity patterns upon both radicals while allowing for secondary differences between the systems, such as in the product yields or stereochemistry."

As mentioned earlier, the major side reaction with aminium radicals is the electrophilic chlorination of olefins which can be made the major process in certain instances. Neale reported that 1,1-diphenylethylene and norbornadiene reacted with chloramines via ionic rather than radical pathways. Further results indicated that

aliphatic terminal olefins would undergo the desired radical addition whereas internal olefins had a tendency to undergo only ionic reactions. This latter observation is especially important in view of some of the results to be discussed later.

Part 3: \( \pi \)-Participation in Carbocyclic Systems.

During the past ten years there have been several reports of solvolysis reactions involving cations which are delocalized by participation of the \( \pi \)-electrons of a suitably substituted double bond. If one examines the valence bond isomers \((43a-c)\) for the norbornyl cation, \(43\), there are two routes possible for generating \(43\).

\[
\begin{align*}
\text{43} & \quad \equiv \quad \begin{bmatrix}
\text{43a} & \quad \text{43b} & \quad \text{43c}
\end{bmatrix}
\end{align*}
\]

Winston has proposed the general term "\(\sigma\)-route" for the formation of bridged ions such as \(43\) in which the three-center, electron deficient bond is formed by \(\sigma\)-delocalization from starting materials such as \(44\). Formation of \(43\) from compounds such as \(45\) by participation of the \(\pi\)-electrons of the double bond was designated the "\(\pi\)-route."

\[25. \text{S. Winston and P. Carter, } J. \text{Am. Chem. Soc., 83, 4485 (1961).}\]
Lawton observed that acetolysis of \( \text{44b} \) gave \( \text{44c} \) as the sole product.

Bartlett and Bank independently observed that solvolysis of \( \text{45a} \) in 50\% acetic acid gave a 92\% yield of \( \text{44c} \) and \( \text{44d} \) in a 60:40 ratio.

Goering and Closson demonstrated \( \pi \)-participation in the solvolysis of cis- and trans-5-cyclodecen-1-yl \( p \)-nitrobenzoates, \( \text{46} \) and \( \text{47} \) respectively. Solvolysis of \( \text{46} \) in 90\% acetone gave \( \text{48} \) in 33\% yield along with 65\% of unreacted \( \text{46} \). Similarly, the solvolysis of \( \text{47} \) gave \( \text{49} \) in 60\% yield and the rearranged \( p \)-nitrobenzoate, \( \text{50} \), in 15\% yield.
The fact that the cis isomer, 46, gave the cis decalyl system and the trans isomer, 47, gave the trans decalyl system requires a trans addition of C1 and solvent across the C5,C6-double bond.

Winstein and Carter extended the "π-route" synthesis of bicyclics to the cyclohexenyl system. Acetolysis of 51 followed by reaction of the solvolysis mixture with lithium aluminum hydride gave a mixture of alcohols which consisted of 37% of 52, 43% of 53, and 20% of 54. The stereochemistry of the bicyclic alcohols requires a trans addition of C1 and solvent across the double bond.

Le Ny likewise observed π-participation in the acetolysis of 55 which gave 56 in approximately 90% yield. However, when 57 was solvolyzed under similar conditions, the only product isolated was 58.

Winstein and Hansen\(^{30}\) also reported participation by the double bond in the rigid system 52. Acetolysis of 52 gave 12% of a rearranged bromobenzenesulfonate, 60, and a single acetate product, 61.

In a five part series of articles, Bartlett\(^{31a-e}\) and co-workers reported several other examples of \(\pi\)-participation involving the formation of bicyclic systems. It is interesting to note that in all the examples of \(\pi\)-participation mentioned above, the double bonds are in the 5,6 position relative to the ionizing center. Bartlett\(^{31c}\)

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observed that the acetolysis of $\text{62}$, in which the double bond is in the 4,5 position, gave only $\text{63}$ with no detectable amounts of cyclization products. Compound $\text{64}$, on the other hand, gave 9 products of which $\text{65}$ was the major component obtained in 42% yield.

\[
\begin{align*}
\text{62} & \xrightarrow{\text{HOAc, NaOAc}} \text{63} \\
\text{64} & \xrightarrow{\text{HOAc, NaOAc}} \text{65}
\end{align*}
\]

In the succeeding paper, Bartlett examined the effect of chain elongation on the rate of solvolysis of $\text{66}$. Acetolysis of $\text{66}$ gave


(b) P. D. Bartlett and G. D. Sargent, ibid., 87, 1297 (1965).

(c) P. D. Bartlett, W. D. Closson and T. J. Cogdell, ibid., 87, 1308 (1965).


67 in greater than 90% yield and the ratio of the rate constants for 66 and its saturated isomer was essentially unity. Both of these observations indicate that there is little or no participation by the double bond. Bartlett also reported that acetolysis of 68 gave about 80% of unicycled acetate, 69, along with 12% of a mixture of four cyclized olefins. This last example is one of the few reported cases where participation by a double bond in the 5,6 position is not observed to any great extent.

The Problem:

The extensive investigations into the \( \pi \)-route synthesis of bicyclic compounds in the carbocyclic series coupled with the results of Gassman and Fox involving alkyl migration to divalent, electron deficient nitrogen suggested an interesting research problem. In theory, nitrenium ions, being the nitrogen counterpart of carbonium ions, should undergo other carbonium ion type reactions. The
The possibility of synthesizing azabicyclic systems via the π-route was deemed worthy of an extensive investigation.

The solvolysis of four different unsaturated amine systems was investigated using various solvent systems. The compounds studied were the N-chloro derivatives of 3-[2-(N-methylamino)ethyl]cyclopentene (70), 4-(N-methylaminomethyl)cyclohexene (71), 4-[2-(N-methylamino)ethyl]cyclohexene (72) and 1-methoxy-4-(N-methylaminomethyl)cyclohexene (73).

\[ \text{Compounds } 70 \text{ and } 71 \text{ were studied initially because the double bond was located in the 5,6 position relative to the nitrogen atom.} \]

As was noted earlier, the carbocyclic examples with the double bond in the 5,6 position relative to the ionizing center gave the greatest amount of π-participation. The results of the solvolyses of 70 and 71 suggested studying compound 72 in which the double bond is in the 6,7 position. The results with 71 suggested studying compound 73 in an attempt to direct the cyclization towards one end of the double bond. The syntheses and results of the solvolyses of compounds 70-73 will be discussed in the following sections.
Synthesis of 3-[2-(N-methylamino)ethyl]cyclopentene (70)

A review of the literature indicated that 70 had not been previously reported. The six step reaction sequence outlined in Scheme 1 was used to prepare 70 in excellent overall yield.

Scheme 1

The procedure of Noller and Adams was used without modification to prepare 77 in good yields. It was reported that attempts to prepare and isolate the acid chloride of 77 led only to black tars. This observation was not checked since it was possible to generate


33. This observation was made by Frances Hoyda, an undergraduate at Ohio State, who did the initial work on the preparation and solvolysis of 70.
the acid chloride in situ by treating a benzene solution of \( \mathcal{R} \) with one equivalent of pyridine and one equivalent of thionyl chloride. Treatment of this solution with gaseous methylamine gave \( \mathcal{S} \) in yields of 70-75%. Reduction of \( \mathcal{S} \) with lithium aluminum hydride in ether proceeded smoothly to give \( \mathcal{T} \) in 85% yield.

**Synthesis of \( 1-(N\text{-methylaminomethyl})\text{cyclohexene (71)} \)**

The synthesis of \( \mathcal{J} \) was accomplished in a manner analogous to that used in the preparation of \( \mathcal{Q} \). The reaction sequence is outlined in Scheme 2.

**Scheme 2**

![Scheme 2](image)

The procedure of Klein was used in the preparation of \( \mathcal{Q} \) from \( \mathcal{R} \). Yields were routinely greater than 90% and the product appeared to be quite stable in contrast to the reported attempt to isolate the acid chloride of \( \mathcal{L} \). Conversion of \( \mathcal{R} \) into its N-methylamide was accomplished by bubbling gaseous methylamine through a solution of \( \mathcal{R} \).

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35. Supplied by the Aldrich Chemical Co.
in benzene until the solution was basic to litmus. Filtration of the precipitated methylamine hydrochloride followed by removal of the solvent gave 81 in 91% yield. Attempts to reduce 81 with lithium aluminum hydride in ether, which had proven so successful in the case of 78, met with failure. Yields were reproducibly lower than 40% with large amounts of unreacted amide being present after workup. However, it was found that yields of 71 in the range 85-90% could be obtained by carrying out the reduction of 81 in a refluxing solution of lithium aluminum hydride in tetrahydrofuran for a period of 3 days.

Synthesis of 4-[2-(N-methylamino)ethyl]cyclohexene (72)

At first glance it appeared that the best route to 72 would be conversion of 72 into the corresponding acid with one more carbon in the side chain followed by the sequence employed in the synthesis of 34. However, Klein had reported that the conversion of 72 into cyclohexen-4-yl acetic acid proceeded in low yield. Since fairly large quantities of 72 were desired, an alternate route outlined in Scheme 3 was used.

Commercially available 82 was reduced with lithium aluminum hydride in ether to give 83. The procedure of Klein was used to convert 83 into its tosylate 84. A small amount of the tosylate was recrystallized from Skelly F to give a sample with a mp 27-28°C. Due to the difficulties in recrystallization and handling of the low melting solid, the crude oily tosylate was used without further purification. The yield of crude 84 was considerably higher than that reported by Klein. Reaction of 84 with potassium cyanide in ethanol according
to the procedure of Klein gave \( \text{85} \) in good yield. Reduction of \( \text{85} \) with lithium aluminum hydride in ether gave \( \text{86} \) in 74% yield along with a higher boiling material which was assumed to be the coupling product of \( \text{86} \) with the imine salt formed in the first stage of the reduction of \( \text{85} \). The primary amine \( \text{86} \) readily reacted with carbon dioxide in the air and had to be stored as its hydrochloride. Reaction of \( \text{86} \) with ethyl formate gave \( \text{87} \) in 96% yield which was reduced with lithium aluminum hydride in ether to give \( \text{72} \) in 78% yield.

**Synthesis of 1-methoxy-4-(N-methylaminomethyl)cyclohexene (73)**

DeGraw reported that the reaction of 2-methoxybutadiene (88) with acrolein gave \( \text{82} \) as the major Diels-Alder product with only a trace amount of the other isomer 90.
It was assumed that 88 would similarly react with ethyl acrylate to give predominantly the 4-substituted ester which could be converted into 72 according to Scheme 4.

Scheme 4

The reaction of 88, prepared according to the procedure of DeGraw, with ethyl acrylate gave 91 in yields ranging from 27-51%. The low yields are undoubtedly a result of the fact that 88 is the limiting reagent in contrast to most Diels-Alder reactions in which the olefin is the limiting reagent. The ester, 91, was shown to be about 90% pure by vapor phase analysis on several columns and was used without further purification. In order to preserve the vinyl ether moiety, a reaction sequence had to be chosen which avoided any acid conditions or acid workups. This excluded the acid chloride.
route which had proven so successful in the preparation of 70 and 71. An attempt to form the amide 92 by heating an ethanolic solution of 91 and methylamine in a sealed tube led only to the recovery of unreacted 91. However, conversion of methylamine into its anion by treatment with butyllithium followed by addition of 91 resulted in a 75% yield of 92. Reduction of 92 with lithium aluminum hydride in ether afforded 72 in 86% yield.

Solvolysis of 3-[2-([N-chloro-N-methylamino]ethyl]cyclopentene (70a)

A. In methanol

When a methanolic solution of 70a was refluxed until the solution gave a negative test for active chlorine, a single cyclization product 93 was obtained in greater than 50% yield along with a small amount of 70.

36. Virtually identical results were obtained when a methanolic solution of silver ion was used.

37. The N-chloramine was prepared by stirring a solution of one gram of amine per 20 ml of commercial bleach for 20-30 min. followed by extraction with Freon 11. The solvent was removed under reduced pressure without heating.
The product was purified by preparative vapor phase chromatography and was shown to be a single compound by vapor phase analysis on several analytical columns. This fact was somewhat interesting since it was anticipated that participation by the double bond followed by solvent incorporation should lead to two azabicyclic ethers. The broad carbon-oxygen stretching vibration at 9.14 μ in the infrared spectrum and the sharp singlet (3H) at 6.82 in the nmr spectrum indicated that the product had incorporated a methoxy group. The lack of an -NH absorption in the infrared spectrum coupled with the disappearance of the vinyl proton signals at 5.55 further indicated that the product was an azabicyclic ether which contained a tertiary amine function. However, it was not possible to distinguish between the two possible isomers, 23 and 24, on the basis of the spectral data.

Thus, it was necessary to undertake a classical degradation of the solvolysis product in order to determine its ring structure. The reaction sequence which was used is outlined in Scheme 5.
Scheme 5

\[ \text{Scheme 5} \]

\[ \text{22} \xrightarrow{1) \text{CH}_3\text{I}} \text{23} \xrightarrow{2) \text{IRA-400}} \text{ion exchange resin} \]

\[ \text{95} \xrightarrow{\Delta} \text{96} \]

\[ \text{26} \xrightarrow{\text{HN}=\text{NH}} \text{98} \xrightarrow{1) \text{CH}_3\text{I}} \xrightarrow{2) \text{IRA-400}} \text{ion exchange resin} \]

\[ \text{99} \xrightarrow{\Delta} [\text{99}] \xrightarrow{\text{H}_2\text{O}^+} \text{5} \]

33
Compound 22 was converted into its quaternary methiodide (23a) by treatment with methyl iodide and was passed through an anion exchange resin in its methoxide form to give the quaternary methoxide 25. Pyrolysis of 25 afforded one major product 26 which was purified by preparative vapor phase chromatography. The nmr spectrum of 26 consisted of a singlet (6H) at $\tau$ 7.82 due to the methyl groups on nitrogen, a singlet (3H) at $\tau$ 6.80 due to the methoxy group and a 14 line multiplet (2H) at $\tau$ 5.05 along with a 7 line multiplet (1H) at $\tau$ 4.05. The fact that the degradation product contained 3 vinyl protons meant that it was either 26 from 23 or 27 from 24. Unfortunately, it was not possible to distinguish between 26 and 27 on the basis of the spectral data. It was reported that an attempt to degrade the quaternary methiodide of 26 led only to the formation of polymers. It was felt that the diene system generated in the degradation was probably unstable under the reaction conditions. Thus, 26 was hydrogenated in an attempt to avoid this complication. Catalytic hydrogenation using 5% palladium on carbon as catalyst gave a 70:30 mixture of products each of which had a retention time different than 26 on an analytical carbowax:KOH column. It was assumed that the allylic center of 26 was isomerizing on the catalyst, thus catalytic
hydrogenation was abandoned in favor of a diimide reduction. Due to the apparent stability of the terminal double bond, it was necessary to recycle 96 three times with diimide in order to effect its complete reduction to 98. The diimide product was shown to have a retention time identical with that of the major product from the catalytic reduction. Quaternization of 22 with methyl iodide followed by anion exchange gave the quaternary methoxide 22. Pyrolysis of 22 followed by hydrolysis of the crude product gave two major products which were separated by preparative vapor phase chromatography to give 22 and 2-ethylcyclopentanone which was identical in all respects to an authentic sample prepared as follows:

Mechanistically, ionic additions to olefins generally yield trans products. In the special case of carbocyclics prepared via
intramolecular cationic cyclization, only trans addition to the double bond was found. In an attempt to demonstrate that the 8-methoxy group of 25 was anti to the nitrogen (trans to the nitrogen containing ring), the nmr spectra of 26a, 100a and 101a were compared.

The nature of the degradation of 25 requires that the vinyl and N,N-dimethylamino groups be cis to each other in the degradation product. Depending upon the stereochemistry of 25, the methoxy group must be either cis or trans to both the vinyl and N,N-dimethylamino groups of the degradation product. In 26a, H_a, which appeared as a quartet centered at $\tau 6.73$, had a coupling constant of 9 cps with H_c and 6 cps with H_b. In the model compound 100a J_{ab} was 6 cps, while in the cis isomer 101a J_{ab} was 4 cps. Although the H_a-H_b coupling constants for 26a and 100a were identical, the proximity of J_{ab} for 101a did not allow an unequivocal assignment of the stereochemistry of the methoxy group in 25. The assignment of the methoxy group anti to the nitrogen was shown to be correct on the basis of results to be discussed later.

38. The author wishes to thank Richard Cryberg for running the 100 MHz nmr spectra of 26a, 100a and 101a and for doing the double and triple resonance studies.
B. In water

Due to the insolubility of 70a in water, it was necessary to use an organic co-solvent in order to run the solvolysis under homogeneous conditions. Tetrahydrofuran proved to be an excellent co-solvent.

As noted earlier, the methanolysis of 70a gave virtually identical results both in the presence and absence of silver ion. However, it was found that in the solvolysis of 70a in 50% water - 50% tetrahydrofuran, silver ion greatly enhanced the reaction and gave a better yield of cyclization product. As in the methanolysis of 70a, a single cyclization product 102 was obtained in 72% yield with only a trace amount of 70 present in the reaction mixture.

\[
\begin{align*}
70a & \xrightarrow{\text{THF/HOH, Ag}^+; \Delta} 102 \\
1) \text{NaH} & \quad 2) \text{CH}_3\text{I} \\
\text{Cl} & \quad \text{OCH}_3 \\
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{I}^-
\end{align*}
\]

The product was purified by preparative vapor phase chromatography and was shown to be structurally related to the methanolysis product 92. Reaction of 102 with sodium hydride followed by the addition of excess methyl iodide gave the quaternary methiodide 93a which was identical in all respects to a sample prepared from 92.

The only feature of the solvolysis reaction which had not been conclusively demonstrated was the absolute stereochemistry about the 8-position of 92 and 102. It was felt that if the epimeric alcohol...
of 102 could be prepared, its hydroxy function should be ideally situated to form a strong hydrogen bond with the nitrogen atom. The conversion of 102 into syn-8-hydroxy-2-methyl-2-azabicyclo[3.2.1]-octane (103) is outlined below. Compound 102 was converted into 104 by a Jones' oxidation. The ketone 104 was found to be fairly unstable and was reduced directly to 103 without purification by treatment with an aqueous solution of potassium borohydride. Vapor phase analysis on a carbowax:KOH column showed that the reduction product was a 3:1 mixture of 103 and 102 respectively. Analysis of the crude ketone on the same column showed it to be a single compound with no trace of unreacted 102 present. Compound 102 had a retention time approximately three times as long as 103 which might be expected if the hydroxy group of 103 was intramolecularly hydrogen bonded to the nitrogen atom. In the case of the known cis- and trans-2-dimethyl-aminocyclopentanols, 101 and 100 respectively, compound 101, which can form an intramolecular hydrogen bond with the nitrogen atom, had a much shorter retention time than 100 on the same carbowax:KOH column used to separate compounds 102 and 103.
One might also predict that the reduction of \( \text{101} \) with potassium borohydride would give predominantly the \textit{syn}-epimer \( \text{103} \) since approach of the negatively charged hydride ion should be impeded on one side by the free electrons on nitrogen. The observed ratio of products is in agreement with this prediction.

Conclusive evidence for the assigned stereochemistry of \( \text{102} \) and \( \text{103} \) came from the positions of the OH stretching vibrations of each in their infrared spectra. The normal solvent for hydrogen bonding studies, carbon tetrachloride, could not be used because it reacted with the amines to give a precipitate upon standing. It was found, however, that 0.01M solutions of the amines in hexane using 1 mm sodium chloride cells gave weak spectra \(^{39}\) from which the positions of the hydroxyl absorptions could be accurately measured. Thus, compound \( \text{102} \) had an OH band at 3625 cm\(^{-1}\), indicative of a free hydroxy group, with no other absorptions in the range 3200-3700 cm\(^{-1}\). Compound \( \text{103} \) on the other hand had a slightly broader band at 3359 cm\(^{-1}\), indicative of a very strong hydrogen bond, with no other absorptions in the range 3200-3700 cm\(^{-1}\). \(^{40}\)

These results also show that compound \( \text{22} \) has the methoxy group anti to the nitrogen since \( \text{102} \) was converted into the methiodide of \( \text{22} \). The fact that the methoxy group of \( \text{22} \) and the hydroxy group of

\(^{39}\) The spectra were obtained on a Beckmann IR-9 recording spectrophotometer. The author wishes to thank John Pascone for running the spectra of the epimeric alcohols.

are both anti to the nitrogen requires that the addition of the nitrogen atom and solvent across the double bond in 70a must have occurred in a trans manner. The formation of a single product in both methanol and water indicates that the transition state leading to product may be highly unsymmetrical such as 105. Incorporation of solvent exclusively at C1 would lead to the formation of the observed products.

Another possible interpretation is that the azabicyclo[3.2.1]-octyl system is thermodynamically more stable than the azabicyclo[3.3.0]octyl system. If this were true, the solvolysis might initially lead to the formation of both bicyclo systems with the [3.3.0] system reverting to the [3.2.1] system under the reaction conditions.

Neither of these possibilities can be ruled out on the basis of the solvolysis results.

Solvolysis of \(4-(N\text{-chloro-}N\text{-methylaminomethyl})\text{cyclohexene (71a)}\)

A. In methanol

When a methanolic solution of 71a was refluxed until the solution gave a negative test for active chlorine, four products were
obtained. The major product $7_4$ was obtained in yields varying from 30-40%. The other products were anti-2-methoxy-7-methyl-7-azabicyclo[3.2.1]octane ($106$) in 6-9% yield, anti-6-methoxy-2-methyl-2-aza­bicyclo[2.2.2]octane ($107$) in 11-14% yield, and syn-2-chloro-7-methyl-7-azabicyclo[3.2.1]octane ($108$) in 5-8% yield.

When the solvolysis was carried out in the presence of silver ion, an additional product $109$ was obtained in about 5% yield. Compound $109$ was shown to be dimethylacetal of 3-cyclohexene-1-carbox­aldehyde ($82$) by conversion of $82$ into $109$ as follows.
It is assumed that 109 is formed via the imine 110 which can be produced by loss of a proton from the nitrenium ion generated from 71a.

The products were separated by preparative vapor phase chromatography and the major product was shown to be 74 by comparison of its infrared spectrum with that of an authentic sample. The nmr spectrum of 106 had a sharp singlet (3H) at $\tau$ 6.76 and a singlet (3H) at $\tau$ 7.58 with no peaks in the olefinic region. The nmr spectrum of 107 had a singlet (3H) at $\tau$ 6.78 and a singlet (3H) at $\tau$ 7.66 with no peaks in the olefinic region. Aside from establishing the presence of methoxy functions in 106 and 107, the nmr spectra could not be used to distinguish the azabicyclo[3.2.1]octyl system from the azabicyclo[2.2.2]octyl system.

**Structure proof of 107**

In 1967 Huffman reported a novel synthesis of substituted isoquinuclidones starting with methyl 3-cyclohexene-1-carboxylate. A slight modification and an extension of Huffman's procedure was used to prove the structure of 107. The reaction sequence which was used is outlined in Scheme 6.

Conversion of 79 into its methyl ester was accomplished by treatment with dimethyl sulfate. Oxidation of 111 with m-chloroperbenzoic acid gave a mixture of the cis and trans epoxides, 112b and

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Scheme 6

79

\[ \text{NaOH, dimethyl sulfate} \rightarrow \text{111} \]

\[ \text{MCPA} \rightarrow \text{112a + 112b} \]

\[ \text{112 (a and b)} \stackrel{\text{4C}6}{\text{CH₃NH₂}} \rightarrow \begin{cases} \text{113a} \\ \text{113b} \end{cases} \]

\[ \text{113 (a and b)} \stackrel{\Delta}{\rightarrow} \begin{cases} \text{114} \\ \text{115} \end{cases} \]

\[ \text{LiAlH₄} \rightarrow \text{115} \]

\[ \text{1) NaH} \rightarrow \text{117a} \]

\[ \text{2) CH₃I} \rightarrow \text{107a} \]
112a, with the trans isomer reported to be the major product. Reaction of the epoxide mixture with aqueous methylamine gave the ring opened products 112a and 113b analogous to the results of Huffman. No attempt was made to separate the mixture at this stage. The crude mixture was heated at 170° for two hours to yield a viscous oil. The pyrolysis of 113b could lead to either a lactone by an intramolecular cyclization or to a polymeric amide. Isomer 113a, however, should lead predominantly to 114 via intramolecular cyclization. Purification of 114 proved difficult and the yield was lower than those reported by Huffman for similar examples.

The crude oil from the pyrolysis of 113 was sublimed to give at first a viscous oil. Repeated washing of the cold finger with ether eventually gave a crystalline sublimate which was recrystallized from Skelly B-ether to give a pure sample of anti-6-hydroxy-2-methyl-2-azon bicyclo[2.2.2]octan-3-one (114). The trans diaxial ring opening of 112a requires that the hydroxy group at the 6-position of 114 be anti to the nitrogen. Reduction of 114 with lithium aluminum hydride in tetrahydrofuran gave anti-6-hydroxy-2-methyl-2-azon bicyclo[2.2.2]-octane (115) which was treated with sodium hydride and methyl iodide to give the methiodide 107a which was identical in all respects to a sample prepared from 107.

Attempted structure proof of 106

Since independent synthesis of 106 in a manner analogous to that used for 107 did not seem practical, it was necessary to devise an alternate approach to the structure proof of 106. It was hoped that
a classical Hofmann degradation would lead to a product which could be independently synthesized utilizing an approach similar to that taken in the structure proof of 93. There are three possible degradation products for the quaternary methoxide of 106.

It was anticipated that $H_a$, which is the most acidic of the $\beta$-substituted hydrogens, should be preferentially abstracted during the degradation. Abstraction of $H_b$, $H_c$, or $H_c'$, should be a much less favored process. When the degradation was carried out, a low yield of products was obtained. Vapor phase analysis showed the presence of several products of which two were present in sufficient quantity to be isolated by preparative vapor phase chromatography. The major product was shown to be 106 by comparison of its infrared spectrum.
with that of an authentic sample. Formation of 106 in the degradation can occur only by nucleophilic attack by methoxide at one of the methyl groups on the quaternary nitrogen atom. This was surprising in view of the results obtained in the degradation of 93.

The minor product had an nmr spectrum with a sharp singlet (3H) at 6.69, a sharp singlet (3H) at 6.74 and a singlet (6H) at 7.69 and with no absorptions in the olefinic region. It was thus assumed that the minor product was arising via attack by methoxide ion at either C-6 to give 116 or at C-2 to give 117.

Since no olefinic products were obtained upon attempted degradation, this approach to the structure proof of 106 was abandoned. The assigned structure of 106 was shown to be correct on the basis of results to be discussed later.

Structure proof of 108

Compound 108 had an elemental analysis consistent with the formula C8H14NCl. The nmr spectrum had a broadened triplet (1H) at 6.21 and a singlet at 7.52 with no absorption in the olefinic region. Aside from supporting the assumption that 108 was an azabicyclic
chloride, the nmr spectrum could not be used to assign its structure. In an attempt to determine the ring structure, 108 was dechlorinated using sodium metal in tetrahydrofuran and t-butyl alcohol according to the procedure of Gassman and Pape. One of the two possible dechlorination products, 2-methyl-2-azabicyclo[2.2.2]octane (118), was prepared by treatment of isoquinuclidone (119) with sodium hydride and methyl iodide to give 120 which was reduced with lithium aluminum hydride.

![Chemical structures](image)

Unfortunately, 118 was not the same as the dechlorination product of 108. Thus an authentic sample of 6-methyl-6-azabicyclo[3.2.1]octane (121) was prepared in a manner analogous to that used by Fox in the synthesis of 119.

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43. The author wishes to thank B. L. Fox for providing an authentic sample of isoquinuclidone.
A sample of \textit{m}-aminobenzoic acid was reduced with hydrogen using 5% ruthenium on carbon as catalyst to give \textit{cis}-3-aminocyclohexanecarboxylic acid (123) in 71% yield. Cyclization to 124 was effected by heating 123 above its melting point and distilling the resultant liquid at atmospheric pressure. Treatment of 124 with sodium hydride and methyl iodide gave the N-methyl derivative 125 which was reduced to 121 with lithium aluminum hydride. The authentic sample of 121 was identical in all respects to the product obtained in the dechlorination of 103.
Having established that the chloride product had the azabicyclo\[3.2.1]\]octyl skeleton, a comparison of the nmr spectra of 106 and 108 was made. If both products had the same stereochemistry about the 2-position, their nmr spectra should be virtually identical with the exception of the methoxy absorption in 106 and the position of the proton at C-2. However, the upfield regions, $\tau$ 7.00 to $\tau$ 9.00, were completely different indicating that 108 might have the opposite stereochemistry of 106.

Further support for assigning the syn stereochemistry to 108 comes from the work of Hobson and Riddell. These authors reported that the solvolysis of 126 in acetone using silver perchlorate as catalyst gave two bicyclic chlorides, 127 and 128, as the major bicyclic products. They also reported that 129 gave 130 as the only bicyclic product under similar conditions.

The authors assigned the stereochemistry of 130 on the basis of the following results. Reaction of 129a with chlorine is reported to give the trans dichloride 131. The base induced cyclization of 131 gave a single product which was identical to the solvolysis product 130. Cyclization of 131 can give rise only to the syn isomer thus establishing the stereochemistry of the solvolysis product. The
formation of the syn isomer in the solvolysis requires a cis addition of nitrogen and chlorine across the double bond which indicates that the products observed by Hobson might be arising by a nonionic mechanism.

There is a remote possibility that 129a may react with chlorine to give the protonated N-chloramine 132 which may be transformed into 130 via a radical mechanism. This seems unlikely, however, because chlorination of the protonated amine followed by rearrangement to 130 would have to occur faster than chlorination of the double bond if 130 was arising from 132 rather than from the base induced cyclization of 131. Since the chlorination of olefins is usually a very rapid reaction, the mechanism involving the intermediacy of 131 is more probable.

Thus, there is some precedent for assigning the syn configuration to the bicyclic chloride 108. It should be pointed out, however, that Hobson used a different solvent system and reported that the bicyclic chloride products were formed only in the presence of silver ion.
B. In water

As in the case of the solvolysis of 70a, solvolysis of 71a in water gave the best results when tetrahydrofuran was used as co-solvent and when silver ion was present. The product mixture consisted of 71 in 14-17% yield, 121 in 13-16% yield, 108 in 9-12% yield, 115 in 16-19% yield, anti-2-hydroxy-7-methyl-7-azabicyclo[3.2.1]octane (133) in 11-14% yield and 82 in 13-18% yield.
Products 71, 82, 108, 115 and 121 were identical in all respects to authentic samples. Compound 133 was converted into 106a by treatment with sodium hydride and methyl iodide. This indicated that 133 and 106 had the same skeletal structure and same stereochemistry at the 2-position but did not guarantee that 133 and 106 had the anticipated azabicyclo[3.2.1]octyl structure. The following sequence of reactions clearly demonstrated that 133 and 106 were the expected azabicyclo[3.2.1]octane derivatives.

\[
\begin{align*}
\text{HO} & \quad \text{CH}_3 \\
\text{N} & \quad \text{CH}_3 \\
\text{CrO}_3 & \quad \text{HSCH}_2\text{CH}_2\text{SH} & \quad \text{BF}_3\text{-etherate} \\
\text{133a} & \quad \text{134} & \quad \text{135} \\
\text{Re/Ni, EtOH} & \quad \text{Picric acid} & \quad \text{Picrate of 121}
\end{align*}
\]
Oxidation of the hydrochloride of 133 with Jones' reagent gave 134 in 83% yield. Conversion of 134 into the bisethylenethioketal 135 was accomplished by treatment with ethanedithiol and boron trifluoride etherate according to the procedure of Fieser. Desulfurization of 135 with Raney nickel gave 131 which was not isolated but instead was converted into its picrate derivative which was identical in all respects to an authentic sample.

The independent synthesis of 115 which was outlined earlier, requires that the hydroxy group be anti to the nitrogen atom. Intuitively, it was assumed that 133 had the anti configuration. Both 115 and 133 were converted to their epimeric alcohols, 136 and 137, by Jones' oxidation followed by potassium borohydride reduction of the ketone intermediates, 138 and 139.
As in the case of the epimeric alcohols 102 and 103, both 136 and 137 had much shorter retention times on a carbowax:KOH column than did 115 and 133. This indicates that the hydroxy groups in 136 and 137 are intramolecularly hydrogen bonded to the nitrogen atoms. The results of the hydrogen bonding studies of the alcohols in hexane conclusively prove that the assigned structures are correct. The anti alcohols, 115 and 133, had hydroxy absorptions at 3623 cm$^{-1}$ and 3628 cm$^{-1}$ respectively, indicative of free hydroxy groups. The syn alcohols, 136 and 137, had hydroxy absorptions at 3490 cm$^{-1}$ and 3539 cm$^{-1}$ respectively, indicative of hydrogen bonded alcohol functions.

DISCUSSION OF RESULTS

It is difficult to envision a single reaction mechanism which would account for all the products. The results of Gassman and Cry-
berg, however, allow one to postulate a mechanism which would account for five of the six observed products. Such a mechanism is outlined in Scheme 7.

Scheme 7

\[ \text{Cl} \quad \text{CH}_3 \quad \text{N} \quad \text{'CH}_3 \quad \text{HOH} \quad + \quad \text{H}_5. \quad + \quad \text{155.} \quad + \quad \text{121} \quad \text{Cl} \quad \text{108} \quad \text{71a} \quad \text{140} \quad \text{82} \quad + \quad \text{115} \quad + \quad \text{133} \quad \text{121} \quad \text{142} \quad \text{141} \quad \text{70a} \]

56
Abstraction of chloride ion by silver ion would produce the singlet nitrenium ion $\text{140}$. This singlet ion could then lose a proton to give the imine $\text{110}$ which would be hydrolyzed to $\text{82}$ during the reaction. The ion $\text{140}$ could also lead to $\text{115}$ and $\text{132}$ by participation of the double bond followed by solvent incorporation. A third possibility would be formation of the triplet nitrenium ion $\text{141}$ via spin inversion of the singlet state. Ion $\text{141}$ could then abstract two hydrogen atoms to give $\text{71a}$ or could cyclize to $\text{142}$ which could abstract two hydrogen atoms to give $\text{121}$. Why only one of the two possible cyclic reduction products is produced cannot be satisfactorily explained on the basis of Scheme 7.

The chloride product $\text{108}$ is thought to arise via a concerted cis addition of the N-Cl bond across the double bond. A molecular model of $\text{71a}$ indicates that in the transition state leading to $\text{108}$, the N-Cl bond is more favorably located than in the transition state leading to $\text{syn-6-chloro-2-methyl-2-azabicyclo[2.2.2]octane (143)}$. This slight difference in geometry might account for the complete absence of $\text{143}$ in the solvolysis mixture.

The chloride product $\text{108}$ was previously assigned the syn stereochemistry on the basis of the differences in the nmr spectra of $\text{106}$ and $\text{108}$. The synthesis of the anti alcohol $\text{135}$ and the syn alcohol $\text{137}$ permitted a more conclusive assignment of the stereochemistry of $\text{108}$. A comparison of the nmr spectra of $\text{108}$ and $\text{135}$ showed them to be quite different. The nmr spectra of $\text{108}$ and $\text{137}$, while not being identical, were similar in the region $\tau 7.00-9.00$ indicating that
both 108 and 137 had the same stereochemistry. Since 137 was previously shown to be the syn derivative, compound 108 must therefore be the syn chloro derivative.

C. In acid

In the silver ion catalyzed reaction of 71a, nitric acid is produced as the reaction proceeds and silver chloride precipitates out of solution. In an attempt to determine whether acid was catalyzing the reaction, the solvolysis was carried out in aqueous acid. Unlike the reactions in water which were run with tetrahydrofuran as co-solvent, the solvolysis of 71a in aqueous acid was run under heterogeneous conditions. As the reaction proceeded, the insoluble N-chloramine was converted into amine products which were soluble in the acid solutions. Both 1M phosphoric and 1M sulfuric acid solutions were used with similar results. The reaction was conducted by refluxing a mixture of the N-chloramine with 1M acid until the solution gave a negative test for active chlorine. The solution was cooled, made strongly basic with potassium hydroxide and continuously extracted with ether. Vapor phase analysis on the crude mixture indicated the presence of three products in a ratio of about 1:8:13 along with a trace amount of one other product. A comparison of the retention times showed that the minor product was 71 and that the major product was 133. The other major product, however, had a retention time different than any of the solvolysis products of 71a in water. The mixture was separated by preparative vapor phase chromatography
to give 71 and 133 which were identical in all respects to authentic samples. The third product, isolated in very small amounts, was shown to be 137 by comparison with an authentic sample. The alcohol, 137, had a retention time identical with the trace component in the solvolysis mixture.

Initially, a product having a retention time identical with 144 was obtained in 80% purity by preparative vapor phase chromatography. Continued vapor phase chromatography of the mixture, however, led to the decomposition of 144 with the formation of a polymeric substance in the injector port of the gas chromatograph. The fact that 144 was stable on an analytical column but not on a preparative column was somewhat surprising.

In an attempt to obtain a pure sample of 144, the mixture was chromatographed on basic alumina. Unfortunately, only a small amount of the product was obtained which was about 90% pure by vapor phase analysis. The product appeared to decompose on the column since 133 was obtained pure in much larger quantities than 144. The infrared spectrum of 144 showed no hydroxy absorption but had a small band in the NH region. The mass spectrum had a parent ion at m/e 141.
indicating that 144 was isomeric with the bicyclic alcohol 133. The nmr spectrum had a broadened doublet at \( \tau 6.85 \), a sharp singlet at \( \tau 7.60 \) and a sharp singlet at \( \tau 8.30 \). An accurate integration of the peaks could not be obtained due to the nearness of the other proton resonance signals. However, the approximate ratio of the peaks was 2:3:1. The only structures which seemed to fit the spectral data were the epoxides 144 and 145.

In an attempt to prepare the epoxides, the hydrochloride of 71 was treated with m-chloroperbenzoic acid in chloroform. After 24 hours, the only isolable product was 71. Use of the stronger oxidizing agent, peracetic acid, also gave only 71 after workup. Treatment of the hydrochloride with trifluoroperacetic acid for 20 minutes gave, after basic workup, a mixture of three products. Vapor phase analysis showed that two of the products had retention times identical with the solvolysis products 133 and 144. Since the crude mixture contained a carbonyl absorption in its infrared spectrum, it was assumed that the third product was an epoxide ring opened product.
The fact that the same two products were obtained in both the solvolysis of \( \text{71a} \) and in the epoxidation of the hydrochloride of \( \text{71} \) indicates that both reactions may be proceeding through the same intermediates. The presence of \( \text{133} \) in the epoxidation mixture can be rationalized on the basis of an intramolecular **trans** diaxial ring opening of epoxide \( \text{145} \). If one assumes that the predominant conformer of \( \text{145} \) is the one in which the methylaminomethyl group is equatorial, **trans** diaxial ring opening to give \( \text{133} \) can only occur when the cyclohexane ring of \( \text{145} \) flips to give the less stable conformer.
The cis epoxide $1^{44}$, which cannot undergo an intramolecular trans diaxial ring opening might be expected to be relatively stable to the basic workup. It was anticipated that if $1^{44}$ was the cis epoxide, it should exist predominantly in the conformer in which the methylaminomethyl group was equatorial. If this were the case, trans diaxial ring opening of the epoxide with lithium aluminum hydride would be expected to give rise to $1^{46}$ as the major product.

In an attempt to demonstrate that $1^{44}$ was the cis epoxide, the crude solvolysis mixture was treated with lithium aluminum hydride in ether. Vapor phase analysis after hydrolysis showed no change in the product ratio. The mixture was then recycled with lithium aluminum hydride in refluxing tetrahydrofuran to give a new product mixture. The products were separated by preparative vapor phase chromatography to give $1^{33}$ and $1^{46}$.

In an attempt to synthesize $1^{46}$ independently, compound $73$ was hydrolyzed with dilute acid. The solution was made basic and was treated with potassium borohydride. It was hoped that a mixture of the cis- and trans-4-methylaminomethylcyclohexanols, $1^{46}$ and $1^{47}$.
would be obtained. Vapor phase analysis showed the presence of one major product which had a retention time slightly longer than 146 and a small amount of a compound which had a retention time identical with 146. It was assumed that the major component was the trans isomer 147 and thus this route was abandoned.

Treatment of the lactone (148) of cis-4-hydroxycyclohexanecarboxylic acid with liquid methylamine at -78° gave the amide 149 in 65% yield. Reduction of 149 with lithium aluminum hydride in tetrahydrofuran gave an authentic sample of 146 which was identical in all respects to the product obtained from the lithium aluminum hydride treatment of the solvolysis mixture.
The formation of the epoxide 144 and the bicyclic alcohol 132 from 145 indicates that the acid catalyzed reaction of 71a proceeds by an entirely different mechanism than the solvolysis of 71a in water with silver ion. As mentioned earlier, Neale reported that the major side reaction of protonated N-chloramines with internal olefins was the electrophilic chlorination of the double bond. The results of the acid catalyzed reaction of 71a can best be interpreted in light of Neale's observation and represents the first case in which this reaction occurs intramolecularly. A possible mechanism for the reaction is outlined in Scheme 8.

In theory, attack of the double bond by positive chlorine can occur with equal facility from either side of the ring. If one assumes a trans diaxial addition of solvent and chloronium ion across the double bond, four possible chlorohydrins can be formed. Treatment of the chlorohydrin mixture with base would result in the formation of only two epoxides, 144 and 145. Compound 145 can then cyclize to give the observed product 132.

Solvolysis of 4-[2-(N-chloro-N-methylamino)ethyl]cyclohexene (72a)

A. In methanol

When a methanolic solution of 72a was refluxed until the solution gave a negative test for active chlorine, a single product was obtained which was purified by preparative vapor phase chromatography and shown to be 72 by comparison with an authentic sample. Trace amounts of several other products were detected but were not present
Scheme 8

\[
\text{Scheme 8}
\]

\[
\begin{align*}
\text{Scheme 8} & \quad \text{Scheme 8} \\
\end{align*}
\]
in sufficient quantities to be isolated. Similarly, when \textit{72a} was refluxed in a methanolic solution of silver ion, the only isolable product was \textit{72}.

**B. In acid**

In an attempt to see if the acid catalyzed reaction was general, a solution of \textit{72a} in 1M sulfuric acid was refluxed until the solution became homogeneous and gave a negative test for active chlorine. After basic workup and extraction with ether, vapor phase chromatographic analysis indicated the presence of three products in an approximate ratio of 1:2:4. Treatment of the crude reaction mixture with picric acid afforded a 37\% yield of the picrate of \textit{151} after recrystallization. The picrates of \textit{72} and \textit{150} are apparently very soluble in ethanol and can be separated from the picrate of \textit{151} quite easily. Regeneration of the free amine from the picrate afforded a pure sample of \textit{151}.

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{CH}_3 & \\
\text{Cl} & \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{CH}_3 & \\
\text{Cl} & \\
\end{align*}
\]

**Structure proof of \textit{151}**

The ring structure of \textit{151} was determined in a manner analogous to that used for \textit{133}. The reaction sequence used is outlined in Scheme 9.
Scheme 9

151a \(\xrightarrow{\text{CrO}_3}\) 152 \(\xrightarrow{\text{HSCH}_2\text{CH}_2\text{SH}}\) 153

153 \(\xrightarrow{\text{Ra/Ni, EtOH}}\) 154 \(\xrightarrow{\text{Picric acid}}\) Picrate of 154
Compound 151 was converted into its hydrochloride which was treated with Jones' reagent in acetone to give 152. The oxidation proceeded in much lower yield than that of 153 even though identical conditions were used. The ketone 152 was treated with ethanedithiol and boron trifluoride etherate according to the procedure of Fieser to give the bisethylenethioketal 153 in 47% yield. Desulfurization of 153 with Raney nickel gave 154 which was not isolated but was converted into its picrate.

An authentic sample of 154 was prepared in an unambiguous manner as outlined in Scheme 10. Catalytic hydrogenation of 155 with 5% palladium on carbon at atmospheric pressure gave a crude sample of 156 which was used without purification. High pressure hydrogenation of 156 using 5% ruthenium on carbon as catalyst gave a crude product which was assumed to be mostly cis-3-aminocyclohexanecarboxylic acid (157). Cyclization of 157 was accomplished by heating it above its melting point according to the procedure of Cronyn. The crude product was sublimed and recrystallized from Skelly B-ether to give a pure sample of 158 in 35% yield. The fact that there was a large amount of residue in the pyrolysis of 157 indicated that the sample of 157 was probably a mixture of the cis and trans isomers accounting for the low yield in the pyrolysis reaction. Treatment of 158 with sodium hydride and methyl iodide gave the N-methyl lactam 159 which was reduced with lithium aluminum hydride to give an authentic sample

Scheme 10

155 \( \xrightarrow{\text{H}_2} \) 156 \( \xrightarrow{\text{H}_2} \) 157 \( \xrightarrow{\Delta} \) 158

158 \( \xrightarrow{1) \text{NaH}} \) 159 \( \xrightarrow{\text{LiAlH}_4} \) 154
of 154. Conversion of 154 into its picrate afforded a sample which was identical in all respects to the product obtained from the desulfurization of 153.

If the same mechanism proposed for the acid catalyzed reaction of 71a also applies to 72a, the expected intermediates would be the epoxides 150 and 160. Intramolecular trans diaxial ring opening of 160 would give 151. The fact that 151 was the only bicyclic alcohol formed strongly supports the proposed mechanism.

\[
\begin{array}{c}
72a \xrightarrow{\text{acid}} \begin{array}{c}
\text{CH}_2\text{CH}_2\text{NHCH}_3 \\
\text{C}\end{array} + \begin{array}{c}
\text{CH}_2\text{CH}_2\text{NHCH}_3 \\
\text{C}\end{array} \xrightarrow{\text{HO}} \begin{array}{c}
\text{CH}_3 \\
\text{N} \\
\text{C}\end{array}
\end{array}
\]

An attempt to purify a sample of 150 by preparative vapor phase chromatography led to a rearranged product which was not characterized. Column chromatography afforded a small amount of a sample which was about 90% pure. The infrared and nmr spectra were very similar to those of 144 and the mass spectrum had a parent ion at m/e 155. Thus the structure of 150 was assigned by analogy with the cis epoxide 144 formed in the acid catalyzed reaction 71a.

It is interesting to note that both 71a and 72a undergo the acid catalyzed reaction which does not require participation by the double bond in the ionization of the N-Cl bond. On the contrary, 72a, in which the double bond is in the 6,7-position, does not undergo
methanolysis with participation of the \( \pi \)-electrons. A molecular model of \( \text{J2a} \) indicates that the nitrogen atom can orient itself nearer the double bond than the nitrogen atom in either \( \text{J0a} \) or \( \text{J1a} \). Thus, one might expect a greater amount of participation by the \( \pi \)-electrons. On the other hand, \( \text{J2a} \) has one more carbon in the side chain than \( \text{J1a} \) and consequently has more degrees of freedom which might result in less participation by the double bond.

As mentioned earlier, studies involving \( \pi \)-participation in carbocyclic systems seemed to indicate that the greatest amount of participation occurred in systems having the double bond in the 5,6-position relative to the ionizing center. The results of the solvolyses of \( \text{J0a}, \text{J1a} \) and \( \text{J2a} \) indicate that the generalizations reported for carbocyclic systems might also apply to their nitrogen analogues.

**Solvolysis of 1-methoxy-4-(N-chloro-N-methylaminomethyl)cyclohexene (73a)**

The fact that \( \text{J1a} \) gave both possible bicyclic ethers when the solvolysis was run in methanol indicated that the transition state leading to these products must be fairly symmetrical. By placing a methoxy group on one end of the double bond, it was hoped that the nitrenium ion would add exclusively to the other end generating the resonance stabilized ion \( \text{161} \) which could then incorporate solvent to give an azabicyclic ketal.
When a methanolic solution of 73a was refluxed until the solution gave a negative test for active chlorine, one major product along with two minor products was obtained. Several trace components were also shown to be present by vapor phase analysis. The products were separated by preparative vapor phase chromatography and one of the minor products was shown to be 72 by comparison with an authentic sample. The other two products were shown to have incorporated a chlorine atom and a methoxy group on the basis of their elemental analyses. The two most logical structures for these products are 162 and 163.
The ratio of 72, 162 and 163 in the crude reaction mixture was 1.7:5.5:1.0 but products 162 and 163 appeared to decompose to a considerable extent during the separation process since the collection efficiency was only 63% based on the weight of distilled product which was chromatographed. A large amount of black residue was also noticed in the injector port after the separation was completed.

The nmr spectrum of the major product had a singlet (1H) at $\tau$ 8.79, a singlet (3H) at $\tau$ 7.94, two slightly overlapping singlets (6H) at $\tau$ 6.78 and $\tau$ 6.72 and a broad multiplet (1H) at $\tau$ 5.70. The nmr spectrum of the minor product was very similar. It had a singlet (1H) at $\tau$ 8.71, a singlet (3H) at $\tau$ 7.53, two slightly overlapping singlets (6H) at $\tau$ 6.61 and $\tau$ 6.58 and a broad multiplet (1H) at $\tau$ 5.97.

While the nmr spectra fit the assigned structures quite nicely, assignment of either 162 or 163 as the major product based on the position of the proton resonance signals is subject to considerable uncertainty.

The major products also underwent some unexpected reactions. An attempt to dechlorinate it, using sodium and t-butyl alcohol, gave only 72.
Since it was initially assumed that the major product was the azabicyclic ketal derived from the resonance stabilized ion $\text{161}$, the product was treated with aqueous acid. The acid phase was made basic and was treated with potassium borohydride in the hope of obtaining syn-2-hydroxy-7-methyl-7-azabicyclo[3.2.1]octane ($\text{137}$). The fact that $\text{137}$ was the only product formed was surprising when it was later determined that the original product contained a chlorine atom. A possible interpretation for this observation is outlined below for $\text{163}$.

![Chemical structures](attachment:image.png)

Treatment of $\text{163}$ with aqueous acid would give the $\alpha$-chloro ketone $\text{164}$. Neutralization of the amine hydrochloride followed by intramolecular displacement of chloride ion would give $\text{139}$ which was previously shown to give $\text{137}$ upon treatment with potassium borohydride. The fact that $\text{164}$ readily cyclized to $\text{139}$ could be interpreted to indicate that the chloro and methylaminomethyl groups were situated trans to each other. However, this does not necessarily require that they be trans to each other in $\text{163}$. It would be possible for the $\alpha$-chloro ketone derived from $\text{162}$ to isomerize to $\text{164}$ under either the
acid or basic conditions used. Thus, either 162 or 163 might be expected to give 137 according to the reaction sequence outlined above. This was not confirmed by experiment due to the scarcity of the minor product.

Thus it becomes necessary to assign the structure of the major product on the basis of the probable mode of formation.

One possible mechanistic interpretation of the observed results involves nucleophilic attack at the chlorine atom of the N-Cl bond by double bond. This would require that the chloro and methylamino-methyl groups cis to each other in the final product. Unfortunately, there are no reports in the literature of nucleophilic attack at the chlorine atom of N-chloramines. Gassman, Cryberg and Trent, however, have observed the reaction of various N-chloramines with

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potassium borohydride to regenerate the amines from which the N-chloramines were derived. This reaction can be viewed as occurring either via nucleophilic attack by hydride on nitrogen to give the free amine and chloride ion or via nucleophilic attack by hydride on chlorine to give the amide anion and hydrochloric acid. By comparison, there are several reports of nucleophilic attack at the nitrogen atom of N-chloramines.\(^{49-53}\)

A second possible interpretation of the results involves the addition of the elements of methyl hypochlorite across the double bond, a process not observed with either 70a or 71a. The addition can be viewed as occurring in a two step process as outlined in Scheme 11. If one assumes that the major conformer of 72 is the one in which the methylaminomethyl group is equatorial, then trans diaxial addition of chloronium ion and methanol across the double bond should lead to the formation of both 163 and 162 with 163 being the major product.

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Thus, $162$ is the expected major product on the basis of the former mechanism while $163$ is the expected major product on the basis of the latter mechanism. Unfortunately, a clearcut decision between the two mechanisms cannot be made on the basis of the results presented in this dissertation.

It is felt that the addition of the nitrenium ion to one end of the double bond might be possible if the methoxy group of $72a$ is replaced by either a methyl or phenyl group.
**EXPERIMENTAL**

All melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord, Model 137. Nuclear Magnetic Resonance spectra were obtained on either a Varian Associates A-60 or HA 100 Megacycle Nuclear Magnetic Resonance Spectrometer using tetramethylsilane as an internal standard. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark and by the Bernhardt Microanalytical Laboratory, West Germany. The azabicyclic alcohols were analyzed as their picrate derivatives due to the hygroscopic nature of the free amines. The commercial bleaches used in the preparation of the N-chloramines included Chlorox, Purex and Pic.

**Preparation of derivatives**

**A. Picrates**

All picrates were prepared by treating the free amines with a saturated ethanolic solution of picric acid. The samples were purified by recrystallization from absolute ethanol.

**B. Methiodides**

All methiodides were prepared by adding excess methyl iodide to an ethereal solution of the free amine. The solution was stirred until precipitation of the methiodide was complete (one hour to two days depending upon the concentration of amine and the amount of
methyl iodide used). The samples were purified by recrystallization from ethyl acetate with a small amount of absolute ethanol added. The methiodides were not analyzed due to their hygroscopic nature.

C. Hydrochlorides

All hydrochlorides were prepared by treating an ethanolic solution of the amine with excess concentrated hydrochloric acid. The solvents were removed under reduced pressure on a rotary evaporator and the residue was recrystallized from tetrahydrofuran with a small amount of absolute ethanol added in some cases.

3-Chlorocyclopentene (74)

The procedure of Noller and Adams was used in the preparation of 74.

Diethyl cyclopent-3-ylmalonate (75)

The procedure of Noller and Adams was used in the preparation of 75.

Cyclopenten-3-ylmalonic acid (76)

The procedure of Noller and Adams was used in the preparation of 76.

Cyclopenten-3-ylacetic acid (77)

The procedure of Noller and Adams was used in the preparation of 77.
N-Methyl-cyclopenten-3-ylacetamide (78)

To a stirred solution of 30.0 g (0.240 moles) of \( \text{I} \), 20.0 g (0.253 moles) of pyridine and 500 ml of benzene cooled to 0° was added dropwise 30.7 g (0.260 moles) of thionyl chloride. The solution was stirred for 20 min after the addition of thionyl chloride was complete and gaseous methylamine was slowly bubbled through the solution until the solution was basic to litmus. The benzene layer was washed with 100 ml of a 10% sodium carbonate solution and was dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed under reduced pressure. Distillation gave 23.3 g (0.167 moles; 70%) of \( \text{I} \), bp 94-97° (0.06 mm).

Anal. Calcd. for C₉H₁₃NO: C, 69.03; H, 9.41; N, 10.06.

Found: C, 68.85; H, 9.47; N, 9.83.

3-[2-(N-Methylamino)ethyl]cyclopentene (70)

To a stirred suspension of 9.70 g (0.256 moles) of lithium aluminum hydride in 300 ml of ether was added dropwise a solution of 23.3 g (0.167 moles) of \( \text{I} \) in 75 ml of ether and the mixture was stirred at room temperature for 30 hr. The mixture was hydrolyzed by the dropwise addition of 40.0 g of a 10% sodium hydroxide solution. The solution was filtered and the solvent was removed by distillation through a packed column. Distillation gave 17.7 g (0.142 moles; 85%) of \( \text{J} \), bp 78-80° (28 mm). The picrate was made in the usual manner but the solution had to be cooled in dry ice to obtain a seed crystal. Recrystallization from absolute ethanol afforded an analytical sample of the picrate, mp 109-110°.
Solvolysis of 3-[2-(N-chloro-N-methylamino)ethyl]cyclopentene (70a)
in methanol

A solution of 1.03 (8.25 mmoles) of 70 in 30 ml of commercial bleach was vigorously stirred for 20 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The residue was refluxed for 4 hr with 70 ml of methanol at which time the solution gave a negative test for active chlorine. The reaction mixture was diluted with 150 ml of a 5% sodium hydroxide solution and was continuously extracted with pentane for 12 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. The residue was distilled at 40 mm to give 0.848 g of material which was separated by preparative vapor phase chromatography on a 10' 10% Carbowax:KOH column to give 0.076 g (0.605 mmoles; 78) of 70 and 0.665 g (4.29 mmoles; 52%) of 92.


Found: C, 69.54; H, 10.82; N, 9.09.

The picrate was made in the usual manner, mp 139-140°.


Found: C, 47.09; H, 5.37; N, 14.57.
When the reaction was run on a larger scale the products were separated by the standard Hinsberg method and \( \text{92} \) was purified by distillation, bp 92-94\(^\circ\) (30 mm).

The methiodide was prepared in the usual manner, mp 120-121\(^\circ\).

Hofmann degradation of \( \text{anti-}8\text{-methoxy-2-methyl-2-azabicyclo[3.2.1]-octane methoxide (95)} \).

The quaternary methoxide was prepared by passing a solution of 4.11 g (14.0 mmles) of the methiodide of \( \text{92} \) in 50 ml of methanol through an IRA-400 anion exchange resin in its methoxide form. The column was eluted with methanol until the eluent was no longer basic to litmus. The solvent was removed under reduced pressure to give a syrupy residue. Pyrolysis gave 2.90 g of a mixture of products, bp 60-115\(^\circ\) (30 mm) which contained one major product, a small amount of \( \text{92} \) and trace amounts of two other products as determined by vapor phase chromatography on an Apiezon L:KOH column. The reaction mixture was separated by preparative vapor phase chromatography on a 10' \( \text{20}^\circ \) Apiezon L:KOH (4:1) on chromosorb G column to give 1.20 g (7.11 mmles; 51\%) of \( \text{trans-2-methoxy-cis-3-dimethylamino-1-vinylcyclopentane (96)} \).

Anal. Calcd. for \( \text{C}_{16}\text{H}_{19}\text{NO} \): C, 70.96; H, 11.32; N, 8.28.

Found: C, 71.09; H, 11.41; N, 8.19.

The picrate was made in the usual manner, mp 156.5-158\(^\circ\).

Anal. Calcd. for \( \text{C}_{16}\text{H}_{22}\text{N}_{4}\text{O}_{8} \): C, 48.24; H, 5.57; N, 14.07.

Found: C, 48.22; H, 5.53; N, 13.97.

The methiodide was made in the usual manner, mp 125-126.5\(^\circ\).
Diimide reduction of \textit{trans-2-methoxy-cis-3-dimethylamino-1-vinyl-cyclopentane} (96)

A solution of 1.10 g (6.50 mmole) of 96 in 75 ml of methanol was mixed with 12.6 g (65.0 mmole) of potassium diazodicarboxylate and was vigorously stirred with a mechanical stirrer. Glacial acetic acid, 14.3 g (235 mmole), was added dropwise and the mixture was stirred at room temperature for 6 hr. The reaction mixture was diluted with 150 ml of water, made basic with sodium hydroxide and extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. Vapor phase analysis on a 10' Quadrol column indicated that only about 50% of the material had been reduced. The crude product was recycled with 36.7 g (189 mmole) of potassium diazodicarboxylate and 45.0 g (739 mmole) of acetic acid. After workup, vapor phase analysis indicated that about 80% of the material had been reduced. The crude product was recycled a third time using 40.0 g (206 mmole) of potassium diazodicarboxylate and 40.0 g (656 mmole) of acetic acid to give a product which was greater than 95% pure. A small amount of \textit{trans-2-methoxy-cis-3-dimethylamino-1-ethylcyclopentane} (98) was purified by preparative vapor phase chromatography on a 10' 10% Quadrol on chromosorb G column and was converted into its picrate, mp 169.5-170.5°.

Anal. Calcd. for C_{16}H_{26}N_{4}O_{8}: \text{C, 47.99; H, 6.04; N, 13.99.}

Found: \text{C, 47.8; H, 6.20; N, 13.7.}
The rest of the crude product, \( \text{28} \), was converted into 0.800 g (2.56 mmoles) of its methiodide (\( \text{28a} \)), mp 205.5-206.5°, in 37% yield based on \( \text{26} \).

Hofmann degradation of trans-2-methoxy-cis-3-dimethylamino-1-ethyl-cyclopentane methoxide (\( \text{99} \))

The quaternary methoxide was prepared by passing a solution of 1.03 g (3.28 mmoles) of the methiodide of \( \text{28} \) in 10 ml of methanol through an IRA-400 anion exchange resin in its methoxide form. The column was eluted with methanol until the eluent was no longer basic to litmus. The solvent was removed under reduced pressure and the residue was pyrolyzed at 120° (40 mm). The product was taken up in 50 ml of dilute hydrochloric acid. After 15 min the solution was made basic with sodium hydroxide and was extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. The mixture was separated by preparative vapor phase chromatography on a 10' 10% Quadrol on chromosorb G column to give a small amount of material which had an infrared spectrum identical with \( \text{92} \) and a small amount 2-ethylcyclopentanone which was identical in all respects to an authentic sample. The 2,4-dinitrophenylhydrazone was prepared and was recrystallized from absolute ethanol, mp 154-155°. Mixture melting point with an authentic sample showed no depression, mp 153-155°.
Ethyl 1-ethyl-2-oxocyclopentanecarboxylate

A solution of sodium ethoxide in ethanol was prepared by dissolving 2.30 g (0.100 moles) of sodium metal in 400 ml of absolute ethanol. A solution of 15.0 g (0.100 moles) of ethyl 2-oxocyclopentanecarboxylate in 100 ml of absolute ethanol was added drop-wise and the solution was stirred at room temperature for 15 min. Thirty grams (0.192 moles) of ethyl iodide was added and the solution was refluxed for 30 min. The reaction mixture was concentrated to about 100 ml on a rotary evaporator and was stirred with 1500 ml of ether to precipitate the sodium iodide. The solution was filtered and the solvent was removed by distillation. Distillation of the residue gave 14.6 g (0.080 moles; 80%) of ethyl 1-ethyl-2-oxocyclopentanecarboxylate, bp 84-89° (1.7 mm), [Lit 54 bp 100° (7 mm)].

2-Ethylcyclopentanone

A solution of 14.6 g (79.5 mmoles) of ethyl 1-ethyl-2-oxocyclopentanecarboxylate, 50 ml of 48% hydrobromic acid, 50 ml of glacial acetic acid and 25 ml of water was refluxed for 7 hr. The solution was diluted with 75 ml of water, made basic with sodium hydroxide and extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. Distillation of the residue gave 6.96 g (62.2 mmoles; 78%) of

54. The sample supplied by the Arapahoe Chemical Co. is a mixture of the methyl and ethyl esters.

2-ethylcyclopentanone, bp 81-83°C (60 mm). The 2,4-dinitrophenylhydrazone was prepared and was recrystallized twice from absolute ethanol, mp 153-155°C. (Lit mp 156-161°C).

2-Bromocyclopentanone

The procedure of Ramirez and Bellet was used in the preparation of 2-bromocyclopentanone.

2-Dimethylaminocyclopentanone

2-Dimethylaminocyclopentanone was prepared in 31% yield according to the procedure of Friess and Baldridge using 2-bromocyclopentanone in place of 2-chlorocyclopentanone.

Reduction of 2-dimethylaminocyclopentanone

The procedure of Friess and Baldridge was used in the reduction of 2-dimethylaminocyclopentanone. The cis- and trans-2-dimethylaminocyclopentanols were separated by preparative vapor phase chromatography on a 10' 10C Carbowax 20M:KOH (4:1) on chromosorb G column with the cis isomer having a much shorter retention time.

cis-2-Dimethylaminocyclopentanol methiodide (101a)

The methiodide was prepared according to the procedure of Friess.


and Baldridge but was recrystallized from ethyl acetate-ethanol rather than from ether-methanol, mp 148.5-149°. (Lit mp 146-147°).

**trans-2-Dimethylaminocyclopentanol methiodide (100a)**

The methiodide was prepared according to the procedure of Friess and Baldridge but was recrystallized from ethyl acetate-ethanol rather than ether-methanol, mp 208.5-209°. (Lit mp 206-207°).

**Solvolysis of 3-[2-(N-chloro-N-methylamino)ethyl]cyclopentene (70a) in water**

A solution of 0.996 g (7.97 mmoles) of 70 in 30 ml of commercial bleach was vigorously stirred for 30 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was added to a solution of 2.00 g (11.8 mmoles) of silver nitrate in 50 ml of water and 50 ml of tetrahydrofuran and the solution was refluxed for 4 hr at which time the solution gave a negative test for active chlorine. The reaction mixture was made acidic with concentrated hydrochloric acid, filtered through celite, made basic with sodium hydroxide and the basic phase was continuously extracted with ether for 18 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. The residue was distilled to give 0.825 g (5.75 mmoles; 73%) of 102, bp 81-85° (1.5 mm). The product was shown to be greater than 95% pure by vapor phase analysis. A small amount was purified by preparative vapor phase chromatography.
on a 10' Carbowax:KOH column. The picrate was made in the usual manner, mp 175-177°.

Anal. Calcd. for C_{14}H_{18}N_4O_8: C, 45.40; H, 4.90; N, 15.13.

Found: C, 45.55; H, 5.00; N, 14.99.

When the reaction was run on a larger scale the bicyclic alcohol was purified by fractional distillation. The major impurity was a small amount of 70.

anti-8-Methoxy-2-methyl-2-azabicyclo[3.2.1]octane methiodide (93a)

To a stirred suspension of 0.034 g (0.845 mmoles) of sodium hydride-mineral oil dispersion in 15 ml of tetrahydrofuran was added a solution of 0.094 g (0.669 mmoles) of 102 in 15 ml of tetrahydrofuran. The solution was refluxed for 6 hr and 2 ml of methyl iodide was added. After stirring for 24 hr, the solvent was removed under reduced pressure and the residue was heated with chloroform. The solution was filtered and the chloroform was removed under reduced pressure. The residue was taken up in acetone and triturated with ether gave 0.139 g (0.468 mmoles; 70%) of 93a, mp 119-121°. The methiodide had an infrared spectrum identical with that of a sample prepared from 92. Mixture melting point showed no depression, mp 118-121°.

syn-8-Hydroxy-2-methyl-2-azabicyclo[3.2.1]octane (103)

To a solution of 1.03 g (7.23 mmoles) of 102 in 50 ml of acetone was added 6 ml of Jones' reagent and the solution was stirred for 75 min. Seventy ml of water was added and the acetone was removed under
reduced pressure. The aqueous phase was made basic with sodium hydroxide and was extracted with chloroform. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Vapor phase analysis of the crude product indicated a 70:30 ratio of ketone to unreacted alcohol. The crude product was added to a solution of 1.00 g (18.5 mmoles) of potassium borohydride in 50 ml of water and the solution was stirred for 2 hr. The solution was extracted with chloroform and the extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The mixture was separated by preparative vapor phase chromatography on a 10' 10% Carbowax:KOH column to give 0.404 g (2.87 mmoles; 40%) of 103 and 0.157 g (1.11 mmoles; 15%) of 102.

The picrate of 103 was made in the usual manner, mp 155-156°.


Found: C, 45.52; H, 5.18; N, 15.03.

3-Cyclohexene-1-carboxyl chloride (80)

The procedure of Klein was used in the preparation of 80.

N-Methyl-3-cyclohexene-1-carboxamide (81)

Gaseous methylamine was bubbled through a solution of 115 g (0.798 moles) of 80 in 500 ml of benzene until the solution was basic to litmus. The solution was filtered and the solvent was removed under reduced pressure. The solid residue was recrystallized from Skelly B-ether to give 100 g (0.722 moles; 91%) of 81, mp 88-90°.
Anal. Calcd. for C₉H₁₂NO: C, 69.03; H, 9.41; N, 10.06.

Found: C, 69.17; H, 9.33; N, 10.19.

4-(N-methylaminomethyl)cyclohexene (71)

To a stirred, refluxing solution of 30.0 g (0.791 moles) of lithium aluminum hydride in 900 ml of tetrahydrofuran was added dropwise a solution of 100 g (0.722 moles) of 8₁ in 350 ml of tetrahydrofuran. The solution was refluxed for 3 days, cooled and hydrolyzed by the dropwise addition of 120 g of a 10% sodium hydroxide solution. The solution was filtered and the salts were thoroughly washed with ether. The solvents were removed by distillation through a packed column. Distillation gave 82.4 g (0.659 moles; 91%) of 7₁, bp 66-67° (15 mm).


Found: C, 76.59; H, 12.19; N, 11.11.

The hydrochloride was prepared in the usual manner, mp 199-201°.

Solvolysis of 4-(N-chloro-N-methylaminoethyl)cyclohexene (7₁a) in methanol

A solution of 40.0 g (0.320 moles) of 7₁ in 550 ml of commercial bleach was vigorously stirred for 15 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was taken up in 800 ml of methanol and the solution was refluxed for 6 hr at which time the solution gave a negative test for active chlorine. The reaction
mixture was acidified with concentrated hydrochloric acid and most of the methanol was removed under reduced pressure. The residue was dissolved in 250 ml of water and the solution was made strongly basic with sodium hydroxide and then was continuously extracted with ether for 4 days. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. Distillation of the residue afforded 27.1 g of a mixture of 4 products. The product mixture was redistilled on a spinning band column to give fractions enriched in each of the 4 components. Samples of each product were purified by preparative vapor phase chromatography on a 10' 10% Apiezon L:KOH on firebrick column. The major product which had the shortest retention time was shown to be \( \text{anti-2-methoxy-7-methyl-7-azabicyclo[5.2.1]octane (106)} \).

**Anal. Calcd.** for \( \text{C}_9\text{H}_{17}\text{NO} \): C, 69.63; H, 11.04; N, 9.02.

**Found:** C, 69.89; H, 11.07; N, 8.82.

The picrate was made in the usual manner, mp 181-182.5°.

**Anal. Calcd.** for \( \text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_8 \): C, 46.87; H, 5.25; N, 14.58.

**Found:** C, 47.08; H, 5.30; N, 14.59.

The methiodide was made in the usual manner, mp 205-207°.

The product with the third longest retention time was \( \text{anti-6-methoxy-2-methyl-2-azabicyclo[2.2.2]octane (107)} \).

**Anal. Calcd.** for \( \text{C}_9\text{H}_{17}\text{NO} \): C, 69.63; H, 11.04; N, 9.02.

**Found:** C, 69.49; H, 11.01; N, 9.07.
The picrate was made in the usual manner, mp 179-179.5°.
Anal. Calcd. for C_{15}H_{20}N_4O_8: C, 46.87; H, 5.25; N, 14.58.
Found: C, 46.92; H, 5.27; N, 14.76.

The methiodide was made in the usual manner, mp 208-209°.
The product which had the longest retention time was syn-2-chloro-7-methyl-7-azabicyclo[3.2.1]octane (108).
Anal. Calcd. for C_{9}H_{14}I Cl: C, 60.18; H, 8.77; N, 8.84; Cl, 22.21.
Found: C, 60.20; H, 8.88; N, 8.70; Cl, 22.03.

The picrate was made in the usual manner, mp 230-231°.
Anal. Calcd. for C_{14}H_{17}N_4O_7Cl: C, 43.25; H, 4.41; N, 14.41; Cl, 9.12.
Found: C, 43.25; H, 4.64; N, 14.28; Cl, 8.94.

The product yields were determined by vapor phase analysis using N-methylaniline as the internal standard. The yields determined in this manner were 7.2 (30-40%), 106 (6-9%), 107 (11-14%) and 108 (5-8%).

3-Cyclohexene-1-carboxaldehyde dimethylacetal (109)
A solution of 10.0 g (90.9 mmoles) of 82, 500 ml of anhydrous methanol and 0.25 g of p-toluenesulfonic acid was stirred at room temperature for two days. The reaction mixture was poured onto 300 ml of a saturated sodium bicarbonate solution and the methanol was removed by distillation. The aqueous phase was extracted with ether and the extracts were dried over anhydrous magnesium sulfate and
filtered. The solvent was removed under reduced pressure and the residue was distilled to give 7.02 g (45.0 mmol; 50\%) of 109, bp 70-71.5° (11 mm). [Lit bp 78-79° (11 mm)]

Methyl 3-cyclohexenoate (111)

To a mechanically stirred solution of 58.7 g (0.466 moles) of 3-cyclohexene-1-carboxylic acid in 1500 ml of acetone was added 25.0 g (0.236 moles) of sodium carbonate. After the appearance of a white, fluffy precipitate, 59.2 g (0.470 moles) of dimethyl sulfate was added and the mixture was refluxed for 18 hr. The salts were dissolved by the addition of 50 ml of water and the layers were separated. The acetone phase was washed with 10% sodium carbonate and with brine. The acetone phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Distillation gave 58.9 g (0.420 moles; 90\%) of 111, bp 77-79° (18 mm). [Lit bp 80-85° (30 mm)]

3-Carbomethoxy-7-oxabicyclo[4.1.0]heptanes (112a) and (112b)

Compound 111 was epoxidized according to the procedure of Huffman, Rao and Kamiya, to give a mixture of the cis and trans epoxides, (112b) and (112a).

anti-6-Hydroxy-2-methyl-2-azabicyclo[2.2.2]octan-3-one (114)

A solution of 15.0 g (96.0 mmol) of (112a) and (112b), 40 ml of methanol and 8 ml of 40% aqueous methylamine was stirred at room

temperature for 3 hr and was refluxed for one hr. The solvents were removed under reduced pressure and the residue was heated in a sublimation apparatus at 170° for 2 hr. The oily residue was sublimed at 130° (0.10 mm) to give initially a viscous oil. Continued washing of the cold finger with ether eventually gave a solid sublimate. The sublimate was recrystallized from Skelly B to give a total of 1.39 g (8.96 mmoles; 91%) of 114, mp 110-112°.

Anal. Calcd. for C₆H₁₃NO₂: C, 61.91; H, 8.44; N, 9.03.

Found: C, 61.7; H, 8.65; N, 8.95.

anti-6-Hydroxy-2-methyl-2-azabicyclo[2.2.2]octane (115)

To a stirred suspension of 0.358 g (9.5 mmoles) of lithium aluminum hydride in 100 ml of tetrahydrofuran was added dropwise a solution of 0.717 g (4.63 mmoles) of 114 in 30 ml of tetrahydrofuran and the solution was refluxed for 3 days. The solution was cooled and 1.10 g of a 10% sodium hydroxide solution was added dropwise. After hydrolysis was complete, the solution was filtered and the solvent was removed under reduced pressure. Distillation gave 0.570 g (2.62 mmoles; 57%) of 115, a viscous liquid, bp 129-130° (22 mm).

The picrate was made in the usual manner, mp 240-241°.


Found: C, 45.44; H, 5.04; N, 14.87.

anti-6-Methoxy-2-methyl-2-azabicyclo[2.2.2]octane methiodide (107a)

To a stirred suspension of 0.327 g (6.80 mmoles) of a 50% sodium hydride-mineral oil dispersion in 50 ml of tetrahydrofuran was added
a solution of 0.370 g (2.62 mmoles) of 115 in 15 ml of tetrahydrofuran. The solution was stirred at room temperature for 7 hr and 2 ml of methyl iodide was added. After stirring for 20 hr, the solvent was removed under reduced pressure and the solid residue was heated with chloroform and filtered. The chloroform was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give 0.504 g (1.70 mmoles; 65%) of 107a, mp 206-207°. Mixture melting point with a sample prepared from 107 showed no depression, mp 205-207°.

Attempted Hofmann degradation of anti-2-methoxy-7-methyl-7-azabicyclo-[3.2.1]octane methoxide (106a)

The quaternary methoxide was prepared by passing a solution of 0.785 g (2.64 mmoles) of the methiodide of 106 in 10 ml of methanol through an IRA-400 anion exchange resin in its methoxide form. The column was eluted with methanol until the eluent was no longer basic to litmus. The solvent was removed under reduced pressure and the residue was pyrolyzed at 150° (50 mm). The distillate was purified by preparative vapor phase chromatography on a 5' 3% Amine 220 on Chromosorb G column to give 106 as the major product. The spectral data on the minor product indicated that it might be either 116 or 117 but it was not completely characterized.

2-Methyl-2-azabicyclo[2.2.2]octan-3-one (120)

To a stirred suspension of 1.70 g (35.5 mmoles) of a 50% sodium hydrate-mineral oil dispersion in 25 ml of tetrahydrofuran was added
a solution of 2.02 g (16.2 mmols) of isoquinuclidone in 30 ml of
tetrahydrofuran. The solution was stirred at room temperature for
20 hr and 5 ml of methyl iodide was added. After stirring for 6 hr,
the solution was concentrated under reduced pressure and stirred
with 250 ml of ether. The solution was filtered and the solvent was
removed under reduced pressure. The residue was sublimed at 1 mm to
give 0.673 g (4.84 mmols; 30%) of 120, mp 61-66°. (Lit 60 mp 69-70°).

2-Methyl-2-azabicyclo[2.2.2]octane (118)

To a stirred suspension of 0.252 g (6.65 mmols) of lithium
aluminum hydride in 20 ml of tetrahydrofuran was added a solution of
0.456 g (3.28 mmols) of 120 in 10 ml of tetrahydrofuran. The solu-
tion was refluxed for 3 days and was hydrolyzed by the dropwise addi-
tion of 1.00 g of a 10% sodium hydroxide solution. The solution was
filtered and the solvent was removed by distillation. The residue
was purified by preparative vapor phase chromatography on a 10% 8%
Amine 220 on Chromosorb G column to give 0.111 g (0.891 mmols; 27%)
of 118. The picrate was made in the usual manner, mp 280-282° (d).
(Lit 60 mp 280-282°)

cis-3-Aminocyclohexanecarboxylic acid (123)

The procedure of Gassman and Fox 61 was used in the preparation
of 123.

6-Azabicyclo[3.2.1]octan-7-one (124)

The procedure of Gassman and Fox was used in the preparation of 124.

6-Methyl-6-azabicyclo[3.2.1]octan-7-one (125)

To a stirred suspension of 3.88 g (81.0 mmole) of a 50% sodium hydride-mineral oil dispersion in 100 ml of tetrahydrofuran was added a solution of 5.00 g (40.0 mmole) of 124 in 30 ml of tetrahydrofuran and the solution was stirred at room temperature for 7 hr. Seven ml of methyl iodide was added and the solution was stirred for 12 hr. The reaction mixture was poured onto 300 ml of ether and the solution was filtered. The solvents were removed under reduced pressure and the residue was distilled to give 4.08 g (29.4 mmole; 74%) of 125, bp 78-79° (0.80 mm).

Anal. Calcd. for C15H18NO: C, 69.03; H, 9.41; N, 10.06.

Found: C, 68.85; H, 9.40; N, 10.06.

6-Methyl-6-azabicyclo[3.2.1]octane (121)

To a stirred suspension of 0.300 g (7.92 mmole) of lithium aluminum hydride in 40 ml of ether was added dropwise a solution of 0.711 g (5.63 mmole) of 125 in 20 ml of ether. The solution was stirred at room temperature for 20 hr and hydrolyzed by the dropwise addition of 1.20 g of a 10% sodium hydroxide solution. The solution was filtered and the solvent was removed by distillation through a packed column. Distillation gave 0.440 g (3.52 mmole; 62%) of 121, bp 65-68° (35 mm).
Found:  C, 76.87; H, 12.10; N, 11.25.

The picrate was made in the usual manner, mp 273-275° (d).

Anal. Calcd. for C₁₄H₁₈N₄O₇:  C, 47.45; H, 5.12; N, 15.81.
Found:  C, 47.63; H, 5.08; N, 15.94.

Dechlorination of syn-2-chloro-7-methyl-7-azabicyclo[3.2.1]octane (108)

Into a 3-neck 100 ml round bottom flask fitted with a condenser, a dropping funnel and a Hirschberg stirrer was placed 25 ml of tetrahydrofuran and one gram of finely cut sodium metal. The solution was brought to reflux and a solution of 0.161 g (2.17 mmoles) of t-butyl alcohol in 5 ml of tetrahydrofuran was added dropwise. A solution of 0.199 g (1.25 mmoles) of 108 in 5 ml of tetrahydrofuran was added dropwise and the solution was refluxed for one hr at which time the sodium metal had lumped into a single piece and the solution had turned purple. The reaction mixture was filtered through wire gauze and the sodium was washed with Skelly F. The reaction mixture was poured onto 75 ml of water and extracted with Skelly F. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvents were removed by distillation. The crude product was separated by preparative vapor phase chromatography on a 10' 15% Carbowax 1500 and 3% KOH on Chromosorb G column to give 0.060 g (0.480 mmoles; 38%) and 0.009 g (0.074 mmoles; 6%) of 71. The picrate of 121 was prepared in the usual manner, mp 271-272.5°. Mixture melting point with an authentic sample showed no depression, mp 271-272.5°.
Solvolysis of 4-(N-chloro-N-methylaminomethyl)cyclohexene (71a) in water

A solution of 2.05 g (16.4 mmoles) of 71 in 50 ml of commercial bleach was stirred for 30 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was added to a solution of 4.10 g (24.1 mmoles) of silver nitrate in 50 ml of water and 50 ml of tetrahydrofuran and the solution was refluxed for 20 hr at which time the solution gave a negative test for active chlorine. The reaction mixture was acidified with concentrated hydrochloric acid and filtered through celite. The acid phase was extracted with pentane and the extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. Distillation of the residue through a molecular still gave 0.246 g (0.243 mmoles; 15%) of 3-cyclohexene-1-carboxaldehyde (82).

The tetrahydrofuran was removed from the aqueous acid phase under reduced pressure and the solution was made basic with sodium hydroxide and was continuously extracted with ether for 2 days. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. The residue was distilled through a molecular still and the product was collected in a flask which was cooled at dry ice temperature. A total of 1.50 g of material was collected which consisted of 6-methyl-6-azabicyclo[3.2.1]octane (121) (15%), 4-(N-methylaminomethyl)cyclohexene (71) (15%), syn-2-chloro-
7-methyl-7-azabicyclo[3.2.1]octane (108) (10%), anti-2-hydroxy-7-methyl-7-azabicyclo[3.2.1]octane (133) (12%), and anti-6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane (115) (17%). The yields are based on the amount of crude product isolated by distillation and on the relative areas of the peaks in the vapor phase analysis of the product mixture. The yields determined in this manner were reproducible to within a few percent. The product mixture was separated by preparative vapor phase chromatography on a 10' 1% Carbowax:KOH column. Products 121, 71, 108, and 115 were identical in all respects to samples characterized earlier. The only new product, 133, was converted into its picrate in the usual manner, mp 223-225°.


Found: C, 45.43; H, 5.00; N, 15.30.

The hydrochloride was prepared in the usual manner, mp 217-218°.

When the reaction was run on a larger scale, the same work up and separation procedures were used.

anti-2-Methoxy-7-methyl-7-azabicyclo[3.2.1]octane methiodide (106a)

To a stirred suspension of 0.090 g (2.25 mmoles) of a 60% sodium hydride-mineral oil dispersion in 10 ml of tetrahydrofuran was added a solution of 0.131 g (0.922 mmoles) of 133 in 15 ml of tetrahydrofuran. The solution was refluxed for 2 hr and 4 ml of methyl iodide was added. After stirring for 27 hr, the solvent was removed under reduced pressure and the residue was heated with chloroform and the solution was filtered. The chloroform was removed under reduced pressure and the residue was recrystallized from ethyl acetate-
ethanol to give 0.204 g (0.637 mmoles; 75%) of 106a, mp 206-207.5°. The methiodide had an infrared spectrum identical with that of a sample prepared from 106. Mixture melting point showed no depression, mp 205.5-207°.

2-Methyl-7-azabicyclo[3.2.1]octan-2-one (134)

A solution of 1.01 g (5.70 mmoles) of the hydrochloride of 133a in 80 ml of acetone was treated with 6 ml of Jones' reagent and stirred at room temperature for 30 min. Twenty ml of water was added and the solution was stirred for an additional hr. The acetone was removed under reduced pressure and the solution was diluted with 150 ml of water and made basic with potassium carbonate. The aqueous phase was continuously extracted with ether for 20 hr and the extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed by distillation through a packed column and the residue was distilled in a molecular still at 20 mm to give 0.657 g (4.73 mmoles; 83%) of 134. The product was analyzed by vapor phase chromatography on a 10' 10% Carbowax:KOH column and was found to be greater than 95% pure. The major impurity was unreacted 133. The picrate was made in the usual manner, mp 211-213° (d).

Anal. Calcd. for C_{14}H_{18}N_{4}O_{8}: C, 45.65; H, 4.38; N, 15.21.

Found: C, 45.43; H, 4.61; N, 15.18.

7-Methyl-7-azabicyclo[3.2.1]octan-2-one bisethylenethioether (135)

A solution of 0.590 g (4.24 mmoles) of 134, 15 ml of acetic acid and 1 ml of ethanedithiol was heated on a steam bath for 5 min. One
105 ml of boron trifluoride etherate was added and the solution was allowed to stand at room temperature for 22 hr. The reaction mixture was poured onto an aqueous sodium hydroxide solution and extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. An infrared spectrum on the crude product indicated the presence of a carbonyl group. The crude product was recycled with 15 ml of acetic acid, 1 ml of ethanedithiol and 3 ml of boron trifluoride etherate. The solution was heated on a steam bath for 30 min during which time the solution became dark red. Workup as before gave a crude product which still contained a carbonyl band in the IR. The crude product was treated with 1 ml of ethanedithiol and 1 ml of boron trifluoride etherate and allowed to stand at room temperature for 18 hr. The reaction mixture was poured onto aqueous sodium hydroxide and heated on a steam bath for one hr. The solution was extracted with chloroform and the extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Distillation of the residue through a molecular still at 3 mm gave 0.672 g (3.13 mmole; 74%) of 135. The product was shown to be greater than 95% pure by vapor phase analysis. The picrate was made in the usual manner, mp 200-205° (d).

Anal. Calcd. for C₁₈H₂₀N₄O₇S₂: C, 43.24; H, 4.54; N, 12.61; S, 14.43.

Found: C, 43.42; H, 4.69; N, 12.62; S, 14.54.
Desulfurization of 7-methyl-7-azabicyclo[3.2.1]octan-2-one bisethylenethioketal (135)

To a suspension of W-5 Raney nickel, prepared from 5.00 g of nickel aluminum alloy, in 80 ml of absolute ethanol was added 0.268 g (1.25 mmoles) of 135 and the solution was refluxed for 28 hr. The reaction mixture was cooled and 30 ml of concentrated hydrochloric acid was added. The solution was stirred until all the nickel had been dissolved and the solvents were removed under reduced pressure. The solid residue was heated with chloroform and the solution was filtered. The chloroform was removed under reduced pressure and the residue was taken up in 40 ml of water, made basic with sodium hydroxide and extracted with ether. The picrate was made from the ether extracts and was recrystallized from absolute ethanol to give 0.143 g (0.356 mmoles) of picrate, mp 270-272° (d). The infrared spectrum of the picrate was identical with that of the picrate of 121. A mixture melting point with an authentic sample showed no depression, mp 270-271.5° (d).

syn-6-Hydroxy-2-methyl-2-azabicyclo[2.2.2]octane (136)

To a solution of 0.885 g (6.27 mmoles) of 115 in 60 ml of acetone was added 8 ml of Jones' reagent and the solution was stirred for 90 min. The acetone was removed under reduced pressure and the residue was taken up in 100 ml of water, made basic with sodium hydroxide and extracted with chloroform. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Vapor phase analysis on the crude
product showed no trace of unreacted alcohol. The crude product was added to a solution of 1.00 g (18.5 mmoles) of potassium borohydride in 20 ml of water and the solution was stirred for 16 hr. The aqueous phase was extracted with chloroform and the extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The mixture was separated by preparative vapor phase chromatography on a 10' 1.0 M Carbowax-KOH column to give 0.283 g (2.00 mmoles; 32%) of 136 and 0.054 g (0.386 mmoles; 6%) of 115.

The picrate of 136 was made in the usual manner, mp 251-253.5°.

Anal. Calcd. for C_{14}H_{18}N_{4}O_{8}: C, 45.40; H, 4.90; N, 15.13.

Found: C, 45.35; H, 5.05; N, 14.95.

**syn-2-Hydroxy-7-methyl-7-azabicyclo[3.2.1]octane (137)**

To a stirred suspension of 0.808 g (4.56 mmoles) of the hydrochloride of 133, in 60 ml of acetone was added 5 ml of Jones' reagent and the solution was stirred for 30 min. About 10 ml of water was added and stirring was continued for one hr. The acetone was removed under reduced pressure and the residue was taken up in 50 ml of water and was extracted with chloroform. Vapor phase analysis showed no trace of unreacted alcohol. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was added to a solution of 0.300 g (5.56 mmoles) of potassium borohydride in 50 ml of water and the solution was continuously extracted with ether for 12 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was
removed under reduced pressure. The residue was purified by preparative vapor phase chromatography on a 10' 10% Carbowax:KOH column to give 0.196 g (1.39 mmoles; 34%) of 137. The small amount of anti alcohol, 133, which was present was not isolated.

The picrate of 137 was made in the usual manner, mp 236-241°.

Anal. Calcd. for C_{14}H_{18}N_{4}O_8:  C, 45.40; H, 4.90; N, 15.13.

Found:  C, 45.47; H, 5.12; N, 15.11.

**Solvolysis of 4-(N-chloro-N-methylaminomethyl)cyclohexene (71a) in acid**

A solution of 6.00 g (48.0 mmoles) of 71 in 100 ml of commercial bleach was stirred for 30 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was added to 100 ml of 1M sulfuric acid and the solution was refluxed for 90 min. The solution was cooled, made strongly basic with potassium hydroxide and was continuously extracted with ether for 24 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was diluted to 100 ml in a volumetric flask with tetrahydrofuran and half of the solution was refluxed with 1.00 g (26.4 mmoles) of lithium aluminum hydride for 20 hr. The solution was hydrolyzed by the dropwise addition of 4.00 g of a 10% sodium hydroxide solution, filtered and the solvent was removed under reduced pressure. The residue was separated by preparative vapor phase chromatography on a 10' 10% Carbowax:KOH column.
to give 0.555 g (3.94 mmole) yield based on 71a) of anti-2-hydroxy-7-methyl-7-azabicyclo[3.2.1]octane (132) and 0.325 g (2.30 mmole) of cis-4-(N-methylaminomethyl)cyclohexanol (146). The sample of 146 was purified by sublimation, mp 60-64°. Mixture melting point with an authentic sample showed no depression, mp 61-64°.

The other half of the reaction mixture was treated with an ethanolic solution of picric acid and the resulting picrate was re-crystallized from ethanol to give 1.78 g (5.20 mmole) of the picrate of 132, mp 224-225.5°. Mixture melting point with an authentic sample showed no depression, mp 223-225°.

In a previous experiment, a small amount of a pure sample of 144 was obtained by preparative vapor phase chromatography on a 10'C10 Carbowax:KOH column on an F & M Model 810 gas chromatography. Attempts to purify 144 on an Aerograph A-700 gas chromatograph gave large amounts of decomposition products in the injector port. An exact mass determination on the pure sample of 144 indicated that 144 had the elemental formula C₉H₁₅NO⁺.

Calc. for C₉H₁₅NO⁺: m/e = 141.115369.
Found: m/e = 141.115073.

**Epoxidation of 4-(N-methylaminomethyl)cyclohexene hydrochloride**

To a stirred solution of 0.50 ml (19.3 mmole) of 90% hydrogen peroxide in 25 ml of chloroform maintained at 0° was added 4.03 g (19.3 mmole) of trifluoroacetic anhydride and the solution was stirred for 15 min. A solution of 1.15 g (7.04 mmole) of the
hydrochloride of 71 in 15 ml of chloroform was added dropwise and the solution was stirred for 20 min. The reaction mixture was poured onto 50 ml of 10% sodium hydroxide and the mixture was vigorously stirred. The layers were separated and the chloroform phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Vapor phase analysis on the crude product indicated the presence of 3 components. Two of the products had retention times identical with 133 and 144, the same products obtained in the acid catalyzed reaction of 71a. The third product was thought to have incorporated the trifluoroacetate group on the basis of the carbonyl band in the infrared spectrum of the crude product. Column chromatography on basic alumina gave only one pure product, 133, which had an infrared spectrum identical to that of an authentic sample.

**Attempted conversion of 1-methoxy-4-(N-methylaminomethyl)cyclohexene (73) into cis-4-(N-methylaminomethyl)cyclohexanol (146)**

A solution of 0.600 g (3.87 mmole) of 73 in 50 ml of a 5% hydrochloric acid solution was stirred for 15 min. The solution was made slightly basic with sodium bicarbonate and 0.600 g (11.1 mmole) of potassium borohydride was added. The solution was stirred for 6 hr and then was extracted with chloroform. Vapor phase analysis indicated the presence of one major product which had a retention time slightly longer than that of 146 and a minor product with a retention time identical with 146. No attempt was made to isolate either product.
2-Oxabicyclo[2.2.2]octan-3-one (148)

The procedure of Noyce was used in the preparation of 148.

N-Methyl-cis-4-hydroxy-1-cyclohexanecarboxamide (149)

About 20 ml of methylamine was condensed into a flask which contained 1.23 g (9.76 mmoles) of 148. The solution was stirred for one hr and the excess methylamine was allowed to evaporate off overnight. The oily residue was taken up in 50 ml of a 10% sodium hydroxide solution and the aqueous phase was continuously extracted with ether for 2 days. The product did not appear to be very soluble in ether so the extracts were not dried over anhydrous magnesium sulfate. Instead, the extracts were concentrated under reduced pressure and the residue was dried by adding benzene and removing the combined solvents under reduced pressure to give 0.992 g (6.32 mmoles; 65%) of 149, mp 125-127.5°. An analytical sample, mp 126.5-127.5°, was prepared by sublimation at 0.05 mm and recrystallization from hexane-isopropanol.

Anal. Calcd. for C$_8$H$_{15}$NO$_2$: C, 61.12; H, 9.62; N, 8.91.

Found: C, 61.21; H, 9.73; N, 8.63.

cis-4-(N-Methylaninomethyl)cyclohexanol (146)

To a stirred suspension of 0.300 g (7.92 mmoles) of lithium aluminum hydride in 25 ml of tetrahydrofuran was added dropwise a solution of 0.204 g (1.30 mmoles) of 149 in 25 ml of tetrahydrofuran and the solution was refluxed for 20 hr. The solution was hydrolyzed by the dropwise addition of 1.20 g of a 10% sodium hydroxide solution,
filtered and the solvent was removed under reduced pressure. The residue was purified by preparative vapor phase chromatography on a 10% Carbowax:KOH (4:1) on Chromosorb G column and was sublimed at 0.05 mm to give 0.092 g (0.644 mmole; 49%) of 146, a waxy solid, mp 61-65°.

Found: C, 66.93; H, 11.83; N, 9.78.

4-(Hydroxymethyl)cyclohexene (83)

The procedure of Klein was used in the preparation of 83.

4-(Hydroxymethyl)cyclohexene tosylate (84)

The tosylate was prepared according to the procedure of Klein but was extracted with chloroform rather than benzene. A small amount of the tosylate was recrystallized from hexane, mp 27-28°. The crude, oily tosylate was used without further purification due to the difficulties in recrystallization and handling of the low melting solid.

3-Cyclohexene-1-acetonitrile (85)

The procedure of Klein was used in the preparation of 85.

4-(2-Aminoethyl)cyclohexene (86)

To a stirred suspension of 16.3 g (0.430 moles) of lithium aluminum hydride in 600 ml of ether was added dropwise a solution

of 52.1 g (0.430 moles) of $8\alpha$ in 200 ml of ether. The solution was
stirred at room temperature for 22 hr and was hydrolyzed by the
dropwise addition of 72.0 g of a 10\% sodium hydroxide solution. The
solution was filtered and the solvent was removed under reduced
pressure. Distillation gave 39.6 g (0.317 moles; 74\%) of $8\alpha$, bp 86-
92° (20 mm). The hydrochloride was made in the usual manner, mp 199-
200°.

Found: C, 59.28; H, 9.98; N, 8.68.

4-[2-(N-Formylamino)ethyl]cyclohexene ($8\beta$)
A solution of 39.6 g (0.317 moles) of $8\alpha$ and 25.9 g (0.350 moles)
of ethyl formate was refluxed for 3 hr. The excess ethyl formate and
liberated ethanol were removed under reduced pressure. Distillation
gave 46.5 g (0.304 moles; 96\%) of $8\beta$, bp 110-115° (0.03 mm).

Found: C, 70.24; H, 10.01; N, 9.11.

4-[2-(Methylamino)ethyl]cyclohexene ($7\alpha$)
To a stirred suspension of 11.5 g (0.303 moles) of lithium
aluminum hydride in 400 ml of ether was added dropwise a solution of
46.0 g (0.301 moles) of $8\beta$ in 75 ml of ether. The solution was
stirred at room temperature for 2 days and then hydrolyzed by the
dropwise addition of 50.0 g of a 10\% sodium hydroxide solution. The
solution was filtered and the solvent was removed under reduced
pressure. Distillation gave 32.7 g (0.235 moles; 78\%) of $7\alpha$, bp
94-96° (22 mm).

Anal. Calcd. for C₉H₁₇N: C, 77.63; H, 12.31; N, 10.06.

Found: C, 77.45; H, 12.28; N, 9.99.

The hydrochloride was made in the usual manner, mp 144-147°, but was not analyzed.

**Solvolysis of 4-[2-(N-chloro-N-methylamino)ethyl]cyclohexene (72a) in methanol**

A solution of 1.00 g (7.20 mmoles) of 72 in 25 ml of commercial bleach was stirred for 30 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure without heating. The N-chloramine was taken up in 50 ml of methanol and the solution was refluxed for 48 hr at which time the solution gave a negative test for active chlorine. The solution was diluted with 50 ml of 5% sodium hydroxide solution and was continuously extracted with pentane for 12 hr. Vapor phase analysis showed the presence of one major product which had a retention time identical with that of 72. Trace amounts of several other products were present but not in sufficient quantities to be isolated. A small amount of the crude product was purified by vapor phase chromatography and was shown to be 72 by comparison of its infrared spectra with that of an authentic sample.
Solvolysis of 4-[2-(N-chloro-N-methylamino)ethyl]cyclohexene (72a) in acid

A solution of 4.55 g (32.7 mmoles) of 72 in 125 ml of commercial bleach was stirred for 30 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was added to 100 ml of a 1M solution of sulfuric acid and the solution was refluxed for 90 min at which time the solution gave a negative test for active chlorine. The solution was cooled, made strongly basic with potassium hydroxide and was continuously extracted with ether for 2 days. Vapor phase analysis indicated the presence of three products in an approximate ratio of 1:2:4. The solvent was removed by distillation and the residue was treated with an ethanolic solution of picric acid until the solution became acidic to litmus. The picrate thus formed was recrystallized from absolute ethanol to give 4.63 g (12.1 mmoles; 37%) of the picrate of 15J, mp 232-233.5°.


Found: C, 46.85; H, 5.36; N, 14.58.

In a previous experiment, a small portion of the product was purified by preparative vapor phase chromatography and the minor product was shown to be 72 by comparison with an authentic sample. Column chromatography on basic alumina using chloroform as the eluent gave a small amount of 150 which was about 90% pure by vapor phase analysis. Attempted purification of 150 by preparative vapor phase
chromatography led only to decomposition in the injector port.

2-Methyl-2-azabicyclo[3.3.1]nonan-8-one (152)

A solution of 0.645 g (4.16 mmoles) of 151a in 10 ml of ethanol was made acidic with concentrated hydrochloric acid and the solvents were removed under reduced pressure. The oily residue was taken up in 75 ml of acetone and the solution was stirred vigorously causing the hydrochloride to precipitate. The mixture was treated with 15 ml of Jones' reagent and was stirred vigorously for one hr. The mixture was diluted with 20 ml of water and stirred an additional 20 min. The acetone was removed under reduced pressure and the solution was diluted with 200 ml of water, made basic with sodium hydroxide and was continuously extracted with ether for 18 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation through a packed column. Distillation of the residue in a molecular still at 40 mm gave 0.284 g (1.86 mmoles; 47%) of 152. The picrate was made in the usual manner, mp 218-219° (d).

Anal. Calcd. for C_{15}H_{16}N_{4}O_{3}:  C, 47.12; H, 4.75; N, 14.66.

Found:  C, 47.16; H, 4.87; N, 14.62.

2-Methyl-2-azabicyclo[3.3.1]nonan-8-one bisethylenethioketal (153)

A solution of 0.184 g (1.23 mmoles) of 152, 0.5 ml of ethanedi-thiol and 2 ml of boron trifluoride etherate was heated on a steam bath for 30 min and allowed to stand at room temperature for 20 hr. The reaction mixture was poured onto 30 ml of aqueous sodium
hydroxide and heated on a steam bath for 30 min. The solution was extracted with ether and the extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was distilled in a molecular still at 0.10 mm to give 0.133 g (0.581 mmoles; 47%) of 153. The cold finger was washed with absolute ethanol and the picrate was made in the usual manner from the washings, mp 176-179°.

Anal. Calcd. for C17H21N4O7S2: C, 44.53; H, 4.84; N, 12.22; S, 13.99.

Found: C, 44.53; H, 4.81; N, 12.12; S, 13.93.

Desulfurization of 2-Methyl-2-azabicyclo[3.3.1]nonan-8-one bisethyl-ethioketal (153)

To a suspension of W-5 Raney nickel, prepared from 2.60 g of nickel aluminum alloy, in 60 ml of absolute ethanol was added 0.133 g (0.581 mmoles) of 153 and the suspension was refluxed for 25 hr. The reaction mixture was cooled and 12 ml of concentrated hydrochloric acid was added. The solution was stirred until all the nickel had been dissolved and the solvents were removed under reduced pressure. The solid residue was heated with chloroform and the solution was filtered. The chloroform was removed under reduced pressure and the residue was taken up in 25 ml of water, made basic with sodium hydroxide and extracted with ether. The picrate was made from the ether extracts and was twice recrystallized from absolute ethanol to give 0.072 g (0.196 mmoles; 34%) of picrate, mp 257-257.5°.
The infrared spectrum of the picrate was identical to that of the picrate of 154. Although the melting point was slightly lower than that of an authentic sample, a mixture melting point showed no depression. In fact, a slight increase was noted, mp 259-260° (d).

**m-Aminophenylacetic acid (156)**

A solution of 3.80 g (21.0 mmoles) of m-nitrophenylacetic acid, 200 ml of ethanol and 0.40 g of 5% palladium on carbon catalyst was hydrogenated on a Parr apparatus until the uptake of hydrogen ceased. The mixture was filtered through celite and the solvent was removed under reduced pressure. The residue was dried overnight in a vacuum oven to give 2.87 g (19.0 mmoles; 90%) of crude 156, mp 104-135°. The crude product was used without further purification. (Lit mp 146-148°)

**cis-3-Aminocyclohexylacetic acid (157)**

A solution of 2.87 g (19.0 mmoles) of 156 in 25 ml of water and 25 ml of t-butyl alcohol was charged to a stainless steel bomb and was hydrogenated under 1700 lbs/in² of hydrogen at 100° for 5 hr using 0.50 g of 5% ruthenium on carbon as catalyst. The mixture was filtered through celite and the solvents were removed under reduced pressure.

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63. The sample of m-nitrophenylacetic acid supplied by the Aldrich Chemical Co. was found to contain at least 23% sodium chloride as determined by dissolving 4.94 g of the sample in 200 ml of ethanol and filtering off 1.14 g of an insoluble material which was shown to be sodium chloride by standard qualitative tests.
pressure. The residue was dried overnight in a vacuum oven to give 2.32 g (14.8 mmoles; 78%) of 157. A small amount was recrystallized from ethanol-water, mp 254-256°. (Lit mp 272-273°)

2-Azabicyclo[3.3.1]nonan-3-one (158)

Solid 157, 2.32 g (14.8 mmoles), was placed in a solid distillation flask and was heated above its melting point with a flame. The distillate and pot residue were taken up in benzene and dried over anhydrous magnesium sulfate. About a gram of material was insoluble in benzene and was discarded. The solution was filtered and the solvent was removed under reduced pressure. The oily residue was sublimed at 3 mm and the sublimate was recrystallized from hexane-ether to give 0.721 g (5.19 mmoles; 35%) of 158, mp 162-164°. (Lit mp 163.5-165.5°)

2-Methyl-2-azabicyclo[3.3.1]nonan-3-one (159)

To a stirred suspension of 0.153 g (3.82 mmoles) of a 60% sodium hydride-mineral oil dispersion in 30 ml of tetrahydrofuran was added a solution of 0.431 g (3.10 mmoles) of 158 in 10 ml of tetrahydrofuran. After refluxing for 90 min, the mixture was cooled to room temperature and 10 ml of methyl iodide was added. The solution was stirred for one hr and poured onto 300 ml of ether. The solution was filtered and the solvents were removed under reduced pressure. Distillation gave 0.291 g (1.90 mmoles; 61%) of 159, bp 84-110° (0.70 mm). Although the product distilled over a large range, it was shown to be greater than 98% pure by vapor phase analysis. A small
amount was purified for analysis by preparative vapor phase chromatography on 10' 10% Carbowax:KOH (4:1) on Chromosorb G column.

Found: C, 70.30; H, 9.90; N, 8.95.

2-Methyl-2-azabicyclo[3.3.1]nonane (154)

To a stirred suspension of 0.196 g (5.17 mmoles) of lithium aluminum hydride in 30 ml of ether was added a solution of 0.206 g (1.35 mmoles) of 152 in 10 ml of ether. The mixture was stirred at room temperature for 16 hr and 0.78 g of a 10% sodium hydroxide solution was added dropwise. After hydrolysis was complete, the solution was filtered and the solvent was removed by distillation. Distillation of the residue in a molecular still at 15 mm gave 0.172 g (1.24 mmoles; 92%) of 154. The picrate was made in the usual manner, mp 262-263° (d).

Found: C, 48.94; H, 5.52; N, 15.00.

2-Methoxybutadiene (88)

The procedure of DeGraw, Goodman and Baker was used in the preparation of 88.

Ethyl 4-methoxy-3-cyclohexeneoate (91)

A mixture of 50.5 g (0.601 moles) of 88, 72.0 g (0.720 moles) of ethyl acrylate, 150 ml of benzene and 0.50 g of hydroquinone was charged to a stainless steel bomb and was heated at 140° for 3½ hr. The solution was filtered and the solvent was removed under reduced
pressure. Distillation gave 37.8 g (0.206 moles; 34%) of 91, bp 69-73° (1 mm). Vapor phase analysis indicated that the product was greater than 90% pure. A small amount was purified by preparative vapor phase chromatography on a 10' 10% Carbowax 20M:KOH (4:1) on Chromosorb G column.

Anal. Calcd. for C_{10}H_{16}O_{3}: C, 65.19; H, 8.75.

Found: C, 65.00; H, 8.81.

H-Methyl-4-methoxy-3-cyclohexenecarboxamide (92)

About 200 ml of methylamine was condensed into a 1 liter 3-neck flask fitted with a mechanical stirrer, a dry ice condenser and a gas inlet tube. The inlet tube was replaced by a septum and 160 ml of a 15.12% n-butyllithium solution (0.256 moles) in hexane was added by means of a syringe. The reaction mixture was maintained at -30° as a solution of 35.1 g (0.191 moles) of 91 in 50 ml of hexane was added. The solution was stirred at -30° for 90 min and was allowed to slowly warm to room temperature. The solution was poured onto 200 ml of water and extracted with chloroform. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Sublimation of the residue gave 24.3 g (0.144 moles; 75%) of 92. Recrystallization from Skelly B-ether gave an analytical sample, mp 100.5-101.5°.

Anal. Calcd. for C_{9}H_{15}NO_{2}: C, 63.88; H, 8.94; N, 8.28.

Found: C, 63.92; H, 8.81; N, 8.17.
**1-Methoxy-4-(N-methylaminomethyl)cyclohexene (73)**

To a stirred suspension of 1.82 g (8.0 mmol) of lithium aluminum hydride in 250 ml of ether was added 6.00 g (37.8 mmol) of 92. The solution was stirred at room temperature for 19 hr and was hydrolyzed by the dropwise addition of 7.28 g of a 10% sodium hydroxide solution. The solution was filtered and the solvent was removed under reduced pressure. Distillation gave 5.05 g (32.6 mmol; 86%) of 73, bp 66-68° (1 mm).


Found: C, 69.6; H, 11.01; N, 9.18.

**Solvolysis of 1-methoxy-4-(N-chloro-N-methylaminomethyl)cyclohexene (73a) in methanol**

A solution of 2.40 g (15.5 mmol) of 73 and 40 ml of commercial bleach was stirred for 20 min and the solution was extracted with Freon 11. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure without heating. The N-chloramine was taken up in 100 ml of methanol and the solution was refluxed for 12 hr at which time the solution gave a negative test for active chlorine. The reaction mixture was made strongly basic with 100 ml of aqueous sodium hydroxide and was continuously extracted with pentane for 24 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was distilled to give 2.19 grams of products, bp 70-95° (0.2 mm). The products were separated by preparative vapor phase chromatography on a 10' 15% Carbowax:KOH
column on Chromosorb W to give 0.188 g (0.121 mmoles; 69%) of 13 in 0.902 g (4.09 mmoles; 26%) of 162 and 0.193 g (0.874 mmoles; 69%) of 162. The collection efficiency was only about 63% with a large amount of decomposition occurring in the injector port.

Anal. for 163:
Calcd. for \( \text{C}_{10} \text{H}_{26} \text{NO}_2 \text{Cl} \): C, 54.17; H, 9.09; N, 6.32; Cl, 15.99.

Found: C, 54.22; H, 9.08; N, 6.07; Cl, 15.58.

Anal. for 162:
Calcd. for \( \text{C}_{10} \text{H}_{26} \text{NO}_2 \text{Cl} \): C, 54.17; H, 9.09; N, 6.32; Cl, 15.99.

Found: C, 54.11; H, 9.19; N, 6.18; Cl, 14.29.

Dechlorination of trans-3-chloro-4,4-dimethoxy-1-methylaminomethyl-cyclohexane (163)

To a refluxing solution of 1.1 g of finely cut sodium metal in 25 ml of tetrahydrofuran was added 0.134 g (1.81 mmoles) of t-butyl alcohol in 5 ml of tetrahydrofuran. A solution of 0.214 g (1.13 mmoles) of 163 in 10 ml of tetrahydrofuran was added dropwise and the solution was refluxed for 3½ hr. The solution was filtered through wire gauze and the filtrate was poured onto 50 ml of water and the aqueous phase was extracted with pentane. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by preparative vapor phase chromatography on a 10' x 10\( ^6 \) Carbowax:KOH column to give 0.069 g (0.446 mmoles; 42%) of 1-methoxy-4-(N-methylaminomethyl)cyclohexene (72). No other products were detected by vapor phase analysis.
Conversion of trans-3-chloro-4,4-dimethoxy-1-methylaminomethylcyclohexane (163) to syn-2-hydroxy-7-methyl-7-azabicyclo[3.2.1]octane (137)

A solution of 0.244 g (1.10 mmoles) of 163 in 25 ml of 5% hydrochloric acid was stirred at room temperature for one hr. The solution was made basic with sodium hydroxide and 0.150 g (2.73 mmoles) of potassium borohydride was added. The solution was stirred for one hr and was continuously extracted with ether for 20 hr. The extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. The residue was purified by preparative vapor phase chromatography on a 10' x 105 Carbowax:KOH column to give 0.045 g (0.319 mmoles; 29%) of 137 and 0.010 g (0.071 mmoles; 6%) of 133. The picrate of 137 was made in the usual manner, mp 236-242°. Mixture melting point with an authentic sample showed no depression, mp 236-241.5°.
60 MHz nmr spectrum of

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\begin{align*}
&\text{HO} \\
\end{align*}
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60 MHz nmr spectrum of

\[
\begin{align*}
&\text{N-CH}_3 \\
\end{align*}
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60 MHz nmr spectrum of

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\begin{align*}
&\text{Cl} \\
\end{align*}
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60 MHz nmr spectrum of

\[
\begin{align*}
&\text{OH} \\
\end{align*}
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BIBLIOGRAPHY

1. The term "nitrenium ion" will be used to designate a divalent, positively charged nitrogen species. The singlet state in which the free electrons are paired will be represented by R-N-R. The triplet state in which the free electrons are unpaired will be represented by R-N-R.


33. This observation was made by Frances Hoyda, an undergraduate at Ohio State, who did the initial work on the preparation and solvolysis of 70.


35. Supplied by the Aldrich Chemical Co.

36. Virtually identical results were obtained when a methanolic solution of silver ion was used.

37. The N-chloramine was prepared by stirring a solution of one gram of amine per 20 ml of commercial bleach for 20-30 min. followed by extraction with Freon 11. The solvent was removed under reduced pressure without heating.

38. The author wishes to thank Richard Cryberg for running the 100 Hz nmr spectra of 96a, 100a and 101a and for doing the double and triple resonance studies.

39. The spectra were obtained on a Beckmann IR-9 recording spectrophotometer. The author wishes to thank John Pascone for running the spectra of the epimeric alcohols.


43. The author wishes to thank B. L. Fox for providing an authentic sample of isoquinuclidone.


54. The sample supplied by the Arapahoe Chemical Co. is a mixture of the methyl and ethyl esters.


63. The sample of m-nitrophenylacetic acid supplied by the Aldrich Chemical Co. was found to contain at least 23° sodium chloride as determined by dissolving 4.94 g of the sample in 200 ml of ethanol and filtering off 1.14 g of an insoluble material which was shown to be sodium chloride by standard qualitative tests.