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THE GENERATION OF NITRENIIUM IONS
FROM HYDROXYLAMINE DERIVATIVES

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

By
George David Hartman, B.S.

The Ohio State University
1973

Approved by:

[Signature]
Adviser
Department of Chemistry
ACKNOWLEDGEMENTS

The authors wishes to thank Dr. Paul G. Gassman for suggesting this problem and for encouragement and advice throughout the course of this work.

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November 18, 1972..............Married Mary Jane Conrath of Marietta, Ohio.

March, 1973.......................Ph.D., The Ohio State University.
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Mary Jane
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INTRODUCTION

Part I. Historical

During the past few years the identification of divalent, positive nitrogen (the nitrenium ion) as the key intermediate in a variety of solvolytic processes has gained varied experimental support.\(^1\) The nitrenium ion, possessing six electrons in its valence shell, is isoelectronic with the carbonium ion, however due to the greater electronegativity of nitrogen relative to carbon, the nitrenium ion is predicted to be more reactive. A further dichotomy arises from the possibility that the unshared electron pair on the nitrogen atom of a nitrenium ion may exist in either of two spin states. If the non-bonding electrons have paired spins one is speaking of a singlet nitrenium ion (1), while if they have unpaired spins a triplet

\[
\begin{array}{c}
\end{array}
\]
nitrenium ion (2) is involved. Lee and Morokuma (3) have calculated that the ground state of the nitrenium ion is the triplet, some 45 kcal/mole lower in energy than the singlet. Furthermore, their calculations suggest that the triplet is linear or nearly linear while the optimum equilibrium bond angle for the singlet is ca. 115°. They also found that the energy level structure for the nitrenium ion was very similar to that of the isoelectronic carbene moiety. The energy separation between the triplet and singlet states was predicted to decrease as the angle between the two covalently bonded groups decreased.

Calculation of charge distribution (shown below) of the singlet nitrenium ion and singlet methylene in comparison with that for the carbonium ion (4) led Lee and Morokuma to the following conclusions:

\begin{align*}
\text{(2)} & \quad \text{P.G. Gassman and R.L. Cryberg, J. Amer. Chem. Soc., 91, 5176 (1969).} \\
\text{(3)} & \quad \text{S.T. Lee and K. Morokuma, ibid., 93, 6863 (1971).} \\
\text{(4)} & \quad \text{R.E. Kari and I.G. Scismadia, J. Chem. Phys., 46, 1817 (1967).}
\end{align*}
1. All three species have a 2pσ orbital completely or almost completely unoccupied and therefore will react as electrophiles with this 2pσ orbital pointing toward the substrate.

2. Methylene, CH₂, should be the weakest electrophile.

3. Comparison of reactivity of CH₃⁺ and NH₂⁺ depends on both net charge in the 2pσ orbital and the electron affinity of the cation. For planar CH₃⁺ this charge is +1.0 while at θ = 120° for NH₂⁺ the charge is +0.87, a relatively small deviation from +1.0, and thus NH₂⁺ would be a stronger electrophile because of its larger electronegativity.

In an analogous manner, a second group of workers⁵ also found the triplet to be the ground state, 1.56 eV (36 kcal/mole) lower in energy than the singlet. They predicted the triplet to have a minimum energy configuration at a bond angle of ca. 140° and the singlet to be most stable at a bond angle of ca. 120°.

Generation of a nitrenium ion in a solvolytic process would necessarily lead to the singlet species (1) which, if no other favorable reaction path were available, would spin invert to the energetically more stable triplet (2). This behavior is reminiscent of that of the carbene moiety and in fact, spin inversion in both cases has been shown to be enhanced by generation of the intermediate in heavy atom solvents.² The duality of spin states, each possessing a unique geometry and charge distribution leads to a dichotomy in chemical

---

behavior; the singlet exhibiting carbonium ion-like behavior and the triplet reacting as a diradical.

The history of nitrenium ions most probably began with the experiments of Stieglitz and co-workers\(^6\) who investigated the rearrangement of various trityl-N-chloroamines and tritylhydroxylamines and found that an aryl group would readily migrate from nitrogen to carbon. This same reaction Stieglitz found, did not seem to occur with

\[
\begin{align*}
\text{H} & \quad \text{(C}_6\text{H}_5\text{)}_3\text{C-N-OH} \quad \xrightarrow{} \quad \text{(C}_6\text{H}_5\text{)}_2\text{C}=\text{N-C}_6\text{H}_5 \\
\text{H} & \quad \text{(C}_6\text{H}_5\text{)}_3\text{C-N-Cl} \quad \xrightarrow{} \quad \text{(C}_6\text{H}_5\text{)}_2\text{C}=\text{N-C}_6\text{H}_5
\end{align*}
\]

disubstituted hydroxylamines or disubstituted N-chloroamines leading him to postulate a monovalent nitrogen (nitrene) intermediate in the rearrangement. Later work, however, showed that disubstituted compounds can also be smoothly rearranged,\(^7\) allowing rearrangement of both the mono- and disubstituted species to be explained in terms of divalent, positive nitrogen.

\(^{(6)}\) J. Stieglitz and P.N. Leech, Ber., \(46\), 2147 (1913); J. Stieglitz and P.N. Leech, J. Amer. Chem. Soc., \(36\), 272 (1914); J. Stieglitz and B.A. Stagner, \textit{ibid.}, \(36\), 2046 (1914); J. Stieglitz and I. Vosburgh, \textit{ibid.}, \(56\), 2081 (1916).

\(^{(7)}\) R.T. Conley and H. Brandman, unpublished results.
In 1955 Newman and Hay\(^8\) investigated the phosphorus pentachloride catalyzed rearrangement of tritylhydroxylamines and found that the order of decreasing migratory amplitude was \(\text{p-CH}_3\text{C}_6\text{H}_4^- \rightarrow \text{p-ClC}_6\text{H}_4^- \rightarrow \text{p-NO}_2\text{C}_6\text{H}_4^-\), i.e., electron releasing groups in the phenyl moiety enhanced migration. This result coupled with the observation\(^9\) that the thermal decomposition of tritylazides, almost certainly via a nitrene intermediate, is insensitive to the nature of the aryl group, lends strong support to the notion of a nitrenium ion intermediate in the Stieglitz rearrangement.

An example of a classical reaction which may in some cases involve a nitrenium ion is the Beckmann rearrangement. In this reaction, ketoximes which have had their hydroxyl function converted into a suitable leaving group (often \(\text{CHO}\) or an ester) are converted to substituted amides. The literature contains many examples of Beckmann rearrangements in which the groups \textit{trans} to the hydroxyl function migrates, leading many researchers to suggest that the migration of the group from carbon to nitrogen occurred \textit{via} a concerted mechanism.\(^{10}\)


Subsequently, however, it was shown that in certain cases the group cis to the hydroxyl migrates and that when both \( R_1 \) and \( R_2 \) are alkyl, mixtures of the two possible amides are produced. Therefore, since it does seem possible for rearrangements to occur by other than a concerted, backside attack by the group trans to the hydroxyl function, one may suggest that a discrete, unsaturated nitrenium ion may be involved in the process.

In order to test this hypothesis of an unsaturated nitrenium ion in the Beckmann rearrangement, Lansbury and co-workers\(^\text{11}\) studied the rearrangement of various indanone oximes. These workers reported that when steric considerations precluded the possibility of prior isomerization of the oxime and made aryl migration unlikely due to steric compression in the transition state, an alkyl group cis to the hydroxyl function migrated preferentially (see Table 1). The authors considered iminium cations as possible intermediates in this reaction and support for this proposal was obtained by a novel intramolecular insertion reaction.

Lansbury and co-workers\(^\text{12}\) reported that when 4-bromo-7-t-butyl-

\( \text{\small \begin{align*} \text{N} & \quad \text{OH} \\ \text{R}_1 \text{C} & \quad \text{R}_2 & \rightarrow & \text{O} \\ & \quad \text{R}_2 \text{C-N-R}_1 \end{align*}} \)

---

1-indonone oxime (2) was treated with polyphosphoric acid, a 75% yield of imine 4 was obtained. In the insertion reaction leading

<table>
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<th>% Alkyl Migration</th>
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| \[
\begin{array}{c}
  \text{CH}_3 \\
  \text{N} \\
  \text{CH}_3 \\
  \text{N} \\
  \text{CH}_3
\end{array}
\] | 37               | 63                |
| \[
\begin{array}{c}
  \text{C(CH}_3\text{)}_3 \\
  \text{N} \\
  \text{CH}_3 \\
  \text{N} \\
  \text{CH}_3
\end{array}
\] | 15               | 85                |
to $^1_3$, it was possible that the species attacking the proximal C-H bond could be either the cationic nitrogen intermediate $^2_3$, or the vinyl nitrene $^6$.

In order to distinguish between these two possible intermediates, rearrangement of oxime $^2_3$ was carried out in polyphosphoric acid. If the reaction was proceeding through the iminium cation $^2_3$ no deuterium would be found in the product, while if the nitrene $^6$ were the intermediate, the product should have one deuterium atom at the carbon adjacent to the imine carbon. Since no deuterium was found in the product, the authors concluded that the unsaturated nitrenium ion was the intermediate.
In an extension of the above study Lansbury and Briggs\(^{13}\) sought to determine whether the nitrenium ion which underwent the insertion reaction reported above was the singlet \(I\) or the triplet \(\delta\). Toward this goal they synthesized indanone oxime \(2\), labeled with deuterium in the methyl groups. Analysis of the insertion product for deuterium

\[
\begin{array}{c}
\text{CD₃}\text{C} & \text{CD₃} \\
\text{CH₃} & \text{N} \text{OH} \\
\text{Br} & \\
\text{2} \\
\text{CD₃}\text{C} & \text{CD₃} \\
\text{CH₃} & \text{N} \text{OH} \\
\text{Br} & \\
\text{10} \\
\text{CD₃}\text{C} & \text{CD₂} \\
\text{CH₃} & \text{N} \\
\text{Br} & \\
\text{11} \\
\end{array}
\]

in the methylene unit adjacent to nitrogen allowed determination of the isotope effect as $k_H/k_D = 1.6$. The authors concluded that this isotope effect was indicative of reaction by the singlet species since $k_H/k_D = 1.5$ for singlet \( \overset{\cdot}{\text{N}}-\text{CO}_2\text{C}_6\text{H}_5 \) inserting into cyclohexane\(^\text{14}\) while $k_H/k_D = 4.1$ for triplet \( \overset{\cdot}{\text{Ph}}-\overset{\cdot}{\text{N}} \) abstracting the tertiary hydrogen atom in isobutane.\(^\text{15}\)

Perhaps the earliest worker to implicate dialkyl nitrenium ions as reaction intermediates was Emmons\(^\text{16}\) who investigated the acid

\[
\begin{align*}
\text{RCO}_2\text{H} \rightarrow& \quad \overset{\cdot}{\text{N}}=\text{C}-\overset{\cdot}{\text{R'}} \\
\overset{\cdot}{\text{N}}-\overset{\cdot}{\text{C}}(\text{CH}_3)_3
\end{align*}
\]

---

catalyzed opening of oxazirane rings. He found that 2-t-buty1-3-
phenyloxazirane (12) upon treatment with aqueous acid gave benzalde-
hyde and t-buty1hydroxylamine (13) most likely via the indicated car-onium ion. This sequence involved protonation on oxygen, cleavage
of the C-O single bond, followed by simple hydrolysis. However, when
the carbon of the oxazirane ring did not possess a phenyl group, a
different mode of reaction occurred. The action of aqueous acid on
2-n-butyloxazirane (14) afforded acetaldehyde, ammonia and butyralde-
hyde, while 2-t-butyloxazirane (15) gave acetaldehyde, methylamine

\[
\begin{align*}
\text{CH}_2 & \quad \text{N-(CH}_2)_3\text{CH}_3 \\
& \quad \xrightarrow{H^+} \\
& \quad \text{CH}_2-N-(\text{CH}_2)_3\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2O + \text{NH}_3 + \text{CH}_3(\text{CH}_2)_2\text{CHO} & \leftrightarrow \\
& \quad \text{CH}_2-N-(\text{CH}_2)_3\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 & \quad \text{N-C(CH}_3)_3 \\
& \quad \xrightarrow{H^+} \\
& \quad \text{CH}_2-N-C(CH}_3)_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2O + \text{CH}_3\text{NH}_2 + \text{CH}_3\text{CCH}_3 & \leftrightarrow \\
& \quad \text{CH}_2-N-C(CH}_3)_2
\end{align*}
\]
and acetone. In both cases initial protonation of oxygen was followed by cleavage of the N-O bond to give a nitrenium ion, followed by either hydrogen or methyl migration to the electron deficient nitrogen site.

In 1961 Gassman and co-workers began a systematic approach to the elucidation of nitrenium ion reactions based on the priority of establishing that alkyl migration could occur to a divalent, electron deficient nitrogen atom where both substituents on nitrogen were alkyl groups. This approach was dictated by the tendency of alkyl groups to migrate to cationic and not to radical centers. Thus, the migration of an alkyl group from carbon to divalent nitrogen would indicate that the nitrogen was sufficiently electron deficient.

When N-chloroisouquinuclidine (16) was refluxed in a methanolic solution of silver nitrate, a 60% yield of 2-methoxy-1-azabicyclo[3.2.1]octane (17) was obtained. This skeletal rearrangement clearly required the migration of an alkyl group with its pair of bonding electrons from carbon to nitrogen. The reaction could either involve loss of chloride ion to leave the nitrenium ion (18) as a discrete intermediate which could undergo alkyl migration to give (19), or might possibly involve concerted loss of chlorine and migration of the alkyl group to give (19) directly. Analogously, solvolysis of 4,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (20) in methanol.

gave 21, 22, and 23 in 59%, 20% and 7% yields, respectively.

Unfortunately, the observations discussed above did not allow distinction to be made between a divalent nitrogen species with a unit positive charge and a slightly electron deficient nitrogen species which represented only a transitory point on the reaction pathway. The first substantive evidence for the existence of a discrete nitrenium intermediate with a unit positive charge was given by a quantitative study of the spin inversion of singlet nitrenium ions to triplets.\(^2\)

It was postulated that the solvolytically generated singlet nitrenium ion (\(24\)) could either undergo an alkyl migration or spin invert to triplet (\(25\)), which could then abstract two hydrogen atoms from solvent to give the protonated form of the starting amine (\(27\)).

\[
\begin{align*}
R-N-R & \rightarrow R-N^+R & \rightarrow R-N^+R & \rightarrow R-N^+R \\
\text{24} & & \text{25} & & \text{26} & & \text{27}
\end{align*}
\]

In order to test this hypothesis, Gassman and Cryberg\(^2\) carried out the solvolysis of bicyclic chloramine \(20\) in solvents such as bromoform and chloroform which contain heavy atoms. They found that the presence of the heavy atom solvent increased the percentage of starting secondary amine (\(23\)) in the product mixture. Since heavy
atom solvents are known to catalyze spin inversion, the occurrence of starting amine in the product mixture was due to hydrogen abstraction by the triplet nitrenium ion followed by neutralization of the protonated amine in the work-up. In order for spin inversion to occur, the nitrenium ion must have existed as a discrete entity with unit positive charge on nitrogen.

Alkyl migration to a nitrenium ion center in a nonbicyclic system was carried out in an intriguing series of ring expansion and contraction reactions. When 28 was solvolyzed in methanol containing

\[
\text{28} \quad \begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{N-Cl} \\
\text{CH}_3
\end{array} + \text{AgCl} \rightarrow \begin{array}{c}
\text{N}+ \text{C}_6\text{H}_5 \\
\text{CH}_3 \\
\text{CH}_3
\end{array} \left[ \begin{array}{c}
\text{N}+ \\
\text{C}_6\text{H}_5 \\
\text{CH}_3 \\
\text{CH}_3
\end{array} \right]
\]


silver trifluoroacetate, a mixture of \(32\) (87\%) and \(30\) (7\%) was obtained, while methanalysis of \(33\) in the presence of silver ion gave benzaldehyde and a mixture of \(35\) and \(36\). Both reactions seem best explained by heterolytic cleavage of the N-Cl bond to give a singlet nitrenium ion, followed by alkyl migration producing a resonance stabilized species which is then hydrolyzed.

\[
\begin{align*}
\text{H} & \quad \text{C}_6\text{H}_5 \\
\text{N} & \quad \text{Cl}
\end{align*}
\rightarrow
\begin{align*}
\text{N} & \quad \text{C}_6\text{H}_5 \\
\text{C} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CHO} & \quad + \quad \text{H}_2\text{N(CH}_2\text{)}_2\text{OCH}_3 & \quad + \quad \text{H}_2\text{N(CH}_2\text{)}_2\text{OH}
\end{align*}
\]

Firm kinetic evidence for the existence of nitrenium ions was obtained by a study of \(N\)-chloroaziridine solvolyses in polar solvents. Studies\(^{21,22}\) of the concerted electrocyclic ring opening of cyclo-


propyl cations to allylic cations have shown that a consideration of electronic and steric effects coupled with molecular orbital symmetry arguments permit prediction and explanation of the observed rates. Analogous opening of N-chloroaziridines would involve a disrotatory process in which the groups trans to the leaving group would rotate outwards as indicated below.

It has been reported that solvolysis of various N-chloroaziridines (37 a-f) in methanol proceeds with widely divergent rate constants to yield in all cases a product mixture which upon hydrolysis gives two moles of carbonyl compound and one mole of ammonium chloride. As indicated in Table 2, when no carbonium ion stabilizing groups are available, as in 37a, the reaction is slow. However, when methyl groups are available to stabilize the incipient carbonium ion, the effect must be balanced with steric strain generated during the disrotatory ring opening. The solvolysis of N-chloroaziridines exhibited kinetic behavior identical to that of the cyclopropyl cation. This indicates that heterolytic cleavage of the N-Cl bond was involved.

Since the theoretical and mechanistic basis of nitrenium ions was laid, several synthetic schemes utilizing this species have been


\[ \text{TABLE 2} \]

Rates and Products of N-Chloroaziridine Solvolysis

<table>
<thead>
<tr>
<th>N-Chloroaziridine</th>
<th>( k_{\text{rel}} )</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>37a: ( R_1=) ( R_2=) ( R_3=) ( R_4=\text{H} )</td>
<td>1</td>
<td>2 ( \text{CH}_2\text{O} + \text{NH}_4\text{Cl} )</td>
</tr>
<tr>
<td>37b: ( R_1=) ( R_2=) ( R_3=\text{H} ); ( R_4=\text{CH}_3 )</td>
<td>15</td>
<td>( \text{CH}_3\text{CHO} + \text{CH}_2\text{O} + \text{NH}_4\text{Cl} )</td>
</tr>
<tr>
<td>37c: ( R_1=) ( R_2=) ( R_4=\text{H} ); ( R_3=\text{CH}_3 )</td>
<td>210</td>
<td>( \text{CH}_3\text{CHO} + \text{CH}_2\text{O} + \text{NH}_4\text{Cl} )</td>
</tr>
<tr>
<td>37d: ( R_1=) ( R_3=\text{H} ); ( R_2=) ( R_4=\text{CH}_3 )</td>
<td>1490</td>
<td>2 ( \text{CH}_3\text{CHO} + \text{NH}_4\text{Cl} )</td>
</tr>
<tr>
<td>37e: ( R_1=) ( R_3=\text{H} ); ( R_3=) ( R_4=\text{CH}_3 )</td>
<td>1860</td>
<td>( \text{CH}_3\text{COCH}_3 + \text{CH}_2\text{O} + \text{NH}_4\text{Cl} )</td>
</tr>
<tr>
<td>37f: ( R_1=R_4=\text{H} ); ( R_2=R_3=\text{CH}_3 )</td>
<td>155,000</td>
<td>2 ( \text{CH}_3\text{CHO} + \text{NH}_4\text{Cl} )</td>
</tr>
</tbody>
</table>
published. Gassman and co-workers\textsuperscript{25} showed that certain azabicyclics could be generated \textit{via} intramolecular addition of a nitrenium ion intermediate to a double bond in a "'route'" synthesis. Thus, solvolysis of N-chloroamine \textsuperscript{38} in the presence of silver ion gave \textsuperscript{39}

\begin{equation}
\begin{array}{c}
\text{CH}_{3} \\
\text{(CH}_{2}\text{)}_{2}-\text{N-Cl} \\
\text{CH}_{3}
\end{array}
\xrightarrow{\text{Ag}^{+}}
\begin{array}{c}
\text{RO} \\
\text{H} \\
\text{NCH}_{3}
\end{array}
\end{equation}

\textsuperscript{38} in good yield, while cyclization of \textsuperscript{40} gave \textsuperscript{41} and \textsuperscript{42} as the major bicyclic products. In both cases the nucleophile added \textit{trans} to the attacking nitrenium ion.

The solvolysis of an N-chloraziridine was used by Horwell and Rees\textsuperscript{26} in a novel synthesis of isoquinoline. These workers converted

\begin{equation}
\begin{array}{c}
\text{CH}_{3} \\
\text{CH}_{2}-\text{N-Cl} \\
\text{CH}_{3}
\end{array}
\xrightarrow{\text{CH}_{3}\text{OH}}
\begin{array}{c}
\text{CH}_{3} \text{O} \\
\text{H} \\
\text{NCH}_{3}
\end{array} + \begin{array}{c}
\text{NCH}_{3} \\
\text{H} \\
\text{OCH}_{3}
\end{array}
\end{equation}

\textsuperscript{40} \quad \textsuperscript{41} \quad \textsuperscript{42}


aziridine $h_3$ to its N-chloro derivative ($h_4$) and then solvolysis afforded isoquinoline ($h_6$) as the final product. The mechanism most likely involves heterolytic cleavage of the N-Cl bond, as described previously for aziridines, with formation of iminium ion $h_5$, which then loses a proton to give $h_6$.

An intriguing and synthetically useful transannular insertion reaction of a nitrenium ion into a C-H bond was discovered by Edwards and co-workers. These researchers found that when N-chloroaza-cyclononane ($h_7$) was treated with silver ion, a 65% yield of indolizidine $h_8$ was obtained. The reaction was proposed to proceed through a mechanism involving hydride abstraction followed by ring closure to give the protonated tertiary amine ($h_9$).

Hobson and Riddell\textsuperscript{28} have reported that treatment of N-chloramine\textsuperscript{50} with silver perchlorate in a homogeneous acetone solution gave, in 

addition to starting amine 51, the two rearranged bicyclics 52 and 53. Further, with an equivalent amount of silver perchlorate in hot acetone 24 afforded 55 as the sole product. These workers, however, were skeptical of a mechanism involving free nitrenium ions, suggesting either a radical-chain addition of nitrogen to the double bond

\[
\begin{align*}
\text{CH}_3 & \quad \text{Ag}^+ \\
& \quad \rightarrow \\
\text{N-Cl} & \quad \text{Cl} \\
\end{align*}
\]

or metal complexation with the nitrogen atom of the N-chloramine followed by homolysis or heterolysis of the N-Cl bond leading to intramolecular addition.

In 1969 Rautenstrauch reported23 that the silver ion promoted methanolysis of epimeric N-chloramines 56 and 58 gave 57 and 59, respectively, as the sole products and postulated the indicated mechanism. The N-chloramines 56 and 58 were shown to undergo slow nitrogen inversion at room temperature. It was also demonstrated that 56 solvolyzed much more rapidly than 58.

An interesting ring expansion reaction was carried out by Kovacic and co-workers30 in which treatment of 1-N,N-dichloroamino-


adamantane (60) at low temperature with aluminum chloride in methylene chloride gave 61 which could be trapped by methoxide to yield 62 in ca. 50% yield. The alkyl migration in the present work is to a nitrenium ion site which is attached to a relatively unstrained ring system in contrast to the strained systems previously studied by Gassman.17,18,20
More recently Kovacic and co-workers\(^{31}\) found that treatment of 1-N,N-dichloroaminoapocamphane (63) with 2 equivalents of aluminum chloride in methylene chloride at ca. \(75^\circ\) provided 1-chloro-3,3-

dimethyl-2-azabicyclo[2.2.2]octane (64) in 10% yield. The major nonbasic products 65, 66, and 67 from rearrangement of 63, result from α scission of the carbon-carbon bond present in the shortest bridge. Since little or no inhibition was apparent when radical inhibitors were added, the authors concluded that the reaction involved an ionic type fission of the N-Cl bond.

In 1968 Gassman and co-workers\textsuperscript{32,33} began a systematic study of the aryl substituted nitrenium ion 68, i.e., anilenium ion, which greatly enlarged the scope and synthetic utility of the divalent, positive, nitrogen species. Earlier workers\textsuperscript{34} had demonstrated that

\begin{center}
\begin{tabular}{c}
\textbf{68}
\end{tabular}
\end{center}


chlorination of anilines with certain halogenating agents produced o- and p-chloroanilines and that N-chlorination preceded chlorination of the aromatic nucleus. The mechanism of this reaction had not been elucidated and two pathways seemed possible. The N-chloroaniline could either ionize to form amide anion and positive chlorine followed by electrophilic attack of chlorine on the aromatic nucleus (path a), or cleave to form an anilinium ion and chloride anion followed by

\[ \text{N-R} \quad \xrightarrow{\text{Cl}^+} \quad \text{N-R} \quad \xrightarrow{\text{Cl}^-} \]

nucleophilic attack of chloride on the aromatic ring. In order to distinguish between the two, a series of substituted N-chloramines was synthesized and the rates of solvolysis were measured. The substituents gave an excellent correlation with Hammett $\sigma^+$ values, yielding a rho ($\rho$) of -6.35. This large negative rho provides convincing evidence that the thermal rearrangement of N-chloramines
proceeds via an anilenium ion, in which the positive charge is extensively delocalized into the aromatic nucleus.

In a more synthetic vein, it was found\(^3\) that the silver promoted methanolysis of a series of aryl N-chloramines resulted in a product mixture consisting of the o- and p-chloro as well as the o- and p-methoxy isomers. Quantitative product studies revealed that as the substituents on the aromatic ring became increasingly electron-withdrawing, incorporation of solvent into the aromatic nucleus decreased. The incorporation of chloride was consistent with the silver ion catalyzed formation of a 'tight ion pair' (69), which became 'tighter' as the ring substituents became more electron-withdrawing (anilenium ion stability decreases). This 'tighter' complex led to increased amounts of ring-chlorinated products.

\[
\text{R} \quad \text{N} \quad \text{Cl}^- \quad \text{Ag}^+ \\
\text{6+} \quad \text{6+} \quad \text{6+} \quad \text{6+}
\]

Recently, it has been demonstrated that nitrenium ions can be readily generated from precursors other than N-chloramines. For example, when the hydrochloride of 70 was treated with 1.1 equivalents of isoamyl nitrite at 50° in methanol,\(^3\) a 21% yield of

rearranged ether \( T_1 \) was obtained, in close analogy with previous work.\(^{18}\) A similar rearrangement was observed by Gassman and coworkers\(^{36} \) upon treatment of \( N \)-bromamine \( T_2 \) with a methanolic silver perchlorate solution. Reaction at \( 25^\circ \) for thirty minutes gave \( T_4 \) as the only isolable product in \( 70\% \) yield, while solvolysis at \( 0^\circ \) for thirty minutes led to the isolation of a \( 55\% \) yield of \( T_2 \) and a \( 20\% \) yield of \( T_4 \). Thus, a significant portion of \( T_4 \) possibly arises

---

by initial nitrenium ion generation, Wagner-Meerwein rearrangement with recapture of bromide ion to give \( \text{Z} \) and subsequent solvolysis.
Part II. The Problem

The research upon which this thesis is based can be divided into three related areas: (1) the development of a general synthetic procedure for the preparation of dialkylhydroxylamines and the synthesis and solvolysis of their benzoate and tosylate esters; (2) a determination of the relative migratory amplitudes of the phenyl, methyl and hydrogen groups to an adjacent nitrenium ion generated in a solvolytic process; and (3) an investigation of the effect of solvent on the rate of formation of a secondary nitrenium ion, to include protic and aprotic solvents of high dielectric constant. In each of these areas, the main objective was to ascertain, through careful product and kinetic studies, whether nitrenium ions were present and how the chemistry of this species was affected by changing factors such as solvent and the mode of generation.

When this work was begun, the use of dialkylhydroxylamines as nitrenium ion precursors had virtually no analogy in the literature,37

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(37) We have recently been informed by Professor C.F. Wilcox of the unpublished results of K.K. Pohl on the solvolysis of p-nitrobenzoate and trichloroacetate esters of N,N-dialkylhydroxylamines in ethanol-water mixtures (K.K. Pohl, Ph.D. Thesis, Cornell University, 1963). Their preliminary results seemed to be more complex than ours, presumably due to the solvent system chosen. We wish to thank Professor Wilcox for this information.
Despite the fact that simple dialkylhydroxylamines could be synthesized in a straightforward manner.\(^{38}\) However, it had been reported\(^{39}\) that the benzenesulfonate ester of diethylhydroxylamine decomposed violently at room temperature to give acetaldehyde and ethylamine, most likely through a nitrenium ion intermediate. During the course of the present work, two articles appeared which independently claimed generation of dialkyl nitrenium ions from hydroxylamine precursors.\(^{40-42}\)

It was reported\(^{41}\) that reaction of various trisubstituted imines with cyclopentadiene led to the formation of a Diels-Alder adduct in stereospecific fashion. These compounds appeared to be quite stable.

\[
\begin{align*}
R_1 \quad \text{C=N} \quad OR_3 \\
R_2 \\
\text{+} \\
\text{Cyclic} \\
\rightarrow \\
R_1 \quad \text{N} \quad OR_3 \\
\text{R}_2 \\
\text{R}_3 = -\text{SO}_2\text{C}_6\text{H}_5, -\text{COOC}_2\text{H}_5, -\text{COOCH}_3, -\text{CONH}_2 \\
\text{R}_3 = -\text{SO}_3\text{C}_6\text{H}_5, -\text{CH}_3, -\text{SO}_2\text{CH}_3, -\text{COC}_2\text{H}_4, -\text{NO}_2, -\text{COC}_6\text{H}_5
\end{align*}
\]


\(^{40}\) For a comprehensive review of phenylhydroxylamine derivatives as possible nitrenium ion precursors see: J.A. Miller, Cancer Research, 30, 559 (1970), and references cited therein.


Solvolyis of 75 in aqueous dioxane at 25° with sodium carbonate buffer proceeded with a pseudo first-order rate constant of \( k = 4.6 \times 10^{-7} \text{ sec}^{-1} \) to give only isomer 77. The authors concluded that the rearrangement most likely proceeded through an intermediate such as 76, in direct analogy to the work of Gassman and Cryberg.\(^{18}\)

The second extension of the generation of dialkylnitrenium ions to hydroxylamine precursors was reported by Wasserman, et. al.,\(^{42}\) who found that the 0-benzoyl derivative of N-t-butylhydroxylamine 78

\[
\text{78} \quad \text{79} \quad \text{80}
\]

\[
\begin{align*}
\text{78} & \quad + \quad \text{C}_6\text{H}_5\text{C}-\text{ONHC(CH}_3\text{)}_3 \\
\text{79} & \quad \text{80} \quad + \quad \text{C}_6\text{H}_5\text{CO}_2\text{H}
\end{align*}
\]
reacted directly with cyclopropanone in ether at -78° to form the β-lactam 80 in 40% yield. The proposed mechanism involves the rapid decomposition of the intermediate benzoate ester 79 and alkyl migration (ring expansion) to the electron deficient nitrogen site.

Despite the interesting results gathered by both groups of workers, several questions directly associated with that work remained unanswered. Since the Diels-Alder reaction used by Biehler, et. al., was reported only for imines possessing strong electron-withdrawing groups, the reaction was probably not a good general synthetic method for the preparation of unsubstituted or alkyl substituted bicyclic hydroxylamine derivatives. A good synthetic procedure for these compounds was therefore still needed. Also, one might question what effect the presence of two powerful electron-withdrawing groups adjacent to the nitrenium ion site had on the rate of formation, nature, and subsequent fate of that species. Finally, a comprehensive study of the effect of leaving group on the generation of nitrenium ions was specifically indicated due to the somewhat conflicting reports of stable 41 and unstable 39 hydroxylamine tosylates and unstable hydroxylamine benzoates. 42
RESULTS AND DISCUSSION


In seeking to implicate divalent, positive nitrogen in the solvolytic decomposition of hydroxylamine derivatives, we felt that the ideal systems to investigate were those azabicyclic systems which had already been shown to undergo facile skeletal rearrangement when their nitrogen function was converted into a nitrenium ion. Two such systems were 2-azabicyclo[2.2.2]octane (81) and 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (82). The synthetic approach to the

\[ \text{CH}_3 \quad \text{CH}_3 \]

\[ \text{N} \]

81

\[ \text{CH}_3 \quad \text{CH}_3 \]

\[ \text{N} \]

82
corresponding hydroxylamine derivative for each system was analogous to the procedure developed by Rogers\(^{38}\) for the preparation of simple dialkylhydroxylamines. As shown below, reaction of 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (83) with ethyl acrylate in tetrahydrofuran solution at reflux afforded a 76\% yield of N-(2-carboethoxyethyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (84). This clear oil was dissolved in chloroform and oxidized with m-chloroperbenzoic acid

-34-
to yield, after filtration of the precipitated acid, the N-oxide \( \text{85} \) as a clear, viscous oil. The unpurified N-oxide was then dissolved in 1 M aqueous sodium hydroxide solution and heated to 90° over the course of 1 hr. Continuous extraction of the resultant aqueous phase with ether gave N-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (86) as a fragrant, white solid in 54% yield.
In an analogous manner, 2-azabicyclo[2.2.2]octane\(^{43}\) (91) was converted into 92 in 91\% yield. This adduct was then oxidized with \(m\)-chloroperbenzoic acid to the tertiary N-oxide, which was subjected to aqueous base to give the desired hydroxylamine \(94\) as a stable white solid.

By analogy to carbonium ion chemistry, it might be anticipated that the conversion of dialkylhydroxylamines into the corresponding tosylates should provide a simple route to nitrenium ions. This idea was supported by the work\(^{41}\) previously mentioned and was the initial plan of our investigation.

\[ \text{91} \quad + \quad \text{CH}_2=\text{CHCO}_2\text{C}_6\text{H}_5 \quad \rightarrow \quad \text{92} \]

\[ \begin{align*}
\text{94} & \quad \text{N-OH} \\
\text{93} & \quad \text{N-CH}_2\text{CH}_2\text{CO}_2\text{C}_6\text{H}_5
\end{align*} \]

\(({}^{43}\)) See experimental for synthetic details.
The preparation of hydroxylamine tosylates was first attempted by reaction of the hydroxylamine with p-toluenesulfonyl chloride in pyridine at low temperature. Reaction in this manner, followed by either aqueous or non-aqueous work-up, resulted in the formation of dark intractable materials. However, reaction of N-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (66) in either ether or hexane with an equivalent amount of n-butyllithium (to generate the hydroxylamine anion) and then with p-toluenesulfonyl chloride at 0-10° resulted in a smooth reaction in which the theoretical amount of lithium chloride was precipitated in less than five minutes. Filtration of the reaction solution and solvent removal on the rotary evaporator at 10-15° gave an oil which solidified on cooling. This product was identified on the basis of infra-red and nuclear magnetic resonance spectra data, as well as independent synthesis\(^{44}\) to be 3,3,4-trimethyl-2-tosyloxy-1-azabicyclo[2.2.1]heptane (68), the product of skeletal rearrangement. This product most probably arose by initial formation of tosylate 67, which under the reaction conditions underwent heterolytic cleavage of the N-O bond to give a nitrenium ion: tosylate ion pair. This ion pair then underwent Wagner-Meerwein rearrangement to give a secondary carbonium ion which recaptured the tosylate group. The rearranged secondary tosylate was recovered in

\(^{44}\) We wish to thank Dr. K. Shudo for performing this synthesis; P.G. Gassman and K. Shudo, unpublished results.
virtually quantitative yield, and within the limits of analysis by nuclear magnetic resonance spectroscopy, no other compound was present.

Since the hydroxylamine tosylate 87 proved to be extremely reactive even at the low temperature and in the non-polar media used above, it seems likely to us that the practical use of the p-toluene sulfonate anion as a leaving group was limited to specific molecules in which the hydroxylamine function is flanked by strong electron-
withdrawing groups. At least, in the absence of such electron-withdrawing groups, the initially formed sulfonate esters are extremely unstable. However, the facile rearrangement of $87$ to $88$ indicates that hydroxylamines which have had their hydroxyl function converted into a suitable leaving group, should serve as excellent nitrenium ion precursors. For this reason, we turned our attention to the use of benzoate anions as leaving groups in the generation of nitrenium ions.

The literature contains numerous synthetic methods for preparing benzoate esters of hydroxylamines. However, we discovered that an extremely mild way of affecting this conversion was to react the hydroxylamine with an equivalent amount of acid chloride in an ethereal suspension of powdered sodium hydroxide at $-55^\circ$ for 1.5 hr. If the reactants were mixed at temperatures greater than $-10^\circ$, immediate discoloration and decomposition occurred. That this technique was a good general procedure is shown in Table 3, which lists the yields of $p$-nitrobenzoate esters of various hydroxylamines, and in Table 4 which lists six different benzoate esters of $N$-hydroxypiperidine.

An unexpected benefit of this procedure was that one need not have rigorously pure samples of hydroxylamine. For example, the hydroxylamine, often contaminated with small amounts of amine,

---

underwent reaction rapidly at the low temperature while the amine, which could have reacted with the acid chloride to form an amide, remained inert. The hydroxylamine ester was then readily separated from the amine contaminant by simple recrystallization.
In order to evaluate the effects of using various benzoate anions as leaving groups, we studied rates of methanolysis of the piperidin-1-yl benzoates listed in Table 4. Despite the good pseudo first-order kinetics obtained conductometrically, the rates were anomalous in that all of the compounds listed in Table 4 appeared to solvolyze at about the same rate, although there was a drastic difference in the nature of the leaving groups. This result was distressing until a product analysis revealed that two competing reactions were occurring, one which gave a nitrenium ion (101) and benzoate anion (102), and a second, which produced N-hydroxypiperidine (103) and the appropriate methyl benzoate (104). The conversion of 101 to 105 in methanol is readily rationalized in terms of a singlet to triplet interconversion of the nitrenium ion, followed by hydrogen abstraction.246 Table 5 lists the yields and ratios of products obtained in these solvolyses. Through a series of trial experiments it was determined that of the four compounds which made up the product mixture, none by itself gave a significant conductance, and of the possible pairs, the amine:benzoic acid combination was the only one which could account for the observed conductance changes. Further, addition of either methyl benzoate or hydroxylamine (or both) to a solution of the amine and benzoic acid altered the conductance only slightly.

(46) Solvolysis of N-chloropiperidine in methanol also gives piperidine as the only isolable product (P.G.Gassman and J.E. Trent, unpublished results).
TABLE 4
Methanalysis Rates of Piperidin-l-yl Benzoates

<table>
<thead>
<tr>
<th>Compound</th>
<th>( k \times 10^6 \text{sec}^{-1} )</th>
<th>Partial Rate Factor (( k_n \times 10^6 \text{sec}^{-1} )) for Nitrenium Ion Formation</th>
<th>( k_{rel} ) for Partial Rate Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N-O-C-OC-CH}_3 )</td>
<td>23.6 ± 0.5</td>
<td>2.36</td>
<td>1.0</td>
</tr>
<tr>
<td>( \text{N-O-C-CI} )</td>
<td>15.5 ± 0.3</td>
<td>2.80</td>
<td>1.2</td>
</tr>
<tr>
<td>( \text{N-O-C-H} )</td>
<td>20.4 ± 0.5</td>
<td>4.50</td>
<td>1.9</td>
</tr>
<tr>
<td>( \text{N-O-C-Cl} )</td>
<td>16.2 ± 0.3</td>
<td>6.15</td>
<td>2.6</td>
</tr>
<tr>
<td>( \text{N-O-C-NO}_2 )</td>
<td>13.7 ± 0.2</td>
<td>11.8</td>
<td>5.0</td>
</tr>
<tr>
<td>( \text{N-O-C-NO}_2 )</td>
<td>43.8 ± 0.7</td>
<td>37.6</td>
<td>15.9</td>
</tr>
</tbody>
</table>

\(^a\)Partial rate factors were determined by multiplying the overall rates by the product ratio for 103 and 105 shown in Table 5 (vide post).
Thus, the observed conductance increment is due solely to the formation of products along path a, the nitrenium ion pathway. It can be shown for the case of two parallel reactions, the rate constant calculated from the appearance of either one of the products, and

TABLE 5

Products from the Methanolysis of Piperidin-1-yl Benzoates

<table>
<thead>
<tr>
<th>Starting Benzoate</th>
<th>Ratio of Piperidine to N-Hydroxy-piperidine</th>
<th>Yield of Benzoic Acid and Methyl Benzoate</th>
<th>Ratio of Benzoic Acid to Methyl Benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>10:90</td>
<td>87%</td>
<td>10:90</td>
</tr>
<tr>
<td>96</td>
<td>18:82</td>
<td>88%</td>
<td>15:85</td>
</tr>
<tr>
<td>97</td>
<td>22:78</td>
<td>80%</td>
<td>25:75</td>
</tr>
<tr>
<td>98</td>
<td>38:62</td>
<td>86%</td>
<td>39:61</td>
</tr>
<tr>
<td>99</td>
<td>86:14</td>
<td>82%</td>
<td>85:17</td>
</tr>
<tr>
<td>100</td>
<td>86:14</td>
<td>90%</td>
<td>85:15</td>
</tr>
</tbody>
</table>

using the appropriate parameters, is actually the sum of the rate constants for both of the parallel reactions. Thus, the conductometric rate constants, $k_c$, shown in Table 4 are actually the sum of the rate constants for nitrenium ion formation, $k_n$, and for transesterification, $k_t$. This is shown in equation (1). Further, since in

$$k_c = k_n + k_t \hspace{1cm} (1)$$

$$\frac{k_n}{k_t} = \frac{x}{1-x} \hspace{1cm} (2)$$

$$k_n = xk_c$$

$$k_t = (1-x)k_c \hspace{1cm} (3)$$
parallel reactions the ratio of rate constants is equal to the ratio of products, we can write equation (2), where \( x \) is the fraction of reaction proceeding via nitrenium ions. Thus, one may calculate the partial rate factor for nitrenium ion generation \( k_n \) for each ester by multiplying \( k_c \) (Table 4) by \( x \) (Table 5) for the same ester.

A plot of the partial rate factors for nitrenium ion generation vs Hammett \( \sigma \) values\(^{48}\) gave an excellent straight line (correlation coefficient 0.995) with \( \rho = +0.68 \). This linear plot is approximately what one would have expected, since the heterolytic cleavage of the nitrogen ester to give a nitrenium ion and benzoate anion is analogous to the ionization of a substituted benzoic acid to yield a proton and benzoate anion. Therefore, the linear free energy parameters which

\[
\text{\begin{align*}
\text{O} & \\
\text{HO-C} & \\
\text{\textcircled{X}} & \\
\text{X} & \\
\text{H+} & \\
\end{align*}}
\]

were

\[
\text{\begin{align*}
\text{N+} & + \\
\text{O} & \\
\text{\textcircled{X}} & \\
\text{X} & \\
\end{align*}}
\]

\[
\text{\begin{align*}
\text{O} & \\
\text{HO-C} & \\
\text{\textcircled{X}} & \\
\text{X} & \\
\text{H+} & \\
\end{align*}}
\]

\[
\text{\begin{align*}
\text{N+} & + \\
\text{O} & \\
\text{\textcircled{X}} & \\
\text{X} & \\
\end{align*}}
\]

Figure 1. $\sigma p$ Plot for the formation of benzoic acids from 1-hydroxypiperidine benzoates in methanol.
correlate benzoic acid ionization should also correlate nitrenium ion generation. Experimentally, this has been shown to be the case.

The rho of +0.68 may initially be compared with the rho value of +1.37 determined for the ionization of p-substituted benzoic acids in methanol. However, for a more suitable comparison we prepared and solvolyzed the six benzoate esters of 1-phenylcyclohexanol shown below.

\[
\begin{align*}
106: & \quad R = 3,5\text{-Dinitrophenyl} \\
107: & \quad R = p\text{-Nitrophenyl} \\
108: & \quad R = p\text{-Chlorophenyl} \\
109: & \quad R = \text{Phenyl} \\
110: & \quad R = p\text{-Methylphenyl} \\
111: & \quad R = p\text{-Methoxyphenyl}
\end{align*}
\]

Pseudo first-order rate constants were determined titrimetrically and are shown in Table 6. A plot of \(\log k vs \sigma\) gave a rho of +1.34 (correlation coefficient 0.969). This value appears to compare favorably with the rho of +1.34 obtained for the ionic rearrangement of perbenzoates and with the rho of +1.75 obtained for the ethanoly-sis of various cyclobutyl sulfonates.

TABLE 6

Rates of Methanolysis of 1-Phenylcyclohexyl Benzoates at 85°

<table>
<thead>
<tr>
<th>Compound</th>
<th>$k \times 10^6$ (sec$^{-1}$)</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>87.8 ± 1.9</td>
<td>160</td>
</tr>
<tr>
<td>107</td>
<td>10.7 ± 0.2</td>
<td>20</td>
</tr>
<tr>
<td>108</td>
<td>2.73 ± 0.06</td>
<td>5.0</td>
</tr>
<tr>
<td>109</td>
<td>1.16 ± 0.02</td>
<td>2.1</td>
</tr>
<tr>
<td>110</td>
<td>0.722 ± 0.03</td>
<td>1.3</td>
</tr>
<tr>
<td>111</td>
<td>0.547 ± 0.008</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The smaller rho value observed for the generation of nitrenium ions from 105-100 than for carbonium ions from 106-111 indicates to us that the transition state for ionization of an N-O bond occurs earlier in the bond breaking process than the transition state for ionization of a comparable C-O bond. This is presumably related to the weaker nature of the N-O bond (48 kcal/mole) relative to the C-O bond (78 kcal/mole).

The lower value of rho obtained for the nitrenium ion process relative to the carbonium ion process may also be the result of increased nucleophilic participation by solvent in the transition state. Swain and Langsdorf$^{52}$ have indicated that when the transition

state for solvolysis is less than limiting, charge development and hence the value of rho should reflect the nucleophilic character of the transition state. Thus, in a solvolytic process which would generate a carbonium ion or nitrenium ion, the rho value for formation of that ion would be initially negative and should become more positive as the nucleophilic participation of solvent in the transition state increased. The nitrenium ion is at the same time a less stable and less sterically hindered ion than the tertiary carbonium ion generated in our model system and therefore should be affected to a greater extent by nucleophilic interaction with methanol. Any such assistance by methanol would be expected from the above arguments to result in a diminished rho value. This interpretation is questionable though, as it anticipates the formation of the methyl ether of the starting hydroxylamine. This compound was not observed in the product mixture.

As an alternate explanation, one might suggest that for the case of the nitrogen esters, the amine and benzoic acid might arise from a homolytic cleavage of the N-O bond to give a nitrogen radical and

\[ \text{N-O-} \quad \text{X} \quad \rightarrow \quad \text{N}^\bullet \quad + \quad \text{X} \quad \text{O-C} \]
a benzoyl radical. However, this possibility is unlikely since it has been shown, both for benzoyl peroxide \((\rho = -0.38)^{53}\) and for \(t\)-butylperbenzoate esters \((\rho = -0.90)^{54}\) \((\rho = -0.347)^{55}\) that the formation of a benzoyl radical in a unimolecular process is characterized by a negative rho value. Therefore, the positive rho value observed for the methanolysis of the nitrogen benzoate esters 95-100 strongly supports the notion of heterolytic N-O bond cleavage with formation of a divalent, positive nitrogen species.

In the course of studying the benzoate esters of \(1\)-phenylcyclohexanol we also sought to investigate the effect of leaving group on the solvolysis product ratio. It has been shown \(^{56,57,58}\) that in solvolysis reactions of the same substrate, the more basic the leaving group the greater the fraction of olefin that is formed. This is attributed to removal by the anion (leaving group) of a proton from the carbonium ion, while still in the initial intimate ion

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(54) A.T. Blomquist and I.A. Berstein, ibid., 73, 5546 (1951).
pair stage. In the 1-phenylcyclohexyl system, solvolysis in methanol of the benzoate esters 106-111 leads to a product mixture composed of 1-phenylcyclohexene (112), 1-methoxy-1-phenylcyclohexane (113) and the theoretical amount of the appropriate benzoic acid. However, at the solvolysis temperature (85°), 113 was readily converted to

![Chemical Structure](image)

112. The use of triethylamine as a buffer eliminated the conversion of 113 to 112 in standard solutions utilizing equivalent amounts of 112, 113, and benzoic acid. But when the cyclohexyl benzoates were solvolysed in the presence of triethylamine, the product ratio 112/113 varied with time (number of half-lives) and with the amine concentration. The shorter the reaction time and the greater the concentration of amine, the greater the relative amount of olefin was formed. It seems probable that the amine was removing a proton from the intermediate carbonium ion. Unfortunately, this same behavior was also displayed by pyridine, 2,6-lutidine, diphenylamine and sodium carbonate, thus preventing any useful appraisal of the
leaving group effect on product ratio. The action of these bases in altering the ratio \( \frac{112}{113} \) was quite surprising in view of the many reports in the literature indicating they could be successfully used as buffers while not affecting the product ratio.

In retrospect, an interesting point emerges upon comparison of the solvolysis rate of piperidin-1-yl \( p \)-nitrobenzoate (92) with that calculated for cyclohexyl \( p \)-nitrobenzoate (117). These two solvolysis rates should reflect the ease of formation of a nitrenium ion or a carbonium ion in a six-membered ring system, and one might expect that since the same leaving group is being used, the more stable species, the carbonium ion, would be formed faster. Estimation of the solvolysis rate of cyclohexyl \( p \)-nitrobenzoate involves extrapolation from cyclohexyl tosylate to cyclohexyl chloride using Brown's formula (59) and then consideration of the rate differences of chlorides and \( p \)-nitrobenzoates. In this manner we calculated a solvolysis rate for cyclohexyl \( p \)-nitrobenzoate at \( 50^\circ \) of \( 10^{-11} \) sec\(^{-1}\). In this case, therefore, the nitrenium ion is formed at least one million times more rapidly than is the carbonium ion. Since the carbonium ion should indeed be more stable than the nitrenium ion, the explanation for the rate order probably lies in the notion that the ground

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(60) For comparisons of carbon \( p \)-nitrobenzoates and chlorides see:
(a) A. Fainberg and S. Weinstein, J. Amer. Chem. Soc., 78, 2770 (1956); (b) C. Wilcox, Jr., and M. Mesirov, ibid., 84, 2757 (1962);
(c) R. Buckson and S. Smith, J. Org. Chem., 32, 634 (1967);
The state of the nitrogen ester is much higher in energy than is that of the carbon ester. Specifically, the N-O bond is some 30 kcal higher in energy than is the C-O bond.

Having shown convincing kinetic evidence for the intermediacy of nitrenium ions in hydroxylamine benzoate solvolysis, we next endeavored to observe alkyl migration to a divalent, positive nitrogen site generated in the above manner. The hydroxylamine \( \text{H}_2 \text{O} \) was readily converted to the \( p \)-nitrobenzoate derivative (118) in 75%.

yield. Solvolysis of (118) in methanol proceeded to give five products:
83 (13%), 119 (1%), p-nitrobenzoic acid (32%), 86 (60%) and methyl p-nitrobenzoate (64%). The products and product ratios seem best explained by postulating reaction along two paths, the first producing 83, 119 and p-nitrobenzoic acid, while the second yields 86 and methyl p-nitrobenzoate by transesterification. Since 119 was formed in significant amounts, and since it has already been identified as the product expected from nitrenium ion formation followed by alkyl migration, we feel that the notion of ionic cleavage of the N-O bond of 118 is strongly supported. The rate of disappearance of 118 was followed conductometrically and the observed pseudo first-order rate constant was found to be (7.80 ± 0.37) x 10^-6 sec^{-1} at 50°. This results in a partial rate factor (k_n) for nitrenium ion formation from 118 of 2.36 x 10^{-6} sec^{-1} at 50°.

Having established that a definite portion of the solvolysis reaction of N-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane p-nitrobenzoate (118) proceeded via nitrenium ions, we next endeavored to trap the intermediate ionic species 120 or 121.

In a series of elegant experiments Carey and Tremper\(^{62}\) showed that hydride may be effectively transferred to a carbonium ion site from various silicon and germanium hydrides. In these experiments the carbonium ions were generated from alcohols in either pure acetic acid or methylene chloride containing trifluoroacetic acid. Since

these hydride transfer reagents had been effective in relatively non-polar media, we felt that similar reaction was reasonable in methanol, the solvolysis medium for \textbf{118}.

As shown above, the two possible substrates of hydride transfer were either the nitrenium ion \textbf{120}, to give amine \textbf{83}, or the secondary carbonium ion \textbf{121} to give \textbf{122}. However, when \textbf{118} was solvolyzed in methanol in the presence of an excess of either triphenylgermanium hydride or triphenylsilicon hydride, the product ratio (from vpc analysis) was identical to that obtained in the absence of transfer reagent, i.e., the ratio of \textbf{83} to rearranged methyl ether \textbf{119} was
the same in all cases. Also, there was no evidence (vpc) for the formation of 122. Thus, there seemed to be no apparent trapping of either ionic species under these conditions.

To return to the significance and use of the Hammett rho value for the benzoate leaving group, we felt that this parameter might be a sensitive measure of the amount of bond breaking in the transition state of a given solvolytic reaction. The technique of measuring leaving group parameters in order to gain insight into transition state characteristics is not in itself new. Previous workers\textsuperscript{63} have effectively used the ratio \( k_{\text{OTS}}/k_{\text{Br}} \) as an indication of the amount of bond breaking in the transition state, in seeking to determine the extent of nucleophilic participation by solvent. More recently, Crossland, et al., \textsuperscript{64} have suggested that the ratio \( k_{\text{tosylate}}/k_{\text{triflate}} \) would give a better indication because the large differences in leaving group hydrogen bonding ability, size, and symmetry between the tosylate and bromide groups were absent.

Along these same lines we felt that the Hammett rho value for the benzoate group should be a measure of transition state C-O bond cleavage and would vary over the three systems (114, 115, 116).


shown below in a predictable manner. We felt it reasonable to ex-
pect that as the stability of the incipient carbonium ion increased,
i.e., progressing from 114 to 116, the value of \( \rho \) would increase,
indicating a more fully developed negative charge on the benzoate
moiety.

The synthesis of the six benzoate esters of systems 114 and 116
was accomplished in similar fashion to that already described for
115. We initially attempted to prepare that system containing a
p-methoxyphenyl group on the cyclohexyl ring, but were unsuccessful
due to the apparent instability of the corresponding esters.
Purification of the benzoate esters of 116 was accomplished by column
chromatography on deactivated silica gel while chromatography on
basic alumina afforded pure esters of 114.

Solvolysis of the benzoate esters of 116 was carried out at 85\(^\circ\),
except for the 3,5-dinitrobenzoate which was studied at three lower
temperatures and the rates extrapolated to 85\(^\circ\) as shown in Table 7.
Each ester in Table 7 may be identified from the following:
A plot of log k for the solvolysis of the esters in system 114 vs the appropriate Hammett σ values afforded a rho value at 85° of +1.60 (correlation coefficient 0.988). A similar plot for the esters of 116 gave a rho value of +1.58 (correlation coefficient 0.995) at 85°. These values should be compared with the previously observed rho value of +1.34 for the phenylcyclohexyl esters 115 under the same conditions.

In analyzing the data, it should be noted that the solvolysis rates in each series were very well correlated by the Hammett equation utilizing the σ constants. Further, correlation coefficients for each
TABLE 7
Rates of Solvolysis of Phenyl-Substituted Cyclohexyl Benzoates in Methanol

<table>
<thead>
<tr>
<th>Compound</th>
<th>Temp (+0.01 °C)</th>
<th>$k_{sec^{-1}}$</th>
<th>$\Delta H^\ddagger$ (kcal/mole)</th>
<th>$\Delta S^\ddagger$ (e.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>114a</td>
<td>160.0</td>
<td>$(78.4 \pm 1.5) \times 10^{-5}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>$(37.3 \pm 0.7) \times 10^{-5}$</td>
<td></td>
<td>26.7</td>
</tr>
<tr>
<td></td>
<td>140.0</td>
<td>$(17.0 \pm 0.31) \times 10^{-5}$</td>
<td></td>
<td>-11.8</td>
</tr>
<tr>
<td></td>
<td>85.00$^a$</td>
<td>$9.81 \times 10^{-7}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114b</td>
<td>170.0</td>
<td>$(25.4 \pm 0.55) \times 10^{-5}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160.0</td>
<td>$(14.7 \pm 0.50) \times 10^{-5}$</td>
<td></td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>$(5.51 \pm 0.12) \times 10^{-5}$</td>
<td></td>
<td>-9.14</td>
</tr>
<tr>
<td></td>
<td>85.00$^a$</td>
<td>$7.59 \times 10^{-8}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114c</td>
<td>170.0</td>
<td>$(5.41 \pm 0.13) \times 10^{-5}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160.0</td>
<td>$(2.31 \pm 0.06) \times 10^{-5}$</td>
<td></td>
<td>30.7</td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>$(1.10 \pm 0.03) \times 10^{-5}$</td>
<td></td>
<td>-9.42</td>
</tr>
<tr>
<td></td>
<td>85.00$^a$</td>
<td>$1.14 \times 10^{-9}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114d</td>
<td>170.0</td>
<td>$(2.99 \pm 0.08) \times 10^{-5}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160.0</td>
<td>$(1.55 \pm 0.02) \times 10^{-5}$</td>
<td></td>
<td>28.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-14.9</td>
</tr>
<tr>
<td>Compound</td>
<td>Temp (+0.01 °C)</td>
<td>( k_{\text{sec}^{-1}} )</td>
<td>( \Delta H^\mp ) (kcal/mole)</td>
<td>( \Delta S^\mp ) (e.u.)</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>(0.671 ± 0.001) x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.00^a</td>
<td>1.12 x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>170.0</td>
<td>(1.91 ± 0.04) x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114e</td>
<td>160.0</td>
<td>(0.851 ± 0.01) x 10^{-5}</td>
<td>28.9</td>
<td>-15.6</td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>(0.295 ± 0.001) x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.00^a</td>
<td>6.57 x 10^{-9}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>170.0</td>
<td>(1.42 ± 0.03) x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114f</td>
<td>160.0</td>
<td>(0.606 ± 0.012) x 10^{-5}</td>
<td>30.3</td>
<td>-13.0</td>
</tr>
<tr>
<td></td>
<td>150.0</td>
<td>(0.295 ± 0.001) x 10^{-5}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.00^a</td>
<td>3.35 x 10^{-3}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.00</td>
<td>(17.6 ± 0.09) x 10^{-4}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116a</td>
<td>50.00</td>
<td>(6.62 ± 0.06) x 10^{-4}</td>
<td>22.1</td>
<td>-4.37</td>
</tr>
<tr>
<td></td>
<td>40.00</td>
<td>(2.05 ± 0.02) x 10^{-4}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.00^a</td>
<td>2.78 x 10^{-2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compounds</td>
<td>Temp (+0.01 °C)</td>
<td>$k_{sec^{-1}}$</td>
<td>$\Delta H^\ddagger$ (kcal/mole)</td>
<td>$\Delta S^\ddagger$ (e.u.)</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>116b</td>
<td>85.00</td>
<td>$(1.92 \pm 0.02) \times 10^{-3}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116c</td>
<td>85.00</td>
<td>$(5.20 \pm 0.03) \times 10^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116d</td>
<td>85.00</td>
<td>$(2.18 \pm 0.01) \times 10^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116e</td>
<td>85.00</td>
<td>$(1.50 \pm 0.01) \times 10^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116f</td>
<td>85.00</td>
<td>$(1.11 \pm 0.01) \times 10^{-4}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Extrapolated from other temperatures.*
TABLE 8
Rho Values for Aryl-Substituted Cyclohexyl Benzoates in Methanol at 85°

<table>
<thead>
<tr>
<th>R</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>+1.58</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>+1.34</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>+1.60</td>
</tr>
</tbody>
</table>

individual kinetic determination, as well as for the calculation of the rho value, were consistently ca. 0.99. Despite this, the three rho values obtained are most likely within experimental error of each other and hence no conclusion can be drawn concerning the extent of bond cleavage in the transition states other than saying that the differences, and therefore the ultimate effect on rho, seem quite small. This is somewhat disturbing in that the three carbonium
ions which are formed are quite different in stability, as shown by the rate differences of $10^{-5}$-$10^{-6}$ between systems 114 and 116 for solvolysis involving the same leaving group. One might therefore argue that the transition states for all three systems lie much closer to reactants than products, since in all cases a tertiary, benzylic species is formed, and thus, that variation in the phenyl substituent has negligible effect on the rho value. However, even if the transition state species have only slight differences, these should be uniform and predictable. This should be reflected by the rho value. Thus, it seems a more accurate kinetic determination of the rate constants is needed to obtain the desired information.

In Table 9 are shown the rate constants for solvolysis in methanol of the esters of 114 and 116 at 85°. In addition to the rho value associated with the benzoate leaving group, there should also be a similar Hammett correlation for the substituents on the phenyl group in the phenylcyclohexyl carbonium ion produced upon solvolysis of the indicated esters. Since this ion is benzylic, one would expect that the experimental rate constants would be correlated by the

(65) The Hammond postulate suggests that the more stable the intermediate species in an Sn 1 process, the more the transition state will be 'reactant-like'; G. Hammond, J. Amer. Chem. Soc., 77, 334 (1955).

Brown $\sigma^+$ constants.\textsuperscript{67} In considering the magnitude of the rho value for this correlation, a $\rho$ value between -3 to -5 would be expected.\textsuperscript{68} Thus, since the magnitude of this rho value is greater than that for the benzoate leaving group, it might be anticipated that the $\rho$ for the phenyl group may be a slightly more sensitive diagnostic parameter for determining differences in transition state bond cleavage. However, as shown in Table 9, this does not seem to be the case, since the rho value varies from -3.34 to -3.80 in an unpredictable manner. In Figure 2 we have plotted $\log k$ for the appropriate esters vs the requisite $\sigma^+$ value. There are six "lines" shown in this figure, one for each of the six benzoate leaving groups studied. The three points which determine each "line" represent the rate data for the p-methylphenyl, phenyl, and 3,5-di(trifluoromethyl)phenyl cyclohexylcarbonium ions which are generated upon solvolysis of the given esters. There is a good correlation between solvolysis rates

\begin{center}
\includegraphics[width=0.5\textwidth]{figure.png}
\end{center}

\textsuperscript{(68)} M.S. Silver, \textit{ibid.}, \textbf{83}, 404 (1961).
TABLE 9

Methanolation Rates and Rho Values for

Benzoate Esters at 85°

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>R-H</th>
<th>R-CH₃</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,5-Di(NO₂)</td>
<td>981 x 10⁻⁹</td>
<td>878 x 10⁻⁶</td>
<td>277 x 10⁻⁴</td>
<td>-3.42</td>
</tr>
<tr>
<td>p-NO₂</td>
<td>75.9 x 10⁻³</td>
<td>107 x 10⁻⁶</td>
<td>19.2 x 10⁻⁴</td>
<td>-3.34</td>
</tr>
<tr>
<td>p-Cl</td>
<td>11.4 x 10⁻⁶</td>
<td>27.3 x 10⁻⁶</td>
<td>5.20 x 10⁻⁴</td>
<td>-3.80</td>
</tr>
<tr>
<td>p-H</td>
<td>11.2 x 10⁻⁶</td>
<td>11.6 x 10⁻⁶</td>
<td>2.18 x 10⁻⁴</td>
<td>-3.43</td>
</tr>
<tr>
<td>p-CH₃</td>
<td>6.57 x 10⁻⁹</td>
<td>7.22 x 10⁻⁶</td>
<td>1.50 x 10⁻⁴</td>
<td>-3.47</td>
</tr>
<tr>
<td>p-OCH₃</td>
<td>3.35 x 10⁻⁹</td>
<td>5.47 x 10⁻⁶</td>
<td>1.11 x 10⁻⁴</td>
<td>-3.64</td>
</tr>
<tr>
<td>ρ = 1.60</td>
<td>ρ = 1.34</td>
<td>ρ = 1.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

and the indicated σ⁺ substituent constants, however, the slopes of these lines (ρ value in Table 9) are very close to one another.

Again, very little can be said about the degree of bond breaking for each series of esters from consideration of the rho values for formation of the cyclohexyl carbonium ion. The fact that these rho values, as well as that for the benzoate leaving group, show only small changes over the systems studied indicates that this method will probably need more accurate kinetic determinations to be useful.
Figure 2. Plot of $\log k$ for Aryl Substituted Cyclohexyl Esters vs $\sigma^+$ Values.
Part II. A Comparison of Migratory Amplitudes to a Nitrenium Ion Site.

The literature of carbonium ion rearrangement reactions abounds with information (and warnings) pertaining to the comparison of migratory amplitudes for aryl and alkyl groups to an adjacent carbonium ion site. The results cover a variety of substrates, reaction types and experimental variables. Previous work noted herein has shown that migration of either an aryl or alkyl group to a nitrenium ion site will occur in a variety of systems and via reactions of various precursors. However, there is in this latter literature relatively little information comparing migratory characteristics of aryl and alkyl groups to an electron deficient nitrogen site. We therefore felt that a quantitative determination of these migration parameters would be interesting.

In 1955 Newman and Hay® reinvestigated the Stieglitz rearrangement and found that various tritylhydroxylamines, when subjected to phosphorus pentachloride, underwent facile reaction with migration of an aryl group from carbon to nitrogen. Further, they noted that starting with a hydroxylamine possessing different phenyl groups, one

could ascertain whether any group had migrated preferentially simply by identifying the hydrolysis products, which were a ketone and an aniline derivative. They found that the order of migratory amplitude from carbon to nitrogen was \( p-CH_3 C_6 H_4^- \rightarrow p-C\text{Cl}C_6H_4^- \rightarrow p-NO_2 C_6H_4^- \). Thus, they concluded that the migratory amplitude of the aryl group increased as the para substituent of the aryl group became more electron releasing. This, one may readily note, is what would be expected for migration of an aryl group to an electron deficient nitrogen site.

A more relevant experiment for our purposes was that carried out by Emmons \(^6\) who studied the acid catalyzed cleavage of oxaziranes. Emmons found that when 2-n-butyl-3-isopropylloxazirane (125) was subjected to acidic hydrolysis three products were formed: ammonia, butyraldehyde, and isobutyraldehyde. His proposed mechanism involved protonation on oxygen, cleavage of the N-O bond to generate the divalent positive nitrogen species and then migration of hydrogen. In a second experiment it was discovered that when 2-(\(\alpha\)-phenethyl)-3-isopropylloxazirane (124) was subjected to acidic hydrolysis only
three products were observed: isobutyaldehyde, aniline and acetaldehyde. In this case, acid catalyzed cleavage of the N-O bond was
followed by exclusive migration of the phenyl group to the nitrenium ion site. Allowing that the stepwise or concerted nature of this reaction was still unknown, Emmons concluded that the order of migration to nitrogen was phenyl > hydrogen > alkyl.

We endeavored to expand on the above observations for several reasons. First, we desired a firm quantitative appraisal of these migratory amplitudes. Second, the reaction utilized above to obtain the migration parameters decomposed components of the product mixture. Third, we wondered whether there would be a significant difference in the migration parameters when the nitrenium ion was generated in a solvolytic process, perhaps generating an intermediate ion energetically different from that studied above. Fourth, one may raise the mild objection that the comparison made above is not unequivocally valid, since it compares the migration of methyl and hydrogen in one system, 122, and phenyl migration in a second system, 124. We therefore sought to ascertain whether this order was valid for migration within the same system. What we saw as the ideal case was the generation of a nitrenium ion adjacent to 'migratable' phenyl, alkyl and hydrogen groups (as in 124), and to have all three migrate to some extent in the same solvolytic process.

We chose for our study of migratory amplitudes the N-methyl-N-(dimethylbenzyl)hydroxylamine (125) substrate. The synthetic
approach to 125 involved the dimethylation\(^7\) of benzylcyanide (126) followed by hydrolysis to give 2-methyl-2-phenylpropanoic acid (128).

\[
\text{C}_6\text{H}_5\text{CH}_2\text{CN} \rightarrow \text{C}_6\text{H}_5-\text{C} \rightarrow \text{C}_6\text{H}_5-\text{C} \rightarrow \text{C}_6\text{H}_5-\text{CO}_2\text{H}
\]

This acid was then converted to its acyl azide and Curtius rearrangement afforded dimethylbenzylamine (129) in 60% yield. The tertiary amine was then oxidized\(^7\) in an acetone-water suspension of potassium permanganate to give a 66% yield of 1-methyl-1-phenylnitroethane.


which was then reacted\textsuperscript{72} with twice the equivalent amount of methyllithium to give the desired hydroxylamine\textsuperscript{125}. This hydroxylamine\textsuperscript{73} which decomposed even at low temperatures, was converted in the normal manner to its p-nitrobenzoate derivative\textsuperscript{98} which was stable at room temperature.

Solvolysis of N-methyl-N-(dimethylbenzyl)hydroxylamine p-nitrobenzoate (131) to a nitrenium ion could theoretically proceed along any or all of the four paths, a-d shown below. In path a, the initially formed singlet nitrenium ion is shown to spin invert to the triplet proceeding by abstraction of hydrogen atoms from the solvent to give "starting amine"\textsuperscript{132}. In paths b, c, and d, the initially formed singlet nitrenium ion undergoes phenyl, hydrogen or methyl migration, respectively, to yield initially in each case an iminium ion. Hydrolysis of the iminium ion produces, in each case, a different amine and carbonyl compound. Thus, one may determine both the type of reaction, singlet to triplet conversion or rearrangement of the singlet, as well as the migrating group from an investigation of the reaction products.

As was the case with all the other hydroxylamine benzoates, solvolysis of 131 in methanol proceeded along two paths. Trans-

\begin{itemize}
\item \textsuperscript{73} Although elemental analysis was not possible, infrared and nuclear magnetic resonance spectral data along with an exact mass determination confirmed the identity of the hydroxylamine.
\end{itemize}
esterification of \( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NHCH}_3 \) led to a 75\% yield of methyl p-nitrobenzoate and starting hydroxylamine \( \text{C}_6\text{H}_5\text{NH}_2 \), forming the major part of reaction. However, a 23\% yield of p-nitrobenzoic acid was isolated, indicating that ca. one quarter of reaction had proceeded via nitrenium ions.

As shown in Table 10, vpc analysis of the remaining reaction solution indicated the presence of three amines: \( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NHCH}_3 \) (6.7\%), the product of singlet to triplet spin inversion; \( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NH}_2 \) (3.7\%), the product of phenyl migration; and \( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NH}_2 \) (8.3\%), the product of hydrogen migration. No acetophenone was present indicating the absence of any significant methyl migration to the nitrenium ion site. Trial experiments

**TABLE 10**

<table>
<thead>
<tr>
<th>Product</th>
<th>Leaving Group (X)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-( \text{CO-C}_6\text{H}_4\text{-NO}_2 )-p</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NHCH}_3 ) (132)</td>
<td>6.7%</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{NHCH}_3 ) (133)</td>
<td>3.7%</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{NH}_2 ) (134)</td>
<td>8.3%</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{COCH}_3 )</td>
<td>0</td>
</tr>
</tbody>
</table>
indicated that acetophenone should have survived reaction, work-up and isolation procedures intact.

Thus, we have observed three of the four possible modes of reaction for the initially formed singlet nitrenium ion. After correction for the statistical factor of three possible hydrogen atoms which could migrate as opposed to only one phenyl group, the ratio of phenyl to hydrogen migration was ca. 1.1 to 1.0, and the overall qualitative order of migratory amplitude was phenyl > hydrogen > methyl. We may note that this was also the order observed by Emmons, however, his results with compound 124, which directly compares migration of phenyl and hydrogen, indicated that phenyl migration occurred to the exclusion of hydrogen migration, in strong contrast to the present results.

Solvolyis of 131 in methanol was carried out at 50° and the changing conductance of the solution monitored to give excellent pseudo first-order kinetics with a rate constant of \((1.21 \pm 0.02) \times 10^{-6}\) sec\(^{-1}\). Again, consideration of the fraction of reaction proceeding via nitrenium ions (ca. 2\%\) allowed determination of the partial rate factor for nitrenium ion formation as \(2.90 \times 10^{-6}\) sec\(^{-1}\).

In a separate experiment N-methyl-N-(dimethylbenzyl)-hydroxylamine (125) was reacted with n-butyllithium and then with p-toluene-sulfonyl chloride to generate the tosylate (136). Filtration of the precipitated lithium chloride and solvent removal below room temperature left an oil which decomposed on standing and exposure to the
atmosphere. This oil was dissolved in methanol and refluxed for thirty minutes. Work-up and product identification was as indicated for the p-nitrobenzoate derivative. The three solvolysis products were identified as: dimethylbenzylamine (131), N-methyl-aniline (133), and N-methyl-N-(dimethylbenzyl)amine (132) in an approximate ratio of 1.4:3.6:1.0, respectively. These numbers which represent the average of two runs, are only approximate due to several troublesome experimental problems including impure starting hydroxylamine and product decomposition during solvolysis. Thus, despite the absence of quantitative migration parameters, the presence of the same three products as observed in p-nitrobenzoate solvolysis, and the absence in both cases of the fourth possible product, strongly supports the notion of a divalent, positive nitrogen intermediate common to both solvolyses.
Part III. Solvent Effects on Rates of Formation of Nitrenium Ions

Throughout the work discussed so far, we have been concerned specifically with elucidating the nature and fate of the transient, divalent, positive nitrogen species when generated in methanol. The technique of generating a particular ion in a variety of solvents has allowed workers in the area of carbonium ions to describe many subtle transition state characteristics of that species. Our initial intention therefore was to attempt to generate a secondary nitrenium ion in a variety of solvents and then compare the rates of formation of this ion with those for the carbonium ion.

A suitable nitrenium ion precursor was the N-methyl-N-t-butyl-hydroxylamine system (\( \text{140} \)) which was readily prepared in 57% yield by treatment of one equivalent of t-nitrobutane with two equivalents of methyllithium followed by appropriate work-up. This hydroxylamine

\[
2 \text{CH}_3\text{Li} + (\text{CH}_3)_3\text{C}-\text{NO}_2 \rightarrow (\text{CH}_3)_3\text{C}-\text{N}-\text{OH}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
(\text{CH}_3)_3\text{C}-\text{N}-\text{OTs} & \quad (\text{CH}_3)_3\text{C}-\text{N}-\text{OENB}
\end{align*}
\]

\( \text{140} \)

was readily converted into its p-nitrobenzoate (1\(\text{H}1\)) in the normal manner in excellent yield. In hopes of using (1\(\text{H}1\)) as the nitrenium ion precursor, it was solvolyzed in methanol, yielding a conductometric rate constant of \(9.48 \times 10^{-6} \text{ sec}^{-1}\) at 50°. Subsequent product study revealed that 1\(\text{H}1\) underwent ca. 15% transesterification, to give hydroxylamine 1\(\text{H}0\) and methyl o-nitrobenzoate, and ca. 81% nitrenium ion reaction, to give p-nitrobenzoic acid and two amines: N-methyl-N-t-butylamine (1\(\text{H}3\)) and t-butylamine (1\(\text{H}4\)) in a 1:1 ratio. Thus, reaction of the nitrenium ion involved singlet to triple spin inversion to give 1\(\text{H}3\) and hydrogen migration to give 1\(\text{H}4\) to the

![Chemical structure](image-url)
exclusion of methyl migration. It should be noted that these are the same two products as were observed in the methanolysis of N-methyl-N-t-butylchloramine. The partial rate factor for nitrenium ion formation from 141 was calculated to be $7.67 \times 10^{-8} \text{sec}^{-1}$ at 50°C.

It was decided not to use 141 as the nitrenium ion precursor because of the difficulty in determining the ratio between transesterification and nitrenium ion formation in the solvent chosen for kinetic study. The p-toluenesulfonate derivative $142$ was therefore generated by reaction of the hydroxylamine 140 with one equivalent of n-butyllithium in hexane followed by p-toluenesulfonyl chloride at room temperature. After fifteen minutes the solvent was removed on the rotary evaporator below room temperature to leave an oil which showed no hydroxylamine O-H absorption in the infra-red and which discolored on warming. Carbon tetrachloride solutions of this tosylate exhibited a constant nuclear magnetic resonance spectrum at the normal probe temperature, however, a methanolic solution showed drastic changes in the nuclear magnetic resonance spectrum within a few minutes at the same temperature. An initial product study revealed that when tosylate 106 was taken up in methanol and refluxed for thirty minutes, the two amines $143$ and $144$ were formed in a ratio of 1.0:1.8, respectively, in analogy to the solvolysis of p-nitrobenzoate 105, indicating that again a nitrenium ion was being formed.

(75) P.G. Gassman and J.E. Trent, unpublished results.
The experimental technique for obtaining kinetic parameters consisted of the addition of the desired solvent to the cold tosylate \((\text{I}^\text{42})\) and rapid filtration through glass wool into an nmr tube which was immediately placed into the probe already equilibrated to the proper temperature. The resonance due to the \(_t\)-butyl hydrogens (ca. 9.1 \(\tau\)) was monitored throughout the course of solvolysis and this decreasing peak area was compared to the constant area of the tetramethyilsilane protons (10.00 \(\tau\)) used as an internal standard. It was not possible to monitor the rest of the spectrum for product absorptions due to the presence of strong signals at ca. 6-8 \(\tau\) from the solvent being used. \(N\)-methyl-\(_t\)-butylhydroxylamine tosylate \((\text{I}^\text{42})\) was solvolyzed in four different solvents and the pseudo first-order rate constants calculated from nmr data at 50\(^\circ\) are shown in Table 11, as are the first-order rate constants for solvolysis of \(_t\)-butylchloride at 120\(^\circ\) in various solvents.\(^7\)\\n\\nSeveral interesting observations can be made from the data presented. For whatever the reason, the rate constant for secondary

TABLE 11

Solvent Effects on Rates of Formation of
Nitrenium Ions (50°) and Carbonium Ions (120°)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
<th>CH₃(CH₃)₂CN-OTS (k x 10⁴ sec⁻¹)</th>
<th>(CH₃)₃C-Cl (k x 10⁴ sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅NO₂</td>
<td>34.6</td>
<td>3.73 ± 0.18</td>
<td>0.098</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>37.5</td>
<td>21.4 ± 1.1</td>
<td>0.98</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>32.6</td>
<td>101 ± 4.8</td>
<td>175</td>
</tr>
<tr>
<td>HCON(CH₃)₂</td>
<td>36.7</td>
<td>352 ± 12⁸</td>
<td>314</td>
</tr>
</tbody>
</table>

Extrapolated from lower temperatures

<table>
<thead>
<tr>
<th>Temp.</th>
<th>k(sec⁻¹)</th>
<th>ΔH⁺</th>
<th>ΔS⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10°</td>
<td>1.52 x 10⁻⁴</td>
<td>14.9 kcal/mole</td>
<td></td>
</tr>
<tr>
<td>0°</td>
<td>3.82 x 10⁻⁴</td>
<td>-19.2 e.u.</td>
<td></td>
</tr>
<tr>
<td>+10°</td>
<td>12.5 x 10⁻⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nitrenium ion formation is indeed dependent on the solvent and varies in a manner analogous to that observed for t-butylchloride. No obvious correlation between rate constant and bulk dielectric constant of the medium appeared to hold. The activation parameters are reasonable for what would be expected of an ionic reaction. Finally, it is difficult to speculate on the role of solvent with respect to
factors such as solvation and nucleophilic assistance. In line with the conclusions of the above workers\textsuperscript{73} that "...the problem of medium effects on the rates of solvolysis does not exist any more; it is replaced by two more definitive problems of medium effects on ground and transition states", there also exists the possibility that our results may in essence reflect a serendipitous interplay of ground and transition state factors.
EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord Spectrophotometer as neat liquids, solutions in carbon tetrachloride, or powdered solids in potassium bromide disks. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 A Spectrometer and are reported in tau (τ) units relative to tetramethyldisilane (τ = 10.00) as the internal standard. Elemental analyses were performed by the Scandanavian Microanalytical Laboratory, Herlev Denmark.

\[ \text{N-(2-Carboethoxyethyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (84)} \]

To a stirred solution of 3.0 g (0.0216 mol) of 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane\(^{18}\) in 20 ml of tetrahydrofuran was added dropwise 3.3 g (0.33 mol) of freshly distilled ethyl acrylate in 15 ml of tetrahydrofuran over the course of 1 hr at room temperature. The clear reaction solution was heated at reflux for two days, then cooled and the solvent removed on the rotary evaporator. The clear, viscous residue was distilled through a short-path condenser to give 3.9 g (76%) of \( \text{84} \) as a clear oil: bp 85-87° (0.2 mm); \( n_D^{25} = 1.5262; \)

ir (neat) 1050, 1148, 1180, 1290, 1380, 1385, 1460, and 1740 cm\(^{-1}\);

nmr (CDCl\(_3\)) 9.24 \( \tau \) (5H, s), 9.17 \( \tau \) (3H, s), 9.03 \( \tau \) (3H, s), 8.82 \( \tau \)

\[ \text{84} \]
(3H, t), 7.45 τ (6H, m), 5.98 τ (2H, q).

Analytical. Caled for C14H25NO2: C, 70.25; H, 10.53; N, 5.85.

Found: C, 70.47; H, 10.60; N, 5.82.

N-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (86).

To 1.0 g (0.0042 mol) of N-(2-carboethoxyethyl)-2-azabicyclo[2.2.1]heptane (84) in 20 ml of methylene chloride cooled to 0-10°C in an ice bath was added dropwise a solution of 1.0 g (0.0058 mol) of m-chloroperbenzoic acid in 15 ml of methylene chloride. After the addition was complete the ice bath was removed and the reaction solution stirred at room temperature for 12 hr. The solvent was removed under vacuum to leave a clear oil, which was then dissolved in 20 ml of 1 N aqueous sodium hydroxide solution and heated with stirring at 85-90°C for 1.5 hr. The reaction solution was cooled and extracted with four 100-ml portions of ether. The extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed on the rotary evaporator to leave a waxy, white solid. This solid was sublimed at 110°C (10 mm) to give 0.35 g (54%) of pure 86; mp 153-154°C; ir (KBr) 825, 1382, 1385, 1460, and 3170 cm⁻¹; nmr (acetone-d₆) 9.22 τ (3H, s), 9.13 τ (3H, s), 8.98 τ (3H, s), 8.5 τ (2H, m).


Found: C, 69.71; H, 10.85; N, 8.75.
Attempted Preparation of N-Hydroxy-\(1,1,7\)-trimethyl-2-azabicyclo-
[2.2.1]heptane p-Toluenesulfonate (87).

To 100 mg (0.69 mmol) of 2-hydroxy-\(1,1,7\)-trimethyl-2-azabicyclo-
[2.2.1]heptane (86) in 20 ml of hexane or ether was added 0.43 ml
(0.69 mmol) of a 1.6 N solution of n-butyllithium in hexane under a
nitrogen atmosphere at room temperature. This solution was added
dropwise to a stirred solution of 0.134 g (0.69 mmol) of p-toluene-
sulfonyl chloride in 15 ml of hexane at 0-10°C. A white precipitate
appeared almost immediately and after five minutes the reaction
mixture was filtered and the solvent removed under vacuum at room
temperature to yield 195 mg (98%) of 3,3,4-trimethyl-2-tosyloxy-1-
azabicyclo[2.2.1]heptane (88), which was identical in all respects
to an authentic sample.\(^{44}\) The tosylate was purified by distillation
on a molecular still at 105-110°C (0.05 mm): mp 51-52°C; ir (neat)
710, 848, 970, 1276, 1280, 1340 cm\(^{-1}\); nmr (CCl\(_4\)) \(\delta 10.10 \tau \) (3H, s),
9.07 \(\tau \) (3H, s), 9.02 \(\tau \) (3H, s), 7.60 \(\tau \) (3H, s), 5.32 \(\tau \) (1H, d),
2.42 \(\tau \) (4H, q).

cis-4-Aminocyclohexane Carboxylic Acid (89).

This compound was synthesized from \(p\)-aminobenzoic acid by the

2-Azabicyclo[2.2.2]octane-3-one (90).

In a round bottom flask was placed 120 g (0.82 mol) of cis-4-
aminocyclohexane carboxylic acid and the flask connected by a side-
arm to another flask. The neat acid was then heated at atmospheric pressure with a Bunsen burner until no more material distilled. The distillate was taken up in benzene, dried over anhydrous magnesium sulfate, filtered, and the solvent removed on the rotary evaporator to yield a white solid which was the desired lactam 90. Recrystallization from petroleum ether gave 61.2 g (64%) of 90, mp 195-196°.

2-Azabicyclo[2.2.2]octane (91).

This compound was prepared from 90 by the method of F.J. Villani and C.A. Ellis, J. Med. Chem., 2, 185 (1966).

N-(2-carbothoxyethyl)-2-azabicyclo[2.2.2]octane (92).

To 1.0 g (0.00925 mol) of 2-azabicyclo[2.2.2]octane (91) in 10 ml of anhydrous ether was added dropwise 1.5 g (0.015 mol) of freshly distilled ethyl acrylate in 10 ml of tetrahydrofuran with stirring and ice bath cooling. The resulting solution was then refluxed for three days, cooled, and the solvent removed on the rotary evaporator to give a yellow oil. Distillation of this oil through a short-path condenser gave 1.87 g (97%) of the desired adduct 92 at 91-92° (0.5 mm); ir (neat) 1048, 1090, 1155, 1350, 1450, 1732, and 2870 cm⁻¹; nmr (CCl₄) 8.75 τ (3H, s), 8.38 τ (8H, d), 7.45 τ (8H, m), 5.87 τ (2H, q).

Anal. Calcd for C₁₂H₂₁NO₂: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.03; H, 9.98; N, 6.59.
N-Hydroxy-2-azabicyclo[2.2.2]octane (2½).

Reaction was carried out as for the preparation of 86 to yield the desired bicyclic hydroxylamine 2½ in 20% yield: mp 123-124°; ir (KBr) 694, 750, 1450, 1525, 2860, 3300 cm⁻¹; nmr (CDCl₃) 8.38 τ (8H, d), 6.82 τ (2H, m), 2.41 τ (1H, s).

Anal. Calcd for C₇H₁₃NO; C, 66.10; H, 10.30; N, 11.01.

Found: C, 66.37; H, 10.09; N, 10.52.

Esterification of Hydroxylamines--General Procedure.

To a vigorously stirred ethereal solution of one equivalent of hydroxylamine at -55° was added an excess of powdered sodium hydroxide followed by the dropwise addition of an ethereal solution of one equivalent of the requisite benzoyl chloride. Reaction at higher temperatures led to spontaneous discoloration and decomposition. The suspension was stirred for 1.5 hr, poured onto ice water and quickly extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered, and the solvent removed on the rotary evaporator to yield in all cases either a yellow solid or an oil which crystallized upon cooling.

N-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane p-Nitrobenzoate (118).

Recrystallization from hexane afforded a 75% yield of 118 as a white solid: mp 114-116°; ir (KBr) 716, 854, 872, 1199, 1275, 1350, 1530, and 1730 cm⁻¹; nmr (CDCl₃) 9.06 τ (3H, s), 9.01 τ (3H, s),
8.79 τ (3H, s), 8.22 τ (5H, m), 6.42 τ (2H, s), 1.70 τ (4H, d).

Found: C, 63.18; H, 6.66; N, 9.11.

Piperidin-1-yl 3,5-Dinitrobenzoate (100).

Recrystallization from hexane afforded the desired ester in 59% yield as a white solid which turned pink within 15 minutes after exposure to the atmosphere: mp 119-120°; ir (CCl₄) 715, 920, 1145, 1250, 1348, 1540, and 1760 cm⁻¹; nmr (CCl₄) 8.15 τ (6H, m), 6.77 τ (4H, m), 0.7 τ (3H, m); mass spectrum: parent peak at (m/e) 295.

Piperidin-1-yl p-Nitrobenzoate (99).

Recrystallization from hexane afforded a 90% yield of 99: mp 69-71°; ir (KBr) 718, 848, 1094, 1250, 1344, 1540, and 1750 cm⁻¹; nmr (CDCl₃) 8.10 τ (6H, m), 6.70 τ (4H, s), 1.67 τ (4H, d).

Anal. Calcd for C₁₂H₁₄N₂O₄: C, 57.59; H, 5.64; N, 11.20.
Found: C, 57.61; H, 5.77; N, 11.12.

Piperidin-1-yl p-Chlorobenzoate (98).

Recrystallization from hexane gave a 78% yield of 98 as pure white needles: mp 67-68°; ir (CCl₄) 845, 1010, 1080, 1240, 1585, and 1750 cm⁻¹; nmr (CCl₄) 8.25 τ (6H, m), 5.90 τ (4H, m), 2.37 τ (4H, q).

Anal. Calcd for C₁₂H₁₄NO₂Cl: C, 60.38; H, 5.91; N, 5.87.
Found: C, 60.07; H, 5.89; N, 5.72.
Piperidin-1-yl Benzoate (27).

Recrystallization from hexane gave 27 as a white solid in 65% yield: mp 63-64°; ir (CCl4) 703, 1015, 1060, 1070, 1175, 1240, 1350, and 1755 cm⁻¹; nmr (CCl4) 8.20 τ (6H, m), 6.32 τ (4H, m), 2.65 τ (5H, s).

Anal. Calcd for C12H15NO2: C, 70.22; H, 7.37; N, 6.82.
Found: C, 70.40; H, 7.23; N, 6.58.

Piperidin-1-yl p-Methylbenzoate (26).

Recrystallization from hexane afforded a 71% yield of 26: mp 64-65°; ir (CCl4) 1015, 1030, 1075, 1175, 1250, 1610, and 1750 cm⁻¹; nmr (CCl4) 8.25 τ (6H, m), 7.60 τ (3H, s), 6.90 τ (4H, m), 2.50 τ (4H, q).

Anal. Calcd for C13H17NO2: C, 71.20; H, 7.82; N, 6.39.
Found: C, 71.43; H, 7.83; N, 6.39.

Piperidin-1-yl p-Methoxybenzoate (25).

Recrystallization from hexane gave an 85% yield of 25: mp 55-56°; ir (CCl4) 1040, 1080, 1173, 1250, 1512, 1620, and 1755 cm⁻¹; nmr (CDCl3) 8.27 τ (6H, m), 6.95 τ (4H, m), 6.20 τ (3H, s), 2.60 τ (4H, q).

Found: C, 66.45; H, 7.34; N, 5.77.
N,N-Diethylhydroxylamine p-Nitrobenzoate.

Commercial N,N-diethylhydroxylamine was reacted with p-nitrobenzoyl chloride as described above. Recrystallization from hexane afforded an 88% yield of the desired ester as long, yellow needles: mp 46-47°C; ir (KBr) 717, 854, 880, 1250, 1351, 1465, 1530, 1610, and 1755 cm⁻¹; nmr (CDCl₃) 8.78 τ (6H, t), 6.84 τ (4H, q), 6.65 τ (4H, s) and 1.63 T (4H, s).

Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.45; H, 5.92; N, 11.76.

Found: C, 55.43; H, 5.88; N, 11.61.

Morpholin-1-yl p-Nitrobenzoate.

Commercial N-hydroxymorpholine was reacted as above and recrystallization from hexane afforded the desired ester in 82% yield: mp 61-62°C; ir (KBr) 717, 862, 880, 1098, 1105, 1264, 1352, 1525, and 1732 cm⁻¹; nmr (CDCl₃) 6.65 τ (4H, m), 6.00 τ (4H, m), 1.72 τ (4H, d).

Anal. Calcd for C₁₁H₁₂N₂O₅: C, 52.38; H, 4.80.

Found: C, 52.23; H, 4.90.

N-Hydroxy-2-azabicyclo[2.2.2]octane p-Nitrobenzoate.

Reaction of the requisite bicyclic hydroxylamine 9₂ in the above manner and recrystallization from hexane afforded the desired ester as clear crystals in 65% yield: mp 90-91°C; ir (CCl₄) 713, 1070, 1090, 1265, 1350, 1535, and 1755 cm⁻¹; nmr (CDCl₃) 8.81 τ (9H, d), 4.48 τ (3H, s), 1.64 τ (4H, d).
**Conductometric Kinetics.**

Solvolysis of each piperidin-1-yl benzoate was carried out in methanol which had been distilled from anhydrous magnesium sulfate, stored over molecular sieves and degassed with nitrogen immediately prior to each kinetic run. A 0.01 M solution of benzoate ester in methanol was prepared and the solution pipetted into a 3 ml conductivity cell which was then sealed. The conductivity cell was placed in an oil bath equilibrated at 50 ± 0.01°C, attached to a YSI Model 31 Conductivity Bridge, and the changing conductance of the solution was monitored and recorded. First-order rate constants, obtained from a least squares treatment of the appropriate conductance parameters, varied by less than 3% in duplicate runs. Control experiments carried out subsequent to the product analysis indicated that none of the four products individually had a significant conductance and that the benzoic acid:amine combination was responsible for almost all of the observed conductance increment.

**Product Analysis--General Procedure.**

The requisite piperidin-1-yl benzoate was solvolyzed in methanol for at least 5 half-lives, the reaction solution then made acidic with concentrated hydrochloric acid, and the solvent was removed on the rotary evaporator. The gummy residue was extracted with
several portions of hexane to remove the methyl benzoate component and then with ether to remove the benzoic acid component. The residue was then made basic with aqueous sodium hydroxide solution and extracted with several portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solution concentrated by distillation through a 6' Vigreaux column. VPC analysis on a 10' 10% Carbowax 20M:KOH on 60/80 Chrom W column indicated two components, samples of which were obtained via isolation from a 10' 10% Carbowax 20M:KOH on Chrom W preparative vpc column. The two components were shown to be piperidine and N-hydroxypiperidine through comparison with authentic samples. Indicated yields of these compounds are from vpc analysis of crude reaction mixtures utilizing N-methylaniline as an internal standard.

1-Phenylcyclohexanol.

This compound was synthesized in 70% yield according to the procedure of G. Baddeley, J. Chadwick and H.T. Taylor, J. Chem. Soc., 451 (1956).

Synthesis of Benzoate Esters of 1-Phenylcyclohexanol.

In a three-neck flask equipped with nitrogen inlet, serum cap and additional funnel was placed a solution of one equivalent of 1-phenylcyclohexanol in dry ether under a nitrogen atmosphere. With ice-bath cooling, one equivalent of n-butyllithium in hexane was added through the serum cap, followed by enough tetrahydrofuran to
dissolve the resulting precipitate. To this cooled, homogeneous solution was added dropwise, 1.1 equivalent of the requisite acid chloride dissolved in tetrahydrofuran and the resulting suspension was stirred for 1 hr at room temperature. The reaction mixture was then poured into a saturated aqueous sodium chloride solution and quickly extracted twice with ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed on the rotary evaporator to yield in each case an oil which crystallized readily upon cooling.

1-Phenylcyclohexyl 3,5-Dinitrobenzoate (106).

Recrystallization from carbon tetrachloride gave 106 in 86% yield: mp 117-119°; ir (CCl₄) 690, 715, 1125, 1160, 1235, 1265, 1275, 1338, 1540, and 1740 cm⁻¹; nmr (CCl₄) 8.18 τ (8H, s), 7.20 τ (2H, m), 2.61 τ (5H, d), 0.89 τ (3H, m).

Anal. Calcd for C₁₅H₁₄N₂O₆: C, 61.61; H, 4.90; N, 7.56.

Found: C, 61.44; H, 4.96; N, 7.52.

1-Phenylcyclohexyl p-Nitrobenzoate (107). Recrystallization from carbon tetrachloride gave 107 in 71% yield as a white solid: mp 133-135°; ir (CCl₄) 693, 717, 1098, 1118, 1245, 1265, 1290, 1350, 1534, and 1740 cm⁻¹; nmr (CCl₄) 8.32 τ (8H, s), 7.33 τ (2H, m), 2.74 τ (5H, s), 1.85 τ (4H, s).


Found: C, 70.09; H, 5.93; N, 4.29.
1-Phenylcyclohexyl p-Chlorobenzoate (108).

Recrystallization from hexane afforded an 84% yield of 108 as clear crystals: mp 98-99°; ir (CCl₄) 695, 850, 1015, 1100, 1240, 1272, 1290, 1438, 1596, 1732 cm⁻¹; nmr (CCl₄) 8.28 t (6H, s), 7.36 τ (2H, m), 2.72 τ (5H, s), 2.38 τ (4H, q).

Anal. Calcd for C₁₅H₁₇O₂Cl: C, 72.39; H, 6.08; Cl, 11.26. Found: C, 72.36; H, 6.23; Cl, 11.44.

1-Phenylcyclohexyl Benzoate (109).

Recrystallization from hexane gave 109 in 79% yield as clear crystals: mp 76-77°; ir (CCl₄) 709, 1105, 1240, 1267, 1282, 1305, 1445, 1730 cm⁻¹; nmr (CCl₄) 8.38 t (8H, s), 7.37 t (2H, m), 7.43 τ (2H, m), 2.77 τ (2H, m).


1-Phenylcyclohexyl p-Methylbenzoate (110).

Recrystallization from hexane afforded an 83% yield of 110 as clear crystals: mp 104-105°; ir (CCl₄) 690, 1098, 1233, 1264, 1280, and 1728 cm⁻¹; nmr (CCl₄) 8.33 t (8H, s), 7.66 τ (5H, s), 7.37 τ (2H, m), 2.84 τ (7H, m), 2.15 τ (2H, d).

Anal. Calcd for C₂₀H₂₂O₂: C, 81.60; H, 7.53. Found: C, 81.48; H, 7.56.
1-Phenylcyclohexyl p-Methoxybenzoate (I)

Recrystallization from hexane afforded an 80% yield of I as clear crystals: mp 70-72°; ir (CCl₄) 691, 1030, 1098, 1158, 1248, 1274, 1290, 1605, and 1750 cm⁻¹; nmr (CCl₄) 8.34 τ (6H, s), 7.40 τ (2H, m), 6.29 τ (3H, s), 2.82 τ (5H, d), 2.69 τ (4H, q).


Found: C, 77.13; H, 7.10.

Titrimetric Kinetics.

Reagents. Reagent grade absolute methanol was stirred over anhydrous magnesium sulfate and then distilled at atmospheric pressure.

Procedure. The standard ampoule technique was used with slight modification. Either a standard solution of ester in methanol was made up with equal aliquots taken and carefully pipetted into different ampoules, or the same amount of ester was individually weighed and placed in each ampoule, followed by dilution with methanol. Trial runs showed these techniques to give rate constants within experimental error. The titrant was 0.01 N aqueous sodium hydroxide solution and titrations were performed on Metrohm Herisau Potentiograph Model E 436. Rate constants were determined by the process of linear regression and the computations were carried out on a Wang 360 K Programmable Calculator.
1-Methoxy-1-phenylcyclohexane (II3).

To 4.0 g (0.023 mol) of 1-phenylcyclohexanol in dry ether was added 0.025 mol of n-butyllithium in hexane with ice cooling of the reaction vessel. A precipitate formed rapidly and 10 ml of tetrahydrofuran was added to make the system homogeneous. Then, 3.22 g (0.023 mol) of methyl iodide in tetrahydrofuran was added dropwise and the solution stirred at room temperature for 1 day. The solvent was then removed on the rotary evaporator and the residue distilled through a short-path condenser to give 4.10 g (91\%) of II3 as a clear oil, bp 72-75°C (0.4 mm).

1-Phenylcyclohexene (II2).

To 5.0 g (0.0283 mol) of 1-phenylcyclohexanol dissolved in benzene was added 1.0 g of p-toluenesulfonic acid. The solution was stirred at 60°C for 1 hr and then heated to boiling. After all the water had distilled from the solution, the flask was cooled and the contents poured into a separatory funnel. The benzene phase was then extracted twice with saturated sodium bicarbonate solution and then once with dilute sodium hydroxide solution. The benzene layer was then dried over anhydrous magnesium sulfate, filtered and the solvent removed on the rotary evaporator to leave a slightly yellow residue which was distilled through a short-path condenser to give 3.0 g (81\%) of the desired olefin II2: bp 69°C (0.5 mm).
Product Analysis of 1-Phenylcyclohexyl Benzoate Solvolysis.

Each ester was allowed to solvolyze in methanol for at least seven half-lives. Each solvolysis solution was then subjected to vpc analysis on a 6' SE-30 analytical column. The expected products 112 and 113 were present in each case, however, when solvolysis of a given ester was interrupted at different stages, the ratio of 112 to 113 varied in each case. It was found that 113 in the presence of 3,5-dinitrobenzoic acid under the solvolysis conditions was almost completely converted to 112 after four hours. The other benzoic acids also caused conversion of 113 to 112 at slightly slower rates.

In order to prevent the conversion of 113 to 112, several buffers were investigated. Standard solutions were prepared containing equivalent amounts of 113, 3,5-dinitrobenzoic acid and triethylamine and subjected to solvolysis conditions. Even over extended periods no conversion of 113 to 112 was apparent. However, when the 1-phenylcyclohexyl benzoates were solvolyzed in methanol in the presence of triethylamine, the ratio of 112 to 113 varied with the extent of reaction and with the initial concentration of amine. The more the amine and the greater the number of half-lives, the greater the relative amount of olefin 112 as compared to 113. Other buffers were found which prevented the conversion of 113 to 112, such as pyridine, 2,6-lutidine, diphenylamine and sodium bicarbonate, however each also altered the product ratio in the manner already described.
Product Study of the Methanolysis of \( \text{N-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane p-Nitrobenzoate (118)} \).

A 5.0 g quantity of 118 was solvolyzed in purified methanol for ca. 10 half-lives. The cooled reaction solution was then made acidic with concentrated hydrochloric acid and the solvent was removed on the rotary evaporator. The gummy residue was extracted with several portions of hexane, the extracts combined and the solvent evaporated to yield 0.87 g (31.9\%) of methyl p-nitrobenzoate as a white solid. The gummy residue was then extracted with several portions of ether, the ether extracts combined, dried over anhydrous magnesium sulfate, filtered and the solvents removed to yield 1.98 g (64.0\%) of p-nitrobenzoic acid as a white solid. The residue was then made basic with aqueous sodium hydroxide solution and extracted with four 30-ml portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, filtered, the solution concentrated on the rotary evaporator, and the resulting oil subjected to vpc analysis on a 10' 20\% Apiezon L:KOH on Firebrick preparative column. There were three components and in order of collection off the column these were shown to be \( 4,7,7\)-trimethyl-2-azabicyclo[2.2.1]heptane (83), \( \text{N-hydroxy-4,7,7-trimethyl-2-azabicyclo-[2.2.1]heptane (86)} \), and \( 2\)-exo-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (119). The reaction was repeated and analysis by vpc on a 10' 20\% Apiezon L:KOH on 60/80 Chrom P analytical column (vs \( \text{N,N-dimethylaniline as internal standard} \)) gave 13.4\% of 83,
1-(p-Tolyl)cyclohexanol.

The Grignard reagent of p-bromotoluene (50 g, 0.292 mol) was prepared in dry ether and to it was added with cooling 28.6 g (0.292 mol) of cyclohexanone dissolved in 50 ml of ether over the course of fifteen minutes. After addition was complete, the mixture was refluxed for 1 hr. The cooled reaction mixture was neutralized with saturated aqueous ammonium chloride solution at 0-10°C. The phases were separated and the aqueous phase was extracted with two 100-ml portions of ether. The combined ethereal extracts were washed with saturated sodium bisulfite solution and then dried over anhydrous sodium sulfate. The ethereal solution was then filtered through glass wool and the solvent removed on the rotary evaporator to give a yellow oil, which showed a strong 0-H absorption in the infra-red spectrum. Distillation of this oil through either un-washed or base-washed glassware caused elimination to take place with formation of the corresponding olefin. The crude oil was therefore chromatographed on basic alumina and eluted with 25% ether:hexane to give 21.2 g (39%) of the desired alcohol as a clear viscous oil: ir (neat) 312, 2970, 1030, 1150, 1252, 1450, 1502, 3000, 3800 cm⁻¹; nmr (CCl₄) 8.38 τ (8H, s), 7.75 τ (3H, s), 7.50 τ (1H, s), 2.88 τ (4H, q).

Molecular weight. Calcd. for C₁₆H₁₆O: 190.15575.

Found: 190.13591.
Synthesis of Esters of 1-(p-Tolyl)cyclohexanol.

Benzoate esters were prepared as for 1-phenylcyclohexanol. In each case either a solid or oil was obtained which was purified as described below. Chromatography on basic alumina, neutral alumina, silica gel and Florasil led to virtual quantitative decomposition of the benzoate esters. Small quantities of the desired esters could be isolated by molecular distillation of the crude reaction solution, however, the yields were very low.

1-(p-Tolyl)cyclohexyl 3,5-Dinitrobenzoate (116a).

Reaction yielded a dark yellow oil which was dissolved in carbon tetrachloride and decolorized. Solvent removal gave a yellow solid which was recrystallized from carbon tetrachloride to give the desired ester as a white solid: mp 102-104°; ir (neat) 719, 730, 787, 918, 1155, 1272, 1340, 1449, 1540, 1625, 1730, and 2995 cm⁻¹; nmr (CDCl₃) 8.20 τ (6H, s), 7.70 τ (3H, s), 7.29 τ (2H, m), 2.78 τ (4H, q), 0.63 τ (3H, m); mass spectrum: parent peak at (m/e) 384.

1-(p-Tolyl)cyclohexyl p-Nitrobenzoate (116b).

Reaction gave a yellow solid which was recrystallized from carbon tetrachloride to give a 60% yield of the desired ester; mp 124-126°; ir (CCl₄) 836, 874, 900, 1010, 1098, 1103, 1240, 1262, 1280, 1345, 1530, 1730, and 2995 cm⁻¹; nmr (CCl₄) 8.36 τ (6H, s), 7.81 τ (3H, s), 7.40 τ (2H, d), 2.95 τ (4H, q), 1.92 τ (4H, s).
Molecular Weight: Calcd for C_{20}H_{21}NO_{4}: 339.14704.
Found: 339.14753.

Anal. Calcd for C_{20}H_{21}NO_{4}: C, 70.78; H, 6.24; N, 4.13
Found: C, 70.31; H, 6.22; N, 4.06.

1-(p-Tolyl)cyclohexyl p-Chlorobenzoate (116c).

Reaction afforded a yellow oil which was chromatographed on a deactivated silica gel column and eluted with pentane to give a 72% yield of a clear oil which crystallized upon cooling. Recrystallization from hexane gave the desired ester as a white solid: mp 102-103\(^\circ\); ir (CCl\(_4\)) 849, 902, 908, 1015, 1100, 1162, 1246, 1265, 1290, 1390, 1445, 1590, 1735, and 2995 cm\(^{-1}\); nmr (CCl\(_4\)) 8.37 \(\tau\) (6H, s), 7.80 \(\tau\) (3H, s), 7.40 \(\tau\) (2H, m), 2.85 \(\tau\) (6H, m), 2.10 \(\tau\) (2H, d).

Molecular Weight. Calcd for C_{20}H_{21}O_{2}Cl: 328.12299.
Found: 328.12329.

Anal. Calcd for C_{20}H_{21}O_{2}Cl: C, 73.05; H, 6.44; Cl, 10.78.
Found: C, 72.85; H, 6.56; Cl, 10.86.

1-(p-Tolyl)cyclohexyl Benzoate (116d).

Reaction gave a yellow oil which was chromatographed on a deactivated silica gel column and eluted with hexane to give the

(77) Deactivation was effected by stirring 300 g of silica gel with 500 ml of water for fifteen minutes. After filtration through a sintered glass funnel, the wet silica gel was heated at 90\(^\circ\) for eight hours with stirring every 45 minutes.
desired ester in 42% yield as a fragrant, clear oil: \( n_D^{25} = 1.5629 \); ir (neat) 710, 809, 903, 1025, 1060, 1100, 1175, 1240, 1265, 1310, 1445, 1755, and 3007 cm\(^{-1}\); nmr (CCl\(_4\)) 8.38 \( \tau \) (6H, d), 7.83 \( \tau \) (3H, s), 7.40 \( \tau \) (2H, m), 2.88 \( \tau \) (6H, m), 2.02 \( \tau \) (2H, m).

l-(\( p \)-Tolyl)cyclohexyl \( p \)-Methoxybenzoate (116e).

Reaction afforded a yellow oil which was chromatographed on deactivated silica gel and eluted with hexane to yield the desired ester in 51% yield as a clear oil: \( n_D^{25} = 1.5857 \); ir (neat) 719, 840, 900, 1012, 1103, 1236, 1290, 1310, 1445, 1755 cm\(^{-1}\); nmr (CCl\(_4\)) 8.37 \( \tau \) (6H, s), 7.65 \( \tau \) (3H, s), 7.32 \( \tau \) (3H, s), 2.81 \( \tau \) (6H, m), 2.02 \( \tau \) (2H, d).

l-(\( p \)-Tolyl)cyclohexyl \( p \)-Methoxybenzoate (116f).

Reaction gave a yellow oil which was chromatographed on deactivated silica gel and eluted with hexane to give the desired ester in 40% yield as a clear oil: \( n_D^{25} = 1.5777 \); ir (neat) 690, 768, 805, 845, 903, 1030, 1170, 1249, 1503, 1600, 1730, and 2997 cm\(^{-1}\); nmr (CCl\(_4\)) 8.37 \( \tau \) (6H, d), 7.83 \( \tau \) (3H, s), 7.45 \( \tau \) (2H, m), 6.30 \( \tau \) (3H, s), 2.86 \( \tau \) (6H, m), 2.17 \( \tau \) (2H, d).

l-[3,5-Di(trifluoromethyl)phenyl]cyclohexanol.

The Grignard reagent was prepared from 40 g (0.137 mol) of 3,5-di(trifluoromethyl)bromobenzene and 6.5 g (0.27 mol) of magnesium turnings in ether. To this black solution was added 13.4 g (0.137
mol) of cyclohexanone in ether drop-wise with cooling. The solution was then heated at reflux on a steam bath for 1 hr. The brown suspension was then cooled in an ice-bath and hydrolyzed with saturated aqueous ammonium chloride solution. The aqueous layer was extracted twice with ether and the combined ethereal extracts were washed with 10% aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. The ethereal extract was then filtered and the solvent removed on the rotary evaporator to give a brown oil which solidified upon cooling. Recrystallization from hexane afforded a 60% yield of the desired alcohol as white needles: mp 103-104°; ir (CCl₄) 676, 703, 842, 885, 1140, 1177, 1275, 1375, 1450, 2995, and 3650 cm⁻¹; nmr (CCl₄) 8.25 τ (1H, s), 8.18 τ (1H, s), 2.11 τ (3H, d).

Anal. Calcd for C₁₄H₁₄F₆O: C, 55.85; H, 4.50
Found: C, 55.82; H, 4.57.

Synthesis of Benzoate Esters of 1-[3,5-Di(trifluoromethyl)phenyl]-cyclohexanol.

To 1 equivalent of 1-[3,5-di(trifluoromethyl)phenyl]cyclohexanol in ether was added 1 equivalent of n-butyllithium in hexane under nitrogen atmosphere. The resulting clear solution was stirred at 0-10° for 10 minutes and then 1 equivalent of the requisite acid chloride in ether was added dropwise. Following addition, the reaction solution was stirred at room temperature for 1 hr. The reaction solution was then poured into a separatory funnel containing
ether and ice water and the resulting phases quickly separated.
The ethereal extract was dried over anhydrous magnesium sulfate, and
the solvent removed on the rotary evaporator to yield either an
crystal or solid as indicated below.

1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] 3,5-Dinitrobenzoate (114a).

Reaction yielded an oil which crystallized upon standing. The
yellow solid was then recrystallized from carbon tetrachloride to
give a 71% yield of 114a as a fluffy, white solid: mp 132-133°C;
ir (CCl₄) 882, 1140, 1178, 1225, 1342, 1540, and 1735 cm⁻¹; nmr
(CCl₃) 8.15 τ (8H, s), 7.12 τ (2H, m), 2.06 τ (3H, s), 0.75 τ (3H,
q).

Anal. Calcd for C₂₁H₁₄F₆N₂O₆: C, 49.81; H, 3.18; N, 5.53.

Found: C, 49.85; H, 3.18; N, 5.41.

1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] 2-Nitrobenzoate (114b).

Reaction afforded a yellow solid which was recrystallized from
carbon tetrachloride to give an 88% yield of the desired ester as a
white solid: mp 125-126°C; ir (CCl₄) 675, 699, 713, 841, 885, 1130,
1174, 1265, 1342, 1370, 1515, 1730, and 2999 cm⁻¹; nmr (CCl₃) 8.18 τ
(6H, s), 7.22 τ (2H, m), 2.15 τ (3H, s), 1.78 τ (4H, s).


Found: C, 54.67; H, 3.75; N, 3.03.
1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] p-Chlorobenzoate (114a).

Reaction afforded an oil which was chromatographed on basic alumina and eluted with 1% ether:hexane to give the desired ester in 68% yield as a clear oil which crystallized upon standing as clear plates: mp 79-80\(^0\); ir (neat) 688, 700, 760, 889, 1020, 1128, 1175, 1280, 1382, 1590, 1730, and 2940 cm\(^{-1}\); nmr (CCI\(_4\)) 8.22 \(\tau\) (6H, s), 8.30 \(\tau\) (2H, m), 3.58 \(\tau\) (2H, d), 2.05 \(\tau\) (5H, m).

Anal. Calcd for C\(_{21}\)H\(_{17}\)ClF\(_6\)O\(_2\): C, 55.95; H, 3.80; Cl, 7.86.
Found: C, 56.08; H, 3.83; Cl, 7.90.

1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] Benzoate (114d).

Reaction afforded an oil which was chromatographed on basic alumina and eluted with 1% ether:hexane to give the ester in 65% yield as a clear oil which crystallized upon standing: mp 77-78\(^0\); ir (neat) 677, 710, 841, 886, 1023, 1140, 1175, 1250, 1280, 1388, 1460, and 1755 cm\(^{-1}\); nmr (CCI\(_4\)) 8.22 \(\tau\) (6H, s), 7.29 \(\tau\) (2H, m), 2.31 (6H, m).

Anal. Calcd for C\(_{21}\)H\(_{19}\)F\(_6\)O\(_2\): C, 60.58; H, 4.36.
Found: C, 60.61; H, 4.57.

1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] p-Methylbenzoate (114e).

Reaction afforded a yellow oil which was chromatographed on basic alumina and eluted with 1% ether:hexane to give a 62% yield of the desired ester as a clear oil which formed plates upon standing: mp 70-71\(^0\); ir (neat) 676, 700, 753, 847, 888, 1138, 1175, 1230, 1382,
1455, 1615, 1738, and 2995 cm⁻¹; nmr (CCl₄) 8.22 τ (6H, s), 7.61 τ (3H, s), 7.28 τ (2H, m), 2.50 τ (7H, m).

Found: C, 61.36; H, 4.78.

1-[3,5-Di(trifluoromethyl)phenylcyclohexyl] p-Methoxybenzoate (114f).

Reaction afforded a yellow oil which was chromatographed on basic alumina and eluted with 1% ether:hexane to give the desired ester in 77% yield as a clear oil: nD²⁵ = 1.6636; ir (neat) 677, 766, 885, 1027, 1125, 1264, 1370, 1510, 1600, 1720, 2995 cm⁻¹; nmr (CCl₄) 8.20 τ (6H, s), 7.78 τ (2H, m), 6.27 τ (3H, s), 3.17 τ (2H, d), 2.68 τ (1H, s), 1.55 τ (4H, m).

Found: C, 59.51; H, 4.79.

Dimethylbenzylcyanide (127).

This compound was prepared from benzylcyanide (126) by the method of A.C. Cope, et al., to yield a product mixture which contained dimethyl- and monomethyl products in a ratio of 95:5 from vpc analysis on a 10' 10% Carbowax 20M:KOH on 60/80 Chrom W analytical column. Recycling gave a mixture which was greater than 99% the desired compound.

2-Methyl-2-phenylpropanoic acid (128).

A solution of 8.25 g (0.057 mol) of dimethylbenzylcyanide (127) in 70 ml of 25% aqueous sodium hydroxide solution was refluxed for four
days. After cooling, the reaction solution was extracted with 125 ml of ether and the aqueous phase was made acidic with concentrated hydrochloric acid. The resulting white solid was collected by filtration, air dried overnight and then extracted with several 100-ml portions of hot hexane. The hexane extracts were then concentrated on the rotary evaporator to yield a white crystalline solid which was the desired acid in 95% yield: mp 69-71° (lit. mp 68.69°).

Dimethylbenzylamine (129).

To 5.0 g (0.0305 mol) of 2-methyl-2-phenylpropanoic acid was added 13 ml of thionyl chloride and the yellow solution refluxed for 1 hr. The excess thionyl chloride was then removed on the rotary evaporator to leave the acid chloride as a yellow oil. This oil was taken up in 50 ml of acetone and added dropwise to a solution of 4.2 g (0.062 mol) of sodium azide in 25 ml of water at 0-5° and stirred for 1.5 hr. The reaction mixture was then extracted with two 50-ml portions of benzene and the extracts were combined, dried over anhydrous magnesium sulfate, filtered and then added dropwise to 50 ml of boiling benzene. After refluxing for 1 hr, during which nitrogen was smoothly evolved, the solution was cooled and the total volume reduced to 30 ml on the rotary evaporator. This solution was then added to 25 ml of concentrated hydrochloric acid and after stirring at room temperature for 30 minutes, water was added and the phases separated. The aqueous phase was extracted with ether, made basic with aqueous sodium hydroxide and then
extracted with two 100-ml portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent was removed on the rotary evaporator to yield a yellow oil which was distilled through a 6' Vigreaux column to give 2.54 g (60%) of the desired amine: bp 64-66° (0.7 mm).

1-Methyl-1-phenylnitroethane (130).

In 62 ml of acetone was dissolved 5.0 g (0.037 mol) of dimethylbenzylamine (129) and 15.5 ml of water. To the stirred solution was added 3.72 g of anhydrous magnesium sulfate followed by 23.6 g (0.15 mol) of potassium permanganate over 0.5 hr with ice-bath cooling. The resulting dark suspension was stirred at room temperature for three days and then heated in an oil bath until almost all of the acetone had distilled out. Then, 50 ml of water was added and the mixture steam distilled with the distillate being approximately a 50:1 mixture of water:nitro compound. After no more organic component would steam distill, the distillate was extracted with two 100-ml portions of ether, and the ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and solvent was removed to yield a yellow oil. Distillation of this oil through a short-path condenser afforded the desired nitro compound as a clear liquid in 66% yield: bp 82-84° (0.5 mm) (lit. bp 75-76° (0.35 mm): nD25 = 1.5522.
N-Methyl-N-(dimethylbenzyl)hydroxylamine (125).

To a 0.049 mol of methyllithium72 (31 ml of a 7% solution in ether) in 30 ml of dry ether under a nitrogen atmosphere was added dropwise 2.0 g (0.0122 mol) of 1-methyl-1-phenyl-nitroethane with ice-bath cooling. The cloudy solution was stirred at room temperature for twelve hours, and with cooling 5 ml of ethanol was carefully added followed by the dropwise addition of 25 ml of water. The phases were separated and the ether layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed on the rotary evaporator to give a yellow oil which upon vpc analysis on a 10' Carbowax 2CM:KOH on 60/80 Chrom W analytical column showed two components in a ratio of 1:1. These two components were most likely the desired hydroxylamine and the corresponding nitrooxide.72 The oil was then taken up in methanol, made acidic with 2 ml of concentrated hydrochloric acid, and was stirred at room temperature for 1 hr. The solvent was then removed on the rotary evaporator to leave a yellow, oily residue. This oil was made basic with aqueous sodium hydroxide solution, extracted twice with ether, and the ether extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent was removed on the rotary evaporator to yield a yellow solid. This solid was washed with cold hexane to give the desired hydroxylamine as white crystals (38%) which discolored quickly when exposed to the air: mp 63-65°; ir (CCl4) 700, 1030, 1185, 1360, 1385, 1460, 1496, and 3300 cm⁻¹; nmr (CDCl₃)
8.39 τ (6H, s), 7.30 τ (3H, s), 2.50 τ (6H, m).

Molecular Weight. Calcd for C₁₀H₁₅NO: 165.1155.
Found: 165.1150.

N-Methyl-N-(dimethylbenzyl)hydroxylamine p-Nitrobenzoate (131).

The ester was prepared as described previously for dialkyl-hydroxylamines, affording a 75\% yield of the desired compound as a white solid: mp 92-95°; ir (CCl₄) 695, 712, 847, 1065, 1079, 1252, 1270, 1350, 1528, and 1755 cm⁻¹; nmr (CDCl₃) 8.30 τ (6H, s), 7.12 τ (3H, s), 2.45 τ (5H, m), 1.78 τ (4H, q).

Anal. Calcd for C₁₇H₁₆N₂O₄: C, 64.95; H, 5.77; N, 8.91.
Found: C, 64.82; H, 5.74; N, 8.77.

Solvolyis of N-Methyl-N-(dimethylbenzyl)hydroxylamine p-Nitrobenzoate (131).

A 4.3 g (0.0137 mol) quantity of 131 was solvolyzed in refluxing methanol at 65° for five days. The cooled reaction solution was acidified with 3 ml of concentrated hydrochloric acid and the solvent removed on the rotary evaporator. The residue was extracted with several portions of hexane, removing 1.86 g (75\%) of methyl p-nitrobenzoate, and then extracted with several portions of ether, removing 0.52 g (23\%) of p-nitrobenzoic acid. The residue was then made basic with aqueous sodium hydroxide solution and extracted with several portions of ether. The extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent was removed
by distillation through a 6' Vigreaux column to leave a yellow oil. This oil showed four components on a 10' x 20% (4:1) Apiezon L:KOH on 60/80 Chrom P analytical column. Three components were separated on a 10' x 1/4' 20% (4:1) Apiezon L:KOH on 60/80 Firebrick preparative column, collected, and shown to be N-methylaniline (122), dimethylbenzylamine (124), and N-methyl-N-(dimethylbenzyl)amine (132) by comparison with authentic samples. Actual yields of these three components were determined from vpc analysis on the indicated analytical column, utilizing N,N-dimethylaniline as internal standard, and were found to be 3.7% of 122, 8.5% of 124, and 6.7% of 132 based on starting p-nitrobenzoate. The fourth component decomposed upon attempted preparative vpc isolation and was subsequently identified as N-methyl-N-(dimethylbenzyl)hydroxyamine (125) from vpc retention times on three different columns. No accurate vpc yield of this compound could be obtained due either to decomposition during reaction or vpc analysis.

Preparation and Solvolysis of N-Methyl-N-(dimethylbenzyl)hydroxyamine p-Toluenesulfonate (136).

The tosylate was prepared as for 86. Filtration of lithium chloride and evaporation of the solvent on the rotary evaporator below room temperature gave a yellow oil which was immediately taken up in methanol and refluxed for thirty minutes. Longer reaction times led to increased decomposition. The reaction solution was acidified with 3 ml of concentrated hydrochloric acid and the solvent
was removed on the rotary evaporator. The residue was made basic with aqueous sodium hydroxide solution, extracted with several portions of ether, and the extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation through a 6' Vigreaux column. The residue showed four components upon vpc analysis on a 10' 20% (4:1) Apiezon L:KOH on 60/80 Chrom P analytical column: N-methylaniline (133), dimethylbenzylamine (134), N-methyl-N-(dimethylbenzyl)amine (132) and starting hydroxylamine (125). Two trial runs to determine quantitative product ratios afforded values differing by ca. 10% and hence, the approximate ratio for the amine products was 133 (3.8), 134 (1.4), and 132 (1.0). There was no indication of acetophenone in the reaction solution, and trial experiments proved that it should have survived the reaction, work-up and isolation procedures.

t-Nitrobutane.

This compound was prepared in 48% yield by the method of Kornblum, et. al., J. Amer. Chem. Soc., 78, 4003 (1956).

N-Methyl-N-t-butylhydroxylamine (140).

To 0.10 mol of methylithium in ether under a nitrogen atmosphere was added dropwise 5.0 g (0.05 mol) of t-nitrobutane in ether over the course of fifteen minutes. The addition caused a mild exotherm which was controlled by ice-bath cooling. Within five minutes a white precipitate started forming and the reaction mixture
was stirred for eighteen hours at room temperature. The yellow solution was then cooled, and as 50 ml of water was carefully added to dissolve the precipitate, the solution turned green in color. The layers were separated and the aqueous phase was extracted twice with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate and the solvent stripped on the rotary evaporator to give an oil which showed the presence of two major components on a 10' Carbowax 20M:KOH analytical column. These products were most likely the desired hydroxylamine and the corresponding nitroxide. The oil was then redissolved in ether and to it was added a solution of 2 ml of concentrated hydrochloric acid in 20 ml of methanol and then the solution was stirred vigorously at room temperature for 1 hr. The solvent was removed on the rotary evaporator and the residue was made basic with aqueous sodium hydroxide solution and subjected to continuous extraction with ether for twenty hrs. The ethereal extract was then dried over anhydrous magnesium sulfate and vpc analysis showed only one component. The solvent was removed on the rotary evaporator to give an oil which was distilled through a short-path condenser to give 4.0 g (80%) of the desired hydroxylamine: bp 65-66° (0.4 mm).

N-Methyl-N-t-butylhydroxylamine p-Nitrobenzoate (141).

N-methyl-N-t-butylhydroxylamine and p-nitrobenzoyl chloride were reacted in the normal manner for ester preparation to give an 82% yield of 141 as a white solid: mp 101-102°C; ir (KBr) 723, 851, 1010, 1062, 1080, 1250, 1345, 1500, 1740 cm⁻¹; nmr (CCl₄) 8.78 τ (9H, s), 7.18 τ (9H, s), 7.18 τ (3H, s), 1.75 τ (4H, d).

Found: C, 57.09; H, 6.38; N, 11.00.

Nuclear Magnetic Resonance Kinetics.

All solvents were commercial samples and were distilled prior to use. The kinetic measurements were carried out on a Varian Associates Model A-60 Nuclear Magnetic Resonance Spectrometer. The probe temperature was determined in the normal manner utilizing the ethylene glycol resonances and was monitored immediately prior to and after every kinetic run. The precise temperature variance was impossible to determine since the nmr solvolysis tube could not be removed from the probe during a run, but in considering only initial and final temperature, the increment was normally ±3°C. The indicated pseudo first-order rate constants are the average of two runs, except for the low temperature runs in dimethylformamide, and were obtained from a least squares treatment of the appropriate data.

For each run 100 mg (0.001 mol) of N-methyl-N-t-butylhydroxylamine (140) in ether was reacted with an equivalent amount of n-butyllithium in hexane for five minutes and then was added an
equivalent of p-toluenesulfonyl chloride in ether. The solution was stirred for fifteen minutes at room temperature and the solvent was removed on the rotary evaporator below room temperature. The resulting oil was the desired tosylate and could be stored in ice for up to two hours without decomposing. For each kinetic determination, the solvent was added to the cold tosylate and the solution quickly passed through a glass wool filter into the nmr tube which was then placed in the probe and the timer engaged. The portion of the spectrum from 9.0 τ to 10.0 τ was scanned repeatedly at a scanning speed setting of 250 seconds. The areas of the t-butyl (0.1 τ) and tetramethylsilane peaks were obtained by triangulation and the constancy of the internal standard peak area was taken to mean that no correction of the t-butyl peak area was needed.
REFERENCES


33. P.G. Gassman and G.A. Campbell, ibid., 93, 2567 (1971), and references cited therein.


37. We have recently been informed by Professor C.F. Wilcox of the unpublished results of K.K. Pohl on the solvolysis of p-nitrobenzoate and trichloracetate esters of N,N-dialkyl-hydroxylamines in ethanol-water mixtures (K.K. Pohl, Ph.D. Thesis, Cornell University, 1965). Their preliminary results seemed to be more complex than ours, presumably due to the solvent system chosen. We wish to thank Professor Wilcox for this information.


40. For a comprehensive review of phenylhydroxylamine derivatives as possible nitrenium ion precursors, see: J.A. Miller, Cancer Research, 30, 759 (1970), and references cited therein.


43. See Experimental for synthetic details.

44. We wish to thank Dr. K. Shudo for performing this synthesis; P.G. Gassman and K. Shudo, unpublished results.


46. Solvolysis of N-chloropiperidine in methanol also gives piperidine as the only isolable product (P.G. Gassman and J.E. Trent, unpublished results).


50. P.D. Bartlett and J.L. Kice, ibid., 75, 5591 (1953).


60. For comparisons of carbon p-nitrobenzoates and chlorides see: (a) A. Fainberg and S. Weinstein, J. Amer. Chem. Soc., 78, 2770 (1956); (b) C. Wilcox, Jr., and M. Mesirov, ibid., 84, 2757 (1962); (c) R. Buckson and S. Smith, J. Org. Chem., 22, 634 (1957); (d) O. Benfey, E. Hughes and C.K. Ingold, J. Chem. Soc., 2488 (1952).


65. The Hammond postulate suggests that the more stable the intermediate species in an Sn 1 process, the more the transition state will be "reactant-like"; G. Hammond, ibid., 77, 334 (1955).

66. For discussions concerning classical and non-classical ions with relation to the Hammond postulate see: H.C. Brown, F.J. Chloupek and M.-H. Rei, ibid., 86, 1246 (1964); S. Winstein, ibid., 87, 381 (1965).


69. W.E. Bachmann and M. Steinberg, ibid., 56, 170 (1934); W.E. Bachmann and J.W. Ferguson, ibid., 26, 2081 (1934); J.D. Roberts, ibid., 74, 5943 (1952); V.F. Raen and C.J. Collins, ibid., 80, 1409 (1958).


73. Although elemental analysis was not possible, infrared and nuclear magnetic resonance spectral data along with an exact mass determination confirmed the identity of hydroxylamine.


75. P.G. Gassman and J.E. Trent, unpublished results.


77. Deactivation was effected by stirring 300 g of silica gel with 500 ml of water for fifteen minutes. After filtration through a sintered glass funnel, the wet silica gel was heated at 90° for eight hours with stirring every 45 minutes.