CARBON-NITROGEN DOUBLE BOND-FORMING ELIMINATION REACTIONS INVOLVING 2-ALKYL- AND 2-ARYLPYRROLIDINES

by

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GENERAL INTRODUCTION

1.0 General Aspects of Carbon-Nitrogen Double Bonds

1.1 Introduction

The nitrogen atom plays an important role in nature. It occurs in a wide variety chemical compounds, ranging from molecular nitrogen and nitrogen oxides in air to inorganic nitrates in soil to organic compounds with varying complexity in the plant and animal kingdom. Among these, the compounds having a C=N group play an important part in chemistry.

The C=N group is in many respects intermediate between the C=C and C=O functions. All three groups have two electrons in π orbitals and these account for most of their characteristic properties. Whereas both atoms of the C=C and C=N groups can be located at internal positions in chains and rings, the oxygen atoms of C=O groups are by necessity in terminal positions. The nitrogen and oxygen atoms in the C=N and C=O groups possess lone pairs of electrons which account for other characteristic properties of these groups.

1.2 Internuclear Distances, Bond Energies, and Dipole Moments

Although important organic compounds having C=N bonds have been frequently studied by various methods such as quantum mechanics and ultraviolet and infrared spectroscopy, the C=N unit itself has received less attention. Quantities such as dipole moments, bond energies, and interatomic distances for C=C and C=O groups are plentiful in the literature. But this is not the case for C=N mainly due to the unstable character of the simplest C=N containing compounds.

According to Layton, Kross, and Fassel,[1] typical carbon-nitrogen intermolecular distances are 1.47 Å for the C-N bond and 1.29-1.31 Å for isolated and 1.35-1.36 Å for azaaromatic C=N bonds. In Table 1[2] are recorded some typical lengths of CC, CN, NN, and CO bonds for comparison purposes.

TABLE 1

Some Typical Bond Lengths (Å)

C-C	1.537	C-N	1.47	N-N	1.47	C-O	1.40
C=C (Benzene)	1.397	C=N ring conj.	1.36			C=O strongly conj.	1.29
C=C (Ethylene)	1.338	C=N	1.30	N=N	1.24	C=O	1.21
C≡C (Acetylene)	1.205	C≡N	1.16	N≡N	1.09		

The C=N bond dipole moment is estimated to be close to 1 D.[2,3] Table 2 contains some typical dipole moments.

TABLE 2

Some Typical Dipole Moments[2]

C=C	0.0 D	C=O	2.3	N=O	2.0 D
C=N	0.9 D	C=S	2.6	C≡N	3.5 D

The bond energy $E_{C=N}$ is one of the less well-known bond energies. It was calculated by Cottrell[4] to be 147.0 kcal/mole. Palmer[5] gives a calculated value of 142 kcal/mole. The $E_{C=N}$ values vary by about 10 kcal/mole from molecule to molecule. Table 3 summarizes some of Cottrell's and Palmer's findings.

TABLE 3

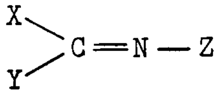
Some Typical Bond Energies

Bond	Bond Energy (kcal/mole) as Calculated by	
	Cottrell	Palmer
C-C	82.8	83
C=C	145.8	146
C≡C	199.6	200
C-N	72.8	69
C=N	147.0	142
C≡N	212.4	214

1.3 Infrared Spectroscopy[2,6]

The C=N stretching frequency is in most cases a strong and fairly sharp band. It is located at lower frequencies then the bands of C=O and close to C=C stretching frequencies in similar environments. In a purely aliphatic environment, in the absence of strain, steric hinderance or other complicating factors, the values for stretching frequency (ν in cm^{-1}) and molar absorptivity (ϵ in L/mole-cm) for C=O and C=N are 1715, 1670 and 400-1000, 100-300, respectively, in dilute solutions. These correspond to respective force constant of 11.9 and 10.6 dynes/cm for C=O and C=N, respectively, calculated using a harmonic oscillator approximation.

There is very little difference between infrared and Raman frequencies of imines and also between the spectra of pure liquids and solids and their solutions in not very associative solvents. The factors affecting the C=N stretching frequency include the physical state of the compound, the nature of the subsituents, the conjugation with either carbon or nitrogen or both, and hydrogen bonding.



1

For the compounds 1 where X, Y, Z, may be hydrogen, alkyl, or aryl groups, the C=N stretching frequencies occur in the region of 1603-1680 cm^{-1}. This a considerably narrower region than the 1471-

1689 cm^{-1} region described for all the C=N containing compounds.

The stretching frequency for saturated aliphatic aldimine type C=N bonds occurs in the region 1665-1680 cm^{-1}. For compounds with alkyl groups both on nitrogen and carbon, the chain length or chain branching does not affect the frequency of absorption. The lack of an alkyl group on the carbon atom of a C=N group shifts the frequency to lower values. A small reduction in frequency is also seen when a single ethylenic double bond is in conjugation with the C=N bond. An unconjugated phenyl group on the aliphatic chain reduces the frequency only very little. Whereas conjugation with an aromatic ring lowers the range to 1638-1650 cm^{-1} for the compounds where X=Ar, Y=H, Z=R. A second aromatic ring on nitrogen, X, Z=Ar and Y=H, reduces the stretching frequency even further to 1626-1637 cm^{-1}.

Ketimines show C=N stretching frequencies in the region 1614-1650 cm^{-1}. The substitution and conjugation effects observed for ketimines are similar to those for aldimines.

1.4 Electronic Spectra[2]

Very little is known about the electronic spectrum of the C=N group in a purely aliphatic environment. The few compounds for which the far ultraviolet absorption spectrum are reported have spectra which consist of broad bands. Therefore interpretation is difficult and only estimated figures are given. The $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transitions are estimated to occur around 170 nm and 210 nm, respectively. In Table 4 are recorded the positions of the $n \longrightarrow \pi^*$ band for various unconjugated lone pair-containing groups for comparison.

TABLE 4

The Position of the $n \longrightarrow \pi^*$ Band for Unconjugated Lone Pair-Containing Groups

Group	$n \longrightarrow \pi^*$ (nm)
$>C=N-$	190-200
$-NO_2$	270
$>C=O$	280
$-N=N-$	370
$>C=S$	550
$-N=O$	680

Much more data is available for compounds in which the C=N group has aromatic ring substituents. Jaffe, Yeh, and Gardner[7] have compared the spectrum of benzalaniline, $C_6H_5CH=NC_6H_5$, with the spectra of stilbene and azobenzene. Stilbene has no lone pair electrons and the $n \longrightarrow \pi^*$ transition was naturally missing from its spectrum. The analysis of the spectrum of benzalaniline suggested the presence of a weak band near 360 nm with ϵ_{max} about 100, which was been assigned to a $n \longrightarrow \pi^*$ transition. In azobenzene, an extremely broad band around 420 nm was observed due to superposition of two nearly degenerate $n \longrightarrow \pi^*$ transitions. The n level in benzalaniline occurs at almost the same energy as in azobenzene, but the π^* level lies considerably higher.

This results in a blue-shift for the $n \longrightarrow \pi^*$ transition between azobenzene and benzalaniline. The $\pi \longrightarrow \pi^*$ transitions are complicated by the presence of two conjugated benzene groups and therefore the interpretations of these transitions will not be attempted here. For further information the Reader is referred to the original work.[7]

1.5 Analysis of Imines[6]

There have been relatively few qualitative chemical methods developed which are specifically designed for compounds having C=N groups. In most cases, the method is based on hydrolysis of the C=N group to the corresponding amine and carbonyl compound and subsequent identification of these products.

The quantitative methods which have been developed for measuring the C=N group are based either on the basic properties of the group or on the determination of the hydrolysis products of the imine.

The titration technique employs the basic character of imines for the quantitative analysis. Perchloric acid is used generally as the titrant and glacial acetic acid, chloroform, or acetonitrile is commonly used as solvent. Potentiometric titration of an imine in acetonitrile with perchloric acid in dioxane solution is recommended as the acidimetric method of greatest utility.

The ease with which imines hydrolyse, especially under acidic conditions, is used for the quantitative analysis of this group. The C=N bearing compound is first hydrolysed in either dilute HCl or dilute H_2SO_4 and the resulting carbonyl compound is quantitatively determined using 2,4-dinitrophenylhydrazine, bisulfite, or hydroxylamine reagents.

2.0 Methods of Formation of Carbon-Nitrogen Double Bonds

2.1 Introduction

There are numerous methods for the synthesis of carbon-nitrogen double bonds. An attempt will be made to only cover some of the important methods here. For a more detailed coverage the Reader is referred to the review by S. Dayagi and Y. Degani.[8]

2.2. Condensations of Aldehydes and Ketones with Amines

One of the most important synthetic routes to form C=N is the condensation reaction of amines with carbonyl compounds. This reaction has many applications. It has been used for preparation of imines; for identification, detection, and determination of aldehydes and ketones; for purification of carbonyl and amino compounds; and for the protection of amino or carbonyl groups.

Eq-1 $$R_1R_2C{=}O + R_3NH_2 \rightleftharpoons R_1R_2C{=}NR_3 + H_2O$$

The condensation of primary amines with carbonyl compounds was first reported by Schiff[9] and products are often referred as "Schiff bases". The reaction is acid-catalysed and it is recommended that water be removed as it is formed to drive the reaction to completion. The variety of compounds containing amino groups which undergo this reaction include: hydroxylamine and its derivatives, hydrazine and its derivatives, carbamates, sulphenamides, nitramine, chloramine, and triazine derivatives.[8] Aldehydes and ketones are not the only compounds to react with amines to give imines. Thioamides, enols, enol ethers, phenols, <u>gem</u>-dihydroxy compounds, and <u>gem</u>-dihalides also react with amines.[8]

A new C=N bond can be formed from an existing C=N bond by the action of either amines or carbonyl compounds.

Eq-2 $$R_2C{=}NR' + R''NH_2 \rightleftharpoons R_2C{=}NR'' + R'NH_2$$

Eq-3 $$Me_2C{=}NR + R'_2C{=}O \rightleftharpoons Me_2C{=}O + R'_2C{=}NR$$

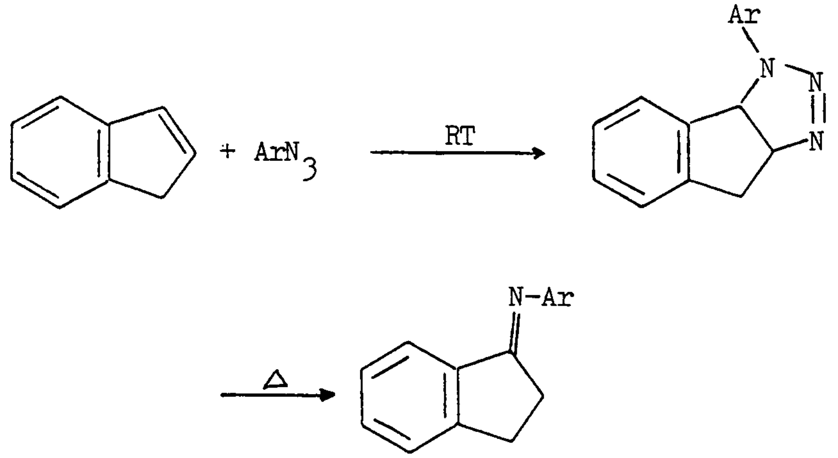
2.3 Additions to Carbon-Carbon Double or Triple Bonds

Compounds containing a C=C group activated by a strong electron-attracting group react with amines to give imines by cleavage of the carbon-carbon double bond.

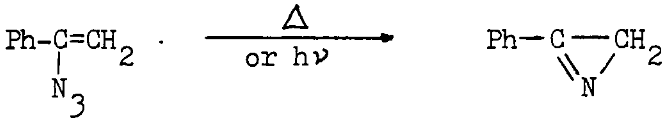
Eq-4 $$RCH{=}CX_2 + R'NH_2 \longrightarrow RCH{=}NR' + CH_2X_2$$

Azides add to double bonds activated by aromatic systems to form imines (Equation 5). α-Azidoethylenes undergo internal cycloaddition with subsequent elimination of nitrogen on heating or by irradiation to form azirenes (Equation 6).

Eq-5

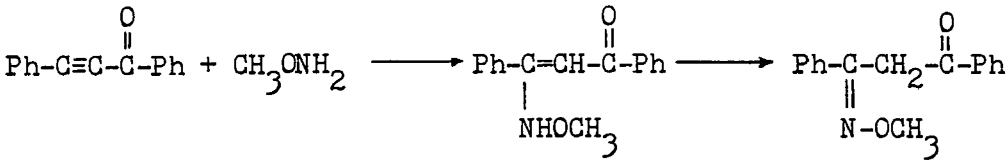


Eq-6



Simple acetylenes reluctantly add amines, but those which are activated with strong electron-attracting groups react much more readily. The enamine formed might undergo a tautemeric shift to form imine (Equation 7).

Eq-7

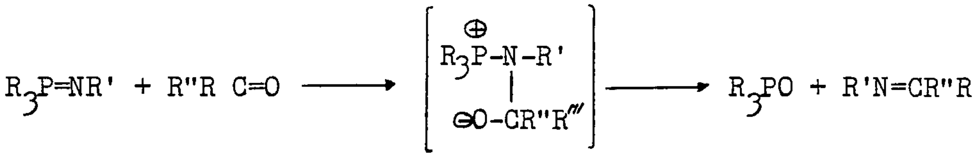


$$\mathrm{Ph{-}C{\equiv}C{-}\overset{\overset{O}{\|}}{C}{-}Ph} + \mathrm{CH_3ONH_2} \longrightarrow \mathrm{Ph{-}\underset{\underset{NHOCH_3}{|}}{C}{=}CH{-}\overset{\overset{O}{\|}}{C}{-}Ph} \longrightarrow \mathrm{Ph{-}\underset{\underset{N{-}OCH_3}{\|}}{C}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}Ph}$$

2.4 Formation of C=N Bonds Through Ylids

Ylids which are extensively employed to form carbon-carbon double bonds also find use in forming carbon-nitrogen double bonds. The mechanism of the reaction involves the formation of a betaine intermediate

(Equation 8).

Eq-8 

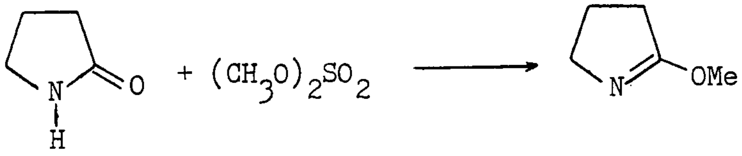
$$R_3P{=}NR' + R''R\ C{=}O \longrightarrow \left[\begin{array}{c}\oplus\\ R_3P\text{-}N\text{-}R'\\ | \\ \ominus O\text{-}CR''R'''\end{array}\right] \longrightarrow R_3PO + R'N{=}CR''R$$

Sulfur ylides, phophoramide anions, and phosphazines also react in similar fashion.

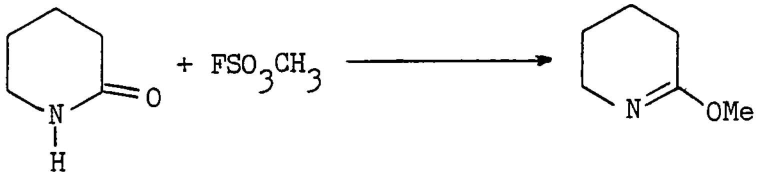
2.5 Tautemerization of Amides and Thioamides

Amides usually are alkylated by alkyl halides under basic conditions to give N-alkyl amides. However, if more reactive alkylating reagents such as dimethyl sulfate or methyl fluorosulfonate are used O-alkylation is observed (Equation 9 and 10).

Eq-9[10]

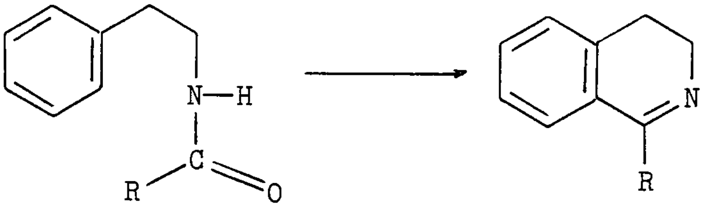


Eq-10[11]



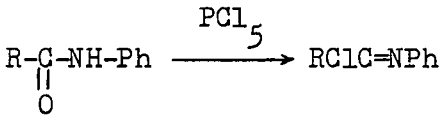
Suitable amides cyclize to give various kinds of products. N-(β-Arylethyl)-amides form dihydroisoquinolines under the influence of acidic catalysts. This reaction is called Bischer-Napieralsky reaction.[12]

Eq-11



The first step in the Sonn and Müller aldehyde synthesis is the formation of an imidoyl chloride from anilide and PCl_5.[13]

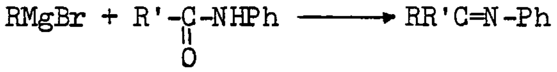
Eq-12



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}Ph} \xrightarrow{\mathrm{PCl_5}} \mathrm{RClC{=}NPh}$$

Anilides also react with Grignard reagents to give imines.[14]

Eq-13



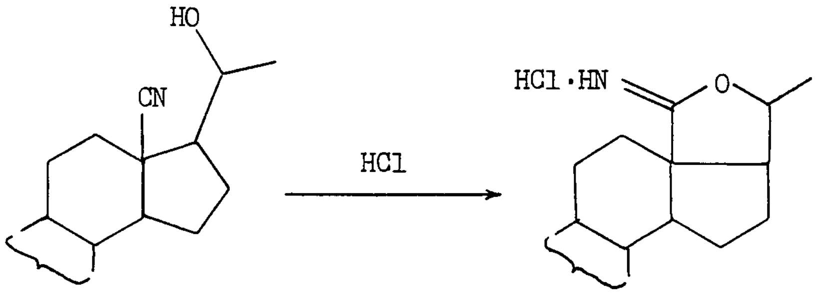
$$\mathrm{RMgBr + R'{-}\underset{\underset{O}{\|}}{C}{-}NHPh} \longrightarrow \mathrm{RR'C{=}N{-}Ph}$$

2.6 Addition Reactions of Nitriles

The controlled addition of hydrogen in the catalytic hydrogenation of nitriles to form imines is very difficult to control due to secondary reactions. However, the reduction using $LiAlH_4$ is much more controllable and, in some cases, imines can be obtained in good yields.

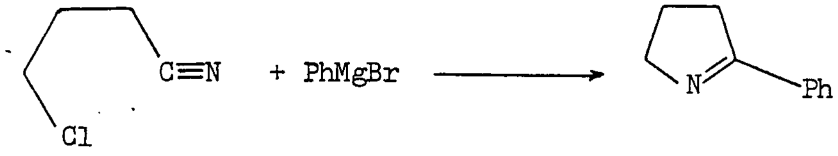
Alcohols, thiols, and amines add to nitriles to form imines.

Eq-14[15]



One of the most attractive methods for preparing imines is by addition of a Grignard reagent to a nitrile.

Eq-15[16]



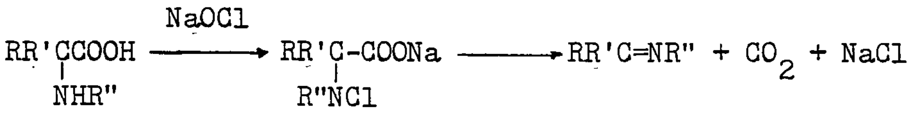
2.7 Oxidation of and Elimination from Nitrogen Compounds

Oxidation or dehydration processes are only seldomly used to prepare imines, since it is difficult to control the reactions and usually secondary products are obtained. Both primary[17] and secondary[18] amines may be oxidized by hypochlorites to imines. The reaction proceeds through a N-chloramine intermediate.

Eq-16

$$R_2CHNH_2 \xrightarrow{t\text{-}BuOCl} R_2CHNHCl \xrightarrow{-HCl} R_2CH{=}NH$$

α-Amino acids[19] also undergo a similar oxidation with hypohalites in which CO_2 and Cl^- are eliminated from the intermediate to give the corresponding imine.

Eq-17 

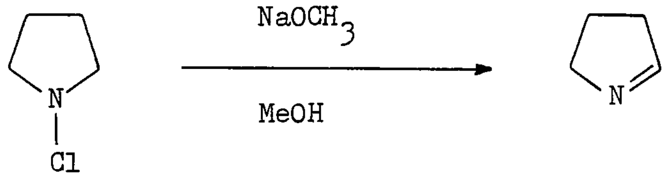
$$\underset{\displaystyle NHR''}{RR'CCOOH} \xrightarrow{NaOCl} \underset{\displaystyle R''NCl}{RR'C\text{-}COONa} \longrightarrow RR'C{=}NR'' + CO_2 + NaCl$$

Other oxidizing agents such as, mercuric acetate, chromic acid, ferric chloride, silver oxide, $S_2O_8^{2-}/Ag^+$, and lead tetracetate are reported to oxidize amines to imines or immonium salts.[8]

Although primary amines give mixtures of products upon catalytic dehydrogenation, secondary amines give imines with Ni, Pt, or Cr catalysts.[8]

Amines which are substituted on the nitrogen by an anionic leaving group X eliminate HX easily to give an imine. N-Haloamines may be eliminated by the action of alkalis or by heating.

Eq-18[20]



Other leaving groups include nitroso,[21-23] nitro,[24] tosyl,[25-27] benzoyloxy,[28] and arylsulfonyloxy.[29]

2.8 Rearrangements

Various kinds of compounds containing C=N groups have been synthesized using rearrangement reactions. The simplest type of rearrangement to give C=N is a prototopic shift which is spontaneous in most cases. These include the azo-hydrazo shift (Eq-19), enamine-imine transformation (Eq-20), C-nitroso-oxime shift (Eq-21), and transformation between two isomeric imines (Eq-22).

Eq-19 $$>\text{CH-N=N-} \rightleftharpoons\ >\text{C=N-NH-}$$

Eq-20 $$>\text{C=CH-NH-} \rightleftharpoons\ >\text{CH-CH=N-}$$

Eq-21 $$>\text{CH-N} \rightarrow \text{O} \rightleftharpoons\ >\text{C=N-OH}$$

Eq-22 $$>\text{CH-N=C}< \rightleftharpoons\ >\text{C=N-CH}$$

There are many rearrangement reactions involving nitrene intermediates leading to molecules having C=N groups. Many of these reactions are name reactions such as the Beckmann, Hoffmann, Lossen, Curtius, and Stieglitz rearrangements. These have reviewed recently by Abramovitch and Davies.[30]

3.0 Elimination Reactions[31-33]

3.1 Introduction

The formation of a double bond $>\text{C=X}$, where X is C, N, or S by the loss of HY from $\text{H-}\overset{|}{\underset{|}{\text{C}}}\text{-X-Y}$ is very common in organic chemistry. The reaction is promoted by solvent or a base and is named as the "1,2 elimination reaction" or "β-elimination reaction". There are three main types of mechanism operating in these reactions (Figure 1); a) E1

(Equation 23), b) E2 (Equation 24), and c) E1cB (Equation 25).

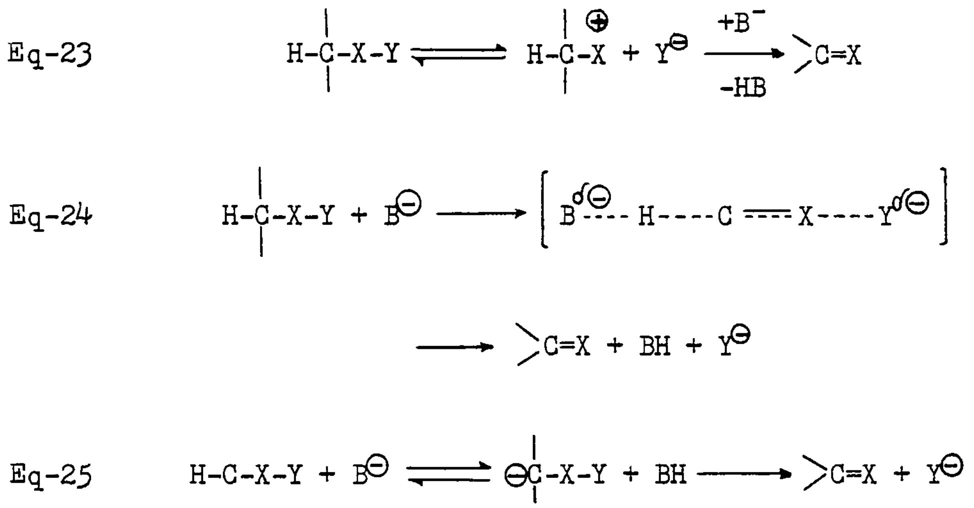
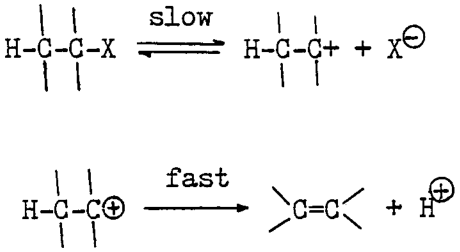


Figure 1 The Mechanisms of β-Elimination Reactions

The formation of carbon-carbon double bonds by 1,2 elimination has been examined extensively, but carbon-nitrogen and carbon-sulfur double bond-forming β-elimination reactions have not been investigated with the same thoroughness. Since carbon-carbon double bond-forming eliminations have been investigated in more detail, the following discussions for the different mechanisms will be given for alkene-forming eliminations.

3.2 The E1 Mechanism

Elimination reactions can occur in the absence of an added base under some conditions. The mechanism by which these eliminations occur is called E1, which stands for elimination-unimolecular. It is a two step process in which the rate-determining step is the ionization of the substrate by the loss of the leaving group to give a carbonium ion intermediate which then in the second step rapidly loses a β proton to give the product.



Step 1:

$$\text{H-C-C-X} \xrightleftharpoons{\text{slow}} \text{H-C-C}^{+} + \text{X}^{\ominus}$$

Step 2:

$$\text{H-C-C}^{\oplus} \xrightarrow{\text{fast}} \text{>C=C<} + \text{H}^{\oplus}$$

For a pure E1 reaction, in which the carbonium ion intermediate is free to adopt its most stable conformation, the elimination should occur in a completely nonstereospecific fashion. That is, the probability of the loss of a β hydrogen from either the same (syn) or the opposite (anti) side of the molecule as the original leaving group, will be equal. The following facts are observed for E1 mechanism:

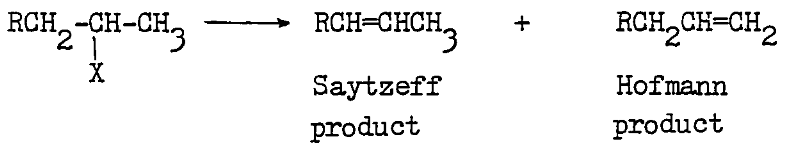
a) The reaction exhibits kinetics which are first order in substrate and zero order in base. Possible involvement of the solvent as a base in the rate-determining step can be checked by adding a small amount of the conjugate base of the solvent. If the rate shows no increase in the presence of this more powerful base, it is highly unlikely that solvent is involved as the base in the rate-determining step.

b) For the reactions performed on two molecules differing only in the leaving group under identical conditions, the ratio of elimination to substitution should be the same, since both will give the same carbonium ion intermediate.

c) The steric environment of the β hydrogen is not important and the thermodynamically more stable olefin is predominantly formed.

d) The reaction is accompanied by rearrangements since the carbonium ion intermediate is susceptible to rearrangement.

For compounds having two different kinds of β protons, two different olefinic products may be obtained. The elimination to give the more highly substituted product of the two is called "Saytzeff orientation" and the one to give the less substituted product is called "Hofmann orientation". Since the transition state for the product-determining step has double bond character, the lowest-energy transition state will be the one leading to the most stable double bond. It is a well known fact that alkyl groups lower the energy of double double bonds through hyperconjugation. Therefore E1 reactions give predominantly the Saytzeff product.

Eq-26 

$$RCH_2\text{-}\underset{X}{\underset{|}{C}}H\text{-}CH_3 \longrightarrow \underset{\text{Saytzeff product}}{RCH{=}CHCH_3} + \underset{\text{Hofmann product}}{RCH_2CH{=}CH_2}$$

So far this discussion has involved symmetrically solvated carbonium ions. It is known that for E1 reactions in solvents of low ionizing power, the generalizations described above do not hold. In solvents of low ionizing power intimate ion pairs are formed. The following observations are made for these kind of systems:

a) The ratio of elimination to substitution products depends on the nature of the leaving group.

b) A syn elimination takes place since the leaving group rather than the solvent acts as the base to remove the β hydrogen.

c) Hofmann products predominate as the leaving group becomes more basic. This can be explained by the Hammond postulate. The more basic the ion which removes the hydrogen, the more the transition state for the product determining step will resemble a carbonium ion and consequently have less double bond character. Therefore the orientation of the double bond will depend more on the acidity of the β hydrogens and less on the relative stabilities of the two possible double bonds. Since alkyl group substitutions will make the hydrogens on the same carbon atom less acidic, the Hofmann product dominates.

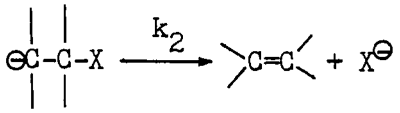
3.3 E1cB Mechanism

Combination of a poor leaving group and a highly acidic β proton may lead to the elimination mechanism called E1cB, which stands for "elimination, unimolecular, from the conjugate base". This mechanism is frequently discussed as an alternative to the E2 mechanism. In many cases, it is very difficult to distinquish between these to mechanisms.

Eq-27

$$B^{\ominus} + H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + {\ominus}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X$$

Eq-28



$$\ominus\text{C-C-X} \xrightarrow{k_2} \text{C=C} + X^{\ominus}$$

Depending on the relative magnitudes for the rate constants, k_1, k_{-1}, and k_2, four distinct kinetic possibilities can be observed. Assuming a steady-state concentration for the intermediate carbanion the overall rate equation for this mechanism can be derived.

Eq-29

$$\text{rate} = \frac{k_1k_2\,[\text{SHX}]\,[\text{B}^{\ominus}]}{k_{-1}\,[\text{BH}] + k_2}$$

3.3.1 $(\text{E1cB})_R$

A limiting case for the E1cB mechanism occurs when k_{-1} is comparable to k_1, but k_2 is quite small ($k_1 \sim k_{-1} \gg k_2$). In this case, the intermediate anion forms from the starting material in a rapid equilibrium and the leaving group departs in a subsequent slow step. The mechanism is called $(\text{E1cB})_R$ ("R" for reversible). The rate equation reduces to:

Eq-30

$$\text{rate} = \frac{k_1k_2\,[\text{SHX}]\,[\text{B}^{\ominus}]}{k_{-1}\,[\text{BH}]}, \text{ when } k \sim k_{-1} \gg k_2$$

The rate is first-order in substrate and first-order in base. The inverse dependence on the conjugate acid of the base concentration makes it easy to distinguish this mechanism from an E2 process. This reaction should be independent of the base concentration if the buffer ratio, $[B^\ominus]/[BH]$, is kept constant. This means it should show specific base catalysis. If the solvent contains deuterium then the reactant, SHX, should become isotopically labeled. On the other hand deuterium labeled reactant, SDX, should rapidly lose its label according to this mechanism.

3.3.2 $(E1cB)_{ip}$

This mechanism is closely related to $(E1cB)_R$. The difference between these two mechanisms is that in $(E1cB)_{ip}$ ("ip for ion-pair) the anion formed does not exist as a free anion, but as an ion pair which collapses to give the products or the reactants without equilibration with the solvent. Therefore, no deuterium exchange is observed with the solvent. Since, $k_2 \ll k_{-1}$ the influence of deuterium at C_β on k_2 (secondary isotope effect) and on k_1/k_{-1} (equilibrium isotope effect) is negligible. Since there is no free anion formed the observed rate is not dependent on $[BH]^{-1}$. This mechanism is more likely to be seen in solvents of low ionizing and solvating power and occurs generally with amine bases.

3.3.3 $(E1cB)_{irr}$

When the leaving group becomes so good that the carbonion formed goes on to give product much more rapidly than it returns to substrate, $k_2 \gg k_{-1}[BH]$, then the abstraction of the proton becomes rate-determining, and the rate equation reduces to:

Eq-31 $$\text{rate} = k_1\,[B]\,[SHX] \quad \text{when } k_2 \gg k_{-1}\,[BH]$$

The reaction is general base catalysed and kinetically indistinguishable from the E2 reaction.

3.3.4 $(E1)_{anion}$

If the acidities of the substrate and conjugate acid of the base are similar and the leaving group is poor, then in the presence of excess base, the substrate will be almost completely converted into its conjugate base, which then will lose the leaving group in a rate-determining step. This leads to a rate expression:

$$\text{Eq-32} \quad \text{rate}(E1)_{anion} = k_2 \left[SHX\right] \quad ; \text{ when} \quad k_1 \gg k_{-1} \left[BH\right] > k_2$$

For this mechanism, the following kinetic predictions can be made: i) there will be a significant leaving group isotope effect or element effect; ii) electron-donating groups on C_α should increase the rate of elimination; iii) electron-withdrawing groups on C_β should retard the elimination, by causing delocalization of the electron pair at C_β and making it less effective in aiding cleavage of the C_α-X bond; iv) if a β-deuterium labeled substrate is used and if $k_{exchange} \gg k_{elimination}$, then complete or extensive exchange with protic solvent is expected. Reactions which follow this mechanism are rare due to the high acidity requirement for the β-hydrogen.

A summary of the various E1cB reaction mechanisms is given in Table 5.[32]

Numerous more or less succesful methods have been developed in an

TABLE 5

Kinetic Predictions for Base-Induced β-Eliminations

Mechanism	Kinetic Order	β-Hydrogen exchange faster than elimination	General or Specific Base catalysis	k_H/k_D	E-with-drawal at C_β Rate:	E-release at C_β Rate:	Leaving group isotope or element effect
$(E1)_{Anion}$	1	Yes	-	1.0	decrease	increase	Substantial
$(E1cB)_R$	2	Yes	Specific	1.0	small increase	small increase	Substantial
$(E1cB)_{ip}$	2	No	General	1.0 ⟶ 1.2	small increase	small increase	Substantial
$(E1cB)_{irr}$	2	No	General	2 ⟶ 8	increase	little effect	small to negligible
E2	2	No	General	2 ⟶ 8	increase	small increase	small

effort to distinquish E1cB mechanisms from the E2 mechanism. The classical method is the isotope exchange. A deuterium exchange between the labeled solvent and unlabeled substrate, or $C\beta$ labeled substrate and the unlabeled solvent is indicative of an E1cB mechanism. But the reverse is not true, $(E1cB)_{ip}$ and $(E1cB)_{irr}$ mechanisms will show no isotope exchange. The rate of reaction by the $(E1cB)_R$ mechanism depends on the buffer ratio $[B^{\ominus}]/[BH]$. Increasing the base concentration without changing the buffer ratio should not affect the rate of the $(E1cB)_R$, but the rate of an E2 or the other E1cB mechanisms should increase linearly. The dependence on the base concentration may change when the buffer concentration is changed. One can expect $k_2 > k_{-1}[BH]$ at low buffer concentrations, but at higher buffer concentrations one may find $k_{-1}[BH] > k_2$ and the reaction will become independent of the buffer concentration, that is Equation-29 will reduce to Equation-30.

The leaving group effect may be used to distinquish between the E2 and $(E1cB)_{irr}$ mechanisms. In the $(E1cB)_{irr}$ process, the only influence of the leaving group on the rate should be through an inductive or field effect. In the E2 mechanism the weaking of the $C\alpha$-X bond should lower the energy of the transition-state below that for a $(E1cB)_{irr}$ stepwise process. This should cause a faster reaction rate than expected from a simple electrostatic effect.

Carbon-halogen bond strengths increase markedly in the series $I<Br<Cl<F$, therefore a concerted reaction should show steeply decreasing relative rates in the order $RI>RBr>RCl>RF$. On the other hand, differences in the inductive effect should be rather small, so that the effect on the relative rates of an $(E1cB)_{irr}$ process should be minor.

When the leaving group is a substituted benzensulfonate group, its effect on rate will be indicative of the mechanism. Hammet rho values for a concerted reaction should be moderately large, but for a E1cB mechanism (the substituent being sufficiently remote from the site of proton removal) should be very small. The difficulty in this method lies in the fact that it is very hard to say when the Hammet rho value is small enough to indicate no weakening of the carbon-leaving group bond.

The acidity function, H-, has been suggested for distinguishing between $(E1cB)_R$ and $(E1cB)_{irr}$ or E2 mechanisms. Anbar, <u>et</u>. <u>al</u>.[34] have derived relationships between H- and rate to be expected for the two cases. For a fast, reversible equilibrium followed by a slow rate determining step, log k_{obs} follows H_- and for $(E1cB)_{irr}$ or E2 log k_{obs} follows $H_- + \log [H_2O]$. The actual cases are more complex than this simple relationship indicates.

3.4 E2 Reaction Mechanism

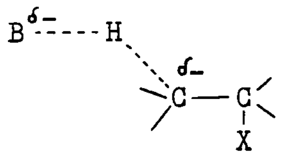
Unlike the other two mechanisms, E1 and E1cB, the E2 mechanism is a one step reaction. That is the C-H and C-X bond-breaking and C=C bond forming all occur at the same time. It has been found that the rates for these reactions are a) second-order, first-order in substrate and first-order in base; b) decreased for C_β deuterium substituted substrates; and c) strongly dependent on the character of the leaving group. The substituent and isotope effects suggest that there must be a spectrum of transition states with varying extents of C-H and C-X bond breaking.

3.4.1 The Variable Transition State Theory

The E2 transition state involves a concerted breaking of a carbon-hydrogen bond and carbon-leaving group bond and formation of a carbon-carbon double bond. To explain the experimental data, the variable transition state theory suggests that the balance and timing of the bond-making and bond-breaking processes involved may vary depending upon the reactant structure and reaction conditions while the mechanism remains a single-step E2 process without any detectable intermediates. That is one or more of the process of C-H and C-X bond breaking and C=C bond formation may be farther advanced than the others at the transition state and the less advanced ones catch up during the subsequent downhill path to the products. The possible variations in the transition state structure will be discussed in the following three sections.

The E1cB-E1 Elimination Spectrum

One can imagine a spectrum of E2 transition states. At one extreme there is the E1cB-like transition state, 2, in which only the C-H bond is extremely stretched through synchronous or central transition states, 3, in which both C-H and C-X bonds are equally stretched with considerable C=C formation, to the E1-like transition state, 4, in which only the C-X bond is extremely stretched, on the other extreme.



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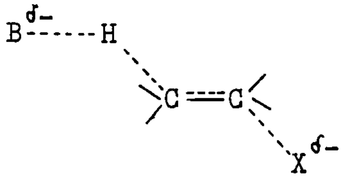

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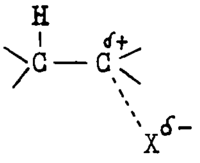

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The transition state 2 possesses carbanion character. Therefore it should be stabilized by electron-withdrawing and destabilized by electron-donating substituents on C_β. The central transition state 3 has double-bond character and should be stabilized by the factors which stabilize the final product. On the other hand, the transition state 4 possesses carbonium-ion character on C_α and therefore should be stabilized by the factors which stabilize carbonium ions.

Reactant-like to Product-like Transition States

Even though the amount of bond-breaking for C-H and C-X can be equal, the extent of such rupture may vary. This will result in varying degrees of double bond formation. Thus, if each bond, C-H and C-X, is only 25% ruptured the double bond formed will be only 25%, resembling the reactants. On the other hand, a 75% bond rupture of the C-H and C-X bonds will give a 75% double bond formation and the transition state will resemble the products. Therefore, a spectrum of transition state of the central type is possible. Figure 2 summarizes these transition state types as well as those from the previous section.

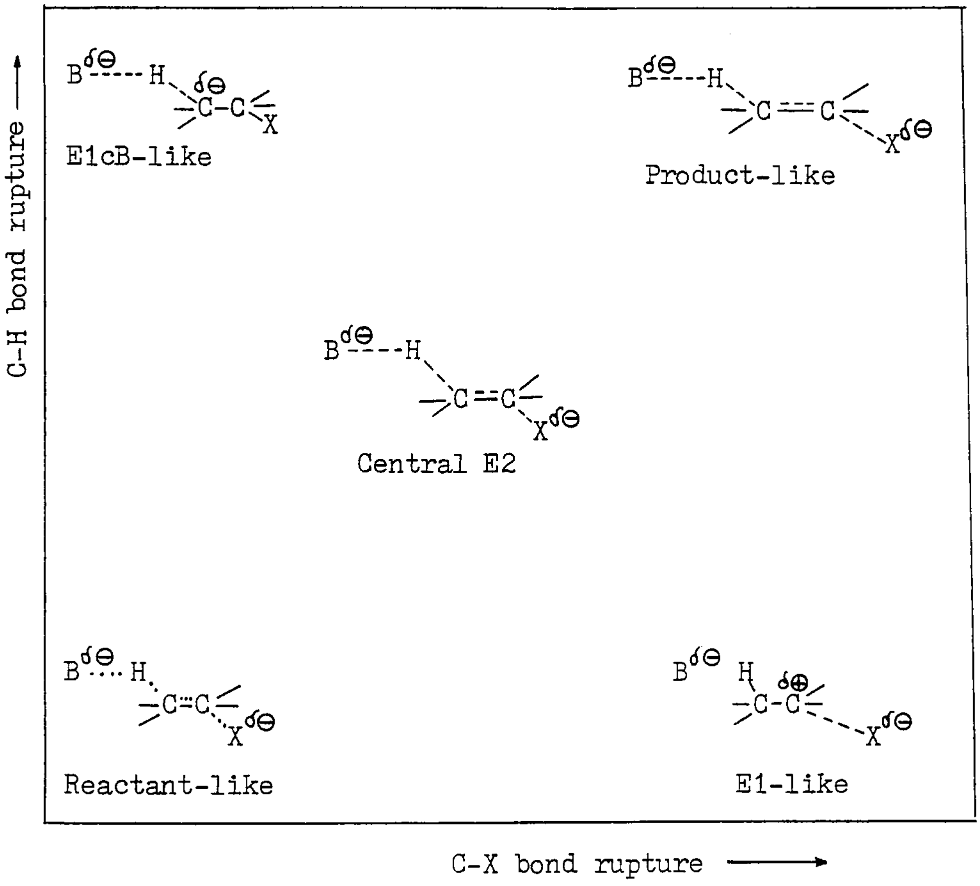
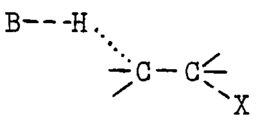


Figure 2 E2 Transition States

E2H and E2C Transition States

It is generally assumed that strong bases are more effective than weak bases in promoting elimination reactions. But it was found by Winstein and Parker[35] that not only strong proton bases (hard bases) but also weak bases (weak toward hydrogen but strong toward carbon, soft bases) are effective in promoting certain elimination reactions. To explain this behaviour Winstein and Parker devised a spectrum of transition states for E2 reactions.



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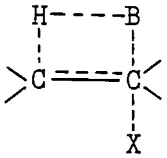

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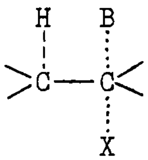

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They proposed that hard bases attack on hydrogen to give the E2H transition state, 5, on one extreme. On the other extreme, soft bases attack on C_α to give E2C transition states, 7. The actual transition state in most elimination reactions falls between these extremes and is represented by a structure such as 6. When hard bases are used for the elimination reaction, the rate depends on the proton basicity of the reagent (Equation 33). On the other hand, when soft bases are used, the rate depends on the nucleophilicity of the reagents which can be expressed by their ability to perform S_N2 reactions (Equation 34).

Eq-33 $$\log k^E = \log pK_A + \text{constant}$$

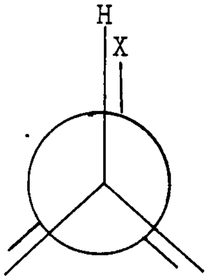
Eq-34 $$\log k^E = X \log k^S + \text{constant}$$

Parker and Winstein have surveyed substituent effects in E2H and E2C reaction mechanisms. From product distributions and overall rates the partial rates for elimination and substitution processes were determined. They have found methyl groups at both C_α and C_β accelerate the E2C reactions, but hinder or have little effect on the E2H reactions. A phenyl group at C_β has the same effect as methyl on an E2C reaction, but strongly accelerates an E2H reaction. On the other hand, a phenyl substituent at C_α accelerates an E2C reaction, but has little effect on an E2H reaction. The substituent effects and the effect of changing solvents on rates suggest that the E2C transition state must be rather loose (both base and leaving group must be highly solvated) and the transition state must have highly developed double bond character. The latter point was also demonstrated by the orientation data, in which the proportion of the more stable alkene approaches the equilibrium mixture of product alkenes. It was also suggested that the low kinetic deuterium isotope effect on C_β in E2C mechanism was due to the nonlinear configuration of the C·····H·····Base bond in the transition state.[33]

3.4.2 The Stereochemistry of E2 Reactions

In general, atoms in a transition state prefer to occupy certain definite positions with respect to each other. The reaction site of an E2 process involves four atoms from the substrate and one atom from the base.

There are two extreme cases for the arrangement of the leaving group X and the β-hydrogen with respect to each other on the same side of the molecule, 8, or on the opposite sides of the molecule, 9. The dihedral angle between C-X and C-H bonds is approximately 0° for 8 and this arrangement is called syn-periplanar. Whereas in the other extreme, the dihedral angle is 180° for 9 and the arrangement is designated anti-periplanar. There are two more intermediate conformations: syn-clinal, 10, and anti-clinal, 11, with dihedral angles of 60° and 120°, respectively.



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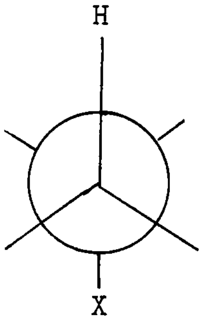
Syn-periplanar
(syn)



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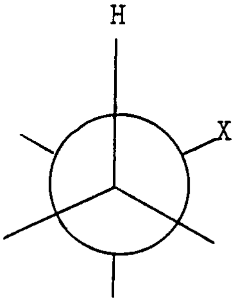
Anti-periplanar
(anti)



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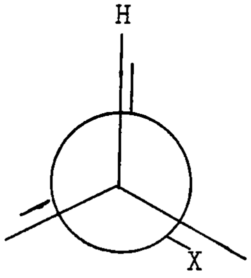
Syn-clinal



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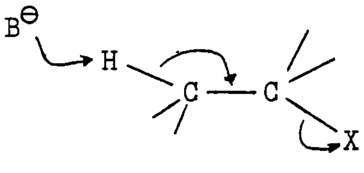
Anti-clinal

The dihedral angles given for each structure generally include all the angles $\pm 30^{\circ}$ from the stated one. It is usually impossible, except for structurally rigid compounds, to distinquish experimentally between syn-periplanar and syn-clinal on the one hand and anti-periplanar and anti-clinal on the other.

When possible, E2 elimination reactions generally prefer the anti configuration. Hückel[37] proposed that electrostatic repulsion in the syn configuration between the base and the leaving group would make this configuration less favorable than anti. However, the results of his calculations could not account the large difference between anti and syn eliminations.

Another explanation involves quantum chemical reasoning. During the course of the reaction, the α- and β-carbon atoms rehybridize from sp^3 to sp^2, and the C-H and C-X σ-bonds become p-orbitals to form the π-bond. The best overlap could be obtained either for syn-periplanar or anti-periplanar arrangements. Eliel, et. al.[38] made the analogy that the anti-periplanar conformation is like a linear conjugated system. such as butadiene. On the other hand, the syn-periplanar conformation resembles cyclobutadiene. Since the former is of lower energy, the anti-periplanar conformation should be preferred.

The most common electronic argument for the prefence of anti elimination is that the electrons of the C-H bond are performing a displacement of the leaving group like in an S_N2 reaction. By analogy, since a backside attack is preferred in a S_N2 reaction, the anti-periplanar conformation in an E2 reaction should be preferred, 12.



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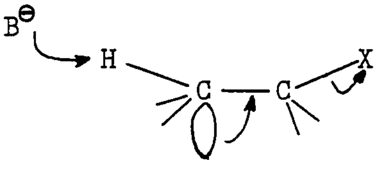

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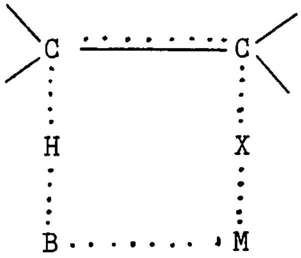
One can arrive at the same conclusion when the argument is done in terms of electron repulsion effects. The electrons in the C-H and

C-X bonds will prefer to stay as far apart as possible during the progress along the reaction coordinate. This is best accomplished by an anti arrangement. An exception is when the C-H bond is so ionic that there is greater electron density on the opposite side of the C-H bond. This would lead to the syn configuration, 13. The preferred backside attck will be done by the back lobe of the C-H σ-bond as shown in 13. This also predicts a syn configuration.

It is found that syn elimination is possible for E2H reactions when: a) the structure permits a syn-periplanar but not an anti-periplanar conformation; b) a syn hydrogen is more reactive than the anti one; c) elimination is preferred due to steric reasons (the anionic base used remains coordinated with its cation which also coordinates to the leaving group). The transition state for the last case is shown in 14.



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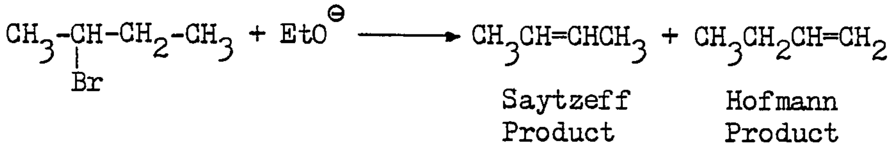
3.4.3 Orientation in E2 Reactions

Whenever the possibility exists for obtaining two or more different olefins from a single substrate, the problem of orientation arises. When the substrate has two different types of β-hydrogens, the two possible products will have the carbon-carbon double bond in different positions. This kind of orientation is called positional orientation. An example for this kind orientation is the reaction of 2-butyl bromide with a base which can give either 2-butenes or 1-butene (Equation 35).

Eq-35 

$$CH_3-\underset{Br}{\underset{|}{C}}H-CH_2-CH_3 + EtO^{\ominus} \longrightarrow \underset{\text{Saytzeff Product}}{CH_3CH{=}CHCH_3} + \underset{\text{Hofmann Product}}{CH_3CH_2CH{=}CH_2}$$

Another category of orientation is geometrical orientation. The 2-butene, for example, in Equation 35 will be a mixture of trans- and cis-2-butenes.

The factors which control orientation are very important from a synthetic chemist's point of view, since proper choice of reaction conditions will enable him to obtain the maximum yield of the desired isomer of the product. It is also important from a theoretical point of view since it gives valuable information on relative reactivities. All the reaction paths of a given substrate have the same ground state. Therefore, for the product proportions reflect the relative free energies of the different transition states. This enables one to discuss the various available paths of a substrate under given specific reaction conditions. On the other hand, it is difficult to compare results obtained for a different substrate or for the same substrate under different reaction conditions.

Saytzeff and Hofmann Orientations

When positional isomerism is possible and if the preferred olefin is the one bearing the greater number of alkyl groups on the double bond, then the reaction is said to give "Saytzeff orientation". It is known that these olefins are almost always thermodynamically more stable than the others. One can conclude that the transition states of the E2 elimination reactions which give Saytzeff orientation possess sufficient double-bond character so that they are stabilized by the same factors that stabilize the product alkenes.

It has been found that in elimination reactions when the substrate is a tetraalkylammonium hydroxide[39,40] or trialkylsulfonium hydroxide[41] the less substituted alkene is formed instead of the more highly subsituted alkene. These reactions are said to give "Hofmann orientation".

It has been found that in elimination reactions of a number of quaternary ammonium hydroxides, the first alkyl substitution of the β-carbon atom causes a dramatic decrease in relative rate of elimination.[42] The second alkyl substitution or the lenghthening the alkyl chain has rather minor effect. Also α-alkyl substitution does not have the same effect as β-alkyl substitution. In $(CH_3CH_2)R_1\overset{+}{N}Me_2{}^{-}OH$, where R_1 is either isopropyl or tert-butyl, R_1 is lost more readily than the ethyl group.

Several explanations were suggested to explain these observations. It was argued that these positively-charged leaving groups increase the acidity of the β-hydrogens by an inductive effect and β-alkyl substituents will counteract this and therefore decrease the rate.[43] Similarly, it was suggested that since trialkylammonio and dialkylsulfonio groups are relatively poor leaving groups, there is a considerable negative charge build-up on the Cβ in the transition state.[44] The transition state will have considerable carbanion and limited double-bound character. Therefore, electron-repelling alkyl groups on the β-carbon atom will destabilize this transition state and reduce the rate. A different kind of explanation was given by Brown.[45,46] He suggested that the steric interactions between the leaving group and the β-alkyl substituents in the transition state for an anti elimination are important particularly for a large leaving group like trialkylammonio. Therefore, the more substitution on Cβ, the more interaction, and the slower is the reaction rate. A word of caution about this latter explanation is in order. Although there is no doubt that steric effects contribute to some extent to Hofmann orientation, its mode of action cannot be as simple as described above because it is known that the eliminations from quaternary ammonium salts often occur with mixed anti and syn stereochemistry.

3.4.4 The Effect of Structure and Reaction Conditions on Orientation

The Leaving Group Effect

The two alternative explanations for Hofmann orientation were given in the previous section. The attempt will be made to distinguish between these two theories.

The products from the reactions of pentyl halides with ethoxide ion in ethanol are given in Table 6.[47]

TABLE 6

Products from Reactions of 2-Pentyl Halides with $EtO^-/EtOH$

Halide	%1-Pentene	trans/cis-2-Pentene
F	82	2.6
Cl	35	3.5
Br	25	3.8
I	20	4.1

The expected order for the steric requirements for the leaving group is F<Cl<Br<I. On the other hand, the difficulty of heterolytic bond breaking of C-X should be F>Cl>Br>I. Some question has arisen concerning the steric requirements of the various halogens. In monohalocyclohexanes, the prefence for an equatorial halogen atom is found to be F<I<Br<Cl;[48] whereas for 3,3-dimethyl-halocyclohexanes this order was calculated to be F<Cl<Br<I.[49] In either case, fluorine is the smallest hydrogen. Therefore the difference in percent of 1-pentene between the fluoride and the other halides is inconsistent with the steric theory.

It is evident that the variable transition theory can be used to rationalize the observed results.

Bartsch and Bunnett[50-52] have determined rates and products of elimination from 2-hexyl derivatives with wide variety of leaving groups. They have found that the olefin product ratios obtained from the 2-hexyl halides were in excellent accord with the variable E2 transition state theory, provided that the 2-hexyl iodide transition states were central or toward the E1cB-like side. As the leaving group becomes poorer, I ⟶ F, the transition state shifts toward E1cB-like extreme, with consequent decrease in both 2-hexenes/1-hexene and trans/cis ratios. They have demonstrated that a relationship between orientation and reactivity (the logarithm of 2-hexene/1-hexene or trans-/cis-2-hexene versus the logarithm of rate of formation of 1-hexene) exists, but is perturbed by other factors which may be partly steric.

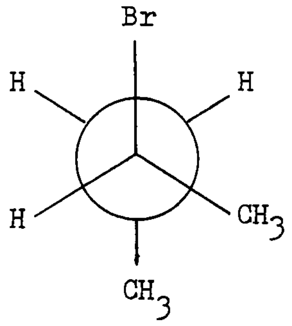
Experiments in which steric effects were held constant and the electronic effects of the leaving group varied are inconclusive. The results of Colter and Johnson[53] obtained for 2-pentyl m- and p-substituted benzenesulfonates showed the expected selectivity as predicted by the variable transition state theory. However, the changes were barely beyond experimental error. The overall change in orientation was larger for the 2-methyl-3-pentyl arenesulfonates, but the trend was irregular.[54] The conclusions drawn from these experiments was that the inductive effect of the uncharged leaving group on the acidity of the β-hydrogen cannot be an important factor.

It has been found that the more reactive leaving groups give higher trans/cis ratios. Since better leaving groups give transition states with more double bond character, they will be more susceptible to eclipsing effects, and more _trans_- than _cis_-isomer will be formed. There are instances where this explanation does not hold. Sometimes _trans_/_cis_ ratios change without concominant change in positional orientation. This means the factors controlling geometrical and positional orientation are not necessarily the same. Most of these irregularities in the _trans_/_cis_ ratios are attributed to the effects of base/solvent or to the variations in mechanism.

Substituent Effects

In previous sections, the effects of β-substituents in Hofmann and Saytzeff orientations were explained using electronic and steric effects. The electronic effects of alkyl substituents can be exerted as an inductive effect on the developing charge in the transition state or they can stabilize a developing double bond in the transition state. The steric effects can be observed in α- and β-alkyl group interactions (eclipsing effects), or α- or β-alkyl group and leaving group or attacking base interactions. Since the electronic effects have been discussed earlier, this section will be devoted to the steric effects.

Even for a simple system such as 2-butyl bromide steric effects may operate. The most stable conformation of 2-butyl bromide is _15_ but for an anti elimination the molecule should take either conformation _16_ or _17_. On the other hand, a methyl hydrogen can become anti to bromine without disturbing the stable conformation _15_. This should results in 1-butene as product. Since 2-butene is the preferred



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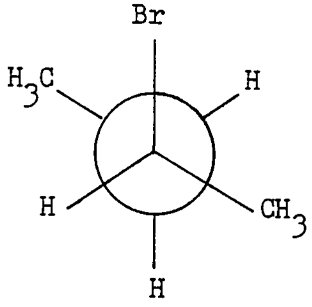

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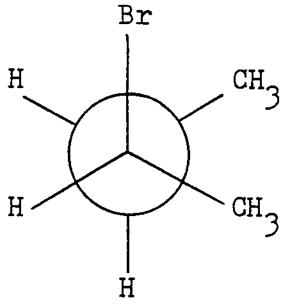
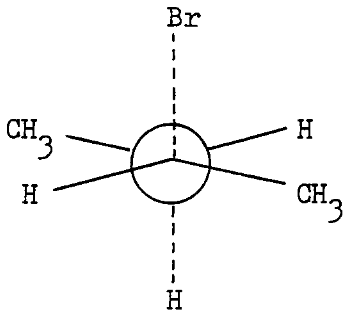


17

product, the conformational stabilizing effect for elimination from 15 must not be very important in this case. *trans*-2-Butene and *cis*-2-butene will arise from conformations 16 and 17 respectively. Since the steric interactions in conformation 16 are less than those in 17, more *trans*- than *cis*-2-butene should be obtained. These arguments are based on a reactant-like transition state. In product-like transition states, the α- and β-carbon atoms will be nearly sp^2-hybridized and the geometry of transition state for anti elimination may be represented by either 18 or 19.



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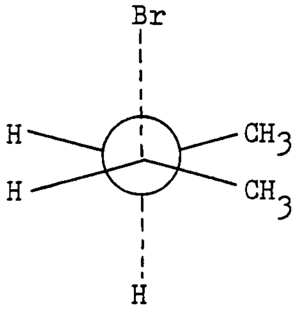
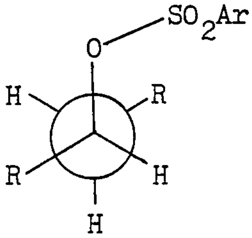


19

Even though the interactions between the leaving group and alkyl groups are minimized, the interactions between the alkyl groups increases in going from the ground state to the transition state. Therefore, both of these arguments predict the trans/cis ratio will be greater than one. A trans/cis ratio close to or below unity suggests the operation of some other factor than alkyl group eclipsing effects.

The eclipsing effect can be important if the only way to relieve a strong alkyl-alkyl interaction is to change the orientation. It has been found that in elimination reactions of $RCH_2C(CH_3)_2Br$ when R is changed from methyl to ethyl to isopropyl to t-butyl, the amount of 1-ene formed increases.[55] This trend can be explained by noticing that the larger the R group the more important is the destabilizing effect by eclipsing. Therefore the 1-ene formation is enhanced since eclipsing effects are not important in its transition states.

When the leaving group is not symmetrical, its preferred conformation may have significant effects on other groups in the transition state. For example, the arenesulfonate leaving group prefers a conformation where the sulfur group is anti to the α-alkyl group, as in 20 and 21. This will result in steric interactions between the leaving



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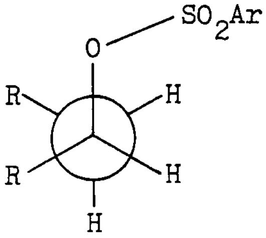

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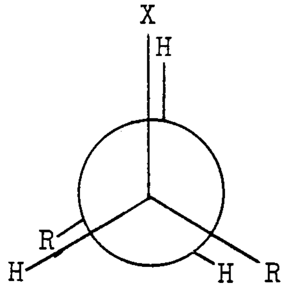
group and the β-alkyl group in transition state 20. It is evident that this kind of interaction is avoided in 21. Therefore the trans/cis ratio should be decreased. In eliminations from 2-halo or 2-tosyloxy substituted hexanes with t-BuOK-t-BuOH, lower trans/cis were observed for the tosylate leaving group.[51] 2-Pentyl tosylate gives lower trans/cis ratios than 3-pentyl tosylate in RO$^-$-ROH (R=n-Bu; s-Bu; and t-Bu) base-solvent systems.[56] These observations are consistent with the presented argument.

A change in the stereochemistry of elimination should result in different steric effects than the ones presented for coplanar anti eliminations. The bonds involved in elimination may not be coplanar. In syn eliminations, the α- and β-alkyl groups are eclipsed even in a reactant-like transition state as shown in 22 and 23. The steric



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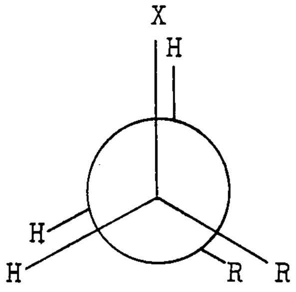


23

interactions will be greater in 23. Therefore there should be a strong preference for the formation of trans over cis olefin in syn eliminations. The trans/cis ratio should be even greater than the one predicted from the relative thermodynamic stabilities of the trans and cis olefin.

So far alkyl substituents and their effects in trans/cis ratios and orientation have been discussed. In general, any group situated on the β-carbon atom which can stabilize either a developing negative charge or a developing double-bond will cause elimination predominantly towards the β-carbon atom bearing this particular group. Whenever there is much carbanion character in the transition state and the steric interactions become important this rule partially breaks down and elimination products into the other alkyl chains becomes more important.

Effects of Base and Solvent

The reactivity of a base in an elimination reaction, or in other proton transfer reactions, depends strongly on the solvent. Most elimination reactions are conducted in protic solvents. An added base will form the conjugate base of the solvent (Equation 36). The rate of

Eq-36 $$\mathrm{ROH} + \mathrm{B}^{\ominus} \rightleftharpoons \mathrm{RO}^{\ominus} + \mathrm{BH}$$

elimination may depend on $[\mathrm{B}^{\ominus}]$, or $[\mathrm{RO}^{\ominus}]$, or both. Only when $\mathrm{B}^{\ominus}$ is very much weaker than $\mathrm{RO}^{\ominus}$ it is safe to assume the involvement of $\mathrm{RO}^{\ominus}$ is insignificant in the elimination process. In order to avoid this complication, it is customary to use the conjugate base of the solvent as the added base. Then, a change in base must be accompanied by a change in solvent. But this leads to the problem of deciding whether the changes are caused by the change of base or the change of solvent or both.

The effect of branched alkoxide in alcohol base-solvent systems on the elimination products from alkyl bromides are shown in Table 7.[57]

TABLE 7

The Olefin Compositions from the Reaction of Alkyl Bromides with RO^- in ROH

	% 1-Ene in the Product when RO^- Is			
RBr	EtO^-	*t*-BuO^-	Me_2EtCO^-	Et_3CO^-
2-BuBr	19	53	-	-
2-PenBr	29	66	-	-
2-$PrMe_2CBr$	21	73	81	92
t-PenBr	30	72	77	88
neo-Pen$(Me)_2CBr$	86	98	-	97

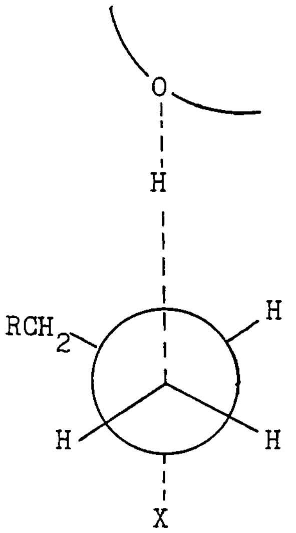
Branching of the alkyl group of the alkoxide causes more terminal olefin to be formed. This has a great synthetic utility. Terminal olefins can be prepared from alkyl bromides without having to prepare the corresponding ammonium or sulfonium salts.

Various groups have attempted to explain the observed positional orientation trends. Brown[58] proposed that the branched alkoxides will have greater steric requirements and this will make the attack on β-hydrogens at interior positions more difficult and hence will reduce the formation of 2-ene. Then 1-ene predominates. Froemsdorf[59] and Bunnett[60] attributed these changes in orientation to the changes in charge distribution in the transition state. They argued that as the base strength increases, C-H bond breaking in the transition state increases and the transition state will have more carbanion character. Since the hydrogens on the terminal carbon atom are more acidic they should be more reactive and hence more 1-ene is produced. Thornton argued that the increase in the yield of 1-ene was due to the reactant-like transition state arising from the attack of strong bases. Such transition states will have less double bond character and will be less susceptible to Saytzeff orientation and the product ratio of the olefins should approach a statistical value with complete loss of preference.

Bartsch[62] has clarified this controversy by demonstrating the effects of base association upon positional and geometrical orientation. For potassium and sodium alkoxides, significant base-counterion pairing exist at synthetically useful base concentrations (Equation 37). It has been found that for eliminations from 2-bromobutane induced by t-BuOK/t-BuOH, positional and geometrical orientation are

Eq-37 $$RO^{\ominus} + M^{\oplus} \rightleftharpoons (RO^{\ominus}M^{\oplus}) \rightleftharpoons (RO^{\ominus}M^{\oplus})_n$$

dependent upon base concentration. It was proposed that both dissociated and associated base species are important in this base/solvent system. The greater 1-butene yield and lower *trans*/*cis* 2-butene ratios observed at higher base concentration are postulated to arise from a greater portion of elimination being promoted by associated *t*-BuOK. Addition of a complexing agent, dicyclohexano-18-crown-6, which should shift the equilibrium in Eq-37 to the left (dissociated base), results in the reverse trend. That is, a lower 1-butene yield and higher *trans*/*cis*-2-butene ratio are observed. The effects of base association are attributed to the steric destabilization introduced by large aggregates of alkali metal-alkoxide ion pairs in the transition states 24-26. The steric interactions should increase in the order 24<25<26. As the steric requirements of base aggregates increase the transition



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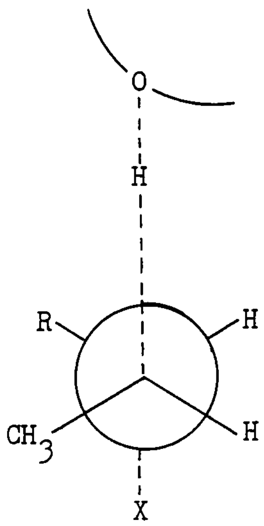

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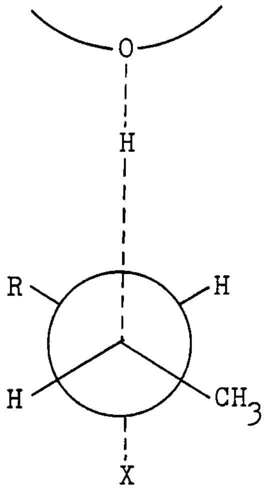
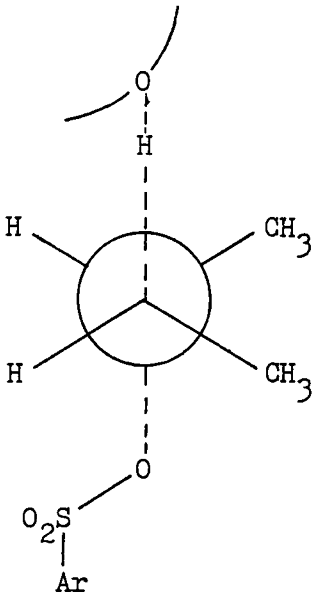


26

state 24 will be favored and the percentage of 1-butene will increase. In 25 the bulky base can be tilted away from alkyl groups which should lessen the steric destabilization due to alkyl group-bulky base interactions. The transition state 26 cannot do this and, therefore, the formation of cis-2-butene should be favored. According to this theory, the change from a dissociated base to a bulky associated base should increase the percentage of 1-alkene and decrease the trans/cis-2-alkene ratio. The experimental observations verifty this prediction.

Bartsch[62] has also shown that a linear relationship exists between free energy differences for formation of 1-butene and trans-2-butene (or cis-2-butene) and pK_a of conjugate acids of variety of anionic oxygen, nitrogen, and carbon bases in Me_2SO (a solvent which should suppress complicating base association). It was concluded that the fundamental control of positional orientation is by base strength, not size, for dissociated bases. Therefore, steric effects of the base are only important for associated bases and highly ramified for dissociated bases.

Using the same approach, Bartsch[62] has rationalized low trans/cis ratios obtained in eliminations of 2-alkyl tosylates induced by $RO^{\ominus}/ROH$ (R=n-Bu, s-Bu; t-Bu).[51,56,62] It was suggested that the transition state 27 will be lower in energy than 28 for an associated base and cis isomer will predominate. When dicyclohexano-18-crown-6 was added, the trans/cis ratio increased as it should for a dissociated base.



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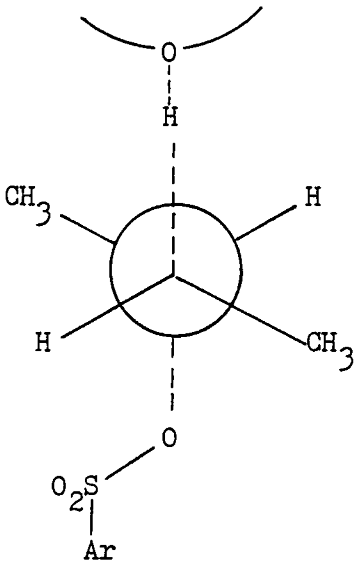


28

3.5 Carbon-Nitrogen Double Bond Forming Eliminations

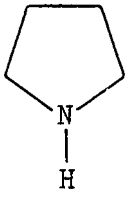
There are relatively few examples in the literature for carbon-nitrogen double-bond forming eliminations.[20-29,63-69] Kinetic investigations of base-promoted imine formation are even scarcer.[70-75] Recently, Bartsch and Cho measured positional isomerization in eliminations from N-chlorobenzyl-*n*-butylamine induced by several base-solvent systems (RO^--ROH, where R= Me, Et, and *t*-Bu, and *t*-BuOK-hexane).[74] A regiospecific elimination to give the conjugated imine was observed. This was attributed to considerable carbon-nitrogen double-bond development in the transition states. Dehydrochlorination of N-chloro-benzylmethylamines induced by MeONa-MeOH and *t*-BuOK/ *t*-BuOH base solvent systems also give exclusively the conjugated imine.[75] In this system, Bartsch and Cho found Hammet ρ values +1.52 and 1.68, primary deuterium isotope effect values of 6.0 and 5.9, and leaving group element effects, k_{Br}/k_{Cl}, of 11.9 and 10.8 for reactions with MeONa-MeOH and t-BuOK/t-BuOH, respectively. From these results, these authors concluded that the transition states for base-promoted eliminations from N-chlorobenzylmethylamine have appreciable C-H and N-Cl bond breaking, significant carbon-nitrogen double bond character, and limited carbanionic character. Thus the transition states lies somewhat to the E1cB side of central in the spectrum of E2 transition states. A 1000-fold rate enhancement was observed over closely-related olefin-forming eliminations. This rate difference was attributed to enthalpic (energy of bond-making and bond-breaking) factors, since the entropies for the closely related imine- and olefin-forming eliminations were found quite similar. When the base was changed from disassociated (MeONa-MeOH) to associated (t-BuOK-t-BuOH), the Hammet ρ value increased slightly and the primary deuterium isotope effect value remained the same. A similar change in base-solvent for eliminations from 1-phenyl-2-propyl bromide resulted in a large decrease in the Hammet ρ values. Also this change in base-solvent system for eliminations from 1-phenyl-2-propyl chloride produced a large increase in k_H/k_D. It was concluded that the imine-forming transition states were relatively insensitive to change in base-solvent system.

4.0 Pyrrolidines and 1-Pyrrolines

4.1 Natural Occurrence

The pyrrolidine ring occurs in nature in various oxidation states.

Pyrrolidine, 29, and 1-pyrroline, 30, and their derivatives will be covered in this discussion. Honneger[76] has found the parent amine, 29 is one constituents of the unbound volatile amines in brains of pig and cat. 1-Pyrroline, 30, has been detected among the volatile constituents of the white bread crust.[77] One of volatile nitrogeneous bases emanating from desert Locust (Schistocerca Gregaria) has been found to be 1-pyrroline.[78] Hasse and Maisack[79] have suggested that 1-pyrroline is formed from putrescine (1,4-diaminobutane) by an enzymatic oxidation (diamine oxidase).



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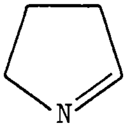

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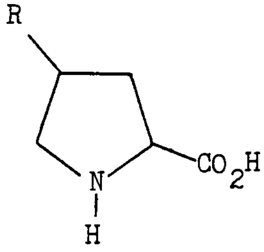
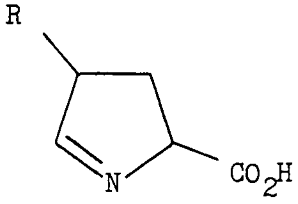


31

a) R=H
b) R=OH
c) R=Me



32

a) R=H
b) R=OH

Proline, 31a, is one of the non-essential amino acids (those which can be formed within the human body). Proline 31a, and 3-hydroxyproline, 31b, are important constituents of collagen which found in insoluble proteins.[80] 1-Pyrroline derivatives, 1-pyrroline-5-carboxylate 32a and 1-pyrroline-3-hydroxy-5-carboxylate 32b, have been proposed as intermediates in the formation of proline and

3-hydroxyproline from and metabolization to glutamate (Figure 3).[80-88]

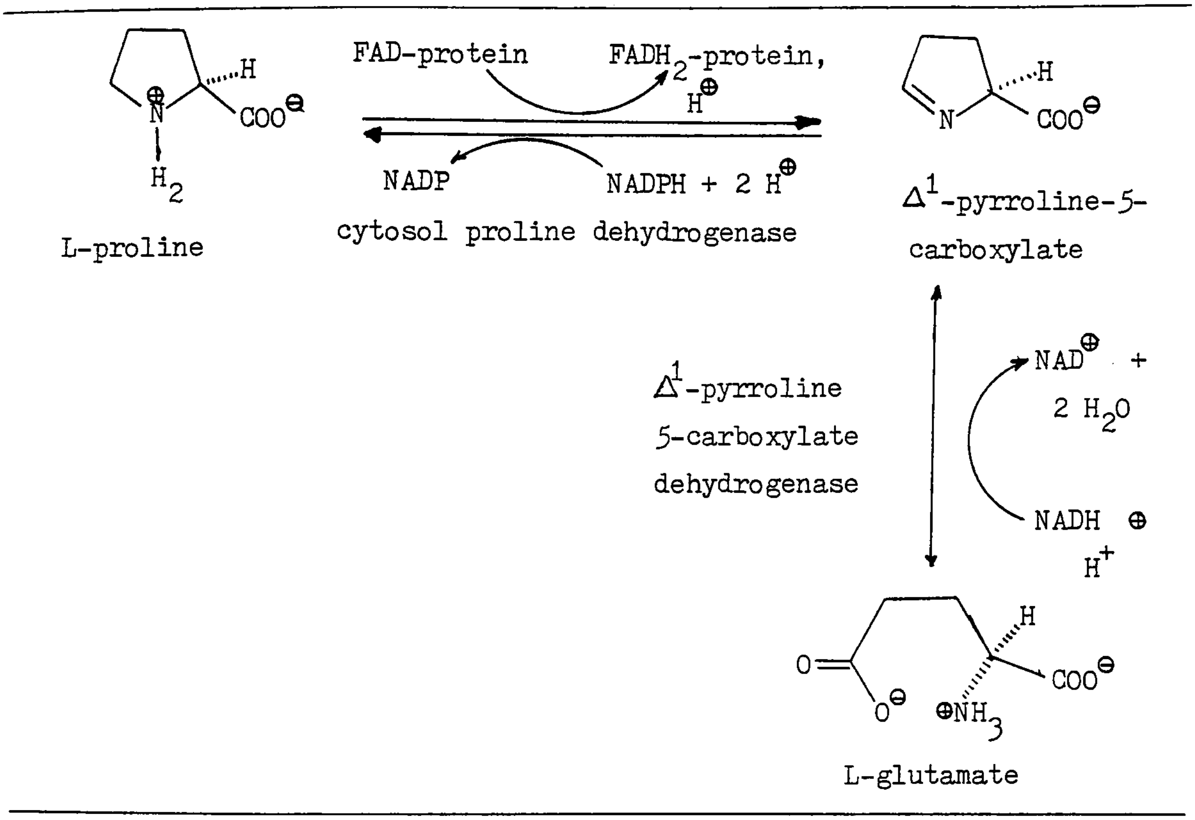
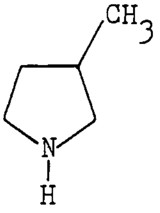


Figure 3[81] Proline, Formation from or Conversion to Glutamate

Proline, 3-hydroxyproline, and 3-methylproline have also been isolated from plants.[89]

A large number of structurally diverse alkaloid skeletons incorporate various perturbations of the pyrrolidine ring system.[90-94]

The presence of pyrrolidine, N-methylpyrrolidine, N-methylpyrroline in tobacco has been established.[91] 3-Methylpyrrolidine, 33, found in black pepper (Piper nigrum)is classified as terpenoid alkaloid.[93] Other pyrrolidine alkaloids include hygrine, 34, hygroline, 35, and cuscohygrine, 36. The alkaloids obtained from tobacco contain a number of pyridine alkaloids which have a pyrrolidine ring. These include



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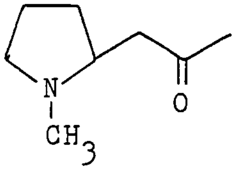

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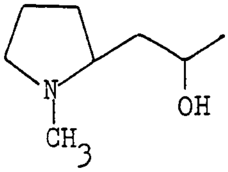

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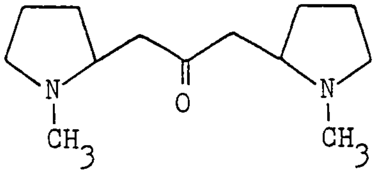

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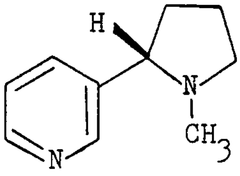
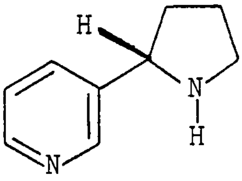


37

nicotine



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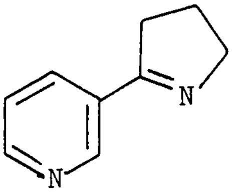
nornicotine



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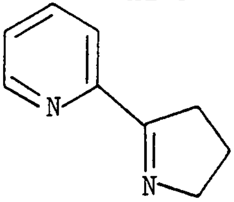
myosmine



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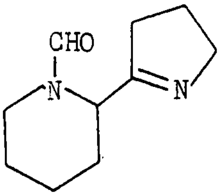
apoferrrorosamine



41

smipine

Figure 4 Some of the Alkaloids Containing a Pyrrolidine or Pyrroline Ring nicotine, 37, nornicotine, 38, myosmine, 39, and apoferrorosamine, 40. Recently, Djerassi[95] has isolated a novel piperdyl alkaloid, smipine, 41, which has a completely reduced pyridine ring from *Lupinus formosus*.

1-Pyrroline, 30, and the N-methyl-1-pyrrolinium cation, 42 have been proposed as intermediates in the alkaloid biosynthesis.[90,93] Figure 5 shows the proposed paths for the biosynthesis of nicotine.

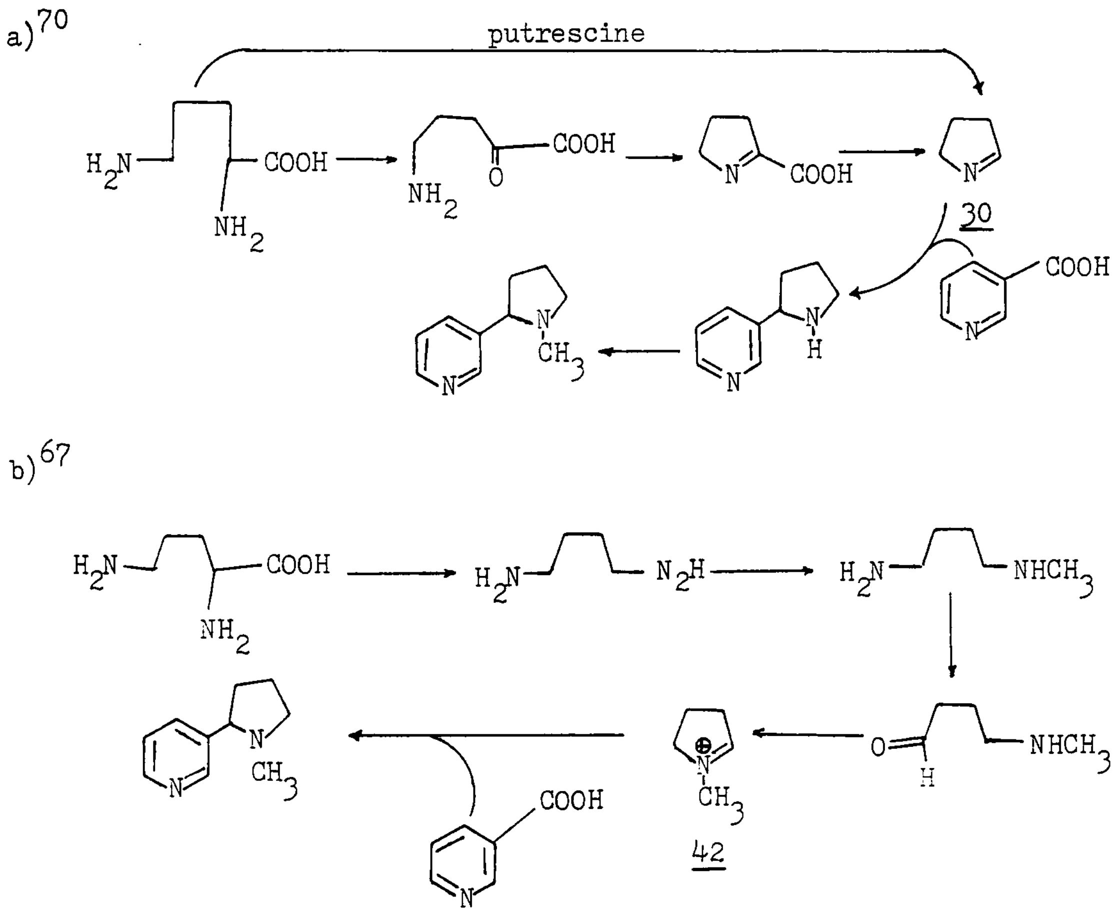


Figure 5 Pathways to Nicotine

Pyrroline, 30, and its derivatives have been used for synthesis of alkaloids.[90,96-99] The synthesis of erythriane in Figure 6 is given as an example.

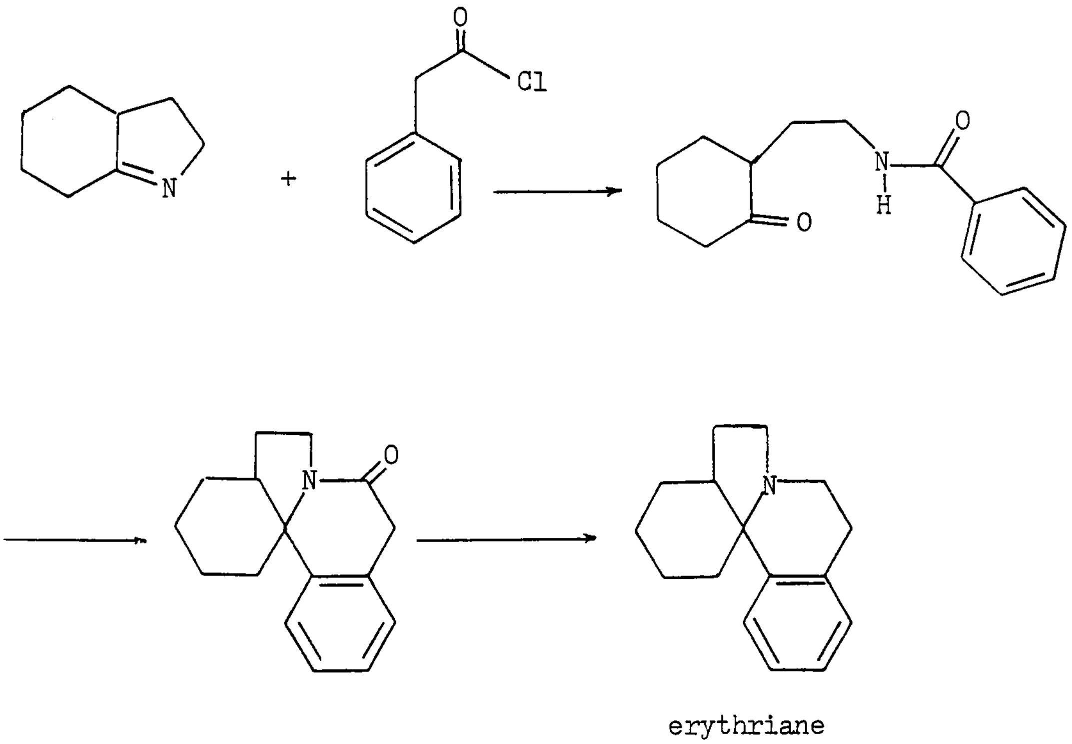
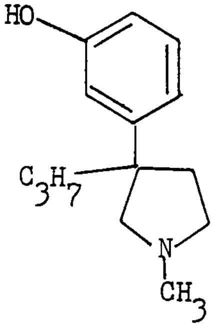


Figure 6 Synthesis of Erythriane

Pyrrolidine is a chemical attraction agent for the olive fly (Dacus oleae Gmel)[100] and also in its cationic form[101] has fungistatic activity against germination of Penicillium digitatum spores. Pyrrolidines show analgesic characteristics. Bowman[102] has prepared a potent analgesic, Profadol, 43.

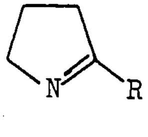


43

4.2 Synthesis of 2-Substituted Pyrrolines

4.2.1 Introduction

One can formulate five different structures for a 2-substituted pyrroline (44-48) depending upon the position of the double bond. Only one structure is possible for 2-substituted pyrrolidine (49). The compounds 44 and 45 are called 1-pyrrolines or Δ^1-pyrrolines, 46 and 47 are 2-pyrrolines or Δ^2-pyrrolines, and 48 is 3-pyrroline. The current interest lies in 1-pyrrolines (44 and 45). There has been a controversy concerning the structures of 1- and 2-pyrrolines. Early workers in the field arbitrarily assigned a Δ^2 structure to their compounds. Using spectroscopy Witkop[103] concluded that the structure of



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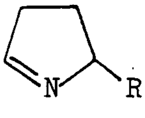

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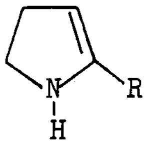

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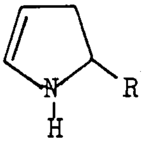

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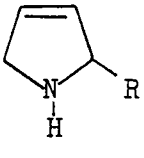

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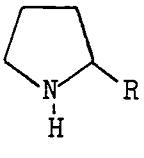


49

these compound should be Δ^1 rather than Δ^2 and suggested there are no authentic 2-pyrrolines. Maginnity and Cloke,[104] using the Zerevitinov method of determining active hydrogen, have shown that these compounds should have a Δ^1 structure. However an anomaly still exists. Evans[105] has noted that even carefully-dried 2-methyl-1-pyrroline has a weak band at 3.02μ in its infrared spectrum where N-H and O-H absorption lies, but Maginnity and Cloke[104] found no active hydrogen for this compound. In spite of this discrepancy, the universally accepted structures for these compounds are now Δ^1.

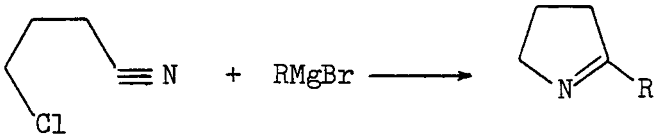
Several 2-substituted-1-pyrrolines, 44, can be found in the literature. The only example for the structure 45 is Δ^1-pyrroline-5-carboxylic acid, 32a. This compound has been synthesized from γ,γ-dicarbethoxy-γ-acetamidobutyraldehyde, but no proof for its structure has been given except its reaction with o-amino-benzaldehyde and and catalytic reduction to proline.[84,88] A Δ^1-pyrroline-2-carboxylic acid should give the same reactions. Therefore it is safe to say that to our knowledge no authentic 1-pyrroline corresponding to the structure 45 has been synthesized. The various kinds of synthetic methods used to obtain 2-substituted-1-pyrrolines will be discussed in the following sections.

4.2.2 Organometallic Reagents

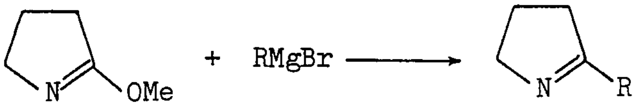
One of the most common methods is the reaction of a Grignard reagent, RMgX, with 4-chlorobutanenitrile to yield a 2-substituted-1-pyrroline (Equation 38).[15,104,106-117] Both 2-alkyl and 2-aryl-1-

pyrrolines have been prepared by this reaction. Alkyl or aryl Grignard reagents also react with 2-methoxy-1-pyrrolide[117-122] (Equation 39) and 2-pyrrolidone[116,123-125] (Equation 40) to yield 2-substituted-1-pyrrolines. Organolithium reagents also react with N-vinyl-2-pyrrolidone to form 2-substituted-1-pyrrolines[126,127] (Equation 41).

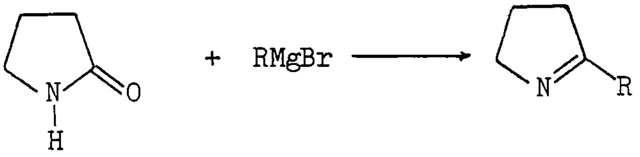
Eq-38



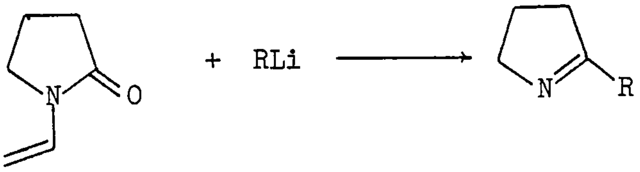
Eq-39



Eq-40



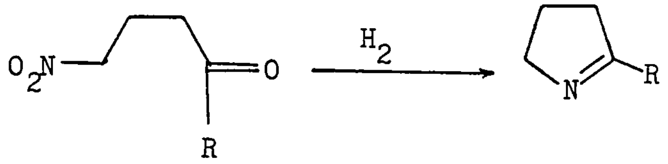
Eq-41



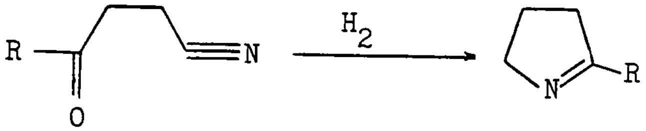
4.2.3 Cyclization Reactions

Various of compounds have been cyclized to obtain 1-pyrrolines. The most common method involves the reductive cyclization of γ-nitroketones, (Equation 42)[115,128-133] It is important to stop the reaction at the imine stage since further reduction can take place to give pyrrolidines.[131] Reduction of cyanoketones also provides 1-pyrrolines (Equation 43).[116,134-136]

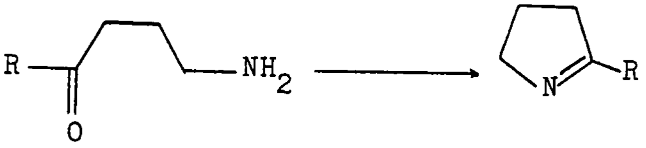
Eq-42



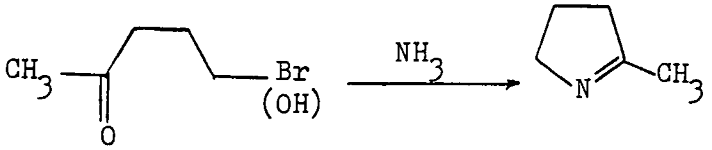
Eq-43



Eq-44



Eq-45



γ-Aminoketones and their precursers have been used for synthesis of 1-pyrrolines (Equation 44).[123,132,137-142] 5-Bromo-2-pentanone[143] and 5-hydroxy-2-pentanone[144] (Equation 45) were convrted into 2-methyl-1-pyrroline in the presence of ammonia with[144] or without[143] any catalyst.

4.2.4 Reduction of Pyrrols

The partial reduction of pyrrols to 1-pyrrolines is difficult to control and usually complete reduction to pyrrolides is observed.[145-

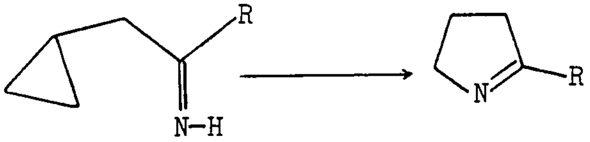
[149] However, succesful reductions of pyrrols to 1-pyrrolines have been achieved in some cases.[105,150-152]

4.2.5 Rearrangement of Cyclopropylimines and N-Acyllactams

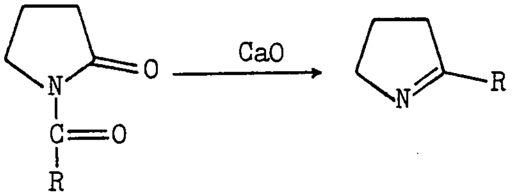
The rearrangement of cyclopropylimines could give either Δ^1- or Δ^2-pyrrolines. Maginnity and Cloke have observed the pyrrolines prepared by this method are identical with the ones prepared by the action of Grignard reagents on γ-chlorobutanenitrile which have a Δ^1 structure.[104] Both alkyl and aryl pyrrolidines may be prepared by this method (Equation 46).[104,106,112,153-155]

When heated in the presence of calcium oxide, N-acyllactams rearrange to 2-substituted Δ^1-pyrrolines (Equation 47).[156,157]

Eq-46



Eq-47



4.2.6 Miscellaneous

Various other less common methods are used to obtain 2-substituted-1-pyrrolines. Elimination of N-chloropyrrolidine with sodium methoxide in methanol gave 1-pyrroline.[20] 2-Methyl-1-pyrroline was obtained by oxidation of 2-methylpyrrolidine with mercuric acetate[158] and decomposition of 5-hexenylazide.[159]

4.3 Synthesis of 2-Substituted Pyrrolidines

As stated in section 4.2.3, 2-substituted pyrrolidines can be obtained from reduction of 2-substituted pyrrols.[144-149] Also the reduction of 1-pyrrolines is a general method for synthesis of pyrrolidines.[110,115,118,123,124,135,140,151,154] Lesser known methods include the reduction of 5-alkyl-2-pyrrolidones with $LiAlH_4$[160,161] or Na/alcohol[162,163] to give 2-alkylpyrrolidines. γ-Haloamines cyclizes in the presence of base to yield pyrrolidines.[164-166] Also 4-aminohexanol cyclizes in concentrated HBr to produce 2-ethylpyrrolidine in 44% yield.[131] Octyl-[167] and heptylazides have been photolyzed to produce 2-n-butyl- and 2-n-propylpyrrolidines. Mono-N-chloramines were cyclized in the presence of Fe^{2+} salts to give 2-alkylpyrrolidines.[169,170]

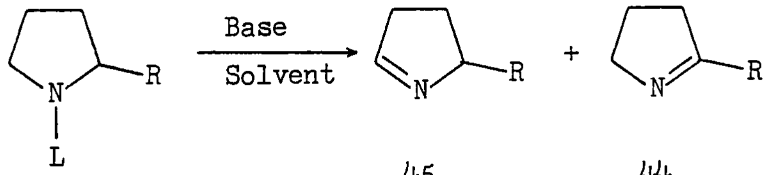
5.0 Purpose and Formulation of Research Plan

As was dicussed earlier, the available information concerning elimination reactions which form carbon-nitrogen double bonds is quite limited. In known examples, whenever positional isomerism was possible the Saytzeff product has been obtained.[67,69,74,75] The only exception is the amine-induced elimination of N-alkyl-N-(p-nitrobenzenesulfonyloxy)-benzylamines, which yields both positional isomers.[73] The reasons for obtaining only the Saytzeff product could be the use of only dissociated bases, or the lack of complete analysis of reaction products, or the use of a substituent which forces the reaction to give only the Saytzeff product.

It was mentioned in Section 4.2, 1-pyrrolines are biologically important molecules. These compounds can also serve as intermediates[97] in the synthesis of biologically important molecules due to the ability of the carbon-nitrogen double bond to undergo a number of reactions.[171]

Therefore an examination of base-promoted, imine-forming eliminations from 50 was undertaken. Variation of the leaving group, L, the base-solvent system, and the alkyl group, R, was to be conducted to provide insight in carbon-nitrogen double bond forming eliminations and hopefully lead to new synthetic methods for heretofore unknown 5-substituted 1-pyrrolines, 44 (Equation 48).

Eq-48



50 45 44

The transition states for base-promoted imine formation are to be probed further by kinetic examination of eliminations from N-chloro-2-arylpyrrolidines. Hammet ρ values, deuterium isotope effect values, leaving group isotope effect values are to be determined.

CHAPTER II

BASE INDUCED DEHYDROCHLORINATION OF N-CHLORO-2-ALKYLPYRROLIDINES

1.0 Experimental

1.1 Materials and Instrumentation

The reagents used in the experiments discussed in this chapter are listed below with the companies from which they were purchased given in paranthesis:

Methylene chloride (Ashland), magic methyl (FSO_3CH_3, Aldrich), 2-pyrrolidone (GAF), sodium hydroxide (Fisher), anhydrous diethyl ether (MCB), sodium sulfate (Fisher), magnesium turnings (American Drug and Chemical), benzene (MCB), ethyl bromide (Mallinckrodt), hydrochloric acid (Fisher), ammonium chloride (MCB), n-propyl bromide (Aldrich), isopropyl bromide (Aldrich), t-butyl lithium (Aldrich), potassium hydroxide (MCB), 5-methyl-2-pyrrolidone (Pflatz and Bauer), lithium aluminum hydride (Alfa), sodium borohydride (Alfa), methanol (Fischer), t-butyl alcohol (Fischer), standardized HCl (Fischer), o-xylene (Aldrich), anisole (Aldrich), Carbowax 400 (Applied Science Lab.), Chromosorb W (John Mansville), Chromosorb WAW-DMCS (Supelco). Methanol was dried by distilling from magnesium.[172] t-Butyl alcohol was dried by distilling twice from potassium. Benzene was purified by a literature method[172] and dried by distilling from sodium-wire. The other solvents were used as received.

The 2-alkyl-1-pyrrolines and 2-alkylpyrrolidines were identified by comparing their bp's with literature values and their ir, proton nmr, and mass spectra with the anticipated spectral values. The boiling points are given in degrees Centrigade and are uncorrected. Infrared spectra were taken with a Perkin-Elmer 457 instrument and were recorded in cm^{-1}. The proton nmr spectra were taken either with a Varian XL100, Varian A60, or Varian EM360 spectrophotometer and were recorded in ppm with respect to the internal standard tetramethylsilane (s= singlet, d=doublet, t=triplet, m=multiplet). The gc-mass spectra were recorded with Varian Mat 311 mass spectrometer coupled with Varian Aerograph 2700 gas chromatograph and are given m/e (P^+ stands for the parent peak). The relative peak intensities could not be obtained due to a computer break-down. For preparative gas chromatography either a Varian Aerograph 1520 or Antek 400 (with thermal conductivity detectors) instruments were employed. For analyses of elimination products an Antek 400 flame ionization detector gas chromatograph was used. The reaction mixtures were centrifuged with a Fisher Safety Centrifuge.

1.2 Synthesis of 2-Substituted 1-Pyrrolines

1.2.1 2-Methoxy-1-pyrroline

A solution of 36.00 g (0.424 mole) of freshly distilled 2-pyrrolidone in 500 ml of methylene chloride was placed into a three-necked, round-bottomed flask fitted with a reflux condenser and a pressure-equilizing dropping funnel. Magic methyl (FSO_3CH_3, 33.0 ml, 0.396 mole) was introduced dropwise. After the addition was complete, the solution was stirred at room temperature for two hours. The adduct was decomposed by the addition of a solution of 18.0 g of sodium hydroxide in 56.0 ml of water (8.0 N) and stirring at room temperature for 15 minutes. The organic layer was separated and the aqueous layer was extracted once with methylene chloride (100 ml) and with ether (3x100 ml). The organic layers were combined and dried over Na_2SO_4. The solvents were removed by a careful distillation using a Vigreux column. The residue was distilled to yield 25.83 g (66%) of 2-methoxy-1-pyrroline, bp 114-116°C (literature[120] bp 118-120°C); ir (neat): 3030, 2980, 2960, 2890, 1665 (C=N), 1460, 1450, 1350, 1310, 1000, 990, 730; nmr ($CDCl_3$): 3.83 ppm (s, 3.0 H), 3.96-3.56 ppm (m, 1.9 H), 2.67-1.73 ppm (m, 4.0 H).

1.2.2 General Procedure for Synthesis of Some 2-Alkyl-1-pyrrolines

2-Ethyl-, n-propyl-, and isopropyl-1-pyrrolines were synthesized according to the literature procedure[118] by the action of alkyl Grignard reagents on 2-methoxy-1-pyrroline. A three-necked, round-bottomed flask was fitted with an efficient reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a pressure-equilizing dropping funnel. All of the glassware was dried in an oven (130°), assembled while hot, and allowed to cool under a purging nitrogen atmosphere. Magnesium turnings were washed with anhydrous diethyl ether and placed into the round-bottomed flask. A crystal of iodine and 25-50 ml of anhydrous diethyl ether were added. A solution of the alkyl bromide in anhydrous diethyl ether was placed into the dropping funnel. A few ml of alkyl bromide solution was run into the flask. The initiation of the reaction could be judged by the disapperance of the iodine color and the refluxing of ether. After the reaction started, the addition rate of the alkyl bromide solution was adjusted to maintain a gentle reflux. After the addition was complete, the solution was refluxed for 30 minutes. The solvent was then exchanged with anhydrous benzene (dried with sodium) via simultaneous distillation of diethyl ether and addition of benzene. When the solvent exchange was complete, the Grignard reagent precipitated as a brown solid. An anhydrous benzene solution of 2-methoxy-1-pyrroline was added dropwise to the refluxing Grignard reagent under nitrogen atmosphere. The mixture was then refluxed for 17-23 hours and allowed to cool. The adduct was decomposed by the addition of an aqueous solution of either NaOH or NH_4Cl. The benzene layer was decanted and the aqueous layer (an emulsion) was extracted with ether. The organic layers was combined and dried over Na_2SO_4. The solvent was removed and the crude products were purified by distillation.

2-Ethyl-1-pyrroline

The Grignard reagent was prepared from 7.294 g (0.30 mole) of magnesium and 32.67 g (0.30 mole) ethyl bromide in 200 ml of anhydrous diethyl ether. After the solvent was exchanged by benzene, a solution of 9.9 g (0.10 mole) of 2-methoxy-1-pyrroline in 200 ml of anhydrous benzene was added dropwise and the mixture was refluxed for 17 hours.

The adduct was decomposed by the addition of 75 ml of 6.0 N sodium hydroxide solution. 2-Ethyl-1-pyrroline, 4.0 g, was isolated directly from the reaction mixture by extraction with diethyl ether. The emulsion in the aqueous layer was treated with water and steam distilled. The distillate was made acidic with concentrated HCl and concentrated in vacuo. The residue was treated with concentrated NaOH solution and extracted with ether. After the removal of solvent and distillation, 1.0 g (10.3%) 2-ethyl-1-pyrroline was obtained. The combined yield was 5.0 g (51.5%), bp 118-122°C (Literature[118] bp 127-129); ir (neat): 2980, 2950, 2880, 1655 (C=N), 1465, 1440, 1375, 1345, 1300, 960; nmr (CCl_4): 3.86-3.58 ppm (t, 1.9 H), 2.55-1.52 ppm (m, 6.0 H), 1.23-0.97 ppm (t, 3.1 H); mass spec: 97 (P^+), 96, 82, 70, 69, 68, 56, 55, 42, 41, 39.

2-n-Propyl-1-pyrroline

The n-propyl magnesium bromide was prepared from 24.6 g (0.20 mole) of n-propyl bromide and 4.86 g (0.20 mole) of magnesium turnings in 200 ml of anhydrous diethyl ether. After the solvent was exchanged with benzene, a solution of 9.9 g (0.1 mole) of 2-methoxy-1-pyrroline in 100 ml of dry benzene was added dropwise and the reaction mixture was refluxed for 18 hours. The adduct was decomposed by the addition of 50 ml of 25% NH_4Cl solution. The product was isolated from the reaction mixture by extraction in the usual manner, 4.54 g (43%), bp 140-142°C (Literature[118] 146-150); ir (neat): 2970, 2880, 1655 (C=N), 1470, 1440, 1390, 1305, 1010, 970; nmr (CCl_4): 3.72-3.50 ppm (t, 2.0 H), 2.48-1.25 ppm (m, 8.0 H), 1.00-0.80 (t, 2.9 H); mass spec: 111 (P^+), 110, 96, 83, 82, 70, 69, 68, 55, 54, 43, 42, 41, 39.

2-Isopropyl-1-pyrroline

The Grignard reagent was prepared from 4.86 g (0.20 mole) of magnesium turnings and 24.6 g (0.20 mole) of isopropyl bromide in 200 ml of anhydrous diethyl ether. The solvent was exchanged with benzene and a solution of 6.46 g (0.065 mole) of 2-methoxy-1-pyrroline in 100 ml of dry benzene was added dropwise. The mixture was refluxed for 23 hours, allowed to cool, and treated with 50 ml of 25% NH_4Cl solution. 2-Isopropyl-1-pyrroline, 2.4 g (33%), was isolated from the reaction mixture in the usual manner, bp 134-138°C (Literature[127] bp 142-143°C/760 mm, 138°C/740 mm); ir (neat): 2980, 2890, 1650 (C=N), 1475, 1300, 960; nmr (CCl_4): 3.83-3.50 ppm (t, 2.0 H), 2.65-2.20 ppm (m, 3.1 H), 2.03-1.6 (m, 2.2 H), 1.16 and 1.06 ppm (d, 6.0 H); mass spec: 111 (P^+), 110, 96, 83, 70, 69, 68, 56, 55, 54, 43, 42, 41, 39.

1.2.3 Synthesis of 2-t-Butyl-1-pyrroline

A three-necked 100 ml round-bottomed flask was fitted with a septum, (for an argon inlet), a reflux condenser, a pressure-equilizing addition funnel, and a magnetic stirrer. The glassware was dried in an oven (130°C), assembled while hot and allowed to cool under a purging argon atmosphere. Then 33 ml of a 1.5 M solution of t-butyllithium (0.0495 mole) in pentane was introduced into the flask and cooled to -78°C with a dry ice-acetone bath. 2-Methoxy-1-pyrroline, 4.95 g

(0.05 mole), was added dropwise. A yellow solid was formed. The reaction mixture was stirred overnight. The temperature slowly rose to room temperature as the dry ice evaporated. Next 75 ml of diethyl ether was added and the adduct was decomposed by the addition of 18 ml of water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3x50 ml). The organic layers were combined dried over KOH, and the solvent was removed. The residue was vacuum distilled to give 2.7 g (33%) of crude product, 70-78°/55 mm, which was purified by preparative gas chromatography (20'x1/4" column of Carbowax 400 on Chromosorb WAW-DMCS) (Literature[157] bp 110°/15 mm); ir (neat): 2980, 2880, 1645 (C=N), 1485, 1470, 1370, 1220, 1100, 970; nmr (neat): 3.92-3.57 ppm (m, 2.0 H), 2.72-2.35 (m, 2.1 H), 2.3-1.65 ppm (m, 1.9 H), 1.10 ppm (s, 9.0 H); mass spec: 125 (P^+), 110, 82, 70, 69, 68, 57, 55, 42, 41, 39.

1.2.4 2-Methyl-1-pyrroline

N-Chloro-2-methylpyrrolidine was prepared from 1.0 g (11.8 mmole) of 2-methylpyrrolidine and 3.14 g (23.5 mmole) of N-chlorosuccinimide in 50 ml of _n_-hexane by stirring at room temperature for 3 hours. The mixture was filtered and the solid was washed with _n_-hexane (2x25 ml). The hexane layers were combined and 2.04 g (18 mmole) of _t_-BuOK was added. After the mixture had been stirred at room temperature for 18 hours, it was centrifuged. 2-Methyl-1-pyrroline was isolated from the hexane solution by preparative gas chromotography on 20'x1/4" column of Carbowax 400 on Chromosorb W column (column temperature 90°C)

(Literature[118] bp 106); ir (CCl_4): 2970, 2930, 2880, 1665 (C=N), 1388, 1320; nmr (CCl_4): 3.80-3.43 ppm (m, 2.0 H), 2.53-2.20 ppm (m, 2.0 H), 2.03-1.37 ppm (m, 2.1 HO, 1.93 ppm (s, 3.0 H); mass spec: 83 (P^+), 55, 54, 42, 41, 40, 39.

1.3 Synthesis of 2-Alkylpyrrolidines

1.3.1 2-Methylpyrrolidine

The method developed by Karrer and Erhardt[160] was followed. A three-necked 500 ml round-bottomed flask was fitted with an efficient reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a pressure-equilizing dropping funnel. All of the glassware was dried in oven (130°C), assembled while hot, and allowed to cool under a purging nitrogen atmosphere. Then 5.35 g (0.140 mole) of $LiAlH_4$ and 100 ml anhydrous diethyl ether were placed into the flask and a solution of 11.0 g (.111 mole) of 5-methyl-2-pyrrolidone in 100 ml of anhydrous diethyl ether was added dropwise. After the addition was complete, the mixture was refluxed for 20 hours. The reaction mixture was allowed to cool, was treated with 15 ml of H_2O, and was stirred overnight. The white precipitate was filtered and washed with diethyl ether. The ether layers were combined and dried over Na_2SO_4. The solvent was removed by a careful distillation using a Vigreux column. The residue was distilled to give 5.45 g (58%) of 2-methylpyrrolidine, bp 90-92°C (Literature[160] bp 93-96°C/730 mm); ir (neat): 3200, 2970, 2880, 1465, 1380, 1145, 1110, 770; nmr (neat): 3.19-2.5 ppm (m, 3.0 H), 2.65 ppm (s, 1.0 H), 1.98-1.28 ppm (m, 4.0 H), 1.10-1.03 (d, 3.0 H).

1.3.2 General Procedure for Reduction of Some 2-Alkyl-1-pyrrolines

2-Alkylpyrrolidines (alkyl=ethyl, n-propyl, isopropyl, t-butyl) were obtained by the reduction of corresponding 2-alkyl-1-pyrrolines with sodium borohydride. The method of Billman and Diesing[173] was modified. A three-necked 250 ml round-bottomed flask was fitted with a reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a pressure-equilizing dropping funnel. The glassware was dried in oven, assembled while hot, and allowed to cool under a purging nitrogen atmosphere. An anhydrous methanolic solution of 2-alkyl-1-pyrroline (2.5-4.0% by weight) was placed into the reaction vessel and a solution of sodium borohydride in absolute methanol (3.1% by weight, 3.9-4.5 molar excess) was added dropwise. After the addition was complete, the solution was refluxed for 30 minutes. The reaction mixture was allowed to cool and was treated with an aqueous solution (5.86 M) of sodium hydroxide which was double the molar amount of sodium borohydride used. After the addition of 200 ml of water, the reaction mixture was distilled (steam distillation *in situ*). The distillate was made acidic with concentrated HCl and concentrated *in vacuo*. The residue was made basic with a concentrated solution of NaOH and extracted with diethyl ether (3x100 ml). The ether layers were combined and dried over $MgSO_4$ (Na_2SO_4 was used in the preparation of 2-t-butylpyrrolidine). The solvent was removed by a careful distillation using a Vigreux column and the residue was distilled to yield 2-alkylpyrrolidines.

2-Ethyl-pyrrolidine

A solution of 2.00 g (20.6 mmole) of 2-ethyl-1-pyrroline in 50 ml of absolute methanol was reduced with a solution of 3.07 g (81.2 mmole) of sodium borohydride in 100 ml of absolute methanol. The adduct was decomposed with 28 ml of an aqueous solution of 5.86 M NaOH.

The product was obtained from the reaction mixture in the usual manner, 0.75 g (37%), bp 118°C (Literature[118] 119-123); ir (neat): 3300, 2980, 1460, 1360; nmr (CCl_4): 3.03-2.51 ppm (m, 2.7 H), 2.09-0.74 ppm (m, 10.0 H).

2-n-Propylpyrrolidine

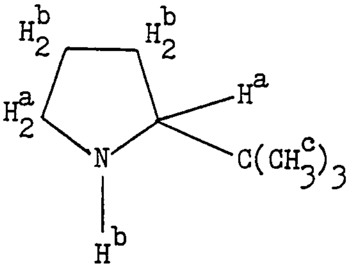
2-n-Propyl-1-pyrroline (2.00 g, 18.0 mmole) in 50 ml of absolute methanol was reduced with a solution of 3.07 g (81.2 mmole) sodium borohydride in 100 ml of absolute methanol in the usual manner. The decomposition of the adduct was accomplished by the addition of 28 ml of 5.86 M sodium hydroxide solution. The product (1.5 g, 75%) was obtained after distillation, bp 142-145°C (Literature[118] 145-
ir (neat): 3300, 2970, 2880, 1470, 1420, 1340, 1290; nmr (CCl_4): 3.83-3.53 ppm (m, 2.0 H), 2.53-1.3 ppm (m, 9.8 H), 1.05-0.83 ppm (t, 3.0 H).

2-Isopropylpyrrolidine

2-Isopropylpyrrolidine was obtained from the reduction of a solution of 2.00 g (18.0 mmole) of 2-isopropyl-1-pyrroline in 50 ml of absolute methanol with a solution of 3.07 g (81.2 mmole) of sodium borohydride in 100 ml of absolute methanol in the usual manner (28 ml of 5.86 M NaOH was used to free the amine), bp 136-138°C, 1.10 g

(54%) (Literature[147] 48-51°/20 mm); ir (neat): 3300, 2980, 2880, 1470, 1390, 1265, 1080; nmr (CCl_4): 2.73-2.4 ppm (m, 3.0 H), 1.9-1.1 ppm (m, 6.2 H), 0.96-0.91 (d, 3.0), 0.86-0.80 (d, 3.0).

2-t-Butylpyrrolidine



The reduction of 1.25 g (10.0 mmole) of 2-t-butyl-1-pyrroline in 50 ml of absolute methanol with a solution of 1.51 g (40.0 mmole) of $NaBH_4$ was accomplished in the usual manner (14 ml of 5.85 M NaOH was used), to yield 0.645 g (51%) of 2-t-butylpyrrolidine, bp 148-150°C. ir (neat): 3300 (N-H), 2950, 2870, 1470, 1395, 1365, 1090; nmr (neat): 2.93-2.60 ppm (m, 3.0 H^a), 1.73-1.10 ppm (m, 5.1 H^b), 0.88 ppm (s, 8.8 H^c); mass spec: 127 (P^+), 70, 69, 68, 43, 42, 41, 39.

1.4 Elimination Studies

1.4.1 Preparation of Base-Solvent Systems

Sodium Methoxide in Methanol

A three-necked round-bottom flask was fitted with a reflux condenser, a gas inlet adaptor, and a magnetic stirrer. The glassware was dried in an oven, assembled while hot, and cooled under a purging nitrogen atmosphere. An appropriate amount of absolute methanol was placed into the flask. Freshly cut sodium was weighed in xylene, cut into small pieces, washed first with pentane, then in two successive absolute methanol baths, and dropped into the flask. After all the sodium had dissolved, the base-solvent was transferred into a round-bottomed flask equipped with an adaptor for dispensing solvents under inert atmosphere and stored under positive nitrogen atmosphere. The molarity was determined by titration with standardized HCl using phenolphtalein as an indicator. There was no discoloration of the solution upon prolonged storage.

Potassium t-Butoxide in t-Butyl Alcohol

Potassium t-butoxide in t-butyl alcohol was prepared by the same method given for sodium methoxide in methanol (refer to previous section). Heating with stirring was generally necessary in order to react all of the potassium. The base-solvent yellowed upon standing and was prepared fresh if coloration was evident.

Potassium t-Butoxide in Hexane

Commercially available potassium t-butoxide was used as received. The white powdery base was weighed under nitrogen atmosphere and rapidly transferred to the solution of N-chloroamine in hexane.

1.4.2 Preparation of N-Chloro-2-alkylpyrrolidines

N-Chloro-2-alkylpyrrolidines were prepared from 2-alkylpyrrolidines (0.51-2.75 mmole) by stirring the amine with a 1.57-3.74 molar excess of N-chlorosuccinimide in either 10 ml of pentane (for MeONa-MeOH and _t_-BuOK-_t_-BuOH induced eliminations) or 10 ml of hexane (for _t_-BuOK-hexane induced eliminations) at room temperature for 1-3 hours. The reaction mixture was filtered and the hexane solutions were used directly. To the pentane solutions 1 ml of the appropriate solvent, absolute methanol or _t_-butyl alcohol, was added and the volume of the liquid was reduced to 0.5 ml _in vacuo_ without applying any heat to give alcoholic solutions of the N-chloro-2-alkylpyrrolidines.

1.4.3 Preparation of Authentic Samples of Elimination Products

The authentic 2-alkyl-1-pyrrolines, except for 2-methyl-1-pyrroline, were obtained by the action of organometallic reagents (RMgBr, where R=Et, _n_-Pr, Isopr and _t_-BuLi) on 2-methoxy-1-pyrroline. The Reader is referred to Sections 1.2.2 and 1.2.3.

The 5-alkyl-1-pyrrolines and 2-methyl-1-pyrroline were obtained from large scale reactions of N-chloro-2-alkylpyrrolidines with _t_-BuOK-hexane. The hexane solutions of the resulting imines were subjected to preparative gas chromatography (20'x1/4" column of 10% Carbowax 400 on Chromosorb W, 20'x1/4" column of 10% Carbowax 400 on Chromosorb WAW-DMCS, or 30'x1/4" column of 10% Carbowax 400 on Chromosorb WAW-DMCS at column temperatures 90-100°C). The imines were identified by comparing their infrared, proton nmr, and mass spectra with the anticipitated spectral values. The mass spectra of both the

5-alkyl- and 2-alkyl-1-pyrrolines were recorded by gc-mass spectra analysis. Spectral evidence for the 5-alkyl-1-pyrrolines is summarized as follows.

5-Methyl-1-pyrroline

ir (CCl_4): 3040, 2980, 1635 (C=N), 1460, 1435. nmr (CCl_4): 7.34 ppm (unresolved, 1.0 H), 4.0-3.93 ppm (m, 1.0 H), 2.59-2.40 ppm (m, 2.0 H), 2.14-1.80 ppm (m, 2.0 H), 1.26-1.18 ppm (d, 3.0 H). mass spec: 83 (P^+), 68, 56, 55, 41, 39.

5-Ethyl-1-pyrroline

ir (CCl_4): 3020, 2980, 2880, 1630 (C=N), 1465, 1440. nmr (CCl_4): 7.43 ppm (unresolved, 0.9 H), 4.30-3.45 ppm (m, 1.1 H), 2.8-0.8 ppm (m, 6.0 H), 1.15-0.93 ppm (t, 3.0 H). mass spec: 97 (P^+), 82, 70, 69, 68, 56, 55, 54, 42, 41, 39.

5-n-Propyl-1-pyrroline

ir (neat): 3020, 2970, 2880, 1630 (C=N), 1465, 1440, 1325, 1230, 920. nmr (CCl_4): 7.30 ppm (unresolved, 0.7 H), 4.10-3.60 ppm (m, 0.9 H), 2.65-0.8 ppm (m, 11.0 H). mass spec: 111 (P^+), 110, 96, 83, 69, 68, 56, 55, 54, 43, 42, 41, 39.

5-Isopropyl-1-pyrroline

ir (CCl_4): 3020, 2970, 2880, 1635 (C=N), 1475, 1390, 1370. nmr (CCl_4): 7.44 ppm (unresolved, 0.9 H), 3.82-3.54 ppm (m, 1.0 H), 2.58-2.36 ppm (t, 1.9 H), 2.02-1.36 ppm (m, 3.2 H), 1.04-0.98 ppm (d, 3.0 H), 0.94-0.87 ppm (d, 3.0 H). mass spec: 111 (P^+), 96, 83, 82, 70, 69, 68, 56, 55, 43, 42, 41, 39.

5-t-Butyl-1-pyrroline

ir (CCl_4): 3020, 2980, 2920, 2880, 1640 (C=N), 1480, 1470, 1380. nmr (CCl_4): 7.67 -7.50 ppm (unresolved, 1.0 H), 3.88-3.48 ppm (m, 1.0 H), 2.32-2.72 ppm (m, 2.0 H), 2.18-1.43 ppm (m, 2.1 H), 0.89 (s, 8.7 H). mass spec: 125 (P^+), 110, 82, 70, 69, 68, 57, 55, 42, 41, 39.

1.4.4 Molar Response Ratios

Pentane or hexane solutions of authentic imines with a respective internal standard (o-xylene or anisole) were analysed by gas chromatography (20'x1/8" column of 10% Carbowax 400 on Chromosorb W (or WAW-DMCS at 80-90°C). From the known weights of the compounds used and the relative peak areas, the molar responses were calculated (Equation 49). The relative ratios from at least three chromatograms were averaged (Table 8).

$$\text{Eq-49} \quad \text{Molar Response} = \frac{\text{Moles of Internal Standard} \times \text{Peak Area of Imine}}{\text{Moles of Imine} \times \text{Peak Area of Internal Standard}}$$

1.4.5 Elimination Reaction Procedures

The MeONa-MeOH and t-BuOK-t-BuOH solutions were added to the appropriate alcoholic solutions of the N-chloro-2-alkylpyrrolidines. A

Table 8

Molar Response Ratios of Some Imines

Imines	Internal Standard	Molar Response
5-Methyl-1-pyrroline	*o*-Xylene	0.521 ± 0.003
2-Methyl-1-pyrroline	*o*-Xylene	0.537 ± 0.005
5-Ethyl-1-pyrroline	Anisole	0.87 ± 0.02
2-Ethyl-1-pyrroline	Anisole	0.86 ± 0.02
2-*n*-Propyl-1-pyrroline	*o*-Xylene	0.65 ± 0.02
2-Isopropyl-1-pyrroline	*o*-Xylene	0.75 ± 0.01
2-*t*-Butyl-1-pyrroline	*o*-Xylene	0.924 ± 0.002

weighed amount of commercial *t*-BuOK was added directly to the hexane solutions of N-chloro-2-alkylpyrrolidines. The reaction mixtures were stirred at room temperature for 1-24 hours, centrifuged, and the clear supernatant solutions were decanted. A measured amount of imine solution was mixed with a measured amount of a solution of the desired internal standard in the appropriate solvent and the mixture was analysed by gas chromatography. The gc colums used were: 20'x1/8" column of 10% Carbowax 400 on Chromosorb W, 20'x1/8" column of 10% Carbowax 400 on Chromosorb WAW-DMCS, and 30'x1/8" column of 10% Carbowax 400 on Chromosorb WAW-DMCS. The column temperatures employed were 80, 90, and 100°, the injector temperatures were set at 130-

185°C, and the detector temperature was 220°C. The product and internal standard peak areas were measured by an electronic integrator and corrected for the molar responses to calculate the relative ratios of products and the yields. Whenever the peak areas could not be determined by the electronic integrator, they were estimated by cutting and weighing using aluminum foil. The relative ratios of peak areas from at least three chromatograms were averaged.

2.0 Results

2.1 2-Alkyl-1-pyrrolines

The majority of 2-alkyl-1-pyrrolines (2-ethyl-, 2-n-propyl-, 2-isopropyl-1-pyrroline) were prepared by the method of Etienne and Correria.[118] The alkyl magnesium bromides were reacted with 2-methoxyl-1-pyrroline to give the 2-alkyl-1-pyrrolines. This method failed for preparations of 2-methyl- and 2-t-butyl-1-pyrrolines. It is probable that 2-methyl-1-pyrroline was lost during the isolation step from the reaction mixture. Therefore, the authentic 2-methyl-1-pyrroline was isolated by preparative gas chromatography from the dehydrochlorination products in a reaction of N-chloro-2-methylpyrrolidine with t-BuOK-hexane as the base-solvent system. For the attempted synthesis of 2-t-butyl-1-pyrroline using a Grignard reagent, the failure might be due to difficulty in forming the elusive Grignard reagent with a t-butyl group. It was necessary to use a different organometallic reagent, t-butyllithium, for the synthesis of 2-t-butyl-1-pyrrolidine. The results of the 2-alkyl-1-pyrroline syntheses are presented in Table 9.

Table 9

2-Alkyl-1-pyrrolines from 2-Methoxy-1-pyrroline

Alkyl Group of 2-Alkyl-1-pyrroline	Organometallic Reagent	% Yield of imine
Ethyl	CH_3CH_2MgBr	51.5
_n_-Propyl	$CH_3CH_2CH_2MgBr$	43
Isopropyl	$(CH_3)_2CHMgBr$	33
_t_-Butyl	$(CH_3)_3CLi$	33

2.2 2-Alkylpyrrolidines

All the 2-alkylpyrrolidines, except 2-methylpyrrolidine, were prepared by the reduction of corresponding 2-alkyl-1-pyrrolines with sodium borohydride. 2-Methylpyrrolidine was obtained by the reduction of 5-methyl-2-pyrrolidone with lithium aluminum hydride. The results are tabulated in Table 10.

2.3 5-Alkyl-1-pyrrolines

2.3.1 Introduction

The 5-alkyl-1-pyrrolines were isolated as dehydrochlorination products which resulted from reactions of N-chloro-2-alkylpyrrolidines with _t_-BuOK-hexane. The compounds were separated from the accompanying 2-alkyl-1-pyrrolines by preparative gas chromatography. It was found

Table 10

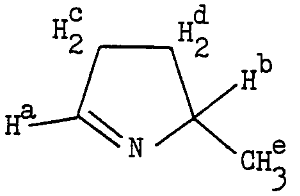
2-Alkylpyrrolidines

Alkyl Group of 2-Alkylpyrrolidine	Precursor	Reducing Agent	% Yield of 2-Alkylpyrrolidine
Methyl	2-pyrrolidone	$LiAlH_4$	58
Ethyl	1-pyrroline	$NaBH_4$	37
_n_-Propyl	1-pyrroline	$NaBH_4$	75
Isopropyl	1-pyrroline	$NaBH_4$	54
_t_-Butyl	1-pyrroline	$NaBH_4$	51

that, 5-alkyl-1-pyrrolines were stable when exposed to the various base-solvent systems and did not isomerize (the Reader is referred to Section 2.4). However, the 5-alkyl-1-pyrrolines decomposed rapidly once they were isolated in pure form. It was possible to keep these imines at -78°C for a period of 24 hours and their CCl_4 solutions at -5°C for a similar period of time. Due to this instability, the elemental analyses of the 5-alkyl-1-pyrrolines was not attempted. The structures of 5-alkyl-1-pyrrolines were verified by their infrared, proton magnetic resonance and mass spectra. Specific spectral assignments for each compound are attempted with the aid of information in References 174-182.

2.3.2 5-Methyl-1-pyrroline

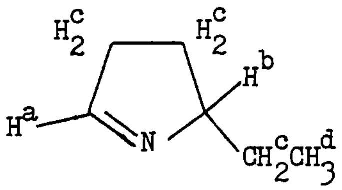
The olefinic $C-H^a$ stretching frequency in the infrared spectrum



51

was observed as a weak absorbtion at 3040 cm^{-1}. The 1635 cm^{-1} band was assigned to the C=N stretching frequency. The absorptions observed in the proton nmr spectrum are identified as follows: 7.34 ppm (unresolved, 1.0 H^a), 4.05-3.93 ppm (m, 1.0 H^b), 2.59-2.40 ppm (m, 2.0 H^c), 2.14-1.80 ppm (m, 2.0 H^d), and 1.26-1.18 ppm (d, 3.0 H^e). The mass spectrum of 5-methyl-1-pyrroline was interpreted as shown in Figure 7. Only the intense peaks are mentioned. The spectral evidence strongly supports the structure proposed for this imine.

2.3.3 5-Ethyl-1-pyrroline



52

The infrared spectrum of compound 52 showed unsaturated C-H stretch and C=N double bond stretching absorbtions at 3020 and 1630

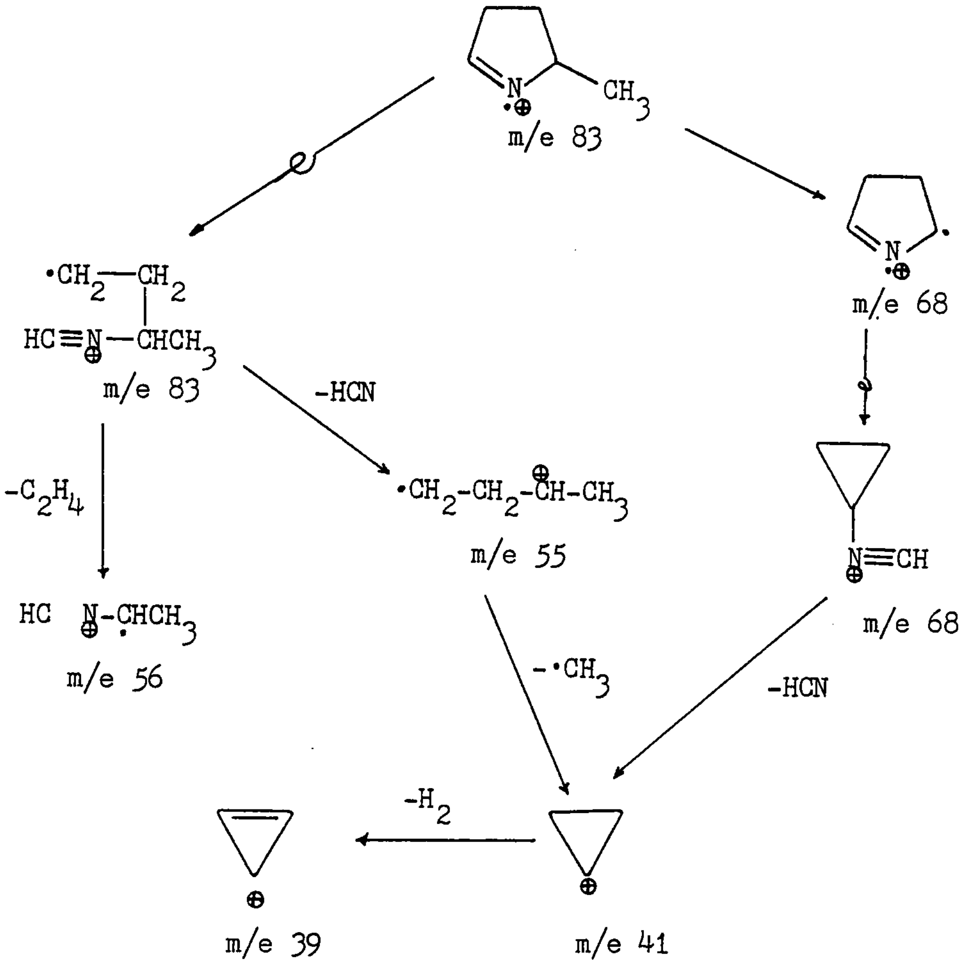


Figure 7 Interpretation of Mass Spectrum for 5-Methyl-1-pyrroline

cm^{-1}, respectively. The following assignments can be made for the proton nmr absorbtions: 7.43 ppm (unresolved, 0.9 H^a), 4.30-3.45 ppm (m, 1.1 H^6), 2.8-0.8 ppm (m, 6.0 H^c), 1.15-.093 (t, 3.0 H^d). The interpretation of fragmentation pattern for the mass spectrum of the compound 52 is given in Figure 8. The spectral evidence argues strongly for the proposed structure for 52.

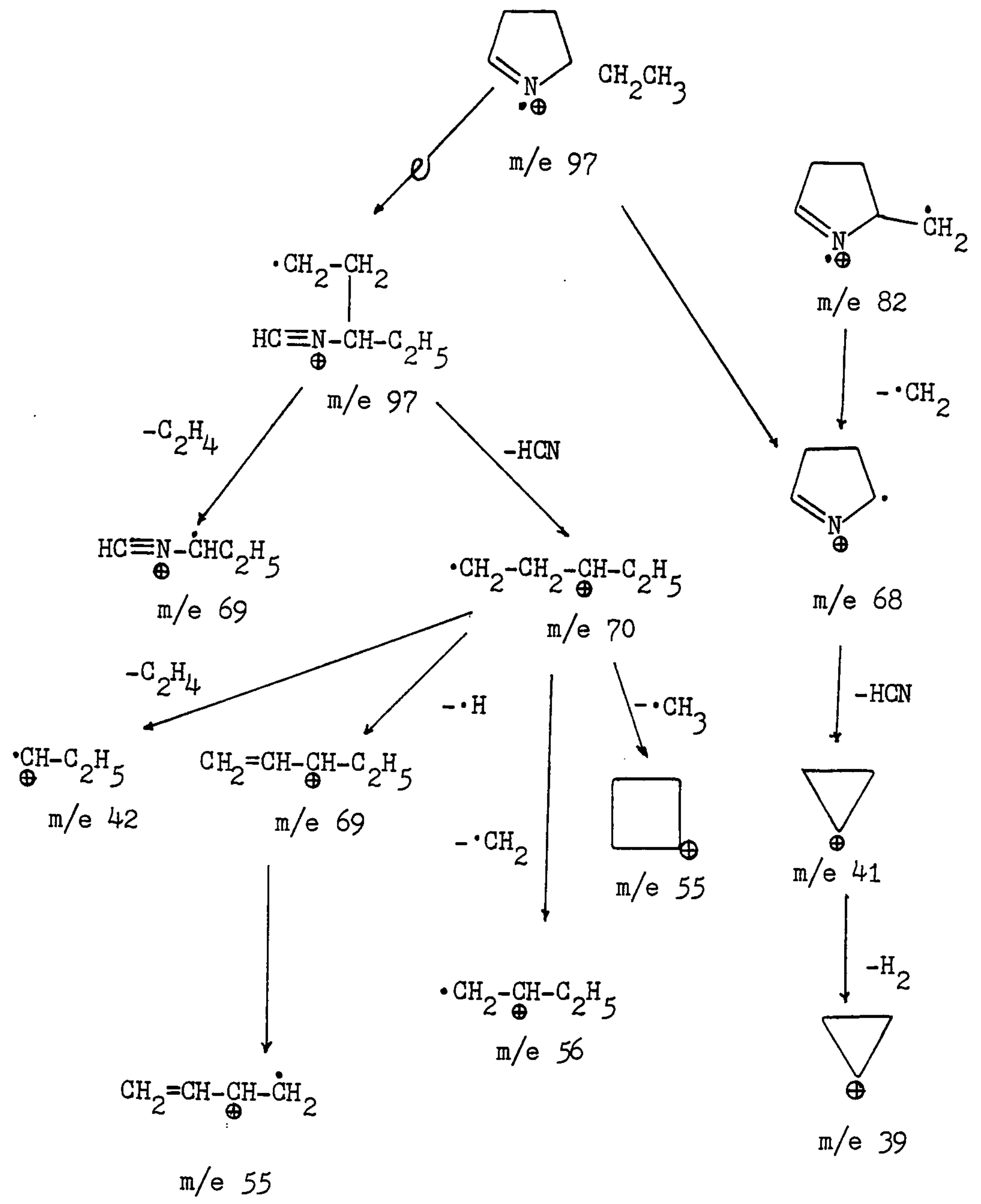
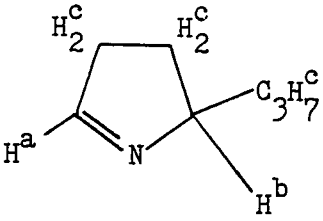


Figure 8 Interpretation of Mass Spectrum of 5-Ethyl-1-pyrroline

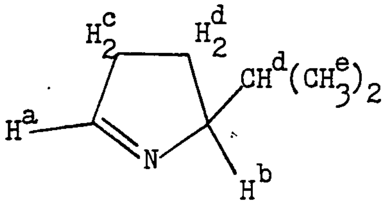
2.3.4 5-n-Propyl-1-pyrroline



53

The infrared spectrum of 53 has the unsaturated (N=C-H) carbon-hydrogen stretching absorption at 3020 cm^{-1} and the C=N stretching band is observed at 1630 cm^{-1}. The protons H^{a} and H^{d} have absorptions 7.30 ppm (unresolved, 0.7 H^{a}) and 4.10-3.60 ppm (m, 0.9 H^{b}) in the nmr spectrum of 53, respectively. The rest of the protons show a complex multiplet at 2.65-0.80 ppm (11.0 H^{c}). The fragmentation pattern of the mass spectrum of 53 is shown in Figure 9. All the spectroscopic evidence support the proposed structure of 53.

2.3.5 5-Isopropyl-1-pyrroline



54

The unsaturated (N=C-H) carbon-hydrogen stretching band and

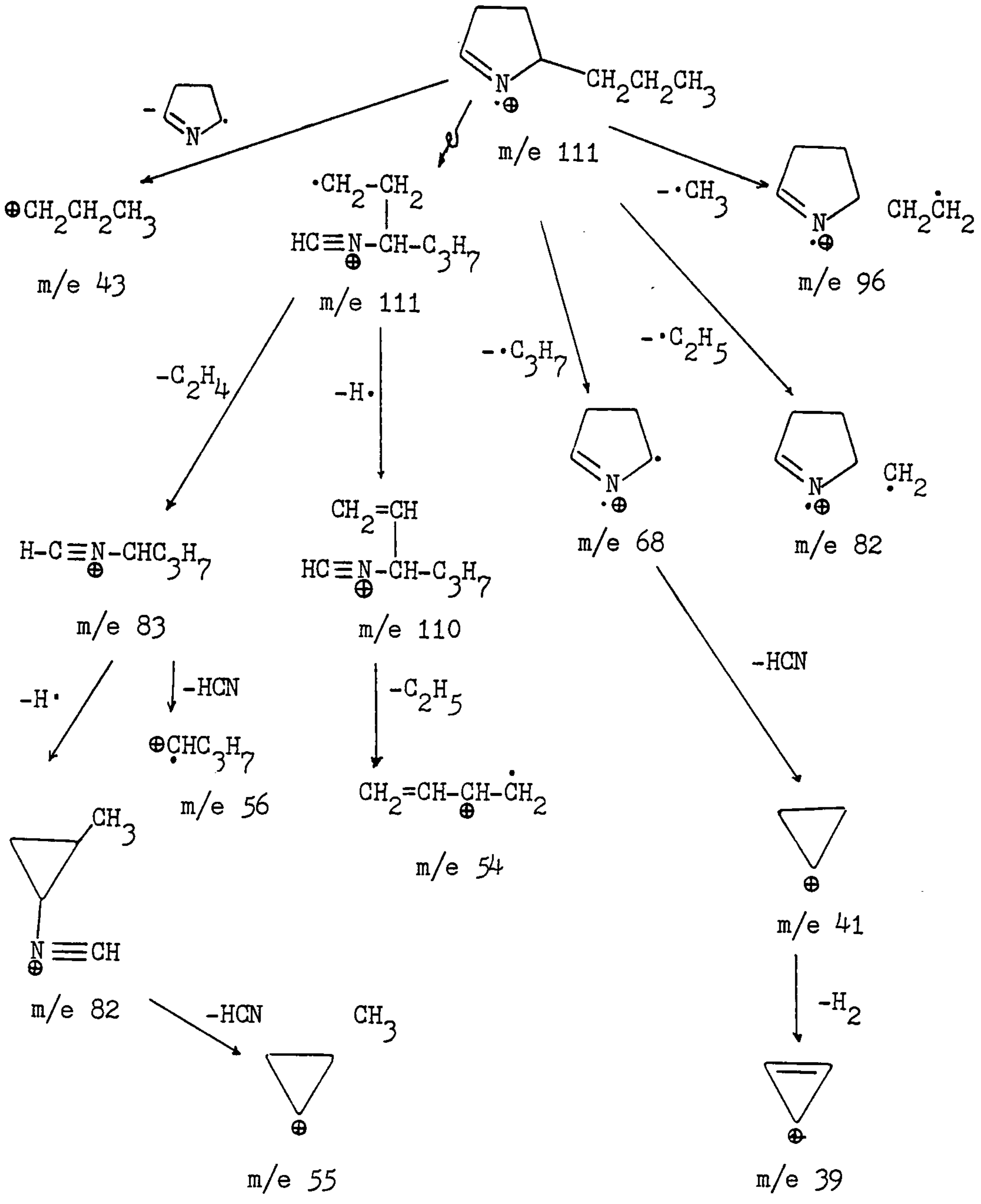
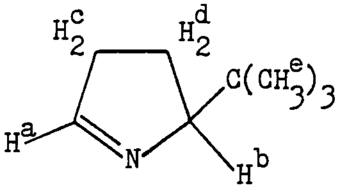


Figure 9 Interpretation of Mass Spectrum of 5-n-Propyl-1-pyrroline

carbon-nitrogen double bond (C=N) stretching absorption were observed at 3020 and 1635 cm^{-1}, respectively. The proton nmr spectrum was interpreted as follows: 7.44 ppm (unresolved, 0.9 H^a), 3.82-3.54 ppm (m, 1.0 H^b), 2.58-2.36 ppm (t, 1.9 H^c), 2.02-1.36 ppm (m, 3.2 H^d), 1.04-0.98 ppm (d, 3.0 H^e), and 0.94-0.87 ppm (d, 3.0 H^e). The interpretation of the mass spectrum of 54 is given in Figure 10. The spectral data for this compound, 54, verifies the proposed structure.

2.3.6 5-t-Butyl-1-pyrroline



55

The following spectral evidence was obtained for the compound 55. The infrared spectrum showed the presence of an unsaturated carbon-hydrogen stretching absorption (N=C-H) at 3020 cm^{-1} and a carbon-nitrogen double bond stretching band at 1640 cm^{-1}. The proton nmr showed an unresolved peak at 7.67- 7.50 ppm (1.0 H^a), a multiplet at 3.88-3.48 ppm (1.0 H^b), a multiplet at 2.32-2.72 ppm (2.0 H^c), another multiplet at 2.18-1.43 ppm (2.1 H^d), and a singlet at 0.89 ppm (8.7 H^e). The mass spectrum of 55 is given in Figure 11. All the spectral evidence strongly support the structural assignment of 55.

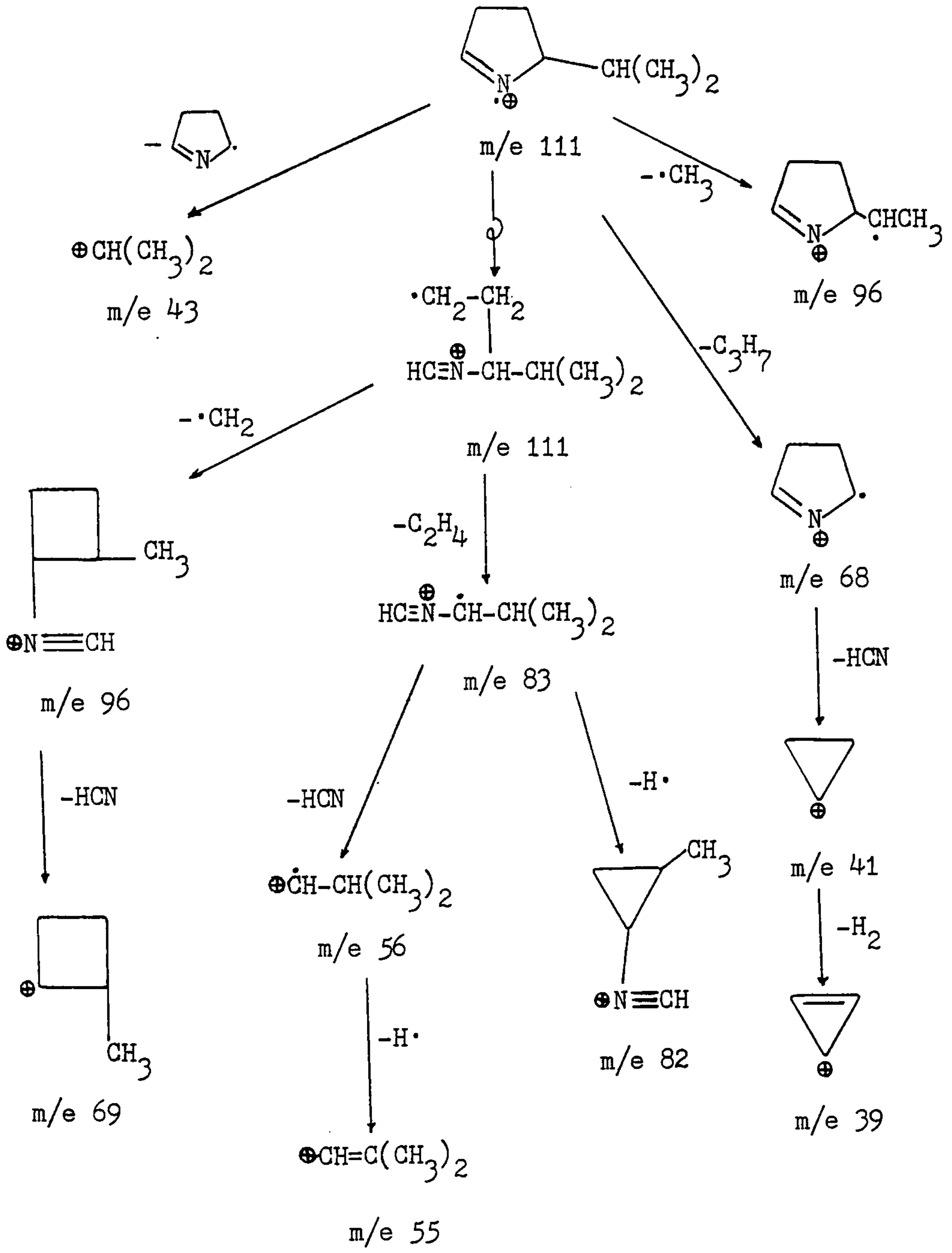


Figure 10 Interpretation of Mass Spectrum of 5-Isopropyl-1-pyrroline

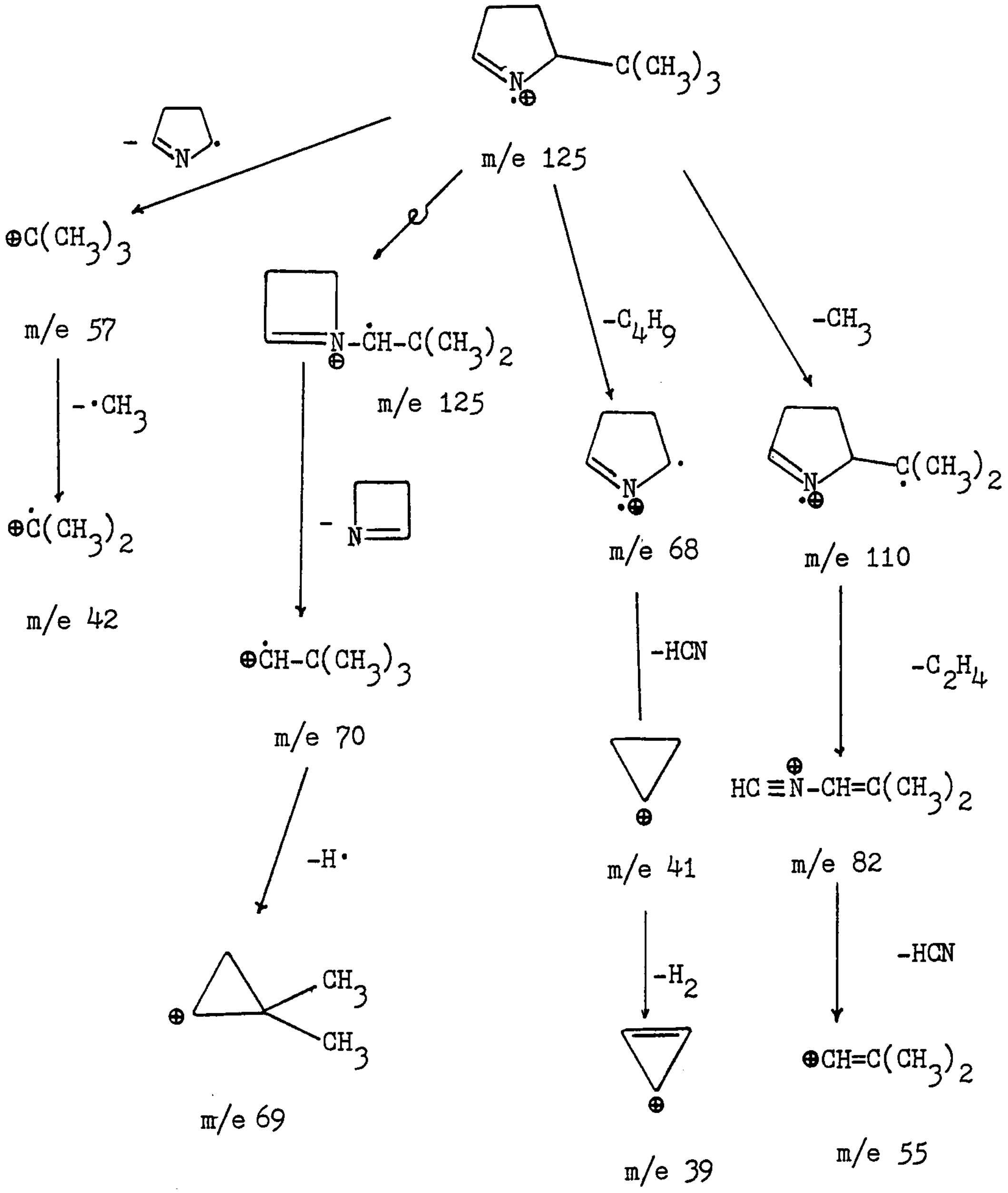


Figure 11 Interpretation of Mass Spectrum of 5-t-Butyl-1-pyrroline

2.4 Results of Elimination Reactions

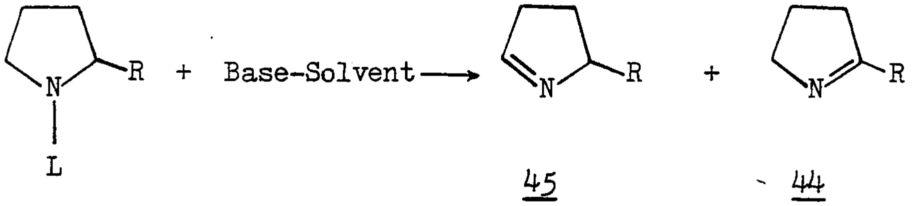
The 2-alkylpyrrolidines were N-chlorinated with N-chlorosuccinimide in pentane. Due to instability and potential hazard (explosiveness),[183] the resulting N-chloroamines were used in elimination reactions without prior isolation and characterization. The incomplete conversion of 2-alkylpyrrolidine into N-chloro-2-alkylpyrroline should produce an amine peak along with the elimination products in the gas chromotographic analysis of the elimination reaction mixtures. No amine peak was observed. The conversion of various amines into N-chloroamines by N-chlorosuccinimide is reported[74,75,184] to proceed in very high yield (usually quantitative). For these reasons, it was assumed that the conversion of 2-alkylpyrrolidines into N-chloro-2-alkylpyrrolidines was quantitative. Therefore, the yields of the imines resulting from dehydrochlorination reactions of the N-chloro-2-alkylpyrrolidines were based on the parent amines, 2-alkylpyrrolidines. The results of base induced dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines are given in Tables 11-15 (the relative percentages of imines and total imines yields and the standard deviations were calculated from at least three gc analyses of a given reaction mixture). The lower than quantitative yields which were obtained in some cases (Tables 11-15) are attributed to losses in the <u>in situ</u> preparation of N-chloro-2-alkylpyrrolidines (these losses most probably occurred in the filtration and solvent exchange steps) or to evaporation of the surprisingly volatile 2- and 5-alkyl-1-pyrrolines prior to product analysis. It appears that the conversion of 2-alkylpyrrolines via dehydrochlorination of N-chloro-2-alkylpyrrolidines with base was quantitative. Within experimental error, drastically lengthening the reaction time did not affect the product distribution (Table 14 No 2; Table 15 No 2). This demonstrates that there is no isomerization of the product imines in the basic solutions and that they are stable under these conditions.

3.0 Discussion

3.1 Identification of Elimination Products

The base-promoted dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines, 50 (L=Cl) may give two isomeric 1-pyrrolines because there are two different kinds of Cβ-H bonds. Depending upon which Cβ-H breaks either 5-alkyl-1-pyrroline, 45, or 2-alkyl-1-pyrroline, 44, will be formed (Equation 48).

Eq-48

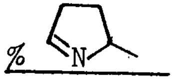
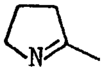


50 45 44

Gas chromatographic analysis of the product mixtures which resulted from base-promoted dehydrochlorination of N-chloro-2-alkylpyrrolidines showed that only two compounds were present. These compounds were isolated by preparative gas chromatography. One of the compounds was identified as the 2-alkyl-1-pyrroline by comparison of

Table 11

Base-Induced Dehydrochlorinations of N-Chloro-2-methylpyrrolidine (NCl)

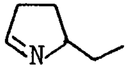
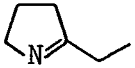
No	Base-Solvent	[NCl], M	[Base], M	Reaction Time	% 	% 	% Yield
1	MeONa-MeOH	0.302	1.98	45 min	2.2 ± 0.3*	97.8 ± 0.3	59 ± 3
2	MeONa-MeOH	0.372	0.99	30 min	2.4 ± 0.1	97.6 ± 0.1	98 ± 3
3	t-BuOK-t-BuOH	0.167	0.29	18 hr	9 ± 1	91 ± 1	42 ± 2
4	t-BuOK-Hexane**	0.129	0.296	23 hr	15.0 ± 0.2	85.0 ± 0.2	72.9 ± 0.5
5	t-BuOK-Hexane**	0.137	0.299	5 hr	15.3 ± 0.1	84.7 ± 0.1	100
6	t-BuOK-Diethyl Ether**	0.247	0.450	24 hr	7.7 ± 0.2	92.3 ± 0.2	40 ± 2

* Standard deviations from multiple analysis.

** Heterogeneous base-solvent combinations.

Table 12

Base-Induced Dehydrochlorinations of N-Chloro-2-ethylpyrrolidine (NCl)

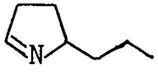
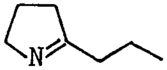
No	Base-Solvent	[NCl] ,M	[Base] ,M	Reaction Time	% 	% 	% Yield
1	MeONa-MeOH	0.386	1.65	1 hr	3.4 ± 0.1*	96.5 ± 1	100
2	t-BuOK-t-BuOH	0.295	0.435	1 hr	28 ± 1	72 ± 1	41
3	t-BuOK-t-BuOH	0.024	0.230	1 hr	27.5 ± 0.4	72.5 ± 0.4	—
4	t-BuOK-t-BuOH	0.120	0.133	1 hr	26.1 ± 0.5	73.9 ± 0.5	100
5	t-BuOK-Hexane**	0.103	0.305	overnight	41.4 ± 0.3	58.6 ± 0.3	99 ± 4
6	t-BuOK-Hexane**	0.079	0.199	24 hr	41.0 ± 0.2	59.0 ± 0.2	100

* Standard deviations from multiple analysis.

** Heterogeneous base-solvent combinations.

Table 13

Base-Induced Dehydrochlorinations of N-Chloro-2-n-propylpyrrolidine (NCl)

No	Base-Solvent	[NCl],M	[Base],M	Reaction Time	% 	% 	% Yield
1	MeONa-MeOH	0.191	0.501	1.5 hr	2.8 ± 0.2[*]	97.2 ± 2	56 ± 2
2	MeONa-MeOH	0.162	0.342	overnight	2.7 ± 0.3	97.2 ± 0.3	72.7 ± 0.2
3	t-BuOK-t-BuOH	0.230	0.222	1.5 hr	25.3 ± 0.2	74.7 ± 0.2	90 ± 2
4	t-BuOK-t-BuOH	0.16	0.348	2 hr	27.8 ± 0.1	72.7 ± 0.1	100
5	t-BuOK-Hexane[**]	0.275	0.707	23 hr	54.7 ± 0.3	45.3 ± 0.3	100

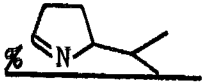
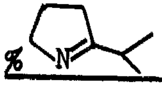
---

[*] Standard deviation from multiple analysis.

[**] Heterogeneous base-solvent combination.

Table 14

Base-Induced Dehydrochlorinations of N-Chloro-2-isopropylpyrrolidine (NCl)

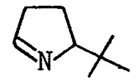
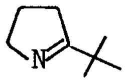
No	Base-Solvent	[NCL],M	[Base],M	Reaction Time	% 	% 	% Yield
1	MeONa-MeOH	0.157	0.342	overnight	3.4 ± 0.3*	96.6 ± 0.3	87 ± 1
2	*t*-BuOK-*t*-BuOH	0.140	0.342	2 hr	72.8 ± 0.7	27.2 ± 0.7	77 ± 1
				20 days	71 ± 1	29 ± 1	78 ± 3
3	*t*-BuOK-*t*-BuOH	0.207	0.202	20 hr	77.2 ± 0.4	22.8 ± 0.4	
4	*t*-BuOK-*t*-BuOH	0.151	0.353	17 hr	78.3 ± 0.2	21.7 ± 0.2	100
5	*t*-BuOK-Hexane**	0.140	0.598	34 hr	82.4 ± 0.7	17.6 ± 0.7	77 ± 2

* Standard deviations from multiple analysis.

** Heterogeneous base-solvent combination.

Table 15

Base-Induced Dehydrochlorinations of N-Chloro-2-*t*-butylpyrrolidine (NCl)

No	Base-Solvent	NCl ,M	Base ,M	Reaction Time	% 	% 	% Yield
1	MeONa-MeOH	0.111	0.514	19 hr	6.3 ± 0.3*	93.7 ± 0.3	86.5 ± 0.3
2	*t*-BuOK-*t*-BuOH	0.098	0.438	1 hr	49 ± 2	51 ± 2	-
				3 days	49.6	50.4	68
3	*t*-BuOK-*t*-BuOH	0.143	0.382	17 hr	52.9 ± 0.3	47.1 ± 0.3	100
4	*t*-BuOK-Hexane**	0.142	0.778	22 hr	83.2 ± 0.6	16.8 ± 0.6	-
5	*t*-BuOK-Hexane**	0.104	0.215	19 hr	76.1 ± 0.1	23.9 ± 0.1	62 ± 3
6	*t*-BuOK-Benzene**	0.094	0.142	3 days	84.2 ± 0.4	15.8 ± 0.4	84.6 ± 0.1

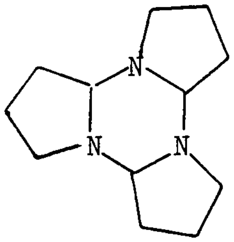
* Standard deviations from multiple analysis.

** Heterogeneous base-solvent combinations.

its ir, nmr, and mass spectra with those of the authentic compounds prepared by different method (except 2-methyl-1-pyrroline). The second components were shown to be 5-alkyl-1-pyrrolines by their ir, nmr, and mass spectra.

The 5-alkyl-1-pyrrolines have not previously been reported in the literature. The only 5-monosubstituted-1-pyrroline mentioned is 5-carboxy-1-pyrroline. However no spectral evidence was given for this compound and the structural assignment was made intuitively.

Fuhlhage and VanderWerf[68] have synthesized 1-pyrroline employing various methods and have found (based on the infrared evidence) that 1-pyrroline exists to a large extent as a trimer 56 along with a slight amount of dissociated monomer or dimer. The C=N obsorbtion of the monomer was observed at 1620 cm^{-1}. Bonnett [158] and his coworkers



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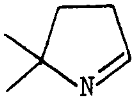

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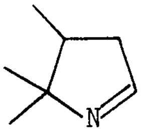

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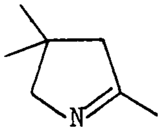


59

have reported C=N stretching frequencies for R-C=N- and H-C=N- at 1650 and 1620 cm^{-1}, respectively. The 5,5-dimethyl-1-pyrroline, 57, and 4,5,5-trimethyl-1-pyrroline, 58, have C=N stretching bands at 1621 and 1617 cm^{-1}, respectively. Whereas, the C=N absorbtion for 2,4,4-trimethyl-1-pyrroline, 59, was at 1644 cm^{-1}. Thus, the stretching absorbtions for a R-C=N- group is expected to be 20-30 cm^{-1} lower than that for an analogous H-C=N- linkage.

Table 16

The C=N Stretching Frequencies (cm^{-1}) for Prepared 5-Alkyl- and 2-Alkyl-1-pyrrolines

Alkyl	2-Alkyl-1-pyrroline	5-Alkyl-1-pyrroline
Me	1665	1635
Et	1655	1630
_n_-Pr	1655	1635
Isopr	1650	1630
_t_-Bu	1645	1640

A number of 2-alkyl substituted 5-membered,[68,185-187] 6-membered,[66, 67, 186, 188, 189] and 7-membered[127] cyclic imines have been examined by infrared spectroscopy. The C=N stretching absorbtions for these compounds were observed at 1667-1650 cm^{-1}. The C=N stretching bands observed for the prepared 2-alkyl-1-pyrrolines lie well within this range (Table 16). Compared with the 2-alkyl-1-pyrrolines, a reduction of 20-30 cm^{-1} in the C=N stretching frequencies for 5-alky-1-pyrrolines was generally observed (Table 16). This is entirely consistent with the findings of Fuhlhage and VanderWerf[68] and Bonnett.[158]

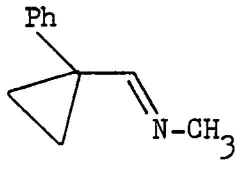
For the discrepancy observed in the 5-t-butyl- and 2-t-butyl-1-pyrroline systems there is no explanation at present. Even though the reduction in the frequency is small (5 cm^{-1}), it is in the right direction.

The proton nmr spectra of 5-alkyl-1-pyrrolines showed an absorbtion at 7.30-7.59 ppm which was assigned to C_2-H (Table 17). Stevens and his coworkers[155] have investigated the thermal rearrangement of cyclopropyl imines. The imines 60 and 61 had N=C-H absorbtions in the proton nmr at 7.57 and 7.80 ppm, respectively. The 2-pyrroline, 62, had a N=C-H absorbtion at 6.47 ppm, Ruenitz and Smissman[189] have prepared the imine 63 which exhibited a one-proton multiplet centered at 7.86 ppm for N=C-H. Considering these data, the assignment of the 7.30-7.50 absorption peaks in the proton nmr spectra to the C_2-H

Table 17

The N=C-H Absorption in Proton NMR for 5-Alkyl-1-pyrrolines

5-Alkyl	N=C-H (ppm)
Me	7.34
Et	7.43
n-Pr	7.30
Isopr	7.44
t-Bu	7.59



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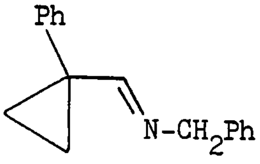

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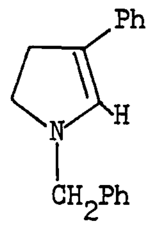

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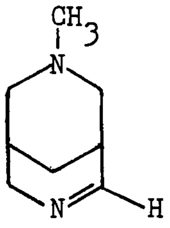

63

proton of a 5-alkyl-1-pyrroline structure seems reasonable.

Combining the ir, nmr, and mass spectral evidence for the second components isolated from the base-promoted dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines, the assigned 5-alkyl-1-pyrroline structures are well-supported.

3.2 N-Chloro-2-alkylpyrrolidines

Amines can be N-chlorinated by various chemicals under a variaty of conditions.[183] For the preparation of N-chloro-2-alkylpyrrolidines, pentane solution of 2-alkylpyrrolidines were treated with N-chlorosuccinimide at room temperature. This system was chosen because a) the reaction was quantitative, b) the excess N-chlorosuccinimide and resulting succinimide were insoluble in pentane and could be easily removed via filtration, c) pentane had a low boiling point and could be easily removed *in vacuo*, thereby making a solvent exchange easy.

N-Chloroamines decompose rapidly in the pure form and their toxic and explosive characteristics in this state must be taken into account.[183,190] Although the purification of N-chloropyrrolidine[191] and

N-chloro-2-alkylpiperidines[67] by distillation have been reported, the yields were low (probably due to decomposition during the distillation[192,193]). For these reasons, no attempt was made to isolate and purify the N-chloro-2-alkylpyrrolidines.

Gassman and his coworkers[194-197] have found that N-chloro derivatives of various cyclic secondary amines solvolytically ionize in protic solvents to give a number of products. Among these products the HCl salts of parent amines were identified. The formation of amines was rationalized by assuming that a heterolytic cleavage of the N-Cl bond of the N-chloroamines produced a singlet nitrenium ion, which was then converted into a triplet nitrenium ion by spin inversion. The resulting nitrogen cation radical then abstracts hydrogen from the solvent to give the parent amines.

Under the reaction conditions employed in this study, the parent amine or any other nitrogen containing compound would be in the free base form and would be easily recognizable during the gas chromatographic analysis. No compounds other than 5-alkyl- and 2-alkyl-1-pyrrolines were found in the reaction mixture of base-promoted dehydrochlorinations of N-chloro-2-alkylpyrrolidines. This fact combined with quantitative yields of the imines produced demonstrates that the solvolytic decomposition under the reaction conditions employed is negligible.

Lambert, Oliver, and Packard[191] have studied pyramidal inversion in saturated, cyclic amines containing from four to seven members and their N-chloro derivatives. The nmr spectra of the parent amines in tetrahydrofuran remained unchanged down to -150° because of rapid intermolecular exchange of the hydrogen on nitrogen. The activation parameters for N-chloroamines are given in Table 18. For the four-, five-, and seven-membered rings, nitrogen inversion was the rate-determining process. Whereas for the six-membered ring, ring reversal is the rate-determining process. The low activation parameters for N-chloropyrrolidine indicate that nitrogen inversion in for N-chloro-2-alkylpyrrolidines would be rapid which would make an anti-periplanar arrangement of C_β-H and N_α-Cl easily accessible, thus making an anti elimination possible. It has been found that in N-chloro-2-alkylpiperidines, a conformation with a 2-alkyl group equatorial and the chlorine axial, was preferred over one with both the 2-alkyl and chlorine substituents equatorial.[198]

TABLE 18

Activation Parameters for Nitrogen Inversion or Ring Reversal in Cyclic N-Chloramines

Compound	Solvent	E_a (kcal/mole)	$\Delta H^\ddagger$ (25°, kcal/mole)	$\Delta S^\ddagger$ (25°, eu)
Azetidine	$CHClF_2$	16.0	-	-
Pyrrolidine	$CFCl_3$	13.8	13.2	14.5
Piperidine	CH_2Cl_2	17.0	16.4	10.6
Homopiperidine	CH_2Cl_2	11.2	15.0	8.2

3.3 Dehydrochlorinations of N-Chloro-2-alkylpyrrolidines

3.3.1 Introduction

N-Chloroamines have been used for converting amines to their carbonyl derivatives and imines are postulated intermediates in these reactions.[64,199] Only a few examples are known where the reaction stopped at the imine stage.[67,199] Because of the difficulty of handling imines, it is customary to hydrolyse the imines to their carbonyl and amine components and analyse these more stable compounds (Chapter I Section 1.5). The hydrolysis is usually accomplished in acidic medium.

The possibility of double bond isomerization prior to the hydrolysis and the analysis of secondary reaction products made such a procedure unattractive for the present work. Therefore, the reaction mixtures were directly analysed using gas chromotography. Isolation of 5-alkyl-1-pyrrolines in the monomer form by preparative gas chromatography and the 1:1 correspondance of their molar response ratios with those for 2-alkyl-1-pyrrolines strongly suggests that there is either no or negligible polymerization or decomposition durind the analysis.

The base-promoted dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines proceeded smoothly at room temperature and were complete within a time period of 10-20 minutes for homogeneous reactions (MeONa-MeOH and t-BuOK-t-BuOH induced eliminations) and 1-2 hours for heterogeneous reactions (t-BuOK-hexane). For comparison, it was found that the dehydrochlorination of 2-chlorohexane by t-BuOK-t-BuOH required elevated temperatures (99°C) and long reaction period

(20 hours).[51] The facility of the dehydrochlorination reaction of the N-chloro-2-alkylpyrrolidines can be attributed to: a) lower stability of the heteroatom-leaving group bond (E_{C-Cl} in CCl_4= 78.2 kcal/mole and E_{N-Cl} in NCl_3= 46 kcal/mole)[4], b) increased acidity of β-hydrogen due to neighboring more negative nitrogen atom, and c) the larger energy difference between carbon-nitrogen single and double bonds compared to carbon-carbon single and double bonds (Table 3, $E_{C=N}-E_{C-N}=$ 74.2 kcal/mole and $E_{C=C}-E_{C-C}=$ 63.1 kcal/mole).

The 2-alkyl substituent and base-solvent effects on the regioselectivity of the base-promomed dehydrochlorinations of N-chloro-2-alkylpyrrolidines are summarized in Table 19.

3.3.2 2-Alkyl Substituent Effect

The effects of β-substituents in Hofmann and Saytzeff orientations have earlier been explained using electronic and steric effects. The Reader is referred to Chapter I Sections 3.4.3 and 3.4.4. Brown, et.al.[45,46] have examined dehydrobromination reactions of tertiary bromides, $RCH_2CBr(CH_3)_2$, with R=Me, Et, Isopr, and t-Bu in various base-solvent systems. Some of their results are tabulated in Table 20.

The preferential formation of the 2-alkene when R=Me was explained by the hyperconjugative interactions of the hydrogen atoms of the methyl groups with the incipient double bond. The reduction of these interactions by successive replacement of the hydrogen atoms in one of the methyl groups by one, two, and three methyl groups would reduce the preference of the formation of 2-alkene. But, it was

TABLE 19

Base-Promoted Dehydrochlorinations of N-Chloro-2-alkylpyrrolidines*

Base- Solvent	1-Pyrrolines %5-Me / %2-Me	%5-Et / %2-Et	%5-*n*-Pr / %2-*n*-Pr	%5-Isopr / %2-Isopr	%5-*t*-Bu / %2-*t*-Bu
MeONa- MeOH	2/98	3/97	3/97	3/97	6/94
t-BuOK- *t*-BuOH	9/91	26/74	28/72	78/22	53/47
t-BuOK- Hexane	15/85	41/59	55/45	82/18	83/17

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*Summarized data collected from Tables 11-15.

TABLE 20

Base-Promoted Dehydrobrominations of Alkyldimethylcarbinyl Bromides

Alkyl	EtOK-EtOH	*t*-BuOK-*t*-BuOH
	%1-ene-/%2-ene	%1-ene-%2-ene
Me	30/70	72.5/27.5
Et	50/50	—
Isopr	54/46	—
t-Bu	86/14	98/2

thought that this decreased propensity for hyperconjugative stabilization of the transition state leading to the 2-olefin could not account for the large increases in the 1-/2-alkene ratios. It was proposed, that as the steric requirements of R were increased, there would be increasing steric interactions between the groups R and Br in the transition state leading to the 2-olefin, whereas the transition state leading to the 1-olefin will not be effected and this would increase 1-/2-olefin ratio.

Bartsch, *et.al*.[200] have examined the influence of β-alkyl groups upon orientation. The pertinent data is given in Table 21.

It was found that positional orientations depended on the base strength in dimethyl sulfoxide solvent. With the highly ramified bases (Table 21 # 4-6) the correlation between positional orientation and

TABLE 21

Base-Promoted Dehydroiodinations of Alkyl Iodides in Dimethyl Sulfoxide

No	Base	%1-Alkene from 2-Butyl Iodide	%1-Alkene from 4-Methyl-2-pentyl Iodide
1	MeONa	17.0	-
2	EtONa	17.1	21.9
3	t-BuOK	19.7	38.7
4	2,6-(t-Bu)$_2$C$_6$H$_3$OK	19.2	51.4
5	(C$_6$H$_{11}$)$_3$COK	27.2	58.3
6	(2-Norbornyl)$_3$COK	29.4	66.1
7	t-BuOK(in t-BuOH)	29.9	82.3

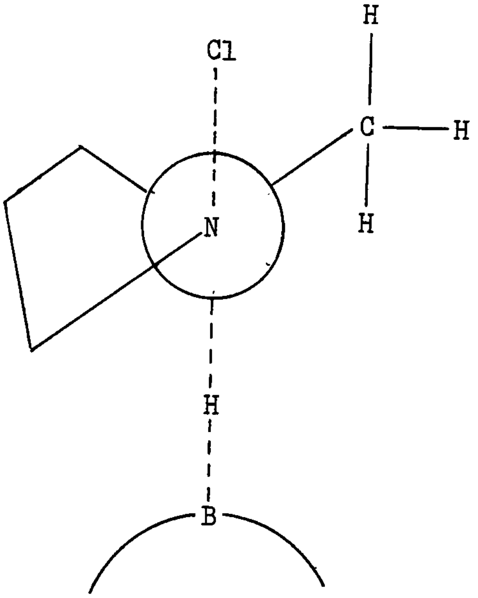
[a] Solvent=Me$_2$SO unless stated otherwise.

base strength broke down because of base steric effects. By changing the substrate from 2-butyl iodide to 4-methyl-2-pentyl iodide the threshold for base steric interactions occurred with bases of lesser complexity (Table 21 # 3). Although positional orientation in eliminations from 4-metyl-2-pentyl iodide was more sensitive to steric effects of dissociated bases than from 2-butyl iodide, associated bases such as t-BuOK-t-BuOH gave more terminal alkene than any dissociated base.

In contrast to Brown's findings for the dehydrobrominations of alkyldimethylcarbinyl bromides induced by the dissociated base, EtOK-

EtOH, (Table 20), no significant increase in the percentage of the Hofmann elimination products was found for the dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines promoted by a dissociated base, MeONa-MeOH, as the steric requirements of the alkyl group were increased from Me, Et, n-Pr, Isopr, to t-Bu (Table 19). The percentages of Hofmann orientation products, 5-alkyl-1-pyrrolines, obtained from dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines with MeONa-MeOH system were very small (2-6%) compared to Brown's results for alkyl bromides (30-86%) and Bartsch's findings with alkyl iodides (17-30%). Therefore, it can be concluded that the steric factors for the elimination reactions of N-chloro-2-alkylpyrrolidines with a dissociated base, MeONa-MeOH, are not important. The relative stabilities of the incipient carbon-nitrogen double bond dictates the orientation. This suggests considerable double bond formation in the imine-forming transition states.

When the base was changed from a dissociated base, MeONa-MeOH, to an associated base, t-BuOK-t-BuOH or t-BuOK-Hexane, steric interactions of 2-alkyl substituents with base were observed (Table 19). When the alkyl group is methyl the steric interactions between methyl and base is quite small, as depicted in 64 and Saytzeff orientation is dominant, 91% (t-BuOK-t-BuOH) and 85% (t-BuOK-Hexane). When one of the hydrogens on the 2-methyl group was replaced with a methyl group, the steric interaction is increased and the percentage of Hofmann orientation becomes enhanced, 26% (t-BuOK-t-BuOH) and 41% (t-BuOK-Hexane). Although the replacement of the 2-ethyl group with an 2-n-propyl



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group showed no significant change in the amount of 5-alkyl-1-pyrroline in the t-BuOK-t-BuOH system (26% 5-ethyl- and 28% 5-n-propyl-1-pyrroline), for the more sterically demanding heterogeneous base-solvent system, t-BuOK-Hexane, more 5-n-propyl-1-pyrroline (55%) than 5-ethyl-1-pyrroline (41%) was obtained. When two of the hydrogens of the 2-methyl group of 64 were replaced with methyl groups, thereby making the 2-substituent considerably more sterically demanding, Hofmann orientation dominated (5-isopropyl-1-pyrroline 78% and 82% for t-BuOK-t-BuOH and t-BuOK-Hexane, respectively). It was anticipated that continuing the trend by replacing all of the hydrogens of the 2-methyl group in 64 by methyl groups should have resulted in even more dramatic steric interactions between the 2-t-butyl group and the associated bases. However, a drop in the percentage of the Hofmann orientation product (53% 5-t-butyl-1-pyrroline) for the t-BuOK-t-BuOH base-solvent system and no change for the t-BuOK-Hexane system (83% 5-t-butyl-1-pyrroline) were observed as the 2-alkyl group was changed from 2-isopropyl to 2-t-butyl. At present the reasons for this anomalous result are uncertain. Possible explanations include a change of the preferred elimination stereochemistry.

The data in Table 19 clearly establish that base-β-alkyl group steric interactions are operative in the dehydrochlorination reactions of N-chloro-2-alkylpyrrolidines promoted by associated bases. Therefore, positional orientation may be controlled by such interactions in carbon-nitrogen double bond-forming eliminations in much the same manner to that previously demonstrated for carbon-carbon double bond-forming eliminations.

3.3.3 Base-Solvent Effects

The effect of base-solvent combinations on the positional orientation of carbon-carbon double bond-forming eliminations has already been discussed in Chapter I (Section 3.4.4). It was concluded that, except for oversized bases, the base strength for the dissociated bases and the base size for the associated bases were the important factors in determining orientation for olefin-forming elimination reactions. In this study one dissociated base, MeONa-MeOH and two associated base systems, t-BuOK-t-BuOH and t-BuOK-hexane, were used. Trends consistent with those observed in base-promoted olefin-forming elimination reactions were found for imine-forming dehydrohalogenations. As the base-solvent system was changed from a dissociated base to an associated base, the amount of 5-alkyl-1-pyrroline (Hofmann orientation) formed from the dehydrochlorination reactions of all the N-chloro-2-alkylpyrrolidines increased accordingly.

4.0 Conclusion

The regioselectivity of base-promoted imine formation was probed using N-chloro-2-alkylpyrrolidines as substrates. Dehydrochlorination of N-chloro-2-alkylpyrrolidines produced two isomeric imines, 5-alkyl- and 2-alkyl-1-pyrrolines. Although 2-alkyl-1-pyrrolines may be prepared by several methods (Chapter I Section 4.2), 5-alkyl-1-pyrrolines were previously unknown. The use of specific base-solvent systems allowed viable syntheses 5-alkyl-1-pyrrolines. Of the base-solvent systems studied, the heterogeneous base-solvent combination, t-BuOK-hexane, gave the best yields of 5-alkyl-1-pyrrolines. The synthetic utility of the base-promoted dehydrochlorination reactions have been dramatically demonstrated for the N-chloro-2-isopropyl- and 2-_t_-butylpyrrolidine systems (Table 18). By choosing either a dissociated base, MeONa-MeOH, or an associated base, _t_-BuOK-Hexane, either 5-alkyl-1-pyrroline or 2-alkyl-1-pyrroline may be obtained in high yield.

Preliminary results of base-promoted dehydrochlorination reactions involving N-chloro-2-methyl- and 2-ethylpiperidines are not encouraging. Only 2-alkyl-1-piperidienes were obtained. Whether this is attributable to the six-membered ring or the analytical techniques remains to be demonstrated. The investigation by Lambert and his coworkers[191] of cyclic N-chloramine inversion showed that among the four-, five-, six-, and seven-membered cyclic amines, the six-membered ring is unique. The N-chloroamine derivatives of these amines, except for the six-membered N-chloropiperidine, showed a prefrence for nitrogen inversion over ring reversal. It was found that ring reversal was preferred by the N-chloropiperidine. Whether this uniqueness of the six-membered rings extends to elimination reactions may be explored by examining base-promoted eliminations of N-chloro derivatives of four- and seven-membered cyclic amines.

CHAPTER III

BASE-PROMOTED ELIMINATIONS FROM N-AROYLOXY-2-ALKYLPYRROLIDINES

1.0 Experimental

1.1 Materials and Instrumentation

The following chemicals were used in this part of the research and the companies from which they were purchased are given in parentheses: benzoyl peroxide (Fisher); potassium carbonate (Fisher); sodium hydride (Alfa); anhydrous diethyl ether (Mallinckrodt); benzene (MCB); silica gel (Sargent-Welch); silica gel tlc plates (Analtech); sodium peroxide (Allied Chemical); *p*-nitrobenzoyl chloride (Eastman); toluene (Phillips 66); *p*-anisic acid (Aldrich); thionyl chloride (Eastman); 2-methylpiperidine (Reilly Tar and Chemicals); sodium hydroxide (Fisher); proton sponge (Aldrich), pentane (Phillips 66); *n*-butyl lithium (Aldrich); anisole (Aldrich); *o*-xylene (Aldrich). *t*-Butyl alcohol was dried by distilling twice from potassium. Benzene was purified by distillation using an efficient fractionating column. The other solvents were used as received.

The N-aroyloxy-2-alkylpyrrolidines were identified by comparing their ir and proton nmr with the anticipated spectral values. Infrared spectra were taken either with a Perkin-Elmer 457 or Beckman 33 instrument and were recorded in cm^{-1}. The proton nmr spectra were taken either with Varian XL100, Varian A60, or Varian EM360 spectrophotometer and were recorded in ppm with respect to the internal standard tetramethylsilane (s=singlet, d=doublet, t=triplet, m=multiplet). For analyses of elimination products an Antek 400 flame ionization detector gas chromatograph was used.

1.2 Synthesis of Substituted Benzoyl Peroxides

1.2.1 p-Nitrobenzoyl Peroxide

The method by Price and Krebs[201] was used to synthesize p-nitrobenzoyl peroxide. A 500 ml three-necked round-bottomed flask containing 100 ml of water was fitted with a mechanical stirrer, a thermometer, and a pressure-equilizing dropping funnel and immersed in an ice-water bath. When the temperature of the water had dropped to 3°C, 10.0 g (0.13 mole) of sodium peroxide was added. This was followed, with vigorous stirring, by a dropwise addition of a solution of 37.0 g (0.20 mole) of p-nitrobenzoyl chloride in 150 ml of toluene over a period of 30 minutes. After the addition of p-nitrobenzoyl chloride was complete, the reaction mixture was stirred for an additional 1.5 hours. The precipitate formed was filtered and washed with 250 ml of ice-water. The pale yellow crystals were dried under high vacuum over $CaCl_2$ to yield 31.0 g (93.4%) of the peroxide. The p-nitrobenzoyl peroxide was used without any further purification.

1.2.2 p-Anisoyl Peroxide

p-Anisoyl chloride was prepared from 30.4 g of p-anisic acid and 25.5 ml of thionyl chloride following the procedure given in Vogel[202] to yield 30.9 g (90.6%) of the desired acid chloride. p-Anisoyl peroxide was prepared by the method of Price and Krebs[201] as outlined in Section 1.2.1 from 5.0 g (0.064 mole) of sodium peroxide in 50 ml of water and a solution of 17.05 g (0.10 mole) of p-anisoyl chloride in 55 ml of toluene. The yield of p-anisoyl peroxide was 14.6 g (96.6%) after vacuum drying. The p-anisoyl peroxide was used without further purification.

1.3 Synthesis of Substrates

1.3.1 N-Benzoyloxy-2-methylpyrrolidine

A 250 ml three-necked round-bottomed flask was fitted with a reflux condenser, a pressure-equilizing dropping funnel, and a mechanical stirrer. Anhydrous diethyl ether (100 ml) was placed into the flask and cooled to 0°C with an ice-bath. Benzoyl peroxide 2.42 g (10.0 mmole) and 8.29 g (60.0 mmole) of potassium carbonate was added. A solution of 850 mg (10.0 mmole) of 2-methylpyrrolidine was introduced dropwise over one hour at 0°C. The reaction mixture was stirred at 0°C for 3.5 hours and filtered. The ether layer was washed with 60 ml of saturated aqueous sodium bicarbonate solution and dried over $MgSO_4$ in the refrigerator overnight. The solvent was removed to yield 1.85 g of crude material. Tlc (silica gel, benzene:ether=9:1) showed the presence of three compounds. The crude product was purified by column chromatography using silica gel as adsorbant and benzene-ether

(9:1) as aluant to yield 882 mg (43%) of N-benzoyloxy-2-methylpyrrolidine as an oil; ir (neat): 3100, 3080, 2980, 2930, 2870, 1735 (C=O), 1600, 1585, 1480, 1450, 1255, 1090, 1065, 1025, 710, 680; nmr ($CDCl_3$): 8.06-7.96 ppm (m, 2.0 H), 7.66-7.32 ppm (m, 3.1 H), 3.72-2.90 ppm (m, 3.0 H), 2.16-1.46 (m, 4.1 H), 1.30-1.23 (d, 3.0 H).

1.3.2. N-(p-Nitrobenzoyloxy)-2-methylpyrrolidine

N-(p-Nitrobenzoyloxy)-2-methylpyrrolidine was prepared by a method analogous to that given in Section 1.3.1. To a suspension of 3.32 g (10.0 mmole) of p-nitrobenzoyl peroxide and 8.29 g (60.0 mmole) of potassium carbonate in 100 ml of anhydrous diethyl ether at 0°C, a solution of 0.85 g (10.0 mmole) of 2-methylpyrrolidine in 80 ml of anhydrous diethyl ether was added dropwise. The reaction mixture was stirred at 0°C for one hour and at room temperature for 24 hours. It was filtered and the ether layer was washed with 100 ml of saturated sodium bicarbonate solution. After drying over $MgSO_4$ and removal of the solvent, 1.73 g of crude product was obtained which was purified using chromatography (silica gel; benzene:ether=9:1). The yield of product (an oil) was 0.994 g (48.3%); ir (neat): 3120,3090, 2990, 2880, 1750 (C=O), 1610, 1530, 1348, 1260, 1080, 845, 710; nmr ($CDCl_3$): 8.35-8.12 ppm (m, 3.9 H), 3.74-2.96 ppm (m, 3.0 H), 2.28-1.48 ppm (m, 4.2 H), 1.31 and 1.25 ppm (d, 3.0 H).

1.3.3 N-(p-Anisoyloxy)-2-methylpyrrolidine

A method similar to that given in Section 1.3.1 was followed. To a suspension of 3.02 g (10.0 mmole) p-anisoyl peroxide and 8.29 g (60.0 mmole) of potassium carbonate in 100 ml of anhydrous diethyl ether at 0°C, a solution of 0.850 g (10.0 mmole) of 2-methylpyrrolidine in 90 ml of anhydrous diethyl ether was added dropwise. The reaction mixture was stirred at 0°C for one hour and then at room temperature for 20 hours. It was filtered and the ether layer was washed with 60 ml of saturated sodium bicarbonate solution. The product was recovered from the reaction mixture in the usual manner and after column chromatography (silica gel; benzene:ether=9:1) 1.03 g (46%) of N-(p-anisoyloxy)-2-methylpyrrolidine as an oil was obtained; ir (neat): 3030, 2980, 2950, 2860, 1735 (C=O), 1610, 1585, 1515, 1250, 1165, 1070, 840, 760; nmr ($CDCl_3$): 8.02-7.92 ppm (d, 2.0 H), 6.97-6.87 ppm (d, 2.0 H), 3.84 ppm (s, 3.0 H), 3.74-2.93 ppm (m, 3.0 H), 2.22-1.48 ppm (m, 4.1 H), 1.28 and 1.22 ppm (d, 3.2 H).

1.3.4 N-(p-Anisoyloxy)-2-ethylpyrrolidine

A three-necked round-bottomed flask was fitted with a reflux condenser, a gas inlet adaptor, a magnetic stirrer and a septum. Sodium hydride (480 mg, 50% oil dispersion, 10.0 mmole) was introduced into the flask and washed with pentane (3X20 ml). Anhydrous diethyl ether (30 ml) was added. Then a solution of 990 mg (10.0 mmole) of 2-ethylpyrrolidine in 120 ml of anhydrous diethyl ether was introduced into the flask and stirred for 5 minutes. p-Anisoyl peroxide (3.02 g, 10.0 mmole) was added and the mixture was refluxed for 24 hours. The reaction mixture was allowed to cool, was filtered, and the solid was washed with ether. After removal of solvent, the crude product (2.44 g) was purified by column chromatography (silica gel; benzene:ether= 9:1) to yield 1.11 g (45%) of N-(p-anisoyloxy)-2-ethylpyrrolidine; ir (neat): 3080, 2970, 2940, 2880, 2850, 1740 (C=O), 1610, 1515, 1465, 1315, 1255, 1165, 1020, 840, 755; nmr ($CDCl_3$): 8.07-7.93 ppm (d, 2.0 H), 7.00-6.85 ppm (d, 2.0 H), 3.89 ppm (s, 3.0 H), 3.70-2.80 ppm (m, 3.0 H), 2.27-1.22 ppm (m, 6.0 H), 1.10-0.83 (t, 3.2 H).

1.3.5 N-(p-Anisoyloxy)-2-n-propylpyrrolidine

The general method outlined in Section 1.3.4 was used. A 0.48 g sample of a 50% oil dispersion of sodium hydride (10.0 mmole) was washed with pentane and 50 ml of ether was added. The sodium hydride suspension was allowed to react with a solution of 1.13 g (10.0 mmole) of 2-n-propylpyrrolidine in 100 ml of diethyl ether for 5 minutes and then 3.02 g (10.0 mmole) of p-anisoyl peroxide was added. The mixture was stirred at room temperature for 2.5 hours and then refluxed for 23 hours. The reaction mixture was allowed to cool, was filtered, and the solvent was removed. The crude product was purified by column chromatography (silica gel; benzene:ether=9:1) to yield 1.56 g (59%) of N-(p-anisoyloxy)-2-n-propylpyrrolidine; ir (neat): 3080, 2960, 2940, 2870, 1738 (C=O), 1610, 1585, 1510, 1460, 1315, 1245, 1110, 1065, 1020, 840, 755; nmr ($CDCl_3$): 8.04-7.90 ppm (d, 2.0 H), 6.98-6.83 ppm (d, 1.9 H), 3.87 ppm (s, 2.9 H), 3.67-2.80 ppm (m, 3.0 H), 2.23-0.77 ppm (m, 11.1 H).

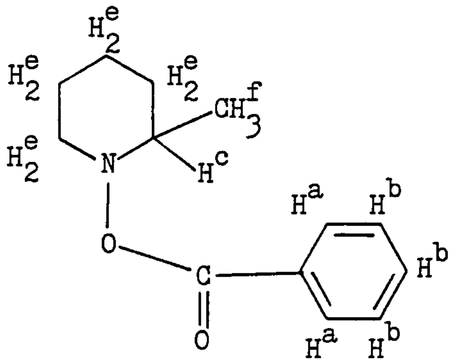
1.3.6 N-(p-Anisoyloxy)-2-isopropylpyrrolidine

The general method given in Section 1.3.4 was used. Sodium hydride (0.480 g of a 50% oil dispersion, 10.0 mmole) was washed with pentane and reacted with a solution of 1.13g (10.0 mmole) of 2-isopropylpyrrolidine in 150 ml of diethyl ether for 5 minutes. Then, 3.02 g (10.0 mmole) of p-anisoyl peroxide was added. The mixture was stirred at room temperature for 15 hours and refluxed for 24 hours. After the reaction mixture had been allowed to cool, it was filtered and the solvent was removed *in vacuo* to give 3.0 g crude product. After purification by column chromatography (silica gel; benzene: ether=9:1) 1.56g (59%) N-(p-anisoyloxy)-2-isopropylpyrrolidine was obtained; ir (neat): 3090, 2990, 2900, 2860, 1745 (C=O), 1615, 1590, 1520, 1470, 1320, 1255, 1075, 1025, 845, 760; nmr ($CDCl_3$): 8.05-7.90 ppm (d, 2.0 H), 7.00-6.85 ppm (d, 2.1 H), 3.87 ppm (s, 3.0 H), 3.80-2.80 ppm (m, 3.0 H), 2.20-1.50 ppm (m, 5.0 H), 1.07-.90 ppm (d of d, 6.0 H).

1.3.7 N-(p-Anisoyloxy)-2-t-butylpyrrolidine

The general method given in Section 1.3.4 was used. Sodium hydride (0.283 g of 50% oil dispersion, 5.9 mmole) was washed with pentane and reacted with a solution of 0.737 g (5.8 mmole) of 2-t-butylpyrrolidine in 100 ml of diethyl ether for 5 minutes. After the addition of 1.78 g (5.9 mmole) of p-anisoyl peroxide, the reaction mixture was stirred at room temperature for 4 hours and then refluxed for 24 hours. The product was recovered from the reaction mixture in the usual manner. After column chromatography (silica gel, benzene:ether= 9:1) 0.331 g (21%) of N-(p-anisoyloxy)-2-t-butylpyrrolidine was obtained; ir (neat): 3080, 2960, 2880, 1740 (C=O), 1610, 1590, 1515, 1250, 1165, 1070, 1020, 840, 760; nmr ($CDCl_3$): 7.97-7.83 ppm (d, 1.8 H), 6.91-6.77 ppm (d, 2.0 H), 3.78 ppm (s, 3.0 H), 3.57-2.73 ppm (m, 2.8 H), 2.05-1.50 ppm (m, 4.0 H), 0.94 ppm (s, 8.8 H).

1.4 Synthesis of N-Benzoyloxy-2-methylpiperidine



In order to develop a good synthetic method for the preparation of N-aroyloxy-2-alkylpyrrolidines, the synthesis of N-benzoyloxy-2-methylpiperidine was attempted under various reaction conditions. The crude reaction products were purified using column chromatography. Silica gel was used as the adsorbant and the compounds were eluted with a benzene-diethyl ether (9:1) mixture. Interpretation of the ir and nmr spectra are given below: ir (neat) 3080 and 3040 (Ar-H stretch), 2980, 2950, 2870, and 2850 (saturated C-H stretch), 1750 (C=O), 1610 and 1595 (aromatic C=C), 1250 (C-O), 760 and 700 (mono-substitution on benzene); nmr ($CDCl_3$): 8.10-7.99 ppm (m, 2.1 H^a), 7.64-7.30 ppm (m, 3.1 H^b), 3.66-3.48 ppm (m, 1.0 H^c), 3.10-2.56 ppm (unresolved, 2.1 H^d), 2.10-1.40 ppm (unresolved, 5.9 H^e), 1.22-1.15 ppm (d, 3.0 H^f).

1.4.1 Sodium Hydroxide-Diethyl Ether (-5°-0°C)

A 250 ml three-necked round-bottomed flask containing 100 ml of anhydrous diethyl ether and 4.84 g (20.0 mmole) of benzoyl peroxide was fitted with a reflux condenser, a magnetic stirrer, and a pressure-equilizing dropping funnel and placed into an ice-salt bath. When the temperature had dropped to -3°C, 5.0 g (125 mmole) of powdered sodium hydroxide was added. A solution of 1.98 g (20.0 mmole) of 2-methylpiperidine in 100 ml of anhydrous diethyl ether was added dropwise over a period of 30 minutes. After the addition had been completed, the reaction mixture was stirred at 0° to -5°C for 3.5 hours, was filtered and the ether layer was washed with 100 ml of saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and the solvent was removed to give 4.6 g of crude product which was purified in the usual manner to give 1.19 g (27.5%) of the desired product.

1.4.2 Sodium Hydroxide-Diethyl Ether (Reflux)

A mixture of 1.98 g (20.0 mmole) of 2-methylpiperidine, 4.84 g (20.0 mmole) of benzoyl peroxide, 5.0 g (125.0 mmole) of powdered sodium hydroxide, and 150 ml of anhydrous diethyl ether was refluxed for 20 hours. The reaction mixture was allowed to cool and was filtered. The organic layer was washed with 100 ml of saturated sodium bicarbonate solution, dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified in the usual manner to yield 2.16 g (49.2%) of N-benzoyloxy-2-methylpiperidine.

1.4.3 Triethylamine-Diethyl Ether (Reflux)

To a solution of 0.99 g (10.0 mmole) 2-methylpiperidine and 1.01 g (10.0 mmole) of triethylamine in 100 ml of anhydrous diethyl ether, 2.42 g (10.0 mmole) of benzoyl peroxide was added. The reaction mixture was stirred at room temperature for 24 hours. The color of the solution became darker as time progressed. Since tlc showed the presence of benzoyl peroxide, the reaction mixture was refluxed for 24 hours. A brown oil appeared at this point. The reaction mixture was allowed to cool and the ether layer was decanted. After washing the ether layer with saturated sodium bicarbonate solution and drying over $MgSO_4$, the solvent was removed in vacuo to give 0.557 g of crude product. A very small amount of N-benzoyloxy-2-methylpiperidine was obtained from the crude product in the usual manner.

1.4.4 1,8-Bis-(dimethylamino)-naphthalene-Diethyl Ether (Reflux)

To a solution of 0.99 g (10.0 mmole) of 2-methylpiperidine and 2.143 g (10.0 mmole) of 1,8-bis-(dimethylamino)-naphthalene (proton sponge) in 100 ml of anhydrous diethyl ether, 2.42 g (10.0 mmole) of benzoyl peroxide was added and the reaction mixture was stirred at room temperature for 24 hours. The color of the solution became darker as the time passed. Since the presence of benzoyl peroxide was observed by tlc, the reaction mixture was refluxed for 24 hours. An oil separated. The ether layer was separated, washed with saturated solution of sodium bicarbonate (2X50 ml), and dried over $MgSO_4$. After the solvent had been removed *in vacuo*, the crude product (356.2 mg) gave only a small amount of N-benzoyloxy-2-methylpiperidine.

1.4.5 Sodium Hydroxide-Benzene (Reflux)

2-Methylpiperidine (1.98 g, 20.0 mmole) and 4.84 g (20.0 mmole) of benzoyl peroxide were dissolved in 100 ml of benzene and stirred at room temperature for 10 minutes. Then, 5.0 g (125.0 mmole) of powdered sodium hydroxide was added. The suspension was stirred at room temperature for 1 hour. Additional benzene (60 ml) was added and the mixture was refluxed for 20 hours. The reaction mixture was allowed to cool, filtered, and the solvent removed. According to tlc (silica gel, benzene:ether=9:1) the residue contained a single compound. The ir and nmr spectra of the crude product showed the compound to be N-hydroxy-2-methylpiperidine. The crude product was purified by distillation, bp 47-48°C/0.5 mm Hg. The crude yield was quantitative. However due to loss in the distillation step only 1.47 g (64%) of purified N-hydroxy-2-methylpiperidine was obtained.

1.4.6 Sodium Hydride-Diethyl Ether-Benzene (Reflux)

A three-necked round-bottomed flask was fitted with a reflux condenser, a gas inlet adaptor, a magnetic stirrer, and a rubber septum. Sodium hydride (0.96 g of a 50% oil dispersion, 20.0 mmole) was placed into the flask and was washed with pentane (3X30 ml) under nitrogen atmosphere. After the residual pentane had been removed via purging with a nitrogen atmosphere, 30 ml of anhydrous diethyl ether was added. The septum was replaced by a pressure-equilizing addition funnel. A solution of 1.98 g (20.0 mmole) of 2-methylpiperidine in 50 ml of anhydrous diethyl ether was added dropwise. After the addition had been completed, the reaction mixture was refluxed for 5 minutes, and was allowed to cool to room temperature. An attempt was made to dissolve 4.84 g (20.0 mmole) of benzoyl peroxide in 100 ml of anhydrous diethyl ether. Most of it did not dissolve. The clear ether layer was decanted and the remaining peroxide was dissolved in 30 ml of benzene. The ether layer and benzene solution were added dropwise to the amine solution consecutively. The reaction mixture was stirred at room temperature for 17 hours. Since the presence of benzoyl peroxide was detected by tlc, the mixture was refluxed for 24 hours. N-Benzoyloxy-2-methylpiperidine was obtained from the reaction mixture in the usual manner, 3.15 g (72%) yield.

The reaction was repeated on $\frac{1}{2}$ scale and the reaction time at room temperature was decreased to 1 hour and the reflux time to 20 hours. The N-benzoyloxy-2-methylpiperidine was then obtained in 56% yield.

1.4.7 Potassium Carbonate-Benzene (Reflux)

To a solution of 0.99 g (10.0 mmole) of 2-methylpiperidine in 150 ml of benzene, 6.91 g (50.0 mmole) of potassium carbonate and

2.42 g (10.0 mmole) of benzoyl peroxide were added and the mixture was refluxed for 22 hours. The crude product (1.64 g) was recovered from the reaction mixture but was not purified any further (purified yield might have been around 50%).

1.4.8. n-Butyl Lithium-Hexane-Benzene (Room Temperature)

A three-necked flask was fitted with a reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a septum, placed into a dry-ice-acetone bath, and charged with a 7.7 ml of a solution of n-butyl lithium (10.0 mmole) in n-hexane (1.34 M) under argon atmosphere. The rubber septum was replaced by a pressure-equilizing dropping funnel. A solution of 0.99 g (10.0 mmole) of 2-methylpiperidine in 10 ml of n-hexane was added dropwise. The solution was allowed to warm to room temperature and a solution of 2.42 g (10.0 mmole) of benzoyl peroxide was added dropwise. After the addition had been completed, the reaction mixture was stirred at room temperature for 24 hours. No N-benzoyloxy-2-methylpiperidine could be detectected by tlc.

1.4.9 Potassium Hydride-Diethyl Ether (Reflux)

A three-necked round-bottomed flask was fitted with a reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a rubber septum and was charged with 1.688 g (9.26 mmole) of a 22% oil dispersion of potassium hydride. The hydride was washed with pentane (3X20 ml) under nitrogen atmosphere. The septum was replaced with a pressure-equilizing dropping funnel and a solution of 0.917 g (9.26 mmole) of

2-methylpiperidine in 100 ml of anhydrous diethyl ether was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes and 2.24 g (9.26 mmole) of benzoyl peroxide was added in small portions. After stirring at room temperature for 1 day, the reaction mixture was refluxed for 45 hours. N-Benzoyloxy-2-methylpiperidine (1.58 g, 78%) was obtained in the usual manner.

1.4.10 Sodium Hydride-Diethyl Ether (Reflux)

Sodium hydride (0.48 g of 50% oil dispersion, 10.0 mmole) was washed with pentane (3X20 ml) in the usual manner. Anhydrous diethyl ether (30 ml) was added. After the dropwise addition of a solution of 0.99 g (10.0 mmole) of 2-methylpiperidine in 120 ml of anhydrous diethyl ether had been completed, 2.42 g (10.0 mmole) of benzoyl peroxide was added in one portion. The mixture was refluxed for 20 hours. N-Benzoyloxy-2-methylpiperidine was isolated from the reaction mixture in the usual manner (1.48 g, 68% yield).

1.5 Elimination Procedures

The t-BuOK-t-BuOH base solvent system was prepared according to the procedure given in Chapter II Section 1.4.1. A measured amount of (4-5 ml) of t-BuOK-t-BuOH was added directly to the N-aroyloxy-2-alkylpyrrolidines. The mixtures were stirred at room temperature for 1 hour, centrifuged, and the clear supernatant solutions were analysed.

The t-BuOK-diethyl ether induced eliminations were done by adding a weighed amount (under nitrogen atmosphere) of commercial t-BuOK to an anhydrous diethyl ether solution of the N-aroyloxy-2-alkylpyrrolidines. The mixtures were stirred at room temperature for 4 hours, centrifuged, and the clear supernatant solutions were analysed.

A measured amount of internal standard solutions (anisole for 2- and 5-ethyl-1-pyrrolines and o-xylene for the rest of the 2- and 5-alkyl-1-pyrrolines) was mixed with a measured amount of the reaction solutions and the resulting solutions were analysed by gas chromatography. A 30'x1/8" column of 10% Carbowax 400 on Chromosorb WAW-DMCS was used for the analysis of the imines. The column temperatures employed were 90°C for methyl-, ethyl-, and n-propyl-1-pyrrolines and 100°C for isopropyl-and t-butyl-1-pyrrolines. The injector temperature was 170°C for methyl-1-pyrrolines and 165°C for the remainder of the alkyl-1-pyrrolines. The detector temperature was set at 220°C.

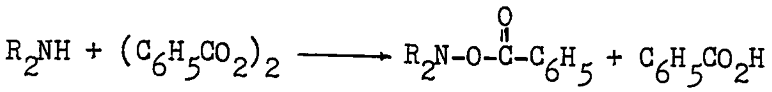
The relative ratios of the peak areas from at least three chromatograms were averaged and were corrected for molar responses (Chapter II Section 1.4.4). The relative percentage of the imines formed and actual imine yields were calculated from the corrected ratios of peak areas.

2.0 Results

2.1 N-Benzoyloxy-2-methylpiperidine

Secondary aliphatic amines react with benzoyl peroxide to give N,N-dialkyl-O-benzoylhydroxylamines and benzoic acid (Equation 51).[203] The mechanism involves nucleophilic attack by the amine on the perox-

Eq-51



$$R_2NH + (C_6H_5CO_2)_2 \longrightarrow R_2N\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}C_6H_5 + C_6H_5CO_2H$$

ide to give a pair of ions which undergo proton transfer to form the products. Since the overall reaction uses two moles of amine per one mole of peroxide[28,203], the liberated benzoic acid must react with a second mole of the amine to form an unreactive ammonium benzoate salt. Although the yields from secondary aliphatic amine reactions with benzoyl peroxide are good when calculations are based on two moles of amine per one mole of peroxide, it was desirable to search for an improved synthesis which would require only one mole of a secondary amine (ultimately 2-alkylpyrrolidines for this dissertation research). As a model compound 2-methylpiperidine was employed because it is commercially available. Thus, the synthesis of N-benzoyloxy-2-methylpiperidine was examined under various reaction conditions (Table 22). A second base was added in an attempt to improve the conversion of the amine to its N-benzoyloxy derivative. Both soluble bases, triethylamine, 1,8-bis-(dimethylamino)-naphthalene (proton sponge), and n-butyl lithium (Table 22, # 3,4,9), and insoluble, heterogenous bases, sodium hydroxide, sodium hydride, potassium carbonate, and potassium hydride (Table 22, # 1,2,5-8,10,11) were used.

It was found that the soluble bases produced very little or no N-benzoyloxy-2-methylpiperidine. Among the insoluble bases sodium hydride and potassium hydride were the most effective (68-78% yield based on 1:1 reaction ratio of amine to benzoyl peroxide). Diethyl

TABLE 22

Preparation of N-Benzoyloxy-2-methylpiperidine[1]

No	Base	Solvent	Time (hr)	Temp	%Yield
1	NaOH	Et_2O	3.5	-3°C	22
2	NaOH	Et_2O	20	reflux	49
3	Et_3N	Et_2O	24	reflux	-[2]
4	Proton Sponge[3]	Et_2O	24	reflux	-[2]
5	NaOH	Benzene	20	reflux	0
6	NaH	Et_2O-Benzene	24	reflux	72
7	NaH	Et_2O-Benzene	20	reflux	55
8	K_2CO_3	Benzene	22	reflux	-[4]
9	n-BuLi	Hexane-Benzene	24	25°C	0
10	KH	Et_2O	45	reflux	78
11	NaH	Et_2O	20	reflux	68

[1] All yields given are based on isolated purified product.

[2] Less than 10%, not isolated.

[3] 1,8-Bis-(dimethylamino)-naphthalene.

[4] Less than 50%, not isolated.

ether or a combination of diethyl ether and benzene proved to be appropriate solvents for these reactions. When reactions were run at room temperature or below the yields were low and the isolation of the product was complicated by the presence of the unreacted benzoyl peroxide. Refluxing the reaction mixture both increased the yield and destroyed the unreacted benzoyl peroxide.

2.2 N-Aroyloxy-2-alkylpyrrolidines

The N-aroyloxy-2-alkylpyrrolidines were prepared from 2-alkylpyrrolidines and aroyl peroxides, $(\underline{p}\text{-}XC_6H_4CO_2)_2$ where X= H, NO_2, or OMe, by refluxing in diethyl ether in the presence of K_2CO_3 or NaH. The results are tabulated in Table 23. The percentage yields of the isolated products were based on 2-alkylpyrrolidines.

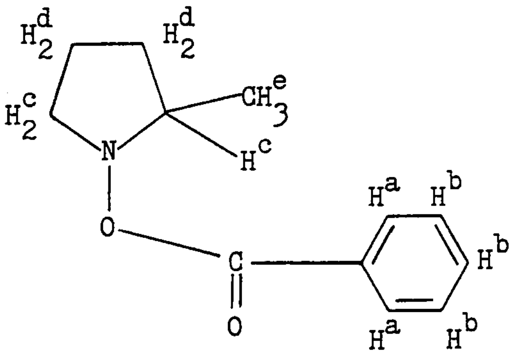
TABLE 23

N-Aroyloxy-2-alkylpyrrolidines $(RC_4H_7NO_2CC_6H_4\text{-}\underline{p}\text{-}X)$

R	X	Added Base	%Yield
Methyl	H	K_2CO_3	43
Methyl	NO_2	K_2CO_3	48
Methyl	OMe	K_2CO_3	46
Ethyl	OMe	NaH	45
n-Propyl	OMe	NaH	59
Isopropyl	OMe	NaH	59
t-Butyl	OMe	NaH	21

The isolated N-aroyloxy-2-alkylpyrrolidines were relatively stable when kept cold in a refrigerator, but decomposed in a few hours at room temperature. Due to this instability, elemental analyses of the compounds were not attempted. The structures were verified by ir and nmr spectra. Mass spectra of these compounds could not be obtained because the Varian Mat 311 mass spectrometer was inoperative and samples which were sent to the University of Texas (Austin) decomposed before mass spectrometric analysis was performed. The interpretations of the spectral data are given in the following sections.[177,180-182]

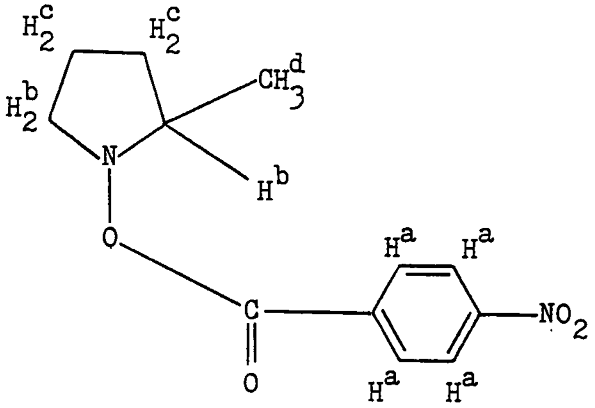
2.2.1 N-Benzoyloxy-2-methylpyrrolidine



Ir (cm^{-1}): 3100 and 3080 (Ar-H), 2980, 2930, and 2870 (saturated C-H), 1735 (C=O), 1600, 1585 (aromatic C=C), 1255 (C-O), 710 and 680 (Ar-H, monosubstituted benzene)

Nmr (ppm): 8.06-7.96 (m, 2.0 H^a), 7.66-7.32 (m, 3.1 H^b), 3.72-2.90 (m, 3.0 H^c), 2.16-1.46 (m, 4.1 H^d), 1.30-1.23 (d, 3.0 H^e).

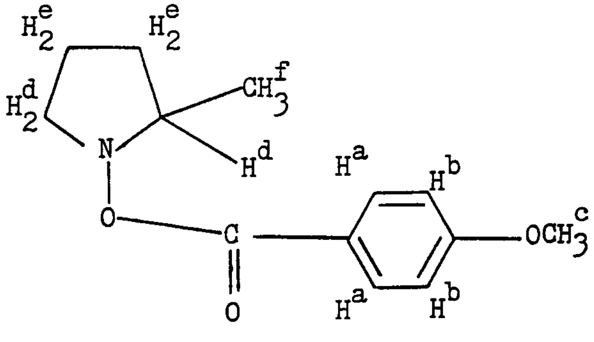
2.2.2 N-(p-Nitrobenzoyloxy)-2-methylpyrrolidine



Ir (cm^{-1}): 3120 and 3090 (Ar-H), 2990 and 2880 (saturated C-H), 1750 (C=O), 1610 (aromatic C=C), 1530 and 1348 (Ar-NO_2), 1260 (C-O), 845 (Ar-H, 1,4-disubstitution).

Nmr (ppm): 8.35-8.12 (m, 3.9 H^a, an AA'BB' pattern), 3.74-2.96 (m, 3.0 H^b), 2.28-1.48 (m, 4.2 H^c), 1.31 and 1.25 (d, 3.0 H^d).

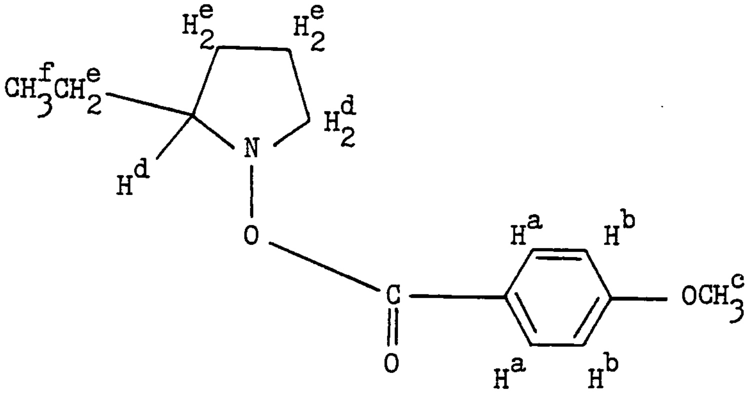
2.2.3 N-(p-Anisoyloxy)-2-methylpyrrolidine



Ir (cm^{-1}): 3030 (Ar-H), 2980, 2950, and 2860 (saturated C-H), 1735 (C=O), 1610 (aromatic C=C), 1250 (C-O), 1070 (Ar-OCH_3), 840 (Ar-H, 1,4-disubstitution).

Nmr (ppm): 8.02-7.92 (d, 2.0 H^a), 6.97-6.87 (d, 2.0 H^b), 3.84 (s, 3.0 H^c), 3.74-293 (m, 3.0 H^d), 2.22-148 (m, 4.1 H^e), 1.28-1.22 (d, 3.2 H^f). The absorbtions of aromatic protons resembled an AB pattern of two distorted doublets. However, closer inspection showed additional splitting.

2.2.4 N-(p-Anisoyloxy)-2-ethylpyrrolidine

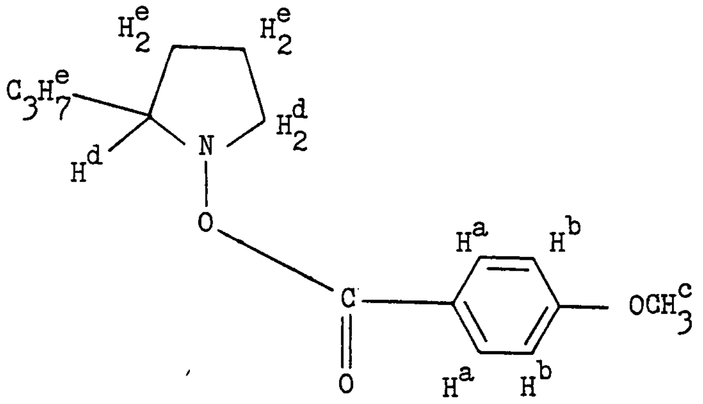


Ir (cm^{-1}): 3080 (Ar-H stretch), 2970, 2940, 2880, 2850 (saturated C-H), 1740 (C=O), 1610 (aromatic C=C), 1255 (C-O), 1070 (Ar-OCH_3), 840 (Ar-H, 1,4-disubstitution).

Nmr (ppm): 8.07-7.93 (d, 2.0 H^a), 7.00-6.85 (d, 2.0 H^b), 3.89 (s, 3.0 H^c), 3.70-2.80 (m, 3.0 H^d), 2.27-1.22 (m, 6.0 H^e), 1.10-0.83 (t, 3.2 H^f). The absorbtions of aromatic protons resembled an AB pattern of two distorted doublets. However, closer inspection showed additional splitting.

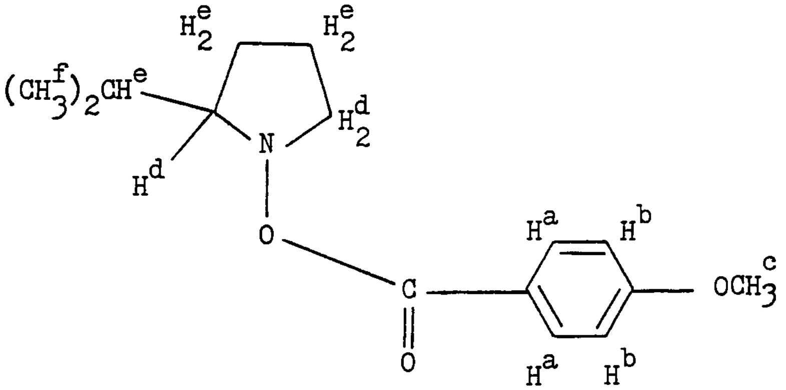
2.2.5 N-(p-Anisoyloxy)-2-n-propylpyrrolidine

Ir (cm^{-1}): 3080 (Ar-H stretch), 2960, 2940, 2870 (saturated C-H), 1738 (C=O), 1610, 1585 (aromatic C=C), 1245 (C-O), 1065 (Ar-OCH_3), 840



(Ar-H, 1,4 disubstitution).

Nmr (ppm): 8.07-7.90 (d, 2.0 H^a), 6.98-6.83 (d, 1.9 H^b), 3.87 (s, 2.9 H^c), 3.67-2.80 (m, 3.0 H^d), 2.23-0.77 (m, 11.1 H^e). The aromatic protons showed two sets of doublets with additional fine splitting (AB pattern).

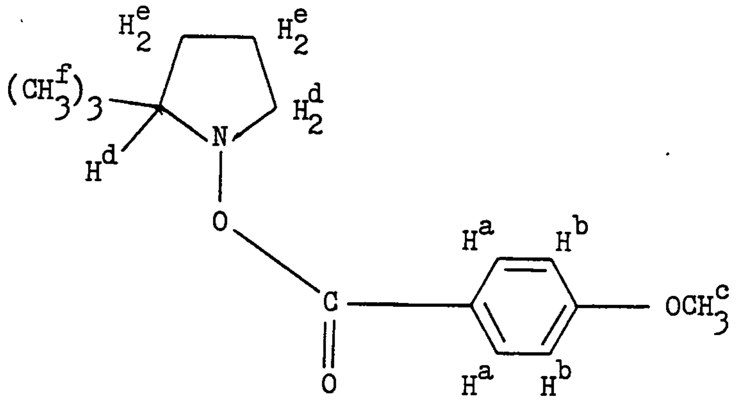


2.2.6 N-(p-Anisoyloxy)-2-isopropylpyrrolidine

Ir (cm^{-1}): 3090 (Ar-H stretch), 2990, 2900, 2860 (saturated C-H), 1745 (C=O), 1615, 1590 (aromatic C=C), 1255 (C-O), 1075 (Ar-OCH_3), 845 (Ar-H, 1,4-disubstitution).

Nmr (ppm): 8.05-7.90 (d, 2.0 H^a), 7.00-6.85 (d, 2.1 H^b), 3.87 (s, 3.0 H^c), 3.80-2.80 (m, 3.0 H^d), 2.20-150 (m, 5.0 H^e), 1.07-0.90 (d, of d's, 6.0 H^f). The absorbtion pattern of benzene protons resembled an AB pattern of two distorted doublets with additional fine splitting.

2.2.7 N-(p-Anisoyloxy)-2-t-butylpyrrolidine



Ir (cm^{-1}): 3080 (Ar-H); 2960, 2880 (saturated C-H); 1740 (C=O); 1610, 1590 (aromatic C=C); 1250 (c-O); 1070 (Ar-OCH_3) 840 (A-H 1,4-disubstitution).

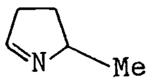
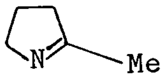
Nmr (ppm): 7.97-7.83 (d, 1.8 H^a), 6.91-6.77 (d, 2.0 H^b), 3.78 (s, 3.0 H^c), 3.57-2.73 (m, 2.8 H^d), 2.05-1.50 (m, 4.0 H^e), 0.94 (s, 8.8 H^f). The absorbtion of the aromatic protons resembled an AB pattern of two distorted doublets with additional fine splitting.

2.3 Elimination Reactions of N-Aroyloxy-2-alkylpyrrolidines

In order to probe the electronic effect of the leaving group on the positional isomerism and product yield base-promoted eliminations from N-benzoyloxy-, N-(p-nitrobenzoyloxy)-, and N-(p-anisoyloxy)-2-methylpyrrolidine were conducted. The effect of the β-alkyl substituent was examined by varying the alkyl group to include methyl, ethyl, n-propyl, isopropyl, and t-butyl in base promoted elimination reactions of N-anisoyloxy-2-alkylpyrrolidines. The results are tabulated

TABLE 24

Base-Promoted Eliminations from N-Benzoyloxy-2-methylpyrrolidine (BMP)

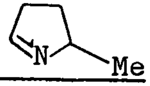
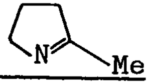
Base-Solvent	[BMP],M	[Base],M	Reaction Time	% 	% 	% Yield
MeONa-MeOH	0.230	0.835	3 days	-	-	-
t-BuOK-t-BuOH	0.106	0.293	1.5 h	24.7 ± 0.9*	75.3 ± 0.9	59 ± 1
t-BuOK-Hexane**	0.103	0.567	18.0 h	24.3 ± 0.1	75.7 ± 0.1	55 ± 2
t-BuOK-Hexane**	0.098	0.60	16.0 h	22.9 ± 0.4	77.1 ± 0.1	61 ± 2
t-BuOK-Et_2O**	0.124	0.597	5.0 h	35.3 ± 0.3	64.7 ± 0.3	66 ± 1

* Standard deviation from multiple analysis.

** Heterogeneous base-solvent system.

TABLE 25

Base-Promoted Eliminations from N-(p-Nitrobenzoyloxy)-2-methylpyrrolidine (NBP)

Base-Solvent	[NBP],M	[Base],M	Reaction Time	% 	% 	% Yield
t-BuOK-t-BuOH	0.183	0.293	1.5 h	28.4 ± 0.2*	71.6 ± 0.2	31.5 ± 0.5
t-BuOK-Et$_2$O**	0.065	0.557	5.0 h	41.7 ± 0.6	58.3 ± 0.6	50 ± 1

---

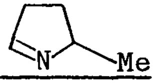
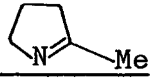
* Standard deviation from multiple analysis.

** Heterogeneous base-solvent system.

TABLE 26

Base-Promoted Eliminations from N-(p-Anisoyloxy)-2-alkylpyrrolidines (AP)

N-(p-Anisoyloxy)-2-methylpyrrolidine

Base-Solvent	[AP], M	[Base], M	Reaction Time	% 	% 	% Yield
t-BuOK-t-BuOH	0.102	0.293	1.0 h	23.0 ± 0.2*	77.0 ± 0.2	77.8 ± 0.2
t-BuOK-Hexane**	0.124	0.980	18.5 h	27.4 ± 0.7	72.6 ± 0.7	62.2 ± 0.8
t-BuOK-Et_2O**	0.114	0.563	5.0 h	36.2 ± 0.2	63.8 ± 0.2	79 ± 2

N-(p-Anisoyloxy)-2-ethylpyrrolidine

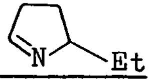
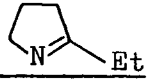
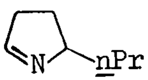
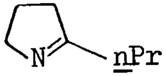
Base-Solvent	[AP], M	[Base], M	Reaction Time	% 	% 	% Yield
t-BuOK-t-BuOH	0.099	0.293	1.0 h	61 ± 2	39 ± 2	37.5 ± 0.5
t-BuOK-Et_2O**	0.111	0.565	4.0 h	59.6 ± 0.6	40.4 ± 0.6	73.5 ± 0.1

TABLE 26 continued

N-(p-Anisoyloxy)-2-n-propylpyrrolidine

Base-Solvent	[AP],M	[Base],M	Reaction Time	% 	% 	% Yield
t-BuOK-t-BuOH	0.102	0.293	1.0 h	61.0 ± 0.5	39.0 ± 0.5	50.6 ± 0.1
t-BuOK-Et_2O**	0.120	0.579	4.0 h	66.9 ± 0.2	33.1 ± 0.2	100

N-(p-Anisoyloxy)-2-isopropylpyrrolidine

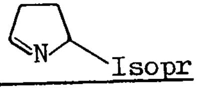
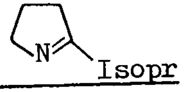
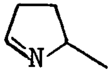
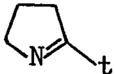
Base-Solvent	[AP],M	[Base],M	Reaction Time	% 	% 	% Yield
t-BuOK-t-BuOH	0.112	0.293	1.0 h	9.0 ± 0.5	9.0 ± 0.5	49.4 ± 0.4
t-BuOK-Et_2O**	0.099	0.460	4.0 h	84.1 ± 0.7	15.9 ± 0.7	86.0 ± 2

TABLE 26 continued

N-(p-Anisoyloxy)-2-t-butylpyrrolidine

Base-Solvent	[AP],M	[Base],M	Reaction Time	%  t-Bu	%  t-Bu	% Yield
t-BuOK-t-BuOH	0.095	0.293	1.0 h	64.0 ± 0.9	36.0 ± 0.9	30.8 ± 0.2
t-BuOK-Et_2O**	0.090	0.440	4.0 h	67.0 ± 0.3	33.0 ± 0.3	38.2 ± 0.6

* Standard deviation from multiple analysis.

** Heterogeneous base-solvent system.

in Tables 24-26. The yields given are the combined yields of both of the imines.

3.0 Discussion

3.1 Introduction

The effect of leaving group on positional orientation was explained with the help of variable E2 transition state in Chapter I (Section 3.4.4). Bartsch and Bunnett[51] have examined the leaving group effect in the elimination reactions of 2-substituted hexanes promoted by MeONa-MeOH and t-BuOK-t-BuOH. Some of their data is represented in Table 27.

TABLE 27

Percent of 1-Hexene in Base-Promoted Eliminations from 2-Substituted Hexanes

Leaving Group, X	% of 1-Hexene (MeONa-MeOH)	Temp, °C
Cl	33.3	100.0
OTs[a]	34.5	44.3
OBs[b]	41.7	100.0
OTMB[c]	63.2	164.4

[a] p-Toluenesulfonoxy group.

[b] p-Bromobenzenesulfonoxy group.

[c] 2,4,6-Trimethylbenzoyloxy group.

The percentage of 1-hexene increased as the neutral leaving group was varied Cl~OTs < OBs < OTMB. By analogy, one might expect the regioselectivity for formation of 5-alkyl-1-pyrrolines in the elimination from N-X-2-alkylpyrrolidines (X=neutral leaving group) to increase with a similar leaving group variation.

O-Sulfonate esters of most N,N-dialkylhydroxyamines have been found to be too unstable for convenient handling.[203] On the other hand, N-aroyloxy derivatives of N,N-dialkylamines can be easily prepared and handeled.[28,203,204] This anticipated ease of synthesis and manipulation and the expected higher regioselectivity for the Hoffmann orientation product made the aroyloxy leaving group an attractive possibility for improving the yields 5-alkyl-1-pyrrolines in eliminations from N-X-2-alkylpyrrolidines.

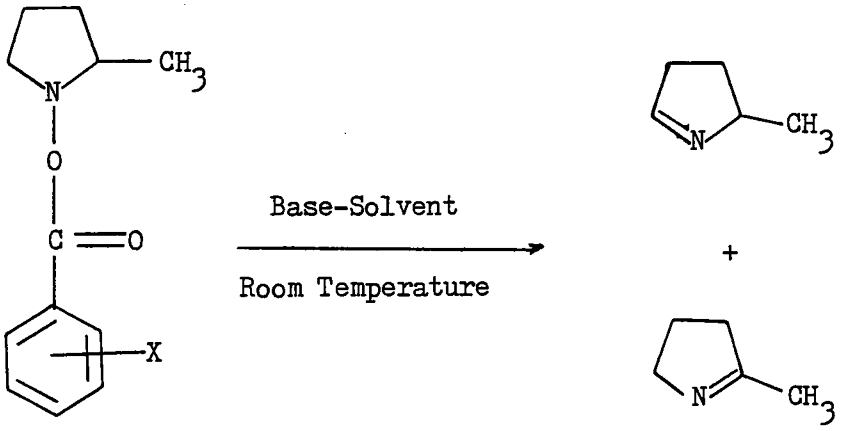
3.2 Preparation of N-Aroyloxy-2-alkylpyrrolidines

Gassman and Hartman[203] have prepared N-aroyloxypiperidines by reacting the corresponding hydroxylamines with aroyl chlorides in the presence of sodium hydroxide at -50°. The hydroxylamines were prepared by a general sequence of reactions: Addition of a secondary amine to ethyl acrylate in a Michael-type reaction produced a tertiary amine, which was oxidized with m-chloroperbenzoic acid to give an N-oxide. The N-oxide was heated with 1M sodium hydroxide to give the hydroxylamine.

The N-aroyloxy derivatives of secondary amines can also be prepared by the reaction of secondary amines with aroyl peroxides.[28,203]

TABLE 28

Base-Promoted Eliminations from N-Aroyloxy-2-methylpyrrolidine



Base-Solvent	%5-Methyl-1-pyrroline/%2-Methyl-1-pyrroline[a]		
	X=H	X=p-NO$_2$	X=p-OCH$_3$
MeONa-MeOH	b	-	-
t-BuOK-t-BuOH	25/75 (59)	28/72 (32)	23/77 (78)
t-BuOK-Hexane	23/77 (61)	-	27/73 (62)
t-BuOK-Et$_2$O	35/65 (66)	42/58 (50)	36/64 (79)

---

[a] The numbers in the parantheses are the percent yields of total imine production.

[b] No imines could be detected even though reaction was evident.

Blomquist and Buselli[205] have prepared a large number of substituted benzoyl peroxides. Because of availability of aroyl peroxides and the simplicity and higher yields of the latter method, it was chosen over the method of Grassman and Hartman.

Since the secondary amines used in this study were time-consuming and expensive to prepare, an attempt was made to improve the yields in reactions of secondary amines with aroyl peroxides. As a model system, a commercially-available secondary amine, 2-methylpiperidine, was reacted with benzoyl peroxide under various different reaction conditions (Table 22). At this time, the reasons for the much lower yields observed in the presence of the soluble bases (triethylamine, Proton Sponge, n-BuLi) are not known. The best yields were obtained when the bases were potassium and sodium hydride (78% and 72% respectively). The application of this method to 2-alkylpyrrolidines gave lower yields (21-59%) of the N-aroyloxy-2-alkylpyrrolidines (Table 23).

3.3 Studies of Eliminations from N-Aroyloxy-2-alkylpyrrolidines

3.3.1 Eliminations from N-Aroyloxy-2-methylpyrrolidine

In order to study the effects of aryl ring substituents on the regioselectivity of imine-forming reactions and the overall yields of the imines produced, base-promoted eliminations from N-benzoyloxy-, N-(p-nitrobenzoyloxy)-, and N-(p-anisoyloxy)-2-pyrrolidine were studied (Table 28).

In the reactions of N-aroyloxy-2-methylpyrrolidines with bases, there are three places where the base can attack. Reaction at the 2-H or 5-H on the pyrrolidine ring with the aroyloxy group leaving would produce the 1-pyrrolines. Alternatively, it can attack the carbonyl carbon of the aroyloxy group to produce hydroxylamine. The elimination reaction of N-benzoyloxy-2-methylpyrrolidine with MeONa-MeOH did not produce any elimination product. Apparently attack with a small base like MeONa occurs exclusively at the carbonyl carbon. This is not without precedent, Denney and Denney[204] have reported that N-benzoyloxydibenzylamine gave dibenzylhydroxylamine when treated with EtONa. The reactions of N-benzoyloxy-2-methylpyrrolidine with associated base-solvent combinations gave the expected imines. The large steric requirement for these bases most probably hinders attack on the carbonyl carbon. The p-substituents on the aryl ring will effect the charge on the carbonyl carbon and relative rate of base attack at that position. An electron-withdrawing group at the para position should make the carbonyl carbon more susceptile to a base attack and thereby reduce the yield of elimination products. An electron-donating group should have the opposite effect and the attack on β-H should increase. This prediction is fulfilled by the observed imine yields (Table 28). The p-nitrobenzoyloxy leaving group gave the lowest yields of imines and the p-anisoyloxy leaving group produced the highest yields of elimination products (Table 28).

In the eliminations from the N-aroyloxy-2-methylpyrrolidines, the steric effect of the leaving group was held constant and the electronic effects were changed. There was little influence of p-substituents upon positional orientation (Table 28). This suggests that the leaving group ability is not affected very much by the p-substituent. Gassman and Hartman[203] have found that the rate of heterolysis of N-aroyloxypiperidines to give a nitrenium ion increased silightly, (five-fold), when the p-substituent was changed from a methoxy to a nitro group. This was for an S_N1 reaction which requires almost complete N-O bond rupture in the transition state. For an E2 reaction in which N-O bond should have undergone much less rupture, the leaving group effect would be expected to be even less. This is consistent with the negligible effect of para substituents upon the regioselectivity of eliminations from N-aroyloxy-2-alkylpyrrolidines.

3.3.2 Comparison of Imine- and Alkene-Forming Eliminations Involving Aroyloxy Leaving Group

Base-promoted eliminations from N-aroyloxy-2-alkylpyrrolidines took place at room temperature and were complete in a short period of time (1-4 hours). By comparison, olefin-forming eliminations from 2-(2,4,6-trimethylbenzoyloxy)-hexane with t-BuOK-t-BuOH required a temperature of 99.0°C and a reaction time of 60 hours. The facility of the base-promoted elimination reactions of the N-aroyloxy-2-alkylpyrrolidines can be attributed to: a) lower stability of the heteroatom-leaving group bond (E_{C-O}=85.5 kcal/mole and E_{N-O} in H_2NOH=48 kcal/mole)[4], b) increased acidity of the β-hydrogen due to a more electronegative α-atom (nitrogen vs. carbon), and c) the larger energy difference between carbon-nitrogen single and double bonds compared with carbon-carbon single and double bonds (Table 3).

The lower yields observed for the alkene-forming eliminations (0.2-4% total alkene yield[51]) than with the aroyloxy leaving group can be attributed to the slower rate of elimination for the former which enhances the proportion of the reaction that proceeds by base attack at the carbonyl carbon.

2.3.3 Eliminations from N-(p-Anisoyloxy)-2-alkylpyrrolidines

Since the influence of the p-substituents on the aroyloxy leaving group was found to affect regioselectivity negligibly, and since the reactions with the p-anisoyloxy leaving group gave the highest total imine yields in eliminations from N-aroyloxy-2-methylpyrrolidine, the p-anisoyloxy leaving group was chosen for the studies of 2-alkyl substituent and base-solvent effects upon the base-promoted eliminations of the N-aroyloxy-2-alkylpyrrolidines. The heterogeneous base-solvent system t-BuOK-Et_2O was chosen over t-BuOK-Hexane because of the better solubility of the N-aroyloxy-2-alkylpyrrolidines in Et_2O. The results are tabulated in Table 29.

As it was in the eliminations from N-chloro-2-alkylpyrrolidines, steric interactions of the base and 2-alkyl substituent play an important role in controlling the regioselectivity of associated base-promoted eliminations from N-(p-anisoyloxy)-alkylpyrrolidines. As the steric requirements of the 2-alkyl group were increased in the order methyl, ethyl, isopropyl, the percentage of Hofmann orientation was enhanced in both base-solvent systems. The steric requirements of ethyl and n-propyl groups seem to be very similar for t-BuOK-t-BuOH

TABLE 29

Base-Promoted Eliminations from N-(p-Anisoyloxy)-2-alkylpyrrolidines

1-Pyrrolines	Base-Solvent	
	t-BuOK-t-BuOH	t-BuOK-Et_2O
%5-Me/%2-Me	23/77	36/64
%5-Et/%2-Et	61/39	60/40
%5-n-Pr/%2-n-Pr	61/39	67/33
%5-Isopr/%2-Isopr	91/9	84/16
%5-t-Bu/%2-t-Bu	64/36	67/33

base-solvent system. The sterically more demanding heterogeneous base-solvent system, t-BuOK-Et_2O showed a slight enhancement in the percentage of Hofmann elimination product (60% for 2-ethyl and 67% for 2-n-propyl). It was anticipated that a 2-t-butyl substituent should have resulted in the largest percentage of Hofmann orientation. However, a drop in the percentage was observed in going from 2-isopropyl to 2-t-butyl (91% to 64% and 84% to 67% in t-BuOK-t-BuOH and t-BuOK-Et_2O, respectively). A similar phenomenon was also observed in the eliminations from N-chloro-2-alkylpyrrolidines. At present the reasons for this anomalous result are uncertain. Possible explanations include a change of the preferred elimination stereochemistry.

A change of base-solvent system from t-BuOK-t-BuOH to t-BuOK-Et_2O in the elimination reactions of N-(p-anisoyloxy)-2-alkylpyrrolidines did not have as much influence as the base was changed from t-BuOK-t-BuOH to t-BuOK-Hexane in eliminations from N-chloro-2-alkylpyrrolidines (Table 20). A possible explanation is the better solvating ability of diethyl ether.

In order to allow for ready comparison of the regioselectivities of base-promoted eliminations from N-chloro- and N-(p-anisoyloxy)-2-alkylpyrrolidines, the percentages of 5-alkyl-1-pyrroline which result from reactions with t-BuOK-t-BuOH are given in Table 30.

TABLE 30

The Relative Percentage Yields of 5-Alkyl-1-pyrrolines in Elimination Reactions of N-Chloro- and N-(p-Anisoyloxy)-2-alkylpyrrolidines with t-BuOK-t-BuOH

Alkyl Group	Leaving Group	
	Chloro-	p-Anisoyloxy
Methyl	9	23
Ethyl	26	61
n-Propyl	28	61
Isopropyl	78	91
t-Butyl	53	64

The 2-alkyl substituent effects in both of the elimination reactions are very similar. The Hofmann orientation product percentage increases in both systems in the order Me<Et=n-Pr<Isopr. The t-butyl

group has the same anamolous result in both systems. For all 2-alkyl groups, the yield of 5-alkyl-1-pyrrolines is greater with the p-anisoyloxy leaving group than with the chloro leaving group.

4.0 Conclusion

The results obtained in this part of the dissertation research show the synthetic utility of base-promoted elimination reactions from N-aroyloxy-2-alkylpyrrolidines to form 5-alkyl-1-pyrrolines. The substrates for the elimination reaction can be easily prepared by the reaction of aroyl peroxides with pyrrolidines. Table 30 shows that the aroyloxy leaving group is superior to chloro in producing the Hofmann orientation product.

Even though the relative bond strengths of N-Cl and N-O are very similar (E_{N-Cl} in NCl_3=46 and E_{N-O} in H_2NOH=48[4]) the N-aroyloxy leaving group produced more Hofmann orientation product than N-Cl. Therefore some other factor than the relative ease of nitrogen-leaving group bond rupture for determining the regioselectivity is involved. Thus, a closer look into other leaving groups is in order.

CHAPTER IV

BASE-PROMOTED DEHYDROCHLORINATION OF N-CHLORO-2-ARYLPYRROLIDINES

1.0 Experimental

1.1 Materials and Instrumentation

The reagents used in the experiments discussed in this chapter are listed below with the companies from which they were purchased given in parentheses:

Bromobenzene (Eastman), aryl bromides other than bromobenzene (Aldrich), magnesium turnings (American Drug and Chemical), sodium borohydride (Alfa), sodium borodeuteride (SIC), sodium sulfate (Fisher), magnesium sulfate (MCB), potassium _t_-butoxide (Aldrich), absolute diethyl ether (Mallinckrodt), _t_-butyl alcohol (Fisher), methanol (Fisher), benzene (MCB), pentane (Phillips 66), N-chlorosuccinimide (Parish). Methanol was dried by distilling from magnesium.[173] _t_-Butyl alcohol was dried by distilling twice from potassium. Benzene was purified by the literature method[173] and dried by distilling from sodium-wire. Absolute ether and pentane were used as received.

The 2-aryl-1-pyrrolines and 2-arylpyrrolidines were identified by comparing their bp's and mp's with literature values and their ir, proton nmr, and mass spectra with the anticipated spectral values. The boiling points are given in degrees Centigrade/torr (°/mm). The melting points were taken with a Fischer-Johns Melting Point Apparatus and are uncorrected. Infrared spectra were taken with Perkin-Elmer 457 instrument and recorded in cm^{-1}. The proton nmr spectra were taken either with Varian A60 or Varian EM360 spectrophotometer and were recorded in ppm with respect to the internal standard tetramethylsilane (s=singlet, d=doublet, t=triplet, m=multiplet). The UV spectra (presented in nm) and kinetic runs were recorded using a Beckman Acta V spectrophotometer.

1.2 General Procedure for Preparation of 2-Aryl-1-pyrrolines

2-Aryl-1-pyrrolines were synthesized according to the literature procedure[118] by the action of aryl Grignard reagents on 2-methoxy-1-pyrroline. A three-necked, round-bottomed flask was fitted with an efficient reflux condenser, a magnetic stirrer, a gas inlet adaptor, and a pressure-equilizing dropping funnel. All of the glassware was dried in an oven (130°C), assembled while hot, and allowed to cool under a purging nitrogen atmosphere. Magnesium turnings were washed with anhydrous diethyl ether and placed into the round-bottomed flask. A crystal of iodine and 25-50 ml of anhydrous diethyl ether were added. A solution of the aryl bromide in anhydrous diethyl ether was placed into the dropping funnel. A few ml of the aryl bromide solution was run into the flask. The initiation of the reaction could be judged by the disapperance of the iodine color and refluxing of the ether. After the reaction had started, the addition rate of the aryl bromide solution was adjusted to maintain a gentle reflux. After the addition was complete, the solution was refluxed for one hour. In some cases not all of the magnesium had reacted after this time interval. In those cases, reflux of the Grignard mixture was continued until almost all of the magnesium had reacted. After the preparation of the aryl Grignard reagent was complete, the solvent was exchanged by anhydrous benzene via simultaneous distillation of diethyl ether and addition of benzene. When the solvent exchange was complete, the Grignard reagent precipitated as a brown solid. An anhydrous benzene solution of 2-methoxy-1-pyrroline was added dropwise to the refluxing Grignard reagent under a nitrogen atmosphere. The mixture was then refluxed for 15-24 hours and allowed to cool. The adduct was decomposed by the addition of a 25% aqueous solution of NH_4Cl. The benzene layer was decanted and the aqueous layer (a paste) was extracted with ether. The organic layers were combined and dried over Na_2SO_4. The solvent was removed and the crude products were purified by vacuum distillation.

1.2.1 2-Phenyl-1-pyrroline

The Grignard reagent was prepared from 2.43 g (0.10 mole) of magnesium turnings and 15.7 g (0.10 mole) of bromobenzene in 125 ml of anhydrous diethyl ether. It was refluxed for one hour and the solvent was exchanged by addition of 100 ml of anhydrous benzene with simultaneously distillation of ether. A solution of 4.5 g (0.0455 mole) of 2-methoxy-1-pyrroline in 200 ml of dry benzene was added and the mixture was refluxed for 17 hours. After work-up, the crude product was distilled to give 5.19 g (79%) of pure 2-phenyl-1-pyrroline, bp 66-

70°C/0.3-0.4 mm (Literature[116] mp 44-45); ir (neat, cm^{-1}): 3080 and 3050 (Ar-H), 2980 and 2880 (C-H), 1630 (C=N), 1600 and 1585 (aromatic C=C), 750 and 690 (Ar-H, monosubstitution); nmr (CCl_4 ppm): 1.73-2.1 ppm (m, 2.1 H), 2.6-3.0 ppm (t of m, 2.0 H), 3.73-4.05 ppm (t of m, 2.0 H), 7.0-7.45 ppm (m, 3.2 H), 7.5-7.8 ppm (m, 2.0 H).

1.2.2 2-(p-Methylphenyl)-1-pyrroline

The Grignard reagent was prepared from 1.82 g (0.075 moles) of magnesium turnings and 13.1 g (0.075 moles) of p-bromotoluene in 125 ml of anhydrous diethyl ether. It was refluxed for one hour and the solvent was exchanged with anhydrous benzene (100 ml). A solution of 4.96 g (0.05 moles) of 2-methoxy-1-pyrroline was added and the mixture was refluxed for 20 hours. After the usual work-up, the crude product was distilled to give 4.2 g (53%) of 2-(p-methylphenyl)-1-pyrroline; bp 102-105°C/0.72 mm Hg (Literature[112] 123-124°C/7 mm Hg); ir (neat, cm^{-1}): 3030 (Ar-H), 2980 and 2880 (saturated C-H), 1630 (C=N), 1600 and 1590 (aromatic C=C), 810 (p-disubstitution); nmr (CCl_4): 7.67-7.54 (broad d, 1.8 H), 7.07-6.93 (broad d, 2.0 H), 4.02-3.70 (t of m, 2.0 H), 2.83-2.50 (t of m, 2.0 H), 2.27 (s, 3.2 H), 2.03-1.48 (broad pentet, 2.0 H).

1.2.3 2-(m-Methylphenyl)-1-pyrroline

3-Tolyl magnesiumbromide was prepared from 2.43 g (0.10 mmole) of magnesium turnings and 17.28 g (0.10 mole) of 3-bromotoluene in 200 ml of anhydrous diethyl ether. It was refluxed overnight and the solvent was exchanged by adding anhydrous benzene (300 ml) and simultaneously distilling the diethyl ether. A solution of 4.95 g (0.05 mole) 2-methoxy-1-pyrroline in 100 ml of dry benzene was added and the mixture was refluxed for 17.5 hours. The product was isolated from the reaction mixture in the usual manner. After distillation 7.5 g (94%) of 2-(m-methylphenyl)-1-pyrroline was obtained, bp 86-88°C/0.35 mm (Literature bp 137-138°C/15 mm Hg[112], mp 65°C[135]); ir (neat, cm^{-1}): 3040 (Ar-H), 2985, 2925, and 2875 (saturated C-H), 1630 (C=N), 1615 and 1595 (aromatic C=C), 770 and 690 (Ar-H, m-disubstitution); nmr (CCl_4): 7.53-7.00 (m, 4.3 H), 4.04-3.72 (t of m, 2.0 H), 2.93-2.57 (t of m, 2.0 H), 2.31 (s, 3.3 H), 2.23-1.71 (m, 2.1 H).

1.2.4 2-(p-Methoxyphenyl)-1-pyrroline

The Grignard reagent was prepared from 1.82 g (0.075 moles) of magnesium turnings and 14.03 g (0.075 moles) of p-bromoanisole in 100 ml of anhydrous diethyl ether. It was refluxed overnight in order to get all of the magnesium to react. The solvent was exchanged with dry benzene (100 ml). A solution of 4.96 g (0.05 moles) of 2-methoxy-1-pyrroline in 75 ml of dry benzene was added and the mixture was refluxed for 19.5 hours. After the usual work-up, the product was distilled to yield 4.83 g (55%) of 2-(p-methoxy-1-pyrroline); bp 137-140°C/0.8 mm Hg, mp 72-3°C (Literature bp 95-6°/0.3 mm[116], mp 74° (69°)[135]); ir (KBr, cm^{-1}): 3030 (Ar-H), 2980 and 2880 (saturated C-H), 1620 (C=N), 1590 (aromatic C=C), 1250 ($ArO\text{-}CH_3$), 1030 (Ar-OMe), 820 (Ar-H, p-disubstitution); nmr ($CDCl_3$): 7.78-7.64 (broad d, 2.0 H), 6.89-6.73 (broad d, 2.0 H), 4.11-3.64 (t of m, 2.1 H), 3.78 (s, 3.0 H), 3.03-2.68 (t of m, 2.0 H), 2.23-1.64 (broad pentet, 2.0 H).

1.2.5 2-(m-Methoxyphenyl)-1-pyrroline

3-Anisyl magnesium bromide was prepared from 1.22 g (0.05 mole) of magnesium turnings and 9.35 g (0.05 mole) of 3-bromoanisole in 200 ml of anhydrous diethyl ether. Since the usual methods failed to initiate the reaction, a small amount of ethyl bromide (ca 1 g 0.009 mole) was added. The solution was refluxed overnight and the solvent was exchanged by adding dry benzene (200 ml) and distilling the ether simultaneously. A solution of 3.0 (0.0303 mole) 2-methoxy-1-pyrroline in 100 ml benzene was added and the reaction mixture was refluxed for 23 hours. The crude product was isolated from the reaction mixture in the usual manner and was distilled to yield 3.9 g (74%) of pure 2-(m-methoxyphenyl)-1-pyrroline, bp 110-112°C/0.4 mm Hg, (Literature[116] 77-78°C); ir (neat, cm^{-1}): 3080 and 3020 (Ar-H), 1635 (C=N), 1610 and 1590 (aromatic C=C), 1220 ($ArO-CH_3$), 1040 (Ar-OMe), 780 and 690 (Ar-H, m-disubstitution); nmr (CCl_4, ppm): 7.55-6.75 (m, 4.3 H), 4.15-3.6 (m, 2.0 H), 3.79 (s, 3.0 H), 2.95-2.6 (t of m, 2.0 H), 2.2-1.65 (pentet, 1.9 H).

1.2.6 2-(p-Chlorophenyl)-1-pyrroline

The Grignard reagent was prepared from 1.82 g (0.075 mole) of magnesium turnings and 14.36 g (0.075 mole) of p-chlorobromobenzene in 100 ml of anhydrous diethyl ether. The solution was refluxed for one hour and the solvent was exchanged with anhydrous benzene (100 ml). A solution of 4.26 g (0.043 moles) of 2-methoxy-1-pyrroline in 50 ml of anhydrous diethyl ether was added and the mixture was refluxed for 15 hours. After the usual work-up, the crude was vacuum distilled to yield 3.4 g (44%) of 2-(p-chlorophenyl)-1-pyrrolidine, bp 105°C/0.07 mm Hg, mp 64-65°C (Literature bp 136-138°C/10 mm Hg[151], mp 67[135]). Ir spectrum (neat) showed bands at 3040 (Ar-H), 2960, 2920 and 2860 (C-H saturated), 1635 (C=N stretch), 1600, 1570 (C=C aromatic), 1080 (Ar-Cl), 830 (p-disubstitution pattern of benzene ring), Nmr spectrum showed 1.88-2.30 ppm (m, 2.1 H), 2.72-3.10 ppm (m, 2.0 H), 3.94-4.25 ppm (m, 1.9 H), 7.35-7.93 ppm (m, p- pattern, 3.9 H).

1.2.7 2-(m-Chlorophenyl)-1-pyrroline

3-Chlorophenyl magnesium bromide was formed from 1.216 g (0.05 mole) of magnesium turnings and 9.573 g (0.05 mole) of 3-bromochlorobenzene in 150 ml of anhydrous ether. It was refluxed overnight and solvent exchanged (200 ml dry benzene). A solution of 4.0 g (0.040 moles) of 2-methoxypyrroline in 100 ml of dry benzene was added. After refluxing for 20 hours, the crude product was obtained in the usual manner. After distillation 3.8 g (42%) of 2-(m-chlorophenyl)-1-pyrroline was obtained, bp 97-98°C/0.4 mm Hg, (Literature[151] bp 147-150°C/16 mm Hg); ir (neat, cm^{-1}): 3080 (Ar-H), 2980, 2940, and 2880 (saturated C-H), 1630 (C=N), 1610, 1600 and 1580 (aromatic C=C), 1080 (Ar-Cl), 750 and 680 (Ar-H, m-disubstitution): nmr (CCl_4, ppm): 7.70-7.07 (m, 4.3 H), 4.07-3.77 (t of m, 1.9 H), 2.90-2.55 (t of m, 2.0 H), 2.13-1.57 (broad pentet, 2.0 H).

1.2.8 2-(p-Bromophenyl)-1-pyrroline

The Grignard reagent was prepared from 1.82 g (0.075 moles) of magnesium turnings and 17.7 g (0.075 moles) of p-dibromobenzene in 150 ml of anhydrous diethyl ether. It was refluxed for two hours to complete the reaction. The solvent was exchanged with anhydrous benzene (100 ml) and a solution of 4.96 g (0.05 moles) of 2-methoxy-1-pyrroline in 75 ml of dry benzene was added. The mixture was refluxed for 18 hours. After the usual work-up the crude product was distilled to give 2.04 g (18%) of 2-(p-bromophenyl)-1-pyrroline, bp 135-140°C/0.9 mm Hg, ir (neat, cm^{-1}): 3060 and 3030 (Ar-H), 2980, 2940, and 2880 (saturated C-H), 1630 (C=N), 1600 (aromatic C=C), 820 (Ar-H, p-disubstitution; nmr (CCl_4, ppm): 7.70-7.17 (m, 4.1 H), 4.07-3.75 (t of m, 2.0 H), 2.92-2.52 (t of m, 2.0 H), 2.12-1.63 (p, 2.0 H).

1.3 General Method for Synthesis of 2-Arylpyrrolidines

2-Arylpyrrolidines were generated by the reduction of 2-aryl-1-pyrrolines with sodium borohydride. The 2-deuterated analogs were obtained using sodium borodeuteride. A modified method of Billman and Diesing[172] was employed. A 250 ml, three-necked flask, a reflux condenser, a pressure-equalizing addition funnel, and a gas inlet adaptor were dried in oven. They were assembled while hot and then cooled under a purging nitrogen atmosphere. A solution of 2-aryl-1-pyrroline (2.0-6.4% by weight) in absolute methanol was placed into the flask and a solution of sodium borohydride (1.5-4.5% by weight), 3-8.5 times the molar amount of imine, was introduced dropwise. When the decomposition rate of sodium borohydride in methanol was fast, the addition of the hydride solution to the imine solution was performed rather rapidly. After the addition was complete, the solution was refluxed for 30 minutes. It was cooled and the amine was liberated by the addition of a solution of sodium hydroxide (5.9-7.6 M) in double the molar amount of sodium borohydride used. Then 200-500 ml of water was added and the mixture was steam distilled. The distillate was made acidic with concentrated HCl and concentrated using a rotary evaporator. The residue was made strongly basic with concentrated sodium hydroxide solution (ca 50%) and extracted many times with diethyl ether. The ether layers were combined and dried over Na_2SO_4. After removal of the ether in vacuo, the crude product was purified by distillation.

1.3.1 2-Phenylpyrrolidine

2-Phenyl-1-pyrroline, 3.0 g (0.0207 mole), in 55 ml of absolute methanol was reduced with a solution of 2.39 g (0.062 mole) of sodium borohydride in the usual manner. The crude product was distilled to give 2.3 g (76%) of 2-phenylpyrrolidine, bp 70-71°C/0.6 mm (Literature bp 99-100°C/4.5 mm Hg[116], 241°C/771 mm Hg[135]); ir (neat, cm^{-1}): 3320 (N-H), 3080 and 3040 (Ar-H), 2980 and 2880 (saturated CH), 1610 (aromatic C=C), 735 and 690 (Ar-H, monosubstitution); nmr (CCl_4 ppm): 7.23 broad s, 5.0 H), 4.10-3.87 (t, 1.0 H), 3.31-2.65 (m, 2.1 H), 2.20-1.37 (m, 5.0 H).

1.3.2 2-(p-Methylphenyl)-pyrrolidine

The 2-(p-methylphenyl)-1-pyrroline, 3.18 g (0.02 mole), in 50 ml of absolute methanol was reduced with a solution of 3.07 g (0.081 mole) of sodium borohydride in 100 ml of absolute methanol in the usual manner to generate 1.86 g (58%) of 2-(p-methylphenyl)-pyrrolidine, bp 78°/0.55 mm (Literature[110] bp 128-130°C/8-10 mm Hg); ir (neat, cm^{-1}): 3320 (N-H), 3030 (Ar-H), 2980, 2880 (saturated C-H), 1620 (aromatic C=C), 810 (Ar-H, p-disubstitution); nmr (CCl_4, ppm): 7.23-6.74 (m, 4.0 H), 4.07-3.82 (t, 1.0 H), 3.23-2.67 (m, 2.0 H), 2.30 (s, 3.1 H). 2.00-1.33 (m, 5.0 H).

1.3.3 2-(m-Methylphenyl)-pyrrolidine

2-(m-Methylphenyl)-pyrrolidine was obtained in 65% yield (2.1 g) from the reduction of a solution of 3.18 g (0.02 mole) of 2-(m-methylphenyl)-1-pyrroline in 50 ml of absolute methanol with a solution of 2.27 g (0.06 mole) sodium borohydride in 100 ml of absolute methanol, bp 71-71.5°C/0.36 mm Hg (Literature[110] 128-130°C/8-10 mm Hg); ir (neat, cm^{-1}): 3320 (N-H), 3030 (Ar-H), 2960 and 2870 (saturated C-H), 1615 and 1600 (aromatic C=C), 780 and 695 (Ar-H, m-disubstitution); nmr (CCl_4, ppm): 7.07-6.70 (m, 4.2 H), 4.03-3.77 (t, 1.0 H), 3.17-2.63 (m, 2.2 H), 2.30 (s, 3.0 H), 2.00-1.37 (m, 5.1 H).

1.3.4 2-(p-Methoxyphenyl)-pyrrolidine

2-(p-Methoxyphenyl-1-pyrroline, 2.5 g (0.0143 mole), in 50 ml of absolute methanol was reduced with a solution of 4.5 g (0.12 mole) of sodium borohydride in 100 ml of methanol in the usual manner to yield 1.6 g (63%) of 2-(p-methoxyphenyl)-pyrroline, bp 103-104°C/0.45 mm Hg (Lierature[135] 284°C/760 mm Hg); ir (neat, cm^{-1}): 3320 (N-H), 3080 and 3040 (Ar-H), 2980, 2880, and 2840 (saturated C-H), 1620 and 1595 (aromatic C=C), 1250 ($ArO-CH_3$), 1035 ($Ar-OCH_3$), 825 (Ar-H, p-disubstitution); nmr (CCl_4, ppm): 7.23-7.07 (d, 2.0 H), 6.74-6.60 (d, 2.0 H), 4.03-3.77 (t, 1.0 H), 3.70 (s, 3.1 H), 3.17-2.73 (m, 2.0 H), 2.17-1.33 (m, 5.1 H).

1.3.5 2-(m-Methoxyphenyl)-pyrrolidine

2-(m-Methoxyphenyl)-1-pyrroline, 2.625 g (0.015 mole), in 50 ml of absolute methanol was reduced with a solution of 1.701 g (0.045 mole) of sodium borohydride in 75 ml of absolute methanol in the usual manner to produce 1.7 g (64%) of 2-(m-methoxyphenyl)-pyrrolidine, bp 84-87°C/0.22 mm Hg; ir (neat, cm^{-1}): 3350 (N-H), 3070 (Ar-H), 2970, 2880, and 2850 (saturated C-H), 1610 and 1595 (aromatic C=C), 1260 ($ArO-CH_3$), 1045 ($Ar-OCH_3$), 780 and 695 (Ar-H, m-disubstitution); nmr (CCl_4, ppm): 7.23-6.53 (m, 4.0 H), 4.07-3.83 (t, 0.9 H), 3.70 (s, 2.9 HO, 3.30-2.67 (m, 2.1 H), 2.00-1.37 (m, 5.0 H).

1.3.6 2-(p-Chlorophenyl)-pyrrolidine

The reduction of 2.5 g (0.014 mole) 2-(p-chlorophenyl)-1-pyrroline in 50 ml of absolute methanol with a solution of 4.5 g (0.12 mole) of sodium borohydride in 100 ml of absolute methanol produced 1.76 g (70%) of 2-(p-chlorophenyl)-pyrrolidine, bp 97-100°C/0.72 mm Hg

(Literature[151] 124-127°C/10 mm Hg); ir (neat, cm^{-1}): 3020 (N-H), 3040 (Ar-H), 2980 and 2880 (saturated C-H), 1610 (aromatic C=C), 1090 (Ar-Cl), 820 (Ar-H, p-disubstitution); nmr (CCl_4, ppm): 7.24 (s, 3.8 H), 4.10-3.87 (t, 1.0 H), 3.23-1.30 (m, 5.2 H).

1.3.7 2-(m-Chlorophenyl)-pyrrolidine

The reduction of 2.0 g (0.0114 mole) 2-(m-chlorophenyl)-1-pyrroline in 50 ml of absolute methanol with a solution of 1.68 g (0.0444 mole) of sodium borohydride in 100 ml of absolute methanol resulted in 0.75 g (37%) of 2-(m-chlorophenyl)-pyrrolidine, bp 75°/0.07 mm Hg (Literature[151] bp 138-141°/16 mm Hg); ir (neat, cm^{-1}): 3300 (N-H), 3080 (Ar-H), 2970 and 2880 (saturated C-H), 1605 and 1580 (aromatic C=C), 1070 (Ar-Cl), 775 and 685 (Ar-H, m-disubstitution); nmr (CCl_4 ppm): 7.20 (s, 1.2 H), 7.03 (s, 2.9 H), 3.87-3.60 (t, 1.0 H), 2.93-2.53 (m, 2.0 H), 1.97-1.00 (m, 5.0 H).

1.3.8 2-(p-Bromophenyl)-pyrrolidine

The reduction of 1.5 g (0.007 mole) 2-(p-bromophenyl)-1-pyrroline in 75 ml of absolute methanol with a solution of 0.76 g (0.02 mole) of sodium borohydride in 50 ml of absolute methanol produced 0.70 g (46%) of 2-(p-bromophenyl)-pyrrolidine, bp 89-90°C/0.22 mm Hg; ir (neat, cm^{-1}): 3360 and 3300 (N-H), 3020 (Ar-H), 2980 and 2880 (saturated C-H), 1600 (aromatic C=C), 820 (Ar-H, p-disubstitution); nmr (CCl_4, ppm): 7.47-7.10 (m, 4.1 H), 4.10-3.88 (t, 1.0 H), 3.23-2.87 (m, 2.0 H), 2.26-1.33 (m, 5.0 H).

1.3.9 2-Deuterio-2-phenylpyrrolidine

A solution of 1.013 g (0.00698 mole) 2-phenyl-1-pyrroline in 50 ml of absolute methanol was reduced with 0.93 g (0.02225 mole) of sodium borodeuteride in 70 ml of absolute methanol employing the procedure developed for the sodium borohydride reductions to yield 0.70 g (68%) of 2-deuterio-2-phenylpyrrolidine bp 83°C/1.2 mm Hg; ir (neat, cm^{-1}), 3370, 300 (N-H), 3080 and 3050 (Ar-H), 2.980 and 2890 (saturated C-H), 1615 and 1605 (aromatic C=C), 735 and 695 (Ar-H, p-disubstitution); nmr (CCl_4 ppm): 7.30 (broad s, 5.0 H), 3.27-2.83 (m, 2.0 H), 2.30 (s, 1.2 HO, 2.03-1.46 (m, 4.0 H). Since the nmr spectrum of 2-deuterio-2-phenylpyrrolidine showed no absorbtion due to a 2-H proton (a triplet at 4.10-3.87 ppm, Section 1.3.1), the incorporation of deuterium at the 2-position was assumed to be quantitative.

1.3.10 2-Deuterio-2-(m-chlorophenyl)-pyrrolidine

The reduction of 0.60 g (0.00335 mole) of 2-(m-chlorophenyl)-1-pyrroline in 50 ml of absolute methanol with 0.42 g (0.0099 mole) sodium borodeuteride in 70 ml of absolute methanol was performed via the method developed for the sodium borohydride reductions to yield 0.34 g (56%) of 2-deuterio-2-(m-chlorophenyl)-pyrrolidine, bp 111°C/1.1 mm Hg); ir (neat, cm^{-1}): 3300 (N-H), 3080 (Ar-H), 2980 and 2880 (saturated C-H), 1610, 1600, and 1585 (aromatic C=C), 755 and 680 (Ar-H, monosubstitution); nmr (CCl_4, ppm): 7.27 (s, 1.2 H), 7.13 (s, 2.9 H), 3.93 (s, 1.0 H), 3.20-2.67 (m, 2.0 H), 2.20-1.27 (m, 4.2 H). Since the nmr spectrum of 2-deuterio-2-(m-chlorophenyl)-pyrrolidine showed no absorption due to a 2-H proton (a triplet at 4.10-3.87 Section 1.3.6), the incorporation of deuterium at the 2-position was assumed to be quantitative.

1.4 Base Induced Eliminations

1.4.1 Large Scale Elimination of N-Chloro-2-phenylpyrrolidine

N-Chloro-2-phenylpyrrolidine was prepared from 230 mg (1.57 mmole) 2-phenylpyrrolidine and 300 mg (2.25 mmole) of N-chlorosuccinimide by stirring the reagents in 10 ml of pentane at room temperature for one hour. The mixture was filtered and the solid was washed twice with small amounts of pentane. Ten ml of absolute methanol was added to the pentane solution and the pentane was removed _in vacuo_. To this methanolic solution was added 15 ml of 1.063 N MeONa-MeOH. The reaction solution was stirred at room temperature for 1 hour and refluxed for 24 hours. After cooling, diethyl ether was added and the mixture was filtered. The solvent was removed _in vacuo_. The residue was extracted with pentane. After the pentane was removed, the ir and nmr spectra were taken to show that this product is identical with authentic 2-phenyl-1-pyrroline. No spectral evidence was found for any other product.

1.4.2 Determination of λ_{max} and ϵ Values for 2-Aryl-1-pyrrolines

Solutions of 2-aryl-1-pyrrolines in absolute methanol or _t_-butyl alcohol were prepared by weighing carefully a small amount of the compound into a 1 or 2 ml volumetric flask and adding the appropriate solvent. The uv spectra of the 2-aryl-1-pyrrolines were determined by diluting these solutions. The λ_{max} values were determined from these spectra. By using three different concentrations the ϵ values could be calculated for these compounds.

1.4.3 Preparation of Base-Solvent Solutions

The base-solvent solutions, MeONa-MeOH and t-BuOK-t-BuOH, were prepared in the usual manner as outlined in Chapter II Section 1.4.1.

1.4.4 Synthesis of N-Chloro- and N-Bromo-2-arylpyrrolidines

The 2-arylpyrrolidines (0.35-0.72 mmole for NaOMe-MeOH induced eliminations and 0.49-0.81 mmole for t-BuOK-t-BuOH induced eliminations) were dissolved in 10 ml of pentane and N-chlorosuccinimide (NCS) was added (0.56-1.1 mmole and 0.85-1.4 mmole for NaOMe-MeOH and t-BuOK-t-BuOH induced eliminations, respectively). The mixtures were stirred at room temperature for one hour. They were filtered and washed with a few ml's (2-5 ml) of pentane. Ten ml of absolute methanol or absolute t-butyl alcohol was added and the pentane was removed with a rotary evaporator without applying any heat. The methanol and t-butyl alcohol solutions were put into 10 ml volumetric flask and the appropriate solvent was added to replace the amount lost during the removal of pentane.

1.4.5 Kinetic Runs

For MeONa-MeOH systems, MeOH was used in the reference uv cell.

In t-BuOK-t-BuOH systems, the same base-solvent was used in both uv cells. When the bath temperature was changed, a minimal six hour waiting period was used to insure the equilibration of bath temperature. To insure the equilibration of the temperature of base-solvent systems, a 30 minute waiting time was used after the base-solvent solution had been placed in the cuvette. After this time interval, the cuvette was removed from the spectrophotometer, a measured amount of a N-chloramine solution was injected into the uv cell containing the base-solvent solution, and the cuvette was shaken for a few seconds. It was placed back into the instrument and the absorbance (A_t), measured at the λ_{max} for the 2-aryl-1-pyrroline, versus time (t) was recorded at least for 2 half lives. To insure the pseudo-first-order conditions base/N-chloramine ratios of at least 151/1 and 68/1 (for MeONa-MeOH and t-BuOK-t-BuOH, respectively) were used. The pseudo-first-order rate constants and correlation coefficients were calculated using least squares method (TI, SR-51-II calculator). In order to insure the linearity, the points were also plotted by hand and the straight line was drawn.

The data for kinetic runs in different base concentrations at 39.0°C are tabulated in Tables 31 and 32. The activation parameters were determined by conducting the kinetic runs at three different temperatures, 29.6°, 39.0°, and 48.5°C, and the data is tabulated in Tables 33 and 34. The Hammett ρ values were obtained from kinetic runs of N-chloro-2-arylpyrrolidines substituted at the meta or para position of the aryl group. The data is presented in Tables 35 and 36. To measure the primary deuterium isotope effects, N-chloro-2-deuterio-2-phenylpyrrolidine and N-chloro-2-deuterio-2-(3-chlorophenyl)-pyrrolidine were used as substrates, Tables 37 and 38. For the leaving group element effect, the elimination reaction was also performed using N-bromo-2-phenylpyrrolidine (Table 39).

2.0 Results

2.1 Synthesis of 2-Aryl-1-pyrrolines and 2-Arylpyrrolidines

The various methods for preparation of 2-substituted 1-pyrrolines are given in Chapter I, Section 2. The synthesis of 2-aryl-1-pyrrolines used in this portion of the dissertation research was the reaction of 2-methoxy-1-pyrroline with arylmagnesium bromides. A number of 2-alkyl- and 2-aryl-1-pyrrolines have been synthesized by the same method by various groups.[117,118,120,122] The method developed by Etienne and Correia[118,120] was modified and the products were identified by their ir and nmr spectra. The results are tabulated in Table 40.

The uv spectra of 2-aryl-1-pyrrolines were recorded in absolute methanol and absolute t-butyl alcohol. The λ_{max} and ϵ values for 2-aryl-1-pyrrolines are presented in Table 41.

2-Arylpyrrolidines were generated from the corresponding 2-aryl-1-pyrrolines by reduction with sodium borohydride. A modification of the method of Billman and Diesing[172] for reduction of imines with sodium borohydride was used. The integrity of the products obtained was

TABLE 31

Kinetic Data for Eliminations of HCl from N-Chloro-2-phenylpyrrolidine (NCA) Induced by Different Concentrations of MeONa-MeOH at 39.0°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.300	33.3	0.230	50	0.163
8.3	0.370	66.7	0.305	100	0.216
16.7	0.441	100.0	0.371	150	0.263
25.0	0.494	133.3	0.428	200	0.313
33.3	0.544	166.7	0.478	250	0.353
41.7	0.584	200.0	0.525	300	0.394
50.0	0.621	233.3	0.556	350	0.428
58.3	0.656	266.7	0.600	400	0.465
66.7	0.686	300.0	0.638	450	0.498
75.0	0.709	333.3	0.659	500	0.525
∞	0.916	∞	0.881	∞	0.883

[a] [Base]=0.1063 N; [Base]: [NCA]=1510:1; quantitative yield.

[b] [Base]=0.0267 N; [Base]: [NCA]=390:1; quantitative yield.

[c] [Base]=0.01063 N; [Base] : [NCA]=151:1; quantitative yield.

TABLE 32

Kinetic Data for Eliminations of HCl from N-Chloro-2-phenylpyrrolidine (NCA) Induced by Different Concentrations of *t*-BuOK-*t*-BuOH at 39.0°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
1.7	0.663	6.7	0.442	13.3	0.347
3.3	0.696	13.3	0.497	26.7	0.398
5.0	0.721	20.0	0.550	40.0	0.445
6.7	0.744	26.7	0.594	53.3	0.491
8.3	0.763	33.3	0.631	66.7	0.529
10.0	0.778	40.0	0.663	80.0	0.566
11.7	0.790	46.7	0.690	93.3	0.597
13.3	0.801	53.3	0.713	106.7	0.625
15.0	0.808	60.0	0.734	120.0	0.653
16.7	0.818	66.7	0.751	133.3	0.675
∞	0.863	∞	0.856	∞	0.888

[a] [Base]=0.0577 N; [Base]:[NCA]=748:1; yield=90%.

[b] [Base]=0.0133 N; [Base]:[NCA]=173:1; yield=90%.

[c] [Base]= 0.00527 N; [Base]=[NCA]=71:1; yield=96%.

TABLE 33

Kinetic Data for Eliminations of HCl from N-Chloro-2-phenyl pyrrolidine (NCA) Induced by MeONa-MeOH at Different Temperatures

Temperature 48.5°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
25.0	0.084	0.0	0.203	6.7	0.338
50.0	0.113	16.7	0.293	13.3	0.443
75.0	0.144	33.3	0.374	20.0	0.529
100.0	0.165	50.0	0.438	26.7	0.600
125.0	0.191	66.7	0.493	33.3	0.650
150.0	0.213	83.3	0.549	40.0	0.702
175.0	0.234	100.0	0.591	46.7	0.738
200.0	0.250	116.7	0.629	53.3	0.769
225.0	0.269	133.3	0.662	60.0	0.788
250.0	0.284	150.0	0.688	66.7	0.809
∞	0.875	∞	0.881	∞	0.884

[a] $[\text{Base}]=0.01063$ N; $[\text{Base}]:[\text{NCA}]=155:1$; quantitative yield.

[b] $[\text{Base}]=0.0267$ N; $[\text{Base}]:[\text{NCA}]=390:1$; quantitative yield.

[c] $[\text{Base}]=0.1063$ N; $[\text{Base}]:[\text{NCA}]=1552:1$; quantitative yield.

TABLE 33 Continued

Temperature 39.0°C, [Base]=0.0267 N

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.200	0.0	0.219	0.0	0.230
33.3	0.284	33.3	0.291	33.3	0.305
66.7	0.353	66.7	0.356	66.7	0.371
100.0	0.416	100.0	0.417	100.0	0.428
133.3	0.475	133.3	0.463	133.3	0.478
166.7	0.519	166.7	0.513	166.7	0.525
200.0	0.564	200.0	0.550	200.0	0.556
233.3	0.601	233.3	0.584	233.3	0.600
266.7	0.635	266.7	0.616	266.7	0.638
300.0	0.664	300.0	0.647	300.0	0.659
∞	0.833	∞	0.859	∞	0.881

[a] [Base]:[NCA]=390:1; quantitative yield.

[b] [Base]:[NCA]=401:1; quantitative yield.

[c] [Base]:[NCA]=390:1; quantitative yield.

TABLE 33 Continued

Temperature 29.6°C, [Base]=0.0267 N

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.172	0.0	0.210	0.0	0.219
50.0	0.234	50.0	0.268	50.0	0.274
100.0	0.288	100.0	0.321	100.0	0.324
150.0	0.334	150.0	0.369	150.0	0.371
200.0	0.381	200.0	0.414	200.0	0.413
250.0	0.422	250.0	0.454	250.0	0.451
300.0	0.463	300.0	0.491	300.0	0.486
350.0	0.526	350.0	0.526	350.0	0.519
400.0	0.528	400.0	0.556	400.0	0.549
450.0	0.556	450.0	0.586	450.0	0.576
∞	0.875	∞	0.898	∞	0.878

[a] Base : [NCA]=390:1; quantitative yield.

[b] Base : [NCA]=378:1; quantitative yield.

[c] Base : [NCA]=390:1; quantitative yield.

TABLE 34

Kinetic Data for Eliminations of HCl from N-Chloro-2-phenylpyrrolidine Induced by t-BuOK-t-BuOH (0.0133 N) at Different Temperatures

Temperature 48.5°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
3.3	0.588	3.3	0.545	3.3	0.516
6.7	0.613	6.7	0.584	6.7	0.554
10.0	0.634	10.0	0.614	10.0	0.588
13.3	0.656	13.3	0.639	13.3	0.612
16.7	0.676	16.7	0.659	16.7	0.638
20.0	0.694	20.0	0.676	20.0	0.654
23.3	0.708	23.3	0.693	23.3	0.669
26.7	0.716	26.7	0.706	26.7	0.684
30.0	0.725	30.0	0.719	30.0	0.700
33.3	0.736	33.3	0.728	33.3	0.706
∞	0.801	∞	0.815	∞	0.794

[a] [Base]: [Substrate]=200:1; yield=90%.

[b] [Base]: [Substrate]=200:1; yield=91%.

[c] [Base]: [Substrate]=193:1; yield=86%.

TABLE 34 Continued

Temperature 39.0°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
6.7	0.422	6.7	0.442	6.7	0.423
13.3	0.483	13.3	0.497	13.3	0.478
20.0	0.534	20.0	0.550	20.0	0.530
26.7	0.576	26.7	0.594	26.7	0.571
33.3	0.613	33.3	0.631	33.3	0.610
40.0	0.643	40.0	0.663	40.0	0.643
46.7	0.669	46.7	0.0.690	46.7	0.672
53.3	0.691	53.3	0.713	53.3	0.694
60.0	0.713	60.0	0.734	60.0	0.718
66.7	0.731	66.7	0.751	66.7	0.734
∞	0.835	∞	0.856	∞	0.850

[a] [Base] : [Substrate] =173:1; yield=87%

[b] [Base] : [Substrate] =173:1; yield=90%

[c] [Base] : [Substrate] =173:1; yield=89%

TABLE 34 Continued

Temperature 29.6°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
13.3	0.669	13.3	0.664	13.3	0.654
26.7	0.685	26.7	0.681	26.7	0.674
40.0	0.698	40.0	0.697	40.0	0.688
53.3	0.706	53.3	0.707	53.3	0.700
66.7	0.714	66.7	0.715	66.7	0.713
80.0	0.722	80.0	0.724	80.0	0.724
93.3	0.728	93.3	0.731	93.3	0.733
106.7	0.734	106.7	0.737	106.7	0.740
120.0	0.739	120.0	0.740	120.0	0.745
133.3	0.741	133.3	0.744	133.3	0.750
∞	0.763	∞	0.767	∞	0.778

[a] [Base] : [Substrate] =200: 1; yield=86%.

[b] [Base] : [Substrate] =200: 1; yield=86%.

[c] [Base] : [Substrate] =193: 1; yield=84%.

TABLE 35

Kinetic Data for Eliminations of HCl from N-Chloro-2-arylpyrrolidines Induced by NaOMe-MeOH (0.0267 N) at 39.0°C

N-Chloro-2-(m-methylphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.106	66.7	0.159	66.7	0.172
50.0	0.219	133.3	0.297	133.3	0.309
100.0	0.316	200.0	0.409	200.0	0.422
150.0	0.397	266.7	0.500	266.7	0.509
200.0	0.466	333.3	0.572	333.3	0.578
250.0	0.525	400.0	0.633	400.0	0.638
300.0	0.578	466.7	0.681	466.7	0.684
350.0	0.622	533.3	0.719	533.3	0.719
400.0	0.656	600.0	0.749	600.0	0.758
450.0	0.688	666.7	0.775	-	-
∞	0.866	∞	0.878	∞	0.875

[a] [Base] : [Substrate]=391: 1; quantitative yield.

[b] [Base] : [Substrate]=378; 1; quantitative yield.

[c] [Base] : [Substrate]=378: 1; quantitative yield.

TABLE 35 Continued

N-Chloro-2-(p-methylphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
50.0	0.094	0.0	0.169	0.0	0.194
100.0	0.178	100.0	0.356	100.0	0.369
150.0	0.253	200.0	0.488	200.0	0.503
200.0	0.318	300.0	0.575	300.0	0.600
250.0	0.375	400.0	0.661	400.0	0.669
300.0	0.422	500.0	0.716	500.0	0.724
350.0	0.463	600.0	0.756	600.0	0.761
400.0	0.499	700.0	0.784	700.0	0.781
450.0	0.528	800.0	0.806	800.0	0.813
500.0	0.556	900.0	0.823	900.0	0.831
∞	0.719	∞	0.872	∞	0.872

[a] [Base]: [Substrate]=585: 1; quantitative yield.

[b] [Base]: [Substrate]=473: 1; quantitative yield.

[c] [Base]: [Substrate]=512: 1; quantitative yield.

TABLE 35 Continued

N-Chloro-2-(m-methoxyphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
66.7	0.169	66.7	0.211	66.7	0.175
133.3	0.278	133.3	0.344	133.3	0.328
200.0	0.359	200.0	0.443	200.0	0.447
266.7	0.421	266.7	0.516	266.7	0.534
333.3	0.466	333.3	0.572	333.3	0.600
400.0	0.499	400.0	0.614	400.0	0.653
466.7	0.524	466.7	0.646	466.7	0.689
533.3	0.544	533.3	0.672	533.3	0.719
600.0	0.559	600.0	0.689	600.0	0.743
666.7	0.569	666.7	0.703	666.7	0.757
∞	0.603	∞	0.747	∞	0.809

[a] [Base]: [Substrate]=453: 1; quantitative yield.

[b] [Base]: [Substrate]=377: 1; quantitative yield.

[c] [Base]: [Substrate]=331: 1; quantitative yield.

TABLE 35 Continued

N-Chloro-2-(p-methoxyphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
66.7	0.131	66.7	0.167	66.7	0.219
133.3	0.225	133.3	0.278	133.3	0.317
200.0	0.300	200.0	0.366	200.0	0.400
266.7	0.363	266.7	0.444	266.7	0.466
333.3	0.417	333.3	0.503	333.3	0.522
400.0	0.459	400.0	0.556	400.0	0.569
466.7	0.494	466.7	0.598	466.7	0.606
533.3	0.525	533.3	0.631	533.3	0.641
600.0	0.555	600.0	0.659	600.0	0.668
666.7	0.569	666.7	0.688	666.7	0.689
∞	0.672	∞	0.680	∞	0.803

[a] [Base] : [Substrate]=669: 1; yield=90%.

[b] [Base] : [Substrate]=585: 1; yield 94%.

[c] [Base] : [Substrate]=585: 1; yield=94%.

TABLE 35 Continued

N-Chloro-2-(m-chlorophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
33.3	0.134	16.7	0.100	16.7	0.138
66.7	0.300	33.3	0.225	33.3	0.244
100.0	0.416	50.0	0.316	50.0	0.328
133.3	0.500	66.7	0.389	66.7	0.400
166.7	0.563	83.3	0.450	83.3	0.463
200.0	0.606	100.0	0.506	100.0	0.516
233.3	0.634	116.7	0.554	116.7	0.559
266.7	0.656	133.3	0.594	133.3	0.597
300.0	0.672	150.0	0.626	150.0	0.629
333.3	0.682	166.7	0.655	166.7	0.656
∞	0. 13	∞	0.817	∞	0.806

[a] [Base]: [Substrate]=406: 1; quantitative yield.

[b] [Base]: [Substrate]= 382: 1; quantitative yield.

[c] [Base]: [Substrate]= 382: 1; quantitative yield.

TABLE 35 Continued

N-Chloro-2-(p-chlorophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
16.7	0.134	16.7	0.134	16.7	0.144
33.3	0.218	33.3	0.216	33.3	0.229
50.0	0.300	50.0	0.289	50.0	0.304
66.7	0.356	66.7	0.353	66.7	0.368
83.3	0.410	83.3	0.409	83.3	0.421
100.0	0.459	100.0	0.458	100.0	0.472
116.7	0.503	116.7	0.503	116.7	0.516
133.3	0.539	133.3	0.543	133.3	0.553
150.0	0.572	150.0	0.574	150.0	0.586
166.7	0.600	166.7	0.606	166.7	0.616
∞	0.797	∞	0.813	∞	0.824

[a] [Base]: [Substrate]=556: 1; yield=93%.

[b] [Base]: [Substrate]=556: 1; yield=95%.

[c] [Base]: [Substrate]=556: 1; yield=96%.

TABLE 35 Continued

N-Chloro-2-(p-bromophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.134	0.0	0.094	0.0	0.097
25.0	0.250	25.0	0.216	25.0	0.217
50.0	0.341	50.0	0.314	50.0	0.318
75.0	0.419	75.0	0.397	75.0	0.402
100.0	0.480	100.0	0.459	100.0	0.468
125.0	0.531	125.0	0.514	125.0	0.523
150.0	0.571	150.0	0.556	150.0	0.569
175.0	0.603	175.0	0.591	175.0	0.606
200.0	0.631	200.0	0.620	200.0	0.638
225.0	0.651	225.0	0.644	225.0	0.661
∞	0.756	∞	0.758	∞	0.794

[a] [Base]: [Substrate]=580: 1; quantitative yield.

[b] [Base]: [Substrate]=580: 1; quantitative yield.

[c] [Base]: |Substrate|=561: 1; quantitative yield.

TABLE 36

Kinetic Data for Eliminations of HCl from N-Chloro-2-arylpyrrolidines Induced by t-BuOK-t-BuOH (0.0080 N) at 39.0°C

N-Chloro-2-(m-methoxyphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absoebance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
6.7	0.293	6.7	0.227	6.7	0.239
13.3	0.336	13.3	0.272	13.3	0.283
20.0	0.378	20.0	0.316	20.0	0.326
26.7	0.416	26.7	0.356	26.7	0.366
33.3	0.448	33.3	0.390	33.3	0.399
40.0	0.478	40.0	0.423	40.0	0.430
46.7	0.506	46.7	0.454	46.7	0.459
53.3	0.529	53.3	0.484	53.3	0.485
60.0	0.550	60.0	0.509	60.0	0.508
66.7	0.570	66.7	0.530	66.7	0.530
∞	0.776	∞	0.744	∞	0.732

[a] [Base]: [Substrate]=113: 1; quantitative yield.

[b] [Base]: [Substrate]=113: 1; quantitative yield.

[c] [Base]: [Substrate]=125: 1; quantitative yield.

TABLE 36 Continued

N-Chloro-2-(p-methoxyphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
16.7	0.194	16.7	0.234	16.7	0.203
33.3	0.259	33.3	0.327	33.3	0.264
50.0	0.317	50.0	0.417	50.0	0.322
66.7	0.368	66.7	0.477	66.7	0.371
83.3	0.410	83.3	0.538	83.3	0.415
100.0	0.448	100.0	0.591	100.0	0.455
116.7	0.481	116.7	0.636	116.7	0.490
133.3	0.509	133.3	0.675	133.3	0.519
150.0	0.533	150.0	0.710	150.0	0.548
166.7	0.555	166.7	0.742	166.7	0.570
∞	0.712	∞	0.921	∞	0.724

[a] [Base] : [Substrate]=175: 1; yield=92%.

[b] [Base] : [Substrate]=140: 1 yield=95%.

[c] [Base] : [Substrate]=184: 1; yield=98%.

TABLE 36 Continued

N-Chloro-2-(p-chlorophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
6.7	0.327	6.7	0.254	6.17	0.318
13.3	0.401	13.3	0.331	13.3	0.407
20.0	0.452	20.0	0.391	20.0	0.462
26.7	0.515	26.7	0.444	26.7	0.508
33.3	0.563	33.3	0.490	33.3	0.546
40.0	0.587	40.0	0.525	40.0	0.578
46.7	0.615	46.7	0.554	46.7	0.605
53.3	0.641	53.3	0.580	53.3	0.620
60.0	0.660	60.0	0.599	60.0	0.636
66.7	0.678	66.7	0.613	66.7	0.661
∞	0.765	∞	0.700	∞	0.738

[a] [Base] : [Substrate] =183: 1; yield=93%.

[b] [Base] : [Substrate] =195: 1; yield=90%.

[c] [Base] : [Substrate] =195: 1; yield=95%.

TABLE 36 Continued

N-Chloro-2-(m-chlorophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
3.3	0.339	3.3	0.321	3.3	0.319
6.7	0.390	6.7	0.371	6.7	0.374
10.0	0.436	10.0	0.418	10.0	0.419
13.3	0.475	13.3	0.456	13.3	0.459
16.7	0.509	16.7	0.493	16.7	0.494
20.0	0.541	20.0	0.526	20.0	0.528
23.3	0.569	23.3	0.553	23.3	0.555
26.7	0.593	26.7	0.577	26.7	0.581
30.0	0.613	30.0	0.599	30.0	0.603
33.3	0.631	33.3	0.616	33.3	0.621
∞	0.797	∞	0.778	∞	0.794

[a] [Base]: [Substrate]=120: 1; quantitative yield.

[b] [Base]: [Substrate]=120: 1; quantitative yield.

[c] [Base]: [Substrate]=120: 1; quantitative yield.

TABLE 36 Continued

N-Chloro-2-(p-methylphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[b]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
16.7	0.250	16.7	0.291	16.7	0.249
33.3	0.347	33.3	0.408	33.3	0.343
50.0	0.428	50.0	0.506	50.0	0.427
66.7	0.497	66.7	0.594	66.7	0.498
83.3	0.555	83.3	0.675	83.3	0.557
100.0	0.604	100.0	0.731	100.0	0.609
116.7	0.648	116.7	0.785	116.6	0.651
133.3	0.684	133.3	0.827	133.3	0.687
150.0	0.714	150.0	0.868	150.0	0.719
166.7	0.743	166.7	0.901	166.7	0.747
∞	0.891	∞	1.086	∞	0.907

[a] [Base] : [Substrate]=144: 1; yield=89%.

[b] [Base] : [Substrate] :115: 1; yield=87%.

[c] [Base] : [Substrate]=144: 1;yield=90%.

TABLE 36 Continued

N-Chloro-2-(m-methylphenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[b]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
16.7	0.236	16.7	0.225	16.7	0.306
33.3	0.341	33.3	0.333	33.3	0.384
50.0	0.429	50.0	0.425	50.0	0.464
66.7	0.504	66.7	0.500	66.7	0.525
83.3	0.571	83.3	0.568	83.3	0.576
100.0	0.624	100.0	0.625	100.0	0.619
116.7	0.669	116.7	0.673	116.7	0.657
133.3	0.709	133.3	0.713	133.3	0.691
150.0	0.745	150.0	0.749	150.0	0.721
166.7	0.774	166.7	0.778	166.7	0.748
∞	0.935	∞	0.949	∞	0.876

[a] $[\text{Base}] : [\text{Substrate}] = 107 : 1$; quantitative yield.

[b] $[\text{Base}] : [\text{Substrate}] = 100 : 1$; quantitative yield.

[c] $[\text{Base}] : [\text{Substrate}] = 110 : 1$; quantitative yield.

TABLE 36 Continued

N-Chloro-(p-bromophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
6.7	0.367	6.7	0.348	3.3	0.301
13.3	0.460	13.3	0.444	6.7	0.358
20.0	0.533	20.0	0.521	10.0	0.410
26.7	0.590	26.7	0.582	13.3	0.457
33.3	0.641	33.3	0.632	16.7	0.500
40.0	0.680	40.0	0.672	20.0	0.540
46.7	0.715	46.7	0.708	26.7	0.574
53.3	0.741	53.3	0.736	-	-
60.0	0.762	60.0	0.760	-	-
66.7	0.778	66.7	0.781	-	-
∞	0.880	∞	0.888	∞	0.918

[a] [Base] : [Substrate]=175: 1; quantitative yield.

[b] [Base] : [Substrate]=175: 1; quantitative yield.

[c] [Base] : [Substrate]=163: 1; quantitative yield.

TABLE 37

Kinetic Data for Deuterium Isotope Effect Studies in MeONa-MeOH (0.0267 N) Base-Solvent System at 39.0°C

N-Chloro-2-deuterio-2-phenylpyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
333.	0.113	333	0.119	117	0.335
667	0.303	667	0.303	333	0.378
1000	0.419	1000	0.416	500	0.413
1333	0.501	1333	0.494	667	0.444
1667	0.559	1667	0.549	833	0.469
2000	0.600	2000	0.581	1000	0.484
2333	0.632	2333	0.617	1167	0.507
2667	0.655	2667	0.639	1333	0.524
3000	0.671	3000	0.655	1500	0.538
3333	0.683	3333	0.666	1667	0.550
∞	0.718	∞	0.706	∞	0.618

[a] $[\text{Base}]:[\text{Substrate}] = 473:1$; quantitative yield.

[b] $[\text{Base}]:[\text{Substrate}] = 493:1$; quantitative yield.

[c] $[\text{Base}]:[\text{Substrate}] = 567:1$; quantitative yield.

TABLE 37 Continued

N-Chloro-2-deuterio-2-(m-chlorophenyl)-pyrrolidine

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.314	0.0	0.315	66.7	0.288
100.0	0.425	100.0	0.425	133.3	0.371
200.0	0.508	200.0	0.508	200.0	0.441
300.0	0.571	300.0	0.573	266.7	0.498
400.0	0.623	400.0	0.621	333.3	0.544
500.0	0.661	500.0	0.659	400.0	0.584
600.0	0.693	600.0	0.689	466.7	0.620
700.0	0.716	700.0	0.714	533.3	0.651
800.0	0.736	800.0	0.734	600.0	0.675
900.0	0.751	900.0	0.747	666.7	0.696
∞	0.808	∞	0.806	∞	0.822

[a] [Base] : [Substrate] =378: 1; quantitative yield.

[b] [Base] : [Substrate] =378: 1; quantitative yield.

[c] [Base] : [Substrate] =366 :1; quantitative yield.

TABLE 38

Kinetic Data for Deuterium Isotope Effect Studies in t-BuOK-t-BuOH Base-Solvent System at 39.0°C

N-Chloro-2-deuterio-2-phenylpyrrolidine

(Base = 0.0133 N)

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
0.0	0.219	0.0	0.200	0.0	0.188
20.0	0.308	20.0	0.294	20.0	0.288
40.0	0.380	40.0	0.356	40.0	0.363
60.0	0.441	60.0	0.434	60.0	0.425
80.0	0.494	80.0	0.484	80.0	0.479
100.0	0.543	100.0	0.532	100.0	0.528
120.0	0.581	120.0	0.575	120.0	0.566
140.0	0.618	140.0	0.602	140.0	0.600
160.0	0.649	160.0	0.632	160.0	0.631
180.0	0.673	180.0	0.659	180.0	0.656
∞	0.906	∞	0.893	∞	0.875

[a] [Base] : [Substrate] =193: 1; yield=98%.

[b] [Base] : [Substrate] =193: 1; yield=97%.

[c] [Base] : [Substrate] =207: 1; yield= quantitative.

TABLE 38 Continued

N-Chloro-2-deuterio-2-(m-chlorophenyl)-pyrrolidine

(Base = 0.008 N)

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
13.3	0.403	13.3	0.369	13.3	0.313
26.7	0.449	26.7	0.409	26.7	0.355
40.0	0.488	40.0	0.444	40.0	0.391
53.3	0.523	53.3	0.476	53.3	0.424
66.7	0.555	66.7	0.506	66.7	0.453
80.0	0.581	80.0	0.529	80.0	0.478
93.3	0.603	93.3	0.552	93.3	0.499
106.7	0.624	106.7	0.571	106.7	0.519
120.0	0.641	120.0	0.586	120.0	0.536
133.3	0.656	133.3	0.601	133.3	0.551
∞	0.775	∞	0.713	∞	0.664

[a] [Base] : [Substrate]=112: 1; quantitative yield.

[b] [Base] : [Substrate]=122: 1; quantitative yield.

[c] [Base] : [Substrate]=131: 1; quantitative yield.

TABLE 39

Kinetic Data for Elimination of N-Bromo-2-phenylpyrrolidine (NBA) Induced by MeONa-MeOH (0.0267 N) at 39.0°C

Run # 1[a]		Run # 2[b]		Run # 3[c]	
Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)	Time (sec)	Absorbance (A_t)
3.3	0.447	3.3	0.544	3.3	0.344
6.7	0.504	6.7	0.577	6.7	0.378
10.0	0.553	10.0	0.603	10.0	0.406
13.3	0.594	13.3	0.628	13.3	0.429
16.7	0.626	16.7	0.649	16.7	0.450
20.0	0.654	20.0	0.666	20.0	0.466
23.3	0.676	23.3	0.678	23.3	0.478
26.7	0.694	26.7	0.688	26.7	0.489
30.0	0.709	30.0	0.697	30.0	0.498
33.3	0.723	33.3	0.705	33.3	0.506
∞	0.778	∞	0.731	∞	0.537

[a] [Base]: [NBA] =406: 1; yield=98%.

[b] [Base]: [NBA] =401: 1; yield=91%.

[c] [Base]: [NBA] =394: 1; yield=66%.

TABLE 40

2-Aryl-1-pyrrolines from 2-Methoxy-1-pyrroline (MPy) and Aryl Magnesium Bromides (AMB)

Aryl Group	AMB / MPy [a]	Reflux time (hr)	% Yield of 2-Aryl-1-pyrroline[b]
Phenyl	2.2	17	79
p-Anisyl	1.5	19.5	55
m-Anisyl	1.7	23	74
p-Tolyl	1.5	20	53
m-Tolyl	2	17.5	94
p-Chlorophenyl	1.7	15	44
m-Chlorophenyl	1.2	20	42
p-Bromophenyl	1.5	18	18

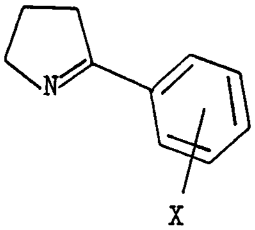
---

[a] The ratio of moles of reagents used.

[b] Yields are based on isolated, purified compounds.

TABLE 41

The λ_{max} and ϵ Values of 2-Aryl-1-pyrrolines



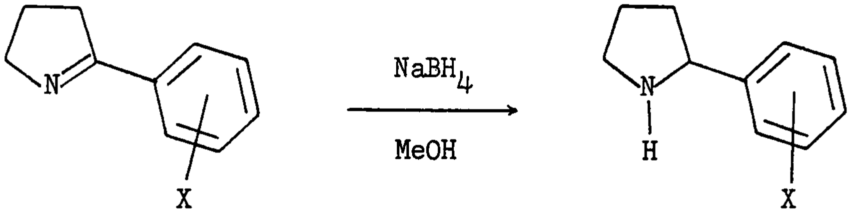
X	Methanol		t-Butyl Alcohol	
	λ_{max} (nm)	ϵ (x10^4)[a]	λ_{max} (nm)	ϵ (x10^4)[a]
H	241.5	1.21 ± 0.02	243	1.24 ± 0.07
3-OMe	246	0.92 ± 0.01	246	0.91 ± 0.02
4-OMe	263	1.87 ± 0.08	263	1.69 ± 0.05
3-Me	245	1.12 ± 0.01	146	1.10 ± 0.02
4-Me	250	1.56 ± 0.02	250	1.80 ± 0.01
3-Cl	242	1.07 ± 0.01	245	0.99 ± 0.01
4-Cl	250	1.78 ± 0.01	250	1.89 ± 0.01
4-Br	248	1.48 ± 0.01	251	1.32 ± 0.08

---

[a] The ϵ values presented are the average of three determinations, at 39°C.

TABLE 42

Reduction of 2-Aryl-1-pyrrolines with Sodium Borohydride



X	Hydride / Imine [a]	% Yield of 2-Aryl-1-pyrroline
H	3.0	79
p-OCH_3	8.4	63
m-OCH_3	3.0	64
p-CH_3	4.0	58
m-CH_3	3.0	65
p-Cl	8.5	70
m-Cl	3.0	37
p-Br	3.0	46

---

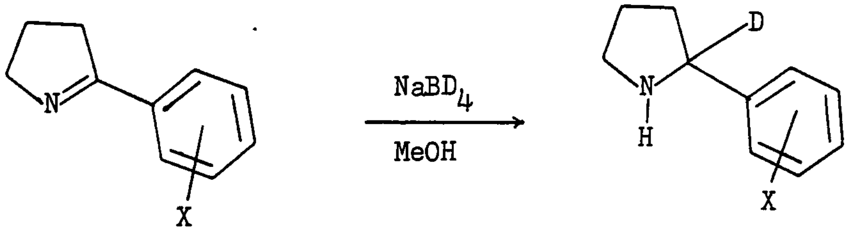
[a] The ratio of moles of reagents used.

[b] The yields are based on isolated, purified amines.

established by their ir, nmr, and mass spectra and comparison of their boiling points with literature values (Table 42). The 2-deuterio derivatives were obtained by reduction of the corresponding 2-aryl-1-pyrrolines with sodium borodeuteride following the same procedure developed for sodium borohydride reductions. The results are presented in Table 43.

TABLE 43

Reduction of 2-Aryl-1-pyrrolines with Sodium Borodeuteride



X	Deuteride / Imine [a]	% Yield of Amine[b]
H	3.2	68
3-Cl	2.8	56

[a] The molar ratio of the reagents used.

[b] The isolated and purified yields.

2.2. Elimination of HCl from N-Chloro-2-phenylpyrrolidine

A large scale elimination reaction was performed on N-chloro-2-

phenylpyrrolidine using the MeONa-MeOH base-solvent system. The crude product was analysed by infrared and nuclear magnetic spectroscopy. The crude product was found to be 2-phenyl-1-pyrroline. There was no spectral evidence for the presence of any other product.

2.3 Kinetic Runs

2.3.1 Introduction

Eliminations from N-chloro-2-arylpyrrolidines (NCA) were induced by mixing an alcoholic solution of N-chloroamine with MeONa-MeOH or t-BuOK-t-BuOH, $\left[B^{\ominus}\right]$. Pseudo-first-order conditions were employed (base in at least 70 fold excess). This simplifies the kinetic Equation 53 to 54. The Equation 54 can be integrated to give Equation 55. Pseudo-first-order rate constants were obtained by measuring the appearance

Eq-53
$$-\frac{d\ \text{NCA}}{dt} = k_2 \left[\text{NCA}\right] \left[B^{\ominus}\right]$$

Eq-54
$$-\frac{d\ \text{NCA}}{dt} = k \left[\text{NCA}\right];\ \text{where } k = k_2 \left[B^{\ominus}\right]$$

Eq-55
$$-\ln \left[\text{NCA}\right] = k \quad + \text{constant}$$

of absorption at the λ_{max} for the 2-aryl-1-pyrrolines in the region 241-263 nm as a function of time. The difference of absorption at infinite time, A_{∞}, and absorption at a given time, A_t, is proportional to the concentration of N-chloroamine. Therefore the plot of $-\ln(A_{\infty} - A_t)$

versus time should give straight line with the slope k (pseudo-first-order rate constant). Excellent pseudo-first-order kinetic plots were obtained with corrolation coefficients better than r= 0.999. This provides ample evidence that the elimination reactions are first order in N-chloro-2-arylpyrrolidines. Some representative plots are shown in Figures 12 and 13. The second-order rate constants, k_2, were obtained by dividing the pseudo-first-order rate constants by the base concentration. The kinetic runs were performed three times for each system and the average values are taken to insure reproducability.

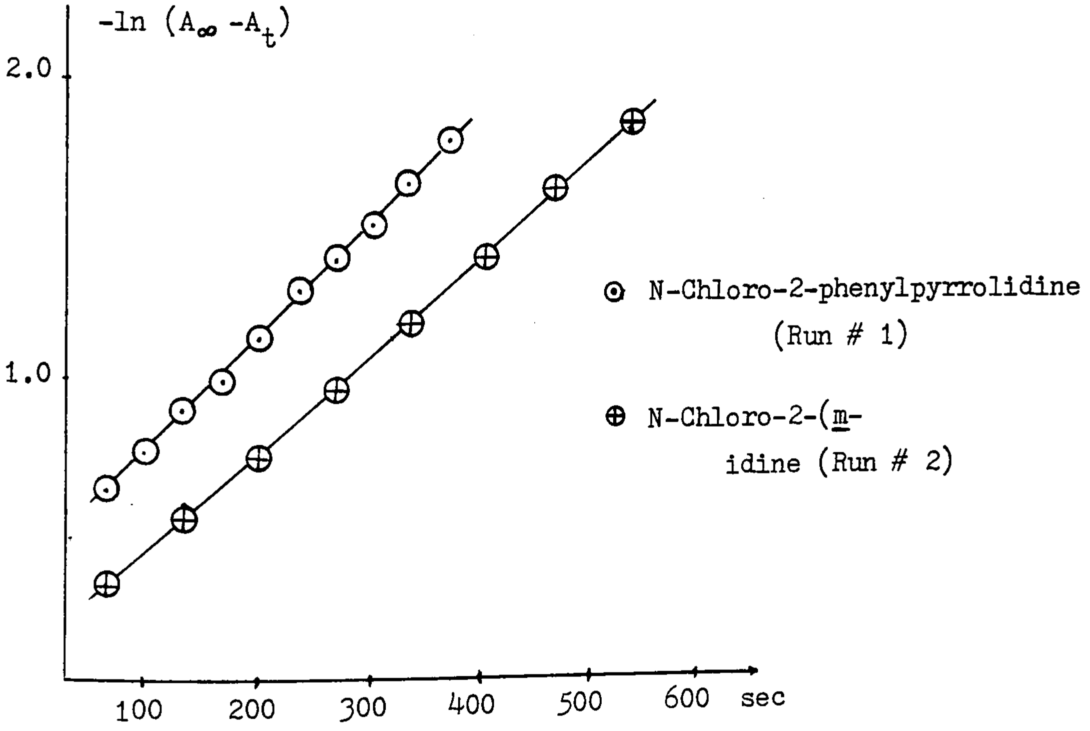


Figure 12 Some Representative Kinetic Plots in MeONa-MeOH at 39.0°C

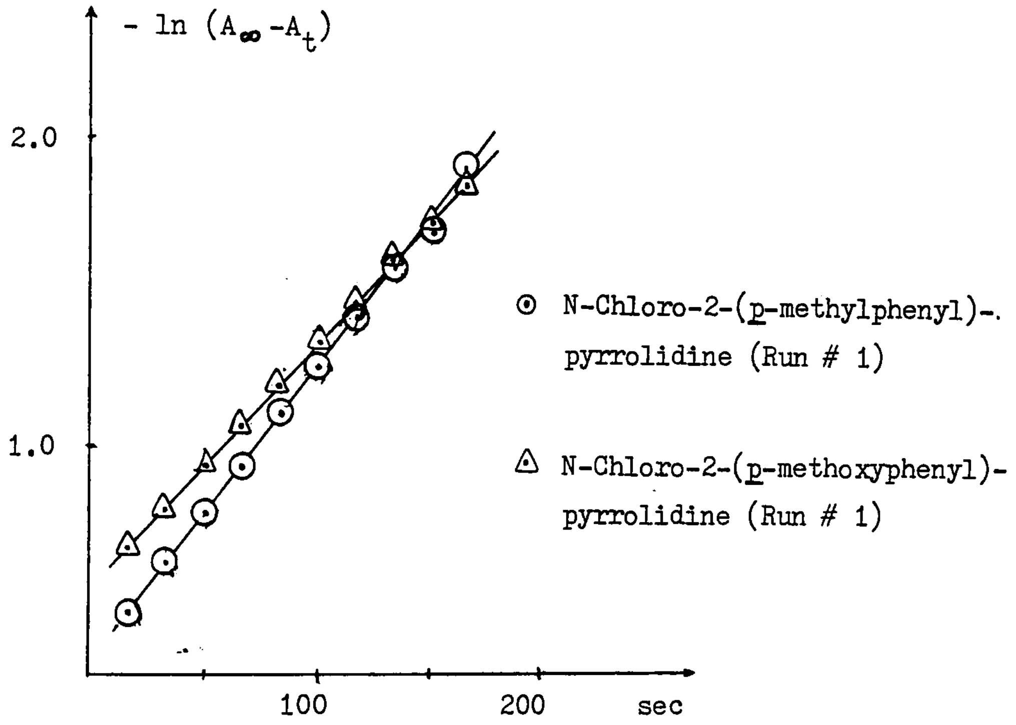


Figure 13 Some Representative Kinetic Plots in t-BuOK-t-BuOH at 39.0°C

By comparison of the absorption in infinity samples with that for authentic 2-aryl-1-pyrrolines, the product yields were calculated. Elimination of HCl from N-chloro-2-arylpyrrolidines induced by MeONa-MeOH and t-BuOK-t-BuOH at 29.6-48.5°C produced 84-100% yields of 2-aryl-1-pyrroline (based upon the original 2-arylpyrrolidines). The cases where lower than quantitative yields were observed might be due to moderate losses occurring the generation of N-chloro-2-arylpyrrolidines from the parent amines and the errors encountered during the injection of alcoholic solutions of N-chloroamines into the base-solvent solutions. In view of the lack of evidence for other possible products (see Section 2.2) and the regiospecificity exhibited for eliminations from N-chlorobenzyl-_n_-butylamine[74] and N-chlorobenzylmethylamine[75] with several base-solvent systems, the yields of 2-aryl-1-pyrrolines were assumed to be quantitative.

When N-chloro-2-phenylpyrrolidine was heated in methanol at 48.5° C for a period of time similar to that needed for infinity samples in base-promoted eliminations from N-chloro-2-phenylpyrrolidine, no absorbtion due to 2-phenyl-1-pyrroline was observed. Therefore solvolytic elimination from N-chloro-2-arylpyrrolidines was demonstrated to be unimportant.

2.3.2 Order of Base

The second-order rate coefficients presented in Tables 44 and 45 for the base-solvent combinations of MeONa-MeOH and _t_-BuOK-_t_-BuOH, respectively, were determined for differing base concentrations (_ca_. 10 fold variation). The constancy of these values establishes that the elimination reactions are first order in base.

2.3.3 Activation Parameters

Rates of elimination from N-chloro-2-phenylpyrrolidine induced by MeONa-MeOH and _t_-BuOK-_t_-BuOH were measured at three temperatures spanning nearly 20°C. The results are tabulated in Table 46 and 47.

The Arrhenius equation which defines the activation energy, E_a, is given by the Equation 56. Therefore a plot of $-\ln k_2$ versus $1/T$

TABLE 44

Rate Coefficients for Eliminations from N-Chloro-2-phenylpyrrolidine (NCA) Induced by MeONa-MeOH at 39.0°C

[MeONa] ,M	[MeONa] : [NCA]	k_2, M^{-1} s^{-1}
0.1063	1510: 1	0.140[a]
0.267	390: 1	0.138 ± 0.004[b]
0.0.01063	151: 1	0.145[a]

[a] Single run.

[b] Standard deviation from average value for three runs.

TABLE 45

Rate Coefficients for Eliminations from N-Chloro-2-phenylpyrrolidine (NCA) Induced by *t*-BuOK-*t*-BuOH at 39.0°C

[*t*-BuOK] ,M	[*t*-BuOK] : [NCA]	k_2, M^{-1} s^{-1}
0.0577	748: 1	1.69[a]
0.0133	173: 1	1.72 ± 0.06[b]
0.00527	71: 1	1.56[a]

[a] Single run.

[b] Standard deviation from average value for three runs.

TABLE 46

Rate Constants for Eliminations from N-Chloro-2-phenylpyrrolidine Induced by MeONa-MeOH at Different Temperatures

Temp, °C	k_2, M^{-1} s^{-1}
48.5	0.328 ± 0.02
39.0	0.138 ± 0.004
29.6	0.0654 ± 0.0002

TABLE 47

Rate Constants for Eliminations from N-Chloro-2-phenylpyrrolidine Induced by _t_-BuOK-_t_-BuOH at Different Temperatures

Temp, °C	k_2, M^{-1} s^{-1}
48.5	2.9 ± 0.1
39.0	1.69 ± 0.04
29.6	0.93 ± 0.02

should give a straight line with the slope of E_a/R. The Arrhenius

Eq-56
$$\ln k = -\frac{Ea}{RT} + \ln A$$

plots shown in Figures 14 and 15 exhibited excellent linearity (correlations better than 0.99).

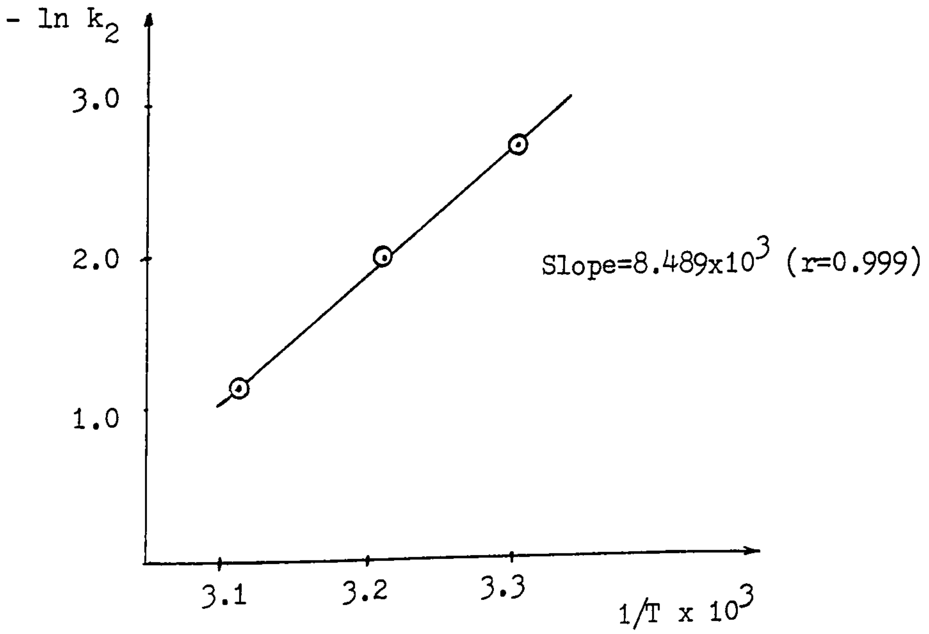


Figure 14 Arrhenius Plot for the Eliminations from N-Chloro-2-phenylpyrrolidine Induced by MeONa-MeOH

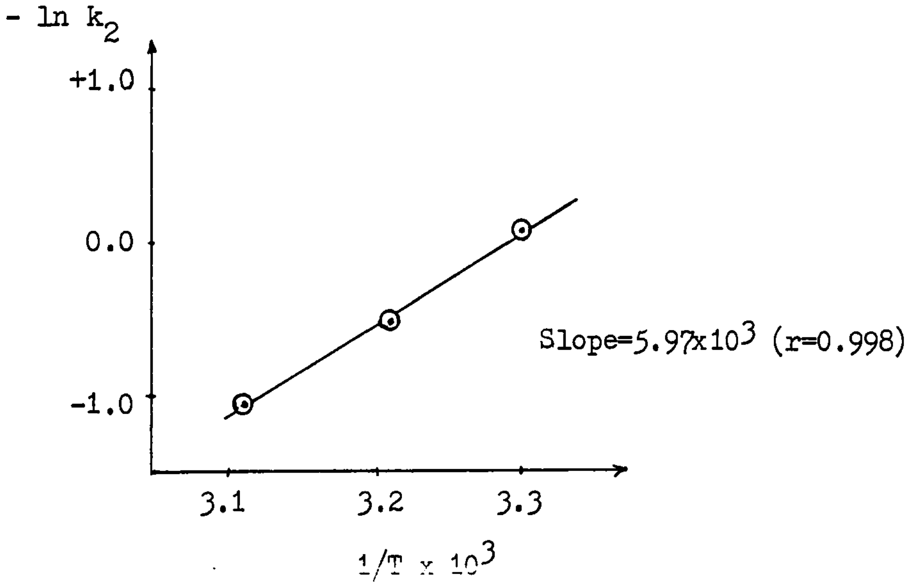


Figure 15 Arrhenius Plot for the Eliminations from N-Chloro-2-phenylpyrrolidine Induced by t-BuOK-t-BuOH

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be calculated with the help of Equations 57 and 58. The results are tabulated in Table 48.

Eq-57 $$\Delta H^{\ddagger} = E_a - RT$$

Eq-58[206] $$\Delta S^{\ddagger} = 4.756\ (\log k_2 - 10.753 - \log T + \frac{E_a}{4.576\ T})$$

2.3.4 Hammet ρ Values

In order to observe the effect of aryl substituents upon elimination rates, elimination reactions from N-chloro-2-(m- or p-substituted

TABLE 48

Activation Parameters for Base-Promoted Eliminations from N-Chloro-2-phenylpyrrolidine at 39.0°C

Base-Solvent	E_a (kcal/mole)	$\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (eu)
MeONa-MeOH	16.9 ± 0.8	16.2 ± 0.8	-10.9 ± 2.4
t-BuOK-t-BuOH	11.9 ± 0.6	11.3 ± 0.6	-22.4 ± 1.2

TABLE 49

Rate Constants for Base-Promoted Dehydrochlorination Reactions of N-Chloro-2-arylpyrrolidines at 39.0°C

No	Substituent	k_2, M^{-1} s^{-1} (MeONa-MeOH)	k_2, M^{-1} s^{-1} (t-BuOK-t-BuOH)
1	H	0.138 ± 0.003	1.62 ± 0.06
2	3-Me	0.123 ± 0.003	1.22 ± 0.01
3	4-Me	0.112 ± 0.001	1.20 ± 0.02
4	3-OMe	0.157 ± 0.001	1.81 ± 0.04
5	3-OMe	0.159 ± 0.001	- -
6	4-OMe	0.105 ± 0.003	1.04 ± 0.05
7	4-OMe	0.101 ± 0.001	- -
8	3-Cl	0.370 ± 0.002	4.28 ± 0.07
9	4-Cl	0.297 ± 0.004	3.40 ± 0.04
10	4-Br	0.291 ± 0.01	3.33 ± 0.08

phenyl)-pyrrolidines were performed using MeONa-MeOH and t-BuOK-t-BuOH at 39°C. The results are presented in Table 49.

The entries 4,5 and 6,7 in Table 49 demonstrate the reproducibility of the rate constant determination.

The influence of aryl ring substituents upon elimination rates correlated satisfactorily with the Hammet
(Equation 59).

Eq-59 $$\log k_X/k_H = \sigma^- \rho$$

The Hammett plots for these reactions are given in Figures 16 and 17 and the Hammett ρ values and correlation coefficients are given in Table 50.

TABLE 50

Hammett Correlations for Eliminations from N-Chloro-2-arylpyrrolidines Promoted by MeONa-MeOH and t-BuOK-t-BuOH at 39.0°C

Base-Solvent	ρ^a (r^b)	ρ^c (r^b)
MeONa-MeOH	0.992 (0.959)	1.02 (0.982)
t-BuOK-t-BuOH	1.13 (0.975)	1.15 (0.988)

[a] ρ value obtained using all the substituents.

[b] r= correlation coefficient.

[c] ρ value obtained using all substituents except 3-OMe.

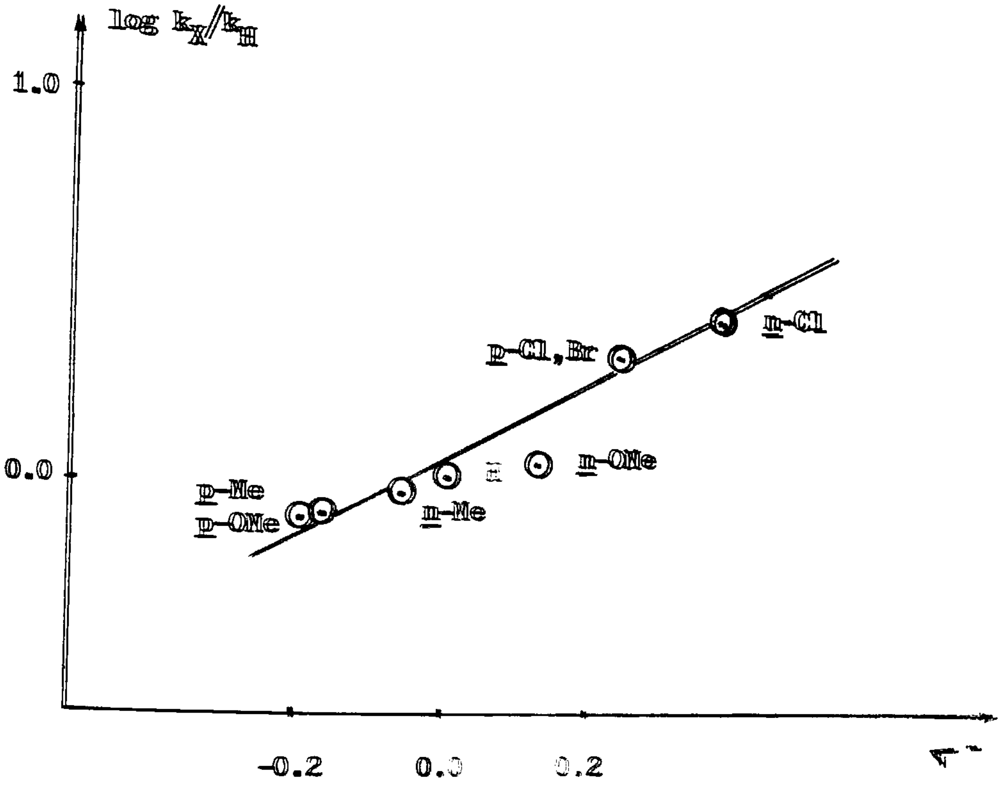


Figure 16 Hammett Plot for Dehydrochlorination Reactions of N-Chloro-2-arylpyrrolidines with MeONa-MeOH at 39.0°C

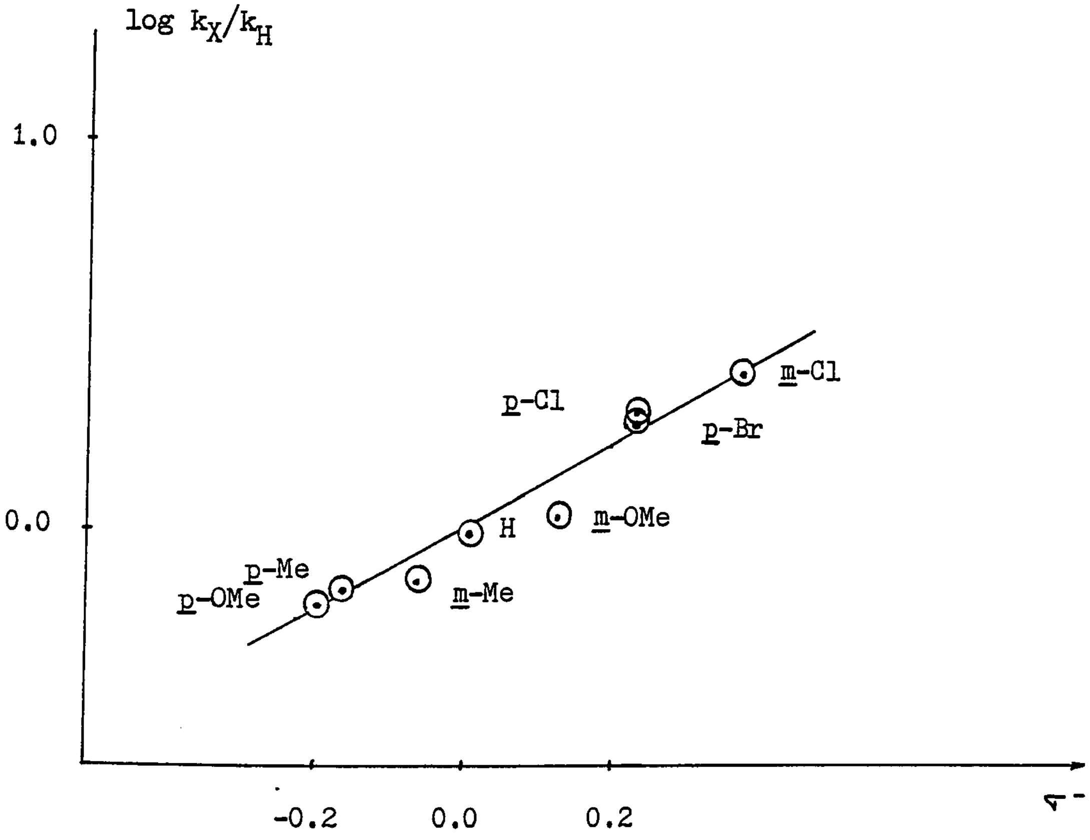


Figure 17 Hammett Plot for Dehydrochlorination Reactions of N-Chloro-2-arylpyrrolidines with t-BuOK-t-BuOH at 39.0°C

The data point for the 3-OMe substituent did not correlate well with those for the other substituents. This is not without precedent. Bartsch and Cho[75] noted that the data point in the Hammett plots for the eliminations from N-chloro-(3-methoxybenzyl)-methylamine did not correlate well with the data points for the other ring-substituted N-chlorobenzylmethylamines. Repeating the dehydrochlorination reaction of N-chloro-2-(m-methoxy)-pyrrolidine gave the same k_2 value within experimental error (Table 46 # 5) which proves that the deviation is real. There is no explanation for the anomalous behaviour of the 3-OMe substituent at the present time.

2.3.5 Deuterium Isotope Effects

In order to determine the primary deuterium isotope effect values, dehydrochlorination reactions of N-chloro-2-deutero-2-phenylpyrrolidine and N-chloro-2-deutero-2-(m-chlorophenyl)-pyrrolide were performed with MeONa-MeOH and t-BuOK-t-BuOH. The rate constants and the primary deuterium isotope effect values are given in Table 51.

2.3.6 Leaving Group Element Effect

In order to observe the leaving group element effect 2-phenylpyrrolidine was N-brominated with N-bromosuccinimide employing the general method developed for the N-chlorination reactions. The k_2 value observed for eliminations from N-bromo-2-phenylpyrrolidine induced by MeONa-MeOH was $2.3 \pm 0.1\ M^{-1}\ s^{-1}$ which gave a leaving group element effect of $k_{Br}/k_{Cl}=16.7$. The eliminations from N-bromo-2-phenylpyrrol-

TABLE 51

Rate Constants and Deuterium Isotope Effect Values for Eliminations from N-Chloro-2-deuterio-2-arylpyrrolidines with MeONa-MeOH and t-BuOK-t-BuOH at 39.0°C

	Aryl = Phenyl		Aryl = 3-Chlorophenyl	
Base-Solvent	k_2, M^{-1} s^{-1}	k_H/k_D	k_2, M^{-1} s^{-1}	k_H/k_D
MeONa-MeOH	$(3.46 \pm 0.01)x10^{-2}$	3.98	$(8.93 \pm 0.01)x10^{-3}$	4.15
t-BuOK-t-BuOH	0.46 ± 0.01	3.68	1.19 ± 0.01	3.66

idine promoted by t-BuOK-t-BuOH proved to be too fast to follow with the kinetic technique employed in this study.

3.0 Discussion

3.1 Introduction

Very few kinetic investigations of base-promoted imine formation from CH-NX compounds have appeared in the literature. The majority of these employ a substrate, leaving group, or base-solvent system which has little analogy in previously-studied reactions leading to olefins.[70-73] Most recently, Bartsch and Cho have investigated dehydrochlorination reactions of N-chlorobenzyl-n-butylamine[74] and N-chlorobenzylmethylamine[75] and compared the kinetic data obtained for these imine-forming eliminations with that for olefin-forming reactions.

Kinetic investigations of base-promoted dehydrochlorinations from N-chloro-2-arylpyrrolidines will increase our knowledge in imine-forming transition states and similarities and differences between imine- and alkene-forming elimination reactions.

3.2 Mechanism of Elimination from N-Chloro-2-arylpyrrolidines

The kinetic investigation provides convincing evidence that eliminations from N-chloro-2-arylpyrrolidines promoted by MeONa-MeOH and *t*-BuOK-*t*-BuOH proceed via an E2 mechanism. Solvolytic elimination was demonstrated to be negligible for N-chloro-2-phenylpyrrolidine in methanol, the more polar alcoholic solvent employed. Also the observed second-order kinetics, first-order in chloroamine and first-order in base, rule out all but bimolecular pathways. A reversible E1cB mechanism was negated by substantial values of the primary deuterium isotope effect (Table 51). The E2 and $(E1cB)_{irr}$ mechanisms may be differentiated by the leaving group element effect.[31] From eliminations from N-halo-2-phenylpyrrolidine, a leaving group element effect (k_{Br}/k_{Cl}) value of 16.7 was determined with MeONa-MeOH. Bartsch and Cho[75] have calculated a k_{Br}/k_{Cl} value of 80 for E2 elimination from 2-halo-1-phenylpropanes induced by EtONa-EtOH at 25°C. Since the differences in bond energies between N-Br and N-Cl bonds is anticipated to be significantly less than that between C-Br and C-Cl bonds a k_{Br}/k_{Cl} value of 16.7 is consistent with an E2 mechanism for base-promoted dehydrochlorination reactions of N-chloro-2-arylpyrrolidines.

3.3 Regioselectivity in Eliminations from N-Chloramines

Eliminations from N-chloro-2-arylpyrrolidines promoted by MeONa-MeOH and t-BuOK-t-BuOH produced quantitative yields of the conjugated imine, 2-aryl-1-pyrrolines. Detection of only the conjugated imine has previously been reported in base-promoted dehydrochlorination reactions of N-chlorobenzyl-n-butylamine[74] and N-chlorobenzylmethylamines.[75] The regiospecificity observed in these systems parallels observations for alkoxide-induced eliminations from 2-halo-1-phenylpropanes[207] and suggests well-developed double bond character in the imine-forming transition states. In contrast to the high regioselectivity observed for alkoxide-induced eliminations from N-chloro-2-arylpyrrolidines and other N-chloramines,[74,75] 2-halo-1-phenylpropanes,[207] and 1-phenyl-2-tosyloxypropane,[207] Hoffman and Cadena[73] have noted the formation of both conjugated and unconjugated imine products in reactions of $PhCH_2N(R)OSO_2C_6H_4$-p-NO_2 with amine bases in water-THF-ethylacetate at -10°C. At this time, the reasons for the much lower regioselectivity observed with the Hoffman and Cadena system than with ours remain uncertain.

3.4 Comparison of the Rates of Imine- and Alkene-Forming Eliminations

Activation parameters for base-promoted eliminations from N-chloro-2-phenylpyrrolidine, N-chlorobenzylmethylamine,[75] N-chloro-α-methylbenzylmethylamine,[208] and 2-chloro-1-phenylpropane[206] are presented in Table 55.

It was reported by Bartsch and Cho that the second-order rate

TABLE 52

Activation Parameters for Some Base-Promoted Eliminations

Substrate	Base-Solvent	Temp, °C	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
N-Chloro-2-phenyl-pyrrolidine	MeONa-MeOH	39.0	16.9	-10.9
	t-BuOK-*t*-BuOH	39.0	11.9	-22.4
N-Chloro-α-methyl-benzylmethylamine	MeONa-MeOH	39.0	19.2	-6.4
	t-BuOK-*t*-BuOH	39.0	14.6	-17.3
N-Chlorobenzyl-methylamine	MeONa-MeOH	39.0	16.6	-12.1
	t-BuOK-*t*-BuOH	39.0	11.7	-21.1
2-Chloro-1-phenyl-propane	EtONa-EtOH	25.0	22.3	-10.1
	t-BuOK-*t*-BuOH	25.0	17.9	-19.4

constant for reaction of N-chlorobenzylmethylamine with MeONa-MeOH at 29.6°C was 1.53×10^{-2} M^{-1} s^{-1} and that for reaction of 2-chloro-1-phenylpropane with EtONa-EtOH at 25.0°C was 1.86×10^{-6} M^{-1} s^{-1}.[75] Taking into account the slightly different reaction conditions, the replacement of an α-carbon with an α-nitrogen produced a minimal 1000-fold enhancement in elimination rate. From comparison of activation parameters (Table 52), the large rate enhancement for eliminations from N-chlorobenzylmethylamine was attributed to enthalpic (energy of bond-making and bond-breaking) factors, since the entropies of activation were similar for base-solvent combinations of similar type (dissociated or associated bases). The same argument holds also for the alkoxide-induced eliminations from N-chloro-2-arylpyrrolidines. The similarity of activation entropies for imine- and alkene-forming elimination reactions provides additional additional evidence for a common E2 mechanism for both types of the reactions.

3.5 Transition States for Eliminations from N-Chloramines

Measurements of the primary deuterium isotope effect and determination of the Hammett ρ value for β-aryl groups have been instrumental in assessing the character of the E2 transition state.[31-33] A collection of primary deuterium isotope and Hammett ρ values of some elimination reactions are given in Table 53.[75,208]

For the reactions of N-chloro-2-arylpyrrolidines with MeONa-MeOH and t-BuOK-t-BuOH at 39.0°C, Hammett ρ values calculated were 1.02 and 1.15, respectively. The indicated carbanionic character at β-carbon in the transition state appears to be somewhat less than those reported for alkoxide-promoted eliminations from N-chloro-α-methylbenzylmethylamine,[208] N-chlorobenzylmethylamine,[75] and 1-phenyl-2-bromopropane.[207] For imine-forming eliminations, the ρ value increases very slightly as the base is changed from dissociated, MeONa-MeOH, to associated t-BuOK-t-BuOH. A similar change in base-solvent combination produces a considerable larger decrease in ρ value for olefin-forming eliminations (Table 53). At the present, the factors responsible for the opposing effects observed in ρ values for alkene- and imine-forming reactions brought about by the change of base and solvent are not clear. However,

TABLE 53

Hammett Correlations and Deuterium Isotope Effects of Some Alkene- and Imine-Forming Elimination Reactions

Substrate	Base-Solvent	Temp, °C	k_H/k_D	ρ
N-Chloro-2-phenyl-pyrrolidine	MeONa-MeOH	39.0	3.98	1.02
	_t_-BuOK-_t_-BuOH	39.0	3.68	1.15
N-Chloro-α-methyl-benzylmethylamine	MeONa-MeOH	39.0	4.4	1.36
	_t_-BuOK-_t_-BuOH	39.0	4.5	1.55
N-Chlorobenzyl-methylamine	MeONa-MeOH	39.0	6.0	1.52
	_t_-BuOK-_t_-BuOH	39.0	5.9	1.68
1-Phenyl-2-chloro propane	EtONa-EtOH	25.0	6.1	-
	_t_-BuOK-_t_-BuOH	25.0	8.7	-
1-Phenyl-2-bromo propane	EtONa-EtOH	50.0	-	1.84
	_t_-BuOK-_t_-BuOH	50.0	-	1.37

the results suggest a lesser sensitivity of E2 transition state character to variation of the base-solvent system for the imine-forming elimination reactions.

The primary deuterium isotope effect values indicate considerable Cβ-H bond rupture in the transition states for the alkoxide-promoted eliminations from N-chloro-2-arylpyrrolidines.

The change of base from dissociated, EtONa-EtOH, to associated, t-BuOK-t-BuOH, for eliminations from 2-chloro-1-phenylpropane produces a large increase in k_H/k_D values. On the other hand, a similar chage of base-solvent system for imine-forming eliminations produces a slight decrease in k_H/k_D value, consistent with the small increase in the ρ value. The primary deuterium isotope effect values are consistent with the insensitivity of imine-forming transition-state character to change in base-solvent system indicated by the ρ values.

Comparison of the kinetic data for eliminations from N-chloro-2-arylpyrrolidines with that for the structurally-related N-chloro-α-methylbenzylmethylamines studied by Cho[208] is revealing. In changing the substrate in imine-forming eliminations from N-chloro-α-methylbenzylmethylamine to N-chloro-2-phenylpyrrolidine a rate enhancement of 14-fold for MeONa-MeOH and 25-fold for t-BuOK-t-BuOH was observed at 39.0°C. The more rapid rates result from substantial decreases in the enthalpies of activation with somewhat offsetting decreases in entropies of activation for the heterocyclic substrate (Table 52). The primary deuterium isotope effect and Hammett ρ values are consistently lower for eliminations from N-chloro-2-arylpyrrolidines (Table 53). Likewise, the leaving group element effect of $k_{Br}/k_{Cl}=16.7$ found for eliminations from N-halo-2-phenylpyrrolidines promoted by MeONa-MeOH at 39.0°C is smaller than the value of 28.8 reported by Cho[208] for eliminations from N-halo-α-methylbenzylmethylamine under the same conditions. Thus, the kinetic data demonstrate that compared with N-chloro-α-methylbenzylmethylamines, elimination transition states for N-chloro-2-arylpyrrolidines have less C_β-H and N-Cl bond rupture and less carbanionic character at C_β. These results indicate a shift to a more reactant-like transition state. A more reactant-like transition state is also consistent with the observed reaction rate increases because, according to the Hammond Postulate, the transition state should have more resemblance to the reactants for a less endothermic reaction.

4.0 Conclusion

The combined results indicate that the transition states for base-promoted eliminations from N-chloro-2-arylpyrrolidines have appreciable C_β-H and N_α-Cl bond rupture, significant carbon-nitrogen double bond character, and limited carbanionic character. Thus, it appears that the transition states lie around central-E2 in the spectrum of the E2 transition states. Also the transition-state structure is rather insensitive to variations of the base-solvent system.

By changing the substrate in imine-forming eliminations from N-chloro- α-methylbenzylmethylamine[208] to N-chloro-2-phenylpyrrolidine the imine-forming transition states changed. The comparison of Hammett ρ values, deuterium isotope effects, and leaving group element effects indicate that there is less C_β-H and N_α-Cl bond rupture and less carbanionic character in the imine-forming transition states of N-chloro-2-phenylpyrrolidine than those for N-chloro-α-methylbenzylmethylamines. Also, the rates of elimination reactions increase when both the C_β and N_α are part of a cyclic system. The kinetic investigagations of elimination reactions of N-chloro-2-aryl substituted four-, six-, and seven-membered cyclic secondary amines should provide an insight into the effect of ring size in imine-forming eliminations. This might help clarify the observed failure to obtain any 6-alkyl-1-piperidines in base-promoted eliminations from N-chloro-2-alkylpiperidines.

Kinetic investigations of eliminations from N-substituted-2-arylpyrrolidines which contain more reluctant leaving groups would increase our knowledge of imine-forming transition states. Preparation of N-aroyloxy-2-arylpyrrolidines could be accomplished by the method given in Chapter III for N-aroyloxy-2-alkylpyrrolidines. Even though the dissociated base, MeONa-MeOH, would probably produce no imines, the t-BuOK-t-BuOH induced eliminations would give valuable data.

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