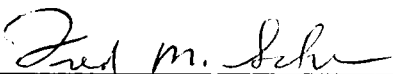
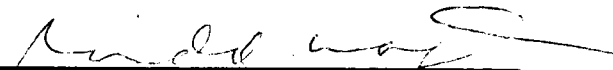


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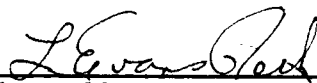
I am submitting herewith a thesis written by Jacalyn Mary Schremmer, entitled "Synthesis of Indolizidine from N-Chloro Octahydro-1-Pyridine." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.


Fred M. Schell, Major Professor

We have read this thesis
and recommend its acceptance:


Richard Pagni

Accepted for the Council:


Vice Chancellor
Graduate Studies and Research

SYNTHESIS OF INDOLIZIDINE FROM

N-CHLOROOCCTAHYDRO-1-PYRINDINE

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Jacalyn Mary Schremmer

June 1981

3051774

DEDICATION

The author would like to dedicate this thesis to Robert L. Wykle, whose support and encouragement were invaluable to her during her graduate career.

ACKNOWLEDGMENT

Deepest gratitude is extended to Dr. Fred M. Schell for his continual guidance, encouragement and inspiration to attain a high degree of competence in the field of chemistry.

Thanks are also extended to the faculty and staff of the Department of Chemistry for their patience, and to The University of Tennessee, Knoxville, for a Graduate Teaching Assistantship.

The author would also like to express her appreciation to Mr. Paul R. Williams for his invaluable advice and for obtaining cmr spectra. Thanks are extended to Ms. Patsy Graves for typing this thesis.

ABSTRACT

A model study was undertaken to investigate the rearrangement of N-chloro-octahydro-1-pyrindine. Cyclopenteno-2,3-pyridine was reduced catalytically to a mixture of the cis- and trans-isomers of octahydro-1-pyrindine. The N-chloramines were prepared, and rearrangement was accomplished by stirring these with silver tetrafluoroborate in benzene under a nitrogen atmosphere. The indolizidinium ion which resulted was isolated and reduced with sodium cyanoborohydride. Indolizidine was obtained in 85% yield, based on recovered octahydro-1-pyrindine. Attempts are described to capture the indolizidinium ion with various nucleophiles.

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LIST OF SYMBOLS

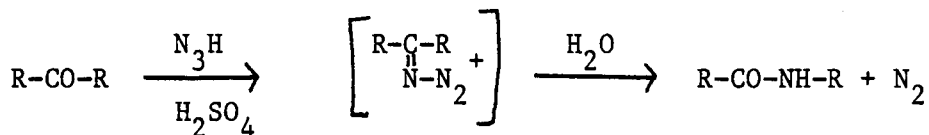
bs	Broad singlet
Bu ^t or tBu	tertiary-butyl group
cm ⁻¹	Reciprocal centimeters (wave number)
cmr	Carbon-13 nuclear magnetic resonance
d	Doublet
GLC	Gas liquid chromatography
ir	Infrared
m	Multiplet
Me	Methyl
ml	milliliter
nmr	Nuclear magnetic resonance
p	Para
Ph	Phenyl
pmr	Proton nuclear magnetic resonance
ppm	Parts per million from tetramethylsilane
q	Quartet
R	Alkyl, aryl, acyl, etc.
s	Singlet
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrohydrofuran
tlc	Thin layer chromatography
TMS	Tetramethylsilane
δ	Parts per million from tetramethylsilane

CHAPTER I

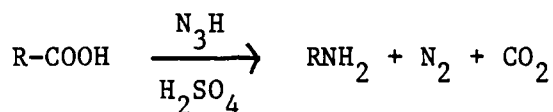
HISTORICAL SURVEY

Migration of chemical groups from one atom to a neighboring electron deficient nitrogen atom has long been recognized and are well documented.¹ This change presumably occurs to alleviate formation of a first period element with only a sextet of electrons in its valence shell. Whether this process involves formation of a discrete electron deficient species, or migration in concert with loss of a substituent on the heteroatom, or whether the formation of a new bond occurs by an entirely different mechanism is still a topic in question.

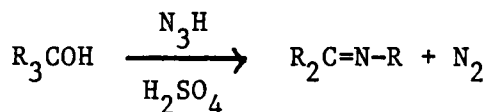
Migration of alkyl, aralkyl, aryl, alkylidene, and acyl groups to nitrogen proceeds with the ejection of a stable species such as N_2 , H_2O , or the anion of a strong acid. Many of the examples of such rearrangements have recognized names. Inclusive in these are rearrangements of azides, hydroxylamines, and haloamines. The Schmidt rearrangement entails the reaction of carbonyl compounds with hydrogen azide in the presence of a strong acid. Inclusive in this group of reactions are the rearrangement of ketones and aldehydes to amides via the intermediate $R_2C=N-N_2^+$ (Equation 1). Carboxylic acids rearrange to form amines (Equation 2), and olefins and alcohols yield aldimines and ketimines (Equation 3). The Curtius rearrangement yields isocyanates in the same fashion from acyl azides, but requires no acid catalysis (Equation 4). Representative of hydroxylamine rearrangement are the



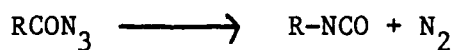
Equation 1



Equation 2

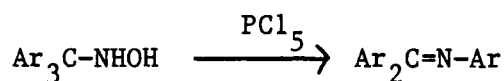


Equation 3

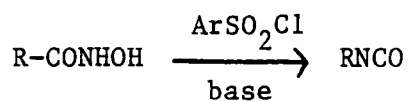


Equation 4

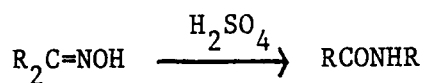
Steiglitz (Equation 5), the Lossen (Equation 6), and the Beckmann (Equation 7) rearrangements, which yield ketimines, isocyanates, and amides, respectively. The Tiemann rearrangement involves acyl migration from a carbonimidyl group (Equation 8), while base catalyzed conversion of O-sulfonyl oximes to α -amino ketones via an azirene intermediate is known as the Neber reaction (Equation 9). The Steiglitz rearrangement



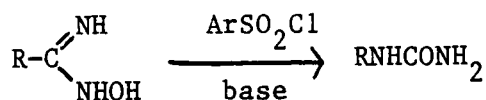
Equation 5



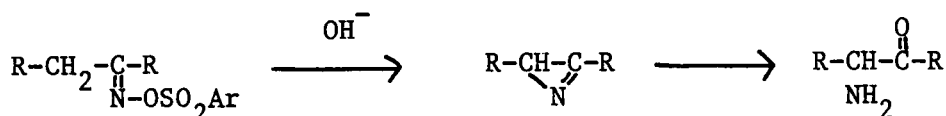
Equation 6



Equation 7

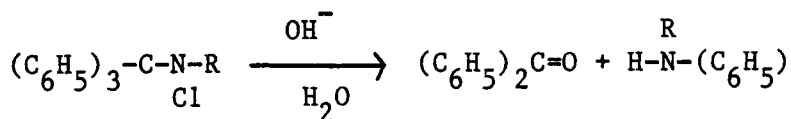


Equation 8

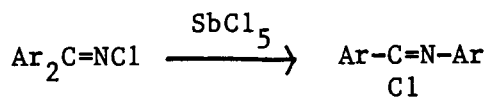


Equation 9

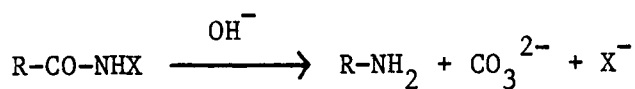
of N-trityl haloamines to ketimines occurs in fashion analogous to that of hydroxylamines (Equation 10). Rearrangement of N-halo-ketimines is considered a variation of the Beckmann rearrangement (Equation 11). The best known rearrangement of haloamines is the Hofmann rearrangement of haloamides (Equation 12).



Equation 10



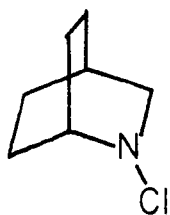
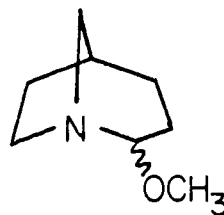
Equation 11



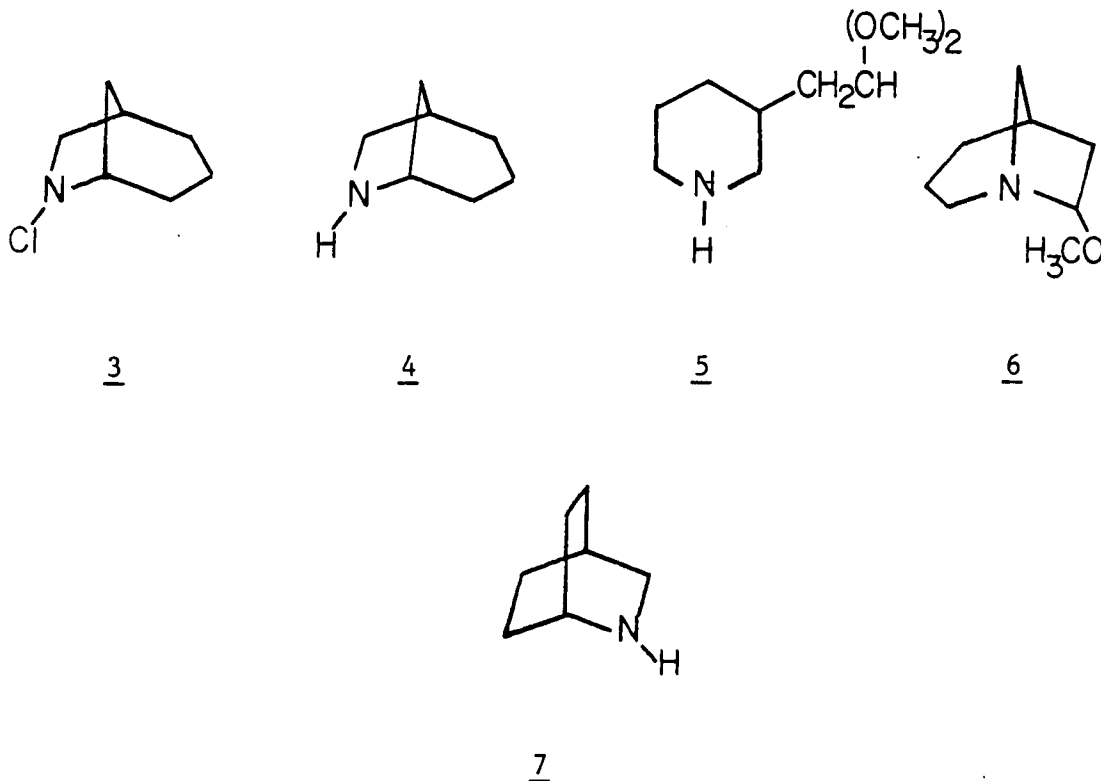
Equation 12

Most of these reactions are thought to proceed via a nitrene-like intermediate. However, Stieglitz reported that trityl N-chloramines fail to rearrange when R is methyl (Equation 10), but that rearrangement is facile when R is hydrogen. So he assumed that a univalent nitrogen species (nitrene) is involved.² However, since protons are easily transferred, it is hard to ascertain whether the reactive intermediate in this reaction and in the acid catalyzed decomposition of alkyl azides and certain monosubstituted hydrazines is a nitrene or a protonated nitrene (nitrenium ion). In the early 1960's, Gassman undertook the study of N-haloamines for utilitarian purposes as well as for mechanistic considerations. He surmised that if nitrenium ions are intermediates in the reaction of these compounds, where both substituents on nitrogen were alkyl groups, then bond migration is likely to occur in a fashion analogous to carbonium ion rearrangement.³ Of course, since $R-\overset{+}{N}-R$ should be of higher energy and thus harder to form than its sister carbonium ion $R-\overset{+}{C}-R_2$, the driving force for such a reaction would be expected to be supplied by migration synchronous with the reaction that gives rise to the positive nitrogen species.

In 1966, Gassman reported the rearrangement of N-chloroisoquinuclidine (1) in refluxing methanolic silver nitrate to yield 2-methoxy-1-azabicyclo[3.2.1]octane (2) in 60% yield.⁴ Also examined was

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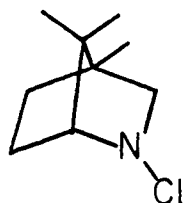
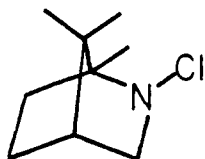
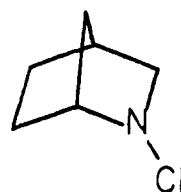
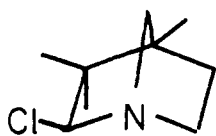
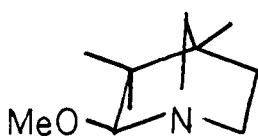
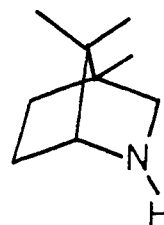
6-chloro-6-azabicyclo[3.2.1]octane (3), which, in methanolic silver nitrate, yielded 36% of 4, 8% of 5, and 1% of 6.³ On the other hand, thermolysis of 1 gave 20% of 7, 11% of 2, and eleven other unidentified components along with decomposition products. Thermolysis of 3 gave



mostly secondary amine (4) and trace amounts of 6. Gassman interpreted these results to indicate a homolytic cleavage of the N-Cl bond in the thermal reaction versus a predominant heterolytic mechanism in the reactions involving silver nitrate. The latter reaction was viewed as occurring with complete loss of chlorine anion followed by alkyl migration and solvent addition, particularly in the case of the formation of stereochemically pure ether (2). A 200-fold increase in reaction rate

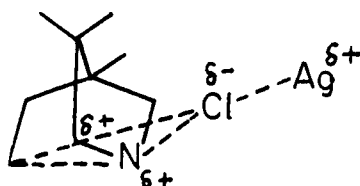
in the silver ion catalyzed reaction over thermolysis is in agreement with this proposal.

Other systems investigated by Gassman include 4,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (8),⁵ 1,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (9),⁶ and 2-chloro-2-azabicyclo[2.2.1]heptane (10).⁷ Treatment of 8 with AgClO_4 in refluxing methanol yields 78% of 11, 8% of 12, and 4% of parent amine 13. Omission of the silver ion

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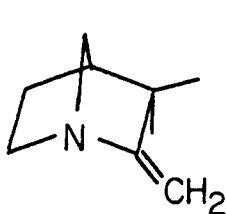
results in 59% of 11, 20% of 12, and 7% of 13. The silver ion seems to play a dramatic role in breaking the N-Cl bond, as demonstrated by a half-life of less than one minute for the silver catalyzed reaction versus 83 minutes for the solvolysis reaction. However, only small amounts of AgCl are formed, making the mechanism of rearrangement questionable. Concerted transfer of chlorine via a transition state similar to 14 explains the increase in chlorine retention in the silver ion

catalyzed reaction. Not only is solvation of less importance here, but shielding of the side of the molecule where methanol would add by silver ion promotes internal return of chlorine.

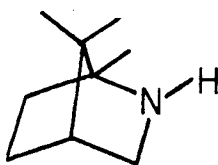


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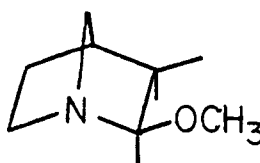
Treatment of 9 with silver perchlorate gave 13% of 15, 5% of 16, 64% of 17 and 12% of 18. Methanolysis studies were not reported. The



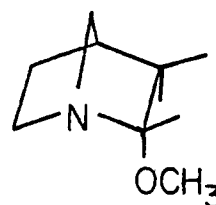
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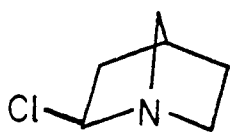
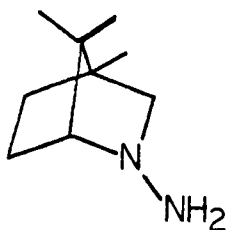
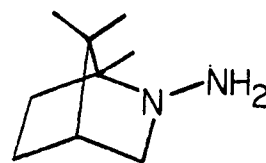
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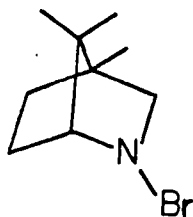
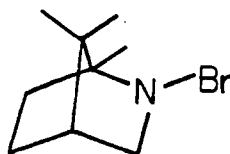
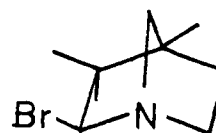
increase in methyl-ether rearrangement products is a strong argument for nitrenium ion formation. This is followed by rearrangement and formation of a trisubstituted carbonium ion, which by nature of its stability is long-lived, and thus more apt to solvate than the secondary carbonium ion produced in the rearrangement of 8. Silver ion catalyzed rearrangement of 10 gave 19 in 52% yield.

Nitrenium ions were also generated from the dialkyl hydrazine and N-bromo-derivatives of 8 and 9.⁸ Nitrous acid deamination of 20 yielded 67% of 13 (p 6) and 21% of 12 (p 6). The same treatment of 21 yielded

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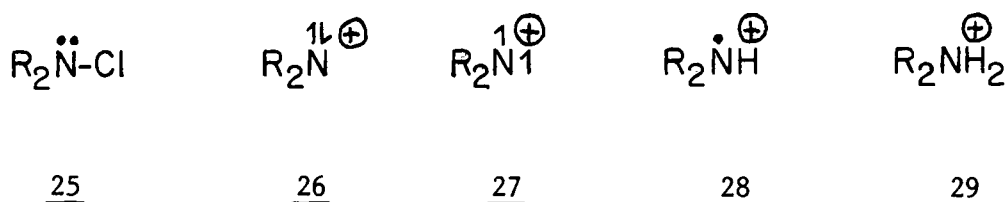
54% of 16 (p 7), 16% of 17 (p 7), 9% of 18 (p 7), and 2% of 15 (p 7).

The formation of secondary amine is thought to arise from transfer of hydrogen to the ring nitrogen by a diazotic acid intermediate formed in the reaction with nitrous acid, followed by elimination of N_2O , which was identified as a major gaseous product. Silver perchlorate treatment of 22 in methanol at 25° gave 70% of 12 (p 6). The same treatment of 23 gave 11% of 15 (p 7), 10% of 16 (p 7), and ca 67% of a mixture of 17 (p 7) and 18 (p 7). When 22 was treated in the same manner at 0° for 30 minutes, 55% of 24 and 20% of 12 (p 6) were formed. The inherent reactivity of bromamines leads to the greater formation of ether products at room temperature.

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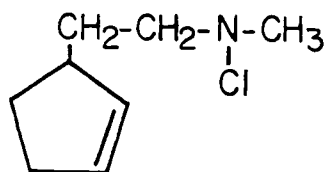
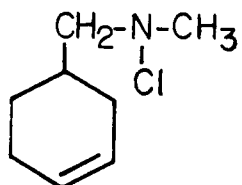
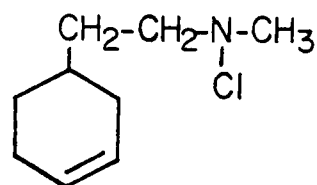
Most of the rearrangements presented so far produce some of the secondary parent amine. Gassman believes this is due to the conversion of singlet nitrenium ions into their triplet spin states.⁹ Thus,

heterolytic cleavage of 25 would produce 26, which then spin-inverts to produce triplet nitrenium ion 27, presumably an efficient hydrogen abstractor,¹⁰ since it should behave like a nitrogen cation radical. Methanol is a good source of hydrogen atoms, and reaction with 27 provides radical cation 28, another good hydrogen abstractor, which reacts with methanol to provide 29. To substantiate this postulated mechanism, Gassman

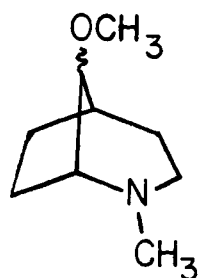
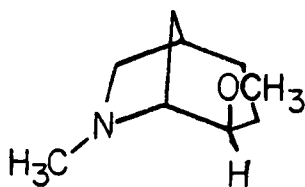
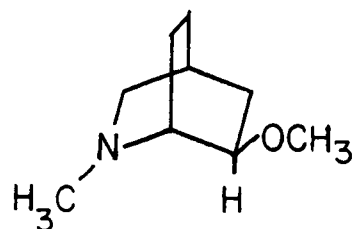
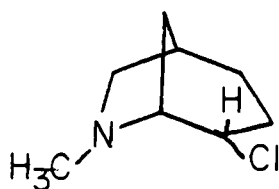
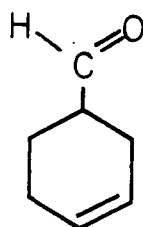
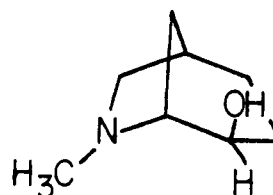


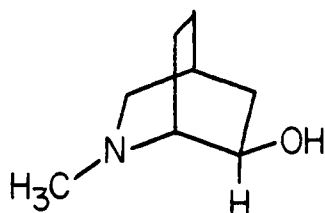
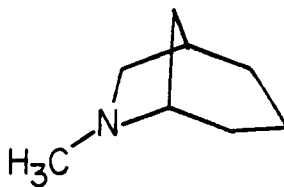
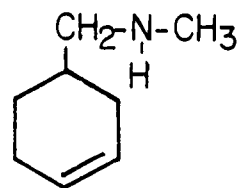
investigated the methanolysis of 8 (p 6) in heavy atom solvents, which enhance the probability of singlet to triplet inversion through coupling of spin and orbital angular momenta.^{11,12} Indeed, solvolysis of 8 (p 6) in a one to one mixture of methanol/bromoform resulted in a 500-fold increase in triplet products. This change in singlet-triplet product ratios cannot be attributed to solvent polarity. Solvolysis of 8 (p 6) in one to one methanol/hexane, the least polar mixture tested, gave product mixtures similar to those obtained by solvolysis in pure methanol, the most polar solvent tested. The same qualitative results are obtained with carbon tetrachloride as with chloroform and bromoform. This rules out the possibility that the latter two solvents are better sources of hydrogen atoms for abstraction by a nitrogen radical that might be formed from homolytic cleavage of the N-Cl bond in these solvents.

Investigations by Gassman and others on the solvolysis of olefinic N-chloramines prove interesting from both the synthetic and mechanistic vantage points. Gassman looked at the solvolysis of 30-32 as a synthetic

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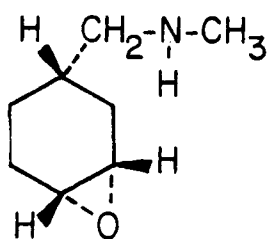
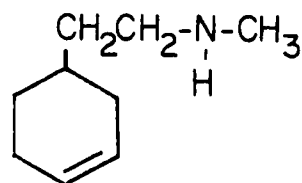
π -route to azabicyclic compounds.^{13,14,15} Amino ether 33 was obtained in 65% yield when 30 was refluxed in methanol both in the presence and absence of silver ion. In refluxing methanol, 31 gave 15% of 34, 23% of 35 and 13% of 36. The product mixture from reflux of 31 in THF-water with silver ion catalysis was more complex, yielding 9-12% of 36, 13-18% of 37, 11-14% of 38, 16-19% of 39, 13-16% of 40, and 14-17% of parent amine 41. Gassman attributes the formation of 34, 35, 36, 38 and 39

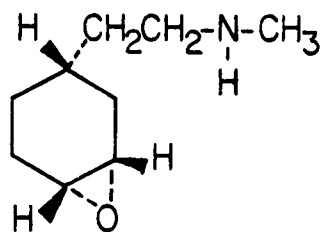
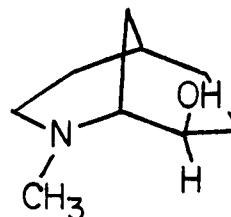
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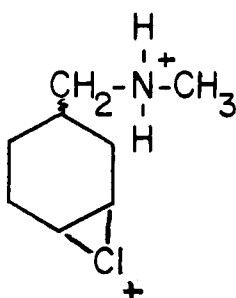
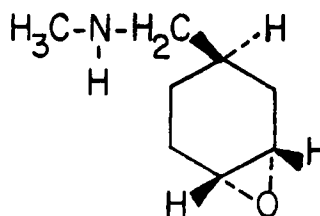
to the addition of a singlet nitrenium ion to the double bond, followed by internal return of chloride ion or nucleophilic attack by solvent. Hydrogen ion loss from the singlet nitrenium ion followed by hydrolysis explains the formation of 37. Gassman suggests that addition of the triplet nitrenium ion to the double bond, followed by hydrogen abstraction explains the formation of 40.

The solvolysis of 31 (p 10) in one molar sulfuric acid or one molar phosphoric acid differs considerably from solvolysis in aqueous THF. Reflux of 31 (p 10) in these acids produced a 1:13:8 mixture of 41, 38 (p 10), and 42. Similar treatment of chloramine 32 (p 10), whose solvolysis proved unsatisfactory for the synthesis of azabicyclics, yielded 43, 44, and 45 in a 1:2:4 mixture. Gassman suggests that the protonated N-chloramine ionizes to form a positive chlorine ion and

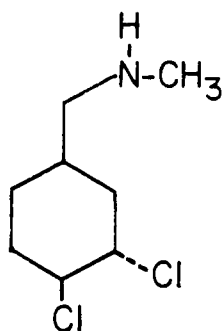
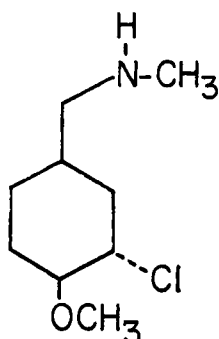
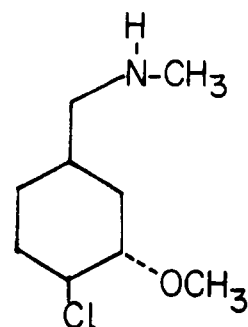
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parent amine. Protonation of the parent amine followed by the reaction of the chloronium ion with the double bond yields 46, which, on hydrolysis, yields epoxides 42 (p 11) and 47. Intramolecular epoxide opening of 47 results in the formation of 38 (p 10).

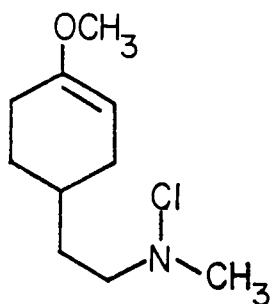
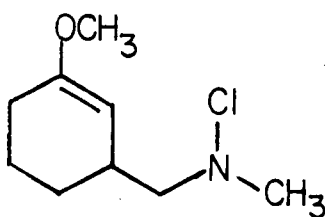
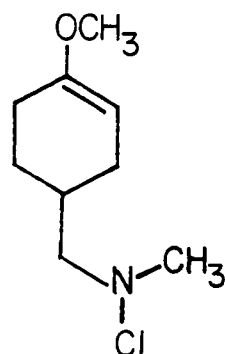
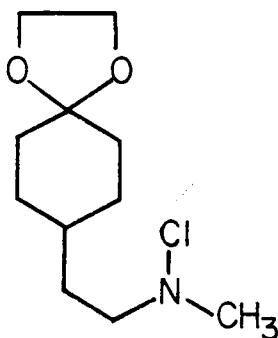
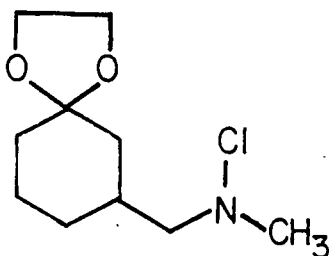
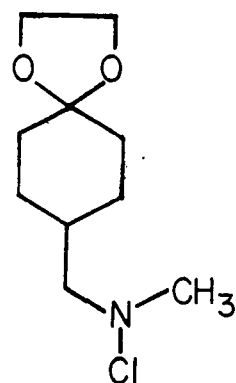
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Edwards et al. also examined solvolysis of 31 (p 10) in acidic methanol.¹⁶ After two hours at room temperature in the presence of excess p-toluenesulfonic acid, a mixture of salts formed which were converted into free bases 48, 49, and 50. Subsequent reflux of methanol solutions of these products resulted in the formation of 36 (p 10) from 48 and 34 (p 10) from 49, while base 50 failed to cyclize. Formation of 34 (p 10) and 36 (p 10) are understandable in terms of electrophilic chlorination followed by cyclization. But Edwards invokes a homolytic mechanism to explain observed products, in that 36 (p 10) is the only

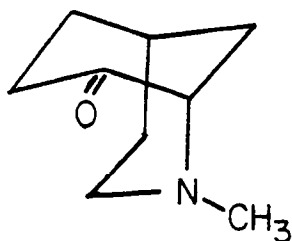
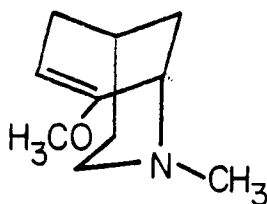
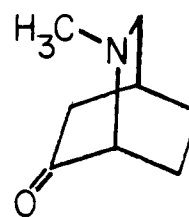
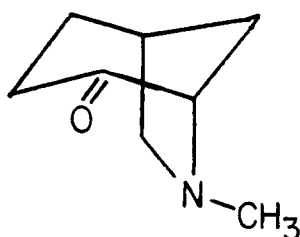
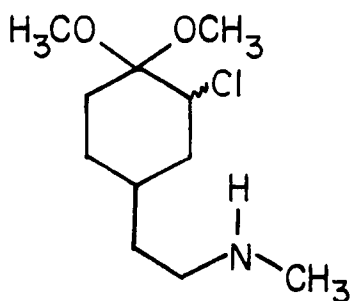
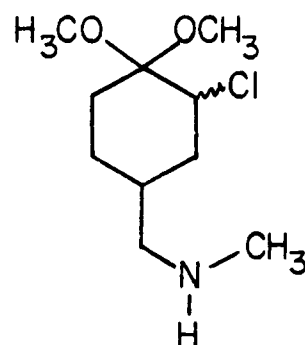
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bicyclic product formed unless the free bases are heated in methanol, and this would demand that 48 cyclize much faster than 49. Thermolysis of 31 (p 10) under N_2 showed a marked induction period followed by rapid decomposition of chloramine. Benzoyl peroxide eliminated the induction period. O_2 markedly slowed the reaction and the major product observed was parent secondary amine 41 (p 11). Other than these differences, the products were the same as those determined by Gassman. From these data Edwards concludes that homolytic cleavage of the N-Cl bond and radical mechanisms account for all the observed products from the thermolysis of 31 (p 10) rather than nitrenium ion addition to the double bond or electrophilic chlorination and cyclization.

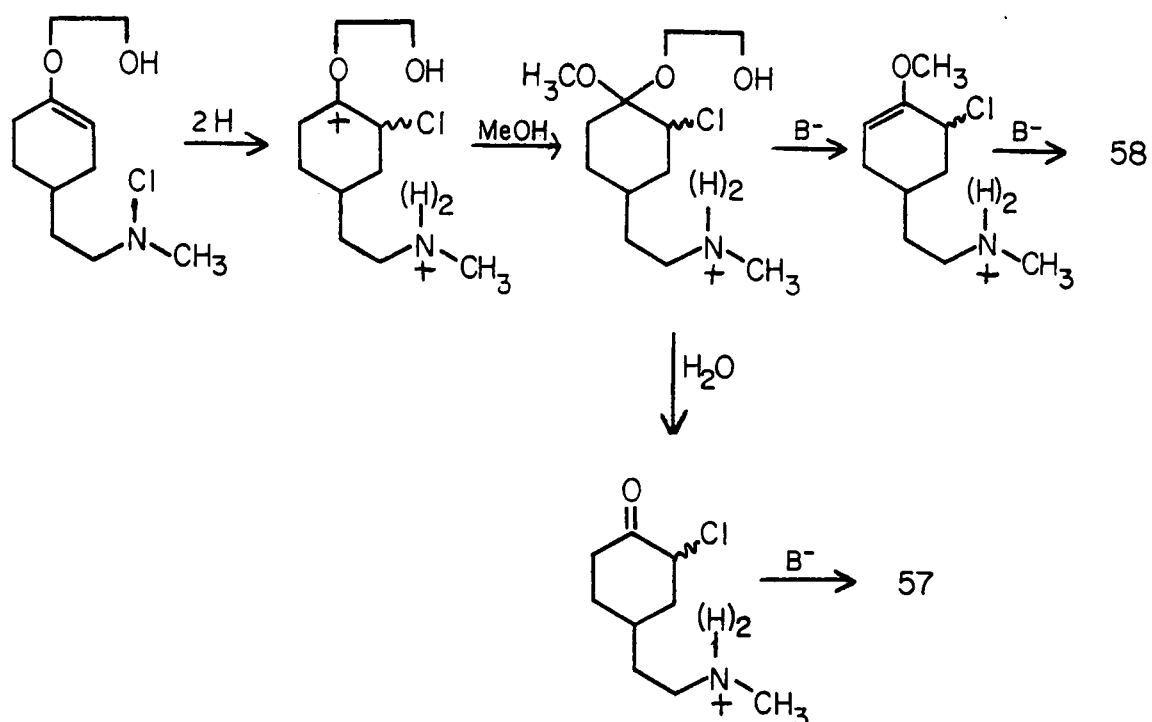
Waegell's group examined the solvolysis of enol ether and ethylene ketal N-chloramines in acid media and, like Gassman, postulated that an electrophilic chlorination of the double bond was responsible for the observed products.¹⁷ Examined were methyl ethers 51, 52 and 53, and the corresponding dioxolane derivatives 54, 55 and 56. In cooled ($0^\circ C$) anhydrous trifluoroacetic acid, 51 cyclized to produce 77% of 57

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and 19% of 58. Enol ether 52 yielded 15% of 59, and 53 yielded 75% of 60. The corresponding ethylene ketals produced lower yields of the same bicyclic amines. Reaction of 54, 55, and 56 yielded 10% of 57, 5% of 59, and 25% of 60, respectively. When methanol is included in the reaction mixture, 51 and 52 produce high yields of chloro-ketals (61) and (62), respectively. The dioxolanes give higher yields of their respective cyclization products in methanol than in pure TFA: 50% of

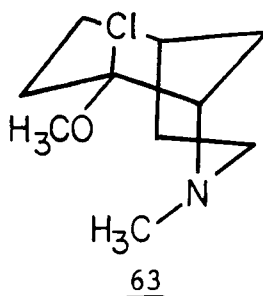
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57 from 54, 60% of 59 from 55, and 50% of 60 from 56. Waegell believes that the high yields of chloro-ketals obtained in the presence of methanol exclude both nitrenium ion and radical intermediates from possible reaction mechanisms. Cyclization in the presence of oxygen, short reaction times, and a strong solvent effect favor a process involving electrophilic chlorination of the enol ether double bond, rather than a radical process. The higher amounts of bicyclic products obtained when the dioxolanes are solvolized in TFA-methanol can be explained by attack by methanol on the open forms of the ketals (Scheme 1). These intermediates can then eliminate ethylene glycol and cyclize.

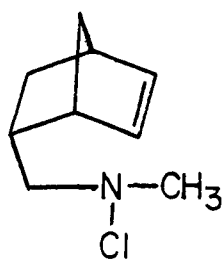
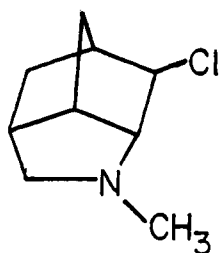
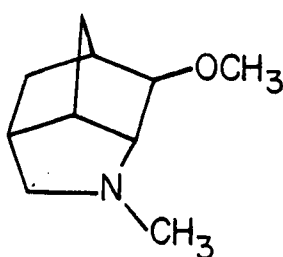
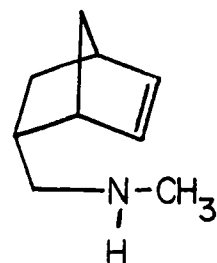


Scheme 1

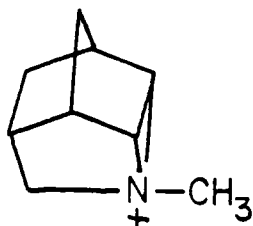
Edwards believes that the high yield of electrophilic chlorination products obtained from 51 (p 14) in methanol is due to the high nucleophilic potential of the enol ether.¹⁶ He suggests that the origin of bicyclic enol ether 58 (p 15) formed in TFA is the chloromethoxy compound 63 that is produced from a radical process.



Waegell also studied the thermolysis of chloramine 64 in neutral media.¹⁸ In methanol, 5% of 65, 74% of 66 and 18% of parent amine 67

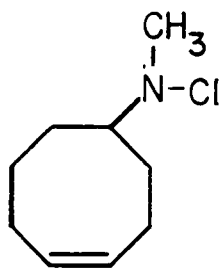
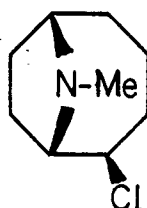
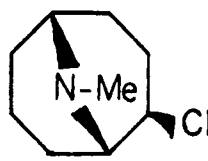
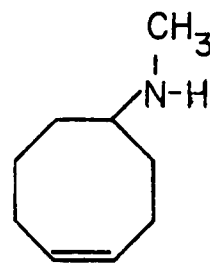
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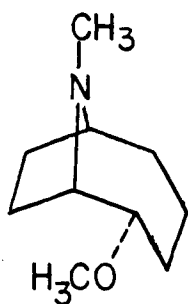
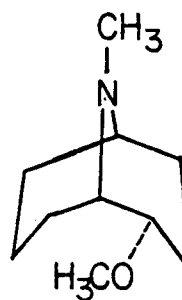
were observed. In chloroform, no methyl ether was detected, and the amount of starting amine observed was unchanged relative to the amount formed in methanol, a fact which argues against the "heavy atom theory" that Gassman used to justify starting amine formation via nitrenium ion inversion to the triplet state. When the reaction was catalyzed by silver nitrate, no starting amine was produced, but overall yields dropped. Reaction yield and rate increased when the thermolysis was carried out under a nitrogen atmosphere. The observed induction period for the disappearance of N-chloramine vanished when the rearrangement was initiated by Tollens' reagent, silver oxide, or benzoyl peroxide, all of which favor radical formation.¹⁹ These data suggest homolytic cleavage of the N-Cl bond. In addition, 65 is not observed when the silver nitrate catalyzed reaction is carried out for extended periods of time. This fact, along with the lack of formation of 66 when chloroform is the solvent of choice, argues that 66 is formed from tricyclic chloride 65 via an aziridinium ion (68). Waegell concludes that the increased rate of cyclization observed with silver nitrate and silver oxide can be accounted for by reduction of metallic silver by traces of amine in the starting material.²⁰ Ag° then induces homolytic cleavage of the N-Cl

68

bond. Although addition of a neutral amino radical to a non-activated double bond is an unfavorable process,²¹ an excellent entropy is supplied by the close proximity of the radical to the double bond. In cases where this advantage does not exist, it is possible that the amino radical could be oxidized to a nitrenium ion by silver ion, and the type of reaction that results will depend on the reaction rate relative to cyclization or hydrogen abstraction.

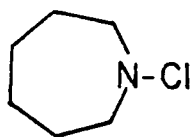
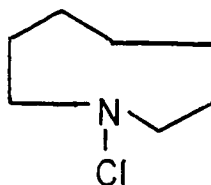
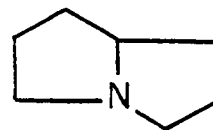
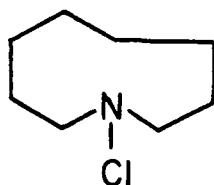
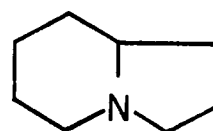
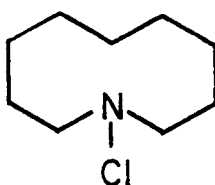
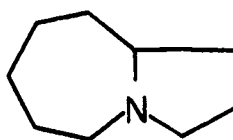
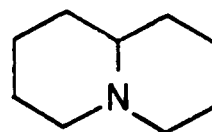
Hobson et al. examined the transannular cyclization of cycloolefinic N-chloramines,²² and decided that the mechanism of this reaction involves homolysis of the N-Cl bond. When refluxed in cyclohexane, acetone, or acetonitrile, 69 gave only bicyclic chlorides 70, 71 and parent amine 72. Upon addition of methanol, α -methyl ethers 73 and 74 were observed, once again indicating that the 2- β -chloro-derivatives were precursors of the 2- α -methoxy-9-azabicyclononanes. Rearrangement thus appears to proceed via an aziridinium ion intermediate, which

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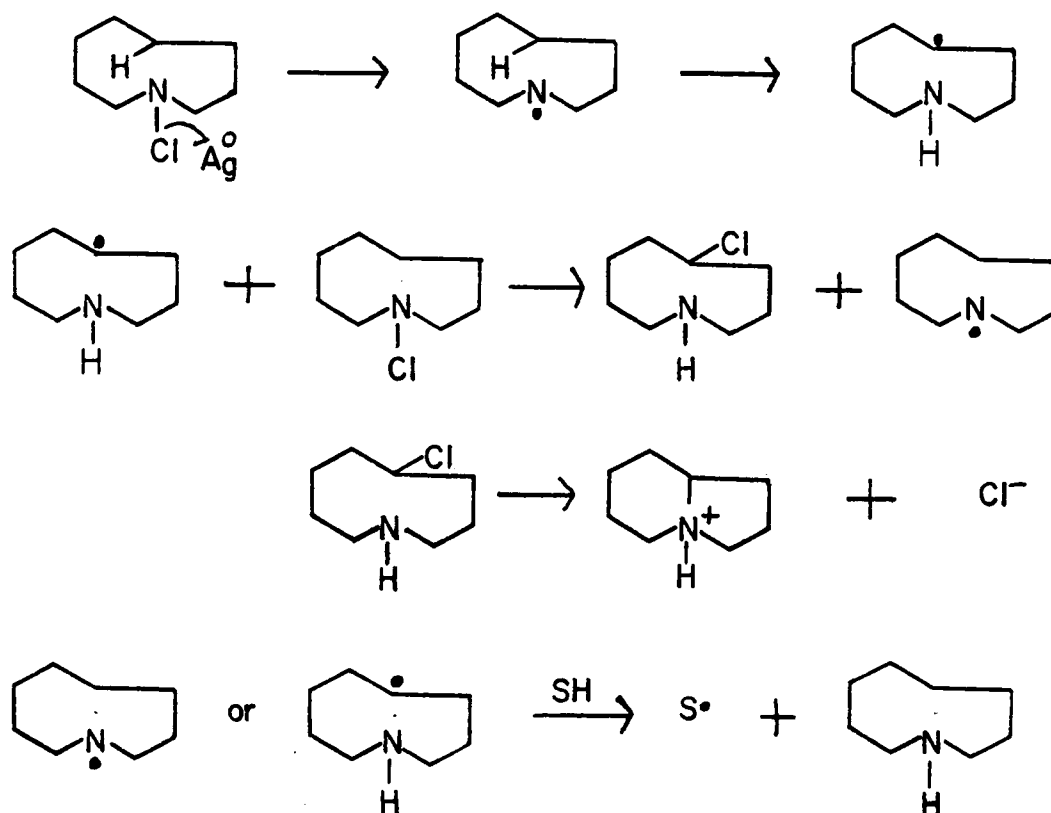
accounts for the cis configurations of the products. Catalysis by silver perchlorate caused a substantial acceleration of the reaction but no variation in the proportion of products. When azobisisobutyronitrile, a common radical initiator, was included in the reaction mixture, the nature and proportion of the products were the same as for the silver perchlorate catalyzed reaction, suggesting the formation of a similar radical intermediate under these conditions. Further substance is lent to the homolysis argument by the fact that radical traps such as O_2 and diphenylpicrylhydrazyl suppress the formation of bicyclic products. Hobson suggests that methyl hypochlorite is a possible radical chain initiator for the cyclization reaction in methanol. In neutral protic solvents, aminyl radicals are generated, but hydrogen abstraction prevails over intramolecular cyclization.

A final argument in behalf of the homolysis of N-chloramine is presented by Edwards, who examined the cyclization of medium ring chloramines in the presence of Ag(0) and Ag(1) in a variety of solvents.²³ N-Chloroazacycloheptane (75) gave negligible amounts of bicyclic products. N-Chloroazacyclooctane (76) yielded pyrrolizidine (77). N-Chloroazacyclononane (78) gave indolizidine (79) as the major product.

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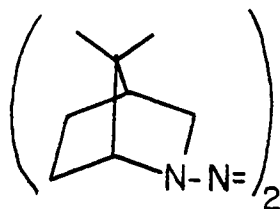
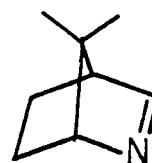
N-Chloroazacyclodecane (80) gave 1-azabicyclo[5.3.0]decane (81) as the major product and quinolizidine (82) as a minor product. Evidence for the homolytic mechanism includes increased formation of parent amines in the presence of Ag(0), and decrease in the reaction rate and formation of bicyclic products in the presence of air. Again, Tollens' silver is a good initiator, and is converted into silver chloride during the reaction. An explanation for the high efficiency of transannular hydrogen abstraction could be absorption of the nitrogen radical to the surface

of the silver oxide catalyst long enough that carbon radicals are formed before the nitrogen radicals come in contact with other hydrogen donors. Edwards recommends Scheme 2 as the mechanism for the reaction of medium ring chloramines.



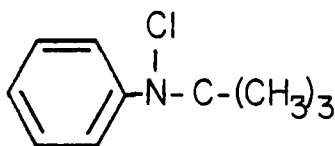
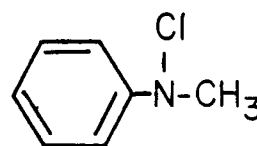
Scheme 2

In response to all the evidence for homolytic cleavage of the N-Cl bond, Gassman generated the amino radical of 8 (p 6) in methanol by three methods: photolysis of 8 (p 6), photolysis of tetrazene 83 and benzoyl peroxide treatment of 8 (p 6).²⁴ Photolysis of 8 (p 6) in methanol gave 37% of 13 (p 6), 33% of 84, and 10% of 11 (p 6). Photolysis of 83 in methanol gave 63% of 13 (p 6), and 34% of 84. Methanolysis of 8 (p 6) in the presence of 0.1 equivalent of benzoyl peroxide yielded 10% of 13 (p 6), 5% of 12 (p 6), 25% of 11 (p 6), and, most

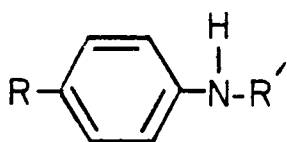
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significantly, 21% of 84. Formation of 11 (p 6) and 12 (p 6) indicates that some heterolysis is occurring in these solvolyses. But formation of 84 in these radical promoting processes indicates that nitrogen radicals follow reaction pathways that differ from those attributed to nitrenium ions. This indicates that both the silver ion promoted and noncatalyzed methanolysis of 8 (p 6) proceed via heterolytic cleavage of the N-Cl bond.

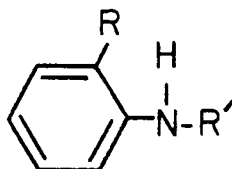
Chloramines have been utilized for their synthetic utility, as mentioned earlier. Along with his study of bicyclic chloramines, Gassman investigated several other systems. One of these was of the substitution of N-chloroanilines.²⁵ Methanolysis of N-chloro-N-butylaniline (85) and N-chloro-N-methylaniline (86) were studied in the presence and absence of silver perchlorate. When the reaction was catalyzed by AgClO_4 , 85 gave 39% of 87, 6% of 88, 6% of 89, 2.8% of 90, plus 10% of parent amine 91. Under the same conditions, 86 gave a similar product

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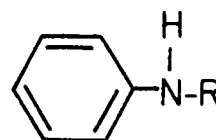
distribution of 30% of 92, 1% of 93, 6% of 94, 9% of 95, and 3% of secondary amine 96. The non-silver catalyzed reaction of 85 (p 22) resulted in the formation of 8% of 91, 52% of 90, and 14% of 89. This reaction was considerably slower. Heterolytic cleavage of the N-Cl bond and delocalization of the resultant positive charge on nitrogen into the ring, followed by attack of chloride ion or solvent accounts for the formation of all the observed products.



87 R = OMe
R' = tBu



88 R = OMe
R' = tBu



91 R = tBu

89 R = Cl
R' = tBu

90 R = Cl
R' = tBu

96 R = CH₃

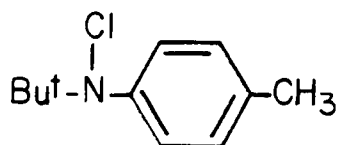
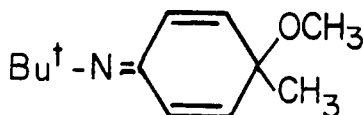
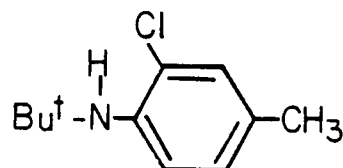
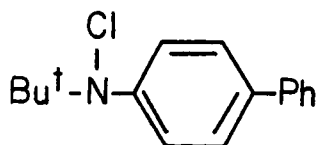
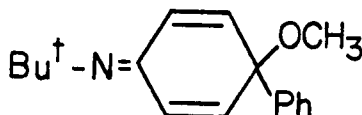
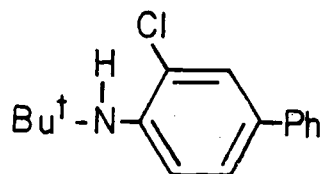
92 R = OMe
R' = CH₃

93 R = OMe
R' = CH₃

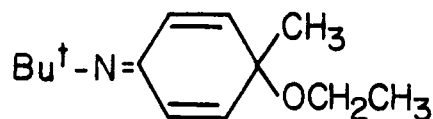
94 R = Cl
R' = CH₃

95 R = Cl
R' = CH₃

Cyclohexa-2,5-dienone derivatives can be synthesized via the silver ion assisted solvolysis of substituted N-chloroanilines.²⁶ N-Chloro-N-(t-butyl)-p-toluidine (97) gave 70% of 98 and 17% of 99 when added to a methanolic solution of silver trifluoroacetate at 0-5°C. N-Chloro-N-t-butyl-4-aminobiphenyl (100) yielded 62% of 101 and 5% of 102 under the same conditions. The mechanism of the chlorination of

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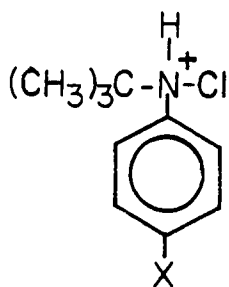
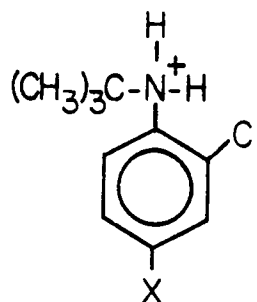
these aromatic amines was investigated by Gassman.^{27,28} He synthesized analogues of 85 (p 22) substituted in the para position with groups ranging from CH_3 (electron donating) to $\text{C}\equiv\text{N}$ (electron withdrawing). An overall rate decrease of 1.8×10^6 resulted in going from the para-methyl to the para-cyano analogue when rearrangement was carried out in buffered ethanol. The major products in all cases were ortho-chlorinated aniline derivatives, although the para-methyl derivative also gave para-substituted product, as previously observed.²⁶ The amount of parent amine increased from 1% (p- CH_3) to 28% (pC $\equiv$ N) reflecting decreased delocalization of the positive charge on nitrogen, generated by heterolysis of the N-Cl bond, into the aromatic ring. A ρ value of -6.35 correlates well with this proposed scheme of charge delocalization. The difference in the solvolytic properties of ethanol and methanol are reflected in the formation of 10% of 2,5-cyclohexadienone derivative 103 in ethanol and a 32% yield of 98 in methanol from chloramine 97.



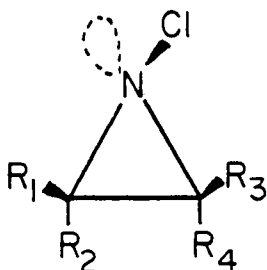
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Gassman proposes that, as the electron withdrawing ability of the para-substituent increases, the stability of the anilinium ion decreases, and a tight ion complex of the anilinium ion, chlorine anion, and the silver cation is favored. This complex then collapses to ring chlorinated products. In the case of the p-CH₃ analogue, 17% of ortho-chlorinated N-t-butylaniline is formed, and 65% in the case of the p-NO₂ analogue. In the absence of either catalyst or buffer, a mechanistic change in ring chlorination is probable, as indicated by the generation of 99% and 94% of ortho-chlorinated products in the cases of p-carboxyethyl- and p-cyano- substituted N-t-butyl-N-chloroanilines, respectively. Absence of parent amine in the product mixtures resulting from these chloramines is also observed.²⁹ Gassman suggests that in the presence of acid a chlorammonium ion (104) is generated whose heterolysis to parent amine and positive chlorine ion is facilitated by electron withdrawing groups. Electrophilic attack and rearomatization readily produces 105. It is to be noted that catalytic amounts of acid have no effect on the rearrangement of N-alkyl-N-chloroanilines substituted with electron donating groups.

Gassman also studied the noncatalyzed solvolyses of N-chloroaziridines 106 through 111 in methanol and water.³⁰ The solvolytic

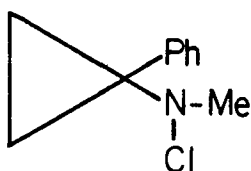
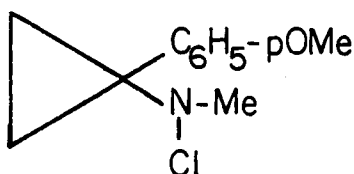
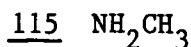
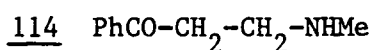
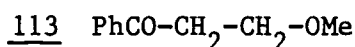
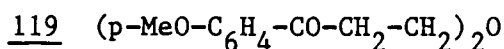
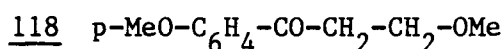
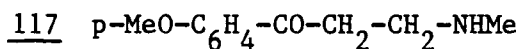
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behavior of these compounds is analogous to that of cyclopropyl tosylates. Methyl substitution on the aziridine ring results in a larger rate of acceleration than analogous methyl substitution on the cyclopropyl system. This probably reflects the delocalization of positive charge that develops with heterolysis of the N-Cl bond in concert with the disrotatory cleavage of the carbon-carbon bond. The delocalization would be expected to be greater for the aziridine case than for the analogous cyclopropyl system, since nitrogen is less likely to tolerate a positive charge than carbon. The rate increase in going from 106 to 111 is 150,000. The rate also increased when the solvent for the reaction was changed from methanol to water, further demonstrating the polar nature of the transition state. These findings support the theory

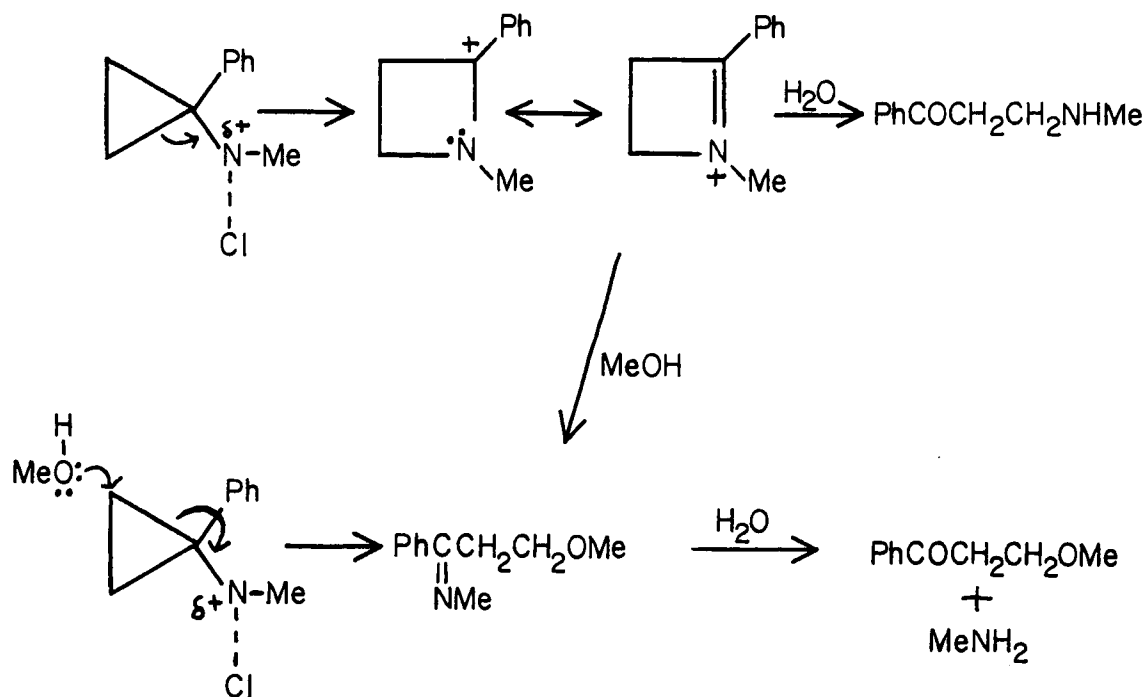
106 $R_1 = R_2 = R_3 = R_4 = H$ 107 $R_1 = R_2 = R_4 = H; R_3 = CH_3$ 108 $R_1 = R_2 = R_3 = H; R_4 = CH_3$ 109 $R_1 = R_4 = H; R_2 = R_3 = CH_3$ 110 $R_1 = R_2 = H; R_3 = R_4 = CH_3$ 111 $R_1 = R_3 = H; R_2 = R_4 = CH_3$

that N-chloramines, under solvolytic conditions, experience heterolytic cleavage of the N-Cl bond to give a chlorine anion and an electron deficient positive nitrogen species.

N-Chloramines have been examined by Gassman for their application to expansion and contraction of ring systems.^{31,32} N-Chloro-N-methyl-1-phenylcyclopropylamine (112) was solvolyzed in methanol at -30° for 4 hours. Products included 85% of 113, 7% of 114 and 80% of methylamine (115). Similarly, the p-methoxy-phenyl-analogue (116) rearranged to yield 11% of 117, 56% of 118, 1% of 119, and 66% of methylamine (115).

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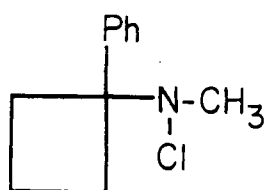
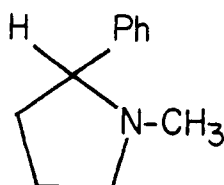
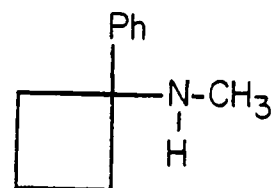
These results are analogous to those obtained from ring cleavage of the cyclopropyl carbinyl cation. Gassman suggests that, just as the existence of the carbinyl cation is improbable, so too is the formation of a cyclopropyl nitrenium ion with unit positive charge on nitrogen. Instead, migration probably occurs in concert with the heterolysis of the N-Cl bond. This forms a cyclobutane intermediate which is then hydrolyzed to the observed products as presented in Scheme 3. The methyl ethers could also be explained by direct attack of solvent on the cyclopropylamine



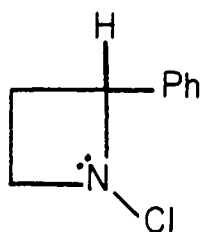
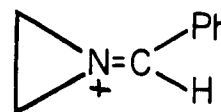
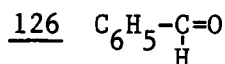
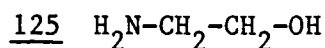
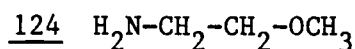
Scheme 3

ring in concert with loss of chlorine, also depicted. The mechanism for the formation of 119 (p 27) is unknown.

Ring expansion of cyclobutylamines was also accomplished by Gassman.³² When 120 was treated with a methanolic solution of silver trifluoroacetate, immediate precipitation of silver chloride was observed. Upon neutralization and reduction with sodium borohydride, 121 was obtained in 36% yield and 122 in 24% yield. This serves as a

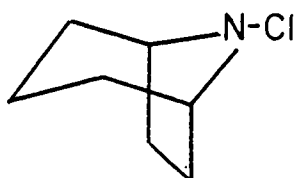
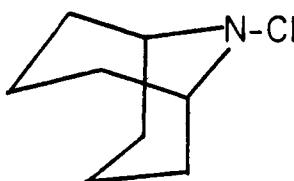
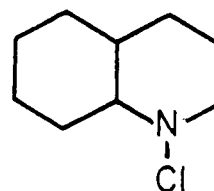
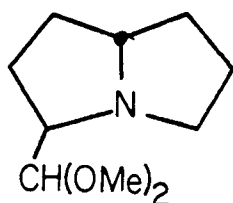
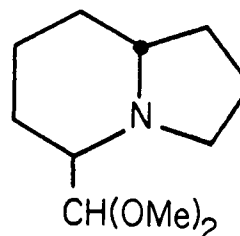
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good model for expansion of carbocyclic rings to adjacent nitrenium ion centers. N-Chloro-2-phenyl-azetidine (123), on the other hand, serves as a model for ring contraction via the same mechanism. When treated with methanolic silver trifluoroacetate, rapid precipitation of silver chloride was again observed. Hydrolysis, followed by neutralization and addition of benzoyl chloride gave derivatives of the reaction products: 39% of 124, 36% of 125, plus 67% of benzaldehyde (126). These products are explained by heterolysis of the N-Cl bond to give an azetidine nitrenium ion. Bond migration from carbon to nitrogen then gives aziridinium salt (127). Hydrolysis of the immonium ion yields benzaldehyde and protonated aziridine, which opens under the reaction conditions to give a mixture of 124 and 125. Solvent opening of 127 followed by hydrolysis of the imine linkage can also provide the observed products under the reaction conditions used.

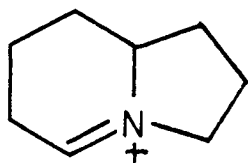
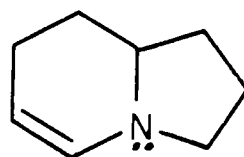
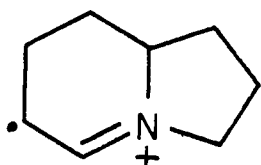
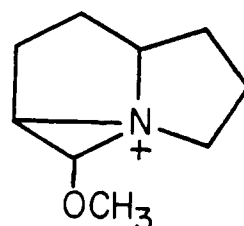
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Schell et al. have recently taken advantage of the rearrangement of cyclic N-chloramines to approach the synthesis of pyrrolizidine and indolizidine ring systems.³³ They first achieved the synthesis of pyrrolizidine (77) (p 20) in 35% yield from N-chloronortropane (128) via reflux in methanolic silver nitrate solution. This was followed by reduction by sodium borohydride, treatment with acetic anhydride, and alkaline workup. However, when the same reaction was tried with

N-chlorogranatanine (129) and N-chloro-trans-decahydroquinoline (130), neither indolizidine (79) (p 20) nor 1-azabicyclo[5.3.0]decane (81) (p 20) were observed. Instead, acetal (131) was formed in 25% yield from 129 and acetal (132) formed in 13% yield from 130 along with

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N-acetyl derivatives of the starting material. Acetals (131) and (132) can be explained by β -haloenamine rearrangement.^{34,35} However, when two equivalents of silver nitrate are used in the rearrangement of 129, 0.91 equivalents of Ag° are isolated relative to 131. A mechanism which explains these results is hydrogen atom abstraction from immonium ion (133) by a triplet nitrenium ion or amino radical, or by silver oxidation of 134 to yield 135. Reaction with solvent and further oxidation by silver or chloramine provides 136, which readily adds solvent to yield the observed products.

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Ganguly was able to prevent the oxidation of immonium ion intermediates by carrying out the rearrangement reactions in a benzene solution of silver tetrafluoroborate at room temperature.³⁶ The immonium ion precipitates along with the silver chloride that is formed, thus protecting it from oxidation. Upon reduction with sodium borohydride (129) (p 30) yielded 92% indolizidine (79) (p 20), 128 (p 30) gave pyrrolizidine (77) (p 20), and 130 (p 30) gave 81 (p 20) in equally high yields. Furthermore, carbon-13 nmr analysis of the silver ion rearrangement products of 129 (p 30) showed that immonium ion was indeed in hand! This represents the first ionic product isolated from silver ion induced rearrangements of N-chloramines.

The high yields of anticipated rearrangement products using the benzene silver tetrafluoroborate procedure set the stage for synthesis

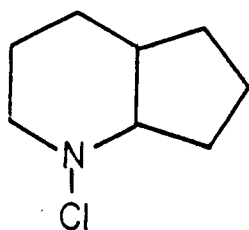
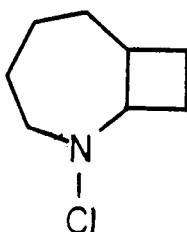
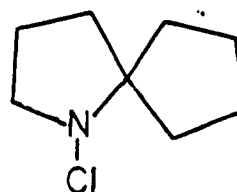
of natural products from bicyclic N-chloramines. This is especially true for those systems containing the pyrrolizidine and indolizidine ring systems. A model study for the synthesis of the indolizidine system is outlined in the next section.

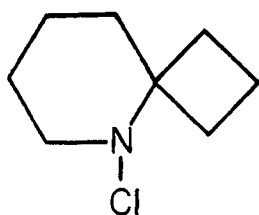
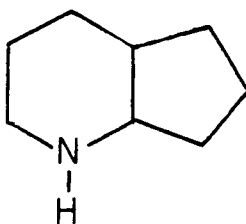
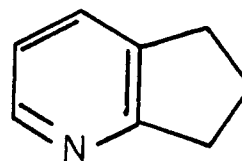
CHAPTER II

RESULTS AND DISCUSSION

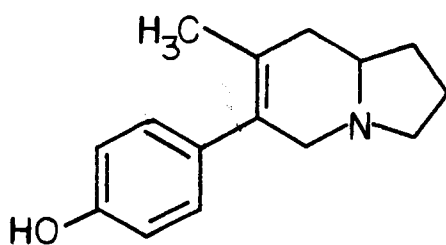
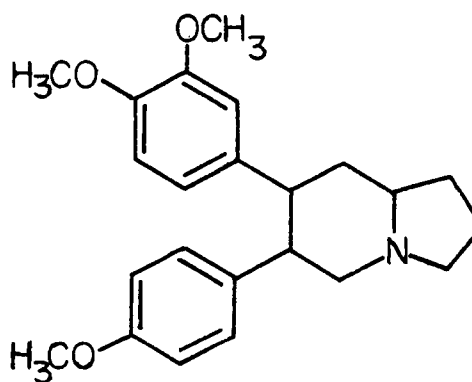
In the first chapter it was outlined how indolizidine (79) (p 20) has been synthesized from two different N-chloramines. Edwards used N-chloroazacyclononane (78) (p 20) to form indolizidine in 68% yield, and Ganguly accomplished its synthesis in 92% yield via a rearrangement of N-chlorogranatanine (129) (p 30). A vast number of physiologically active substances contain indolizidine ring systems.³⁷ Among these are several of the Dendrobates alkaloids, including gephyrotoxin, pulmatoxin A, and their derivatives. Some of these compounds are in short supply, and their substitution patterns on the bicyclic framework are quite complex. These facts lend themselves to investigation of new synthetic schemes that will potentially lead to these natural products.

In addition to N-chlorogranatinine (129) (p 30), there are four other bicyclic systems, 137-140, which can give rise to indolizidine via rearrangement. N-Chloro-octahydro-1-pyridine (137) is an attractive model for study, since the parent amine (141) is easily obtained through reduction of 2,3-cyctopentenopyridine (142).³⁸ This compound can be

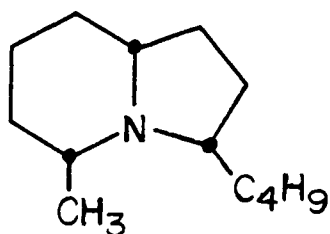
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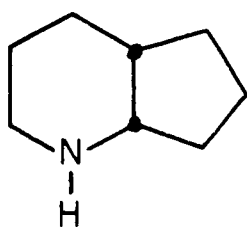
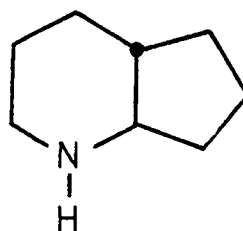
modified via nucleophilic substitution on the pyridine ring, and by electrophilic substitution on the cyclopentene ring. Thus, the synthesis of ipalbidine (143) and septicine (144) can be approached by making appropriate substitutions on the methylene carbons of 2,3-cyclopentenopyridine (142) prior to its reduction and subsequent rearrangement of its N-chloro-derivative. Likewise, the synthesis

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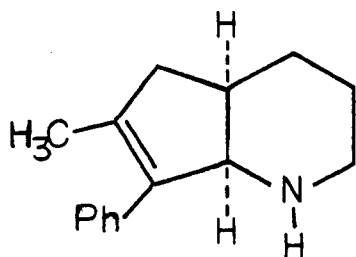
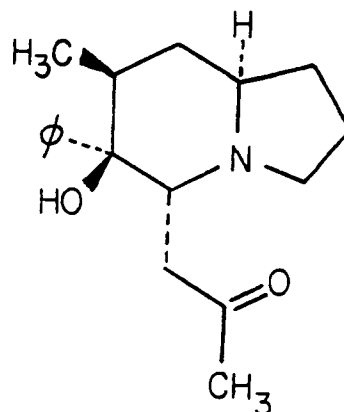
of monomorine (145) can be approached by the butylation of 142, followed by hydrogenation, N-chlorination, ring interchange, and capture of the rearrangement product by the appropriate nucleophile.

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An advantage is gained if 142 (p 34) is reduced stereospecifically to yield octahydro-1-pyridine (141) (p 34) with either cis (146) or trans (147) stereochemistry at the ring juncture carbons. For

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example, if the cis stereochemistry is obtained upon reduction of 142 (p 34), then this could help determine the stereochemical course of subsequent steps. An example is the hydrogenation of 148, which is a conceivable intermediate in the synthesis of crepidamine (149), to yield the correct stereochemistry at C₆. Several methods are available for the stereospecific production of reduced pyridanes. Reduction by hydrogen in the presence of platinum should give the cis isomer as the major product, by virtue of the stereochemistry obtained by reduction of

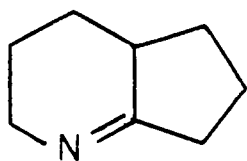
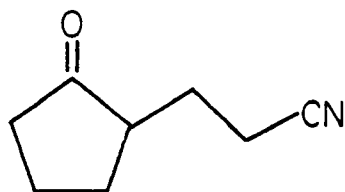
148149

analogous systems.³⁹ In the presence of a small amount of catalyst under high pressure, delivery of hydrogen from the catalyst's surface to one side of the pyridane ring should produce cis perhydropyrindine (146) (p 36) as the major reduction product.⁴⁰ When 2,3-cyclopentenopyridine (142) (p 34) was submitted to these conditions, a mixture of the cis and trans perhydropyrindines resulted. The carbon-13 spectrum exhibited twelve peaks instead of the anticipated sixteen. Single frequency analysis indicated that four of the signals were assignable to the ring juncture carbons of the cis and trans perhydropyrindines. The remaining eight signals gave triplet spin patterns typical of methylene carbons. Attempts to separate the isomers by chromatography on silica gel columns or by preparative thin-layer chromatography were unsuccessful, as were efforts to obtain a ratio of the two isomers by gas-liquid chromatographic analysis.

Failure of the catalytic reduction to yield one isomer of the desired product was not a problem at this stage, since there are several

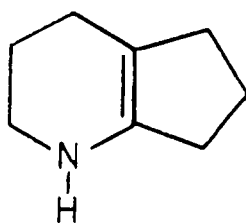
published methods for the stereospecific synthesis of octahydro-1-pyrindine (141) (p 34). Prelog and Szpilfogel describe a reduction of 2,3-cyclopentenopyridine (142) (p 34) by sodium in ethanol, which yields 76% of liquid trans-octahydro-1-pyrindine (147) (p 35).⁴¹ This procedure was repeated. Pyrindane (142) (p 34) was refluxed in dry ethanol with twenty equivalents of sodium. On workup, a mixture of the cis and trans perhydropyrindines was again obtained. The spectrum was this time resolved into fifteen lines, due to an increase in the trans isomer. Comparison of this spectrum with that of the catalytic reduction products allowed us to assign overlapping cis and trans chemical shifts on the latter spectrum, and assured us that we were obtaining mixed isomers of octahydro-1-pyrindine (141) (p 34) by that method. Unfortunately, it did not solve the problem concerning synthesis and isolation of a single isomer of octahydro-1-pyrindine (141) (p 34).

Another scheme for the stereospecific synthesis of perhydropyrindines was reported by Henshall and Parnell, who used as their starting material a piperidine.⁴² Hexahydro-1-pyrindine (150) was prepared from 2-(2'-cyanoethyl)cyclopentanone (151). Upon reduction of 150 by sodium in ethanol, the authors report that solid trans-octahydro-1-pyrindine (147) (p 35) was obtained, with no specific yield indicated. The picrolonate

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derivative of the product had the same melting point as the product synthesized by Prelog and Szpilfogel, but the base they obtained was a solid, whereas the product of the dissolving metal reduction was a liquid. Henshall and Parnell also submitted the piperidine to reduction in acetic acid over Adams' catalyst. They obtained a mixture of isomeric bases, from which an N-tosyl derivative was isolated in 60% yield. This tosyl derivative had a different melting point, 68-69°C, than the tosyl derivative of the product of the dissolving metal reduction, m.p. 101.5-102.5, and so was assigned the cis-configuration.

An efficient synthesis of hexahydro-1-pyridine (150) (p 37) was found in Grundon and Reynolds' preparation of Δ 1-piperidines from N-chloramines.⁴³ N-Chloro derivatives of the octahydro-1-pyridine isomers obtained from the catalytic reduction of 142 (p 34) were prepared by stirring these products in a one-to-one mixture of methylene chloride/chlorox for approximately one hour at room temperature. Thin layer chromatographic analysis indicated that none of the starting material remained. The chloramines were stirred with 12% potassium hydroxide in methanol for two hours at room temperature, after which time tlc of the reaction mixture showed that none of the chloramines remained. Instead, two new spots of greater polarity appeared on the chloroform developed alumina plates. The carbon-13 spectrum obtained from the products of the dehydrohalogenation reaction was complex, and indicated that more than two products were present. A peak at 169.69 ppm downfield from TMS corresponds to the imine carbon under nitrogen in 150 (p 37). But another absorbance at 88.04 ppm suggests that enamine 152 is present. A single frequency spectrum was not obtained, so these

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assignments are not conclusive. Some of the observed peaks correspond with *cis*-perhydropyrindine (146) (p 35).

Without further analysis or purification, these products were subjected to dissolving sodium metal reduction in dry ethanol at room temperature for several hours. Workup and subsequent carbon-13 analysis of the products produced a sixteen line spectrum not dissimilar to that obtained from direct dissolving metal reduction of 2,3-cyclopenteno-pyridine (142) (p 34). Thus, efforts at this point failed to produce a single isomer of perhydropyrindine desired for rearrangement studies.

Mistryukov indicated that he obtained the same results when piperideine (150) (p 37) was hydrogenated over PtO_2 in methanol.⁴⁴ A mixture of *cis*- and *trans*-octahydro-1-pyrindines was produced, and not mainly the *cis* isomer, as indicated by Henshall and Parnell.⁴² Therefore, catalytic reduction of hexahydro-1-pyrindine was ruled out for the purpose of this study. On the other hand, Mistryukov indicates that reductive cyclization of 2-oxocyclopentanepropionitrile (151) (p 37) goes with a high degree of stereospecificity.⁴⁴ He reported that hydrogenation of 151 over nickel in absolute alcohol at 70 atmospheres and 120°C produces pure *cis*-octahydro-1-pyrindine (146) (p 35), after

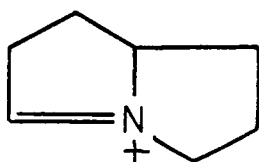
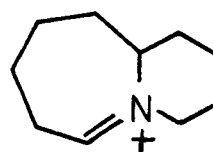
crystallization of the perhydropyrindine hydrochlorides. The cis isomer accounted for 90% of the products obtained. 2-Oxocyclopentanepropionitrile (151) (p 37) can also be converted into hexahydro-1-pyrindine (150) (p 37) according to the procedure outlined by Henshall and Parnell.⁴² This method may yield pure piperidine rather than the mixture that resulted from dehydrohalogenation of the mixed N-chlorooctahydro-1-pyrindines. Reduction by sodium in ethanol should then yield trans-octahydro-1-pyrindine (147) (p 35).

The synthesis of indolizidine was continued using the cis and trans mixture of octahydro-1-pyrindines that resulted from catalytic hydrogenation of 2,3-cyclopentenopyridine (142) (p 34). These compounds were efficiently chlorinated in a mixture of methylene chloride and commercial bleach, as recommended by Kerwin et al.⁴⁵ Carbon-13 analysis demonstrated the expected downfield shift of the methylene and methine carbons neighboring the chloramine group in 137 (p 33). The yield of yellow oil was quantitative.

Following the methods of Schell and Ganguly,³⁶ the chloramines were dissolved in benzene and added dropwise to a solution of silver tetrafluoroborate in dry benzene. The reaction was carried out at room temperature under a nitrogen atmosphere and in the dark to prevent photoreduction of the silver tetrafluoroborate.⁴⁶ Immediate precipitation of silver chloride was observed. After two to three hours of additional stirring, the silver salt was caked on the sides of the reaction vessel. At this point, lithium chloride was added to the mixture to precipitate excess silver ion. After another 30 minutes of stirring, the benzene was filtered and the silver chloride was washed

with methylene chloride. The filtrates were combined and the solvents were evaporated under reduced pressure. A brown oil resulted whose proton nmr was identical to that obtained when Ganguly treated N-chloro-granatanine (129) (p 30) with silver tetrafluoroborate. The carbon-13 nmr chemical shifts of the rearrangement product obtained by Ganguly (CH carbons at δ 174.9 and 62.1; CH₂ carbons at δ 54.9, 296., 27.1, 24.7, 20.4 and 15.4) were characteristic of the expected immonium ion (133) (p 31). Since that species is identical to the rearrangement product expected from N-chloro-octahydro-1-pyrindine, an identical proton nmr spectrum is convincing evidence that the ring interchange reaction desired was accomplished.

Since reduction of immonium ion intermediates 133 (p 31), 153 and 154 by sodium borohydride in methanol yielded near quantitative yield of saturated bicyclic products without complication, no problems were anticipated for the reduction of 133 (p 31) obtained from this new ring interchange scheme. However, analysis of products obtained from the

153154

borohydride reduction of 133 (p 31) showed clearly that products other than indolizidine were present. Attempts to separate the reduction products by making N-benzoyl derivatives or picrates failed. The carbon-13 nmr spectrum of the mixture exhibited a downfield peak at δ 167.37, characteristic of an sp² carbon α to nitrogen. A possible

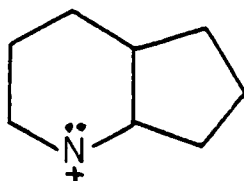
product which accounts for the observed chemical shifts in enamine (134) (p 31). Formation of 134 can be expected in basic media, which results when sodium borohydride is dissolved in methanol, due to proton abstraction by either methoxide anion or the parent secondary amine. Carbon-13 nmr also demonstrated the presence of octahydro-1-pyrindine, probably due to inefficient chlorination or rearrangement.

Several unsuccessful attempts to obtain indolizidine (79) (p 20) via sodium borohydride reduction of the indolizidinium ion (133) (p 31) prompted an effort to avoid the complications of reduction in basic media. Borch et al. report that cyanohydridoborate is an effective reducing agent at pH three to four.⁴⁷ Thus, the immonium ion (133) (p 31) was added to a solution of sodium cyanoborohydride in methanol, and the mixture was stirred overnight at room temperature. Workup yielded a clear oil whose ir spectrum was identical to that of indolizidine (79) (p 20). The carbon-13 nmr chemical shift values were also identical to published values for indolizidine.⁴⁸ However, eight more peaks were present in the carbon spectrum which had chemical shifts identical to those of cis-octahydro-1-pyrindine (146) (p 35). Analysis by gas-liquid chromatography on a OV101 column indicated an 84% yield of indolizidine, based on recovered cis-perhydropyrindine. An authentic sample of the mixed perhydropyrindines had the same retention time as the secondary amine found in the rearrangement product mixture. In addition to indolizidine and parent amine, GLC demonstrated the presence of a decidedly more polar product which accounted for approximately 15% of the mixture. However, no extra peaks were apparent in the carbon-13

spectra, so no further attempts were made to isolate and identify this product.

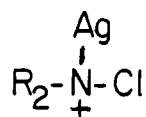
Several attempts were made to capture the immonium ion intermediate (133) (p 31) with efficient nucleophiles. Dimethyl malonate was included in the benzene silver tetrafluoroborate mixture. Chloramine (137) (p 33) was added and the rearrangement was carried out as described earlier. Workup yielded quantitative recovery of the capture agent and a mixture of rearrangement products which were not characterized. Since it is possible that precipitation of the immonium ion-tetrafluoroborate salt prevents its further reaction in benzene, the capture reaction was tried with isolated 133 (p 31). However, reflux of 133 (p 31) with dimethyl malonate or methyl acetoacetate in benzene, and with 2,4-pentanedione in ethanol, failed to produce new identifiable products. Quantitative recovery of the nucleophile was obtained in all cases. The enol ether 4-methoxypent-3-ene-2-one was prepared according to the method of Chong and Clezy,⁴⁹ and 1.1 equivalents were refluxed with the immonium ion - BF_4 salt in ethanol. But even this agent failed to result in a substituted indolizidine derivative. It is apparent that capture of the rearrangement product from 137 (p 33) is not as straightforward as it would appear. It is desirable to find the exact conditions for nucleophilic capture, since it would provide a method by which to modify indolizidine (79) (p 20) and serve as a model for substitution of chloramine rearrangement products.

The mechanism of rearrangement of 137 (p 33) is not clear. Gassman has invoked nitrenium ion formation as the mechanism of rearrangement of many chloramines,¹³ but their existence has never generally been

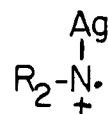
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proven. It is possible that nitrenium ion (155) is an intermediate in the rearrangement of N-chloro-octahydro-1-pyrindine (137) (p 33). The ionic nature of the ring interchange reaction is suggested by the formation of immonium ion (133) (p 31). It is hard to conceive of a way by which 133 could be produced by a homolytic mechanism, although the yield of secondary amine (141) (p 34) decreases when the rearrangement is conducted under argon, a condition which favors a radical mechanism. Low recovery of parent amine in the rearrangements of 128, 129 and 130 (p 30) in benzene is probably due to the absence of a source of abstractable hydrogen. In methanol, spin inversion of a nitrenium ion intermediate to the triplet state, followed by hydrogen abstraction from solvent or other rearrangement products could account for the high yields of secondary amine observed.³³ But formation of parent amines in benzene, as well as failure to trap the nitrenium ion intermediate with anisole³³ argue against formation of a discrete electron deficient species. It is possible that the chloride anion is lost with σ bond participation, or that a very tight ion complex is formed upon heterolysis of the N-Cl bond. Schell proposes that complexes such as 156 or radical cation 157 could be responsible for the formation of observed products in the rearrangement of 128 and 129 (p 30) in benzene.³⁶ This mechanism would involve bond migration to positive nitrogen in concert

with loss of chlorine anion, or reduction of 157 to provide an ammonium ion-silver complex.



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Recovery of starting amine in the rearrangement of 137 (p 33) is higher than in the systems studied by Ganguly, but only cis-octahydropyrindine (146) (p 35), and none of its isomer, is observed. No reason is envisioned for more facile rearrangement of the trans-chloramine over the cis. Perhaps this phenomenon is simply due to a higher percentage of cis-chloramine in the starting material and inefficient rearrangement to product in the given reaction time. Reduction of unreacted chloramine by borohydride then produces starting amine. Studies on the rearrangement of one isomer of octahydropyrindine will help explain if recovery of cis-secondary amine is purely artifactitious, or is indeed attributable to slower rearrangement of the cis-chloramine.

CHAPTER III

EXPERIMENTAL DATA

Pmr spectra were recorded on a Varian T-60A spectrometer.

Spectra were taken in deuteriochloroform solution with TMS as an internal standard. Cmr spectra were recorded on a Nicolet TT-14 spectrometer using deuteriochloroform as a solvent and internal standard. Chemical shifts are reported as ppm downfield from TMS. Proton splitting patterns are designated as s, bs, d, t, q and m (see List of Symbols). Ir spectra were recorded "neat" on a Perkin-Elmer 257 Grating Infrared Spectrophotometer. The absorptions are reported in cm^{-1} and are standardized against polystyrene absorbances. Gas-liquid chromatographs were recorded on a Varian Series 2700 gas-liquid chromatograph equipped with an OV101 column.

All solvents were distilled immediately before use. Dry benzene was obtained by distillation from benzophenone and sodium wire. Ethanol was dried overnight over CaO, distilled under argon, then refluxed over magnesium turnings overnight, and redistilled under argon. Thin layer chromatographic analyses were performed on microscope slides coated with Woelm Alumina G, prepared by dipping the slide in a slurry of the stationary phase in chloroform. Column chromatography was carried out using Merck Silica Gel.

Octahydro-1-pyridine (141, p 34): Method 1

2,3-Cyclopentenopyridine was obtained from Aldrich and distilled. Ten g was dissolved in 100 ml of acetic acid and placed in a 500 ml reaction bottle. PtO_2 (200 mg) was added, along with a few drops of

sulfuric acid. The sample was then reduced under 55.5 psi hydrogen gas for approximately 48 hours. When the bottle pressure gauge indicated no further pressure drop, the reaction was stopped. The mixture was filtered and the acetic acid removed by distillation. The product was dissolved in aqueous KOH and extracted with methylene chloride. The extract was dried over K_2CO_3 , filtered, and the solvent removed by means of a rotary evaporator. The product was distilled under reduced pressure to yield 10.4 g of cis- and trans-octahydro-1-pyridine in an approximate ratio of two to one, as indicated by cmr: pmr δ 1.3 (s,1H), 1.7 (m,8H), 2.4 (m,5H), 3.0 (bs,1H); cmr methylenes δ 18.8, 20.8, 24.1, 25.4(2), 27.7(2), 29.3(2), 31.3, 44.3(2), methines δ 37.9, 46.2, 57.5, 63.6; ir 3290 (N-H stretch), 2950 (CH_2 stretch), 1470 (N-H bend), 1350 (C-H bend).

Octahydro-1-pyridine (141, p 34): Method 2

Sodium metal was added to a refluxing solution of 5.09 g of 2,3-cyclopentenopyridine (142) (p 34) in 300 ml of dry ethanol until no more metal would dissolve. The solution was refluxed an additional hour, after which time ethanol was added to dissolve the excess sodium. Water was added to dissolve the sodium ethoxide salt, and the mixture was extracted with hexane. The picrate of the product was made by dropping saturated picric acid solution into the hexane until crystals no longer formed. The picrate was filtered, dissolved in ethanol, and an unsuccessful attempt was made to recrystallize the picrate from that solution. The ethanol was distilled and saturated KOH solution was added to hydrolyze the picrate. The perhydropyridines were extracted with methylene chloride. The extract was dried over K_2CO_3 , filtered,

and the solvent removed under reduced pressure. A mixture of cis- and trans-octahydro-1-pyrindine in a ratio of 1:2 was obtained, as indicated by cmr: pmr δ 1.2 (m,4H), 1.2 (s,3H), 1.6 (m,14H), 2.1 (s,1H), 2.3 (s,4H), 2.7 (m,2H), 3.0 (s,2H); cmr methylenes δ 19.9, 21.8, 25.1, 26.4, 26.7, 28.8, 30.0, 30.3(2), 32.1, 45.1, 45.4, methines δ 38.8, 47.2, 58.6, 64.5.

N-chloro-octahydro-1-pyrindine (137, p 33)

Octahydro-1-pyrindine (141) (p 34) (1.25 g) prepared by Method 1 was dissolved in 50 ml of methylene chloride. Commercial Chlorox bleach (5% NaClO), (50 ml) was added and the solution was stirred at room temperature for 30 minutes. At this point, tlc of an aliquot of the reaction mixture in 80/20/1 - acetone/methanol/water indicated that no starting material remained. The chloramine was extracted with methylene chloride, the extract was dried over K_2CO_3 , filtered, and the solvent removed under reduced pressure. Quantitative yield of the product was obtained: pmr δ 1.0-2.9 (complex m,12H), 3.1 (m,1H), 3.3 (m,1H); cmr methylenes δ 18.5, 21.0, 23.4, 23.9, 26.5, 27.6, 28.8, 29.5, 30.3, 30.7, 64.1, 64.2, methines δ 42.2, 45.9, 74.2, 77.8.

1,2,3,4,5,6,7-hexahydro-1-pyrindine (150, p 54)

N-Chloro-octahydro-1-pyrindine (137) (p 33) (3.5 g) in 25 ml methanol was added dropwise to a solution of 12% KOH in methanol. KCl precipitated immediately. The mixture was stirred for 2 hours at room temperature until tlc of the reaction mixture in chloroform showed that no chloramine remained. The salt was filtered and the products extracted with hexane. The extract was dried over K_2CO_3 , filtered, and

the solvent removed under reduced pressure. A yellow liquid was obtained, tlc of which showed that two compounds were present.

Octahydro-1-pyrindine (141, p 34): Method 3

Immediately following its preparation, the piperidine (150) was dissolved in 50 ml. of dry ethanol under argon. Sodium was added, and the mixture was stirred, while the sodium dissolved. After several hours, the solution was neutralized with HCl, made alkaline with aqueous K_2CO_3 , and the products were extracted with methylene chloride. The extract was dried over K_2CO_3 , filtered, and the solvent removed under reduced pressure. Carbon-13 analysis showed an approximate 1:1 mixture of cis- and trans-octahydro-1-pyrindine: cmr methylenes δ 19.8, 21.7, 25.0, 26.4, 26.7, 28.7, 30.2, 31.7, 44.8, 45.3, methines δ 38.5, 47.1, 58.2, 64.6.

1,2,3,6,7,8,8a-heptahydroindolizinium tetrafluoroborate (133, p 31):

Chloramine (137) (10 moles) was dissolved in 50 ml of benzene, and added dropwise to 2.5 g (1.3 equivalents) of silver tetrafluoroborate in 250 ml dry benzene, in the dark. Silver chloride precipitated immediately upon addition of the chloramine. The solution was stirred for 4 hours under a nitrogen atmosphere. By this time, most of the precipitate had adhered to the sides of the flask. Lithium chloride was added to precipitate excess silver ion, and the solution was stirred for an additional 30 minutes. The reaction solution was then filtered through celite, and the precipitate was washed well with methylene chloride. The two filtrates were combined and the solvents removed under reduced pressure. A brown oil remained: pmr δ 1.8 (m, 10H), 3.0 (m, 2H), 3.4 (m, 1H), 4.1 (m, 1H).

Octahydroindolizine (79, p 20)

Sodium cyanoborohydride (5 g) was dissolved in 100 ml methanol, along with 10 mg bromocresol green. HCl was added until a yellow color persisted. The indolizidinium ion (133) (p 31) prepared as above was added dropwise in a solution of methanol, and more HCl was added to keep the reaction mixture acidic. This solution was stirred for 18 hours, after which time aqueous KOH was added to make the mixture alkaline. The product was extracted with methylene chloride, and the extract was dried over potassium carbonate, filtered, and the solvent removed under reduced pressure. A yellow oil was obtained in 92.8% yield whose purity was established at 85% by GLC: pmr δ 1.0-2.0 (m, 14H), 3.0 (bs, 1H); cmr methylenes δ 20.1, 24.0, 25.0, 30.0, 30.6, 52.5, 53.7, methines δ 63.8; ir 2930 (CH_2 stretch), 2780 (C-H stretch), 1445 (C-H bend).

4-methoxypent-3-ene-2-one (p 65)

Dimethyl sulfate (0.53 mole) 2,4-pentanedione (0.49 mole), and anhydrous potassium carbonate were dissolved in acetone and refluxed for 4 hours. Tlc of the mixture on alumina plates in chloroform showed that most of the 2,4-pentanedione had reacted. The mixture was stirred for two days at room temperature. The salt was filtered, the acetone was removed under reduced pressure, and the product was dissolved in ether. Excess dimethyl sulfate was removed by extracting one time with cold aqueous NaOH. The ether fraction was dried over Na_2SO_4 , filtered, and the ether removed under reduced pressure. A 50% yield of the desired product was obtained: pmr δ 2.2 (s, 3H), 2.3 (s, 3H), 3.7 (s, 3H), 5.5 (s, 1H).

5-[(3)-2,4-dioxopentane] octahydroindolizine

A solution of the immonium ion (133) (p 31) in ethanol was added dropwise to a solution of 2,4-pentanedione (5 ml) in refluxing ethanol (20 ml). After 30 minutes, two new spots were observed by tlc of the reaction mixture on alumina plates in chloroform. After 2 hours, the mixture was acidified and the excess capture agent was extracted with methylene chloride. The remaining solution was made alkaline by the addition of K_2CO_3 , and the remaining products were extracted with methylene chloride, dried over anhydrous K_2CO_3 , filtered, and the solvent evaporated under reduced pressure. Quantitative yield of the 2,4-pentanedione was obtained, indicating that no capture had occurred. The remaining products were separated by preparative tlc on 1000 micron alumina G.F. plates (Analtech) in chloroform. One new product fraction was isolated (200 mg), but was not identifiable by pmr.

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APPENDIX

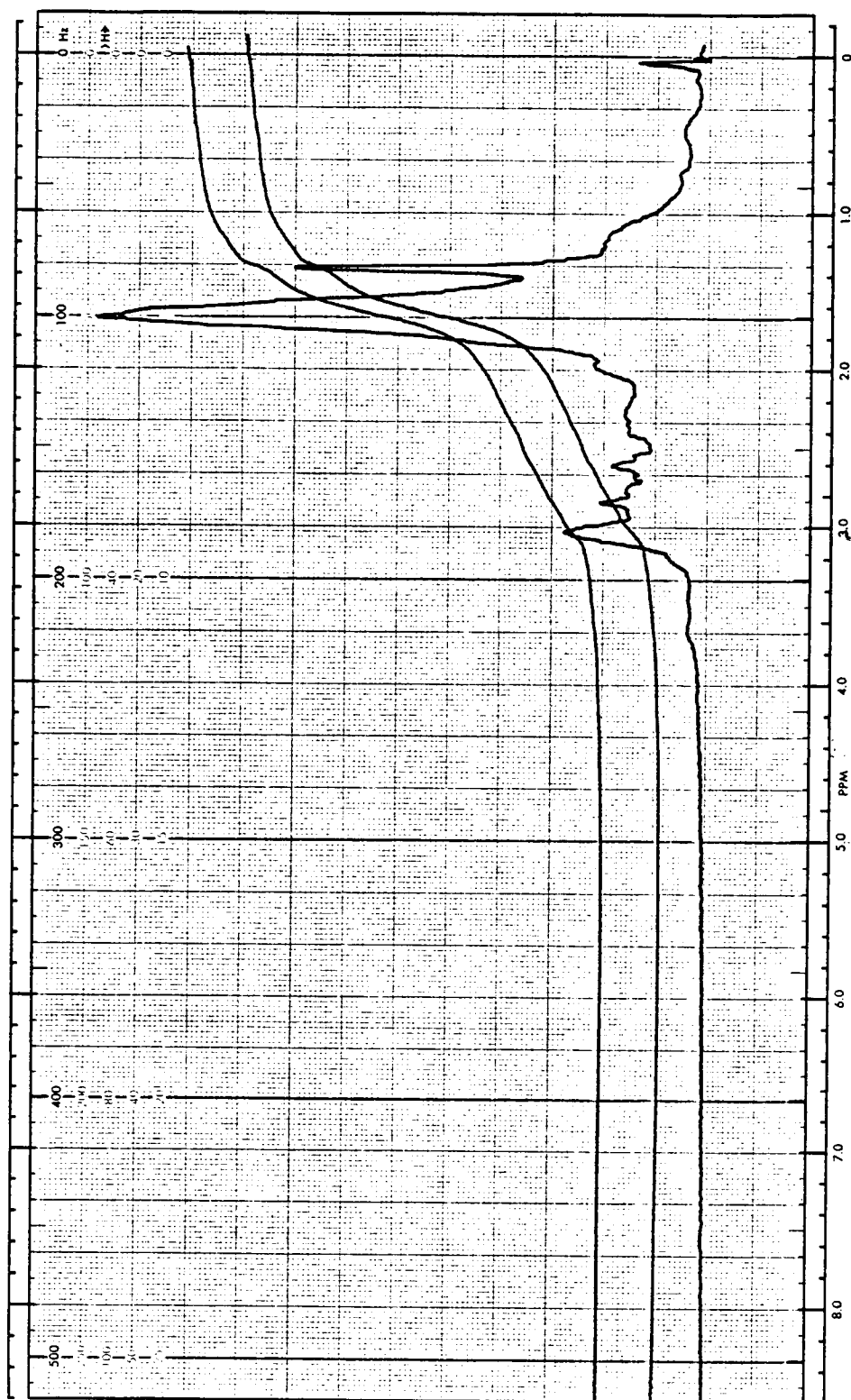


Figure 1. Proton magnetic resonance spectrum of octahydro-1-pyridine (141)

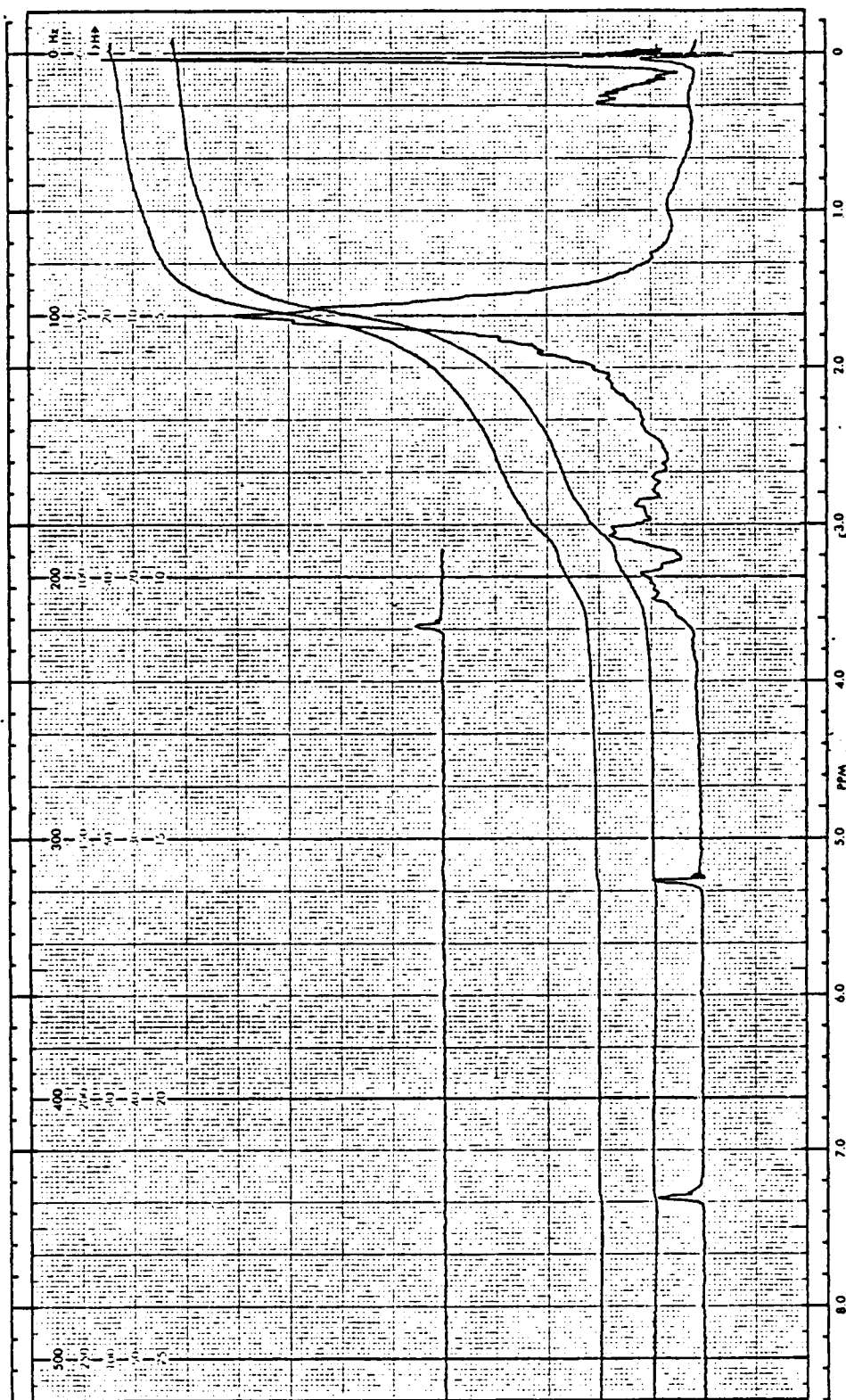


Figure 2. Proton magnetic resonance spectrum of N-chloro-octahydro-1-pyridine (137)

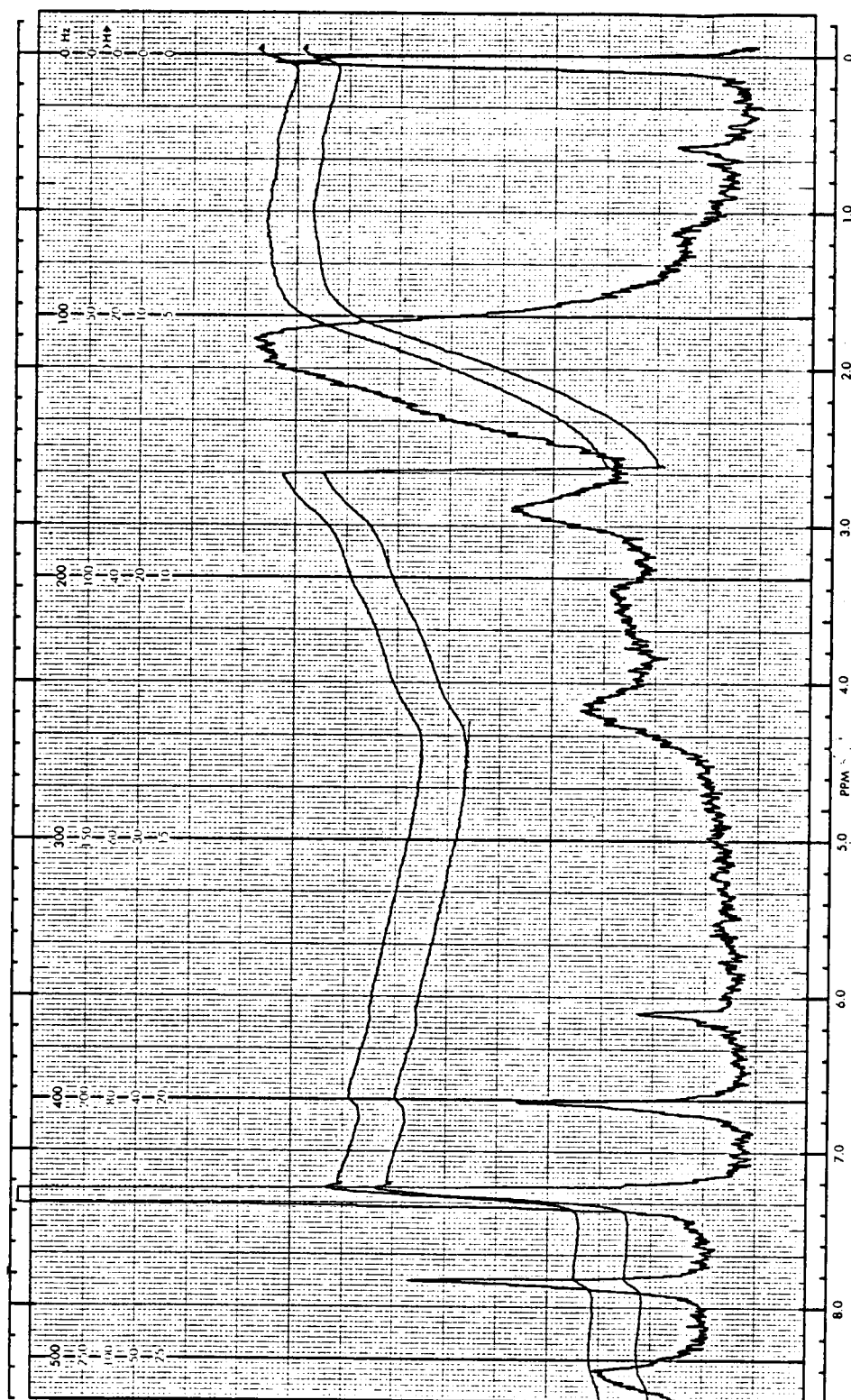


Figure 3. Proton magnetic resonance spectrum of 1,2,3,6,7,8,8a-heptahydroindolizinium (133)

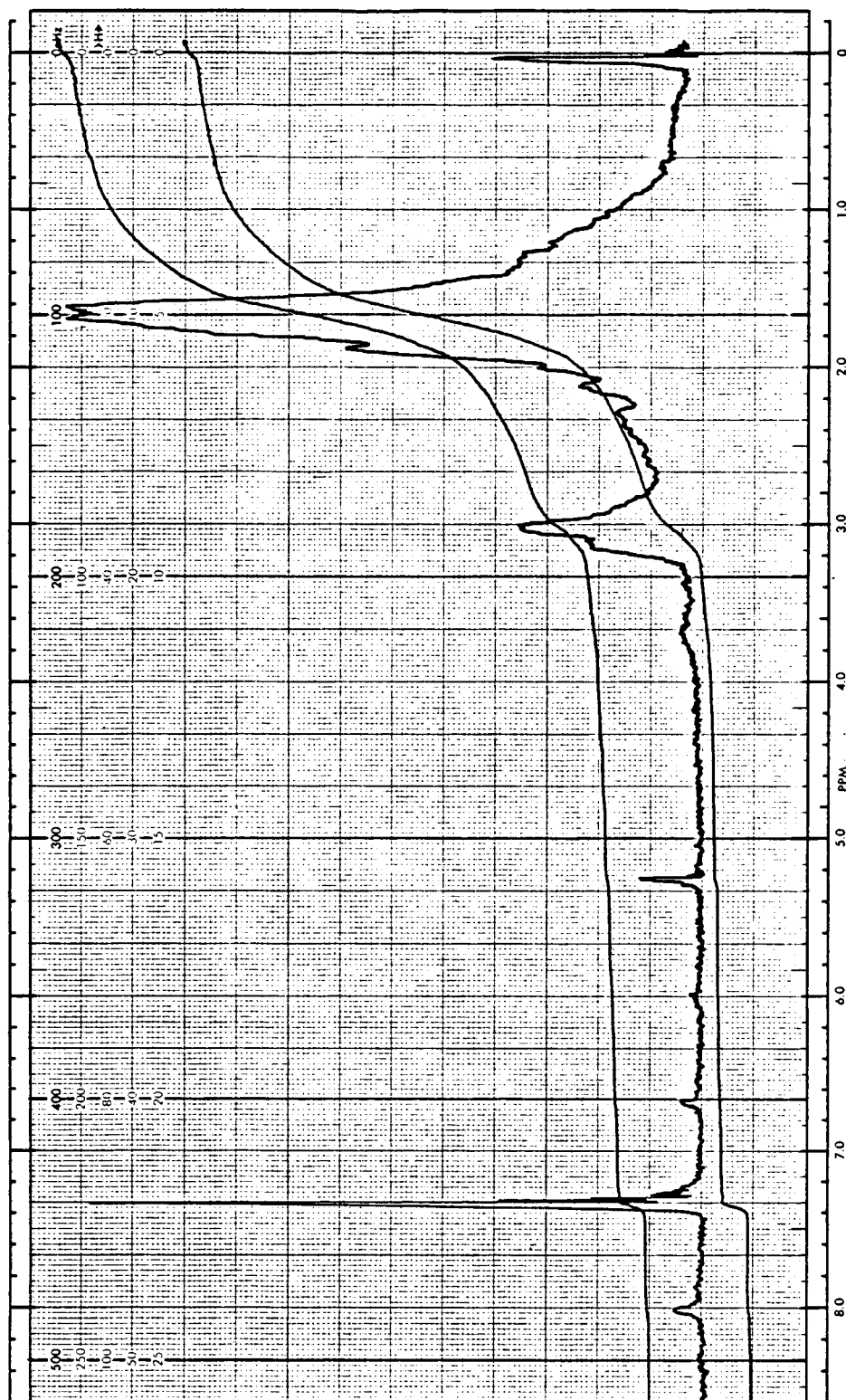


Figure 4. Proton magnetic resonance spectrum of octahydroindolizine (79)

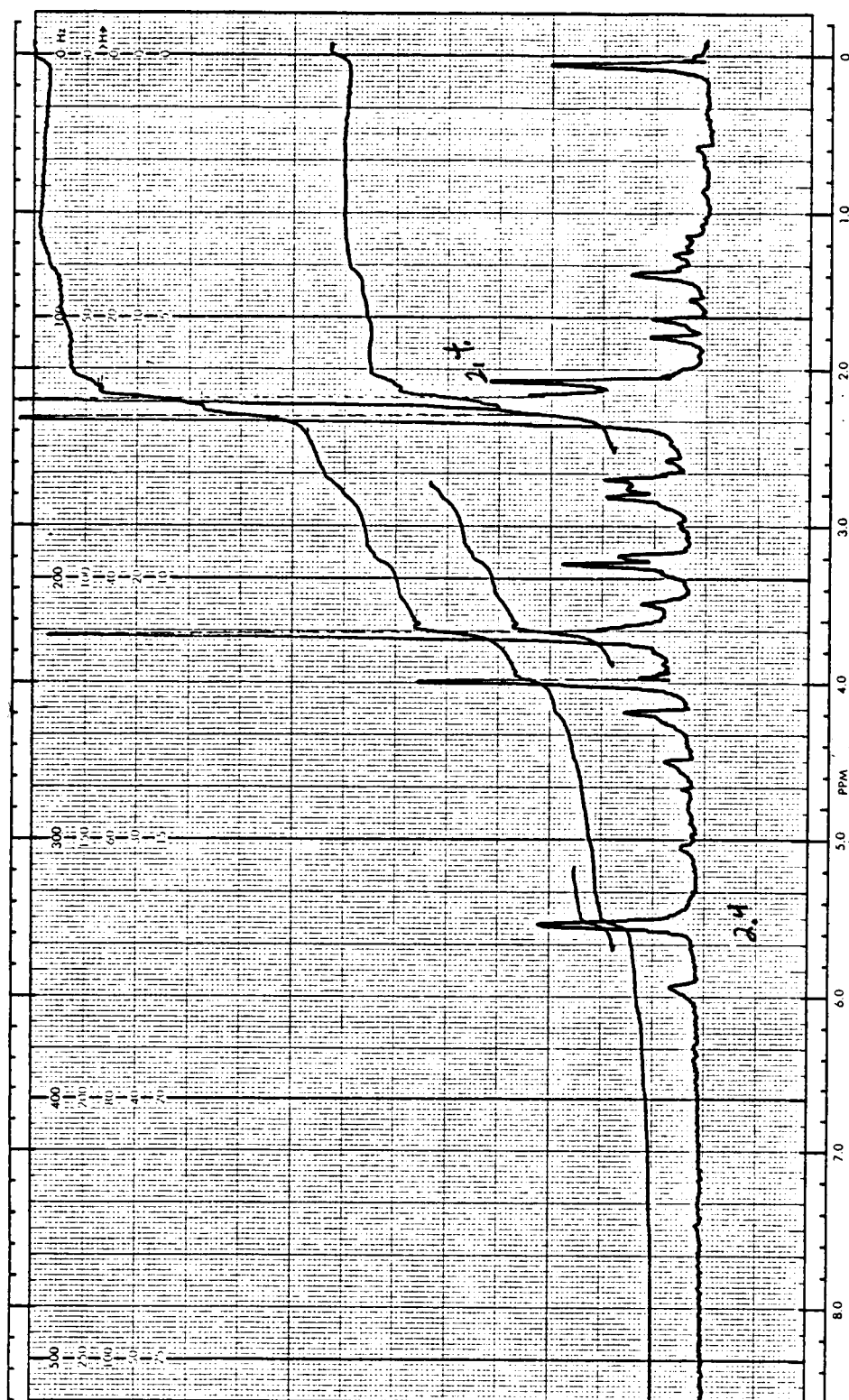


Figure 5. Proton magnetic resonance spectrum of 4-methoxypent-3-ene-2-one

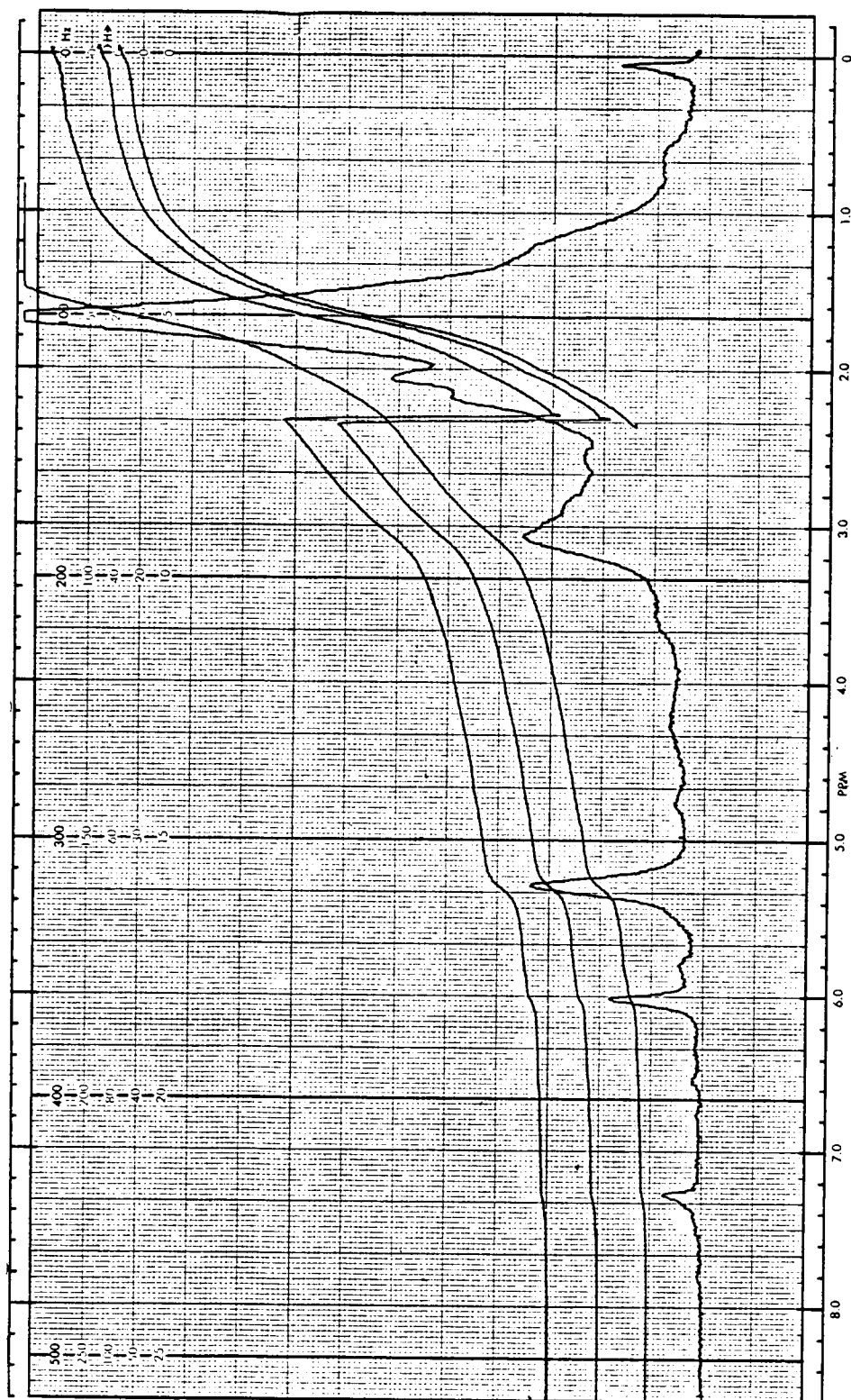


Figure 6. Proton magnetic resonance spectrum of crude product mixture arising from capture of $(^{133})$ with 2,4-pentanedione

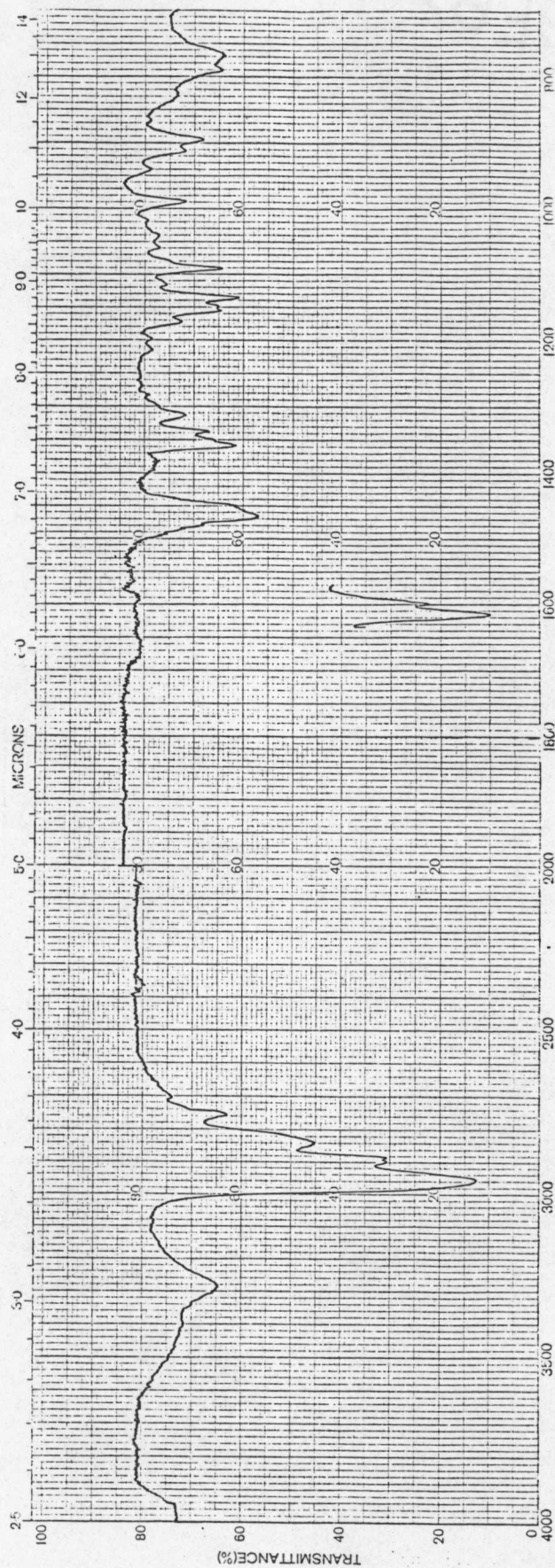


Figure 7. Infrared spectrum of octahydro-1-pyrindine (141)

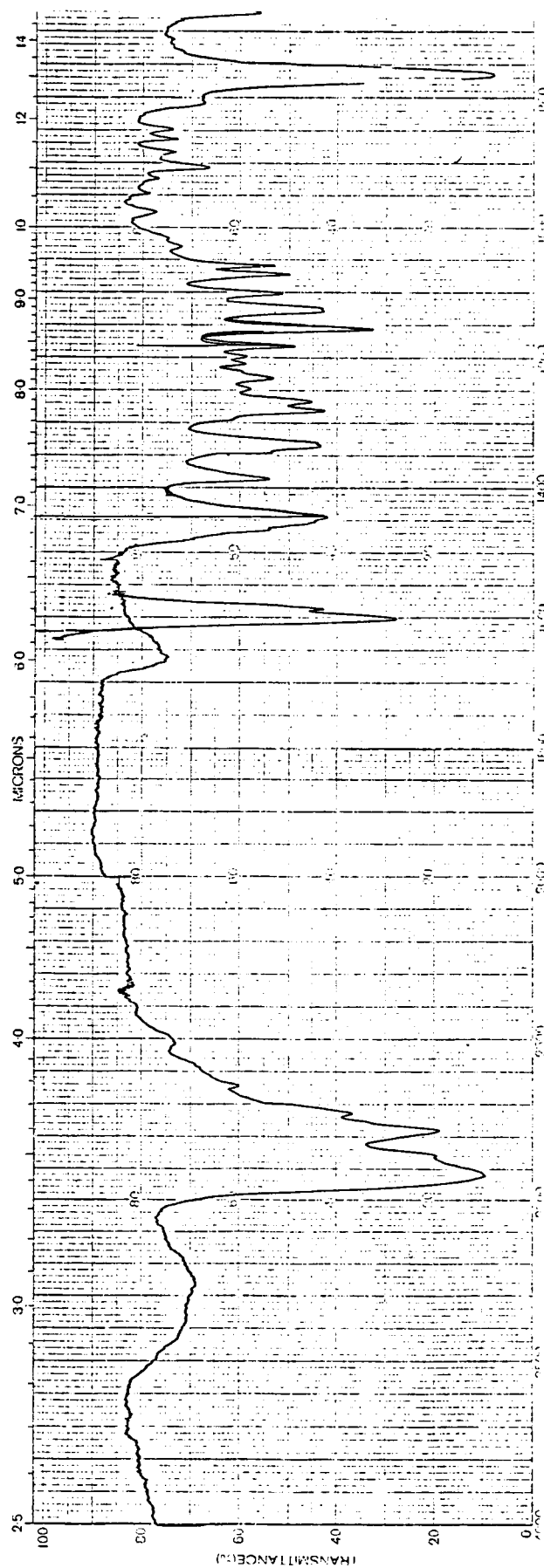


Figure 8. Infrared spectrum of octahydroindolizine (79)

VITA

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