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I am submitting herewith a dissertation written by Kenneth Alan Cole entitled "The Silver Ion Induced Rearrangement of N-Chloro-octahydropyrindines: A synthesis of Monomorine I." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Fred M. Schell, Major Professor

We have read this dissertation
and recommend its acceptance:

Accepted for the Council:

Vice Provost
and Dean of The Graduate School

THE SILVER ION INDUCED REARRANGEMENT OF N-CHLORO-OCTAHYDROPYRINDINES: A SYNTHESIS OF MONOMORINE I

A Disseration

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Kenneth A. Cole

May 1990

DEDICATION

For their continued support, love, and encouragement, the author wishes to dedicate this dissertation to his father and his late wife, Barbara.

ACKNOWLEDGMENTS

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ABSTRACT

The effect of treating N-chloro-octahydro-1-pyrindines with silver tetrafluoroborate and subsequent hydride or trapping of the imminium ion intermediate results in good yields of indolizidines. The rearrangement of N-chloro-octahydro-1-pyrindine to indolizidine seems independent of a cis or trans fussion of the pyrindine rings and occurs with preference over alkyl substituent migration in the C-2 substituted case. Efficient trapping with cyanide and utilization of the chemistry this functionality provides led to a synthesis of monorine I.

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LIST OF SYMBOLS

APT	attached proton test
bm	broad multiplet
bs	broad singlet
d	doublet
LAH	lithium aluminum hydride
M	molar concentration
m	multiplet
mL	milliliter
mmol	millimole
NMR	nuclear magnetic resonance
NCS	N-chlorosuccinimide
ppm	parts per million
q	quartet
R	alkyl
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
δ	parts per million from TMS

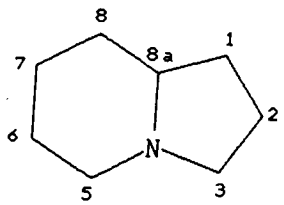
CHAPTER I

HISTORICAL SURVEY

Since the inception of the field of chemistry, it has been the ambition of the chemist to isolate, define, duplicate, and ameliorate the processes and products of nature. Motivation behind this objective has arisen from nature's generosity in providing products that are of biological significance to man. These products have provided him with a means to control and understand the mechanisms of disease and pestilence, as well as to explore and control the physiological responses of himself and other organisms. Unfortunately, nature has provided many of these compounds on a scale too small to be utilized by man, thereby challenging him with devising schemes to efficiently synthesize these often complex compounds. Indeed, much of modern synthetic organic chemistry has been focused not only on the synthesis of these natural products, but also on the development of new techniques of synthesis which can rival nature's efficiency in creating these compounds.

One of the largest, as well as most structurally and biodynamically diverse type of organic natural products is the alkaloids. An alkaloid can be defined as "... a cyclic organic compound containing nitrogen in a negative oxida-

tion state which is of limited occurrence in living organisms."[1] Compounds possessing a nitrogen in a negative oxidation state include amines, amine oxides, amides, and ammonium salts. A brief discussion of the occurrence and biological activities of alkaloids would provide insight to the cogent reasons to develop methods leading to their synthesis. However, to even briefly survey the various classifications of alkaloids and their biodynamics is beyond the scope of this dissertation. Therefore, discussion will be limited to only those alkaloids possessing the indolizidine (1) ring system. The diversity of structural complexity, as well as physiological activity exhibited even within this narrow category can be considered exemplatory of all classifications of alkaloids.

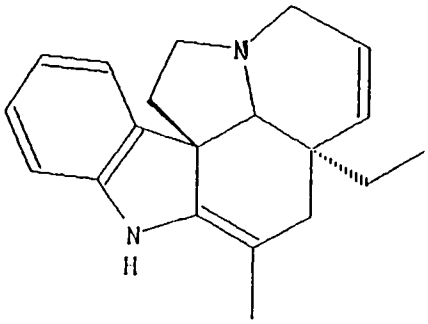


1

Indolizidine: Occurrence and Biological Activity.

The indolizidine ring system is well represented among the alkaloid natural products. It appears as a structural moiety in many classes of alkaloids in which biogenetic and structural considerations indicate a preference to another heterocyclic system such as the indole ring or isoquinoline

ring system. Alkaloids containing the indolizidine ring can be found in the Aspidosperma (tabersonine 2), Amaryllidaceae (lycorine 3), Erythena (Erythraline 4), and the steroidal Solanoaceae (solanidine 5) families.



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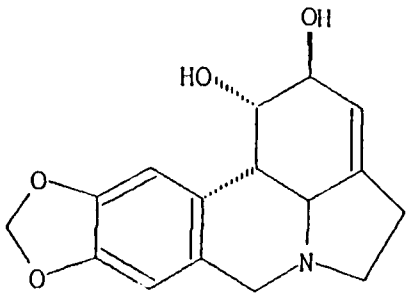

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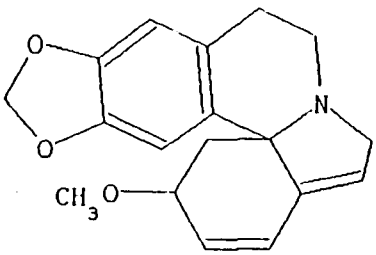

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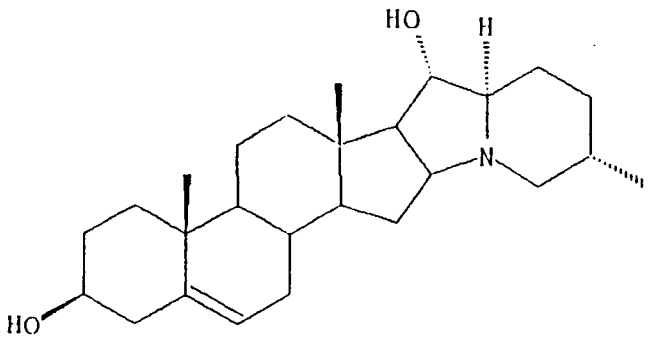

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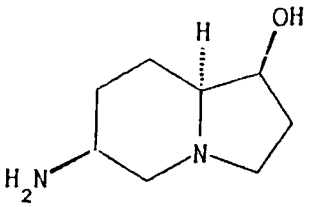
Alkaloids in which the prime structural feature is the indolizidine ring system have been found in fungi, higher plants, insect, amphibian, and mammal sources. Much interest has been shown in the indolizidine alkaloids in recent years due to their toxicity, pharmacological potential, and occurrence in animals.[2]

The consumption of locoweeds (Astrgenlus and Oxytropis species of the family Leguminosae) in the western United

States, and of the Darling Pea (Swainosina canescena) in western Australia produces locomotor disturbances in range animals known respectively as "locoism" and "peastruck".[3] This disease has been a serious economic problem for livestock owners in these two countries for more than 100 years.[4] Recognition of biochemical and pathological simularities between "locoism" or "peastruck" and mannosidosis, a genetic-controlled lyposomal storage disease which produces similar symptoms in humans, prompted investigation into the etiology of "locoism." [5] This investigation led to the isolation of swainosine 6, which is a potent inhibitor of α-D-mannosidases.[5] Inhibition of this enzyme causes accumulation of oligosaccharides within the cell which eventually disrupts cellular function, especially in neurons.[7] The isolation of this alkaloid makes available a tool for inducing and reversing phenocopy of genetic mannosidosis and allows for controlled monitoring of a disease which could only be studied in animals that were chance carriers of the deviant gene.[8] Swainosine has also been used for the investigation of the role of the oligosaccharide moiety in glycoprotein metabolism.[9]

Slaframine (7) is another indolizidine alkaloid which has posed a serious problem in veterinary medicine, yet holds promise for human pharmacological use. This powerful cholinegeric stimulator of the exocrine glands[10] is isolated from Rhizoctonia legumineosla, a fungus which infects



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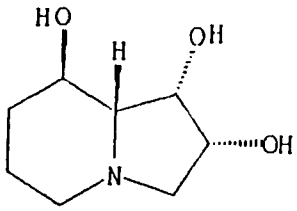
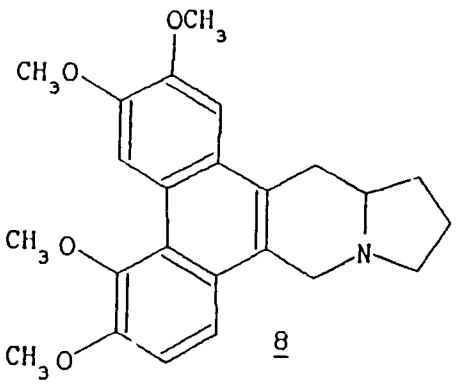


7

red clover[10], and is the agent responsible for the disorder known as "slobbers," the excessive salivation it causes in cattle.[11] In view of its ability to stimulate the exocrine glands, slaframine has been suggested as a possible agent for diseases involving cholingeric dysfunction such as cystic fibrosis.[12]

Tylocrebine (8) is representative of the phenanthraindolizidines found in the Aselepidaceae, Moraceae, and Urticaceae plant families.[13] Alkaloids of this type have vesicant activity.[13] Tylocrebine is very effective against L1210 leukemia,[14] however, clinical trials of the alkaloid were terminated because of central nervous system toxicity, primary ataxia, and disorientation.[14]

Cyclizidine (9), with its novel cyclopropane moiety, has recently been isolated from a Streptomyces species indigenous to the soil in northern England.[16] This alkaloid exhibits non-selective immunostimulatory effects and its secondary monoacetate exhibits β-blocking activity.[17] Another strain of Streptomyces produces the antibiotic indolizomycin 10 .[18]



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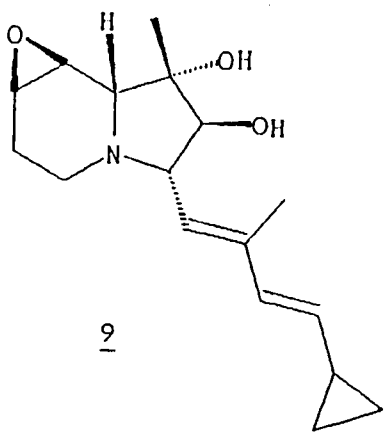

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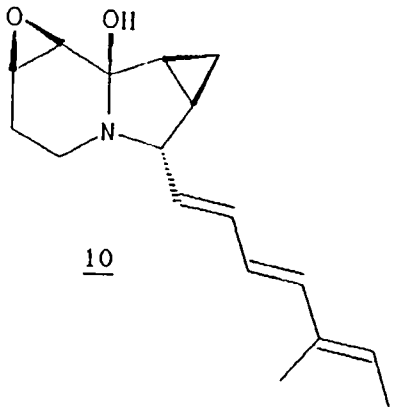

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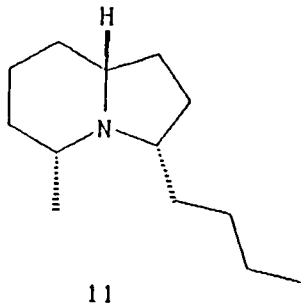

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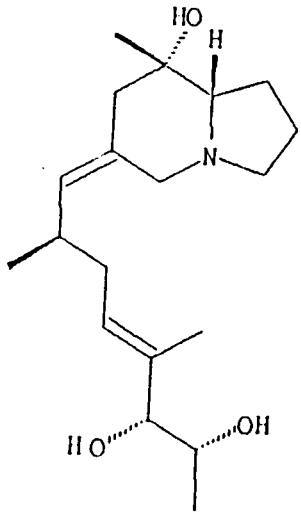
Many indolizidines have been isolated from animal sources. Several 3,5-dialkylindolizidines have been found in ants. Monomorine I (11) is one of the trail pheromones of the Pharoah ant (Monomorium pharoanas).[19] The queen's venom of the thief ant Solenopis contains the all cis stereoisomer of 3-(n-hexyl)-5-methylindolizidine as the sole alkaloidal component.[20]

The defensive skin secretions of several species of amphibians have yielded many novel and interesting indolizidines.[21] Pumiliotoxin B (12), a powerful cardiotonic

agent, is isolated from the Panamanian poison frog Dendrobates pumilio.[22] Gephrotoxin (13) is another such alkaloid isolated from the Dendrobates family.[22]

The musk glands of the Canadian beaver, the source of the perfume fixative castolatum, contains 5-(3-furyl)-8-methylindolizidine.[23]



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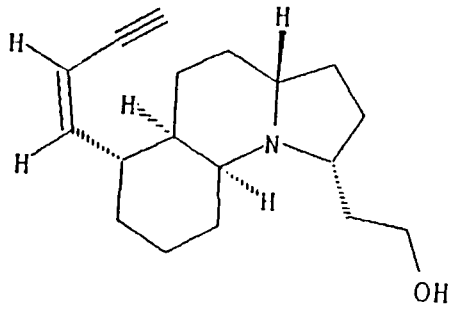

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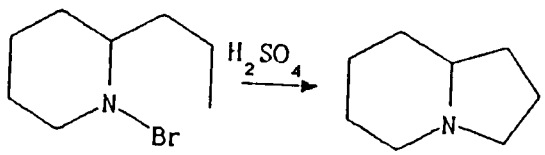
Interest in the study and exploitation of the biodynamic properties of indolizidine alkaloids has spurred parallel interests in the development of synthetic methodologies which would afford these compounds. A historical overview of the methods of preparation of these compounds is therefore warranted. The number of individual syntheses of these alkloids is almost as numerous as the alkaloids themselves and it is beyond the scope of this manuscript to review them all. Therefore, coverage will be limited to

those techniques which show applicability in the synthesis of the indolizidine ring system and exhibit potential for the synthesis of similar ring systems which also possesses a bridgehead nitrogen. For simplicity of coverage these techniques will be categorized as follows: cyclizations onto nitrogen; cyclizations α to nitrogen; transannular cyclizations; cycloadditons; and miscellaneous methods.

Cyclizations onto Nitrogen.

The first method which afforded an indolizidine ring was discovered serendipitously in the 1880's when A. W. Hofmann treated N-bromoconiine (14) with hot sulfuric acid and obtained a tertiary amine.[24] This was later shown to be δ-coniceine or indolizidine (1, p.2)[25,26] (Scheme 1). The Hofmann-Loffler-Freytag reaction, as this free radical reaction is known,[27] is of historical value only and has not received much use.

Scheme 1



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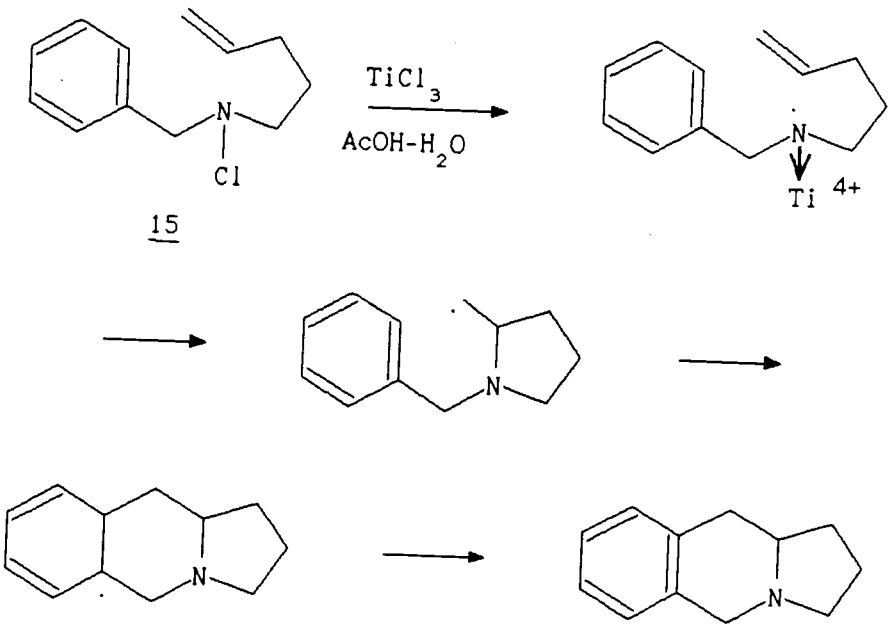
Surzur and Stella[28] have employed another aminyl radical reaction to provide indolizidines. When N-chloro-N-

benzyl-4-pentenylamine (15) in aqueous acetic acid is treated with titanium trichloride, hexahydropyrrolo[1,2b]-isoquinoline (16) is produced in 19% yield (Scheme 2). When N-allyl-N-chloro-4-pentylamine is reacted under the same conditions, 2-chloromethylpyrrolizidine is obtained in 78% yield.[29] The more difficult intramolecular aromatic substitution in the second cyclization step below is attributed for the lower yield in the previous case.

Scheme 2



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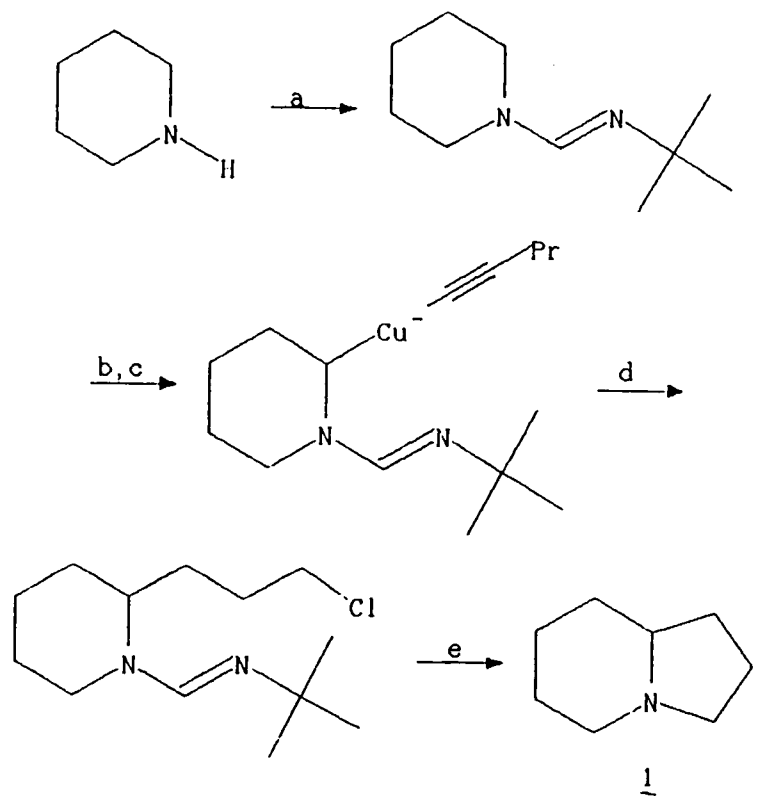
Cycloalkylations of amino halides and amino alcohols are another method which has been utilized in the preparation of indolizidines. Edwards and Meyers[30] have developed a versatile method which provides these compounds from 2-(ω-chloroalkyl)piperidines and -pyrrolidines (Scheme 3).

In this method N-t-butylformamidine derivatives of pyrrolidine and piperidine undergo α-lithiation upon treatment with t-butyllithium. Pentynlcopper is then used to produce the cuprate which will react with an α,ω-chloroiodoalkane to produce a product which cyclizes upon exposure to base. In this fashion δ-coniceine (1,p.2) was synthesized in 85% yield.

Scheme 3

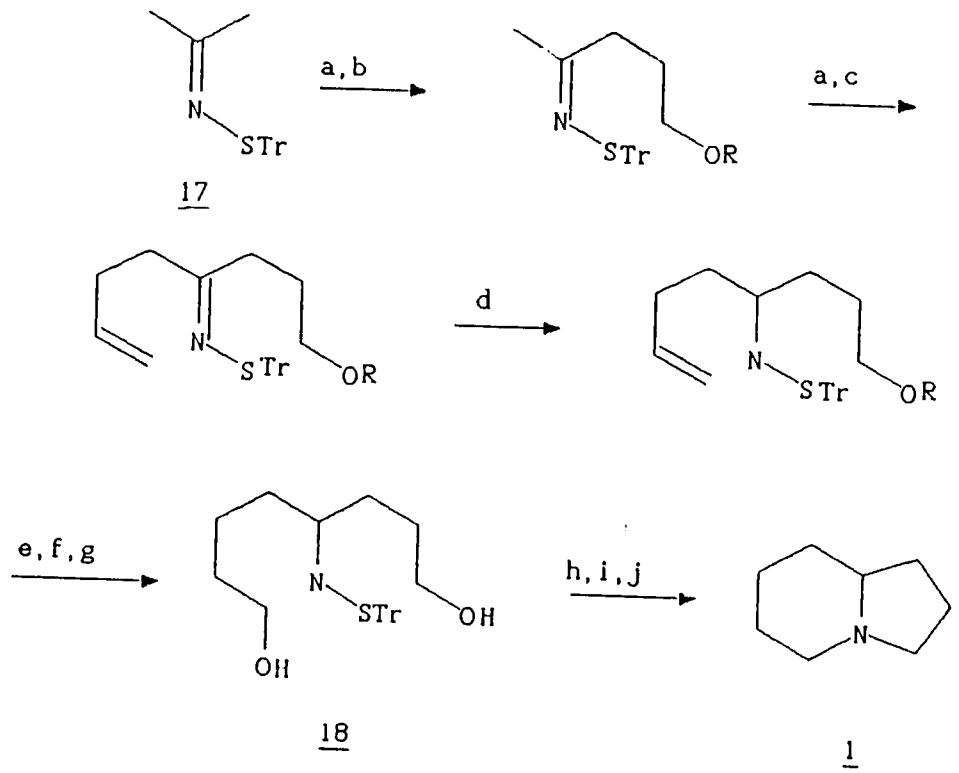


1

Reagents: a) N,N-dimethyl-N′-t-butylforamidine; b) t-BuLi, THF; c) CuC≡CPr; d) $I(CH_2)_3Cl$; e) KOH.

Branchaud[31] synthesized 1 in 18% yield from acetone tritylsulfenimine (17) by constructing the amino diol 18 then cyclizing it with base as its dimesylate (Scheme 4).

Scheme 4

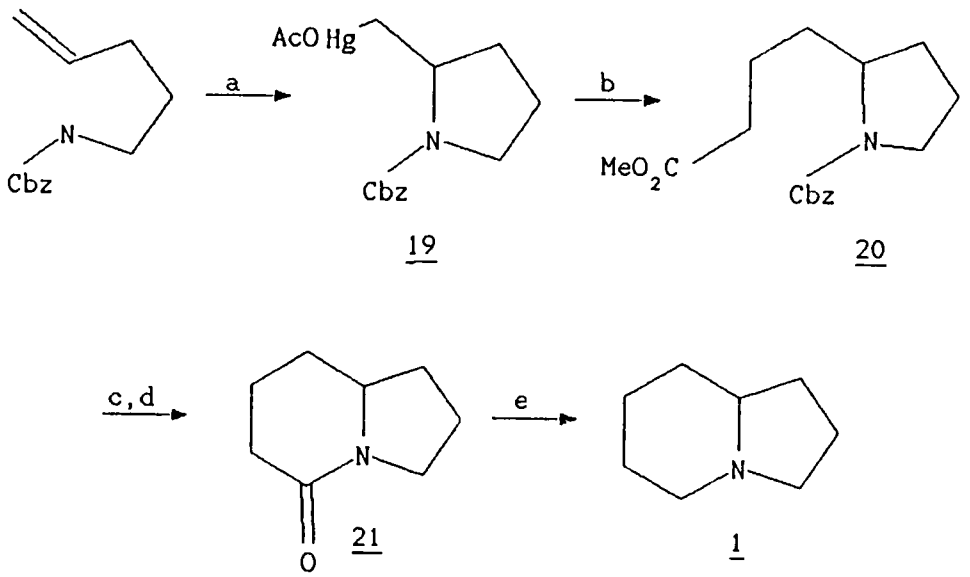


Reagents: a) s-BuLi/THF, -78°C; b) $BrCH_2CH_2OTBDMS$; c) $ICH_2CH{=}CH_2$; d) $NaCNBH4/CF_3COOH$/THF pH4; e) B_2H_6/THF; f) $NaOH{-}H_2O_2/H_2O$; g) $n\text{-}Bu_4NF$/THF; h) $MsCl/CH_2Cl_2$/DMAP 0°C; i) $(CH_3)_3SiI/CDCl_3$; j) Na_2CO_3, Na_2SO_4/D_2O.

In Danishefsky's[33] four-step synthesis of 2, a novel ureidomercuration step was used to form 19. Treatment with trimethoxyborohydride and trapping the resulting radical with methyl acrylate gives 20 (Scheme 5). The protecting

group on the nitrogen is removed by hydrogenolysis and cyclization occurs to give lactam 21. The synthesis is completed by lithium aluminum hydride reduction.

Scheme 5



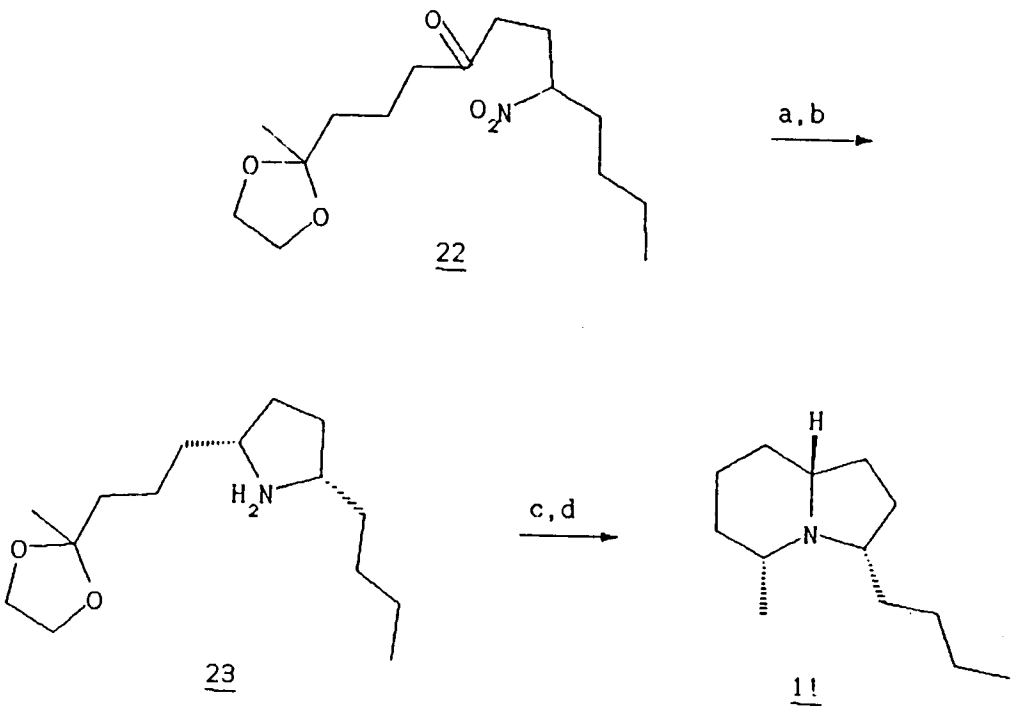
Reagents: a) $Hg(OAc)_2$; b) $Na(CH_3O)_3BH$, CH_2Cl_2, $CH_2=CHCO_2CH_3$; c) H_2/ 5% Pd-carbon d) Δ; e) $LiAlH_4$.

In another approach, Stevens and Lee[33] (Scheme 6) stereospecifically cyclized nitroketone 22 over palladium on carbon to pyrrolidine acetal 23. Hydrolysis of this compound gave the endocyclic enamine 24 which was reduced with sodium cyanoborohydride to give monomorine I (11).

Reductive cyclization is highly versatile in the conversion of sugars into alkaloids as demonstrated by Fleet's synthesis of swainsonine (6)[34] (Scheme 7). The azido man-

nose derivative 25 is modified by a Wittig reacton after oxidation to give 26. Hydrogenation reduces the azide and olefin, and reductive cyclization occurs producing the piperidine ring of 27. Upon changing the catalyst from

Scheme 6



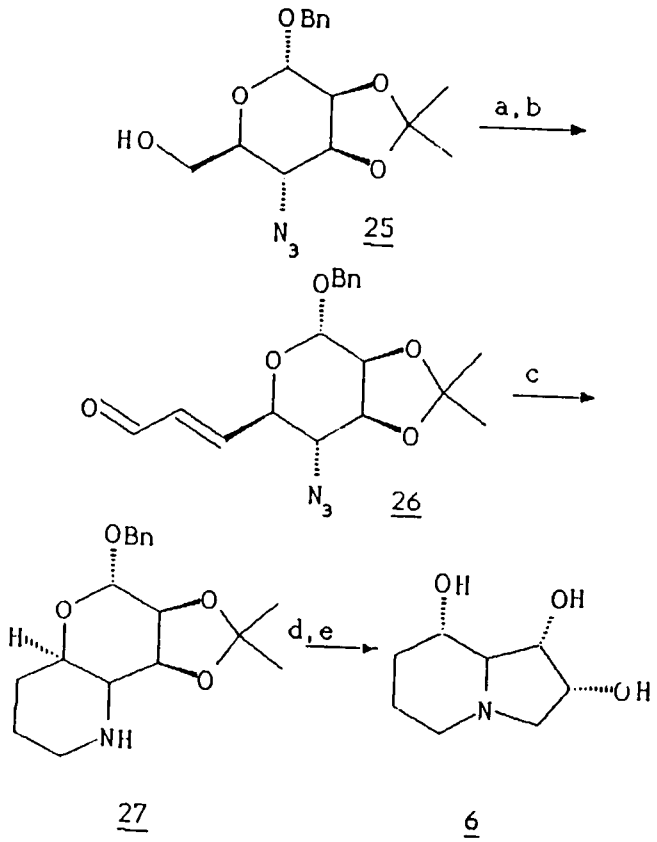
Reagents: a) H_2, 10% Pd-C, anhydr. Na_2SO_4; b) oxalic acid; c) H_3O^+ pH3.8-5.4; d) $NaCNBH_3$.

palladium to platinum black, debenzylation occurs and the resulting acetal through its open-chain form undergoes a second reductive cyclization to give 6 in 87% yield from 25.

Several mixed-method cyclizations have also been used in the conversion of sugars into alkaloids. Suami, et

al.,[35,36] formed the pyrrolidine 29 by the displacement of a tosyloxy group from C-6 of an open-chain mannose derivative 28 (Scheme 8). A Wittig reaction followed by reduction afforded an amino ester whose hydrolyzed

Scheme 7



27 6

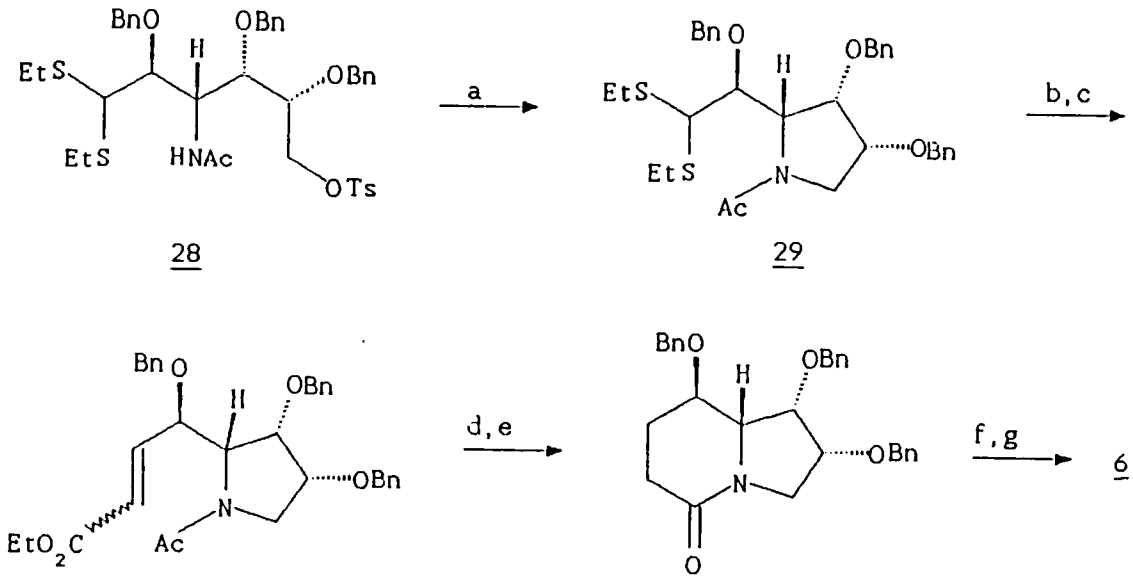
Reagents: a) py·HCl-CrO_3, molecular sieve; b) Ph_3P=CHCHO; c) H_2, 10% Pd-C, CH_3OH; d) H_2, Pd black, AcOH; e) 80% CF_3CO_2H-D_2O, H_2O work-up.

derivative cyclized on exposure to base to give 30. Lithium aluminum hydride reduction of the carbonyl followed by debenzylation produced swainsonine (6, p.9).

Cyclization α to Nitrogen.

Cyclization to a position α to nitrogen has been the focus of some of the more versatile and imaginative syntheses of alkaloids. One such method that has had much success in terms of the number of structures it provides

Scheme 8



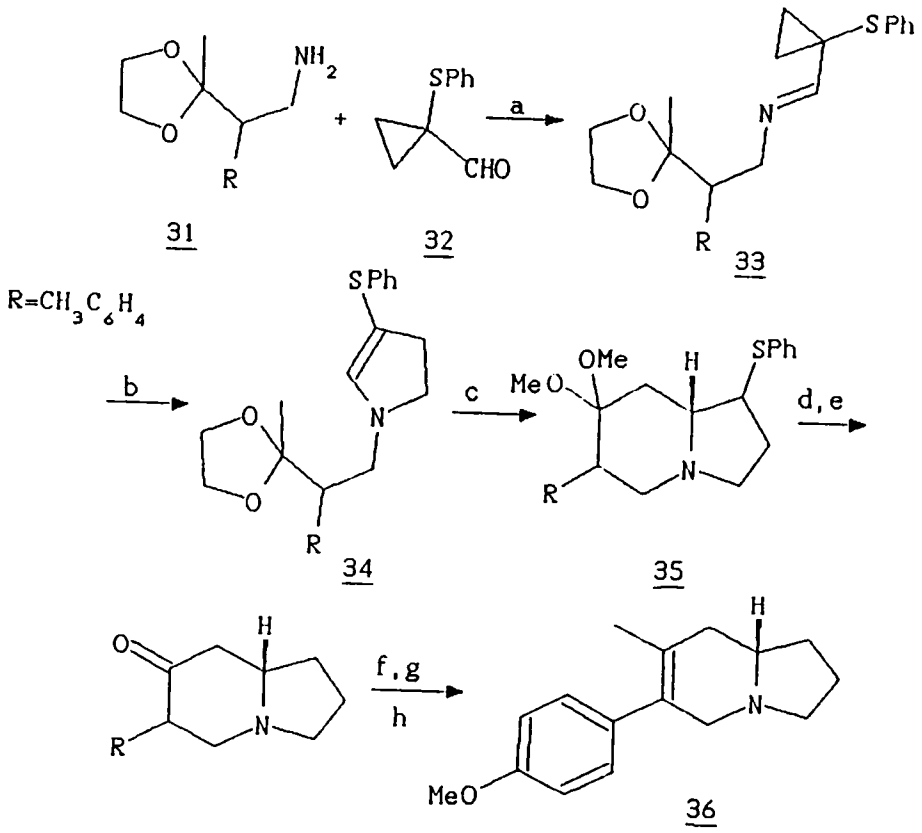
28 29 30

Reagents: a) 1M NaOH, dioxane,Δ; b) $HgCl_2$, $CaCO_3$, CH_3CN-H_2O; c) $(EtO)_2POCH_2CO_2Et$, NaH, THF; d) H_2 (1 atm.), Raney-NI, EtOH; e) KOH, EtOH-H_2O, 90°C; f) $LiAlH_4$, THF,Δ; g) 20% $Pd(OH)_2$, cyclohexane, EtOH,Δ.

access to is the rearrangement of a cyclopropylimine to a Δ^2-pyrrolidine.[37] Stevens and co-workers[38] formed the imine 33 from the condensation of 31 and 32 (Scheme 9). Rearrangement of the imine is then accomplished by refluxing in xylene with NH_4Cl. The resulting endocyclic enamine 34 is treated with methanolic HCl to induce cycli-

zation to 35, effectively accomplishing a Mannich reaction. Desulfurization and deprotection of the ketone allowed for the introduction of a methyl group. Dehydration then afforded ipalbidine (36).[39]

Scheme 9

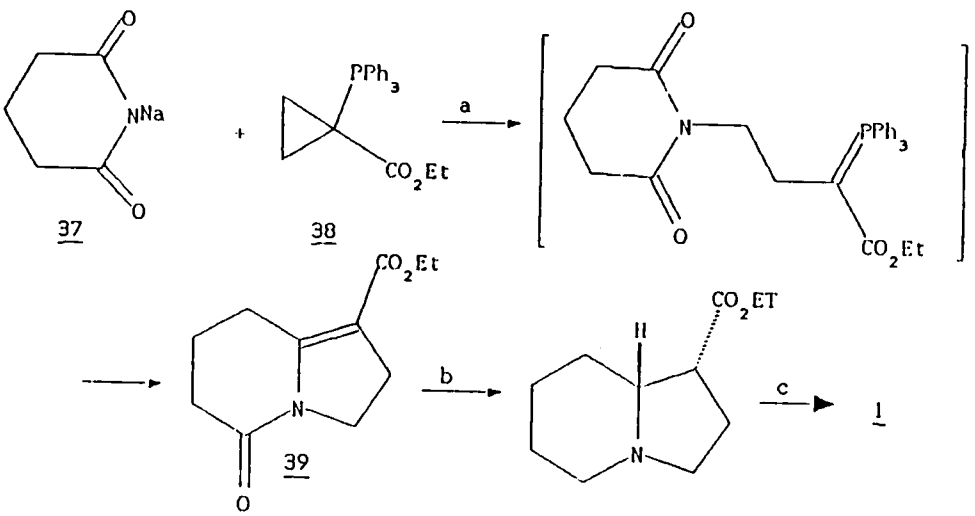


Reagents: a) C_6H_6,Δ; b) NH_4Cl, xylene, Δ: c) HCl, CH_3OH, $(CH_3O)_3CH$; d) H_2 (60psi), Raney-Ni, EtOH; e) 1M HCl,CH_2Cl_2; f) CH_3Li; g) H_2SO_4; h) $AlCl_3$, CS_2.

The reaction of sodium glutarimide (37) with the cyclopropylphosphonium salt 38 (Scheme 10) allowed Flitsch and Wernsmann[40] to synthesize 39 in 68% yield via an intramolecular Wadsworth-Emmons reaction.

A procedure utilizing the cyclization of an α-acylamino radical was the basis of Hart's synthesis of (±)-heliotridane (43) and δ-coniceine (1) (Scheme 11).[41] The α-acylamino radical is generated by the treatment of

Scheme 10

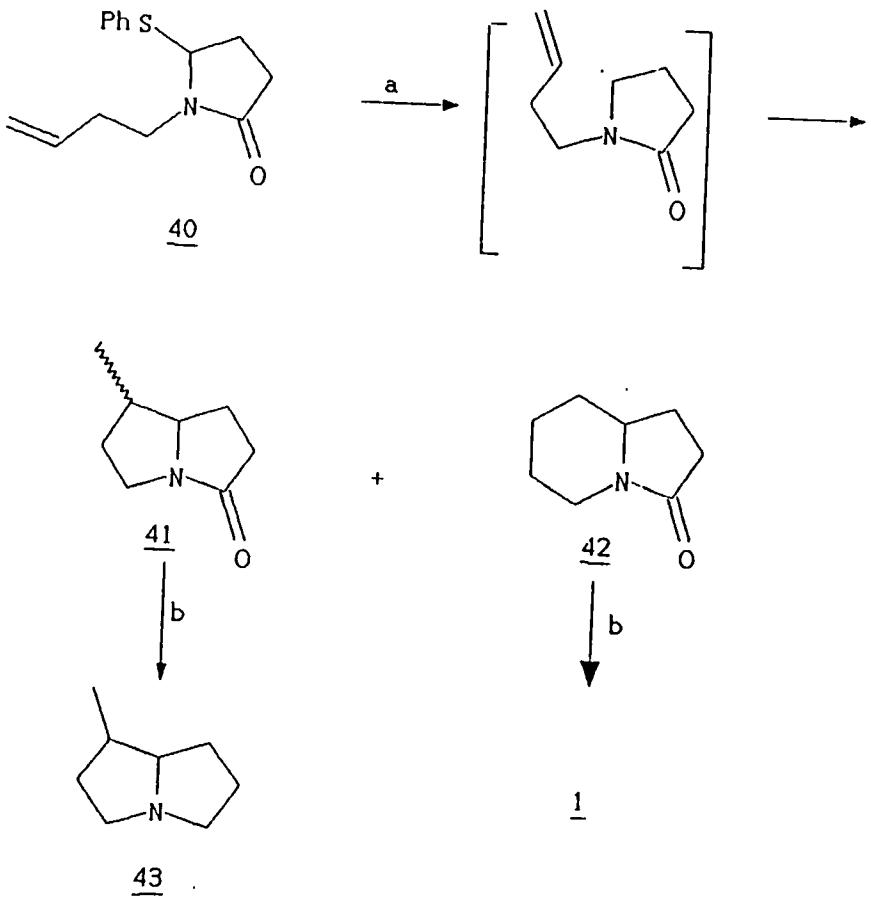


Reagents: a) Benzene, Δ; b) PtO_2, AcOH; c) $LiAlH_4$.

phenylthiolactam 40 with tri-n-butyltin hydride in the presence of 2,2'-azobisisobutyronitrile. The radical adds intramolecularly to the olefin to give 41 as a 11:1 mixture of stereoisomers in 49% yield and the indolizidone 42 in 23% yield. Lithium aluminum hydride reduction afforded the products. The kinetic partitioning of the radical between cyclizaton pathways is believed to account for the product ratio.[42]

The cyclization of an α-acyliminium ion is another method which has met with success in its ability to provide access to a multitude of structures.[43] This technique developed by Speckamp has been utilized by his group to synthesize elaeokanine B (48) (Scheme 12). Ketoimide 44 is

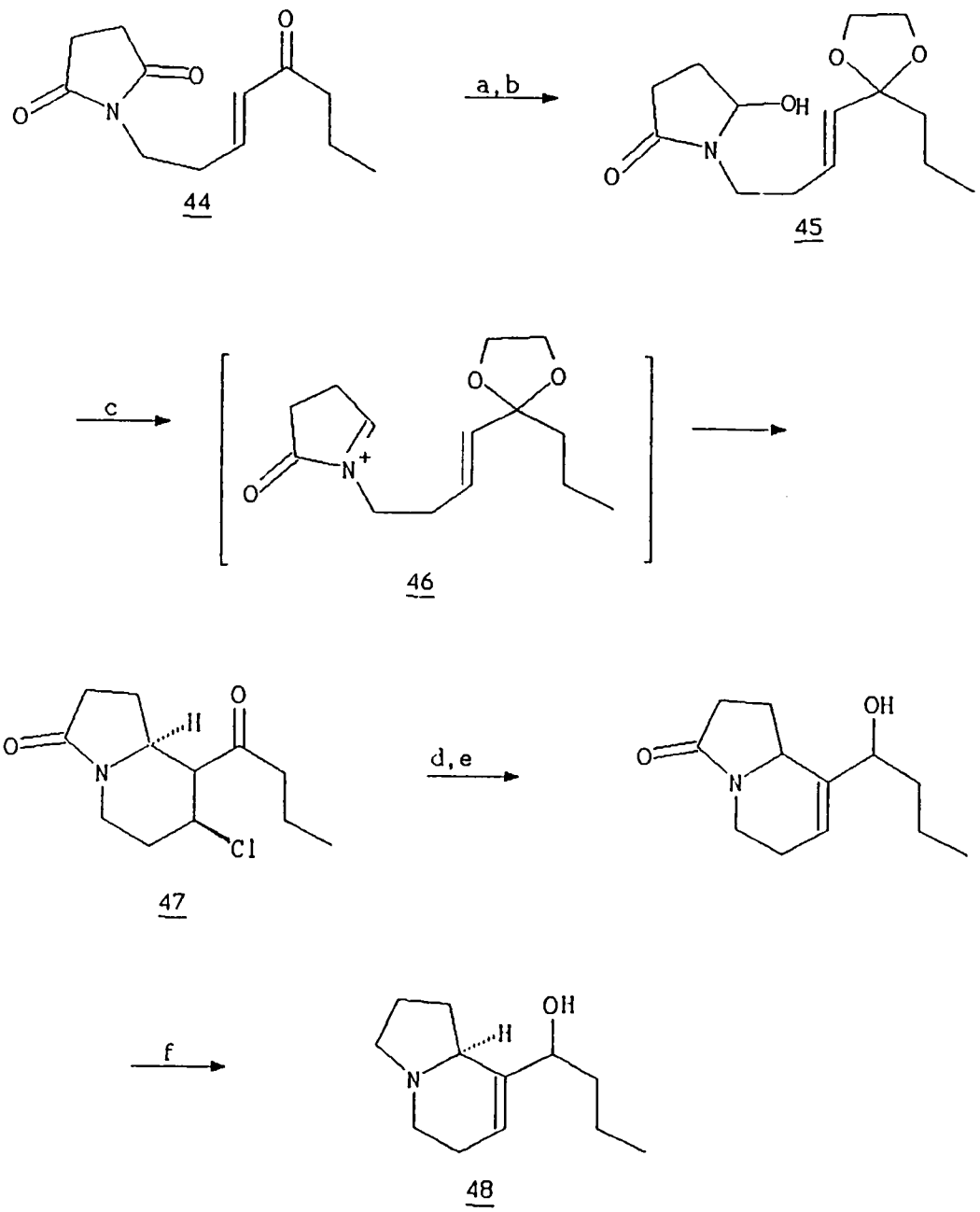
Scheme 11



Reagents: a) n-Bu_3SnH, AIBN, C_6H_6; b) $LiAlH_4$.

protected and partially reduced and the cyclization initiated by the dehydration of the resulting hydroxylactam 45

Scheme 12



44 45 46 47 48

Reagents: a) $(CH_2OSiCH_3)_2$, CH_3SiOtf, -8-0 °C; b) $NaBH_4$, H^+; c) HCl, CH_3OH, 0-5 °C; d) DBN, $C_6H_6CH_3$, Δ; e) $NaBH_4$, 0°C; f) i-Bu_2AlH, Et_2O.

to produce the acyliminium 46. The highly stereo- and regiospecific cyclization produces 47. Dehydrohalogena-

tion, borohydride reduction of the ketone and diisobutyl aluminum hydride reduction affords 48 in 51% yield.

Since endo- and exocyclic closure of the ring can be competitive in this method, the choice of a terminator must be judicious.[44] In addition to the terminators mentioned, olefinic[45] and vinylsilane[46,47] terminators have been used in this reaction.

Transannular Cyclizations.

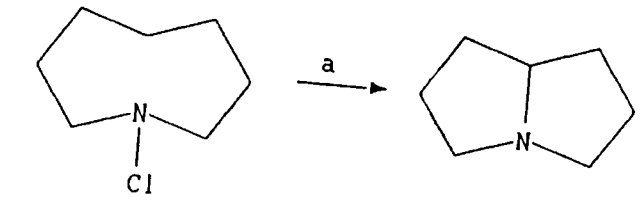
Ring compounds of 7-12 atoms are known to be strained and will adopt configurations which can facilitate the interactions between moieties that are juxtapositional.[48] Given that the proper functionality exists, these rings may undergo collapse to give bicyclic compounds. Due to the conformational constraints necessary for interactions of these groups, the ring will collapse with a moderate degree of stereochemical specificity.[49]

Edwards, Vocelle, and ApSimmon[50] synthesized unsubstituted pyrrolizidine and indolizidine ring systems in 78% and 68% yields respectively by the silver-induced transannular cyclizations of N-chloroazacyclooctane (49) and N-chloroazacyclononane (50) in aqueous dioxane (Scheme 13).

Edwards, et al. studied the mechanism of this reaction to determine whether nitrenium ions were involved and concluded that a nitrogen radical was involved. Further discussion of this mechanism will follow later in this disser-

tation.

Scheme 13



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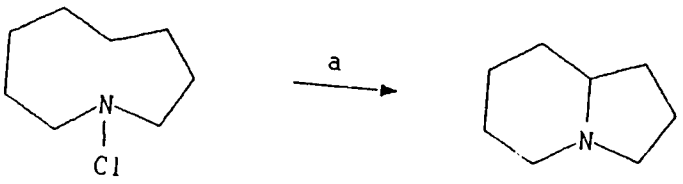


50

1

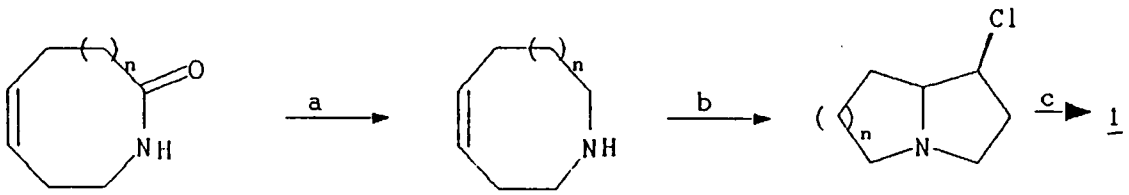
Reagents: $AgClO_4$, 80:20 Dioxane-H_2O

Wilson and Sawiciki[51] have developed a method for general entry into the indolizidine and pyrrolizidine rings through the reaction of an amine with a transannular double bond. This procedure involves the reduction of an unsaturated lactam obtained by a Beckman rearrangement. Collapse of the resulting olefinic amine ring is accomplished by exposure to an electrophile followed by nucleophilic attack by the amine (Scheme 14).

In this fashion, Wilson and Sawicki synthesized coniceine in 75% yield by treatment of amine 51 with mercuric

chloride in tetrahydrofuran followed by sodium borohydride reduction.[52]

Scheme 14

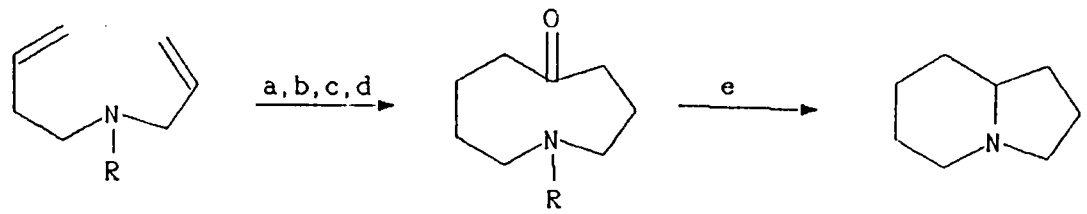


51

Reagents: a) $LiAlH_4$, THF; b) $HgCl_2$.

Coniceine (1,p.2) has been synthesized by Garst and Bonfiglio in 35% yield using hydroboration-carbonylation of a bisolefinic amine followed by reductive cyclization of the cycloaminone 52[53] (Scheme 15).

Scheme 15



R=CBz

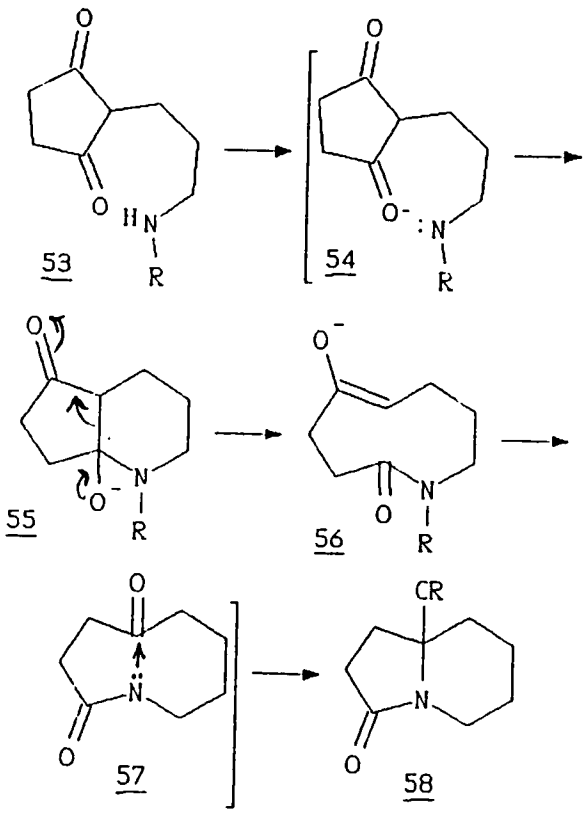
52

Reagents: a) Thexylborohydride; b)KCN; c) $(CF_3CO)_2O$; d) H_2O_2; e) H_2/Pd CH_3OH.

Ban, et al.,[54] have developed a novel annulation technique (Scheme 16) in which a 1,3-diketone bearing the

appropriate amino side chain (53) is converted into a bicyclic ring (58) in one step.

Scheme 16



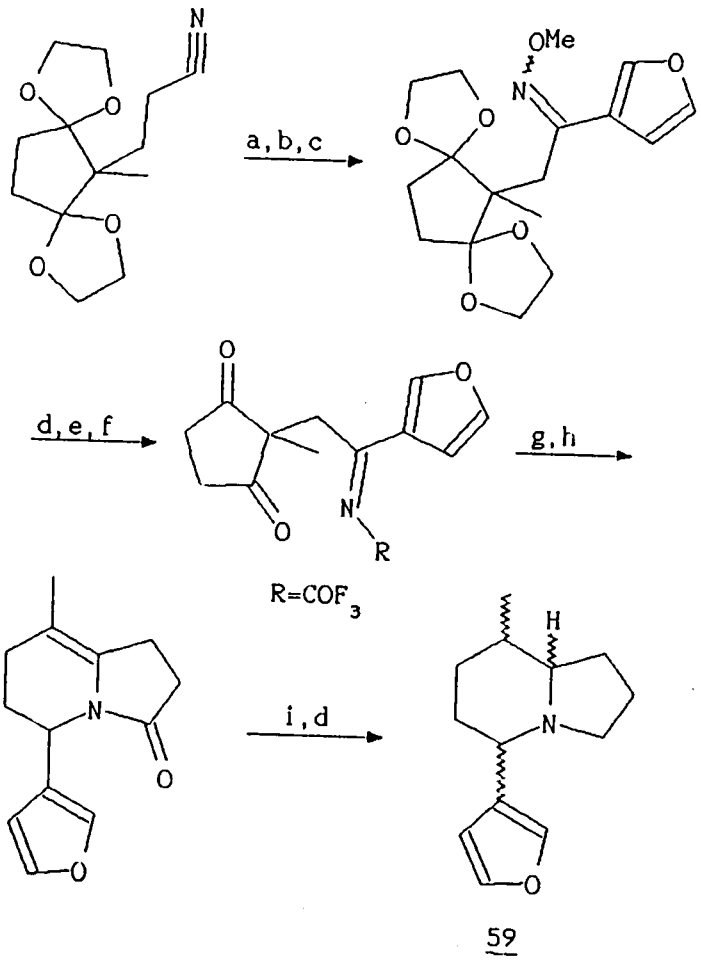
The process involves the formation of 55 followed by a retro-aldol type ring opening to give 56, tautomerization to the ketolactam 57 is followed by transannular cyclization. This technique has been used to synthesize nuphor indolizidine (59) (Scheme 17).

Cycloaddition.

1,3-Dipolar cycloadditions constitute another way in which indolizidine rings can be formed. Pizzorno and

Albonico[55,56] have developed an efficient two-step stereospecific synthesis of these compounds using N-acylpipecolic acid (60) (Scheme 18).

Scheme 17



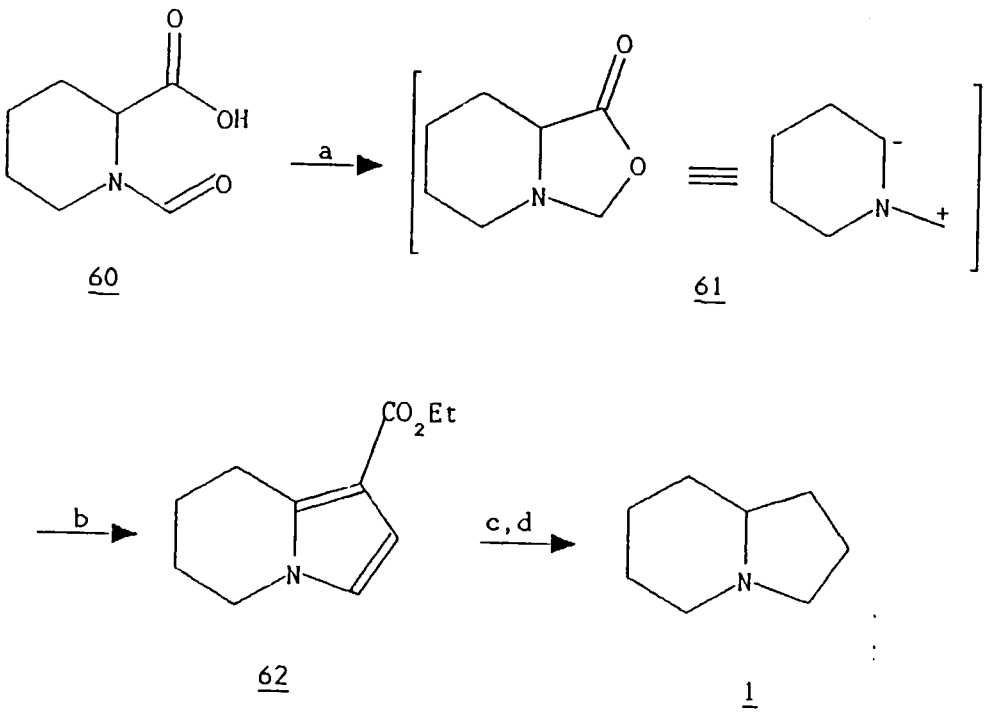
59

Reagents: a) 3-furanyl lithium; b) H_2O c) NH_2-OCH_3; d) $LiAlH_4$, THF, Δ; e) $(CF_3O)_2O$, Py; f) aq. CF_3COOH; g) LiOH, CH_3OH-H_2O, 65°C; h) HCl, CH_3OH; i) $NaCNBH_4$, CH_3OH.

In this reaction, ethyl propiolate adds via the oxazolonone intermediate (61) which serves as an effective

1,3-dipole precursor to produce a pyrrole. Hydrolysis and decarbonylation of 62, followed by hydrogenation affords δ-coniceine in 67% overall yield.

Scheme 18

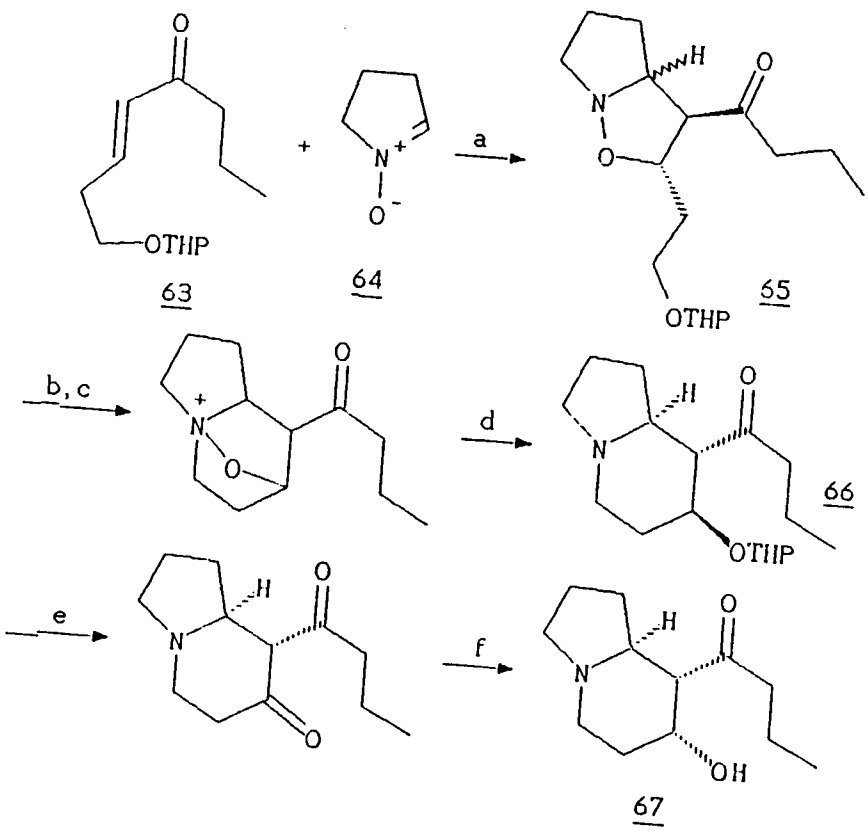


Reagents: a) CH_3COOH; b) $HC{\equiv}CCO_2Et$.

Cycloaddition of nitrones has been developed into a versitile tool for the formation of alkaloids.[57] Kametani and his colleagues[58] employed a nitrone cyclization in their synthesis of elaeokanine C (67) (Scheme 19). The addition of Δ^1-pyrroline-1-oxide (64) to the trans enone 63 produced 65 as a 2:3 mixture of diastereomers. Cyclization and N-O bond cleavage with epimerization of the proton

adjacent to the carbonyl yields 66. Jones' oxidation followed by reduction to provide the correct alcohol stereochemistry completed the synthesis.

Scheme 19



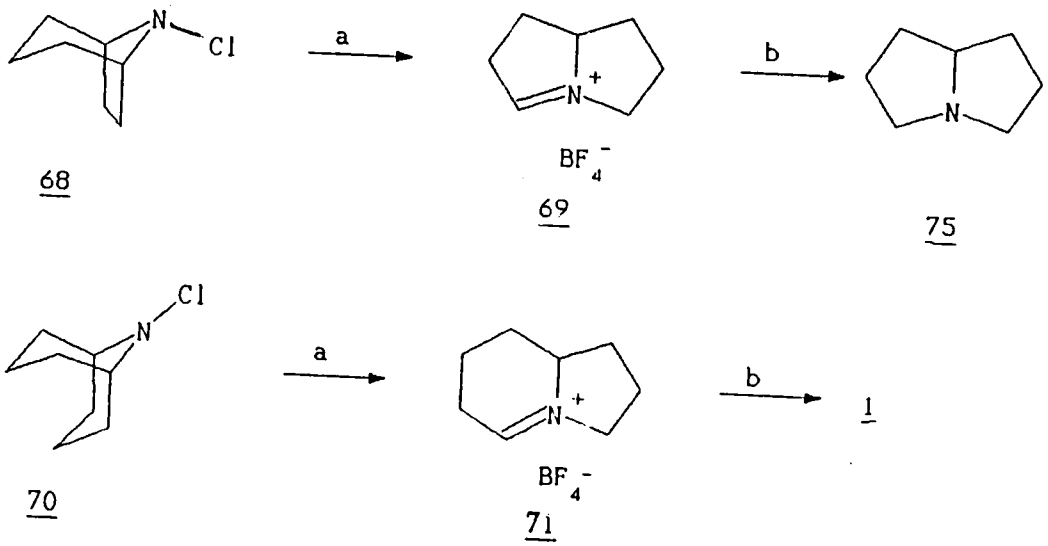
Reagents: a) $C_6H_6CH_3$, Δ; b) 1M HCl, THF; c) MsCl, py; d) Zn, HOAc-H_2O; e) Jone's oxidation; f) $NaBH_4$.

Micsellaneous Methods.

The silver-induced rearrangement of N-chloroamines is the basis for a method used by Schell and co-workers in the synthesis of pyrrolizidine and indolizidine nuclei[59,60]

(Scheme 20). N-Chloronortropane (68) on exposure to silver tetrafluoroborate in benzene underwent a rearrangement to form the unisolated intermediate iminium ion 69. Sodium cyanoborohydride reduction gave 75 in high yield. Similarly, N-chlorogranatinine (70) produced 1 by way of the iminium ion 71 in 92% yield.

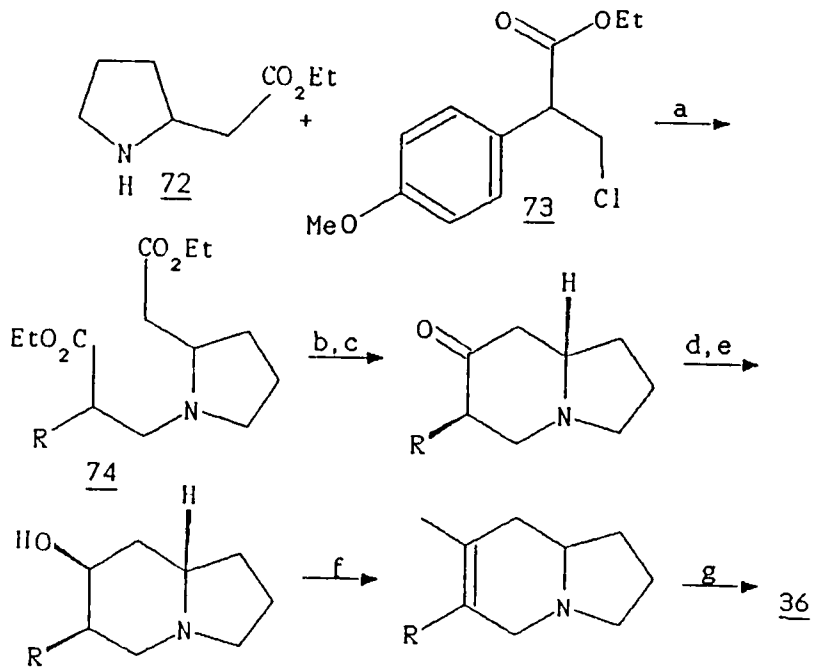
Scheme 20



In a synthesis of ipalbidine (36), Govindachari's group used a Dieckmann condensation to accomplish the formation of the indolizidine ring system[61] (Scheme 21). N-Alkylation of ethyl 2-pyrrolidinylacetate (72) with phenethyl chloride 73 produced the diester 74 whose Dieckmann reaction followed by immediate hydrolysis and decarboxylation of the Dieckmann products provided the needed indolizidine ketone. The synthesis was completed by the addition

of methyllithium to the carbonyl followed by dehydration and removal of the methyl ether on the aromatic ring.

Scheme 21



Reagents: a) K_2CO_3, $C_6H_6CH_3$, Δ; b) PhCK, Et_2O-THF; c) 2M HCl, Δ; d) CH_3Li, THF-Et_2O; e) 2M HCl; f) H_2SO_4, H_2O, Δ; g) $AlBr_3$, CS_2.

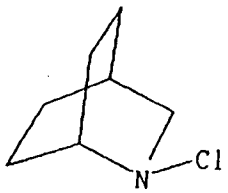
CHAPTER II

RESULTS AND DISCUSSION

Of the many imaginative and creative methods described in the previous chapter, most fail at the problematic task of stereochemical control. Typically, the strategies focus on a cyclization to form a pyrrolidine or piperidine ring in the final step and, consequently, generate epimers in those systems which lack sufficient intramolecular interactions to prejudice the mode of cyclization. One approach to this problem is to create an intermediate in which the stereochemical centers can be introduced readily and with high efficiency. A bond migration is then induced which would maintain the integrity of the stereochemical centers while producing the desired ring system. The silver induced rearrangement of a secondary N-chloramine is one method in which this may be accomplished and is the focus of this chapter.

The chemistry of N-chloramines has been studied by several groups interested in understanding the mechanisms of the reactions and in developing new synthetic reactions. The most notable work has been that of Gassman and co-workers who studied the rearrangement reactions of a number of cyclic N-chloramines.[62] In their first reported example, N-chloroisoquinuclidine (75) was rearranged to the amino ether 76 in 60% yield using refluxing methanolic silver

nitrate.[63,64] Cyclobutylamine 77 was shown to undergo ring expansion to give pyrrolidine 78 after sodium borohydride reduction.[65] Bicyclic N-chloramines 79 and 80 were rearranged to give 81 and 82 respectively.[66,67]



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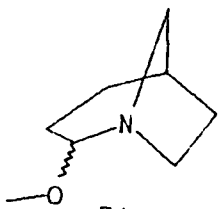

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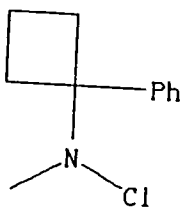

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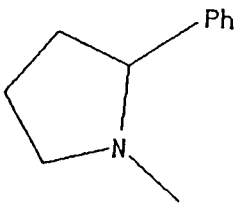

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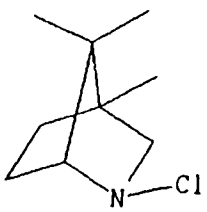

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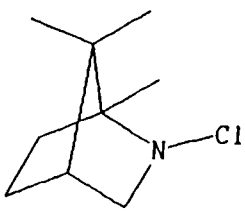

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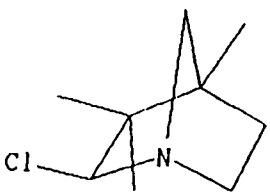

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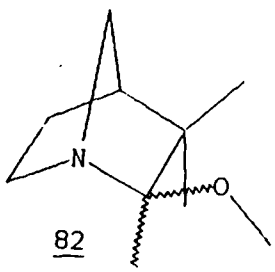
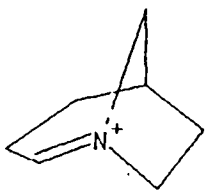


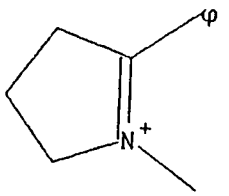
82

The alkyl migrations in each of the above cases paralleled those that would be predicted in the analogous carbocyclic cation systems and, therefore, indicated that an electron-deficient nitrogen species, or nitrenium ion,

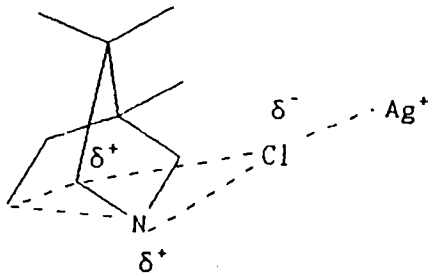
might be involved. Alkyl migration to such a nitrenium ion would produce an imminium ion. Gassman concluded that the products he observed were derived from this imminium ion. Solvent attack on imminium ion 83 would provide 76. Reduction of 84 would afford 78. Gassman reasoned that internal return of chloride in a complex such as 85 would account for the chlorine found in 81.[66]



83



84



85

The parent amine was obtained in many of the rearrangements studied. Gassman attributes this to hydrogen abstraction by a triplet state nitrenium ion.[62] It can be postulated that the N-Cl bond breaks heterolytically in the

presence of silver to form a singlet nitrenium ion (86). Once produced, this species can undergo the rearrangement reaction or intersystem crossing to a triplet nitrenium ion (87). Abstraction of a hydrogen by the triplet would afford a radical cation (88) which is an efficient hydrogen abstractor[68] and could provide 89.



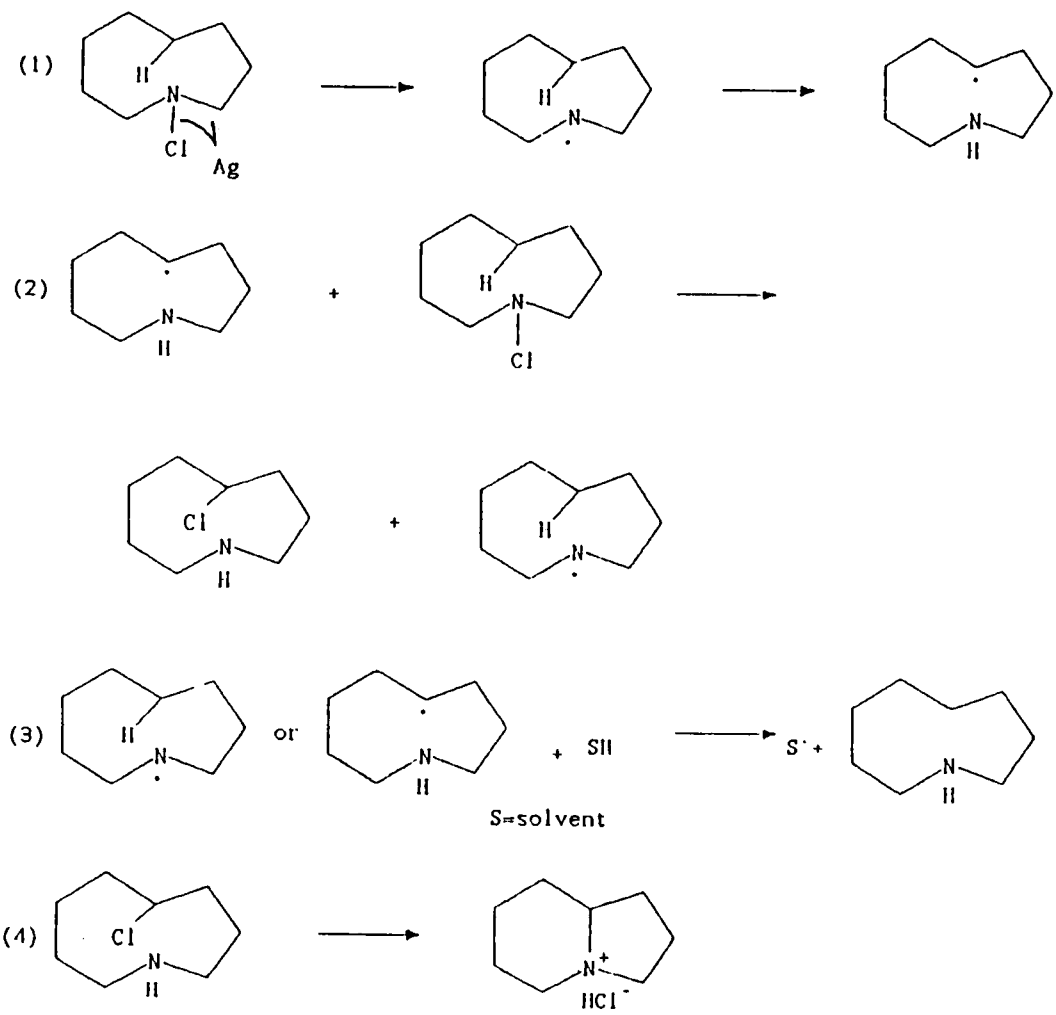
86 87 88 89

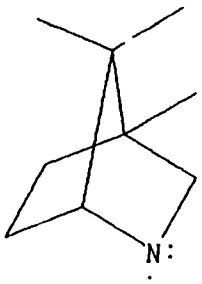
Edwards and collaborators in exploring the cyclization of N-chloroazacyclononane (50) to indolizidine (1) (Scheme 13, p.21) came to a different conclusion concerning the involvement of nitrenium ions.[50] They attribute the appearance of parent amine in the reaction to be a product of homolytic cleavage of the N-Cl bond. The amount of parent amine increased in the presence of Ag^{o}. Furthermore, the reaction was found not to give bicyclic products upon exposure to air. Based upon this evidence, Edwards forwarded the radical mechanism as shown in Scheme 22.

On the basis of the aforementioned results and other results, Edwards concluded that "nitrenium ions are not generated from simple secondary chloramines in the presence of silver ions at room temperature."[69] In response to this, Gassman generated the aminyl radical 90 in the ground and excited states and compared its reactions to those of 79.[70] In each radical case the main product obtained was 91, a

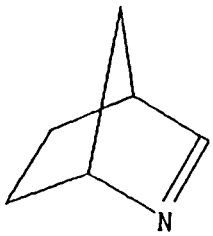
product that was absent in the silver induced rearrangement of 79.

Scheme 22





90



91

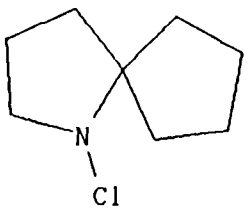
Schell and co-workers,[59,60] in a study preliminary to the work outlined in Scheme 20 (p.27), observed ring contraction reactions when N-chloronortropane (68, p.27), N-chlorogranatanine (70, p.27), and N-chloro-trans-decahydroquinoline (92) were treated with refluxing methanolic silver nitrate. When the products of these reactions were reduced with sodium cyanoborohydride, it was observed that 68 produced 35% of pyrrolizidine (75,p.27), 70 yielded 25% of pyrrolizidine acetal 93, and 92 yielded 13% of acetal 94. It is plausible that acetals 93 and 94 are derived from the formation and rearrangement of a β-chloroenamine produced after the formation of an imminium ion intermediate.[71,72]

To reduce the possibility of side reactions, Schell and Ganguly[60] explored the action of silver tetrafluoroborate on N-chloramines in anhydrous benzene. They speculated that the poor hydrogen atom donating ability of

benzene would reduce hydrogen abstraction side reactions, and that the reaction conditions would force the precipitation of the imminium ion intermediate which would reduce undesirable oxidation reactions. When N-chloramine 70 was exposed to these conditions it underwent rearrangement to 95 which precipitated from solution with the silver chloride. Carbon-13 NMR spectroscopy of the crude reaction product confirmed that only 95 had been present. This marked the first occasion that an ionic product was isolated from a silver-induced rearrangement of a N-chloramine. Reduction of 95 with sodium borohydride produced indolizidine (1, p.2) in near quantitative yield. With a high yielding N-chloramine rearrangement reaction at hand, it was desired to apply this reaction to the synthesis of indolizidine alkaloids.

Indolizidine system.

There are four bicyclic systems, (96-99), in addition to N-chlorogranatinine (70, p.27), which may give rise to the indolizidine ring system upon rearrangement. System 98



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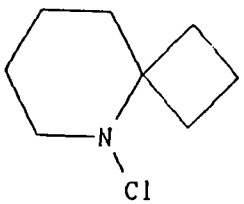

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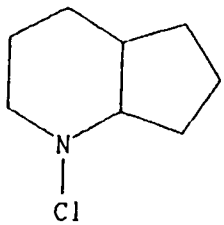

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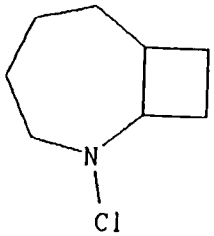
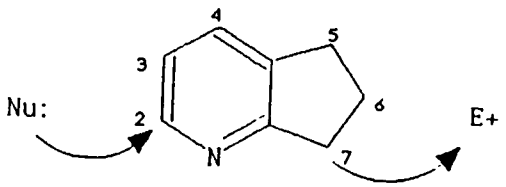


99

is an attractive system since its parent amine is readily obtained by the reduction of 6,7-dihydro-5*H*-1-pyrindine (2,3-cyclopentenopyridine) (100). The parent pyrindine, 100 possesses much potential for the incorporation of substituents[73] by nucleophilic addition on the pyridine ring or addition of an electrophilic species at C-7 as shown. Nucleophiles such as alkyllithiums and Grignard reagents

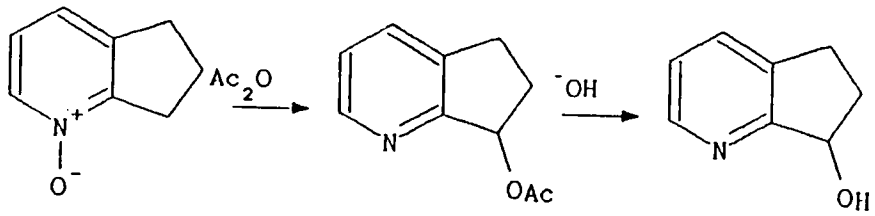


100

have a preference for attack at the C-2 position of the pyridine ring.[74] Attack at C-4 is generally not observed. Modification of the pyrindine by formation of the N-oxide, quaternization with alkyl or acyl groups, or by replacement of the C-2 proton by a halide can be used to facilitate reaction with a nucleophile.[73,74]

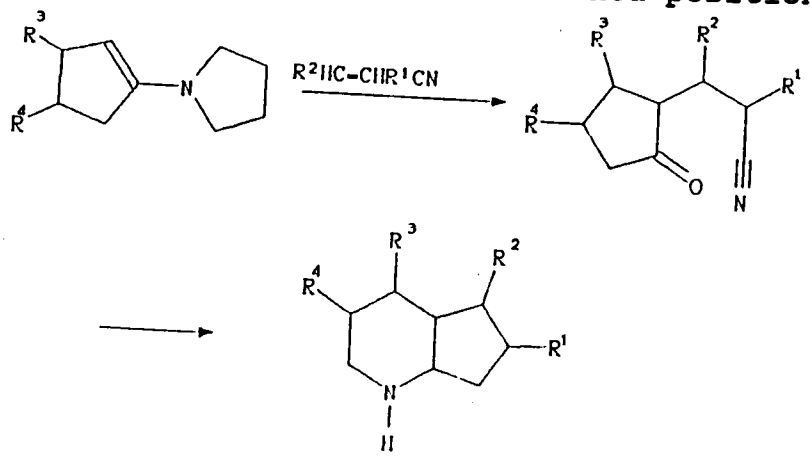
C-7 of 100 has been shown to undergo condensation reactions very readily with aldehydes.[75] The 7-lithio salt of 100 is readily made at dry ice temperatures by the addition of an alkyl lithiate. This allows for substituent incorporation at this position by an S_N2 reaction with the appropriate electrophile.[73] Modification of C-7 may also be accomplished by rearrangement reactions of an acylated

N-oxide of 100 which leads to the incorporation of an acyloxy group at C-7.[76]

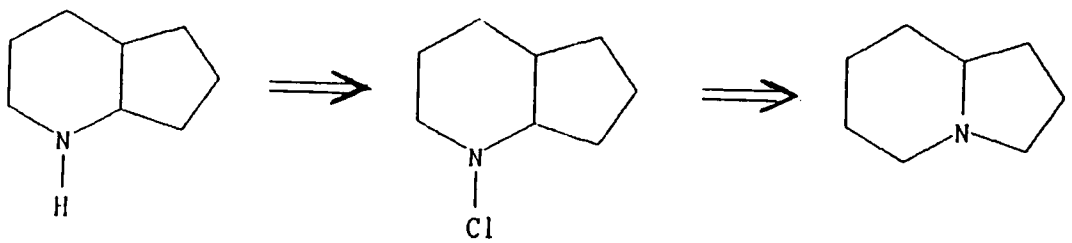


Hydrolysis to the alcohol followed by oxidation to the carbonyl provides a site for nucleophilic addition and modification of C-6 by its interaction with electrophiles. Displacement of the C-7 acyloxy substituent (or its derivative, tosylate,etc.) would also allow alteration of this site by nucleophilic substitution.

Pyrindines of other substitution patterns and their reduced forms are also readily available.[73] Michael addition of a substituted cyclopentanone enamine to an acrylonitrile followed by reductive cyclization provides a method of incorporating substituent at the C-3, 4, 5, and 6 positions in addition to the aforementioned positions. [77]



Many of the stereochemical relationships between substiuents in the indolizidine precurser can be established by judicious choice of the method of reduction of the pyrindine. For example, reduction of the pyridine ring by dissolving metal techniques favors the establishment of a trans relationship between the brigehead protons[78] while catalytic reduction with hydrogen provides a cis relationship at the bridgehead protons[79]. Catalytic reduction often introduces a cis relationship between the bridgehead protons and the protons present at other substitution sites on the pyridine ring. [79] The combination of partial reduction by a metal hydride and one of the above techniques may also be used to introduce desired stereochemical patterns into the octahydropyrindine. Indolizidine synthesis could therefore be envisioned as the reduction of a suitably substituted pyrindine followed by rearrangement of its N-chloramine.



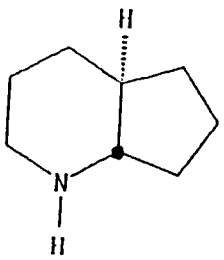
Schremmer and Schell[80] instituted a model-study using a mixture of cis and trans octahydro-1-pyrindine obtained by the reduction of 2,3-cyclopentenopyridine. N-Chlorina-

tion followed by exposure to silver tetrafluoroborate in anhydrous benzene produced an immediate precipitation of silver chloride. Carbon-13 NMR spectroscopy of the crude product indicated a compound identical to the imminium ion 71 observed when Ganguly treated N-chlorogranatanine (70, p.27) with silver tetrafluoroborate.[59] Sodium cyanoborohydride reduction of the crude product yielded indolizidine (1, p.2), cis octahydro-1-pyrindine, and an unidentified product. Since the product mixture was free of any trans-octahydro-1-pyrindine, it was important to explore the differences in the reactivity of the cis and trans isomers. This exploration is the starting point for this research into the use of N-chlorooctahydro-1-pyrindine as a precursor of indolizidine.

The sodium metal reduction[78] of 2,3-cyclopentenopyridine in ethanol produced a 1:5 mixture of cis and trans-octahydro-1-pyrindines. Recrystallization of the hydrochloride salts of the mixture from 95% ethanol afforded pure trans octahydro-1-pyrindine hydrochloride as determined by its melting point.[78] Carbon-13 NMR spectroscopy of the free base (101) of this compound indicated eight carbon species present. C-2, C-4a, C-7a were found to have chemical shifts of 47.70, 45.61, and 65.08 ppm respectively. These chemical shifts are comparable to the observed chemical shifts of 47.33, 43.34, and 62.09 ppm for

the analogous C-2, C-4a, C-8a in trans decahydroquinoline.[81]

Hydrogenation of 2,3-cyclopentenopyridine in glacial acetic acid with Adams' catalyst[79] produced a 4:1 mixture of cis- and trans- isomers. Repetitive recrystallization of the hydrochloride salts from 95% ethanol gave pure cis octahydro-1-pyrindine hydrochloride as determined by melting point.[79] Carbon-13 NMR spectroscopy of the corresponding free amine (102) also indicated eight carbon species with C-2 at 46.23 ppm, C-4a at 39.81 ppm and C-7a at 59.33 ppm. These chemical shifts are comparable to the observed chemical shifts of 46.58, 35.85, and 55.03 ppm for the analogous C-2, C-4a, and C-8a in cis decahydroquinoline.[81]



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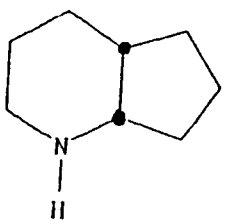


102

Comparison of the possible conformations of the cis and trans octahydropyrindines reveals that the cis-octahydropyrindine should have gauche butane like interactions

which are not present in the trans compound.[82] These steric interactions should represent themselves in the carbon-13 NMR spectra as signals shifted up-field relative to the analogous resonances in the trans compound.[83,84] Analysis of the carbon-13 NMR spectra of the dissolving metal reduction product and the product obtained from the catalytic hydrogenation indicates that the chemical shifts assigned to the bridgehead carbons (C-4a and C-7a) are 5.8 ppm further upfield in the catalytic product relative to the dissolving metal product. This indicates that the product obtained from the catalytic reduction is indeed the cis fused ring system.

N-Chlorination of these amines was accomplished by treatment with a saturated solution of N-chlorosuccinimide in methylene chloride.[85] Attempts to purify the N-chloramine led to the isolation of a compound which was extremely sensitive to shock and heat. Early literature on N-haloamines indicate that this property can be considered common among compounds of this category.[86] Of interest is N-chlorogranatinine isolation as a stable compound.[59] N-Chlorogranatinine may owe its stability to a reluctance to undergo elimination reactions that are possible in other N-chloramines.

The crude N-chloro-octahydropyrindine was added to

silver tetrafluoroborate in anhydrous benzene at 40°C. When the trans isomer was subjected to these reaction conditions, a precipitate formed, and thin layer chromotagraphy indicated no starting chloramine after one-half hour. Work-up of the reaction mixture followed by sodium cyanoborohydride reduction gave indolizidine as the only product in 90% yield. The cis isomer, under these reaction conditions, appeared to react at a similar rate as the trans but produced indolizidine and an unknown compound which did not correspond to either of the parent amines. Appearance of this unknown was unreproducible and conditions were explored to try to enhance its production. When the cis isomer was exposed to the same conditions at room temperature only indolizidine was obtained without any side products or starting amine present. It was observed that when these reaction conditions were repeated with silver tetrafluoroborate that had been exposed to the atmosphere, or when meticulous care was not exercised to exclude moisture from the reaction, some parent amine could be found in the reaction products.

A dramatic change was seen in the reaction when the solvent was changed to purified methylene chloride. Upon introduction of a mixture of cis and trans N-chloramine, immediate precipitation of silver chloride was observed and the starting materials were exhausted within 10 min. This

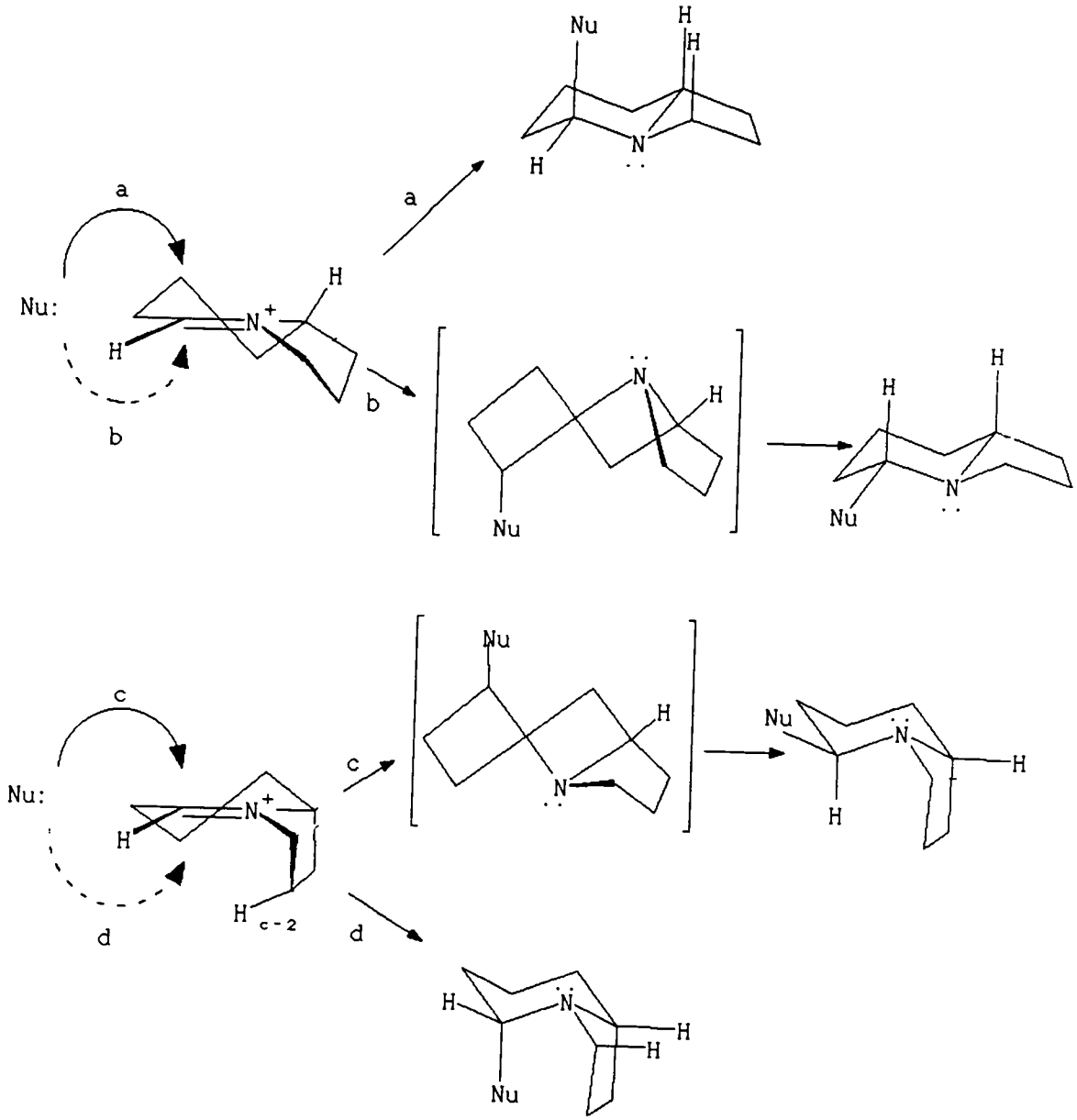
is approximately three times faster than the disappearance of the same cis-trans mixture at the same temperature and concentration in benzene. Silver salts are known to exist as complexes with aromatic compounds such as benzene.[87] This complexation may account for the higher temperatures required and lower rate of reaction in benzene as compared to methylene chloride. Product yields of the rearrangements in each of these solvents compared well. Purified methylene chloride was therefore selected for use in subsequent rearrangements due to the milder conditions, higher rate of reaction, and experimental simplicity it allowed.

Since many indolizidine alkaloids possess substitution at C-5, it would be advantageous to trap the imminium ion intermediate with a nucleophile that would enable further construction at that position. Cyanide ion has been found be an efficient nucleophile for this task.[88]

Stevens had studied nucleophilic attack upon indolizidine imminium ions and had observed a stereochemical preference for attack on the molecule.[33] His rationale is outlined in Scheme 23.

There are four possible conformations in which maximum orbital interaction with respect to the nucleophile and the developing lone pair on the nitrogen can be maintained. Attack of the nucleophile by two of these pathways, b and c, are disfavored due to the involvement of a higher energy

Scheme 23

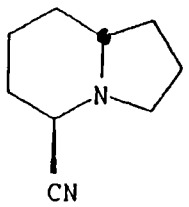


boat-like transition state they adopt in order to fulfill stereoelectronic demands. A third, shown by d, has a severe peri interaction with the proton on C-2. The remaining interaction, a, would lead to a product with an axial

substituent at C-5. This axial incorporation has been observed in the addition reaction of cyanide to tetrahydropyrindines.[89]

Trapping of the rearrangement products was accomplished by the addition of an aqueous solution of sodium cyanide at pH 5 to a reaction of silver tetrafluoroborate with cis and trans N-chloropyrindines in methylene chloride. This afforded an 86% yield of cis-5-cyanoindolizidine (103) upon work-up. An upfield shift of 6.7 ppm was observed for C-8a, as well as, upfield shifts of 4.1 and 4.0 ppm for C-3 and C-7 respectively. The large γ-effects observed here indicate that the cyano group is axial and are consistent with the literature values of -4 ppm and -5.5 ppm for γ_{CCC} and γ_{CNC}-effects for an axial cyano group on a piperidine ring.[89] An α-shift of -2.4 ppm for C-5 and an α-shift of 1.8 ppm for C-6 are also consistent with the literature values of -2 ppm and +2 ppm for an axial cyano group on a piperidine ring.[89] Proton NMR spectroscopy reveals the C-5 proton as a overlapping doublet of doublets with coupling constants of 4.26 and 2.55 Hz. Molecular mechanics calculations using Allinger's MM2[90] program indicate that an equatorial proton at C-5 should have dihedral angles of 53 and 63 degrees to the axial and equatorial protons of C-6 respectively. The coupling constants corresponding to these angles are 4.35

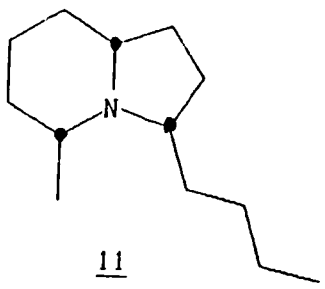
and 2.01 Hz[91] and are in agreement with the observed values. Calculations for an axial C-5 proton yield dihedral angles of 173 and 55 degrees with corresponding coupling constants of 11.80 and 3.42 Hz.



103

Monomorine I:

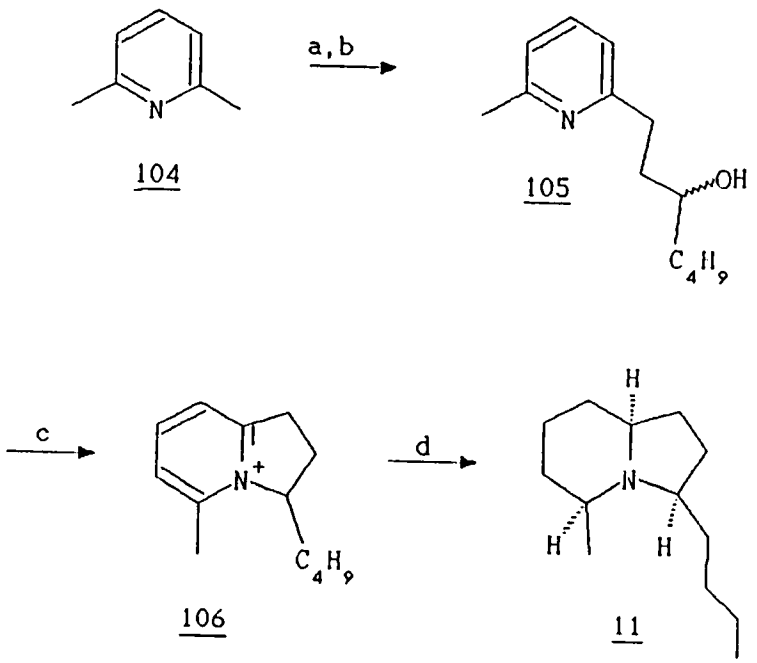
Monomorine I (11), a 3,5-dialklyindolizidine found in the trail pheromone mixture of the Pharaoh ant,[19] seemed to be a likely candidate for the application of this silver-induced ring interchange technique to the synthesis of a natural product. This compound possesses an all-cis relationship between the bridgehead carbon, and the alkyl substituents.[92]



11

Several syntheses of this intriguing alkaloid have appeared in the literature. A synthesis by Stevens has already been discussed (Scheme 6, p.12). For comparative purposes, a review of some of these methods is warranted. The first synthesis of monomorine I was accomplished by Sonnet and Oliver[93] (Scheme 24). Sequential treatment of 2,6-lutidine (104) with n-butyllithium and hexene 1-oxide gave the alcohol 105. Cyclization of 105 with triphenylphosphine dibromide provided the dihydroindolizium bromide 106. Hydrogenation of 106 over Adams' catalyst gave the all-cis monomorine I.

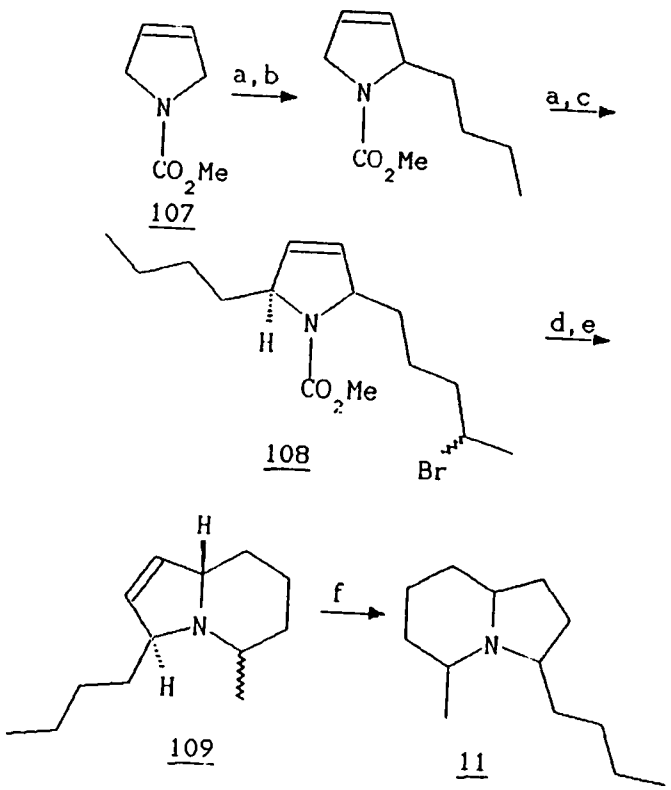
Scheme 24



Reagents: a) BuLi; b) hexene-1-oxide; c) Ph_3P^+Br; d) H_2, PtO_2.

A synthesis by Macdonald focuses on the alkylation and cyclization of a substituted 3-pyrroline.[94] The anion of 1-(methoxycarbonyl)-3-pyrroline (107) was alkylated with 1-bromobutane and the product subsequently alkylated a second time with 1,4-dibromopentane to give the trans-2,5-dialkyl-pyrroline 108. N-Decarbomethoxylation of the pyrroline and

Scheme 25



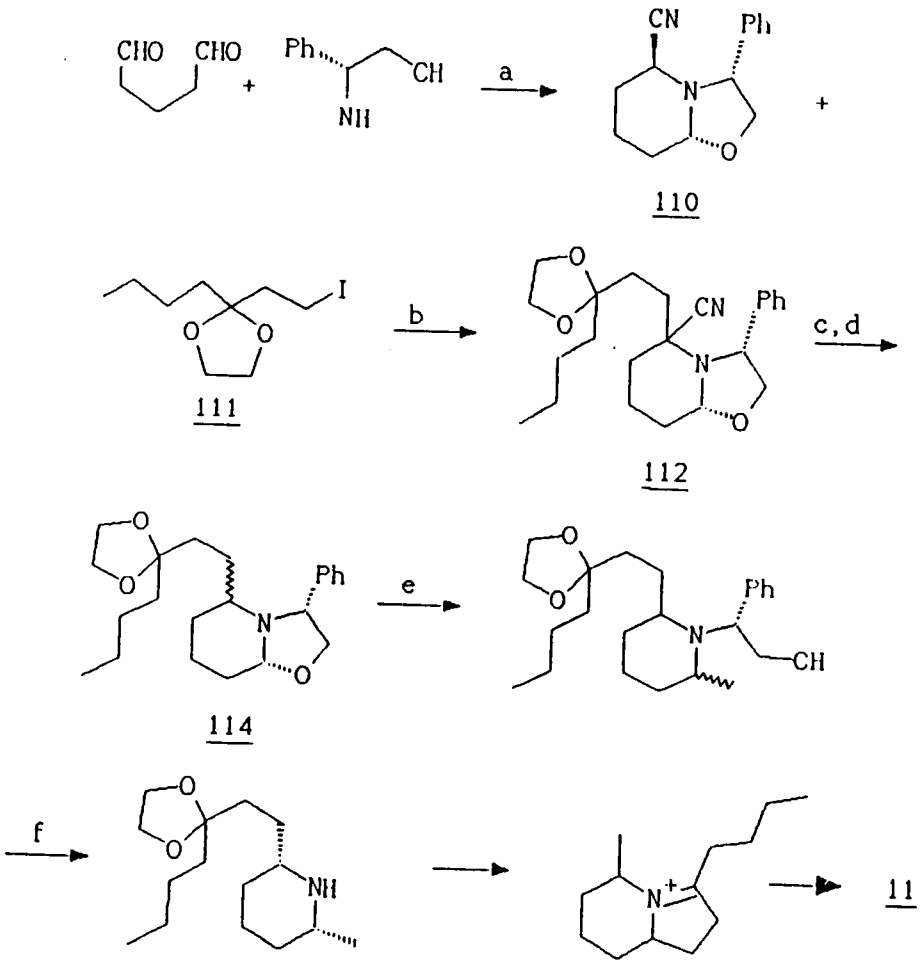
107 108 109 11

Reagents: a) LDA, THF; b) $CH_3CH_2CH_2Br$; c) 1,4-dibromopentane; d) KOH; e) PtO_2, AcOH.

indolizidine formation by cyclization at the nitrogen gave dehydroindolizidine 109 as a 1:1 mixture of C-5 epimers. Catalytic reduction of 109 led to monomorine I in an overall yield of 15% (Scheme 25).

An enantiomeric synthesis of (-)-monomorine I was accomplished by Royer and Husson[95] using the non-racemic

Scheme 26

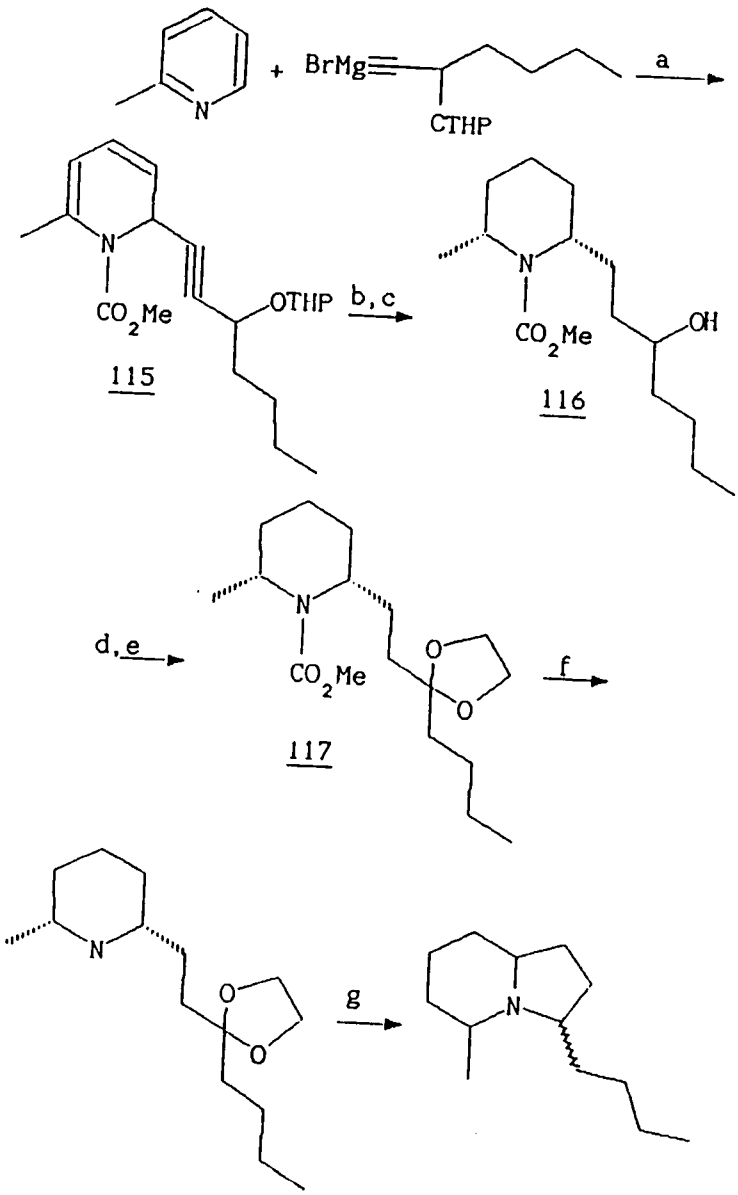


Reagents: a) KCN, pH3-4; b) LDA, THF; c) $AgBF_4$, THF; e) $Zn(BH_4)_2$; e) CH_3MgI; f) H_2, 10% Pd-C.

intermediate 2-cyano-6-oxazolopiperidine 110. This compound was prepared by the one-pot reaction of (-)-phenylglycinol, glutaraldehyde, and potassium cyanide. Alkylation of the anion of 110 with iodo ketal 111 led to the formation of 112. Decyanation of 112 was accomplished by complexation of the nitrile with silver tetrafluoroborate followed by reduction with zinc borohydride to give 113 as a 3:2 mixture of oxazolines. Reaction of 113 with methylmagnesium iodide afforded a 4:1 mixture of alcohol 114 and its trans epimer. Exposure of 114 to catalytic hydrogenation conditions resulted in hydrogenolysis of the chiral auxiliary, liberation of the ketal and reductive cyclization to give a 9:1 mixture of monomorine I and its C-3 epimer. The overall yield of monomorine from 110 was 19% (Scheme 26).

Yet another approach utilizing a cyclization onto nitrogen was provided by Yamaguchi and co-workers[96] (Scheme 27). 2-Methylpyridine was allowed to react with 3-(2-tetrahydropyranyloxy)heptynylmagnesium bromide in the presence of methyl chloroformate to give the α-alkylated 1,2-dihydropyridine 115. Hydrogenation of 115 over 5% Pd-C catalyst and deprotection of the alcohol produced the cis-piperidine 116. Subsequent Jones' oxidation and ethylene glycol protection of the resulting ketone gave 117. Hydrolysis of the urethane and ketal followed by catalytic reduction afforded monomorine I in 32% overall yield .

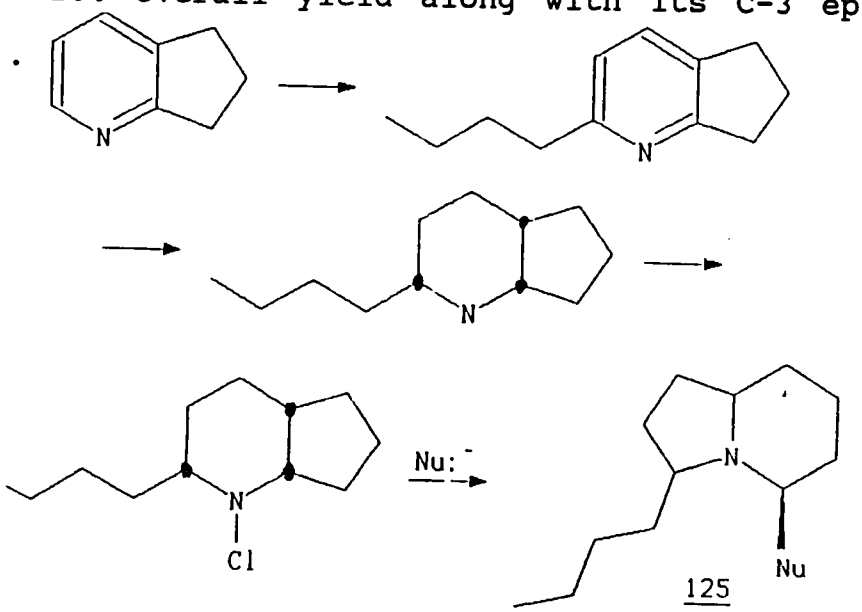
Scheme 27



Reagents: a) $ClCO_2Me$, THF; b) H_2, Pt-C/MeOH; c) Amberlyst H-15, MeOH; d) CrO_3-H_3O^+, acetone; e) $(CH_2OH)_2$, p-TsOH, PhH; f) KOH, NH_2NH_2, H_2O, $(CH_2OH)_2$; g) aq. HCl/THF.

Most recently there appeared in the literature a synthesis by Kibayashi, et al. employing a nitroso-Diels-Alder

cycloaddition[97]. Periodate oxidation of the hydroxamic acid 118 generated the acyl nitroso compound 119 *in situ* which underwent an intramolecular [4+2] cycloaddition to give the bicyclic 1,2-oxazine 120. Hydrogenation of 120 followed by a Grignard reaction and dehydration afforded enamine 121 which was hydrogenated to give 122 as a single isomer. Reductive cleavage of 122 with zinc in aqueous acetic acid and protection of the nitrogen furnished the cis-2,6-dialkylpiperidine 123. Collins' oxidation of 123 provided the ketone 124. Reductive cyclization of 124 under conditions which removed the Cbz group afforded monomorine I in 20% overall yield along with its C-3 epimer (Scheme 28).



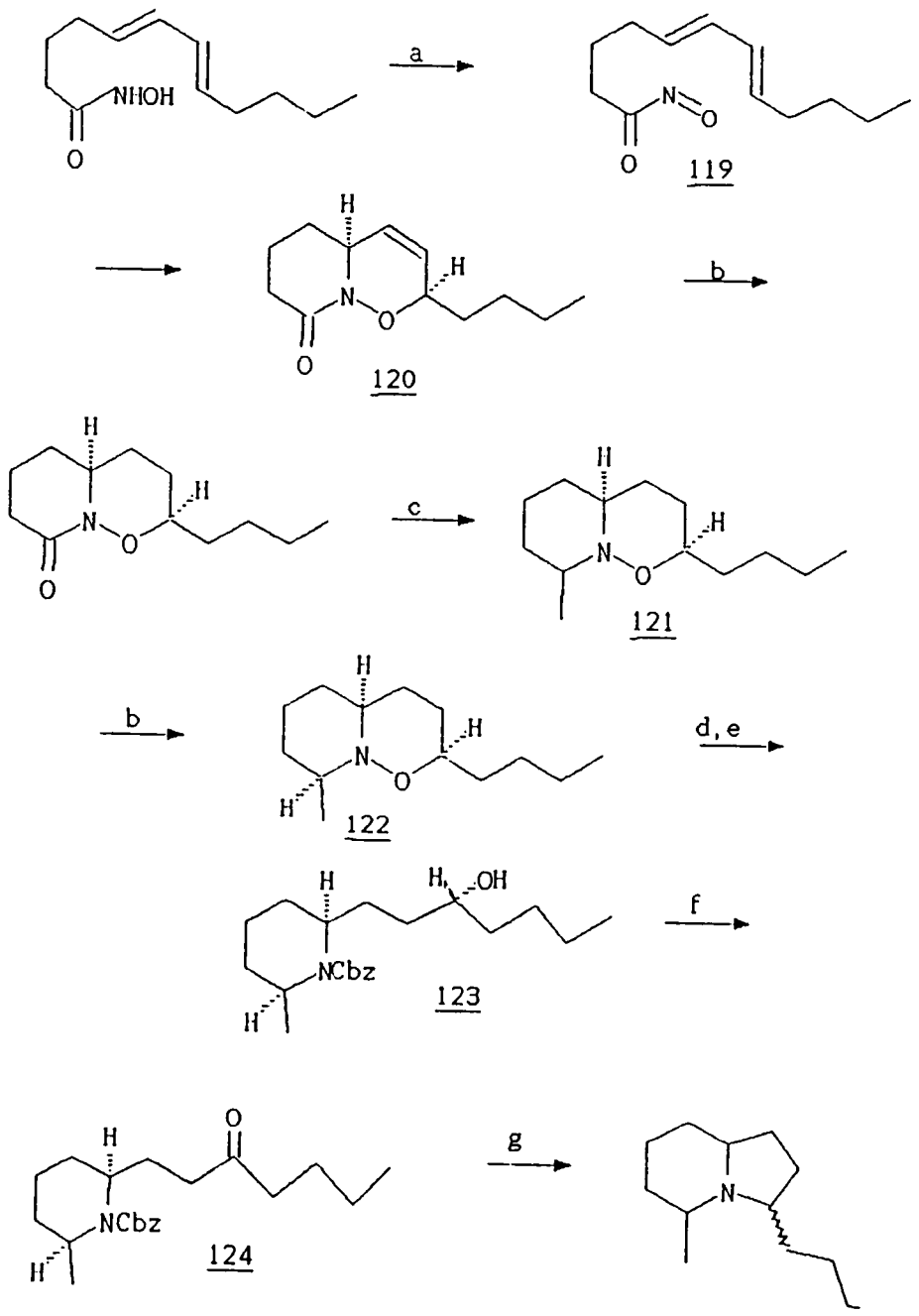
125

Synthesis of this compound by the silver induced ring interchange trapping method described earlier in this chapter could be envisioned as the incorporation of the n-butyl group on C-2 of 6,7-dihydro-5H-1-pyrindine followed by stereospecifc reduction of the pyridine ring to give a cis

relationship between the butyl group and the bridgehead carbons. N-Chlorination and rearrangement of this substituted octahydropyrindine could be followed by trapping of the resulting indolizidinium ion to give substitution at C-5.

The introduction of the alkyl group at C-5 may be accomplished by trapping with an alkyl lithium. Trapping with such a nucleophile, based on the cyanide trapping of the indolizidinium ion described earlier and the work done by Stevens,[33] would most likely attack by path a as shown in Scheme 23 (p 44) to produce a compound (125) whose methyl group at that position is epimeric to that desired in monomorine I. Alternatively, the indolizidinium ion could be captured using the cyanide ion as was done in the earlier study. This would enable the manipulation of the C-5 site by taking advantage of the acidic nature imparted to the proton at this location by the cyano group. A methyl group could thus be introduced by the base induced epimerization of the cyano group to the equatorial position followed by reduction first to an aldehyde and then by a Wolff-Kishner reduction to the methyl group. Another method would be to create an anion by abstraction of the C-5 proton with a base and then exposing the anion to an electrophile such as iodomethane. The cyano group could subsequently be removed by exposure to silver tetrafluoro-

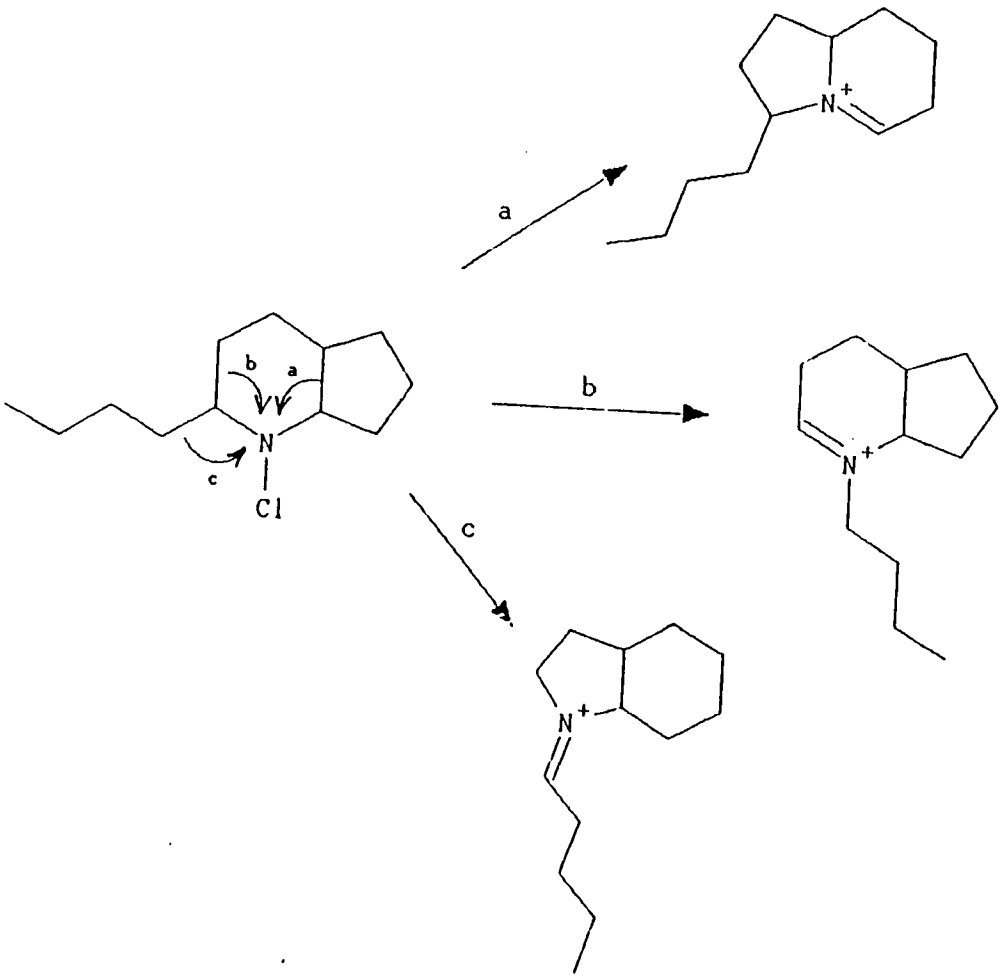
Scheme 28



Reagents: a) n-$Pr_4N(IO_4)$; b) MeMgBr, Et_2O; c) $NaBH_3C$; d) Zn, Na_2CO_3, CH_2Cl_2; f) CrO_3-2Py, CH_2Cl_2; g) H_2, 5%Pd-C, MeOH.

borate[98] and the resulting imminium ion reduced with sodium cyanoborohydride. The latter method would be able to take advantage of the stereochemical preference exhibited by the indolizinium ion for attack on the side leading to the cis product.

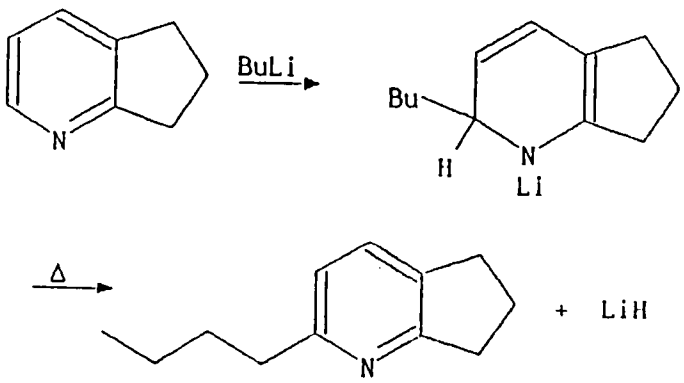
In addition to being a good candidate for synthesis, this compound also would make an interesting model for the



study of migratory aptitudes of alkyl groups on a tertiary carbon adjacent to the N-chloramine. It could give some insight whether the ring interchange process (bond migration a) competes with butyl migration (bond migration b) or with ring contraction (bond migration c).

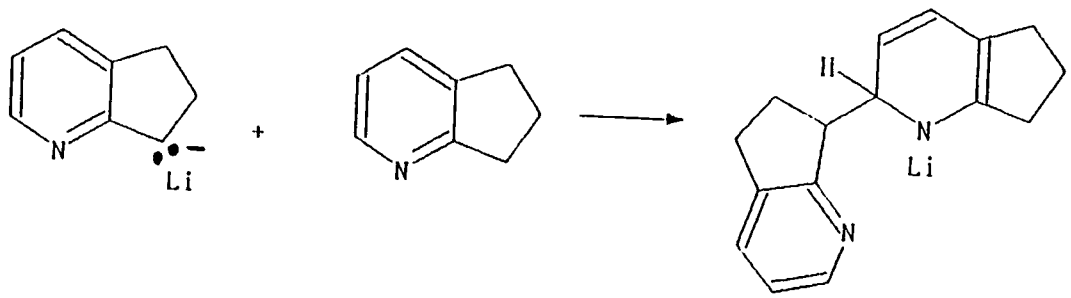
Alkylation of the pyrindine was accomplished by the method of Ziegler[99]. This method involves the nucleophilic attack of an orgnaometallic compound, in this case n-butyllitium, upon the pyridine ring. This attack occurs with preference at the C-2 position and produces a dihydropyridine intermediate which undergoes rearomatization when lithium hydride is thermally removed.[100] This alkylation process is outlined in Scheme 29.

Scheme 29



Addition of n-butyllithium to cyclopentenopyridine in refluxing toluene produced only a 40% yield of 2-butyl-1-pyrindine (125) after completion of the reflux period and reaction workup. A large amount of oligomeric material was

also recovered from the reaction. This is presumably the result of nucleophilic attack of the 7-lithiopyrindine, formed by the abstraction of the benzylic proton[71], upon the aromatic pyridine ring of another pyrindine and subsequent reactions of the dimeric, partially reduced materials. The yields for this reaction were lower than those observed for pyridine and may be due a higher electron density in the aromatic ring produced by the 7-lithio salt which reduces the ease of attack by the nucleophile.



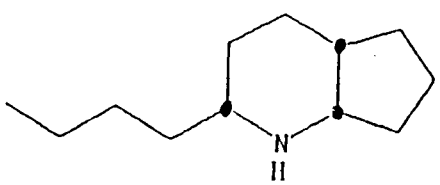
A variety of methods were employed to try to increase the yield of the 2-butylpyrindine. Neither reverse addition nor manipulation of the temperature made any improvement in yield. The organometallic reagent was changed to n-butylmagnesium bromide. This reduced the amount of oligomeric material, but also provided a lower yield of the desired product than n-butyllithium. The pyrindine was converted into the N-oxide in anticipation that the lithium oxide would facilitate the rearomatization of the ring by being a better leaving group. Again this failed to produce

an increase in yield. Conversion of the N-oxide to an ester group was also attempted. Not surprisingly, it was found that saponification of the ester occurred preferentially to the nucleophilic attack on the ring.

Reduction of a multiply-substituted pyridine ring by hydrogenation over Adams' catalyst has been demonstrated to be effective in producing piperidines in which the primary reduction product has an all-cis configuration between the substituents on the ring.[101] Hydrogenation of the 2-butylpyrindine under the same conditions utilized for the reduction of pyrindine to the cis-octahydropyrindine produced little of the fully reduced compound. Reduction of the pyrindine as its hydrochloride salt under the same conditions also produced little perhydro compound. Upon changing the solvent to anhydrous ethanol, the 2-butylpyrindine hydrochloride reduced readily and nearly quantitatively in a few hours.

Carbon-13 NMR analysis of the hydrogenation mixture indicated only 12 carbon species present and hence only one product was obtained instead of the mixture of isomers obtained in the reduction of the unsubstituted pyrindine. The chemical shift assignments were made on the basis that no significant differences were expected from the parent unsubstituted heterocycle other than those due to induced substituent effects. The bridgehead carbons, C-4a and C-

7a, where found to have chemical shifts of 59.14 and 38.97 ppm, respectively, which are comparable to the shifts of 59.33 and 39.81 ppm observed in the unsubstituted cis-octahydropyrindine. The nearly identical value observed for C-7a indicates an almost negligible γ-effect from the butyl substituent on C-2. This is consistent with the literature value[102] of a γ-effect for an equatorially oriented alkyl group on a piperidine ring.[102] Had the alkyl group assumed an axial orientation the γ-effect observed would be approximately -6.4 ppm. C-2 was found to have a chemical shift of 56.21 ppm which represents an α-shift of +9.95 ppm which is consistent with the expected +9.3 ppm shift for an equatorial alkyl group on C-2 of a piperidine ring.[102] The reduction compound was therefore assumed to be 126.



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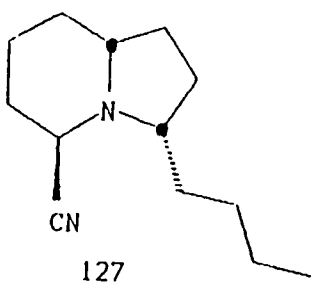
Further conversion of the 2-(n-butyl)-octahydropyrindine into the indolizidine was accomplished by first chlorination of the amine with N-chlorosuccinimide in methylene chloride.[85] The N-chloramine was added in one portion to a slurry of silver tetrafluoroborate in methylene chloride when a white precipitate formed immediately. Thin layer chromatography revealed that no chloramine was present after 15 minutes, at which time an aqueous solution of 10 equivalents of sodium cyanide at pH 4 was added and allowed to stir for 3 hr. The resultant oil was found to consist of only one product as determined by carbon-13 NMR. A chemical shift of 59.10 ppm was assigned to C-8a and is comparable to the chemical shift of 57.79 ppm observed in the 5-cyanoindolizidine. It represents a γ-effect of -5.19 ppm from the axial cyano group on C-5 and a negligible γ-effect for the equatorial butyl group on C-3. This is consistent with a reported γ-effect of -5.5 ppm for a axially oriented cyano group on a piperidine[89] and a γ-effect of 0 ppm for an equatorial butyl group on a pyrrolidine.[103] C-3 was assigned a shift of 61.03 ppm which is consistent with a +14.8 α-effect observed in butylcyclopentane[104] plus a γ-effect of -5.5 ppm for the C-5 cyano group.

Molecular mechanics calculations using the Allinger MM2 program[90] predict that an equatorial proton on C-5 would have dihedral angles of 54° and 62° with the vicinal

protons which would translate into coupling constants of 4.17 and 2.39 Hz respectively. The C-5 proton appears as a doublet of doublets with coupling constants of 4.3 and 2.2 Hz which is in agreement with the calculated values. Based upon these assignments, the structure for the 3-(n-butyl)-5-cyanoindolizidine was determined to be 127.



127

With the cyano group established as being epimeric to the one desired in monomorine I, a decision had to be made to either introduce the methyl group to this position by epimerization of the cyano group followed by a two-step reduction to the methyl group or by alkylation followed by decyanation and reduction. In the first case the epimerization step would most likely lead to a mixture of axially and equatorially oriented products since one could expect some problems due to the buttressing of the equatorial cyano group with the butyl group. Reduction of this

compound would also require the rather violent conditions of a Wolff-Kishner reduction. In the latter case, α-alkylation of a nitrile,[105] decyanation with silver tetrafluoroborate,[98] and reduction of the resulting immium ion[106] all have precedent for being relatively facile and good yielding. Therefore the later method was selected.

Alkylation of 127 did not occur as readily as anticipated. Initially the compound was exposed to lithium diisopropylamide at -78°C for about 15 minutes and then iodomethane was added. Upon work-up of the reaction mixture, starting material was obtained with no epimerization of the cyano group implying that the anion had not been formed or that the nitrile was in the more stable position. The alkylation procedure was repeated at 0°, again without success. Performing the reaction at room temperature resulted in the immediate formation of a precipitate, presumably lithium iodide. Carbon-13 analysis of the product obtained from this reaction revealed that three compounds were present; starting material, the C-5 cyano epimer and mostly N-alkylated material.

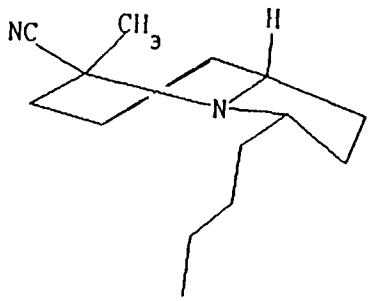
In an attempt to facilitate the formation of the α-anion, the 3-butyl-5-cyanoindolizidine was added to a THF solution of lithium diisopropylamide containing two equivalents of hexamethylphosphoramide. The initial temperature of addition was -78°. The solution was allowed to warm to

0° for 30 minutes at which time TLC indicated that no starting material remained. The solution was cooled to -78° and iodomethane was added. This solution was stirred at -78° for six hours during which time a precipitate formed. The reaction was warmed to room temperature and then quenched with water. Chromatography of the product mixture on alumina provided 37 mg of starting material and a compound whose carbon-13 NMR indicated fourteen carbon species. APT demonstrated that the C-5 position had become quaternary indicating that alkylation had indeed occurred at that site.

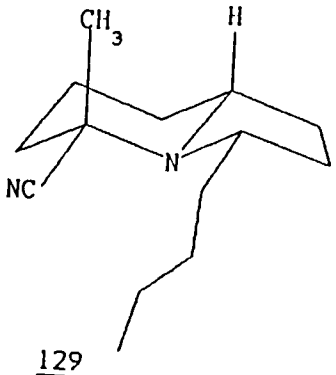
Carbon-13 NMR chemical shift assignments other than the ones obvious from APT experiments were difficult to assess presumably due to ring distortions caused by eclipsing of the C-3 butyl group and the geminal substitutents on C-5. Utilizing the arguments presented earlier for the attack of a nucleophile on the indolizidinium ion, the anion should be of similar conformation due to the general nature of an anion to assume a more planar conformation. The peri interaction of the butyl group would therefore also dictate an addition in the direction which would result in an axial orientation of the methyl group. Since the removal of the cyano group would form the same indolizidinium ion regardless of its original orientation the position of the methyl group in this intermediate is

irrelevant to the eventual synthetic outcome.

Molecular mechanics calculations of the possible conformations of this compound indicate that a twist-boat conformation (128) would reduce the amount of eclipsing between the substitutents and would be 1.61 kcal lower in energy than the normal chair-half-chair conformation[107] (129) assumed by indolizidine compounds.



128



129

Removal of the cyano group was accomplished by the addition of silver tetrafluoroborate to a solution of 128 in anhydrous THF. Following completion of the decyanation, sodium cyanoborohydride in anhydrous methanol at pH 5 was added. Reaction work up and chromatography on an alumina micro column produced 83.4 mg (94%) of a light brown oil whose carbon-13 NMR spectroscopy showed it to be a single product.

Comparison of this compound to the unsubstituted indo-

lizidine revealed that C-1, C-7, C-8, and C-8a did not differ significantly and implies that neither the C-3 butyl group nor the C-5 methyl group are axial. An axial C-3 substiuent would exert a large γ-effect on C-1 and C-8a while an axial C-3 group would exert a similarly large γ-effect on C-7 and C-8a. The chemical shift at 60.13 ppm was assigned to C-5 and represents an α-effect of +7.05 ppm. An α-effect of +5.6 ppm has been observed for an equatorial methyl in piperidine rings.[108] C-2 was determined to have a β-shift of +8.94 ppm which is in agreement with the observed β-effect of +9.1 ppm for methylpyrrolidine.[103] The 62.77 ppm shift which was assigned as the C-3 resonance represents an α-effect of 8.46 ppm. This is consistent with the +9.3 ppm α-effect observed for an equatorial methyl on a pyrrolidine[103] but does not agree well with a +14.8 ppm shift observed in n-butylcyclopentane.[104] This does suggest that the substiuent may assume a psuedoequatorial position due to a syn interaction with the methyl on C-3. This is further supported with a large downfield shift for the α-methylene of the butyl group at 39.59 ppm. Comparison of the carbon-13 assignments and spectra, as well as the mass spectra, infrared spectra and proton NMR spectra with those in the literature for monomorine I indicate that the compound produced by this sequence of reactions is identical to that isolated and synthesized earlier.[19,92,94-97]

In conclusion it has been shown that the silver induced rearrangement of an octahydropyrindine to an indolizidine is a high yielding and viable method of synthesizing the indolizidine ring system. The ring interchange occurs in both the cis and the trans-fused octahydropyrindines without the production of side products. In the case of an equatorially positioned C-2 group on an octahydropyrindine, the ring interchange process is favored over alkyl migration to the nitrogen or with ring contraction to the pyrrolidine. The rearrangement products can be easily trapped and modified to other functionalities.

This method possesses the potential to be expanded into other ring systems such as the pyrrolizidine ring system[109] and the homoerythena ring system. Intramolecular trapping of the indolizidinium ion by a substituent attached to C-2 would allow the introduction of a third ring to the system and introduction to the gephrotoxin type ring system.

CHAPTER III

EXPERIMENTAL

General Information and Procedures.

Proton NMR spectra were recorded with a Nicolet NT-200 WB (200 MHz), Jeol FX-90Q (90 MHz), Varian T-60 (60 MHz), or a Nicolet TT-14 (60 MHz) spectrometer with deuteriochloroform as a solvent and referenced to tetramethylsilane unless otherwise noted. Proton-decoupled ^{13}C NMR spectra were obtained using a Nicolet NT-200 WB (50.31 MHz, with use of APT to determine carbon type), Jeol FX-90Q (22.5 MHz, with use of SFORD to determine carbon type), or a Nicolet TT-14 (15.087-MHz, with use of SFORD to determine carbon type) spectrometer with deuteriochloroform as the solvent and internal standard, unless otherwise noted. All chemical shifts are reported in ppm downfield from tetramethylsilane.

Infrared spectra were recorded using a Perkin-Elmer 1330 infrared spectrometer or a Digilab FTS-7 Fourier transform infrared spectrometer through sodium chloride plates as either neat films (in the case of liquids) or as KBr pellets (in the case of solids). Infrared absorptions are reported in cm^{-1} and are referenced to polystyrene.

Mass spectra were obtained with a Hewlett-Packard HP-5970 GC-MSD system or with a VG Analytical ZAB/EQ mass

spectrometer.

Melting points were determined on a Thomas 40 Micro Hot Stage equipped with a polarizing field viewer and are uncorrected.

Anhydrous solvents were prepared as follows: benzene and tetrahydrofuran were distilled from sodium benzophenone ketyl under an argon atmosphere; toluene was distilled from calcium hydride under argon; diethyl ether was distilled from lithium aluminum hydride under argon; dichloromethane was distilled from P_2O_5 under argon; ethanol and methanol were distilled from their magnesium salts prepared by treating the solvent with magnesium turnings and a small amount of iodine. Chromatographic solvents were distilled through a 50-cm Vigreux column, or if HPLC grade, were used without further purification.

Analytical thin-layer chromatography plates were prepared by dipping a microscope slide into a chloroform slurry of Merck Silica Gel G or Woelm Alumina G. Developed plates were visualized with iodine vapor after drying. Preparative chromatographic plates were used as supplied by Analtech Laboratories. Flash chromatography refers to the medium-pressure technique as described by W. C. Still[100] and was performed using Merck Silica Gel 60 (200 mesh). Davisil 62 silica gel (Davison Chemical Co. 60-200 mesh) and Fisher neutral alumina (Brockman activity I 80-200 mesh) were used for open column chromatography. Analytical

HPLC was performed on a Waters 6000A analytical chromatograph using a C-18 reverse-phase column.

Silver tetrafluoroborate (Aldrich Chemical Company) was stored under argon in opaque containers. This reagent was transferred into anhydrous glassware sealed with rubber septa in an inert atmosphere polyethylene glove bag (I^2R Corporation).

Stock solutions of N-chlorosuccinimide were prepared by dissolving N-chlorosuccinimide (Eastman Kodak) in freshly distilled dichloromethane until saturation was achieved. The solution was then filtered and standardized either by gravimetric analysis or titration against silver nitrate. Typical concentrations were of 0.1 M. The solution was stored in foil-wrapped bottles under argon and discarded after two weeks.

Hydrogenations were implemented with a Series 3910 Hydrogenation Apparatus (Parr Instrument Company) equipped to handle a 500-mL Parr flask. Typical hydrogenations were performed by dissolving the compound to be reduced in approximately 100 mL of solvent in a 500-mL Parr flask and adding the appropriate catalyst. The flask was placed into the explosion guard, connected to the hydrogen inlet, and clamped into the shaker. The flask was evacuated by vacuum pump until the solvent could be seen boiling. Hydrogen was then introduced to give a slight positive pressure (2-5

psi) and the flask reevacuated. The process of evacuation pressurization was repeated three times before pressurizing the flask to 55 psi. After cessation of hydrogen uptake, the shaker was stopped and the flask was depressurized. The catalyst was vacuum filtered from the solution and the solvent removed by distillation.

Trans-octahydro-1-pyrindine (101,p.40)

Method 1:[78]

In a 1-L three-necked round-bottomed flask equipped for reflux , 5.0 mL (5.09 g, 0.041 mol) cyclopentenopyridine, and 300 mL of absolute ethanol were placed and brought to reflux. Sodium metal, 25 g, was added in small pieces over one hour at a rate to maintain a steady amount of gas evolution and a blue color to the solution. An additional 100 mL of ethanol was added to the solution during the sodium addition to prevent the solution from becoming too viscous to be stirred. Once all of the sodium was dissolved, the solution was cooled and 250 mL of water added. The solution was extracted five times with 100 mL portions of dichloromethane. The combined organic were dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the solvent removed by distillation *in vacuo* to yield 7.24 g of a brown liquid. The liquid was dissolved in 100 mL of diethyl ether, and hydrogen chloride gas was bubbled through the solution. The

solution was filtered to give 5.62 g of a tan-colored crystals. Recrystallization from 95% ethanol gave 3.5 g (54%) of pure trans-octahydro-1-pyrindine hydrochloride, mp 187.5-188°C (lit. mp 187-188°C)[78]. ^{13}C NMR: δ 65.08, 45.61 (methines), 47.70, 31.05, 30.83, 29.37, 26.95, 20.52 (methylenes). ^{1}H NMR: δ 3.07 (bm, 1H), 2.94 (dt, 1H), 2.58 (bm, 1H), 2-1.3 (bm, 12H). Infrared: 3412 (N-H), 2919, 2889, 2515 (C-H stretch), 1581 (asym. N-H), 1456 (asym. C-H).

Method 2:[78]

Approximately 250 mL of liquid ammonia was condensed into a 500-mL three-necked flask equipped with a cold finger condenser and immersed in a dry-ice/acetone bath. To the ammonia was added 30 mL (30.5 g, 25.5 mmol) of cyclopentenopyridine and 15 mL of anhydrous ethanol. Lithium metal (2 g) was slowly added to the ammonia solution at reflux at a rate to maintain a blue color. Upon completion of the addition of the lithium, the color was allowed to dissipate and the ammonia allowed to evaporate. The resulting pale residue was suspended in 50 mL of water and was extracted six times with 50 mL portions of diethyl ether. The organic layers were combined and dried over anhydrous potassium carbonate. The solution was filtered and the ether removed <u>in vacuo</u>. The remaining liquid was distilled via Kugelrohr distillation (130-138°C/ 28 torr)

to produce 0.83 g (26%) of a clear liquid whose carbon-13 NMR was identical to that obtained in method 1.

cis-Octahydro-1-pyrindine (102, p.40)[79]

A solution of 10 mL (10.18 g, 0.085 mol) of freshly distilled cyclopentenopyridine (Aldrich Chemical Co.), 90 mL of glacial acetic acid, and 8.5 mL of concentrated hydrochloric acid was placed in a 500-mL Parr reaction flask along with 500 mg of Adams' catalyst. The flask was connected to the Parr hydrogenator and exposed to a hydrogen atmosphere as previously described.

Upon cessation of hydrogen uptake, the apparatus was discharged and disassembled. The solution was vacuum filtered to remove the catalyst and concentrated to approximately 30 mL by distillation of the acetic acid. The solution was then cooled in an ice bath and a solution of saturated potassium hydroxide added until the solution was basic to litmus paper. The solution was extracted five times with 100-mL portions of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate. The solution was filtered and the solvent removed *in vacuo* to yield 10.05 g (94%) of a red liquid. HPLC analysis (reverse phase, 60% methanol-water) of this liquid indicated it to be a mixture of 79% cis and 21% trans isomers. Kugelrohr distillation (121-125°C/20 torr) of this mixture produced 8.41 g of a clear liquid. The liquid was

dissolved in 50 mL of diethyl ether and converted into its hydrochloride salt by passing hydrogen chloride gas through the solution. The hydrochloride salt was recrystallized three times from 95% ethanol to produce 7.82 g (40%) of pure cis-octahydro-1-pyrindine hydrochloride, mp 189-190°C (lit. mp 188-189°C)[79]. ^{13}C NMR: δ 59.33, 39.81 (methines), 46.26, 33.55, 27.04, 25.93, 22.75, 22.43 (methylenes). ^{1}H NMR: δ 3.1 (dm, 1H), 2.63 (td, 1H), 2.2 (bm, 1H), 1.92 (bs, 3H), 2-1.1 (bm, 2H), 1.68 (m, 4H), 1.25 (s, 1H), 1.06 (bm, 2H). Infrared: 3286 (N-H stretch), 2965, 2820, 2735 (C-H stretch), 1455 (asym. C-H stretch).

Rearrangement of trans-Octahydro-1-pyrindine[80]

A solution of 0.54 g (4.5 mmol) of trans-octahydro-1-pyrindine in 10 mL of dichloromethane was added to 70 mL of 0.097 M N-chlorosuccinimide in dichloromethane. The solution was allowed to stir for 30 min under a nitrogen atmosphere at which time it was poured into a solution of 30 mL of saturated sodium bicarbonate. The layers were separated and the organic layer extracted with an additional 30 mL of saturated sodium bicarbonate. The organic solution was dried over anhydrous potassium carbonate. The solution was filtered and the solvents removed in vacuo at room temperature to yield a light-yellow slurry which was immediately redissolved in 25 mL of anhydrous benzene.

A solution of silver tetrafluoroborate was prepared by

dissolving 1.67 g (8.6 mmol) of silver tetrafluoroborate in 80 mL of anhydrous benzene with the aid of heat under an atmosphere of nitrogen. Using a Dean-Stark trap, 20 mL of solvent was removed and the solution then cooled to room temperature. The above N-chloramine was added in one portion via a syringe. The solution was stirred for 2 hr before 3 mL of 3.1 M lithium chloride in methanol was added. The solution was vacuum-filtered through a 2-cm pad of celite on a fritted funnel and the filtrate washed liberally with dichloromethane. The solvents were removed in vacuo to afford a yellow residue. The residue was dissolved in anhydrous methanol and added to a solution of sodium cyanoborohydride prepared by dissolving 1.96 g sodium cyanoborohydride and a small amount of bromocresol green in 50 mL of anhydrous methanol and acidifying with an anhydrous HCl/methanol solution until a yellow end point was achieved. The solution was allowed to stir overnight (14 hr), then poured into 100 mL of 1 M sodium hydroxide. The solution was extracted six times with 100-mL portions of dichloromethane. The combined organic layers were extracted with 100 mL of saturated sodium chloride and dried over anhydrous potassium carbonate. The solution was filtered and the solvents removed in vacuo to produce 0.42 g (78%) of indolizidine as a yellow oil. ^{13}C NMR: δ 64.29 (methine), 54.31, 53.08, 31.19, 30.59, 25.61, 24.65, 20.71 (methylenes).

Rearrangement of cis-Octahydro-1-pyrindine[80]

A solution of 0.84 g (6.7 mmol) of cis-octahydro-1-pyrindine in 10 mL of purified dichloromethane was added to 100 mL of 0.1 M N-chlorosuccinimide in dichloromethane and stirred for 40 minutes under a nitrogen atmosphere. The solution was poured into 100 mL of saturated sodium bicarbonate. The layers were separated and the dichloromethane fraction extracted with an additional 100 mL of sodium bicarbonate. The organic fraction was dried over anhydrous potassium carbonate. The solution was filtered and the solvent removed by distillation in vacuo at room temperature to produce a white slurry which was redissolved in 15 mL of anhydrous benzene.

A solution of silver tetrafluoroborate was prepared by dissolving 2.35 g (12 mmol) of silver tetrafluoroborate in 85 mL of anhydrous benzene with the aid of heat under a nitrogen atmosphere. After removal of 25 mL of benzene via a Dean-Stark trap, the solution was cooled to room temperature and the N-chloramine solution added in one portion by syringe. After 2 hr, TLC (silica/benzene) indicated no N-chloramine remaining, and 5 mL of 3.1 M lithium chloride in methanol was added to precipitate the remaining dissolved silver. The solution was vacuum-filtered through a 2-cm pad of celite on a fritted funnel and the filtrate washed copiously with dichloromethane. The solvents were removed

in vacuo to provide a yellow-green slush. The residue was dissolved in 20 mL of anhydrous methanol and added in one portion to a solution of sodium cyanoborohydride which had been prepared as follows: 2.35 g of sodium cyanoborohydride and a small amount of bromocresol green were dissolved in 50 mL of anhydrous methanol and acidified to a yellow end point using an anhydrous HCl/methanol solution. The solution was allowed to stir overnight (14 hr) before pouring it into 100 mL of 1 M sodium hydroxide. The solution was extracted seven times with 100-mL of portions of dichloromethane. The combined organic layers were extracted with 100 mL saturated sodium chloride and dried over anhydrous potassium carbonate. The solution was filtered and the dichloromethane removed in vacuo to provide 0.70 g (83%) of indolizidine as a light-yellow liqiud.

Rearrangement of cis- and trans-1-Chlorooctahydropyrindine in Benzene.

A 0.14 g (1.09 mmol) mixture of cis-trans octahydro-1-pyrindines obtained from the catalytic reduction of cyclopentenopyridine was added to 10 mL of 0.145 M N-chlorosuccinimide in dichloromethane and stirred for 30 minutes. The solution was then extracted with 25 mL of saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the solvent distilled in vacuo at room temperature. The slushy

white crystals were dissolved in 10 mL of anhydrous benzene and added in one portion to a solution of 0.49 g (2.2 eq.) of silver tetrafluoroborate in 40 mL of anhydrous benzene under an argon atmosphere. The solution was stirred and was monitored by TLC (silica-benzene). After 30 minutes, TLC indicated no starting chloramine remaining, and 2 mL of 3.1 M lithium chloride in methanol was added to the milky solution. The solution was vacuum-filtered through a pad of celite and the benzene removed in vacuo. The resulting black solid was dissolved in 5 mL of anhydrous methanol and added to an excess of sodium cyanoborohydride in 10 mL of anhydrous methanol acidified to pH 5 with HCl/methanol. The solution was stirred overnight. The solution was poured into 20 mL of 1 M sodium hydroxide and extracted five times with 25-mL portions of dichloromethane. The combined organic layers were extracted with 25 mL of saturated sodium chloride and dried over anhydrous potassium carbonate. The solution was filtered and the dichloromethane removed in vacuo to provide 0.119 g (87%) of indolizidine as a light yellow liquid.

Rearrangement of cis- and trans-1-Chlorooctahydro-1-pyrindine in Dichloromethane.

A 0.14 g (1.1 mmol) mixture of cis-trans octahydro-1-pyrindines were added to 10 mL of 0.145 M N-chlorosuccinimide in dichloromethane and allowed to react in the same

manner as the benzene rearrangement. The resulting N-chloramine was dissolved in 10 mL of dichloromethane and added to a slurry of 0.44 g (2.2 eq.) of silver tetrafluoroborate in 50 mL of dichloromethane. A white precipitate formed immediately. TLC indicated no starting N-chloramine present after 10 minutes. The reaction was treated identically to the benzene rearrangement of the same mixture described above to yield 0.13 g (94%) of indolizidine as a clear liquid.

5-Cyanoindolizidine (103, p.45)[88]

To a solution of 80 mL of 0.097 M N-chlorosuccinimide in dichloromethane was added 0.77 g (6.1 mmol) of a mixture of cis- and trans-octahydro-1-pyrindine in 10 mL of dichloromethane. The solution was stirred for 35 min at room temperature under a nitrogen atmosphere. The solution was then poured into 50 mL of saturated sodium bicarbonate. The layers were separated and the organic layer extracted with an additional 50 mL of saturated sodium bicarbonate. The organic layer dried over anhydrous potassium carbonate for 20 min. The desiccant was removed by filtration and the solvent distilled *in vacuo*. The residue was redissolved in 10 mL of anhydrous benzene and added in one portion via syringe to a stirring solution of 1.14 g of silver tetrafluoroborate in 90 mL of anhydrous benzene under a nitrogen atmosphere. A white precipitate formed

immediately. The solution stirred for 30 min at which time thin layer chromatography (silica gel-benzene) indicated no starting N-chloramine. A solution of 5.3 g of sodium cyanide in 30 mL of water was adjusted to pH 5 with acetic acid and added to the silver-N-chloramine solution. The pH was readjusted to 4.5 with acetic acid and the mixture allowed to stir for 3 hr at room temperature. Anhydrous sodium carbonate was added cautiously to the solution until no more effervescence occurred. The solution was diluted with 300 mL of dichloromethane and the layers separated. The aqueous portion was extracted with three 150-mL portions of dichloromethane. The combined organic layers were extracted with 100 mL of water and dried over anhydrous sodium sulfate overnight (12 hr). The solution was then filtered and the solvent removed <u>in vacuo</u> at room temperature to produce a brown oil. Chromatography of this oil on silica with dichloromethane afforded 0.69 g (75%) of 5-cyanooctahydroindolizidine as a light brown liquid and 0.14 g of cis-octahydro-1-pyrindine as a light brown oil. ^{13}C NMR: δ 115.97 (CN), 57.79, 50.99 (methines), 50.54, 30.08, 29.74, 27.97, 20.38, 19.97 (methylenes). ^{1}H NMR: δ 4.09 (dd, 1H), 3.4 (m, 1H), 2.96 (m, 1H), 2.45 (q, 1H), 2.22 (m, 1H), 2.1-1.2 (bm, 9H). Infrared: 2945, 2866, 2820 (C-H stretch), 2216 (CN), 1445 (asym. C-H stretch). MS: 150 (M), 121 (B), 107.

2-n-Butyl-6,7-dihydro-5H-1-pyrindine

Method 1:[99]

A solution of 4.65 g (39 mmol) of cyclopentenopyridine, freshly distilled from pulverized potassium hydroxide, and 50 mL of anhydrous toluene was brought to reflux in a 500-mL two-necked round-bottomed flask. To this solution, 60 mL (2.3 eq) of 1.55 M n-butyllithium in hexanes was added dropwise over 35 min. The solution turned dark red as the alkyl lithium was added. The solution was refluxed overnight (11 hr) during which a dark precipitate formed. Upon cooling the solution to ice temperature, 20 mL of water was added very cautiously producing much effervescence. The solution was filtered through a fluted filter and the organic layer separated. The aqueous layer was extracted with two 20-mL aliquots of toluene. The organic layers were combined and dried over pulverized potassium hydroxide. The solution was filtered and the toluene removed in vacuo to yield a black liquid. The liquid was filtered through a 2 cm X 10 cm alumina column with dichloromethane to give 5.64 g of a yellow liquid. This liquid was was submitted to flash chromatography on silica with 1:1 benzene:ethyl acetate to give 2.83 g (40%) 2-n-butyl-6,7-dihydro-5H-1-pyrindine as a clear liquid. ^{13}C NMR: δ 157.18, 152.64, 139.27 (aromatic C), 139.98, 122.65 (aromatic C-H), 30.57, 30.00, 29.33,

28.37, 21.68, 20.26 (methylenes), 11.91 (methyl). MS: 174 (M+), 133 (B), 146.

Method 2:[99]

A solution of 11 g (49 mmol) of 70% meta-chloroperbenzoic acid (MCPBA) in 100 mL of dichloromethane was added over 5 minutes to a stirring solution of 5.00 mL (42.7 mmol) of cyclopentenopyridine in 120 mL dichloromethane. The solution exhibited effervescence upon the addition. After 30 minutes thin layer chromatography (silica, 1:1 benzene:ethyl acetate) indicated no starting pyridine present. The solution was extracted 2 X 100 mL of 1 M sodium hydroxide, once with 100 mL of saturated sodium chloride and dried over anhydrous potassium carbonate. The solution was filtered and the dichloromethane removed in vacuo to yield 4.05 g of a white solid. The solid was immediately dissolved in 75 mL of anhydrous benzene and added dropwise over 70 minutes to a solution of 30 mL of 1.5 M n-butyllithium in hexanes and 150 mL of anhydrous benzene at reflux under a nitrogen atmosphere. The solution turned red then black during the addition. After 8 hr, 100 mL of water was added cautiously. The layers were separated and the aqueous layer extracted with two 100-mL aliquots of dichloromethane. The combined organic fractions were extracted with 75 mL of saturated sodium chloride. The solution was dried over anhydrous sodium sulfate. The

solution was filtered and the solvent removed in vacuo to afford 3.96 g of a black oil which separated into a black liquid 0.591 g (10.9%) whose carbon-13 NMR was identical to that of 2-(n-butyl)-6,7-dihydro-5*H*-1-pyrindine and 3.35 g of a black tar.

Method 3:[111]

A 500-mL three-necked round-bottomed flask equipped with reflux condenser and dropping funnel was flame-dried under a nitrogen atmosphere. The flask was then charged with 7 g of magnesium turnings, 15 mL of anhydrous tetrahydrofuran and 2 mL of 1-bromobutane. Upon commencement of the Grignard reaction, as evident by the turbid brown color and vigorous boiling, the solution was diluted with 100 mL of anhydrous tetrahydrofuran. A solution of 28 mL of 1-bromobutane in 50 mL of tetrahydrofuran was added dropwise over 40 minutes at a rate to maintain a reflux. The reaction was cooled to room temperature and 3.71 g (25.4 mmol) 1-pyrindine N-oxide in 50 mL of anhydrous tetrahydrofuran was added over 30 min. The solution was heated to reflux for 5 hr. The solution was cooled to 0°C and 100 mL of saturated ammonium chloride was added dropwise to the solution producing a vigorous reaction. The solution was allowed to stir overnight to destroy the last traces of magnesium metal. The layers were separated and the aqueous fraction extracted with seven 100-mL aliquots of dichloro-

methane. The combined organic fractions were dried over anhydrous sodium sulfate. The solution was filtered and the solvents removed in vacuo to give 3.82 g of a red liquid. Flash chromatography on silica with 1:1 benzene:ethyl acetate afforded 1.06 g (32%) of 2-(n-butyl)-6,7-dihydro-5*H*-1-pyrindine as a light red liquid, 1.59 g of starting material as a red oil, and 1.37 g of a resinous material.

2-(n-Butyl)-octahydro-1-pyrindine (126, p.59)

In a 500-mL Parr flask was combined 100 mL of anhydrous ethanol, 3.99 g (18.9 mmol) 2-(n-butyl)-6,7-dihydro-5H-1-pyrindine, and 1 g of Adams' catalyst. The flask was fitted to the hydrogenation apparatus and utilized as previously described. Upon cessation of hydrogen uptake, the apparatus was depressurized, disassembled, and the clear colorless liquid filtered. The ethanol was removed by distillation in vacuo to yield 4.02 g (97.6%) of a light-tan solid. Carbon-13 NMR of the crude solid indicated only one product present. Recrystallization of the solid from 95% ethanol gave 3.57 g (16.4 mmol, 86.6%) of 2-(n-butyl)-octahydro-1-pyrindine. ^{13}C NMR: δ 59.12, 56.20, 39.04 (methines), 36.84, 33.40, 27.98, 27.75, 26.11, 24.99, 22.63, 22.11 (methylenes), 13.78 (methyl). ^{1}H NMR: δ 4-2 (bm, 2H), 1.74 (bm, 7H), 1.32 (m, 10H) 0.96 (t, 3H). Infrared: 3311 (N-H stretch), 2948, 2925, 2880 (C-H

stretch), 1581 (asym. N-H stretch), 1444 (asym. C-H stretch). MS: 180 (M+), 124 (B), 107, 96.

3-butyl-5-cyanoindolizidine (127, p. 60):

To a solution of 25 mL of 0.12 M N-chlorosuccinimide in dichloromethane was added 0.40 g (2.22 mmol) of 2-butyl-octahydro-1-pyrindine in 15 mL of dichloromethane. The solution was stirred for 25 min before extracting with 25 mL of saturated sodium bicarbonate. The layers were separated and the organic layers dried over anhydrous sodium sulfate. The solution was filtered and the solution concentrated by distillation in vacuo. The N-chloramine was then added in one portion via syringe to a solution of 0.54 g (2.78 mmol) of silver tetrafluoroborate in 50 mL of freshly distilled dichloromethane under a nitrogen atmosphere. A white precipitate formed immediately. A solution of 1 g of sodium cyanide in 10 mL of water at pH 4 was added to the the rearrangement mixture. The pH was checked with pH paper and readjusted to pH 4. The solution then stirred at room temperature for 4 hr. Solid anhydrous sodium carbonate was added slowly to the reaction until the effervescence subsided. The solution was extracted four times with 50 mL portions of dichloromethane . The organic layers were combined and extracted with 25 mL of water. The organic phase was then dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the

solvent removed in vacuo to yield 0.77 g of a brown oil. The oil was chromatographed on silica with 3:2 hexane:diethyl ether to produce 0.41 g (90.4%) of 3-butyl-5-cyanoindolizidine as a light-yellow oil.

^{13}C NMR: δ 116.11 (CN), 61.03, 59.10, 49.00 (methines), 32.07, 30.40, 28.51, 28.05, 27.72, 22.64, 20.52 (methylenes), 13.70 (methyl). ^{1}H NMR: δ 4.1 (dd, 1H), 2.45 (bm, 1H), 1.86 (m, 5H), 1.78 (m, 4H), 1.35 (m, 8H), 0.98 (t, 3H). MS: 206 (M), 205 (M+), 180, 149, 122. Infrared: 2956, 2930, 2857 (aliphatic C-H strectch), 2203.9 (CN stretch), 1465.9, 1459.4, 1451.6 (asym. C-H stretch).

3-butyl-5-cyano-5-methylindolizidine (128, P.63)

A solution of lithium diisopropylamide (LDA) was prepared by adding 0.856 mL of a 2.5 M solution of n-butyllithium in hexanes to 0.300 mL of diisopropylamine in 15 mL of anhydrous THF at -78°C under a nitrogen atmosphere. After stirring for 10 min, 0.350 mL of hexamethylphosphoramide (HMPA) was added and the solution stirred an additional 10 min.

A solution of 0.188 g (0.91 mmol) 3-butyl-5-cyanoindolizidine in 2 mL of anhydrous THF was added to the LDA/HMPA mixture. The reaction was allowed to warm to 0°C for 30 min. The solution was then cooled to -78°C and 88

uL (1.4 mmol) iodomethane was added. The solution was stirred for 6 hr before being allowed to come to room temperature at which time the reaction was quenched with 5 mL of water. The mixture was diluted with 15 mL of dichloromethane and the layers separated. The aqueous layer was washed with 10 mL of dichloromethane and the combined organic fractions were washed with 10 mL of saturated sodium chloride and dried over anhydrous sodium sulfate. The solution was filtered and the solvent removed in vacuo to yield 0.214 g of a light-brown oil. Chromatography of this oil on alumina with 9:1 hexane:diethyl ether provided 0.135 g (67%) of 3-butyl-5cyano-5-methylindolizidine and 37 mg of starting material as a mixture of epimers.

^{13}C NMR: δ 120.28 (CN), 62.54, 59.56, 59.12 (methines), 39.22, 38.76, 30.06, 29.18, 29.10, 28.41, 27.80, 22.19 (methylenes), 22.68, 13.95 (methyls). MS: 219 (M+), 193, 178, 163, 136 (B). Infrared: 2950.6, 2928.9, 2856.0 (aliphatic stretch), 2200.6 (CN stretch).

(5Z,9Z)-3-n-Butyl-5-methylindolizidine (Monomorine I)

To a solution of 98.3 mg (0.045 mmol) of 3-butyl-5-cyano-5-methylindolizidine (128) in 15 mL of anhydrous THF was added 0.195 g (2 eq., 1 mmol) silver tetrafluoroborate in 2 mL of anhydrous THF. The solution was allowed to stir for 15 min. A white precipitate formed almost immediately. A solution of 0.314 g (8 eq.) of sodium cyanoborohydride at

pH 5 in 3 mL of anhydrous methanol was then added to the THF solution. The solution was readjusted to pH 5 and allowed to stir for 3 hr at room temperature. The reaction was basified by the addition of 5 mL of 1 M sodium hydroxide. The mixture was then vacuum-filtered through a fritted funnel containing a 2-cm thick layer of Celite. The filtrate was washed copiously with dichloromethane. The layers were separated and the aqueous layer washed with 10 mL of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the solvent removed *in vacuo* at room temperature. The resulting pink liquid was chromatographed on an alumina column with 9:1 hexane:diethyl ether to give 83.4 mg (0.42 mg, 94%) of monomorine I as a clear liquid. ^{13}C NMR: δ 67.04, 62.77, 60.13 (methines), 39.59, 35.73, 30.80, 30.22, 29.65, 24.80, 22.80 (methylenes), 22.74, 14.05 (methyls). ^{1}H NMR: δ 2.49 (m 4, .5H), 2.16 (m, 1.5H), 1.7 (bs+m, 8H) 1.6-1.1 (bm, 9H). MS: 195 (M), 194, 180, 138 (B), 122. Infrared: 2964.5, 2927.9, 2857.7 (aliphatic C-H stretch), 1459 (asym. C-H stretch).

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APPENDIX

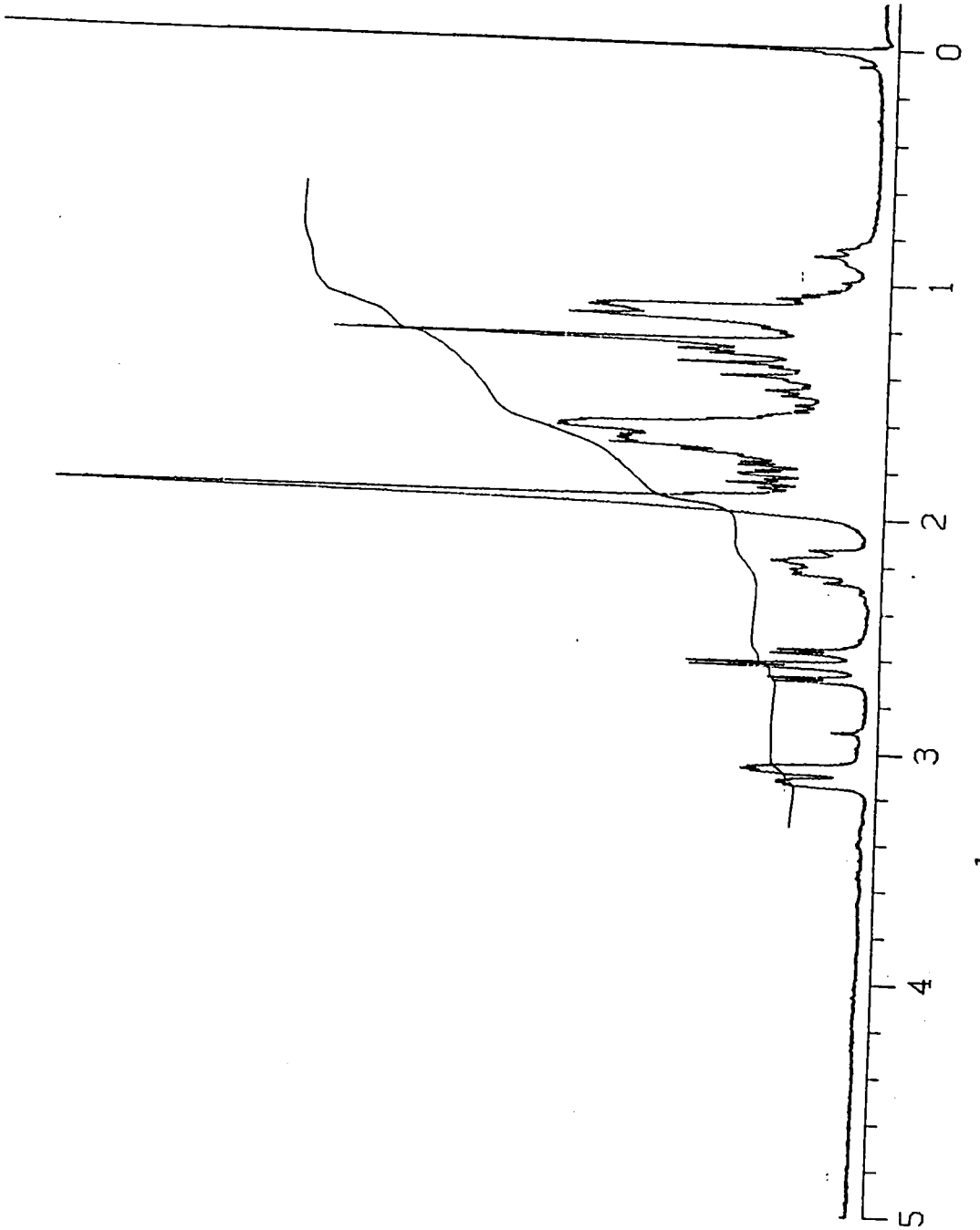

Figure 1: ^{1}H NMR spectrum of cis-octahydro-1-pyrindine.

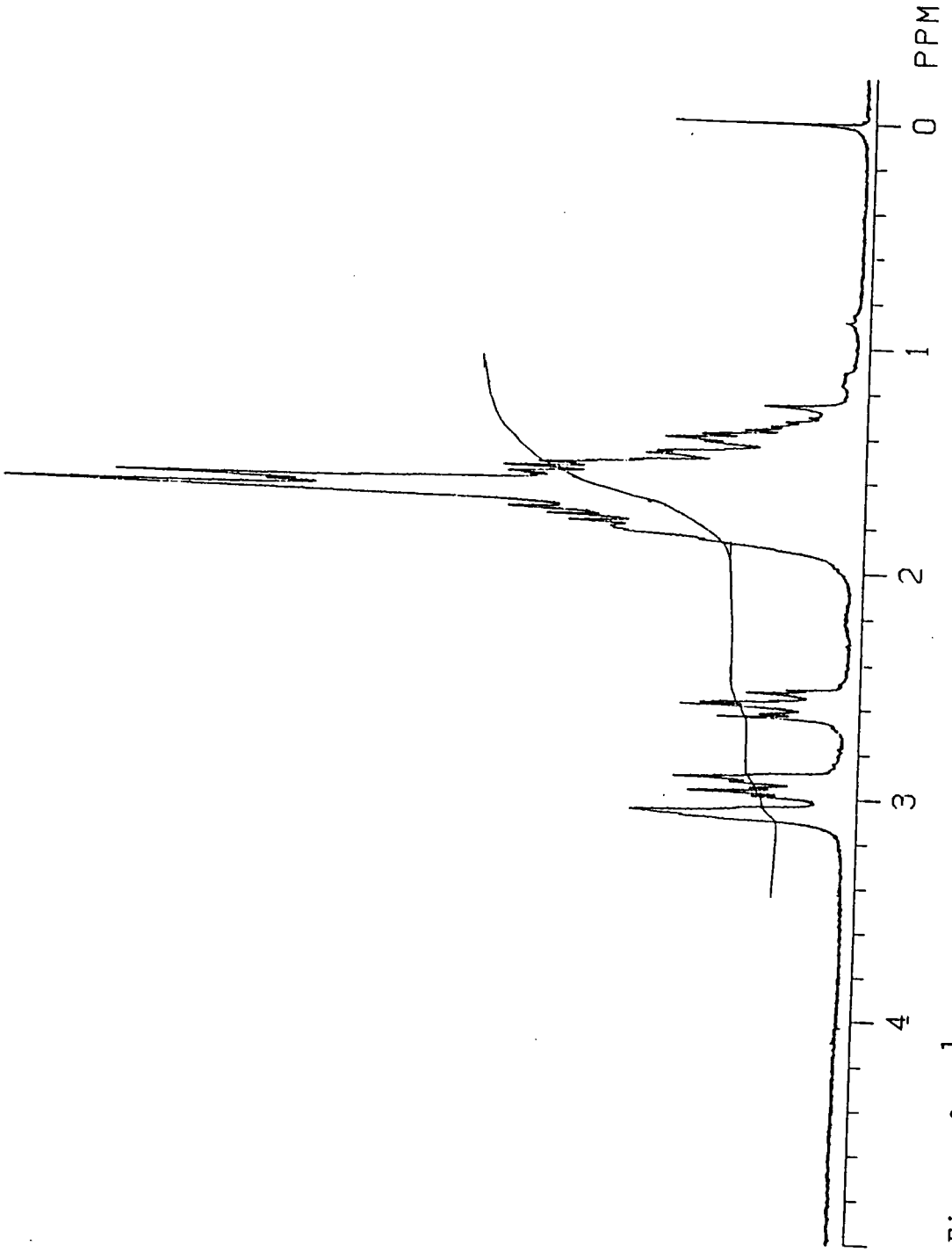

Figure 2: ^{1}H NMR spectrum of trans-octahydro-1-pyrindine.

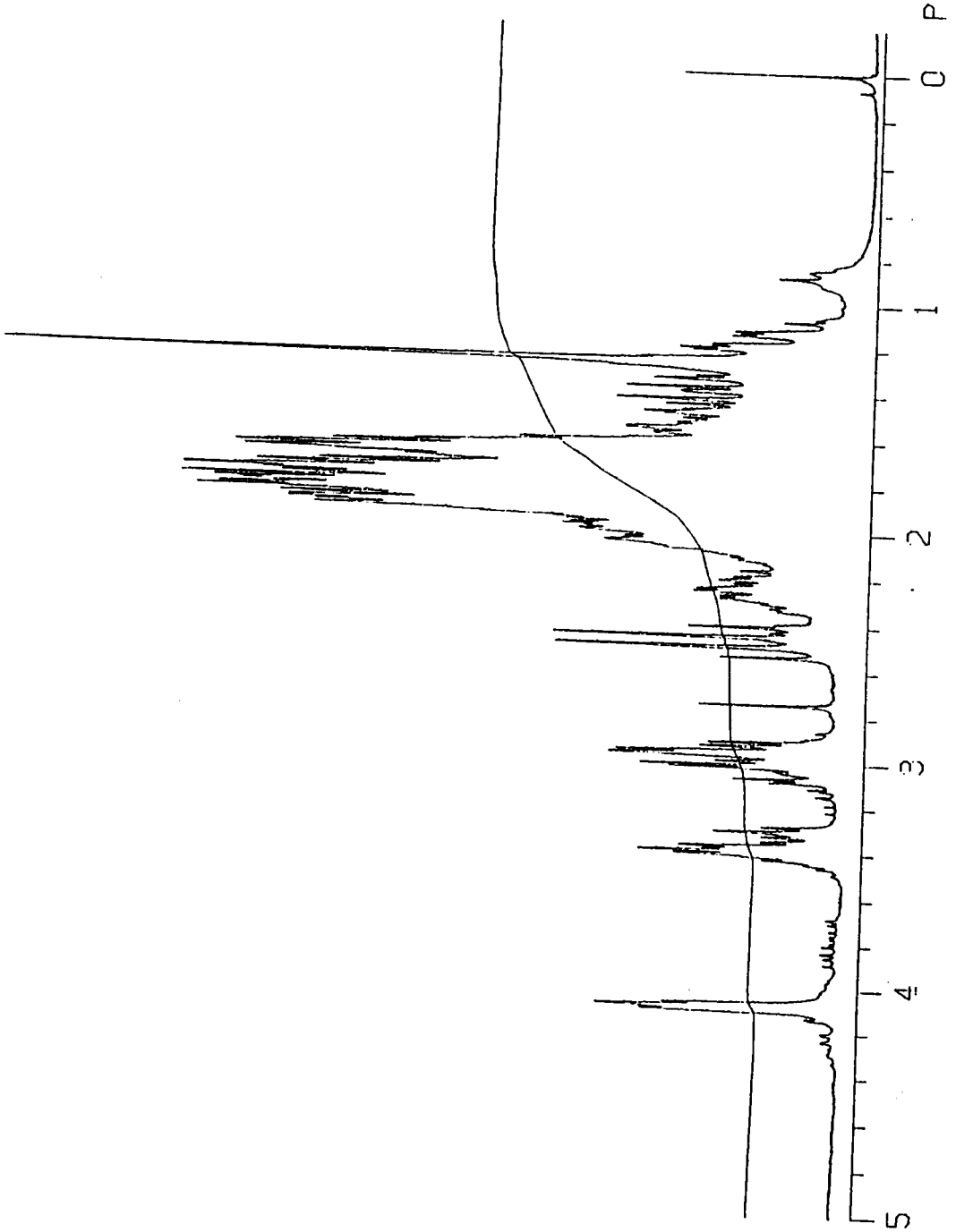

Figure 3: ^{1}H NMR spectrum of 3-cyanoindolizidine.

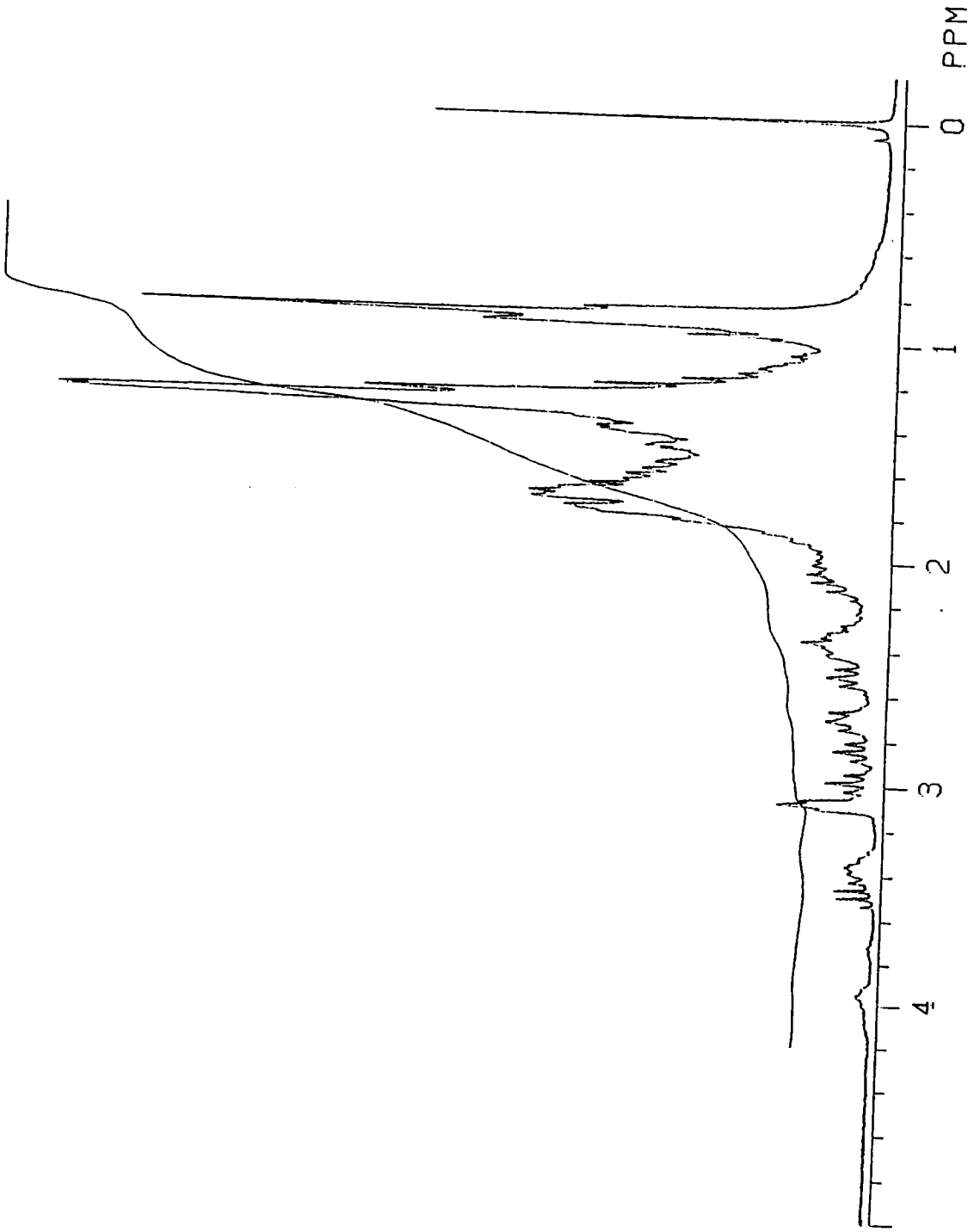

Figure 4: ^{1}H NMR spectrum of cis 2-(n-butyl)-octahydro-1-pyrindine.

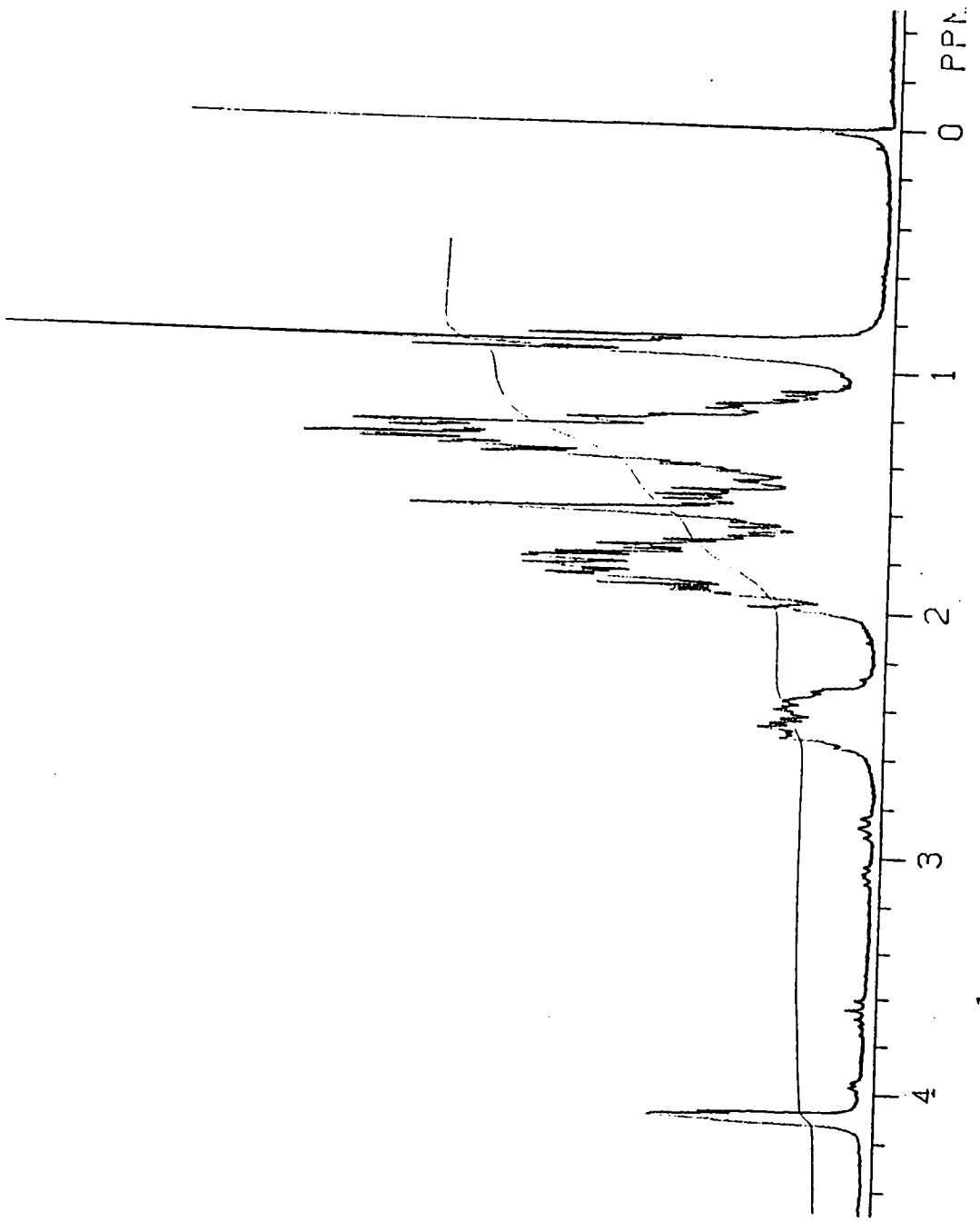

Figure 5: ^{1}H NMR spectrum of 3-(n-butyl)-5-cyanoindolizidine.

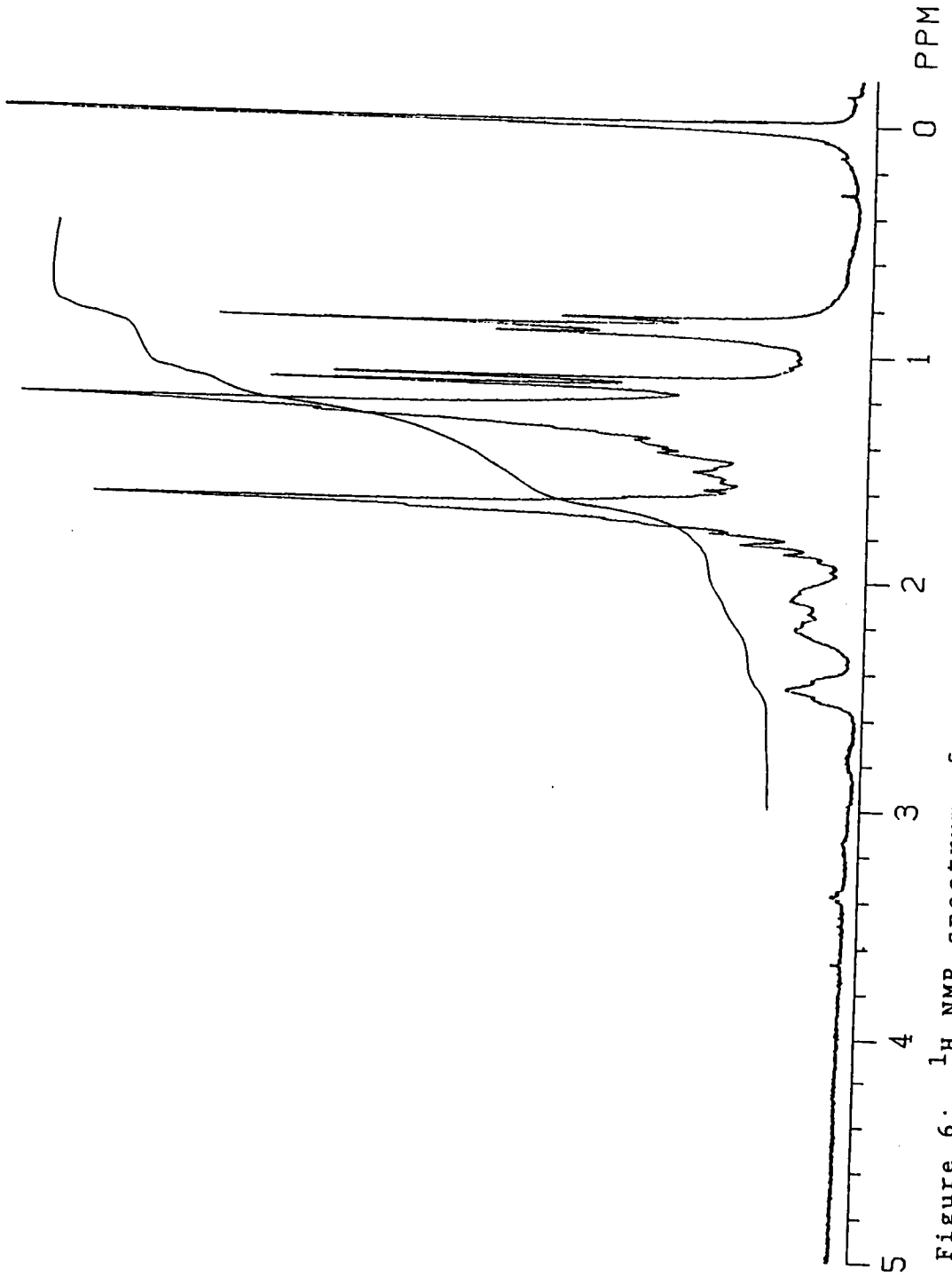

Figure 6: ^{1}H NMR spectrum of monomorine I.

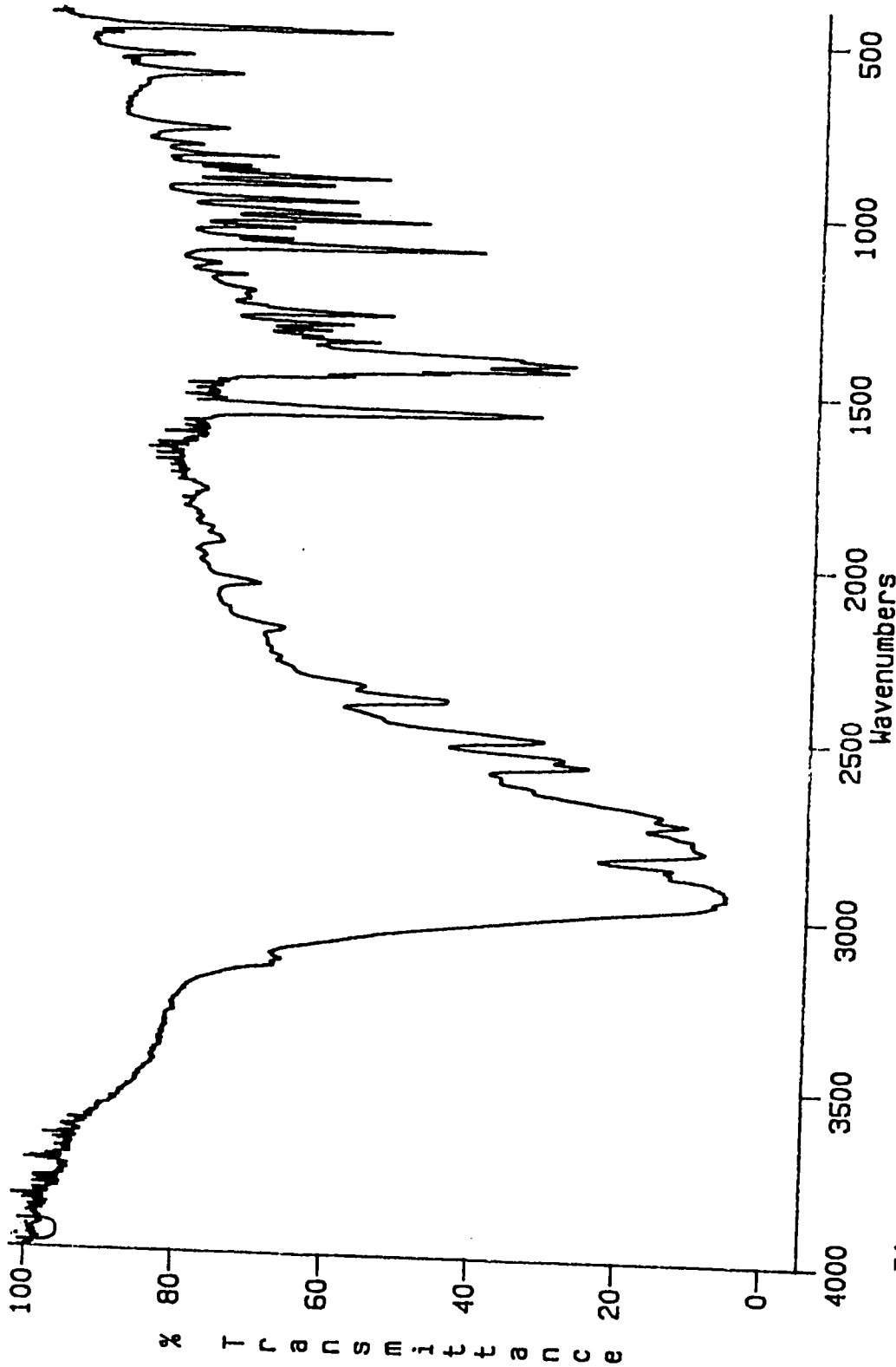

Figure 7: FT-IR spectrum of cis-octahydropyrindine.

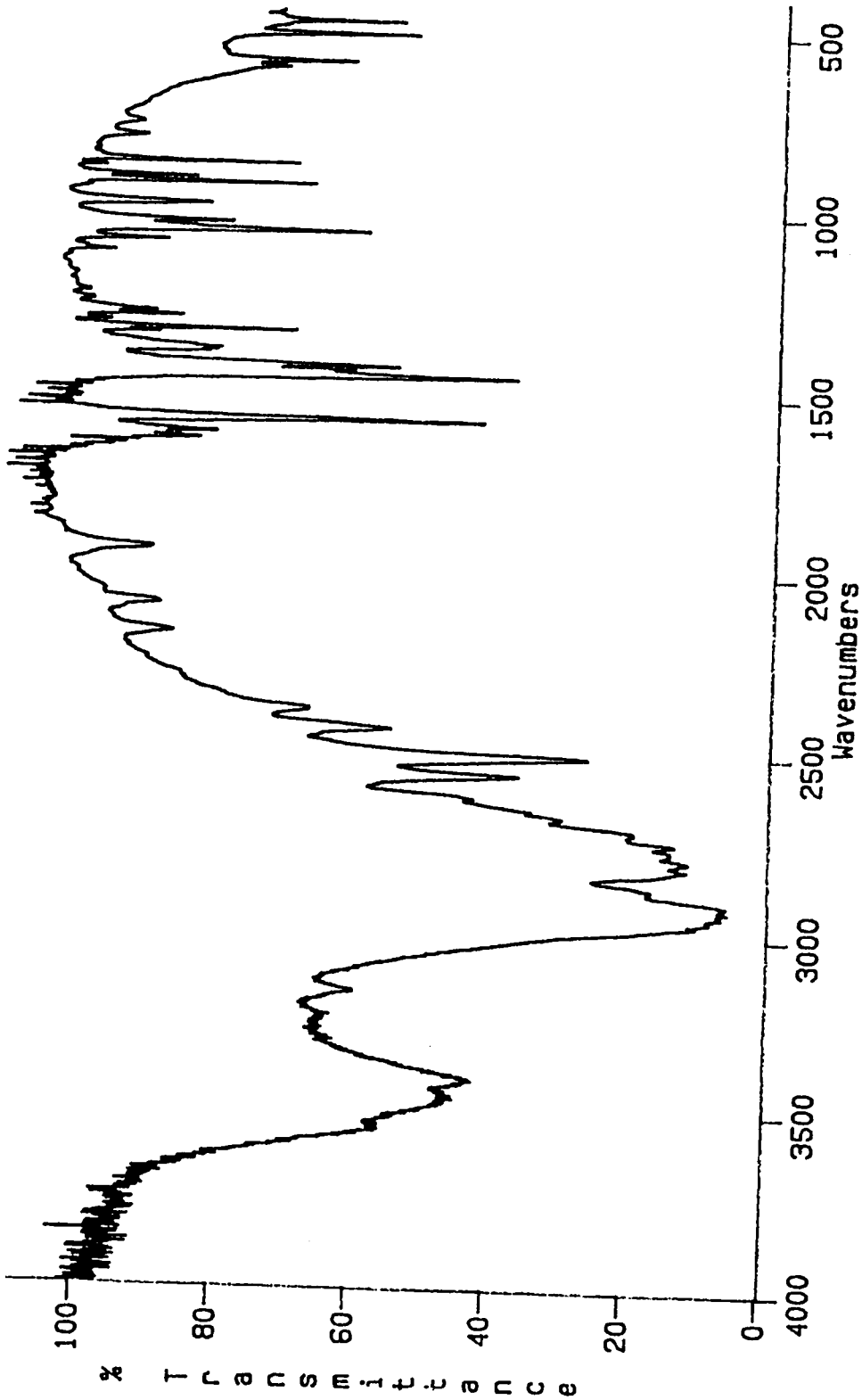

Figure 8: FT-IR spectrum of trans-octahydro-1-pyrindine.

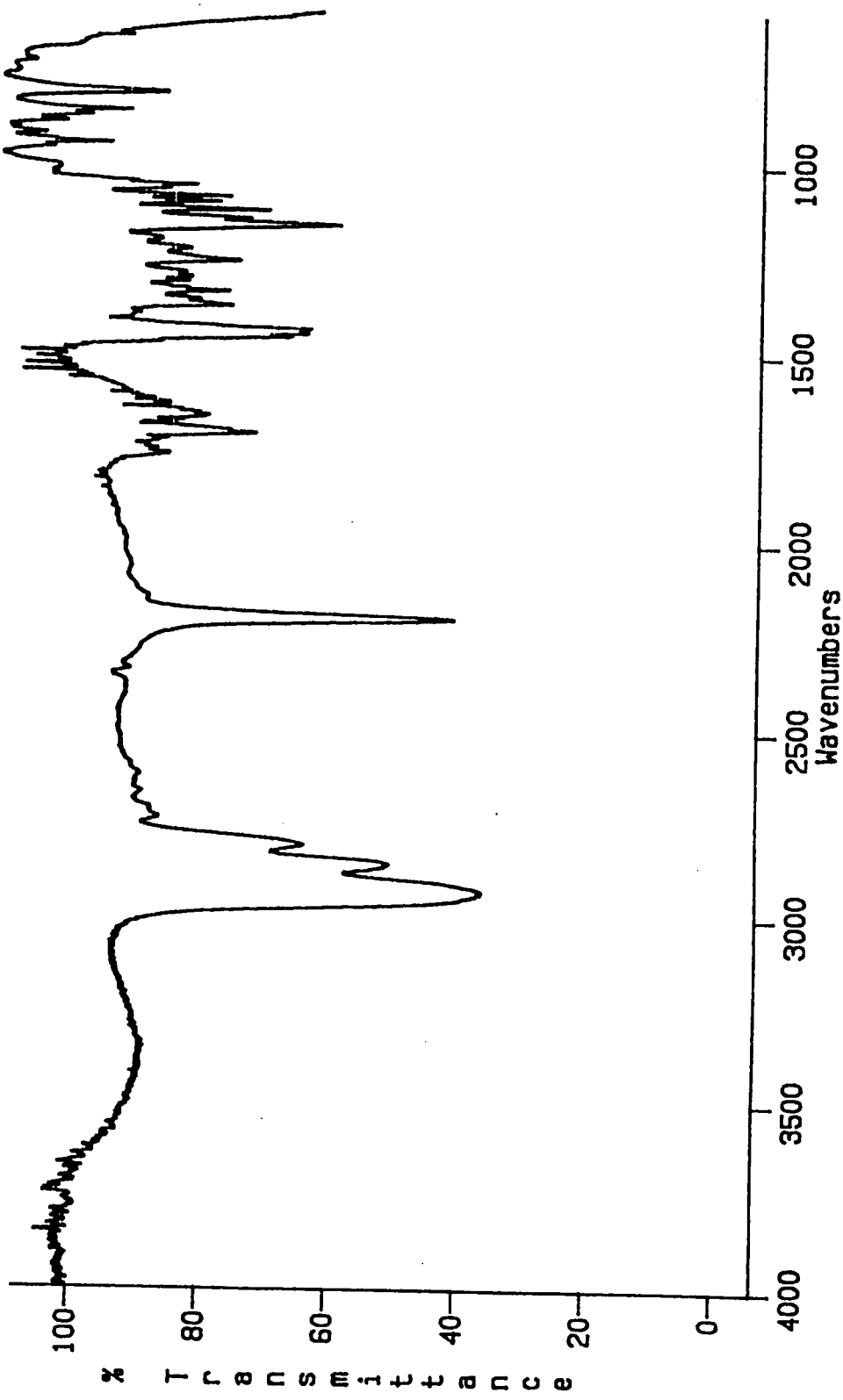

Figure 9: FT-IR spectrum of 3-cyanoindolizidine.

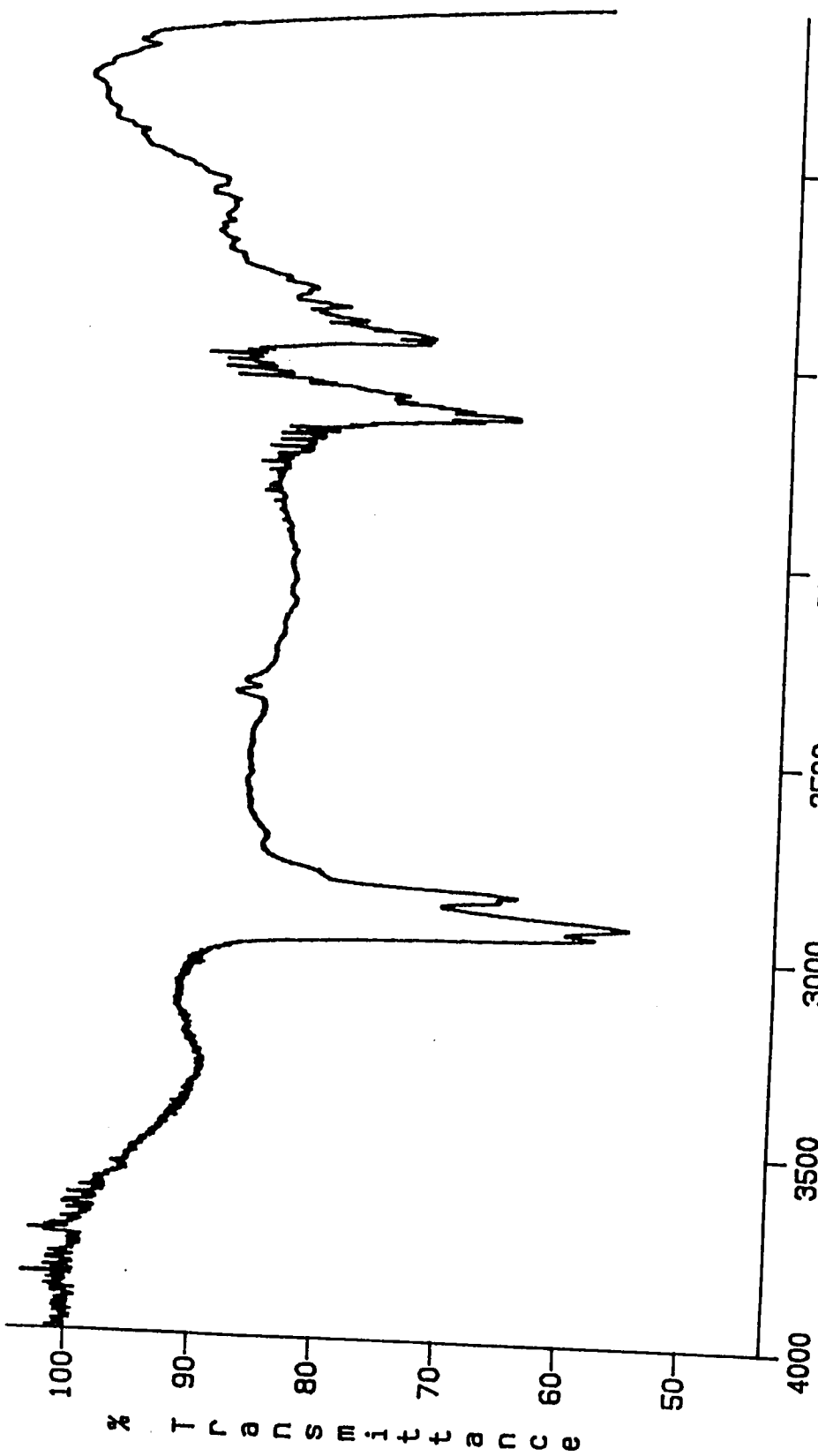

Figure 10: FT-IR spectrum of cis 2-(n-butyl)-octahydro-1-pyrindine.

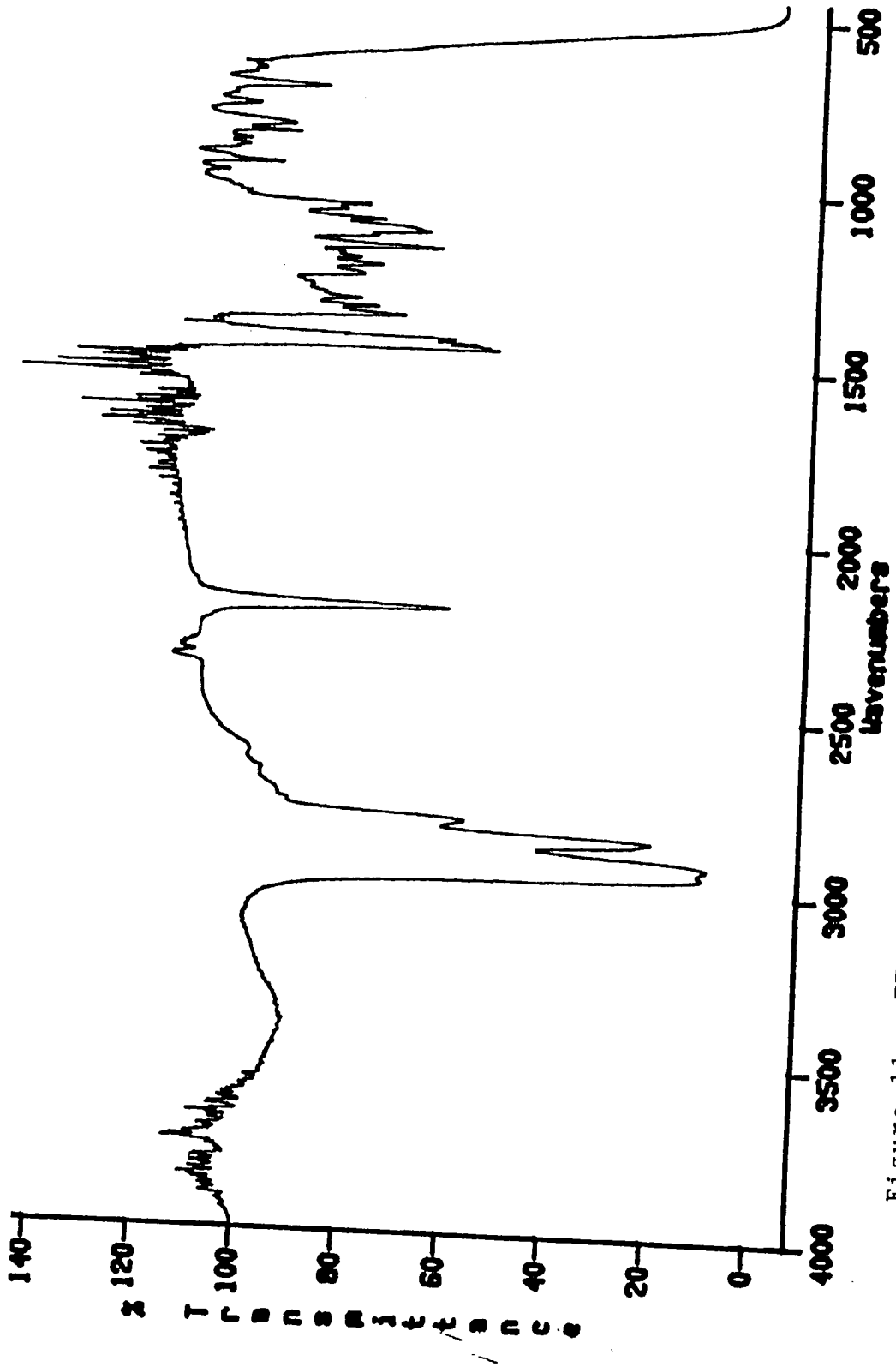

Figure 11: FT-IR spectrum of 3-(n-butyl)-5-cyanoindolizidine.

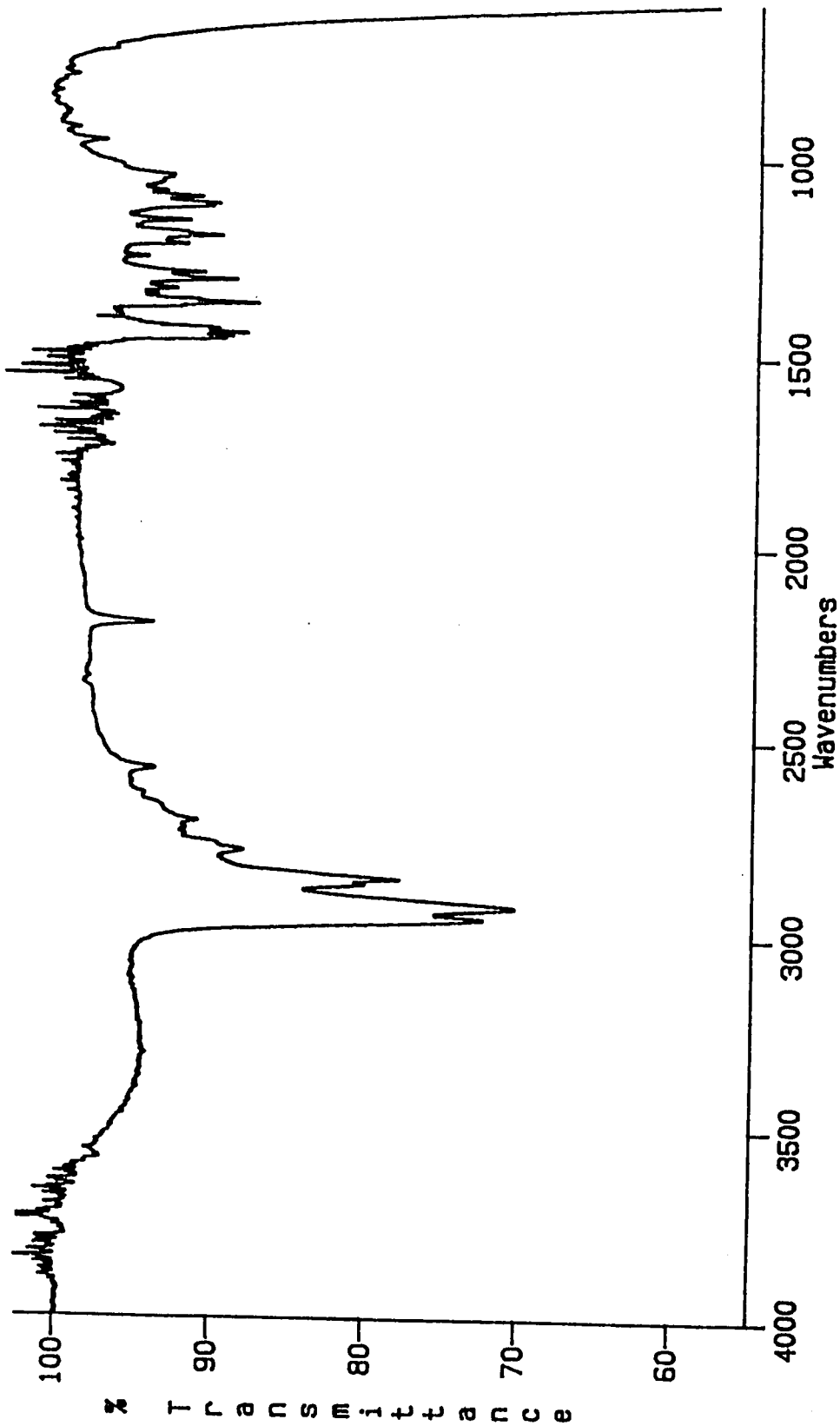

Figure 12: FT-IR spectrum of monomorine I.

VITA

Kenneth Alan Cole was born in Great Falls, Montana on November 3, 1957. He was graduated from James Robinson High School in Fairfax, Virginia in June of 1975. In August of that same year he entered Roanoke College, and in May of 1979 recieved a Bachelor of Science degree in Chemistry, cum lauda. Shortly after his graduation, he was employed by the Fermentation Chemistry Division of the NCI Fredrick Cancer Research Center.

In August of 1980 he married Barbara Lee Brennan and in September of that year entered The University of Tennessee, Knoxville and began study toward a Doctorate degree. This degree was awarded in May 1990. On July 14, 1989 he accepted a commission as a Lieutenant in the United States Navy Medical Service Corps. LT Cole is presently assigned to the Armed Forces Radiobiology Research Institute in Bethesda, Maryland.