

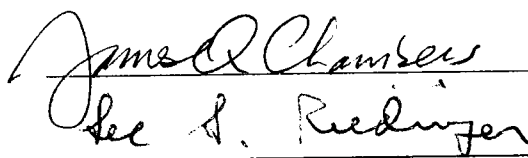
To the Graduate Council:

I am submitting herewith a dissertation written by Edward L. Brown entitled "Formation of N-Chloramine:Silver Ion Complexes, Isolation of a Stable Nitrenium Ion and the Silver Ion-Induced Rearrangement of N-Chlorocyclobutylamines." 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:



Associate Vice Chancellor and
Dean of the Graduate School

FORMATION OF N-CHLORAMINE:SILVER ION COMPLEXES,
ISOLATION OF A STABLE NITRENIUM ION AND THE SILVER ION-
INDUCED REARRANGEMENT OF N-CHLOROCYCLOBUTYLAMINES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Edward L. Brown

December 1995

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DEDICATION

To my loving wife

Robin

for her unending encouragement

and

To my beautiful daughter

Cassie

for her inspiration

and

To my parents

Ray and Carolyn Brown

for their wisdom, support and Christian example

ACKNOWLEDGEMENTS

I would like to thank the contributors that made this work possible. Professor Fred M. Schell for his technical guidance in the writing of this dissertation and for the countless hours spent discussing this and related research; the faculty and staff at the University of Tennessee provided much assistance; Drs. Al Tuinman and Bill Boggess for timely mass spectrometry results; Dr. Clifton Woods, Jonathon Pollitte and Jonathon Diminie for X-ray crystallographic analysis; and Holger Försterling for Low-Temperature NMR results.

Gratitude is extended to Lee College for providing employment for the past five years, and offering encouragement and support during those summers to finish this research and prepare this manuscript.

Special friends made life more pleasant throughout the time spent here. Bill King, Rikki W. Collier, Jane Doll, Anthony Hipps, and Bill and Gladys Holt provided many fond memories and excellent friendships.

Financial assistance awarded by the Science Alliance and ARCO, a teaching assistantship position awarded by The University of Tennessee Department of Chemistry, and the fellowships awarded by the Appalachian College Association, Inc. are also gratefully acknowledged.

ABSTRACT

Several secondary N-chloramines were characterized by both proton and carbon NMR revealing predictable chemical shift effects. The addition of silver ion to some of these N-chloramines produced N-chloramine:silver ion complexes that were studied using proton NMR. From this NMR study, it is clear that the site of silver complexation in these compounds occurs predominately at the nitrogen unshared electrons. Precipitation of silver chloride from one of these complexes left behind a crystalline material that was stable at ambient temperature to atmospheric moisture and air. Subsequent characterization by X-ray crystallography revealed a central nitrogen with two sigma bonds and a tetrafluoroborate counterion, hence a nitrenium ion. Proton and carbon NMR of this nitrenium ion were also obtained.

N-Chloramines, which undergo rearrangement following the introduction of silver ion, are thought to do so through the intermediacy of nitrenium ions. Specifically, certain N_b -chloro- N_b -cyclobutyltryptamines and N_b -chloro-1-spiro-1'-cyclobutyl-1,2,3,4-tetrahydro- β -carbolines were utilized in the preparation of 2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole. In both cases reaction was initiated with silver tetrafluoroborate. Subsequent addition of either concentrated

hydrochloric acid or sodium cyanoborohydride, respectively, provided the desired tetracycle in yields ranging from 16-66%.

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LIST OF SYMBOLS

Å	Angstrom
BMS	Borane Methyl Sulfide Complex
bs	broad singlet
C	Celsius
d	doublet
EI	Electron Impact
eq	equivalent
FAB	Fast Atom Bombardment
g	gram
h	hour
Hz	Hertz
K	Kelvin
LAH	Lithium Aluminum Hydride
m	multiplet
M	Molarity
M ⁺	Molecular ion
Mg	Megagram
MHz	Megahertz

LIST OF SYMBOLS (continued)

min	minute
mL	milliliter
mmol	millimole
m/z	mass to charge ratio
NCA	N-chloramine
NCS	N-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
ppm	parts per million
psi	pounds per square inch
q	quartet
R	alkyl
s	singlet
t	triplet
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
δ	parts per million from TMS

CHAPTER I

HISTORICAL SURVEY

The human quest for knowledge has rewarded our species with a vast amount of information concerning our universe and more specifically our planet. While some gazed at the stars and dreamed, others sought to explore the properties and potential uses of physically attainable resources. Very quickly, it was discovered that numerous compounds, once isolated, could have a large impact on many aspects of life. Earliest recordings of many cultures have described practices where crude extracts of flowers, plants, and insects were used as pigments, perfumes, healing agents, or as a quick release from life itself. Thus, the thrust of chemical inquiry in the eighteenth and nineteenth centuries was inevitably drawn toward the chemical nature of these traditional substances. Indeed, it was the realization that these materials exhibit different properties than metal salts and rock materials that led Jöns Jacob Berzelius (1779-1848) in 1807 to first coin the term *organic* to describe substances isolated from living things. This definition was unchallenged until Friedrich Wöhler (1800-1882) accidentally synthesized urea from an inorganic compound, ammonium cyanate, in 1828. Although Wöhler's work broke the barrier between organic and inorganic chemistry, to a great extent the field of chemistry is still divided along these lines.

The field of organic chemistry was initially limited exclusively to the study of natural products,^a and was first intensively pursued in France by Dumas and his colleagues. They made very little progress in this area, however, despite many accurate analyses and observations, since the concept of covalency and electrovalency of organic compounds had not yet evolved. In fact, it was not until 1859 that Couper and Kekulé independently proposed the constant tetravalency of carbon and wrote the first organic structural formulas.

The last half of the nineteenth century saw a rapid evolution of organic structural theory which necessarily arose when structural challenges presented by natural products were surmounted. A major portion of this theory was advanced once stereoisomerism was observed in the tartaric acids by Pasteur and later expanded upon by Van't Hoff.

Most natural products are obtained from plants or microorganisms and the research into these sources had been limited to only those from which useable chemicals could be isolated. In fact, it is probably fair to say that less than five per cent of all plant species have been scrutinized to determine their chemical constituents.¹

^aThe term "natural product", as used here, refers to those organic compounds isolated from plant, animal, or microorganism which have historically been of interest to the traditional organic chemist. This definition suffers in that it excludes nucleic acids, proteins, polysaccharides, coenzymes, fatty acids, and vitamins. It should be noted that the line which has historically separated these areas is rapidly fading.

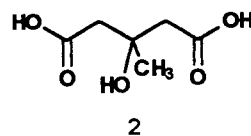
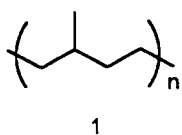
The first problem posed by a natural compound once isolated is the elucidation of its structure. In a rough way the classical approach may be divided into four phases: determination of the elemental composition and types of functional groups; delineation of the carbon skeleton and location of the groups on it; clarification of the stereochemistry; and synthesis of the molecule in confirmation. Historically, structure determination was initiated by chemical degradation of the natural compound, synthesis of the simpler compounds so derived, and reconstruction of the original molecule by inference. In this procedure, melting and/or boiling points, optical rotation, and chromatography were the only physical measurements available for structure identification. However, much of the tedium involved in structure determination has now been eliminated due to the advent of ultraviolet (UV) measurements in the 1930's, the development of infrared (IR) spectroscopy in the 1940's, the growth of nuclear magnetic resonance (NMR) spectroscopy in the 1950's, the rise of the potentially illuminating mass spectroscopy (MS) in the 1960's, and more recently the resurgence of X-ray crystallography due to ever increasing computer capabilities. Great gains in each of these fields of physical inquiry have made the determination of a compound's structure essentially guaranteed with a few well-planned experiments utilizing the technology present in the above techniques.

With the ease of structure determination came understanding of the

biogenesis of natural products. Three major groups of compounds have emerged - the **acetogenins**, the **terpenes**, and the **alkaloids**. The acetogenins are compounds formed from head-to-tail condensation of acetic acid which results in a linear chain of alternating ketone and methylene groups, viz.,



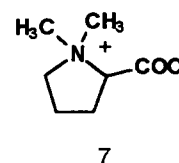
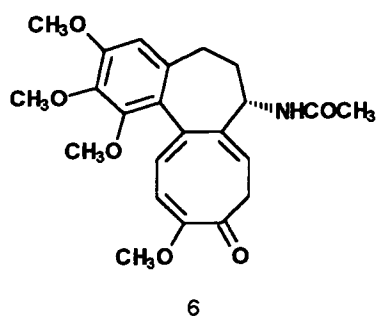
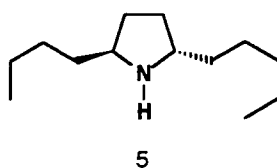
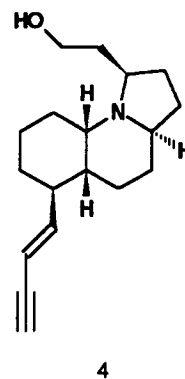
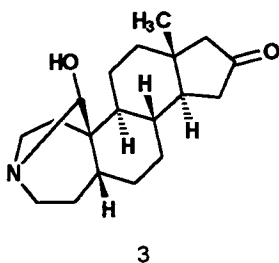
These chains can then cyclize via aldol condensation between an enolic methylene and a ketone six atoms away. Terpenoid structures are characterized by chains formed from the head-to-tail union of "isoprene units" [1]. The detailed biosynthesis of this basic five-carbon unit has been found to arise from the substituted glutaric acid **2** through the branched condensation of three acetic acid molecules. Subsequent decarboxylation and dehydration allow chains of from two to eight isoprene units to form and this can be followed by cyclization. The formation of alkaloids typically involves the conversion of amino acids, $\text{RCH}(\text{NH}_2)\text{COOH}$, into amines, RCH_2NH_2 , and aldehydes, RCHO , which can be united via a Mannich reaction.



The term alkaloid was first coined in 1818 by Meissner² and implies a compound similar to an alkali, referring to its basic property. Of all the classes of

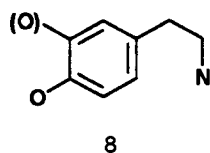
naturally occurring organic substances, the alkaloids possess the most diverse structural variance.² One of the first attempts to define alkaloids in order to further aid in their study was suggested by Winterstein and Trier.³ Simply, an alkaloid is a compound of complex structure isolated from a member of the plant kingdom, containing a basic nitrogen as part of a heterocyclic system and displaying significant physiological activity. However, this definition is severely limited in light of the significant number of natural products isolated from animals which are now considered to be alkaloids. Included among these are cycloneosamandione [3]⁴ isolated from the skins of the European fire salamander, gephyrotoxin [4]⁵ found in skin extracts of a Columbian frog, and 2,5-dialkyl-pyrrolidines [5]⁶ isolated from the venom of the fire ant, Solenopsis invicta, which is still classified as an alkaloid despite its comparatively simple chemical structure. In addition, many neutral compounds and quaternary nitrogen salts are now considered alkaloids, including colchicine [6] found in the autumn crocus, and stachydrine [7] present in alfalfa and Chinese artichoke. These and many other examples make Winterstein and Trier's definition too exclusive for the many compounds regarded as alkaloids in the field of organic chemistry today.

The major thrust in structure elucidation of alkaloids involved the proposal of their biosynthetic pathways by Pictet and Robinson. These pathways were first worked out solely by inference from the existence of common structural features,



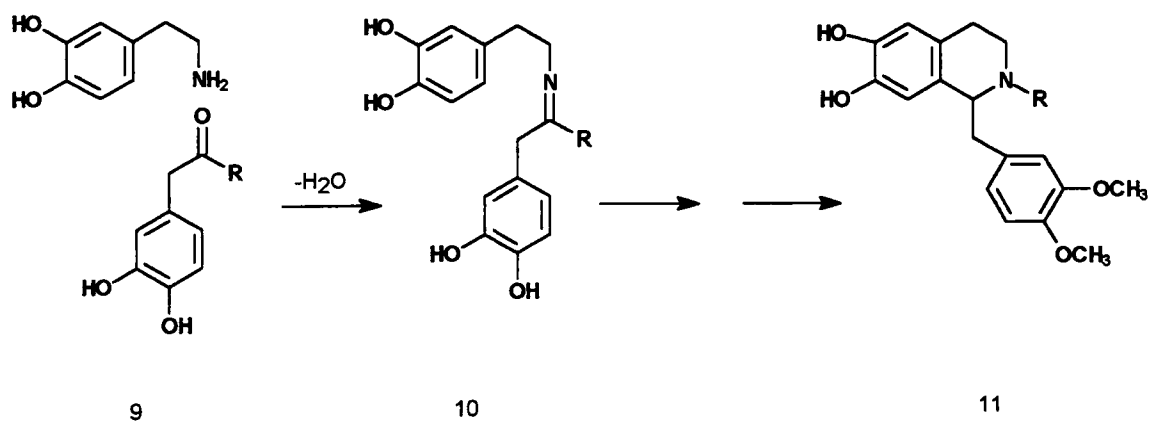
a brilliant intellectual achievement indeed! Since that time, radioactive tracer work has generally confirmed their speculations and added much solid detail as well. We are now in a position to appreciate in broad outline the wonderful simplicity of Nature's design for the synthesis of these intricate molecules.

Most of the alkaloids contain aromatic rings and in many of these the structural unit 8 can be discerned. This was first recognized by Pictet and



coworkers,^{7,8} who further observed that the benzyloquinoline alkaloids (cf. laudanosine [11, R=CH₃]) contained two such units, which might be synthesized by the condensation shown in Scheme I-1.

SCHEME I-1



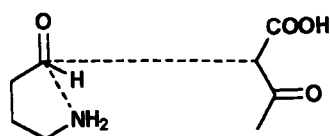
This reaction is representative of a generalized Mannich condensation where an aldehyde condenses with an amine [e.g. 9, R=H], yielding imine 10 (R=H) which may then be attacked by a nucleophilic carbon (such as that found in an enol or phenol) to form a carbon-carbon bond as illustrated in 11. Subsequently it was

shown by Schöpf⁹ that such a condensation occurred with great facility *in vitro* at neutral pH and room temperature and so was a reasonable candidate for a biosynthetic pathway.

While the generalized Mannich reaction affords a suitable reaction for biosynthesis, the structural unit **8** suggests that the common amino acids phenylalanine and tyrosine, known from biochemical studies¹⁰ to suffer oxidation to the *o*-dihydroxyphenyl derivative and decarboxylation to the amine, are acceptable starting materials. In addition, oxidative deamination and decarboxylation to the aldehyde commonly occurs in metabolic situations.

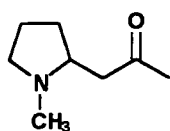
These amino acids along with tryptophan, lysine and ornithine are the basic ingredients for the synthetic elaboration of alkaloid molecules in living tissue and afford a convenient classification of alkaloids into three large groups: the alicyclic group, the phenylalanine group, and the indole group.

The simplest alkaloids are those found in the alicyclic group. Their biogenesis was first outlined by Robinson who regarded acetone-dicarboxylic acid as the source compound. In general, acetoacetic acid, formed from the decarboxylation of acetone-dicarboxylic acid, can be used as the precursor of the alicyclic group. Hygrine [**13**] is typical of the pyrrolidines arising, as implied in **12**, from ornithine (with acetoacetic acid acting as the nucleophile for the Mannich reaction). Methyl-isopelletierine [**14**] from pomegranate root and coniine [**15**], the

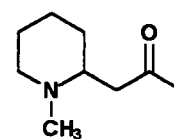


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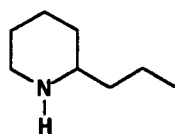
major alkaloid of Socrates' poison cup, are examples of piperidines, the homologous structures deriving from lysine. Similarly, tropine [16] ($R_1 = R_2 =$



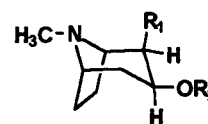
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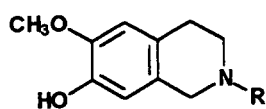


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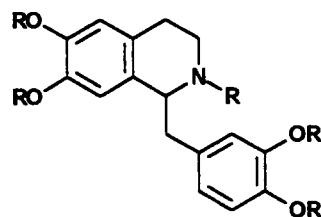
H) is an oxidized (to an imine) and further cyclized hygrine with the ketone subsequently reduced. The basic skeleton in tropane alkaloids is the azabicyclo[3.2.1]octane system exemplified by cocaine [16] ($R_1 = \text{COOCH}_3$; $R_2 = \text{C}_6\text{H}_5\text{CO}-$). The ganglion-blocking and central nervous system-stimulating effects of cocaine are well known and are exhibited in varying degrees by other members of this important alkaloid system.¹¹ Other tropane alkaloids include

atropine [16] ($R_1 = H$; $R_2 = C_6H_5CH(CH_2OH)CO-$) and other constituents of such plants as henbane, mandrake, and deadly nightshade - known even in medieval times for their hallucinogenic qualities.

The phenylalanine group is characterized primarily by 1-benzylisoquinoline skeletons [17, $R=CH_3$], although some simple isoquinolines are known, such as corypalline [17, $R=H$], which may arise simply by cyclization of the imine formed from a formaldehyde equivalent. Subsequent methylation affords the opium constituent laudanosine [11] which (with phenolic or methylenedioxy variants) may be regarded as the protean compound 18, where further oxidations would yield most of the main alkaloids of this group.

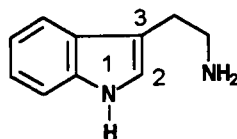


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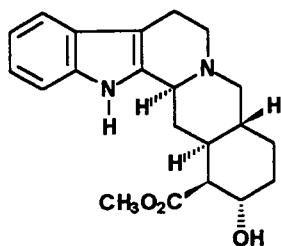
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The indole group is structurally the most varied of the three groups. Despite its superficial complexity, it can be seen that the majority of its members are formally derived from a Mannich condensation of tryptamine [19] with a ten carbon aliphatic aldehyde, derived from two mevalonic acids,^{12,13} at the 2- or 3-positions of the indole nucleus. Perkin and Robinson¹⁴ were the first to report that the

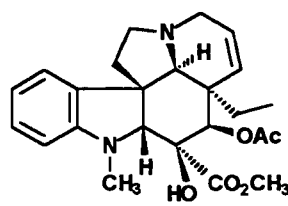


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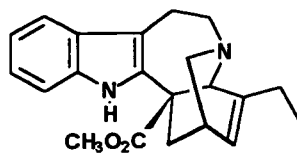
aromatic portion in the indole alkaloids is derived from tryptophan which has undergone decarboxylation to tryptamine. Experimental evidence for this decarboxylation has been obtained by Battersby¹⁵ and coworkers. The majority of the indole alkaloids may be included under essentially three broad classes which differ in the skeleton of the C₁₀ unit. These may be exemplified by the *Corynanthe* alkaloids, e.g. yohimbine [20] (class I); *Aspidosperma* alkaloids, e.g. vindoline [21] (class II); and the *Iboga* alkaloids, e.g. catharanthine [22] (class III). A number of



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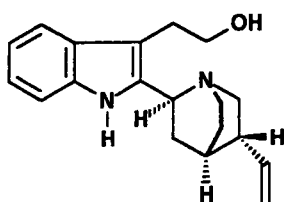


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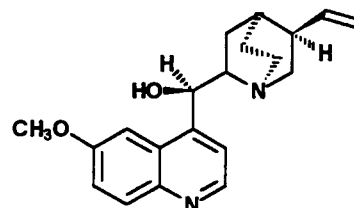


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other alkaloids are biogenetically derived from some of the above by a few further transformations, as in the conversion of cinchonamine [23] (class I) into the quinine [24] family skeleton via opening of the indole ring and reclosure of the aniline nitrogen on the hydroxy ethyl side chain.



23

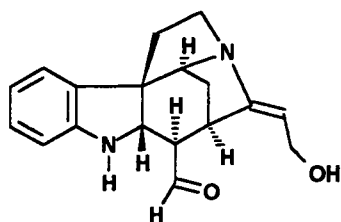


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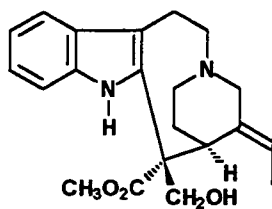
Legend has it that the Countess Chinchon, wife of the Viceroy of Peru, was the first European cured of malaria by the bark of the *quina-quina* tree in 1638 and subsequently it was introduced into medical practice. In any case, Linnaeus bestowed her (misspelled) name on the *Cinchona* species, and Pelletier and Calventou isolated quinine from its bark in 1820. The medical importance of the drug and its availability in quantity spurred active chemical study in the nineteenth century. In fact, it may be said that the commercial production of synthetic dyes, the first, and for a long time the major organic chemical industry, sprang from Perkins' famous, if naïve attempt, to synthesize quinine in 1856. He obtained instead the dye "mauve" which soon became the rage of *fin-de-siècle* fashion.

Somewhat more involved schemes can be proposed to explain the origin of

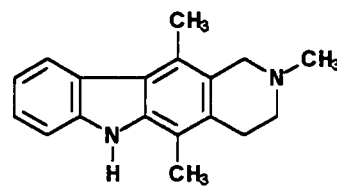
stemmadenine [26], ellipticine [27], and gelsemine [28] from a starting point of the caracurine [25] type.¹⁶



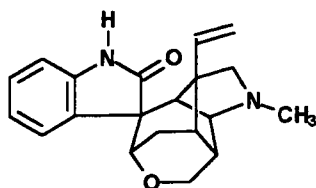
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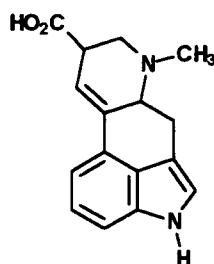
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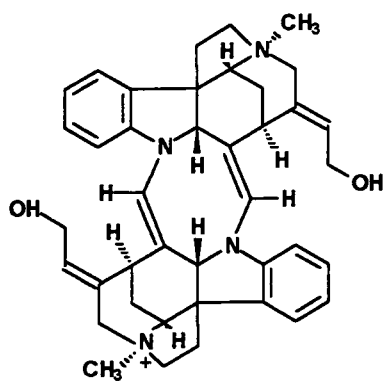
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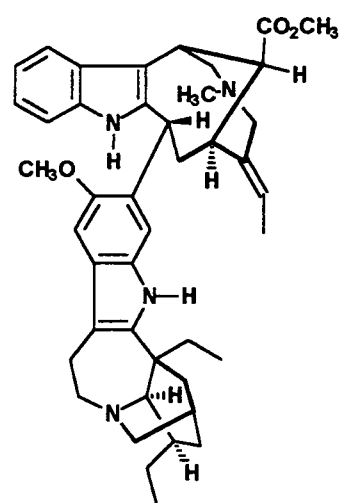
29

The hallucinogens from the rye fungus (ergot), thought to have been the cause of St. Vitus's Dance in medieval times, are peptide amides of the interesting lysergic acid [29], shown to be a biosynthetic product of tryptamine and mevalonic acid. The most complex bases are the dimeric indole alkaloids such as the many constituents of calabash curare, derived from caracurine [25] by a simple dehydrative dimerization and exemplified in the common toxiferine [30]. Other dimeric examples include voacamine [31] and the very similar vinblastine [32], an anticancer agent isolated from the periwinkle.

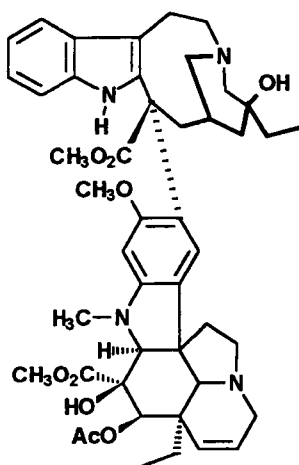
The discovery of alkaloids with increasing complexity, forced synthetic chemists to devise more sophisticated experimental designs to meet the challenges inherent in their syntheses. This indirect cooperation has given synthetic chemists tangible goals to use as tests of newly developed synthetic strategies and has given discoverers of these natural products conclusive proof of an alkaloid's structure through its total synthesis by chemical means.



30



31

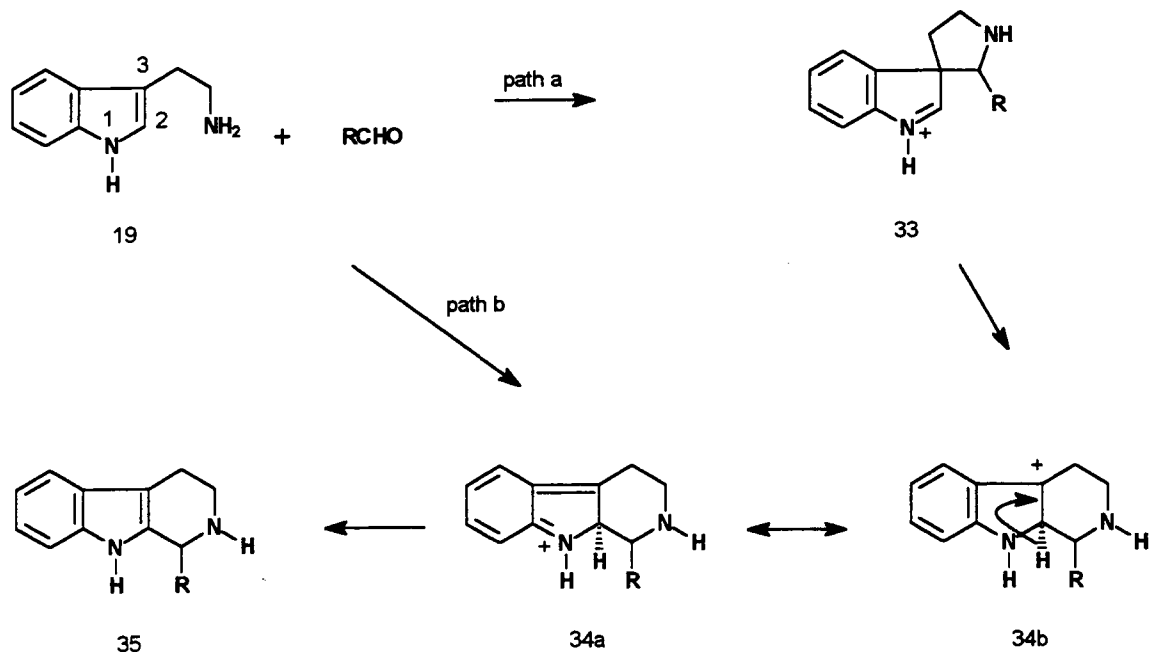


32

The synthesis of compounds containing the tetrahydro- β -carboline nucleus is of interest because this ring system occurs in a number of physiologically active indole alkaloids [e.g. **20**] and some hormones. The preparation of 1,2,3,4-tetrahydro- β -carbolines [**35**] has been accomplished by the Pictet-Spengler condensation,^{17,18,19,20} the Fischer indole cyclization, and the Bischler-Napieralski reaction.¹⁷ Other methods¹⁷⁻²¹ have also been employed and will be discussed later. The earliest route to this system, modelled on the Pictet-Spengler tetrahydroisoquinoline synthesis,¹⁷ was first reported by Tatsui^{22,23} and by Akabori and Saito.²⁴ In its simplest form the synthesis consists of the acid-catalyzed Mannich reaction of tryptamine [**19**] with an appropriate aldehyde (RCHO) to afford the observed condensation product **35** (Scheme I-2). Two principal mechanistic pathways have been proposed for the Pictet-Spengler condensation: the spiroindolenine route (path a) or the simpler approach (path b) which involves the direct formation of the cationic intermediate **34a** by electrophilic attack of the Schiff base at the 2-position of the indole. The idea that the aldehyde could condense directly at the 2-position was questioned once the reaction mechanism was studied by Jackson and coworkers.²⁵ The mechanism proposed for path b involves an energetically unfavorable transition state in which the nitrogen lone pair disrupts the aromatic π cloud leading to intermediate **34a**. Although the formation of a spiroindolenine (path a) would form the same intermediate (e.g. **34b** which is a

resonance contributor of **34a**) the transition state leading to **34b** is presumably lower in energy since the resonance energy of the aromatic ring has not been disturbed.

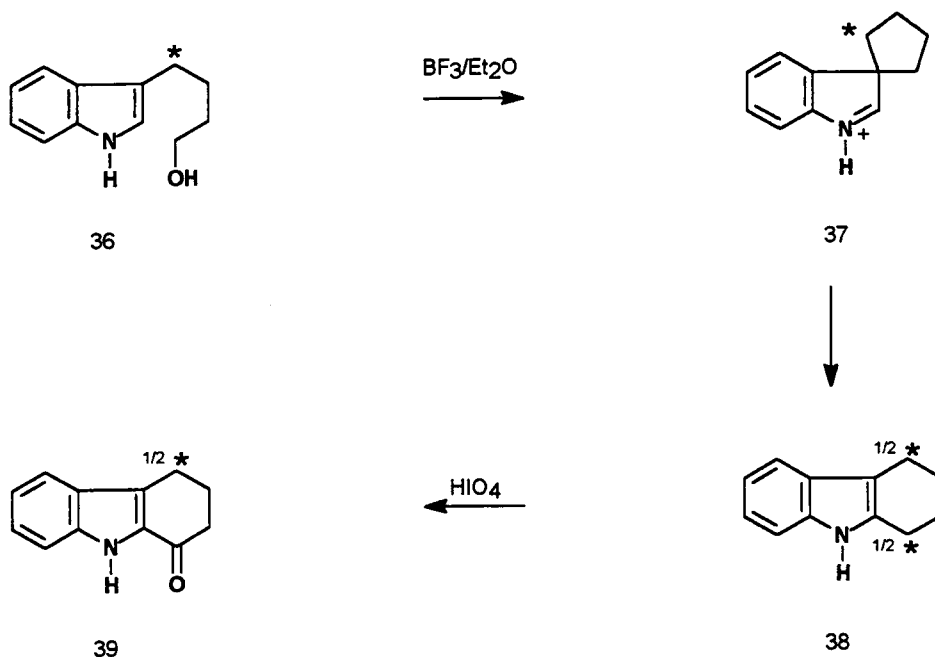
SCHEME I-2



The origin of the spiroindolenine hypothesis is attributed to Woodward^{26,27} who proposed a spiroindolenine as an intermediate for the biosynthesis of *Strychnos* alkaloids. Much mechanistic proof has been collected by Jackson and Smith from investigations of the electrophilic nature of the 2,3-indole double bond.^{28,29} In one case, tritium was incorporated on the carbon atoms which bear the asterisk (Scheme I-3). Cyclization of the alcohol to **38** followed by oxidation with periodic acid gives the ketone **39** with only half of the radioactivity of the preceding compounds. The

reaction is thought to proceed through the formation of the symmetrical spirocyclic indolenine **37** which would make positions 1 and 4 equivalent upon rearrangement to **38**. This would distribute the radioactivity equally such that half is lost upon oxidation.

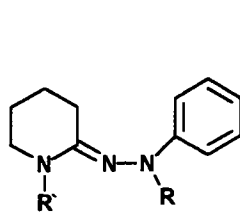
SCHEME I-3



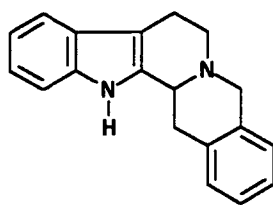
Further proof for the intermediacy of indolenines was obtained when the carbinolamine **40** was rearranged under extremely mild acidic conditions to the tetrahydro- β -carboline **41**.²⁹



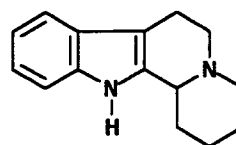
Another very versatile route to the tetrahydro- β -carboline ring system is the Fischer indole synthesis. Cyclization of 3-piperidone phenylhydrazone derivatives [e.g. **42**] were employed to initially synthesize pentacyclic derivatives [e.g. **43**] related to the yohimbe alkaloids.^{30,31,32} Later this scheme was extended to the synthesis of tetracyclic compounds [e.g. **44**].³³



42

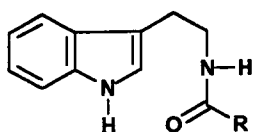


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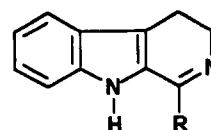


44

Tetrahydro- β -carbolines also result from the reduction of 3,4-dihydro- β -carbolines [e.g. **46**] which are produced in the Bischler-Napieralski reaction. Introduced by Asahina and Osada³⁴ and extended by Späthe and Lederer,^{35,36} the reaction consists of a cyclodehydration of a tryptamine amide [45] by means of phosphorous pentoxide, phosphorous oxychloride, polyphosphoric acid, or polyphosphate ester³⁷ to yield the 3,4-dihydro- β -carboline **46**.



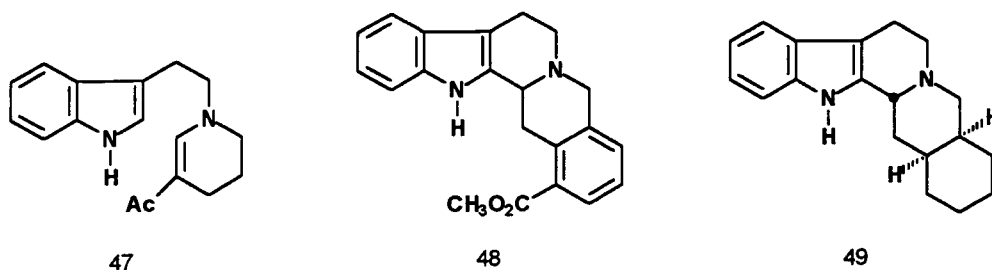
45



46

The use of indolyl-3-ethylpyridines [e.g. **47**] in various states of oxidation has also generated the tetrahydro- β -carboline structure when an electrophilic site

on the pyridine ring is attacked by the indole ring to afford cyclized product. Acid catalyzed Pictet-Spengler cyclization of tetrahydropyridines [i.e. **47**] has been used extensively by Wenkert and co-workers^{38,39} in the synthesis of various compounds including *d,l*-dihydrogambirtannine [**48**]⁴⁰ and *d,l*-epialloyohimbane [**49**].³⁵

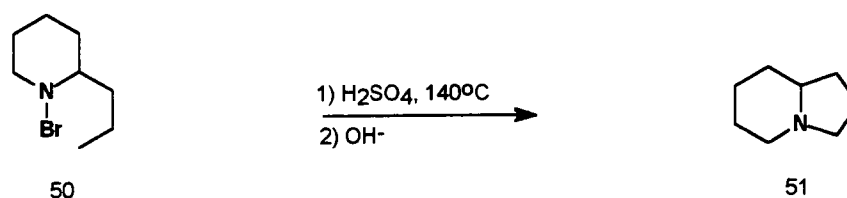


Chemical reduction of indolylethylpyridinium salts by LiAlH_4 in THF has also been shown to give the tetrahydro- β -carboline skeleton.⁴¹ Additionally, oxidation of 3-indolylethylpiperidines with mercuric acetate has been used by Wenkert and Wickberg⁴² to effect the above-mentioned cyclization. While there are many other reported syntheses of the 1,2,3,4-tetrahydro- β -carboline, the versatility of the above syntheses allow them to be representative of the different approaches to this ring system. In addition, the following chapters describe two other routes to this ring system involving a Pictet-Spengler cyclization: the cyclization of an imine formed from tryptamine and a cyclic ketone; and heterolytic cleavage of a nitrogen-chlorine bond followed by a skeletal rearrangement that ultimately leads to the formation of the β -tetrahydro-carboline framework. A brief review of

N-chloramine chemistry, both homolytic and heterolytic cleavage, seems in order prior to a discussion of the skeletal rearrangement that has been found to stem from heterolysis of the nitrogen-chlorine bond, the emphasis of this investigation.

The first reported homolytic cleavage of an N-haloamine was discovered serendipitously in the 1880's when A. W. Hofmann treated N-bromo-2-propylpiperidine [50] with hot sulfuric acid and obtained a tertiary amine.⁴³ This was later shown to be δ -coniceine or indolizidine [51] (Scheme I-4).^{44,45}

SCHEME I-4

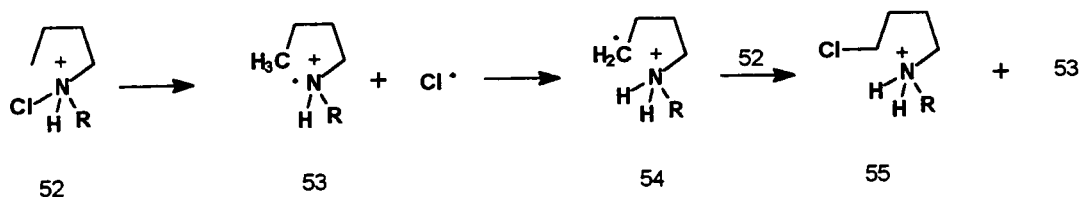


The experimental proof that these particular conditions encompassed a general pyrrolidine synthesis was collected by Löffler⁴⁶ and Freytag⁴⁷ some 20 years later. Many investigators^{48,49,50,51,52} have since refined and extended the reaction which has acquired the name "Hofmann-Löffler-Freytag reaction."⁵²

About 70 years after its discovery, two groups^{49,50,51} found evidence to support a free radical chain mechanism (Scheme I-5) in which a protonated N-haloamine **52** undergoes a homolytic cleavage under the influence of heat, light, or radical initiator to produce a protonated aminyl radical **53**. Intramolecular

abstraction of a positionally favorable hydrogen atom by the aminyl radical gives an alkyl radical [54] which abstracts a halogen atom and forms a haloalkylammonium ion [55] and another species [53] which continues the chain reaction. Species 55 cyclizes during the normal workup procedure (addition of base) to yield a pyrrolidine ring.

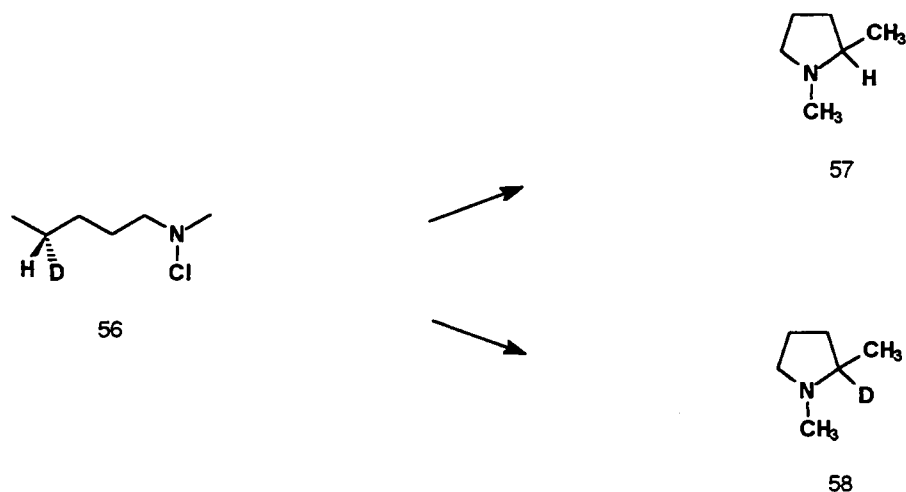
SCHEME I-5



The characterization of the Hofmann-Löffler-Freytag reaction in terms of stereochemistry, isotope effect, reaction intermediates, initiation and acid catalysis, and geometrical requirements of hydrogen abstraction has been investigated by Corey and Hertler.⁴⁹ The optically active N-chloramine of (-)-methyldiamine-4-d [56] was cyclized (Scheme I-6) under Hofmann-Löffler-Freytag conditions to give two products: 1,2-dimethylpyrrolidine [57] and 1,2-dimethylpyrrolidine-2-d [58]. These products were found to be optically inactive leading one to envision an intermediate in which C₄ adopts a trigonal planar sp^2 hybridization. An isotope effect (k_H/k_D) of 3.54, compared to a maximum theoretical isotope effect at 95°C of 4.7,⁵³ led Corey to reason that the breaking of the C-H(D) bond had proceeded

to a considerable extent in the transition state of the rate-determining step. This step involves a 1,5-intramolecular hydrogen (deuterium) shift which forms a cyclohexane-like transition state. This transition state is energetically more favorable than transition states which might arise from a 1,6-hydrogen shift (cycloheptyl-like transition state), a 1,4-hydrogen shift (cyclopentyl-like transition state), or a 1,3-hydrogen shift (cyclobutyl-like transition state).

SCHEME I-6



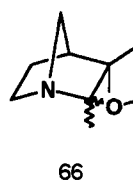
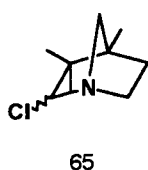
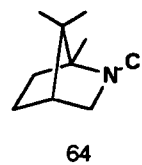
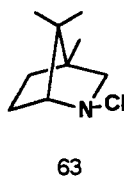
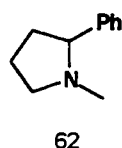
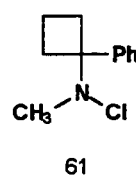
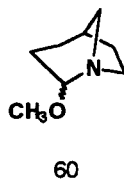
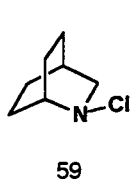
Although both N-bromo- and N-chloramines have been used in the Hofmann-Löffler-Freytag reaction, the greater thermal instability of N-bromoamines and their sometimes explosive nature^{43,54} soon favored N-chloramines as reagents of choice in these chain reactions. Synthetically, N-chloramines can be produced by saturating a cooled mixture of dilute sodium hydroxide, the amine, and ligroin with chlorine gas,⁵⁴ by treatment of a solution of

the amine hydrochloride with sodium hypochlorite⁵⁵ or by treatment of an ether solution of the free amine with N-chlorosuccinimide.⁵⁶

The previously mentioned aminyl radicals have been formed, though complexed with metals, through the treatment of the corresponding N-chloramines with catalytic amounts of reducing metal salts in neutral media.^{57,58} Complexation of the metal is assumed to occur at nitrogen's lone pair of electrons to enhance the electrophilic character of the aminyl radical, but not to the extent of the protonated aminyl radical.⁵⁹ In chemical reactions, metal-complexed aminyl radicals display characteristics between those shown by protonated and neutral aminyl radicals. Like neutral aminyl radicals, the complex does not undergo Hofmann-Löffler-Freytag reactions or selective hydrogen atom abstractions,⁶⁰ yet like protonated species, there is no tendency to dimerize or disproportionate, and addition to alkenes, dienes, and acetylenes is very successful.^{61,62} These characteristics of metal-complexed aminyl radicals have been demonstrated through the cyclization of several olefinic N-chloramines^{63,64} and the reaction has enjoyed several applications in the synthesis of natural products.^{65,66}

The most notable work in the area of heterolytic cleavage of the N-Cl bond in N-chloramines has been that of Gassman and coworkers who studied the rearrangement reactions of a number of cyclic N-chloramines.⁶⁷ Using refluxing methanolic silver nitrate, Gassman successfully rearranged N-chloroisoquinuclidine

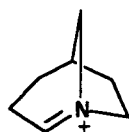
[59] to the amino ether **60** in 60% yield.^{68,69} Cyclobutylamine **61** was shown to undergo ring expansion to give pyrrolidine **62** after sodium borohydride reduction.⁷⁰ Bicyclic N-chloramines **63** and **64** were rearranged to give **65** and **66** respectively.^{71,72}



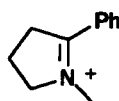
The alkyl migrations evident in the above cases parallel those that would be expected in the analogous carbocyclic cation systems and is indicative of an electron deficient nitrogen species - a nitrenium ion. While there are superficially many similarities between nitrenium ions and carbocations, there are also some obvious differences. Nitrogen is considerably more electronegative than carbon and, unlike

carbocations, nitrenium ions have a non-bonding electron pair which theoretically permits its existence in either the singlet or triplet form. In addition to the inference of nitrenium ions by product formation, the UV spectra of nitrenium ions generated during cyclic voltametry of di-*p*-anisylamine^{73,74} and the NMR spectra of the nitrenium ions generated in super acid from *p*-substituted nitrosobenzenes and benzoquinone monoximes⁷⁵ have been reported.

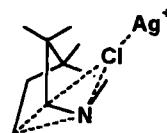
Gassman concluded that the observed products [60, 62, 65, 66] were derived from an imminium ion that formed subsequent to chloride loss and alkyl migration. Specifically, the formation of 60, 62, 65 and 66 can be attributed respectively to solvent attack on imminium ion 67, reduction of 68, internal return of chloride to the complex 69, and solvent attack on the imminium ion formed from 64.⁷⁰



67



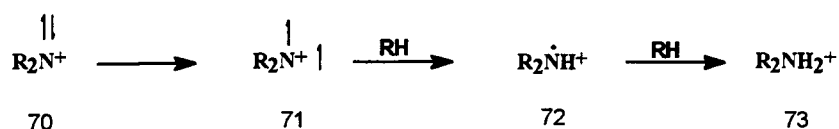
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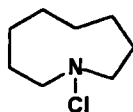
69

In many of these reactions involving N-chloramines, the formation of parent amine was seen as a significant side reaction. Gassman has proposed that the parent amine forms from abstraction of a hydrogen from the solvent by a triplet state nitrenium ion.⁶⁷ Upon heterolytic breakage of the N-Cl bond, a singlet nitrenium ion 70 is produced which can either undergo the rearrangement reaction or

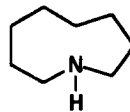
intersystem crossing to a triplet nitrenium ion **71**. Abstraction of a solvent hydrogen atom by the triplet would afford radical cation **72** which is itself an efficient hydrogen abstractor⁵² that could then provide ammonium salt **73**. Finally, during the basic workup procedure, this ammonium salt is deprotonated to the parent amine.



Another view concerning the formation of starting amine in the product mixture has been forwarded by Edwards and collaborators.⁷⁶ They propose that the parent amine arises from the homolytic cleavage of the N-Cl bond by silver metal contaminant present in the silver salt due to the photoreduction of the silver cation. Experimental support for this view came when N-chloramine **74** formed both the parent amine **75** and indolizidine [51] when placed together with silver metal. Furthermore, the reaction was found **not** to give bicyclic products upon exposure



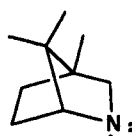
74



75

to air, thus implying a radical mechanism. These and other results led Edwards to conclude that "nitrenium ions are not generated from simple secondary chloramines in the presence of silver ions at room temperature."⁷⁷

In response, Gassman generated the aminyl radical **76** in both the ground and excited states to compare its behavior to that of **63**.⁷⁸ In each of these radical reactions, the main product obtained was **77**, a product that was absent in the silver



76

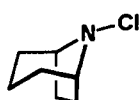


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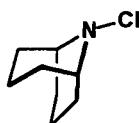
induced rearrangement of **63**. As these two groups have shown, the outcome of reactions involving N-chloramines is highly dependent on their structure and the reaction conditions - in cases where rearrangement is possible (and favored), nitrenium ion formation *can* explain the origin of observed products; in cases where metals favoring radical formation are present, hydrogen abstraction can be the favored route if the structure permits; and, as will be shown in the next chapter, in cases where rearrangement is possible, but not favored, both an N-chloramine:silver complex and a stable nitrenium ion have been observed.

Schell and co-workers,^{79,80} have observed that ring contraction occurred when N-chloronortropine [**78**], N-chlorogranatamine [**79**], and N-chloro-*trans*-

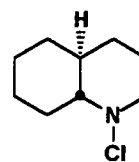
decahydro-quinoline [80] were treated with refluxing methanolic silver nitrate. Following reduction of the reaction mixture with sodium cyanoborohydride,⁸¹ **78** produced 35% of pyrrolizidine [81], **79** yielded 25% of pyrrolizidine acetal **82**, and **80** gave 13% of acetal **83**. The acetals **82** and **83** are thought to arise from the formation and subsequent rearrangement of a β -chloroenamine produced from the imminium ion intermediate.^{82,83}



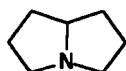
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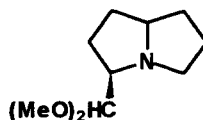
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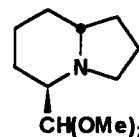
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81



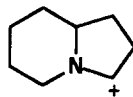
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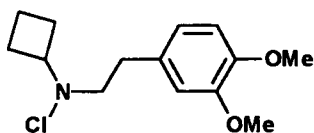
In an attempt to reduce the possibility of side reactions, notably attack by solvent, Schell and Ganguly⁸⁰ explored the action of silver tetrafluoroborate on N-chloramines in anhydrous benzene (a non-nucleophilic solvent which resists hydrogen abstraction). When N-chlorogranatanine [79] was exposed to these conditions it underwent rearrangement to **84** which precipitated from the solution along with silver chloride. This marked the first time that an ionic product was

isolated from a silver-induced rearrangement of an N-chloramine. Reduction of this precipitate produced indolizidine [51] in near quantitative yield.

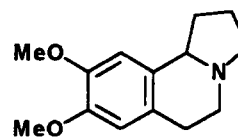


84

Ring expansion of N-chlorocyclobutylamines, which has also been observed by Schell and Smith,⁸⁴ leads to imminium ions in the presence of silver cation. Specifically, **85** was subjected to rearrangement conditions in which the resulting imminium ion (in the presence of concentrated HCl) was trapped by the aromatic ring, followed by reformation of the aromatic ring, to yield the tricyclic **86** (67%).



85



86

Schell and Cole⁸⁵ found that rearrangement of certain N-chloramines in methylene chloride occurs readily at room temperature in only about 10 min. This is presumably due to the absence of solvent complexation of silver ion typically seen when benzene or toluene is used as the medium.⁸⁶

The initial thrust of the present investigation was focused on the migratory ability of substituents adjacent to the nitrogen-chlorine bond. As has been shown,

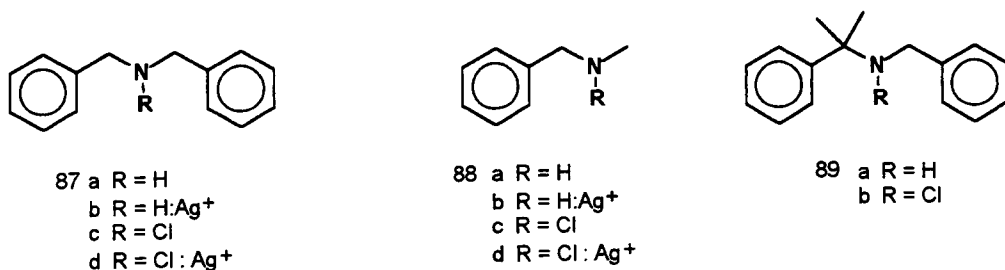
N-chloro-N-cyclobutyl groups inherently possess the ability to ring expand in the presence of silver ion, presumably to relieve angle strain. However, similar investigation in systems lacking the ability to ring open, had received limited attention. A study of secondary benzylic amines proved extremely fruitful in that the existence of an N-chloramine:silver complex was observed when substituent migration did not occur. Furthermore, once phenyl migration was observed, the competition between migration and ring expansion seemed an important area of research to explore in the tetrahydro- β -carboline system.

CHAPTER II

N-CHLORAMINE:SILVER COMPLEXES AND ISOLATION OF A NITRENIUM ION

The initial focus of the work reported herein was directed toward examining the boundaries of the silver catalyzed N-chloramine rearrangement in aprotic solvents in systems devoid of ring strain. While Edwards and coworkers^{76b,77} had shown that medium ring chloramines and simple aliphatic chloramines were inert at room temperature to silver ions in aqueous dioxane, tetrahydrofuran, or acetonitrile, rearrangements in acyclic systems had been observed by others for several aryl substituted N-chlorotritylamines^{87,88} and for N-chloro-N-methyltritylamine.⁸⁹ An investigation of migratory aptitudes of aryl groups in tritylhydroxylamines⁹⁰ furnished results similar to those obtained from the rearrangement of substituted pinacols.⁹¹ Foremost in our minds were the following questions: would rearrangement similar to that in the trityl substituted amines be found in compounds which have only one aryl substituent under conditions described by Schell and Ganguly;⁸⁰ if these rearrangements are observed, do the migratory aptitudes of hydrogen, methyl, and phenyl parallel those seen in carbocation rearrangements; and, finally, can the results of these acyclic cases be used to predict the rearrangement potential in non-strained, non-rigid cyclic

systems? In the attempt to resolve these questions, we initiated a study of a series of appropriately substituted secondary amines (i.e. dibenzylamine [87a], N-benzylmethylaniline [88a] and N-benzyl-1-methyl-1-phenethylamine [89]). These were converted into the corresponding N-chloramines [87c, 88c, 89b] and their interaction with the silver cation observed.



At the beginning of this investigation, we found it necessary to unequivocally identify the N-chloramines that were formed. While the amount of chlorine has been determined by some using iodometric analysis,⁷¹ the most routine method used to determine conversion of the parent amine into its N-chloramine derivative, prior to this work, was thin-layer chromatography (TLC). Typically, silica gel plates with methylene chloride as the mobile phase, provided a medium where the N-chloramine was observed with iodine vapor. The R_f value of a particular N-chloramine is always much greater than the R_f for the parent amine (0.85-0.95 vs. 0.0-0.1). Although TLC generally showed no evidence of starting amine after reaction with one equivalent of N-chlorosuccinimide (NCS), we utilized another method to fully establish the formation of the N-chloramine, namely Nuclear

Magnetic Resonance Spectroscopy (NMR). Interestingly, few reported cases of N-chloramines subjected to NMR are found in the literature⁷¹ owing probably to their reactive nature.

The N-chloramines, to be studied by proton NMR, were prepared by treatment of the corresponding secondary amines with N-chlorosuccinimide in methylene chloride. Following removal of succinimide by water extraction, the N-chloramines were isolated from the solvent by rotary evaporation at room temperature. Heating was avoided in the removal of solvent due to the unpredictable nature of N-haloamines and in light of rapid decomposition of purified N-chloramines related by others in our group.⁹² It has been the experience of the author, though, that most N-chloramines are stable enough to be purified by liquid chromatography (alumina or silica) and then to be safely analyzed by NMR. In fact, a mass spectrum (electron impact) of N-chlorodibenzylamine has been obtained which contains the parent ion peak (m/z of 231 corresponding to the M^+ peak for the molecular ion containing ^{35}Cl)!

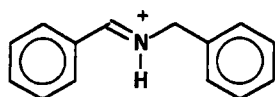
After observing the ease with which the N-chloramine travelled on TLC (silica/methylene chloride), we were curious if the N-chloramine nitrogen was basic enough to form a hydrochloride salt. Since such a species had not been encountered in the literature, it was a simple process to saturate a methylene chloride solution of N-chlorodibenzylamine [87c] with HCl gas. The solution turned a yellow-green

color and smelled of chlorine. A salt did form in the reaction, which after neutralization, proved to be the parent amine in nearly quantitative yield. Since chloride ion is a weak nucleophile it appeared that N-protonation occurred followed by chloride attack on nitrogen bound chlorine. Although chloride is too weak a nucleophile to dechlorinate unprotonated N-chloramines, it seemed likely that addition of a strong nucleophile could lead to dechlorination. In fact, when **87c** was treated with *n*-BuLi, followed by aqueous sodium bicarbonate, the parent amine was once again isolated in high yields. Similar results with Grignard reagents have been reported.^{93,94} Since previous reactions^{70,79,80} of certain N-chloramines produced an imminium ion that is usually reduced, it appeared likely that this reducing agent might also be able to dechlorinate any unreacted N-chloramine. Again formation of parent amine was observed when sodium cyanoborohydride was added to a methanolic solution of N-chlorodibenzylamine.

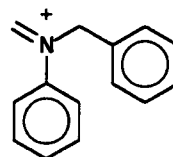
Since we demonstrated that dechlorination of N-chloramines could be accomplished by HCl gas or aqueous hydrochloric acid (both followed by adding base to the resulting hydrochloride salt), methanolic sodium cyanoborohydride reduction, or attack on the chlorine by *n*-butyllithium, it seemed likely that the formation of parent amine, reported by other groups,^{67,69,70,71,76,78,80,84,95} could be the result of incomplete reaction of the N-chloramine with silver ion with subsequent dechlorination during workup. Some groups reported the use of

concentrated hydrochloric acid, either to remove silver ion^{71,76b} or to initiate Pictet-Spengler cyclization⁸⁴, while others^{70,80} reported the use of sodium borohydride to reduce the newly formed imminium ion. Although many of the groups which saw return of parent amine did not report experimental detail, workup procedures similar to the ones reported above are expected and could explain the formation of parent amine.

Attempted rearrangements of compounds **87-89**, similar to the process observed in the trityl case,^{87,88,89} succeeded only in the last member of the group (*vide infra*). While the other two did not rearrange, they did exhibit signs of interaction with the silver ion. Specifically, the chlorination of dibenzylamine followed by addition of silver tetrafluoroborate showed no signs of rearrangement by either hydride migration to provide **90** or phenyl migration to provide **91**. Even



90

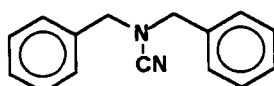


91

though TLC (silica/chloroform) of the reaction mixture showed no N-chloramine, the parent amine was nonetheless isolated after reduction with sodium cyanoborohydride.

Even more interesting results were obtained when this same N-

chloramine:silver mixture was quenched with an aqueous acidic cyanide solution, a proven nucleophilic medium for this task.⁹⁶ After neutralization with sodium bicarbonate, an equimolar mixture of N-chlorodibenzylamine [87c] and N-cyanodibenzylamine [92] was isolated and separated chromatographically (silica



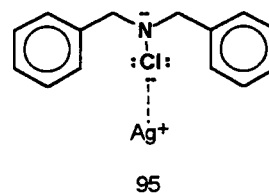
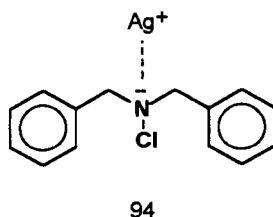
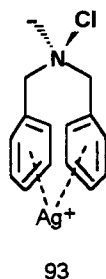
92

gel/methylene chloride). The results were consistent regardless of whether the solvent was benzene or methylene chloride, the reaction was at room temperature or above, or the atmosphere was nitrogen or oxygen. The N-chloramine 87c was easily identified by the presence of a methylene singlet signal at δ 4.09 in the ^1H NMR. Infrared spectroscopy (IR) of 92 revealed the characteristic nitrile stretch at 2199.5 cm^{-1} . The parent ion of 92 was located in the mass spectrum (MS) at 223 which is the m/z ratio for the protonated parent peak formed in the Fast Atom Bombardment (FAB) experiment. Although the proton NMR contained aromatic absorptions at δ 7.35-7.20 and the methylene singlet signal at δ 4.03, it was the carbon NMR that contained the most useful information - the nitrile carbon absorption at δ 118.1.

In addition, when 87c and aqueous acidic cyanide were mixed without the benefit of silver's influence, no displacement of chloride by cyanide was noted. At

this point, it seemed likely that an N-chloramine:silver complex [87d] could be responsible for the mysterious results above. The N-chloramine *appeared* absent on TLC, since it was complexed to silver ion which affected its R_f value. During reductive workup, addition of sodium cyanoborohydride to this complex resulted in the formation of silver and the parent amine. The enhanced reactivity of the N-chloramine toward a strong nucleophile, CN^- , after silver ion was added is also consistent with an N-chloramine:silver complex. In a related experiment, 87d was quenched with 6 M hydrochloric acid which resulted in copious amount of precipitated silver chloride. Presumably, this released the N-chloramine 87c from the silver complex 87d, rendering it susceptible to conversion into the ammonium salt of the parent amine by excess HCl (*vide supra*). Alkaline workup affords the parent amine.

Several structures [93 - 95] for this silver:N-chloramine complex have been envisioned, and all have some precedence in the literature. The existence of donor-

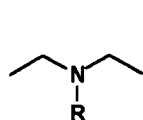


acceptor complexes between aromatic moieties and Ag(I) [e.g. 93] has been known for some time.^{97,98} Although the 1:1 complexes are well known, solution

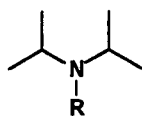
evidence,^{99,100} composition phase diagrams,¹⁰¹ and temperature composition diagrams¹⁰² have indicated aromatic-to-silver ratios different from 1:1. The nature of the bonding between Ag(I) and aromatics has been discussed by Mulliken¹⁰³ and Dewar,¹⁰⁴ and molecular orbital calculations¹⁰⁵ have been made to predict the positioning of the silver ion in substituted benzenes and other aromatics. In addition, silver:nitrogen complexes of amines are also well documented in the literature;¹⁰⁶ hence we may have a complex such as **94**. With the formation of silver chloride in systems which undergo rearrangement by polar means comes the likelihood that a silver:chlorine complex [**95**] might be formed which should resemble the one assumed to form when secondary or tertiary alkyl halides react with silver ion. In reality, a combination of these interactions may be occurring to further complicate the situation.

Since results similar to those observed for dibenzylamine were also seen in the benzylmethanamine [**88a**] case, we decided to thoroughly investigate the interaction of these two amines and their N-chloramines with silver ion by NMR. Obviously X-ray analysis would provide more information about the structure of this complex, but all attempts at growing single crystals of the silver complex failed. Several new compounds were also selected, primarily on a functional group and structural basis, to help ascertain the type of interaction between silver cation and aryl containing N-chloramines. Insight into this interaction could be useful in

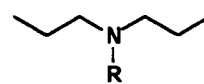
proposing a mechanism for reactions in which N-chloramines do undergo structural rearrangements (see pages 23-24, and 27-29). Some of the selected compounds (diethylamine [96a], diisopropylamine [97a], dipropylamine [98a], and dibutylamine [99a]) have no aryl substituents, allowing interaction only at nitrogen or chlorine. Another group (toluene [100], and ethylbenzene [101]) was selected to illustrate the interaction of the aryl group in the absence of nitrogen or chlorine. The remaining compounds (dibenzylamine [87a], benzylmethylamine [88a],



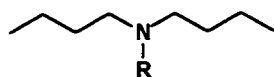
96 a R = H
b R = H:Ag⁺



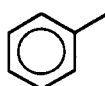
97 a R = H
b R = H:Ag⁺
c R = Cl
d R = Cl:Ag⁺



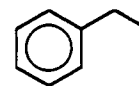
98 a R = H
b R = H:Ag⁺
c R = Cl
d R = Cl:Ag⁺



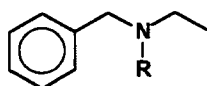
99 a R = H
b R = H:Ag⁺
c R = Cl
d R = Cl:Ag⁺



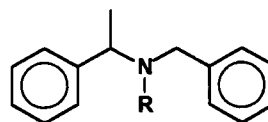
100



101



102 a R = H
b R = H:Ag⁺
c R = Cl
d R = Cl:Ag⁺



103 a R = H
b R = H:Ag⁺
c R = Cl
d R = Cl:Ag⁺

benzylethylamine [102a], and benzyl-1-phenethylamine [103a]) possess all three functional groups with which interaction is possible and can be compared to the first two groups to gain insight into the site or sites of silver's interaction. The proton NMR chemical shifts of these compounds, the complexes formed from these compounds and silver ion, their N-chloramines, and their N-chloramine:silver complexes are shown in Table II-1. The changes in chemical shifts that occurred between the free amine and the amine:silver complex (a→b), the free amine and the N-chloramine (a→c), and the N-chloramine and the N-chloramine:silver complex (c→d) are shown in Table II-2.

The α and β hydrogens of the dialkylamines [96a - 99a] shifted downfield in the proton NMR by 0.11 to 0.25 ppm when silver ion was complexed to nitrogen's lone pair [e.g. 96b - 99b]. A similar change (.18-.28 ppm) was observed when the dialkyl-N-chloramines [97c - 99c] were mixed with 1 equivalent of silver tetrafluoroborate to form 97d - 99d. This leads one to believe that complexation is occurring at nitrogen and not at chlorine. Additionally, the alkyl substituent on toluene and ethylbenzene appears to be unaffected by silver ion ruling out significant chemical shift contribution from aryl complexation. This result is similar to those seen in other non-rigid aromatic compounds.¹⁰⁷ An interesting upfield shift (0.01 - 0.06 ppm) is seen for the α^* hydrogens in 87, 88, and 104 when silver ion is added. A similarly small change (-0.03 to +0.07 ppm) is

Table II-1: Proton NMR Chemical Shifts of Certain Secondary Amines, the Amine:Silver Complex, the N-Chloramine, and the N-Chloramine:Silver Complex

Compound Structure	Compound #	Aryl	α^*	α'	β	γ	δ	N-H
$(\text{CH}_3\text{CH}_2)_2\text{N-R}$	96a R = H			2.656	1.111			1.42
	96b R = H:Ag ⁺			2.906	1.3			3.42
$((\text{CH}_2)_2\text{CH})_2\text{N-R}$	97a R = H			2.88	0.99			1
	97b R = H:Ag ⁺			3.1	1.2			3.17
	97c R = Cl			3.27	1.15			
	97d R = Cl:Ag ⁺			3.55	1.39			
$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{N-R}$	98a R = H			2.57	1.51	0.92		1.23
	98b R = H:Ag ⁺			2.71	1.62	0.96		2.83
	98c R = Cl			2.88	1.69	0.93		
	98d R = Cl:Ag ⁺			3.12	1.87	1.03		
$(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{N-R}$	99a R = H			2.6	1.5	1.36	0.92	1.18
	99b R = H:Ag ⁺			2.78	1.63	1.39	0.93	3.28
	99c R = Cl			2.91	1.65	1.36	0.93	
	99d R = Cl:Ag ⁺			3.16	1.84	1.45	0.98	
$\text{C}_6\text{H}_5\text{CH}_3$	100	7.12 - 7.24	2.34					
$\text{C}_6\text{H}_5\text{CH}_3 : \text{Ag}^+$	100	7.19 - 7.3	2.36					
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$	101	7.16 - 7.35	2.64		1.23			
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3 : \text{Ag}^+$	101	7.16 - 7.29	2.65		1.24			
$(\text{C}_6\text{H}_5\text{CH}_2)_2\text{N-R}$	87a R = H	7.2 - 7.37	3.78					1.66
	87b R = H:Ag ⁺	7.1 - 7.29	3.72					3.18
	87c R = Cl	7.26 - 7.42	4.09					
	87d R = Cl:Ag ⁺	7.26 - 7.45	4.16					
$(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)\text{N-R}$	88a R = H	7.2 - 7.32	3.73	2.44				1.53
	88b R = H:Ag ⁺	7.2 - 7.3	3.68	2.51				3.38
	88c R = Cl	7.3 - 7.4	4.05	2.94				
	88d R = Cl:Ag ⁺	7.5 - 7.35	4.02	3.24				
$(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3\text{CH}_2)\text{N-R}$	102a R = H	7.2 - 7.31	3.78	2.67	1.12			1.36
	102b R = H:Ag ⁺	7.25 - 7.35	3.85	2.83	1.07			4.37
	102c R = Cl	7.25 - 7.35	4.08	3.01	1.25			
	102d R = Cl:Ag ⁺	7.33 - 7.6	4.12	3.33	1.3			
$(\text{C}_6\text{H}_5(\text{CH}_2)\text{CH})(\text{C}_6\text{H}_5\text{CH}_2)\text{N-R}$	103a R = H	7.16 - 7.4	3.61	3.79	1.35			1.56
	103b R = H:Ag ⁺	7.1 - 7.4	3.6	3.86	1.35			3.75
	103c R = Cl	7.2 - 7.45	3.93	4.15	1.63			
	103d R = Cl:Ag ⁺	7.27 - 7.5	3.96	4.26	1.64			

* The benzylic CH₂ or CH₃

Table II-2: The Chemical Shift Change (Δ) Observed in the ^1H NMR when the Parent Amine Interacts With Silver Ion (a-b), when the Parent Amine is Converted to the N-Chloramine (a-c), and when the N-Chloramine interacts with Silver Ion (c-d).

Compound Structure	#	$\Delta \alpha^*$ a → b	$\Delta \alpha^*$ a → c	$\Delta \alpha^*$ c → d	$\Delta \alpha'$ a → b	$\Delta \alpha'$ a → c	$\Delta \alpha'$ c → d	$\Delta \beta$ a → b	$\Delta \beta$ a → c	$\Delta \beta$ c → d
$(\text{CH}_3\text{CH}_2)_2\text{N-R}$	97				0.25			0.19		
$((\text{CH}_3)_2\text{CH})_2\text{N-R}$	98				0.22	.39	.28	0.19	0.16	.24
$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{N-R}$	99				0.14	.31	.24	0.11	0.18	.18
$(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{N-R}$	100				0.18	.31	.25	0.13	0.15	0.19
$\text{C}_6\text{H}_5\text{CH}_3$	101	0.02								
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$	102	0.01						0.01		
$(\text{C}_6\text{H}_5\text{CH}_2)_2\text{N-R}$	87	-0.06	0.31	0.07						
$(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)\text{N-R}$	88	-0.05	0.32	-0.03	0.07	0.5	0.30			
$(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_2\text{CH}_3)\text{N-R}$	103	0.07	0.3	0.04	0.16	0.34	0.32	-0.05	0.13	0.05
$(\text{C}_6\text{H}_5(\text{CH}_3)\text{CH})(\text{C}_6\text{H}_5\text{CH}_2)\text{N-R}$	104	-0.01	0.32	0.03	0.07	0.36	0.11	0	0.28	0.01

* The benzylic CH_2 or CH_3

observed for these same hydrogens when the corresponding N-chloramines [87c, 88c, 103c, 104c] are placed in the presence of silver ion. Very different results for 88c were obtained after a particular experiment in which the N-chloramine was allowed to interact with silver ion overnight. After solvent removal and dissolution of the remaining material, the proton NMR showed absorptions at δ 7.27-7.41, 4.11, and 2.72, corresponding to aromatic, benzylic, and methyl hydrogen absorptions, respectively. These results are markedly different than those observed when the N-chloramine 88c, in a deuterated solvent, is allowed to interact with silver ion for only a few minutes. It is very possible that these chemical shifts

might be representative of a nitrenium ion, since such an ion has been observed when **87c** is allowed prolonged exposure to silver ion (*vide infra*).

While the scope of the data is insufficient to allow extensive speculation, it is apparent that an N-chloramine:silver complex is formed and that the predominant site of this complexation is at the nitrogen. While it is true that the presence of an aromatic moiety does lead to smaller chemical shift changes for the α^* benzylic hydrogens (-0.03 - 0.07 ppm for compounds **87**, **88**, **103**, and **104 c→d**), compared to the aliphatic α' hydrogens (0.25 -0.28 ppm for compounds **98** - **100 c→d**), the extent of aromatic participation can not be determined from NMR data. In fact, the α' hydrogens of the N-alkyl group in **88c→d** and **102c→d**, show chemical shift changes (0.30 and 0.32, respectively) very close to those observed for the aliphatic α' hydrogens (0.25 -0.28 ppm) mentioned previously. This leads one to envision a structure for these N-chloramine:silver complexes which is very similar to **94**.

Also of interest, is the change in chemical shift that occurs when N-H is converted into N-Cl (a→c). The hydrogens adjacent (both α^* and α') to the nitrogen exhibit an average shift of 0.35 ppm with a range of 0.3 - 0.5 ppm. As expected, the hydrogens β to the nitrogen show a smaller, but still significant, average chemical shift change (0.18 ppm) with a range of 0.13 - 0.28 ppm. Thus the substituent effect of chlorine on neighboring hydrogens seems to be fairly

constant regardless of whether the hydrogens are benzylic or alkyl.

In an attempt to determine the saturation point of silver ion in this complex, the ratio of silver cation to N-chlorodibenzylamine was varied. The maximum chemical shift change occurred when the $\text{Ag}^+:\text{N-chloramine}$ was 3:1. At this ratio, the methylene singlet absorbed at δ 4.24 in the ^1H NMR. In a related experiment, one equivalent of silver tetrafluoroborate was treated with one equivalent of N-chlorodibenzylamine in an NMR tube. After the proton NMR was obtained, a sequential addition of N-chloramine to the NMR tube resulted in an upfield shift of the methylene hydrogens (Table II-3). The concentration of the added N-chloramine **87c** was comparable to the concentration already present in the NMR tube. The same NMR tube was used for all of the cases reported in Table II-3 and no reshimming was performed so that any chemical shift variance would be eliminated. The chemical shift information contained in Table II-3 demonstrates the facile movement of silver ion between the molecules of N-chloramine **87c**. If the complexation constant for this complex is large, one would expect to see an absorption for the complex and one for the N-chloramine when added in excess. However, if the silver ion "jumps" from one N-chloramine to another, faster than the NMR time scale, one would see an average absorption for the mixture. The chemical shift of the complex would then vary with its composition.

From the information in Table II-3, one can see that both the aromatic and

Table II-3: ^1H NMR Chemical Shifts of N-Chloramine:Silver Ion Mixtures of Varying Composition

	δ Aromatic Hydrogens	δ Methylene Hydrogens
N-chloramine (NCA)	7.20-7.34	4.0318
NCA + 1 Eq AgBF_4	7.30-7.4	4.177
+ 2 drops NCA	7.30-7.42	4.168
+ 4 more drops NCA	7.30-7.417	4.158
+ 5 more drops NCA	7.299-7.41	4.150
+ 10 more drops NCA	7.29-7.39	4.136
+ 20 more drops NCA	7.288-7.38	4.119

the methylene hydrogens are affected by the complexation of the silver ion. With each addition of N-chloramine (NCA), the chemical shift of the upfield absorption in the aromatic region is moving toward the 7.20 ppm mark (the chemical shift of the most upfield portion of N-chlorodibenzylamine). Also, the methylene peak is moving from 4.18 ppm (when N-chloramine:silver ion is 1:1) toward 4.03 ppm (the chemical shift of the methylenes of N-chlorodibenzylamine) as more NCA is added. These results are consistent with the formation of a weak association silver and the N-chloramine.

A low temperature (200 K) proton NMR study was also conducted in which the methylene signal of dibenzyl-N-chloramine [87c] at 200 K was observed (Figure II-1) and compared to the methylene signal of the dibenzyl-N-chloramine:silver complex [87d] also at 200 K (Figure II-2). At room temperature, a singlet was

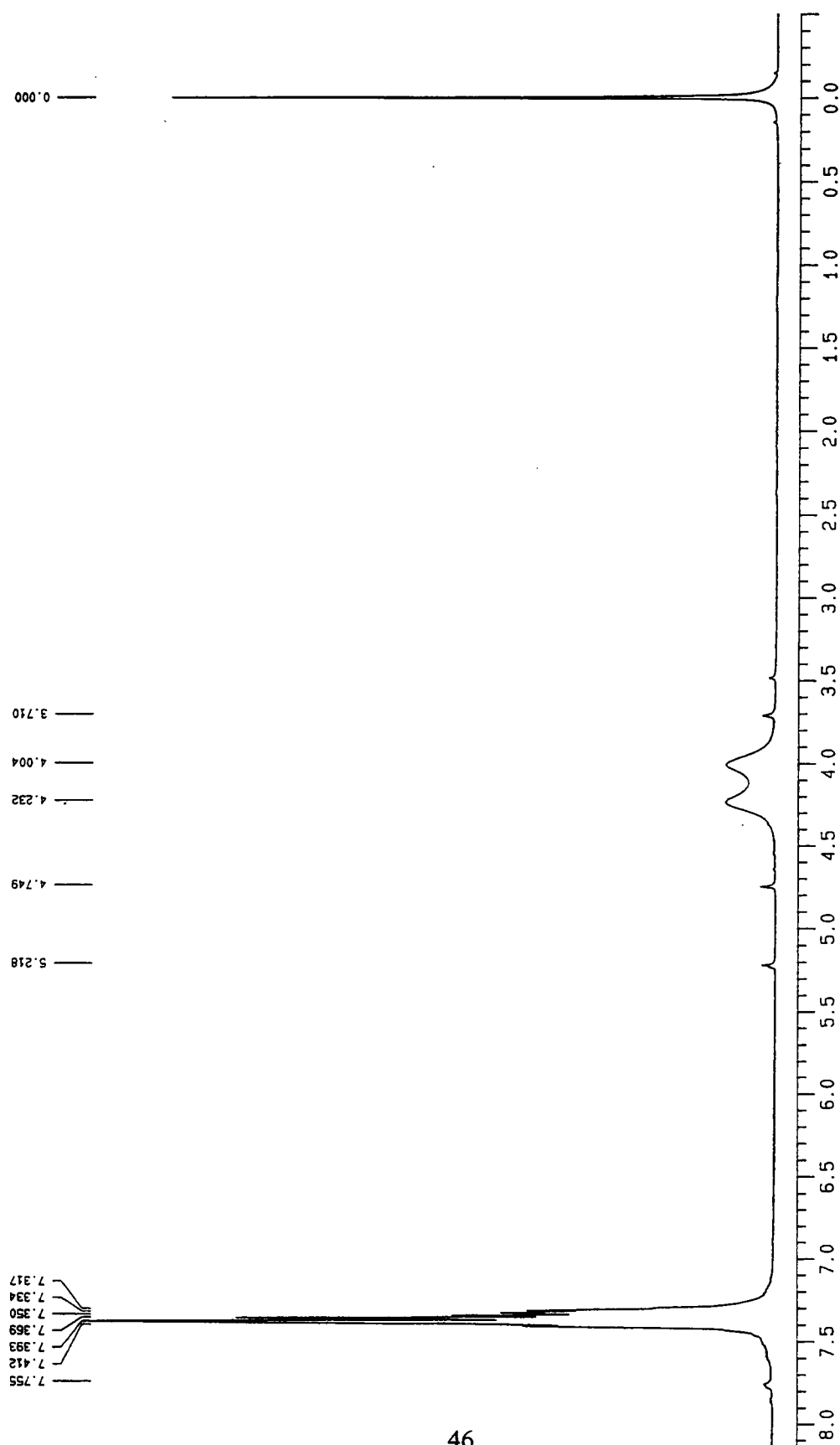


Figure II-1: Low Temperature (200 K) ^1H NMR of Dibenzyln-N-Chloramine [87c]

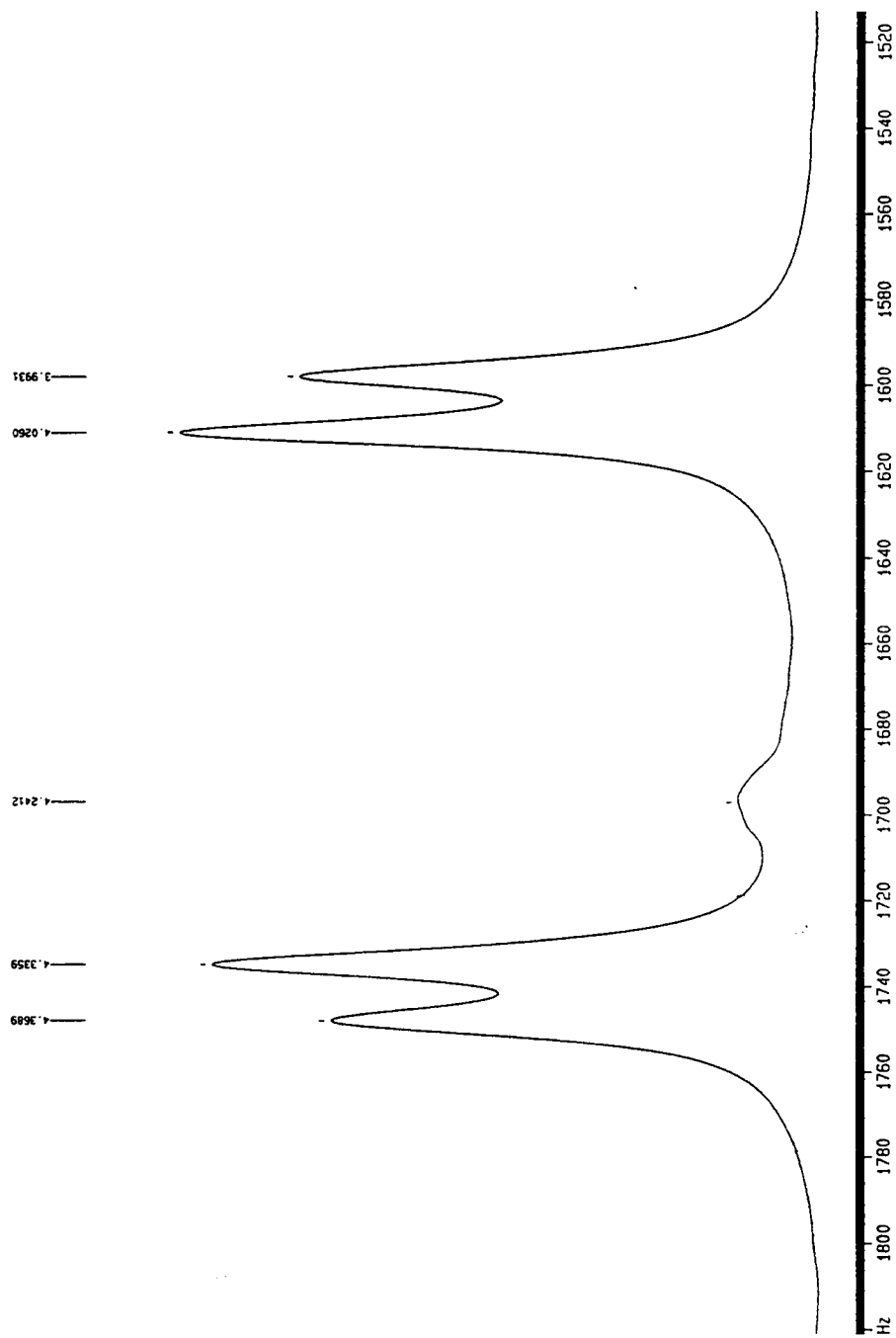


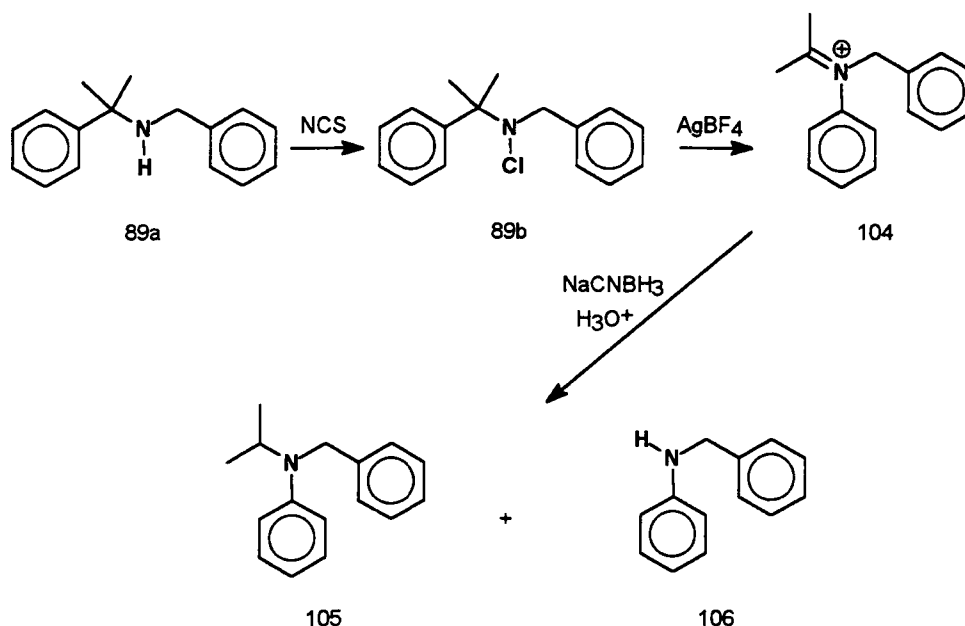
Figure II-2: Low Temperature (200 K) ^1H NMR of Dibenzy1-N-Chloramine:Silver Ion Complex [87d]

observed at δ 4.11 for **87c**. This signal split into two broad singlets positioned at δ 4.00 and δ 4.23 at 200 K. The average of these two peaks (δ 4.11) coincides with the room temperature peak observed previously. It appears that nitrogen inversion has stopped or at least is slower than the NMR time scale so that the methylene hydrogens are now different. However, the coupling between these hydrogens appears to be small, resulting in a broad singlet. Complexation of the N-chloramine with 1 equivalent of silver tetrafluoroborate afforded an interesting ^1H NMR at 200 K (Figure II-2); two doublets at δ 4.01 and δ 4.353, each with J values of 13.2 Hz. The center of the two doublets comes at δ 4.18, which is similar to the room temperature value reported in Table II-1 for **87d**. In this situation, the temperature is low enough that the silver ion is limited in movement and remains complexed to the N-chloramine long enough that the complex is seen by ^1H NMR. Consequently, the two methylene hydrogens are sufficiently different that a geminal coupling constant of 13.2 Hz is observed. Also present in the N-chloramine:silver spectrum is a peak at δ 4.24 which corresponds to one of the peaks seen in the low temperature spectrum of the N-chloramine. Presumably, the other half of this doublet is present, but buried under the upfield doublet of the complex. Thus silver ion exchange between N-chloramine molecules is also slowed at low temperature.

Unlike the compounds in Table II-1, N-benzyl-1-methyl-1-phenethylamine

[89b] underwent rearrangement when exposed to silver ion similar to the trityl substituted amines. Compound **89a** was generated from the reduction of the benzamide, formed from 1-methyl-1-phenethylamine and benzoyl chloride, by lithium aluminum hydride. The 1-methyl-1-phenethylamine was synthesized starting from 2-phenyl-2-propanol as described by Kalir.¹⁰⁸ This involved converting the alcohol to a mixture of 2-chloro-2-phenylpropane and the styrene when reacted with concentrated hydrochloric acid. Both products reacted with aqueous acidic azide to afford the alkyl azide which was reduced to 1-methyl-1-phenethylamine by lithium aluminum hydride. Compound **89a** was chlorinated with N-chlorosuccinimide and treated with silver tetrafluoroborate in methylene chloride to give the imminium ion **104**. Evidence of the imminium ion was seen in the proton NMR - a singlet at δ 5.40 integrated for two hydrogens and two other singlets at δ 2.98 and 2.37 integrated for three hydrogens each. Reduction of **104** by sodium cyanoborohydride in methanol gave the starting amine, the reduced product **105**, and the hydrolyzed product **106**, in 30, 35, and 35% yield, respectively (Scheme II-1). Molecular formula verification of **105** and **106** was accomplished by MS, where the parent ions had m/z ratios of 225 and 183, respectively. Structure determination was easily carried out by carbon NMR - **105** showed ortho and para carbon absorptions at δ 116.4 and 113.2, respectively, indicative of aniline formation and N-isopropyl at δ 48.2 and δ 19.9. Aniline

SCHEME II-1



formation was further supported by the presence of aromatic hydrogens at δ 6.75-6.6 in the proton NMR. The isopropyl group was also seen in the proton NMR containing its characteristic splitting pattern of a septet and a doublet at δ 4.27 and 1.20, respectively. Similar aromatic carbon absorptions were seen for **106** (δ 117.6 and 112.8), but the aliphatic region of the proton NMR contained only two unsplit absorptions at δ 4.13 (CH₂) and 1.25 (N-H). Three carbons and their hydrogens were clearly missing from both the proton and carbon NMR spectra of **106**. This is consistent with the MS observations reported above.

It appears that **89b** might have an advantage over other similarly substituted N-chloramines [**87**, **88**, **102c**, and **103c**] toward rearrangement. While there is no obvious conformational bias available to **89b** that is unavailable to the others, there

is an energy factor which must be considered. The source of the difference in energies of the various imminium ions, derived from **87**, **88**, **89**, **102**, or **103** can be attributed to the degree of alkyl substitution present at the sp^2 carbon, since alkyl groups are known to be electron-donating. A resonance contributor of **104** contains a dialkyl substituted carbenium ion while the imminium ions from other compounds [**87**, **88**, **102**, and **103**] would contain either two hydrogens or one hydrogen and one alkyl group at this carbon atom.

As mentioned previously, all attempts to grow crystals of an N-chloramine:silver ion complex had met with failure. In each case, a purple non-crystalline silver ion precipitate had formed on the sides of the container which was subsequently discarded after several weeks due to absence of crystal formation. One such experiment, however was left in the dark at 5 °C for about one year during which time the solvent partially evaporated. Crystal growth was observed extending from the walls of the container, which were coated with non-crystalline silver ion precipitate, inward to the center of the test tube. Careful decantation of the solvent left behind crystal growth that was gently dislodged to give orthorhombic crystals suitable for structure analysis. X-ray crystallography revealed the molecular structure (Figure II-3) by direct methods using the SHELXTL PLUS software.¹⁰⁹ The crystal was found to contain no silver and no chlorine. The crystal data, collection data, and solution and refinement data are

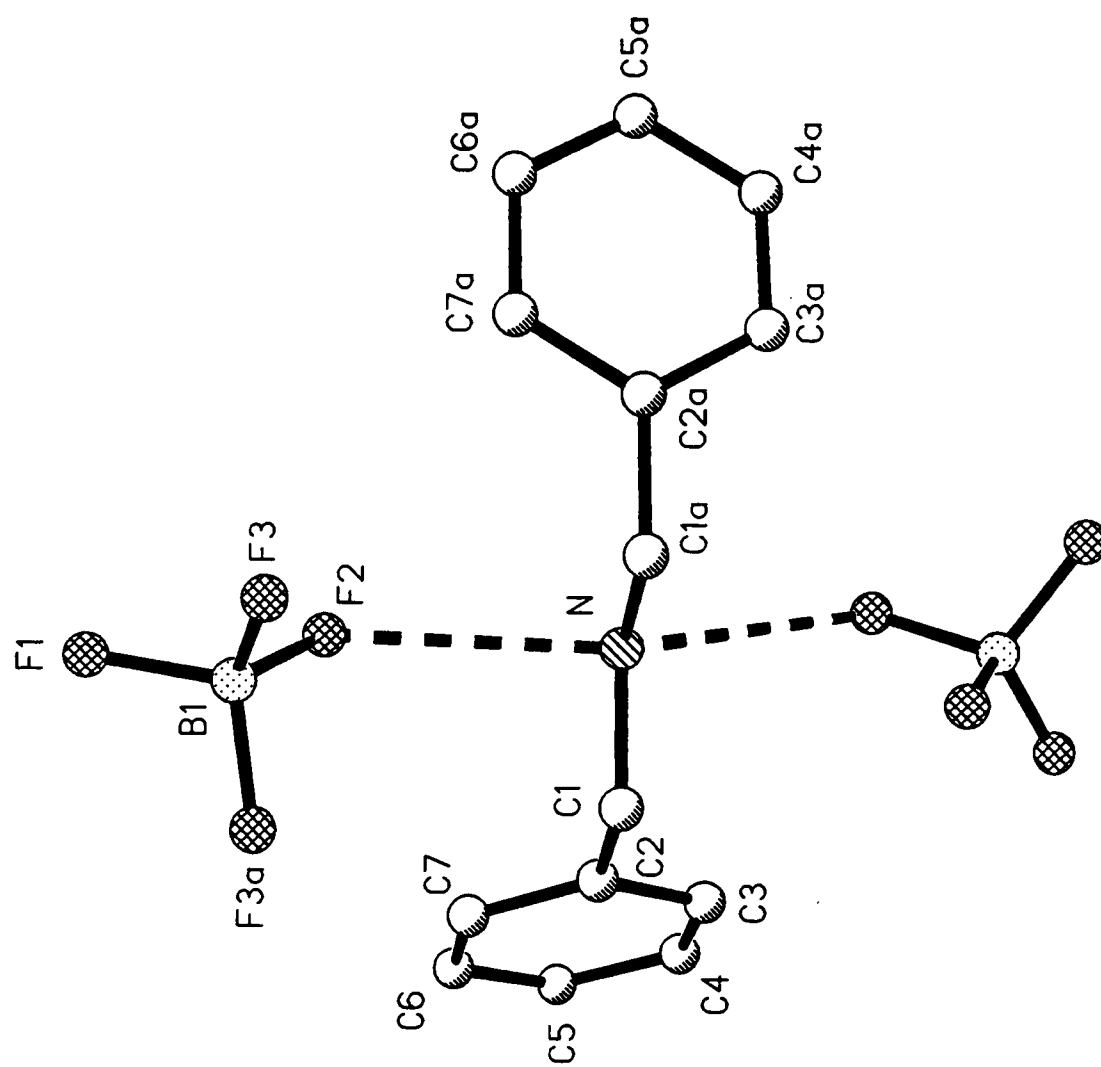


Figure II-3: Ball-and-Stick Depiction of Dibenzylnitrenium Tetrafluoroborate

given in Table A-1, Table A-2, and Table A-3 (pages 137-139), respectively. The atomic positional parameters are given in Table A-4 (page 140) and bond distances and angles are given in Table A-5 and Table A-6 (pages 140-141), respectively. Anisotropic displacement coefficients are given in Table A-7 (page 141). The coordination geometry of the nitrogen atom is that of a distorted see-saw (Figure II-4) which is likely the result of crystal packing phenomena. The N-C(1) bond distance is 1.506(4) Å and the C(1)-N-C(1a) bond angle is 113.8(4)°. This bond angle is consistent with an sp^2 center containing a lone electron pair that compresses the σ bond angles relative to the ideal angle of 120°. The presence of the tetrafluoroborate anion dictates that the nitrogen atom possess a positive charge, hence a **nitrenium ion**. While spin conservation requires that the first formed ion is a singlet, the triplet state can be reached by intersystem crossing. Which of these two states is the ground state is still a matter of intense discussion. Initial work in this area by Lee and Morokuma¹¹⁰ using *ab initio* SCF-CI calculations on the nitrenium ion NH_2^+ predicted an almost linear triplet ground state. This geometry is consistent with Walsh's prediction that the singlet NH_2^+ is bent and the triplet is almost linear.¹¹¹ Later, Ford and Scribner, using semi-empirical methods (MNDO), concluded that aryl nitrenium ions possessed a singlet ground state.¹¹² More recent work by Falvey and Cramer (using correlated CISD, *ab initio* calculations) generally support the conclusions above in that nitrenium ions

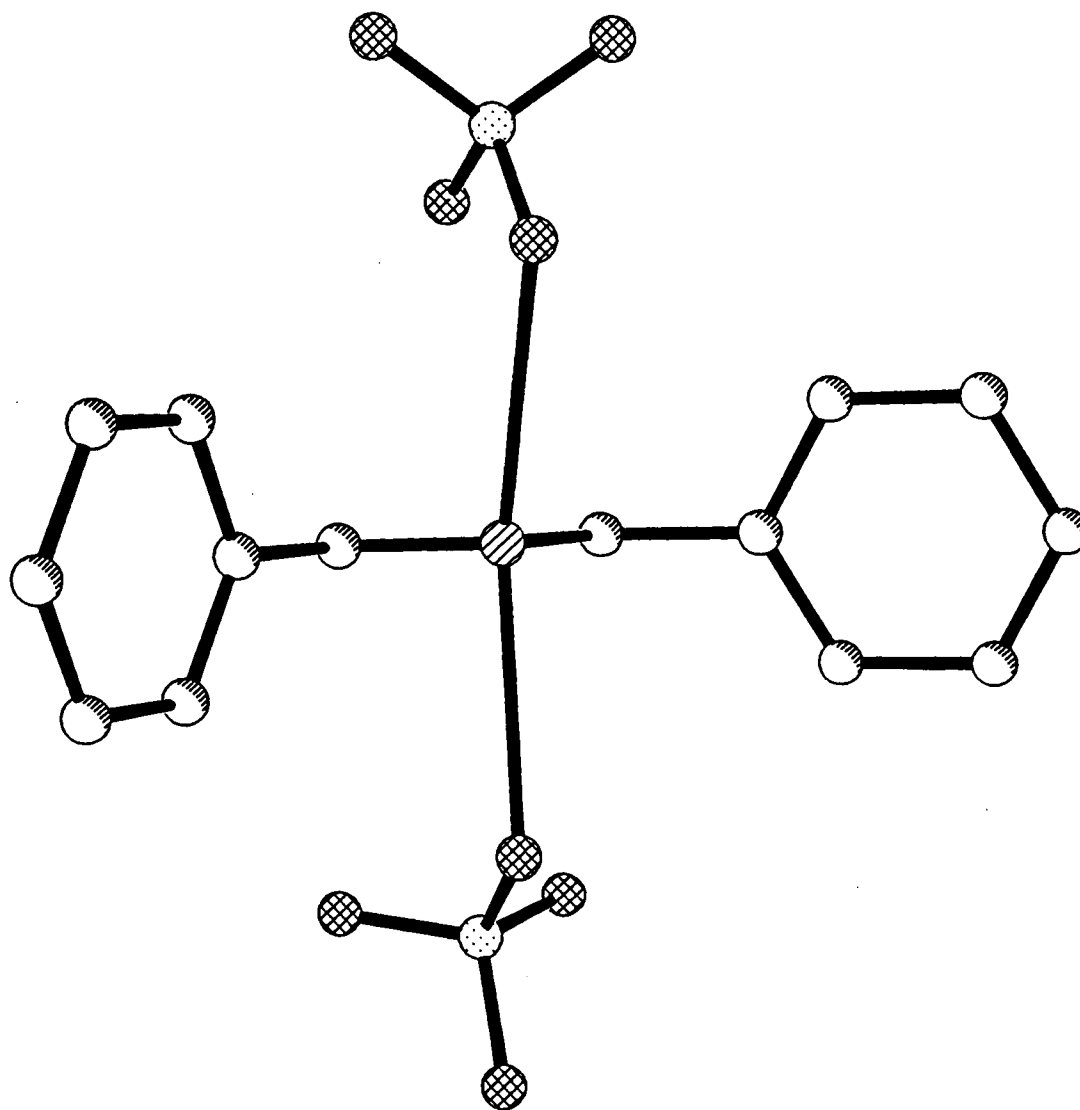


Figure II-4: Distorted See-Saw Geometry of Dibenzylnitrenium Tetrafluoroborate

containing electron deficient π systems will favor the triplet state while electron rich π systems will favor the singlet state.¹¹³ The R-N-R' bond angle of both triplet and singlet states has been calculated to be between 150 - 160° and 110 - 130°, respectively. Thus, if nitrogen is found in a small ring, the triplet state will be destabilized due to its inability to adopt the preferred bond angle. Conversely, the presence of bulky groups in acyclic nitrenium ions is predicted to destabilize the singlet state by sterically preventing the formation of more favorable angles.¹¹³ However, solid-state analysis of dibenzylnitrenium tetrafluoroborate indicates that the two electrons on nitrogen are contained in the same orbital which is orthogonal to the unhybridized p orbital interacting with the tetrafluoroborate anion. While this is consistent with a singlet state geometry, it is surprising since other dialkylnitrenium ions have been predicted with triplet ground states.¹¹³

The proton NMR spectrum of dibenzylnitrenium tetrafluoroborate (Figure II-5) in deuterated chloroform shows the aromatic singlet at δ 7.38 and the methylene singlet at δ 4.05. Since these values are very similar to those observed for the N-chloramine (δ 4.14), a sample of the nitrenium ion was mixed with the N-chloramine and two absorptions were found at δ 4.14 and 4.06. These results also dispell any notion that the nitrenium ion and the N-chloramine are interconverting. Additionally, it was thought that the nitrenium ion may be crossing

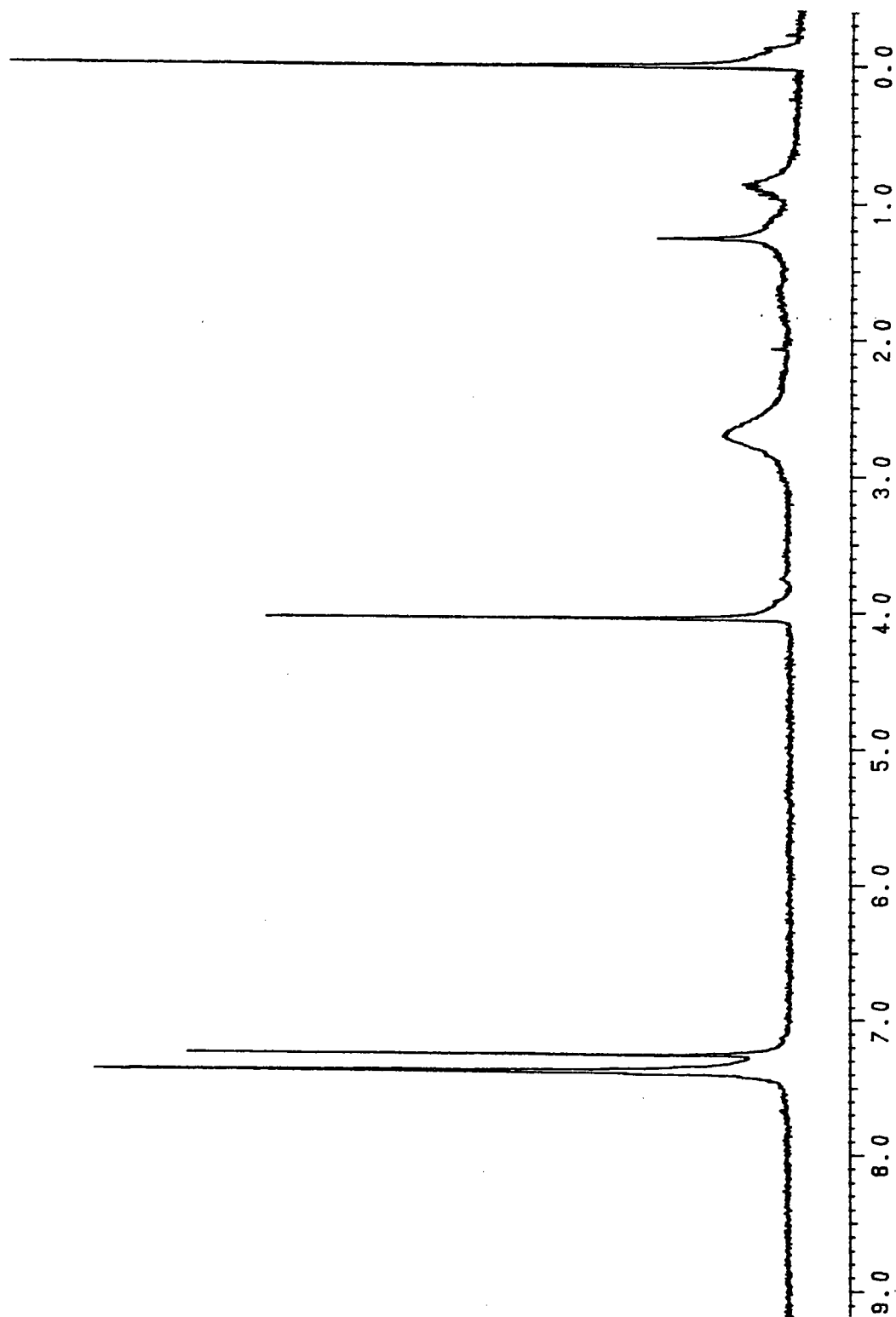


Figure II-5: ^1H NMR of Dibenzylnitrenium Tetrafluoroborate

to the triplet state and abstracting deuterons from the NMR solvent and that the deuterated parent ammonium ion was responsible for the proton NMR absorptions above. However, the proton NMR of the deuterated dibenzylammonium ion revealed methylene hydrogen absorption at δ 3.82. More spectroscopic support in favor of the nitrenium ion came from the carbon NMR spectrum (Figure II-6), where the methylene carbons absorbed at δ 50.8 and the aromatic carbons absorbed at δ 130.9, 129.6 (2C) and 129.4; these absorptions were different from those observed for the parent amine [87a], the N-chloramine [87c], or the deuterated dibenzylammonium ion.

The isolation and characterization of nitrenium ions has long been a goal of many researchers. Prior to this work, the only direct observation of nitrenium ions was reported using ^{15}N NMR.¹¹⁴ Like dibenzylnitrenium tetrafluoroborate, these nitrenium ions were stable at ambient temperature to atmospheric moisture and air. Other reported nitrenium ions might be more accurately be described as highly resonance stabilized carbenium ions in super-acid medium,¹¹⁵ or as filled-octet oxonium ions¹¹⁶ and ammonium or imminium ions¹¹⁷ in electrochemical oxidations leading to formal nitrenium ions. In addition, aryl nitrenium ions have been proposed as intermediates which covalently bind guanine residues¹¹⁸ on DNA leading to carcinogenesis.¹¹⁹ With a stable nitrenium ion in hand, it may be possible to gain some insight into the mechanism of this DNA-damaging step.

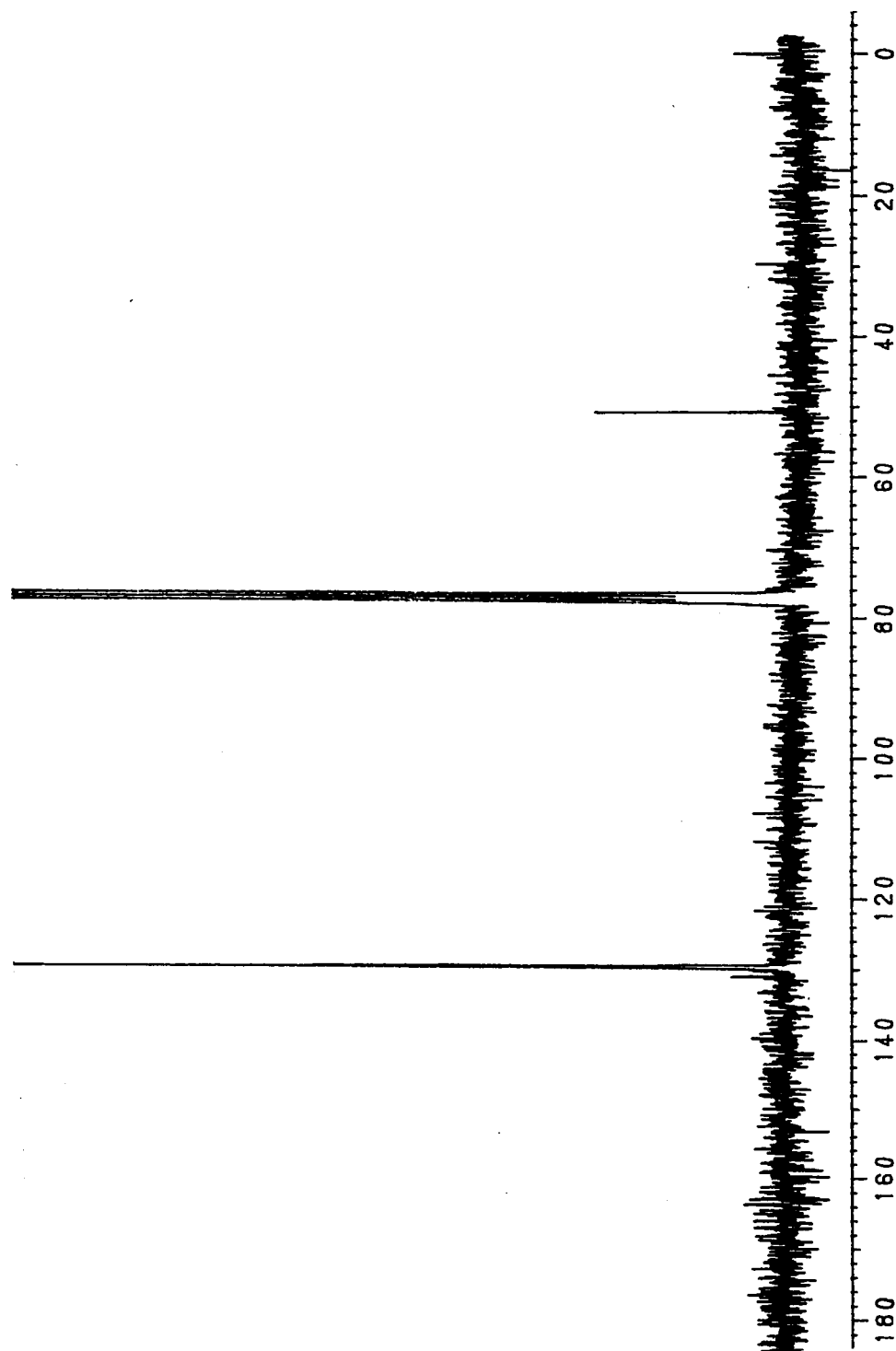


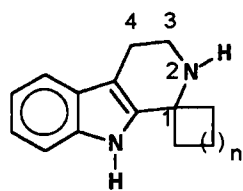
Figure II-6: ^{13}C NMR of Dibenzylnitrenium Tetrafluoroborate

CHAPTER III

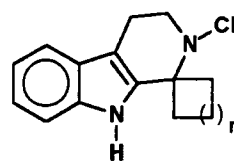
N-CHLORAMINE REARRANGEMENTS FORMING THE 1,2,3,4-TETRAHYDRO- β -CARBOLINE SYSTEM

At this point, our research focus was drawn toward finding a system in which the knowledge gained from the study of the secondary amines [87 - 89, 96 - 99, 102 and 103] could be used to support a synthetic project. Specifically, this system would form a stabilized imminium ion, either by ring expansion or arene migration. The indole alkaloids, as a group, offer a fertile synthetic field in which we could apply the chemistry learned previously. They provide an exceptional opportunity for the development of new strategies and designs. Elaboration of complex molecular frameworks, invention of new methods for carbon-carbon bond formation, and selective functional group interconversions are some of the intellectual challenges available in this field of inquiry. Specifically, the 1,1-dialkyl-1,2,3,4-tetrahydro- β -carboline system was selected because bond migration, in an appropriately substituted precursor, such as 107, would lead to valuable models [110 or 111] for indole alkaloid systems (Scheme III-1). It was envisioned that the spirocycle 107 could be chlorinated at the N_b nitrogen [e.g. 108] to form a reactive electrophilic intermediate via the action of silver ion. This intermediate could then either undergo ring expansion (path a) to form the imminium ion 109,

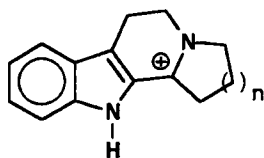
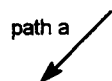
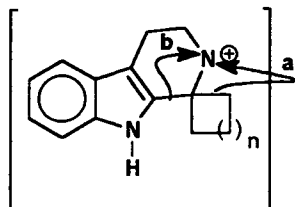
SCHEME III-1



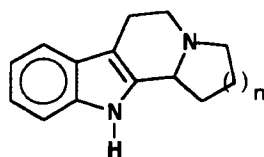
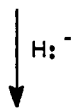
107 a n = 1
b n = 2



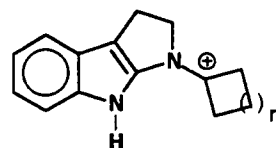
108 a n = 1
b n = 2



109 a n = 1
b n = 2



110 a n = 1
b n = 2



111 a n = 1
b n = 2

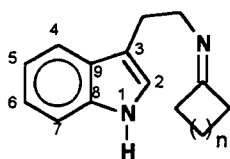
or aryl migration (path b) to produce the physostigmine framework. Subsequent reduction with sodium cyanoborohydride would afford **110** or **111**, respectively.

To avoid confusion in numbering the indole and carboline systems, the indole numbering system [e.g. **112**] will be used throughout to refer to particular carbons and hydrogens. A partial numbering of the carboline skeleton [e.g. **107**] will be helpful in understanding the nomenclature of these compounds.

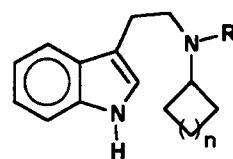
Attempts to form **107** involved a Pictet-Spengler cyclization (see Scheme I-2, page 16). It is well known that the condensation of tryptamine and substituted tryptamines with aldehydes and with α -keto acids in aqueous solution yields 1-alkyl and 1-alkyl-1-carboxy-1,2,3,4-tetrahydro- β -carbolines, respectively.¹⁷ 6-Hydroxy- and alkoxytryptamine derivatives also react quite readily with acetone in aqueous solution, affording the expected 1,1-dimethyl-1,2,3,4-tetrahydro- β -carboline derivatives.¹²⁰ Tryptamine and 5-methoxy-tryptamine, on the other hand, do not undergo facile cyclization with simple ketones to any appreciable extent under the same conditions; however, treatment of the Schiff bases, derived from the amines and ketones, with dilute sulfuric acid¹²¹ or phosphorus oxychloride¹²⁰ results in the formation of the 1,1-dialkyltetrahydro- β -carbolines. In addition, the 1,1-dimethyl derivative (from tryptamine and acetone) has been prepared with ethyl polyphosphate¹²² as catalyst in 66% yield. Derivatives of tryptamine and cycloalkanones^{123,124,125} or 1,2-cycloalkadiones¹²⁶ have also been synthesized using

either mineral acid or ethyl polyphosphate. All of these reactions create a more electrophilic imminium ion from the Schiff base which is trapped by the 2,3-indolic double bond.

The formation of tetrahydro- β -carbolines [e.g. 107] from uncyclized Schiff bases [e.g. 112] can easily be detected by both ^1H and ^{13}C NMR. The characteristic feature in the carbon NMR of the tetrahydro- β -carboline system is the presence of four protonated and four non-protonated aromatic signals. In the proton NMR spectrum, the absence of the indolic C-2 hydrogen singlet confirms cyclization. In addition, cyclization causes the downfield shift of approximately 16 ppm for the indole C-2 carbon absorption. Uncyclized indoles [e.g. 112 and 113] contain five protonated aromatic signals in their carbon NMR spectrum, along with the C-2 hydrogen singlet in the proton NMR spectrum.



112 a $n=1$
b $n=2$



113 a $n=1$; $R=H$
b $n=2$; $R=H$
c $n=1$; $R=Cl$

Since many of the conditions used to form 1,1-dialkyltetrahydro- β -carbolines from tryptamines and ketones are potentially damaging to highly functionalized materials, an incremental approach to mild ring closure was sought. Due to the heightened reactivity of ketone groups contained in small rings, cyclobutanone was

added to tryptamine in hopes of forming spirocycle **107a**. Even in the absence of acid, **107a** was discovered, albeit in very low yield, in the product mixture after reductive workup (NaCNBH_3). Proof of its formation was unmistakable: the carbon NMR spectrum contained the spiranic carbon at δ 56.8 and the C-2 signal at δ 138.3; the C-2 hydrogen singlet was missing in the aromatic region of the proton NMR spectrum; and, the mass spectrum showed the molecular ion ($M + 1$) at 213. The ratio of the major product, N_b -cyclobutyltryptamine [**113a**], to **107a** was 96:4. This ratio was increased to 90:10 upon the addition of a catalytic amount (ca 15 mg *p*TSA/g tryptamine) of *p*-toluene sulfonic acid (*p*TSA) to the reaction. A phenomenal shift in the ratio of **113a** to **107a** (26:74) was subsequently realized when the imine was refluxed with both *p*TSA and silica gel in benzene. Prolonged heating at 78 °C (24 hrs) followed by purification (alumina/chloroform) gave yields of **107a** as high as 90%. The addition of the silica gel was prompted by the desire of the author to influence the formation of the spirocyclic amine from the imine by introducing a surface that might preferentially bind to the amine, thus shifting the equilibrium to the side of amine formation. However, the exact function of the silica gel is not clear. After uncovering its utility in this reaction it was discovered that Hudlicky and coworkers¹²⁷ had noted the catalytic use of silica gel in the Pictet-Spengler reaction of tryptamine and phenylpyruvic acid. Since only the rate of reaction of phenylpyruvic acid was increased in the reported case and since catalytic

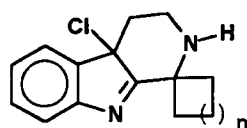
quantities of silica gel had no significant effect on the reaction using the simple ketones reported here, it is likely that the silica gel is providing a different effect in the two systems. We tested this assumption by placing pure spirocycle **107a** in a flask containing silica gel, *p*TSA, and benzene, and heating for five hours in an attempt to isomerize it to imine **112a**. Only the spirocycle was isolated. Absence of imine led us to conclude that the silica gel is not responsible for final product [**107a**] formation. Apparently it does facilitate the initial reaction at the β -position (see Scheme I-2, page 16) and the indolenine subsequently rearranges to the observed product. It seems likely that surface of the silica gel is able to hold the imine in an orientation that is optimal for attack by the indole π electrons and at the same time participate in the expeditious movement of protons that has to occur during the course of this reaction. It is worth noting that **both** silica gel and catalytic *p*TSA are necessary for the spirocycle to dominate in the product mixture.

Cyclopentanone was similarly converted into spirocycle **107b**, to study its potential usefulness as a precursor of the *Corynanthe* model [e.g. **43**] (page 18). The ring-expansion of cyclopentyl-N-chloramines has long been a goal of our group, but has continually met with dismal results. Successful ring expansion of cyclopentylamines to the corresponding piperidines has been reported in the solvolysis of N-(arylsulfonyl)amines, provided there is a tertiary carbon at the migration origin.¹²⁸ Other reactions that accomplish this type of change (ring-

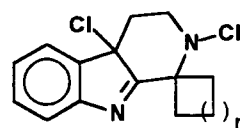
expansion and insertion of nitrogen) include the Beckmann rearrangement¹²⁹ and the Schmidt reaction¹³⁰ of cyclic ketones, which are converted into ring-expanded cyclic amides through the agency of hydroxylamine and hydrazoic acid, respectively. With the formation of spirocycle **107b**, it seemed that rearrangement similar to that seen in the solvolysis of N-(arylsulfonyl)amines might be possible since **107b** has a tertiary carbon at the migrating center.

The ring-expansion reaction of **107a** and **107b** required the synthesis and silver-induced rearrangement of the N_b-chloramines **108a** and **108b**, respectively. Since the cyclopentyl derivative **107b** was in greater supply, experiments directed to selective chlorination at N_b were carried out first with this material.

The desired chlorination of **107b** proved to be difficult due to the formation of mono- and di-chlorinated products [**108b**, **114b**, and **115b**]. A mixture of chloroindolenine **114b** and the N_b-chlorinated spirocycle **108b** resulted when one equivalent of N-chlorosuccinimide was added to **107b**. However, upon standing in a methylene chloride solution, most of the N_b-chlorinated compound isomerized to the C-chlorinated adduct **114b**. The chloroindolenine **114b** was easily identifiable in the carbon NMR spectrum by several distinct features: presence of the C=N carbon absorption at δ 182.6, movement of the C-7 absorption from δ 110.7 (in the spirocycle **107b**) to δ 121.23, and movement of the C-3 absorption from δ 108.5 to δ 69.4.



114 a n = 1
b n = 2

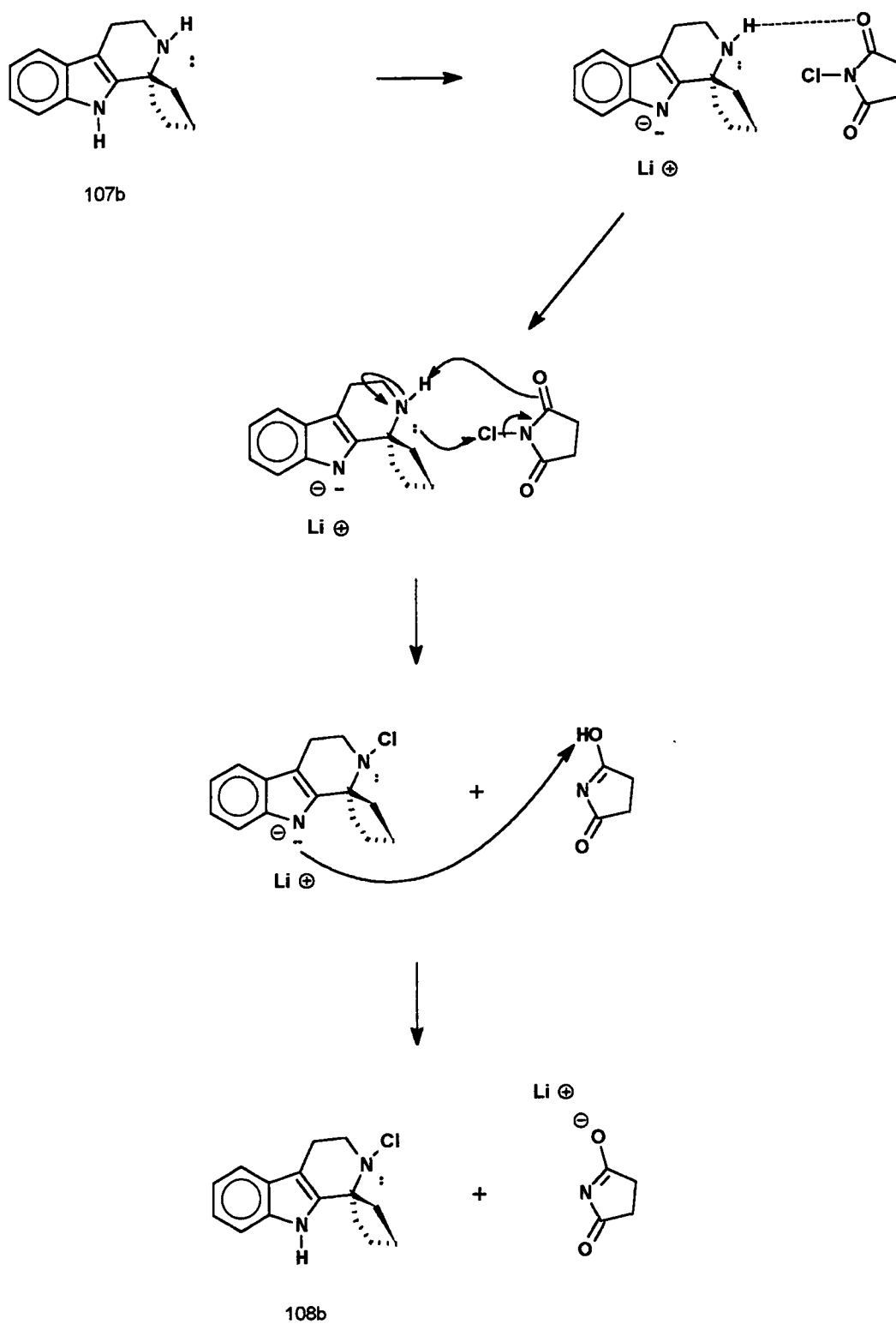


115 a n = 1
b n = 2

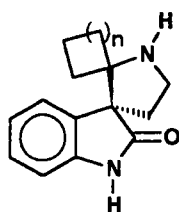
High initial yield of N-chloramine **108b** was achieved when **107b** was first deprotonated with *n*-BuLi and then chlorinated with N-chlorosuccinimide. However, the N-chloramine generated in this manner must be used immediately to minimize isomerization to chloroindolenine **114b**. The preference for the N_b position by N-chlorosuccinimide is not initially obvious. From pK_a values¹⁸, it is apparent that the N_a hydrogen is much more acidic than the N_b hydrogen and is the one removed by the *n*-BuLi. This leaves a nitrogen bound hydrogen only at the N_b position which can hydrogen bond with the N-chlorosuccinimide oxygen prior to hydrogen/chlorine exchange, resulting in chlorine attachment only at the N_b position (Scheme III-2).

Addition of two equivalents of N-chlorosuccinimide to **107b** provided the dichlorinated spirocycle **115b** in good yields as determined by NMR. However, when **115b** was subjected to column chromatography (alumina/chloroform), decomposition resulted giving purified yields of only 30%. Again, this compound

SCHEME III-2



had distinct spectral absorptions which made its identification straightforward. Similar carbon NMR trends to those seen in the chloroindolenine **114b** were also seen for **115b** where the C=N absorption appeared at δ 178.1, the C-7 absorption at δ 121.6, and the C-3 absorption at δ 68.2. Compound **115b** possesses an additional chlorine attached to the N_b nitrogen which produces distinctive upfield shifts for C-11 and the spiranic carbon (both are β to the chlorine). The spiranic carbon shifted from δ 66.3 (in compound **114b**) to δ 77.3, while C-11 changed from δ 45.7 (in compound **114b**) to δ 51.8. Attempts to dechlorinate **115b** to **114b**, in a manner similar to previously mentioned N-chloramine dechlorinations, required that the dichlorinated spirocycles be exposed to either HCl gas or NaCNBH₃. When **115b** was exposed to HCl gas, **114b** was produced in 50% yield. In addition, a significant portion (30%) of the product mixture consisted of the oxindole **116b**.



116 a n = 1
b n = 2

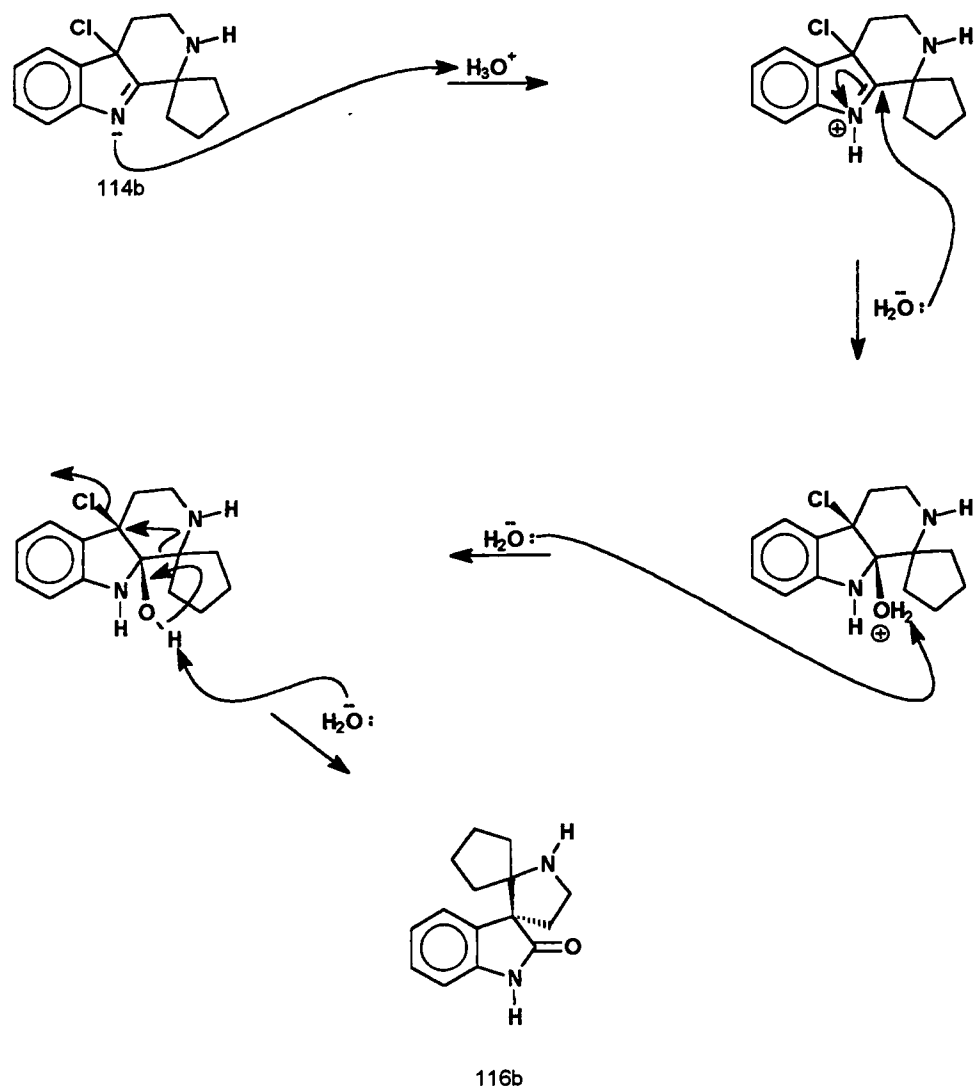
Oxindole formation arises from the attack of electrophilic agents at the 3-position of the indole nucleus¹³¹ followed by subsequent reaction. Typically, these

electrophilic agents generate a 3-hydroxy or 3-chloroindolenine intermediate upon reaction with the indole nucleus which can then be converted into the oxindole. The former compounds can be prepared by the reduction of hydroperoxyindolenines (the primary autoxidation product of indoles) or by treatment of certain indoles with peracids; the latter compounds are generated through the action of hypochlorite or N-chlorosuccinimide. The reaction of peracid with the tetrahydro- β -carboline system yields only the N_b -oxides¹³² unless the N_b -nitrogen is first rendered non-basic *via* acylation.¹³³ On the other hand, many reliable methods exist where electrophilic chlorine is added to both basic (unacylated)¹³⁴ and nonbasic (acylated)¹³⁵ N_b -nitrogen analogs. These chloroindolenines, once generated, can be converted into their corresponding oxindole (Scheme III-3) when either acid¹³⁶ or base¹³⁷ in refluxing methanol attack the 2-position.

Using acid catalysis, **114b** was converted into **116b** in 52% yield. Formation of the carbonyl group initiates the alkyl bond migration from the 2- to the 3-position with the required expulsion of chloride ion from this latter position. Our observation of **114b** to **116b** represents the first known case where a dichlorinated (C-3 chloro and N_b -chloro) tetrahydro- β -carboline was rearranged to its corresponding oxindole.

Much higher yields (66% from **114b**, 83% from **115b**) of **116b** were realized when the chloroindolenine **114b** or the dichlorinated adduct **115b** was taken up in

SCHEME III-3

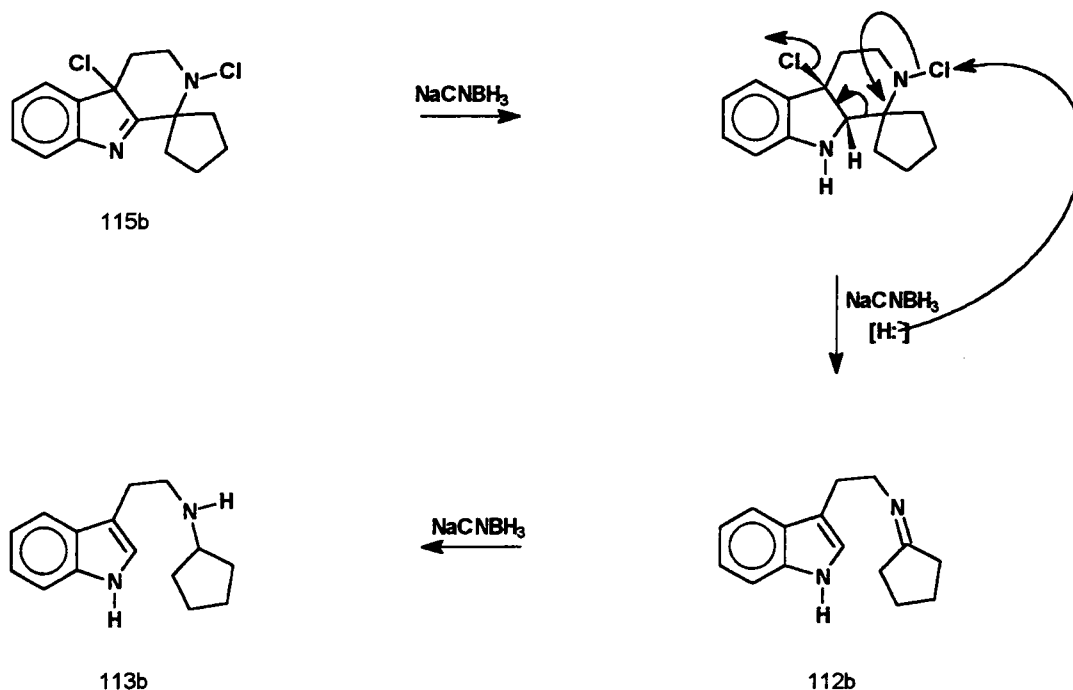


dry benzene and allowed to react with solid aluminum trichloride (3 eq) followed by aqueous acidic (H_2SO_4) methanol at room temperature. Addition of aluminum trichloride to **114b** or **115b**, produced a precipitate which was used without characterization. This precipitate may be the salt that results when the aluminum

trichloride bonds to the N_a-nitrogen in an acid-base reaction. This would render the C-2 carbon electronically more susceptible to attack by hydrolytic nucleophiles added later, facilitating conversion to the oxindole. The N_b-Cl group is probably dechlorinated when it encounters the acidic conditions associated with the methanol addition in analogy to previously described conversion, e.g. **87c** to **87a**.

Attempts to dechlorinate **115b** with sodium cyanoborohydride resulted in the expected product **114b** as well as the ring-opened N_b-cyclopentyltryptamine **113b**. This ring-opening is thought to occur by the initial reduction of the indolenine double bond, hydride induced removal of the N_b chlorine and opening of the

SCHEME III-4

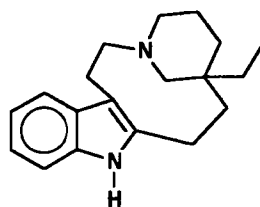


carboline C ring as portrayed in Scheme III-4 to regenerate the indole nucleus with expulsion of chloride ion. The imine formed in the unravelling step is subsequently reduced to the amine with excess borohydride that was present.

With the chlorination problems well in hand, we generated the N_b-chloro-spirocycle **108b** and subjected it to conditions known to cause bond rearrangement (Ag⁺ in benzene, followed by borohydride reduction). Unfortunately, all attempts to convert **108b** into **110b** (via **109b**) resulted in only the production of the oxindole **116b** (from the chloroindolenine) and the spirocycle **107b** (presumably by dechlorination of **108b** during borohydride workup). In view of our isolation of dibenzylnitrenium tetrafluoroborate from N-chlorodibenzylamine, other pathways must be considered. This is, perhaps, a case where sigma bond participation is not involved in the heterolysis of the N_b-Cl bond,⁴³ and the formation of an nitrenium ion may explain the unreactivity toward ring-expansion by the cyclopentyl moiety. This nitrenium ion may exist as a ground state triplet which can abstract available hydrogens, thus forming the spirocycle **107b** during basic workup. Other results from our group are consistent with those above in that the spirocycle of tryptamine and 2-indanone also failed to rearrange to the yohimbine framework.¹³⁸

With the failure of the cyclopentylamine to ring-expand, our interest was directed toward **108a** which contains a cyclobutyl group - a system known for its ring-expansion reactions.^{70,84} It seemed likely that the N_b-chlorination of the

cyclobutyl spirocycle **108a**, followed by ring-expansion and reduction, would afford hexahydro-indolo-indolizidine **110a**. A compound with this skeletal framework has been transformed by Takano¹³⁹ into the *Aspidosperma* alkaloid, ($\pm$) quebrachamine [**117**]; and, thus, similar application seemed a worthy field in which to ultimately implement any successes encountered with the cyclobutyl case.

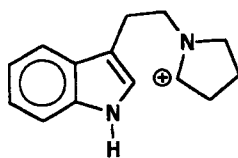


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Cyclobutanone reacted in a manner analogous to all the reactions reported previously for cyclopentanone with the exception of the rearrangement reaction. Most importantly, **107a** was converted into **108a** by the sequential addition of *n*-BuLi and N-chlorosuccinimide. As expected, the cyclobutyl spirocyclic ring in **108a** expanded to the five-membered ring imminium ion **109a** (path a, Scheme III-1, page 60) in the presence of silver ion and was subsequently reduced with sodium borohydride to form the hexahydro-indolo-indolizidine [**110a**] in 66% yield. Other products included the spirocycle **107a** in 20% yield, and the N_b-cyclobutyltryptamine [**113a**] in 11% yield. The latter product probably resulted from borohydride reduction of chloroindolenine **114a** (see Scheme III-4, page 71)

formed as a by-product either during the chlorination step or by isomerization of **108a** as noted in our preliminary chlorination studies (page 66). Recrystallization of **110a** from aqueous methanol afforded white crystals with melting point (171.8-173.0 °C) consistent with that reported by Corsano.¹⁴⁰ In addition, the ¹³C NMR clearly contained six aliphatic absorptions, all protonated (determined by 2D NMR - heteronuclear ¹H-¹³C coupled spectrum), at δ 57.0, 49.4, 46.0, 29.5, 23.4, and 17.9. These shifts lie in the range of what would be expected for three carbons adjacent to nitrogen (57.0, 49.4, and 46.0) and three carbons β to nitrogen.

The conversion of tryptamine into **110a**, described above, was accomplished by utilizing a Pictet-Spengler cyclization to afford spirocycle **107a**, followed by ring-expansion. We now sought to explore the synthesis of **110** through an alternate approach. In the ideal case, ring-expansion of **113a** would afford imminium ion **118**, which could then be trapped by a Pictet-Spengler cyclization. Attempted



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chlorination of N-cyclobutyltryptamine [**113a**] at room temperature gave an inextractable blue mixture possibly due to chlorination of the indole nucleus and subsequent reaction. Chlorination at -78°C appeared (by low temperature NMR)

to produce predominantly the N_b-chloramine **113c**. Introduction of silver ion and acidification with HCl did produce **110**, albeit in only 16% yield. The major product was the parent amine [**113a**], presumably formed from the dechlorination of the N-chloramine when HCl was added. It seemed apparent that some control in the outcome of the chlorination step might lead to higher yields of the desired tetracycle **110a**. Since the chlorination at the 3-position of the indole nucleus is due to high electron density associated with the N_a-nitrogen lone pair of electrons, replacement of the N-H hydrogen with an appropriate substituent could serve to limit the participation of this nitrogen lone pair and thus terminate this chlorination reaction.

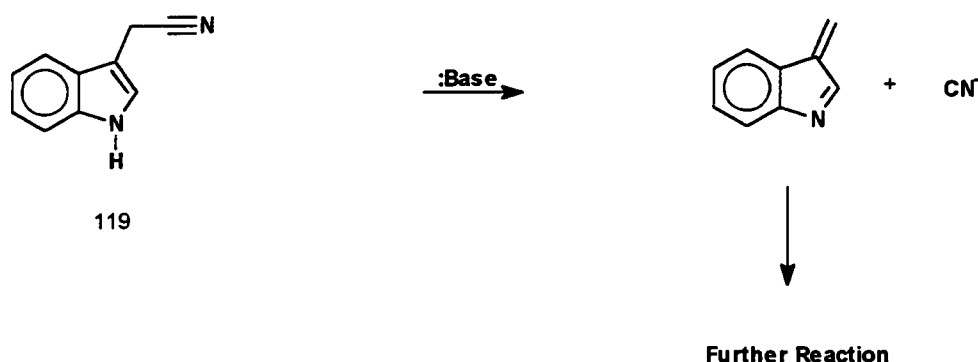
The protection of indolic nitrogen has been accomplished by conversion into the sulfonamide,¹⁴¹ carbamate,¹⁴² trialkylsilylamine^{143,144} and alkylamide¹⁴⁵. Care must be taken, though, to insure that the protecting group is added to the indolic nitrogen (N_a) and not at the secondary amine (N_b) where chlorination will later take place. To circumvent problems associated with this latter requirement, the protection of the indolic nitrogen was accomplished prior to the conversion of the tryptamine nitrogen into a secondary amine. Three different approaches were used to protect the indolic nitrogen as either a sulfonamide or a carbamate without interference by the N_b-nitrogen: first, the tosyl group was attached to N_a while N_b was part of a nitrile group; second, the *tert*-butoxy carbonate group (*t*-Boc) was

attached to N_a while N_b was part of an amide functionality; and finally, the *t*-Boc group was attached to N_a while N_b was part of an imine group.

Initial attempts to attach a tosyl group to the N_a-position of indole-3-acetonitrile [119] were met with failure. While it seemed obvious that treatment of indole-3-acetonitrile with a strong base followed by tosyl chloride should yield **120**, all attempts with many different bases (*n*-BuLi, C₆H₅Li, C₆H₅MgBr, and NaH) and with different sulfonyl chlorides (tosyl chloride and benzene sulfonyl chloride) resulted only in isation of starting material. Further investigation revealed that the hydrogens α to the nitrile group were being removed by the strong base. Evidence of this was seen in the carbon NMR spectrum when D₂O was added after deprotonation by *n*-BuLi. A triplet in the proton-decoupled carbon NMR spectrum of the recovered indole-3-acetonitrile at δ 13.9 revealed the attachment of a deuterium at the α position. Finally, details outlining the use of a phase transfer agent¹⁴¹ were discovered that provided a route to the tosylated nitrile **120**. A two-phase solution, consisting of aqueous sodium hydroxide, ether, and N-benzyltributylammonium bisulfate, afforded a medium where hydroxide could remove the N_a hydrogen, forming an anion that subsequently reacted with tosyl chloride. While the reported yield was 60%,¹⁴¹ the maximum yield achieved in this investigation was 48% yield. Many attempts to increase the reaction yield had little or no effect. A slight enhancement of yield was realized when an equivalent of

sodium cyanide was added to the heterogenous mixture. The cyanide is thought to perform a dual role: act as a base to assist in the removal of the proton on nitrogen, and limit the production of by-products that result when cyanide is expelled from the initially formed anion (Scheme III-5).

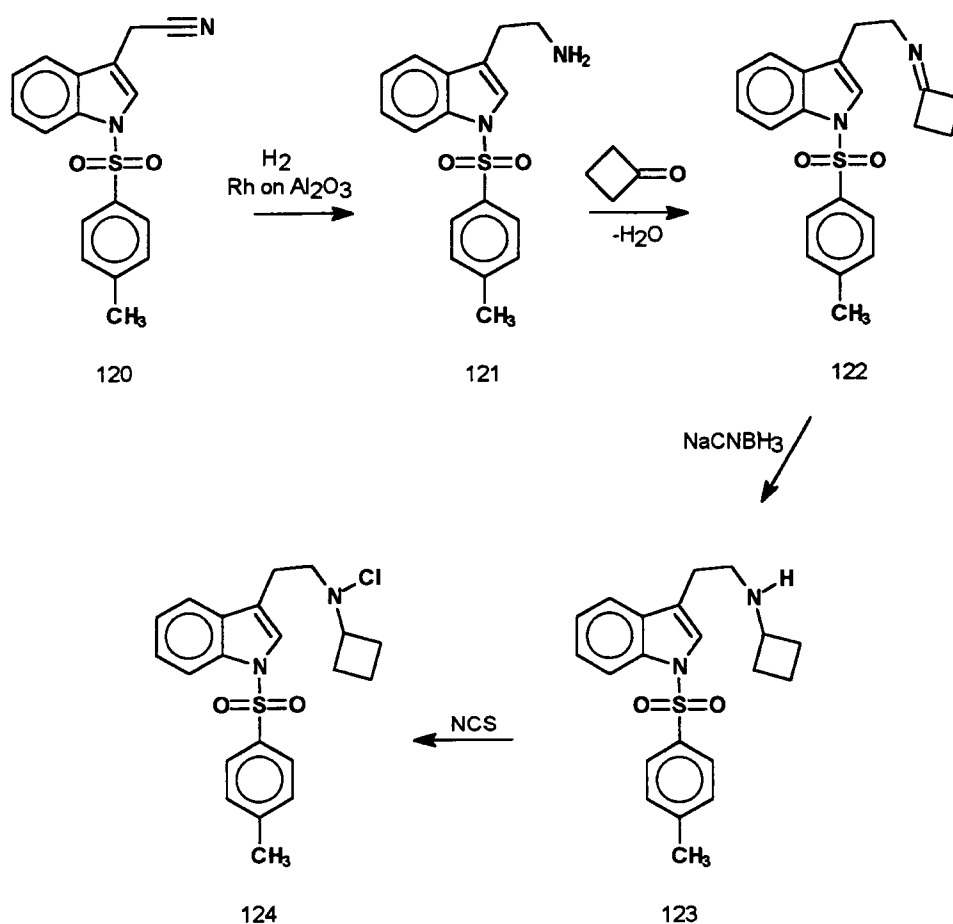
SCHEME III-5



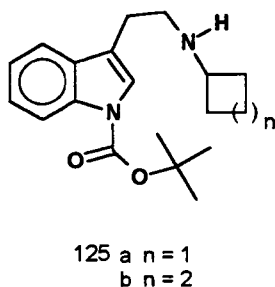
Reduction of **120** to the tosylated tryptamine **121** with hydrogen absorbed on a rhodium/aluminum oxide surface,¹⁴¹ proceeded in 95% yield. Reaction of **121** and cyclobutanone with concomitant removal of water in refluxing benzene gave imine **122** that was further reduced with sodium cyanoborohydride to the tosylated amine **123** (Scheme III-6). Chlorination with N-chlorosuccinimide occurred exclusively at N_b to give **124**. Treatment of **124** with silver tetrafluoroborate followed by concentrated HCl, gave a myriad of products, the major component being **123** in 50% yield. This was unexpected due to facile rearrangement of other cyclobutyl N-chloramines in the presence of silver ion.¹⁴⁶ Although three

equivalents of silver were added, it is likely, in view of previous results, that the tosyl aromatic ring or the sulfonamide oxygens are complexing the silver, either singly or in conjunction with the N-chloramine. This could form a complex that would be unreactive toward ring-expansion and then be destroyed by the acidic conditions encountered later.

SCHEME III-6



At this point, a group was needed that could protect the indole nucleus from chlorination, be free of functional groups that could complex silver, and be removed during the acidic treatment of the rearrangement product. The obvious candidate was the *tert*-butoxy carbonyl group (*t*-Boc). Two separate routes were pursued to afford the synthesis of the protected tryptamine **125b**. It should be noted, that the utility of these routes were first investigated using cyclopentyl as the N-substituted moiety due to its more favorable affordability. These cyclopentyl adducts were never subjected to rearrangement conditions since the cyclopentyl spirocycle **107b**, arguably the most favorable cyclopentyl candidate for rearrangement, failed to react under the same conditions.



The first attempt to synthesize **125b** involved the conversion of indole-3-acetic acid into the cyclopentylamide **126b** by treating its corresponding acid chloride with cyclopentylamine. While the purified yields of **126b** were never more than 50%, this process did afford a reasonable amount of **126a** when cyclobutylamine was used in place of cyclopentylamine. With the desired

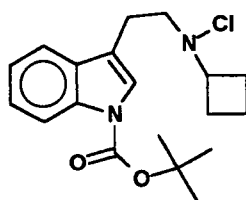
attachment of the cyclobutyl moiety accomplished, we set out to protect the N_a position with the *t*-Boc group. Addition of *n*-butyl lithium to **126a** in tetrahydrofuran, followed by Boc-anhydride afforded the protected amide **127**. However, attempts to reduce the amide by treatment with Meerwein's reagent followed by sodium borohydride reduction gave back only starting material.



In another route, the N_a hydrogen of imine **112b**, (formed from the condensation of tryptamine and cyclopentanone) was deprotonated with *n*-BuLi to give an anion to which was added Boc anhydride followed by sodium cyanoborohydride dissolved in methanol. This one-pot synthesis of N_a-Boc-N_b-cyclopentyltryptamine [**125b**] was accomplished in 60% yield.

Having developed a successful approach to **125b**, the cyclobutyl system **112a** was treated in exactly the same manner to produce **125a**. Proton NMR provided the most conclusive data that the N_a position had been protected. The absence of the N_a hydrogen absorption between δ 8-9 established the attachment site of the *t*-Boc group which appeared as a singlet at δ 1.65 that integrated for nine hydrogens.

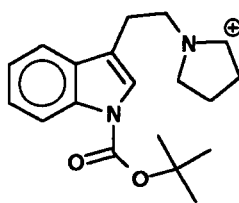
Carbon-13 NMR showed evidence of the *t*-Boc group at δ 149.7, 83.3 and 28.2 corresponding to the carbonyl, quaternary, and methyl carbons, respectively and chemical shifts for an unperturbed cyclobutyl ring attached to a secondary nitrogen. Next, **125a** was converted into N-chloramine **128** in the usual fashion. Treatment of **128** with silver tetrafluoroborate in methylene chloride followed by acidification with 4 N HCl in methanol produced three major products, detected by ^{13}C NMR. These were separated by column chromatography ($\text{Al}_2\text{O}_3/\text{CHCl}_3$) and identified as the hexahydro-indolo-indolizidine [**110a**], the spirocycle **107a**, and the N_b -cyclobutyltryptamine [**113a**] (33%, 32%, and 20% yields, respectively).



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The hexahydro-indolo-indolizidine [**110**] undoubtedly arose by trapping the imminium ion **129** with the 2,3-indolic double bond after the *t*-Boc was removed by hydrochloric acid. The formation of the spirocycle **107a** undoubtedly arose from the cyclobutyl imine **112a**. This is a surprising observation since simple elimination products (imines) have not previously been encountered in silver ion induced reaction of N-chlorocyclobutylamines.^{84,146} However, once formed, it is

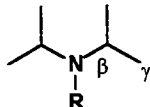
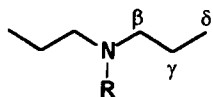
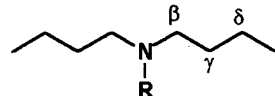
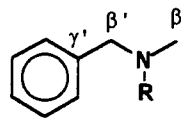
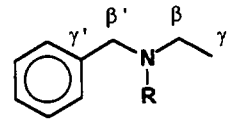
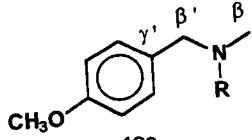
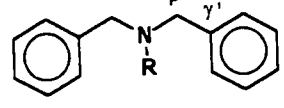
reasonable that **112a** would be trapped by the indolic double bond under the strong acid conditions. The formation of **113a** can be attributed to the action of HCl on the unreacted N-chloramine **128** - both the chlorine on N_b and the *t*-Boc group on N_a would be converted to N-H by such treatment.

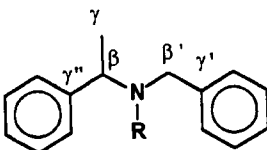
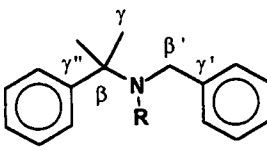
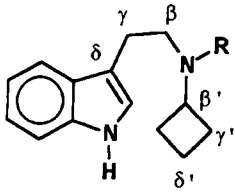
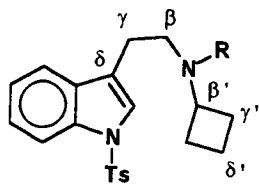
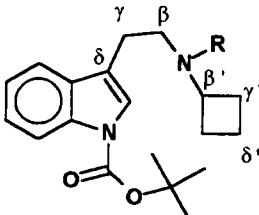
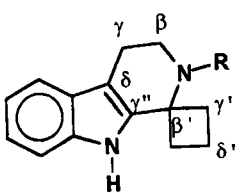


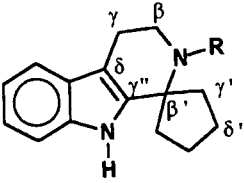
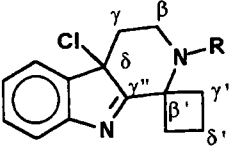
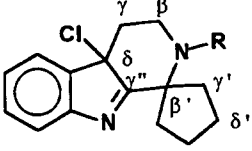
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During the course of both the NMR study of the interaction of N-chloramines and silver ion and the synthesis of various N-chloramines derived from N-alkylated tryptamines and tetrahydro- β -carbolines, we characterized the N-chloramines by both proton and carbon NMR. In the carbon NMR spectra, the chlorine on nitrogen exhibits some distinct substituent effects on the carbons in the β , γ , and δ positions. Table III-1 lists the various carbon NMR chemical shifts and chemical shift changes for the parent amine and the corresponding N-chloramine. It should be noted that these β , γ , and δ effects refer only to the number of bonds between the chlorine and a particular carbon and does not reflect any stereochemical considerations. Although the chlorine on nitrogen is assumed to be equatorial, no attempts have been made to verify this assumption. The most dramatic chemical

Table III-1: Carbon NMR Chemical Shifts of Certain N-Chloramines and their Parent Amines

Structure		#	β	γ	δ	β'	γ'	δ'	γ''
 97	R=H	97a	45.2	23.4					
	R=Cl	97c	56.6	20.2					
	Δ		11.4	-3.2					
 98	R=H	98a	52.0	23.4	11.8				
	R=Cl	98c	66.1	21.2	11.3				
	Δ		14.1	-2.2	-0.5				
 99	R=H	99a	49.9	32.5	20.6				
	R=Cl	99c	64.1	30.1	20.1				
	Δ		14.2	-2.4	-0.5				
 88	R=H	88a	36.0			56.1	140.2		
	R=Cl	88c	51.9			70.1	136.9		
	Δ		15.9			14.0	-3.3		
 102	R=H	102a	43.7	15.3		54.0	140.6		
	R=Cl	102c	57.5	13.1		67.9	137.1		
	Δ		13.8	-2.2		13.9	-3.5		
 130	R=H	130a	35.7			55.1	132.0		
	R=Cl	130b	51.5			69.4	130.2		
	Δ		15.8			14.3	-1.8		
 87	R=H	87a				53.1	140.3		
	R=Cl	87c				66.9	136.9		
	Δ					13.8	-3.4		

Structure		#	β	γ	δ	β'	γ'	δ'	γ''
 103	R=H	103a	57.5	24.5		51.6	140.7		145.6
	R=Cl	103c	68.8	19.5		64.1	137.7		141.7
	Δ		11.3	-5.0		12.5	-3.0		-3.9
 89	R=H	89a	56.1	29.7		47.6	141.3		147.8
	R=Cl	89b	67.0	25.1		60.4	138.4		146.1
	Δ		10.9	-4.6		12.8	-2.9		-1.7
 113	R=H	113a	46.9	25.9	113.7	53.9	30.8	14.8	
	R=Cl	113c	60.1	24.0	112.5	66.0	30.0/ 28.2	13.5	
	Δ		13.2	-1.9	-1.2	12.1	-0.8/ -2.6	-1.3	
 123	R=H	123	45.9	25.9	121.0	53.9	31.1	14.8	
	R=Cl	124	58.9	21.4	120.0	65.7	28.2	13.3	
	Δ		13.0	-4.5	-1.0	11.8	-2.9	-1.5	
 125a	R=H	125a	46.2	25.9	118.7	54.1	31.1	14.8	
	R=Cl	128	59.4	23.6	118.0	65.9	28.3	13.5	
	Δ		13.2	-2.3	-0.7	11.8	-2.8	-1.3	
 107a	R=H	107a	40.2	22.2	107.7	56.8	34.4	14.9	138.3
	R=Cl	108a	52.1	18.5	105.6	66.6	29.6	13.4	137.2
	Δ		11.9	-3.7	-2.1	9.8	-4.8	-1.5	-1.1

Structure		#	β	γ	δ	β'	γ'	δ'	γ''
	R=H	107b	40.6	22.8	108.5	61.9	40.2	24.9	139.3
	R=Cl	108b	54.3	18.9	105.7	73.0	39.5	25.6	137.2
	Δ		13.7	-4.1	-2.8	11.1	-0.7	+0.7	-2.1
	R=H	114a	37.8	44.8	69.1	60.2	32.0/ 29.8 ^a	15.8	181.4
	R=Cl	115a	50.0	37.8	68.2	70.2	32.4/ 28.7	14.1	177.9
	Δ		12.2	-7.0	-0.9	10.0	0.4/ -1.1	-1.7	-3.5
	R=H	114b	38.1	45.7	69.4	66.3	38.6/ 34.4 ^a	25.0/ 22.9 ^a	182.6
	R=Cl	115b	51.8	38.2	68.2	77.3	37.1/ 35.9	25.2/ 22.7	178.1
	Δ		13.7	-7.5	-1.2	11.0	-1.5/ +1.5	0.2/ -0.2	-4.5

^aSpectra taken at -60 °C, the nitrogen has stopped inverting and there appears to be hindered rotation about the N_b-cyclobutyl bond. The methylene carbons of the cyclobutyl moiety are no longer equivalent.

^bThe cyclobutyl and cyclopentyl methylenes are nonequivalent in these compounds due to their relationship to the C3 chlorine.

shift change occurs for the carbons β to the chlorine - an average of 12.75 ppm downfield shift, with the range of values between 9.8 and 15.92 ppm. The carbons in the γ position have an average upfield shift of 2.86 ppm with the range of values between 7.5 ppm upfield and 1.5 ppm downfield; while the carbons in the δ position have an average upfield shift of 1.04 ppm with the range of values between

2.8 ppm upfield and .7 ppm downfield. It should be noted, that in several cases absolute assignment of the carbon NMR chemical shifts for the parent amines was possible only after forming the N-chloramine, consulting its carbon NMR spectra, and noting these characteristic chemical shift changes that occur when the parent amine is N-chlorinated.

Overall, treatment of N-chloro-1,1-spirocyclobutyltetrahydro- β -carboline [108a] with silver ion and subsequent borohydride reduction results in good yields of the ring-expanded compound [110a]. Product formation is thought to be the result of favorable orbital overlap of the emptying orbital on nitrogen and a carbon-carbon bond of the cyclobutyl ring. Unfortunately, results similar to those seen with 108a, were not realized with the corresponding cyclopentyl compound 108b. In spite of seemingly favorable orbital overlap, all attempts to convert the N_b-chlorocyclopentyl spirocycle [108b] to the ring-expanded 110b were unsuccessful. Rearrangement in aprotic solvent of the N_b-chloro-N_b-cyclobutyltryptamine [113a] yields product 110a, consistent with the capture of an imminium ion by an internal nucleophile, namely the carbon-carbon double bond of the indole moiety. Attempts to limit chlorination at C-3 and still retain the nucleophilic nature of the 2,3-indolic double bond was accomplished by protecting the N_a position with the *tert*-butoxy carbonate group. This group permitted selective chlorination at N_b, which when followed by exposure to silver ion formed imminium ion 129. Subsequent addition

of hydrochloric acid liberated the *t*-Boc group, as carbon dioxide and isobutylene, and returned nucleophilicity to the 2,3-indolic double bond, permitting attack on the imminium ion **129** to effect ring closure.

An N_b-chlorocyclobutyltryptamine **124** containing the N_a sulfonamide protecting group failed even to ring-expand. This may be due to the formation of either a silver complex or a nitrenium ion that is unreactive toward ring expansion. Acyclic amine:silver complexes that are unreactive toward bond migration have been observed by proton NMR in aliphatic secondary amines some of which contain aryl substituents in the aliphatic groups. It has become clear from this NMR study that a complex between the N-chloramine and silver ion has formed, but the degree of involvement by aromatic moieties has not been determined. While the exact position of the silver ion in this complex is not known, there is evidence that the silver ion is interacting strongly with the nitrogen unshared electrons.

All information concerning the role of the silver ion, both in the cases that undergo rearrangement and in those that form only an N-chloramine:silver complex, can serve to better prepare the synthetic chemist who wishes to use this ring-expanding reaction to achieve a target molecule. The many examples of products formed as a result of silver ion treatment of N-chlorocyclobutylamines show that the reaction has promise in the synthesis of alkaloids having a pyrrolidine moiety.

CHAPTER IV

EXPERIMENTAL

General Information and Procedures:

NMR spectra were recorded with a Jeol FX-90Q (90 MHz for ^1H , 22.5 MHz for ^{13}C) or a Bruker AC-250 (250 MHz for ^1H , 62.88 MHz for ^{13}C) spectrometer with deuteriochloroform as the solvent and referenced to internal tetramethylsilane (δ 0.0) for ^1H NMR or deuteriochloroform (δ 77.1) for ^{13}C NMR unless otherwise noted. All NMR experiments were performed at 300 K for solutions of ca. 5 - 50 mg of compounds dissolved in 0.5 mL of CDCl_3 . The homonuclear ^1H - ^1H and heteronuclear ^1H - ^{13}C chemical shift-correlated 2D diagrams were obtained using the standard COSY 90 and HETCOR pulse sequences, respectively.

Infrared spectra were recorded using a Digilab FTS-7 Fourier transform infrared spectrometer as neat films on sodium chloride plates (in the case of liquids) or as KBr pellets (in the case of solids). The infrared absorptions are reported in cm^{-1} .

EI or FAB^+ direct introduction mass spectra were obtained with a VG Analytical ZAB/EQ apparatus. Mass assignments and molecular formulas were confirmed by "peak matching" measurements.

Melting points were determined on a Thomas 40 Micro Hot Stage equipped

with a polarizing field viewer and are uncorrected.

All reactions were carried out in oven-dried glassware, under a nitrogen atmosphere, unless specified otherwise. 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.

Silver tetrafluoroborate (Aldrich Chemical Company) was transferred into anhydrous glassware, sealed with rubber septa, and stored under argon in opaque containers.

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 200 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 degassing. Hydrogen was then introduced to give a slight positive pressure (2-5 psi) and the flask re-evacuated. 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 *in vacuo*.

NMR Study of Silver Tetrafluoroborate - Amine Complexes:

The conversion of amines **87a**, **88a**, **96a-99a**, and **102a-103a** into their respective amine:silver tetrafluoroborate complexes (**87b**, **88b**, **96b-99b**, and **102b-103b**) was achieved by adding 0.05 g of the amine, dissolved in 0.5 mL of CDCl_3 , to 1 equivalent of silver tetrafluoroborate and then placing the resulting solution, void of any undissolved solids, into an NMR tube (5mm) and recording the spectrum. Only the ^1H NMR spectra were taken.

Dibenzylamine:silver tetrafluoroborate [**87b**]: ^1H NMR: δ 7.24-7.29 (bs, 6H), 7.10-7.14 (bs, 4H), 3.72 (s, 4H), 3.18 (bs, 1H).

Benzylmethanamine:silver tetrafluoroborate [88b]: ^1H NMR: δ 7.2-7.35 (bs, 5H), 3.68 (s, 2H), 3.38 (s, 1H), 2.51 (s, 3H).

Diethylamine:silver tetrafluoroborate [96b]: ^1H NMR: δ 3.43 (s, 1H, N-H), 2.90 (q, 4H, $J = 7.3$ Hz), 1.31 (t, 6H, $J = 7.1$ Hz).

Diisopropylamine:silver tetrafluoroborate [97b]: ^1H NMR: δ 3.18 (s, 1H), 3.10 (septet, 2H, $J = 6.3$ Hz), 1.21 (d, 12H, $J = 6.3$ Hz).

Dipropylamine:silver tetrafluoroborate [98b]: ^1H NMR: δ 2.83 (s, 1H), 2.71 (t, 4H, $J = 7.7$ Hz), 1.62 (sextet, 4H, $J = 7.5$ Hz), .96 (t, 6H, $J = 7.4$ Hz).

Dibutylamine:silver tetrafluoroborate [99b]: ^1H NMR: δ 3.28 (s, 1H), 2.78 (t, 4H, $J = 7.8$ Hz), 1.63 (pentet, 4H, $J = 7.95$ Hz), 1.39 (sextet, 4H, $J = 7.5$ Hz), .93 (t, 6H, $J = 7.2$ Hz).

Benzylethylamine:silver tetrafluoroborate [102b]: ^1H NMR: δ 7.25-7.4 (s, 5H), 4.3-4.4 (bs, 1H), 3.85 (s, 2H), 2.83 (q, 2H, $J = 7.1$ Hz), 1.07 (t, 3H, $J = 7.1$ Hz).

Benzyl-1-phenethylamine:silver tetrafluoroborate [103b]: ^1H NMR: δ 7.1-7.4 (m, 10H), 3.87 (q, 1H, $J = 6.7$ Hz), 3.75 (s, 1H, N-H), 3.68 (d, 1H, $J = 12.3$ Hz), 3.52 (d, 1H, $J = 12.3$ Hz), 1.34 (d, 3H, $J = 6.6$ Hz).

General Procedure for N-Chloramine Preparation:

Method A: The conversion of amines 87a-89a, 97a-99a, and 102a-103a into their

respective N-chloramines (**87c-89c**, **97c-99c**, and **102c-103c**) was accomplished in a typical fashion: in a 100-mL Erlenmeyer flask, at room temperature, was placed the amine (.005 mol) in a stirred solution of dichloromethane (20 mL). N-Chlorosuccinimide (1.1 eq) was then added and the reaction was followed via TLC (silica gel/methylene chloride). The formation of the N-chloramine was essentially quantitative and instantaneous. The N-chloramine was purified by extracting the contaminating succinimide into a saturated solution of sodium bicarbonate (three times). The organic layer was dried over sodium sulfate, filtered, and the solvent removed at room temperature by distillation *in vacuo* to give a clear liquid that consisted of only one spot on TLC.

Method B: The formation of the N-chloramine was accomplished in the same manner as in Method A. The purification step, however, was streamlined by omitting the bicarbonate wash and filtering the N-chloramine solution through a pad of silica gel (20 g silica/0.5 g N-chloramine) using methylene chloride as the eluent. This process removed the succinimide and any unchlorinated parent amine. Removal of solvent at room temperature afforded the purified N-chloramine in high yields (> 95% all cases).

N-Chlorodibenzylamine [**87c**]: ^{13}C NMR: δ 136.86, 128.86, 128.15, 127.62 (aromatics), 66.91 (methylene). ^1H NMR: δ 7.23-7.47 (bm, 10H), 4.09 (s, 4H). MS (EI $^+$) m/z (relative intensity): 233 (M^+ for ^{37}Cl , 13), 231 (M^+ for ^{35}Cl , 35),

196 (10), 106 (28), 91 (100), 84 (100), 58 (100).

N-Chlorobenzylmethylamine [**88c**]: ^{13}C NMR: δ 136.86, 129.2 (2C), 128.37 (2C), 127.97 (aromatics), 70.13 (methylene), 51.94 (methyl). ^1H NMR: δ 7.3-7.4 (s, 5H), 4.05 (s, 2H), 2.94 (s, 3H)

N-Chloro-N-benzyl-2-phenyl-2-propylamine [**89b**]: ^{13}C NMR: δ 146.1, 138.44, 128.53 (2C), 128.40 (2C), 128.13 (2C), 127.27 (2C), 126.22 (2C) (aromatics), 67.01 (quarternary), 60.41 (methylene), 25.07 (methyl). ^1H NMR: δ 7.61 (d, 2H, $J = 8.1$ Hz), 7.2 - 7.37 (m, 8H), 3.76 (s, 2H), 1.65 (s, 6H).

N-Chlorodiisopropylamine [**97c**]: ^{13}C NMR: δ 56.59 (2C), 20.22 (4C). ^1H NMR: δ 3.28 (septet, 2H, $J = 6.3$ Hz), 1.18 (d, 12H, $J = 6.3$ Hz).

N-Chlorodipropylamine [**98c**]: ^{13}C NMR: δ 66.1 (2C; $\alpha\text{-CH}_2$), 21.19 (2C; $\beta\text{-CH}_2$), 11.27 (2C; CH_3). ^1H NMR: δ 2.88 (t, 4H, $J = 7.1$ Hz), 1.69 (sextet, 4H, $J = 7.2$ Hz), 0.93 (t, 6H, $J = 7.5$ Hz).

N-Chlorodibutylamine [**99c**]: ^{13}C NMR: δ 64.09 (2C; $\alpha\text{-CH}_2$), 30.05 (2C; $\beta\text{-CH}_2$), 20.08 (2C; $\gamma\text{-CH}_2$), 13.96 (2C; CH_3). ^1H NMR: δ 2.91 (t, 4H, $J = 7.3$ Hz), 1.65 (pentet, 4H, $J = 7.7$ Hz), 1.36 (sextet, 4H, $J = 7.6$ Hz), 0.93 (t, 6H, $J = 7.3$ Hz).

N-Chlorobenzylethylamine [**102c**]: ^{13}C NMR: δ 137.12, 129.17 (2C), 128.32 (2C), 127.79 (aromatics), 67.89 (benzylic- CH_2), 57.52 ($\alpha\text{-CH}_2$), 13.08 (CH_3). ^1H NMR: δ 7.25-7.4 (m, 5H), 4.08 (s, 2H), 3.01 (q, 2H, $J = 6.9$ Hz), 1.25 (t, 3H,

$J = 6.9 \text{ Hz}$).

N-Chloro-N-benzyl-1-phenethylamine [103c]: ^{13}C NMR: δ 141.68, 137.72, 128.8 (2C), 128.43 (2C), 128.23 (2C), 127.81 (2C), 127.54, 126.71 (aromatics), 68.79 (α -CH), 64.08 (α -CH₂), 19.47 (CH₃). ^1H NMR: δ 7.2-7.5 (m, 10H), 4.16 (q, 1H, $J = 6.6 \text{ Hz}$), 3.99 (d, 1H, $J = 13.9 \text{ Hz}$), 3.88 (d, 1H, $J = 13.8 \text{ Hz}$), 1.63 (d, 3H, $J = 6.5 \text{ Hz}$).

Silver Tetrafluoroborate Complexes of N-Chloramines and Arenes:

The conversion of the N-chloramines [87c-88c, 97c-99c, and 102c-103c] and arenes [100 and 101] into their respective N-chloramine:silver tetrafluoroborate (87d-88d, 97d-99d, and 102d-103d) and arene:silver tetrafluoroborate (100 and 101) complexes was accomplished by placing the N-chloramine (.01 mole) or arene (.01 mole) in 0.5 mL CDCl_3 and adding this solution to one equivalent of solid silver tetrafluoroborate. The resulting solution, minus any undissolved solids, afforded a sample suitable for NMR analysis. In some of the cases, only the proton NMR data were obtained.

N-Chlorodibenzylamine:silver tetrafluoroborate [87d]: ^{13}C NMR: δ 136.9, 129.27 (2C), 128.61 (2C), 128.22 (aromatics), 67.7 (methylenes). ^1H NMR: δ 7.3-7.5 (bm, 10H), 4.18 (s, 4H).

N-Chlorobenzylmethanamine:silver tetrafluoroborate [88d]: ^{13}C NMR: δ 134.08,

128.53 (2C), 128.22 (2C), 128.06 (aromatics), 56.7 (methylene), 37.5 (methyl).

^1H NMR: δ 7.25-7.4 (m, 5H), 4.11 (s, 2H), 2.73 (s, 3H)

N-Chlorodiisopropylamine:silver tetrafluoroborate [**97d**]: ^{13}C NMR: δ 60.6 (2C; CH), 21.24 (4C; CH_3). ^1H NMR: δ 3.55 (septet, 2H, $J = 6.1$ Hz), 1.40 (d, 12H, $J = 6.1$ Hz).

N-Chlorodipropylamine:silver tetrafluoroborate [**98d**]: ^{13}C NMR: δ 68.5 (2C; $\alpha\text{-CH}_2$), 23.27 (2C; $\beta\text{-CH}_2$), 10.79 (2C; CH_3). ^1H NMR: δ 3.12 (t, 4H, $J = 7.7$ Hz), 1.87 (sextet, 4H, $J = 7.4$ Hz), 1.03 (t, 6H, $J = 7.4$ Hz).

N-Chlorodibutylamine:silver tetrafluoroborate [**99d**]: ^{13}C NMR: δ 66.78 (2C; $\alpha\text{-CH}_2$), 32.25 (2C; $\beta\text{-CH}_2$), 19.77 (2C; $\gamma\text{-CH}_2$), 13.92 (2C; CH_3). ^1H NMR: δ 3.16 (t, 4H, $J = 7.8$ Hz), 1.84 (pentet, 4H, $J = 7.3$ Hz), 1.45 (sextet, 4H, $J = 7.5$ Hz), .98 (t, 6H, $J = 7.4$ Hz).

N-Chlorobenzylethylamine:silver tetrafluoroborate [**102d**]: ^1H NMR: δ 7.35-7.45 (m, 3H), 7.46-7.6 (m, 2H), 4.12 (s, 2H), 3.33 (q, 2H, $J = 6.8$ Hz), 1.30 (t, 3H, $J = 6.9$ Hz).

N-Chloro-N-benzyl-1-phenethylamine:silver tetrafluoroborate [**103d**]: ^1H NMR: δ 7.24-7.55 (m, 10H), 4.26 (q, 1H, $J = 6.5$ Hz), 4.0 (d, 1H, $J = 13.6$ Hz), 3.91 (d, 1H, $J = 13.6$ Hz), 1.64 (d, 3H, $J = 6.5$ Hz).

N-Cyanodibenzylamine [92]: The reaction of N-chlorodibenzylamine:silver tetrafluoroborate complex with cyanide was performed in both benzene and methylene chloride, at room temperature, 0°C, and -78°C, and under both an inert atmosphere and an oxygen atmosphere, with the product outcome being essentially unchanged. Into a stirring solution of N-chlorodibenzylamine (.5 g, .002 mol) in 50 mL of solvent (methylene chloride or benzene) in a round-bottomed flask was added 1 equivalent of silver tetrafluoroborate (.42 g, .002 mol). The reaction was monitored by TLC (silica/methylene chloride) and stopped when no further reaction was evident (about 8 hours), by the addition of sodium cyanide (0.86g, 0.018 mol) in 10 mL of water at a pH of 5 (adjusted with acetic acid). Two products were formed in the reaction as indicated by TLC and spectroscopic analysis. Separation of the two products was effected by liquid chromatography using silica gel/methylene chloride to give N-chlorodibenzylamine [**87c**] (R_f .95 [silica gel/methylene chloride], 50% yield) and the N-cyanoamine **92** (R_f .8 [silica gel/methylene chloride], 50% yield). ^{13}C NMR: δ 134.14 (2C), 128.6 (4C), 128.3 (4C), 128.09 (2C) (aromatics), 54.02 (2C; methylene). ^1H NMR: δ 7.2-7.35 (bm, 10H), 4.031 (s, 4H). IR: 3060.8, 3029.7, 2922.6 (C-H stretch), 2199.5 (C=N), 1470.7, 1452.5 (asym. C-H stretch), 1343.2, 1257.5, 1207.8, 1176.6, 1122.5, 1072.9, 1027.9, 961.2, 810.5, 730.5, 690.3, 537.4, 478.3. MS (FAB) m/z (relative intensity): 223 ($M+1$, 36), 131 ($M - \text{C}_6\text{H}_5\text{CH}_2$, 13), 91 (100), 65 (7).

N-benzyl-N-phenyl-isopropyliminium tetrafluoroborate [104]: The N-chloramine **89b** (.30 g; 1.16 mmol) was placed in a dry 50-mL round-bottomed flask along with dry methylene chloride (30 mL) and purged with N₂. Silver tetrafluoroborate (.3 g; 1.5 mmol) in dry methylene chloride was then added via syringe and a silver chloride precipitate was immediately formed. After stirring overnight, a bluish-green solution formed which was filtered and concentrated to give a crude mixture containing predominantly the imminium ion **104**: ¹H NMR (CDCl₃) δ 7.15 - 7.7 (m, 10H), 5.35 (s, 2H), 2.92 (s, 3H), 2.34 (s, 3H).

N-benzyl-N-isopropylaniline [105] and N-benzylaniline [106]: The crude mixture containing the imminium ion **104** was taken up in benzene and placed in a 100 mL round-bottomed flask. Treatment with NaCNBH₃ (.22 g; 3.4 mmol) in methanol at a pH of 5.5 (adjusted with HOAc) was followed by stirring at room temperature for 30 min. The solution was washed with a saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give three organic products which were separated by preparative TLC (SiO₂/CH₂Cl₂): N-benzyl-2-phenyl-2-propylamine [**90a**], N-benzyl-N-isopropylaniline [**105**], and N-benzylaniline [**106**] in 30, 35, and 35% yields respectively from the starting amine **90a**. Higher yields (65%) of **105** were obtained when solid sodium

cyanoborohydride was added first to the benzene solution followed by methanol (pH 5.5).

N-Benzyl-N-isopropylaniline [105]: ^{13}C NMR: δ 148.9, 137.7, 129.1 (2C), 128.4 (2C), 126.4, 126.2 (2C), 116.4, 113.2 (2C) (aromatics), 48.4 (CH_2), 48.2 (CH), 19.9 (CH_3). ^1H NMR: δ 7.4-7.1 (m, 7H), 6.75-6.6 (m, 3H), 4.41 (s, 2H), 4.27 (septet, 1H, $J = 6.6$ Hz), 1.20, (d, 6H, $J = 6.6$ Hz). MS (EI^+) m/z (relative intensity): 225 (M^+ , 56), 210 ($\text{M} - \text{CH}_3$, 100), 183 (24), 167 (8), 152 (4), 132 (3), 118 (7).

N-Benzylaniline [106]: ^{13}C NMR: δ 148.1, 139.4, 129.2 (2C), 128.6 (2C), 127.5 (2C), 127.2, 117.6, 112.8 (2C) (aromatics), 48.3 (CH_2). ^1H NMR: δ 7.4-7.25 (m, 5H), 7.17 (t, 2H, $J = 7.5$ Hz), 6.70 (t, 1H, $J = 7.3$ Hz), 6.63 (d, 2H, $J = 7.7$ Hz), 4.31 (s, 2H), 1.25 (s, 1H, N-H). MS (EI^+) m/z (relative intensity): 183 (M^+ , 100), 182 ($\text{M} - 1$, 65), 106 ($\text{M} - \text{C}_6\text{H}_5$, 50).

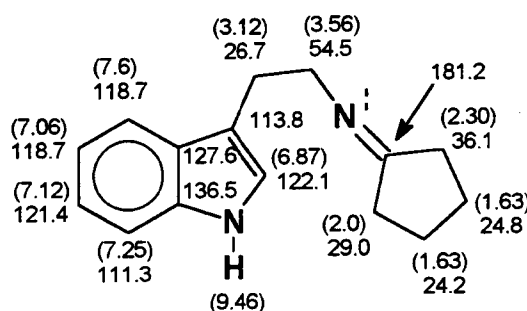
Dibenzylnitrenium tetrafluoroborate (Figure II-3): Silver tetrafluoroborate (1 g) was dissolved in 80 mL of dry benzene with heating as necessary. After cooling the solution to room temperature, dibenzyl-N-chloramine (1 g) was added in 15 mL of dry benzene. The tube was stoppered and placed in the refrigerator for one year.

Periodic observations noted extensive silver precipitation. At the end of a year, the benzene solution was carefully decanted to reveal crystal growth extending from the walls of the test tube inward. The crystals were dislodged to afford several samples suitable for X-ray crystallographic analysis. The selected crystal was a colorless parallelepiped of dimensions 0.2 X 0.15 X 0.8 mm. X-ray data were collected on a Siemens R 3mV diffractometer using the ω method. A total of 1889 reflections were recorded in the 2θ range 3.5-45° using MoK α radiation. Of the 956 independent reflections, 756 reflections with $F_o > 6.0\sigma(F_o)$ were used in full-matrix least-squares refinement. Final residuals were $R(F) = 0.0630$ and $R_w(F) = 0.0828$. The atoms were located by direct methods using the SHELXTL PLUS software. The hydrogen atoms were placed at their calculated positions. The crystallographic data are given in Tables A-1 to A-7, pages 137-141.

Cyclobutylidene-[2-(1H-indol-3-yl)-ethyl]amine [112a]: Into a 50-mL round-bottomed flask containing 25 mL benzene and equipped with Dean-Stark trap, condensor, and N₂ inlet, was placed tryptamine (0.50 g; 3.12 mmol) and cyclobutanone (0.24 g, 3.44 mmol). The mixture was stirred at room temperature for 30 min, heated to reflux (2 hrs), cooled and checked for conversion into the imine by NMR analysis. Subsequent additions (2 X .25 eq, 0.06 g) of cyclobutanone and additional heating at reflux (1 hr) were required in order to

maximize the conversion to the imine. The solvent was removed *in vacuo* and the imine was used without further purification. ^{13}C NMR: δ 173.1 (C=N), 136.5, 128.3, 121.9, 121.7, 119.0, 118.8, 114.2, 111.1 (aromatics), 52.4, 37.8, 34.6, 26.5, 13.1. ^1H NMR: δ 9.28 (bs, 1H), 7.7-6.6 (m, 5H), 3.5 (t, 2H), 3.2-1.5 (m, 8H).

Cyclopentylidene-[2-(1H-indol-3-yl)-ethyl]amine [112b]: Using the procedure described for **112a**, cyclopentanone was converted into **112b**. However, no subsequent addition of cyclopentanone was needed to maximize the conversion of amine to imine presumably due to the lower volatility of cyclopentanone.



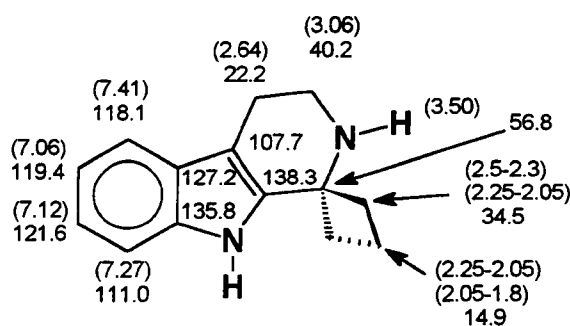
112b

^{13}C NMR: δ 181.2 (C=N), 136.5, 127.6, 122.1, 121.4, 118.7, 118.7, 113.8, 111.3 (aromatics), 54.5, 36.1, 30.0, 26.7, 24.7, 24.2. ^1H NMR: δ 9.5 (bs, 1H),

7.6 (d, 1H, J = 7.4 Hz), 7.3 (d, 1H, J = 7.6 Hz), 7.12 (t, 1H, J = 6.7 Hz), 7.06 (t, 1H, J = 6.8 Hz), 6.87 (s, 1H), 3.6 (t, 2H, J = 7.3 Hz), 3.12 (t, 2H, J = 7.5 Hz), 2.3 (bs, 2H), 2.0 (bs, 2H), 1.63 (bs, 4H). (HETCOR: Figure A-1, page 142)

1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1-spiro-1'-cyclobutane [107a]:

To a benzene solution of imine **112a** in a 50-mL round-bottomed flask was added a catalytic amount of p-toluenesulfonic acid (*ca* .1 g) along with oven-dried silica gel (5 g). The heterogenous mixture was maintained at reflux (78°C) for 24 hrs under a nitrogen atmosphere. The silica gel was removed by vacuum filtration, washed with methanol, and the combined organic fractions were concentrated to give a brownish oil which was taken up in methylene chloride and extracted with a saturated solution of sodium bicarbonate (3 X 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give a yellowish-



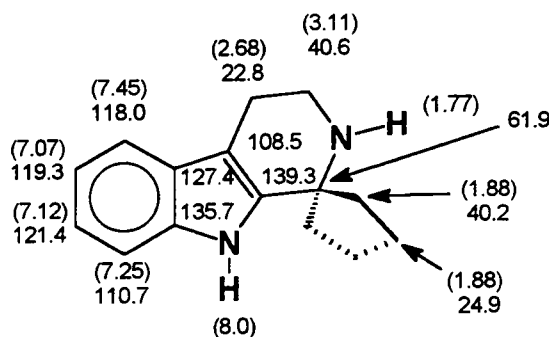
107a

brown solid. Purification by liquid chromatography ($\text{Al}_2\text{O}_3/\text{CHCl}_3$) provided the spirocycle **107a** in 90% yield. ^{13}C NMR: δ 138.3, 135.8, 127.1, 121.6, 119.4, 118.1, 110.96, 107.7 (aromatics), 56.8, 40.2, 34.4 (2C), 22.2, 14.9. ^1H NMR: δ 8.6 (s, 1H), 7.41 (d, 1H, $J = 7.3$ Hz), 7.27 (d, 1H, $J = 7.7$ Hz), 7.12 (t, 1H, $J = 7.1$ Hz), 7.06 (t, 1H, $J = 7.4$ Hz), 3.51 (s, 1H, N-H) 3.06 (t, 2H, $J = 5.6$ Hz), 2.64 (t, 2H, $J = 5.6$ Hz), 2.41 (m, 2H), 2.16 (m, 3H), 1.91 (m, 1H). IR: 3407, 3262, 3055, 2929, 2844, 1587, 1451, 1384, 1345, 1299, 743. MS (FAB^+) m/z (relative intensity): 213 ($\text{M}^+ + 1$, 100), 196 (25), 168 (9), 144 (27), 130 (10), 115 (5). HRMS: calculated for $\text{C}_{14}\text{H}_{17}\text{N}_2$ ($\text{M}^+ + 1$) m/z 213.1392, found 213.1387. (^1H NMR: Figure A-2, page 143; ^{13}C NMR: Figure A-3, page 144; HETCOR: Figure A-4, page 145)

1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1'-spiro-1'-cyclopentane [107b]:

Using the procedure described for **107a**, the imine **112b** was converted into **107b** in 80% yield (m.p.¹²³ 138-139 °C). ^{13}C NMR: δ 139.3, 135.7, 127.4, 121.4, 119.3, 118.0, 110.7, 108.5 (aromatics), 61.9, 40.6, 40.2 (2C), 24.9 (2C), 22.8. ^1H NMR: δ 8.0 (s, 1H), 7.45 (d, 1H, $J = 6.7$ Hz), 7.25 (d, 1H, $J = 6.95$ Hz), 7.12 (t, 1H, $J = 7.02$ Hz), 7.07 (t, 1H, $J = 7.12$ Hz), 3.11 (t, 2H, $J = 5.7$ Hz), 2.68 (t, 2H, $J = 5.7$ Hz), 1.88 (m, 8H), 1.77 (s, 1H). IR: 3407, 3054, 2949, 2868, 1463, 1448, 1295, 908, 740. MS (FAB^+) m/z (relative intensity): 227 (M^+ ,

35), 210 (3), 197 (15), 109 (5). HRMS: calculated for $C_{15}H_{19}N_2$ ($M^+ + 1$) m/z 227.1548, found 227.1497. (1H NMR: Figure A-5, page 146; HETCOR: Figure A-6, page 147; COSY: Figure A-7, page 148)



107b

N_b -Chloro-1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1-spiro-1'-cyclobutane

[108a]: The formation of **108a** was accomplished by two different methods, the first method giving higher yields as determined by NMR. Absolute yield of purified material was not determined since the N-chloramine isomerizes to the chloroindolenine upon standing.

Method A: Into an ice-water cooled 100-mL round-bottomed flask, under a nitrogen atmosphere, was placed the spirocycle **107a** (420 mg, 2 mmol) and 20 mL of dry tetrahydrofuran. Addition of *n*-BuLi (1 mL, 2M solution) was followed by treatment of the resulting anion with N-chlorosuccinimide (290 mg, 1.1 eq). Immediately, the proton and carbon NMR were obtained which showed

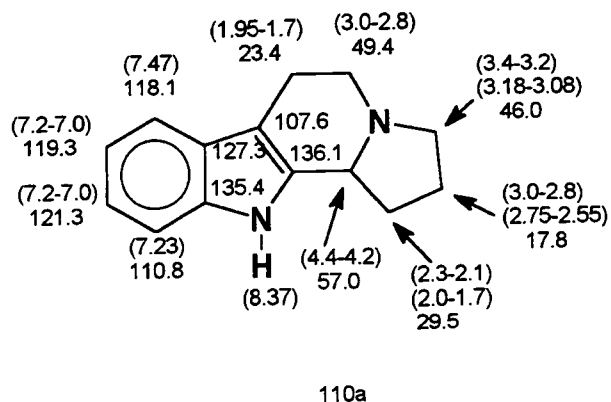
predominately the N_b-chloramine as well as the succinimide by-product.

Method B: Into a 125-mL Erlenmeyer flask was placed 20 mL methylene chloride, spirocycle **107a** (100 mg, .47 mmol), N-chlorosuccinimide (69 mg, 1.1 eq) and alumina (5 g). After swirling for 2 min the mixture was filtered to remove the alumina and concentrated *in vacuo* at room temperature. This formed the N_b-chloramine in approximately 70% yield (as determined by NMR). Since the proton NMR of **108a** was difficult to analyze due the formation of mixtures (previously described in text, page 65) and since we were unable to purify the N-chloramine due to its subsequent isomerization to the chloroindolenine, only crude ¹³C NMR data is available: δ 135.9, 130.2, 127.1, 121.9, 119.7, 118.4, 111.0, 105.6 (aromatics), 66.6, 52.1, 29.6, 18.5, 13.4.

N_b-Chloro-1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1'-spiro-1'-cyclopentane [108b]: Using the procedures described for **108a** (Method A), the spirocycle **107b** was converted to **108b**. ¹³C NMR: δ 137.2, 135.9, 126.5, 121.8, 119.6, 118.3, 110.9, 105.7 (aromatics), 73.0, 54.3, 39.5 (2C), 25.6 (2C), 18.9.

2,3,5,6,11,11b-Hexahydro-1H-indolizino[8,7-b]indole [110a]: The spirocycle **[107a]** (420 mg, 2 mmol) was dissolved in 50 mL of dry benzene and placed in a 100-mL round-bottomed flask, equipped with a nitrogen inlet and a magnetic

stirring bar. After cooling to 0°C, *n*-BuLi (1.1 eq, 2M solution in hexane) was added via syringe to the reaction and the solution was stirred for 10 min. A solution of N-Chlorosuccinimide (.29g, 1.1 eq.) in benzene was then added via syringe. **Immediately** this solution was poured into a flask containing silver tetrafluoroborate (1.16 g, 6 mmol) that had previously been dissolved in 50 mL of dry benzene. The reaction was stirred under nitrogen for five hrs before sodium cyanoborohydride (.16 g, 5 eq.) in methanol (pH 6, adjusted with acetic acid) was added to quench the reaction. Three identifiable products were formed and subsequently separated by column chromatography (Al₂O₃/CHCl₃): the expected product - hexahydro-indolo-indolizidine [110a] in 66% yield, the parent amine 107a in 20% yield, and the N_b-cyclobutyltryptamine [113a] in 11% yield.



¹³C NMR: δ 136.1, 135.4, 127.3, 121.3, 119.3, 118.1, 110.8, 107.6 (aromatics), 57.0, 49.4, 46.0, 29.5, 23.4, 17.9. ¹H NMR: δ 8.37 (s, 1H), 7.47 (d, 1H, J =

7.4 Hz), 7.23 (d, 1H, $J = 7.3$ Hz), 7.11 (m, 2H), 4.25-4.1 (bs, 1H), 3.35-3.2 (d, 1H), 3.16-3.0 (m, 1H), 3.0-2.8 (m, 3H), 2.75-2.55 (d, 1H), 2.4-2.0 (m, 1H), 2.0-1.5 (m, 3H). IR: 3053, 2923, 2849, 2730, 1451, 1370, 1335, 1307, 1163, 1063, 742. MS (FAB⁺) m/z (relative intensity): 213 ($M^+ + 1$, 80), 167 (12). HRMS: calculated for $C_{14}H_{17}N_2$ ($M^+ + 1$) m/z 213.1392, found 213.139 (¹H NMR: Figure A-8, page 149; ¹³C NMR: Figure A-9, page 150; HETCOR: Figure A-10, page 151; COSY: Figure A-11, page 152)

Cyclobutyl-[2-(1H-indol-3-yl)-ethyl]-amine [113a]: Imine **112a** (50 mg; .24 mmol) was taken up in 20 mL of anhydrous methanol and placed in a 100 mL round-bottomed flask. Sodium cyanoborohydride (3 eq.) in methanol (50 mL, pH adjusted to 6 with acetic acid) was added to the solution at room temperature and stirred for 30 min.. The reaction mixture was then concentrated to give a light brown oil which was taken up in methylene chloride and extracted with a saturated solution of sodium bicarbonate (3 X 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give **113a** in 80% yield. ¹³C NMR: δ 136.5, 127.4, 122.2, 121.8, 119.0, 118.7, 113.2, 111.3 (aromatics), 53.8, 46.8, 30.7 (2C), 22.7, 14.8. ¹H NMR: δ 9.02 (s, 1H), 7.58 (d, 1H, $J = 7.5$ Hz), 7.26 (d, 1H, $J = 7.8$ Hz), 7.15 (t, 1H, $J = 7.0$ Hz), 7.08 (t, 1H, $J = 7.6$ Hz), 6.9 (s, 1H), 3.26 (m, 1H), 2.93 (d, 2H, $J = 5.4$ Hz), 2.88 (d, 2H, $J = 5.1$

Hz), 2.15 (m, 2H), 1.61 (bs, 5H). IR: 3413, 3307, 2857, 1619, 1453, 1384, 1353, 1223, 1147, 1122, 1062, 1008, 858, 741. MS (FAB⁺) *m/z* (relative intensity): 215 (M⁺ + 1, 75), 144 (38), 130 (15), 117 (4). HRMS: calculated for C₁₄H₁₉N₂ (M⁺ + 1) *m/z* 215.1548, found 215.1544. (¹H NMR: Figure A-12, page 153; HETCOR: Figure A-13, page 154)

Cyclopentyl-[2-(1H-indol-3-yl)-ethyl]-amine [113b]: Using the procedure described for **113a**, the imine **112b** was converted into **113b** in 77% yield. ¹³C NMR: δ 136.5, 127.4, 122.2, 121.7, 119.0, 118.8, 113.5, 111.2 (aromatics), 59.8, 48.7, 33.1, 26.0, 24.1. ¹H NMR: δ 9.0 (s, 1H), 7.60 (d, 1H, J = 7.3 Hz), 7.28 (d, 1H, J = 7.9 Hz), 7.16 (t, 1H, J = 7.0 Hz), 7.11 (t, 1H, J = 7.85 Hz), 6.92 (s, 1H), 3.07 (pentet, 1H, J = 6.9 Hz), 2.96 (s, 4H), 1.25-1.95 (m, 9H).

N_b-Chlorocyclobutyl-[2-(1H-indol-3-yl)-ethyl]-amine [113c]: A methylene chloride solution (20mL) of **113a** (150 mg, .7 mmol) was cooled to -78 °C prior to the addition of N-chlorosuccinimide (103 mg, .77 mmol). This solution was not concentrated, but was used as described below. NMR analysis of the N-chloramine was obtained by performing the reaction in an NMR tube with CD₂Cl₂ as the solvent. Good yields (>80% - as determined by NMR) were obtained as long as the solution was kept below -60 °C. Low temperature NMR (-60 °C) revealed the

following N-chloramine carbon absorptions: 136.2, 127.3, 122.7, 121.9, 119.2, 118.9, 112.5, 111.7 (aromatics), 66.01, 60.11, 29.96, 28.22, 24.0, 13.49.

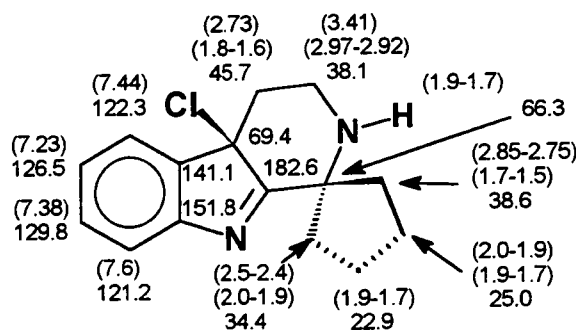
Rearrangement of N_b-Chlorocyclobutyl-[2-(1H-indol-3-yl)-ethyl]-amine [113c]:

The N-chloramine **113c** (obtained from 150 mg of **113a**) was kept at -60 °C until it was added, in one portion, to a room temperature solution of silver tetrafluoroborate (.41 g, 2.1 mmol) and 25 mL of anhydrous CH₂Cl₂ which had previously been heated to reflux to dissolve the silver compound and remove any residual water. The reaction mixture immediately turned a milky brown color with the formation of a precipitate. TLC of the mixture after one hour showed no trace of the N-chloramine. At this point, gaseous HCl was bubbled into the flask and copious amounts of AgCl was formed. The reaction was allowed to stir at room temperature for another hour before filtering through celite. The filtrate was placed in a separatory funnel and washed with a saturated solution of NaHCO₃ (3 X 30 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a brown oil. Crude NMR revealed the formation of hexahydro-indolo-indolizidine [**110a**]. Purification by liquid chromatography (Al₂O₃/2%hexane-chloroform) provided **110a** and **113a** in 16% and 60% yields, respectively.

4a-Chloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclobutane [114a]: Into a benzene solution of the dichlorinated spirocycle **115a** in an Erlenmeyer flask, was bubbled HCl gas until a saturated solution resulted. The reaction was neutralized by washing with a saturated sodium bicarbonate solution, followed by drying the organic layer over anhydrous sodium sulfate and concentrating the solution *in vacuo*, to give the chloroindolenine **114a** and a minor impurity (30%) identified as the corresponding oxindole **116a**. Purification by column chromatography ($\text{Al}_2\text{O}_3/\text{CH}_2\text{Cl}_2$) gave **114a** in 60% yield. ^{13}C NMR: δ 181.4 (C=N), 152.3, 140.9, 129.98, 126.6, 122.5, 121.4, (aromatics), 69.1, 60.2, 44.8, 37.8, 32.0, 29.8, 15.8. ^1H NMR: δ 7.61 (d, 1H, $J = 7.3$ Hz), 7.44 (d, 1H, $J = 7.3$ Hz), 7.36 (t, 1H, $J = 7.8$ Hz), 7.24 (t, 1H, $J = 7.8$ Hz), 3.40-2.95 (m, 2H), 2.85-2.75 (m, 2H), 2.73 (bs, 1H), 2.5-2.4 (m, 1H), 2.0-1.9 (m, 3H), 1.7-1.5 (m, 2H).

4a-Chloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [114b]: Using the procedures described for **114a**, the dichlorinated spirocycle **115b** was converted into **114b** in 65% yield along with oxindole **116b** in 28% yield. ^{13}C NMR: δ 182.6 (C=N), 151.8, 141.1, 129.8, 126.5, 122.3, 121.2 (aromatics), 69.4, 66.3, 45.7, 38.6, 38.1, 34.5, 24.97, 22.9. ^1H NMR: δ 7.60 (d, 1H, $J = 7.4$ Hz), 7.44 (d, 1H, $J = 7.3$ Hz), 7.38 (t, 1H, $J = 7.7$ Hz), 7.26 (t, 1H, $J = 7.6$ Hz), 3.41 (t, 1H, $J = 12.3$ Hz), 3.0-2.95 (m, 1H), 2.85-2.75 (m, 1H), 2.73 (bs,

1H), 2.5-2.4 (m, 1H), 2.0-1.9 (m, 2H), 1.9-1.7 (m, 5H), 1.7-1.5 (m, 1H). IR: 2956, 2251, 1566, 1453, 908, 734, 649. MS (EI⁺) *m/z* (relative intensity): 260 (M⁺, 9), 225 (M⁺ - ³⁵Cl, 100), 197 (13), 167 (7). HRMS: calculated for C₁₅H₁₇ClN₂ (M⁺) *m/z* 260.10803, found 260.1077. (¹H NMR: Figure A-14, page 155; HETCOR (8.2-6.9 ppm vs. 138-114 ppm): Figure A-15, page 156; HETCOR (3.0-1.4 ppm vs. 48-20 ppm): Figure A-16, page 157; COSY: Figure A-17, page 158)

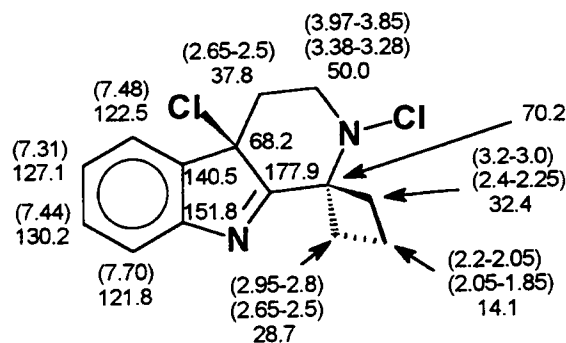


114b

2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclobutane [115a]:

Into a 125 mL Erlenmeyer flask was placed 20 mL CH₂Cl₂, spirocycle **107a** (2 mmol), and N-chlorosuccinimide (0.59 g; 2.2 eq). After swirling for 2 min the succinimide was removed by washing the organic solution with saturated sodium bicarbonate (3 X 20 mL) followed by drying over anhydrous sodium sulfate and concentrating *in vacuo* at room temperature. The product was generally used

without further purification (70% yield, as determined by NMR) due to marked loss of product upon purification by liquid chromatography ($\text{Al}_2\text{O}_3/\text{CH}_2\text{Cl}_2$).

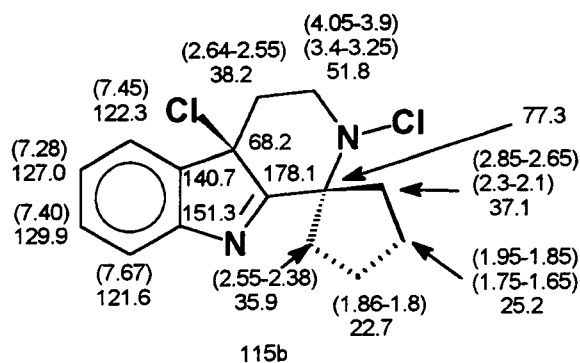


115a

^{13}C NMR: δ 177.9 (C=N), 151.8, 140.5, 130.2, 127.1, 122.5, 121.8 (aromatics), 70.2, 68.2, 50.0, 37.8, 32.4, 28.7, 14.1. ^1H NMR: δ 7.70 (d, 1H, $J = 7.6$ Hz), 7.48 (d, 1H, $J = 7.02$ Hz), 7.44 (t, 1H, $J = 7.7$ Hz), 7.31 (t, 1H, $J = 7.6$ Hz), 3.91 (ddd, 1H, $J = 14.4, 10.1, 4.3$ Hz), 3.33 (ddd, 1H, $J = 14.3, 2.9, 2.9$ Hz), 3.15-3.01 (m, 1H), 2.95-2.82 (m, 1H), 2.80-2.69 (m, 2H), 2.63-2.47 (m, 1H), 2.39-2.24 (m, 1H), 2.2-2.04 (m, 1H), 1.83-2.0 (m, 1H).

2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [115b]:

Using the procedures described for 115a, the spirocycle 107b was converted into 115b in 70% yield.



^{13}C NMR: δ 178.1 (C=N), 151.3, 140.7, 129.9, 127, 122.3, 121.6 (aromatics), 77.3, 68.2, 51.8, 38.2, 37.1, 35.9, 25.2, 22.7. ^1H NMR: δ 7.67 (d, 1H, $J = 7.7$ Hz), 7.45 (d, 1H, $J = 6.6$ Hz), 7.40 (t, 1H, $J = 7.6$ Hz), 7.28 (t, 1H, $J = 7.5$ Hz), 3.97 (ddd, 1H, $J = 15, 7.5, 7.5$ Hz), 3.33 (ddd, 1H, $J = 15, 3.0, 2.9$ Hz), 2.8-2.65 (m, 1H), 2.65-2.55 (m, 2H), 2.55-2.44 (m, 1H), 2.44-2.3 (m, 1H), 2.3-2.1 (m, 1H), 2.0-1.6 (m, 4H). IR: 3048, 2955, 2870, 1705, 1636, 1571, 1455, 1025, 871, 767, 747. MS (EI^+) m/z (relative intensity): 294 (M^+ , 18), 259 (294 - ^{35}Cl , 54), 223 (259 - ^{35}Cl , 100), 195 (21), 178 (10), 167 (14), 154 (8), 115 (10). HRMS: calculated for $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2$ (M^+) m/z 294.0691, found 294.0684. (^1H NMR: Figure A-18, page 159; HETCOR (8-7 ppm vs. 132-120 ppm): Figure A-19, page 160; HETCOR 4.4-1.5 ppm vs. 60-10 ppm): Figure A-20, page 161; COSY: Figure A-21, page 162)

2'-Spiro-2'-cyclobutyl-1H-spiro[indole-3,3'-pyrrolidin]-2-one [116a]: The oxindole **116a** was prepared *via* the formation of both the chloroindolenine **114a**

and the dichlorinated adduct **115a** by the same procedure, with the only deviation being the amount of N-chlorosuccinimide used. The general procedure is as follows: to an Erlenmeyer flask was added **110a** (50 mg, .24 mmol), CH₂Cl₂ (20 mL), and N-chlorosuccinimide (1.1 eq. to prepare **114a**, 2.2 eq. to prepare **115a**). After stirring for 5 min at room temperature, the organic layer was washed with a saturated sodium bicarbonate solution (2 X 20 mL) and a brine solution (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give the chlorinated material. To this compound in 20 mL of dry benzene was added aluminum trichloride (3 eq.) and, after 5 minutes, 2 mL of 1 M H₂SO₄ in methanol (20 mL). The solution immediately turned green, but changed to brown when 6M NH₃ (20 mL) was added 30 min later. The organic layer was washed with a saturated sodium bicarbonate solution (30 mL) and a brine solution (30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the oxindole **116a** in 70% yield from **114a** and 85% yield from **115a**. The oxindole was purified by column chromatography (Al₂O₃) using CHCl₃ with 3% methanol. ¹³C NMR: δ 182.3 (C=O), 141.7, 130.9, 127.9, 124.6, 122.2, 109.9 (aromatics), 71.9, 60.1, 43.6, 36.0, 29.8, 28.3, 15.5. ¹H NMR: δ 7.35 (s, 1H), 7.23 (t, 1H, J = 6.6 Hz), 7.21 (d, 1H, J = 7.4 Hz), 7.05 (t, 1H, J = 6.9 Hz), 6.95 (d, 1H, J = 7.4 Hz), 3.37-3.08 (m, 2H), 2.4-2.22 (m, 2H), 2.2-2.05 (m, 2H), 2.05-1.93 (m, 1H), 1.93-1.75 (m, 3H), 1.5-1.25 (m, 1H).

2'-Spiro-2'-cyclopentyl-1H-spiro[indole-3,3'-pyrrolidin]-2-one [116b]: Using the procedure described for **116a**, the spirocycle **107b** was converted into **116b** in 83% yield. ^{13}C NMR: δ 183.3 (C=O), 141.8, 130.4, 127.8, 125.2, 122.0, 109.8 (aromatics), 77.4, 60.3, 43.7, 36.3, 33.4, 33.2, 24.2, 23.5. ^1H NMR: δ 9.01 (s, 1H), 7.25 (t, 1H, $J = 5.6$ Hz), 7.20 (d, 1H, $J = 7.7$ Hz), 7.02 (t, 1H, $J = 7.5$ Hz), 6.92 (d, 1H, $J = 7.5$ Hz), 3.37-3.12 (m, 2H), 2.89 (s, 1H, N-H), 2.4-2.13 (m, 2H), 1.9-1.6 (m, 4H), 1.58-1.22 (m, 4H). IR: 3288, 2957, 2872, 1701, 1616, 1469, 1329, 1245, 1184, 1112, 966. MS (FAB $^+$) m/z (relative intensity): 243 ($\text{M}^+ + 1$, 40). HRMS: calculated for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}$ ($\text{M}^+ + 1$) m/z 243.1497, found 243.1489.

[1-(Toluene-4-sulfonyl)-1H-indol-3-yl]-acetonitrile [120]: An aqueous solution (75 mL distilled water) of NaOH (8 g), NaCN (1 g) and tetra-*n*-butylammonium hydroxide (.5 g) was added in one portion to an ice-cooled solution of indolylacetonitrile (8 g, 51.2 mmol) dissolved in ether (50 mL). The reaction was allowed to stir for five minutes prior to the partial addition (1 g of 19 g total) of tosyl chloride. The reaction mixture immediately turned red and was allowed to stir for two minutes between each subsequent addition of tosyl chloride (1 g every 2 min). After the addition period was complete, the reaction was stirred thirty minutes longer at room temperature. The solid that had formed in the reaction flask

was removed and dissolved in a minimal amount of hot methylene chloride. This solution was poured, in one portion, into four times its volume of ether and stirred vigorously. Copious amounts (7.54 g, 48% yield) of the purified tosylated nitrile, mp 160-161°C (lit. mp 160-162°C)¹⁴¹ crystallized from the solution and were collected by vacuum filtration. ¹³C NMR: δ 145.3, 135.0, 134.8, 129.9 (2C), 128.6, 126.7 (2C), 125.4, 124.3, 123.5, 118.7, 116.7, 113.7 (aromatics), 111.3 (C≡N), 21.4, 14.2. ¹H NMR: δ 8.00 (d, 1H, J = 7.7 Hz), 7.77 (d, 2H, J = 8.3 Hz), 7.60 (s, 1H), 7.48 (d, 1H, J = 7.7 Hz), 7.37 (t, 1H, J = 7.9 Hz), 7.28 (t, 1H, J = 7.1 Hz), 7.23 (d, 2H, J = 8.3 Hz), 3.73 (s, 2H), 2.33 (s, 3H). IR: 3117, 2982, 2921, 2258, 1763, 1595, 1449, 1364, 1307, 1283, 1210, 1175, 1123, 1095, 979, 814, 756, 703, 671, 644, 586, 534. MS (EI⁺) *m/z* (relative intensity): 310 (M⁺, 100), 155 (92), 128 (25), 101 (24), 91 (100), 77 (19), 65 (35).

2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl]-ethylamine [121]: Into a Parr flask containing absolute ethanol (300 mL) saturated with anhydrous ammonia at 0 °C was placed the nitrile **120** (9 g, .029 mol) and the catalyst (.5 g, Rh on Al₂O₃). The flask was charged with 55 psi hydrogen and shaken for 24 hrs. The heterogenous reaction mixture was filtered through Celite and concentrated *in vacuo* to give a viscous oil (8.6 g, 95%). ¹³C NMR: δ 144.7, 135.4, 135.3, 130.9, 129.7 (2C), 126.7 (2C), 124.7, 123.3, 123.0, 120.6, 119.4, 113.8 (aromatics), 41.4, 29.2,

21.4. ^1H NMR: δ 7.99 (d, 1H, $J = 8.1$ Hz), 7.74 (d, 2H, $J = 8.4$ Hz), 7.48 (d, 1H, $J = 7.5$ Hz), 7.38 (s, 1H), 7.34-7.17 (m, 4H), 2.99 (t, 2H, $J = 6.9$ Hz), 2.80 (t, 2H, $J = 6.7$ Hz), 2.31 (s, 3H), 1.28 (s, 2H, NH_2). IR: 3381, 2930, 2865, 1595, 1447, 1366, 1278, 1208, 1171, 1120, 1086, 1018, 978, 877, 813, 748, 702, 669, 600, 572, 539, 498. MS (EI^+) m/z (relative intensity): 314 (M^+ , 6), 285 (12), 155 (15), 130 (100), 102 (23), 91 (55), 77 (19), 65 (32). HRMS: calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (M^+) m/z 314.1089, found 314.1065. Purification of **121** was accomplished by converting it into its hydrochloride salt and recrystallizing it from methanol/ether. The amine **121** was stored in this form and converted back into its free base prior to use.

Cyclobutylidene-{2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl}-ethyl}-amine [122]:

Into a 50-mL round-bottomed flask equipped with Dean-Stark trap, condensor, N_2 inlet, and benzene (25 mL), was placed the tosylated tryptamine **121** (.50 g; 1.59 mmol) and cyclobutanone (.12 g, 1.75 mmol). The mixture was stirred at room temperature for 30 min, heated to reflux (2 hrs), cooled and checked for conversion to the imine by NMR analysis. Subsequent addition (.1 g) of cyclobutanone was required and further heating (1 hr) in order to maximize the conversion to the imine. The solvent was removed *in vacuo* and the imine was used without further purification. NMR showed 80% conversion into the imine with the only other

product being unreacted amine. ^{13}C NMR: δ 173.1 (C=N), 145.3, 134.6, 134.2, 130.0, 129.7 (2 carbons), 128.2, 126.7 (2 carbons), 124.5, 123.1, 121.3, 119.5, 113.6 (aromatics), 51.3, 37.7, 34.5, 26.1, 21.5, 13.0. ^1H NMR: δ 7.98 (d, 1H, $J = 6.9$ Hz), 7.75 (d, 2H, $J = 8.6$ Hz), 7.6-7.0 (m, 5H), 7.36 (s, 1H), 3.47 (t, 2H, $J = 7.8$ Hz), 3.05-2.65 (m, 4H), 2.57 (t, 2H, $J = 7.8$ Hz), 2.32 (s, 3H), 2.2-1.6 (m, 2H).

Cyclobutyl-{2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl}-ethyl}-amine [123]: Imine **122** (470 mg; 1.27 mmol) was taken up in 20 mL of anhydrous methanol and placed in a 100-mL round-bottomed flask. Sodium cyanoborohydride (.24 g; 3 eq.) in methanol (50 mL, pH adjusted to 6 with acetic acid) was added to the solution at room temperature which was stirred for 30 min. The reaction mixture was then concentrated to give a light brown oil which was taken up in methylene chloride and washed with a saturated solution of sodium bicarbonate (3 X 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give **123** in 80% yield. ^{13}C NMR: δ 144.7, 135.3, 135.1, 130.9, 129.7 (2 carbons), 126.6 (2 carbons), 124.7, 123.2, 123.1, 121.0, 119.5, 113.7 (aromatics), 53.9, 45.9, 31.1 (2 carbons), 25.9, 21.4, 14.8. ^1H NMR: δ 8.01 (d, 1H, $J = 7.97$ Hz), 7.72 (d, 2H, $J = 8.33$ Hz), 7.48 (d, 1H, $J = 7.52$ Hz), 7.39 (s, 1H), 7.29 (t, 1H, $J = 7.14$ Hz), 7.19 (t, 1H, $J = 7.4$ Hz), 7.12 (d, 2H, $J = 7.99$ Hz), 3.24 (pentet,

1H), 2.82 (s, 4H), 2.23 (s, 3H), 2.20-2.10 (m, 2H), 1.70-1.30 (m, 5H). MS (FAB⁺) *m/z* (relative intensity): 369 (M + 1, 28), 277 (9), 215 (7), 185 (83), 93 (100), 84 (5), 75 (23), 57 (9). HRMS: calculated for C₂₁H₂₄N₂O₂S (M⁺) *m/z* 368.1559, found 368.1557. (¹H NMR: Figure A-22, page 163; HETCORR: Figure A-23, page 164)

N_b-Chloro-N_b-cyclobutyl-{2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl}-ethyl}-amine [124]: Into a 125-mL Erlenmeyer flask was placed 20 mL of methylene chloride, **123** (300 mg, 8.15 mmol), and N-chlorosuccinimide (120 mg, 8.96 mmol). After swirling for 2 min., the succinimide was removed by washing the organic solution with saturated sodium bicarbonate (3 X 20 mL), followed by drying over anhydrous sodium sulfate, and concentrating *in vacuo* at room temperature. ¹³C NMR: δ 144.7, 135.1, 135.0, 130.7, 129.7 (2 carbons), 126.6 (2 carbons), 124.6, 123.2, 123.0, 120.0, 119.3, 113.6 (aromatics), 65.7, 58.9, 28.2 (2 carbons), 23.4, 21.4, 13.3. ¹H NMR: δ 7.98 (d, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.53-7.35 (m, 1H), 7.40 (s, 1H), 7.3-7.1 (m, 4H), 3.51 (pentet, 1H), 3.03 (s, 4H), 2.3 (s, 3H), 2.25-1.5 (m, 6H).

Attempted Rearrangement of N_b-Chloro-N_b-cyclobutyl-{2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl}-ethyl}-amine: The N-chloramine **124** was immediately

taken up in anhydrous methylene chloride (20 mL) and placed in an addition funnel following its purification. A 100-mL round-bottomed flask, fitted with a N₂ inlet and a Dean-Stark trap was charged with .32 g of silver tetrafluoroborate and 25 mL of anhydrous methylene chloride. This mixture was heated to remove any residual water before the N-chloramine (from 300 mg of **123**) was added. The reaction mixture turned a yellowish-brown color with the formation of a precipitate. TLC of the mixture showed no presence of the N-chloramine. At this point, gaseous HCl was bubbled into the flask and copious amounts of AgCl was formed and the reaction turned a light brown color. The reaction was allowed to stir at room temperature for 1 hour. The mixture was filtered through celite and placed in a separatory funnel with a saturated solution of NaHCO₃. TLC at this step showed many spots with one predominant spot as indicated by I₂ adsorption. The major spot was identified as the starting amine **123** in 50% recovered yield.

N-Cyclopentyl-2-(1H-indol-3-yl)-acetamide [126b]: Into a 100-mL round-bottom flask, equipped with nitrogen inlet and cooled to 0°C, was placed anhydrous ether (20 mL), pyridine (.68 g; 8.6 mmol), and indole-3-acetic acid (.5 g; 2.85 mmol); the mixture was stirred for 20 min before thionyl chloride (.21 mL; 2.85 mmol) (freshly distilled from isoquinoline) was slowly added over 2 min. The reaction was allowed to stir for 30 min during which time it turned a pinkish color.

Cyclopentylamine (.25 g; 2.9 mmol) was then added slowly over 2 min with continued cooling. The reaction was warmed to room temperature and allowed to stir for one hour. The pyridine and unreacted cyclobutylamine were removed by converting them into their hydrochloride salts and extracting them into the aqueous layer in a separatory funnel. The organic layer was removed *in vacuo* to give a solid material that was purified by column chromatography (silica gel/chloroform) to give .34 g (50%) of a waxy solid. ^{13}C NMR: δ 171.4 (C=O), 136.6, 126.9, 123.9, 122.3, 119.8, 118.5, 111.6, 108.6 (aromatics), 51.2, 33.6, 32.8 (2C), 23.5 (2C). ^1H NMR: δ 9.09 (s, 1H), 7.53 (d, 1H, $J = 7.53$ Hz), 7.40 (d, 1H, $J = 7.97$ Hz), 7.20 (t, 1H, $J = 6.5$ Hz), 7.12 (t, 1H, $J = 7.2$ Hz), 7.07 (s, 1H), 5.77 (d, 1H), 4.21 (sextet, 1H, $J = 7.1$ Hz), 3.72 (s, 2H), 1.95-1.75 (m, 2H), 1.55-1.35 (m, 4H), 1.35-1.05 (m, 2H). IR: 3273, 2943, 2868, 1614, 1557, 1384, 1220, 1101, 738, 680, 560.

N-Cyclobutyl-2-(1H-indol-3-yl)-acetamide [126a]: Using the procedure described for **126b**, indole-3-acetic acid was converted into **126a** in 48% yield. ^{13}C NMR: δ 171.4, 136.7, 127.0, 124.3, 122.1, 119.6, 118.4, 111.8, 108.0 (aromatics), 44.8, 33.4, 30.7 (2C), 15.0. ^1H NMR: δ 9.17 (s, 1H), 7.48 (d, 1H, $J = 7.65$ Hz), 7.27 (d, 1H, $J = 7.96$ Hz), 7.14 (t, 1H, $J = 7.3$ Hz), 7.1 (t, 1H, $J = 7.46$ Hz), 6.85 (s, 1H), 6.18 (d, 1H, $J = 7.9$ Hz), 4.34 (sextet, 1H), 3.68 (s, 2H), 2.25-

2.05 (m, 2H), 1.75-1.35 (m, 4H). IR: 3385, 3319, 3051, 2972, 1654, 1523, 1455, 1412, 1336, 1258, 1226, 1150, 1093, 1039, 926, 847, 796, 741, 620, 585, 517. MS (FAB⁺) *m/z* (relative intensity): 229 (*M* + 1, 100), 200 (23), 154 (10), 130 (100). HRMS: calculated for C₁₄H₁₇N₂O (*M* + 1) *m/z* 229.1341, found 229.1299.

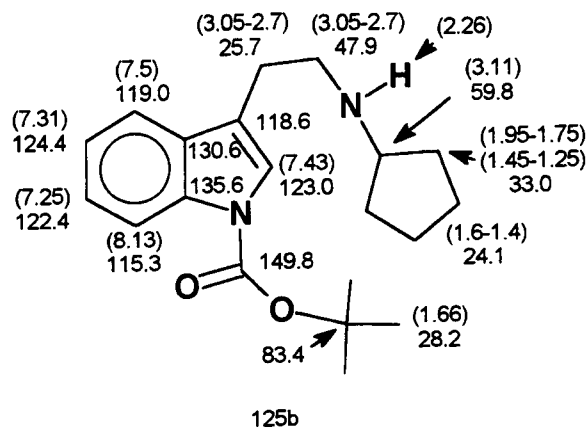
3-Cyclobutylcarbamoylmethylindole-1-carboxylic acid *tert*-butyl ester [127]: To a stirring solution of amide **126a** (200 mg, .83 mmol) in 7 mL of dry tetrahydrofuran at -78°C under N₂ atmosphere was added dropwise .47 mL *n*-BuLi (2.0 M) over 2 min. After stirring at the same temperature for 30 min, BOC-anhydride (.20 g, .94 mmol) was added during a 1 min interval. TLC analysis (silica gel/methylene chloride) indicated that the reaction was complete 20 min after the BOC-anhydride addition. The solution was then partitioned between a saturated sodium bicarbonate solution and diethyl ether, dried with anhydrous sodium sulfate, filtered, and concentrated to give a viscous oil. The residue was chromatographed on 60 g of silica gel by using gradient elution (10% hexane:methylene chloride to pure methylene chloride) to provide 215 mg of the amide (75%). ¹³C NMR: δ 169.4 (amide), 149.5 (carbamate), 135.5, 130.0, 124.7, 124.65, 122.8, 119.1, 115.3, 114.1 (aromatics), 83.7, 44.9, 33.1, 30.8 (2 carbons), 28.1 (3 carbons), 15.0. ¹H NMR: δ 8.14 (d, 1H, *J* = 7.93 Hz), 7.54 (s, 1H), 7.50 (d, 1H, *J* =

7.74 Hz), 7.32 (t, 1H, $J = 7.36$ Hz), 7.21 (t, 1H, $J = 7.17$ Hz), 6.48 (bs, 1H), 4.45-4.25 (bs, 1H), 3.58 (s, 2H), 2.3-2.15 (m, 2H), 1.85-1.5 (m, 4H), 1.65 (s, 9H). IR: 3255, 3058, 2983, 2943, 2867, 1736, 1630, 1549, 1457, 1370, 1339, 1276, 1257, 1228, 1160, 1139, 1083, 1016, 751. MS (FAB⁺) m/z (relative intensity): 329 ($M + 1$, 80), 273 (30), 244 (35), 229 (30), 200 (10), 174 (9). HRMS: calculated for C₁₉H₂₅N₂O₃ ($M + 1$) m/z 329.1865, found 329.1841.

3-(2-Cyclopentylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [125b]:

Imine **112b** (200 mg, .87 mmol) was dissolved in 10 mL of anhydrous THF, placed in a 50-mL round-bottomed flask under a nitrogen atmosphere, and cooled to -78 °C. The addition of *n*-BuLi (435 μ L, .87 mmol) was followed immediately with the introduction of solid Boc-anhydride (167 mg, .96 mmol). The reaction was allowed to warm to room temperature with stirring before it was poured into a methanolic sodium cyanoborohydride solution (pH 6 - made acidic with acetic acid) containing 274 mg (4.4 mmol) of the borohydride. The reaction was left stirring for 2 hrs before most of the solvent was removed via rotary evaporation. The evaporated residue was taken up in methylene chloride (30 mL), washed with a saturated sodium bicarbonate solution (3 X 30 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give a brown oily residue. Purification

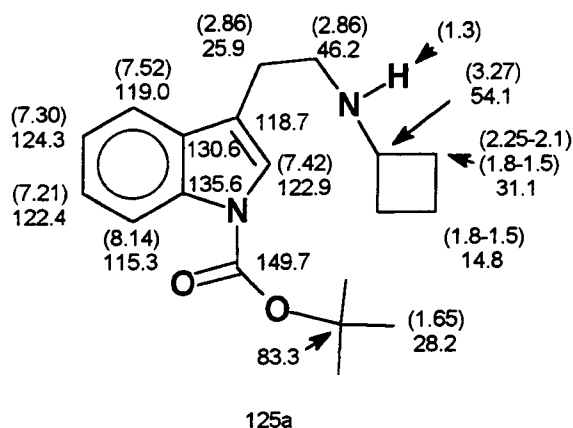
by column chromatography (alumina/10% hexane-chloroform) afforded a 60% yield of **125b**.



¹³C NMR: δ 149.78 (C=O), 135.63, 130.61, 124.36, 123.01, 122.41, 119.0, 118.64, 115.29 (aromatics), 83.39, 59.83, 47.88, 30.02 (2 carbons), 28.24 (3 carbons), 25.69, 24.1 (2 carbons). ¹H NMR: δ 8.13 (d, 1H, J = 7.7 Hz), 7.55 (d, 1H, J = 6.98 Hz), 7.43 (s, 1H), 7.31 (t, 1H, J = 6.9 Hz), 7.22 (t, 1H, J = 7.35 Hz), 3.11 (pentet, 1H, J = 6.83 Hz), 3.05-2.7 (m, 4H), 2.26 (bs, 1H), 2.0-1.8 (m, 2H), 1.66 (s, 9H), 1.6-1.4 (m, 4H), 1.4-1.15 (m, 2H). MS (FAB⁺) *m/z* (relative intensity): 329 (M + 1, 45), 273 (25), 144 (60), 130 (33), 98 (100), 67 (15). HRMS: calculated for C₂₀H₂₉N₂O₂ (M + 1) *m/z* 329.2229, found 329.2219. (¹H NMR: Figure A-24, page 165; HETCORR: Figure A-25, page 166)

3-(2-Cyclobutylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [**125a**]:

Using the procedure described for **125b**, imine **112a** was converted to **125a** in 66%



yield. ^{13}C NMR: δ 149.73 (C=O), 135.64, 130.61, 124.34, 122.95, 122.39, 118.97, 118.71, 115.3 (aromatics), 83.31, 54.08, 48.18, 31.06 (2C), 28.20 (3C), 25.93, 14.83. ^1H NMR: δ 8.14 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 7.50 Hz), 7.42 (s, 1H), 7.30 (t, 1H, J = 7.2 Hz), 7.21 (t, 1H, J = 7.21 Hz), 3.98 (pentet, 1H, J = 5.64 Hz), 2.86 (s, 4H), 2.3-2.1 (m, 2H), 1.8-1.5 (bs, 13H), 1.44 (s, 1H, N-H). MS (FAB $^+$) m/z (relative intensity): 315 (M + 1, 45), 257 (10), 187 (12), 144 (42), 130 (28), 84 (58), 57 (100). HRMS: calculated for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2$ (M + 1) m/z 315.2073, found 315.2074. (^1H NMR: Figure A-26 page 167; ^{13}C NMR: Figure A-27 page 168; HETCORR: Figure A-28, page 169)

N_b -Chloro-3-(2-Cyclobutylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester

[128]: Into a 125-mL Erlenmeyer flask was placed 20 mL CH_2Cl_2 , **125a** (200 mg,

0.57 mmol), and N-chlorosuccinimide (84 mg, 0.63 mmol). After swirling for 2 min., the succinimide was removed by washing the organic solution with saturated sodium bicarbonate (3 X 20 mL), followed by drying over anhydrous sodium sulfate, and concentrating *in vacuo* at room temperature. Although the **128** was used without further purification, NMR showed predominantly (>90%) the N-chloramine. ^{13}C NMR: δ 149.8 (carbamate), 135.5, 130.6, 124.4, 123.0, 122.5, 118.9, 118.0, 115.3 (aromatics), 83.5, 65.9, 59.4, 28.3 (2C), 28.3 (3 CH_3), 23.6, 13.5. ^1H NMR: δ 8.12 (d, 1H, $J = 7.9$ Hz), 7.54 (d, 1H, $J = 7.8$ Hz), 7.43 (s, 1H), 7.33-7.18 (m, 2H), 3.53 (pentet, 1H, $J = 7.67$ Hz), 3.07 (s, 4H), 2.2-1.8 (m, 4H), 1.8-1.55 (m, 2H), 1.66 (s, 9H).

Rearrangement of N₁-Chloro-3-(2-Cyclobutylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [128]: The N-chloramine **128** (obtained from 200 mg of **125a**) was taken up in anhydrous CH_2Cl_2 (20 mL) and placed in an addition funnel without further purification. The N-chloramine was then added (10 min) to a 100-mL round-bottomed flask, fitted with a N_2 inlet and a Dean-Stark trap, that had previously been charged with .34 g (3 eq) of silver tetrafluoroborate and 25 mL of anhydrous CH_2Cl_2 which had been heated to remove any residual water. The reaction mixture turned a milky brown color with the formation of a precipitate. TLC of the mixture showed no presence of the N-chloramine. At this point,

gaseous HCl was bubbled into the flask and copious amounts of AgCl was formed. The reaction was allowed to stir at room temperature for 1 hr before filtering through celite. The filtrate was placed in a separatory funnel and washed with a saturated solution of NaHCO₃ (3 X 30 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a light brown foam. Crude NMR revealed the formation of hexahydro-indolo-indolizidine [110a]. Purification by liquid chromatography (Al₂O₃/2%hexane-chloroform) provided 110a, the spirocycle 107a, and the N_b-cyclobutyltryptamine [113a] in 33%, 32%, and 20% yields, respectively.

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APPENDIX

Table A-1: Structure Determination Summary - Crystal Data

Empirical Formula	$C_{14}H_{14}BF_4N$
Color; Habit	COLORLESS PARALLELEPIPED
Crystal Size (mm)	0.2 X 0.15 X 0.8
Crystal System	Orthorhombic
Space Group	Pnma
Unit Cell Dimensions	$a = 11.309 (4) \text{ \AA}$ $b = 22.859 (6) \text{ \AA}$ $c = 5.473 (2) \text{ \AA}$
Volume	$1414.8 (8) \text{ \AA}^3$
Z	4
Formula Weight	283.1
Density (calc.)	1.329 Mg/m^3
Absorption Coefficient	0.108 mm^{-1}
F(000)	584

Table A-2: Structure Determination Summary - Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoK α ($\lambda = 0.71073 \text{ \AA}$)
Temperature	173 K
Monochromator	Highly oriented graphite crystal
2 θ Range	3.5 to 45°
Scan type	ω
Scan Speed	Constant; 3.00°/min. in ω
Scan Range (ω)	0.60°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 97 reflections
Index Ranges	$-12 \leq h \leq 12, -24 \leq k \leq 24, 0 \leq l \leq 5$
Reflections Collected	1889
Independent Reflections	956 ($R_{\text{int}} = 7.50\%$)
Observed Reflections	756 ($F > 4.0\sigma(F)$)
Absorption Correction	N/A

Table A-3: Structure Determination Summary - Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Absolute Structure	N/A
Extinction Correction	$\chi = 0.0005$ (6), where $F^* = F[1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding Model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0012F^2$
Number of Parameters Refined	98
Final R indices (obs. data)	R = 6.30 %, wR = 8.28 %
R indices (all data)	R = 8.02 %, wR = 8.92 %
Goodness-of-Fit	1.80
Largest and Mean Δ/σ	0.001, 0.000
Data-to-Parameter Ratio	7.7:1
Largest Difference Peak	0.70 eÅ ⁻³
Largest Difference Hole	-0.33 eÅ ⁻³

Table A-4: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement*

coefficients ($\text{\AA}^2 \times 10^3$)

	x	y	z	U(eq)
F(1)	9181(3)	2500	-2294(6)	39(1)
F(2)	10531(3)	2500	706(6)	43(1)
F(3)	10889(3)	2016(2)	-2776(6)	85(1)
B	10397(6)	2500	-1827(12)	33(2)
N	12698(4)	2500	3171(8)	27(1)
C(1)	13079(3)	3052(2)	1892(7)	31(1)
C(3)	13299(4)	3796(2)	5250(8)	38(1)
C(2)	12657(3)	3578(2)	3289(7)	28(1)
C(7)	11586(4)	3840(2)	2704(8)	39(1)
C(6)	11175(4)	4308(2)	4095(10)	52(2)
C(4)	12875(5)	4259(2)	6610(8)	50(2)
C(5)	11806(5)	4513(2)	6034(9)	53(2)

*Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table A-5: Bond lengths ($\text{\AA}$)

F(1) - B	1.398 (7)	F(2) - B	1.395 (7)
F3 - B	1.344 (5)	B - F(3A)	1.344 (5)
N - C(1)	1.506 (4)	N - C(1A)	1.506 (4)
C(1) - C(2)	1.503 (5)	C(3) - C(2)	1.388 (6)
C(3) - C(4)	1.380 (6)	C(2) - C(7)	1.388 (5)
C(7) - C(6)	1.393 (6)	C(6) - C(5)	1.362 (7)
C(4) - C(5)	1.377 (7)		

Table A-6: Bond angles (°)

F(1)-B-F(2)	106.8 (5)	F(1)-B-F(3)	109.7 (3)
F(2)-B-F(3)	109.8 (3)	F(1)-B-F(3A)	109.7 (3)
F(2)-B-F(3A)	109.8 (3)	F(3)-B-F(3A)	111.0 (5)
C(1)-N-C(1A)	113.8 (4)	N-C(1)-C(2)	110.1 (3)
C(2)-C(3)-C(4)	120.7 (4)	C(1)-C(2)-C(3)	121.0 (3)
C(1)-C(2)-C(7)	120.3 (3)	C(3)-C(2)-C(7)	118.6 (3)
C(2)-C(7)-C(6)	119.8 (4)	C(7)-C(6)-C(5)	121.0 (4)
C(3)-C(4)-C(5)	120.3 (4)	C(6)-C(5)-C(4)	119.6 (4)

Table A-7: Anisotropic displacement coefficients ($\text{\AA}^2 \times 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(1)	27(2)	58(2)	33(2)	0	-5(1)	0
F(2)	25(2)	70(2)	35(2)	0	-4(2)	0
F(3)	70(2)	105(2)	78(2)	46(2)	0(2)	-40(2)
B	24(3)	45(4)	30(4)	0	4(3)	0
N	31(3)	19(2)	31(3)	0	1(2)	0
C(1)	27(2)	29(2)	37(2)	-2(2)	8(2)	4(2)
C(3)	42(2)	30(2)	40(3)	-1(2)	-2(2)	-1(2)
C(2)	30(2)	21(2)	32(2)	-4(2)	5(2)	4(2)
C(7)	38(2)	31(2)	48(3)	4(2)	-1(2)	2(2)
C(6)	47(3)	37(2)	71(3)	12(2)	5(3)	2(3)
C(4)	72(3)	34(2)	44(3)	-6(2)	-1(2)	-6(2)
C(5)	71(3)	33(3)	56(3)	12(2)	11(3)	-3(2)

The anisotropic displacement exponent takes the form:

$$-2\pi^2(h^2a^{*2}U_{11} + \dots + 2hka^*b^*U_{12})$$

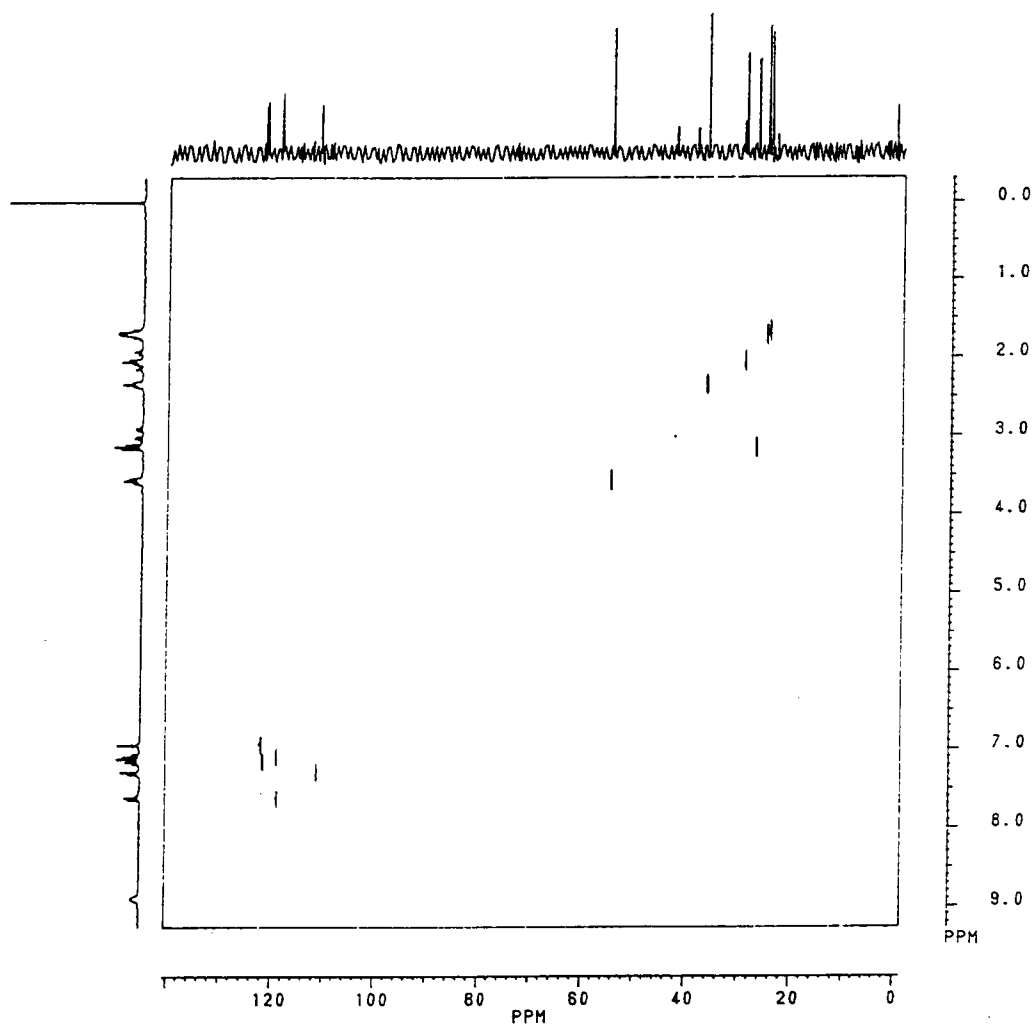


Figure A-1: 2-Dimensional HETCOR spectrum of Cyclopentylidene-[2-(1H-indol-3-yl)-ethyl]amine [112b]

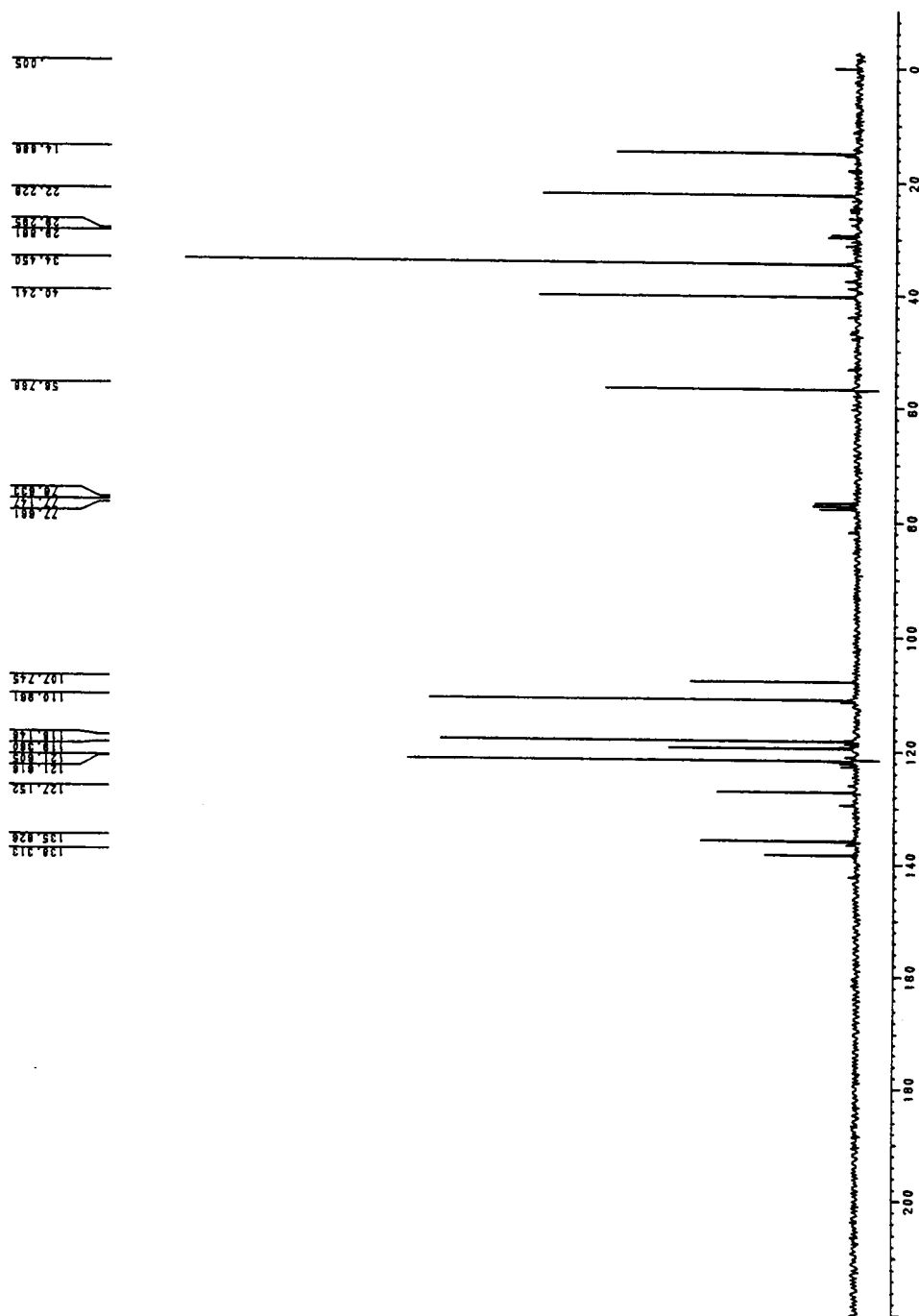


Figure A-3: ^{13}C NMR spectrum of 1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1'-spiro-1'-cyclobutane [107a]

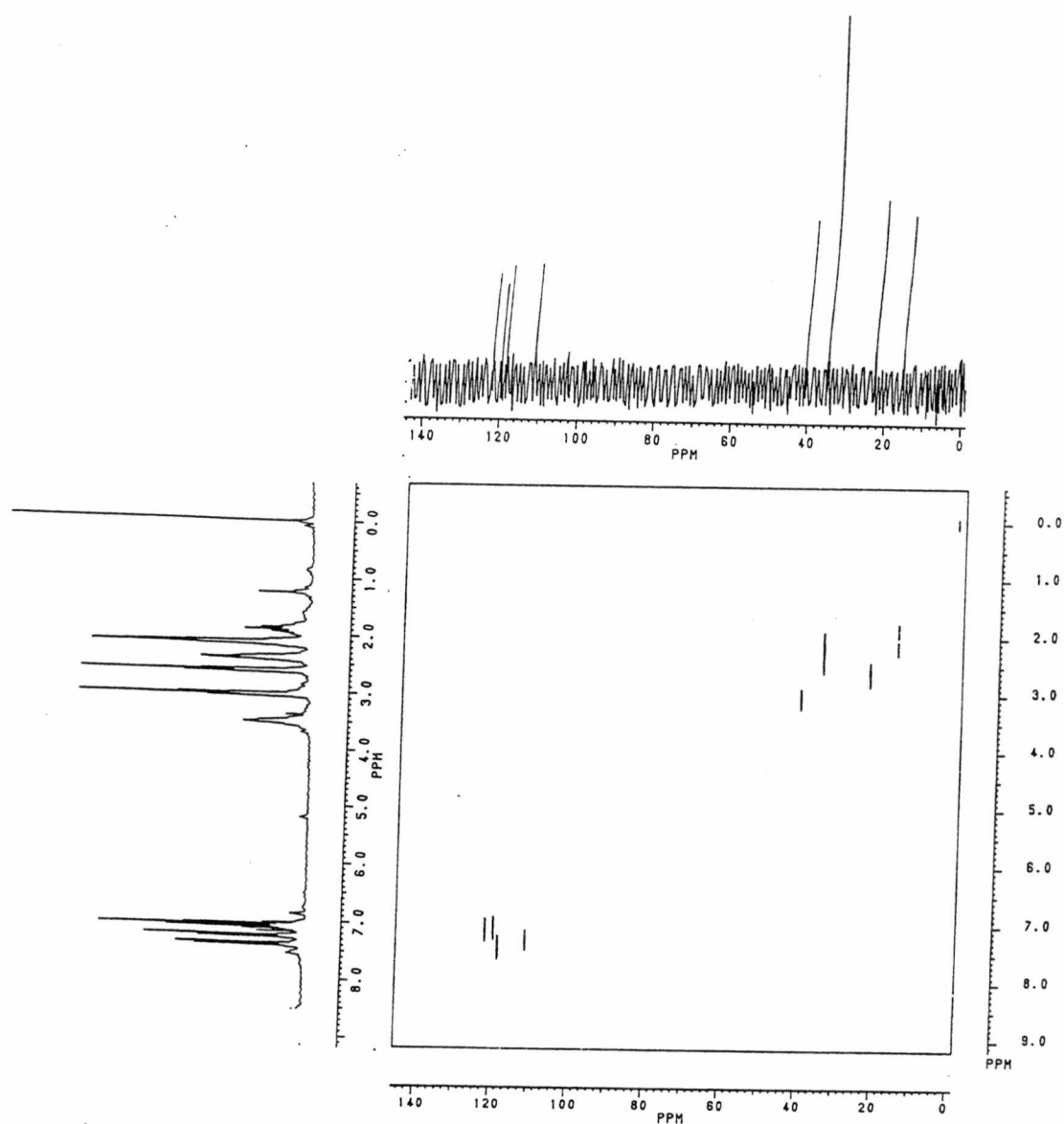


Figure A-4: 2-Dimensional HETCOR spectrum of 1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1-spiro-1'-cyclobutane [107a]

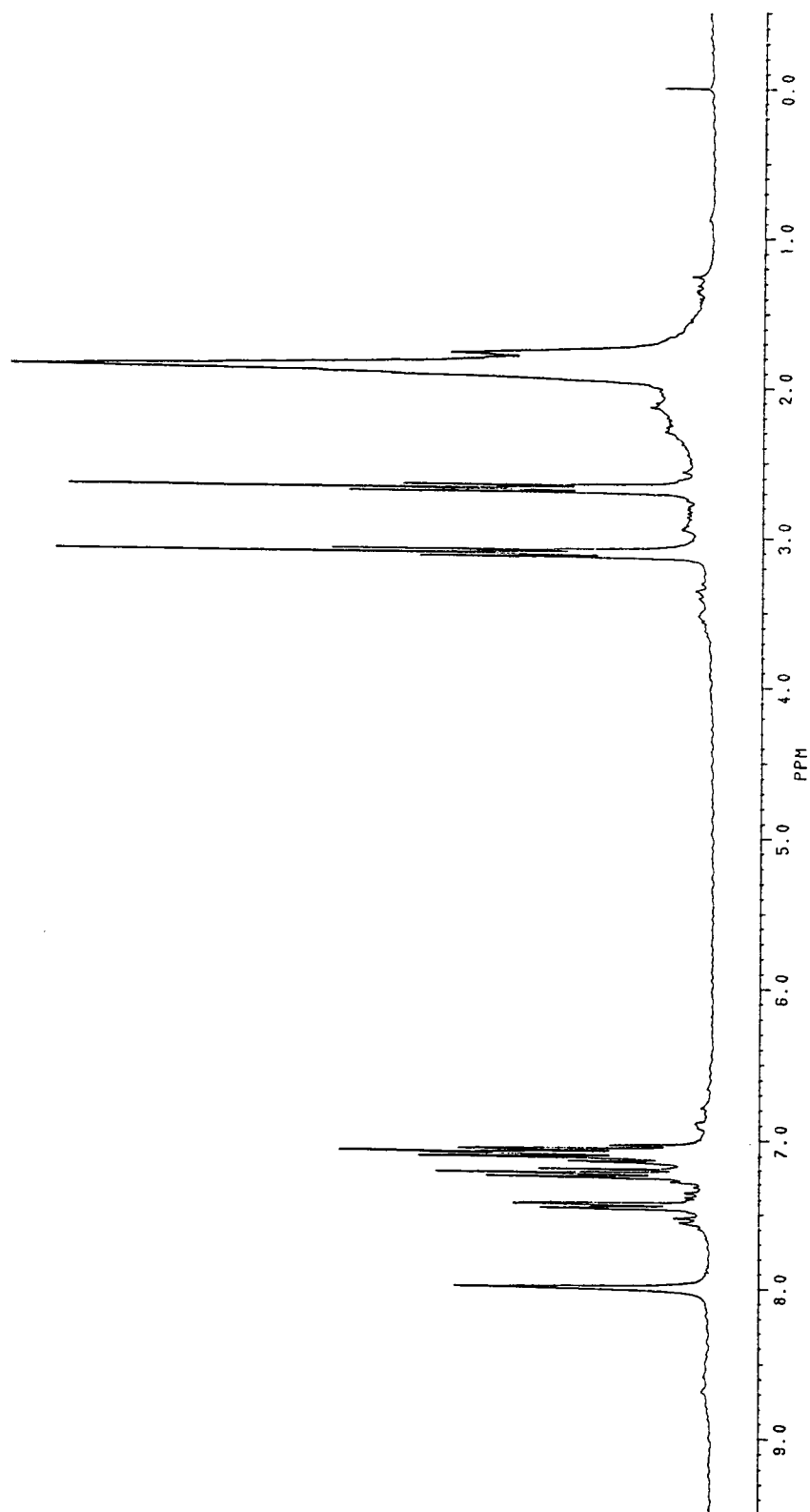


Figure A-5: ^1H NMR spectrum of 1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1'-spiro-1'-cyclopentane [107b]

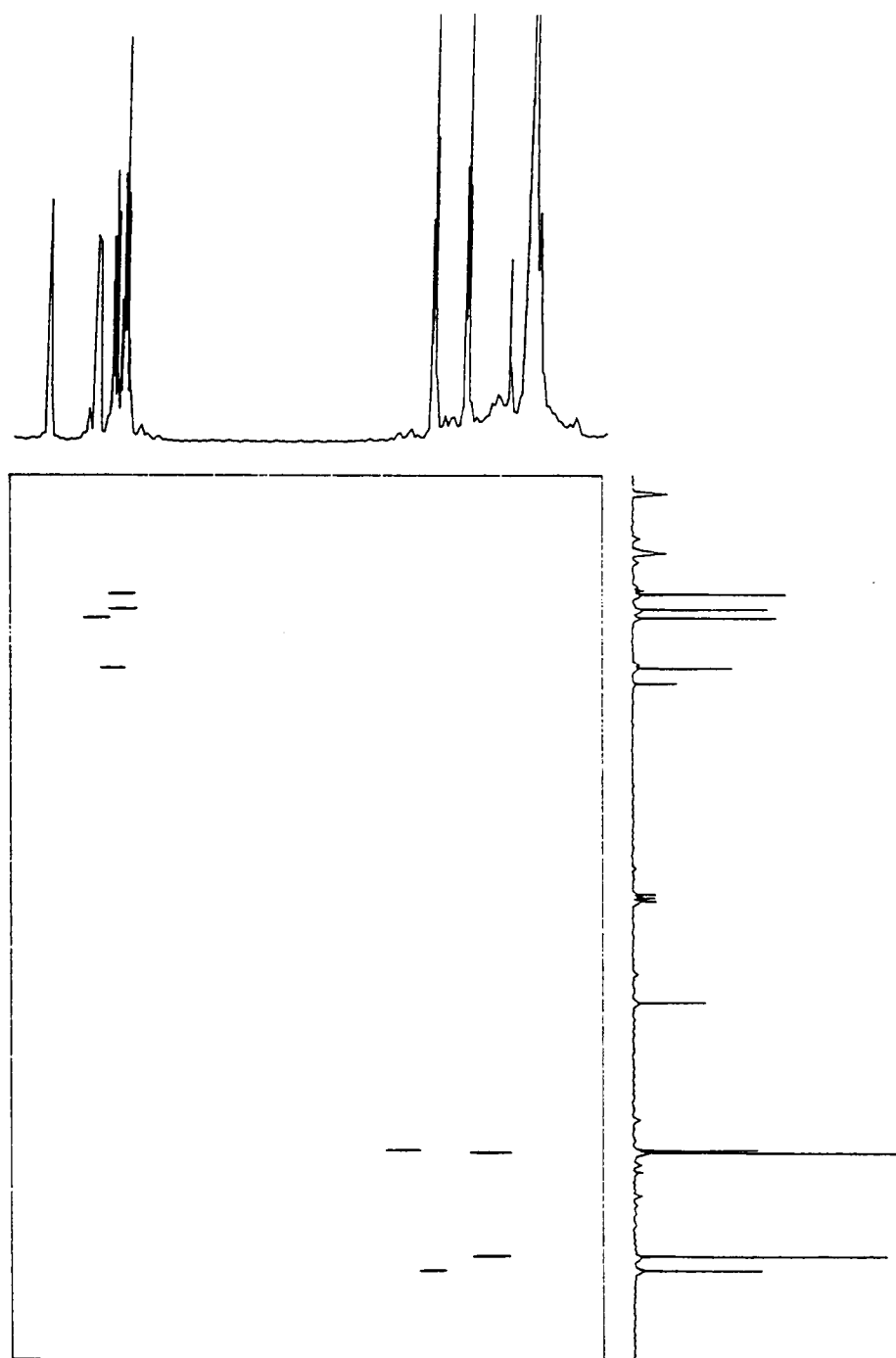


Figure A-6: 2-Dimensional HETCORR spectrum of 1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1-spiro-1'-cyclopentane **[107b]**

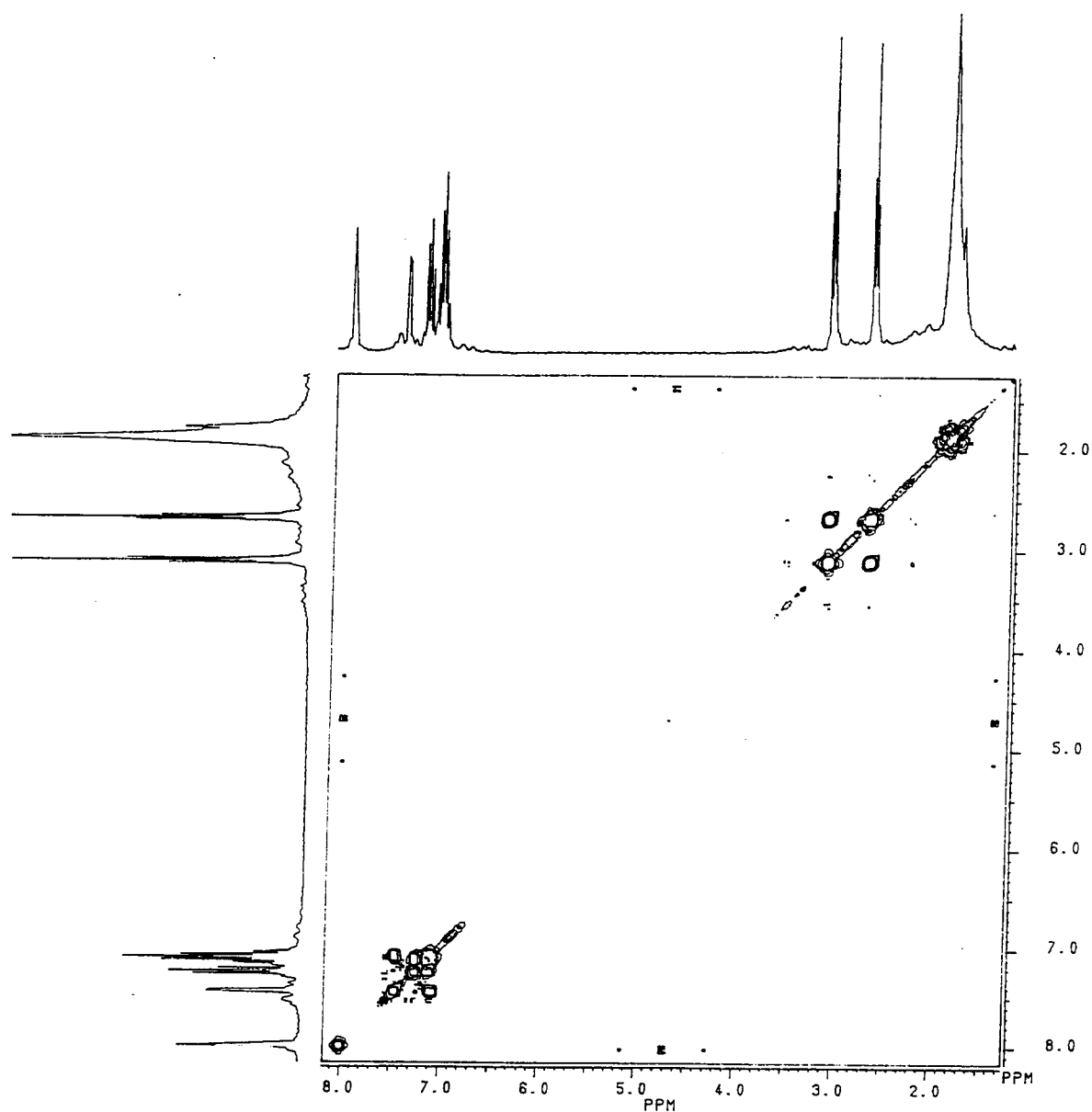


Figure A-7: 2-Dimensional COSY spectrum of 1,2,3,4-tetrahydro-(9H)-pyrido[3,4-b]-indole-1-spiro-1'-cyclopentane [**107b**]

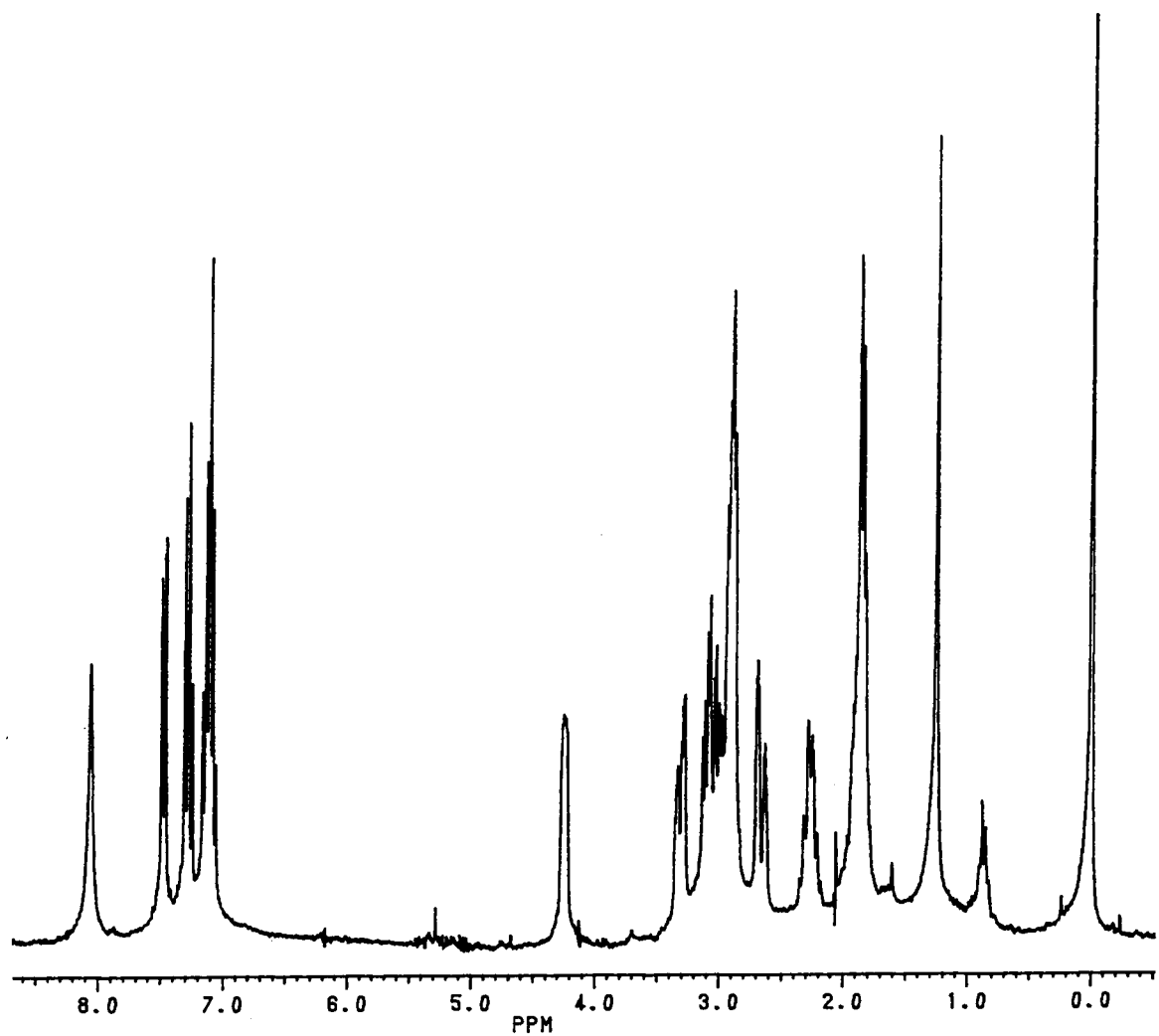


Figure A-8: ^1H NMR spectrum of 2,3,5,6,11,11b-Hexahydro-1H-indolizino[8,7-b]indole [110a]

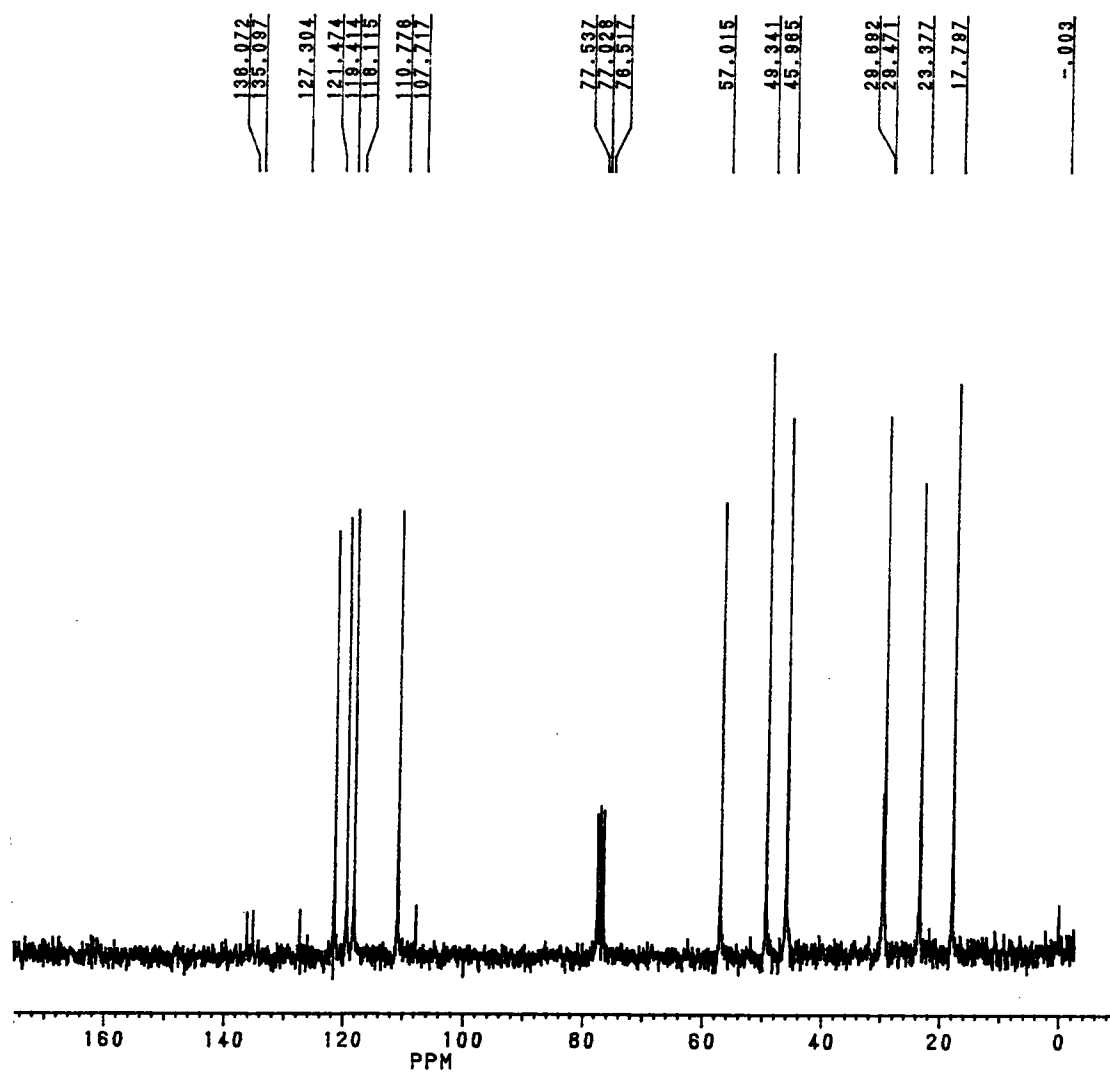


Figure A-9: ^{13}C NMR spectrum of 2,3,5,6,11,11b-Hexahydro-1H-indolizino[8,7-b]indole [110a]

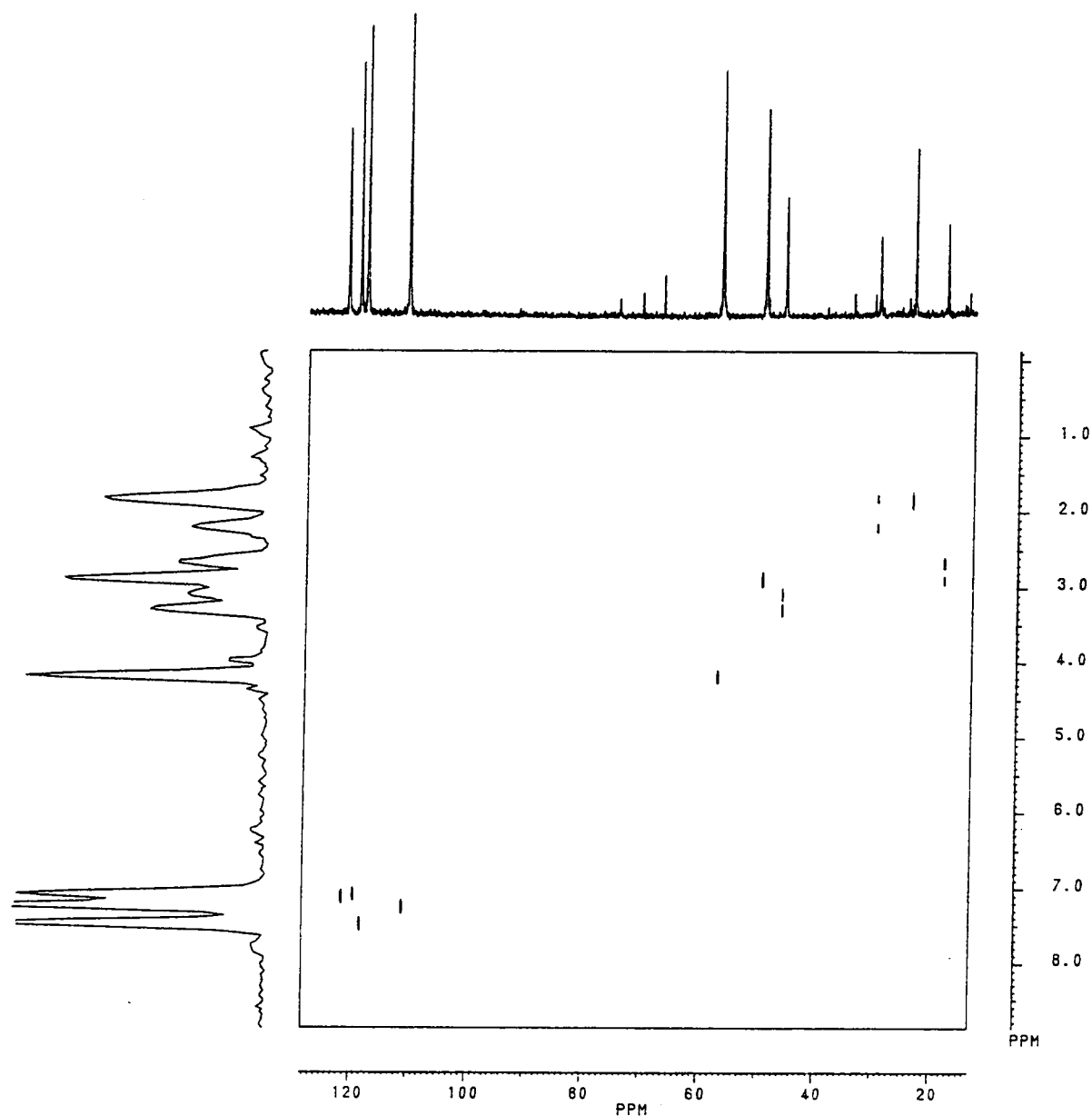


Figure A-10: 2-Dimensional HETCORR spectrum of 2,3,5,6,11,11b-Hexahydro-1H-indolizino[8,7-b]indole [110a]

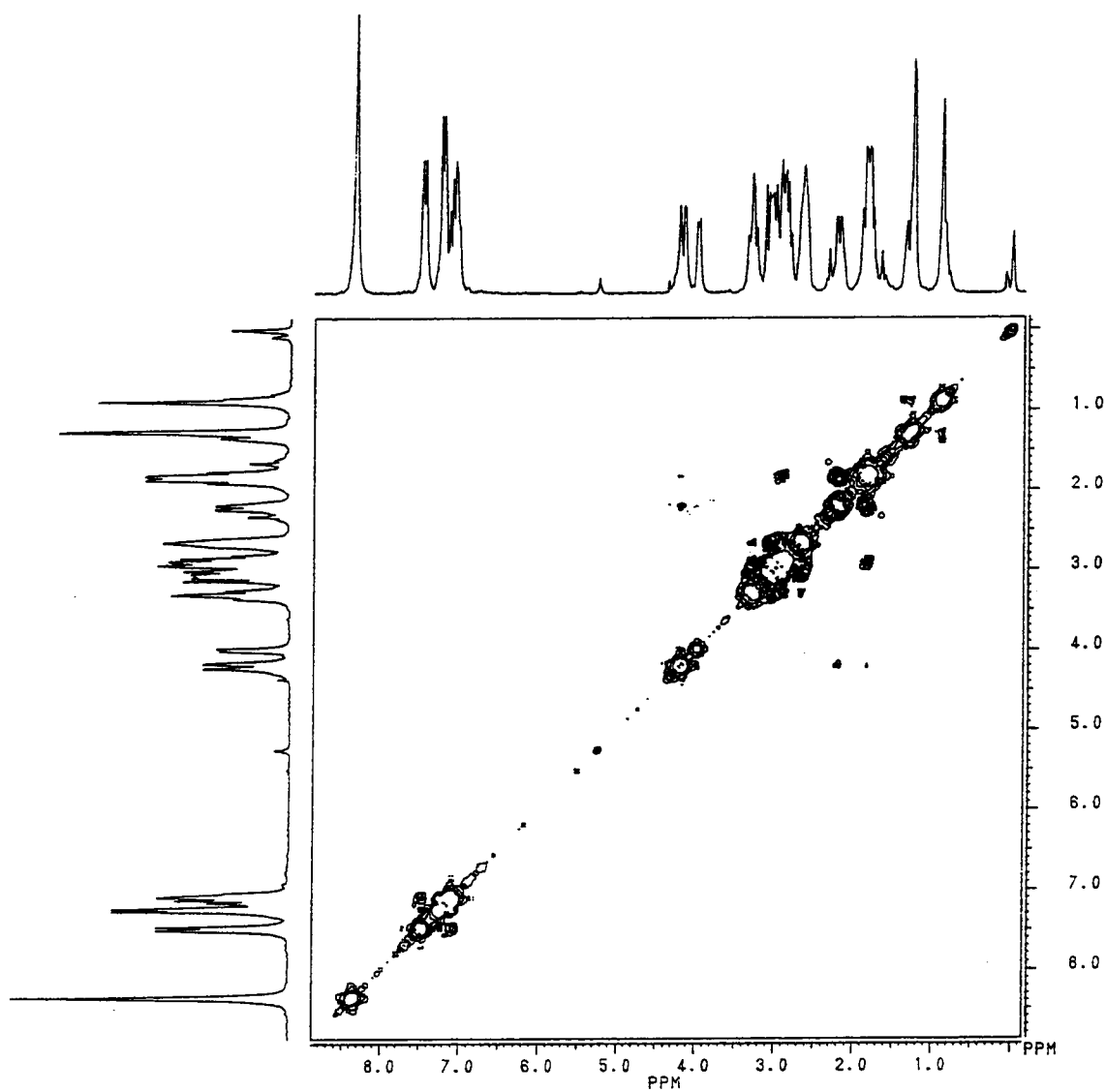


Figure A-11: 2-Dimensional COSY spectrum of 2,3,5,6,11,11b-Hexahydro-1H-indolizino[8,7-b]indole [110a]



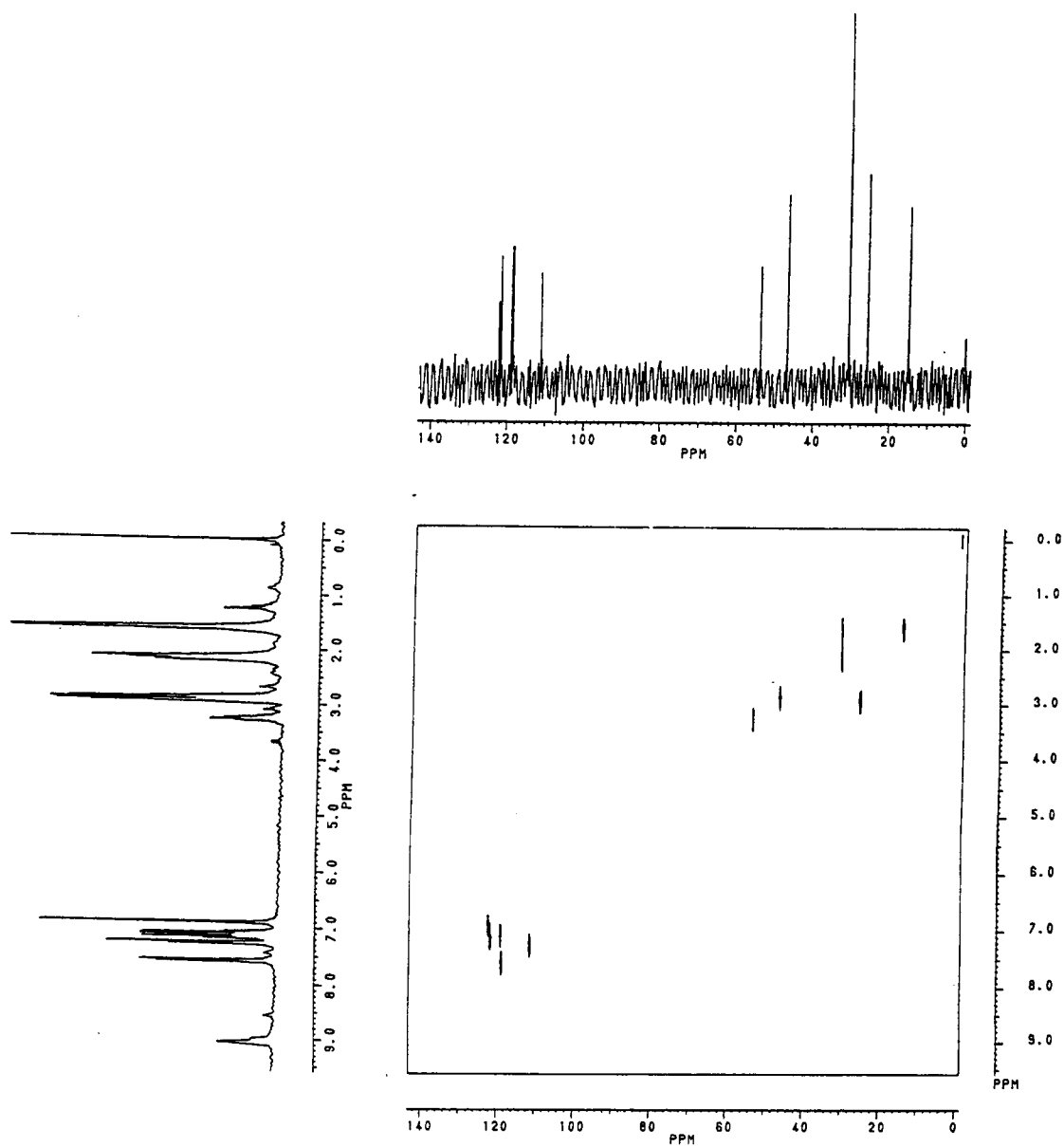


Figure A-13: 2-Dimensional HETCORR spectrum of Cyclobutyl-[2-(1H-indol-3-yl)-ethyl]-amine [113a]

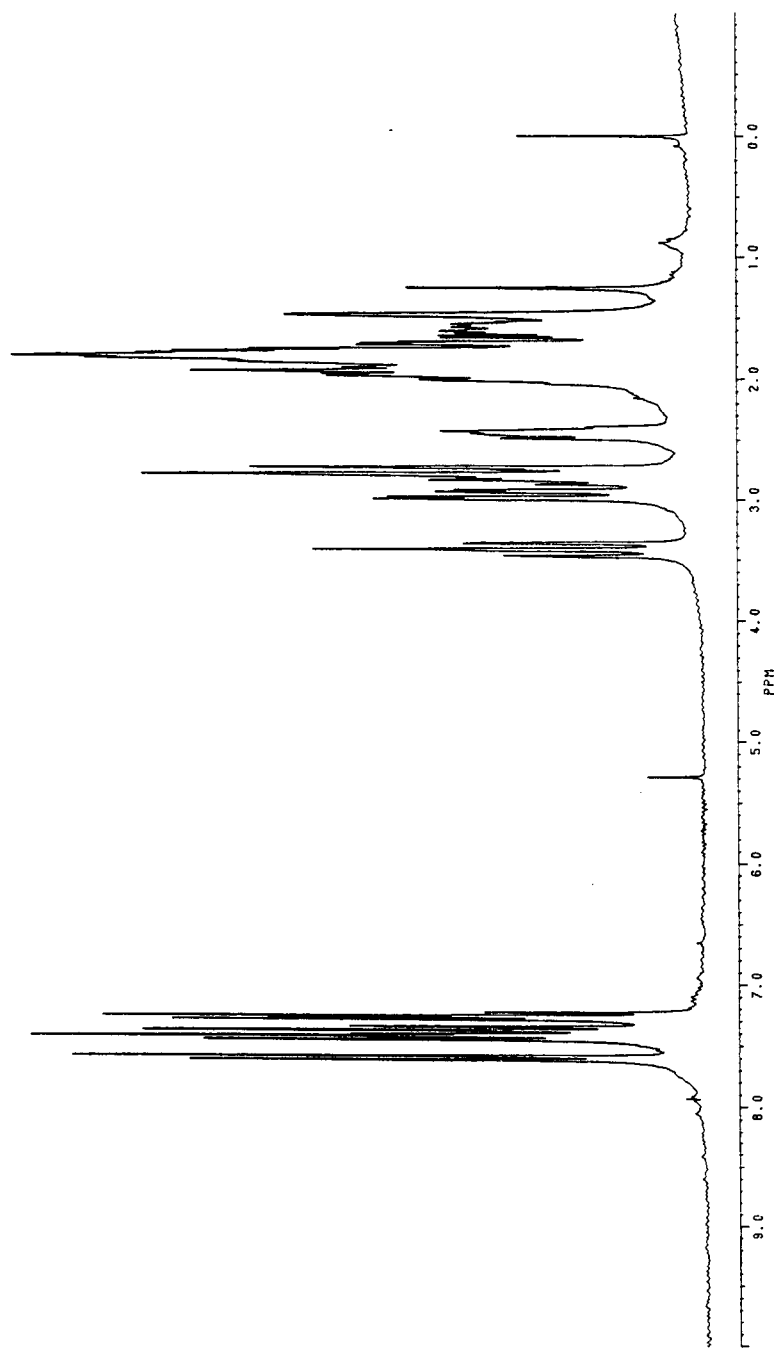


Figure A-14: ¹H NMR spectrum of 4a-Chloro-2,3,4,4a-tetrahydro-β-carboline-1-spiro-1'-cyclopentane [114b]

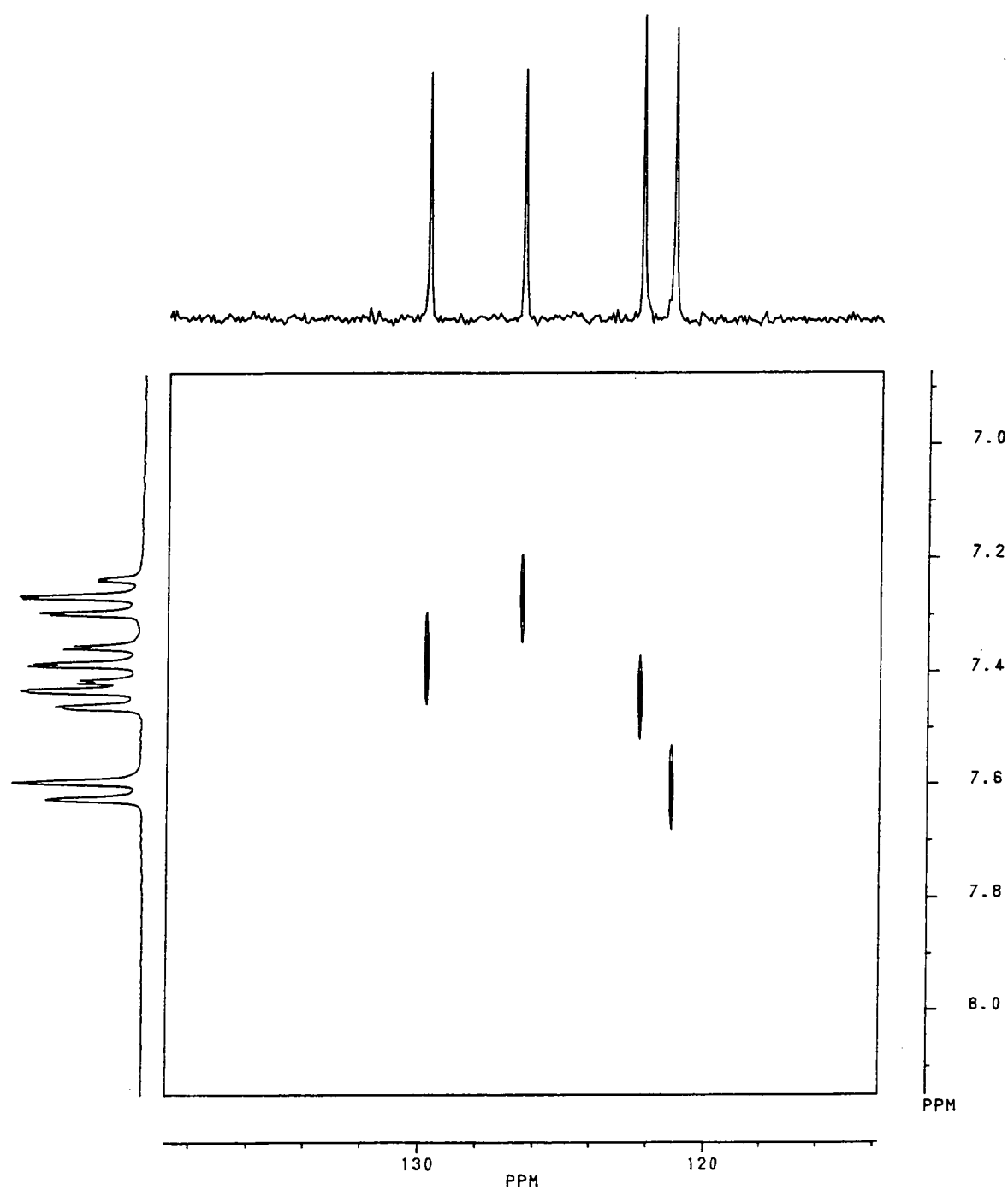


Figure A-15: 2-Dimensional HETCORR spectrum (8.2-6.9 ppm vs. 138-114 ppm) of 4a-Chloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [114b]

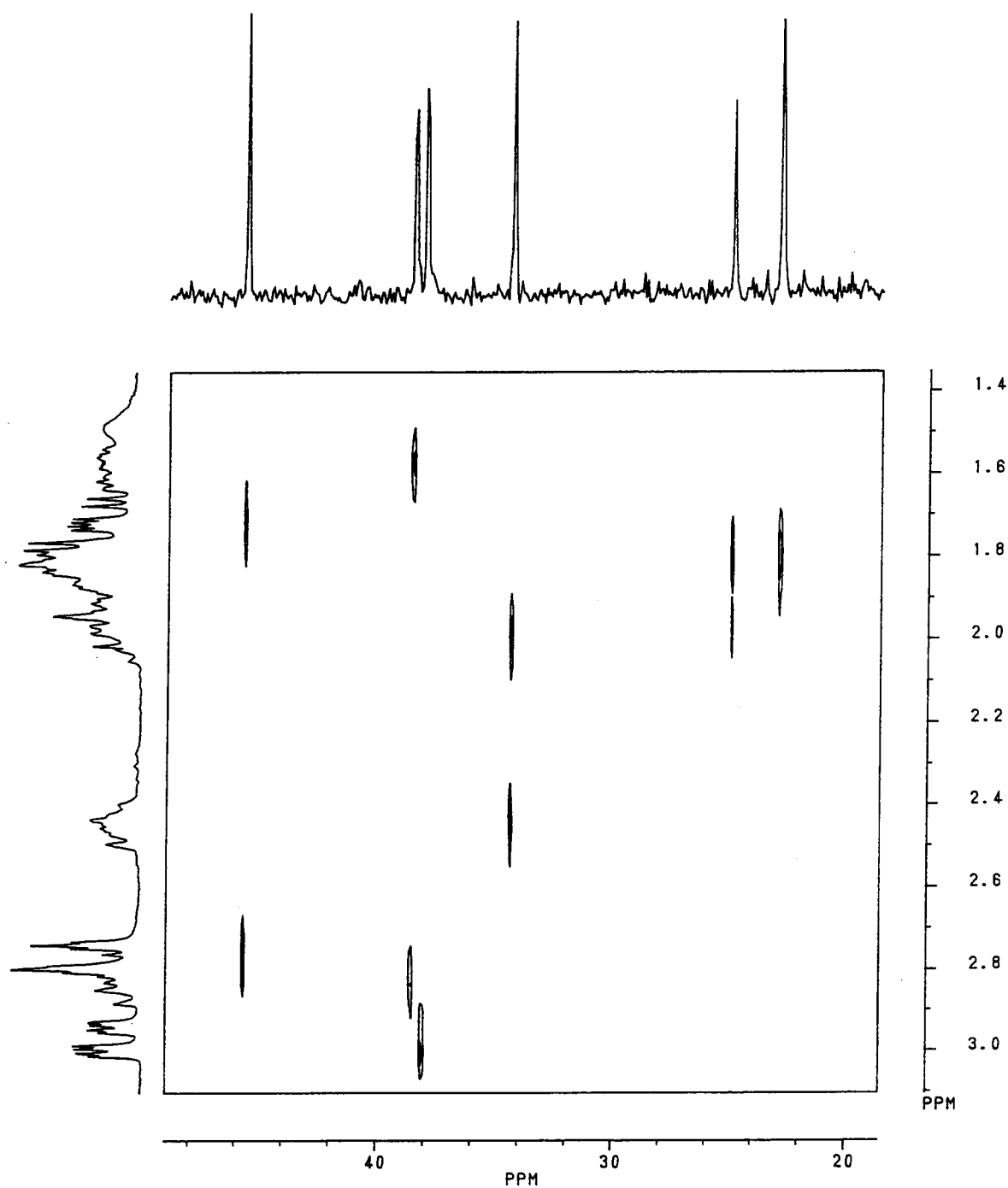


Figure A-16: 2-Dimensional HETCORR spectrum (3.0-1.4 ppm vs. 48-20 ppm) of 4a-Chloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [**114b**]

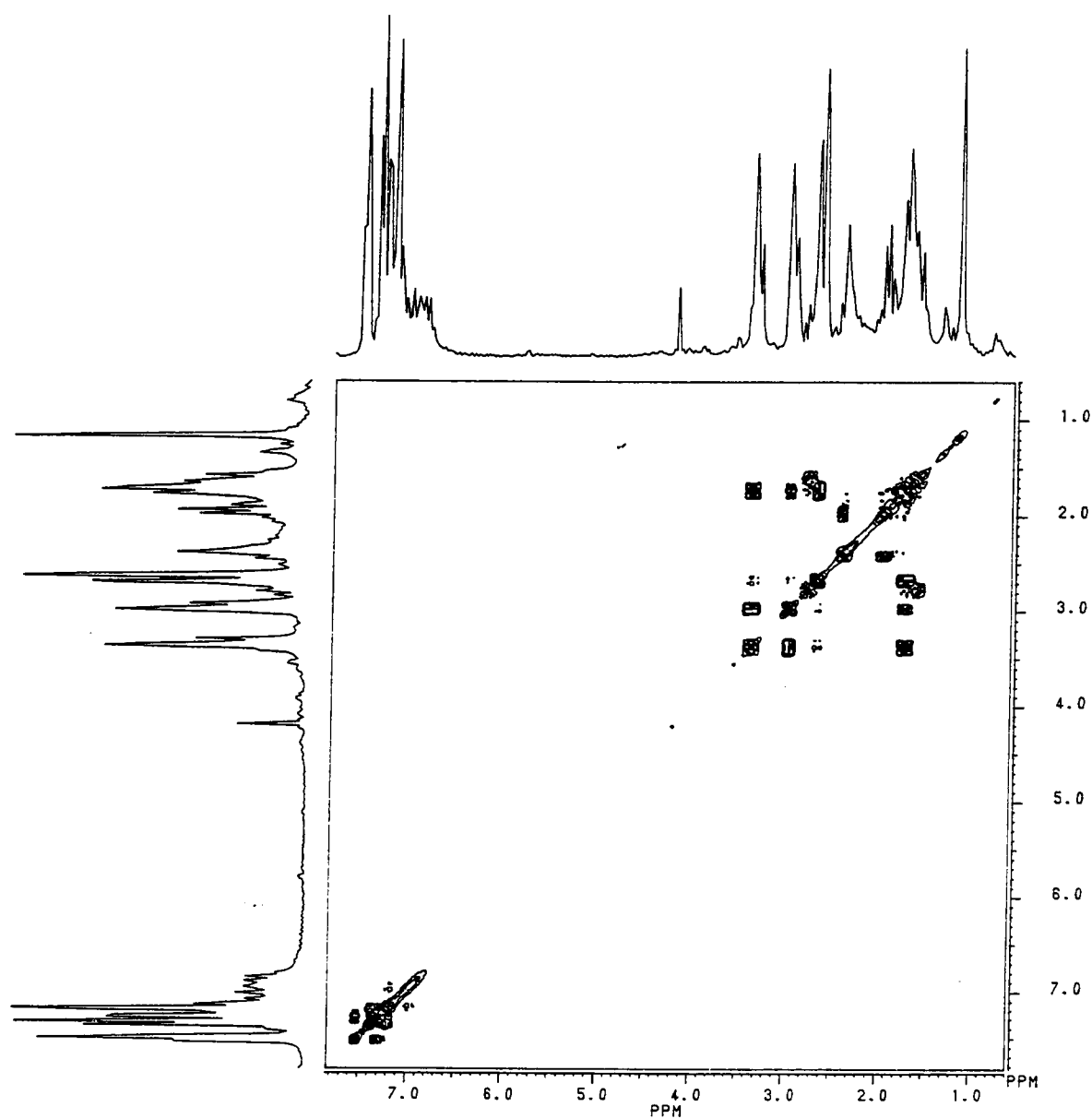


Figure A-17: 2-Dimensional COSY spectrum of 4a-Chloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [114b]

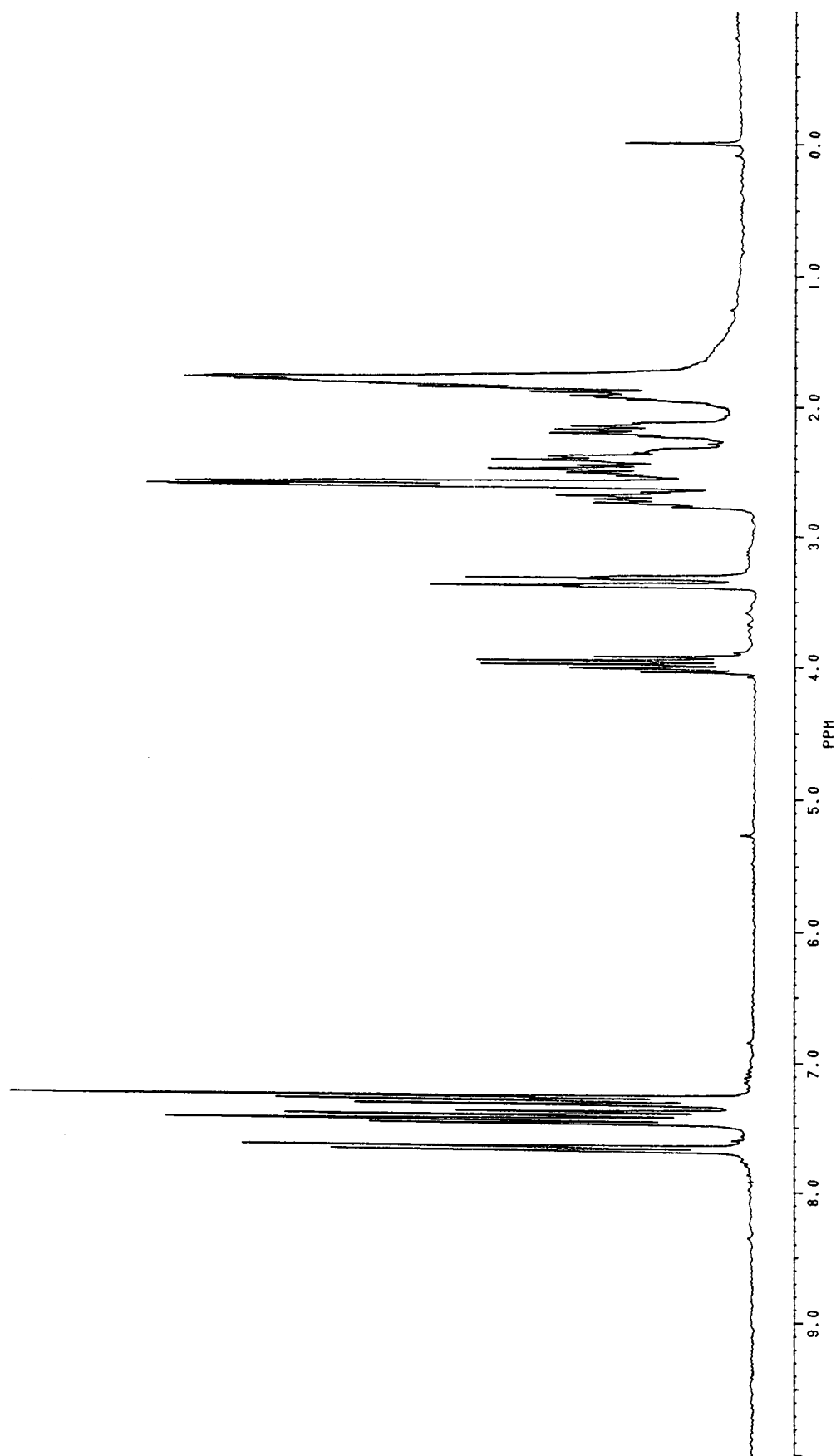


Figure A-18: ^1H NMR spectrum of 2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [115b]

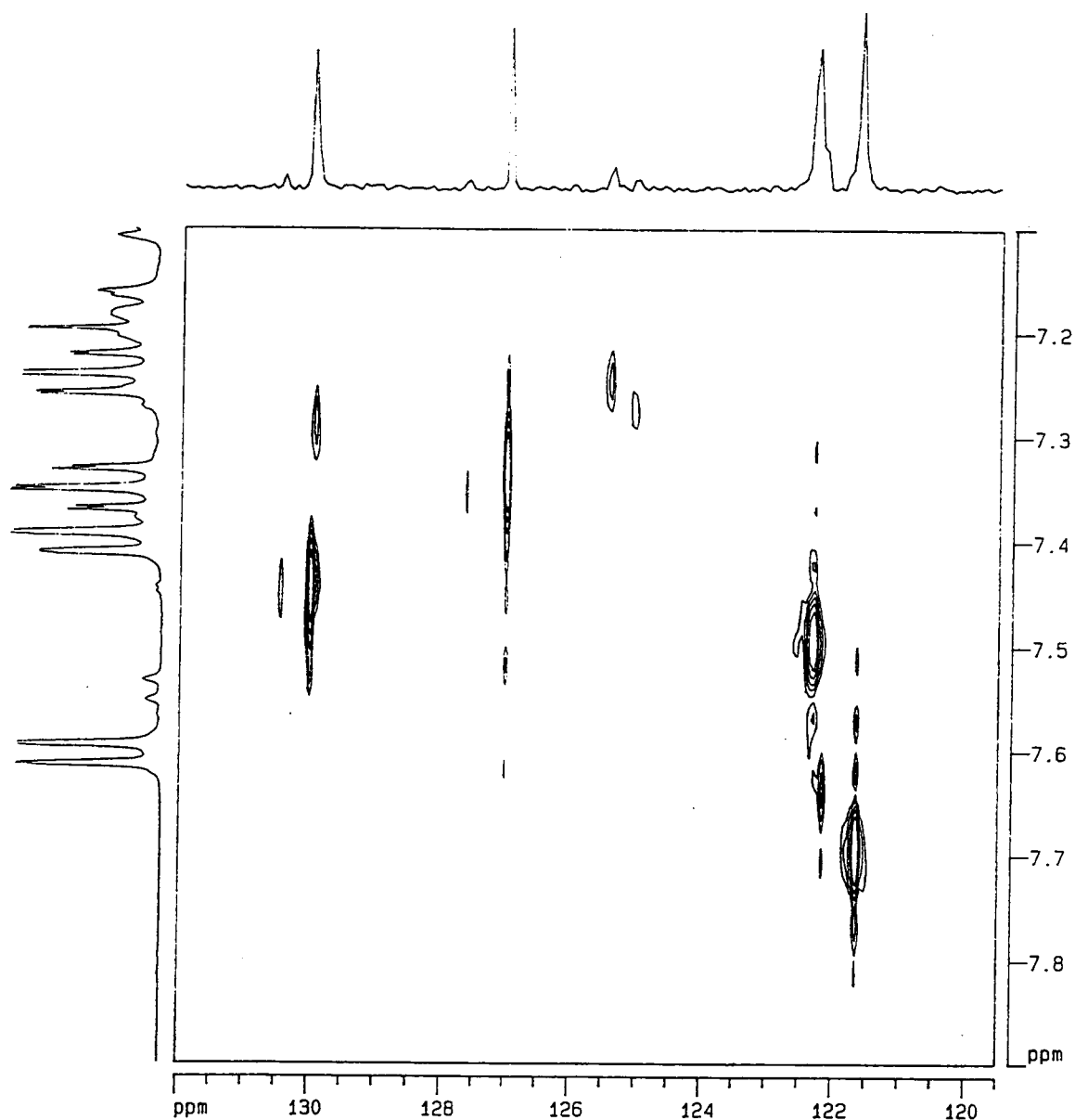


Figure A-19: 2-Dimensional HETCORR spectrum (8-7 ppm vs. 132-120 ppm) of 2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [**115b**]

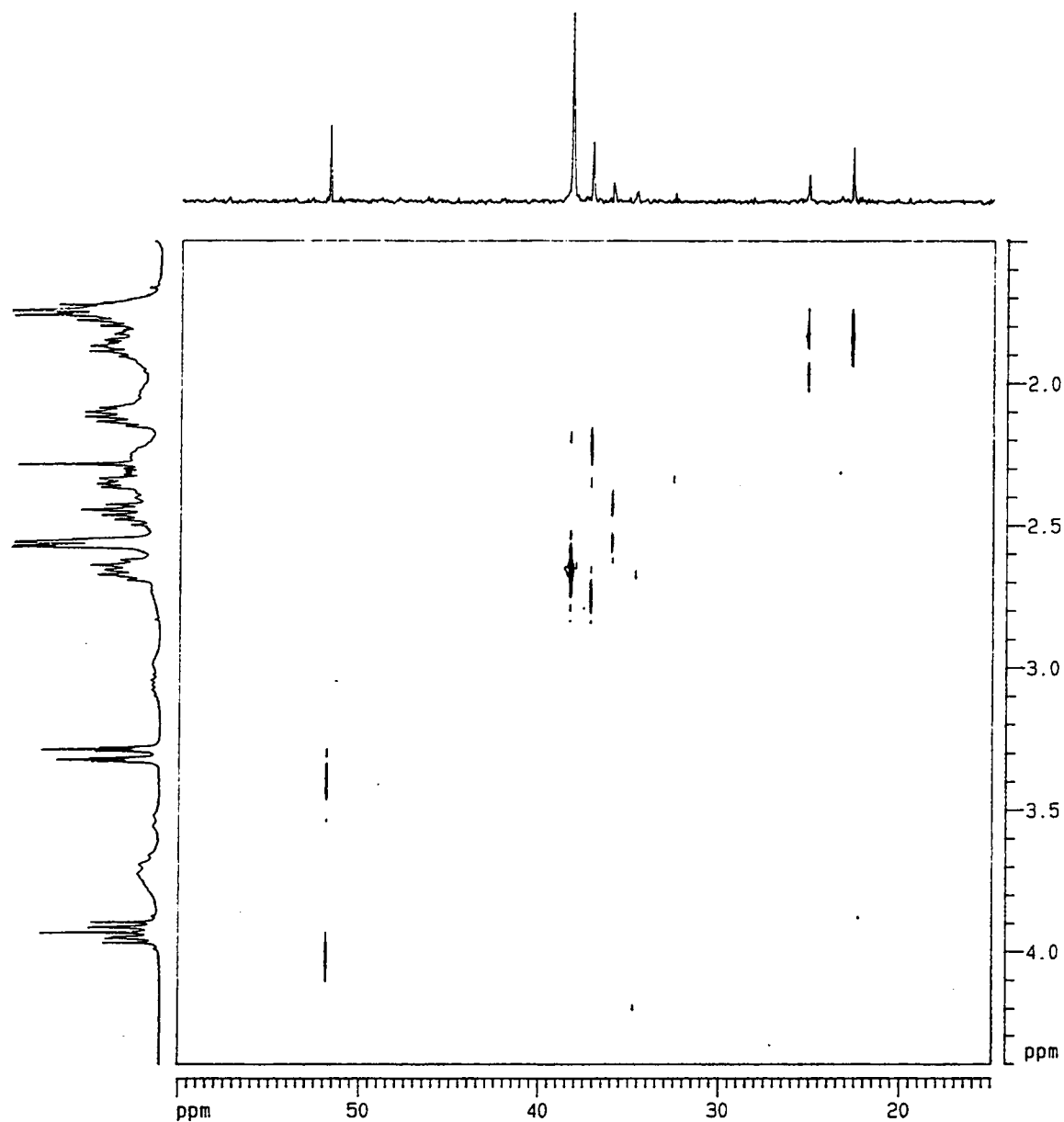


Figure A-20: 2-Dimensional HETCORR spectrum (4.4-1.5 ppm vs. 60-10 ppm) of 2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [**115b**]

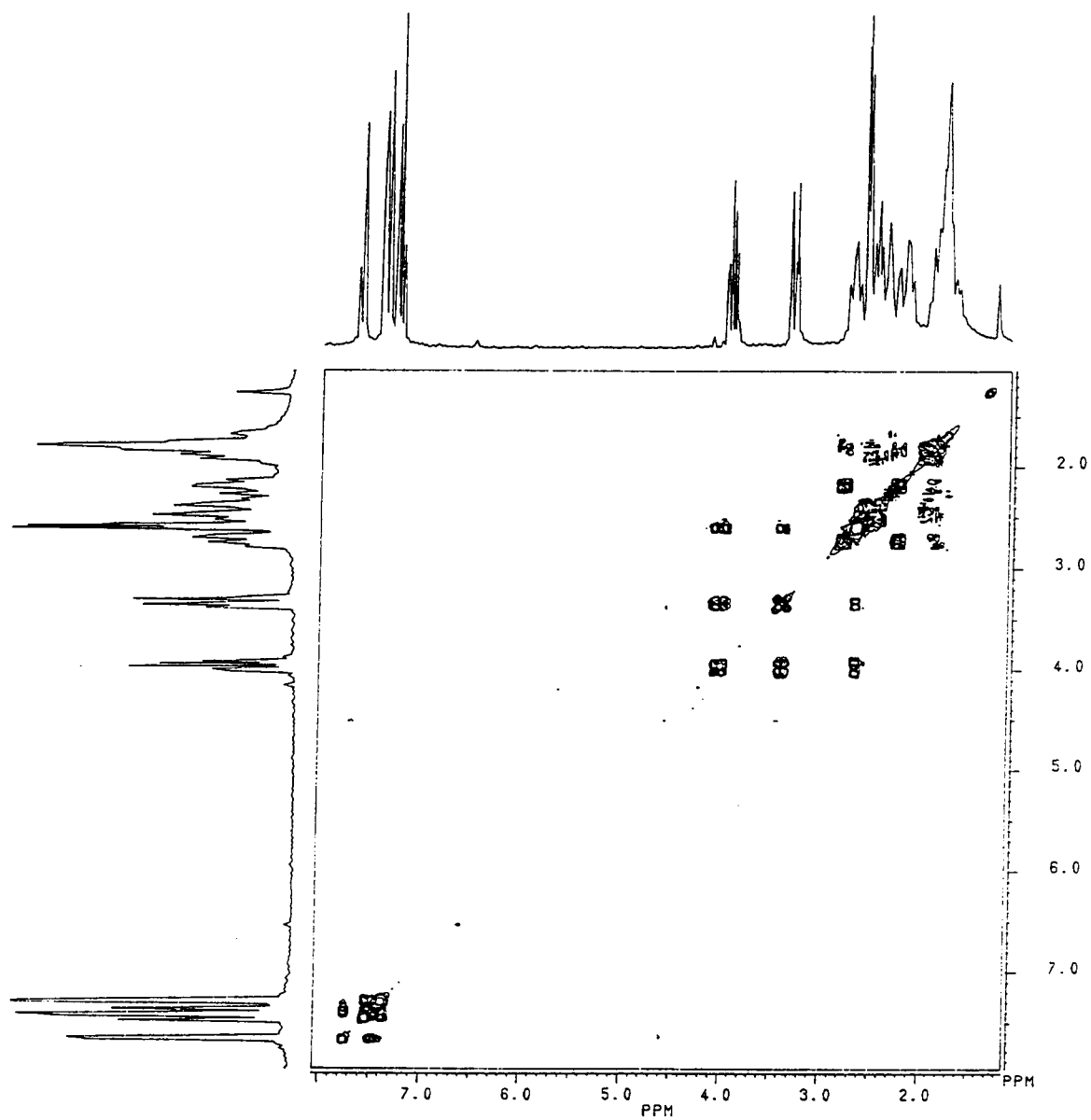


Figure A-21: 2-Dimensional COSY spectrum of 2,4a-Dichloro-2,3,4,4a-tetrahydro- β -carboline-1-spiro-1'-cyclopentane [115b]

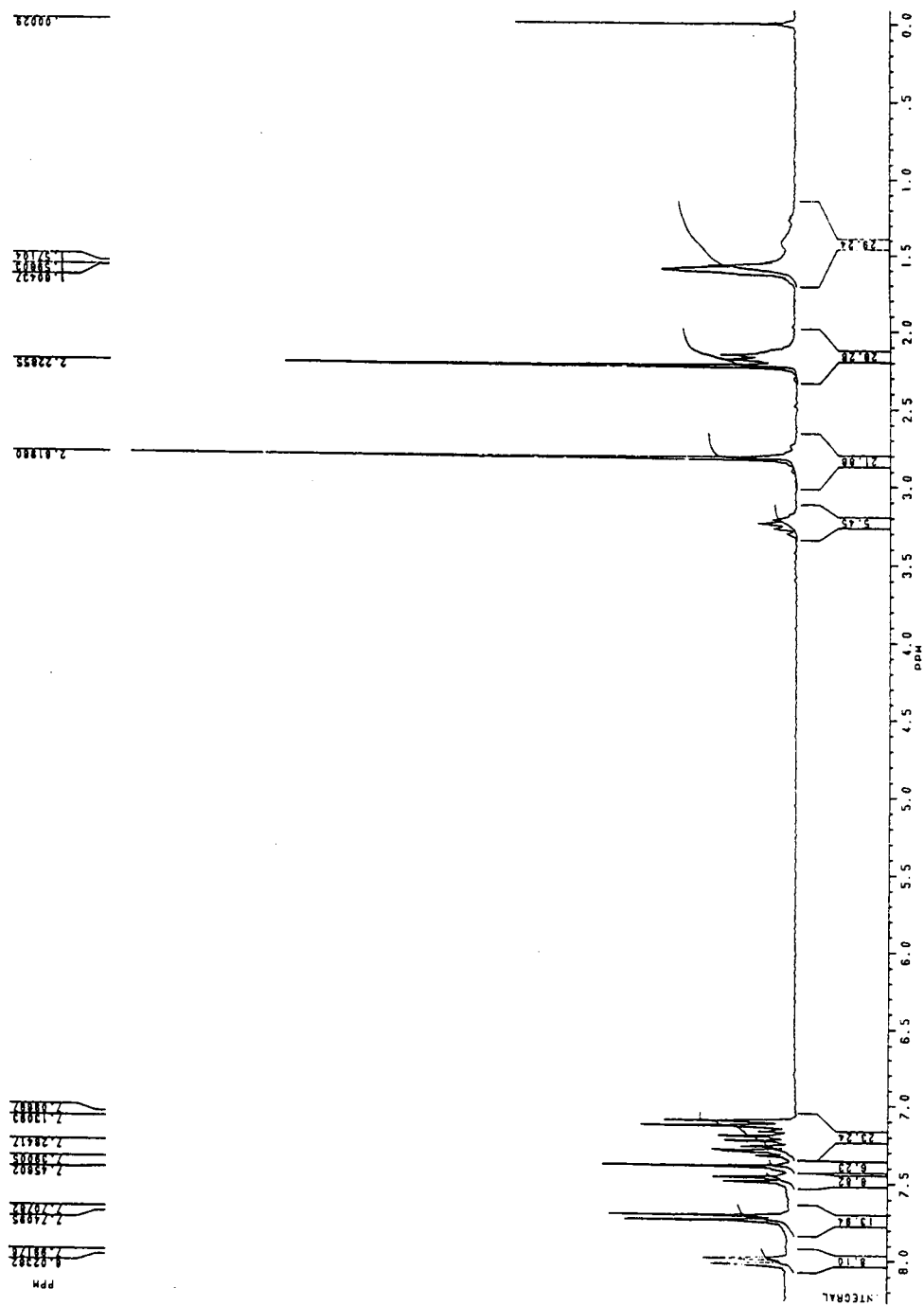


Figure A-22: ^1H NMR spectrum of Cyclobutyl-(2-[1-Toluene-4-sulfonyl]-1H-indol-3-yl)-ethyl-amine [123]

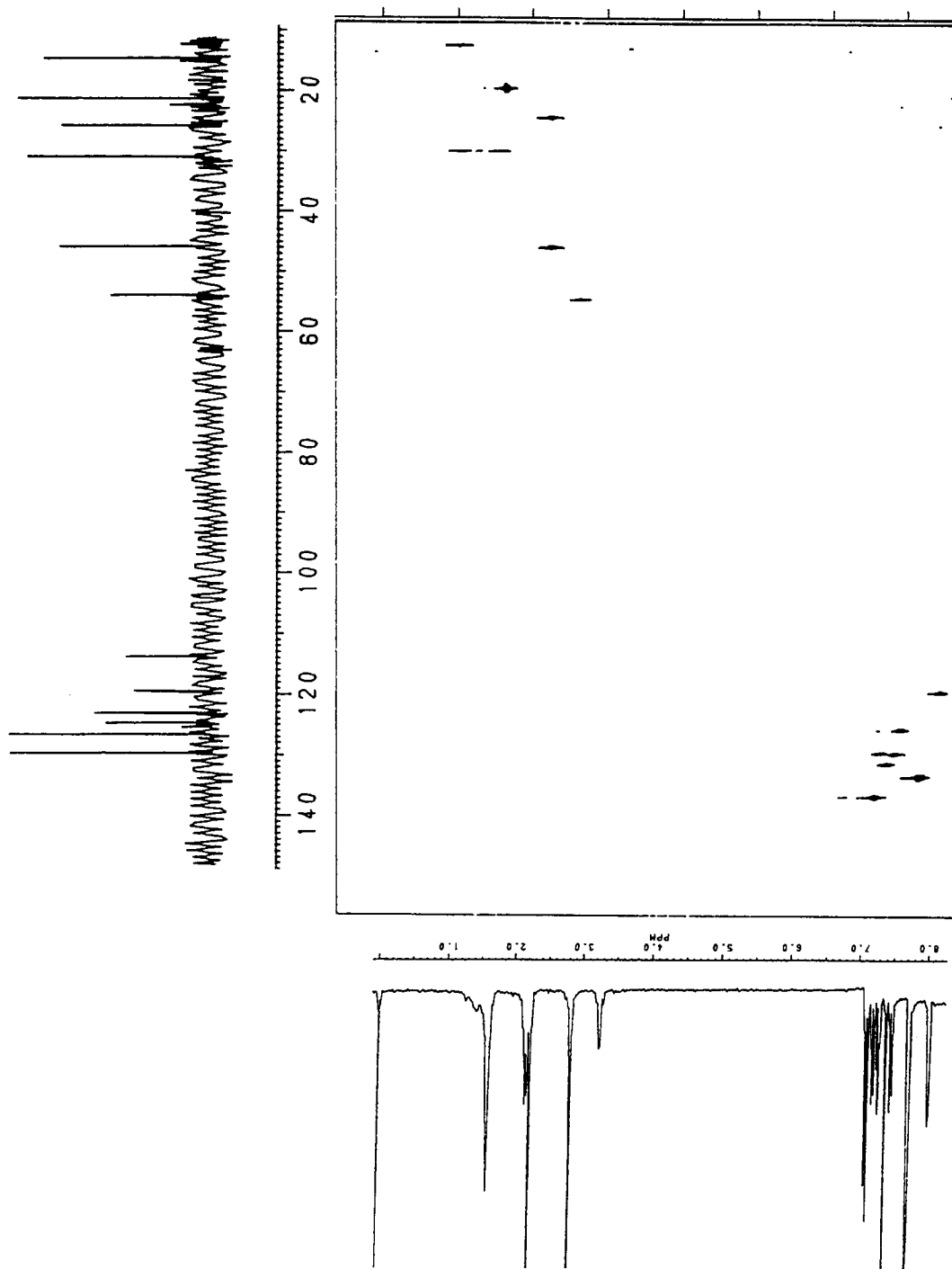


Figure A-23: 2-Dimensional HETCOR spectrum of Cyclobutyl-{2-[1-Toluene-4-sulfonyl)-1H-indol-3-yl]-ethyl}-amine [123]

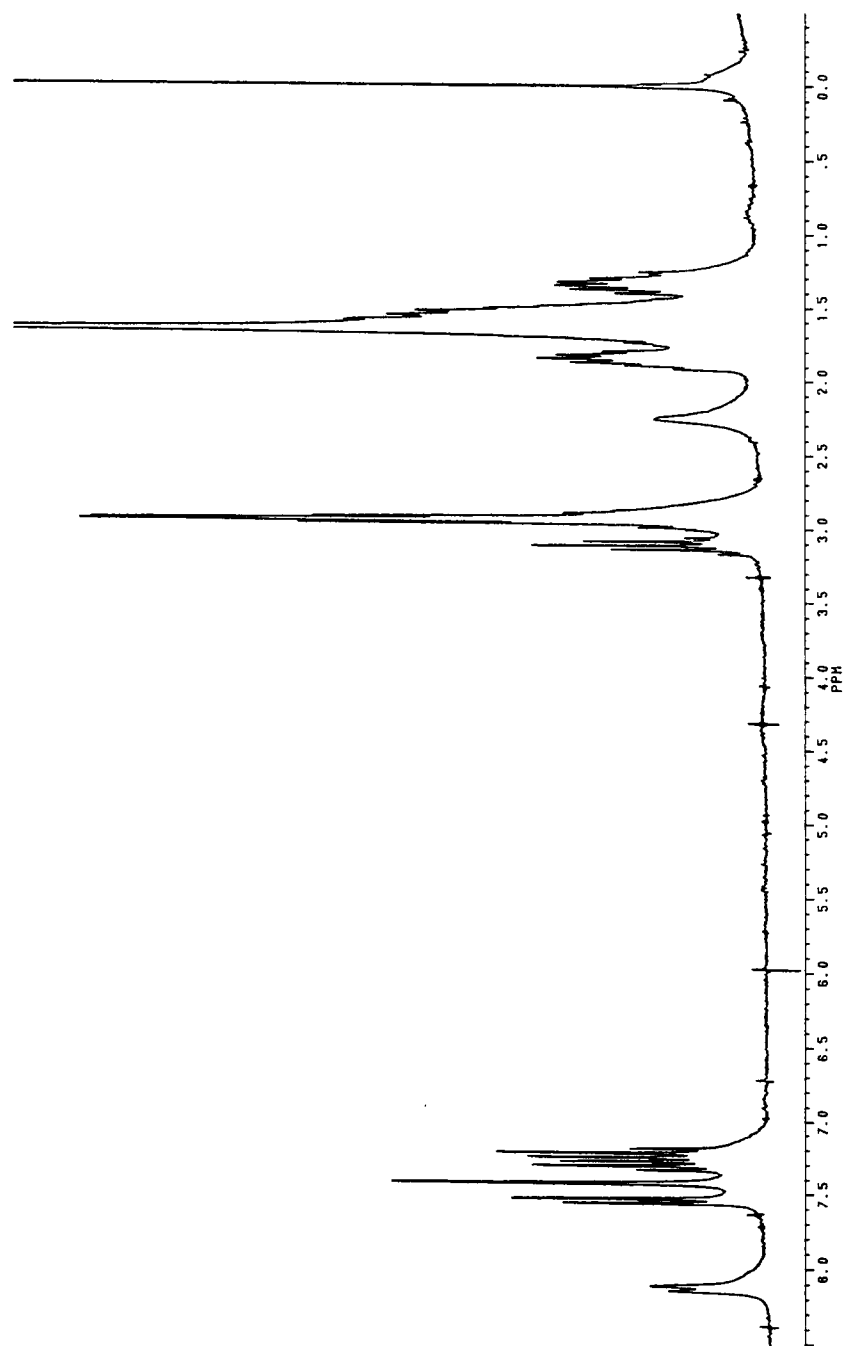


Figure A-24: ^1H NMR spectrum of 3-(2-Cyclopentylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [125b]

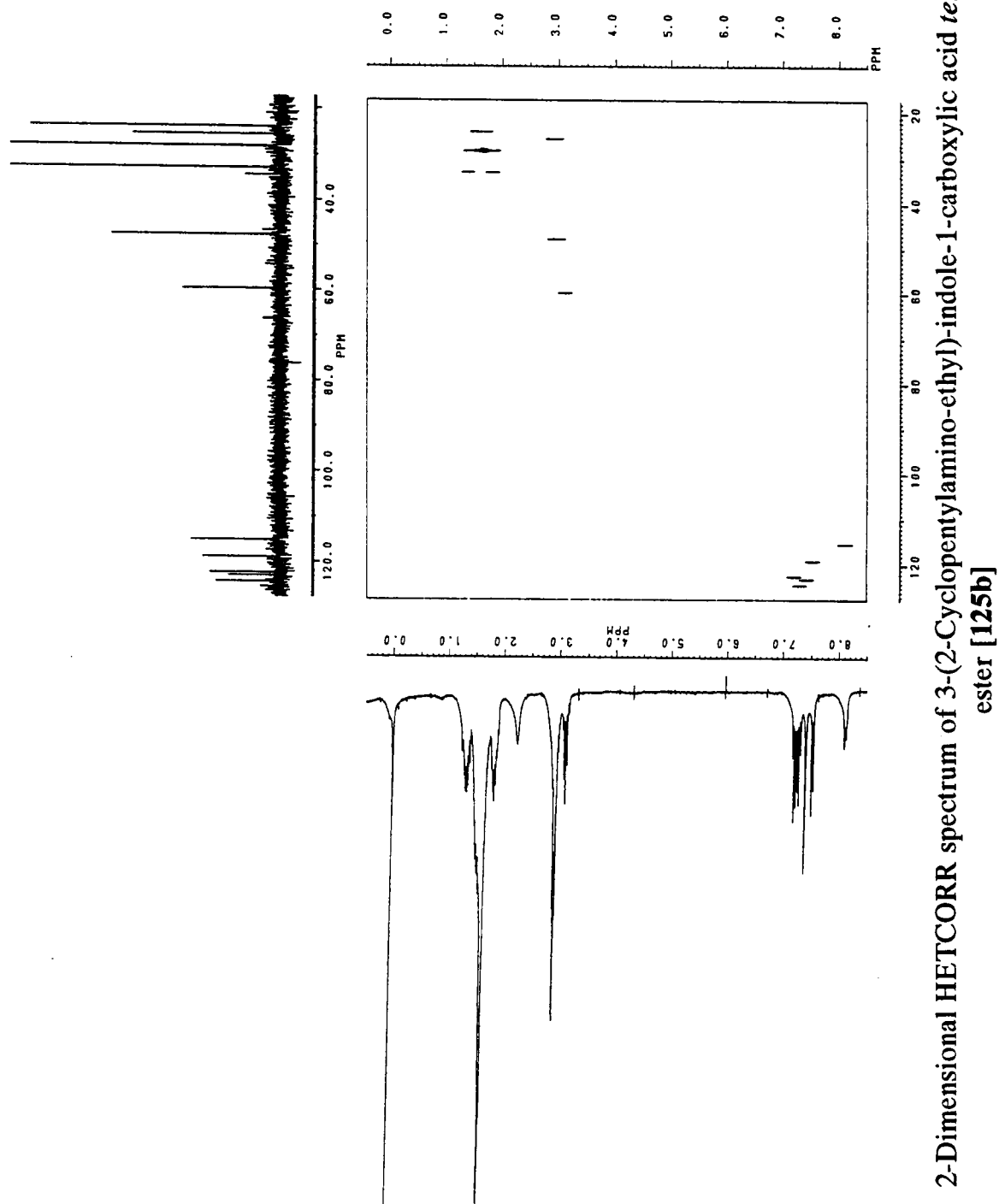


Figure A-25: 2-Dimensional HETCOR spectrum of 3-(2-Cyclopentylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [125b]

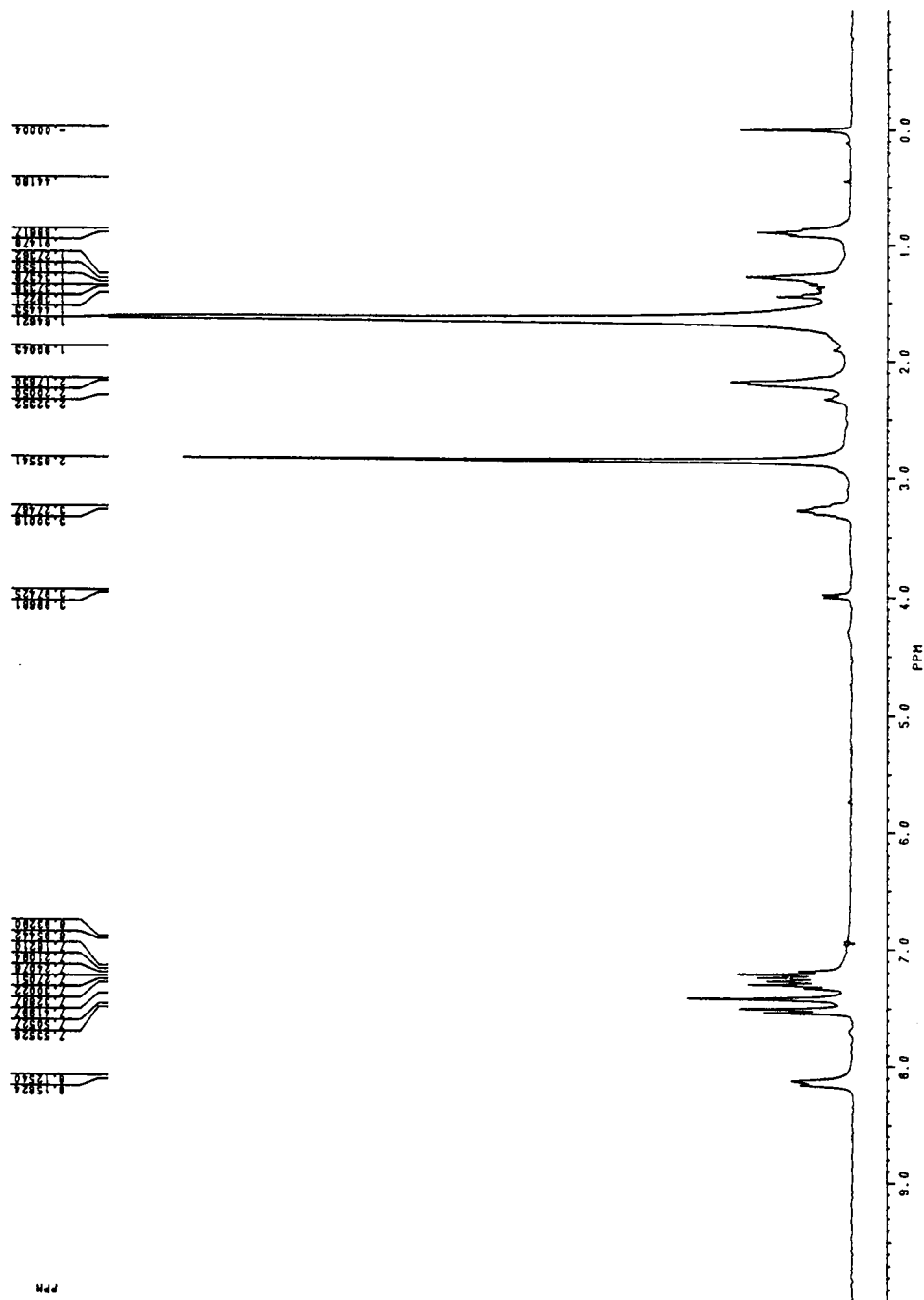
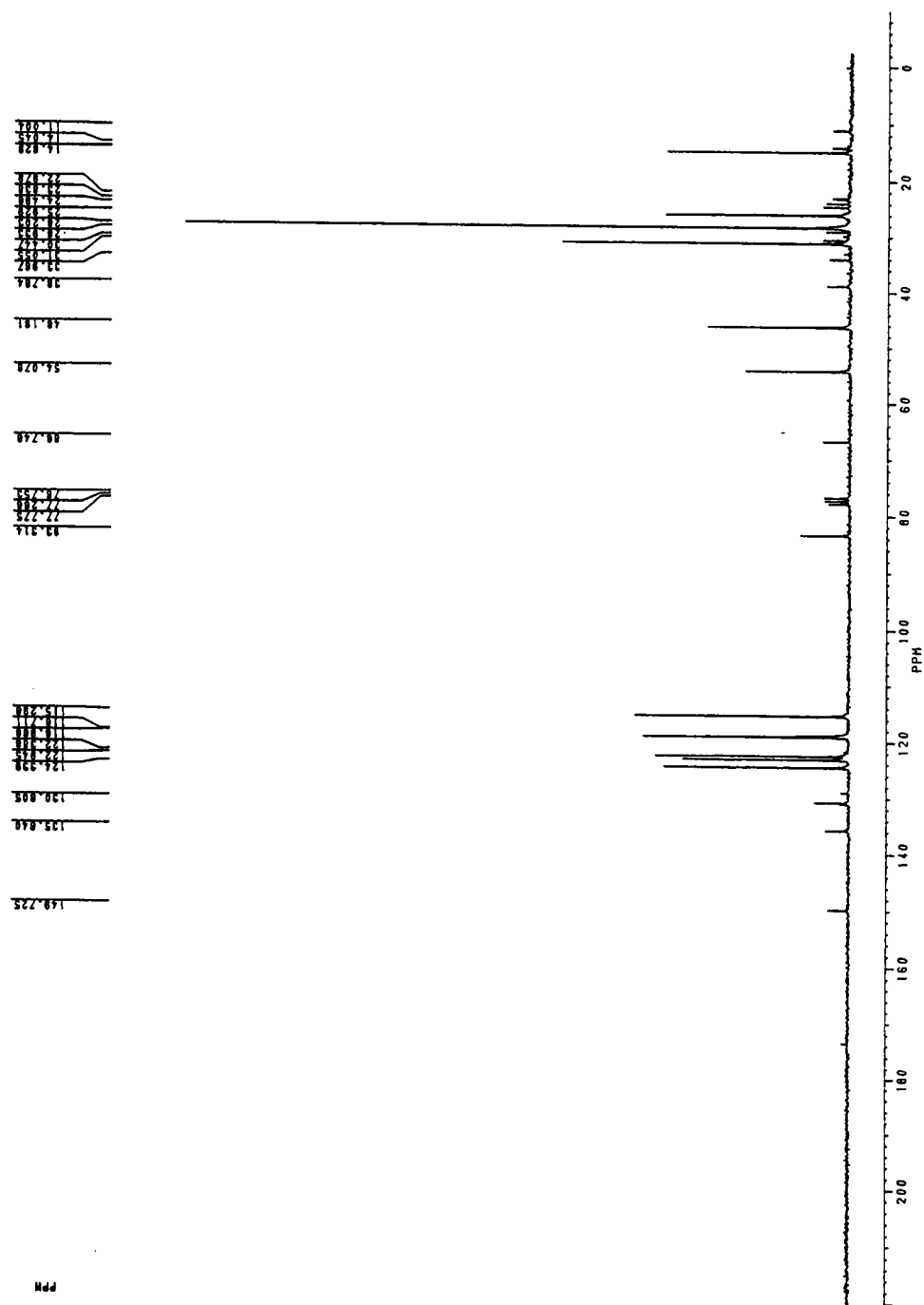


Figure A-26: ¹H NMR spectrum of 3-(2-Cyclobutylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [125a]



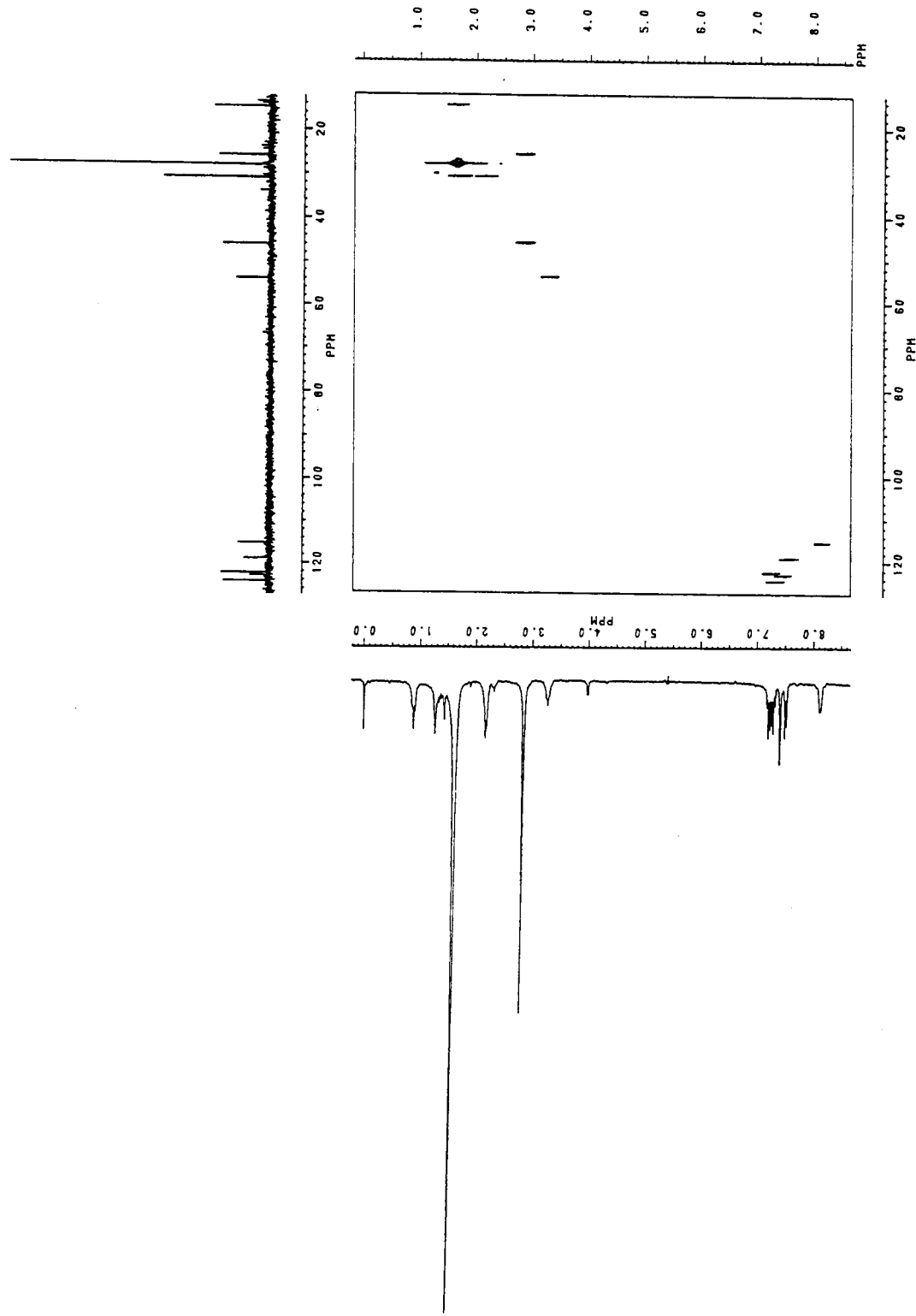


Figure A-28: 2-Dimensional HETCOR spectrum of 3-(2-Cyclobutylamino-ethyl)-indole-1-carboxylic acid *tert*-butyl ester [125a]

VITA

Edward Brown, son of Ray and Carolyn Brown, was born in Dallas, Texas on August 6, 1961. He graduated from New Hope High School in Columbus, Mississippi in May 1979. In the fall of 1979, he entered Lee College in Cleveland, Tennessee. Eddie graduated *magna cum laude* in May 1983 with a Bachelor of Science in Chemistry. In the fall of 1983, the author entered graduate school at the University of Tennessee where he served as both an organic and general chemistry teaching assistant and a departmental NMR operator. In 1990, Eddie was hired by his alma mater to teach general, organic, and biochemistry.

Eddie is married to Robin Whittaker and currently resides in Ten Mile, Tennessee. They have a daughter, Sarah Catherine "Cassie" Brown, born May 5, 1995. After graduation, Eddie will continue teaching and directing undergraduate research at Lee College in Cleveland, Tennessee.