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Cycloadditions of isoquinolinium salts: A new route to benz[cd]indoles

Soll, Clifford E., Ph.D.

City University of New York, 1991

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CYCLOADDITIONS OF ISOQUINOLINIUM SALTS: A NEW ROUTE TO BENZ[cd]INDOLES

by

CLIFFORD E. SOLL

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1991

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

12-17-90
date

Richard Frech
Chairman of Examining Committee

12-17-90
date

Richard Pigsen
Executive Officer

A David Baker

Supervisory Committee

The City University of New York

Abstract

Cycloadditions of Isoquinolinium Salts:

A New Route To Benz[cd]Indoles

by

Clifford E. Soll

Adviser: Professor Richard W. Franck

Text: The Bradsher cycloaddition of isoquinolinium salts involving isoquinolines substituted at the 5-position with nitrogen were investigated as a new route to benz[cd]indoles. Upon ring opening of the initial tricyclic adducts, the 5-position nitrogen interacts with the aldehyde generated to construct the basic carbocyclic skeleton of this ring system. Dehydration followed by functional group interconversions led to the synthesis of Uhle's Ketone, a known precursor to the ergot alkaloid framework.

This type of cycloaddition using methoxycyclohexene was used to construct the carbon skeleton of the hapalindoles. These are a class of compounds, extracted from the blue-green alga, *Hapalosiphon Fontanalis* that exhibit antibacterial and antimycotic activity.

During the course of our work we developed a new method for the dedinitrophenylation of our ring opened cycloadducts. This reaction using aqueous lithium borohydride was investigated as a general procedure for the deprotection of 2,4-dinitrophenylamines.

Acknowledgments

I wish to express my deep sense of appreciation to Prof. R.W. Franck for his guidance, patience and encouragement during this work. I am indebted to Prof. K. Grohmann for his guidance and helpful discussions even when I was not prepared to heed his ideas. I would like to thank Dr. M. Blumenstein for his help with many NMR experiments and for the opportunity to learn how to "fix the GE QE300". I would like to thank Prof. K.D. Onan at Northeastern University and Prof. G. Quigley and S. Chen at Hunter College for their x-ray crystallographic work. My gratitude is expressed to Waldemar Cieniewicz, our electronics technichian and Richard Krumm from the machine shop for the countless times that I have required their help.

I am especially grateful to Mike Pencak for his assistance in life, which includes all things besides chemistry, some chemistry and homebrewing beer. If it was not for Mike, "I would only have graduated with a Ph.D!".

I would also like to thank the members of Prof. Franck's research group who have contributed help in their individual ways. These people include Drs. R.B. Gupta, C.S. Subramaniam, V. Bhat, S. Ramesh, G. Grewal, N. Kaila, H. Yin, R. Tripathy, A. Chowdhury and my other labmates T. Nicolas, Xiaoming Ye, and Aloma Geer.

Most important, I thank my mother Edith Soll, for support (financial and moral) and my girlfriend, Lynn A. Frischmann, without whom I would never have been able to complete this undertaking.

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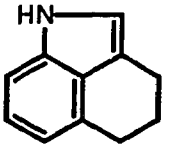
CHAPTER I. INTRODUCTION

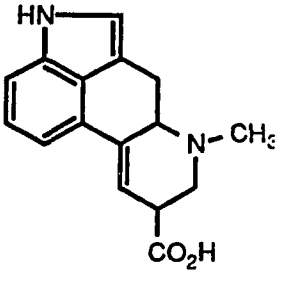
A.THE BENZ[cd]INDOLE FRAMEWORK

1.1 Ergot Alkaloid Framework

The Benz[cd]indole skeleton **I** is the basic framework for a host of extremely pharmacologically active compounds. The most well known and studied of these compounds is Lysergic Acid **II**. The family of compounds derived from this



I. 1,3,4,5-Tetrahydrobenz[cd]indole



II. Lysergic Acid

Figure I. Benz[cd]Indole Skeleton

structure, which upon hydrolysis yield Lysergic acid, are the Ergot alkaloids. Ergot is the name given to the parasitic fungus Claviceps Purpurea, that infects wheat and rye grain and produces these alkaloids. Ergotism or poisoning by eating bread made from infected grain was common in the seventeenth and eighteenth centuries, especially during times of famine when the infected grain could not be wasted.

The symptoms of ergotism varied with the amount ingested and the time frame over which the poisoning occurred. The characteristics of ergot poisoning

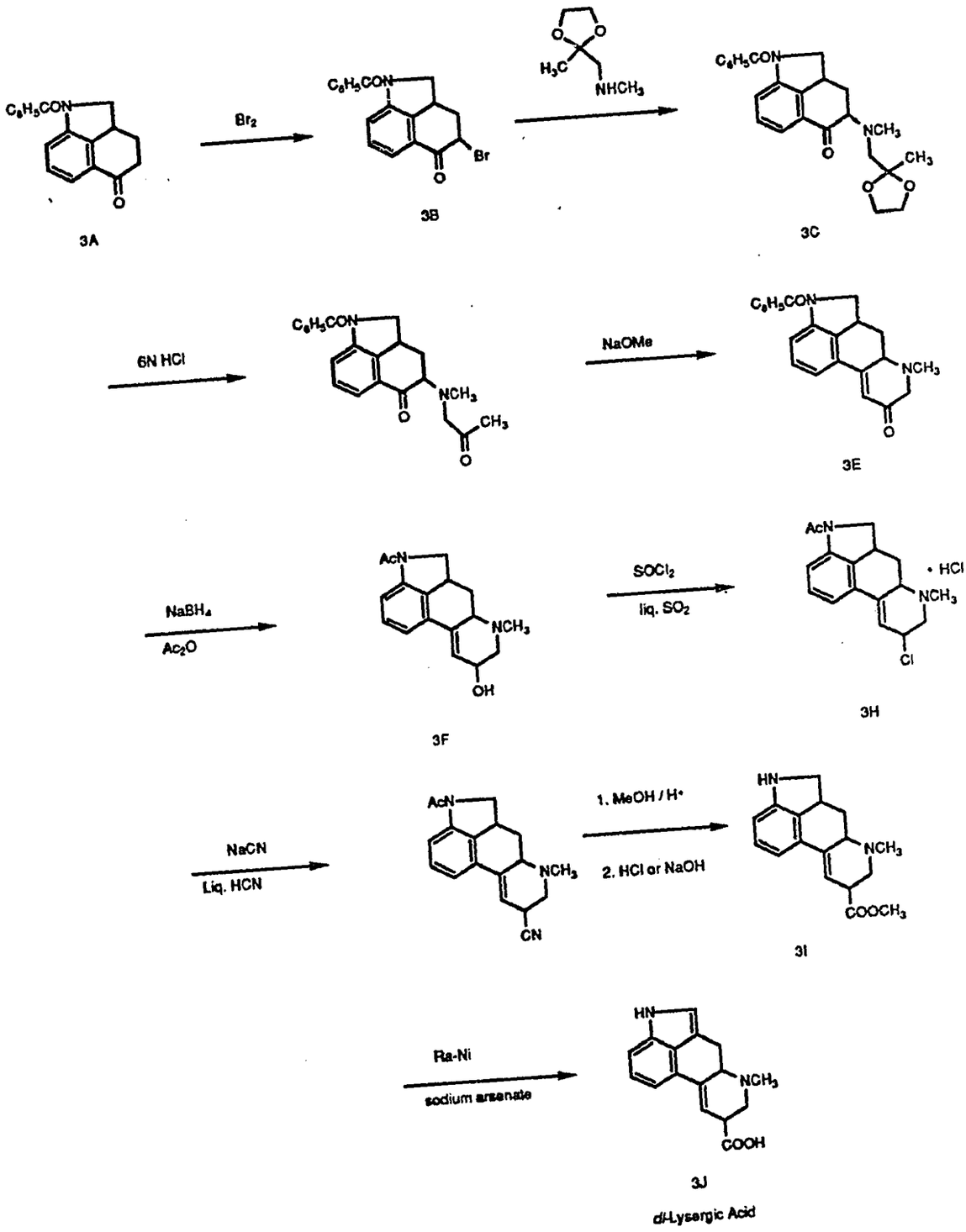
are intense vasoconstriction and effects to the central nervous system. The skin becomes dry and cold and the victim feels intense pain from the muscles in the extremities. Effects on the central nervous system include: vomiting, dizziness, headache, confusion, unconsciousness and convulsions. Ergot also causes contractions of the uterus and induces abortion.

The ergot alkaloids are a group of twelve naturally occurring compounds incorporating six different pairs of epimers at C_6. They are all amide derivatives of Lysergic acid and have different functionalities attached to the amide nitrogen. It was this fact that upon hydrolysis all of these compounds yield Lysergic acid that a synthetic interest was generated.

1.2 Lysergic Acid

The first reported synthesis of Lysergic acid diethylamide, LSD, was in 1938 by Albert Hofmann a pharmacologist working at Sandoz Laboratories in Basel Switzerland.[1] Five years after reporting this synthesis Dr. Hofmann accidently discovered the significant psychic properties of this compound which stirred up a huge interest by other researchers and curious people.

In 1958 Woodward[2] reported another synthesis (scheme I) of Lysergic acid that started with 1-Benzoyl-1,2,2a,3,4-hexahydro-benz[cd]indol-5(1H)-one **3A**. Compound **3A** was brominated to give the alpha bromo compound **3B** using pyridine hydrobromide perbromide in acetic acid. This was followed by alkylation with methylaminoacetone ethylene ketal to give the ketal **3C**. Deblocking with aqueous HCl followed by treatment with sodium methoxide produced the octa-



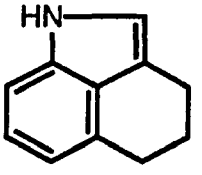
Scheme I. Woodward's Lysergic Acid Synthesis

hydroindolo[4,3-fg]quinoline **3E**. Reduction of the ketone with sodium borohydride, followed by treatment with HCl and then acetylation gave the alcohol **3F**.

The alcohol was converted to the chloro compound **3H** with thionyl chloride and subsequently transformed to the nitrile with sodium cyanide. Hydrolysis of the nitrile with sulfuric acid and methanol gave the ester **3I**. Treatment of the ester with potassium hydroxide followed by dehydrogenation with Raney-nickel produced (±) Lysergic Acid **3J**.

1.3 Retrosynthetic Disconnection

Subsequent to Woodward's synthesis a sizable interest was generated in order to form the basic carbon skeleton of Lysergic Acid. This basic skeleton, 1,3,4,5-tetrahydrobenz[cd]indole **I**,



I. 1,3,4,5-Tetrahydrobenz[cd]indole

Figure II. Benz[cd]indole Skeleton

The general synthetic approaches to this heterocyclic framework have involved various disconnections to the tricyclic ring system. Two obvious disconnections,

a and **b**, are shown below. In **a**, the indole would be constructed on to an existing tetrahydronapthalene. In **b**, the third ring could be formed by alkylation of the existing indole ring. A variety of these strategies have been used to build this heterocyclic skeleton.

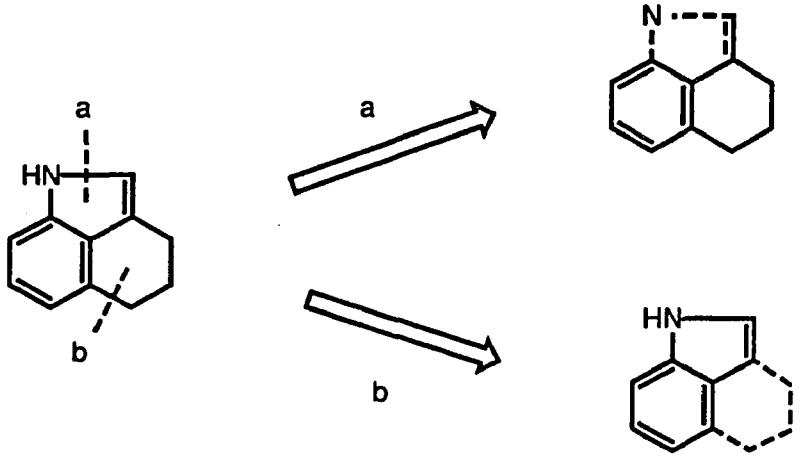
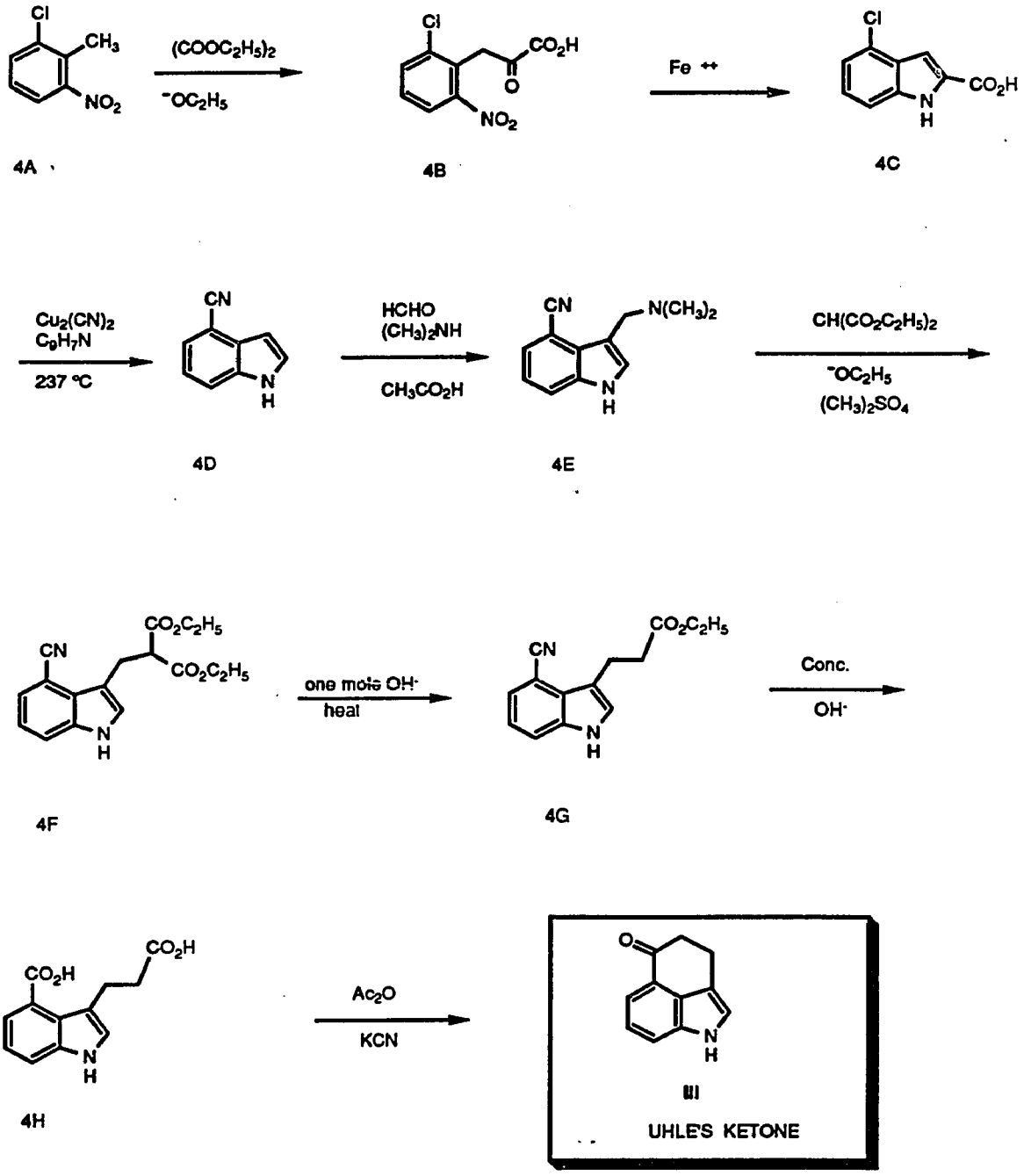


Figure III. Disconnection of Benz[cd]Indole Skeleton

1.4 Uhle's Ketone Synthesis

Uhle's ketone, 3,4-dihydrobenz[cd]indol-5(1H)-one, first synthesized in 1949 by F.C. Uhle[3] has generated considerable synthetic interest because of Woodward's Lysergic Acid synthesis and because it consists of a large portion of the carbon framework of the acid. Uhle's synthetic strategy (scheme **III**) started with 2-nitro-6-chlorotoluene **4A**. The first step was alkylation with ethyl oxalate using sodium methoxide to give the α-keto acid **4B**. The nitro group was reduced with Fe^{2+} followed by cyclization to give the indole carboxylic acid **4C**. The next step was decarboxylation with copper cyanide which also caused nucleophilic

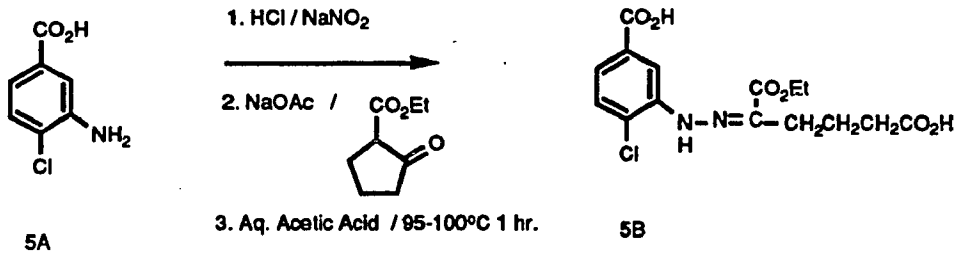


Scheme II. F.C. Uhle's Synthesis

displacement of the chlorine by cyanide to give 4-cyanoindole **4D**. The indole was then alkylated in the 3-position with the mannich base to give the N,N-dimethylamino-methyl-indole **4E**. Quaternization of the amine by dimethylsulfate, followed by alkylation with diethylmalonate gave the diester **4F**. Treatment with one mole of hydroxide caused cleavage of one ester group followed by decarboxylation to give the monoester **4G**. Further treatment by concentrated hydroxide caused cleavage of the other ester group and hydrolysis of the nitrile to give the diacid **4H**. Treatment of the diacid **4H** with acetic anhydride and potassium cyanide caused cyclization to the desired ketone, 3,4-dihydro benz[cd]indol-5(1H)-one **III**.

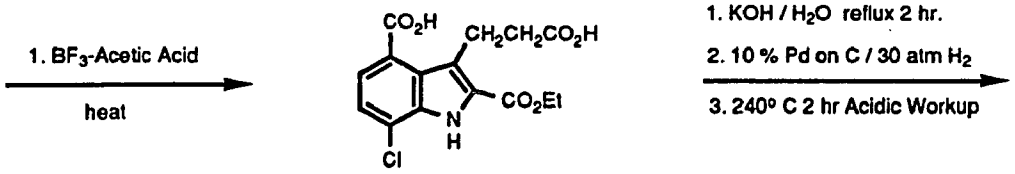
A synthesis reported by Bowman et al[4] in 1973 started with 4-chloro-3-hydrazinobenzoic acid, using a Fischer cyclization to generate the indole and a condensation to produce the third ring. 4-chloro-3-aminobenzoic acid **5A** was dissolved in concentrated hydrochloric acid followed by addition of ice and water. To this suspension was added a solution of sodium nitrite followed by sodium acetate and then ethyl 2-oxocylopentanecarboxylate. An oil separated from the mixture and gradually solidified to an orange solid. Filtration of the solid yielded and ensuing treatment with aqueous acetic acid and heating to 95 °C for 1 hour gave the hydrazone carboxylate **5B**. A suspension of **5B** in glacial acetic acid and a boron trifluoride-acetic acid complex was heated to 90 °C. After the ensuing exothermic reaction occurred the reaction was refluxed for 4 hours. After cooling, the resulting indole ester **5C** crystallized from the solution. This indole ester was

next treated in three successive steps without purification. Treatment in boiling water containing potassium hydroxide followed by distillation of ethanol, hydrolyzed

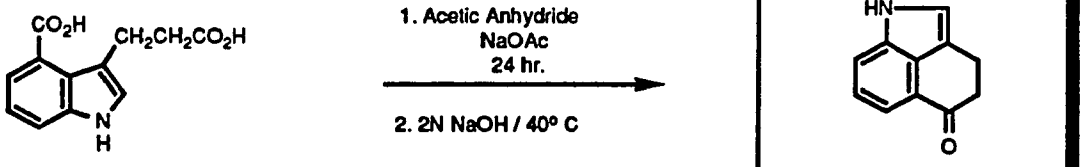


5A

5B



5C



5D

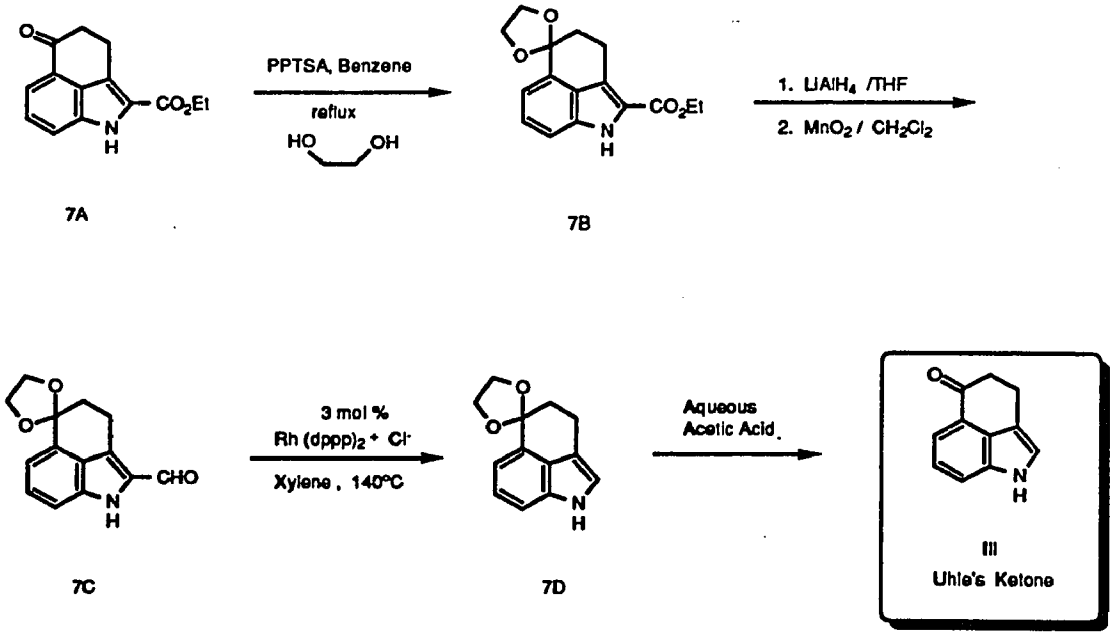
III

Uhle's Ketone

Scheme III. Bowman Uhle's Ketone Synthesis

the ester. The product was shaken in an autoclave containing 10 % palladium on carbon and 30 atmospheres of hydrogen. After filtration of the catalyst the resulting dehalogenated product was heated to 240 °C for 2 hours. After cooling and acidification the 4-carboxyindole-propionic acid **5D** was obtained. The indole-propionic acid was dissolved in acetic anhydride containing sodium acetate and the mixture heated to reflux for 24 hours. After workup the resulting N-acetyl derivative was dissolved in ethanol and treated with 2N sodium hydroxide for 15 minutes. Removal of the ethanol afforded Uhle's ketone **III** as a yellow-brown solid.

In 1984 Meyer and Kruse[5] synthesized Uhle's Ketone (scheme **IV**) from 2-ethylcarboxylate-3,4-dihydrobenz[cd]indol-5(1H)-one **7A** that was prepared by

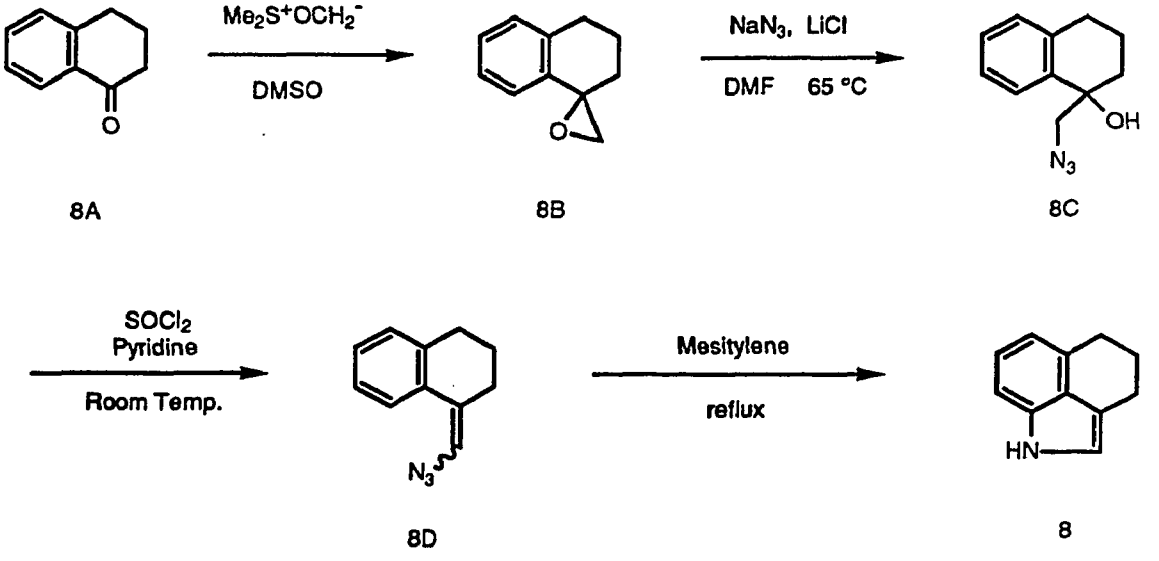


Scheme **IV**. Meyer and Kruse Synthesis of Uhle's Ketone

Nagasaka and Ohki.[6] The synthesis would appear to be a simple decarboxylation of the ethyl ester at the 2-position of the indole but classical methods gave poor yields. In their synthesis the 5-keto group was protected as the ethylene ketal using ethylene glycol and para-toluenesulfonic acid to give **7B**. The ester was reduced to the alcohol with LAH followed by oxidation to the aldehyde **7C** using manganese dioxide. Decarboxylation of the aldehyde was accomplished using a rhodium catalyst in xylene at 140 °C to give the ketal **7D**. Deprotection of the ketal **7D** was accomplished using aqueous acetic acid to give Uhle's ketone **III**.

1.5 Tetrahydrobenz[cd]indole Synthesis

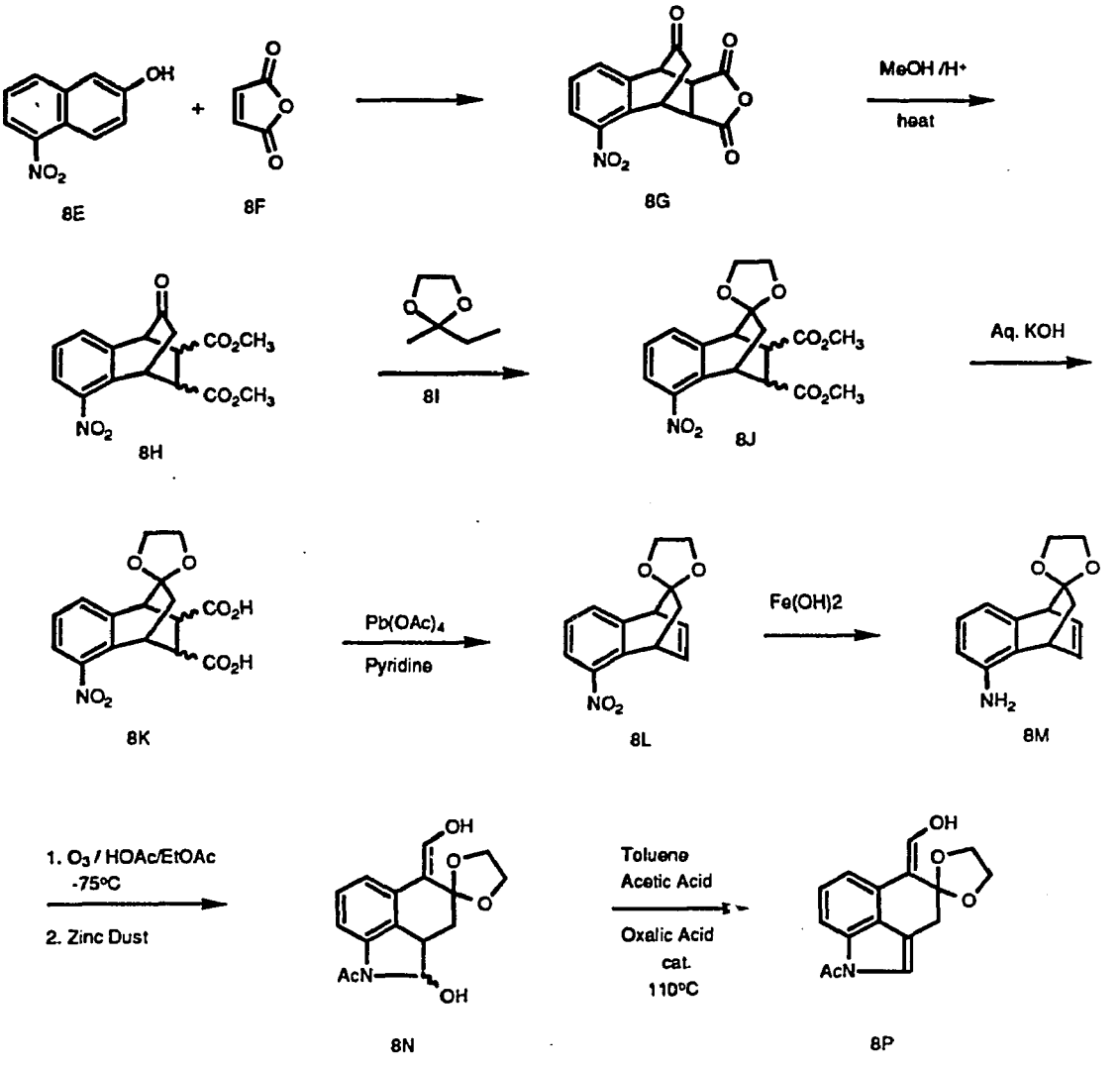
In another recent synthesis, while not of the ketone but rather 1,2,4,5-tetrahydrobenz[cd]indole **8**, Moody, Beck, and Coates (scheme **V**) started their



Scheme **V**. Moody, Beck and Coates - Tetrahydrobenz[cd]indole Synthesis

scheme using tetralone **8A**.[7] The keto group was converted to the epoxide **8B** with dimethylsulfoxinium ylid in DMSO. The epoxide was opened using sodium azide in DMF to give the azido alcohol **8C**. Conversion of the alcohol to the chloro compound using thionyl chloride followed by elimination with pyridine gave the vinyl azide **8D**. Cyclization to the final product **8** was accomplished by refluxing in mesitylene.

Also of interest is work published by Plieninger and Lehnert.[8] Their interesting synthetic strategy to this framework commenced with the high pressure Diels-Alder reaction between 5-nitro-2-napthol **8E** and maleic anhydride **8F**. The product of the reaction is the adduct **8G**. Treatment of adduct **8G** with acidic methanol and heat, hydrolyzed the anhydride to give the diester **8H**. Trans ketalization of the keto group of **8H** with the ethylene ketal of methyl ethyl ketone gave the ketal **8J**. Treatment of **8J** with aqueous potassium hydroxide cleaved the esters to give the diacid **8K**. When **8K** was subjected to lead tetraacetate and pyridine, bis-decarboxylation occurred to form the unsaturated compound **8L**. Reduction of the nitro group of **8L** using iron(II) hydroxide yielded the unsaturated amino compound **8M**. Ozonolysis of the double bond in **8M** followed by reduction with zinc dust gave the hydroxyindoline **8N**. Dehydration of **8N** was accomplished by treatment with acetic acid and catalytic oxalic acid in refluxing toluene to give the substituted benz[cd]indole **8P**.



Scheme **Va**. Plieninger Synthetic Strategy

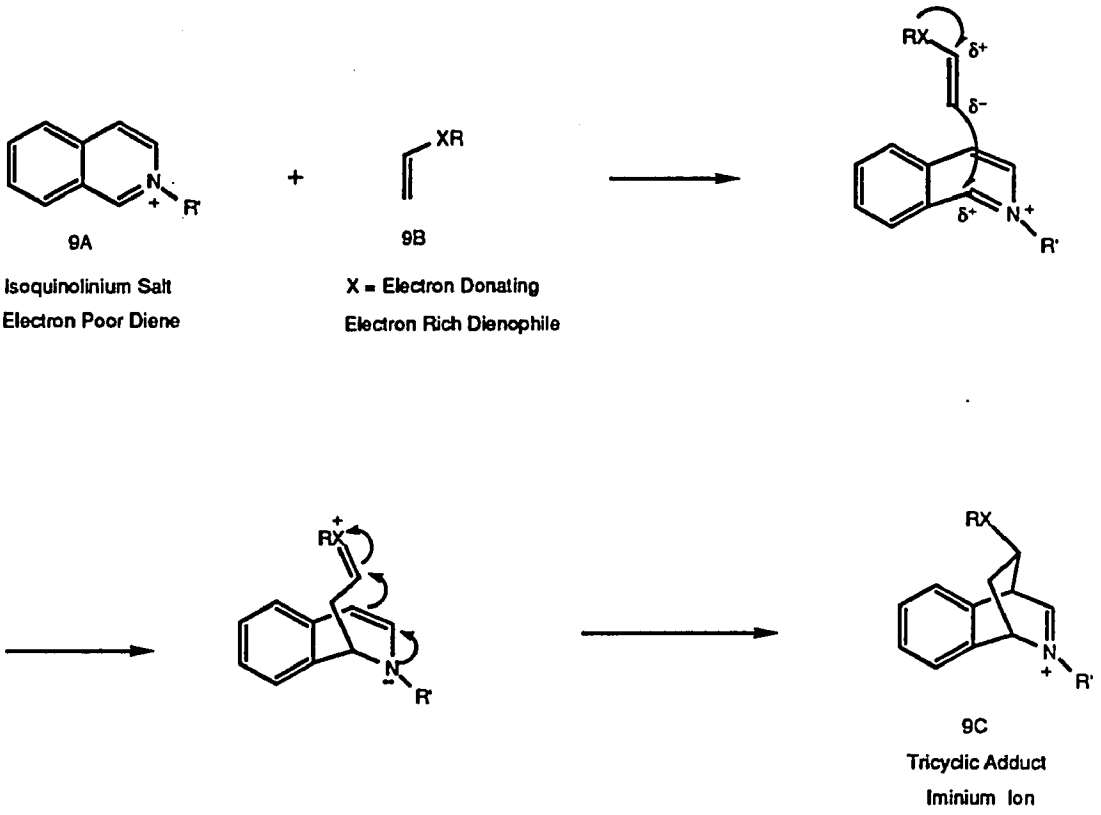
New synthetic approaches to this framework are important because of the extraordinary pharmacological activity exhibited by these compounds. A few of the

many published procedures have been examined in the previous pages. Our approach to this skeleton involves utilization of the Bradsher cycloaddition of isoquinolinium salts.

B. CYCLOADDITION OF ISOQUINOLINIUM SALTS

1.6 Bradsher Cycloaddition of Isoquinolinium Salts

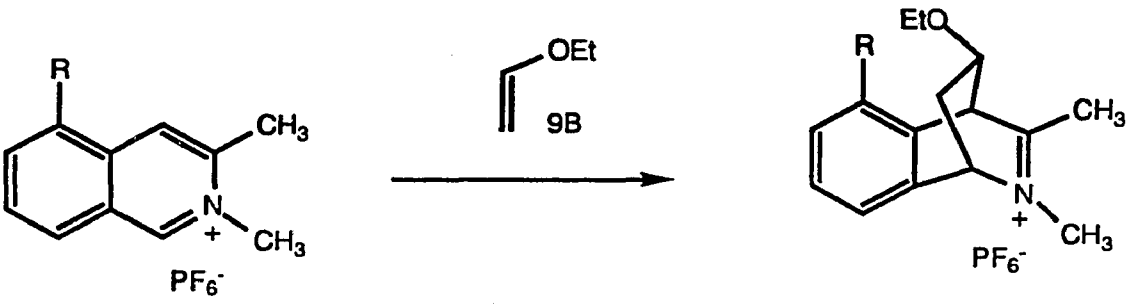
The cycloaddition of isoquinolinium salts with vinyl ethers are one example of inverse electron demand Diels-Alder reactions. The reaction of the isoquinolinium



Scheme VI. Inverse Electron Demand Diels Alder Reaction

salt **9A** (scheme **VI**) an electron poor diene with a vinyl ether **9B**, an electron rich dienophile was first discovered by Bradsher[9] in 1971. The reaction proceeds to give the tricyclic iminium ion product **9C**.

The reaction was found to be regiospecific and highly stereoselective. When the 2,3-dimethyl-isoquinolinium salt **9D** reacts with ethyl vinyl ether **9E** the resulting tricyclic adduct **9F** is obtained.

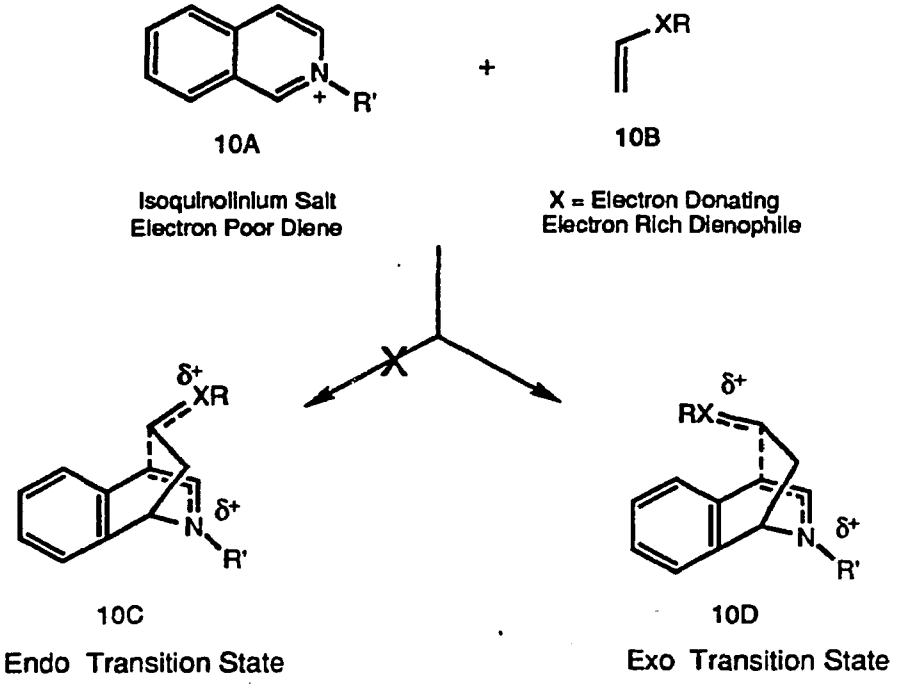


9A 9C

a. R = H
b. R = NO_2
c. R = NHCOMe

Scheme **VI**. Bradsher Cycloaddition of Isoquinolinium Salts

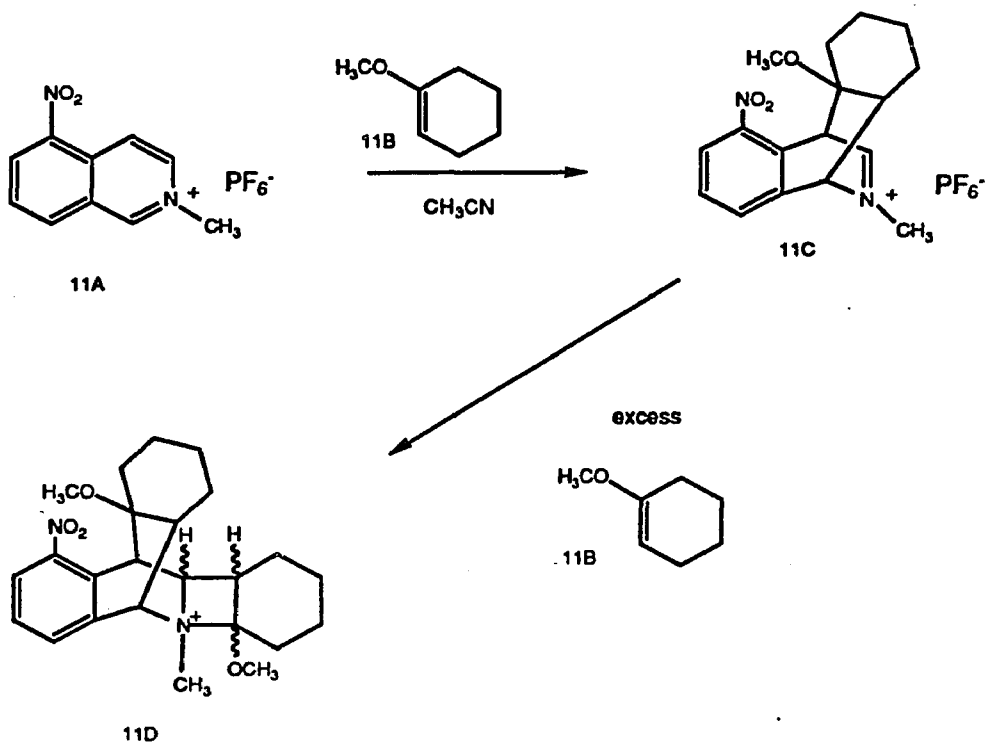
The stereoselectivity of this reaction, that gives predominantly exo product, was thought to arise because this adduct would give the maximum like charge separation in the transition state. In the *endo* transition state, **10C**, the developing positive charge on the electron donating substituent of the dienophile **10B** will be in close proximity to the positively charged nitrogen of the diene **10A**. In the *exo* transition state **10D** the developing positive charges are at maximum distances to each other.



Scheme **VII**. Bradsher Cycloaddition

1.7 Bradsher Double Addition

The resulting iminium ion tricyclic adduct is an inordinately reactive species and may react with a second molecule of dienophile to give a "double adduct". When 5-nitro-2-methylisoquinolinium hexafluorohosphate **11A** was reacted with excess 1-methoxycyclohexene **11B**, a simple cycloaddition to give **11C** was not the result. Based on mechanistic rationalizations and NMR evidence the product was reported to be the "double adduct" **11D** (Scheme **VIII**).[10]

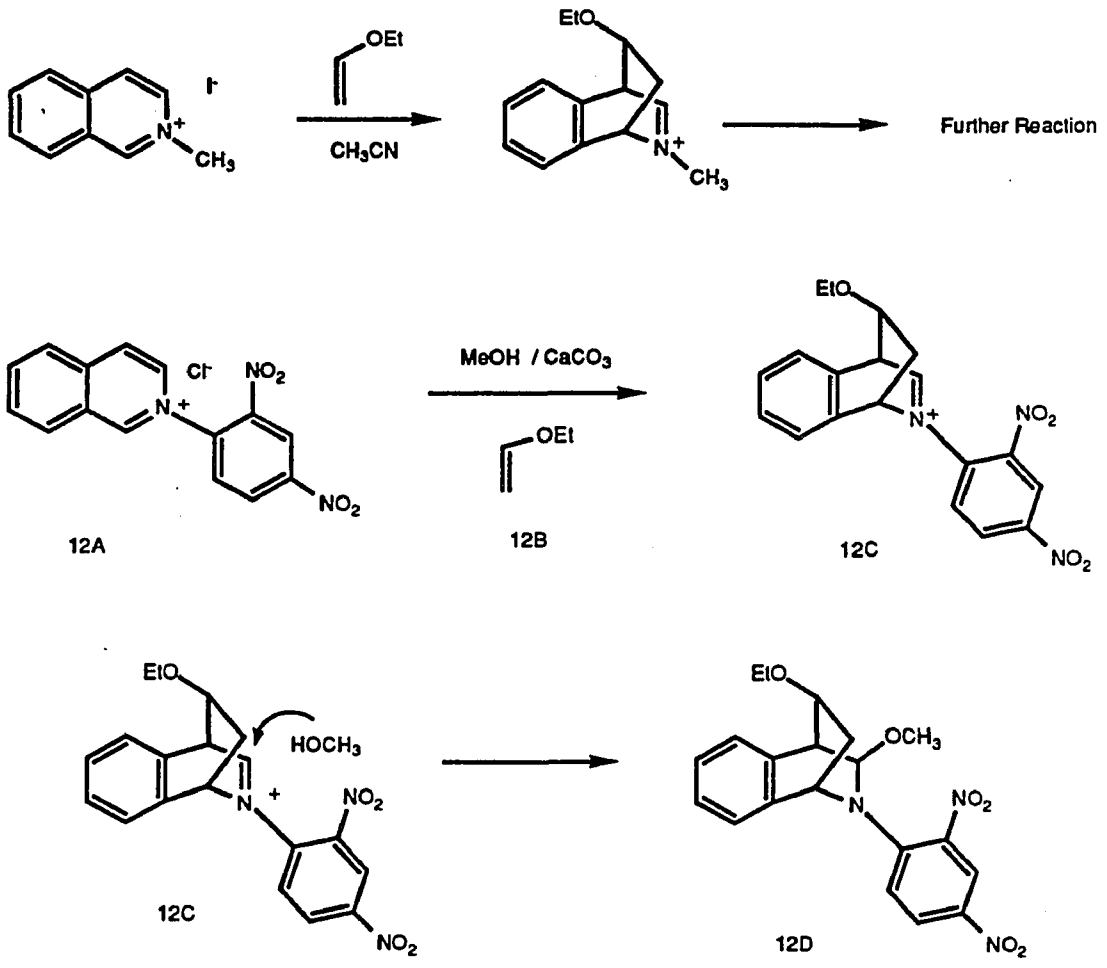


Scheme **VIII.** Double Addition

One initial resolution to this problem was found when it was observed that isoquinolines substituted in the 3-position with an alkyl group did not undergo this type of addition.

1.8 Falck Modification of Bradsher Reaction

Another solution to this problem was reported by Falck and Mioskowski[11], in which the isoquinoline was quaternized as the 2,4-dinitrophenyl (DNP) salt and the reaction was carried out in anhydrous methanol as the solvent and calcium carbonate as a buffer. When the DNP salt **12A** was treated in methanol with ethyl vinyl ether **12B** in the presence of calcium carbonate the tricyclic adduct **12C**

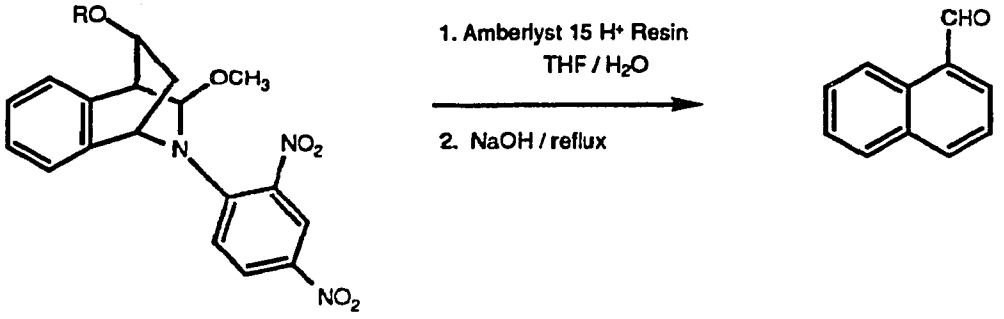


Scheme **IX.** Falck Modification To Bradsher Reaction

was formed as an intermediate, but the methanol solvent acts a nucleophile that traps the iminium ion to give the cycloadduct **12D**. Calcium carbonate is used to buffer the HCl formed during the reaction to prevent decomposition of the enol ether.

1.9 Ring Opening With Water

The synthetic utility of this reaction was advanced by the discovery that the tricyclic adduct could undergo acid hydrolysis. When the adduct **13A** was treated in tetrahydrofuran / water with Amberlyst-15 acidic resin followed by treatment with refluxing NaOH the napthaldehyde **13B** was produced.

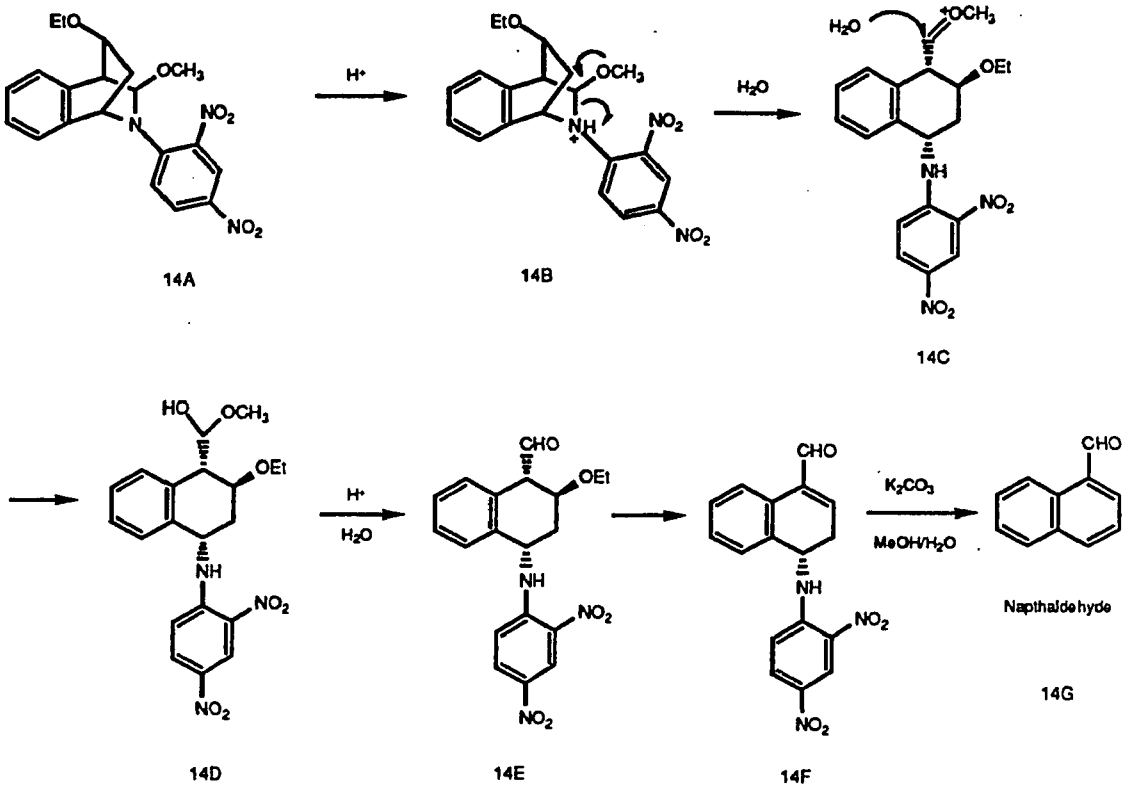


13A **13B**

Scheme **X.** Aromatization of Cycloadduct

The mechanism for the hydrolysis first involves the protonation of the 2,4-DNP-amino nitrogen of the cycloadduct **14A.** This is followed by ring cleavage of the C(3)-N bond due to participation of the lone pair of electrons on the oxygen (**14B**) at C(3) to form the ring opened oxocarbonium ion **14C.** The oxocarbonium ion **14C** is now trapped with water to give the hemiacetal **14D** which upon further reaction with the acid gives the aldehyde **14E.** Under the acidic conditions the aldehydes **14E** usually give some of the α,β-unsaturated elimination product **14F.**

It is this mixture of aldehyde and unsaturated aldehyde that is treated with base to give the napthaldehyde **14G**.

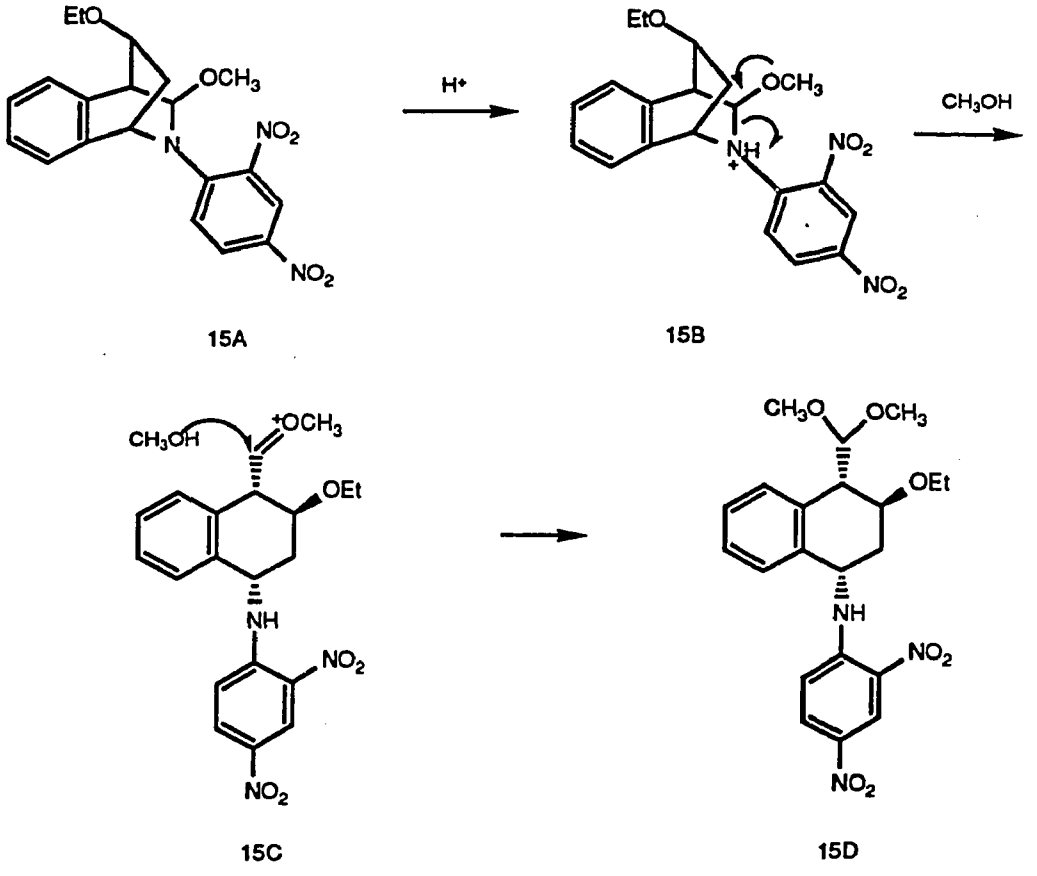


Scheme **XI**. Ring Opening With Water

1.10 Ring Opening With Anhydrous Methanol

In another method that was developed in our lab[12], the tricyclic adduct **15A** is treated with Dowex-50X8-H^+ resin in anhydrous methanol to give the tetralin **15C** where the aldehyde is blocked as a dimethyl acetal. As in the previous case the first step involves protonation of the N(2) nitrogen of the cycloadduct **15A** followed

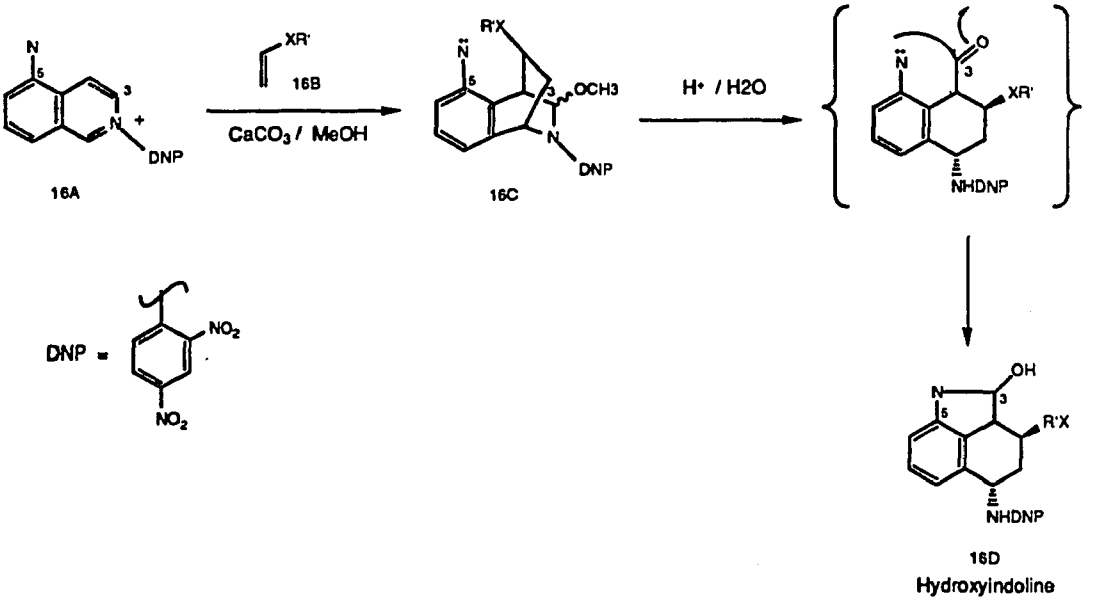
by C(3)-N(2) bond cleavage to give the oxocarbonium ion **15B**. In this case the oxocarbonium ion **15B** reacts with methanol to give the dimethyl acetal **15C**. The tetralins obtained by this reaction are stable and survive chromatography as well as basic conditions.



Scheme **XII**. Ring Opening With Anhydrous Methanol.

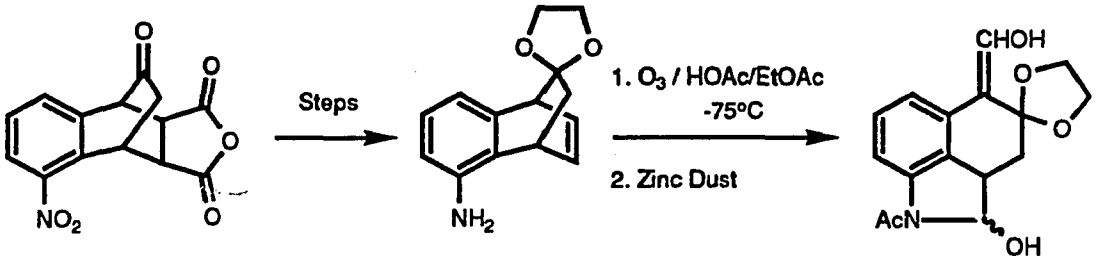
1.11 Participation of 5-Position Nitrogen In Ring Opening

It was the formation of the oxocarbonium ion intermediate that we envisioned would enable us to make the benz[cd]indole framework. If the cycloaddition was performed, with an isoquinoline substituted at the 5-position with nitrogen **16A** reacting with an electron rich dienophile **16B**, one would expect to get the tricyclic adduct **16C**. Upon ring opening the intermediate oxocarbonium should be in a position to be trapped by the peri nitrogen atom to give the hydroxyindoline product **16D**.



Scheme **XIII**. Cycloaddition With 5-Position Nitrogen

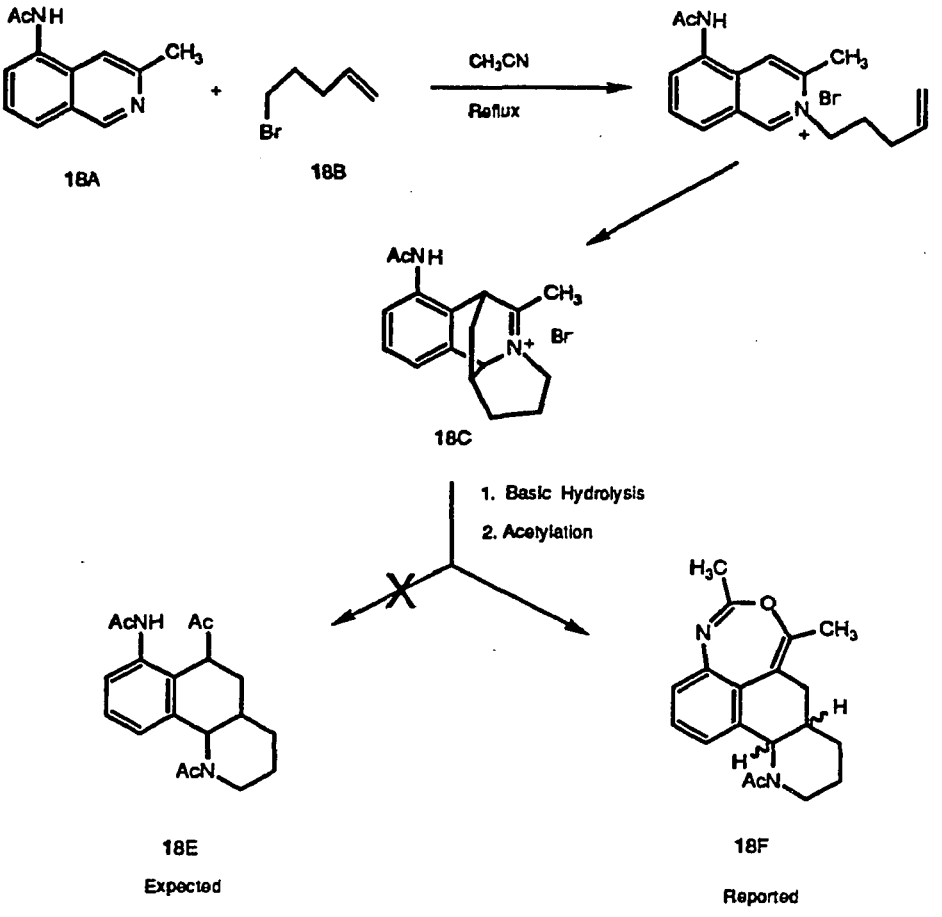
The concept of this interaction between the 5-position nitrogen and a neighboring carbonyl group is not new. Plieninger[8,13] reported examples of these type of hydroxyindolines after ozonolysis of **8M** formed from the high pressure Diels-Alder adduct **8G** (Scheme **XIV** and **Va**).



8G 8M 8N

Scheme **XIV**. *Plieninger Hydroxyindoline Formation*

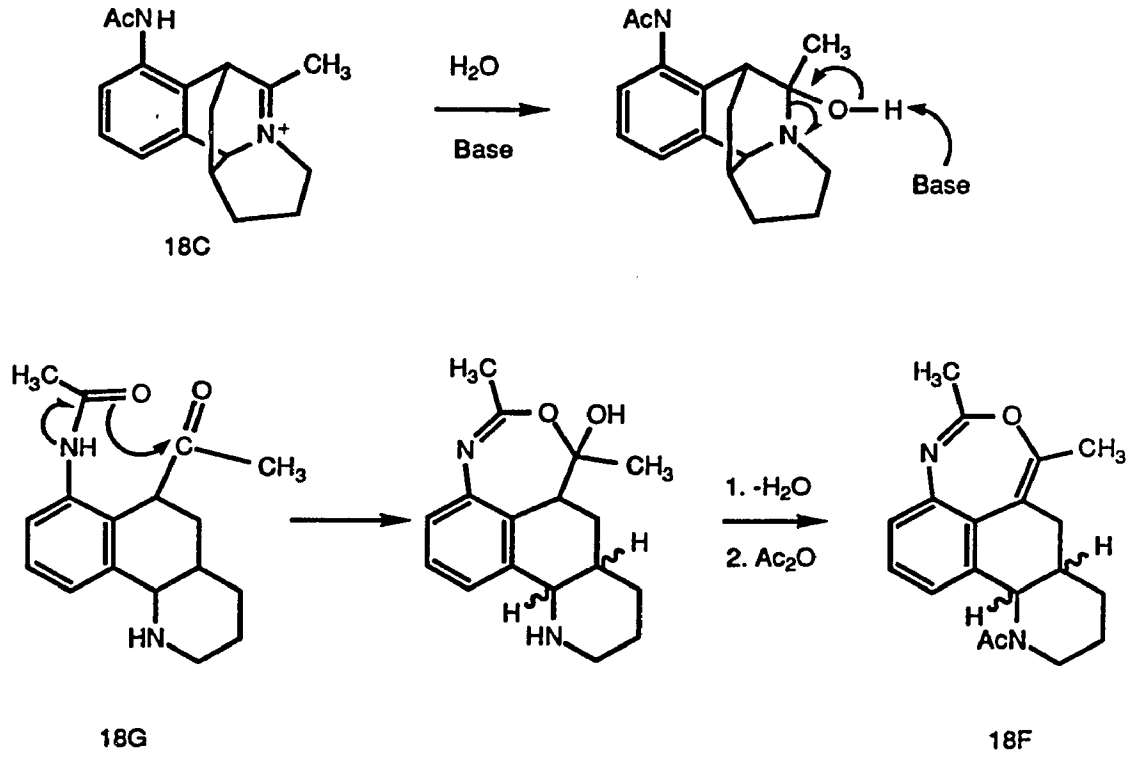
In fact there is also a report by Sammes[14] showing the intramolecular cycloaddition of a 5-acetylaminoisoquinolinium salt followed by hydrolysis in which it is reported the product is a benzoxazepine structure rather than derived from a hydroxyindoline (Scheme **XV**). The 5-acetylamino-3-methyl-isoquinoline **18A** was quaternized, by heating with 5-pentenyl bromide **18B** followed by cycloaddition to give the cycloadduct **18C** as an unstable salt. Basic hydrolysis of the cycloadduct **18D** followed by acetylation did not give the expected product **18E** but was reported as the fused oxazepine ring system **18F**.



Scheme **XV**. Sammes Intramolecular Cycloaddition

The mechanism for product formation of this type would involve the attack of water at the 6-position of the adduct **18C** followed by deprotonation and C(6)-N(5) ring cleavage to give the expected ring opened product **18G**. The fused oxazepine structure **18F** would result from attack by the oxygen of C(8) acetylamino group on the carbonyl group of the C(7) acetyl group followed by dehydration and acetylation.

This product appears to be in contrast to the interaction reported by Pleininger. Our prediction of the interaction would be to give the hydroxyindoline but the cycloaddition and its hydrolysis will have to be tested to see if the desired product is obtained.



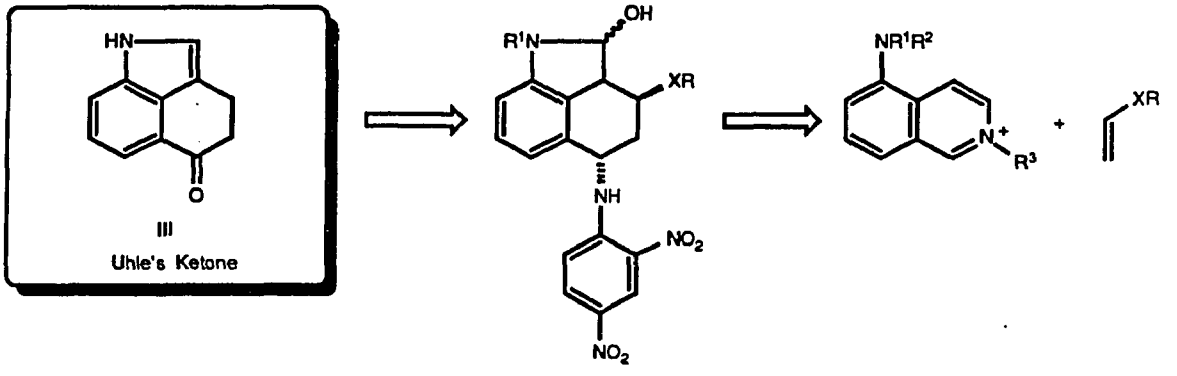
Scheme **XVI**. Sammes Mechanism For Oxazepine Formation

CHAPTER II. RESULTS AND DISCUSSION

A. 5-NITROISOQUINOLINIUM CYCLOADDITIONS

2.1 Retrosynthetic Analysis

In order to achieve our target molecule, Uhle's Ketone **I**, we proposed a retrosynthetic scheme as shown below.



Scheme **I**. Retrosynthetic Scheme

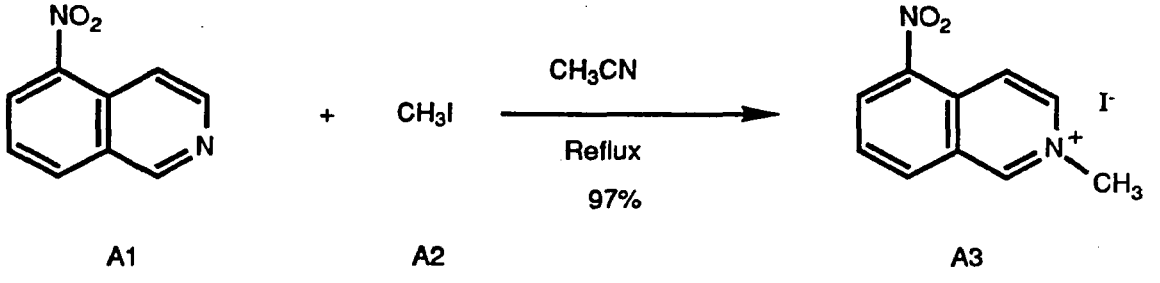
The three selections to be made are the choice of (1) the nitrogen functional group R^1 and R^2 at the 5-position of the isoquinoline, (2) the quaternizing group R^3at the N(2) of the isoquinoline and (3) the electron donating substiuent (**X**) and its substituent **R** on the dieneophile.

Since the target ketone requires removal of the electron donating substiuent and its substituent it seemed appropriate that **X** = sulfur and **R** = Phenyl because there are known methods for removal. The chosen dienophile would therefore be phenyl vinyl sulfide a commercially available reagent.

For initial studies it was decided to use the Nitro (NO_2) substituent at the 5-position of the isoquinoline as it was reported by Bradsher[9] that this group causes a rate increase by a factor of 5 times over the 5-H isoquinoline. The quaternizing agent chosen was methyl iodide.

2.2 5-Nitroisoquinolinium Iodide Reactions

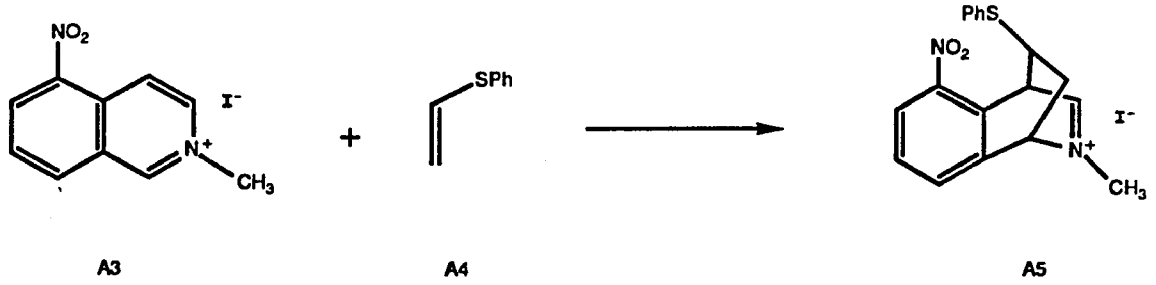
Commercially available 5-nitroisoquinoline **A1** was dissolved in acetonitrile, treated with excess iodomethane **A2** and heated to reflux for 1.5 hours. The product resulting from solvent removal in vacuo was 2-methyl-5-nitroisoquinolinium iodide salt **A3** in 97 % yield.



A1 A2 A3

Scheme **II**. 5-Nitroisoquinolinium Methiodide Formation

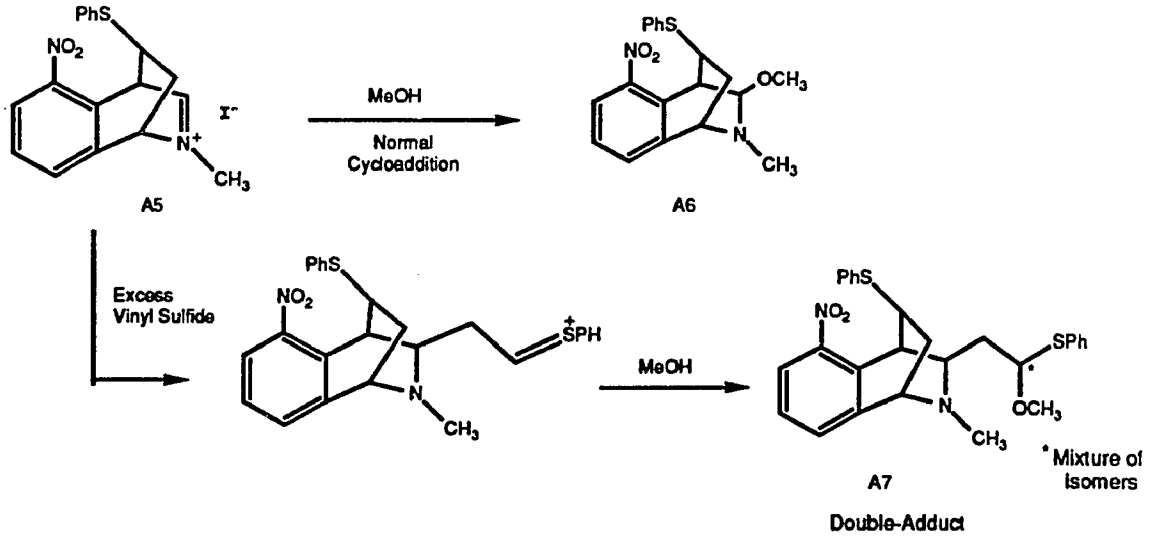
The cycloaddition of 5-nitroisoquinolinium methiodide **A3** with phenyl vinyl sulfide **A4** has produced many interesting results. The conditions under which this reaction is run are critical to the amounts and types of products that are obtained. The cycloaddition takes place readily to give the resulting iminium ion **A5** that is normally expected as shown in scheme **III**. The iminium ion **A5** is usually attacked by the alcoholic solvent methanol to give the normal cycloadduct **A6** but in certain



A3 A4 A5

Scheme III. Cycloaddition of 2-Methyl-5-Nitroisoquinolinium Methiodide

cases is attacked by another molecule of vinyl sulfide with the sulfur lone pair of electrons causing the β-carbon to act as a nucleophile. In the N-methyl caseeven if the iminium ion is trapped by methanol the lone pair of electrons on the nitrogen is readily available to aid in eliminating the methoxyl group to reform the iminium

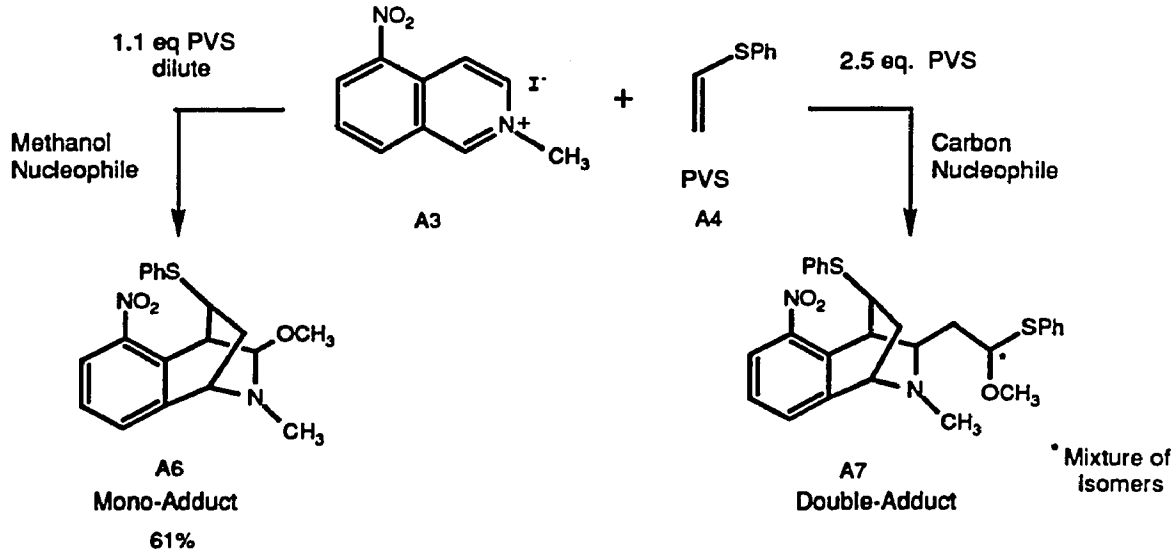


Scheme IV. Single and Double Addition Products

ion. If the iminium ion reacts with another molecule of vinyl sulfide to form a "double adduct", **A7**, one would not expect the process to be reversible due to the formation of a carbon-carbon bond. This is illustrated in scheme **IV**. In the reaction one equivalent of HI is produced which probably aids in reversing the solvent attack.

2.3 Single vs. Double Addition

In order to favor the formation of the single adduct **A6** the reaction must be run at high dilution with 6-7 equivalents of calcium carbonate present with constant stirring. The conditions favoring the double adduct were those with high concentrations of vinyl sulfide under concentrated conditions. When the reaction was run with 2.5 equivalents of phenyl vinyl sulfide at a concentration of 0.38 mM

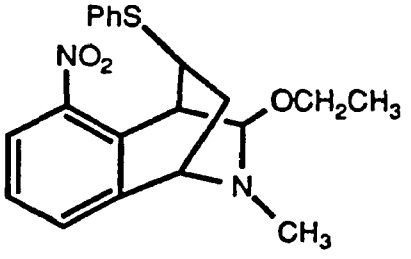


Scheme **V**. Conditions For Single vs. Double Addition

and 1.0 equivalent of isoquinolinium salt present in 0.94 mM, the double adduct was obtained in 59 % yield as a mixture of isomers that have been separated by radial chromatography. In this reaction there is approximately 10 % yield of the mono adduct. This is shown in scheme **V**.

2.4 Monoadduct X-ray Structure

Using the reaction conditions that favored the mono adduct we were able to obtain the product in 61% yield after radial chromatography as a light yellow solid as shown in scheme **IV**. The product was crystallized from ethanol to yield pale yellow crystals that gave the following x-ray structure:



A8
Mono-Adduct
X-Ray

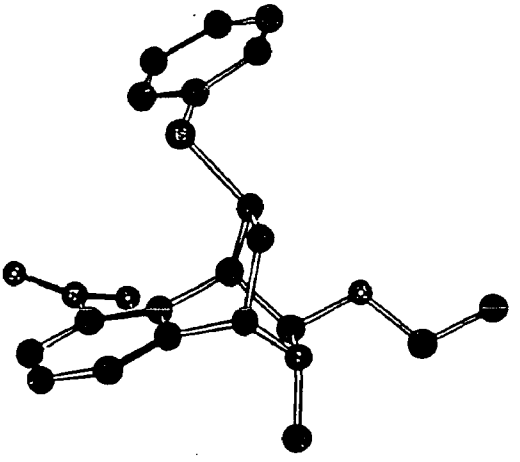
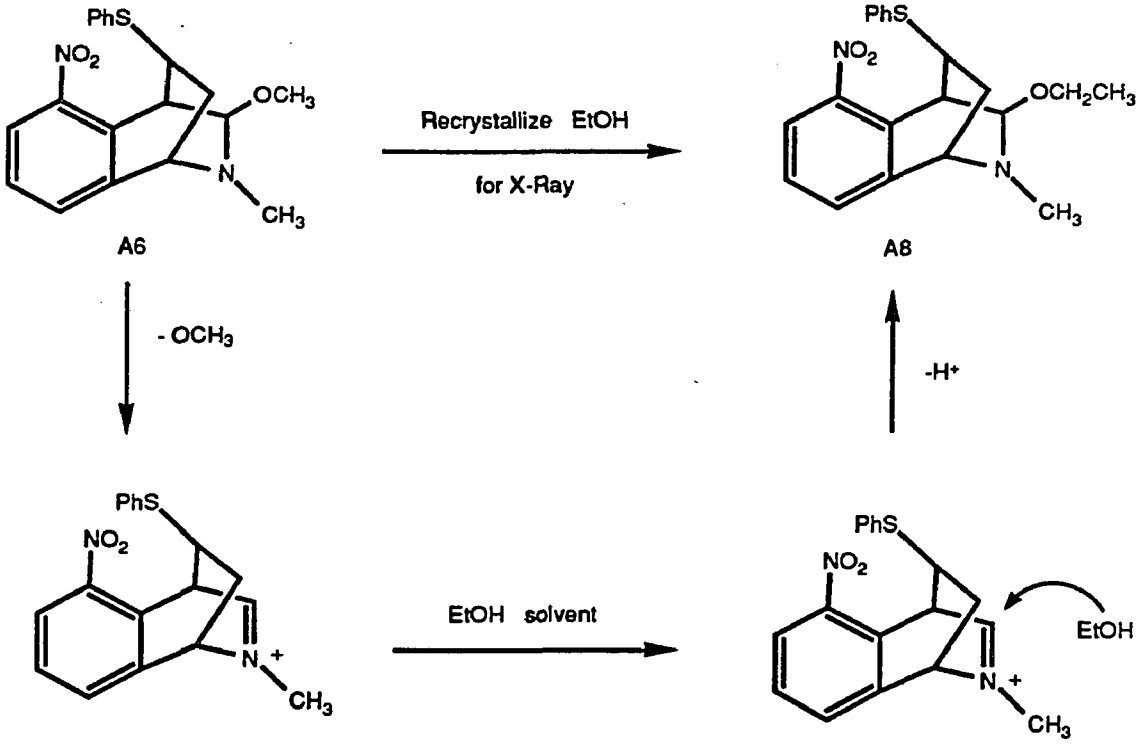


Figure **IV**. X-Ray Structure of Mono-Adduct.

As can be seen from the structure the methoxyl group on C-3 was replaced by ethoxyl. The x-ray analysis shows the ethoxyl group to be syn to the bridge in the bicyclic adduct but NMR analysis in solution shows the presence of approximately

10% of the epimer at C-3 giving further evidence of this reversibility. The x-ray structure of this product allowed the correlation of NMR data for other members of the series obtained from other work in the lab[15].

The replacement of the methoxyl group by ethoxyl during recrystallization from ethanol, lends further evidence to the reversibility of the iminium ion formation in this series. The facile replacement of the group at C-3 as shown in scheme VI



Scheme VI. Facile Solvent Exchange of Mono-Adduct

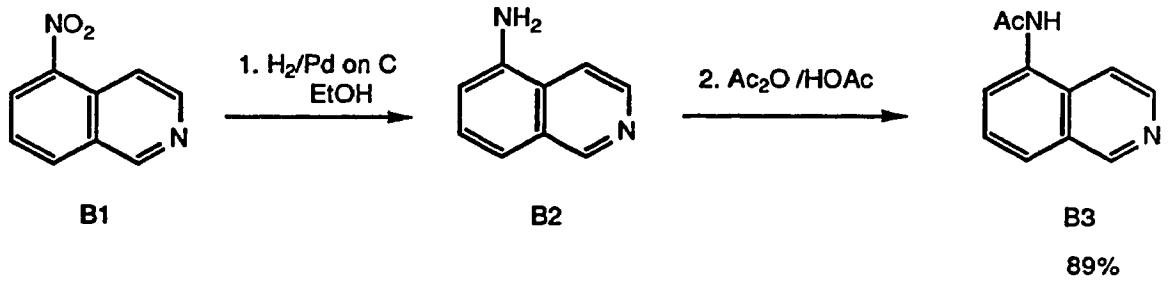
is presumably due to the availability of the lone pair of electrons on the 2-position nitrogen.

It is interesting to note that the double adduct is never seen in the case where the quaternizing agent is the 2,4-dinitrophenyl group and a sulfur analog of the enol ether is used. In this case the lone pair of electrons on nitrogen is delocalized on the aromatic ring and helps prevent expulsion of the methoxyl group. The next step in our sequence would have been the acid catalyzed ring opening of the bicyclic adduct to yield a carbonyl type intermediate that could be trapped by the nitrogen at the 5-position of the isoquinoline. This step was not practical probably due to the availability of the lone pair on the nitrogen. The hydrolysis probably requires a deactivated nitrogen (ie. one with a 2,4 dinitrophenyl attached). Because of this we decided to continue our work involving the cycloaddition of 2,4-dinitrophenyl-5-acetylaminoisoquinoline with phenyl vinyl sulfide.

B. 5-ACETYLAMINOISOQUINOLINIUM CYCLOADDITIONS

3.1 5-Acetylaminoisoquinolinium Salt Formation

Due to the ring opening problems associated with the 2-methyl isoquinolinium salt our attention focused on effecting the cycloaddition using the 2,4-dinitrophenyl salt used successfully by Falck and our lab. We decided to start the synthetic sequence with 5-nitroisoquinoline **B1** followed by reduction to 5-aminoisoquinoline **B2** and blocking the amino group as the acetyl derivative **B3**, a known procedure[16]. The reduction is carried out in a Parr Hydrogenator with 10% palladium on charcoal in ethanol solution. It can also be effected in equivalent yields using Raney-Nickel in ethanol. The 5-aminoisoquinoline is protected with acetic anhydride in acetic acid without further purification to give 5-acetyl-aminoisoquinoline **B3**. The product is isolated in 89% yield as an off white solid by precipitation from the reaction mixture using concentrated ammonium hydroxide

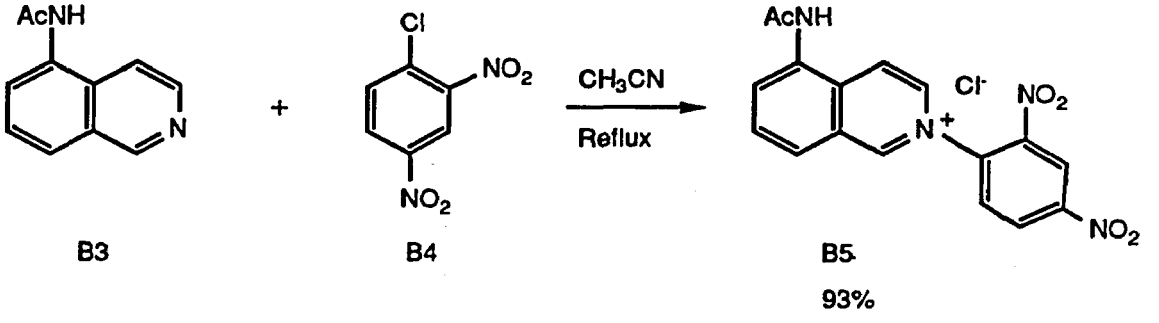


B1 B2 B3

89%

Scheme **VII**. Formation of 5-N-Acetylaminoisoquinoline

followed by filtration. Salt formation is accomplished by treating the 5-acetyl-aminoisoquinoline **B3** with 1-chloro-2,4-dinitrobenzene **B4** in refluxing acetonitrile. After solvent removal the 2-2,4-dinitrophenyl-5-acetylaminoisoquinolinium chloride **B5**, an orange solid is washed with anhydrous methylene chloride to give the product in 93% yield.



B3 B4 B5

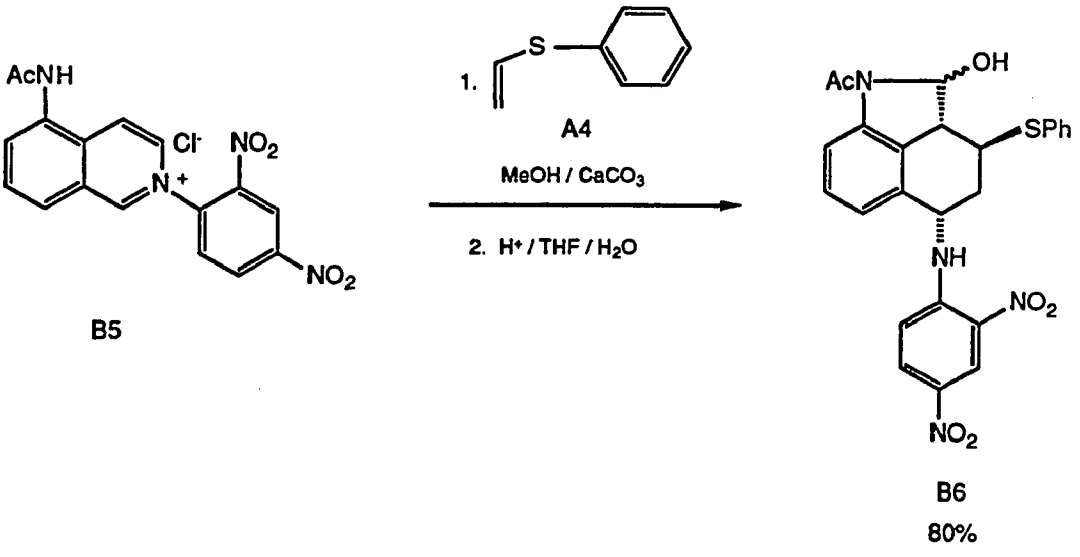
93%

Scheme **VIII**. N-Acetyl Salt Formation

The subsequent step would be to carry out the cycloaddition. The decision was made to perform the cycloadditon followed by immediate acid treatment to give the ring opened product. As stated before the ring opening of the tricyclic adduct is of vital importance to the synthetic scheme because it could give the hydroxyindoline that is needed and as reported by Pleininger or it could give a fused oxazapine as reported by Sammes.

3.2 Hydroxyindoline Formation

The cycloaddition was carried out by dissolving the isoquinolinium salt **B5** in anhydrous methanol followed by subsequent addition of 6-7 equivalents of anhydrous calcium carbonate and the dieneophile, phenyl vinyl sulfide **A4**. The reaction proceeded smoothly in 24 hours under an argon atmosphere. After filtration of the reaction mixture through celite to remove the calcium carbonate followed by washing the filter pad with tetrahydrofuran the intermediate adduct was dried in vacuo. The mixture was immediately dissolved in tetrahydrofuran and treated with dilute aqueous hydrochloric acid. The product of the reaction was isolated as a bright yellow solid by precipitation with water in 80 % yield. NMR of the product showed that the product is the desired 1-acetyl-2-hydroxy-3-thiophenyl-5-(2,4-dinitrophenyl)-amino-1,2,2a,3,4,5-hexahydro-benz[cd]indole **B6**.

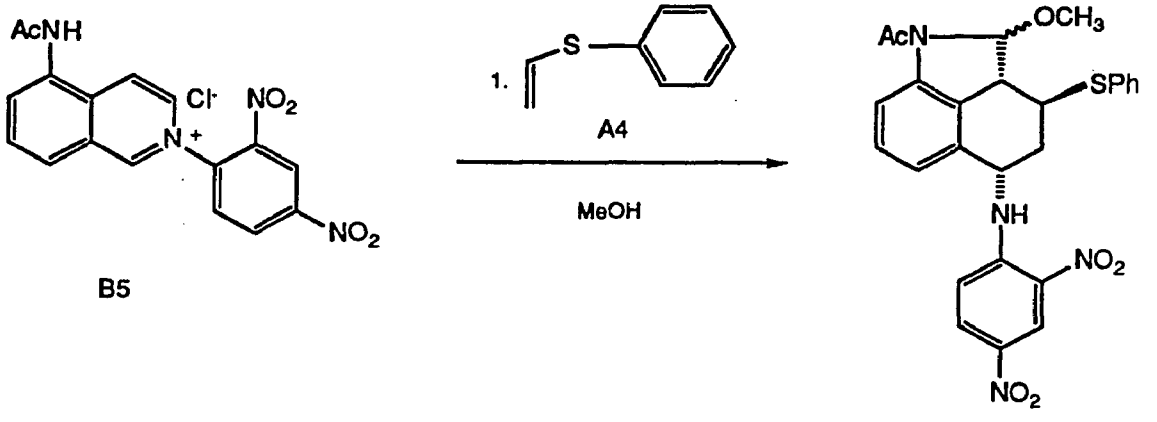


Scheme **IX**. Acetylamino Salt Cycloaddition

The aromatic region displayed a total of 13 protons which would be expected based on the 11 aromatic protons plus the amino proton on the dinitrophenyl group and the C_{2a} amino acetal proton. The three protons on the 2,4-dinitrophenyl ring along with the N-H (δ = 8.3 ppm) proton had the typical appearence for a ring opened cycloadduct. An indication that we did have the product based on the cyclization of the amine with the aldehyde is the presence of the acetal type proton as a doublet (δ=6.93 ppm, J=8.75 Hz). Decoupling experiments showed this proton to be coupled to the C_{2a} benzylic proton (δ=5.95 ppm). The hydroxyl proton appeared at δ=2.30 ppm. The aliphatic region displayed a total of 9 protons which is expected if one includes the 3 protons of the -OAc, the hydroxyl proton, the C_{2a} benzylic proton, and the protons alpha to the sulfur and amino functional groups. The ^{13}C spectrum showed a total of 6 carbons below 100 ppm. The amino-acetal type carbon appears at 85.8 ppm and the 2 carbons attached to the 2,4-DNP amine and the thiophenyl group appear in the 45-50 ppm range. The C_{2a} carbon and the C_4 carbon have chemical shifts at 36-38 ppm. The methyl group of the acetal shows up at 23 ppm.

When phenyl vinyl sulfide **A4** was used as the dienophile, the cycloaddition could be run without the presence of the acid scavenger $CaCO_3$. Vinyl sulfides are more stable to acid and can therefore survive the equivalent of acid produced in the reaction. When the reaction is run (Scheme **IXa**) the product is the 2-methoxy indoline **B6a** although the yield is only 51%. ^1H NMR of this product was similar to the hydroxyindoline reported above but instead of having a hydroxyl peak at

δ=2.3 ppm the spectrum displayed a singlet for the methoxyl group at δ=3.49 ppm. There were slight differences in the chemical shifts between the two compounds but these may be attributed to the difference in solvents used to take the NMR, $CDCl_3$ vs DMSO-d_6.

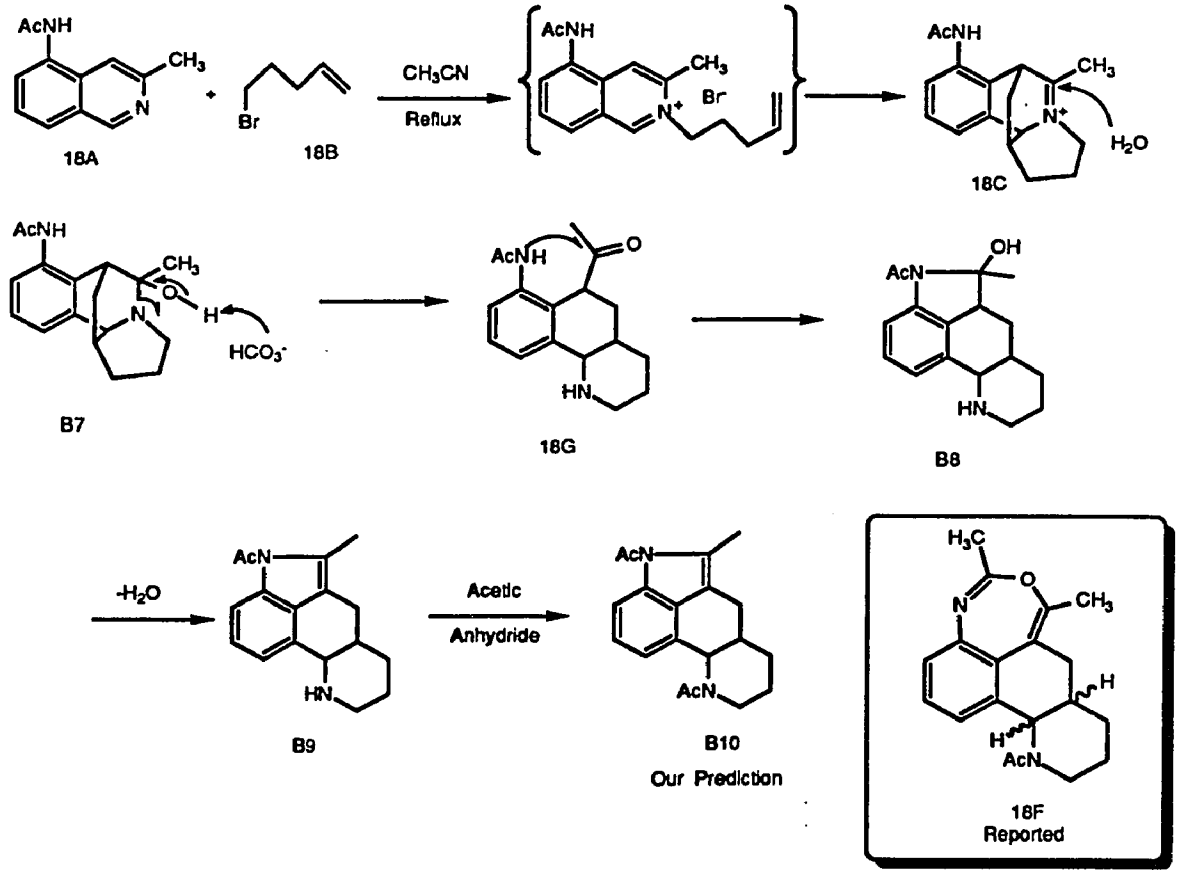


Scheme **IXa**. Acetylamino Cycloaddition Without Calcium Carbonate

3.3 Sammes Work - Our View

Based on the our results from the above work, we decided to reexamine the results reported by Sammes. It would seem that the product obtained by Sammes may not have been the fused oxazepine but rather an indole derivative as shown in scheme **X** below. As Sammes reported, the intramolecular cycloaddition proceeded to give the cycloadduct **18C** but the hydrolysis probably did not produce

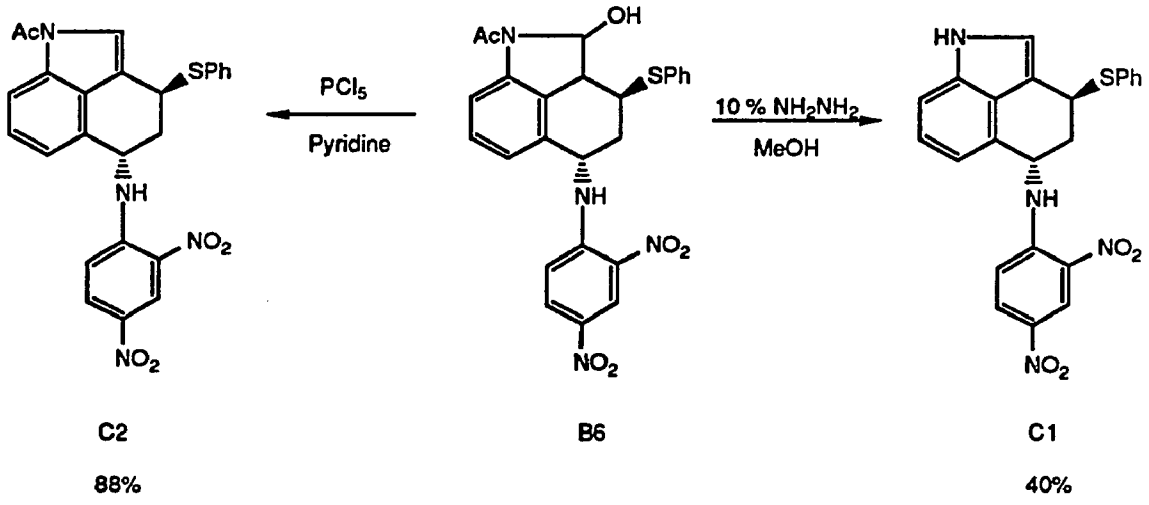
the reported fused oxazapine **18F**. According to our results the iminium ion adduct was trapped as the intermediate **B7** which is then deprotonated followed by C-N bond cleavage to give the ring opened hydroxyindoline **B8** which is also tertiary alcohol. Under the reaction conditions the alcohol could dehydrate to give the indole **B9**. After acetylation, we predict the product obtained is the indole derivative **B10** and not the fused oxazapine derivative reported (See Scheme **XV**. on page 27). Sammes NMR data is consistent with either structure **18F** or **B10**, but our evidence for indole formation suggests strongly that our structure proposal for his result is more reasonable.



Scheme **X**. Sammes Work - Our View

3.4 Indole Formation

With our synthetic scheme, the next step would be the dehydration of the 2-hydroxyindoline to give the indole. Unfortunately the dehydration could not be effected using general acid or base catalysis. The first successful attempt was achieved when the hydroxyinoline **B6** was treated with a solution of 10% hydrazine in methanol. The product obtained was the deacetylated indole **C1** with the thiophenyl and the 2,4-dinitrophenylamino group still attached in 33% yield. One problem with this reaction was the insolubility of the hydroxyindoline in the reaction medium. Dehydration to the indole can be achieved in very high yield by treatment of the hydroxyindolene with phosphorus pentachloride in pyridine solvent (Scheme **XI**).



C2 88%

B6

C1 40%

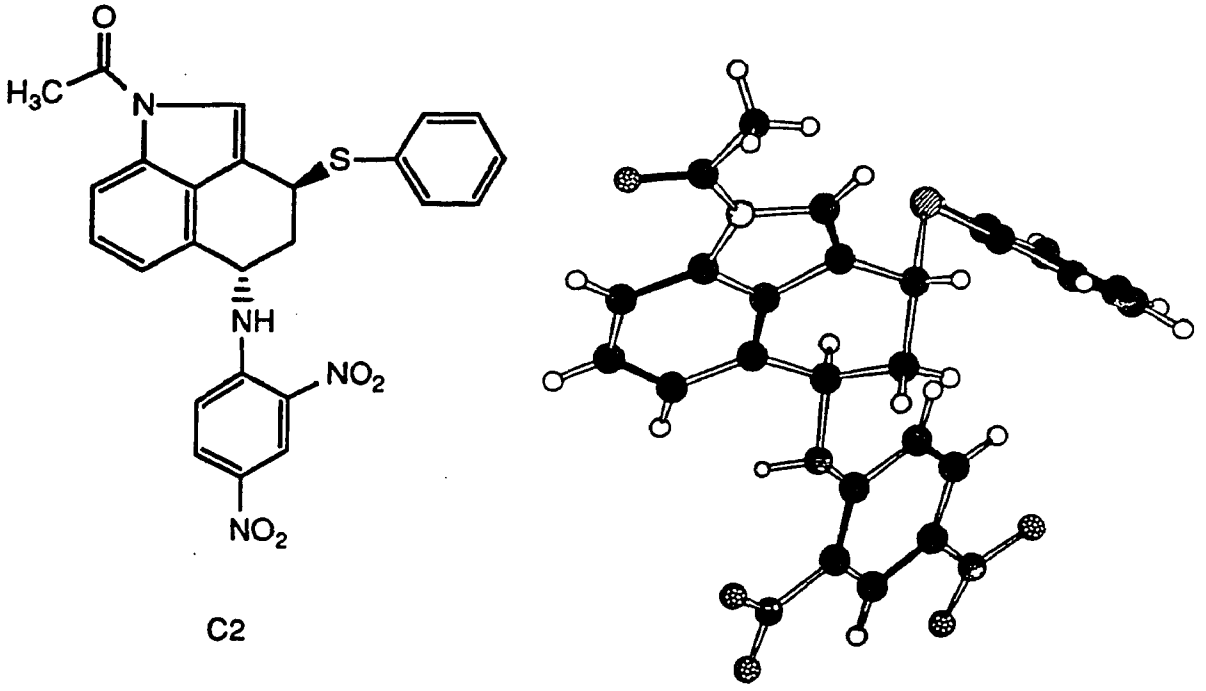
Scheme **XI**. Formation of Indole

The product of this reaction is 1-acetyl-3-thiophenyl-5-(2,4-dinitrophenyl)-amino-tetrahydrobenz[cd]indole **C2** in 88% yield after chromatography. The solubility of the hydroxyindoline was much greater in pyridine than in the previous reaction conditions. Evidence for this was the appearence of broad singlet at δ = 7.1 ppm in the ^{1}H NMR spectrum that is typical of an indole C-2 proton. The ^{1}H NMR spectrum exhibits four protons below δ=6 ppm which would be expected for the dehydrated product. A downfield shift of the C_3 proton from δ=3.25 ppm to δ=4.95 ppm due to the presence of the new double bond. Disappearance of two signals at δ = 85.9 (C-2 acetal type carbon) and δ = ~ 50 ppm (C-2a benzylic carbon) in the ^{13}C NMR spectrum and the appearence of two extra signals in the δ = 110 - 120 ppm also would indicate the indole formation. It is noteworthy to point out that the cycloaddition and dehydration have been carried out on a large scale of approximately 20 grams and have worked equally well. The cycloaddition produced a higher yield on the larger scale, 80% vs. 63% and was most probably due to less loss of product during filtration and washing. The dehydration exhibited the opposite result giving 80 % yield on the large scale as opposed to 88% on a small (1 mm) scale.

3.5 Indole X-Ray Structure

The indole could be recrystallized from a solution of ethyl acetate by slow precipitation by petroleum ether. This was done by placing the solution of the indole in a flask inside a closed chamber containing a larger amount of petroleum ether. An x-ray crystallographic structure of the indole was obtained and revealed

many interesting features about the molecule during the process. According to the initial data on the molecule, it had a very high density of 1.42. This was confirmed by observing that the crystals would sink in dichloromethane ($\rho = 1.325$) and float in chloroform ($\rho = 1.492$). The high density of the molecule indicated that the



C2

Figure V. X-Ray Structure of Indole **C2**

unit cell was very tightly packed and in fact it was found to contain a total of eight molecules. The structural proof that we did indeed have the correct molecule is shown in figure **V**. The structure shows that the 3-thiophenyl group and the 5-(2,4-

dinitrophenyl)-amino group are trans to each other. This would be expected based on the mechanism of the cycloaddition. One would also expect to see two enantiomers present due to attack by the vinyl sulfide dieneophile from both faces of the isoquinolinium salt. This was in fact observed but much to our surprise the two species observed in each assymetric unit of the unit cell were not merely enantiomers but conformers. This is illustrated in figure **VI**. The two molecules are enantiomers with respect to C-3 and C-5 but their ring conformations are different.

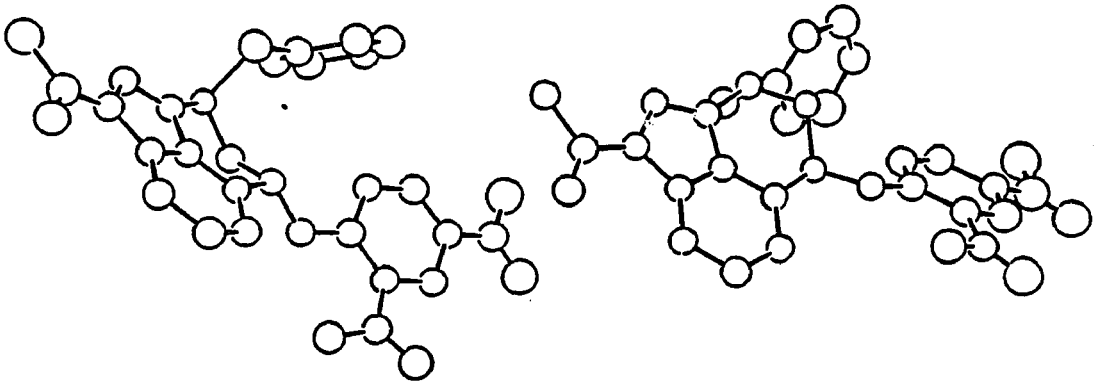


Figure **VI**. Conformers of Indole **C2**

Each enantiomer was present in its other conformer which are corresponding enantiomers giving a total of four observable species. Since there is a C_2 axis present for the crystal structure this would give rise to eight molecules per unit cell which is what is observed.

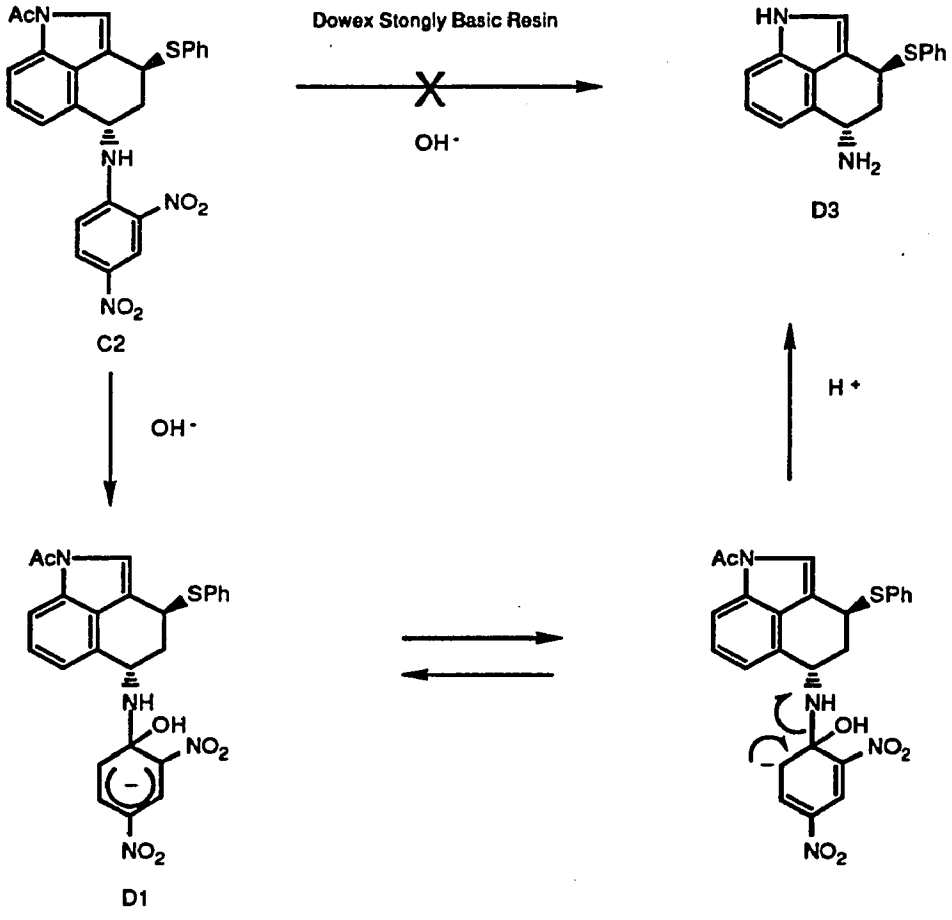
3.6 Removal of the 2,4-Dinitrophenyl Group

The ensuing stage for our synthetic scheme would either require the removal of the 3-thiophenyl group or the dinitrophenyl group from the 5-amino substituent. The choice was to dedinitrophenylate rather than desulfurize the molecule because the reagents generally used for desulfurization would probably interfere with the dinitrophenyl group. Raney-nickel would almost certainly reduce the nitro groups and the radical chain reaction of tributyltin hydride might react with these groups also.

The standard dedinitrophenylation procedure is carried out using Amberlyst OH^- strongly basic resin in acetone[17] solvent and usually does not give exceptional yields. The reaction proceeds by nucleophilic substitution on the 1-position of the dinitrophenyl ring to give the Meisenheimer adduct **D1** shown in scheme **XII**. The reaction can then either reverse to give hydroxide ion and starting DNP-amine or eliminate the $R\text{-}NH^-$ which protonates to give the deblocked amine **D3**. One general problem with this procedure is that the acetone solvent, in which the reaction is carried out reacts with the basic resin to give a variety of condensation products. These are generally not easily separated from the reaction product. The reaction mixture is normally subjected to high vacuum and heated

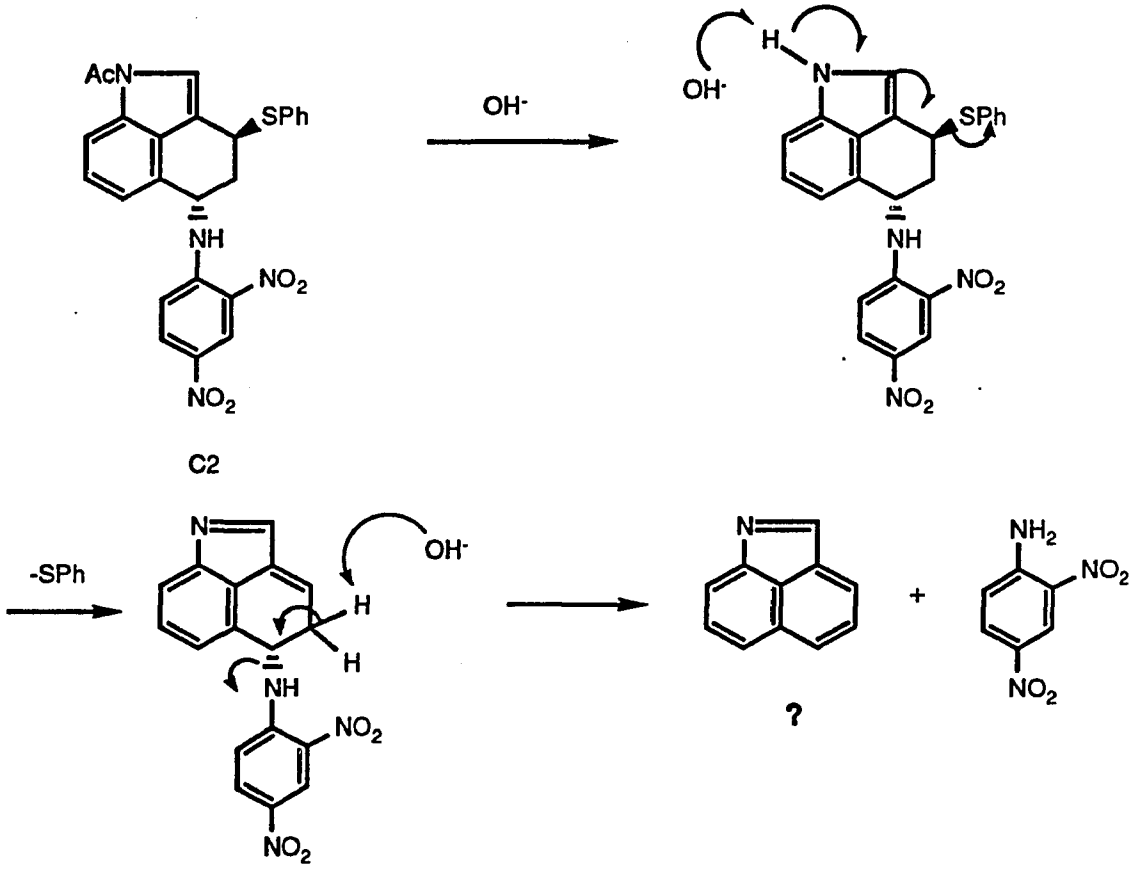
for extended periods of time in order to evaporate these side products.

When our indole **C2** was subjected to the standard reaction conditions, it turned from yellow to dark brown in color, and gave no identifiable products other than some starting material as evidenced by the NMR spectrum of the crude product. This was also the case when indole **C2** was treated with sodium hydroxide in tetrahydrofuran. One problem that could arise here is the



Scheme **XII**. Standard Dedintrophenylation Mechanism

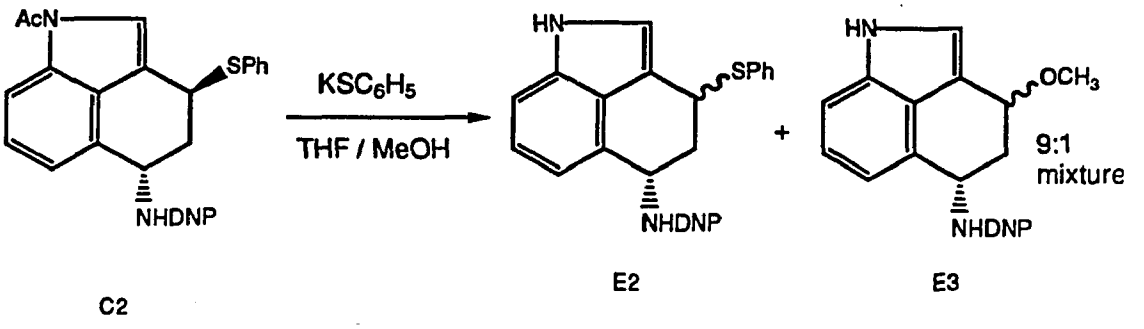
reaction of base sensitive groups attached to the molecule. If the indole was deacetylated the molecule could undergo further elimination and aromatization (scheme **XIII**) through loss of 2,4-dinitroaniline and thiophenol although no explicit proof of this was observed.



Scheme **XIII**. Possible Reaction of Indole and Strong Base

Because of the potential problems with using a strong base we decided to try a better nucleophile in the form of thiophenoxide anion. The indole **C2** was treated

with 4.0 equivalents of potassium thiophenoxide **E1** in THF / MeOH (2:1) in the presence of 18-crown-6 to give a mixture of isomers of the two products shown in scheme **XIV**.



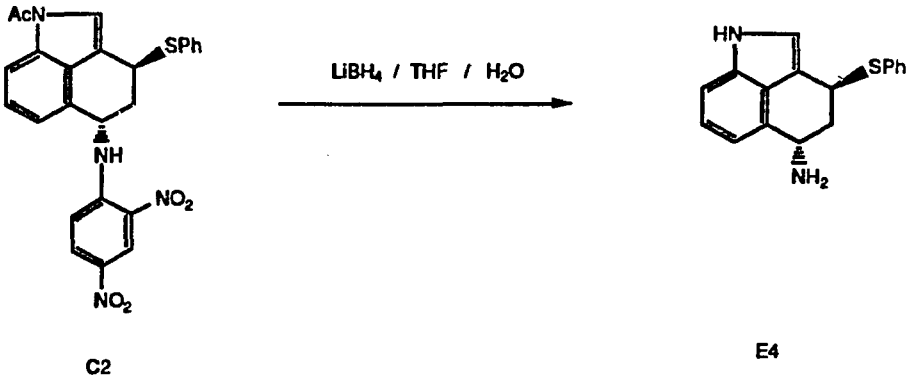
Scheme **XIV**. Reaction of Indole and Thiophenoxide

All of the compounds had the indole deprotected based on the disappearance of the acetyl peak in ^{1}H NMR. The products were a mixture of isomers at the carbon next to the thiophenyl group **E2** and a mixture of isomers where the thiophenyl group was replaced by a methoxyl group **E3**. The thiophenyl mixture appears to have undergone epimerization at the C_3 carbon based on the ^{1}H NMR which shows all the peaks doubled up. For the product where the thiophenyl group was replaced by a methoxy group, the product appeared to be a 9:1 ratio (based on the ratios of the two methoxyl peaks in the NMR) of epimers. The main diastereomer displayed the methoxyl peak at δ=3.40 ppm and there was a slight upfield shift of the C_3-H to 4.71 ppm from δ=4.95 ppm in the thiophenyl substituted

compound. There were also small changes in the chemical shift of the C_4 protons. This lends further evidence to the base sensitivity of the compound. Since the replacement of the thiophenyl group was taking place so readily we thought it would be nice if it could be replaced by a hydrogen nucleophile in the form of a hydride.

3.7 $LiBH_4$ Dedinitrophenylation

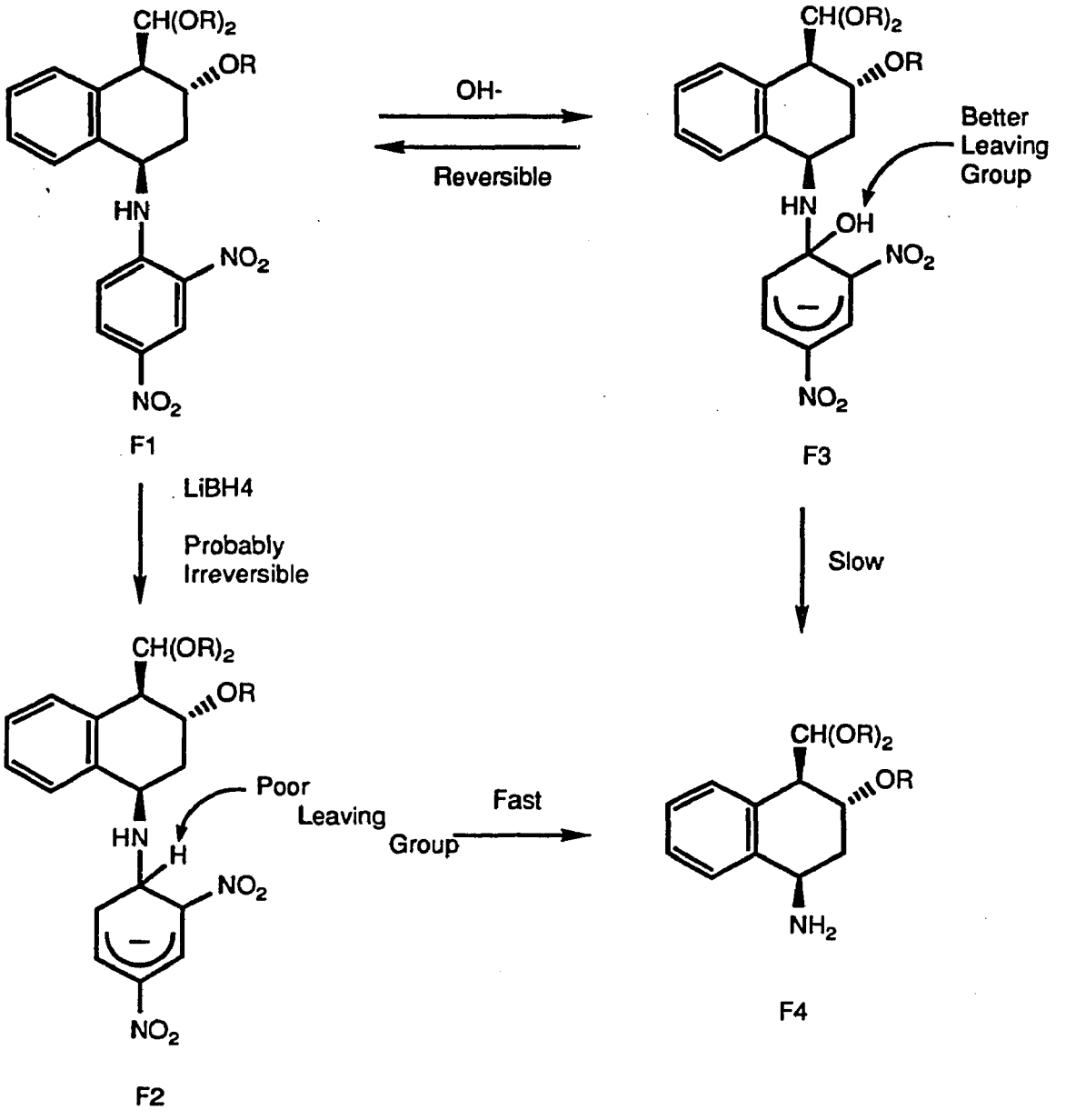
When the indole **C2** dissolved in THF was treated with a borohydride dissolved in isopropanol containing one equivalent of water the yellow solution immediately turned deep red in color. This color in these compounds is usually a sign of some anionic species due to nucleophilic attack on the 2,4-dinitrophenyl ring. After approximately 1 hr the solution became pale yellow in color again. The reaction was worked up by addition of water and bicarbonate to make the solution basic followed by extraction into organic solvent. After concentration, crude ^{1}H NMR, much to our surprise, showed the 2,4-dinitrophenyl group was removed along with the acetyl group (Scheme **XV**). The three protons for the 2,4-dinitrophenyl group at δ= 9.2, 8.25 and 7.0 ppm were not present. The singlet at δ=2.6 ppm for the acetyl group was also not present and a broad singlet at δ=8.08 for the indole N-H was now found. This peak was the only downfield peak below δ=7.6 ppm. The chiral carbon bearing the S-phenyl substituent appeared to be epimerized based on the doubling of the peaks in the aliphatic region.



C2 E4

Scheme **XV**. Reaction of Indole **C2** with Borohydride

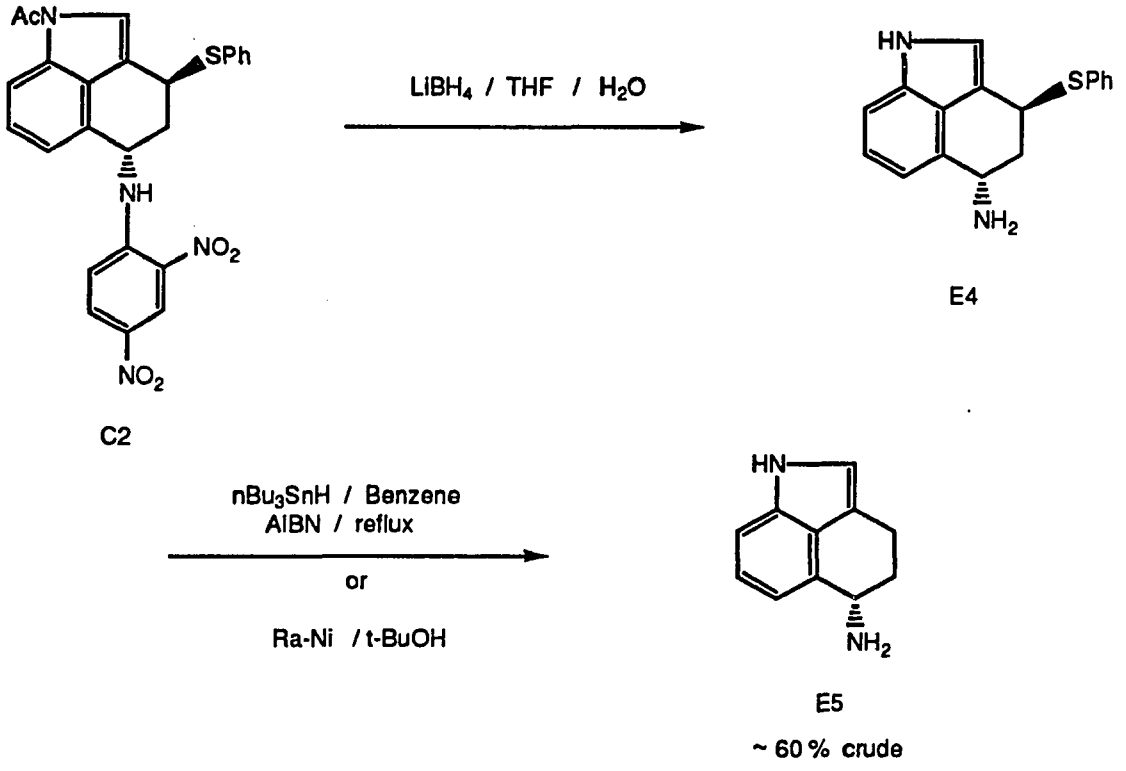
As stated previously, the removal of the 2,4-dinitrophenyl group by a hydride was an unexpected result. Since the initial step of the dedinitrophenylation involves the nucleophilic attack on the aromatic ring, it is not expected that a hydride would cause the reaction to occur and the superior nucleophile, thiophenoxide would not. Proposing the following reaction mechanism (scheme **XVI**), one can rationalize why the hydride can cause the dedinitrophenylation to occur. The first step in the reaction scheme is attack by the hydride on the ipso position of the 2,4-dinitrophenylamino group to give the Meisenheimer adduct **F2**. Two possibilities exist as to how the adduct can react. Elimination of NH^- can occur followed by protonation to give the amino product **F4** or reversal of the original attack by loss of hydride can occur to give the starting material **F1**. In the case of the hydride, reversal would not be likely because NH^- is a better leaving



Scheme **XVI.** Hydride Dedinitrophenylation Mechanism

group than hydride. This is probably not the case when hydroxide is used. In this situation hydroxide is a better leaving group than NH^- and therefore the reaction proceeds slowly and may be the cause for poor yields observed in some cases.

The 3-thiophenyl-5-amino-1,3,4,5-tetrahydrobenz[cd]indole **E4** was very unstable and we were unable to purify it by chromatography. Due to the compound's instability we decided it was best to take the 3-thiophenyl-5-aminotetrahydro-benz[cd]indole and immediately desulfurize the compound



Scheme **XVII.** Indole Rxn with Borohydride and then Desulfurized

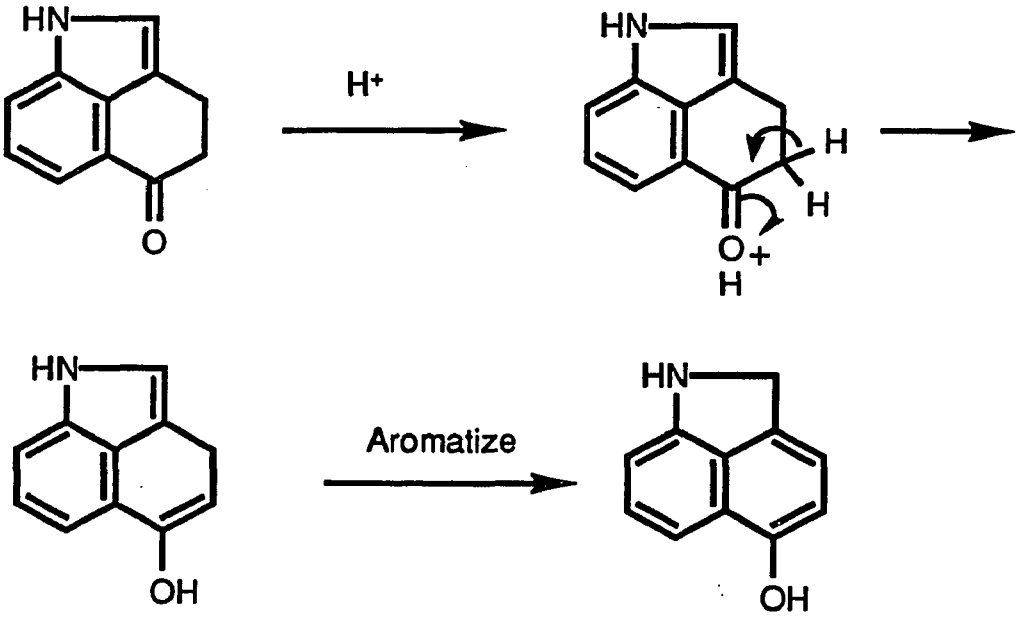
with tributyltin hydride. This synthetic strategy does work and is best accomplished using the conditions described below and illustrated in scheme **XVII.**

The indole dissolved in tetrahydrofuran was treated with lithium borohydride dissolved in isopropanol with one equivalent of water present. When the borohydride solution was injected into the solution containing the indole the yellow solution immediately turned deep red in color. After approximately 1 hour the red solution turned yellow in color again. The product obtained from this reaction after concentration was dissolved in benzene and a catalytic amount of AIBN added. The solution is degassed and then tributyltin hydride added and the mixture set up to reflux. The time for desulfurization varies greatly mainly due to an initiation period for this radical process. The progress of the reaction is monitored by tlc and worked up when the starting material is gone. The aminoindole **E5** was isolated by diluting the mixture with benzene and extracting into 10% aqueous HCl, then neutralizing with sodium bicarbonate and extracting the product into ethyl acetate followed by concentration to give a 60% yield of 5-amino-1,3,4,5-tetrahydrobenz[cd]indole as a dark brown oil. This appears to be a good way of separating the product from any excess tin compounds. Desulfurization can also be effected using Raney-nickel in refluxing t-butanol. The reaction is complete in 24 hours with the product being isolated by filtration through celite followed by concentration in vacuo. ^{1}H NMR (DMSO-d_6) of the aminoindole features five protons in the aromatic region. The indole N-H appears as a broad singlet at δ=10.5 ppm and the three aromatic protons and the indole proton appear between δ=6.9-7.2 ppm. The C_5 proton has now shifted upfield to δ=4.05 due to the elimination of the 2,4-dintrophenyl group. The primary amino protons appear at

δ=3.2 ppm as a broad singlet. Amine **E5** appears to be air sensitive and upon standing, even for short periods of time, turns brown in color. Repeated attempts at purifying the aminoindole such as chromatography (silica gel, florisil and alumina) and recrystallization have not furnished a white solid as was reported in the literature.[18] NMR of this product showed the product to be moderately pure and it is used without further purification.

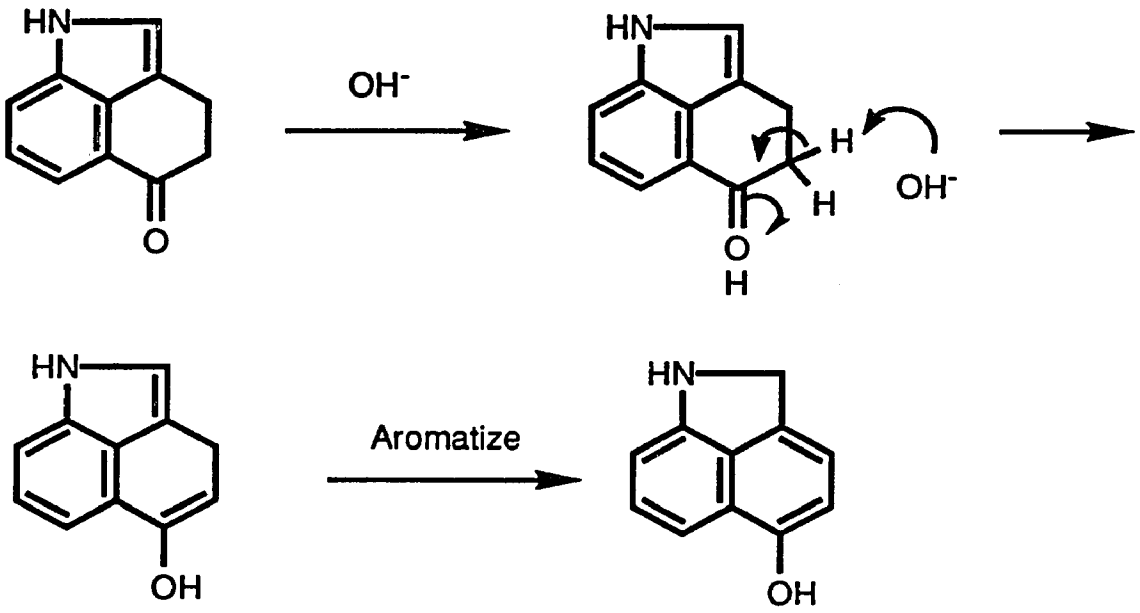
3.8 Oxidation of 5-Amino-Tetrahydrobenz[cd]indole

The next step was to undertake the oxidation of the amine **E5** to the ketone **III**, the final product in our synthetic scheme. Due to the presence of the easily oxidizable indole ring we needed to use a very mild oxidizing agent. This step has proved more difficult than we originally assumed. One must also consider the acid and base sensitivity of the final ketone **III**. If the ketone is treated with acid the



Scheme **XVIIa**. Uhle's Ketone Reacting With Acid

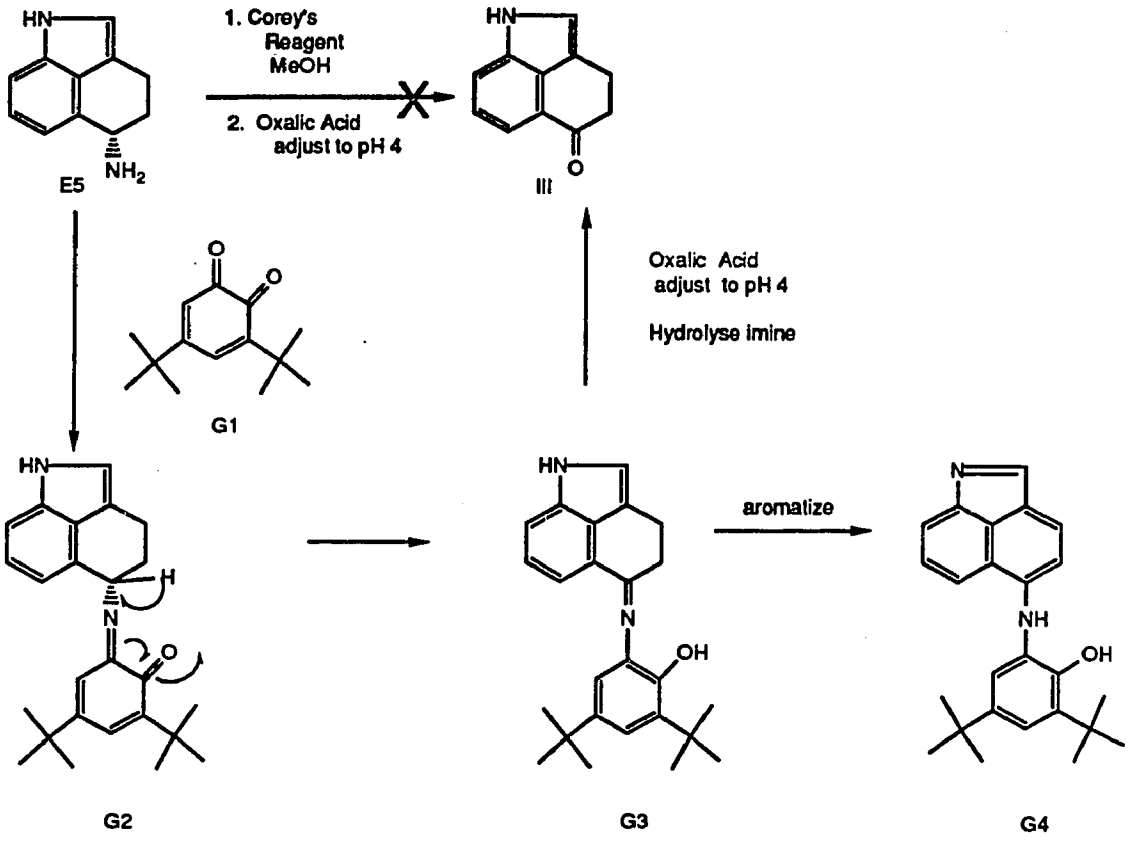
ketone may enolize and then aromatize to the napthenoid compound (Scheme **XVIIa**). The ketone is also base sensitive and may also enolize and rearrange to the napthenoid derivative (Scheme **XVIIb**).



Scheme **XVIIb**. Uhle's Ketone Reacting With Base

We decided to try Corey's reagent 3,5-di-t-butyl-1,2-benzoquinone[19] **G1** since it was used for similar amine oxidations in our lab. When this compound was treated with the reagent in methanol followed by acidification the major product isolated according to NMR data was the fully aromatic compound **G4**. ^{1}H NMR only showed the presence of aromatic protons and the two t-butyl groups at δ =

1.5 ppm and 1.3 ppm. There were no aliphatic protons in the range of δ = 2 to 6 ppm. The aromatic region appears to show on seven protons when one would expect eight according to the structure. It is also not evident from the NMR where

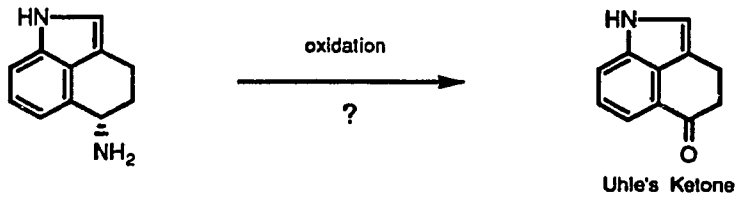


Scheme **XVIII**. Oxidation of Aminoindole With Corey's Reagent

the hydroxyl or amino protons show up. Based on the NMR data the product isolated is not the expected one and reaction was extremely messy according to tlc, showing many spots, including some that were highly colored. This product

probably arises from initial formation of the imine **G2** which tautomerizes to the enamine **G3** which then aromatizes. After the failure of this reagent we began the task of testing a variety of oxidizing agents.

A literature search revealed a number of mild oxidizing agents to be tested. A number of unsucessful attempts have been made with reagents such as nitrosobenzene[20], and diphenylselenic anhydride[21], manganese dioxide, and sodium hypochlorite. The oxidations involving nitrosobenzene and diphenylselenic anhydride did not produce identifiable products. As was seen with Corey's



Uhle's Ketone

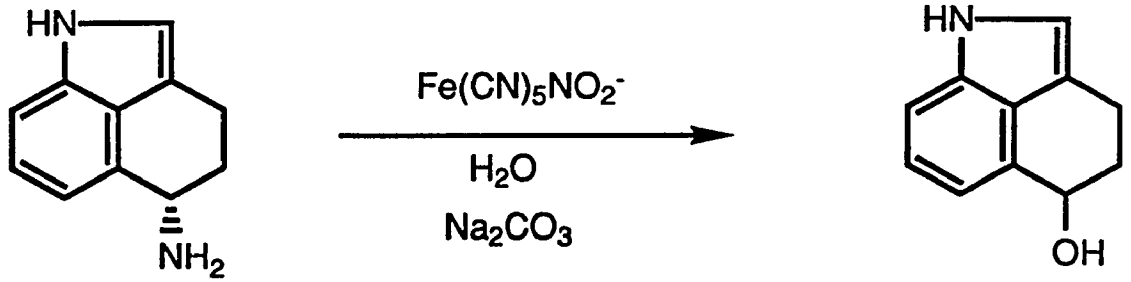
Oxidation Reaction	Reaction Conditions	Result
Corey's Reagent	3,5-di-t-Butyl-1,2-benzoquinone/ MeOH. 2. Adjust to pH 4	Aromatization
MnO_2	MnO_2 / EtOAc	Aromatization
NaOCl	5% NaOCl / CH_2Cl_2 cat. tetrabutylammonium bisulfate	Reacts with Indole
Silver Persulfate	$AgNO_3$/Potassium Persulfate NaOH/ H_2O/THF	Very Low Yield of Ketone

Table I. 5-Amino-Tetrahydrobenz[cd]indole Oxidations

reagent, when the indole was treated with manganese dioxide in ethyl acetate the molecule seemed to aromatize. When the amino indole was treated with sodium hypochlorite the product was a brown messy tar probably due to the hypochlorite reacting with the indole. This same type of reaction was observed when indole was treated with the same reagent. The first reaction with any success was using silver nitrate and persulfate in aqueous solution[22]. The reaction produced the desired ketone but in very poor yield, approximtely 10%.

3.9 Oxidation of Aminoindole to Hydroxyindole

Due to the problems encountered with oxidizing the amine to the ketone we decided to convert the amino group to a hydroxyl group because of the greater variety of oxidizing reageants available and greater stability. Oxidation of the



E5 H1

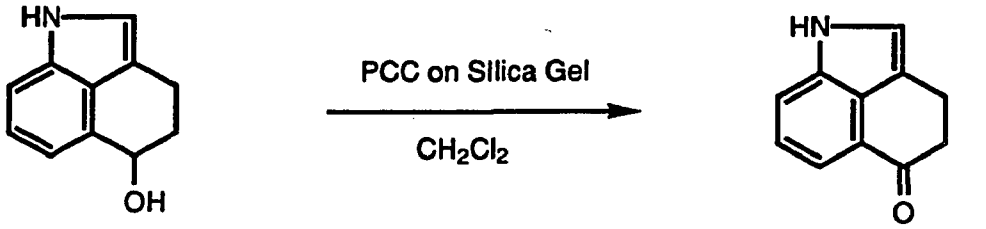
Scheme **XIX**. Oxidation of Aminoindole with Nitroprusside

amine was accomplished with sodium nitroprusside a mild oxidizing agents for amines[23]. The amino indole **E5** was treated sodium nitroprusside and sodium carbonate in water to give 5-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole **H1** (Scheme **XIX**) in 23% yield. ^{1}H NMR displayed the presence of five protons in the aromatic region. The indole N-H appeared at δ=8.00 ppm as a broad singlet followed by the three aromatic protons between δ 7.1-7.4 ppm and the indole proton as a singlet at δ=6.95 ppm. The C_5-H was found at 5.16 ppm and the hydroxyl proton at δ=1.7 ppm as a very broad singlet.

3.10 Oxidation of Hydroxyindole to Uhle's Ketone

The final step of the sythetic sequence was the oxidation of 5-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole **H1** to Uhle's ketone **III**. This step was accomplished by treating the hydroxy compound with pyridinium chlorochromate on silica gel in methylene chloride[24] (Scheme **XX**). After purification by column chromatography the target compound was isolated in 24 % yield but contained a small amount of impurity. Further purification by radial chromatography gave Uhle's Ketone **III** as a yellow solid with a melting point of 162 - 164 °C which matches the published melting point.[3] NMR of the reaction mixture exhibited the characteristic signals published for Uhle's Ketone[5], two triplets at δ = 2.9 and 3.3 ppm, a singlet at δ = 7.1 ppm for the C_2 indole proton, a triplet at δ = 7.3 ppm along with doublet at δ =7.5 and 7.6 ppm for the aromatic protons and a singlet at δ = 8.3 ppm for the indole N-H. For our product the C_3 and C_4 protons appeared

at δ = 2.9 and δ = 3.3 ppm respectively. The indole N-H proton appeared at δ = 8.3 ppm as a broad singlet and the neighboring C_2 proton appeared at δ = 7.1



H1 III

Uhle's Ketone

Scheme **XX**. Oxidation of 5-Hydroxy-1,3,4,5-Tetrahydrobenz[cd]indole

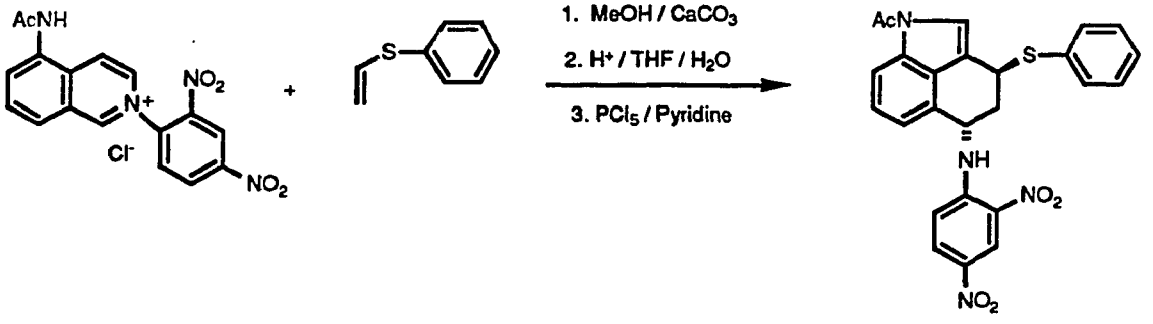
ppm as a singlet. It is also interesting to note that when the ketone was left for 12 hours dissolved in $CDCl_3$ during a ^{13}C NMR spectrum, the color turned from light yellow to purple with some solid matter floating inside the tube. It is possible that decomposition occurs due to the presence of a small amount of hydrogen chloride present in the solvent. The infrared spectrum showed absorbances at 3260 (N-H), 1655 (C=O), along with 1622 and 1605 cm^{-1} (C=C ring system). These compare well with the absorbances of 3260, 1655, 1605, and 1496 cm^{-1} (KBr) published by Meyer and Kruse[5] and 3185, 1645, 1610, 1596, 1491 cm^{-1} (Nujol) published by Bowman et al.[4] High resolution mass spectrum (EI) calculated for $C_{11}H_9NO$ (Uhle's

Ketone) is 171.068 and our reaction product exhibited a molecular ion at 171.0672 also substantiating that our product is indeed Uhle's Ketone **III**, identical with the material obtained previously.

C. HAPALINDOLE FRAMEWORK

4.1 Similar Indole Ring Systems

As has been demonstrated by our previous synthetic route the cycloaddition of isoquinolium salts is a very effective method for constructing the tetrahydrobenz[cd]indole skeleton. Since our construction of 1-acetyl-3-thiophenyl-5-(2,4-dinitrophenyl)amino-tetrahydrobenz[cd]indole shown in scheme I, worked so



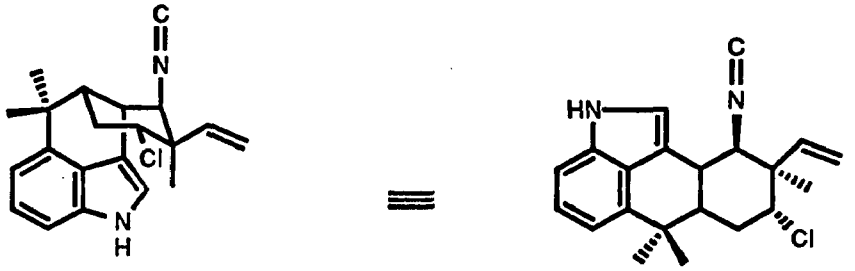
Scheme I. Indole Synthesis I

well we decided to examine the construction of other related indole systems. The construction of the indole system above is basically a two step process and the overall yield for both steps is approximately 70 %.

4.2 First Hapalindoles Isolated

In a 1984 communication, R.E. Moore and coworkers[25] reported the isolation and characterization of two compounds of a related indole system. The compounds were isolated from the marine alga *Hapalosiphon fontinalis* collected in the Marshall Islands and then cultured in the laboratory. These alga have been

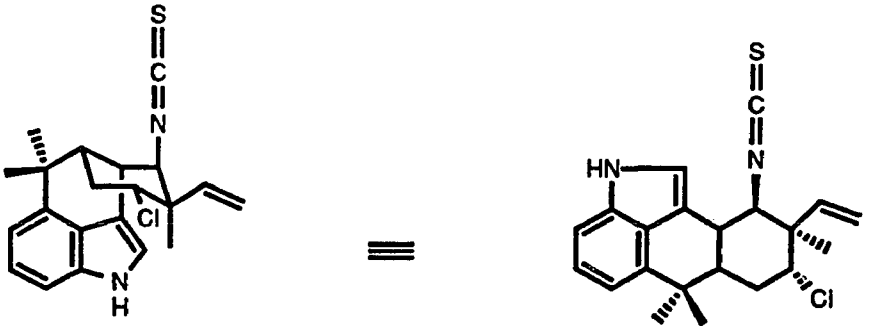
found to have antimycotic and antialgal activity. Separation was accomplished by extracting the freeze dried alga with 1:1 propanol / methylene chloride, with the resulting mixture subject to rapid chromatography on silica gel usin hexane, 1:1 hexane/CH_2Cl_2, CH_2Cl_2, CH_2Cl_2/EtOAc, EtOAc, and EtOAc/EtOH. The fraction containing this new framework, 1:1 hexane / CH_2Cl_2, was further purified by



AA1

Hapalindole A

Small amounts of Related Compounds Including:

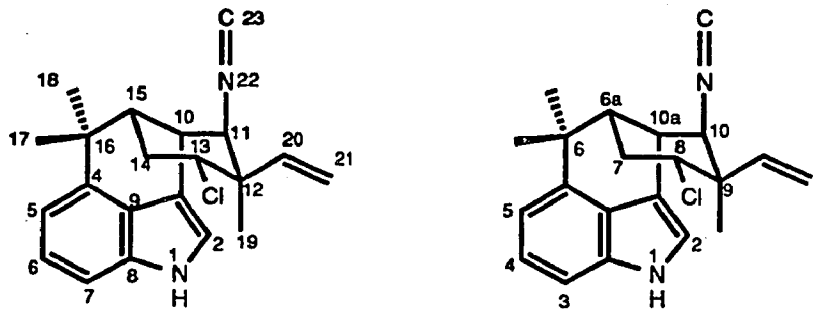


AA2

Figure **VII**. First Hapalindoles Isolated

preparative HPLC to yield Hapalindole A **AA1** as shown above. It was also reported that smaller amounts of several related compounds including **AA2** were isolated. Hapalindole A was reported to be responsible for the antimycotic and

antialgal activity displayed by this alga. It is interesting to note the substiuents on the fourth ring of the tetracyclic structure. The chlorine on C-13, the geminal methyl and allyl groups on C-12, the isonitrile or isocyanate on C-11 and the geminal dimethyl group at C-16 make this an attractive molecule. The numbering procedure for the skeleton of hapalindole A is shown in Figure **VIII**.



Literature Numbering

Chemical Abstracts Numbering

Hapalindole A

Figure **VIII**. Hapalindole A Numbering System

4.3 Other Hapalindoles Isolated

More recently the same authors described the isolation and structure proofs of eighteen more indoles, hapalindoles C-Q and T-V[26]. As can be seen from the structures in Figure **IX**, the stereochemistry and substitution pattern of the different hapalindoles is quite varied. Five of the hapalindoles, C,D,E,F,Q, do not have a tetracyclic ring structure but rather have a tricyclic ring system where the C-4 to C-16 bond is broken.

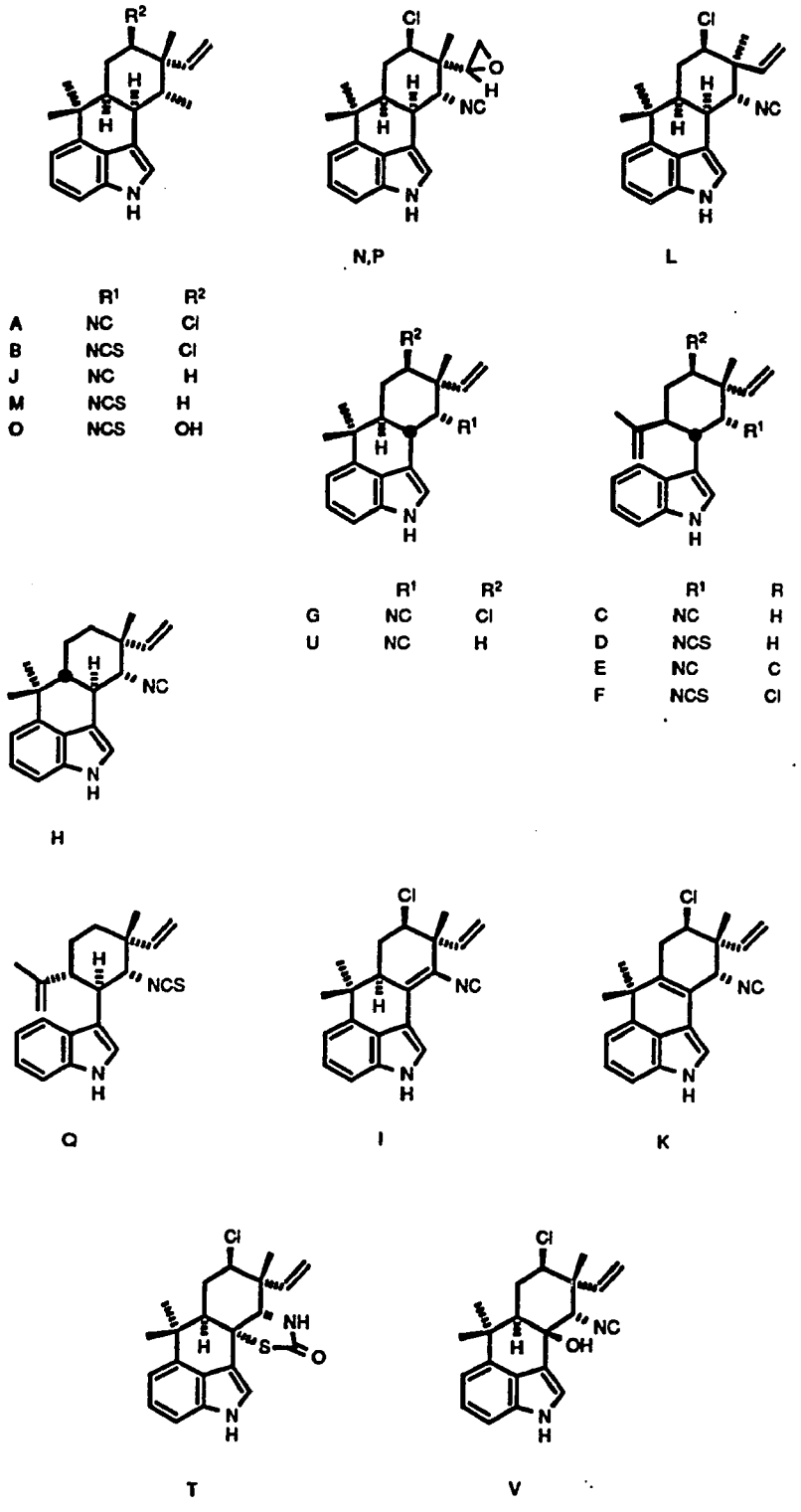
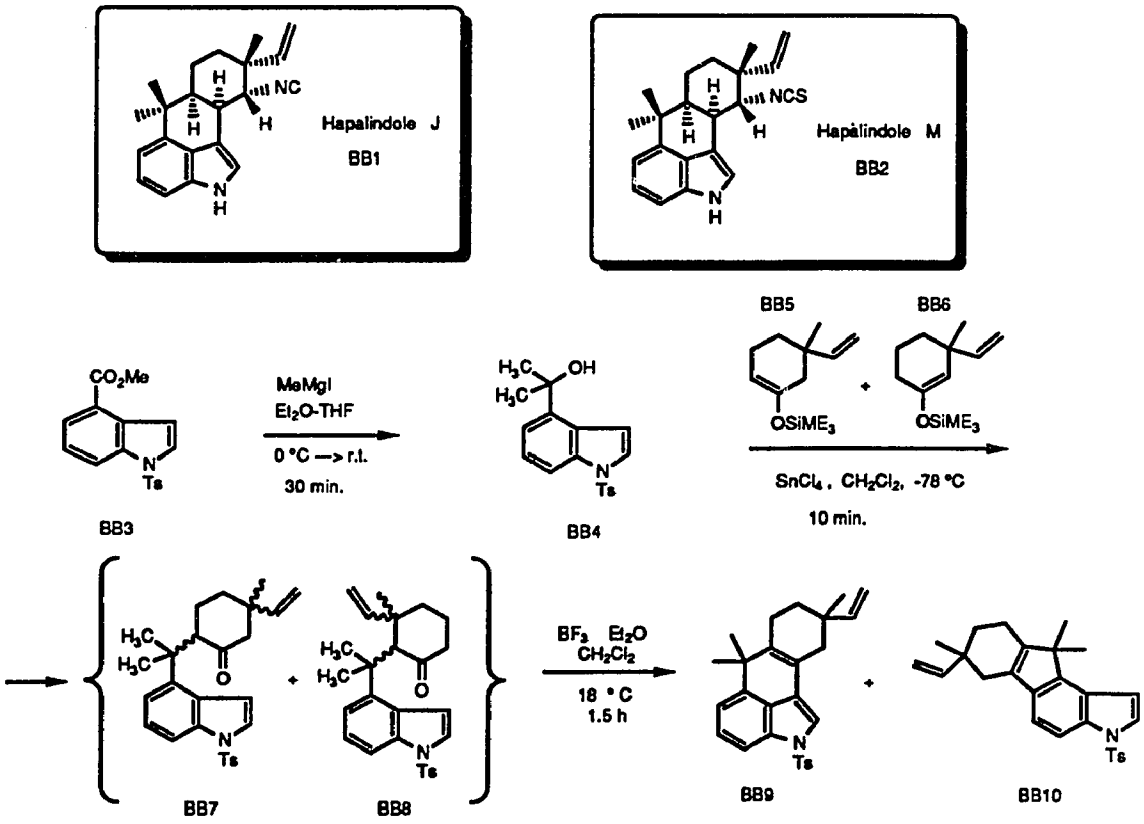


Figure **IX.** Various Hapalindoles Isolated

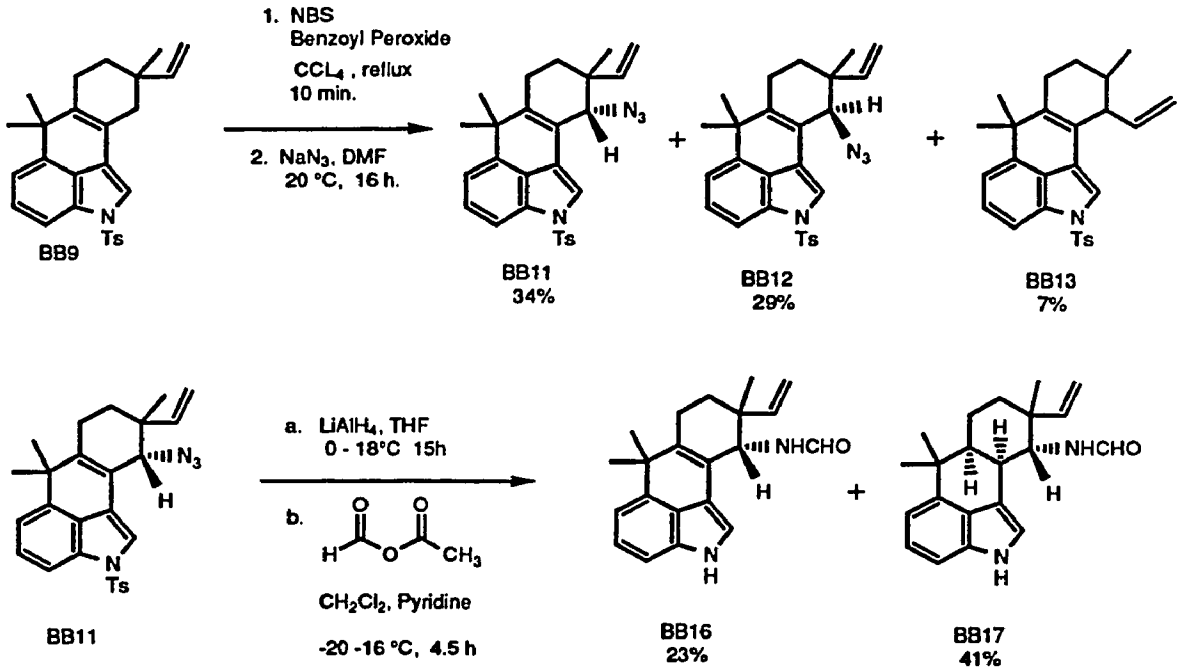
4.4 Synthesis of (±)-Hapalindoles J and M

The first reported synthesis of a hapalindole was in 1989 by Muratake and Natsume[27]. They were able to successfully synthesize (±)-Hapalindoles J (**BB1**) and M (**BB2**). The synthesis started with the tertiary alcohol **BB4** that was prepared from methyl 1-(p-toluenesulfonyl)-4-indolylcarboxylate **BB3**. The first step



Scheme II. Hapalindole Synthesis Part I

in the synthesis involved compound **BB4** reacting with a mixture of enol ethers **BB5** and **BB6**, in the presence of $SnCl_4$ in an interesting carbon-carbon bond forming process. The products formed in this process are the 4-substituted indoles **BB7** and **BB8**. The crude reaction mixture was treated with boron trifluoride etherate to give the tetracyclic indoles **BB9** and **BB10** in 57% and 4.5% yields respectively (Scheme **II**). Compound **BB9** has the correct carbon framework for

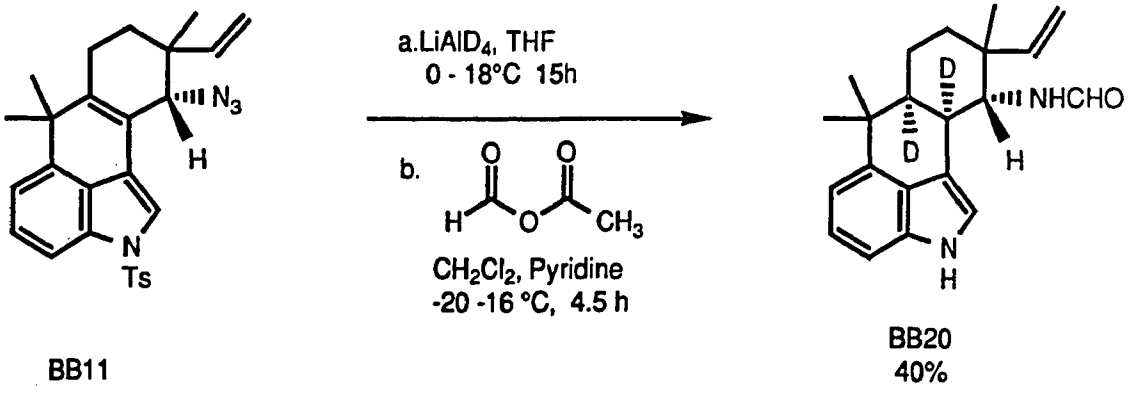


Scheme **III**. Hapalindole Synthesis Part II

the hapalindole series. The next step in the synthesis was the introduction of the nitrogen funtionality at C-11. Compound **BB9** brominated at C-11 by treatment with N-bromosuccinimide. The epimeric bromides obtained were treated with

sodium azide in DMF to give a mixture of **BB11** and **BB12** in yields of 34% and 29% respectively. When **BB11** was treated with with lithium aluminum hydride followed by formylation, the expected reduction product **BB16** was found in 23% yield and the over reduction product **BB17** was isolated in 41% yield (Scheme III).

As the authors have discussed in the paper, it is interesting to note the stereochemical consequence of the over reduction product. The reduction of the double bond was found to be a cis fused ring system where the hydrogens were delivered from the same side of the ring as the nitrogen functionality. When the reaction mixture was quenched with D_2O, no deuterium incorporation was observed, indicating that a stable carbanion salt did not exist. The p-toluene-



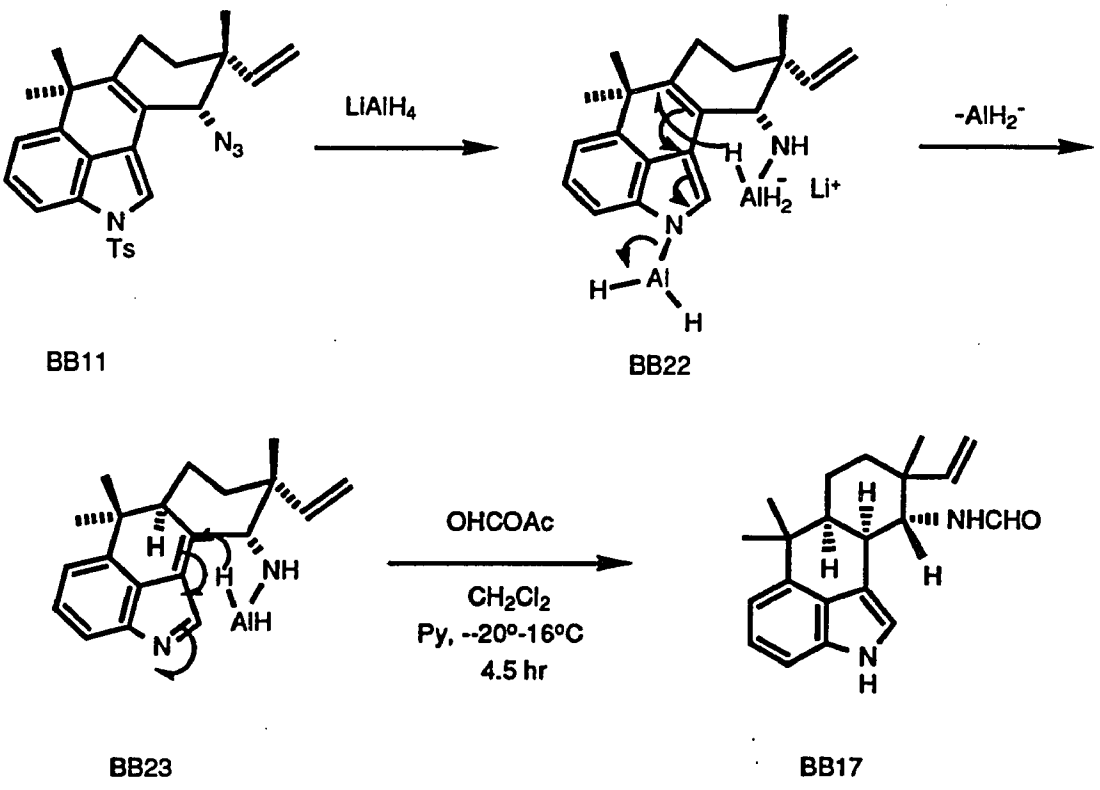
BB11

BB20
40%

Scheme **IV**. $LiAlD_4$ Reduction

sulfonyl group on the indole nitrogen did not appear to play a role, since the same outcome was observed when the reduction was performed on the compound with the free indole. When the reduction was carried out using $LiAlD_4$ followed by formylation, compound **BB20** with two deuterium atoms at C-10 and C-15 was obtained in 40% yield (Scheme **IV**).

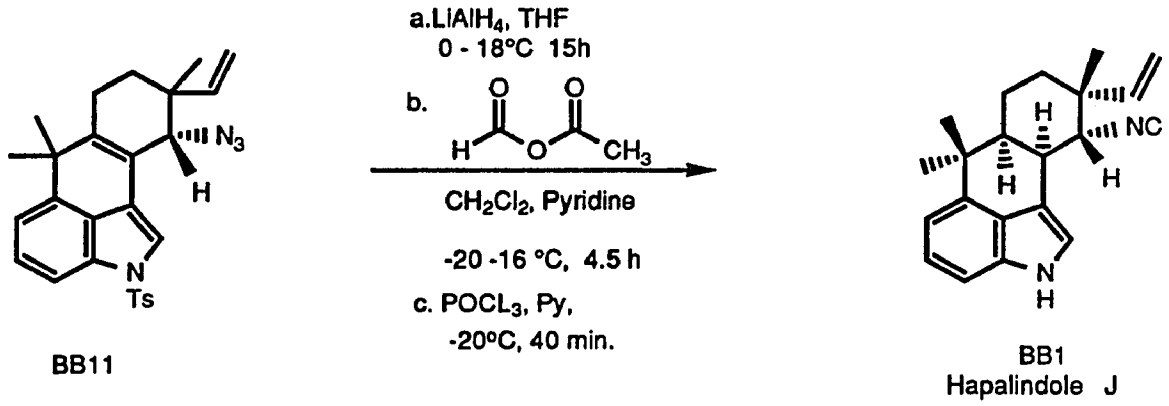
The mechanism proposed by the authors is shown in Scheme **V**. Initially a reductive cleavage of the p-toluenesulfonyl group of **BB11** occurs to form the indolylaluminum compound **BB22** having an additional aluminum chelated nitrogen functionality from the azide. An electron transfer from the double bond to the aluminum on the indole nitrogen along with a concurrent transfer of a hydride to



Scheme **V**. Proposed Reduction Mechanism

C-15, producing **BB23**. Intramolecular attack of a hydride from the chelated aluminum moiety to C-10 gives the fully reduced species which upon formylation gives the reported product **BB17.**

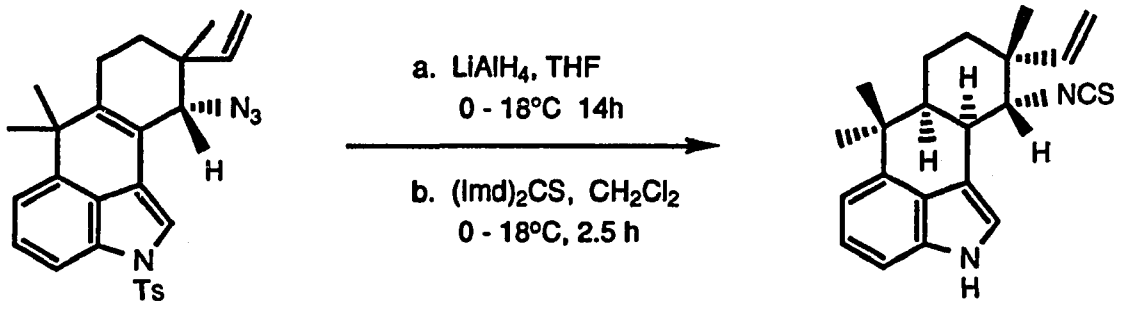
To complete the synthesis of (±)-hapalindole J **BB1**, compound **BB17** was treated with phosphorous oxychloride in pyridine to give the dehydrated product in 76% yield (Scheme **VI**).



Scheme **VI.** Completion of (±)-Hapalindole J

Likewise the completion of the synthesis of (±)-hapalindole M **BB2** was completed along the same lines. Compound **BB11** was reduced with $LiAlH_4$ followed by formylation to give the mixture containing the over reduced compound BB17. Treatment of the mixture with 1,1'-thio-carbonyldiimidazole in methylene

chloride afforded (±)-hapalindole M **BB2** in 35% yield (Scheme **VII**).



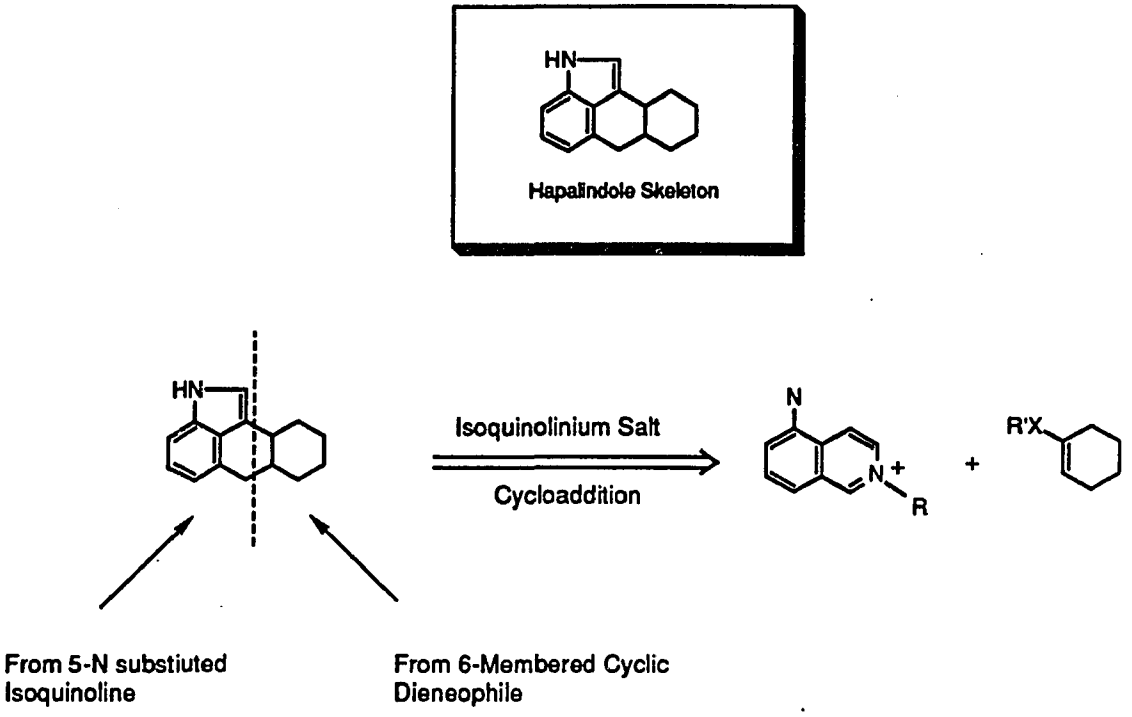
BB11

BB2
Hapalindole M

Scheme **VII**. Completion of (±)-Hapalindole M

4.5 Retrosynthetic Analysis

In order to construct this type of tetracyclic indole system through the Bradsher cycloaddition of isoquinolinium salts we must propose a retrosynthetic scheme. Upon examination of the tetracyclic ring system one can see that the indole portion and the third ring can come from a 5-nitrogen substiuted isoquinoline (Scheme **VIII**). The fourth ring of the system can come from an electron rich 6-memebered cyclic dienophile.



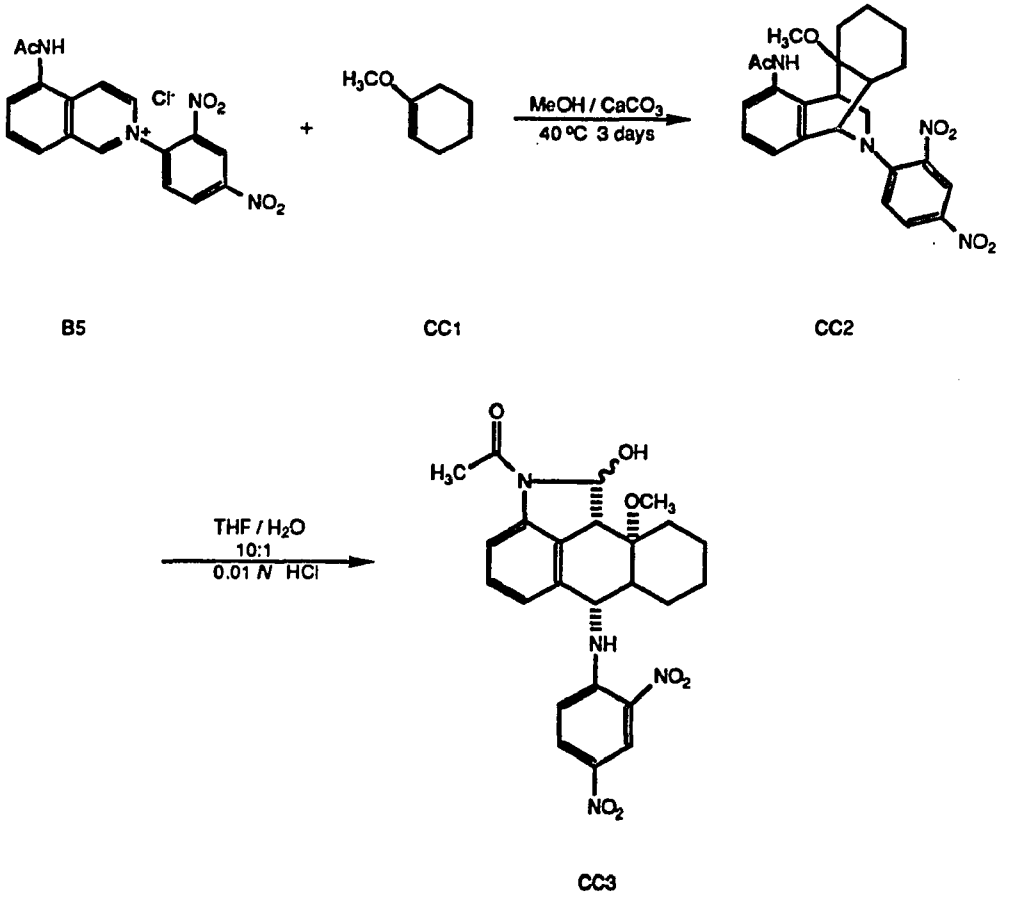
Scheme **VIII.** Retrosynthetic Analysis for Hapalindole Skeleton

Based on the stereochemistry of the cycloaddition, yielding a *cis* fused ring system, our synthesis would have to be confined to the hapalindoles with this type of ring fusion or with an unsaturation. The hapalindoles with cis fused rings include A, B, J, L, M, N, O, and P. The tetracyclic hapalindoles with an unsaturation at the ring junction are I and K.

4.6 Model Study

Since we were undertaking a model study, we decided to form the basic ring system without any of the complex substituents that are asssociated with the

natural products. The cycloaddition was performed by reacting 2-(2,4-dinitrophenyl)-5-acetylamino-isoquinolinium chloride **B5** with 1-methoxycyclohexene **CC1** in the presence of calcium carbonate and methanol. After inital workup the tricyclic intermediate **CC2** was immediately treated with 0.01 *N* HCl in THF / H_2O (10:1) for 24 hours to give the indoline **CC3** containing the basic hapalindole framework (Scheme **IX**). Proton NMR in DMSO-d_6 showed the product to be

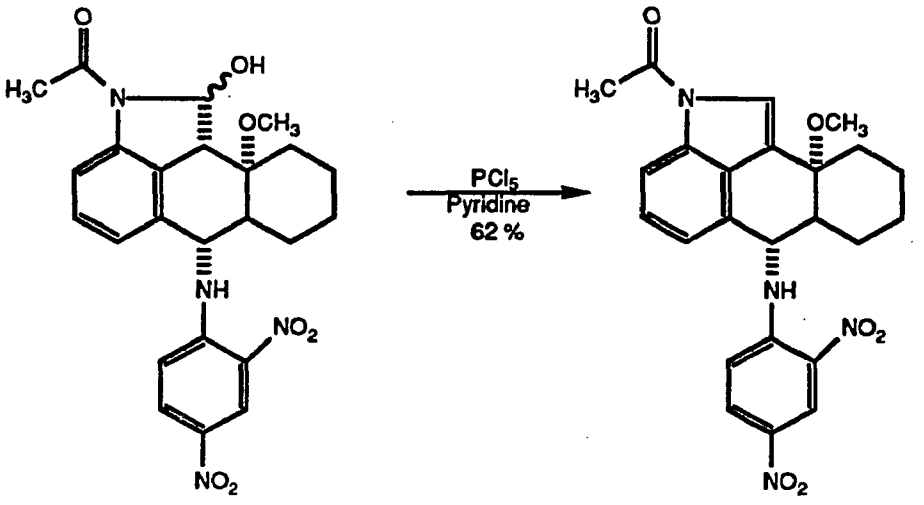


Scheme **IX**. Formation of Hapalindole Framework

approximately a 5:1 mixture of diastereomers based on the doubling of the peaks. The major isomer exhibited the N-H peak at 8.45 ppm, C_{2a}-H at 3.68 ppm, -OCH_3 at 2.89 ppm and acetyl -CH_3 at 2.18 ppm. The minor isomer exhibited the N-H peak at 8.56 ppm, C_{2a}-H at 3.78 ppm, -OCH_3 at 2.93 ppm and acetyl -CH_3 at 2.22 ppm. The stereochemisty of the cycloaddition would give the *cis* orientation and in the case of methoxycyclohexene would give the anti-Bradsher product shown where the methoxyl and dinitrophenylamino group are *cis*[28]. The diastereomers would appear to arise from epimers at C_2 because after dehydration only one indole was isolated.

In order to afford the dehydrated indole, the indoline mixture was treated with phoshorous pentachloride in pyridine as was done previously. The dehydration proceeded smoothly and after chromatography a single indole **CC4** was obtained in 62 % yield (Scheme **X**). The yield for this reaction was lower than in the analogous case the cycloaddition was performed with phenyl vinyl sulfide and the yield was 88 %.

The ^{1}H NMR of indole **CC4** showed the disappearance of the C_2 amino-acetal proton at δ = 5.88 ppm and the C_2a proton at δ = 3.68 ppm. The protons on the 2,4-dinitrophenyl ring appeared at their routine positions and the N-H appeared at 10.37 ppm. The aliphatic protons were assigned based on a 2D COSY experiment. A direct comparison to the ^{1}H NMR of the indole derived from the cycloaddition of phenyl vinyl sufide was not practical because of the differences in their structures. The ^{13}C spectrum showed the carbonyl carbon at δ = 168.4



CC3 CC4

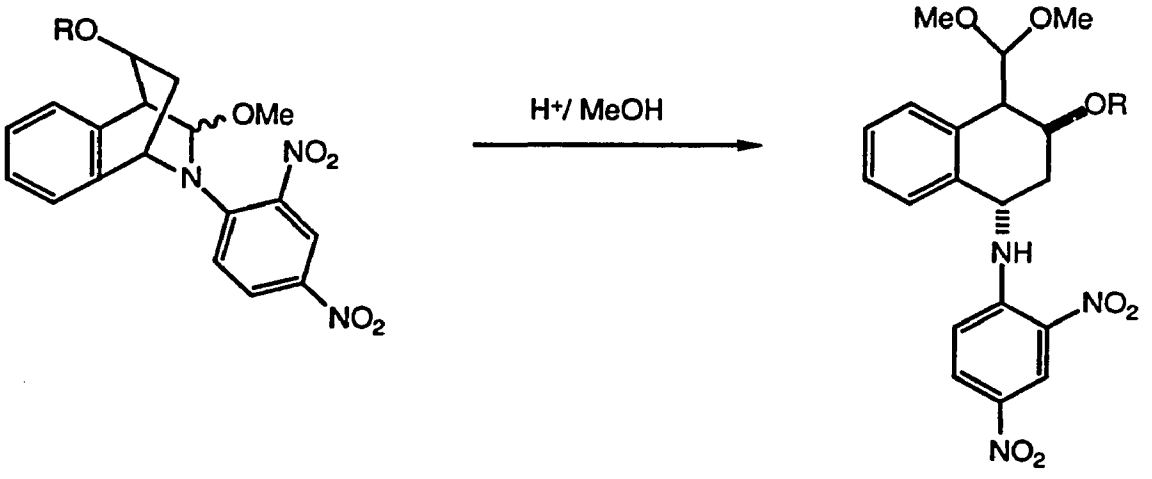
Scheme **X.** Dehydration of Ring Opened Cycloadduct

ppm, 9 upfield carbons ($\delta < 80$ ppm) and the presence of 7 non-quaternary carbons in the aromatic region which would be predicted for this structure. Out of the 7 quaternary carbons in the structure only 2 appeared well resolved but there was a broad signal at $\delta = 116$ ppm that could account for 3 or 4 of these carbons. Based on the above data and the correct high resolution mass spectrum we feel that the structure is correct.

D. 2,4-DINITROPHENYL PROTECTING GROUP FOR AMINES

5.1 Amine Protecting Group

During the course of our work with the cycloadditions of isoquinolinium salts we became exposed various cases where an amino functionality was protected by a blocking group. Since the general product of the ring opening of the tricyclic adduct **FF1** was a substituted tetralin **FF2** where the amino functionality was protected with the 2,4-dinitrophenyl group (Scheme **I**) , the removal of this group was of primary concern. With the lithium borohydride removal technique developed during our 1,3,4,5-tetrahydrobenz[cd]indole synthesis we decided to see if the method could be used as a practical procedure for the dedinitrophenylation of 2,4-DNP-amines. This would facilitate the use of the 2,4-dinitrophenyl group as a more general blocking group for amines.



FF1 FF2

Scheme **I.** Ring Opening of Tricyclic Adduct to Give DNP-Amine

Two general requirements for an effective protecting group are (i) that it reacts selectively in high yield to give the protected functionality and (ii) the group should be able to be removed in high yield in order to regenerate the functional group.[29]

5.2 Common Amine Protecting Groups

Some of the more common blocking groups for the amino functionality are the carbamate, amide and cyclic imide derivatives. Carbamate formation as shown in Scheme **II** involves the reaction of the amino group with an activated acid derivative. The substituent **X** can be chlorine in the case of a chloroformate, N_3 with an azidoformate, -OR' with a carbonate and -OCOOR' with a dicarbonate.

$$R^1R^2NH + R'OCOX \xrightarrow{\text{base}} R^1R^2NCOOR'$$

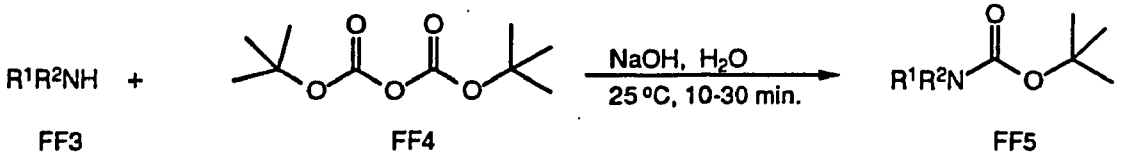
Scheme **II**. Carbamate Formation

The group R' can be diverse but some of the more popular substituents used are methyl (CH_3), t-butyl (BOC) and Benzyl (CBZ).

The methyl carbamate derivative can be formed by refluxing the amine in methyl chloroformate in the presence of potassium carbonate for 12 hours.

Cleavage can be accomplished by treatment with methanolic sodium hydroxide for two hours at room temperature.[30] The overall yield for both protection and deprotection is 90%. Other methods for deprotection such as iodotrimethylsilane (50 °C, 70% yield)[31], aqueous potassium hydroxide in ethylene glycol (100 °C, 12 h, 88% yield)[32], potassium hydroxide in methanol-water (25 °C, 30 min, 100% yield)[33], and hydrogen bromide/acetic acid (25 °C, 18h)[34] can also be used in high yields.

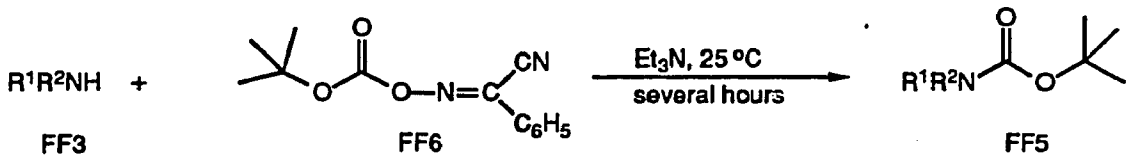
One of the more common carbamate derivatives is the t-butyl carbamate (BOC) **FF5** which can be formed and removed in a variety of ways. If the amine **FF3** is treated with di-tert-butyl dicarbonate **FF4** in the presence of aqueous sodium hydroxide the BOC protected amine is formed in 75-95% yield (Scheme **III**).[35]



FF3 FF4 FF5

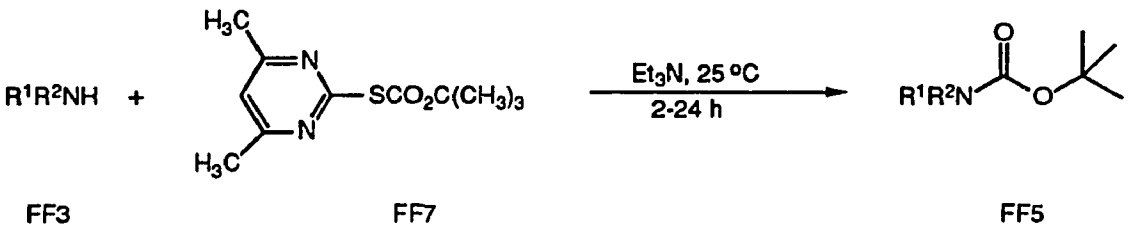
Scheme **III**. Formation of BOC Protected Amine

Treatment of the amine **FF3** with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) **FF6** in triethylamine for several hours gives the BOC derivative **FF4** in 72-100% yield (Scheme **IV**).[36]



Scheme **IV.** Formation of BOC-Amine with 2-(tert-Butoxycarbonyloxyimino-2 -Phenylacetonitrile

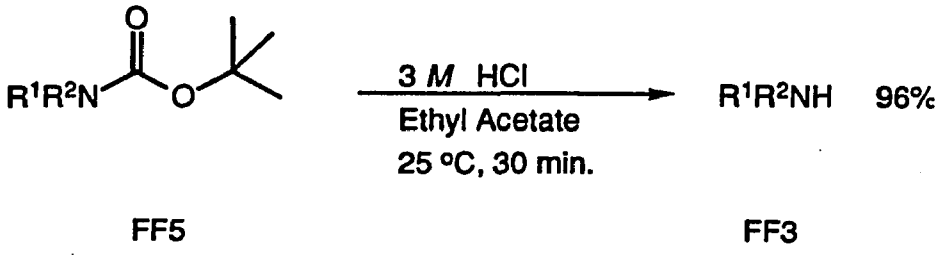
A third method is treatment of the amine **FF3** with *tert*-butyl S-(4,6-dimethylpyrimidin-2-yl)thiocarbonate **FF7** in triethlamine for 2-24 hours produces the *BOC* derivative **FF5** in 80-100% yield (Scheme **V**).[37]



Scheme **V.** Formation of BOC-Amine with *tert*-Butyl-S-(4,6-Dimethylpyrimidin-2-yl)thiocarbonate

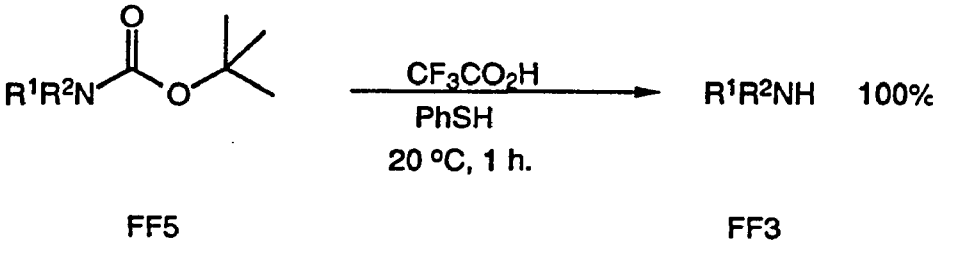
Removal of the *BOC* group can be effected using a variety of reagents and generally in high yield. Upon treatment of the BOC-amine with 3 *M* HCL in ethyl

acetate for 30 min at room temperature, the free amine was liberated in 96% yield (Scheme **VI.**).[38]



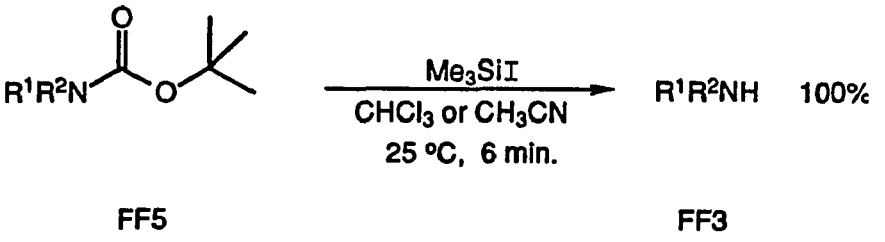
Scheme **VI.** Cleavage of BOC-Amine With 3 *M* HCl

Treatment with thiophenol in trifluoroacetic acid for 1 hour gives the free amine in 100% yield (Scheme **VII.**).[39]



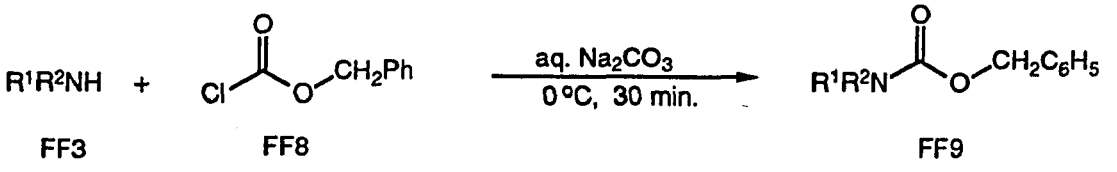
Scheme **VII.** Cleavage of BOC-Amine With Thiophenol

Iodotrimethylsilane in chloroform or acetonitrile at room temperature for 6 minutes cleaves the carbamate in 100% yield (Scheme **VIII**).[40]



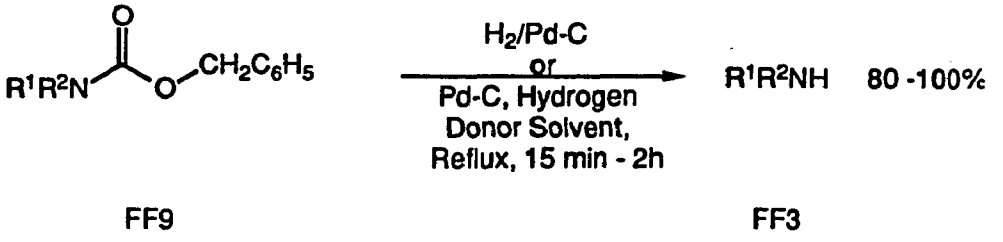
Scheme **VIII**. Cleavage of BOC-Amine with Iodotrimethylsilane

Another popular amino protecting group is the benzyl carbamate (CBZ) group. The benzyl carbamate **FF9** can be formed by treatment of the amine **FF3** with benzyl chloroformate **FF8** in aqueous sodium carbonate for 30 minutes at 0 °C (Scheme **IX**).[41]



Scheme **IX**. Formation of CBZ-Amine

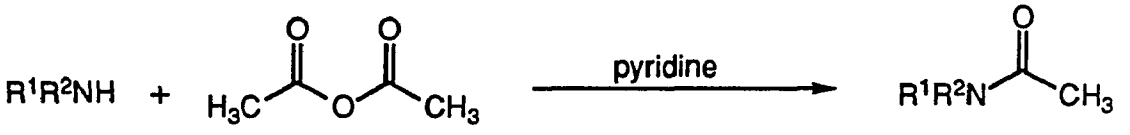
Benzyl carbamates **FF9** are generally cleaved by treatment with with palladium on carbon or palladium black and a hydrogen-donor solvent or by refluxing in ethanol (Scheme **X**).[42,43,44,45,46]



FF9 FF3

Scheme **X**. Cleavage of CBZ-Amine

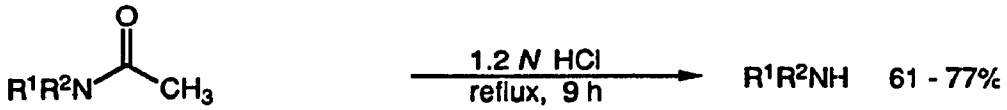
Amines can also be protected as amides of which two common derivatives are the acetamide and the benzamide. Acetamides **FF12** are routinely formed by treatment of the amino compound **FF3** with acetic anhydride **FF11** in pyridine (Scheme **XI**).



FF3 FF11 FF12

Scheme **XI**. Formation of Acetamide Derivative

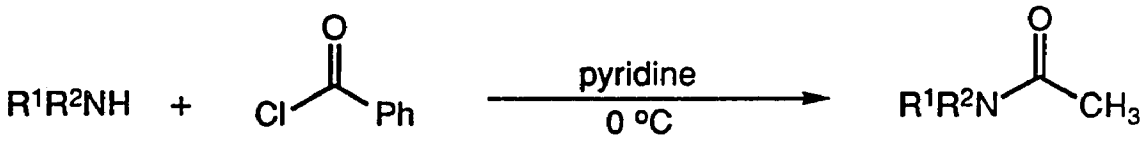
Cleavage can be accomplished by refluxing the acetamide derivative **FF12** with 1.2 *N* HCl for 9 hours to give the deprotected amine in 61 - 77 % yield (Scheme **XII**). [47]



FF12 FF3

Scheme **XII.** Cleavage of Acetamide

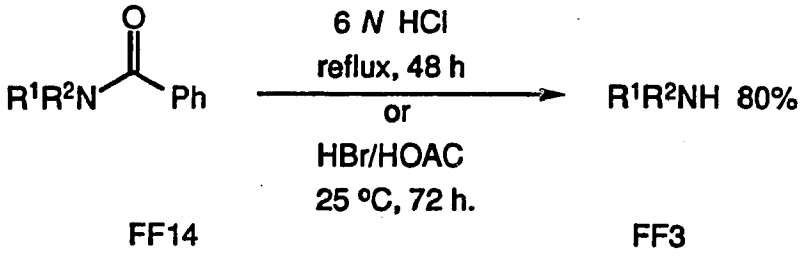
Benzamides are formed in a corresponding way to the acetamides. The amine **FF3** is reacted with benzoyl chloride **FF13** in pyridine at 0 °C to give the benzamide derivative **FF14** in high yield.[48]



FF3 FF13 FF14

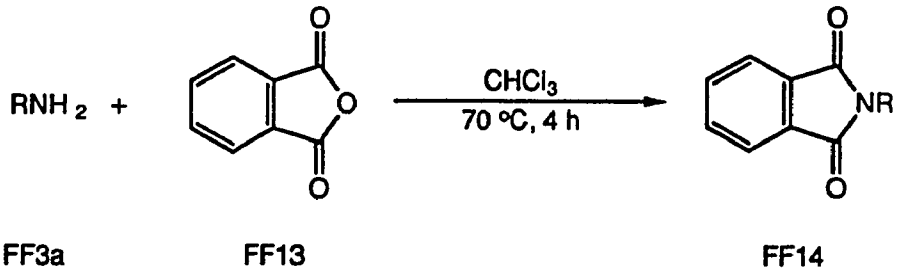
Scheme **XIII.** Benzamide Formation

A standard method for cleavage is by refluxing with 6 *N* HCl for 48 hours or by treatment with hydrogen bromide-acetic acid for 72 hours to give the deprotected amine in 80 % yield.[49]



Scheme **XIV.** Benzamide Cleavage

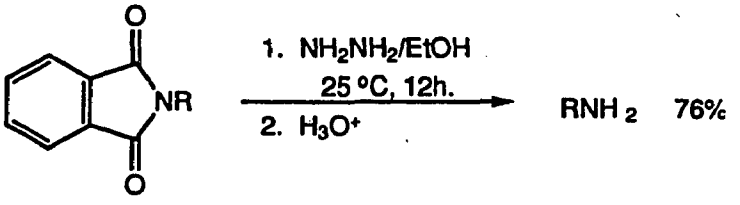
In the case of the cyclic imide derivatives the traditional derivative is the phthalimide. A preparative procedure that has been used to prepare phthalimide derivatives **FF16** of nucleosides involves heating the amine **FF3a** with phthalic anhydride **FF15** at 70 °C in chloroform for 4 hours (Scheme **XV**).[50]



Scheme **XV.** Formation of Phthalimido Derivative of an Amine

Cleavage of the phthalimido derivative is typically carried out by first treating with

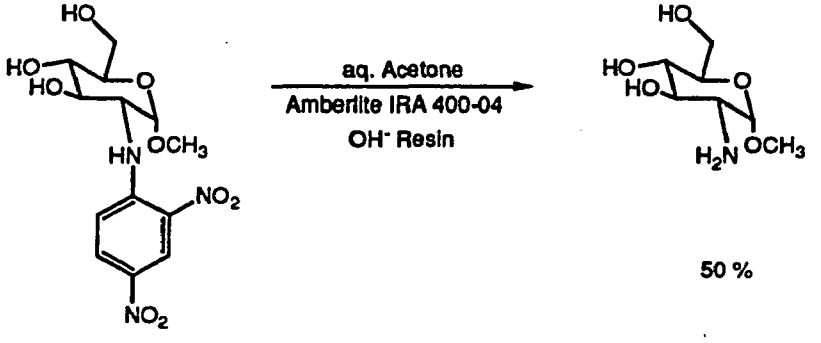
hydrazine in ethanol at room temperature for 12 hours followed by acid treatment to yield the amine in 76 % yield (Scheme **XVI**).50



FF14 FF3a

Scheme **XVI**. Cleavage of Benzamide Derivative

As can be seen with the above examples, the derivatives shown meet the criteria for good protecting groups: (i) that it reacts selectively in high yield to give the protected functionality and (ii) the group should be able to be removed in high yield in order to regenerate the functional group. Also listed as a protecting group for amino compounds is the 2,4-dinitrophenyl group which is also attached to our ring opened cycloaddition product. The group was listed as a protecting group for the amino substituent of an amino sugar.[51] The cleavage of the DNP-group from the DNP-amino-glucopyranoside **FF17** using Amberlite IRA-400-04 basic anion



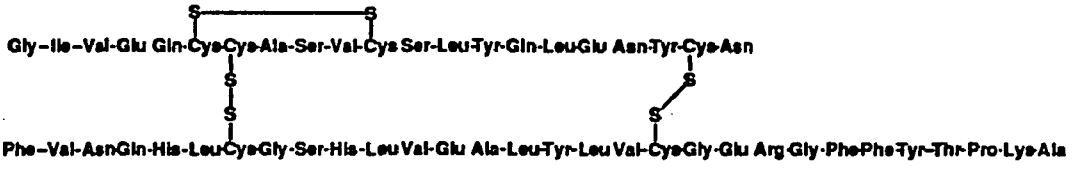
FF17 FF18

Scheme **XVII**. Dinitrophenyl Protecting Group

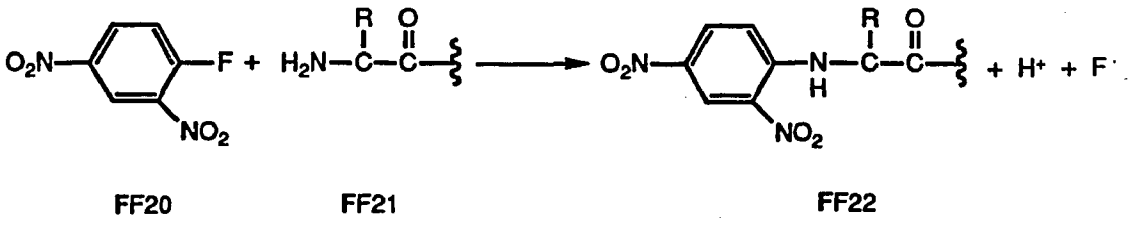
exchange resin in aqueous acetone was modest, providing the amino product FF18 in 50 % yield. It is most probably because of these meager yields that the DNP group has not been more promoted as a blocking group for amines.

5.3 2,4-Dinitrophenyl Group

The 2,4-dinitrophenyl group first achieved great notoriety when Frederick Sanger used 2,4-dinitrofluorobenzene (DNFB) in order to determine the the complete amino acid sequence of the bovine polypeptide hormone insulin. DNFB was used as a label to quantitatively and qualitatively determine the free amino groups of the protein insulin (Scheme **XVIIIa**).[52] The free amino groups of **FF20** react by aromatic nucleophilic substitution, displacing the fluoride ion at the 1-position of 2,4-dinitrofluorobenzene **FF21** to give the DNP amino acid **FF22** (Scheme **XVIIIb**). The resulting DNP-aminoinsulin could be isolated by



Scheme **XVIIIa**. Amino Acid Sequence of the Protein Insulin



FF20 FF21 FF22

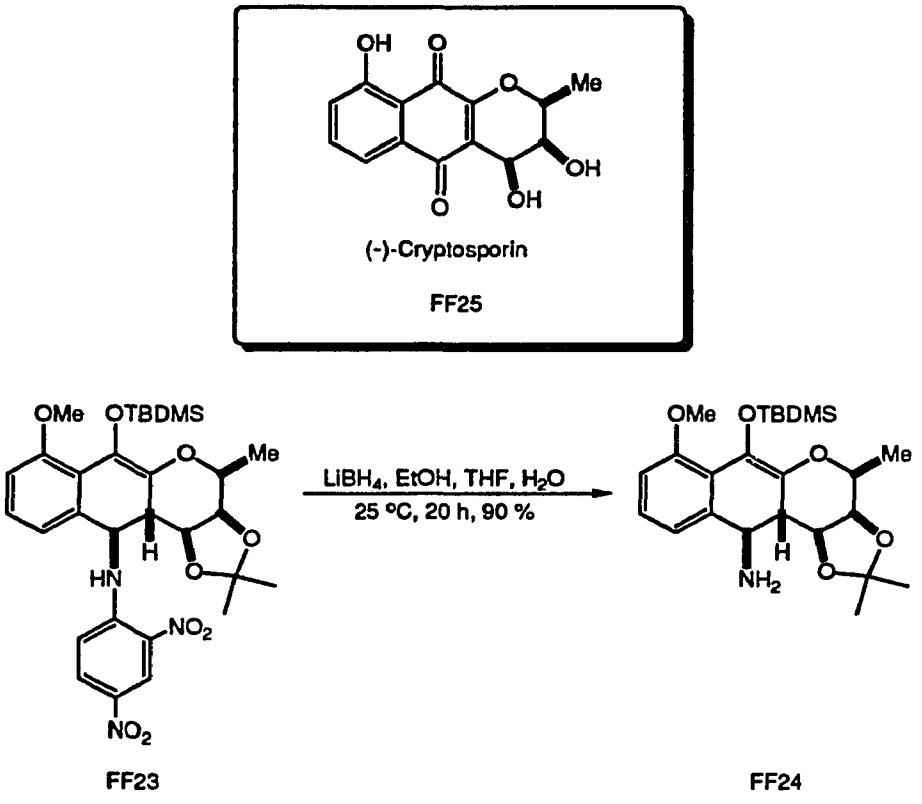
Scheme **XVIIIb**. DNP Labeling of the *N*-Terminal Residue of a Protein

neutralizing the solution with sodium bicarbonate which caused precipitation of the product. The DNP-protein could then be hydrolyzed by treatment with aqueous acid to yield the constituent DNP-amino acids formed from the amino acids present with free amino groups. The amino acids were then seperated chromatographically. The DNP-amino acids obtained were all bright yellow in color with quantitative and qualitative determinations made based on data acquired from DNP-amino acids prepared independently. As a result of Sanger's work, a variety of DNP-amino acids are readily available.

5.4 2,4-Dinitrophenyl Protecting Group

Our interest in trying to promote the use of the DNP group as practical protecting group for amines was spawned by a result by a coworker in our lab. During the proposed synthetic pathway to the yellow fungal metabolite, (-)-Cryptosporin **FF25** [53], problems arose during attempted removal of the DNP group by basic anion exchange resin. Treating the DNP-amino derivative **FF23** (Scheme **XIX**) with $LiBH_4$ dissolved in a mixture of ethanol, tetrahydrofuran, and

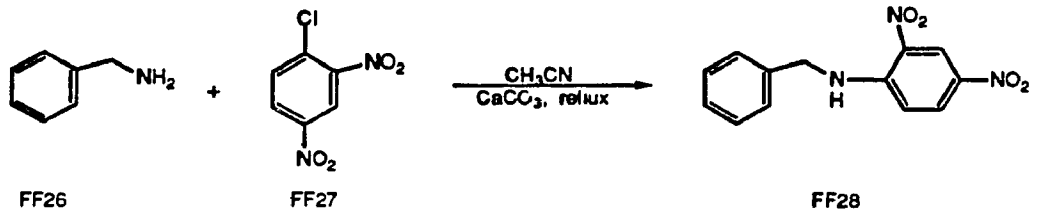
water for 20 hours at 25 °C the free amine **FF24** was obtained in 90 % yield.[54] This was by far the highest yield that we had observed for the removal of the 2,4-dinitrophenyl group.



Scheme **XIX**. Cryptosporin Synthesis Using $LiBH_4$ to Deblock DNP-Amine

Based on our initial result from the isoquinoline work the prospect of having an effective removal method looked promising. Our next step was to test the method on a few more DNP-amines and survey the result. The first amine we decided on was to protect benzylamine with the DNP group. Refluxing

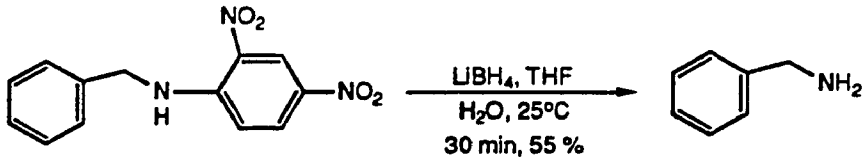
benzylamine **FF26** and 1-chloro-2,4-dinitrobenzene **FF27** in acetonitrile in the presence of calcium carbonate furnished the DNP derivative **FF28** in 94% yield (Scheme **XX**).



FF26 FF27 FF28

Scheme **XX**. Protection of Benzylamine With The 2,4-Dinitrophenyl Group

The next step was to try our deprotection method. When *N*-2,4-dinitrophenyl-benzylamine **FF28** was treated with the borohydride/THF/water mixture the best result for deprotection was 54% yield (Scheme **XXI**). This was not very encouraging.

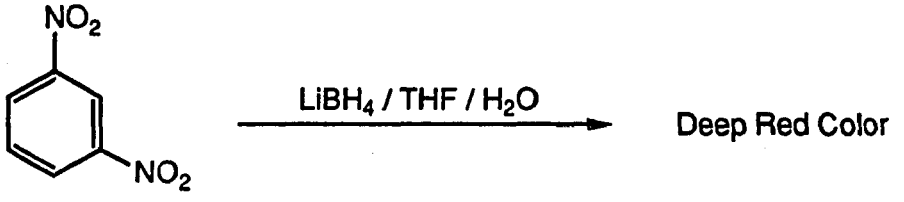


FF28 FF26

Scheme **XXI**. Deblocking of DNP-Benzylamine with $LiBH_4$

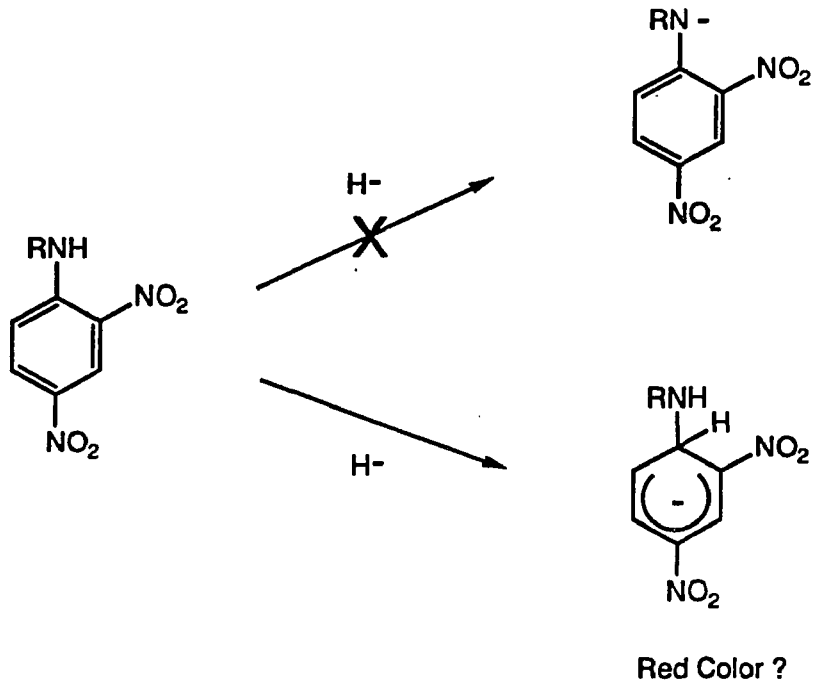
We also noticed that when the reaction was allowed to proceed for extended periods the mixture took on a dark brown color. This was also observed during our isoquinoline work.

Intrigued with the colorful displays of the reaction mixture, going from yellow before addition of borohydride, to deep red after addition, and finally dark brown after extended periods, we decided to test our reaction conditions on meta-dinitrobenzene. When meta-dinitrobenzene was subjected to our reaction conditions the mixture immediately turned the same deep red color as observed



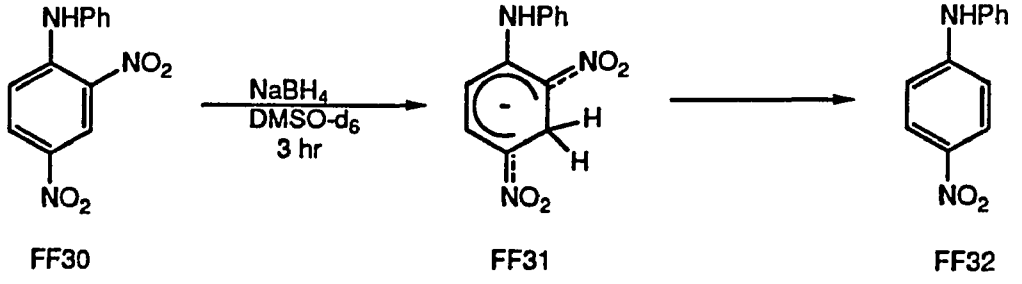
Scheme **XXII**. Reaction of *meta*-Dinitrobenzene With Borohydride

in the DNP-amino compounds. This detail would lead one to surmise that the red color of our reaction mixture is not originating from deprotonation of the secondary amine but conceivably from nucleophilic attack on the aromatic ring (Scheme **XXIII**).



Scheme **XXIII**. Hydride Attack on the DNP Ring

There have been several reports in the literature examining the reaction of aromatic nitro compounds with hydride ion. It was reported that when *N*-phenyl-2,4-dinitroaniline **FF30** was treated with sodium borohydride in DMSO-d_6 the species observed by ^{1}H NMR was assigned as the transient Meisenheimer adduct



Scheme **XIV**. Reaction of *N*-phenyl-2,4-dinitroaniline With Borohydride

FF31.[55] The final product is reported to correspond to the displacement of the 2-position nitro group by a hydride ion to furnish *N*-phenyl-4-nitroaniline **FF32** (Scheme **XIV**). When the reaction as carried out with 1,4-dinitrobenzene under aqueous conditions the amount of water present had a substantial effect on the

% Water[a]	[NC]/[BH][b]	*t*/hrs	% Nitro Loss
0	2.1	146	15
5[c]	0.5	144	100
30[c]	0.5	144	72
23[d]	0.5	19	11

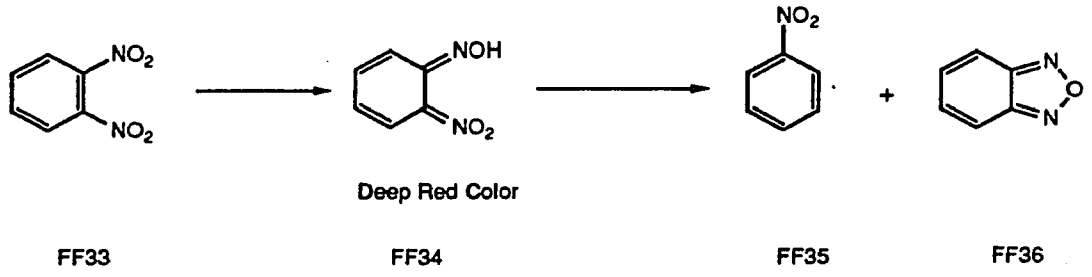
[a] *x* % means *x* volumes of water + (100 - *x*) volumes of DMSO. [b] [NC] = 10^3 [1,4-DNB]/mol dm^{-3}, [BH] = 10^3 [$NaBH_4$]/mol dm^{-1}. 10^{-3} *M* NaOH used in place of water. [d] Solvent composition employed by Bird, Rae, and White[56] who reported no chemical change of 1,4-dinitrobenzene after 1 hour.

Table **II.** Effect of Water on the Reaction of 1,4-Dinitrobenzene with Borohydride

final product ratios (Table **I**). When the reaction is carried out in the absence of water the final product mixture contains 15 % of compounds where the nitro group is lost from the 2-postion of the aromatic ring. When the solvent system is composed of 5 % 10^{-3} M sodium hydroxide the products shows 100% loss of the

nitro group. This may have some correlation to our results where water must be present in order for the dedinitrophenylation to occur.

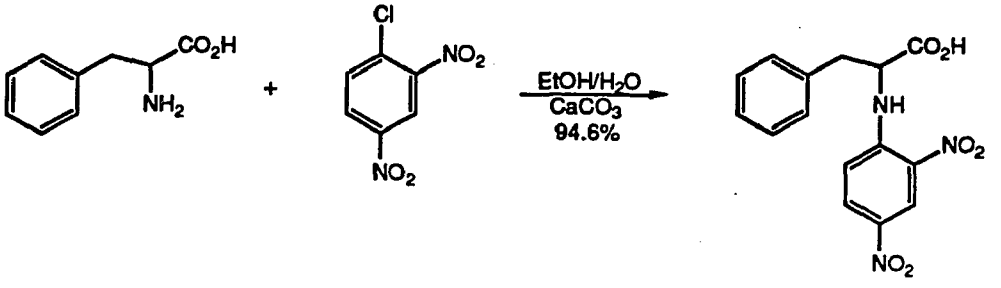
Bird, Rae, and White studied the reaction of *ortho*-dinitrobenzene **FF33** with sodium borohydride in aqueous DMSO. They reported the color of the mother liquor to be deep red when basic then changing to yellow upon neutralization. It was proposed that the red colored intermediate was ortho-benzoquinone dioxime **FF34** (Scheme **XXV**). The final products reported for the reaction are nitrobenzene **FF35** (90%) and benzofurazan **FF36.**



Scheme **XXV**. Reaction of o-Dinitrobenzene in Aqueous Borohydride

Next we decided to test our method on a DNP-amino acid. The derivative prepared was *N*-2,4-dinitrophenyl-L-phenylalanine **GG2.**[52] L-phenylalanine **GG1** was treated with 2,4-dinitrochlorobenzene **B4** in a mixture of ethanol and water the DNP derivative was obtained in 94.6% yield (Scheme **XXVI**). The ^{1}H NMR showed the $CO_2\underline{H}$ proton at δ = 9.85, the N-$\underline{H}$ proton at δ = 7.41 and the benzylic protons at 3.48 ppm. The α-amino proton appeared as a multiplet at δ = 4.66-4.73

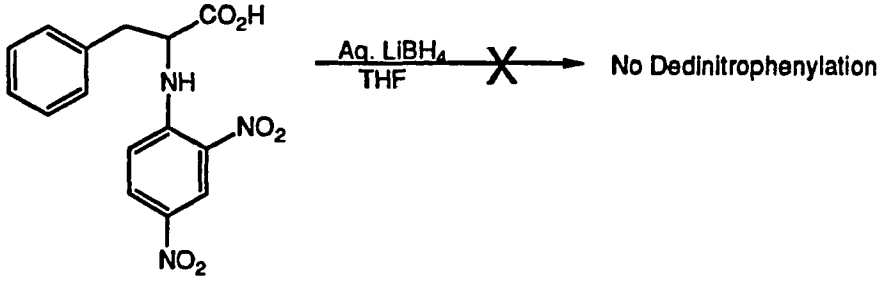
ppm. The ^{13}C NMR spectrum displayed the carboxylic carbon at δ = 175.8 ppm, and showed 10 downfield aromatic carbons along with two upfield carbons due to the benzylic carbon and the carbon containing the amino-acid functionality. This is what would be expected by the structure.



GG1 B4 GG2

Scheme **XXVI**. Formation of *N*-2,4-dinitrophenyl-phenylalanine

When an attempt was made to dedinitrophenylate the DNP-amine **GG2** the reaction did not proceed as planned (Scheme **XXVII**). Upon treatment with the aqueous lithium borohydride solution the color changed to red as usual but even after an extended period of time the mixture did not become colorless. Tlc did not

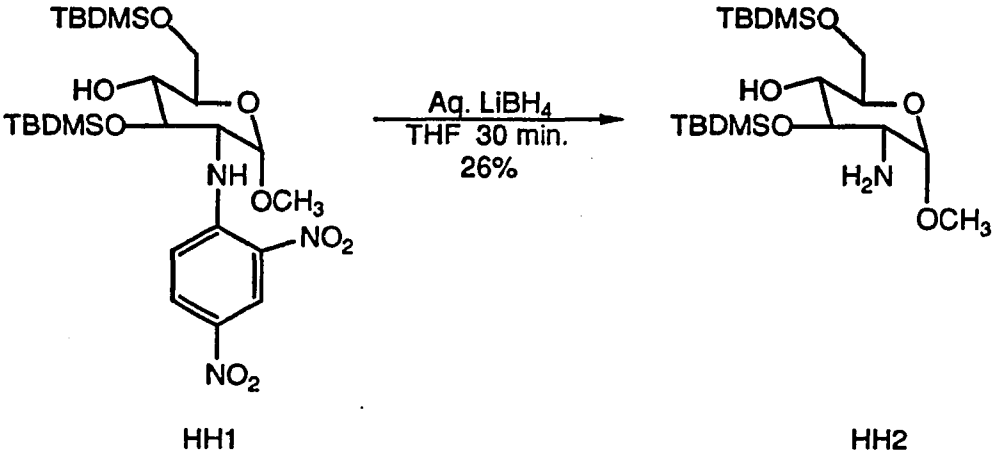


GG2

Scheme **XXVII**. Reaction of *N*-2,4-dinitrophenyl-phenylalanine with Aqueous $LiBH_4$

show any evidence of reforming the starting amino acid. Our best guess as to why the dedinitrophenylation did not occur would be due to some effect of the free carboxylic group. The reaction might have to be tried at a different pH.

This dedinitrophenylation procedure has also been attempted on a DNP-amino sugar.[57] When the dedinitrophenylation reaction was performed on the



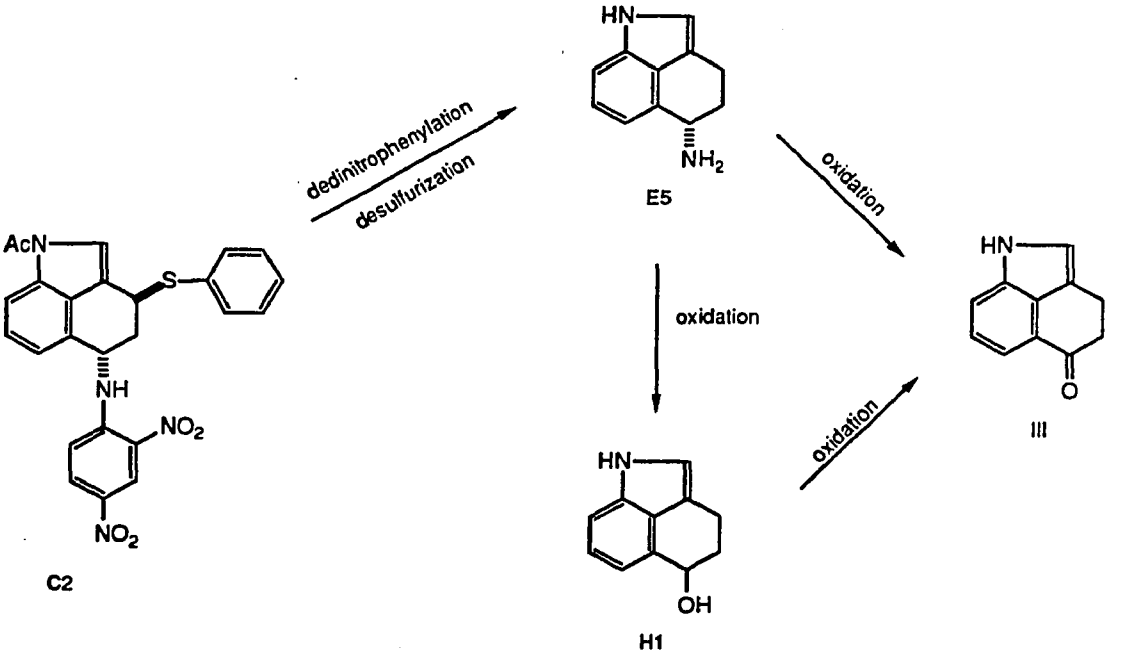
HH1 HH2

Scheme **XXVIII**. Dedinitrophenylation of a Blocked 2-Deoxy-2-(DNP)-Amino-Sugar

2-Deoxy-2-(DNP)-Amino-Sugar **HH1** the reaction went in very low yield (26 %). Further work will have to investigate why this is the case.

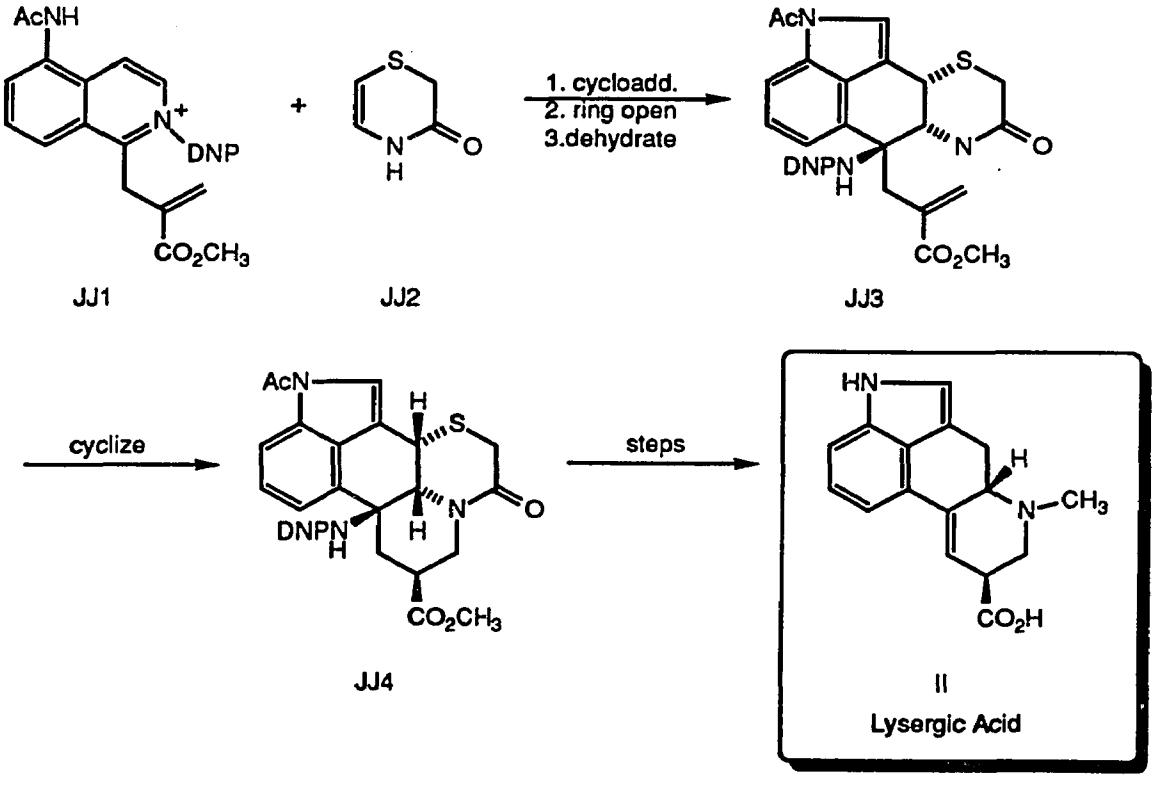
CHAPTER III. CONCLUSIONS

The following section will give a short recapitulation of the work presented in the previous sections. As far as a good method to synthesize Uhle's ketone **III**, the cycloaddition of isoquinolinium salts substituted with a nitrogen at the 5-position would not appear to be a good method in its present form. The method is however a good way to construct the fundamental framework. More work on the removal of the dinitrophenyl group and the subsequent oxidation of the amine **E5** or its conversion to the hydroxy compound **H1**, followed by oxidation to the ketone **III** is needed (Scheme **I**).



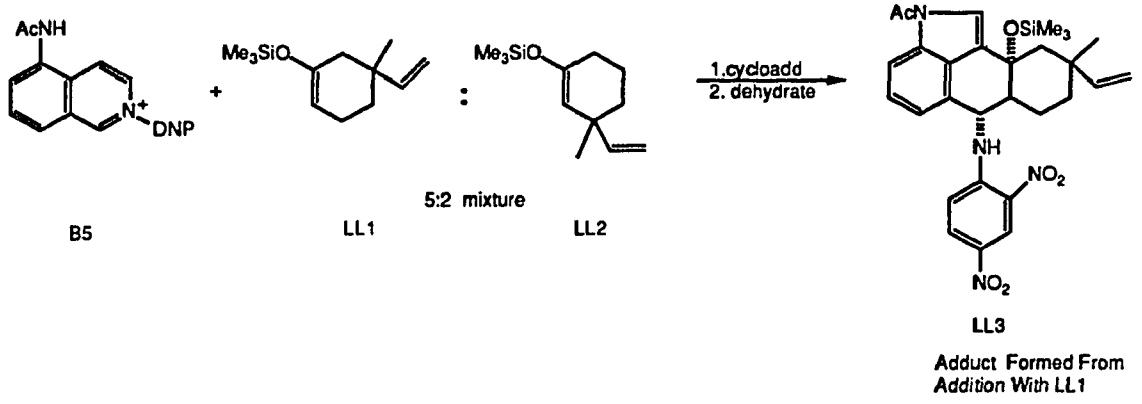
Scheme **I**. Further Work on Uhle's Ketone Synthesis.

As a synthetic route to Lysergic acid **II** one would have to expand the methodology used for the synthesis of Uhle's Ketone **III**. As a proposed route we could envision the cycloaddition of salt **JJ1** with the dienophile **JJ2** which after ring opening and dehydration would give the indole **JJ3**. Cyclization of this intermediate which may occur during the ring opening would give compound **JJ4**. Functional group conversion and manipulation at this stage would require some experimentation but the carbocyclic skeleton is in place in a short number of steps.



Scheme **II**. Proposed Lysergic Acid Synthesis Via Isoquinolinium Salt Cycloadditions

With regard to a total synthesis of a hapalindole natural product, a more complicated enol ether would have to be synthesized in order to generate the highly functionalized ring system of the natural products. The cycloaddition could be performed using the silyl enol ether mixture **LL1** and **LL2** used by Natsume.[27] The adduct resulting from cycloaddition with **LL1** would give upon ring opening and dehydration, indole **LL3**. In order to complete a synthesis of one of the natural products, the 6-position 2,4-dinitrophenylamino group would require a conversion to a gem dimethyl group. This conversion would not be trivial and would probably require careful experimentation.



Scheme **III.** Elaboration of a Hapalindole Synthesis

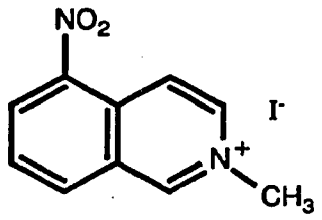
As a useful method for the deprotection of 2,4-dintrophenylamino compounds, the borohydride method developed during our synthetic quest for a

new route to Uhle's ketone **III** will require more work. So far the only reaction in which a promising yield was obtained was for the DNP-amino intermediate it was used on for the synthesis of cryptosporin. The reaction will have to be tried on a more extensive variety of 2,4-dinitrophenylamines and the reaction conditions varied to see if any improvement can be obtained.

CHAPTER IV. EXPERIMENTAL

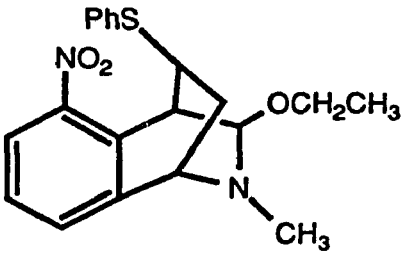
The ^{1}H NMR spectra were recorded on a General Electric QE300 (300 MHz) or Jeol JNM GX400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a General Electric QE300 (75 Mhz) spectrometer. Infrared Spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Elemental analysis were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. High resolution mass spectra were obtained from Rockefeller University, New York. Melting points are uncorrected and were determined on a Fisher-John melting point apparatus. Thin Layer chromatograms were done on precoated TLC sheets of silica gel F_{254} (E. Merck) using short/long wave UV light and 2,4-dinitrophenylhydrazine, potassium permanganate, or ninhydrin for detection. Chromatatron (radial chromatography) plates were prepared using Kieselgel 60 PF_{254} gipshaltig (E. Merck). All experiments were carried out in an inert atmosphere of nitrogen or argon. Solvents were purified and dried using standard procedures.

2-Methyl-5-Nitroisoquinolinium Iodide (A3):



To a stirred solution of 5-Nitroisoquinoline **(A1)** 4.0004 g (23 mm) in 15 ml of acetonitrile (anhydrous) was added iodomethane 3.0 ml (48 mm). The mixture was refluxed for 1 hour at which time the reaction mixture was semisolid due to precipitation of the salt. An additional 5 ml of acetonitrile was added and refluxing continued for 30 additional minutes. The solvent was removed by vacuo and afforded and orange solid weighing 7.0507 g (97%): mp = 203-205 °C. NMR (^{1}H 300 MHz CD_3OD) δ 10.29 (s, 1H, Ar-H), 9.02 (d, 1H, J = 7.81, Ar-H), 8.8 - 9.0 (m, 3H, Ar-H), 8.22 (m, 1H, Ar-H), 4.50 (s, 3H, -CH_3) ppm. ^{13}C NMR (75 MHz DMSO-d_6) δ 152.2, 144.5, 139.0, 137.7, 134.5, 131.0, 129.4, 128.4, 121.6, 48.7 ppm. IR (KBr) 2900, 1620, 1490, 1320, 1250, 1150, 1060 (b) cm^{-1}.

2-Methyl-3(R*)-ethoxy-5-nitro-9(S*)-thiophenyl-1(S*),4(R*)-ethano-1,2,3,4-tetrahydroisoquinoline (A8, x-ray sample):

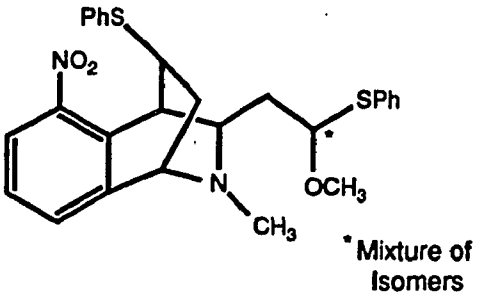


To a stirred mixture of 2-methyl-5-nitroisoquinolinium iodide 300 mg (0.95 mmol), $CaCO_3$ 574 mg (5.7 mmol) and methanol (15 mL) was added phenyl vinyl sulfide **A4** (128 µL, 0.98 mmol) and the reaction mixture stirred at room temperature for 3 days in an atmosphere of argon. The reaction mixture was filtered through Celite, the residue was washed with methanol and the combined filtrate concentrated in vacuo. Radial chromatography (EtOAc/pet. ether, 9:1) afforded 227 mg (61%) of **A6**, but with MeO- in place of EtO- at C3, as a light yellow solid. On recrystallization of the tricyclic adduct from ethanol the methoxy group on C_3 was replaced by ethoxy. The x-ray structure and spectral data were obtained from this adduct **A8**: mp 102-106 °C; IR ($CHCl_3$) 2940, 2860, 2810, 1585, 1525, 1450, 1350, 1120 (br), 1085 (br), 1020, 990, 970, 900 cm^{-1}; ^1H NMR (300

MHz $CDCl_3$) δ 8.00 (dd, 1 H, Ar<u>H</u>), 7.45-7.50 (m, 2 H, Ar<u>H</u>), 7.25-7.40 (m, 5 H, Ar<u>H</u>), 4.43 (m, 1 H, *J* = 2.5, 2.9 Hz, C_4-H), 4.21-4.27 (m, 1 H, *J* = 2.5, 4.9, 9.9 Hz, C_9-H), 3.85 (m, 1 H, C_6-H), 3.65 (d, 1 H, *J* = 2.9 Hz., C_3-H), 3.54-3.65 (m, 1 H, ½ $OC\underline{H}_2CH_3$), 3.40-3.52 (m, 1 H, ½ $OC\underline{H}_2CH_3$), 2.93 (ddd, 1 H, *J* = 3.4, 9.9, 13.9 Hz, ½ C_{10}-CH_2), 2.31 (s, 3 H, N_2-CH_3), 1.32 (m, 1 H, ½ C_{10}-CH_2), 1.26 (t, 3 H, $OCH_2C\underline{H}_3$). NMR analysis indicates that the material contains 10 % of the epimer at C_3. ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 142.8, 135.1, 131.7, 130.7, 129.1, 129.0, 128.8, 127.2, 126.9, 122.9, 94.9, 62.9, 59.0, 43.4, 39.3, 35.5, 15.5; high resolution mass spectrum (CI) calcd for $C_{20}H_{22}N_2O_3S$ + H^+ 371.1429, found 371.1491. Analysis calculated for $C_{20}H_{22}N_2O_3S$, C, 64.84; H, 5.99; N, 7.56; S, 8.65; Found C, 64.75; H, 5.93; N, 7.52; S, 8.45;

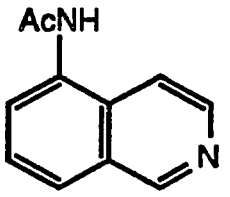
Crystal data $C_{20}H_{22}N_2O_3S$, <u>M</u> = 370.47, Monoclinic, <u>a</u> = 7.920 (5) Å, <u>b</u> = 16.151 (14) Å, <u>c</u> = 20.688 (15) Å, <u>ß</u> = 134.62(3)°, <u>U</u> = 1883 (2) $Å^3$, <u>Z</u> = 4, $\underline{D}_c$ = 1.307 g/cm^3, F(000) = 784. Mo-Kα radiation (λ = 0.71069 Å),μ = 0.2 cm^{-1}. Space group $P2_1/c$ (C_2^5h) from systematic absences: 0<u>k</u>0 when <u>k</u> ≠ 2<u>n</u> and h0l when l ≠ 2<u>n</u>. The structure was solved by direct methods and refined by full-matrix least squares iterations using 1333 data with I ≥ 2σ(I) to R = 0.072, R_w = 0.082. Atomic coordinates, anisotropic thermal parameters for the non-hydrogen atoms, and bond angles are given in Appendix B. on page 161.

2-Methyl-3(R*)-(2-methoxy-2-thiophenyl)-ethyl-5-nitro-9(S*)-thiophenyl-1(S*),4(R*)-ethano-1,2,3,4-tetrahydroisoquinoline (double adduct (A7)).



To a solution of 2-methyl-5-nitro-isoquinolinium iodide **A3** 0.300 g (0.949 mm) dissolved in 2.5 ml of dry methanol was added phenyl vinyl sulfide **A4** 310 ul (2.37 mm). The reaction mixture was stirred under an argon atmosphere for 24 hours. The solvent was removed to leave a red-brown solid. Radial chromatography (silica gel, P.E. / EtOAc 9:1) afforded the double adduct, a light tan solid, total mass 278.1 g (59 %) as two diastereomers. Lower isomer ^{1}H NMR (300 MHz $CDCl_3$) 7.99 (dd, 1H, J=1.75, 7.6, ortho to nitro), 7.2-7.5 (m, 13H), 4.82 (dd, 1H, J=4.8, 9.1, next to methoxy and thiophenyl), 4.16 (bs, 1H), 3.88 (bs, 1H), 3.68 (m, 1H, next to N), 3.39 (s, 3H, $OC\underline{H}_3$), 2.75 (bs, 1H), 2.48 (bs, 3H, $N\text{-}C\underline{H}_3$), 1.6 (m, 2H), 1.38 (m, 1H), 1.1 (m, 1H). Upper Isomer ^{1}H NMR (300 MHz $CDCl_3$) 8.0 (dd, 1H), 7.2-7.45 (m, 13H), 4.06 (m, 1H), 3.86 (m, 1H), 3.65 (m, 1H, next to methoxy and thiophenyl), 3.44 (s, 3H, $OC\underline{H}_3$), 2.95 (m, 1H), 2.74 (m, 1H), 2.42 (s, 3H), 1.55 (m, 1H), 1.40 (m, 1H), 1.09 (m, 1H).

5-Acetylaminoisoquinoline (B3):

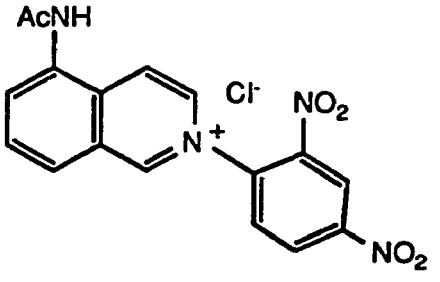


A solution of 5-Nitroisoquinoline **B1** 21.7730 g. (125 mm) dissolved in 350 ml of Ethanol(200 proof) was placed in a 500 ml Parr hydrogenation bottle. To this solution was added 1.112 g of 10% palladium on carbon. The bottle was attached to the Parr hydrogenator, evacuated, flushed with hydrogen and then shaking begun. The reaction mixture was allowed to shake overnight after which time no more hydrogen uptake was observed. The catalyst was removed by filtration through celite followed by repeated washings with ethanol. The reaction mixture was concentrated to approximately 250 ml followed by addition of 1 g of activated charcoal and then heated for 1 hr. Filtration through celite followed by concentration in vacuo yielded 5-aminoisoquinoline **B2** as a light tan solid.

The crude 5-Aminoisoquinoline **B2** was dissolved in 80 ml of Acetic Acid (anhydrous) and Acetic Anhydride 18 ml (190 mm) was added. The mixture was stirred overnight. Water, 70 ml was added to the solution which was then heated to 90 °C for 2 hr in order to decompose any remaining acetic anhydride. The

solution was poured into a 600 ml beakerand cooled in an ice bath. Neutraliztion of the reaction mixture by addition of concentrated ammonium hydroxide caused the product to precipitate. Filtration followed by washing with 2 x 50 ml of water and 2 x 50 ml petroleum ether then drying, yielded 20.888 g (89.7%) of the product **B3** as a light tan solid: mp 162-164 °C (lit[16] 166 °C). NMR (^{1}H 400 MHz $CDCl_3$) δ 9.14ppm (s, 1H, Ar-H), 8.39 (d, 1H, J = 5.50, Ar-H), 8.25 (s, 1H, Ar-H), 7.95 (d, 1H, J = 7.94, Ar-H), 7.70 (d, 1H, J = 7.94, Ar-H), 7.57 (d, 1H, J = 5.49, Ar-H), 7.47 (dd, 1H, J = 7.33, 7.93 Ar-H), 2.24 (s, 3H, Acetyl-CH_3).

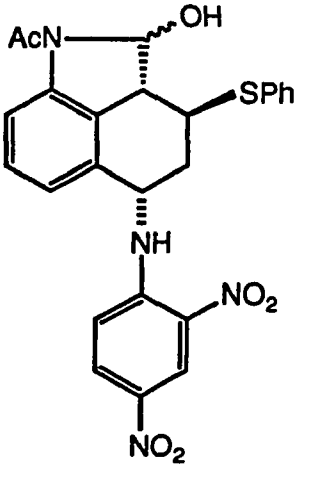
2-(2,4-Dinitrophenyl)-5-Acetylaminoisoquinolinium Chloride (B5):



5-Acetylaminoisoquinoline **(B3)** 370 mg (2.0 mm) was dissolved in 2.5 ml

acetonitrile(anhydrous) and then 2,4-dinitrochlorobenzene **(B4)** 445 mg (2.2 mm) was added. The reaction mixture was refluxed for 8 hours in an oil bath. The reaction mixture was now concentrated and the remaining acetonitrile removed by hi-vac. The product was washed with 3 x 2 ml portions of CH_2Cl_2 to yield 727 mg (94%) of the salt as an orange solid; mp 128-133 °C (dec). NMR (^{1}H 400 MHz DMSO-d_6) δ 9.2 (s, 1H, Ar-H), 8-9 ppm (m, 9H, Ar-H), 2.38 (s, 3H, Acetyl-CH_3).

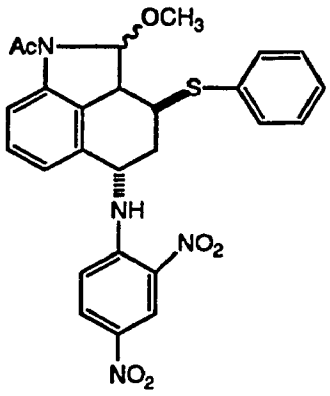
2-Hydroxy-1,2,2a,3,4,5-octahydro-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[c,d]indole (B6):



In a dry 50 ml 2-neck r.b. flask fitted with a stopper, magnetic bar, condensor, and nitrogen adapter were added 180 mg (0.463 mm) of the isoquinolinium salt **B5** followed by addition of 2 ml of anhydrous methanol. The salt was dissolved in the methanol by stirring for a few minutes. To the solution was added 302 mg (3.0 mm) of freshly dried $CaCO_3$. To the stirred suspension was added 90 ul (0.69 mm) of phenyl vinyl sulfide **A4**. The reaction mixture was stirred at 40 °C for 48 hrs. The reaction mixture was filtered through celite and washed with a mixture of CH_2Cl_2 / MeOH (4:1) followed by THF. After concentration by rotovap the product was placed on high vacuum for 20 min. To the product was added 7 ml of THF followed by addition of 3 ml of 0.01 N HCl. The reaction mixture was stirred under an argon atmosphere for 24 hrs. To the reaction mixture was added 10 ml of H_2O to yield an orange colored precipitate. The precipitate was filtered on a Buchner funnel and after drying the product was a yellow colored solid weighing 147 mg (63 % yield): mp 205-207 °C. When the reaction was run on a larger scale (approximately 20 g) the yield was higher (80%), probably due to better recovery of the finely powdered product. ^{1}H NMR (300 MHz DMSO-d_6) δ 8.8 (d, 1H, J=2.7 Hz, Ar-H-between NO_2 groups), 8.3 (d, 1H, J=7.73 Hz, Ar-NH), 8.27 (dd, 1H, J=2.6, 9.5 Hz, C-5-Ar-H on DNP), 7.44 (d, 1H, J=9.8 Hz, Ar-H), 7.33 (m, 2H, Ar-H), 7.1-7.25 (m, 4H), 7.01 (d, 1H, J=7.7 Hz, Ar-H), 6.93 (d, 1H, J=8.75 Hz, AcN-CH-OH), 5.95 (m, 1H, C_{2a}-H), 5.31 (m, 1H, C_5-H), 3.6 (m, 1H, ½-C_4-CH_2), 3.25 (m, 1H, C_3-H) 2.34 (s, 3H, acetyl-CH_3), 2.30 (s, 1H, OH), 2.15 (m,

1H, ½-C_4-C$\underline{H_2}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.5, 146.5, 140.4, 135.4, 132.5, 132.4, 131.7, 131.1, 130.3, 130.2, 130.0, 129.0, 128.8, 127.2, 123.6, 122.4, 115.5, 115.2, 85.9, 49.2, 46.4, 37.0, 36.4, 23.1 ppm. Analysis calculated for $C_{25}H_{22}N_4O_6S$, C, 59.28; H, 4.38; N, 11.06; S, 6.33; Found C, 59.37; H, 4.49; N, 10.94; S, 6.32; Low resolution mass spectra found no molecular ion peak.

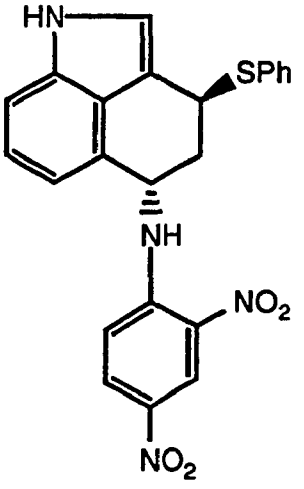
2-Methoxy-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-1,2,2a,3,4,5-Hexahydrobenz[c,d]indole (B6A):



To a solution of 0.2000 g (0.51 mm)2-(2,4-dinitrophenyl)-5-acetyl-aminoisoquinolinium chloride **(B5)** in 2 ml of anhydrous methanol was added 0.135 ml (1.0 mm) phenyl vinyl sulfide **(A4)**. The reaction mixture was stirred under a nitrogen atmosphere for 20 hours. A yellow precipitate was observed in the flask. Water 1 ml was added to the reaction mixture and the flask cooled in an ice bath. The yellow precipitate was filtered and washed with cold methanol. After drying

the product weighed 0.1353 g (51%). NMR (^{1}H 400MHz $CDCl_3$) δ 9.16 (d 1H J=2.44), 8.6 (d 1H J=7.33), 8.27 (dd 1H J=2.44, 9.15), 7.43 (dd 2H), 7.3 (mult. 5H), 6.94 (d 1H J=9.16), 6.85 (d 1H J=7.32), 5.80 (d 1H J=3.66), 4.96 (m 1H), 3.49 (s 3H), 3.25 (m 2H), 2.46 (mult. 1H), 2.32 (s 3H), 2.29 (mult. 1H).

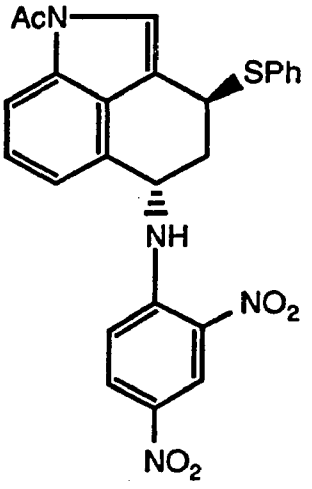
3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[c,d]indole (C1):



To a 14 ml vial was added the N-acetyl-hydroxy-indolene **B6** 20 mg (.040 mm) followed by addition of 2 ml of 10% NH_2NH_2 in MeOH. The indolene did not dissolve well but was allowed to stir over the weekend (72 hrs.) under an argon atmosphere. The reaction mixture was added to 5 ml of water and extracted with

3 x 10 ml portions of CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$, and concentrated to give 17 mg of crude product. Preparative TLC (silica gel-CH_2Cl_2/MeOH 95:5) afforded 5.7 mg (33%) of the indole. NMR (^1H 300MHz $CDCl_3$) δ 9.23 ppm (d 1H), 9.07 (dd 1H), 8.24 (broad s 1H), 8.19 (dd 1H), 7.0-7.6 (mult. 9H), 5.72 (mult. 1H), 5.1 (dd 1H), 2.7 (dt 1H), 2.35 (ddd 1H).

1-Acetyl-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[c,d]-Indole (C2):



In a 100 ml. 2-necked r.b. flask were dissolved 200 mg (0.40 mm) of the hydroxyindolene **B6** in 6 ml of pyridine. To the solution were added 169 mg of phosphorous pentachloride (0.81 mm) and the reaction stirred for 10-15 minutes. The brown reaction mixture was poured into 50 ml of water and extracted with 5 x 25 ml portions of CH_2Cl_2. The organic layers were combined and washed with 25 ml of brine. The organic layer was dried with $MgSO_4$ and concentrated in

vacuo. The resulting product was washed with 2 x 5 ml portions of benzene followed by concentration to remove the remaining pyridine. Column chromatography of the crude product using CH_2Cl_2 as the eluent gave 171 mg (88.4 %) of the indole as a bright yellow solid: mp 218-219 °C. The reaction can be done on a large scale (approximately 15 g) and the product precipitated by addition of water. The product is then washed with cold methanol to yield a useable product in slightly lower yield of 80 %. ^{1}H NMR (300 MHz $CDCl_3$) δ 9.2 (d, 1H, J=2.6), 8.95 (d, 1H, J = 8.2, Ar-N-H), 8.25 (dd, 2H, J = 2.5, 9.4 + m, 1H, Ar-H), 7.4-7.6 (m, 6H, Ar-H), 7.3 (m, 1H), 7.1 (bs, 1H, indole-H), 7.0 (d, 1H, J = 9.6), 5.6 (m, 1H, benzylic next to Ar-N-H), 4.95 (m, 1H, next to S-Ph), 2.7 (m, 1H, ½-CH_2), 2.6 (s, 3H N-Ac), 2.35 (m, 1H, ½-CH_2). ^{13}C NMR (75 MHz $CDCl_3$) δ 168.3, 148.0, 136.5, 134.0, 133.7, 133.1, 131.1, 130.7, 129.5, 129.2, 128.4, 127.7, 126.6, 124.4, 120.7, 118.3, 117.4, 116.3, 114.2, 48.5, 38.9, 35.5, 23.8. High resolution mass spectrum (CI) calcd for $C_{25}H_{20}N_4O_5S$ 488.1154, found 488.1197. Analysis calculated for $C_{25}H_{20}N_4O_5S$, C, 61.47; H, 4.13; N, 11.47; Found C, 61.38; H, 4.04; N, 11.36.

X-RAY DATA: F.W. = 468.54; Space Group: P21/B (#14); a = 23.427(20)Å, b=19.435(0)Å, c = 10.873 (0)Å, α = 90.0(0)°, γ = 113.32 (0)°, V=4546.10 Å^3; Z = 8, D_{calc} = 1.369@; Radiation = Cu K_α (λ = 1.54056A); @ = 15.9 cm^{-1}; F(000) =

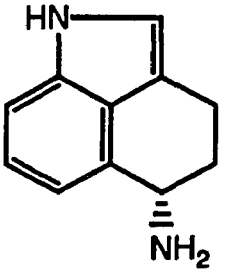
1968; Temperature = 23 @ 1°; Final R = 0.115; Number of Unique Reflections = 6697. Structure was solved by direct methods. Atomic coordinates, anisotropic thermal parameters for the non-hydrogen atoms, and bond distances are given in Appendix B. on page 167.

Reaction of indole C2 with K^+ $^-SC6H5$

In a 25 ml flask was dissolved 45 mg (0.09 mm) of 1-acetyl-3-thiophenyl-5-(2,4-dinitrophenyl)-amino-benz[cd]indole (**C2**) in 2 ml of tetrahydrofuran and 1 ml of methanol. To the mixture was added 54 mg (0.36 mm) of potassium thiophenoxide. After 3 hrs, no reaction was detectable by tlc. In order to make the thiophenoxide ion more nucleophilic, 20 mg of 18-crown-6 ether was added and the mixture heated to reflux. The reaction was allowed to continue overnight. Workup involved pouring the mixture into 25 ml of water and extracting with 3 x 15 ml portions of CH_2Cl_2. The organic layers were combined, washed with 25 ml of water, dried with $MgSO_4$, filtered and concentrated in vacuo to give 41 mg of crude product. The crude product was purified on a small chromatographic column using silica gel and eluting with CH_2Cl_2 followed by 2% MeOH in CH_2Cl_2. The first fraction isolated was 20 mg of a yellow material that was a mixture of epimers at the C_3 carbon where the indole was partially deacetylated. The second fraction isolated was 11 mg of a yellow material that ^1H NMR indicated was a 9:1 mixture of epimers where the C_3-thiophenyl group was replaced by a methoxyl group and the indole was partially deacetylated. Selected NMR data. ^1H (300 MHz $CDCl_3$)

Epimerized C_3-thiophenyl compound: δ 5.69 (m, 1H, epimer-1 C_5-H), 5.34 (m, 1H, epimer-2 C_5-H), 5.06 (m, 1H, epimer-1 C_3-H), 4.86 (m, 1H, epimer-2 C_3-H), the rest of the spectrum also exhibits peak doubling due to the two diastereomers. ^{1}H (300 MHz $CDCl_3$) C_3-methoxy compound: δ 9.22 (d, 1H, J=2.67, Ar-H), 9.06 (d, 1H, J = 8.26, N-H), 8.30 (dd, 2H, J = 2.6, 9.4, Ar-H + indole N-H), 7.35 (d, 1H, J = 8.28, Ar-H), 7.2-7.3 (m, 3H, Ar-H), 7.03 (d, 1H, J = 7.14, Ar-H), 5.57 (m, 1H, C_5-H), 4.71 (m, 1H, C_3-H), 3.40 (s, 3H, OCH_3), 2.78 (m, 1H, ½C_4-CH_2), 2.15 (m, 1H, ½C_4-CH_2), the spectrum also showed the minor epimer where the C_3-OCH_3 appears at δ = 3.47 ppm.

5-Amino-1,3,4,5-tetrahydrobenz[c,d]indole (E5):



In a 100 ml 2-necked r.b. flask fitted with a rubber septa, magnetic bar, and argon inlet was dissolved 300 mg of 1-acetyl-3-thiophenyl-5-(2,4-dinitrophenyl)-amino-benz[c,d]-indole **(C2)** in 20 ml of anhydrous THF. To the stirred solution

was added 57.8 mg (2.65 mm) of $LiBH_4$ dissolved in 10 ml of isopropanol with 12 µl (0.66 mm) of H_2O added. The reaction mixture immediately turned deep red in color. After 30 minutes the solution began to lose the red color and after 40 minutes the solution was yellow in color again. The reaction mixture was poured into 100 of sat'd $NaHCO_3$ solution and extracted with 100 ml of CH_2Cl_2. The aqueous layer was then extracted with 2 x 50 ml portions of CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo.

Desulfurization:

Method A: (Tributyltin hydride).

The material was transferred to a 100 ml r.b. flask for the desulfurization step. In a dry 100 ml 2-necked r.b. flask fitted with a stopper, magnetic bar, condenser and argon inlet was dissolved, with warming, the previous product in 6 ml of dry benzene. To the solution was added 122 mg of AIBN. The reaction mixture was degassed under vacuum and flushed with argon two times. To the solution was 500 ul (1.86 mm) of tributyltin hydride. The reaction mixture was set up to reflux under an argon atmosphere. The reaction must be monitored by tlc because great differences in the reaction time have been observed. Reaction times have varied from 1 hr up to 48 hrs. The reaction mixture is poured into a 125 ml separatory funnel containing 75 ml of hexane. The organic layer is extracted with 40 ml of 10 % HCl followed by 4 x 10 ml portions. The acidic layers were combined and neutralized with $NaHCO_3$. The aqueous layer was extracted with 6 x 50 ml portions of EtOAc followed by 2 x 30 ml portions. The organic layers were

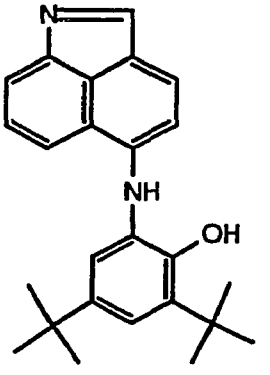
combined, dried with $MgSO_4$, and concentrated in vacuo to give 58 mg (55 %) of the product as a yellow-brown residue. ^1H NMR (300 MHz DMSO-D_6) δ 10.5 (bs, 1H, indole-N<u>H</u>), 6.9-7.2 (m, 4H), 4.05 (dd, 1H, J=3.9, 8.6, C_5-<u>H</u>), 3.2 (bs, 2H, N<u>H_2</u>), 2.3 (m, 2H, allylic-<u>H</u>), 2.05 (m, 1H, ½C_4-CH_2), 1.7 (m, 1H, ½C_4-CH_2).

Method B: Raney-Nickel.

In a dry 100 ml 2-neck r.b. flask fitted with a magnetic bar, stopper, condensor and argon inlet was dissolved 360 mg of 3-thiophenyl-5-amino-tetrahydrobenz[cd]indole (as prepared above) in 10 ml of t-butanol. To the solution was transferred approximately 1 g of raney-nickel W2 that was previously washed with 3 x 1 ml of acetone and 3 x 1 ml of t-butanol. The mixture was setup to reflux under an argon atmosphere for 6 hours. The reaction mixture was transferred to the thimble of a Soxhlet extractor and then setup to reflux for 12 hours. The reaction mixture was concentrated in vacuo to give 105 mg (61 % based on dedinitrophenylation and desulfurization) of the amine as a dark brown oil. An analytical sample was treated with acetic anhydride and pyridine to form the acetyl derivative which after chromatography was a tan solid: $mp_{(EtOAc)}$ 225-226 °C. ^1H NMR (300 MHz DMSO-D_6) δ 7.95 (bs, 1H, indole-N<u>H</u>), 7.19 (m, 1H, Ar-<u>H</u>, partially hidden by $CHCl_3$), 7.12 (t, 1H, J = 7.6, Ar-<u>H</u>), 6.92 (d, 1H, J = 7.0, Ar-<u>H</u>), 6.85 (bs, 1H, Indole-<u>H</u>), 5.68 (bs, 1H, acetyl-N-<u>H</u>), 5.38 (m, 1H, 2.3, C_5-<u>H</u>), 2.87 (m, 2H, C_3-CH_2), 2.22 (m, 1H, ½C_4-CH_2), 2.02 (s, 3H, acteyl-C<u>H_3</u>), 1.95 (m, 1H, ½C_4-C<u>H_2</u>, partially hidden by acetyl C<u>H_3</u>). Low resolution mass spectrum (EI) (m/e)

calculated for $C_{13}H_{14}N_2O$, 214; found 214. Analysis calculated for $C_{13}H_{14}N_2O$, C, 72.87; H, 6.59; N, 13.07; Found C, 72.99; H, 6.70; N, 13.12.

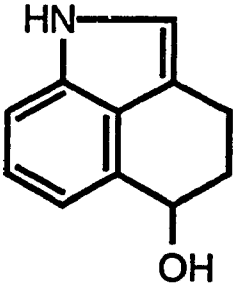
Aromatized Corey's Reagent Product (G4).



In a dry 25 ml 2-necked r.b. flask was dissolved 10 mg of the amino indole (0.58 mm)(E5) in 300 µl of methanol. To the stirred solution was added 12.2 mg of Corey's reagent, 3,5-di-t-butyl-1,2-benzoquinone (0.055 mm) and the reaction mixture stirred for 45 min. The solution was acidifed to pH 4 by addition of oxalic acid. The mixture was stirred for 1.5 hrs until no starting material remained according to tlc. The reaction mixture was poured into 2 ml of water and extracted

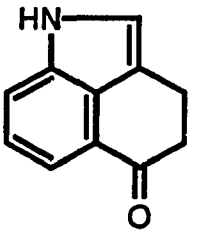
with CH_2Cl_2 (5 x 3 ml). The organic fractions were combined, dried with $MgSO_4$, filtered and concentrated to yield 18 mg of a brown oil. Column chromatography (silica gel - CH_2Cl_2 / MeOH 98:2) gave 12 mg (55 %) of an orange oily material that appears to be the fully aromatized product **G4**. ^1H NMR (300 MHz $CDCl_3$) 8.03 (d, 1H, J=8.00, Ar-H), 8.00 (bs, 1H,), 7.67 (d, 1H, J=7.48, Ar-H), 7.53 (d, 1H, J=8.78, Ar-H), 7.44 (t, 1H, J=7.74, Ar-H), 7.08 (d, 1H, J=2.3, Ar-H), 6.75 (d, 1H, J=8.80, Ar-H), 1.49 (s, 9H, $-C(CH_3)_3$), 1.30 (s, 9H, $-C(CH_3)_3$). The NMR spectrum was run again using acetone-d_6 as the solvent and a proton observed at 7.23 (d) with a meta coupling constant that is connected to the proton at 7.08 ppm. These are the protons from the benzoquinone ring.

5-Hydroxy-1,2,3,4-Tetrahydrobenz[cd]indole (H1):



In a 50ml flask were dissolved 9.1050 g (30.6 mm) of sodium nitroprusside in 30 ml of water. The solution was degassed by bubbling argon through the solution for 20 minutes. In a 250 ml 3-neck flask were combined 864 mg (5.0 mm) of 5-amino-1,3,4,5-tetrahydrobenz[cd]indole **E5**, 30 ml of water and 269 mg (2.5 mm) of sodium carbonate. The solution was degassed by bubbling argon through it for 15 minutes. The amine was not very soluble in the solution. To the amine suspension was added the nitroprusside solution dropwise over a 1 hour period using a syringe pump. The solution was allowed to stir overnight at room temperature. The reaction was still not complete so 1.500g (5.0 mm) of sodium nitroprusside were added and the reaction mixture was heated to 50 °C. After 24 hours another 3.000g (5.0 mm) of nitroprusside were added. After 2 hours the reaction mixture was poured into a 250 ml separatory funnel. Approximately 15 g of potassium carbonate were added to the solution in order to salt out the organic material. The aqueous layer was extracted with 4 x 50 ml of ethyl ether. The organic layers were combined, dried with $MgSO_4$, and filtered through florisil. After concentration 196 mg of a tan solid were obtained. Radial chromatography (alumina, CH_2Cl_2) afforded 120 mg (14 %) of 5-hydroxy-1,3,4,5-tetra-hydrobenz[cd]indole as a tan solid. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.98 (bs, 1H, indole N-H), 7.1-7.3 (m, 3H, Ar-H), 6.95 (s, 1H, indole-H), 5.1 (t, 1H, J=5.1 Hz, C_5-H), 2.9-3.1 (m, 2H, C_4-CH_2), 2.23 (dd, 2H, J=6.0, 11.7 Hz, C_3-CH_2).

5-Keto-1,3,4,5-tetrahydrobenz[cd]indole (Uhle's Ketone) (III)



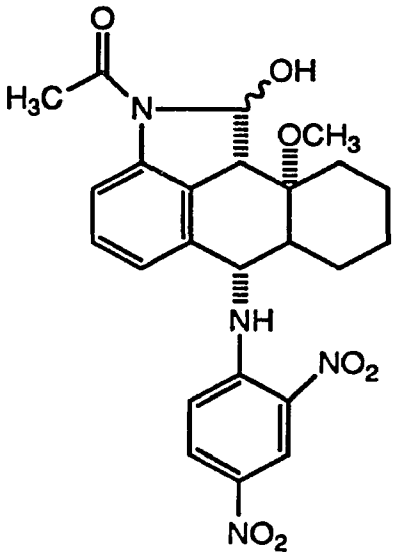
Method A: Oxidation of 5-aminobenz[cd]indole (E5).

In a 10 ml 2-necked r.b. flask fitted with a rubber septum and argon inlet were dissolved 10 mg (0.058 mm) of the aminoindole **E5** in 100 ul of water and 200 ul of THF as a co-solvent. To the stirred solution was added 0.5 mg (0.003 mm) of $AgNO_3$ followed by 2.2 mg (0.055) of NaOH. To the stirred reaction mixture was added an ice cold solution of 55 mg (0.2 mm) of $K_2S_2O_8$ dissolved in 100 µl of water. The reaction mixture was stirred under an argon atmosphere for 3 hrs. The reaction mixture was poured into 2 ml of H_2O and extracted with 3 x 2 ml of EtOAc. The organic layers were combined and shaken with 2 ml of 1 % HCl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to yield 4 mg of crude product. ^1H NMR of the crude reaction mixture indicated that the ketone was present in the mixture. The product was purified by column chromatography (silica gel - $CHCl_3$) to yield 1 mg (10.8 % yield). ^1H NMR (300 MHz $CDCl_3$) δ 8.1 (bs, 1H, indole-N<u>H</u>), 7.6 (d, 1H, J=7.3), 7.54 (d, 1H, J=8.0), 7.35 (m, 1H), 7.1 (s, 1H, C_2-<u>H</u>), 3.27 (t, 2H, J=7.0), 2.93 (t, 2H, J=7.1).

Method B: Oxidation of 5-Hydroxybenz[cd]indole (H1).

In a dry 25 ml r.b. flask fitted with an argon inlet and magnetic stir bar were dissolved 75 mg (0.47 mm) of 5-hydroxy-1,3,4,5-tetrahydrobenz[cd]-indole **H1** in 2.5 ml of CH_2Cl_2. To the solution were added 673 mg of PCC on silica gel followed by addition of 23 μl of acetic acid. The reaction mixture was stirred for 24 hours under an argon atmosphere. To the reaction mixture were added 5 ml ethyl ether and stirring continued for 15 minutes. The reaction mixture was filtered through celite and eluted with 30 ml of ethyl ether. After concentration to approximately 10 ml the solution was transfered to a 25 ml seperatory funnel. The organic phase was extracted with 2 x 2 ml of 5% HOAc, 2 x 2 ml H_2O, 1 x 2ml 5% $NaHCO_3$ and 2 ml of brine. The organic layer was dried and concentrated in vacuo to give 30 mg of a brown oil. Column chromatography (Florisil) using chloroform as the eluent yielded 19 mg (24 %) of the ketone as a yellow brown solid: mp 162-164 °C (lit.[3] 162-164 °C). ^{1}H NMR (300 MHz $CDCl_3$) δ 8.16 (bs, 1H, indole-N<u>H</u>), 7.55 (d, 1H, J=7.4), 7.48 (d, 1H, J=8.0), 7.35 (m, 1H,), 7.1 (s, 1H, C_2-<u>H</u>), 3.21 (t, 2H, J=7.0), 2.87 (t, 2H, J=7.1). IR (Nujol) 3260, 1655, 1622, 1605 cm^{-1}. High resolution mass spectrum (EI) calcd for $C_{11}H_9NO$ 171.068, found 171.0672.

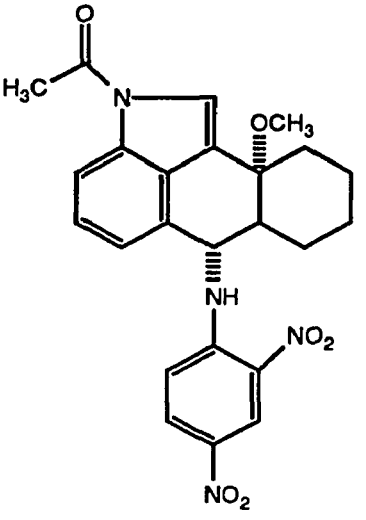
1-Acetyl-6-(2,4-dinitrophenyl)-amino-10a-methoxy-2,2,2a,6,6a,7,8,9,10,10a-decahydro-napth[1,2,3-cd]indole (CC3):



In a dry 100 ml 2-neck r.b. flask fitted with a magnetic bar, stopper, condensor, and argon inlet were dissolved 390 mg (1.0 mm) of 2-(2,4-dinitrophenyl)-5-nitro-isoquinolinium chloride **B5** in 3 ml of anhydrous methanol. To the solution were added 700 mg (6.99 mm) of freshly flame dried $CaCO_3$. To the stirred suspension were added 190 µl (2.1 mm) of methoxycyclohexene. The reaction mixture was stirred at 40 °C under an argon atmosphere. Over a three

day period two more additions of 190 µl (2.1 mm) of methoxycyclohexene were added to the reaction mixture until the isoquinolinium salt was consumed. To the reaction mixture were added 10 ml of CH_2Cl_2 and the reaction mixture was filtered through a sintered funnel to remove the $CaCO_3$. The filter pad was washed with 4 x 10 ml of dimethoxyethane:CH_2Cl_2 (1:1) and the reaction mixture concentrated in vacuo. The reaction mixture was dissolved in a mixture if THF / H_2O (10 : 1) and 2 ml of 0.01 N HCL addded. The reaction mixture was stirred at room temperature for 24 hours under an argon atmosphere. The hydroxyindoline was precipitated by addition of cold water and isolation was accomplished by filtration. The product was washed with 2 x 3 ml of cold methanol followed by 2 x 5 ml of petroleum ether. After drying 265 mg (57 %) of the indoline **CC3** were obtained as a bright yellow solid. ^1H NMR (300 MHz DMSO-d_6) showed the presence of two diastereomers in approxomately 5:1 ratio. Selected NMR data are as follows: Major isomer: δ 8.45 (d, 1H, J = 8.6, N-H), 3.68 (d, 1H, J = 6.9, C_{2a}-H), 2.89 (s, 3H, OCH_3), 2.18 (s, 3H, Acetyl-CH_3) Minor Isomer: δ 8.56 (d, 1H, J = 8.6, N-H), 3.78 (m, 1H, C_{2a}-H), 2.93 (s, 3H, OCH_3), 2.22 (s, 3H, Acetyl-CH_3). Low resolution mass spectrum found no molecular ion.

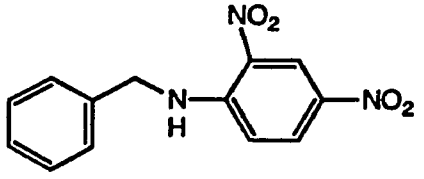
1-Acetyl-6-(2,4-dinitrophenyl)-amino-10a-methoxy-2,6,6a,7,8,9,10,10a-octahydro-napth[1,2,3-cd]indole (CC4):



In a dry 100 ml 2-neck r.b. flask fitted with a magnetic bar, stopper, and argon inlet were dissolved 242 mg (0.5 mm) of the indoline in 10 ml of pyridine. To the solution were added 108 mg of phosphorus pentachloride. The reaction mixture was stiired for 1.5 hours at room temperature under an argon atmosphere. The reaction mixture was poured into a 250 ml seperatory funnel containig 50 ml of water. The aqueous layer was extracted with 1 x 75 ml and 2 x 50 ml portions of CH_2Cl_2. The organic layers were combined, washed with 1 x 50 ml of water, and 2 x 50 ml of brine. The organic layer was dried and concentrated to give a

yellow-brown oil. The oil was azeotroped with 3 successive portions of toluene in order to remove the residual pyridine. Radial chromatography (silica gel) with chloroform provided 152 mg (62 %) of the indole as a bright yellow solid: mp 183-185 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ 10.46 (bs, 1H, N-H), 9.07 (d, 1H, J = 2.77, Ar-H), 8.28 (dd, 1H, J = 2.6, 9.6, Ar-H), 8.13 (bs, 1H, Ar-H), 7.47 (bs, 1H, Ar-H), 7.40 (d, 1H, J = 9.74, Ar-H), 7.25-7.38 (m, 2H, Ar-H), 4.89 (d, 1H, J = 8.81, C_5-H), 3.23 (s, 3H, OCH_3), 2.67 (s, 3H, Acetyl-CH_3), 2.65 (m, 1H, ½-$C_{10}CH_2$), 2.46 (m, 1H, ½-C_6CH_2), 1.78 (m, 1H, ½-C_9CH_2), 1.5-1.7 (m, 3H, ½-C_7CH_2, ½-C_8CH_2, ½-$C_{10}CH_2$), 1.3-1.38 (m, 1H, ½-C_8CH_2), 1.13-1.23 (m, 1H, ½-C_9CH_2), 0.78-0.93 (m, 1H, ½-C_7CH_2). ^{13}C NMR (75 MHz $CDCl_3$) δ 168.4, 146.6, 135.1, 130.2, 130.0, 128.2, 126.5, 125.0, 122.3, 121.6, 116.0-116.5 (appears to be 3 quaternary carbons - not well seperated), 113.2, 76.1, 54.8, 48.8, 48.0, 31.8, 29.2, 25.0, 24.0, 23.2 ppm. High resolution mass spectrum (CI) calcd for $C_{24}H_{24}N_4O_6$ 464.1696, found 464.1685.

_N_-2,4-DNP-Benzylamine (FF28):



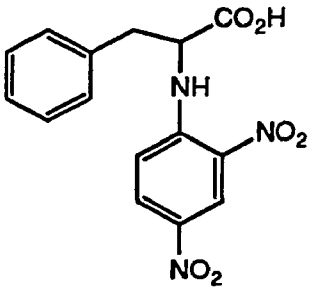
In a dry 250 ml 2-neck r.b. flask fitted with a magnetic bar, stopper, condenser and argon inlet were dissolved 22.0 ml (0.20 m) of benzylamine in 80 ml of acetonitrile. To the solution were added 24.4 g (0.24 m) $CaCO_3$ and 40.85 g (0.20 m) 1-chloro-2,4-dinitrobenzene. The mixture was setup to reflux for 16 hours. The reaction mixture was filtered through a sintered glass funnel and the mixture concentrated in vacuo to give 51.681 g (94%) of the protected amine as a bright yellow solid: mp 116-117 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ 9.14 (d, 1H, J=1.95, Ar-H), 8.92 (bs, 1H, Ar-N-H), 8.23 (dd, 1H, J = 2.48, 9.48, 1H, Ar-H), 7.3-7.4 (m, 5H, Ar-H), 6.93 (d, 1H, J= 9.50, Ar-H), 4.66 (d, 2H, J=5.63, Ph-CH_2). ^{13}C NMR (75 MHz $CDCl_3$) δ 148.2, 136.5, 135.6, 130.8, 130.3, 129.3, 128.3, 127.1, 124.1, 114.4, 47.6 ppm.

Dedinitrophenylation of *N*-2,4-Dinitrophenyl-Benzylamine (FF28):

In a 250 ml 2-neck r.b. flask fitted with a magnetic bar, stopper and argon and argon inlet were dissolved 547 mg (2.0 mm) of *N*-2,4-dinitrophenyl-benzylamine in 40 ml of THF. In a 50 ml Erlenmeyer flask were dissolved 438 mg (20.0 mm) $LiBH_4$ in 30 ml of THF and 4 ml of water. The borohydride suspension was added dropwise to the DNP-amine solution over a 5 minute period. The DNP-amine solution immediately turned red upon addition of the borohydride solution. After 5 minutes the red color faded to yield a clear solution with a white precipitate. The solution was filtered through a sintered funnel and the precipitated washed

with 3 x 10 ml of THF. The reaction mixture was transferred to a 500 ml separatory funnel and 50 ml of water added. The solution was acidified to pH ≈ 4 with acetic acid and the aqueous layer extracted with 3 x 50 ml of ether. The aqueous layer was neutralized with saturated sodium bicaronate solution and extracted with 3 x 50 ml portions of ether. The organic layers were combined, washed with 2 x 25 ml of brine, dried, and concentrated in vacuo to give 140 mg of a yellow oil. The product was applied to a small silica gel column and eluted with CH_2Cl_2 : MeOH (95 : 5) to give 116 mg (54%) of the product, benzylamine as a yellow oil. ^1H NMR (300 MHz $CDCl_3$) δ 7.2-7.5 (m, 5H), 4.95 (s, 2H, $N\underline{H_2}$), 3.95 (s, 2H, $C\underline{H_2}$).

***N*-(2,4-Dinitrophenyl)-L-Phenylalanine :**

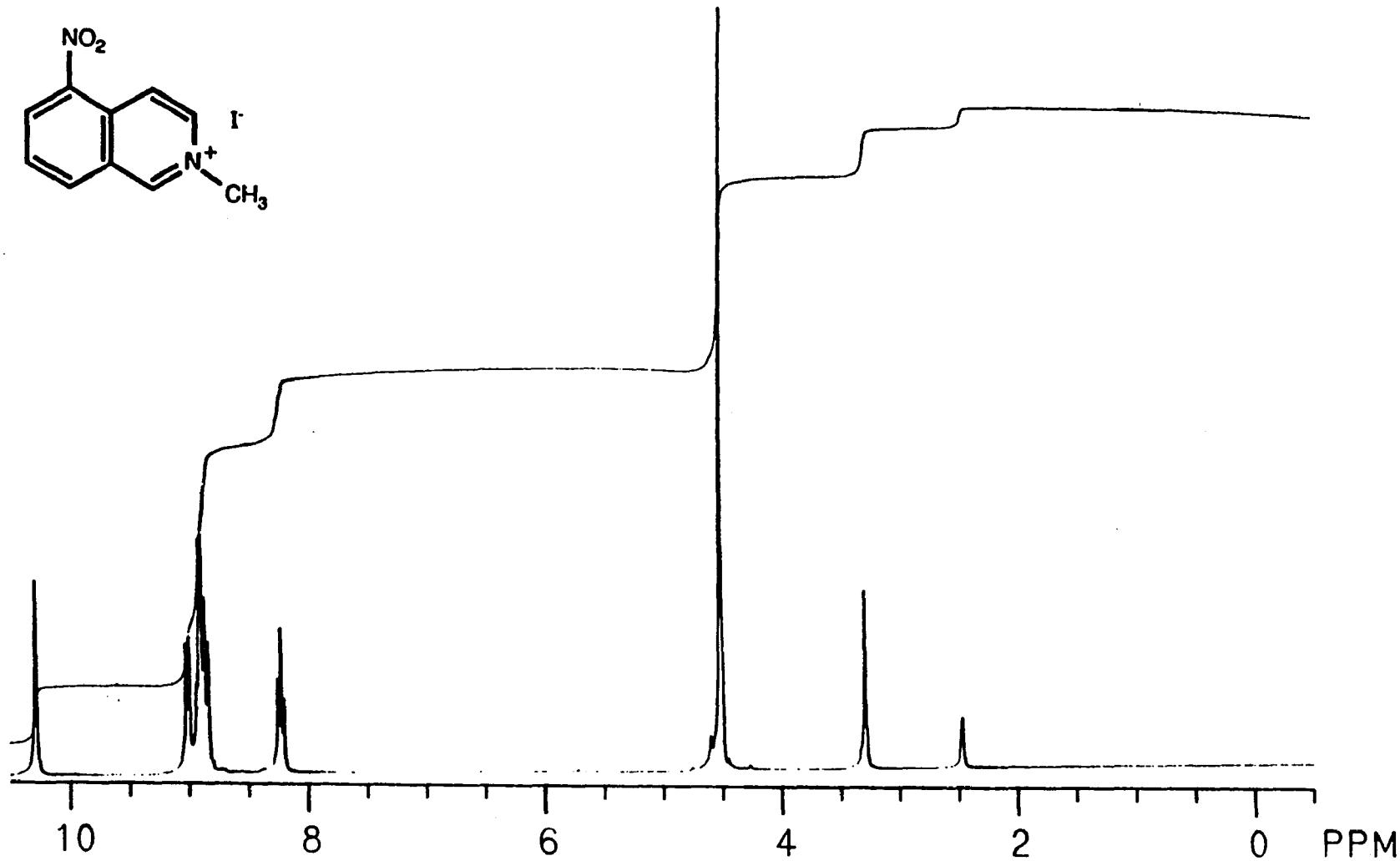


In a 100 ml 2-neck r.b. flask fitted with magnetic bar, stopper and argon inlet were added 1.6527 g (10 mm) of L-phneylalanine to a mixture of 15 ml

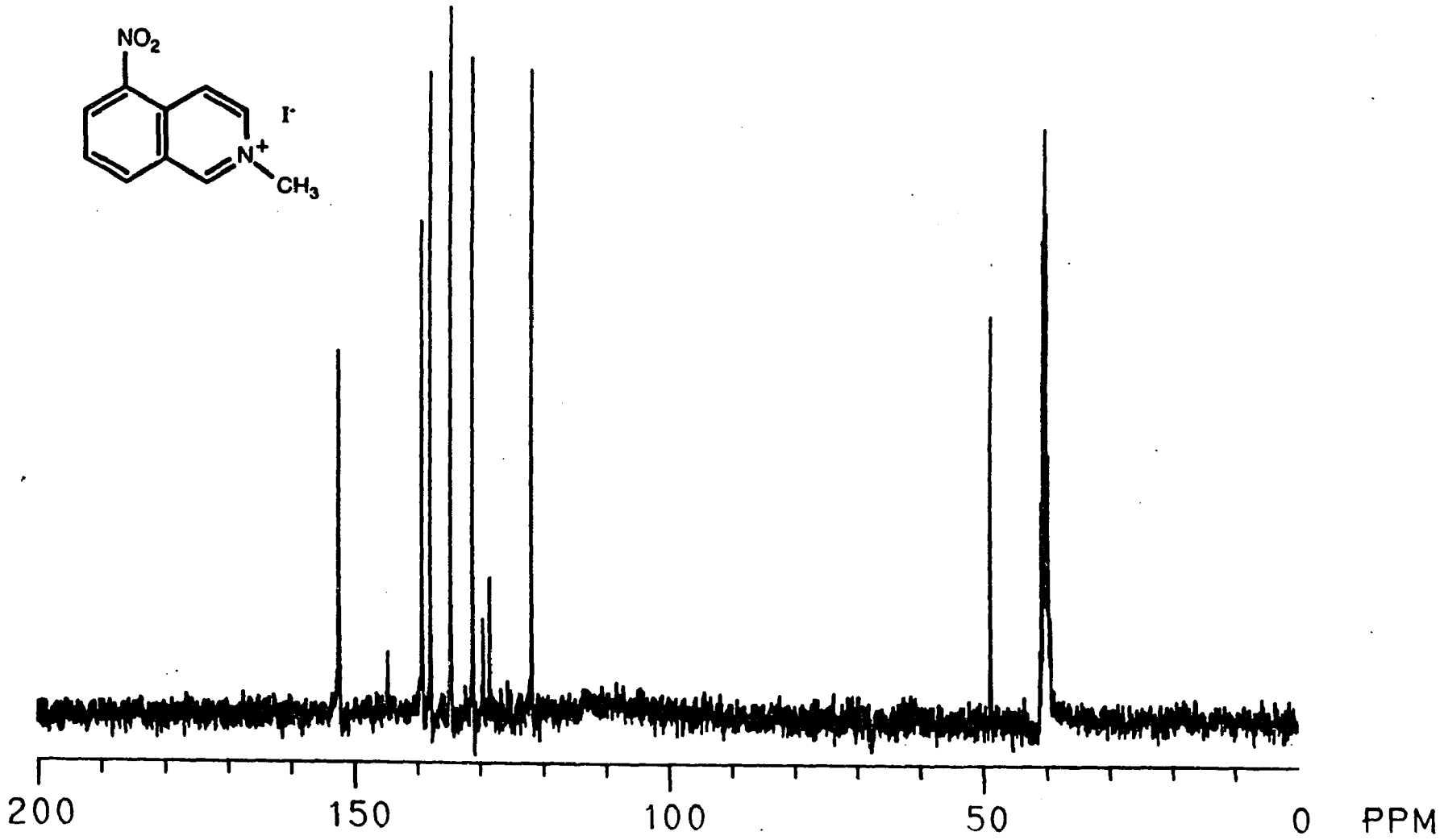
ethanol and 20 ml of water. After addition of 3.18 g (30 mm) sodium carbonate the amino acid appeared to go into solution. To the solution were added 2.026 g (10.0 mm) of 1-chloro-2,4-dinitrobenzene. The reaction was stirred under an argon atmosphere for 4 days. The reaction mixture was filtered through a sintered funnel to remove the sodium carbonate and concentrated. To the residue were added 50 ml of water follwed by acidification to pH ≈ 3 with aqueous HCl. The reaction mixture was transferred to a 250 ml seperatory funnel and extracted with 1 x 150 and 1 x 50 ml of CH_2Cl_2. The organic layer was washed with 1 x 100 ml of 1 *N* acetic acid. The organic layer was concentrated, dried with magnesium sulfate and concentrated in vacuo to give a 3.1351 g (94.6 %) of the DNP-amino acid as a bright yellow solid: mp 180-182 °C (lit[52] 186 °C). ^{1}H NMR (300 MHz $CDCl_3$) δ 9.85 (bs, 1H, CO_2H), 9.13 (d, 1H, J=2.59, Ar-H), 8.89 (d, 1H, J = 7.41 Ar-N-H), 8.23 (dd, 1H, J = 2.55, 9.40, 1H, Ar-H), 7.2-7.4 (m, 5H, Ar-H), 6.74 (d, 1H, J = 9.50, Ar-H), 4.66-4.73 (m, 1H, α-CH), 3.48 (dd, 1H, J = 4.8, 14.0, ½-benzylic-CH_2), 3.31 (dd, 1H, J=7.5, 14.0, ½-benzylic-CH_2). ^{13}C NMR (75 MHz $CDCl_3$) δ 175.8, 148.5, 147.1, 136.9, 134.3, 131.2, 130.3, 129.2, 128.0, 124.2, 114.0, 57.11, 38.3 ppm.

APPENDIX

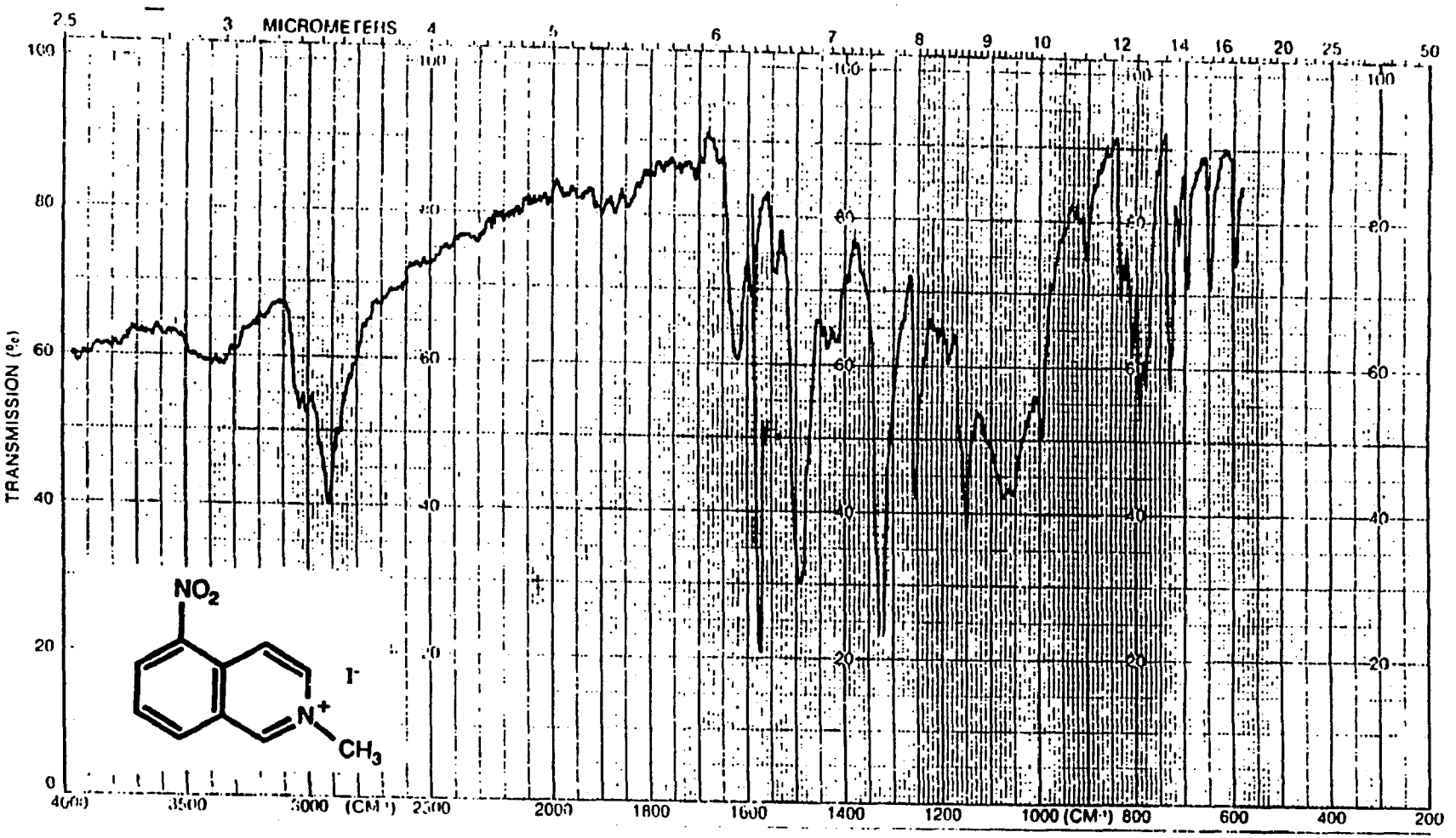
A. SPECTRAL DATA



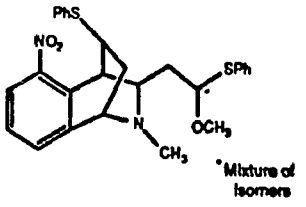
^{1}H NMR (**A3**): 5-Nitroisoquinolinium Methiodide.

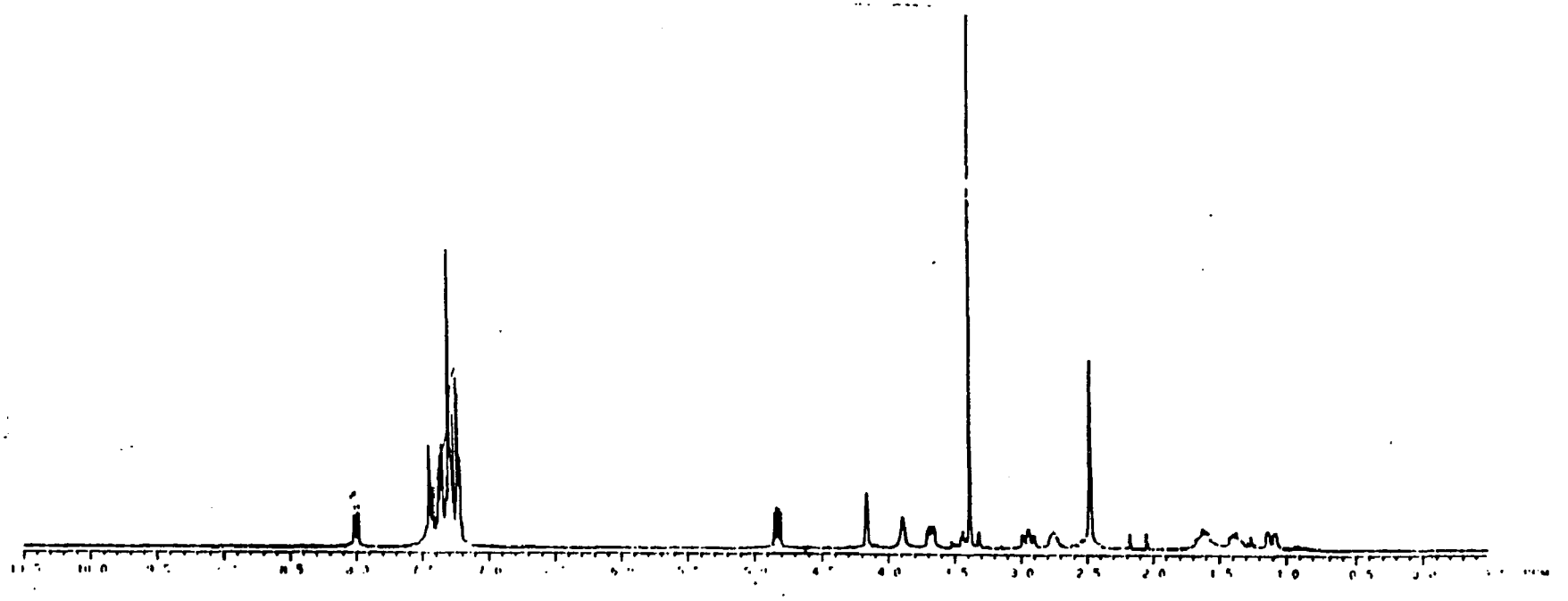


^{13}C NMR **(A3)**: 5-Nitroisoquinolinium Methiodide.

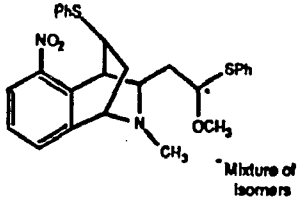


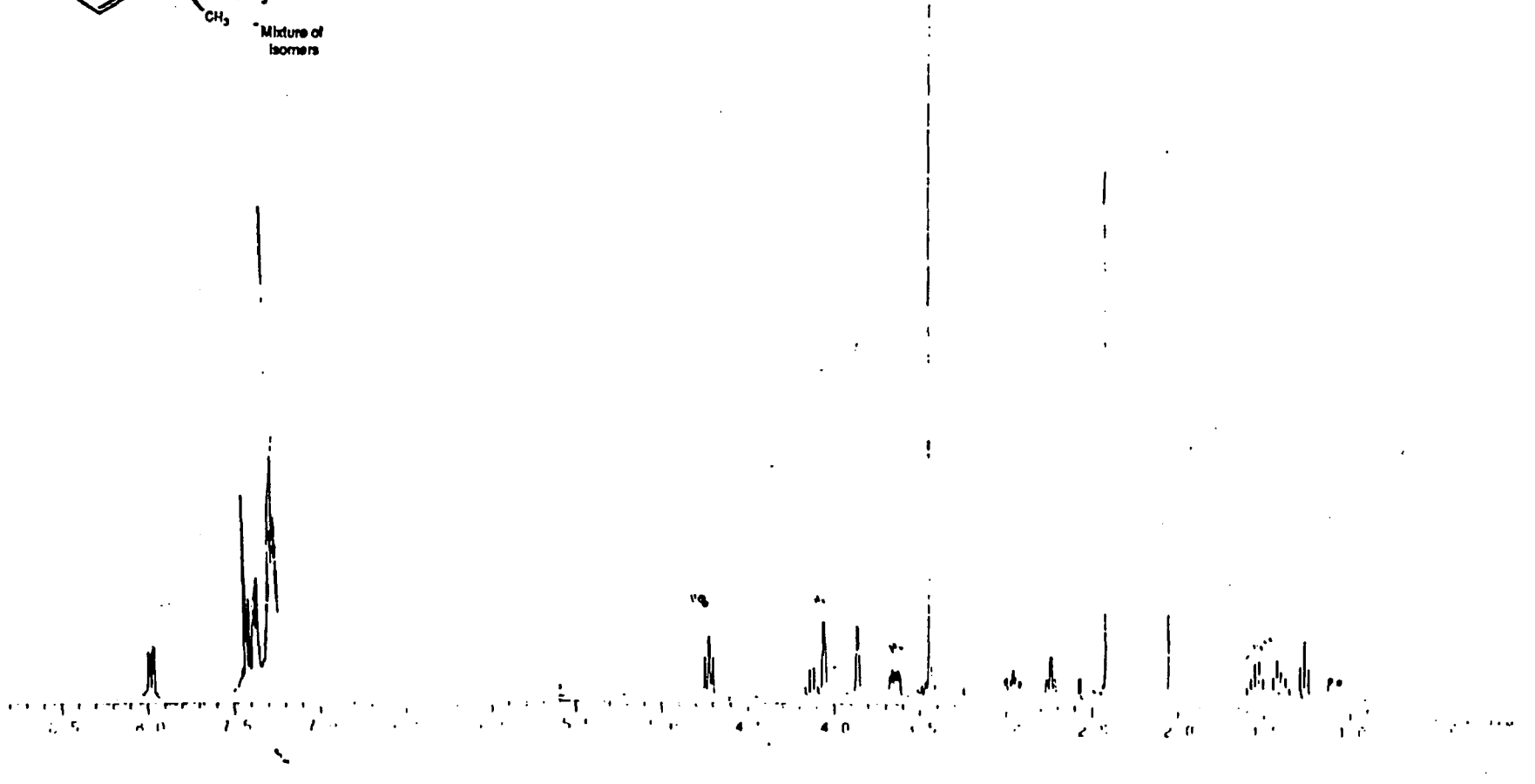
IR (A3): 5-Nitroisoquinolinium Methiodide.



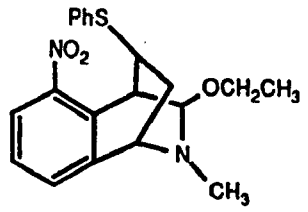


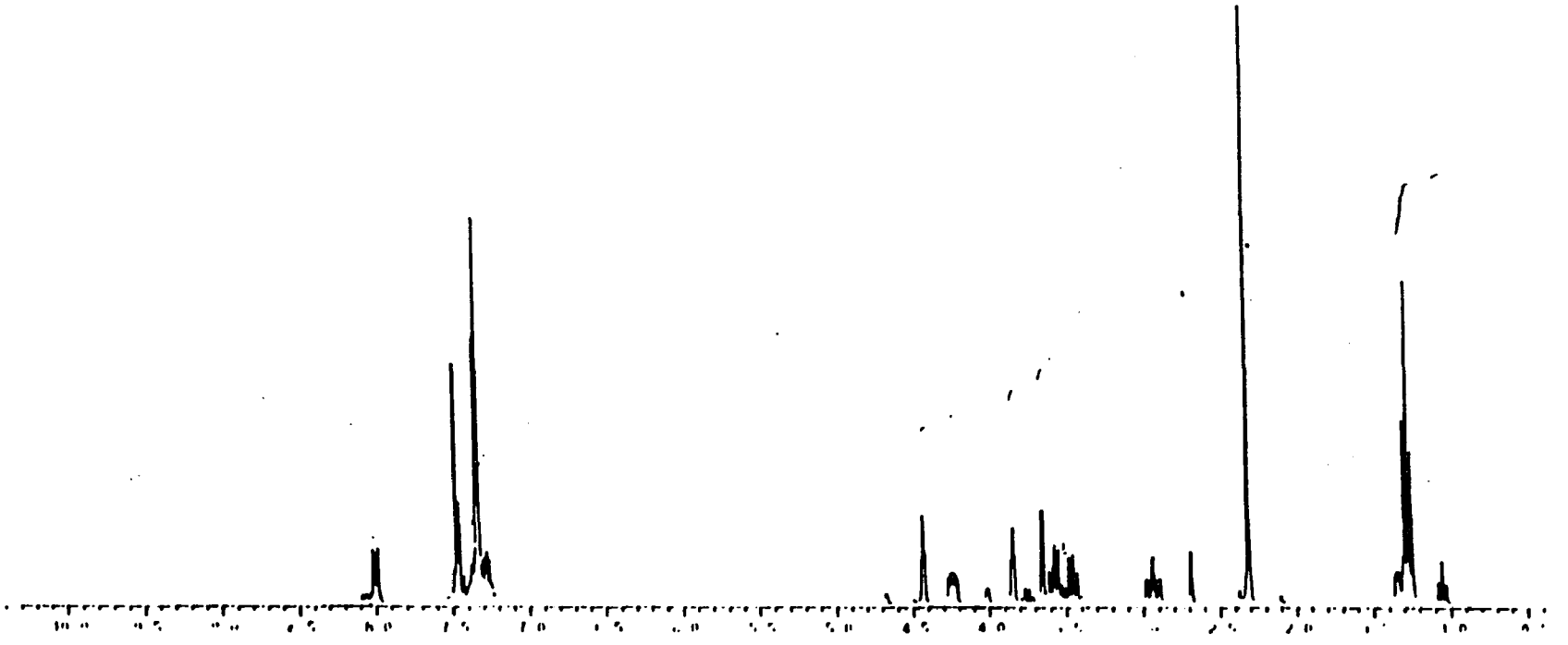
^{1}H NMR (**A7**): 2-Methyl-3(R*)-(2-Methoxy-2-Thiophenyl)-Ethyl-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (Lower Isomer).



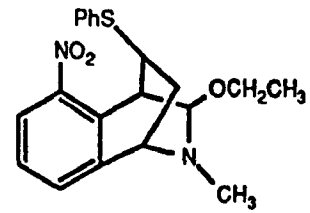


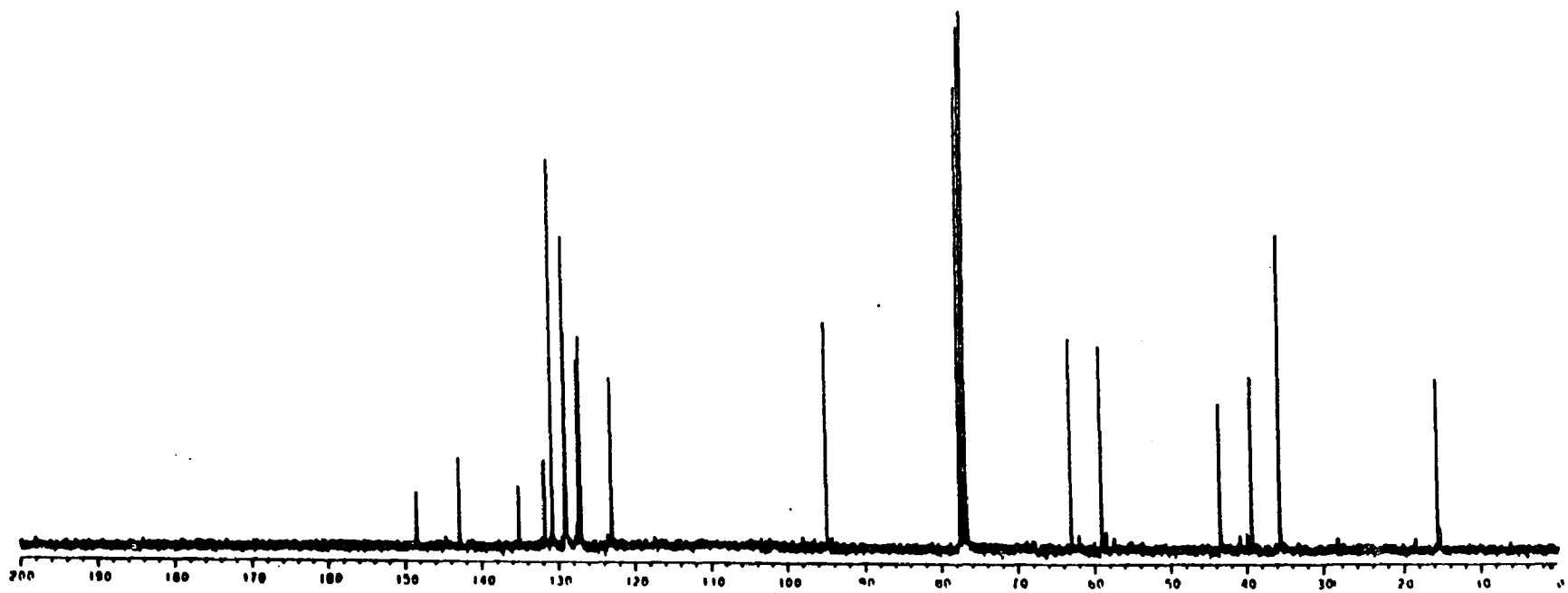
^{1}H NMR (**A7**): 2-Methyl-3(R*)-(2-Methoxy-2-Thiophenyl)-Ethyl-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (Upper Isomer).



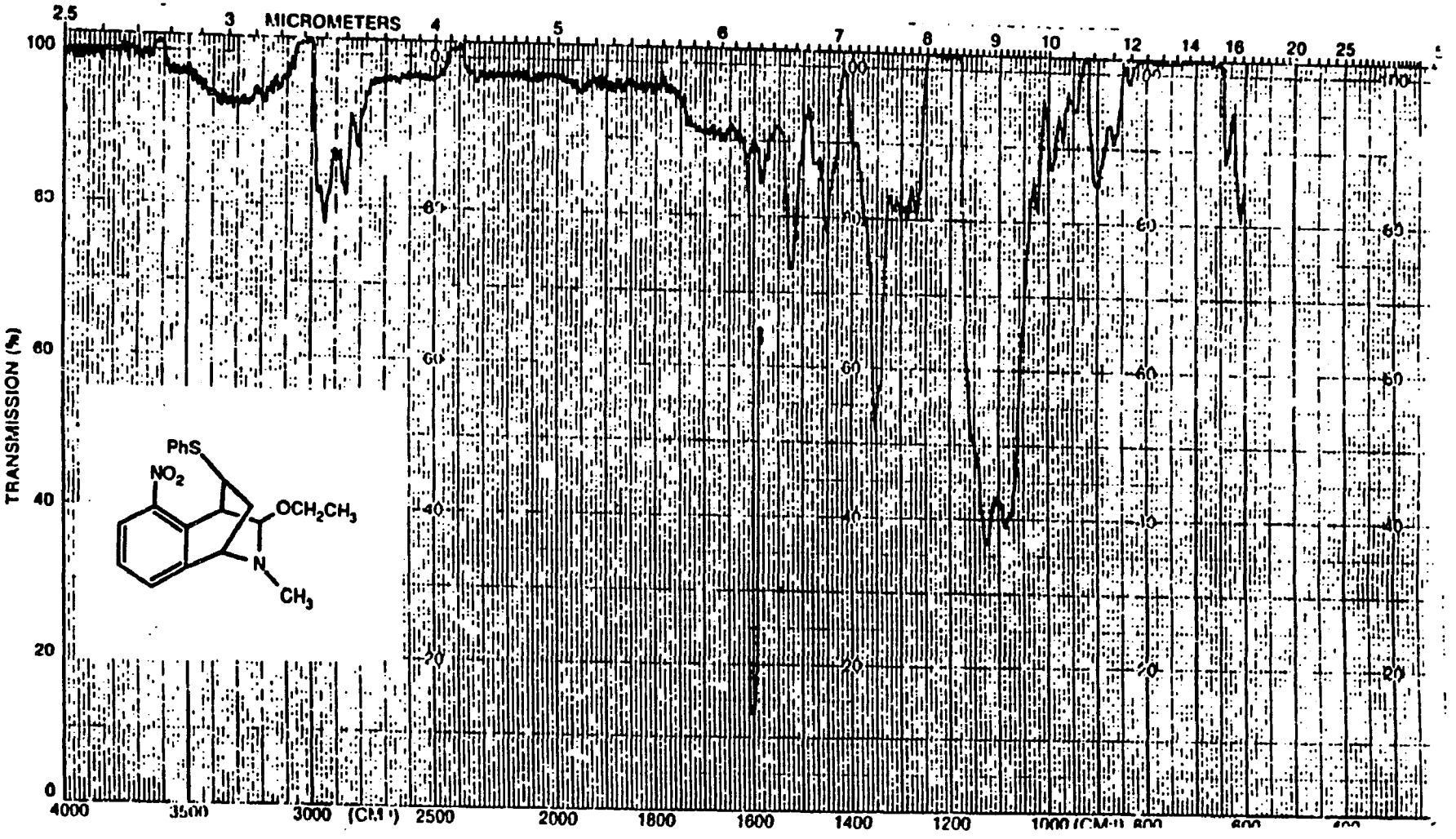


^{1}H NMR (**A8**): 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline.

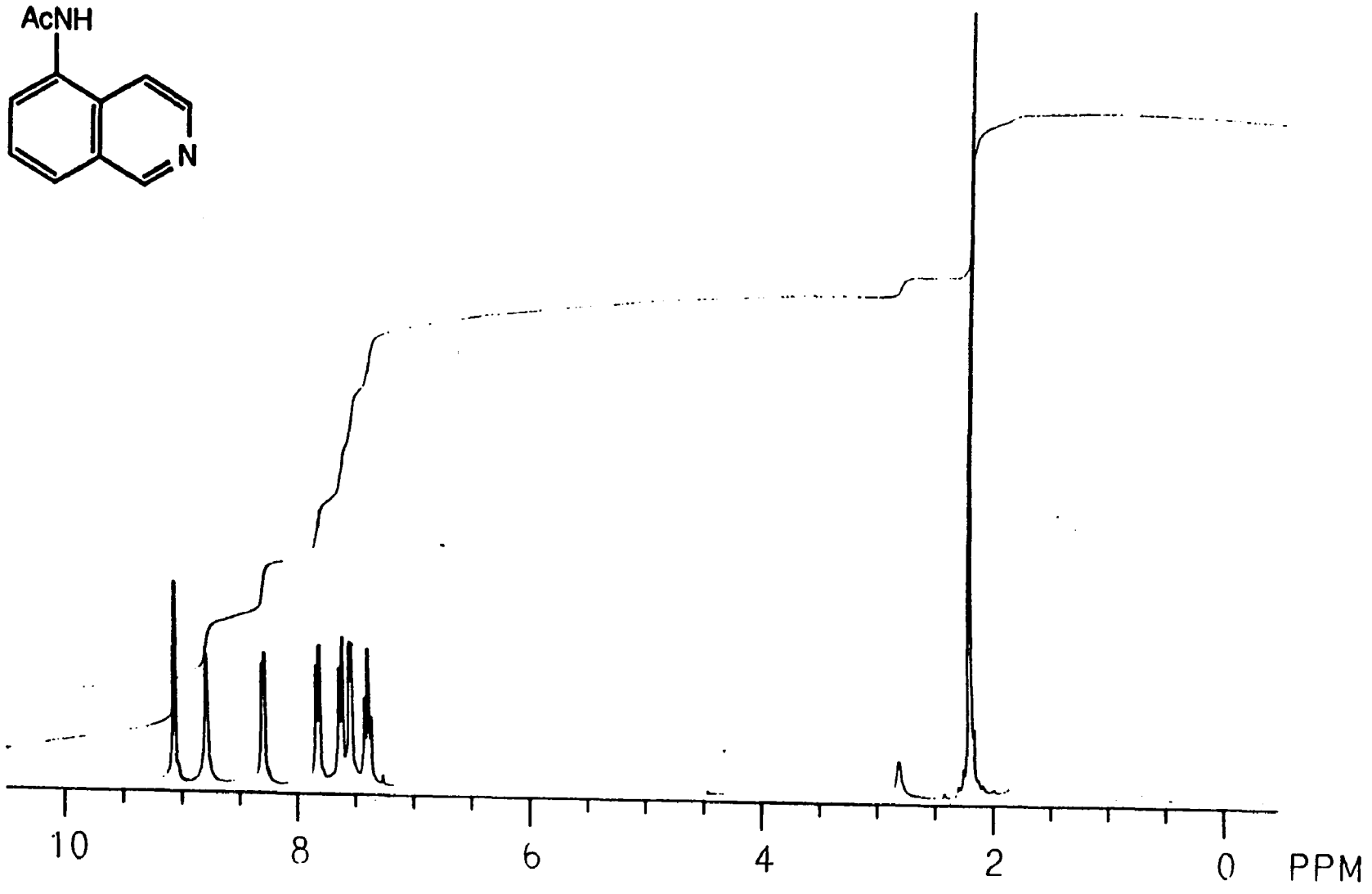




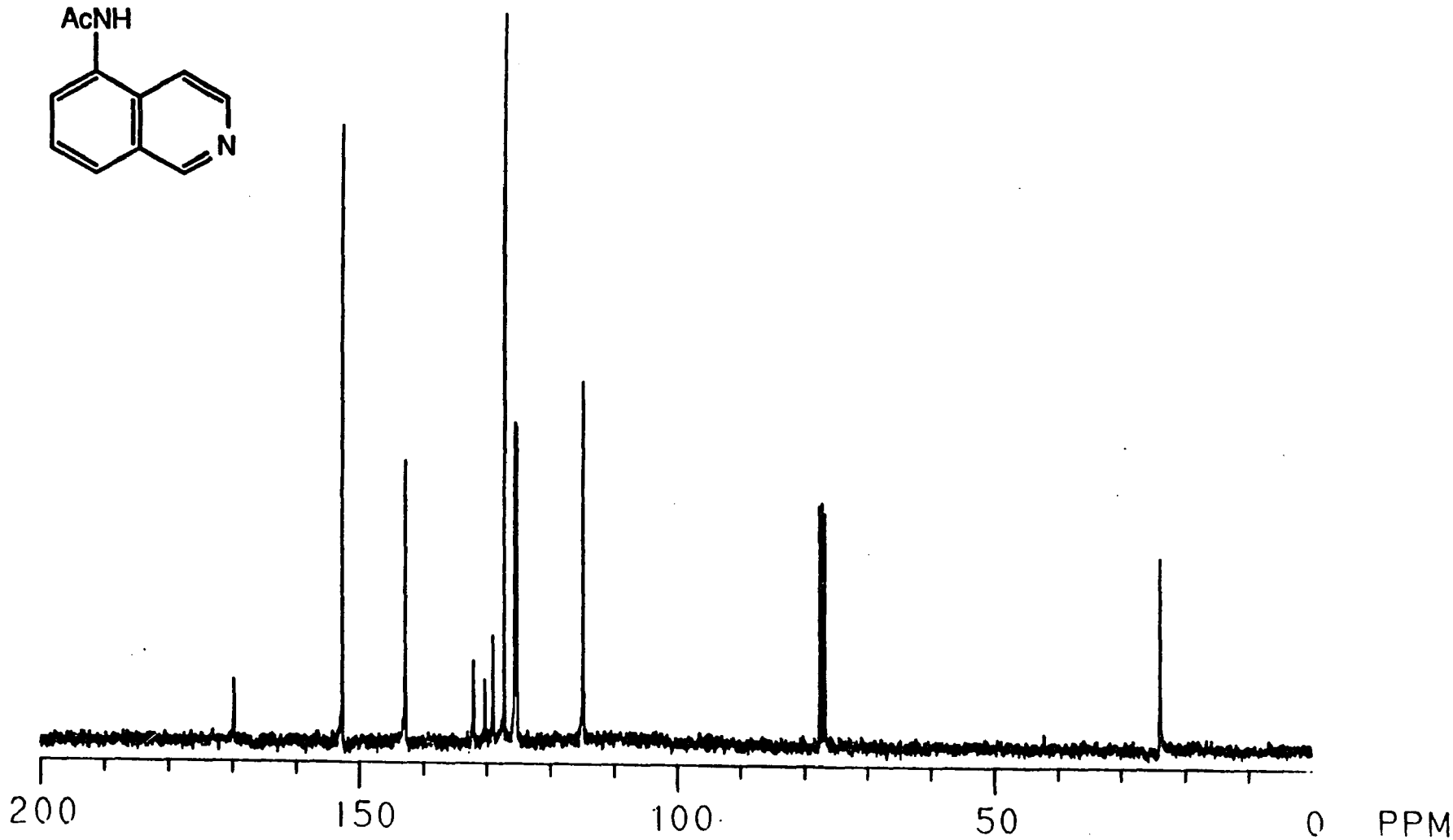
^{13}C NMR **(A8)**: 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline.



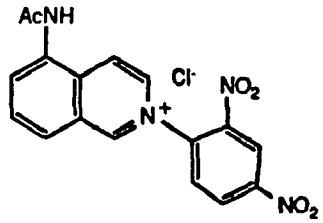
IR (A8): 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline.

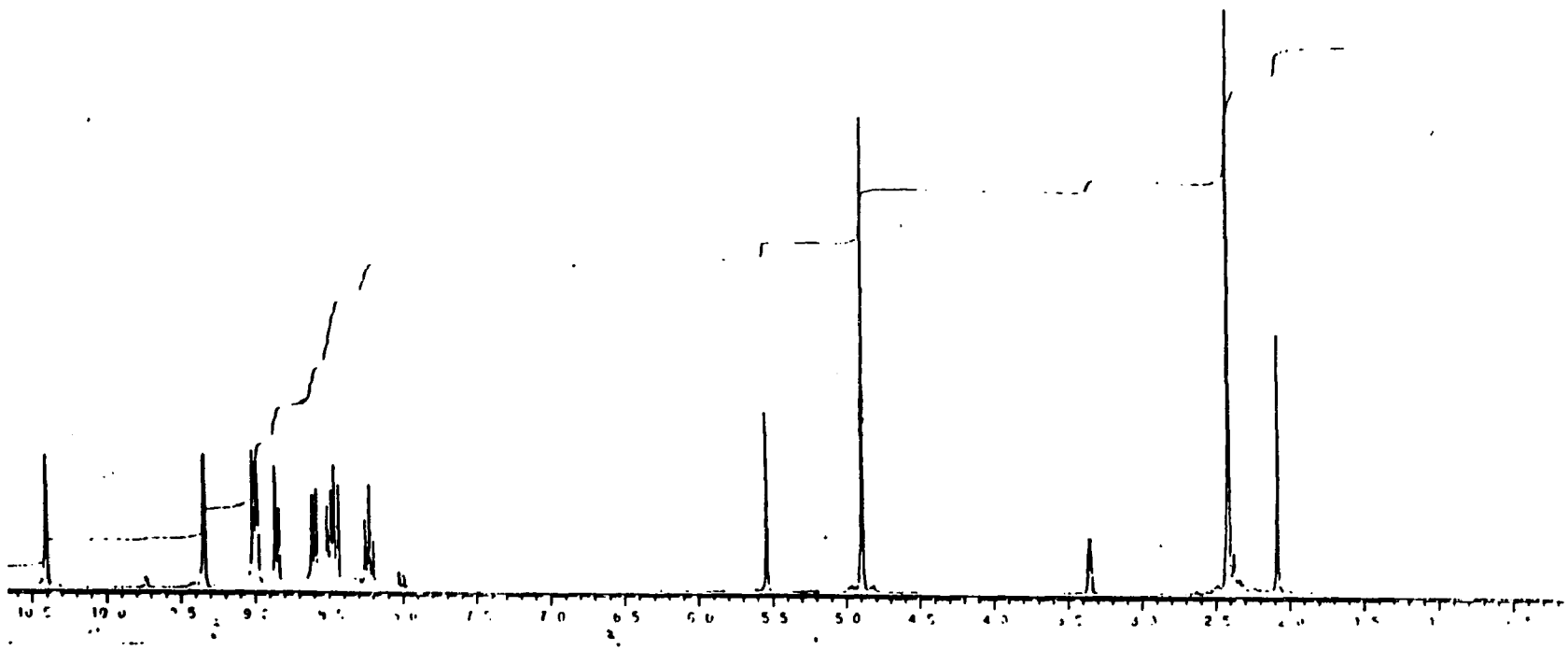


^{1}H NMR (B3): 5-Acetylaminoisoquinoline.

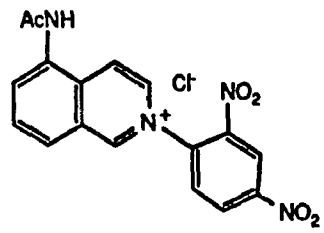


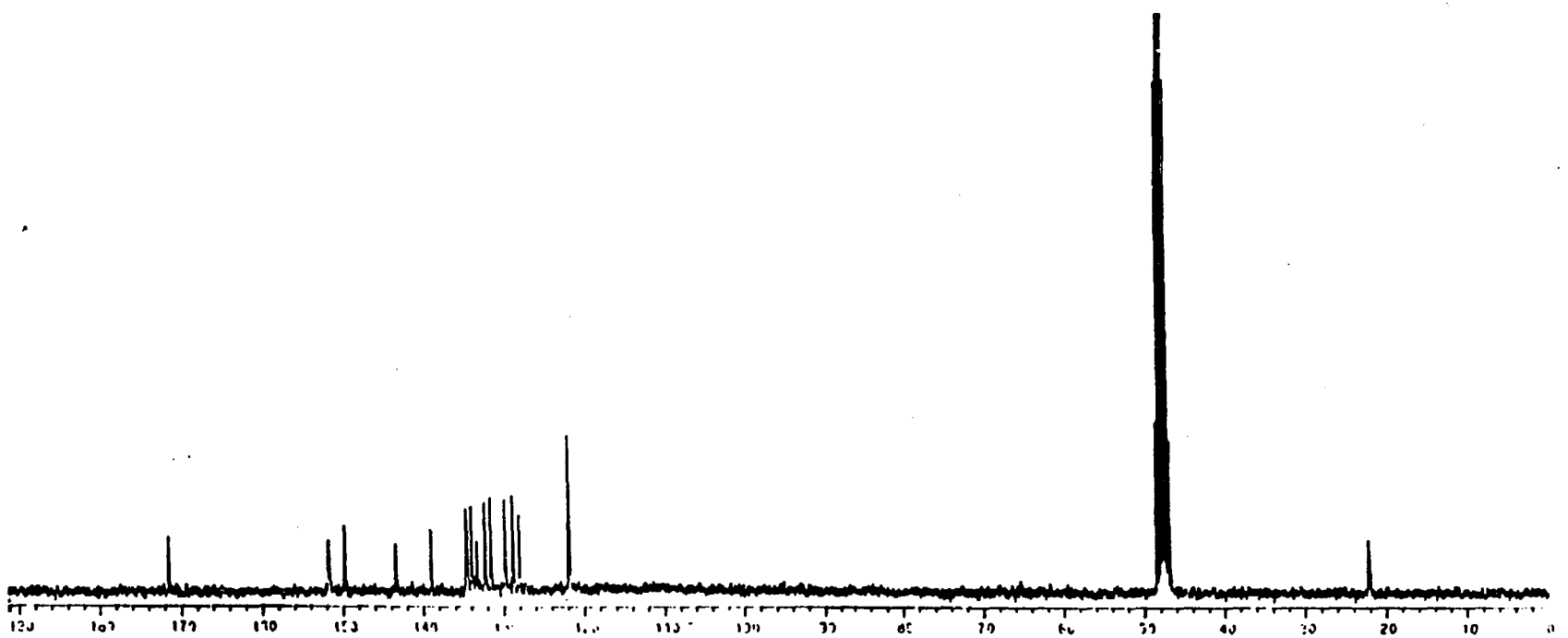
^{13}C NMR (B3): 5-Acetylaminoisoquinoline.



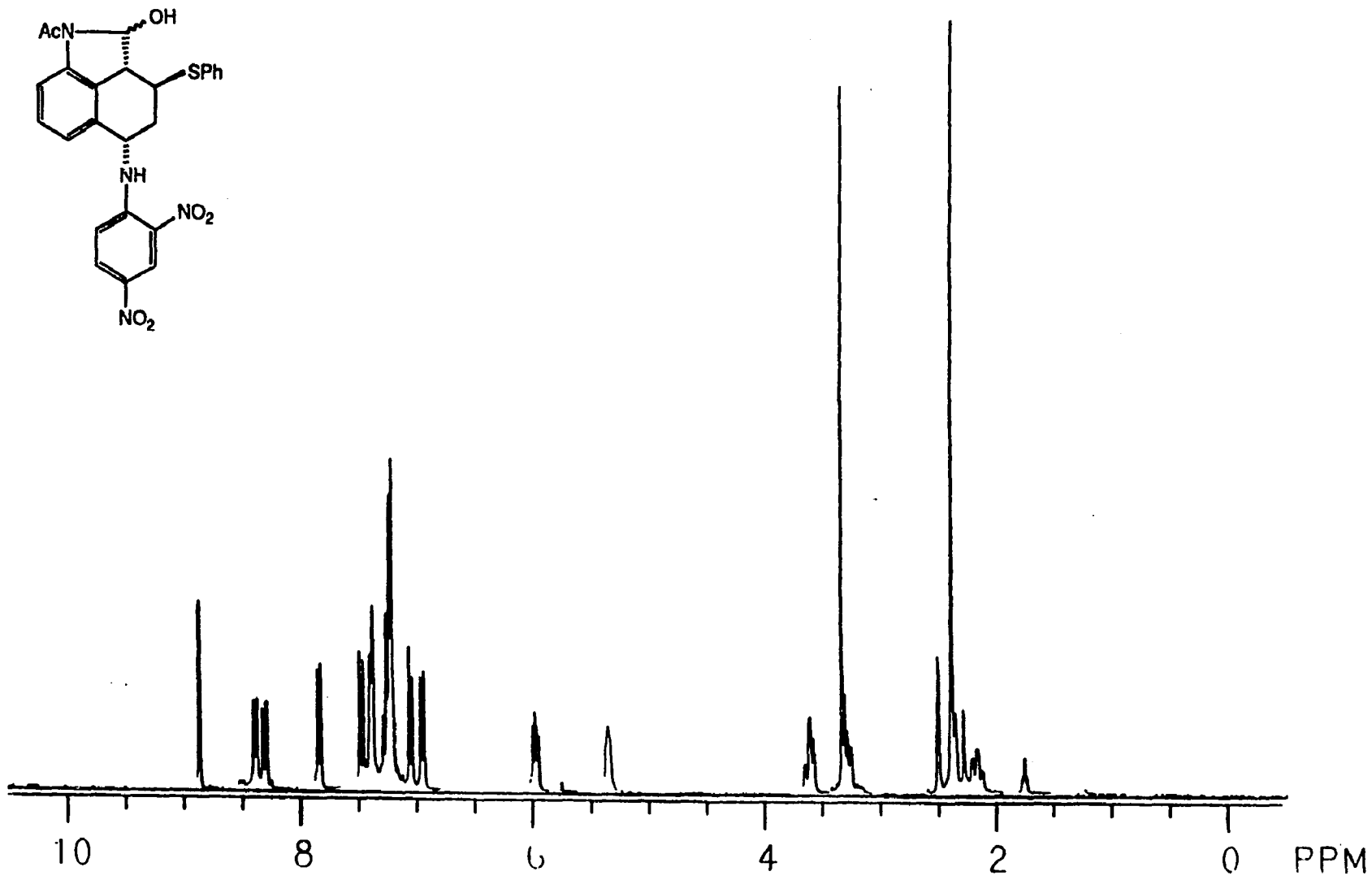


^{1}H NMR (**B5**): 2-(2,4-Dinitrophenyl)-5-Acetylaminoisoquinolinium Chloride.

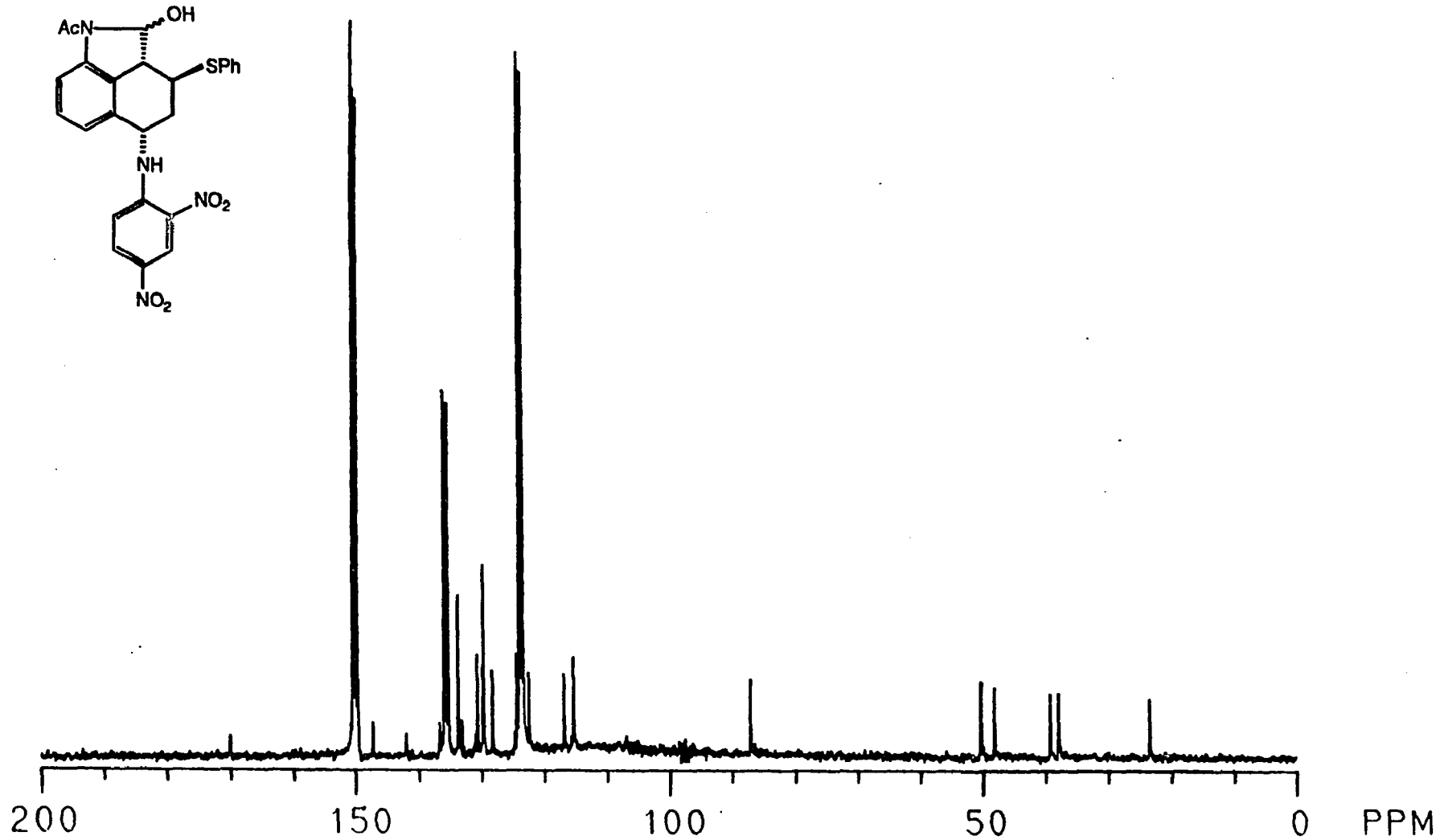




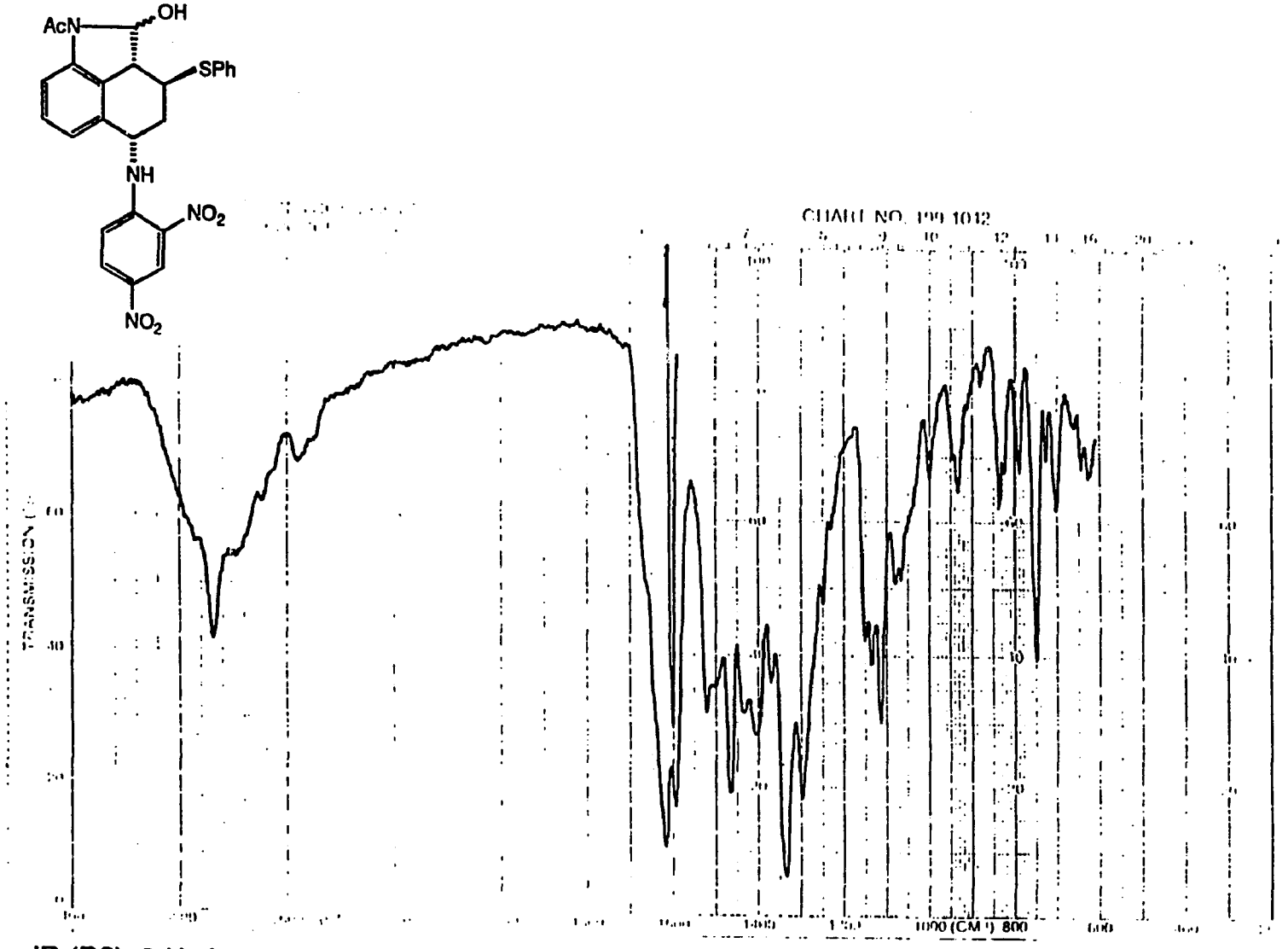
^{13}C NMR **(B5)**: 2-(2,4-Dinitrophenyl)-5-Acetylaminoisoquinolinium Chloride.



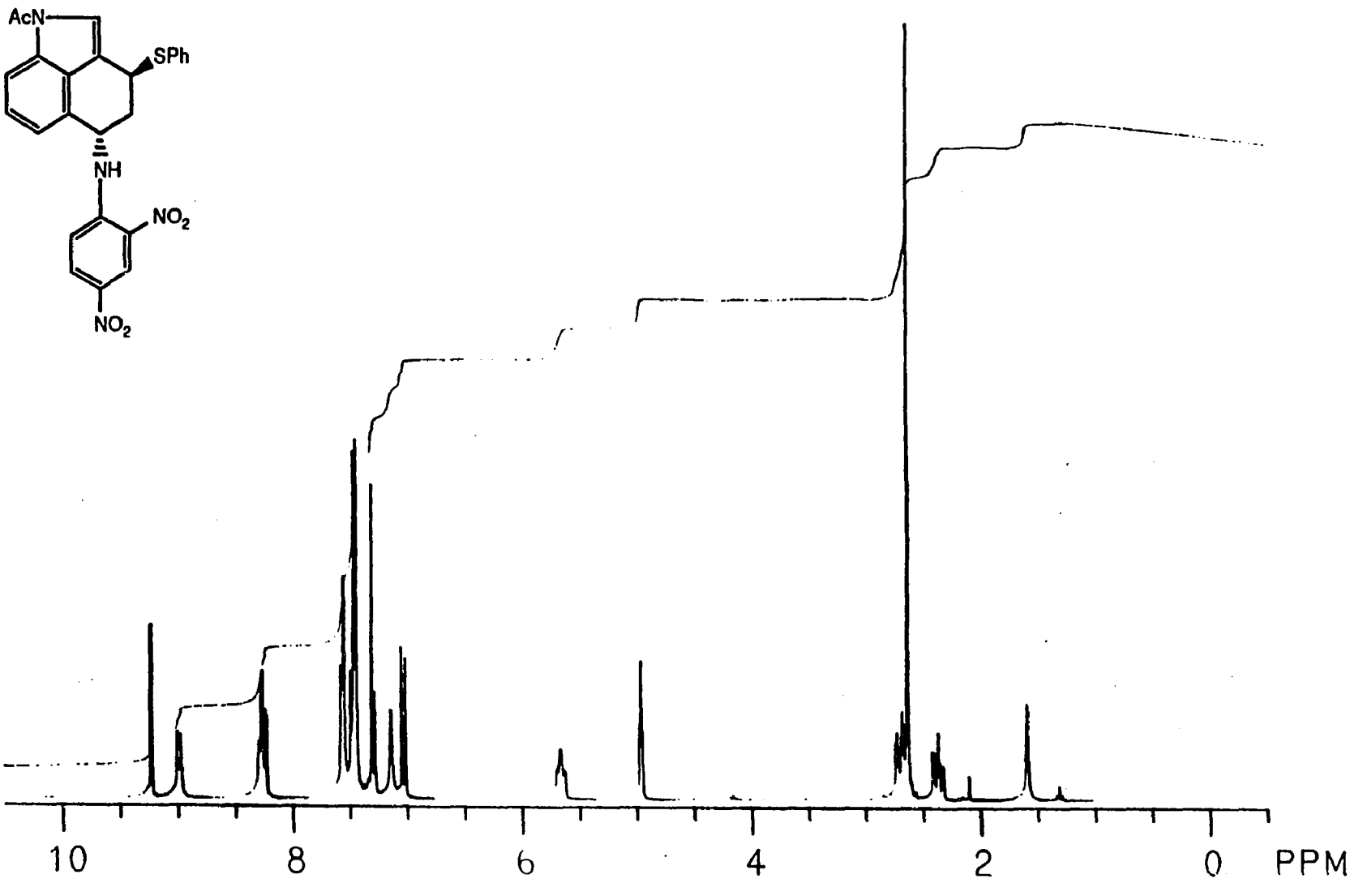
^{1}H NMR (B6): 2-Hydroxy-1,2,2a,3,4,5-Octahydro-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[cd]indole.



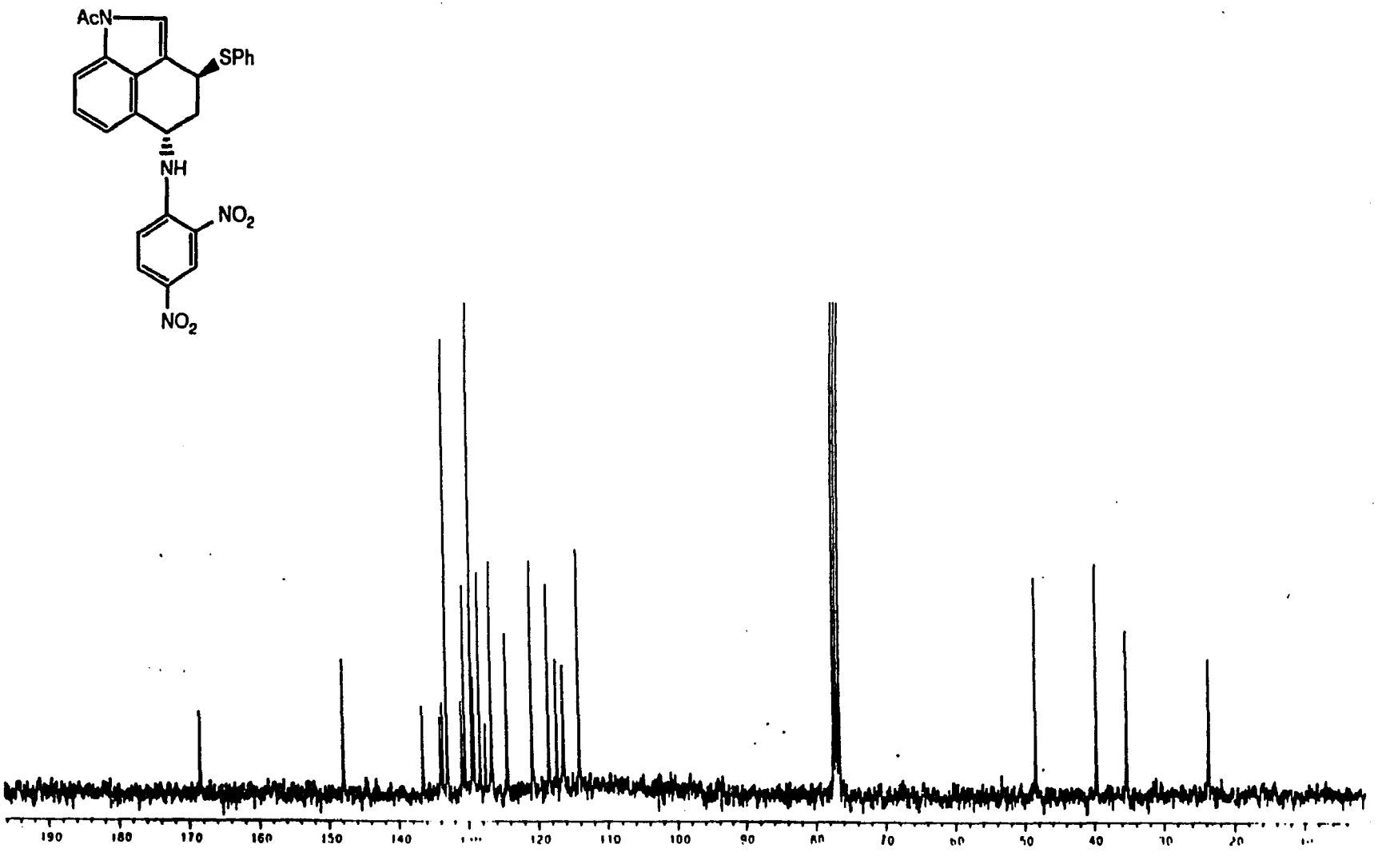
^{13}C NMR (B6): 2-Hydroxy-1,2,2a,3,4,5-Octahydro-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[cd]indole.



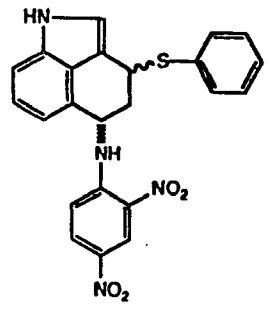
IR (B6): 2-Hydroxy-1,2,2a,3,4,5-Octahydro-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-Benz[cd]indole.

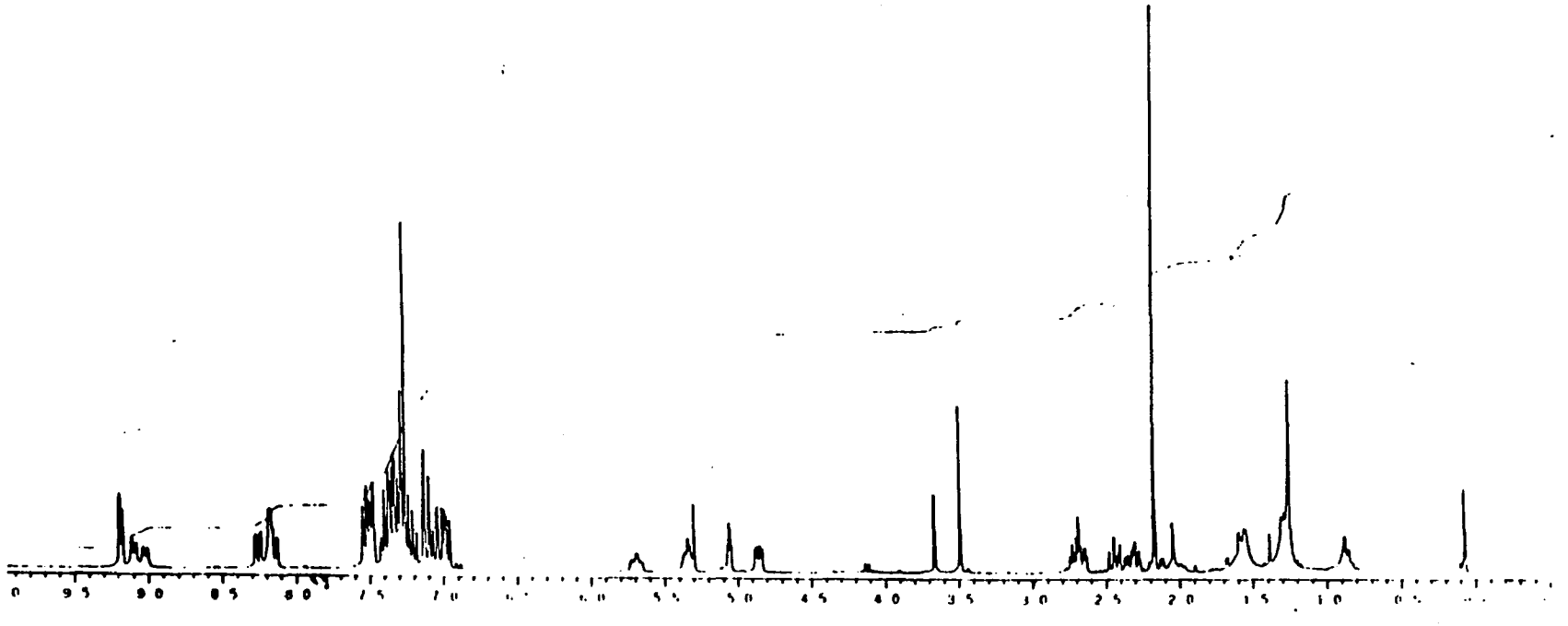


^{1}H NMR (**C2**): 1-Acetyl-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole.

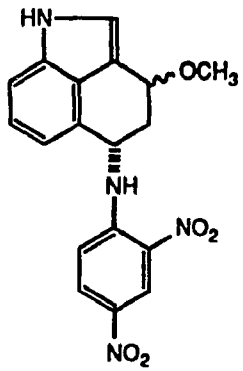


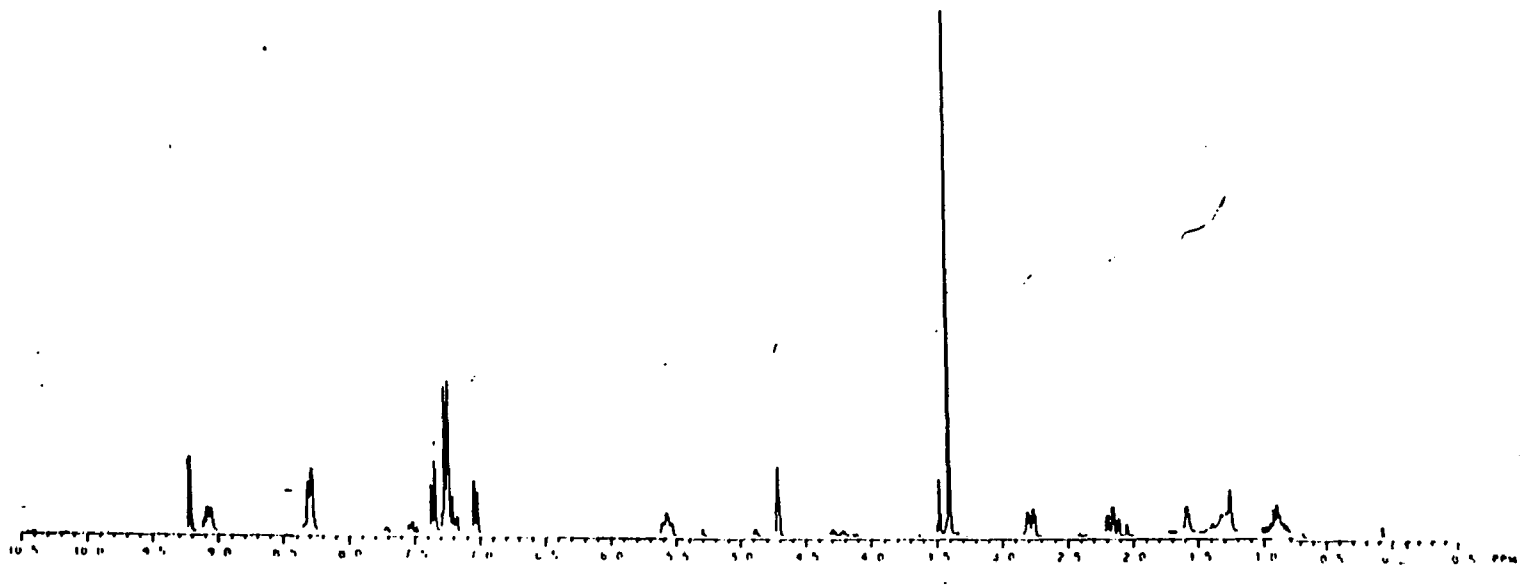
^{13}C NMR (**C2**): 1-Acetyl-3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole.



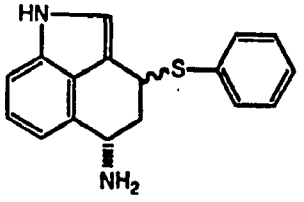


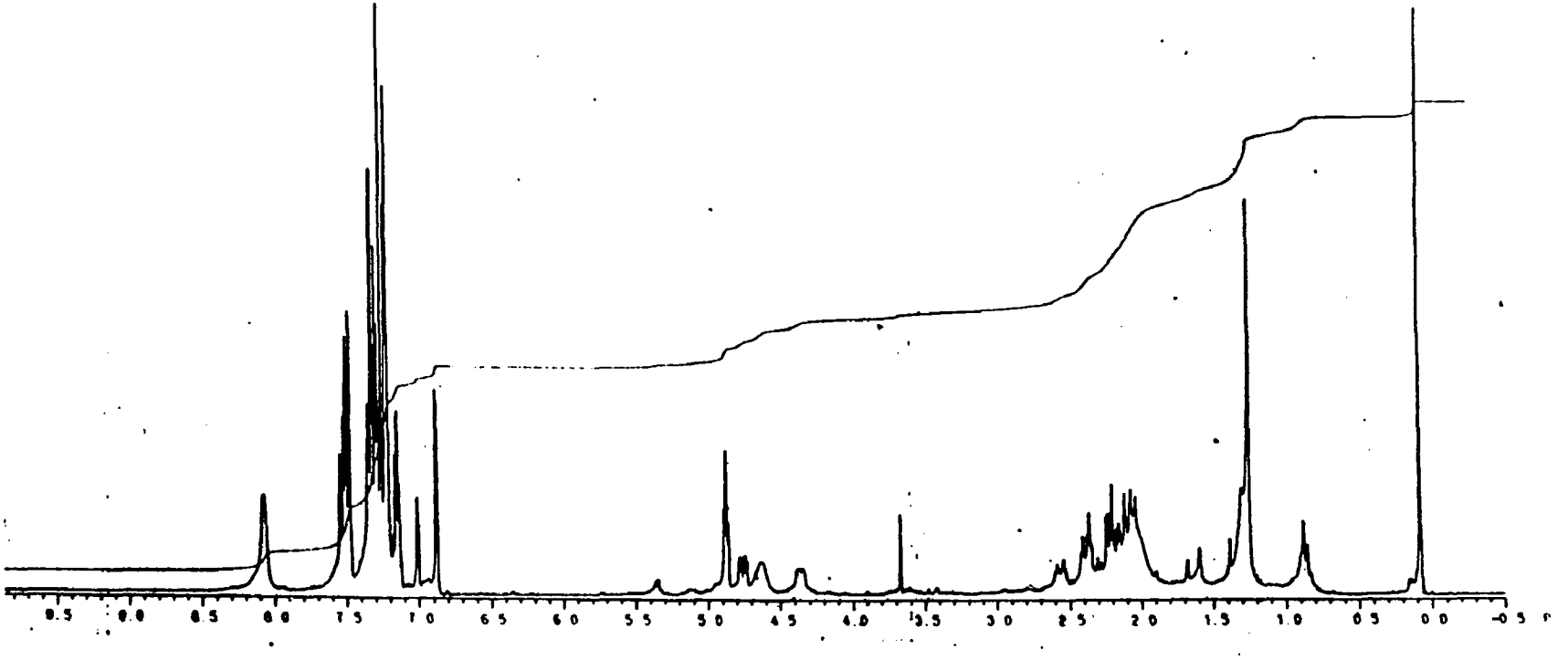
^{1}H NMR **(E2): 3-Thiophenyl-5-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole (mixture of isomers).**



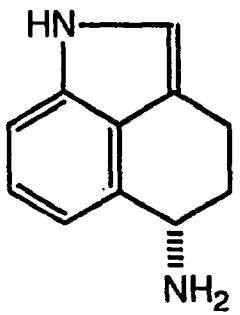


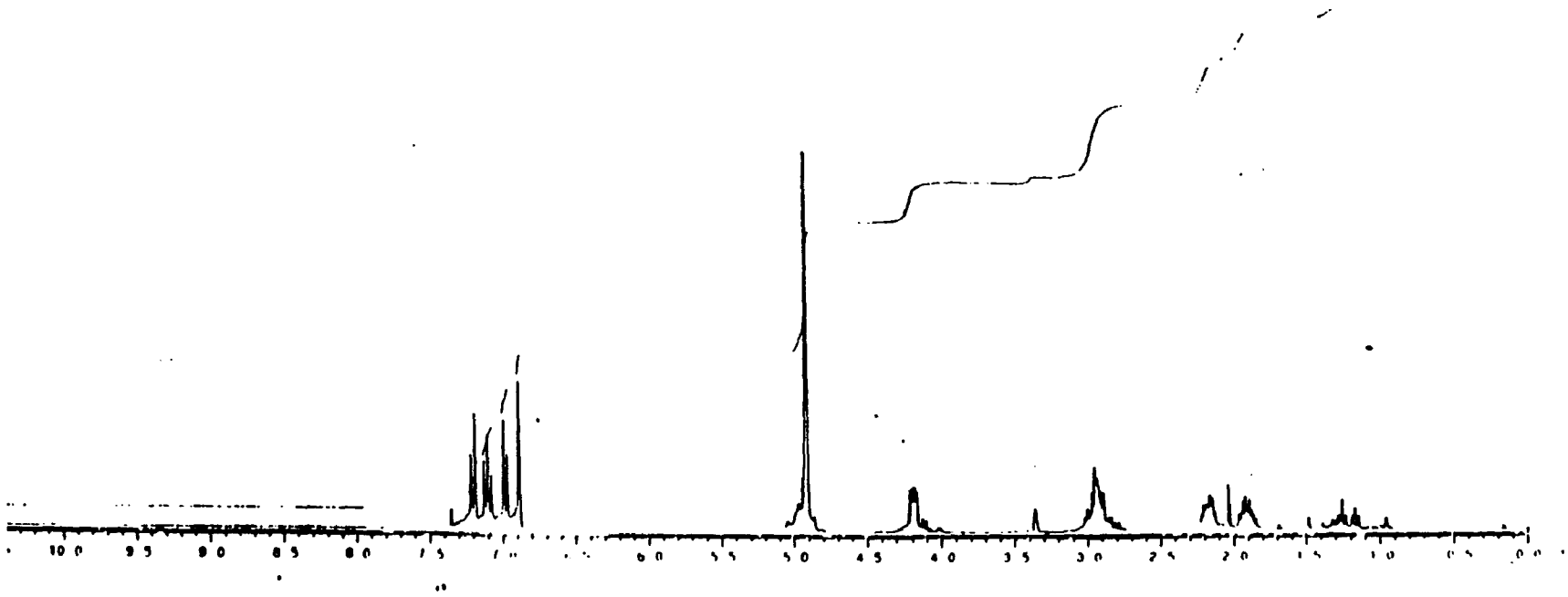
^{1}H NMR (E3): 3-Methoxy-5-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole (mixture of isomers).



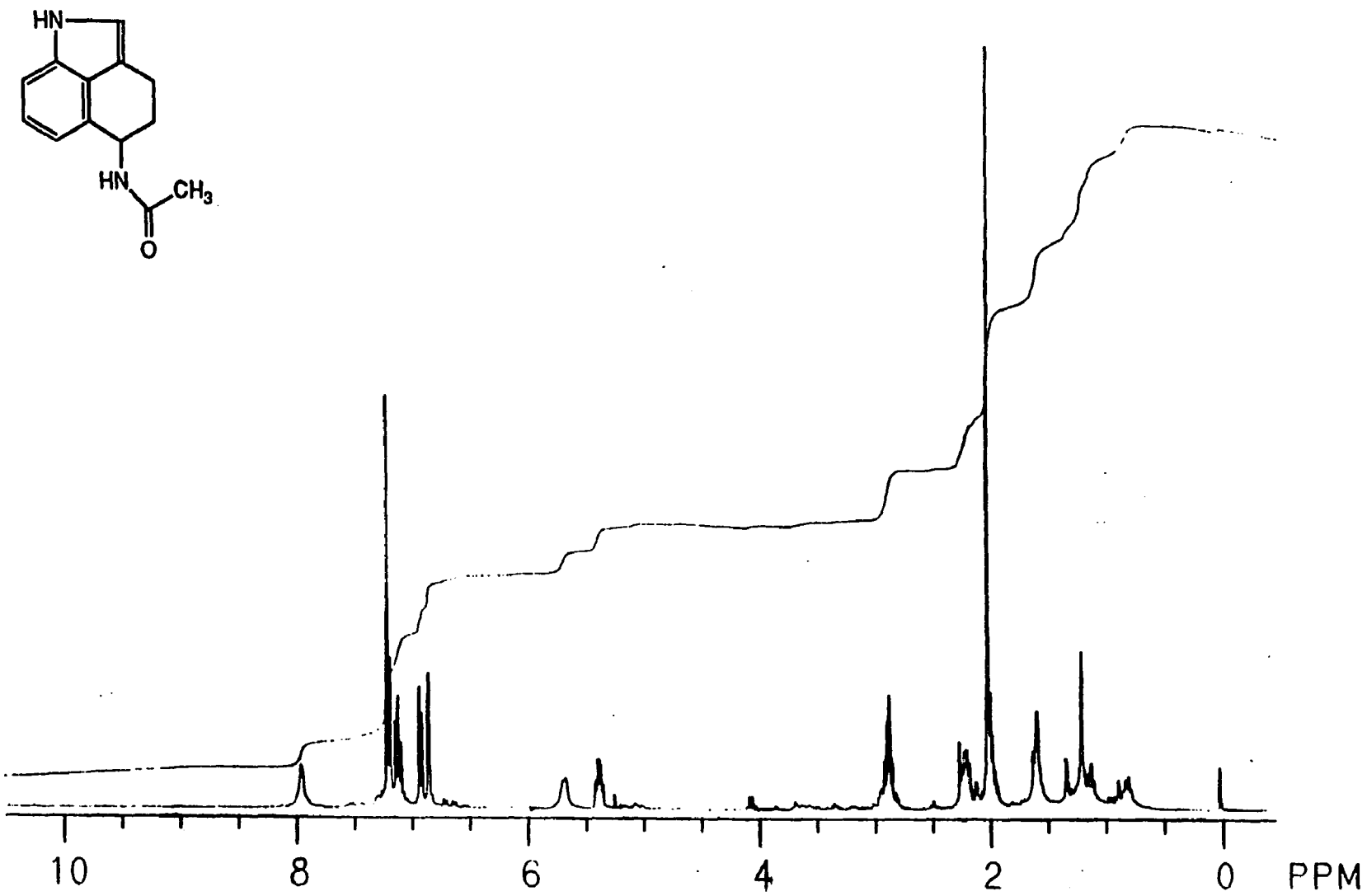


^{1}H NMR (E4): 3-Thiophenyl-5-Amino-1,3,4,5-Tetrahydrobenz[cd]indole.

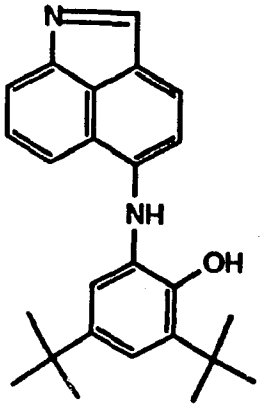


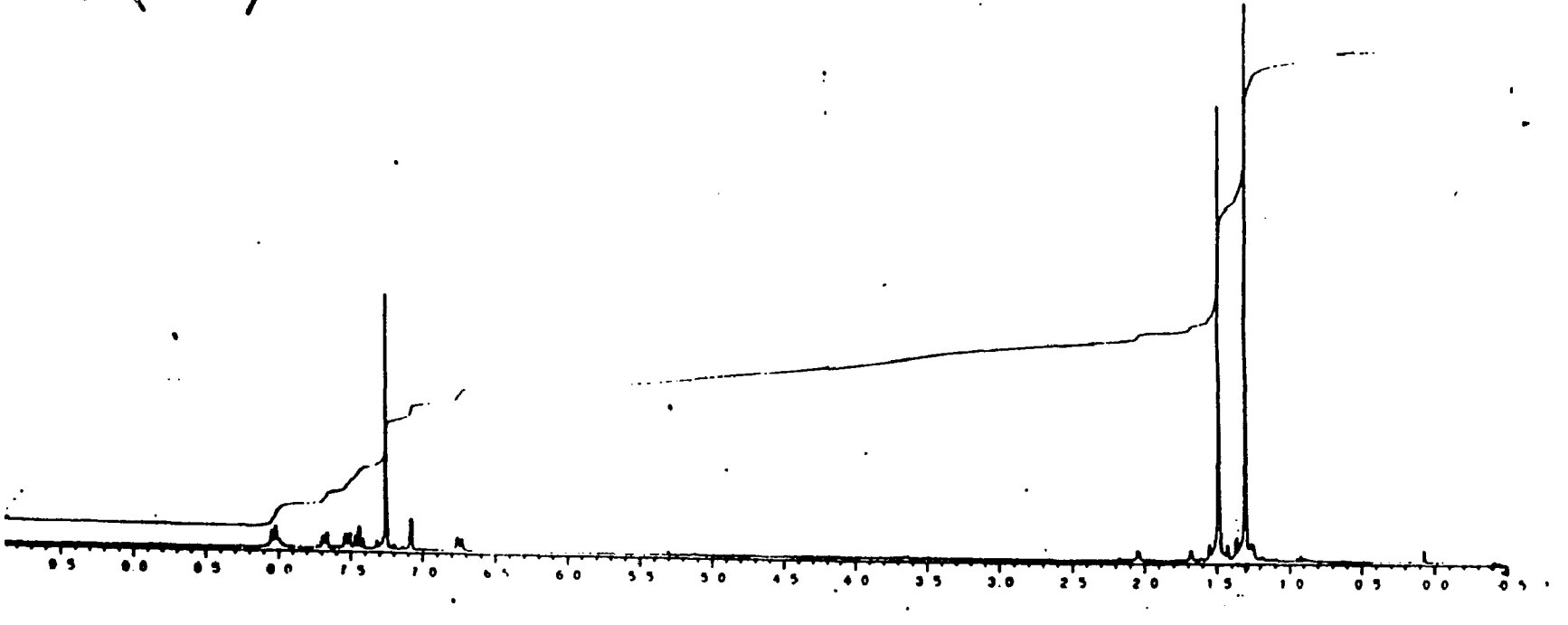


^{1}H NMR (E5): 5-Amino-1,3,4,5-Tetrahydrobenz[cd]indole.

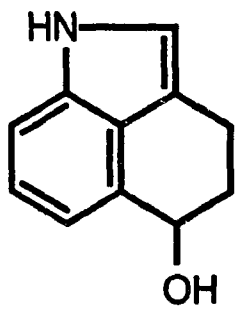


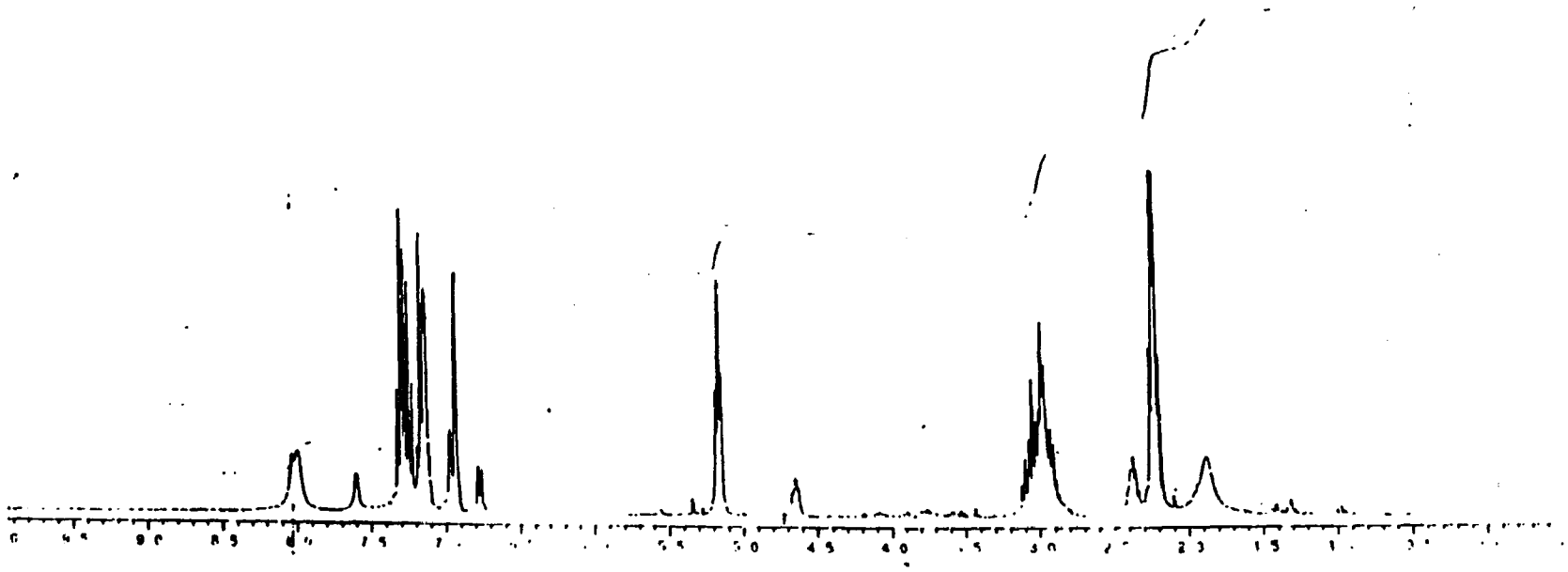
^{1}H NMR: 5-Acetylamino-1,3,4,5-Tetrahydrobenz[cd]indole.



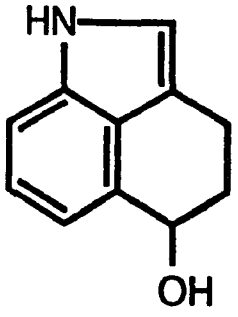


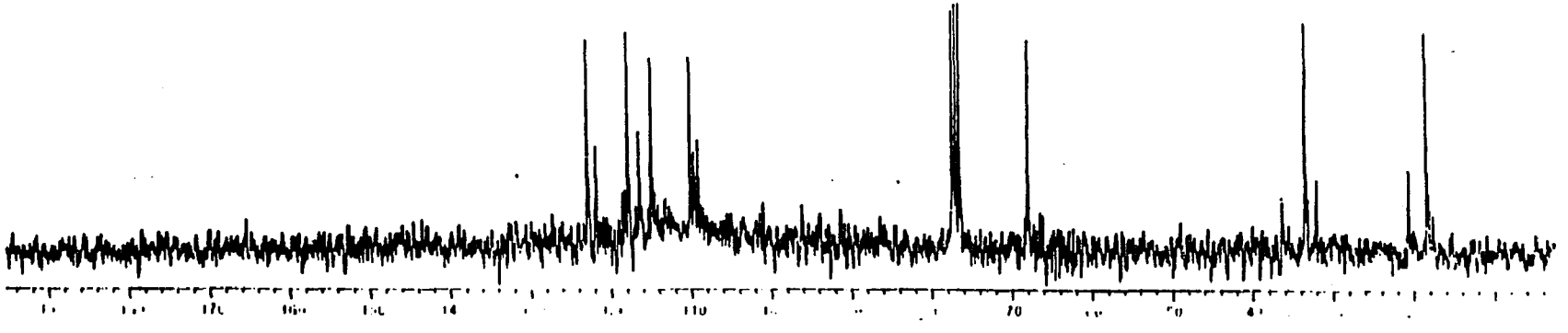
^{1}H NMR (G4): Corey's Reagent Oxidation Product.



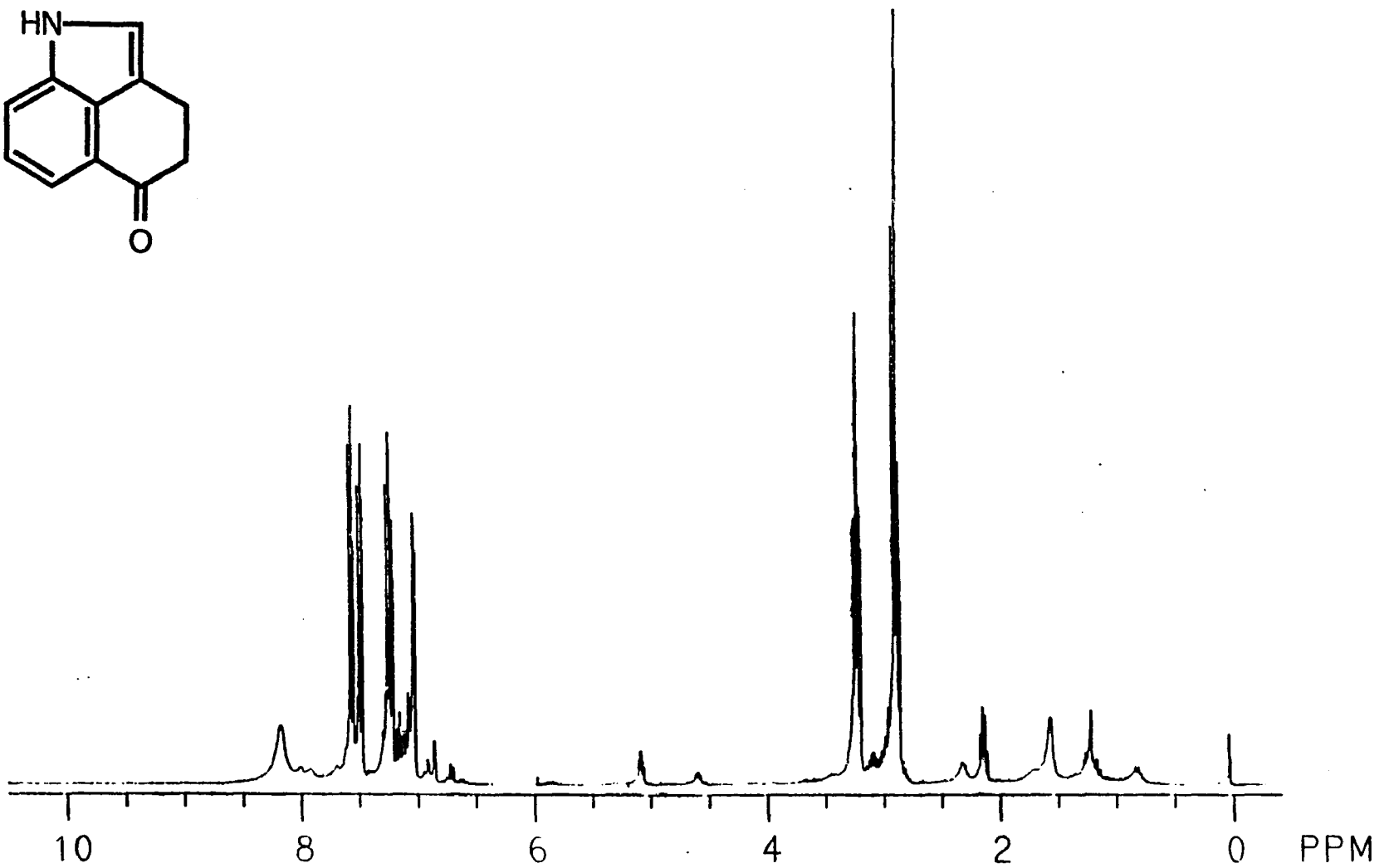


^{1}H NMR (H1): 5-Hydroxy-1,3,4,5-Tetrahydrobenz[cd]indole.

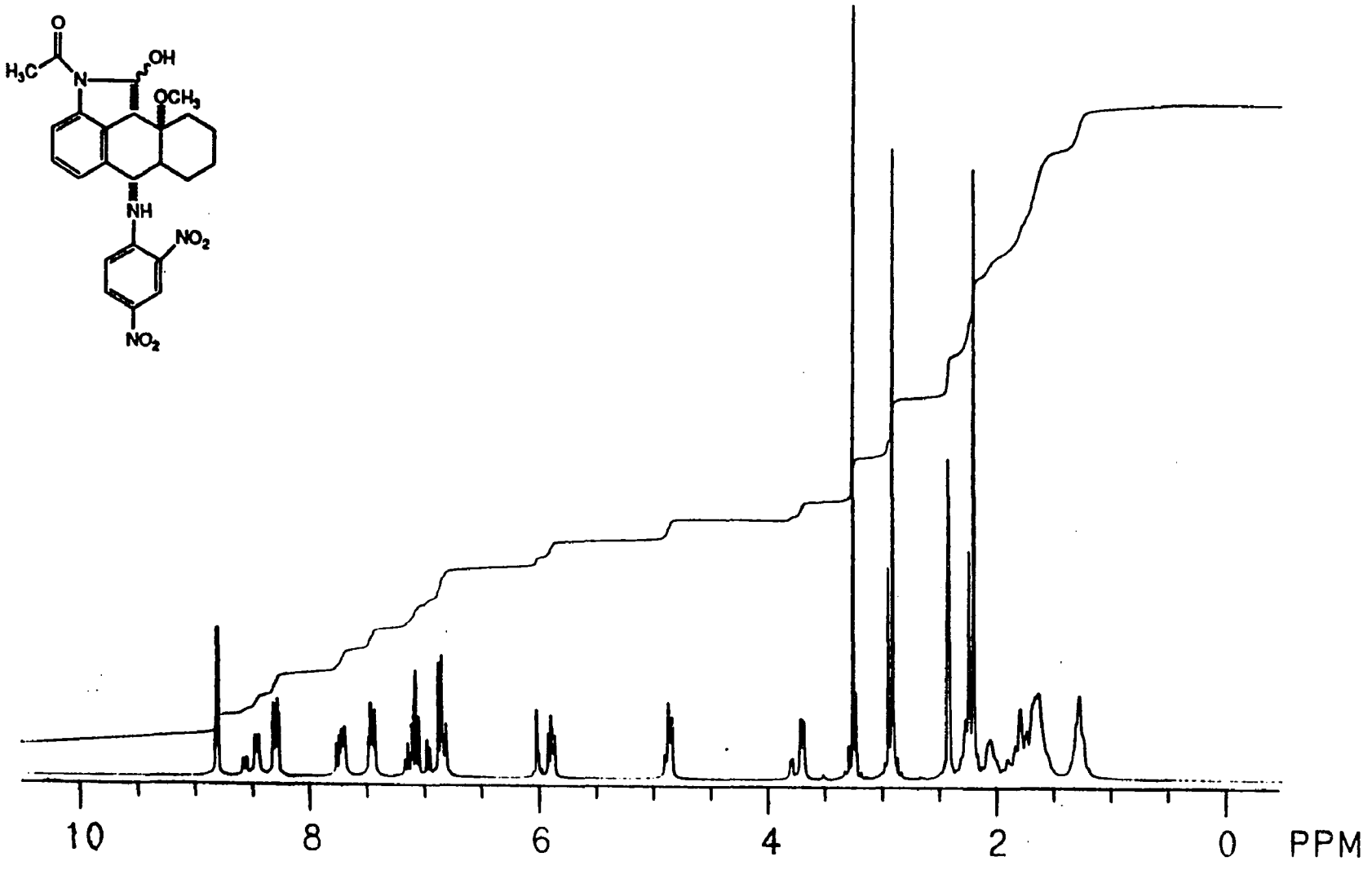




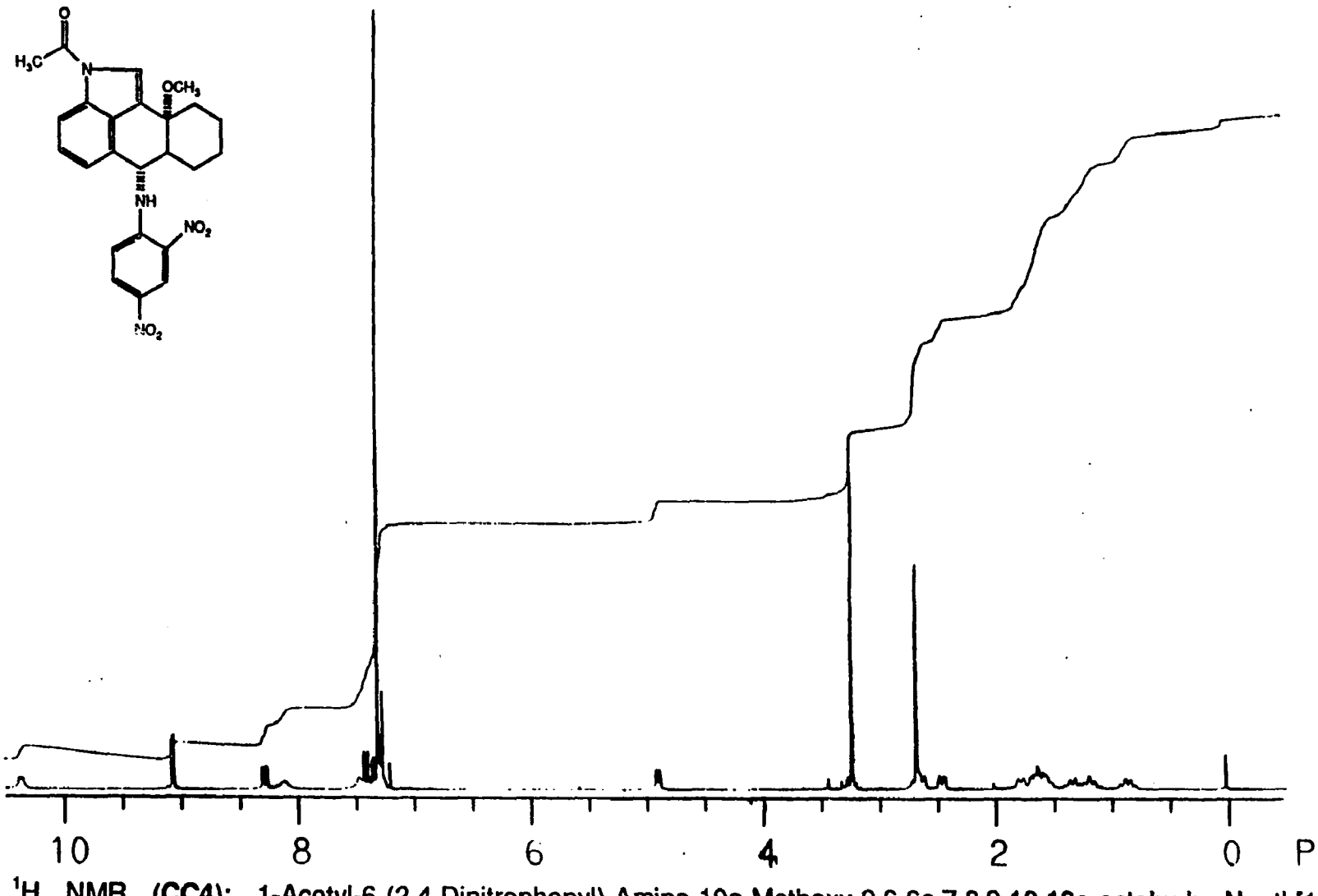
^{13}C NMR (H1): 5-Hydroxy-1,3,4,5-Tetrahydrobenz[cd]indole.



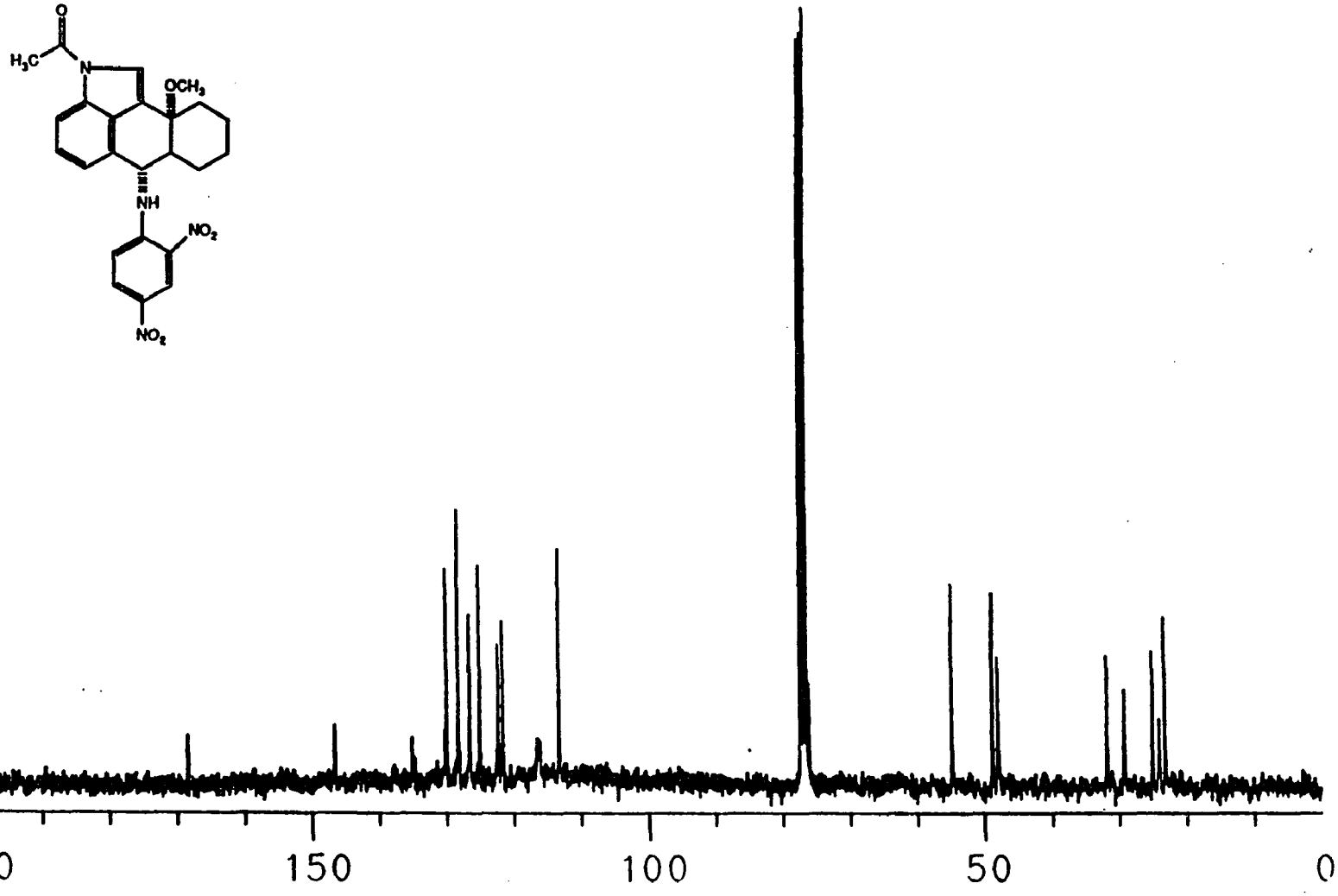
^{1}H NMR (III): 3,4-Dihydrobenz[cd]indol-5(1*H*)-one (Uhle's Ketone).



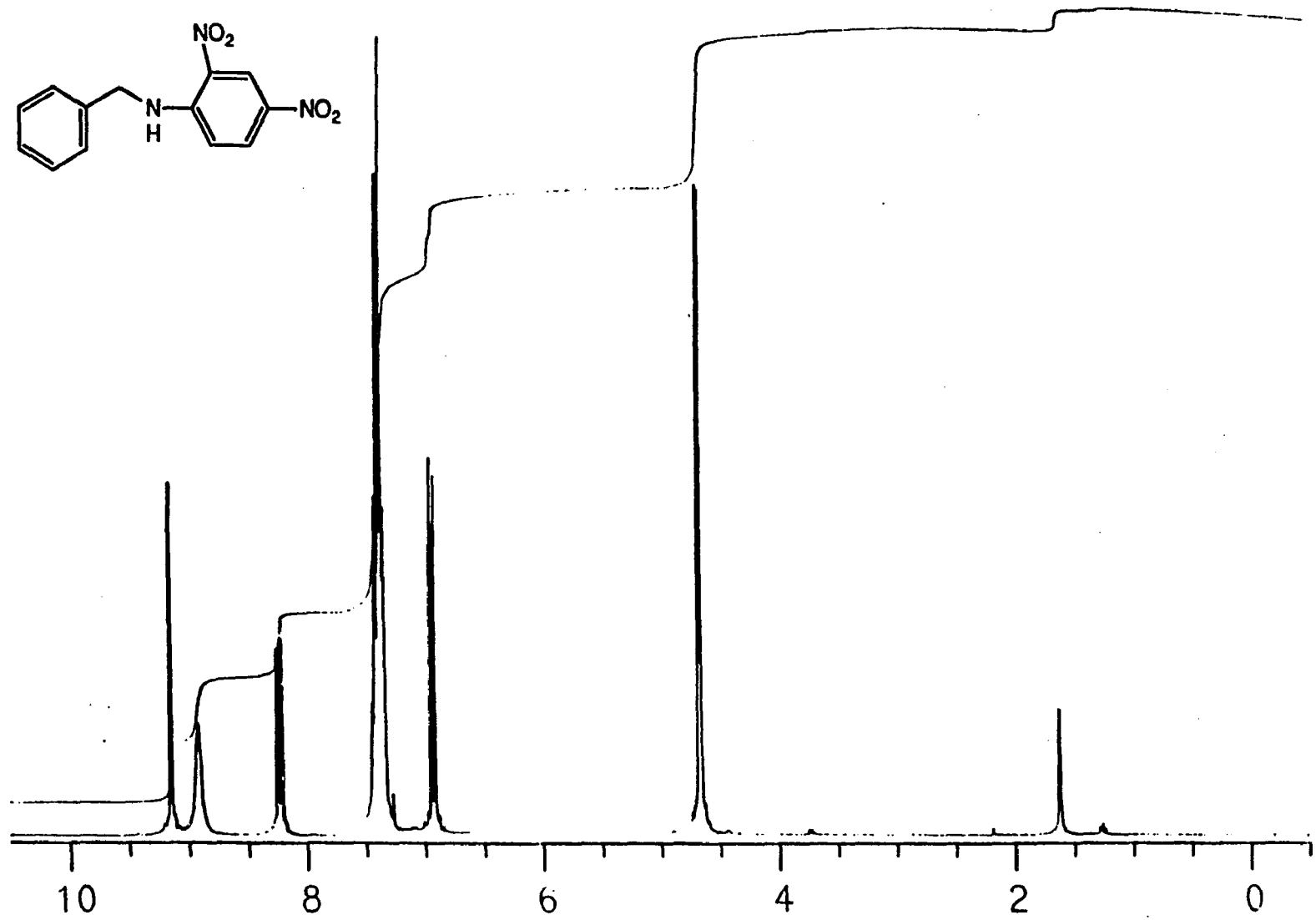
^{1}H NMR (CC3): 1-Acetyl-2-Hydroxy-6-(2,4-Dinitrophenyl)-Amino-10a-Methoxy-2,2,2a,6,6a,7,8,9,10,10a-Decahydro-Napth[1,2,3-cd]indole. (Mixture of Diastereomers)



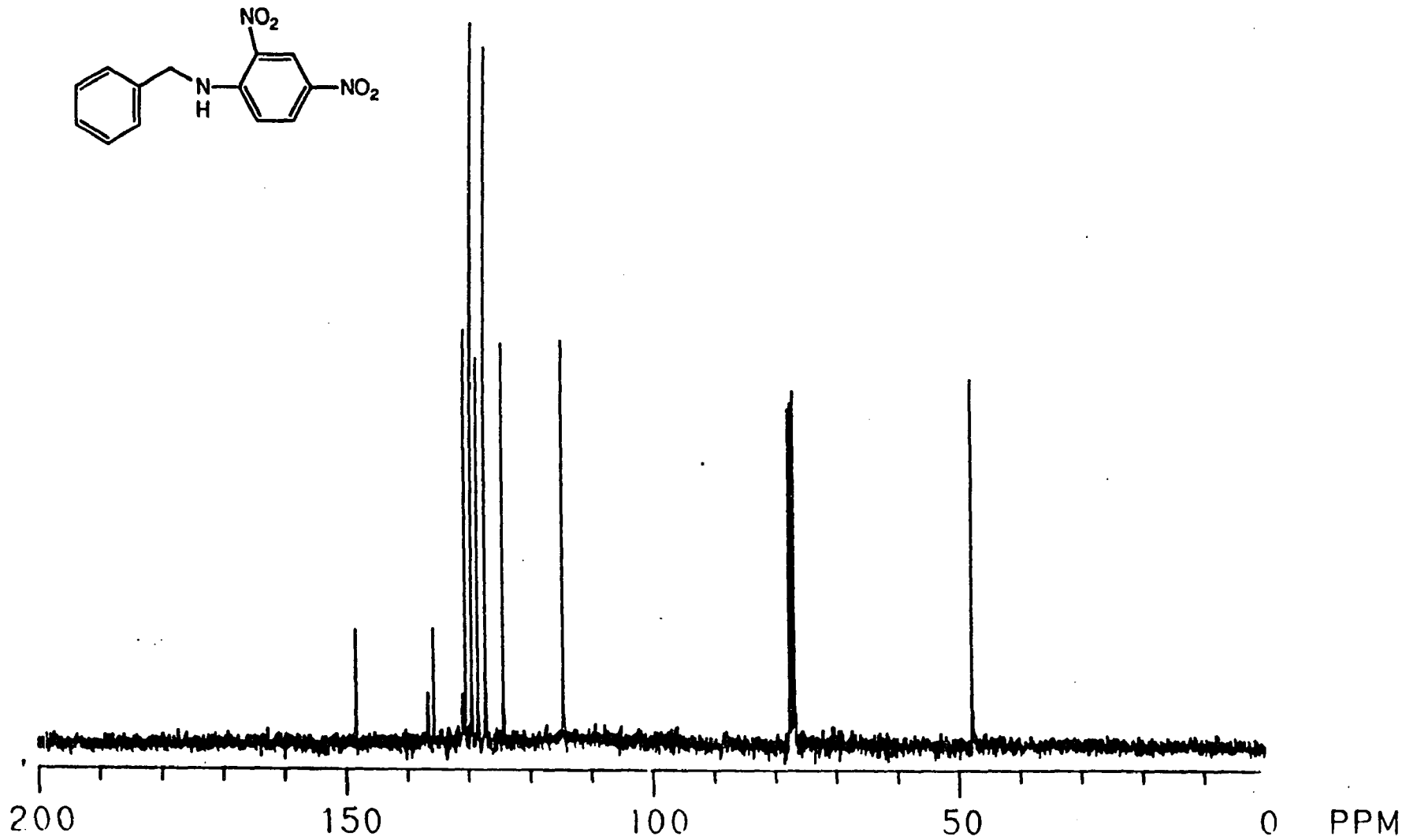
^{1}H NMR (**CC4**): 1-Acetyl-6-(2,4-Dinitrophenyl)-Amino-10a-Methoxy-2,6,6a,7,8,9,10,10a-octahydro-Napth[1,2,3-cd]indole.



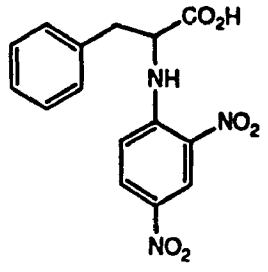
^{13}C NMR (CC4): 1-Acetyl-6-(2,4-Dinitrophenyl)-Amino-10a-Methoxy-2,6,6a,7,8,9,10,10a-octahydro-Napth[1,2,3-cd]indole.

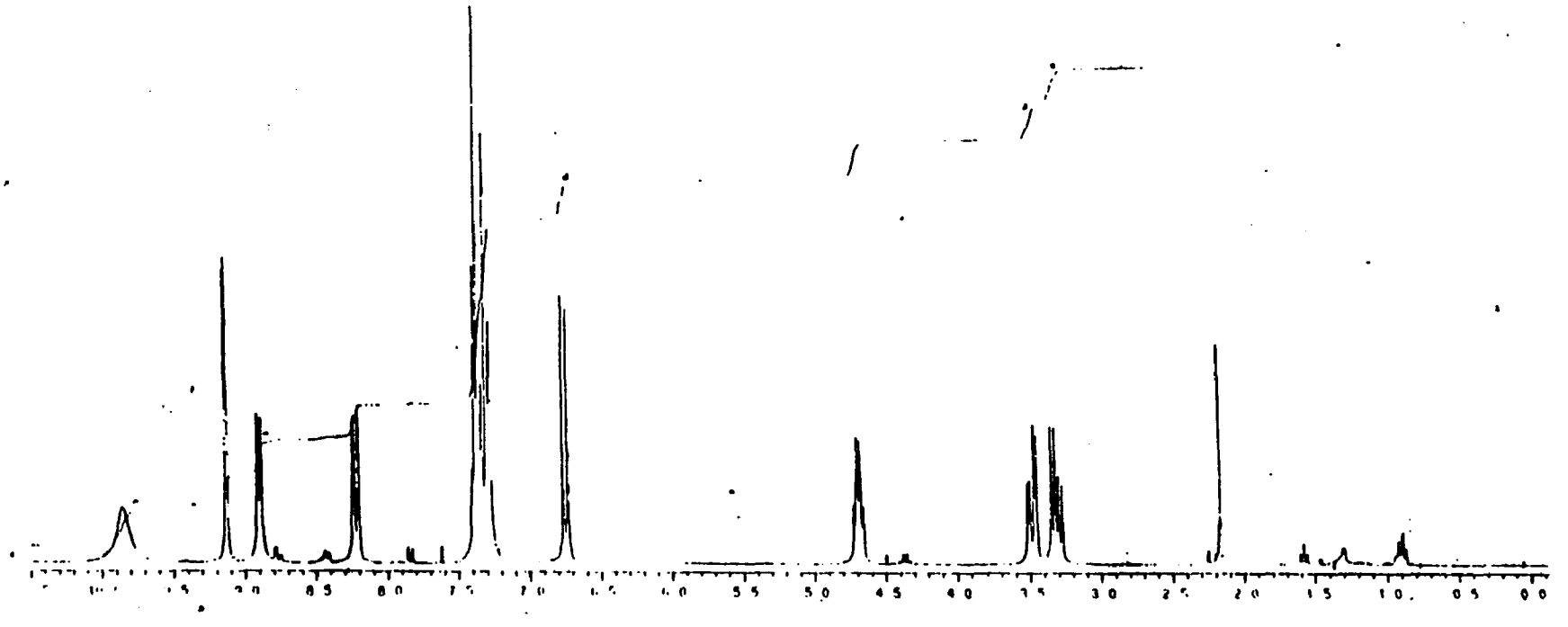


^{1}H NMR (**FF28**): *N*-(2,4-Dinitrophenyl)-Benzylamine.

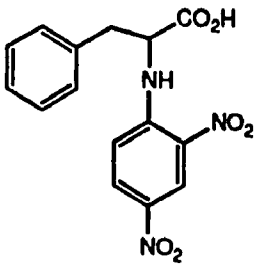


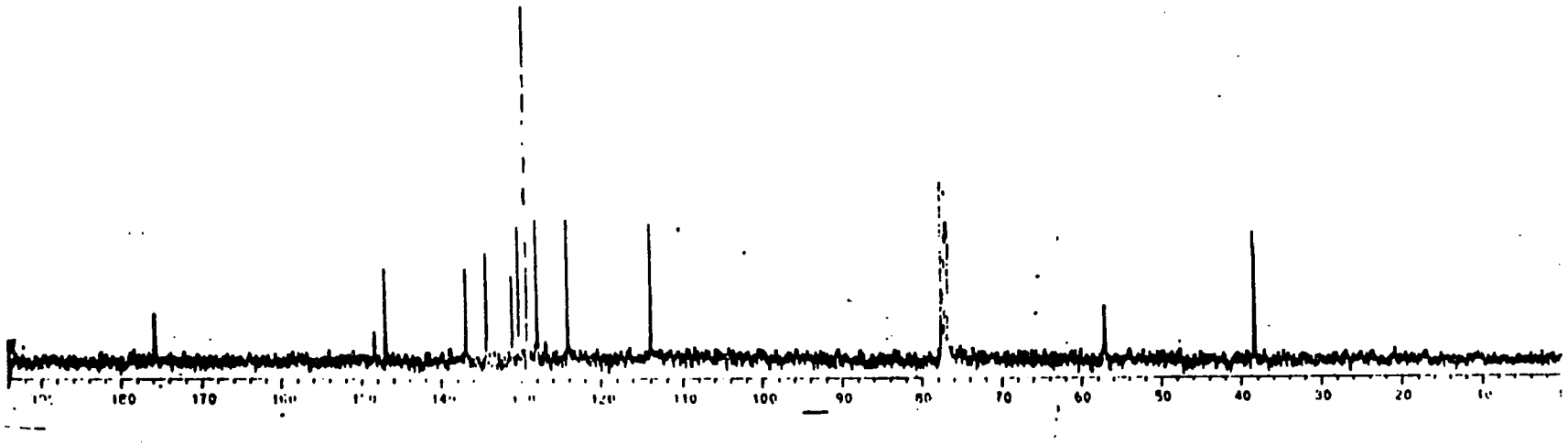
^{13}C NMR (**FF28**): *N*-(2,4-Dinitrophenyl)-Benzylamine.





^{1}H NMR (**GG2**): *N*-(2,4-Dinitrophenyl)-L-Phenylalanine.





^{13}C NMR (GG2): *N*-(2,4-Dinitrophenyl)-L-Phenylalanine.

APPENDIX B. X-RAY DATA.

Table of Positional Coordinates in Fractional Coordinates for 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**).

Atom	X	Y	Z	Sig X	Sig Y	Sig Z
C1	0.30527	0.37737	-0.04676	0.00710	0.00771	0.00710
N2	0.29950	0.41172	-0.11398	0.00603	0.00604	0.00588
C3	0.43134	0.35954	-0.12298	0.00715	0.00757	0.00685
C4	0.53598	0.28483	-0.05961	0.00658	0.00691	0.00668
C4A	0.32854	0.23981	-0.08447	0.00660	0.00715	0.00636
C5	0.24911	0.15992	-0.11159	0.00693	0.00737	0.00689
C6	0.06080	0.12860	-0.12679	0.00808	0.00821	0.00847
C7	-0.05985	0.18105	-0.11900	0.00776	0.01087	0.00895
C8	0.01368	0.26169	-0.09151	0.00756	0.00962	0.00776
C8A	0.20464	0.29154	-0.07514	0.00679	0.00794	0.00715
C9	0.70147	0.31711	0.03808	0.00710	0.00738	0.00703
C10	0.55955	0.37419	0.04440	0.00800	0.00764	0.00742
C11	0.05854	0.43106	-0.20069	0.00947	0.00925	0.00913
O12	0.62821	0.40329	-0.09825	0.00514	0.00551	0.00490
C13	0.55250	0.46840	-0.16801	0.01079	0.01040	0.00937
C14	0.73738	0.51881	-0.13249	0.01170	0.01140	0.01171
N15	0.36974	0.10105	-0.12318	0.00679	0.00681	0.00692
O16	0.45263	0.12734	-0.15158	0.00574	0.00632	0.00584
O17	0.37683	0.02833	-0.10529	0.00749	0.00634	0.00791
S18	0.83841	0.23335	0.12194	0.00209	0.00231	0.00211
C19	1.04345	0.19345	0.12129	0.00721	0.00721	0.00692
C20	1.24123	0.23847	0.15698	0.00765	0.00841	0.00841
C21	1.40186	0.20746	0.15680	0.00918	0.00945	0.00965

Table of Positional Coordinates in Fractional Coordinates for 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**) (continued).

Atom	X	Y	Z	Sig X	Sig Y	Sig Z
C22	1.37448	0.13010	0.12509	0.00875	0.01039	0.00900
C23	1.18945	0.08260	0.09199	0.00966	0.00895	0.00940
C24	1.02109	0.11382	0.08921	0.00916	0.00855	0.00890
H1	0.21150	0.41100	-0.04370	0.00000	0.00000	0.00000
H3	0.32080	0.34050	-0.18430	0.00000	0.00000	0.00000
H4	0.61980	0.24970	-0.06710	0.00000	0.00000	0.00000
H6	0.01040	0.07180	-0.14520	0.00000	0.00000	0.00000
H7	-0.18780	0.16120	-0.12960	0.00000	0.00000	0.00000
H8	-0.06940	0.29840	-0.08540	0.00000	0.00000	0.00000
H9	0.83160	0.34720	0.05150	0.00000	0.00000	0.00000
H10A	0.56640	0.35210	0.09030	0.00000	0.00000	0.00000
H10B	0.62600	0.42830	0.06510	0.00000	0.00000	0.00000
H11A	-0.02770	0.46660	-0.19560	0.00000	0.00000	0.00000
H11B	0.05860	0.45280	-0.24450	0.00000	0.00000	0.00000
H11C	0.00210	0.40340	-0.24640	0.00000	0.00000	0.00000
H13A	0.43920	0.50250	-0.16920	0.00000	0.00000	0.00000
H13B	0.46730	0.44390	-0.21960	0.00000	0.00000	0.00000
H?A	0.69100	0.56060	-0.17580	0.00000	0.00000	0.00000
H?B	0.84850	0.48080	-0.12600	0.00000	0.00000	0.00000
H?C	0.82000	0.53940	-0.07570	0.00000	0.00000	0.00000
H19	1.26270	0.29390	0.18000	0.00000	0.00000	0.00000
H20	1.53630	0.24030	0.18190	0.00000	0.00000	0.00000
H21	1.49070	0.10860	0.12870	0.00000	0.00000	0.00000
H22	1.17390	0.02770	0.07120	0.00000	0.00000	0.00000
H23	0.88020	0.08140	0.06330	0.00000	0.00000	0.00000

Table of Bond Angles for 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**).

Atom A	Atom B	Atom C	Dist. (A-B)	Dist. (B-C)	Angle (ABC)	S.D.
N2	C1	C8A	1.46782	1.49810	108.93638	0.579
N2	C1	C10	1.46782	1.50995	108.82716	0.586
C8A	C1	C10	1.49810	1.50995	109.49812	0.616
C1	N2	C3	1.46782	1.45211	110.82444	0.562
C1	N2	C11	1.46782	1.46581	112.78421	0.605
C3	N2	C11	1.45211	1.46581	113.71992	0.598
N2	C3	C4	1.45211	1.52814	110.72123	0.563
N2	C3	O12	1.45211	1.43945	111.50948	0.587
C4	C3	O12	1.52814	1.43945	106.45827	0.542
C3	C4	C4A	1.52814	1.51853	106.36189	0.545
C3	C4	C9	1.52814	1.53394	107.97178	0.566
C4A	C4	C9	1.51853	1.53394	109.20747	0.542
C4	C4A	C5	1.51853	1.37099	131.72926	0.626
C4	C4A	C8A	1.51853	1.40164	111.32607	0.609
C5	C4A	C8A	1.37099	1.40164	116.93047	0.631
C4A	C5	C6	1.37099	1.38590	123.21425	0.679
C4A	C5	N14	1.37099	1.48202	120.48505	0.619
C6	C5	N14	1.38590	1.48202	116.26891	0.658
C5	C6	C7	1.38590	1.36867	118.46411	0.775
C6	C7	C8	1.36867	1.37609	120.43887	0.757
C7	C8	C8A	1.37609	1.38399	120.22475	0.756
C1	C8A	C4A	1.49810	1.40164	111.97984	0.601
C1	C8A	C8	1.49810	1.38399	127.40421	0.704

Table of Bond Angles for 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**)(continued).

Atom A	Atom B	Atom C	Dist. (A-B)	Dist. (B-C)	Angle (ABC)	S.D.
C4A	C8A	C8	1.40164	1.38399	120.61595	0.737
C4	C9	C10	1.53394	1.52878	108.56722	0.570
C4	C9	S17	1.53394	1.83655	112.66663	0.498
C10	C9	S17	1.52878	1.83655	110.19852	0.494
C1	C10	C9	1.50995	1.52878	109.24390	0.601
C3	O12	C13	1.43945	1.43185	112.20308	0.602
O12	C13	C?	1.43185	1.39478	113.54411	0.841
C5	N14	O15	1.48202	1.22413	118.53538	0.643
C5	N14	016	1.48202	1.22081	117.76012	0.670
O15	N14	O16	1.22413	1.22081	123.59010	0.724
C9	S17	C18	1.83655	1.75611	101.46821	0.337
S17	C18	C19	1.75611	1.38077	120.78257	0.576
S17	C18	C23	1.75611	1.40027	122.06635	0.599
C19	C18	C23	1.38077	1.40027	117.07529	0.714
C18	C19	C20	1.38077	1.36834	120.92431	0.785
C19	C20	C21	1.36834	1.35596	120.35351	0.850
C20	C21	C22	1.35596	1.34001	121.37370	0.867
C21	C22	C23	1.34001	1.38861	119.15221	0.853
C18	C23	C22	1.40027	1.38861	121.05139	0.798

Anisotropic Thermal Parameters* (x 10^3), For Non-Hydrogen Atoms With Estimated Standard Deviations In Parentheses for compound 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**).

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	53(2)	52(4)	51(2)	7(3)	39(1)	-3(3)
N(2)	62(2)	41(3)	52(2)	7(2)	41(1)	3(2)
C(3)	53(2)	45(4)	44(2)	-4(3)	35(1)	-4(2)
C(4)	44(2)	41(4)	41(2)	0(2)	29(1)	3(2)
C(4a)	51(2)	42(4)	46(2)	0(3)	34(1)	-5(3)
C(5)	51(2)	42(4)	46(2)	0(3)	34(1)	-5(3)
C(6)	54(2)	52(5)	66(3)	-15(3)	38(2)	3(3)
C(7)	44(2)	101(7)	83(3)	3(3)	45(1)	6(4)
C(8)	63(2)	86(6)	69(2)	6(3)	52(1)	-2(3)
C(8a)	38(2)	66(5)	46(2)	12(3)	30(1)	10(3)
C(9)	48(2)	41(4)	44(2)	0(3)	31(3)	6(2)
C(10)	73(2)	45(4)	47(2)	10(3)	43(1)	-2(3)
C(11)	75(3)	73(5)	56(3)	37(3)	37(2)	8(3)
O(12)	68(2)	59(3)	49(1)	1(2)	40.8(9)	11(2)
C(14)	156(4)	81(7)	157(4)	4(5)	129(2)	29(4)
N(15)	62(2)	51(4)	69(2)	-19(3)	41(1)	-26(3)

Anisotropic Thermal Parameters* (x 10^3), For Non-Hydrogen Atoms With Estimated Standard Deviations In Parentheses for compound 2-Methyl-3(R*)-Ethoxy-5-Nitro-9(S*)-Thiophenyl-1(S*),4(R*)-Ethano-1,2,3,4-Tetrahydroisoquinoline (**A8**) (continued).

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(16)	103(2)	76(4)	111(2)	-12(2)	88(1)	-30(2)
O(17)	115(3)	48(4)	135(3)	-3(3)	86(2)	-8(3)
S(18)	63.0(5)	70(1)	64.5(6)	19.0(8)	48.3(3)	25.8(8)
C(19)	40(2)	42(4)	31(2)	9(3)	19(1)	11(2)
C(20)	48(2)	56(5)	71(3)	0(3)	40(1)	0(3)
C(21)	70(3)	76(6)	81(3)	-3(4)	51(2)	12(4)
C(22)	64(3)	101(7)	67(3)	23(4)	43(2)	3(4)
C(23)	77(3)	58(5)	63(3)	10(4)	38(2)	-13(3)
C(24)	54(3)	61(5)	44(3)	-1(3)	20(2)	1(3)

*In the form:

$$B \sin^2 \Theta/\lambda^2 = 2\pi^2 \left(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2\,U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^* \right)$$

Table of Positional Parameters and Their Estimated Standard Deviations for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole **C2.**

Atom	x	y	z	B(A2)	Atom	x	y	z	B(A2)
S1	0.2898	0.1634	0.2702	4	C20	-0.3824	-0.4129	0.0128	5
S2	-0.2248	-0.3966	0.2686	4	C21	0.0392	-0.0356	0.3302	4
O1'	-0.5842	-0.4852	0.2407	7	C22	0.1036	-0.0248	0.5113	3
O1	-0.0739	-0.0975	0.2258	8	C25	-0.2886	-0.3511	0.5081	3
O2'	-0.6244	-0.4649	0.406	6	C27	-0.5182	-0.4324	0.4016	3
O2	-0.119	-0.1384	0.3988	7	C28	0.0487	-0.0705	0.5702	3
O3'	-0.4035	-0.3298	0.7557	4	C30	-0.1331	-0.32	0.649	3
O3	0.0968	-0.0696	0.7581	5	C31	-0.5137	-0.4121	0.5228	3
O4'	-0.5026	-0.3922	0.7641	5	C33	0.3211	0.1393	0.5789	2
O4	-0.0024	-0.1208	0.7511	7	C34	-0.1572	-0.3079	0.4478	3
O5'	-0.0125	-0.2943	0.7294	5	C36	0.3548	0.1914	0.7799	3
O5	0.4898	0.2685	0.741	4	C37	-0.009	-0.098	0.5141	4
N1	-0.0739	-0.1092	0.3351	5	C38	-0.1819	-0.3251	0.5711	2
N1'	-0.5798	-0.4624	0.3465	4	C39	0.2451	0.1142	0.7346	3
N2'	-0.4535	-0.3665	0.7066	3	C40	-0.1447	-0.3323	0.7758	3
N2	0.0486	-0.0888	0.7003	4	C41	0.2271	0.1118	0.1733	3
N3'	-0.3433	-0.3417	0.5582	3	C42	-0.205	-0.3518	0.8136	3
N3	0.1601	0.0032	0.564	3	C43	0.4094	0.1752	0.4701	3
N4	0.4242	0.2042	0.5919	2	C44	-0.2543	-0.3588	0.734	3
N4'	-0.0799	-0.301	0.5765	3	C45	0.4832	0.2438	0.6356	3
C1	-0.3356	-0.4673	0.1577	4	C48	0.0966	-0.0073	0.3851	3
C2	-0.2842	-0.3385	0.103	4	C49	0.0296	-0.2731	0.5281	5
C4	-0.2861	-0.3995	0.1696	3	C51	-0.2422	-0.345	0.6087	3

Table of Positional Parameters and Their Estimated Standard Deviations for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole **C2** (continued).

Atom	x	y	z	B(A2)	Atom	x	y	z	B(A2)
C5	-0.4	-0.3716	0.51	3	C52	0.2931	0.1565	0.8143	3
C6	0.3689	0.1815	0.6575	2	C53	0.3059	0.0922	0.36	3
C8	0.5374	0.2554	0.5547	3	C54	0.1728	0.0108	0.0339	4
C10	-0.4675	-0.426	0.3335	3	C58	0.2483	0.0326	0.4179	3
C12	-0.0118	-0.0802	0.3939	4	C60	0.26	0.1056	0.6126	3
C13	-0.384	-0.4741	0.0764	5	C63	0.2144	0.0632	0.5121	3
C14	0.3485	0.1362	0.461	2	C64	-0.2556	-0.2926	0.406	3
C15	-0.4094	-0.3973	0.3849	3	C65	0.1311	0.1019	0.0782	6
C17	-0.3337	-0.3448	0.0249	5	C69	0.2234	0.048	0.1106	4
C17	-0.4551	-0.382	0.574	2	C74	0.1271	0.0376	0.0184	5
C18	-0.0969	-0.2934	0.453	3	C82	0.1814	0.138	0.1585	5
C19	-0.0217	-0.29	0.6176	3					

Anisotropically refined atoms are given in the form of theisotropic equivalent displacement parameter defined as:

$$(4/3)*[a2*B(1,1)+b2*B(2,2)+c2*B(3,3)+ab(\cos\gamma)*B(1,2)+$$

$$ac(\cos\beta)*B(1,3)+bc(\cos\alpha)*B(2,3)]$$

Table of Bond Distances in Angstroms for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole **C2**.

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
S1	C41	1.760	N4'	C18	1.424	C22	C28	1.396
S1	C53	1.851	N4'	C19	1.368	C22	C48	1.438
S2	C4	1.776	N4'	C30	1.395	C25	C51	1.514
S2	C99	1.838	C1	C4	1.373	C25	C64	1.557
O1'	N1'	1.222	C1	C13	1.402	C27	C31	1.368
O1	N1	1.211	C2	C4	1.376	C28	C37	1.385
O2'	N1'	1.213	C2	C17	1.402	C30	C38	1.392
O2	N1	1.202	C5	C15	1.434	C30	C40	1.407
O3'	N2'	1.226	C5	C17	1.408	C33	C60	1.367
O3	N2	1.212	C6	C33	1.389	C34	C38	1.446
O4'	N2'	1.227	C6	C36	1.402	C34	C99	1.508
O4	N2	1.241	C8	C45	1.486	C36	C52	1.383
O5'	C19	1.243	C10	C15	1.369	C38	C51	1.371
O5	C45	1.228	C10	C27	1.362	C39	C52	1.398
N1	C12	1.480	C12	C21	1.356	C39	C60	1.398
N1'	C27	1.453	C12	C37	1.361	C40	C42	1.374
N2'	C17	1.470	C13	C20	1.363	C41	C69	1.387
N2	C28	1.458	C14	C33	1.445	C41	C82	1.366
N3'	C5	1.329	C14	C43	1.329	C42	C44	1.405
N3'	C25	1.466	C14	C53	1.501	C44	C51	1.395
N3	C22	1.343	C17	C20	1.369	C53	C58	1.524
N3	C63	1.458	C17	C31	1.377	C54	C69	1.394
N4	C6	1.388	C18	C34	1.327	C54	C74	1.374
N4	C43	1.427	C19	C49	1.481	C58	C63	1.549
N4	C45	1.372	C21	C48	1.371	C60	C63	1.521
C64	C99	1.537	C65	C74	1.377	C65	C82	1.408

Table of Refined Displacement Parameter Expressions - Beta's for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole **C2**.

Name	"B(1,1)"	"B(2,2)"	"B(3,3)"	"B(1,2)"	"B(1,3)"	"B(2,3)"
S1	0.00313(1)	0.00296(1)	0.00764(1)	0.00152(1)	-0.00247(1)	0.00061(1)
S2	0.00309(1)	0.00480(1)	0.00898(1)	0.00522(1)	-0.00296(1)	-0.00518(1)
O1'	0.00397(1)	0.00577(1)	0.01555(1)	0.00379(1)	0.00001(1)	0.00002(1)
O1	0.00466(1)	0.00678(1)	0.01826(1)	0.00445(1)	0.00001(1)	0.00002(1)
O2'	0.00342(1)	0.00496(1)	0.01337(1)	0.00326(1)	0.00000(1)	0.00001(1)
O2	0.00388(1)	0.00564(1)	0.01521(1)	0.00371(1)	0.00001(1)	0.00002(1)
O3'	0.00247(1)	0.00359(1)	0.00966(1)	0.00236(1)	0.00000(1)	0.00001(1)
O3	0.00293(1)	0.00425(1)	0.01146(1)	0.00279(1)	0.00000(1)	0.00001(1)
O4'	0.00284(1)	0.00412(1)	0.01110(1)	0.00271(1)	0.00000(1)	0.00001(1)
O4	0.00390(1)	0.00567(1)	0.01527(1)	0.00372(1)	0.00001(1)	0.00002(1)
O5'	0.00293(1)	0.00425(1)	0.01146(1)	0.00279(1)	0.00000(1)	0.00001(1)
O5	0.00240(1)	0.00349(1)	0.00940(1)	0.00229(1)	0.00000(1)	0.00001(1)
N1	0.00317(1)	0.00461(1)	0.01243(1)	0.00303(1)	0.00000(1)	0.00001(1)
N1'	0.00263(1)	0.00383(1)	0.01031(1)	0.00251(1)	0.00000(1)	0.00001(1)
N2'	0.00205(1)	0.00298(1)	0.00803(1)	0.00196(1)	0.00000(1)	0.00001(1)
N2	0.00244(1)	0.00355(1)	0.00956(1)	0.00233(1)	0.00000(1)	0.00001(1)
N3'	0.00180(1)	0.00262(1)	0.00705(1)	0.00172(1)	0.00000(1)	0.00001(1)
N3	0.00187(1)	0.00272(1)	0.00733(1)	0.00179(1)	0.00000(1)	0.00001(1)
N4	0.00159(1)	0.00232(1)	0.00624(1)	0.00152(1)	0.00000(1)	0.00001(1)
N4'	0.00168(1)	0.00244(1)	0.00658(1)	0.00160(1)	0.00000(1)	0.00001(1)
C1	0.00244(1)	0.00355(1)	0.00957(1)	0.00233(1)	0.00000(1)	0.00001(1)
C2	0.00236(1)	0.00343(1)	0.00925(1)	0.00226(1)	0.00000(1)	0.00001(1)
C4	0.00195(1)	0.00283(1)	0.00763(1)	0.00186(1)	0.00000(1)	0.00001(1)
C5	0.00165(1)	0.00240(1)	0.00645(1)	0.00157(1)	0.00000(1)	0.00001(1)
C6	0.00153(1)	0.00222(1)	0.00597(1)	0.00146(1)	0.00000(1)	0.00001(1)
C8	0.00212(1)	0.00307(1)	0.00828(1)	0.00202(1)	0.00000(1)	0.00001(1)

Table of Refined Displacement Parameter Expressions - Beta's for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole C2 (continued).

Name	"B(1,1)"	"B(2,2)"	"B(3,3)"	"B(1,2)"	"B(1,3)"	"B(2,3)"
C10	0.00211(1)	0.00307(1)	0.00826(1)	0.00201(1)	0.00000(1)	0.00001(1)
C12	0.00219(1)	0.00318(1)	0.00858(1)	0.00209(1)	0.00000(1)	0.00001(1)
C13	0.00274(1)	0.00399(1)	0.01075(1)	0.00262(1)	0.00000(1)	0.00001(1)
C14	0.00154(1)	0.00223(1)	0.00601(1)	0.00147(1)	0.00000(1)	0.00001(1)
C15	0.00201(1)	0.00292(1)	0.00787(1)	0.00192(1)	0.00000(1)	0.00001(1)
C17	0.00277(1)	0.00403(1)	0.01086(1)	0.00265(1)	0.00000(1)	0.00001(1)
C17	0.00160(1)	0.00233(1)	0.00627(1)	0.00153(1)	0.00000(1)	0.00001(1)
C18	0.00169(1)	0.00245(1)	0.00661(1)	0.00161(1)	0.00000(1)	0.00001(1)
C19	0.00203(1)	0.00295(1)	0.00794(1)	0.00194(1)	0.00000(1)	0.00001(1)
C20	0.00280(1)	0.00407(1)	0.01096(1)	0.00267(1)	0.00000(1)	0.00001(1)
C21	0.00237(1)	0.00345(1)	0.00929(1)	0.00227(1)	0.00000(1)	0.00001(1)
C22	0.00176(1)	0.00255(1)	0.00687(1)	0.00167(1)	0.00000(1)	0.00001(1)
C25	0.00178(1)	0.00258(1)	0.00695(1)	0.00170(1)	0.00000(1)	0.00001(1)
C27	0.00185(1)	0.00269(1)	0.00724(1)	0.00176(1)	0.00000(1)	0.00001(1)
C28	0.00182(1)	0.00265(1)	0.00713(1)	0.00174(1)	0.00000(1)	0.00001(1)
C30	0.00169(1)	0.00245(1)	0.00660(1)	0.00161(1)	0.00000(1)	0.00001(1)
C31	0.00194(1)	0.00282(1)	0.00759(1)	0.00185(1)	0.00000(1)	0.00001(1)
C33	0.00152(1)	0.00220(1)	0.00594(1)	0.00145(1)	0.00000(1)	0.00001(1)
C34	0.00168(1)	0.00244(1)	0.00656(1)	0.00160(1)	0.00000(1)	0.00001(1)
C36	0.00198(1)	0.00287(1)	0.00774(1)	0.00189(1)	0.00000(1)	0.00001(1)
C37	0.00237(1)	0.00345(1)	0.00929(1)	0.00226(1)	0.00000(1)	0.00001(1)
C38	0.00156(1)	0.00227(1)	0.00611(1)	0.00149(1)	0.00000(1)	0.00001(1)
C39	0.00202(1)	0.00294(1)	0.00792(1)	0.00193(1)	0.00000(1)	0.00001(1)
C40	0.00206(1)	0.00300(1)	0.00808(1)	0.00197(1)	0.00000(1)	0.00001(1)
C41	0.00187(1)	0.00272(1)	0.00734(1)	0.00179(1)	0.00000(1)	0.00001(1)
C42	0.00215(1)	0.00312(1)	0.00842(1)	0.00205(1)	0.00000(1)	0.00001(1)

Table of Refined Displacement Parameter Expressions - Beta's for 1-Acetyl-3-Thiophenyl-6-(2,4-Dinitrophenyl)-Amino-1,3,4,5-Tetrahydrobenz[cd]indole **C2** (continued).

Name	"B(1,1)"	"B(2,2)"	"B(3,3)"	"B(1,2)"	"B(1,3)"	"B(2,3)"
C43	0.00175(1)	0.00254(1)	0.00685(1)	0.00167(1)	0.00000(1)	0.00001(1)
C44	0.00212(1)	0.00308(1)	0.00829(1)	0.00202(1)	0.00000(1)	0.00001(1)
C45	0.00176(1)	0.00256(1)	0.00691(1)	0.00168(1)	0.00000(1)	0.00001(1)
C48	0.00212(1)	0.00307(1)	0.00828(1)	0.00202(1)	0.00000(1)	0.00001(1)
C49	0.00294(1)	0.00427(1)	0.01150(1)	0.00280(1)	0.00000(1)	0.00001(1)
C51	0.00170(1)	0.00247(1)	0.00666(1)	0.00162(1)	0.00000(1)	0.00001(1)
C52	0.00216(1)	0.00314(1)	0.00846(1)	0.00206(1)	0.00000(1)	0.00001(1)
C53	0.00178(1)	0.00258(1)	0.00695(1)	0.00170(1)	0.00000(1)	0.00001(1)
C54	0.00264(1)	0.00383(1)	0.01032(1)	0.00252(1)	0.00000(1)	0.00001(1)
C58	0.00183(1)	0.00265(1)	0.00715(1)	0.00174(1)	0.00000(1)	0.00001(1)
C60	0.00165(1)	0.00239(1)	0.00645(1)	0.00157(1)	0.00000(1)	0.00001(1)
C63	0.00173(1)	0.00251(1)	0.00678(1)	0.00165(1)	0.00000(1)	0.00001(1)
C64	0.00179(1)	0.00259(1)	0.00699(1)	0.00170(1)	0.00000(1)	0.00001(1)
C65	0.00359(1)	0.00522(1)	0.01406(1)	0.00343(1)	0.00001(1)	0.00001(1)
C69	0.00217(1)	0.00315(1)	0.00848(1)	0.00207(1)	0.00000(1)	0.00001(1)
C74	0.00307(1)	0.00446(1)	0.01200(1)	0.00293(1)	0.00000(1)	0.00001(1)
C82	0.00305(1)	0.00443(1)	0.01195(1)	0.00291(1)	0.00000(1)	0.00001(1)
C99	0.00181(1)	0.00263(1)	0.00710(1)	0.00173(1)	0.00000(1)	0.00001(1)

The form of the anisotropic displacement parameter is:

"exp[-(B(1,1)*h2 + B(2,2)*k2 + B(3,3)*l2 + B(1,2)*hk + B(1,3)*hl + B(2,3)*kl)]"

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57. Unpublished result by Xiaoming Ye in our lab.