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## A Stereoselective Synthesis of Cis-2,5-Disubstituted Pyrrolidines: Precursors for the (5E, 8Z)-3,5-Dialkyl Pyrrolizidines

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A STEREOSELECTIVE SYNTHESIS OF  
CIS-2,5-DISUBSTITUTED PYRROLIDINES:  
PRECURSORS FOR THE  
(5E,8Z)-3,5-DIALKYL PYRROLIZIDINES

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A Thesis  
Presented to  
The Faculty of the Department of Chemistry  
The College of William and Mary in Virginia

In Partial Fulfillment  
of the Requirements for the Degree of  
Master of Arts

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by  
Mehul Shantilal Shah  
1987

APPROVAL SHEET

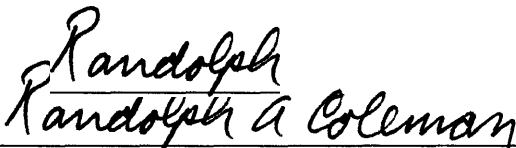
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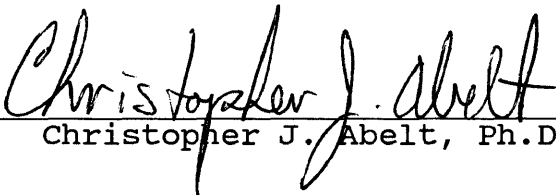
  
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## DEDICATION

This thesis is dedicated to my family, especially my parents, without whose love, encouragement, and thoughtful understanding, life would have little meaning.

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## ABSTRACT

A stereoselective synthesis of cis-2,5-disubstituted pyrrolidines which includes the incorporation of acid sensitive functional groups is reported.

The synthesis utilizes nitron methodology followed by stereoselective reduction using diisobutylaluminum hydride to accomplish the goal.

The appropriate cis-2,5-disubstituted pyrrolidines will be the necessary precursors for the synthesis of (5E,8Z)-3,5-dialkyl pyrrolizidines.

A STEREOSELECTIVE SYNTHESIS OF  
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PRECURSORS FOR THE  
(5E,8Z)-3,5-DIALKYL PYRROLIZIDINES

CHAPTER 1  
ALKALOIDS OF ANT VENOMS

A. INTRODUCTION

The chemistry of glandular secretions of ants has been studied critically only over the past fifteen years, and as such, is still quite limited. The venoms of the subfamily Mermicinae, genera Solenopsis, Monomorium, and Chelaner, however, have been relatively thoroughly investigated and have been shown to be outstanding sources of nitrogenous compounds.<sup>1</sup>

The ability of ants to survive the attacks of their predators is believed to be due to potent defensive secretions containing compounds that are synthesized de novo in specialized exocrine glands. Frequently, the major defensive products in the venom glands are alkaloids, some of which constitute unique natural products. Many of these alkaloids function as chemical signaling agents (pheromones) that transfer information rapidly between individuals; but it is more likely that this function often accompanies the defensive roles of these alkaloids. The alkaloids function admirably in their roles as both pheromones and allomones, demonstrating that these ants have adapted a number of

relatively small, basic, mono- and bicyclic nitrogen heterocycles which are instrumental in a variety of critical biological functions.

In general, the alkaloids are only produced in trace amounts, with submicrogram quantities being the rule. The identification of these compounds has generally required degradative studies in combination with a variety of spectral techniques. Ultimately, direct comparisons with synthetic compounds have been utilized to identify the alkaloids conclusively, especially when questions of stereochemistry or absolute configuration need to be answered.

To date, ants constitute the largest source of saturated nitrogen heterocycles derived from animals.

## B. PIPERIDINES AND PIPERIDEINES

### 1. Distribution

Dialkylpiperidines have been predominantly found as poison gland products of fire ant workers and queens in the genus Solenopsis. These alkaloids have been found in three different subgenera, but, only in the subgenus Solenopsis have all of the species to be analyzed been found to produce dialkylpiperidines, which are often species specific.<sup>1</sup> In the subgenus Diplorhoptrum, workers of three species, S. bondari, S. invicta, and S. richteri, synthesize these alkaloids, as well as one species in the subgenus Euopthalma, S. littoralis.<sup>2</sup>

N-methyl-2,6-dialkylpiperidines have been found in the

venom glands of a few Solenopsis species in the subgenus Diplorhoptrum, and, the Monomorium species M. latinode with the corresponding N-H piperidines.<sup>2</sup>

Two 1-piperideines have been identified as poison gland products in the genus Solenopsis. In S. xyloni, 2-methyl-6-undecyl-1-piperideine (5) is a minor component in the venom, and was hypothesized to serve as a precursor for the corresponding piperidine.<sup>1</sup> The other piperideine has been identified to be 2-(4-penten-1-yl)-1-piperideine (6) as the single component of the poison gland of S. Diplorhoptrum Puerto Rico species A.<sup>2</sup> This alkaloid was of interest because it differed from all previously reported alkaloids, both from Monomorium and Solenopsis, in that it had an even number of carbons and that it departed from the usual disubstituted theme characteristic of ant alkaloids.

## 2. Functions

In humans, the fire ant sting causes pronounced necrosis of the epidermis with the formation of pruritic pustules that are not characteristic of human reactions to the stings of other insects, giving the ants in the subgenus Solenopsis the name fire ants. Other biological activity observed of the venom to possess include: pronounced antibacterial, antifungal, phytotoxic, insecticidal and powerful hemolytic activity. Physiologically, these compounds are capable of inhibiting  $\text{Na}^+$  and  $\text{K}^+$  ATPases, reducing mitochondrial respiration and uncoupling oxidative phosphorylation at low concentrations. Furthermore, they are

capable of blocking neuromuscular junctions, and releasing histamine from mast cells.<sup>1</sup> Many of the above mentioned functions make the alkaloids excellent for their role as defensive compounds.

The piperideines seem to function primarily as deterrents against other ant species.<sup>2</sup>

### 3. Chemistry

#### 3.a. 2-Alkyl-6-methylpiperidines

The known 2-alkyl-6-methylpiperidines of the Solenopsis ant venoms were analyzed by GC/MS. The mass spectra displayed a strong characteristic ion at  $m/z=98$  due to cleavage of the side chain alkyl group, as well as  $M-CH_3$ , and an  $M-1$  ion.

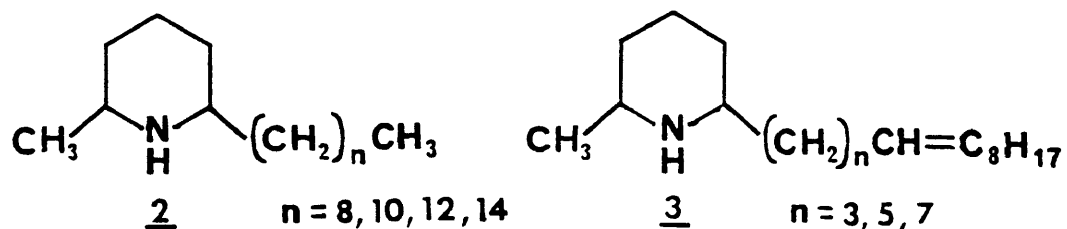


Figure 1. Piperidines.

Secondly, infrared spectroscopy of the alkaloids showed characteristic absorptions for the piperidine ring and could be used to elucidate the geometry of the carbon-carbon double bond on the alkyl chain which proved to always be cis. The homologous 2-alkyl-6-methylpiperidines are represented by structures 2 and 3.



The overall structure and stereochemistry of the 2-alkyl-6-methylpiperidines was confirmed by independent synthesis. A generally applicable synthesis was based on the alkylation of the lithium salt derivative of 2,6-lutidine with the appropriate alkyl bromide or tosylate, followed by reduction of the resulting 2-alkyl-6-methylpyridine.<sup>3</sup> Hydrogenation with rhodium over charcoal provided only the cis-2,6-disubstituted piperidine, whereas reduction with sodium in ethanol yielded an 85:15 cis/trans mixture.

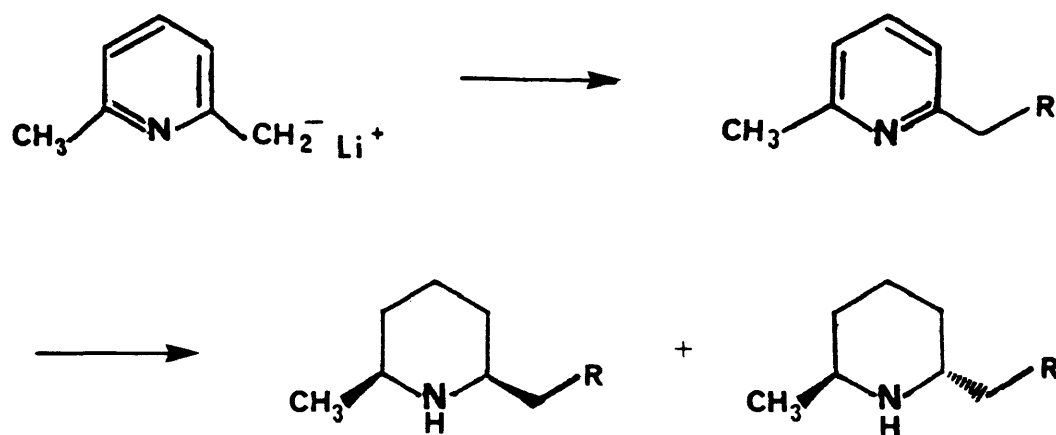


Figure 2. Piperidine synthesis from 2,6-lutidine.

When there was a double bond present in the side chain, the appropriate alkenyl bromides with cis double bonds were prepared using partial hydrogenation of an acetylene in the presence of Lindlar catalyst as the geometry determining step, and carried through the 2,6-lutidine alkylation and reduction which provided products that were chromatographically and spectroscopically identical to the natural

alkaloids.<sup>3</sup>

A recent stereoselective synthesis provided either cis or trans piperidines depending upon the reduction method employed from the appropriate 2-cyanopiperidine.<sup>4</sup> In another report, the reduction of 1-piperidines with lithium aluminum hydride in the presence of trimethylaluminum provided the trans-2,6-disubstituted piperidines.<sup>5</sup> And finally, a synthesis which utilized the nitrene cycloaddition methodology, provided the trans-2-alkyl-6-methylpiperidines stereoselectively.<sup>6</sup>

Direct GLC retention time comparison eluded that the 2-alkyl-6-methylpiperidines in the ant venoms to have predominantly the trans configuration.

### 3.b. N-methyl-2-alkyl-6-methylpiperidines

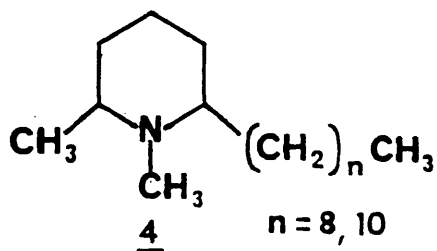


Figure 3. N-Methylpiperidines.

The N-methylpiperidines (4) occurring in Solenopsis and Monomorium species displayed a characteristic base peak in their mass spectra at  $m/z=112$  and were prepared by reductive

methylation of the corresponding N-H piperidine with formaldehyde and formic acid.<sup>2</sup>

### 3.c. Piperideines

The structures of the 1-piperideines occurring in Solenopsis venoms were determined from their reduction products along with their mass spectra. The reduction of 2-methyl-6-undecyl-1-piperideine (5) to its corresponding N-H piperidine by borohydride followed by treatment with t-butylhypochlorite provided both isomers of the piperideine. The mass spectra of the two isomers were quite different with the 1-piperideine having an intense odd-electron ion appearing at  $\underline{m/z}$ =97, whereas the 6-piperideine had an intense odd-electron ion appearing at  $\underline{m/z}$ =111.

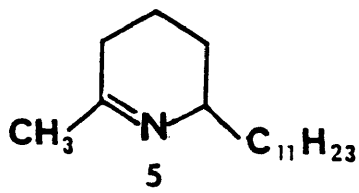


Figure 4. 2-Methyl-6-undecyl-1-piperideine.

Comparison of the natural product to the isomers revealed 5 to have an identical mass spectra and GLC retention time as the 1-piperideine isomer in the ant.<sup>1</sup>

The mass spectrum of 2-(4-penten-1-yl)-1-piperideine (6) also displayed an odd-electron ion at  $\underline{m/z}$ =97 and a weak molecular ion at  $\underline{m/z}$ =151 suggesting the formula  $C_{10}H_{17}N$ . Its

synthesis for comparison purposes was based on the Mundy N-acyllactam rearrangement:<sup>7</sup> N-(5-Hexenoyl)-piperidone, prepared by acylation of the piperidone with 5-hexenoyl chloride, was heated in the presence of calcium oxide to give 6 directly.<sup>8,9</sup>

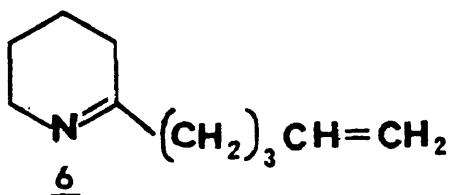


Figure 5. 2-(4-Penten-1-yl)-1-piperidine.

### C. PYRROLIDINES AND PYRROLINES

#### 1. Distribution

A diversity of pyrrolidines and pyrrolines have been identified as venom constituents of ant species in the genera Solenopsis and Monomorium, two taxa in the subfamily Myrmicinae.<sup>1</sup> The first pyrrolidines to be reported, 2-butyl-5-pentylpyrrolidine (7a) and 5-(5-hexen-1-yl)-2-pentylpyrrolidine (7b), were venom gland products of Pharaoh's ant, M. pharaonis, a species that is quite abundant in the Old World tropics. It has become a domestic pest in many nontropical countries and is known to be able to carry pathogenic bacteria and transmit disease.<sup>2</sup> A substantial study of North American ants of the genus Monomorium revealed a number of nineteen carbon pyrrolidines as major

venom components.<sup>10</sup> The venoms of Monomorium species have been shown to contain saturated 2,5-dialkylpyrrolidines as well as the unsaturated pyrrolidines.<sup>10</sup> Occasionally, N-methylpyrrolidines were found to be present in some of the venoms.<sup>2</sup> An Asiatic species, M. latinode, was found to be distinctive in that it produces a venom that is rich in both pyrrolidines and pyrrolines.<sup>2</sup> Finally, in one species, M. ebeninum, an isomeric pair of 1-pyrrolines has been found as the major components of the venom gland.<sup>10</sup>

In the genus Solenopsis, pyrrolidines have been found to occur exclusively in species belonging to the subgenus Diplorhoptrum.<sup>1</sup> Although the venom of the South African ant, S. punctaticeps, contains a complex mixture of both pyrrolidines and pyrrolines,<sup>11</sup> those of other species generally contain a single pyrrolidine.<sup>12</sup>

## 2. Functions

Workers of the Monomorium species, which compete quite successfully with other species of ants at food sources, have been observed to utilize their poison gland secretions as an effective repellent. In addition, some components in the venom have been shown to be trail pheromones. Both workers and queens have a tendency to travel in lines following odor trails secreted by workers. Behavioral studies have shown that the synthetic alkaloids are mutually synergizing since trails laid with the cis/trans mixtures were responded to better by the ants than trails composed of the separate isomers.<sup>2</sup>

The ants belonging to the subgenus Diplorhoptrum are referred to as thief ants because of their propensity for raiding the nests of other species of ants and stealing the larvae for food. This action is made possible by the presence of powerful venomous repellents, which are secreted in offensive contexts by the raiding thief ants. The ant does sting human beings, but reactions to the sting are mild and characterized by transient edema and pruritis.<sup>2</sup>

### 3. Chemistry

#### 3.a. 2,5-Dialkylpyrrolidines

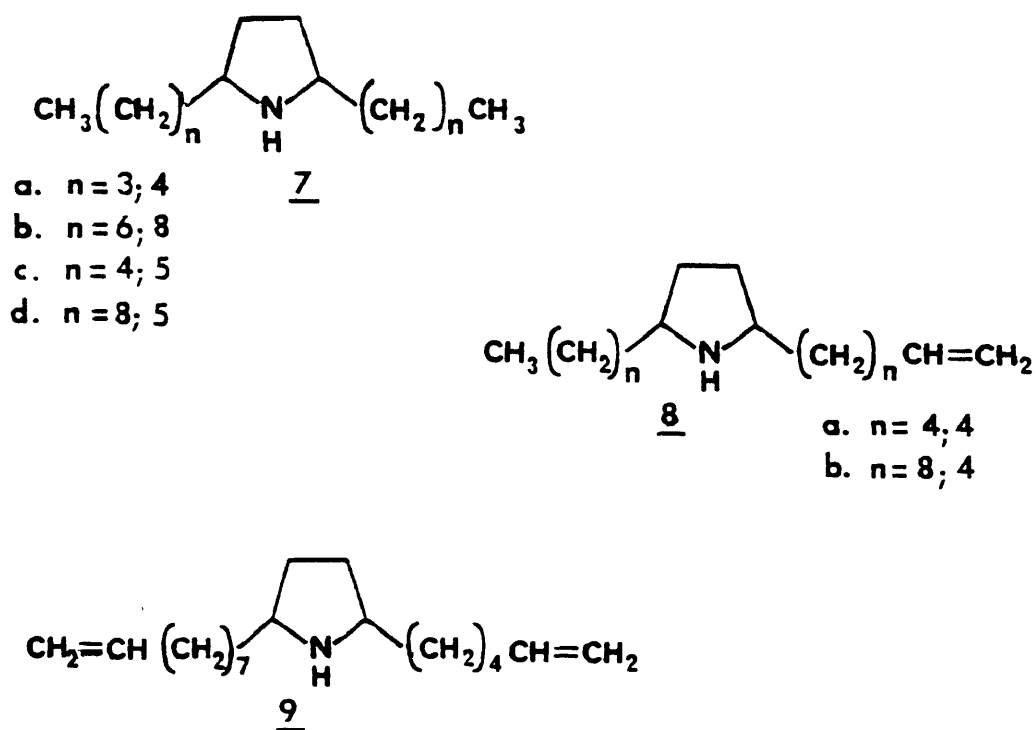


Figure 6. Pyrrolidines.

The mass spectra of the 2,5-dialkylpyrrolidines, 7-9, found in Solenopsis and Monomorium ant species, displayed

two intense ions corresponding to cleavage of the side chains as well as a weak molecular ion, which defined their C-N skeletons, but not their stereochemistry.<sup>11</sup>

Subsequently, a number of synthetic routes have been developed including procedures based on the use of nitrene cycloaddition methodology,<sup>6</sup> the borohydride reduction of the corresponding pyrrolines formed by the Mundy rearrangement,<sup>7</sup> the Hofmann-Löffler reaction,<sup>11</sup> the catalytic hydrogenation of pyrroles,<sup>12</sup> the direct alkylation of N-nitrosopyrrolidine,<sup>13</sup> the pyrroline allylic carbanion alkylation,<sup>14</sup> the synthesis from glutamic acid,<sup>15</sup> and, the reductive amination of 1,4-diketones.<sup>16</sup>

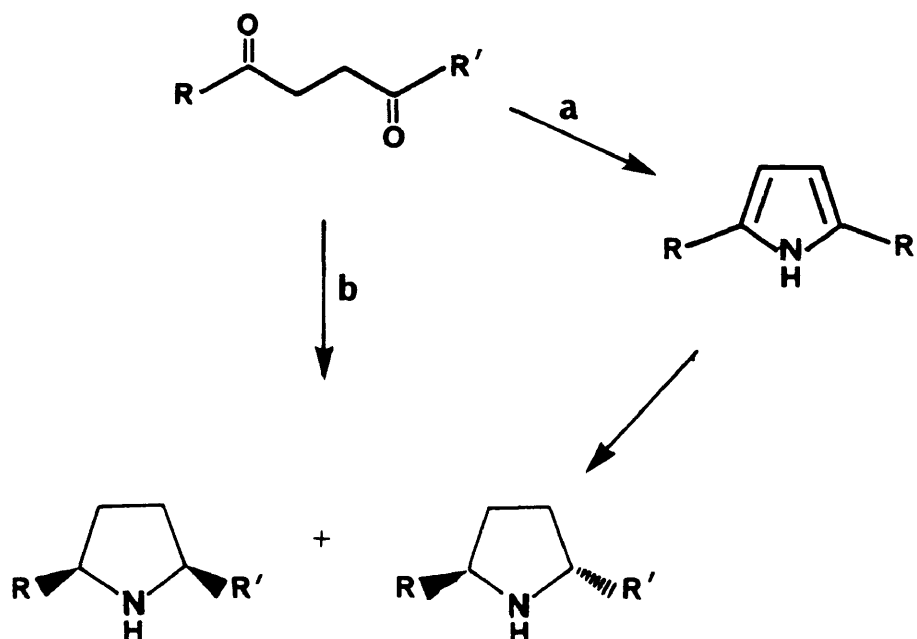


Figure 7. Pyrrolidine synthesis from 1,4-diketones.

Treatment of 1,4-diketones with excess ammonium car-

bonate to gave dialkylpyrroles which were hydrogenated over a rhodium catalyst to provide an 85:15 cis/trans mixture of pyrrolidine.<sup>12</sup> This method, however, was not compatible to the incorporation of terminal double bonds. The more direct reductive amination of 1,4-diketones using ammonium acetate and sodium cyanoborohydride followed immediately by addition of excess sodium borohydride provided a 50:50 cis/trans 2,5-dialkylpyrrolidine mixture,<sup>16</sup> indicating little difference between the isomers in strain and in crowding of the side chains.

The mass spectra of the synthetic 2,5-dialkylpyrrolidines were identical to that of the naturally occurring alkaloids. Comparison by GLC retention time and coinjection showed that the naturally occurring pyrrolidines were of the trans configuration exclusively.<sup>10,16</sup>

### 3.b. N-Methyl-2,5-dialkylpyrrolidines

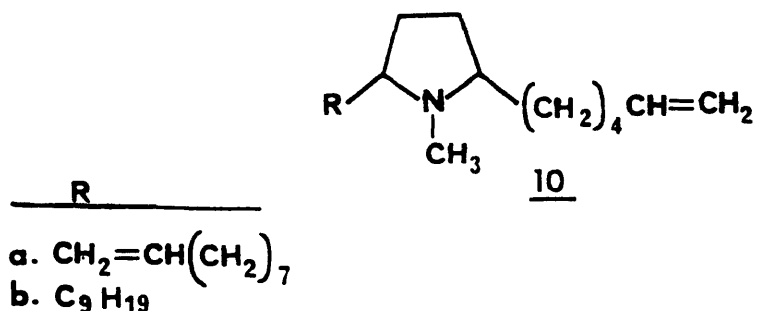


Figure 8. N-Methylpyrrolidines.

The several N-methylpyrrolidines, 10a,b, found to be present in some of the venoms had mass spectra similar to



their corresponding N-H derivatives with all the major fragments shifted up by fourteen units. Their preparation could be achieved by reductive alkylation of the nonmethylated pyrrolidines with formaldehyde in formic acid.<sup>10</sup>

### 3.c. 2,5-Dialkyl-1-pyrroline

The isomeric pair of 1-pyrroline, **11**, had mass spectra which showed the expected allylic cleavage ions from to carbon-nitrogen double bond as well as an odd electron ion from a McLafferty rearrangement and an ion at  $m/z=82$  resulting from the  $\alpha$ -cleavage of an alkyl group from the odd electron ion.<sup>10,11</sup>

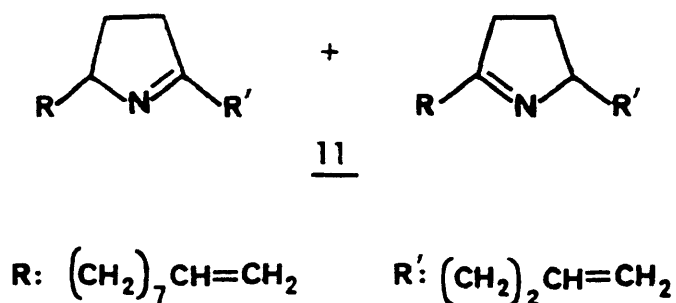


Figure 9. Pyrrolines.

The 1-pyrrolines have been prepared from their parent pyrrolidine by treatment of the N-chloropyrrolidine with aqueous alkali.<sup>12,16</sup>

## D. INDOLIZIDINES

### 1. Distribution

The distribution of dialkylindolizidines is limited to

Pharaoh's ant, M. pharaonis,<sup>2</sup> and two species in Solenopsis (Diplorhoptum), species AA and S. conjurata.<sup>17</sup>

In M. pharaonis, the alkaloids reported to be found were (5Z,9Z) 5-methyl-3-butylindolizidine 12a and (5Z,9Z) 5-methyl-3-(3-hexen-1-yl)indolizidine 12b.<sup>2</sup>

The alkaloidal venom components of the two species of their ants were found to contain (5Z,9Z)-3-hexyl-5-methylindolizidine 13a or a mixture of (5Z,9Z)-3-ethyl-5-methylindolizidine 13b, cis-2-methyl-6-nonylpiperidine 14a, cis-2-methyl-6-undecylpiperidine 14b, and trans-2-methyl-6-nonylpiperidine 15.<sup>17</sup>

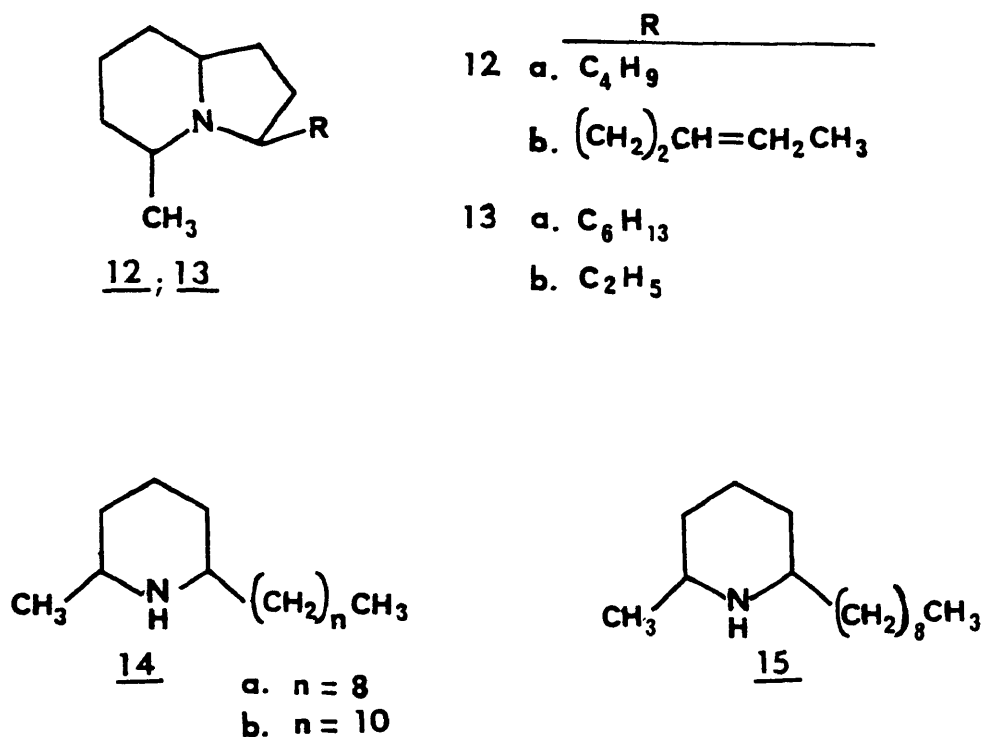


Figure 10. Indolizidines.

It should be noted that the queens of S. (Diplorhoptum)

species AA were found to produce only 13a, whereas workers of S. (Diplorhoptrum) conjurata produce 13b concomitant with 14a,b and 15.<sup>17</sup>

At this point, a brief review of the nomenclature of the bicyclic nitrogen heterocycles (indolizidines and pyrrolizidines) is worth mention. The compounds are numbered beginning with the carbon on the five membered ring alpha to the bridgehead carbon, assigning the number four to nitrogen for indolizidines; or, with the carbon alpha to the bridgehead carbon and proceeding in such a manner as to assign the lowest number to the methine with the substituent occurring first alphabetically for pyrrolizidines. The stereochemistry is designated relative to the three methine hydrogens using the lowest numbered methine hydrogen as the basis of comparison. The other methine hydrogens are labelled Z if they are on the same side of the ring system as the lowest position methine hydrogen, or E if they are on the opposite side.

## 2. Biosynthesis

There are two intriguing facts to consider from these findings: 1) Indolizidines occur in Solenopsis species with the same stereochemical configuration as that of the indolizidines found in M. pharaonis; and 2) Piperidines present that did not have the trans configuration characteristic of all those previously found in Solenopsis species. Since it was hypothesized that the final stereochemistry of the indolizidines was probably determined

during the closure of the last formed ring, the stereochemistry of their monocyclic concomitants is of special interest.<sup>17</sup> To date, there have been no reports of a cis-2,5-dialkylpyrrolidines occurring in either genus, even though the pyrrolidine ring of the indolizidines is cis-2,5-disubstituted. On the other hand, the occurrence of cis and trans-2,6-dialkylpiperidines together is well known with the trans isomer always predominating in the workers. In S. conjurata, however, stereochemical elucidation of 2-nonyl- and 2-undecyl-6-methylpiperidine has shown that they the piperidines had predominantly the cis configuration. Consideration of the stereochemistry of the alkaloids together suggests that in the biogenetic cyclization forming the (5Z,9Z) indolizidines, the six membered ring may be formed and saturated first, followed by the formation of the five membered ring.<sup>17</sup>

### 3. Functions

The indolizidines found in the venoms of Solenopsis and Monomorium species seem to have more of an active role as repellents against other species of ants rather than as natural trail pheromones.<sup>17</sup>

### 4. Chemistry

Although the structures of the 3-alkyl-5-methylindolizidines were suggested by their spectral data, both the structure and stereochemistry were again only established by syntheses of the possible stereoisomers. There are four possible isomers whose stereochemistry was

established by unambiguous synthesis from aromatic precursors, utilizing the principle of cis hydrogenation of an aromatic ring to control the geometry. One approach, and probably the best as it provided a more convenient supply of the natural alkaloid, is the well known indolizidine preparation from 2,6-lutidine.<sup>18,19</sup> The anion of 2,6-lutidine was treated with n-butyllithium and alken-1-oxide to give the alcohol derivative of lutidine. Cyclization of the five-membered ring of the derivative was accomplished by the bromination of the secondary alcohol either before or after reduction of the pyridine ring. Depending on the sequence of reactions and the reduction conditions, a mixture of pairs of isomers was obtained.

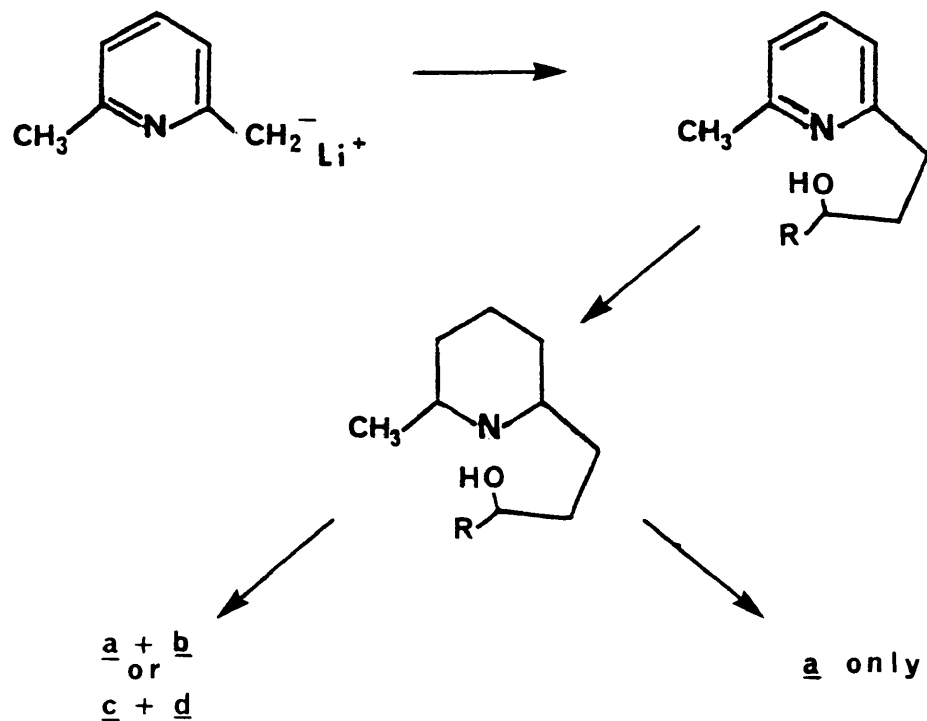


Figure 11. Indolizidine synthesis from 2,6-lutidine.

Alternatively, oxidation of the secondary alcohol gave the ketone which was readily converted to the iminium salt. Catalytic hydrogenation of this salt provided only the all cis (5Z,9Z) dialkylindolizidine isomer.<sup>1</sup> The stereochemical assignments were confirmed by an analysis of the <sup>13</sup>C NMR spectra of each isomer.<sup>20</sup>

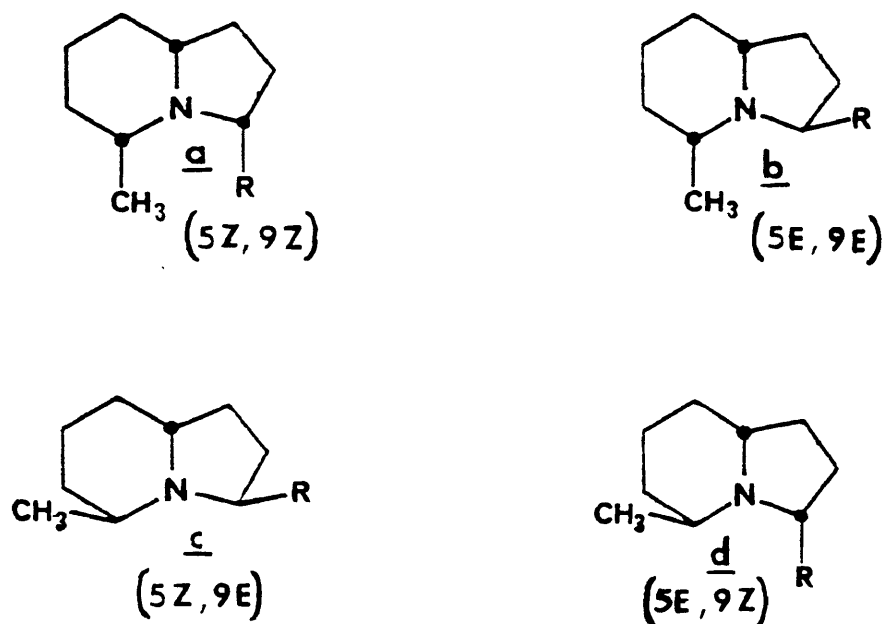


Figure 12. Indolizidine isomers.

The standard reductive amination of a triketone with sodium cyanoborohydride and ammonium acetate provided the four possible isomers in quantities of the same order of magnitude, indicative of the relatively small differences in strain and steric hinderance between the isomers.<sup>17</sup>

Direct comparison of the naturally occurring indolizidines with isomers a-d revealed them to be identical

with isomer a, the all cis isomer.<sup>1</sup>

## E. PYRROLIZIDINES

### 1. Distribution

Until recently, the occurrence of 3,5-disubstituted pyrrolizidines has remained uncommon among formicine venom gland alkaloids, with the exception of a 3-alkyl-5-methylpyrrolizidine found earlier in a thief ant.<sup>1,17,21</sup> A recent study of ants from New Zealand of the genus Chelaner has revealed two 3,5-dialkylpyrrolizidines with the (5E,8Z) stereochemistry to be the major venom components in nearly all the species examined. In many cases the pyrrolizidines were accompanied by small amounts of a trans-pyrrolidine.<sup>22</sup>

In one species, C. antarcticus (White), (5E,8Z)-3-(1-non-8-enyl)-5-(E, 1-prop-1-enyl)pyrrolizidine (1) was shown to be the major alkaloidal component<sup>22,23</sup> as was (5E,8Z)-3,5-di(hex-5-enyl)pyrrolizidine (16) for a second unidentified species, with both species containing trans-2-(5-hexen-1-yl)-5-(8-nonen-1-yl)pyrrolidine (17) as a minor component.<sup>22</sup>

Two 3-alkyl-5-methylpyrrolizidines have also been found. The alkaloids from the ants in collection 85/21 are quite distinctive from the other Chelaner species in having (5Z,8E)-3-methyl-5-(8-nonen-1-yl)pyrrolizidine (18) as the major component, concomitant with trans-2-butyl-5-(8-nonen-1-yl)pyrrolidine (19).<sup>22</sup> The pyrrolizidine 18 has the same stereochemistry as that of (5Z,8E)-3-heptyl-5-methylpyrrolizidine (20) found previously in Solenopsis

(Diplorhoptrum) xenovenenum. 1, 17, 21

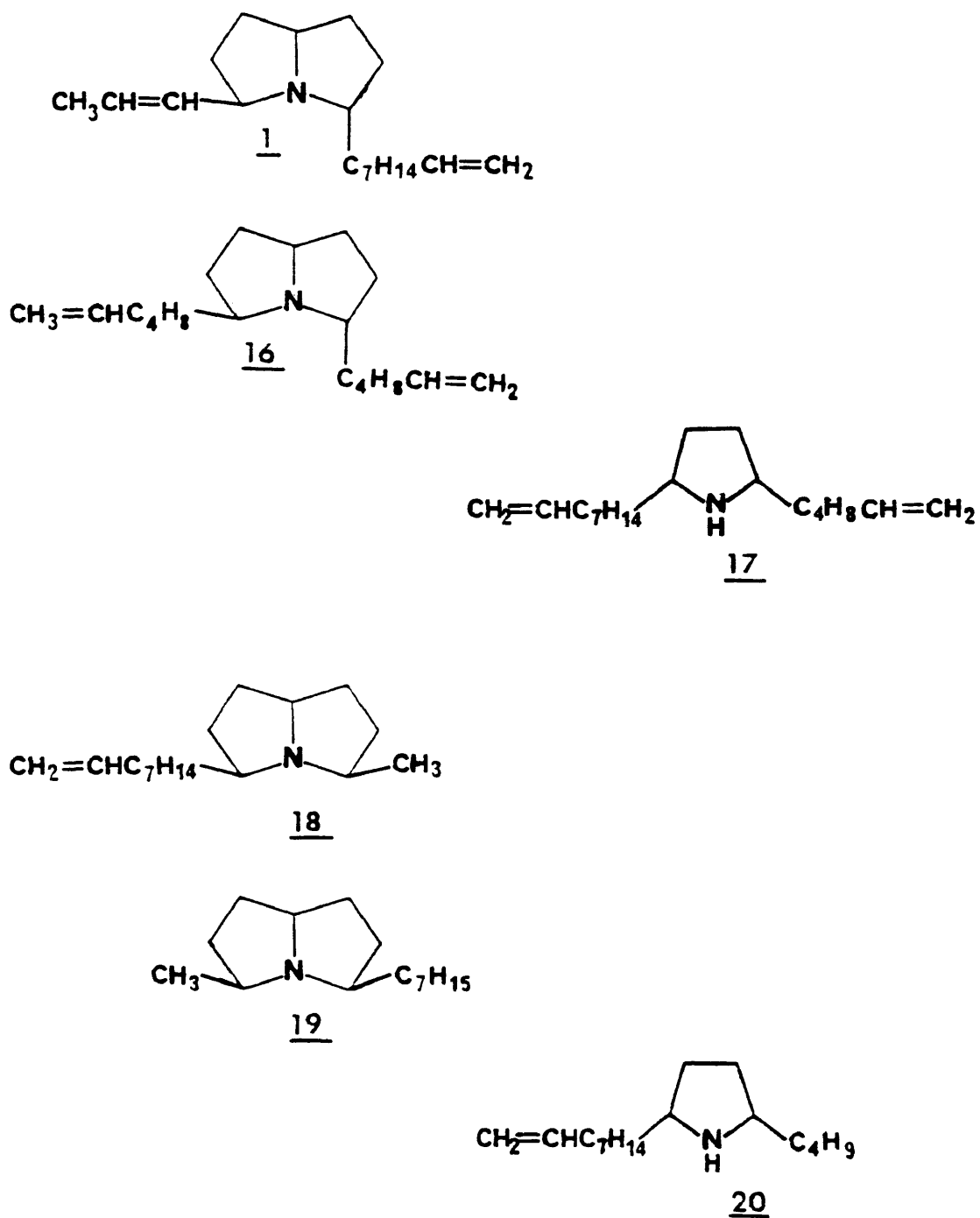


Figure 13. Pyrrolizidines with concomitant trans-pyrrolizidines.



## 2. Biosynthesis

The pyrrolizidines 1 and 16 have been viewed as bicyclic analogues of 17, in which the second ring would be formed from the six-carbon side chain to produce 1, or from the nine-carbon side chain to produce 16. Alternatively, the trans substitution patterns of all the five membered rings in 18 and 19, indicated that 18 is the direct bicyclic homologue of 20.

In every case, the association of the pyrrolidines with the pyrrolizidines suggests a common biological precursor for pyrrolidines and pyrrolizidines with the same carbon skeleton.<sup>22</sup>

## 3. Functions

The 3,5-dialkylpyrrolizidine secretions seemed to act as defensive allomones at the onset,<sup>1</sup> however, their entire functional domain has yet to be established.

## 4. Chemistry

### 4.a. (5E,8Z)-3,5-Disubstituted pyrrolizidines

The mass spectrum of 1 displayed a molecular ion at  $m/z=275$  and a single fragment at  $m/z=150(100)$  due to the loss of  $C_9H_{17}$  from the carbon adjacent to the nitrogen.<sup>23</sup> The mass spectrum of 16 displayed a molecular ion at  $m/z=275$  and a single fragment at  $m/z=192(100)$  due to the loss of  $C_6H_{11}$  from the carbon adjacent to the nitrogen.<sup>22</sup> Hydrogenation experiments indicated the presence of two double bonds in each case.<sup>22,23</sup> To demonstrate the presence of the pyrrolizidine ring system beyond question and determine the

stereochemistry of 1 and 16, nonstereoselective syntheses were carried out. The appropriate triketone was prepared by the thiazolium salt catalyzed condensation of an aldehyde with a vinyl ketone, and subjected to reductive amination with sodium cyanoborohydride and ammonium acetate. In the case of 1, the conjugated double bond was protected by epoxidation which could be removed afterwards to afford the trans double bond. In this way, all four possible isomers of 1 and the three possible isomers of 16 were obtained 1,17,21-23 in the ratio 3:7:10:1,<sup>23</sup> and 1:9:3,<sup>22</sup> respectively.

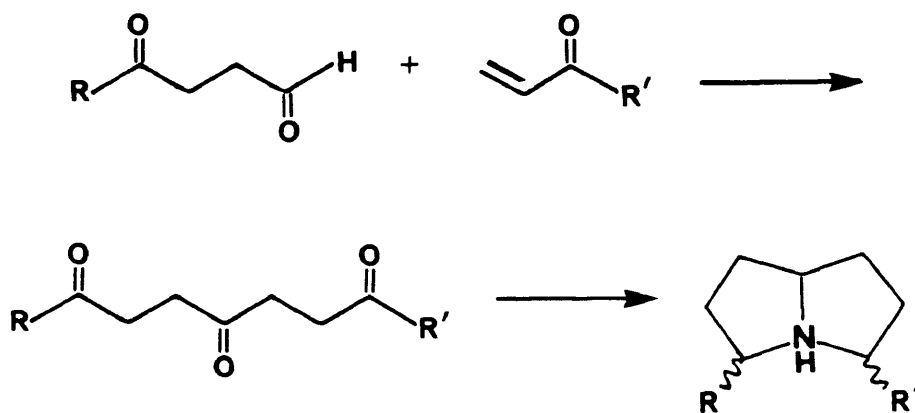


Figure 14. Pyrrolizidine synthesis from triketones.

The stereochemistry of the isomers could be assigned from <sup>1</sup>H NMR and IR data. Isomer a was determined to be the highly strained, trans-fused (5Z,8Z) pyrrolizidine ring system which minimizes steric hinderance between the alkyl groups at C-3 and C-5 relative to the alternative cis isomer. The remaining three isomers b-d were free to assume

the less strained cis-fused pyrrolizidine ring. Isomer **b** was the least strained stereoisomer having both alkyl groups oriented exo, (5Z,8E), to the ring system, which, considering each ring as a separate pyrrolidine, is all trans substituted. Isomers **c** and **d**, had one of the alkyl groups oriented endo to the ring system.<sup>21,23</sup>

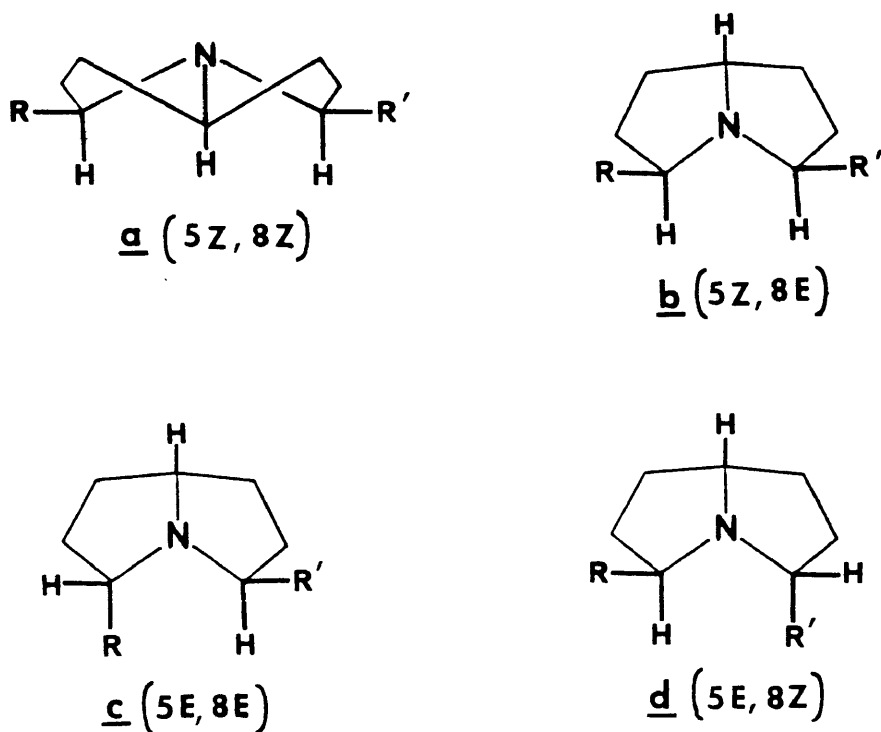


Figure 15. Pyrrolizidine isomers.

Direct comparison of the isomers to the natural products by GLC retention times, IR, and  $^1\text{H}$  NMR revealed the pyrrolizidines to correspond to stereoisomer **d** in which the largest alkyl substituent is oriented endo, (5E,8Z) to the ring system.<sup>22,23</sup> The product ratios from the reductive amination seemed to reflect the relative degree of strain

and steric hinderance of the isomers.<sup>17,21-23</sup>

#### 4.b. (5Z,8E)-3-Alkyl-5-methylpyrrolizidine

The mass spectrum of the major alkaloid 18 in the extracts from the collection 85/21 had a molecular ion at  $m/z=249$  and fragments at  $m/z=234$  and 124(100) indicating the loss of  $CH_3$  and  $C_9H_{17}$ , respectively.<sup>22</sup> Similarly, the mass spectrum of 20 had a molecular ion at  $m/z=223$  and fragments at  $m/z=208$  and 124(100) indicating the loss of  $CH_3$  and  $C_7H_{15}$ , respectively.<sup>21</sup>

The syntheses were much like that previously described, providing all four possible pyrrolizidine isomers. The ratio of the isomers was 1:40:7:3 for 18,<sup>22</sup> and 2:14:2.2:1 for 20.<sup>21</sup>

The stereochemical assignments of the isomers were identical to those previously described.

Direct comparison of the isomers to the natural products by GLC retention times, IR, and  $^1H$  NMR revealed the pyrrolizidines to correspond to stereoisomer b, the major synthetic isomer.<sup>1,17,21,22</sup>

Recently, two novel syntheses have been reported to provide the desired (5Z,8E) stereoisomers. The first synthesis employs a 3-propinoaldehyde and enantioselective epoxidation at the key step,<sup>24</sup> whereas the second employs the cyclization of an allenic oxime to generate a 5-substituted nitron as the key step.<sup>25</sup>

## CHAPTER 2

### CONSIDERATIONS OF PYRROLIZIDINES

#### A. GENERALIZATIONS

From the latest study of the Chelaner species, it is apparent that the 3,5-dialkylpyrrolizidines that characterize the venoms are produced stereoselectively by the ants.<sup>22</sup> Similar stereoselection has been observed for the formation of 3-alkyl-5-methylindolizidines in Monomorium and Solenopsis species,<sup>17</sup> and only (5Z,9Z) indolizidine isomers have been detected in the venoms of Myrmecine ants. On the other hand, Chelaner species produce either the (5Z,8E)-pyrrolizidine when one of the alkyl groups was methyl,<sup>17,21,22</sup> or the (5E,8Z)-pyrrolizidine stereoisomer with the largest alkyl group endo to the ring system,<sup>22,23</sup> depending on the particular collection examined.

Based on the product ratios from triketone reductive amination, there is relatively little difference in strain and hinderance between the possible 3-alkyl-5-methylindolizidine isomers, whereas there is a much greater difference between the corresponding 3,5-dialkylpyrrolizidine isomers.<sup>17,22</sup> The indolizidines are not rigid compounds due to flexibility of the six-membered ring

ring which allows the nitrogen in the bicyclic system to invert.<sup>20</sup> On the other hand, the five-membered rings of pyrrolizidines are much more rigid. In the former case, all of the isomers are formed in nearly equal amounts, and in the latter one, the (5Z,8E) pyrrolizidine isomer predominates over the others by at least an order of magnitude.<sup>17,21,23</sup> Remarkably, the most common 3,5-dialkylpyrrolizidines found in the Chelaner species were the strained and hindered (5E,8Z) isomers 1 and 16.<sup>22,23</sup> However, one should not overlook the fact that the single 3-methyl-5-alkylpyrrolizidine, 18, found in Chelaner collection 85/21 has the same, unstrained (5E,8Z) configuration as an analogous 3-methyl-5-alkylpyrrolizidine 20 isolated from a thief ant.<sup>21</sup>

Since triketone reductive amination provides so little of the (5E,8Z) 3,5-disubstituted pyrrolizidine, a stereoselective synthesis of these compounds is desirable. The diolefinic pyrrolizidine 1 will be the initial target of this synthesis since it has the stereochemistry of interest and seems to be more widely distributed than 16.<sup>22</sup>

#### B. RETROSYNTHESIS OF (5E,8Z) 3,5-DISUBSTITUTED PYRROLIZIDINES

Retrosynthetically, one of the major problems that must be overcome is the selective introduction of the 1-propenyl group at C-5, using an appropriate three carbon nucleophile, exo to a pyrrolizidine nucleus where one of the rings is already cis disubstituted. This may be achieved by the use of bromomagnesium<sup>26</sup> or lithium propynolide<sup>27,28</sup> followed by

the reduction of the triple bond to a trans double bond using lithium aluminum hydride.<sup>29-34</sup> Although this sequence would introduce the propenyl group as an extra step, it does take advantage of the existing stereochemistry. The exo propenyl group would be difficult to obtain based on the reductive amination method where the carbon-nitrogen single bond precursor is a carbonyl group (or its precursor) with the three carbon group already attached, as it requires a subsequent reduction step, which would tend to make the C-5 hydrogen exo.

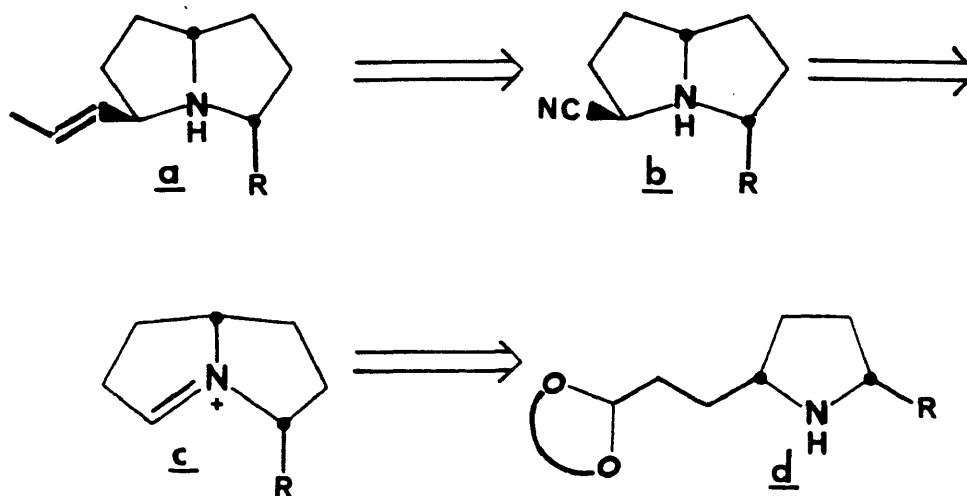


Figure 16. Retrosynthetic plan for (5E,8Z) pyrrolizidines.

However, it can be envisioned that the appropriate pyrrolizidine conformation could be prepared by hydrolysis of the acetal of a cis-2,5-disubstituted pyrrolidine **d** to form the iminium salt **c**,<sup>35-39</sup> which could be converted to the cyanoamine **b** with potassium cyanide.<sup>40-42</sup> This reaction is

reported to be stereospecific; and such cyanoamines serve as latent forms of the corresponding iminium salts. Subsequent treatment with bromomagnesium or lithium propynolide would displace the cyano group with retention of configuration.<sup>40</sup>

### C. RETROSYNTHESIS OF CIS-2,5-DISUBSTITUTED PYRROLIDINES

As indicated above, the cis-2,5-disubstituted pyrrolidine is the key to providing the (5E,8Z) 3,5-disubstituted pyrrolizidine ring system, which is the second major problem. Classically, cis-2,5-disubstituted pyrrolidines are obtained by the hydrogenation of pyrroles,<sup>12</sup> which would not permit the inclusion of side chain double bonds. The more recent syntheses focus on providing the naturally occurring trans-2,5-disubstituted pyrrolidine.<sup>6,14</sup>

We herein report the first stereoselective synthesis of cis-2,5-disubstituted pyrrolidines capable of the inclusion of side chain double bonds. In planning the synthetic route, we thought that the desired stereochemistry could be attained by reduction of the imine bond with a bulky, hindered reagent such as diisobutylaluminum hydride. There is precedent for this selectivity, since 2,6-dialkylpiperidines, less rigid six-membered ring systems, have been shown to give only the cis-2,6-dialkylpiperidines under these conditions.<sup>43,44</sup> Furthermore, it has been shown recently that reduction of a mixture of 2-heptyl-5-butyl-1- and 2-heptyl-5-butyl-5-pyrrolines by diisobutylaluminum hydride gives cis-pyrrolidines predominantly.<sup>45</sup> The appropriate pyrroline b could be prepared by addition of a Grig-



nard reagent<sup>46-48</sup> derived from an acetal<sup>49-54</sup> to a lactim thioether **c**, which would have been previously S-alkylated using an alkyl halide.<sup>54-60</sup> Lactim thioethers are known to react with nucleophilic species such as Grignard reagents to form imines by displacement of the thioalkyl group. The lactim ether **d** would come from thiation of a lactam **e**<sup>54,56,61,62</sup> which would have been prepared by reductive amination of an appropriate ketoester **f** using sodium cyanoborohydride and ammonium acetate.<sup>10,63,64</sup>

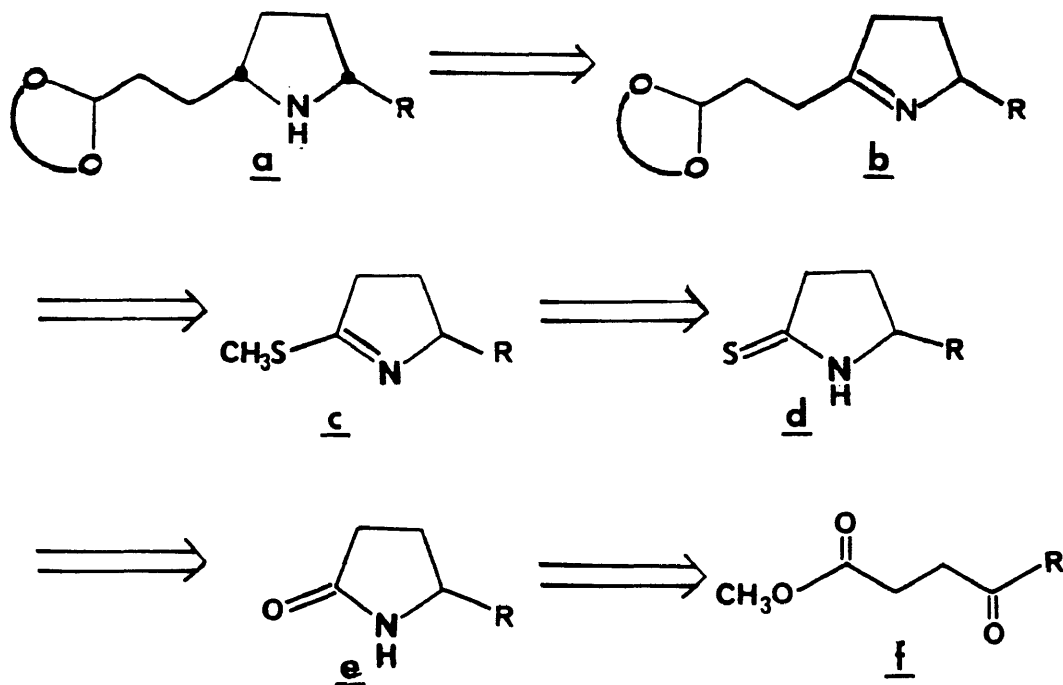


Figure 17. Retrosynthetic plan for cis-pyrrolidine via lactim thioether.

Another possible pathway we envisioned focused on the use of nitron methodology. The N-oxide functional group can readily provide the 1-pyrroline skeleton necessary along

with the versatility of the already attached alkyl groups.

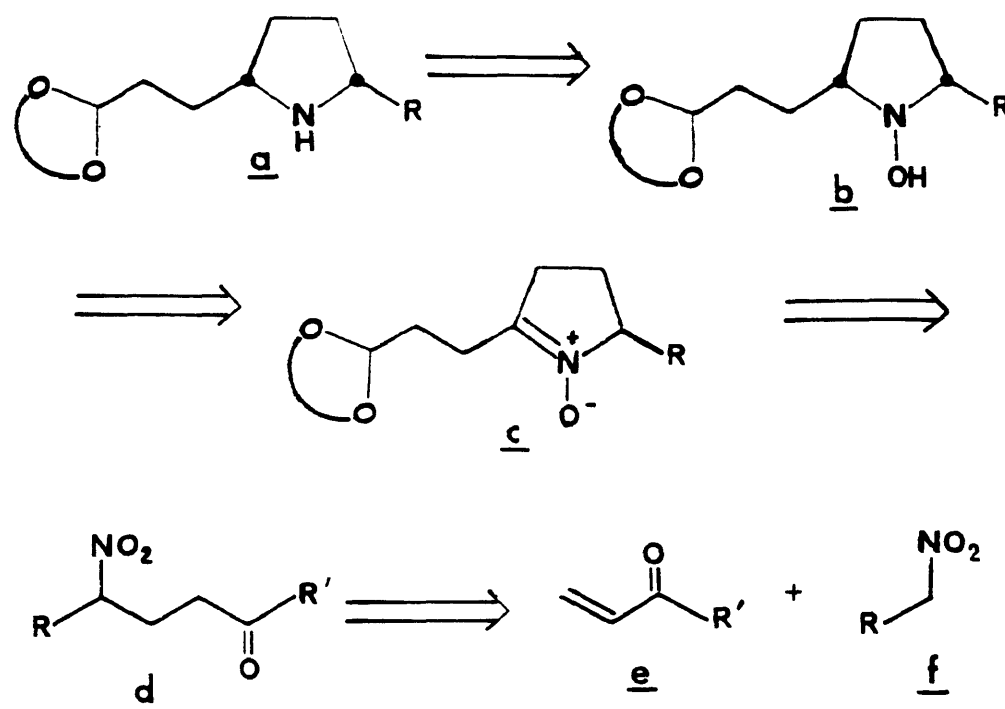


Figure 18. Retrosynthetic plan for cis-pyrrolidine via nitrones.

Reduction of the appropriate nitronium ion **c** to the corresponding N-hydroxide **b** using a bulky, hindered reagent such as diisobutylaluminum hydride promises some sort of selectivity.<sup>65-67</sup> The nitronium ion **c** itself may be easily prepared from a ring closure reduction of a  $\gamma$ -nitro ketone with zinc and ammonium chloride.<sup>6,25,65-70</sup> The required  $\gamma$ -nitro ketone **d** could easily be obtained by the Michael addition of nitroalkanes **f** to vinyl ketones **e**.<sup>35,40,71-81</sup> The synthesis is convergent at this point, as well as being able to accommodate many R and R' groups.

#### D. CONCLUSION

The frequent occurrence of (5E,8Z)-3,5-disubstituted pyrrolizidines in Chelaner species necessitates syntheses. Once the methodology is established, the preparation of any (5E,8Z) pyrrolizidine will simply be a matter of changing the side chain precursors. The synthetic plan described herein takes into account the two major problems of the synthesis, utilizing the cis-2,5-disubstituted pyrrolidine. Given the synthetic material in-hand, their potential entomological interests may be explored to develop a better understanding of the behavioral and taxonomic relationships in the Myrmecine ants.

## CHAPTER 3

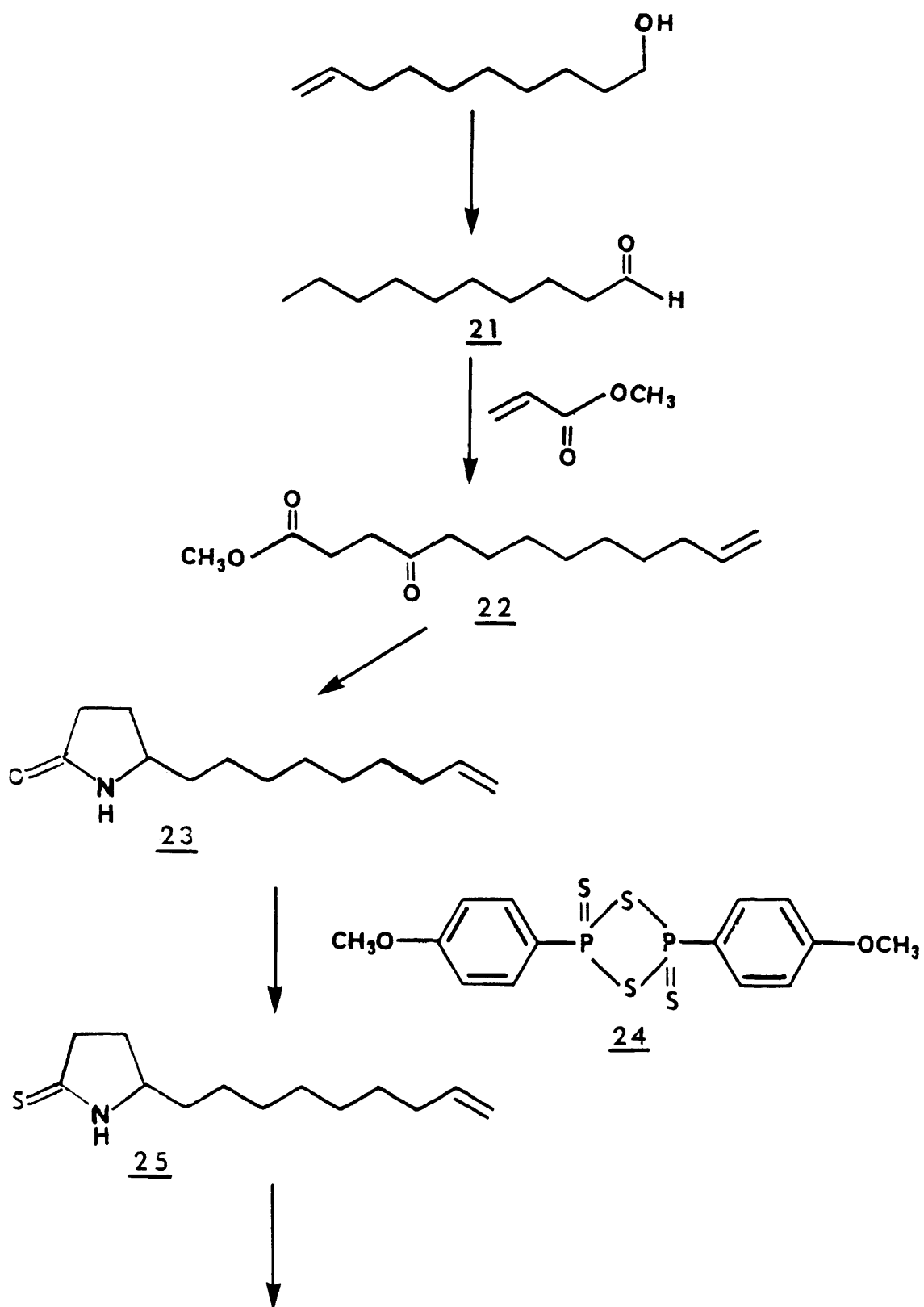
### RESULTS AND DISCUSSION

#### A. SYNTHESIS VIA SCHEME I

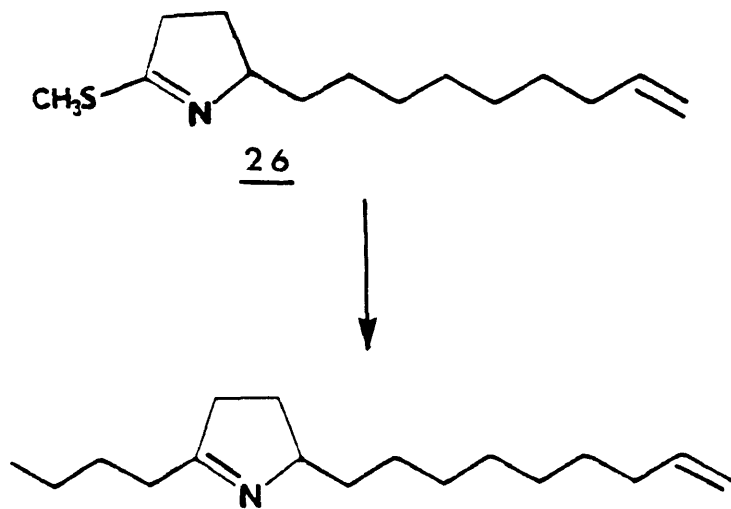
Since the synthesis of cis-2,5-disubstituted pyrrolidines is possible by the stereoselective reduction of 1-pyrrolines, utilization of the thiolactim ether route was first attempted as shown in Scheme I. The incorporation of the terminal double bond, so common in ant venoms, in this methodology was achieved by using the commercially available 9-decen-1-ol (Aldrich). The alcohol was oxidized to its corresponding aldehyde 21 using pyridinium chlorochromate, a readily available, stable reagent that is known to oxidize a wide variety of alcohols to carbonyl compounds with high efficiency.<sup>10,82,83</sup> Usually oxidation of alcohols does not stop at the aldehyde but instead continues to give the carboxylic acids very easily, even in air. The advantage of pyridinium chlorochromate, however, is that the reaction stops at the aldehyde.

The 9-decen-1-al (21) was immediately used in the formation of the ketoester 22 by heating to reflux with methyl acrylate and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (the thiazolium salt catalyst) in

Scheme I



## Scheme I (continued)



1,2-dimethoxyethane and triethylamine.<sup>64,84,85</sup>

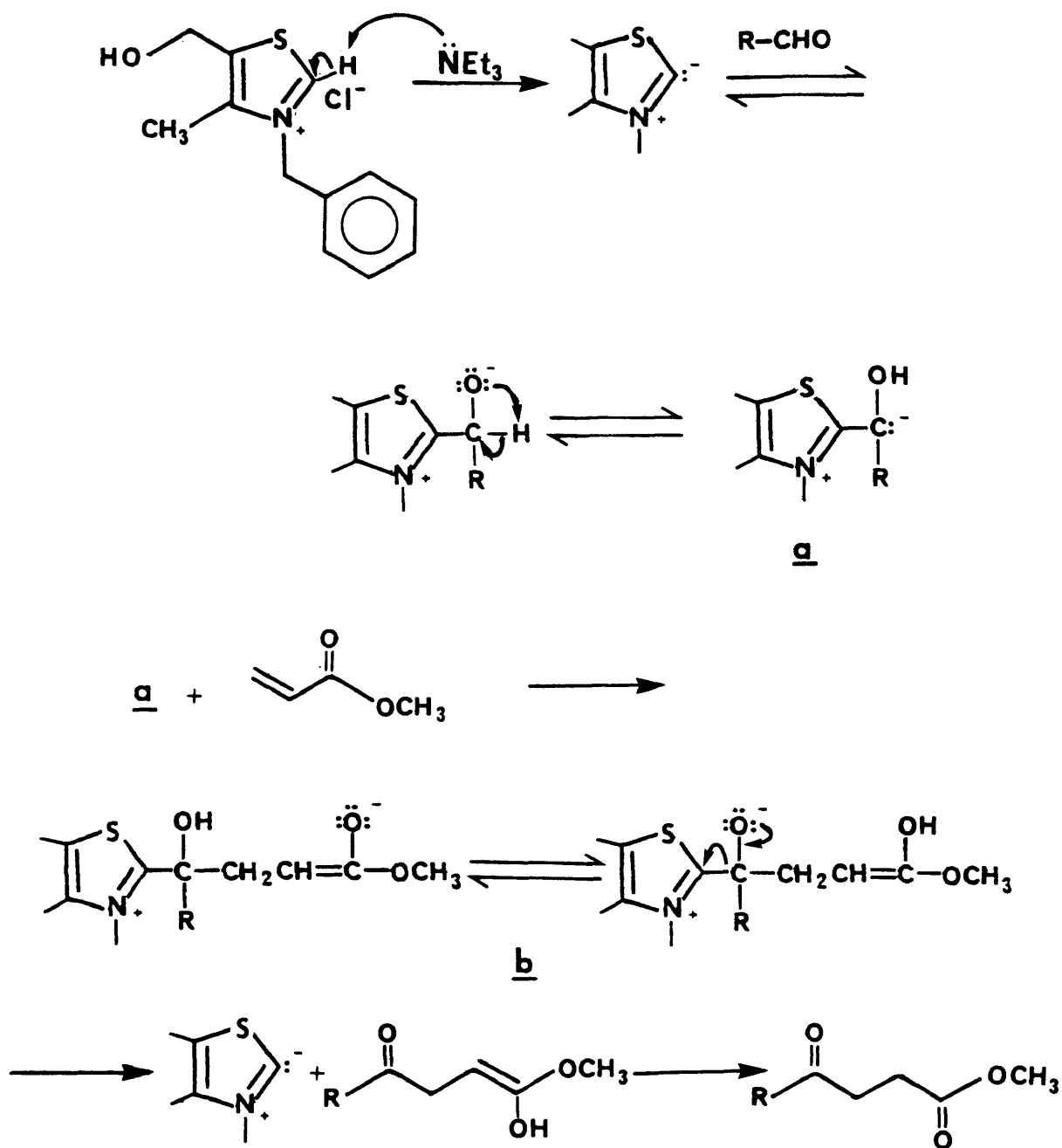


Figure 19. Thiazolium salt catalyzed condensation.

In this reaction, triethylamine acts as a base towards the quaternary thiazolium salt by abstracting a proton to form

an ylide. The carbanion of the ylide then attacks the carbonyl carbon of the aldehyde which has a more "exposed" positive center than the enone. The alkoxide suffers a hydrogen-shift to form the activated nucleophile followed by subsequent conjugate addition of intermediate a to the  $\alpha,\beta$ -unsaturated ketone results in intermediate b, which collapses to give the 4-oxocarboxylic ester 22 and the ylide form of the thiazolium catalyst. It is essential that the reaction be carried out in aprotic solvents. A possible side reaction product, which was encountered once, is due to the acyloin condensation of intermediate a with the aldehyde.<sup>83</sup> The mass spectrum of 22 showed a molecular ion peak at  $m/z=240$  and fragments at  $m/z=209$ , 130, and 115, corresponding to  $M-CH_3O$ , the McLafferty rearrangement, and  $\alpha$ -cleavage of  $C_9H_{17}$  next to the carbonyl, respectively.

The pyrrolidone 23 was afforded by treating the ketoester 22 with ammonium acetate to form an imine, and then reduced in situ to the amine with sodium cyanoborohydride, which subsequently cyclizes to the lactam under basic conditions.<sup>10,63,64</sup> The cyanoborohydride ion is too weak to reduce ketones at normal pH due to the electron withdrawing effect of the nitrile group. Furthermore, electron withdrawal from boron weakens the nucleophilicity of the hydrogens thereby also making them less likely to attack the carbonyl carbon atom of ketones. The carbon atom of an iminium ion has a stronger positive center than ketones due to the greater electronegativity of protonated nitrogen over



oxygen. Thus, cyanoborohydride is the perfect reagent for this reaction because it reduces the imines to amines while leaving ketones untouched. Once formed, the amine nitrogen acts as a nucleophile and attacks the adjacent ketone to form the five-membered ring.<sup>63</sup>

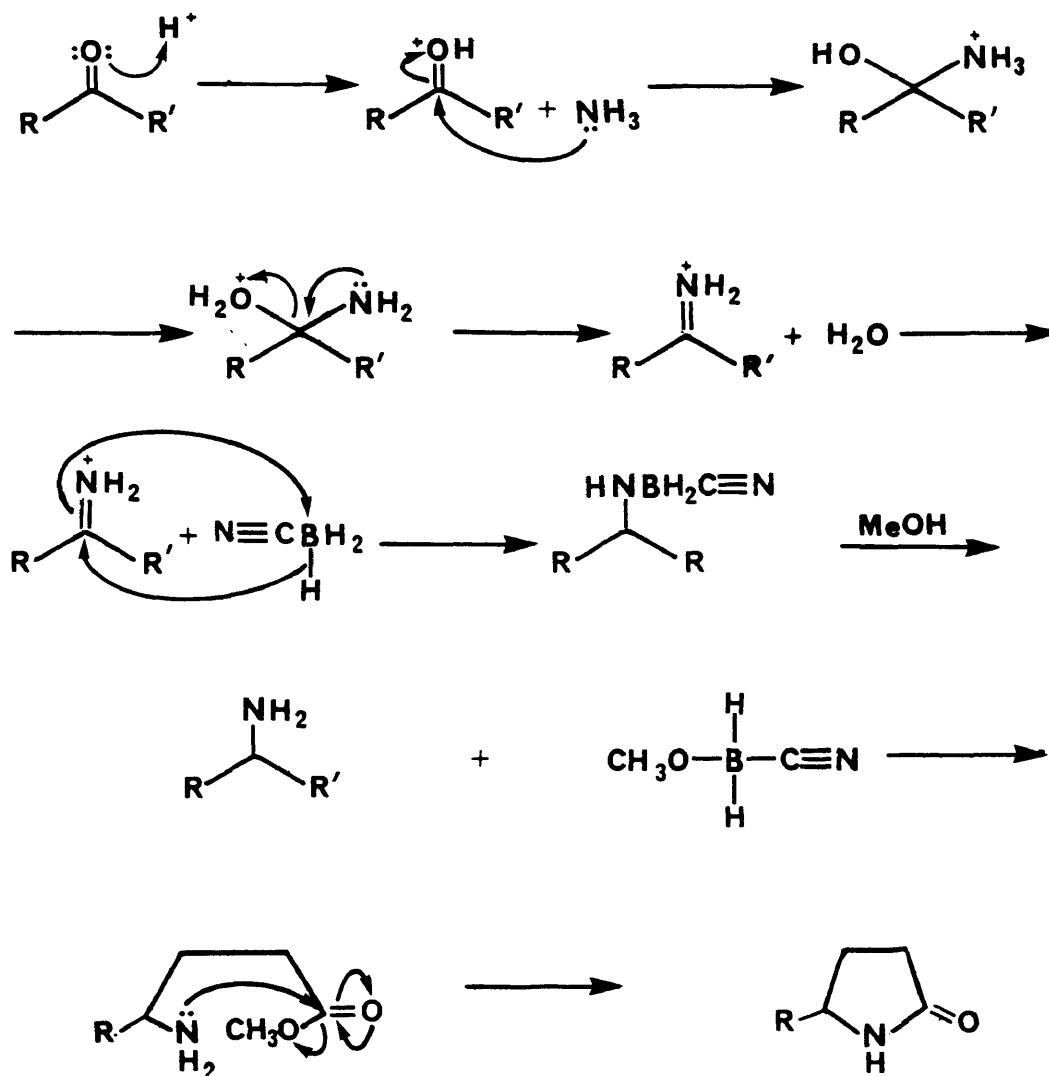


Figure 20. Reductive amination using sodium cyanoborohydride.

The mass spectrum of 23 showed a molecular ion peak at

$m/z=209$  and a base peak at  $m/z=84$  due to the  $\alpha$ -cleavage of the side chain. It was critical that the ammonium acetate used be anhydrous as traces of water caused the formation of the corresponding lactone.

The thiation of the lactam 23 to produce the thiopyrrolidone 25 was accomplished using two different reagents, phosphorus pentasulfide,<sup>54,56,62</sup> and, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiodiphosphetane 2,4-disulfide (24).<sup>61</sup> It was found that a cleaner product mixture and equally good yields were obtained when a 1:1 equivalence of lactam 23:24 in toluene were used. No characterization was carried out as it proved to be difficult to purify 25.

Two different methods were used to attempt the S-alkylation of the lactim ether 25, addition of iodomethane alone,<sup>54,56-60</sup> and, addition of iodomethane with an equivalent amount of sodium hydride.<sup>55</sup> The use of sodium hydride seemed to facilitate the reaction by removal of the secondary amine hydrogen thereby creating a negatively charged thiolactim anion. Nucleophilic attack by the sulfur on the iodomethane could then more readily take place.<sup>55</sup> The mass spectrum of 2-thiomethyl-1-pyrroline 26 showed a molecular ion peak at  $m/z=240$  and a base peak at  $m/z=115$  due to the  $\alpha$ -cleavage of the side chain. The presence of the carbon-nitrogen double bond of the pyrroline was indicated by a band at  $1580\text{ cm}^{-1}$  in the IR spectrum.

The characteristic IR and  $^1\text{H}$  NMR spectra indicated that the terminal double bond had not been altered during this

sequence of reactions.<sup>86</sup> The  $^1\text{H}$  NMR spectra showed two patterns in the olefinic region. The pair of doublets at  $\delta=4.9-5.0$  ppm results from the terminal methylene protons. One doublet had a coupling constant of 10 Hz, characteristic of a single proton being split by a proton cis to it across a double bond. The other doublet had a coupling constant of 18 Hz, characteristic of a single proton being split by a proton trans to it across a double bond. The methine proton on the terminal double bond at  $\delta=5.9$  ppm was a doublet of doublets of triplets. Hence, a set of four triplets having coupling constants of 6 Hz were observed, each triplet due to the splitting of the methine hydrogen by two methylene hydrogens a single bond away. These could be viewed as a set of two doublets having coupling constants of 10 Hz due to splitting of the methine proton by the cis proton across the double bond. Finally, this pair of doublets could be viewed as one doublet having a coupling constant of 18 Hz due to splitting of the methine proton by the trans proton across the double bond. Furthermore, the bands at 3080(w), 1640(w), and 910  $\text{cm}^{-1}$  in the IR spectra were also characteristic of a terminal double bond.

All attempts to add a Grignard reagent (butyl magnesium bromide)<sup>46-48</sup> to displace the thiomethyl group to form the desired 2,5-disubstituted-1-pyrroline were unsuccessful. The subsequent use of N,N,N',N'-tetramethylethylenediamine and later heating (which could not be applied when using a Grignard reagent derived from an acetal<sup>49-53</sup>) of the reac-

tion mixture to promote the addition were also unsuccessful.

At this point, the synthetic plan of Scheme I was abandoned.

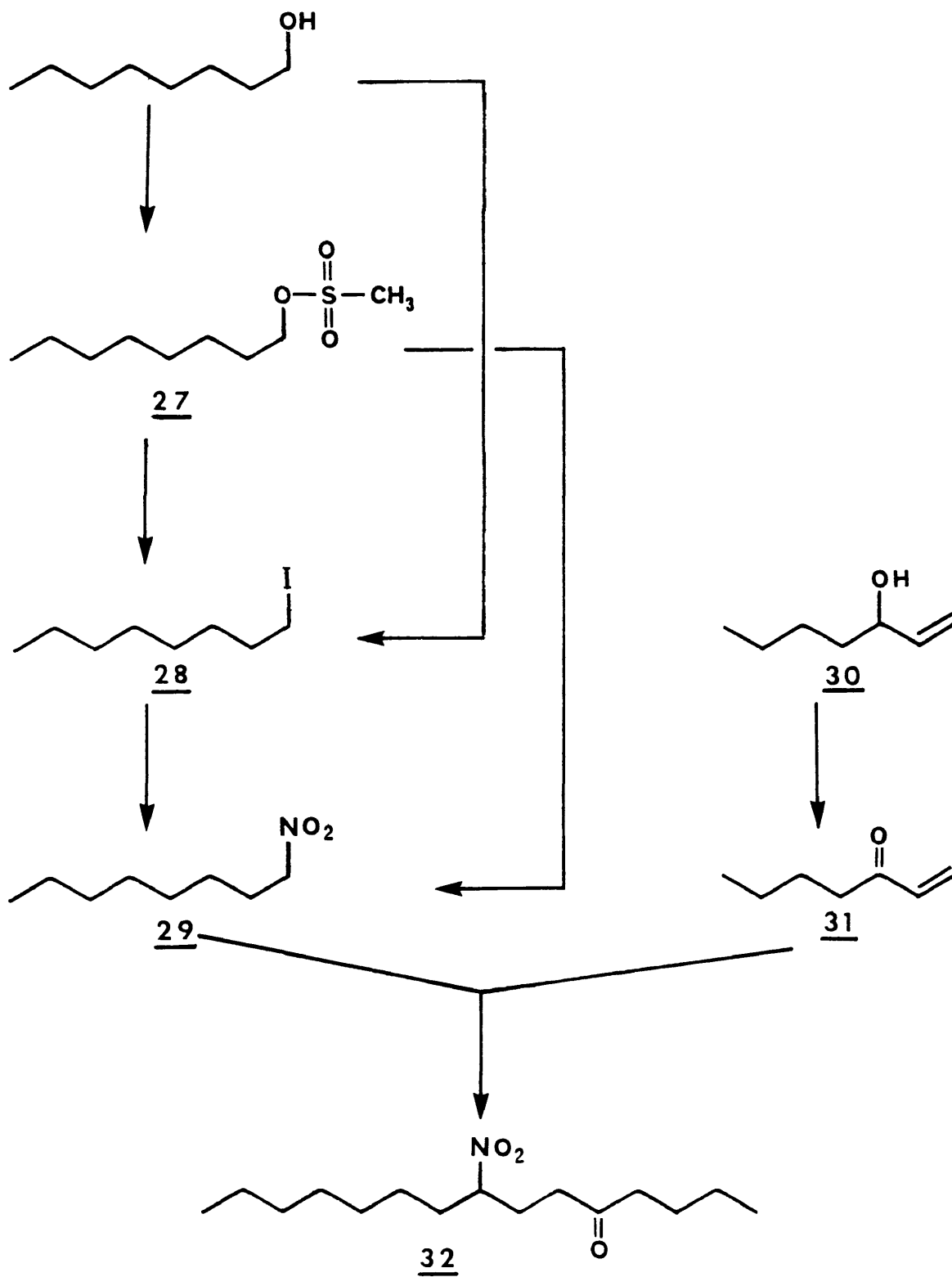
## B. SYNTHESIS VIA SCHEME II

Since the thiolactim ether route in Scheme I was not feasible, we focused on the use of nitron methodology to provide the necessary 2,5-disubstituted pyrroline skeleton. We first determined the feasibility of the synthetic plan with a model system, the goal being the preparation of cis-2-butyl-5-heptylpyrrolidine (35) shown in Scheme II.

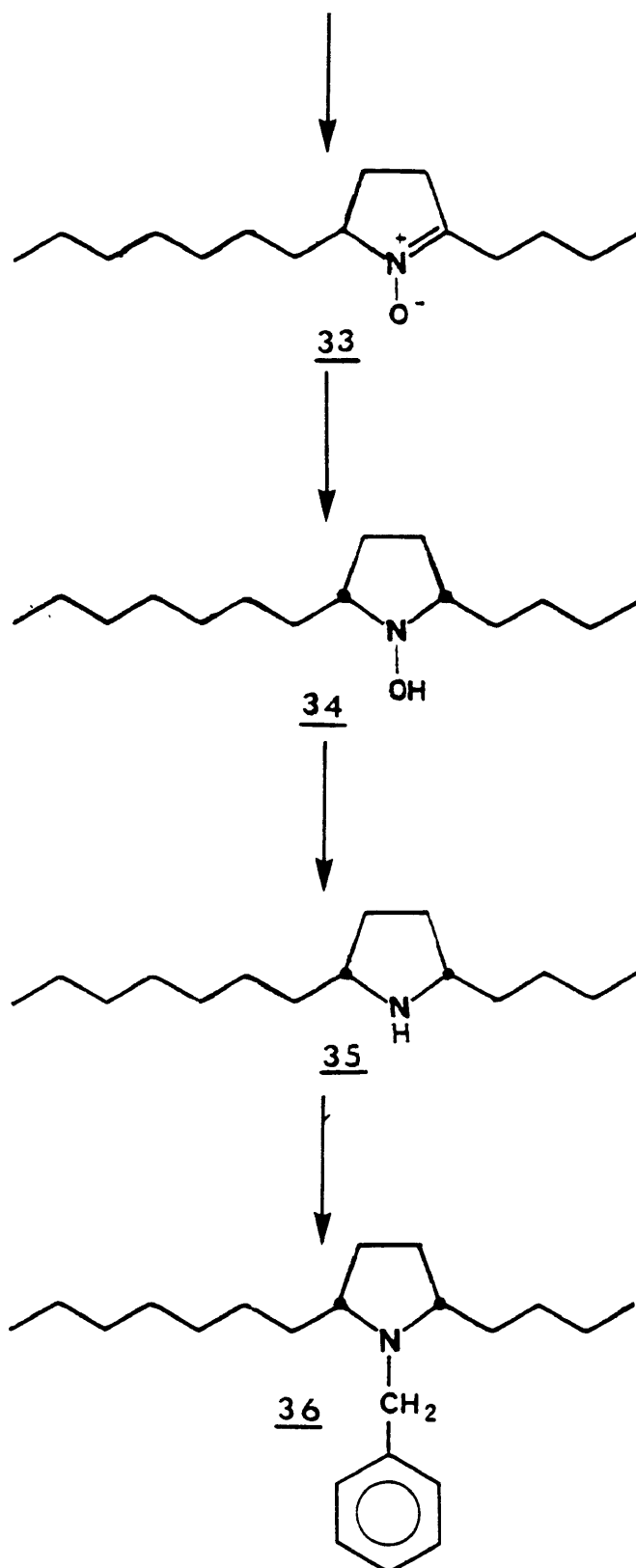
The synthesis began with the conversion of commercially available 1-octanol (Eastman Organic Chemicals) to 1-octylmethane sulfonate (27) using methanesulfonyl chloride in pyridine. The IR spectrum of 27 showed a characteristic sulfur-oxygen double bond band at  $1355\text{ cm}^{-1}$  and a carbon-oxygen single bond band at  $1175\text{ cm}^{-1}$ .

Next, the formation of 1-iodooctane (28) could be achieved by two methods. The first proceeded via an  $\text{SN}_2$  reaction using sodium iodide in acetone. Alternatively, 1-octanol could provide 28 directly by treatment with sodium iodide and chlorotrimethylsilane in acetonitrile.<sup>87-90</sup> The advantage of the latter method is that the sulfonate step could be completely avoided. The high bond energy of the silicon-oxygen bond (90-110 kcal/mol) drives the formation of trimethylsilyl octanol, which can be transformed to another product in a subsequent  $\text{SN}_2$  step.<sup>87</sup> The absence of functional group bands in the IR spectrum of 28 indicated

## Scheme II



## Scheme II (continued)



that the sulfonate group had been displaced presumably by iodine.

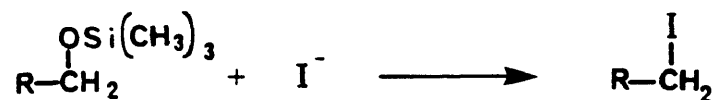


Figure 21. Iodination using chlorotrimethylsilane.

Various methods were employed to provide 1-nitrooctane (29) in an array of yields. The first, and also the most practical, utilized an SN2 reaction between 1-iodooctane (28) and sodium nitrite in DMF. A quantity of urea was added to enhance the solubility of sodium nitrite.<sup>91</sup> This method provided a 66% overall yield of 29. The IR spectrum of 29 showed nitro group bands at 1550 and 1380  $\text{cm}^{-1}$ . An attempt at using sodium nitrite without urea<sup>92</sup> gave an identical yield to that obtained previously. The third method employed silver nitrite, prepared as described by Kornblum et. al.,<sup>93</sup> which gave a quantitative yield of 29. The impracticality of synthesis by this method, however, included the high cost of the reagent, the long time required, the need to control temperature, as well as the strict exclusion of light. The final method, which attempted to avoid the preparation of 28, involved treating the sulfonate 27 directly with sodium

nitrite.<sup>91</sup> This method was dismissed because of the low (40%) yield of 29. In all cases, the other component in the product mixture was reusable 1-octanol which was separated by distillation.

The next step in the synthesis was the oxidation of 1-hepten-3-ol (30).<sup>94</sup> Treatment of the enol with pyridinium chlorochromate<sup>10,82,83</sup> or manganese dioxide<sup>95</sup> in the usual manner provided 1-hepten-3-one (31) in adequate yields, but, the more successful approach was the Swern oxidation. Various sequences, as described by Swern et. al.,<sup>96-102</sup> were attempted to oxidize the alcohol effectively; however, the one which proceeded to give a quantitative yield was the sequence described by Martin et. al.<sup>103</sup> The reaction commences with the "activation" of dimethylsulfoxide (DMSO) by a suitable electrophilic reagent ( $E^+ A^-$ ) such as oxalyl chloride in dichloromethane to yield an unstable intermediate a that instantaneously loses  $CO_2$  and CO to form the intermediate b.<sup>100</sup> Oxalyl chloride reacts explosively with DMSO at room temperature; therefore, successful activation, survival, and use of the requisite intermediate in synthetic applications requires low temperatures (-10 to  $-63^\circ C$ ).<sup>102</sup> The activated DMSO is rapidly attacked by the alcohol on the electropositive sulfur atom of intermediate b with the departure of the leaving group to form the dimethylalkoxysulfonium salt c. Reaction of the salt with a base, typically triethylamine, causes the deprotonation of a methyl group of the salt to form the methylcarbanion or



ylide **d**, which then collapses to form dimethylsulfide and the carbonyl product by an intramolecular hydrogen transfer in high to quantitative yields.<sup>99</sup>

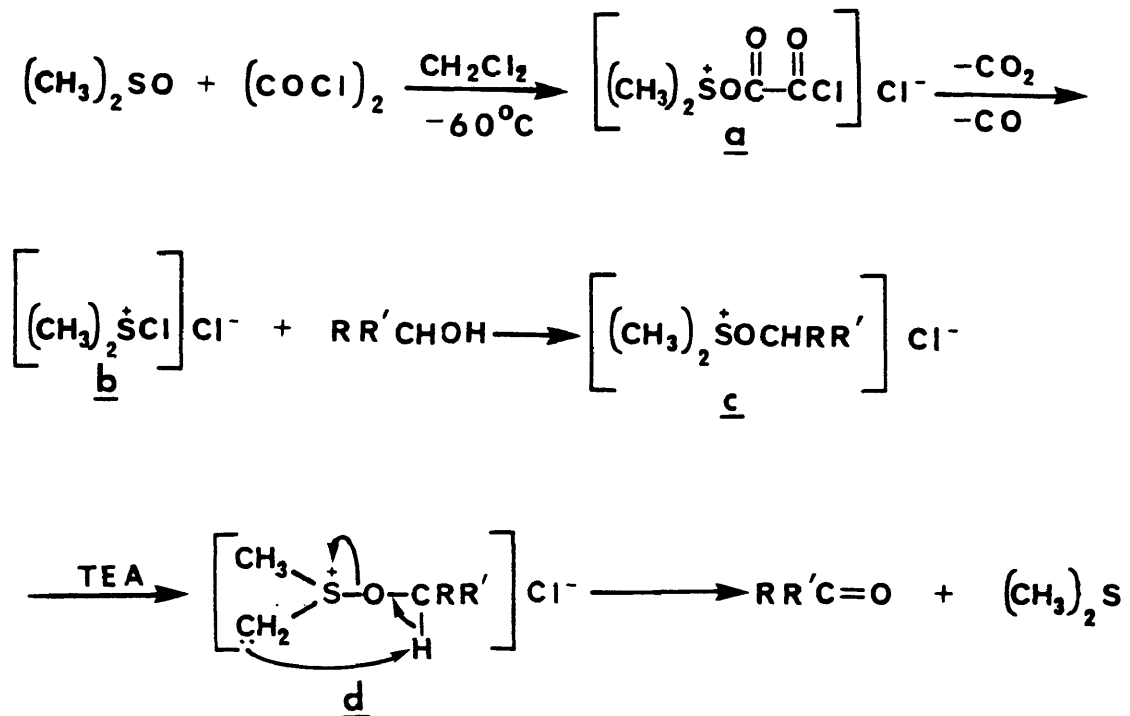


Figure 22. Swern oxidation.

The absence of an alcohol band at  $3350 \text{ cm}^{-1}$  in conjunction with the presence of an unsaturated carbonyl band at  $1675 \text{ cm}^{-1}$  in the IR spectrum of **31** indicated the successful oxidation of the alcohol.

The point of convergence for the synthesis occurred in the process of preparing the required  $\gamma$ -nitro carbonyl compound **32**. The reaction can be most readily effected by a Michael-type addition of the 1-nitrooctane anion to the  $\alpha, \beta$ -unsaturated carbonyl compound **31**. When

tributylphosphine,<sup>79</sup> tetramethylguanidine,<sup>35,40,73-76</sup> and diisopropylamine<sup>76-78</sup> were used to catalyze the reaction, the yields of 32 were quite negligible as determined by GLC analysis. However, tetrabutylammonium fluoride<sup>80,81</sup> proved to be the catalyst of choice as nearly quantitative yields of 32 were obtained.

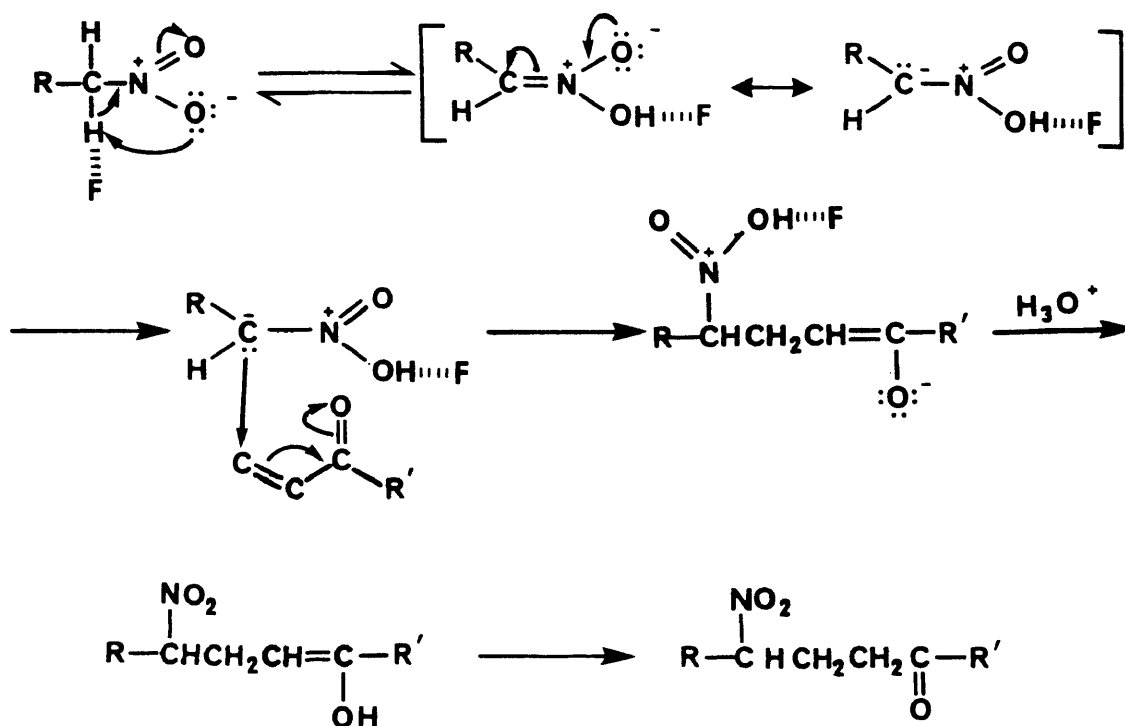


Figure 23. Tetrabutylammonium fluoride catalyzed Michael-type addition.

It is believed that the activity of the catalyst is attributable to the fluoride ion which is a relatively strong base capable of forming strong hydrogen bonds. Primary and secondary nitro-compounds in themselves, possess a site for hydrogen-bonding to fluoride (the hydrogen

directly attached to the nitro-carbon) and through tautomerization possess a particularly powerful hydrogen-bond electron acceptor site (the N-hydroxy hydrogen). A resonance form of the iminium ion converts the nitro-carbon into a carbanion which can then go through nucleophilic addition with the carbon-carbon double bond<sup>80</sup> of the enone 31. Tautomerization of the enol form provided 8-nitro-5-pentadecanone 32. The IR spectrum of 32 showed a carbon-oxygen double bond band at  $1710\text{ cm}^{-1}$  and a carbon-nitro group band at  $1540\text{ cm}^{-1}$ . The mass spectrum of 32 displayed a base peak at  $m/z=85$  corresponding to  $\alpha$ -cleavage next to the carbonyl as well as a  $M-\text{NO}_2$  fragment at  $m/z=225$ .

The formation of 2-butyl-5-heptyl-1-pyrroline N-oxide (33) was afforded by the cyclization of the  $\gamma$ -nitroketone 32 using zinc dust in cold aqueous ammonium chloride to reduce the nitro group to a hydroxylamine.<sup>6,25,65-70</sup>

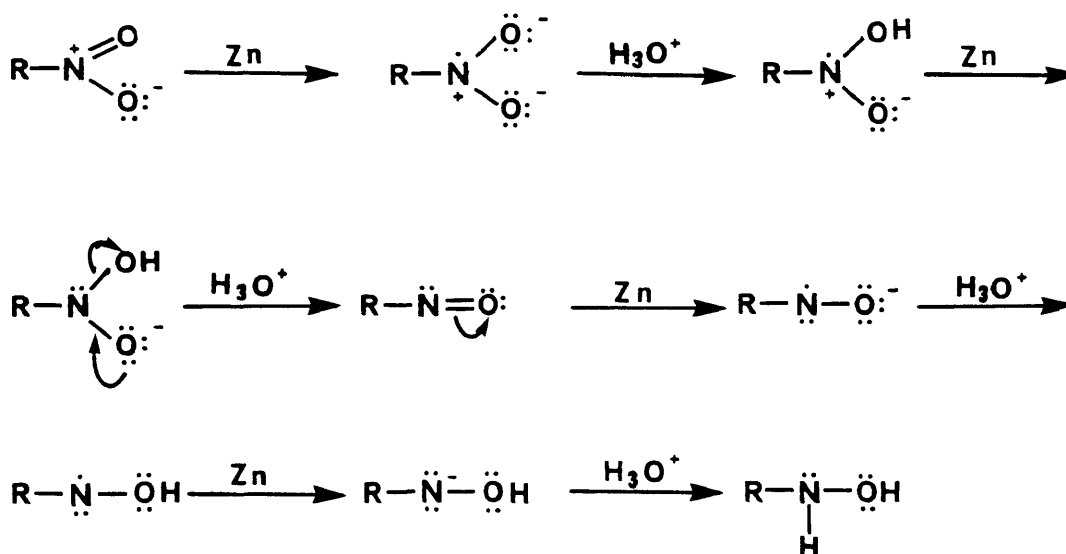


Figure 24. Zinc metal reduction to a hydroxylamine.

In using the zinc dust, it is imperative that it be freshly activated (though not necessarily anhydrous) as described by Fieser and Fieser<sup>104</sup> prior to use. It has been suggested that reduction to the hydroxylamine by the metal and acid follows the pathway described above.<sup>105</sup>

The lone electron pair on the nitrogen may then attack the carbonyl forming an iminium ion. In the aqueous media, the proton on the nitrogen is pulled off and the alcohol is protonated to form a good leaving group. A nitrogen-carbon double bond then forms causing the displacement of water. Finally, removal of the hydroxylamine hydrogen provides the relatively stable zwitterion characteristic of nitrones. The crude hygroscopic nitrone 33 showed a characteristic carbon-nitrogen double bond band<sup>65</sup> at  $1590\text{ cm}^{-1}$  in the IR spectrum.

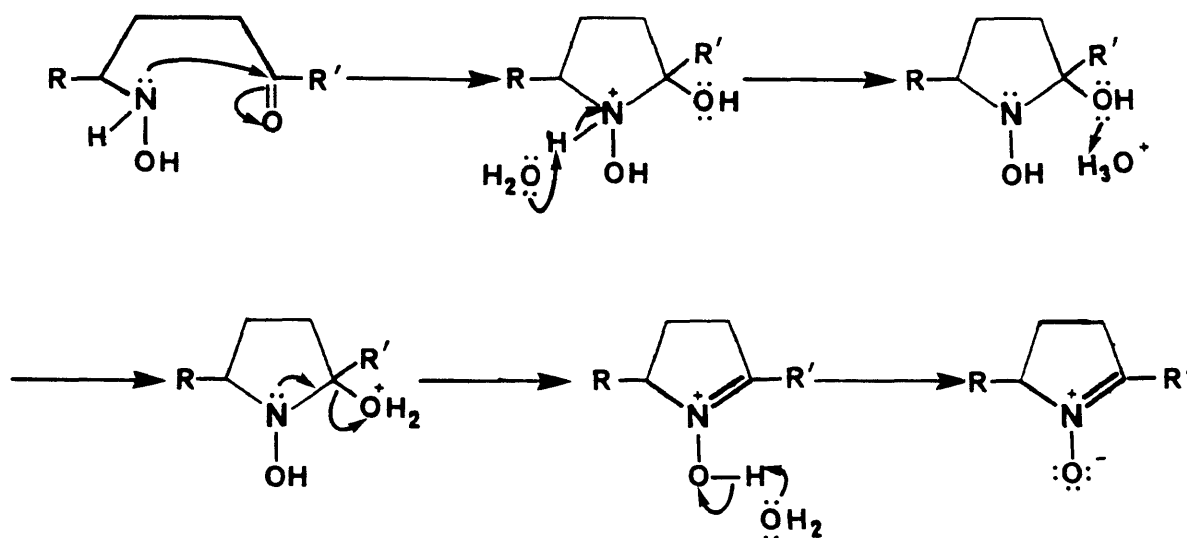


Figure 25. Intramolecular nitrone formation.

No means of purification were attempted for fear of un-

intentional polymerization of the product.

The nitron 33 was immediately subjected to reduction of the carbon-nitrogen double bond with excess diisobutylaluminum hydride<sup>65-67</sup> to form the N-hydroxypyrrolidine 34. The carbon-nitrogen double bond is very similar in functionality to a carbon-oxygen double bond. The long, preattached side chain (heptane) in combination with the bulkiness of diisobutylaluminum hydride insures the cis addition to the double bond of the 1-pyrroline, thus forming N-hydroxy-cis-2-butyl-5-heptylpyrrolidine (34).

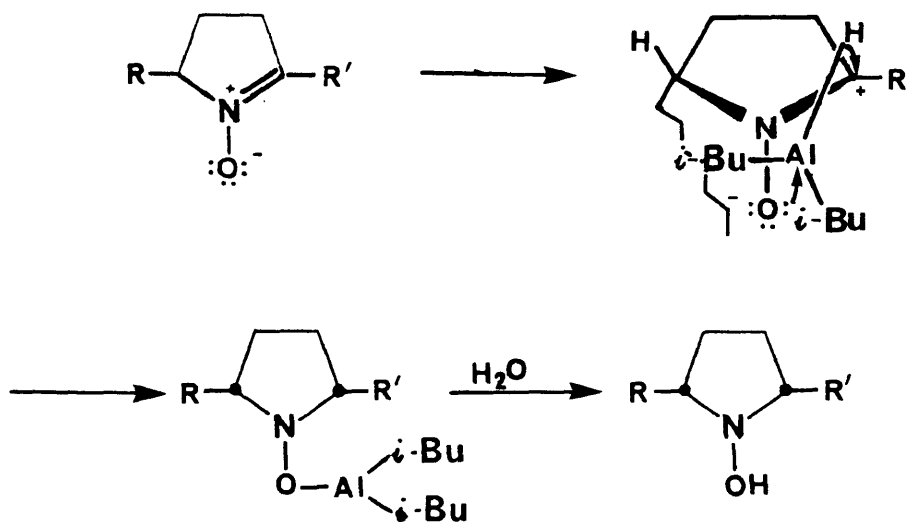


Figure 26. Stereoselective reduction using diisobutylaluminum hydride.

The presence of a hydroxylamine was initially indicated by the positive result obtained from the Rogers' test.<sup>106,107</sup> A characteristic deep purple-red color of the reduction

product provided by the test compound, and triphenyltetrazolium chloride, in the presence of alkali, can be considered to be a positive result. The IR spectrum of 34 showed the presence of an alcohol group band at  $3210\text{ cm}^{-1}$  along with the absence of the previous carbon-nitrogen double bond band which confirmed the result of the Rogers' test.

Finally, the ultimate goal of Scheme II was achieved by the well known dehydroxylation of the hydroxylamine 34 using lithium aluminum hydride<sup>105</sup> to provide the cis-2-butyl-5-heptylpyrrolidine 35. The IR spectrum of 35 showed none of the functional group bands previously reported, and, the  $^1\text{H}$  NMR displayed a complex multiplet in the region for the hydrogens at C-2 and C-5 ( $\delta = 2.85\text{ ppm}$ ) indicating the pyrrolidine ring skeleton. An indication of the stereochemistry of 35 was provided by GLC comparison of retention time and by coinjection of 35 with an authentic cis/trans mixture of 2-butyl-5-heptylpyrrolidine.

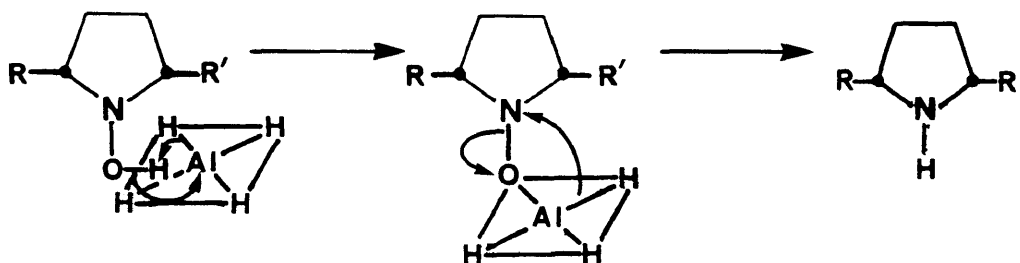


Figure 27. Lithium aluminum hydride reduction to cis-pyrrolidine.

The retention of 35 was identical to that of the first eluting (cis) isomer of the mixture.<sup>12</sup>

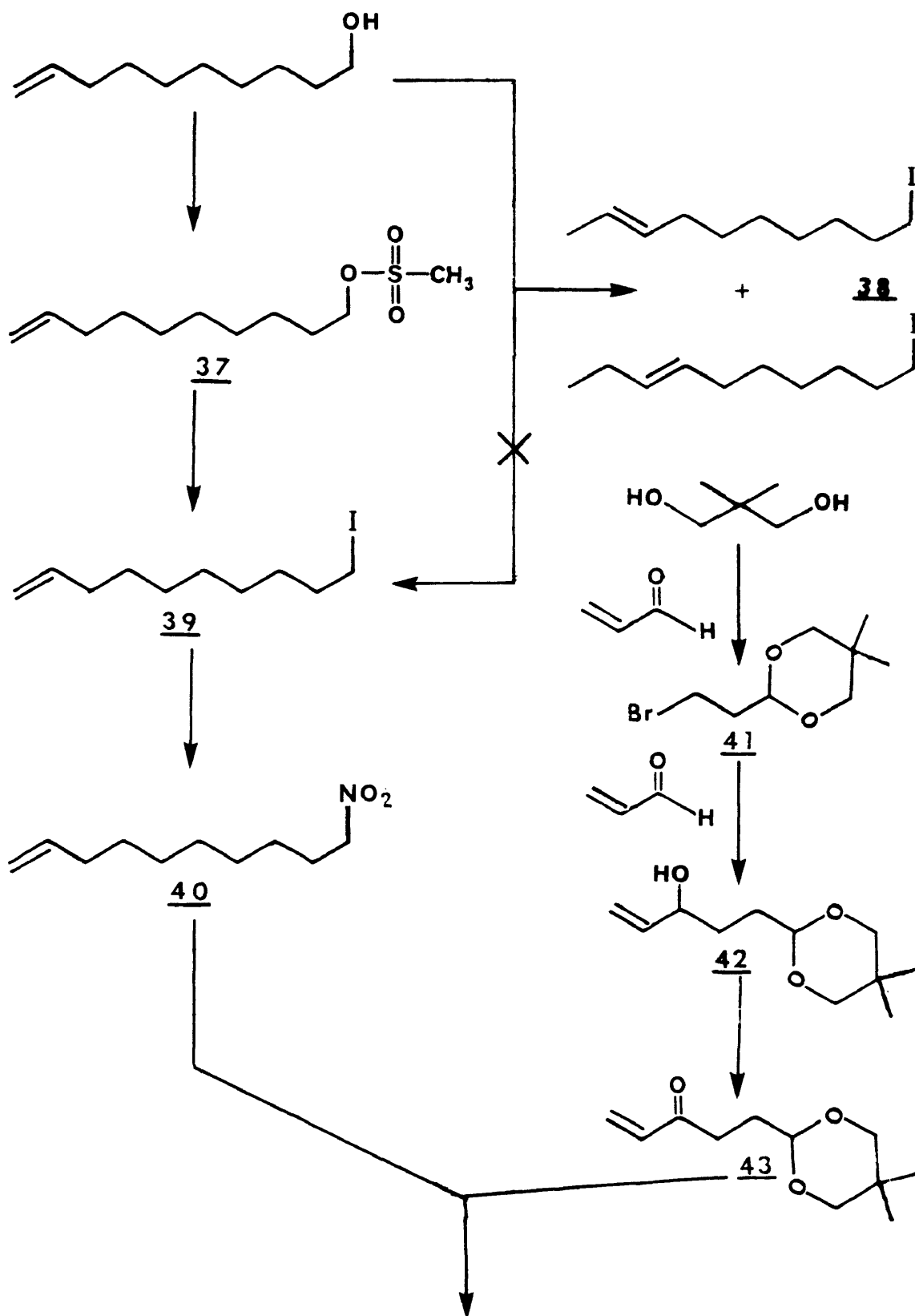
### C. SYNTHESIS VIA SCHEME III

Since the nitron reduction route successfully lead to the formation of cis-2,5-dialkyl pyrrolidine 35 stereoselectively, the synthesis of cis-2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxane-2-yl))ethyl pyrrolidine was conducted in the same manner to examine the feasibility of incorporating an acetal functional group and a terminal double bond.

It was envisioned that the nitroalkene would carry the terminal double bond and that the commercially available 9-decen-1-ol would be a useful precursor. Since the method described by Olah et. al.<sup>85-88</sup> for the preparation of iodoalkane 28 had worked so well previously, it seemed obvious to proceed by the route and avoid the sulfonate derivative. However, the acidic conditions of this procedure resulted in isomerization of the double bond to give a mixture of iododecenes (38). The initial evidence that the terminal double bond had been altered came from the IR spectrum which lacked the characteristic bands. The <sup>1</sup>H NMR spectrum of 38 had multitude peaks in the olefinic region, a triplet at  $\delta=3.78$  ppm for the two methylene hydrogens next to iodine, as well as a terminal methyl group doublet at  $\delta=0.95$  ppm.

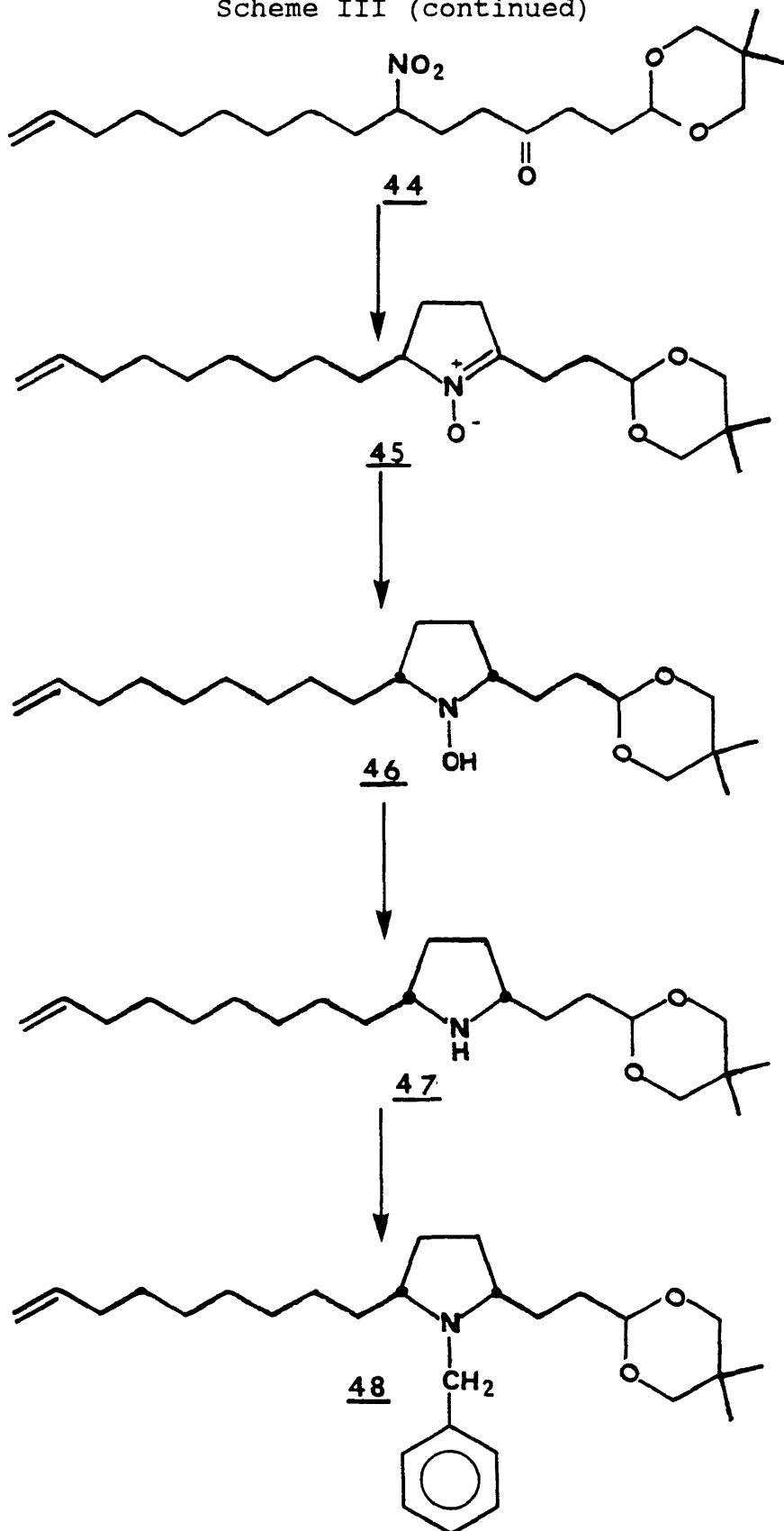
Subsequently, it was necessary to prepare 9-decen-1-methanesulfonate (37) by the usual procedure. The IR

Scheme III





## Scheme III (continued)



spectrum of 37 showed the presence of the terminal double bond by the characteristic bands at 3080, 1640, and 910  $\text{cm}^{-1}$  accompanied by the typical sulfonate functional group bands at 1360 and 1180  $\text{cm}^{-1}$ .

1-Iodo-9-decene (39) was prepared in the same manner as was 28 using sodium iodide without alteration of the terminal double bond, as was evident from its spectral data.

The attempted preparations of 1-nitro-9-decene (40) from 39 included procedures utilizing sodium nitrite with<sup>91</sup> and without urea<sup>92</sup>, as well as the use of silver nitrite<sup>93</sup> described previously. Additionally, a method employing the use of a sonic bath with silver nitrite was investigated.<sup>108</sup> The ultrasound was used to aid in the homogenization of the reaction mixture. The rate of completion of the reaction, as followed by GLC, was dramatically decreased from three days to three hours with equally good yields. The impracticalities of the silver nitrite method for large scale production, including the acquisition of a sonic bath, necessitated the use of the sodium nitrite/urea method. The IR spectrum of 40 showed the nitro group bands at 1545 and 1375  $\text{cm}^{-1}$ . As before, the other component in the product mixture was the starting alcohol due to the acid catalyzed hydrolysis of the nitrite ester<sup>93</sup> which was separated by distillation.

The acetal precursor to the vinyl alcohol chosen was 2(2-bromoethyl)-5,5-dimethyl-1,3-dioxane (41), which was prepared by treatment of acrolein with 2,2-dimethyl-1,3-

propanediol in the presence of anhydrous hydrogen bromide.<sup>49-53</sup> With small unbranched aldehydes, the equilibrium lies to the right. The mechanism shown below involves the initial formation of a hemiacetal, and, is the reverse of that for acetal hydrolysis.<sup>105.109</sup>

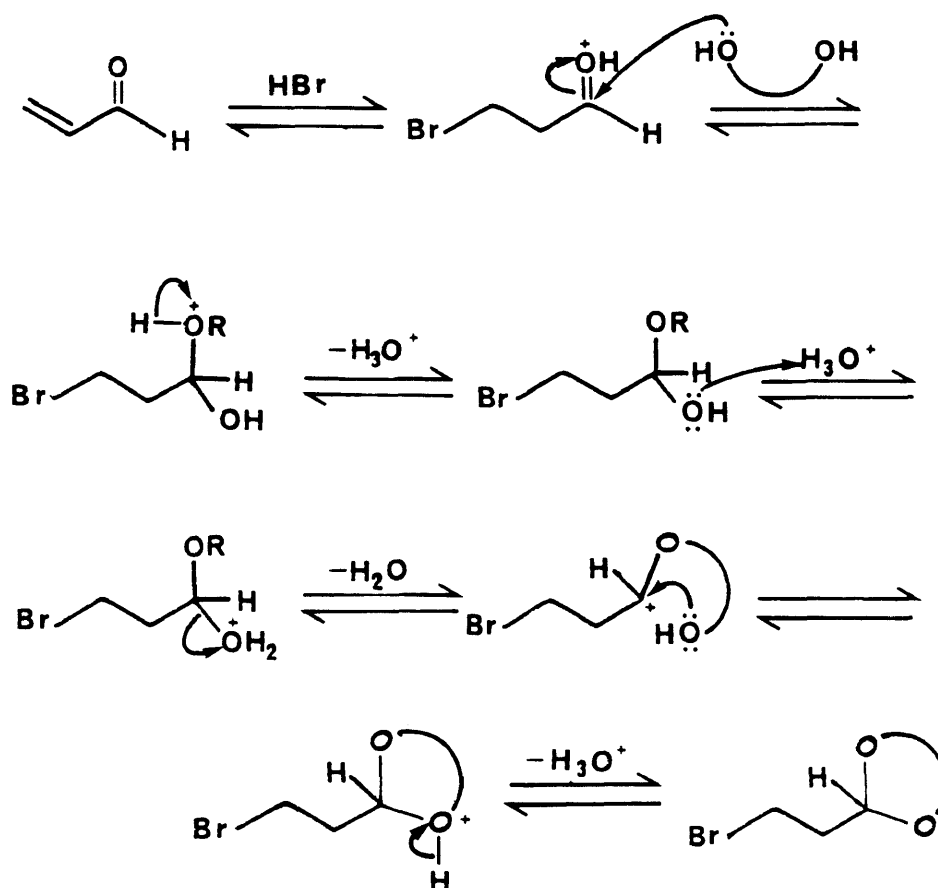


Figure 28. Acetal formation.

The structure of **41** was confirmed by its <sup>1</sup>H NMR spectrum which displayed the methine hydrogen at the C-2 position of the dioxane as a triplet at  $\delta=4.60$  ppm split by two hydrogens on the adjacent carbon with a coupling constant of 5 Hz. The two hydrogens on the carbon next to the bromine

along with the methylene hydrogens next to an oxygen atom gave a multiplet at  $\delta=3.69-3.35$  ppm. The methylene hydrogens one carbon removed from the bromine gave a doublet of triplets at  $\delta=2.21$  ppm, split first by the adjacent methylene hydrogens and then by the methine hydrogen. The equatorial and axial methyl groups appeared as singlets at  $\delta=1.17$  ppm and  $\delta=0.72$  ppm, respectively. The IR spectrum showed a number of sharp bands in the fingerprint region corresponding to the dioxane (1470, 1125, 1020, and 905  $\text{cm}^{-1}$ .)

Subsequent Grignard addition of 2(2-magnesium bromoethyl)-5,5-dimethyl-1,3-dioxane to acrolein in the usual manner<sup>35,40,47,49</sup> afforded 2(4-penten-3-ol)-5,5-dimethyl-1,3-dioxane (42). The Grignard reagent was prepared slowly to avoid the evolution of heat so that it would not react with itself. The IR spectrum of the enol dioxane 42 displayed an alcohol group band at 3440  $\text{cm}^{-1}$ , along with the forementioned characteristic double bond bands. The terminal double bond is well represented in the  $^1\text{H}$  NMR spectrum by a doublet of doublets of doublets for the methine hydrogen at  $\delta=5.87$  ppm, and, broad doublets at  $\delta=5.20$  and  $\delta=5.07$  ppm for each of the methylene hydrogens with their characteristic coupling constants. Furthermore, the methine hydrogen next to the alcohol group gave a multiplet at  $\delta=4.12$  ppm along with the regular pattern for the dioxane.

The Swern oxidation conditions<sup>103</sup> were employed successfully to provide the vinyl ketone 43, as indicated by

the presence of a carbonyl group bands at 1700 and 1680  $\text{cm}^{-1}$  corresponding to the two possible conformational isomers.

The tetrabutylammonium fluoride catalyzed Michael-type addition<sup>80,81</sup> of 1-nitro-9-decene (40) and enone dioxane 43, as used in the preparation of 32, provided 2-(6-nitro-14-pentadecen-3-one)-5,5-dimethyl-1,3-dioxane (44). Although the  $^1\text{H}$  NMR spectrum of 44 was acquired, the presence of all the functional groups was indicated by the IR spectrum alone. The terminal double bond displayed bands at 3080, 1640, and 910  $\text{cm}^{-1}$ ; the carbonyl group band was at 1715  $\text{cm}^{-1}$ ; the nitro group band was at 1550  $\text{cm}^{-1}$ ; and, the dioxane was represented by the bands at 1470, 1130, and 1015  $\text{cm}^{-1}$ .

Cyclization of the  $\gamma$ -nitroketone 44 was accomplished by reduction using ammonium chloride and zinc dust,<sup>6,25,65-70</sup> as in the preparation of 33, to provide 2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl))ethyl-1-pyrroline N-oxide (45). The IR spectrum showed the carbon-nitrogen double bond band<sup>65</sup> at 1605  $\text{cm}^{-1}$  and the absence of the carbonyl and nitro group bands.

Reduction of the nitro compound 45, as in the preparation of 34, to the cis-N-hydroxylamine 46 was afforded by the use of diisobutylaluminum hydride.<sup>65-67</sup> The product, N-hydroxy-cis-2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl))ethyl pyrroline (46), had a positive result for the Rogers' test<sup>106,107</sup> and an alcohol group band at 3370  $\text{cm}^{-1}$  in its IR spectrum.

Finally, dehydroxylation of 46 with lithium aluminum hydride,<sup>105</sup> as in the preparation of 35, gave the desired cis-2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl)) ethyl pyrrolidine (47). Both the IR and <sup>1</sup>H NMR spectra gave data characteristic of the terminal double bond and dioxane as described previously.

The stereochemical relationship of the alkyl groups in the resultant 2,5-disubstituted pyrrolidines 35 and 47 were determined by the method of Hill and Chan.<sup>110</sup> This method permits the configurational assignments to the corresponding N-benzyl amines on the basis of their distinguishable <sup>1</sup>H NMR behavior. The non-equivalent, diastereotopic benzylic protons of the trans-isomer should appear as an AB pattern while the enantiotopic benzylic protons of the cis-isomer should result in a singlet at approximately the same chemical shift.<sup>110</sup>

The requisite benzyl derivatives 36 and 48 were prepared by the benzylation of 35 and 47 using benzoyl chloride and 4-dimethylaminopyridine in pyridine followed by conversion of the resultant amides to the corresponding tertiary benzylic amines with lithium aluminum hydride.<sup>105</sup> Initially, GLC analyses revealed the presence of one of the two isomers to be present in each case. The <sup>1</sup>H NMR spectra revealed the expected benzylic methylene singlet at  $\delta=3.72$  and  $\delta=3.73$  ppm, clearly confirming formation of the cis-isomer exclusively.

All attempts at hydrolysis of the dioxane acetal using

different kinds and concentrations of acids,<sup>35-40</sup> thus forming the cis-fused pyrrolizidine skeleton proved to be unsuccessful. Generally speaking, cyclic acetals and ketals are readily hydrolyzed by acids to their components, however, it has been shown that the rate of hydrolysis can vary depending on ring size and substitution.<sup>111</sup> The ease of hydrolysis is increased by substitution in the C-2 position and decreased by substitution in the C-4 and C-5 positions. In the case of 5,5-dimethyl-1,3-dioxane, hydrolysis would tend to flatten the six-membered ring thus causing unfavorable forcing of the two methyl groups closer to each other. Further, comparable measurements with six- and seven-membered cyclic 1,3-acetals indicate that the seven-membered ring is six times as stable as the six-membered ring which in turn is six times as stable as the five-membered ring.<sup>111</sup>

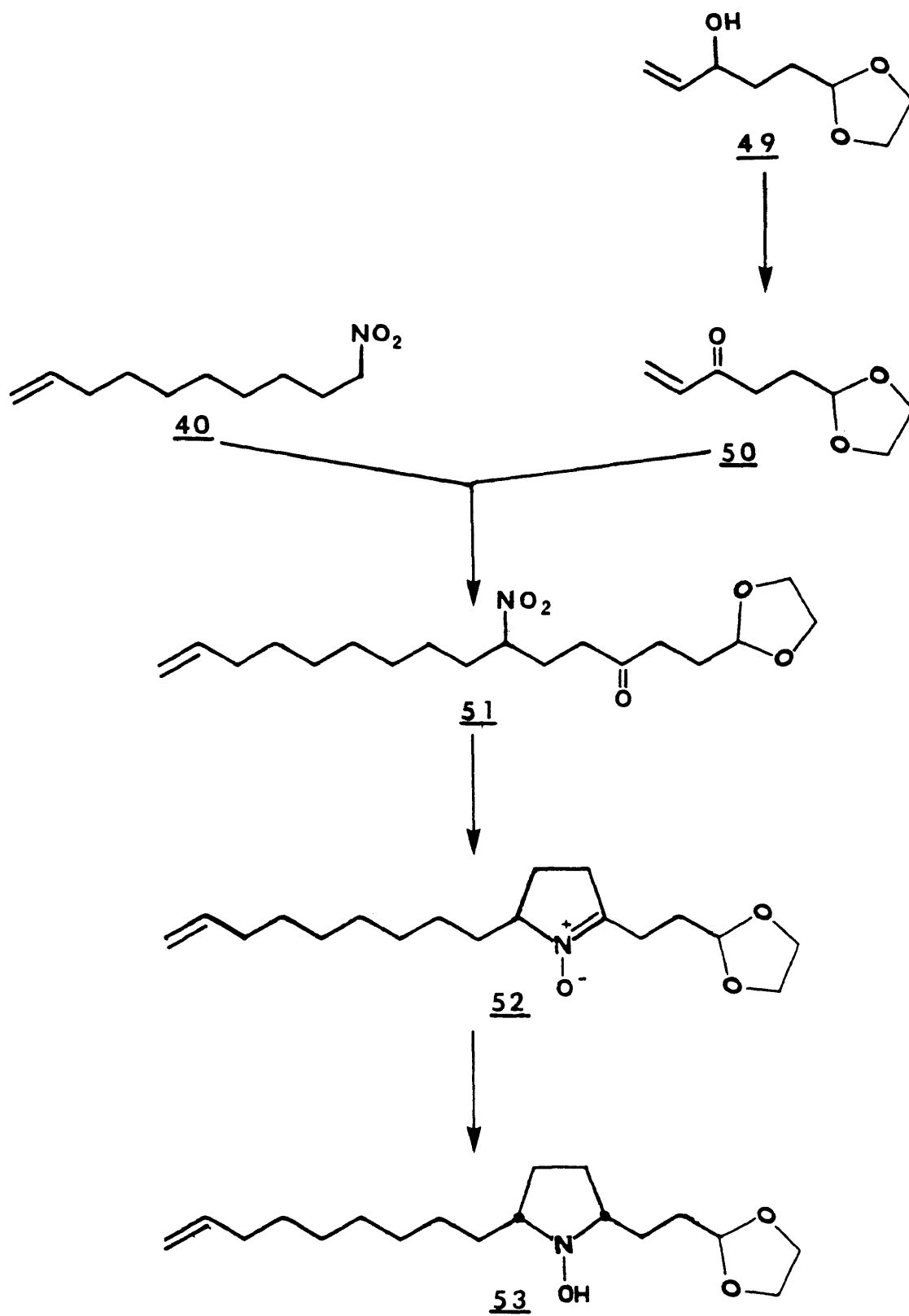
In any case, at this point, synthesis via Scheme III was discontinued.

#### D. SYNTHESIS VIA SCHEME IV

As it appeared that the use of the dioxane acetal could not be hydrolyzed to form a pyrrolizidine ring skeleton, we then resolved to use the more easily hydrolyzed dioxolane acetal<sup>111</sup> as shown in Scheme IV.

Synthesis began with the Swern oxidation<sup>103</sup> of 2(4-penten-3-ol)-1,3-dioxolane (49),<sup>112</sup> as in the preparation of 31, to provide the vinyl ketone 50. The IR spectrum of 50 showed carbonyl group bands at 1700 and 1680  $\text{cm}^{-1}$  corresponding to the two possible conformational isomers, and, the

## Scheme IV





dioxolane band in the fingerprint region at 1400(w), 1140, 1030, and 900  $\text{cm}^{-1}$ .

The Michael-type addition of 1-nitro-9-decene (40) and enone dioxolane 50 catalyzed by tetrabutylammonium fluoride,<sup>80,81</sup> as in the preparation of 32, provided 2-(6-nitro-14-pentadecen-3-one)-1,3-dioxolane (51). The IR spectrum displayed bands for the terminal double bond at 3080, 1640, and 910  $\text{cm}^{-1}$ ; the carbonyl group band at 1715  $\text{cm}^{-1}$ ; the nitro group band at 1550  $\text{cm}^{-1}$ ; and, the characteristic dioxolane bands. The mass spectrum of 51 displayed a molecular ion at  $m/z=341$  and a base peak at  $m/z=73$  resulting from carbon-carbon cleavage at C-2 of the dioxolane. Other fragments occurred at  $m/z=295$ , and 129, corresponding to  $M-\text{NO}_2$ , and  $\alpha$ -cleavage adjacent to the carbonyl on the side of the nitro group, respectively.

The nitrone 52 was afforded by treatment of the  $\gamma$ -nitroketone 51 with zinc dust and ammonium chloride to effect cyclization,<sup>6,25,65-70</sup> as in the preparation of 33. The IR spectrum of 2-(8-nonenyl)-5-(2-(1,3-dioxolan-2-yl))ethyl-1-pyrroline N-oxide (52) showed the carbon-nitrogen double bond<sup>65</sup> at 1605  $\text{cm}^{-1}$ .

Stereospecific reduction of the nitrone 52 using diisobutylaluminum hydride,<sup>65-67</sup> as in the preparation of 34, provided N-hydroxy-2-(8-nonenyl)-5-(2-(1,3-dioxolan-2-yl))ethyl pyrrolidine 53. The N-hydroxylamine 53 gave a positive result to the Rogers' test,<sup>106,107</sup> and, an alcohol group band at 3360  $\text{cm}^{-1}$  in its IR spectrum.

## E. OTHER RESULTS

In anticipation of the final steps in the synthesis of the (5E,8Z) pyrrolizidine 1, preliminary studies were done to provide a means for nucleophilic addition at C-5 of the 1-propenyl group exo to the pyrrolizidine nucleus. One of the means by which this may be accomplished is by the use of lithium diisobutylmethyl-E-1-propenylalanate.<sup>113,114</sup> The required vinylalanes are readily accessible via hydroalumination of alkynes with diisobutylaluminum hydride in ether. This involves a cis addition of the aluminum-hydrogen bond to the triple bond yielding trans-vinylalanes from 1-alkynes.<sup>113</sup> Treatment of the solution of vinylalane with methyllithium in a 1:1 ratio followed by the addition of a carbonyl should yield the trans-enol.

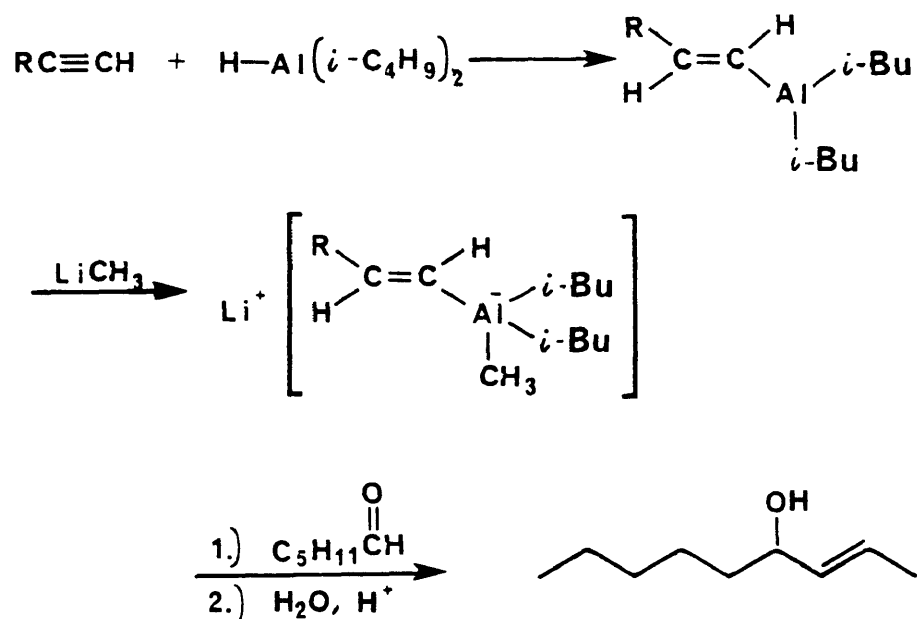


Figure 29. Nucleophilic addition to a carbonyl via lithium diisobutylmethyl-E-1-propenylalanate.

However, in our investigation, GLC analysis of the product mixture revealed the presence of an intractable mixture, with the major component identified as 54 by comparison of GLC retention time, IR, and  $^1\text{H}$  NMR spectra with that of the authentic 2-nonyn-4-ol. In retrospect, it is clear that the trans-vinylalane must never have formed consequently resulting in the formation of lithium propynolide upon the addition of the methyllithium which then reacted with the 1-hexanal to give 54.

It has been shown that disubstituted acetylenes can be reduced with fairly high stereoselectivity to trans-olefins with lithium aluminum hydride in an etheral solvent.<sup>29-34</sup>

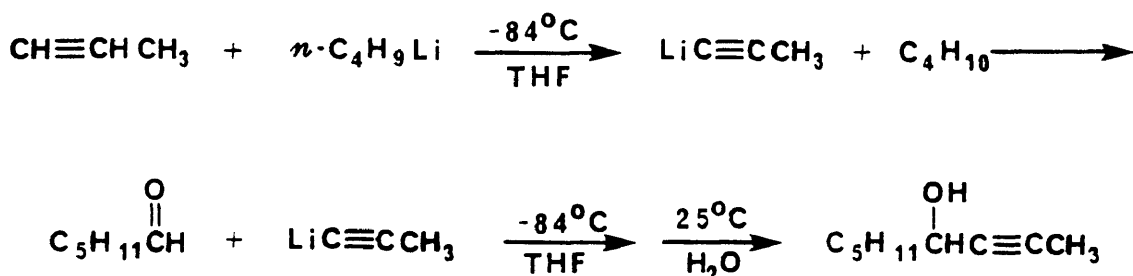


Figure 30. Nucleophilic addition to a carbonyl via lithium propynolide.

Hence, another method employable would be by the use of lithium propynolide<sup>27,28</sup> followed by the reduction of the carbon-carbon triple bond with lithium aluminum hydride. Monolithium acetylide has been shown to react with a variety of aldehydes and ketones under exceptionally mild conditions

to give high yields of the corresponding ethynyl carbinols.<sup>28</sup> We thus decided to study the reaction using 1-hexanal as the model. Addition of 1-propyne to *n*-butyllithium in THF at -84°C resulted in a clear solution, followed by the addition of 1-hexanal and warming to room temperature which gave a nearly quantitative yield of 2-nonyl-4-ol (54). The <sup>1</sup>H NMR spectrum of 54 showed a multiplet at  $\delta=4.33$  ppm for the methine hydrogen attached to the alcohol group. The terminal methyl one carbon away from the carbon-carbon triple bond gave a doublet at  $\delta=1.83$  ppm with a coupling constant of 2 Hz characteristic of long range splitting. The IR spectrum displayed an alcohol group band at  $3350\text{ cm}^{-1}$  as well as a carbon-carbon triple bond band at  $2230(\text{w})\text{ cm}^{-1}$ .

A study was conducted to determine the effective partial reduction of a carbon-carbon triple bond without altering a terminal double bond which consisted of heating to reflux 1-octyne and 9-decen-1-ol with lithium aluminum hydride in THF.<sup>115</sup> The IR and <sup>1</sup>H NMR spectra of the major product of the first reduction revealed the characteristic data for a terminal double bond, hence, 1-octyne had been reduced to 1-octene (55). The IR and <sup>1</sup>H NMR spectra of the second reduction revealed 9-decen-1-ol to remain unchanged upon similar treatment with lithium aluminum hydride.

## CHAPTER 4

### EXPERIMENTAL

**Spectral procedures.** Analytical and preparative gas/liquid chromatography (GLC) were performed on a Varian 920 equipped with a filament detector and a 2 m X 5 mm i.d. aluminum column packed with either 10% SP-2100 on 100/120 Supelcoport, 10% SP-1000 on 80/100 Supelcoport, 10% SE-30 on 60/80 Chromosorb, 3% SE-30 on 60/80 Chromosorb, or 10% Carbowax 20M on 60/80 Chromosorb, using helium as the carrier gas; or, on a GOW-MAC 750P equipped with a flame ionization detector and a 2 m X 2 mm i.d. glass column packed with 5% SP-1000 on 100/120 Supelcoport, using nitrogen as the carrier gas. Infrared spectra (IR) were recorded using neat liquid films on NaCl plates with a Perkin-Elmer 1320 Infrared Spectrometer. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) were recorded on a Varian FT-80 Spectrometer at 80 MHz in deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Mass spectra (MS) were recorded using a LKB-9000 GC/MS equipped with a 2 m X 2 mm i.d. glass column packed with either 1% SP-1000 on 100/120 Supelcoport or 5% OV-101 on 100/120 Supelcoport.

**General procedures.** Tetrahydrofuran (THF) and

1,2-dimethoxyethane were distilled from lithium aluminum hydride under a nitrogen atmosphere. Pyridine and triethylamine were distilled from calcium hydride. Dichloromethane, acetonitrile, dimethylformamide (DMF), and dimethylsulfoxide were distilled from phosphorous pentoxide.

**Methyl-4-oxo-12-tridecenoate (22).** A solution containing 20.60g (129.4 mmol) 21, and 17.83g (207.1 mmol) methyl acrylate in 180 mL 1,2-dimethoxyethane was added dropwise to a magnetically stirred mixture containing 4.36g (16.2 mmol) 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, 17.83g (207.1 mmol) methyl acrylate and 15.72g (155.3 mmol) triethylamine in 200 mL 1,2-dimethoxyethane at 80°C under a nitrogen atmosphere. The resulting mixture was heated to reflux for 20 h. During this time, the mixture became light yellow in color. Upon cooling, the mixture was diluted in 500 mL ether. The organic phase was washed consecutively with dilute HCl, saturated aqueous NaHCO<sub>3</sub>, brine, and dried over anhydrous MgSO<sub>4</sub>. The solvent was removed in vacuo and distillation provided 21.32g (69% yield) of ketoester 22, bp 112-166°C (0.1 mmHg); IR 3080(w), 1740, 1710, 1640(w), 910 cm<sup>-1</sup>; <sup>1</sup>H NMR δ=5.9 (1H, d of d of t, J=18, 10, and 6 Hz, CH<sub>2</sub>=CH-), 5.0 (1H, br d, J=18 Hz, CH<sub>2</sub>=CH-), 4.9 (1H, br d, J=10 Hz, CH<sub>2</sub>=CH-), 3.66 (3H, s, CH<sub>3</sub>-O), 2.77-2.45 (6H, complex m, -CH<sub>2</sub>-CO-), 2.04 (2H, m, CH<sub>2</sub>-CH=CH<sub>2</sub>), 1.31 (10H, br s, -(CH<sub>2</sub>)<sub>5</sub>-); MS m/z (rel. intensity) 240(M), 209(10), 135(25), 130(95), 115(60), 111(25), 98(100), 69(35), 59(15), 55(65), 43(15), 41(35), 31(5).

**5-(8-Nonenyl)-2-pyrrolidone (23).** A mixture containing 21.32g (88.8 mmol) ketoester 22, and 34.24g (444.1 mmol) ammonium acetate (dried in vacuo) in 150 mL methanol was magnetically stirred for 1 h at room temperature. Potassium hydroxide, 1.25g (22.2 mmol), was added and dissolved followed by the addition of 2.50g (40.0 mmol) sodium cyanoborohydride, and the mixture was stirred overnight. The solvent was removed in vacuo and the residue taken up in ether. The mixture was carefully acidified by addition of dilute HCl. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub>, brine, dried over anhydrous K<sub>2</sub>CO<sub>3</sub>, and the solvent removed in vacuo. Kugelrohr distillation gave 9.37g (51% yield) of lactam 23, bp 204-228<sup>o</sup>C (0.1 mmHg); IR 3200, 3080(w), 1690, 1640(w), 910 cm<sup>-1</sup>; <sup>1</sup>H NMR δ=5.9 (1H, d of d of t, J=18, 10, and 6 Hz, CH<sub>2</sub>=CH-), 5.0 (1H, br d, J=18 Hz, CH<sub>2</sub>=CH-), 4.9 (1H, br d, J=10 Hz, CH<sub>2</sub>=CH-), 3.61 (1H, m, CH-NHC(=O)R), 2.27 (2H, complex m, CH<sub>2</sub>-CH=CH<sub>2</sub>), 1.31 (14H, br s); MS m/z (rel. intensity) 210(4, M+1), 209(5, M), 110(7), 85(7), 84(100), 55(7), 41(11).

**5-(8-Nonenyl)-2-thiopyrrolidone (25).** Procedure A using 24. A mixture containing 1.00g (4.8 mmol) distilled lactam 23 and 1.93g (4.8 mmol) 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiodiphosphetane 2,4-disulfide (24), prepared as described by Clausen et. al.,<sup>61</sup> was magnetically stirred under a nitrogen atmosphere for 5 min and 5 ml toluene was injected through the rubber septum. The mixture was heated to reflux for 2.5 h and then cooled to room temperature. The

mixture was taken up in ether, washed with 5% aqueous NaOH, brine, and dried over anhydrous  $\text{MgSO}_4$ . Upon removal of the solvent in vacuo, 0.62g (58% yield) of the crude thiolactam 25 were obtained. GLC analysis showed one major component which could not be purified by preparative GLC.

**Procedure B using phosphorous pentasulfide.** A mixture containing 0.43g (2.1 mmol) distilled lactam 23, and 0.24g phosphorous pentasulfide (1.1 mmol) in 10 mL toluene, was heated to reflux under a nitrogen atmosphere overnight. After the work-up in Procedure A, the crude product yield was 0.11g. GLC analysis revealed a complex mixture.

**5-(8-Nonenyl)-2-thiomethyl-1-pyrroline (26).** Procedure A. A mixture containing 0.62g (2.8 mmol) thiolactam 25 in 15 mL THF and 0.07g (2.8 mmol) pentane washed sodium hydride was magnetically stirred under a nitrogen atmosphere for 1.5 h, followed by the dropwise addition of 0.39g (2.8 mmol) iodomethane. The mixture was stirred for 1.5 h, taken up in ether and washed once with saturated aqueous  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was washed with ether. The combined organic extracts were washed with brine and dried over anhydrous  $\text{MgSO}_4$ . Upon removal of the solvent in vacuo, 0.46g (70% yield) of the crude thiolactim 26 were obtained. GLC analysis revealed one major component which could be isolated by preparative GLC; IR 3080(w), 1640(w), 1580, 1455, 1250, 1130, 1055, 1025, 960, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  = 5.9 (1H, d of d of t,  $J=18, 10, \text{ and } 6$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.0 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.9 (1H, br d ,



$J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 3.95 (1H, m,  $\text{RCH}-\text{N}=\text{C}(\text{SCH}_3)$ ), 2.61 (2H, complex m,  $\text{CH}_2-\text{C}(=\text{N})\text{SCH}_3$ ), 2.44 (3H, s,  $\text{SCH}_3$ ), 2.04 (2H, m,  $\text{CH}_2-\text{CH}=\text{CH}_2$ ), 1.66-1.30 (14H, br s); MS  $m/z$  (rel. intensity) 240(9,M), 224(43), 170(26), 115(100), 114(39).

**Procedure B.** A solution containing 0.67g (3.0 mmol) thiolactam 23 in 10 mL dichloromethane was magnetically stirred and cooled in an ice bath followed by the dropwise addition of 0.45g (3.0 mmol) iodomethane. The mixture was stirred overnight and allowed to warm to room temperature. The mixture was neutralized with solid  $\text{NaHCO}_3$ , and diluted with dichloromethane. The organic phase was washed once with saturated aqueous  $\text{NaHCO}_3$ , twice with brine, and dried over anhydrous  $\text{MgSO}_4$ . The crude product yield was 0.58g. GLC analysis showed one major component along with several others having longer retention times.

**Attempted pyrroline synthesis.** An ethereal solution containing 0.46g (1.9 mmol) thiolactim 26 in 5 mL anhydrous ether was added dropwise to butyl magnesium bromide (prepared from 0.57g (4.2 mmol) 1-bromobutane in 10 mL anhydrous ether and 0.26g (10.6 mmol) magnesium) under a nitrogen atmosphere. A small aliquot was treated with 10% aqueous  $\text{Na}_2\text{CO}_3$ , the ethereal layer was washed once with brine, and dried over anhydrous  $\text{K}_2\text{CO}_3$ . GLC analysis revealed mainly the unreacted thiolactim 26. Subsequently, 0.5 ml of  $N,N,N',N'$ -tetramethylethylenediamine (TMEDA) was added and the mixture heated to reflux overnight. GLC analysis showed no change.

**1-Octylmethanesulfonate (27).** To a magnetically stirred solution containing 8.33g (64.0 mmol) octanol in 20 mL pyridine, cooled to 0°C was added dropwise 11.10g (100.0 mmol) methanesulfonyl chloride. After 1.5 h, the mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was poured over ice and then taken up in ether. The organic phase was washed with dilute HCl, saturated aqueous NaHCO<sub>3</sub>, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Upon removal of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 10.12g (78% yield) 27, bp 90-92°C (0.1 mmHg); IR 1355, 1175, 945 cm<sup>-1</sup>.

**1-Iodooctane (28). Procedure A.** A mixture containing 2.00g (9.6 mmol) 27, and 2.16g (14.4 mmol) sodium iodide, in 80 mL acetone was magnetically stirred overnight at room temperature. After dilution with ether, the organic phase was washed with water and dried over anhydrous MgSO<sub>4</sub>. Upon removal of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 1.67g (72% yield) 28, bp 50-52°C (0.2 mmHg), (lit.<sup>116</sup> 225.5°C (760 mmHg)); IR 1740, 1460, 1240 cm<sup>-1</sup>.

**Procedure B.** A solution containing 1.00g (7.7 mmol) octanol, 2.30g (15.5 mmol) sodium iodide, and 1.67g (15.4 mmol) chlorotrimethylsilane in 10 mL acetonitrile was magnetically stirred under a nitrogen atmosphere for 12 h at room temperature. The reaction mixture was taken up in ether and washed successively with water, 10% aqueous sodium thiosulfate, brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Upon removal

of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 1.29g (69% yield) 28.

**1-Nitrooctane (29) Procedure A.** A mixture containing 0.50g (2.1 mmol) 28, 0.49g (8.2 mmol) urea, and 0.43g (6.2 mmol) sodium nitrite in 10 mL DMF, was magnetically stirred overnight under a nitrogen atmosphere at room temperature. The reaction mixture was poured over ice and extracted with petroleum ether. The aqueous phase was washed three times with petroleum ether. The combined organic phase was dried over anhydrous  $\text{MgSO}_4$ . Upon removal of the solvent in vacuo, GLC analysis revealed the presence of two components; the first eluting was identified as octanol by comparison with authentic sample (GLC retention time, IR). The second eluting component was identified as 29; IR 1550, 1380  $\text{cm}^{-1}$ . The yield was 66% 29 and 33% octanol by GLC analysis. The nitrooctane 29 was obtained pure by careful distillation, bp 60-65°C (0.2 mmHg) (lit.<sup>93</sup> 66°C (2 mmHg)).

**Procedure B.** Treating 2.00g (8.3 mmol) 28 with 1.15g (16.7 mmol) sodium nitrite in the same manner as in Procedure A (without urea) provided a yield of 66% 29 and 33% octanol by GLC analysis.

**Procedure C.** A solution containing 1.00g (4.2 mmol) 28 in 3 mL anhydrous ether was added dropwise to a well stirred mixture of 0.96g (6.3 mmol) silver nitrite<sup>93</sup> in 3 mL anhydrous ether at 0°C with the exclusion of light. The mixture was stirred for 24 h at 0°C and for 48 h at room temperature with strict exclusion of light. After filtration, and

removal of the solvent in vacuo, GLC analysis revealed the presence of 29 exclusively.

**Procedure D.** Treating 1.00g (4.8 mmol) 27 with 0.66g (9.6 mmol) sodium nitrite in the same manner as in Procedure A provided a yield of 40% 29 by GLC.

**1-Hepten-3-one (31). Procedure A.** A solution containing 4.40g (56.4 mmol) dimethylsulfoxide in 15 mL dichloromethane was added dropwise to a magnetically stirred solution containing 5.01g (39.5 mmol) oxalyl chloride in 15 mL dichloromethane, cooled to  $-63^{\circ}\text{C}$  (chloroform/ $\text{N}_2(l)$ ) under a nitrogen atmosphere. After 0.5 h a solution containing 3.0g (26.3 mmol) enol 30 in 20 mL dichloromethane was added dropwise and the mixture was stirred for 1.5 h. Subsequently, 8.71g (86.1 mmol) triethylamine was added, the resulting mixture was allowed to warm to room temperature, and heated to reflux overnight. Following the addition of ether (50 mL), the mixture was washed once with water, and the aqueous phase washed twice with 25 mL portions of ether. The combined organic phase was washed with brine, and dried over anhydrous  $\text{NaSO}_4$ . Upon removal of the solvent in vacuo, GLC analysis revealed one major component, 31, in nearly quantitative yield; bp  $134-140^{\circ}\text{C}$  (760 mmHg); IR 3100(w), 1675(br), 1610(w), 1400(m),  $910\text{ cm}^{-1}$ .

**Procedure B.** A mixture containing 0.52g (4.6 mmol) enol 30 and 5.20g (59.8 mmol) manganese dioxide was allowed to stir overnight at room temperature. The manganese dioxide was removed by filtration. GLC analysis indicated a 80% yield of

the enone 31 and 20% unreacted enol 30.

**Procedure C.** Treating 3.00g (26.3 mmol) enol 30 with 11.30g (52.6 mmol) pyridinium chlorochromate in the usual manner provided 0.66g (22% yield) enone 31.

**8-Nitro-5-pentadecanone (32).** A magnetically stirred mixture containing 1.00g (8.9 mmol) enone 31, and 1.41g (8.9 mmol) 29 in 15 mL THF was cooled to 0°C under a nitrogen atmosphere. Following the addition of 4.5 mL (4.5 mmol) tetrabutylammonium fluoride, the mixture was allowed to warm to room temperature overnight, taken up in ether, washed once with water, and dried over anhydrous MgSO<sub>4</sub>. Upon removal of the solvent in vacuo, GLC analysis revealed one major component which was purified by distillation to provide 2.32g (97% yield) nitroketone 32, bp 135-190°C (0.15 mmHg); IR 1710, 1540 cm<sup>-1</sup>; MS m/z (rel. intensity) 241(1), 225(8), 214(1), 183(3), 123(6), 124(6), 97(10), 95(6), 86(8), 85(100), 83(20), 81(10), 69(17), 67(8), 57(60), 55(55), 43(18), 41(20), 29(16).

GLC analysis revealed the yield of 32 to be negligible when tributylphosphine, tetramethylguanidine, and diisopropylamine were used as catalysts.

**2-Butyl-5-heptyl-1-pyrroline N-oxide (33).** A magnetically stirred solution containing 1.00g (3.7 mmol) nitroketone 32, and 0.40g (7.4 mmol) ammonium chloride in 2.6 mL deionized water was cooled to 0°C. To this was added 1.92g (29.6 mmol) freshly activated zinc dust<sup>104</sup> over the course of 3 h, and then continued to stir for 2 h at room

temperature. After filtration of the zinc dust using methanol, the mixture was concentrated in vacuo, taken up in chloroform, washed with saturated aqueous  $\text{NaHCO}_3$ , and dried over anhydrous  $\text{MgSO}_4$ . Upon removal of the solvent in vacuo, 0.50g (78% yield) crude nitron 33 was obtained; IR 1590, 1465, 1380(w)  $\text{cm}^{-1}$ .

**N-Hydroxy-cis-2-butyl-5-heptylpyrrolidine (34).** A standard solution of 3.2 mL (3.2 mmol) diisobutylaluminum hydride in anhydrous ether was added by syringe to a magnetically stirred solution containing 0.39g (1.6 mmol) nitron 33 in 50 mL anhydrous ether at  $0^\circ\text{C}$ . The solution was allowed to warm to room temperature overnight, followed by careful dropwise addition of water, dilution with ether, extracted once from 5% aqueous NaOH, and dried over  $\text{K}_2\text{CO}_3$ . Removal of the solvent in vacuo provided 34 a waxy solid which had an appropriate IR, and a positive result for the Rogers' test<sup>106,107</sup> for a hydroxylamine. The yield was quantitative; IR 3210(br s), 1470, 1380, 1045, 925  $\text{cm}^{-1}$ .

**cis-2-Butyl-5-heptylpyrrolidine (35).** A magnetically stirred mixture containing 0.53g (2.2 mmol) hydroxylamine 34, and 0.17g (4.4 mmol) lithium aluminum hydride in 15 mL THF was heated to reflux for 3 h under a nitrogen atmosphere. The reaction was terminated by the dropwise addition of water, taken up in ether, washed once with 5% aqueous NaOH, and dried over anhydrous  $\text{K}_2\text{CO}_3$ . Upon removal of the solvent in vacuo, GLC analysis revealed one major component, 35, which could be isolated by preparative GLC; IR 2860,

1460, 1380(w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ =2.85 (2H, complex m,  $\text{RCH-NR}$ ), 1.30 (22H, br s), 0.95 (6H, d,  $\text{CH}_3\text{-R}$ ). No accurate yield could be determined as an emulsion formed and probably had quite a bit of product in it.

**N-Benzyl-cis-2-butyl-5-heptylpyrrolidine (36).** To a magnetically stirred solution containing 0.25g (1.1 mmol) pyrrolidine 35, and 0.04g (0.3 mmol) 4-dimethylaminopyridine in 8 mL pyridine, cooled to  $0^\circ\text{C}$  was added 0.18g (1.3 mmol) benzoyl chloride and allowed to warm to room temperature overnight. The solution was poured over ice, taken up in ether, extracted, and dried over anhydrous  $\text{MgSO}_4$ . Removal of the solvent in vacuo provided N-benzoyl-cis-2-butyl-5-heptylpyrrolidine as a waxy yellow-brown solid. Subsequently, the crude product mixture was taken up in 50 ml anhydrous ether, and 1.00g (26.3 mmol) lithium aluminum hydride was added. The mixture was magnetically stirred under a nitrogen atmosphere for 3 h at room temperature. The standard nonacidic work-up<sup>104</sup> was used and the organic phase dried over anhydrous  $\text{K}_2\text{CO}_3$  to give crude 36. The product was purified by column chromatography over Florisil; TLC over silica gel provided  $R_F=0.72$  using a 9:1, pentane/ethyl acetate mixture; IR 3100, 3070, 3040, 1500, 1450, 730, 695  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ =7.30 (5H, s,  $-\text{C}_6\text{H}_5$ ), 3.72 (2H, s,  $-\text{N-CH}_2\text{-C}_6\text{H}_5$ ), 2.6 (1H, complex m,  $\text{RCH-NR}$ ), 1.23 (22H, d), 0.85 (3H, d,  $\text{CH}_3\text{-R}$ ).

**9-Decen-1-methanesulfonate (37).** Treating 10.00g (64.0 mmol) 9-decen-1-ol with 11.00g (96.0 mmol) methanesulfonyl

chloride in the same manner as in the preparation of 27 provided 12.09g (81% yield) 37, distilling at bp 113-120°C (0.05 mmHg); IR 3080, 1640, 1360, 1180, 970, 940(br), 910  $\text{cm}^{-1}$ .

**1-Iodo-9-decene (39).** Treating 21.92g (93.7 mmol) 37 with 28.08g (187.4 mmol) sodium iodide in the same manner as in the preparation of 28, Procedure A, with stirring for 48 h, provided 23.46g (94% yield) 39; bp 64-69°C (0.1 mmHg); IR 3080, 1640, 1460, 910  $\text{cm}^{-1}$ .

Treating 1.0g (6.4 mmol) 9-decen-1-ol with 1.92g (12.8 mmol) sodium iodide and 1.39g (12.8 mmol) chlorotrimethylsilane in the same manner as in the preparation of 28, Procedure B; provided a mixture of iododecenes 38; IR 960  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  = 5.39 (2H, m, olefinic), 3.78 (2H, t,  $-\text{CH}_2-\text{I}$ ), 2.04-1.31 (4H, complex,  $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$ ), 1.31 (10H, s,  $-(\text{CH}_2)_5-$ ), 0.95 (3H, d,  $\text{CH}_3-$ ).

**1-Nitro-9-decene (40).** Procedure A. Treating 16.38g (61.6 mmol) 39 with 8.50g (123.2 mmol) sodium nitrite, and 1.00g (16.7 mmol) urea in the same manner as in the preparation of 29, Procedure A, provided 6.01g (57% yield) 40 and 4.56g (43% yield) 9-decen-1-ol, with the desired product distilling at 60-70°C (0.1 mmHg); IR 3080, 1640, 1545, 1430, 1375, 910  $\text{cm}^{-1}$ .

Procedure B. Treating 0.25g (0.9 mmol) 39 with 0.13g (1.8 mmol) sodium nitrite in the same manner as in the preparation of 29, Procedure B, provided 66% yield 40 and 33% yield 9-decen-1-ol by GLC analysis.



**Procedure C.** Treating 0.25g (0.9 mmol) **39** with 0.22g (1.4 mmol) silver nitrite<sup>93</sup> in the same manner as in the preparation of **29**, Procedure C, provided 75% yield **40** and 25% yield 9-decen-1-ol by GLC analysis.

**Procedure D.** A mixture containing 3.76g (14.1 mmol) **39**, and 4.49g (28.2 mmol) silver nitrite<sup>93</sup> in 40 mL anhydrous ether was half submerged in a sonic bath and subjected to ultrasound for 3 h. After the work-up in Procedure C, and removal of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 2.01g (77% yield) **40**, bp 70-120°C (0.10 mmHg).

**2(2-Bromoethyl)-5,5-dimethyl-1,3-dioxane (41).** Hydrogen bromide gas was bubbled into a magnetically stirred solution of 78.00g (0.75 mmol) 2,2-dimethyl-1,3-propanediol in 100 mL dichloromethane at 0°C for 0.5 h. Subsequently, 37.76g (0.67 mmol) distilled acrolein was added dropwise while hydrogen bromide gas bubbling was continued over 2 h. The mixture was allowed to warm to room temperature overnight, neutralized with solid NaHCO<sub>3</sub>, and taken up in 150 mL ether. The organic phase was washed (5 X 50 mL) with H<sub>2</sub>O and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. Upon removal of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 131.63g (88% yield) **41**, 60-64°C (0.2 mmHg); IR 2780(w), 2720(w), 2660(w), 1470, 1125, 1020, 970, 905 cm<sup>-1</sup>; <sup>1</sup>H NMR δ = 4.60 (1H, t, J=5 Hz, -O-CHR-O-), 3.69-3.35 (6H, m, Br-CH<sub>2</sub>-; -O-CH<sub>2</sub>-CR-CH<sub>2</sub>-O-), 2.21 (2H, d of t, J=7, and 6 Hz, Br-CH<sub>2</sub>-CH<sub>2</sub>), 1.17 (3H, s, ax -CH<sub>3</sub>), 0.72 (3H, s, eq -CH<sub>3</sub>).

2(4-Penten-3-ol)-5,5-dimethyl-1,3-dioxane (42). A solution of 2.59g (46.0 mmol) distilled acrolein in 80 mL THF was added dropwise to 2(2-magnesium bromoethyl)-5,5-dimethyl-1,3-dioxane (prepared from 10.00g (46.0 mmol) bromodioxane 41 in 100 mL THF and 1.12 (46.0 mmol) magnesium) under a nitrogen atmosphere. The addition of the reagents in both cases were done slowly and carefully such as to evolve the minimum heat. The mixture was stirred for 2.5 h, taken up in ether, washed twice with saturated aqueous  $\text{NH}_4\text{Cl}$ , and dried over anhydrous  $\text{K}_2\text{CO}_3$ . Upon removal of the solvent in vacuo, GLC analysis revealed one major component. Distillation provided 7.92g (88% yield) 42, bp  $85-150^\circ\text{C}$  (0.1 mmHg); IR 3440(br), 3080(w), 2780(w), 2720(w), 2660(w), 1640(w), 1470, 1125, 1010, 975, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  = 5.87 (1H, d of d of d,  $J=18, 10, \text{ and } 6$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.20 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.07 (1H, br d,  $J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.47 (1H, br t,  $-\text{O}-\text{CHR}-\text{O}-$ ), 4.12 (1H, m,  $-\text{CH}(\text{OH})-$ ), 3.50 (4H, m,  $-\text{O}-\text{C}-\text{H}_2-\text{CR}-\text{CH}_2-\text{O}-$ ), 1.73 (4H, m,  $-\text{C}(\text{OH})-(\text{CH}_2)_2-\text{CH}-$ ), 1.18 (3H, s, ax  $-\text{CH}_3$ ), 0.71 (3H, s, eq  $-\text{CH}_3$ ).

2(4-Penten-3-one)-5,5-dimethyl-1,3-dioxane (43). Treating 7.92g (39.6 mmol) enol dioxane 42 with 7.54g (59.4 mmol) oxalyl chloride, 6.19g (79.2 mmol) dimethylsulfoxide, and 23.2g (229.6 mmol) triethylamine in the same manner as in the preparation of 31, Procedure A, provided a nearly quantitative yield of 43 by GLC analysis, and could be isolated by preparative GLC; IR 3100(w), 3030(w), 2780(w),

2720(w), 2660(w), 1700, 1680, 1630, 1470, 1130, 1015, 975, 910  $\text{cm}^{-1}$ .

**2(6-Nitro-14-pentadecen-3-one)-5,5-dimethyl-1,3-dioxane (44)**. Treating 3.05g (16.5 mmol) **40**, and 3.89g (19.5 mmol) enone dioxane **43** with 8.25 mL (8.25 mmol) tetrabutylammonium flouride in the same manner as in the preparation of **32**, provided 5.80g (92% yield) nitroketone **44**. The product was purified by column chromatography over Florisil; TLC over silica gel provided  $R_F=0.13$  using a 9:1, pentane/ether mixture; IR 3080(w), 2780(w), 2720(w), 2660(w), 1715, 1640, 1550, 1470, 1130, 1015, 975, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$ =5.9 (1H, d of d of t,  $J=18, 10, \text{ and } 6$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.0 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.9 (1H, br d,  $J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.40 (1H, complex m,  $\text{CH}-\text{NO}_2$ ), 4.37 (1H, t,  $J=7$  Hz,  $-\text{O}-\text{CHR}-\text{O}-$ ), 3.48 (4H, m,  $-\text{O}-\text{CH}_2-\text{CR}-\text{CH}_2-\text{O}-$ ), 2.51 (2H, br q,  $-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}-$ ), 1.97 (6H, complex m,  $\text{CH}_2-\text{CH}=\text{CH}_2$ ;  $-\text{CH}_2-\text{C}(=\text{O})-\text{CH}_2-$ ), 1.29 (14H, br s), 1.11 (3H, s, ax  $-\text{CH}_3$ ), 0.70 (3H, s, eq  $-\text{CH}_3$ ).

**2-( 8-Nonenyl )-5-( 2-( 5,5-dimethyl-1,3-dioxan-2-yl )) ethyl-1-pyrroline N-oxide (45)**. Treating 1.00g (2.6 mmol) nitroketone **44** with 0.28g (5.2 mmol) ammonium chloride, and 1.35g (20.8 mmol) zinc dust<sup>104</sup> in the same manner as in the preparation of **33**, provided 0.67g (73% yield) nitrone **45**; IR 3080(w), 2780(w), 2720(w), 2660(w), 1640, 1605, 1470, 1130, 1015, 970, 910  $\text{cm}^{-1}$ .

**N-Hydroxy-cis-2-( 8-nonenyl )-5-( 2-( 5,5-dimethyl-1,3-dioxan-2-yl ))ethyl pyrrolidine (46)**. Treating 0.67g (1.9

mmol) nitrene 45 with 3.8 mL (3.8 mmol) diisobutylaluminum hydride in the same manner as in the preparation of 34, provided a quantitative yield of hydroxylamine 46 as a waxy, yellow solid upon removal of the solvent in vacuo, and, having a positive result to the Rogers,<sup>106,107</sup> test; IR 3370(br), 3080(w), 2780(w), 2720(w), 2660(w), 1640, 1470, 1130, 1015, 970, 910  $\text{cm}^{-1}$ .

cis-2-( 8-Nonenyl )-5-( 2-( 5,5-dimethyl-1,3-dioxan-2-yl ))ethyl pyrrolidine (47). Treating 0.74g (2.1 mmol) hydroxylamine 46 with 0.40g (10.5 mmol) lithium aluminum hydride in the same manner as in the preparation of 35, provided 0.60g (86% yield) cis-pyrrolidine 47, using the standard nonacidic work-up<sup>104</sup>. Upon removal of the solvent in vacuo, GLC analysis revealed one major component which could be isolated by preparative GLC; IR 3080(w), 2780(w), 2720(w), 2660(w), 1640, 1460, 1130, 1015, 970, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  =5.9 (1H, d of d of t,  $J=18, 10, \text{ and } 6$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.0 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.9 (1H, br d,  $J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.42 (1H, br t,  $-\text{O}-\text{CHR}-\text{O}-$ ), 3.50 (4H, m,  $-\text{O}-\text{CH}_2-\text{CR}-\text{CH}_2-\text{O}-$ ), 1.97 (2H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 1.63-1.29 (23H, complex), 0.91 (3H, s, ax  $-\text{CH}_3$ ), 0.71 (3H, s, eq  $-\text{CH}_3$ ).

N-Benzyl-cis-2-( 8-nonenyl )-5-( 2-( 5,5-dimethyl-1,3-dioxan-2-yl ))ethyl pyrrolidine (48). Treating 0.22g (0.7 mmol) pyrrolidine 47 with 0.04g (0.3 mmol) 4-dimethylaminopyridine, and 0.18g (1.3 mmol) benzoyl chloride, followed by treating the N-benzoyl derivative with

1.00g (26.3 mmol) lithium aluminum hydride in the same manner as in the preparation of 36, provided the N-benzyl derivative 48 in an unknown quantity. The product was purified by column chromatography over Florisil; TLC over silica gel provided  $R_F=0.77$  using a 9:1, pentane/ethyl acetate mixture; IR 3080(w), 3040(w), 2720(w), 2660(w), 1640, 1470, 1020, 970, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  =7.34 (5H, s,  $-\text{C}_6\text{H}_5$ ), 5.9 (1H, d of d of t,  $J=18, 10, \text{ and } 6$  Hz,  $\text{CH}_2=\text{CH}-$ ), 5.0 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.9 (1H, br d,  $J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.41 (1H, br t,  $-\text{O}-\text{CHR}-\text{O}-$ ), 3.73 (2H, s,  $-\text{N}-\text{CH}_2-\text{C}_6\text{H}_5$ ), 3.49 (4H, m,  $-\text{O}-\text{CH}_2-\text{CR}-\text{CH}_2-\text{O}-$ ), 1.99 (2H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 1.64-1.28 (22H, complex), 0.88 (3H, s, ax  $-\text{CH}_3$ ), 0.70 (3H, s, eq  $-\text{CH}_3$ ).

**Attempted acetal hydrolysis.** GLC & IR analysis of the reaction mixture (obtained by treatment of the cis-pyrrolidine 47 with the acid and under the conditions as indicated) revealed that the starting material was unchanged.

<u>Quantity of 47</u>	<u>Solvent</u>	<u>Acid</u>	<u>Conditions*</u>
0.20g (0.6 mmol)	benzene	0.11 mL 60% $\text{HClO}_4$ ; 0.11 mL EtOAc	3 h; r.t.
0.20g (0.6 mmol)	THF	0.08 mL 50% HOAc	0.5 h; reflux
0.20g (0.6 mmol)	THF	3.00 mL 50% HOAc	3 h; reflux
0.20g (0.6 mmol)	THF	0.06 mL 60% $\text{HClO}_4$	3 h; r.t.
0.20g (0.6 mmol)	THF	0.10 mL 60% $\text{HClO}_4$	5 h; r.t.
0.20g (0.6 mmol)	ethanol	0.22 mL 10% HCl	24 h; r.t.
0.20g (0.6 mmol)	ethanol	0.40 mL 60% $\text{HClO}_4$	24 h; r.t.

0.25g (0.7 mmol) acetone 0.64 mL 10% HCl 3 h; r.t.

0.11g (0.3 mmol) acetone 0.06 mL 50% HCl 3 h; r.t.

\*The solvent and 47 were mixed together and cooled to 0°C prior to the addition of the acid.

**2(4-Penten-3-one)-1,3-dioxolane (50).** Treating 6.12g (38.7 mmol) 2(4-penten-3-ol)-1,3-dioxolane 49 with 7.37g (58.1 mmol) oxalyl chloride, 5.57g (71.3 mmol) dimethylsulfoxide, and 17.42g (172.1 mmol) triethylamine in the same manner as in the preparation of 31, Procedure A, provided a nearly quantitative yield of 50 by GLC analysis, and could be isolated by preparative GLC; IR 1700, 1680, 1615, 1400(w), 1140, 1030, 900 cm<sup>-1</sup>.

**2(6-Nitro-14-pentadecen-3-one)-1,3-dioxolane (51).** Treating 8.98g (48.5 mmol) 40, and 7.57g (48.5 mmol) enone dioxolane 50 with 24.25 mL (24.3 mmol) tetrabutylammonium fluoride in the same manner as in the preparation of 32, provided an unknown quantity of 51. The product was purified by column chromatography over Florisil; TLC over silica gel provided R<sub>F</sub>=0.70 using a 9:1, pentane/ether mixture; IR 3080(w), 1715, 1640, 1550, 1140, 1030, 910 cm<sup>-1</sup>; MS m/z (rel. intensity) 341(1,M), 340(4,M-1), 295(9), 293(7), 142(7), 129(33), 109(8), 101(13), 99(12), 95(15), 87(10), 86(36), 85(33), 83(10), 81(17), 74(9), 73(100), 69(12), 67(17), 57(15), 53(34), 45(25), 43(12), 41(28), 29(14).

**2-( 8-Nonenyl )-5-( 2-( 1,3-dioxolan-2-yl ))ethyl-1-pyrroline N-oxide (52).** Treating 3.04g (8.9 mmol) nitroketone 51 with 0.48g (8.9 mmol) ammonium chloride, and

2.32g (35.8 mmol) zinc dust<sup>104</sup> in the same manner as in the preparation of 52, provided 2.31g (84% yield) 33; IR 3080(w), 1640(w), 1605(w), 1410(w), 1140, 1030, 910(w)  $\text{cm}^{-1}$ .

N-Hydroxy-cis-2-(8-nonenyl)-5-(2-(1,3-dioxolan-2-yl))ethyl pyrrolidine (53). Treating 2.31g (7.5 mmol) nitron 52 with 15 mL (15.0 mmol) diisobutylaluminum hydride in the same manner as in the preparation of 34, provided a crude yield of 2.15g (92% yield) 34, having a positive result for the Rogers,<sup>106,107</sup> test; GLC analysis showed the predominance of the cis isomer; IR 3360(br), 3080(w), 1640(w), 1410(w), 1140, 1030, 910  $\text{cm}^{-1}$ .

2-Nonyn-4-ol (54). A standard solution of 5.2 mL (13.0 mmol) n-butyllithium in hexanes was carefully added by syringe to a magnetically stirred solution containing 50 mL THF and excess propyne cooled to  $-84^{\circ}\text{C}$  (ethyl acetate/ $\text{N}_2$ (l)), under a nitrogen atmosphere and stirred for 15 min. To this solution was added by syringe 1.32g (13.0 mmol) distilled hexanal in 10 mL THF, stirred for 20 min at  $-84^{\circ}\text{C}$  and then allowed to warm to room temperature. Water (40 mL) was added followed by an excess of anhydrous  $\text{K}_2\text{CO}_3$ . The organic phase was decanted and the residue was washed twice with ether. The combined organic phases were dried over anhydrous  $\text{MgSO}_4$ , and the solvent removed in vacuo. GLC analysis revealed a nearly quantitative yield of 54 which could be isolated by preparative GLC; IR 3350(br), 2230(w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  = 4.33 (1H, m, -C C-CH(OH)-), 1.83 (3H, d,  $J=2$  Hz,  $\text{CH}_3$ -C C-), 1.75-1.30 (8H, complex m,  $-(\text{CH}_2)_4-$ ), 0.89

(3H, br t,  $-\text{CH}_3$ ).

Attempted addition of propene to 1-hexanal using lithium diisobutylmethyl-E-1-propenylalunate. A standard solution of 2.0 mL (2.0 mmol) methyllithium in ether was added by syringe to a magnetically stirred solution containing 3.0 mL (3.0 mmol) diisobutylaluminum hydride and excess propyne which had initially been at  $-41^\circ\text{C}$  (acetonitrile/ $\text{N}_2(1)$ ) for 2 h and then warmed to room temperature overnight, under a nitrogen atmosphere. The solution was stirred for 2 h after which 0.30g (3.0 mmol) distilled hexanal was added by syringe at  $-63^\circ\text{C}$  (chloroform/ $\text{N}_2(1)$ ) and allowed to warm to room temperature overnight. The reaction mixture was poured over ice and extracted with ether. The organic phase was washed once with saturated aqueous  $\text{NH}_4\text{Cl}$  and dried over anhydrous  $\text{MgSO}_4$ . Upon removal of the solvent in vacuo, GLC analysis revealed the presence of several components. The major component was identified as 2-nonyl-4-ol by comparison with 54 (GLC retention time, IR,  $^1\text{H}$  NMR).

1-Octene (55). A magnetically stirred solution containing 0.50g (4.5 mmol) 1-octyne and 0.24g (6.4 mmol) lithium aluminum hydride in 2 mL THF was heated to reflux overnight under a nitrogen atmosphere. The standard nonacidic work-up<sup>104</sup> was used and the organic phase dried over  $\text{K}_2\text{CO}_3$ . Upon removal of the solvent in vacuo, GLC analysis revealed a nearly quantitative yield of 55 which could be isolated by preparative GLC; IR 3080(w), 1640, 910  $\text{cm}^{-1}$ ;



$^1\text{H}$  NMR  $\delta$  =5.9 (1H, d of d of t,  $J=18, 10,$  and 6 Hz,  $\text{CH}_2=\text{CH}-$ ), 5.0 (1H, br d,  $J=18$  Hz,  $\text{CH}_2=\text{CH}-$ ), 4.9 (1H, br d,  $J=10$  Hz,  $\text{CH}_2=\text{CH}-$ ), 2.04 (2H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 1.26 (8H, s,  $-(\text{CH}_2)_4-$ ), 0.88 (3H, br t,  $-\text{CH}_3$ ).

Attempted reduction of 9-decen-1-ol using lithium aluminum hydride. Treating 0.50g (3.2 mmol) 9-decen-1-ol with 0.17g (4.5 mmol) lithium aluminum hydride in the same manner as in the preparation 55 provided unchanged starting material as identified by comparison with authentic sample (GLC retention time, IR, and  $^1\text{H}$  NMR).

## CHAPTER 5

### CONCLUSION

The predominant components of the alkaloidal venoms of nearly all the Chelaner species examined have been found to be the (5E,8Z) pyrrolizidines where one of the rings is cis disubstituted. Besides from (5E,8Z)-3-(1-non-8-enyl)-5-(E, 1-prop-1-enyl)pyrrolizidine (1) and (5E,8Z)-3,5-di(hex-5-enyl)pyrrolizidine (16), a third one, identified as 3-allyl-5-(8-nonen-1-yl)pyrrolizidine, whose stereochemistry remains undetermined, is suspected to be an isomer of 1.<sup>22</sup> Until now, there has been no generally applicable methodology to prepare a cis-2,5-disubstituted pyrrolidine.

Herein, we have reported the first stereoselective synthesis of cis-2,5-disubstituted pyrrolidines. It is amenable to acid sensitive functional groups and is convergent thereby allowing a variety of side chain precursors to be incorporated with ease. Focus of the synthesis is on the stereoselective reduction of an appropriate, versatile N-oxide-1-pyrroline. The indisputable conformation of the stereoselectivity has been shown by GLC analysis of 2-butyl-5-heptylpyrrolidine and 2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl))ethyl pyrrolidine under conditions that are

capable of separating a cis/trans mixture of isomers, as well as by  $^1\text{H}$  NMR studies of the N-benzyl derivatives.

Since the 5,5-dimethyl-1,3-dioxane acetal protecting group proved to be intractable, the synthesis using a 1,3-dioxolane acetal protecting group was initiated and carried through the cis-N-hydroxy pyrrolidine stage. The stereochemistry of the new pyrrolidine was suggested by GLC analysis.

Once the methodology for the stereoselective synthesis of 1 is established, the convergent step can be utilized as a point for facile changing of the initial side chain. For example, the synthesis of 16 would commence with 6-heptenol and proceed in an analogous fashion.

The ultimate goal of this work, as mentioned previously, would be to gain a useful understanding of the role of (5E,8Z) pyrrolizidines as pheromones and allomones along with their possible taxonomic relationships in the Myrmecine ants.

## CHAPTER 6

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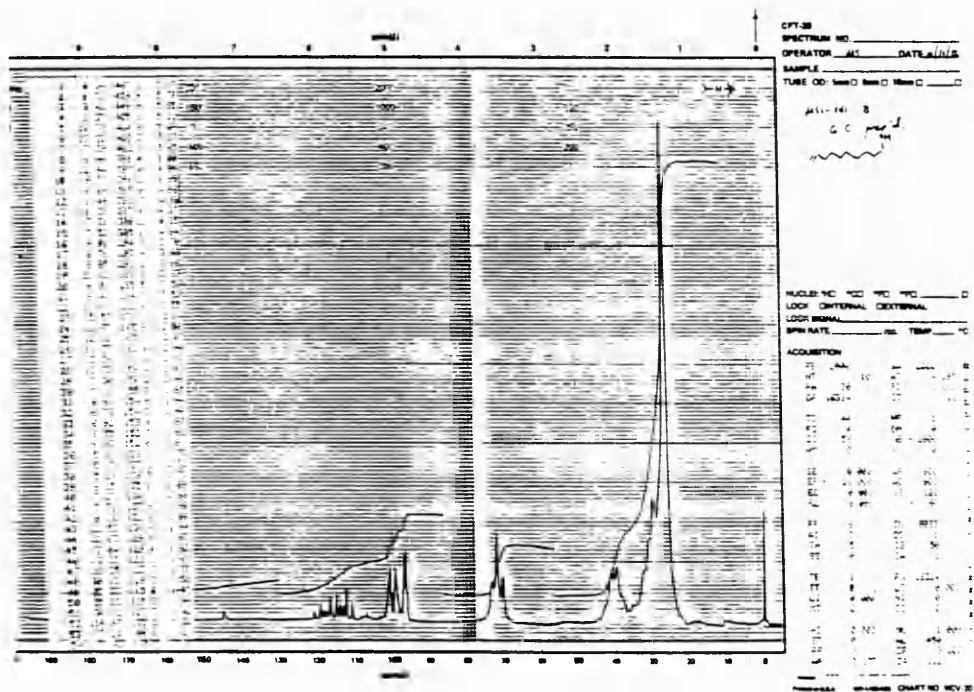
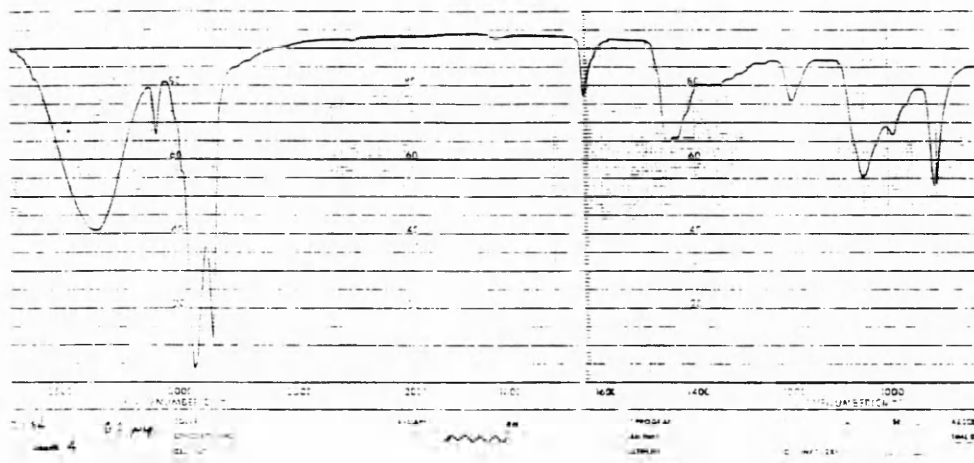
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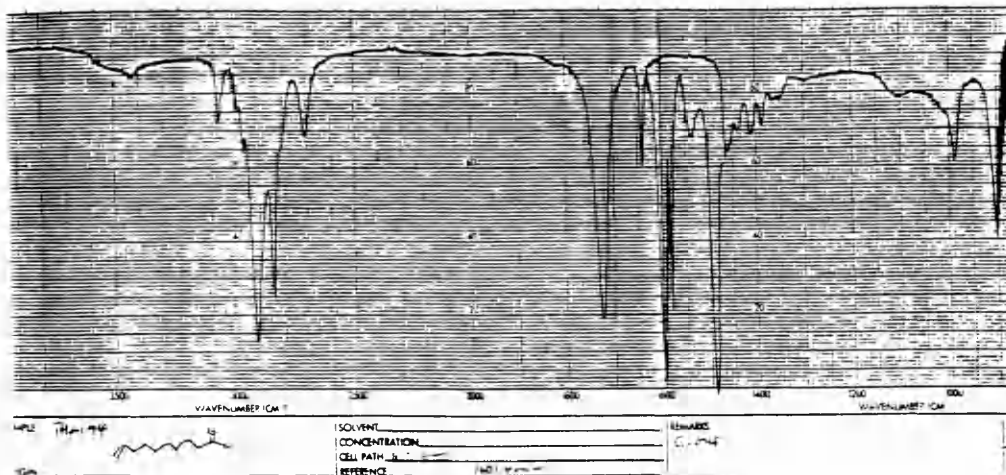
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# APPENDIX

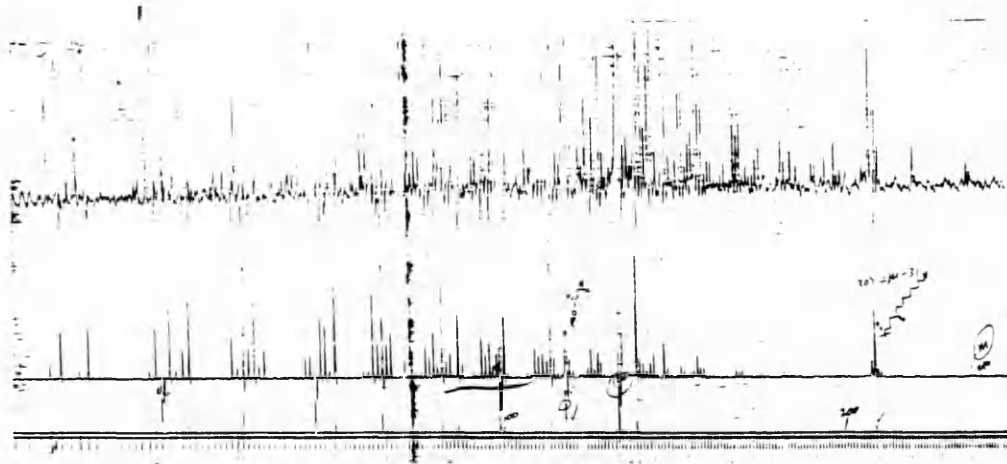
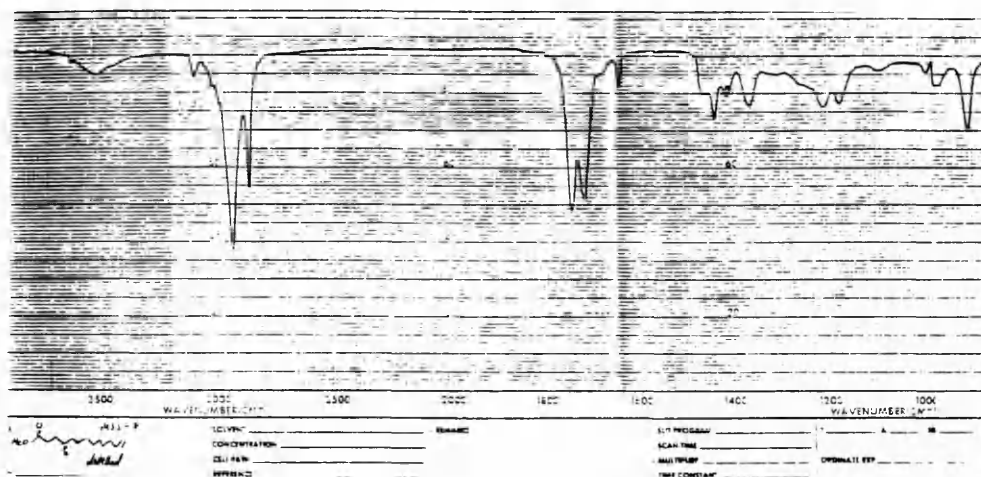
9-Decen-1-ol.



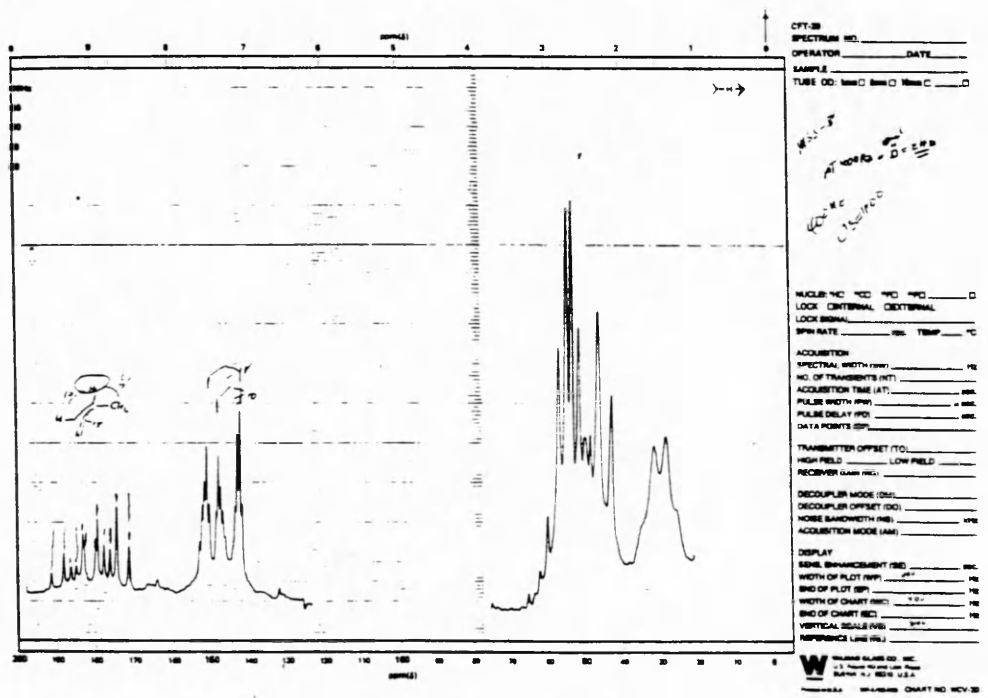
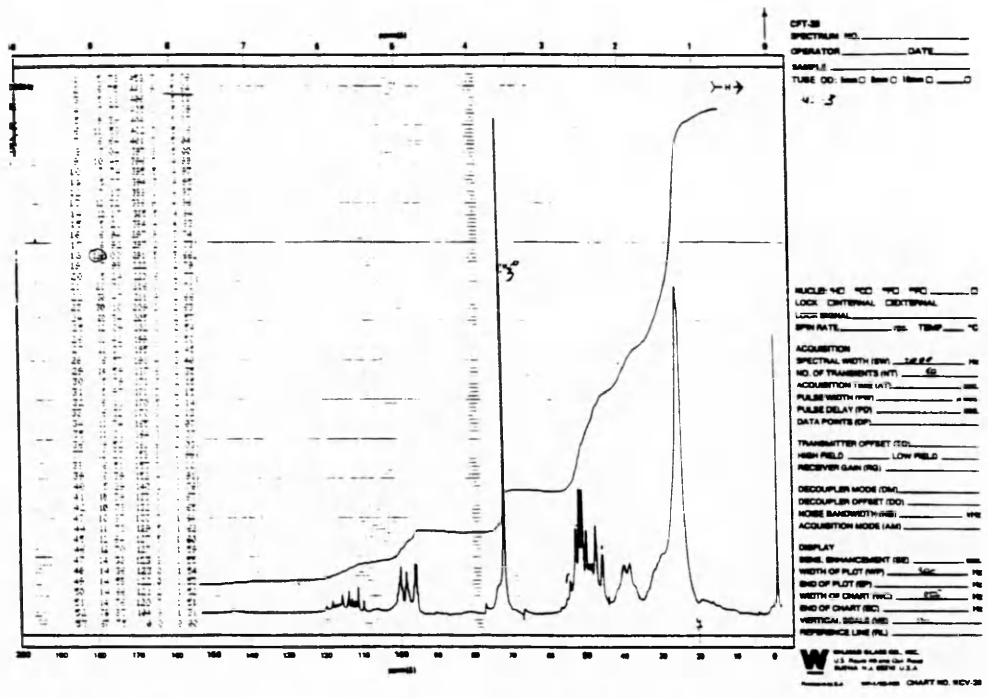
9-Decen-1-al.



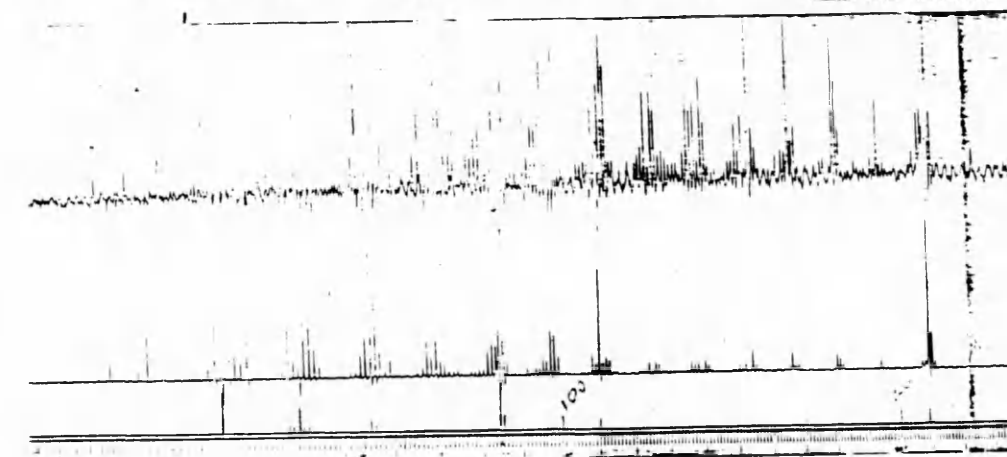
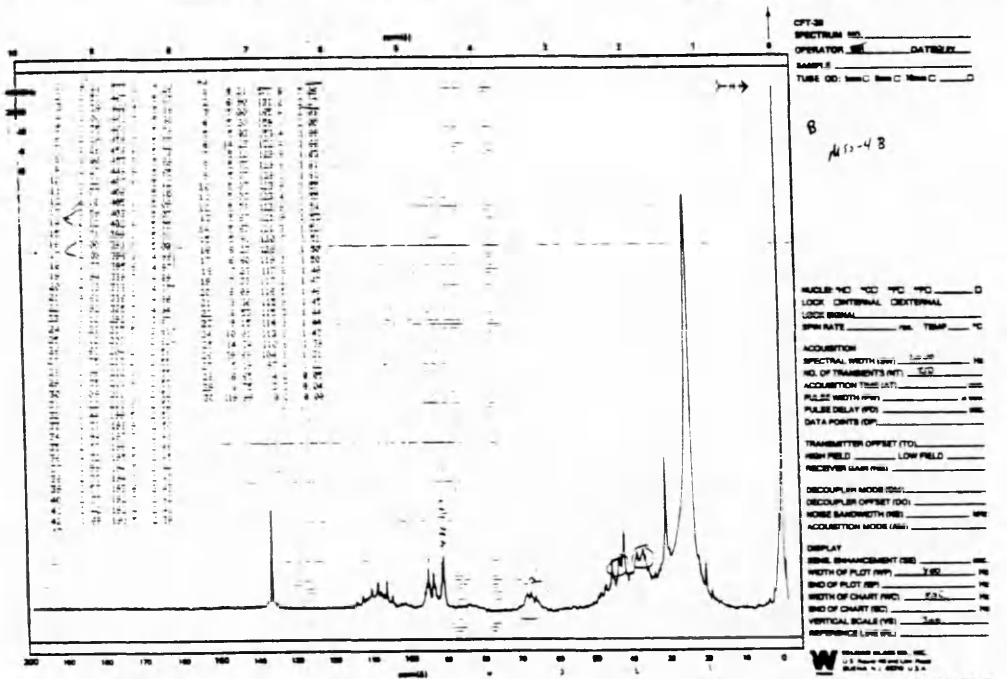
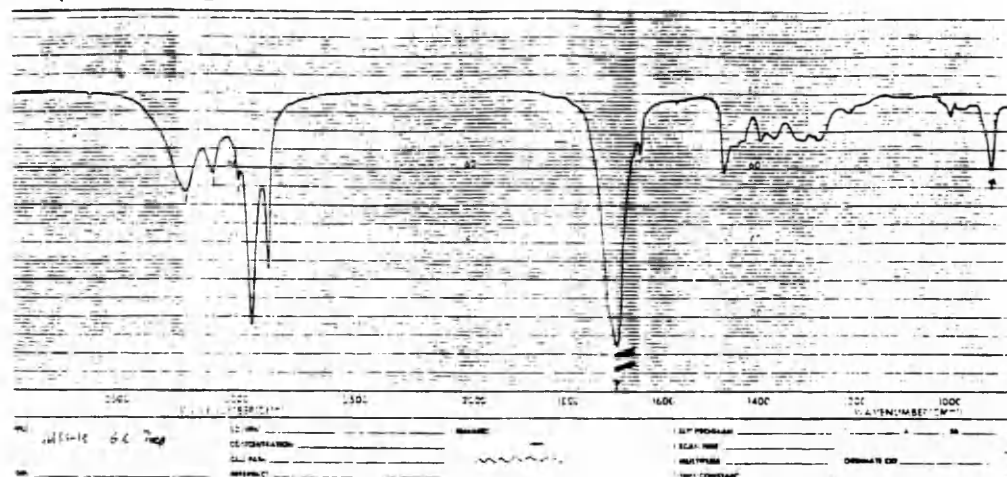
Methyl-4-oxo-12-tridecenoate.



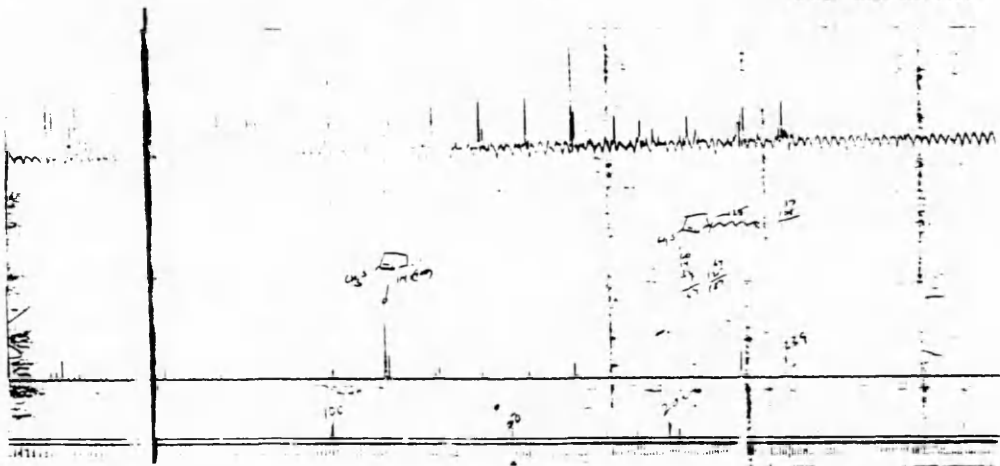
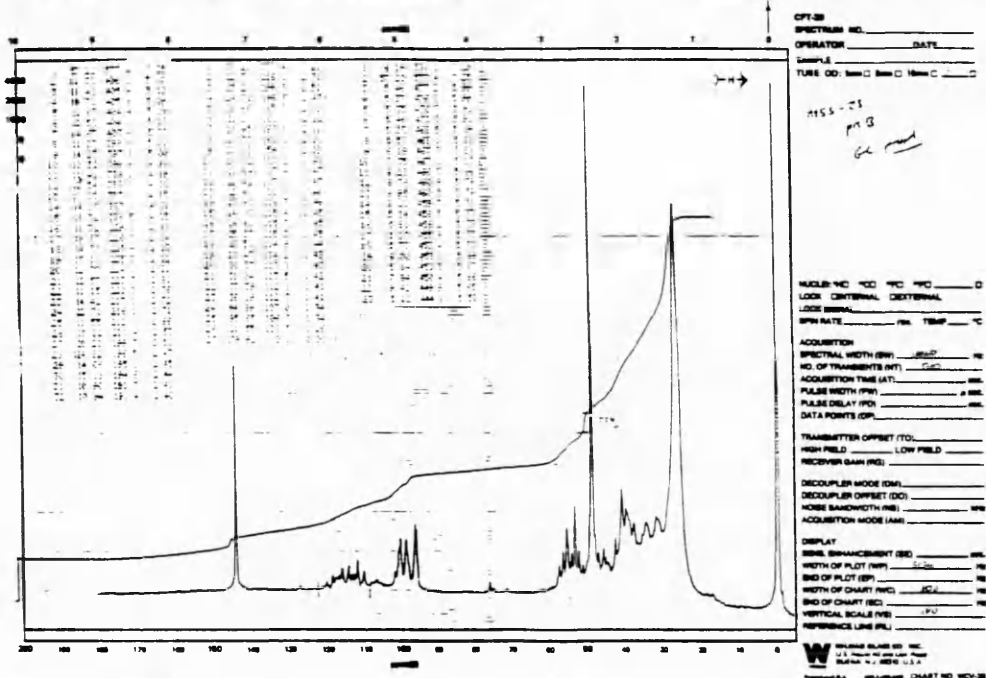
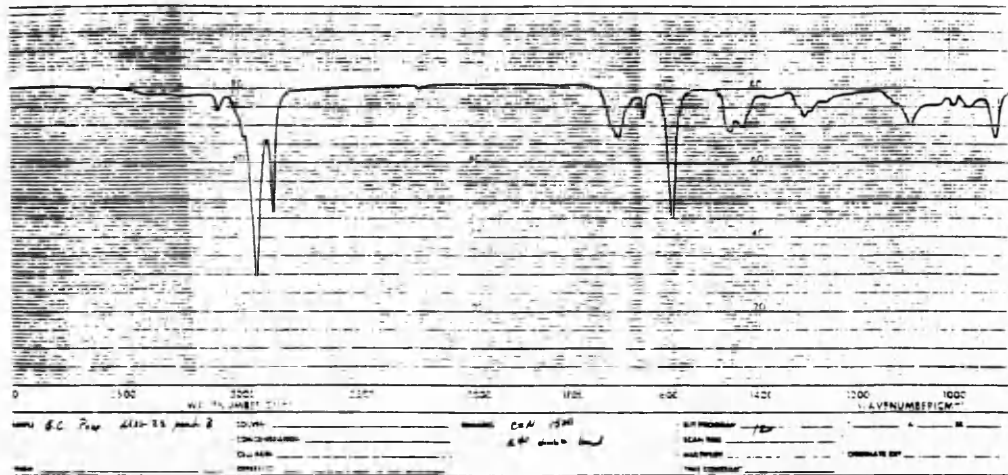
Methyl-4-oxo-12-tridecenoate (cont'd.).



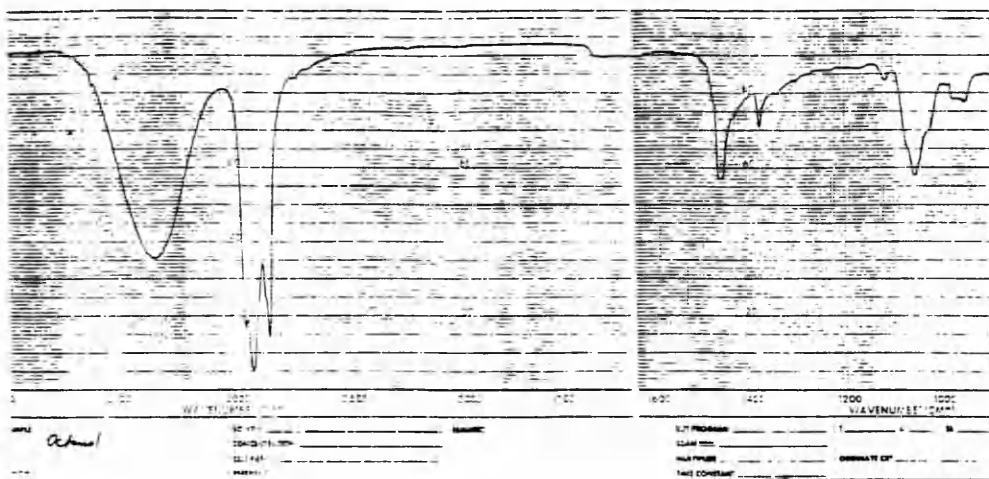
5-(8-Nonenyl)-2-pyrrolidone.



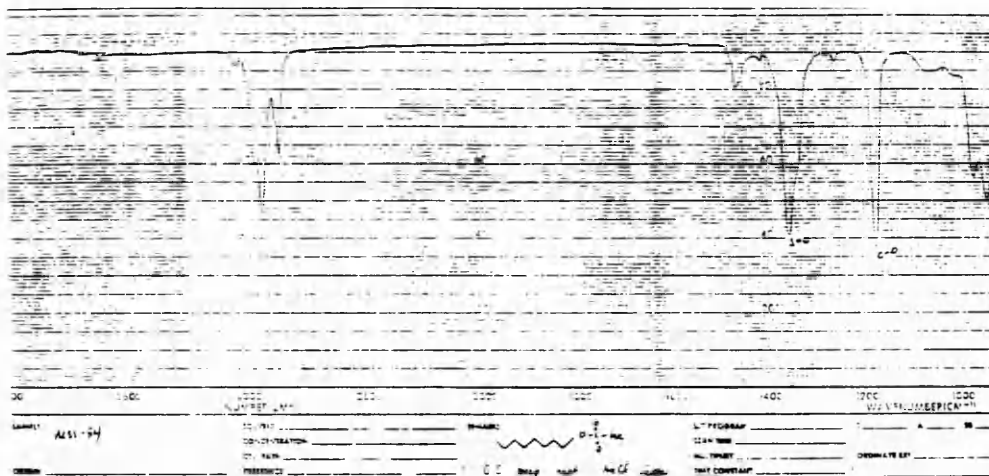
5-(8-Nonenyl)-2-thiomethyl-1-pyrroline.



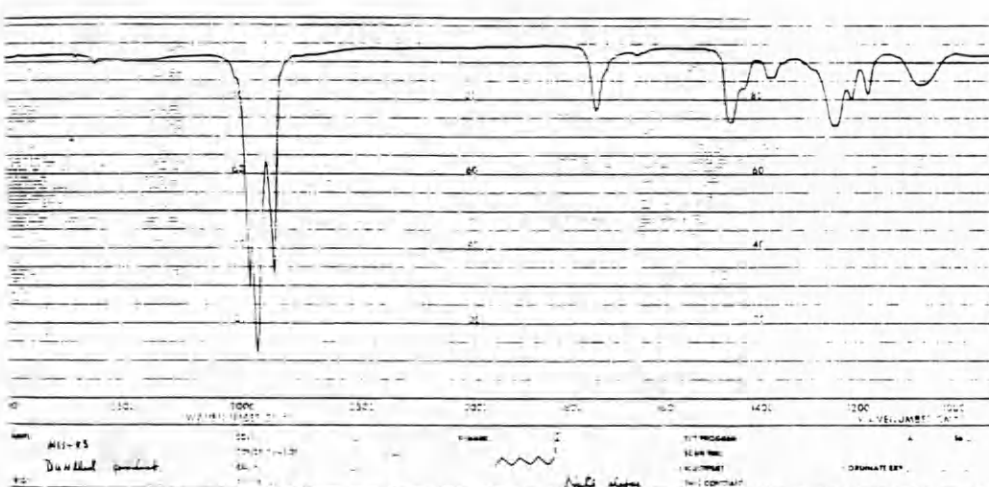
1-Octanol.



1-Octylmethanesulfonate.

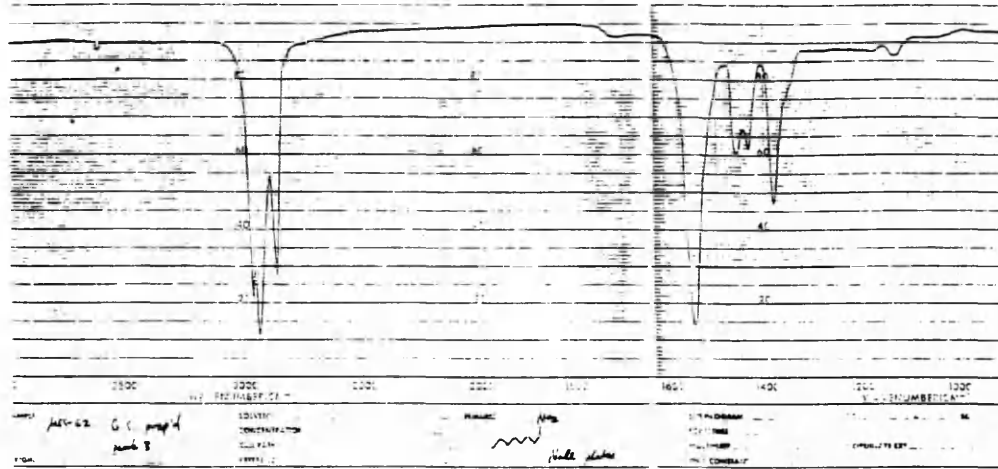


1-Iodooctane.

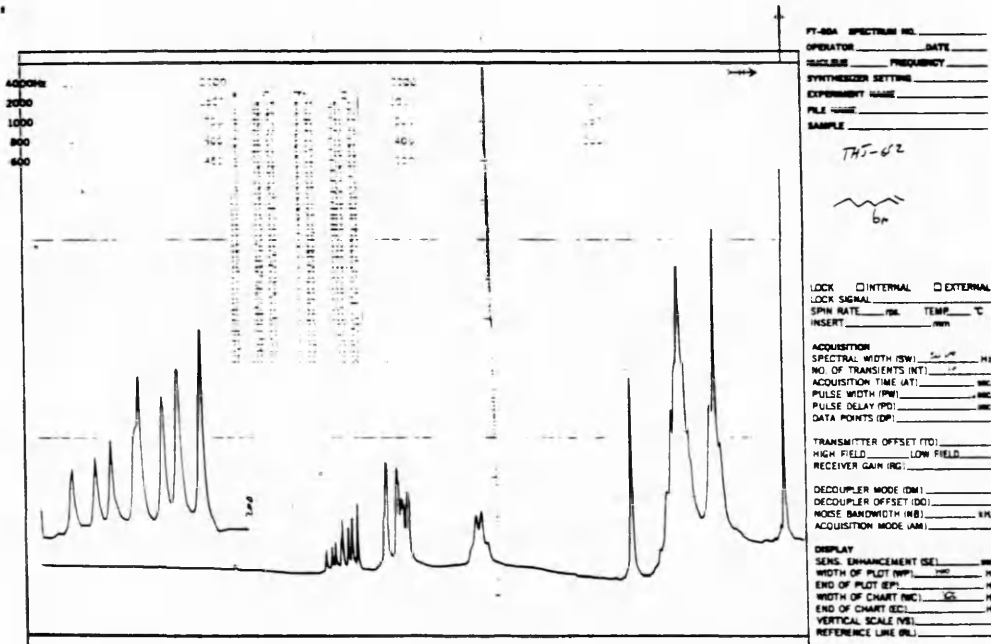
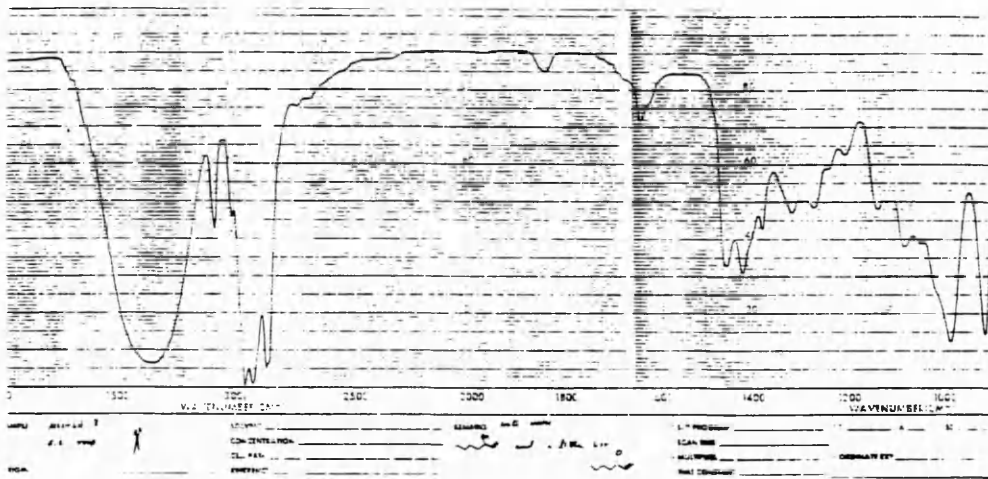




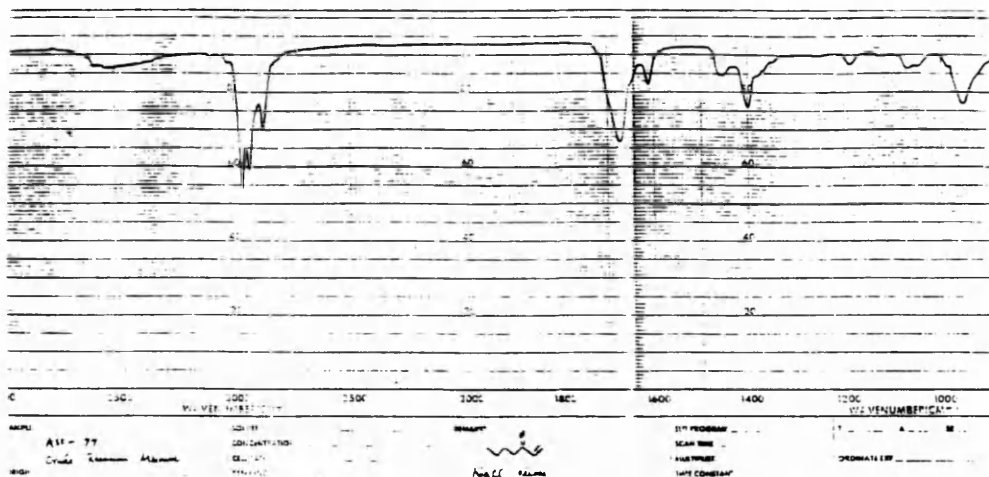
1-Nitrooctane.



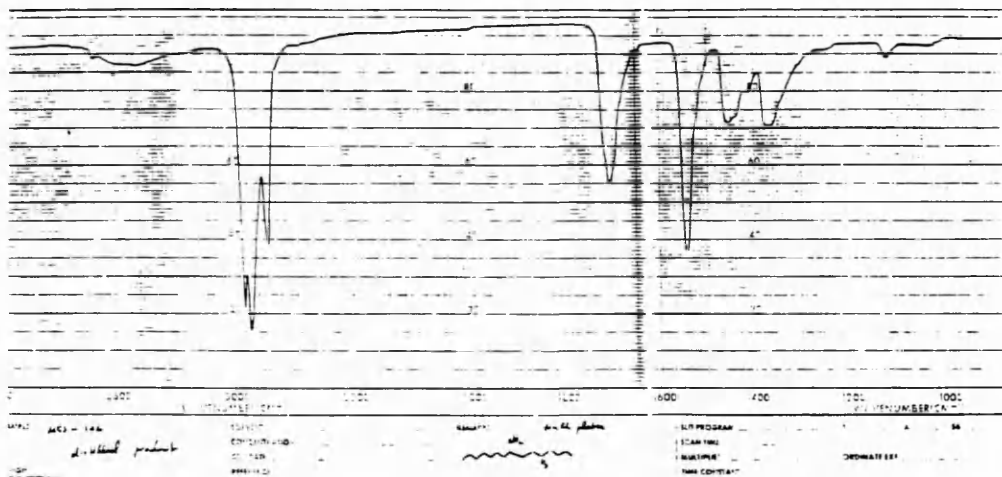
1-Hepten-3-ol.



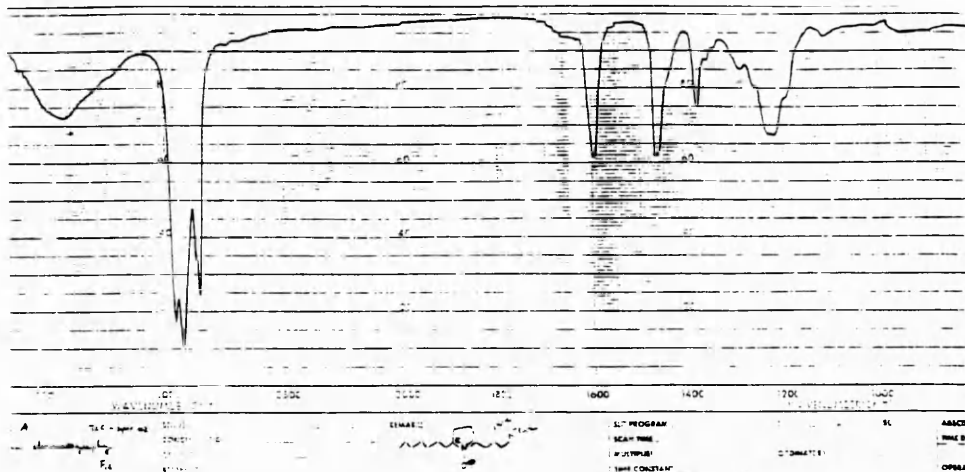
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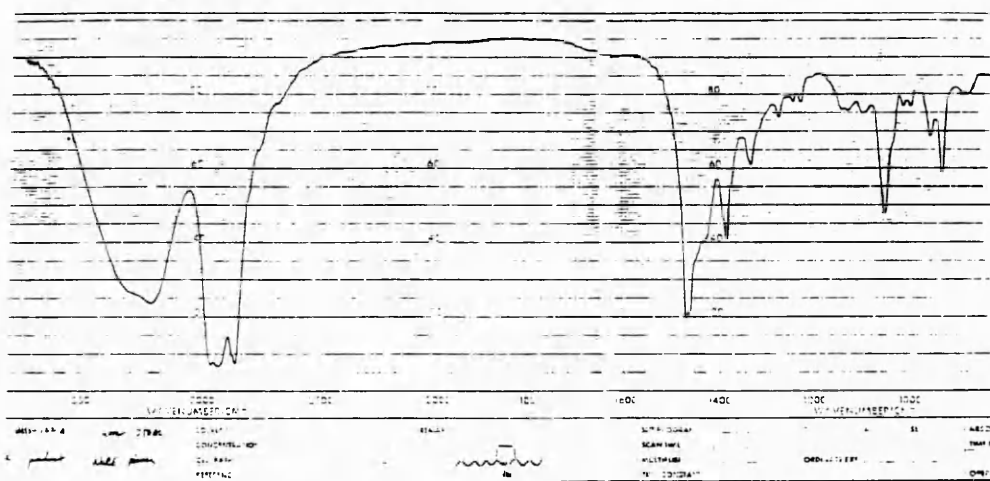
8-Nitro-5-pentadecanone.



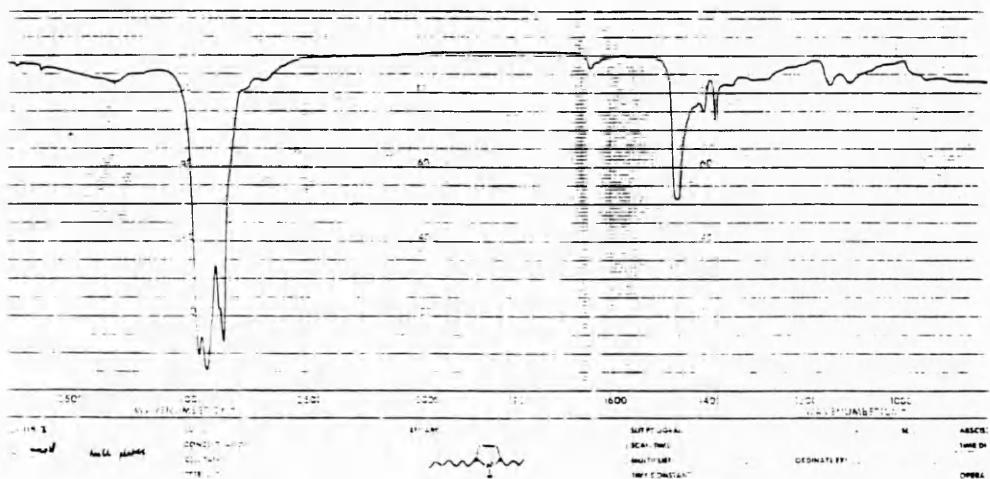
2-Butyl-5-heptyl-1-pyrroline N-oxide.



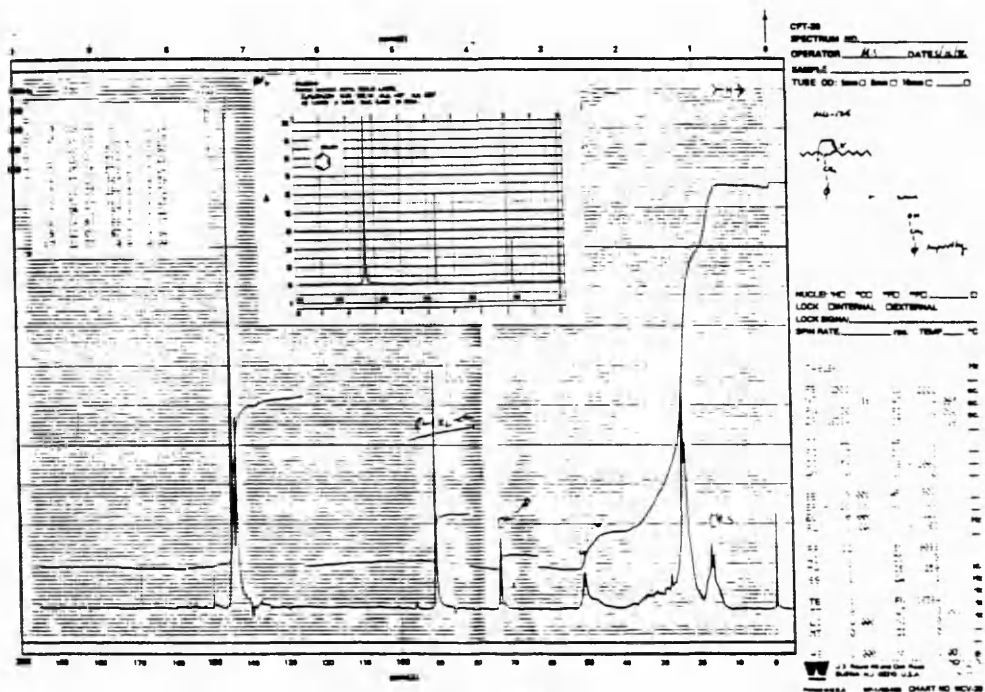
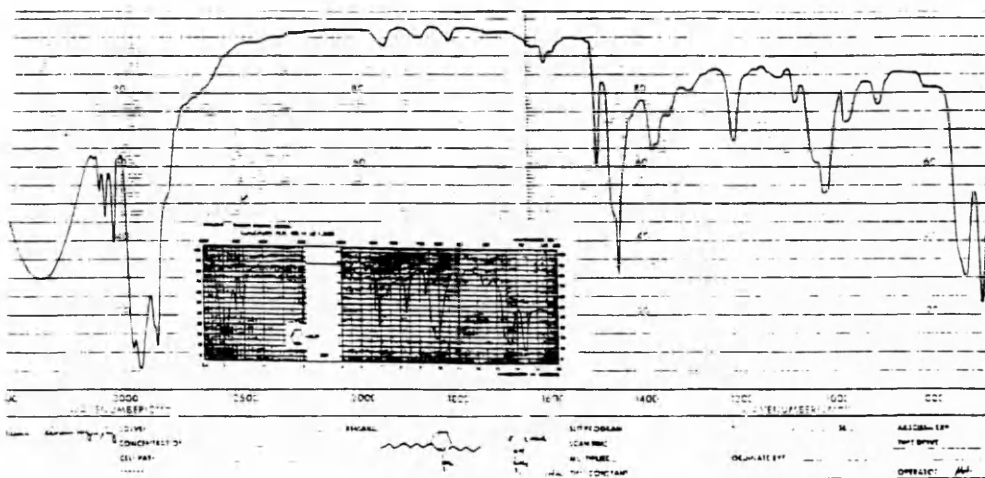
N-Hydroxy-cis-2-butyl-5-heptylpyrrolidine.



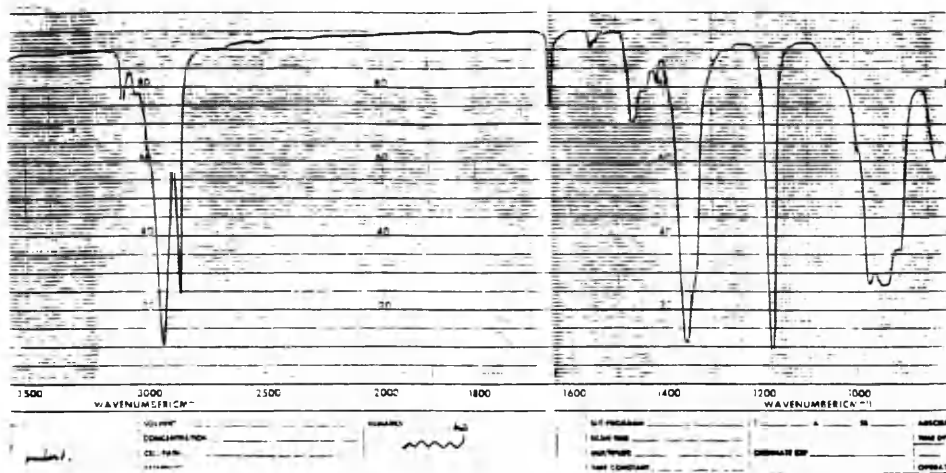
cis-2-Butyl-5-heptylpyrrolidine.



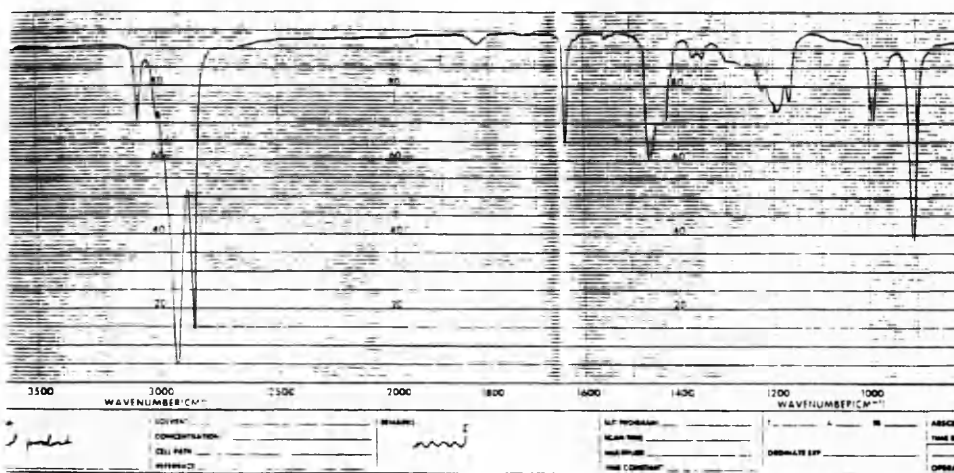
N-Benzyl-cis-2-butyl-5-heptylpyrrolidine.



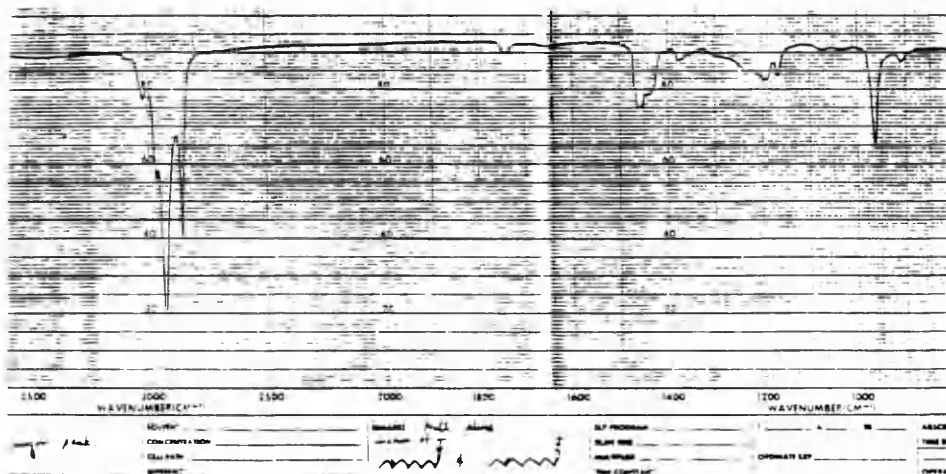
9-Decen-1-methanesulfonate.



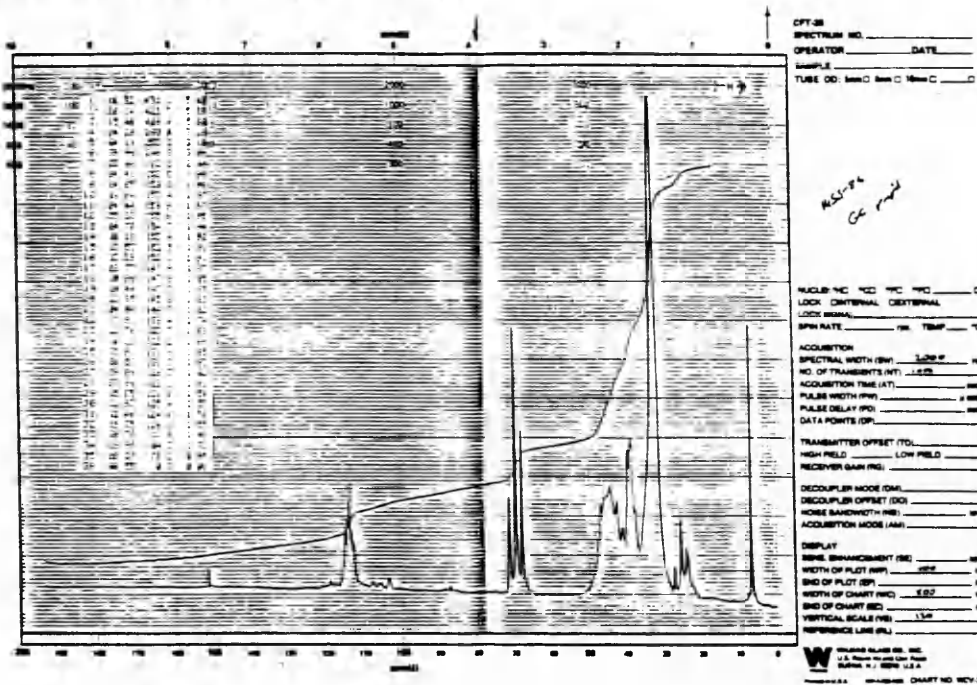
1-Iodo-9-decene.



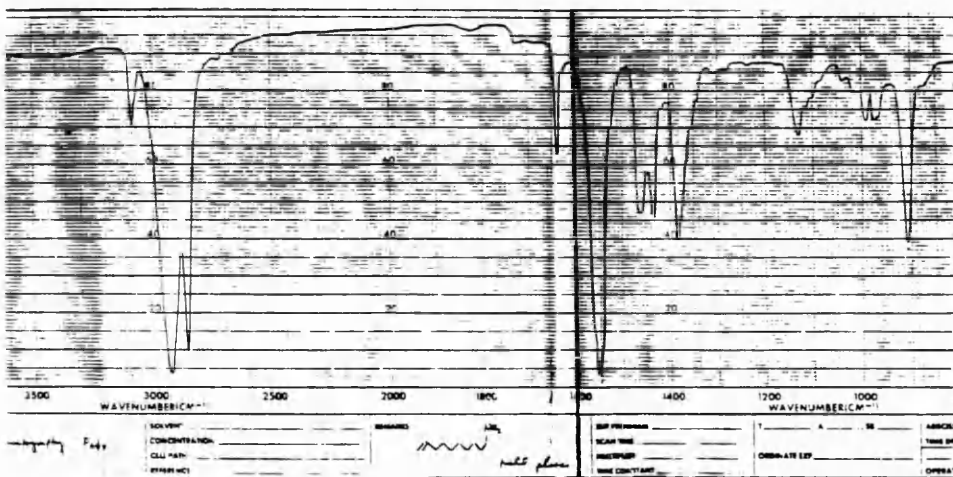
1-Iododecenes.



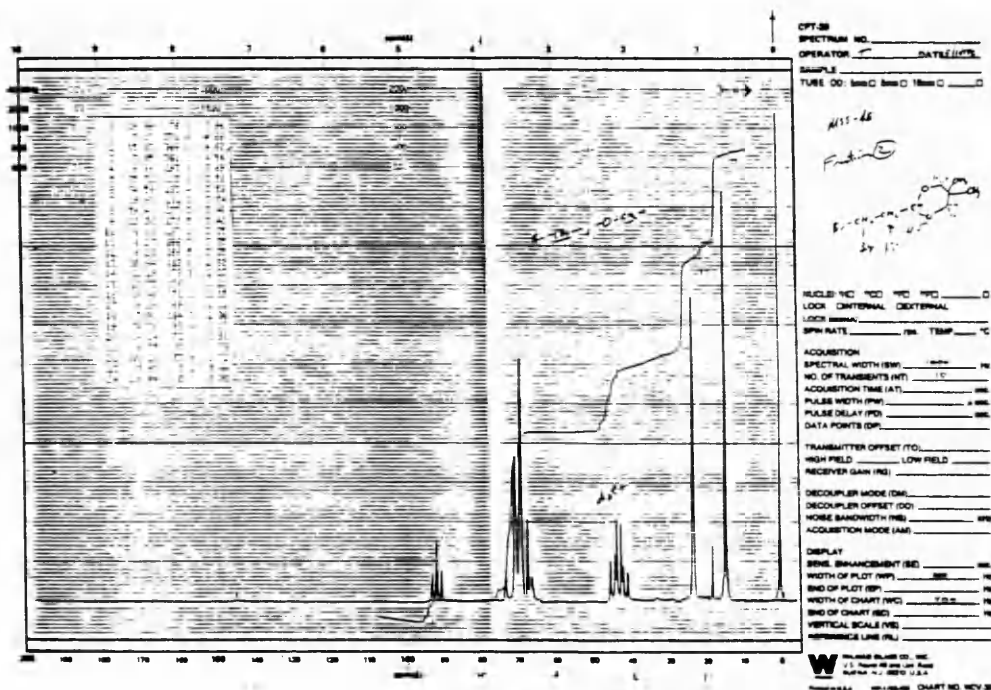
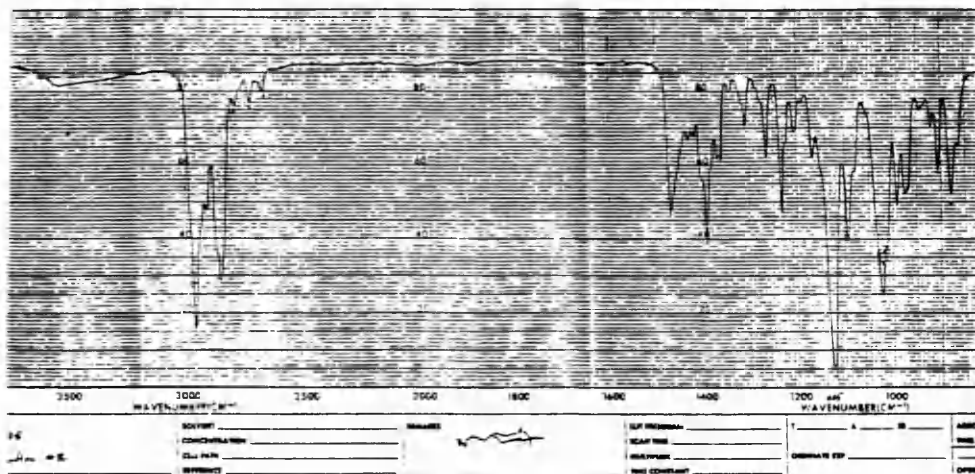
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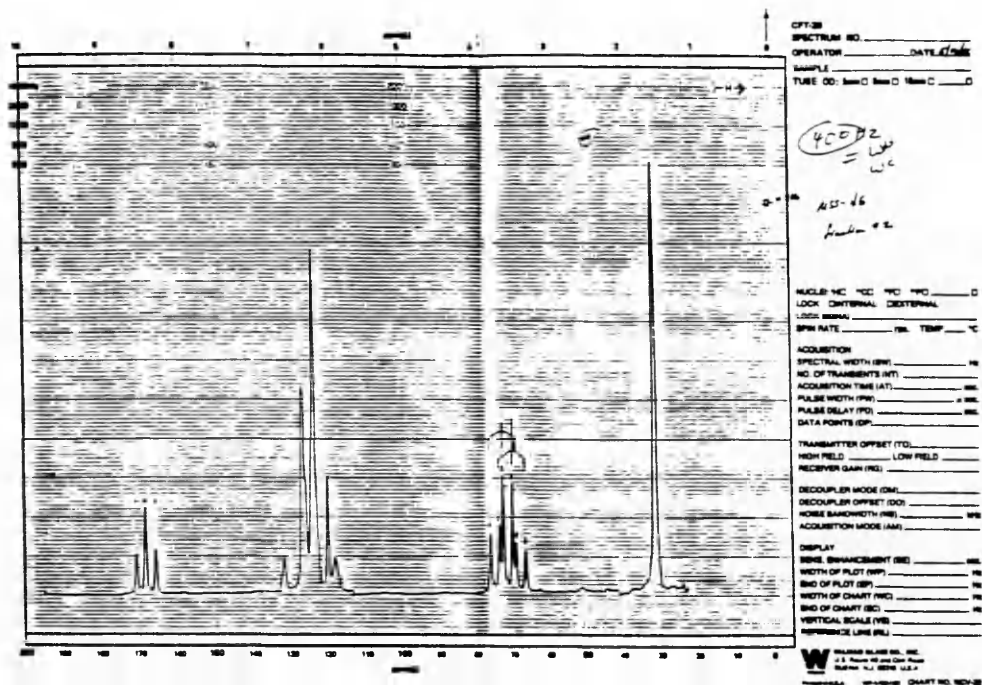
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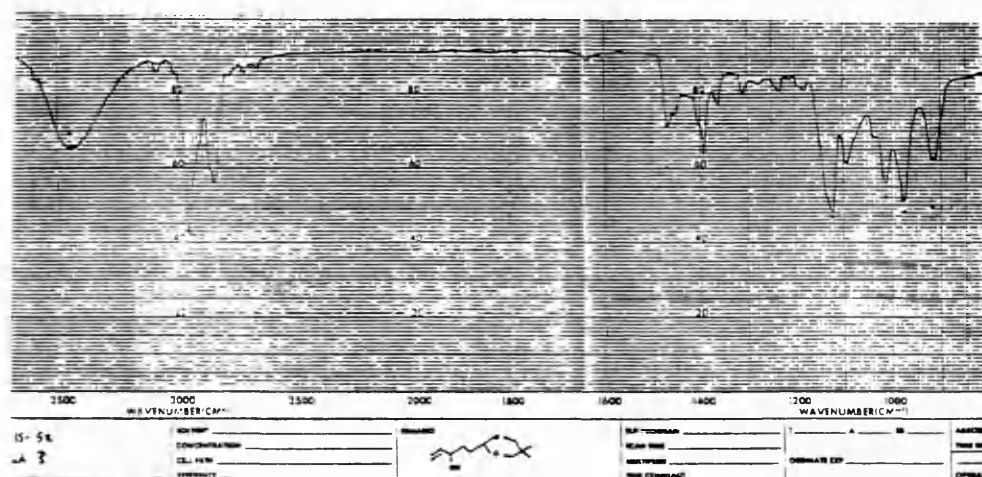
2(2-Bromoethyl)-5,5-dimethyl-1,3-dioxane.



2(2-Bromoethyl)-5,5-dimethyl-1,3-dioxane (cont'd).

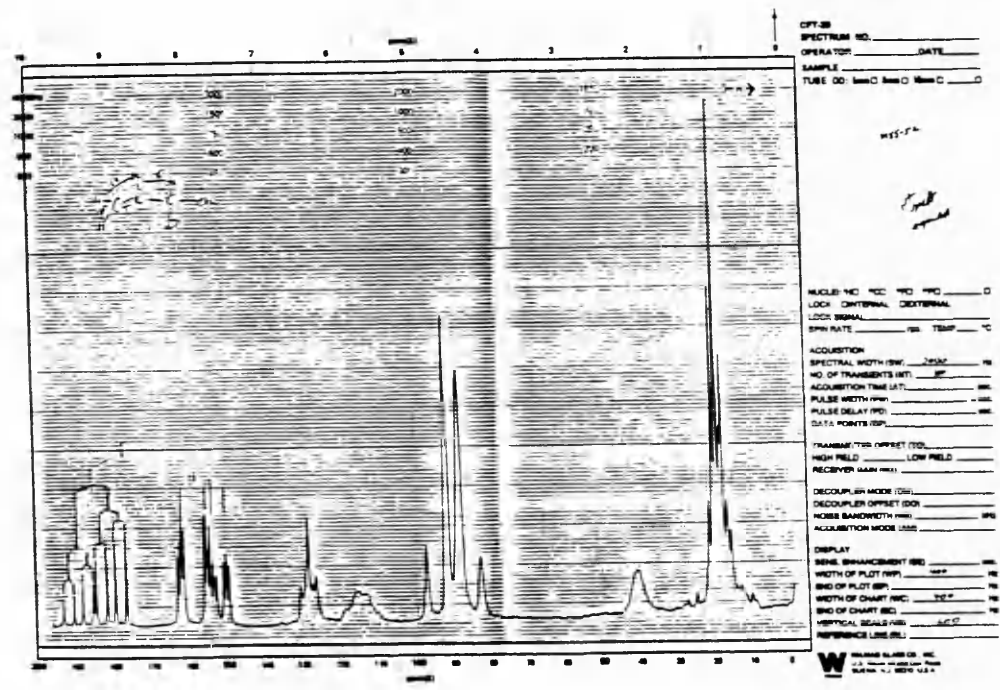
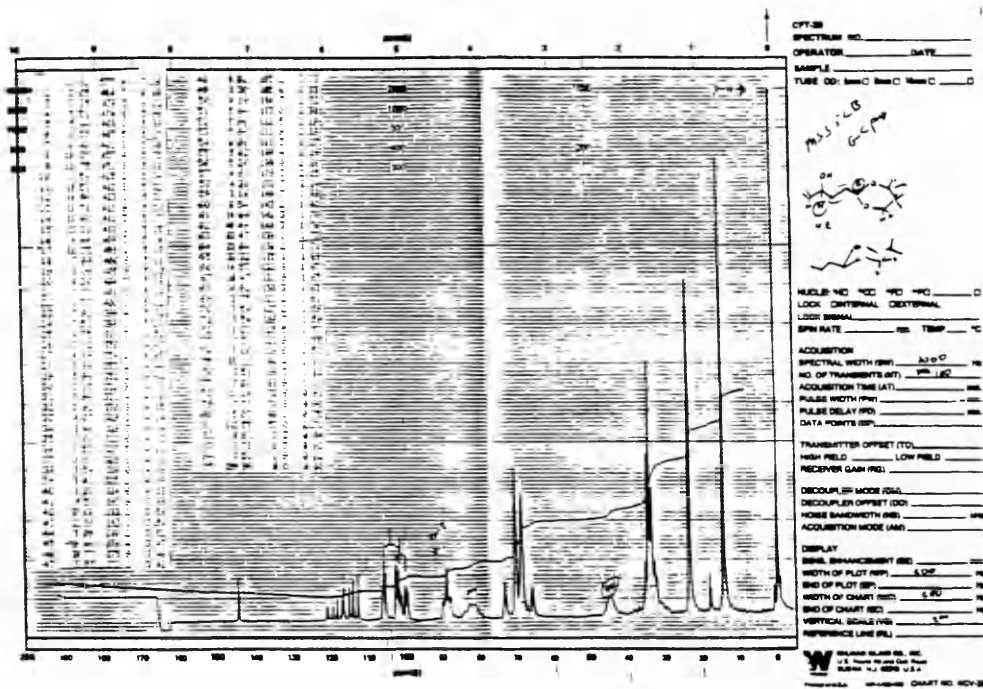


2(4-Penten-3-ol)-5,5-dimethyl-1,3-dioxane.

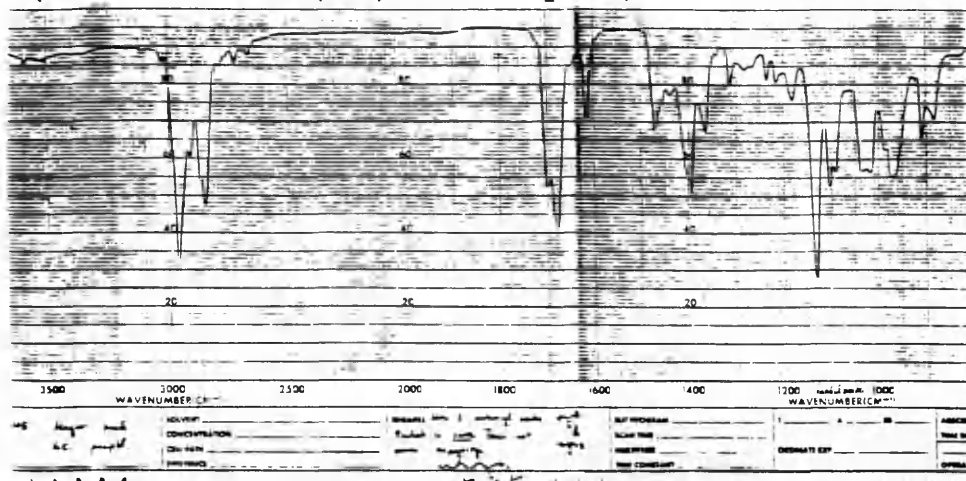




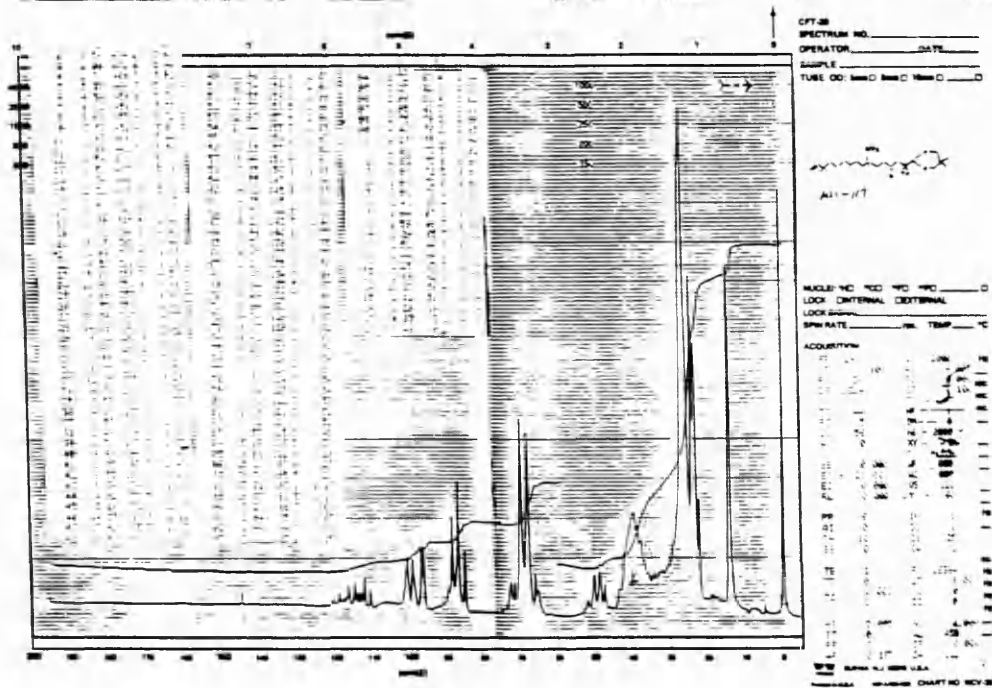
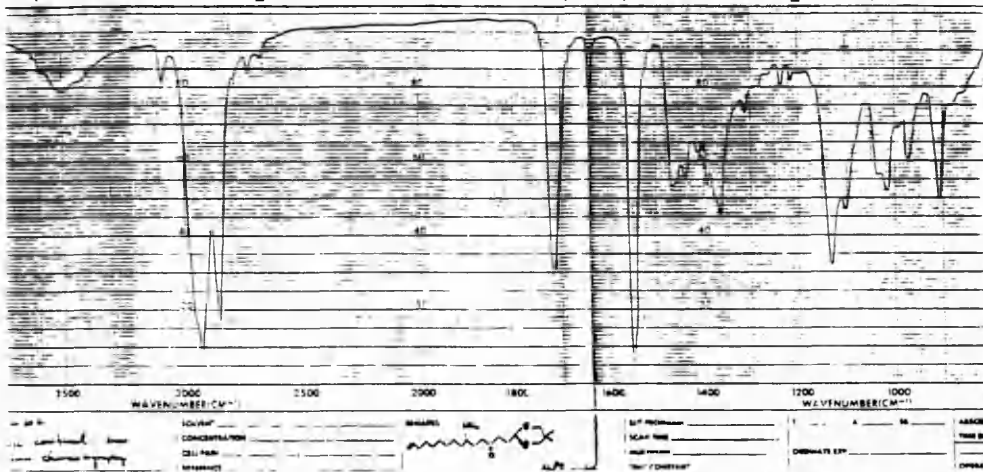
2(4-Penten-3-ol)-5,5-dimethyl-1,3-dioxane (cont'd).



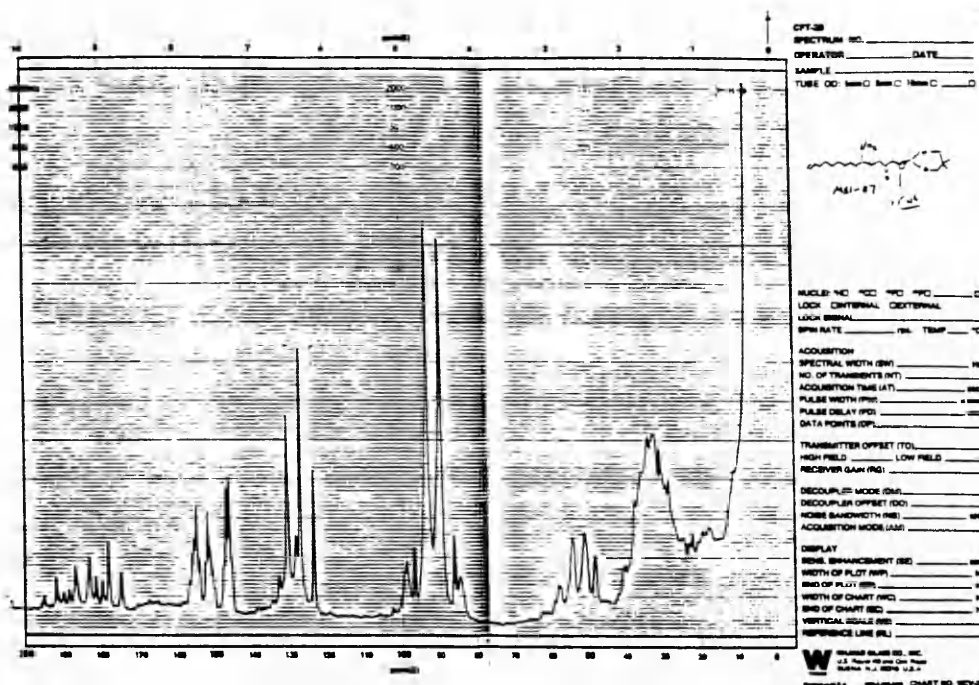
2(4-Penten-3-one)-5,5-dimethyl-1,3-dioxane.



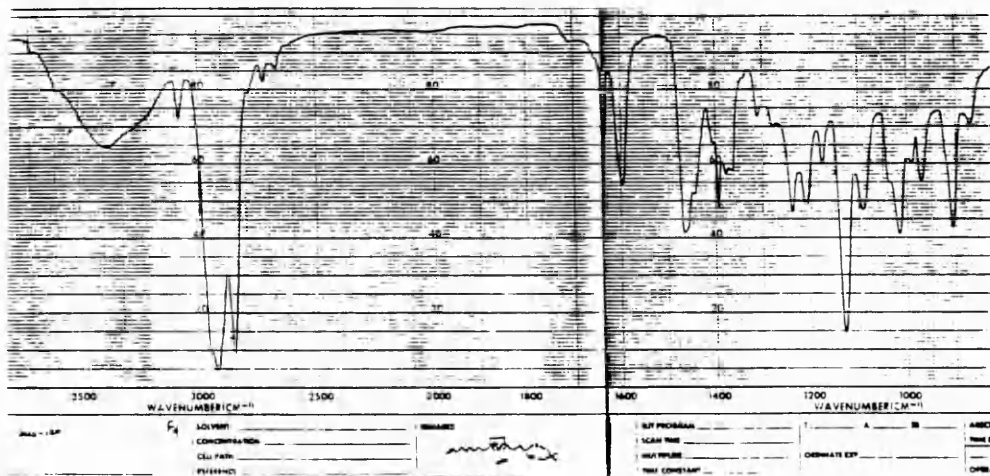
2(6-Nitro-14-pentadecen-3-one)-5,5-dimethyl-1,3-dioxane.



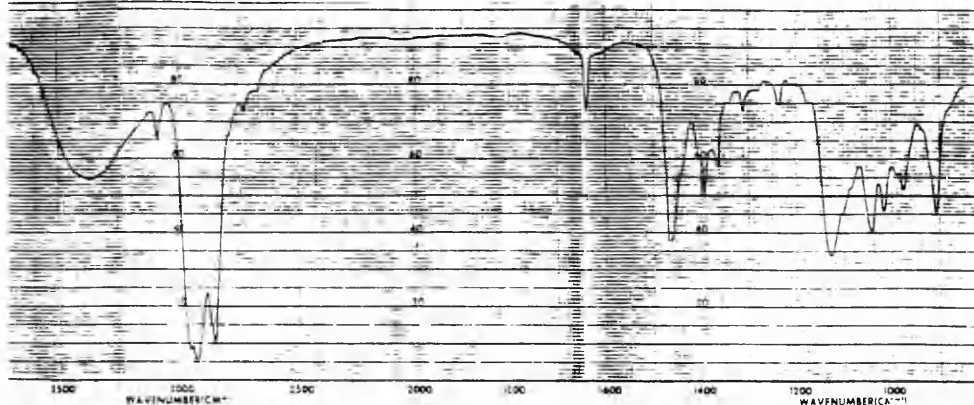
2-(6-Nitro-14-pentadecen-3-one)-5,5-dimethyl-1,3-dioxane (cont'd).



2-(8-Nonenyl)-5-(2(5,5-dimethyl-1,3-dioxan-2-yl))ethyl-1-pyrroline N-oxide.

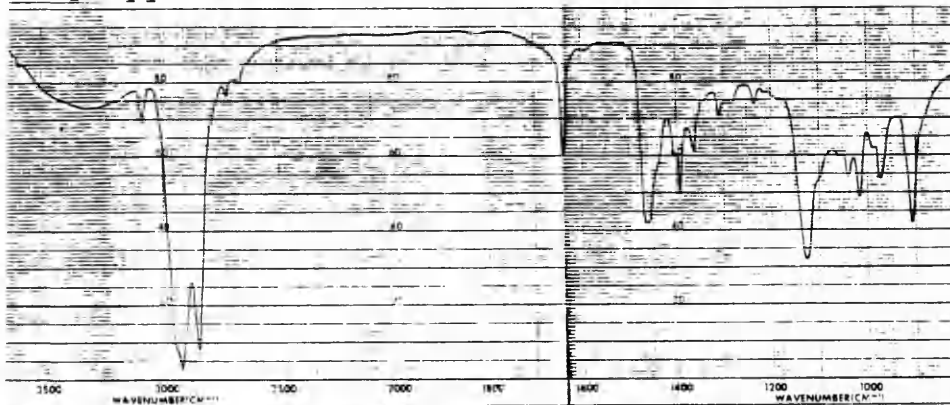


N-Hydroxy-cis-2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl pyrrolidine.

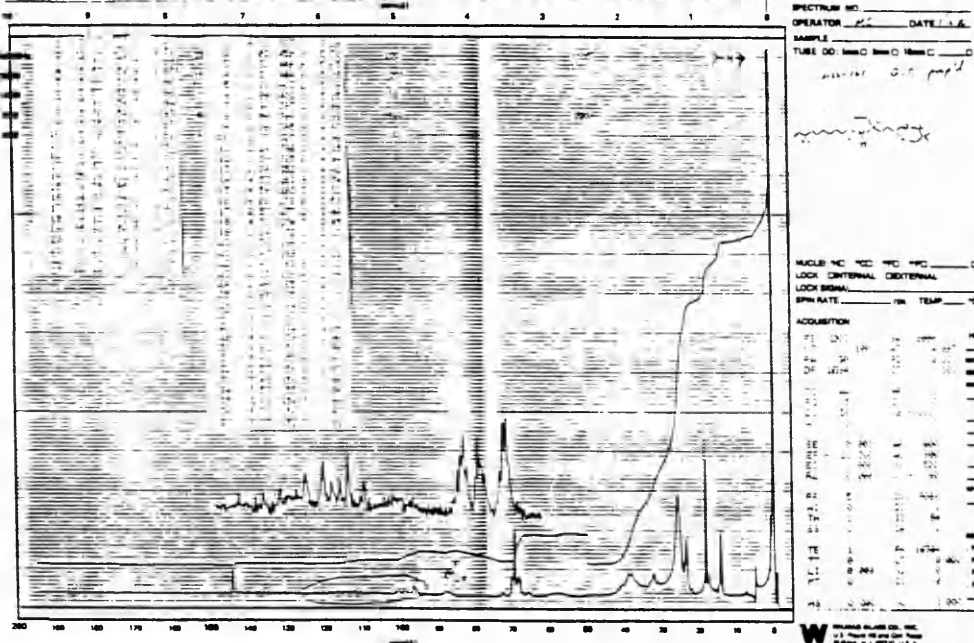


1500 WAVENUMBER (CM<sup>-1</sup>)  
 1000 WAVENUMBER (CM<sup>-1</sup>)  
 7500 WAVENUMBER (CM<sup>-1</sup>)  
 7000 WAVENUMBER (CM<sup>-1</sup>)  
 1800 WAVENUMBER (CM<sup>-1</sup>)  
 1600 WAVENUMBER (CM<sup>-1</sup>)  
 1400 WAVENUMBER (CM<sup>-1</sup>)  
 1200 WAVENUMBER (CM<sup>-1</sup>)  
 1000 WAVENUMBER (CM<sup>-1</sup>)

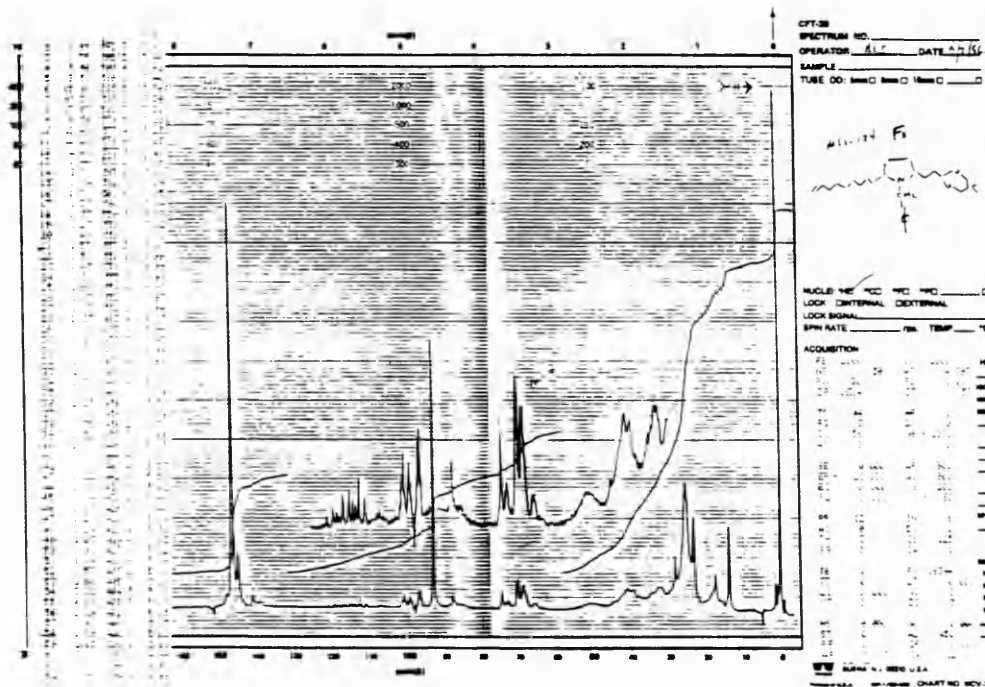
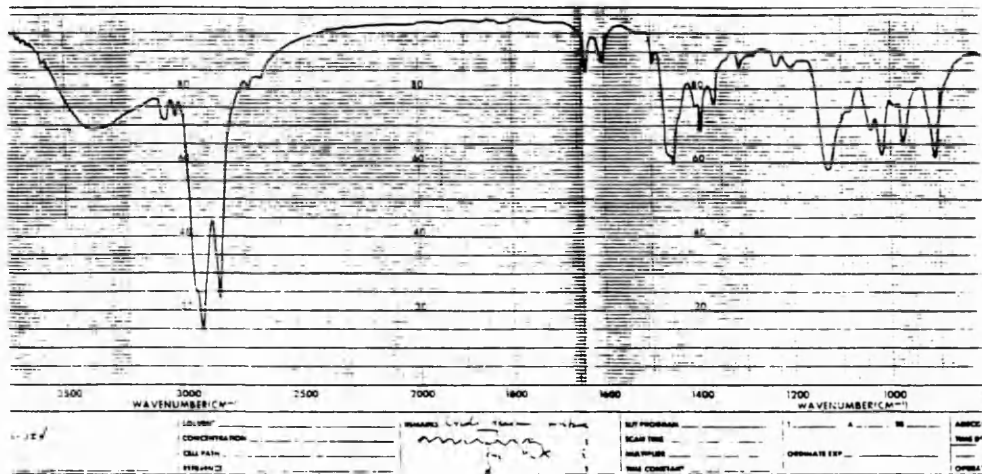
cis-2-(8-Nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl pyrrolidine.



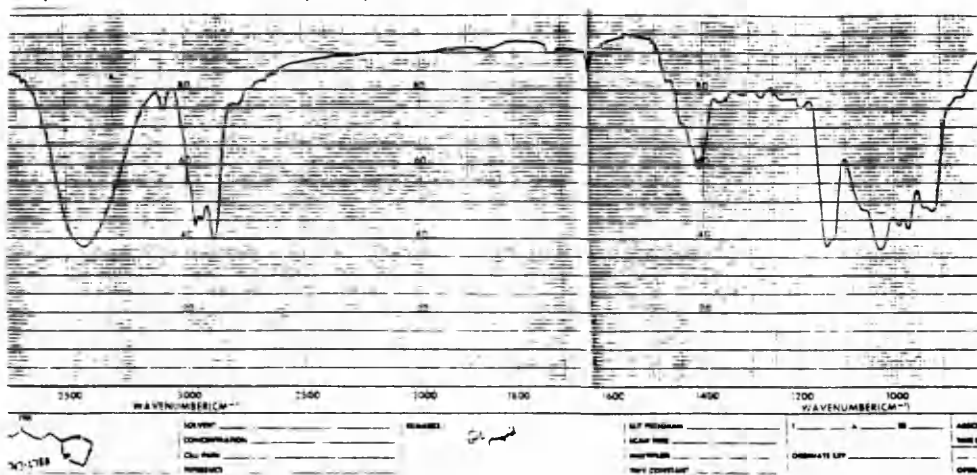
1500 WAVENUMBER (CM<sup>-1</sup>)  
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 7500 WAVENUMBER (CM<sup>-1</sup>)  
 7000 WAVENUMBER (CM<sup>-1</sup>)  
 1800 WAVENUMBER (CM<sup>-1</sup>)  
 1600 WAVENUMBER (CM<sup>-1</sup>)  
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 1000 WAVENUMBER (CM<sup>-1</sup>)



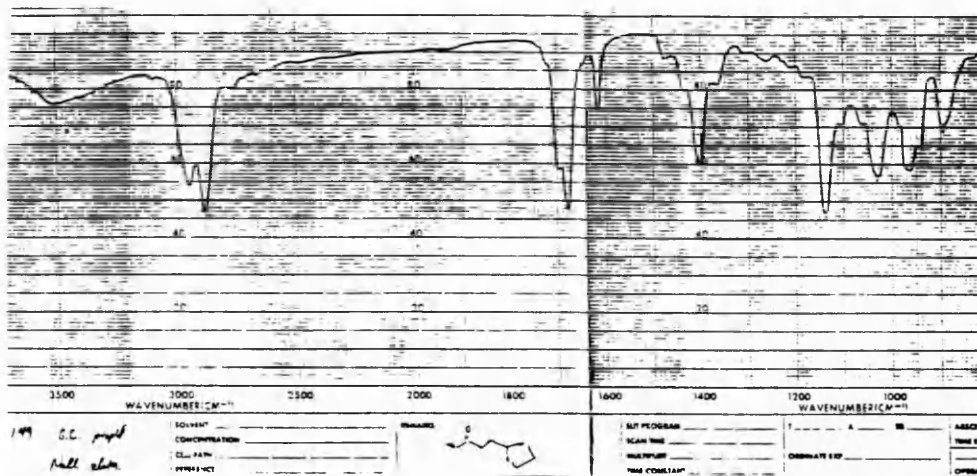
N-Benzyl-cis-2-(8-nonenyl)-5-(2-(5,5-dimethyl-1,3-dioxan-2-yl))ethyl pyrrolidine.



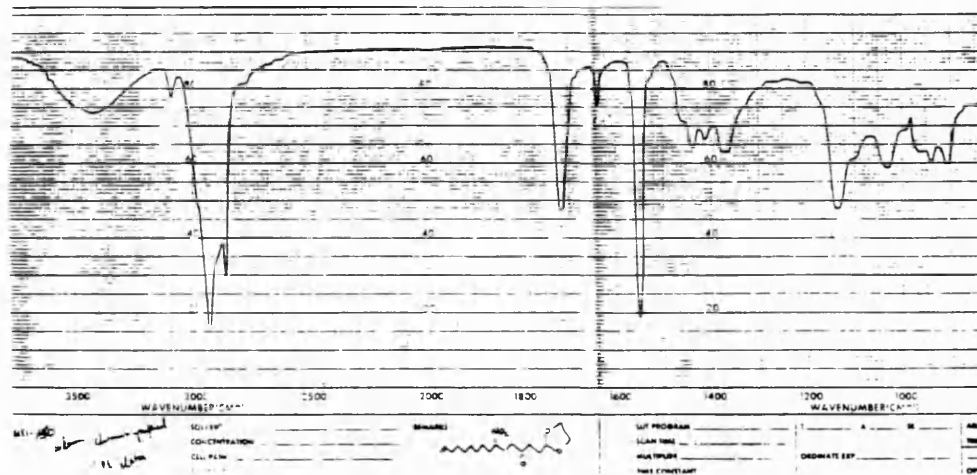
2(4-Penten-3-ol)-1,3-dioxolane.



2(4-Penten-3-one)-1,3-dioxolane.



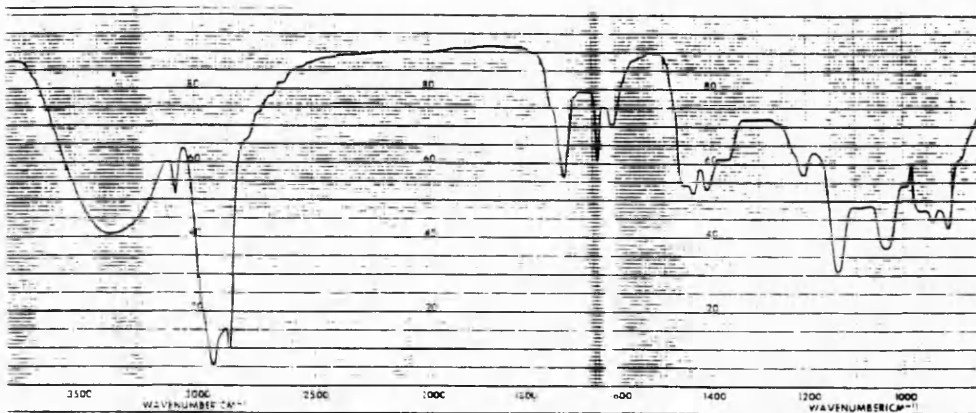
2(6-Nitro-14-pentadecen-3-one)-1,3-dioxolane.



2(6-Nitro-14-pentadecen-3-one-1,3-dioxolane (cont'd.).

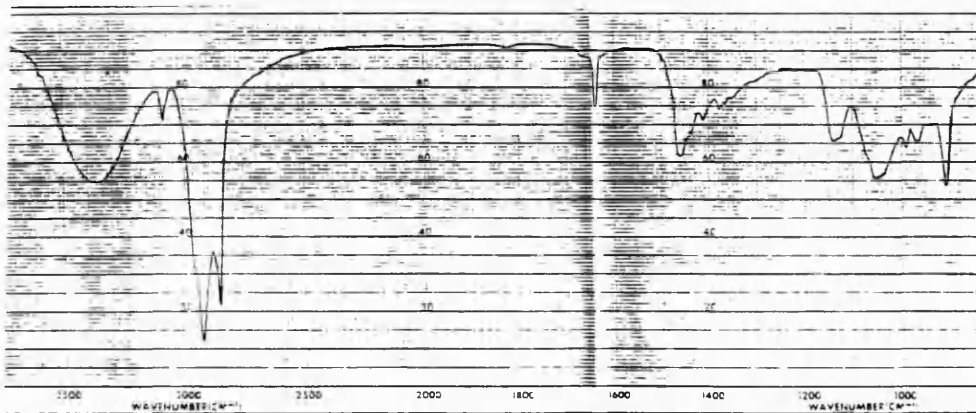


2-(8-Nonenyl)-5-(2-(1,3-dioxolan-2-yl))ethyl-1-pyrroline N-oxide.



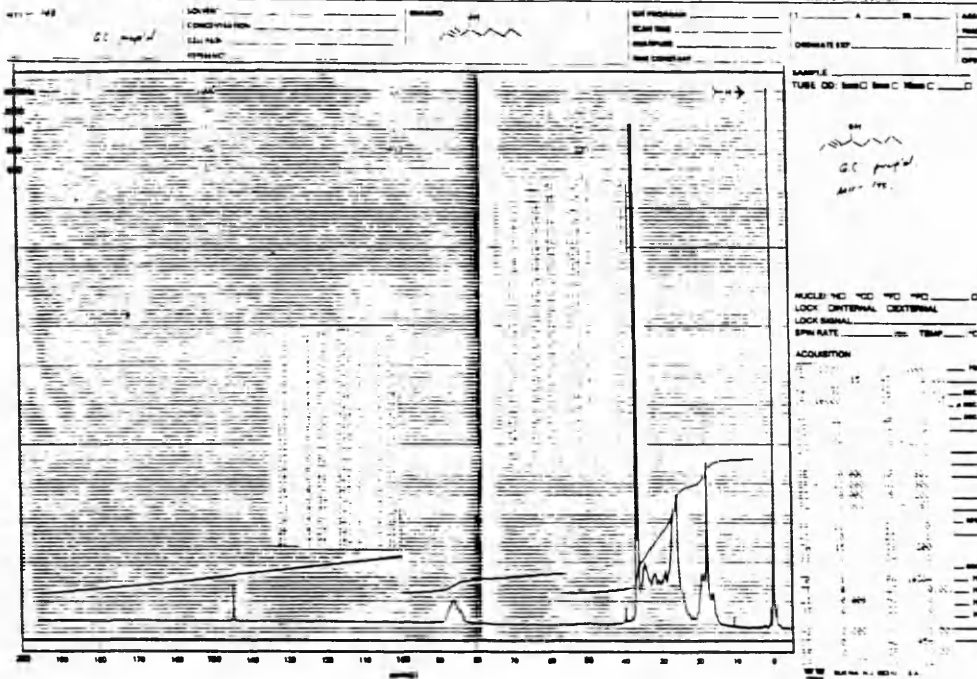
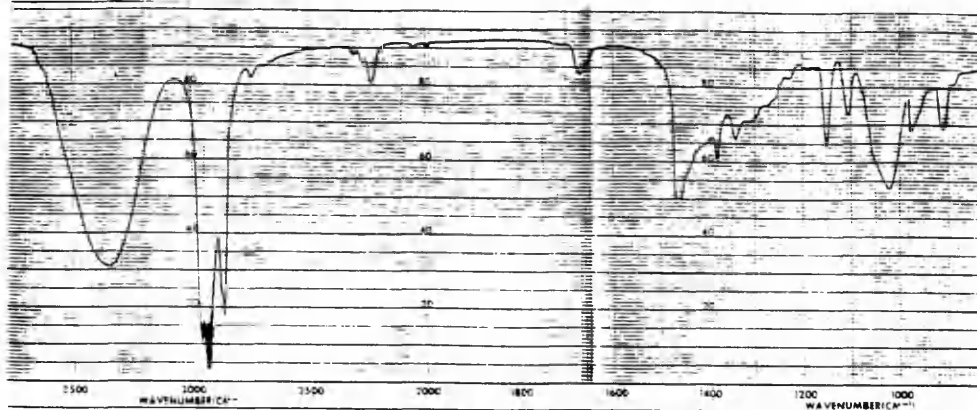
SOLVENT: \_\_\_\_\_  
 CONCENTRATION: \_\_\_\_\_  
 CELL PATH: \_\_\_\_\_  
 REFERENCE: \_\_\_\_\_  
 SAMPLE: C1=CCN(C1)CCOC2OCCO2  
 SUT PROGRAM: \_\_\_\_\_  
 SCAN RATE: \_\_\_\_\_  
 GAIN: \_\_\_\_\_  
 TIME CONSTANT: \_\_\_\_\_  
 ORIGINATE EXP: \_\_\_\_\_  
 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

N-Hydroxy-cis-2-(8-nonenyl)-5-(2-(1,3-dioxolan-2-yl))ethyl pyrrolidine.

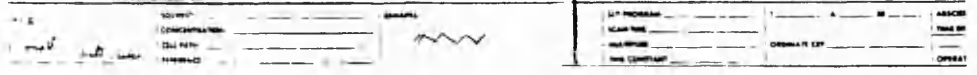
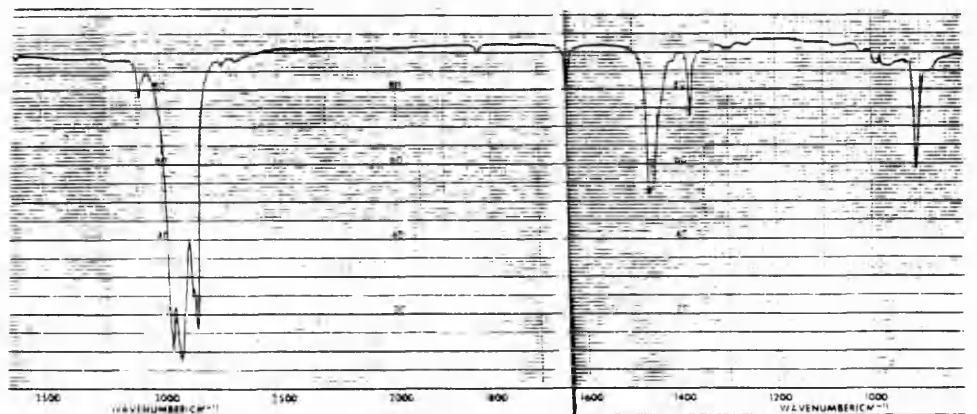


SOLVENT: \_\_\_\_\_  
 CONCENTRATION: \_\_\_\_\_  
 CELL PATH: \_\_\_\_\_  
 REFERENCE: \_\_\_\_\_  
 SAMPLE: C1=CCN(C1)CCOC2OCCO2  
 SUT PROGRAM: \_\_\_\_\_  
 SCAN RATE: \_\_\_\_\_  
 GAIN: \_\_\_\_\_  
 TIME CONSTANT: \_\_\_\_\_  
 ORIGINATE EXP: \_\_\_\_\_  
 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

2-Nonyn-4-ol.

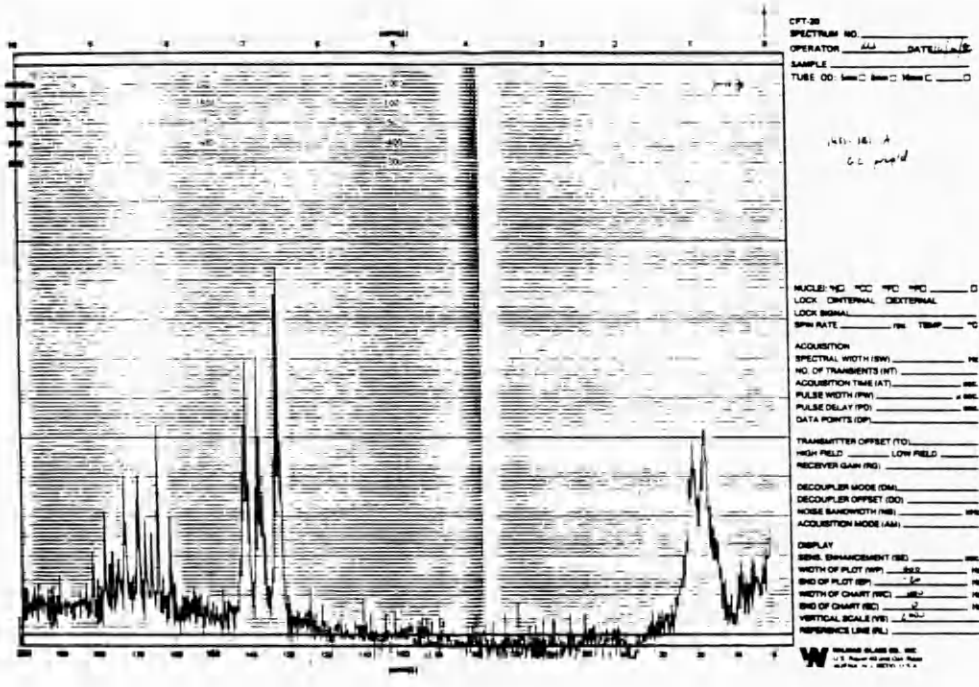
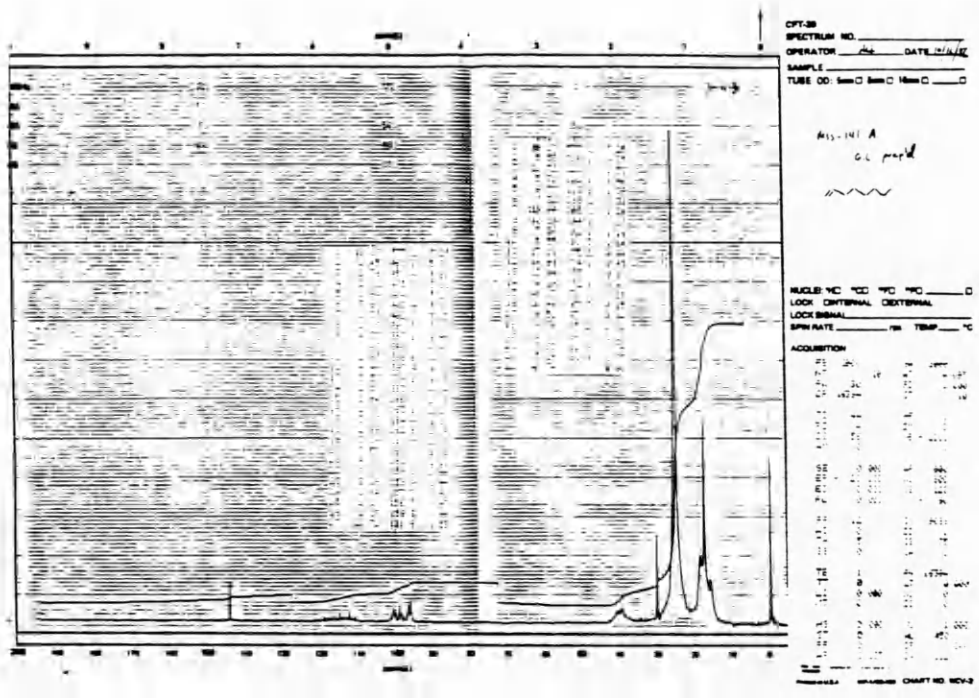


1-Octene.





1-Octene (cont'd.)



## VITA

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