

Calcium oxide catalyzed pyrolysis of N-acyl lactams
by Brent Robert Larsen

A thesis submitted to the Graduate Faculty in partial fulfillment of the requirements for the degree of
MASTER OF SCIENCE in Chemistry
Montana State University
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Abstract:
A calcium oxide pyrolysis of several N-acyl lactams leads to a useful preparation of some pyrroline and piperidine alkaloids.

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Bozeman, Montana

August, 1972

ACKNOWLEDGMENT

I would like to first acknowledge the Endowment and Research Foundation of Montana State University for its support of Dr. B. P. Mundy's research endeavors. I would also like to thank the Department of Chemistry at Montana State University for their financial support in the way of teaching assistantships and tuition waivers. I would like to acknowledge Professor Henry Rapoport for his analytical data and helpful discussion with Dr. Mundy. I would like to thank Dr. Mundy for his continued help and interest not only in the area of my research, but also the overall value of my education at this institution. Without his continued support this thesis would not have been possible. I would also like to acknowledge the help of the staff members and graduate students of the department for their discussion and technical aid to my special problems.

Most importantly I would like to thank my wife, Nancy, for her patience, understanding, and unselfish sacrifices which enabled me to achieve the completion of this phase of my education.

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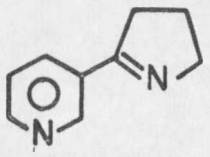
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ABSTRACT

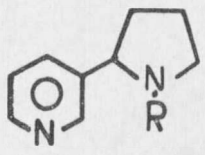
A calcium oxide pyrolysis of several N-acyl lactams leads to a useful preparation of some pyrroline and piperidine alkaloids.

INTRODUCTION

In 1893 workers reported the identification of a class of alkaloid compounds isolated from the tobacco plant genus, Nicotiana.[1] These nicotine alkaloids are assorted derivatives of 2 substituted 3'-Pyridyl pyrroles. These alkaloids were later to become the subject of many synthetic endeavors.



Myosmine



Nornicotine R=H

Nicotine R=CH_3

The first of these endeavors, completed in 1895,[2] was a synthesis of nicotine, the most abundant of the alkaloids. Since then many new avenues have been explored for preparation of these structurally simple but synthetically complex compounds.

Early workers found it necessary to synthesize these alkaloids as a means to unequivocally prove the hypothesized structures stemming from degradative investigations. After the structures of these alkaloids had been well established, interest shifted to synthesis, not to solve fundamental problems, but simply to derive new procedures. In the last decade, chemists' interests have again changed to more versatile synthetic procedures in attempts to label these alkaloids and provide the biochemist with the proper tools for biogenetic studies.

Under the direction of B. P. Mundy, a new approach to the synthetic problem was undertaken by two undergraduates, Lee F. McKenzie and Gary Braden. This new methodology was neither complicated nor elegant. The approach consisted of a pyrolysis of an N-acyl lactam leading to the desired substituted 2-pyrroline. The model system studied to begin this problem, a pyrolysis leading to the preparation of 2-phenyl pyrrolidone, later blossomed into a preparative method far beyond our modest expectations.

This thesis will show the evolutionary refinement of synthetic techniques eventually leading to a relatively simple, high yielding, widely applicable synthesis of pyrrolidine and piperidine alkaloids.

DISCUSSION

Historical Survey of Progress in Synthesis of Tobacco Alkaloids

Although the naturally occurring alkaloids of the Nicotiana species had been known for many years, a structure proof eluded workers until Pinner,[1] in 1893, reported the first detailed degradation of nicotine, the most abundant member of the family. This work pioneered the way for further investigations leading to the structure proof of the other unresolved members of the nicotine family. The first reported synthesis of nicotine was accomplished by A. Pictet and P. Crepieux[2] in 1895.

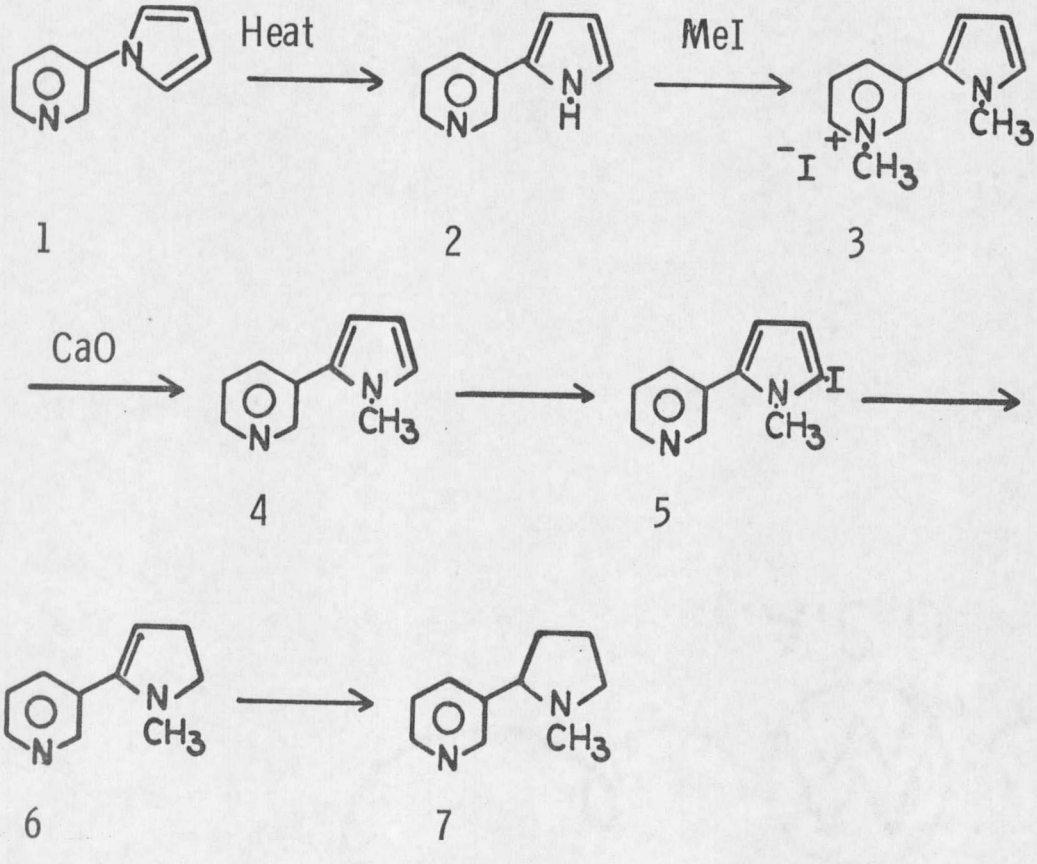
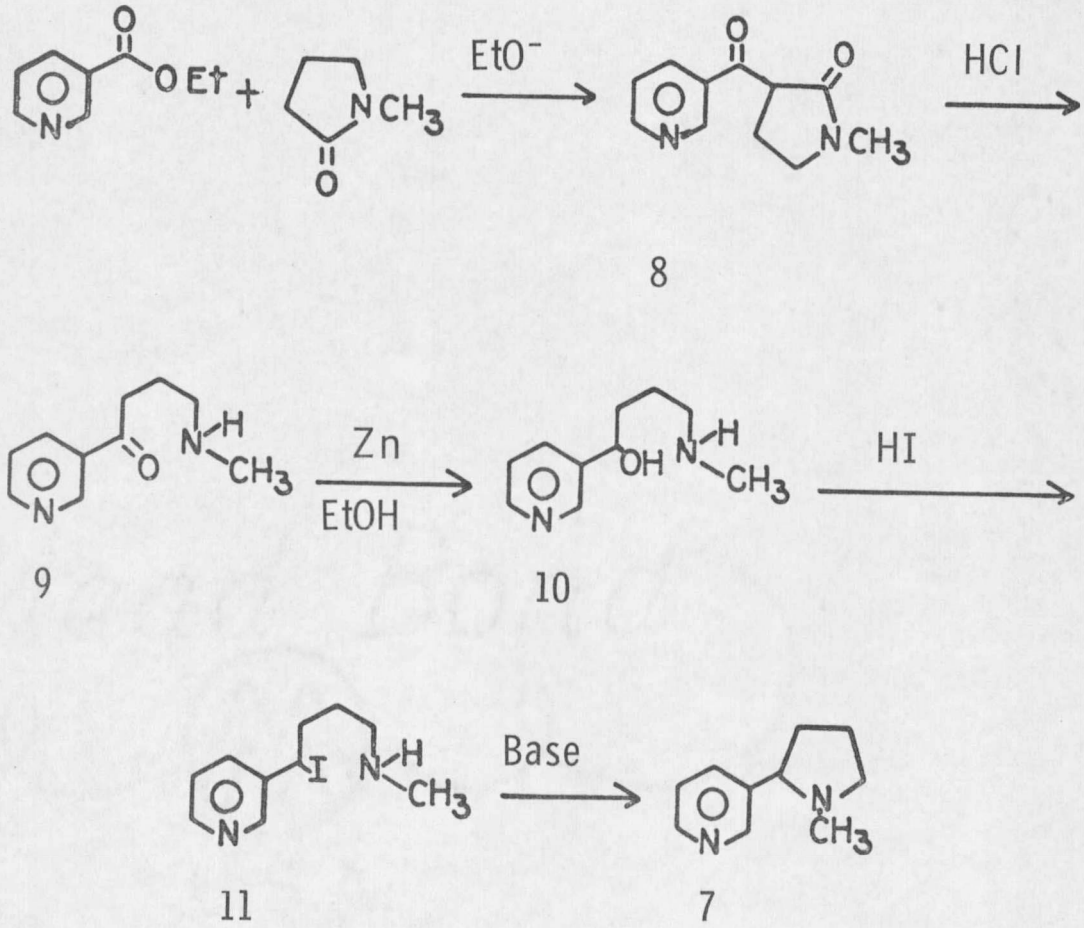


Figure 1. The Pictet Synthesis of Nicotine

This method, as outlined in Figure 1, began with the distillation of 3-aminopyridine mucate to give N-3-pyridylpyrrole (1). With the aid of red heat, a nitrogen to carbon rearrangement to 3'-pyridyl-2-pyrrole (2) was accomplished. Methylation with MeI gave nicotryne methyliodide (3) which was then distilled from calcium oxide yielding nicotryne (4). Reduction of the nicotryne was accomplished in three steps with the use of iodine and bromine. Upon isolation of the iodo compound (5), a



8 9 10 11 7

Figure 2. Spath & Bretschneider Synthesis of Nicotine

simple reduction yielded 4,5-dihydro nicotryne. Bromination followed by hydrogen reduction afforded nicotine (7).

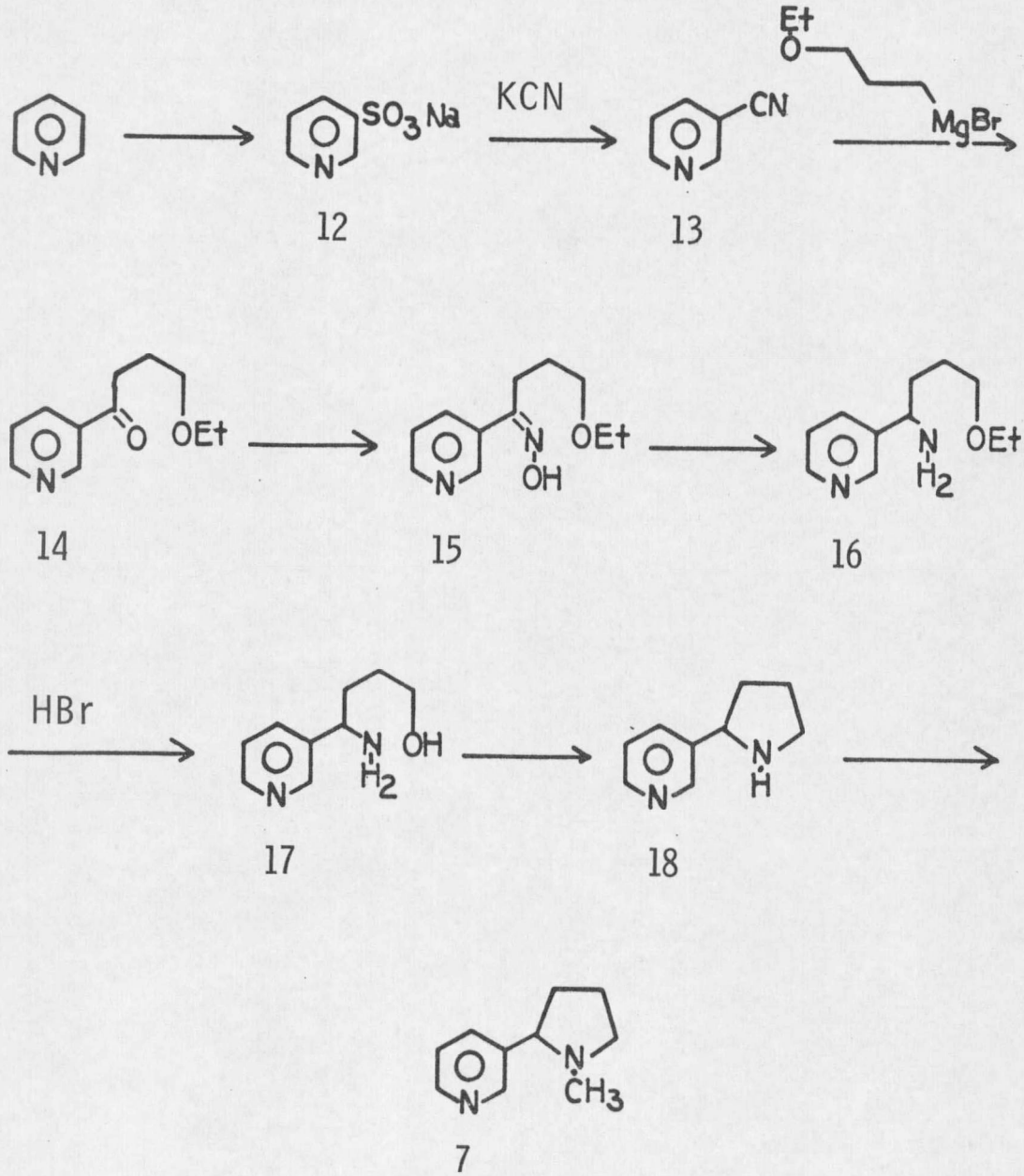


Figure 3. The Craig Synthesis of Nornicotine and Nicotine

Because of Pictet's poor yield and extreme conditions, this method of synthesis was not desirable. In 1928, Spath and Bretschneider[2] proposed a synthesis leading to nicotine shown in Figure 2. This synthesis involved the combination of N-methyl pyrrolidone and ethyl nicotinate in sodium ethoxide to yield the ketone (8). With fuming hydrochloric acid the lactam ring was opened, forming the ketone (9). Reduction with an alcoholic zinc solution afforded the alcohol (10). Displacing the alcohol with iodine formed compound (11) which was then cyclized in strong base to yield d,l-nicotine (7).

A route now existed for the convenient synthesis leading to one of the natural products in the alkaloid family. The other members of the family had, as yet, eluded preparation by simple synthetic techniques. In 1933, L. Craig[4] reported a novel synthesis for another member of the family, nornicotine, as a precursor to nicotine.

To begin his synthesis, Craig devised a method for sulfonation of pyridine with fuming sulfuric acid, yielding (12). The addition of potassium cyanide to displace the sulfinate group afforded the cyano compound (13).[5] A γ-ethoxy-propyl Grignard reagent was then added,[6] yielding a 1-(β-Pyridyl)-γ-ethoxy-propyl ketone (14). After conversion of the ketone to the oxime (15), reduction to the primary amine, 1-(β-Pyridyl)-1-amino-4-ethoxy butane (16) proceeded smoothly. The ethoxy functionality was removed from (16) by addition of hydrogen bromide, resulting in (17). By distillation of the excess hydrogen

bromide from the mixture, followed by addition of strong base, cyclization was induced, giving nornicotine (18). The conversion of nornicotine to nicotine (7) was accomplished by the addition of MeI to a methanolic solution of nornicotine. After equilibration, pure nicotine was isolated by distillation and compared to the natural product.

Although this synthesis provided for preparation of both nornicotime and nicotine, the overall yield of .5% left a need for a more efficient pathway.

In 1936 another of the alkaloids of the nicotine family was synthesized. Spath and Mamoli[7] presented the synthesis of myosmine as shown in Figure 4. As in Spath's previous synthesis, the condensation of benzoic anhydride and pyrrolidone forming the acyl lactam (19) began this synthesis. The ethyl ester of nicotinic acid was then added to the acyl lactam in the presence of sodium ethoxide to provide (20). Without purification, a bomb was charged with fuming hydrochloric acid and (20). It was then postulated that ring opening occurred, forming the intermediate (21). Upon decarboxylation and recyclization, myosmine was obtained. This synthetic method produced approximately 8% of the theoretical amount of myosmine. An improved mode of synthesis using the same general techniques was demonstrated by Korte and Schulze-Steiner[8] in 1962. (Figure 5)

N-Nicotinyl-2-pyrrolidone (23) was formed by the addition of 2-pyrrolidone to a solution of nicotinoyl chloride hydrochloride suspended

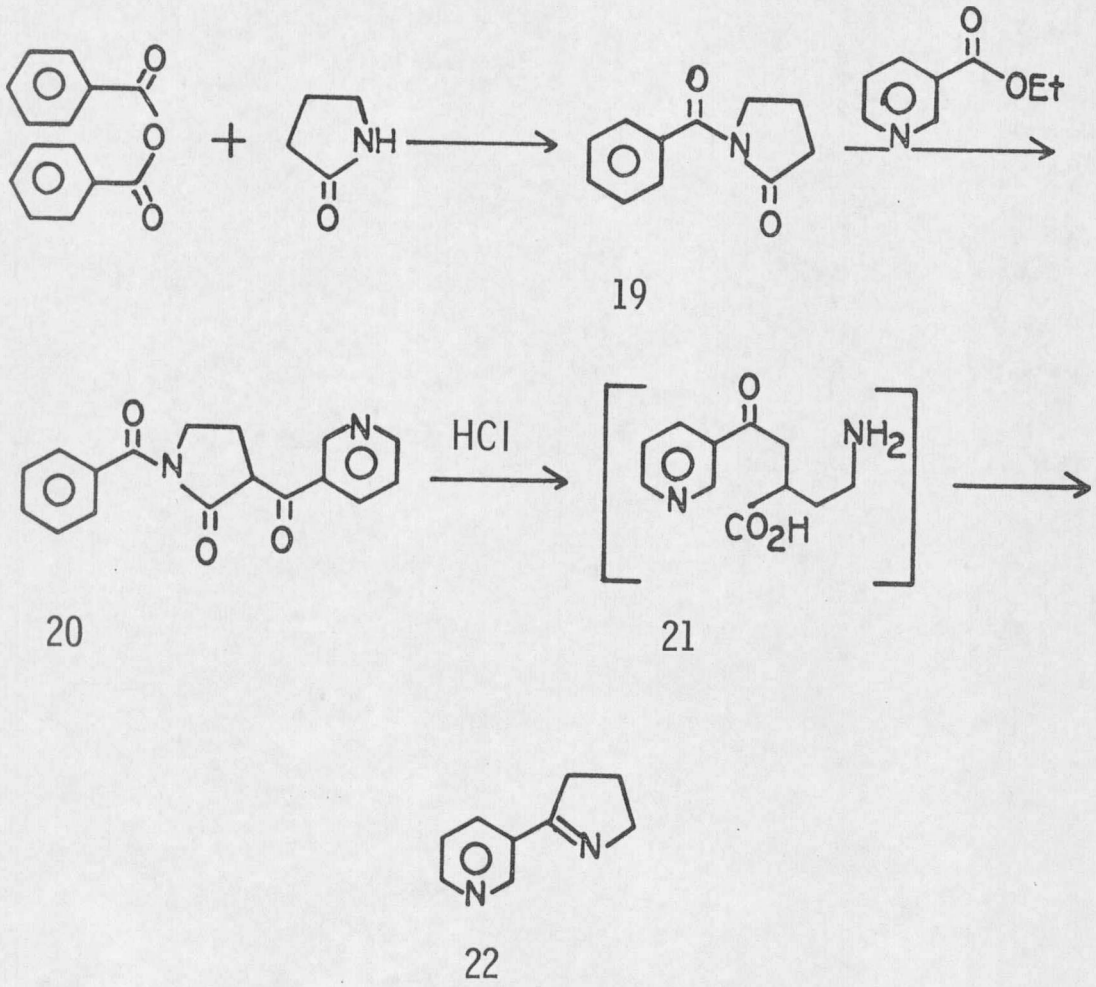


Figure 4. Synthesis of Myosmine by Spath & Mamoli

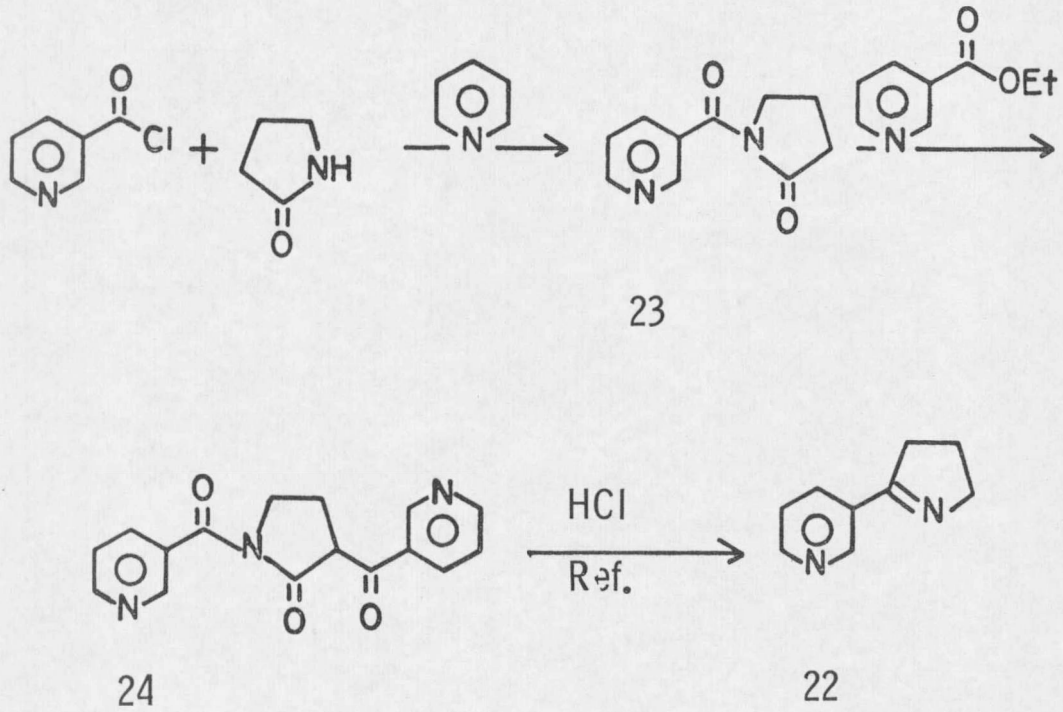


Figure 5. Synthesis of Korte & Schulze-Steiner

in pyridine. The N-nicotinyl-2-pyrrolidone was condensed with ethyl nicotinate in the presence of sodium ethoxide. The resulting compound, dinicotinyl pyrrolidone (24), was refluxed in concentrated hydrochloric acid until the evolution of carbon dioxide terminated. The result of this pathway was a 28% yield of myosmine. Although a vast improvement was observed in the overall yield of this compound, there still remained room for improvements. However, coupling the synthesis of Korte and Schulze-Steiner with two steps performed by Djerassi, the total synthesis of nornicotine and nicotine could be achieved more easily than before. As shown in Figure 6, Djerassi[9] prepared nicotine by the

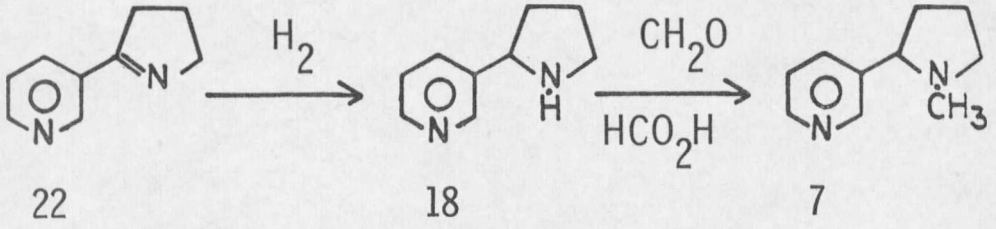
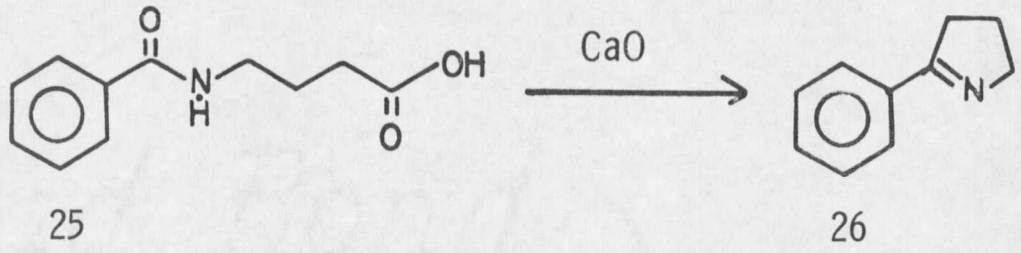


Figure 6. Conversion of Myosmine to Nicotine by Djerassi

above method. Hydrogenation of myosmine (22) with the aid of Platinum oxide afforded a quantitative yield of nornicotine (18). Methylation was then accomplished by refluxing (18) in a solution of formaldehyde and formic acid yielding nicotine (7) in excellent quantities.

A high yield of myosmine coupled with the equally productive Djerassi synthesis would lend itself to satisfyingly efficient preparation of nornicotine and nicotine.

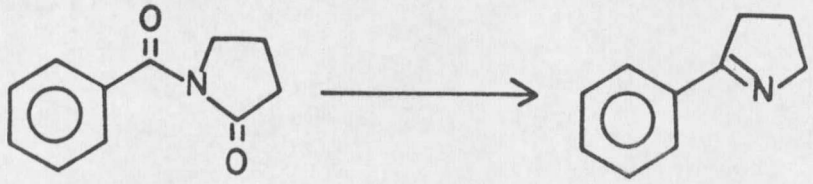
Mundy and McKenzie, realizing this fact, embarked on a synthetic procedure based on the calcium oxide pyrolysis of N-benzoyl-4-aminobutyric acid (25) previously reported by Murakoshi.[10] Using the phenyl-substituted acid, (25), free flame, and calcium oxide as a catalyst, 2-phenylpyrroline (26) was isolated according to the method outlined in Figure 7. Mundy proposed the reaction of Figure 7 to be achieved



25 26

Figure 7. The Murakoshi Synthesis of Phenylpyrroline

through the intermediate acyl lactam (19) which then decomposed, liberating CO_2 and yielding the desired product (Figure 8).



19 26

Figure 8. Suspected Intermediate of the Murakoshi Synthesis

Upon this supposition, work was begun to synthetically produce the acyl lactam intermediate (19). After isolation of 2-(3'-phenyl)-pyrrolidone, (23), a calcium oxide pyrolysis would yield the desired product, if the hypothesis was correct. Figure 9 depicts the synthesis used by Mundy and McKenzie[11] to test their model system. N-benzoyl-2-pyrrolidone (19) was obtained by reacting benzoyl chloride and pyrroli-

done in the same manner as Korte and Schultz-Steiner.[8] After purification and characterization, (19) was mixed with an equal weight of calcium oxide and subjected to a free-flame pyrolysis. The product recovered was shown by boiling point and picrate derivative to be 2-phenylpyrroline.[8]

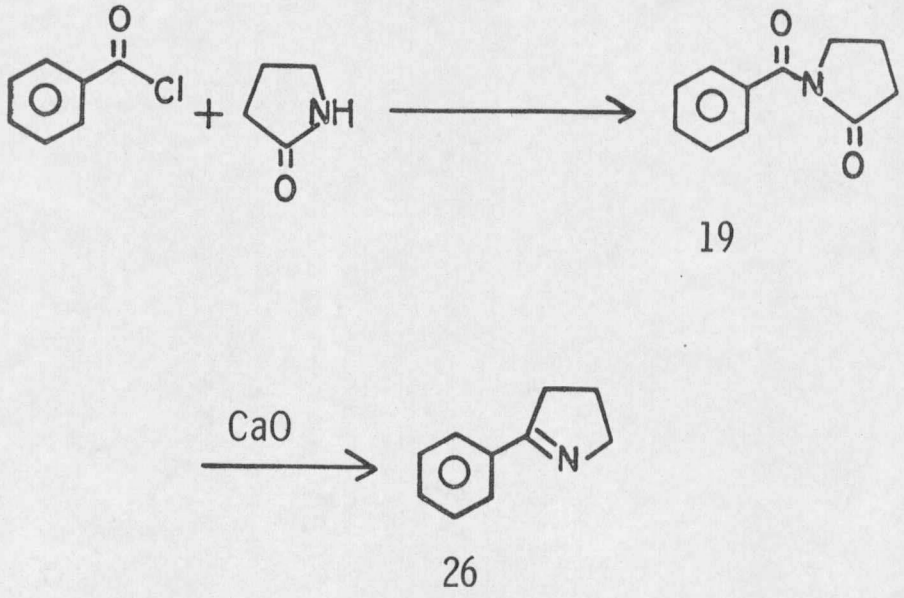
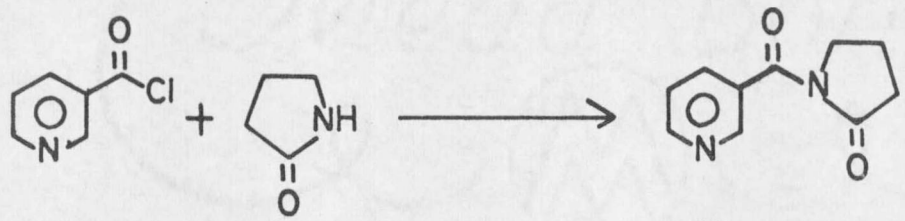


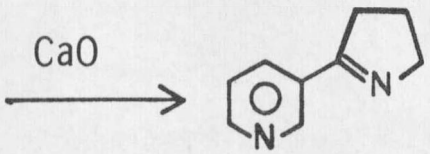
Figure 9. The McKenzie Synthesis of Phenyl Pyrroline

Our Preparation of Myosmine and Similar Pyrroline and Piperidine Compounds

The success of McKenzie's work inspired our continued investigation of a similar pyrolytic synthesis leading to myosmine and other alkaloids. Figure 10 shows the synthetic process that eventually yielded myosmine. The reaction sequence from which (23) was realized is precisely the same as Korte and Schultz-Steiner (Figure 5),[8] a pyridine catalyzed coupling of nicotinyl chloride hydrochloride and 2-pyrrolidone.



23



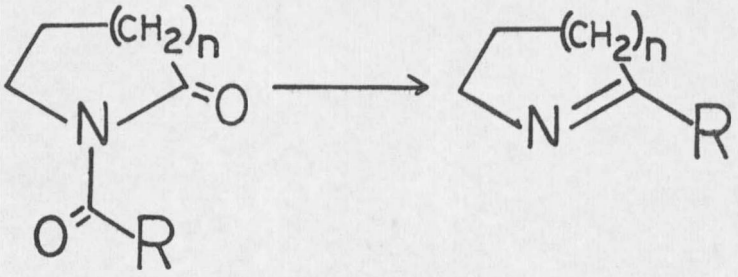
22

Figure 10. Synthesis of Myosmine

After isolation, (23) was mixed with an equal weight of calcium oxide and pyrolized with a free flame. Properties and derivatives of the product isolated compared exactly to the data given for myosmine isolated by other workers.[7] Although the mechanism is unknown, the sequence provided an easy two-step synthesis of myosmine. The pathway shown in Figure 10 is a vast improvement over previous synthetic attempts, providing an overall yield of 56.95% upon final distillation. To now complete the synthesis of nicotine, one must merely apply the reactions of Djerassi.[9] By making use of this new synthetic technique for myosmine, coupled with the simplicity of the Djerassi pathway, a unique method of preparation for the nicotine alkaloids can be envisioned. This simple but efficient mode of preparation would appear to have advantages over the previously presented techniques.

There are other alkaloid compounds, both unnatural and natural products, exhibiting a similar structure to that of myosmine, nornicotine, and nicotine. As shown in Figure 11, these compounds could all lend themselves to synthesis through pyrolysis of an N-acyl lactam. One compound of this nature is anabesene (24a). This compound is very similar to myosmine and in fact was synthesized by Spath and Mamoli,[14] using their same general procedure shown for myosmine (Figure 4).

Our reaction sequence[15] for anabesine is similar to that procedure previously demonstrated for myosmine (Figure 12). We prepared the N-acyl lactam (24a) by condensing nicotinoyl chloride hydrochloride



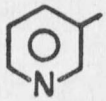
	R	n
24a-25a		2
24b-25b		1
24c-25c		2
24d-25d		1

Figure 11. General Formula of Pyrroline and Piperidine Alkaloids

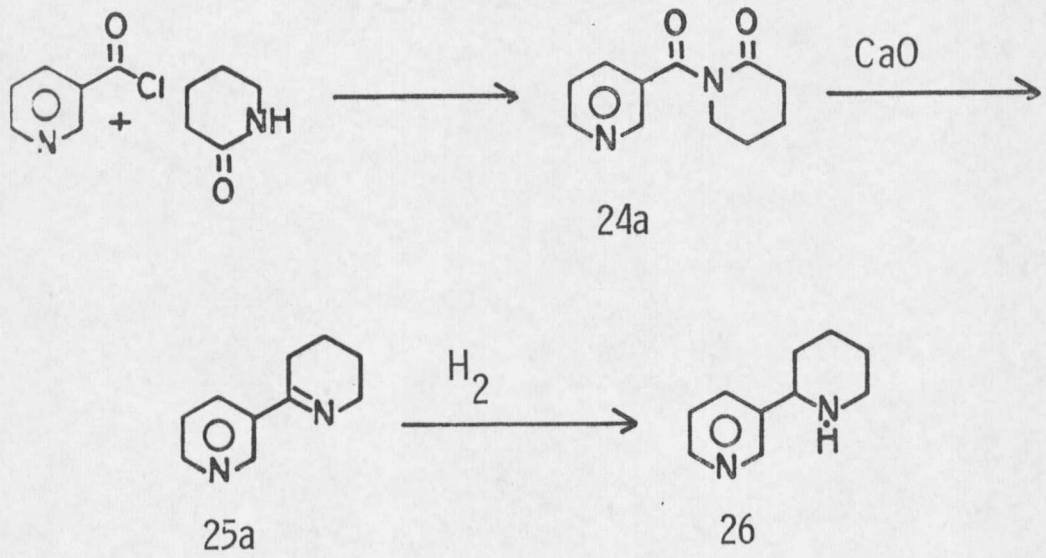


Figure 12. Pyrolysis Production of Anabasene and Anabasine

with δ-valerolactam. Pyrolysis of (24a) using calcium oxide resulted in the formation of anabasene (25a). Simple hydrogenation with platinum oxide as demonstrated by Djerassi,[9] would produce the natural product, anabasine (26). As previously observed, our reaction procedure generated the desired compounds in considerably better yields than the other processes. The further utility of this methodology of synthesis is exemplified by its utility in preparing (25b) and (25c). The latter, (25c), is the naturally-occurring alkaloid, coniine, of the Hemlock species. This synthesis was preceded by the synthesis of (25b) used as a model system. As in the previous examples, the products (25b) and (25c) have been synthesized by other groups using techniques similar to procure the desired alkaloid. Because of the

basic structural similarities with other alkaloids prepared, the methodology for the preparation of (25a) and (25b) followed the previously established N-acyl lactam pyrolysis. The synthesis of 2-(n-propyl)-pyrroline, shown in Figure 13, begins with the condensation of

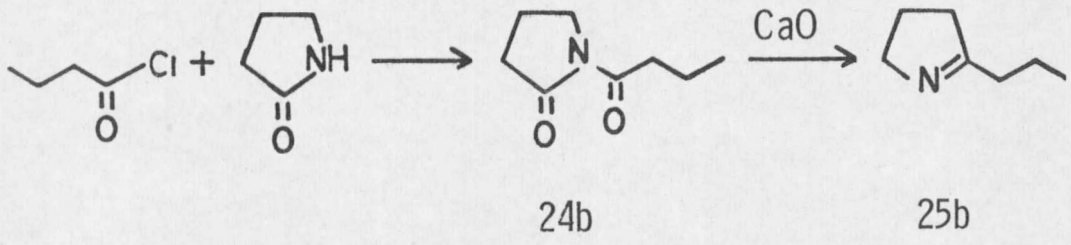


Figure 13. Synthesis of 2-(n-propyl) pyrroline

n-butyryl chloride with 2-pyrrolidone, this time excluding the use of pyridine, to form the N-acyl lactam (24b). Pyrolysis of this product gave a crude mixture which upon distillation provided an excellent overall yield of 2-(n-propyl) pyrroline.

The synthesis of Coniceine[15] was accomplished in the same manner. Figure 14 shows the condensation of n-butyryl chloride and δ-valerolactam to yield the desired N-acyl lactam (24c). Pyrolysis of this compound led to the crude material which upon distillation yielded

coniceine (25c). Djerassi has shown that the saturated coniine (27) can be prepared by the catalytic hydrogenation of coniceine.

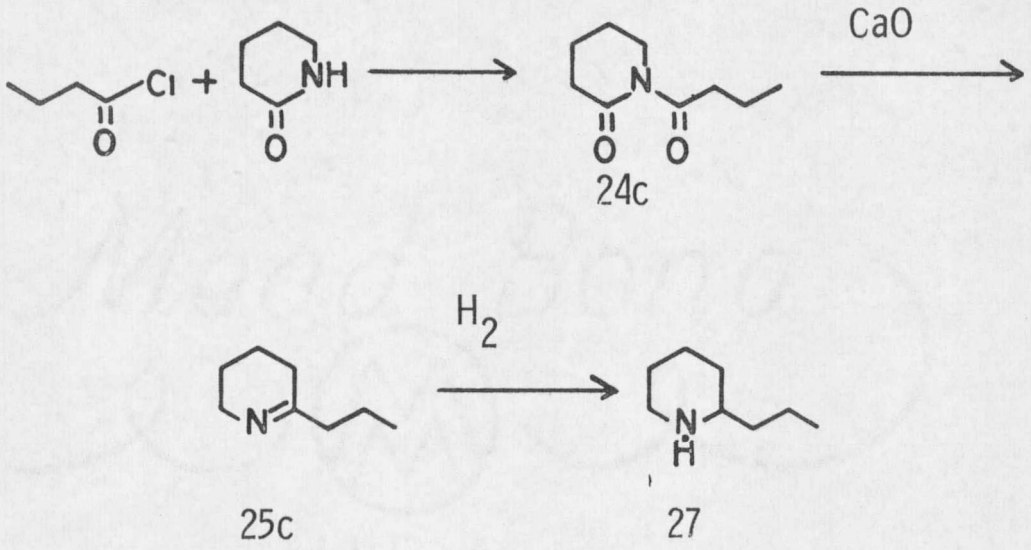


Figure 14. The Synthesis of Coniceine and Coniine

Through the simply pyrolytic reaction described, one is now able to obtain not only the nicotine alkaloids described, but many alkaloids containing the pyrroline or piperidine moiety. Yet with all the excellent results already published, this synthetic method has merely scratched the surface of its utility. The mechanism of the reaction is yet unknown. There has been no evidence as to which side of the lactam is bound to the R-group (Figure 14) after completion of the pyrolysis. There is also no evidence defining the loss of the two oxygens and one carbon, observed by the pyrolysis of the N-acyl lactam. It has been demonstrated, however, that the conditions for the pyrolysis

are gentle enough that no rearrangement of the acyl group can be detected. A very good example of the specificity of the reaction is the pyrolysis shown in Figure 15. Cyclopropanecarboxcylic acid chloride was condensed with 2-pyrrolidone to form the N-acyl lactam (24d). This N-acyl lactam was pyrolized under the same conditions as previously described. The desired product, 2-cyclopropyl pyrroline (25d) upon nmr investigation exhibited an unresolved doublet at 0.8 ppm. Although the doublet represented 4 hydrogens, there was doubt as to whether the doublet represented cyclopropane hydrogens.

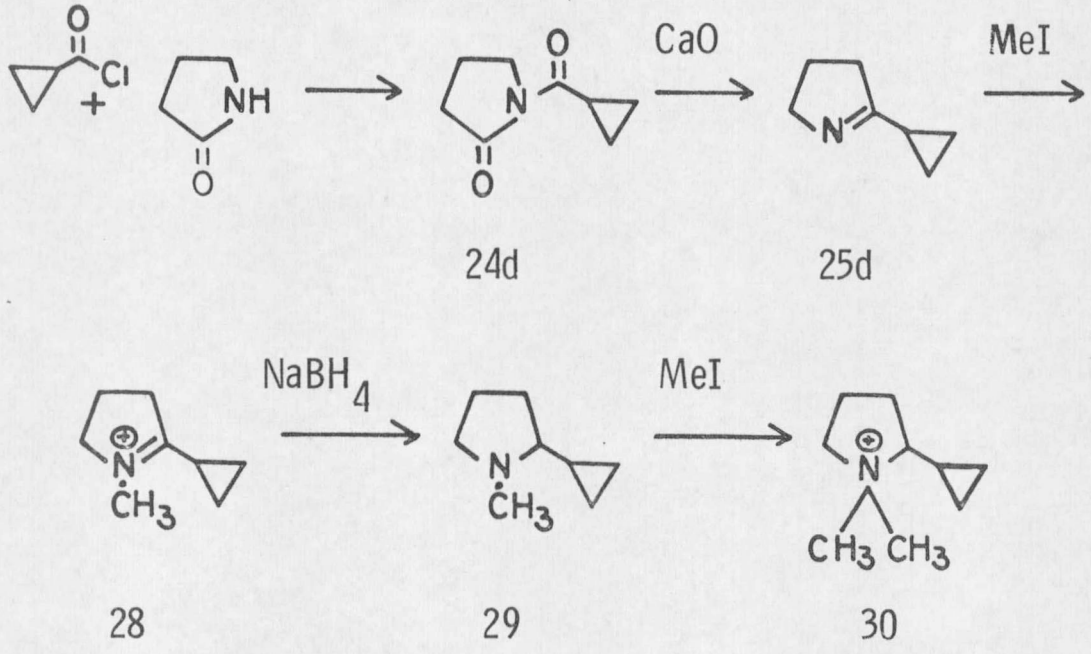


Figure 15. The Synthesis of Cyclopropylpyrroline and Its Derivatives

In an attempt to resolve this problem, a methyl iodide derivative (28) was prepared. The nmr spectrum of the compound isolated from the methyl iodide reaction showed a shift of the doublet to 2.6 ppm and a change in shape to a multiplet. At first the product was thought to be a rearrangement of the former pyrroline (25d), but investigation suggested that due to the quaternary ammonium salt prepared, the cyclopropane hydrogens could be moved the 1.8 ppm depicted by the multiplet. Reduction of the unsaturation of (28) was undertaken by the addition of sodium borohydride. The nmr spectrum of (29) provided substantial proof that the reaction proceeded as predicted. The spectra displayed a multiplet at .3 ppm and a singlet, the N-methyl hydrogens, at 2.4 ppm. This would then suggest that the unsaturated pyrroline had caused the formation of the doublet observed in the nmr of (25d). To finalize the results, the methyl iodide derivative (30) of the tertiary amine was then prepared. Upon nmr investigation of this compound, the cyclopropane hydrogens were again shifted downfield to a position of .8 ppm. It was then proposed that the data were consistent with the suggested structure, (25d), 2-cyclopropylpyrroline.

The Mundy-Rapoport Synthesis for Labeled Nicotine Alkaloids

The present most important reason for an adequate synthesis of these alkaloids is to study their biogenesis. For these types of studies, one must specifically label positions in the alkaloids desired. Therefore, a synthesis should proceed with accuracy (efficiently) of label placement in order to produce as much labeled material as possible. A synthesis designed by Mundy and Rapoport[12] (Figure 16) demonstrates how one can place a label specifically in the 4-position of the pyrroline ring of nornicotine or nicotine. Addition of the carbanion generated by basic action on malonic acid leads to the vinyl diacid (31). Heating the vinyl diacid causes decarboxylation, forming the vinyl acid which, upon esterification leads to the vinyl ester (32). Addition of labeled N-carboxyl glycine forms compounds (33) and (36) in an equilibrium mixture. Pathways 1 and 2 lead to the same empirical product. The difference between the pathways is the position of the labeled carbon upon cyclization. In compound (34) the labeled carbon is in the 4-position of the pyrrolidine ring as opposed to compound (37) where the labeled carbon remains as an ester function branching from the 5-position. Upon removal of the external ester functions of (34) and (37) by hydrolysis, all of the label carbon is removed by the formation of (38), rendering it useless. (34) is now the only compound of concern having its label fixed in the four position. The addition of hydrazine and reduction yields nornicotine (18) which

upon methylation results in specifically labeled nicotine (7).

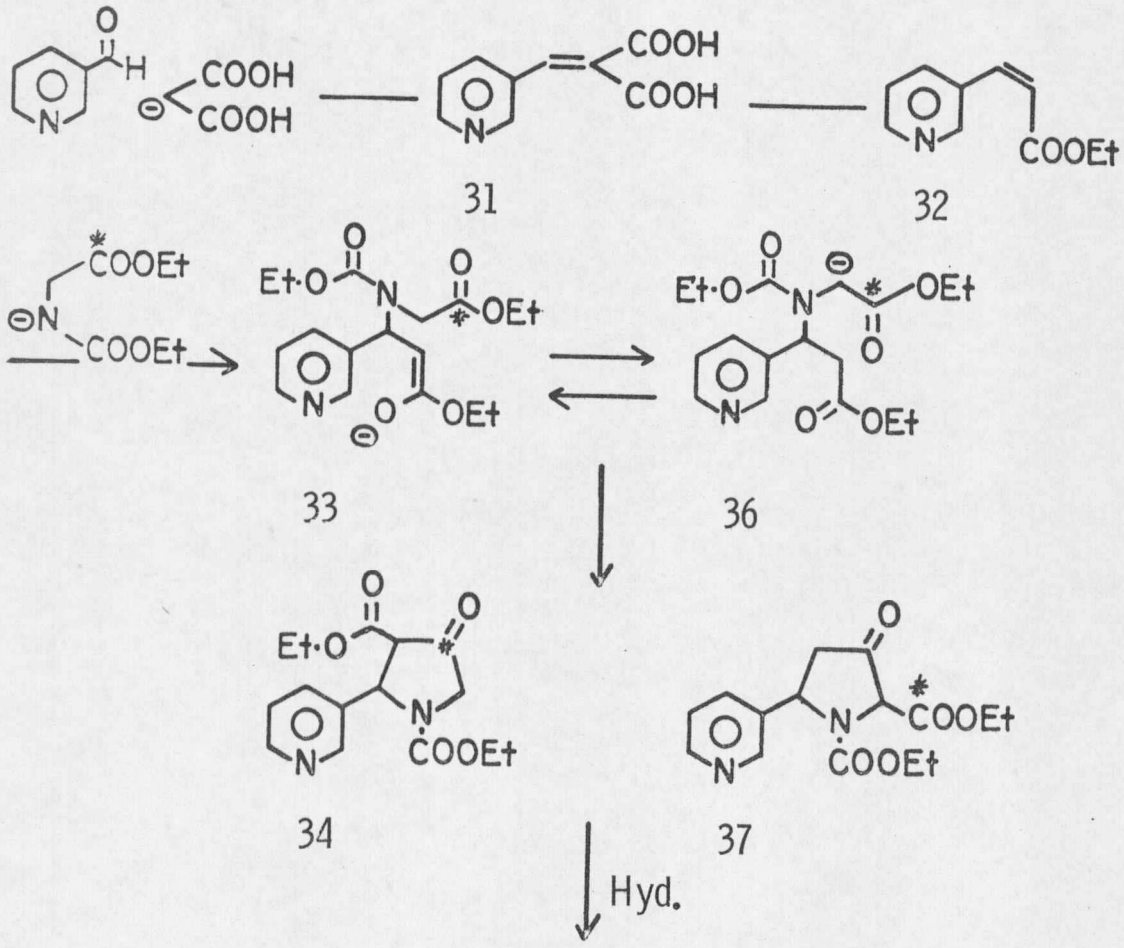


Figure 16. Synthesis of Labeled Nicotine by Mundy and Rapoport
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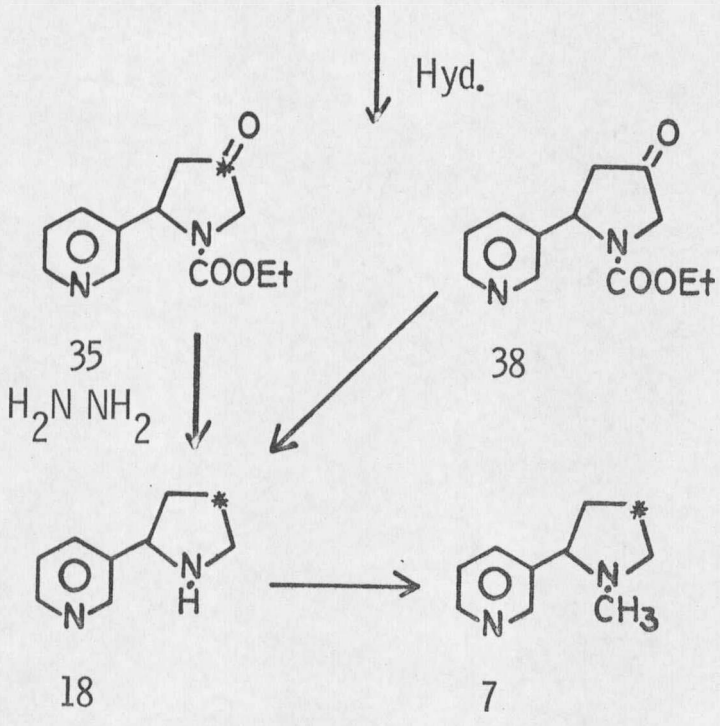


Figure 16. (cont.)

Proposed Application of Our Synthetic Techniques
for the Preparation of Labeled Nicotine Alkaloids

Despite the loss of labeled material, the elegant, but lengthy, synthesis provides placement of the carbon fourteen function with surprisingly high yields.

As an alternative method for labeled alkaloid preparation, realized without the necessity of a lengthy complicated sequence, an adaptation to our synthetic procedure seems possible. By preparing specifically labeled 2-pyrrolidone, the desired natural product can be synthetically generated as illustrated by the former sequences (Figures 6 and 10). The envisioned synthesis, shown in Figure 17, begins with bromohydrin, a readily available starting material, under-

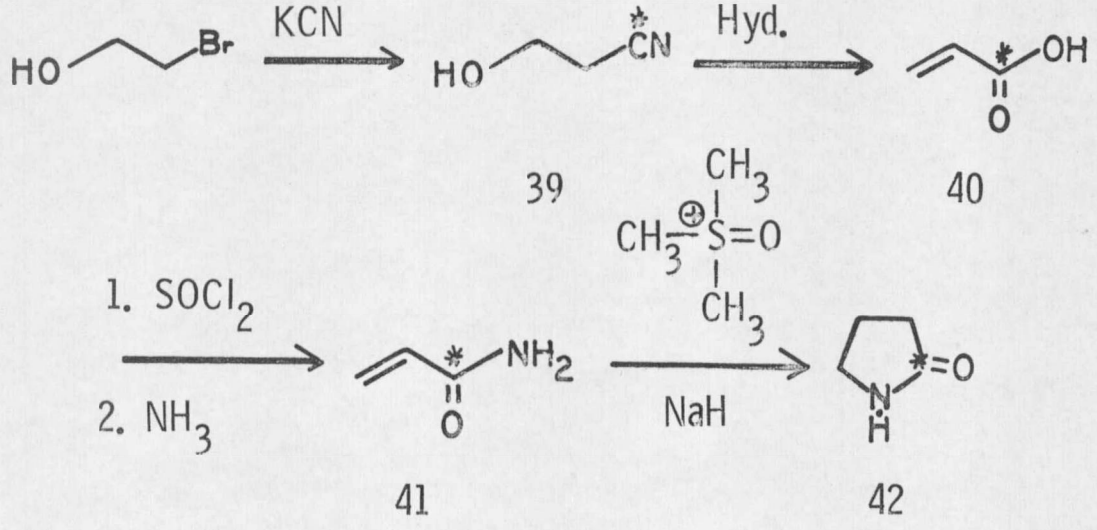


Figure 17. Synthesis of Labeled 2-pyrrolidone

going displacement of the bromine with labeled sodium cyanide to provide labeled cyanohydrin (39). This compound could then be dehydrated and hydrolyzed to produce the acid (40). Reaction of the free acid with refluxing thionyl chloride, isolation of the acid chloride, and reaction with ammonia would produce the amide (41). Cyclization could then be accomplished with the methyl iodide salt of dimethyl sulfoxide in the presence of sodium hydride.[13] This cyclization product (42) would then be specifically labeled 2-pyrrolidone with the label residing at the 2 or carbonyl carbon of the lactam. This reaction sequence could then be coupled with our previously presented synthesis of myosmine yielding, we believe, myosmine labeled in the 2 position. Upon hydrogenation and methylation, nicotine, labeled in the 2 position, would be isolated with very minimal loss of label due to the synthetic procedure.

SUMMARY

With the wealth of evidence presented, we feel the problem warrants further exploration. The synthetic reward offered by this method of synthesis is, perhaps, unlimited. The total potential of the powerful synthetic technique will only be realized upon extensive experimental investigation. But, for the present, this method presents an excellent hypothetical entrance into synthesis of the hard-to-obtain labeled compounds concerned with biogenetic studies. The application of this synthesis in the biosynthesis of the nicotine may well change the classical biogenetic pathways shown for production of the nicotine alkaloids as preliminary investigations by B. P. Mundy have suggested.

EXPERIMENTAL

Nuclear magnetic resonance spectra were run on a Varian A-60 Nuclear Magnetic Resonance Spectrophotometer using deuterochloroform as a solvent and TMS as an internal standard.

Glc recorder tracings were obtained from a Varian Aerograph Model A-700. Work was performed using a 7' x $\frac{1}{4}$" 3% OV-17 on Chromosorb W (90/120 mesh) column. The gas flow in the system was kept at approximately 40 ml/min.

Mass spectra of both solids and liquids were obtained with the aid of a Varian Model CH5 mass spectrophotometer. The liquid samples were introduced into the machine through a 6' x 1/8" column packed with 10% Apeizon-L on Chromosorb W (90/120 mesh) into a helium separator with the aid of a Varian Aerograph Series 1700.

All melting points and boiling points are uncorrected.

Pressures are reported in mm of mercury (e.g. $bp_{10}50^{o}C$ indicates the boiling point was $50^{o}C$ at a pressure of 10 mm of mercury).

General Preparation of the Acylated Lactams:

The similarity of the N-acyl lactam systems lended themselves to a consistent preparation procedure. Unless otherwise noted, reaction times, conditions, and workup procedures remained static for generation of all the systems pyrolized.

A solution prepared by the slow addition of n moles of pyridine to x moles of an acid chloride was stirred for one hour. After this

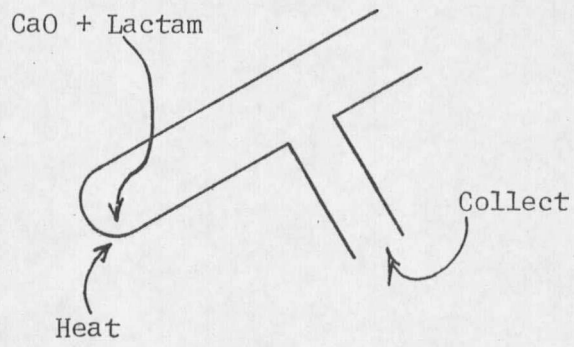
time, y moles of the desired lactam, dissolved in pyridine, were added dropwise to the previous solution. The reaction mixture was then allowed to stir at room temperature. After 8 hours, the crude product was dissolved in methylene chloride, and washed with dilute hydrochloric acid until a pH of 3 was obtained in the aqueous layer. A saturated solution of sodium bicarbonate was then used to raise the pH to 9 eliminating any excess acid. The methylene chloride layer was then dried with anhydrous sodium sulfate and the solvent removed at reduced pressure. The remaining residue was purified by a variety of procedures.

(Note: If the acyl lactam desired contains a pyridine ring, one should not wash the methylene chloride mixture with acid as the compound will be salted out of the organic layer.)

General Rearrangement Procedure of the N-acyl Lactams:

As in the N-acylation general procedure, the pyrolysis conditions of the systems illustrated remained constant from preparation of the reaction mixture to distillation of the crude pyrolysis product.

The N-acyl lactam was mixed thoroughly with an equal weight of calcium oxide and placed in a pyrex tube fitted with a side arm. The mixture was gently heated with the flame of a micro burner. When a melt was observed, the heat was continued until the crude product distilled. This product was then subjected to reduced pressure distilla-



tion, purity being checked by glc (3% OV-17 5'XX.25"). Identification was accomplished by spectral means and by preparation of known derivatives.

Preparation of N-Nicotinoyl-2-Pyrrolidone, (23):

Using the general procedure for acylation, a solution of nicotinoyl chloride hydrochloride (27 g, 0.163 mole) and pyridine (10 g, 0.126 mole) was prepared. After addition of 2-pyrrolidone (40 g, .465 mole) a crude mixture containing (23) was isolated. The crude product was successively recrystallized from a mixture of chloroform and hexane yielding 22.4 g (85% yield) of (23).

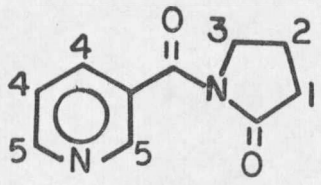
mp. 104°C

Anal: Calc'd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73

Found*: C, 63.78; H, 5.03; N, 14.82

*Analytical data for (23) was kindly provided by Prof. Henry Rapoport, University of California, Berkeley.

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	2.57	2	Triplet
2.	2.12	2	Unresolved Quartet
3.	3.90	2	Triplet
4.	7.59	2	Doublet of Multiplets
5.	8.70	2	Multiplet (unresolved singlet)

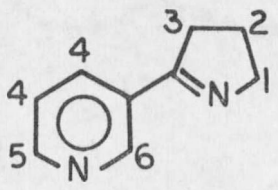
Preparation of Myosmine, (22):

Using the general procedure for rearrangement of N-acyl lactams N-nicotinoyl-2-pyrrolidone (1.5 g, .0085 mole) and calcium oxide (1.5 g, 0.0209 mole) were gently heated providing a crude mixture which upon vacuum distillation yielded .75 g (67% yield) of myosmine.

$bp._{10}$ 82-86°

Picrate derivative mp. 184-185°C , Literature[7] mp. 184-185°C

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	4.05	2	Triplet of Triplets
2.	2.08	2	Quartet
3.	2.91	2	Unresolved Triplet
4.	7.70	2	Doublet of Multiplet
5.	8.60	1	Unresolved Singlet
6.	8.93	1	Unresolved Singlet

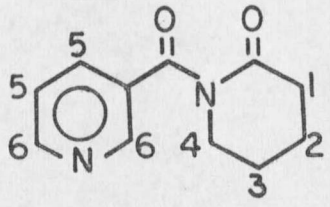
Preparation of N-nicotinoyl-2-Piperidone, (24a):

Using the general procedure for acylation, a solution of nicotinyl chloride hydrochloride (42 g, .252 mole) and pyridine (20 g, .252 mole) was prepared. To this solution, addition of piperidone (10 g, .0101 mole) led to the isolation of a crude product mixture containing the desired acyl lactam (24a). Purification of the product by recrystallization proved to be fruitless. The crude mixture was then eluted through a column containing Bio-Sil-A 100-200 mesh. Elution began with benzene, the solvent used to pack the column, and the product was isolated after 500 mls. of 50:50 benzene chloroform had passed through

the column. After evaporation of the solvents, a solid residue remained which by tlc on silica gel with 10% methanol in chloroform, showed only one spot with an rf value of 4.4. The solid material was subjected to nmr showing the expected peak placement for compound (24a). 11.2 grams of (24a) was isolated according to this procedure affording a 54.5% yield.

mp. 66-68°C

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	2.5	2	Multiplet
2.	1.77	4	Multiplet
3.	1.77	4	Multiplet
4.	3.75	2	Multiplet
5.	7.5	2	Doublet of Multiplet
6.	8.7	2	Multiplet

Preparation of Anabasene, (25a):

The pyrolysis of the N-acyl lactam (24a) proceeded according to the general procedure outlined. The lactam (24a), (1 g, 0.0049 mole) and calcium oxide (1 g, 0. 0156 mole) which upon gentle heating yielded a crude mixture shown by nmr to contain the compound desired (25a). Distillation of the crude material yielded 4.3 grams (62% yield) of (40a).

$bp._{10}$ 70-72°C, Literature[9] $bp._{0.8}$ 25°C

Picrate derivative mp. 171-172°C, Literature[9] mp. 170-172°C

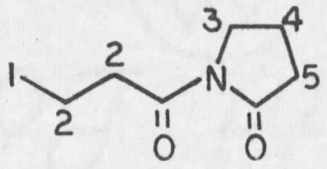
Because of the nature of the compound, no nmr spectrum was taken.

Preparation of N-Butyryl-2-pyrrolidone, (24b):

This preparation deviates from the general procedure in that the best yields of the compound were prepared without the use of pyridine. N-butyryl chloride (15 g, 0.124 mole) suspended in benzene (10 ml) was added directly to a benzene (25 ml) solution of 2-pyrrolidone (24.2 g, 0.285 mole). After one hour of constant stirring, the reaction mixture was taken up in methylene chloride. After the general acid and base washings, the solvent was removed and vacuum distillation yielded 20.8 g (94.5% yield) of the final product, (24b).

$bp._{10}$ 158°C

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	0.92	3	Triplet
3.	3.72	2	Triplet

2, 5, & 4 Unresolved multiplet ranging from 1.25-2.95

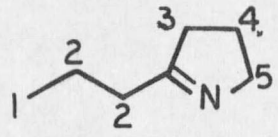
Preparation of 2-(n-propyl)-pyrroline, (25b):

Using the general procedure for pyrolysis, preparation of (25b) was accomplished. (24b), (1.5 g, 0.097 mole) and calcium oxide (1.5 g, 0.029 mole) were reacted yielding a crude product mixture. This crude mixture was then vacuum distilled affording .81 g (75% yield) of (40b).

$bp._{10}$ 38°C

Picrate derivative mp. 105-105.5°C, Literature[17] mp. 104-104.5°C

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	0.95	3	Triplet of Doublet
5.	3.75	2	Multiplet

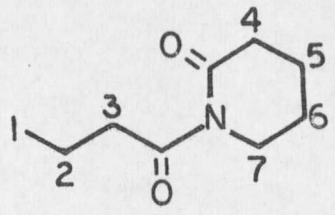
2, 3, & 4 Unresolved multiplet ranging from 1.12-2.67

Preparation of N-Butyryl-piperidone, (24c):

The preparation of this lactam was also found to proceed with maximum efficiency without the use of pyridine. N-butyryl chloride (2.3 g, 0.0225 mole) suspended in benzene (10 ml) was added directly to a benzene solution (15 ml) of 2-piperidone (5 g, 0.0505 mole). After one hour of constant stirring, the reaction mixture was taken up in methylene chloride. After the standard acid and base washings, the solvent was removed and vacuum distillation yielded 2.3 g (61% yield) of (24c).

$bp._{10}$ 155°C, Literature[16] $bp._{0.1}$ 82°C

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	0.9	3	Triplet of Doublets
7.	3.67	2	Unresolved Triplet

2, 3, 4, 5, & 6 unresolved ranging from 1.3-3.0

Preparation of γ-Coniceine, (25c):

The preparation of (25c) was accomplished using the general pyrolysis procedure as outlined. (24c), (1 g, 0.0059 mole) and calcium oxide (1 g, 0.0156 mole) gently heated yielded .51 g (69% yield) of (25c) after vacuum distillation of the crude material.

$bp._{10}$ 54°C, Literature[16] $bp._{9}$ 54°C

Picrate derivative mp. 77-78°C, Literature[16] mp. 77-78°C

Preparation of N-cyclopropanecarboxoyl-2-pyrrolidone, (24d):

Using the general procedure for acylation, a solution of cyprop-anecarboxyl acid chloride (5 g, 0.0484 mole) and pyridine (10 g, 0.0126 mole) was prepared. After addition of the 2-pyrrolidone (8.25 g, 0.0968 mole) a crude mixture containing (24d) was isolated. The

crude product was successfully recrystallized from a mixture of chloroform and hexane yielding 6.965 g (90% yield) of (24d).

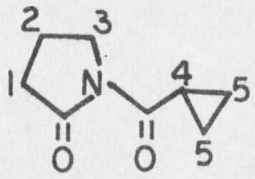
$bp._{.15}$ 136°C

mp. 62-63°C

Anal: Calc'd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1

Found: C, 62.3; H, 7.1; N, 9.3

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	2.61	2	Triplet
2.	1.95	2	Quintet
3.	3.75	2	Triplet
4.	3.17	1	Multiplet
5.	0.97	4	Multiplet

Preparation of 2-cyclopropylpyrroline (25d):

Using the general procedure for pyrolysis, the acyl lactam (24d) (1.5 g, 0.0098 mole) and calcium oxide (1.5 g, 0.029 mole) were reacted yielding a crude mixture containing (25d). The mixture was then distilled yielding 7.84 g (73.5% yield) of (25d).

$bp._{10}$ 45°C

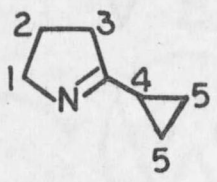
Picrate derivative mp. 150-151°C

Analytical Data (analysis performed on picrate derivatives):

$C_7H_{11}N + C_6H_3N_3O_7$ Calc'd: N, 16.56

Found: N, 16.53

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	3.75	2	Triplet of Triplets unresolved
5.	.81	4	Doublet

2, 3, & 4 unresolved ranging from 1.5-2.57

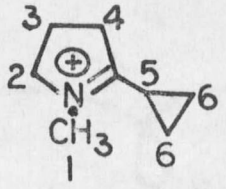
Preparation of the Methyl Iodide Salt of 2-cyclopropyl-pyrroline, (28):

A large excess of methyl iodide was added to an ethereal solution of (25d), (.5 g, 0.00467 mole). The solution was heated to reflux for fifteen minutes and cooled to room temperature. The white crystals of the salt (28) were collected by vacuum filtration.

mp. 34°C

Mass spectra parent peak 124

nmr Data



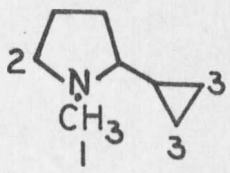
	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	3.72	3	Singlet
2.	4.35	2	Triplet
6.	1.69	4	Multiplet

3, 4, & 5 two peaks at 2.35 and 3.06 unresolved

Preparation of N-methyl-2-cylcopropyl pyrrolidine, (29):

To the solution of (28) and absolute methanol, a large excess of sodium borohydride was added. The reaction was allowed to proceed for one hour. After the allotted time, work-up was effected by the addition of a large excess of water and extraction with methylene chloride, a solution containing the desired product was obtained. Drying with sodium sulfate and evaporation of the methylene chloride yielded a residue showing only one major component by glc (7' x ¼" OV-17 column).

nmr Data

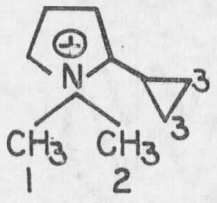


	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1.	2.41	3	Singlet
2.	3.10	2	Multiplet
3.	.5	4	Wide Multiplet

Preparation of the Methyl Iodide Salt of N-methyl-2-cyclopropyl pyrrolidine, (30):

After dissolving the previously prepared n-methyl compound (29) in ether and heating the solution to reflux, a large excess of methyl iodide was added. After refluxing for 15 minutes, the solution was allowed to cool to room temperature at which time white crystals began to form. Collection of the crystals was accomplished by vacuum filtration. The nmr spectrum was the only physical data taken on this compound.

nmr Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
1 & 2	3.47 & 3.22	6	Two Separate Singlets
3.	.9	4	Multiplet

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