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

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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Signature Brent Robert Carlson

Date June 16, 1972

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Approved:

E. W. Gnacker
Head, Major Department

Bradford Philip Mundy
Chairman, Examining Committee

Henry L Parsons
Graduate Dean

MONTANA STATE UNIVERSITY
Bozeman, Montana

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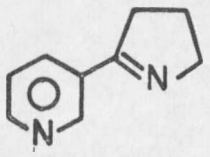
ABSTRACT

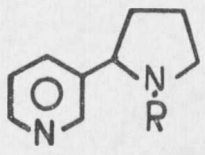
A calcium oxide pyrolysis of several N-acyl lactams leads to a useful preparation of some pyrroline and piperidine alkaloids.

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.

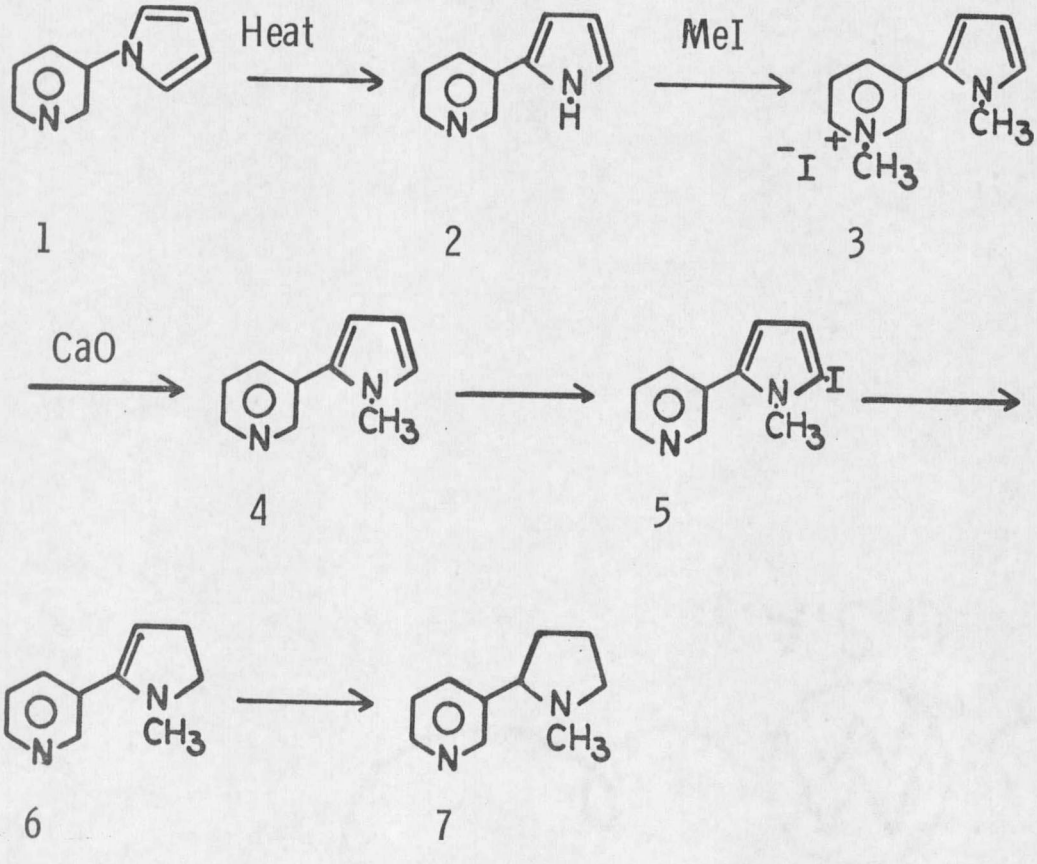
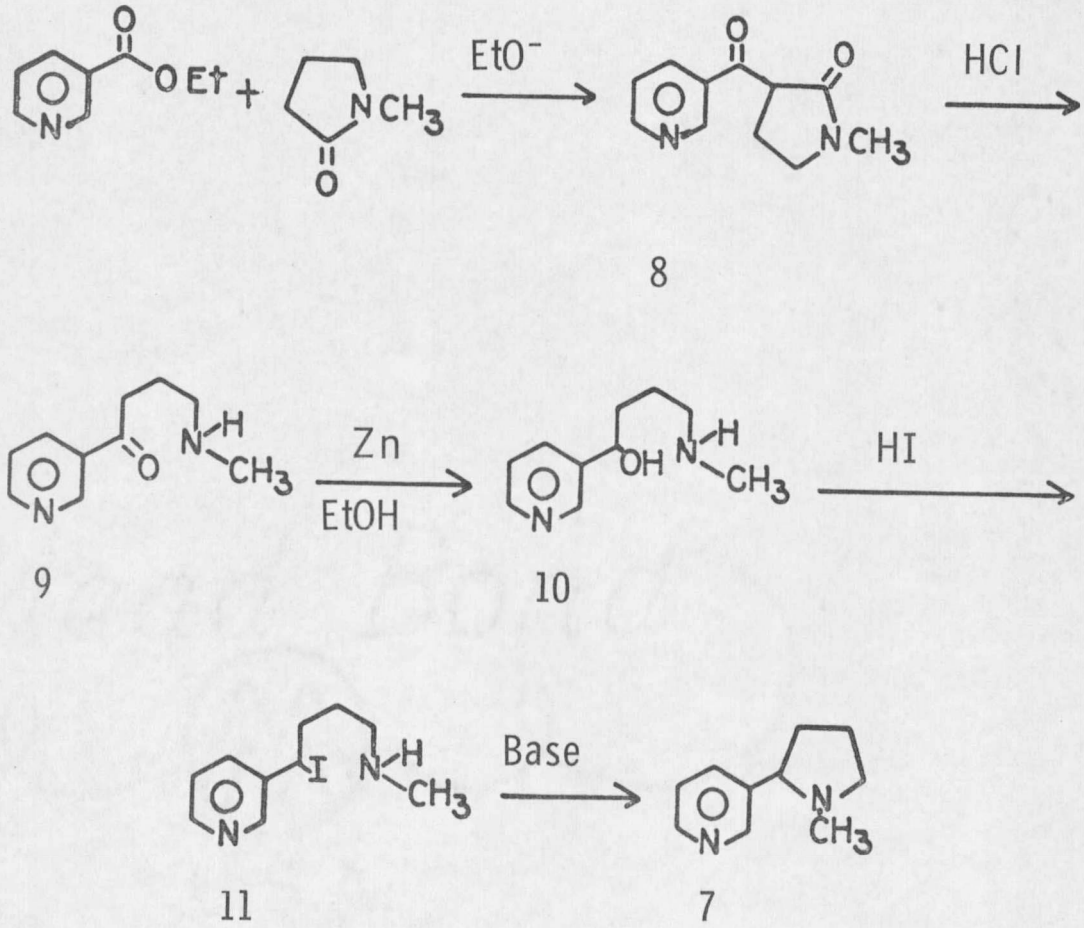


Figure 1. The Pictet Synthesis of Nicotine

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).

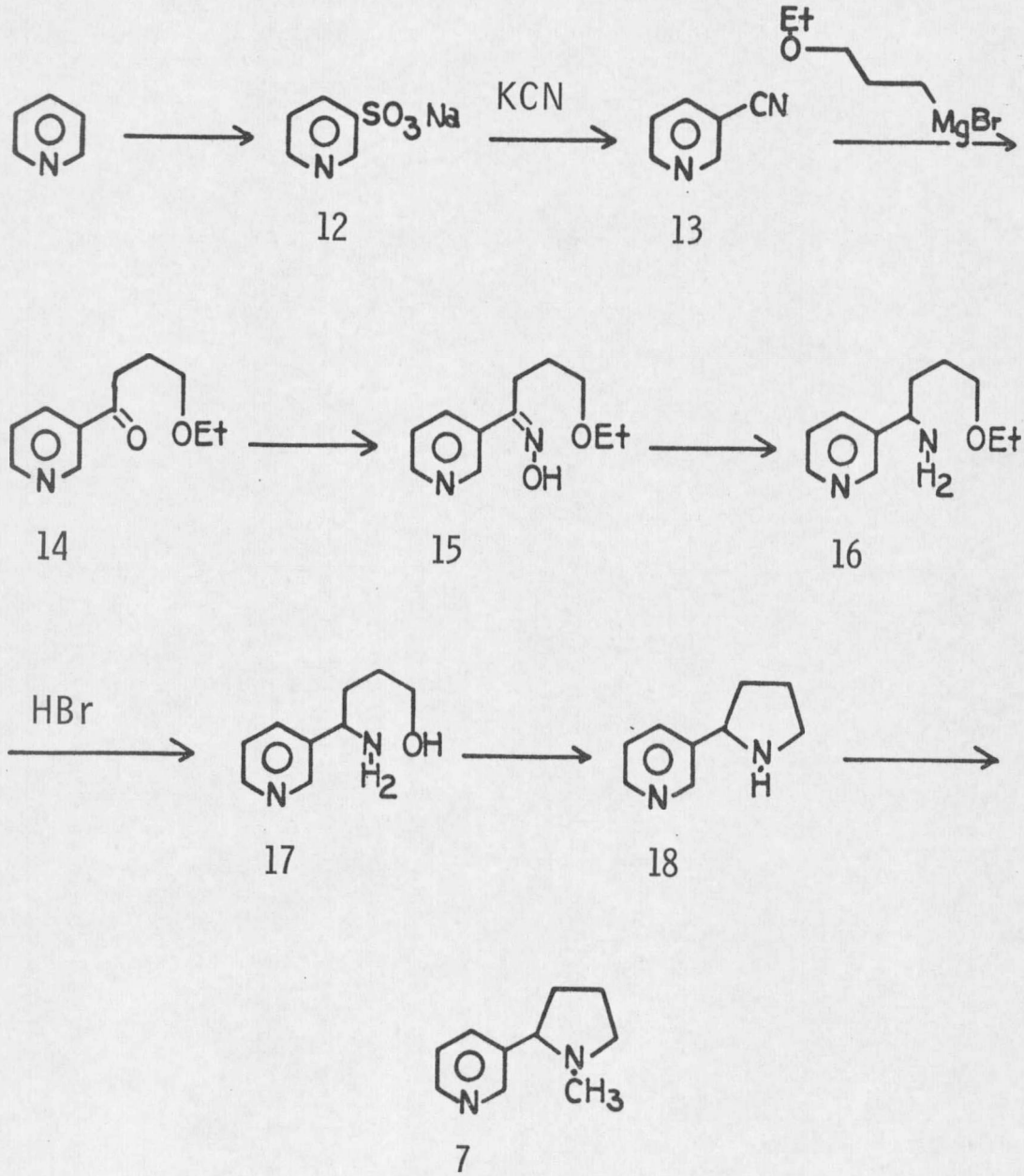


Figure 3. The Craig Synthesis of Nornicotine and Nicotine

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

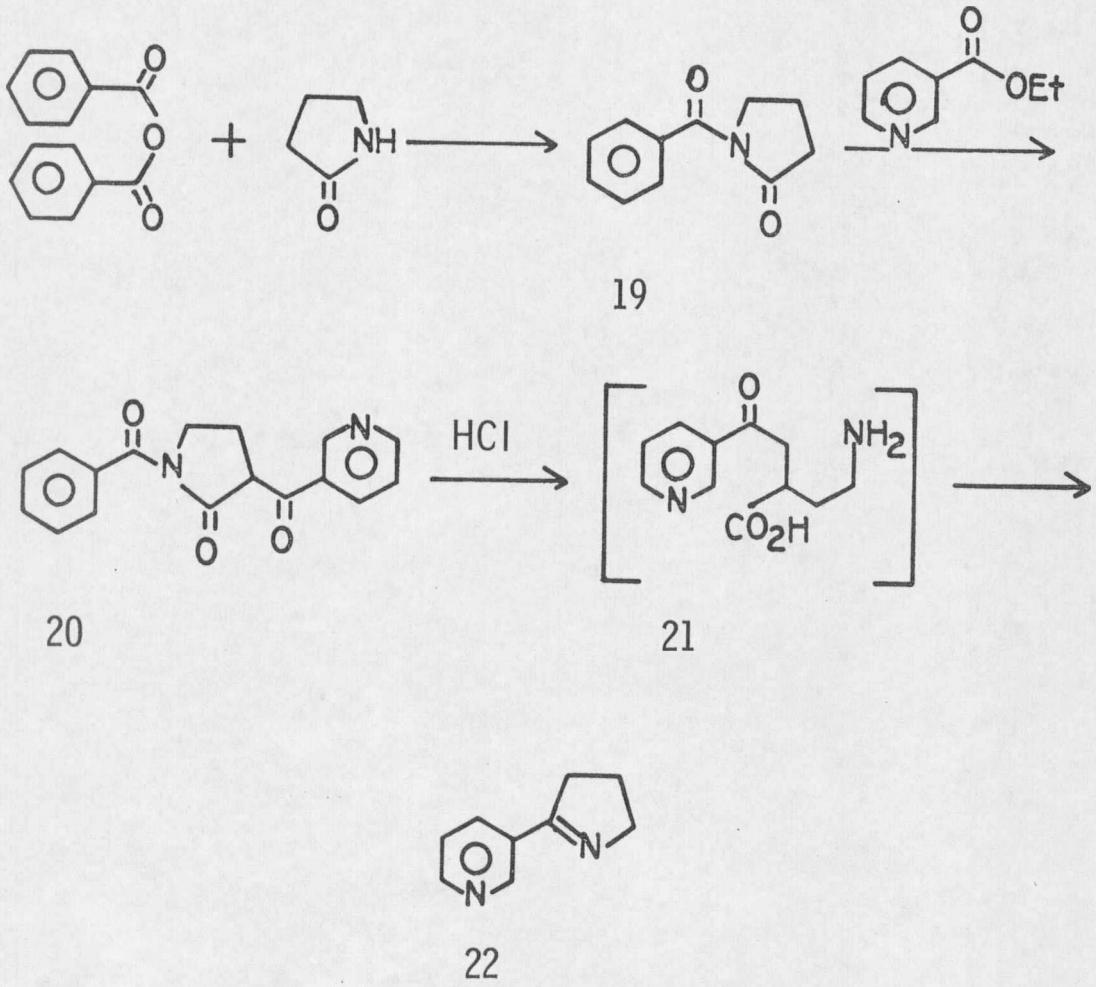


Figure 4. Synthesis of Myosmine by Spath & Mamoli

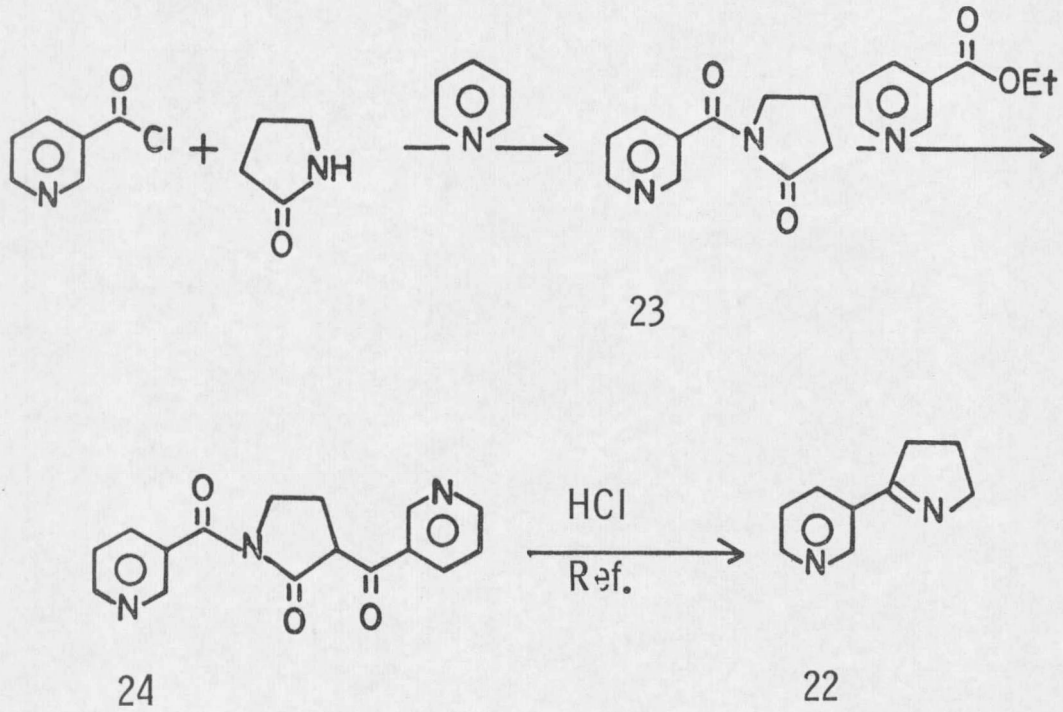


Figure 5. Synthesis of Korte & Schulze-Steiner

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

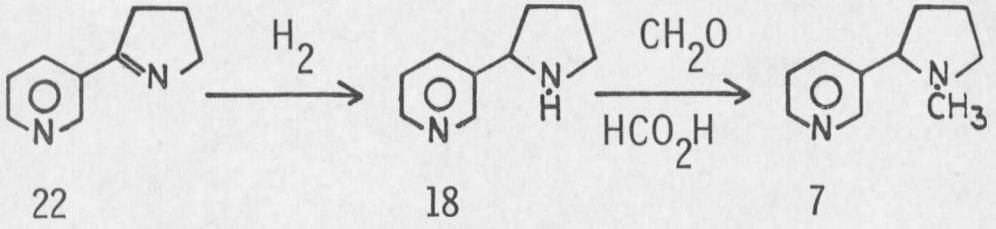
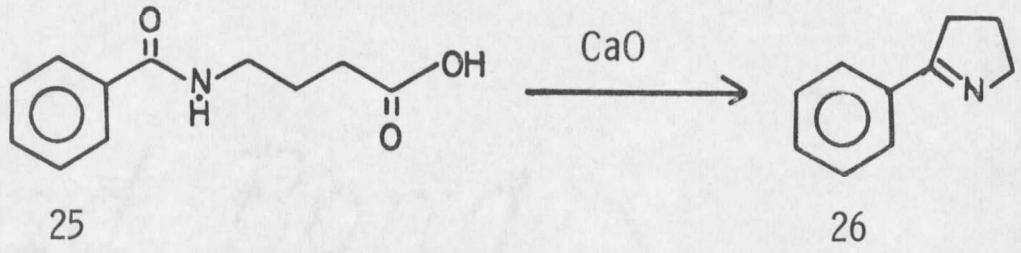


Figure 6. Conversion of Myosmine to Nicotine by Djerassi

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.

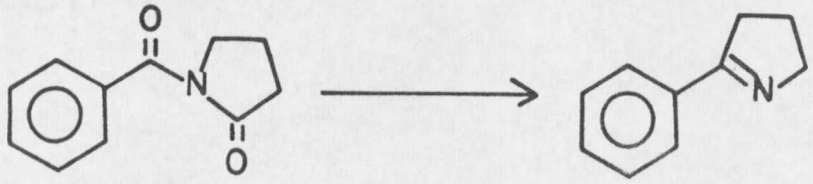
Mundy and McKenzie, realizing this fact, embarked on a synthetic procedure based on the calcium oxide pyrolysis of N-benzoyl-4-aminobutyric acid (25) previously reported by Murakoshi.[10] Using the phenyl-substituted acid, (25), free flame, and calcium oxide as a catalyst, 2-phenylpyrroline (26) was 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]

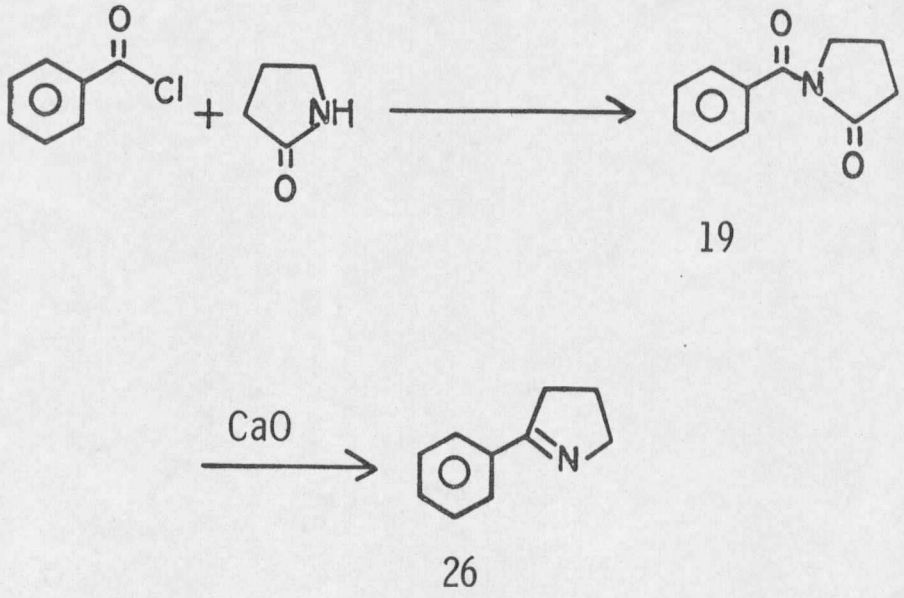
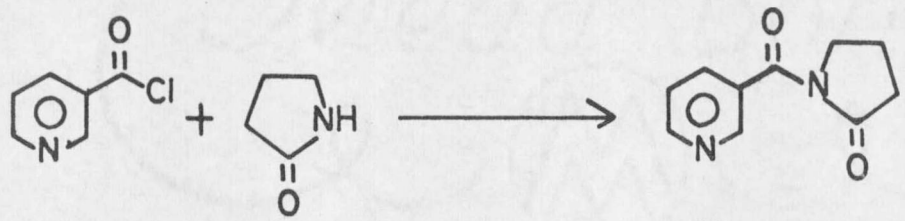


Figure 9. The McKenzie Synthesis of Phenyl Pyrroline

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.



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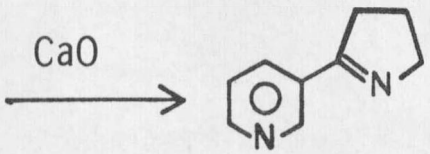

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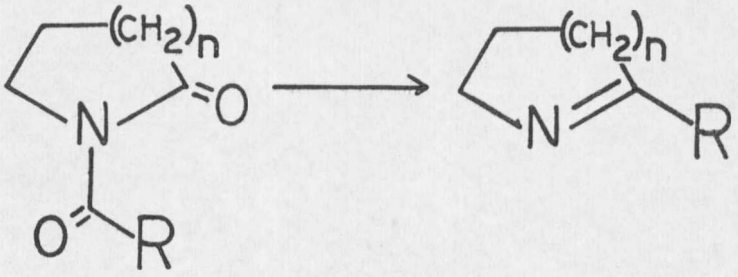
Figure 10. Synthesis of Myosmine

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



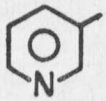
	R	n
24a-25a		2
24b-25b		1
24c-25c		2
24d-25d		1

Figure 11. General Formula of Pyrroline and Piperidine Alkaloids

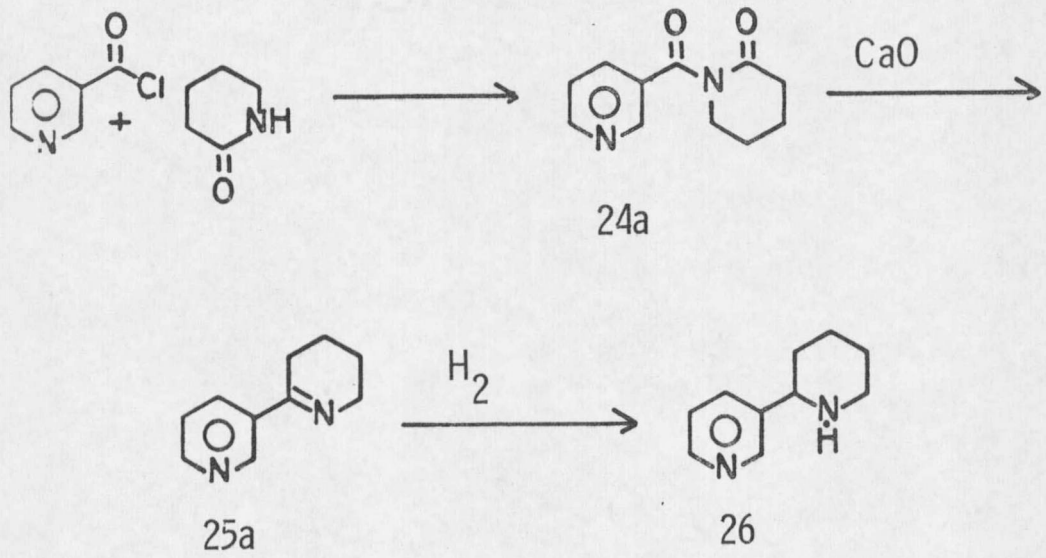


Figure 12. Pyrolysis Production of Anabasene and Anabasine

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

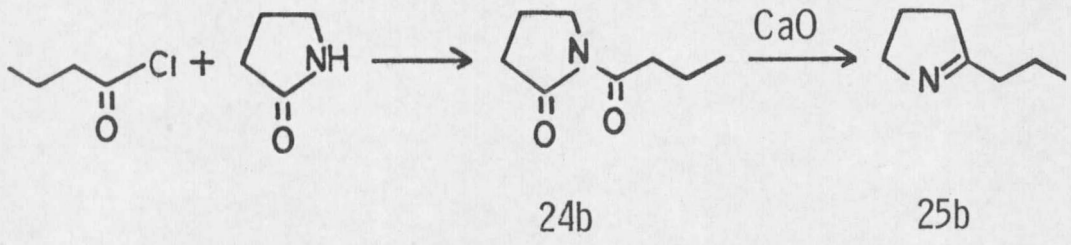


Figure 13. Synthesis of 2-(n-propyl) pyrroline

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