A new approach to substituted piperideines
by Joseph Alan Dibbern

A thesis submitted in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE in Chemistry
Montana State University

Abstract:
The Beckmann and Mundy N-acyllactam rearrangements are utilized to develop a new synthetic approach to alkylated piperideines. A consequence of this work is a new synthesis of coniine.

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Date 6/17/81

to
my parents

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A thesis submitted in partial fulfillment
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Approved:

Bradford P. Mundy
Chairperson, Graduate Committee

Head, Major Department

Henry L. Parsons
Graduate Dean

MONTANA STATE UNIVERSITY
Bozeman, Montana

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ABSTRACT

The Beckmann and Mundy N-acyllactam rearrangements are utilized to develop a new synthetic approach to alkylated piperideines. A consequence of this work is a new synthesis of coniine.

INTRODUCTION

The primary objective of this endeavor was to find an improved method for synthesizing alkylated imines. A general schematic of the proposed methodology is shown below (Figure 1). All yields and further

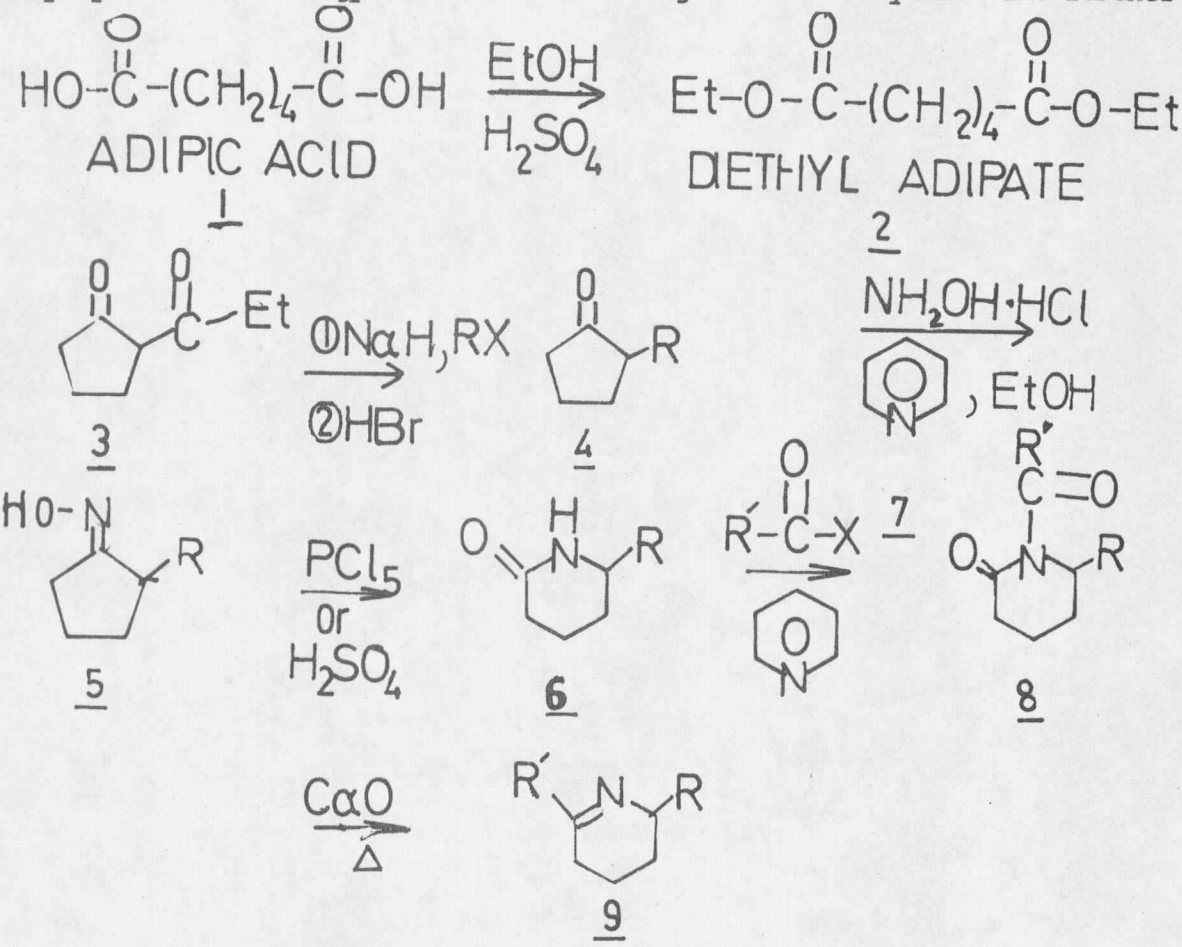
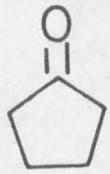


Figure 1. Proposed synthetic methodology

information concerning reaction conditions are reported in the experimental section.

At steps 4 and 5 structurally similar stock chemicals 10 and 11 were used as model compounds to avoid drastic loses of precious synthesized material in alternately tested pathways. When the best



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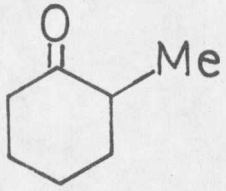

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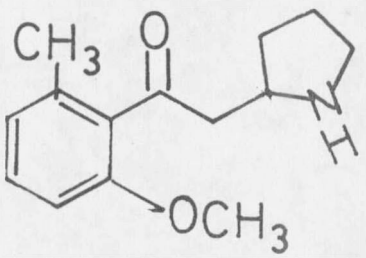
reaction pathway was found the synthesized reagents were used.

HISTORICAL

The 1-pyrroline and piperideine ring systems constitute the backbone of a variety of natural products, biosynthetic intermediates and pharmaceuticals (Table 1). The preparation of these forms of

Table 1. 1-pyrroline and piperideine examples



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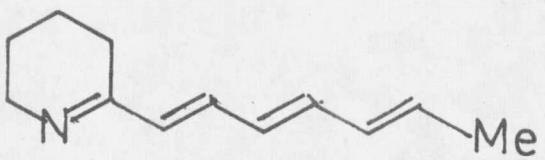
intermediate in the synthesis of elaeocarpine and isoelasocarpine[1].



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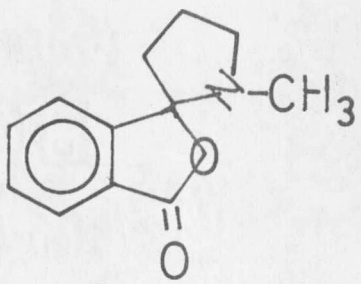
Nigrifactin[2], a natural product, antibiotic



14

Shihunine[3], a natural product

molecules, with various alkylated substituents, would not only serve as an intellectual stimulation but as a great aid in the pursuit of simplified methods for natural products synthesis.

This thesis will be concerned with laying the framework for further study of the synthesis of dialkylated imines via the Mundy N-acyllactam and Beckmann rearrangements. For the purpose of organization, the historical section is divided between reports on the Mundy N-acyllactam rearrangement's and the Beckmann rearrangement's uses and limitations.

The Beckmann rearrangement is a common reaction of oximes. The mechanism involves the production of an electron deficient nitrogen via the loss of water from the protonated oxime, followed by alkyl migration. The resulting cation is attacked by water to form an enol which experiences enol-keto equilibrium[4]. This process is delineated in Figure 2.

This reaction has been further characterized as a stereospecific rearrangement where the group <u>trans</u> or <u>anti</u> to the hydroxyl group migrates (Figure 3). The stereospecific nature has been attempted to be explained by a simultaneous movement of the <u>trans</u> -R group and the -OH forming a transition state, as shown in Figure 4. With the -OH partially bonded to the nitrogen and the carbon, the <u>trans</u> -R group attempts a backside attack while being partially bonded to both the nitrogen and the carbon[5]. However, more modern consideration of

orbital requirements leave this approach to be questionable.

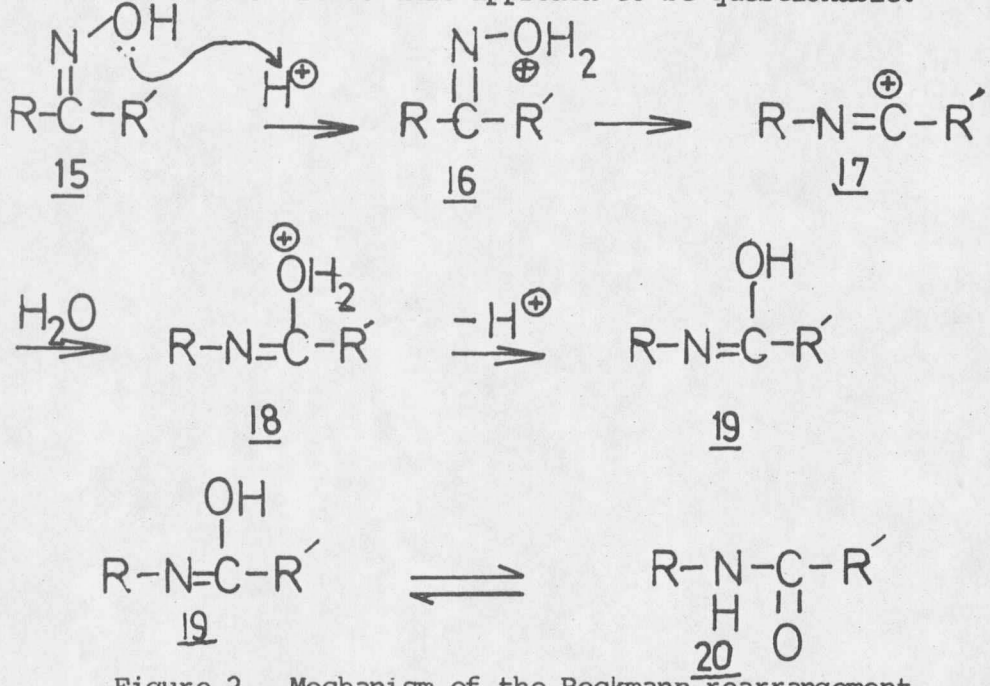


Figure 2. Mechanism of the Beckmann rearrangement

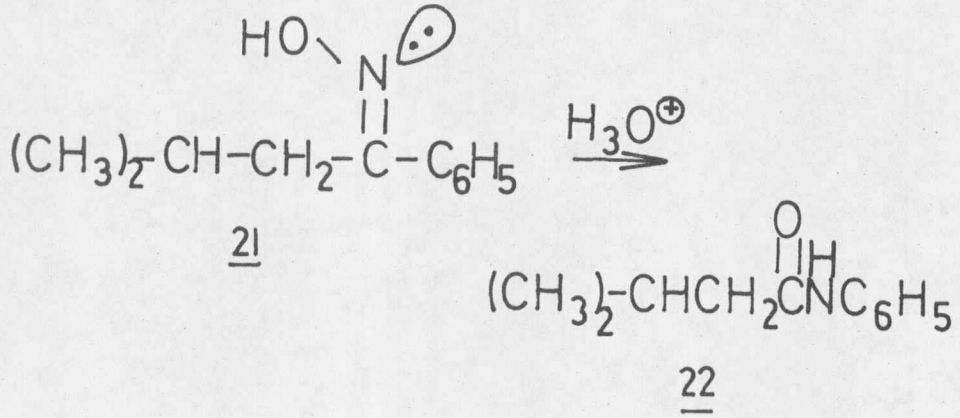


Figure 3. Stereospecific nature of Beckmann rearrangement

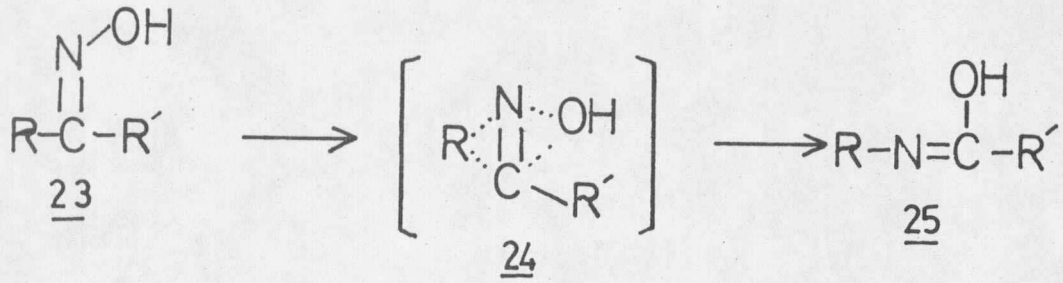


Figure 4. Beckmann transition state

This rearrangement was used extensively in the past for the synthetic preparation of amides, their hydrolysis products, carboxylic acids and amines.

The Mundy N-acyllactam rearrangement[6] was originally developed as a useful method of converting N-acyllactams to their corresponding cyclic imines. As part of an NSF funded Undergraduate Research Participation Program, it was shown that N-benzoyl-2-pyrrolidone was readily converted to 2-phenyl pyrroline[7] (Figure 5).

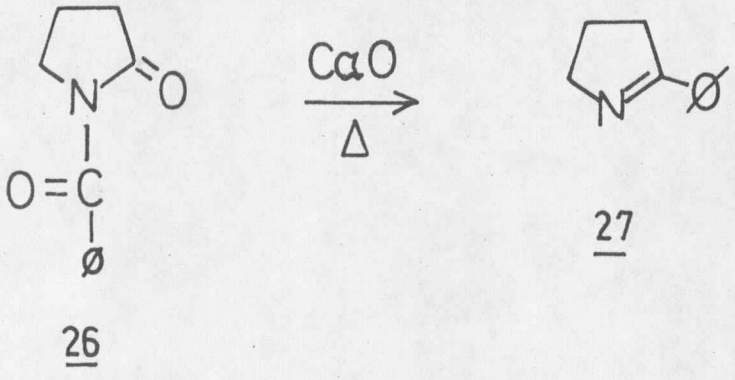


Figure 5. N-acyllactam rearrangement of N-benzoyl-2-pyrrolidone

Myosmine, an alkaloid isolated from the tobacco plant, genus Nicotiana[8], was originally synthesized by Spath and Mamoli[9] via the complex steps outlined in Figure 6 below. Spath and Mamoli's

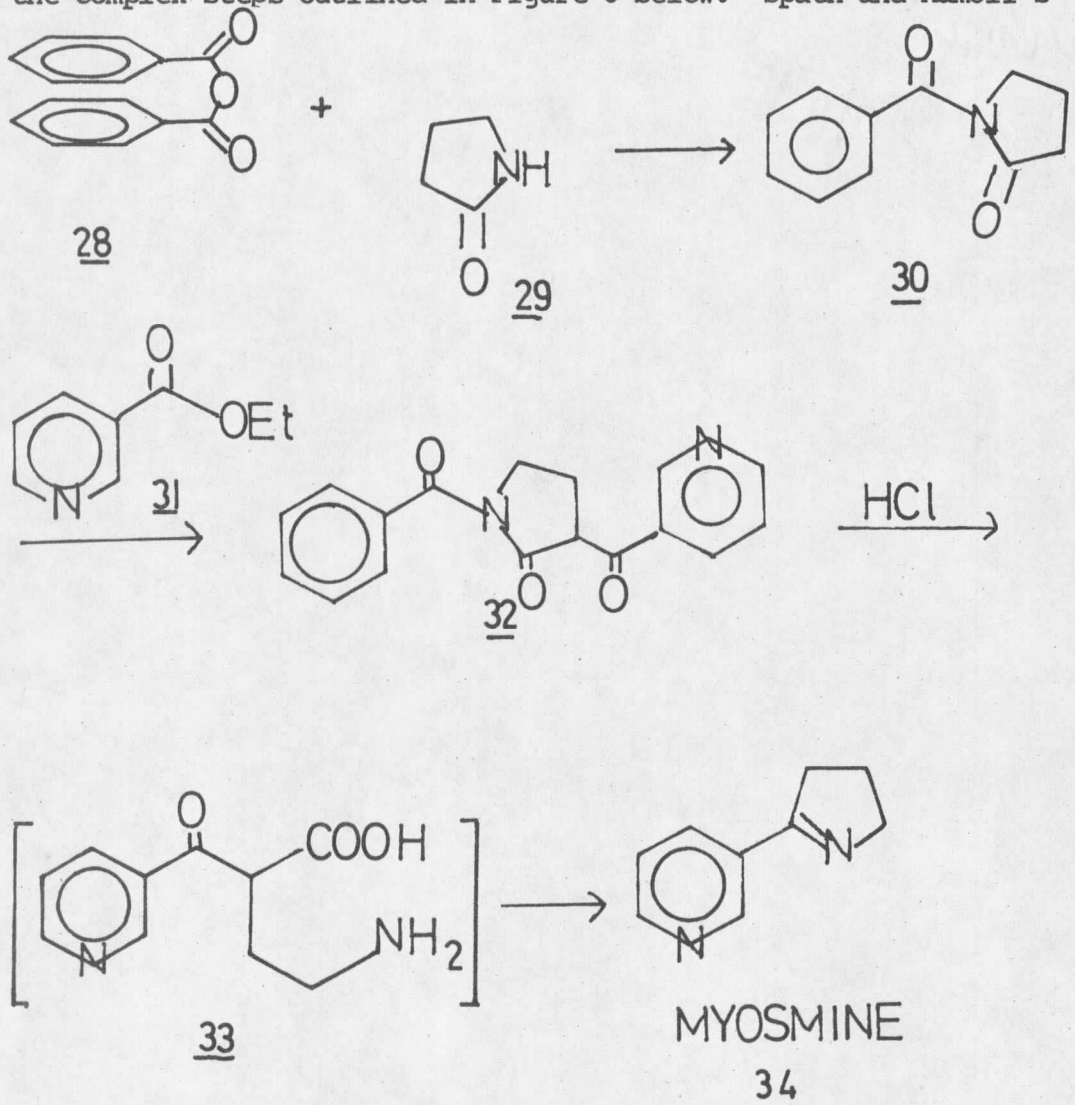


Figure 6. Spath and Mamoli synthesis of Myosmine

synthetic scheme was simplified further by Korte and Schulze-Steiner[10] as shown in Figure 7. These methods had yields of 8% and 28%

respectively.

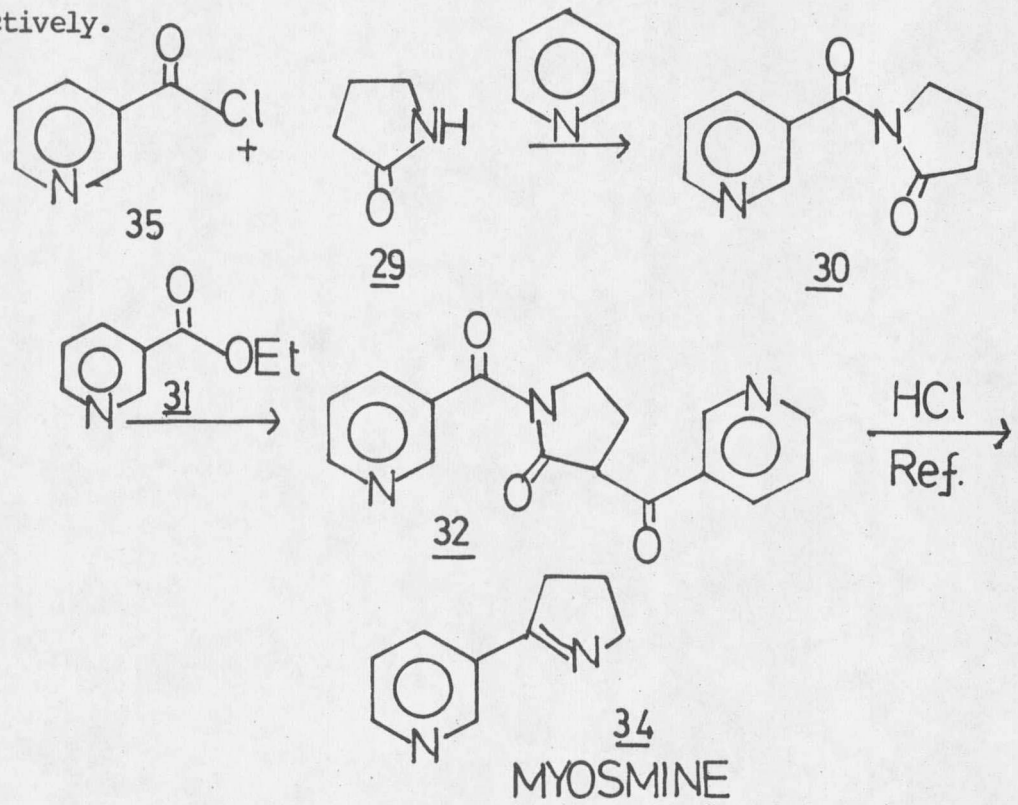
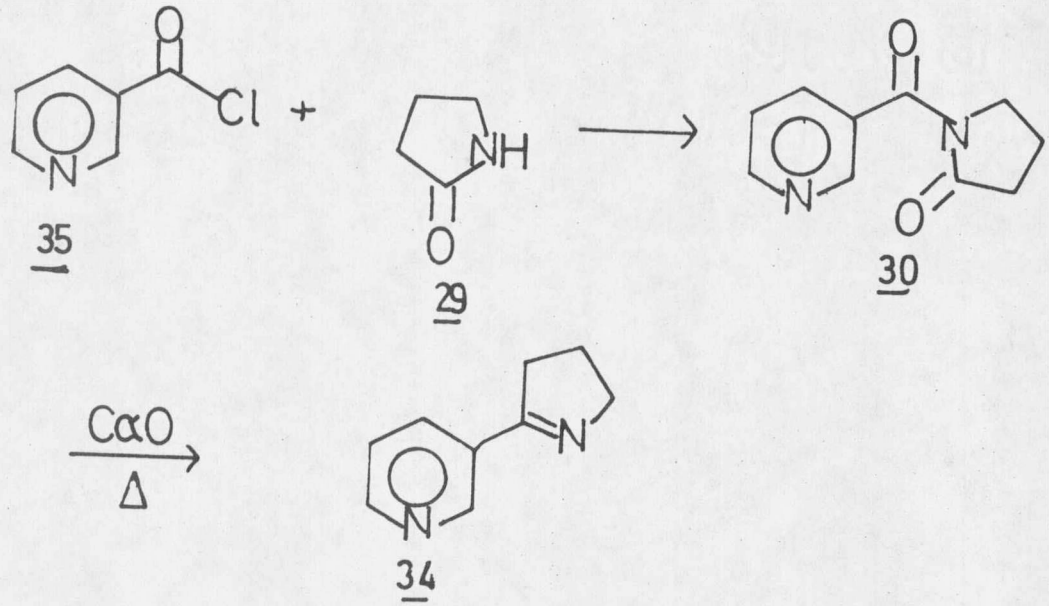


Figure 7. Korte and Schulze-Steiner synthesis of Myosmine

This laboratory adapted the N-acyllactam rearrangement for a two-step synthesis of myosmine with an overall yield of 57% (Figure 8).

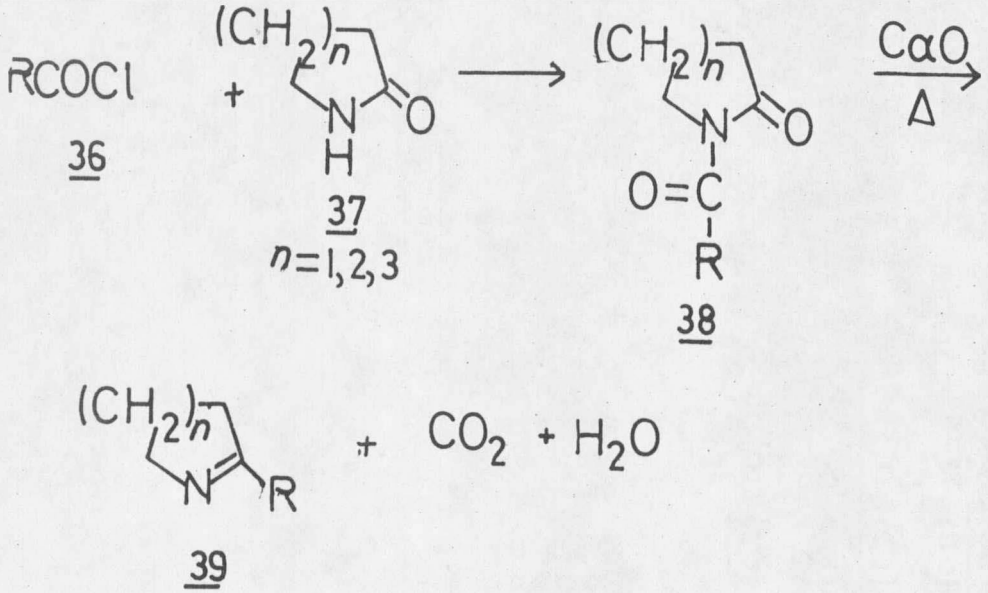
Generally, this rearrangement follows a synthetic scheme of coupling an acid halide where R=alkyl, aryl carbocyclic or heterocyclic, with a 5-, 6- or 7-membered lactam forming the corresponding N-acyllactam. Pyrolysis of this with calcium oxide produces the cyclic imine with, presumably, the loss of CO_2 and H_2O. The general scheme is shown in Figure 9, followed by Table 2 listing

products available via this rearrangement.



35 29 30 34

Figure 8. N-acyllactam synthesis of myosmine

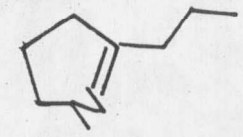


36 37 38 39

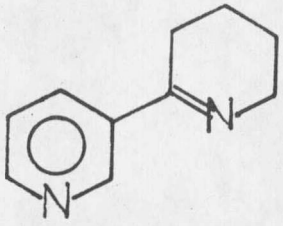
Figure 9. General synthesis of cyclic imines

Table 2

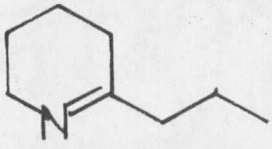
Molecule Available Via N-acyllactam Rearrangement



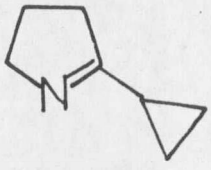
40 2-(n-propyl)pyrroline[11]



41 Anabasene[12]



42 Coniceine[7]



43 2-cyclopropylpyrroline[11]

This rearrangement has been shown to have two possible reaction pathways (Figure 10)[13]. Furthermore, the rearrangment mechanism has been shown via carbon-14 labeling to follow the partial scheme proposed in Figure 11[14].

Up to this point this rearrangement has been a useful synthetic tool, but it has been shown to have drawbacks (Figure 12).

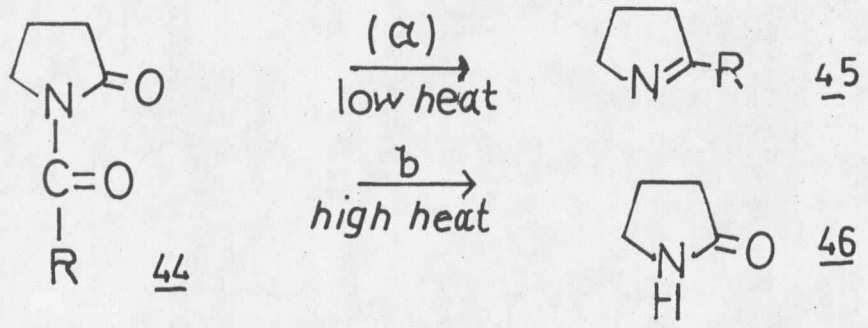


Figure 10. Two possible N-acyllactam pyrolysis routes

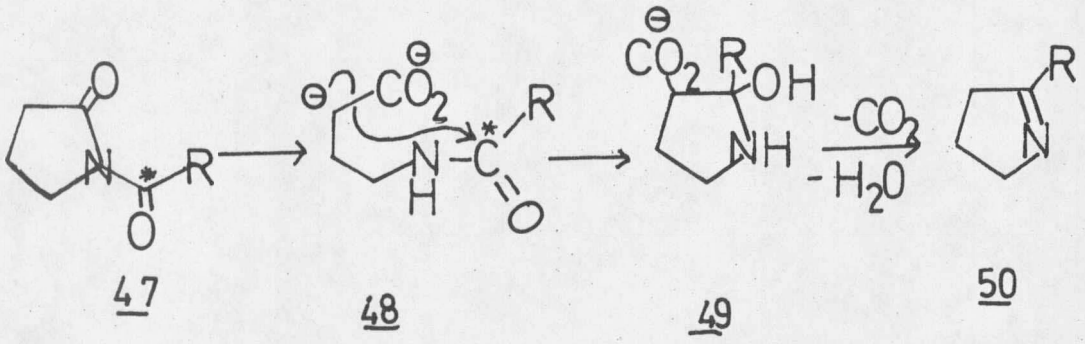


Figure 11. Partial mechanism of N-acyllactam rearrangements

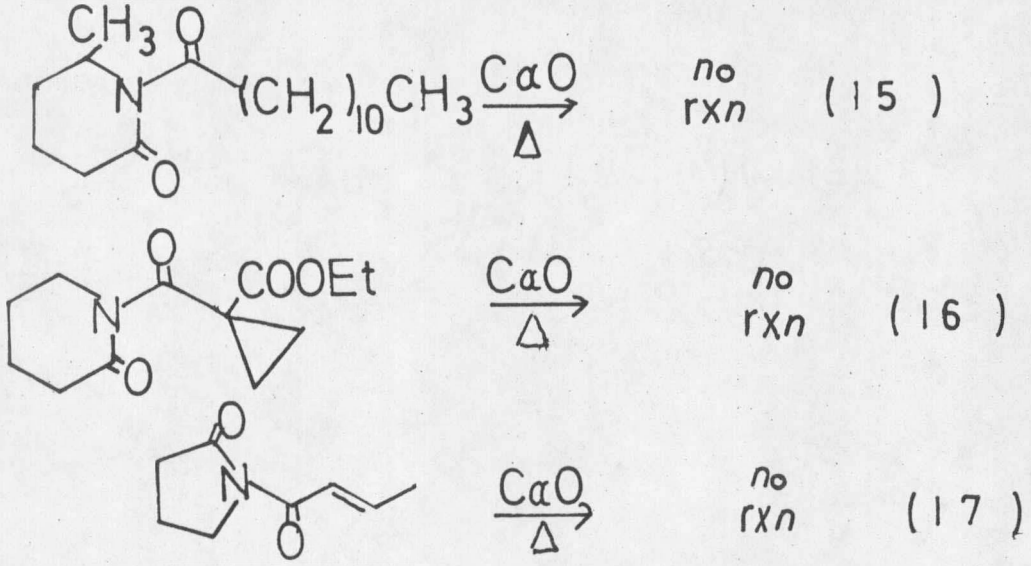


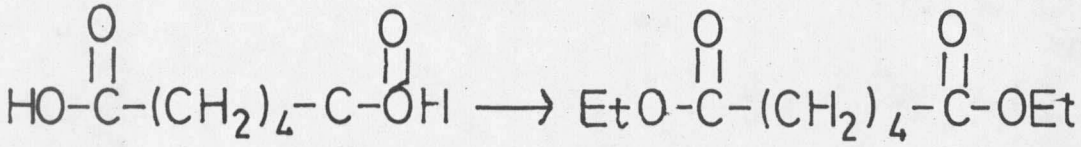
Figure 12. Reactions where the N-acyllactam rearrangement failed

These reactions would lead an investigator to believe very large groups and conjugated systems would not rearrange but further study is warranted to narrow these restrictions. These studies are now being pursued in our laboratory.

Both the Beckmann and N-acyllactam rearrangements have been presented and their independent synthetic usefulness described. My purpose is to show their combined worth and explore these methods for "quick and dirty" synthesis of dialkylated imines from inexpensive starting materials.

RESULTS AND DISCUSSION

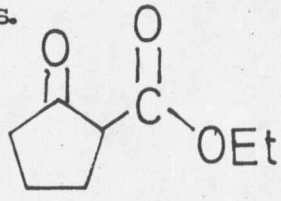
Adipic acid 63 is an inexpensive and readily available chemical which can be easily converted to 64 in reasonable yields, Figure 13.



63 64

Figure 13. Esterification of adipic acid

Subsequently 64 is converted, via the Dieckmann Reaction with sodium hydride to 65, which becomes the important precursor for a variety of possible conversions.



65

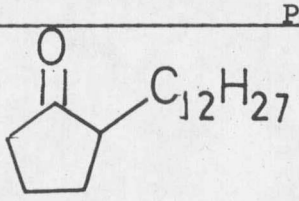
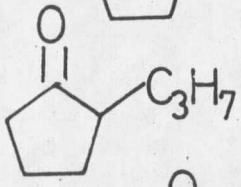
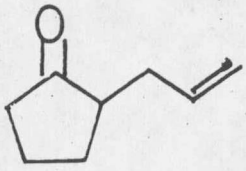
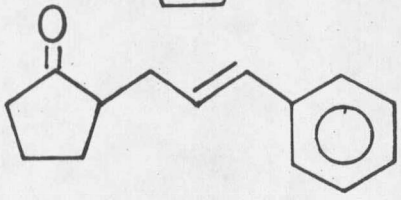
Alkylation of the 2-position of 65 occurs via removal of the hydrogen at the 2-position with sodium hydride, followed by the subsequent alkylation of the resulting enolate with an appropriate alkyl halide. Table 3 lists some of the attempted alkylated products and the respective alkylating agents.

Compound 67 proved to be the easist to synthesize, resulting in an 84% yield. Due to this fact, 67 was the compound of choice for continuation of the synthetic study. Compounds 65, 68, and 69 were

attempted to examine the generality of the alkylating method. The alkylating agents used were chosen primarily due to their ready availability.

Table 3

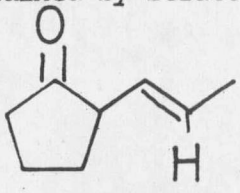
Attempted Alkylation Products

Alkylating Agent	Product
1-chlorododecane	 66
1-iodopropane	 67
3-iodopropene	 68
Cinnamyl chloride	 69

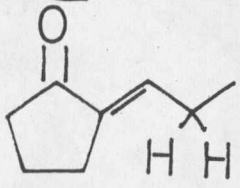
Compound 66 could never be prepared, even after repeated attempts. The problem seemed to be a result of poor displacement, possibly a consequence of -Cl being a poorer leaving group. The formation of a large amount of dodecane from this reaction was confirmed via mass spectral analysis and seemed to indicate that enolate formation was not complete and a reduction had occurred by hydride displacement of

chloride.

The reaction to product 68 gave no predominant product in a complex mixture. Distillation gave six fractions which contained combinations of substances that were not starting materials. Gas Liquid Chromatography (G.L.C.) collections were made of various peaks and used for Nuclear Magnetic Resonance (NMR) analysis. The NMR spectra were of such complex nature that they were not readily evaluated; but, two had prominant features. One spectrum had a methyl doublet (1.15 ppm) and the other a methyl triplet (0.90 ppm) which could be explained by structures 70 and 71. These structures can be



70



71

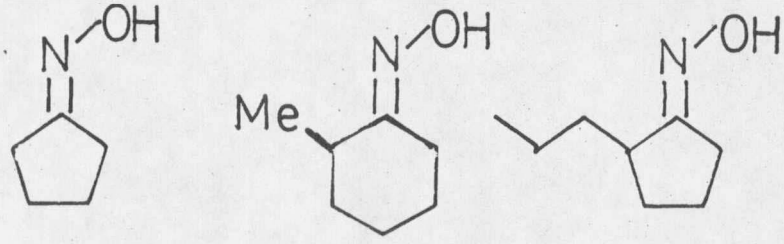
rationalized as products via isomerization of the original desired product, 68, to a conjugated system.

Compound 69 was produced in low yield. It was purified no further than the point where it was T.L.C. collected and its structure verified by I.R. analysis. The I.R. showed strong peaks at 2900 cm^{-1} (C-H stretch) 1740 cm^{-1}(C=O), 751 cm^{-1} and 700 cm^{-1} (mono-substituted aromatic). The mere existance of 69 proves that large groups and conjugated groups could be alkylated onto 65.

The next major hurdle to be assulted was the formation of the

oximes of the alkylated cyclopentanones. Although there are many methods for oximation, few of them produce useful yields of cyclic oximes. A summary of general reagents used, systems tested and resulting yields are shown in Table 4. Not all methods were investigated due to their sketchy descriptions or exotic natures.

Of the methods described in Table 4, the last method held the greatest potential due to the reasonable yields of 72 and 73 (89% and 85% respectively) and fifteen minute reaction time. Also, due to the relatively small number of by-products, the oximes could be purified by simple distillation.



72 73 74

The Beckmann rearrangement was the next step to be examined. Table 5 lists some possible methods for this rearrangement. Of the methods listed, methods a, e and f were attempted due to their higher yields, simplicity, and reoccurrence in the literature. Compound 9 was used as the test subject for all runs followed by 67 via the most promising method.

Table 4

Oximation Methods Available

General Reagents Used	System Oximated	Sources
$NH_2OH \cdot HCl$, 0°C, CO_2 atmosphere	cyclic, aliphatic, and methyl ketones	18
ion exchange columns used as reaction templates	acetone, methyl ethyl ketone furfural, cyclohexanone, acetophenone	90-100%[19]
review article of cyanohydrin synthesis, oxime and semicarbazone formation	_____	20
review article of photosation and oximation of saturated hydrocarbons	_____	21
3° AmOK in 3° AmOH, 1-6 mo at room temperature	very hindered ketones	22
$NH_2OH \cdot HCl$, KOH, 95% ETOH	2-methyl cyclohexanone	81%[23]
$NH_2OH \cdot SO_4$, ETOH, H_2O, $NaCO_3$, pH 6.8	2-methyl cyclohexanone	no rxn[24]
$NH_2OH \cdot HCl$, 50% ETOH, pyridine	2-methyl cyclohexanone 2-(n-propyl)cyclopentanone cyclopentanone	40%, 69%, 92.5%[23]

Method "e" was found twice in the literature and both times the procedure was quite sketchy. A German patent[25] was referred to for more information, but insufficient details were available. In all attempts, the reaction failed to produce any evidence for the formation

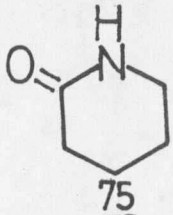
of 75.

Table 5

Methods for Beckmann Rearrangements

General Reagents Used	Systems Studied	Source
a) various concentrations of H_2SO_4 108°C	cyclopentanones, cyclohexanones	59-97%[26]
b) H_2SO_4-HOAc and HCl, heated with oximes	cyclopentanone	27
c) H_2SO_4 solution at various temperatures	aliphatic and alicyclic oximes	28
d) pyridine hydrochloride	benzophenone oximes	29
e) 8% NaOH, benzene sulfonylchloride, ether	thienyl ketoximes	30,25
f) PCl_5, ether, 10 N NaOH	cyclopentanone	95%[31,32]

Method "f" produced 75 as well as several by-products not produced in method "a". Method "a" proved to be the method of choice, giving higher yields (16% versus 12% in "f") and less by-products. Due to its fine performance with 72 all of 74 was committed via this method to produce 76 in 64% yield.



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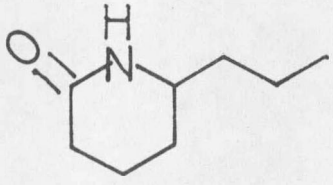
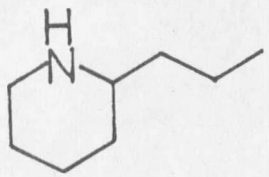


76

At this point a fraction of the stockpiled 76 was reduced with

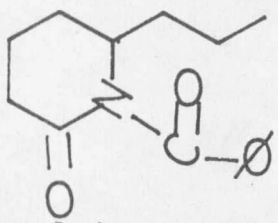
lithium aluminum hydride to form coniine, 77, a natural product of the



77

water hemlock, Coniium maculatum[33]. The product was characterized by making the picrate derivative and comparing its melting point (42-43°C) with the literature value (43°C)[34]. The conversion of 1 to 77 establishes that this method may be useful in providing a general route to 2-substituted piperidines.

It was next of interest to test the possibilities of preparing 2,6-disubstituted piperidines. The remainder of 76 was committed to form the acylation product 78.

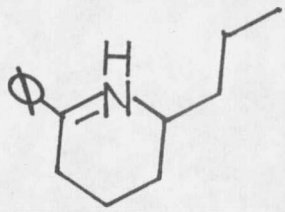


78

The crude reaction products were separated by an aluminum oxide column (3" x 1") with a dichloromethane/ether (50/50) elution, followed by methanol. The later fractions contained unreacted starting material, 76, while the former contained 78. The structure of 78 agreed with analysis via I.R. and NMR of the first fraction. The purity of these fractions was checked by T.L.C. rather than G.L.C due

to their high boiling points.

All of the acylated product 78, was mixed with calcium oxide and an N-acyllactam rearrangement was attempted to produce 79. A few drops of crude reaction products were obtained and an NMR analysis was



79

attempted to confirm aromatic character. A very small aromatic response was noticed, but there was much more evidence of decomposition products, predominantly 76. Much more work needs to be done to define more reproducable reaction conditions.

SUMMARY

Starting with inexpensive materials 63, a synthetic scheme was proposed to produce alkylated piperideines. As a consequence, a new method of synthesizing coniine, 77, was developed and an attempt was made to produce a dialkylated imine, 79.

Although many reaction conditions were reviewed for various steps in the proposed synthetic scheme, numerous research topics could be proposed to further understand the steps used.

Studies could be conducted on the flexibility and usefulness of alternate methods of alkylation. These alternate methods could involve a spectrum of new ways ranging from photochemical means[39] to metal oxide initiated additions[40].

Further study is warranted on the ramifictions of substituent sizes, conjugation and even heteroatom effects. Examination of the effect of various alkyl groups on the Beckmann rearrangement could show them inconsequential[24] or of a much less passive effect[29] then previously proposed.

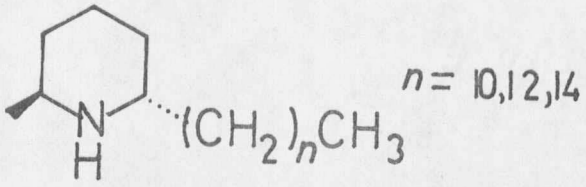
The Mundy N-acyllactam rearrangement could use further clarification as to its limitations, reaction conditions and possible idiosyncrasies. It could be refined and used to prepare compounds like those shown in Table 6.

Clearly, this research has only scratched the surface of a teaming "termite hill" of research topics, some of which are presently

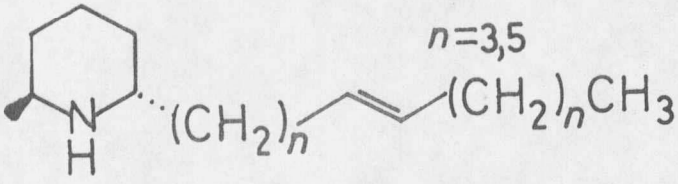
being pursued by this laboratory.

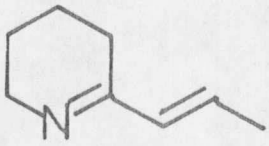
Table 6

Possible N-acyllactam Products



Constituents from the Venom of the "fire" ant, Solenopsis sevissima[41]





An unstable constituent of immature pomegranate leaves[42]

EXPERIMENTAL

Boiling and melting points are uncorrected, NMR spectra were taken from either a Varian A-60 or Bruker 250 MHz instrument using carbon tetrachloride (CCl_4) as a solvent with 1% tetramethylsilane (TMS) as an internal standard or $CDCl_3$ with 1% TMS respectively. Infrared spectra were obtained using a Beckmann IR-5 spectrophotometer and G.L.C. analyses were performed with a Varian 1400 gas chromatograph using an 8' x ⅛", 10% Apiazon on Chromosorb W column.

Unless otherwise specified, the commonly used solvents were purified as follows: tetrahydrofuran (THF) was distilled from lithium aluminum hydride, benzene was distilled from sodium, and pyridine was distilled from barium hydroxide.

Other commonly-needed reagents were used as received: lithium aluminum hydride (LAH) (Alfa Products), sodium hydride (NaH), 50% oil dispersion (K & K Laboratories, Inc.), various other reagents were acquired from Baker and Aldrich Co.

Preparation of Diethyl Adipate (64)

Concentrated sulfuric acid (3 ml) was added to a stirred solution of adipic acid (184.30 g, 1.26 moles) in absolute ethanol (200 ml). This mixture was refluxed overnight. The resulting solution was brought to neutral pH with saturated sodium bicarbonate solution and the ethanol was removed via rotary evaporation. The remaining organic residue was distilled to produce 167 g (66% yield) of 64. Purity was

checked via G.L.C.

B.P.$_{17}$ 146-182°C, literature[35] B.P.$_{760}$ 239-241°C

Preparation of 2-carboethoxycyclopentanone (65)

The reaction vessel was a dry 5 l, 3 neck round bottom flask fitted with condenser, dropping funnel and mechanical stirrer. The vessel was flushed with nitrogen. A sodium hydride oil dispersion (38.95 g, approximately .83 moles) and dry thiophene-free benzene (700 ml) were placed inside. To this stirred suspension, 64 (167.01 g, .83 moles) was added dropwise over a one hour period. If the reaction solidified more benzene was added. The mixture was refluxed overnight. Glacial acetic acid (6.5 ml) was then mixed into the precipitate thoroughly, with the temperature maintained at 0°C. Next, 10% hydrochloric acid (150 ml) was added slowly with the temperature maintained between 0-10°C. Water (200 ml) was added to dissolve the salts and any remaining were removed via suction filtration. The benzene layer was separated and the H_2O layer extracted with additional benzene. All benzene used was then washed with water, 5% sodium bicarbonate, water and then dryed with magnesium sulfate. The drying agent was filtered, the benzene distilled and the remaining organic residue vacuum distilled to produce 59 g 65 (46% yield). Purity was checked via G.L.C.

B.P.$_{20}$ 113-116°C, literature[36] B.P.$_{11}$ 102-104°C

General Preparation for 2-alkylcyclopentanone

One well-accepted alkylation method was used throughout and typical experimental procedure follows. A sodium hydride (50%) oil dispersion (4.26 g, approximately .18 moles) was placed in a 250 ml, 2 neck, round-bottom flask, dry benzene (40 ml) and the suspension was stirred for 15-30 minutes. After the allotted time, the benzene/oil dispersion was removed by pipet and then dry THF (100 ml) was added. Compound 65 (15 g, .096 moles) was then added slowly to the stirred mixture. The solution was allowed to stir for one hour, after which time an equal molar amount of the desired alkyl halide was added and the reaction mixture was refluxed overnight. The mixture was then cooled, the THF removed and water (80 ml) added. This solution was extracted with dichloromethane, which was then dried with magnesium sulfate. The solution was filtered, the solvent removed and 48% hydrobromic acid (69 ml) was added. The mixture was refluxed until no more carbon dioxide was evolved. Water (60-80 ml) was added and the solution was extracted with dichloromethane. The extracts were washed with saturated sodium bicarbonate, water and a saturated sodium chloride solution and then dried with calcium chloride. The solution was filtered and the solvent removed, leaving the crude product for distillation.

Attempted Preparation of 2-n-dodecanecyclopentanone (65)

The general alkylation procedure described earlier was used. Chlorododecane (169.98 g, .83 moles) was used as the alkylating halide but no 66 was ever isolated. Large quantities of dodecane and 10 were found. Compound 10 was identified by coinjection via G.L.C. Dodecane was identified via mass spectrum parent peak 170 as well as the characteristic hydrocarbon fragmentation (-14 mass units).

Preparation of 2-propenecyclopentanone (67)

The general alkylation method was used with 3-iodopropene (89.62 g, .83 moles). Distillation provided six fractions from the reaction mixture, each containing combinations of several products (as indicated by G.L.C.). Various peaks were collected from the G.L.C. and examined by NMR. A methyl doublet (1.15 ppm) and a methyl triplet (0.90 ppm) were individually observed on two spectra, suggesting the formation of 70 and 71, respectively, instead of predominatly 68.

Preparation of 2-n-propylcyclopentanone (67)

The general alkylating method was used with 3-iodopropane (141 g, .83 moles). The final reaction product was distilled and 10.17 g 67 was collected. Purity was checked via G.L.C. and the NMR spectrum was in accord with the proposed structure.

B.P.$_{15}$ 67-73°C, literature[37] $_{760}$ 183°C

Preparation of 2-cinnamylcyclopentanone (69)

The general alkylation method was used with cinnamyl chloride (126 g, .83 moles). No distillation was attempted due to the high boiling point suspected, even for high vacuum distillation. The reaction mixture was cleaned via a silica gel column (10" x 1" diameter) with heptane solvent.

General Preparation of 2-alkylcyclohexanone Oxime

Hydroxylamine hydrochloride (1.26g, .018 moles) in 50% ethanol (5 ml) was added to a stirred solution of 2-alkylcyclopentanone (.016 moles) in pyridine (5 ml). The mixture was refluxed for fifteen minutes, after which the solvents were removed. Dichloromethane (25 ml) and water (20 ml) were added to dissolve the residue. The organic layer was removed and dried with magnesium sulfate. The solution was filtered and the solvent removed. Further purification depended on the particular oxime and ranged from distillation to recrystallization[38].

Preparation of 2-methylcyclohexanone Oxime (73)

The general oxime preparation method was used with these quantities:

25 g (.035 moles) hydroxylamine hydrochloride

10 ml 50% ethanol

3.37 g (.03 moles) 11

10 ml pyridine

The final residue was then recrystallized from anhydrous ether and resulted in the pure white crystalline 73.

m.p. 42-43°C, literature[39] m.p. 43°C

Preparation of 2-(n-propyl) Cyclopentanone Oxime (74)

The general oxime preparation method was used with these quantities:

7.46 g 67 (.059 moles)

18 ml pyridine

4.70 g hydroxylamine hydrochloride (.068 moles)

18 ml 50% ethanol

The resulting residue was G.L.C. checked for purity and an I.R. spectrum showed the disappearance of the C=O (1715 cm^{-1}) peak and appearance of C=N (1533 cm^{-1}), -OH (3175 cm^{-1}) and N-O (968 cm^{-1}) peaks.

Preparation of Cyclopentanone Oxime (72)

The general oxime preparation method was used with these quantities:

60.0 g 10 (.714 moles)

212 ml pyridine

56.68 g hydroxylamine hydrochloride

216 ml 50% ethanol

The final residue was distilled to produce 65 g of 72 (93% yield).

Purity checked via dichloromethane solution injected into G.L.C. An I.R. was taken of dichloromethane-wetted crystals to substantiate structure.

B.P.$_{15}$ 89-90°C, literature[23] B.P.$_{760}$ 196°C.

Preparation of 2-piperidone (75) [26]

The experimental procedure is the same as that of 76 but with these quantities:

10 g 72 (.10 moles)

15 ml 80% sulfuric acid

5 ml 80% sulfuric acid

The method produced 8.35 g crude products. The mixture was coinjected with stock reagents and produced these estimated yields:

15.6% 75

46.5% 72

18.3% 10

19.6% solvents and various minor constituents.

Alternate Preparation of 2-piperidone (75)

Compound 72 (10 g, .10 moles) was stirred at 0°C with enough anhydrous ether to make a slurry. To this slurry, phosphorous pentachloride (21.67 g, .104 moles) was added very slowly. Enough ether was added to maintain a slurry and it was stirred overnight. The ether was removed and the residue dissolved in dichloromethane, then

poured over a slush of 10 N sodium hydroxide (314 ml) and ice. The pH was adjusted to between 10 and 12, the organic layer was separated, dried with magnesium sulfate, decolorized and filtered. The solvent was removed and the components of the organic residue identified via G.L.C. coinjection with stock reagents. The composition of the 3.95 g crude mixture was:

4.7% 10

10.9% 72

11.8% 75

72.6% solvent and numerous by-products

Preparation of 2-(n-propyl)-6-piperidone (76)

In a dropping funnel 74 (3.24 g, .023 moles) and 80% sulfuric acid (35 ml) were mixed. They were added slowly to more acid (1.2 ml) at a maintained temperature of 108°C. After the addition the flask was cooled and the pH was adjusted to basic. Water (11 ml) was added and the mixture was extracted with dichloromethane. The extract was dried with magnesium sulfate, filtered and the solvent removed. The oily residue was distilled and 2.09 g 76 was collected. The purity was checked by G.L.C. inspection of a dichloromethane solution of the white crystals, as was an I.R. An NMR analysis was also used to substantiate the structure. The crystals were further purified by recrystallization with heptane.

m.p. 86-89°C, literature[38] m.p. 91.5-92.4°C.

Preparation of Coniine (77)

To a stirred solution of anhydrous ether (25.0 ml) and LAH (.07 g, .0016 moles), a solution of 76 (.5 g, .0035 moles) and anhydrous ether (10 ml) was added very slowly. After the addition the mixture was refluxed for two hours. The mixture was cooled, water (10 ml) was added, the salts were filtered off and ether rotary evaporated. To the residue 20% hydrochloric acid (20 ml) was added and then extracted with ether. Next the water layer was changed to a basic pH with 20% sodium hydroxide and extracted with ether again. This ether extract was dried with magnesium sulfate, filtered and then the solvent was removed. The .10 g crude residue was converted to the picrate derivative.

m.p. 75°C, literature[39] m.p. 72-75°C.

Preparation of N-benzoyl-2-(n-propyl)-6-piperidone (78)

Compound 76 (1.00 g, .007 moles) was dissolved in a stirred solution of dichloromethane (60 ml) and pyridine (.56 g). Benzoyl chloride (1.00 g, .007 moles) in dichloromethane (20 ml) was added to the stirred solution slowly. After the mixture was allowed to stir overnight it was filtered and the solvent removed to yield 1.51 g of a crude yellowish liquid. This was then separated to two major components by a 3" x 1" aluminum oxide (basic washed) column. Fraction

1 (.75 g) was collected with a dichlormethane/ether wash (50/50, 60 ml). Fraction 2 (.38 g) was collected with a methanol wash (60 ml). Purity of the fractions were checked by an aluminum oxide thin layer chromatography (TLC) plate using dichlormethane/ether solvent (50/50). An I.R. of Fraction 1 showed no N-H peak (3150 cm^{-1}), a C=O (1670 cm^{-1}) and possibly aromatic character (790, 700 cm^{-1}). An NMR spectrum confirmed the aromatic character (6 hydrogen peak, 7.4 ppm)

Fraction 2's I.R. and NMR matched those of the starting material 76.

Attempted Preparation of 2-phenyl-6-(n-propyl)-piperideine (79)

Compound 78 (.51 g, .003 moles) was mixed with an equal weight of calcium oxide and placed in a pyrex tube fitted with a side arm. The mixture was gently heated with a micro burner. When a melt was observed, the heat was continued until a crude product distilled. The crude mixture was analyzed via NMR for aromatic protons. No significant aromatic peaks were observed and with further comparison to the NMR's of 78 and 76 this reaction mixture was deemed to consist of fragmentation products.

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