# REACTIONS OF SIX-MEMBERED ENOL LACTONES AND CORRESPONDING HYDROXY LACTONES WITH AMMONIA AND PRIMARY AMINES

By

DAVID WAYNE SULLINS

Bachelor of Science

Oklahoma State University

Stillwater, Oklahoma

1981

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1987

REACTIONS OF SIX-MEMBERED ENOL LACTONES
AND CORRESPONDING HYDROXY LACTONES
WITH AMMONIA AND PRIMARY AMINES

Thesis Approved:

Thesis Adviser

Dean of the Graduate College

ACKNOWLEDGMENTS

I wish to express my gratitude to my research adviser, Dr. E. J. Eisenbraun, for his guidance and support throughout the course of this work.

I also wish to extend my appreciation to my committee members, Drs. J. I. Gelder, E. M. Holt, and R K. Gholson for their help and advice.

I would like to thank the members of the faculty and staff of the Chemistry Department for their assistance during the course of this work. A special thanks is due to Mr. S. Sigle for obtaining the many NMR spectra

I am grateful to Dr. O. C. Dermer and Joy Steidl for reviewing the manuscript and making many valuable suggestions. I wish to express my appreciation to Mrs. Sue Hiel for assistance in preparing the final manuscript.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SPECTRA

Spectrum Page

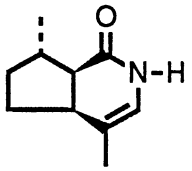
## SYMBOLS AND ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl ($COCH_3$) |
| bp | boiling point |
| br | broad |
| °C | degree Celsius |
| ca. | approximately |
| δ | scale (NMR), dimensionless |
| d | doublet |
| DIBAH | diisobutylaluminum hydride |
| equiv | equivalent |
| g | gram |
| GC | gas chromatography |
| h | hour |
| Hz | Hertz |
| IR | infrared |
| *J* | coupling constant |
| L | liter |
| lit. | literature |
| m | multiplet |
| M | molar |
| MCPBA | *m*-chloroperoxybenzoic acid |
| mg | milligram |
| MHz | megaHertz |
| min | minutes |
| mL | milliliter |
| mmol | millimole |
| mol | mole |
| mp | melting point |
| MS | mass spectrometry |
| *m/z* | mass-to-charge ratio |
| NMR | nuclear magnetic resonance |
| oxidn | oxidation |
| p | page or pentet (NMR) |
| pp | pages |
| ppm | parts per million |
| q | quartet |
| $R_f$ | retardation factor |
| $t_R$ | retention time |
| s | singlet |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TsOH | *p*-toluenesulfonic acid monohydrate |
| TBAB | tetra-*n*-butylammonium bromide |
| UV | ultraviolet |

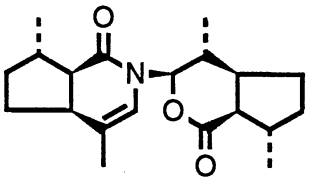
# CHAPTER I

## INTRODUCTION AND HISTORICAL

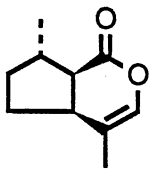
Recently, two new crystalline nitrogen-containing compounds were isolated from a sample of commercial oil of catnip (*Nepeta cataria*). These compounds were later established to be "enelactams"[1] [4a*S*-(4aα,7α,7aα)]-nepetalactam (**1a**) and *N*-(nepetal-3-yl)-nepetalactam (**2**),[2] the latter a mixed "dimer". Since these compounds had not previously been reported to exist in oil of catnip, and because the normal major constituent of oil of catnip, [4a*S*-(4aα,7α,7aα)]-nepetalactone (**3a**),[2] was present in only trace quantities, we proposed that these new enelactams were artifacts resulting from the action of ammonia on **3a**. However, neither the origin of this particular sample of oil of catnip, nor its method of isolation, which might have given information about how these enelactams had arisen, was known. To assist the reader, a glossary of structures is provided on pages 90-94.




**1a**




**2**

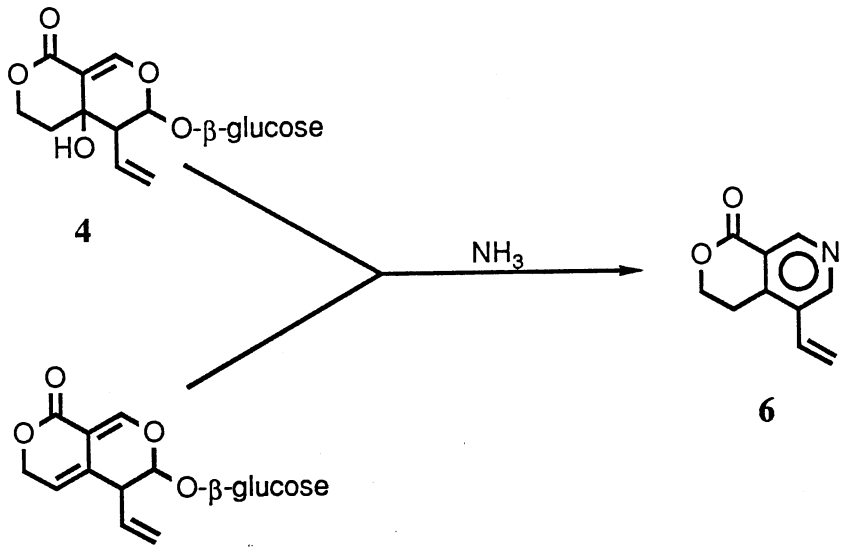



**3a**

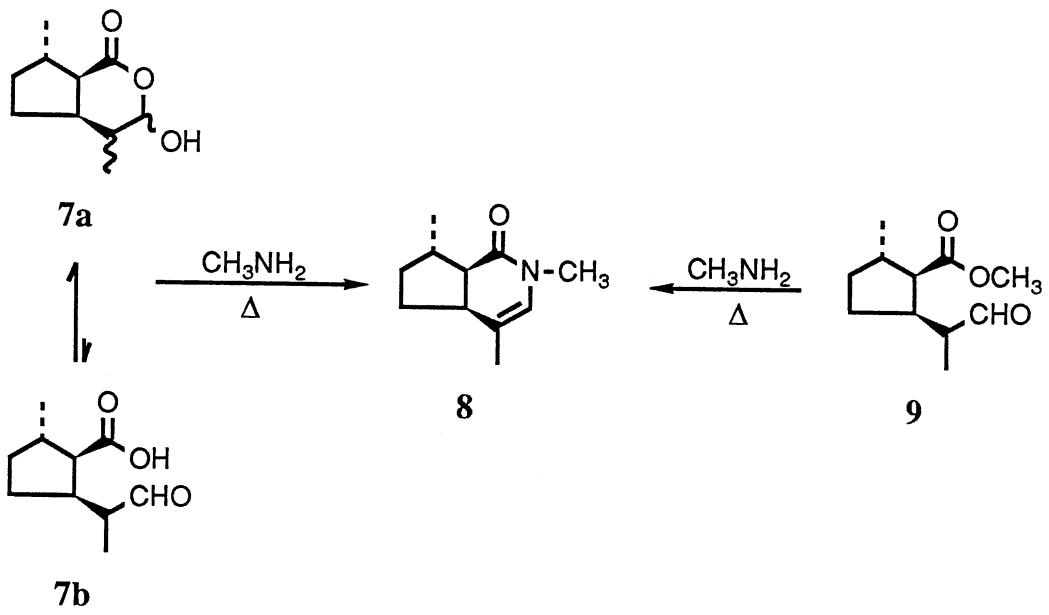
Ammonia has frequently been used during the isolation of natural products,[3] and there are several examples of the recognition that what were initially believed to be nitrogen-containing natural products were actually artifacts resulting from the action of ammonia on a non-nitrogenous natural product .[4]

Perhaps the best known of these nitrogen-containing artifacts is gentianine (**6**). Although **6** appears to be a true natural product of some plants, this alkaloid was isolated

from many others only when an extraction with ammonia was carried out. In these plants, when ammonia was not used as a part of the isolation procedure, **6** was either not found or present only in trace quantities. For example, when $^{15}NH_3$ was used in the isolation procedure, 91% of the nitrogen in **6** isolated from *Gentiana lutea* was labeled.[5] Also, extraction of plant material from *Erythraea centaurium* with chloroform and sodium carbonate solution gave no **6**, but extraction with chloroform and ammonia gave a 0.6% yield of **6**.[5] The non-nitrogenous natural products swertiamarine (**4**) and gentiopicroside (**5**) are apparently the precursors of **6**, since these compounds, frequently isolated from the same plants from which **6** was isolated, have been transformed into **6** by ammonia.



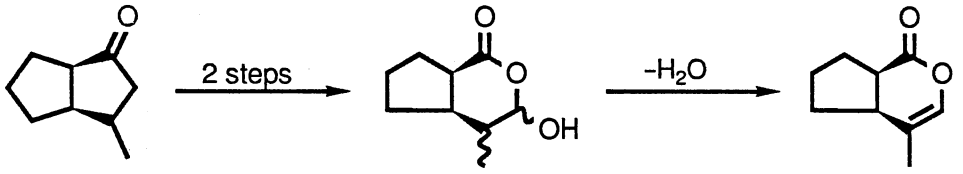

A derivative of **1a** was made during the synthesis of various skytanthine isomers. Nepetalic acid (**7**)[6] and methyl nepetalinate (**9**) were treated with methylamine to form [4a*S*-(4aα,7α,7aα)]-*N*-methyl-nepetalactam (**8a**).[7,8] This result suggests that **7**, which is formed by the hydrolysis of **3a**, might also react with ammonia to give **1a**. However, the formation of the mixed dimer **2** would be more difficult to explain.



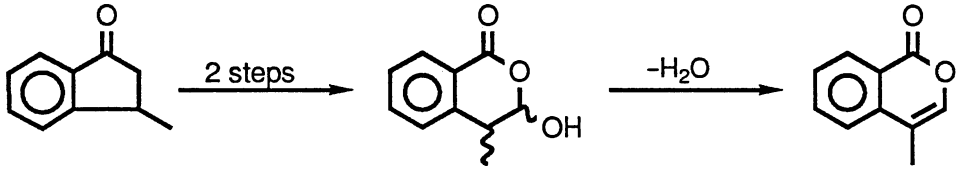

Because our supply of **3a** was limited, we decided to study the reactions of enol lactones with ammonia and primary amines using model compounds to determine the scope of this reaction. We were especially interested in treating these model compounds with primary amines that contained a second functional group. Then, if new compounds were made, further reactions could be carried out on that functional group. Also, we wished to investigate whether different conditions might affect the outcome of the reaction. *cis*-7-Nornepetalactone (**12**)[9] was selected as the ideal model compound because it would be expected to react with ammonia and primary amines in a manner nearly identical to **3a**. While **12** has been made before,[10] we planned to try another route in the hope of obtaining significant quantities of **12**, and the corresponding hydroxy lactone, 7-nornepetalic acid (**11**). If this was successful, many reactions of ammonia and primary amines with both **11** and **12** could then be carried out to determine optimum reaction conditions for the synthesis of enelactams. Also, we hoped that conditions for the formation of the mixed dimer **2** could be found.

In addition to synthesizing **12**, we planned to make 3,4-dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one (**14**) and 4-methyl-1*H*-2-benzopyran-1-one (**15**). The synthesis of **14** and **15** from 3-methyl-1-indanone (**13**) would provide experience useful

for later converting hexahydro-3-methyl-1(2*H*)-pentalenone (**10**) to **12** since the same general scheme was to be used in conversion of either ketone to the corresponding enol lactone. Furthermore, the reaction of **14** and **15** with ammonia and primary amines in itself could provide interesting results.

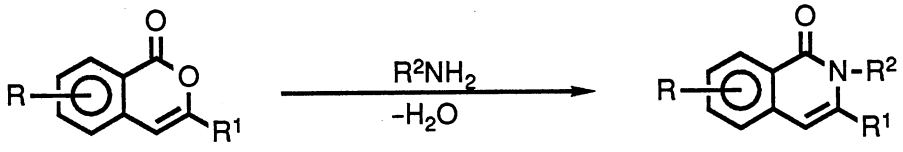



**10** **11** **12**



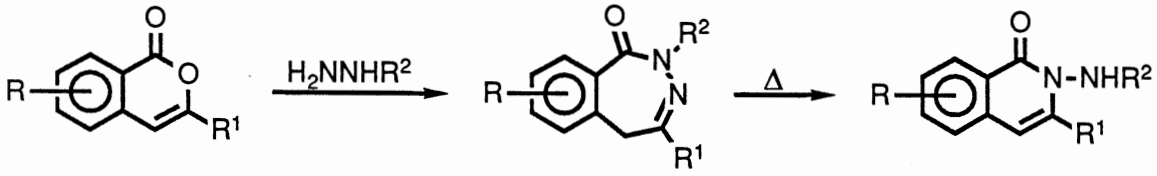

**13** **14** **15**

1*H*-2-Benzopyran-1-ones **A**, commonly called isocoumarins, are known to react with ammonia and primary amines to give 1(2*H*)-isoquinolinones **B**, also called isocarbostyrils.[11,12] These isocoumarins **A** have been treated with aqueous ammonia, ammonium carbonate in acetic acid, aniline, and tryptamine to give various isocarbostyrils **B**. Also, the synthesis of some isoquinoline natural products involved a reaction of an isocoumarin **A** with a primary amine.[12,13]




**A** **B**

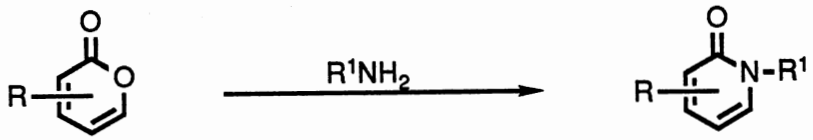
With hydrazines, 3-substituted isocoumarins **A** gave 4-substituted 2,5-dihydro-1*H*-2,3-benzodiazepin-1-ones **C** or 2-amino-1(2*H*)-isoquinolinones **D** depending upon the hydrazine used and reaction conditions.[14]




**A** **C** **D**

While there are many reports of conversions of isocoumarins **A** to isocarbostyrils **B** with ammonia and primary amines, most of these involved 3-substituted isocoumarins **A** ($R^1 \neq H$), These isocoumarins can be thought of as having arisen from the dehydration of keto acids, even though they may have been made in other ways. With the exception of isocoumarin itself (**A**, $R = R^1 = H$), there is little information on the reaction of ammonia and primary amines with isocoumarins not substituted at the 3-position, that is, isocoumarins that could have resulted from the dehydration of aldehydo acids. So, while the reaction of **15** with ammonia and primary amines could be predicted to give the corresponding isocarbostyrils, we felt it was worthwhile to see if indeed an isocoumarin not substituted at the 3-position would react with ammonia and various primary amines in the usual way. Also, we wished to study **15**, as well as the hydroxy lactone **14**, to determine what conditions, if any, promoted the formation of a mixed dimer analogous to **2.**

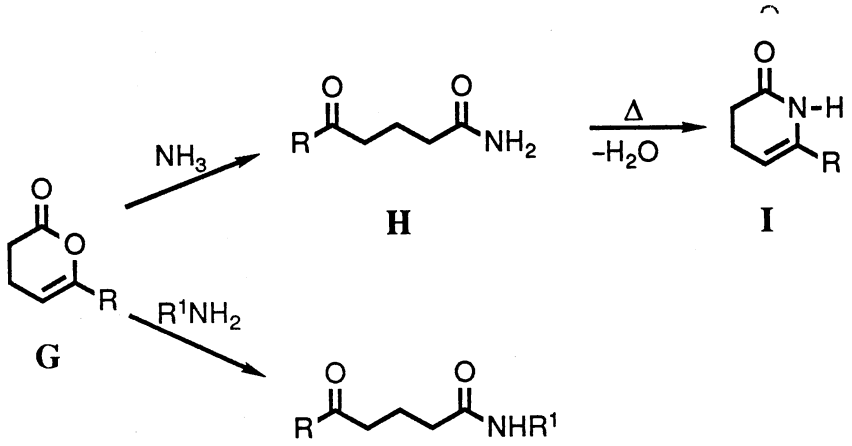
2*H*-Pyran-2-ones **E** are a group of compounds related to the enol lactones. There are numerous examples of their reactions with ammonia and primary amines giving 2(1*H*)-pyridinones **F**, also known as pyridones.[15,16] In one case, addition of aniline to a pyran-2-one **E** gave an intermediate that had incorporated an extra molecule of aniline. However, the corresponding pyridinone **F** ($R^1 = C_6H_5$) was obtained upon



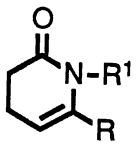

**E** **F**

heating this material with hydrochloric acid.[17] Pyran-2-ones **E** have also been treated with hydrazines to give pyridinones **F** ($R^1 = NH_2$, $NHC_6H_5$).[16,18] There are a few examples of the formation of other types of products from the reaction of pyran-2-ones **E** with primary amines.[19]

More closely related to the structure of nepetalactone (**3a**) are the 3,4-dihydro-2*H*-pyran-2-ones **G.** The reaction of ammonia with enol lactones **G** leads to formation of 5-oxoalkanamides **H**, which can then be dehydrated with varying ease to the corresponding 3,4-dihydro-2(1*H*)-pyridinones **I**.[20] Similarly, primary amines react with enol lactones **G** to give high yields of *N*-substituted 5-oxoalkanamides **J**.[20,21] There is

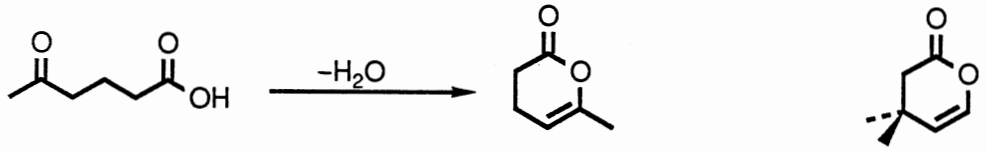



one report of the treatment of enol lactones **G** with hydrazine giving, with loss of nitrogen, enelactams **I**, instead of the expected enelactams **K** ($R^1 = NH_2$).[22] Apparently, no enol lactones **G** have been converted to enelactams **K**, *N*-substituted analogues of **I**, by reaction with primary amines, although such enelactams have been made by other methods.[23]



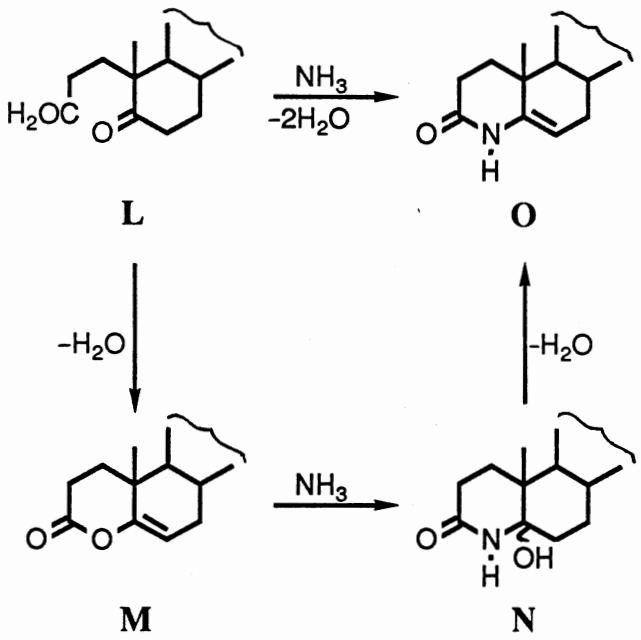

**K**

Because of the simplicity of the enol lactones **G**, study of their reactions with ammonia and primary amines was attractive, since spectra of the products should be easily interpreted. Two of these enol lactones proved to be readily accessible. 3,4-Dihydro-6-methyl-2*H*-pyran-2-one (**17**) could be made from the commercially available 5-oxohexanoic acid (**16**),[24,25] while 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**18**) itself was commercially available. It should be noted that **17** differs from the other enol lactones we proposed to study in that it is formed by the dehydration of a keto acid instead of an aldehydo acid.




**16** **17** **18**

Steroidal enol lactones **M** are another group of six-membered enol lactones that have been found to react with ammonia.[26-28] In addition to **M**, the corresponding steroidal keto acids **L** also reacted with ammonia, both giving azasteroids **O**. In the case of enol lactones **M**, their treatment with ammonia initially gave hydroxy lactams **N**,

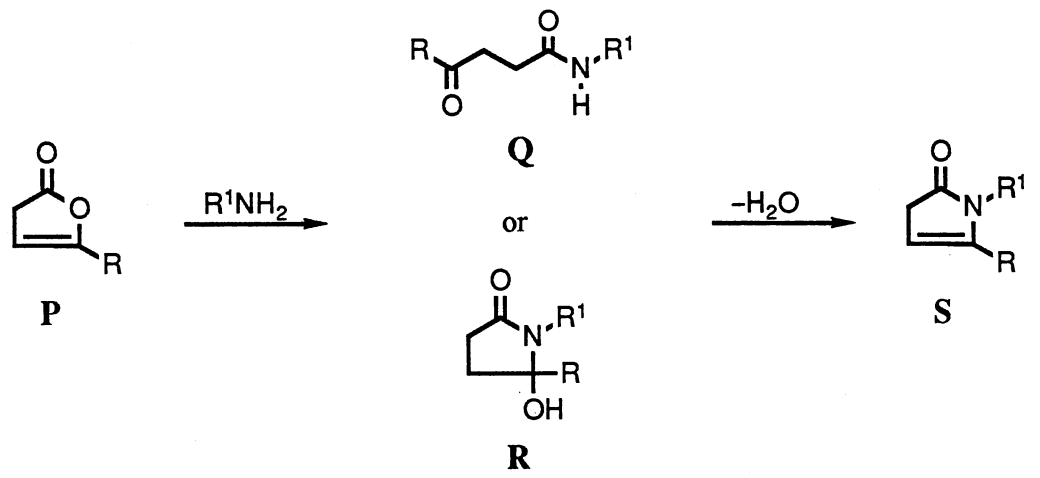



**L** **O**

**M** **N**

which were subsequently dehydrated to the azasteroids **O** by heating above 100 °C, or by treating with an acid catalyst at 25 °C.[27] Direct conversion of keto acids **L** to azasteroids **O** was carried out by treating **L** with concentrated aqueous ammonium hydroxide under pressure,[27] or by heating in the presence of an ammonia solution containing ammonium carbonate.[28] In the conversion of keto acids **L** to azasteroids **O**, no hydroxy lactams **N** were isolated.

Although we were primarily interested in the reactions of ammonia and primary amines with six-membered enol lactones, it is worthwhile to discuss similar reactions with five-membered enol lactones, 2(3*H*)-furanones **P**, for these reactions have been studied more extensively.[29] The reaction of ammonia with an enol lactone **P** was first reported in 1885, for α-angelica lactone (**P**, R = $CH_3$).[30] Although many reactions of enol lactones **P** with ammonia and primary amines have been carried out since that time, prior to the advent of spectroscopy the isolated products were often assigned incorrect structures.[31] However, UV, IR, and especially NMR spectroscopy have been invaluable in determining the exact structures for the products obtained from these reactions.




Chiron and co-workers[21,32,33] carried out a number of reactions of enol lactones **P** with ammonia and primary amines and found that in general 4-oxoalkanamides **Q** are formed. The only exceptions were for some products of the reactions of methylamine

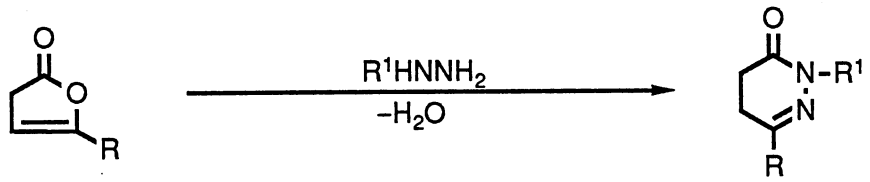
with enol lactones **P** where R was aromatic, in which case substituents on the aromatic ring influenced the structure of the product. Here, electron-withdrawing or weakly electron-donating groups favored the formation of pyrrolidinones **R**, while strongly electron-donating groups favored the formation of the keto amides **Q**.

However, somewhat conflicting results were reported earlier by Jones and Young.[34] When they treated α-angelica lactone (**P**, R = $CH_3$) with aqueous methylamine at 0 °C, and worked up the reaction mixture below 20 °C, they reported the isolation of 5-hydroxy-1,5-dimethyl-2-pyrrolidinone (**R**, R = $R^1$ = $CH_3$), instead of the keto amide **Q** (R = $R^1$ = $CH_3$) reported by Chiron and Graff.[32] With benzylamine, Jones and Young reported that α-angelica lactone (**P**, R = $CH_3$) reacted to form initially the keto amide **Q** (R = $CH_3$, $R^1$ = $CH_2C_6H_5$), which gradually equilibrated with the hydroxy lactam **R** (R = $CH_3$, $R^1$ = $CH_2C_6H_5$) at room temperature. However the keto amide **Q** (R = $CH_3$, $R^1$ = $CH_2C_6H_5$) was isolated when the temperature was kept at 0-5 °C during synthesis and workup. The equilibration between the two structures did not allow them to purify the cyclic isomer. On the other hand, Chiron and Graff mentioned only the keto amide **Q** (R = $CH_3$, $R^1$ = $CH_2C_6H_5$) as the product of the reaction of α-angelica lactone (**P**, R = $CH_3$) with benzylamine.

It should be noted that in general for a series of reactions of enol lactones **P** with primary amines, as the R group of **P** becomes more electron-withdrawing and the $R^1$ group of the primary amine becomes more electron-donating, the formation of the cyclic pyrrolidinone **R** is favored over the linear keto amide **Q**. Furthermore, the addition of substituents, especially *gem*-dialkyl groups, at the 3- and 4-position of the enol lactone **P** also favors the formation of **R** when treated with primary amines. This is an example of the Thorpe-Ingold effect.[35] Usually, either the keto amide **Q** or the pyrrolidinone **R** was isolated after the reaction of **P** with primary amines, but in some cases a mixture of the two was produced, the equilibrium being affected somewhat by solvent and temperature.[31]

Only in the few cases where R was an alkyl group were attempts made to dehydrate the product of the reaction of an enol lactone **P** with a primary amine to an enelactam **S**. When Chiron and Graff[32] distilled the products of the reaction of α-angelica lactone (**P**, R = $CH_3$) and related enol lactones **P** (R = other alkyl) with several primary aliphatic amines including methylamine, dehydration took place to give 1,3-dihydro-2*H*-pyrrol-2-ones **S**. In contrast to these results, attempts by Jones and Young[34] to dehydrate their product of the reaction of α-angelica lactone (**P**, R = $CH_3$) with methylamine, 5-hydroxy-1,5-dimethyl-2-pyrrolidinone (**R**, R = $R^1$ = $CH_3$), by distillation or acid catalysis, resulted in the formation of mixtures not containing any of the enelactam **S** (R = $R^1$ = $CH_3$). Dehydration did not take place when Chiron and Graff distilled the product of the reaction of α-angelica lactone (**P**, R = $CH_3$) with ammonia or benzylamine. Treatment of other enol lactones **P** (R = $C_2H_5$ or *n*-$C_3H_7$ ) with methylamine gave them a mixture of keto amides **Q** and enelactams **S** upon distillation. Finally, when they treated enol lactones **P** with primary aromatic amines, distillation did not cause dehydration to take place and only the keto amides **Q** were obtained. No attempt was made by Chiron and Graff to dehydrate the products of the reaction of primary amines with enol lactones **P** where R was an aromatic substituent.

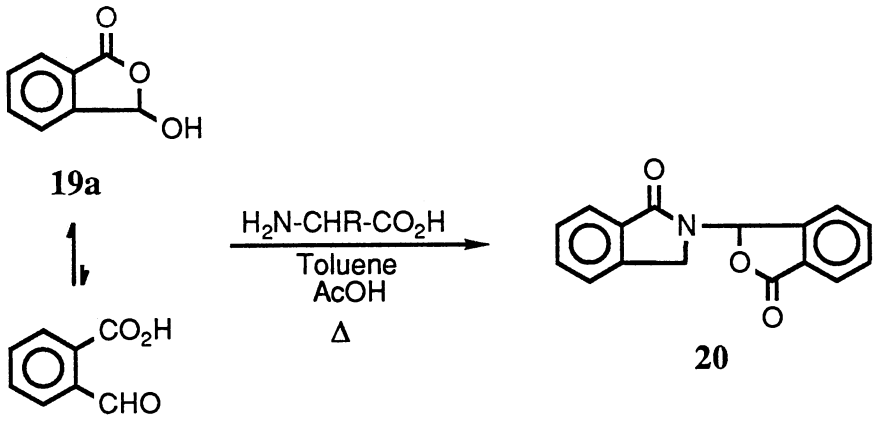
Hydrazines also react with enol lactones **P** to give intermediates which are usually dehydrated to 4,5-dihydro-3(2*H*)-pyridazinones **T** as shown below.[36]



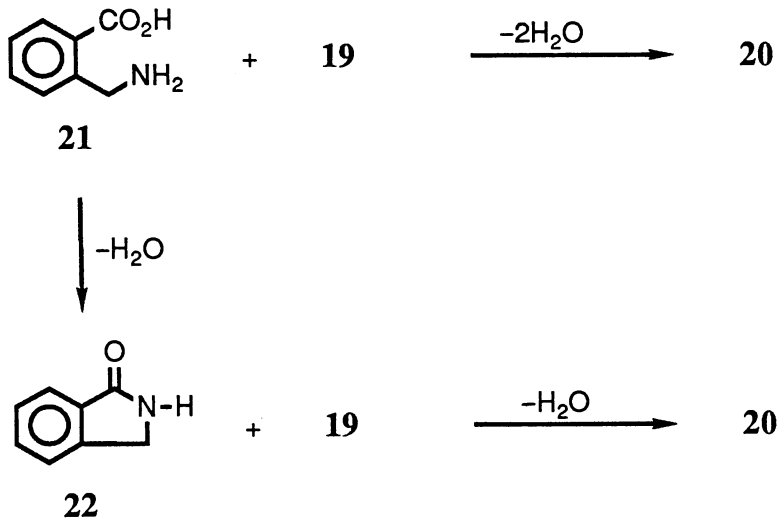

**P** **T**

In the previous examples of reactions of enol lactones and related compounds with ammonia, no report of a compound resembling the mixed dimer **2** was found. However, there is one example of a hydroxy lactone reacting with α-amino acids to give a compound similar to **2**.[37] When 2-formyl-benzoic acid (**19**), which exists primarily as

a hydroxy lactone, was treated with several α-amino acids, transamination took place to give the mixed dimer **20** in 19-66% yield. Also, **20** was produced in 50% yield by




reacting 2,3-dihydro-1*H*-isoindol-1-one (**22**) with **19**. The authors suggested that 2-(aminomethyl)-benzoic acid (**21**) was formed during the reaction, and either reacted with **19** to give the mixed dimer **20** after loss of two molecules of water or lost water first to form **22** which then reacted with **19** to give **20**. While it is quite unlikely that the mixed dimer **2** was formed by a reaction related to this example, it does show that a similar mixed dimer can be made.




It may be concluded from the previous examples that the reaction of various enol lactones or related compounds with ammonia and primary amines is a general one. In

most cases, however, the enol lactones used were those that were made or could be considered to have been made by the dehydration of a keto acid, that is, the enol lactone had a substituent on the olefinic carbon bonded to the ring oxygen. We were more interested in enol lactones similar to nepetalactone (**3a**) that could be made from the dehydration of aldehydo acids. Furthermore, there are few examples of reactions of ammonia and primary amines with six-membered enol lactones such as **3a**. For these reasons, it was of interest to obtain six-membered enol lactones similar to **3a** and study their reactions with ammonia and primary amines.

CHAPTER II

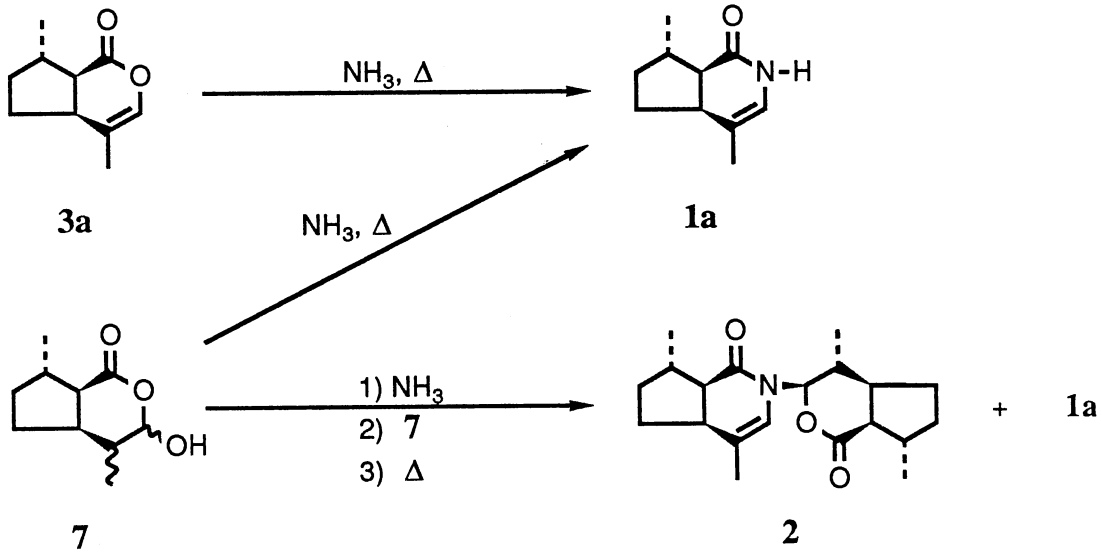
RESULTS AND DISCUSSION

## Synthesis of Nepetalactam and *N*-(Nepetal-3-yl)-nepetalactam

Our interest in reactions of six-membered enol lactones and hydroxy lactones with ammonia and primary amines began with our efforts to determine the origin of nepetalactam (**1a**) and the mixed dimer **2** in a sample of commercial oil of catnip. After some investigation into this problem, we decided to expand our work into related areas. Therefore, this study focuses initially on the synthesis of **1a** and **2**, and later on the synthesis and subsequent reactions of several six-membered enol lactones and the corresponding hydroxy lactones with ammonia and both primary aliphatic and primary aromatic amines.

In early work in this area we found that both nepetalactone (**3a**), the usual major component of oil of catnip, and nepetalic acid (**7**) readily reacted with either anhydrous or aqueous ammonia at room temperature to give intermediates that were converted to **1a** upon distillation. The passage of anhydrous ammonia through a solution of **3a** gave an intermediate material that prior to distillation was by GC analysis identical to **1a**, but by TLC analysis was quite different from **1a**. By either basis, **3a** clearly was not present. Also, the $^{13}C$ NMR spectrum of this intermediate material indicated that although it appeared to be a mixture of compounds, it did not contain either **1a** or **3a.** While the intermediate material from reaction of **3a** with ammonia was soluble in dichloromethane, the passage of anhydrous ammonia through a solution of **7** in dichloromethane immediately caused material to precipitate. This indicates that the two intermediate materials are different, and suggests that in the latter case, the intermediate may be an

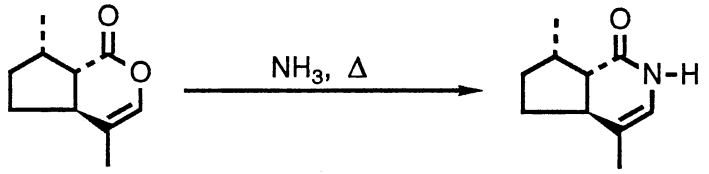
ammonium salt. Nevertheless, distillation of either intermediate gave **1a** as the only product. Since ammonium hydroxide was almost certainly the material used in processing the oil of catnip from which **1a** was isolated, we substituted ammonium hydroxide for anhydrous ammonia to see whether this change would affect the outcome of the reaction. However, this substitution made no apparent difference, as both **3a** and **7** reacted with ammonium hydroxide to give only **1a** upon distillation. In these various treatments of **3a** and **7** with ammonia, no mixed dimer **2** was ever found.



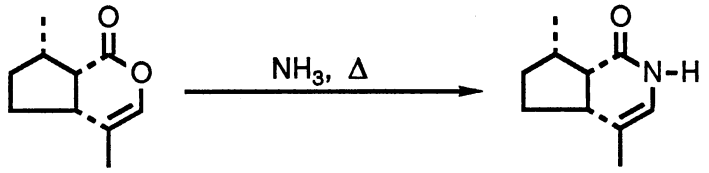

After several attempts we discovered conditions for the formation of **2**. The structure of **2** suggested that one half of the molecule came from **1a**, while the other half came from **3a** or **7**. However, heating mixtures of **1a** with either **3a** or **7** did not produce any **2**. Next, we decided to treat a given amount of **3a** or **7** with ammonia, remove any excess ammonia by vacuum, and then add another equivalent of **3a** or **7**. Provided that only one molecule of ammonia reacted with one molecule of **3a** or **7**, this mixture would be sure to contain one equivalent of ammonia per two equivalents of **3a** or **7**, which is the ratio needed as indicated by the structure of **2**. In this manner, mixtures of **3a** and ammonia and **7** and ammonia were prepared. While distillation of the mixture of **3a** and ammonia gave only **1a**, the distillation of the mixture of **7** and ammonia indeed gave the mixed dimer **2** as well as **1a** in approximately equal amounts.

When **3a** was substituted for **7** either before or after the treatment with ammonia, only **1a** was produced, which suggests that **7** must be present in excess in order for **2** to form. These results support our belief that both **1a** and **2** are artifacts resulting from the use of ammonia during the processing of this sample of catnip oil. However, it does not answer exactly the question of how **2** arose in this oil since **3a**, and not **7**, is normally the major constituent in oil of catnip. However, substantial amounts of **7** have also been found in oil of catnip, as it, like **1a**, is apparently an artifact from the processing of catnip oil.[38] Perhaps a combination of processes took place in this oil to give first **7** and later **2**.

Stereoisomers of **3a**, [4a*S*-(4aα,7α,7aβ)]-nepetalactone (**3b**), the minor component of *Nepeta cataria*, and [4a*S*-(4aα,7β,7aα)]-nepetalactone (**3c**), the major component of *Nepeta mussini*, were also treated with ammonia and gave after distillation **1b** and **1c** respectively.



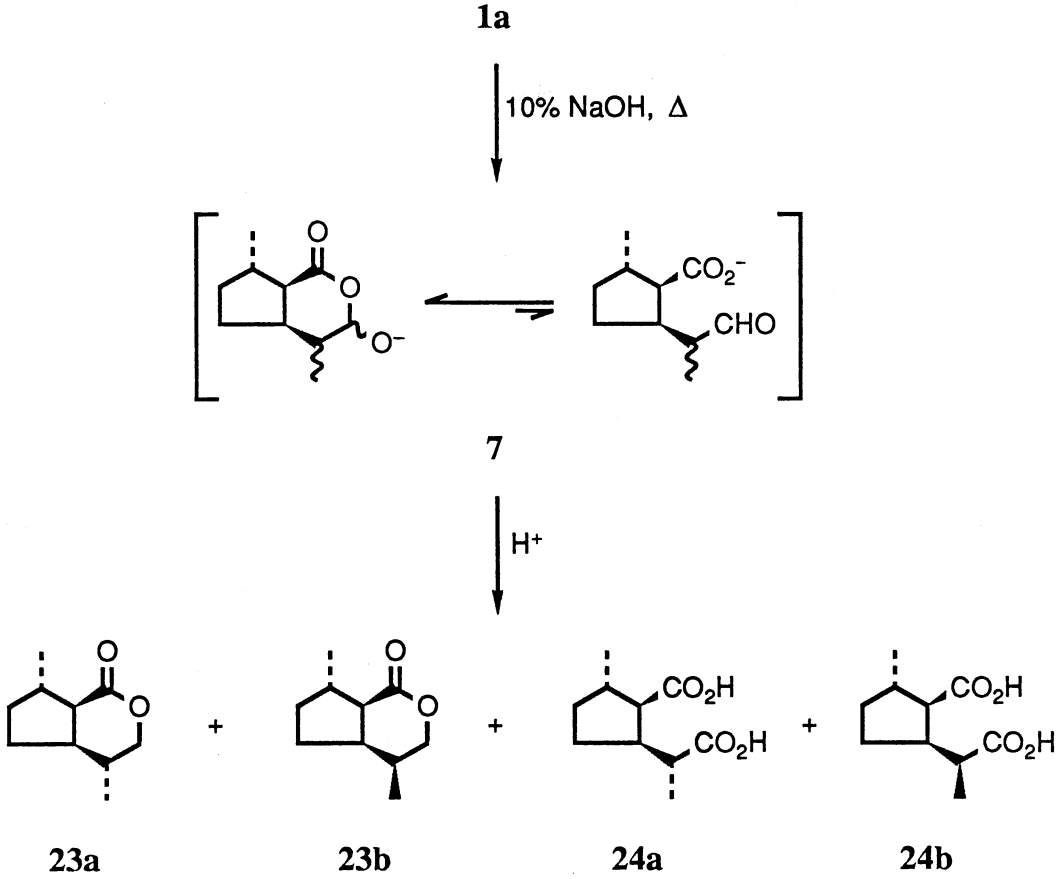

**3b** **1b**




**3c** **1c**

Because our supply of **3a** and **7** was limited, we hoped to convert **1a** into either **3a** or **7** so that we could carry out reactions of either of the two with various primary amines. However, attempts to produce **7**, which in turn may be dehydrated to **3a**, by either acidic or basic hydrolysis of **1a** always gave a mixture of products. While some **7** was produced by acidic hydrolysis, the yield was too low and the product too impure for

this reaction to be useful. On the other hand, basic hydrolysis gave no **7**, but rather four related products. These products were determined to be two dihydronepetalactones, **23a** and **23b**, and two nepetalinic acids, **24a** and **24b**. Apparently, **1a** was initially hydrolyzed to a salt of **7** which under the conditions of the reaction underwent a Cannizzaro reaction to give the four products isolated. The two dihydronepetalactones were separated on the basis of the difference in the rate of their being extracted into a 5% NaOH solution from ether. The two nepetalinic acids could be separated because of the insolubility of the barium salt of **24a** in water.[39]




Since it did not appear feasible to prepare **3a** or **7** from **1a**, we turned our attention toward the synthesis of model compounds. With these compounds, we hoped to determine the generality of the reaction of six-membered enol lactones with ammonia as well as primary amines, and perhaps gain insight into the nature of the intermediate materials formed by addition of ammonia to **3a** and **7**.

## Synthesis of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one and 4-Methyl-1*H*-2-benzopyran-1-one and Their Reactions with Ammonia and Primary Amines

The first of these model compounds to be made and to have its reactions with ammonia and amines studied was hydroxy lactone **14** and its dehydration product, isocoumarin **15**. Hydroxy lactone **14** was made as shown in Figure 1. Synthesis of 3-methyl-1-indanone (**13**) and its conversion to enol acetate **25** proceeded in good yields. However, despite trial of a variety of methods, the ozonolysis of **25** invariably gave low yields (25-42%) of **14**. Dichloromethane and methanol both with and without pyridine were used as solvents, but with little difference in results. Various reductive workup procedures were also tried in the hope of improving the yield. These procedures included catalytic hydrogenation, treatment with potassium iodide, dimethyl sulfide, triphenylphosphine, and zinc in aqueous acetic acid.[40] While the first two treatments described gave mixtures of base-soluble products containing little or no **14**, treatment with the latter three reagents did give **14** as the major component of the base-soluble fraction. Of these, ozonization of **25** in dichloromethane followed by treatment with zinc in aqueous acetic acid proved to be the best procedure. From this workup procedure, the base-soluble material was nearly pure **14**, the yield was somewhat higher than for other methods, and the neutral material consisted mostly of **13** which could be converted to **25** and ozonized again. That **14** exists as a diastereomeric mixture of two hydroxy lactones is indicated by the appearance of its $^{1}H$ and $^{13}C$ NMR. There was no spectral evidence for the presence of the aldehydo acid tautomer of **14**.[41]

Treatment of the material from the ozonization of **25** in methanol with potassium iodide gave as the base-soluble material a half ester of diacid **26a** which was later found to be **26b**. This material was suspected to be a half ester of **26a** because of the appearance of its $^{1}H$ and $^{13}C$ NMR, and was proven to be a half ester by the fact that

treatment of it and **26a** with diazomethane gave the same diester **26d**. However, both **26b** and **26c** were possible structures for this compound. Previously, nepetalic acid (**7**) had been converted to a half ester by first treating **7** with diazomethane and then oxidizing the resulting aldehydo ester **9** to the half ester.[39] A similar process was to be carried out on **14**, to provide a half ester of known structure. However, addition of the usual ether solution of diazomethane to crystalline **14**, or **14** dissolved in methanol, gave mixtures containing some **27**, but also other unidentified material.[42] Later, it was found that addition of diazomethane to a solution of **14** in acetone gave **27** with virtually no side products. Oxidation of **27** using the Jones reagent gave half ester **26c**, which was different by melting point, and $^{1}H$ and $^{13}C$ NMR from the material obtained from potassium iodide workup after the ozonization of **25**, proving that this material was **26b**.

Hydroxy lactone **14** was converted to isocoumarin **15** by either heating **14** to 200 °C, or by refluxing **14** in toluene in the presence of a catalytic amount of acid. Distillation of **14** under vacuum was not sufficient to cause dehydration to take place. Instead, the distillate consisted mostly of unchanged **14**, with the formation of only a slight amount of **15**.

Treatment of hydroxy lactone **14** with ammonia gave isocarbostyril **28a** upon distillation, but isocoumarin **15** did not react with ammonia even when heated to 150 °C. Mixed dimer **29**, analogous to mixed dimer **2** isolated from the oil of catnip, was found in the residual material after the distillation of the reaction product of **14** and ammonia. The formation of **29** from treatment of hydroxy lactone **14** with excess ammonia differs from the analogous reaction of hydroxy lactone **7** with ammonia in that in the latter case, distillation had not given any mixed dimer **2**. Conditions that had led to the formation of **2** were tried with **14**. However, treatment of one equivalent of **14** with ammonia, followed by addition of another equivalent of **14** and distillation of the resulting mixture, increased the yield of **29** only moderately.

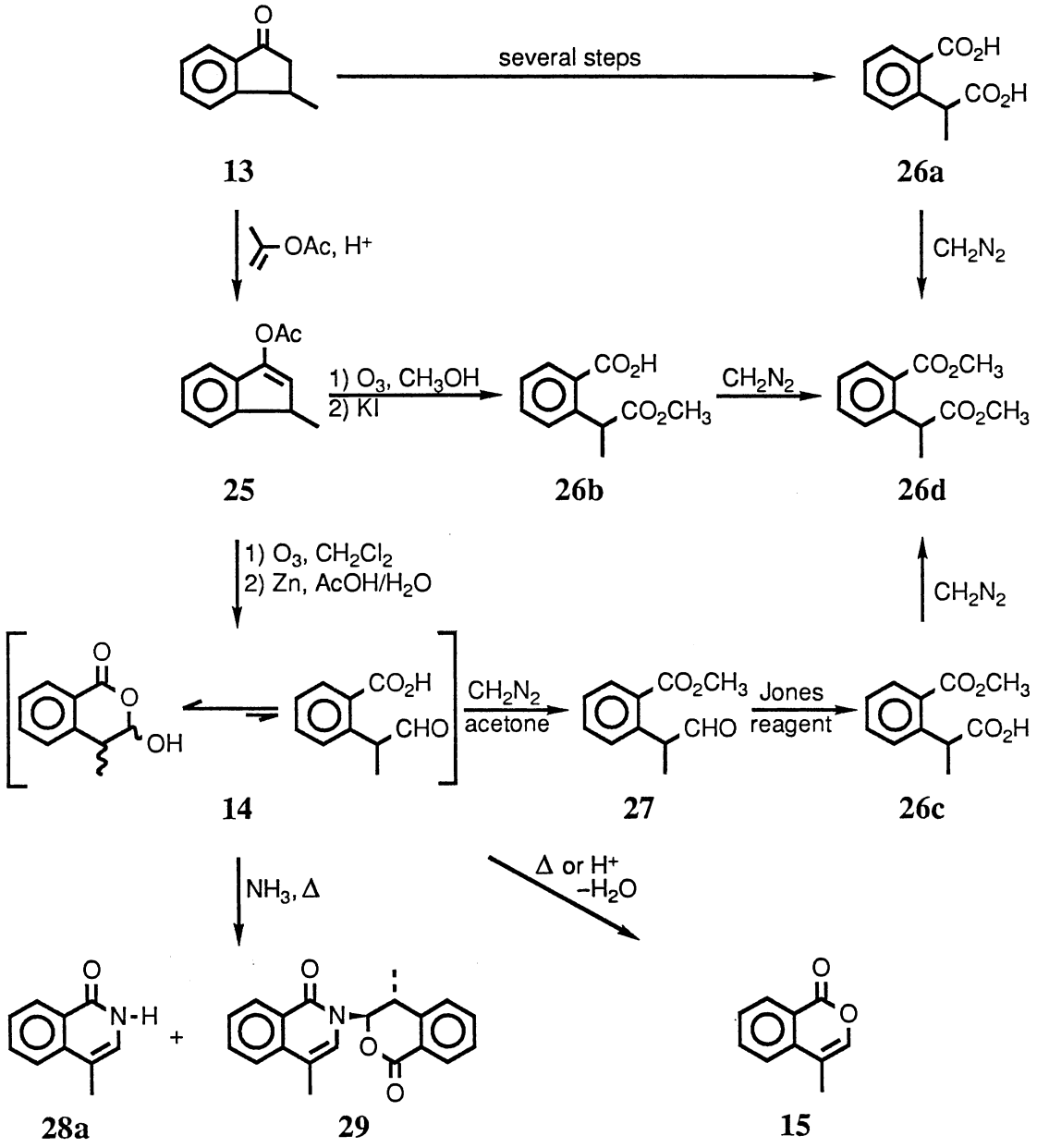



**Figure 1.** Synthesis of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one (**14**) and 4-Methyl-1*H*-2-benzopyran-1-one (**15**) and Related Reactions

Because of the ease with which hydroxy lactone **14** reacted with ammonia relative to isocoumarin **15**, we initially concentrated our studies on the reaction of **14** with primary amines. As shown in Figure 2, we found that in general **14** reacts with many such amines to give various products. We were primarily interested in using amines that contained a second functional group such as 2-aminoethanol ($H_2NCH_2CH_2OH$), 1,3-propanediamine ($H_2NCH_2CH_2CH_2NH_2$), aminoacetaldehyde dimethyl acetal ($H_2NCH_2CH(OCH_3)_2$), and anthranilic acid (2-$H_2NC_6H_4CO_2H$). The presence of this second functional group in the amine did not hinder the reaction of the amine with **14**, but in some cases did influence the product obtained.

In general the amine was added to a methanol solution of **14**. Methanol was chosen as a solvent simply because **14** was more soluble in it than in other common organic solvents. After removal of methanol, distillation of the mixture under vacuum gave the product isocarbostyril in good yields. Since these products were, with one exception, crystalline, recrystallization gave the pure isocarbostyril.

Distillation of the product of the reaction of hydroxy lactone **14** with primary aliphatic amines gave isocarbostyrils **28b-h**. In most cases, addition of 25% excess of the amine to a solution of **14** in methanol was sufficient to rapidly and completely consume **14** as indicated by GC analysis of the solution immediately after addition of the amine. By $^1H$ and $^{13}C$ NMR and TLC, these reaction mixtures even before heating were found to contain the isocarbostyrils isolated after distillation. However, the $^{13}C$ NMR spectra of these mixtures generally contained many broad peaks in addition to the relatively sharp peaks due to the isocarbostyrils. Apparently the reaction of **14** with primary aliphatic amines initially gives intermediate materials, which then gradually change to the isocarbostyril at room temperature. In any case, distillation of these mixtures gave isocarbostyrils **28b-h**, which frequently crystallized during or immediately after distillation.

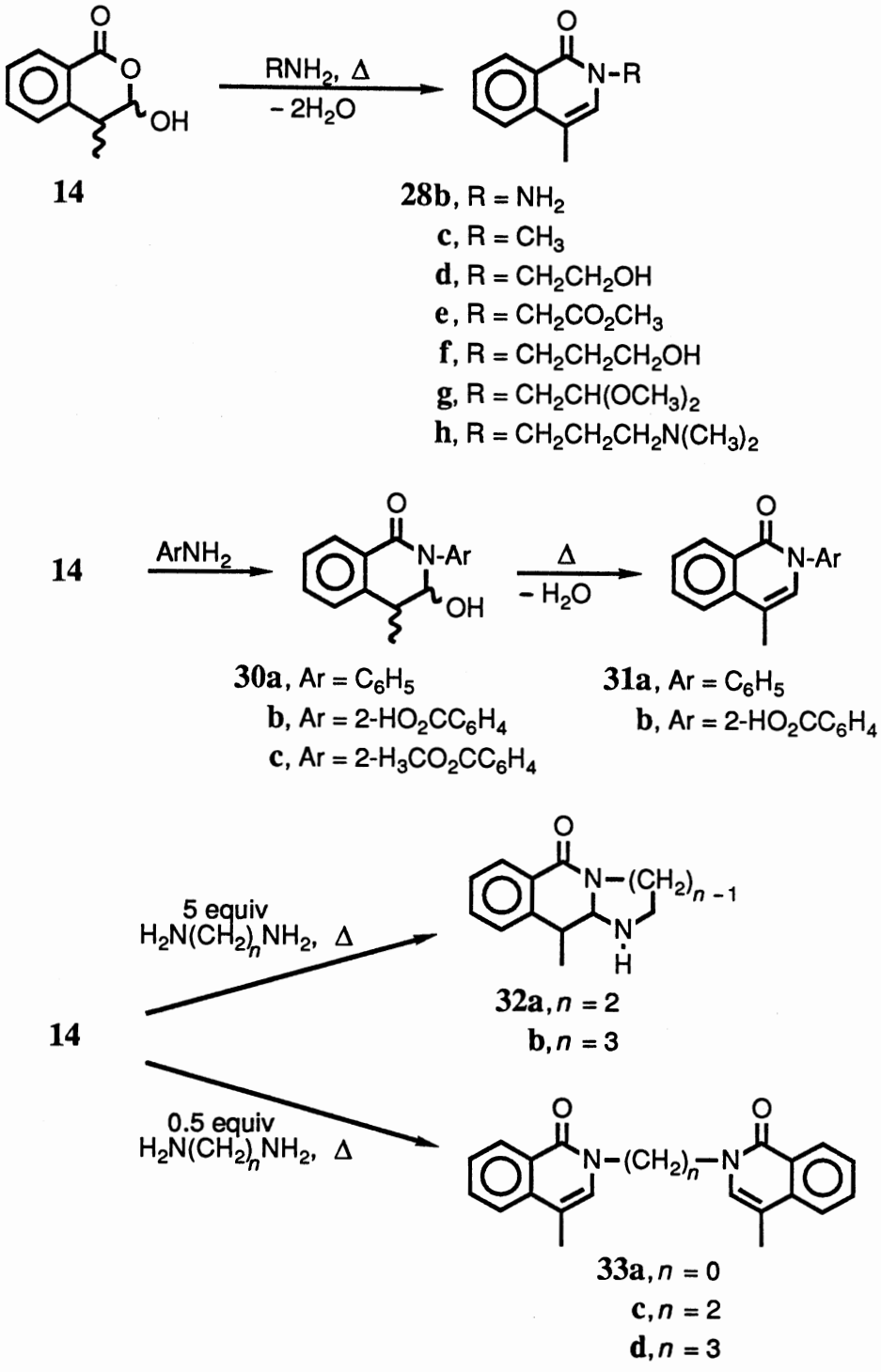
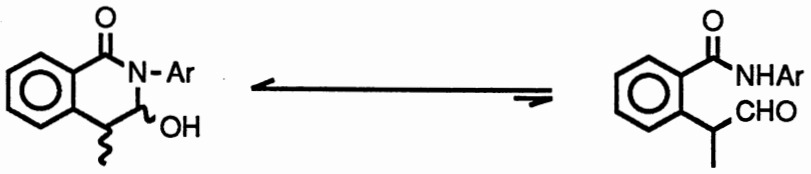



**Figure 2.** Reactions of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one (**14**) with Primary Amines

In contrast to the reaction of **14** with primary aliphatic amines to give apparently unstable intermediates, **14** reacted with three primary aromatic amines to give isolable crystalline compounds prior to distillation. Addition of aniline, anthranilic acid (2-$H_2NC_6H_4CO_2H$), and methyl anthranilate (2-$H_2NC_6H_4CO_2CH_3$) gave diastereomeric mixtures of hydroxy lactams **30a-c**. There are a few examples of similar hydroxy lactams.[43-45] While **30a** and **30b** could be dehydrated by distillation to isocarbostyrils **31a** and **31b** respectively, **30c** was recovered unchanged from distillation. This behavior is similar to that of **14**, which, as noted earlier, was not dehydrated when distilled under vacuum. However, attempts to dehydrate **30c** in a similar manner that **14** had been dehydrated resulted only in the destruction of **30c**. Apparently, the ease of dehydrating a hydroxy lactam varies considerably with a change in the second functional group present in the reacting amine.

In an attempt to ascertain the chemical shift of the hydroxy proton of **30a-c**, $D_2O$ was added to a $CDCl_3$ solution of these hydroxy lactams. Unexpectedly, we found that in addition to the hydroxy proton, the proton bonded to C-4 was also exchanged. This finding suggests that the ring of these hydroxy lactams is opened to give the tautomeric aldehydo amides, and then through the process of keto-enol tautomerization the α-proton of the aldehydo group is replaced by deuterium. However, neither $^1H$ nor $^{13}C$ NMR showed any evidence for the presence of an aldehydo group. Apparently, these hydroxy lactams are similar to nepetalic acid (**7**), which behaves as an aldehyde in some of its reactions, but gives no evidence of the presence of an aldehydo group in either $^1H$ or $^{13}C$ NMR.[6]




**30a-c**

In the case of **30b** and **30c**, the hydroxy proton appears to be intramolecularly hydrogen bonded with the $-CO_2-$ portion of the molecule, as its chemical shift did not change when the concentration of sample was varied. Also, the hydroxy proton signal was split into doublets for each diastereomer of both compounds. This hydrogen bonding apparently stabilizes the hydroxy lactam form of the above equilibrium since under the same conditions, the exchange of the C-4 proton was not so complete in **30b** or **30c** as it was in **30a**.

The $^{13}C$ NMR spectra of hydroxy lactams **30a-c** showed signals around 85-90 ppm for C-3. It should be noted that the intermediate materials obtained from the reaction of **14** with primary aliphatic amines prior to distillation did not show any such signals. Therefore, these materials do not exist as hydroxy lactams. Also, as shall be discussed later, stable hydroxy lactams with aliphatic groups attached to nitrogen could be isolated.

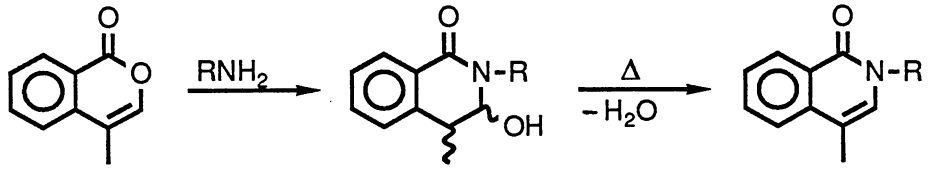
With the exception of **30c**, only did material from the treatment of hydroxy lactone **14** with an excess of two aliphatic diamines not give isocarbostyrils upon distillation. When an excess of ethylenediamine or 1,3-propanediamine was added to **14**, distillation gave the tricyclic products **32a** and **32b**. Despite the possibility of formation of diastereomeric products from each reaction, one major isomer was isolated in each case, with only a trace of a second isomer indicated by $^{13}C$ NMR. However, it is not clear from the NMR data what the stereochemistry of **32a** or **32b** is.

In the $^{1}H$ NMR spectrum of **32b**, the signal of one of the protons of the methylene group adjacent to the lactam nitrogen is shifted significantly downfield (1.9 ppm) relative to that of the other proton. This effect has been noticed before in lactams with the nitrogen at a ring junction,[46] and has been explained by preferential deshielding of the equatorial proton by the nearby carbonyl group. The nonequivalency of these methylene protons is sufficient to cause the off-resonance $^{13}C$ NMR signal of the methylene carbon to be split into a doublet of doublets, instead of the usual triplet.[47] In

**32a**, this deshielding effect is not nearly so great, partly because the methylene protons in the smaller five-membered ring are farther from the carbonyl group, but also because any deshielding should affect the methylene protons more equally, instead of preferentially deshielding the equatorial proton as it does in six-membered rings.[46]

When hydroxy lactone **14** was treated with 0.5 equivalents of hydrazine, ethylenediamine or 1,3-propanediamine, formation of bisisocarbostyrils **33a**, **33c**, and **33d** respectively took place. In the reaction of **14** with ethylenediamine and 1,3-propanediamine the bisisocarbostyrils were present even before distillation of the reaction mixture as indicated by TLC analysis. In all three cases, the bisisocarbostyrils did not actually distill; rather, impurities were removed by distillation and the bisisocarbostyrils were left behind in the undistilled portion of the reaction mixture.

As mentioned earlier, isocoumarin **15** did not appear to react with ammonia even at elevated temperatures, but it was later found that in methanol solution, **15** does react slowly with ammonia and primary aliphatic amines. When a methanol solution of **15** was saturated with ammonia and allowed to stand at room temperature for a few days, **15** was converted to a diastereomeric mixture of hydroxy lactam **34a**. Similarly, when methylamine was passed through such a solution, a diastereomeric mixture of hydroxy lactam **34c** was formed, but in only 30 min. Hydrazine and 2-aminoethanol converted **15** in methanol to hydroxy lactams **34b** and **34d** respectively, which precipitated from



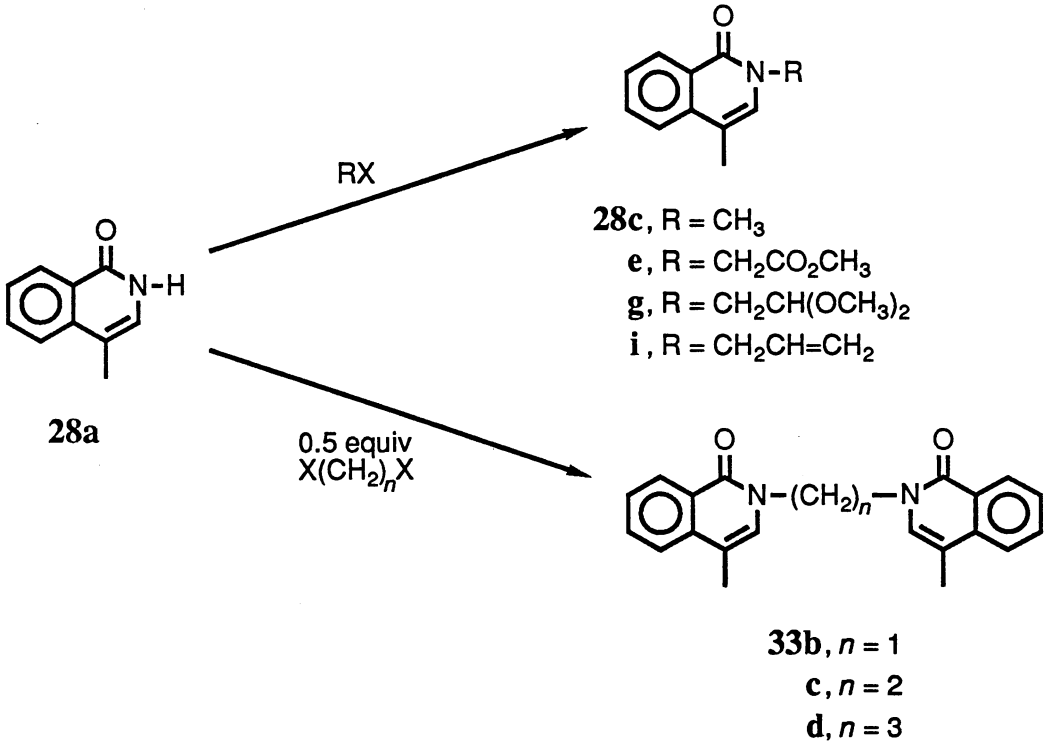

**15**

**34a**, R = H
**b**, R = $NH_2$
**c**, R = $CH_3$
**d**, R = $CH_2CH_2OH$

**28a**, R = H
**b**, R = $NH_2$
**c**, R = $CH_3$
**d**, R = $CH_2CH_2OH$

solution. Hydroxy lactams **34a-d**, unlike **30a-c**, did not appear to exchange the proton bonded to C-4 in the presence of $D_2O$. Distillation of these hydroxy lactams from **15** and primary amines caused dehydration, giving the same isocarbostyrils isolated earlier from similar reactions with hydroxy lactone **14**.

During our efforts to synthesize various *N*-substituted isocarbostyrils, we found that the unsubstituted one, **28a**, could be *N*-alkylated by using a procedure described for the *N*-alkylation of unsubstituted lactams.[48] In this reaction, the alkyl halide was added to a mixture of **28a**, powdered KOH, and the phase-transfer catalyst tetra-*n*-butylammonium bromide in THF. By using this reaction, several isocarbostyrils made by the reaction of hydroxy lactone **14** with primary aliphatic amines were also produced by treatment of **28a** with alkyl halides. As might be expected, this reaction worked well with iodomethane and allyl bromide to give **28c** and **28i** respectively; lower yields were obtained in the synthesis of **28e** and **28g**. In addition, the three bisisocarbostyrils **33b**, **33c**, and **33d** were made by treating **28a** with dihaloalkanes.



## Reactions of 3,4-Dihydro-6-methyl-2*H*-pyran-2-one with Ammonia and Primary Amines

3,4-Dihydro-6-methyl-2*H*-pyran-2-one (**17**) is one of the simplest enol lactones, and has been known since 1897.[24] Enol lactone **17** is made by the cyclodehydration of 5-oxohexanoic acid (**16**). While **16** is commercially available, it was easily made on a 1-2 mole scale by the hydrolysis of the much less expensive 5-oxohexanenitrile. Keto acid **16** has previously been converted to **17** either by heating **16** with acetic anhydride,[24] or by refluxing a benzene solution of **16** with thionyl chloride.[25] Another method for the cyclodehydration of keto acids to enol lactones involves refluxing a solution of the keto acid in isopropenyl acetate containing a catalytic amount of acid.[49] In our hands, treatment of **16** with thionyl chloride gave a 63% yield of **17**. Previously reported yields for this reaction were 52% and 80%.[25] The use of isopropenyl acetate gave us a 92% yield of **17**, and therefore appears to be the best method for preparing **17** from **16**.

The reaction of enol lactone **17** with ammonia gave different results depending on what solvent, if any, was used. The passage of anhydrous ammonia through neat **17** caused the temperature of the reaction mixture to rise above 100 °C within a few seconds. While GC analysis of the product showed only one new peak, the $^{13}C$ NMR spectrum indicated it was a mixture of compounds which was later determined to include **35**, **36a**, and **37a**. After a few days, crystals formed in this material, and because of their relative insolubility in dichloromethane, they could be separated from the rest of the oil. The $^{13}C$ NMR spectrum of these crystals indicated this material was hydroxy lactam **35**. When **17** was dissolved in ether, dichloromethane, or chloroform before passing ammonia through the solution, keto amide **36a** was formed exclusively, and it crystallized upon removal of the solvent. However, when methanol was used as the solvent in the reaction, **36a** was only a minor product. The primary product was not **35**

either, but a compound with a $^{13}C$ NMR spectrum very similar to that of **35**. The major difference was the chemical shift of a signal that was a singlet in off-resonance $^{13}C$ NMR for both compounds. In **35** this signal occurred at 80.9 ppm, while for the material produced in methanol, it occurred at 66.5 ppm. A possible explanation is that an amino group replaced the hydroxy group of **35** to give an amino lactam, but no attempt was made to isolate this compound. As shall be shown later, the formation of amino lactams from reaction of enol lactones with amines is possible.

Under certain conditions, the keto amide **36a** tautomerizes to the hydroxy lactam **35**. As mentioned earlier, passage of ammonia through an ether, dichloromethane, or chloroform solution of **17** gave exclusively **36a**. This was indicated by $^{1}H$ and $^{13}C$ NMR spectra obtained immediately after **36a** was made. A second $^{13}C$ NMR spectrum obtained two weeks later for one sample of **36a** in $CDCl_3$ showed little change from the first except small signals corresponding to the hydroxy lactam **35** were now present. There are several examples of basic materials catalyzing the tautomerization of keto amides to hydroxy lactams.[50] Apparently the conversion of **36a** to **35** is also catalyzed by base, as the addition of of a few drops of triethylamine to this $CDCl_3$ solution of **36a** converted more than half of it to **35** within five days as indicated by $^{13}C$ NMR.

The keto amide **36a** has been mentioned in a few papers,[24,51] and in every case a melting point at about 112-114 °C was reported. However, our melting point for **36a** after recrystallization was 69-70 °C. Furthermore, the melting point of hydroxy lactam **35** was 114-115 °C, very close to that reported for **36a**. Apparently what was previously believed to be the keto amide **36a** was actually the tautomeric hydroxy lactam **35**. Another unexplained aspect of these compounds is that there has been one report of the synthesis of **35**,[52] but a melting point of 140 °C was given. Both the hydroxy lactam **35** and the keto amide **36a** were dehydrated to the enelactam **37a** by distillation.

As shown in Figure 3, enol lactone **17** reacted with several primary aliphatic amines to give the *N*-substituted keto amides **36b-e**. As with ammonia, the reaction of

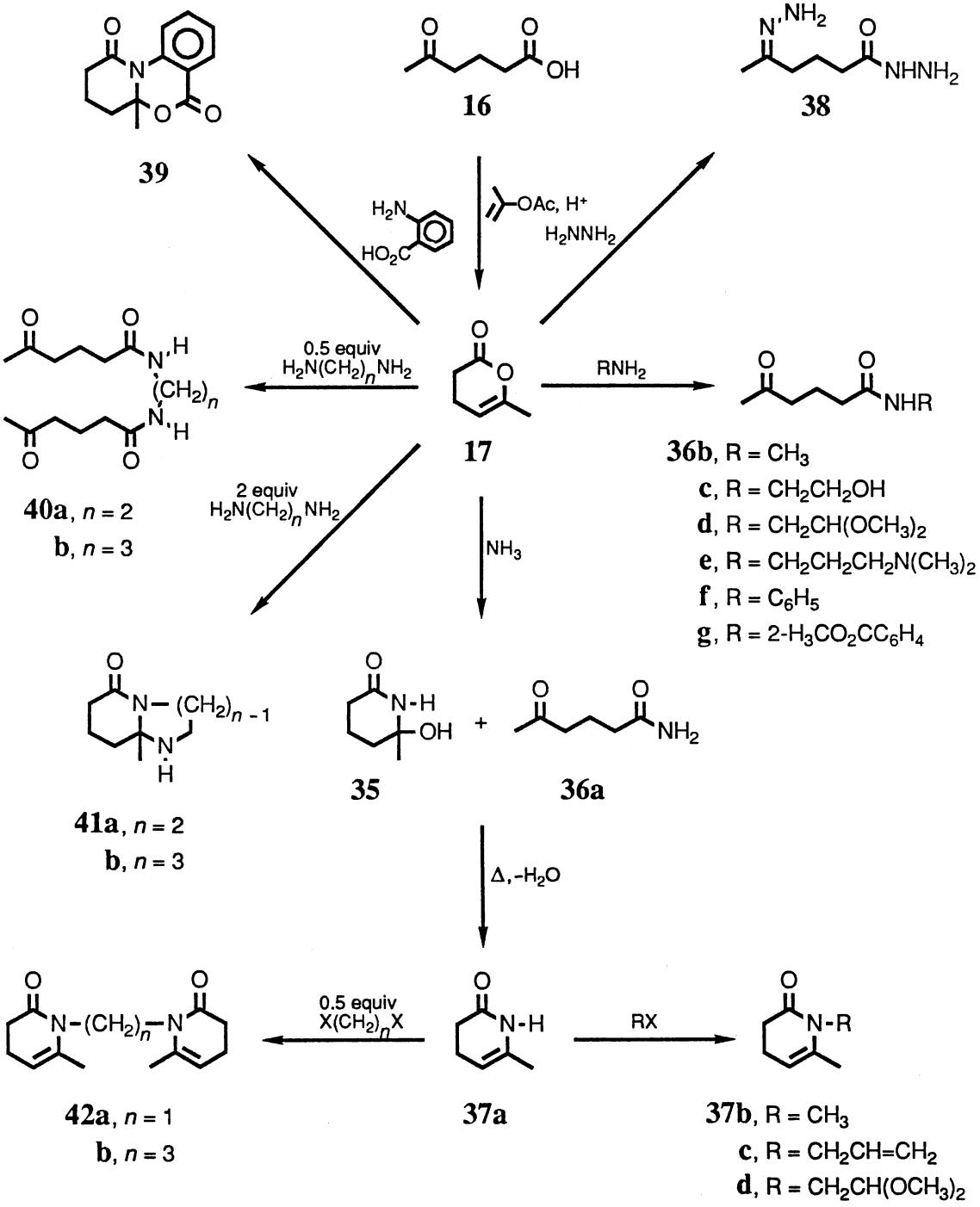


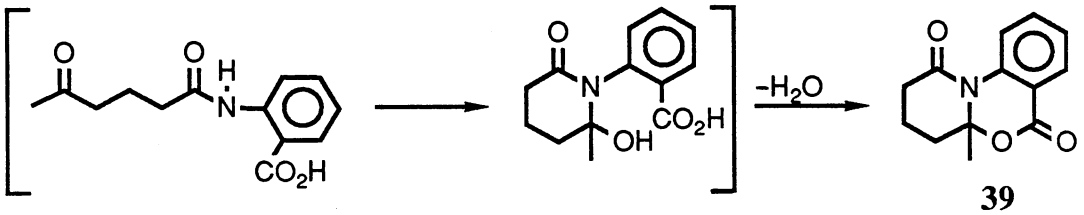

**Figure 3.** Reactions of 3,4-Dihydro-6-methyl-2*H*-pyran-2-one (**17**) with Ammonia and Primary Amines

**17** with these amines was exothermic with temperatures rising rapidly above 100 °C when the amine was added to neat **17**. Distillation of these *N*-substituted keto amides resulted in mixtures consisting predominantly of the unchanged keto amide, accompanied by small amounts of the corresponding enelactams. No attempt was made to separate these mixtures. The $^{13}C$ NMR of these *N*-substituted keto amides gave no evidence of the presence of any cyclic products analogous to **35**, either before or after distillation. However, in a different type of reaction Lukes reported[53] the synthesis of several hydroxy lactams including the cyclic isomer of **36b**, which would be the *N*-methyl derivative of **35**. Many years later, after examining several of these compounds by IR spectroscopy, Lukes revised their structures from cyclic hydroxy lactams to straight-chain keto amides.[45,54] However, this latter study did not include what he earlier believed was the *N*-methyl derivative of **35**. The similarity in the reported melting point of Lukes's compound and that of our keto amide **36b** suggests that Lukes's compound was probably also the keto amide **36b**, which has not yet been reported in the literature. This is likely another example of an incorrect structure assignment to a compound for which two possible tautomeric structures can be written.[31]

With hydrazine, **17** reacted exothermically to form apparently the hydrazide **38**. Treatment of **17** with slightly more than one equivalent of hydrazine gave a mixture of compounds as indicated by $^{13}C$ NMR. However, when at least two equivalents of hydrazine were used $^{1}H$ and $^{13}C$ NMR indicated only one product was present. The lack of a $^{13}C$ signal around 208 ppm present in all of the keto amides just discussed rules out the possibility that this compound has a keto group. The presence of a broad signal that integrates to five in $^{1}H$ NMR supports the hydrazide structure. This compound is quite water-soluble and cannot be extracted from water by ether or dichloromethane

Enol lactone **17** also reacted with several primary aromatic amines. Unlike the rapid exothermic reaction of **17** with aliphatic amines, **17** reacted with aniline slowly, and it took several hours at room temperature before the reaction was complete as

indicated by GC analysis. With methyl anthranilate, there was little if any reaction with **17** at room temperature, and it was necessary to heat the mixture of the two to cause reaction. In both cases, the products were *N*-substituted keto amides. On the other hand, refluxing a solution of **17** and anthranilic acid gave a compound in which a new six-membered ring had formed. Apparently, the initially formed keto amide cyclized to a hydroxy lactam which then lactonized to form the pyrido[1,2-*a*][3,1]benzoxazine **39**. While **17** did react with 1,2-phenylenediamine ($C_6H_4(NH_2)_2$), the result was a mixture of tarry materials that was not separated.




**39**

Depending on the relative amounts of two aliphatic diamines used, **17** reacted to give either bisketo amides or compounds in which a new ring had formed. When 0.5 equivalents of either ethylenediamine or 1,3-propanediamine was added to **17**, an exothermic reaction took place and after cooling the bisketo amides **40a** and **40b** were isolated. If an excess of the diamine was added to **17**, again an exothermic reaction took place, and upon distillation of this material, **41a** and **41b** were isolated, albeit in low yields. The formation of **41a** and **41b** is similar to the previous examples of the formation of **32a** and **32b** from the reaction of **14** with diamines.

As was the case with the unsubstituted isocarbostyril **28a**, the unsubstituted enelactam **37a** may be *N*-alkylated with alkyl halides to give *N*-substituted enelactams as shown in Figure 3. The reaction worked best with iodomethane to give **37b**, with lower yields for the reaction of **37a** with alkyl bromides to give **37c** and **37d**, or with dihaloalkanes to give the bisenelactams **42a** and **42b**.

## Reactions of 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one with Ammonia and Primary Amines

A simple enol lactone that is commercially available is 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**18**). Although **18** is similar in structure to enol lactone **17** previously discussed, and in some cases reacts with amines in similar ways, in general the reaction of **18** with amines gives results different from the reaction of **17** with amines.

The reaction of ammonia with enol lactone **18**, less exothermic than the same reaction with **17**, gave after distillation enelactam **43a**. However, this reaction was plagued by the formation of material that remained as a distillation residue. Apparently, excess ammonia was responsible for the formation of this side product, but efforts to reduce its formation by using one equivalent of ammonia in the form of liquid ammonia or concentrated ammonium hydroxide were not successful and left some **18** unreacted. Dissolving **18** in various solvents before treating with ammonia, or shortening the time ammonia was passed through the solution, did not eliminate the formation of the side product either. This side product was relatively insoluble in various organic solvents, as well as in acidic or basic aqueous solution, and no satisfactory spectral data was obtained for it.

As shown in Figure 4, **18** reacted with several primary aliphatic amines to give two types of products depending on the reaction conditions and the amine used. With methylamine, **18** reacted to give a product that had incorporated two molecules of methylamine as shown by $^{1}H$ and $^{13}C$ NMR. Possibly the first molecule of methylamine adds to **18** to give an intermediate hydroxy lactam which then reacts with a second molecule of methylamine to form amino lactam **44b**. This reaction with a second molecule of methylamine is an intermolecular version of the intramolecular cyclization reaction that took place when enol lactone **17** was treated with ethylenediamine and 1,3-propanediamine as discussed earlier. Distillation of **44b** did not convert it to the

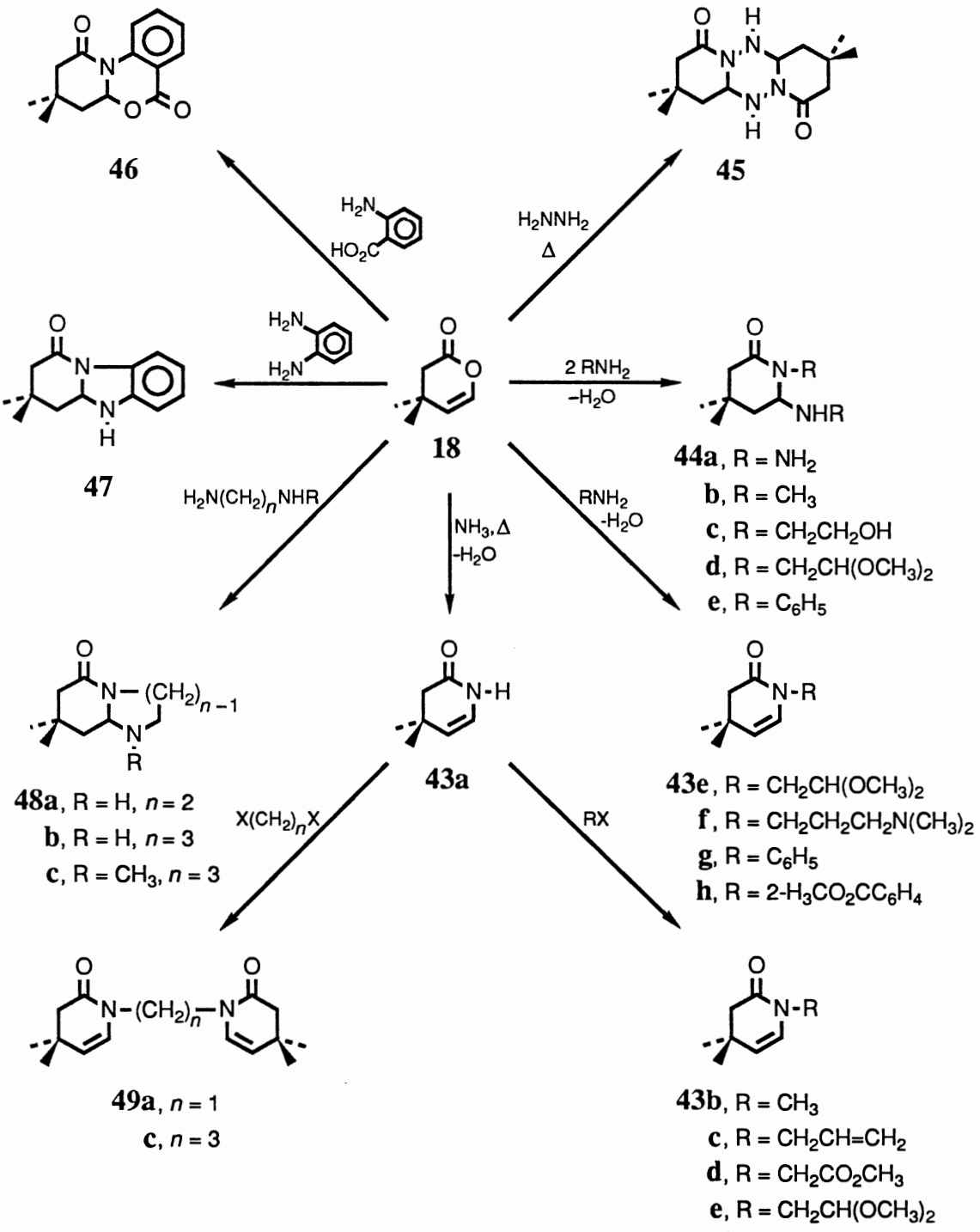
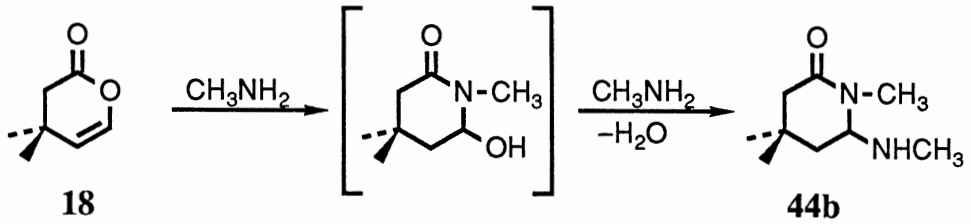



**Figure 4.** Reactions of 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one (**18**) with Ammonia and Primary Amines

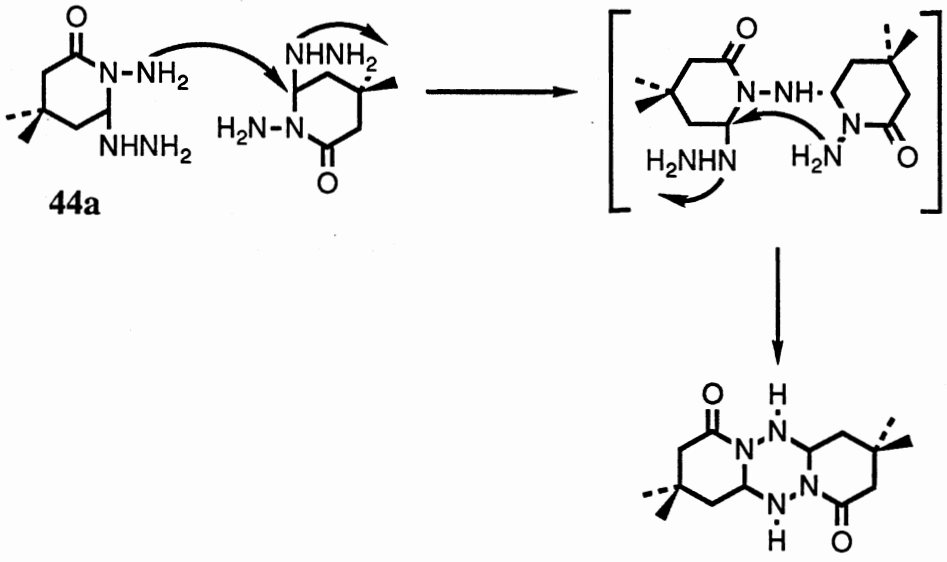



**18** **44b**

corresponding enelactam but only resulted in the recovery of **44b** less pure than before distillation.

When it was discovered that two molecules of methylamine reacted with **18**, slightly more than two equivalents of other aliphatic amines were added to **18** to see if similar amino lactams would form. We found that two molecules of both 2-aminoethanol and aminoacetaldehyde dimethyl acetal added to each molecule of **18** to give amino lactams **44c** and **44d**. When slightly more than one equivalent of aminoacetaldehyde dimethyl acetal was added to **18**, distillation gave predominantly enelactam **43e**. Regardless of amount of amine used, treatment of **18** with *N,N*-dimethyl-1,3-propanediamine gave only a low yield of enelactam **43f**.

With excess hydrazine, **18** apparently also reacts twice to give initially **44a**, based on the similarities of its $^{1}H$ and $^{13}C$ NMR to that of **44b**. Although this material

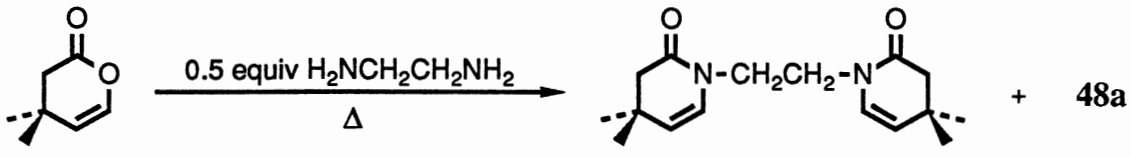



**44a** **45**

is a solid, attempts to recrystallize it were unsuccessful. Upon distillation, **44a** is apparently converted to another solid which has tentatively been assigned structure **45**. The $^{1}H$ and $^{13}C$ NMR spectra of **45** are quite similar to those of **44a**, while the mass spectral data shows a molecular weight of 280, corresponding to that of proposed structure **45**.

Enol lactone **18** did not react with aromatic amines until a mixture containing the two was heated. For example, when a mixture of **18** and aniline was allowed to stand at room temperature for several hours, GC and TLC analysis indicated no reaction was taking place. However, when the two were refluxed in xylene overnight, enelactam **43g** was formed. In a similar manner, **18** and methyl anthranilate reacted to give the enelactam **43h**. In both these cases, slightly more than one equivalent of amine was used. If more than two equivalents of aniline were added to **18**, and the mixture heated, addition of two molecules of aniline took place to give the amino lactam **44e**. As was observed for enol lactone **17**, **18** reacted with anthranilic acid to give a tricyclic product, pyrido[1,2-*a*][3,1]benzoxazine **46**. Enol lactone **18** also reacted with 1,2-phenylenediamine to give initially an unidentified solid that when treated with 10% HCl was converted to pyrido[1,2-*a*]benzimidazol-1(2*H*)-one **47**.

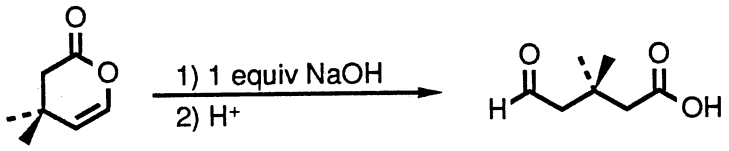
Three aliphatic diamines reacted with **18** to give bicyclic products. When an excess of ethylenediamine, 1,3-propanediamine, or *N*-methyl-1,3-propanediamine was added to **18**, an exothermic reaction took place and after distillation gave **48a-c**. Distillation of a mixture of 0.5 equivalents of ethylenediamine and **18** gave a mixture of bisenelactam **49b** and the bicyclic compound **48a**. However a similar reaction with 0.5 equivalents of 1,3-propanediamine did not give any bisenelactam upon distillation.




**18** **49b**

Unsubstituted enelactam **43a** also undergoes the *N*-alkylation reaction described previously to give **43b-e**. In fact, this reaction gave significantly better results with **43a** than with the similar enelactam **37a**, although the reason for this is not clear. The use of 0.5 equivalents of diiodomethane and 1,3-dibromopropane gave bisenelactams **49a** and **49c**.

Enol lactone **18** was treated with aqueous base to learn whether the corresponding hydroxy lactone could be made. However, while **18** is hydrolyzed with base, $^{1}H$ and $^{13}C$ NMR indicate the product exists as the open chain aldehydo acid **50** instead of as a hydroxy lactone. Treatment of **50** with ammonia or aniline apparently produced salts, which upon distillation gave only small amounts of enelactams **43a** and **43g** respectively. Because of the low yields from these two reactions, no further reactions of **50** with other primary amines were attempted.




**18** **50**

## Synthesis of 7-Nornepetalic Acid and 7-Nornepetalactone and Their Reactions with Ammonia and Primary Amines

In order to make 7-nornepetalactone (**12**) in the same way that we had prepared isocoumarin **15**, ketone **10** was required. As shown in Figure 5, two diastereomers of this ketone were prepared. Since we had on hand a substantial amount of acid **51**, we sought a method to remove the carboxyl group and leave a ketone carbonyl group in its place. While there are many possible ways of doing this, we found after considerable experimentation that the route shown gives the best results. Except for the first reaction, each reaction gave a high yield of product without side reactions. In the conversion of acid **51** to ketone **52** using methyllithium with ether as a solvent, a substantial amount of the tertiary alcohol side product was formed, a common problem with this reaction.

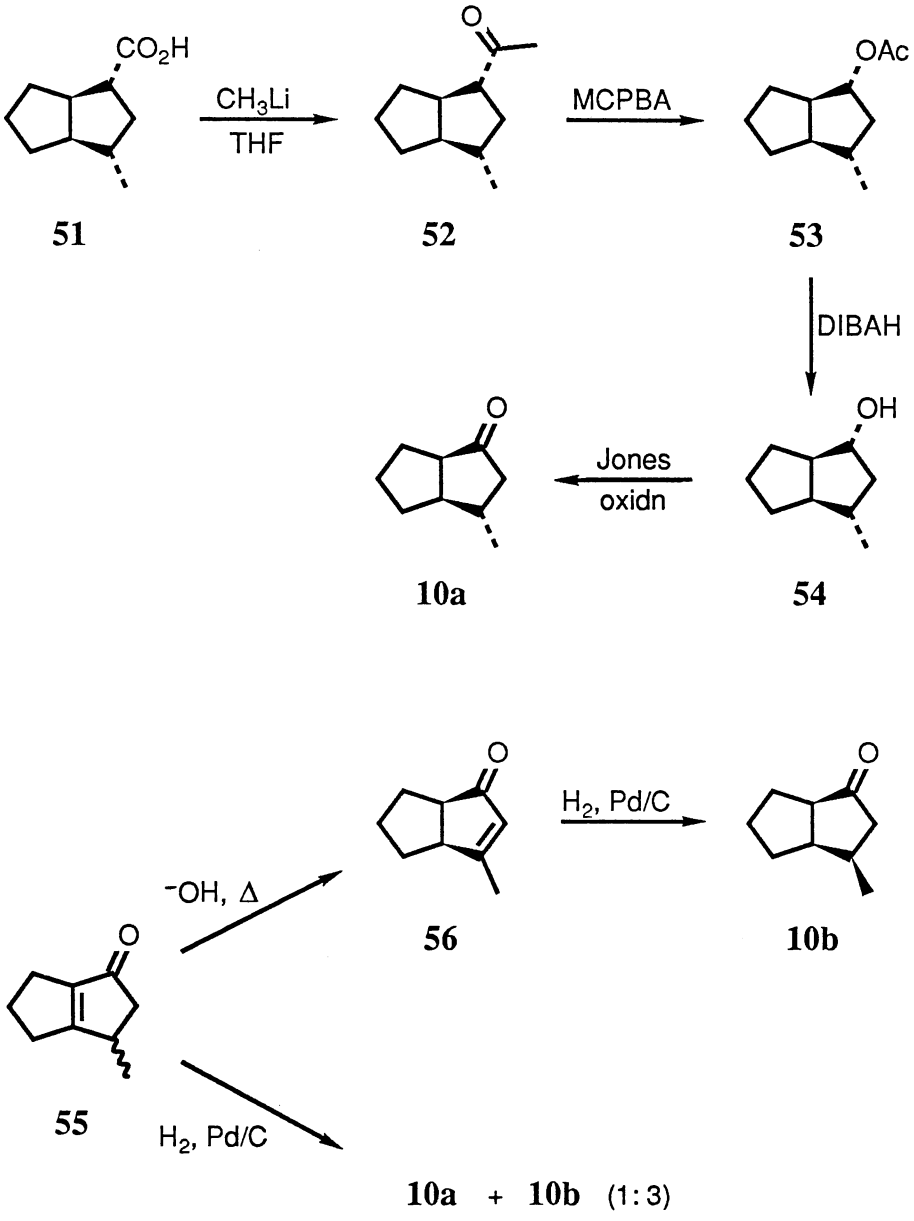



**Figure 5.** Synthesis of Hexahydro-3-methyl-1(2*H*)-pentalenone (**10**)

However, by replacing ether with tetrahydrofuran, the formation of this tertiary alcohol was considerably reduced though not entirely eliminated. After purification, **52** was converted to acetate **53** by Baeyer-Villiger oxidation using *m*-chloroperoxybenzoic acid. Acetate **53** may be converted to alcohol **54** either by basic hydrolysis or by reduction using an hydride reagent. We used diisobutylaluminum hydride in this step with good results. Finally, oxidation of **54** using the Jones reagent gave ketone **10a**.

An isomer of **10a**, ketone **10b**, was prepared in two steps from ketone **55**. Reaction of cyclopentene and crotonic acid in polyphosphoric acid gave ketone **55**.[55] During an attempt to purify **55** we found that heating in the presence of sodium hydroxide caused **55** to isomerize to ketone **56**. In our hands, catalytic hydrogenation of **56** gave only ketone **10b**, while that of **55** gave a mixture of **10a** and **10b** (1:3). An advantage of the synthesis beginning with ketone **55** over the one beginning with acid **51**, is that the starting materials are readily available, and so relatively large quantities of ketone **10b** could be made. Also, only two steps are needed to prepare the desired ketone. However, the yield in the synthesis of **55** is only about 25%, and it is a somewhat tedious reaction to run and work up. Furthermore, **55** was slightly contaminated by side products after workup. It should be noted that for our purposes it did not matter whether we had pure **10a**, pure **10b**, or a mixture of the two since both were later converted to the same compound.

In a manner similar to the conversion of ketone **13** to hydroxy lactone **14** and isocoumarin **15**, both ketone **10a** and **10b** were converted to 7-nornepetalic acid (**11**) and 7-nornepetalactone (**12**) as shown in Figure 6. First, the ketones **10a** and **10b** were refluxed with isopropenyl acetate containing a catalytic amount of acid to give their respective enol acetates **57a** and **57b** in good yield. There was no indication in either case that any enol acetate with the double bond exocyclic to the cyclopentane ring was formed.[56] As in the reaction of enol acetate **25** with ozone to give **14**, reaction of either enol acetate **57a** or **57b** with ozone gave a low yield of **11**. As before, the neutral

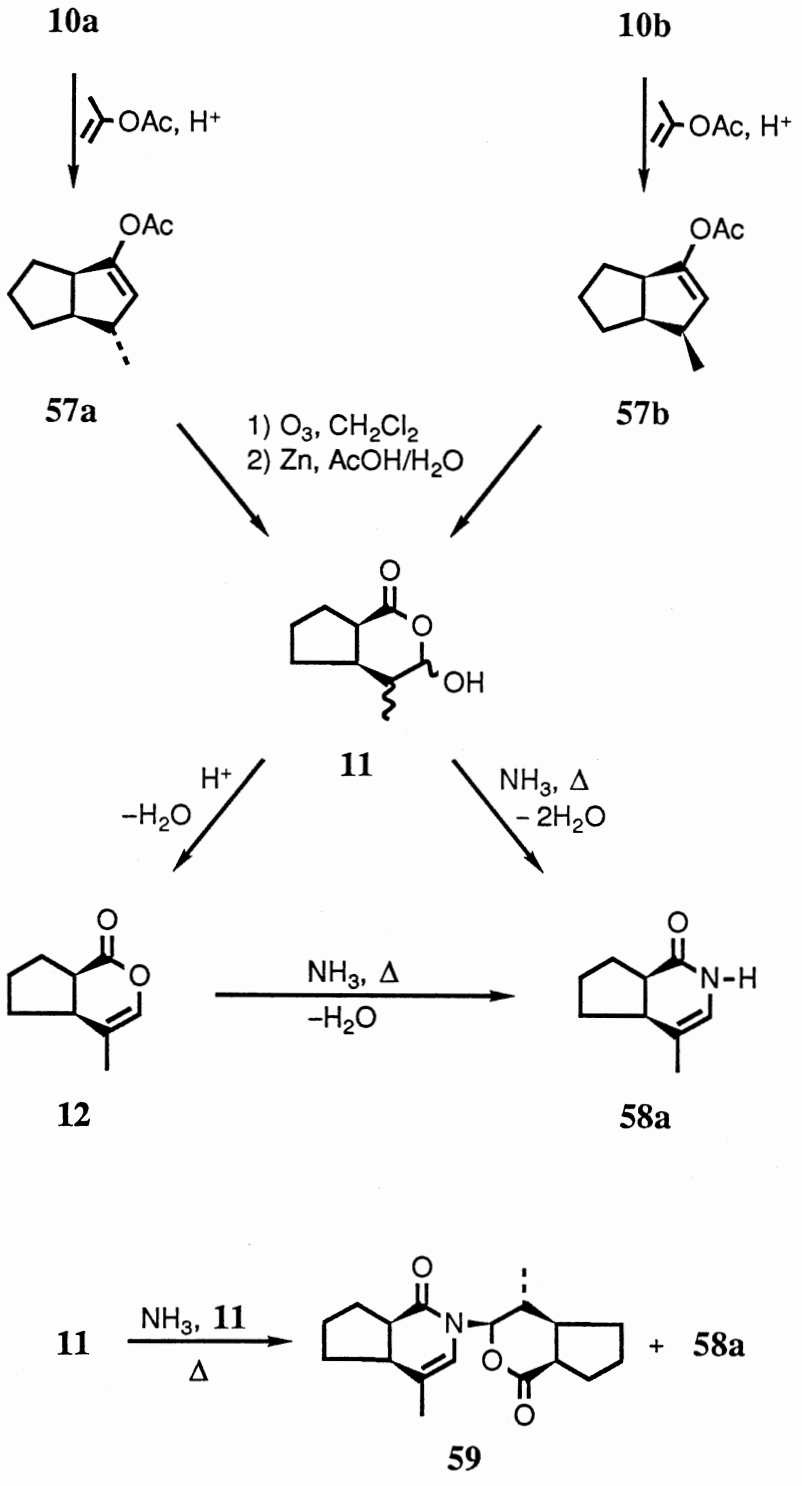
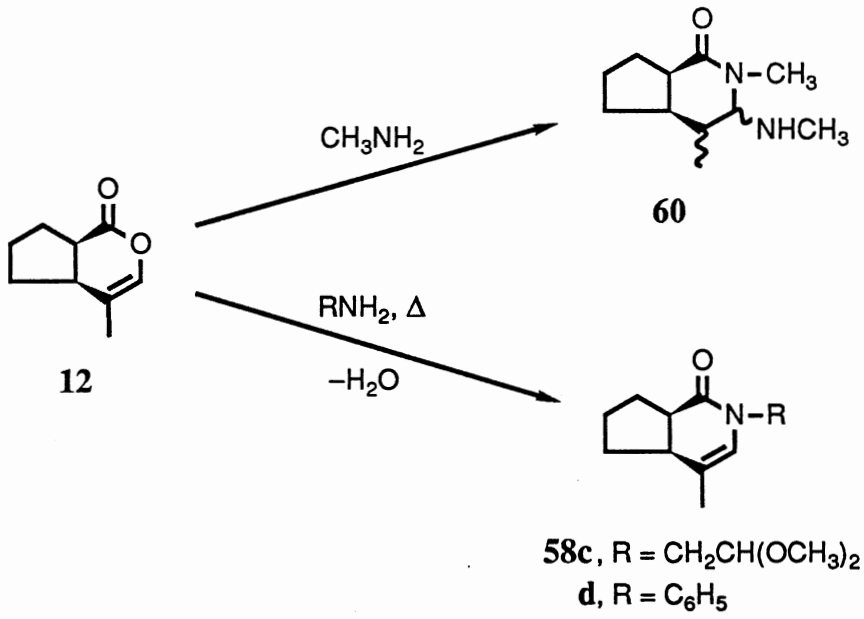



**Figure 6.** Synthesis of 7-Nornepetalic Acid (**11**) and 7-Nornepetalactone (**12**) and Their Reactions with Ammonia

material consisted mostly of recoverable ketone **10.** The hydroxy lactone **11** was dehydrated to enol lactone **12** by refluxing in toluene that contained a catalytic amount of acid. It should be noted that starting materials in both routes to the synthesis of **11** and **12** were racemic, and so then are **11** and **12.**

Like nepetalactone (**3a**) and nepetalic acid (**7**), both 7-nornepetalactone (**12**) and 7-nornepetalic acid (**11**) reacted with ammonia and gave 7-nornepetalactam (**58a**) after distillation. Also, treatment of one equivalent of **11** with ammonia, followed by addition of a second equivalent of **11**, gave, after distillation, a mixture of enelactam **58a** and mixed dimer **59**, analogous to the mixed dimer **2** isolated from oil of catnip.

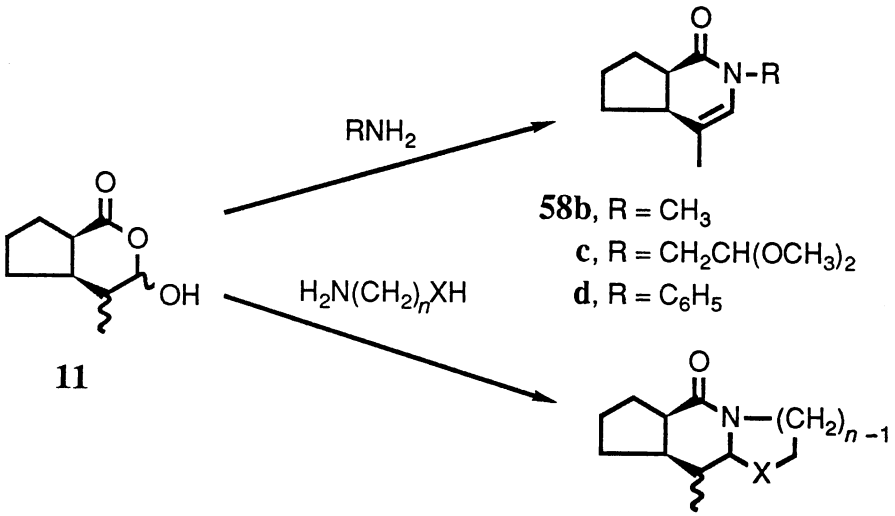
7-Nornepetalactone (**12**) and 7-nornepetalic acid (**11**) also reacted with a few primary amines to give enelactams. With aminoacetaldehyde dimethyl acetal and aniline, **12** reacted to give upon distillation enelactams **58c** and **58d** respectively. In contrast, the reaction of neat **12** with methylamine resulted in addition of two molecules of methylamine to give two diastereomers of amino lactam **60**. This is the same type of



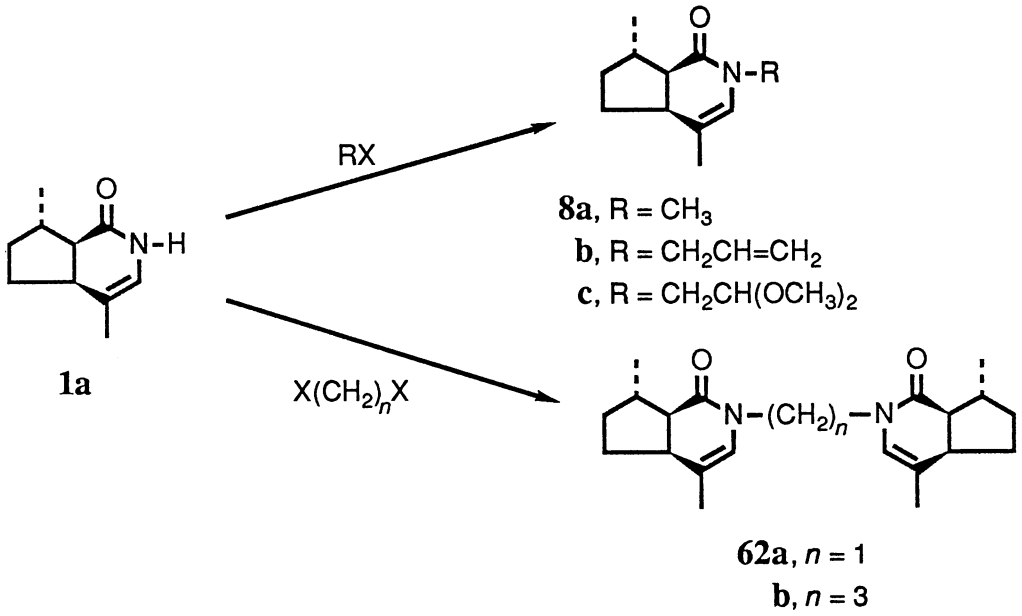

reaction enol lactone **18** underwent when treated with methylamine. Distillation of these diastereomers apparently gave rise to a third diastereomer of **60** plus a trace of enelactam

**58b** as indicated by $^{13}C$ NMR. However, treatment of **11** with methylamine followed by distillation gave only enelactam **58b**.

When **11** was treated with a few simple aliphatic diamines and hydroxy amines, tricyclic products were obtained upon distillation. The reaction of **11** with ethylenediamine gave, as shown by $^{13}C$ NMR, only one isomer of **61a**. However, with 1,3-propanediamine, **11** reacted to give what was apparently a mixture of three diastereomers of **61b**. With 2-aminoethanol and 3-amino-1-propanol, **11** reacted to give only one isomer of the tricyclic compounds **61c** and **61d**. In addition to formation of **61c**, it appeared by $^{13}C$ NMR that the reaction of **11** with 2-aminoethanol gave a small amount of an enelactam.




It is quite likely that nepetalactone (**3a**) and nepetalic acid (**7**) would react with amines in a similar way to their 7-nor analogues **11** and **12**, although this was not confirmed. So, while we did not make any *N*-substituted derivatives of nepetalactam (**1a**) from **3a** or **7**, we found that **1a** could be *N*-alkylated as were other unsubstituted enelactams. Treatment of **1a** with alkyl halides gave enelactams **8a-c**, while treatment with dihaloalkanes gave bisenelactams **62a** and **62b**.



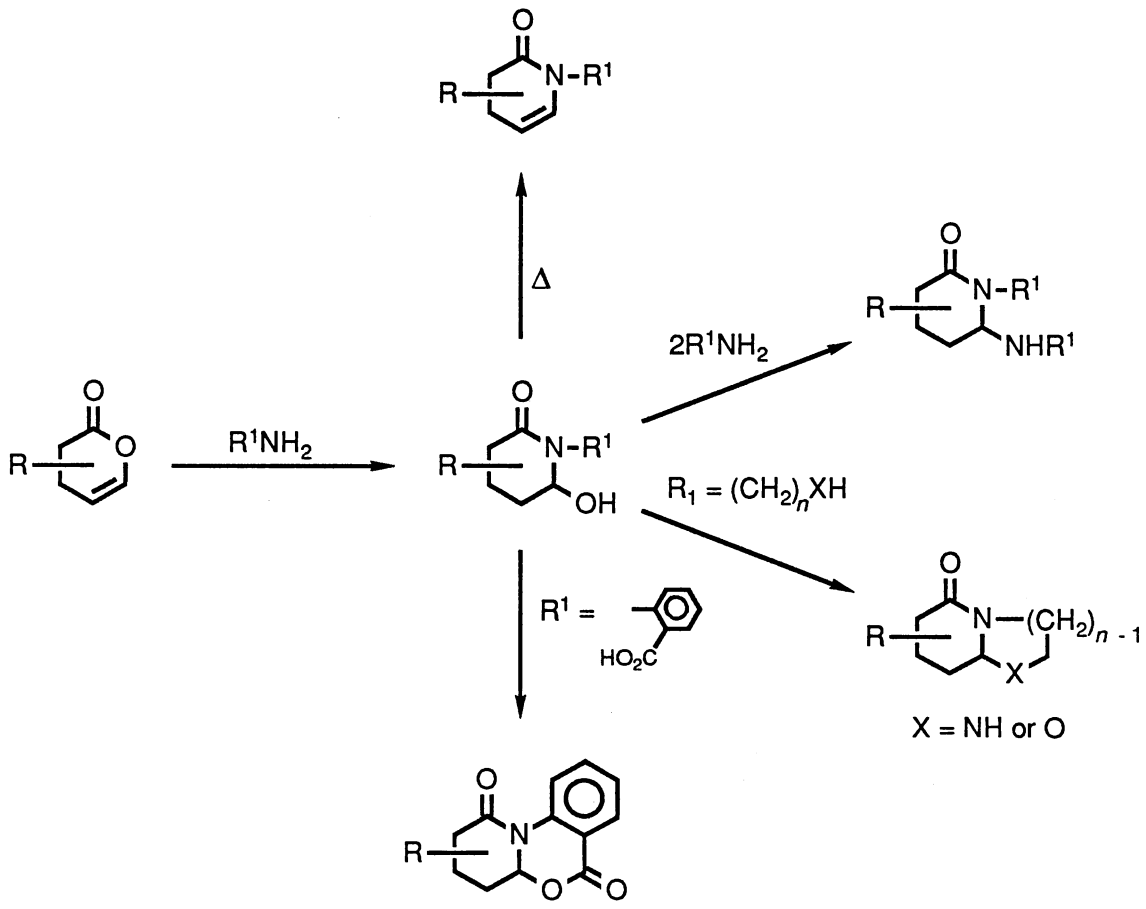

## Conclusions

Our original goal was to determine the origin of nepetalactam (**1a**) and *N*-(nepetal-3-yl)-nepetalactam (**2**), isolated from a sample of commercial oil of catnip. Toward that end, we found that treatment of the usual major constitutent in oil of catnip, nepetalactone (**3a**), with ammonia followed by distillation gave **1a**. Later, we also found conditions for the formation of mixed dimer **2** from nepetalic acid (**7**), a compound that can be derived from **3a**, and has also been found in oil of catnip.

In addition to determining the origins of **1a** and **2**, this study has also explored the reactions of six-membered enol lactones, or corresponding hydroxy lactones, if they exist, with ammonia and primary amines. We have found that, depending on conditions, these reactions give a interesting variety of products, many of which have not been described before. The type of product obtained depends in part on the enol lactone, the amine, the ratio of reactants, and solvent, if any, that are used in the reaction. In addition, distillation of the mixture plays an important role in determining the product finally obtained.

From our work and information available in the literature, it appears enol lactones can be divided into two classes: those that can be derived from aldehydo acids such as nepetalactone (**3a**), and those derivable from keto acids such as **17**. In both cases the enol lactones reacted with ammonia to give the unsubstituted enelactams upon distillation. However, enol lactones derived from aldehydo acids are more easily converted to *N*-substituted enelactams by treatment with various primary amines. Enol lactone **17**, derived from a keto acid, usually gave keto amides when treated with primary amines. This is the trend found in the literature for other enol lactones derived from keto acids.

Although no attempt was made to determine the mechanism of the reactions of enol lactones with amines, the formation of various products from both types of enol lactones suggest that hydroxy lactams may be intermediates. Occasionally a hydroxy



lactam may be isolated, but in most cases it appears to be easily converted to other products. This intermediate hydroxy lactam may dehydrate when heated to give an enelactam. Under certain conditions, the hydroxy group may be replaced by an amino group. This replacement may occur by intermolecular nucleophilic substitution to give amino lactams, or a second amino group, or in one case a hydroxy group, originally from the reacting amine may displace the hydroxy group by intramolecular nucleophilic substitution to give compounds containing a new ring. In the special case of anthranilic acid, the hydroxy group of the hydroxy lactam apparently reacts with the carboxy group originally from anthranilic acid to give lactones.

Finally, we found that unsubstituted enelactams could be *N*-alkylated by various alkyl halides. In some cases, enelactams that could not be made from treatment of enol lactones with primary amines could be made by this *N*-alkylation procedure.

CHAPTER III

EXPERIMENTAL

## General Information

$^1H$ NMR spectra were recorded on a Varian XL-300 spectrometer, and $^{13}C$ NMR spectra on Varian XL-300 or Varian XL-100 spectrometers. In both cases, chemical shifts are reported in ppm (δ) with tetramethylsilane as internal standard. GC analyses were performed on a Micro Tek 220 instrument using a 6 ft x 0.25 in. U-shaped glass column packed with 5% Carbowax 20M on acid-washed G Pak. TLC analyses were carried out with Eastman Kodak precoated sheets (13181 silica gel with fluorescent indicator), and results were visualized by UV light (254 nm). Solutions were routinely dried with anhydrous $MgSO_4$. The term in vacuo means removal of solvents under reduced pressure by rotary evaporator or by vacuum pump. All distillations were carried out with a Kugelrohr apparatus and boiling points refer to oven temperature at time of distillation. Melting points are uncorrected; those below 250 °C were determined with a Thomas Hoover apparatus and those above 250 °C on a Mel-Temp apparatus. Ozonolyses were conducted using a Welsbach T-23 ozonator. Ammonia refers to anhydrous ammonia unless otherwise indicated. Methylamine refers to anhydrous methylamine.

## Synthesis of Nepetalactam and *N*-(Nepetal-3-yl)-nepetalactam

**[4a*S*-(4aα,7α,7aα)]-Nepetalactam (1a). Method A.** Ammonia was passed through a solution of **3a** (100 mg) in $CH_3OH$ (10 mL) for 15 min. Removal of

$CH_3OH$ in vacuo gave an intermediate material that was readily soluble in $CH_2Cl_2$. GC analysis of this material showed a peak with the same $t_R$ as that of **1a**, but TLC analysis indicated the material was not **1a**. Apparently this intermediate material dehydrates to **1a** during GC analysis. $^{13}C$ NMR indicated the presence of several compounds, but not **1a**, in the intermediate material. Distillation of this material at 110-120 °C (0.15 torr) gave 90 mg (91%) distillate which was identical in all respects to **1a** isolated from the Fritzche oil of catnip. When $CH_2Cl_2$ was substituted for $CH_3OH$ in the above reaction, **3a** reacted much more slowly with ammonia as indicated by GC analysis.

**Method B.** Hydroxy lactone **7** (100 mg) was substituted for **3a** in the above reaction. While the intermediate material was not soluble in $CH_2Cl_2$, it was soluble in $CH_3OH$. Again GC analysis of the intermediate material showed a peak with the same $t_R$ as that of **1a**. Distillation of the intermediate material gave 81 mg (90%) of **1a**: mp 95-96 °C (hexane); $^1H$ NMR ($CDCl_3$) δ 1.10-1.28 (m, 1), 1.23 (d, 3, $J$ = 6 Hz), 1.43-1.60 (m, 1), 1.66 (s, 3), 1.78-1.90 (m, 1), 1.98-2.10 (m, 1), 2.26-2.41 (m, 2), 2.74 (q, 1, $J$ = 9 Hz), 5.68-5.76 (m, 1), 7.70 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 17.9 (q), 21.2 (q), 31.9 (t), 33.3 (t), 40.4 (d), 42.6 (d), 51.0 (d), 115.5 (s), 118.3 (d), 174.9 (s). When the above reactions were carried out with concentrated ammonium hydroxide (5 mL) in place of anhydrous ammonia, distillation gave only **1a** as product in approximately the same yields as above.

***N*-(Nepetal-3-yl)-nepetalactam (2).** A solution of **7** (100 mg) in $CH_3OH$ was treated with ammonia for 15 min. After $CH_3OH$ was removed in vacuo, more **7** (100 mg) and $CH_3OH$ (10 mL) were added. After complete solution of the material, $CH_3OH$ was again removed in vacuo. The remaining material was distilled to 120 °C (0.14 torr) to give 103 mg of distillate. The $^{13}C$ NMR spectrum of this distillate showed it to be mostly **1a.** The residual material was then distilled to 180 °C (0.14 torr) to give 81 mg more distillate, which $^1H$ and $^{13}C$ NMR showed was identical to mixed dimer **2** isolated from the oil of catnip: mp 116-117 °C (hexane); $^1H$ NMR ($CDCl_3$) δ 0.87 (d, 3,

$J$ = 7 Hz), 1.14-1.30 (m, 2), 1.17 (d, 3, $J$ = 7 Hz), 1.21 (d, 3, $J$ = 7 Hz), 1.40-1.64 (m, 2), 1.69 (s, 3), 1.76-2.54 (m, 10), 2.71 (q, 1, $J$ = 8 Hz), 5.82 (s, 1), 6.30 (d, 1, $J$ = 10 Hz); $^{13}$C NMR ($CDCl_3$) δ 14.2 (q), 18.6 (q), 20.6 (q), 20.9 (q), 31.7 (t), 32.5 (t), 33.2 (t), 34.9 (t), 38.4 (d), 39.5 (d), 40.7 (d), 42.0 (d), 43.5 (d), 50.2 (d), 51.9 (d), 83.8 (d), 116.4 (d), 118.5 (s), 172.5 (s), 174.9 (s).

**Synthesis of 1b and 1c.** In the same manner that **3a** was converted to **1a,** impure samples of **3b** and **3c** were converted to **1b** and **1c** respectively. Although GC analysis and $^{13}$C NMR indicated both products were moderately impure, no attempt was made to purify either compound.

**[4a*S*-(4aα,7α,7aβ)]-Nepetalactam (1b):** bp 110-120 °C (0.11 torr); $^{13}$C NMR ($CDCl_3$) δ 16.4 (q), 17.5 (q), 25.9 (t), 29.8 (d), 32.0 (t), 39.0 (d), 50.5 (d), 119.2 (d), 119.8 (s), 173.4 (s).

**[4a*R*-(4aα,7β,7aα)]-Nepetalactam (1c):** bp 110-120 °C (0.13 torr); $^{13}$C NMR ($CDCl_3$) δ 16.3 (q), 17.1 (q), 31.5 (t), 32.7 (t), 38.7 (t), 40.3 (d), 47.3 (d), 116.1 (s), 117.1 (d), 173.4 (s).

**Basic Hydrolysis of 1a.** In an attempt to convert **1a** to **7**, a solution of **1a** (1.65 g, 10 mmol) in 10% NaOH (50 mL) was refluxed. The reaction was followed by GC, and it took 2 days before all **1a** was consumed. After cooling, the reaction mixture was neutralized with 10% HCl and products were extracted with ether. The ether layer was then extracted with a saturated solution of $NaHCO_3$. The ether layer was dried, and ether was removed in vacuo to leave a mixture of the lactones **23a** and **23b** (0.69 g). The $NaHCO_3$ layer was neutralized with 10% HCl and products were extracted with ether. The usual workup of this ether layer gave a mixture of the diacids **24a** and **24b** (0.58 g). The conversion of **24a** to its water-insoluble barium salt was carried out to separate **24a** and **24b**.[39] The isolated diacids were identical by $^{13}$C NMR to authentic **24a** and **24b** on hand from previous work.

The lactones **23a** and **23b** were separated on the basis of the more rapid basic hydrolysis of **23a** to the sodium salt of its corresponding hydroxy acid. When a mixture of an ether solution (50 mL) of **23a** and **23b** and 5% NaOH (50 mL) was vigorously stirred, both **23a** and **23b** were hydrolyzed to the sodium salts of their corresponding hydroxy acids. However, when the stirring was stopped about 20 min after it had begun, GC analysis of the ether layer showed that although some **23b** remained, **23a** had virtually been completely removed. After separation of the two layers, the aqueous layer was neutralized and the lactones were extracted with ether. This ether layer was then treated with 5% NaOH as above. By repeating this process several times, **23a** and **23b** were separated. The lactones **23a** and **23b** were further purified by distillation.

**[4*R*-(4α,4aα,7α,7aα)]-Dihydronepetalactone (23a):** bp 75-85 °C (0.45 torr); $^1$H NMR[57] ($CDCl_3$) δ 1.01 (d, 3, $J$ = 7 Hz), 1.12-1.34 (m, 2), 1.20 (d, 3, $J$ = 7 Hz), 1.55-1.69 (m, 1), 1.80-1.92 (m, 1), 2.00-2.19 (m, 2), 2.21-2.31 (m, 1), 2.38 (dd, 1, $J$ = 11, 9 Hz), 3.92 (dd, 1, $J$ = 11, 10 Hz), 4.15 (dd, 1, $J$ = 11, 4 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.5 (q), 20.0 (q), 31.7 (t), 34.2 (t), 35.1 (d), 38.6 (d), 44.4 (d), 48.8 (d), 72.6 (t), 174.8 (s).

**[4*S*-(4α,4aβ,7β,7aβ)]-Dihydronepetalactone (23b):** bp 75-85 °C (0.35 torr); $^1$H NMR[57] ($CDCl_3$) δ 0.90 (d, 3, $J$ = 7 Hz), 1.07-1.28 (m, 1), 1.10 (d, 3, $J$ = 7 Hz), 1.30-1.52 (m, 1), 1.67-1.79 (m, 1), 1.83-2.08 (m, 2), 2.14-2.32 (m, 1), 2.41 (dd, 1, $J$ = 11, 9 Hz), 2.47-2.61 (m, 1), 3.96-4.16 (m, 2); $^{13}$C NMR ($CDCl_3$) δ 13.1 (q), 19.4 (q), 26.4 (t), 31.0 (d), 35.1 (t), 40.5 (d), 41.4 (d), 50.5 (d), 69.9 (t), 174.0 (s).

**[1*R*-[1α(*R**),2α,3β]]-Nepetalinic Acid (24a):** mp 84-85 °C (lit.[39] mp 85 °C); $^1$H NMR ($CDCl_3$) δ 1.07 (d, 3, $J$ = 7 Hz), 1.12-1.28 (m, 1), 1.21 (d, 3, $J$ = 7 Hz), 1.35-1.50 (m, 1), 1.81-2.00 (m, 2), 2.09-2.25 (m, 1), 2.43-2.60 (m, 2), 2.65-2.78 (m, 1), 11.40 (s, 2); $^{13}$C NMR ($CDCl_3$) δ 17.1 (q), 18.8 (q), 30.5 (t), 34.0 (t), 39.5 (d), 41.8 (d), 44.1 (d), 54.6 (d), 182.5 (s), 183.5 (s).

**[1*R*-[1α(*S**),2α,3β]]-Nepetalinic Acid (24b):** mp 115-117 °C (lit.[39] mp 115-117 °C); $^1$H NMR ($CDCl_3$) δ 1.11 (d, 3, $J$ = 7 Hz), 1.28-1.46 (m, 1), 1.39 (d, 3, $J$ = 7 Hz), 1.71-1.90 (m, 1), 1.92-2.05 (m, 1), 2.14-2.28 (m, 1), 2.37-2.60 (m, 2), 2.64-2.70 (m, 1), 2.72-2.84 (m, 1), 11.68 (s, 2); $^{13}$C NMR ($CDCl_3$) δ 17.0 (q), 21.9 (q), 30.3 (t), 33.4 (t), 38.5 (d), 41.4 (d), 45.8 (d), 53.0 (d), 181.9 (s), 182.8 (s).

## Synthesis of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one and 4-Methyl-1*H*-2-benzopyran-1-one

**3-Methyl-1*H*-inden-1-ol Acetate (25).** A mixture of 3-methyl-1-indanone[58] (**13**) (146.0 g, 1.00 mol), isopropenyl acetate (500 mL), and TsOH (5.0 g) was refluxed for 1 h before distilling it to bp 95 °C. Afterwards, refluxing of the mixture was continued until all of **13** was consumed as indicated by TLC. After allowing the reaction mixture to cool, ether was added and the mixture was washed with saturated $NaHCO_3$ solution and water. The solution was dried, and ether and isopropenyl acetate were removed in vacuo. The resulting black oil was distilled at 85-90 °C (0.25 torr) [lit.[59] bp 100-101 °C (1.9 torr)] to give 174.0 g (93%) of **25**: $^1$H NMR ($CDCl_3$) δ 1.29 (d, 3, $J$ = 8 Hz), 2.23 (s, 3), 3.44-3.54 (m, 1), 6.25-6.32 (m, 1), 7.17-7.30 (m, 4); $^{13}$C NMR ($CDCl_3$) δ 16.3 (q), 21.1 (q), 41.3 (d), 117.9 (d), 121.9 (d), 122.7 (d), 125.8 (d), 126.2 (d), 138.1 (s), 147.1 (s), 147.8 (s), 167.8 (s).

**3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one (14).** Ozone was passed through a solution of enol acetate **25** (47.0 g, 0.25 mol) in $CH_2Cl_2$ (500 mL) at –78 °C until the effluent gases turned moist starch-iodide paper dark. After this mixture had been poured into a solution of 50% aqueous acetic acid (500 mL), Zn dust (ca. 50 g) was added and the mixture was stirred overnight. The mixture was diluted with water until it became cloudy, and then extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was extracted several times with saturated $NaHCO_3$ solution. The $CH_2Cl_2$ layer was worked up to give 12.3 g (34%) of ketone **13**. The $NaHCO_3$ layer was neutralized

(10% HCl) and extracted with $CH_2Cl_2$. After the $CH_2Cl_2$ layer was dried, $CH_2Cl_2$ was removed in vacuo to leave an oil which later crystallized. Recrystallization from $CHCl_3$ gave 18.7 g (42%) of **14**: mp 139-142 °C; $^1$H NMR ($CDCl_3$) δ 1.37 and 1.42 (d, 3, $J$ = 8 Hz), 3.14-3.24 and 3.28-3.39 (m, 1), 5.50 (br s, 1), 5.74 and 5.86 (d, 1, $J$ = 3 Hz), 7.31-7.48 (m, 2), 7.63 (t, 1, $J$ = 8 Hz), 8.14 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 13.2 (q), 18.7 (q), 36.4 (d), 37.8 (d), 98.3 (d), 100.2 (d), 123.5 (s), 124.0 (s), 126.6 (d), 127.5 (d), 127.7 (d), 130.1 (d), 134.5 (d), 142.0 (s), 142.7 (s), 165.2 (s), 165.7 (s).

**α-Methyl 2-Carboxy-α-methyl-benzeneacetate (26b).** Enol acetate **25** (18.8 g, 0.10 mol) in $CH_3OH$ (200 mL) at –78 °C was ozonized until the effluent gases turned moist starch-iodide paper dark. To this mixture was added KI[60] (50 g) and glacial acetic acid (50 mL) and the solution was allowed to warm to room temperature. Later, 10% sodium thiosulfate solution was added until the color of the released iodine was removed. Then water was added to the solution until it became cloudy. This solution was extraced with ether, and the ether layer was then extracted with saturated $NaHCO_3$. Neutralization of the $NaHCO_3$ layer followed by the usual workup gave the half ester **26b**: 21% yield; mp 95-96 °C (hexane/ether); $^1$H NMR ($CDCl_3$) δ 1.56 (d, 3, $J$ = 8 Hz), 3.66 (s, 3), 4.81 (q, 1, $J$ = 8 Hz), 7.34 (t, 1, $J$ = 8 Hz), 7.41 (d, 1, $J$ = 8 Hz), 7.54 (t, 1, $J$ = 8 Hz), 8.09 (d, 1, $J$ = 8 Hz), 11.45 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 18.4 (q), 42.1 (d), 52.0 (q), 126.9 (d), 128.0 (s), 128.6 (d), 131.6 (d), 133.2 (d), 142.8 (s), 172.6 (s), 175.0 (s).

**2-Carboxy-α-methyl-benzeneacetic Acid (26a).** Using the method of Chatterjea et al.,[61] ketone **13** was converted to diacid **26a**: mp 149-150 °C (lit.[61] mp 151 °C); $^1$H NMR ($CD_3OD$) δ 1.56 (d, 3, $J$ = 8 Hz), 4.74 (q, 1, $J$ = 8 Hz), 6.11 (br s, 2), 7.35 (t, 1, $J$ = 8 Hz), 7.42-7.59 (m, 2), 8.01 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CD_3OD$) δ 18.2 (q), 42.2 (d), 127.0 (d), 128.5 (d), 129.9 (s), 131.1 (d), 132.6 (d), 142.1 (s), 170.6 (s), 177.5 (s).

**Methyl 2-(Methoxycarbonyl)-α-methyl-benzeneacetate (26d).** To acid **26a** or **26b** was added an ether solution of $CH_2N_2$ to give after removal of ether the diester **26c**: $^1$H NMR ($CDCl_3$) δ 1.54 (d, 3, $J$ = 8 Hz), 3.64 (s, 3), 3.88 (s, 3), 4.66 (q, 1, $J$ = 8 Hz), 7.30 (t, 1, $J$ = 8 Hz), 7.38 (d, 1, $J$ = 8 Hz), 7.48 (t, 1, $J$ = 8 Hz), 7.92 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 18.3 (q), 42.0 (d), 51.9 (q), 52.1 (q), 126.7 (d), 128.4 (d), 129.1 (s), 130.6 (d), 132.2 (d), 141.8 (s), 167.6 (s), 174.8 (s).

**Methyl 2-(1-Methyl-2-oxoethyl)-benzoate (27).** To a solution of **14** (1.78 g, 10 mmol) in acetone (25 mL) was added an ether solution of $CH_2N_2$ until a yellow color persisted in the solution. Removal of solvents in vacuo left the aldehydo ester **27**: $^1$H NMR ($CDCl_3$) δ 1.46 (d, 3, $J$ = 8 Hz), 3.88 (s, 3), 4.54 (q, 1, $J$ = 8 Hz), 7.22 (d, 1, $J$ = 8 Hz), 7.35 (t, 1, $J$ = 8 Hz), 7.52 (t, 1, $J$ = 8 Hz), 8.01 (d, 1, $J$ = 8 Hz), 9.75 (s, 1); $^{13}$C NMR ($CDCl_3$) δ 14.8 (q), 49.5 (dd), 52.1 (q), 127.2 (d), 129.4 (d), 129.5 (s), 131.1 (d), 132.5 (d), 140.1 (s), 167.4 (s), 200.6 (d).

**2-(Methoxycarbonyl)-α-methyl-benzeneacetic Acid (26c).** To a solution of **27** (1.92 g, 10 mmol) in acetone (25 mL) was added the Jones reagent[62] (5.0 mL). This mixture was heated by heat gun for a few minutes, after which GC analysis indicated reaction was complete. Workup gave 1.38 g (66%) of half ester **26c**: mp 118-119 °C (hexane/ether) (lit.[61] mp 115-116 °C); $^1$H NMR ($CDCl_3$) δ 1.55 (d, 3, $J$ = 8 Hz), 3.88 (s, 3), 4.62 (q, 1, $J$ = 8 Hz), 7.32 (t, 1, $J$ = 8 Hz), 7.42 (d, 1, $J$ = 8 Hz), 7.50 (t, 1, $J$ = 8 Hz), 7.92 (d, 1, $J$ = 8 Hz), 11.20 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 17.8 (q), 42.1 (d), 52.2 (q), 126.9 (d), 128.5 (d), 129.1 (s), 130.6 (d), 132.4 (d), 141.1 (s), 168.0 (s), 179.6 (s).

**4-Methyl-1*H*-2-benzopyran-1-one (15). Method A.** Hydroxy lactone **14** (8.90 g, 50 mmol) was heated to 200 °C under nitrogen for 15 min. After cooling, the product was distilled at 90-95 °C (0.10 torr) to give 7.84 g (98%) of isocoumarin **15**.

**Method B.** A solution of **14** (8.90 g, 50 mmol) in toluene (250 mL) containing TsOH (0.25 g) was refluxed for 2 h. At this time, TLC analysis of the reaction mixture indicated the reaction was complete. The usual workup gave 7.12 g (89%) of **15**: mp 64-65 °C (hexane) (lit.[63] mp 63-66 °C); $^1$H NMR ($CDCl_3$) δ 2.12 (s, 3), 7.11 (s, 1), 7.42-7.58 (m, 2), 7.77 (t , 1, *J* = 8 Hz), 8.29 (d, 1, *J* = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 12.8 (q), 112.8 (s), 121.2 (s), 122.9 (d), 128.2 (d), 129.7 (d), 134.7 (d), 137.4 (s), 141.0 (d), 162.6 (s).

## Reactions of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one with Ammonia and Primary Amines

**Reaction of 14 with Ammonia. Method A.** Ammonia was passed through a solution of hydroxy lactone **14** (8.90 g, 50 mmol) in $CH_3OH$ (125 mL) for 1 h. After removal of $CH_3OH$ in vacuo, the material was distilled to 155 °C (0.15 torr) to give **28a** as a crystalline distillate (6.27 g, 79%). The residual material consisted mostly of mixed dimer **29**, which crystallized from an ether/$CH_2Cl_2$ solution. Filtration of the solution gave **29** (1.26 g, 16%).

**Method B.** The conditions that had led to the formation of mixed dimer **2** from hydroxy lactone **7** were reproduced on a larger scale with hydroxy lactone **14**. Through a solution of **14** (1.78 g, 10 mmol) in $CH_3OH$ (25 mL) was passed ammonia for 30 min. After removal of $CH_3OH$ in vacuo, more **14** (1.78 g, 10 mmol) was added and the mixture was dissolved in $CH_3OH$ (25 mL). After removal of $CH_3OH$ in vacuo, the resulting material was distilled to 160 °C (0.07 torr) to give a crystalline material (1.96 g) which TLC analysis indicated was a mixture of isocoumarin **15** and isocarbostyril **28a**. The residual material crystallized from an ether/$CH_2Cl_2$ solution to give 0.90 g (28%) of **29**.

**4-Methyl-1(2*H*)-isoquinolinone (28a):** bp 130-140 °C (0.15 torr); mp 173-174 °C ($CH_2Cl_2$) (lit.[64] mp 173-174 °C); $^1$H NMR ($CDCl_3$) δ 2.22 (s, 3), 7.04 (s,

1), 7.51 (t, 1, $J$ = 8 Hz), 7.59 (d, 1, $J$ = 8 Hz), 7.70 (t, 1, $J$ = 8 Hz), 8.49 (d, 1, $J$ = 8 Hz), 12.05 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q), 112.5 (s), 123.3 (d), 125.5 (d), 125.8 (s), 126.5 (d), 127.6 (d), 132.5 (d), 138.4 (s), 164.2 (s).

**2-(3,4-Dihydro-4-methyl-1-oxo-1*H*-2-benzopyran-3-yl)-4-methyl-1(2*H*)-isoquinolinone (29):** mp 204-205 °C (ether/$CH_2Cl_2$); $^1$H NMR ($CDCl_3$) δ 1.31 (d, 3, $J$ = 8 Hz), 2.32 (s, 3), 3.50-3.64 (m, 1), 7.05 (d, 1, $J$ = 10 Hz), 7.19 (s, 1), 7.41-7.81 (m, 6), 8.15 (d, 1, $J$ = 7 Hz), 8.47 (d, 1, $J$ = 7 Hz); $^{13}$C NMR ($CDCl_3$) δ 12.3 (q), 15.6 (q), 36.1 (d), 84.3 (d), 113.6 (s), 122.8 (d), 123.2 (d), 124.2 (s), 125.2 (d), 127.1 (d), 127.8 (d), 128.6 (d), 130.2 (d), 133.0 (d), 134.6 (d), 136.8 (s), 141.0 (s), 161.7 (s), 164.0 (s).

**General Procedure for the Reaction of 14 with Primary Aliphatic Amines.** To a solution of **14** (1.78 g, 10 mmol) in $CH_3OH$ (25 mL) was added the amine (12.5 mmol). In the case of methylamine, the anhydrous amine was bubbled through the solution of **14** for 30 min. Glycine methyl ester hydrochloride (1.57 g, 12.5 mmol) was dissolved in water (10 mL) and neutralized with 10% NaOH before adding to the solution of **14**. GC analysis of these solutions immediately after addition of the amine always showed complete absence of **14**. Next, $CH_3OH$ was removed in vacuo. At this point, $^{13}$C NMR and TLC invariably showed the intermediate material already contained some of the product isocarbostyril. However, in addition to the sharp peaks of the isocarbostyril, $^{13}$C NMR also showed several broad peaks that were not present after this material was distilled. Similarly, TLC usually showed several spots in addition to one with the same $R_f$ value as that of the isocarbostyril obtained after distillation. During or immediately after distillation the product usually crystallized and was relatively pure as indicated by TLC and $^1$H and $^{13}$C NMR. With the exception of **28h**, the products were solids, and so recrystallization was used for final purification of each isocarbostyril.

**2,4-Dimethyl-1(2*H*)-isoquinolinone (28c):** 95% yield; bp 110-120 °C (0.14 torr); mp 82-83 °C (ether) (lit.[43] mp 80-82 °C); $^1$H NMR ($CDCl_3$) δ 2.23 (s, 3),

3.53 (s, 3), 6.85 (s, 1), 7.48 (t, 1, $J$ = 8 Hz), 7.55 (d, 1, $J$ = 8 Hz), 7.68 (t, 1, $J$ = 8 Hz), 8.44 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q), 36.6 (q), 111.8 (s), 123.0 (d), 125.9 (s), 126.5 (d), 127.9 (d), 130.2 (d), 131.8 (d), 137.3 (s), 162.2 (s).

**2-(2-Hydroxyethyl)-4-methyl-1(2*H*)-isoquinolinone (28d):** 55% yield; bp 145-155 °C (0.11 torr); mp 169-170 °C ($CHCl_3$); $^1$H NMR ($CD_3OD$) δ 2.29 (s, 3), 3.22 (br s, 1), 3.94 (t, 2, $J$ = 5 Hz), 4.14 (t, 2, $J$ = 5 Hz), 7.04 (s, 1), 7.55 (t, 1, $J$ = 8 Hz), 7.64 (d, 1, $J$ = 8 Hz), 7.74 (t, 1, $J$ = 8 Hz), 8.45 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CD_3OD$) δ 15.3 (q), 52.1 (t), 60.7 (t), 112.5 (s), 123.1 (d), 125.6 (s), 126.7 (d), 128.0 (d), 130.2 (d), 132.2 (d), 137.4 (s), 163.0 (s).

**Methyl 4-Methyl-1-oxo-2(1*H*)-isoquinolineacetate (28e):** 64% yield; bp 110-120 °C (0.32 torr); mp 95-96 °C (ether); $^1$H NMR ($CDCl_3$) δ 2.24 (s, 3), 3.76 (s, 3), 4.70 (s, 2), 6.85 (s, 1), 7.50 (t, 1, $J$ = 8 Hz), 7.58 (d, 1, $J$ = 8 Hz), 7.70 (t, 1, $J$ = 8 Hz), 8.45 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q), 49.8 (t), 52.4 (q), 112.2 (s), 122.9 (d), 125.4 (s), 126.6 (d), 128.0 (d), 129.1 (d), 132.1 (d), 137.3 (s), 162.0 (s), 168.4 (s).

**2-(3-Hydroxypropyl)-4-methyl-1(2*H*)-isoquinolinone (28f):** 86% yield; bp 135-145 °C (0.08 torr); mp 90-91 °C (ether/$CH_2Cl_2$); $^1$H NMR ($CDCl_3$) δ 1.96 (p, 2, $J$ = 7 Hz), 2.28 (s, 3), 3.48-3.59 (m, 2), 4.17 (t, 2, $J$ = 7 Hz), 4.23 (br s, 1), 6.94 (s, 1), 7.52 (t, 1, $J$ = 8 Hz), 7.61 (d, 1, $J$ = 8 Hz), 7.72 (t, 1, $J$ = 8 Hz), 8.49 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.2 (q), 32.1 (t), 45.4 (t), 58.0 (t), 112.8 (s), 122.9 (d), 125.3 (s), 126.5 (d), 127.8 (d), 129.2 (d), 131.9 (d), 137.1 (s), 162.2 (s).

**2-(2,2-Dimethoxyethyl)-4-methyl-1(2*H*)-isoquinolinone (28g):** 90% yield; bp 105-115 °C (0.08 torr); mp 78-79 °C (hexane); $^1$H NMR ($CDCl_3$) δ 2.29 (s, 3), 3.45 (s, 6), 4.07 (d, 2, $J$ = 5 Hz), 4.69 (t, 1, $J$ = 5 Hz), 6.97 (s, 1), 7.53 (t, 1, $J$ = 8 Hz), 7.62 (d, 1, $J$ = 8 Hz), 7.72 (t, 1, $J$ = 8 Hz), 8.49 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.4 (q), 51.4 (t), 55.5 (q), 102.9 (d), 111.6 (s), 123.1 (d), 125.7 (s), 126.6 (d), 128.1 (d), 130.7 (d), 132.1 (d), 137.5 (s), 162.2 (s).

**2-[3-(Dimethylamino)propyl]-4-methyl-1(2*H*)-isoquinolinone (28h):** 94% yield; bp 105-115 °C (0.10 torr); $^1$H NMR ($CDCl_3$) δ 1.94 (p, 2, $J$ = 8 Hz), 2.23 (s, 6), 2.27 (s, 3), 2.31 (t, 2, $J$ = 8 Hz), 4.03 (t, 2, $J$ = 8 Hz), 6.97 (s, 1), 7.49 (t, 1, $J$ = 8 Hz), 7.57 (d, 1, $J$ = 8 Hz), 7.67 (t, 1, $J$ = 8 Hz), 8.50 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.2 (q), 26.9 (t), 45.1 (q), 46.9 (t), 56.0 (t), 111.2 (s), 122.7 (d), 125.9 (s), 126.1 (d), 127.8 (d), 129.8 (d), 131.5 (d), 137.0 (s), 161.4 (s).

**General Procedure for the Reaction of 14 with Primary Aromatic Amines.** To a solution of **14** (1.78 g, 10 mmol) in $CH_3OH$ (25 mL) was added the aromatic amine (12.5 mmol). GC analysis indicated that the reaction of **14** with aromatic amines was not nearly as rapid as with aliphatic amines, and so the mixtures were allowed to stand overnight. In each case, the hydroxy lactam crystallized from solution. Filtration of the crystalline material gave the hydroxy lactams **30a-c**. In the case of **30a** and **30b**, distillation caused dehydration to take place to give the isocarbostyrils **31a** and **31b** respectively. However, **30c** was unchanged by distillation under vacuum. Attempts to dehydrate **30c** by heating at atmospheric pressure under nitrogen or by refluxing a solution of **30c** in toluene containing a catalytic amount of TsOH were unsuccessful. GC and TLC analysis indicated that methyl anthranilate and isocoumarin **15** were produced in both cases.

**3,4-Dihydro-3-hydroxy-4-methyl-2-phenyl-1(2*H*)-isoquinolinone (30a):** 81% yield; mp 120-121 °C (ethyl acetate); $^1$H NMR ($CDCl_3$) δ 1.41 and 1.49 (d, 3, $J$ = 7 Hz), 3.16-3.28 and 3.38-3.50 (m, 1), 4.57 (br t, 1, $J$ = 11 Hz), 5.71 and 5.93 (dd, 1, $J$ = 11, 4 Hz), 6.73-6.92 (m, 3), 7.11-7.27 (m, 2), 7.32-7.48 (m, 2), 7.61 (t, 1, $J$ = 8 Hz), 8.12 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 14.2 (q), 17.1 (q), 35.6 (d), 35.9 (d), 86.8 (d), 89.0 (d), 113.6 (d), 114.0 (d), 118.2 (d), 118.5 (d), 124.3 (s), 124.4 (s), 126.9 (d), 127.2 (d), 128.7 (d), 129.1 (d), 133.7 (d), 142.7 (s), 144.0 (s), 145.1 (s), 145.2 (s), 164.3 (s), 164.9 (s).

**4-Methyl-2-phenyl-1(2*H*)-isoquinolinone (31a):** 74% yield; bp 120-130 °C (0.32 torr); mp 107-108 °C (ether); $^1$H NMR ($CDCl_3$) δ 2.08 (s, 3), 7.03 (s, 1), 7.14-7.84 (m, 8), 8.59 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 14.9 (q), 111.6 (s), 122.6 (d), 125.7 (s), 126.3 (d), 127.4 (d), 127.9 (d), 128.7 (d), 129.3 (d), 131.9 (d), 136.8 (s), 140.8 (s), 161.1 (s).

**2-(3,4-Dihydro-3-hydroxy-4-methyl-1-oxo-2(1*H*)-isoquinolinyl)-benzoic Acid (30b):** 91% yield; mp 193-194 °C, with bubbling; $^1$H NMR ($CDCl_3$/$(CD_3)_2SO$) δ 1.46 and 1.51 (d, 3, $J$ = 7 Hz), 3.28-3.39 and 3.43-3.54 (m, 1), 5.83 ($J$ = 9, 5 Hz) and 6.07 ($J$ = 9, 3 Hz) (dd, 1), 6.73-6.85 (m, 1), 7.06-7.18 (m, 1), 7.31-7.54 (m, 3), 7.60-7.70 (m, 1), 7.93 (t, 1, $J$ = 8 Hz), 8.04 (d, 1, $J$ = 8 Hz), 8.88 and 9.04 (d, 1, $J$ = 9 Hz, $D_2O$ exchangeable), 11.05 (br s, 1); $^{13}$C NMR ($CDCl_3$/$(CD_3)_2SO$) δ 14.1 (q), 18.6 (q), 35.9 (d), 37.2 (d), 85.3 (d), 87.5 (d), 112.2 (s), 112.5 (s), 112.8 (d), 112.9 (d), 117.6 (d), 117.7 (d), 124.4 (s), 126.8 (d), 127.1 (d), 127.7 (d), 129.8 (d), 131.8 (d), 134.0 (d), 134.3 (d), 142.0 (s), 142.9 (s), 147.7 (s), 163.9 (s), 164.8 (s), 170.2 (s), 170.4 (s).

**2-(4-Methyl-1-oxo-2(1*H*)-isoquinolinyl)-benzoic Acid (31b):** 83% yield; bp 180-190 °C (0.03 torr); mp 217-219 °C ($CHCl_3$); $^1$H NMR ($CDCl_3$) δ 2.33 (s, 3), 7.00 (s, 1), 7.35 (d, 1, $J$ = 8 Hz), 7.55 (t, 2, $J$ = 8 Hz), 7.63-7.81 (m, 3), 8.15 (d, 1, $J$ = 8 Hz), 8.44 (d, 1, $J$ = 8 Hz), 11.05 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 15.4 (q), 112.7 (s), 123.2 (d), 125.8 (s), 126.9 (d), 128.6 (d), 128.7 (d), 128.9 (d), 129.4 (d), 131.7 (d), 132.5 (d), 133.6 (d), 137.7 (s), 140.7 (s), 162.6 (s), 168.5 (s).

**Methyl 2-(3,4-Dihydro-3-hydroxy-4-methyl-1-oxo-2(1*H*)-isoquinolinyl)-benzoate (30c):** 90% yield; bp 175-185 °C (0.11 torr); mp 136-138 °C ($CH_3OH$); $^1$H NMR ($CDCl_3$) δ 1.49 and 1.51 (d, 3, $J$ = 7 Hz), 3.25-3.36 and 3.40-3.49 (m, 1), 3.76 and 3.83 (s, 3), 5.73 ($J$ = 9, 5 Hz) and 5.97 ($J$ = 9, 3 Hz) (dd, 1), 6.74-6.83 (m, 1), 7.10 and 7.15 (d, 1, $J$ = 10 Hz), 7.33-7.48 (m, 3), 7.57-7.68 (m, 1), 7.92 (t, 1, $J$ = 8 Hz), 8.12 (d, 1, $J$ = 8 Hz), 8.60 and 8.77 (d, 1, $J$ = 9 Hz, $D_2O$

exchangeable); $^{13}C$ NMR ($CDCl_3$) δ 14.2 (q), 18.8 (q), 36.2 (d), 37.5 (d), 51.6 (q), 51.7 (q), 85.5 (d), 87.7 (d), 111.7 (s), 112.0 (s), 113.2 (d), 118.0 (d), 124.5 (s), 126.7 (d), 127.0 (d), 127.9 (d), 130.2 (d), 131.4 (d), 134.3 (d), 134.8 (d), 141.9 (s), 142.8 (s), 147.5 (s), 147.6 (s), 164.1 (s), 165.1 (s), 168.6 (s), 168.7 (s).

**General Procedure for the Reaction of 14 with Aliphatic Diamines. Method A.** To a solution of **14** (1.78 g, 10 mmol) in $CH_3OH$ (25 mL) was added the diamine (50 mmol). After removal of $CH_3OH$ in vacuo, the mixture was distilled to give the product.

**2-Amino-4-methyl-1(2*H*)-isoquinolinone (28b):** 83% yield; bp 115-125 °C (0.20 torr); mp 139-140 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 2.21 (s, 3), 5.19 (br s, 2), 7.16 (s, 1), 7.49 (t, 1, $J$ = 8 Hz), 7.55 (d, 1, $J$ = 8 Hz), 7.67 (t, 1, $J$ = 8 Hz), 8.43 (d, 1, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 15.1 (q), 111.5 (s), 123.2 (d), 125.2 (s), 126.6 (d), 127.9 (d), 130.3 (d), 131.9 (d), 137.0 (s), 161.4 (s).

**2,3,10,10a-Tetrahydro-10-methyl-imidazo[1,2-*b*]isoquinolin-5(1*H*)-one (32a):** 90% yield; bp 120-130 °C (0.11 torr); mp 140-141 °C (ethyl acetate); $^1H$ NMR ($CD_3OD$) δ 1.45 (d, 3, $J$ = 6 Hz), 2.82-3.06 (m, 2), 3.30-3.44 (m, 1), 3.51-3.65 (m, 2), 4.07 (d, 1, $J$ = 10 Hz), 4.34 (br s, 1), 7.24-7.38 (m, 2), 7.47 (t, 1, $J$ = 9 Hz), 7.96 (d, 1, $J$ = 9 Hz); $^{13}C$ NMR ($CD_3OD$) δ 13.9 (q), 37.9 (d), 44.6 (t), 44.9 (t), 77.2 (d), 124.6 (d), 127.0 (d), 127.1 (d), 129.5 (s), 132.2 (d), 140.1 (s), 162.1 (s).

**1,2,3,4,11,11a-Hexahydro-11-methyl-6*H*-pyrimido[1,2-*b*]isoquinolin-6-one (32b):** 91% yield; bp 120-130 °C (0.15 torr); mp 82-83 °C (ether); $^1H$ NMR ($CDCl_3$) δ 1.42 (d, 3, $J$ = 7 Hz), 1.55-1.80 (m, 2), 1.84 (br s, 1), 2.90-3.12 (m, 3), 3.18-3.29 (m, 1), 4.29 (d, 1, $J$ = 4 Hz), 4.84-4.96 (m, 1), 7.26 (d, 1, $J$ = 8 Hz), 7.39 (t, 1, $J$ = 8 Hz), 7.51 (t, 1, $J$ = 8 Hz), 8.21 (d, 1, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 21.5 (q), 26.9 (t), 37.9 (d), 44.8 (dd), 45.7 (t), 76.8 (d), 126.5 (s), 126.9 (d), 127.1 (d), 128.4 (d), 132.2 (d), 141.0 (s), 163.0 (s).

**Method B.** To a solution of **14** (1.78 g, 10 mmol) in $CH_3OH$ (10 mL) was added the diamine (5 mmol). After removal of $CH_3OH$ in vacuo, the mixture was distilled to approximately 175 °C. While the bisisocarbostyril did not distill, the heating insured the conversion of any intermediate to the bisisocarbostyril and removed impurities or unreacted starting material. The undistilled solid material was recrystallized to give the pure bisisocarbostyril.

**2,2'-Bis[4-methyl-1(2*H*)-isoquinolinone] (33a):** 80% yield; mp >300 °C ($CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 2.32 (s, 6), 7.01 (s, 2), 7.58 (t, 2, $J$ = 8 Hz), 7.71 (d, 2, $J$ = 8 Hz), 7.81 (t, 2, $J$ = 8 Hz), 8.52 (d, 2, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 15.4 (q), 113.2 (s), 123.6 (d), 126.5 (s), 127.3 (d), 128.9 (d), 129.2 (d), 133.1 (d), 137.5 (s), 159.8 (s).

**2,2'-(1,2-Ethanediyl)bis[4-methyl-1(2*H*)-isoquinolinone] (33c):** 43% yield; mp 233-234 °C ($CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 2.08 (s, 6), 4.34 (s, 4), 6.80 (s, 2), 7.46-7.59 (m, 4), 7.69 (t, 2, $J$ = 8 Hz), 8.49 (d, 2, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 15.0 (q), 47.7 (t), 112.8 (s), 123.0 (d), 125.3 (s), 126.7 (d), 127.7 (d), 129.5 (d), 132.3 (d), 137.3 (s), 162.1 (s).

**2,2'-(1,3-Propanediyl)bis[4-methyl-1(2*H*)-isoquinolinone] (33d):** 69% yield; mp 193-194 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 2.09 (s, 6), 2.30 (t, 2, $J$ = 7 Hz), 4.08 (t, 4, $J$ = 7 Hz), 6.91 (s, 2), 7.40-7.60 (m, 4), 7.68 (t, 2, $J$ = 8 Hz), 8.49 (d, 2, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 15.1 (q), 28.3 (t), 46.7 (t), 112.0 (s), 122.7 (d), 125.7 (s), 126.3 (d), 127.8 (d), 128.9 (d), 131.7 (d), 137.0 (s), 161.6 (s).

***N*-Alkylation of 28a.[48] Method A.** To a solution of isocarbostyril **28a** (0.80 g, 5 mmol) in THF (25 mL) were added powdered KOH (0.50 g) and tetra-*n*-butylammonium bromide (TBAB, 0.32 g). After addition of the alkyl halide (8 mmol), the mixture was stirred overnight. Filtration of the solution followed by removal of THF in vacuo gave a crude product which was dissolved in $CH_2Cl_2$ and washed with water containing a few drops of 10% HCl. After the solution was dried, $CH_2Cl_2$ was removed

in vacuo. Distillation of the resulting material and recrystallization of the distillate gave the product. Isocarbostyrils **28c** (92%), **28e** (68%), and **28g** (92%) gave the same experimental data as that reported earlier.

**4-Methyl-2-(2-propenyl)-1(2*H*)-isoquinolinone (28i):** 74% yield; bp 105-115 °C (0.06 torr); $^1$H NMR ($CDCl_3$) δ 2.20 (s, 3), 4.61 (dd, 2, $J$ = 6, 2 Hz), 5.16-5.30 (m, 2), 5.90-6.06 (m, 1), 6.86 (s, 1), 7.49 (t, 1, $J$ = 8 Hz), 7.55 (d, 1, $J$ = 8 Hz), 7.66 (t, 1, $J$ = 8 Hz), 8.53 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.2 (q), 50.3 (t), 111.8 (s), 117.5 (t), 122.8 (d), 125.8 (s), 126.3 (d), 128.0 (d), 128.6 (d), 131.7 (d), 132.8 (d), 137.0 (s), 161.3 (s).

**Method B.** The same procedure as above was used with the following changes. Only 2.5 mmol of a dihaloalkane was used. Also, due to the slight solubility of the bisisocarbostyrils in THF, much of the product precipitated from solution during the reaction and so during the filtration step, the solid material was rinsed with sufficient $CH_2Cl_2$ (ca. 100 mL) to dissolve all the product. Finally, after removal of $CH_2Cl_2$, and THF in vacuo, the product was not distilled but simply recrystallized. The bisisocarbostyrils **33c** and **33d** were produced in 51% and 56% yield respectively, and their experimental properties were identical to those given earlier.

**2,2'-Methylenebis[4-methyl-1(2*H*)-isoquinolinone] (33b):** 87% yield; mp 263-265 °C ($CHCl_3$); $^1$H NMR ($CDCl_3$) δ 2.27 (s, 6), 6.12 (s, 2), 7.50 (t, 2, $J$ = 8 Hz), 7.57 (d, 2, $J$ = 8 Hz), 7.64 (s, 2), 7.69 (t, 2, $J$ = 8 Hz), 8.47 (d, 2, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.4 (q), 58.8 (t), 112.4 (s), 123.2 (d), 125.7 (s), 126.8 (d), 128.3 (d), 130.1 (d), 132.7 (d), 137.8 (s), 163.1 (s).

## Reactions of 4-Methyl-1*H*-2-benzopyran-1-one with Ammonia and Primary Amines

**Reactions of 15 with Amines.** A solution of **15** (1.60 g, 10 mmol) in $CH_3OH$ (25 mL) was treated with the amine. In the case of hydrazine (50 mmol) and 2-

aminoethanol (12.5 mmol), crystals formed when the mixture was allowed to stand overnight. Crystals of hydroxy lactams **34b** and **34d** were isolated by filtration. $^{1}H$ and $^{13}C$ NMR of these crystals indicated **34b** consisted mostly of one diastereomer, while **34d** consisted of one diastereomer only. However, the filtrate from isolation of crystals of **34d** contained both diastereomers of **34d** as indicated by $^{1}H$ NMR. Ammonia and methylamine were passed through the solution of **15** in $CH_3OH$ for 30 min. Analysis by TLC indicated that **15** had been completely consumed by this treatment with methylamine, and removal of $CH_3OH$ in vacuo left a mixture of two diastereomers of **34c** in approximately equal proportions as indicated by $^{1}H$ and $^{13}C$ NMR. However, little reaction of **15** with ammonia was indicated by this treatment, and so the solution was allowed to stand for several days at room temperature. After a week TLC indicated **15** had been consumed, and after removal of $CH_3OH$ in vacuo, $^{1}H$ and $^{13}C$ NMR indicated the remaining material was a mixture of diastereomers of **34a**. Unlike hydroxy lactams **30a-c**, hydroxy lactams **34a-d** gave no evidence by $^{1}H$ NMR of exchange of the C-4 proton in the presence of $D_2O$. Dehydration of **34a-d** by distillation gave the corresponding isocarbostyrils.

**3,4-Dihydro-3-hydroxy-4-methyl-1(2*H*)-isoquinolinone (34a):** $^{1}H$ NMR ($CDCl_3$) δ 1.15 and 1.27 (d, 3, $J$ = 7 Hz), 3.01-3.17 (m, 1), 4.84- 4.95 (m, 1), 5.41 (br s, 1), 7.19-7.34 (m, 2), 7.40-7.53 (m, 1), 7.99 (d, 1, $J$ = 8 Hz), 8.15 (d, 1, $J$ = 4 Hz); $^{13}C$ NMR ($CDCl_3$) δ 13.6 (q), 20.2 (q), 36.6 (t), 39.4 (t), 77.8 (d), 79.5 (d), 125.8 (s), 126.0 (s), 126.7 (d), 127.2 (d), 127.4 (d), 127.6 (d), 127.9 (d), 132.7 (d), 140.5 (s), 142.4 (s), 165.7 (s), 166.1 (s).

**2-Amino-3,4-dihydro-3-hydroxy-4-methyl-1(2*H*)-isoquinolinone (34b):** 63% yield; mp 155-157 °C, with bubbling; $^{1}H$ NMR ($CDCl_3/CD_3OD$) major isomer δ 1.32 (d, 3, $J$ = 7 Hz), 3.17-3.30 (m, 1), 4.69 (s, 3), 5.16 (d, 1, $J$ = 3 Hz), 7.33 (d, 1, $J$ = 8 Hz), 7.41 (t, 1, $J$ = 8 Hz), 7.52-7.66 (m, 1), 8.09 (d, 1, $J$ = 8 Hz), minor isomer δ 1.52 (d, 3, $J$ = 7 Hz), 3.36-3.47 (m, 1), 5.18 (d, 1, $J$ = 3 Hz); $^{13}C$

NMR ($CDCl_3/CD_3OD$) major isomer δ 21.0 (q), 40.8 (d), 87.3 (d), 126.1 (d), 127.4 (d), 128.1 (d), 128.5 (d), 133.1 (d), 142.3 (s), 164.4 (s), minor isomer δ 13.7 (q), 37.4 (d), 86.6 (d).

**3,4-Dihydro-3-hydroxy-2,4-dimethyl-1(2*H*)-isoquinolinone (34c):** $^1H$ NMR ($CDCl_3$) δ 1.12 and 1.37 (d, 3, $J$ = 8 Hz), 2.92-3.00 and 3.15-3.27 (m, 1), 3.03 and 3.05 (s, 3), 4.72 ($J$ = 3 Hz) and 4.75 ($J$ = 5 Hz) (d, 1), 5.22 (br s, 1), 7.10-7.30 (m, 2), 7.33-7.48 (m, 1), 7.89 (d, 1, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 13.5 (q), 20.6 (q), 33.4 (q), 34.1 (q), 36.4 (d), 39.7 (d), 85.3 (d), 86.8 (d), 125.2 (d), 126.5 (d), 126.6 (d), 127.3 (d), 127.6 (d), 132.0 (d), 139.0 (s), 141.3 (s), 163.8 (s), 164.3 (s).

**3,4-Dihydro-3-hydroxy-2-(2-hydroxyethyl)-4-methyl-1(2*H*)-isoquinolinone (34d):** 36% yield; mp 152-153 °C; $^1H$ NMR ($CDCl_3$) δ 1.51 (d, 3, $J$ = 8 Hz), 3.31-3.48 (m, 2), 3.78 (br s, 2), 3.79-3.95 (m, 2), 4.29 (dt, 1, $J$ = 15, 4 Hz), 4.97 (d, 1, $J$ = 4 Hz), 7.37-7.47 (m, 2), 7.59 (t, 1, $J$ = 8 Hz), 8.09 (d, 1, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 13.6 (q), 36.5 (d), 50.5 (t), 60.2 (t), 85.3 (d), 125.3 (d), 126.8 (d), 127.7 (d), 127.9 (s), 132.5 (d), 139.5 (s), 164.7 (s).

## Reactions of 3,4-Dihydro-6-methyl-2*H*-pyran-2-one with Ammonia and Primary Amines

**3,4-Dihydro-6-methyl-2*H*-pyran-2-one (17).** A mixture of 5-oxohexanoic acid (130.0 g, 1.00 mol), isopropenyl acetate (500 mL), and TsOH (0.5 g) was refluxed for 3 h.[49] By this time GC analysis indicated the reaction was complete. After cooling, the reaction mixture was diluted with ether, washed with water,[65] dried, and ether and isopropenyl acetate were removed in vacuo. The remaining material was distilled at 60 °C (0.22 torr) to give 103.1 g (92%) of **17**: $^1H$ NMR[25] ($CDCl_3$) δ 1.89 (s, 3), 2.25-2.39 (m, 2), 2.59 (t, 2, $J$ = 8 Hz), 5.02-5.12 (m, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.6 (q), 18.8 (t), 28.3 (t), 99.9 (d), 149.7 (s), 168.8 (s).

**6-Hydroxy-6-methyl-2-piperidinone (35).** Through neat **17** (5.6 g, 50 mmol) was passed ammonia. In less than 1 min, the temperature of the reaction mixture rose past 100 °C. The brown oil that was obtained partially crystallized during the next few days. The crystals were isolated by removing the oil with $CH_2Cl_2$, in which the crystals were not appreciably soluble. Recrystallization of the crude crystals gave **35**: 56% yield; mp 114-115 °C ($CHCl_3$); $^1H$ NMR ($CD_3OD$) δ 1.48 (s, 3), 1.62-2.45 (m, 6), 3.74 (br s, 1), 6.63 (br s, 1); $^{13}C$ NMR ($CD_3OD$) δ 16.9 (t), 29.6 (q), 30.9 (t), 35.5 (t), 80.9 (s), 173.6 (s).

**5-Oxo-hexanamide (36a).** Through a solution of **17** (5.6 g, 50 mmol) in $CH_2Cl_2$ (25 mL) was passed ammonia for 30 min. Removal of $CH_2Cl_2$ left in a quantitative yield **36a**: mp 69-70 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.87 (p, 2, $J$ = 7 Hz), 2.16 (s, 3), 2.25 (t, 2, $J$ = 7 Hz), 2.54 (t, 2, $J$ = 7 Hz), 6.45 (br s, 2); $^{13}C$ NMR ($CDCl_3$) δ 19.5 (t), 29.9 (q), 34.5 (t), 42.5 (t), 175.5 (s), 208.6 (s). Replacement of $CH_2Cl_2$ by ether or $CHCl_3$ in the above reaction gave virtually the same results. When $CH_3OH$ was used as the solvent instead, another compound, possibly 6-amino-6-methyl-2-piperidinone, was the major product as indicated by $^{13}C$ NMR: ($CDCl_3$) δ 17.5 (t), 29.8 (q), 30.8 (t), 36.2 (t), 66.5 (s), 171.9 (s).

**Tautomerization of 36a to 35.** Frequently, the isomerization of keto amides to hydroxy lactams is catalyzed by polar solvents or bases.[50] The keto amide **36a** also behaves in a similar manner. The appearance of a $^{13}C$ NMR spectrum of a solution of **36a** in $CDCl_3$ was little changed after 2 weeks. The addition of a few drops of $CD_3OD$ to this solution caused the formation of some **35** (ca. 5%) as indicated by $^{13}C$ NMR when ran 5 days later. To this solution was added 2 drops of triethylamine and after 5 days more, another $^{13}C$ NMR spectrum was obtained that indicated more than half of **36a** had now been converted to **35**. A $^{13}C$ NMR spectrum of the material obtained immediately after the reaction of neat **17** with ammonia showed the presence of **35**, **36a**, and **37a** in approximately equal amounts. However, after a few days, crystals of

**35** formed in the oil, and $^{13}C$ NMR then showed that **36a** was virtually absent in both the oil and the crystals. Apparently traces of base, either ammonia itself or some other material present in the oil, catalyzed the conversion of **36a** to **35** over the course of a few days.

**3,4-Dihydro-6-methyl-2(1*H*)-pyridinone (37a).** The oil obtained from the reaction of neat **17** (5.6 g, 50 mmol) with ammonia was distilled to give 4.5 g (81%) of **37a**: bp 110-120 °C (0.60 torr); mp 117-118 °C ($CH_2Cl_2$) (lit.[66] mp 119-121 °C); $^1H$ NMR ($CDCl_3$) δ 1.83 (s, 3), 2.22-2.35 (m, 2), 2.44 (t, 2, $J$ = 8 Hz), 4.76-4.84 (m, 1), 9.03 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.6 (q), 20.1 (t), 30.2 (t), 99.9 (d), 133.2 (s), 172.6 (s). Either pure **35** or **36a** could also be distilled to give **37a**. However, in the case of distillation of **36a**, dehydration was sometimes incomplete as apparently the material distills under high vacuum and dehydrates at about the same temperature.

**5-Hydrazono-hexanohydrazide (38).** To a solution of **17** (1.12 g, 10 mmol) in $CH_2Cl_2$ (10 mL) was added anhydrous hydrazine (1.60 g, 50 mmol). Removal of $CH_2Cl_2$ and excess hydrazine in vacuo left **38**: $^1H$ NMR ($CDCl_3$) δ 1.74 (s, 3), 1.76-1.88 (m, 2), 2.17 (t, 2, $J$ = 9 Hz), 2.20 (t, 2, $J$ = 6 Hz), 4.90 (br s, 5); $^{13}C$ NMR ($CDCl_3$) δ 13.7 (q), 22.2 (t), 33.3 (t), 37.7 (t), 150.9 (s), 173.2 (s). The reaction of **17** with a smaller amount of hydrazine (0.40 g, 12.5 mmol) gave a mixture of products as indicated by $^{13}C$ NMR. However, when more hydrazine ( 1.28 g, 40 mmol) was added to this mixture, **38** was obtained.

**General Procedure for the Reaction of 17 with Primary Aliphatic Amines.** To a solution of **17** (2.8 g, 25 mmol) in $CH_2Cl_2$ (25 mL) was added the amine (25 mmol), except for methylamine, which was bubbled through the solution for 30 min. Removal of $CH_2Cl_2$ in vacuo left the keto amide which $^1H$ and $^{13}C$ NMR indicated was pure. Without $CH_2Cl_2$, the temperature of the reaction mixture rose above 100 °C, which caused the formation of side products as indicated by $^{13}C$ NMR. Distillation of **36b** gave mostly unchanged starting material, but some dehydration did

take place as signals corresponding to **37b** were present in the $^{13}C$ NMR spectrum of the distillate. Similarly, distillation of **36d** gave a small amount of the enelactam **37d** as indicated by $^{13}C$ NMR. However, distillation of **37e** caused no changed in the appearance of its $^{13}C$ NMR.

***N*-Methyl-5-oxo-hexanamide (36b):** mp 52-53 °C (ether); $^1H$ NMR ($CDCl_3$) δ 1.88 (p, 2, *J* = 7 Hz), 2.14 (s, 3), 2.21 (t, 2, *J* = 7 Hz), 2.52 (t, 2, *J* = 7 Hz), 2.77 (d, 3, *J* = 7 Hz), 6.52 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.8 (t), 26.1 (q), 29.9 (q), 35.1 (t), 42.6 (t), 173.2 (s), 208.4 (s).

***N*-(2-Hydroxyethyl)-5-oxo-hexanamide (36c):** mp 59-60 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.86 (p, 2, *J* = 7 Hz), 2.15 (s, 3), 2.24 (t, 2, *J* = 7 Hz), 2.53 (t, 2, *J* = 7 Hz), 3.28-3.40 (m, 2), 3.66 (t, 2, *J* = 5 Hz), 5.84 (br s, 1), 7.40 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.7 (t), 29.9 (q), 35.1 (t), 42.2 (t), 42.5 (t), 61.0 (q), 173.5 (s), 208.8 (s).

***N*-(2,2-Dimethoxyethyl)-5-oxo-hexanamide (36d):** $^1H$ NMR ($CDCl_3$) δ 1.86 (p, 2, *J* = 7 Hz), 2.14 (s, 3), 2.23 (t, 2, *J* = 7 Hz), 2.51 (t, 2, *J* = 7 Hz), 3.28-3.44 (m, 2), 3.36 (s, 6), 4.38-4.46 (m, 1), 7.28 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.2 (t), 29.3 (q), 34.5 (t), 40.3 (t), 41.9 (t), 53.4 (q), 101.9 (d), 172.1 (s), 207.7 (s).

***N*-[3-(Dimethylamino)propyl]-5-oxo-hexanamide (36e):** $^1H$ NMR ($CDCl_3$) δ 1.68 (p, 2, *J* = 7 Hz), 1.89 (p, 2, *J* = 7 Hz), 2.17 (s, 3), 2.20 (t, 2, *J* = 7 Hz), 2.26 (s, 6), 2.40 (t, 2, *J* = 7 Hz), 2.54 (t, 2, *J* = 7 Hz), 3.31 (q, 2, *J* = 7 Hz), 7.49 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.8 (t), 26.9 (t), 29.7 (q), 35.1 (t), 37.9 (t), 42.4 (t), 45.0 (q), 57.4 (t), 172.2 (s), 207.4 (s).

**Reaction of 17 with Aromatic Amines.** To neat **17** (5.6 g, 50 mmol) was added the aromatic amine (62.5 mmol). With aniline, **17** reacted over the course of a few hours to give a crystalline product. This material was dissolved in $CH_2Cl_2$ and washed with 10% HCl. With methyl anthranilate and anthranilic acid, the mixture was heated in refluxing xylene (100 mL) overnight with a Dean-Stark trap attached. After

cooling, the xylene solution was washed with 10% HCl. In all three cases, the solution was dried, xylene was removed in vacuo, and the remaining material was distilled to give a solid product which was purified by recrystallization.

**5-Oxo-*N*-phenyl-hexanamide (36f):** 78% yield; bp 150-160 °C (0.08 torr); mp 82-83 °C; (ether/$CH_2Cl$); $^1H$ NMR ($CDCl_3$) δ 1.91 (p, 2, *J* = 8 Hz), 2.06 (s, 3), 2.36 (t, 2, *J* = 8 Hz), 2.47 (t, 2, *J* = 8 Hz), 7.06 (t, 1, *J* = 8 Hz), 7.26 (t, 2, *J* = 8 Hz), 7.57 (d, 2, *J* = 8 Hz), 8.97 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.5 (t), 29.8 (q), 36.0 (t), 42.4 (t), 120.0 (d), 123.9 (d), 128.6 (d), 138.0 (s), 171.2 (s), 208.6 (s).

**Methyl 2-[(1,5-Dioxohexyl)amino]-benzoate (36g):** 65% yield; bp 140-150 °C (0.08 torr); mp 72-73 °C (ether); $^1H$ NMR ($CDCl_3$) δ 2.00 (p, 2, *J* = 8 Hz), 2.15 (s, 3), 2.47 (t, 2, *J* = 8 Hz), 2.58 (t, 2, *J* = 8 Hz), 3.91 (s, 3), 7.06 (t, 1, *J* = 8 Hz), 7.52 (t, 1, *J* = 8 Hz), 8.01 (d, 1, *J* = 8 Hz), 8.70 (d, 1, *J* = 8 Hz), 11.08 (br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.3 (t), 29.9 (q), 37.2 (t), 42.4 (t), 52.3 (q), 114.8 (s), 120.2 (d), 122.4 (d), 130.8 (d), 134.6 (d), 141.5 (s), 168.6 (s), 171.3 (s), 208.0 (s).

**2,3,4,4a-Tetrahydro-4a-methyl-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine-1,6-dione (39):** 63% yield; bp 140-150 °C (0.11 torr); mp 115-116 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.63 (s, 3), 1.82-1.97 (m, 1), 2.00-2.29 (m, 2), 2.38-2.56 (m, 1), 2.68 (t, 2, *J* = 6 Hz), 7.41 (t, 1, *J* = 8 Hz), 7.70 (t, 1, *J* = 8 Hz), 7.85 (d, 1, *J* = 8 Hz), 8.10 (d, 1, *J* = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 16.8 (t), 26.8 (q), 33.7 (t), 36.2 (t), 93.1 (s), 121.2 (s), 127.0 (d), 127.1 (d), 130.0 (d), 134.9 (d), 139.7 (s), 163.4 (s), 170.2 (s).

**Reaction of 17 with Aliphatic Diamines. Method A.** To a solution of **17** (1.12 g, 10 mmol) in $CH_2Cl_2$ (10 mL) was added the diamine (5 mmol). In a short time the bisketo amide precipitated out of solution, and was isolated by filtration.

***N*,*N*'-1,2-Ethanediylbis[5-oxo-hexanamide] (40a):** 90% yield; mp 164-165 °C ($CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.91 (p, 4, *J* = 8 Hz), 2.16 (s, 6), 2.22 (t, 4,

$J$ = 8 Hz), 2.57 (t, 4, $J$ = 8 Hz), 3.39 (s, 4), 6.68 (br s, 2); $^{13}$C NMR ($CDCl_3$) δ 19.7 (t), 29.9 (q), 35.3 (t), 39.8 (t), 42.6 (t), 173.4 (s), 208.4 (s).

***N,N'*-1,3-Propanediylbis[5-oxo-hexanamide] (40b):** 91% yield; mp 133-134 °C ($CHCl_3$); $^1$H NMR ($CDCl_3$) δ 1.63 (p, 2, $J$ = 6 Hz), 1.87 (p, 4, $J$ = 8 Hz), 2.15 (s, 6), 2.21 (t, 4, $J$ = 8 Hz), 2.53 (t, 4, $J$ = 8 Hz), 3.22 (t, 4, $J$ = 6 Hz), 7.26 (br s, 2); $^{13}$C NMR ($CDCl_3$) δ 19.6 (t), 29.0 (t), 29.6 (q), 35.0 (t), 35.9 (t), 42.3 (t), 173.2 (s), 208.7 (s).

**Method B.** To a solution of **17** (1.12 g, 10 mmol) in $CH_2Cl_2$ (10 mL) was added the diamine (20 mmol). After $CH_2Cl_2$ had been removed in vacuo, the remaining material was distilled. The part of the distillate that was soluble in $CH_2Cl_2$ was washed with water and dried. Removal of $CH_2Cl_2$ in vacuo gave the product.

**Hexahydro-8a-methyl-imidazo[1,2-*a*]pyridin-5(1*H*)-one (41a):** 24% yield; bp 100-110 °C (0.05 torr); mp 96-97 °C (ether); $^1$H NMR ($CDCl_3$) δ 1.32 (s, 3), 1.45-1.60 (m, 1), 1.87-2.01 (m, 2), 2.14-2.36 (m, 2), 2.40-2.54 (m, 1), 3.10 (br s, 1), 3.18-3.39 (m, 3), 3.64-3.80 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 17.5 (t), 23.3 (q), 30.2 (t), 34.8 (t), 41.9 (t), 43.2 (t), 77.3 (s), 167.6 (s).

**Octahydro-9a-methyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (41b):** 27% yield; bp 100-110 °C (0.09 torr); $^1$H NMR ($CDCl_3$) δ 1.51 (s, 3), 1.56-1.73 (m, 3), 1.76-1.89 (m, 2), 1.95-2.11 (m, 1), 2.20 (br s, 1), 2.30-2.51 (m, 2), 2.80-3.00 (m, 2), 3.06-3.22 (m, 1), 4.66-4.78 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 16.2 (t), 21.2 (q), 26.7 (t), 31.9 (t), 35.0 (dd), 38.0 (t), 38.6 (t), 69.7 (s), 167.1 (s).

***N*-Alkylation of 37a.**[48] To a solution of enelactam **37a** (1.11 g, 10 mmol) in THF (50 mL) were added powdered KOH (1.00 g) and TBAB (0.64 g). After addition of the alkyl halide (15 mmol) or dihaloalkane (5 mmol), the mixture was stirred overnight. It was necessary to reflux the mixture containing bromoacetaldehyde dimethyl acetal to cause reaction. Filtration of the solution followed by removal of THF in vacuo gave a crude product which was dissolved in ether and washed with water

containing a few drops of 10% HCl. After the solution was dried, ether was removed in vacuo. Finally, distillation of the remaining material gave the enelactam. However, $^{13}C$ NMR usually showed that the distillate contained a minor impurity with signals similar to those of the major product except for the presence of a signal near 90-95 ppm that was a triplet in off-resonance $^{13}C$ NMR. Apparently, under the conditions of the reaction, the double bond of the major product can migrate to the exocyclic position to give a second enelactam. Also, some **37c** was produced during the synthesis of the bisenelactam **42b**, but the two could be separated by distillation.

**3,4-Dihydro-1,6-dimethyl-2(1*H*)-pyridinone (37b):** 78% yield; bp 60-65 °C (0.06 torr); $^1H$ NMR ($CDCl_3$) δ 1.95 (s, 3), 2.09-2.21 (m, 2), 2.45 (t, 2, $J$ = 8 Hz), 3.10 (s, 3), 4.98-5.03 (m, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.3 (q), 19.4 (t), 28.5 (q), 31.6 (t), 103.9 (d), 136.4 (s), 170.4 (s).

**3,4-Dihydro-6-methyl-1-(2-propenyl)-2(1*H*)-pyridinone (37c):** 42% yield; bp 70-75 °C (0.14 torr); $^1H$ NMR ($CDCl_3$) δ 1.94 (s, 3), 2.16-2.27 (m, 2), 2.51 (t, 2, $J$ = 8 Hz), 4.23-4.34 (m, 2), 5.00-5.19 (m, 3), 5.77-5.93 (m, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.9 (q), 19.5 (t), 31.7 (t), 43.2 (t), 104.6 (d), 114.8 (t), 134.0 (d), 136.1 (s), 169.9 (s).

**1-(2,2-Dimethoxyethyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridinone (37d):** 61% yield; bp 80-85 °C (0.12 torr); $^1H$ NMR ($CDCl_3$) δ 1.98 (s, 3), 2.12-2.26 (m, 2), 2.49 (t, 2, $J$ = 8 Hz), 3.44 (s, 6), 3.71 (d, 2, $J$ = 6 Hz), 4.49 (t, 1, $J$ = 6 Hz), 4.98-5.08 (m, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.4 (t), 19.5 (q), 31.8 (t), 44.2 (t), 55.3 (q), 103.5 (d), 104.6 (d), 136.7 (s), 170.9 (s).

**1,1'-Methylenebis[3,4-dihydro-6-methyl-2(1*H*)-pyridinone] (42a):** 74% yield; bp 130-140 °C (0.11 torr); mp 106-107 °C (ether); $^1H$ NMR ($CDCl_3$) δ 2.10 (s, 6), 2.04-2.17 (m, 4), 2.45 (t, 4, $J$ = 8 Hz), 5.04-5.12 (m, 2), 5.42 (s, 2); $^{13}C$ NMR ($CDCl_3$) δ 18.9 (t), 19.0 (q), 32.4 (t), 48.6 (t), 105.9 (d), 137.0 (s), 172.0 (s).

**1,1'-(1,3-Propanediyl)bis[3,4-dihydro-6-methyl-2(1*H*)-pyridinone] (42b):** 34% yield; bp 130-140 °C (0.12 torr); $^1$H NMR ($CDCl_3$) δ 1.83 (p, 2, *J* = 7 Hz), 1.96 (s, 6), 2.11-2.23 (m, 4), 2.46 (t, 4, *J* = 8 Hz), 3.66 (t, 4, *J* = 7 Hz), 5.02-5.14 (m, 2); $^{13}$C NMR ($CDCl_3$) δ 19.1 (q), 19.4 (t), 29.1 (t), 31.8 (t), 38.9 (t), 105.6 (d), 135.7 (s), 170.4 (s).

## Reactions of 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one with Ammonia and Primary Amines

**3,4-Dihydro-4,4-dimethyl-2(1*H*)-pyridinone (43a).** To a solution of enol lactone **18** (12.6 g, 0.10 mol) in ether (200 mL) was added concentrated ammonium hydroxide (5.7 g, 0.10 mol). After this solution was stirred overnight, ether was removed in vacuo and the remaining material was distilled to 130 °C (0.12 torr) to give a crystalline distillate. This distillate was redistilled at 75-85 °C (0.20 torr) and later recrystallized (ether) to give 7.0 g (56%) of **43a**: mp 55-56 °C; $^1$H NMR ($CDCl_3$) δ 1.06 (s, 6), 2.31 (s, 2), 4.89 (d, 1, *J* = 8 Hz), 5.96-6.09 (m, 1), 9.32 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 27.7 (q), 31.3 (s), 45.2 (t), 115.6 (d), 122.5 (d), 171.5 (s).

**1-Amino-6-hydrazino-4,4-dimethyl-2-piperidinone (44a).** To a solution of **18** (1.26 g, 10 mmol) in $CH_2Cl_2$ (10 mL) was added anhydrous hydrazine (1.60 g, 50 mmol). After removal of $CH_2Cl_2$ in vacuo, a waxlike solid remained. Attempts to recrystallize this solid were unsuccessful. While this material was not appreciably soluble in $CHCl_3$ or $CH_2Cl_2$, once dissolved only a fraction of the original material recrystallized. Furthermore, $^{13}$C NMR indicated this recrystallized material was a mixture of **44a** and **45**. The spectral properties of the waxlike solid were as follows: $^1$H NMR ($CDCl_3$) δ 1.00 (s, 3), 1.06 (s, 3), 1-66-1.78 (m, 1), 1.97 (dd, 1, *J* = 14, 11 Hz), 2.17-2.30 (m, 2), 3.73 (br s, 5), 4.27 (dd, 1, *J* = 11, 6 Hz); $^{13}$C NMR ($CDCl_3$) δ 24.9 (q), 29.3 (s), 30.6 (q), 38.5 (t), 45.3 (t), 74.1 (d), 170.8 (s).

**Octahydro-3,3,9,9-tetramethyl-dipyrido[1,2-*b*:1',2'-*e*][1,2,4,5]tetrazine-1,7(2*H*,8*H*)-dione (45).** The amino lactam **44a** was distilled at 190-200 °C (0.09 torr) to give a solid with the following properties: mp 295-298 °C; $^1$H NMR ($CDCl_3$) δ 1.00 (s, 6), 1.08 (s, 6), 1.57 (dd, 2, *J* = 14, 9 Hz), 1.98 (dd, 2, *J* = 14, 6 Hz), 2.30 (s, 4), 4.48-4.54 (m, 2), 5.45 (br s, 2); $^{13}$C NMR ($CDCl_3$) δ 25.9 (q), 29.6 (s), 30.3 (q), 39.2 (t), 45.1 (t), 70.1 (d), 164.4 (s), MS, *m/z* (rel intensity) 280 (18), 182 (17), 141 (41), 126 (21), 83 (100).

**1,4,4-Trimethyl-6-(methylamino)-2-piperidinone (44b).** Through a solution of **18** (1.26 g, 10 mmol) in $CH_2Cl_2$ (25 mL) was bubbled methylamine for 30 min. The removal of $CH_2Cl_2$ in vacuo left **44b**: $^1$H NMR ($CDCl_3$) δ 0.98 (s, 3), 1.05 (s, 3), 1.56-1.68 (m, 1), 1.74-1.86 (m, 1), 2.15-2.22 (m, 2), 2.31 (s, 3), 2.68 (br s, 1), 2.95 (s, 3), 4.18 (dd, 1, *J* = 11, 6 Hz); $^{13}$C NMR ($CDCl_3$) δ 24.6 (q), 28.1 (q), 29.2 (s), 29.6 (q), 30.6 (q), 40.6 (t), 45.8 (t), 71.0 (d), 170.7 (s).

**Reactions of 18 with Two Equivalents of Primary Amines.** To neat **18** (1.26 g, 10 mmol) was added the amine (20 mmol). The mixture from the exothermic reaction of **18** and 2-aminoethanol was dissolved in $CH_2Cl_2$ (10 mL) and then just enough ether was added to cause the solution to become slightly turbid. When this solution was allowed to stand at 0 °C overnight, crystals of **44c** formed. The mixtures from the reaction of **18** with aminoacetaldehyde dimethyl acetal and aniline were heated to 100 °C for 3 h before cooling. In the case of the reaction of **18** with aminoacetaldehyde dimethyl acetal, $^1$H and $^{13}$C NMR indicated the material consisted of only **44d** and was not purified further. The material from the reaction of **18** and aniline partially crystallized after cooling. Ether was used to remove the oil from the reaction, and the remaining crystals were recrystallized to give **44e.**

**1-(2-Hydroxyethyl)-6-[(2-hydroxyethyl)amino]-4,4-dimethyl-2-piperidinone (44c):** 76% yield; mp 89-90 °C (ether/$CH_2Cl_2$); $^1$H NMR ($CDCl_3$) δ 0.98 (s, 3), 1.06 (s, 3), 1.55 (dd, 1, *J* = 14, 9 Hz), 2.07 (dd, 1, *J* = 14, 7 Hz), 2.23 (s,

2), 2.69-2.79 (m, 1), 2.84-2.95 (m, 1), 3.15-3.26 (m, 1), 3.64-3.86 (m, 4 + 3 exchangeable), 4.04-4.16 (m, 2); $^{13}C$ NMR ($CDCl_3$) δ 25.0 (q), 29.6 (s), 30.2 (q), 42.6 (t), 45.9 (t), 46.8 (t), 47.3 (t), 60.9 (t), 61.0 (t), 70.7 (d), 171.0 (s).

**1-(2,2-Dimethoxyethyl)-6-[(2,2-dimethoxyethyl)amino]-4,4-dimethyl-2-piperidinone (44d):** $^1H$ NMR ($CDCl_3$) δ 1.01 (s, 3), 1.06 (s, 3), 1.55 (dd, 1, $J$ = 14, 9 Hz), 1.86 (dd, 1, $J$ = 14, 6 Hz), 2.21 (s, 2), 2.44 (br s, 1), 2.63 (dd, 1, $J$ = 17, 7 Hz), 2.73 (dd, 1, $J$ = 17, 5 Hz), 3.29 (dd, 1, $J$ = 15, 7 Hz), 3.40 (s, 3), 3.42 (s, 3), 3.43 (s, 3), 3.48 (s, 3), 4.04 (dd, 1, $J$ = 15, 4 Hz), 4.44 (dd, 1, $J$ = 7, 5 Hz), 4.51 (dd, 1, $J$ = 9, 6 Hz), 4.63 (dd, 1, $J$ = 7, 4 Hz); $^{13}C$ NMR ($CDCl_3$) δ 24.4 (q), 29.2 (s), 30.6 (q), 42.0 (t), 42.4 (t), 44.4 (t), 46.0 (t), 53.5 (q), 53.9 (q), 54.1 (q), 54.8 (q), 69.0 (d), 103.0 (d), 103.9 (d), 170.5 (s).

**4,4-Dimethyl-1-phenyl-6-(phenylamino)-2-piperidinone (44e):** 63% yield; mp 133-134 °C (ether/$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.12 (s, 3), 1.22 (s, 3), 1.83 (dd, 1, $J$ = 14, 10 Hz), 2.04-2.14 (m, 1), 2.43 (s, 2), 3.98 (br s, 1), 5.20-5.30 (m, 1), 6.32 (d, 2, $J$ = 8 Hz), 6.63 (t, 1, $J$ = 8 Hz), 7.00 (t, 2, $J$ = 8 Hz), 7.14-7.22 (m, 3), 7.25-7.34 (m, 2); $^{13}C$ NMR ($CDCl_3$) δ 25.1 (q), 29.8 (s), 30.4 (q), 43.8 (t), 46.2 (t), 69.2 (d), 113.6 (d), 118.1 (d), 127.2 (d), 128.5 (d), 128.7 (d), 128.8 (d), 140.0 (s), 145.2 (s), 170.1 (s).

**1-(2,2-Dimethoxyethyl)-3,4-dihydro-4,4-dimethyl-2(1*H*)-pyridinone (43e).** A mixture of **18** (1.26 g, 10 mmol) and aminoacetaldehyde dimethyl acetal (1.16 g, 11 mmol) was distilled to give a material which $^{13}C$ NMR showed to be mostly enelactam **43e** with some **44d** present. The distillate was dissolved in ether and washed with 1% HCl which removed **44d** without noticeably affecting the acetal group. After the solution was dried, ether was removed in vacuo and the remaining material was distilled at 80-90 °C (0.07 torr) to give 1.38 g (65%) of **43e**: $^1H$ NMR ($CDCl_3$) δ 1.06 (s, 6), 2.34 (s, 2), 3.40 (s, 6), 3.55 (d, 2, $J$ = 5 Hz), 4.47 (t,

1, $J$ = 5 Hz), 4.95 (d, 1, $J$ = 8 Hz), 5.99 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.6 (q), 31.4 (s), 46.0 (t), 47.5 (t), 54.2 (q), 102.4 (d), 116.3 (d), 128.2 (d), 168.7 (s).

**1-[3-(Dimethylamino)propyl]-3,4-dihydro-4,4-dimethyl-2(1*H*)-pyridinone (43f).** There was no indication by $^{13}$C NMR that heating a mixture of **18** (1.26 g, 10 mmol) and *N,N*-dimethyl-1,3-propanediamine (2.04 g, 20 mmol) gave any amino lactam, but rather upon distillation of the mixture impure enelactam **43f** was produced. To purify the material an ether solution of the distillate was washed with water, dried, and after removal of ether in vacuo, the remaining material was distilled at 90-100 °C (0.05 torr) to give 0.40 g (19%) of **43f**: $^1$H NMR ($CDCl_3$) δ 1.08 (s, 6), 1.74 (p, 1, $J$ = 7 Hz), 2.22 (s, 6), 2.29 (t, 2, $J$ = 7 Hz), 2.35 (s, 2), 3.56 (t, 2, $J$ = 7 Hz), 4.99 (d, 1, $J$ = 8 Hz), 6.03 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 26.6 (t), 27.7 (q), 31.5 (s), 43.9 (t), 45.2 (q), 46.2 (t), 56.4 (t), 116.8 (d), 127.4 (d), 168.5 (s).

**Reaction of 18 with Primary Aromatic Amines.** To a solution of **18** (6.3 g, 50 mmol) in xylene (250 mL) was added the aromatic amine (62.5 mmol). The mixture was then refluxed, a Dean-Stark trap being used to remove water formed during the reaction. With aniline, anthranilic acid, and 1,2-phenylenediamine, refluxing overnight was sufficent to complete the reaction. However, the solution containing methyl anthranilate was refluxed for 5 days and although no more water seemed to be produced, TLC and GC analysis indicated both starting materials remained. Nevertheless, refluxing of this solution was discontinued at this point. With the exception of the material from the reaction of **18** and 1,2-phenylenediamine, the xylene solution was washed with 10% HCl and water, dried, and xylene was removed in vacuo. Distillation of the remaining material gave either **43g**, **43h**, or **46**. In the case of reaction of **18** with 1,2-phenylenediamine, a solid material was formed during the refluxing period, and after the xylene solution cooled, this solid was isolated by filtration. The xylene solution contained a mixture of compounds (TLC) and was discarded. The remaining solid (mp 264-268 °C) was not appreciably soluble in various

common organic solvents or in water, and no satisfactory spectral data was obtained for this material. However, the solid was soluble in 10% HCl and after neutralization, extraction with $CH_2Cl_2$, and the usual workup, **47** was isolated.

**3,4-Dihydro-4,4-dimethyl-1-phenyl-2(1*H*)-pyridinone (43g):** 72% yield; bp 95-105 °C (0.12 torr); mp 83-84 °C (ether); $^1$H NMR ($CDCl_3$) δ 1.10 (s, 6), 2.48 (s, 2), 5.07 (d, 1, $J$ = 8 Hz), 6.12 (d, 1, $J$ = 8 Hz), 7.16-7.25 (m, 3), 7.28-7.38 (m, 2); $^{13}$C NMR ($CDCl_3$) δ 27.3 (q), 31.1 (s), 46.4 (t), 117.3 (d), 125.1 (d), 126.0 (d), 127.5 (d), 128.1 (d), 139.7 (s), 167.6 (s).

**Methyl 2-(3,4-Dihydro-4,4-dimethyl-2-oxo-1(2*H*)-pyridinyl)-benzoate (43h):** 24% yield; bp 120-130 °C (0.15 torr); $^1$H NMR ($CDCl_3$) δ 1.15 (s, 6), 2.48 (s, 2), 3.89 (s, 3), 5.07 (d, 1, $J$ = 8 Hz), 6.06 (d, 1, $J$ = 8 Hz), 7.18 (d, 1, $J$ = 8 Hz), 7.33 (t, 1, $J$ = 8 Hz), 7.51 (t, 1, $J$ = 8 Hz), 7.91 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.9 (q), 31.7 (s), 46.5 (t), 52.0 (q), 116.7 (d), 127.2 (d), 127.7 (d), 127.9 (d), 128.2 (s), 130.6 (d), 132.7 (d), 139.7 (s), 165.4 (s), 168.6 (s).

**2,3,4,4a-Tetrahydro-3,3-dimethyl-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine-1,6-dione (46):** 72% yield; bp 140-150 °C (0.09 torr); mp 109-110 °C (ether/$CH_2Cl_2$); $^1$H NMR ($CDCl_3$) δ 1.12 (s, 3), 1.21 (s, 3), 2.04-2.26 (m, 2), 2.47 (s, 2), 5.65-5.73 (m, 1), 7.31 (t, 1, $J$ = 8 Hz), 7.60 (t, 1, $J$ = 8 Hz), 7.97 (d, 1, $J$ = 8 Hz), 8.04 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.8 (q), 28.0 (q), 29.8 (s), 39.6 (t), 46.7 (t), 85.0 (d), 118.5 (s), 123.0 (d), 125.5 (d), 129.7 (d), 133.9 (d), 140.5 (s), 162.6 (s), 167.6 (s).

**3,4,4a,5-Tetrahydro-3,3-dimethyl-6*H*-pyrido[1,2-*a*]benzimidazol-1(2*H*)-one (47):** 71% yield; mp 177-178 °C ($CHCl_3$); $^1$H NMR ($CD_3OD$) δ 0.81 (s, 3), 1.02 (s, 3), 1.82 (dd, 1, $J$ = 14, 9 Hz), 2.06-2.17 (m, 1), 2.31 (d, 1, $J$ = 15 Hz), 2.48 (dd, 1, $J$ = 15, 3 Hz), 5.10 (br s, 1), 5.75 (dd, 1, $J$ = 9, 6 Hz), 7.14-7.28 (m, 2), 7.50-7.60 (m, 1), 7.73-7.80 (m, 1); $^{13}$C NMR ($CD_3OD$) δ 24.8 (q), 30.0 (q), 31.0 (s),

37.8 (t), 45.6 (t), 77.0 (d), 112.6 (d), 117.7 (d), 122.1 (d), 122.3 (d), 133.7 (s), 141.6 (s), 151.8 (s).

**Reaction of 18 with Aliphatic Diamines.** To **18** (1.26 g, 10 mmol) was added the diamine (20 mmol). The temperature of the reaction rose above 100 °C within a few seconds after addition. Distillation of the mixture followed by recrystallization of the distillate gave the amino lactam.

In the case of ethylenediamine and 1,3-propanediamine, reactions of 0.5 equiv (5 mmol) of the diamine and **18** (1.26 g, 10 mmol) were also carried out to determine if bisenelactams would form. While the distillate of the reaction of **18** with ethylenediamine contained a mixture of the bisenelactam **49b** and the amino lactam **48a**, similar distillation of the material from the reaction of 1,3-propanediamine and **18** gave no bisenelactam, only the amino lactam **48b**. Extraction with 10% HCl of an ether solution of **48a** and **49b** removed **48a**, and the usual workup gave then **49b**.

**Hexahydro-7,7-dimethyl-imidazo[1,2-*a*]pyridin-5(1*H*)-one (48a):** 42% yield; bp 110-120 °C (0.12 torr); mp 96-97 °C (ether); $^1$H NMR ($CDCl_3$) δ 1.09 (s, 3), 1.10 (s, 3), 1.32 (t, 1, $J$ = 12 Hz), 2.02-2.32 (m, 3), 2.61 (br s, 1), 2.97-3.12 (m, 1), 3.27-3.43 (m, 2), 3.60 (q, 1, $J$ = 10 Hz), 4.22 (dd, 1, $J$ = 12, 4 Hz); $^{13}$C NMR ($CDCl_3$) δ 26.3 (q), 30.2 (s), 31.1 (q), 41.1 (t), 43.6 (t), 44.3 (t), 45.2 (t), 71.4 (d), 167.3 (s).

**Octahydro-8,8-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (48b):** 77% yield; bp 100-110 °C (0.10 torr); mp 80-81 °C (ether); $^1$H NMR ($CDCl_3$) δ 0.96 (s, 3), 1.02 (s, 3), 1.34 (dd, 1, $J$ = 13, 11 Hz), 1.48-1.70 (m, 2), 1.71 (br s, 1), 1.84-1.94 (m, 1), 2.18 (s, 2), 2.65 (dt, 1, $J$ = 13, 4 Hz), 2.82 (dt, 1, $J$ = 13, 4 Hz), 3.10-3.20 (m, 1), 4.17 (dd, 1, $J$ = 11, 6 Hz), 4.74-4.84 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 25.0 (q), 27.1 (t), 29.2 (s), 30.5 (q), 40.5 (dd), 43.5 (t), 44.9 (t), 46.0 (t), 69.0 (d), 167.9 (s).

**Octahydro-1,8,8-trimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (48c):** 74% yield; bp 95-105 °C (0.07 torr); mp 72-73 °C (hexane); $^1$H NMR ($CDCl_3$) δ 0.95

(s, 3), 1.05 (s, 3), 1.55 (dd, 1, $J$ = 14, 10 Hz), 1.72-1.93 (m, 2), 2.19 (s, 2), 2.28 (s, 3), 2.41 (dt, 1, $J$ = 13, 4 Hz), 2.48 (dt, 1, $J$ = 13, 4 Hz), 2.94-3.04 (m, 1), 3.60 (dd, 1, $J$ = 10, 6 Hz), 4.78-4.88 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 23.5 (t), 24.7 (q), 29.1 (s), 30.8 (q), 39.7 (q), 40.7 (dd), 40.9 (t), 45.6 (t), 55.9 (t), 75.5 (d), 168.7 (s).

**1,1'-(1,2-Ethanediyl)bis[3,4-dihydro-4,4-dimethyl-2(1*H*)-pyridinone] (49b):** 22% yield; bp 120-130 °C (0.11 torr); $^1$H NMR ($CDCl_3$) δ 1.05 (s, 12), 2.34 (s, 4), 3.67 (s, 4), 4.94 (d, 2, $J$ = 8 Hz), 5.91 (d, 2, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.9 (q), 31.6 (s), 44.9 (t), 45.9 (t), 116.9 (d), 127.4 (d), 169.1 (s).

***N*-Alkylation of 43a.**[48] To a solution of enelactam **43a** (1.25 g, 10 mmol) in THF (50 mL) were added powdered KOH (1.00 g) and TBAB (0.64 g). After addition of the alkyl halide (15 mmol) or dihaloalkane (5 mmol), the mixture was stirred overnight. Filtration of the solution followed by removal of THF in vacuo gave a crude product which was dissolved in ether and washed with water containing a few drops of 10% HCl. The solution was dried, and ether was removed in vacuo. Distillation of the remaining material gave the product. Enelactam **43e**, which was previously described, was obtained in 87% yield.

**3,4-Dihydro-1,4,4-trimethyl-2(1*H*)-pyridinone (43b):** 77% yield; bp 60-65 °C (0.13 torr); $^1$H NMR ($CDCl_3$) δ 1.04 (s, 6), 2.32 (s, 2), 3.05 (s, 3), 4.94 (d, 1, $J$ = 8 Hz), 5.93 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.9 (q), 31.7 (s), 33.1 (q), 45.9 (t), 116.7 (d), 128.1 (d), 168.5 (s).

**3,4-Dihydro-4,4-dimethyl-1-(2-propenyl)-2(1*H*)-pyridinone (43c):** 94% yield; bp 75-80 °C (0.15 torr); $^1$H NMR ($CDCl_3$) δ 1.06 (s, 6), 2.35 (s, 2), 4.10 (d, 2, $J$ = 6 Hz), 4.98 (d, 1, $J$ = 7 Hz), 5.10 -5.23 (m, 2), 5.70-5.86 (m, 1), 5.95 (d, 1, $J$ = 7 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.7 (q), 31.6 (s), 46.0 (t), 47.3 (t), 116.7 (t), 116.8 (d), 126.6 (d), 132.9 (d), 167.9 (s).

**Methyl 3,4-Dihydro-4,4-dimethyl-2-oxo-1(2*H*)-pyridineacetate (43d):** 54% yield; bp 80-90 °C (0.12 torr); $^1$H NMR ($CDCl_3$) δ 1.10 (s, 6), 2.39 (s,

2), 3.73 (s, 3), 4.22 (s, 2), 5.04 (d, 1, $J$ = 8 Hz), 5.92 (d, 1, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.7 (q), 31.9 (s), 45.6 (t), 46.9 (t), 51.9 (q), 117.3 (d), 127.4 (d), 168.8 (s), 168.9 (s).

**1,1'-Methylenebis[3,4-dihydro-4,4-dimethyl-2(1*H*)-pyridinone] (49a):** 91% yield; bp 115-125 °C (0.20 torr); $^1$H NMR ($CDCl_3$) δ 1.06 (s, 12), 2.38 (s, 4), 5.02 (d, 2, $J$ = 8 Hz), 5.23 (s, 2), 6.31 (d, 2, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.6 (q), 31.5 (s), 45.7 (t), 52.5 (t), 117.5 (d), 126.5 (d), 169.2 (s).

**1,1'-(1,3-Propanediyl)bis[3,4-dihydro-4,4-dimethyl-2(1*H*)-pyridinone] (49c):** 85% yield; bp 130-140 °C (0.13 torr); mp 64-65 °C (hexane); $^1$H NMR ($CDCl_3$) δ 1.06 (s, 12), 1.81 (p, 2, $J$ = 8 Hz), 2.34 (s, 4), 3.49 (t, 4, $J$ = 8 Hz), 5.00 (d, 2, $J$ = 8 Hz), 5.95 (d, 2, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$) δ 27.7 (q), 27.8 (t), 31.5 (s), 43.4 (t), 46.0 (t), 117.3 (d), 126.9 (d), 168.4 (s).

**3,3-Dimethyl-5-oxo-pentanoic Acid (50).** Enol lactone **18** (12.6 g, 0.10 mol) was added to a solution of NaOH (4.1 g, 0.10 mol) in water (100 mL) and the mixture was vigorously stirred for 2 h. After neutralizing with 10% HCl, the usual workup gave 13.1 g (91%) of aldehydo acid **50**: mp 63-64 °C (ether); $^1$H NMR ($CDCl_3$) δ 1.06 (s, 6), 2.47 (s, 2), 2.50-2.66 (m, 2), 9.86 (br s, 1), 10.60 (br s, 1); $^{13}$C NMR ($CDCl_3$) δ 27.7 (q), 28.0 (q), 32.3 (s), 32.6 (s), 44.7 (t), 45.5 (t), 53.7 (t), 178.0 (s), 178.2 (s), 202.5 (d). Apparently in $CDCl_3$ **50** exists as a mixture of slowly interconverting monomers and dimers which gives rise to extra signals in its $^{13}$C NMR spectrum.

**Reaction of 50 with Ammonia.** Ammonia was bubbled through a solution of **50** (1.44 g, 10 mmol) in $CH_2Cl_2$ (25 mL) for a few minutes. Within a few seconds, the solution became cloudy and within a few minutes a white precipitate had formed. After removal of $CH_2Cl_2$ in vacuo, the remaining material was distilled to 170 °C (0.12 torr) to give 0.21 g distillate which $^{13}$C NMR indicated was mostly **43a**. When $CH_2Cl_2$

was replaced by $CH_3OH$ in the above procedure, essentially the same results were obtained.

**Reaction of 50 with Aniline.** To a solution of **50** (1.44 g, 10 mmol) in $CH_2Cl_2$ (25 mL) was added aniline (1.16 g, 12.5 mmol). After removal of $CH_2Cl_2$ in vacuo, the material was distilled to 150 °C (0.14 torr) to give 0.68 g distillate, which $^{13}C$ NMR showed to be mostly enelactam **43g**.

## Synthesis of 7-Nornepetalic Acid and 7-Nornepetalactone

**(1α,3α,3aα,6aα)-1-(Octahydro-3-methyl-1-pentalenyl)-ethanone (52).** To a solution of acid **51** (84.0 g, 0.50 mol) in anhydrous THF (1.5 L) was added an ether solution of $CH_3Li$ (1.5 M, 670 mL) dropwise. After this addition GC analysis indicated some unreacted **51** remained so more $CH_3Li$ solution (150 mL) was added. GC analysis indicated that this second addition was sufficient to consume **51**. The reaction was worked up in the usual manner to give the ketone **52** contaminated by some tertiary alcohol (ca. 10%). The ketone **52** was purified by conversion to and recrystallization of its semicarbazone: mp 165-166 °C (ether/$CH_2Cl_2$). Treatment of the semicarbazone with 10% HCl regenerated the ketone which was then distilled at 45-50 °C (0.08 torr) to give 62.2 g (75%) of **52:** $^1H$ NMR ($CDCl_3$) δ 1.01 (d, 3, $J$ = 7 Hz), 1.29-1.67 (m, 8), 1.84-2.02 (m, 2), 2.15 (s, 3), 2.18-2.31 (m, 1), 2.36-2.48 (m, 1); $^{13}C$ NMR ($CDCl_3$) δ 19.0 (q), 25.3 (t), 29.1 (q), 31.6 (t), 33.4 (t), 39.9 (t), 41.9 (d), 46.4 (d), 51.9 (d), 60.4 (d), 210.6 (s). An earlier run of the above reaction using ether as solvent gave substantially more tertiary alcohol (ca. 25%). Also, stirring of the solution was more difficult due to the lower solubility of the lithium salt of **51** in ether than in THF.

**(1α,3α,3aα,6aα)-Octahydro-3-methyl-1-pentalenyl Acetate (53).** To a solution of ketone **52** (71.4 g, 0.43 mol) in $CHCl_3$ (125 mL) was added a solution of 85% MCPBA (100.0 g, 0.49 mol) in $CHCl_3$ (500 mL). This mixture was stirred for 20

h. Workup gave 74.4 g (95%) of ester **53**: bp 40-45 °C (0.08 torr); $^1$H NMR ($CDCl_3$) δ 1.05 (d, 3, $J$ = 7 Hz), 1.20-1.68 (m, 8), 1.98-2.20 (m, 2), 2.04 (s, 3), 2.38-2.48 (m, 1), 4.66-4.76 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 19.8 (q), 21.3 (q), 25.5 (t), 31.7 (t), 31.8 (t), 38.5 (d), 41.1 (t), 49.5 (d), 50.4 (d), 81.8 (d), 170.9 (s).

**(1α,3α,3aα,6aα)-Octahydro-3-methyl-1-pentalenol (54).** To ester **53** (72.8 g, 0.40 mol) was added a solution of DIBAH (128.0 g, 0.90 mol) in toluene (1 L). Workup in the usual manner gave 51.0 g (91%) of alcohol **54**: bp 50-55 °C (0.07 torr); $^1$H NMR ($CDCl_3$) δ 1.02 (d, 3, $J$ = 7 Hz), 1.09-1.67 (m, 8), 1.92-2.13 (m, 2), 2.20-2.33 (m, 1), 2.91 (br s, 1), 3.65-3.77 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 19.8 (q), 25.3 (t), 31.7 (t), 31.8 (t), 38.4 (d), 44.6 (t), 50.6 (d), 52.2 (d), 80.0 (d).

**(3α,3aα,6aα)-Hexahydro-3-methyl-1(2*H*)-pentalenone (10a).** To a solution of alcohol **54** (49.0 g, 0.35 mol) in acetone (500 mL) was added Jones reagent[62] (85 mL) dropwise. After addition was complete, the solution was stirred for 3 h. Workup gave 45.4 g (94%) of ketone **10a**: bp 45-50 °C (0.10 torr); $^1$H NMR[67] ($CDCl_3$) δ 1.12 (d, 3, $J$ = 7 Hz), 1.15-1.26 (m, 1), 1.36-1.66 (m, 3), 1.68-1.90 (m, 3), 1.92-2.12 (m, 1), 2.39-2.48 (m, 2), 2.63-2.82 (m, 1); $^{13}$C NMR[67] ($CDCl_3$) δ 20.7 (q), 25.8 (t), 29.4 (t), 32.3 (t), 35.0 (d), 46.9 (t), 49.2 (d), 51.9 (d), 220.5 (s).

**(3α,3aα,6aα)-3,3a,4,5,6,6a-Hexahydro-3-methyl-1-pentalenyl Acetate (57a).** A solution of ketone **10a** (44.2 g, 0.32 mol), isopropenyl acetate (200 mL), and TsOH (0.5 g) was refluxed for 3 h. After cooling, the solution was diluted with ether and washed with saturated $NaHCO_3$ and water. Ether and isopropenyl acetate were removed in vacuo, and the remaining material distilled at 45-50 °C (0.05 torr) to give 52.4 g (91%) of enol acetate **57a**: $^1$H NMR ($CDCl_3$) δ 1.07 (d, 3, $J$ = 7 Hz), 1.36-1.77 (m, 6), 2.00-2.39 (m, 2), 2.12 (s, 3), 3.18-3.33 (m, 1), 5.29-5.40 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 21.1 (q), 22.5 (q), 25.1 (t), 29.6 (t), 34.8 (t), 44.3 (d), 48.0 (d), 48.1 (d), 117.6 (d), 150.3 (s), 168.0 (s).

***cis*-4,5,6,6a-Tetrahydro-3-methyl-1(3a*H*)-pentalenone (56).** A solution of ketone **55** (68.0 g, 0.50 mol) made by the method of Dev,[55] ethanol (500 mL), and 10% NaOH (50 mL) was refluxed for 3 h. After removal of most of the ethanol in vacuo, ether and water were added. The ether layer was dried, and after ether was removed in vacuo, the remaining material was distilled at 45-50 °C (0.12 torr) to give 47.5 g (70%) ketone **56**: $^1$H NMR[68] ($CDCl_3$) δ 1.11-1.28 (m, 1), 1.53-1.76 (m, 4), 1.80-1.93 (m, 1), 2.12 (s, 3), 2.66-2.78 (m, 1), 3.09-3.23 (m, 1), 5.88 (s, 1); $^{13}$C NMR ($CDCl_3$) δ 17.6 (q), 23.8 (t), 28.4 (t), 29.3 (t), 49.8 (d), 51.3 (d), 130.9 (d), 179.7 (s), 211.6 (s).

**(3α,3aβ,6aβ)-Hexahydro-3-methyl-1(2*H*)-pentalenone (10b).** Hydrogenation of a solution of ketone **56** (34.0 g, 0.25 mol) in ethanol (250 mL) with 10% Pd/C (3.0 g) gave after the usual workup 29.9 g (87%) of ketone **10b**: bp 60 °C (0.10 torr); $^1$H NMR ($CDCl_3$) δ 1.13 (d, 3, $J$ = 7 Hz), 1.18-1.34 (m, 1), 1.40-1.58 (m, 1), 1.60-1.82 (m, 3), 1.85-2.04 (m, 2), 2.22-2.35 (m, 1), 2.38-2.51 (m, 1), 2.54-2.70 (m, 2); $^{13}$C NMR ($CDCl_3$) δ 17.0 (q), 26.5 (t), 26.9 (t), 29.1 (t), 30.8 (d), 43.3 (t), 47.3 (d), 54.8 (d), 222.1 (s). $^{13}$C NMR gave no evidence for the presence of **10a** in the above hydrogenation. However, when ketone **55** (68.0 g, 0.50 mol) was hydrogenated in a similar manner, a mixture of ketones **10a** and **10b** (59.5 g, 86%) was obtained in an approximate ratio of 1:3 as indicated by GC analysis.

**(3α,3aβ,6aβ)-3,3a,4,5,6,6a-Hexahydro-3-methyl-1-pentalenyl Acetate (57b).** By the same method that **10a** was converted to **57a**, ketone **10b** (27.6 g, 0.20 mol) gave 32.4 g (90%) of enol acetate **57b**: bp 50-55 °C (0.06 torr); $^1$H NMR ($CDCl_3$) δ 1.03 (d, 3, $J$ = 7 Hz), 1.39-1.65 (m, 6), 2.14 (s, 3), 2.60-2.72 (m, 1), 2.90-3.01 (m, 1), 3.27-3.39 (m, 1), 5.20-5.26 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 15.9 (q), 21.0 (q), 26.4 (t), 28.0 (t), 29.4 (t), 37.1 (d), 43.6 (d), 49.0 (d), 117.1 (d), 151.2 (s), 168.0 (s). Reaction of the mixture of ketones **10a** and **10b** (55.2 g, 0.40 mol) with isopropenyl acetate gave 64.8 g (90%) of a mixture of enol acetates **57a** and **57b**.

**7-Nornepetalic Acid (11).** Ozone was passed through a solution of enol acetate **57a** (36.0 g, 0.20 mol) in $CH_2Cl_2$ (250 mL) at –78 °C until the solution turned blue. This solution was poured into 50% aqueous acetic acid (500 mL) and over a period of a few minutes, Zn dust (ca. 50 g) was added. After the solution was stirred overnight, the mixture was worked up in the usual way to give 8.9 g (26%) of base-soluble material, which was apparently a mixture of isomers of **11**. The major isomer of **11** had the following spectral properties: $^1$H NMR ($CDCl_3$) δ 1.11, (d, 3, $J$ = 6 Hz), 1.21-2.66 (m, 8), 3.03 (m, 2), 5.52 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 15.6, 25.5, 29.7, 32.8, 38.1, 39.0, 42.3, 99.4, 177.0. The $^{13}$C NMR signals of **11** were generally broad. When enol acetate **57b** or a mixture of enol acetates **57a** and **57b** was ozonized, workup gave material with a very similar $^{13}$C NMR spectrum as above. Apparently, regardless of the stereochemistry of the methyl group of the starting enol acetate, both gave upon ozonolysis the same isomer of **11** as the major product.

***cis*-7-Nornepetalactone (12).** A solution of **11** (8.5 g, 0.05 mol) in toluene (100 mL) containing TsOH (0.5 g) was refluxed overnight, with a Dean-Stark trap to remove water. Workup of the reaction gave 6.10 g (80%) of **12**: bp 60-65 °C (0.21 torr); $^1$H NMR ($CDCl_3$) δ 1.34-1.75 (m, 3), 1.66 (s, 3), 1.92-2.20 (m, 3), 2.60 (q, 1, $J$ = 8 Hz), 2.95 (q, 1, $J$ = 8 Hz), 6.23 (s, 1); $^{13}$C NMR ($CDCl_3$) δ 15.9 (q), 23.7 (t), 29.8 (t), 31.8 (t), 41.2 (d), 41.8 (d), 115.4 (s), 133.9 (d), 170.8 (s).

## Reactions of 7-Nornepetalic Acid and 7-Nornepetalactone with Ammonia and Primary Amines

***cis*-7-Nornepetalactam (58a).** Ammonia was passed through a solution of either **11** (1.70 g, 10 mmol) or **12** (1.52 g, 10 mmol) in $CH_3OH$ (25 mL) for 30 min. Removal of $CH_3OH$ in vacuo, followed by distillation gave **58a**: bp 105-115 °C (0.15 torr); mp 69-70 °C (hexane); $^1$H NMR ($CDCl_3$) δ 1.36-1.62 (m, 3), 1.66 (s, 3), 1.92-2.19 (m, 3), 2.54 (q, 1, $J$ = 8 Hz), 2.79 (q, 1, $J$ = 8 Hz), 5.76 (d, 1, $J$ = 4 Hz), 8.48

(br s, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.2 (q), 23.9 (t), 30.6 (t), 32.7 (t), 42.4 (d), 43.0 (d), 115.5 (s), 117.4 (d), 174.0 (s).

***N*-(7-Nornepetal-3-yl)-7-nornepetalactam (59).** Ammonia was passed through a solution of **11** (0.85 g, 5 mmol) in $CH_3OH$ for 30 min. After $CH_3OH$ was removed in vacuo, more **11** (0.85 g, 5 mmol) was added and this mixture was distilled to 130 °C (0.11 torr) to give a distillate (0.58 g) that consisted mostly of **58a**. The residual material was then distilled to 180 °C (0.12 torr) to give a distillate (0.64 g) that consisted mostly of **59**. This distillate was purified by column chromatography to give **59**: mp 106-107 °C (hexane); $^1H$ NMR ($CDCl_3$) δ 0.91 (d, 3, $J$ = 7 Hz), 1.22-1.80 (m, 7), 1.74 (s, 3), 1.96-2.22 (m, 7), 2.56 (q, 1, $J$ = 8 Hz), 2.88 (q, 1, $J$ = 8 Hz), 3.04 (q, 1, $J$ = 8 Hz), 5.93 (s, 1), 6.35 (d, 1, $J$ = 10 Hz); $^{13}C$ NMR ($CDCl_3$) δ 14.4 (q), 18.9 (q), 23.7 (t), 25.3 (t), 29.0 (t), 30.6 (t), 32.2 (t), 32.7 (t), 39.0 (d), 42.0 (d), 42.5 (d), 42.9 (d), 44.0 (d), 83.1 (d), 115.5 (d), 118.0 (s), 171.2 (s), 173.8 (s).

**Dihydro-3-(methylamino)-7-nornepetalactam (60).** Through neat **12** (0.76 g, 5 mmol) was passed methylamine for 30 min to give a quantitative yield of a mixture of diastereomers of **60**: $^1H$ NMR ($CDCl_3$) major isomer δ 1.03 (d, 3, $J$ = 8 Hz), 1.24-3.11 (m, 10), 2.23 (s, 3), 2.97 (s, 3), 3.88 (d, 1, $J$ = 9 Hz), minor isomer δ 1.06 (d, $J$ = 8 Hz), 2.24 (s), 2.95 (s), 3.81 (d, $J$ = 9 Hz); $^{13}C$ NMR ($CDCl_3$) major isomer δ 16.2 (q), 24.3 (t), 26.0 (t), 29.5 (q), 30.3 (t), 31.8 (d), 32.0 (q), 39.9 (d), 44.4 (d), 77.7 (d), 173.8 (s); minor isomer δ 23.3, 27.8, 29.9, 32.8, 41.0, 45.3, 78.1, 173.3. By $^1H$ NMR the ratio of the major to minor isomer was 3:1. When the above reaction was carried out except with a solution of **12** in $CH_2Cl_2$ (25 mL), virtually the same results were obtained. However, when $CH_3OH$ was used as a solvent, $^{13}C$ NMR indicated several more compounds were present in addition to the two diastereomers of **60**. The presence of $^{13}C$ NMR signals at 85.0 and 85.5 ppm suggested that part of the product contained a methoxy group bonded to C-3, instead of a methylamino group. However, no attempt was made to separate these products. Distillation of the mixture of

the two diastereomers of **60** obtained above gave only a trace of enelactam **58b**; by $^{13}C$ NMR the predominant product was apparently a third diastereomer of **60**: $^{13}C$ NMR ($CDCl_3$) δ 16.9, 25.5, 30.3, 33.2, 34.2, 36.1, 39.5, 39.9, 43.4, 80.5, 173.0. Distillation of the intermediate from treatment of **12** in $CH_3OH$ with methylamine gave mostly enelactam **58b**, but also some of the same material, apparently a third diastereomer of **60**, just described.

***cis*-*N*-Methyl-7-nornepetalactam (58b).** Through a solution of **11** (0.85 g, 5 mmol) in $CH_3OH$ (25 mL) was passed methylamine for 30 min. After removal of $CH_3OH$ in vacuo, the remaining material was distilled at 95-105 °C (0.09 torr) to give 0.56 g (68%) of **58b**: $^1H$ NMR ($CDCl_3$) δ 1.40-1.64 (m, 3), 1.70 (s, 3), 1.92-2.11 (m, 3), 2.58 (q, 1, $J$ = 8 Hz), 2.79 (q, 1, $J$ = 8 Hz), 3.03 (s, 3), 5.76 (s, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.2 (q), 23.7 (t), 30.6 (t), 32.4 (t), 34.0 (q), 42.7 (d), 43.8 (d), 115.6 (s), 123.4 (d), 170.5 (s).

***cis*-*N*-(2,2-Dimethoxyethyl)-7-nornepetalactam (58c).** Distillation of a mixture of aminoacetaldehyde dimethyl acetal (0.79 g, 7.5 mmol) and either **11** (0.85 g, 5 mmol) or **12** (0.76 g, 5 mmol) gave after workup **58c**: bp 95-105 °C (0.05 torr); $^1H$ NMR ($CDCl_3$) δ 1.43-1.66 (m, 3), 1.71 (s, 3), 1.93-2.20 (m, 3), 2.57 (q, 1, $J$ = 8 Hz), 2.83 (q, 1, $J$ = 8 Hz), 2.42 (s, 6), 3.56 (dq, 2, $J$ = 15, 6 Hz), 4.49 (t, 1, $J$ = 6 Hz), 5.78 (s, 1); $^{13}C$ NMR ($CDCl_3$) δ 18.2 (q), 23.6 (t), 30.5 (t), 32.1 (t), 42.4 (d), 43.9 (d), 48.6 (t), 54.5 (q), 102.7 (d), 115.2 (s), 123.3 (d), 170.8 (s).

***cis*-*N*-Phenyl-7-nornepetalactam (58d):** Addition of aniline (0.70 g, 7.5 mmol) to either **11** (0.85 g, 5 mmol) or **12** (0.76 g, 5 mmol) gave after distillation and workup **58d**: bp 120-130 °C (0.11 torr); $^1H$ NMR ($CDCl_3$) δ 1.46-1.64 (m, 3), 1.68 (s, 3), 1.91-2.04 (m, 1), 2.13 (q, 2, $J$ = 8 Hz), 2.64 (q, 1, $J$ = 8 Hz), 2.93 (q, 1, $J$ = 8 Hz), 5.92 (s, 1), 7.14-7.40 (m, 5); $^{13}C$ NMR ($CDCl_3$) δ 18.1 (q), 23.5 (t), 30.3 (t), 32.0 (t), 42.5 (d), 44.6 (d), 116.0 (s), 123.6 (d), 125.9 (d), 126.4 (d), 128.6 (d), 141.1 (s), 170.3 (s).

**General Procedure for the Reaction of 11 with Diamines and Amino Alcohols.** To a solution of **11** (0.85 g, 5 mmol) in $CH_3OH$ (10 mL) was added the diamine or amino alcohol (10 mmol). After removal of $CH_3OH$ in vacuo, the remaining material was distilled. Ether was added to the distillate and the solution was washed with water. After the solution was dried, ether was removed in vacuo to give the product.

**Decahydro-9-methyl-5*H*-cyclopent[*d*]imidazo[1,2-*a*]pyridin-5-one (61a):** bp 125-135 °C (0.09 torr); $^1$H NMR ($CDCl_3$) δ 1.07-1.25 (m, 1), 1.11 (d, 3, $J$ = 5 Hz), 1.36-1.59 (m, 2), 1.63-1.80 (m, 2), 1.91-2.10 (m, 3), 2.73 (q, 1, $J$ = 9 Hz), 2.94-3.10 (m, 1), 3.12 (br s, 1), 3.27-3.58 (m, 3), 3.94 (d, 1, $J$ = 9 Hz); $^{13}$C NMR ($CDCl_3$) δ 15.8 (q), 24.9 (t), 29.8 (t), 31.4 (t), 40.3 (d), 42.6 (d), 44.4 (t), 44.8 (d), 45.0 (t), 78.3 (d), 170.4 (s).

**Decahydro-10-methyl-cyclopenta[4,5]pyrido[1,2-*a*]pyrimidin-6(2*H*)-one (61b):** 65% yield; bp 130-140 °C (0.08 torr); $^1$H NMR ($CDCl_3$) δ 1.11 (d, 3, $J$ = 6 Hz), 1.20-1.36 (m, 1), 1.41-2.00 (m, 8 + 1 exchangeable), 2.07-2.26 (m, 1), 2.50-2.80 (m, 3), 3.08-3.20 (m, 1), 3.78 (d, 1, $J$ = 9 Hz), 4.64-4.83 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 16.0 (q), 22.7 (t), 26.5 (t), 29.5 (t), 29.9 (t), 36.6 (d), 40.4 (dd), 40.8 (d), 44.3 (t), 45.4 (d), 75.8 (d), 170.8 (s). Signals due to a minor isomer (ca. 30%) were as follows: $^1$H NMR ($CDCl_3$) δ 1.03 (d, $J$ = 6 Hz), 4.09 (d, $J$ = 4 Hz); $^{13}$C NMR ($CDCl_3$) δ 14.5, 23.3, 26.9, 30.1, 33.5, 39.2, 43.4, 44.9, 46.1, 74.9, 171.2.

**Octahydro-9-methyl-cyclopent[*d*]oxazolo[3,2-a]pyridin-5(5a*H*)-one (61c):** 80% yield; bp 95-105 °C (0.12 torr); $^1$H NMR ($CDCl_3$) δ 1.10 (d, 3, $J$ = 7 Hz), 1.18-1.31 (m, 1), 1.41-1.60 (m, 2), 1.64-1.80 (m, 2), 1.92-2.04 (m, 2), 2.07-2.20 (m, 1), 2.74 (q, 1, $J$ = 9 Hz), 3.41-3.52 (m, 1), 3.73 (q, 1, $J$ = 9 Hz), 3.90 (q, 1, $J$ = 7 Hz), 4.13-4.25 (m, 1), 4.42 (d, 1, $J$ = 10 Hz); $^{13}$C NMR ($CDCl_3$) δ 14.9 (q), 25.0 (t), 29.5 (t), 31.0 (t), 39.6 (d), 40.7 (d), 43.3 (t), 45.1 (d), 65.1 (t), 91.6 (d), 170.6 (s). The presence of signals at 114.9 and 123.5 ppm indicated some enelactam was also formed during the above distillation.

**Octahydro-10-methyl-2*H*-cyclopenta[4,5]pyrido[2,1-*b*][1,3]oxazin-6(6a*H*)-one (61d):** 74% yield; bp 100-110 °C (0.20 torr); mp 65-66 °C (hexane); $^1$H NMR ($CDCl_3$) δ 1.08 (d, 3, $J$ = 8 Hz), 1.52-1.98 (m, 9), 2.13-2.28 (m, 1), 2.64 (q, 1, $J$ = 9 Hz), 2.75 (dt, 1, $J$ = 13, 4 Hz), 3.64 (dt, 1, $J$ = 12, 3 Hz), 4.06-4.14 (m, 1), 4.30 (d, 1, $J$ = 9 Hz), 4.68-4.80 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 15.6 (q), 22.8 (t), 25.0 (t), 29.4 (t), 29.6 (t), 35.5 (d), 39.6 (dd), 40.1 (d), 45.2 (d), 66.9 (t), 91.3 (d), 171.2 (s).

## *N*-Alkylation of Nepetalactam

***N*-Alkylation of 1a.**[48] To a solution of **1a** (0.41 g, 2.5 mmol) in THF (25 mL) were added powdered KOH (0.5 g) and TBAB (0.16 g). After addition of the alkyl halide (5 mmol) or dihaloalkane (1.25 mmol) the reaction mixture was stirred overnight. The mixture was then filtered, and THF was removed in vacuo. Ether was added to the crude product and the solution was washed with water containing a few drops of 10% HCl. After the solution was dried, ether was removed in vacuo and the remaining material was distilled to give the final product.

**[4a*S*-(4aα,7α,7aα)]-*N*-Methyl-nepetalactam (8a):** bp 95-105 °C (0.11 torr); $^1$H NMR ($CDCl_3$) δ 1.06-1.28 (m, 1), 1.19 (d, 3, $J$ = 6 Hz), 1.38-1.57 (m, 1), 1.65 (s, 3), 1.73-1.86 (m, 1), 1.92-2.06 (m, 1), 2.21-2.35 (m, 2), 2.72 (q, 1, $J$ = 9 Hz), 3.01 (s, 3), 5.66 (s, 1); $^{13}$C NMR ($CDCl_3$) δ 17.8 (q), 21.0 (q), 31.4 (t), 33.0 (t), 33.9 (q), 40.0 (d), 42.4 (d), 51.1 (d), 115.5 (s), 123.2 (d), 170.6 (s).

**[4a*S*-(4aα,7α,7aα)]-*N*-(2-Propenyl)-nepetalactam (8b):** bp 100-105 °C (0.07 torr); $^1$H NMR ($CDCl_3$) δ 1.07-1.28 (m, 1), 1.19 (d, 3, $J$ = 6 Hz), 1.42-1.57 (m, 1), 1.66 (s, 3), 1.75-1.88 (m, 1), 1.93-2.07 (m, 1), 2.23-2.38 (m, 2), 2.72 (q, 1, $J$ = 9 Hz), 3.94-4.17 (m, 2), 5.08-5.21 (m, 2), 5.64 (s, 1), 5.68-5.85 (m, 1); $^{13}$C NMR ($CDCl_3$) δ 17.9 (q), 21.0 (q), 31.4 (t), 33.0 (t), 40.1 (d), 42.3 (d), 48.0 (t), 51.2 (d), 115.6 (s), 116.5 (t), 121.6 (d), 133.1 (d), 170.1 (s).

**[4a*S*-(4aα,7α,7aα)]-*N*-(2,2-Dimethoxyethyl)-nepetalactam (8c):** bp 100-105 °C (0.03 torr); $^1$H NMR ($CDCl_3$) δ 1.10-1.31 (m, 1), 1.21 (d, 3, *J* = 6 Hz), 1.45-1.61 (m, 1), 1.68 (s, 3), 1.78-1.91 (m, 1), 1.96-2.09 (m, 1), 2.28-2.40 (m, 2), 2.75 (q, 1, *J* = 9 Hz), 3.41 (s, 3), 3.42 (s, 3), 3.47 (dd, 1, *J* = 15, 6 Hz), 3.60 (dd, 1, *J* = 15, 6 Hz), 4.49 (t, 1, *J* = 6 Hz), 5.78 (s, 1); $^{13}$C NMR ($CDCl_3$) δ 17.9 (q), 20.9 (q), 31.3 (t), 32.9 (t), 40.0 (d), 42.1 (d), 48.5 (t), 51.3 (d), 54.3 (q), 54.5 (q), 102.7 (d), 114.9 (s), 123.2 (d), 170.7 (s).

***N*,*N'*-Methylenebis[[4a*S*-(4aα,7α,7aα)]-nepetalactam] (62a):** mp 97-98 °C (hexane); $^1$H NMR ($CDCl_3$) δ 1.15-1.35 (m, 2), 1.20 (d, 6, *J* = 6 Hz), 1.45-1.60 (m, 2), 1.65 (s, 6), 1.78-1.90 (m, 2), 1.95-2.10 (m, 2), 2.22-2.40 (m, 4), 2.73 (q, 2, *J* = 9 Hz), 4.15 (s, 2), 6.08 (s, 2); $^{13}$C NMR ($CDCl_3$) δ 17.9 (q), 20.8 (q), 31.2 (t), 32.9 (t), 39.9 (d), 42.1 (d), 51.2 (d), 54.3 (t), 115.7 (s), 121.7 (d), 171.6 (s).

***N*,*N'*-(1,3-Propanediyl)bis[[4a*S*-(4aα,7α,7aα)]-nepetalactam] (62b):** mp 73-74 °C (hexane); $^1$H NMR ($CDCl_3$) δ 1.16-1.31 (m, 2), 1.23 (d, 6, *J* = 6 Hz), 1.46-1.62 (m, 2), 1.70 (s, 6), 1.75-1.90 (m, 4), 1.95-2.10 (m, 2), 2.22-2.37 (m, 4), 2.75 (q, 2, *J* = 9 Hz), 3.48 (q, 4, *J* = 7 Hz), 5.73 (s, 2); $^{13}$C NMR ($CDCl_3$) δ 18.0 (q), 21.0 (q), 27.4 (t), 31.3 (t), 32.9 (t), 40.0 (d), 42.3 (d), 44.2 (t), 51.4 (d), 115.8 (s), 122.0 (d), 170.4 (s).

## BIBLIOGRAPHY AND NOTES

(1) Enamide has been the term normally used for the nitrogen analogues of both acyclic enol esters and cyclic enol lactones. However, enelactam seems to be a suitable term for the nitrogen analogues of enol lactones such as **1a** and **2**, and is used throughout this work.

(2) The *Chemical Abstracts* name for **1a** should be [4a*S*-(4aα,7α,7aα)]-2,4a,5,6,7,7a-hexahydro-4,7-dimethyl-1*H*-2-pyrindin-1-one, and for **3a** is [4a*S*-(4aα,7α,7aα)]-5,6,7,7a-tetrahydro-4,7-dimethyl-cyclopenta[*c*]pyran-1(4a*H*)-one. It is not clear at this time how *Chemical Abstracts* would name **2**.

(3) For a simplified description of the isolation of alkaloids, including the use of ammonia, see: Cordell, G. A. *Introduction to Alkaloids*; Wiley-Interscience: New York, 1981; pp 12-14.

(4) Cordell, G. A. *Alkaloids (N. Y.)* **1977**, *16*, 447-448, 452-453, 456, 470, 495. Manske, R. H. F. *Alkaloids (N. Y.)* **1977**, *16*, 529.

(5) Wildman, W. C.; Le Men, J.; Wiesner, K. In *Cyclopentanoid Terpene Derivatives*; Taylor, W. I.; Battersby, A. R., Eds.; Marcel Dekker: New York, 1969; pp 247-248.

(6) The *Chemical Abstracts* name for **7** is [1*R*-[1α,2β,5α(*R**)]]-2-methyl-5-(1-methyl-2-oxoethyl)-cyclopentanecarboxylic acid. Despite this name, **7** exists predominantly as a mixture of two hydroxy lactones: Eisenbraun, E. J.; Browne, C. E.; Eliel, E. L.; Harris, D. L.; Rahman, A; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 3302-3305.

(7) Casinovi, C. G.; Delle Monache, F.; Marini-Bettolo, G. B.; Bianchi, E.; Garbarino, J. A. *Gazz. Chim. Ital.* **1962**, *92*, 479-487; *Chem. Abstr.* **1962**, *57*, 13813e. In this paper the structures are drawn in the opposite absolute configuration of the correct formulation. Also, it is unclear whether both **7** and **9** were converted to **8a**, since the discussion section and a scheme indicates only **7** reacting with methylamine to give **8a**, while the experimental section mentions only **9** as being treated with methylamine to give **8a**.

(8) Casinovi, C. G.; Delle Monache, F.; Marini-Bettolo, G. B.; Bianchi, E.; Garbarino, J. A. *Sci. Rep. Ist. Super. Sanita* **1961**, *1*, 588-590; *Chem. Abstr.* **1965**, *63*, 4349d. Here, the abstract mentions **7**, but not **9**, as being treated with methylamine to give **8a**.

(9) The *Chemical Abstract* name for **12** is *cis*-(±)-5,6,7,7a-tetrahydro-4-methyl-cyclopenta[*c*]pyran-1(4a*H*)-one.

(10) Trave, R.; Merlini, L.; Garanti, L. *Chim. Ind. (Milan)* **1958**, *40*, 887-895. Ficini, J.; d'Angelo, J.; Eman, A.; Touzin, A. M. *Tetrahedron Lett.* **1976**, 683-686.

(11) Livingstone, R. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: New York, 1977; Vol. IV, Part E, p 294 and references cited therein. Ellis, G. P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; McKillop, A., Eds.; Pergamon: New York, 1984; Vol. 3, p 685.

(12) Barry, R. D. *Chem. Rev.* **1964**, *64*, 244-245.

(13) Shamma, M. *Org. Chem. (N. Y.)* **1972**, *25*, 517-518. Kametani, T. J.; Fukumoto, K. *Chem. Heterocycl. Compd.* **1981**, *38*, 208.

(14) Popp, F. D.; Noble, A. C. *Adv. Heterocycl. Chem.* **1967**, *8*, 32 and references cited therein. Rose, A.; Buu-Hoï, N. P. *J. Chem. Soc. C* **1968**, 2205-2208. Flammang, M.; Wermuth, C. G. *C. R. Seances Acad. Sci., Ser. C* **1980**, *290*, 361-3. Guzzi, U.; Omodei-Sale, A.; Galliani, G. Ger. Offen. 2 943 286, 1980; *Chem. Abstr.* **1980**, *93*, 186360r. Omodei-Sale, A.; Favara, D. Ger. Offen. 2 942 195, 1980; *Chem. Abstr.* **1980**, *93*, 239418z.

(15) von Pechmann, H.; Welsh, W. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2384-2395. von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2396-2399. Wiley, R. H.; Smith, N. R.; Knabeschuh, L. H.; *J. Am. Chem. Soc.* **1953**, *75*, 4482-4484. Wiley, R. H.; Knabeschuh, L. H.; Duckwall, A. L.; Smith, N. R. *J. Am. Chem. Soc.* **1954**, *76*, 625-627. Brody, F.; Ruby, P. R. *Chem. Heterocycl. Compd.* **1960**, *14*(1), 177-194. Livingstone, R. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: Amsterdam, 1977; Vol. IV, Part E, p 15 and references cited therein. Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; McKillop, A., Eds.; Pergamon: New York, 1984; Vol. 2, pp 499-500.

(16) Wiley, R. H.; Slaymaker, S. C. *J. Am. Chem. Soc.* **1956**, *78*, 2393-2398 and references cited therein.

(17) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963; p 85.

(18) Al-Farkh, Y. A.; Al-Hajjar, F. H.; El-Rayyes, N. R.; Hamoud, H. S. *J. Heterocycl. Chem.* **1978**, *15*, 759-763.

(19) Shusherina, N. P.; Lapteva, V. L. *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 852-855.

(20) Shusherina, N. P.; Levina, R. Y. *Russ. Chem. Rev. (Engl. Transl.)* **1968**, *37*, 198-208 and references cited therein.

(21) Chiron, R.; Graff, Y. *Bull. Soc. Chim. Fr.* **1971**, 2145-2153. In one case, an enol lactone **G** reacted with methylamine to give a cyclic tautomer of **J**, a six-membered hydroxy lactam.

(22) Al-Farkh, Y. A.; Al-Hajjar, F. H.; Hamoud, H. S. *J. Heterocycl. Chem.* **1979**, *16*, 1-6.

(23) For a few examples see: Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2212-2213. Aranda, V. G.; Barluenga, J.; Gotor, V. *Tetrahedron Lett.* **1974**, 977-978. Wrobel, J. T.; Cybulski, J.; Dabrowski, Z. *Synthesis* **1977**, 686-688.

(24) Vorländer, D.; Knötzsch, A. *Justus Liebigs Ann. Chem.* **1897**, *294*, 317-336.

(25) Shiroyan, F. R.; Khazhakyan, L. V.; Mkrtchyan, A. R.; Terzyan, A. G.; Tatevosyan, G. T. *Arm. Khim. Zh.* **1967**, *20*, 649-658; *Chem. Abstr.* **1968**, *69*, 10387v. Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102-4107.

(26) Uskokovic, M.; Gut, M. *Helv. Chim. Acta* **1959**, *42*, 2258-2261. Gut, M.; Uskokovic, M. *J. Org. Chem.* **1961**, *26*, 1943-1944.

(27) Doorenbos, N. J.; Huang, C. L.; Tamorria, C. R.; Wu, M. T. *J. Org. Chem.* **1961**, *26*, 2546-2548.

(28) Shoppee, C. W.; Killick, R. W.; Krüger, G. *J. Chem. Soc.* **1962**, 2275-2285.

(29) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 370-371. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 677-678.

(30) Wolff, L. *Justus Liebigs Ann. Chem.* **1885**, *229*, 249-285.

(31) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum: New York, 1985; pp 57-62.

(32) Chiron, R.; Graff, Y. *Bull. Soc. Chim. Fr.* **1970**, 575-583.

(33) Ramachandran, R.; Chiron, R.; Graff, Y. *Bull. Soc. Chim. Fr.* **1972**, 1031-1040.

(34) Jones, J. B.; Young, J. M. *Can. J. Chem.* **1966**, *44*, 1059-1068.

(35) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum: New York, 1985; pp 27, 257-258.

(36) Nour, T. A.; Baddar, F. G.; Fateen, A. *J. Chem. Soc.* **1964**, 5302-5306. Rao, Y. S. *Chem. Rev.* **1964**, *64*, 371-372. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 676-677.

(37) Panetta, C. A.; Miller, A . L. *J. Org. Chem.* **1978**, *43*, 2113-2115.

(38) McElvain, S. M.; Bright, R. D.; Johnson, P. R. *J. Am. Chem. Soc.* **1941**, *63*, 1558-1563.

(39) McElvain, S. M.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1599-1605.

(40) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 1066 and references cited therein.

(41) For a discussion of the structures of compounds related to **14** see: Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum: New York, 1985; pp 37-38.

(42) The expected product, aldehydo ester **27**, may undergo further reaction with diazomethane, as it is known that aldehydes and ketones react with diazomethane: March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 976-978.

(43) Horning, D. E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.* **1971**, *49*, 2785-2796.

(44) Valter, R. E. *Russ. Chem. Rev. (Engl. Transl.)* **1973**, *42*, 464-476 and references cited therein.

(45) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum: New York, 1985; pp 82-83.

(46) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1969**, *34*, 165-170 and references cited therein.

(47) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; p 256.

(48) Takahata, H; Hashizume, T.; Yamazaki, T. *Heterocycles* **1979**, *12*, 1449-1451.

(49) Cragoe, E. J.; Pietruszkiewicz, A. M. *J. Org. Chem.* **1957**, *22*, 1338-1345.

(50) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum: New York, 1985; pp 60-62, 64, 72 and references cited therein.

(51) Shusherina, N. P.; Levina, R. Y.; Lur'e, M. Y. *Zh. Obshch. Khim.* **1956**, *26*, 750-755; *Chem. Abstr.* **1956**, *50*, 14701c. Terent'ev, A. P., Kost, A. N.; Saltykova, Y. V.; Ershov, V. V. *Zh. Obshch. Khim.* **1956**, *26*, 2925-2928; *Chem. Abstr.* **1957**, *51*, 8011e. Shusherina, N. P.; Levina, R. Y.; Lur'e, M. Y. *Vestn. Mosk. Univ., Ser. Mat., Mekh., Astron., Fiz., Khim.* **1957**, *12*, 173-198; *Chem. Abstr.* **1959**, *53*, 2175c.

(52) Gramain, J. C.; Remuson, R.; Troin, Y. *Tetrahedron* **1979**, *35*, 759-765.

(53) Lukes, R.; Gorocholinskij, J. *Collect. Czech. Chem. Commun.* **1936**, *8*, 223-235; *Chem. Abstr.* **1936**, *30*, 5989[9].

(54) Lukes, R.; Fabryova, A.; Dolezal, S.; Novotny, L. *Collect. Czech. Chem. Commun.* **1960**, *25*, 1063-1069; *Chem. Abstr.* **1960**, *54*, 13114f.

(55) Dev, S. *J. Indian Chem. Soc.* **1957**, *34*, 169-177.

(56) There are few pentalene compounds that contain a exocyclic double bond: Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1699-1701.

(57) Parts of the $^1$H NMR spectral data for **23a** and **23b** have been reported: Sakan, T.; Isoe, S.; Hyeon, S. B.; Katsumura, R.; Maeda, T.; Wolinsky, J.; Dickerson, D.; Slabaugh, M.; Nelson, D. *Tetrahedron Lett.* **1965**, 4097-4102.

(58) Koelsch, C. F.; Hochmann, H.; Le Claire, C. D. *J. Am. Chem. Soc.* **1943**, *65*, 59-60.

(59) Friedrich, E. C.; Taggart, D. B.; Saleh, M. A. *J. Org. Chem.* **1977**, *42*, 1437-1443.

(60) Bailey, P. S.; Erickson, R. E. *Org. Synth.* **1961**, *41*, 41-45.

(61) Chatterjea, J. N.; Bhakta, C.; Vakula, T. R. *J. Indian Chem. Soc.* **1972**, *49*, 1161-1168.

(62) The Jones reagent was prepared by dissolving $CrO_3$ (95 g) in a minimum amount of water, then adding $H_2SO_4$ (81 mL), and finally diluting the resulting solution with water to 350 mL.

(63) Kirby, G. W.; Mackinnon, J. W. M.; Elliott, S.; Uff, B. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1298-1302.

(64) Dijksman, D. J.; Newbold, G. T. *J. Chem. Soc.* **1951**, 1213-1218.

(65) Apparently **17** is hydrolyzed even by weak base, as addition of a saturated solution of sodium bicarbonate to an ether solution of **17** caused much bubbling and served only to lower the yield of **17**.

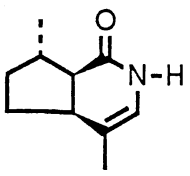
(66) Vill, J. J.; Steadman, T. R.; Godfrey, J. J. *J. Org. Chem.* **1964**, *29*, 2780-2781.

(67) Our $^1H$ and $^{13}C$ NMR spectral data for **10a** are consistent with that previously reported: Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878-3882.

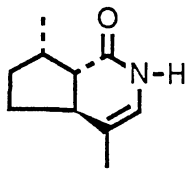
(68) Our $^1H$ NMR spectral data for **56** is consistent with that previously reported: Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621-1626.

# APPENDIX A

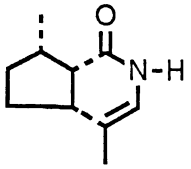
# GLOSSARY OF STRUCTURES



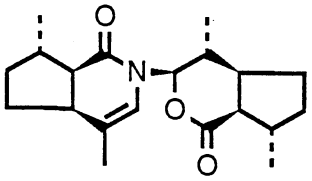
**1a**



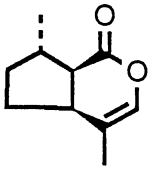
**1b**



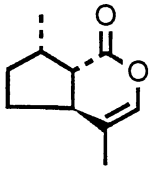
**1c**



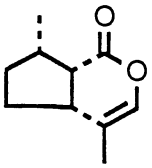
**2**



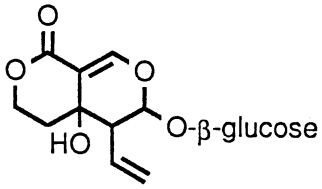
**3a**



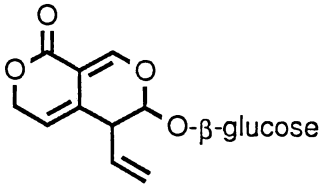
**3b**



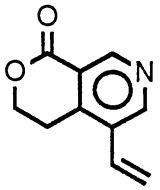
**3c**



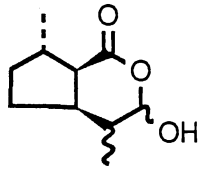

**4**



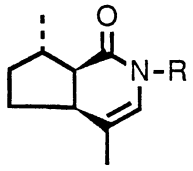

**5**



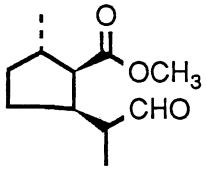
**6**



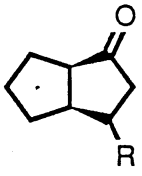
**7**



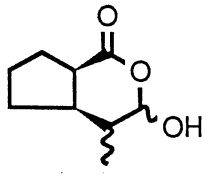
**8a**, R = $CH_3$
**b**, R = $CH_2CH{=}CH_2$
**c**, R = $CH_2CH(OCH_3)_2$



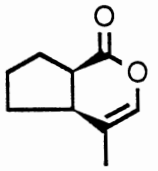
**9**



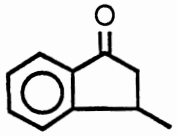
**10a**, R = ···$CH_3$
**b**, R = —$CH_3$



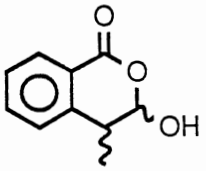
**11**



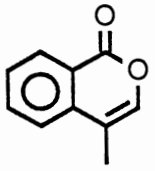
**12**



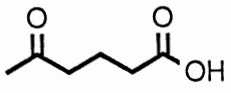
**13**



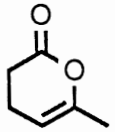
**14**



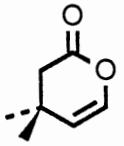
**15**



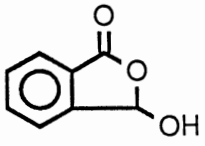
**16**



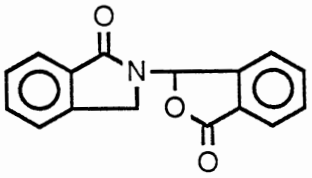
**17**



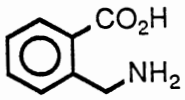
**18**



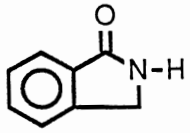
**19**



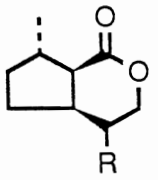
**20**



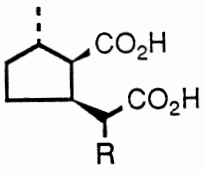
**21**



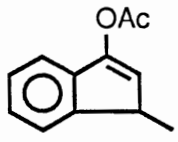
**22**



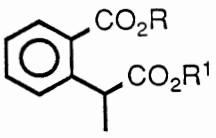
**23a**, R = ··CH$_3$
**b**, R = ⁃CH$_3$



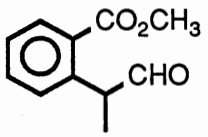
**24a**, R = ··CH$_3$
**b**, R = ⁃CH$_3$



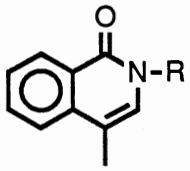
**25**



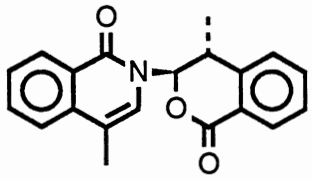
**26a**, R = R$^1$ = H
**b**, R = H, R$^1$ = CH$_3$
**c**, R = CH$_3$, R$^1$ = H
**d**, R = R$^1$ = CH$_3$



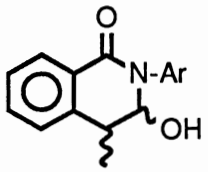
**27**



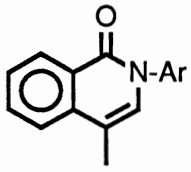
**28a**, R = H
**b**, R = $NH_2$
**c**, R = $CH_3$
**d**, R = $CH_2CH_2OH$
**e**, R = $CH_2CO_2CH_3$
**f**, R = $CH_2CH_2CH_2OH$
**g**, R = $CH_2CH(OCH_3)_2$
**h**, R = $CH_2CH_2CH_2N(CH_3)_2$
**i**, R = $CH_2CH{=}CH_2$



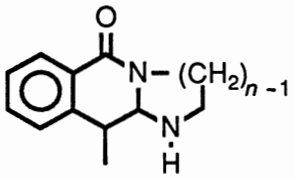
**29**



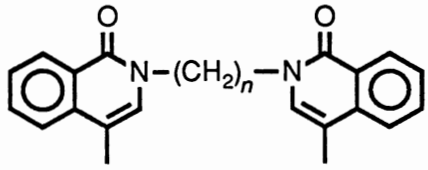
**30a**, Ar = $C_6H_5$
**b**, Ar = 2-$HO_2CC_6H_4$
**c**, Ar = 2-$H_3CO_2CC_6H_4$



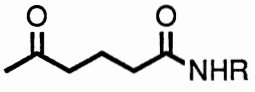
**31a**, Ar = $C_6H_5$
**b**, Ar = 2-$HO_2CC_6H_4$



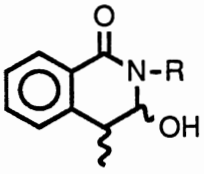
**32a**, *n* = 2
**b**, *n* = 3



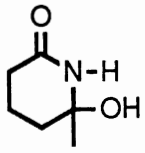
**33a**, *n* = 0
**b**, *n* = 1
**c**, *n* = 2
**d**, *n* = 3



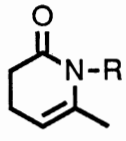
**36a**, R = H
**b**, R = $CH_3$
**c**, R = $CH_2CH_2OH$
**d**, R = $CH_2CH(OCH_3)_2$
**e**, R = $CH_2CH_2CH_2N(CH_3)_2$
**f**, R = $C_6H_5$
**g**, R = 2-$H_3CO_2CC_6H_4$



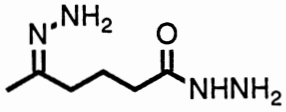
**34a**, R = H
**b**, R = $NH_2$
**c**, R = $CH_3$
**d**, R = $CH_2CH_2OH$



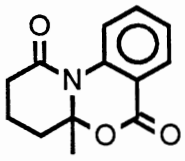
**35**



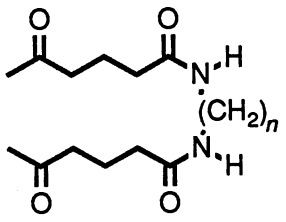
**37a**, R = H
**b**, R = $CH_3$
**c**, R = $CH_2CH{=}CH_2$
**d**, R = $CH_2CH(OCH_3)_2$



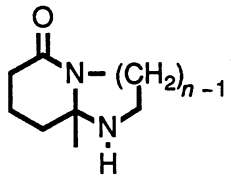
**38**



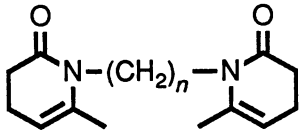
**39**



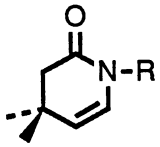
**40a**, $n = 2$
**b**, $n = 3$



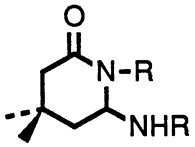
**41a**, $n = 2$
**b**, $n = 3$



**42a**, $n = 1$
**b**, $n = 3$

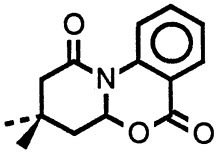


**43a**, R = H
**b**, R = $CH_3$
**c**, R = $CH_2CH{=}CH_2$
**d**, R = $CH_2CO_2CH_3$
**e**, R = $CH_2CH(OCH_3)_2$
**f**, R = $CH_2CH_2CH_2N(CH_3)_2$
**g**, R = $C_6H_5$
**h**, R = 2-$H_3CO_2CC_6H_4$

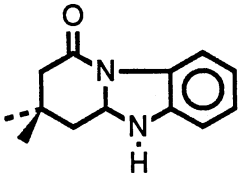


**44a**, R = $NH_2$
**b**, R = $CH_3$
**c**, R = $CH_2CH_2OH$
**d**, R = $CH_2CH(OCH_3)_2$
**e**, R = $C_6H_5$

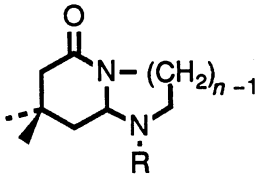
**45**



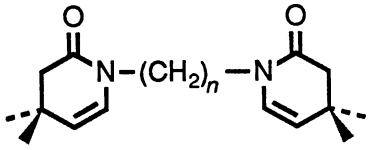
**46**



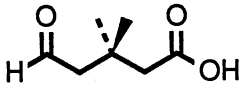
**47**



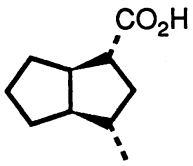
**48a**, R = H, $n = 2$
**b**, R = H, $n = 3$
**c**, R = $CH_3$, $n = 3$



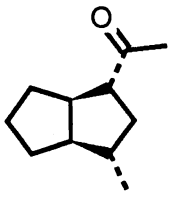
**49a**, $n = 1$
**b**, $n = 3$



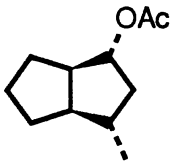
**50**



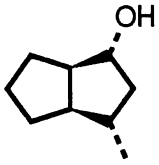
**51**



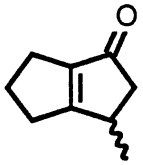
**52**



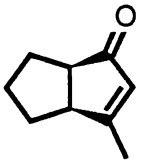

**53**



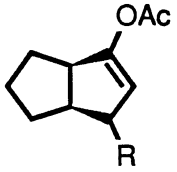

**54**



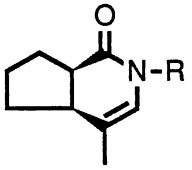

**55**



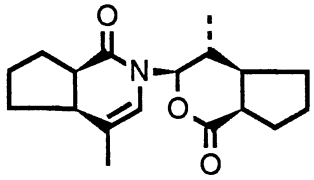

**56**



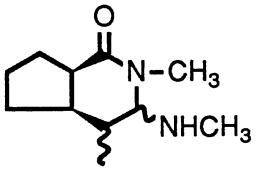

**57a**, R = ···CH$_3$
**b**, R = ▬CH$_3$



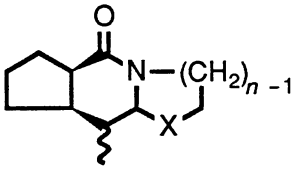

**58a**, R = H
**b**, R = $CH_3$
**c**, R = $CH_2CH(OCH_3)_2$
**d**, R = $C_6H_5$



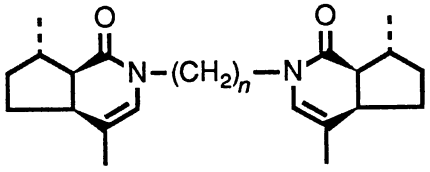

**59**




**60**



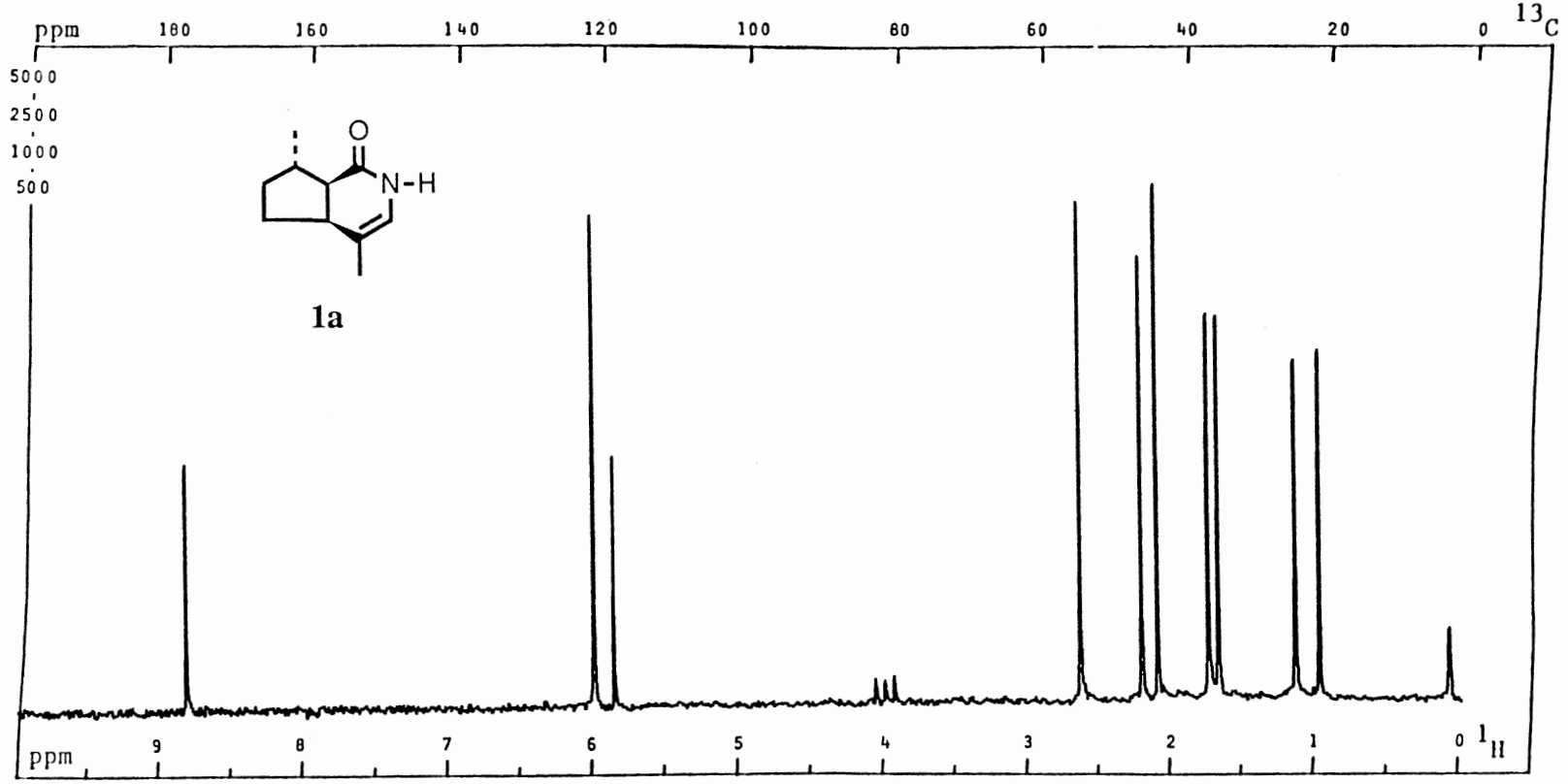

**61a**, X = NH, $n$ = 2
**b**, X = NH, $n$ = 3
**c**, X = O, $n$ = 2
**d**, X = O, $n$ = 3



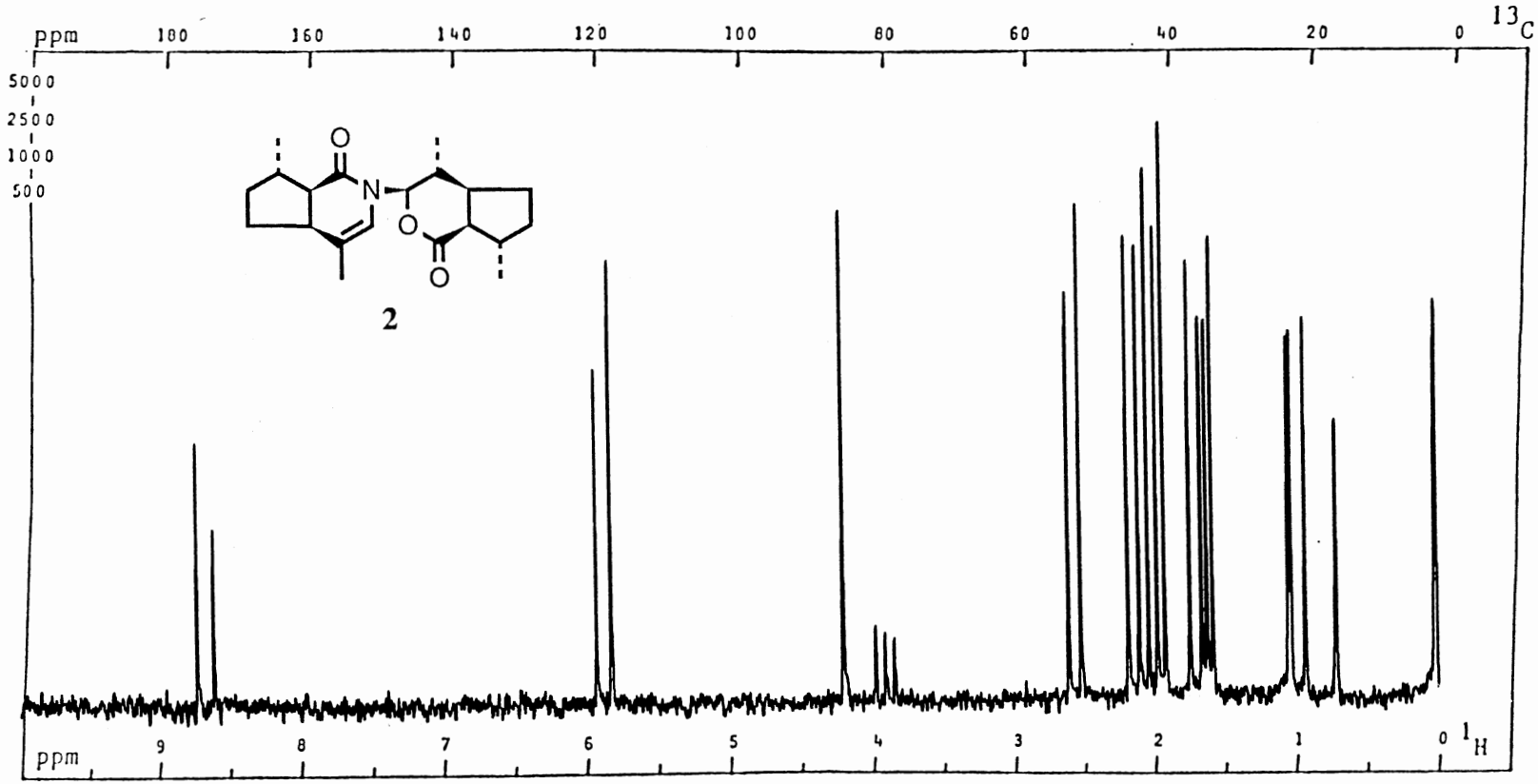

**62a**, $n$ = 1
**b**, $n$ = 3

# APPENDIX B

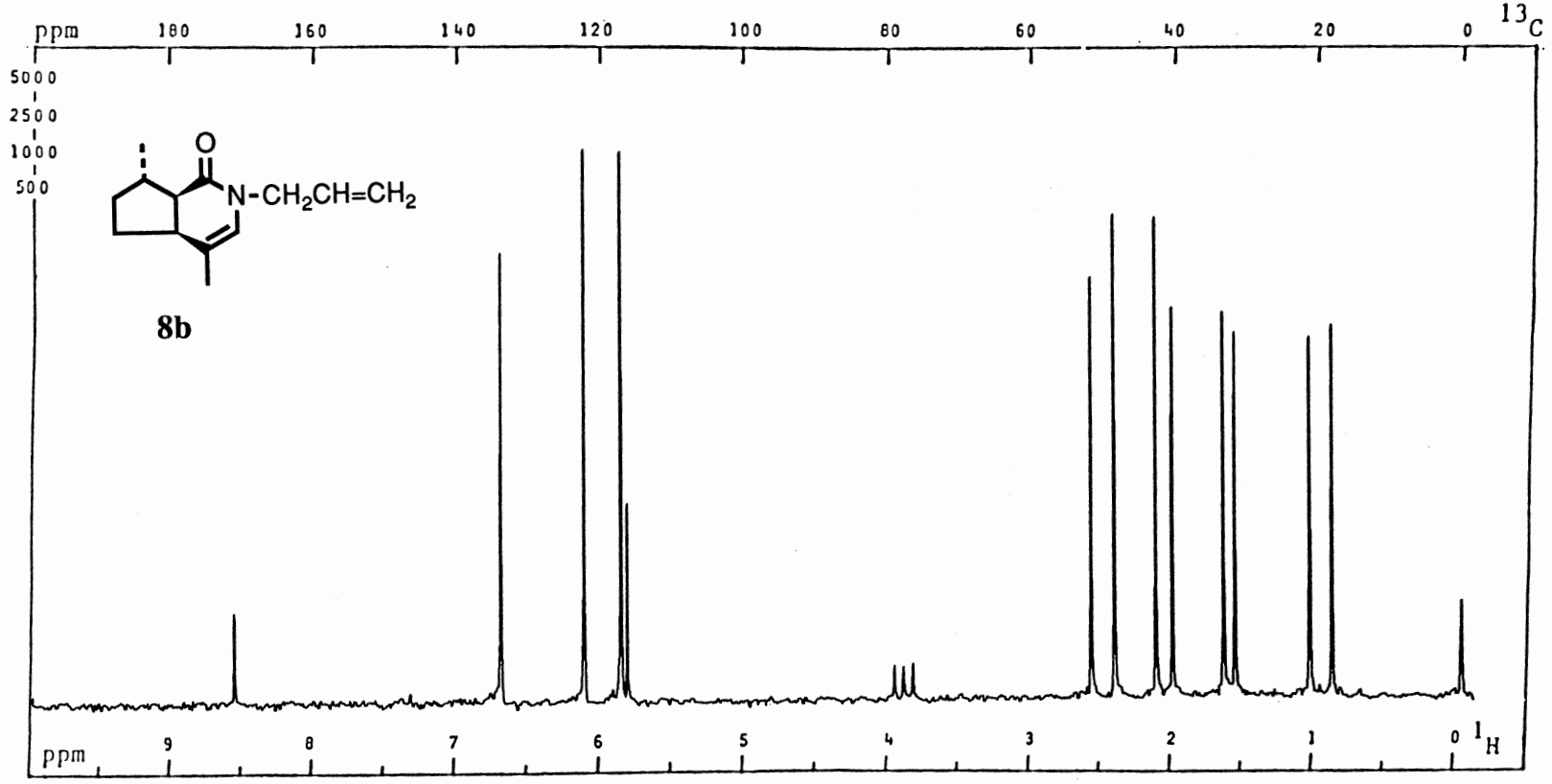
## SELECTED $^{13}C$ NMR SPECTRA



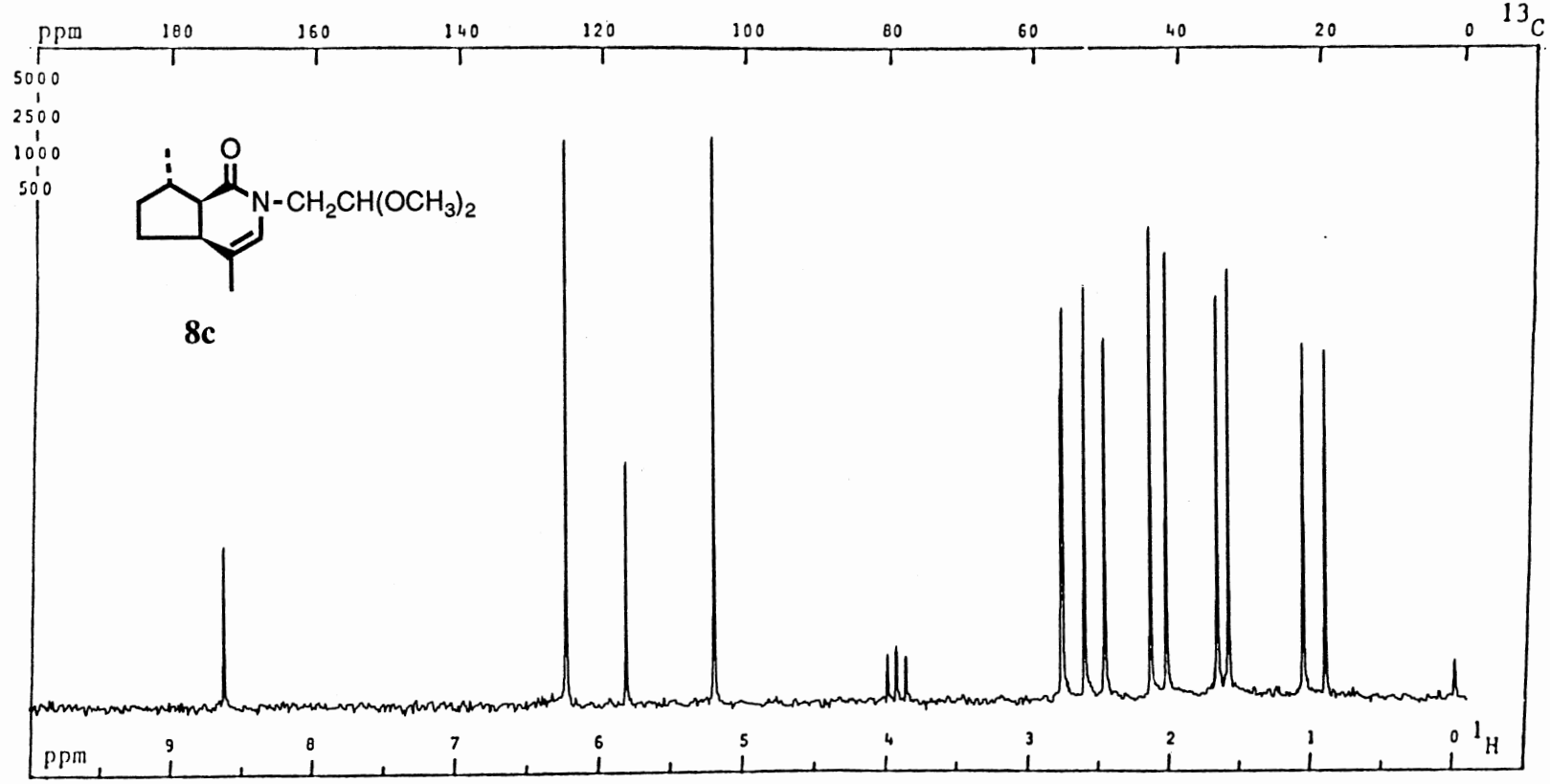

**Spectrum 1.** $^{13}C$ NMR of [4a*S*-(4aα,7α,7aα)]-Nepetalactam (**1a**)



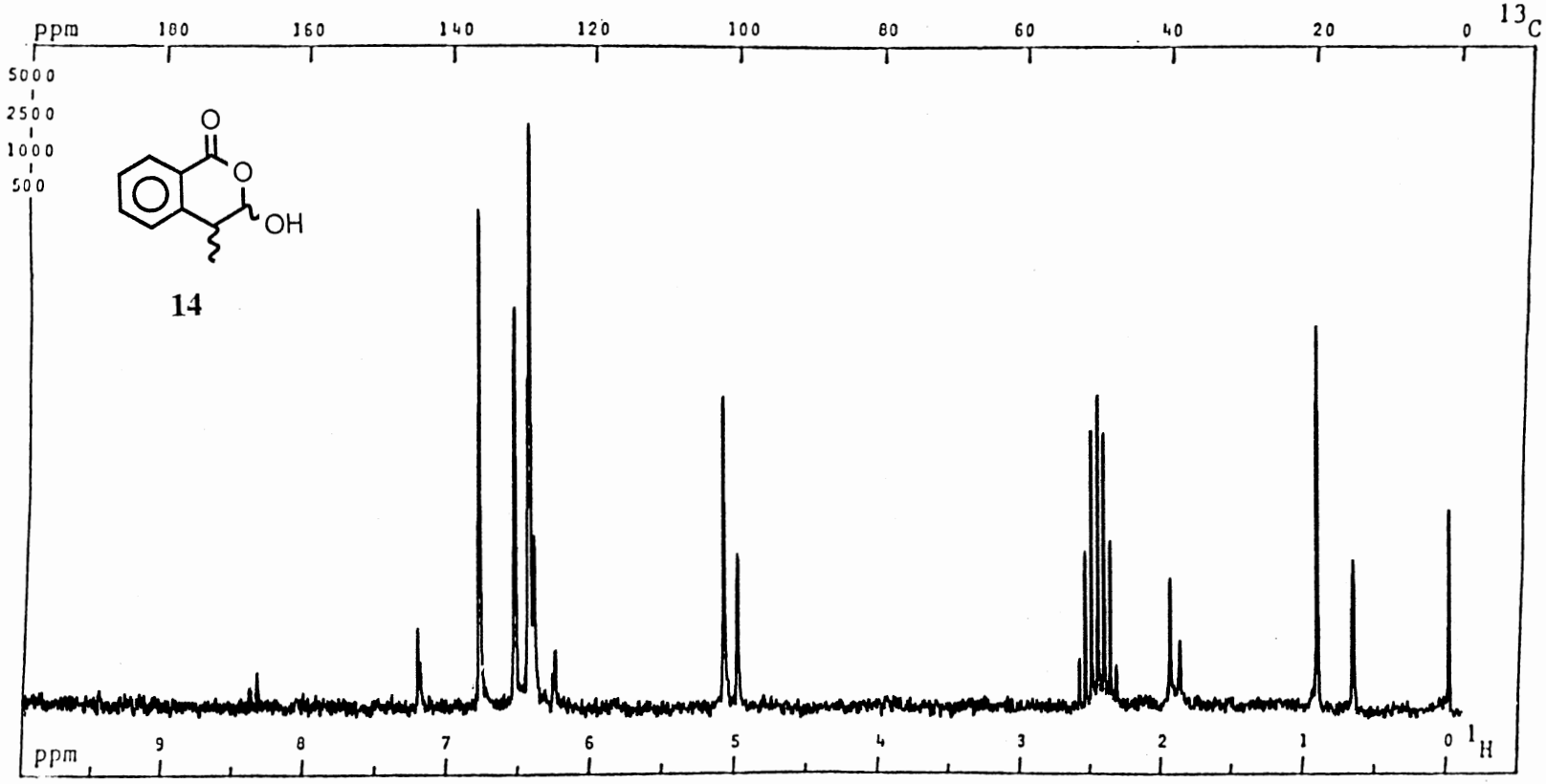

**Spectrum 2.** $^{13}C$ NMR of *N*-(Nepetal-3-yl)-nepetalactam (**2**)



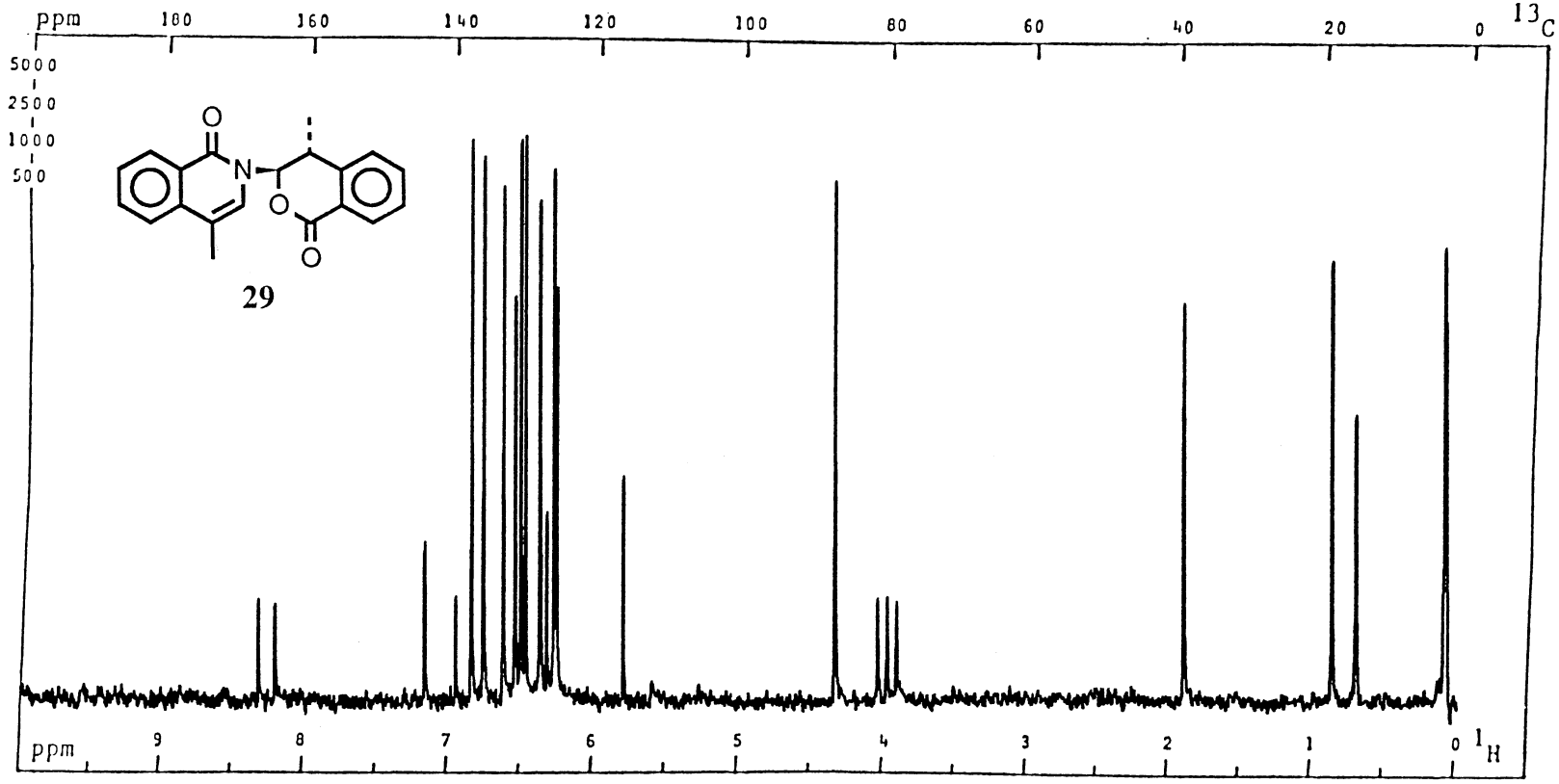

**Spectrum 3.** $^{13}C$ NMR of [4a*S*-(4aα,7α,7aα)]-*N*-(2-Propenyl)-nepetalactam (**8b**)



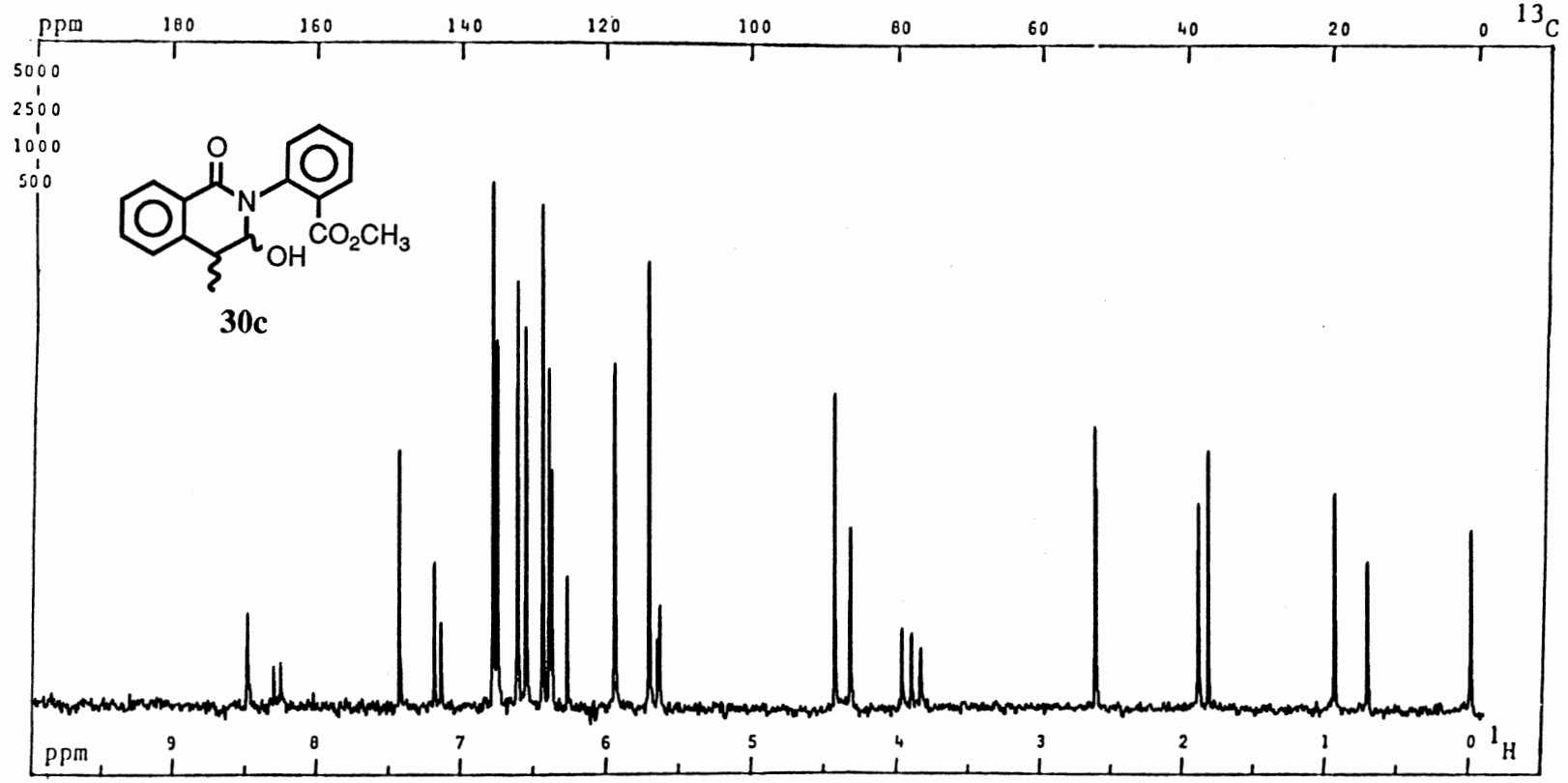

**Spectrum 4.** $^{13}C$ NMR of [4a*S*-(4aα,7α,7aα)]-*N*-(2,2-Dimethoxyethyl)-nepetalactam (**8c**)



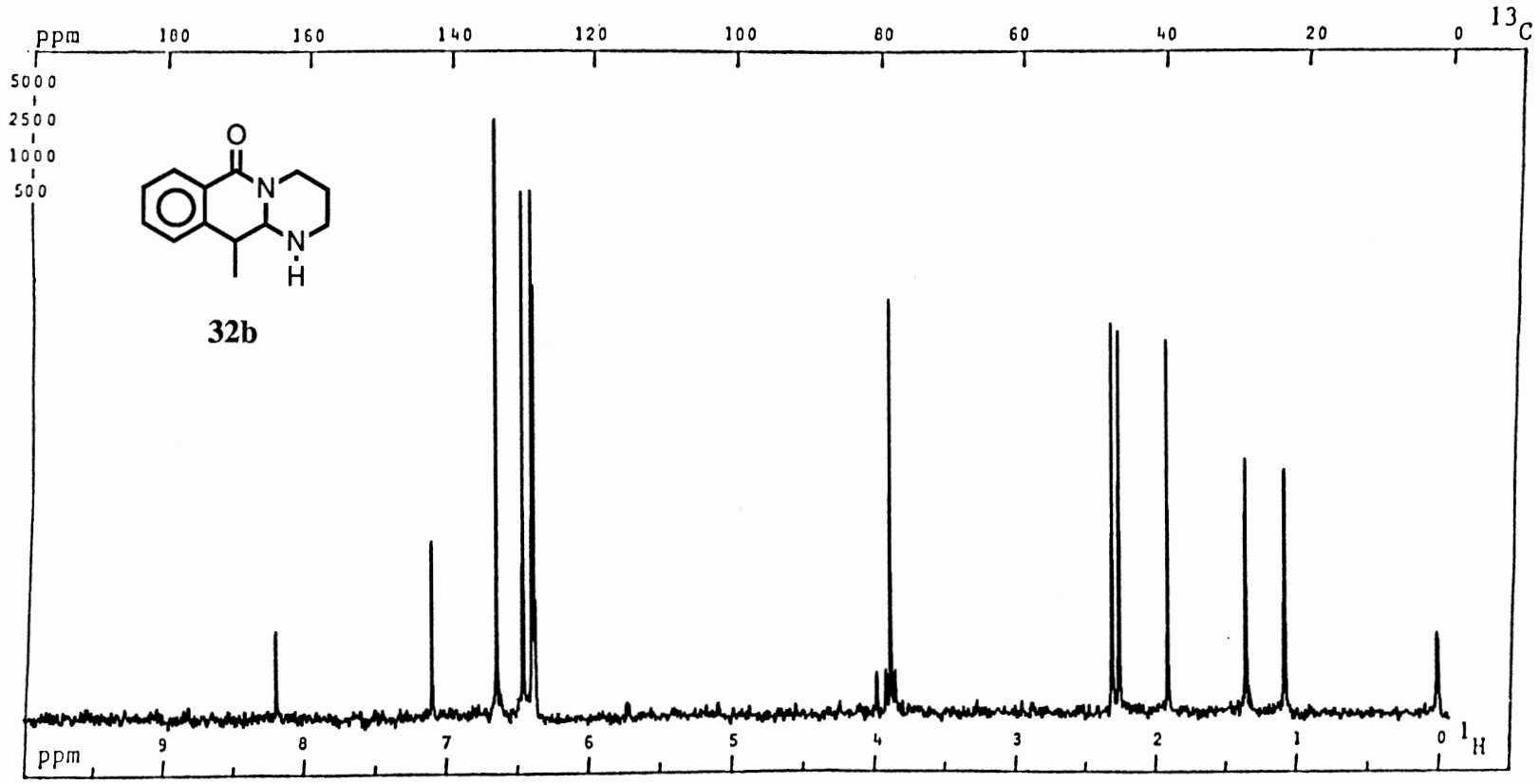

**Spectrum 5.** $^{13}C$ NMR of 3,4-Dihydro-3-hydroxy-4-methyl-1*H*-2-benzopyran-1-one (**14**)



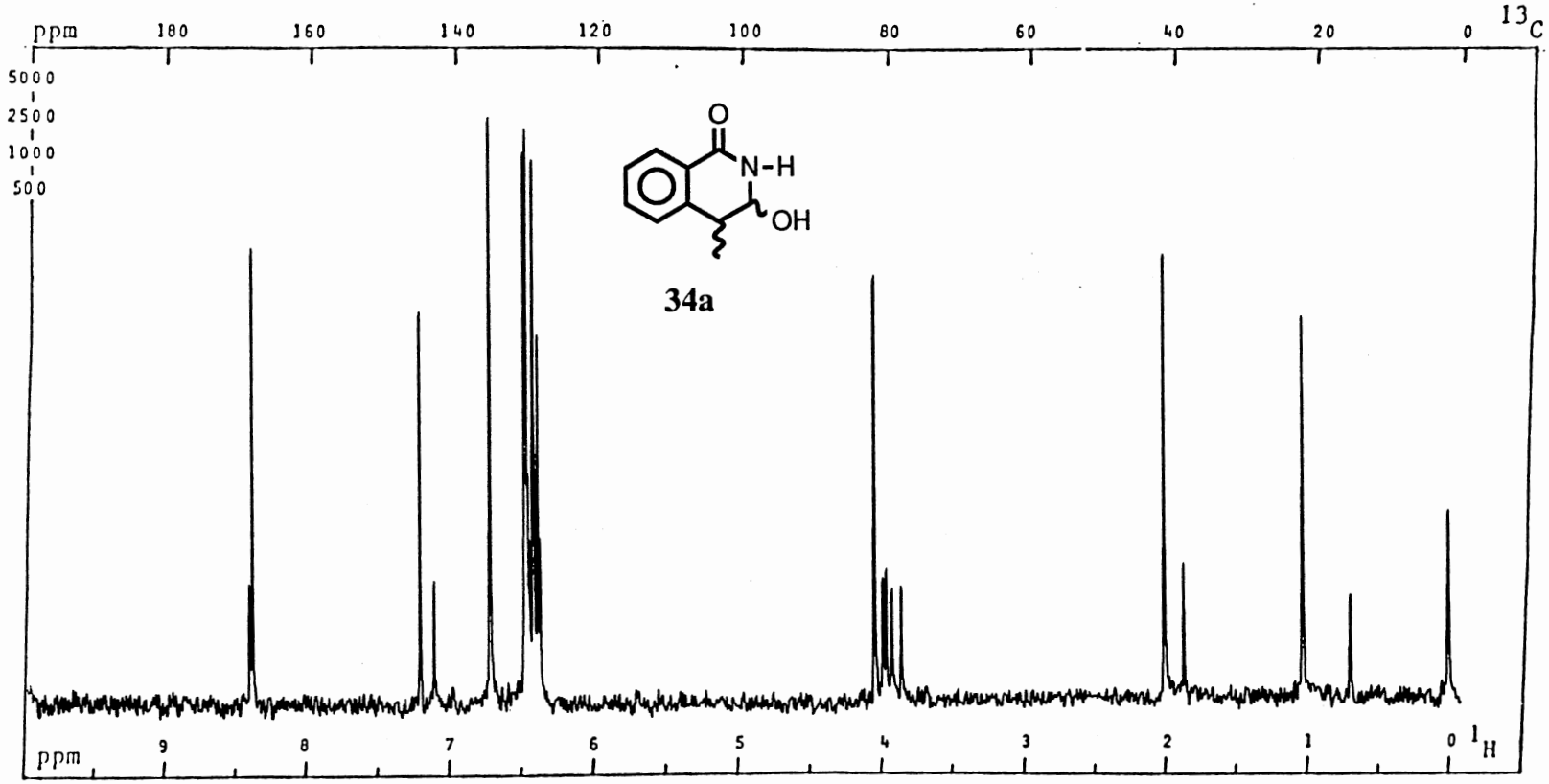

**Spectrum 6.** $^{13}C$ NMR of 2-(3,4-Dihydro-4-methyl-1-oxo-1*H*-2-benzopyran-3-yl)-4-methyl-1(2*H*)-isoquinolinone (**29**)



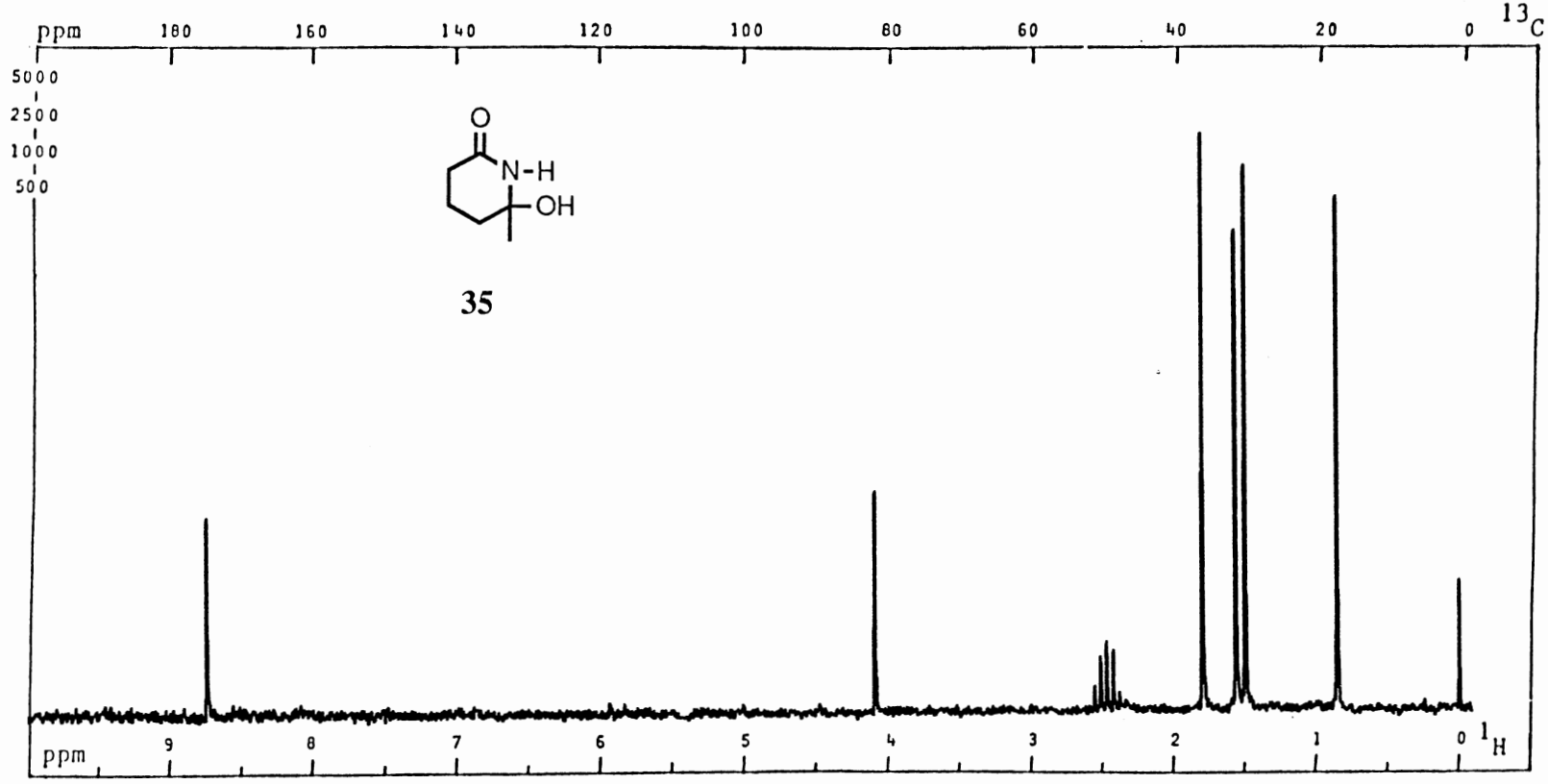

**Spectrum 7.** $^{13}C$ NMR of Methyl 2-(3,4-Dihydro-3-hydroxy-4-methyl-1-oxo-2(1*H*)-isoquinolinyl)-benzoate (**30c**)



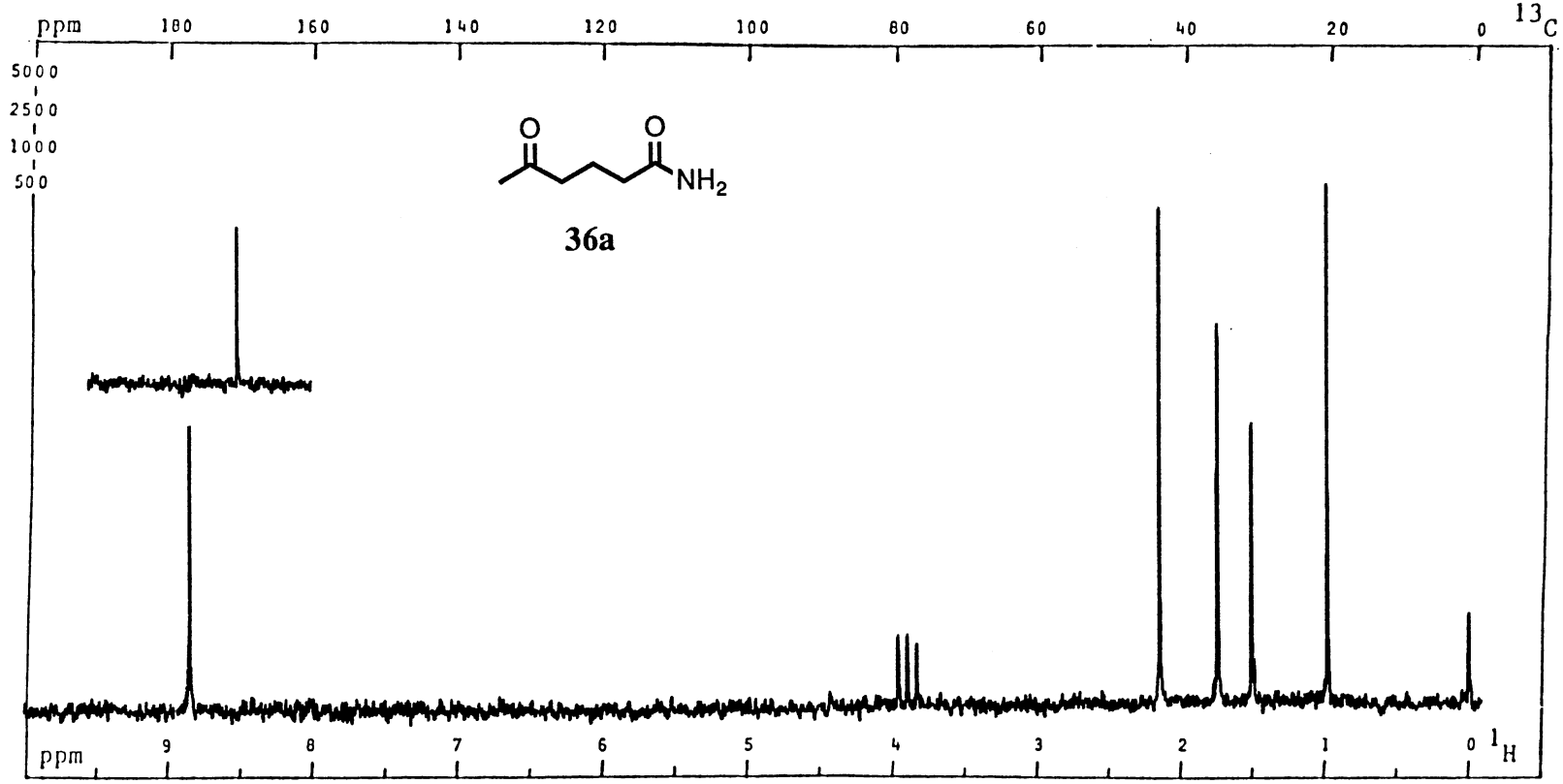

**Spectrum 8.** $^{13}C$ NMR of 1,2,3,4,11,11a-Hexahydro-11-methyl-6*H*-pyrimido[1,2-*b*]isoquinolin-6-one (**32b**)



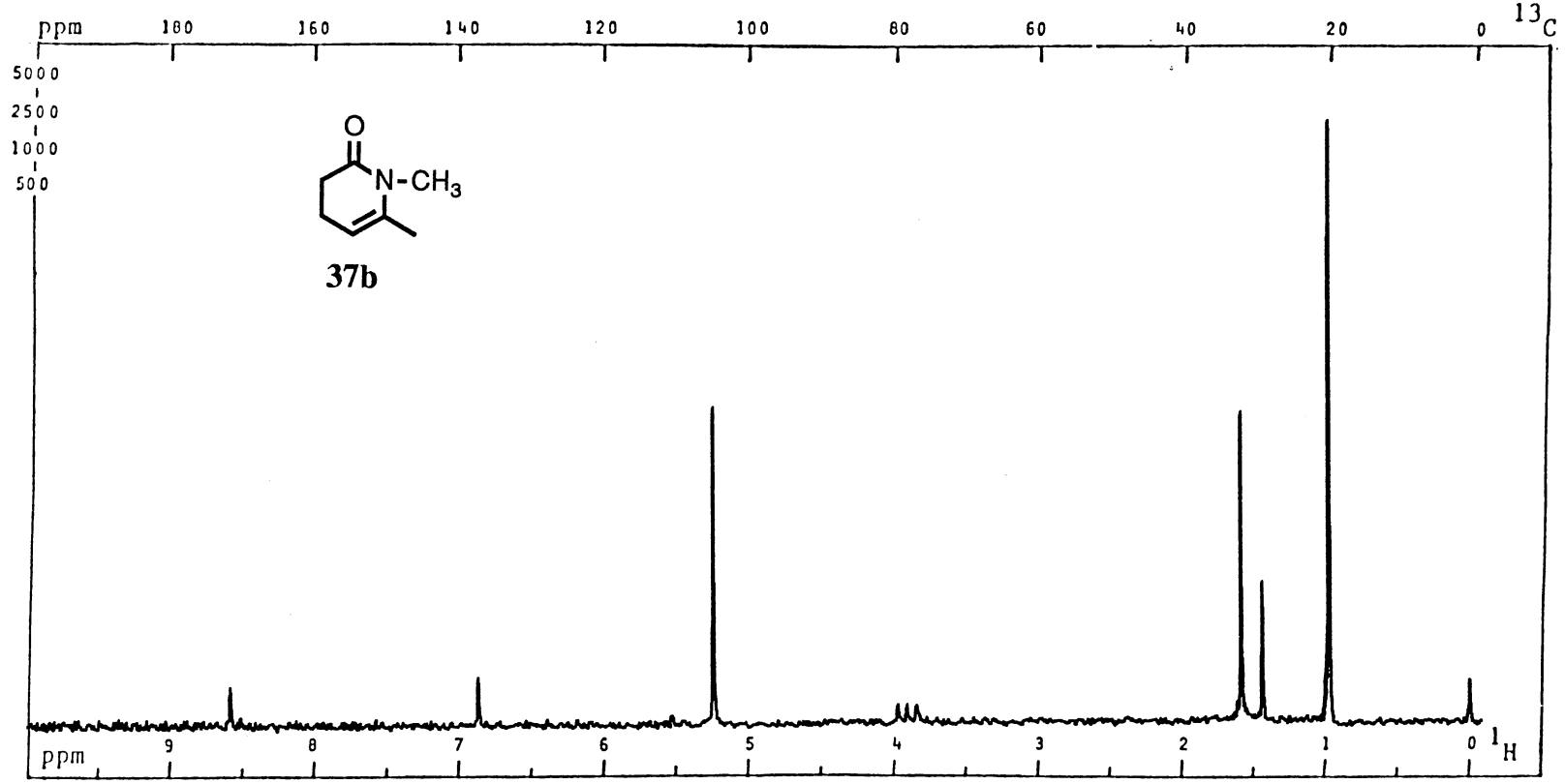

**Spectrum 9.** $^{13}C$ NMR of 3,4-Dihydro-3-hydroxy-4-methyl-1(2*H*)-isoquinolinone (**34a**)



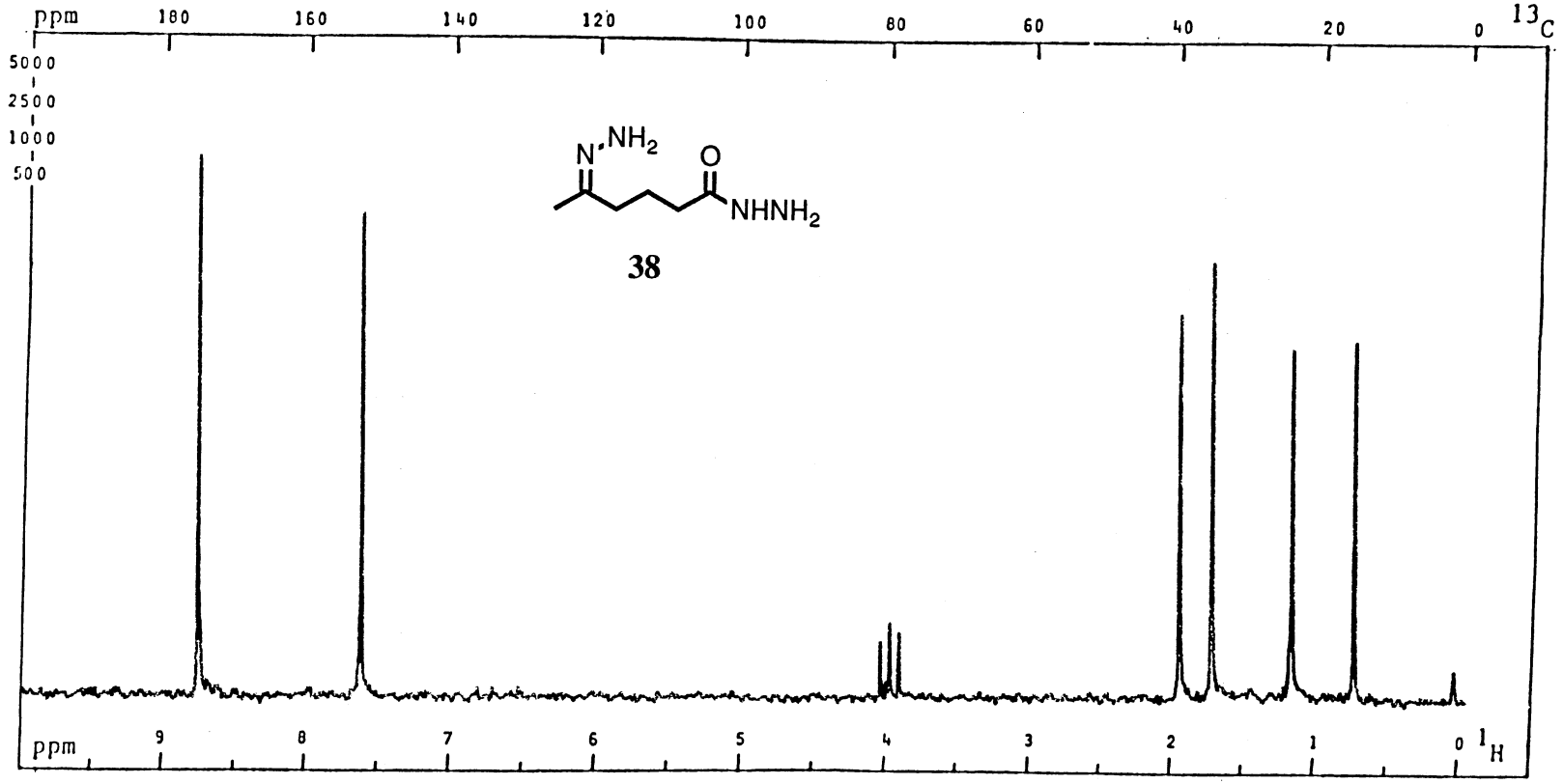

**Spectrum 10.** $^{13}C$ NMR of 6-Hydroxy-6-methyl-2-piperidinone (**35**)



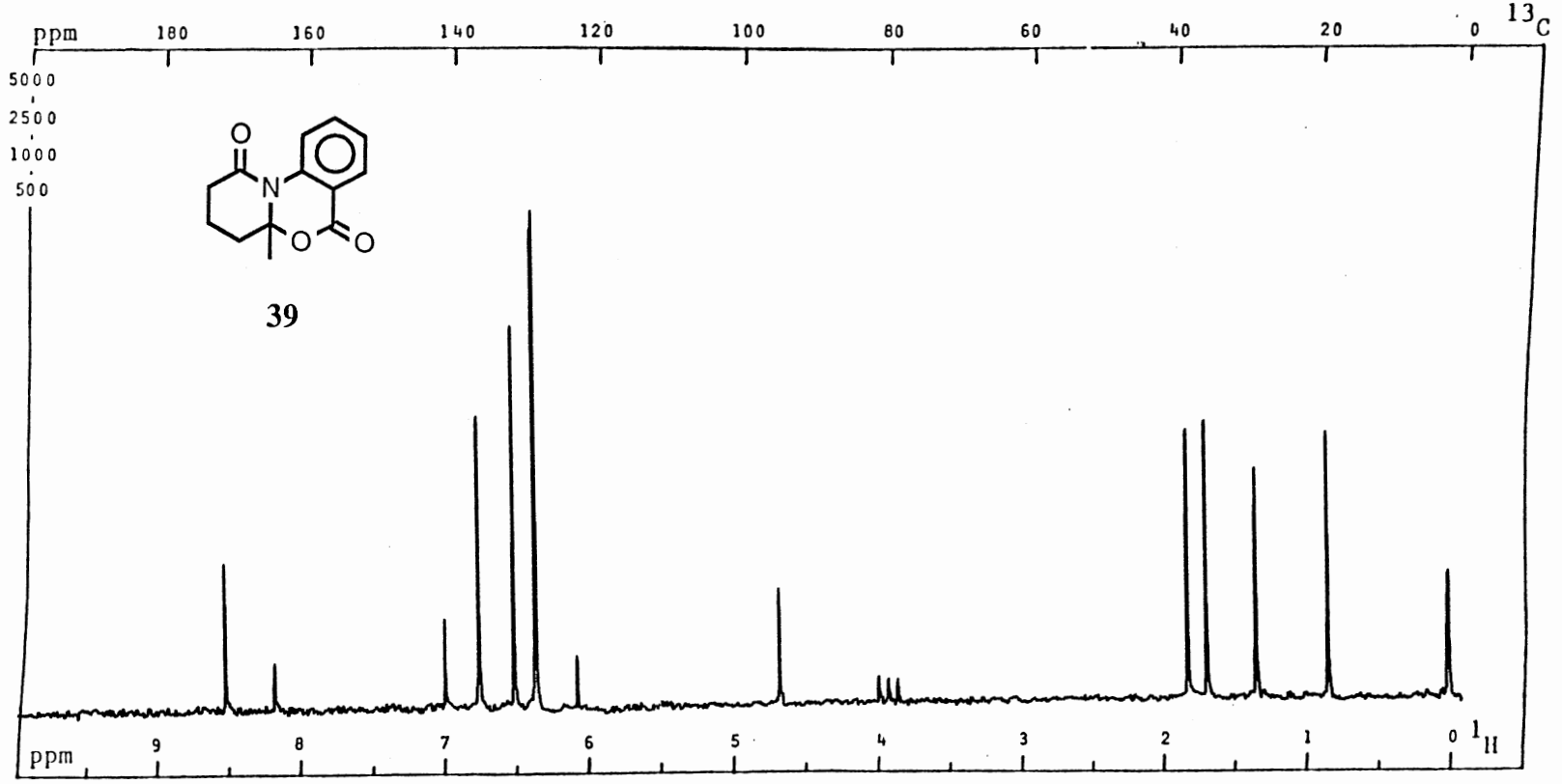

**Spectrum 11.** $^{13}C$ NMR of 5-Oxo-hexanamide (**36a**)



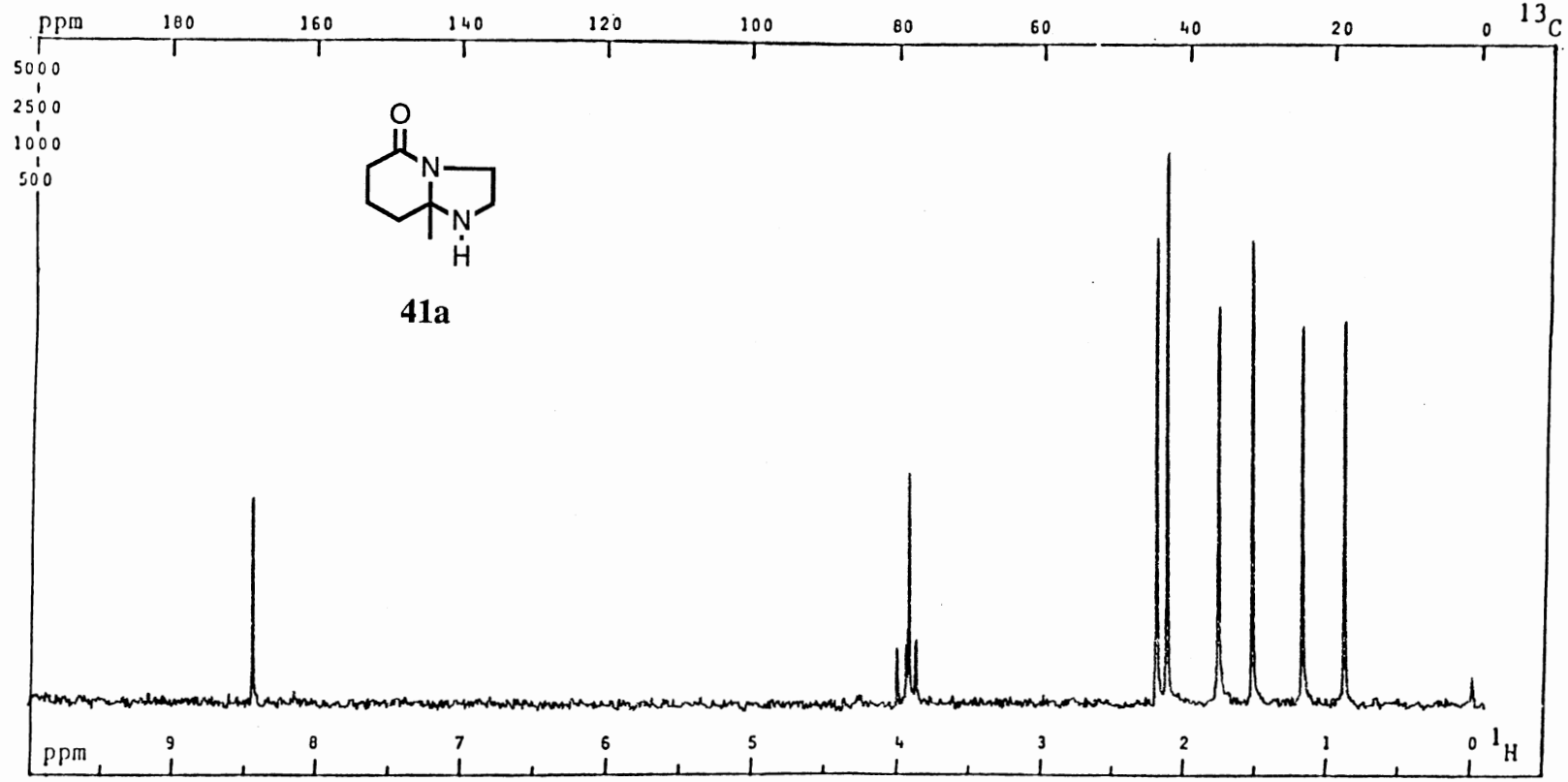

**Spectrum 12.** $^{13}C$ NMR of 3,4-Dihydro-1,6-dimethyl-2(1*H*)-pyridinone (**37b**)



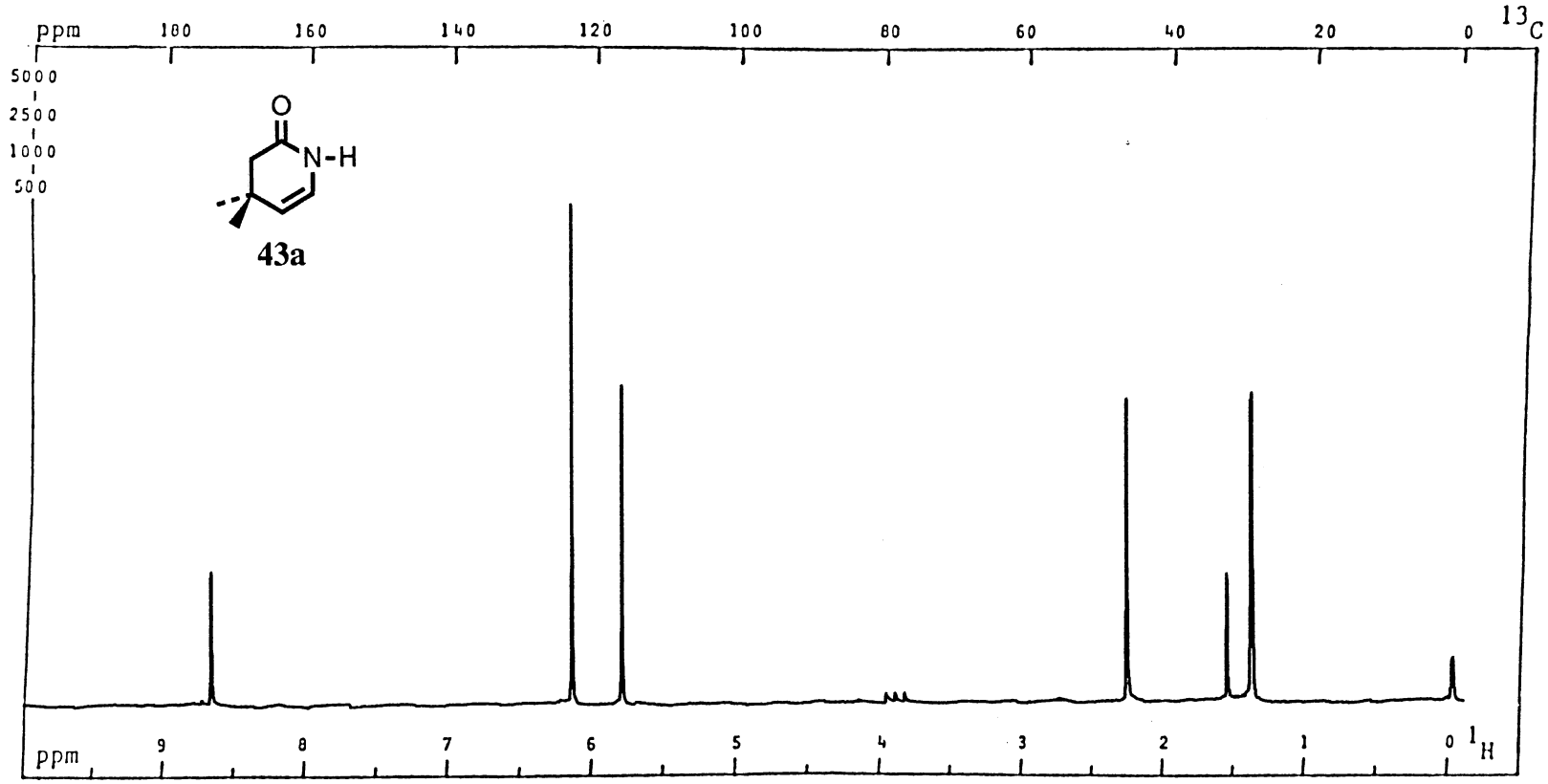

**Spectrum 13.** $^{13}C$ NMR of 5-Hydrazono-hexanohydrazide (**38**)



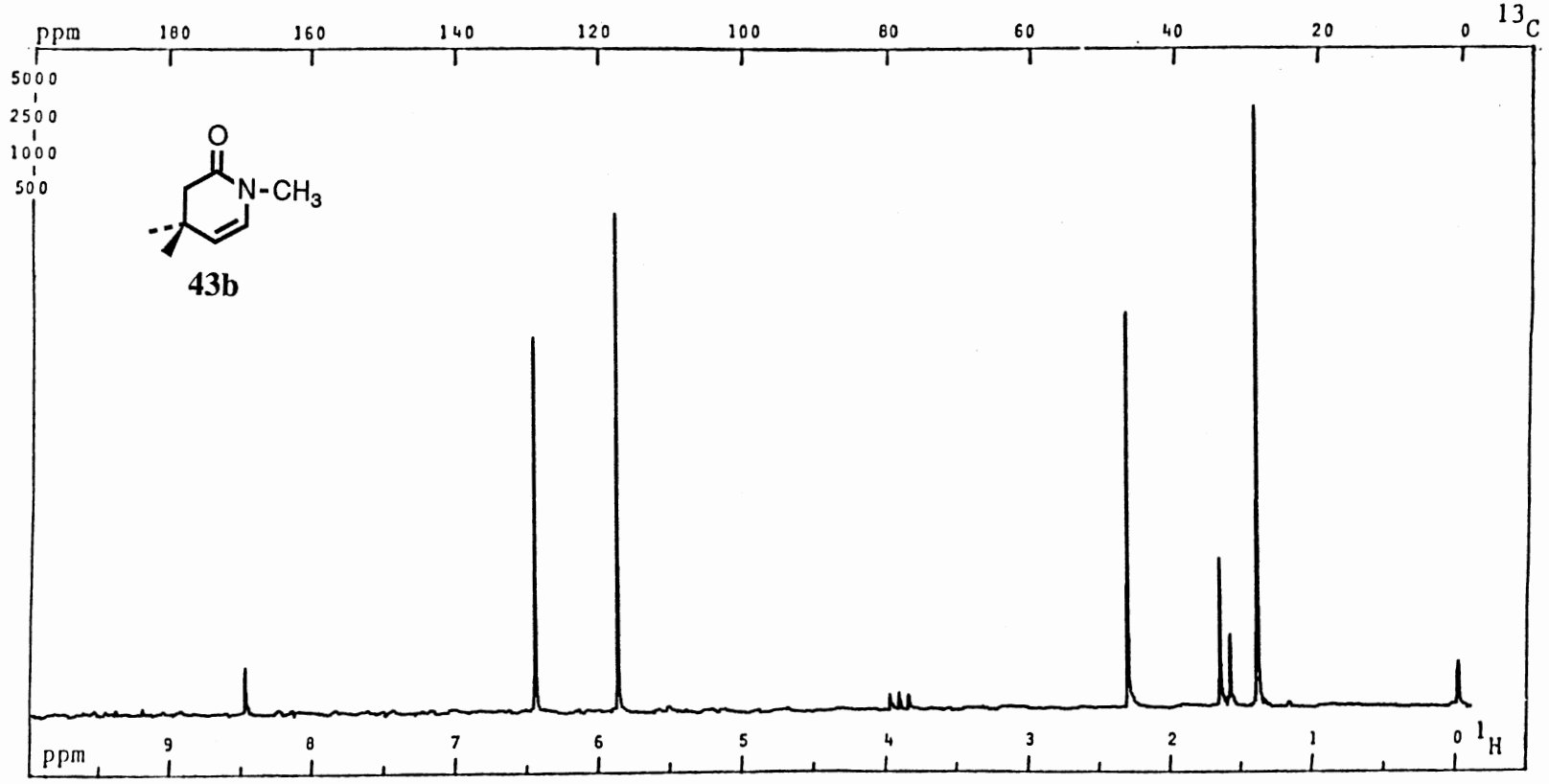

**Spectrum 14.** $^{13}C$ NMR of 2,3,4,4a-Tetrahydro-4a-methyl-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine-1,6-dione (**39**)



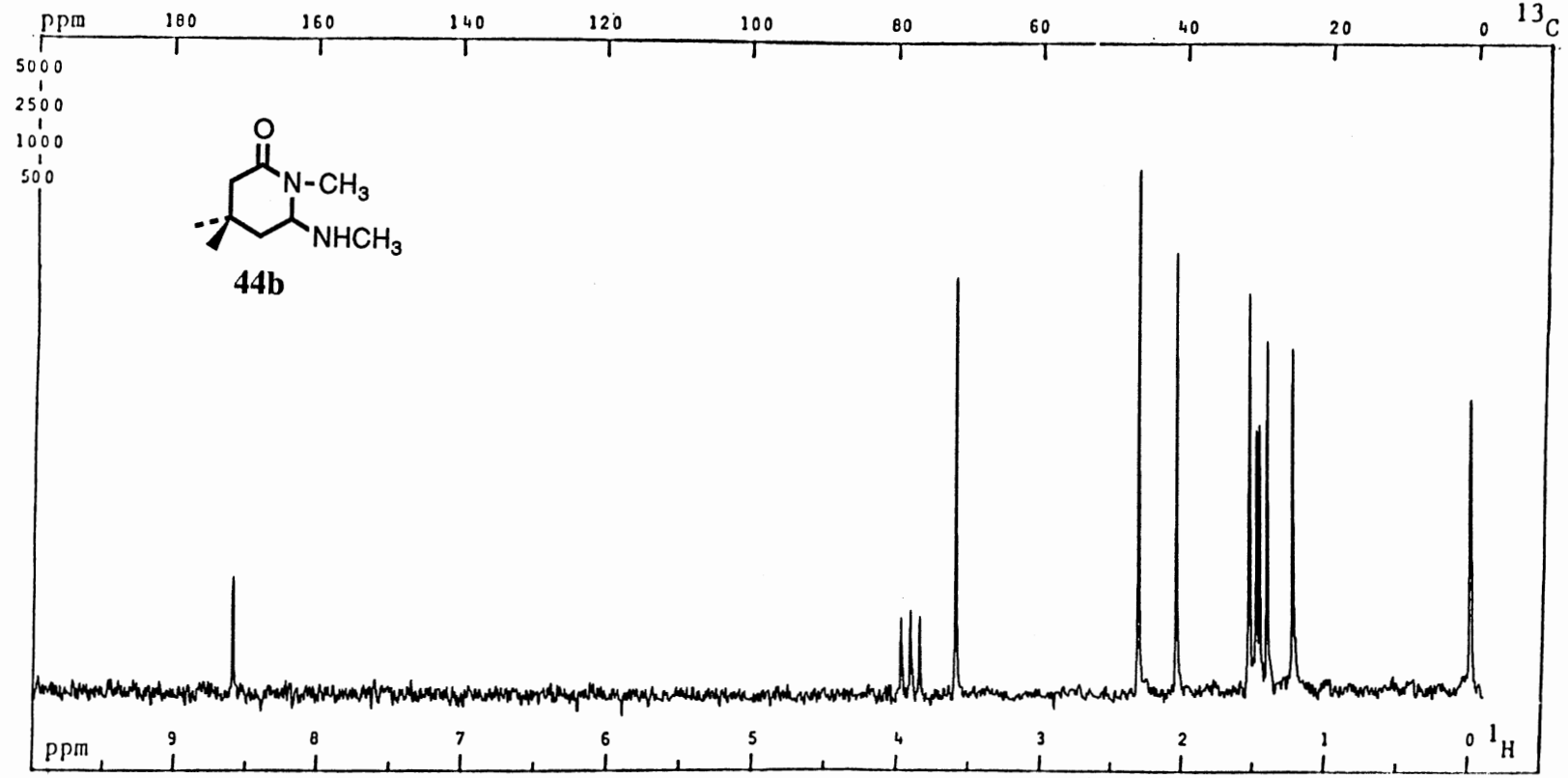

**Spectrum 15.** $^{13}C$ NMR of Hexahydro-8a-methyl-imidazo[1,2-*a*]pyridin-5(1*H*)-one (**41a**)



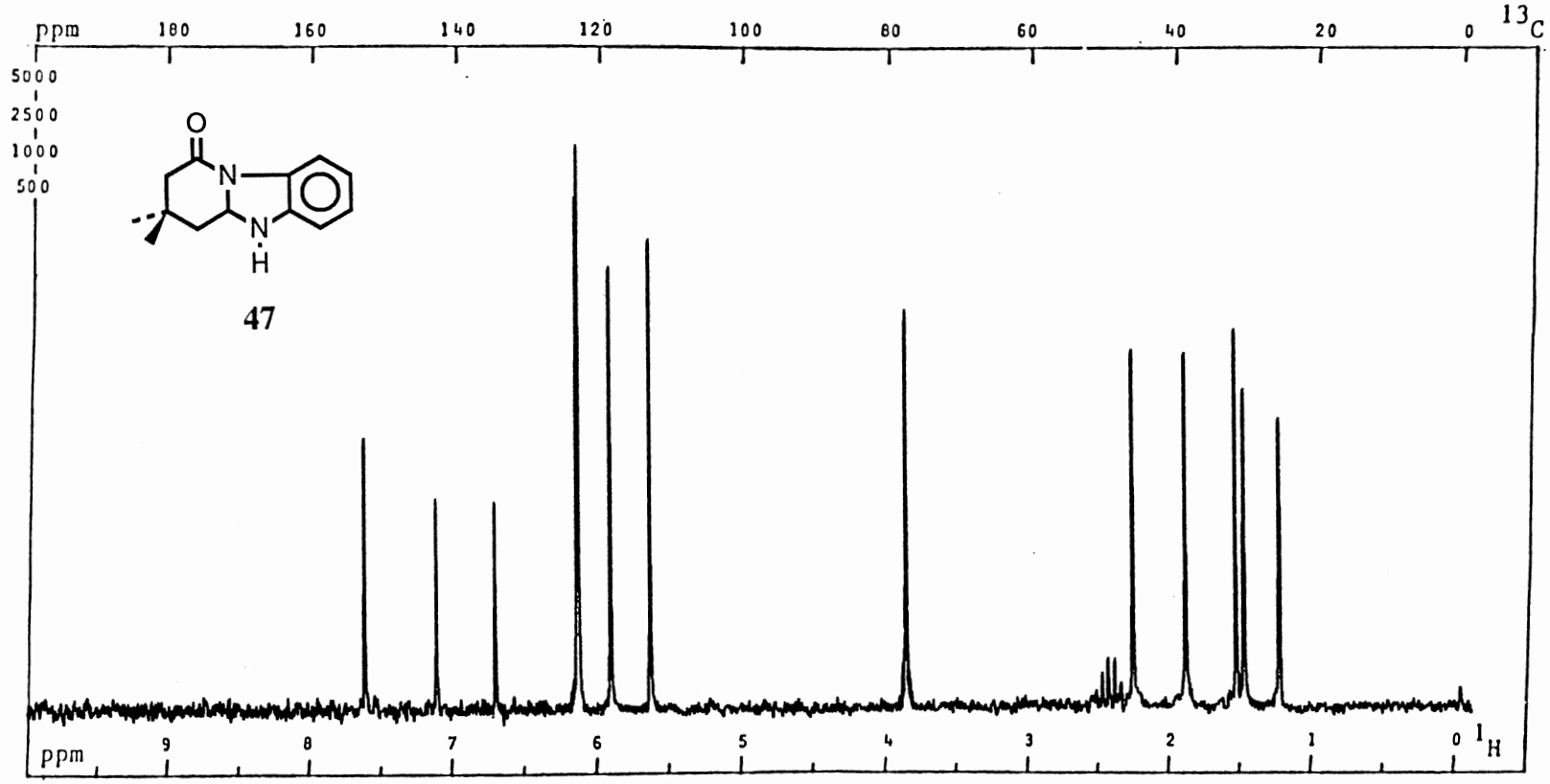

**Spectrum 16.** $^{13}C$ NMR of 3,4-Dihydro-4,4-dimethyl-2(1*H*)-pyridinone (**43a**)



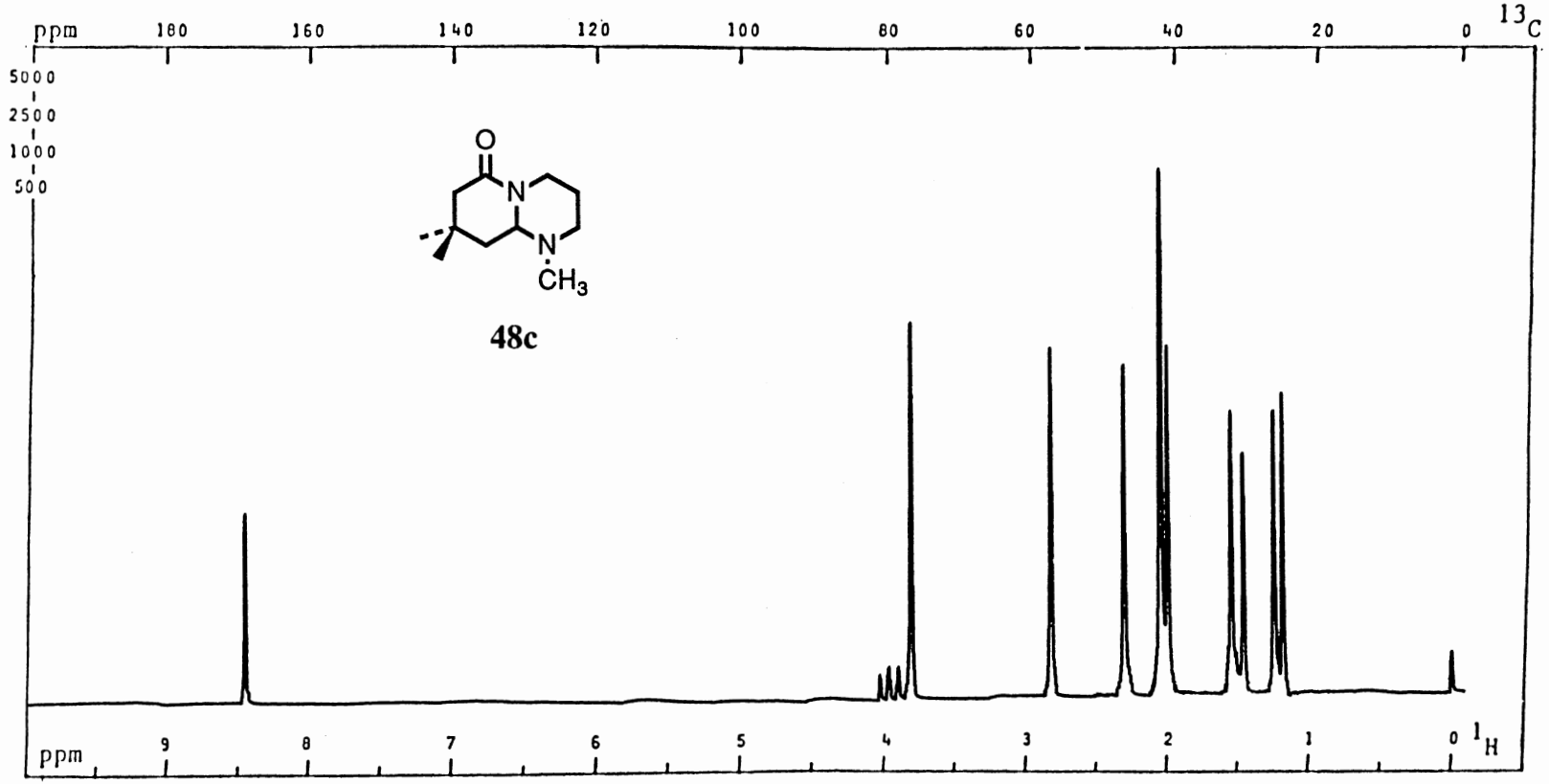

**Spectrum 17.** $^{13}C$ NMR of 3,4-Dihydro-1,4,4-trimethyl-2(1*H*)-pyridinone (**43b**)



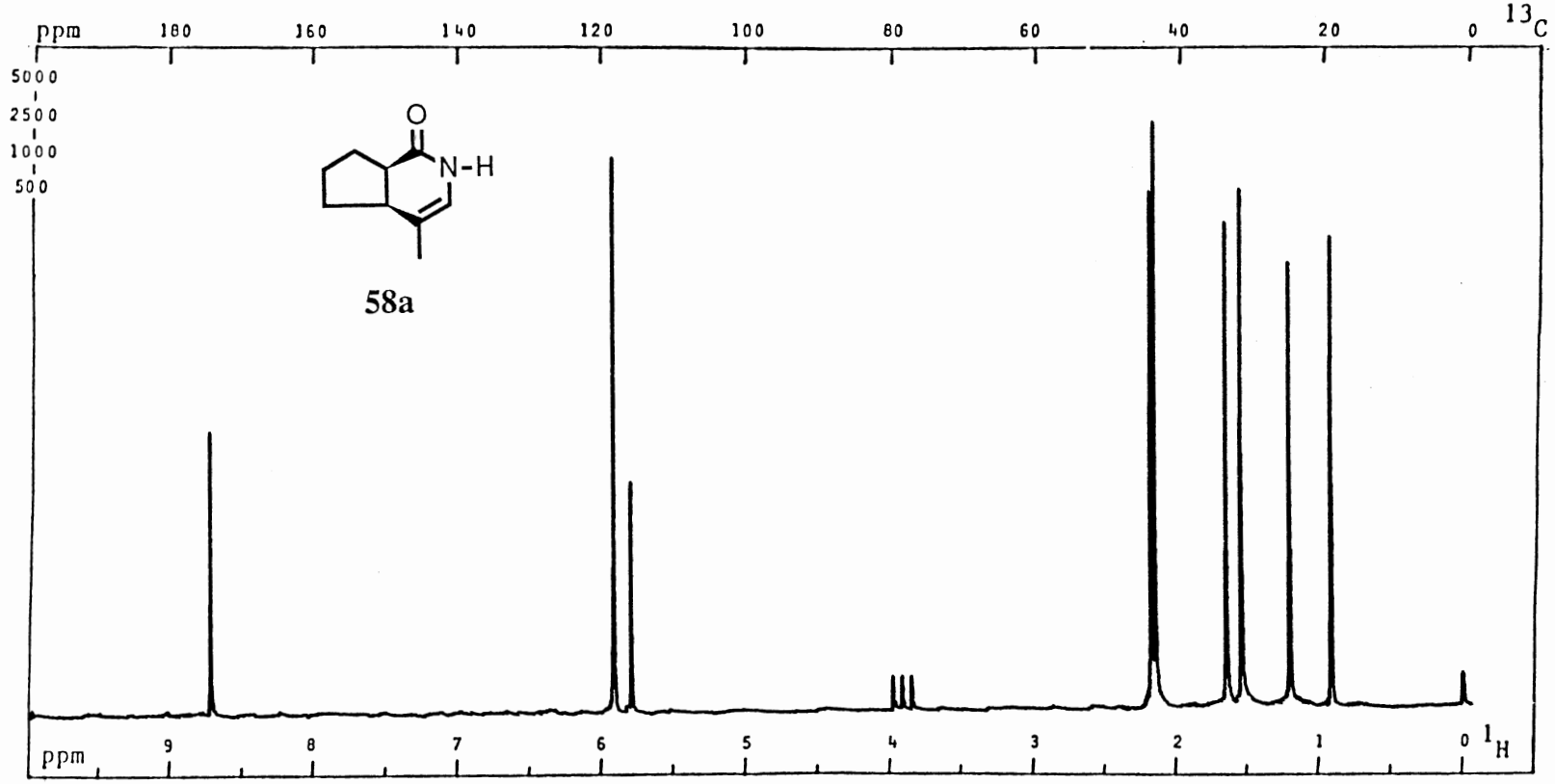

**Spectrum 18.** $^{13}C$ NMR 1,4,4-Trimethyl-6-(methylamino)-2-piperidinone (**44b**)



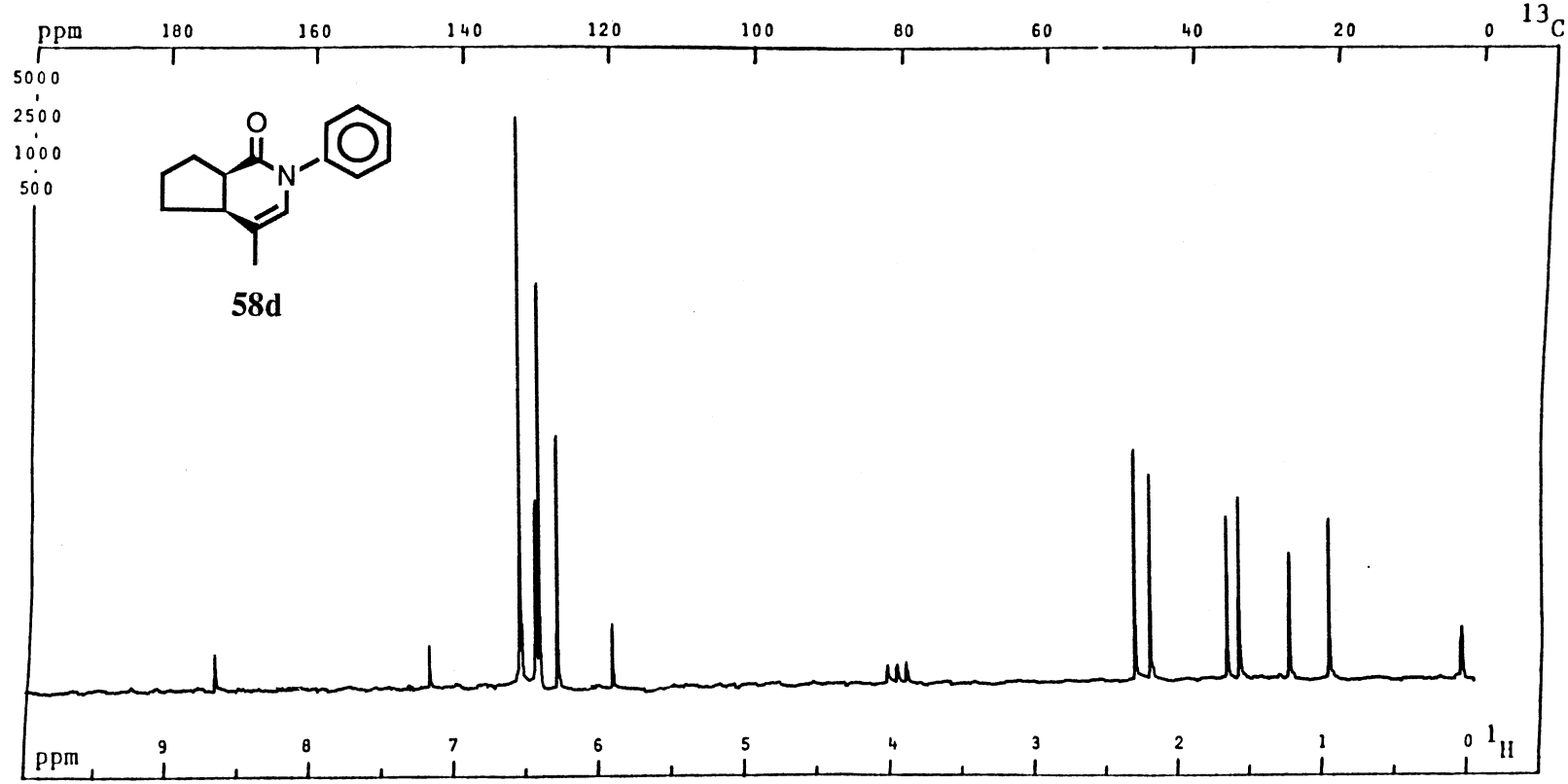

**Spectrum 19.** $^{13}C$ NMR of 3,4,4a,5-Tetrahydro-3,3-dimethyl-6*H*-pyrido[1,2-*a*]benzimidazol-1(2*H*)-one (**47**)



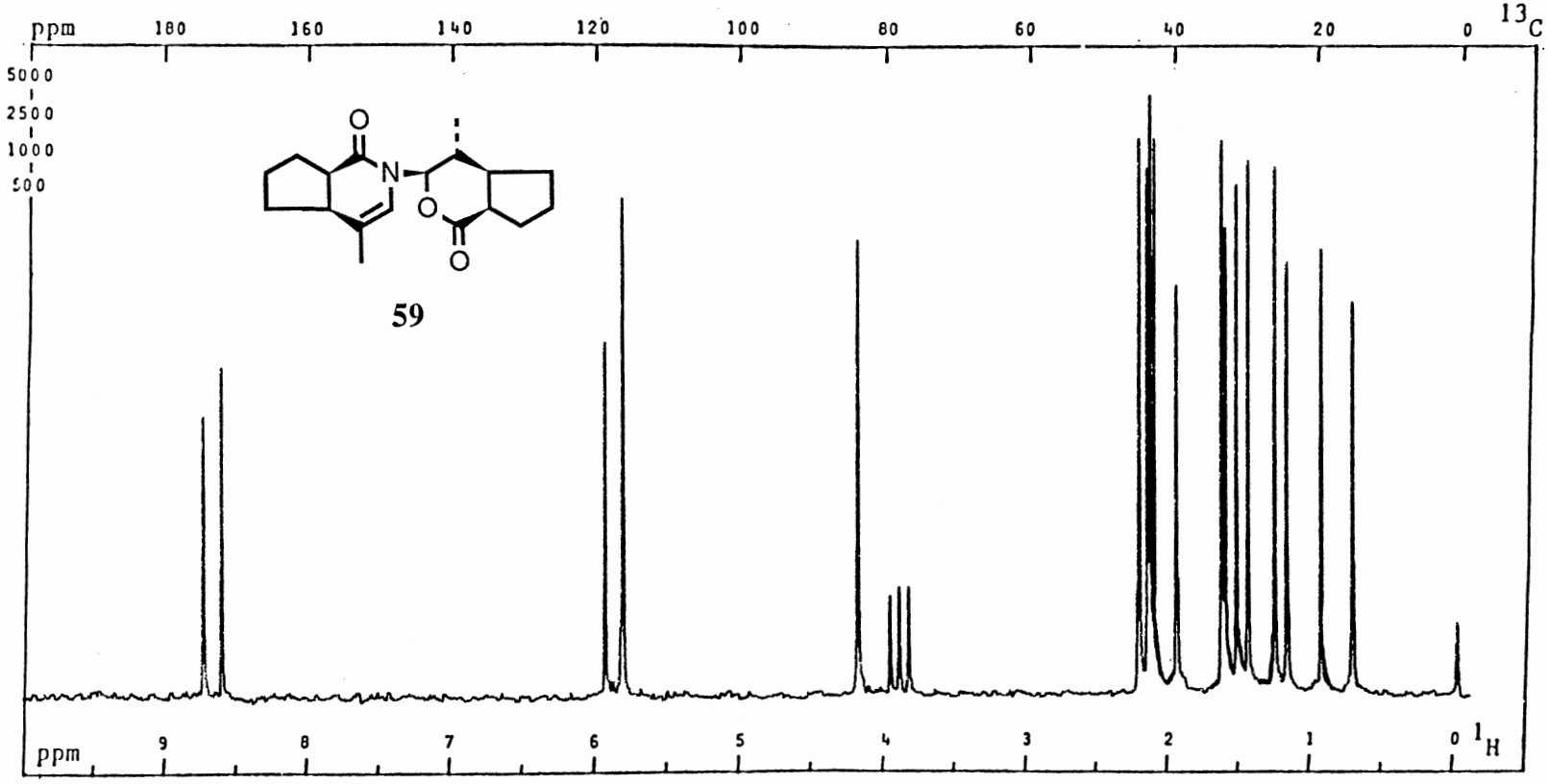

**Spectrum 20.** $^{13}C$ NMR of Octahydro-1,8,8-trimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**48c**)



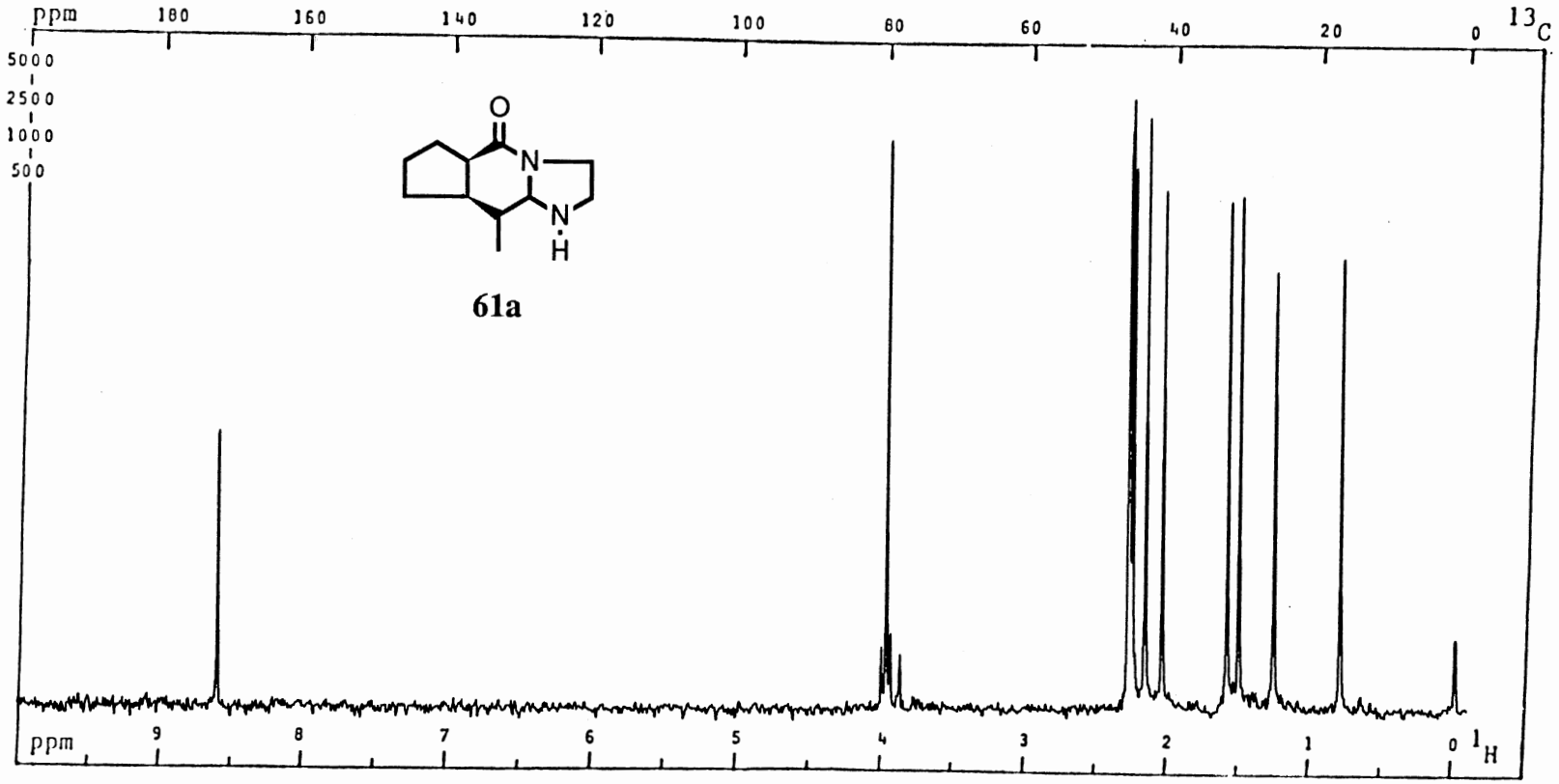

**Spectrum 21.** $^{13}C$ NMR of *cis*-7-Nornepetalactam (**58a**)



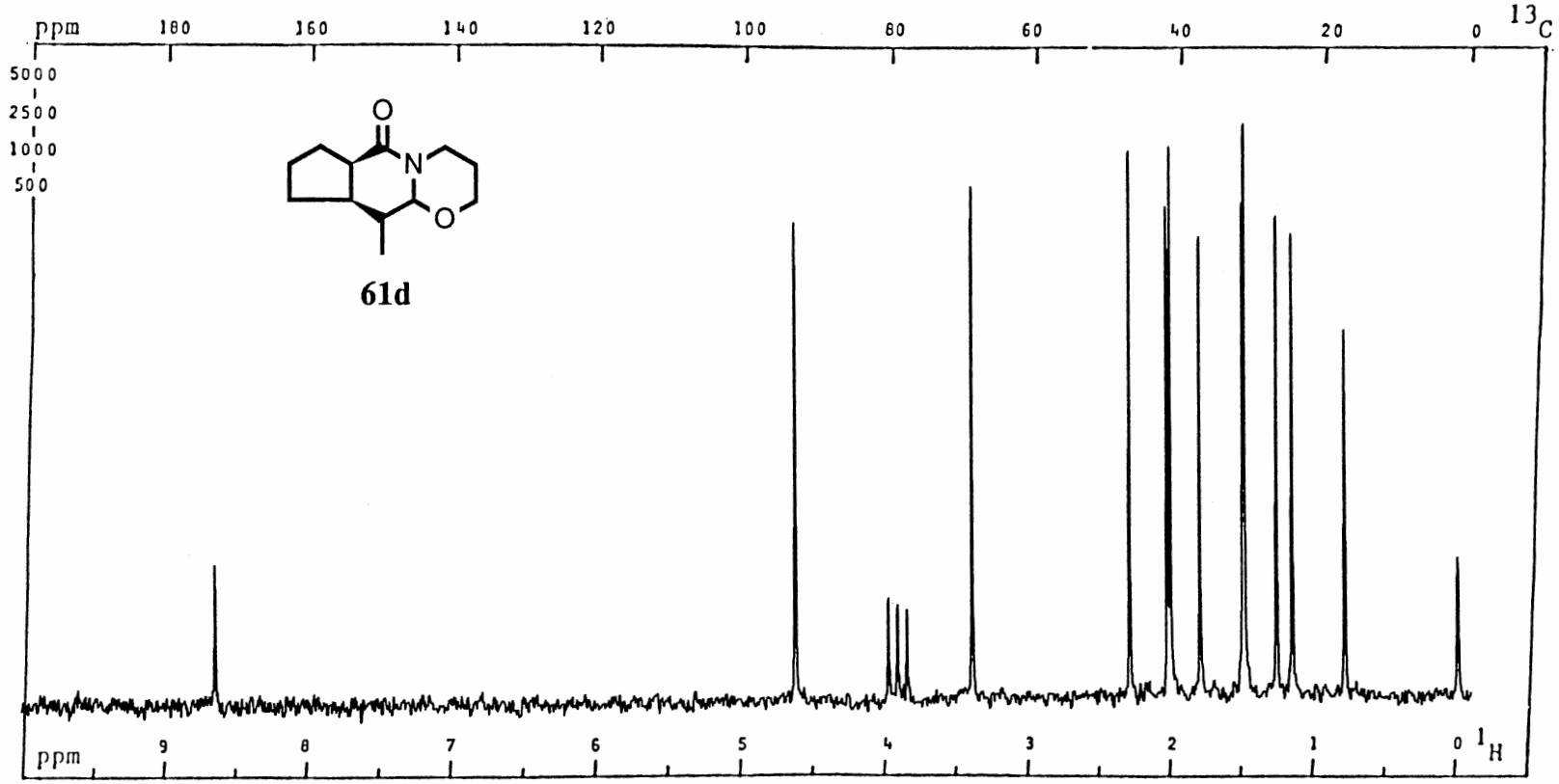

**Spectrum 22.** $^{13}C$ NMR of *cis-N*-Phenyl-7-nornepetalactam (**58d**)



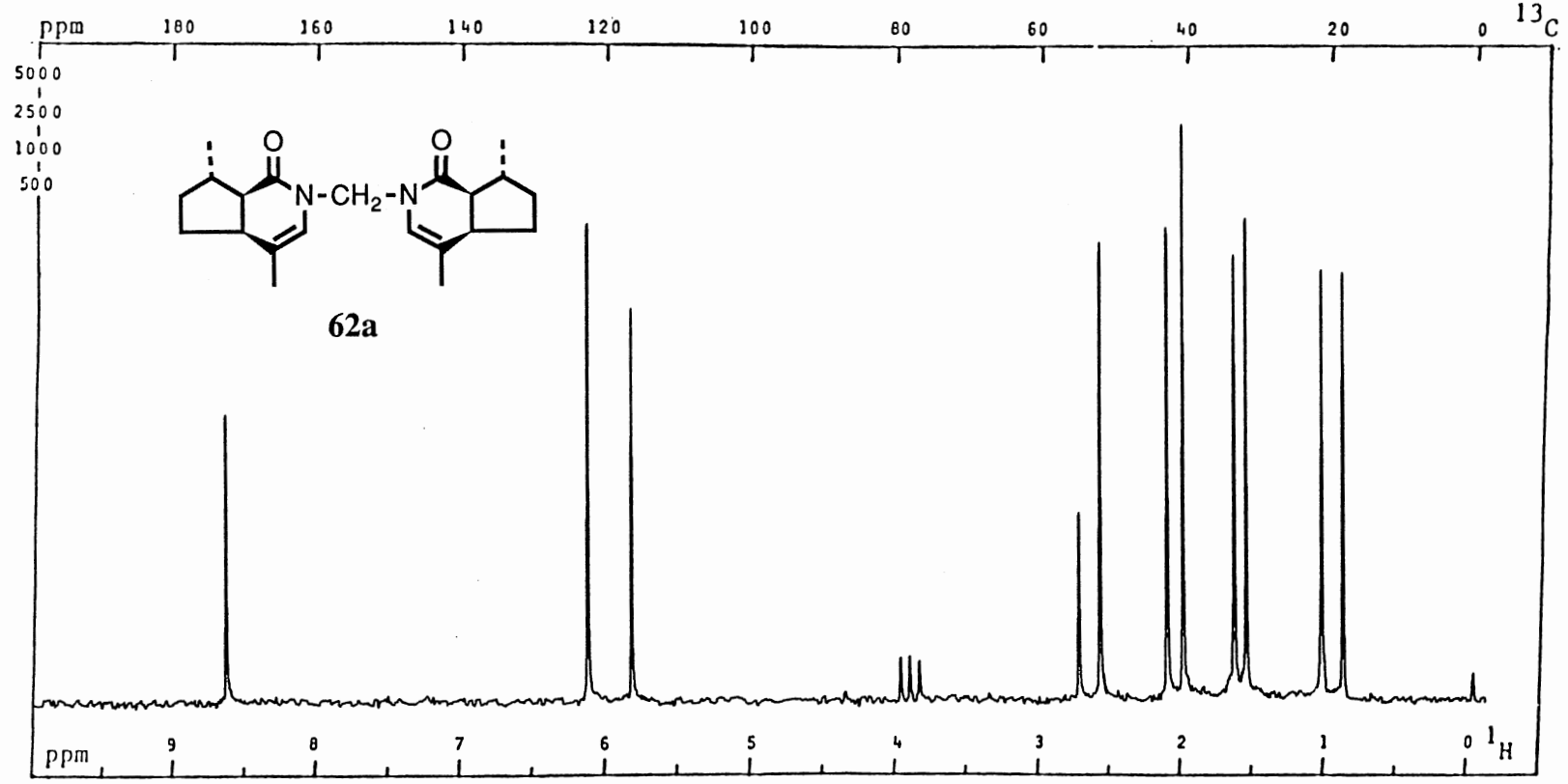

**Spectrum 23.** $^{13}C$ NMR of *N*-(7-Nornepetal-3-yl)-7-nornepetalactam (**59**)




**Spectrum 24.** $^{13}C$ NMR of Decahydro-9-methyl-5*H*-cyclopent[*d*]imidazo[1,2-*a*]pyridin-5-one (**61a**)




**Spectrum 25.** $^{13}C$ NMR of Octahydro-10-methyl-2*H*-cyclopenta[4,5]pyrido[2,1-*b*][1,3]oxazin-6(6a*H*)-one (**61d**)




**Spectrum 26.** $^{13}C$ NMR of *N,N'*-Methylenebis[[4a*S*-(4aα,7α,7aα)]-nepetalactam] (**62a**)

v

# VITA

David Wayne Sullins

Candidate for the Degree of

Doctor of Philosophy

Thesis: REACTIONS OF SIX-MEMBERED ENOL LACTONES AND CORRESPONDING HYDROXY LACTONES WITH AMMONIA AND PRIMARY AMINES

Major Field: Chemistry

Biographical:

Personal Data: Born in Hoboken, New Jersey, October 31, 1958, the son of Alvin Ray and Shirley Ann Sullins.

Education: Graduated from Blackwell High School, Blackwell, Oklahoma, in May, 1976; received Associate of Science Degree in Chemistry from Northern Oklahoma College in May, 1978; Received Bachelor of Science Degree in Chemistry from Oklahoma State University in May, 1981; completed requirements for Doctor of Philosophy degree at Oklahoma State University in May, 1987.

Professional Experience: Teaching Assistant, Department of Chemistry, Oklahoma State University, 1981-1986; Skinner Fellow, Oklahoma State University, 1981-1982; Conoco Summer Fellow, Oklahoma State University, 1982, 1983, and 1985; Dow Summer Fellow, Oklahoma State University, 1984; Phillips Summer Fellow, Oklahoma State University, 1986; Graduate Research Assistant, Department of Chemistry, 1986. Member of Phi Lambda Upsilon, Honorary Chemical Society, and the American Chemical Society.