# LACTAMS FROM THE REACTIONS OF ENELACTONES WITH AMINO ACIDS AND AMINO ESTERS

By

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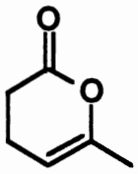
| | | | |
|---|---|---|---|
| Ar | aromatic | q | quartet |
| $^{o}C$ | degrees Celcius | s | singlet |
| $\delta$ | chemical shift in ppm downfield from TMS | TMS | tetramethylsilane |
| | | t | triplet |
| COSY | correlation spectroscopy | | |
| DMSO | dimethyl sulfoxide | | |
| dd | doublet of doublets | | |
| qd | quartet of doublets | | |
| EI | electron impact | | |
| HETCOR | heteronuclear correlation | | |
| HR | high resolution | | |
| g | gram(s) | | |
| h | hour(s) | | |
| mp | melting point | | |
| m | multiplet | | |
| M | moles per liter | | |
| mg | milligram(s) | | |
| min | minute(s) | | |
| mL | milliliter(s) | | |
| mmol | millimole(s) | | |
| NMR | nuclear magnetic resonance | | |
| ppm | parts per million | | |

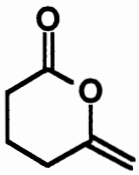
CHAPTER I

## Introduction and Historical

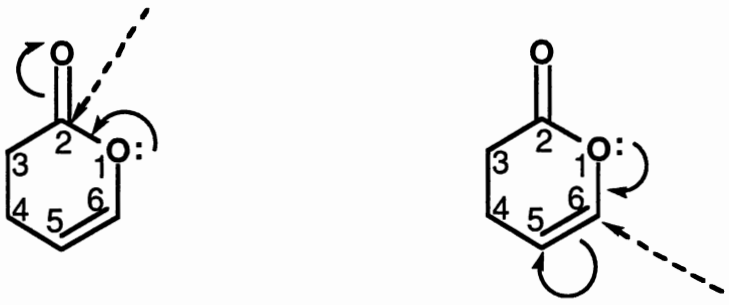
Gamma- and δ-enelactones (enol-lactones), products derived from γ- and δ–oxoacids, have long been known to possess biological activity. The heart action of the cardiac glycoside digitalin[1] is an example of the activity of a γ-enelactone. The recently established identity of nepetalactone as a sex pheromone in aphids[2] and the well-known response of felines[3] to the nepetalactones derived from *Nepeta cataria L.*[4] and *Nepeta mussini L.* [5] demostrate that the δ–enelactones also can have a pronounced physiological activity.

The double bond adjacent to the heteroatom, either endo or exo to the ring as shown for the following examples, is responsible for the chemical behavior of δ-enelactones.[6]

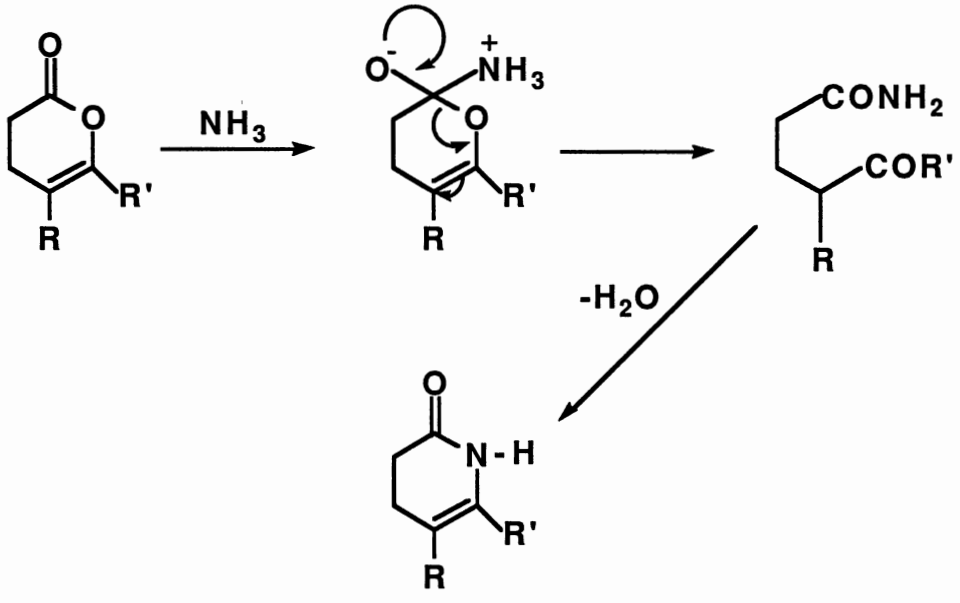




The ring carbon atoms 2 and 6 relative to the hetero oxygen atom are partially positively charged. Thus, this type of enelactone becomes highly reactive toward nucleophilic reagents. The initial attack of these reagents at one of the carbon atoms mentioned above has been reported to cleave the 1,2- or the 1,6-bond to form an open-chain intermediate.[6,7]

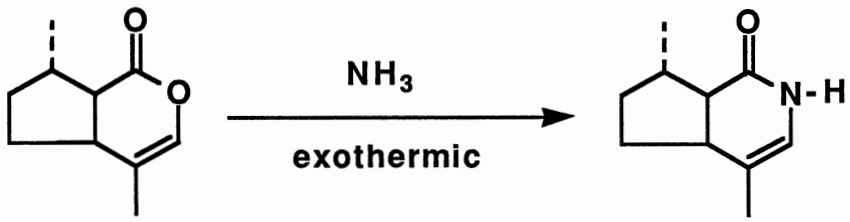


Ammonia and amines have been known to cleave the δ-enelactone ring at the 1,2-bond. Delta-aldehydo or keto amides are formed which, depending on their structure, can be dehydrated with varying ease into the corresponding 5,6-enelactams.[6]

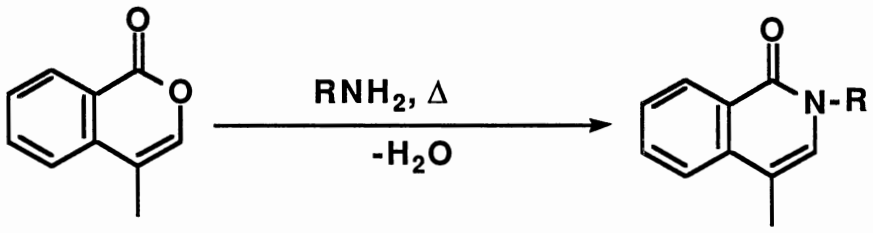



**where R = $CH_2CH_3$ and R' = $C_6H_5$**

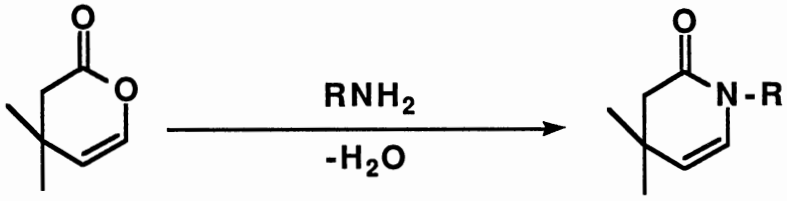
Earlier work in this laboratory [8,9] established that nepetalactone is readily converted to nepetalactam by direct exposure to ammonia as follows:



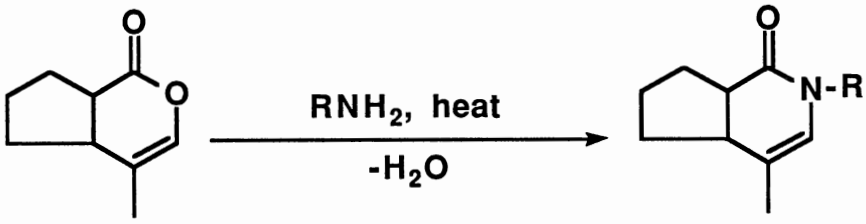
It has also been shown that treatment of other δ-enelactones, with ammonia, hydrazine, primary aliphatic and aromatic amines, and primary amines that contained a second functional group provides a general route[9,10,11] to N-substituted enelactams as shown below.




R = H, $NH_2$, $CH_3$, $CH_2CH_2OH$




R = $CH_2CH(OCH_3)$, $(CH_2)_3N(CH_3)_2$, $C_6H_5$, 2-$H_3CO_2CC_6H_4$




R = H, $CH_2CH(OCH_3)$, $C_6H_5$

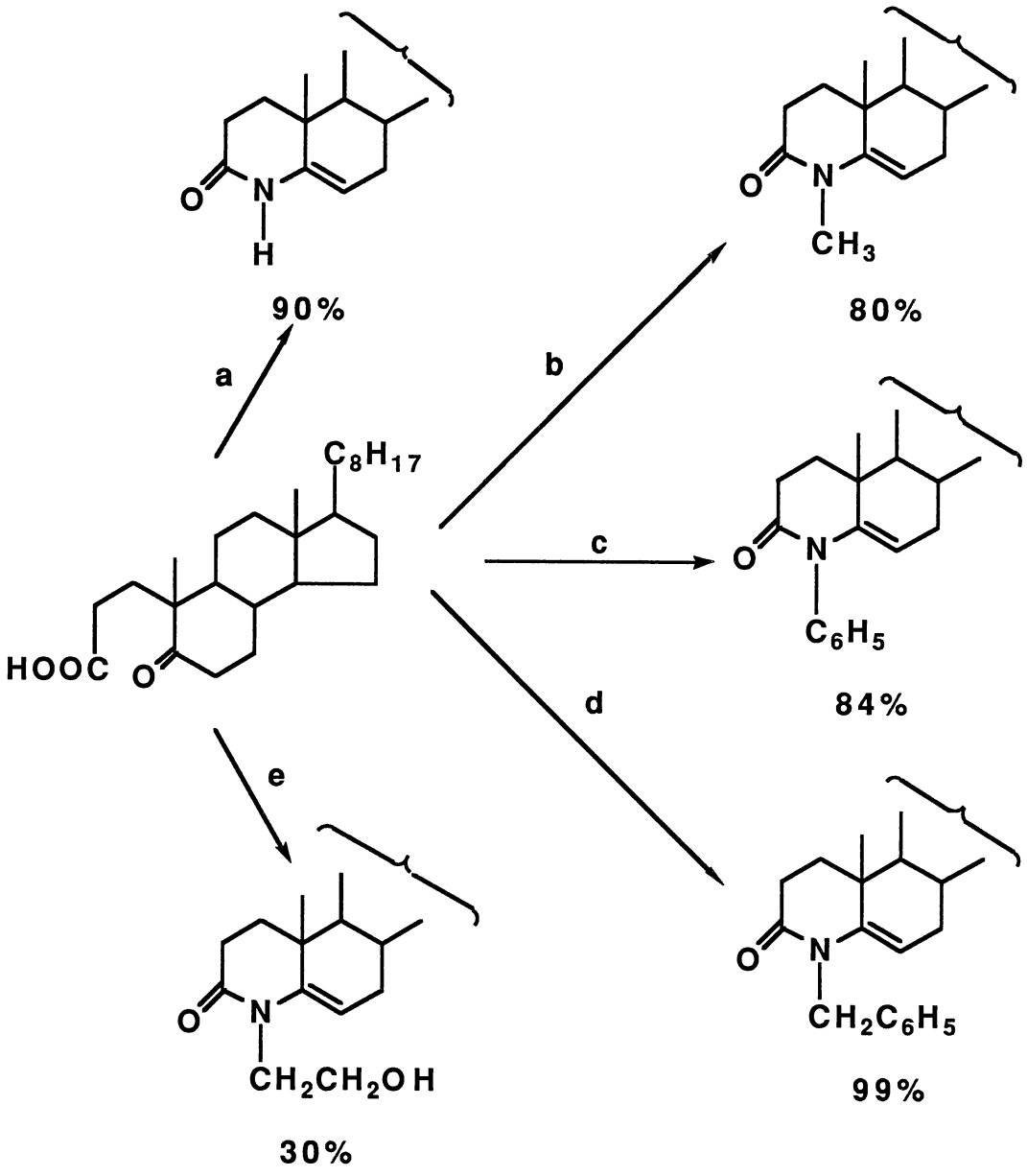
Steroids containing nitrogen also have been prepared to study their biological activity and for use as synthetic intermediates.[12] Nitrogen atoms have been introduced into the steroid nucleus in the form of lactams prepared from seco-keto acids (Figure 1) and oxa-steroids (Figure 2) under varying reaction conditions.

3-Benzylidenephthalide, a γ-enelactone, has been studied extensively. It is known to react with aqueous ammonia to form 3-benzylidenephthalimidine.[13-16] Its reaction with primary aliphatic and aromatic amines and phenylhydrazine gave N-substituted benzylidenephthalimidenes as shown below in Figure 3.[17-25]

3-Benzylidenephthalide has been known to contaminate clinically used phenindione (2-phenyl-1,3-indandione) tablets and was found to possess a high protein reactivity. At physiological conditions of pH and temperature, this contaminant reacts readily with proteins and amino acids in aqueous solutions to form N-substituted 3-benzyl-3-hydroxyphthalimidine derivatives.[26] The analysis of 3-benzylidenephthalide in phenindione tablets involved mixing a dioxane solution of the isolated contaminant with an aqueous alkaline (pH 9.5) solution of glycine and heating the mixture on a steam bath for 5 h to give 2-carboxymethyl-3-hydroxy-1-oxo-3-phenylmethyl-1*H*-isoindole (Figure 4). The dehydration to form 2-carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole was effected with concentrated acetic acid. The above reaction sequence is related to the work in this thesis.

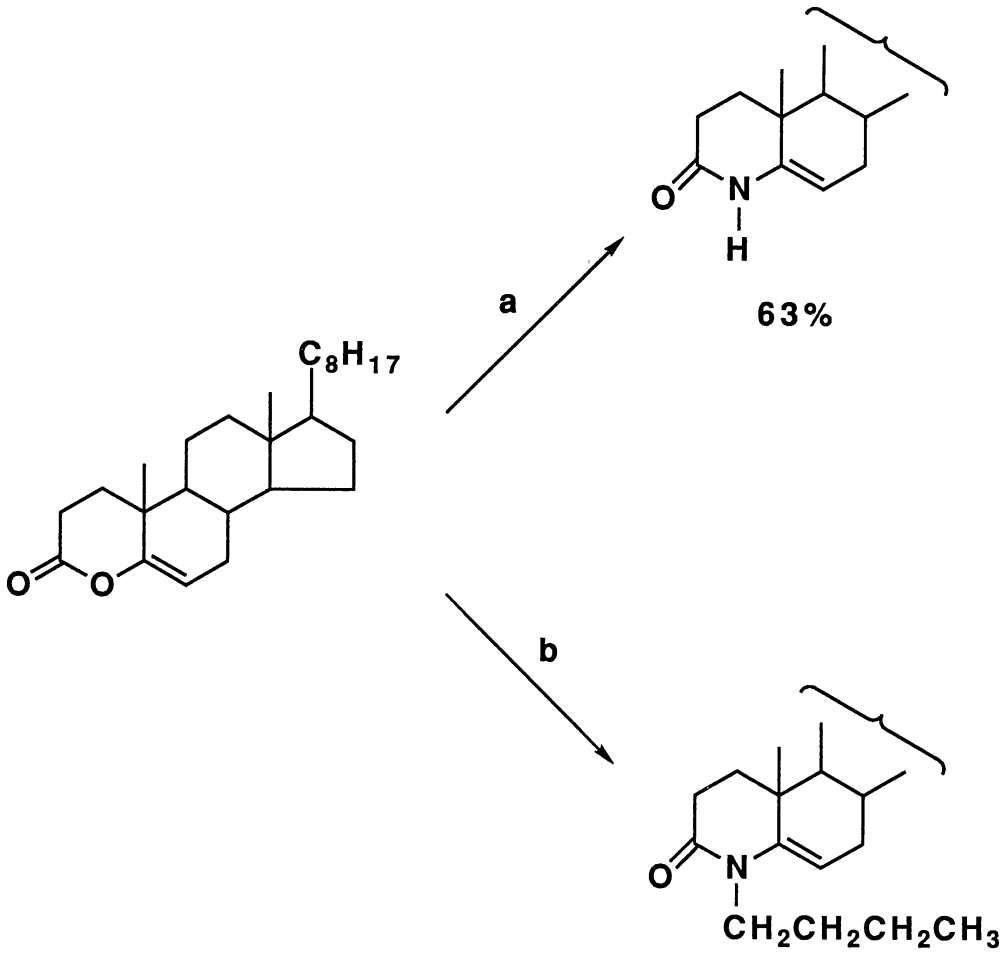
The formation of 2-carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole and its conversion to methyl ester upon treatment with diazomethane has been reported (Figure 5).[27]

A number of substituted pyrrole derivatives have been reported as products from the reaction of 3-benzylidenephthalide with α-amino acids (Figure 6).[28]



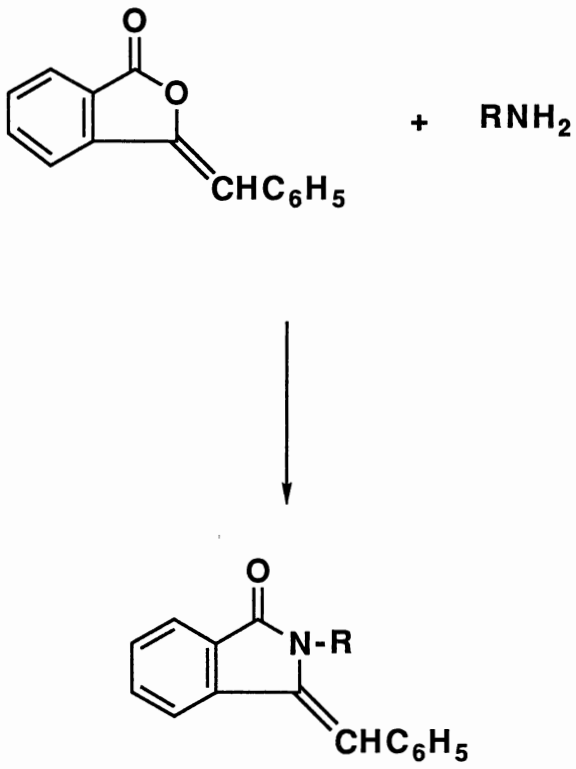

[a]"$NH_3$ solution", $(NH_4)_2CO_3$, 200 $^0$C, 40 h; [b]$CH_3NH_2$, $CH_3CH_2OH$, 140 $^0$C, 8 h; [c]$C_6H_5NH_2$, $N_2$, 180 $^0$C, 11 h; [d]$C_6H_5CH_2NH_2$, 180 $^o$C, 1 h, $N_2$; [e]$HOCH_2CH_2NH_2$, $C_6H_6$, $\Delta$, 8 h.

**Figure 1.** Steroid Lactams From Seco-keto Acids.




[a]$NH_4OH$, 200 [0]C, 48 h; [b]$CH_3CH_2CH_2CH_2NH_2$.

**Figure 2.** Steroid Lactams From Oxa-steroids.




R = H, $C_6H_5$, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$,
$C_6H_4CONHCH_2COOH$-p, $C_6H_4CH_2COOH$-p,
$C_6H_4COOH$-p, $C_6H_4COCH_3$-p, $NHC_6H_5$

**Figure 3**. Reactions of 3-Benzylidenephthalide With Aqueous Ammonia, Aliphatic and Aromatic Amines, and Phenylhydrazine.

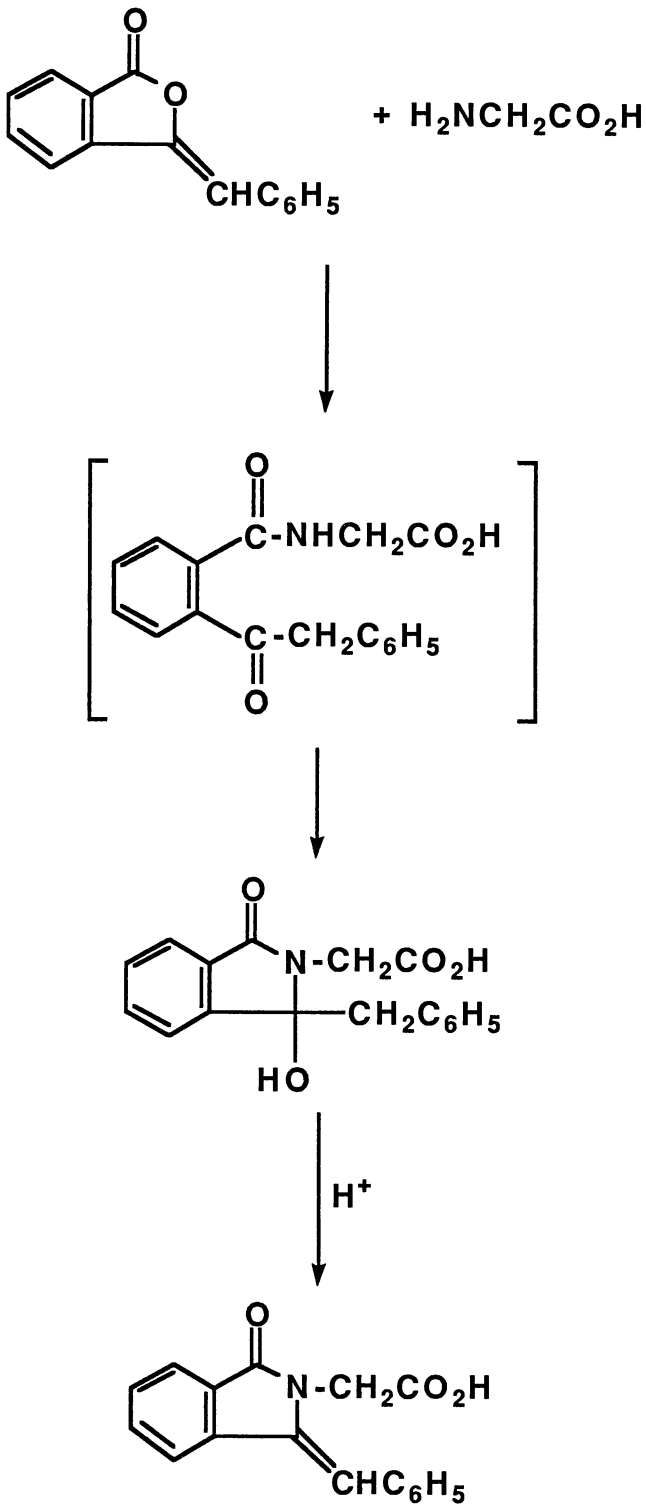
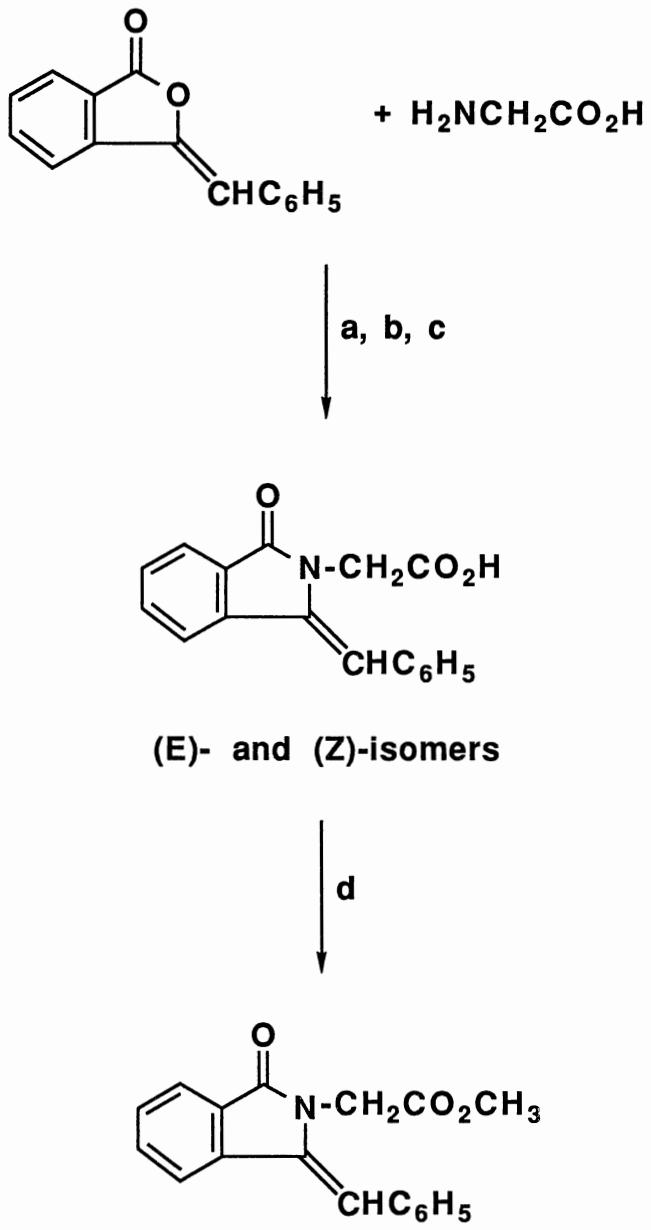
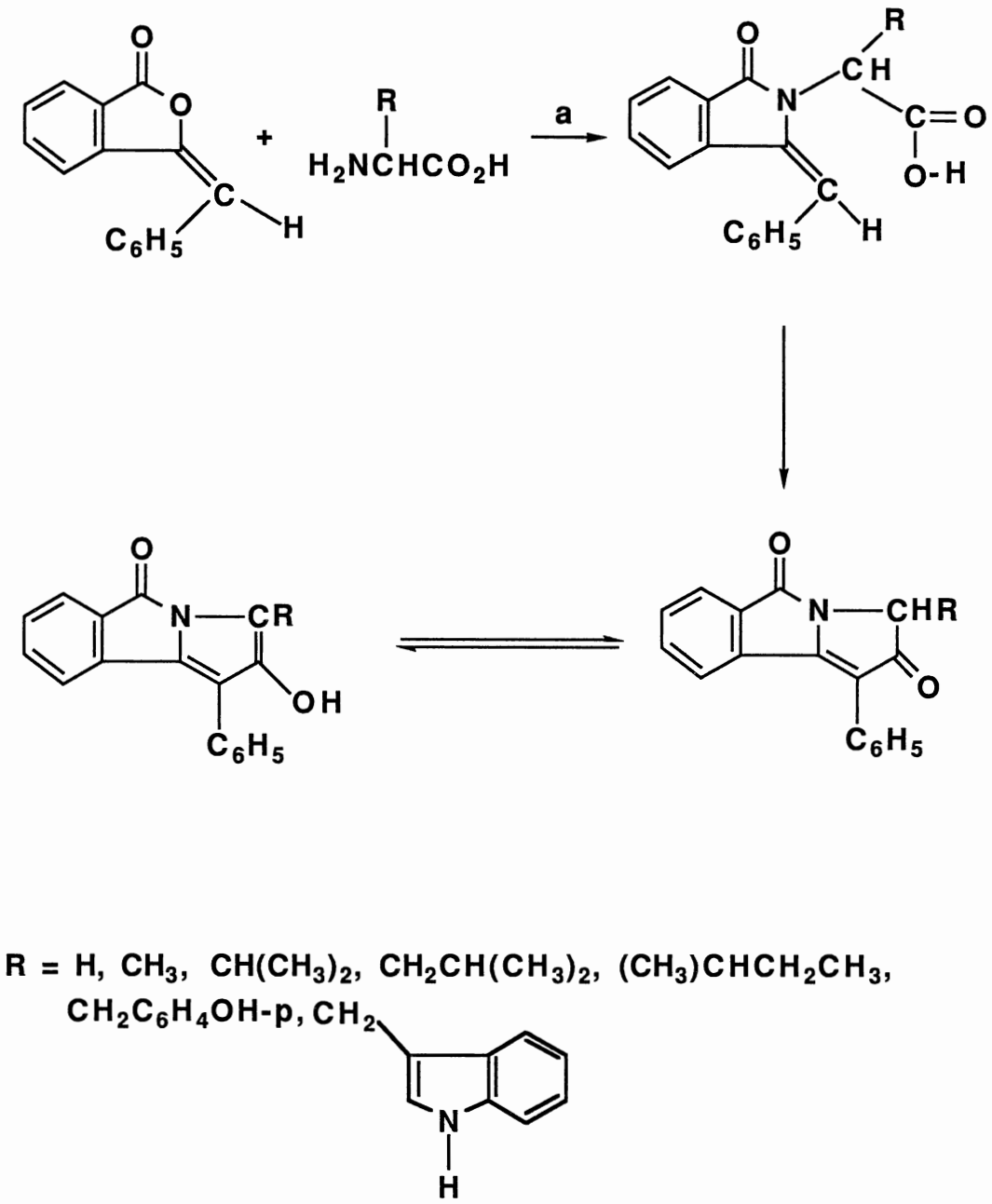



**Figure 4.** Formation of 2-Carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole.




[a]$OH^-$, Δ; [b]$H^+$; [c]Δ; [d]$CH_2N_2$.

**Figure 5**. Formation of 2-Methoxycarbonylmethyl-1-oxo-3-phenylmethylene-1*H*-isoindole.




R = H, $CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $(CH_3)CHCH_2CH_3$, $CH_2C_6H_4OH$-p, $CH_2$




[a] Δ, 220 °C, 5 min.

**Figure 6**. Reactions of 3-Benzylidenephthalide With α-Amino Acids.

CHAPTER II

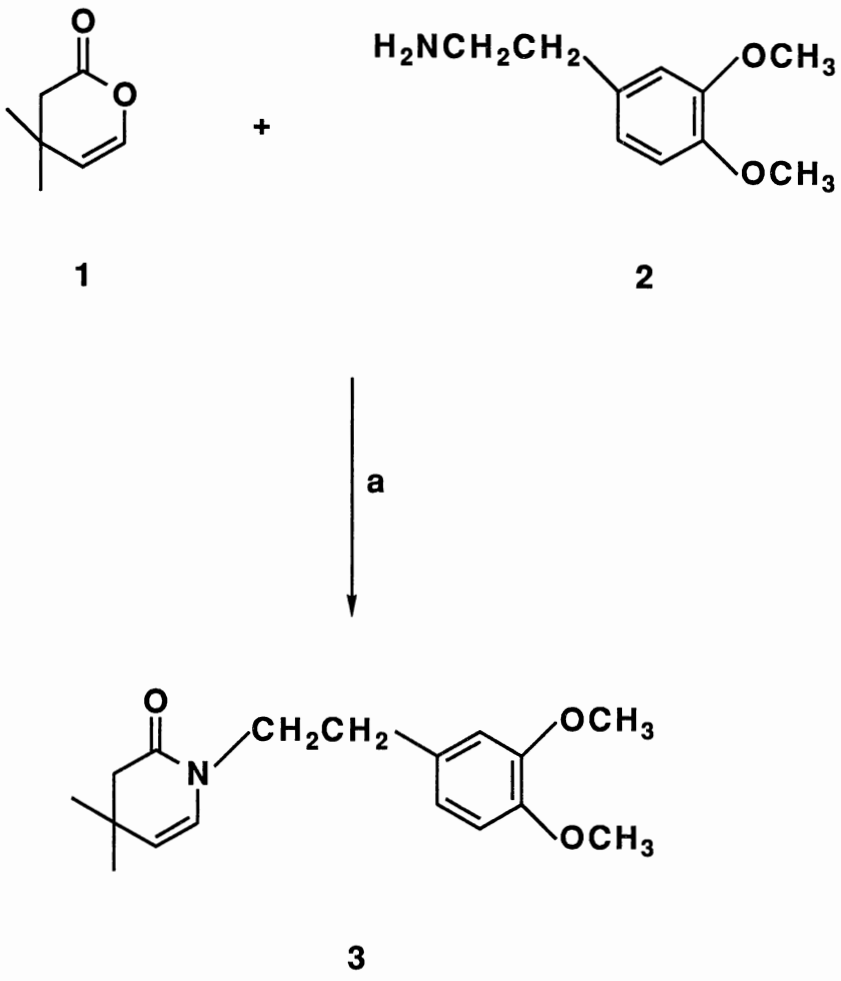
## Results and Discussion

The purpose of this study is to functionalize lactams with carboxylic acid or carboxylate side chains so that they resemble amino acids and amino esters and thus provide a site recognition capability for their assimilation into mammalian biological systems.

In order to gain familiarity with the reaction of 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**1**) with an amine, a trial run of **1** and β-(3,4-dimethoxyphenyl)ethylamine (**2**) was carried out. This reaction was also intended to provide experience in isolating, purifying, and collecting spectral data of the product.

**Preparation of 3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (3).** The addition of **2** to **1** raised the temperature of the reaction mixture to ~40 °C. Refluxing the reaction mixture in toluene for 3 h gave **3** (Figure 7). The structural proof of **3** is based on spectral analyses. The exact mass data were in agreement with structure **3** (MW = 289.1684). The $^{13}C$ NMR spectrum reveals the presence of one carbonyl carbon atom, two olefinic carbon atoms, six aromatic carbon atoms (three ArH and three substituted), two methoxy carbon atoms, and five alkane carbon atoms. The gem-dimethyl carbons were not separated. The olefinic region of the $^{1}H$ NMR spectrum integrates to two protons, the aromatic region to three protons, and the methoxy groups to six protons as two singlets.

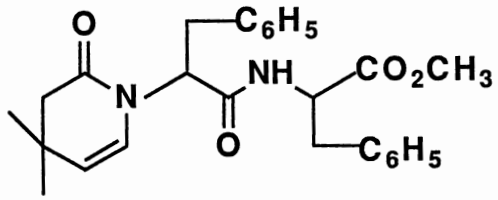
With the experience gained from the above reaction, **1** was then reacted with amino esters and an amino acid.



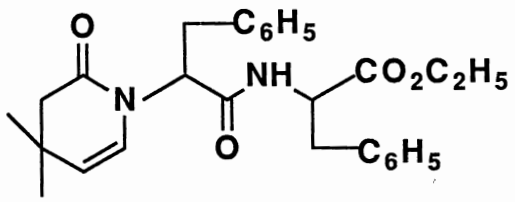

[a]toluene, reflux.

**Figure 7.** Formation of 3,4-Dihydro-1-(2-(3,4-dimethoxypheny)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (**3**).

**Lactams From α-Amino Esters.** Based on exact mass data, enelactone **1** reacted with L-phenylalanine methyl ester (**4b**) and L-phenylalanine ethyl ester (**4c**) to form products with molecular weights of 434.2207 and 448.2366, respectively. It was initially thought that these molecular weights correspond to the following compounds:

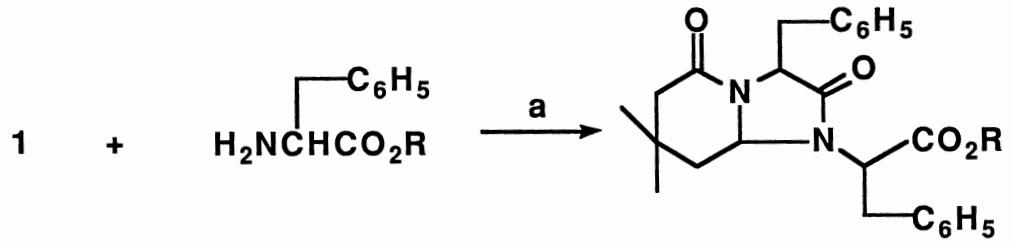


MW = 434.2207



MW = 448.2366

The methyl and ethyl ester carbons were observed in the $^{1}H$ and $^{13}C$ NMR spectra. While three peaks were observed in the $^{13}C$ carbonyl region and the expected eight peaks for the two phenyl rings for both compounds also were found, the expected vinyl absorptions for the alkene double bonds were not observed in either case. To account for these missing absorptions, the following structures are proposed in which cyclization consumed the missing double bonds in the formation of **5** and **6** shown in Figure 8.



**4b** R = $CH_3$
**4c** R = $C_2H_5$

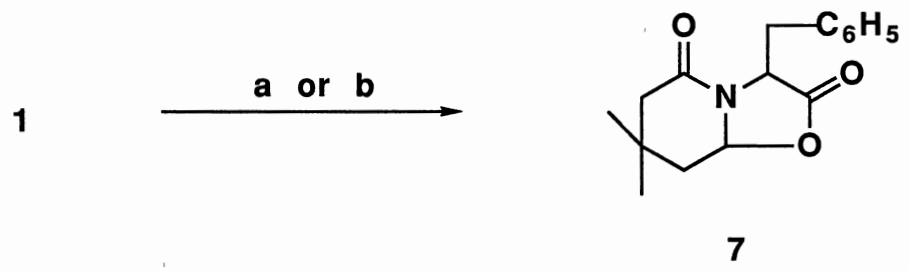
**5** R = $CH_3$
**6** R = $C_2H_5$

[a]**toluene, reflux.**

**Figure 8.** Reactions of 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one (**1**) With L-Phenylalanine Esters.

**Preparation of 3-Benzyl-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-8,8a-dihydro-7*H*-oxazolo[3,2-*a*]pyridine (7).** In an attempt to prepare a noncyclic 1:1 reaction product from **1** and **4b**, Bundgaard's reaction conditions in which 1,4-dioxane was substituted for toluene were used[26]. This author reacted 3-benzylidenephthalide and glycine to form a product with a carboxylic acid side chain as shown in Figure 4. In the

current study, **1** was reacted with **4b** in 1,4-dioxane at pH 8-9. This gave a neutral and a bicarbonate soluble fraction. The bicarbonate soluble fraction was acidified and extracted into ether but it failed to give a homogenous product. The neutral fraction, however, gave a product with a molecular weight of 273.1377. The $^{13}C$ NMR spectrum revealed the presence of two carbonyl carbon atoms, four aromatic carbon atoms, and eight alkane carbon atoms. The gem-dimethyl carbons were separated. This product was assigned structure **7** with incorporation of one molecule of **1** for each molecule of **4b** (Figure 9). Obviously **4b** was hydrolyzed or otherwise reacted to cyclize to **7**.



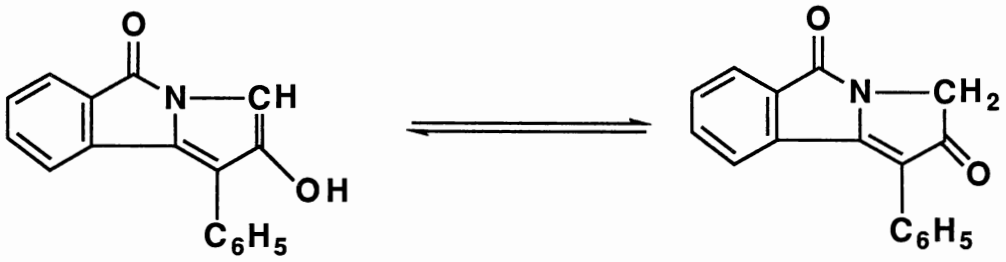

**7**

**[a] $H_2NCH(CH_2C_6H_5)CO_2CH_3$ . HCl, $H_2O$, $K_2CO_3$, 1,4-dioxane, reflux; [b] L-$H_2NCH(CH_2C_6H_5)CO_2H$, $H_2O$, $NaHCO_3$, 1,4-dioxane, reflux.**

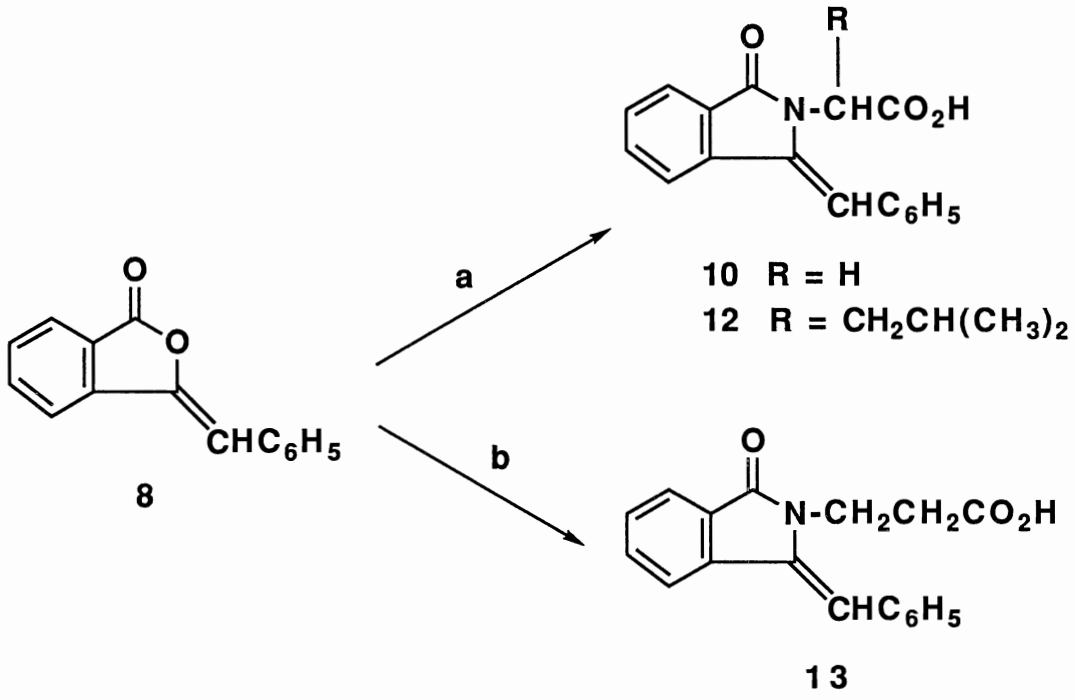
**Figure 9**. Formation of 3-Benzyl-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-8,8a-dihydro-7*H*-oxazolo[3,2-*a*]pyridine (**7**).

Since the solubility of L-phenylalanine (**4a**) in toluene is considerably less than its esters **4b** or **4c**, it became necessary to use 1,4-dioxane as the solvent for the reaction of **1** with **4a** (Figure 9). The reaction products were found to be a mixture of a neutral product and a bicarbonate soluble material. The bicarbonate soluble fraction could not be purified. The neutral fraction showed spectral data identical with that of **7** obtained from the reaction described earlier for **1** and **4b**.

**Enelactams From Amino Acids.** Hassan and co-workers[28] claimed that heating 3-benzylidenephthalide (**8**) and glycine (**9a**) at 220 °C for 5 min gave the substituted pyrrole derivative (MW = 261) shown below.




Their reaction was repeated several times. In contrast to the expected results, spectral analysis of the product showed that the reaction of **8** with **9a** gave 2-carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole (**10**) (Figure 10). The exact mass data gave a molecular weight of 279.0894 for **10**. The $^{1}H$ NMR spectrum indicated the presence of one vinyl proton, nine aromatic protons, and two methylene protons based on integration. Peaks for two carbonyl carbons, 12 aromatic carbons (ten peaks), two olefinic carbons, and one alkane carbon were observed in the $^{13}C$ NMR spectrum.




$^{a}H_2NCHRCO_2H$, Δ; $^{b}H_2NCH_2CH_2CO_2H$, Δ.

**Figure 10.** Reactions of 3-Benzylidenephthalide With Amino Acids.

Bundgaard[26] reacted **8** and **9a**, as shown in Figure 4, in an aqueous solution of dioxane at an alkaline pH on a steam bath and obtained **10**. He reported a melting point of 204-205 °C. There was no mention of the stereochemistry of this compound in his report. We observed a melting point of 204-207 °C for **10** obtained by heating **8** and **9a** at 220 °C for 5 min[28]. The (E)- and (Z)-isomers of **10** (Figure 5) were reported by Scartoni and co-workers[27] to have melting points of 207-209 °C and 188-190 °C, respectively. Their assignment of the (E)- and (Z)-isomers was based on $^1$H NMR data. Thus, it was concluded that **10** is the (E)-isomer.

As shown in Figure 10, the reaction of **8** with DL-leucine (**9b**) and β-alanine (**11**) under the reaction conditions (heating at 220 °C for 5 min) described by Hassan and co-workers[28] also did not produce substituted pyrrole derivatives. Instead, an alkali-soluble product, 2-(1-carboxy-3-methylbutyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**12**) was obtained from the reaction of **8** with **9b**. The exact mass data were in agreement with structure **12** (MW = 335.1524). The $^1$H NMR spectrum of **12** indicated the presence of one vinyl proton and nine aromatic protons based on integration. Peaks for two carbonyl carbons, 12 aromatic carbons (ten peaks), two olefinic carbons, and five alkane carbons were observed in the $^{13}$C NMR spectrum. The reaction of **8** with β-alanine (**11**) also gave an alkali-soluble product, 2-(2-carboxyethyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**13**) in Figure 10. The $^1$H NMR spectrum of **13** showed the presence of one vinyl proton, nine aromatic protons, and four methylene protons based on integration. Peaks for two carbonyl carbons, 12 aromatic carbons (ten peaks), two olefinic carbons, and two alkane carbons were observed in the $^{13}$C NMR spectrum. The exact mass data gave a molecular weight of 293.1052 consistent with that of structure **13**.

**Consideration of Mechanisms Leading to the Cyclic Product 5 From the Reaction of 1 With Amino Esters**. The reaction of **1** with L-phenylalanine esters **4b** and **4c** (Figure 8) to give products that consistently incorporated two molecules of the amino ester for each molecule of enelactone **1** was puzzling. Initially, it was

considered that the amino esters would behave in a manner similar to primary amines as illustrated for the formation of **3** shown in Figure 11.

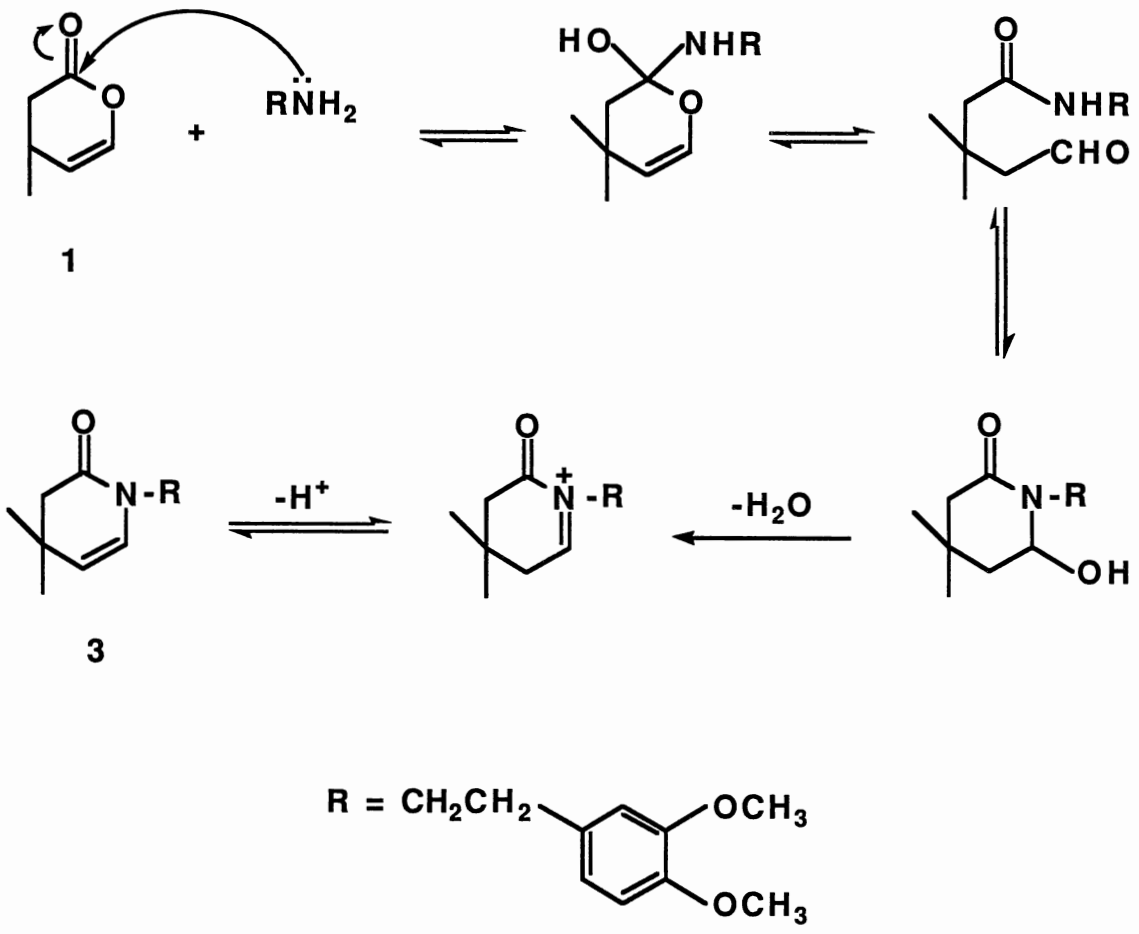
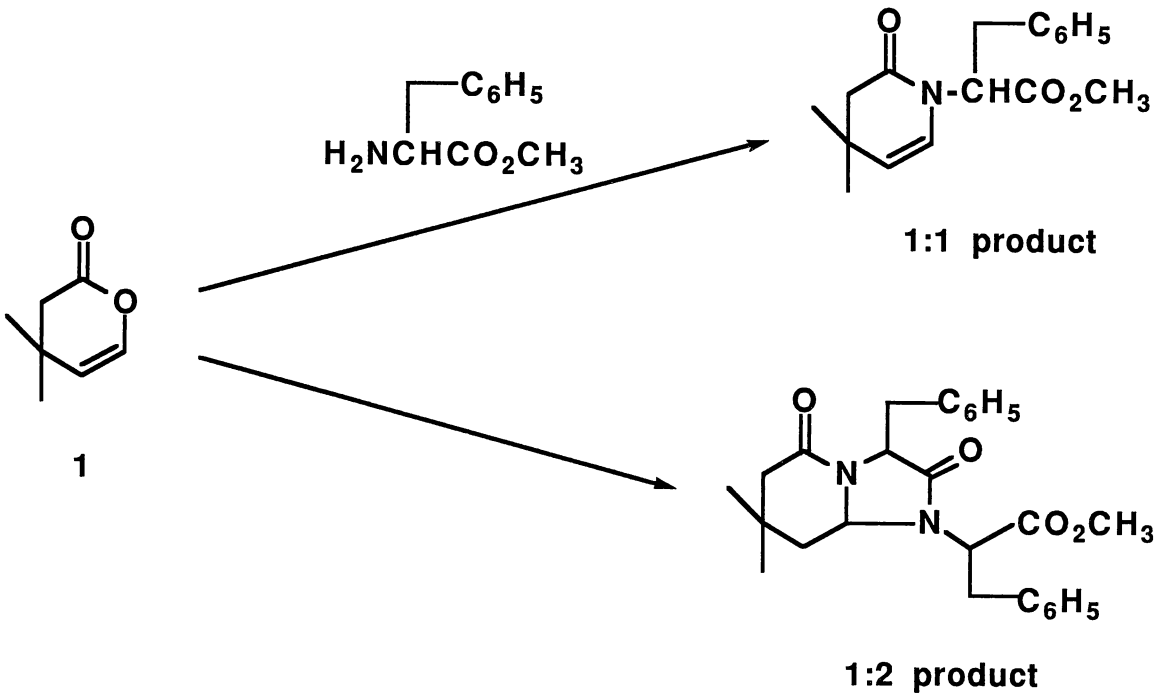



**Figure 11**. Proposed Route for the Formation of 3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (**3**).

Application of this mechanism to the reaction of **1** and L-phenylalanine methyl ester **4b** should have resulted in the formation of the 1:1 product shown below.




Our attempt to identify the 1:1 product (shown above) through the use of mass spectrometry showed that the 1:2 product **5** was formed instead. In addition $^{13}C$ NMR clearly supports the structure of **5** since three carbonyl peaks were observed which would be inconsistent with the structure of the 1:1 product. Thus, it became of interest to collect evidence to explain why the 1:2 product formed so readily. Several routes are being considered and these will be shown in Figures 12, 13, and 14.

Since the 1:2 product implies an intact phenylalanylphenylalanine (phe-phe) skeleton, it was considered possible that L-phenylalanine methyl ester (**4b**) could rapidly dimerize and then react as shown in Figure 12.

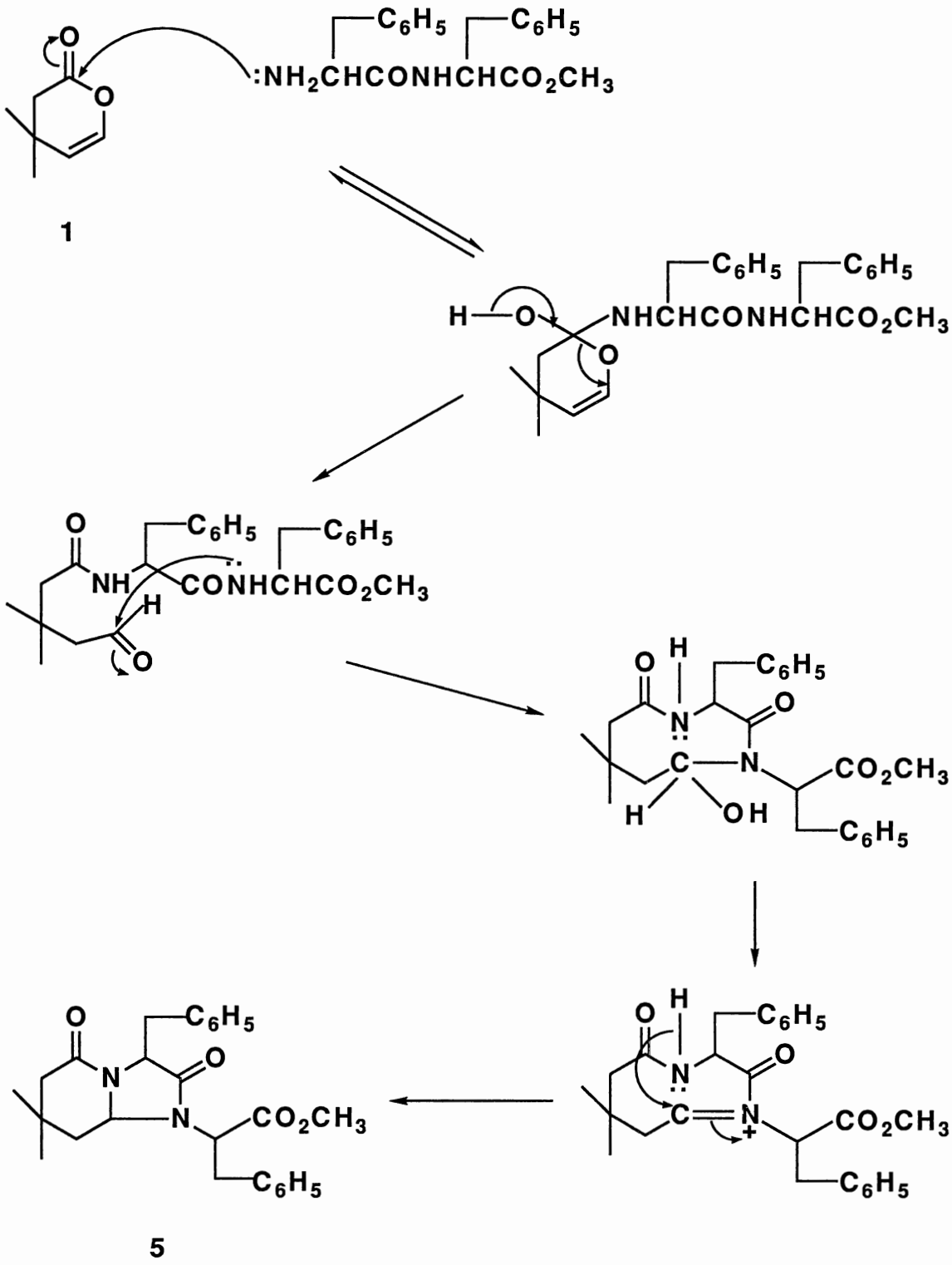



**Figure 12.** Route for the Formation of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).

Figure 12, however, has a serious weakness in that the formation of a nine-membered ring is involved although the subsequent collapse to **5** seems reasonable. Evidence for the formation of the dipeptide (phe-phe methyl ester) from the methyl ester of L-phenylalanine was sought by subjecting L-phenylalanine methyl ester to simulated reaction conditions in the absence of enelactone **1**. Despite a literature suggestion that L-phenylalanine methyl ester may dimerize on release from the hydrochloride salt[29], it was found that the $^{1}H$ and $^{13}C$ NMR spectra of the methyl ester **4b** in $CDCl_3$ and 1,4-dioxane-$d_8$ remained unaltered over a considerable period of time. A noncyclic dimer of **4b** is expected to show two different carbonyl carbons. At no time was the expected second carbonyl absorption (amide carbonyl of a dipeptide) observed. However, in time, formation of a cloudy suspension was observed in all of the NMR tubes. This was thought to be the dipeptide ester or a polymer. A polymer of **4b** should show at least two different carbonyl carbons, one peak for the internal carbonyl carbon (amide) and another peak for the terminal carbonyl carbon (ester), the former increasing in intensity as the number of units increase. This material redissolved on warming the NMR tubes but the $^{13}C$ NMR spectrum did not show a second carbonyl peak and the general appearance of the spectrum remained unchanged. It is possible that the ester peak could diminish in intensity because of the amide groups increasing in number but this would require that all amide carbonyl peaks of the polymer would appear at the same position in the $^{13}C$ NMR spectrum. The material did not reprecipitate until after the NMR studies were complete. Isolation of the material responsible for the cloudy suspension through filtration has not been successful since the material is sticky and noncrystalline.

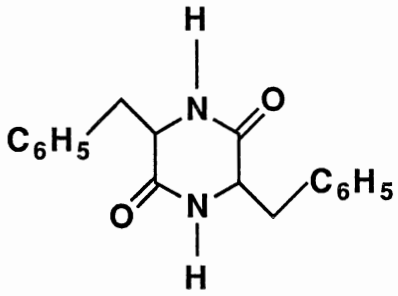
It seems unlikely that the carbonyl peaks of an amido ester (methyl ester of phe-phe) would give a single value in a $^{13}C$ NMR spectrum and thus the suspended material in the NMR tubes does not appear to be phe-phe methyl ester or a higher polymer.

To promote dimerization of **4b**, the amino ester was subjected to two heating conditions. A sample of neat **4b** was heated in an Abderhalden drying apparatus at the temperature of refluxing toluene (109 $^{o}$C) and a second sample of **4b** was dissolved in toluene and heated at reflux temperature. The $^{1}$H and $^{13}$C NMR spectra of **4b** subjected to the above heating conditions and unheated **4b** were compared. The NMR spectra in $CDCl_3$ in all three cases were identical. The solid formed from **4b** dissolved in toluene and heated at reflux showed similar $^{1}$H and $^{13}$C NMR spectra as those of the three cases described above. Detailed information about the spectral data for the NMR studies in this section are presented in the experimental section.

The EI mass spectrum of the solid formed after allowing a sample of neat **4b** to stand at room temperature showed a molecular ion peak of 179. This molecular weight corresponds to that of **4b**. This question was studied further. EI uses 70eV which causes considerable fragmentation. Thus, it is possible that electron impact mass spectrometry is only detecting monomeric amino ester.

Another sample of neat **4b** was allowed to stand at room temperature until solidification occurred. This solid included a yellow oil. To isolate the solid from the oil, the mixture was wrapped in several layers of filter paper and thoroughly pressed in a vise so that the oil was absorbed by the filter paper. The solid was washed with ether several times. A mass spectrum of the pure solid was obtained using Liquid Secondary Ion Mass Spectrometry (LSIMS) which is a milder ionization technique than EI. The LSIMS spectrum showed an $[M+H]^{+}$ ion peak at 295.

The pressed solid was insoluble in most organic solvents. It was dissolved in DMSO and the mixture was heated until a solution was formed. The $^{13}$C NMR spectrum of the pure solid in DMSO showed the presence of one carbonyl carbon, four aromatic carbons, and one alkane carbon. The peak due to the methoxy group was absent in the spectrum. These data are consistent with a cyclic dimer of **4b** (3,6-dibenzyl-2,5-piperazinedione) shown below.




**14**

This structure requires two alkane carbon peaks. The missing alkane carbon appeared in the solvent region.

Thus, the solid formed in the NMR studies of **4b** is the cyclic dimer. It was not detected in the NMR spectra due to its low concentration in the solution.

Alternatively, the phe-phe skeleton in **5** could result from an initial reaction resulting in a 1:1 product and the 1:1 product subsequently incorporating an additional molecule of L-phenylalanine methyl ester. Since a 1:1 product has not been found, this final step must be very rapid and a reactive intermediate must be involved. Two routes to **5**, shown in Figures 13 and 14, are under consideration.

In Figure 13 enelactone **1** is attacked by L-phenylalanine methyl ester **4b** to give the open-chain, amido-aldehyde structure **b**. This structure can cyclize and eliminate water to produce the expected 1:1 product **d** previously shown on p. 18. Structure **d** will be discussed as part of Figure 14. Structure **b** (Figure 13) is that of an aldehyde and, therefore, reactive to amines which are known to readily form enamines such as **f** or imines such as **g**. The imine **g** can cyclize through formation of the cyclic aminal **h**. Once **h** forms, the collapse to **5** through loss of methanol would be expected.

A final alternative for the formation of **5** is shown in Figure 14 in which the methoxycarbonyl group of **d** from Figure 13 becomes involved. The methoxycarbonyl group of **d** is in close proximity to the lactam carbonyl of **d** and, thus, an interaction as shown in structure **i** can be expected. If loss of methanol occurs as shown for step **i** to **j**, **j** can be expected to be receptive to attack by the amino ester to satisfy the plus charge of **j** as

shown. The succeeding steps of formation of the enamine **l** with subsequent equilibration to the acyl iminium ion **m**, and the cyclization to **5** also appear reasonable. At present, we can not distinguish between the routes in Figures 13 and 14. However, either of these routes seem preferable to a prior formation of phe-phe methyl ester and the route shown in Figure 12.

**NMR Studies of a Mixture of 1 and 4b in 1,4-Dioxane-$d_8$.** An attempt has been made to study the interaction of enelactone **1** and L-phenylalanine methyl ester **4b** in 1,4-dioxane-$d_8$ in the hope that conditions could be found which would enable carrying out preparative-scale reactions and, thus, isolate intermediates or provide clues to support or deny the mechanisms shown in Figures 12, 13, and 14. However, the NMR study of the carbonyl region in the $^{13}C$ NMR spectrum in 1,4-dioxane-$d_8$ showed a very complex process as described below.

One hour after mixing **1** and **4b**, six carbonyl carbons (δ 167.87, 168.50, 170.64, 172.04, 173.12, 176.16) were observed in the $^{13}C$ NMR spectrum, two of which were the carbonyl carbons of pure **1** (δ 167.87) and **4b** (δ 176.16). These four new peaks representing carbonyl carbons were present with increasing intensities in the $^{13}C$ NMR spectra until 24 h after mixing. Only one of the other four peaks may correspond to one of the three carbonyl carbons of **5** (δ 167.35, 170.74, 171.48). The carbonyl carbon peak of **4b** disappeared from the $^{13}C$ NMR spectrum on the third day while the carbonyl carbon of **1** remained on the twelfth day and after heating the solution in a water bath for 1 h. However, after heating for 6 h, it then disappeared. The other peaks in the carbonyl region increased from four to eight on the twelfth day before heating the solution in a water bath for 1 h. There were 11 more carbonyl carbon peaks other than the carbonyl carbon of **1** after heating the solution in a water bath for 1 h. Seven more carbonyl carbons appeared in the $^{13}C$ NMR spectrum after the solution was heated in a water bath for 6 h.

At this time it is not clear why the spectrum did not simplify to that of **5** since the product was readily obtained from the reaction in toluene.

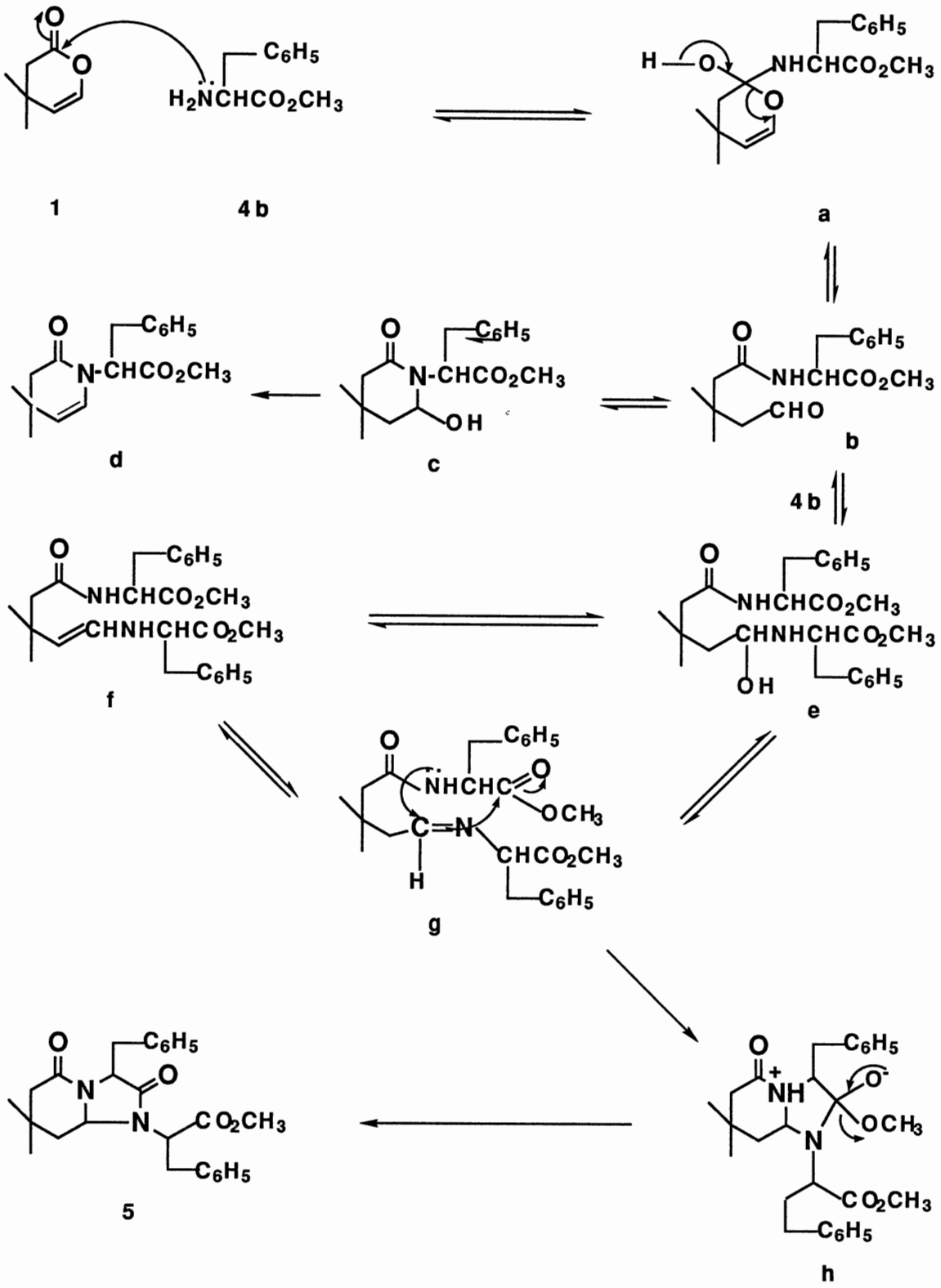



**Figure 13**. Route for the Formation of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).

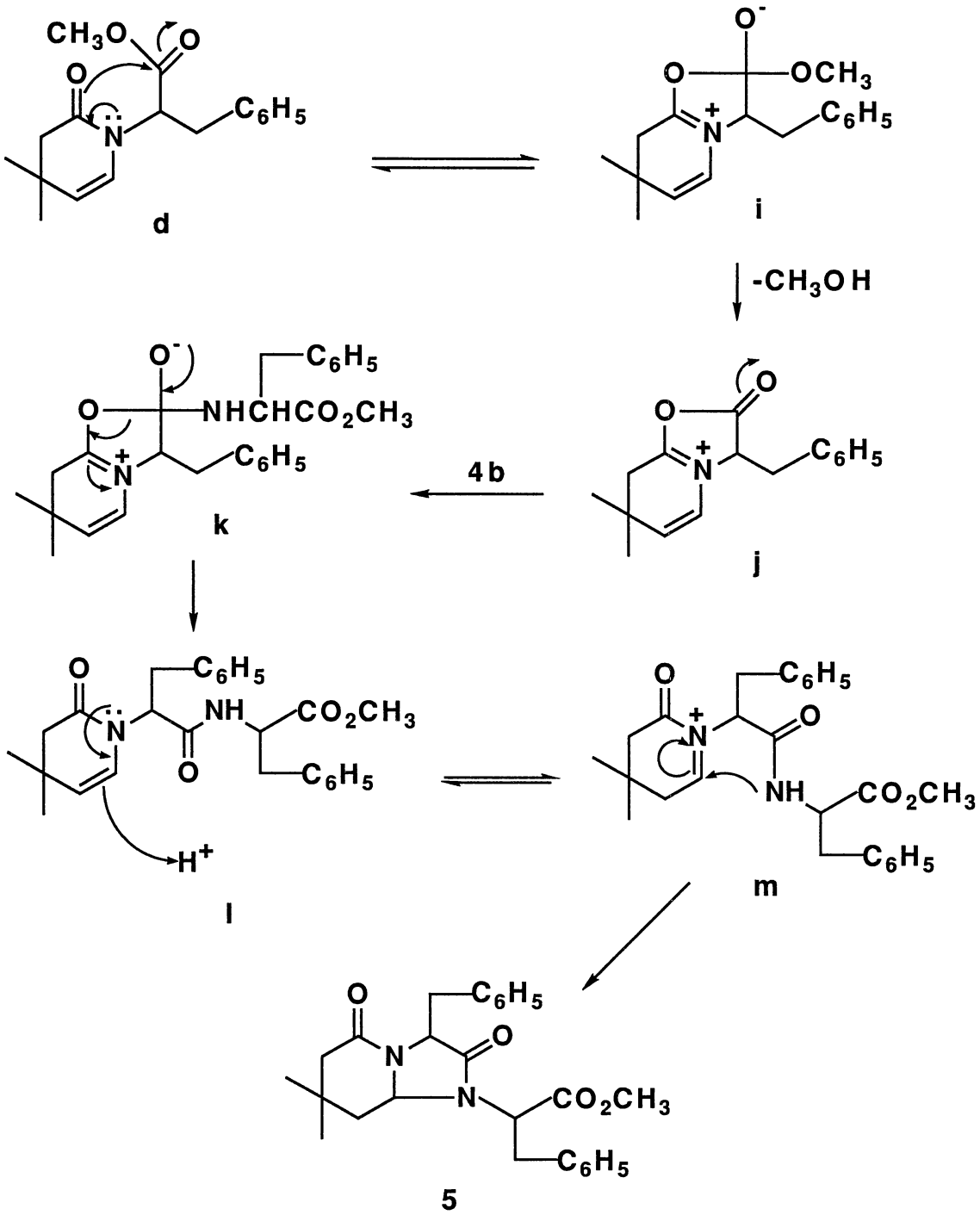



**Figure 14**. Alternate Route to 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).

**NMR Studies of a Mixture of 1 and 4b in $CDCl_3$.** In contrast to the experience with L-phenylalanine methyl ester **4b** in which only one carbonyl peak was observed in the $^{13}C$ NMR spectrum, the $^{13}C$ NMR spectrum of the mixture of **1** and **4b** one h after mixing showed peaks for six carbonyl carbons. Three of these peaks (δ 168.32, 168.44, 171.17, 171.84, 172.59, 175.32) were different from those of **1** (δ 168.32 or 168.44) and **4b** (δ 175.32). These three carbonyl peaks were present with increasing intensities in the $^{13}C$ NMR spectra until 6 h after mixing. After 24 h, the mixture became cloudy and five more carbonyl carbons (δ 168.52, 171.42, 171.48, 172.60, 173.73) appeared in the $^{13}C$ NMR spectrum. Only one of these carbonyl carbons corresponds to one of the three carbonyl carbons of **5** (δ 167.97, 169.89, 171.15). On the twenty-fourth day, the three peaks for the carbonyl carbons of **5** became dominant in the $^{13}C$ NMR spectrum.

CHAPTER III

## Experimental Section

Melting points are uncorrected and were measured using a Thomas Hoover apparatus for temperatures below 250 °C and a Mel-Temp apparatus for temperatures above 250 °C. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. EI-mass spectra were obtained on a VG Tritech TS-250 trisector tandem mass spectrometer with EBE geometry. LSIMS and exact mass data were recorded on a VG ZAB2-SE double focusing high resolution mass spectrometer with a BE geometry. EI was used as the ionization technique in obtaining the exact mass data.

All chemicals were of reagent grade quality and were used without further purification. 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one, β-(3,4-dimethoxyphenyl) ethylamine, 3-benzylidenephthalide, and β-alanine were purchased from Aldrich Chemical Co. L-Phenylalanine methyl ester hydrochloride, L-phenylalanine ethyl ester hydrochloride, L-phenylalanine, glycine, and DL-leucine were obtained from Lancaster Synthesis Inc.

**3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (3).** A solution of **1** (1.260 g, 10 mmol) and **2** (2.172 g, 12 mmol) in toluene (50 mL) was heated at reflux for 3 h. Toluene was removed in vacuo. The residue was triturated with hexane and recrystallized from ether. The resulting solid was extracted through a Soxhlet column containing acidic alumina with toluene as solvent. The residue left on acidic alumina after toluene extraction was extracted with ether to give 0.420 g of crude **3** (15%); mp 55-58 °C (ether/pet ether); $^{1}H$ NMR ($CDCl_3$) δ 1.02 (s, 4-$CH_3$), 2.33

(s, 2-$CH_aH_b$), 2.81 (t, Ar'-$CH_2$, J = 7.5 Hz), 3.68 (t, N-$CH_2$, J = 7.5 Hz), 3.85 (s, $OCH_3$), 3.87 (s, $OCH_3$), 4.89 (d, 5-H, J = 7.7 Hz), 5.78 (d, 6-H, J = 7.7 Hz), 6.73-6.78 (m, 3H, aromatic); $^{13}C$ NMR ($CDCl_3$) δ 27.80 (4-$CH_3$'s), 31.64 ($C_4$), 34.48 (Ar'-$CH_2$), 46.26 (N-$CH_2$), 47.79( $C_3$), 55.87 ($OCH_3$), 55.91 ($OCH_3$), 111.27, 112.15, 117.25 ($C_5$), 120.84, 127.35 ($C_6$), 131.16, 147.63, 148.89, 169.07 (C=O); HR-EI ($M^+$) calcd for $C_{17}H_{23}NO_3$: 289.1678. found: 289.1684 .

**3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (5).** L-Phenylalanine methyl ester hydrochloride (10 g, 46 mmol) was added to a solution of $NaHCO_3$ (3.864 g, 46 mmol) in water (125 mL). The solution was extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and stripped of solvent to give **4b** (85%) as a light yellow liquid. A solution of **4b** (1.343 g, 7.5 mmol) and **1** (0.630 g, 5 mmol) in toluene (50 mL) was refluxed for 6 h. The crude product was washed with 0.2 M HCl (2 x 20 mL) and then with water (2 x 20 mL). Toluene was removed in vacuo to yield 1.107 g of crude **5** (68%); mp 108-110 °C (ether/pet ether); $^1H$ NMR ($CDCl_3$) δ 0.33 (t, 8-$CH_aH_b$, J = 11.6 Hz), 0.83 (s, 7-$CH_3$), 0.86 (s, 7-$CH_3$), 1.37 (qd, 8-$CH_aH_b$, J = 1.8, 11.6 Hz), 1.98 (d, 6-$CH_aH_b$, J = 17.9 Hz), 2.22 (dd, 6-$CH_aH_b$, J = 1.8, 17.9 Hz), 2.91 (dd, Ar"-$CH_aH_b$, J = 8.5, 13.7 Hz), 3.12 (d, Ar"-$CH_aH_b$, J = 6.9 Hz), 3.18 (d, Ar'-$CH_aH_b$, J = 3.5 Hz), 3.27 (dd, Ar'-$CH_aH_b$, J = 6.0, 13.7 Hz), 3.71 (s, $OCH_3$), 4.16 (dd, 8a-H, J = 4.1, 11.6 Hz), 4.22 (dd, 1-CH, J = 6.9, 8.5 Hz), 4.72 (dd, 3-H, J = 3.5, 6.0 Hz), 7.10-7.31 (m, 10H, aromatic); $^{13}C$ NMR ($CDCl_3$) δ 25.98 (7-$CH_3$), 28.89 ($C_7$), 31.33 (7-$CH_3$), 34.16 (Ar"-$CH_2$), 35.47 (Ar'-$CH_2$), 39.45 ($C_8$), 44.84 ($C_6$), 52.58 ($OCH_3$), 55.99 (1-CH), 58.46 ($C_3$), 69.87 ($C_{8a}$), 127.00, 127.02, 128.27, 128.62, 129.33, 130.07, 136.16, 137.32, 167.97 ($C_5$), 169.89 ($C_2$), 171.15 (O=C-O-$CH_3$); HR-EI ($M^+$) calcd for $C_{26}H_{30}N_2O_4$: 434.2206. found: 434.2207.

**3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-ethoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (6).** L-Phenylalanine ethyl ester hydrochloride (1.532 g, 6.7 mmol) in ether (50 mL) was extracted with a saturated solution of $NaHCO_3$ (2 x 12.5 mL). The aqueous layer was extracted with ether (25 mL). The combined ether extracts was washed with water, dried ($MgSO_4$), and stripped of solvent to give **4c** (90%) as a colorless liquid. Enelactone **1** (0.880 g, 7 mmol) and **4c** (1.161 g, 6 mmol) were heated at reflux in 50 mL toluene for 4 h. Toluene was removed in vacuo to give 0.103 g of pure **6** (8%); mp 129-132 °C (ether); $^1$H NMR ($CDCl_3$) δ 0.50 (t, 8-$CH_aH_b$, J = 12.2 Hz), 0.85 (s, 7-$CH_3$), 0.88 (s, 7-$CH_3$), 1.24 (t, $CH_2C\underline{H}_3$, J = 7.2 Hz), 1.45 (qd, 8-$CH_aH_b$, J = 1.7, 12.2 Hz), 2.00 (d, 6-$CH_aH_b$, J = 17.9 Hz ), 2.22 (dd, 6-$CH_aH_b$, J = 1.7, 17.9 Hz), 2.83 (dd, Ar"-$CH_aH_b$, J = 8.1, 13.7 Hz), 3.08 (d, Ar"-$CH_aH_b$, J = 7.5 Hz), 3.16 (d, Ar'-$CH_aH_b$, J = 3.7 Hz), 3.25 (dd, Ar'-$CH_aH_b$, J = 6.1, 13.7 Hz), 4.18 (q, $OCH_2$, J = 7.2 Hz), 4.23 (d, 8a-H, J = 3.8 Hz), 4.34 (t, 1-CH, J = 7.5 Hz), 4.73 (dd, 3-H, J = 3.7, 6.1 Hz), 7.11-7.31 (m, 10H, aromatic); $^{13}$C NMR ($CDCl_3$) δ 14.10 ($CH_2\underline{C}H_3$), 26.05 (7-$CH_3$), 28.95 ($C_7$), 31.37 (7-$\underline{C}H_3$), 34.26 (Ar"-$CH_2$), 35.65 (Ar'-$CH_2$), 39.81 ($C_8$), 44.89 ($C_6$), 56.04 ($OCH_2$), 58.44 (1-CH), 61.78 ($C_3$), 69.77 ($C_{8a}$), 126.99, 127.07, 128.32, 128.62, 129.31, 130.05, 136.22, 137.31, 167.97 ($C_5$), 169.50 ($C_2$), 171.23 (O=$\underline{C}$-O-$CH_2CH_3$); HR-EI ($M^+$) calcd for $C_{27}H_{32}N_2O_4$: 448.2362. found: 448.2366.

**3-Benzyl-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-8,8a-dihydro-7*H*-oxazolo[3,2-*a*]pyridine (7).** (a) A solution of **1** (0.630 g, 5 mmol) in 1,4-dioxane (9.030 g) was added to an alkaline solution (pH = 8-9) of L-phenylalanine methyl ester hydrochloride (2.157 g, 10 mmol), $K_2CO_3$ (1.380 g, 10 mmol), and water (9.030 g).[26] The mixture was refluxed for 5 h. 1,4-Dioxane was removed in vacuo. The residue was acidified with 5 M HCl solution to pH ~ 2. A precipitate formed. This was filtered, washed with water (3 x 20 mL), and extracted with ether. The ethereal solution was extracted with a saturated solution of $NaHCO_3$. The fraction that remained in the ether

layer was washed with water, dried ($MgSO_4$), and stripped of solvent to furnish **7**; mp 118-120 °C (ether).

(b) A mixture of **4a** (1.652 g, 10 mmol), $NaHCO_3$ (2.520 g, 30 mmol), 1,4-dioxane (40 mL), water (25 mL), and **1** (0.630 g, 5 mmol) was heated at reflux for 5 h.[26] 1,4-Dioxane was removed in vacuo. The residue was acidified with 2 M HCl solution to pH ~ 2. The resulting precipitate was extracted with ether and washed with water. The ether layer was extracted with a saturated solution of $NaHCO_3$. The fraction that remained in the ether layer was washed with water, dried ($MgSO_4$), and stripped of solvent to give 0.328 g of crude **7** (24%); mp 123-125 °C (ether); $^1H$ NMR ($CDCl_3$) δ 0.87 (s, 7-$CH_3$), 1.04 (s, 7-$CH_3$), 1.42 (dd, 8-$CH_aH_b$, J = 10.0, 12.7 Hz), 1.88 (qd, 8-$CH_aH_b$, J = 2.1, 12.7 Hz), 2.21 (d, 6-$CH_aH_b$, J = 18.1 Hz), 2.35 (dd, 6-$CH_aH_b$, J = 2.1, 18.1 Hz), 3.30 (d, Ar'-$CH_2$, J = 4.3 Hz), 4.20 (dd, 8a-H, J = 4.7, 10.0 Hz), 4.86 (t, 3-H, J = 4.3 Hz), 7.21-7.31 (m, 5H, aromatic); $^{13}C$ NMR ($CDCl_3$) δ 25.97 (7-$CH_3$), 28.88 ($C_7$), 31.01 (7-$CH_3$), 35.77 (Ar'-$CH_2$), 39.96 ($C_8$), 44.83 ($C_6$), 56.80 ($C_3$), 87.36 ($C_{8a}$), 127.72, 128.91, 129.60, 135.30, 167.79 ($C_5$), 172.14 ($C_2$); HR-EI ($M^+$) calcd for $C_{16}H_{19}NO_3$: 273.1365. found: 273.1377.

**2-Carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole (10).** A mixture of **8** (5.550 g, 25 mmol) and **9a** (2.346 g, 31 mmol) was added to a 150-mL test tube equipped with a thermocouple and heated in a Woods' metal bath at 220 °C for 5 min. The product was recrystallized three times from 95 % ethanol to give after three recrystallization 1.613 g of **10** (23%); mp 204-207 °C; $^1H$ NMR (DMSO-$d_6$) δ 4.64 (s, $CH_2$), 6.75 (s, =CH), 7.32-7.82 (m, 9H, aromatic); $^{13}C$ NMR (DMSO-$d_6$) δ 40.79 ($CH_2$), 110.89 (=CH), 122.52, 122.86, 127.80, 128.65, 129.21, 129.33, 129.61, 132.09, 134.56, 134.64, 135.07 (=C-N), 165.38 (O=C-N), 169.36 (O=C-OH); HR-EI ($M^+$) calcd for $C_{17}H_{13}NO_3$: 279.0895. found: 279.0894.

**2-(1-Carboxy-3-methylbutyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (12).** Enelactone **8** (11.100 g, 50 mmol) and **9b** (6.550 g, 50 mmol) were heated at

250 °C in a Thermowell mantle for 5 min in a 250-mL round bottom flask equipped with a condenser. NaOH solution (5%) and ether were added to the crude product. The aqueous layer was washed with ether. Concentrated HCl was added dropwise to the aqueous layer until no additional precipitate formed. The precipitate was dissolved in ether. The ether solution was washed with water, dried ($MgSO_4$), and stripped of solvent to give 2.961 g of pure **12** (18%); mp 112-114 °C (ether); $^1$H NMR ($CDCl_3$) δ 0.95 (d, CHC$\underline{H}_3$, J = 6.6 Hz), 1.00 (d, CHC$\underline{H}_3$, J = 6.6 Hz), 2.16 (m, 3H), 5.31 (m, 1H), 6.56 (s, 1H), 7.18-7.86 (m, 9H, aromatic); $^{13}$C NMR ($CDCl_3$) δ 21.82 (CH-$\underline{C}H_3$), 23.12 (CH-$\underline{C}H_3$), 25.24 ($\underline{C}$H-$CH_3$), 37.78 ($\underline{C}H_2$-CH), 51.92 ($\underline{C}$H-$CO_2H$), 112.11 (=CH), 123.42, 123.55, 128.03, 128.73, 129.27, 129.36, 129.57, 132.00, 134.79, 135.11, 135.22 (=C-N), 167.18 (O=C-N), 174.65 (O=C-OH); HR-EI ($M^+$) calcd for $C_{21}H_{21}NO_3$: 335.1521. found: 335.1524.

**2-(2-Carboxyethyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (13).** To a 150-mL test tube equipped with a thermocouple was added **8** (5.550g, 25 mmol) and **11** (2.759 g, 31 mmol). The mixture was heated in a Woods' metal bath at 220 °C for 5 min. After cooling, saturated $NaHCO_3$ solution (200 mL) and ether (300 mL) were added to the crude product. The aqueous layer was extracted with ether (100 mL). Concentrated HCl was added dropwise to the aqueous layer until precipitation ceased. The precipitate was filtered, washed with water, and recrystallized from isopropyl alcohol to give 3.884 g of pure **13** (53%); mp 208-211 °C; $^1$H NMR (DMSO-$d_6$) δ 2.65 (t, C$\underline{H}_2CO_2H$, J = 7.4 Hz), 4.10 (t, N-$CH_2$, J = 7.4 Hz), 6.88 (s, =CH), 7.27-7.78 (m, 9H, aromatic); $^{13}$C NMR (DMSO-$d_6$) δ 32.75 ($\underline{C}H_2CO_2H$), 34.91 (N-$CH_2$), 111.04 (=CH), 122.50, 122.66, 127.73, 128.58, 129.30, 129.47, 129.56, 131.79, 134.44, 134.61, 134.88 (=C-N), 165.05 (O=C-N), 172.29 (O=C-OH); HR-EI ($M^+$) calcd for $C_{18}H_{15}NO_3$: 293.1052. found: 293.1052.

**NMR and MS Studies of L-Phenylalanine Methyl ester (4b).** A series of five NMR spectra of **4b** were obtained as follows:

**a**. $CDCl_3$ at room temperature; $^1H$ NMR ($CDCl_3$) δ 2.84 (m, 1H), 3.07 (m, 1H), 3.69 (s, 3H), 3.72 (m, 1H), 7.16-7.31 (m, 5H, aromatic); $^{13}C$ NMR ($CDCl_3$) δ 40.79 (CH-$\underline{C}H_2$), 51.65 ($OCH_3$), 55.51 ($\underline{C}H$-$CH_2$), 126.53, 128.27, 128.99, 136.95, 175.11 (C=O).

**b**. After a white solid formed in sample **a**, (48 days) the NMR tube was warmed to dissolve the solid. The solid remained dissolved until after the NMR was run; $^1H$ NMR ($CDCl_3$) δ 2.85 (m, 1H), 3.07 (m, 1H), 3.69 (s, 3H), 3.73 (m, 1H), 7.17-7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 41.07, 51.92, 55.80, 126.80, 128.54, 129.25, 137.22, 175.38.

**c**. A neat sample which has been heated in an Abderhalden drying apparatus for 4 h at 109 °C (toluene reflux) was allowed to cool, dissolved in $CDCl_3$ and the NMR spectrum was obtained; $^1H$ NMR ($CDCl_3$) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.70 (s, 3H), 3.73 (m, 1H), 7.16-7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 41.07, 51.93, 55.79, 126.81, 128.55, 129.26, 137.21, 175.39.

**d**. A sample of **4b** was dissolved in toluene and heated at reflux for 5 h. Toluene was stripped and pumped (oil pump) from the sample of **4b**. The NMR was obtained in $CDCl_3$; $^1H$ NMR ($CDCl_3$) δ 2.84 (m, 1H), 3.07 (m, 1H), 3.68 (s, 3H), 3.72 (m, 1H), 7.16-7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 41.10, 51.89, 55.81, 126.78, 128.52, 129.25, 137.26, 175.38.

**e**. The sample from **d** was allowed to stand until solidification occurred (97 days). The $CDCl_3$ was removed, the sample was dissolved in DMSO-$d_6$ by heating and the NMR was recorded after cooling. The sample stayed in solution during collection of the spectrum but on standing, solid formed; $^1H$ NMR (DMSO-$d_6$) δ 2.77 (m, 1H), 2.87 (m, 1H), 3.57 (s, 3H), 3.59 (m, 1H), 7.16-7.30 (m, 5H); $^{13}C$ NMR (DMSO-$d_6$) δ 41.65, 52.22, 56.64, 127.17, 129.02, 130.09, 138.84, 176.30.

A sample of neat **4b** was allowed to stand at room temperature until solidification occurred. The slippery solid was dried in vacuo for several days. The melting point and the mass spectrum of the solid were recorded; mp 300-305 °C; MS (m/e) 179 ($M^+$).

**NMR Studies of 4b in 1,4-Dioxane-$d_8$.** The $^1H$ and $^{13}C$ NMR spectra of **4b** in 1,4-dioxane-$d_8$ were recorded every 30 min for the first 3 h, every 3 h for the next 9 h, and every 12 h for the next 36 h. The solution was allowed to stand at room temperature until solidification of **4b** occurred on the twenty-sixth day. The mixture was heated in a water bath until the solid dissolved completely. The $^1H$ and $^{13}C$ NMR spectra of the resulting solution was recorded. The NMR data were the following: **(a) upon mixing**; $^1H$ NMR (1,4-dioxane-$d_8$) δ 2.77 (m, 1H), 2.94 (m, 1H), 3.56 (s, 3H), 3.58 (m, 1H), 7.14-7.26 (m, 5H); $^{13}C$ NMR (1,4-dioxane-$d_8$) δ 41.67, 51.52, 56.52, 126.89, 128.70, 129.87, 138.75, 176.05; **(b) 36 h after mixing**; $^1H$ NMR (1,4-dioxane-$d_8$) δ 2.78 (m, 1H), 2.94 (m, 1H), 3.57 (s, 3H), 3.58 (m, 1H), 7.13-7.27 (m, 5H); $^{13}C$ NMR (1,4-dioxane-$d_8$) δ 41.67, 51.51, 56.51, 126.88, 128.69, 129.86, 138.74, 176.03; **(c) 4b heated in water bath after solidification**; $^1H$ NMR (1,4-dioxane-$d_8$) δ 2.77 (m, 1H), 2.94 (m, 1H), 3.57 (s, 3H), 3.60 (m, 1H), 7.15-7.26 (m, 5H); $^{13}C$ NMR (1,4-dioxane-$d_8$) δ 41.68, 51.52, 56.52, 126.89, 128.70, 129.87, 138.75, 176.05;

**NMR Studies of a Mixture of 1 and 4b in 1,4-Dioxane-$d_8$.** The $^1H$ and $^{13}C$ NMR of **1** (61 mg, 0.486 mmol) in 1,4-dioxane-$d_8$ were taken. The $^1H$ and $^{13}C$ NMR of **4b** (87 mg, 0.486 mmol) in 1,4-dioxane-$d_8$ were also recorded. The two solutions were then mixed and the $^1H$ and $^{13}C$ NMR spectra were recorded immediately. The $^1H$ and $^{13}C$ NMR spectra were taken 3h and 6 h after mixing. The $^1H$ and $^{13}C$ NMR spectra were recorded every 24 h for 12 days. On the twelfth day, the solution was heated in a water bath for 1 h. The $^1H$ and $^{13}C$ NMR spectra were taken. The solution was heated for another 6 h and the $^1H$ and $^{13}C$ NMR spectra were again recorded.

**NMR Studies of a Mixture of 1 and 4b in $CDCl_3$.** A solution of **1** (61 mg, 0.486 mmol) in $CDCl_3$ was added to a solution of **4b** (87 mg, 0.486 mmol) in $CDCl_3$. The solution was mixed and the $^1H$ and$^{13}C$ NMR spectra were recorded immediately. The $^1H$ and $^{13}C$ NMR spectra were recorded 3 h and 6 h after mixing. The solution was allowed to stand at room temperature for 24 h until the next $^1H$ and $^{13}C$

NMR spectra were recorded. The solution was allowed to stand at room temperature for the next 23 days and the $^{1}H$ and $^{13}C$ NMR spectra were again recorded.

**Formation, Isolation, and Identification of 3,6-Dibenzyl-2,5-piperazinedione (14).** A neat sample of L-phenylalanine methyl ester (**4b**), released from L-phenylalanine methyl ester hydrochloride, was allowed to stand at room temperature until it gave a semi-solid appearance (about one week). The oily solid was placed between sharkskin filter paper contained between layers of qualitative filter paper and paper towels. The resulting sandwich was pressed in a vise to squeeze out the oil. This procedure was repeated until a dry, white solid resulted. The solid was washed with ether and dried in vacuo. The solid decomposes on melting at 298 $^{o}C$; $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 55.84 (N-CH), 126.92, 128.61, 130.25, 136.97, 166.60 (C=O). The benzylic methylene appeared in the solvent region.

## BIBLIOGRAPHY


(1) *Merck Index*; Stecher, P. G. Ed.; Merck: New Jersey, 1968; p 363.

(2) Dawson, G. W.; Griffiths, D. C.; Janes, N. F.; Mudd, A.; Pickett, J. A.; Wadhams, L. J.; Woodcock, C. M. *Nature* **1987**, *325*, 614-616.

(3) Hatch, R. C. *Am. J. Vet. Res.* **1972**, *33*, 143-155.

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

(5) Eisenbraun, E. J.; Browne, C. E.; Irvin-Willis, R. L.; McGurk, D. J.; Elliel, E. L.; Harris, E. L. *J. Org. Chem.* **1980**, *45*, 3811-3814.

(6) Shusherina, N. P.; Levina, R. Ya. *Russ. Chem. Rev. (Engl. Trans.)* **1968**, *37*, 198-208.

(7) Brody, F.; Ruby, P. R. *Chem. Heterocycl. Comp.* **1960**, *14*(1), 177-194.

(8) Eisenbraun, E. J.; Sullins, D. W.; Browne, C. E.; Shoolery, J. N. *J. Org. Chem.* **1988**, *53*, 3968-3972.

(9) Sullins, D. W. Ph.D. Thesis, Oklahoma State University, 1987.

(10) Schmidt, H. G. **Ger. Patent 3 427 146**, 1986; *Chem. Abstr.* **1986**, *106*, 638.

(11) Schmidt, H. G. **Ger. Patent 3 427 147**, 1986; *Chem. Abstr.* **1986**, *105*, 606.

(12) Tökes, L. In *Steroid Reactions An Outline for Organic Chemists*; Djerassi, C. Ed.; Holden-Day: San Francisco, 1963; pp 457-535.

(13) Sam, J.; Lopez, A. V.; Shafik, R. M. *J. Pharm. Sci.* **1968**, *57*, 1755-1759

(14) Natelson, S.; Gottfried, S. P. *J. Am. Chem. Soc.* **1941**, *63*, 487-489.

(15) Salazkin, S. N.; Fedoseenko, N. M.; Korshak, V. V.; Vinogradova, S. V. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, (1), 137-14; *Chem. Abstr.* **1978**, *88*, 504.

(16) Belen'kaya, S. K.; Salazkin, S. N.; Rafikov, S. R. *Deposited Doc.* **1982**, VINITI 3730-3782; *Chem. Abstr.* **1983**, *99*, 594.

(17) Scartoni, V.; Tognetti, T. *J. Heterocycl. Chem.* **1984**, *21*, 1499-1503.

(18) Bedair, A. H.; Lamphon, R. Q.; Ghazal, S. A. *J. Chem. Soc. Pak.* **1988**, *10*(4), 404-409; *Chem. Abstr.* **1990**, *112*, 491.

(19) Mund, A.P.; Behera, R.K.; Nayak, A.; Behera, G. B. *Indian J. Chem.*, Sect. B **1979**, *17B*, 404-405.

(20) Abdel Rahman, S. M.; Ismail, M. F.; Ismail, Z. M. *Rev. Roum. Chim.* **1976**, *21*(6), 889-895.

(21) Bedair, A. H.; Lamphon, R. Q. *J. Prakt. Chem.* **1987**, *329*(4), 675-680.

(22) Marsili, A.; Scartoni, V.; Morelli, I.; Pierangeli, P. J. *Chem. Soc., Perkin Trans. 1* **1977**, *9*, 959-965.

(23) Farley, J. M.; Cassidy, P. E. *Macromolecules* **1988**, *21*(12), 3372-3378.

(24) Marsili, A.; Scartoni, V. *Gazz. Chim. Ital.* **1972**, *102*, 806-817.

(25) Scartoni, V.; Morelli, I.; Marsili, A.; Catalano, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, *20,* 2332-2336.

(26) Bundgaard, H. *Acta Pharm. Suec.* **1975**, *12,* 333-348.

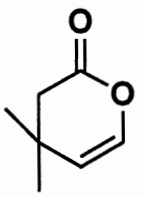
(27) Scartoni, V.; Fiaschi, R.; Catalano, S.; Morelli, I.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, *6,* 1547-1551.

(28) Hassan, KH. M.; EL-Garby Younes, M.; EL-Maghraby, M. A. *Indian J. Chem.* **1974,** *12,* 1031-1032.

(29) Ilan, Y.; Kfir, A. *Inorg. Chim. Acta* **1989**, *156*, 221-226.

# APPENDIX A

# GLOSSARY OF STRUCTURES



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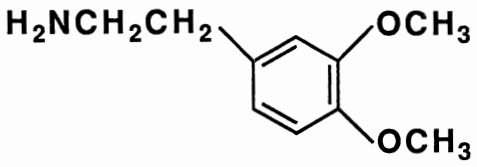

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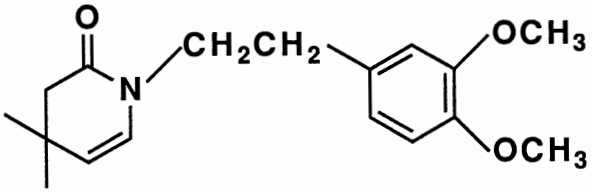

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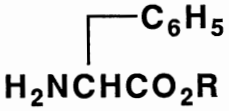
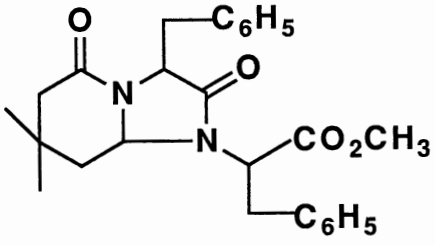


4a R = H
4b R = $CH_3$
4c R = $C_2H_5$



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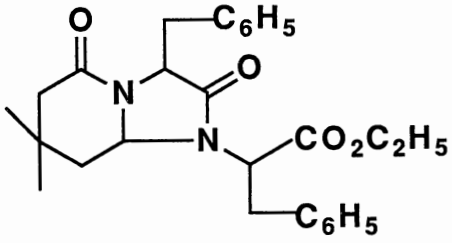

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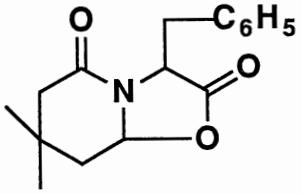

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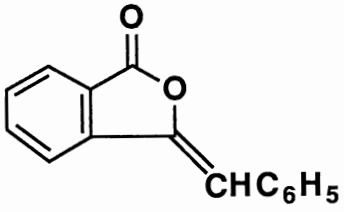

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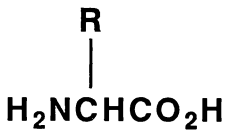
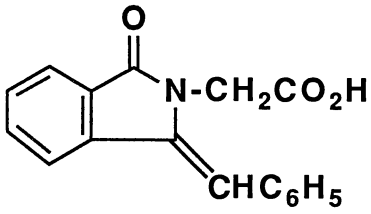


9a R = H
9b R = $CH_2CH(CH_3)_2$



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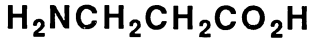

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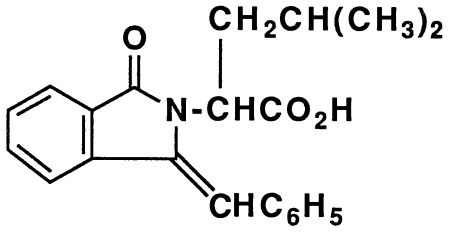

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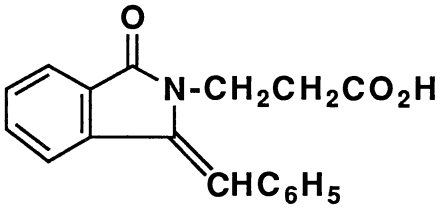

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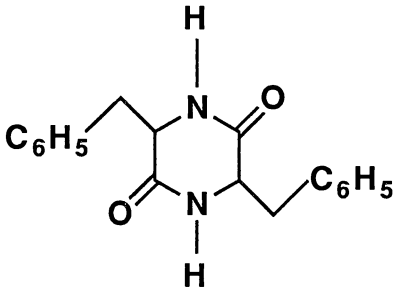
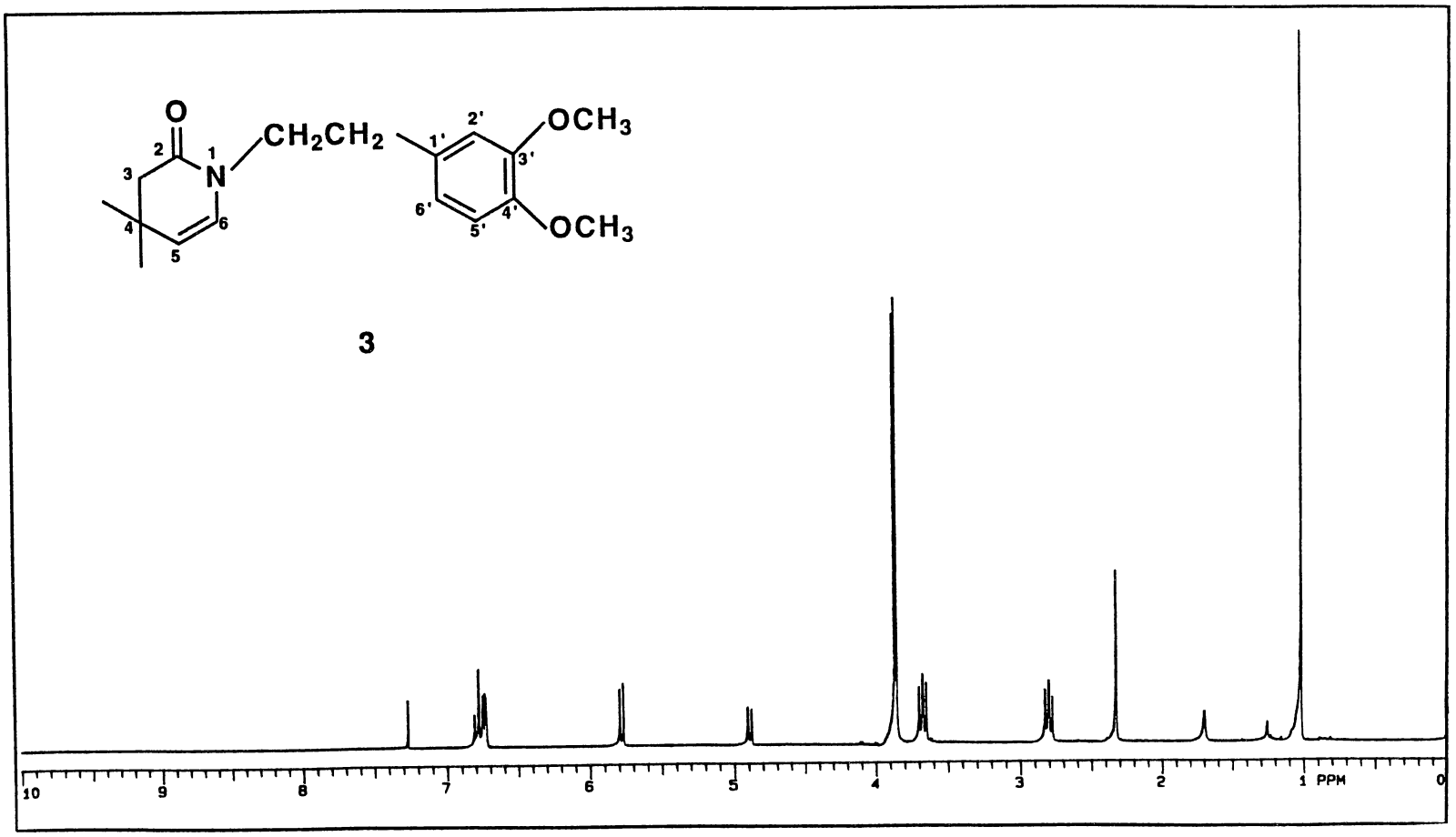


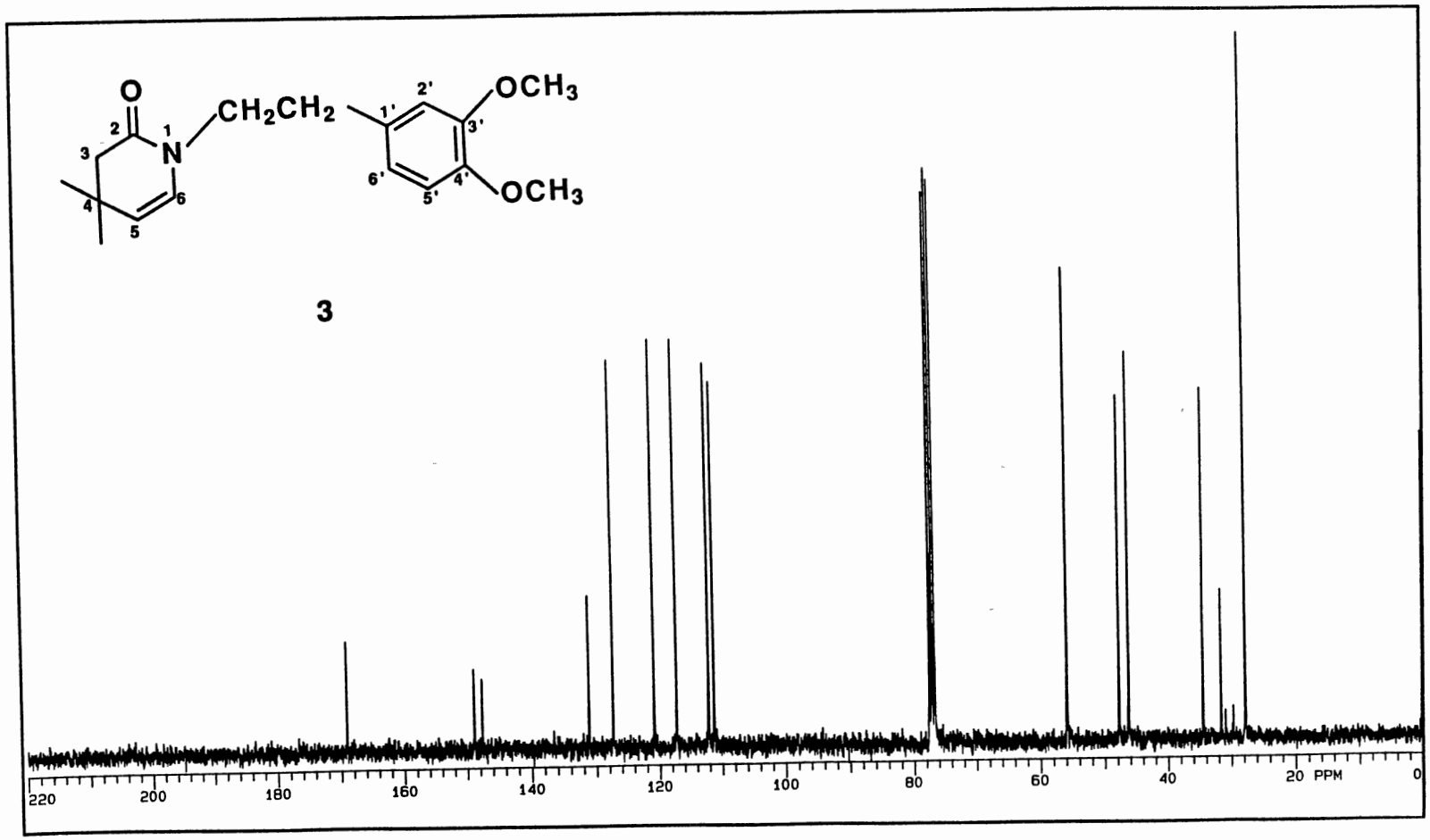
14

# APPENDIX B

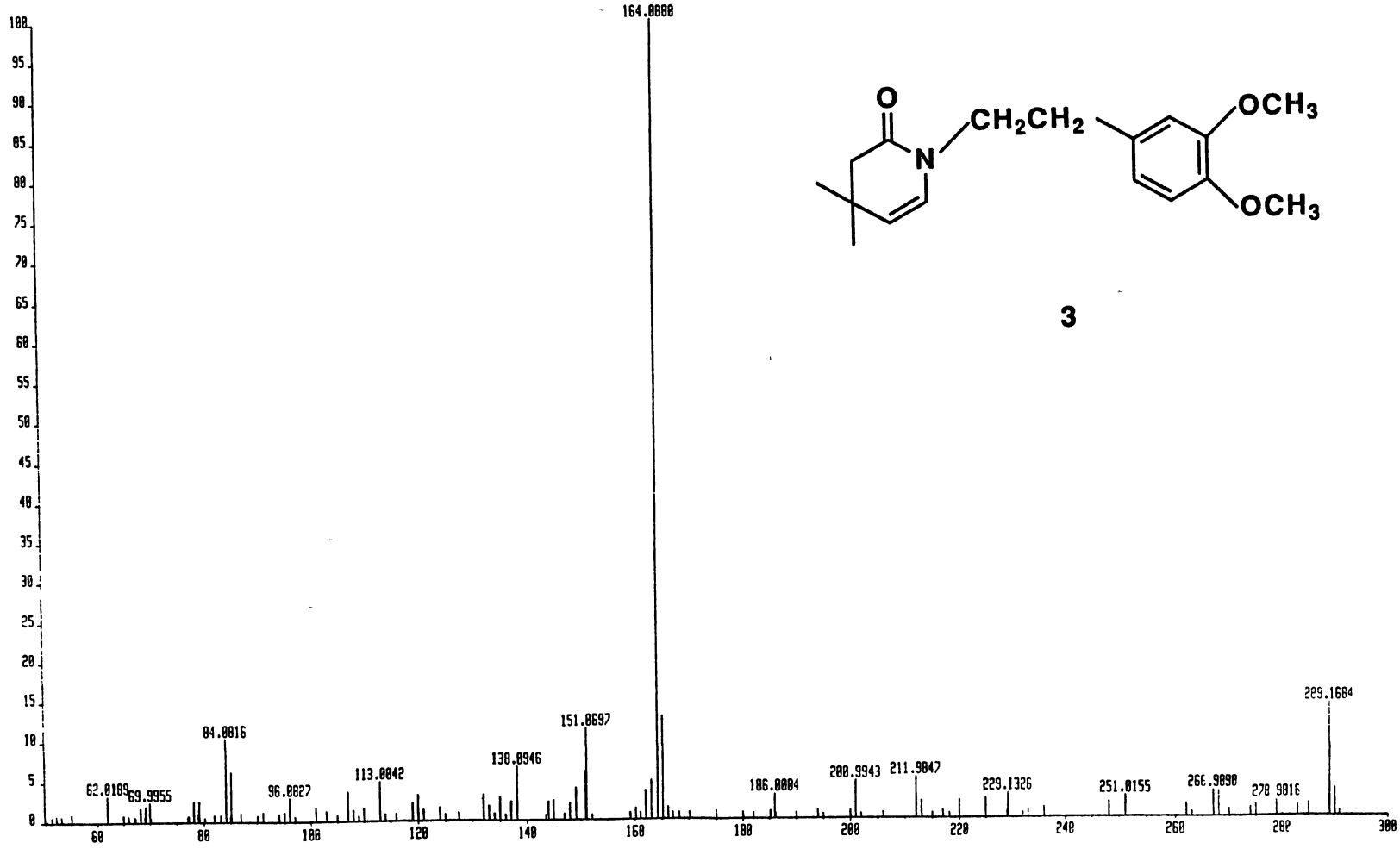
## SELECTED NMR AND MS SPECTRA



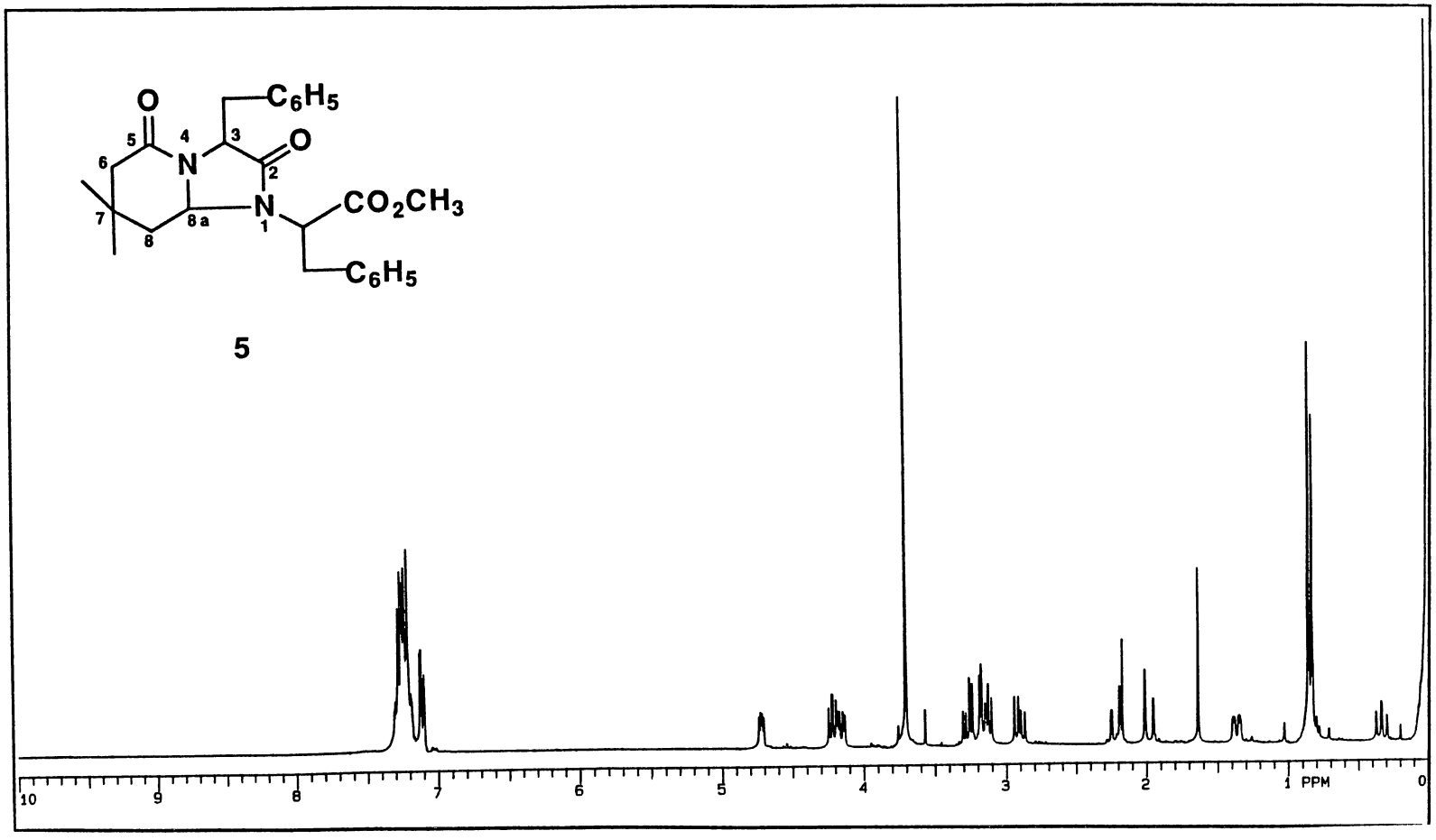

**Spectrum 1.** $^{1}$H NMR Spectrum of 3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (**3**).



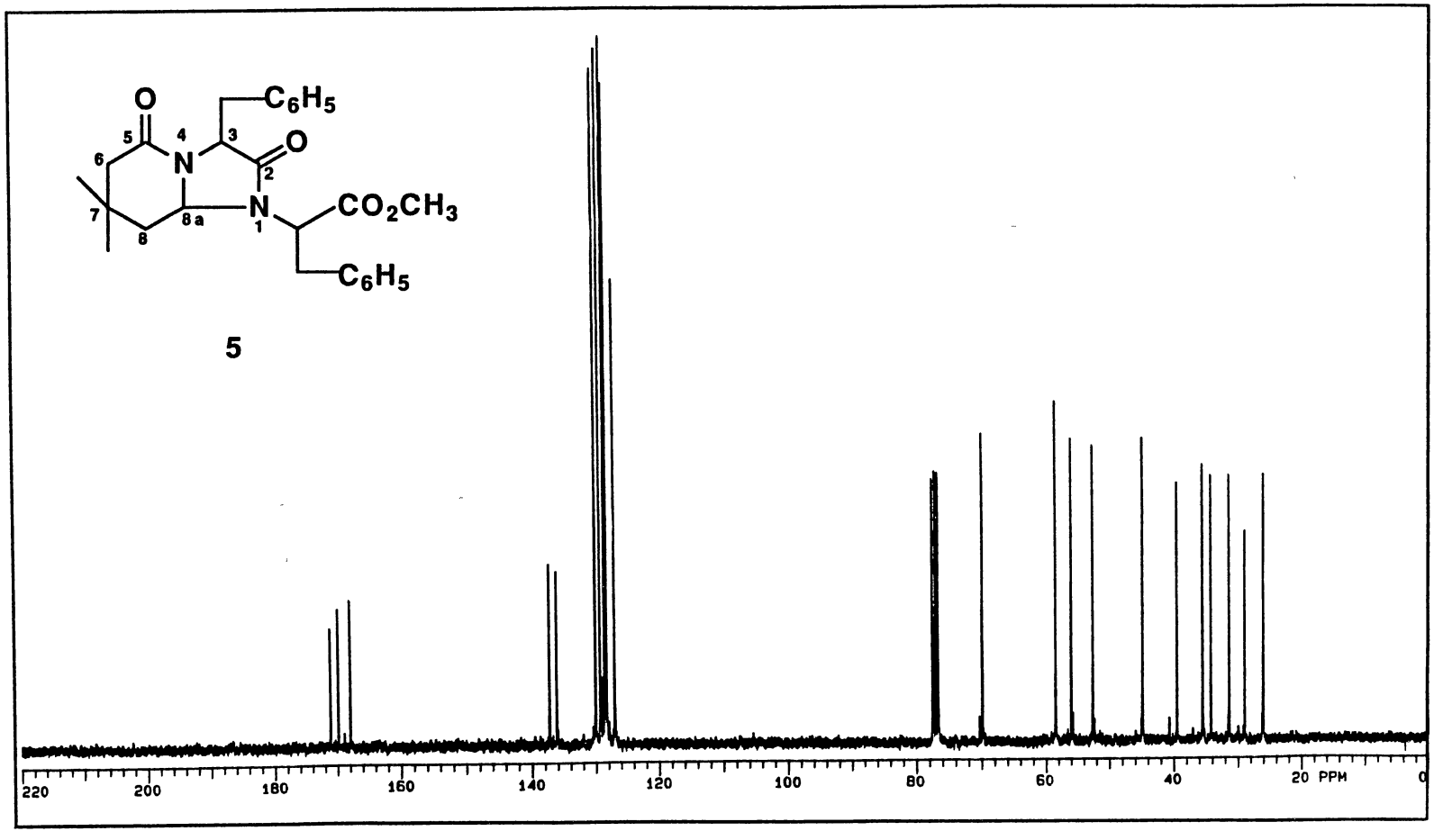

**Spectrum 2.** $^{13}C$ NMR Spectrum of 3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (**3**).



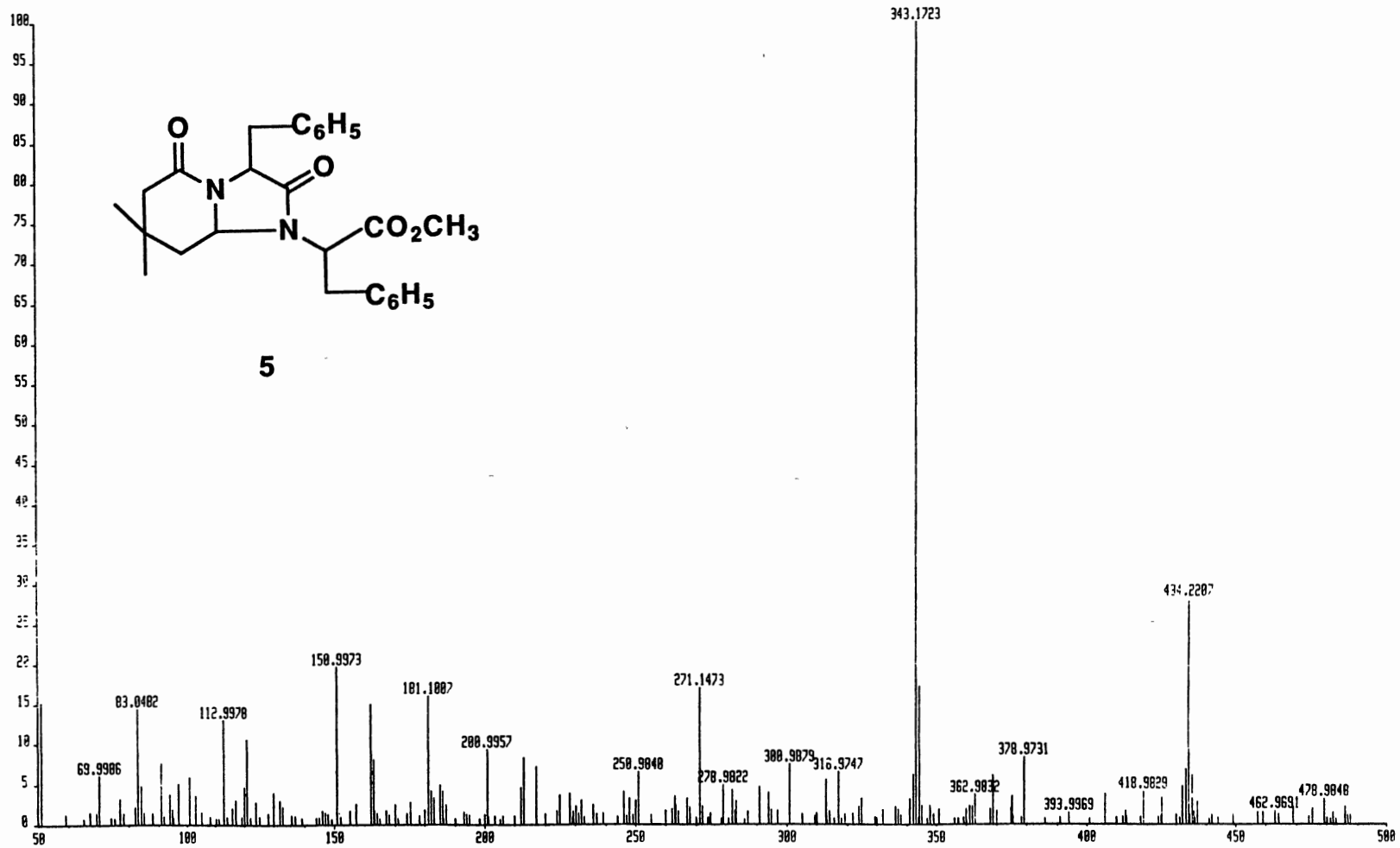

**Spectrum 3**. Exact Mass Spectrum of 3,4-Dihydro-1-(2-(3,4-dimethoxyphenyl)ethyl)-4,4-dimethyl-2(1*H*)-pyridinone (**3**).



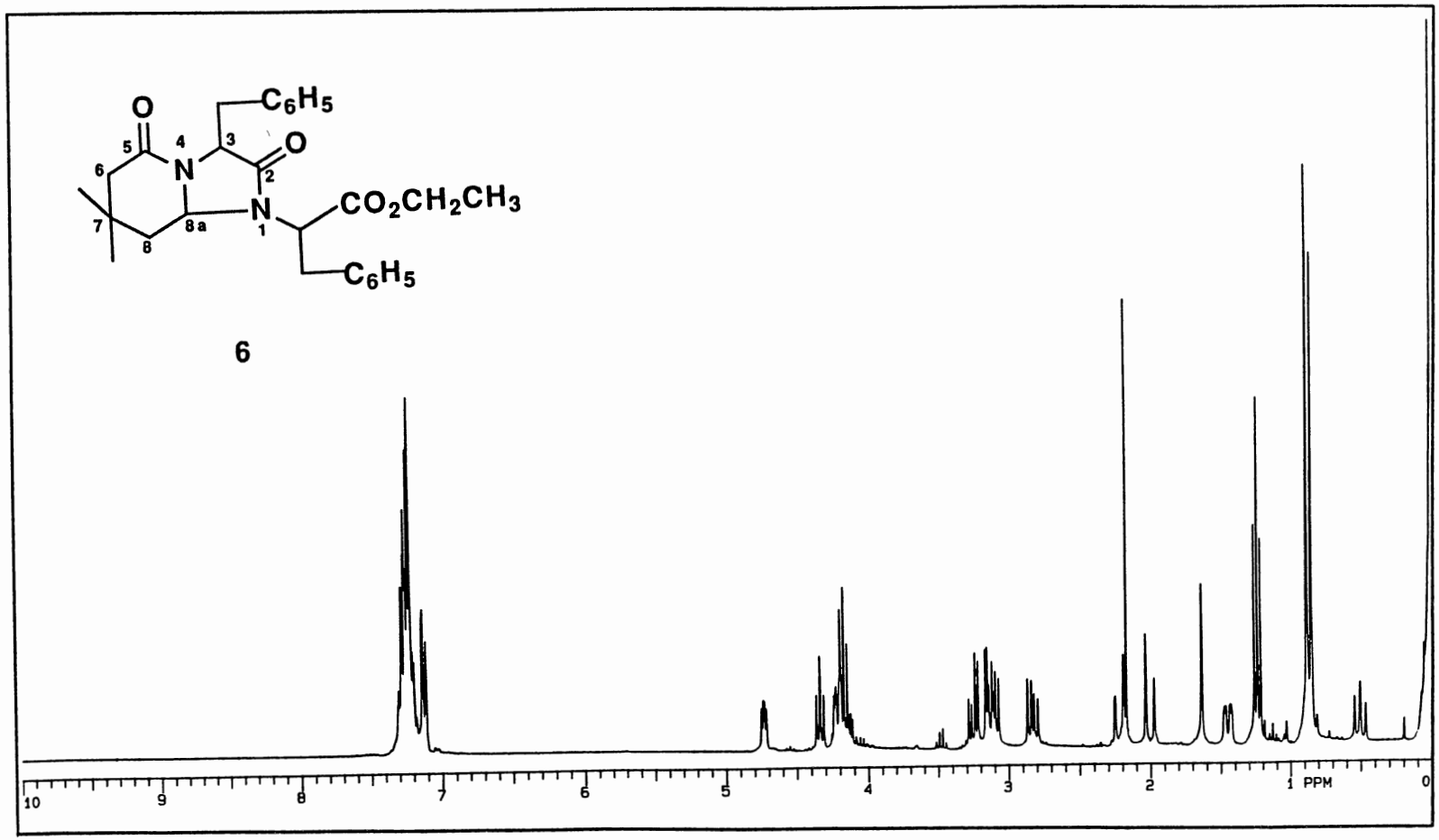

**Spectrum 4**. $^1$H NMR Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).



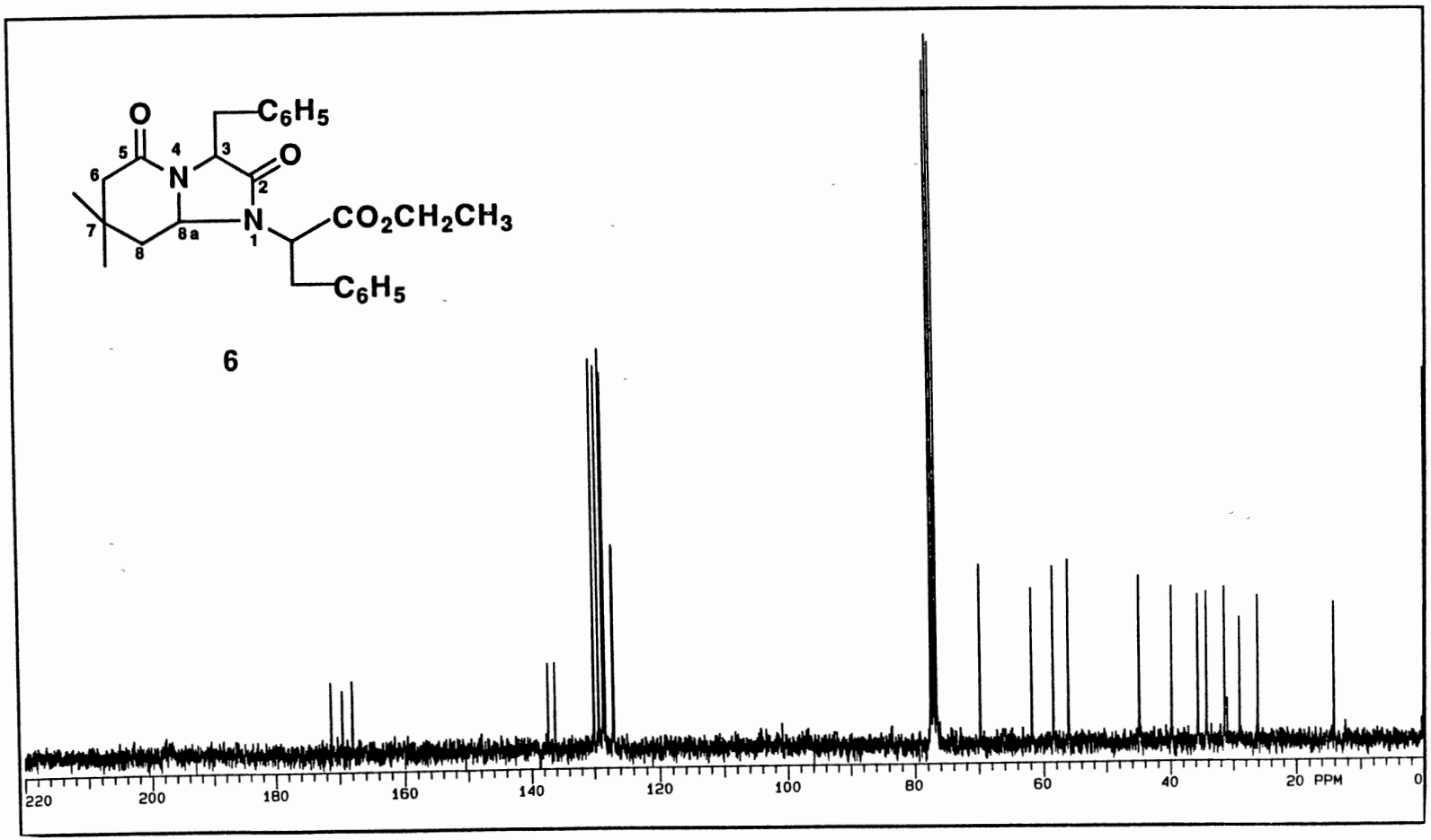

**Spectrum 5.** $^{13}C$ NMR Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).



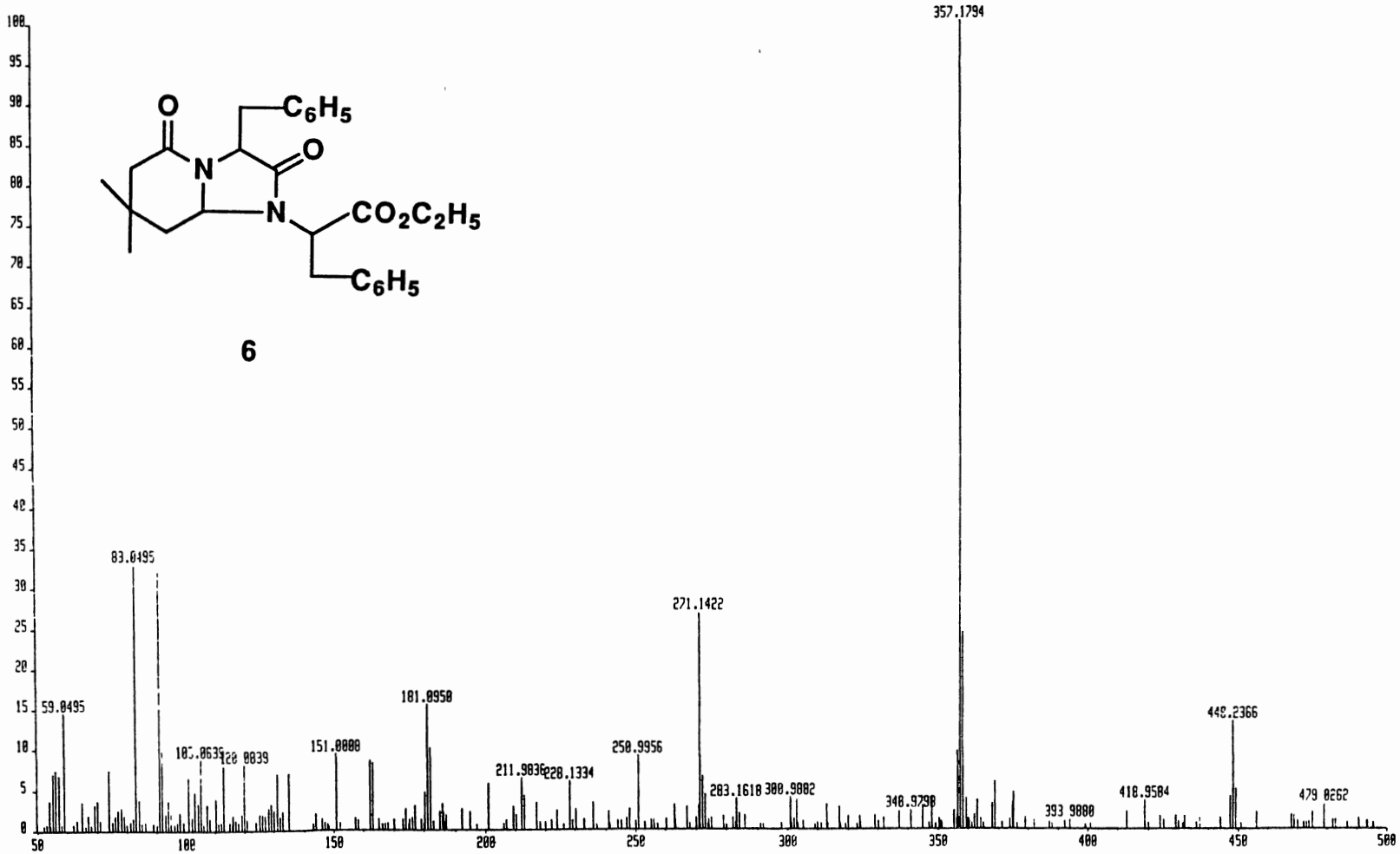

**Spectrum 6**. Exact Mass Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-methoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**5**).



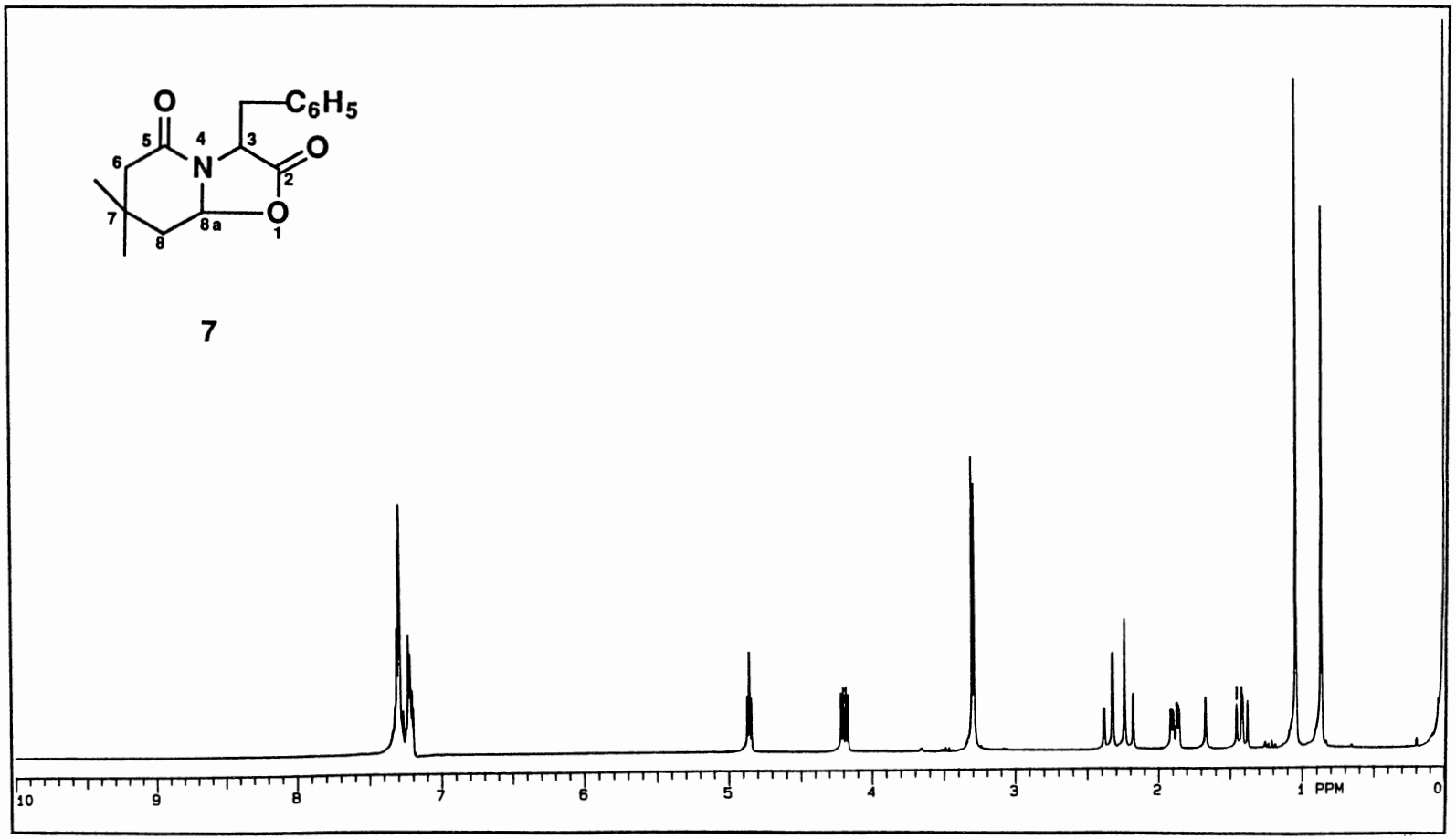

**Spectrum 7**. $^{1}$H NMR Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-ethoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**6**).



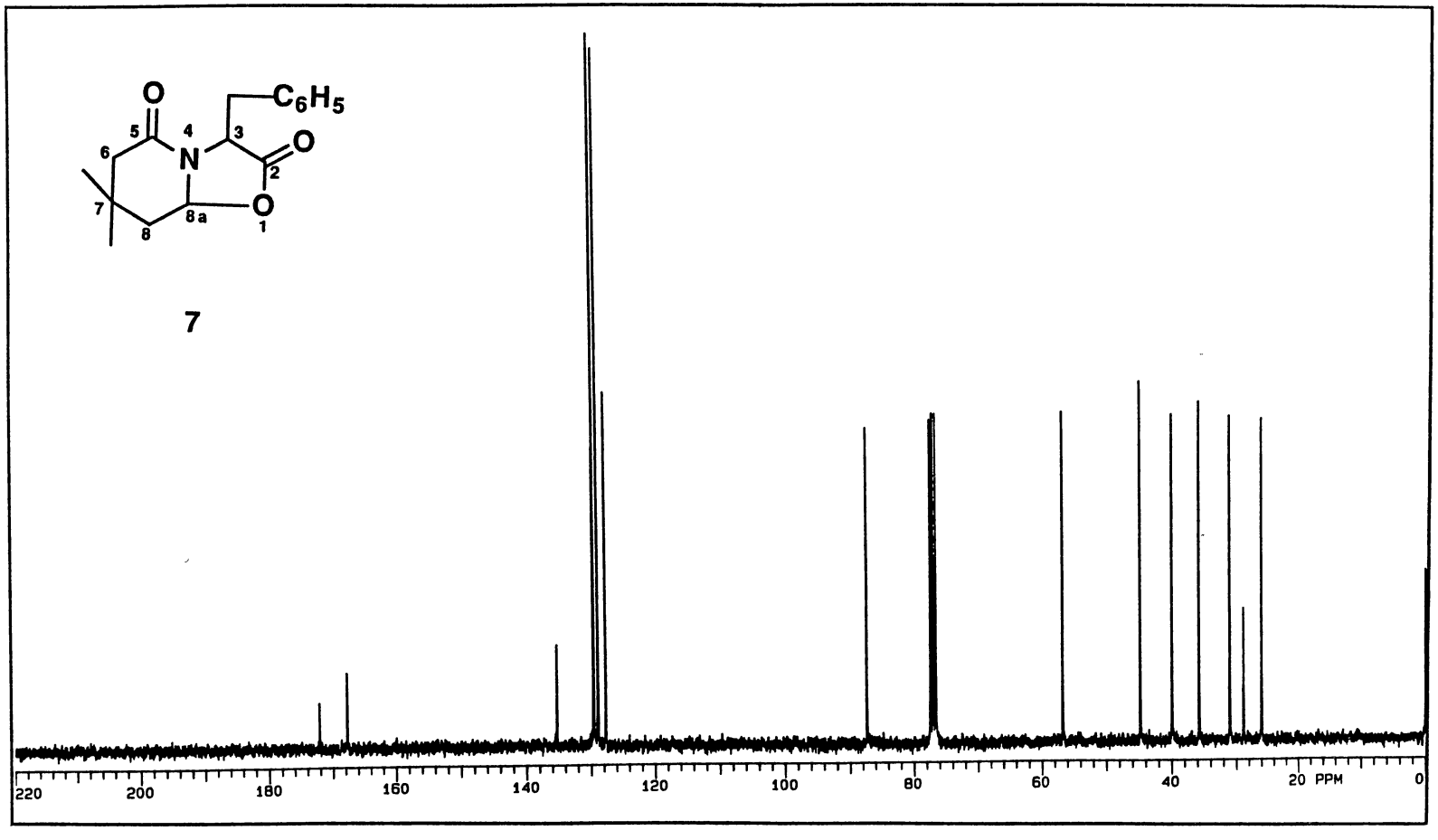

**Spectrum 8.** $^{13}C$ NMR Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-ethoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**6**).



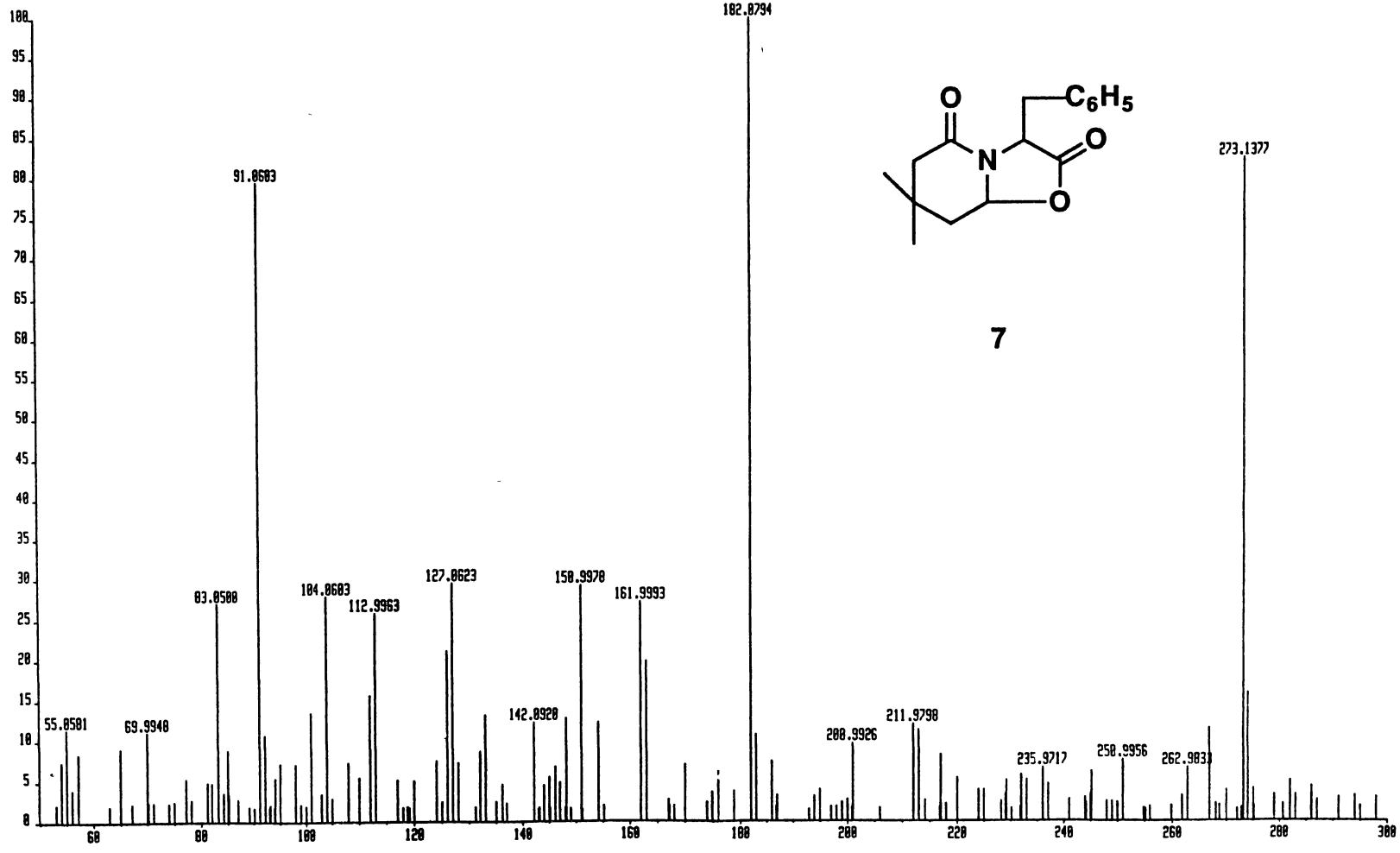

**Spectrum 9**. Exact Mass Spectrum of 3-Benzyl-8(7*H*),8a(1*H*)-dihydro-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-1-(1-ethoxycarbonyl-2-phenylethyl)imidazo[1,2-*a*]pyridine (**6**).



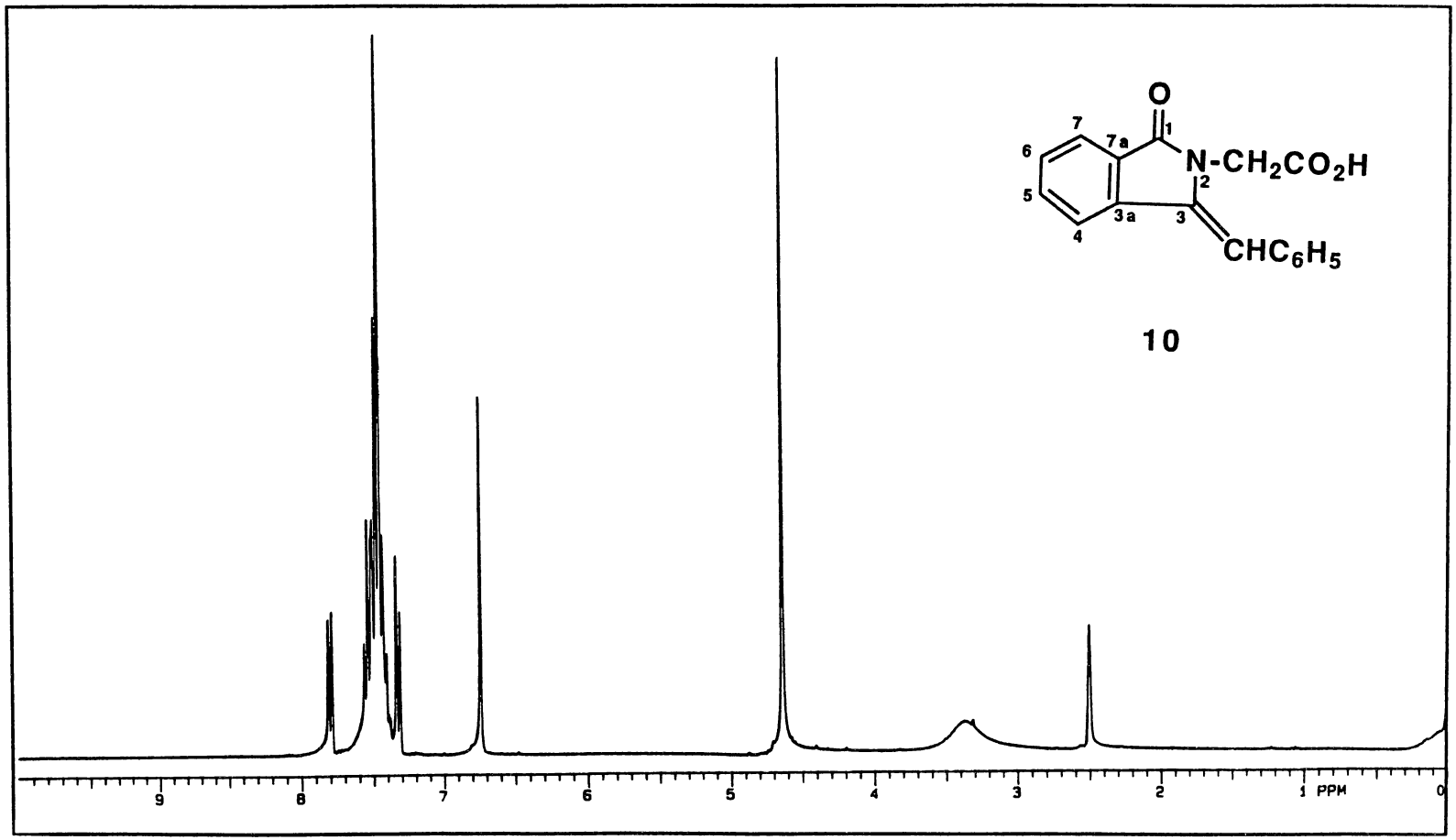

**Spectrum 10**. $^{1}$H NMR Spectrum of 3-Benzyl-7,7-dimethyl-2(3*H*),5-dioxo-5,6,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine (**7**).



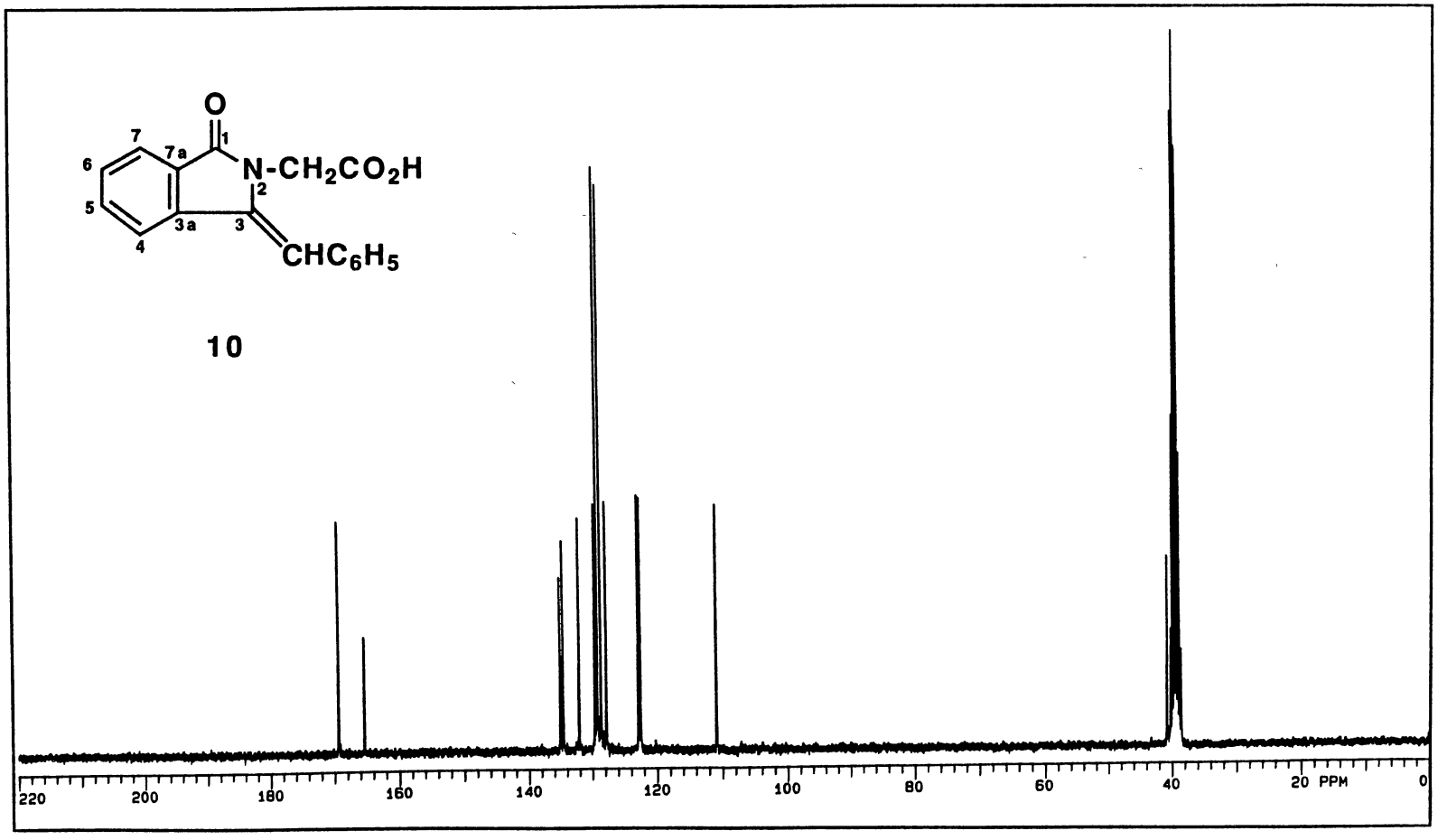

**Spectrum 11.** $^{13}C$ NMR Spectrum of 3-Benzyl-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-8,8a-dihydro-7*H*-oxazolo[3,2-*a*]pyridine (**7**).



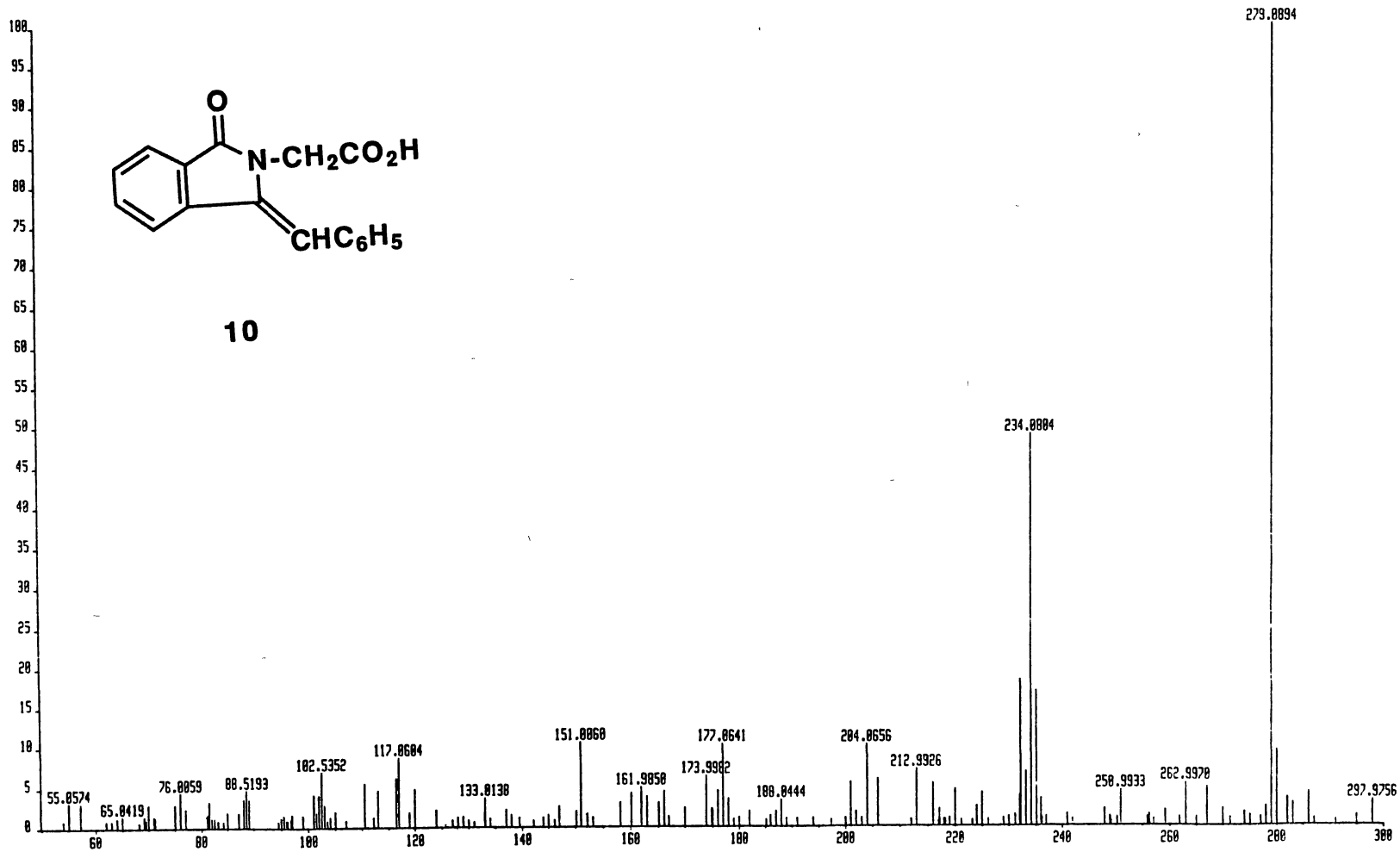

**Spectrum 12.** Exact Mass Spectrum of 3-Benzyl-7,7-dimethyl-2(3*H*),5(6*H*)-dioxo-8,8a-dihydro-7*H*-oxazolo[3,2-*a*]pyridine (**7**).



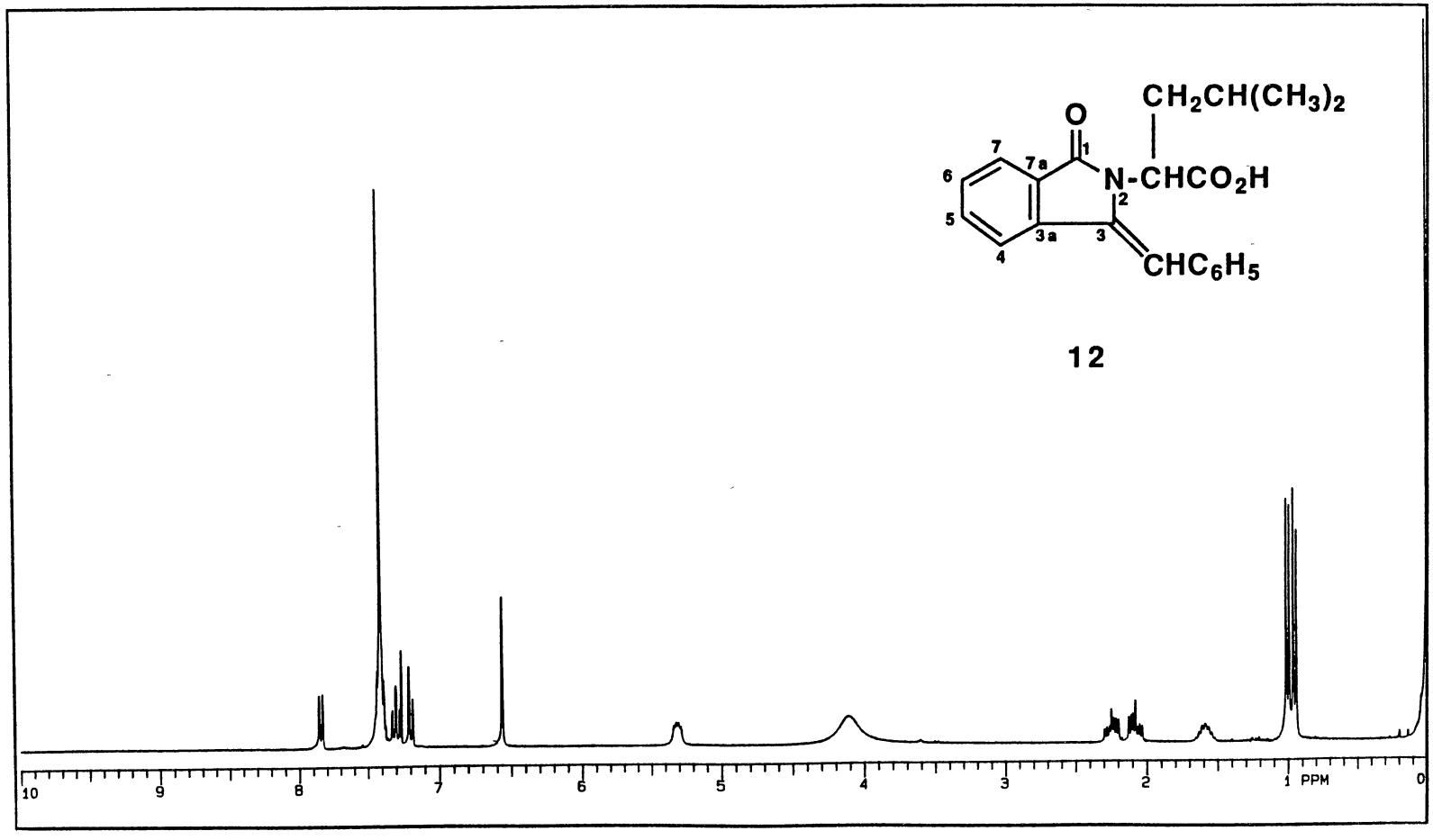

**Spectrum 13.** $^{1}H$ NMR Spectrum of 2-Carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole (**10**).



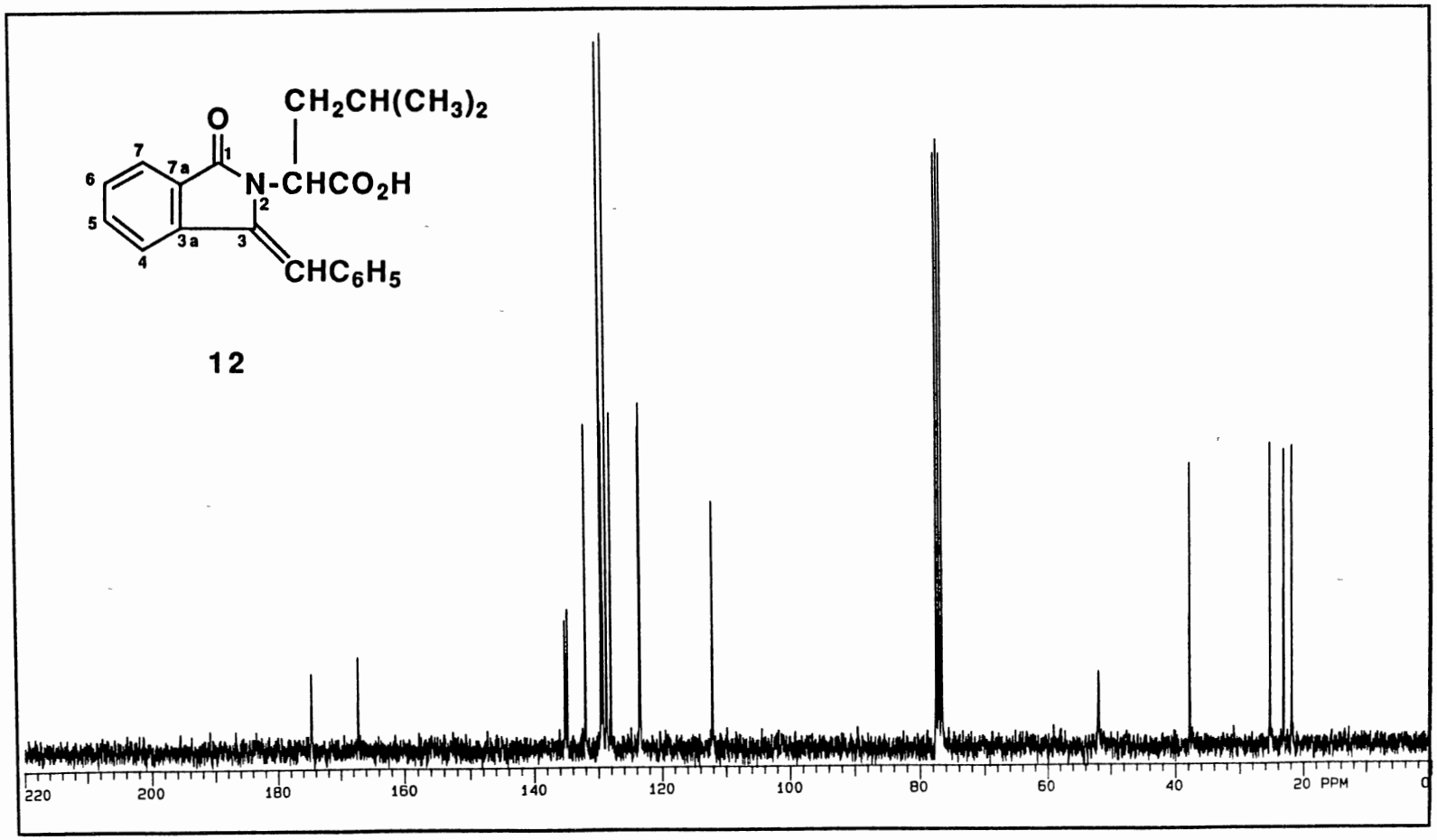

**Spectrum 14.** $^{13}C$ NMR Spectrum of 2-Carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole (**10**).



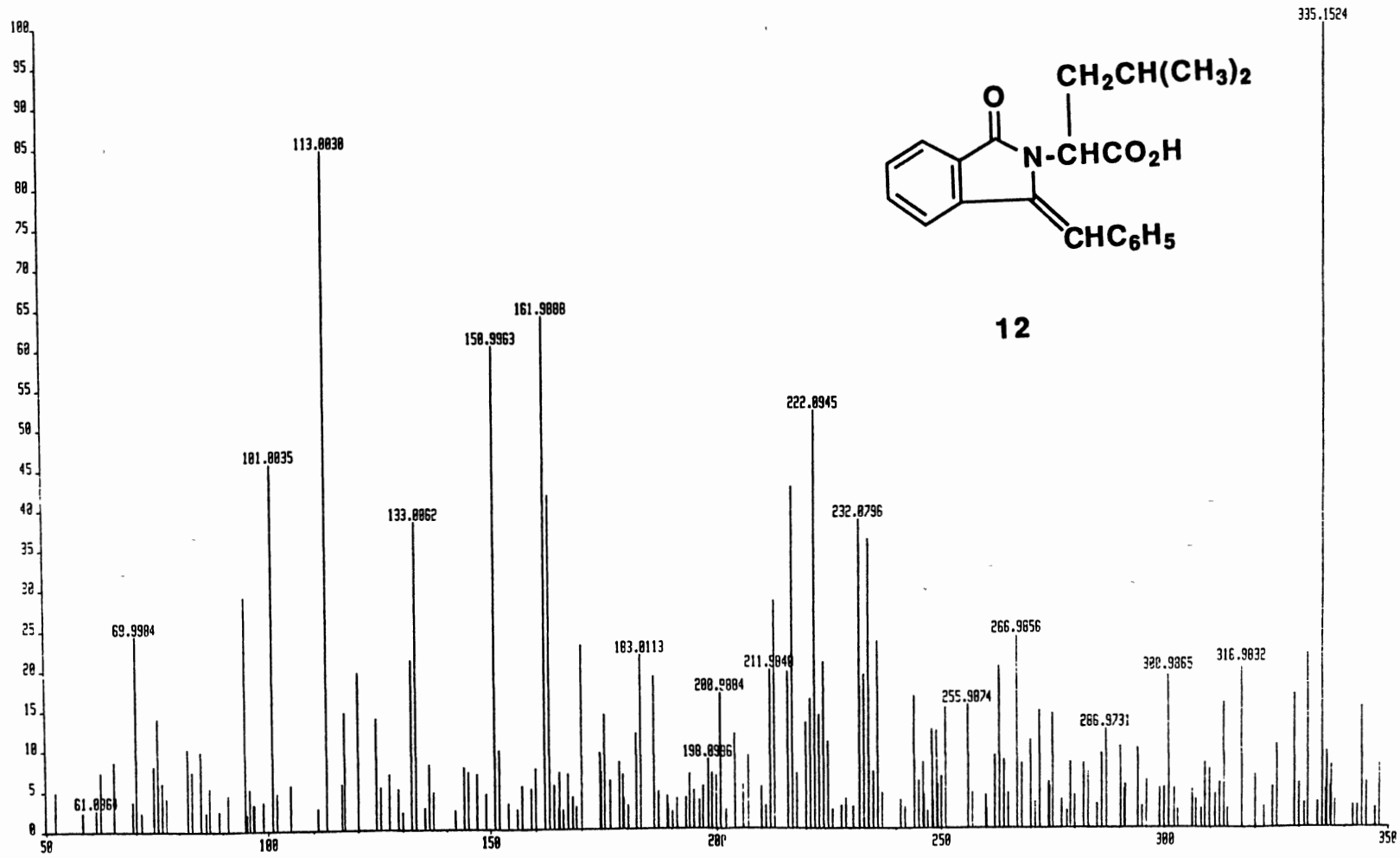

**Spectrum 15.** Exact Mass Spectrum of 2-Carboxymethyl-1-oxo-3-phenylmethylene-1*H*-isoindole (**10**).



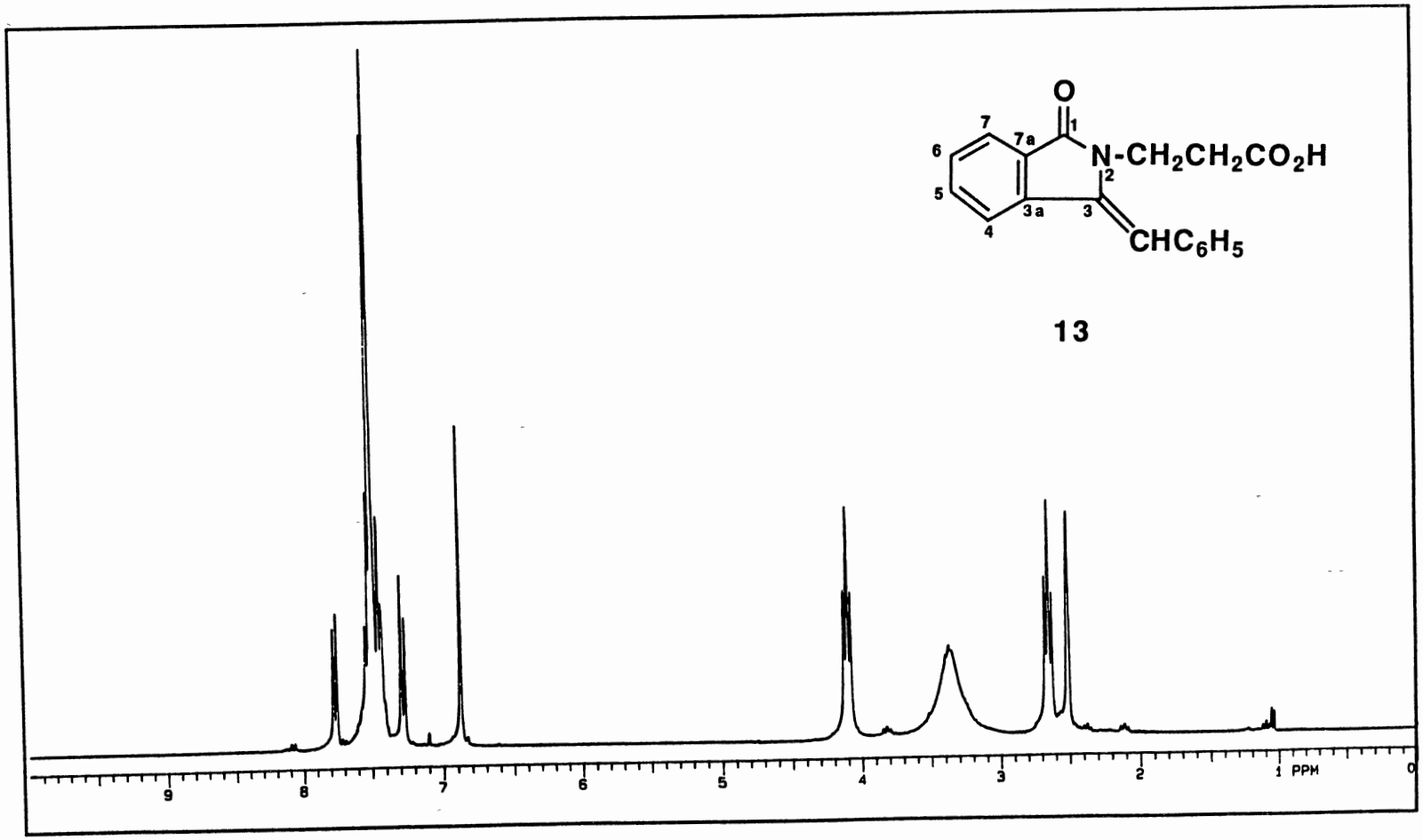

**Spectrum 16.** $^{1}H$ NMR Spectrum of 2-(1-Carboxy-3-methylbutyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**12**).



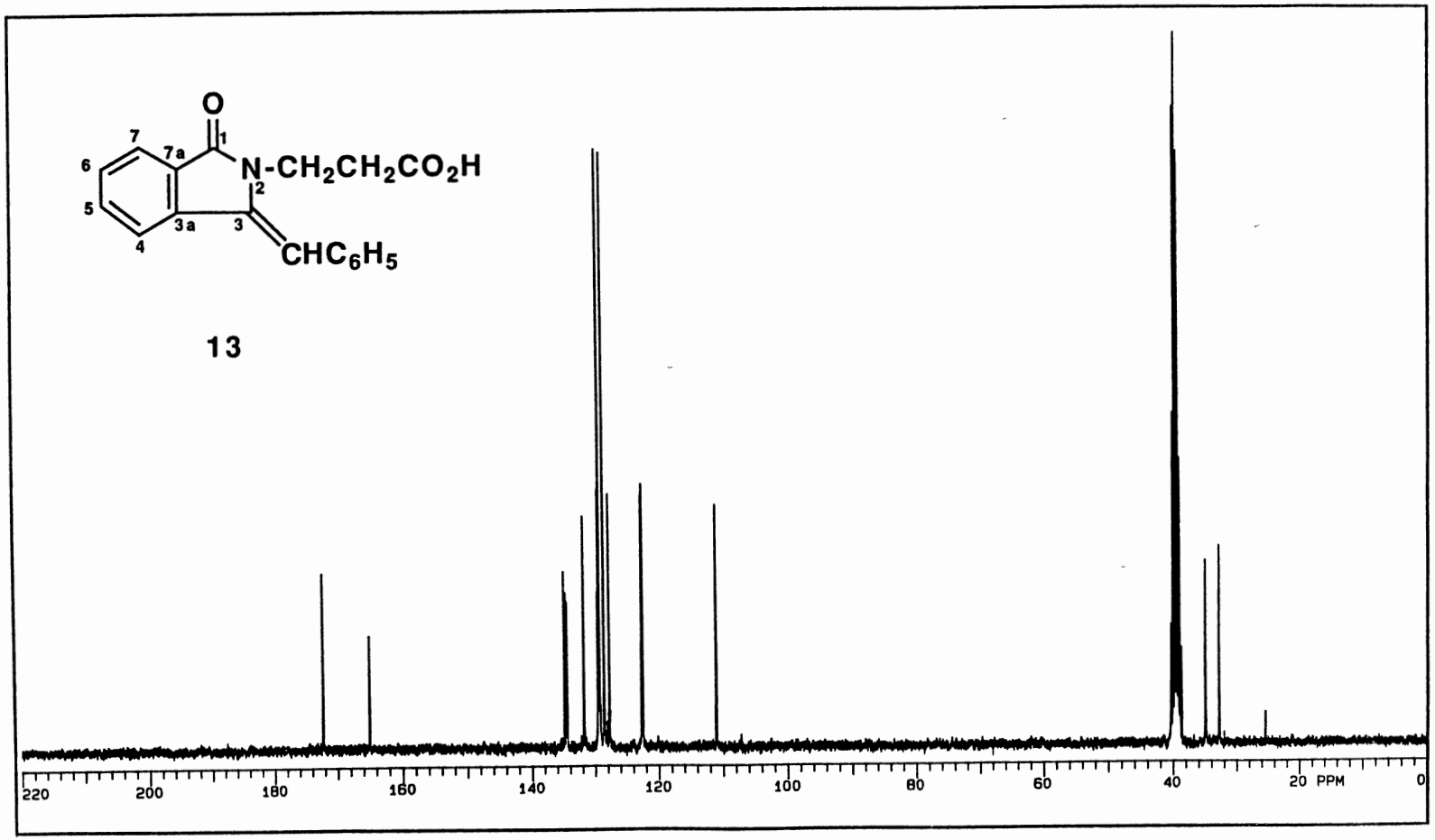

**Spectrum 17.** $^{13}C$ NMR Spectrum of 2-(1-Carboxy-3-methylbutyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**12**).



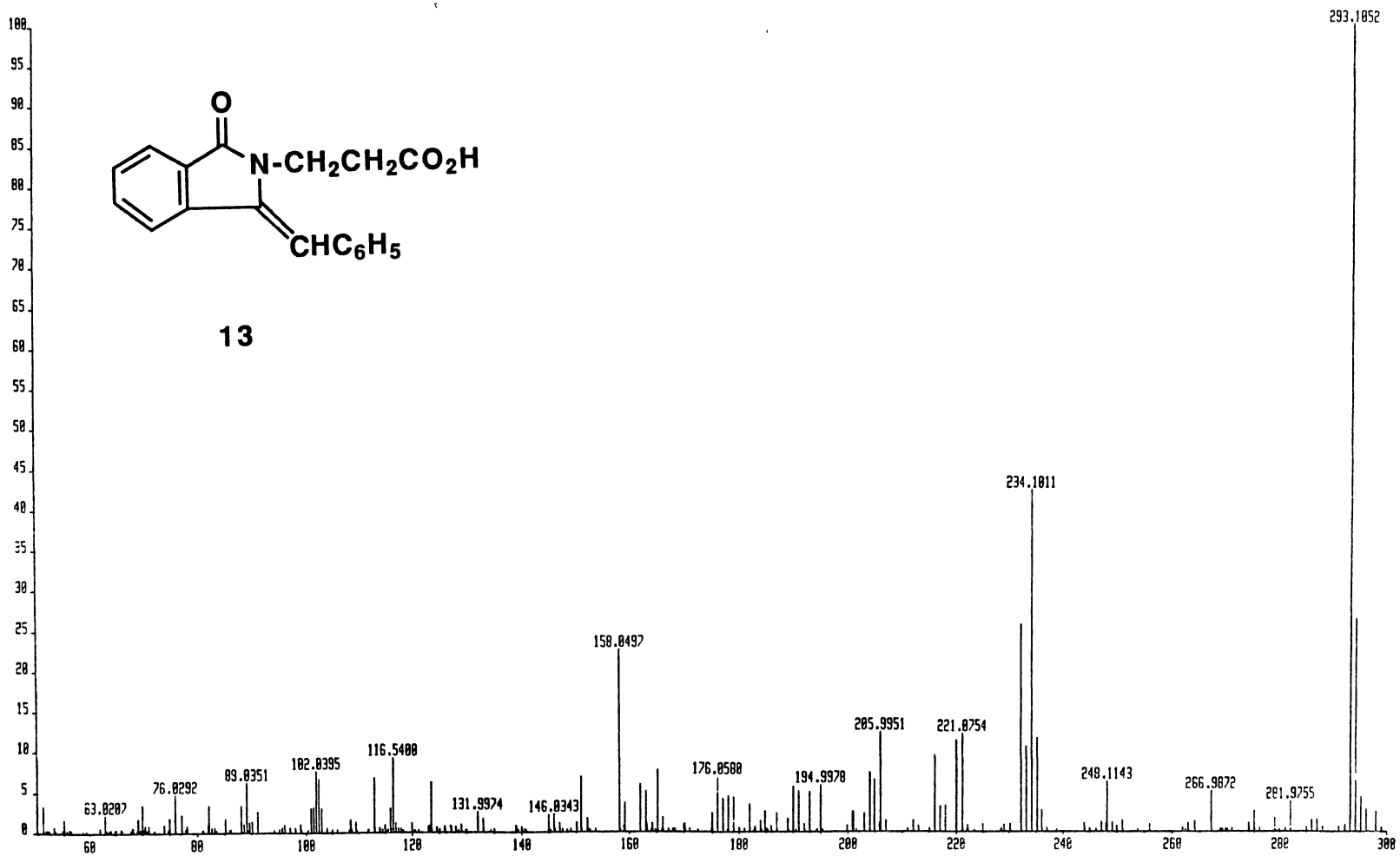

**Spectrum 18.** Exact Mass Spectrum of 2-(1-Carboxy-3-methylbutyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**12**).



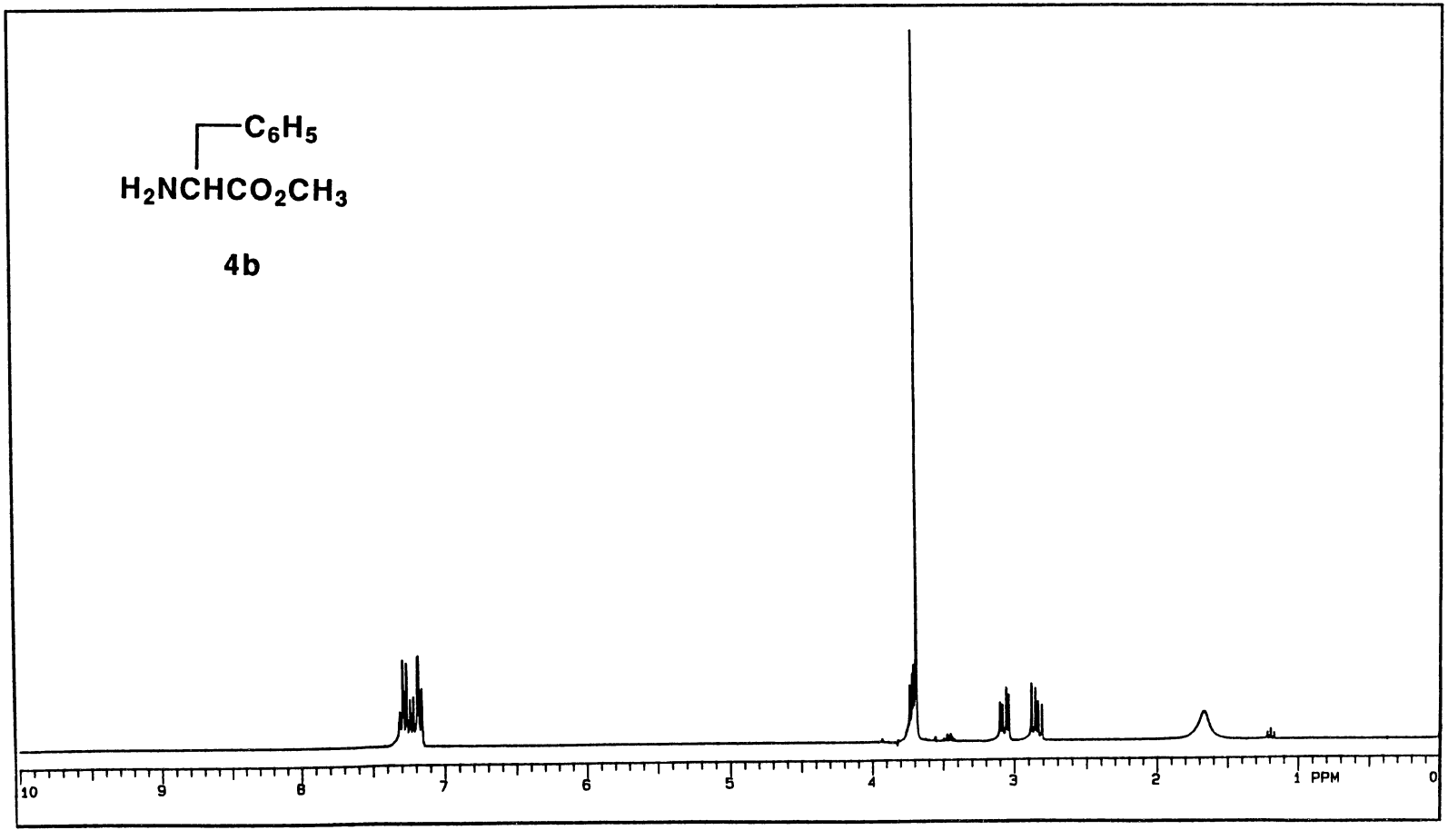

**Spectrum 19.** $^{1}$H NMR Spectrum of 2-(2-Carboxyethyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**13**).



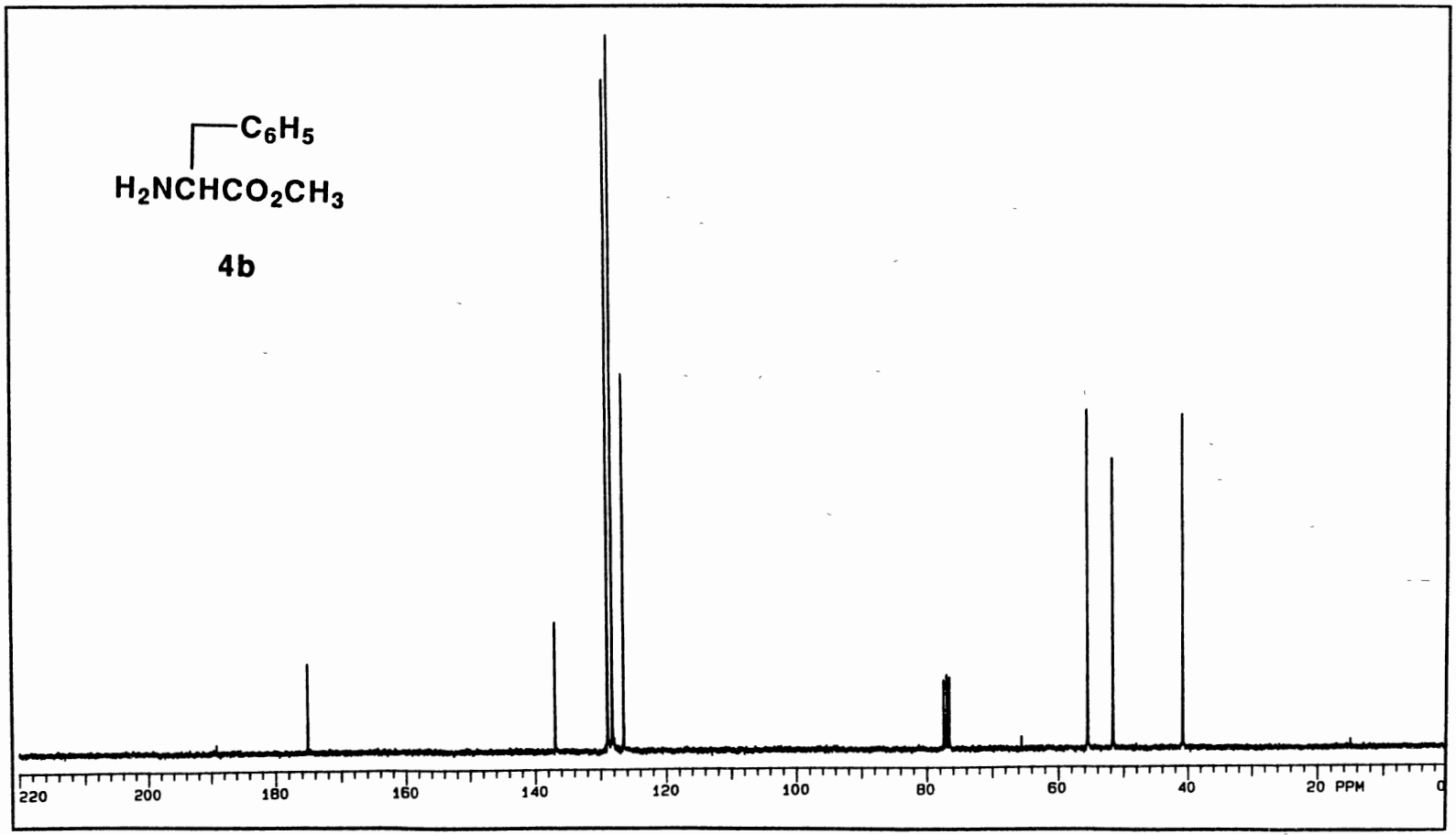

**Spectrum 20.** $^{13}C$ NMR Spectrum of 2-(2-Carboxyethyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**13**).




**Spectrum 21.** Exact Mass Spectrum of 2-(2-Carboxyethyl)-1-oxo-3-phenylmethylene-1*H*-isoindole (**13**).




**Spectrum 22.** $^{1}H$ NMR Spectrum of L-Phenylalanine Methyl Ester (**4b**).




**Spectrum 23.** $^{13}C$ NMR Spectrum of L-Phenylalanine Methyl Ester (**4b**).

VITA

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