INVESTIGATIONS

INTO THE

REACTIONS

OF

IMINES AND ENAMINES

by

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To My Family

"Is life what you make of it,

or is your destiny simply faith"

DECLARATION

The experimental work described in this thesis was carried out in the Department of Chemistry, University of Natal, Durban, under the supervision of Professor P.W. Hickmott.

This study represents original work by the author and has not been submitted in any other form to another university. Where use was made of the work of others it has been duly acknowledged in the text.

Signed : 

H.A Mahomed B.Sc (Hons) (Natal)

I hereby certify that the above statement is correct.

Signed : 

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ABSTRACT

Recent work in our laboratory has led to a new synthesis of the 2-oxo-$\Delta^{8,8a}$-hexahydroquinoline ring system. This involved the condensation of ß-alkylaminopropanoates with 2-methylcyclohexanone. Further reactions of ß-aminopropanoates with other cyclic ketones and acyclic ketones have been investigated and are now reported. These reactions are found to be sensitive to steric effects, the stability of the ketone and the presence of molecular sieves and have led not only to the synthesis of the quinolone ring system but also to the inden-7-one and pyridone ring systems.

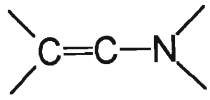
A new one pot synthesis of the bicyclo[2.2.2]octan-5-one ring system from acyclic precursors has recently been reported. Reaction of two equivalents of phenyl vinyl ketone with one equivalent of N-2-butylidenebenzylamine has lead to the synthesis of 2-benzoyl-4-methyl-1-phenylbicyclo[2.2.2]octan-5-one as a mixture of two isomers. This reaction has now been extended to N-2-(4-phenylbutylidene)propylamine and ethyl N-propyl-4-iminopentanoate and our findings are reported.

CONTENTS

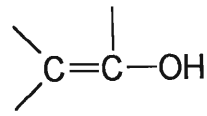
INTRODUCTION

1.0 INTRODUCTION

The term enamine was first introduced by Wittig and Blumenthal[1] in 1927 and indicated an unsaturated amine structure (1a) which is analogous to an enol (1b).



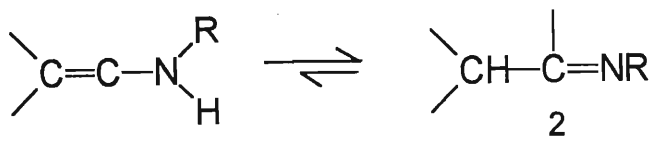
1a



1b

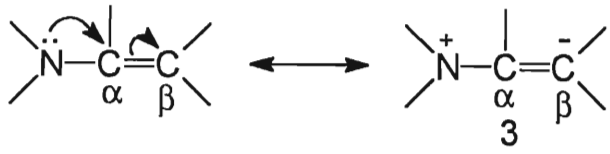
The amino group may be primary, secondary or tertiary with the tertiary enamine being very important synthetically. Since the pioneering work of Stork *et al.*[2] the preparation and reaction of enamines have received appreciable attention.

Opitz *et al.*[3] have shown that if the amine used is primary or secondary then the imine (Schiffs base) tautomer is most favourable (2), unless the enamine tautomer is stabilized by further conjugation with, usually, a carbon-carbon or carbon-oxygen double bond.



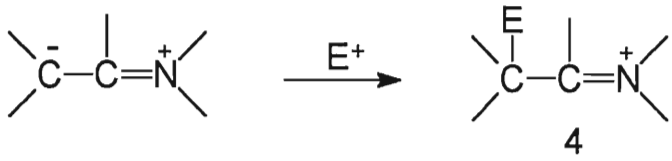
2

A permanent polarization and an increased electron density of the ß-carbon atom[4,5] of the enamine molecule, results from the interaction between the orbital of the nitrogen atom containing the lone pair of electrons and the π-electrons of the carbon-carbon double bond, thereby giving rise to the other canonical form of the enamine (3).



3

As a result of this excess electron density, electrophilic attack may occur at the ß-carbon atom of the enamine giving the iminium cation (4) or, to a varying extent, at the nitrogen atom to give the enammonium cation (5).



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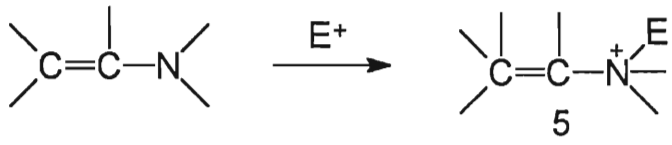


5

As previously mentioned, the full scope of using enamines as reactive intermediates in organic synthesis was foreseen after Stork published his reports on enamines derived from aldehydes and ketones. The C-alkylation and acylation of a carbonyl group via an enamine intermediate, has consequently become known as the Stork reaction.[6]

The many publications of Stork *et al.* in the area of enamine chemistry referred to factors effecting structure and reactivity[7], spectroscopic data, alkylation with alkyl halides and electrophilic olefins, preparations, synthesis of carbocyclic compounds, the tosylation of enamines[8], synthesis of bridged bicyclic compounds and ring enlargement[9],

heterocyclic synthesis,[10,11] natural product synthesis,[12] and the formation and reactions of metallo-enamines.[13]

Further research in the field of enamine chemistry since 1954 has shown that the Stork reaction is dependent on various experimental conditions including changes in solvent, amine moiety in the enamine, reaction temperature, presence of a catalyst, molar proportion of reactants, and order and temperature of mixing. Therefore, the same enamine and the same electrophile can give completely different products on relatively trivial changes in experimental conditions. Because of the diversity of products obtained, Hickmott[6] has proposed an extension to the definition of the Stork reaction to include "**conversion of an aldehyde or ketone into a C-alkylated, acylated, carbocyclic, or heterocyclic derivative by reaction of an electrophile with an enamine intermediate**". Unlike other methods for carbon-carbon bond formation the enamine reaction is a mild and reliable method which readily produces mono-alkylated/acylated products free from O-substituted and, to some extent, disubstituted impurities.

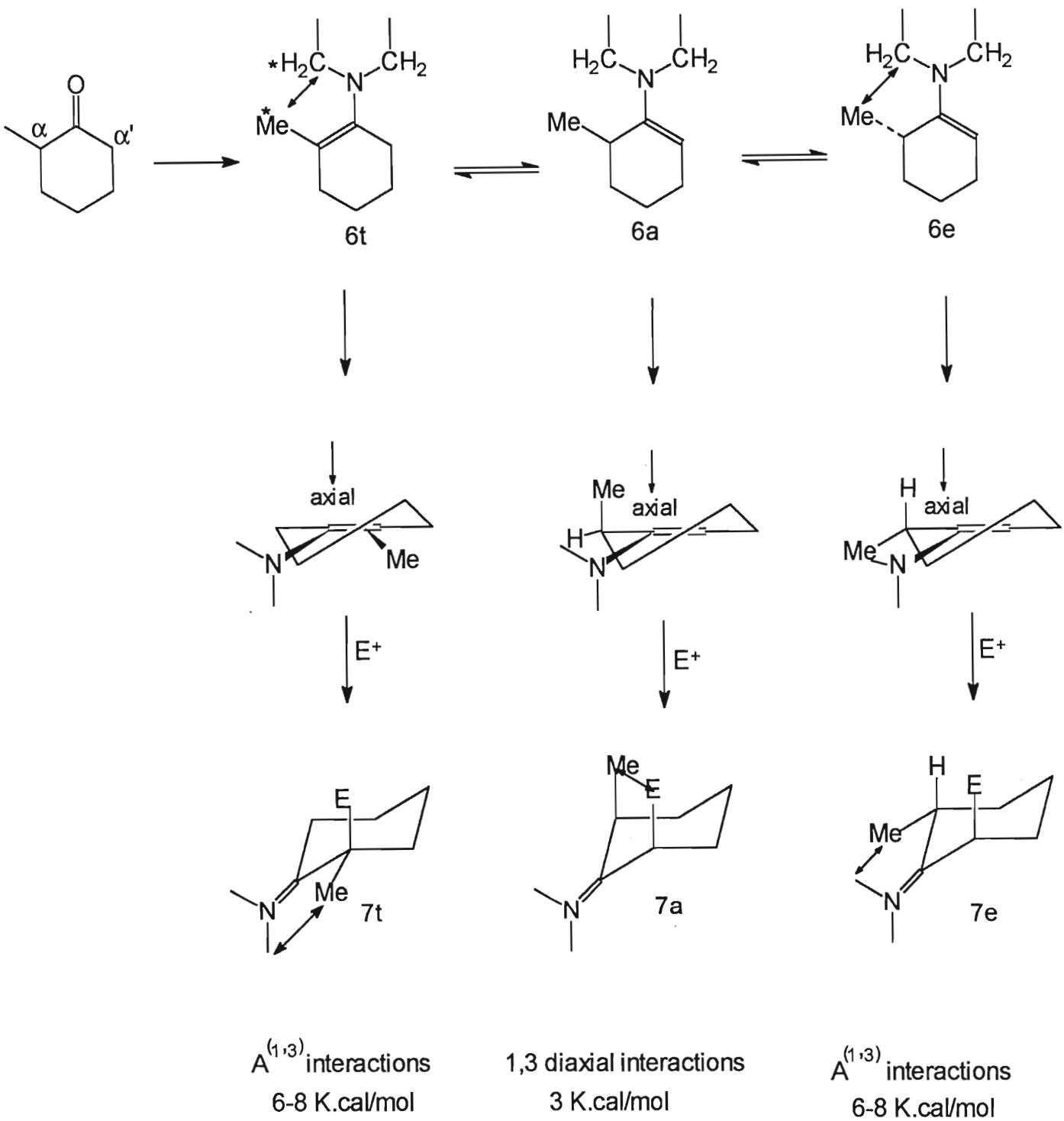
1.1 STRUCTURE AND REACTIVITY

Enamines obtained from unsymmetrical ketones such as 2-alkylcyclanones and branched chain acyclic ketones are generally present as mixtures of structurally isomeric enamines. Johnson *et al.*[14] have shown that these enamines undergo rapid equilibration in acid, but no base or thermal catalysed equilibration has been observed.

Gurowitz and Joseph[15] have reported that enamines derived from 2-methylcyclohexanone, existing as the isomer with the less substituted double bond (6e,a) rather than the more substituted isomer (6t), is highly dependent on the substituent on the nitrogen and the 2-methyl substituent.

The pyrrolidine enamine of 2-methylcyclohexanone exists as approximately 10 % in the more substituted form, whereas the morpholine and piperidine enamines exist in approximately equal proportions of both isomers, while the diethylamine enamine exists as 25 % in the less substituted form and 75 % in the more substituted form.

The more substituted isomer (6t) has a tetrasubstituted double bond and is therefore destabilized by large steric interactions, allylic strain, between the 2-methyl substituent and the α-methylene group of the amine moiety. If in the ground state there is rotation about the N-C (sp^2) bond, then the steric interactions between the α-methylene and methyl group could be reduced, but such rotation reduces the orbital

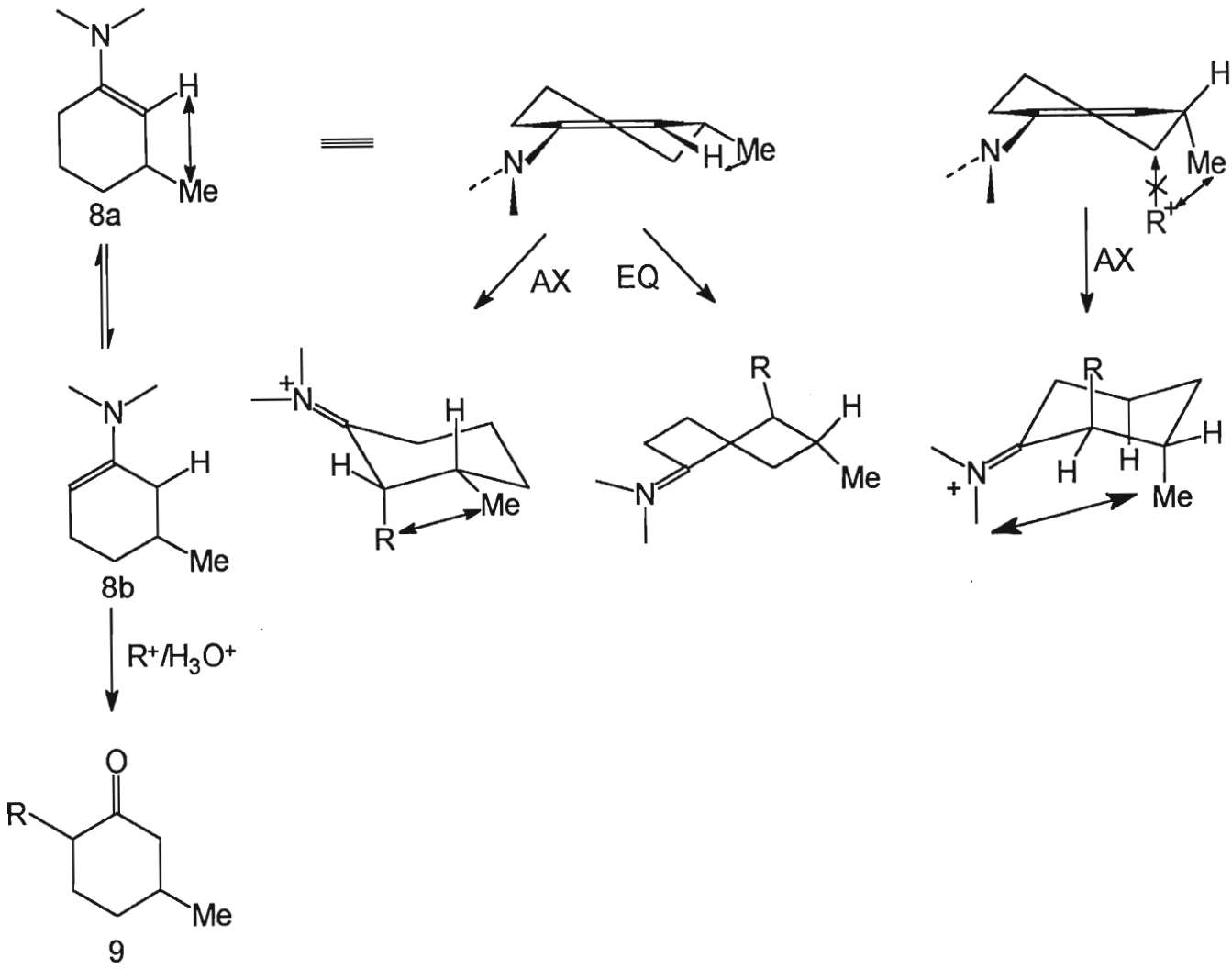


a = quasi-axial; e = quasi-equatorial; t = tetrasubstituted

SCHEME 1

interaction between the nitrogen lone pair and the π-electrons of the double bond. Therefore, in order to minimise the energy of the more substituted double bond isomer (6t) a compromise must be achieved between these two conflicting requirements. The less substituted double bond isomer (6a,e) exists either with the methyl substituent in the quasi-equatorial position (6e) or with the group in the quasi-axial position (6a). The former is destabilized by less severe allylic, $A^{(1,2)}$ strain, interactions and (6a) is therefore the most stable isomer, all other factors being equal. The fact that the methyl group in 2-methylcyclohexanone enamines should be axial was first reasoned by Williamson.[16] This has significant consequences in that α,α-dialkylation of ketones via their enamines is rarely observed since, for maximum orbital interaction between the nitrogen lone pair and the π-electrons of the double bond, the starred groups in (6t) must be coplanar. A product-like transition state should be destabilized by the increasing $A^{(1,3)}$-interactions. Therefore further alkylation or acylation takes place at the less substituted α'-position (of the ketone) but at slower rate due to developing 1,3-diaxial interactions as shown in (7a), or due to developing steric effects associated with a twist or boat conformation if attack occurs from the equatorial side (7e). Hickmott[6] considers axial attack on (6e) to be a higher energy process than axial attack on (6a) due to developing $A^{(1,3)}$ strain interactions in the transition state. It also appears that equatorial attack is less favoured. However α,α-dialkylation of

2-methylcyclohexanone can be achieved by alkylation of the 2-methylcyclohexanone "imines" with electrophilic alkenes.[17]



AX = axial attack of electrophile R^+
EQ = equatorial attack

SCHEME 2

Allylic strain can also account for enamines of 3-methylcyclohexanones existing mainly in the form of isomer (8b) and alkylation[18], acylation[19], and halogenation[20], of the

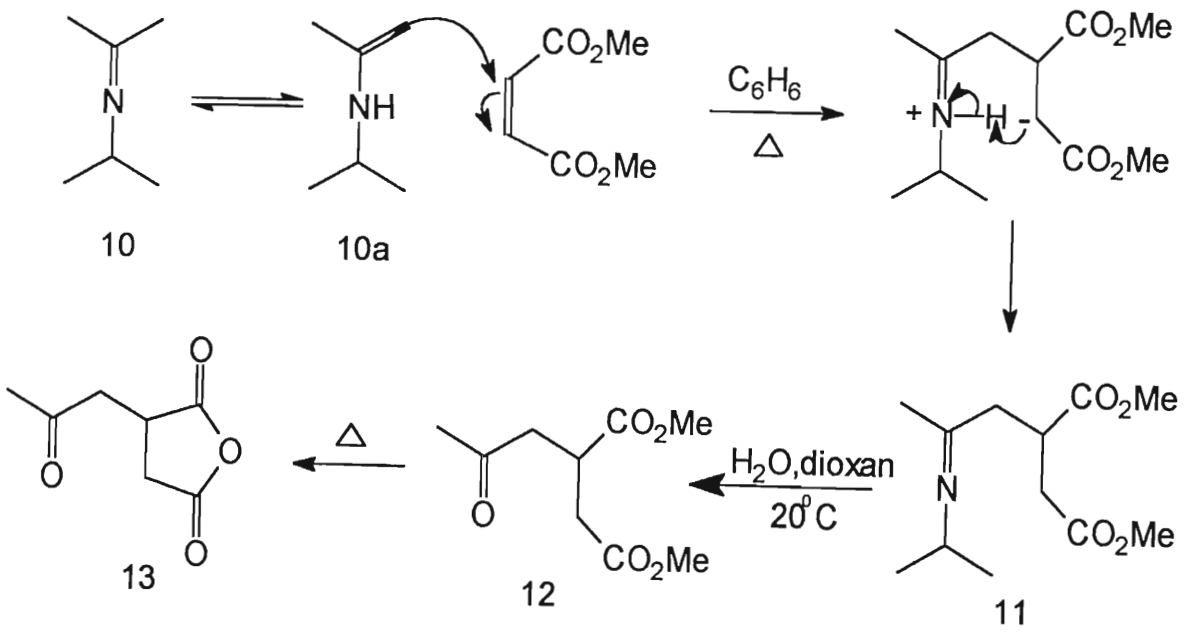
enamine mixture (8a,b) has been shown to give 2-substituted-5-methylcyclohexanones as the major product. Nevertheless, this regioselectivity cannot be attributed to enamine isomer distribution since according to the Curtin-Hammett[21] principle, the population of various structurally isomeric enamines in equilibrium, have no bearing on the course of the reaction provided that the activation energy for enamine interconversion is much lower than that for the reaction. 2,5-disubstituted cyclohexanones have been obtained in yields much higher than the percentage of isomer (8b) present in the parent enamine[18], thus clearly showing the rapid equilibration between the enamine isomers. For product like transition states, formation of 2-substituted-3-methylcyclohexanones are inhibited by developing steric interactions as shown in scheme 2.

1.2 IMINES

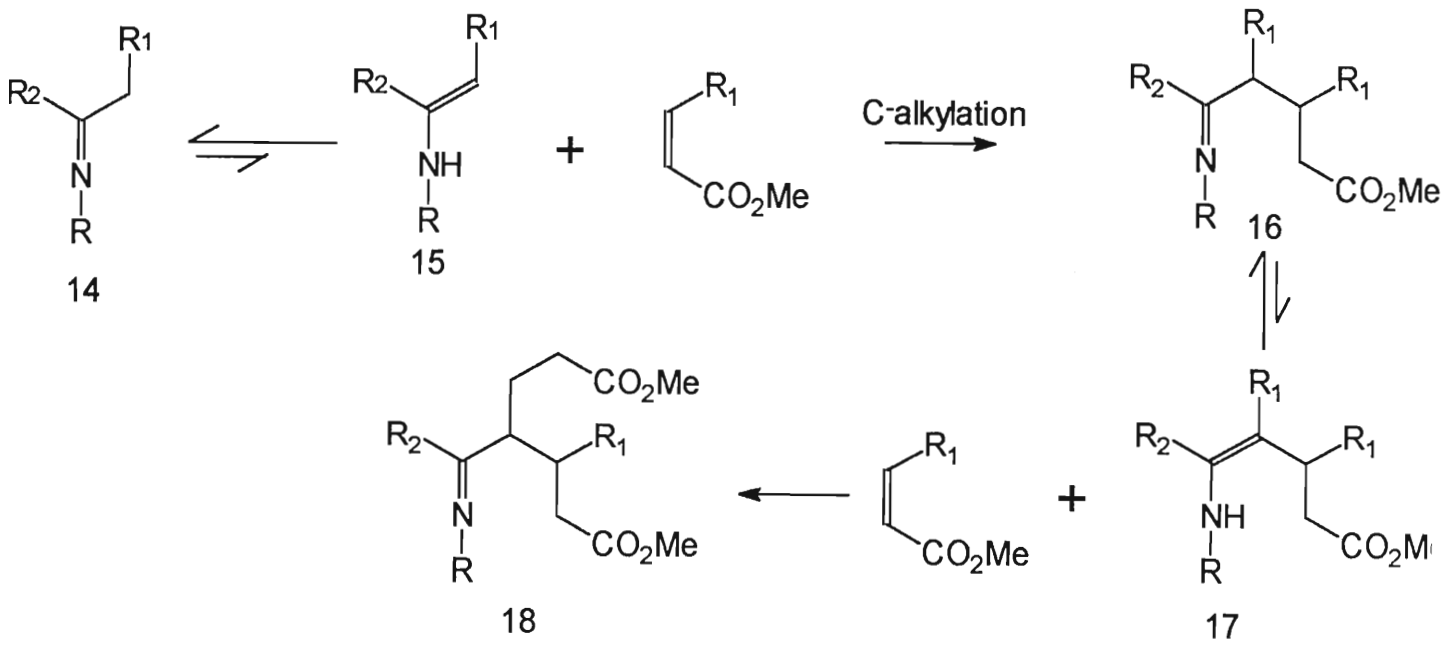
Various spectroscopic studies[22,23] of imine-enamine tautomerism show that, unless the enamine is stabilised by further conjugation with an unsaturated system such as a carbonyl[22,24] or imine group[25] or an aromatic system[26,27] the equilibrium is almost completely in favour of the imine form. However imine-enamine tautomerism has been clearly demonstrated in reactions which involve the enamine form reacting with a variety of electrophilic reagents at the α-position to the original carbonyl function[23,28a,29-32]. Despite their instability, methods have been developed for the isolation of enamines.[33]

Pfau and Ribiere[28,29a] have clearly demonstrated the existence of imine-enamine tautomerism. They reacted equimolecular solutions of N-isopropylideneisopropylamine and dimethyl maleate in boiling benzene or dioxane and obtained the three C-alkylated products (11-13) (Scheme 3). The addition product (13) was isolated in 86% yield.

To check the validity of the imine-enamine equilibrium the proton n.m.r of (10) was recorded in both methanol and deuteriomethanol. In methanol, no olefinic signals were observed in the spectrum, however in deuteriomethanol an immediate suppression of the signals at δ_H 1.94 and δ_H 2.01 which correspond to the two methyl groups (magnetically non-equivalent) attached to the imine bond was observed. This



SCHEME 3



R = cyclohexyl, R_1 = H, R_2 = Me

SCHEME 4

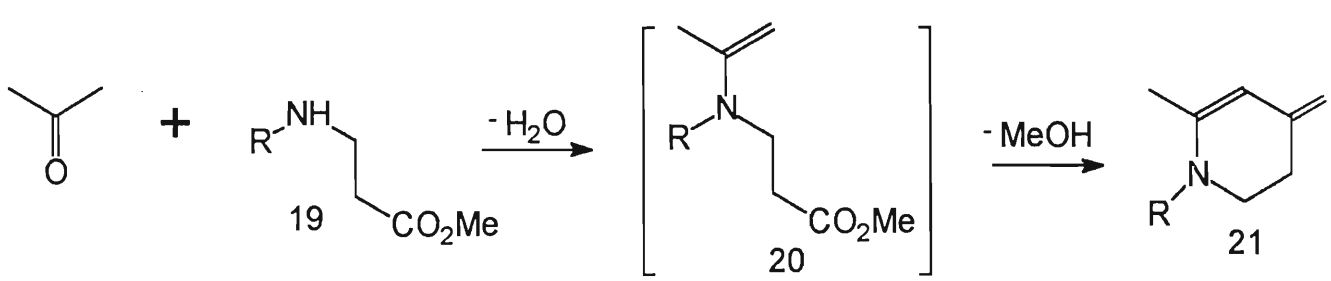
result confirms that although at equilibrium the imine (10) is almost the exclusive form, the six hydrogen atoms of these methyl groups are exchanged rapidly via the enamine form (10a).

The reaction between N-isopropylidenecyclohexylamine (14) and methyl acrylate (Scheme 4) was reinvestigated by Pfau[34] since it was previously claimed that only N-alkylation had occurred.[35]

The results obtained by Pfau showed that several reactions occurred, particularly the C-alkylation reaction yielding iminoesters (17) and (18); but that no N-alkylation had occurred.

To check the stability of enamine (20), which could have been formed had N-alkylation occurred, Pfau decided to synthesize the compound by another pathway, viz. enamination of acetone with the secondary amine (19). The major product isolated was the enaminoketone (21).

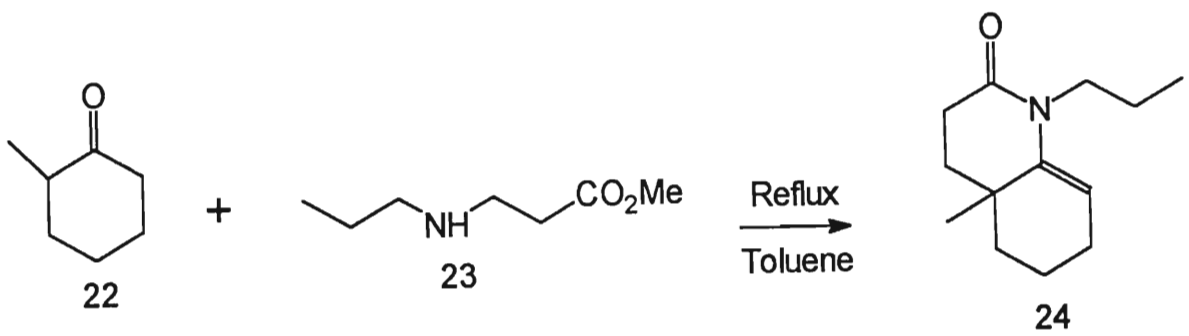
Pfau proposed that the N-alkylated enamine (20) cyclises spontaneously to the cyclic-vinylogous lactam (21).



R = cyclohexyl

SCHEME 5

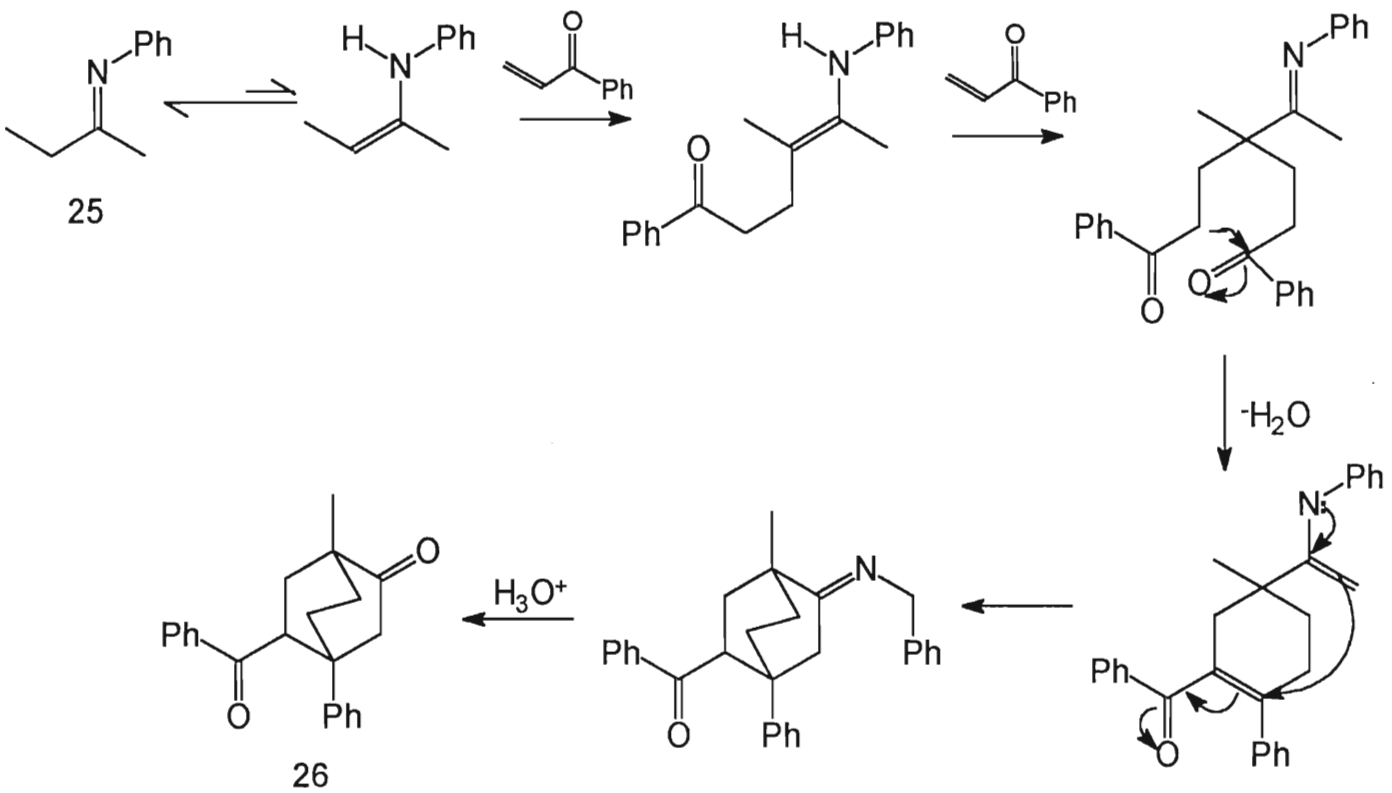
This proposal initiated the recent work of Jutle[36], in which the reactions of ß-aminopropanoates with asymmetric cyclic ketones resulted in the new synthesis of the quinoline ring system. It was found that the ß-aminopropanoate (23) reacted with 2-methylcyclohexanone (22) to produce 4a-methyl-1-N-propyl-3,4,4a,5,6,7-hexahydro-2-quinolone (24).



22 23 24

Recent work[37] in this laboratory has shown that this method can be extended to acyclic ketones as well as symmetrical cyclic ketones. Investigations into these reactions has been continued and it has been found that the pathway of these reactions is sensitive to steric effects and the presence of molecular sieves. These results will be discussed later.

Hickmott and Rae[38] have recently illustrated how imines react via their enamine tautomers with phenyl vinyl ketone (PVK). This reaction has lead to the synthesis of the bicyclo[2.2.2]octan-5-one ring system.



SCHEME 6

Two equivalents of PVK react three times with the butanone imine (25), once at C-1 and twice at C-3 resulting in the bicyclo[2.2.2]octanone structure (26). Four different carbon-carbon bonds are formed sequentially in this reaction (Scheme 6) which as far as the authors are aware constitutes the first one step synthesis of a bridged bicyclic system from acyclic precursors.

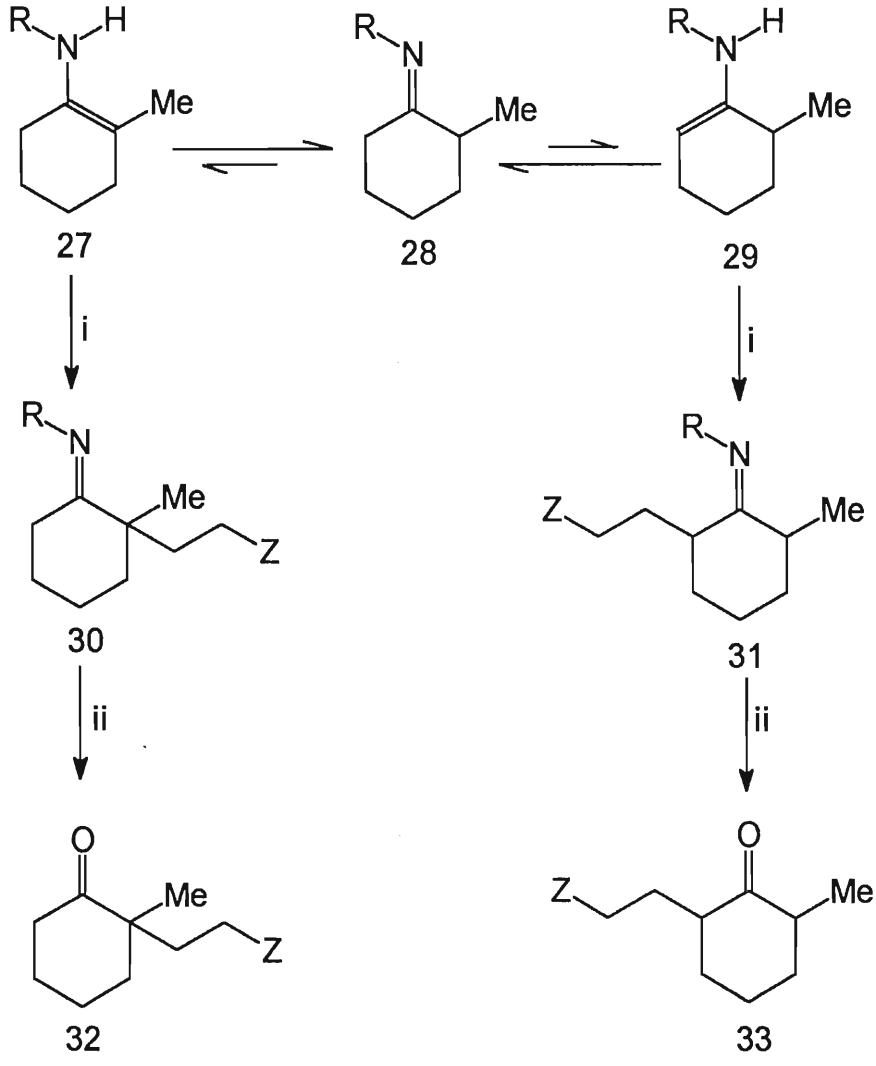
This work has now been continued to try and improve the yields of the bicyclic compounds obtained, and in order to determine the generality of the bicyclo-octanone synthesis from imines of methyl ketones. These results will be discussed later.

1.3 REGIOSELECTIVITY

The regioselectivity of reactions between electrophilic alkenes and imines has been extensively studied.[22,23] As previously mentioned, spectral studies of imine-enamine tautomerism have shown that the equilibrium favours the imine tautomer unless the enamine tautomer is stabilised by further conjugation with an unsaturated system.

Alkylation of an unsymmetrical ketone such as 2-methylcyclohexanone with a primary amine, will result in the preferred structure of the enamine being (27) (Scheme 7) rather than the less substituted isomer (29). This is because the enamine (27) is stabilised over enamine (29) by the hyperconjugative interaction between the methyl group and the double bond without any allylic destabilisations occurring. Such destabilisation is normal in a tertiary enamine but since one of the N-alkyl substituent has been replaced by a hydrogen atom, no $A^{(1,3)}$ interactions exist in structure (27). Hence the more substituted isomer is more predominant. Since there is now no $A^{(1,3)}$ strain present in the structure alkylation of enamine (27) with electrophilic alkenes should give the 2,2- disubstituted cyclohexanone product (32) on hydrolysis rather than the 2,6-disubstituted product (33). Hickmott *et al.*[17,39] have shown that alkylation of 2-substituted cyclohexanones with electrophilic alkenes such as methyl acrylate and acrylonitrile occurs at the more substituted α-position of the derived secondary enamine to give the

2,2-disubstituted ketone (32) on hydrolysis.

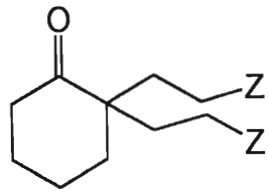


Reagents : (i) CH_2=CH-Z (-H^+) ; (ii) H_2O, Δ , Z = CO_2Me, CN, SO_2Ph

SCHEME 7

It has also been shown that more reactive electrophilic alkenes such as methyl acrylate and phenyl vinyl sulphone react twice with benzylamine or cyclohexylamine imines of

cyclohexanone to give the 2,2-disubstituted cyclohexanones on hydrolysis (34, Z = CO_2Me,SO_2Ph).



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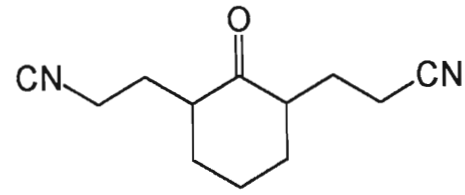


35

However, under identical conditions, the less reactive acrylonitrile gives only the 2,6 disubstituted product (35). It has also been shown that 2,2 and 2,6 - dialkylation does occur, to a small extent, on changing to the less sterically impeded propylamine imine. This work has shown that a complete reversal in the regioselectivity of the alkylation process from α,α′ to α,α-disubstitution, is achieved by changing the amine component from a tertiary to a secondary amine. This then provides a mild and highly regioselective route to α,α-disubstitution.

The regioselectivity of the alkylation of imines of acyclic ketones with electrophilic alkenes such as methyl acrylate, acrylonitrile and phenyl vinyl sulphone has also been investigated.[40]

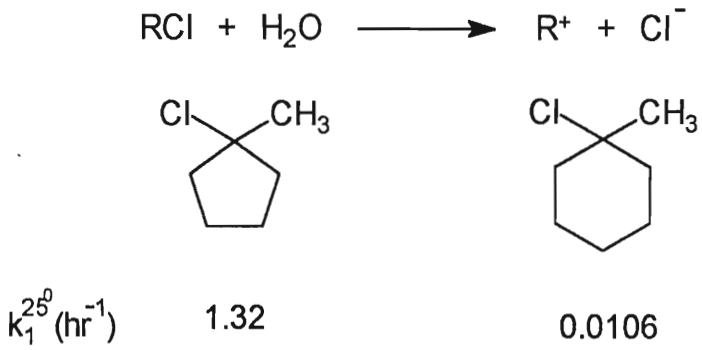
The benzyl or propylamine imines of acyclic ketones including butanone, pentan-2-one and pentan-3-one were treated with electrophilic olefins and the reaction path was found to be sensitive to steric effects, since only monoalkylation had occurred. The regioselectivity however, was not as great as

the corresponding alkylation of 2-substituted cyclohexanone.

For unsymmetrical imines the regioselectivity depends largely on the substituents present in the imine and to a lesser extent on the alkylating agent. The reactions varied from 100 % attack on the more substituted α-position to 70 % attack at the less substituted α'- position, depending on the steric hindrance presence and on the stabilisation of the competing secondary enamine tautomers.

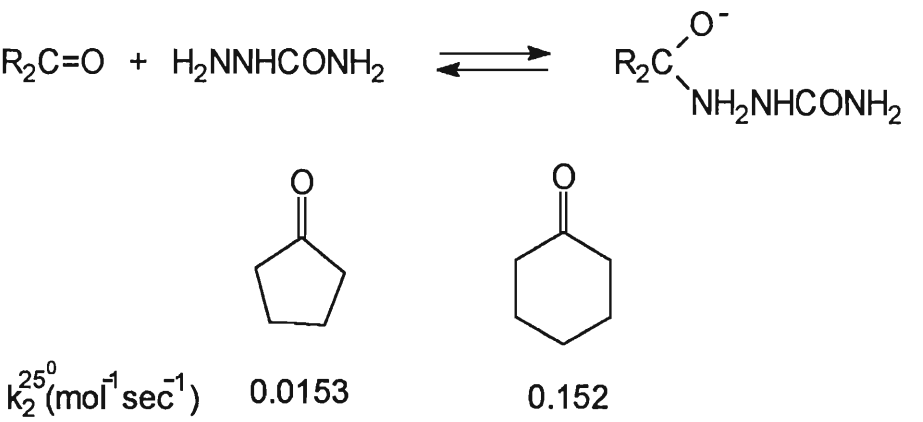
1.4 THE CHEMICAL REACTIVITY OF 5- AND 6- MEMBERED RING COMPOUNDS

The chemical reactivity of 5- and 6- membered ring compounds has previously been investigated.[41,42,43] It has been pointed out that reactions which involve changes in the coordination number of a ring atom from four to three proceed relatively rapidly in cyclopentane derivatives, when compared to cyclohexane derivatives. An example of this type of behaviour is the solvolysis of tertiary halides in aqueous (80%) ethanol[44].



SCHEME 8

On the other hand, reactions which involve changes in coordination number from three to four proceed relatively slowly in 5-membered rings when compared to 6-membered rings. An example of this type of behaviour is the reaction of ring ketones with semicarbazide[45].



SCHEME 9

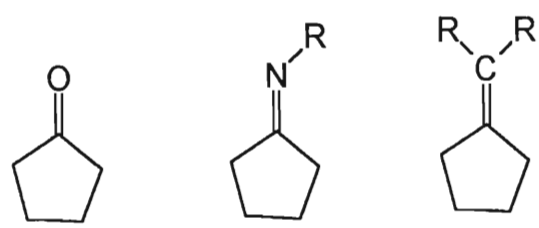
There must therefore be an important factor which in a cyclohexane ring atom favours the change in coordination number from three to four and opposes the change from four to three.

The cyclohexane ring with six tetrahedral carbon atoms is highly symmetrical and stable, with hydrogen-hydrogen repulsions reduced to a minimum in the chair form as a result of the fully staggered conformation permitted by this form[46a,b,a].

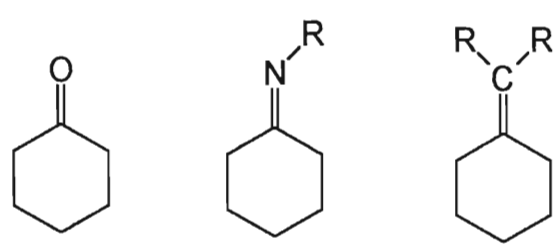
Enlargement of one of the ring (C-C-C) angles will decrease the symmetry, decrease the puckering, and increase the hydrogen-hydrogen repulsions. The increase in the angle will lead to an increase in internal strain (positive internal-strain). Therefore in cyclohexane derivatives internal-strain will oppose reactions of cyclohexane derivatives involving a change in covalency of a ring atom from four to three.

Conversely, in these compounds a change in covalency from three to four will involve a decrease in internal strain (negative internal-strain). Such reactions will be strongly favoured.[42]

On the other hand, 5-membered rings are appreciably strained, primarily because of the torsional forces about C-C single bonds.[46-48] It is proposed that the introduction of an atom with a preferred 120 degree angle leads to a decrease in internal strain. Therefore internal-strain will favour reactions involving changes in coordination numbers from four to three and oppose reactions involving covalency changes from three to four. Justification for this concept is furnished by the observation that 5-membered carbon rings are under considerable strain, whereas 6-membered rings are relatively strain free.[42] It can therefore be concluded that in 5-membered ring compounds the trigonal structure for one of the ring atoms is strongly favoured over the tetrahedral arrangements, and the reverse is true for six membered rings.[41,43]



more stable, less reactive



less stable, more reactive

Now if this result is true for all 5- and 6-membered rings then it may be assumed that an exo double bond in a 5-membered ring

system will be more stable towards changes involving loss of the exocyclic double bond when compared to the corresponding exo double bonds in 6-membered ring systems.[39,41]

If one further assumes that differences in stability between double bonds exo to 5- and 6-membered rings is larger than the difference in stability between endo double bonds in these ring systems[41] (this assumption is based on thermochemical data), then it follows that for a first approximation attention may be focussed on the relative stabilities of exo double bonds and the differences in stabilities of the endo double bonds may be ignored.

It can therefore be generalized that "Double bonds which are exo to a 5-ring are less reactive and more stable to the related double bonds which are exo to a 6-ring. Reactions which involve the formation or retention of an exo double bond in a 5-ring derivative will be favoured over corresponding reactions which involve the formation or retention of an exo double bond in a 6-ring derivative. Reactions which involve the loss of an exo double bond will be favoured in the 6-ring as compared to the corresponding 5-ring derivative".[43]

Brown[41] has utilised an empirical approach in developing the above generalization and has shown, with a few exceptions, how the generalisation is consistent with available thermochemical data.

The generalization includes such diverse substances as cyclic

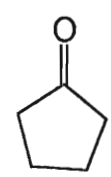
ketones, lactones and lactals, cyclic imides, the sugar aldehydes and acids, exo and endo tautomers and isomers, and the terpene hydrocarbons.

Since misinterpretations have arisen in the past[49,50] it must be stressed that the above generalisation only compares the reactivity of 5- and 6-membered rings, having exo double bonds, and in no way compares exo versus endo stability in either a 5- or 6-ring system.

Brown[41] goes a step further in explaining the effect of the carbonyl group in stabilizing the cyclopentane ring and destabilising the cyclohexane ring.

The effect of the carbonyl group in stabilising the cyclopentane ring is attributed to a decrease in the number of bond oppositions[46a,b]. In the idealized planar structure for cyclopentane the number of bond oppositions will be 10. In cyclopentanone the carbonyl group will be in the staggered conformation with respect to the two alpha methylene groups. The number of bond oppositions will therefore be reduced to six.

10 bond opposition
10 K.cal strain
(idealized planar model)



6 bond opposition
6 K.cal strain
(idealized planar model)

Although the situation will be altered by readjustment of the structure to a somewhat less strained, non polar structure, there is little reason to doubt that the ring ketone will continue to be stabilised relative to the hydrocarbon by the reduction of the number of unfavourable conformations.

On the other hand the parent cyclohexane structure is nicely staggered with no bond oppositions. Introduction of a trigonal atom alters the nice symmetrical arrangement and introduces some measure of unfavourable conformations.

Therefore according to this interpretation, the introduction of the carbonyl group stabilises the cyclopentane ring and destabilises the cyclohexane ring largely by altering the number and degree of unfavourable conformations involving the two α-methylene groups. However even in the absence of one or both methylene groups the same effect is observed.

In the course of the discussion in this thesis we will attempt to show how the reactivity of cyclopentanone and cyclohexanone affect the isomer distribution of the products formed by the reaction of ß-aminopropanoates with these ketones.

DISCUSSION

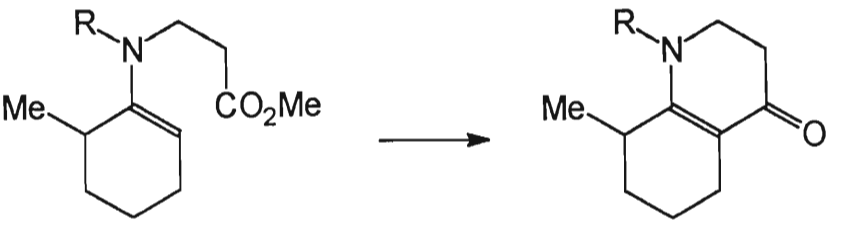
2.0 DISCUSSION

2.1 Reactions of ß-aminopropanoates

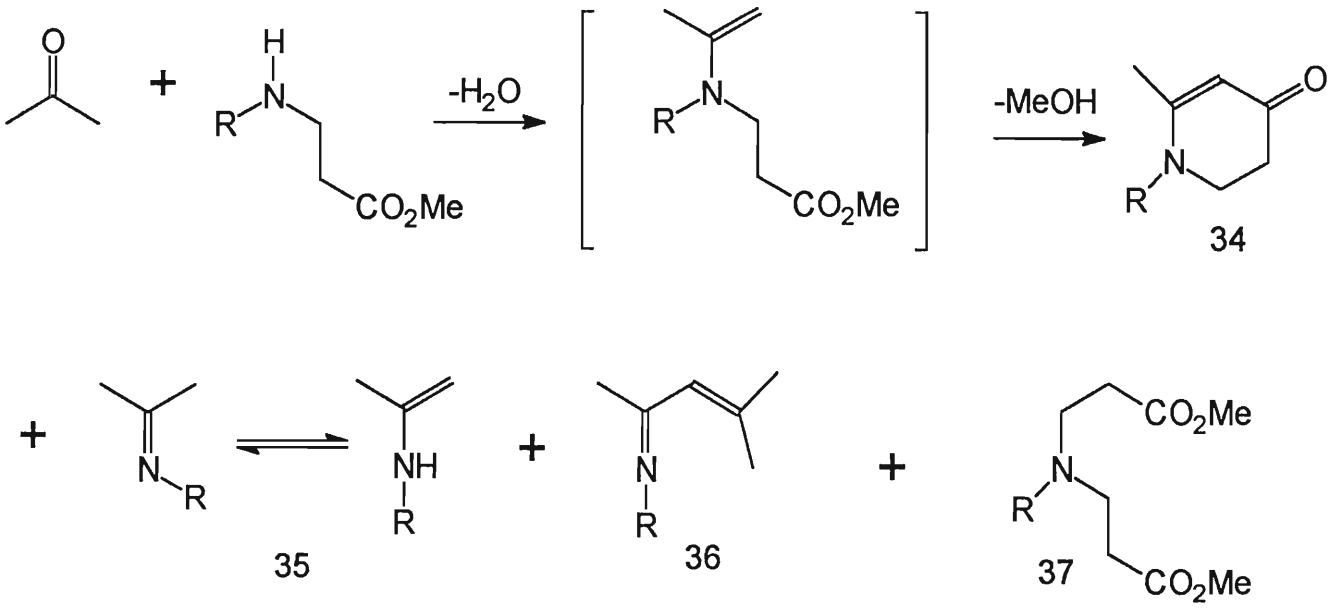
Previous work carried out in this laboratory by Jutle[36] has shown that alkylation of a cyclic ketone with a secondary amine resulted in a new synthesis of the 2-oxo-$\Delta^{8,8a}$-hexahydroquinoline ring system. This work has recently been extended[37] and has resulted in the synthesis of the hexahydro-$\Delta^{3a,7a}$-inden-7-one ring system and we now report the synthesis of the pyridone ring system by this method.

The pyridone ring system was first synthesized, using the above method, by Pfau *et al.* [34]. They treated acetone with methyl 3-(N-cyclohexylamino)propanoate (Scheme 10), using a silica / alumina catalyst and molecular sieves. The experiment was performed at 50°C in benzene and a slow reaction took place yielding 1-N-cyclohexyl-2-methyl-5,6-dihydro-4-pyridone (34) as the major product. Other compounds which were isolated included the cyclohexylamine imines (35) and (36) and the tertiary amine (37).

This result initiated the work of Jutle[36], since it was wished to be ascertained whether cyclic ketones would behave in a similar fashion. That is, would initial N-alkylation to give (38) be followed by spontaneous cyclisation to give (39).



38 39

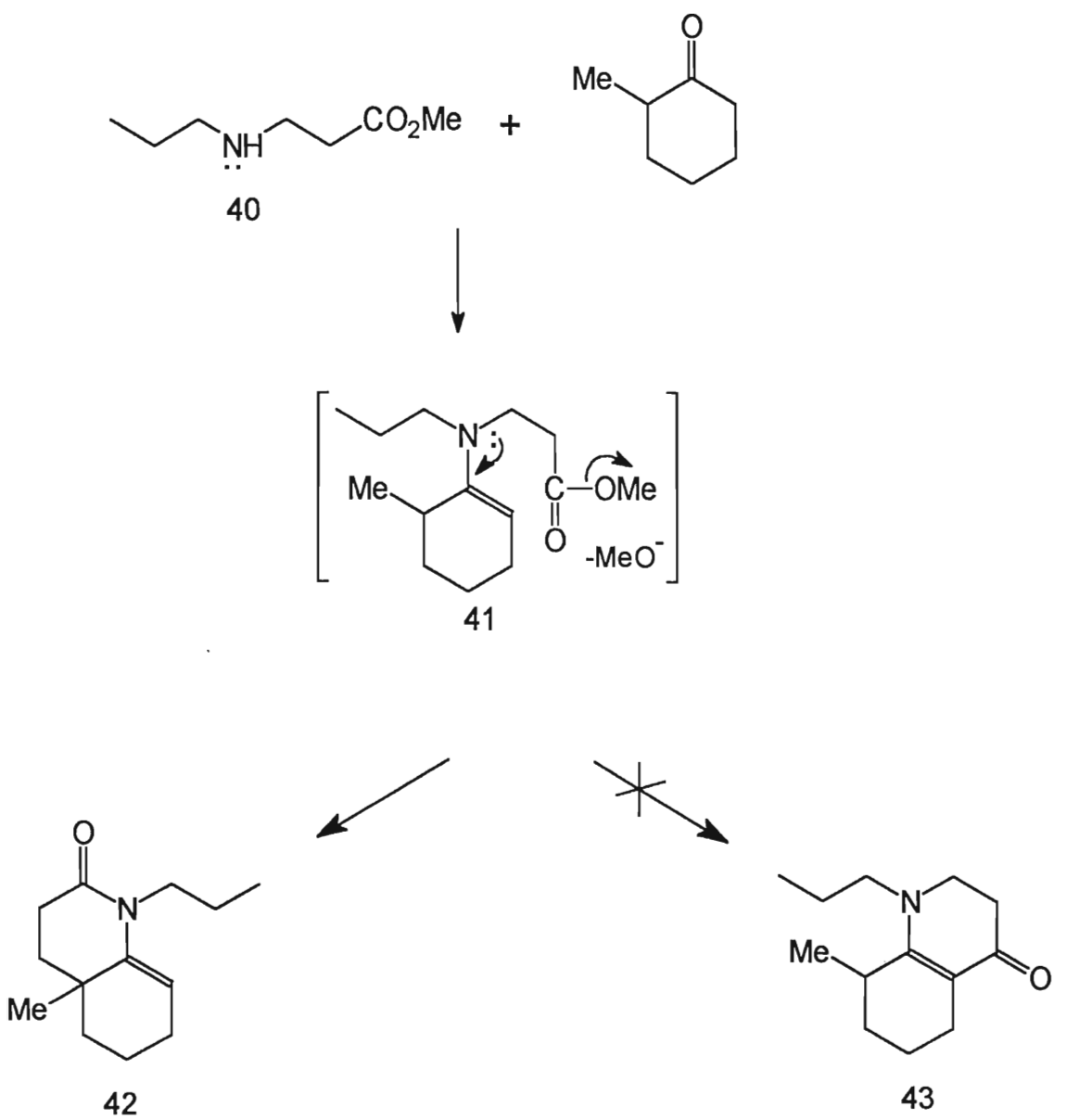


R = cyclohexyl

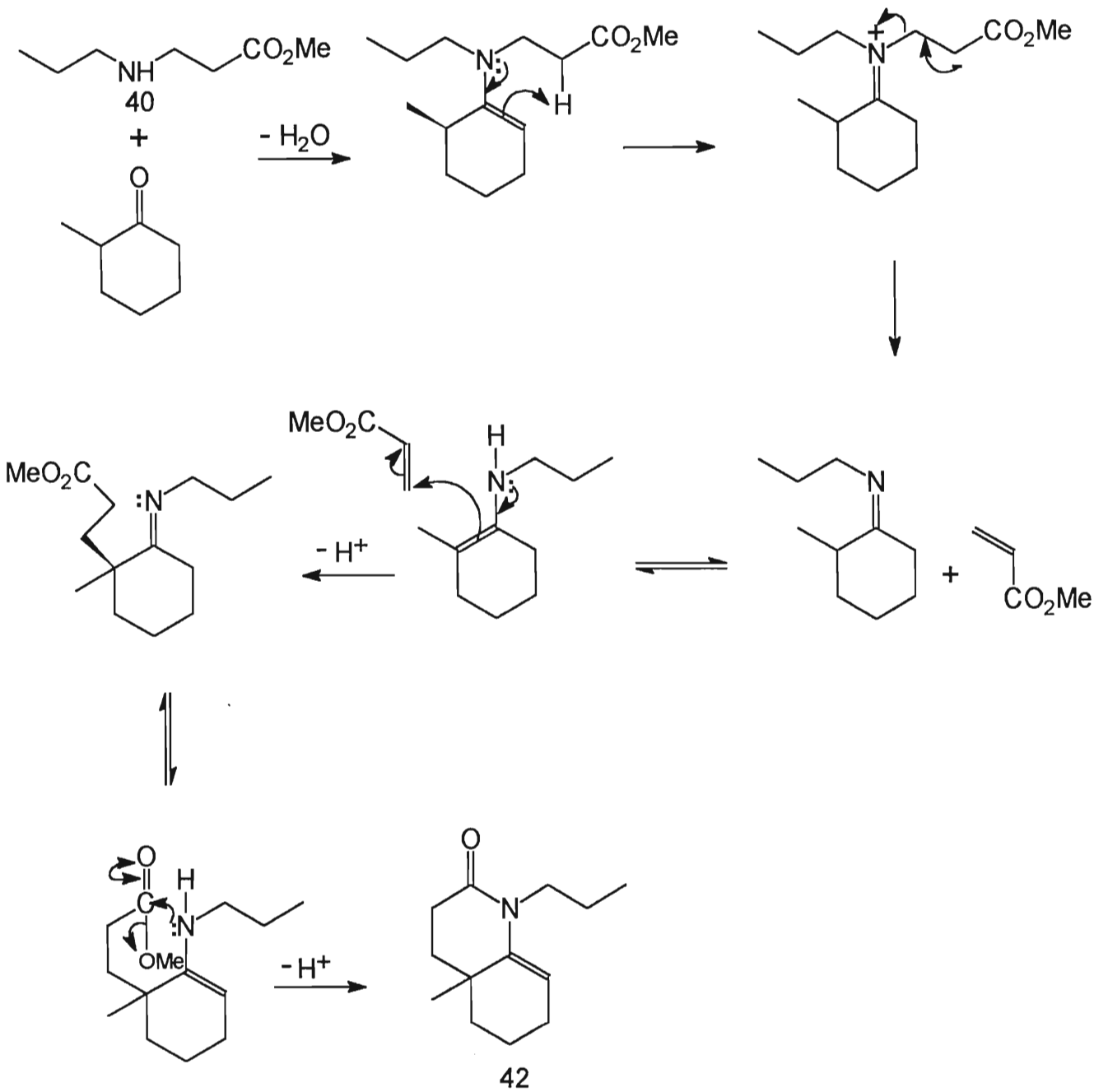
SCHEME 10

Accordingly the methyl 3-(N-propylamino)propanoate (40) (Scheme 11) was synthesized and heated under reflux with 2-methylcyclohexanone in dry toluene, over activated molecular sieves. However the product formed was found to be 4a-methyl-2-oxo-1-propyl-$\Delta^{8,8a}$-hexahydroquinoline (42) instead of compound (43). It seems that rearrangement occurred prior to cyclisation.

It was uncertain as to the mechanism of formation of (42), namely, if it was of an intermolecular nature (Scheme 12) or an intramolecular nature (Scheme 13). Attempts were made to demonstrate the intra- or intermolecular nature of the rearrangement process, however the only conclusion reached was that rearrangement was, at least in part, an intermolecular one.



SCHEME 11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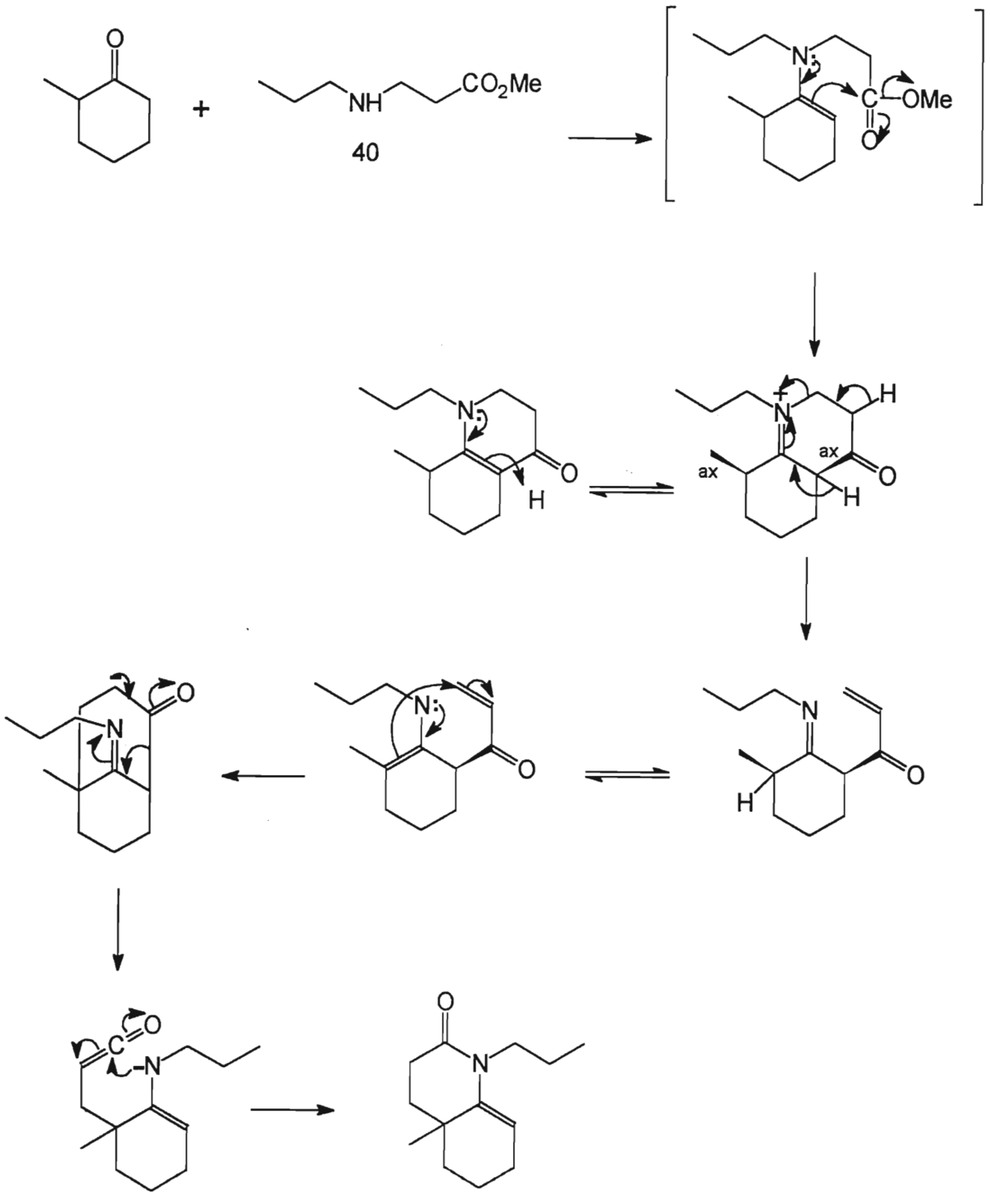
CO2Me
40
+
O
- H2O
N:
H
CO2Me
N
CO2Me
MeO2C
:N
MeO2C
H
N:
- H+
N
+
CO2Me
O
C
H
:N
OMe
- H+
O
N

42

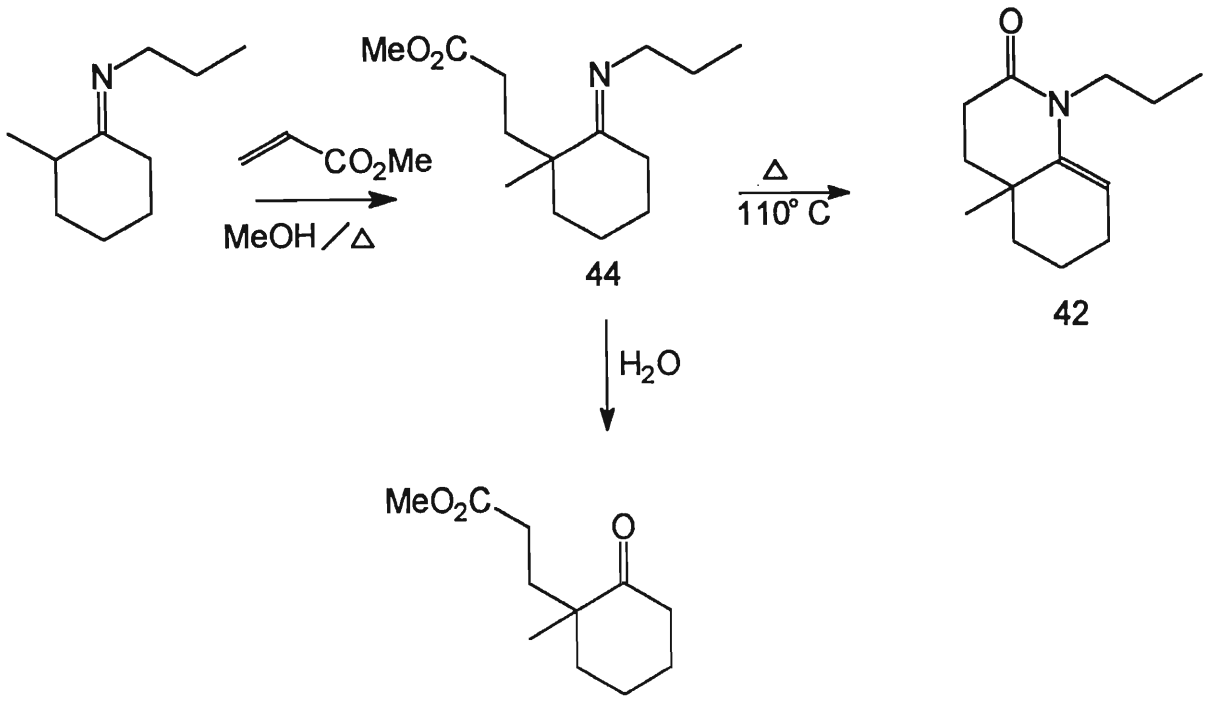
SCHEME 12



SCHEME 13

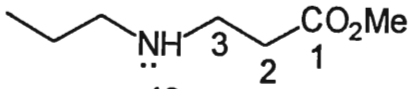
This was determined by selectively trapping any methyl acrylate which was liberated during rearrangement. The reagent used for trapping methyl acrylate was cyclopentadiene, since this undergoes rapid cycloaddition with methyl acrylate, even at room temperature, to give the Diels Alder adduct methyl bicyclo[2.2.1]hept-5-en-2-carboxylate. The Diels Alder adduct was isolated from the reaction mixture indicating indeed that the reaction mechanism is in part an intermolecular process.

If methyl acrylate is liberated as indicated in Scheme 12 and attacks the α-position of the propylamine imine of cyclohexanone,[17] then this could be checked by reacting the propylamine imine of 2-methylcyclohexanone with methyl acrylate. Jutle did investigate this possibility and found that heating the 2,2-disubstituted product (44) in toluene gave the octahydroquinolone (42) (Scheme 14).



SCHEME 14

During the course of the discussion we will show that this work was probably not necessary since nearly all our reaction mixtures contained the tertiary amine (52) which could only be formed by the reaction of the secondary amine (40) with methyl acrylate, and the possibility of any tertiary amine being present at the start of the reaction has been eliminated.



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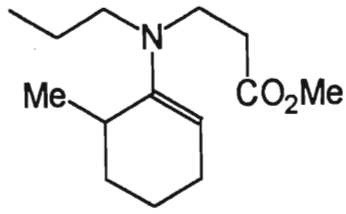
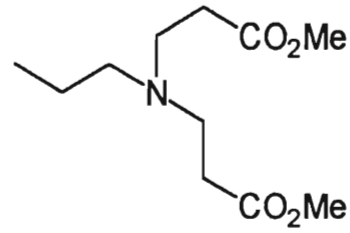


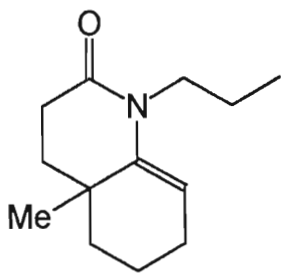
41



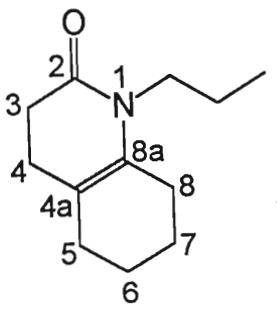
52

In our recent work[37] we tried to isolate the intermediate (41) (Scheme 11). This would have shown that the reaction mechanism could also be of an intramolecular nature, but we were unsuccessful in our attempts.

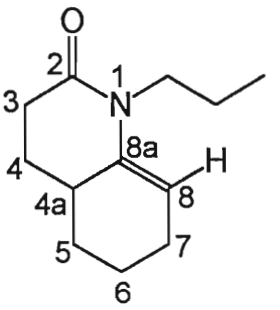
We did however find that the reaction of cyclohexanone with methyl 3-(N-propylamino)propanoate (40) in refluxing toluene resulted in the synthesis of 1-N-propyl-3,4,5,6,7,8-hexahydro-2-quinolone (45/45a), the rearranged product, and 1-N-propyl-2,3,5,6,7,8-hexahydro-4-quinolone (46), the expected cyclised product. The reaction was carried out in the presence of a silica / alumina catalyst as used by Pfau[34] and we initially suspected that the catalyst affected the course of the reaction allowing both compounds (45/45a) and (46) to form instead of compound (45/45a) only.



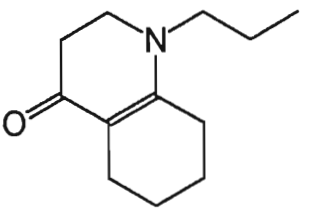
42



45



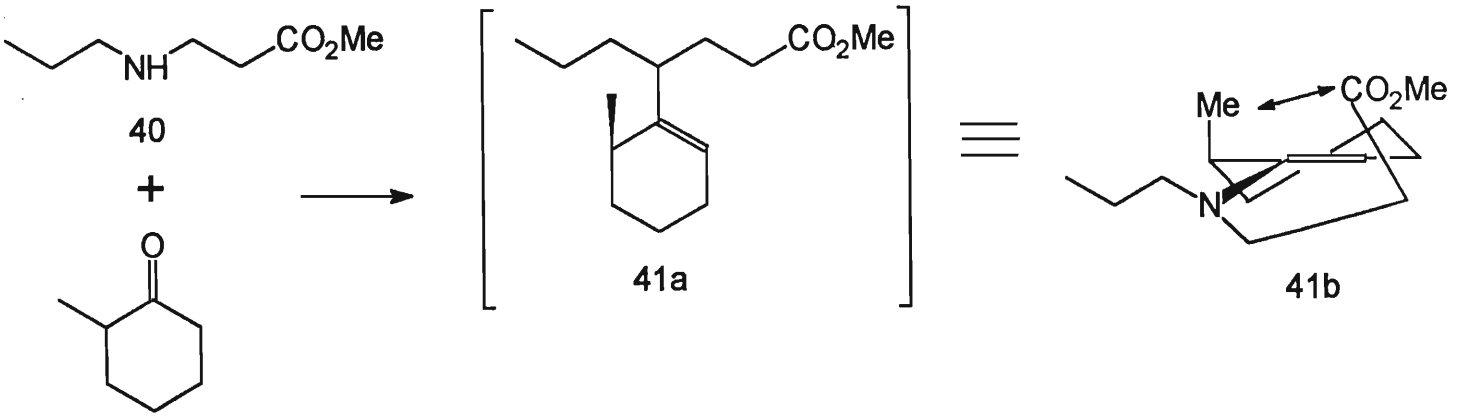
45a



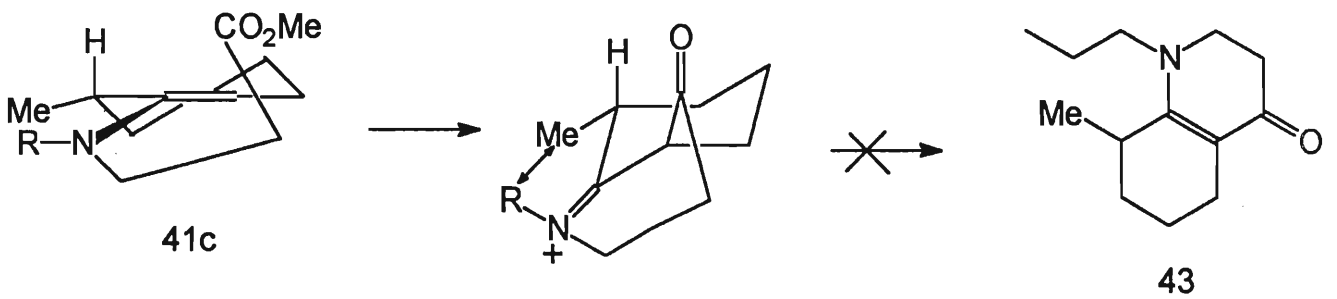
46

This is because Jutle did not use the silica / alumina catalyst for the reaction between 2-methylcyclohexanone and methyl 3-(N-propylamino)propanoate (40) and had only isolated product (42). However, further investigations ruled out this possibility and the synthesis of both isomers was explained by consideration of the stereochemistry and steric effects of the intermediates, as follows:

2-Methylcyclohexanone and the ß-aminoester (40) react to form what we think to be the enamine intermediate (41a). The methyl group is assumed to be in the axial orientation in order to eliminate allylic strain[14,15] and therefore the conformation (41b), leading to the transition state for cyclisation of the enamine onto the ester group from an axial direction, is destabilised by steric interactions shown in Scheme 15. The transition state for cyclisation from the other side (equatorial attack) would of course be destabilised by eclipsed interactions associated with a boat conformation of the six membered ring.



SCHEME 15



$A^{(1,3)}$ interactions

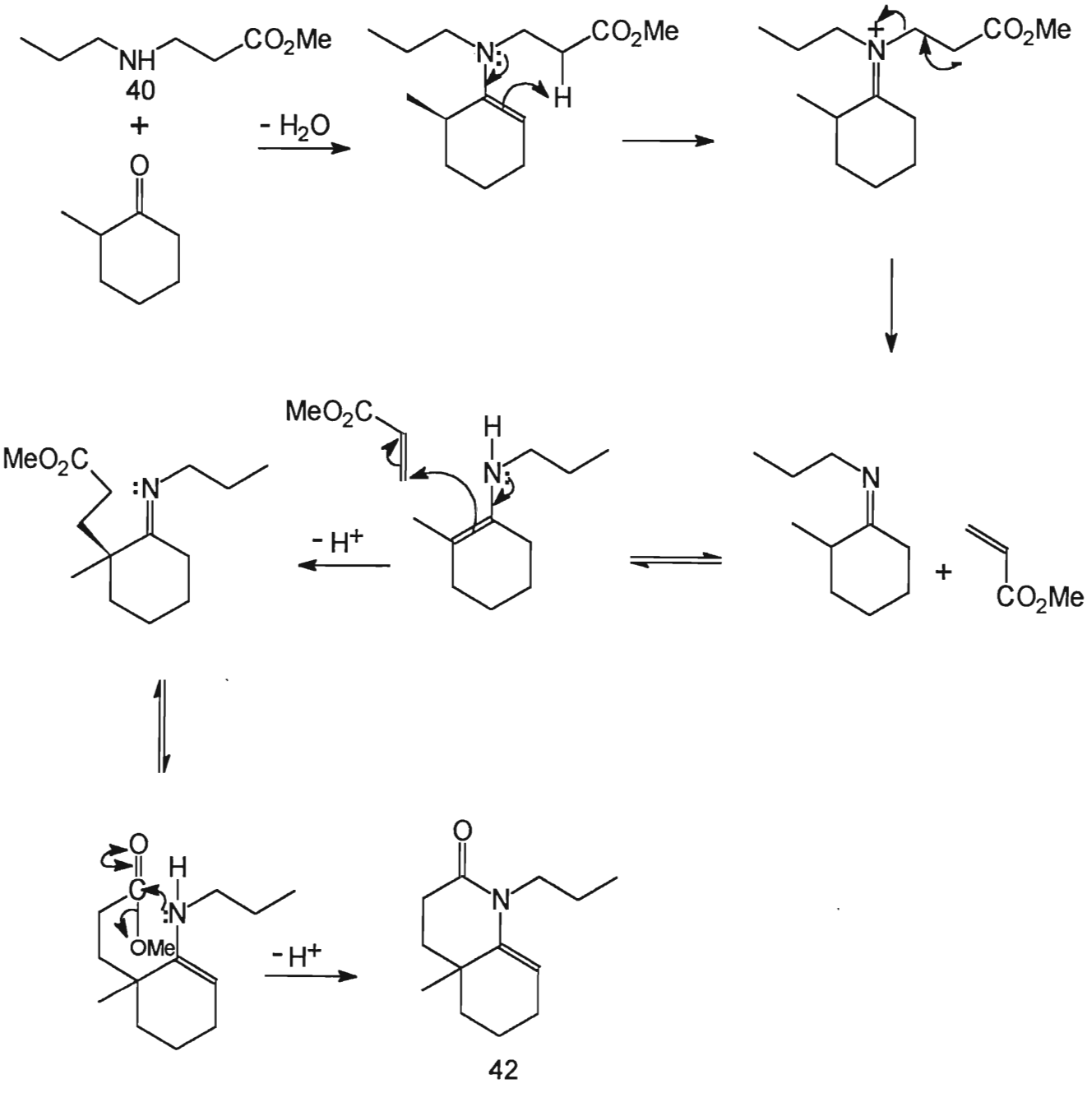
SCHEME 16

Even if the methyl group was in the equatorial position (41c) the transition state for cyclisation would still be destabilised, but now by developing $A^{(1,3)}$ interactions as shown

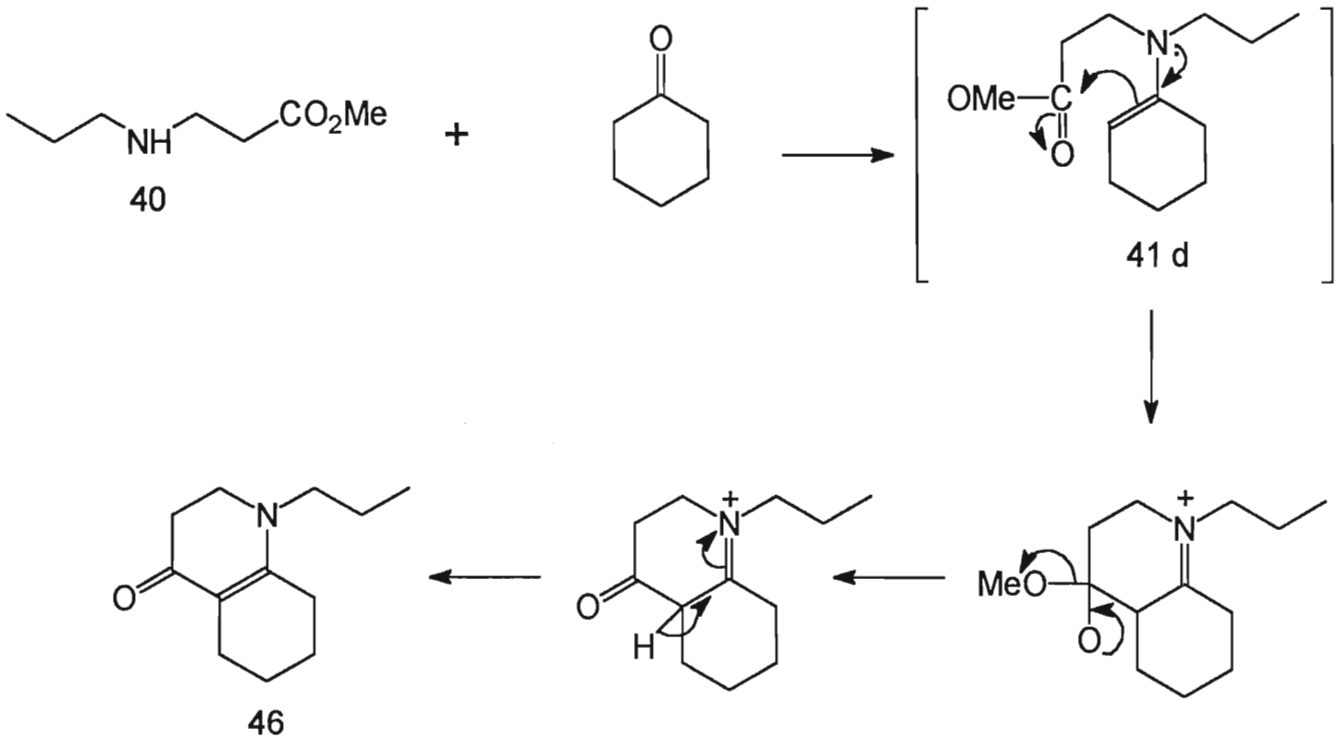
in Scheme 16. Formation of structure (43) would therefore be inhibited by these developing destabilising steric interactions.

The reaction mechanism for the formation of (42) is shown in Scheme 12. Instead as acting as a nucleophile the enamine function presumably acts as a base, removing the proton alpha to the ester group to form a carbanionic centre which provides the "push" for the elimination of methyl acrylate. The transition state for this process would not be destabilised by the aforementioned steric interactions since the ester group can now be orientated away from the axial methyl group. The methyl acrylate then alkylates the α-position of the propylamine imine of 2-methylcyclohexanone via the secondary enamine tautomer to give the 2,2-disubstituted product[17,39] which then cyclises by nucleophilic attack by the amine on the ester group thus resulting in the formation of (42).

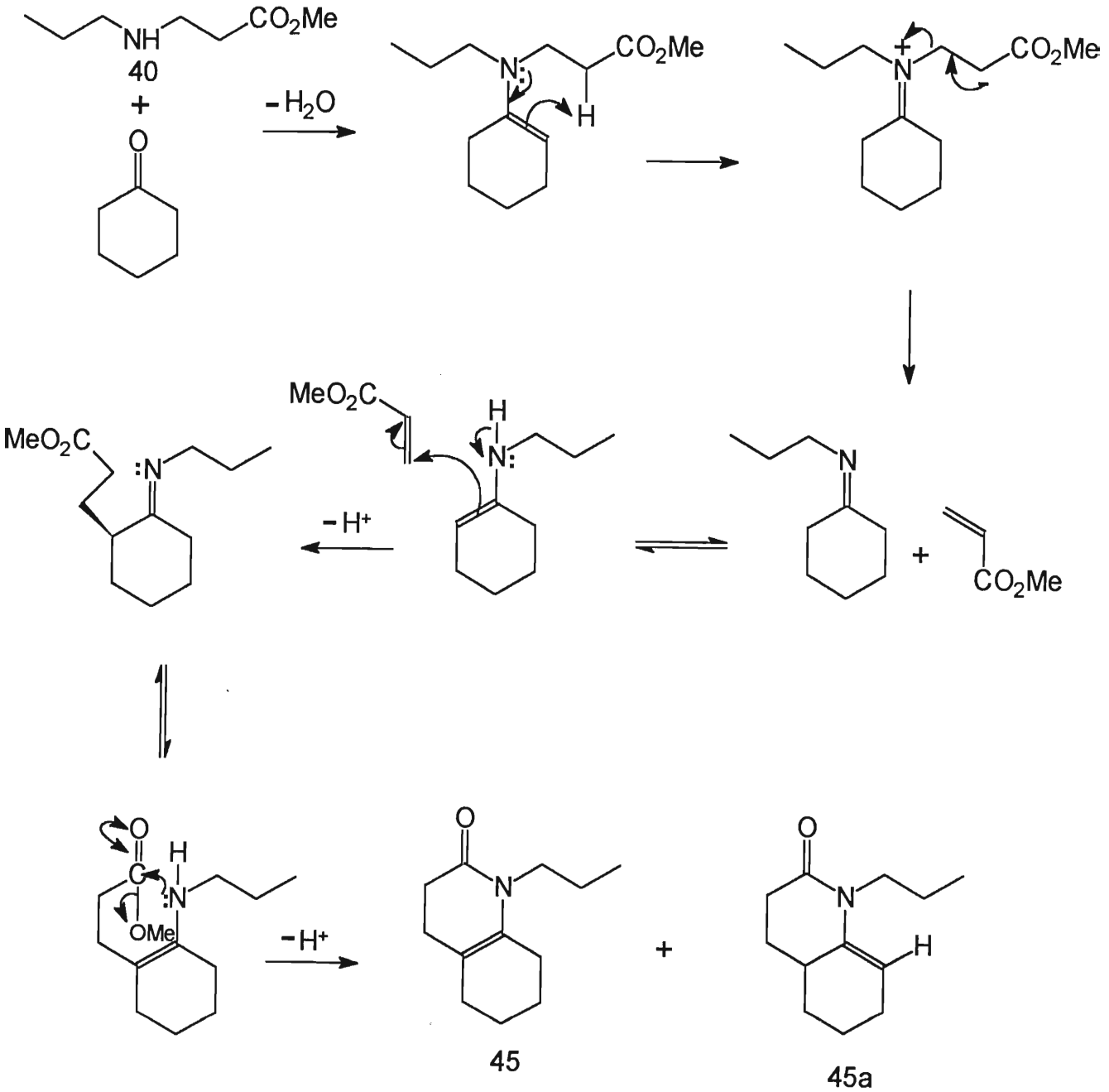
In the corresponding reaction of cyclohexanone with the ß-amino ester (40) there are no steric interactions to affect the course of the reaction. We propose that the formation of the enamine intermediate (41d) (intramolecular mechanism, Scheme 17) is followed by spontaneous cyclisation to (46). This path competes directly with the intermolecular mechanism (Scheme 18) leading to the formation of compound (45/45a).


NH
40
CO2Me
+
O
- H2O
N:
H
CO2Me
N
CO2Me
MeO2C
:N
MeO2C
H
N:
- H+
N
+
CO2Me
O
C
H
:N
OMe
- H+
O
N
42

SCHEME 12



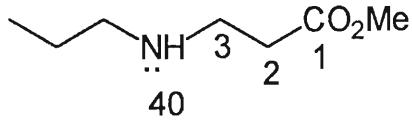
SCHEME 17



45 45a

SCHEME 18

We next reacted cyclopentanone with the secondary amine (40) and expected to isolate compounds (47) and (48).



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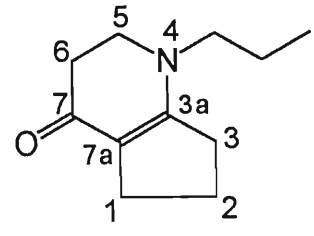
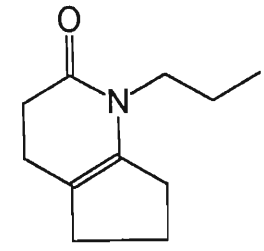


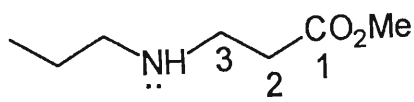
47



48

Compound (47), 4-propyl-4-azahexahydro-$\Delta^{3a,7a}$-inden-7-one, was isolated, but its isomer (48), although present in the reaction mixture as indicated by GC/MS, could not be isolated due to its low yield (≈ 4 %) and because of its similar polarity to other by-products which were present in low yields. The reason for the low yield of compound (48) will be discussed later.

In an attempt to isolate intermediate (41d) (Scheme 17), methyl 3-(N-propylamino)propanoate (40) was reacted with cyclohexanone in the presence of $TiCl_4$.[54] The residue which formed was extracted with dichloromethane and left a white crystalline material after removal of the solvent.



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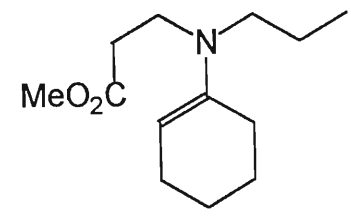


41d

The GC/MS showed a molecular ion corresponding to M^+ 240 and the g.l.c showed the product to have a $t_R \approx 11.7$ min. The i.r spectrum showed the presence of -CH deformations and $-CH_2$ stretching peaks.

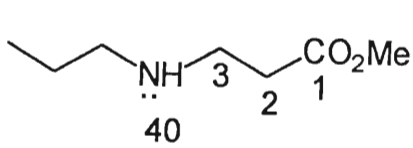
The ^1H n.m.r spectrum showed the presence of two singlets at δ_H 1.77 and 2.57, and upon resolution enhancement these signals appeared as multiplets.

The ^{13}C n.m.r spectrum showed the presence of only three signals, two doublets at δ_C 23.10 and 26.85, and a singlet at δ_C 132.57.

The product was identified as 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (49) formed by sequence of events such as that depicted in Scheme 19.

Elemental analysis of the material isolated verified the proposed structure (49).

We next turned our attention to the attempted isolation of compound (48) from the reaction of cyclopentanone with methyl 3-(N-propylamino)propanoate (40). Unlike our previous work the reaction was now carried out in the absence of molecular sieves, to see if this would have any effect on the amount of compound (48) that formed.



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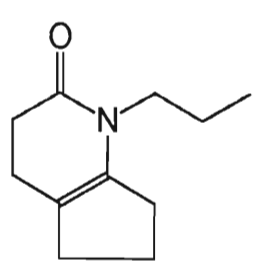
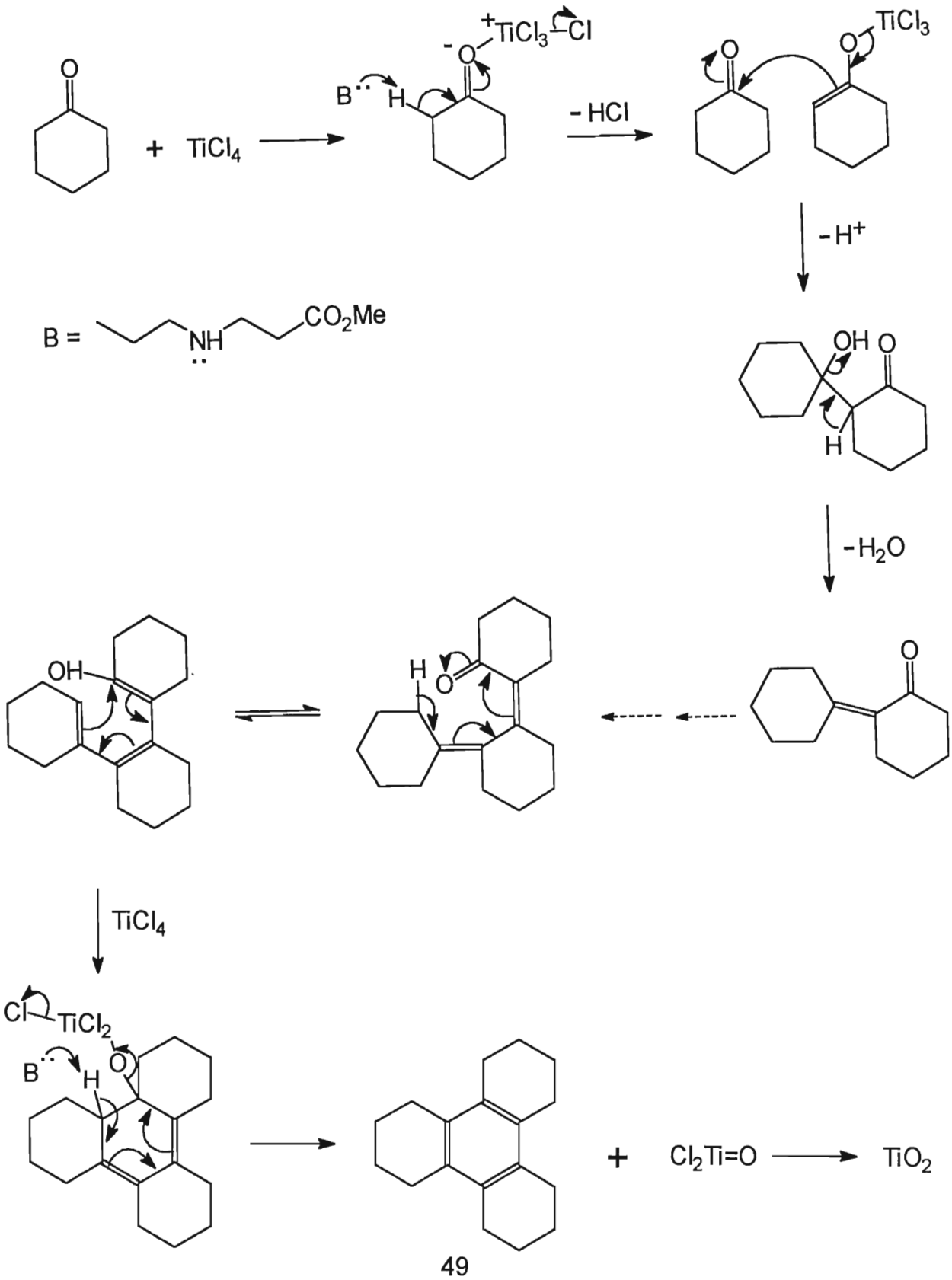


48



49

SCHEME 19

However the absence of molecular sieves did alter the course of the reaction as indicated by GC/MS and g.l.c (*vide infra*).

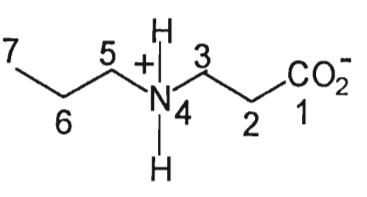
First a white crystalline material was filtered off from the reaction mixture and recrystallised from dichloromethane. This material was found to be hygroscopic.

The GC/MS showed a molecular ion corresponding to M^+ 131 and the g.l.c showed the product to have a $t_R \approx 3.1$ min. The i.r spectrum showed a broad absorption at 2500-3750 cm^{-1} which corresponds to a $>NH_2^+$ stretching peak. The i.r spectrum also showed absorptions at 1575 cm^{-1} and 1400 cm^{-1}, which corresponds to antisymmetric and symmetric stretching of a carboxylate ion.

The ^1H n.m.r spectrum showed the presence of a propyl group [δ_H - 0.99 (t), 1.70-1.83 (m), 2.87 (t)] and two triplets at δ_H 2.51 (C-2) and 3.05 (C-3). The methylene protons of C-2 and C-3 showed coupling to each other (COSY).

The ^{13}C n.m.r spectrum showed the presence of one quartet at δ_C 11.60, four triplets at δ_C 19.69 (C-6), 31.71 (C-2), 44.59 (C-3), and 48.72 (C-5), and one singlet at δ_C 176.91 (C=O).

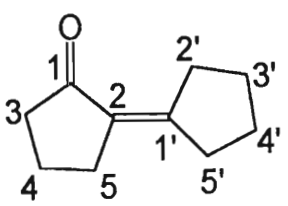
Based on the above spectral data the compound was identified as the zwitterionic salt of N-propyl-aminopropionic acid (50) and was isolated in 4.5 % yield.



50

A portion of the crude reaction mixture was subjected to flash chromatography and a light yellow oil was isolated in 12 % yield, and identified as 2-cyclopentylidenecyclopentanone (51).

The GC/MS showed a molecular ion corresponding to M^+ 150 and the g.l.c showed the product to have a $t_R \approx 4.7$ min. The i.r spectrum showed absorptions at 1635 cm^{-1} (C=C) and 1705 cm^{-1} (C=O), which corresponds to the α,ß-unsaturated five-membered cyclic ketone. This was confirmed by the u.v spectrum which showed λ_{max} at 266 nm (ϵ = 27000).



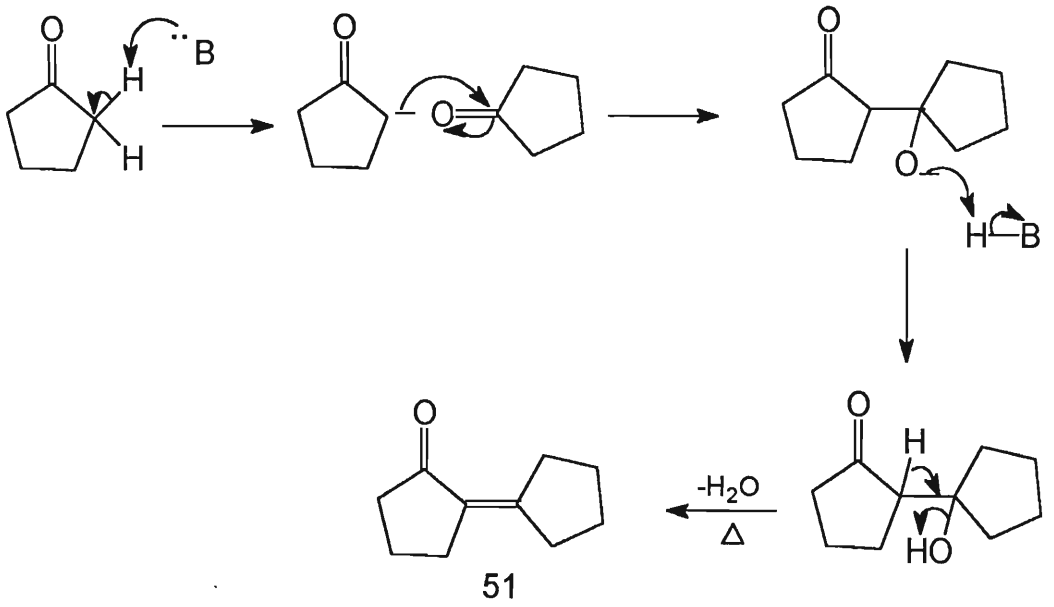
51

The ^1H n.m.r spectrum showed a multiplet at δ_H 1.78-1.89 (C-4). These methylene protons showed coupling to the protons responsible for the c.m.e at δ_H 2.18-2.25 (C-3 and C-5′) and to the methylene protons at δ_H 2.42-2.50 (C-5) (COSY). The protons at δ_H 2.18-2.25 (C-3 and C-5′) also showed coupling to the protons responsible for the c.m.e at δ_H 1.56-1.70 (C-3′ and C-4′) (COSY). These latter protons also showed coupling to the methylene protons at δ_H 2.69-2.72 (C-2′) (COSY).

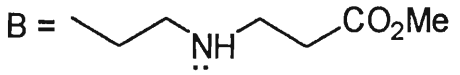
The ^{13}C n.m.r spectrum showed the presence of seven triplets and three singlets. The singlets appeared at δ_C 127.76 (C-2), 158.56 (C-1′) and 207.27 (C=O).

The above spectral data is in accord with the structure (51)

and the following mechanism (Scheme 20) has been proposed. Cyclopentanone presumably undergoes an Aldol reaction with methyl 3-(N-propylamino)propanoate (40) acting as a base for initial proton abstraction at C-2 of cyclopentanone.



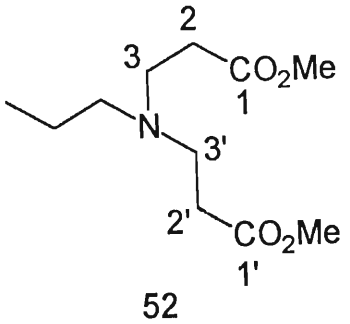
51



40

SCHEME 20

Also isolated by flash chromatography was the tertiary amine, N,N-di(ß-methoxycarbonylethyl)propylamine (52) in 3 % yield.



52

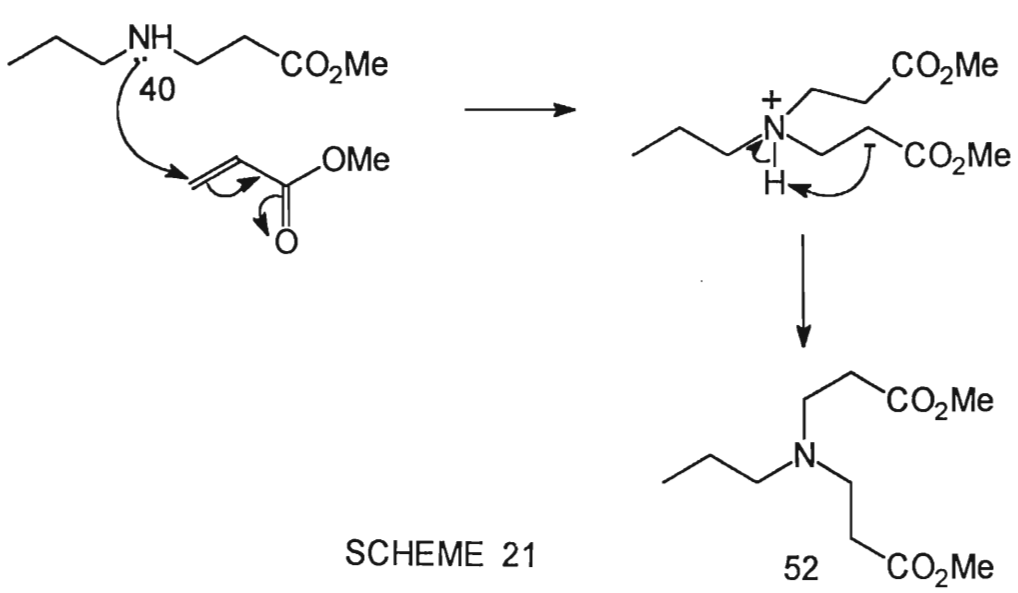
The GC/MS showed a molecular ion corresponding to M^+ 231 and

the g.l.c showed the product to have a $t_R \approx 5.5$ min. The i.r spectrum showed an absorption at 1737 cm^{-1} (C=O).

The ^1H n.m.r spectrum showed the presence of a propyl group [δ_H - 0.82 (t), 1.36-1.44 (m), 2.33 (t)]. The spectrum also showed two triplets at δ_H 2.41 (C-2 and C-2′) and δ_H 2.73 (C-3 and C-3′) and the protons responsible for these signals showed coupling to each other (COSY). The ^1H n.m.r spectrum also showed a singlet at δ_H 3.63 corresponding to the methoxy groups.

The ^{13}C n.m.r spectrum showed the presence of two quartets at δ_C 11.68 and 51.50 (OCH_3), four triplets and one singlet at δ_C 173.10 (C=O, C-1 and C-1′).

The mechanism proposed for the formation of compound (52) is shown in Scheme 21.



SCHEME 21

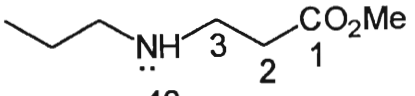
Also isolated by flash chromatography was 4-propyl-4-azahexahydro-$\Delta^{3a,7a}$-inden-7-one (47) in 4 % yield.

This compound has been isolated in our previous work.

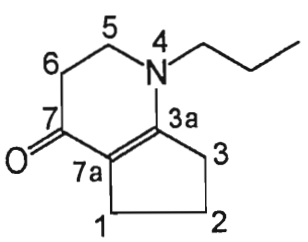
The I.R spectrum of (47) showed absorptions at 1560 cm^{-1} and 1625 cm^{-1} corresponding to an enaminone.

The ^{1}H n.m.r showed the presence of a propyl group [δ_H - 0.88 (t), 1.52-1.59 (c.m.e), 3.16 (t)] and a pair of triplets at δ_H 2.39 (C-6) and δ_H 3.42 (C-5) and the protons responsible for these signals showed coupling to each other (COSY). The spectrum also showed a multiplet at δ_H 1.78-1.92 (C-2) and a c.m.e at δ_H 2.48-2.57 (C-1 and C-3). The protons responsible for these signals showed coupling to each other (COSY).

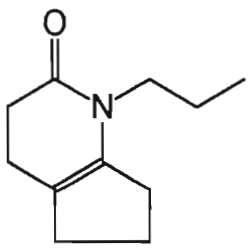
The ^{13}C n.m.r spectrum showed three singlets at δ_C 108.58 (C-7a) and 168.08 (C-3a) and 187.39 (C=O) and the required number of quartets and triplets.



40



47



48

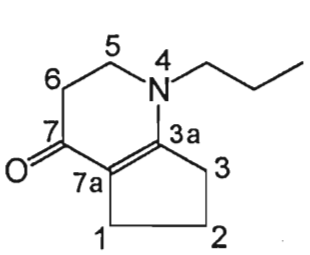
The fact that this structure is (47) and not its isomer (48) was confirmed by u.v spectroscopy. Compound (47) showed a λ_{max} at 333 nm (ϵ = 32000) in the u.v spectrum because of the conjugated enaminone chromophore. The mechanism proposed for the formation of compound (47) is shown later in Scheme 22. Formation of the enamine intermediate is followed by

spontaneous cyclisation to give compound (47).

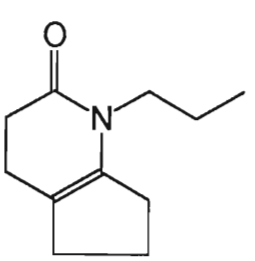
To our disappointment we were again unable to isolate compound (48), which we suspect to have a $t_R \approx 5.9$ min. The GC/MS shows a molecular ion corresponding to M^+ 179 and the g.l.c showed the compound to be present in 3 % yield. The fact that this compound does have the structure (48) is confirmed by the presence of the tertiary amine (52), since in order for compound (52) to form, methyl acrylate must be present and this is only possible if compound (48) forms. This is clearly illustrated later, in Scheme 23.

We next repeated the reaction of cyclopentanone with methyl 3-(N-propylamino)propanoate (40) in refluxing toluene, but now in the presence of molecular sieves. The reaction mixture was purified by flash chromatography and found to contain 4-propyl-4-azahexahydo-$\Delta^{3a,7a}$-inden-7-one (47) in 15.5 % yield.

The GC/MS of the crude reaction mixture also showed the presence of 2-cyclopentylidenecyclopentanone (51) (Scheme 20) and the tertiary amine (52) (Scheme 21) but these were present in a less that 1% yield and were not isolated.



47



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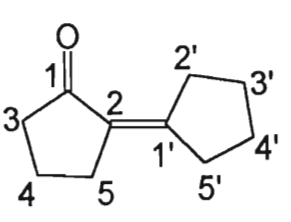

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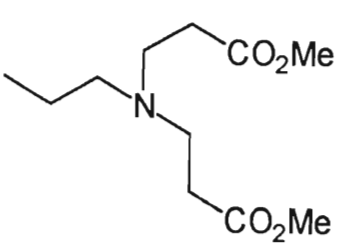
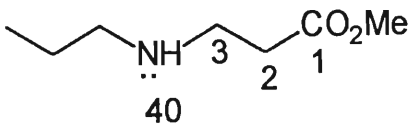


52

Once again we tried to isolate compound (48), which was present

in a 4% yield, as indicated by g.l.c data, but again we were unsuccessful.

Now from our studies we have seen that the reaction of cyclohexanone and methyl 3-(N-propylamino)propanoate (40) in the presence of molecular sieves results in the formation of the isomers (45/45a) and (46) in yields of 11 % and 10 % respectively. Also the reaction of cyclopentanone and methyl 3-(N-propylamino)propanoate (40) in the presence of molecular sieves results in the formation of compound (47) and also what we think to be compound (48) in 15.5 % and 3 % yields respectively. We attribute the low yield of compound (48) to the greater stability of a double bond exo to 5-membered ring relative to one exo to a six-membered ring.



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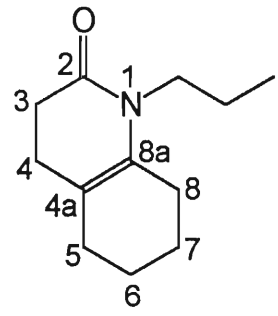

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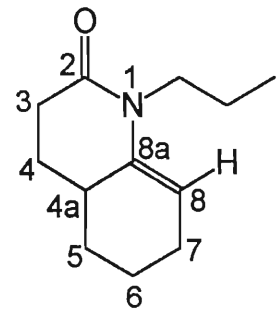
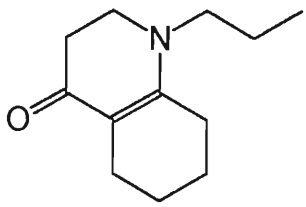
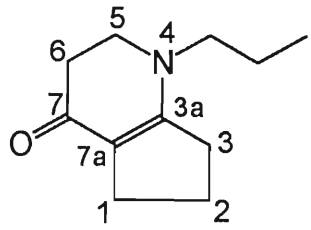


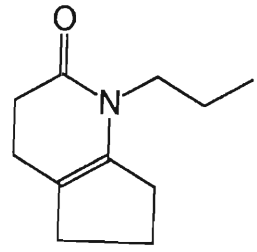
45a



46



47



48

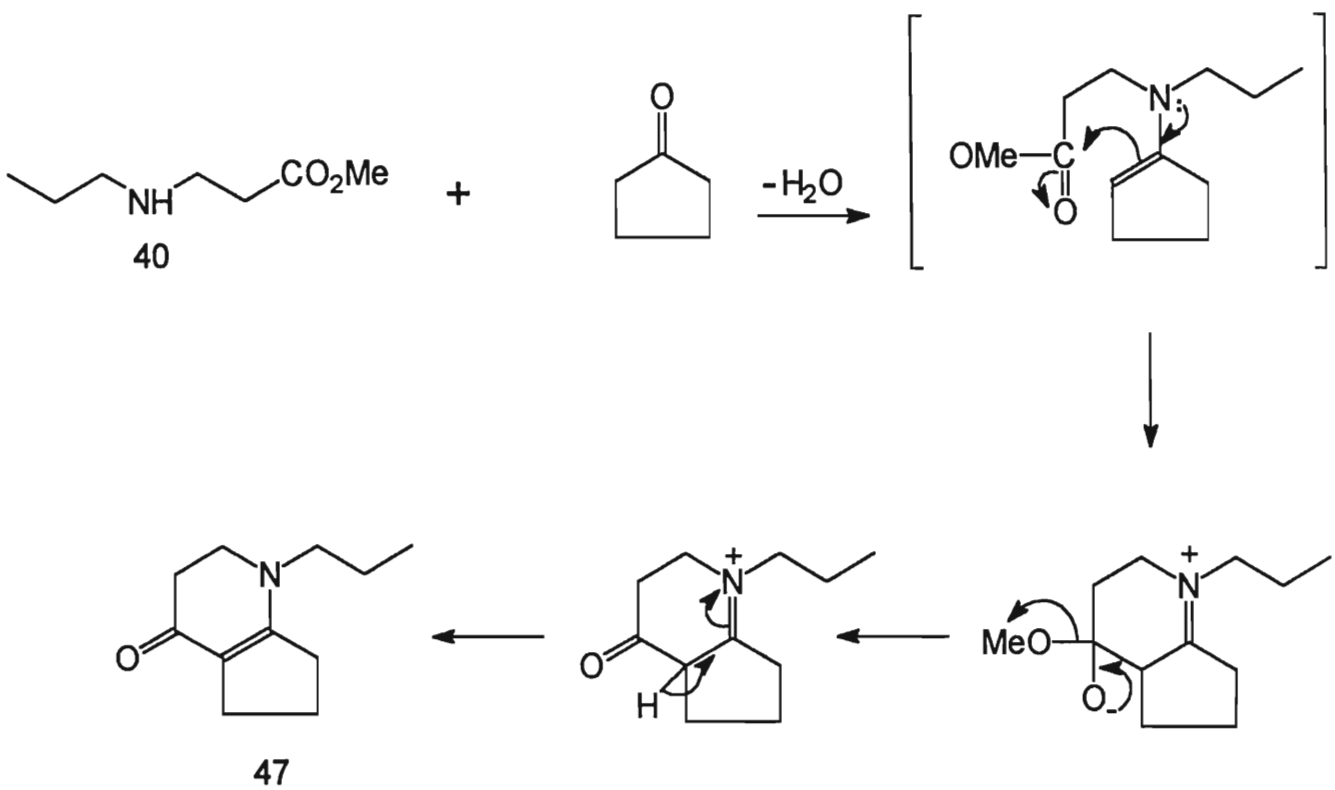
It has already been stated in the introduction to this work that "double bonds which are exo to a 5-ring are less reactive

and more stable compared to the related double bonds exo to a 6-ring. Reactions which involve the formation or retention of an exo double bond in a 5-ring derivative will be favoured over corresponding reactions which involve the formation or retention of an exo double bond in a 6-ring derivative. Reactions which involve the loss of an exo double bond will be favoured in the 6-ring as compared to the corresponding 5-ring derivative".[43]

When considering the reaction of methyl 3-(N-propylamino)propanoate (40) with cyclopentanone it is possible for the reaction to follow the paths shown in both Scheme 22 and Scheme 23.

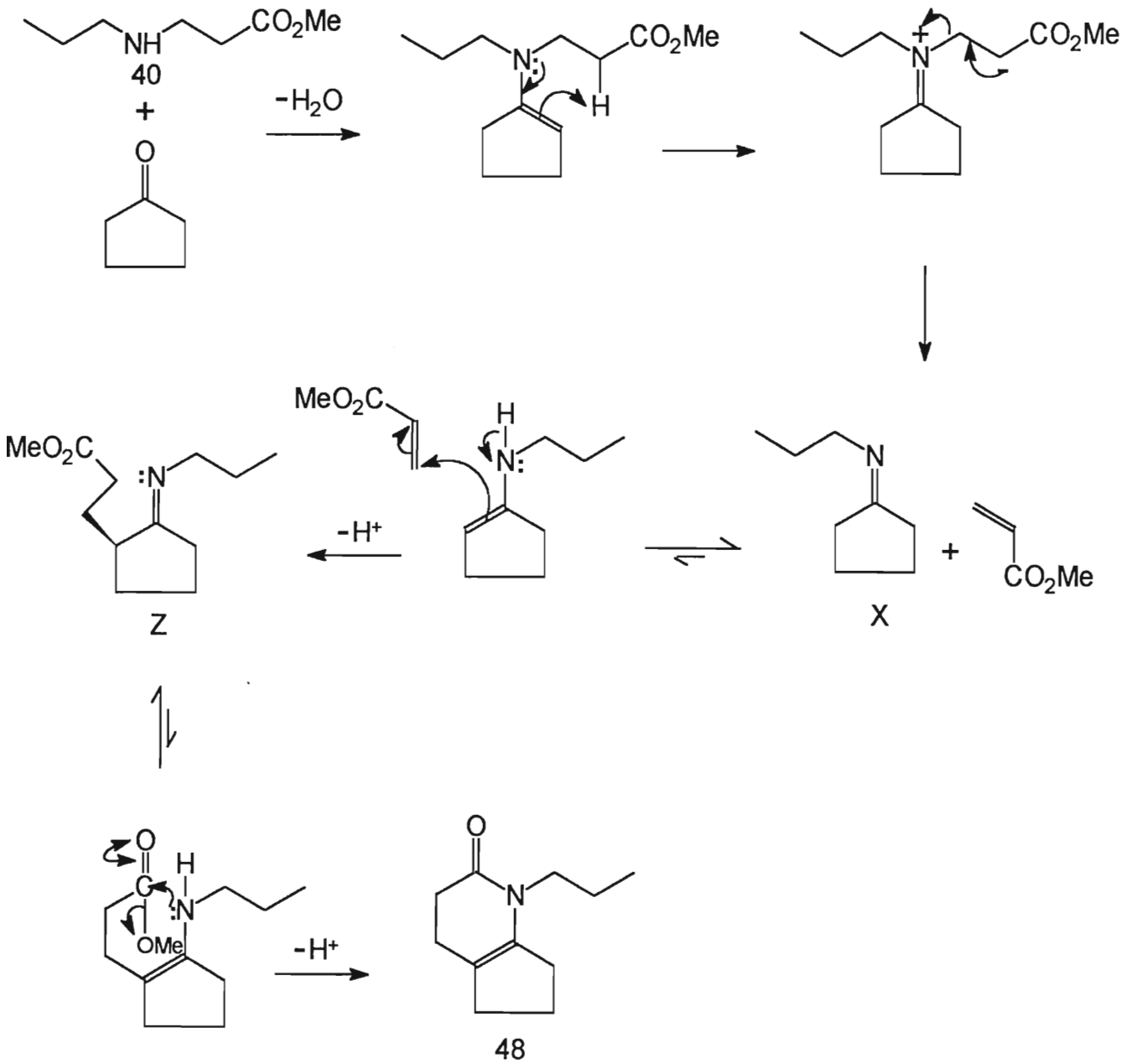
In Scheme 22 the exo double bond is reformed in the initial cyclisation step leading to compound (47).

In Scheme 23 the exo double bond is lost in the cyclisation step. It is therefore possible that the reduced yield of the 2-pyridone system, when fused to a 5-membered ring as in (48), may be attributed to the decreased tendency for tautomeric interconversion into the secondary enamine in both the initial alkylation step (ie. X → Z) and the cyclization step (Z → 48). The low yield of compound (48) is therefore attributed to the stability of this exo double bond.



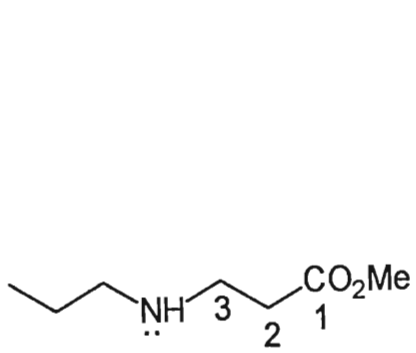
SCHEME 22

*Compound (47) is formed *via* a concerted type process, while (48) is formed *via* a non-concerted process, which could possibly explain the low yield (3%) of (48). However, if this is true then surely we would expect the yield of (46) to be higher that of (45/45a) in the corresponding cyclohexanone reaction. This is not the case since (45/45a) and (46) were isolated in yields of 11 % and 10 % respectively.


NH
CO2Me
40
+
O
-H2O
N:
H
CO2Me
N
+
CO2Me
MeO2C
:N
Z
-H+
MeO2C
H
N:
N
+
CO2Me
X
O
C
H
:N
OMe
-H+
O
N
48

SCHEME 23

Since the absence of molecular sieves had affected the course of the reaction between cyclopentanone and methyl 3-(N-propylamino)propanoate (40) we decided to repeat the reaction of cyclohexanone with methyl 3-(N-propylamino)propanoate but now in the absence of molecular sieves. The reaction mixture was purified by flash chromatography and 1-N-propyl-3,4,5,6,7,8-hexahydro-2-quinolone (45/45a) was isolated.



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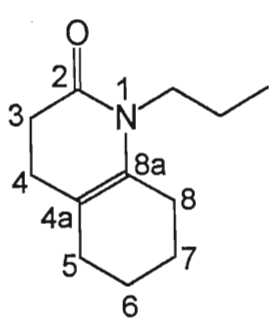

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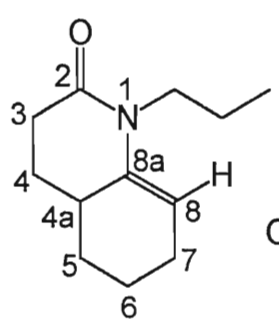
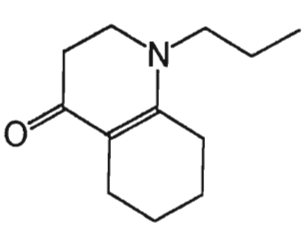


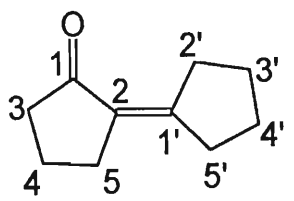
45a



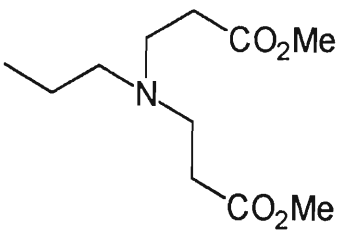
46

This product was also isolated when the reaction was carried out in the presence of molecular sieves, but its isomeric compound (46) was not isolated, but was detected by GC/MS and found to be present in 1.5 % yield from the g.l.c data. A molecular ion corresponding to M^+ 178 was also detected by GC/MS. Although this compound was not isolated we suspect it to be compound (53) which is similar to compound (51) which was isolated, in a 12 % yield, from the corresponding cyclopentanone reaction. We must however emphasize that we cannot unequivocally state this to be the structure.

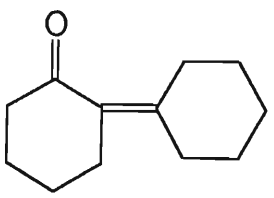
Also isolated from the reaction mixture was the tertiary amine (52) in 2.5 % yield.



51

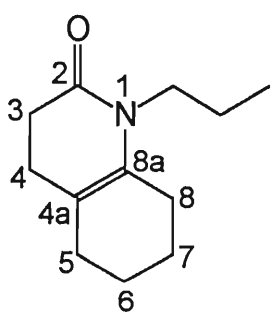


52

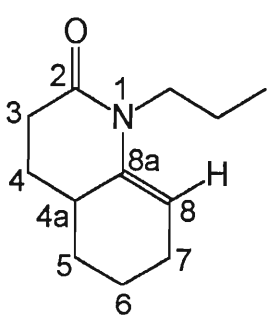


53

In our recent work[37] we failed to see that compound (45) was in fact a mixture of compounds (45) and (45a). We initially believed that the extra peaks in the ^{13}C n.m.r spectrum were due to an impurity, however since the product was isolated in 99 % purity on this occasion we were positive that two compounds were present. The ^{13}C n.m.r and ^{1}H n.m.r spectra showed compounds (45) and (45a) to be present in a ratio of 7:2 respectively.



45



45a

The GC/MS for (45/45a) showed a molecular ion corresponding to M^+ 193 and the g.l.c showed the product to have a $t_R \approx 6.9$ min. The u.v spectrum showed λ max(MeOH) at 247 nm (ϵ = 7000).

The ^{1}H n.m.r spectrum showed the presence of a propyl group [δ_H - 0.82 (t), 1.36-1.68 (c.m.e), 3.46 (t)] and a broad singlet at δ_H 5.00 [C-8, 0.22H, (45a)]. This signal showed coupling (COSY)

to the protons responsible for the c.m.e at δ_H 1.98-2.15 [C-4, C-6, C-7]. The protons responsible for the latter signals also showed coupling to the protons responsible for the c.m.e at δ_H 1.36-1.68 [C-5, C-8 (45), $-CH_2CH_3$, C-4a (45a)] (COSY). The methylene protons of C-3 appeared as a triplet at δ_H 2.38 and showed coupling to the protons at δ_H 1.98-2.15 [C-4, C-6, C-7] (COSY).

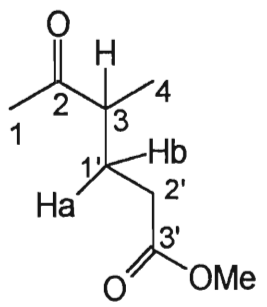
The ^{13}C n.m.r spectrum showed two sets of peaks in the ratio of ≈ 7:2. The peaks of higher intensity correspond compound (45) and those of lower intensity correspond to compound (45a). The following high intensity peaks were observed : The presence of one quartet, eight triplets, and three singlets at δ_C 115.35 (C-4a), 131.02 (C-8a) and 168.75 (C=O).

The ^{13}C n.m.r spectrum showed the following low intensity peaks: The presence of one quartet, seven triplets, two doublets at δ_C 34.89 (C-4a) and 103.65 (C-8) as well as two singlets at δ_C 138.38 (C-8a) and 168.75 (C=O).

This mixture of compounds (45/45a) was confirmed by the i.r spectrum which showed a strong absorption at 1670 cm^{-1} (C=O) and weak absorptions at 1685 cm^{-1} (C=C) and 1640 cm^{-1} (C=C).

We next turned out attention to the reaction of butanone with methyl 3-(N-propylamino)propanoate. The reaction was carried out in boiling dry toluene over activated molecular sieves. The crude reaction mixture was purified directly by flash

chromatography, without a hydrolytic work up, to give a pale yellow oil (54).



54

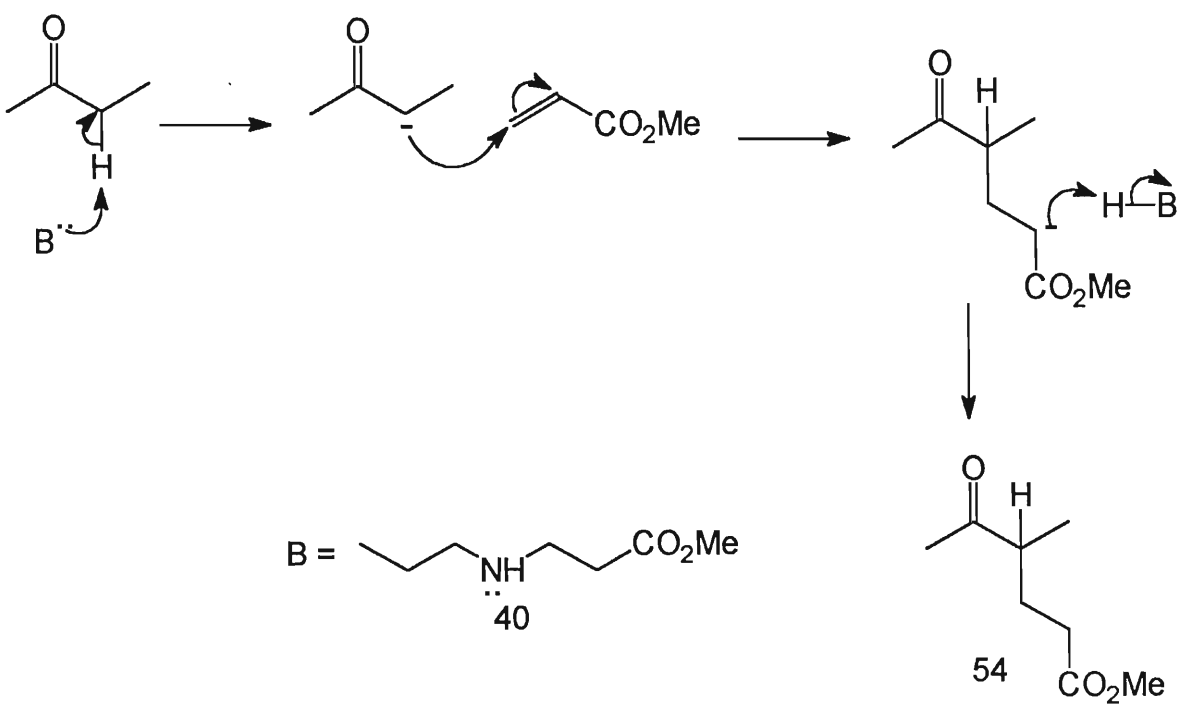
The GC/MS showed a molecular ion corresponding to M^+ 126 and the g.l.c showed the product to have a $t_R \approx 2.8$ min. The i.r spectrum showed absorptions at 1710 cm^{-1} (C=O) and 1735 cm^{-1} (C=O), and the u.v spectrum did not indicate any α,ß-unsaturation.

The ^1H n.m.r spectrum showed the presence of a doublet at δ_H 1.09 ($CH\underline{CH_3}$, C-4) and a multiplet at δ_H 2.52-2.60 (H-3) and the protons responsible for these signals showed coupling to each other (COSY). The spectrum also showed a doublet of multiplets at δ_H 1.62-1.68 (J =7.26 Hz, 1'Ha or 1'Hb) and at 1.94-2.01 (J = 7.32 Hz, 1'Ha or 1'Hb). These protons were geminally coupled (COSY). C-2' appeared as a triplet at δ_H 2.28 with the methylene protons being coupled to 1H'a and 1H'b at δ_H 1.62-1.68 and δ_H 1.94-2.01 (COSY). The ^1H n.m.r spectrum also showed the presence of two singlets at δ_H 2.13 (CH_3-C=O, C-1) and at 3.65 (OCH_3).

The ^{13}C n.m.r spectrum showed the presence of three quartets at δ_C 28.19 (C-1), 16.21 (C-4), and 51.60 (OCH_3), two triplets at

δ_C 27.46 (C-1') and 31.52 (C-2'), one doublet at δ_C 46.08 (C-3), and two singlets which occurred at δ_C 173.62 (C-3') and 211.71 (C-2).

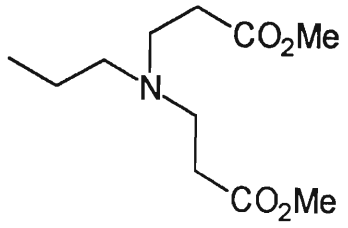
The above data is in accord with the proposed structure methyl 5-oxohexanoate (54) except for M^+ 126 which corresponds to [M - MeOH]. We propose the following sequence of events (Scheme 24) for the formation of (54). Methyl 3-(N-propylamino)propanoate (40) acts a base abstracting a proton from C-3 of butanone. The carbanion then undergoes a Michael addition reaction with methyl acrylate resulting in the formation of compound (54).



SCHEME 24

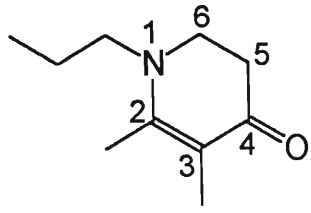
Also isolated from the reaction mixture was the tertiary amine, N,N-di(ß-methoxycarbonylethyl)propylamine (52) (Scheme

21) in 3.5 % yield.



52

Another portion of the reaction mixture was subjected to repeated flash chromatography to give a pale yellow oil, which was identified as 1-N-propyl-2,3-dimethyl-5,6-dihydro-4-pyridone (55). This compound was isolated in only 1.5 % yield.



55

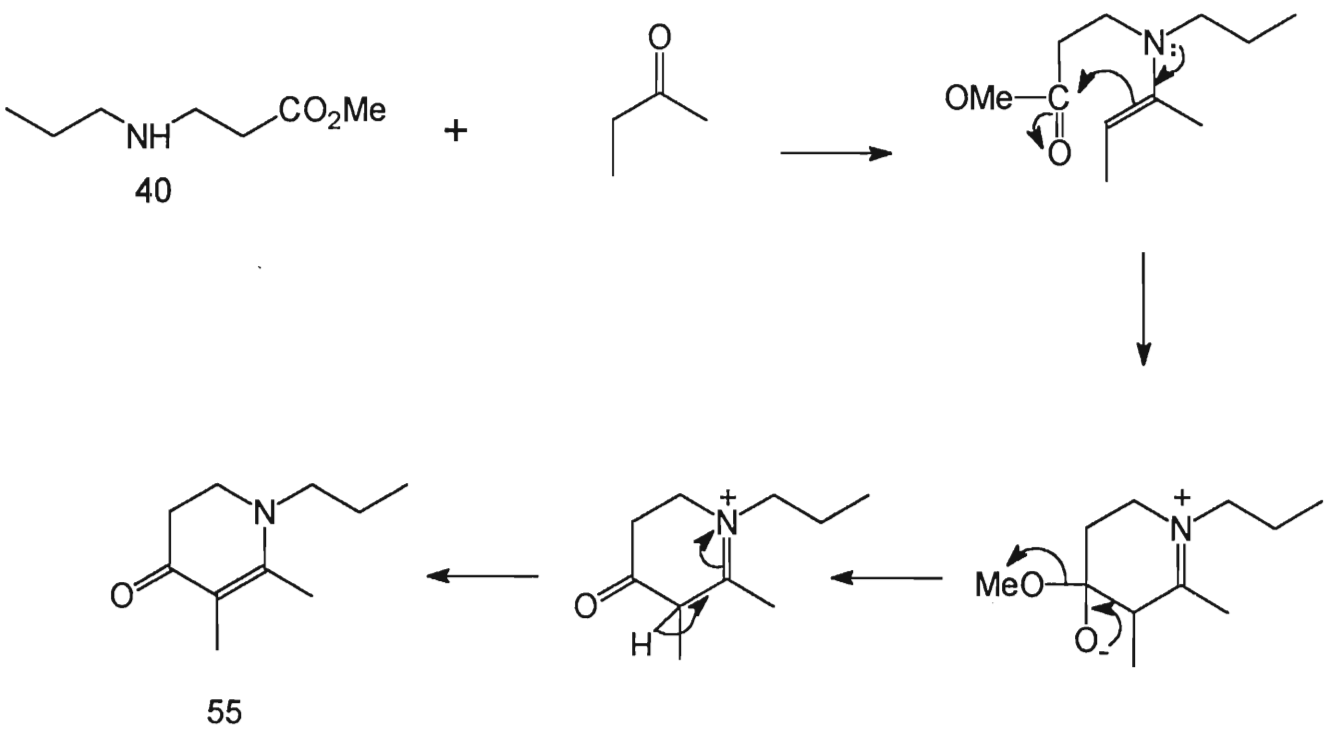
The GC/MS showed a molecular ion corresponding to M^+ 167 and the g.l.c showed the product to have a $t_R \approx 6.4$ min. The i.r showed absorptions at 1605 cm^{-1} (C=O) and 1540 cm^{-1} (C=C) corresponding to an α,ß-unsaturated ketone. This was confirmed by the u.v spectrum which showed λ_{max} (MeOH) at 337 nm (ϵ = 15000).

The ^1H n.m.r spectrum showed the presence of a propyl group [δ_H - 0.90 (t), 1.50-1.62 (m), 3.22 (t)] and the presence of two singlets at δ_H 1.74 and 2.00 which correspond to the methyl groups on C-3 and C-2 respectively. The spectrum also showed two triplets at δ_H 2.37 (C-5) and 3.38 (C-6) and there was evidence of vicinal coupling between the methylene protons

of C-5 and C-6 (COSY).

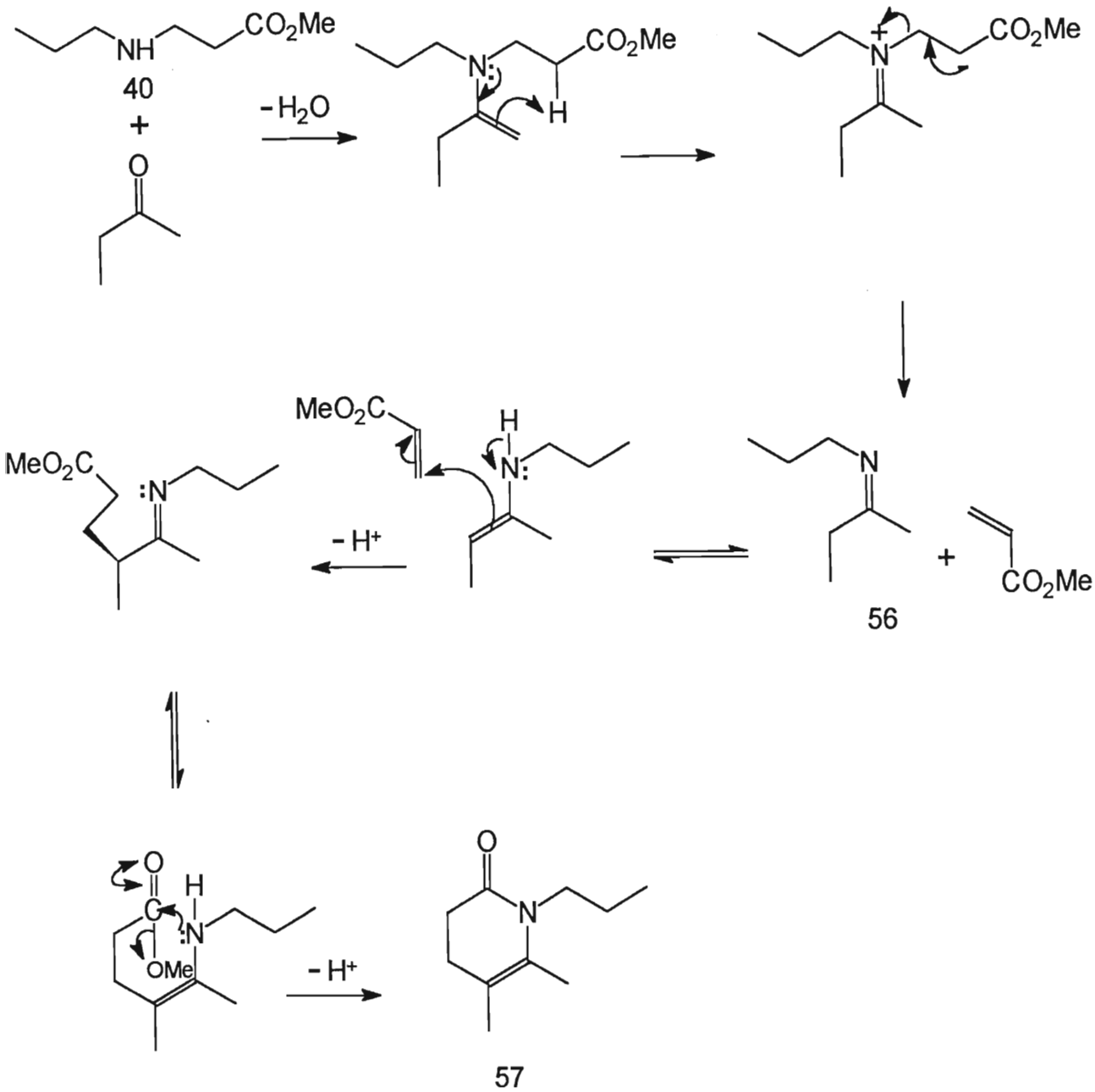
The ^{13}C n.m.r spectrum showed the presence of three quartets, four triplets and three singlets at δ_C 104.56 (C-3), 159.78 (C-2) and 189.63 (C-4, C=O) which is consistent with the proposed structure (55).

The mechanism which we propose for structure (55) is shown in Scheme 25. Formation of the enamine intermediate is followed by spontaneous cyclisation to (55).



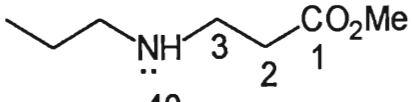
SCHEME 25

The GC/MS of the crude reaction mixture showed another compound corresponding to M^+ 167. We were not able to isolate this compound, however we suspect this compound to have structure (57) (Scheme 26). The g.l.c showed the compound to be present in a 2 % yield and having a $t_R \approx 4.7$ min.

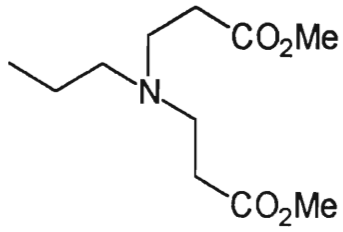


SCHEME 26

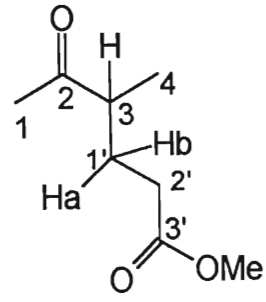
Again as in the cyclopentanone reaction, we are sure that this is the compound since in order for it to form (Scheme 26), methyl acrylate is liberated at a certain stage of the mechanism and it is this methyl acrylate which is essential for the formation of compound (54) (Scheme 24) and compound (52) (Scheme 21).



40



52



54

We next turned our attention to the reaction of $\Delta^{8,8a}$-2-octalone with methyl 3-(N-propylamino)propanoate (40). The reaction was carried out in dry boiling toluene over activated molecular sieves. GC/MS of the crude reaction mixture showed two peaks corresponding to M^+ 245 and g.l.c data showed these peaks to have $t_R \approx 10.6$ min and 10.9 min. Upon subjection of the reaction mixture to flash chromatography these compounds could not be separated and are probably in equilibrium.

The ^1H n.m.r of the mixture proved to be very complex and since these compounds were present in low yield (≈ 5 %), we considered this reaction not to be of sufficient synthetic interest and no further work has been carried out.

In conclusion to this section, it must be stated that the yields of the products obtained from these reactions are not very good (1.5 % - 15.5 %) and the work is not as yet of great synthetic interest. However attention must be paid to variety of compounds isolated and the competition of the various reaction routes for the different starting materials.

These reactions have certainly been interesting and have added

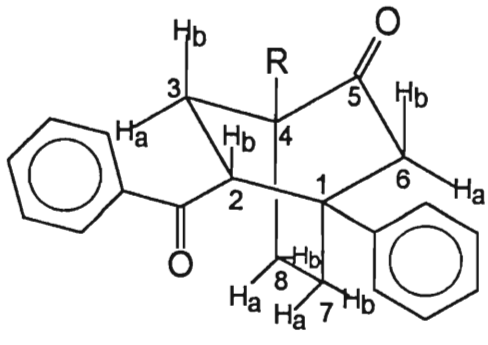
to the various " Analysis of Multipath Reactions" work which has been conducted in our laboratory.

2.2 Reactions of Imines with Phenyl Vinyl Ketone (PVK)

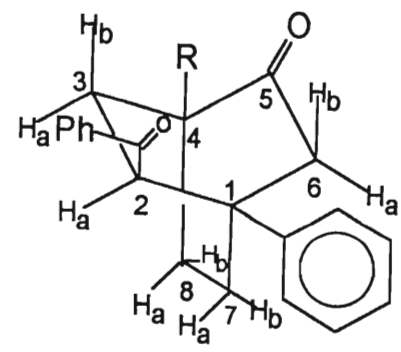
Previous work[38] carried out in this laboratory has resulted in a new one-pot synthesis of the bicyclo[2.2.2]octan-5-one ring system from acyclic precursors.

The reaction of one equivalent of PVK with one equivalent of N-2-butylidenebenzylamine (64a) in boiling dry methanol, followed by hydrolytic work-up, has resulted in the synthesis of 2-benzoyl-4-methyl-1-phenylbicyclo[2.2.2]octan-5-one (65a) (Scheme 27).

It was proposed that two equivalents of PVK add to C-1 of the imine (64a), followed by cyclization where the imine undergoes an intramolecular 1,4-addition reaction to give the bicyclic compound as a mixture of the two isomers, (66a) and (67a), which were isolated in 5.6 % and 1.3 % yield respectively.



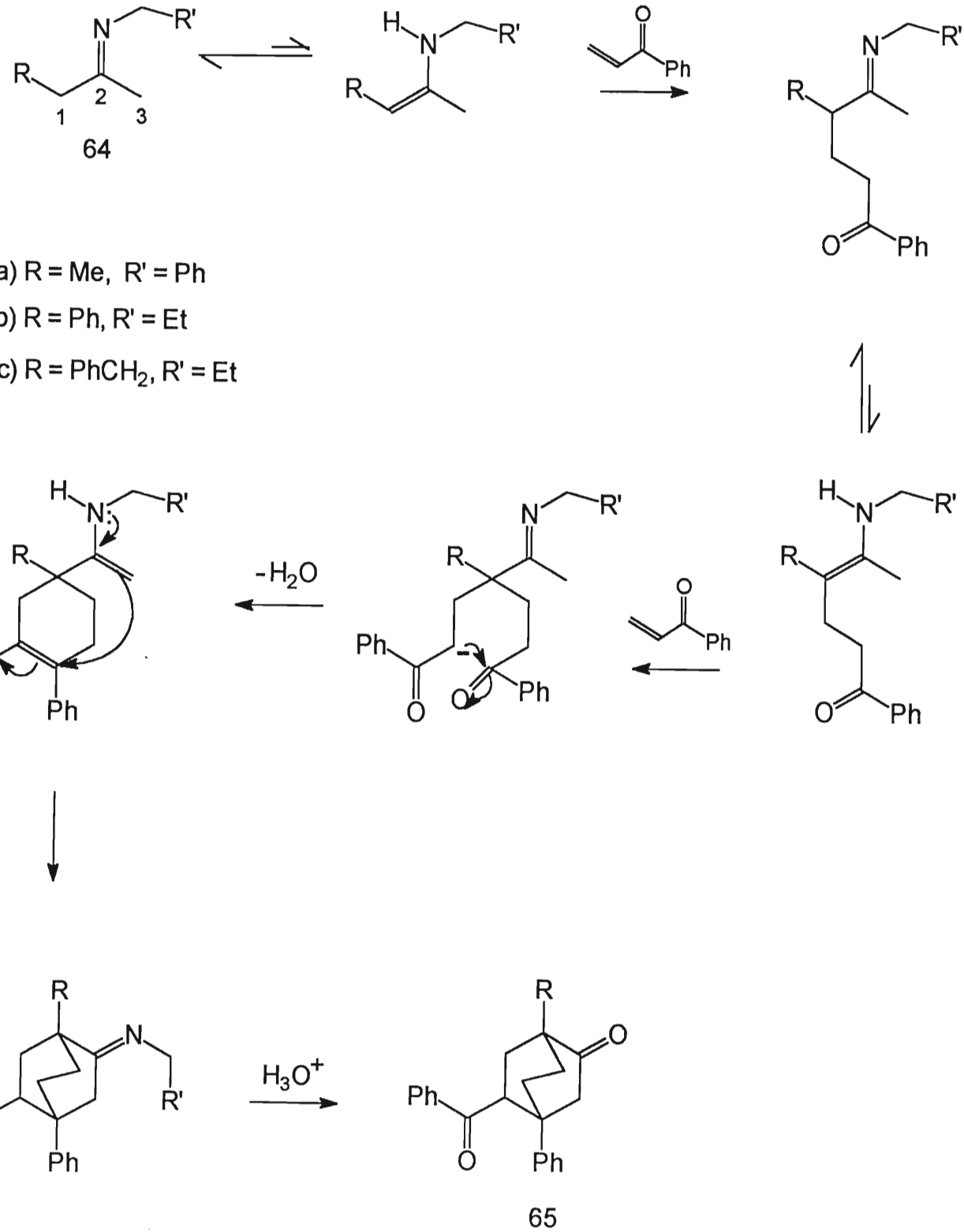
66



67

a) R=Me, b) R=Ph c) R=PhCH$_2$ d) R=CH$_2$CO$_2$Et

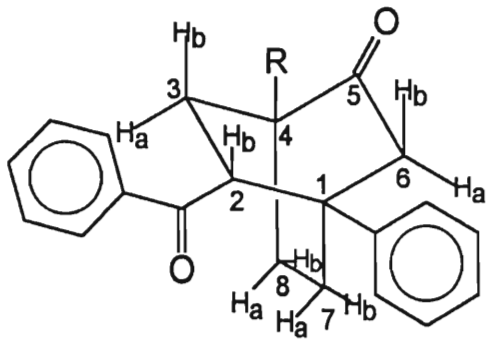
The above structures were confirmed by 500 MHz n.m.r spectroscopy and single crystal X-ray structure determination. The reaction was then repeated using two equivalents of PVK and



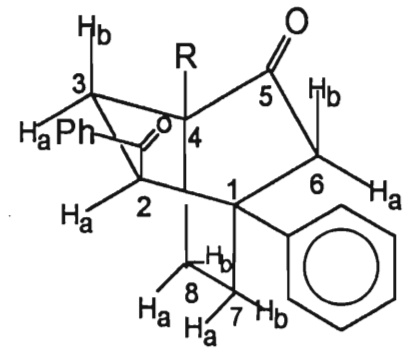
SCHEME 27

the yield of (66a) increased to 35 %, none of isomer (67a) being isolated.

Since any water given off in the initial cyclization step could result in the partial hydrolysis of the imine enamine mixture, the reaction was repeated in the presence of molecular sieves and resulted in the yield of compound (66a) being increased from 35 % to 50 %.



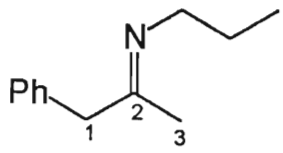
66



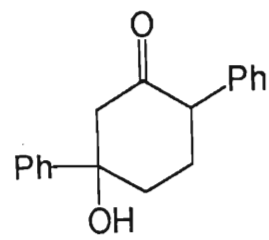
67

a) R=Me, b) R=Ph c) R=PhCH$_2$ d) R=CH$_2$CO$_2$Et

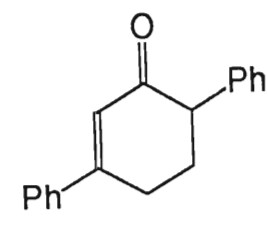
To determine the generality of the bicyclo-octanone synthesis Rae[51] examined the reaction of the propylamine imine of 1-phenylpropan-2-one (64b) (Scheme 27) with PVK. However the yield of the bicyclo-octanone (66b) was only found to be 4 % under conditions which gave a 50 % yield of compound (66a). The reaction gave the monocyclisation products (68) and (69) which form by initial reaction at C-1 of the imine (64b) followed by cyclisation at C-3.



64b

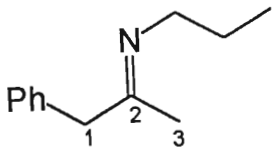


68

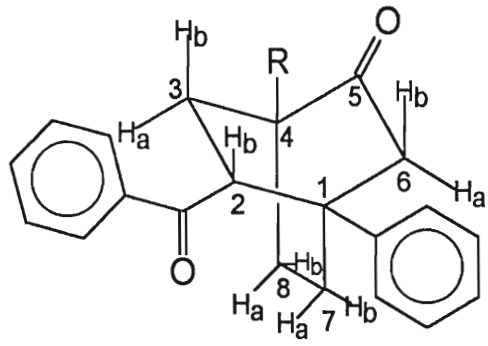


69

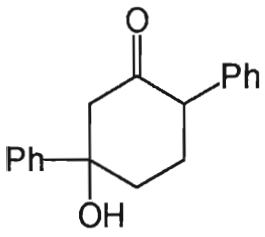
The low yield of compound (66b) was attributed to the bulky phenyl group which impedes reaction at C-1 of the imine (64b) (Scheme 27) with a second equivalent of PVK, and thereby favours cyclization to (68) and (69).



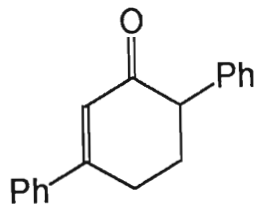
64b



66



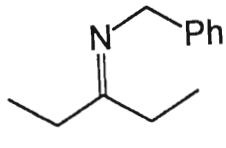
68



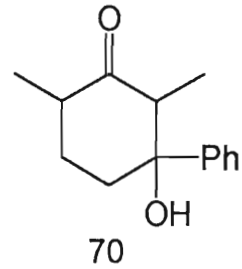
69

a) R = Me, b) R = Ph c) R = $PhCH_2$ d) R = CH_2CO_2Et

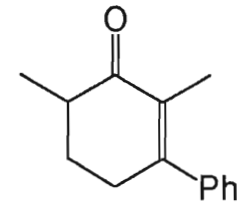
When the reaction of the benzylamine imine of pentan-3-one (64e) was carried out with PVK it followed a different course. In this reaction, only one equivalent of PVK reacted with one equivalent of the imine, and this was followed by cyclization onto C-2 to produce after hydrolysis, 3-hydroxy-2,6-dimethyl-3-phenylcyclohexanone (70) in a 11 % yield and 2,6-dimethyl-3-phenylcyclohex-2-enone (71) in a 45 % yield.



64e



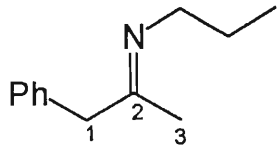
70



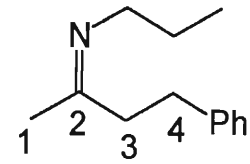
71

Our work begins by investigating the reaction of the propylamine imine of benzylacetone (64c) with two equivalents of PVK.

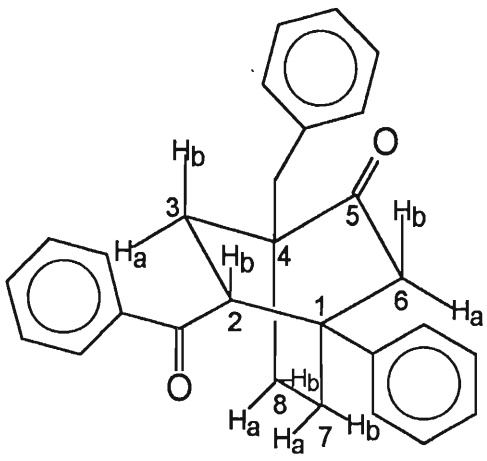
Successful formation of compounds (66c) and (67c) would support the explanation, that the bulky phenyl group impedes reaction at C-1 of imine (64b) (Scheme 27) with a second equivalent of PVK, since the bulky phenyl group is now further removed from the reaction site.



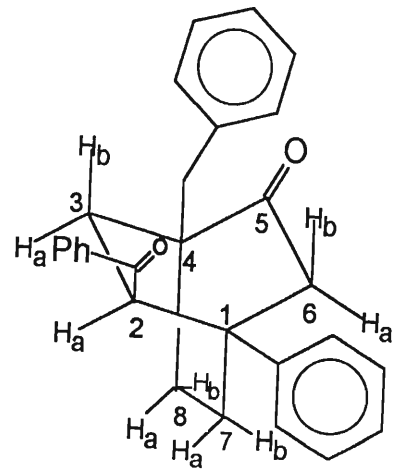
64b



64c



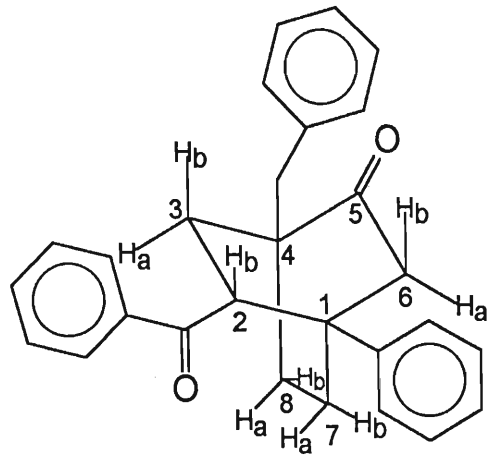
66c



67c

The reaction was carried out in boiling methanol over activated molecular sieves and the resulting mixture was subjected to a hydrolytic work-up, followed by flash chromatography which resulted in the isolation of the two isomers, rel-(1R,2R,4S)-2-benzoyl-4-benzyl-1-phenylbicyclo[2.2.2]octan-5-one (66c) and rel-(1R,2S,4S)-2-benzoyl-4-benzyl-1-phenylbicyclo[2.2.2]octan-

5-one (67c) in yields of 28.5 % and 4 % respectively.

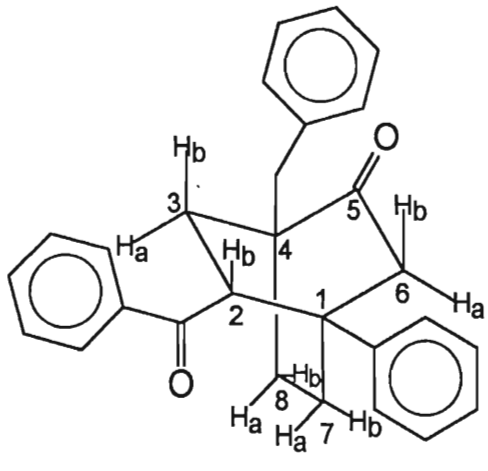


66c

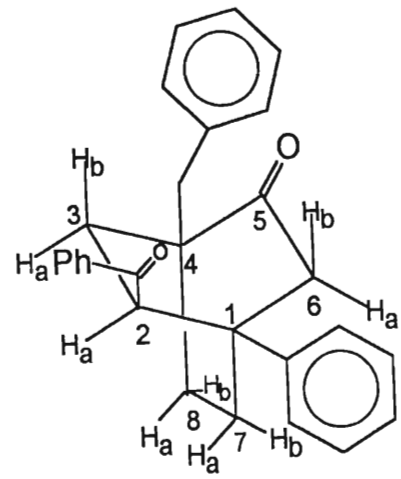
The major product is assigned structure (66c) based on the following n.m.r spectral assignments. The signal due to C-2 appears at δ_C 48.30 (DEPT) and the attached proton 2-Hb appears as a quartet of doublets at δ_H 4.03 (HETCOR). This is vicinally coupled (COSY) to two protons at approximately δ_H 2.0 and forms the X part of an ABX spin system. The further weak splitting of the four lines is attributed to W-coupling to 7-Hb at approximately δ_H 1.75; C-7 therefore appears at δ_C 24.80 and 7-Ha at approximately δ_H 2.95 (HETCOR). The signal at δ_H 2.0 is assigned to the two 3-H protons and C-3 appears at δ_C 33.46 (HETCOR). A sharp doublet at δ_H 2.44 (J 18.6 Hz) is assigned to 6-Ha since this has no path available for W-coupling; 6-Hb appears at approximately δ_H 3.0 (COSY) overlaid by the signal due to 7-Ha, and C-6 appears at δ_C 51.74 (HETCOR). The benzyl methylene protons are non-equivalent and give an AB quartet centred at δ_H 2.90 (δ_C 39.19/HETCOR). The remaining methylene

(C-8) gives a signal at δ_C 28.32 and 8-Ha and 8-Hb appear at approximately δ_H 2.14 and 1.75 (HETCOR) respectively.

The relative stereochemical assignment of (1R*,2R*,4S*) is therefore confirmed by the W-coupling observed between 2-Hb and 7-Hb. Further confirmation is obtained from the steric compression effect exerted by the C-2 benzoyl group on C-7 which appears at higher field (δ_C 24.80) than C-7 in the isomer (67c) (δ_C 34.30) and the deshielding influence of the benzoyl group on 7-Ha which appears at lower field (δ_H 2.95) than 7-Ha in the isomer (67c) (δ_H 2.32) .



66c



67c

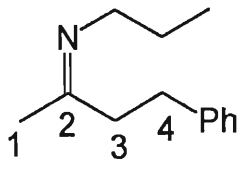
Confirmation that the minor product may be assigned the structure (67c) is based on similar n.m.r spectral assignments. The signal due to C-2 appears at δ_C 46.96 (DEPT) and the attached proton 2-Ha at δ_H 4.12 (HETCOR). This signal is a quartet of unequally split doublets (doublet splitting ranging from 1.4 to 1.65 Hz) and forms the X part of an ABX spin system owing to vicinal coupling with the two 3-H protons at approximately δ_H 2.0 (COSY) and the further fine splitting due

to W-coupling with 6-Ha (δ_H 2.52). The latter is a doublet of doublets (J 18.6, 1.6 Hz) due to geminal coupling with 6-Hb at δ_H 3.7 (COSY); C-6 appears at δ_C 44.12 (HETCOR). The 6-Hb proton is W-coupled (J 3.4 Hz) to a proton appearing as a doublet of multiplets at δ_H 2.32 (COSY) which is therefore assigned to 7-Ha; C-7 therefore appears at δ_C 34.30 and 7-Hb at approximately δ_H 1.75 (HETCOR).

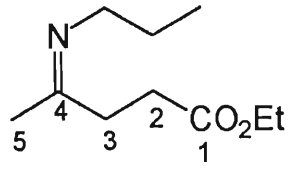
The benzyl methylene carbon and C-3 give signals at δ_C 38.86 and 32.82 (HETCOR) respectively, and the remaining methylene (C-8) appears at δ_C 28.17. The two 3-H and two 8-H protons, together with 7-Hb form a series of overlaid multiplets at δ_H 1.60-2.15.

This partial assignment has enabled the relative stereochemistry to be assigned as (1R*,2S*,4S*) in this structure, since only then can both 6-H protons show W-coupling (6-Ha to 2-Ha and 6-Hb to 7-Ha). Furthermore 6-Hb is the lowest field methylene proton since it bears a 1,3-diaxial relationship to the C-2 benzoyl group.

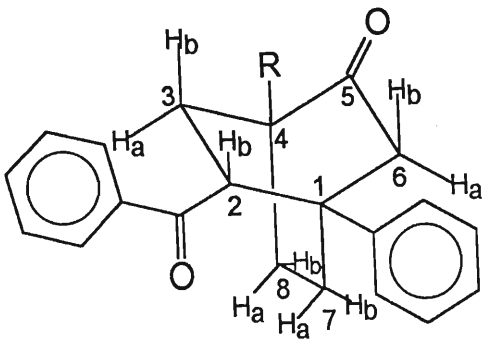
The reaction of imine (64c) with PVK (Scheme 27) was repeated using ethanol as the solvent medium. Hydrolytic work-up and flash chromatography of the reaction mixture led to the isolation of compound (66c) in a 41 % yield and its isomer (67c) was isolated in a 6 % yield.



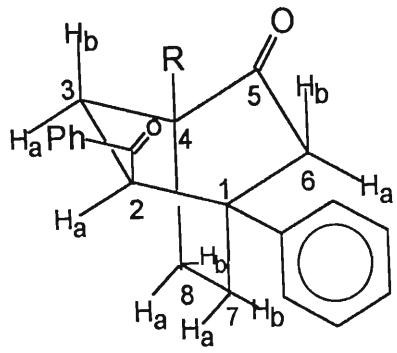
64c



72



66



67

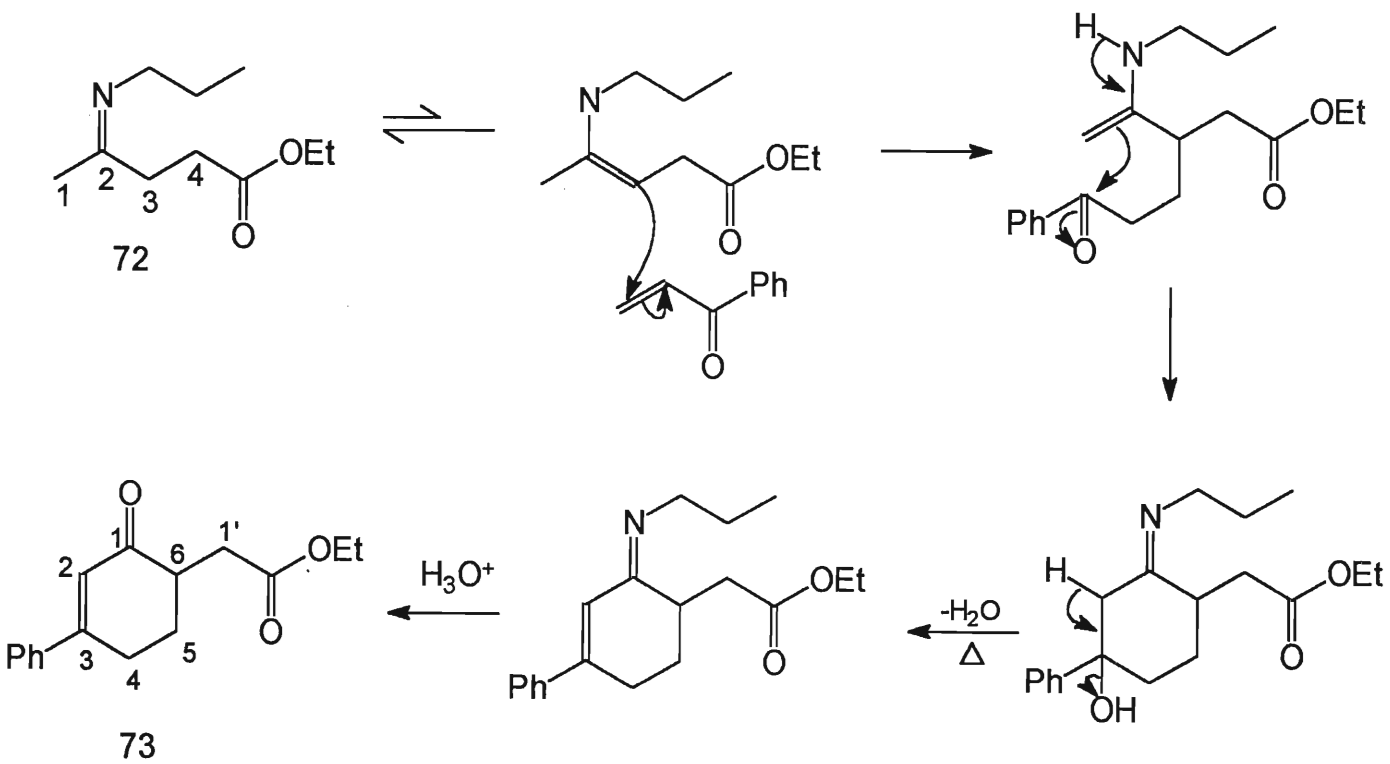
a) R=Me, b) R=Ph c) R=PhCH$_2$ d) R=CH$_2$CO$_2$Et

The reaction of imine (64c) with PVK (Scheme 27) was also repeated by adding the imine to boiling PVK in methanol. Hydrolytic work-up and flash chromatography of the reaction mixture led to the isolation of compound (66c) in a 14 % yield and its isomer (67c) was isolated in a 3 % yield.

We next turned our attention to the reaction of the propylamine imine of ethyl levulinate (72) (Scheme 28) with two equivalents of PVK. The reaction was carried out in boiling dry ethanol, over activated molecular sieves. Hydrolytic work-up of the resulting mixture followed by flash chromatography did not give the expected products (66d) and (67d).

The only product isolated by flash chromatography has

been tentatively assigned as the monocyclisation product 6-ethoxycarbonylethyl-3-phenylcyclohex-2-enone (73), which is formed by initial reaction at C-3 of the imine (72) followed by cyclization at C-1 (Scheme 28).



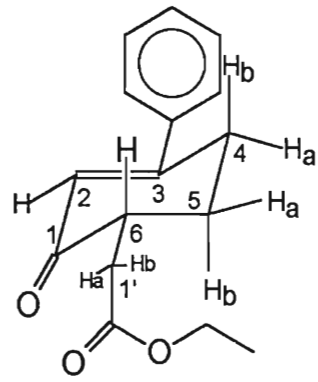
SCHEME 28

The GC/MS showed one peak corresponding to M^+ 258 and the g.l.c showed the product to have a $t_R \approx 12.3$ min. The i.r spectrum showed absorptions at 1730 cm^{-1} (CO_2Et), 1660 cm^{-1} (C=O) and 1605 cm^{-1} (C=C).

The signal for H-2 appears at δ_H 6.42 and there is evidence for long range allylic coupling to 4-Ha (COSY) at δ_H 2.82-3.05. C-4 therefore appears at δ_C 28.12 (HETCOR) and C-2 appears at δ_C

124.65 (HETCOR). The signal for C-6 appears at δ_C 42.93 (DEPT) and H-6 therefore appears as a complex multiplet at δ_H 2.82-3.05 (HETCOR) together with 4-Ha, 4-Hb and 1'Ha or 1'Hb. These protons are coupled to the protons responsible for the c.m.e at δ_H 2.25-2.40 (1'Ha or 1'Hb and 5Ha or 5Hb) which are in turn coupled to the proton responsible for the c.m.e at δ_H 1.85-2.05 (5Ha or 5Hb). The signals for C-5 and C-1' therefore appear at δ_C 28.70 and 34.64 respectively (HETCOR).

The ethoxy group appeared as triplet at δ_H 1.29 ($\underline{CH_3}$-CH_2-O) and a quartet at δ_H 4.13-4.24 ($\underline{CH_2}$-O) and the carbon signals appeared at δ_C 14.23 and 60.56 respectively (HETCOR).



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The ^{13}C n.m.r spectrum showed three doublets at δ_C 126.06, 128.76 and 130.04 which were assigned to the phenyl group and four singlets at δ_C 138.44 (Ph), 159.12 (C-3), 172.59 (C=O) and 199.50 (C=O, C-1), and the required number of quartets and triplets.

Clearly further work is required with regard to the alkylation, using PVK, of the propylamine imine of ethyl levulinate (72) (Scheme 28) and related imines derived from ketones of the form $MeCO-CH_2-CH_2-CO_2R$.

EXPERIMENTAL

3.0 EXPERIMENTAL

Foreword to Experimental

Instrumental :

Nuclear Magnetic Resonance Spectroscopy (n.m.r)

^{1}H n.m.r and ^{13}C n.m.r spectra were recorded with either a 200 MHz or a 300 MHz Gemini spectrometer using $CDCl_3$ as solvent. The spectra were referenced against the central line of the deuteriochloroform triplet at δ_C 77.09 ppm or the deuteriochloroform singlet at δ_H 7.24 ppm.

Infra Red Spectroscopy (i.r)

Infra red spectra were recorded with a Shimadzu I.R - 408 spectrometer and were calibrated against the 1601 cm^{-1} peak of polystyrene.

Gas Liquid Chromatography (g.l.c)

The g.l.c analyses were carried out with a Varian 3400 gas chromatograph. The ß-aminopropanoate work was carried out using ultra-high purity nitrogen as the carrier gas (flow rate: 24 ml/min), a 14.75 m glass capillary column (Phase: SPB.1; I.D - 0.25 microns) and a flame ionization detector. The g.l.c spectra for all samples were obtained at initial column temperature : 140°C; ramp rate : 16°C/min for 10 minutes, final column temperature : 300°C; auxiliary temperature: 280°C; and detector temperature 300°C.

The phenyl vinyl ketone work was carried out using ultra-high purity nitrogen as the carrier gas (flow rate: 30 ml/min), a 30 m glass capillary column (Phase: PS25S; I.D 0.53 microns) and a flame ionization detector. The g.l.c spectra for these compounds were recorded at column temperature : 230°C; injection temperature : 240°C, and auxiliary temperature : 250°C.

Experimental yields quoted are from the masses of the crude reaction mixtures using g.l.c percentage (based on integrated peak areas), unless stated otherwise.

Gas Chromatography/Mass Spectroscopy (GC/MS)

GC/MS spectra were recorded with a Finnigan 1020 automated spectrometer operating at 70 eV.

C/H/N - Analyses

Microanalyses were carried out by the Department of Chemistry of the University of Natal in Pietermaritzburg.

Melting Points

Melting points were measured on a Kofler micro-hot stage melting point apparatus and are uncorrected.

General Chromatography

Silica gel (0.2 mm) containing fluorescent indicator (F_{254}) on aluminium backed plates (Merck: Art 5554) was used for t.l.c and silica gel (Merck : Art 9385) was used for flash

chromatography. The t.l.c plates were developed using anisaldehyde:concentrated H_2SO_4:methanol [1:2:97] as spray reagent followed by heating.

Solvents

The solvents were dried using the following methods :

Ethanol : was dried following the method in Vogel[52]. The super dry ethanol was prepared by heating magnesium turnings (2,60 g), iodine (0,26 g) and ethanol (50 ml) under reflux, the condenser being fitted with a drying tube. After all the magnesium had been consumed, ethanol (450 ml) was added and the mixture was refluxed for a further hour. The ethanol was then fractionally distilled (b.p. 78°C) and stored over molecular sieves (3A).

Methanol: was dried using the method in Vogel used for drying ethanol. The methanol was fractionally distilled (b.p. 64.5°C) and stored over molecular sieves (3A).

Methyl Acrylate : was stirred overnight with magnesium sulphate, filtered, and distilled from quinol (b.p. 77.5°C) and stood over molecular sieves (5A) for 12 hours prior to use.

Benzene : was dried overnight with calcium chloride, and distilled (b.p. 79°C) from the desiccant and stood over molecular sieves (3A).

Toluene : was dried by standing over anhydrous calcium chloride for 24 hours followed by distillation (b.p. 110°C)

into a vessel containing molecular sieves (5A).

Hexane : was dried overnight with calcium chloride and distilled from the desiccant (b.p. 67.5°C) and stood over sodium wire for 24 hours prior to use.

Phenyl Vinyl Ketone : was prepared according to the method outlined in the experimental section and dried over molecular sieves (4A) for 12 hours prior to use.

Ether : was dried over sodium wire.

Methylene Dichloride : was dried over anhydrous calcium chloride and distilled onto molecular sieves (4A) (b.p. 41°C).

In all purifications and reactions, the molecular sieves were activated by heating at 400°C for 15 hours and 60-80 g were used per litre of solvent.

Abbreviations

^{1}H n.m.r - proton nuclear magnetic resonance spectroscopy

^{13}C n.m.r - carbon nuclear magnetic resonance spectroscopy

t.l.c - thin layer chromatography

g.l.c - gas-liquid chromatography

i.r - infra red spectroscopy

b.p. - boiling point

GC/MS - gas chromatography/mass spectroscopy

u.v - ultra violet spectroscopy

The following abbreviations have been used when assigning spectra:

s - singlet

d - doublet

q - quartet

t - triplet

m - multiplet

c.m.e - complex methylene envelope

bs - broad singlet

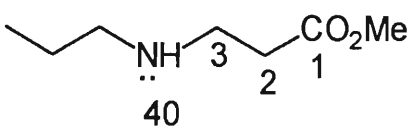
qd - quartet of doublets

dd - doublet of doublets

3.1 REACTIONS OF ß-AMINOPROPANOATES

3.1.1 THE PREPARATION OF METHYL 3-(N-PROPYLAMINO)PROPANOATE

Methyl acrylate (51.66 g; 0.6 mol) was slowly added to propylamine (35.46 g; 0.6 mol) in methanol (80 ml). The mixture was stirred for 24 hours at room temperature. The solvent was removed in *vacuo* and the crude product purified by vacuum distillation to give the secondary amine (73.20 g; 84 %), b.p. 50°C / 0,5 mm Hg.



The GC/MS spectrum showed : one peak, M^+ 145

The i.r spectrum showed : υ (NaCl) cm^{-1}

1735 (C=O) and

3350 (N-H stretching)

The ^1H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

0.92 (3H, t, CH_3)

1.34 (1H, bs, N-H)

1.44-1.56 (m, 2H, -$\underline{CH_2}$-CH_3)

2.50-2.60 (4H, c.m.e, 2 X CH_2)

2.88 (2H, t, CH_2)

3.68 (3H, s, -OCH_3)

The GC/MS of the crude reaction mixture showed the presence of the tertiary amine in low yield, M^+ 231. This is a higher boiling pale yellow liquid (b.p. 100-106°C / 0.1 mm Hg)[36]

3.1.2 THE REACTION OF METHYL 3-(N-PROPYLAMINO)PROPANOATE WITH CYCLOHEXANONE IN THE PRESENCE OF TITANIUM TETRACHLORIDE

A three necked round bottom flask was fitted with a reflux condenser containing a nitrogen inlet, a pressure equalizing dropping funnel and a mechanical stirrer. The whole apparatus was flushed with dry nitrogen.

Methyl 3-(N-propylamino)propanoate (8,71 g ; 0,06 mol) in dry hexane (100 ml) was introduced into the flask and cooled in ice to 0°C. Titanium tetrachloride (4 ml ; 0,036 mol) was added drop wise to methyl 3-(N-propylamino)propanoate with stirring and under a positive pressure of dry nitrogen. After the addition was completed the cyclohexanone (3,92 g ; 0,04 mol) was added in one portion to the flask. After the mixture had risen to room temperature, it was raised to the boil and heated under reflux for 14 hours. The residue which formed was extracted with dichloromethane (4 x 50 ml). The combined extracts were filtered through oven dried diatomaceous earth contained in a sintered glass funnel (porosity 3). The dichloromethane was then removed in *vacuo* leaving a pale yellow solid which was recrystallized from dichloromethane leaving a white crystalline material (1.06 g; 12 %) (actual mass). This material was identified as *1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene* (49).

Melting Point : 232°C

The GC/MS spectrum showed : one peak M^+ 240

g.l.c showed : one peak $t_R \approx 11.7$ min

The i.r spectrum showed : υ (KBr) cm^{-1}

1440, 1555 (-CH deformations)

2850-2950 (CH_2 stretching)

The H^1 n.m.r spectrum (200 MHz) showed : δ_H (ppm)

1.74-1.79 (m, 12H, C-2, C-3, C-6, C-7, C-10, C-11)

2.53-2.60 (m, 12H, C-1, C-4, C-5, C-8, C-9, C-12)

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_c (ppm)

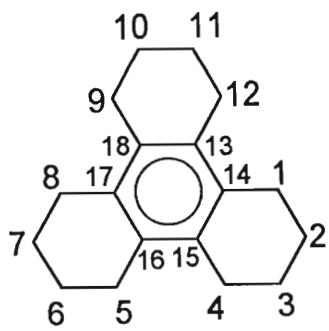
23,10 (t, C-2, C-3, C-6, C-7, C-10, C-11)

26,85 (t, C-1, C-4, C-5, C-8, C-9, C-12)

132,57 (s, C=C, C-13, C-14, C-15, C-16, C-17, C-18)

C/H/N analysis : Found C: 89.78 % H: 10.42 %

Calculated for $C_{18}H_{24}$ C: 89.94 % H: 10.06 %



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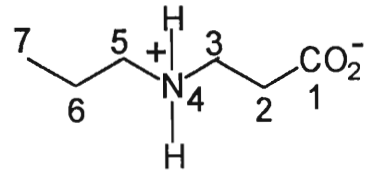
3.1.3 THE REACTION OF CYCLOPENTANONE WITH METHYL 3-(N-PROPYLAMINO)PROPANOATE IN THE ABSENCE OF MOLECULAR SIEVES

Cyclopentanone (30.4 g; 0.35 mol) and methyl 3-(N-propylamino)propanoate (17.46 g; 0.12 mol) in dry toluene (100 ml) were heated under reflux for 48 hours, the condenser being fitted with a drying guard. The solvent was removed in *vacuo* and the crude mixture was filtered to give a white crystalline material. This material was recrystallized from dichloromethane and identified as the zwitterionic salt of *N-propyl ß-aminoproprionic acid* (50) (0.70 g; 4.5 %) (actual mass) and was found to be hygroscopic.



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The GC/MS spectrum showed : one peak M^+ 131

g.l.c showed : one peak $t_R \approx 3.1$ min

The i.r spectrum showed : υ(NaCl) cm^{-1}

2500-3750 - broad absorption - ($>NH_2^+$)

1575 and 1400 - (CO_2^-, antisymmetric and symmetric stretching respectively)

The ^1H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

0.99 (t, 3H, CH_3, C-7)

1.70-1.83 (m, 2H, -$\underline{CH_2}$-CH_3, C-6)

2.51 (t, 2H, N-CH_2, C-2)

2.87 (t, 2H, $\underline{CH_2}$-CH_2-CH_3, C-5)

3.05 (t, 2H, N-CH_2-$\underline{CH_2}$, C-3)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

11.16 (q, CH_2-$\underline{C}H_3$, C-7)

19.69 (t, $\underline{CH_2}$-CH_3, C-6)

31.71 (t, N-$\underline{CH_2}$, C-2)

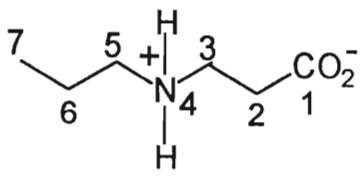
44.59 (t, N-CH_2-$\underline{CH_2}$, C-3)

48.72 (t, $\underline{CH_2}$-CH_2-CH_3, C-5)

176.91 (s, C=O, C-1)

A portion (2.50 g) of the crude reaction mixture (38.39 g) was subjected to flash chromatography using hexane: methylene chloride: ethyl acetate [18:12:1] as eluent and taking 15 (≈ 40 ml fractions). Fractions (2-5) were combined on the basis of t.l.c and g.l.c and found to contain

2-cyclopentylidenecyclopentanone (51) (6.15 g; 12 %)



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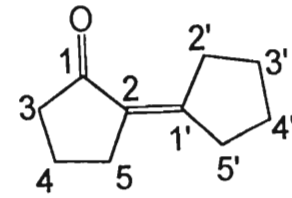

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The GC/MS showed : one peak M^+ 150

g.l.c showed : one peak t_R ≈ 4.7 min

The i.r spectrum showed : υ (NaCl) cm^{-1}

1635 (C=C)

1705 (C=O)

The u.v spectrum showed : λ_{max} (MeOH) 266 nm (ϵ = 27000)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

1.56-1.70 (c.m.e, 4H, C-3′ and C-4′)

1.78-1.89 (m, 2H, C-4)

2.18-2.25 (c.m.e, 4H, C-3 and C-5′)

2.42-2.50 (m, 2H, C-5)

2.69-2.72 (m, 2H, C-2′)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

19.94 (t, C-4)

25.10 (t)

26.80 (t)

29.38 (t, C-5)

32.41 (t, C-2′)

34.16 (t)

39.64 (t)

127.76 (s, C=C, C-2)

158.56 (s, C=C, C-1′)

207.27 (s, C=O, C-1)

Fractions (8-11) were combined on the basis of g.l.c and t.l.c and found to contain *N,N-di(ß-methoxycarbonylethyl)propylamine* (0.80 g; 3 %) (52).

The GC/MS showed : one peak M^+ 231

g.l.c showed : one peak $t_R \approx 5.5$ min

The i.r spectrum showed : υ (NaCl) cm^{-1}

1737 (C=O)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

0.82 (t, 3H, CH_3)

1.36-1.44 (m, 2H, $\underline{CH_2}$-CH_3)

2.33 (t, 2H, $\underline{CH_2}$-CH_2-CH_3)

2.41 (t, 4H, 2 X CH_2, C-2 and C-2′)

2.73 (t, 4H, 2 X CH_2, C-3 and C-3′)

3.63 (s, 6H, 2 X OCH_3)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

11.68 (q, CH_3)

20.29 (t, $\underline{CH_2}$-CH_3)

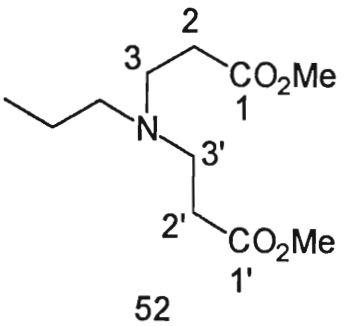
32.57 (t, N-$\underline{CH_2}$, C-2 and C-2′)

49.29 (t, N-CH_2-$\underline{CH_2}$, C-3 and C-3′)

51.50 (q, OCH_3)

55.72 (t, $\underline{CH_2}$-CH_2-CH_3)

173.10 (s, C=O, C-1 and C-1′)



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Another portion (2.5 g) of the crude reaction mixture (35.89 g) was purified by flash chromatography using methylene chloride: hexane: ethyl acetate [3:1:11] as eluent and taking 45 (≈ 40 ml fractions). Fractions (24-40) were combined on the basis of t.l.c and g.l.c and found to contain *4-propyl-4-azahexahydro-$\Delta^{3a,7a}$-inden-7-one* (47) (0.86 g; 4 %).

The GC/MS spectrum showed : one peak M^+ 179

g.l.c showed : one peak t_R ≈ 7.8 min

The i.r spectrum showed : υ (NaCl) cm^{-1}

1560 cm^{-1} (C=C)

1625 cm^{-1} (C=O)

The u.v spectrum showed : λ_{max}(MeOH) 333 nm (ϵ = 32000)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H(ppm)

0.88 (t, 3H, CH_2-$\underline{CH_3}$)

1.52-1.59 (m, 2H, $\underline{CH_2}$-CH_3)

1.78-1.92 (m, 2H, C-2)

2.39 (t, 2H, C-6)

2.48-2.57 (4H, overlaid triplets, C-1 and C-3)

3.16 (t, 2H, N-CH_2)

3.42 (t, 2H, C-5)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

11.10 (q)

21.14 (t, C-2)

21.79 (t, $\underline{C}H_2$-CH_3)

27.20 (t, C-1)

32.51 (t, C-3)

35.87 (t, C-6)

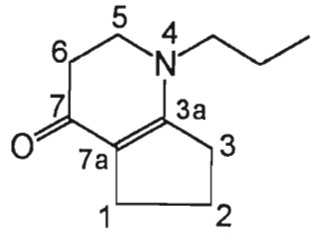
48.53 (t, C-5)

53.60 (t, N-CH_2)

108.58 (s, C=C, C-7a)

168.08 (s, C=C, C-3a)

187.39 (s, C=O, C-7)



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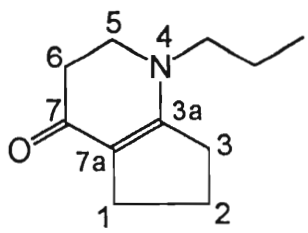
3.1.4 THE REACTION OF CYCLOPENTANONE WITH METHYL 3-(N-PROPYLAMINO)PROPANOATE IN THE PRESENCE OF MOLECULAR SIEVES

Cyclopentanone (5.96 g; 0.07 mol) and methyl 3-(N-propylamino)propanoate (8.85 g; 0.06 mol) in dry toluene (100 ml) were heated under reflux over molecular sieves (3A) for 84 hours, the condenser being fitted with a drying guard. The reaction mixture was filtered through a sintered glass funnel (porosity 3) and the solvent was removed in *vacuo*.

A portion (2.50 g) of the crude reaction mixture (8.89 g) was subjected to flash chromatography using methylene chloride: hexane: ethyl acetate [12:18:1] as eluent and taking 35 (≈ 40 ml fractions). The eluent was then changed to methylene chloride: hexane: methanol [3:1:7], taking another 10 fractions. Fractions (40-41) were combined on the basis of t.l.c and g.l.c to give *4-propyl-4-azahexahydro-$\Delta^{3a,7a}$-inden-7-one* (47) (1.72 g; 15.5 %).



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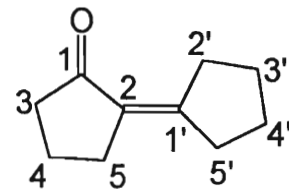

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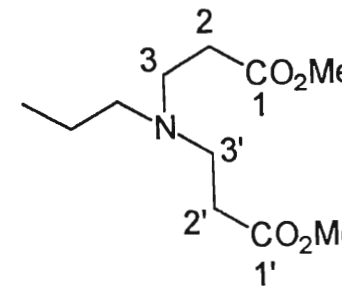

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The GC/MS of the crude reaction mixture showed the presence of M^+ 231 and M^+ 150 which correspond to (52) and (51) respectively, however these compounds where present in low yield (< 1 %) as evidenced by g.l.c and were not isolated.

The GC/MS also showed another peak corresponding to M^+ 179 and this was present in ≈ 4 % yield as evidenced by g.l.c data. This compound has not been isolated.

3.1.5 THE REACTION OF CYCLOHEXANONE WITH METHYL 3-(N-PROPYLAMINO)PROPANOATE IN THE ABSENCE OF MOLECULAR SIEVES

Cyclohexanone (3.50 g; 0.036 mol) and methyl 3-(N-propylamino)propanoate (5.08 g; 0.035 mol) in dry toluene (50 ml) were heated under reflux for 100 hours, the condenser being fitted with a drying tube. The solvent was removed in *vacuo*. A portion (2.5 g) of the crude product (10.97 g) was subjected to flash chromatography using methylene chloride: hexane: ethyl acetate [6:9:4] as eluent.

Fractions (1-2) (≈ 40 ml fractions) were collected under pressure and fractions (3-15) were collected under gravity. Fractions (6-7) were combined on the basis of t.l.c and g.l.c and found to contain
1-N-propyl-3,4,5,6,7,8-hexahydro-2-quinolone (45) and
1-N-propyl-3,4,4a,5,6,7-hexahydro-2-quinolone (45a)
(1.00 g; 15 %)

The GC/MS showed : one peak M^+ 193

g.l.c showed : one peak $t_R \approx 6.9$ min

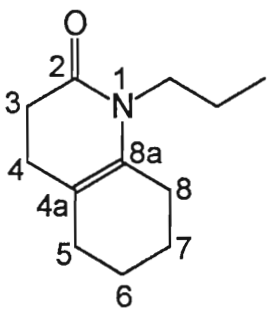
The i.r spectrum showed : υ (NaCl) cm^{-1}

1685 (C=C)

1670 (C=O)

1640 (C=C)

The u.v spectrum showed : λmax(MeOH) - 247 nm (ϵ = 7000)



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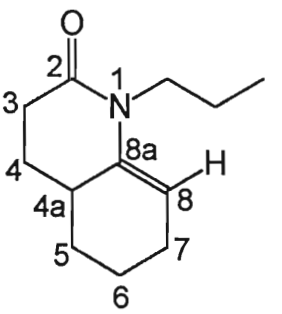


45a

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

0.82 (3H, t, CH_2-$\underline{CH_3}$)

1.36-1.68 (c.m.e, 6.22H, $\underline{CH_2}$-CH_3, C-5, C-8 (**45**), C-4a [**45a**])

1.98-2.15 (c.m.e, 6H, C-4, C-6, C-7)

2.38 (t, 2H, CH_2, C-3)

3.46 (t, 2H, N-CH_2)

5.00 (s, 0.22H, C-8 [**45a**])

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

[**45**]

11.10 (q, CH_3)

22.07 (t, $\underline{CH_2}$-CH_3)

22.38 (t)

22.87 (t)

25.25 (t)

25.37(t)

28.98 (t)

31.73 (t, C-3)

41.86 (t, N-CH_2)

115.35 (s, C=C, C-4a)

131.02 (s, C=C, C-8a)

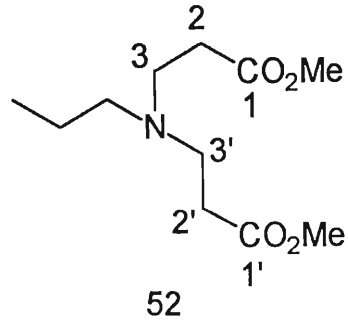
169.98 (s, C=O)

[45a]

11.25 (q, CH_3)	32.76 (t)
20.20 (t)	34.89 (d, C-4a)
21.37 (t)	44.03 (t)
24.45 (t)	103.65 (d, C-8)
27.43 (t)	138.38 (s, C-8a)
30.49 (t)	168.75 (s, C=O)

^{1}H n.m.r and ^{13}C n.m.r spectra indicated the product to be a mixture of isomers (45) and (45a) in the ratio of ≈ 7:2 respectively. This was confirmed by i.r spectrum which showed the presence of two (C=C) absorptions at 1640 cm^{-1} and 1685 cm^{-1}.

Fractions (11-14) were combined on the basis of t.l.c and g.l.c and were found to contain the tertiary amine, *N,N-di(ß-methoxycarbonylethyl)propylamine* (52) (0.21 g; 2.5 %)



52

The GC/MS of the crude reaction showed a product corresponding to M^{+} 178 and this was present in a 3 % yield as evidenced by g.l.c data. This compound has not been isolated.

3.1.6 THE REACTION OF BUTANONE WITH METHYL-3-(N-PROPYLAMINO)PROPANOATE IN THE PRESENCE OF MOLECULAR SIEVES

Butanone (5.1 g; 0.07 mol) and methyl 3-(N-propylamino)propanoate (8.73 g; 0.06 mol) in dry toluene (100 ml) were heated under reflux over molecular sieves (3A) for 60 hours, the condenser being fitted with a drying tube. The reaction mixture was filtered through a sintered glass funnel (porosity 3) and the solvent was removed in *vacuo*.

A portion (2.5 g) of the crude reaction mixture (8.02 g) was subjected to flash chromatography using hexane: methylene chloride: ethyl acetate [18:12:1] as eluent and taking 30 (≈ 40 ml) fractions. Fractions (9-12) were combined on the basis of g.l.c and t.l.c and found to contain *methyl 5-oxohexanoate* (54) (0.52 g; 5.5 %)

The GC/MS showed : one peak M^+ 126 [M - MeOH]

g.l.c showed : one peak $t_R \approx 2.8$ min

The i.r spectrum showed : υ (NaCl) cm^{-1}

1710 (C=O)

1735 (C=O)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

1.09 (d, 3H, $\underline{CH_3}CH$, C-4)

1.62-1.68 (m, 1H, J 7.26, 1'Ha or 1'Hb)

1.94-2.01 (m, 1H, J 7.32, 1'Ha or 1'Hb)

2.13 (s, 3H, $COCH_3$)

2.28 (t, 2H, $CH-CH_2-\underline{CH_2}$, C-2')

2.52-2.60 (m, 1H, $\underline{CH}CH_3$, C-3)

3.65 (s, 3H, OCH_3)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

16.21 (q, C-4)

27.46 (t, $CH-\underline{C}H_2$, C-1')

28.19 (q, C-1)

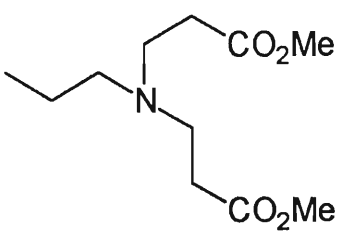
31.52 (t, $CH-CH_2-\underline{C}H_2$, C-2')

46.08 (d, CH, C-3)

51.60 (q, OCH_3)

173.62 (s, C=O, C-3')

211.71 (s, C=O, C-2)



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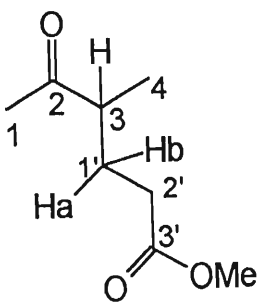
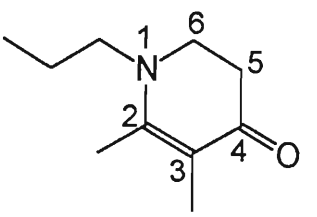


54

Fractions (15-18) were combined on the basis of t.l.c and g.l.c and found to contain the tertiary amine *N,N-di(ß-methoxycarbonylethyl)propylamine* (52) (0.48 g; 3.5 %).

The eluent was then changed to hexane: methylene chloride: methanol [18:12:0.75] and fractions (21-45) were collected. Fractions (34-40) were combined on the basis of t.l.c and

subjected to flash chromatography using hexane: methylene chloride: methanol [18:12:1.5] as eluent and taking 15 fractions. Fraction 9 was found to contain *1-N-propyl-2,3-dimethyl-5,6-dihydro-4-pyridone* (55) (0.15 g; 1.5 %).



55

The GC/MS showed : one peak M^+ 167

g.l.c showed : one peak $t_R \approx 6.4$ min

The i.r spectrum showed : υ (NaCl) cm^{-1}

1605 (C=O)

1540 (C=C)

The u.v spectrum showed : λ_{max} (MeOH) 337 nm (ϵ = 15000)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

0.90 (t, 3H, $\underline{CH_3}$)

1.50-1.62 (m, 2H, $\underline{CH_2}$-CH_3)

1.74 (s, 3H, CH_3, C-3)

2.00 (s, 3H, CH_3, C-2)

2.37 (t, 2H, CH_2, C-5)

3.22 (t, 2H, N-$\underline{CH_2}$-CH_2-CH_3)

3.38 (t, 2H, CH_2, C-6)

The ^{13}C n.m.r spectrum (75 MHz) showed : δ_C (ppm)

10.77 (q, C-3)

11.10 (q, $\underline{C}H_3-CH_2$)

16.53 (q, C-2)

22.26 (t, $\underline{C}H_2-CH_3$)

35.72 (t, C-5)

48.72 (t, C-6)

53.57 (t, $N-\underline{C}H_2-CH_2-CH_3$)

104.56 (s, C=C, C-3)

159.78 (s, C=C, C-2)

189.63 (s, C=O, C-4)

3.1.7 THE PREPARATION OF 1-N-PYRROLIDINYLCYCLOHEXENE

Cyclohexanone (31.36 g; 0.32 mol), pyrrolidine (34.08 g; 0.48 mol) and toluene-4-sulphonic acid (0.1 g) were heated under reflux in dry benzene (200 ml), until no more water was liberated. The water was removed azeotropically using a Dean and Stark head. The solvent and excess pyrrolidine were removed in *vacuo* and the residue was distilled under reduced pressure to give *1-N-pyrrolidinylcyclohexene* (58) (45.51 g; 94 %) b.p - 72°C / 0.9 mm Hg.

The GC/MS showed : one peak M^+ 151

The i.r spectrum showed : υ (NaCl) cm^{-1}

1640 (C=C)

The ^1H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

1.45-1.55 (m, 2H, $N-CH_2-CH_2$)

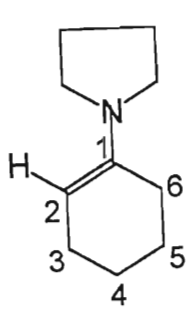
1.56-1.70 (m, 2H, $N-CH_2-CH_2$)

1.73-1.83 (c.m.e, 4H, C-4 and C-5)

1.98-2.18 (c.m.e, 4H, C-3 and C-6)

2.90-3.00 (m, 4H, CH_2-N-CH_2)

4.22 (bs, 1H, =CH)



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3.1.8 THE PREPARATION OF THE PYRROLIDINE DIENAMINE OF $\Delta^{1,8a}$-2-OCTALONE

1-N-pyrrolidinylcyclohexene (27.18 g; 0.18 mol), and methyl vinyl ketone (12.60 g; 0.18 mol), were refluxed in dry toluene (100 ml) for 24 hours, the condenser being fitted with a drying tube. The solvent was removed in *vacuo* and the residue was distilled under reduced pressure to give the pyrrolidine dienamine of $\Delta^{1,8a}$-2-octalone as a viscous oil (27.61 g; 75.5 %) b.p. 145°C / 1 mm Hg.

The GC/MS showed : one peak M^+ 203

The i.r spectrum showed : υ (NaCl) cm^{-1}

1600 (C=C)

1630 (C=C)

The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

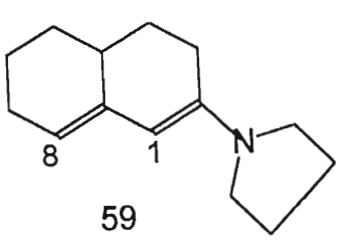
1.10-2.41 (complex methylene / methine envelope)

3.08-3.13 (c.m.e, 4H, CH_2-N-CH_2)

4.30 (s, 0.3H, H-1 endo)

4.85 (s, 0.7H, H-1 exo)

5.10 (s, 0.7H, H-8 exo)



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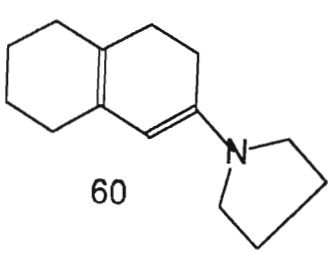


60

^{1}H-n.m.r measurements indicated the dienamine to be a mixture

of the exo and endocyclic isomers (59) and (60) in the ratio of ≈ 7:3 respectively.

3.1.9 THE PREPARATION OF ^{1,8a}-2-OCTALONE

$\Delta^{1,8a}$-2-octalone was prepared by the hydrolysis of the pyrrolidine dienamine of $\Delta^{1,8a}$-2-octalone. The dienamine (12.00 g; 0.06 mol) was heated under reflux with a buffer solution[53] of sodium acetate (5 g) and acetic acid (10 ml) in water (10 ml) for 4 hours. The reaction mixture was extracted with ether (3 X 25 ml) and the combined extracts were washed successively with 2M hydrochloric acid (3 X 25 ml), saturated sodium bicarbonate solution (25 ml), and saturated sodium chloride solution (3 X 25 ml). The ether layer was then dried over anhydrous magnesium sulphate and filtered. The solvent was then removed in *vacuo* and the residue was distilled under reduced pressure to give *$\Delta^{1,8a}$-2-octalone* (5,40 g; 60%) b.p. 84°C / 0.7 mm Hg.

The GC/MS showed : one peak M^+ 150

The i.r spectrum showed : υ (NaCl) cm^{-1}

1620 (C=C)

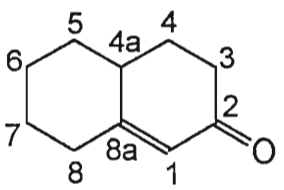
1675 (C=O)

1715 (C=O)

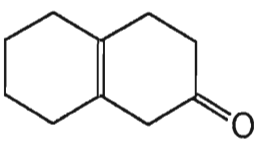
The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

1.10-2.50 (complex methylene/methine envelope)

5.81 (s, 0.8 H, =CH)



61



62

^{1}H n.m.r measurements indicated the product to be a mixture of αß- and ßγ-unsaturated isomers (61) and (62) in the ratio 4:1 respectively. This was confirmed by the i.r spectrum which showed a non-conjugated carbonyl absorption at 1715 cm^{-1}.

3.1.10 THE REACTION OF $\Delta^{1,8a}$-2-OCTALONE WITH METHYL 3-(N-PROPYLAMINO)PROPANOATE

$\Delta^{1,8a}$-2-octalone (3.22 g; 0.021 mol) and methyl 3-(N-propylamino)propanoate (3.38 g; 0.023 mol) in dry toluene (100 ml) were heated under reflux over molecular sieves (3A) for 48 hours, the condenser being fitted with a drying tube. The crude reaction mixture was filtered through a sintered glass funnel (porosity 3) and the solvent was removed in *vacuo*.

The GC/MS showed : two peaks corresponding to M^+ 245

g.l.c showed : the M^+ 245 peaks at t_R of 10.6 min and 10.9 min

3.2 REACTIONS OF IMINES WITH PHENYL VINYL KETONE

3.2.1 THE PREPARATION OF ß-DIMETHYLAMINOPROPIOPHENONE HYDROCHLORIDE

A solution of acetophenone (60.01 g; 0.50 mol), dimethylamine hydrochloride (40.03 g; 0.49 mol) and paraformaldehyde (15.00 g; 0.17 mol) was transferred to a round bottom flask. Concentrated HCl (0.5 ml) in 95 % ethanol (80 ml) was added to the flask and the mixture was heated under reflux for two hours. Acetone (150 ml) was then added to the warm reaction mixture. The mixture was allowed to cool and the crystals were collected and dried at 40-50°C.

3.2.2 THE PREPARATION OF PHENYL VINYL KETONE (PVK)

ß-Dimethylaminopropiophenone hydrochloride (20.00 g; 0.13 mol) was steam distilled for 4 hours to give PVK, which was extracted from the distillate with dichloromethane (3 X 50 ml). The solution was dried over anhydrous magnesium sulphate and the solvent was removed in *vacuo* to give *PVK* (63) (9.20 g; 62%). Quinol was used as a polymerization inhibitor during the distillation and extraction processes.

The i.r spectrum showed : υ(NaCl) cm^{-1}

1610 (C=C)

1670 (Ph-C=O)

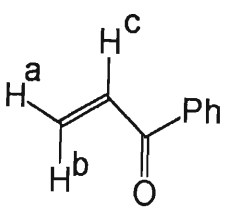
The ^{1}H n.m.r spectrum (300 MHz) showed : δ_H (ppm)

5.88 (dd, 1H, b, J = 12.3 Hz, J = 1.80 Hz)

6.40 (dd, 1H, a, J = 18.9 Hz, J = 1.80 Hz)

7.12 (q, 1H, c)

7.40-7.95 (complex, 5H, Ph)



63

3.2.3 THE PREPARATION OF N-2-(4-PHENYLBUTYLIDENE)PROPYLAMINE

4-Phenyl-butan-2-one (36.19 g; 0.24 mol), propylamine (16.09 g; 0.27 mol) and toluene-4-sulphonic acid (0.10 g) were heated under reflux in benzene (200 ml) for 16 hours, the water being removed azeotropically using a Dean and Stark separator. The solvent was removed in *vacuo* and the residue was vacuum distilled to give *N-2-(4-phenylbutylidene)propylamine* (64c) (28.20 g; 62 %) b.p - 114-118°C / 0.5 mm Hg.

The GC/MS showed : one peak M^+ 189

The i.r spectrum showed : υ(NaCl) cm^{-1}

1663 (C=N)

The ^1H n.m.r spectrum (200 MHz) showed : δ_H (ppm)

0.91 (t, 3H, $\underline{CH_3}$-CH_2)

1.49-1.65 (m, 2H, $\underline{CH_2}$-CH_3)

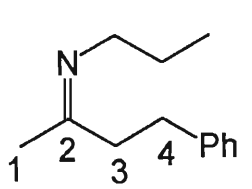
1.68 (s, 3H, CH_3, C-1)

2.38-2.52 (m, 2H, CH_2, C-3)

2.78-2.87 (m, 2H, CH_2, C-4)

3.15 (t, 2H, N-$\underline{CH_2}$)

7.05-7.24 (complex methine envelope, 5H, Ph)



64c

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_C (ppm)

12.07 (q, CH_2-CH_3)

17.39 (q, CH_3-C=N)

24.08 (t)

32.74 (t)

44.04 (t)

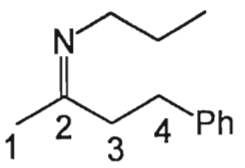
53.15 (t)

125.75 (d, Ph)

128.25 (d, Ph)

128.35 (d, Ph)

141.82 (s, C=N, C-2)



64c

3.2.4 THE REACTION OF PHENYL VINYL KETONE WITH N-2-(4-PHENYLBUTYLIDENE)PROPYLAMINE USING METHANOL IN THE PRESENCE OF MOLECULAR SIEVES

N-2-(4-phenylbutylidene)propylamine (1.79 g; 0.0095 mol) was added to PVK (2.51 g; 0,019 mol) in super dry methanol (45 ml) and the resulting mixture was heated under reflux for 4 hours in the presence of activated molecular sieves (4A). Water (10 ml) was then added, and the reaction mixture was refluxed for a further hour. The reaction mixture was then filtered through a sintered glass funnel (porosity 3) and the solvent was removed in *vacuo* and the residue extracted with dichloromethane (3 X 20 ml). The organic layer was then washed with 2M HCl (3 X 20 ml), saturated sodium hydrogen carbonate solution (3 x 20 ml), water (20 ml) and saturated sodium chloride solution (20 ml) and then dried over anhydrous magnesium sulphate. Filtration and evaporation of the dichloromethane gave a dark brown oil.

A portion (2,50 g) of the crude product (2.66 g) was purified by flash chromatography with ethyl acetate: hexane: methylene dichloride [1:48:24] as the eluent and taking 25 (≈ 50 ml) fractions.

Fractions (9-11) were combined on the basis of t.l.c and recrystallized from acetonitrile to give rel-*(1R, 2R, 4S)-2-benzoyl-4-benzyl-1-phenylbicyclo[2.2.2] octan-5-one* (66c) (1.00 g; 28.5 %)

Melting point : 214-215°C (from isopropyl alcohol- ethyl acetate)

The GC/MS showed : one peak M^+ 394

g.l.c showed : one peak $t_R \approx 22.0$ min

The i.r spectrum showed : $\upsilon(CH_2Cl_2)$ cm^{-1}

1716 (C=O)

1675 (Ph-C=O)

The ^1H n.m.r spectrum (200 MHz) showed : δ_H (ppm)

1.60-2.20 (complex, 5H, 3-Ha,b, 7-Hb, 8-Ha,b)

2.44 (d, 1H, J 18.7, 6-Ha)

2.82-3.10 (complex, 4H, 6-Hb, 7-Ha, Ph-CH_2)

4.03 (qd, 1H, 2-Hb)

6.90-7.55 (complex, 15H, 3Ph)

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_C (ppm)

24.80 (t, C-7) 28.32 (t, C-8)

33.46 (t, C-3) 39.19 (t, Ph-CH_2)

42.70 (s, C-1) 47.04 (s, C-4)

48.30 (d, C-2) 51.74 (t, C-6)

125.89, 126.23, 126.61, 127.82, 128.02, 128.08, 128,27,

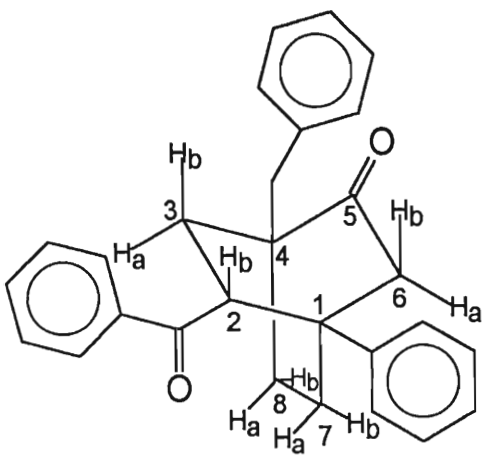
130.77, 132.50 (all d, 3 Ph)

137.64, 137.79, 143.02 (all s, 3 Ph)

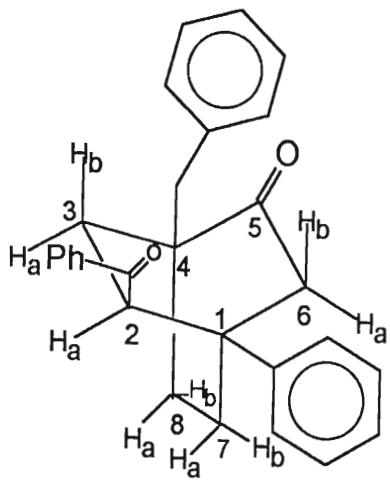
202.71 (s, Ph-C=O) 214.85 (s, C=O, C-5)

C/H/N analyses : Found C: 85.29 % H: 6.82 %

Calculated for $C_{28}H_{26}O_2$ C: 85.25 % H: 6.64 %



66c



67c

Fractions (18-23) were combined and washed with 5 % ethyl acetate in hexane and recrystallised from ethyl acetate to give *rel-(1R,2S,4S)-2-benzoyl-4-benzyl-1-phenylbicyclo[2.2.2]octan-5-one* (67c) (0.15 g; 4 %)

Melting point : 145-146°C

The GC/MS showed : one peak M^+ 394

g.l.c showed : one peak $t_R \approx 21.0$ min

The i.r spectrum showed : $\upsilon(CH_2Cl_2)$ cm^{-1}

1720 (C=O)

1675 (Ph-C=O)

The ^1H n.m.r spectrum (200 MHz) showed : δ_H (ppm)

1.60-2.15 (complex, 5H, 3-Ha,b, 7-Hb, 8-Ha,b)

2.25-2.45 (complex, 1H, 7-Ha)

2.52 (dd, 1H, J 1.6 Hz, 18.6 Hz, 6-Ha)

2.86 (s, 2H, Ph-CH_2)

3.70 (dd, 1H, J 3.4 Hz, 18.6 Hz, 6-Hb)

4.12 (qd, 1H, 2-Ha)

6.92-7.55 (complex, 15H, 3Ph)

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_C (ppm)

28.17 (t, C-8) 32.82 (t, C-3)

34.30 (t, C-7) 38.86 (t, Ph-CH_2)

42.87 (s, C-1) 44.12 (t, C-6)

46.78 (s, C-4) 49.96 (d, C-2)

125.73, 126.24, 126.51, 127.79, 127.85, 127.92, 128,06, 128.14,

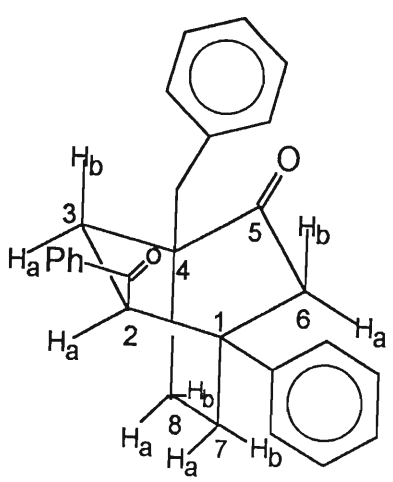
128.25, 130.80, 132.58 (all d, 3 Ph)

137.65, 137.68, 143.01 (all s, 3 Ph)

203.04 (s, Ph-C=O) 214.09 (s, C=O, C-5)

C/H/N analyses : Found C: 85.38 % H: 6.96 %

Calculated for $C_{28}H_{26}O_2$ C: 85.25 % H: 6.64 %



67c

3.2.5 THE REACTION OF PHENYL VINYL KETONE WITH N-2-(4-PHENYLBUTYLIDENE)PROPYLAMINE USING METHANOL IN THE PRESENCE OF MOLECULAR SIEVES

N-2-(4-phenyl-butylidene)propylamine (1.79 g, 0.0095 mol) was added to boiling PVK (2.51 g; 0.019 mol) in super dry methanol (45 ml) containing activated molecular sieve (4A). The mixture was refluxed for 4 hours and hydrolytic work up was as before. The crude product (2.94 g) was subjected to flash chromatography as before and taking 25 (≈ 50 ml) fractions. Fractions (9-11) were combined to give *rel-(1R,2R,4S)-2-benzoyl-4-benzyl-1- phenylbicyclo[2.2.2]octan-5-one* (66c) (0.51 g; 14 %) and fractions (16-19) were combined to give *rel-(1R,2S,4S)-2-benzoyl-4-benzyl-phenylbicyclo[2.2.2]octan-5-one* (67c) (0.10g ; 3.0 %).

3.2.6 THE REACTION OF PHENYL VINYL KETONE WITH N-2-(4-PHENYLBUTYLIDENE)PROPYLAMINE USING ETHANOL IN THE PRESENCE OF MOLECULAR SIEVES

N-2-(4-phenyl-butylidene)propylamine (1.79 g; 0.0095 mol) was added to PVK (2.51 g; 0.019 mol) in super dry ethanol (50 ml) containing activated molecular sieve (4A). The mixture was refluxed for 4 hours and hydrolytic work up was as before. The crude product (2.95 g) was subjected to flash chromatography as before and taking 25 (≈ 50 ml) fractions. Fractions (8-10) were combined to give *rel-(1R,2R,4S)-2-benzoyl-4-benzyl-1-phenyl bicyclo[2.2.2]octan-5-one* (66c) (1.52 g; 41 %) and fractions (16-19) were combined to give *rel-(1R,2S,4S)-2-benzoyl-4-benzyl-phenylbicyclo[2.2.2]octan-5-one* (67c) (0.23 g; 6.0 %).

3.2.7 THE ATTEMPTED PREPARATION OF THE PROPYLAMINE IMINE OF ETHYL LEVULINATE

Ethyl levulinate (36.63 g; 0.25 mol), propylamine (16.63 g; 0.28 mol) and toluene-4-sulphonic acid (0.10 g) were heated under reflux in benzene (200 ml) for 88 hours, the water being removed azeotropically using a Dean and Stark separator. The solvent was removed in *vacuo* and the residue distilled under reduced pressure to give three fractions, none of which gave the imine as evidenced by the absence of the molecular ion in the GC/MS, and the absence of the C=N absorption in the i.r, run on each fraction.

3.2.8 THE PREPARATION OF THE PROPYLAMINE IMINE OF ETHYL LEVULINATE

Following the method of Carlson and Nilsson[55] for the preparation of enamines, a three necked round bottom flask was fitted with a reflux condenser containing a nitrogen inlet, a pressure equalising dropping funnel and the middle inlet was stoppered (use of thermometer). The whole apparatus was flushed with dry nitrogen. Propylamine (28.38 g; 0.48 mol) in dry hexane (150 ml) was introduced into the flask and cooled in ice/water to 0°C. Titanium tetrachloride (8 ml; 0.072 mol) was added drop wise to the propylamine with stirring (magnetic stirrer) and under a positive pressure of dry nitrogen. After the addition had been completed the ethyl levulinate (11.56 g; 0.08 mol) was added in one portion to the flask. After the solution had risen to room temperature, it was raised to the

boil and heated under reflux for 2 hours. The mixture was then filtered through oven dried diatomaceous earth contained in sintered glass funnel (porosity 3). The solvent was removed in *vacuo* leaving *ethyl N-propyl-4-iminopentanoate* (72) (4.66 g; 31.5 %).

The GC/MS showed : one peak M^+ 185

The i.r spectrum showed : υ(NaCl) cm^{-1}

1665 (C=N)

1735 (C=O)

The ^1H n.m.r spectrum (200 MHz) showed : δ_H (ppm)

0.93 (t, 3H, CH_2-CH_2-$\underline{CH_3}$)

1.30 (t, 3H, O-CH_2-$\underline{CH_3}$)

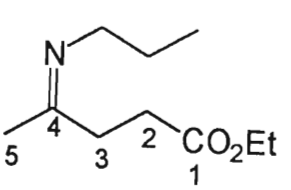
1.48-1.72 (m, 2H, CH_2-$\underline{CH_2}$-CH_3)

1.84 (s, 3H, C-5)

2.57 (s, 4H, C-2 and C-3)

3.20 (t, 2H, N-CH_2)

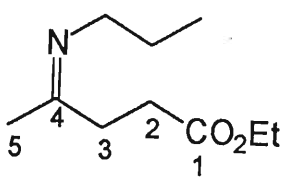
4.08-4.19 (q, 2H, OCH_2)



72

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_C (ppm)

11.99 (q, 3H, CH_2-CH_2-$\underline{CH_3}$)	14.24 (q, OCH_2-$\underline{CH_3}$)
17.88 (q, 3H, C-5)	24.00 (t)
30.52 (t)	36.31 (t)
52.93 (t)	60.20 (t, OCH_2)
166.61 (s, C-4)	173.63 (s, C=O)



72

3.2.9 THE REACTION OF PHENYL VINYL KETONE WITH THE PROPYLAMINE IMINE OF ETHYL LEVULINATE

Ethyl N-propyl-4-iminopentanoate (1.76 g; 0,0095 mol) was added to PVK (2.55 g; 0.019 mol) in super dry ethanol (45 ml) and the resulting mixture was heated under reflux for 4 hours in the presence of activated molecular sieves (4A). Water (10 ml) was then added, and the reaction mixture was refluxed for a further one hour. The reaction mixture was filtered through a sintered glass funnel (porosity 3) and the solvent was removed in *vacuo*. The residue was extracted with dichloromethane (3 X 20 ml). The organic layer was then washed with 2M HCl, saturated sodium hydrogen carbonate solution (3 X 20 ml), water (20 ml) and saturated sodium chloride solution (20 ml) and then dried over anhydrous magnesium sulphate.

A portion (2,50 g) of the crude mixture (2,67 g) was subjected to flash chromatography using hexane: dichloromethane: ethyl acetate [12:3:2] as eluent and taking 35 (≈ 50 ml) fractions.

Based on t.l.c and g.l.c data, fraction 6 was subjected to flash chromatography using hexane: dichloromethane: ethyl acetate [20:3:2] and taking 10 fractions. Fraction 4 was found to contain *6-ethoxycarbonylmethyl-3-phenylcyclohex-2-enone* (73) (0.31 g; 13 %)

The GC/MS showed : one peak M^+ 258

g.l.c showed : one peak $t_R \approx 12.3$ min

The i.r spectrum showed : υ(NaCl) cm^{-1}

1730 (CO_2Et)

1660 (C=O)

1605 (C=C)

The ^1H n.m.r spectrum (200 MHz) showed : δ_H (ppm)

1.29 (t, 3H, $\underline{CH_3}$-CH_2-O)

1.85-2.05 (c.m.e, 1H, 5Ha or 5Hb)

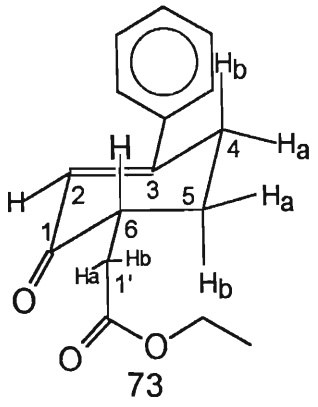
2.25-2.40 (c.m.e, 2H, 1'Ha or 1'Hb, 5Ha or 5Hb)

2.82-3.05 (c.m.e, 4H, H-6, 4 Ha,Hb, 1' Ha or 1'Hb)

4.13-4.24 (q, 2H, CH_2-O)

6.42 (s, 1H, =CH)

7.3-7.6 (complex methine envelope, 5H, Ph)



73

The ^{13}C n.m.r spectrum (50 MHz) showed : δ_C (ppm)

14.23 (q, CH_2-$\underline{C}H_3$)

28.12 (t, C-4)

28.70 (t, C-5)

34.64 (t, C-1')

42.93 (d, C-6)

60.56 (t, $\underline{C}H_2O$)

124.65 (d, C-2)

126.06, 128.76, 130.04 (all d,Ph)

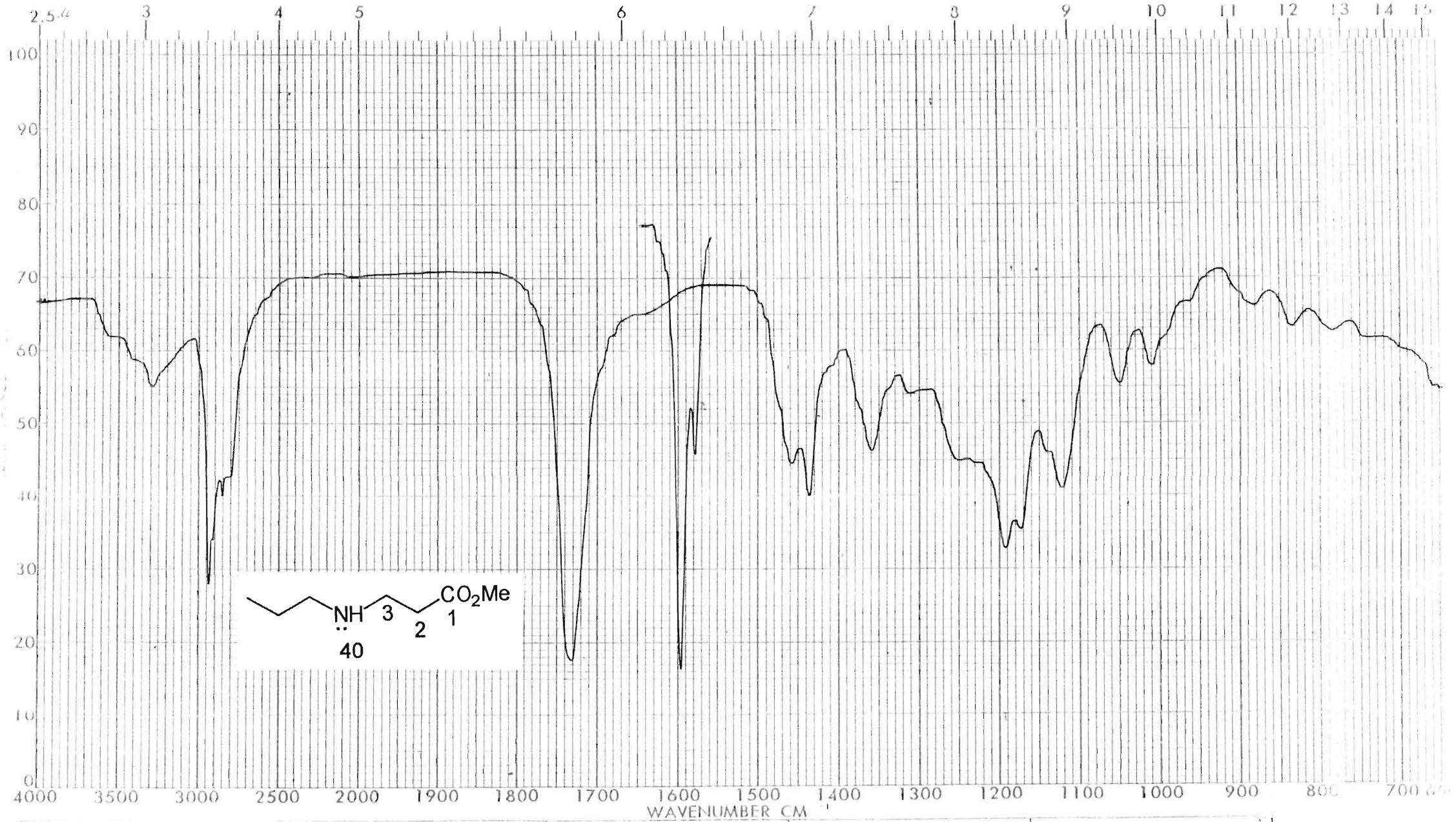
138.44 (s, Ph)

159.12 (s, C-3)

172.59 (s, C=O)

199.50 (s, C=O, C-1)

SPECTRA



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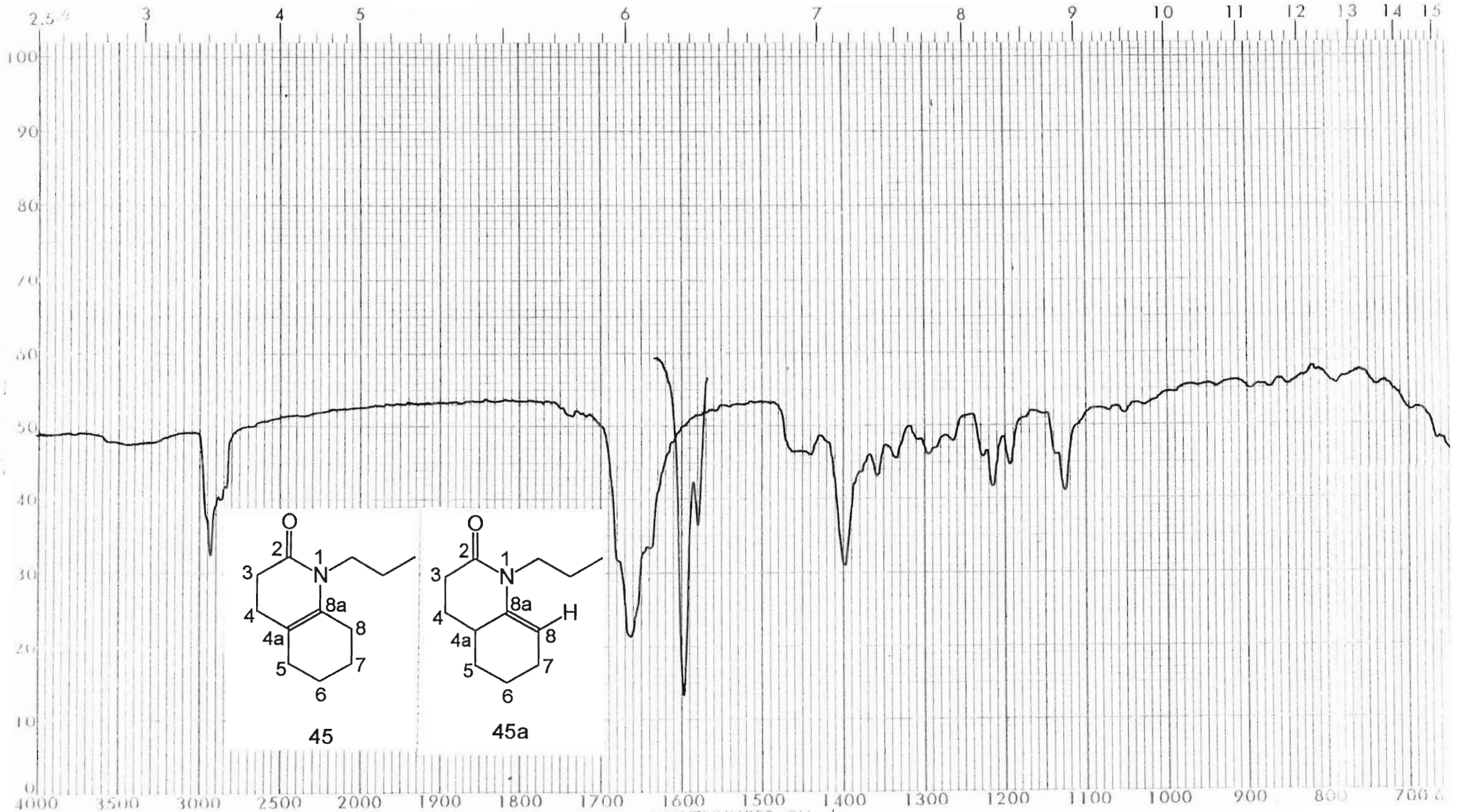
SAMPLE	SOLVENT	REFERENCE		
	CONCENTRATION	SCAN TIME		OPERATOR

PRINTED IN JA



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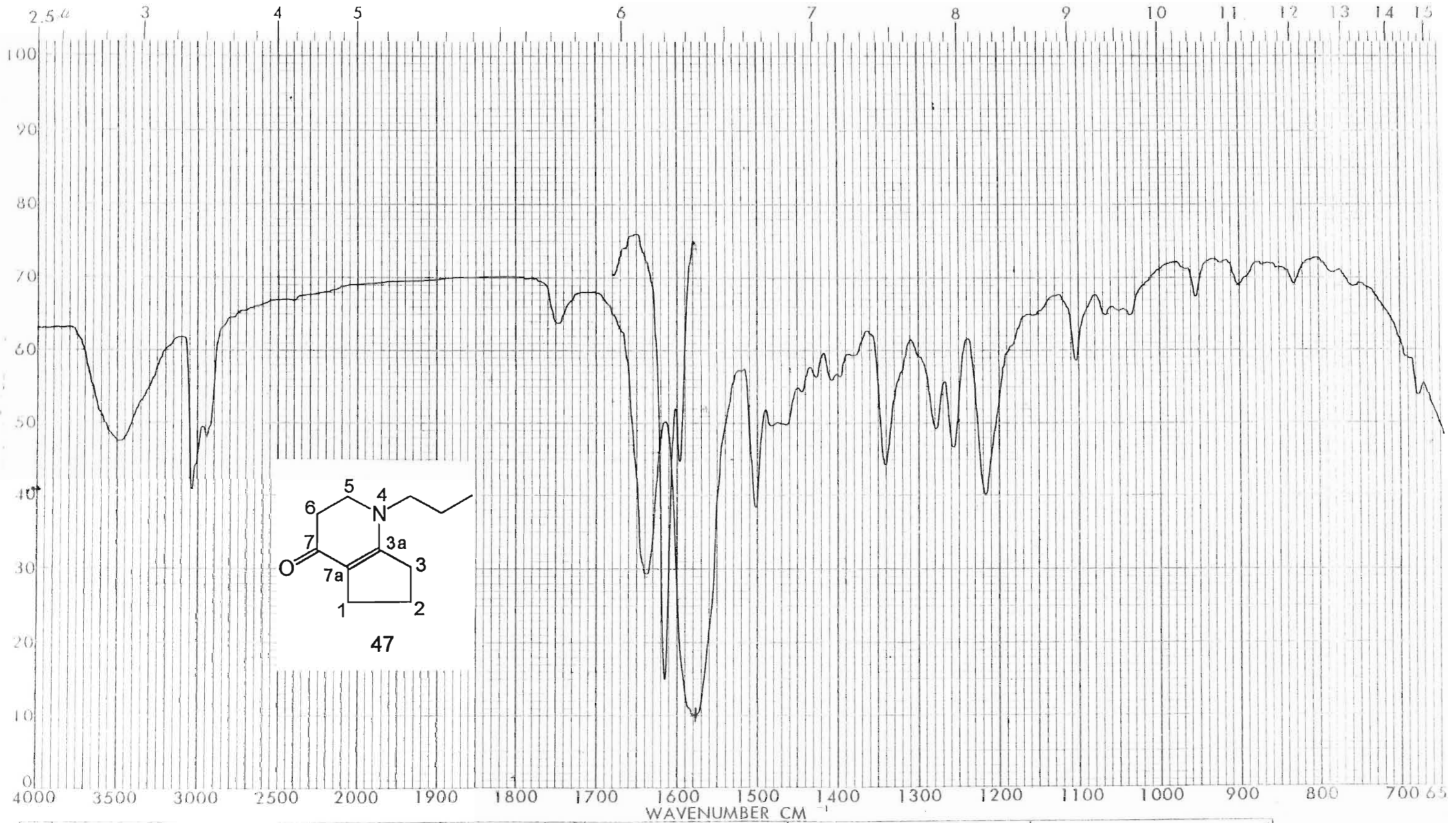


47

SPECTRUM NO.
SAMPLE

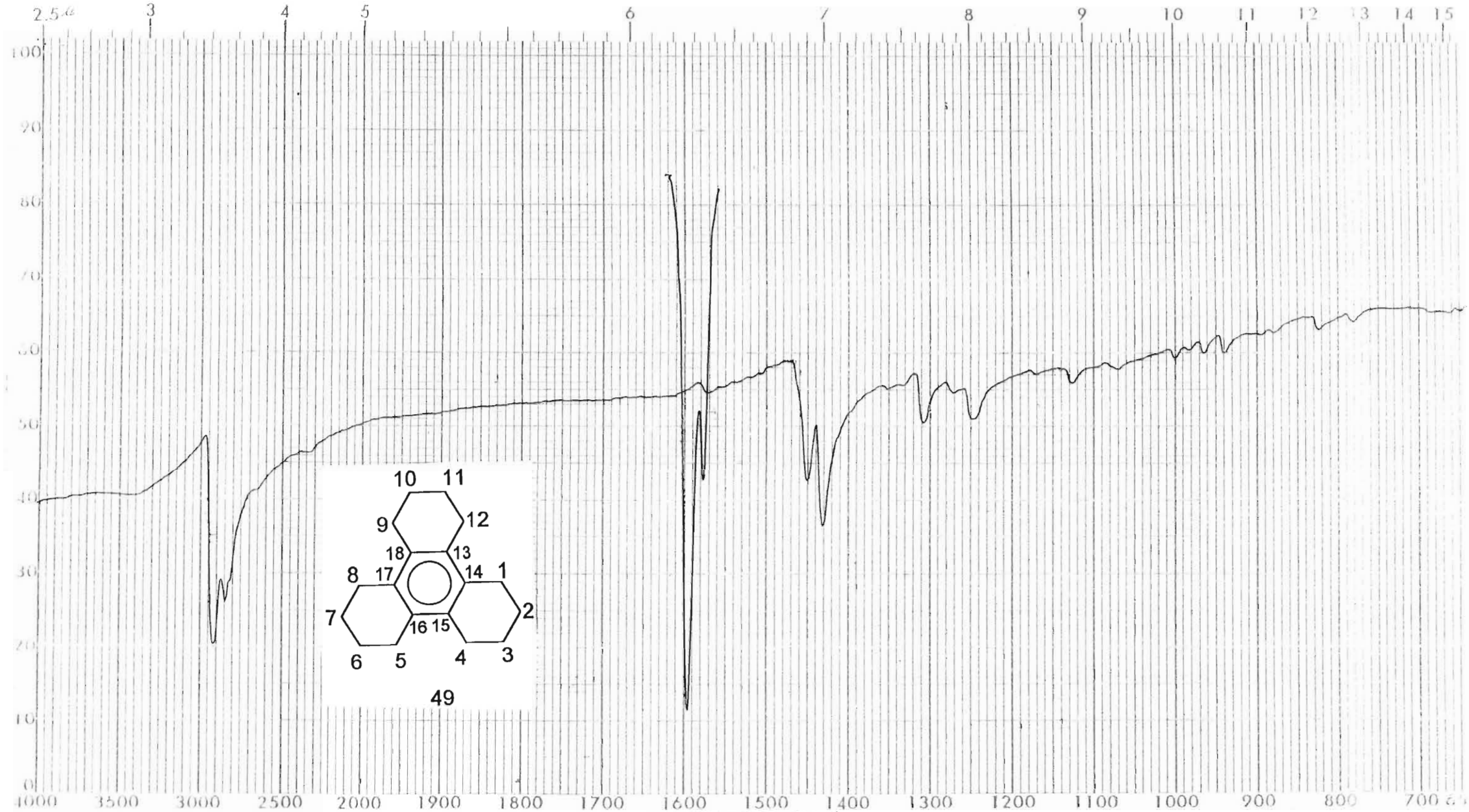
PHASE
SOLVENT
CONCENTRATION

THICKNESS
REFERENCE
SCAN TIME

REMARKS

DATE
OPERATOR

PRINTED IN JAPAN



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SAMPLE	SOLVENT	REFERENCE		
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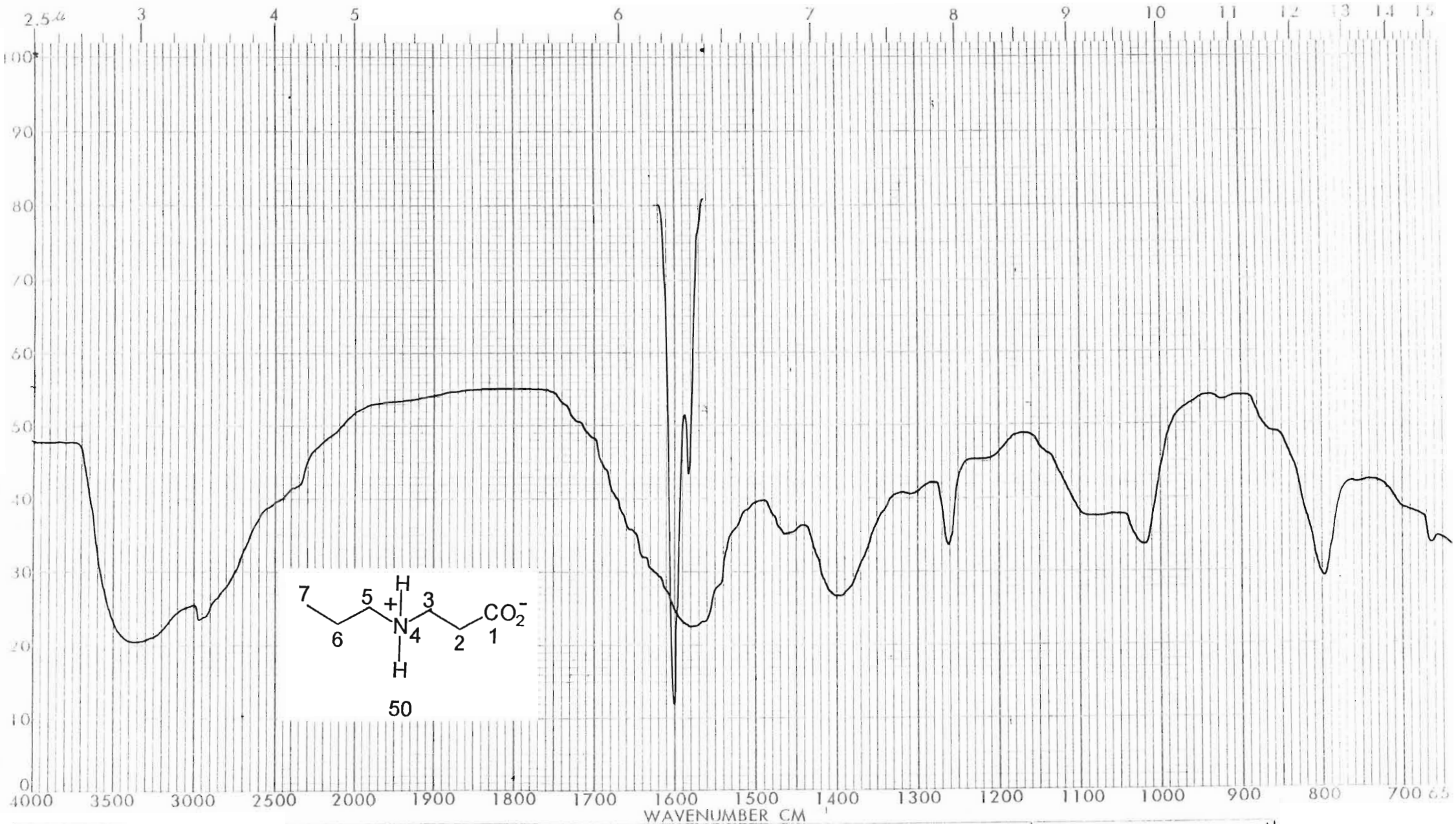

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SAMPLE	SOLVENT	REFERENCE		
	CONCENTRATION	SCAN TIME		OPERATOR

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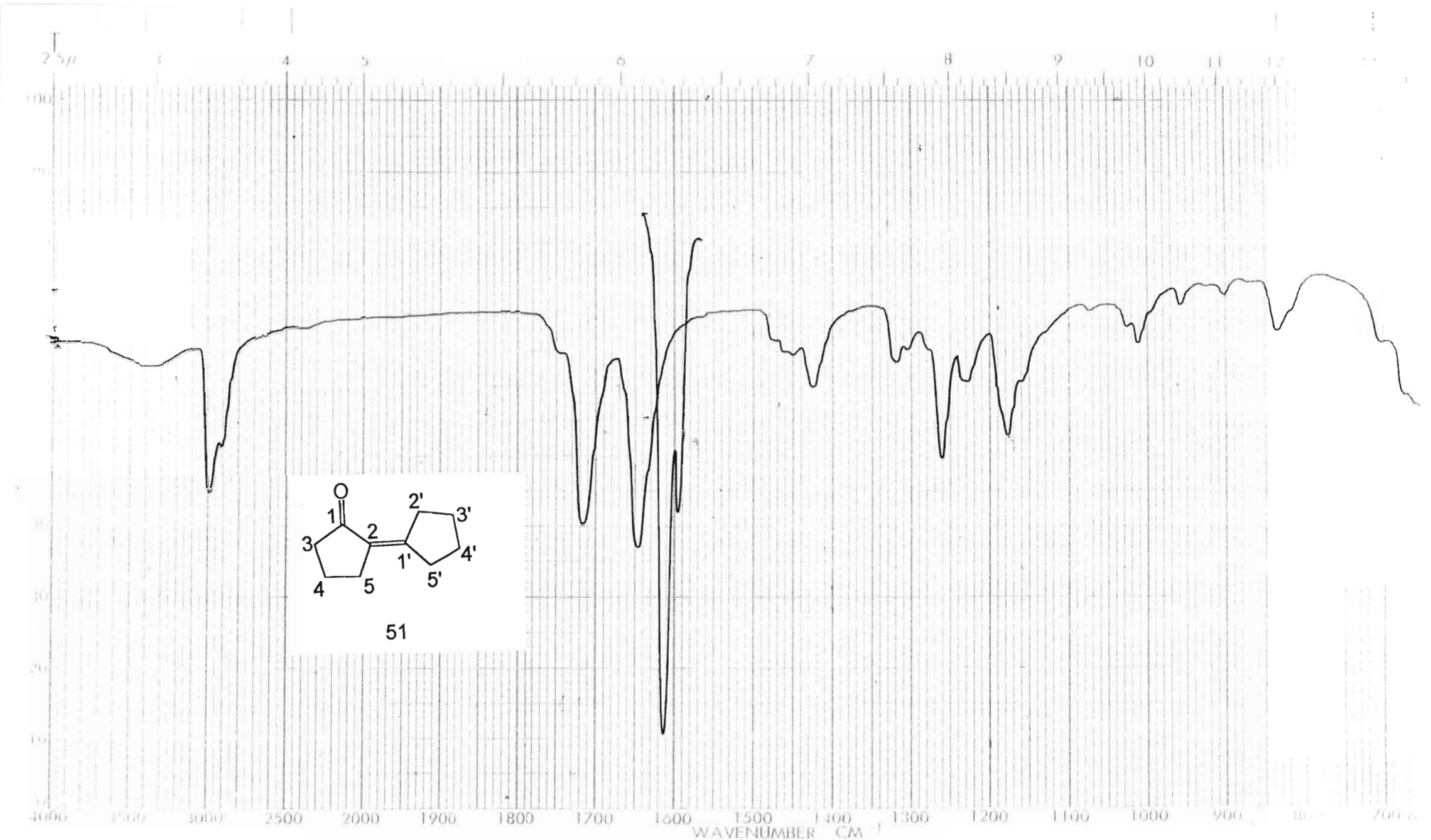
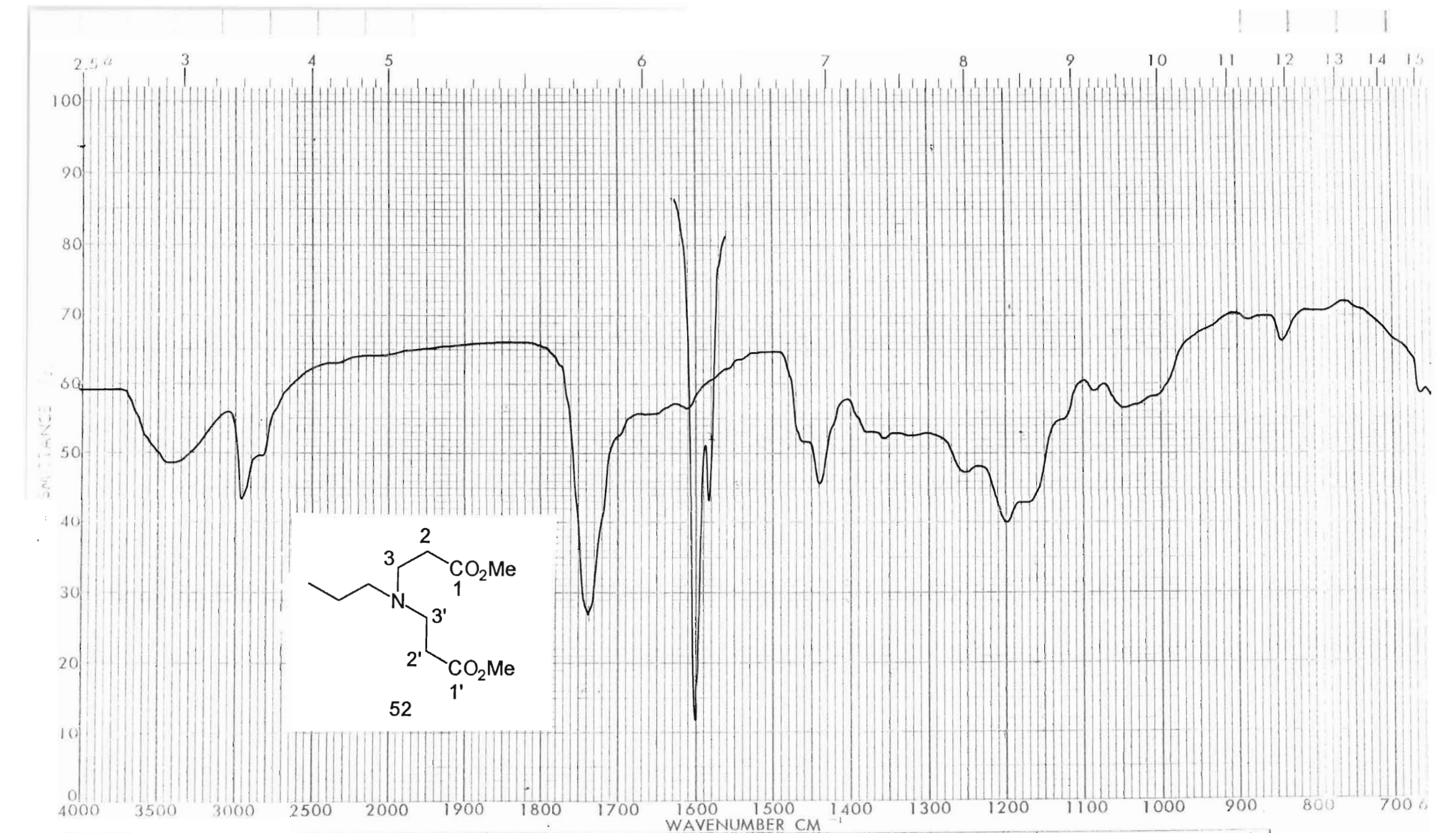


51

PHASE
SOLVENT
CONCENTRATION
THICKNESS
REFERENCE
SCAN TIME
REMARKS
DATE
OPERATOR



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SAMPLE	SOLVENT	REFERENCE		OPERATOR
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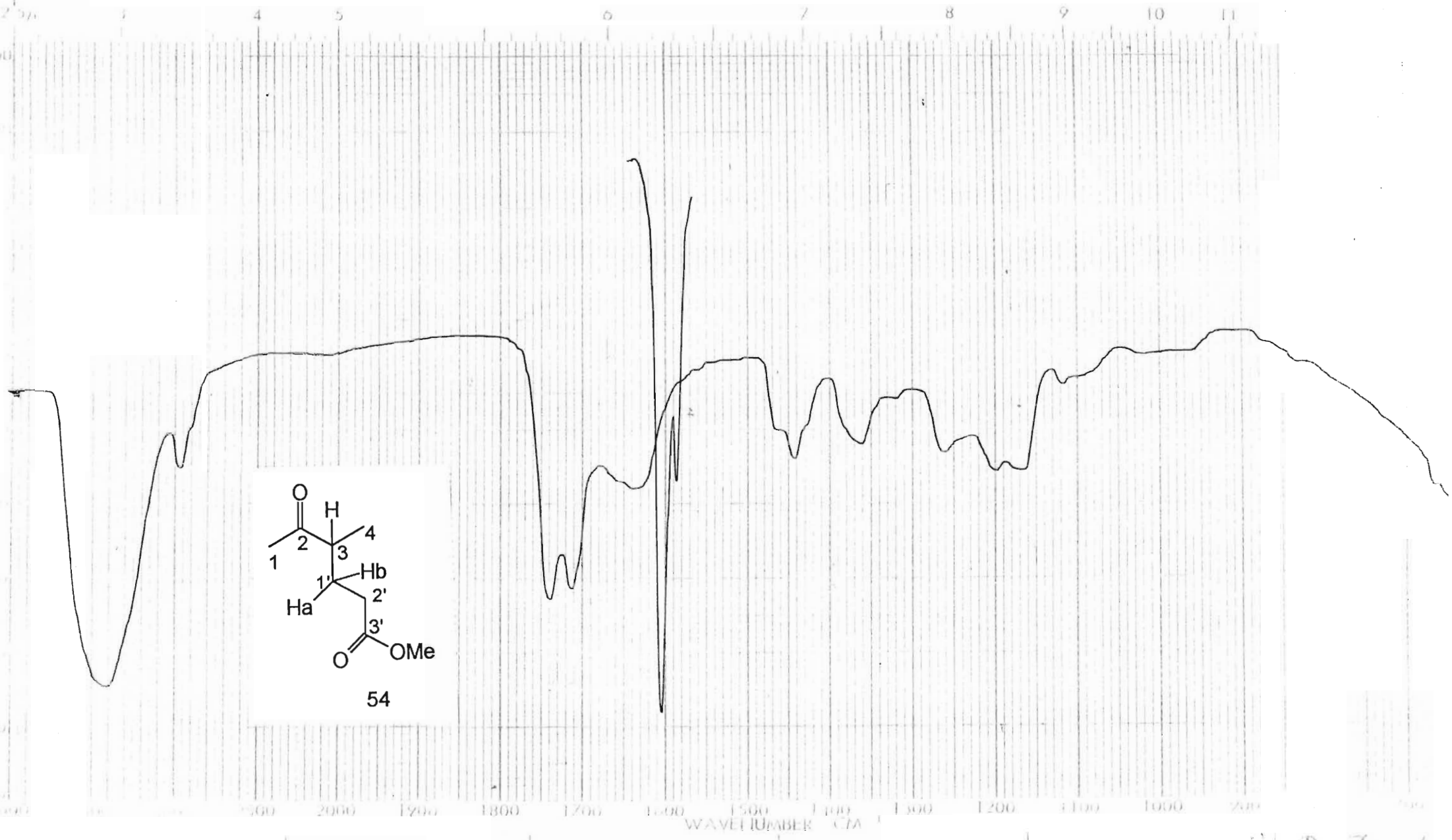

54

PHASE
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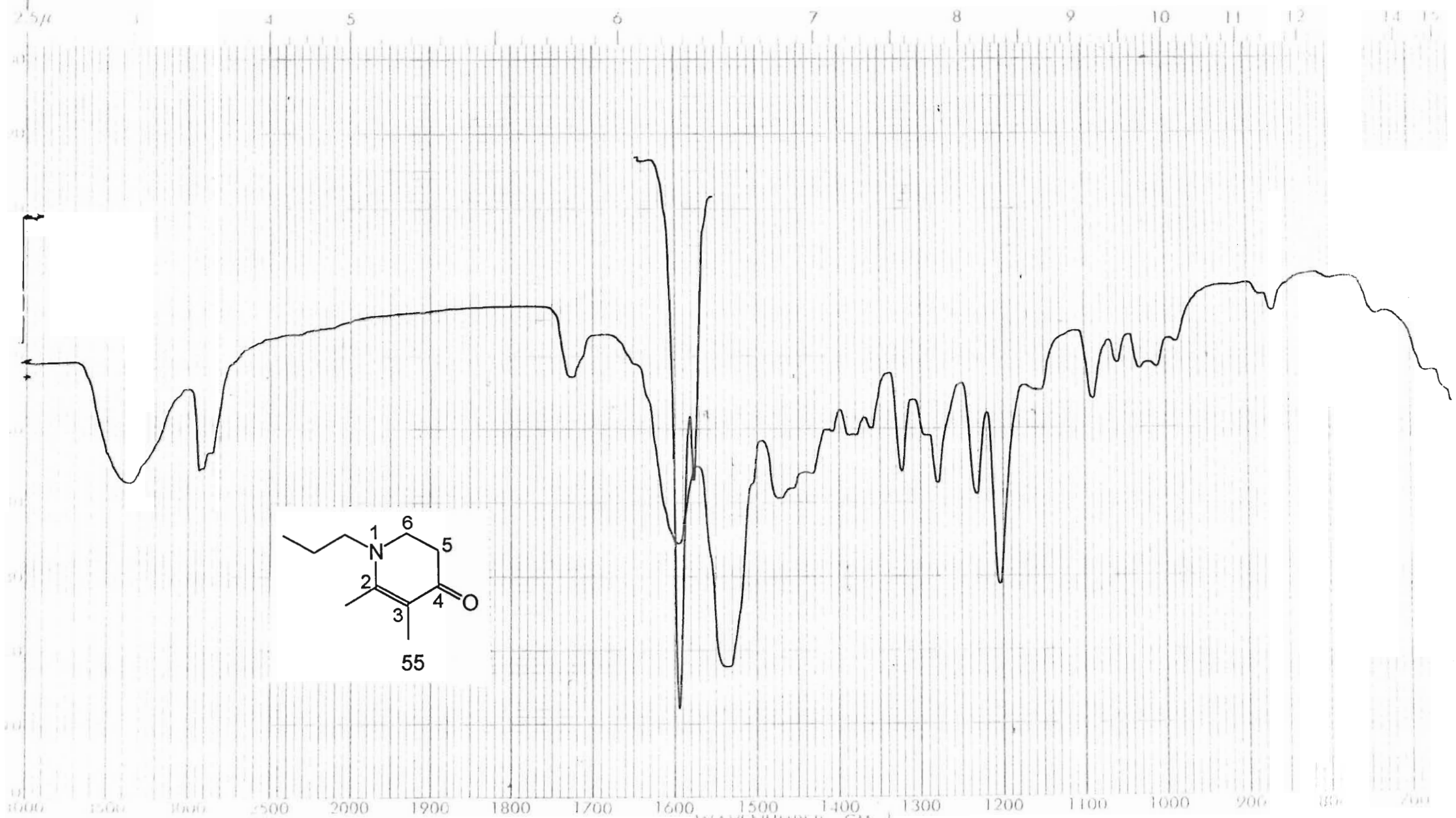
DATE
OPERATOR



PHASE
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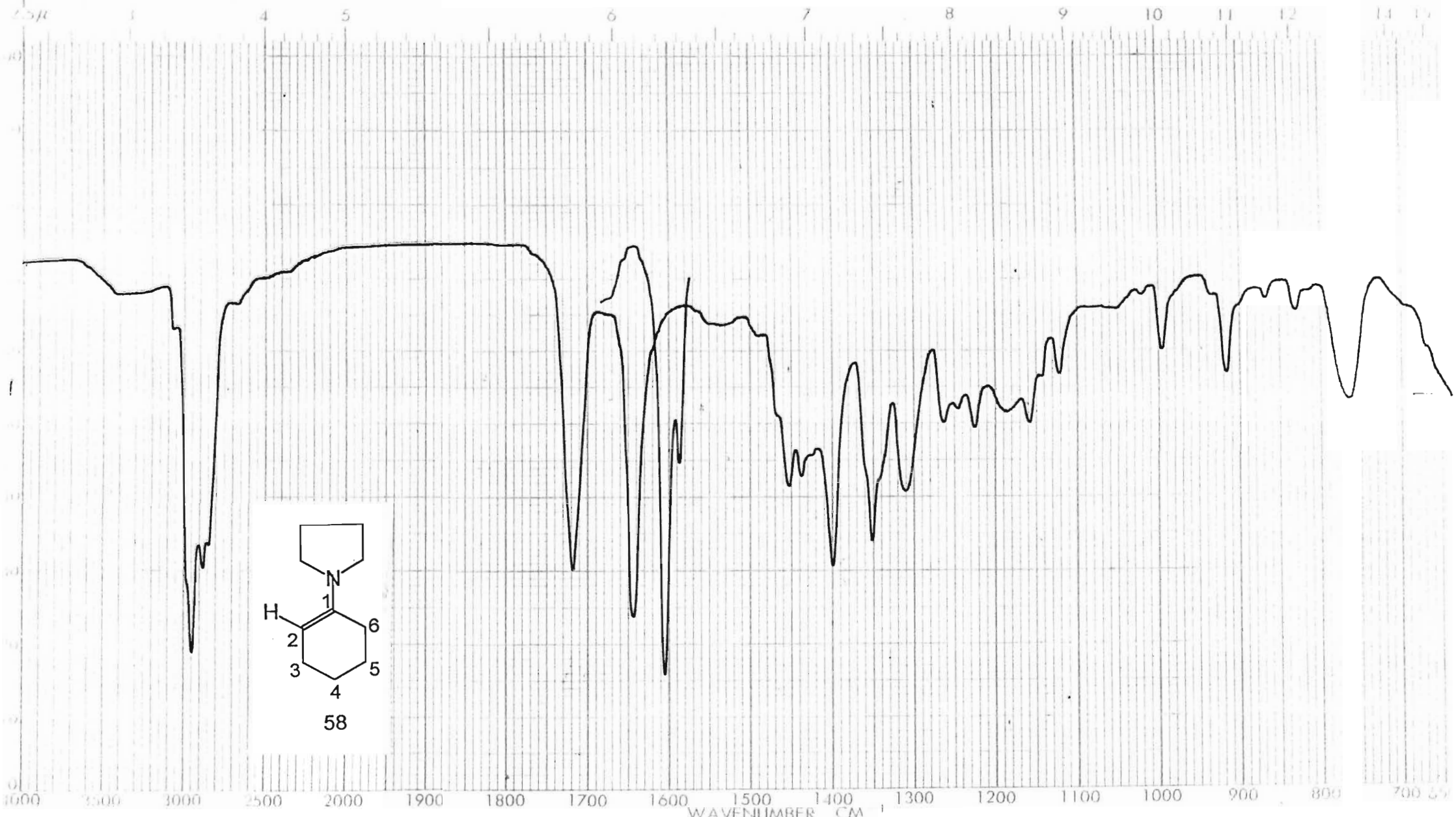
CONCENTRATION
THICKNESS
REFERENCE
SCAN TIME
REMARKS
DATE
OPERATOR



58

SPECTRUM NO

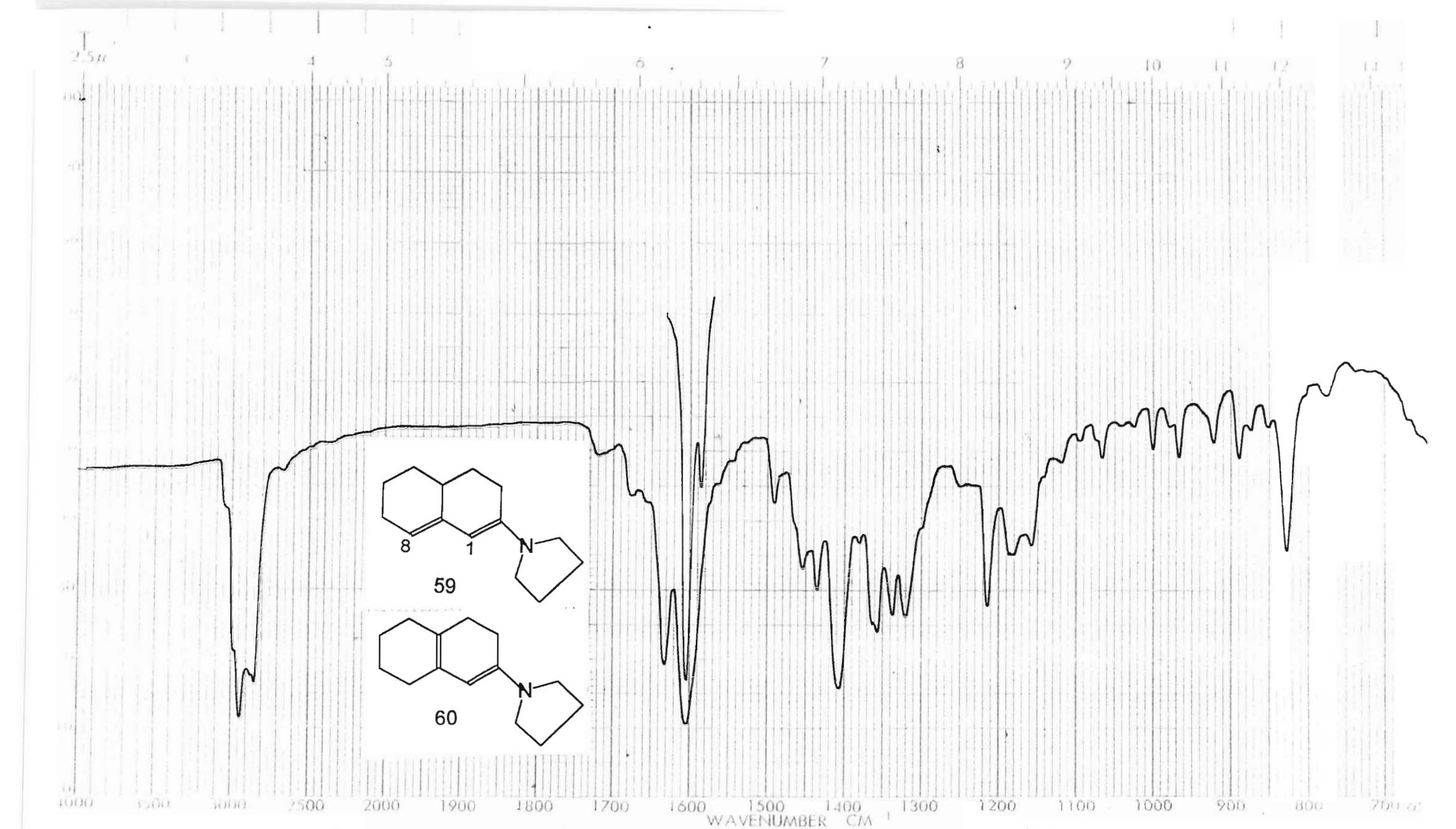
PHASE
SOLVENT
CONCENTRATION

THICKNESS
REFERENCE
SCAN TIME

REMARKS

DATE
OPERATOR

Perkin-Elmer



SPECTRUM NO.

SAMPLE

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SOLVENT

CONCENTRATION

THICKNESS

REFERENCE

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REMARKS

DATE

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⊕ Schmidt

PART NO. 28615

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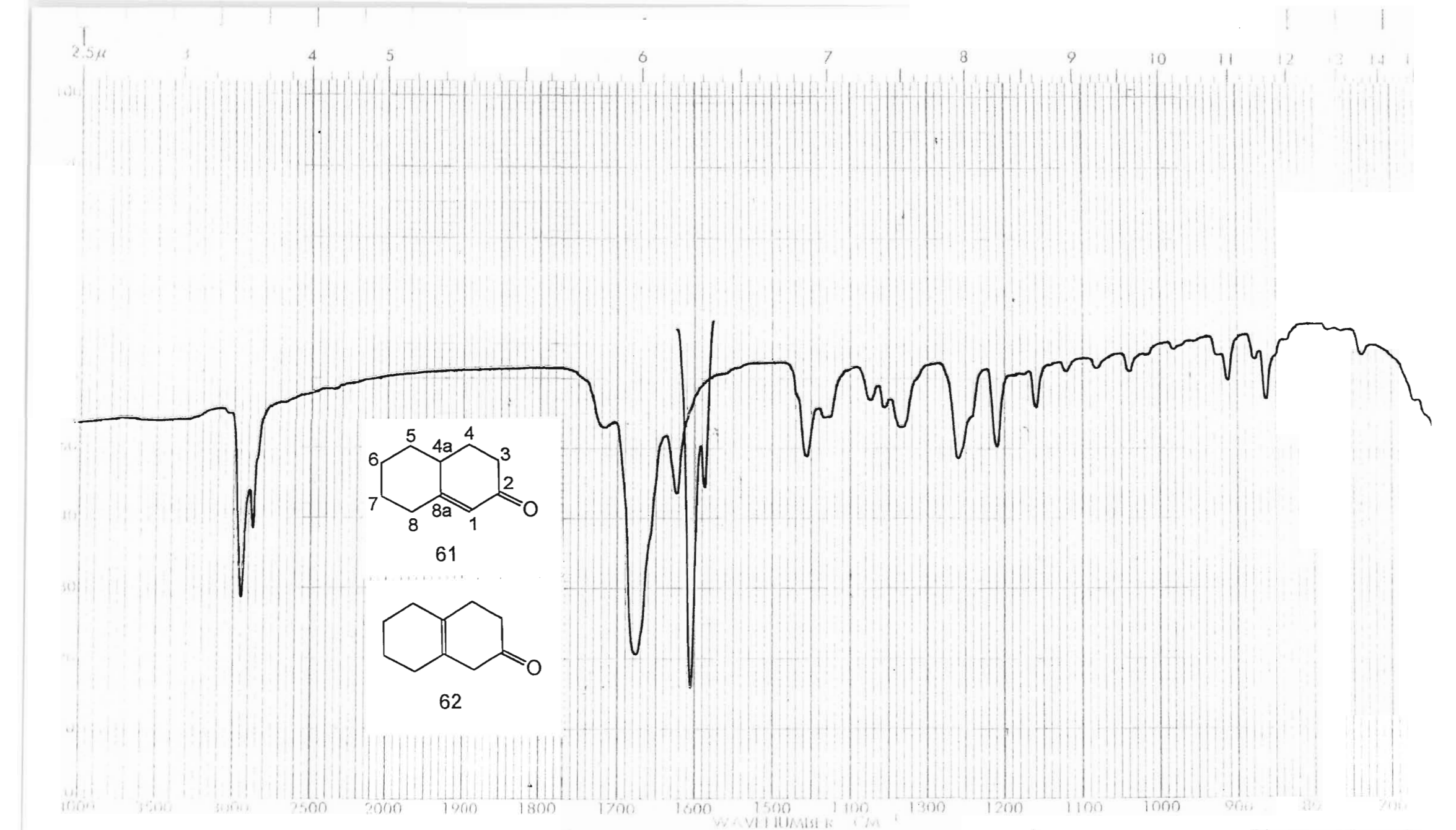

SPECTRUM #

SAMPLE

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CONCENTRATION

THICKNESS

REFERENCE

SCALE TIME

REMARKS

DATE

OPERATOR

Shimadzu

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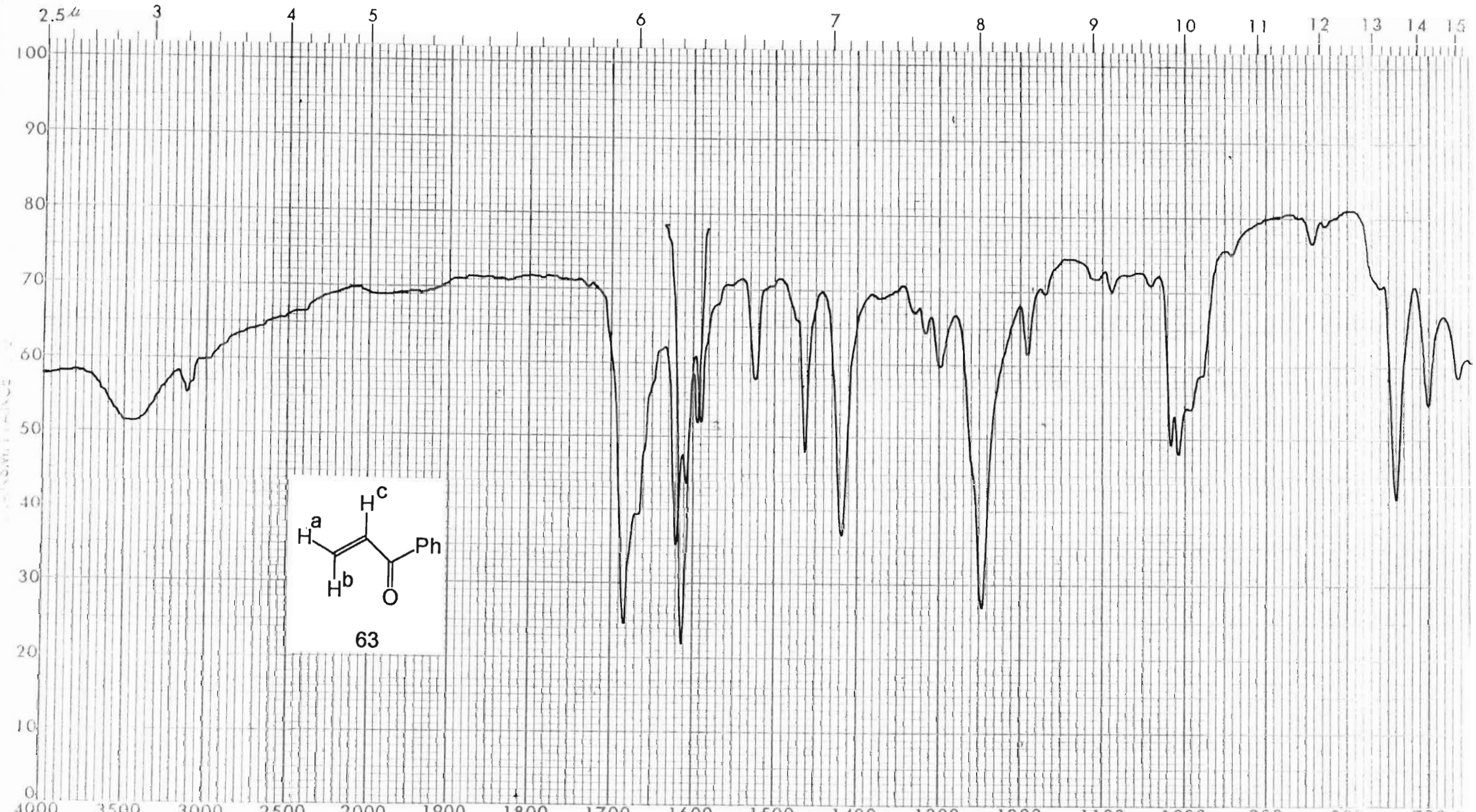

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SAMPLE	SOLVENT	REFERENCE		
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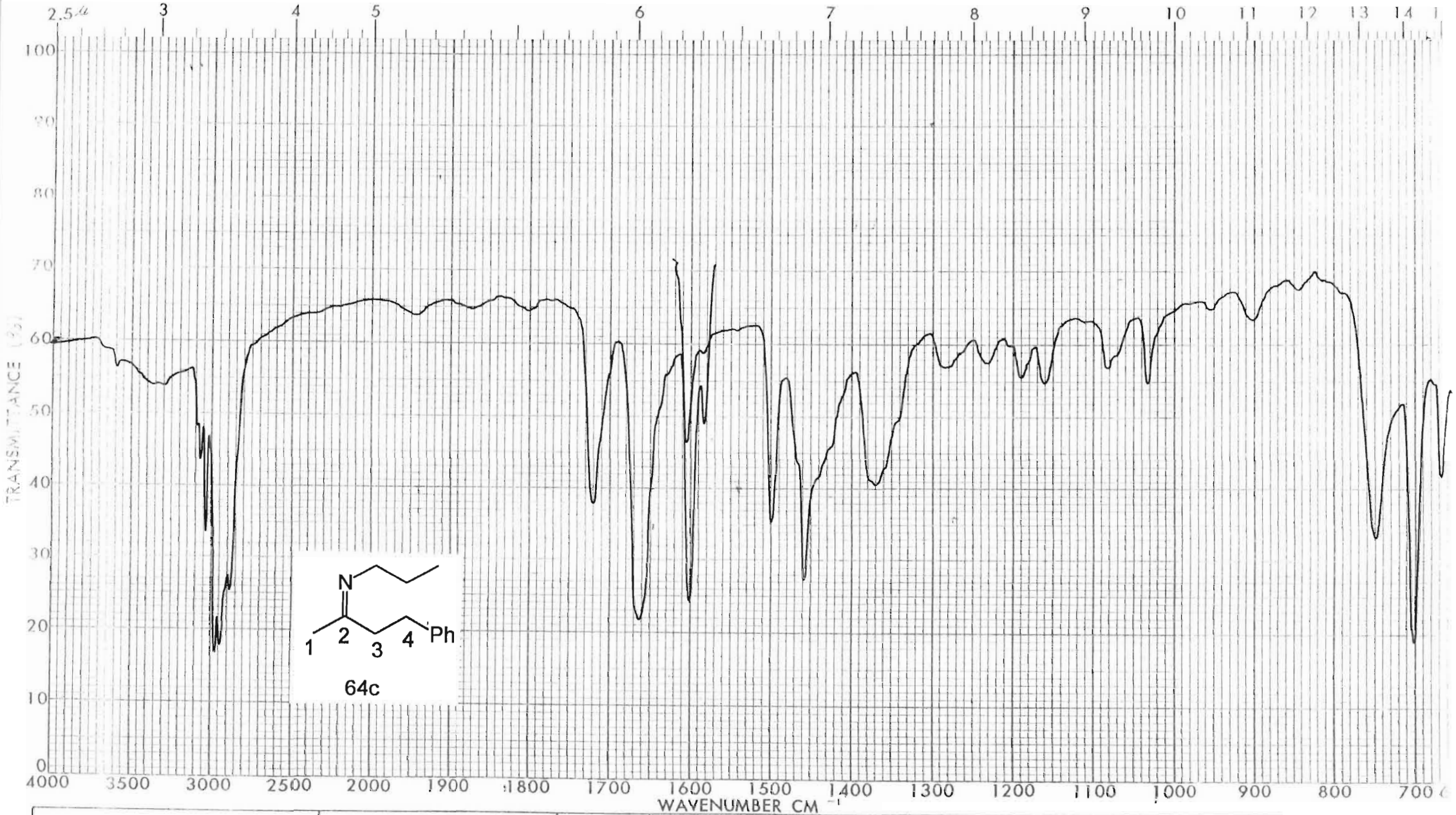

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SAMPLE	SOLVENT	REFERENCE		OPERATOR
	CONCENTRATION	SCAN TIME		

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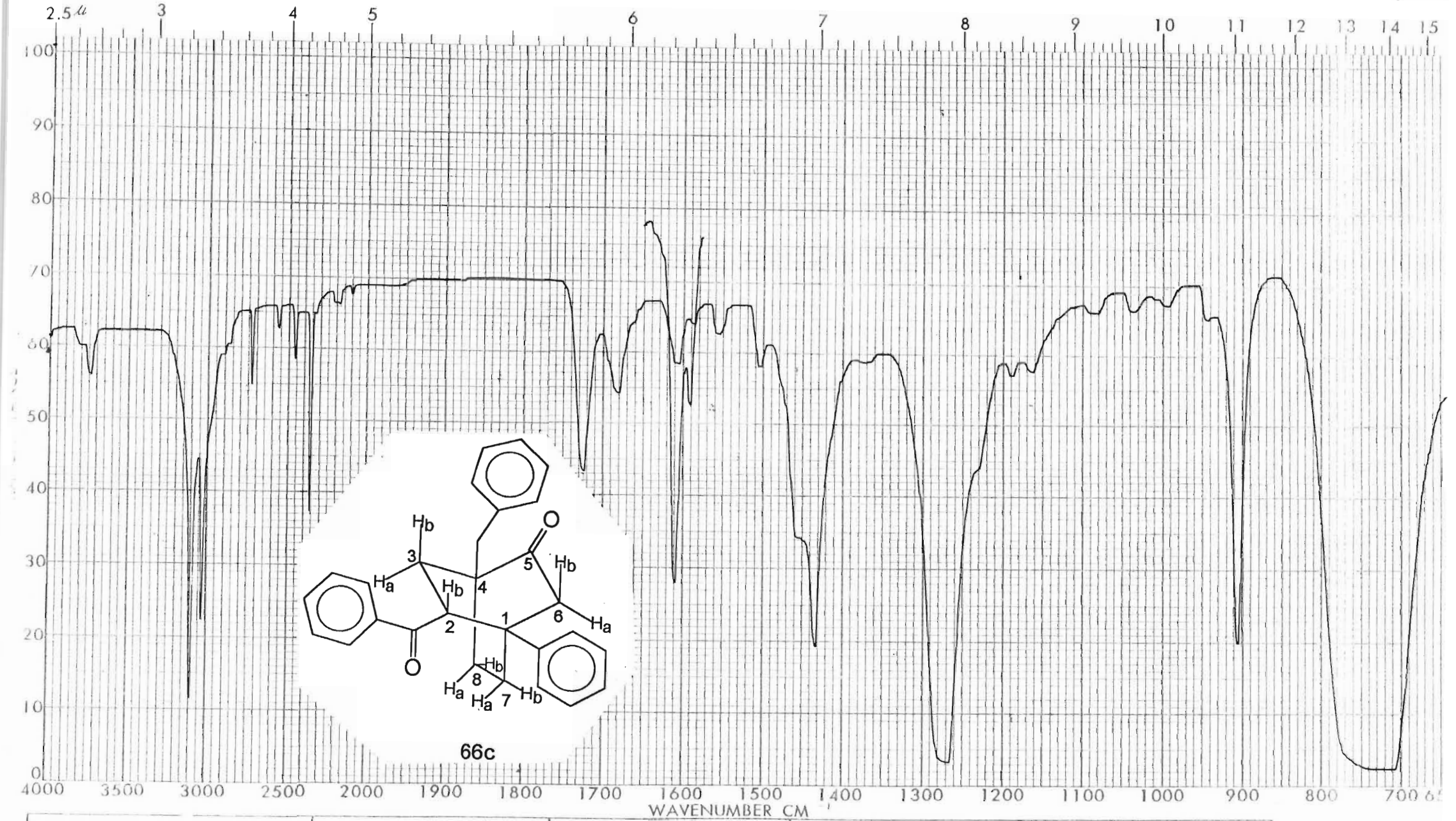

66c

SPECTRUM NO.	PHASE	THICKNESS	REMARKS	DATE
SAMPLE	SOLVENT	REFERENCE		
	CONCENTRATION	SCAN TIME		OPERATOR

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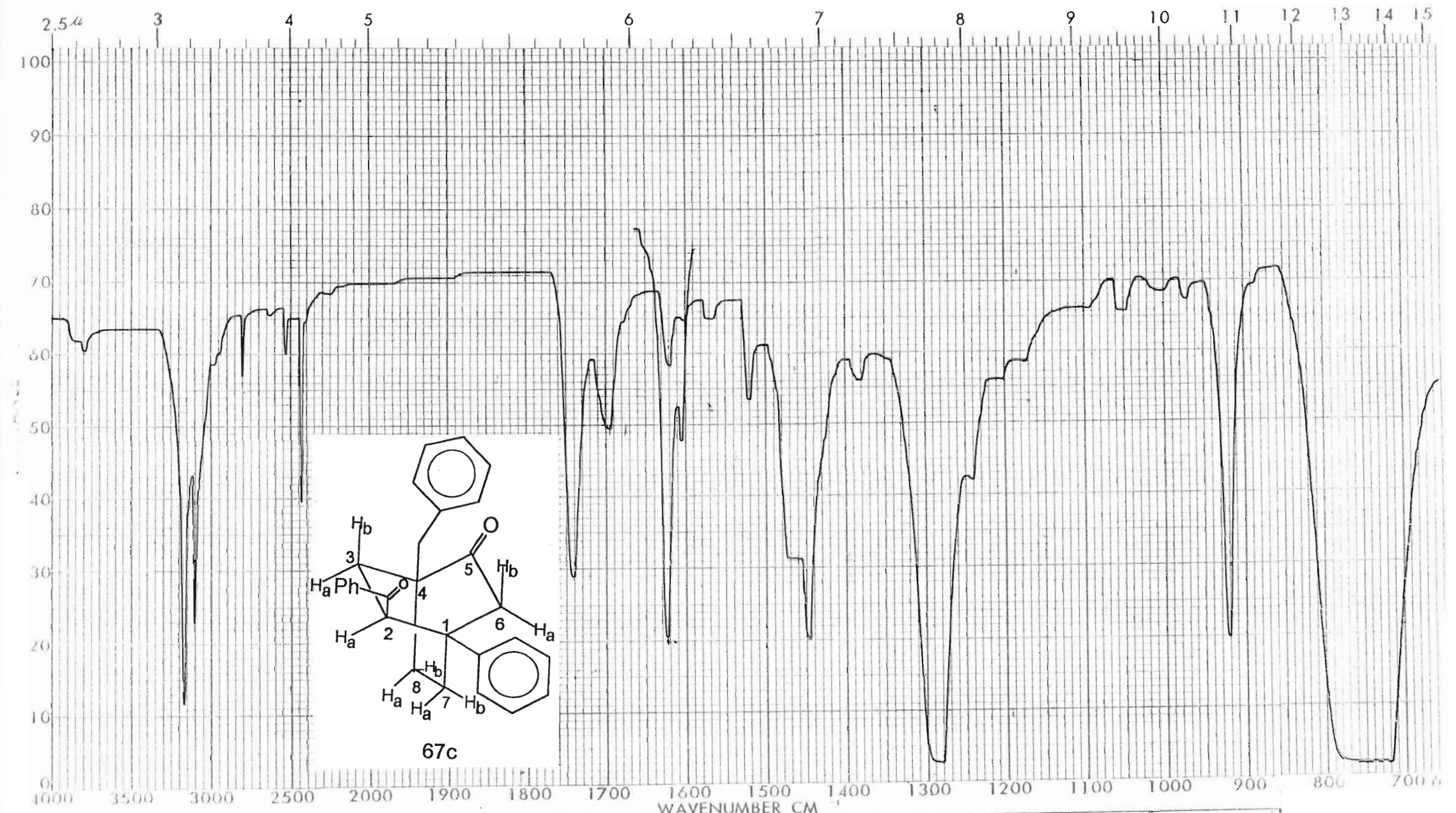
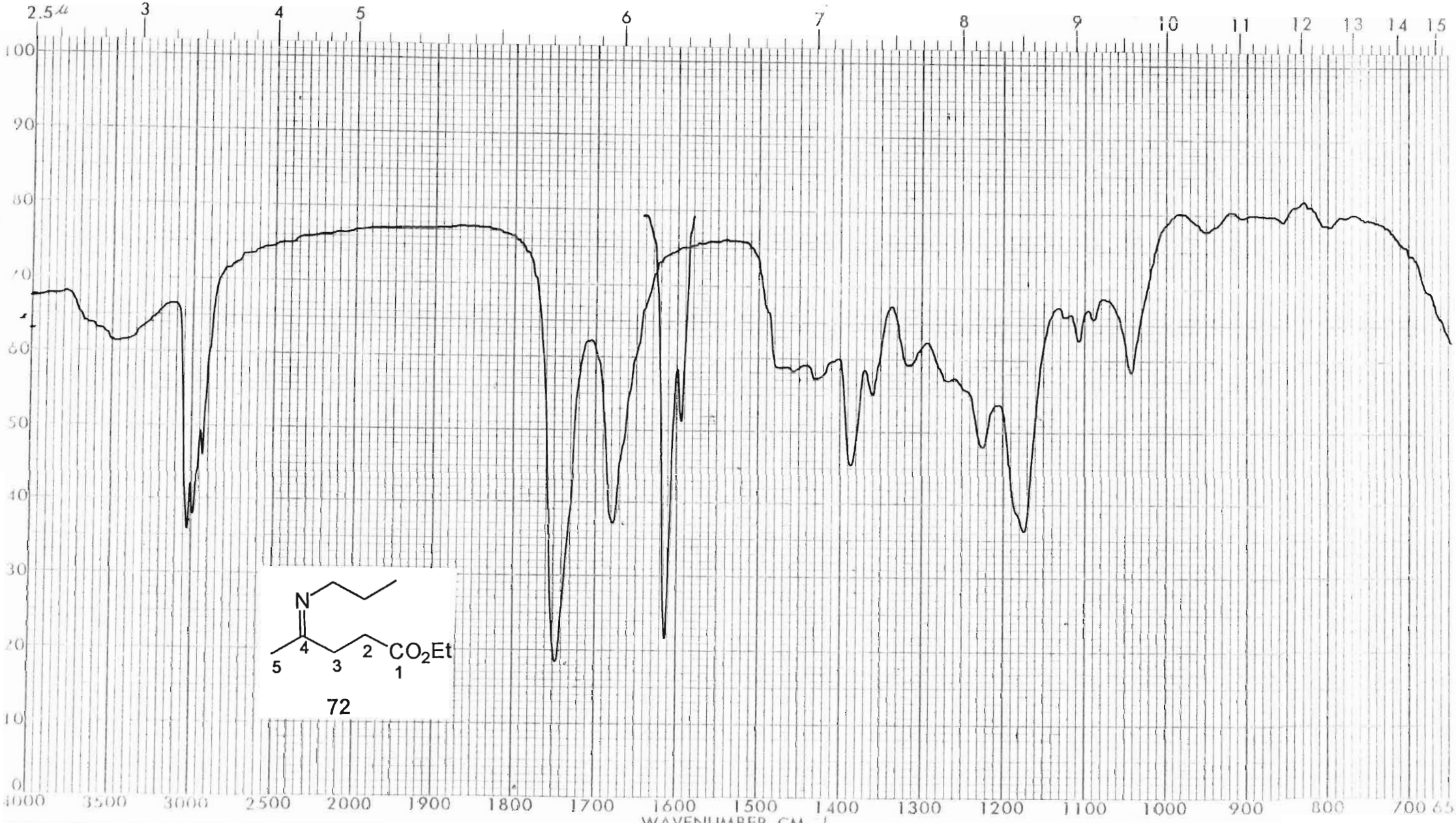


SPECTRUM NO.	PHASE	THICKNESS	REMARKS	DATE
SAMPLE	SOLVENT	REFERENCE		OPERATOR
	CONCENTRATION	SCAN TIME		



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SAMPLE	SOLVENT	REFERENCE		
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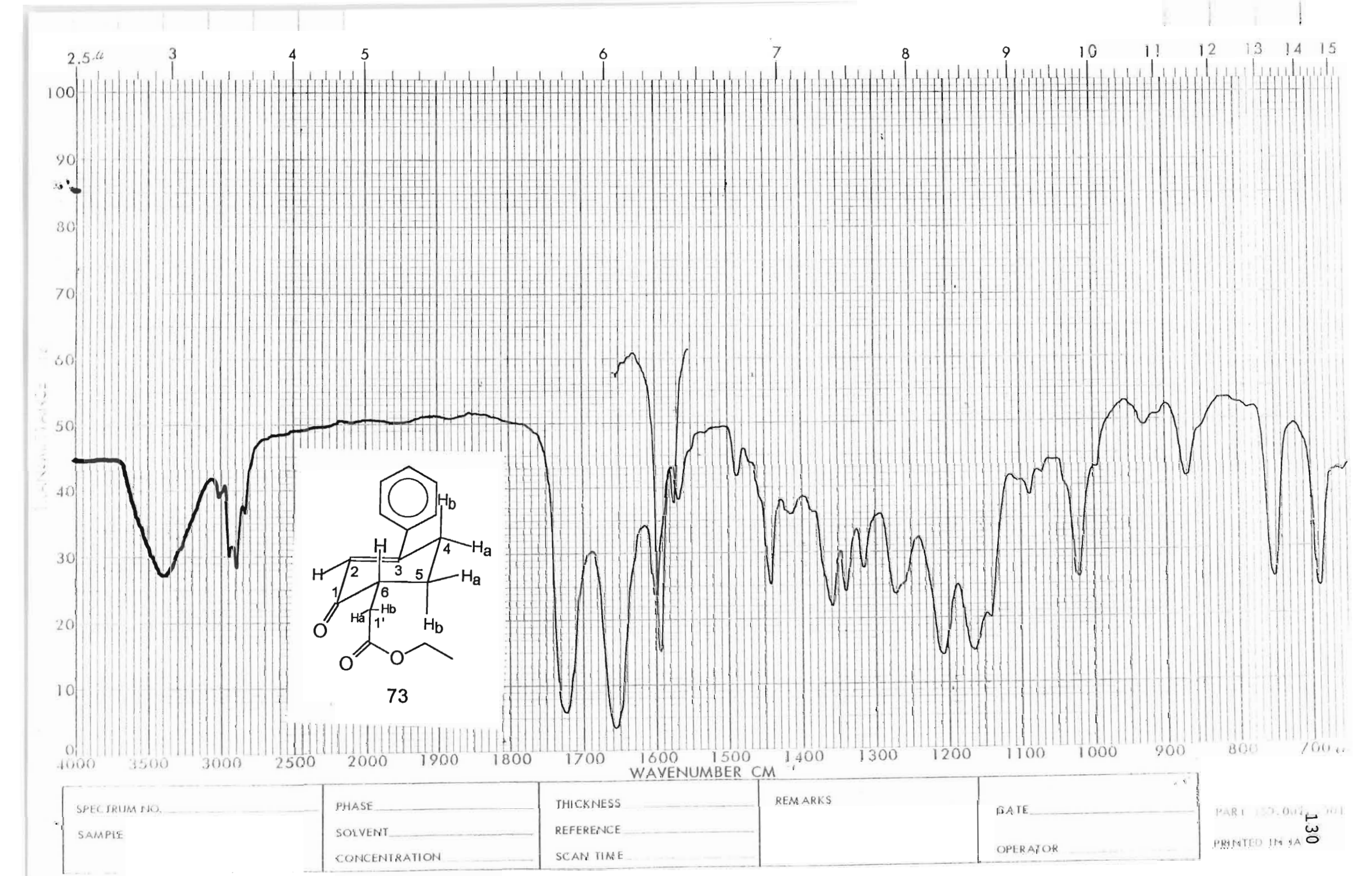

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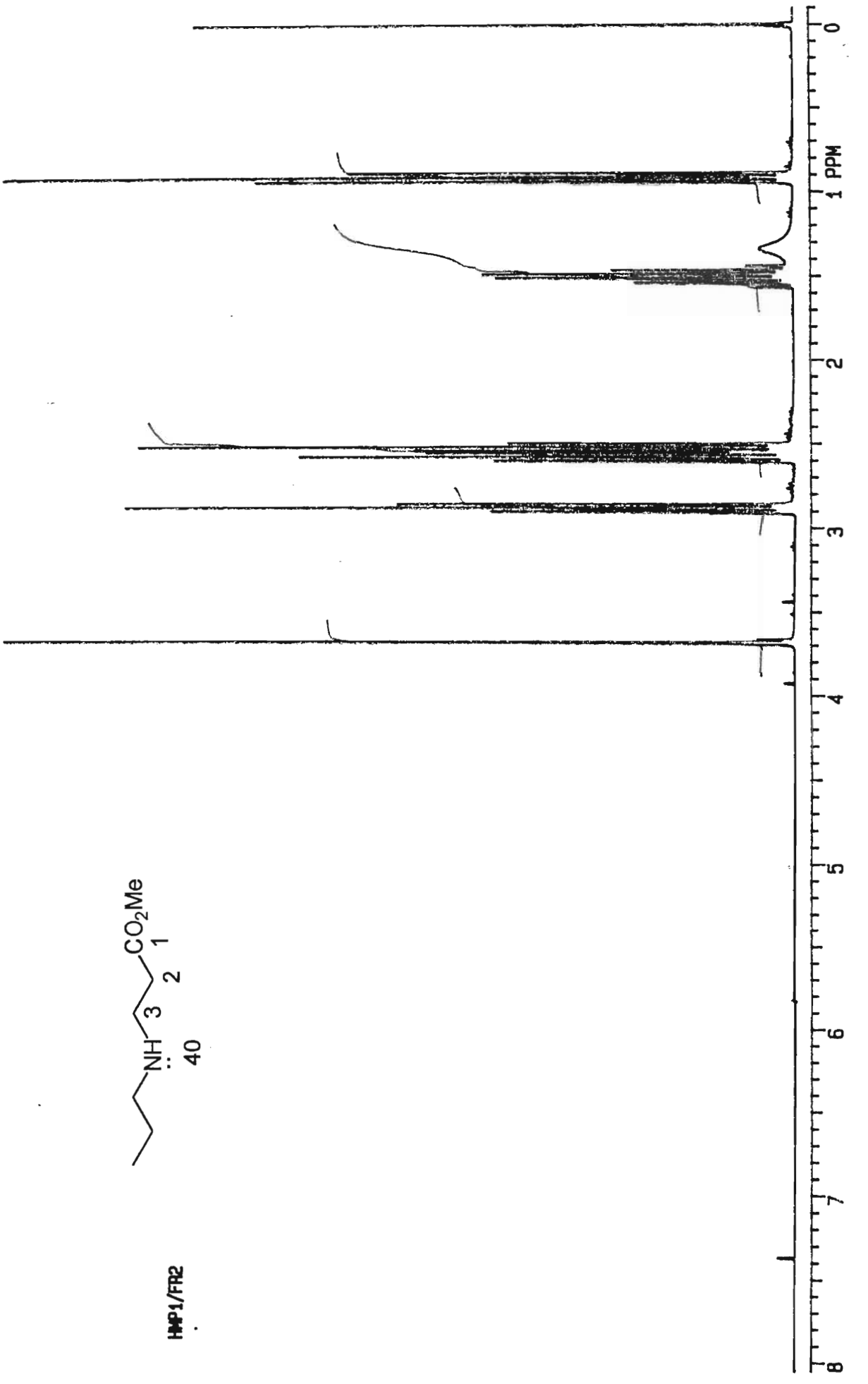
SAMPLE	SOLVENT	REFERENCE		
	CONCENTRATION	SCAN TIME		OPERATOR

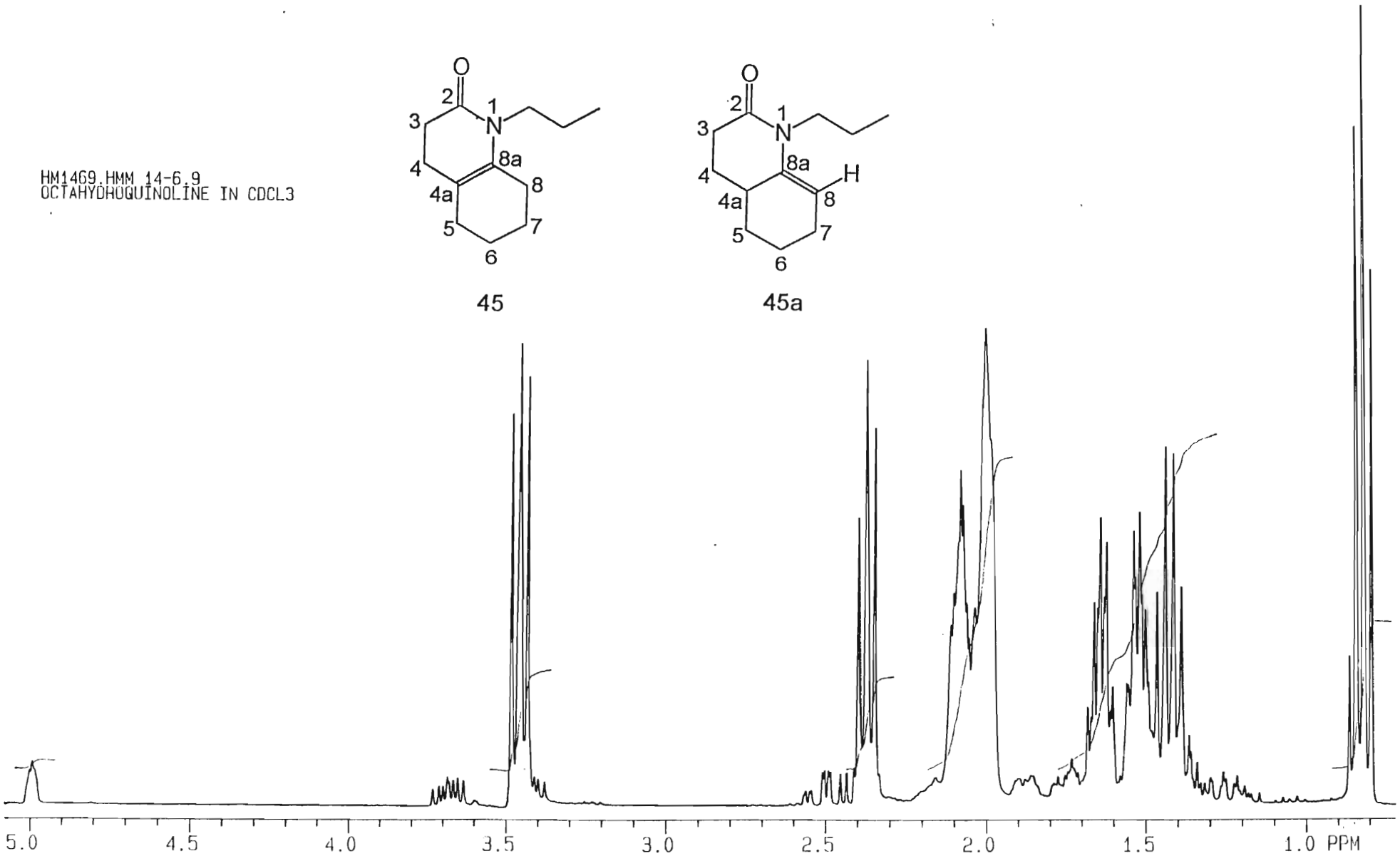
PRINTED IN U.S.A.


HMP1/FR2
NH
3
2
1
CO2Me
40
8
7
6
5
4
3
2
1 PPM
0

HM1469.HMM 14-6.9
OCTAHYDROQUINOLINE IN CDCL3

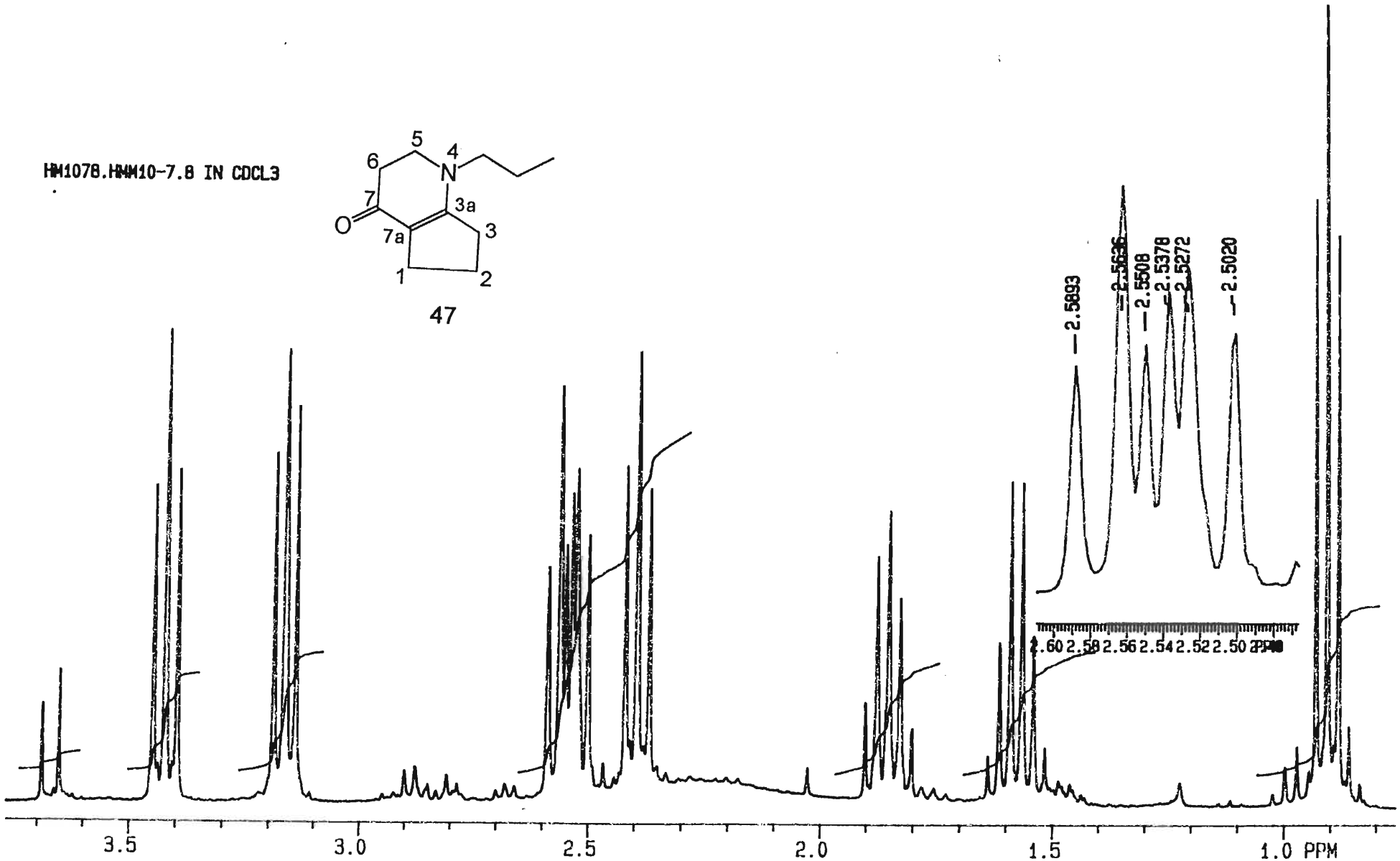
45

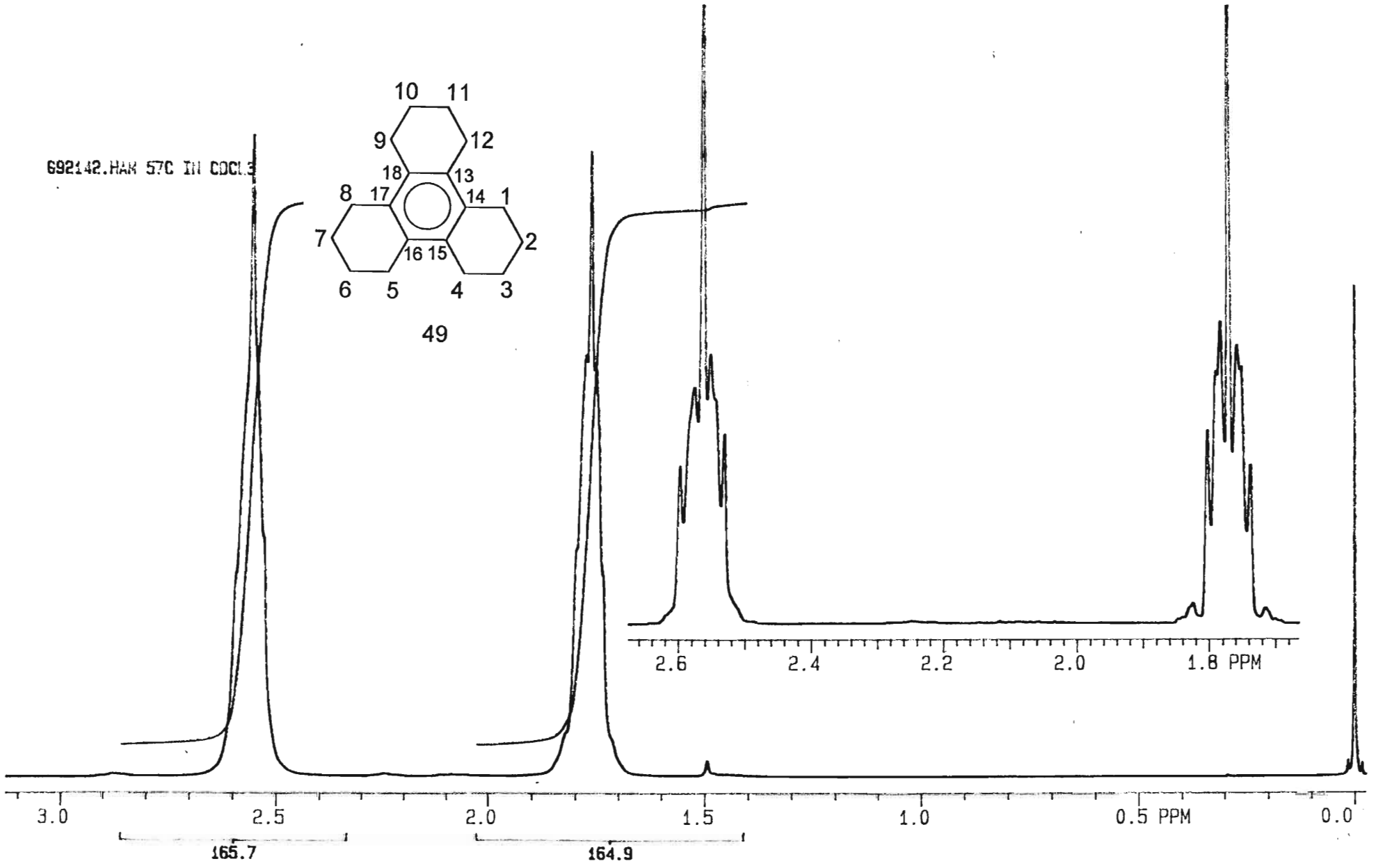
45a



HM1078.HMM10-7.8 IN CDCL3

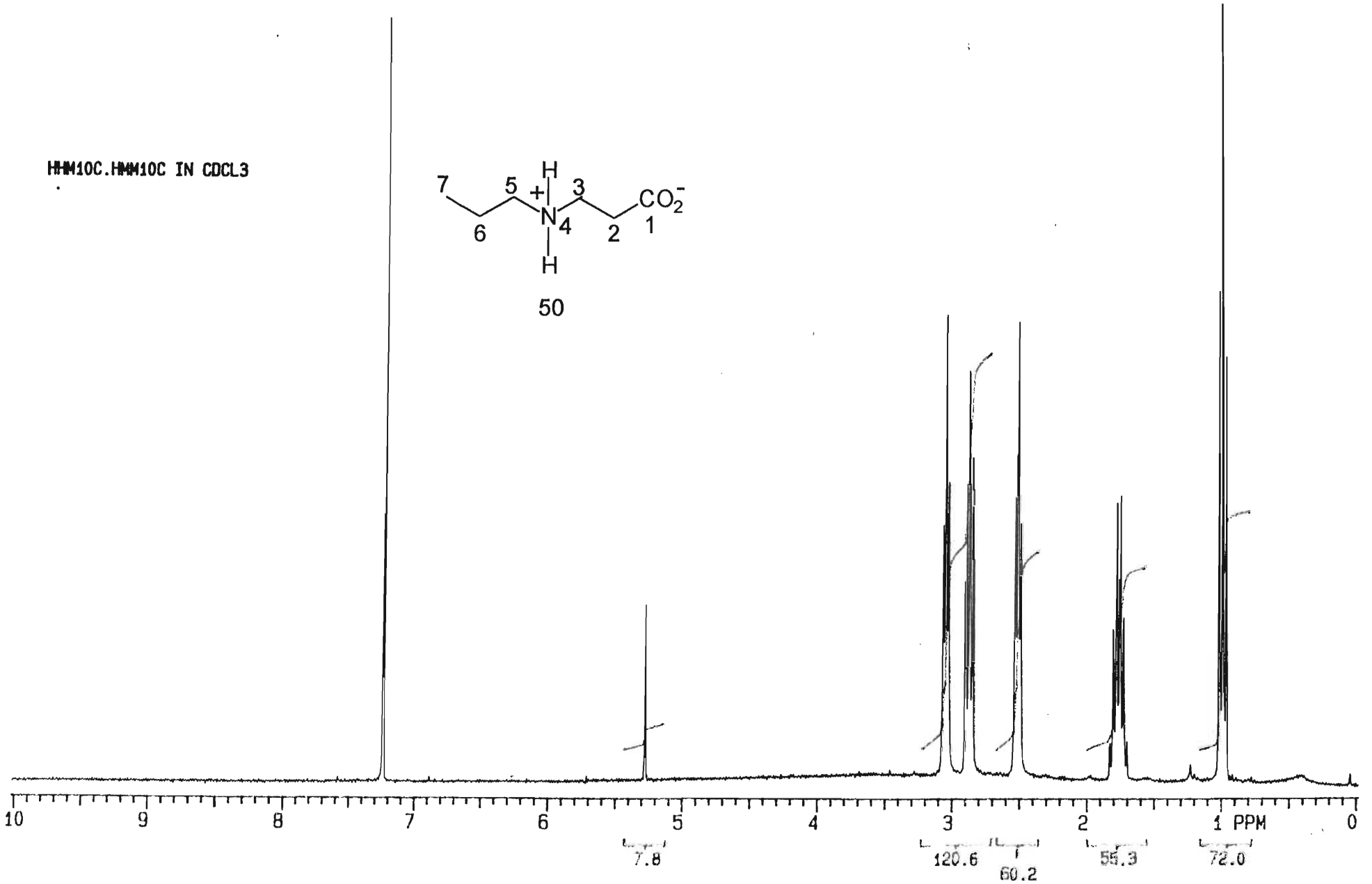
47

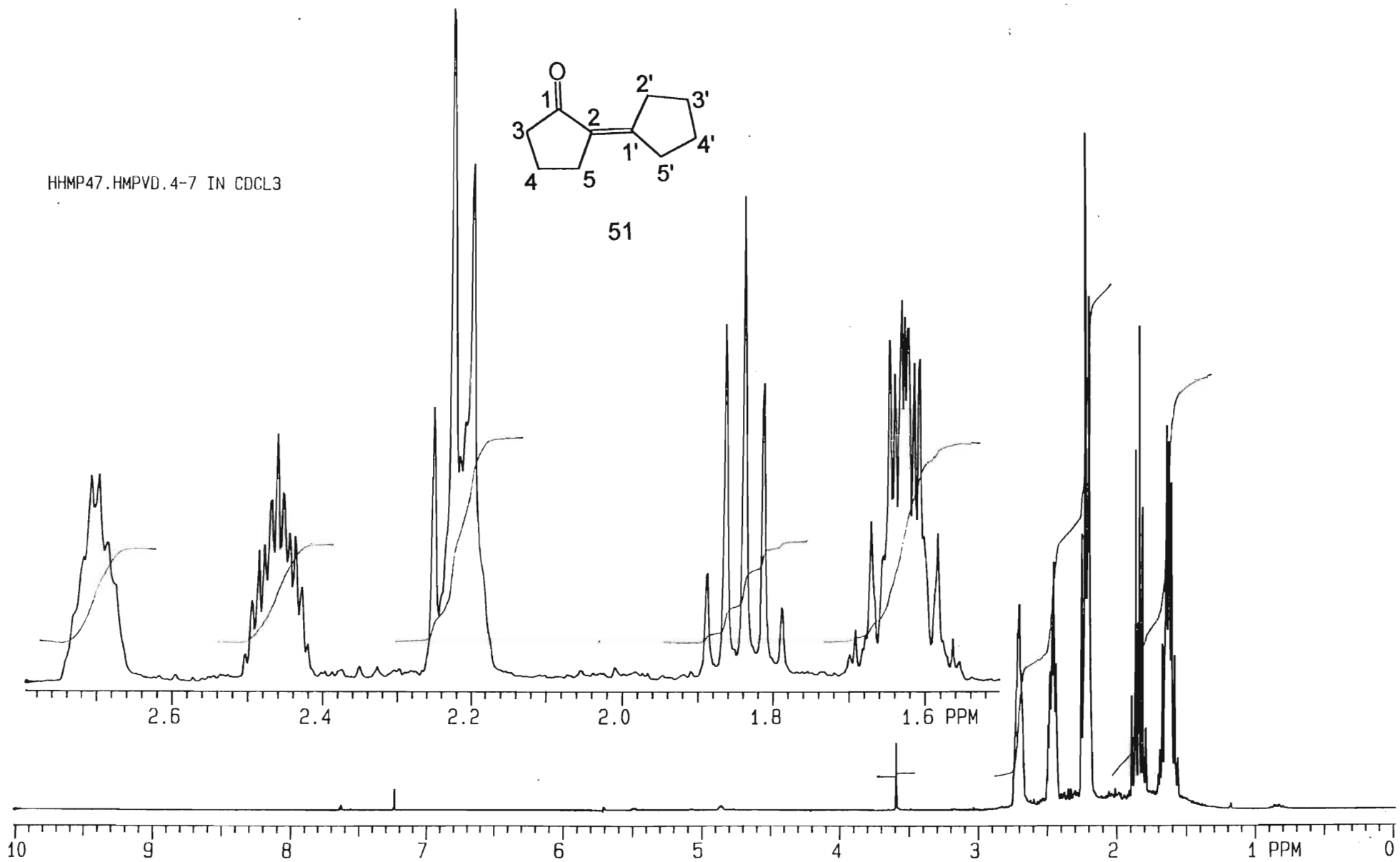


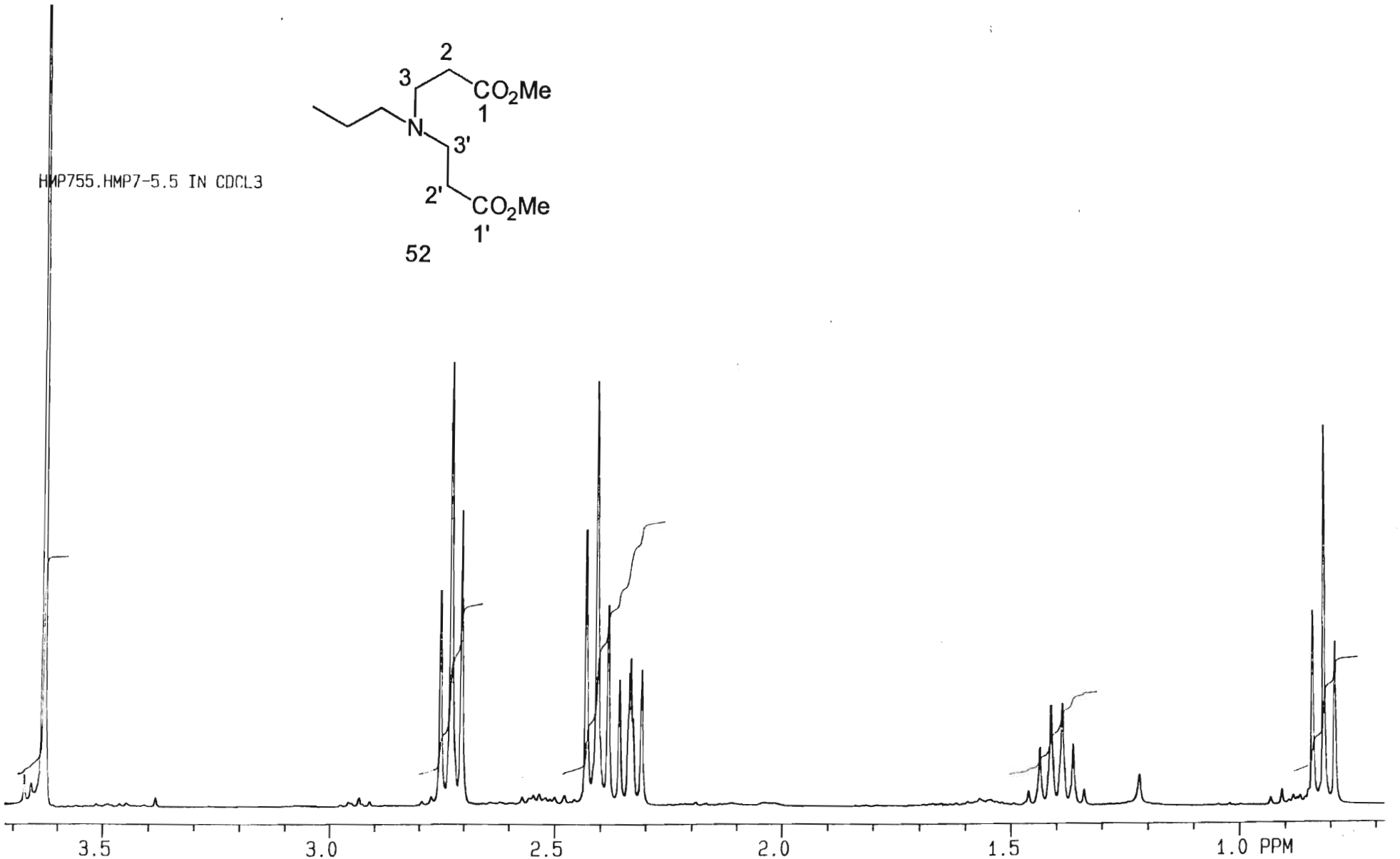

692142.HAN 57C IN CDCL3
10 11
9 12
18 13
8 17 14 1
7 2
16 15
6 5 4 3
49
2.6 2.4 2.2 2.0 1.8 PPM
3.0 2.5 2.0 1.5 1.0 0.5 PPM 0.0
165.7
164.9

HMM10C.HMM10C IN CDCL3

50




HHMP47.HMPVD.4-7 IN CDCL3
O
1
2
3
4
5
1'
2'
3'
4'
5'
51
2.6
2.4
2.2
2.0
1.8
1.6 PPM
10
9
8
7
6
5
4
3
2
1 PPM
0


HMP755.HMP7-5.5 IN CDCL3
2
3
CO2Me
1
N
3'
2'
CO2Me
1'
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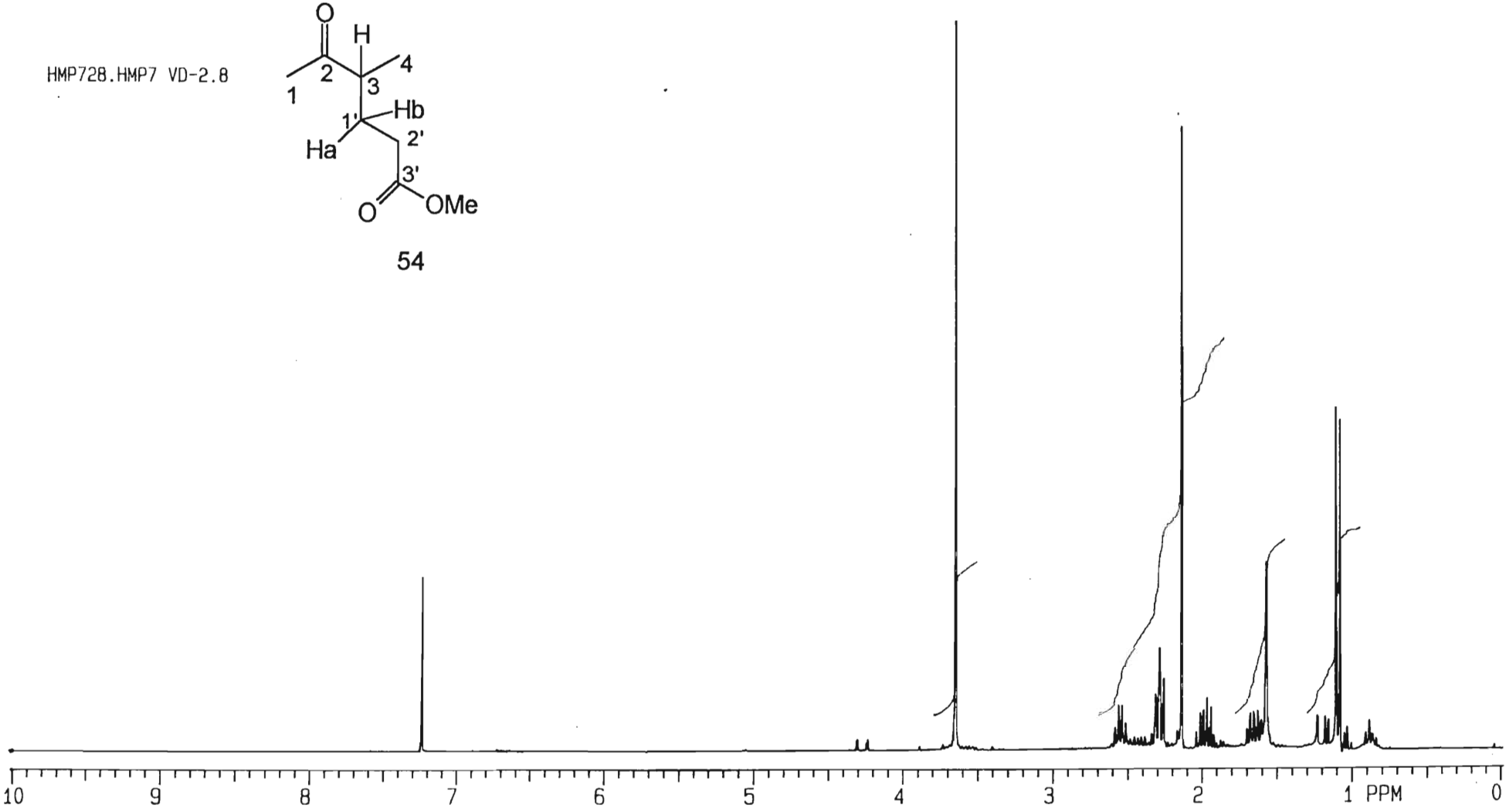
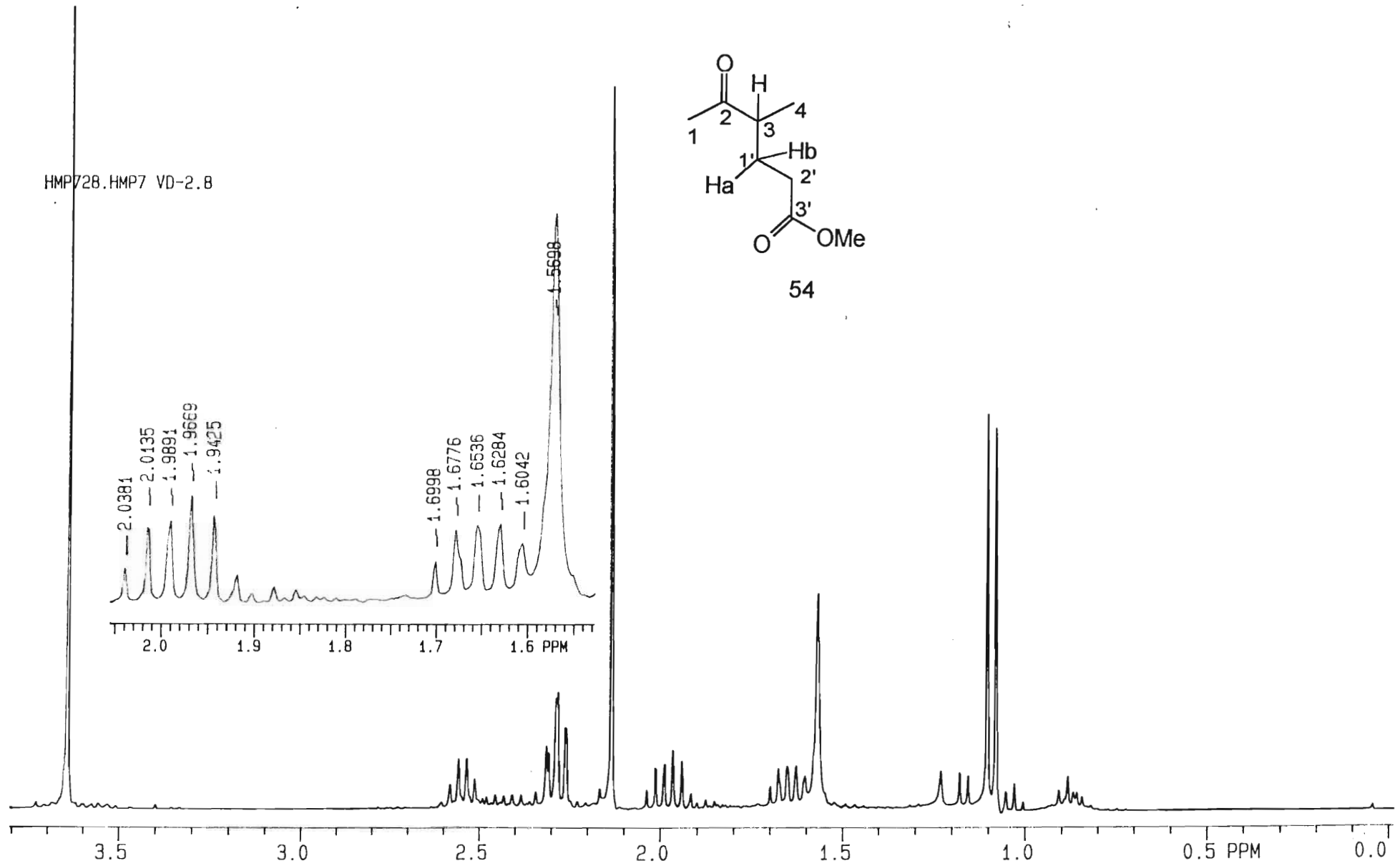
3.5
3.0
2.5
2.0
1.5
1.0 PPM

HMP728.HMP7 VD-2.8

54




HMP728.HMP7 VD-2.8
O
H
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2
3
4
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Hb
Ha
2'
3'
O
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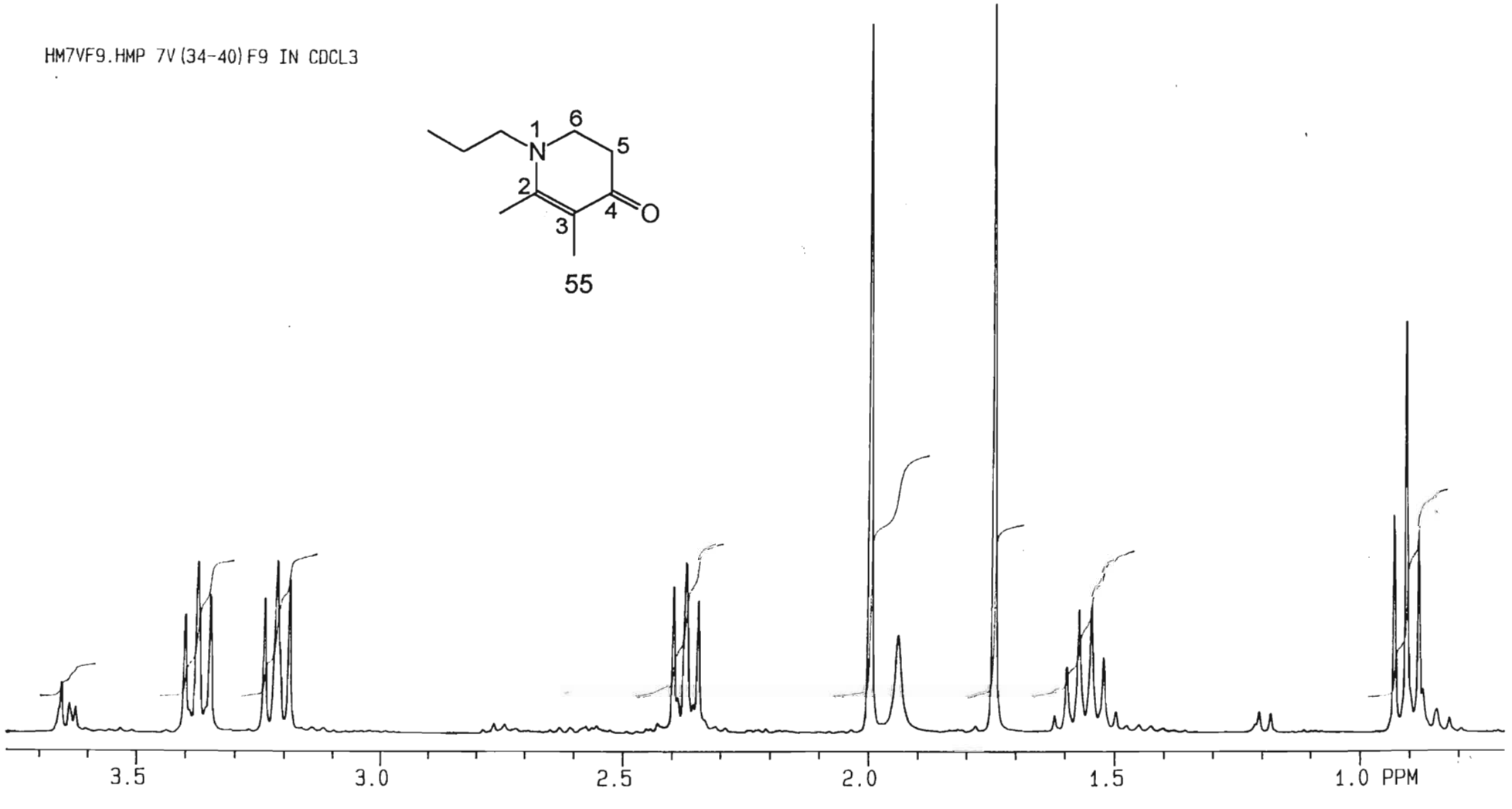
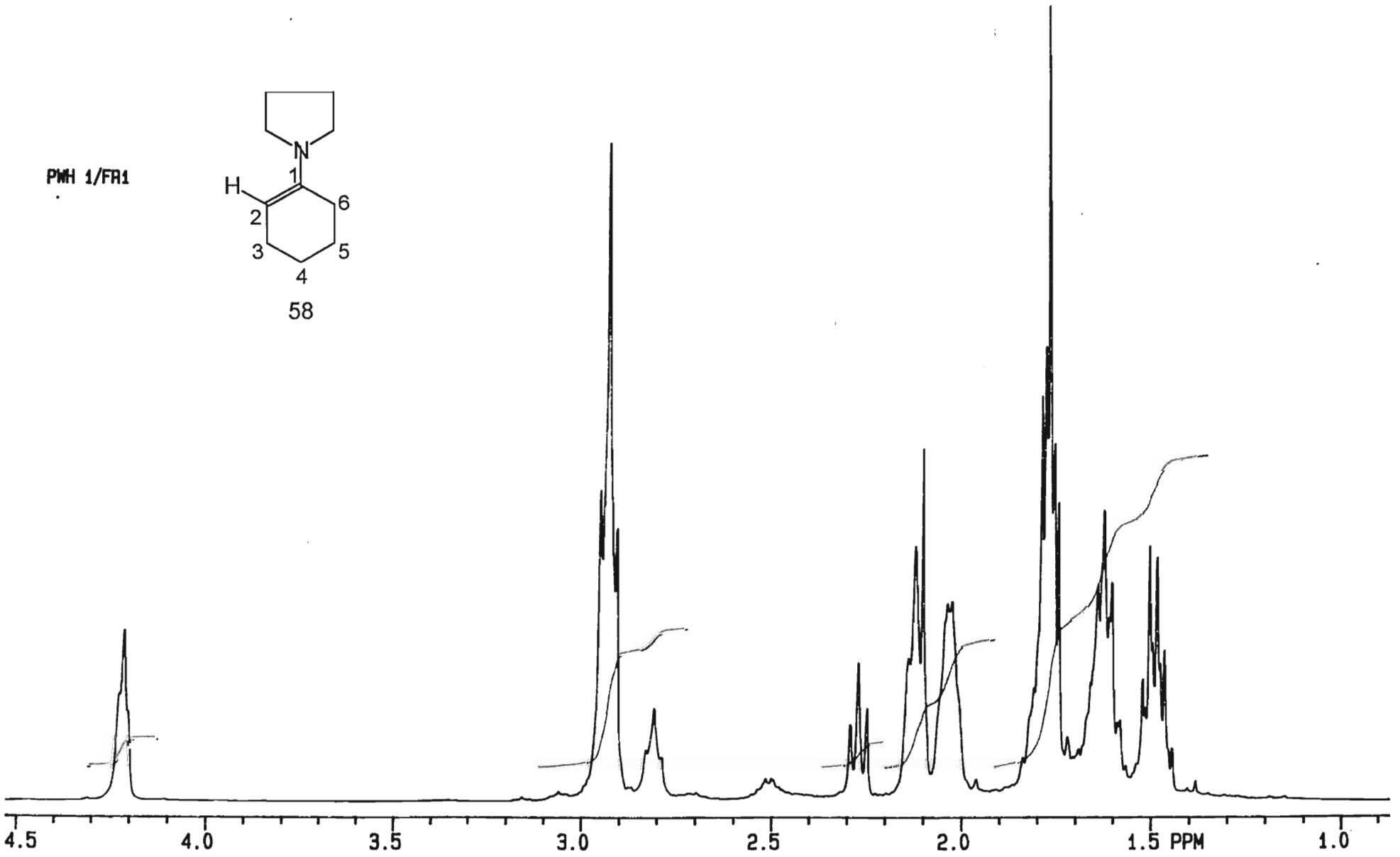
1.9891
1.9669
1.9425
1.6998
1.6776
1.6536
1.6284
1.6042
1.5698
2.0
1.9
1.8
1.7
1.6 PPM
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
0.0


HM7VF9.HMP 7V(34-40)F9 IN CDCL3
1
6
5
N
2
4
O
3
55
3.5
3.0
2.5
2.0
1.5
1.0 PPM

PMH 1/FR1

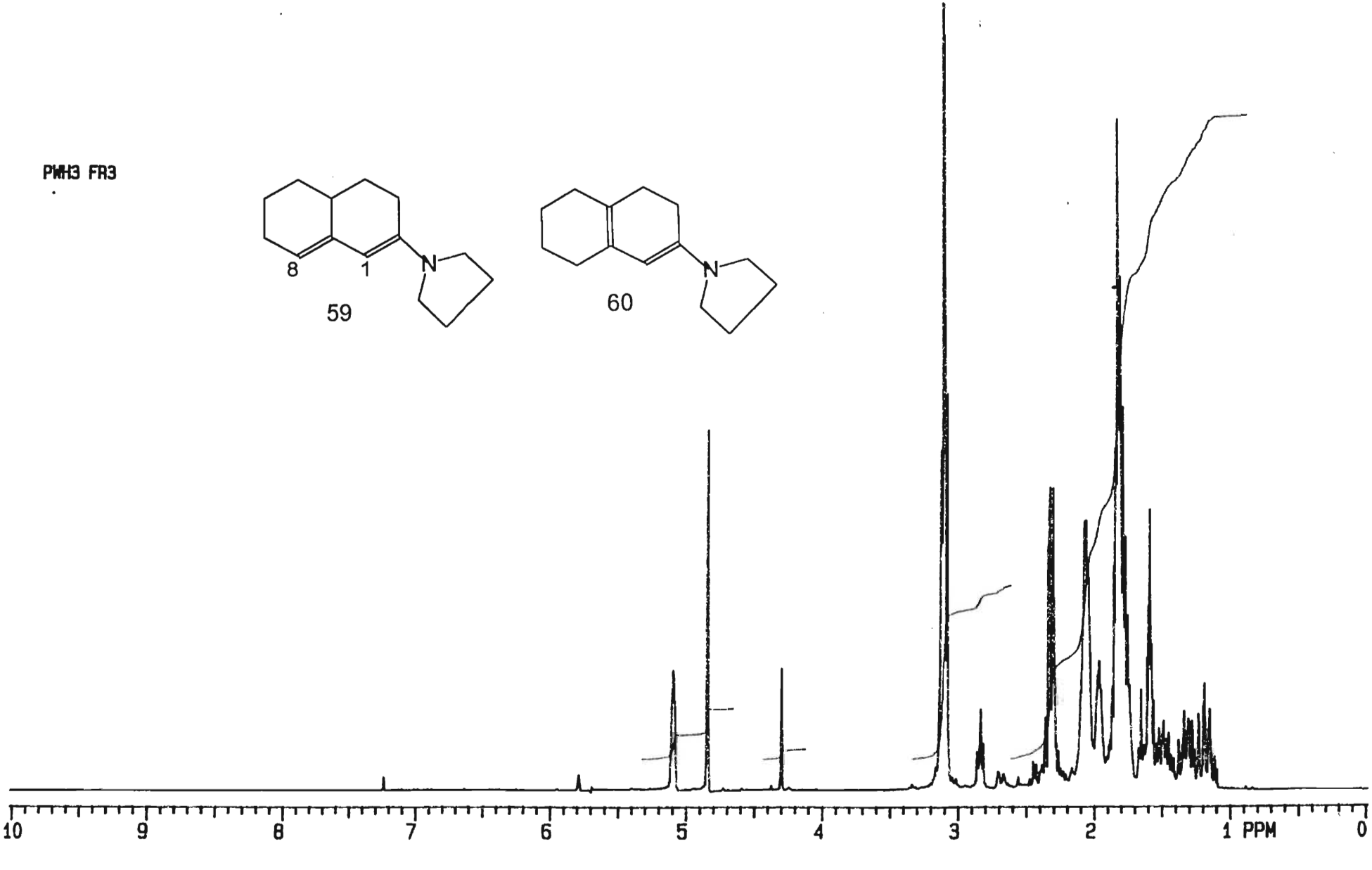
58

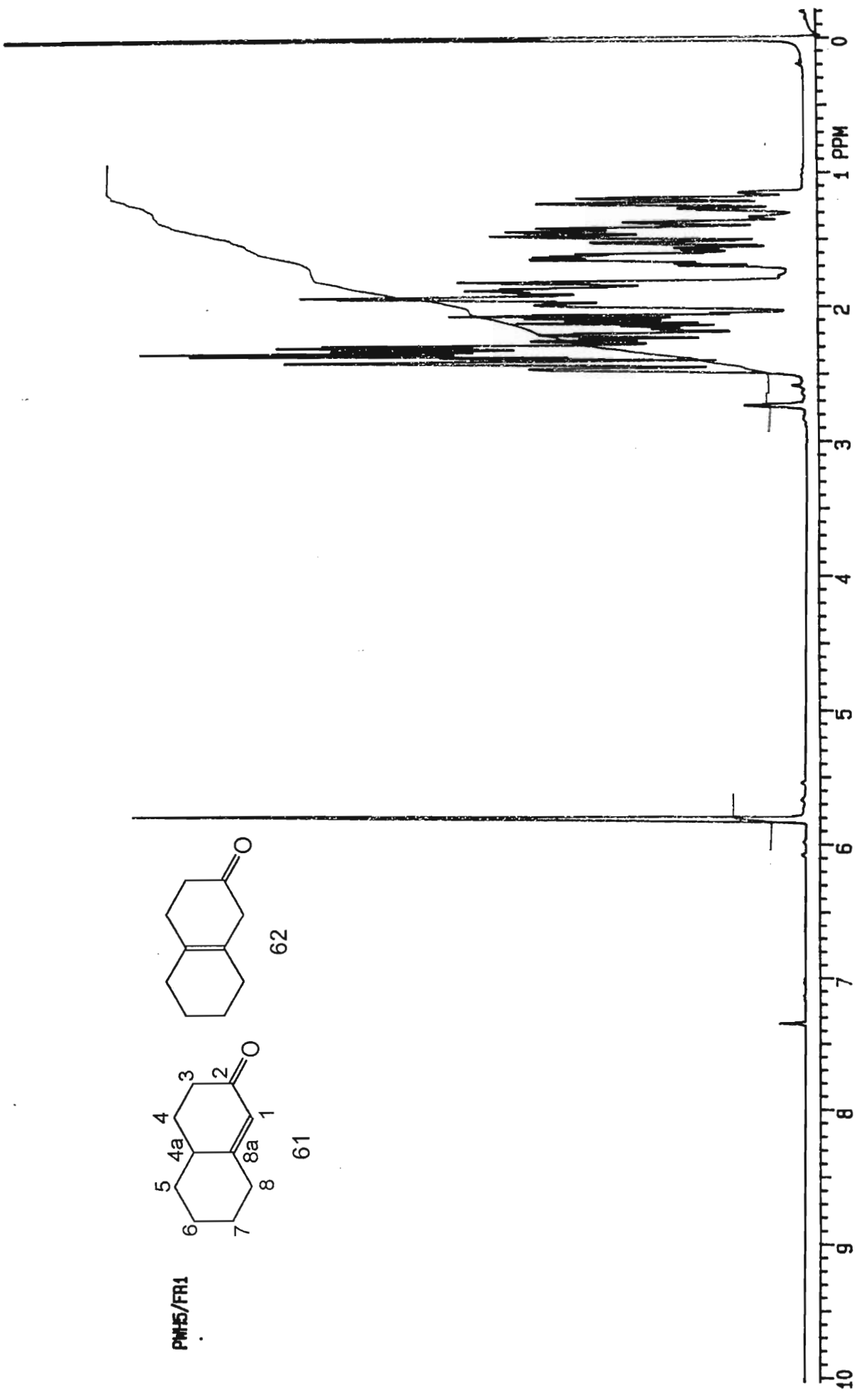


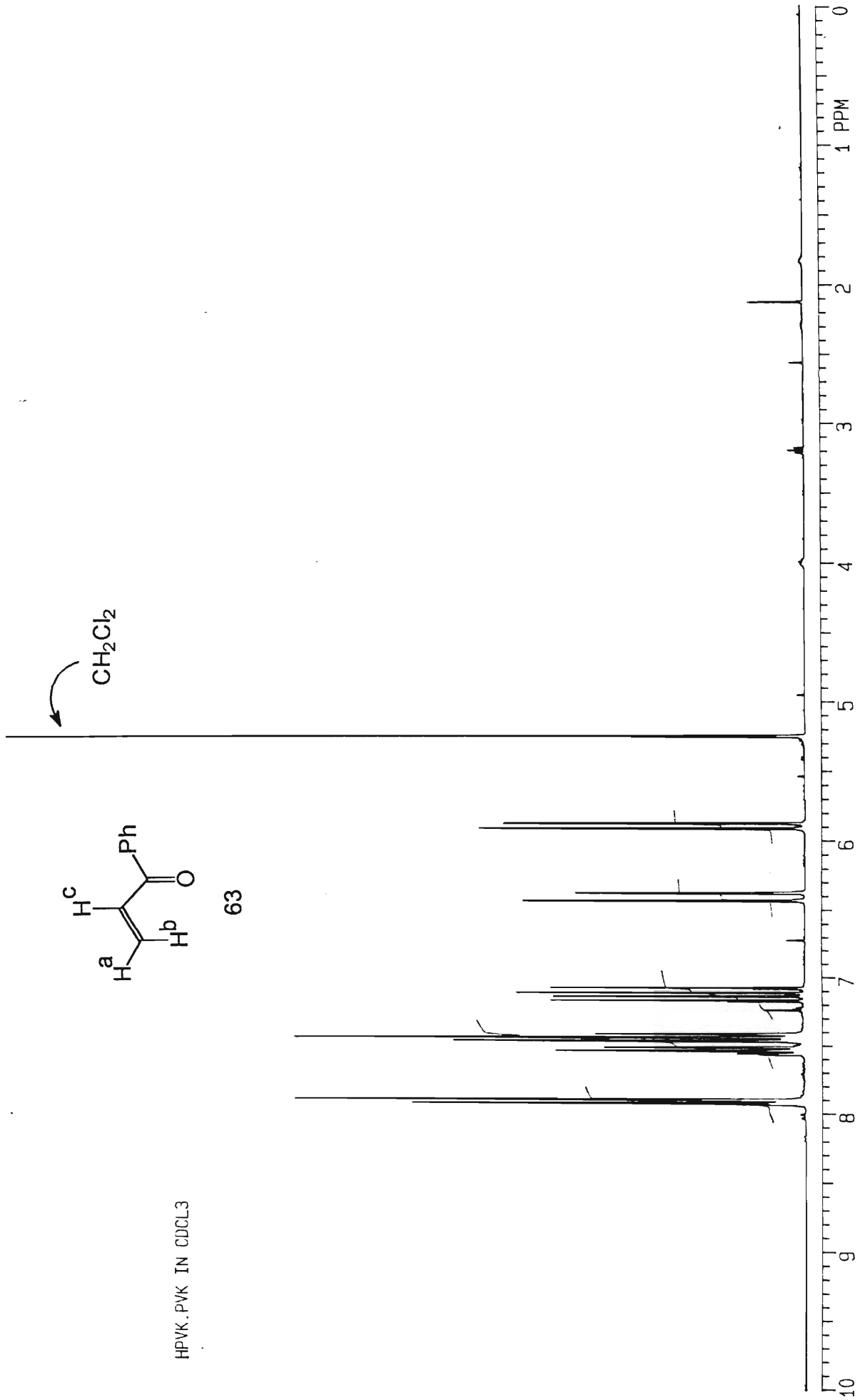
PMH3 FR3

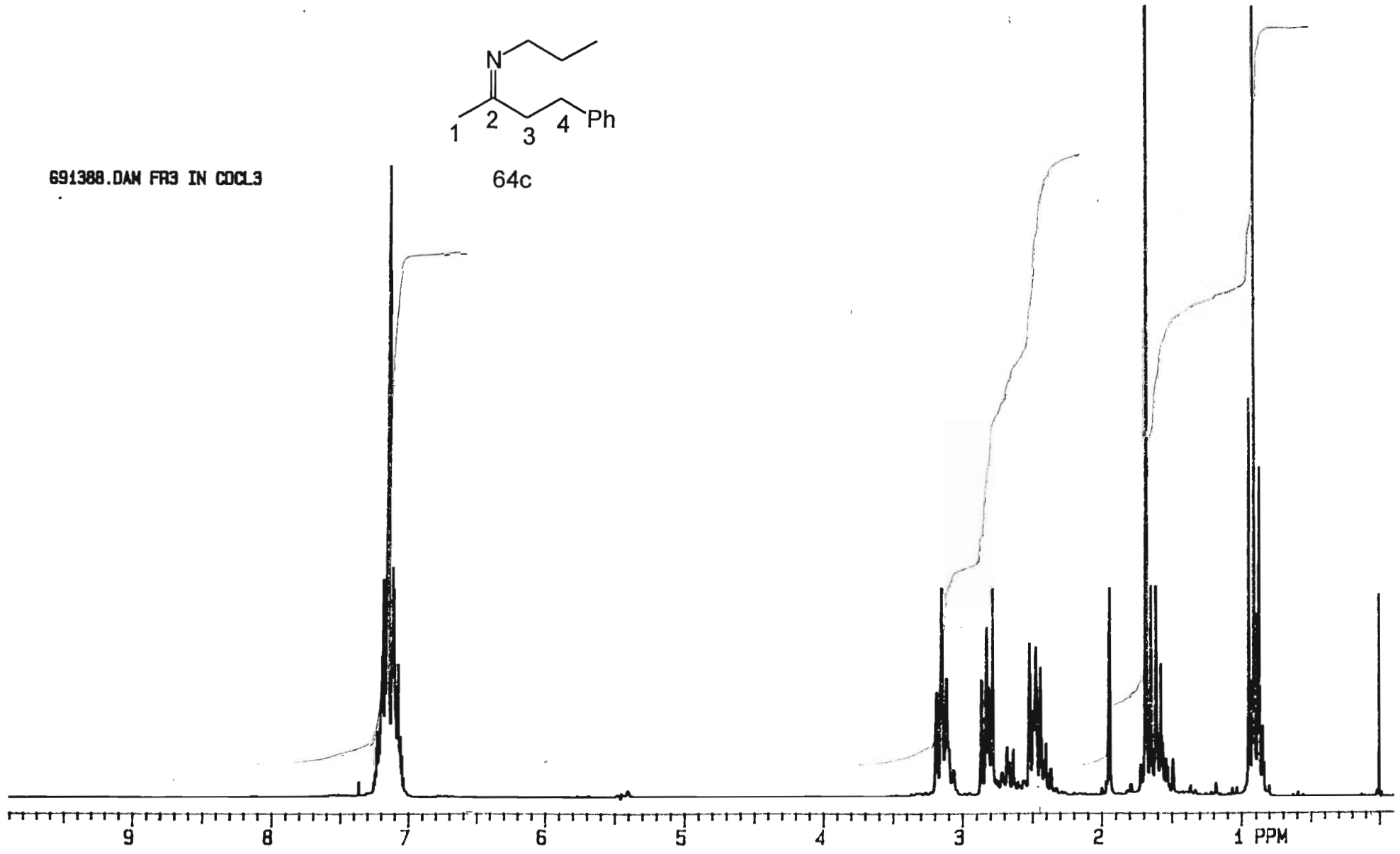
59

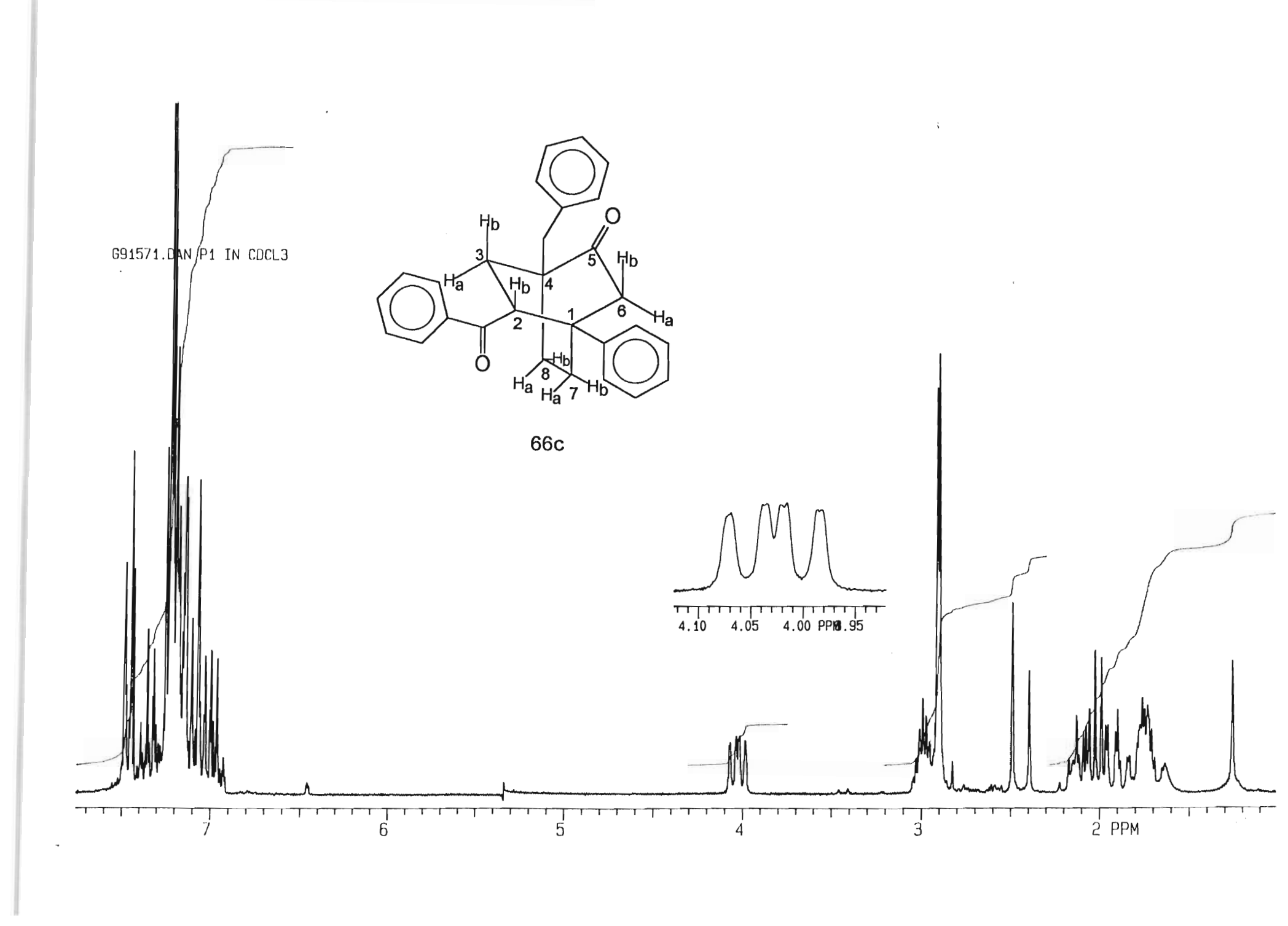
60



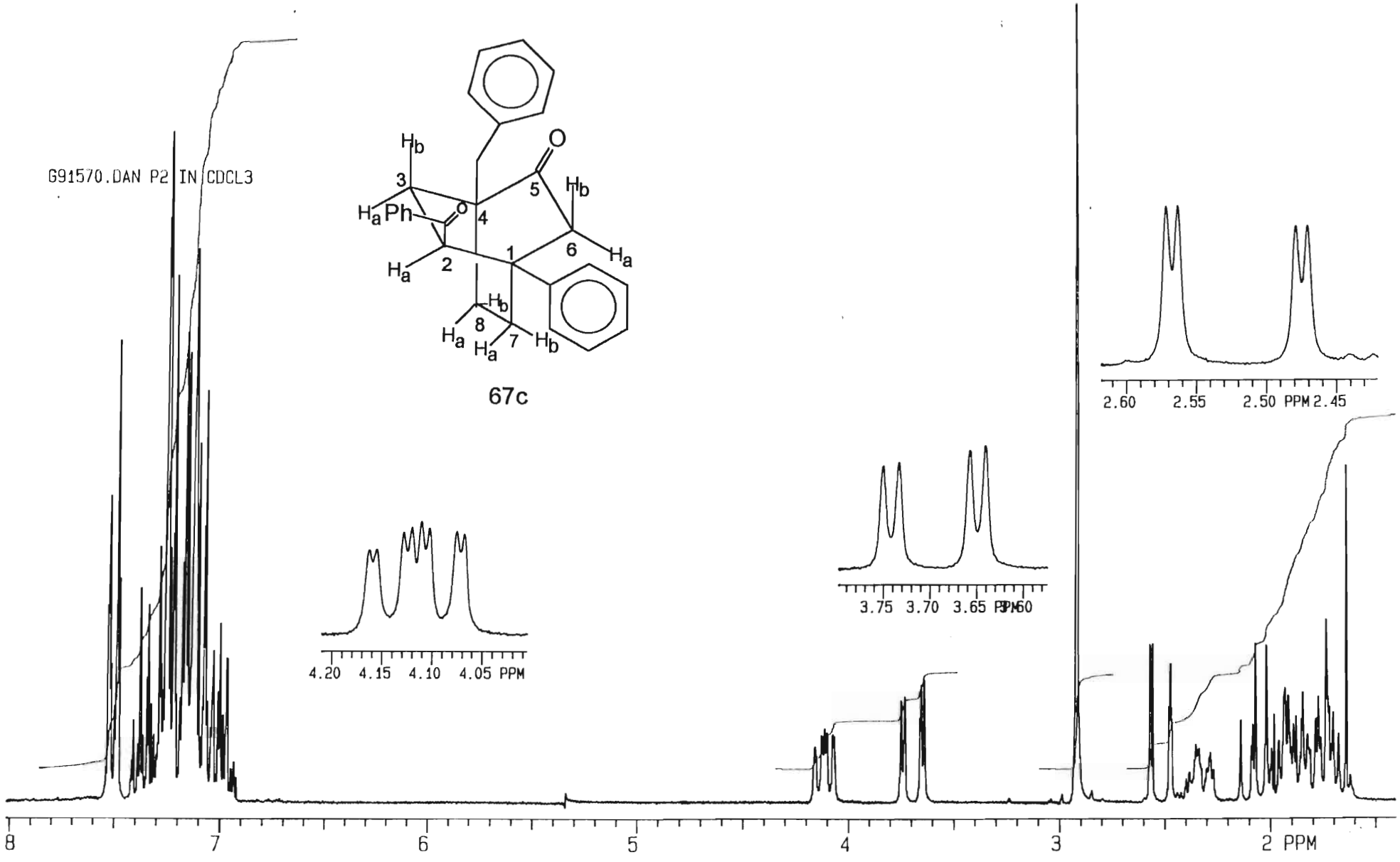

PWH5/FR1
1 PPM
0
1
2
3
4
5
6
7
8
9
10
O
O
1
2
3
4
4a
5
6
7
8
8a
61
62


HPVK.PVK IN CDCL3
63
Ph
O
H^c
H^b
H^a
CH_2Cl_2
10
9
8
7
6
5
4
3
2
1 PPM
0


N
1
2
3
4
Ph
691388.DAM FR3 IN CDCL3
64c
9
8
7
6
5
4
3
2
1 PPM

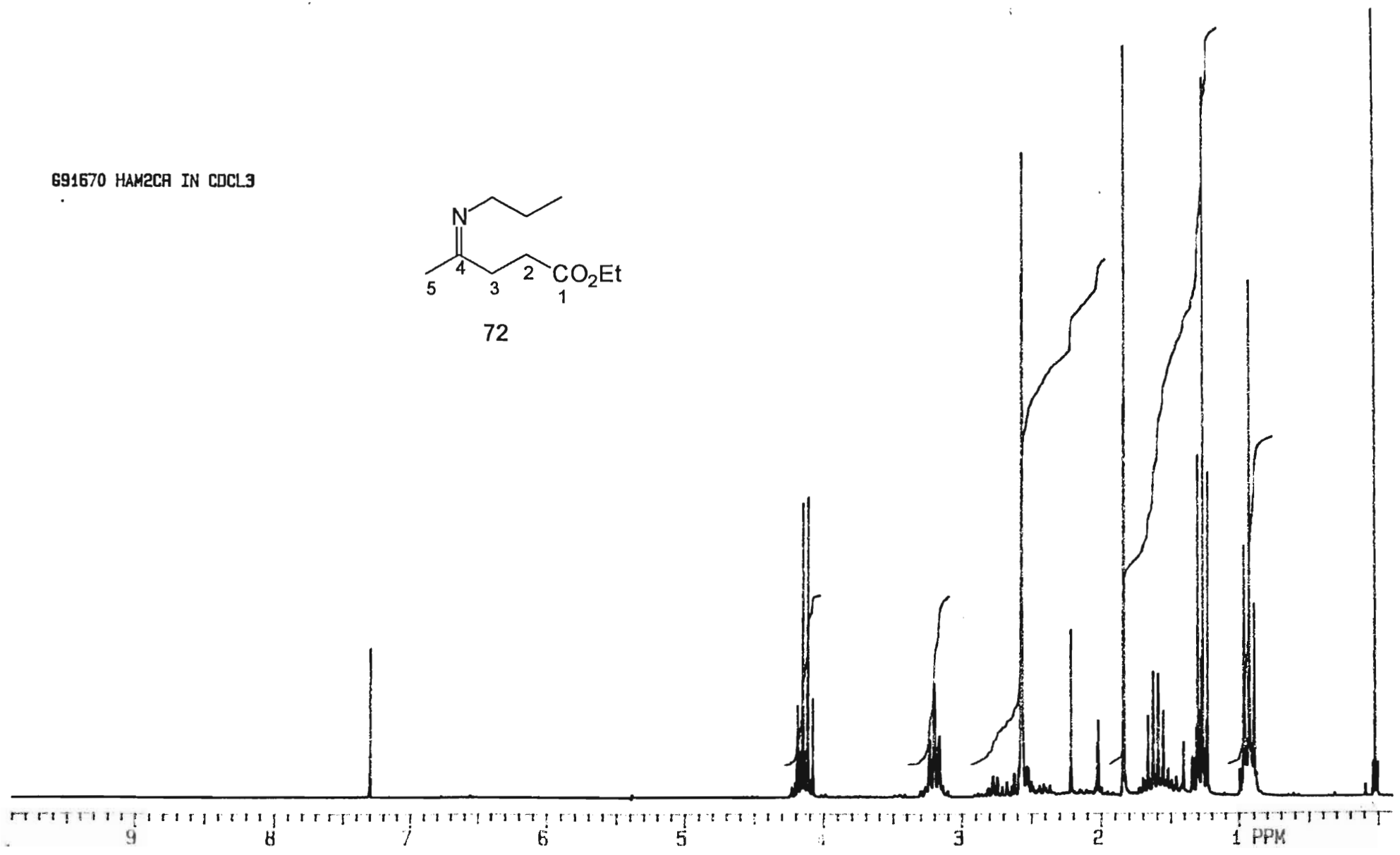

G91571.DAN/P1 IN CDCL3
Hb
3
Ha
Hb
4
5
O
Hb
6
Ha
1
2
O
Hb
8
Ha
Ha
7
Hb
4.10
4.05
4.00 PPM
3.95
7
6
5
4
3
2 PPM

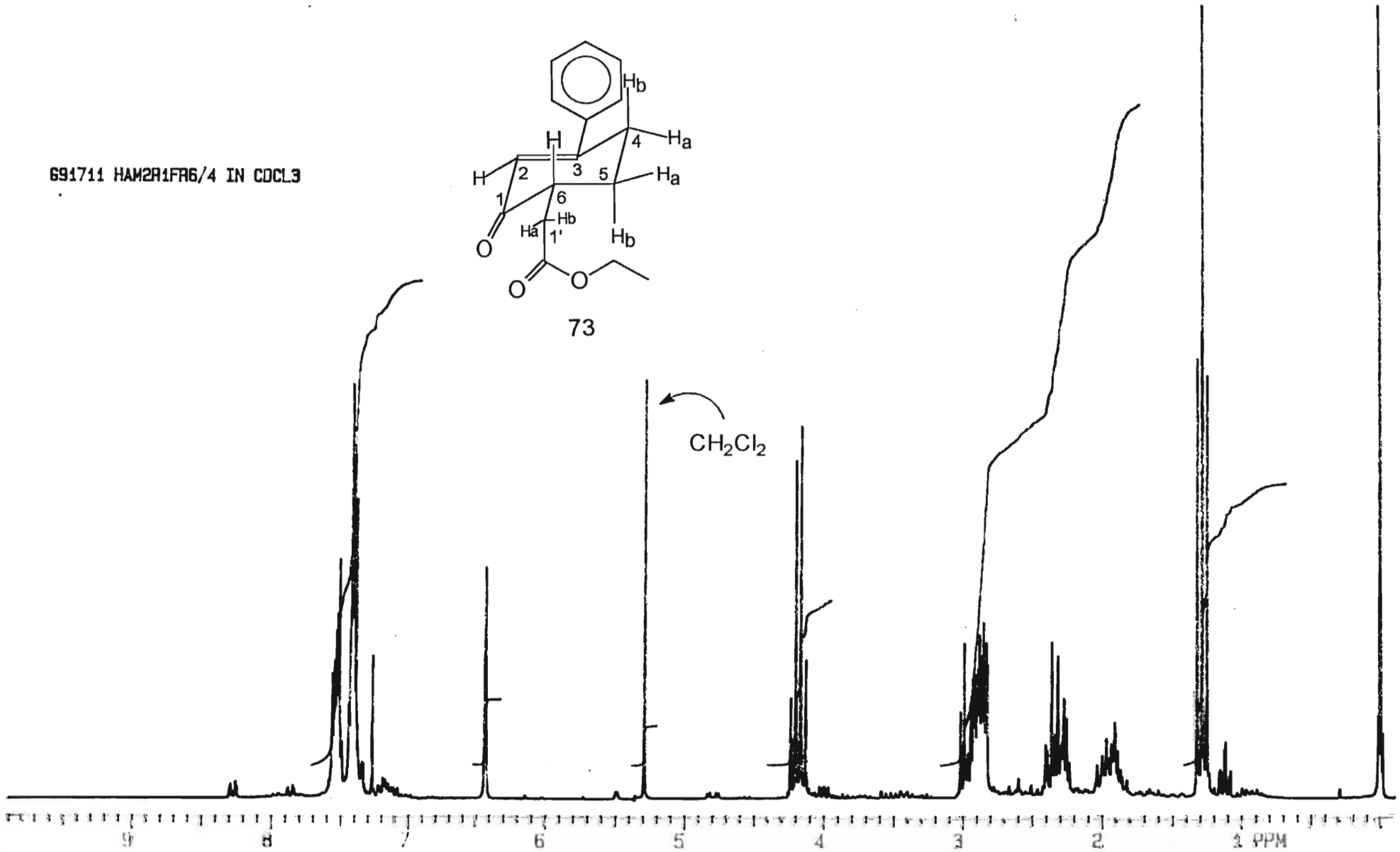
66c


G91570.DAN P2 IN CDCL3
Hb
3
HaPh
O
4
5
O
Hb
Ha
2
1
6
Ha
Hb
8
Ha
Ha
7
Hb
67c
4.20 4.15 4.10 4.05 PPM
3.75 3.70 3.65 PPM
2.60 2.55 2.50 PPM 2.45
8
7
6
5
4
3
2 PPM

691670 HAM2CR IN CDCL3

72



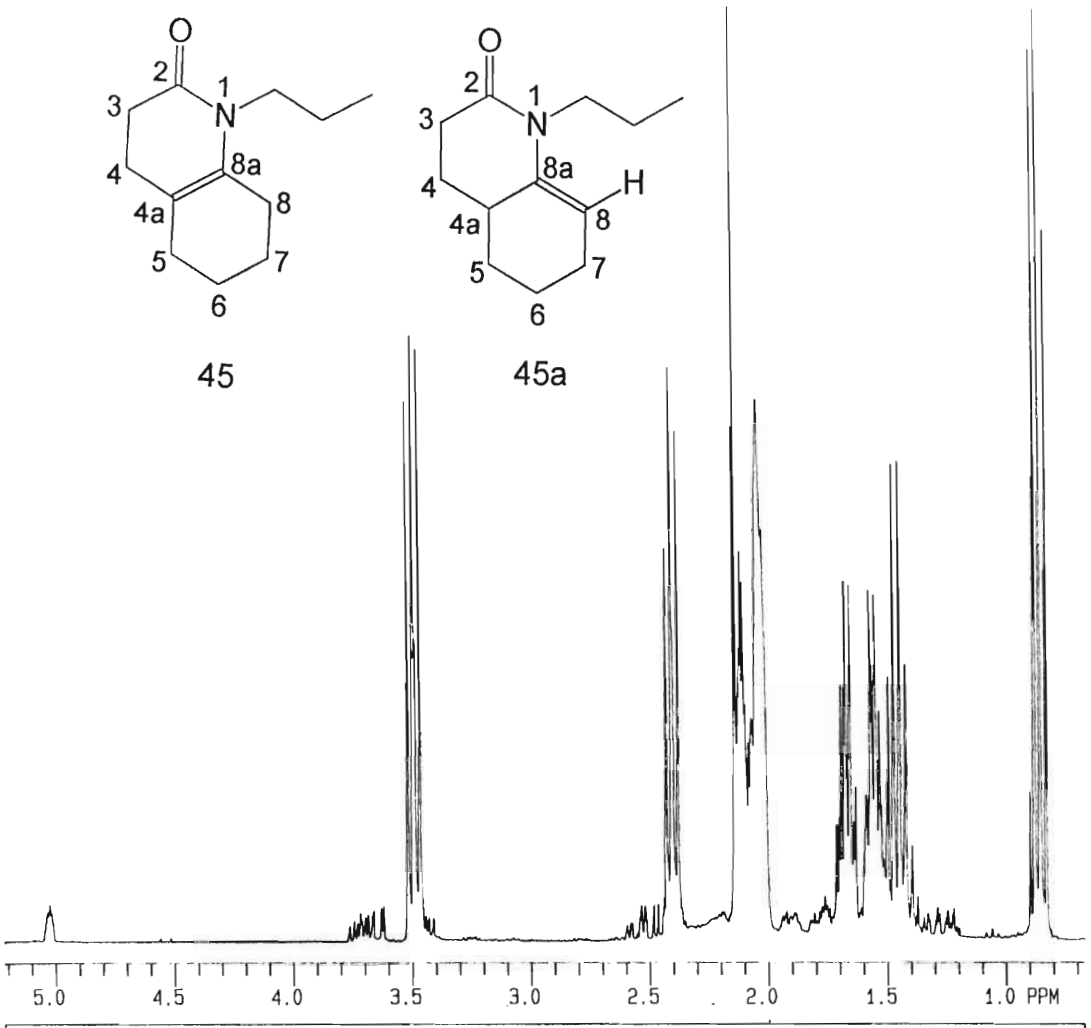

691711 HAM2R1FR6/4 IN CDCL3
Hb
H
4
Ha
H
2
3
5
Ha
1
6
Hb
Ha
1'
Hb
O
O
O
73
CH2Cl2
9
8
7
6
5
4
3
2
1 PPM

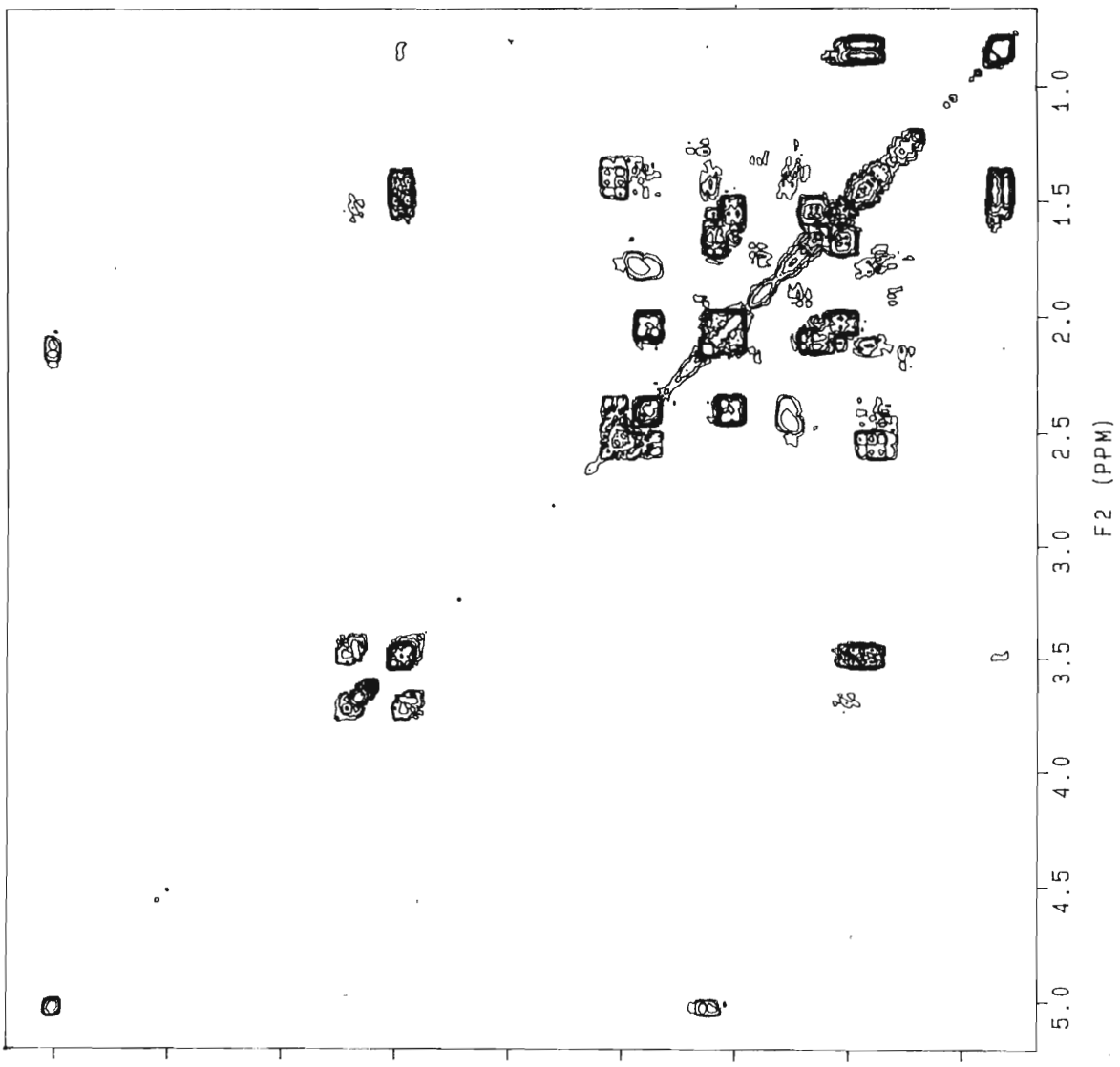
O
2
1
N
3
4
8a
4a
8
5
7
6

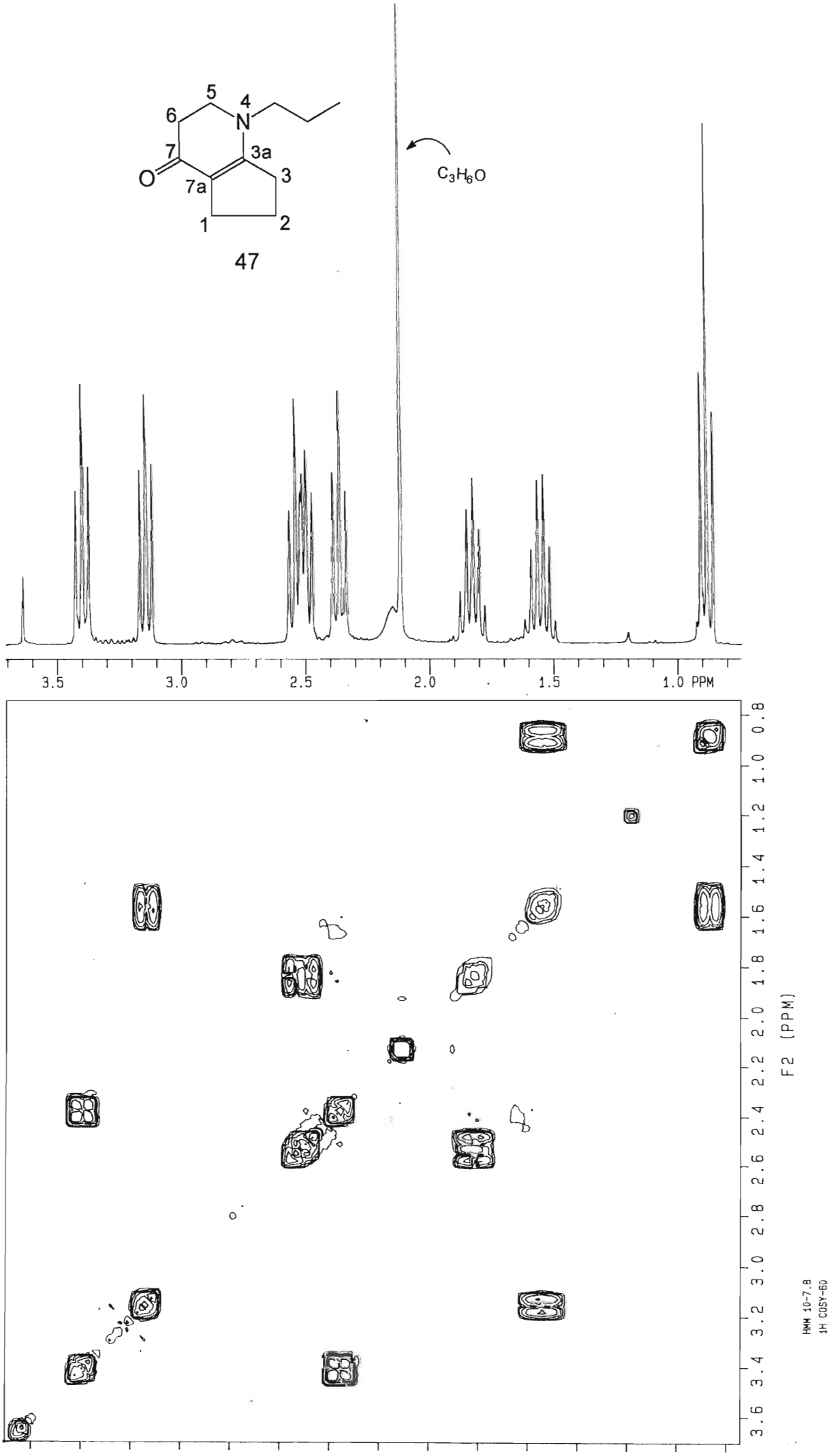
45

O
2
1
N
3
4
8a
H
4a
8
5
7
6

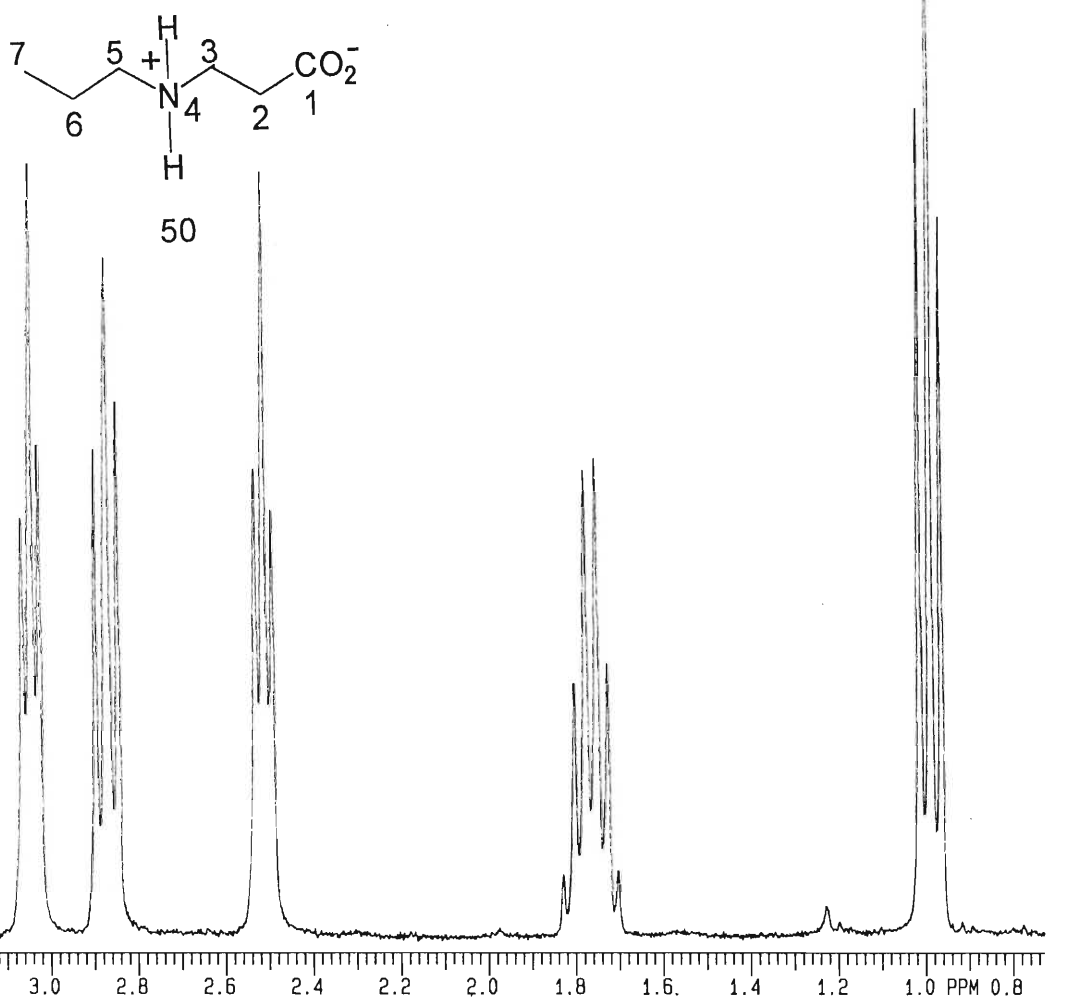
45a

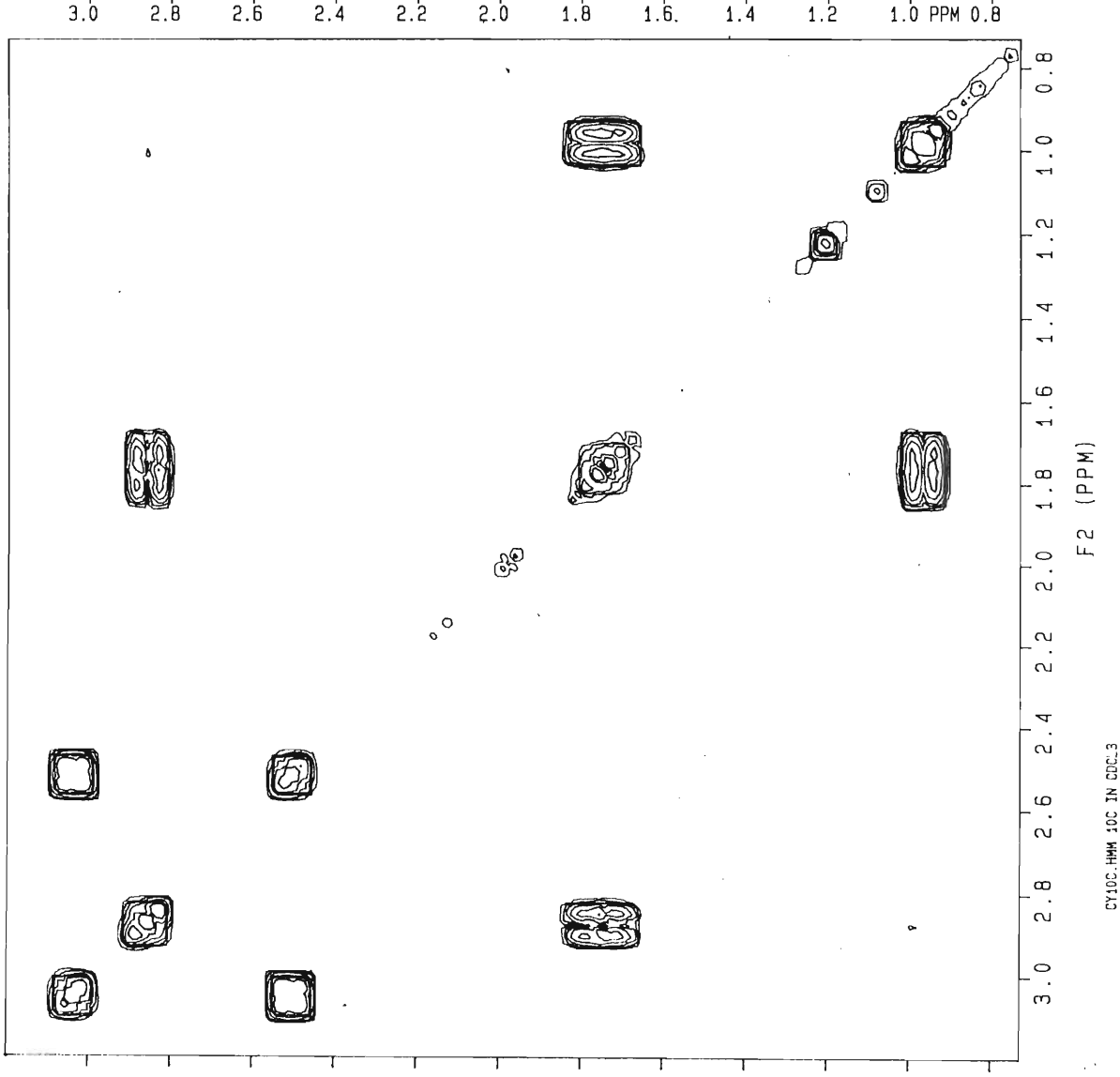

5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0 PPM


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
F2 (PPM)
HMP 14-5.9
1H COSY-60


5
4
6
N
7
3a
O
3
7a
1
2
C_3H_6O
3.5
3.0
2.5
2.0
1.5
1.0 PPM
F2 (PPM)
HMM 10-7.8
1H COSY-60

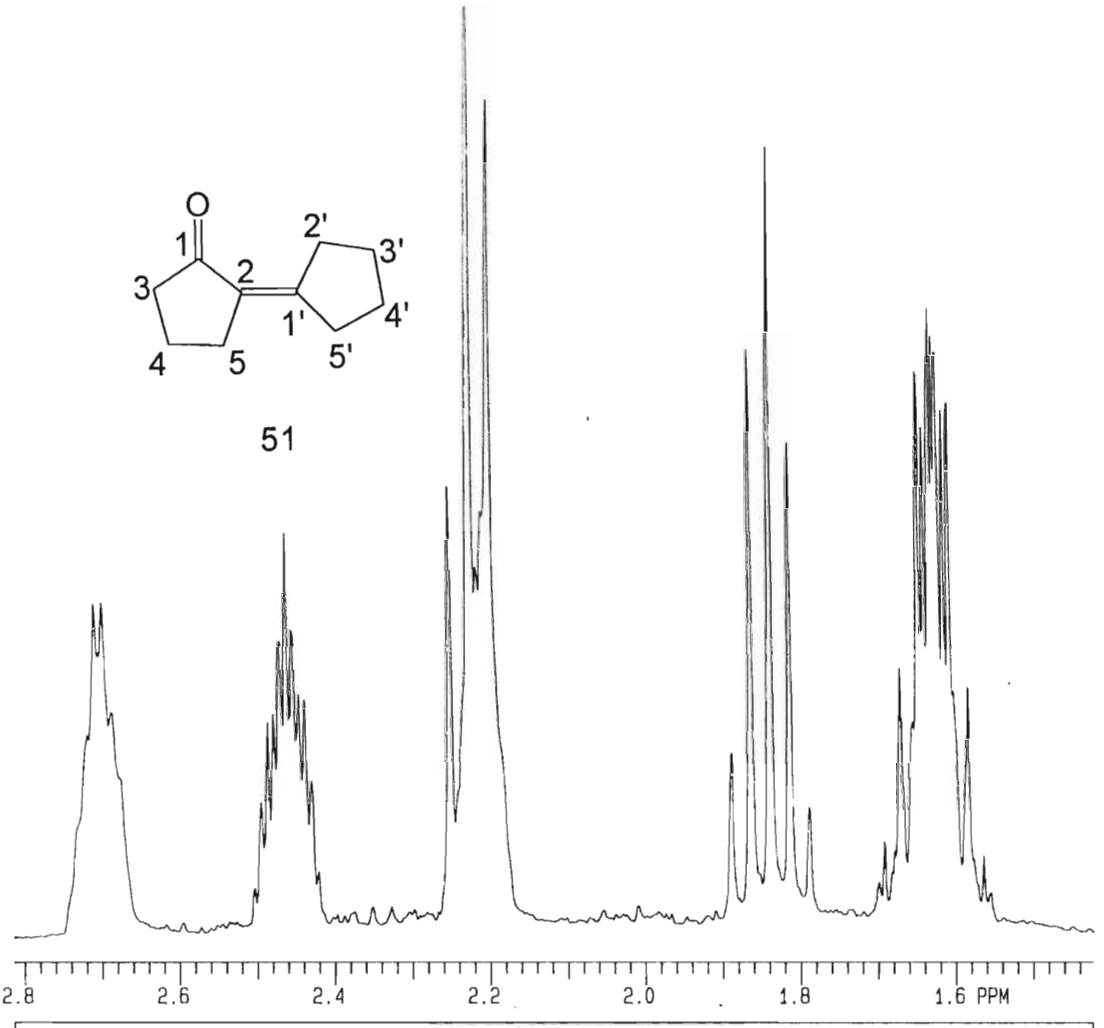
47

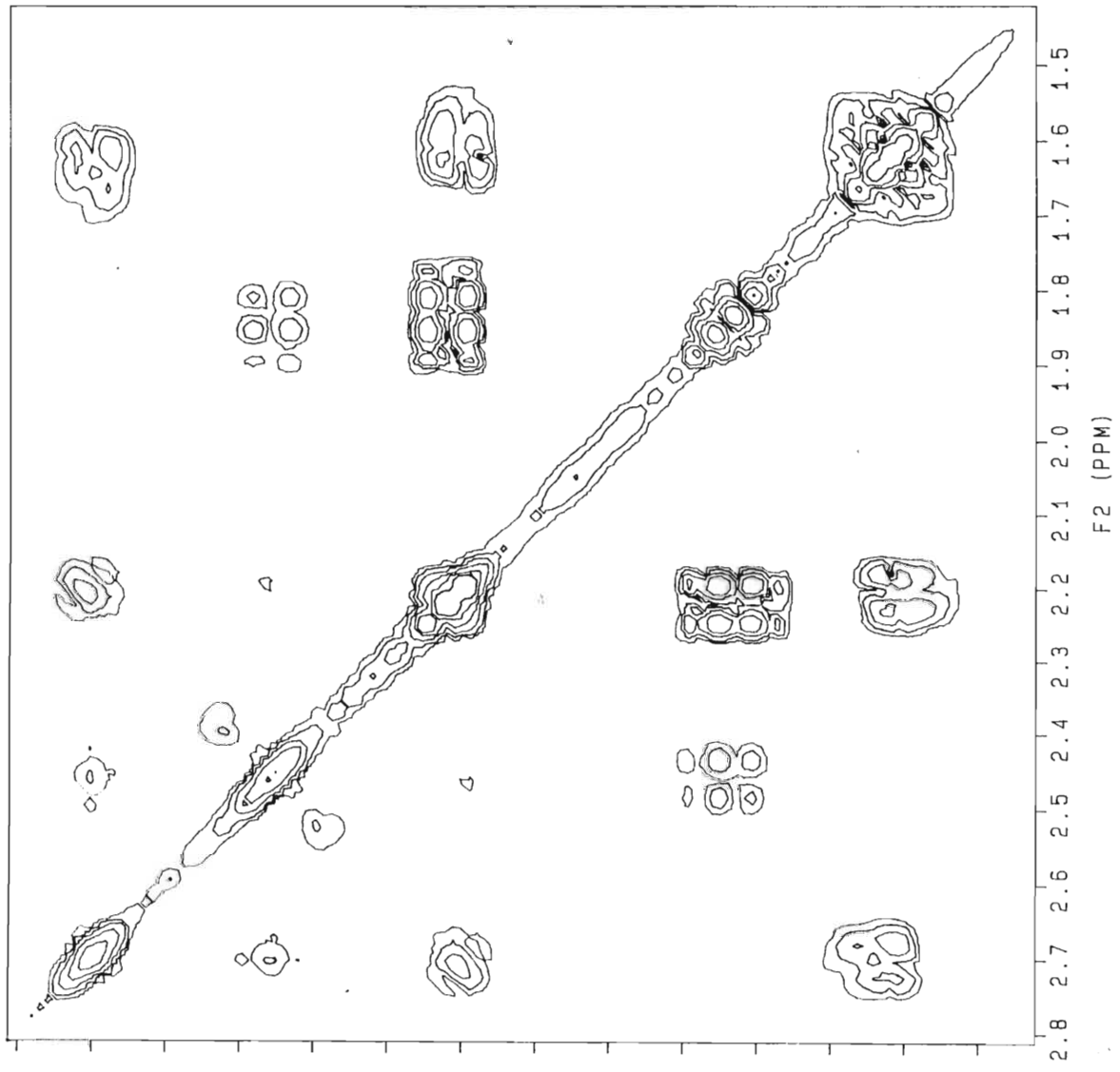

H
7
5
+
3
CO2-
N
4
2
1
6
H
50
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0 PPM 0.8

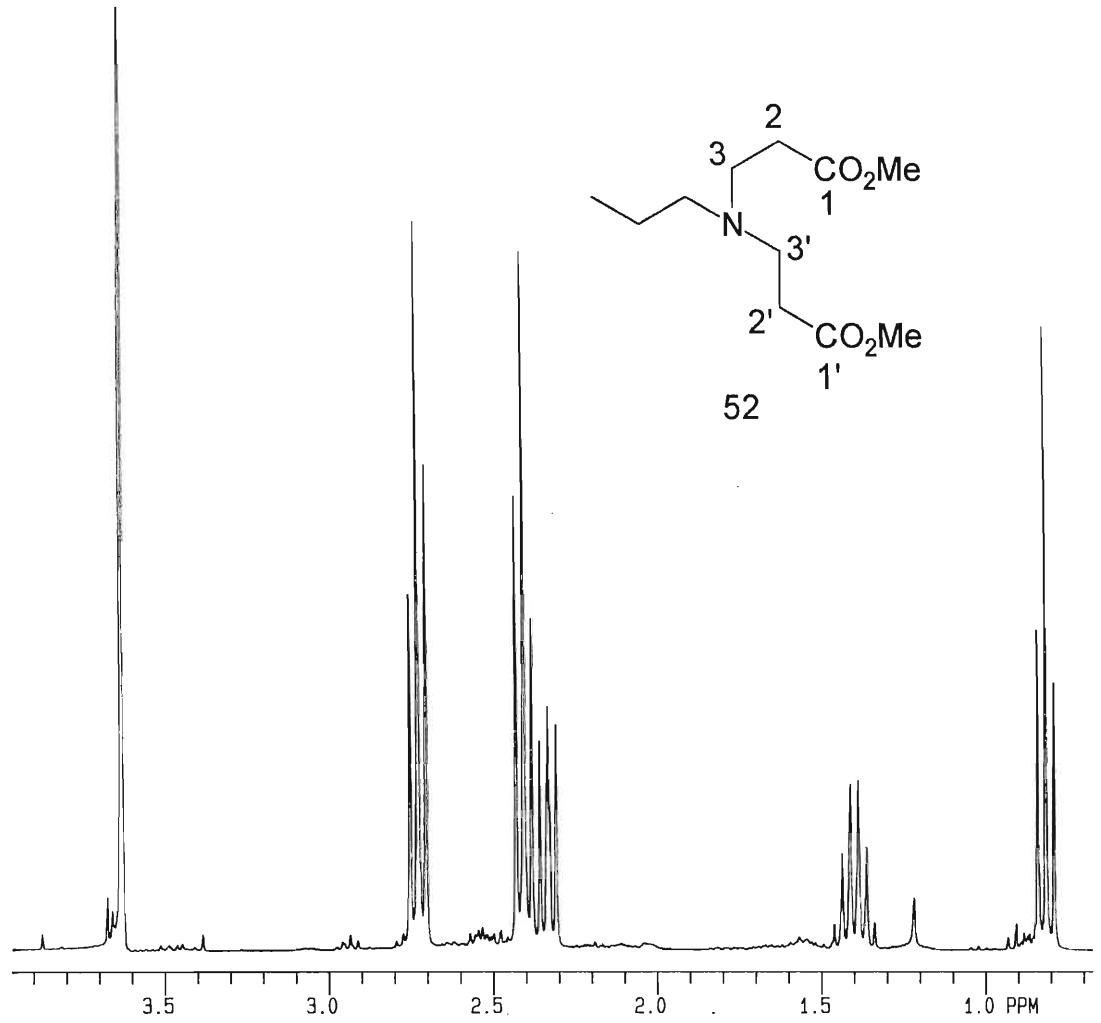

0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
F2 (PPM)
CY10C.HMM 10C IN CDCL3
1H COSY-60

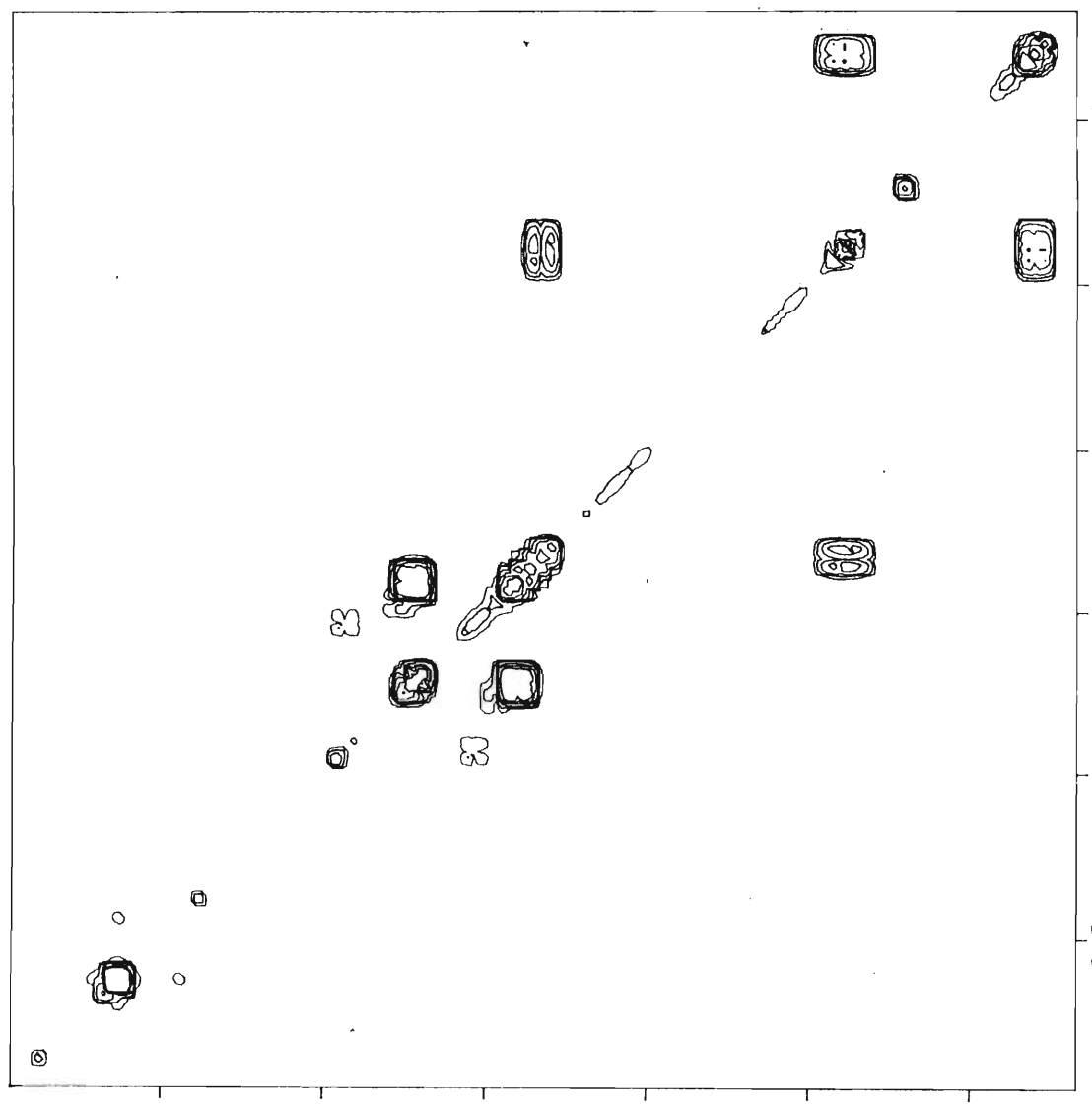
O
1
2
3
4
5
1'
2'
3'
4'
5'

51


2.8
2.6
2.4
2.2
2.0
1.8
1.6 PPM

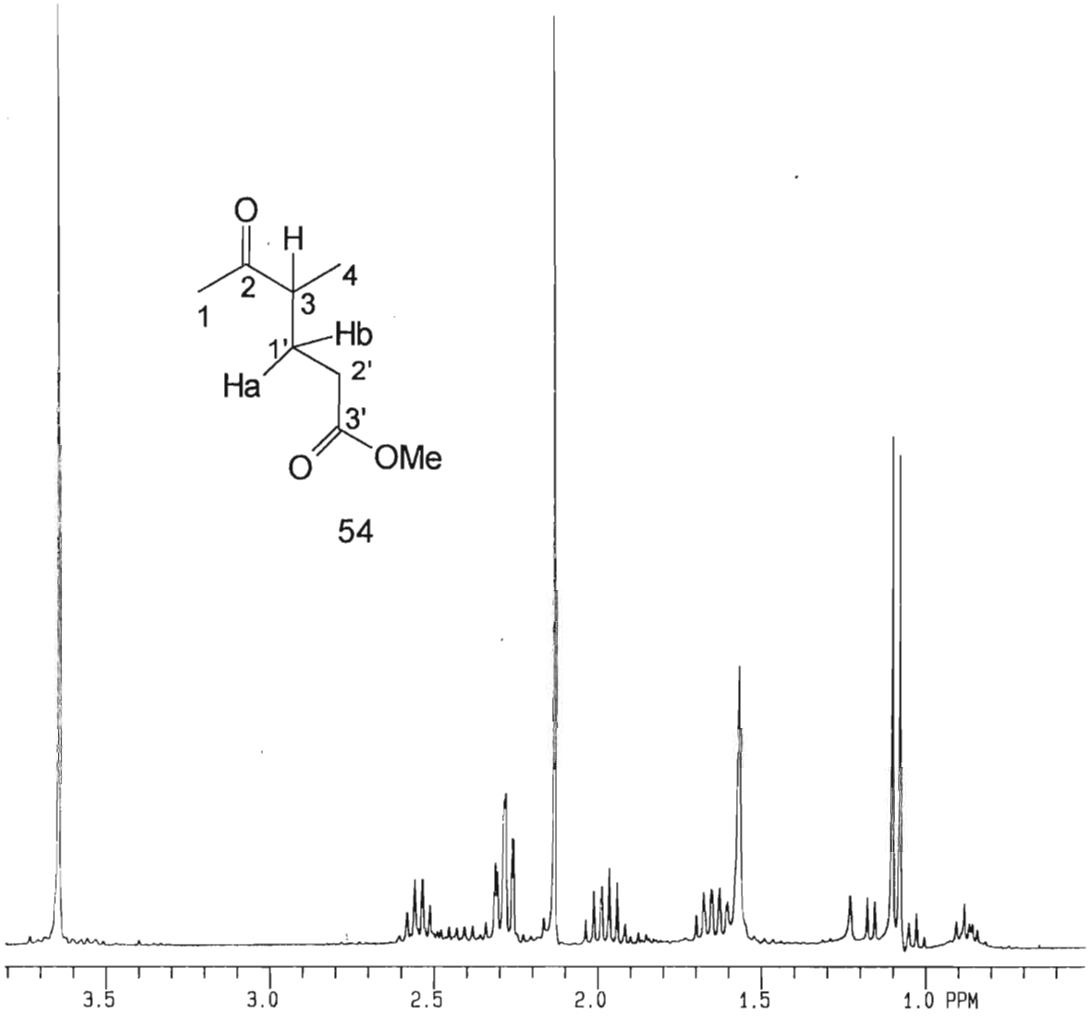

F2 (PPM)
2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5
CYTHN47.HMPYD.4-7 IN CDCL3
1H COSY-60

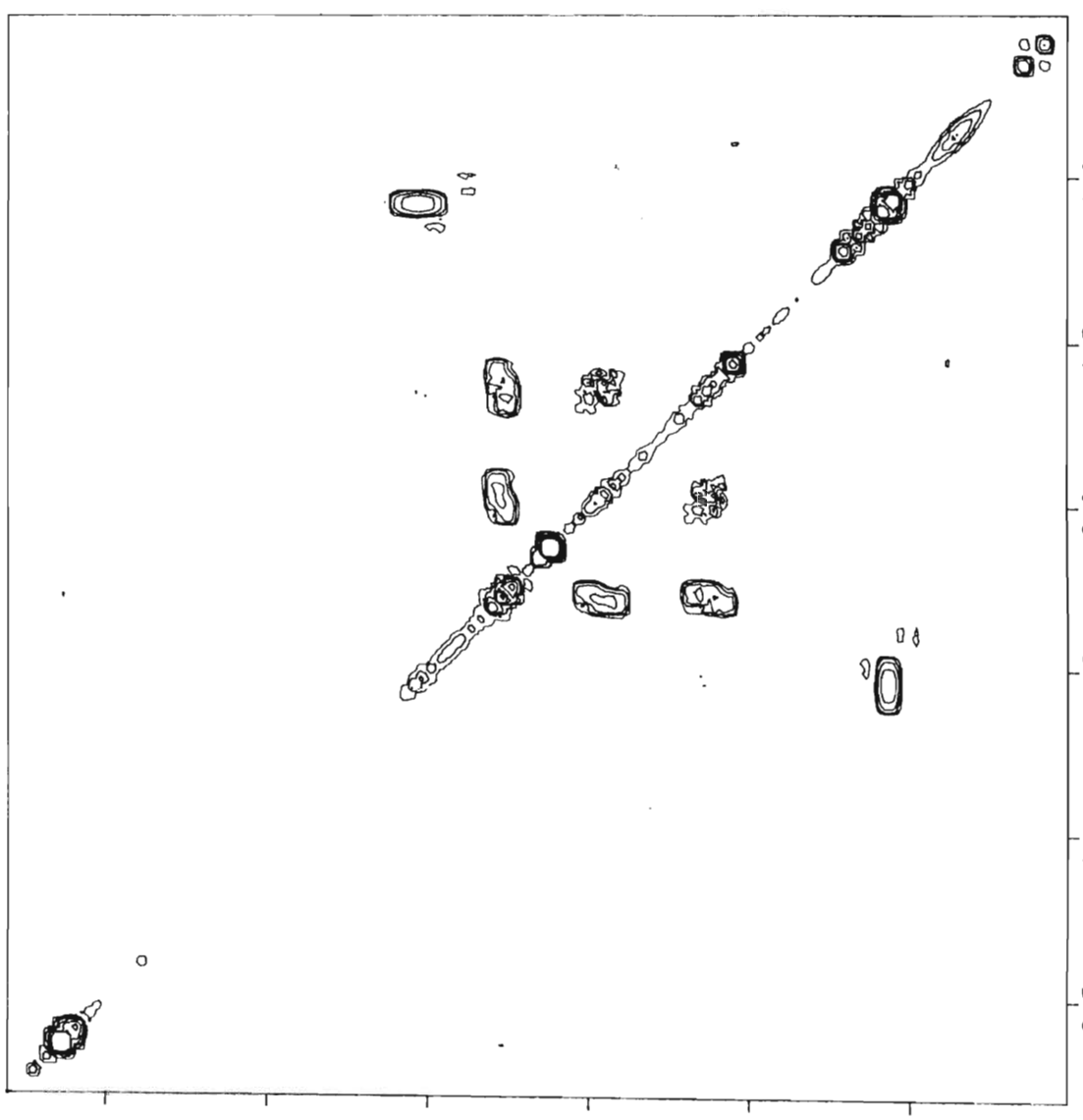

2
3
CO2Me
1
N
3'
2'
CO2Me
1'
52
3.5
3.0
2.5
2.0
1.5
1.0 PPM

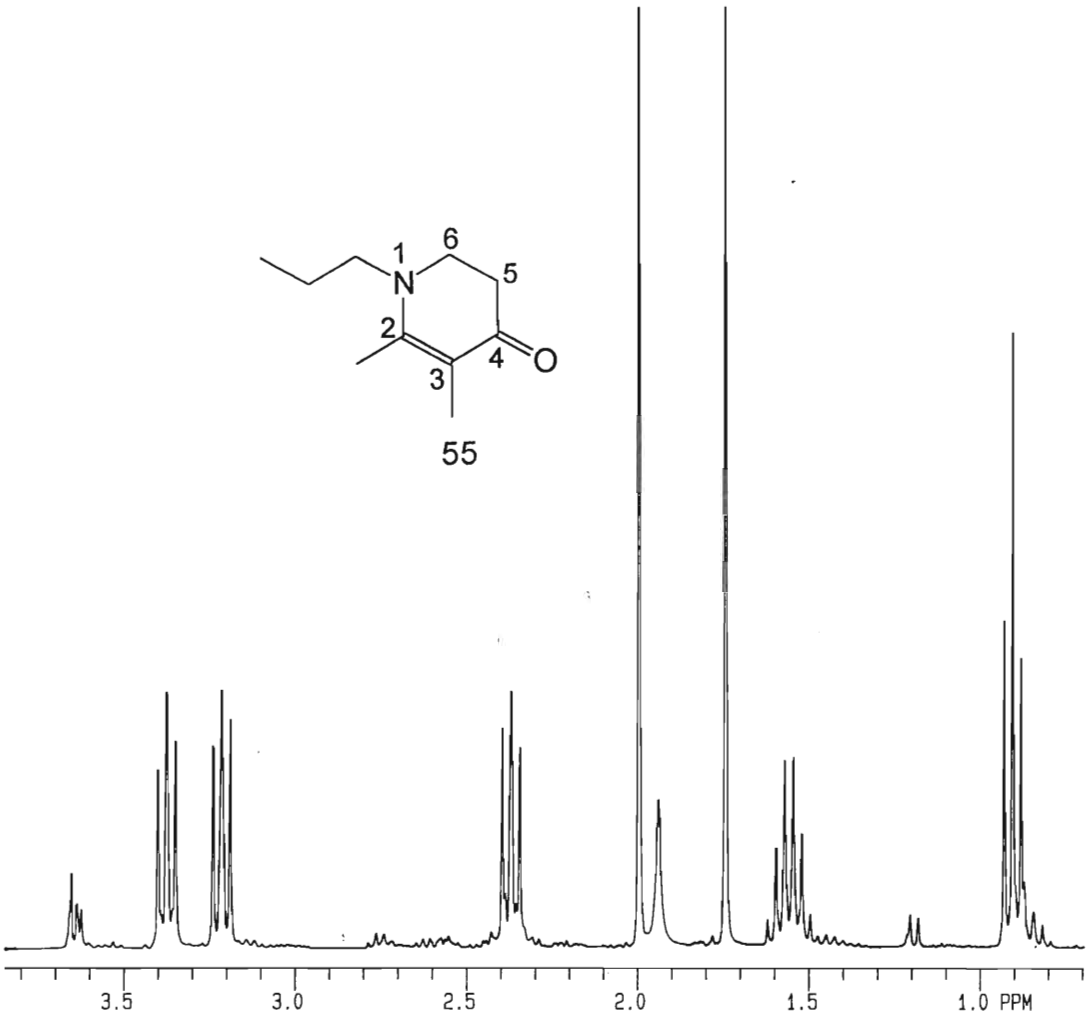

1.0
1.5
2.0
2.5
3.0
3.5
F2 (PPM)
CY755.HWP7-5.5 IN CDCL3
1H COSY-60

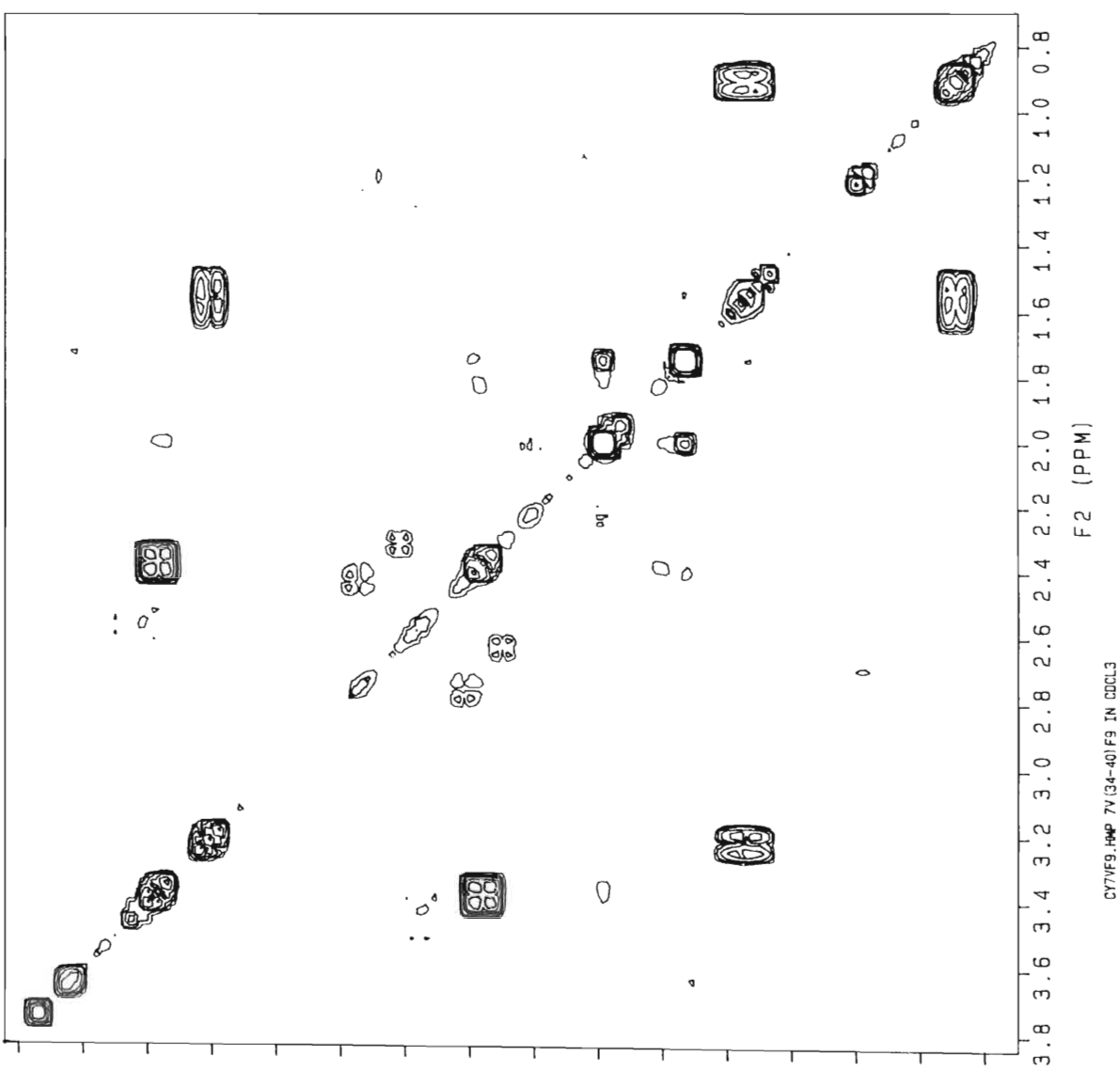
O
H
2
3
4
1
1'
Hb
2'
Ha
3'
O
OMe

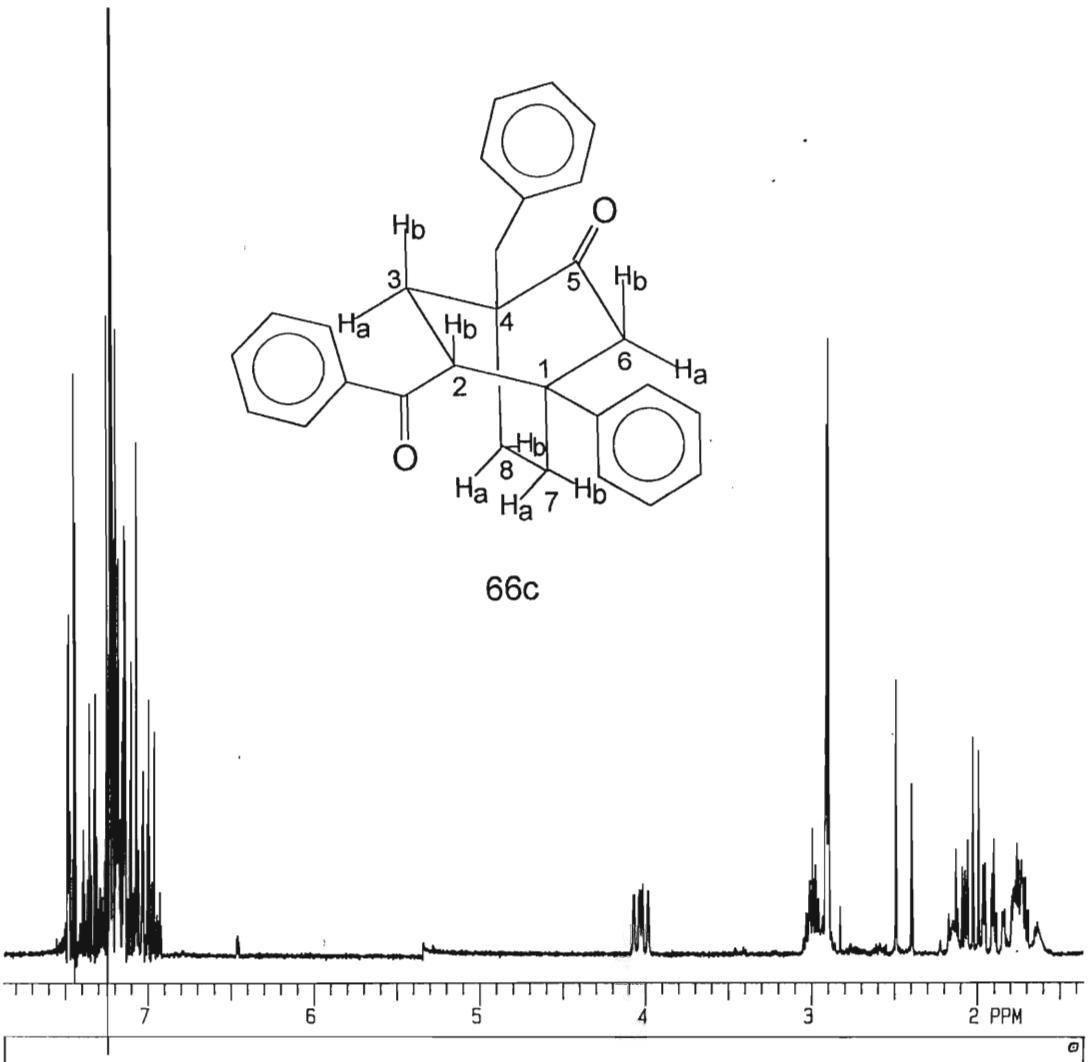
54


3.5
3.0
2.5
2.0
1.5
1.0 PPM

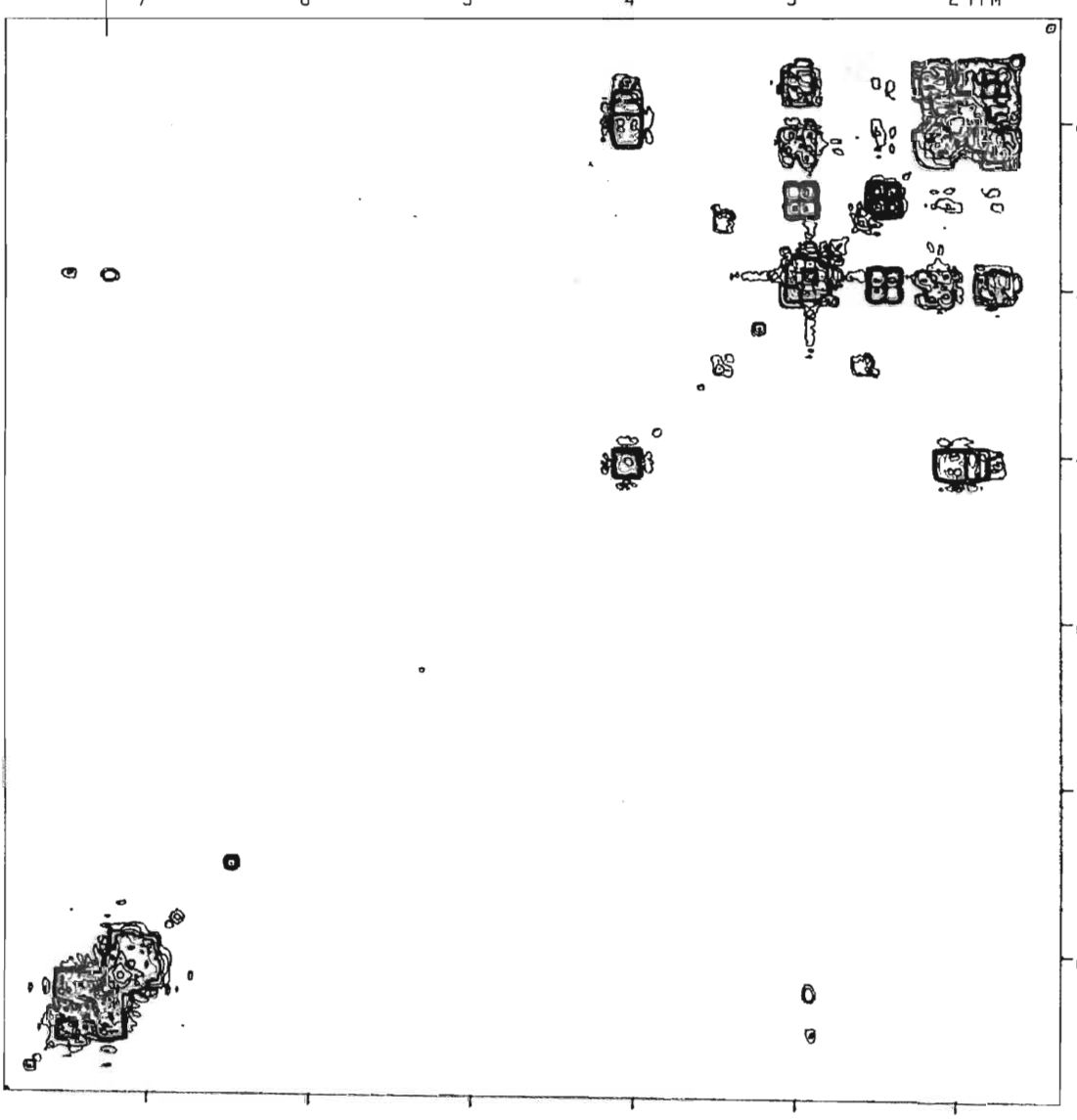

1.0
1.5
2.0
2.5
3.0
3.5
F2 (PPM)
CY728.HAP7 VD-2.8 IN CDCL3
1H COSY-60

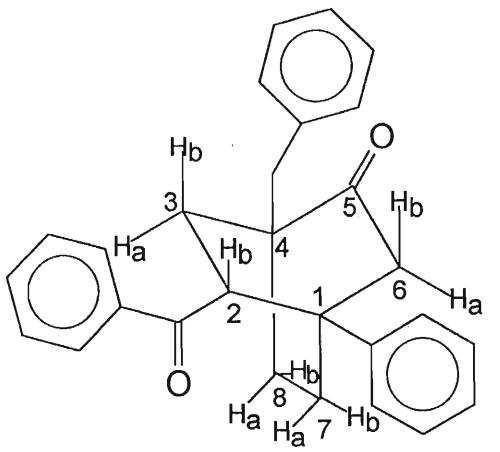

1
6
5
N
2
4
O
3
55
3.5
3.0
2.5
2.0
1.5
1.0 PPM


3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
F2 (PPM)
CY7VF9.HAP 7V(34-40)F9 IN CDCL3
1H COSY-60

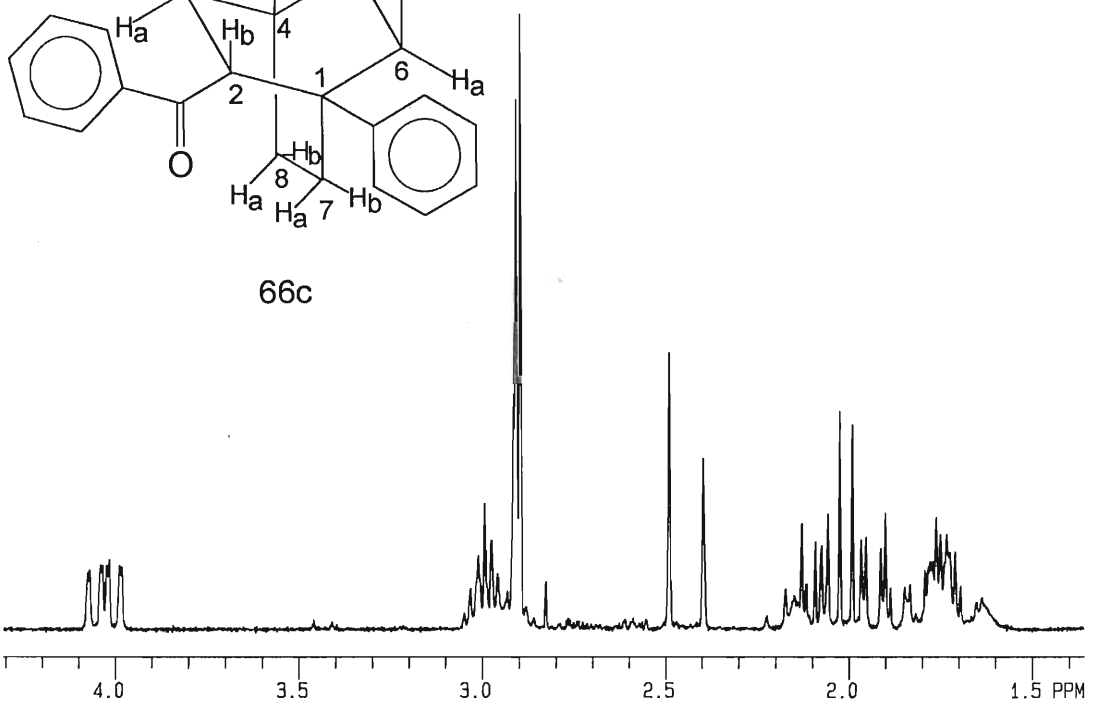

Hb
O
3
5
Hb
Ha
Hb
4
1
6
Ha
2
O
Hb
8
Ha
Ha
7
Hb
7
6
5
4
3
2 PPM

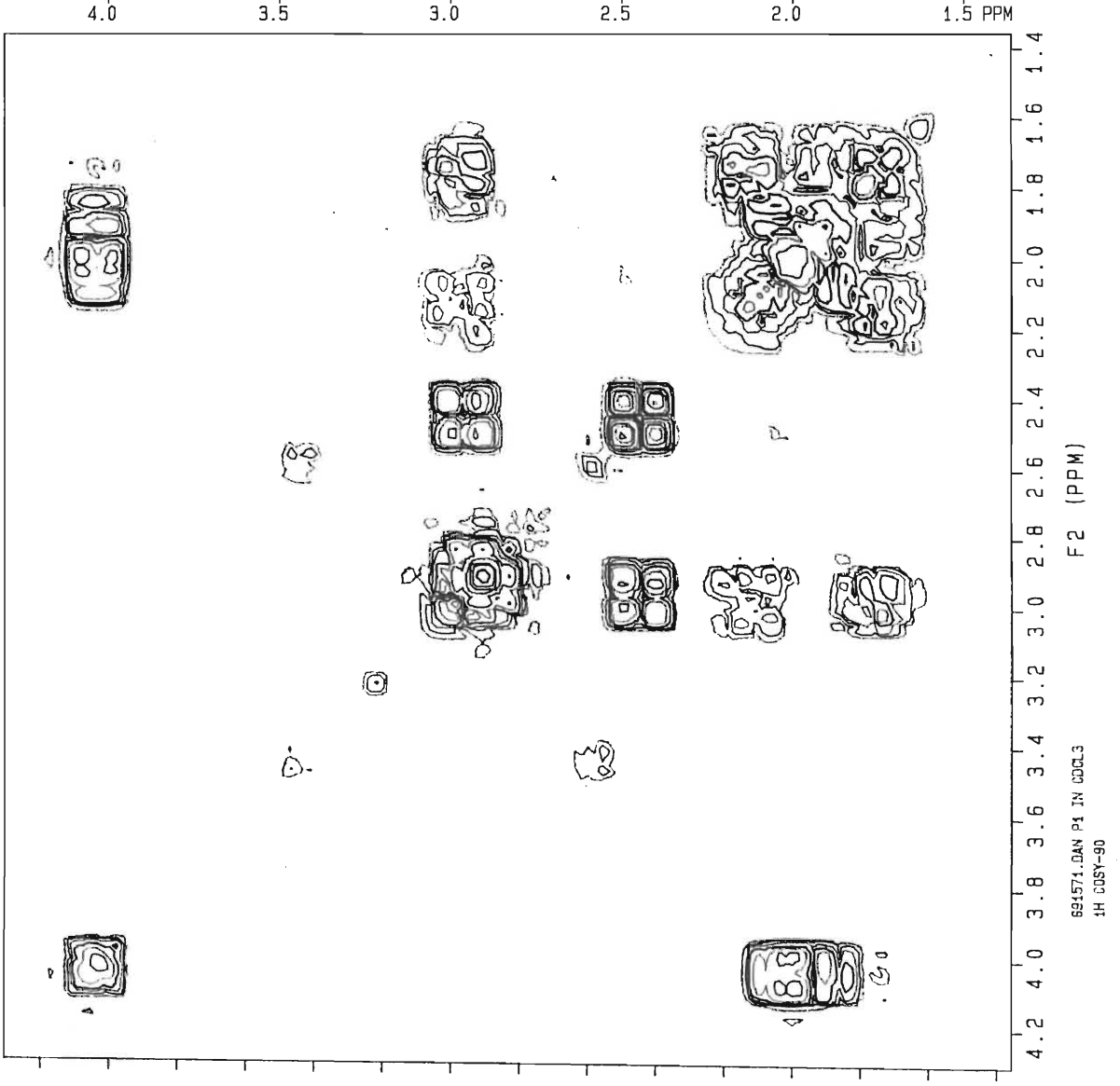
66c

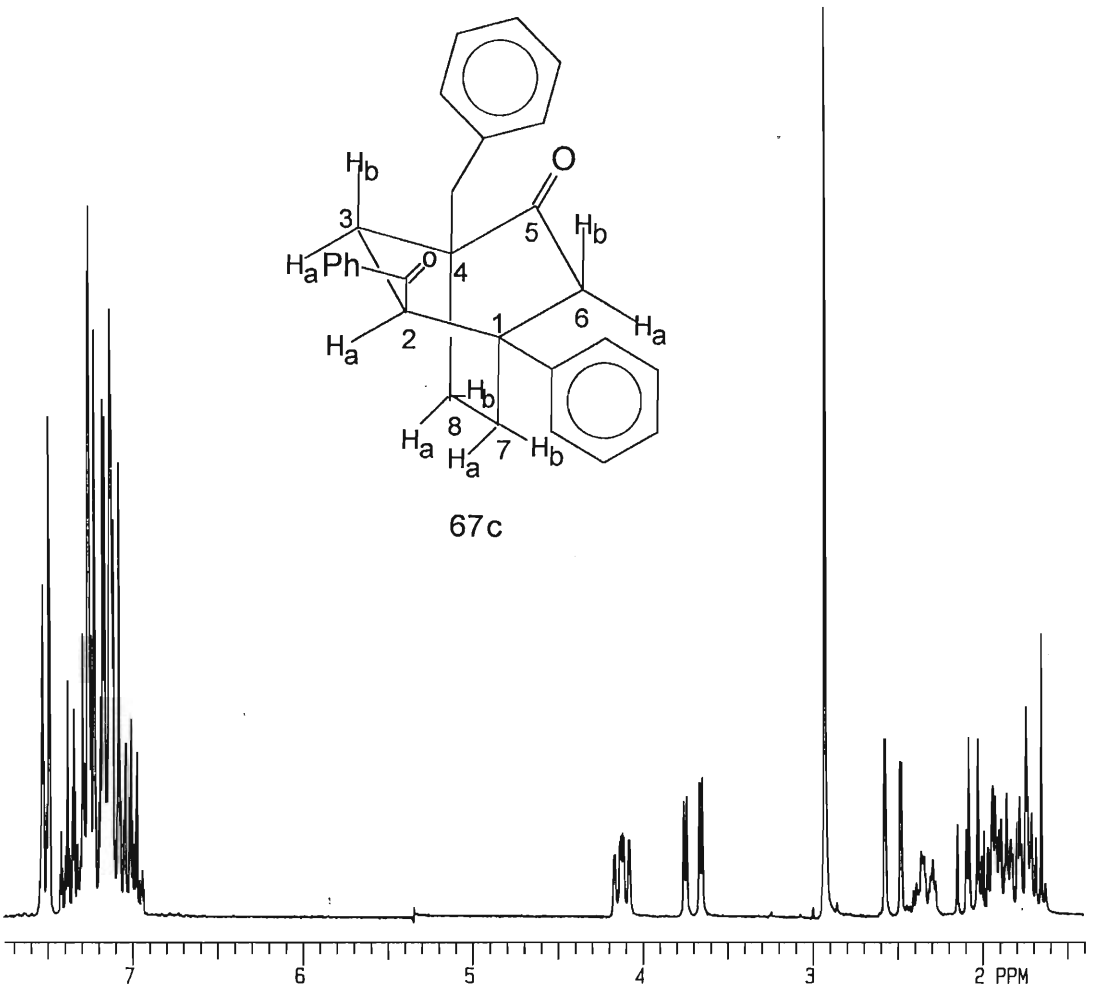

F2 (PPM)
691571.DAN P1 IN CDCL3
1H COSY-90


Hb
3
Ha
Hb
4
5
O
Hb
6
Ha
1
2
O
Hb
8
Ha
Ha
7
Hb

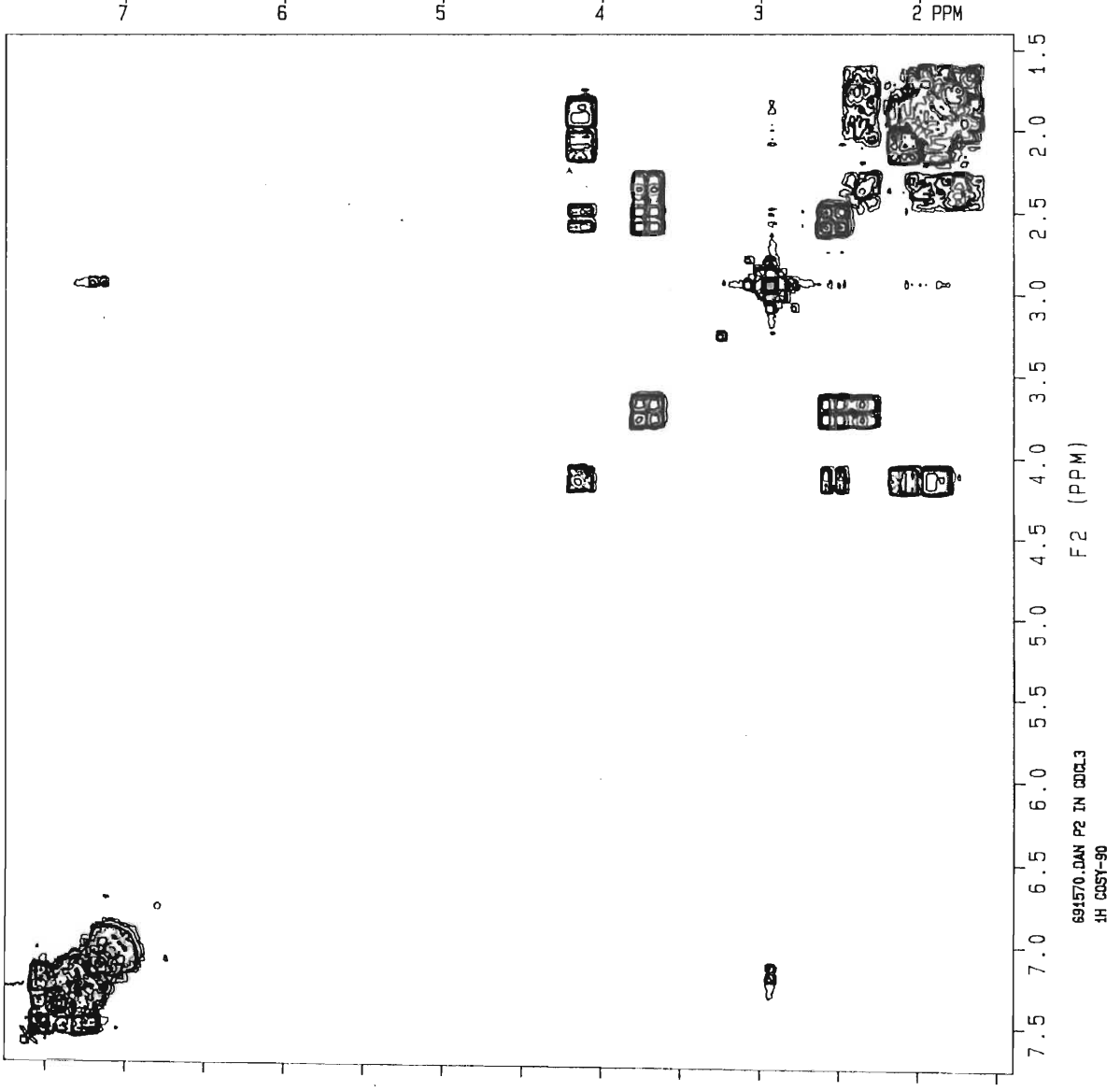
66c


4.0
3.5
3.0
2.5
2.0
1.5 PPM


4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
F2 (PPM)
691571.DAN P1 IN CDCL3
1H COSY-90

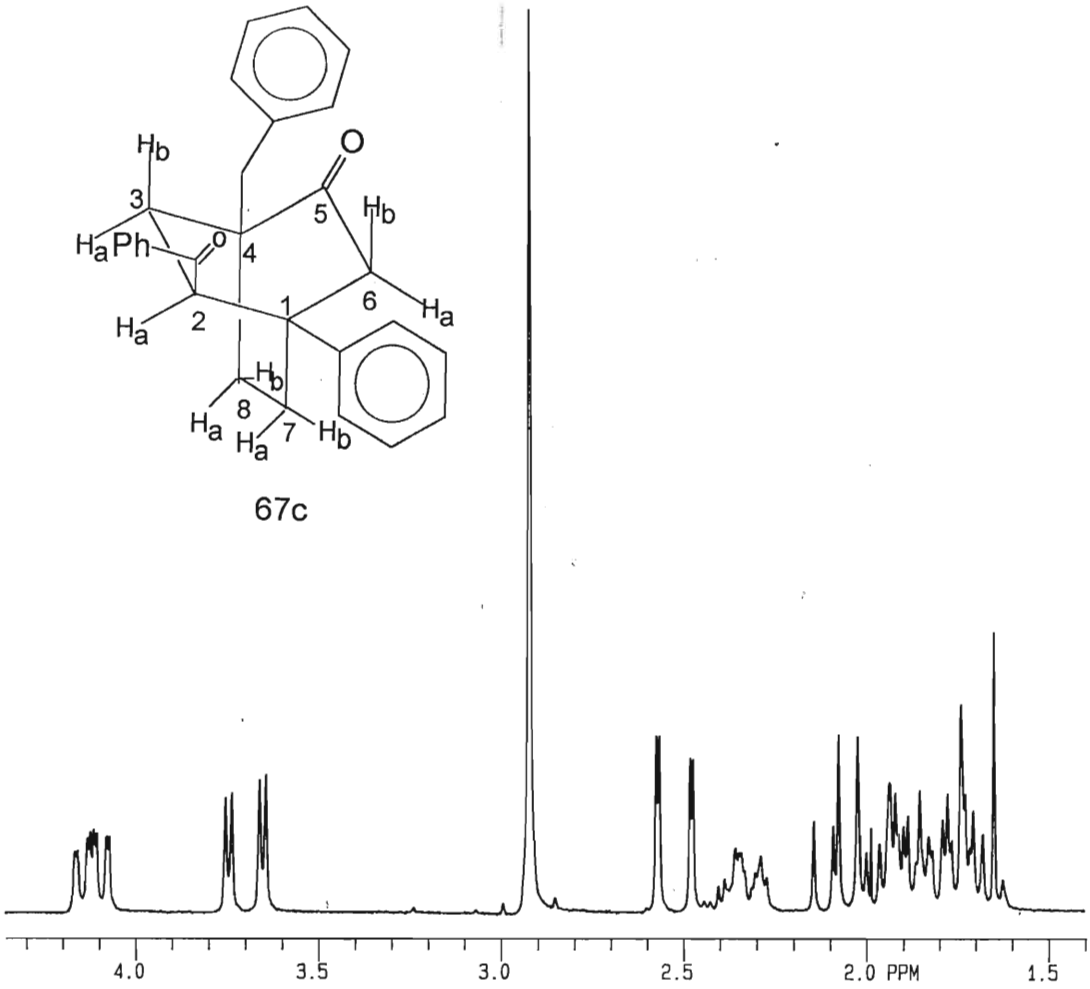

Hb
O
3
5
Hb
HaPh
O
4
6
Ha
Ha
2
1
Hb
8
Ha
Ha
7
Hb
7
6
5
4
3
2 PPM

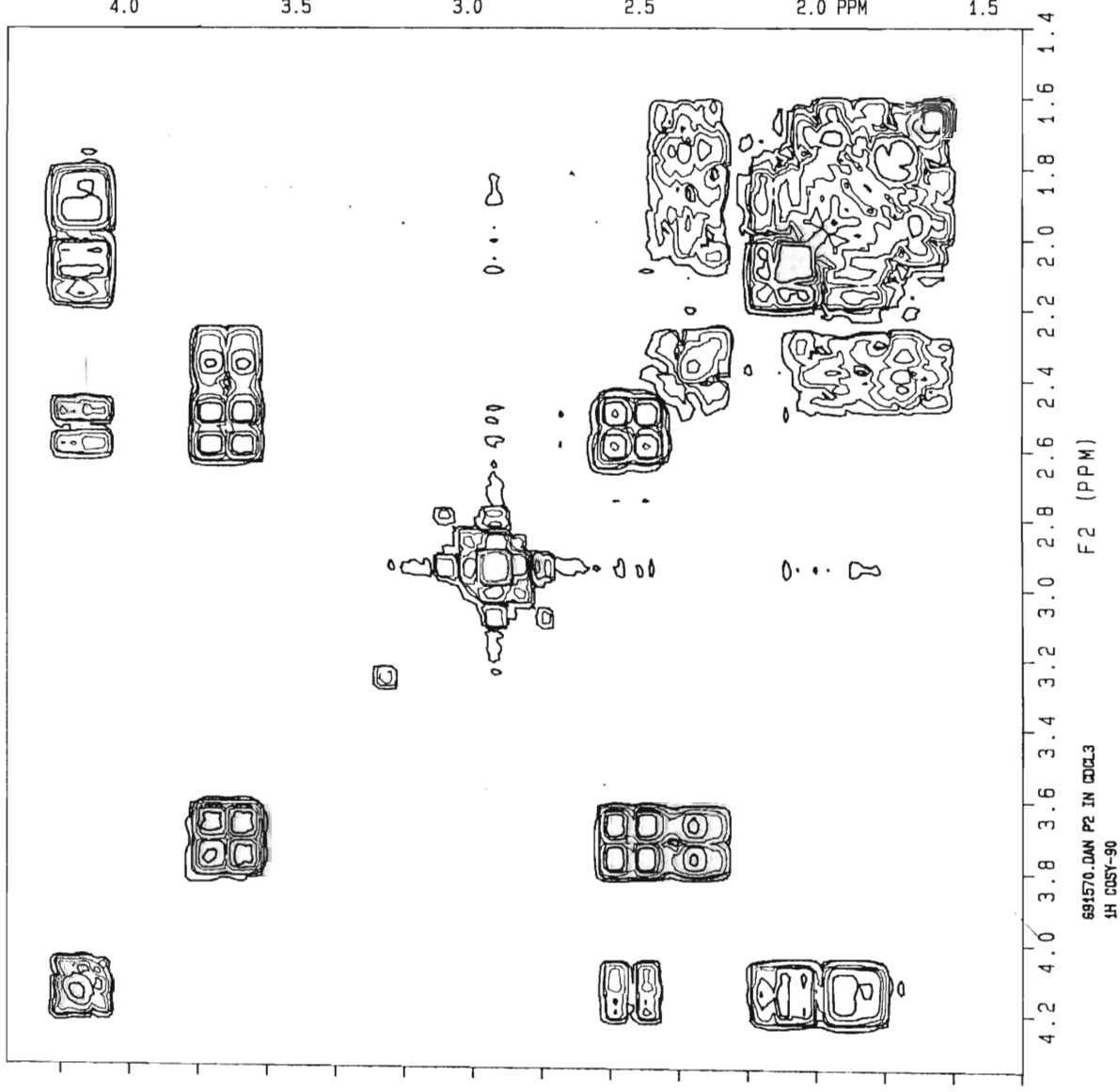
67c

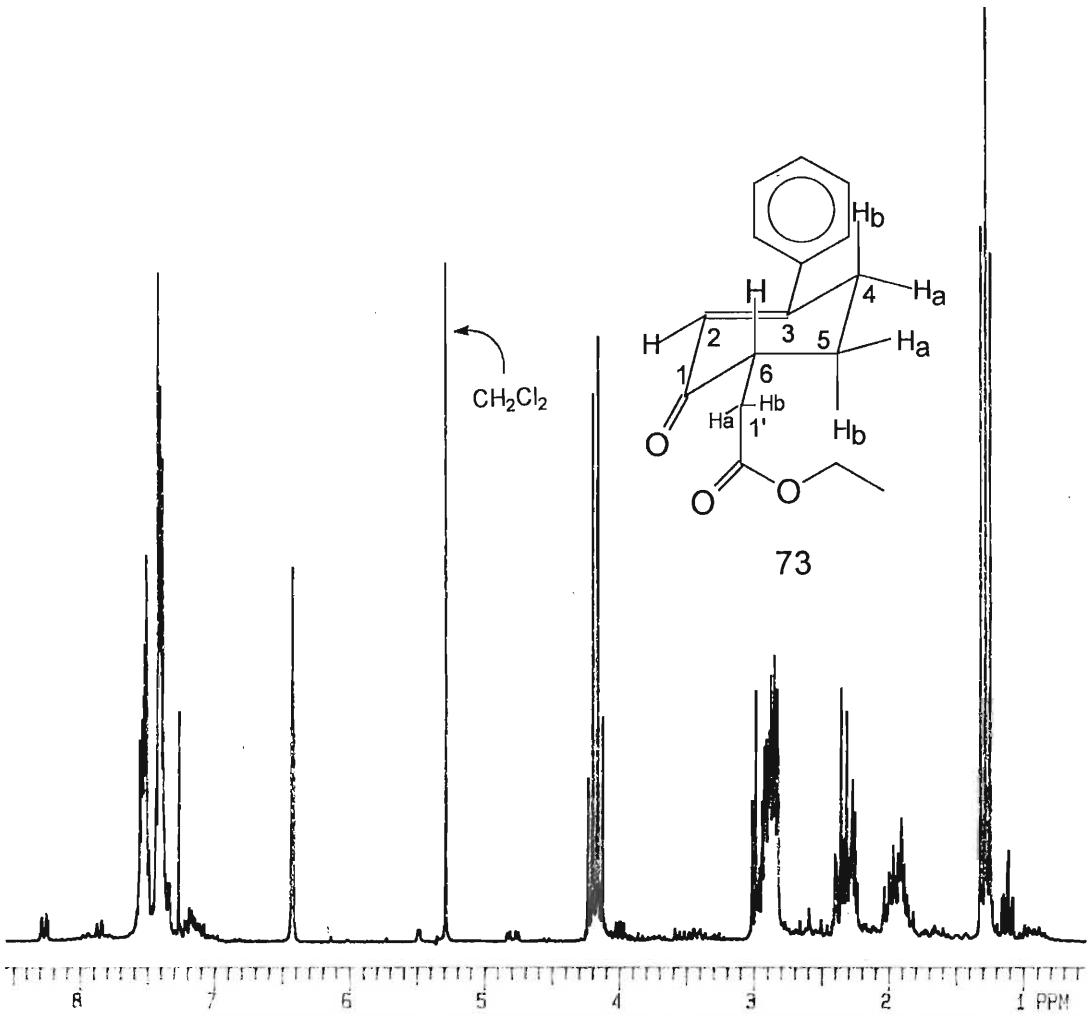

1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
F2 (PPM)
691570.DAN P2 IN CDCL3
1H COSY-90

Hb
O
3
5
Hb
HaPh
o
4
1
6
Ha
2
Ha
Hb
8
7
Ha
Ha
Hb

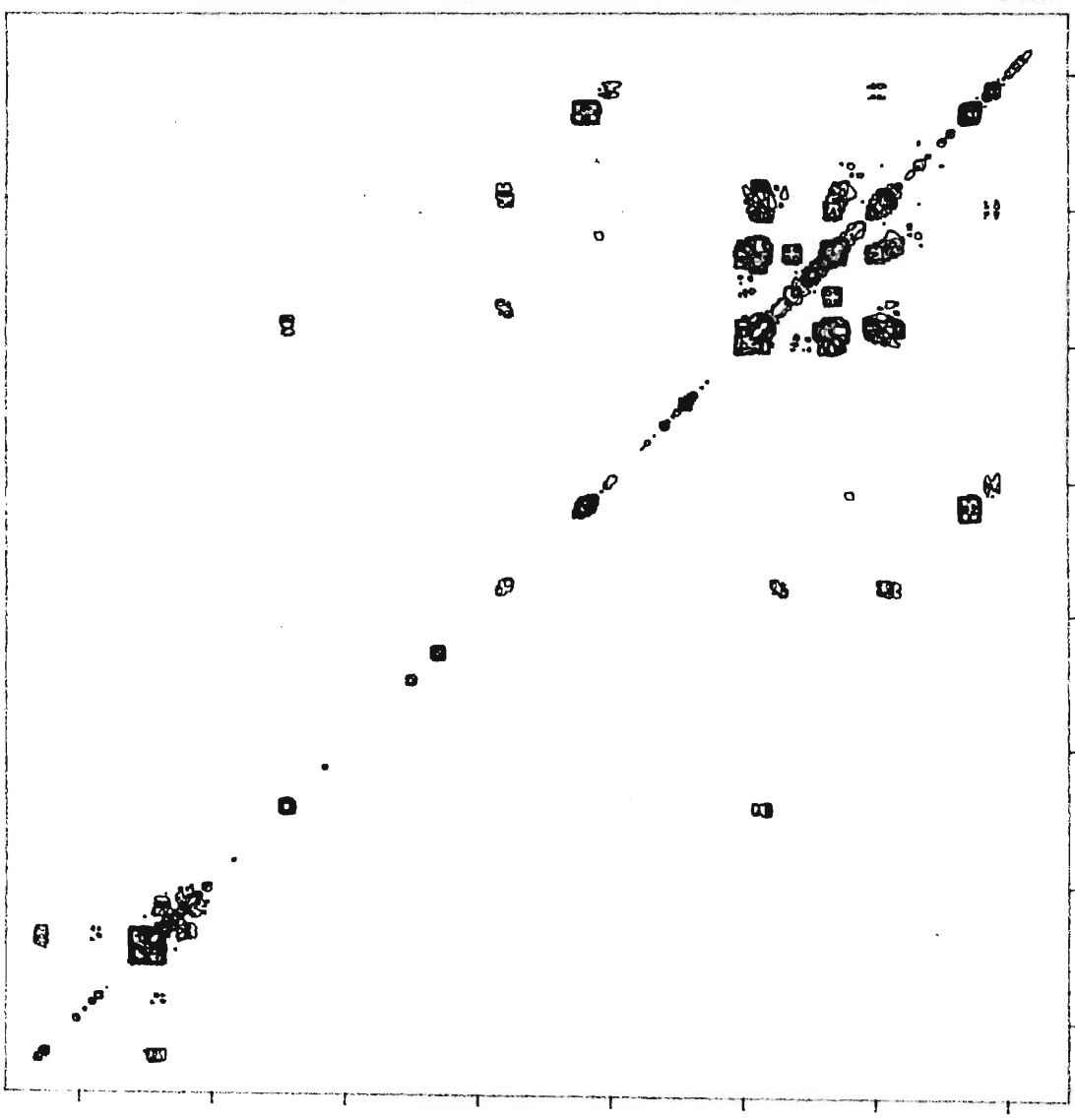
67c


4.0
3.5
3.0
2.5
2.0 PPM
1.5

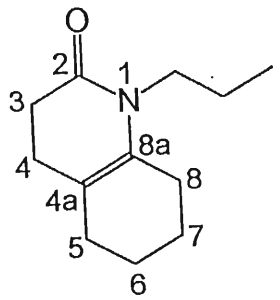

4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
F2 (PPM)
891570.DAN P2 IN CDCL3
1H COSY-90


Hb
H
4
Ha
H
2
3
5
Ha
1
6
Ha
Hb
1'
Hb
O
O
O
CH_2Cl_2
8
7
6
5
4
3
2
1 PPM

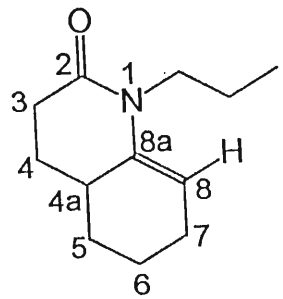
73


F2 (PPM)
891711 HAMZAFRB/4 IN CDCL3
1H COSY 60

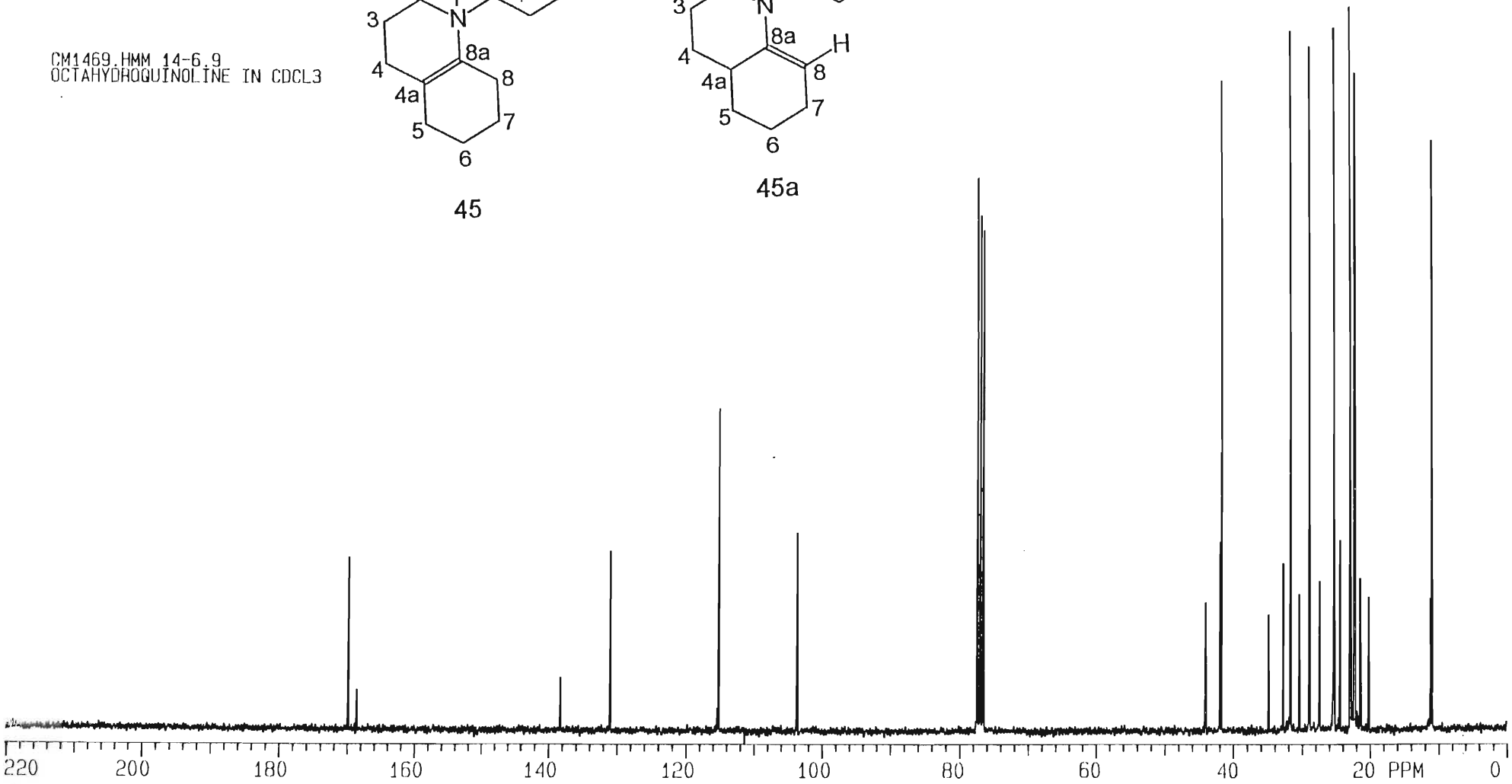
CM1469.HMM 14-6.9
OCTAHYDROQUINOLINE IN CDCL3



45

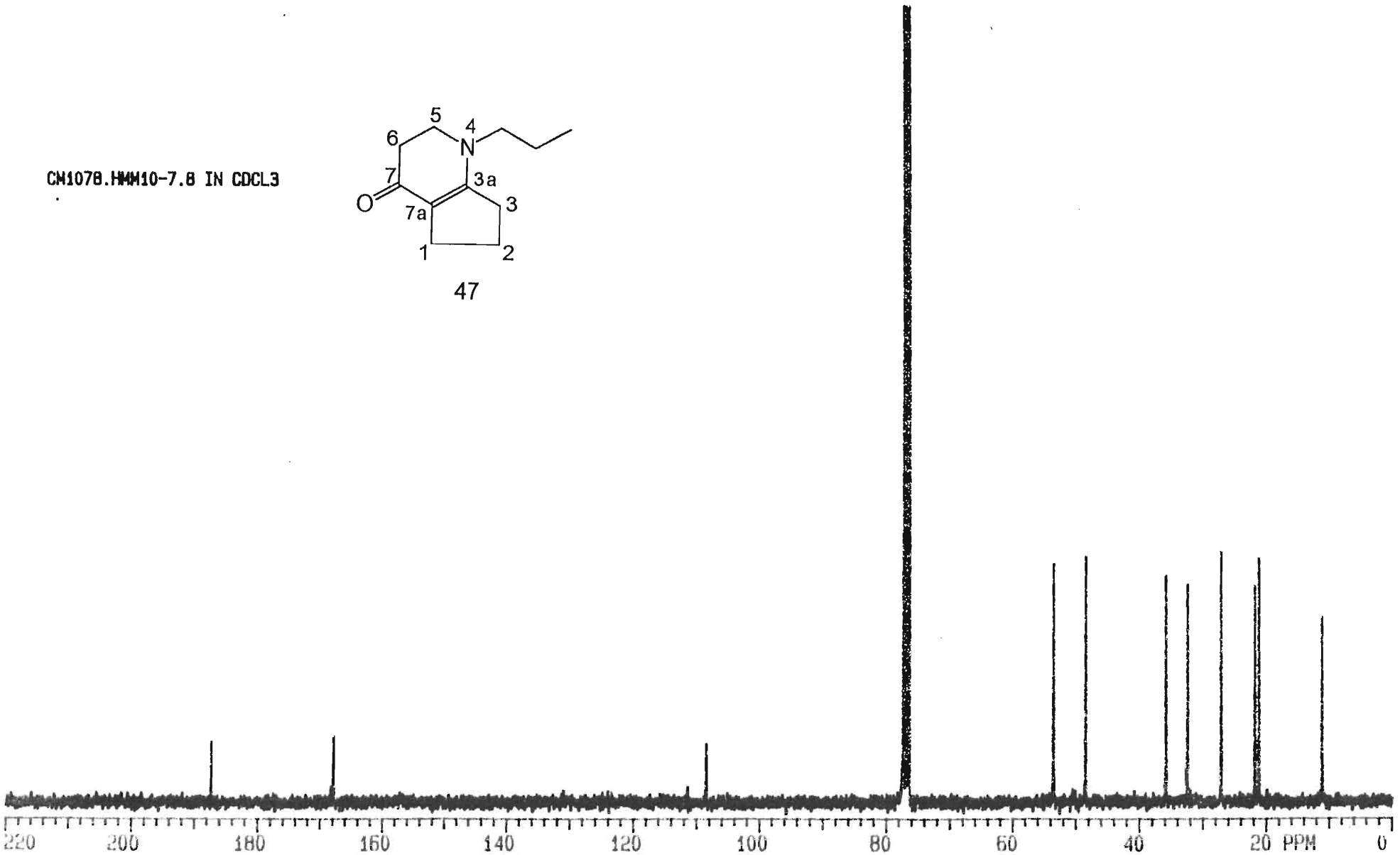


45a



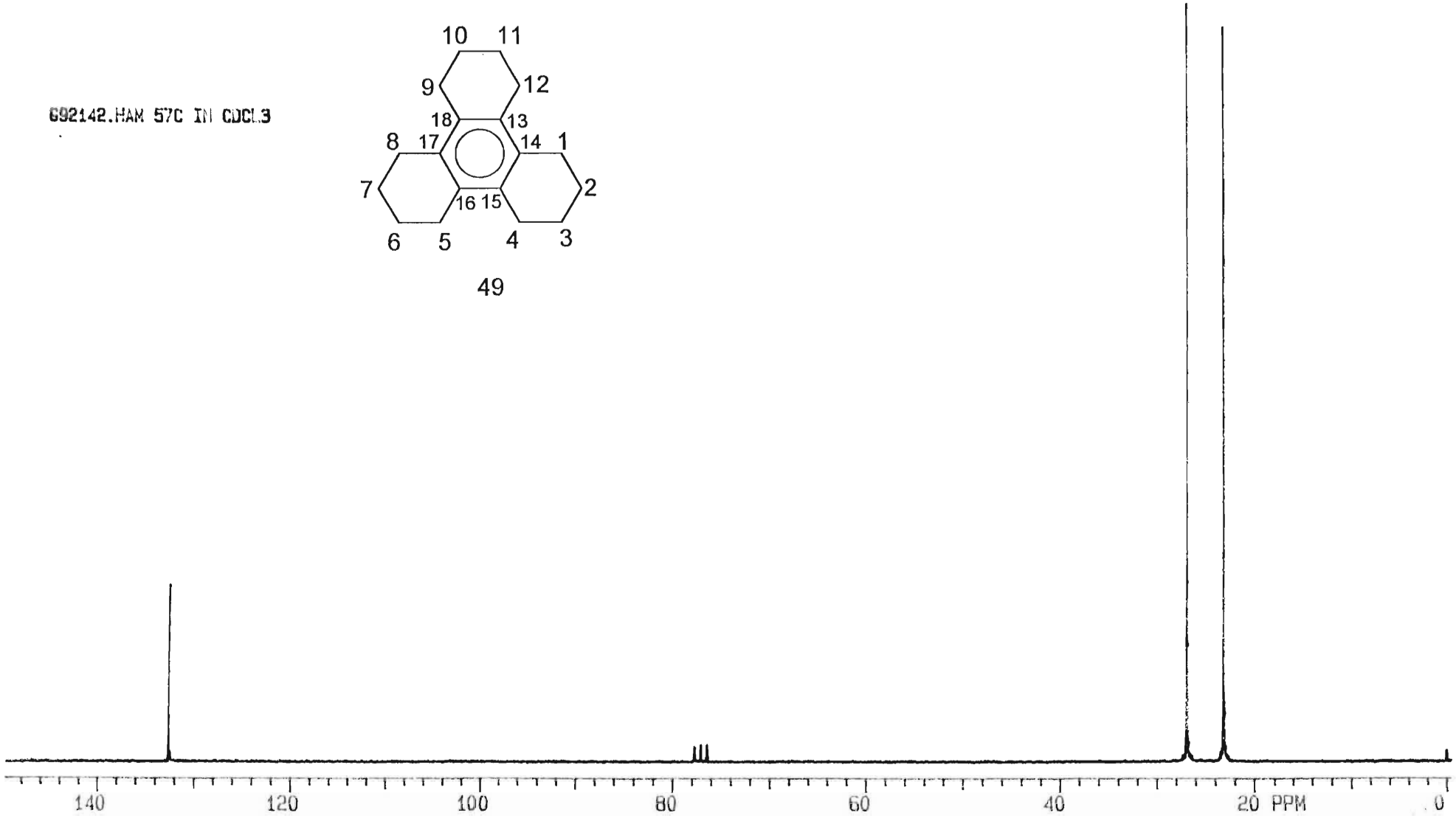
CM1078.HMM10-7.8 IN CDCL3

47



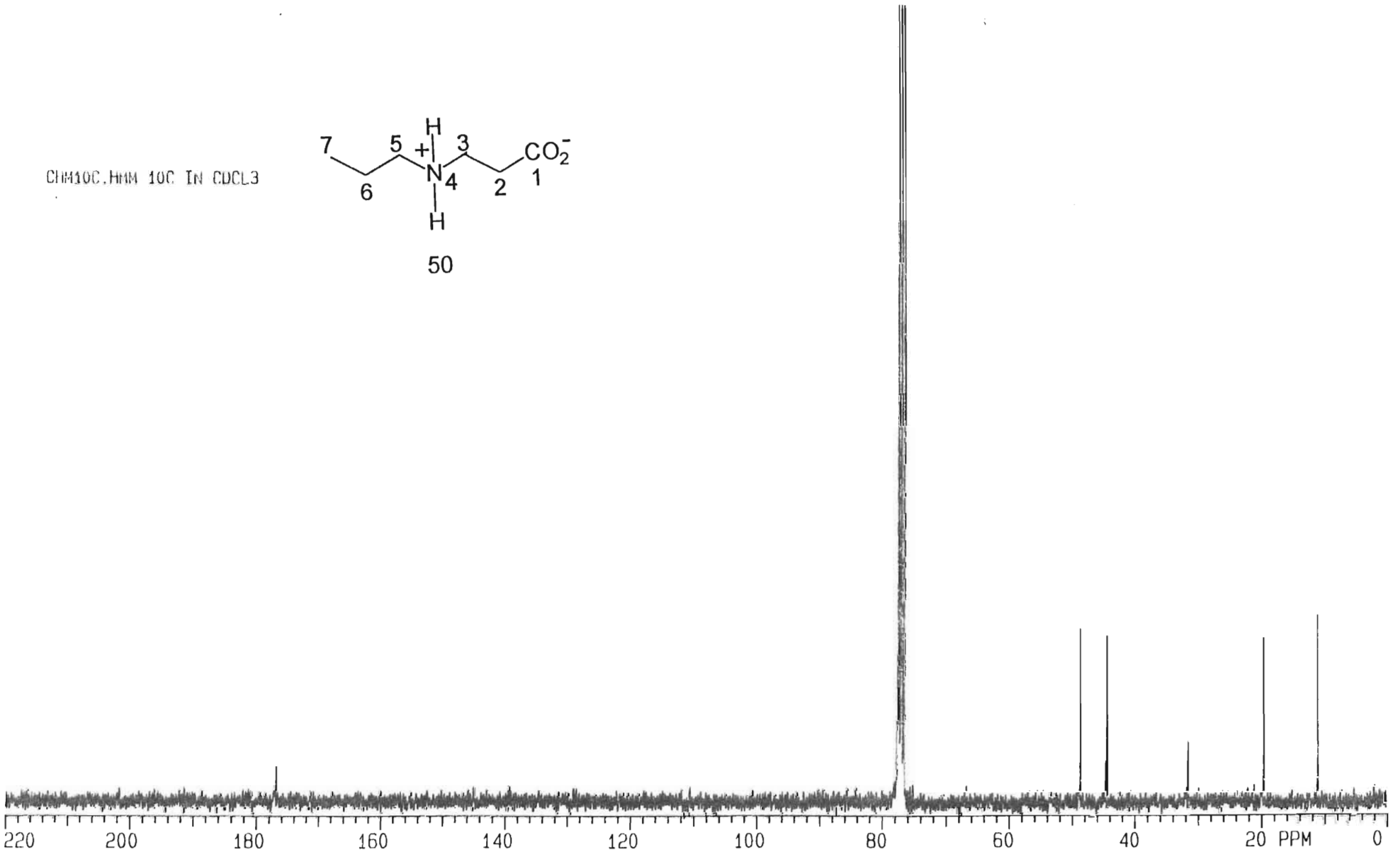
G92142.HAM 57C IN CDCL3

49

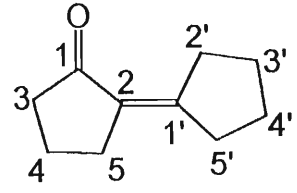


CHM10C.HNM 10C IN CDCL3

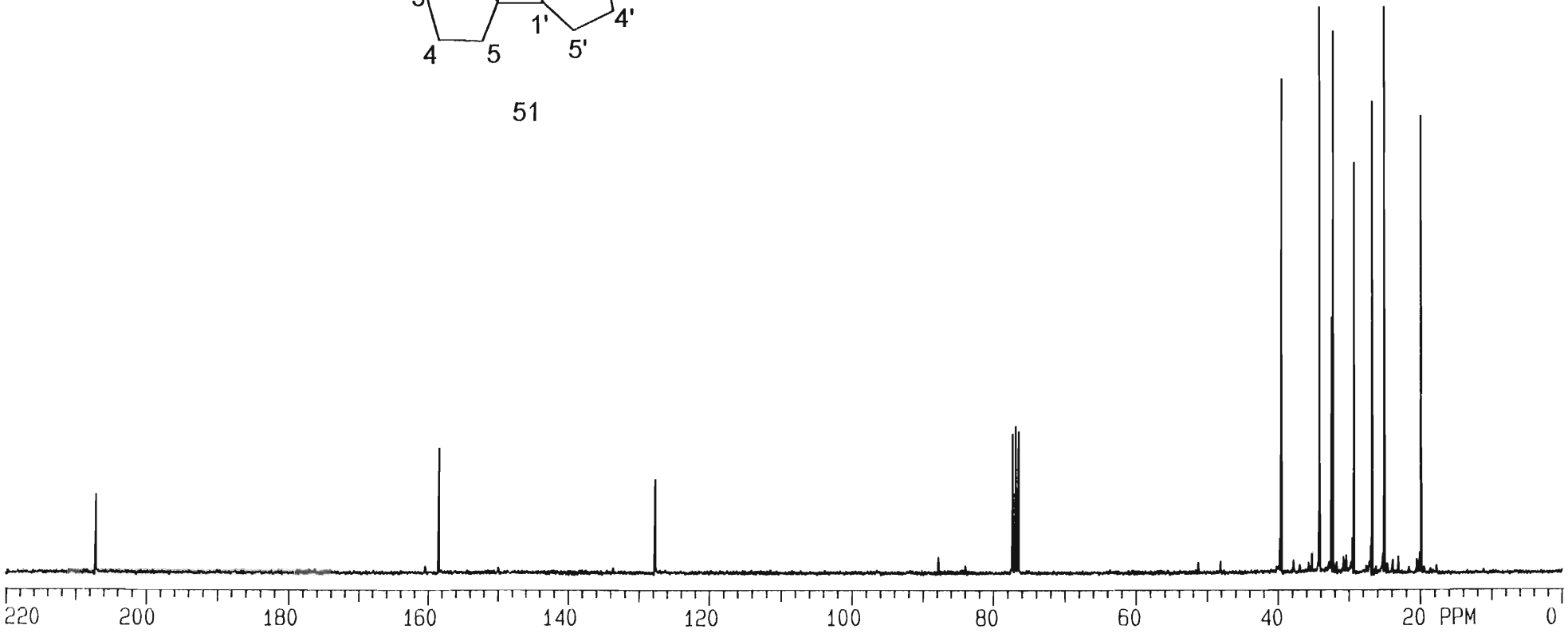
50

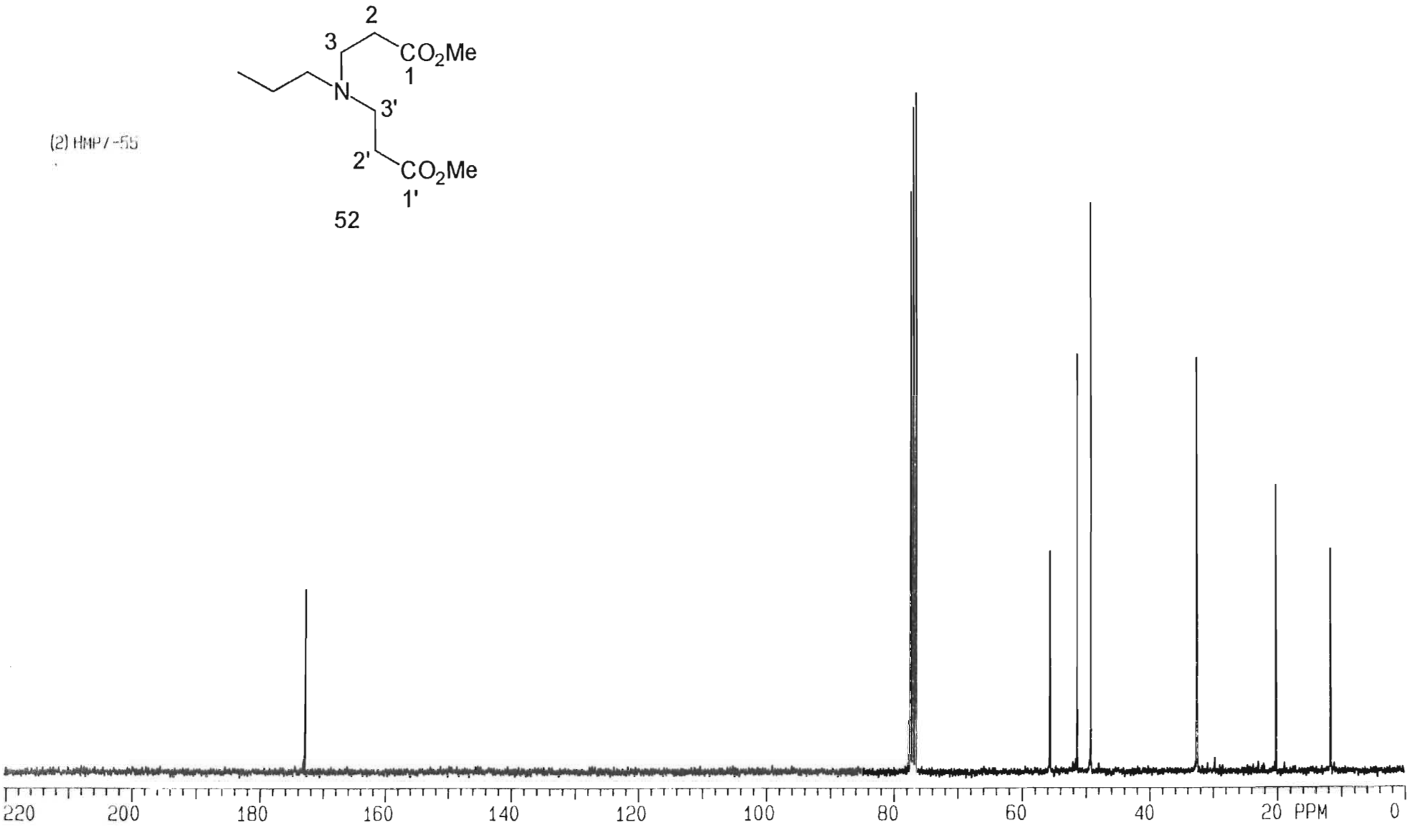


CHMP47.HMPVD.4-7 IN CDCL3



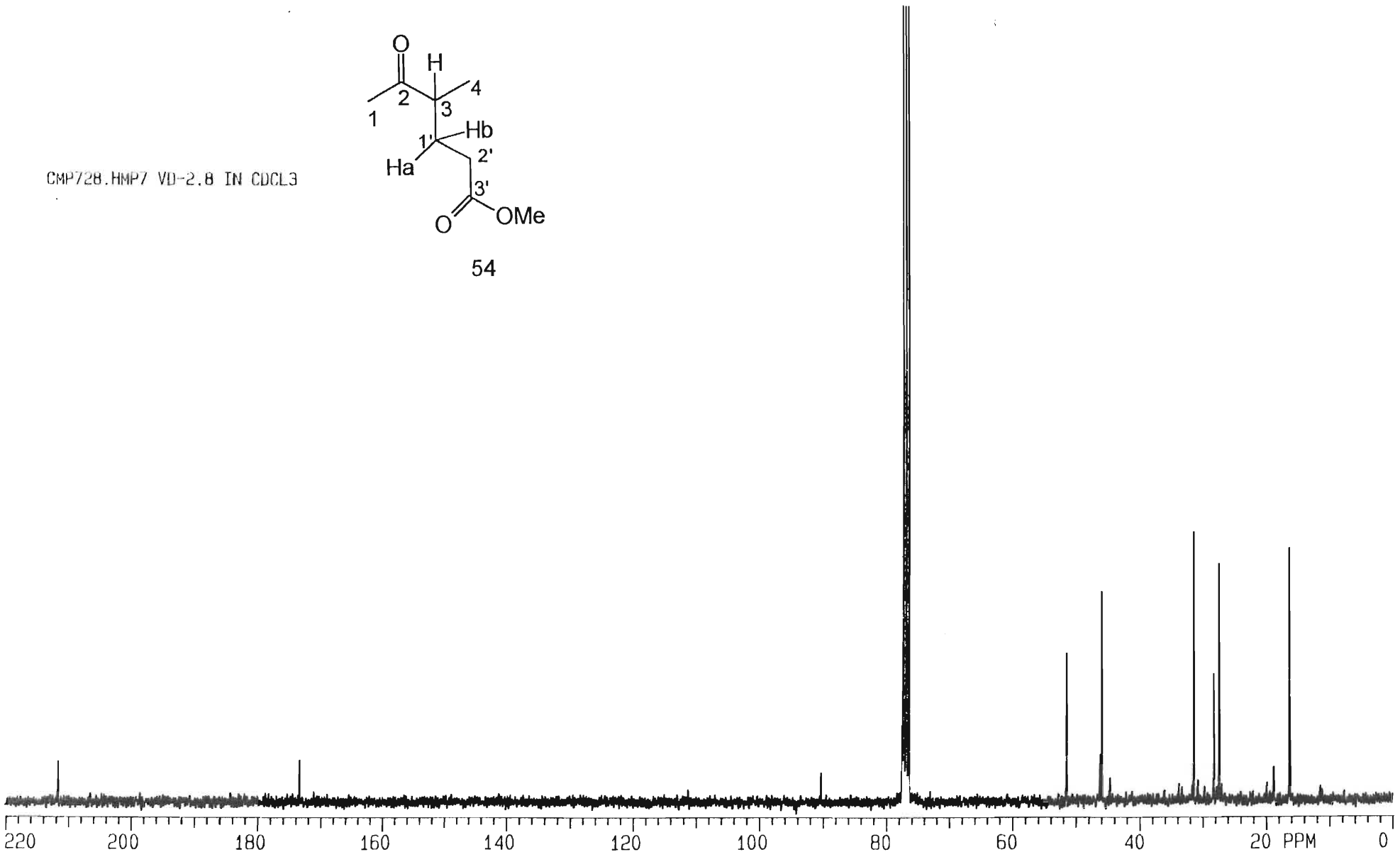
51




(2) HMP / -55
2
3
CO2Me
1
N
3'
2'
CO2Me
1'
52
220
200
180
160
140
120
100
80
60
40
20 PPM
0

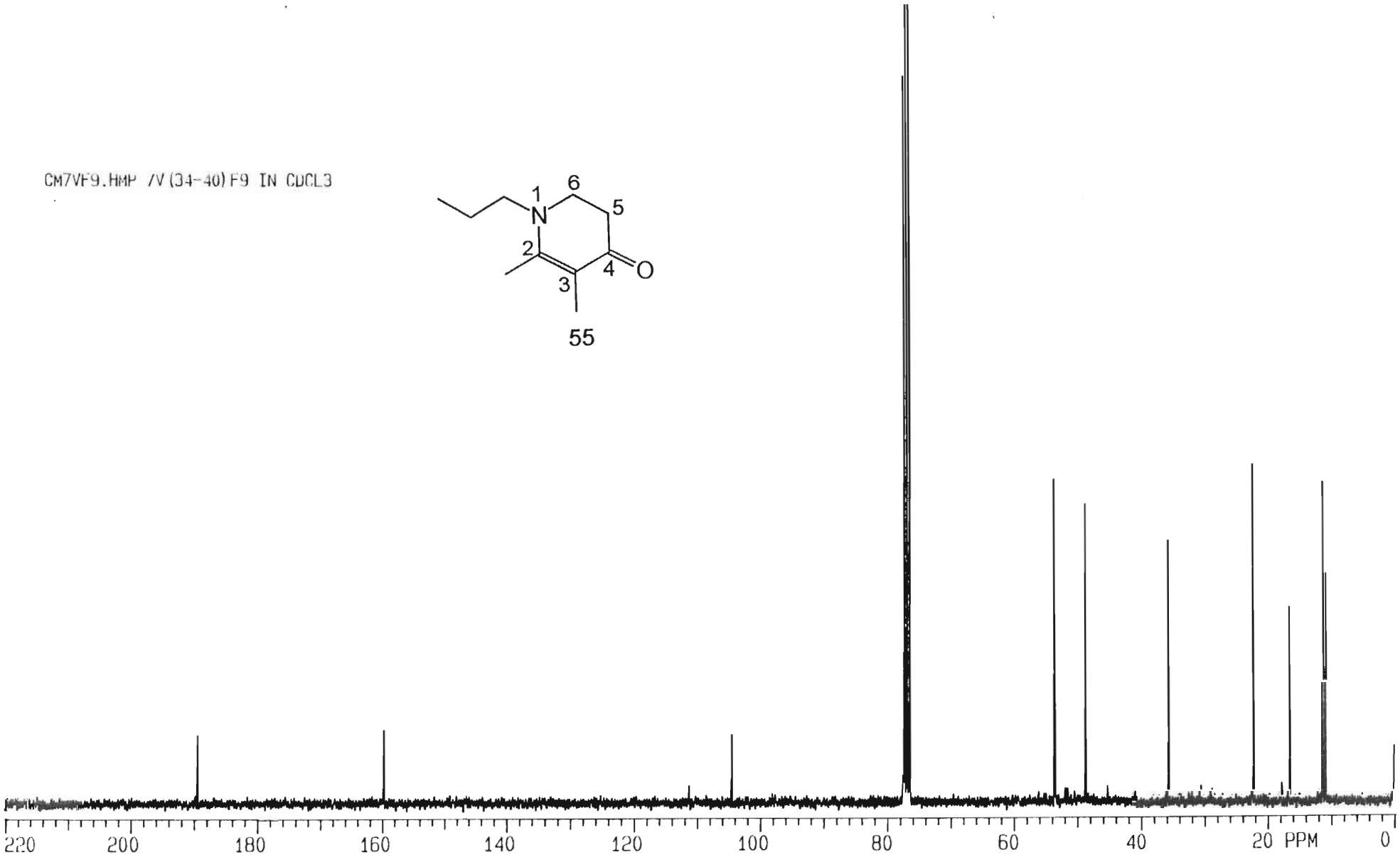
CMP728.HMP7 VD-2.8 IN CDCL3

54



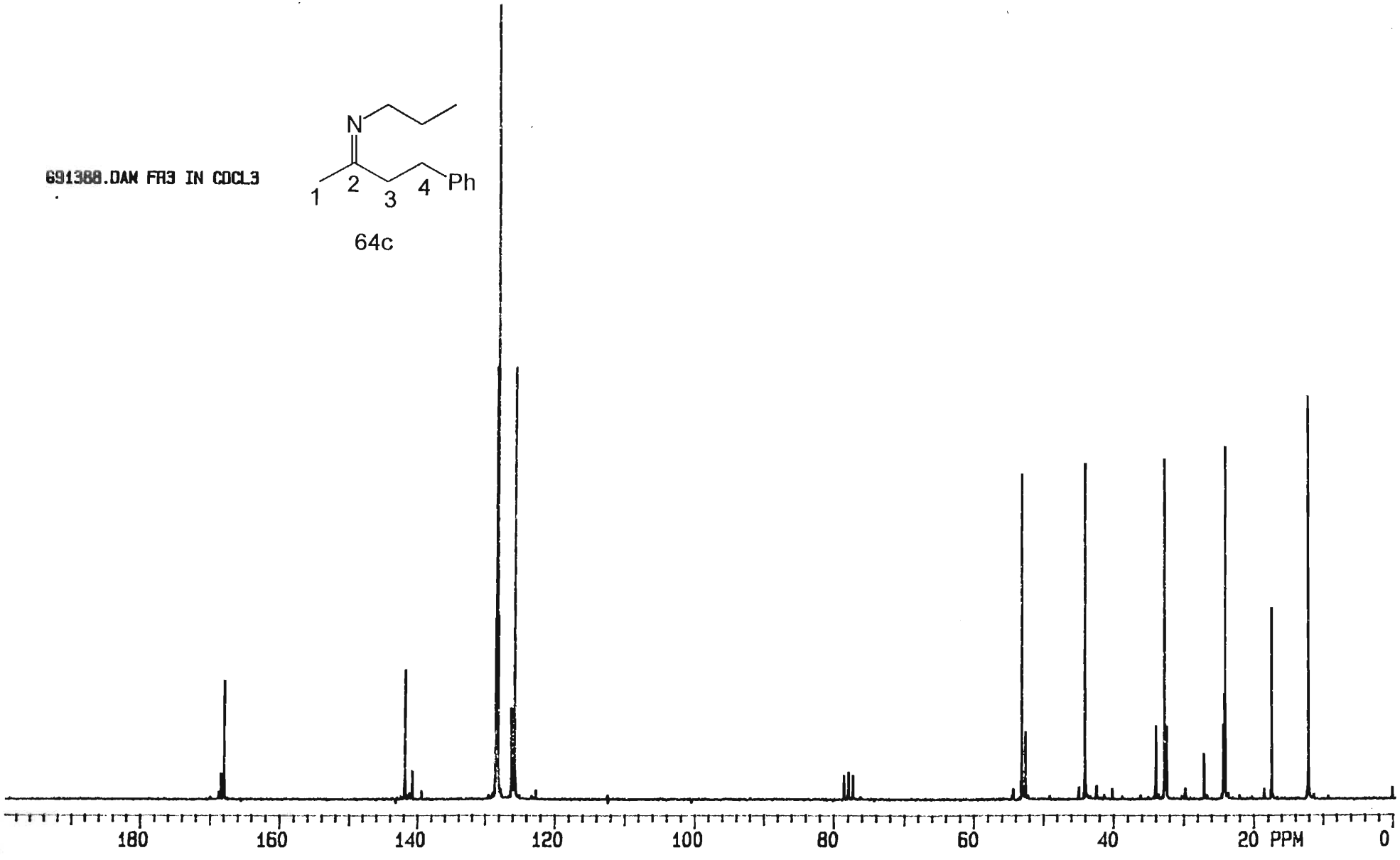
CM7VF9.HMP /V(34-40)F9 IN CDCL3

55

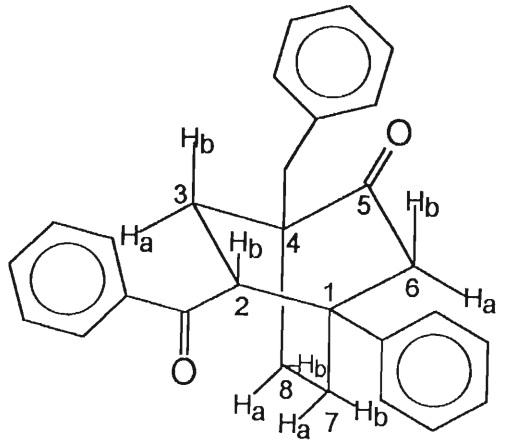


691388.DAM FR3 IN CDCL3

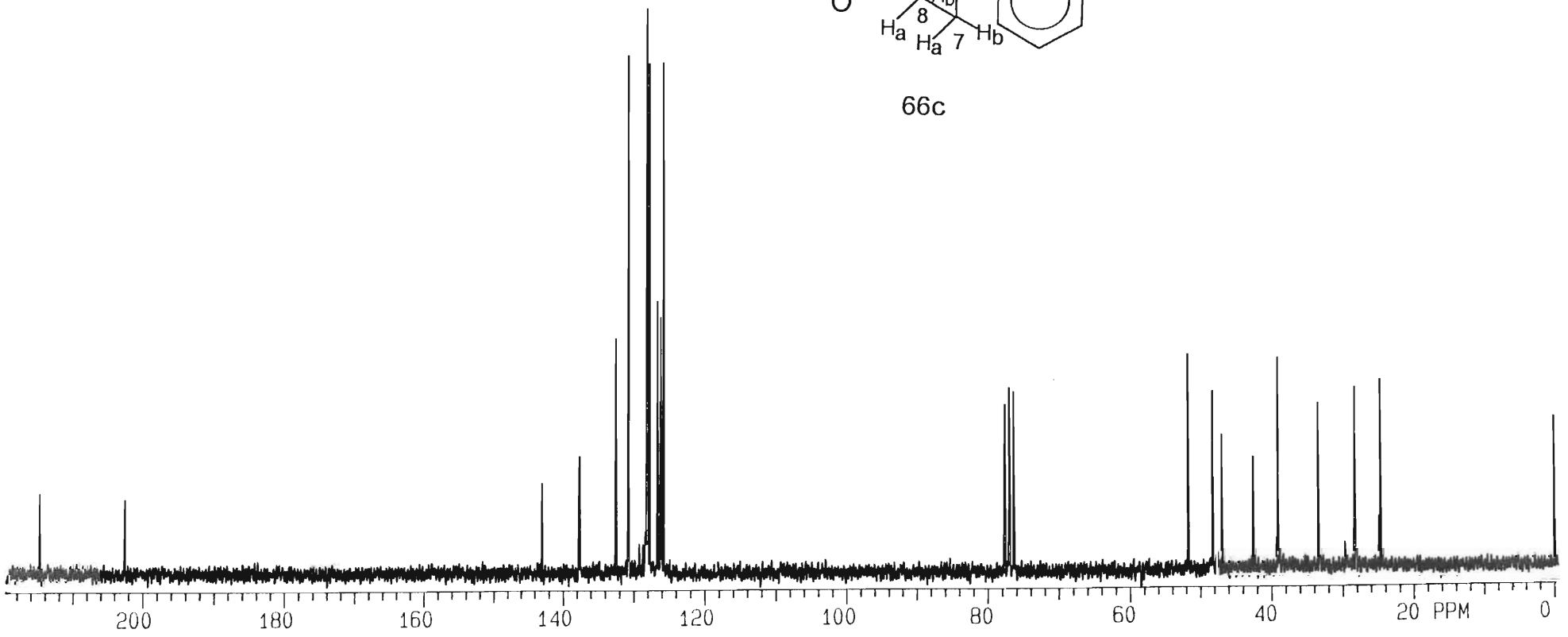
64c

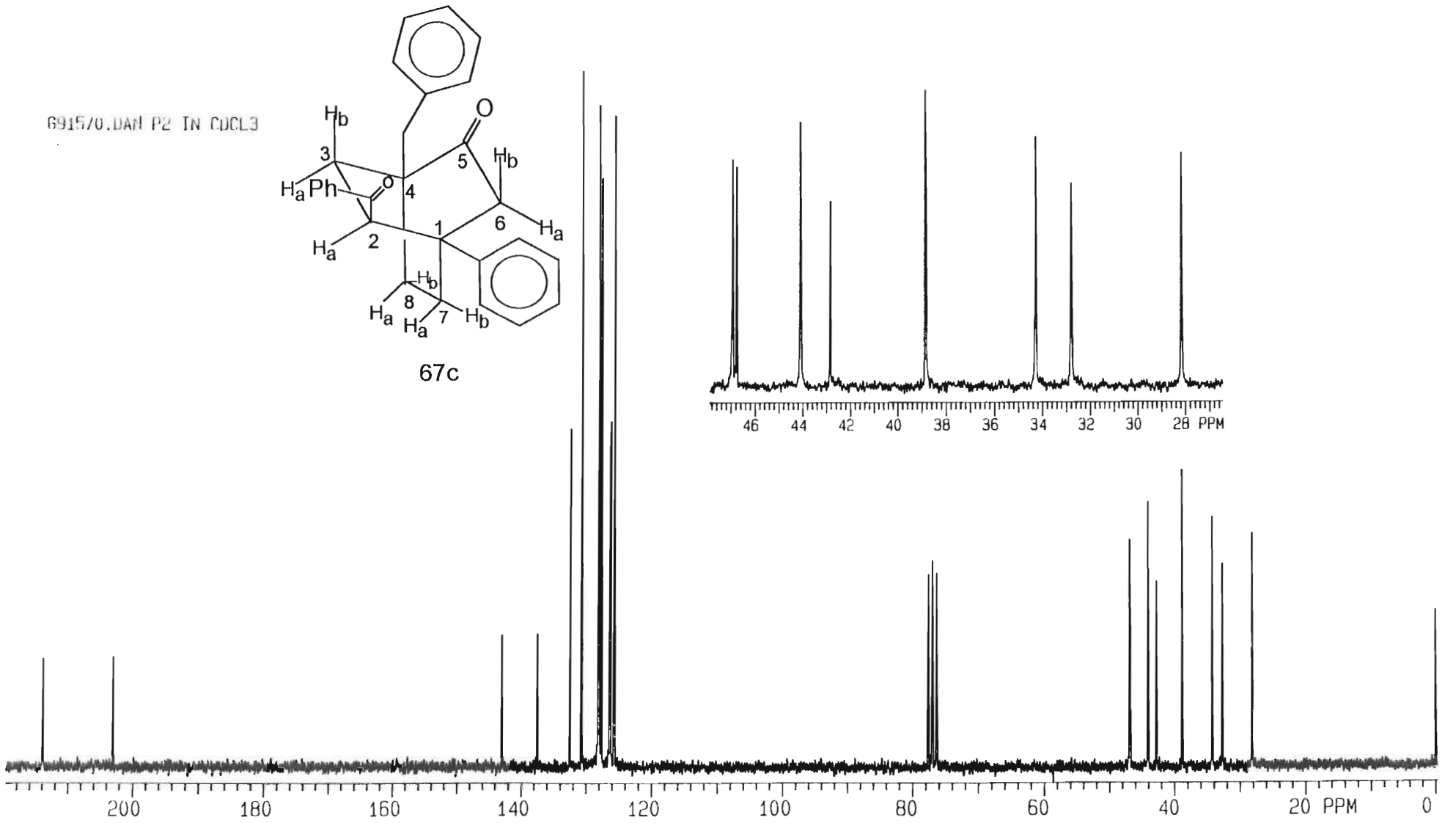


G9157/1.DAN P1 IN CDCL3

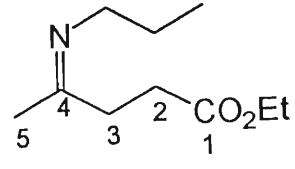


66c

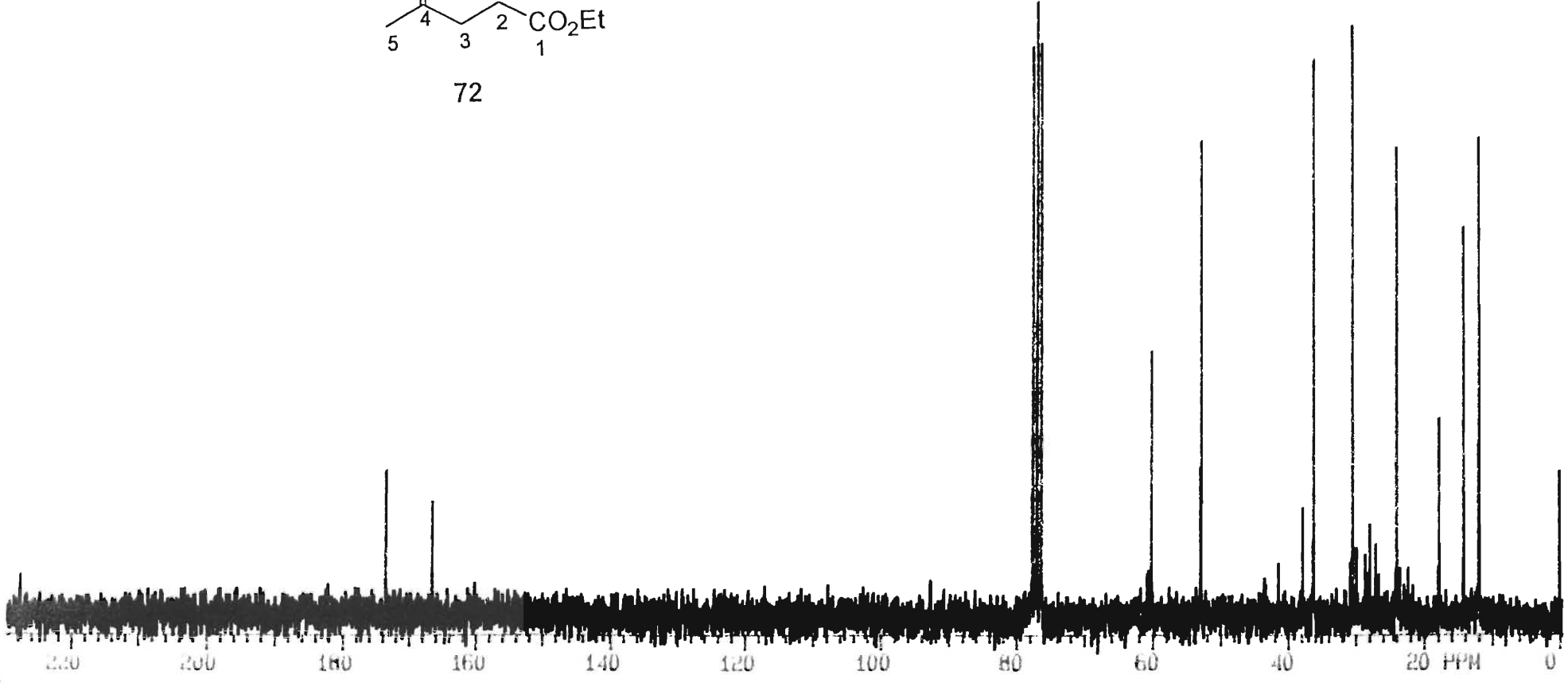



691570.DAN P2 IN CDCL3
Hb
3
Ha Ph
O
4
5
O
Hb
1
6
Ha
2
Ha
Hb
8
Ha
7
Ha
Hb
67c
46
44
42
40
38
36
34
32
30
28 PPM
200
180
160
140
120
100
80
60
40
20 PPM
0

691670 HAM2CR IN CDCL3

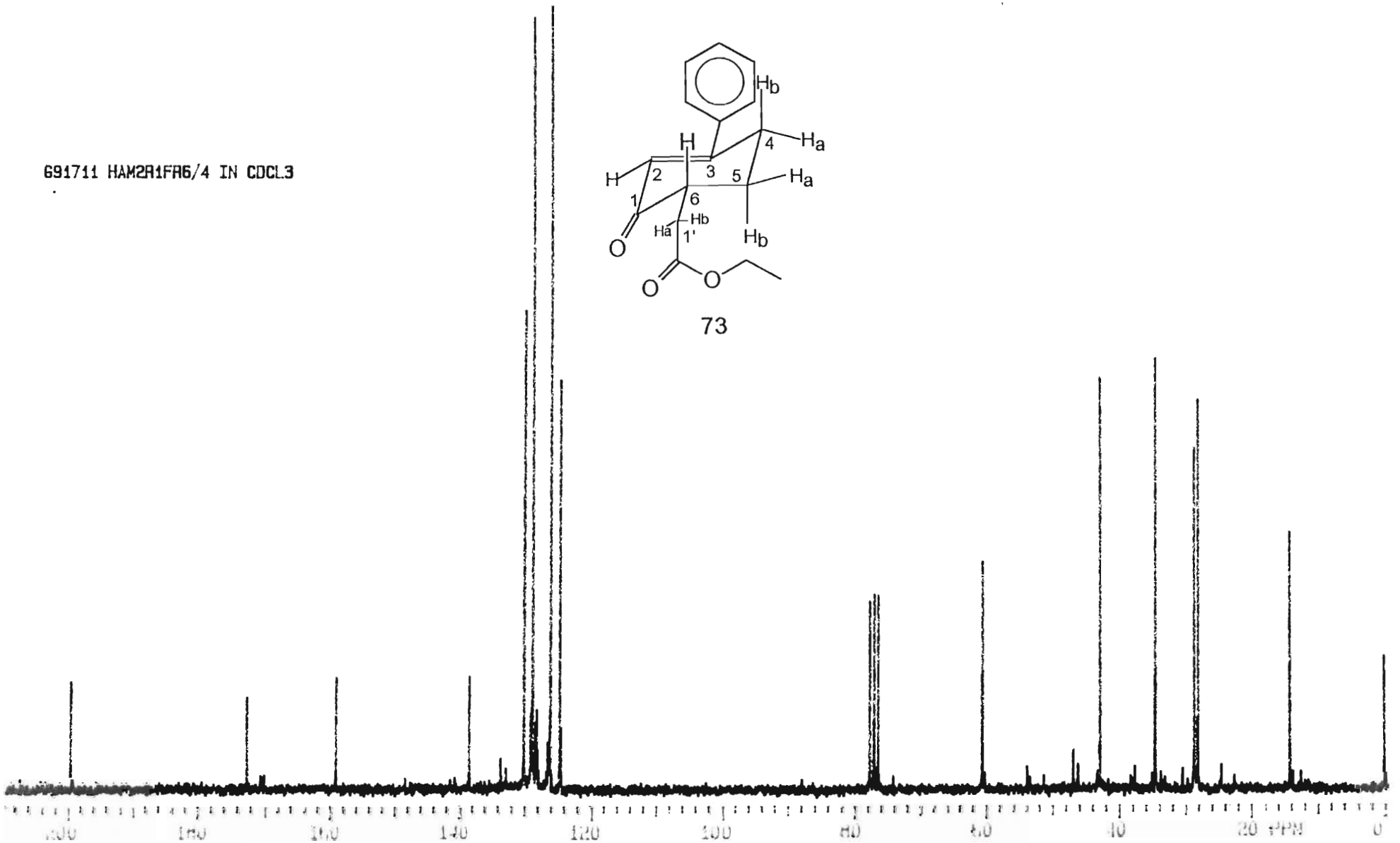


72

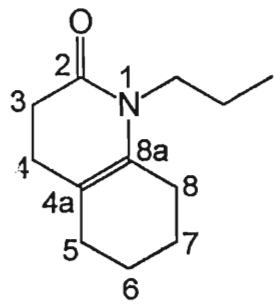


691711 HAM2R1FR6/4 IN CDCL3

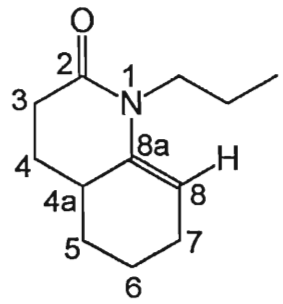
73



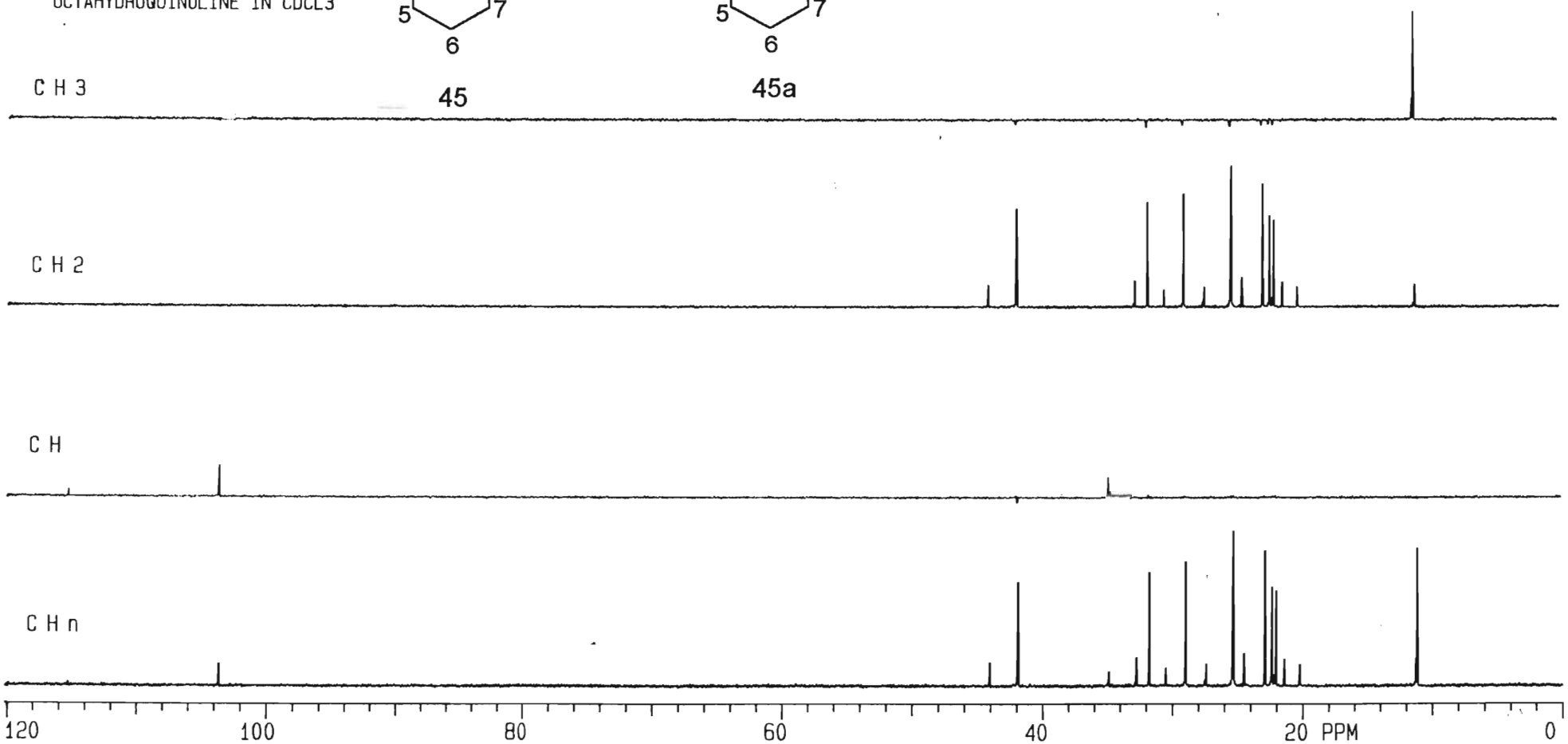
DM1469.HMM 14-6.9
OCTAHYDROQUINOLİNE IN CDCL3



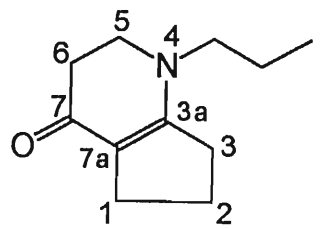
45



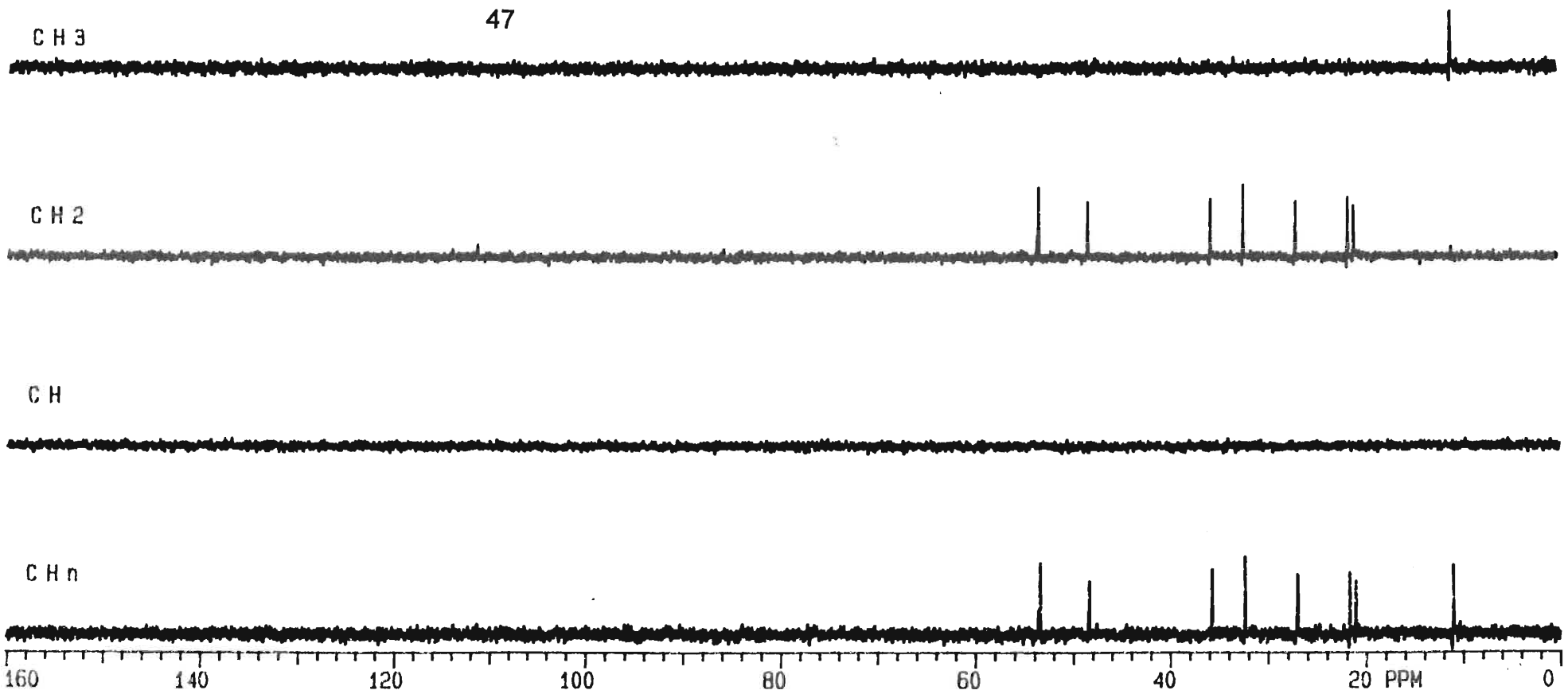
45a

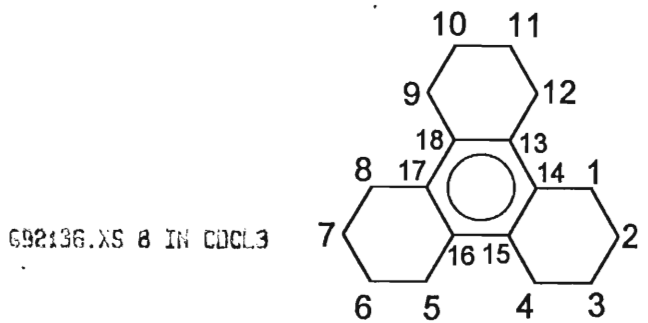


DM1078.HMM10-7.8 IN CDCL3



47





692136.XS 8 IN CDCL3

49

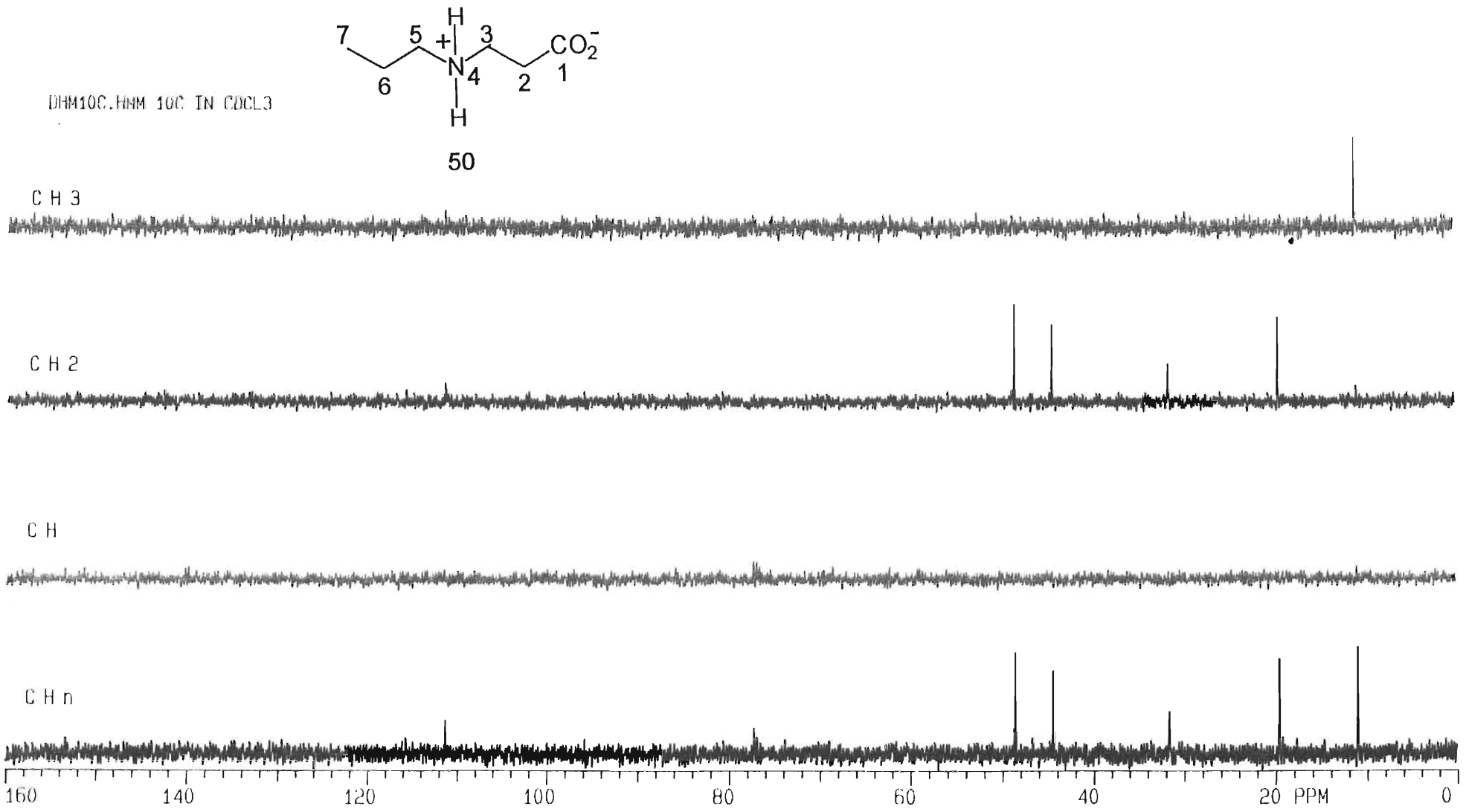
CH3

CH2

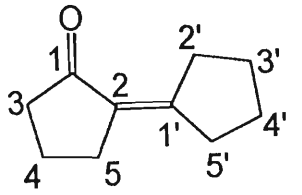
CH

CHn

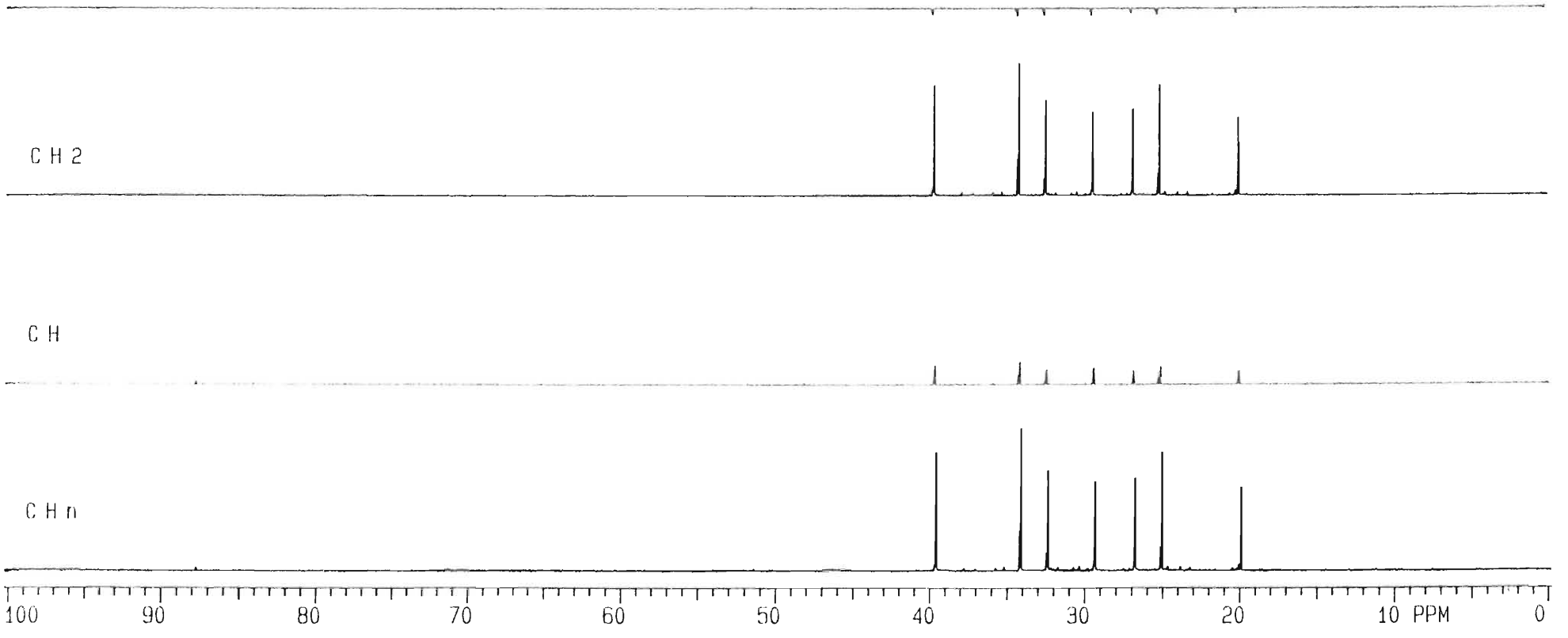
28 26 24 22 20 18 16 14 12 10 8 6 4 2 PPM 0

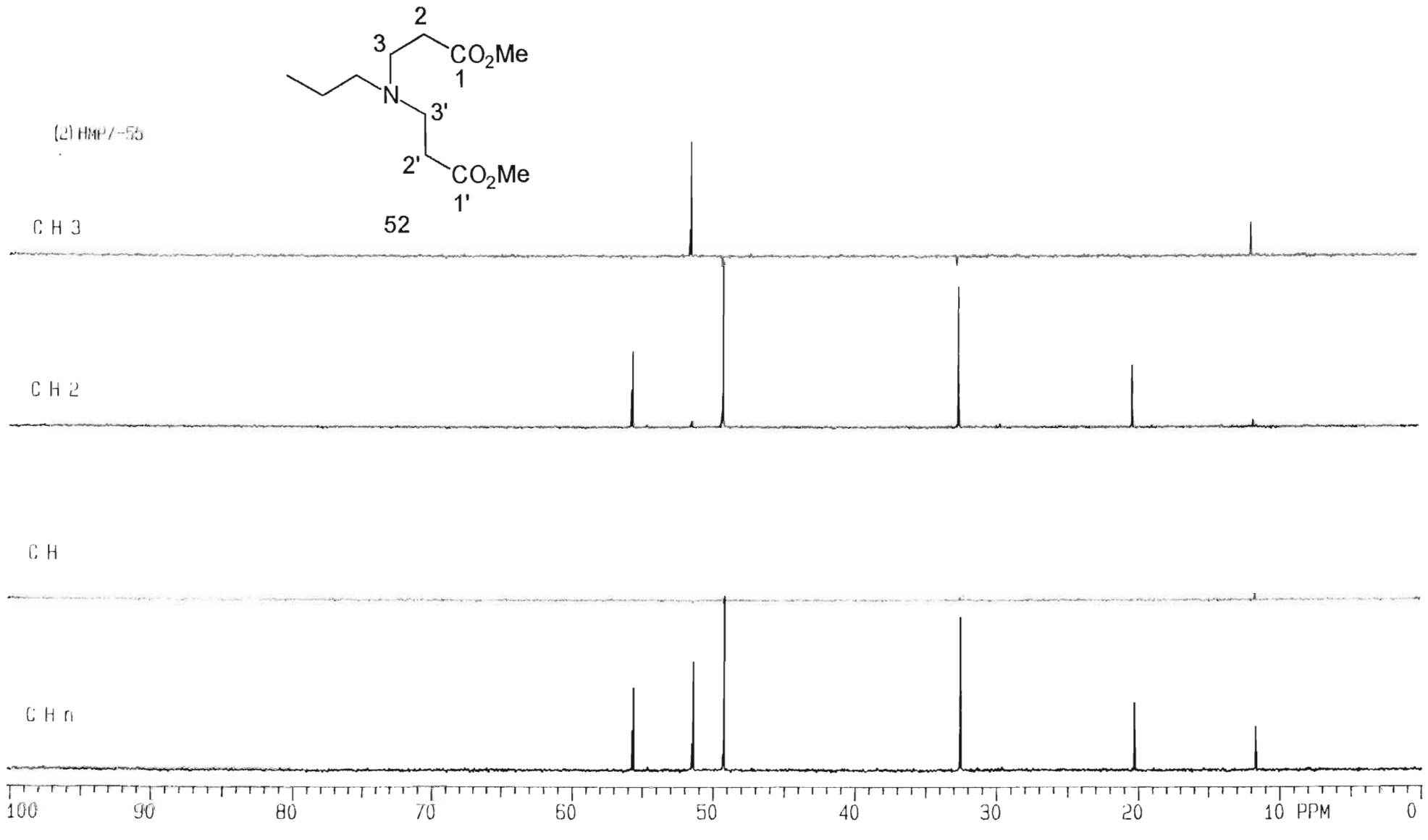

DHM10C.HNM 10C IN CDCL3
7
5
+
H
3
CO_2^-
6
N
4
2
1
H
50
C H 3
C H 2
C H
C H n
160
140
120
100
80
60
40
20 PPM
0

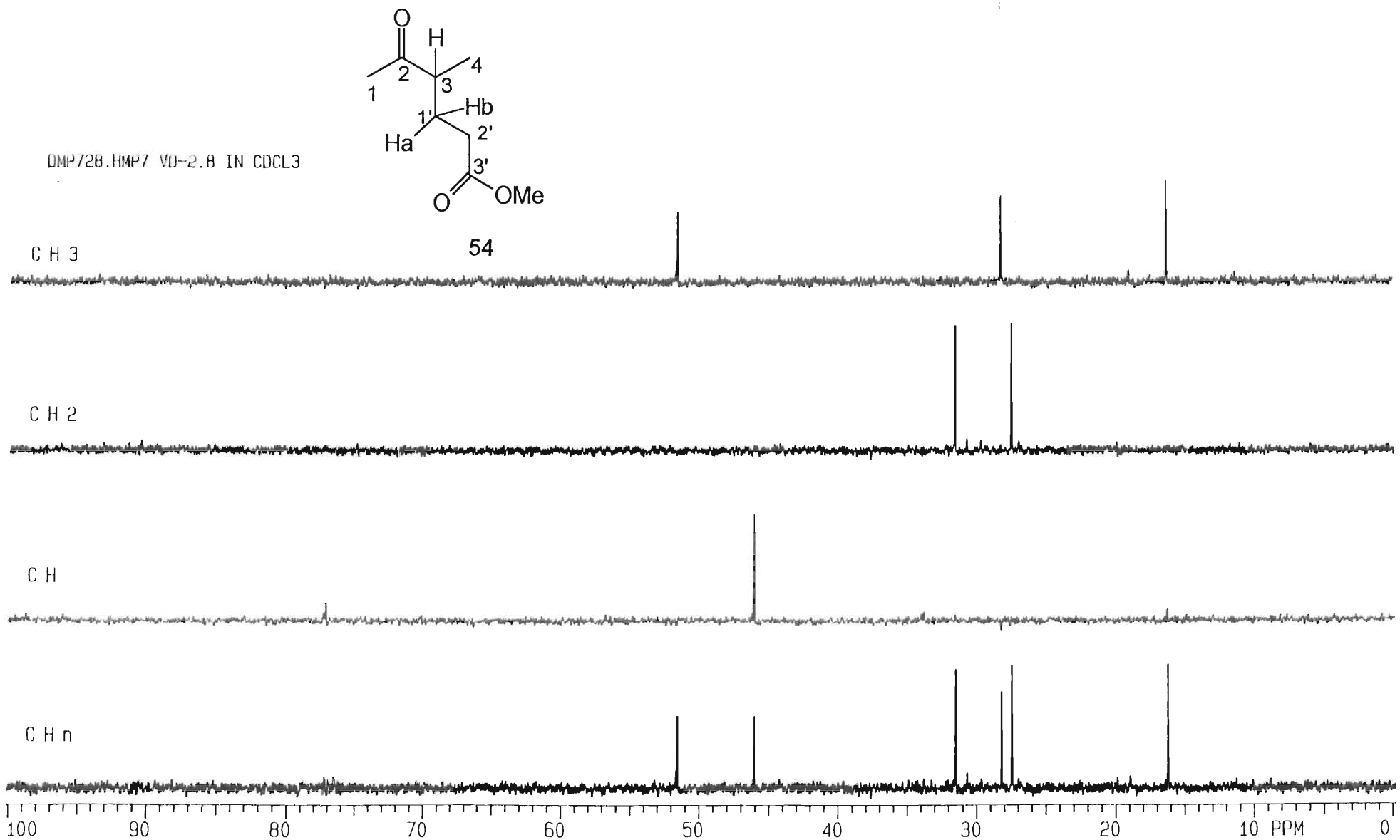
DHMP47.HMPVD.4-7 IN CDCL3

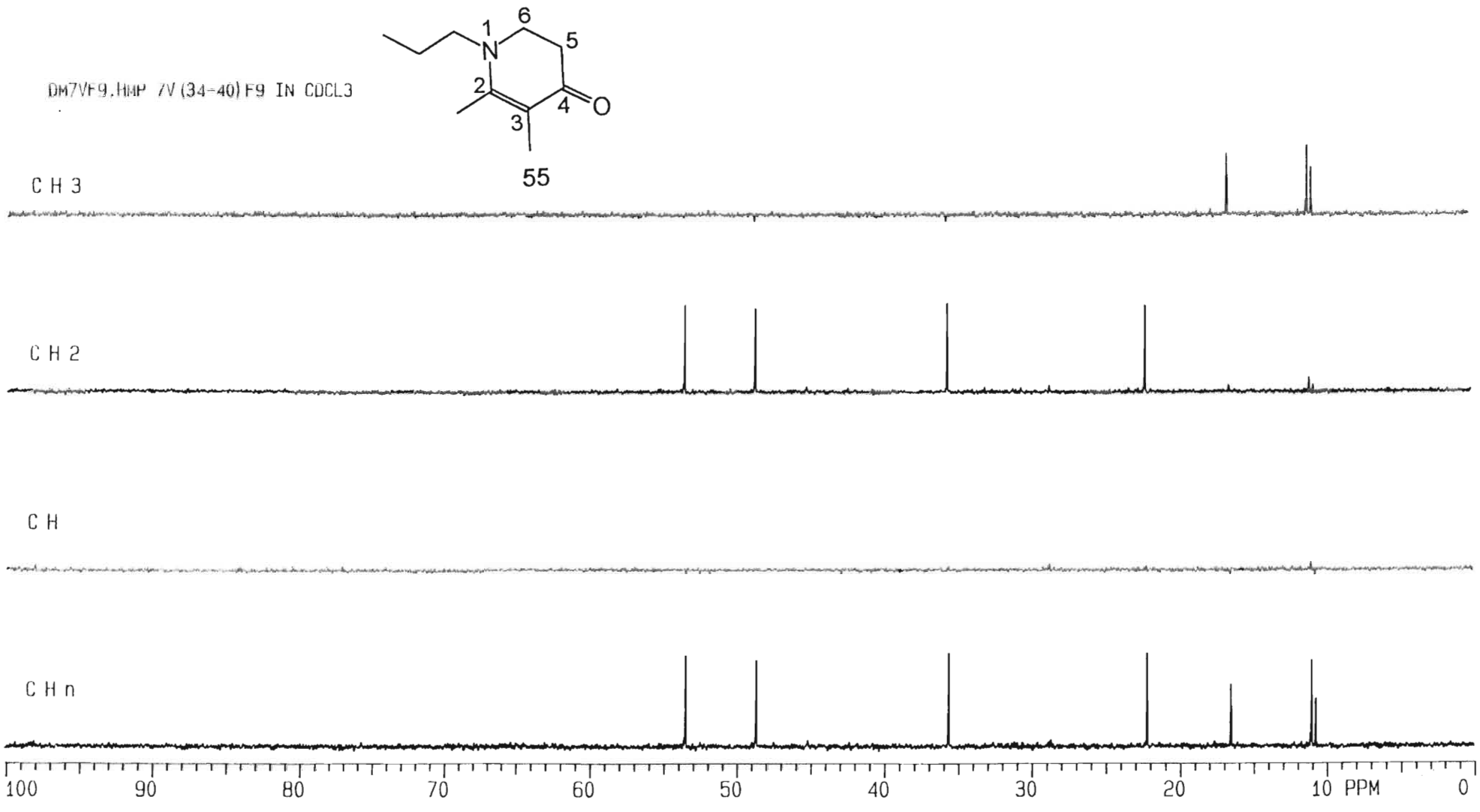


51

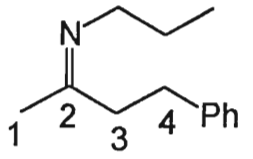



2
3
CO2Me
1
N
3'
2'
CO2Me
1'
52
(2) HMP/-55
C H 3
C H 2
C H
C H n
100
90
80
70
60
50
40
30
20
10 PPM
0

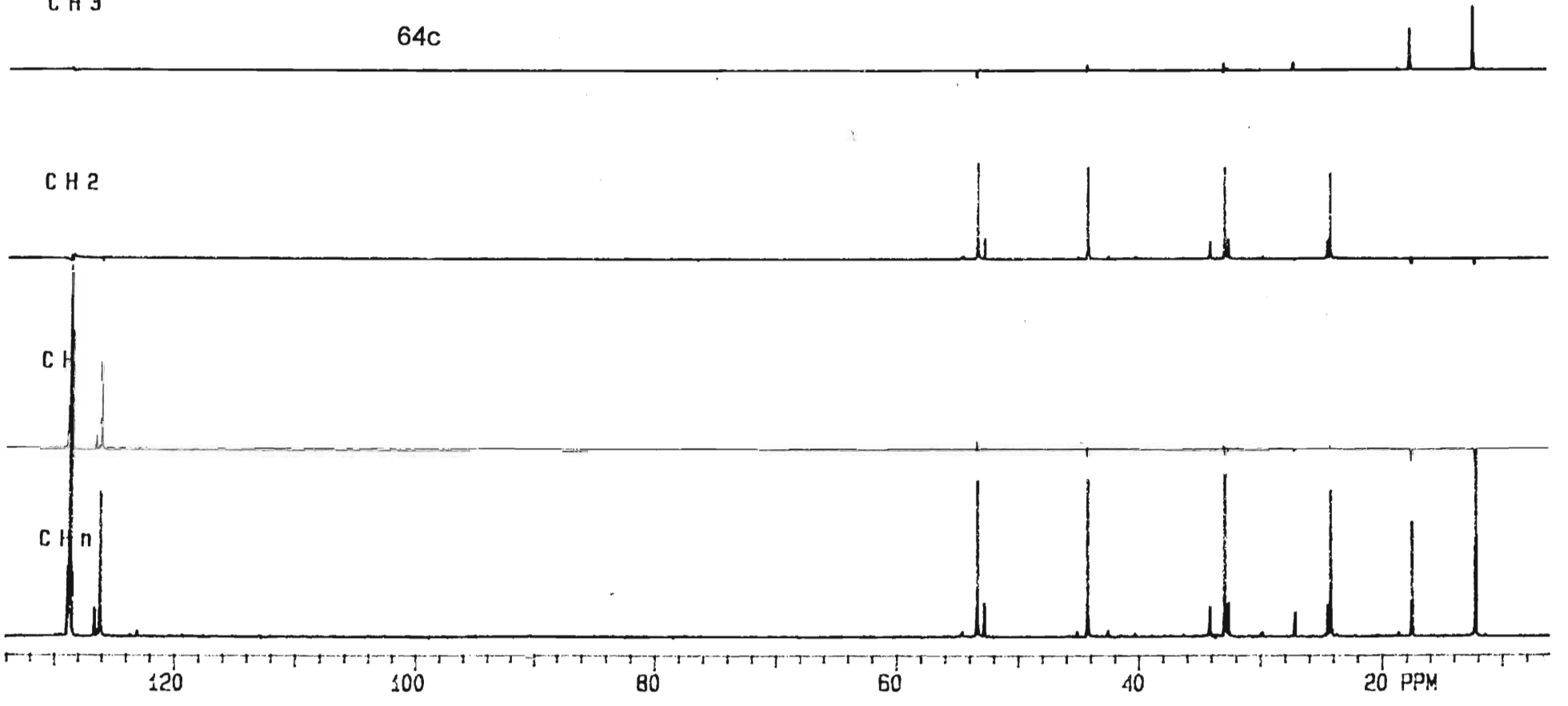

DMP728.HMP7 VD-2.8 IN CDCL3
O
H
2
3
4
1
1'
Hb
Ha
2'
3'
O
OMe
54
C H 3
C H 2
C H
C H n
100
90
80
70
60
50
40
30
20
10 PPM
0

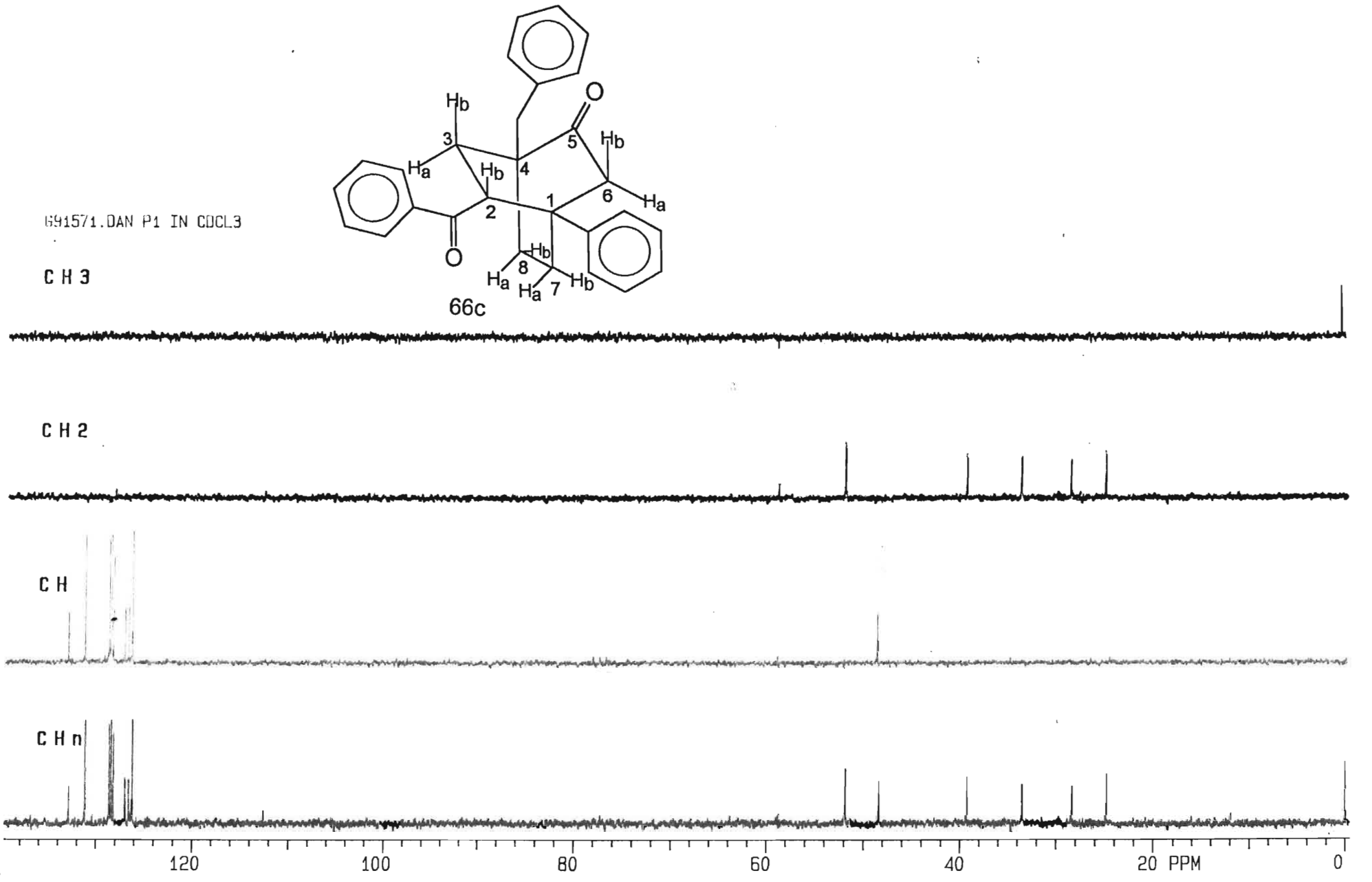

DM7VF9.HMP 7V(34-40)F9 IN CDCL3
1
2
3
4
5
6
N
O
55
C H 3
C H 2
C H
C H n
100
90
80
70
60
50
40
30
20
10 PPM
0

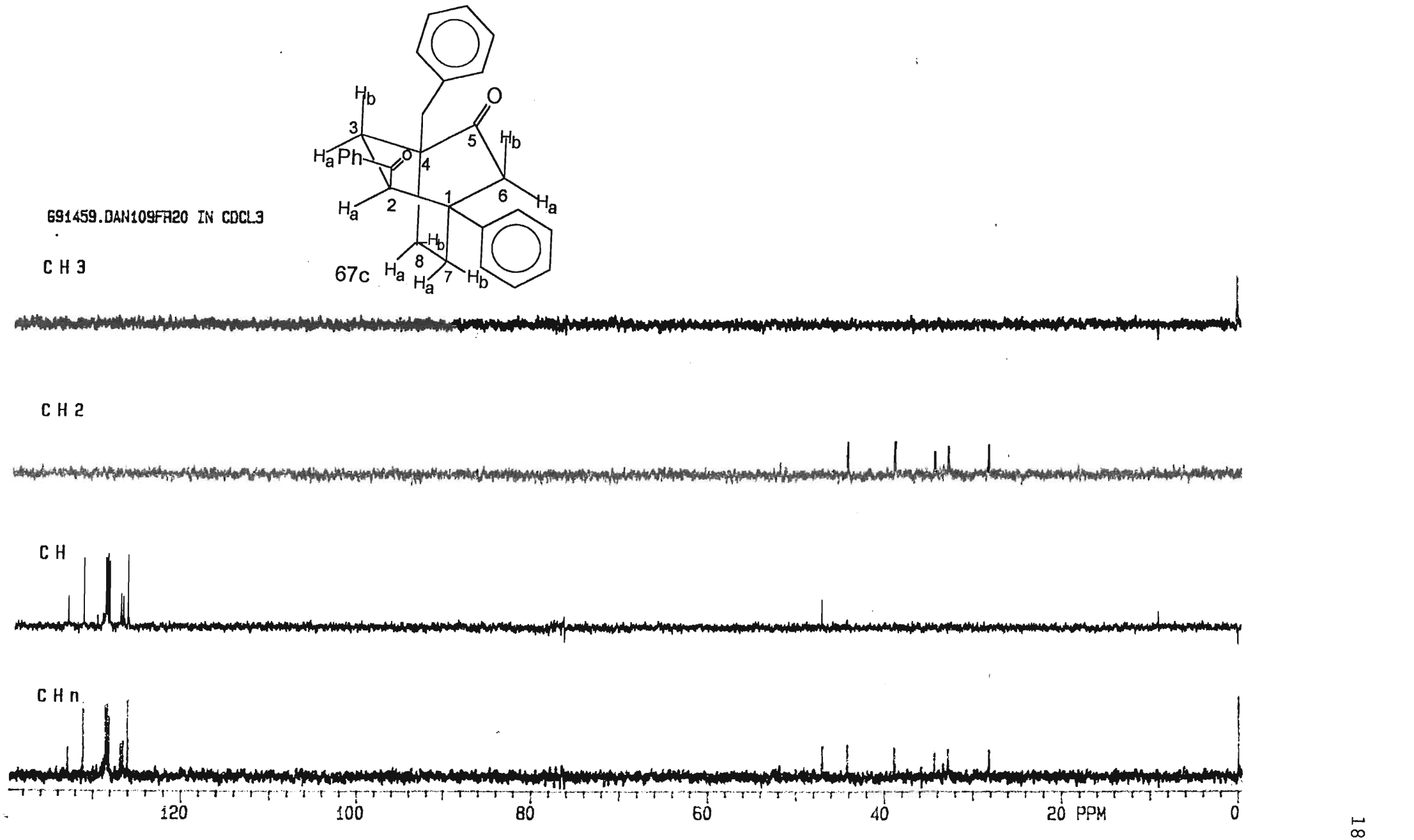
691388.DAM FR3 IN CDCL3



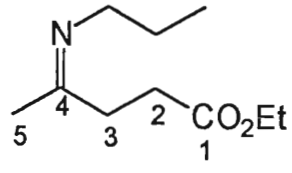
64c



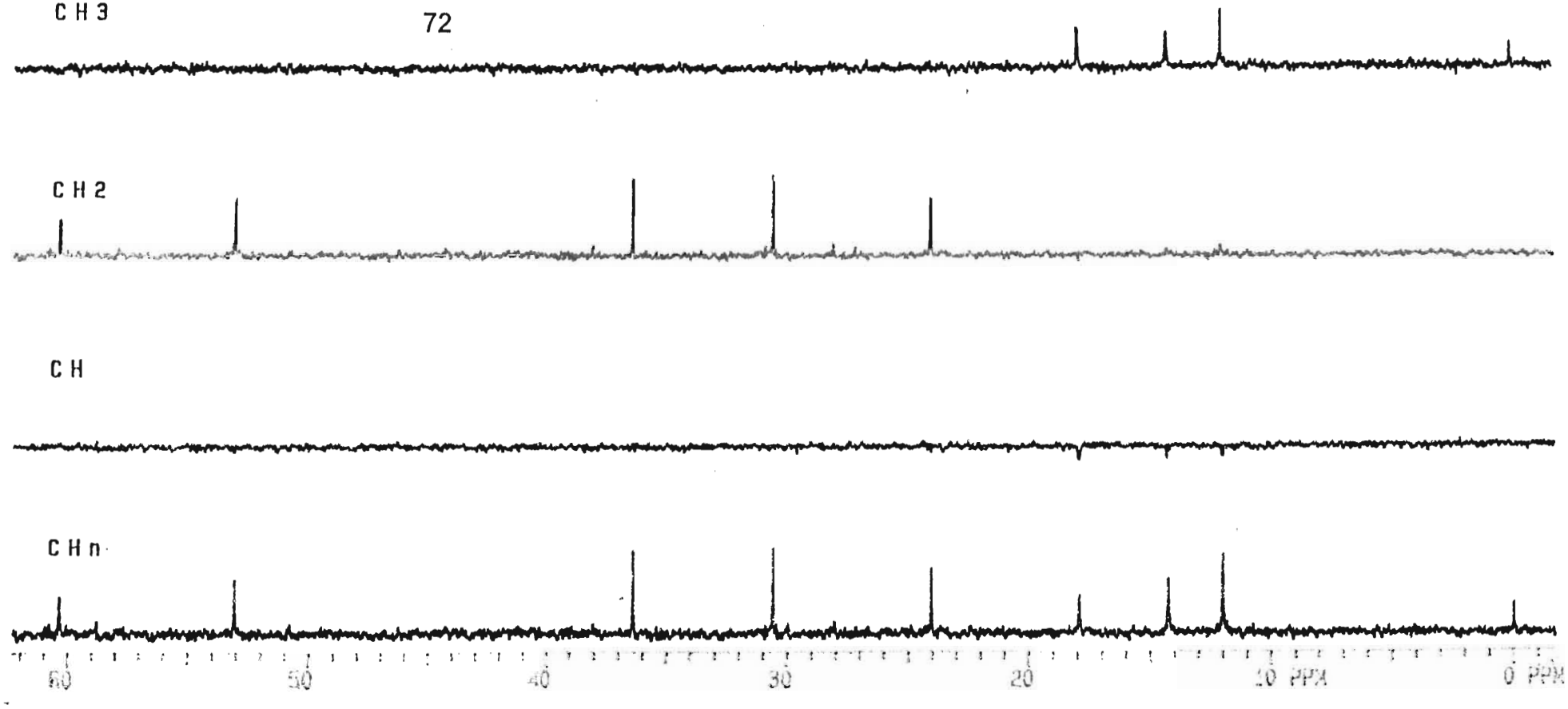

G91571.DAN P1 IN CDCL3
CH3
CH2
CH
CHn
Hb
3
Ha
Hb
4
5
O
Hb
6
Ha
1
2
O
Hb
8
Ha
Ha
7
Hb
66c
120
100
80
60
40
20 PPM
0

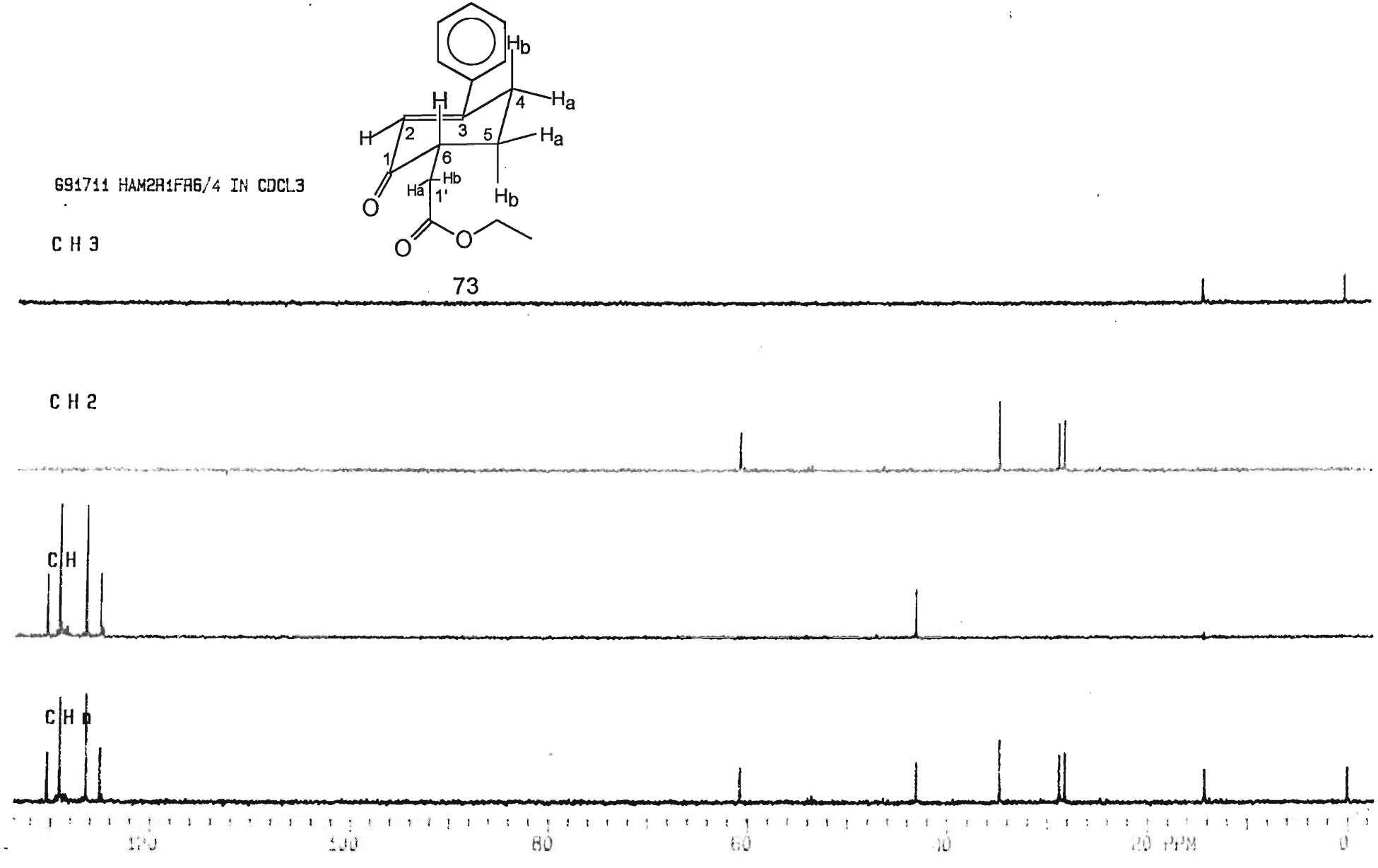

691459.DAN109FR20 IN CDCL3
C H 3
C H 2
C H
C H n
67c
Hb
O
3
5
Hb
Ha Ph
O
4
Ha
2
1
6
Ha
Hb
8
Ha
7
Hb
120
100
80
60
40
20 PPM
0

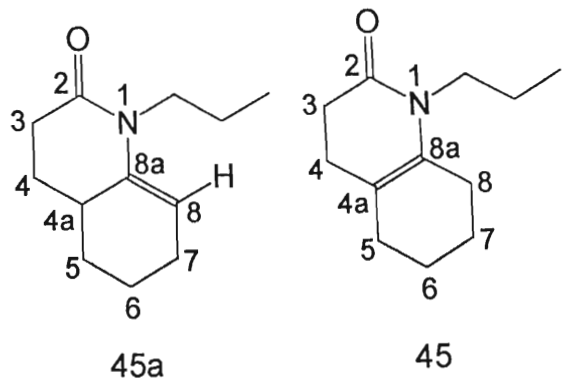
691670 HAM2CR IN CDCL3



72



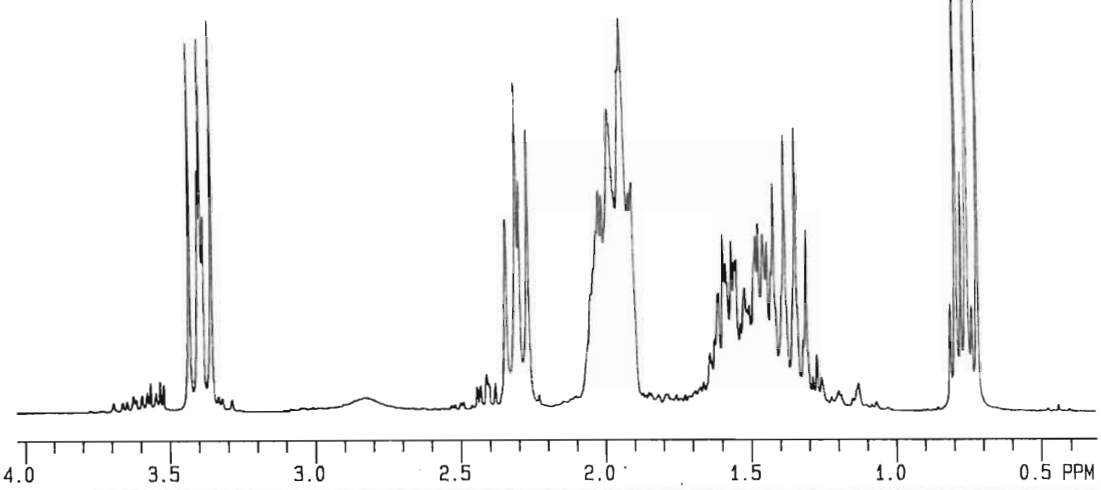

G91711 HAM2R1FR6/4 IN CDCL3
C H 3
C H 2
C H
C H
Hb
H
4
Ha
H
2
3
5
Ha
1
6
Hb
Ha
1'
Hb
O
O
O
73
180
160
80
60
40
20 PPM
0

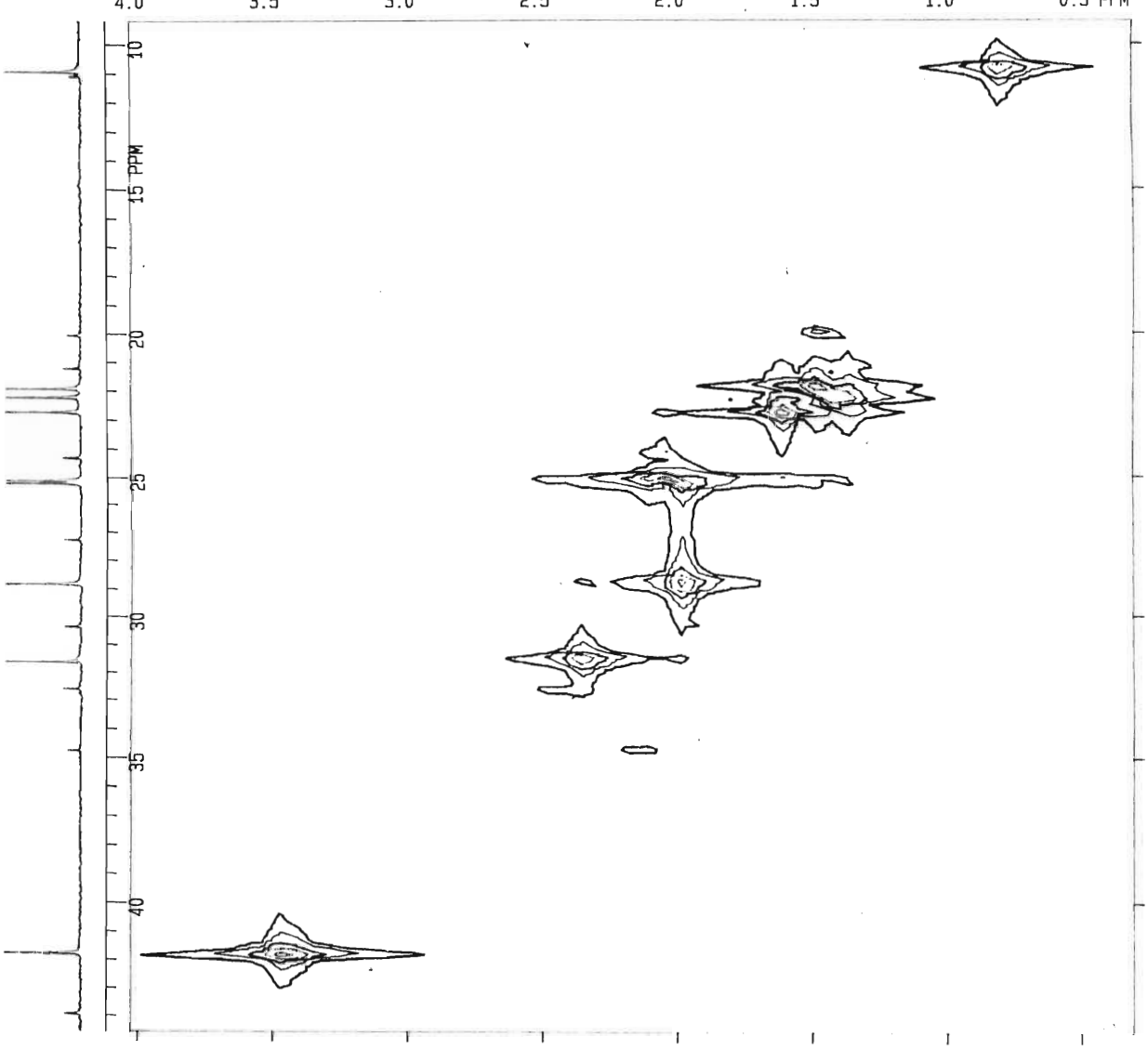

O
2
1
N
3
4
8a
H
4a
8
5
7
6

45a

O
2
1
N
3
4
8a
4a
8
5
7
6

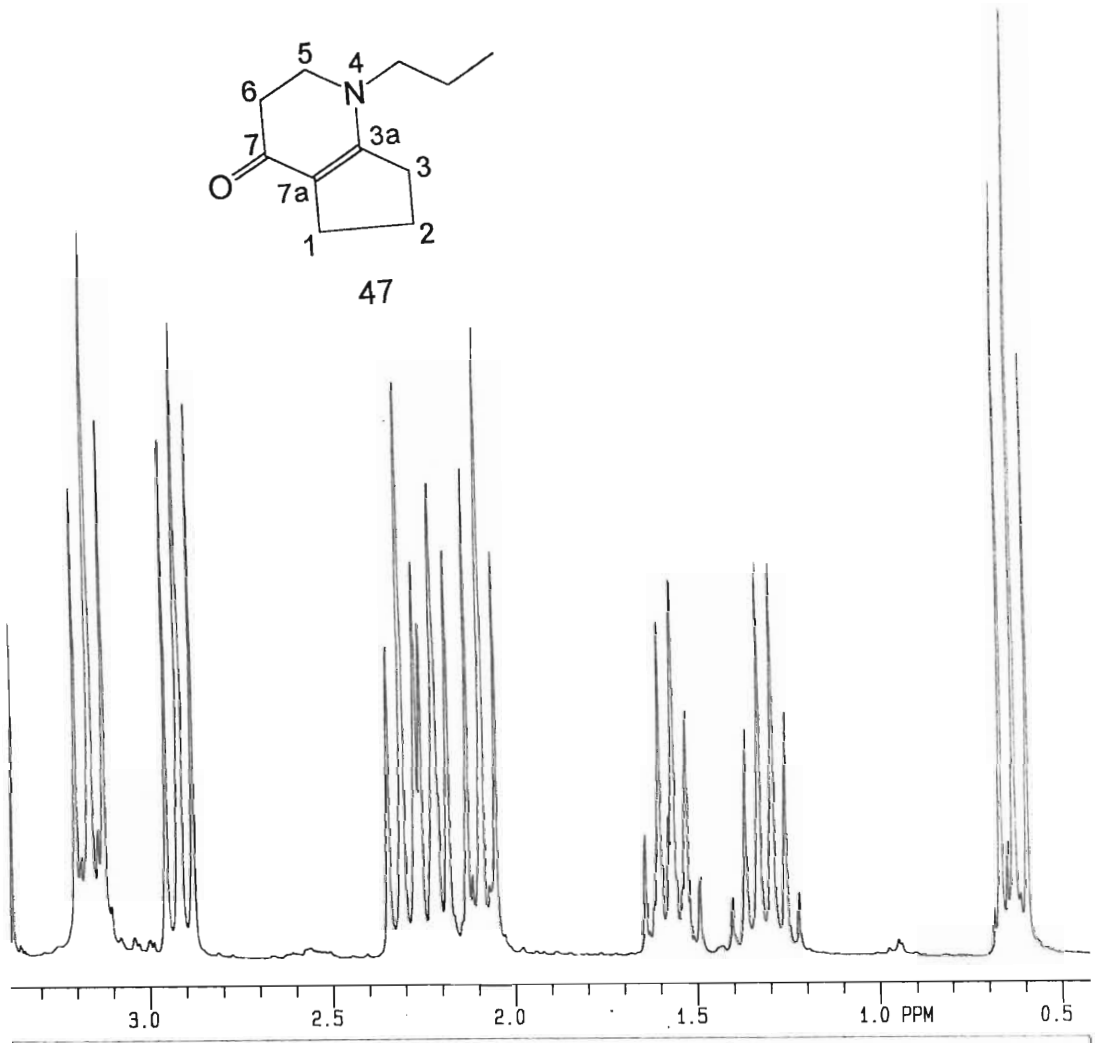
45

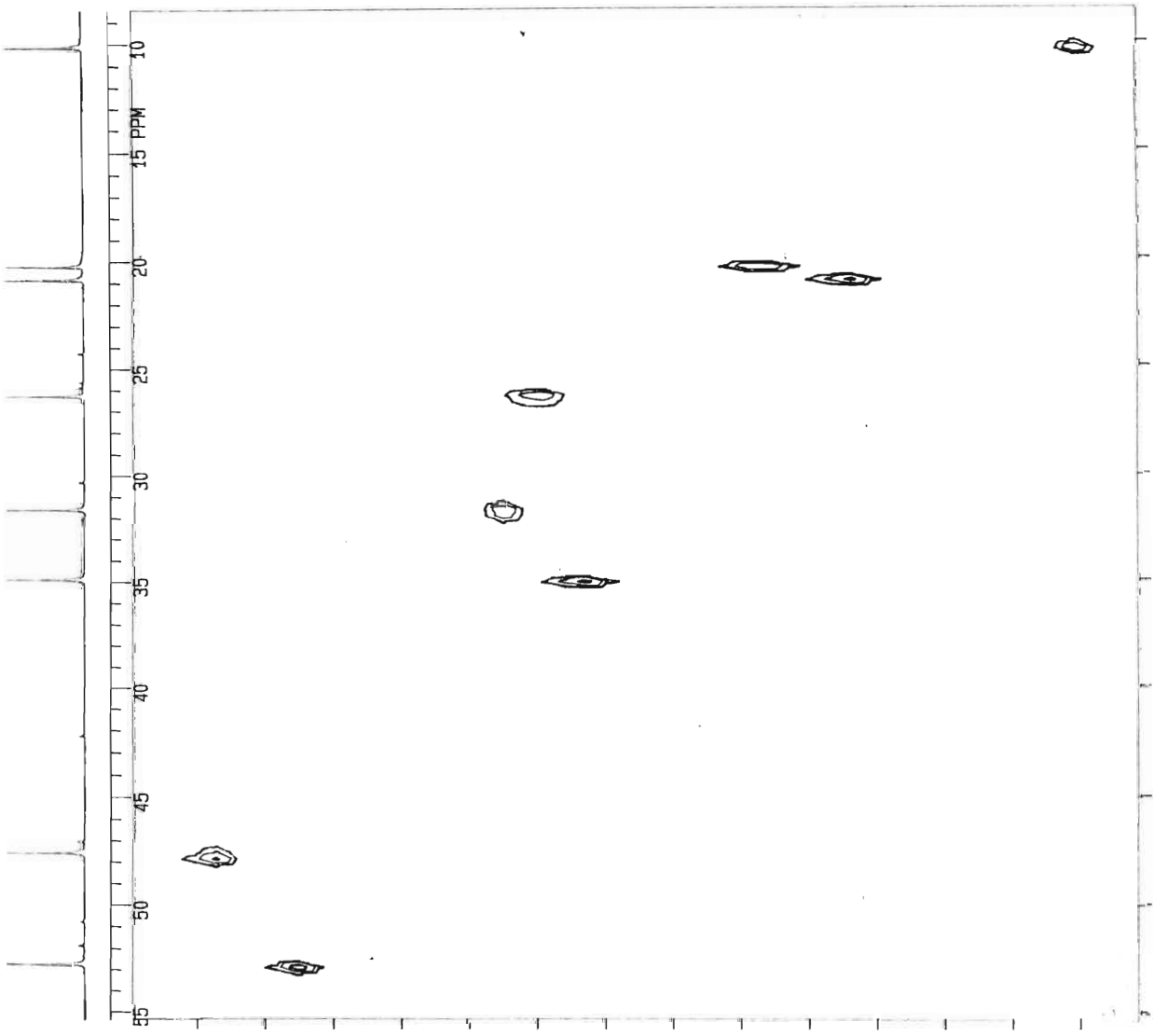

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM


10
15 PPM
20
25
30
35
40
692629 HAN55-7.5 IN CDCL3

5
4
6
N
7
3a
O
3
7a
1
2

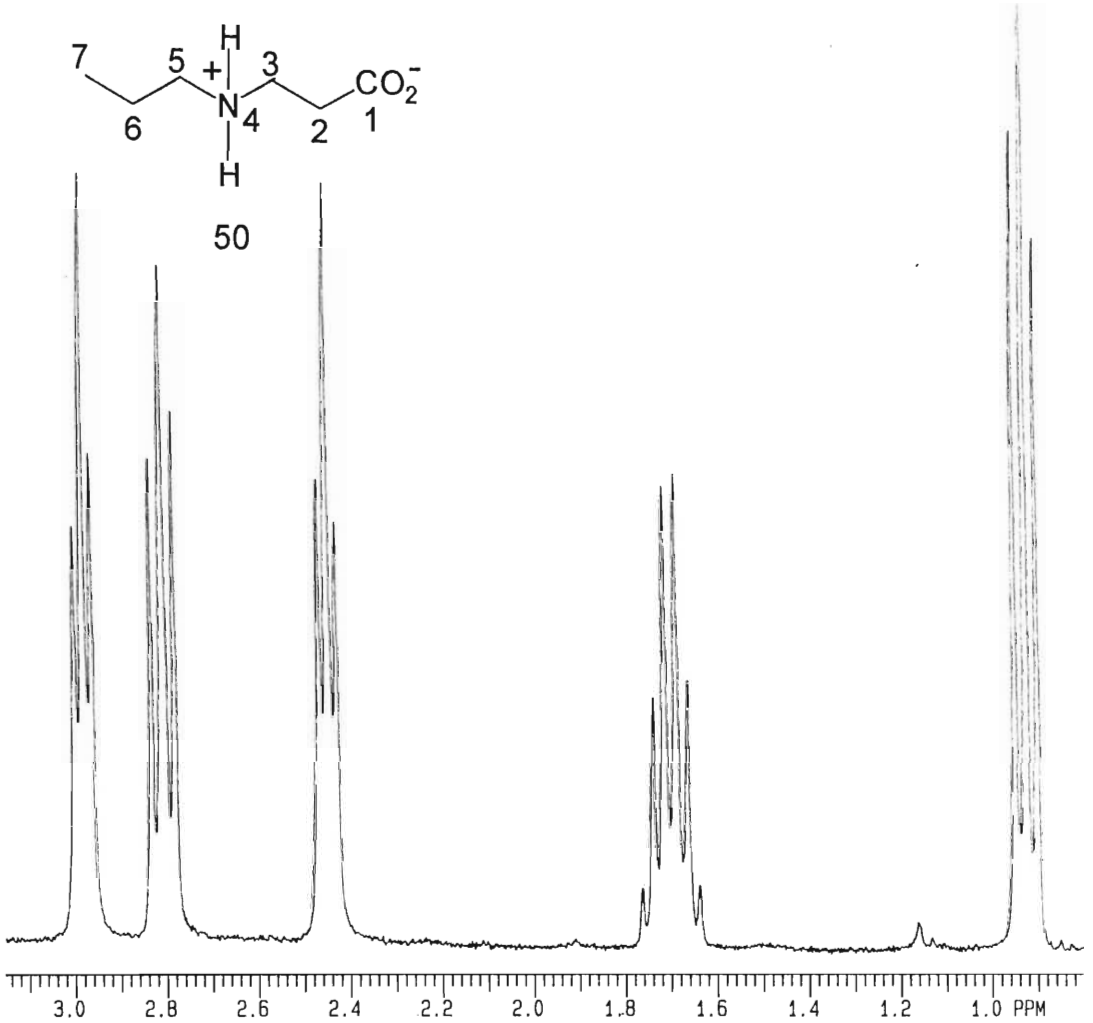
47

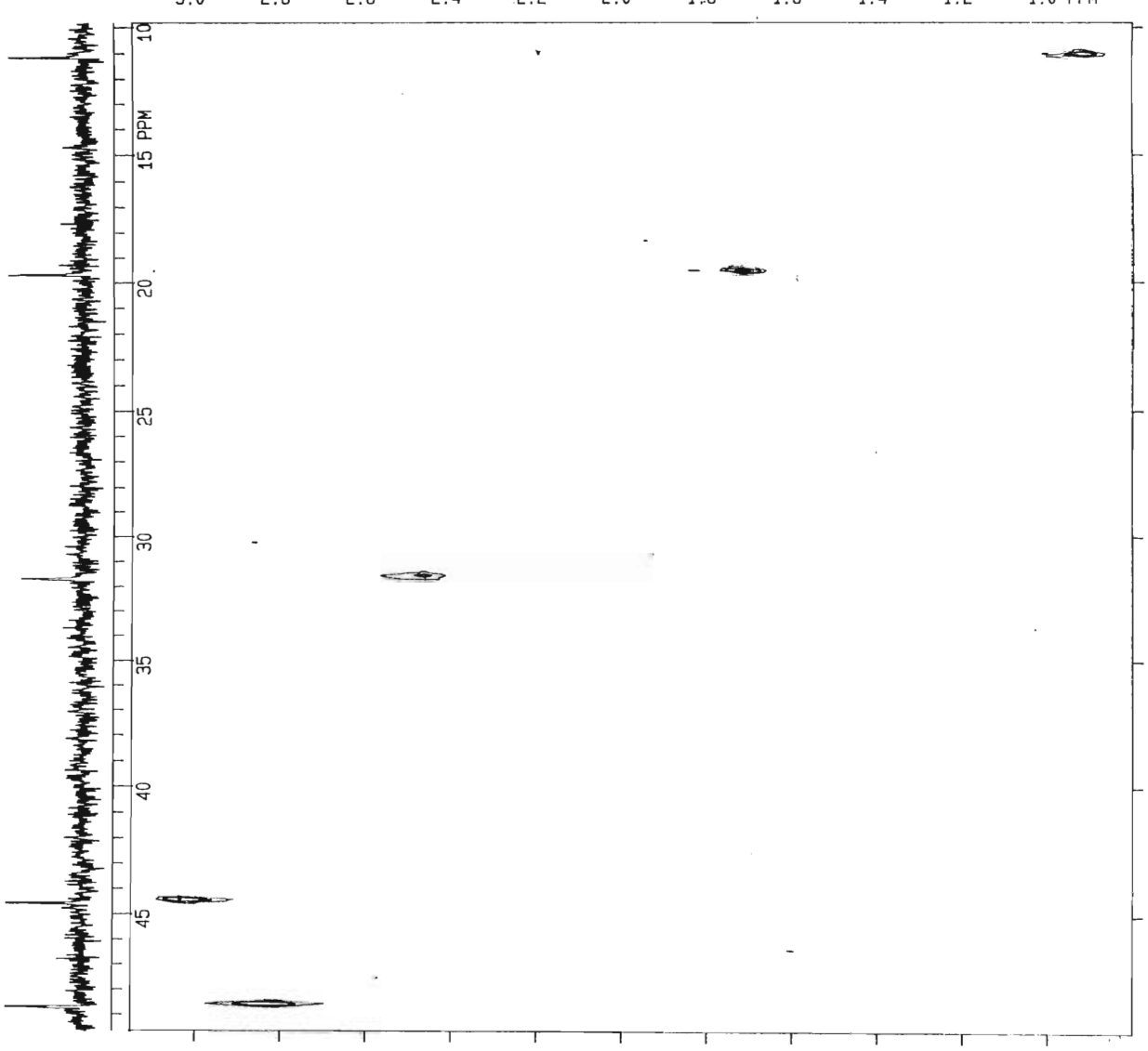

3.0
2.5
2.0
1.5
1.0 PPM
0.5


10
15 PPM
20
25
30
35
40
45
50
55
692624 HMPB-8.2 IN CDCL3
1H-13C HETCOR

7
6
5
+
N
H
H
4
3
2
1
CO_2^-

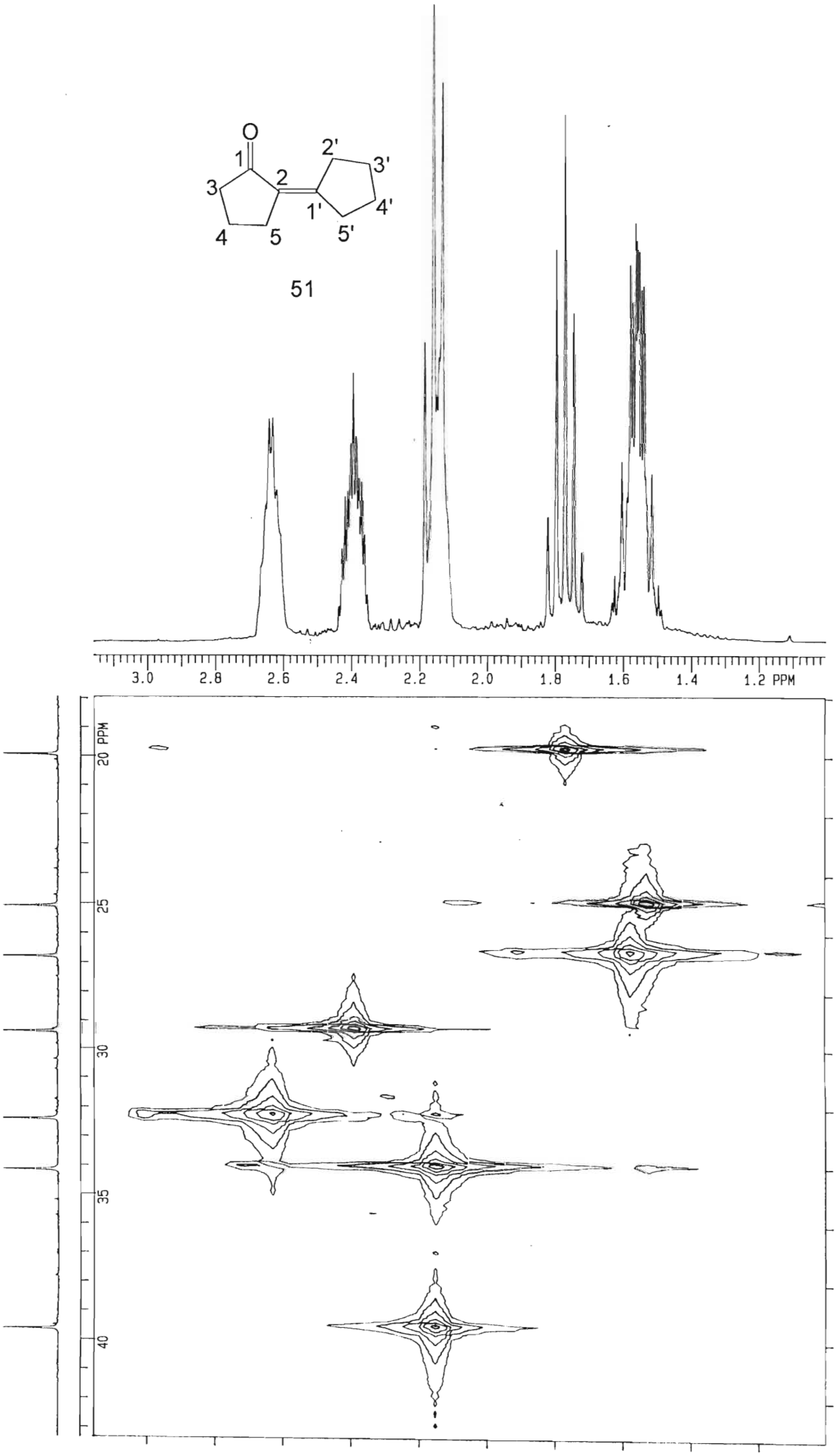
50

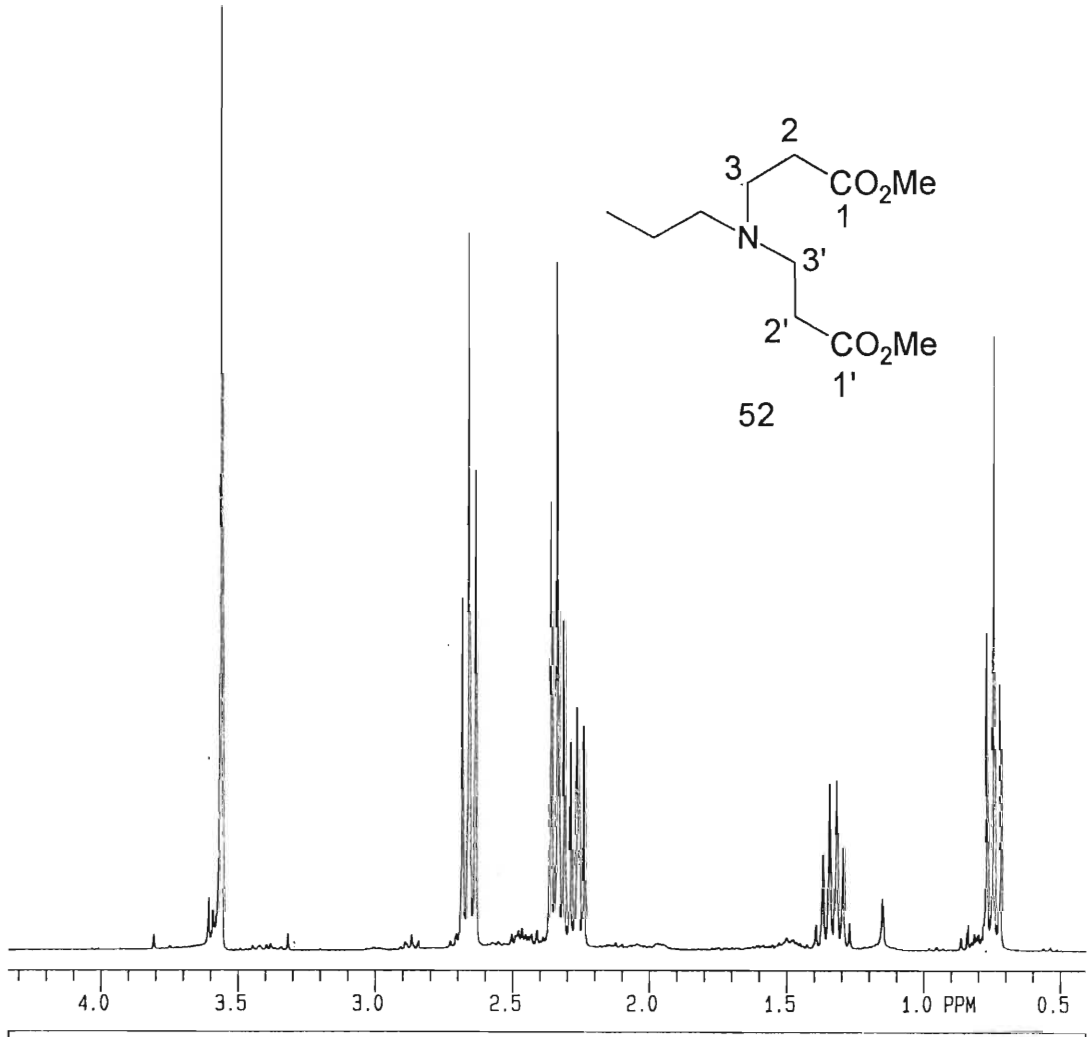

3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0 PPM

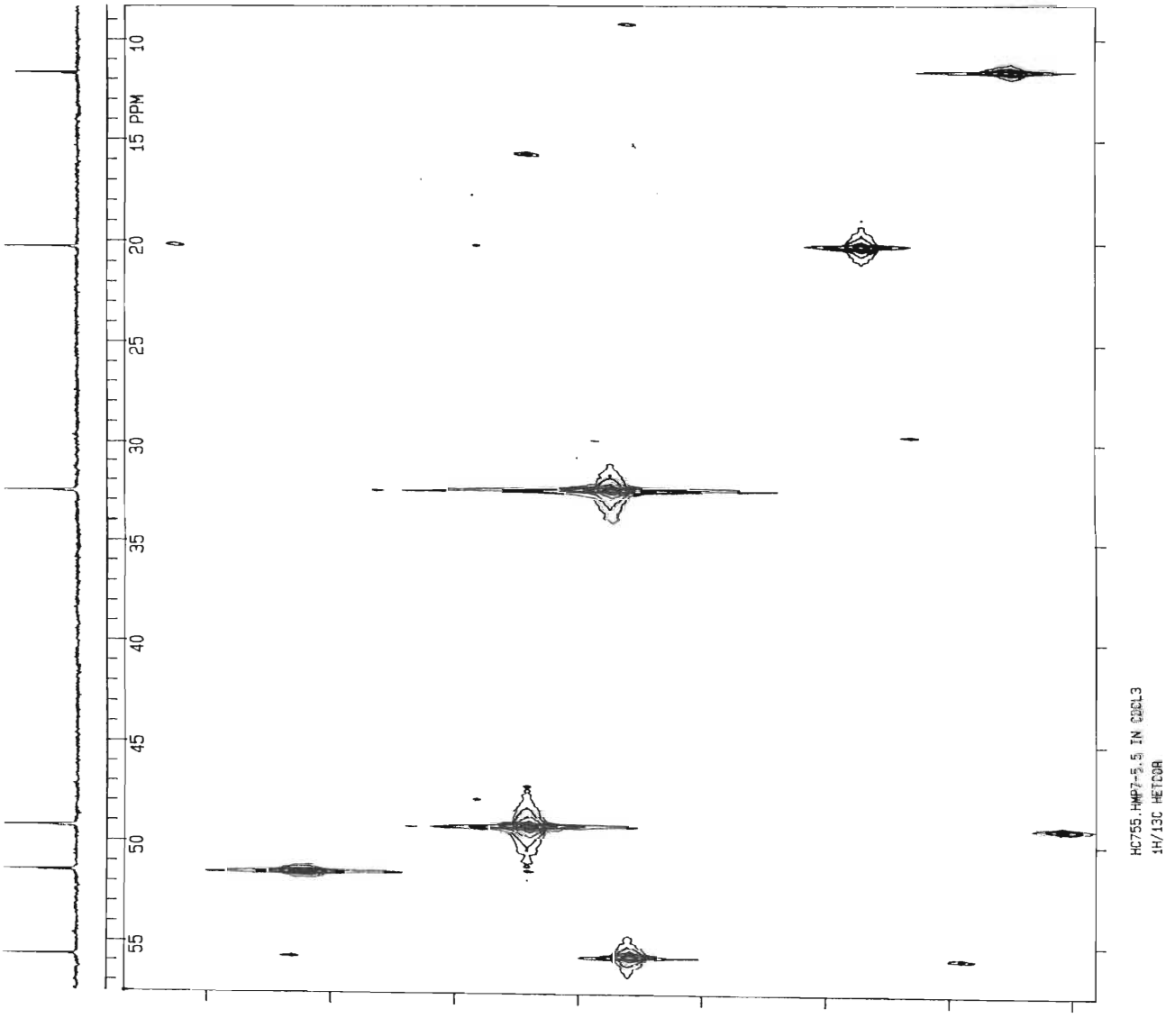

10
15 PPM
20
25
30
35
40
45
HCM10C.HMM10C IN CDCL3
1H/13C HETCOR

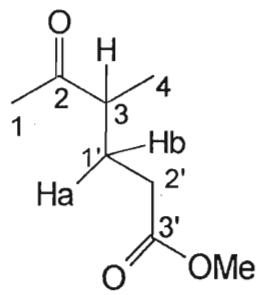
O
1
2
3
4
5
1'
2'
3'
4'
5'

51

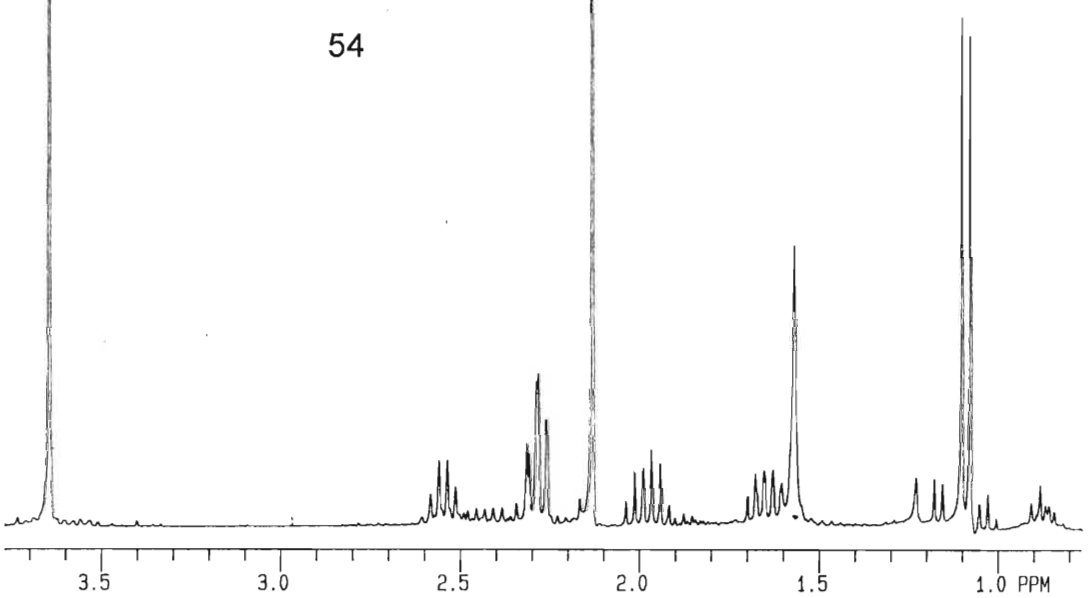

3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2 PPM
20 PPM
25
30
35
40
HCHM47.HMP VD.4.7 IN CDCL3
1H/13C HETCOR

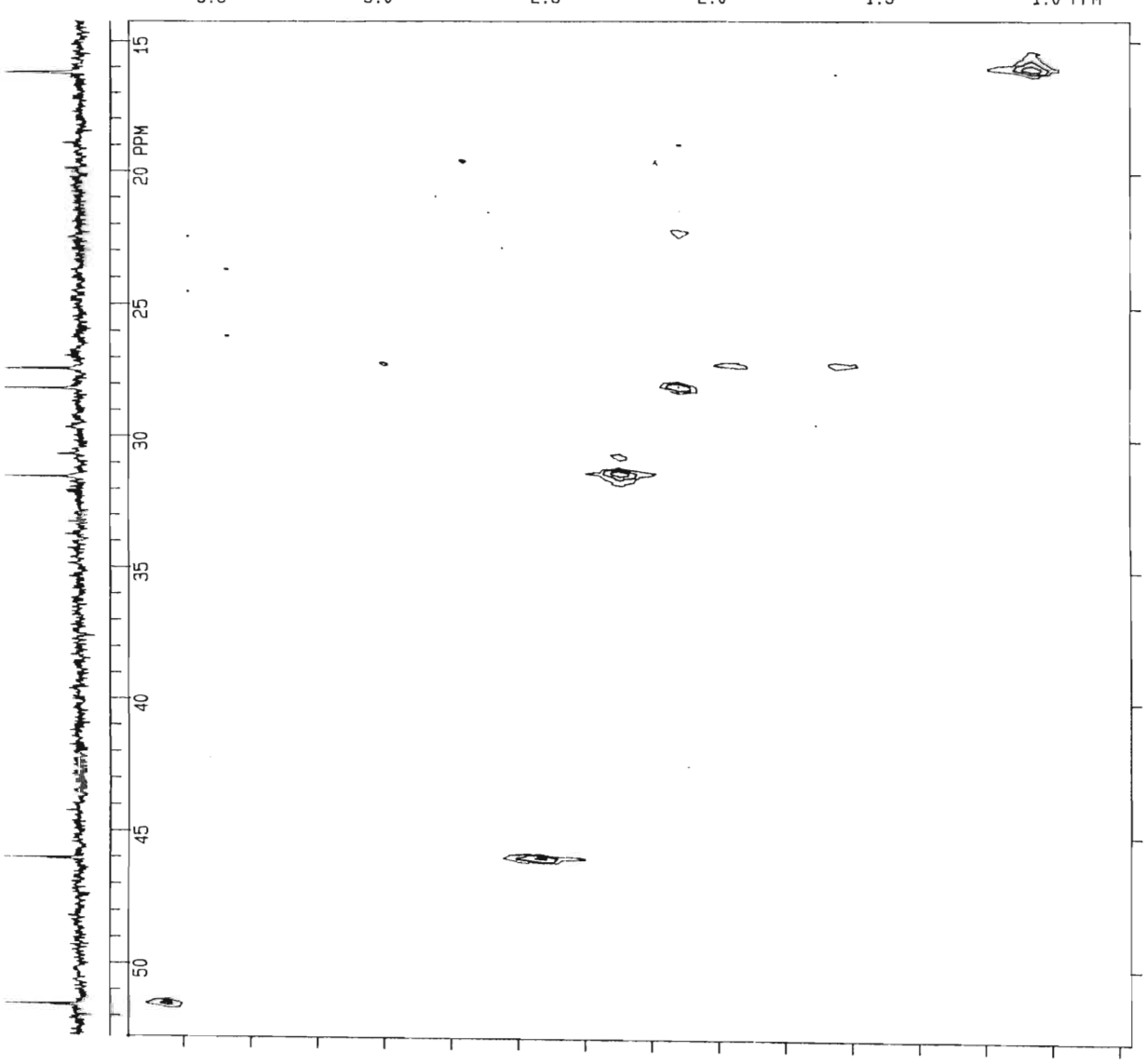

2
3
CO2Me
1
N
3'
2'
CO2Me
1'
52
4.0
3.5
3.0
2.5
2.0
1.5
1.0 PPM
0.5


10
15 PPM
20
25
30
35
40
45
50
55
HC755.HMP7-5.5 IN CDCL3
1H/13C HETCOR



54

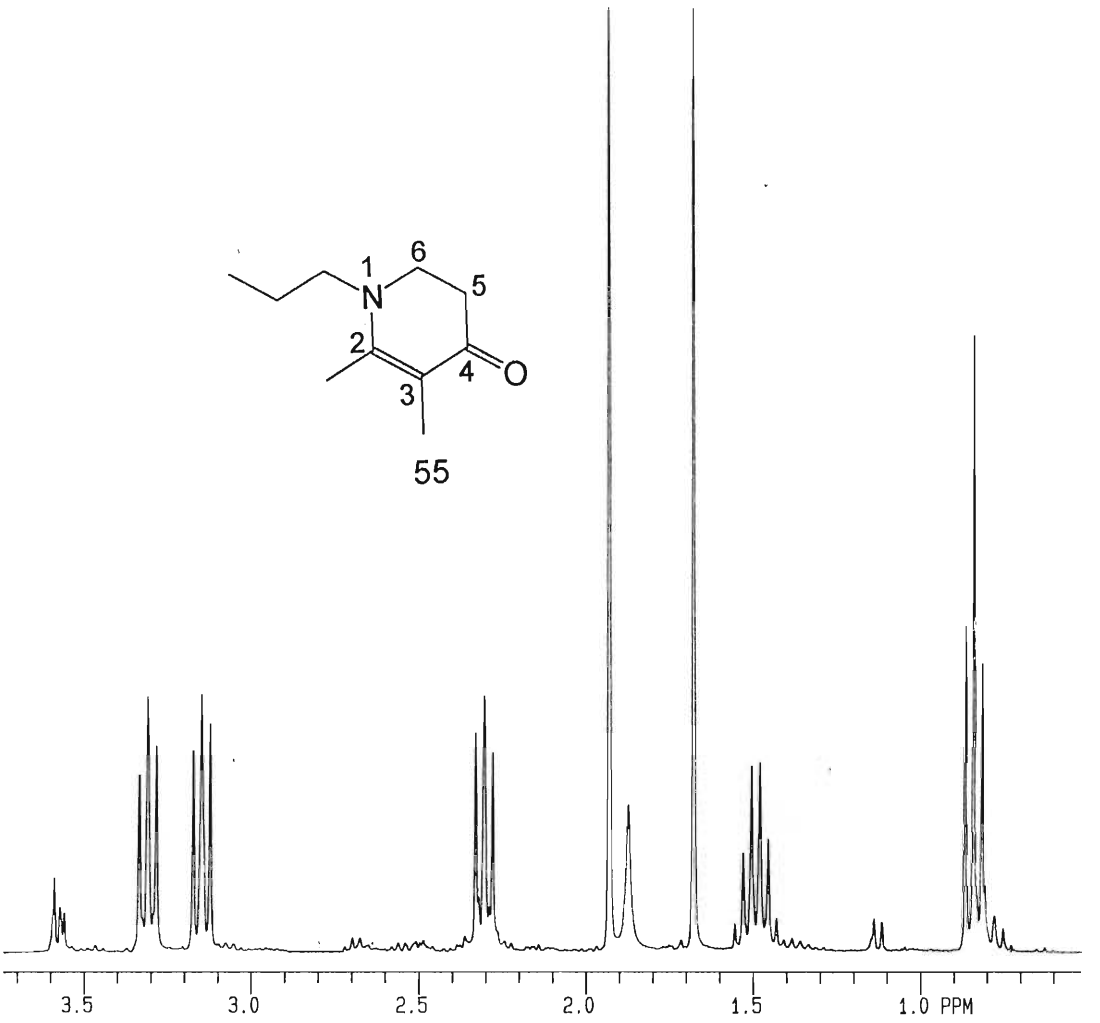


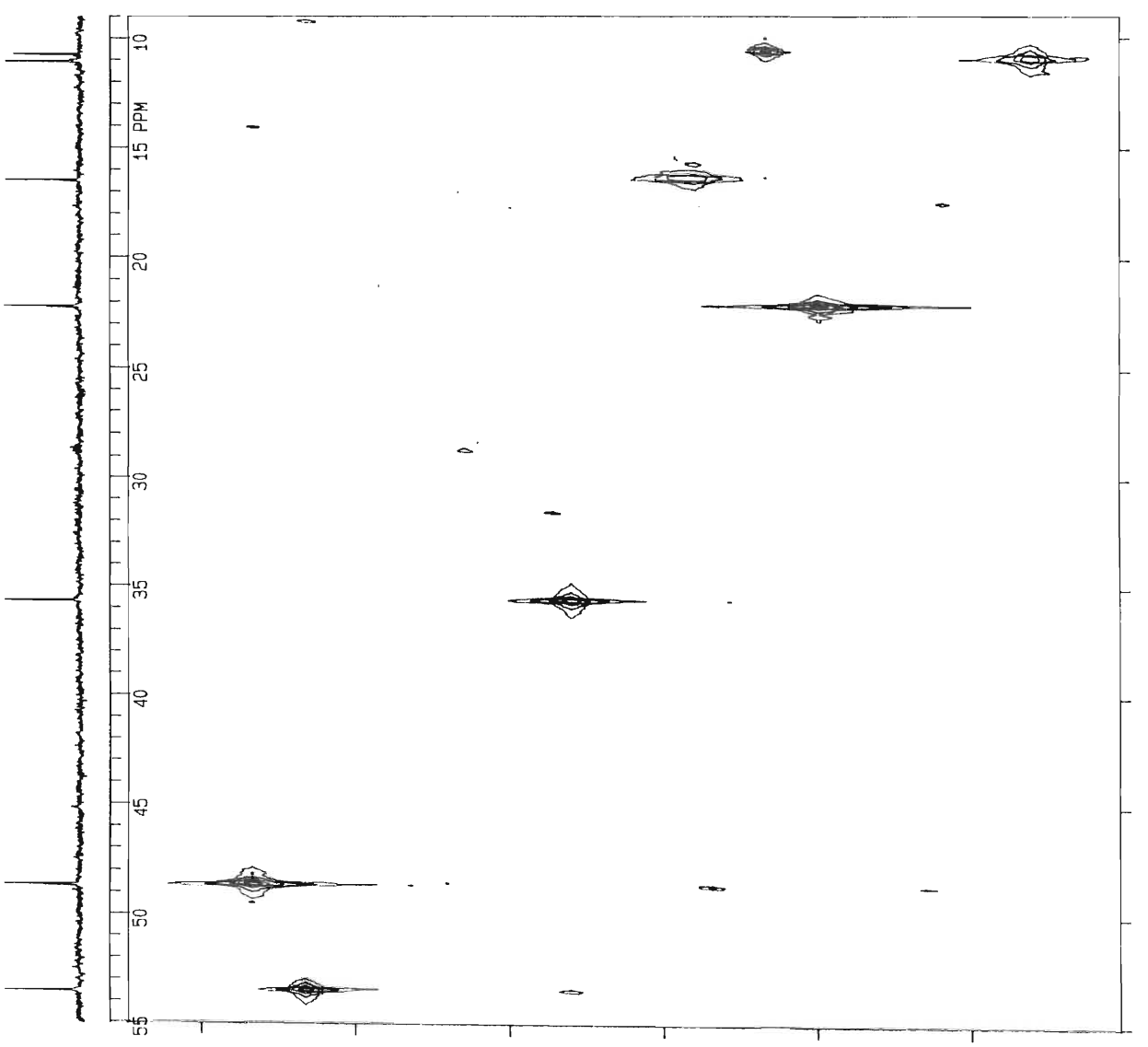


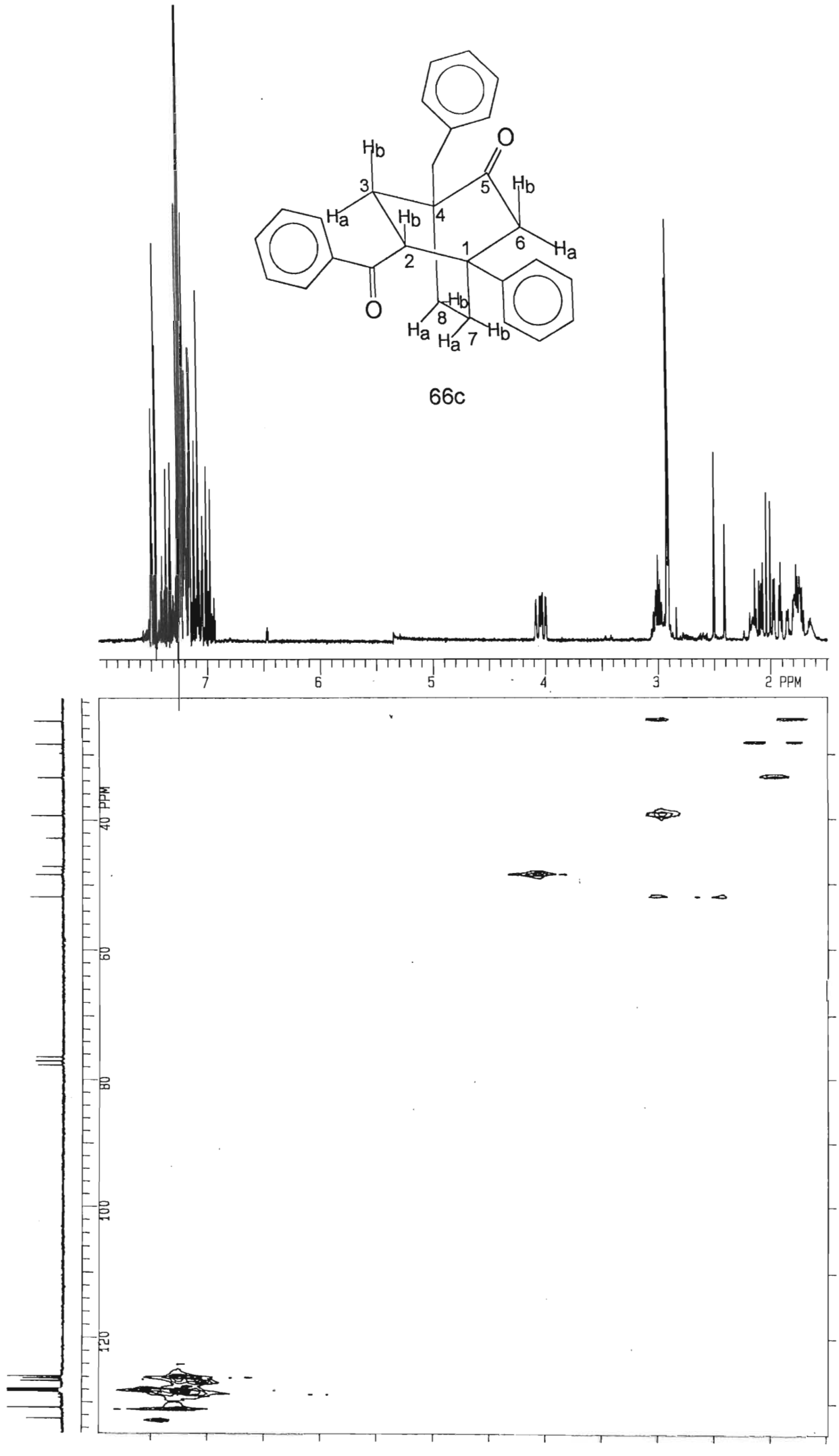
HC:28.HMP 7VD-2.8 IN CDCL3
1H/13C HETCOR

1
6
N
5
2
4
O
3

55

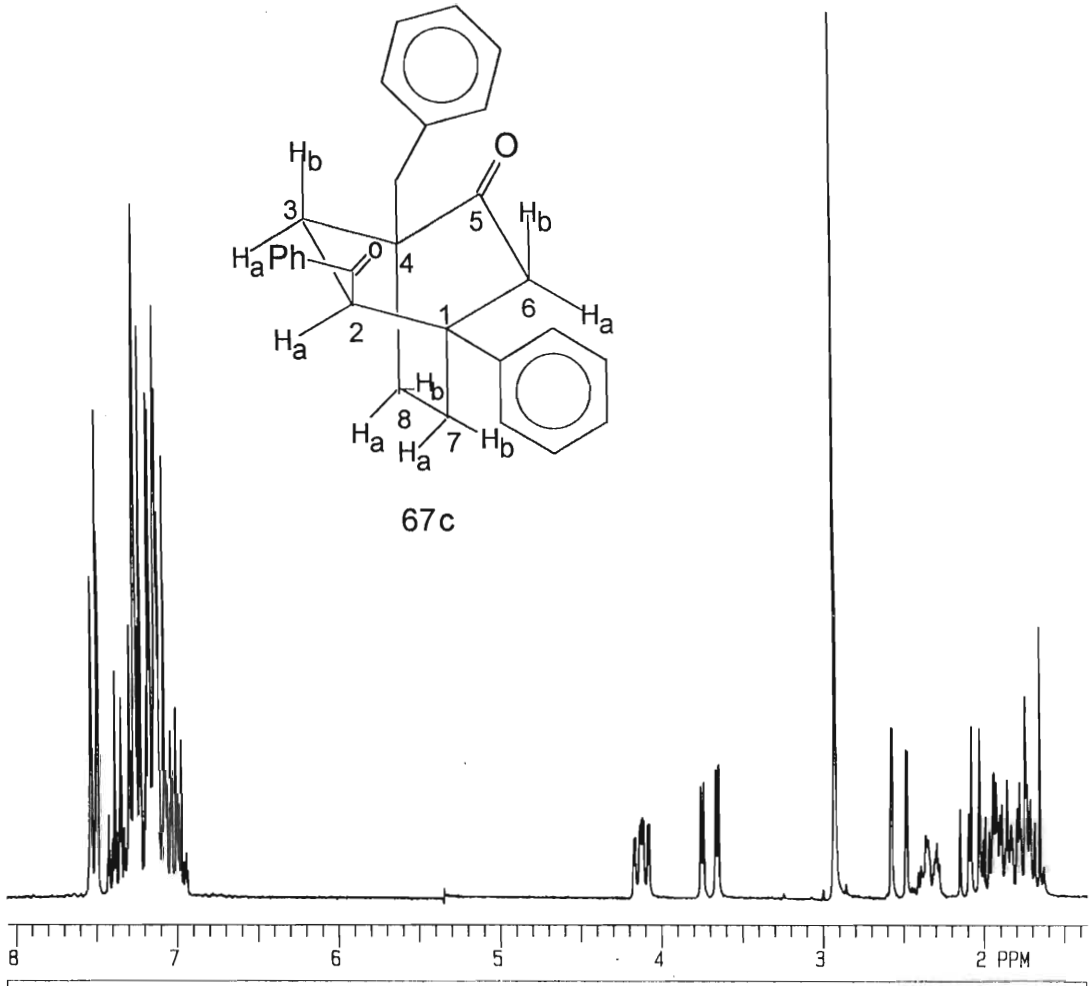

3.5
3.0
2.5
2.0
1.5
1.0 PPM

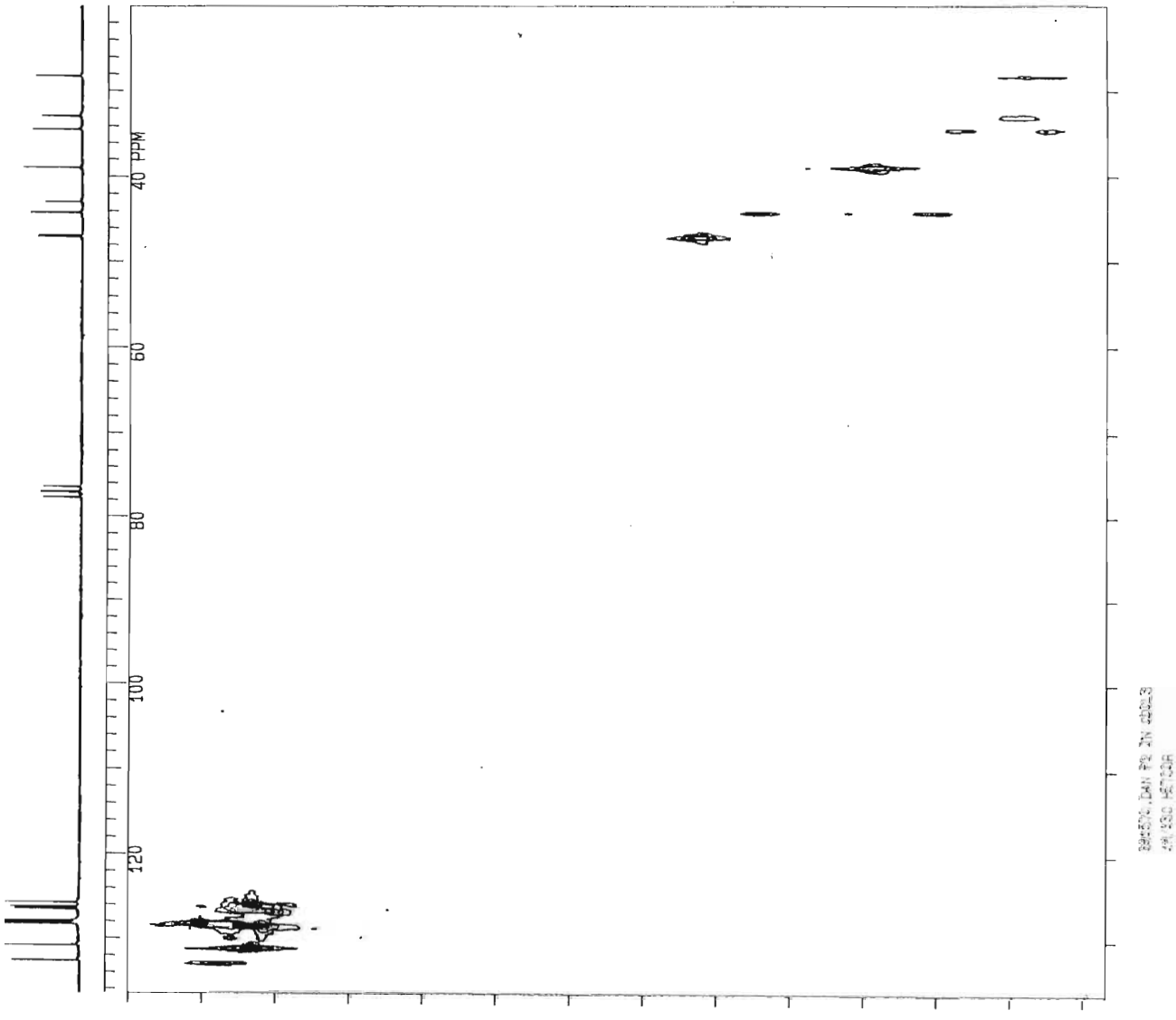

10
15 PPM
20
25
30
35
40
45
50
55
HC7VF9.HMP 7V(34-40)F9 IN CDCL3
1H/13C HETCOR

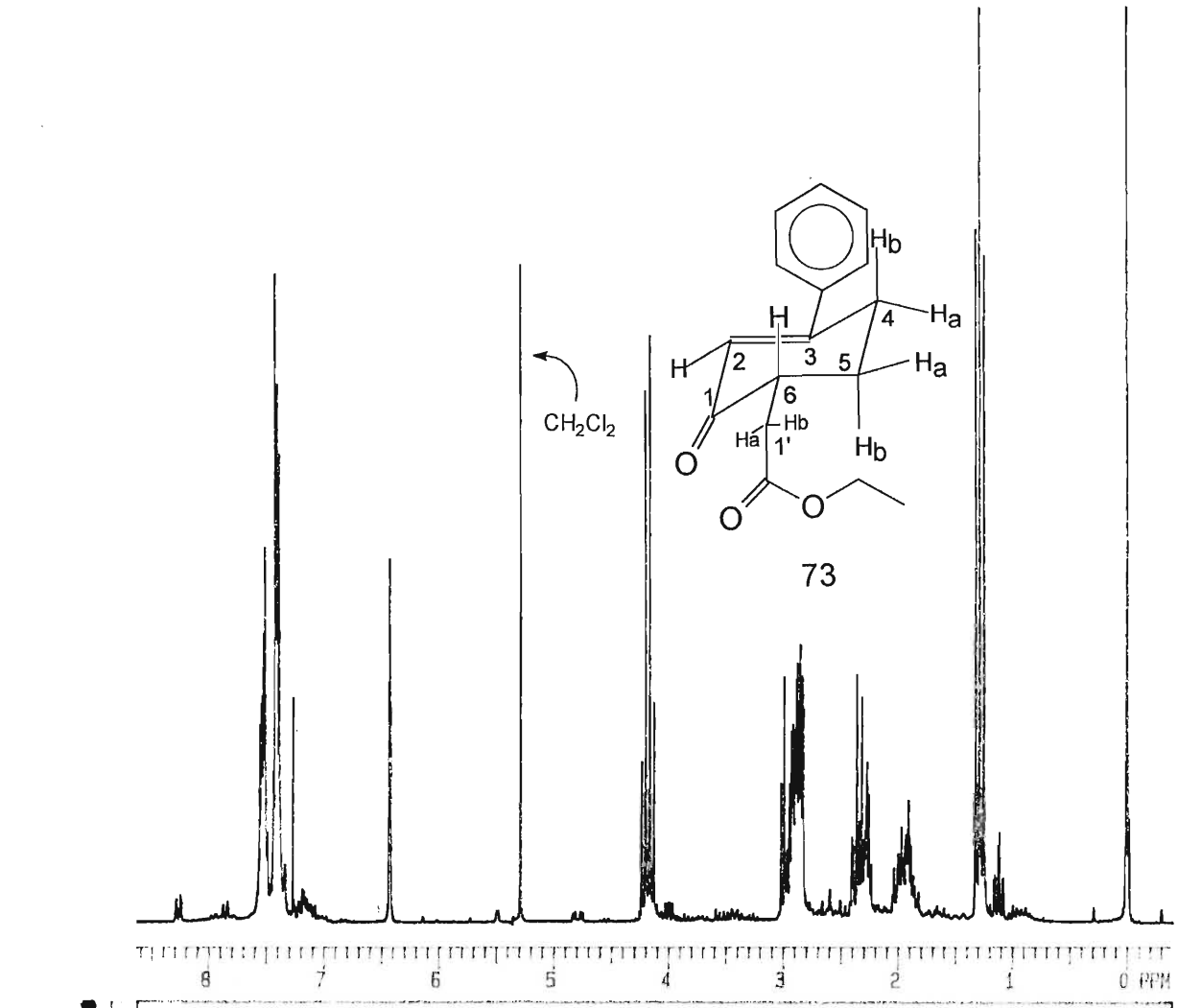

Hb
O
3
5
Hb
Ha
Hb
4
6
Ha
1
2
O
Hb
8
Ha
Ha
7
Hb
66c
7
6
5
4
3
2 PPM
40 PPM
60
80
100
120
691571.DAN P1 IN CDCL3
1H/13C HETCOR

Hb
O
3
5
Hb
HaPh
O
4
2
1
6
Ha
Ha
Hb
8
Ha
Ha
7
Hb

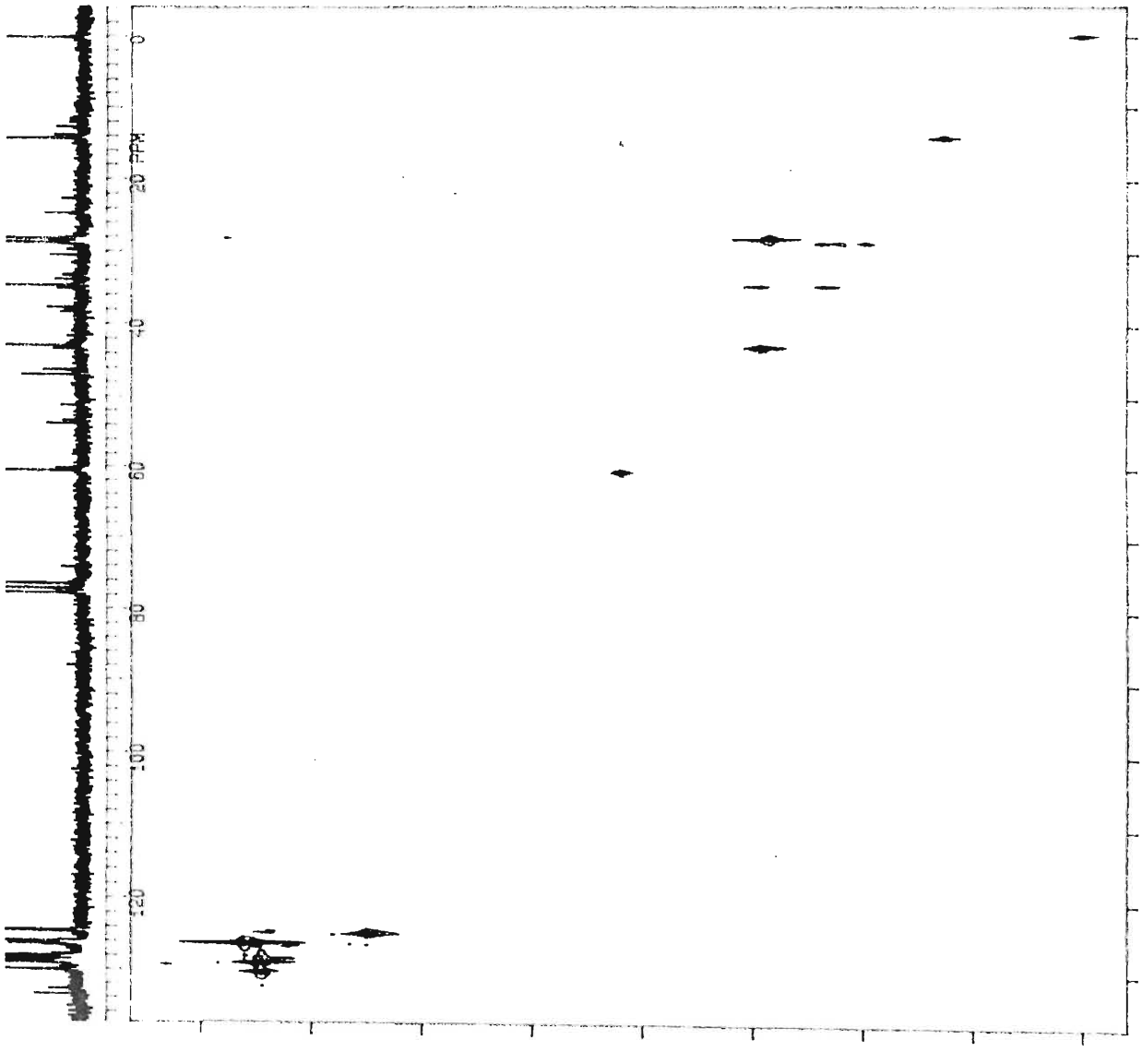
67c


8
7
6
5
4
3
2 PPM


40 PPM
60
80
100
120


Hb
H
4
Ha
H
2
3
5
Ha
1
6
Hb
Ha
1'
Hb
O
O
O
CH_2Cl_2
8
7
6
5
4
3
2
1
0 PPM

73


0
20 PPM
40
60
80
100
120
691711 HAMZA1FR6/4 IN CDCL3
1H-13C HETCOR

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