An Approach to the Synthesis of Chiral Carbamates

BY

Kathryn M. Lea

DECLARATION

I hereby certify that this research is the result of my own investigation which has not been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed:.....

K. M. LEA

We hereby certify that this statement is correct.

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January 1996

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ABBREVIATIONS

SYMBOL	DEFINITION
$[\alpha]_D$	optical rotation
Ar	aryl
BOC	*tert*-butoxycarbonyl
BuLi	*n*-butyllithium (in hexane)
C_2	symmetry axis
CAL	*Candida antartica* lipase (enzyme)
d	days/ doublet
d.e.	diasteriomeric excess
DABCO	diazabicyclo[2.2.2]octane
DCC	N,N-dicyclohexylcarbodiimide
dd	doublet of doublets
DIBAL	diisobutylaluminium chloride
DMC	dimethylcarbonate
DMF	dimethylformamide
DMG	Directing Metalation Group
DoM	Directed *ortho* Metalation
dq	doublet of quartets
dt	doublet of triplets
E	*Entgegen* (geometric isomer)
e.e.	enantiomeric excess
eq.	equivalents
Eqn	equation
EX	electrophile
g	grams
GC-MS	Gas Chromatography Mass Spectroscopy
h	hours
i	*iso*
IUPAC	International Union of Pure and Applied Chemists
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

m	*meta*
m	multiplet
M	molar
ml	millilitres
mol (mmol)	moles (millimoles)
n	*normal*
naph	naphthyl
NEt_3	triethylamine
NMR	Nuclear Magnetic Resonance Spectroscopy
o	*ortho*
p	*para*
Ph	phenyl
PPTS	*para*-phenyltoluene sulfonate
py	pyridine / pyridyl
q	quartet
R	alkyl / carbon based group
R.T.	Room Temperature
RX	electrophile / alkyl halide
s	*sec* (secondary)
t	*tert* (tertiary)
t	triplet
Tf	triflate (trifluoro-methylsulfonate)
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	N,N,N',N'-tetramethyl-1,2-ethylenediamine
TMS	tetramethylsilane / trimethylsilyl
Ts	tosyl (toluenesulfonic acid)
Z	*Zusammen* (geometric isomer)

ABSTRACT

An attempt to obtain chiral induction across the carbamate linkage (-NCOO-), using chiral amines and the benzyl carbamate, was embarked upon. Initial studies centred around the benzyl carbamate protected form of α,α-diphenylpyrrolidinemethanol. The inability to protect the alcohol in this compound led to further investigations into differently structured molecules, these being 2-(1-phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine and N-biphenyl benzyl carbamate. Chiral induction was not achieved, but the investigations therein led to two new fields of study.

A trans-carbamation type cyclisation reaction was found to occur in the α,α-diphenyl-(2-pyrrolidine-N-benzyl carbamate)methanol compound yielding the bicyclic 2-oxazolidone, 3-oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one, with nitrogen at the bridgehead position. Sodium hydride was the base used to facilitate this reaction. Further studies into this reaction and this class of compounds were inconclusive.

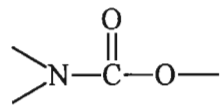
The second field of study was the initial investigation into novel N-monosubstituted carbamate rearrangement reactions to yield a substituted alcohol, of the benzyl alcohol type. The rearrangement occurs when the carbamate is treated with butyllithium at 0°C and the reaction allowed to warm to room temperature. The rearrangement was shown to occur when the substituent on the nitrogen is aromatic in nature, this group being able to contain a hetero-atom and be substituted. A positive result was also obtained when the O-carbamate moiety was the benzyl or cinnamyl group and to a much lesser degree the allyl group. The products obtained from the rearrangement of the benzyl carbamates were α-aryl-α-phenylmethanols (substituted benzyl alcohols / benzhydrols), with the analogous product, 1-aryl-3-phenylprop-2-en-1-ol, being obtained from the cinnamyl alcohol. A benzylic substituted benzyl carbamate rearranged to give the tertiary alcohol. It was found that the rearrangement occurred to the position on the aryl substituent to which the nitrogen had been attached. From the results obtained no conclusive mechanistic details could be determined, but it was proposed that the reaction intermediate contained a five-membered cyclic structure. It is assumed that the rearrangement occurs with concomitant loss of cyanic acid (HNCO).

1. INTRODUCTION

1.1 CARBAMATES

1.1.1 GENERAL

Compounds belonging to the class of organic molecules known as carbamates all contain, as a major feature, the carbamate bond or linkage, depicted below.



The class name of carbamates is derived from the name of the simplest parent compound, carbamic acid (H_2NCOOH). Carbamic acid itself has never been isolated[1]. It is only known as a reaction intermediate, as it is unstable, particularly in acidic media where it decomposes to give ammonia and carbon dioxide[2]. However, carbamic acid is a useful compound on which the carbamate naming system has been based. Esters of the acid, *i.e.* substituents on the oxygen, or alcohol derived moieties, are referred to as alkyl or aryl carbamates, and occasionally as O-alkyl or O-aryl moieties. Substituents on the nitrogen are designated using the N-prefix[1, 2]. Thus PhNHCOOEt is named ethyl N-phenyl-carbamate[1]. Recently it seems to be becoming popular and acceptable to name carbamate substituents the other way around, for example the previous compound's name becomes N-phenyl ethyl carbamate.

Historically carbamates were called urethanes or urethans, names derived from the class of polymers called polyurethanes which contain the carbamate linkage. Ethyl carbamate ($H_2NCOOEt$) is traditionally known as urethan and methyl carbamate ($H_2NCOOMe$), to a lesser degree, as urethylan[1].

Carbamates have been known for a long time, becoming known at about the same time that modern organic chemistry was begun. One of the first reported syntheses is of ethyl carbamate by Wohler in *ca.*1840[1]. Interest in carbamates through the years has been extensive and varied.

1.1.2 PROPERTIES

Physical properties: Methyl carbamate is a white solid with melting point of 54°C and boiling point of 177°C (760 mmHg). Ethyl carbamate is also a white solid with melting point of 48°C and boiling point of 185°C (760 mmHg). It sublimes and is hydrophilic. Ethyl carbamate is soluble in lower alcohols, ketones, ethers, esters, chlorinated hydrocarbons and water, partially soluble in aromatic hydrocarbons and insoluble in aliphatic hydrocarbons. Carbamates of higher alcohols are crystalline solids which have melting point ranges always higher than the corresponding acetate[1]. More complex, that is substituted, carbamates may be liquids or crystalline solids and tend to absorb moisture[3].

Spectral properties: In Infrared absorption spectra the major peaks occur in the carbonyl region. The ester characteristics of the carbamate linkage dominate the amide characteristics of the bond. Carbonyl absorption for N-unsubstituted carbamates occurs in the 1725 cm^{-1} region and for N-monosubstituted carbamates in the 1714 cm^{-1} region. Many carbamates, like esters, have what appears to be a -C-O-C- stretching band in the 1050 - 1000 cm^{-1} region. In mono- and unsubstituted carbamates the amide band is found in the 1620 cm^{-1} region. The N-H stretch absorption band is, like open chain amides, found in the 3300 - 3250 cm^{-1} region[1].

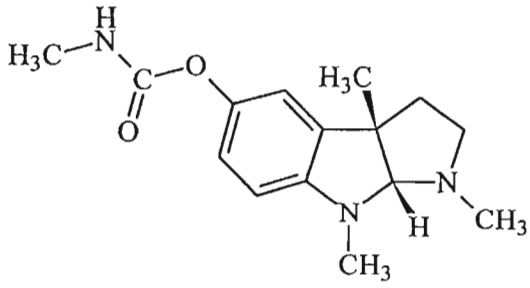
Chemical properties: Carbamates exhibit characteristic properties of both esters and amides. Some of their reactions resemble reactions involving esters, amides, enols and isocyanates[1].

1.1.3 USES

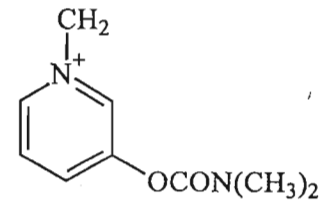
The uses of carbamates are extensive and range from agricultural applications through medical, biological and industrial applications to their synthetic utility in chemistry.

Ethyl carbamate has historically been used extensively in the medical field. It inhibits mitosis, and thus cell growth, and has therefore been used against leukemia[1]. Ethyl carbamate also acts as a nervous system depressant and has thus been used as an antidote

against central nervous system stimulant poisons such as strychnine. It and other simple carbamates have been used as antiseptics, local anaesthetics[1] and anticonvulsants[4,5]. Ethyl carbamate inhibits the enzyme acetylcholinesterase only slightly; however other carbamate compounds are far more active in this regard[6]. Acetyl choline is one of the main messengers in nerve synapses and is acted upon by the enzyme acetylcholinesterase. If the enzyme is inhibited it allows for an increase in concentration of acetylcholine in the nerve synapse, this situation becoming fatal to the organism if these concentrations become too high. The carbamate compound physostigmine **(1)**, and its HP290 analogue which has an altered carbamate moiety, are showing excellent results in tests against Alzheimer's disease. Sufferers have too low a concentration of acetylcholine in the brain nerve synapses and thus suffer from memory loss. Carefully administered doses of enzyme inhibitor therefore allows for these levels to be kept at a suitable concentration. Acetylcholinesterase is also the target of many nerve gases and the compound pyridostigmine **(2)** has therefore been used by the military as it has the ability to bind reversibly to the enzyme, therefore preventing poisoning initially by the gas or later by enzyme inhibition. Carbamates have also been used as prodrugs for amino-functional drugs (β-blockers) to improve drug delivery to man by increasing the drug's permeation through membranes[7].



(1)



(2)

Industrially carbamates have extensive use as they form a large class of polymers, namely the polyurethanes. Other applications of carbamates include the use of substituted alkyl carbamates as plasticisers for natural and synthetic rubbers[8] and the use of ethyl or propyl carbamate as a plasticiser for melamine-isocyanate resins and laminates[9]. Carbamates have also been used in hair setting agent preparations[10] and as crease-resistant finishes for cottons[11].

By far one of the largest uses of carbamates, other than their use as polyurethanes, is in the agricultural sphere where they are used extensively as pesticides[12], insecticides[13], herbicides and fungicides[14]. Here their mode of action is believed to be the deadly build-up of acetylcholine in the organism, by inhibition of the enzyme. Carbamates form a more desirable class of pesticides as they do not remain active in the soil for extended periods of time, unlike such compounds as DDT.

The synthetic utility of carbamates will be discussed in **1.1.5.6**.

1.1.4 FORMATION REACTIONS OF CARBAMATES

Although in the history of carbamate preparations the number of methods are numerous, only a few classes have developed to a level of significance.

1.1.4.1 REACTION OF ALCOHOLS WITH UREA[1]

The preparation of carbamates by the reaction of alcohols with urea **(Eqn 1)** is of more industrial than laboratory importance. Methyl and ethyl carbamate are commercially prepared by this method. For the preparation of ethyl carbamate ethanol and urea have to be heated under pressure to approximately 150°C for a number of hours. Due to these conditions, the high temperatures being necessary for the optimum dissociation of urea into its reactive intermediates, cyanic acid and ammonia, this method is limited to the preparation of carbamates from higher boiling alcohols. Metal salts, for example zinc and cobalt chlorides, lead acetate and metal salts of weak organic acids, are known to have a catalytic effect on the reaction, reducing reaction time and improving yields. Unfortunately this reaction is unsuitable for reactions involving tertiary alcohols, phenols or urea reactive groups. N-substituted ureas can be used, giving the alkyl carbamate or N-alkyl alkyl carbamate, or mixtures of these **(Eqn 2)**.

$$H_2NCONH_2 + ROH \longrightarrow H_2NCOOR + NH_3 \quad \textbf{(Eqn 1)}$$

$$R'NHCONH_2 + ROH \longrightarrow \begin{matrix} R'NHCOOR + NH_3 \\ H_2NCOOR + R'NH_2 \end{matrix} \quad \textbf{(Eqn 2)}$$

1.1.4.2 REACTION OF AMINES AND CHLOROFORMATES

The reaction of chloroformates with amines is a general reaction for the laboratory preparation of carbamates[1] **(Eqn 4)**. Most alcohols in the presence of base will react with phosgene ($COCl_2$) to give the corresponding chloroformate, which may then be used in the reaction **(Eqn 3)**. Unfortunately phosgene is an exceptionally dangerous reagent, being toxic and difficult to handle as it is a gas, which makes this preparation method undesirable. However phosgene equivalents, such as triphosgene[15,16] ($Cl_3COCOOCCl_3$) and trichloromethyl chloroformate[17] (Cl_3COOCl), which are safer have been developed, along with improved preparation methods for these reagents.

$$ROH + COCl_2 \longrightarrow ROCOCl + HCl \quad \textbf{(Eqn 3)}$$

$$ROCOCl + NHR'R'' \longrightarrow ROCONR'R'' + HCl \quad (R',R'' \text{ can} = H) \quad \textbf{(Eqn 4)}$$

1.1.4.3 TRANSESTERIFICATION METHODS

When carbamates, particularly methyl and ethyl carbamate, are heated together with higher boiling alcohols exchange of the alcohol portions occurs to give a more complex carbamate **(Eqn 5)**. The reaction occurs with N-substituted and unsubstituted systems and with primary and secondary alcohols, but is unsuitable for exchange with tertiary alcohols or phenols. The reaction is catalysed by aluminium isopropoxide, as well as a number of other organometallic compounds being reported[1].

$$ROCONR'R'' + R'''OH \longrightarrow R'''OCONR'R'' + ROH \quad \textbf{(Eqn 5)}$$

1.1.4.4 REACTION OF CARBAMOYL CHLORIDES WITH ALCOHOLS

N-monosubstituted carbamoyl halides are unstable, decomposing to the isocyanate and hydrogen halide, and therefore this preparation method may only be used for the preparation of N,N-disubstituted carbamates, from the correspondingly more stable N,N-disubstituted carbamoyl halides (usually chloride). The N,N-disubstituted carbamoyl chlorides are invariably prepared by the reaction of secondary amines with phosgene [2], or phosgene equivalents **(Eqn 6)**. Reaction of the carbamoyl chloride with the desired alcohol, usually in the presence of base such as pyridine[18] or NEt_3, yields the desired carbamate[1,2] **(Eqn 7)**.

$$R'_2NH + COCl_2 \longrightarrow R'_2NCOCl + HCl \quad \textbf{(Eqn 6)}$$

$$R'_2NCOCl + ROH \longrightarrow R'_2NCOOR + HCl \quad \textbf{(Eqn 7)}$$

1.1.4.5 REACTION OF ISOCYANATES WITH ALCOHOLS

The wide availability of isocyanates makes the reaction of isocyanates with alcohols an excellent general method for the preparation of N-substituted carbamates[1] **(Eqn 8)**. The reaction is rapid and quantitative for alcohols, but is slower for phenols, usually being catalysed by tertiary amines[2]. The versatility of products available from this preparative route is further increased by trapping with the alcohol the isocyanate intermediates in the Curtius, Lossen, Hofmann and other rearrangement reactions[2].

$$R{-}N{=}C{=}O + R'OH \longrightarrow R{-}\underset{H}{N}{-}\overset{O}{\overset{\|}{C}}{-}OR' \quad \textbf{(Eqn 8)}$$

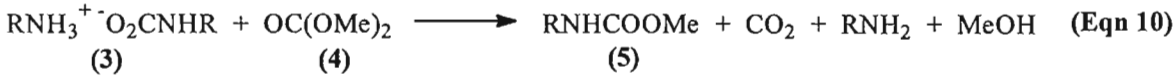
1.1.4.6 AMINOLYSIS OF CARBONATE ESTERS

Carbamates may also be prepared by the aminolysis of carbonate esters (dialkyl carbonates)[2] **(Eqn 9)**. This reaction is most successful when the two alkyl portions are identical, or if there is a large difference in leaving abilities between the two groups. This method cannot be used for the preparation of carbamates with good leaving groups, *i.e.* phenyl carbamate, as the carbamate formed is more reactive that the starting material carbonate.

(Eqn 9)

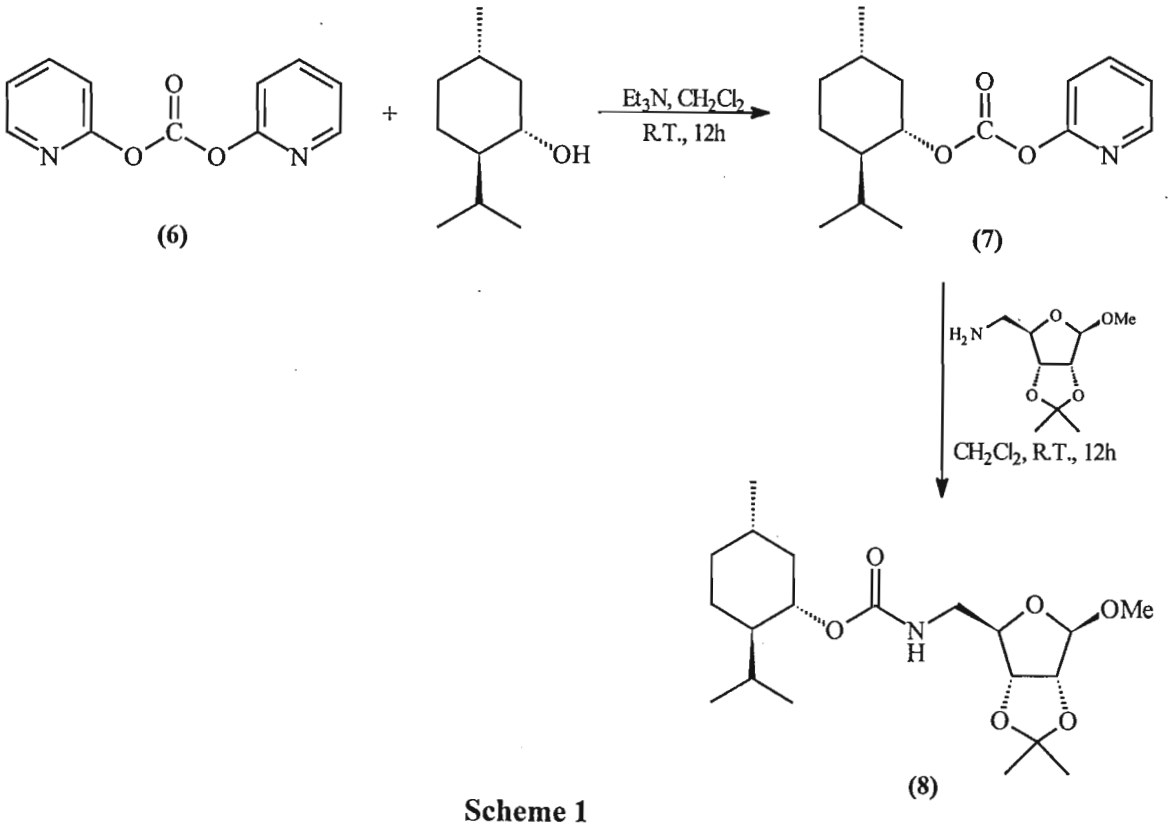
The reaction between primary and secondary amines and dialkylcarbonates needs to be catalysed to achieve satisfactory conversion rates. Some examples of catalysts are strong bases, such as alkali metal alkoxides, and Zn, Co, Sn, Al and Ti compounds for the carboxylation of aromatic amines and Lewis acids, such as $AlCl_3$, $SnCl_2$, $ZnCl_2$ and $FeCl_3$, for the effective conversion of *n*-propylamine and diethylcarbonate to N-propyl ethyl carbamate[19].

Recently the use of carbon dioxide has been reported[19]. Initially alkylammonium N-alkyl carbamates **(3)** are formed by saturating amine solutions with CO_2 and then these are reacted with dimethylcarbonate (DMC) **(4)** to yield the N-alkyl methyl carbamates **(5)** **(Eqn 10)**.



(3) **(4)** **(5)** **(Eqn 10)**

The preparation of functionalised and complex carbamates has recently been reported using di(2-pyridyl)carbonate **(6)** to promote the alkoxycarbonylation of amines[20]. Di(2-pyridyl)carbonate **(6)** may be reacted with a variety of alcohols, including hindered secondary and tertiary alcohols and protected glycols, to give the mixed carbonate **(7)**. This is then reacted with the amine, even complex amines and those containing functional groups, to efficiently obtain the carbamate **(8)**, by replacement of the second pyridyl moiety by the amine. An example of this reaction is shown below **(Scheme 1)**.



(6) (7) (8)

Scheme 1

1.1.4.7 MISCELLANEOUS METHODS

A variety of other methods have been used for the preparation of carbamates. Some of historical interest are the following reactions: a mixture of amine, alcohol and urea, when heated, gives both N-alkyl carbamates and unsubstituted carbamates[1]; phenyl cyanate when hydrolysed by acid yields phenyl carbamate[1]; aminoethyl carbamates have been formed by the reaction of urea and ethylene oxide[1]; heating an alcohol with urea nitrate, in the

presence of zinc chloride, yields the corresponding carbamate[1]; and the reaction of cyanic acid (usually obtained from the thermal decomposition of cyanuric acid) with alcohols also produces carbamates; however allophanates ($ROCONHCONH_2$) may also be formed[1, 2].

Recently a number of reports have appeared in the literature for the preparation of carbamates directly from carbon dioxide, amines and alkyl groups. Butcher[21] reports the formation of a wide variety of carbamates from primary, secondary and aromatic amines, various electrophiles (RX) and CO_2 in the presence of inorganic bases. Caesium carbonate is the most effective of these bases allowing for the highest percentage production of carbamate over tertiary amine, the other product of the reaction. The reaction is solvent dependent. Yoshida and co-workers[22] also report the formation of carbamates from carbon dioxide, aliphatic amines and alkyl halides. They found that the highest yields were obtained with secondary alkyl bromides and that the addition of DMF to the reaction mixture promoted product formation. It is their belief that this reaction proceeds by a S_N2 displacement type reaction mechanism where the halide is displaced from the alkyl halide by the carbamate anion product of the reaction of the CO_2 with the amine. Dixneuf and co-workers[23,24] have produced vinyl carbamates from the reaction of secondary amines and terminal alkynes with carbon dioxide, under pressure, using mono- or trinuclear Ru complexes as catalysts.

The autoxidation of α-sulfenyl-α-aminonitriles to carbamates has been achieved by reaction of the sulfenyl aminonitrile with metal alkoxides under an oxygen atmosphere[25].

A new range of carbamate compounds, N-(methylene-4-oxocoumarinyl) carbamates[26], have been found to be the products of the reaction of 4-hydroxycoumarin with simpler carbamates, such as ethyl, butyl and benzyl carbamate, in refluxing 2-propanol in the presence of ethyl orthoformate ($CH(OEt)_3$).

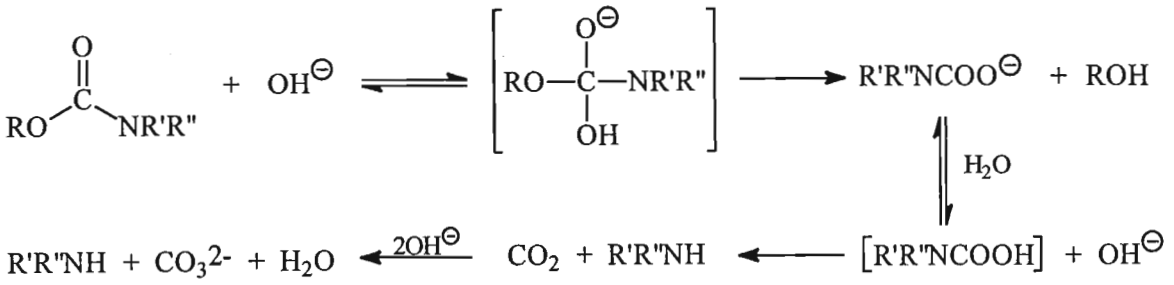
1.1.5 REACTIONS OF CARBAMATES

1.1.5.1 THERMAL DECOMPOSITION

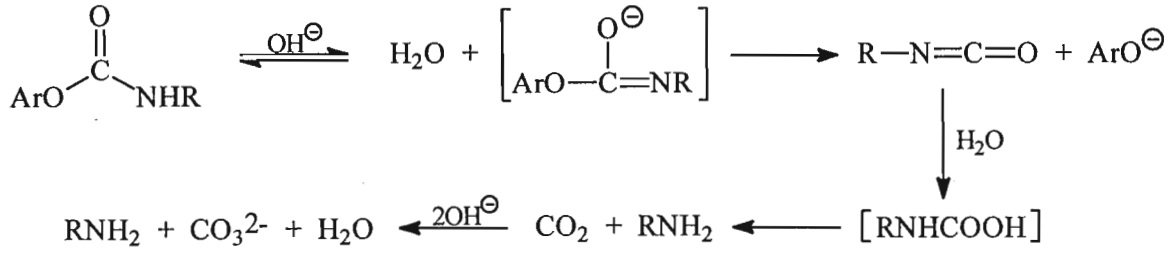
The thermal stability of carbamates depends to a large extent on the degree of N-substitution[1]. N,N-disubstituted carbamates are relatively resistant to thermal decomposition, this rarely occurring cleanly when it does occur. N-monosubstituted carbamates undergo decomposition at elevated temperatures giving largely isocyanates and alcohols and to a lesser extent ureas, CO_2, olefins and carbodiimides. On heating they may undergo three general reactions[2]: (a) elimination of an alcohol and formation of an isocyanate, (b) fragmentation to form an amine, CO_2 and an alkene and (c) loss of CO_2. Decomposition temperatures vary and may be as high as 200°C. Aryl carbamates decompose at approximately 150°C, *via* path (a) above; however *t*-butyl carbamates decompose even at approximately 50°C. Unsubstituted carbamates decompose quite readily above 130°C to cyanic acid derivatives, cyanuric acid, alcohols and allophanates. Metal salts in even trace quantities accelerates this decomposition[1].

1.1.5.2 HYDROLYSIS[1]

Base hydrolysis: All carbamates derived from aliphatic alcohols undergo alkaline hydrolysis by the mechanism depicted in **Equation 11** to give an amine, CO_2 carbonate and water. Carbamates derived from aromatic alcohols decompose by a different mechanism, depicted in **Equation 12**, and are hydrolysed more rapidly. The driving force in this mechanism is the ease of departure of the phenoxide ion. N,N-disubstituted carbamates are unable to form the isocyanate intermediate and thus decompose very slowly by the first mechanism **(Eqn 11)**.



Equation 11



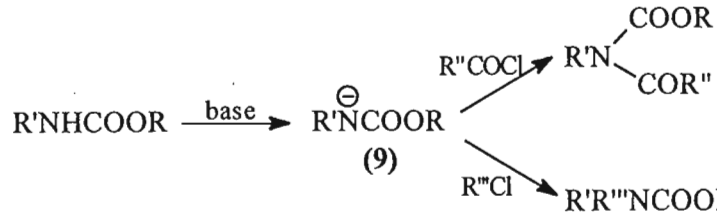
Equation 12

Acid hydrolysis: Carbamates are generally quite stable to acids under most conditions. However, carbamates in glacial acetic acid when treated with HCl or HBr yield CO_2, ammonium halide and alkyl halide. It is believed that the nitrogen is first protonated then the alkoxy group attacked by the halide ion. When heated with 30-60% oleum unsubstituted or monosubstituted carbamates become sulfonated on the nitrogen prior to cleavage, giving sulfamic acids as products.

1.1.5.3 REACTIONS AT THE AMIDO GROUP

Carbamates, that is the N-monosubstituted or unsubstituted carbamates, are themselves potential nucleophiles, although poor ones in comparison with amides. They may be acylated at the nitrogen by a number of compounds including esters, acid halides, anhydrides and ketenes, generally being more readily acetylated than ordinary acid amides. Diacid chlorides, such as oxalyl chloride may even react with two equivalents of carbamate to yield a biscarbamate[1]. When treated with sodium or with strong base N-

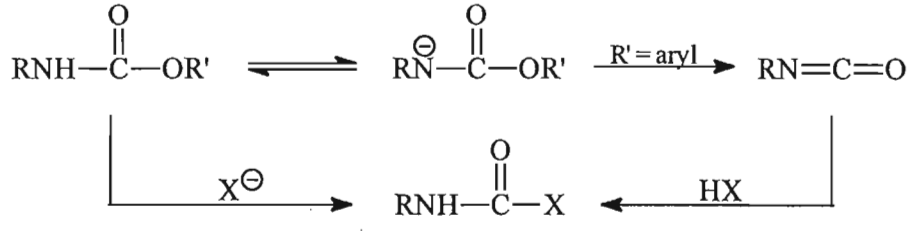
monosubstituted or unsubstituted carbamates can be converted to the formal carbamate anion **(9)** and can therefore act as better nucleophiles in reactions with electrophiles, such as alkyl or acyl halides, to give the corresponding N-alkyl or N-acyl derivatives **(Eqn 13)**. These reactions will only be successful if the carbamate anion is stable, a factor determined by the carbamate ester group. If this group is a poor leaving group the anionic carbamate will not be able to undergo rapid elimination of this -OR group to yield the isocyanate[2].



(Eqn 13)

1.1.5.4 REACTIONS AT THE ESTER GROUP

The reaction of carbamates with nucleophiles is one of the most characteristic reactions of the class. Displacement of the aryloxy or alkoxy group by amines yields ureas, and by alcohols leads to transesterification products. The reactivity of alkyl carbamates bears a closer resemblance to that of amides than that of esters and forcing conditions are needed in the reactions of these compounds. In aryl carbamates the aryloxy group is a good leaving group and the loss of this group is the rate determining step in the base catalysed reaction of unsubstituted or monosubstituted carbamates, giving an isocyanate as an intermediate which is readily trapped by nucleophiles to give the substitution product[2] **(Scheme 2)**.



Scheme 2

When carbamates and amines are reacted together at elevated temperatures substituted ureas are normally the products obtained[1]. Heating ethyl carbamate with ammonia in a sealed system yields urea and ethanol and N,N-dialkylureas can be formed by heating the N-alkylcarbamate and the corresponding amine at 230°C **(Eqn 14)** or by heating, at 150°C, ethyl carbamate and the amine **(Eqn 15 & 16)**. Few examples exist of the formation of monosubstituted ureas from amines and carbamates. However, reaction of primary or secondary alkylamines with an alkyl carbamate, with removal by fractional distillation of the alcohol formed, yields N-alkylureas in excellent yields **(Eqn 17)**. It has been shown that the reaction of an alkylamine with a N-unsubstituted carbamate in the presence of the hydrochloride salt leads to amine interchange yielding the N-substituted carbamate **(Eqn 18)**. Cleavage of the ester bond of the carbamate is achieved by chemical reduction, *e.g.* $LiAlH_4$ reduces carbamates to the corresponding N-methylamines **(Eqn 19)**[1]. Transesterification reactions have already been discussed in **1.1.4.3**.

$$RNHCOOEt + RNH_2 \longrightarrow RNHCONHR + EtOH \qquad \textbf{(Eqn 14)}$$

$$H_2NCOOEt + RNH_2 \longrightarrow H_2NCONHR + EtOH \qquad \textbf{(Eqn 15)}$$

$$H_2NCONHR + RNH_2 \longrightarrow RNHCONHR + NH_3 \qquad \textbf{(Eqn 16)}$$

$$NHR'R'' + R'''NHCOOR \longrightarrow R'R''NCONHR''' + ROH \quad R'=H,alkyl \qquad \textbf{(Eqn 17)}$$

$$H_2NCOOEt + RNH_2 \xrightarrow{RNH_3Cl} RNHCOOEt + NH_4Cl \qquad \textbf{(Eqn 18)}$$

$$RNHCOOR' \xrightarrow{[H]} RNHCH_3 + R'OH \qquad \textbf{(Eqn 19)}$$

1.1.5.5 MISCELLANEOUS REACTIONS

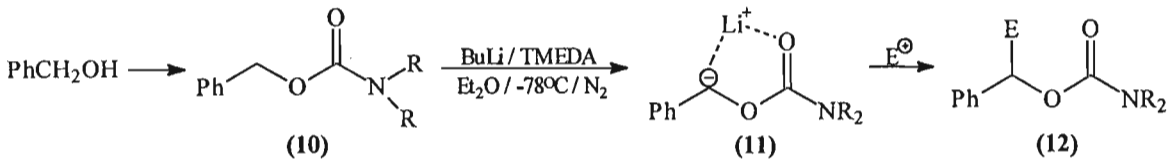
N-unsubstituted carbamates react with carbonyl compounds, but the reaction is very slow except with the most reactive aldehydes[2]. Methylenebiscarbamates [R'R"C(NHCOOR)$_2$] are formed in the reaction of aldehydes with two moles of carbamate in the presence of trace amounts of mineral acid[1]. Carbocations react with carbamates and allow for alkylation at either the nitrogen, for active alkyl halides, or the carbonyl oxygen, more precisely the hydroxyl group of the enolic form of the carbamate, with less active alkyl

halides. This latter reaction is followed by loss of an alkyl halide, resulting in the exchange of the alkoxy group[1]. The carbamate linkage is also able to act as an internal nucleophile towards acyl or alkyl centres if present. In neutral solution reaction at the oxygen is the norm, while the anion reacts at the nitrogen, thus making the carbamate an ambident nucleophile. This aforementioned reaction yields cyclic products, some of which may be hydrolysed to yield the amine, thus removing the carbamate protecting group[2].

1.1.5.6 CARBAMATES AS SYNTHETIC INTERMEDIATES

One of the major synthetic uses of carbamates is in the protection of amine functionalities, usually in biologically related compounds and for peptide synthesis. *Tert*-butyl (BOC), butyl and benzyl carbamates are the most commonly applied, most likely due to their easy removal at later stages, their lack of involvement in subsequent reactions, that they do not undergo many side reactions and that they prevent racemisation of intermediates. Ethyl and methyl carbamate are also used.

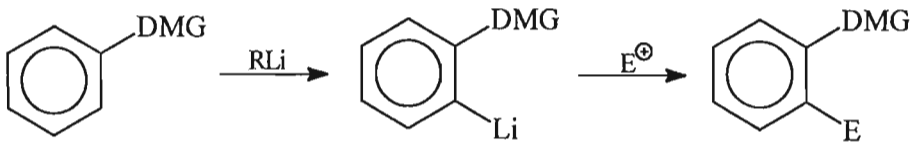
The carbamate linkage is able to activate the position *alpha* to the ester portion of the bond to proton abstraction and metalation. This feature has been employed extensively by Hoppe and co-workers and is described in detail later in **1.2.2.** N,N-dialkyl carbamates of benzyl alcohol **(10)** allow for the functionalisation of the benzylic position in the otherwise fairly unreactive benzyl alcohol, the alcohol usually being the only functionality available for functionalisation. Hoppe and Brönneke[27] showed that N,N-dialkyl benzyl carbamates **(10)** are deprotonated at the benzylic position by BuLi and TMEDA to yield the stable lithio derivative **(11)** which can be reacted with a number of electrophiles to yield the more complex carbamate **(12)**, and ultimately the substituted benzyl alcohol on removal of the carbamate **(Scheme 3)**. These anions **(11)** are stable and do not undergo the Wittig rearrangement, unlike the alkyl benzyl ethers used in the past. Zhang and Gawley[28] have however contradicted Hoppe and claim that these lithiated anion species **(11)** may undergo [1,2]-rearrangement of the amide portion of the carbamate to the benzylic position.



(10) (11) (12)

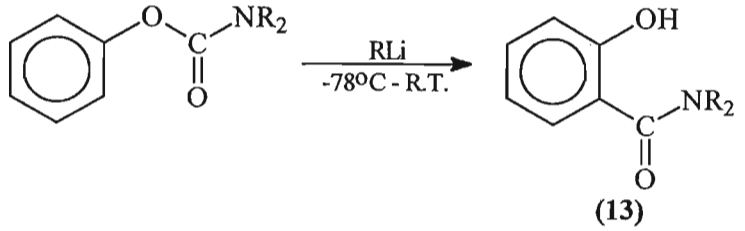
Scheme 3

Carbamates have been used very successfully in Directed *ortho* Metalation (D*o*M) reactions (Eqn A of **Scheme**) where the carbonyl group of the carbamate allows for co-ordination of the metal base in a position which allows for *ortho* abstraction of the proton[29]. This reaction is analogous to β-activation or metalation by the carbamate. In many instances the D*o*M reaction involves migration of the amide portion of the carbamate, after metalation, to the *ortho* position, yielding the *o*-substituted phenol **(13)** (Eqn B of **Scheme**). This rearrangement occurs when no electrophile is added and the reaction is allowed to warm from -78°C to room temperature (R.T.). This reaction amounts to an anionic equivalent of the *ortho*-Fries rearrangement. In some instances the carbamate derivative of benzyl alcohol also undergoes migration of the amide portion to yield the *o*-substituted benzyl alcohol[28].



(Eqn A)

DMG = directing metallation group



(Eqn B)

(13)

Scheme 4

In addition to the above main synthetic uses of carbamates they, or the carbamate linkage, have also played a large role in other fields, some examples of which follow.

- The N-alkyl carbamate form of α-allylic alcohols has been used to yield, by palladium catalysed arylation, the N-alkyl O-cinnamyl carbamates[30]. Without the carbamate

present the analogous reaction (Heck type arylation) would yield the arylated alkyl carbonyl compound.

- N-acylhydroxylamine-*O*-carbamates have been shown to rearrange by a [3,3] sigmatropic shift under basic conditions to yield α-amino acid amide derivatives[31].
- The carbamate protected N-cyclic-ene carbamates have been used to activate these systems to [2+2] cycloaddition reactions with ketenes. This reaction has been used in the synthesis of the important Geissman-Waiss Lactone[32].
- Activated N-methylcarbamates have been used in the preparation of anti-cancer compounds[17].
- N,N-dimethyl carbamates of allylic alcohols undergo high-yield equilibration of the allylic system, by rearrangement of the carbamate under conditions of mercuric trifluoroacetate catalysis[33].
- Another example is their use in the Pirkle chromatographic resolution of alcohols, hydroxy esters and thiols[34].

1.2 STEREOSELECTIVITY IN CARBAMATES

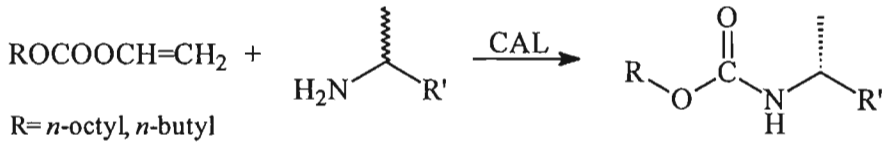
Stereoselectivity in carbamates falls into two categories, that of induced chirality in the substituents on the carbamate linkage and that of regioselectivity around alkenyl systems, with associated diastereoselective addition within these systems.

1.2.1 INDUCED CHIRALITY IN CARBAMATES

Obviously chirality in carbamates can be achieved by using chiral reagents in the preparation of the carbamate, so long as the chirality is maintained throughout the preparation method, which in almost all methods would be the case.

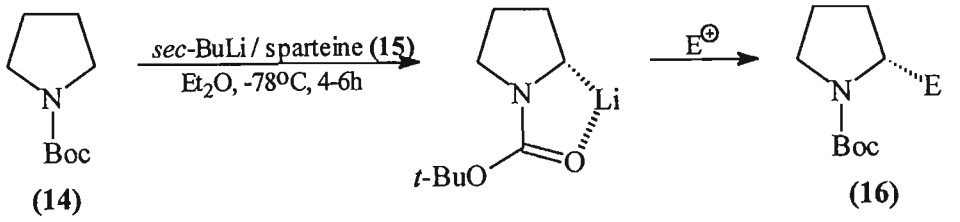
The introduction of chirality to a compound that already contains the carbamate bond has not been very successful at all and only a handful of examples are reported. No examples of strict chiral induction were found in the literature.

Pozo and Gotor[35] have successfully achieved the synthesis of chiral carbamates using an enzymatic alkoxycarbonylation reaction. They reacted a number of racemic primary amines with vinyl carbonates (*n*-octyl vinyl carbonate and *n*-butyl vinyl carbonate), prepared by the reaction of the alkyl alcohol and vinyl chloroformate, in the presence of the enzyme CAL (*Candida antartica* lipase SP 435A immobilised on acurrell) in various solvents **(Scheme 5)**. These long chain alkyl carbonates were chosen due to their previous success in other reactions with CAL. The reactions were successful with the lipase being enantioselective towards the *R* enantiomer, as expected from previous studies. These authors also showed that solvent and substrates do affect the overall enantiospecific success of the reaction.



Scheme 5

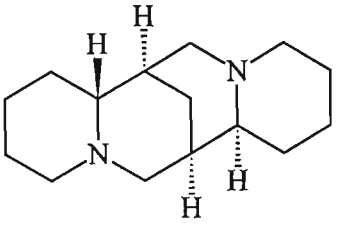
Kerrick and Beak[36] have successfully achieved asymmetric deprotonations to give enantioselective synthesis in a N-pyrrolidine *t*-butyl carbamate system **(14)**. They achieved enantioselective deprotonation of the 2-pyrrolidine position using *s*-butyllithium and (-)-sparteine **(15)**. Reaction with electrophiles gives the substituted product **(16)** with excellent enantiomeric excesses being obtained (88 - 96%), the products having the (R)-configuration, which in the case of proline is the unnatural form.



(14) **(16)**

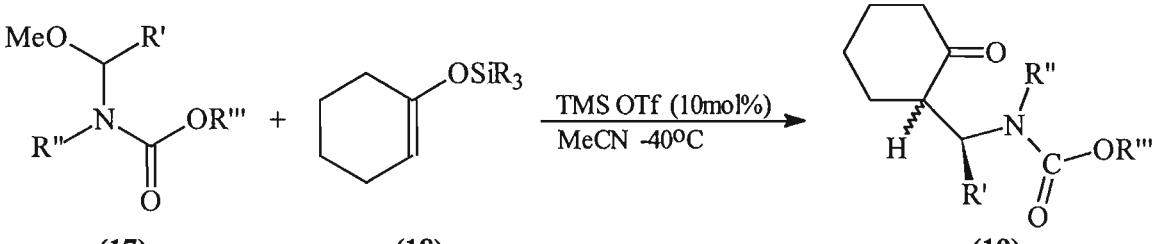
Boc = *tert*-butoxycarbonyl

Scheme 6



(-)-sparteine **(15)**

Brown[37] *et al.* obtained approximately 60% diastereomeric excesses (d.e.) for the reaction of alkyl/benzyl N-alkyl-N-[(aryl/alkyl(methoxy)methyl)methyl]carbamates **(17)** with trialkylsilyl enol ethers **(18)** in the presence of catalytic amounts of trialkylsilyl triflates to yield the corresponding β-ketocarbamates **(19)** **(Scheme 7)**.



(17) **(18)** **(19)**

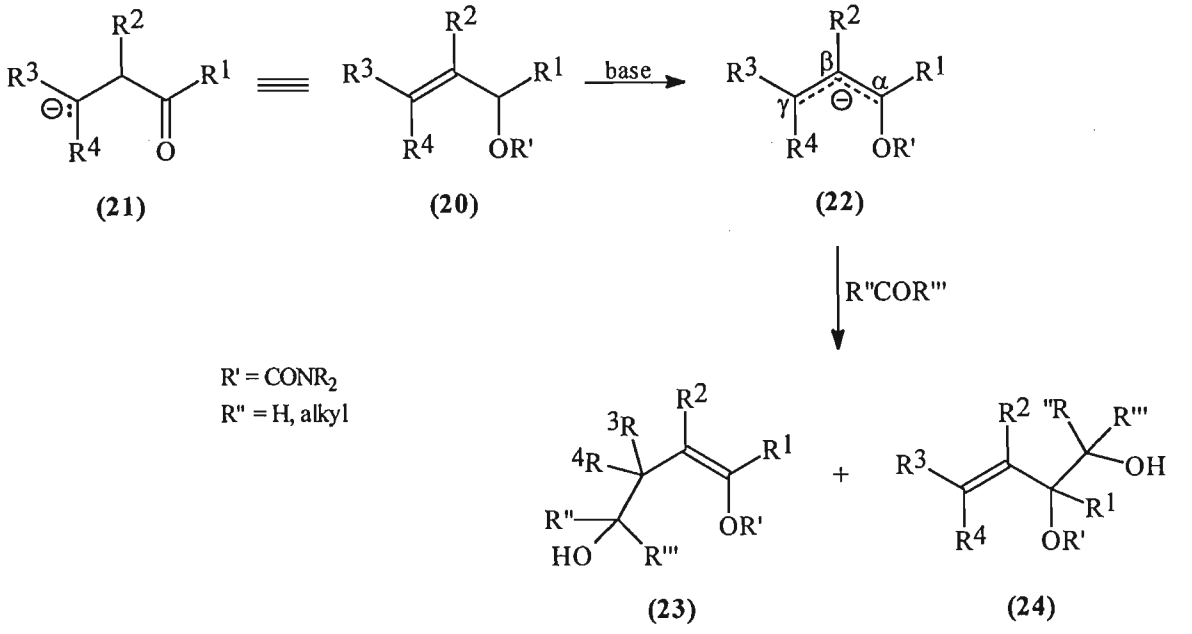
Scheme 7

Barner and Mani[38] attempted to induce chirality across the carbamate linkage using the N-*t*-butyl benzyl carbamate system. They hoped that the configuration of the compound, aided by the *t*-butyl structure, would allow for the enantiospecific abstraction of one of the benzylic protons. Their work was unsuccessful with only racemic products being obtained and they do not report any further successful results. They did however show that this system, once cleavage of the carbamate using DIBAL has been achieved, is a route for the high yielding general synthesis of alkylated benzylic systems.

1.2.2 REGIO - AND DIASTEREOSELECTIVITY IN CARBAMATES - The work of Hoppe and co-workers

The diastereoselective and regioselective studies of Hoppe and co-workers on the whole centre around 1-alkoxy-2-propenyl systems **(20)**. These systems are of interest as they form the starting materials for the production of homoenolate equivalents which are highly desirable for syntheses, as they are synthetic equivalents for the unknown aldehyde or ketone homoenolates **(21)**[18,39]. Traditionally the carbonyl has been protected as the ether, with alkyl, aryl or trialkylsilyl groups, and the anion formed after reaction with base generally reacts regioselectively at the γ-position for the addition of alkyl groups to form the enol ether, but undesirably at the α-position for the addition of carbonyl compounds. Due to the lack of acidity in the system it can be at most monosubstituted to still allow for deprotonation. Unfortunately these systems are also prone to side reactions taking place, such as the Wittig rearrangement[39]. When the carbonyl is protected as the N,N-dialkyl carbamate the acidity of the system is increased to such an extent that, even on reaction with carbonyl compounds, the γ-adduct **(23)** is preferentially formed, with only trace amounts of the α-adduct **(24)** being obtained[18,39]. This regioselectivity is enhanced as the size of the N-alkyl substituent on the carbamate is increased, N,N-di-*iso*-propyl carbamate giving better results than N,N-diethyl carbamate which gives greatly improved results over N,N-dimethyl carbamate[18]. Generally the Z-configuration in the enol ether product predominates over the other isomers[18,39]. The products are formed by the reaction of the N,N-dialkyl carbamates **(20)**, prepared from the alcohols and carbamoyl chlorides, with organometallic bases, such as LDA[18] or *n*-BuLi complexed with TMEDA (N,N,N',N'-tetramethylethylenediamine)[39] to give the anion **(22)**. This is then reacted with an electrophile (carbonyl) to give the γ-adduct **(23)**. Should further terminal protons be available for abstraction the reaction may be repeated to give a disubstituted product[18], with another electrophile (EX). The reaction using the carbamate protecting group, unlike those traditionally used, is even successful in poly-substituted systems[40]. It is believed that due to the greatly increased acidity of the α-position the counter cation preferentially chelates to this position, aided by complexation to the carbonyl, thus allowing for the

preferential γ-addition. The anion intermediate **(22)** is very stable at the reaction temperature of -70°C.



(21) **(20)** **(22)**

R' = $CONR_2$

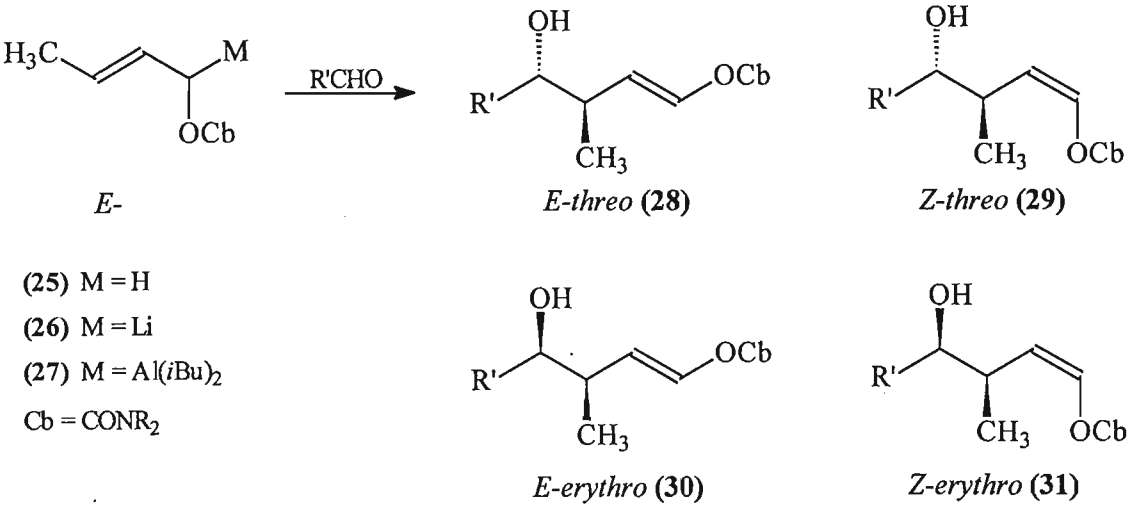
(23) **(24)**

Scheme 8

The carbonyl group can also be "electronically protected" and not only sterically by the use of N-monoalkyl carbamates. Deprotonation at the nitrogen with *n*-BuLi and TMEDA yields the lithium salt, thus reducing this regions electrophilicity. Double deprotonation of these allyl N-substituted carbamate systems with BuLi and TMEDA yields a dilithiated ester anion, and subsequent reaction with an electrophile also yields predominantly the Z-configured γ-adducts[40].

Diastereoselective homoaldol reactions have been achieved by similar methods to those above, but also utilising transmetalation procedures. If the starting materials are (*E*)-2-butenyl N,N-dialkyl carbamates **(25)** then transmetalation of the α-lithium compound **(26)** with bis-*iso*-butylaluminium chloride to yield the aluminium derivative **(27)** and subsequent reaction with aldehydes yields predominantly the E- **(28)** or Z-*threo/anti*-configured **(29)** products of the four possible diastereomers[41] **(Scheme 9)**. If the transmetalation reaction is carried out using chlorotris(diethylamino)titanium to yield the

crotyltitanium derivative then subsequent reaction with an aldehyde yields almost exclusively the Z-configured (*threo*)-δ-hydroxyenol carbamate[42] **(29)**. In addition to this diastereoselectivity further regioselectivity in this reaction can be attained by using an α-substituted starting material, thus giving the γ-adduct free of other isomers. When the (*Z*)-2-butenyl carbamates are used as starting materials[43] then, using the same aluminium exchange and carbonyl addition reaction above, the E-*erythro/syn*-products **(30)**, predominate. Lithium exchange with methanesulfonate also increases the regioselectivity.

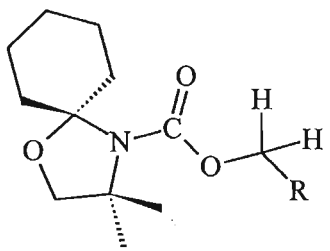


Scheme 9

Using the identical titanium reaction to that above, but with a varied starting material some interesting results relating to chirality were found[44]. When the starting materials were α-chiral α-substituted (for larger groups, *e.g. i*-butyl) 2-alkenyl carbamates abstraction of the α-proton by Li-TMEDA occurs with retention of configuration and if this intermediate is reacted with the carbonyl compound the expected (*Z*)-products predominate. However, if transmetalation with Ti (as above) is carried out with subsequent addition of the carbonyl compound only one product, the (*Z*)-(+)-*anti*-diastereomer, is obtained. Thus inversion of configuration had occurred and there had been 1,3-chirality transfer, the configuration at C1 determining the configuration at C3 and not the position of the aldehyde in the transition complex. The metalated intermediates in these reactions are stable to racemisation. The reaction of the α-lithiated intermediates, derived from (*E*)- or (*Z*)-

configured starting materials similar to those just described, with chlorotrimethylstannane yields predominantly the γ-stannylated (*Z*)-configured products, also with 1,3-chirality transfer, with respect to the chiral configuration of the lithium complex chelation[45].

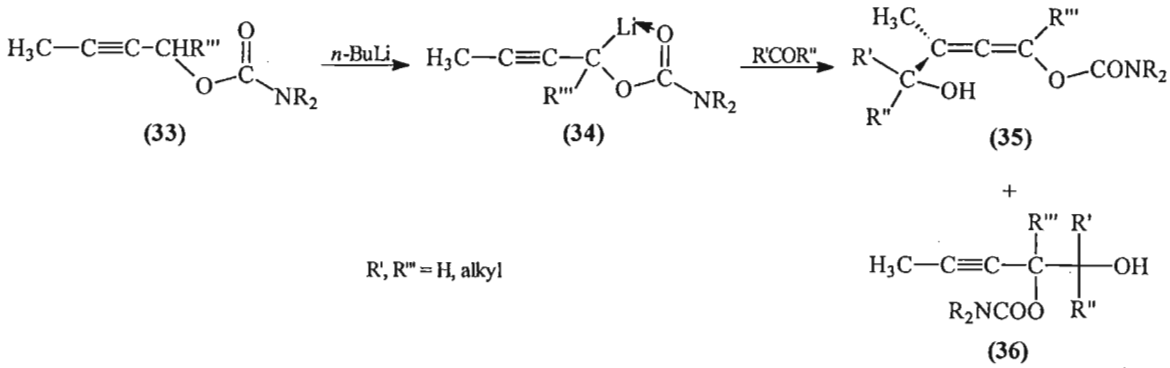
The above reactions utilise α-chiral starting materials with retention of configuration on metalation. However, prochiral starting materials can be used and enantiotopic deprotonation achieved using second-order asymmetric induction with *s*-BuLi complexed with an enantiomerically pure diamine, (-)-sparteine **(15)**[46,47,48]. Proton abstraction occurs but only one enantiomer of the complex rapidly crystallises out of solution, giving the pure (R)-configured product. Direct reaction of this solid with tetra(*iso*-propoxy)titanium results in the complex going into solution. Subsequent reaction of the Ti-complex with carbonyl compounds yields diastereomerically pure products with high enantiomeric excess (e.e.). Derivatives of α-prochiral alcohols where the rest of the molecule does not contain a stabilising factor, such as aryl or alkenyl systems, are also enantiospecifically deprotonated by *sec*-BuLi and (-)-sparteine **(15)**[49]. However, in this case the alcohol must be protected as a sterically demanding carbamate **(32)**. Treatment of this compound with the Li-diamine complex yields the (S)-configured product and consequent substitution with electrophiles is believed to occur with retention of configuration. Removal of the spirocyclic oxazolidine carbamate **(32)** yields the substituted alcohols with high e.e. This same reaction is also successful in the case of diols, or their carbamate derivatives, with the *si*-face also being enantiotopically deprotonated[50,51].



(32)

The chiral products of many of the above reactions themselves become intermediates in the formation of a number of further products, for example chiral substituted lactones[43], furans (lactols[39] and lactol ethers[41, 52]), 3-buten-4-olides[18] and acetals[41, 42].

Similar results to the alkene systems have been obtained for alkyne systems. α-Lithiation results on the treatment of the N,N-dialkyl carbamate derivative of 2-butynol **(33)** with BuLi[53,54]. Reaction of this complex **(34)** with carbonyl compounds leads to their regioselective addition to mainly the γ-position to yield (4-hydroxy-3-methyl-1,2-alkadienyl) carbamates **(35)**, with some of the α-adduct also being obtained **(36)** **(Scheme 10)**. Li-Ti exchange before addition of the carbonyl compounds leads to exclusively the γ-adduct, in high diastereomeric yield. After protection of the 4-hydroxy group the compounds **(35)** can undergo a further α-proton abstraction (R'''= H) and lithiation (with LDA) to allow for substitution with (mostly) retention of configuration. If the 4-oxy group is a good leaving group then 1,4-elimination in a *syn*-stereospecific manner occurs, before substitution is achieved, to yield the very reactive 3-alken-1-ynyl carbamate[55]. Protection of the 4-hydroxy group in **(35)** with a ketene N,O-acetal leads to an allene Claisen rearrangement with 1,4-chirality transfer[56].



(33) **(34)** **(35)** **(36)**

R', R''' = H, alkyl

Scheme 10

1.3 CHIRAL AMINES FOR CHIRAL INDUCTION

As this section ultimately did not form an integral part of my Master's research it will only be touched on briefly and generally.

Acquiring optically active, or chiral, molecules may be done in three ways, these being the optical resolution of racemic mixtures, the transformation of "chiral pool" materials and the synthesis of a chiral centre where one previously did not exist (asymmetric synthesis)[57]. There are a number of ways of creating a chiral centre in a molecule, including reaction of a prochiral centre such as a carbonyl or alkene and substitution reactions, *i.e.* abstraction of a functionality, including H, with subsequent addition of another group at this point. These methods may also be achieved in two ways, one by using a chiral reagent and the other by allowing a chiral centre slightly removed from the reaction point to influence the reaction and the chirality at the centre in question. In fact in some cases a chiral, or asymmetric, reagent does not have to be used to create chirality at a centre but rather a dissymmetric molecule lacking a chiral centre, *i.e.* one that lacks mirror or inversion symmetry[58]. Chiral, or dissymmetrical, reagents can themselves be divided into two classes, namely chiral ligands or auxiliaries and "free" reagents. Some reagents in these classes may also fall into the category of chiral catalysts.

On the whole chiral amines have been used as ligands, with metals such as B, Li and Zn, to achieve chiral induction. These ligands may be monodentate, bidentate or even polydentate. Often in the case of amines the functional groups for co-ordination are not only amine derivatives but also alcohol, and even phosphine, derivatives. Some examples of these classes, derived from recent literature, follow.

- Chiral amino alcohols have been extensively used, co-ordinated to boron, to form oxazaborolidines, for the asymmetric reduction of a number of ketone related functions. (S)-α,α-diphenyl-(indolin-2-yl)methanol[59] and (1R,3R,5R)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane[60] have both been successfully employed for the enantioselective reduction of ketones, generally containing some aromatic group. Itsuno *et al.*[61] have used a range of α,α-diphenyl-β-amino alcohols, prepared from naturally

occurring amino acids, in conjunction with borane to achieve excellent results in the asymmetric reduction of ketones, ketones containing functional groups and ketone oxime ethers. In another paper[62] they detail this last reaction of reduction of ketoxime *O*-alkyl ethers to optically active primary amines, using a combination of sodium borohydride ($NaBH_4$), Lewis acids and the chiral amino alcohols. Chiral hydride reagents, including amino alcohols and oxazaborolidones, have been employed in the asymmetric reduction of N-substituted ketimines to give the corresponding secondary amines[63].

- Amino alcohols used in catalytic or stoichiometric amounts in conjunction with dialkylzinc reagents have allowed for the enantioselective alkylation of carbon-nitrogen double bonds, in N-diphenylphosphinoylimines. From these alkylated products chiral amines can be readily obtained[64]. The enantioselective addition of diethylzinc to benzaldehyde has been achieved using catalytic amounts of β-(*s* or *t*)-amino alcohols[65]. The β-*t*-amino alcohols were found to give the best results. This paper proposes the formation of a dinuclear zinc complex as the intermediate in the chiral addition to the aldehyde.
- A chiral β-amino ether has been used to mediate the enantioselective alkylation of aldimines with organolithium reagents[66].
- The enantioselective deprotonation of cyclohexene oxide, to (S)-2-cyclohexen-1-ol, has been achieved with varying degrees of success using a range of bi- and tri-dentate chiral lithium amines, derived from di- or triamine ligands[67].
- A number of monodentate amino auxiliaries, with C_2 axes of symmetry, co-ordinated to lithium have been reported[58]. Some examples are 2,5-dialkylpyrrolidines and N,N-di-1-phenylethylamine which have generally been used in addition reactions to vinyl systems. The same review reports the extensive use of *trans*-2,5-bis(methoxymethylene)pyrrolidine for addition/substitution reactions, when this compound is added to the molecule on which substitution is to be achieved in the form of an amide linkage. Organolithium reagents are used in the abstraction step and it is believed that one of the oxygens in the auxiliary is effective as a ligand.
- A chiral phosphonamide ylide based on a cyclohexyl diamine has been employed for olefination, with good stereochemical control at remote centres[58].

However, chiral amines have also been used for induction as single reagents, that is not as ligands. Some examples follow.

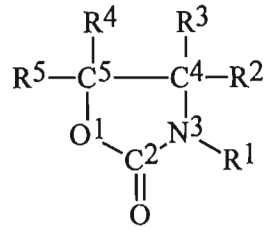
- Fuji *et al.* report the use of the hydrochlorides of chiral piperazine derivatives for asymmetric protonation of 1-acetoxy-2-benzylcyclohexene and similarly structured compounds[68].
- (S)-(-)-1-Amino-2-methoxymethylpyrrolidine (SAMP) and (R)-(+)-1-amino-2-methoxymethylpyrrolidine (RAMP) are well known chiral auxiliaries that form hydrazones when reacted with carbonyls[69]. When these adducts are reacted with bases, such as LDA, with subsequent addition of groups, usually alkyl, to the α position this addition occurs stereoselectively. Using organocerium reagents additions to SAMP-hydrazones has been achieved to give, ultimately, chiral amines[70].
- The chirality inherent in the (-)-2-cyano-6-phenyloxazolopiperidene molecule can be used for the selective functionalisation of either the α-amino nitrile or the α-amino ether positions and subsequently the formation of a number of chiral compounds derived from this chiral precursor[71,72,73,74,].

The number of instances where chiral centres in an amine based molecule have been used to induce chirality at another centre are numerous, particularly in natural product synthesis, and will not be dealt with here.

1.4 OXAZOLIDONES (CYCLIC CARBAMATES)

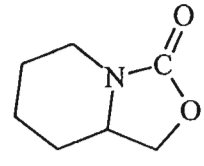
1.4.1 GENERAL

Cyclic carbamates belong to the class of heterocyclic compounds generally known as oxazolidones. They are in fact 2-oxazolidones. The numbering system in oxazolidones is shown below[75] **(37)**.



(37)

If the carbamate linkage falls within a bicyclic structure the system is named according to IUPAC multicyclic systems, with the hetero-atoms being numbered as if they were carbons. If all bridges are equal then the hetero-atom bridge takes preference. When the nitrogen falls at the bridgehead position it is numbered as one (1) with the bicyclic rings being numbered next and the hetero-atoms being assigned numbers in this system[76], for example **(38)** is named 8-oxa-1-azabicyclo[4.3.0]nonan-9-one.



(38)

The parent compound in this class (R=H in **(37)**) is also referred to as 2-oxazolidinone, oxazolid-2-one, oxazolidin-2-one, oxazolidone-2 and oxazolidinone-2[75]. This author will use the name oxazolidone.

2-Oxazolidones, both the substituted monocyclic and the bicyclic systems, have been known for many years, the first known preparation being achieved in about 1890[77]. The number of examples of these compounds, and their applications, are vast. It was not until 1980 that the first bicyclic system with the nitrogen at the bridgehead position was reported[76], it being previously believed that this would be impossible to achieve as the compound would violate Bredt's Rule[76,78].

Structurally 2-oxazolidones favour the carbamate linkage being in a five-membered ring system[79,80], although other ring sizes may be found.

1.4.2 PROPERTIES

Physical Properties: Most 2- oxazolidones are stable solids[75,76,77] and most are soluble in water[75,76].

Spectral Properties: In the infrared spectra the carbonyl absorption band usually occurs at high energy, occurring above approximately 1680 cm^{-1} and generally being found above 1740 cm^{-1} [75,76]. In addition the 2-oxazolidone ring is reported to have a characteristic absorption band in the 1029 - 1059 cm^{-1} region[75].

Chemical Properties: 2-Oxazolidones are generally stable to acid or alkaline hydrolysis[77] and solutions of non-functional group substituted compounds are essentially neutral and therefore do not form salts with either acids or bases[75,77]. 2-Oxazolidones are cyclic urethans and in some cases the ring can be opened and polymerisation initiated. In the bicyclic and hetero-atom bridgehead examples this depends largely on ring strain[76,78].

1.4.3 USES

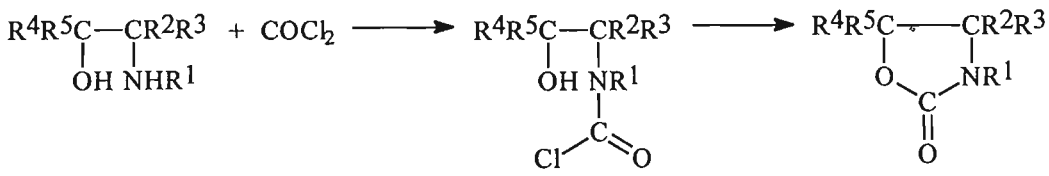
Examples of the uses of 2-oxazolidones are vast and varied. Historically these include antibacterials against a large number of organisms, growth regulators, psycho-and neuropharmacological agents, central nervous system depressants and relaxants and polymers or copolymers with a vast variety of applications[75]. More recent examples include their use in polymer products[81,82,83]; as antibacterial[84], antifungal[85] and antialgicidal[86] agents; as an agent for the removal of NO_x gases from flue gases[87]; as antidotes for organophosphate poisoning[88] and as nervous system agents *i.e.* as tranquillisers, antidepressants and antipsychotics[89].

1.4.4 FORMATION REACTIONS

1.4.4.1 FROM β-AMINO ALCOHOLS

The formation of 2-oxazolidones from β-aminoalcohols forms the biggest class in the preparation of these cyclic carbamates. Numerous compounds have been used to complete the cyclisation. Of these the use of phosgene or dialkyl carbonates are the most common. The production of β-aminoalcohols can be from numerous starting materials, or from natural products such as some of the amino acids. Their formation is beyond the scope of this discussion. Obviously the use of γ-aminoalcohols leads to the formation of six membered cyclic carbamates, should the molecular orientation and reaction conditions allow their formation.

Using Phosgene: One of the first reported syntheses of 2-oxazolidone is the reaction of ethanolamine with phosgene[77]. The amino group, which must have one available hydrogen attached, has greater nucleophilicity than the hydroxyl group and the phosgene therefore initially reacts at this group[75], in almost all cases. The general reaction is shown in **Equation 20.**

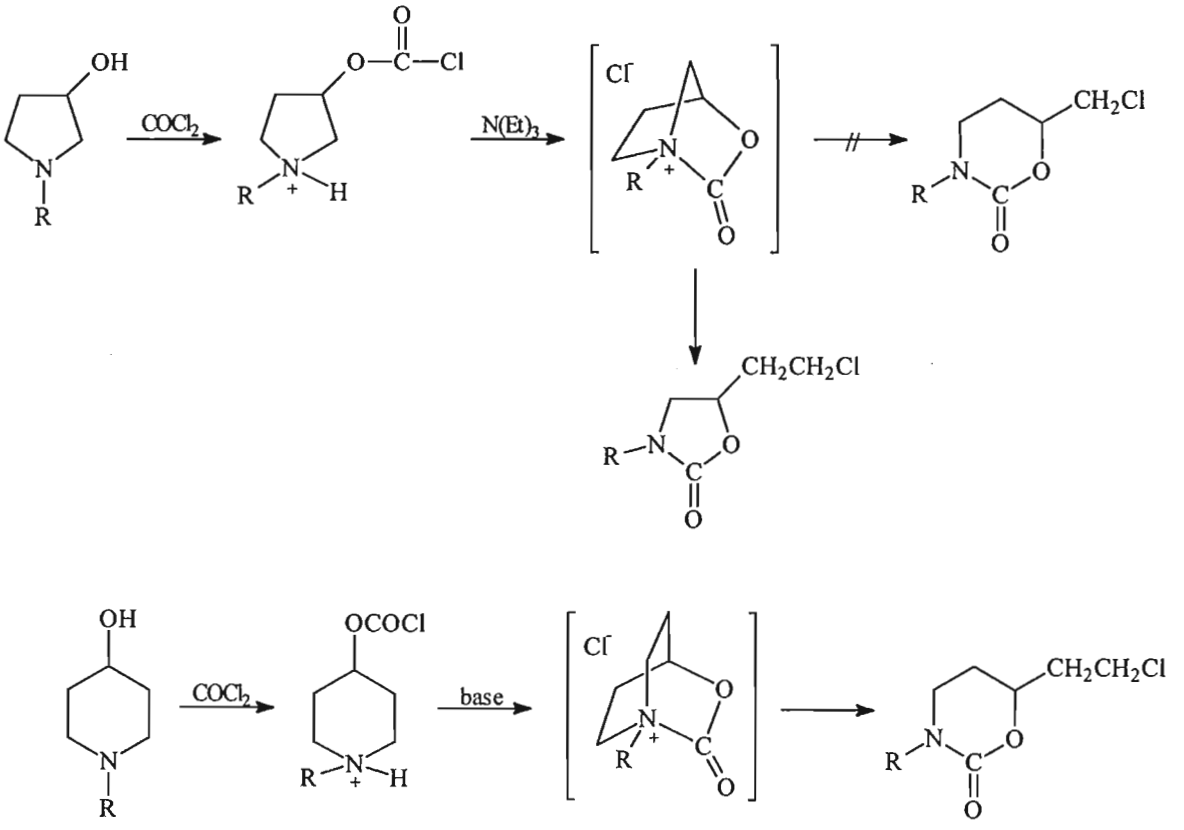


(Eqn 20)

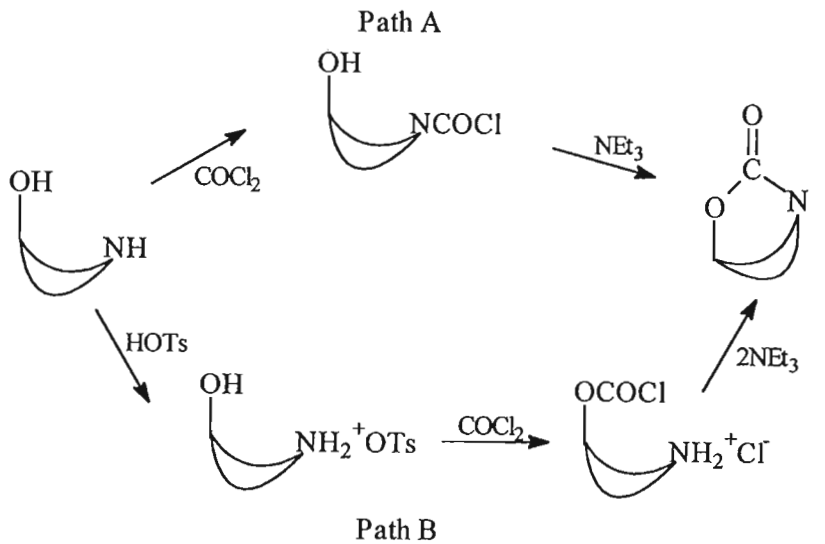
The conditions for the above reaction vary greatly and numerous mono and bicyclic examples have been prepared. Triphosgene has also been used successfully[16]. In these reactions the stereochemistry, if present in the amino alcohol, is not altered[16, 75].

If the amine is a tertiary amine, in a cyclic structure, reaction of the phosgene will occur at the alcohol. Cyclisation is initiated using base and a bicyclic oxazolidone containing a quaternary ammonium cation is formed as an intermediate. This structure is unstable and the ring systems strained and therefore the one ring opens to give a substituted 2-oxazolidone, the five membered ring, if present in the bicyclic system, being the most favoured[80]. If the two rings in the bicyclic structure are symmetrical then only one product can form. This can be seen in **Scheme 11.**

The first bicyclic oxazolidones with nitrogen at the bridgehead position (anti-Bredt Urethanes) were prepared similarly to those above[76]. However, in this case secondary amines in a cyclic structure were used. Two preparation routes are possible **(Scheme 12)**. The first reacts phosgene with the amine and then cyclisation is initiated by base (Path A). In the second the amine is protected as a salt and the phosgene then reacts with the alcohol function. Once again cyclisation is achieved by adding base (Path B).

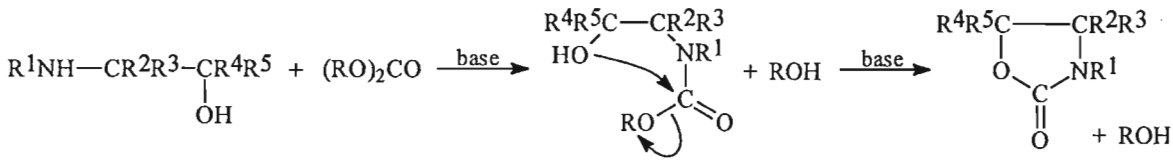


Scheme 11



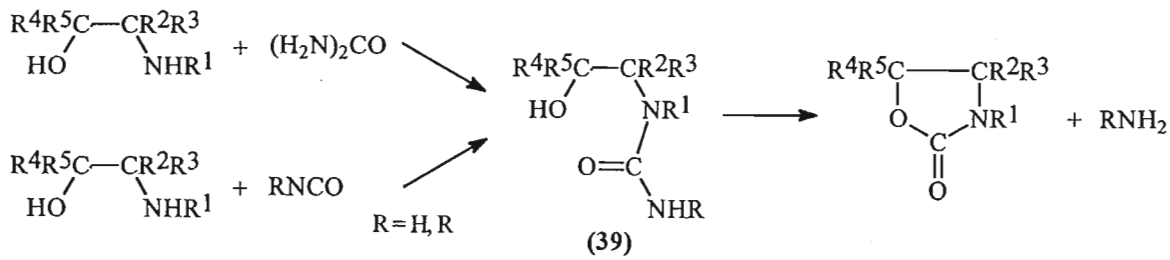
Scheme 12

Using Dialkyl Carbonates[75]: The reaction of a β-aminoalcohol with a dialkyl carbonate was also one of the first methods used for preparing 2-oxazolidones. This reaction is of great importance and is preferable to that using phosgene. This general reaction has wide scope in the synthesis of the cyclic carbamates. The reaction occurs in two stages **(Scheme 13)**. The first is the base catalysed addition of the amine to the dialkyl carbonate, giving the carbamate derivative and loss of alkoxide occurring. In the second stage base catalysed attack at the carbonyl takes place to give the cyclic product with the loss of the second alkoxide group as the alcohol. The reaction has been shown to be overall third order, being first order in the dialkyl carbonate and second order in the aminoalcohol.



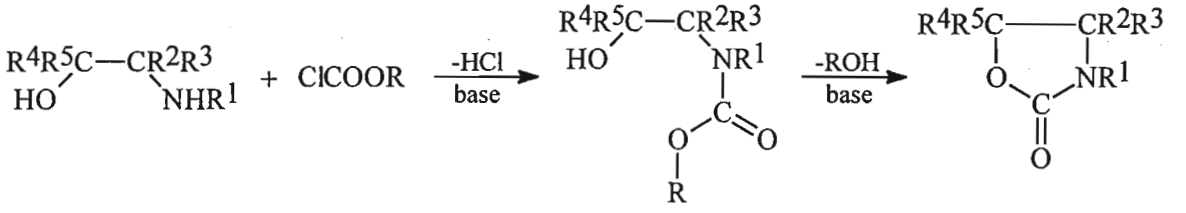
Scheme 13

Using Urea or Isocyanates[75]: The reaction of a β-aminoalcohol with urea is carried out under conditions of fusion above the melting points of the reacting compounds. The urea decomposes to form cyanic acid which reacts with the amino group to give a β-hydroxyethylurea derivative **(39)**, which in turn cyclises to the oxazolidone with loss of ammonia. Alternately the β-hydroxyethylurea **(39)** derivative can be formed by reacting organic or inorganic isocyanates with the amine. Cyclisation is usually achieved by heating, with the loss of ammonia or an amine **(Scheme 14)**.



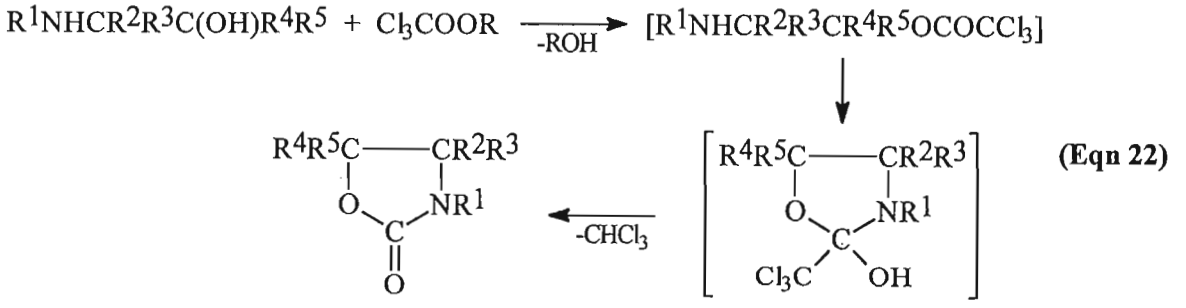
Scheme 14

Using Chloroformates: In the presence of bases chloroformates react with the amine to give a β-hydroxy carbamate, which then cyclises with loss of an alkylhydroxide derived originally from the chloroformate[75,90] **(Eqn 21)**. Pyrolysis of β-hydroxyalkylcarbamates, or ureas, also gives 2-oxazolidones[77].



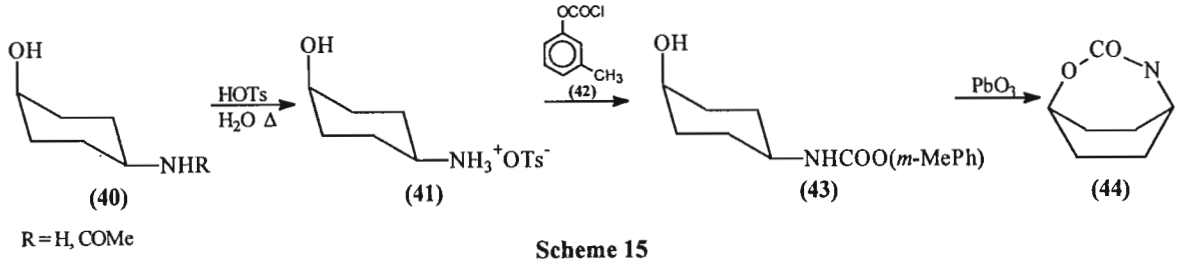
Equation 21

Miscellaneous: Esters of trichloroacetic acid[75] have been used to facilitate cyclisation of the β-aminoalcohols. Reaction occurs at the alcohol to form a trichloroester and then nucleophilic attack on the carbonyl by the nitrogen occurs, with subsequent elimination of chloroform **(Eqn 22)**.



(Eqn 22)

Bicyclic oxazolidones have also been prepared from γ-aminoalcohols of cyclohexane[78] **(40)**. The amine, or acetal, is first converted to the hydrotosylate salt **(41)**, which is in turn reacted with an oxycarbonyl **(42)** to give a carbamate **(43)**. Cyclisation to the bicyclic oxazolidone **(44)** is facilitated by heating the carbamate compound **(43)** with litharge (Pb_3O_4) **(Scheme 15)**.



Scheme 15

1.4.4.2 MISCELLANEOUS FORMATIONS

There are numerous other ways that have been used to prepare oxazolidones.

The first production of 2-oxazolidone was achieved from a β-haloamine by Gabriel, who reacted β-bromoethylamine hydrobromide with silver carbonate, and later sodium bicarbonate[75,77].

Oxazolidones have been prepared from[75]:

- β-haloalcohols using urea, sodium cyanamide, carbamates, inorganic cyanates and cyanuric acid
- epoxides using cyanuric acid, organic isocyanates, inorganic cyanates, isothiocyanates, urea and substituted ureas, carbamates, cyanamide, the cyanide ion, dithiolanes and oxathiolanes
- carbamates by pyrolytic, alkaline and acidic cyclisation
- 1,2-glycols using urea and urethan ($H_2NCOOEt$)
- cyclic carbonates (2-dioxolanones) using isocyanates, formamide and ammonium carbonate and potassium cyanide
- acetylenic alcohols using isocyanates and amines with carbon dioxide
- acetylenic amines using carbon dioxide
- β-hydroxy isocyanates
- α-ketols using isocyanates and potassium cyanide with ammonium carbonate
- 1,2-dihalides

- nitrenes
- (β-hydroxyalkyl)semicarbazides
- β-amino chloroformates
- oxazolines and oxazolinones
- 2-aminooxazolidines.

Recent reports in the literature have described the preparation of oxazolidones by the following methods:

- the reaction of ketone oximes with dimethyl carbonate in an autoclave in the presence of potassium carbonate[91]
- the cyclisation of 2-butenylene dicarbamates using Pd(0) as catalyst, giving 4-vinyl-2-oxazolidones[92]
- from the rearrangement of tertiary α-allenic alcohol carbamates. This reaction occurs on reaction of the carbamate allenic alcohol with base, followed by addition of an electrophile, to yield 4-vinyl-5-alkyl- or substituted-2-oxazolidones with high stereoselectivity[93,94,95,96].

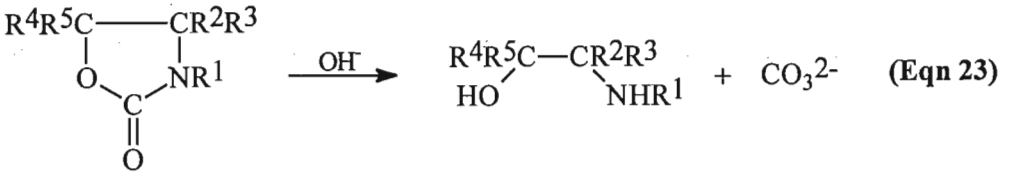
1.4.5 REACTIONS OF OXAZOLIDONES

The reactions of oxazolidones vary greatly and there are numerous examples. Only those reactions affecting the oxazolidone ring itself, or where the ring plays an integral role in the progress of a reaction, will be discussed. Reactions of groups on the ring will not be discussed as they are outside the scope of this research.

1.4.5.1 DECOMPOSITION AND RING OPENING REACTIONS[75]

The five membered oxazolidone ring tends to be quite stable[77]. However ring opening and decomposition can be induced. Hydrolysis with NaOH or KOH, usually in aqueous or alcoholic media, yields the β-aminoalcohol **(Eqn 23)**. These alkaline hydrolyses have

usually been carried out to prove structure or stereochemistry. Reduction with lithium aluminium hydride also yields the β-aminoalcohol. The cyclic carbamate ring is not affected in attempted oxidation with permanganate[77].



(Eqn 23)

N,N'-disubstituted urea is the major product obtained when oxazolidones are reacted with equivalent amounts of primary aliphatic amines. If aromatic primary amines or araliphatic amines (*e.g.* benzylamine) are used in the reaction the products are N,N'-disubstituted urea and a 2-imidazolidone. β-Aminoethyl carbamate is produced when the parent compound 2-oxazolidone (i.e. R's = H) is reacted with aqueous ammonia. 2-Oxazolidones when reacted with hydrazines yield semicarbazides.

Reaction of oxazolidones with dilute HCl produces the hydrochlorides of the β-aminoalcohols. Reaction with anhydrous HCl gives the hydrochloride of the β-chloroamine. In some cases refluxing in HCl yields the β-aminoalcohol with loss of CO_2[77].

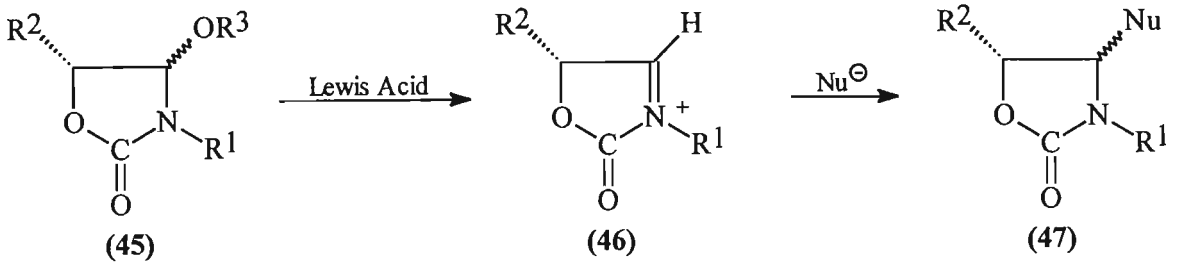
Pyrolysis of unsubstituted 2-oxazolidone itself yields CO_2 and polyethylenimine. If an amine or polyamide is present polymerisation is prevented and the compound decomposes to CO_2 and ethylenimine. There are a number of examples where N-substituted oxazolidones when heated give low weight polymers of the corresponding ethylenimine. Bicyclic oxazolidones may also be polymerised using various catalysts[78]. The ability to polymerise in these systems depends largely on ring strain or stability.

1.4.5.2 REACTIONS ON THE OXAZOLIDONE RING

Reactions on the ring occur mainly at the nitrogen. The hydrogen attached to the endocyclic nitrogen is acidic in nature. Alkylation at the nitrogen is achieved usually under basic conditions and the alkylating reagents have been alkyl halides, alkyl sulfates and olefins. Ethers have also been used as alkylating agents utilising mercuric acetate either alone, with benzoic acid, or with benzyl alcohol. Sulfuric and hydrochloric acids have also been used as catalysts for this reaction. Acylation at the nitrogen may be achieved using acidic or basic media and carbamylation has been achieved using phosgene followed by ammonia. Nitrosation of the nitrogen has been accomplished with nitrous acid and nitrosyl chloride. Nitration has been achieved using nitric acid either with sulfuric acid or with acetic anhydride. The nitro group can be reduced to give the amine attached to the endocyclic nitrogen of the oxazolidone. The nitrogen also reacts with carbonyl compounds in the presence of additional amine to give a N-aminomethyl oxazolidone derivative. Substituted 2-oxazolidones react, in the presence of pyridine or NEt_3, with aryl isocyanates to give carbanilides[75].

Boiling 2-oxazolidone in aniline yields an imidazolidone, where the cyclic oxygen has been replaced by the amine[77].

Stereoselective addition to the α-carbon in oxazolidones has recently been reported[97]. Oxazolidones where all three possible points of substitution are substituted, with an alkoxy group in the *alpha* position **(45)**, are precursors for N-acyl iminium ions **(46)**. Lewis acid attack at the α-alkoxy group removes this group to give the N-acyliminium ion **(46)** and subsequent nucleophilic attack yields nucleophilic substitution at the *alpha* position **(47)** **(Scheme 16)**. Depending on the chiral orientation of the bulky substituent at the *beta* position (or the *gamma* position in a six membered oxazolidone) and on the reagents used for substitution, the orientation of the substitution at the *alpha* position can be controlled.



(45) (46) (47)

Scheme 16

2-Oxazolidones, where there is no substituent on the nitrogen, are potentially tautomeric, it being possible to have both the keto **(48)** and enol **(49)** forms present[75,77]. This tautomerism appears to be weak with the keto form being the more favorable[75]. Little research appears to have been done in this regard and with regard to potential reactions.

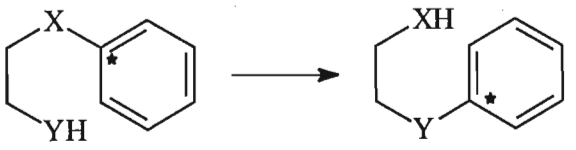
(48) (49)

1.5 REARRANGEMENT REACTIONS

Of all the rearrangement reactions we were able to find reported in the literature none closely resembled the reaction we discovered in which N-monosubstituted carbamates rearrange to secondary, or tertiary, alcohols. Previous preparations of the alcohols prepared by ourselves were by more traditional methods and yielded no assistance. Those few rearrangement reactions we were able to find bearing a vague resemblance to, or shedding some light on, our reaction are briefly discussed below.

1.5.1 SMILES AROMATIC REARRANGEMENT

The Smiles rearrangement is an aromatic rearrangement which results in the migration of an aromatic system from one heteroatom to another[98,99] **(Scheme 17)**. This rearrangement reaction in effect involves an intramolecular nucleophilic substitution[98,100].



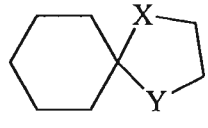
Scheme 17

The mechanism[100] involves initial conversion of the YH function to the anion by the action of sodium hydroxide, or other strong base, followed by nucleophilic attack of this Y^- function on the carbon to which the X atom is attached. This attack results in the displacement of the X function as its anion, which is then converted to XH.

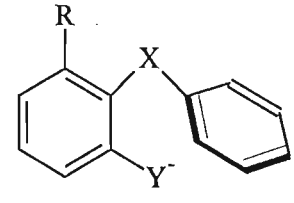
In the original studies by Smiles the X function was a sulfone, the YH function an alcohol and the two carbon bridge between the heteroatoms belonged to an aromatic system[101,102,103]. Since then the reaction has been shown to proceed with a variety of heteroatoms and heteroatom functionalities[99,100,102,103], the instances where these are N and O having relevance for the present study. The carbon bridge does not have to belong to an aromatic ring and may even be part of an acyclic system[102]. It may also contain a carbonyl function, usually adjacent to the YH function and usually forming an amide[102,99]. When the YH function is a NHR group, where R=acyl group, maximum reactivity is achieved. Initially, and still most often, the aromatic ring on which the rearrangement takes place must be activated, usually by a nitro ($-NO_2$) group in the *para* position, but non-activated aromatic systems have been used[104]. *Ortho* and *para* electron withdrawing effects aid the reaction and recently an arene chromium tricarbonyl complex system has also been used to create an electron withdrawing environment[105]. Substitution on the ring to which the bridge belongs has varying effects. The Smiles rearrangement also occurs on the pyridyl ring and with dipyridyl systems[103].

The Truce-Smiles rearrangement is an interesting extension of the Smiles reaction that was discovered in 1958[103]. In this reaction the YH function is a methyl group and *n*-butyllithium is used to form the anion. The X function is a sulfone and the bridge belongs to an aromatic system. The reaction only occurs when there is a methyl group in the *ortho* position to the point of attachment of the X function on the "bridge" phenyl ring. A similar reaction occurs if the methyl group is bonded to a naphthalene system.

The transition state in the rearrangement is believed to be a *spiro*-transition state **(50)** with the charges being dissipated, depending on the heteroatoms and the ring substituents, between a heteroatom and the ring or over the ring and the activating group. Steric effects have been shown to affect the reaction[99,100,103]. Excessive bulk attached to the carbon bridge or to an amine function may hinder the formation of the five-membered *spiro*-transition state and thus prevent the reaction from occurring[99]. It has been shown that a methyl, or alkyl, group in the α position to the X function (or β position to the Y function) on the "bridge" aromatic ring enhances the reaction rate[100,103]. This feature is believed to be due to steric considerations in the formation of the transition state. The molecule takes on a "V" shape around the X function. The two phenyl rings therefore have various positions in the planes to take up with regards to one-another. A substituent in the α position limits the number of conformations available and favours the formation of a conformation in which the phenyl rings are perpendicular to each other, with the alkyl substituent away from the other ring and not in close proximity. This means that the anion is in a position of close proximity to the ring on which rearrangement takes place, enabling the transition state to be readily achieved **(51)**.

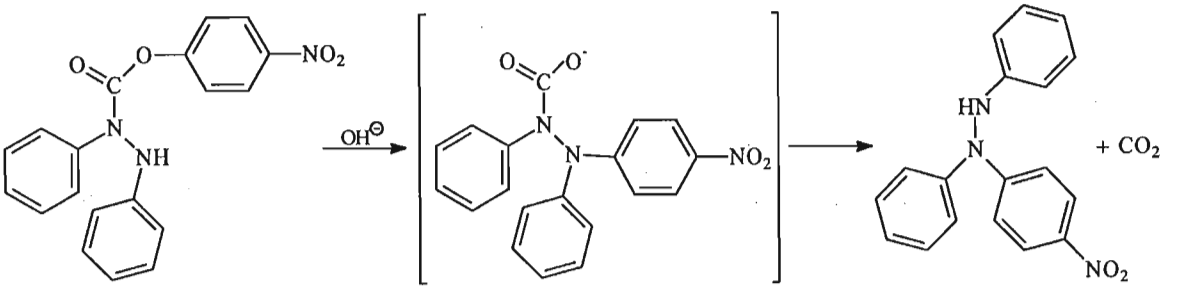


(50)



(51)

An interesting variation on the Smiles rearrangement is a reaction reported by Backer[103] **(Scheme 18)**.

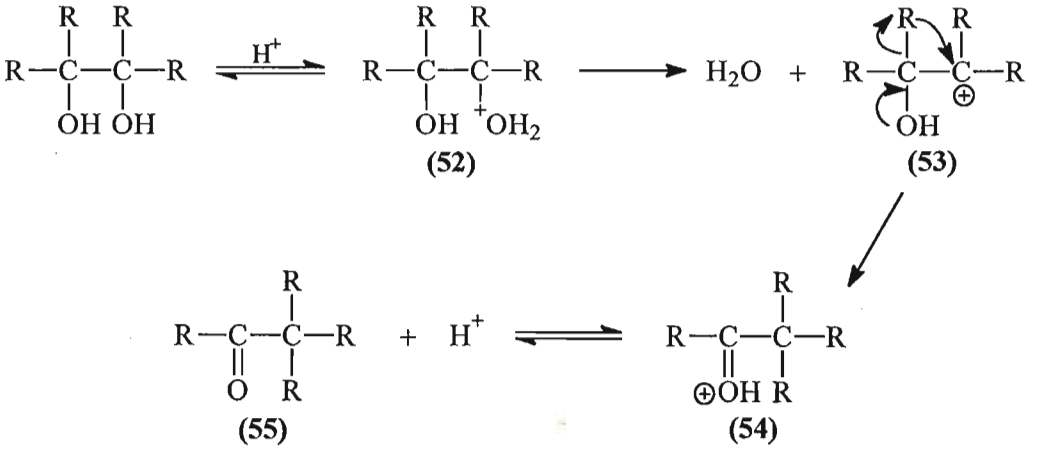


Scheme 18

1.5.2 PINACOL REARRANGEMENT[106]

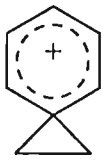
The Pinacol Rearrangement acquires its name from the rearrangement and dehydration of pinacol (2,3-dimethyl-2,3-butanediol) to pinacolone (*tert*-butyl methyl ketone) upon treatment with mineral acids. This same rearrangement occurs in other 1,2-diols.

The rearrangement occurs in two steps, the first involving dehydration from the protonated diol **(52)** to yield a carbocation **(53)** and the second being the rearrangement , by 1,2-shift, of the carbocation **(53)** to yield the protonated ketone **(54)**, and then ketone **(55)** **(Scheme 19)**.



Scheme 19

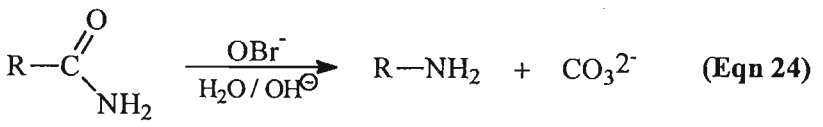
The pinacol rearrangement involves migration of a group to an electron deficient carbon centre. Due to the nature of the reaction, and particularly if the 1,2-diol contains many different substituents, there is usually more than one reaction product. However, the reaction product can often be predicted due to preferential carbocation formation and preferential movement of aryl groups compared to alkyl groups. Within the aryl group preferential migration depends on the ability of the aromatic ring to accommodate a positive charge. This feature is due to the fact that a three membered transition state is formed in the migration step, with the π-electrons of the aryl ring donating electrons to the electrophilic centre. This transition state is analogous to the intermediate in aromatic electrophilic substitution, with creation of the benzenonium ion **(56)**.



(56)

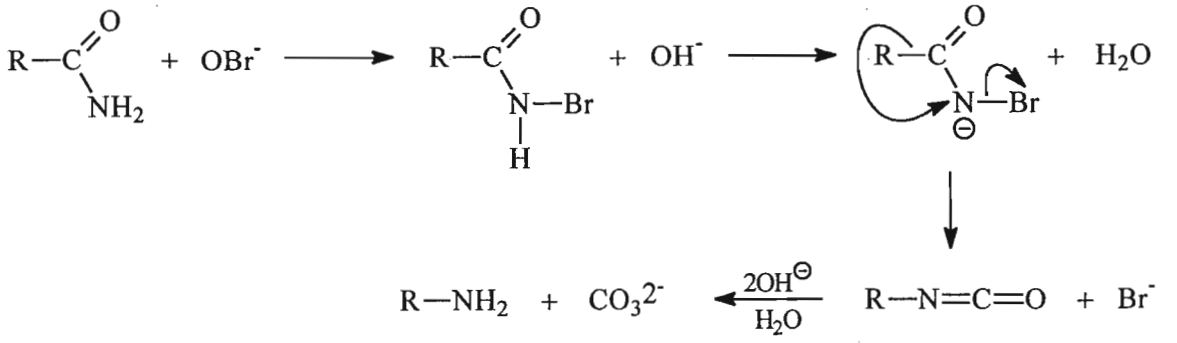
1.5.3 HOFMANN REARRANGEMENT[107]

The Hofmann rearrangement is essentially the degradation of an amide to an amine **(Eqn 24)**.



(Eqn 24)

In this reaction rearrangement occurs with the migration of the alkyl group originally attached to the carbonyl portion of the amide to the nitrogen. The mechanism of the rearrangement is believed to be as follows **(Scheme 20)**:



Scheme 20

The first steps involve removal of the hydrogens and halogenation of the nitrogen. In the next stage the 1,2-shift of the alkyl group occurs to the nitrogen, which is electron deficient due to the departure of the halogen, creating an isocyanate. This rearrangement is believed to be a concerted process. The last stage involved the hydrolysis of the isocyanate to the amine and carbonate. In an absence of water the last stage does not occur. The rearrangement reaction is intramolecular in nature and the stereochemistry of the migrating group is generally maintained.

The three membered transition state is also believed to occur in the Hofmann rearrangement, including the creation of the benzenonium ion **(56)** if the migrating group is aromatic in character.

1.5.4 CURTIUS REARRANGEMENT[108,109]

The decomposition of acid azides, acid hydrazides and acyl azides to isocyanates and nitrogen is known as the Curtius rearrangement **(Eqn 25)**. This rearrangement therefore is a preparative method for isocyanates and compounds derived therefrom. If the Curtius rearrangement is coupled with a hydrolytic step it provides a procedure for the replacement of a carboxyl group by an amino group, this process of converting an acid through its azide to the amine being referred to as the Curtius reaction **(Eqn 26)**.

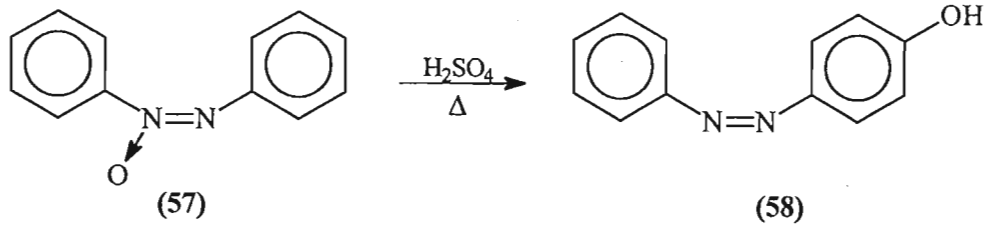
$$RCON_3 \longrightarrow RN{=}C{=}O + N_2 \qquad \textbf{(Eqn 25)}$$

$$RCO_2H \longrightarrow RCON_3 \longrightarrow RN{=}C{=}O \longrightarrow RNH_2 \qquad \textbf{(Eqn 26)}$$

Carbamates do not react readily with azides, but the corresponding carbamyl chlorides do. The resultant semicarbazide, from *O*-carbamates, or substituted semicarbazide, from *N*- and *O*-carbamates, yields carbamyl azides with nitrous acid. The azide derived from carbamic acid rearranges only with difficulty and monosubstituted carbamyl azides ($RNHCON_3$) do not rearrange. This is believed to be due to the formation of an isourea structure - $RN{=}C(OH)N_3$. The disubstituted carbamyl azides rearrange and this rearrangement is facilitated if one of the substituents is aromatic, cyclisation to the ring usually following rearrangement.

1.5.5 WALLACH AZOXYBENZENE REARRANGEMENT[110]

The Wallach azoxybenzene rearrangement, simply and generally, involves the conversion of azoxybenzene **(57)** into *p*-hydroxyazobenzene **(58)**, by migration of the oxygen, on addition of concentrated sulfuric acid **(Scheme 21)**.

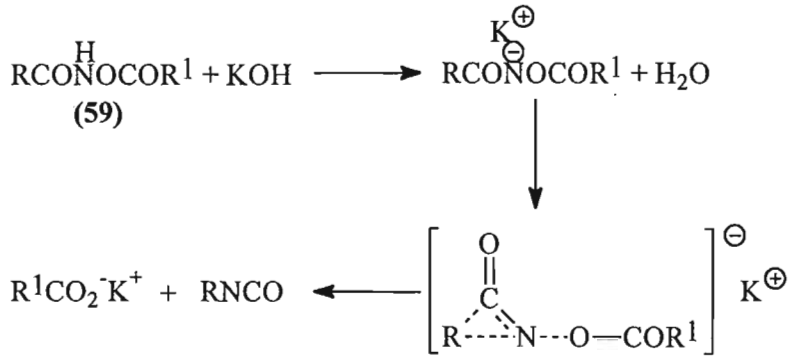


(57) **(58)**

Scheme 21

1.5.6 LOSSEN REARRANGEMENT[111,112]

The Lossen rearrangement allows for the rearrangement of O-acyl hydroxamic acid derivatives **(59)**, *via* isocyanates, with base or heat to amines or urea derivatives. Like the Curtius reaction it also allows for the conversion of a carboxylic acid, through the hydroxamic acid, to an amine. An example of the rearrangement, including the mechanism, is shown below **(Scheme 22)**.



Scheme 22

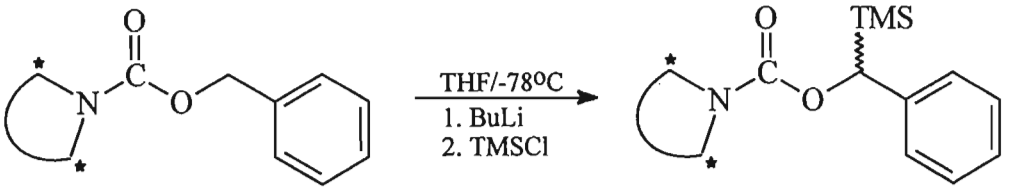
2. DISCUSSION

2.1 CHIRAL INDUCTION IN CARBAMATES

The initial aim of this Masters project was to obtain and determine chiral induction across the carbamate linkage using chiral amines. To date little success has been achieved in obtaining induced chirality in a carbamate system (See **1.2**). An ideal situation would be to use the chirality inherent in one portion of the molecule to induce chirality in another portion (asymmetric induction), particularly if the initial chirality was needed in future stages of the reaction scheme or in the final product. Chirality in carbamates is needed as many carbamate compounds are, or are used as precursors for, biologically active compounds, it being well known that nature tends to be chiral specific. For this reason chiral induction in carbamates is of interest and worthy of investigation.

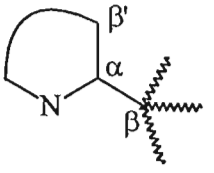
Initially chiral induction was to be attempted using the more stable and bulky benzyl carbamate. The benzyl carbamate is not as prone to side reactions as are other alkyl or alkenyl systems. Molecular modelling studies showed the benzyl carbamate system to be conformationally stable in nature and to exist favourably in only a few conformations. Because of this more ridged nature and due to the bulk of the phenyl ring the chance of achieving successful chiral induction is greater. This may be achieved by either asymmetric induction from another portion of the molecule, due to the more limited configurations of this part of the molecule in relation to the benzyl configuration and the phenyl bulk, or from the use of chiral proton abstraction agents as these would have limited angles of approach to the benzylic protons due to the phenyl ring and the rest of the molecule. Methods are known for the ready removal of carbamates, allowing for cleavage of the amine once chiral induction had been achieved.

The envisaged approach was to prepare chiral secondary amines and then use these to form the carbamate. Chiral induction was to be tested by determining if butyllithium, or LDA, if the additional steric bulk became necessary, would preferentially abstract one of the benzylic protons, and the resultant anion reacted with, for example, TMSCl **(Scheme 23)**.



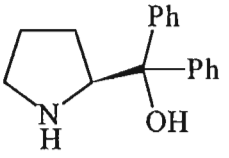
Scheme 23

After an initial search through the available literature it became obvious that numerous chiral amines had been prepared, although many of these preparations were not simple. It was decided to choose a few of the more promising examples and model them using the computer programme ALCHEMY[113] and molecular models to determine which of these examples would theoretically give good chiral induction. It became immediately obvious that for there to be any hope of success the chiral centre had to be preferably α to the nitrogen of the amine and that the major group attached to this point had to be a minimum of three carbons long. If the chiral centre moved β' to the nitrogen the attached group had to be much longer and far more bulky. Phenyl groups or ring systems β to the nitrogen **(60)** appeared to show more promise than alkyl chains as their position was more fixed, unlike the flexible alkyl chains. Based on the above conditions most of the chiral amines mentioned in the literature had to be abandoned.



(60)

One group of molecules that showed some hope of success was the one that had been used as oxazaborolidines for the chiral reduction of ketones, the compound α,α-diphenyl-2-pyrrolidinemethanol **(61)** showing particular promise and appearing simple to prepare. It was therefore decided to start with this molecule and further compounds would be chosen according to the success of this compound.

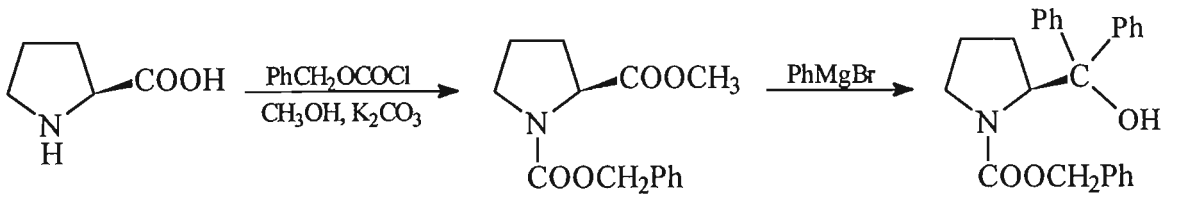


(61)

2.1.1 PREPARATION OF BENZYL 2-(HYDROXYDIPHENYLMETHYL)-PYRROLIDINE-1-CARBOXYLATE (64)

There are a number of procedures in the literature for the preparation of this compound (or the de-carbamated form thereof **(61)**)[36, 114, 115].

Initial attempts to prepare the desired compound were based on a recent publication by Kanth and Periasamy[116] where they detail a shortened two step procedure using proline **(62)** as the starting compound **(Scheme 24)**.

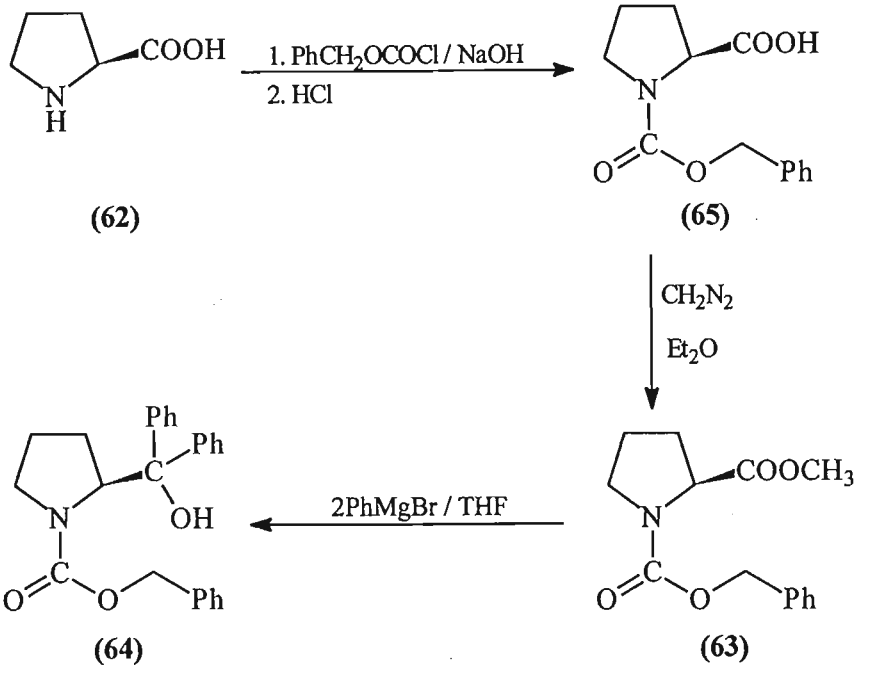


(62) **(63)** **(64)**

Scheme 24

The first step of this reaction sequence was repeated a number of times, but on all occasions the GC-MS results were inconclusive and the NMR spectra did not correspond to the required N and O protected molecule **(63)**, as there always appeared to be unnecessary peaks present, particularly in the δ3,5 region of the ^{1}H spectrum and a doubling up of peaks in the ^{13}C spectrum. Owing to this and the belief that the reaction was unsuccessful the above preparation procedure was abandoned and a multiple single step reaction strategy followed instead **(Scheme 25)**.

The preparation of N-benzyloxycarbonyl-L-proline **(65)** was readily achieved by the reaction of L-proline **(62)** with benzyl chloroformate[117]. The methyl ester **(63)** was formed by reaction of the N-protected proline with diazomethane[118] (made from N-methyl-N-nitrosourea[119]). A Grignard reaction[116] on this product yielded the desired product of the benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** in good yield.



Scheme 25

Upon analysis of these reaction intermediates it was realised that the initial reaction scheme **(Scheme 24)** tried had probably worked, as the same NMR spectra were obtained for the methyl ester **(63)**. Kanth and Periasamy[116] do not quote the occurrence of these excess peaks in their paper. These additional, or doubled-up peaks, in the NMR spectra of the carbamate protected proline methyl ester **(63)** could be due to conformational isomerism, due to the flexibility of the proline structure. This movement is readily seen in a model with the five-membered proline ring structure being able to twist and bend around its major plane into two conformations, with the methyl group being in two distinct and different environments. However, these additional peaks are more likely explained by the occurrence of rotamers[120]. This would occur when the compound was in two distinct conformations which interconvert slowly on the NMR timescale. Due to the pyrrolidine ring the amide portion of the carbamate bond is limited in the number of orientations it can assume, and thus also the benzyl carbamate portion This orientation prevents the free rotation of the methyl ester group, which will cause the methoxy portion to exist in mainly two conformations, these being when it is situated above and below the plane of the proline structure. Hence two sets of peaks are observed in the NMR spectra. Variable temperature NMR studies would have possibly allowed for further elucidation of this phenomenon.

All that remained was to protect the alcohol, as this would interfere with the chiral abstraction of the benzylic proton by BuLi. This step; however, proved to be far more difficult than expected and ultimately could not be achieved. The following protections were attempted:

- methyl protection with diazomethane in ether and with diazomethane and a neutral alumina catalyst[121]
- benzyl protection using DCC and benzoic acid in dichloromethane
- methyl protection with methyl iodide
- methyl protection with Me_2SO_4 and K_2CO_3 in acetone[122]
- tetrahydropyranyl protection[123]
- ethyl vinyl ether protection with PPTS in dichloromethane[124]
- phenyl ester protection with benzoyl chloride and triethylamine
- benzyl ether protection using benzyl chloride and triethylamine and using benzyl chloride and silver oxide catalyst in DMF[125].

None of the above protections was successful, as the required product could not be isolated.

Protection with many other groups, such as the TMS group, were not attempted as modelling studies showed that the conformation of the molecule would be changed to such an extent that chiral induction did not look feasible.

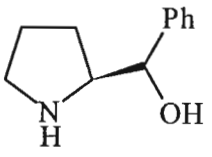
The reason for protection not being successful cannot be explained as modelling studies showed that there should have been sufficient space for protection to occur; however the reason could still have been steric hindrance. It is also generally known that tertiary alcohols are the least reactive in the alcohol series, which may also account for difficulty in achieving successful protection reactions.

No basic or basic medium protections could be attempted due to the occurrence of a *trans*-carbamation type reaction. This reaction became evident from GC-MS analysis data and was also proven by chemical means (to be discussed later in **2.2**).

It was very unfortunate that no protection of the alcohol could be achieved as in the proton NMR spectrum of the benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** molecule the two benzylic protons (δ5.10 - δ5.17) were already appearing in a split pattern, showing that these protons were not equivalent. Should the alcohol have been protected it follows that chiral induction may have been successful, to some degree at least.

At this point it was decided to abandon studies with this molecule and attempt other molecules before returning to this one and attempting the lengthy procedure of removing the carbamate, protecting the alcohol and then replacing the carbamate.

Due to the difficulty of protecting this alcohol, it was decided in future to avoid all similar molecules, such as α-phenylpyrrolidinemethanol[126] **(66)** and (S)-α,α-diphenyl-(indolin-2-yl)methanol[59] **(67)**, when choosing compounds for attempted chiral induction.



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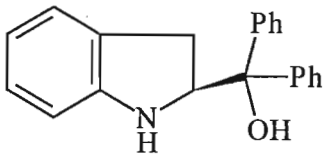
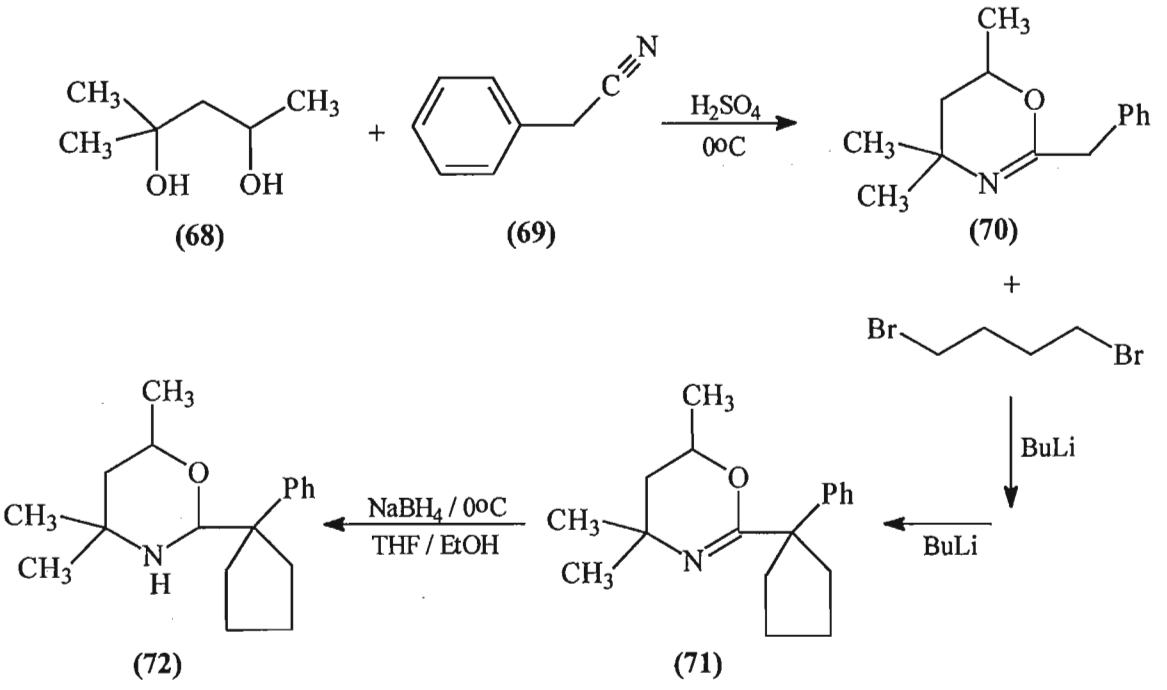


(67)

2.1.2 PREPARATION OF 2-(1-PHENYLCYCLOPENTYL)-4,4,6-TRIMETHYL-TETRAHYDRO-1,3-OXAZINE (72)

Due to the difficulties encountered in achieving results in the previous compound it was decided to attempt the reaction sequence shown in **Scheme 26,** using a racemic substrate to determine the success of the preparative route. Should the reactions be successful a chiral analogue would be prepared to determine the success of chiral induction. The title compound **(72)** is an oxazine and is structurally weighted on one side and modelling studies showed that this type of structure might give some success at a later stage for chiral induction.

The 2-(1-phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine **(72)** was prepared using the tried and tested method of Politzer and Meyers[127] **(Scheme 26)**.



Scheme 26

The synthesis was readily completed, except for the fact that the high yields that the authors claimed could never be attained. In the first stage for the preparation of the 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine **(70)**, phenyl acetonitrile **(69)** had to be added extremely slowly to sulfuric acid at 0-5°C, after which 2-methyl-2,4-pentanediol **(68)** was added extremely slowly once again to keep the reaction temperature at a minimum. In contrast to the method given, after pouring this reaction mixture over ice no organic washes could be made as these washed the desired product **(70)** from the reaction. The entire solution was made alkaline with a sodium hydroxide solution and then extracted. Purification was achieved by Kugelrohr distillation to give a disappointing yield.

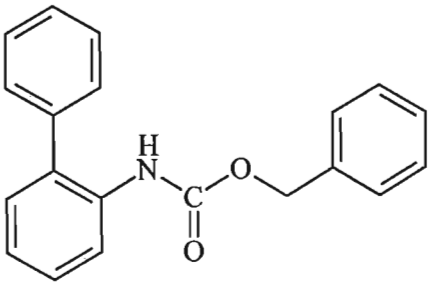
The attachment of the cyclopentyl portion was readily achieved, the first anion colour on addition of the BuLi being the expected dark orange and the second anion colour being an unexpected bright emerald green. For the hydrogenation step the reaction conditions had to be altered from -45°C to 0°C to avoid the occurrence of a binary phase system.

The final step in preparation of the compound was the conversion of the amine to the carbamate. Unfortunately after many attempts using different methods this could not be achieved as in each case the 2-(1-phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine **(72)** molecule disintegrated into numerous, mostly unidentifiable, fragments. Those that could be identified were 1-phenylcyclopentanecarboxaldehyde and 2-methyl-2,4-pentanediol, these being the products of acidic cleavage of the oxirane. Methods attempted to add the benzyl chloroformate included the use of the bases triethylamine, sodium hydride and DABCO as catalysts.

Once again the molecule had to be abandoned and further ones sought in an attempt to achieve the aim of obtaining and determining chiral induction.

2.1.3 FURTHER ATTEMPTS AT CHIRAL INDUCTION

It was observed from molecular models and using the ALCHEMY[113] modelling programme that the biphenyl structure was bulky and that the unsubstituted phenyl ring, in its minimum energy conformation, was in a perpendicular position in relation to the substituted phenyl ring and moieties attached to this ring. These studies showed that the 2-aminobiphenyl molecule **(73)** and derived structures showed some promise due to the close proximity of the second phenyl ring to the benzylic carbon. It was therefore decided to make an attempt using this molecule, by forming the carbamate **(73)** and substituting the other hydrogen of the amine with various electrophiles, to determine if this structure **(74)** would give a predicted result that could be expanded on. Chiral moieties could then be attached to either of the phenyl rings or a chiral structure substituted on the nitrogen.



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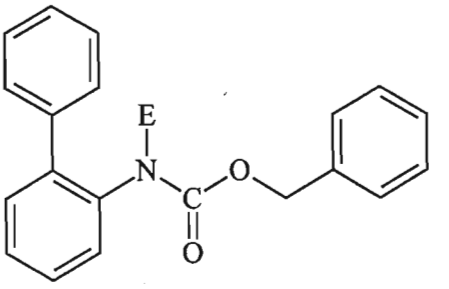


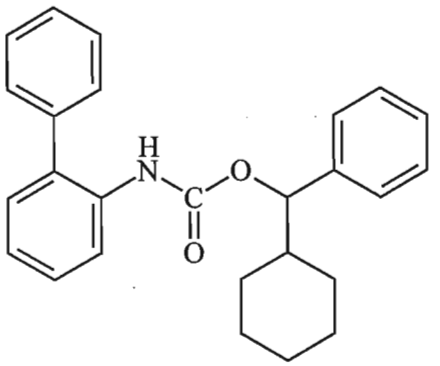
(74)

Initial attempts to alkylate the amine with the benzyl group prior to carbamate formation proved unsuccessful, and it was decided to initially form the carbamate and then substitute the now more activated hydrogen on the nitrogen in the second stage. It was also decided to avoid in future alkylating groups such as the benzyl group due to the presence of the acidic protons adjacent to the phenyl ring which were likely to cause interference in the chiral induction step (by abstraction with BuLi).

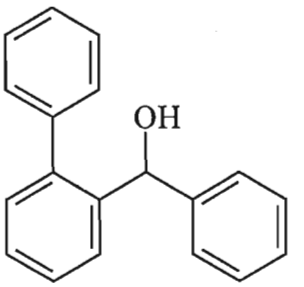
The formation of the carbamate **(73)** was readily achieved by reacting the primary amine with benzyl chloroformate, in THF, with the presence of sodium hydride. It was then decided to introduce the cyclohexyl group, for its bulk, onto the nitrogen of the carbamate. Introduction of the preferable phenyl group could not be attempted due to its inability to act as an electrophile (*i.e.* to have nucleophilic attack on the phenyl ring by the nitrogen ion in the carbamate). In addition, the cyclohexyl ring does not posses acidic protons, and the structure would therefore not interfere in the proton abstraction reaction step.

The substitution reaction was attempted at -78°C using BuLi. The desired product was not obtained although, surprisingly, a low yield of the carbamate benzylic substituted product, N-2-(1,1'-biphenyl) (cyclohexylphenyl)methyl carbamate **(75)**, was isolated, opposing the theory that the N-monosubstituted carbamate amine hydrogen was the more acidic by far. The reason that this substitution did not take place could have been steric hindrance, although this should not have posed a problem. However, it was decided to attempt the same reaction, but at 0°C, to determine if the carbamate could be N-alkylated at this higher temperature. The desired product was once again not obtained but a good yield of a

surprise product, 1'-phenyldiphenylmethanol **(76)**, was obtained giving rise to evidence of a new rearrangement reaction (to be discussed in detail in **2.3**).



(75)



(76)

2.1.4 CONCLUSION

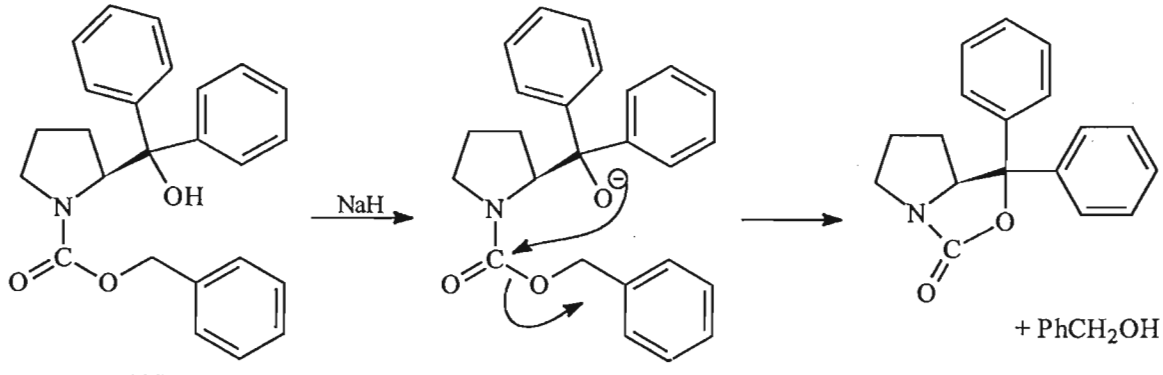
Due to the emergence of the above rearrangement reaction it was decided to study it further and abandon attempts at chiral induction, returning to this topic at a later stage if time allowed. The initial aim of the Master's project, of chiral induction across the carbamate linkage using chiral amines, was therefore never realised, but the investigation therein yielded two interesting categories of research, namely the *trans*-carbamation cyclisation reaction and the carbamate to alcohol rearrangement.

2.2 FORMATION AND PREPARATION OF OXAZOLIDONES (CYCLIC CARBAMATES)

2.2.1 3-OXA-1-AZA-4,4-DIPHENYLBICYCLO[3.3.0]OCTAN-2-ONE (77)

Evidence for a *trans*-carbamation type reaction to give an oxazolidone, or cyclic carbamate, first appeared in the preparation of the benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** compound. In GC-MS analysis of the compound no molecular ion peak could be obtained, but rather two peaks were observed, one with molecular mass of 108 and the other with molecular mass of 297. The fragmentation patterns correlated well with those predicted for benzyl alcohol and the cyclised elimination product, 3-oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one **(77)**, respectively.

To test the theory of this *trans*-carbamation type elimination reaction by chemical means, and not thermal as in the GC-MS occurrence, it was decided to react benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** with sodium hydride, as a base, and determine if the cyclisation occurred **(Scheme 27)**. TLC analysis of this reaction showed that the desired reaction had taken place in high yield and this was confirmed by product analysis after separation.



(64) **(77)**

Scheme 27

The above reaction mechanism **(Scheme 27)** is suggested by Kanth and Periasamy[116] for a portion of the elimination reaction of the carbamate protecting group in the preparation of α,α-diphenyl-2-pyrrolidinemethanol **(61)**, with the oxazolidone **(77)** as a predicted intermediate. However, their reaction takes place under very strongly basic conditions and therefore goes to completion for the hydrolytic elimination. Due to our milder conditions we were able to obtain the oxazolidone **(77)**, the intermediate in the reaction for the elimination of the carbamate protecting group.

An extensive search of the literature indicated that this compound, 3-oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one **(77)**, had not been prepared before, as well as the fact that the formation of oxazolidones by this *trans*-carbamation type reaction using sodium hydride was not reported, although the formation of oxazolidones from protected β-amino alcohols is one of the most common methods for their synthesis (see **1.4.4.1**).

Under the impression that this compound was newly synthesised an extensive structural characterisation study was undertaken and a crystal structure analysis finally proved our findings, also bringing to light some interesting aspects to the conformation of this molecule. The crystal analysis structure may be seen in **diag. 1**. The bicyclic portion of the molecule sits in a butterfly shape with the angle between carbons 4, 5 and 6 being 120.6°. The angle between the two phenyl rings is 78.3° and the angle of the two bonds to the phenyl rings at carbon 4 is 109.6°. Presumably due to the presence of the phenyl rings this molecule has an exceptionally large polarisability, with the $[\alpha]_D^{27}$ value being -215.1 (0.5058 g/100 ml).

A few months after completing our studies of this compound a publication by Delauhay and Le Corre[90] appeared, only later discovered by ourselves, in which they describe their isolation of this oxazolidone intermediate **(77)**. However, their preparation is *via* a different procedure, using that of Kanth and Periasamy[116] but using a much weaker basic solution (of KOH) and carrying out the reaction at room temperature and not at reflux.

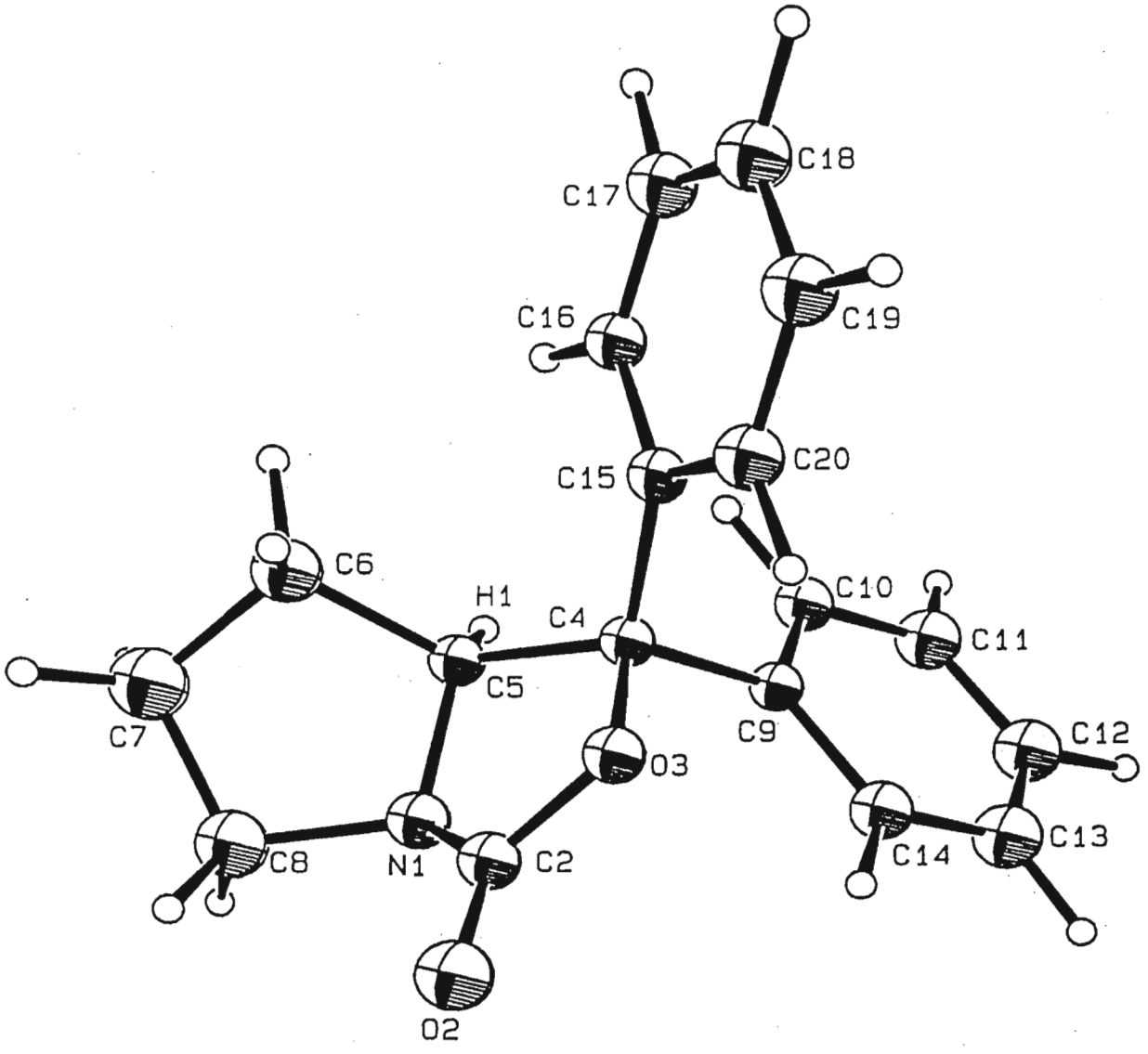
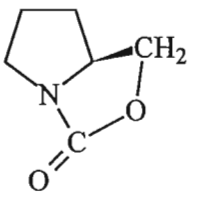


DIAGRAM 1: ORTEP diagram of 3-Oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one **(77)**

From TLC analysis of the initial Grignard reaction for the formation of the benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** it was obvious that this cyclisation reaction was occurring as a minor side reaction under the conditions of the Grignard reaction. It was our experience that this *trans*-carbamation elimination cyclisation reaction occurred very readily in this compound.

Due to the unusual nature of this reaction it was decided to investigate it further, in conjunction with the then chiral induction studies and later the rearrangement studies. The generality of this reaction was to be investigated and this was begun by attempting to form an unsubstituted bicyclic oxazolidone, 3-oxa-1-azabicyclo[3.3.0]octan-2-one **(78)**.



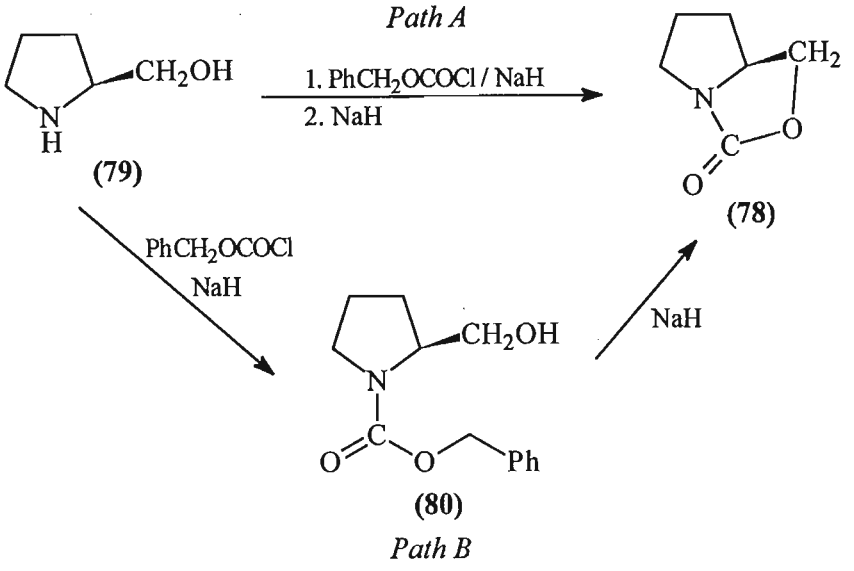
(78)

2.2.2 FURTHER STUDIES ON CYCLIC CARBAMATE FORMATION

The preparation of the simple/unsubstituted bicyclic oxazolidone **(78)** did not prove as simple, or occur as readily, as was the case with the substituted derivative. Two methods were attempted for its preparation (Path A and B of **Scheme 28)**

Initial attempts to form the carbamate of prolinol *via* an adaptation of the method used to form the carbamate from proline[117] were not successful. The reaction of prolinol **(79)** and benzyl chloroformate was then carried out in THF using sodium hydride. The reaction to form the carbamate **(80)** was observed to have occurred by TLC analysis and by NMR analysis of the unpurified products of the reaction, evidenced by the benzylic proton shift from δ4.8 to δ5.12. These unpurified products were dissolved in THF once again and a further equivalent of sodium hydride added to initiate cyclisation (Path B) - but to no effect. It was decided to try a more direct one pot method (Path A) and the first stage of

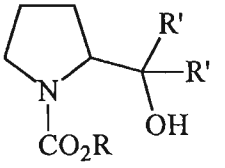
the reaction was repeated, except in this case no work-up was undertaken, and the second equivalent of sodium hydride was added directly to the reaction mixture after it had been stirring for an hour. In both instances reaction appeared to have occurred to some degree, as could be seen by GC-MS and NMR analysis, but even after numerous attempts none of the oxazolidone **(78)** could be isolated.



Scheme 28

It was the belief of Delauhay and Le Corre[90], which they subsequently proved incorrect, that the cyclisation reaction to form the oxazolidones was dependent on the nature of the carbamate *O*-alkyl portion. The results of their study for the cyclisation of the N-carbamate protected β-amino alcohols are summarised in **Table 1**. It was our theory, which was never proved, that the lack of success in the formation of the unsubstituted oxazolidone in comparison to the ease of formation of the diphenyl substituted compound lay in the fact of unsubstitution *i.e.* the difference between a primary and a tertiary alcohol. Possibly, without the presence of electron donating and stabilising groups, such as the phenyl group, for the oxygen ion, attack on the carbonyl and the stability of the intermediates is not as successful. This theory is, in essence, supported by the results of Delauhay and Le Corre who quote lower yields for the less electron-donating alkyl substituted compounds in comparison to the aryl substituted compound, as can be seen in **Table 1**. No reference is made to the unsubstituted oxazolidone.

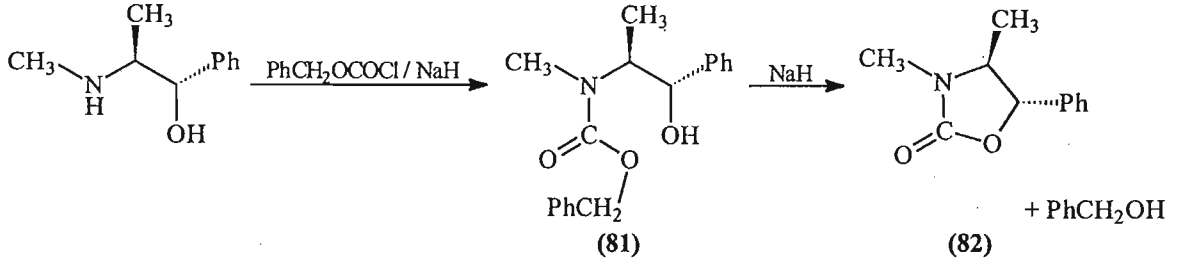
Table 1: Preparation of oxazolidones by base cyclisation of N-protected β-amino alcohols[90].



R	R'	Yield (%)
Me	Ph	92
Me	Et	75
Me	Bu	70
Me	2-Naphthyl	80
Et	Ph	94
CH_2Ph	Ph	93

Attempts to create a bicyclic oxazolidone from pyrrole and pyrrole-2-carboxaldehyde were abandoned due to the inherent instability of the pyrrole ring and its rapid polymerisation.

As the preparation procedure for the oxazolidones had not been reported before it was decided to test the methodology on an acyclic compound that should rapidly undergo cyclisation, namely the carbamate derivative of ephedrine **(81)**. The ephedrine oxazolidone **(82)** is well documented in the literature, prepared by other means from the β-amino alcohol and other methods[128]. It was initially decided to attempt this synthesis as a two stage one pot synthesis **(Scheme 29)**.



(81) **(82)**

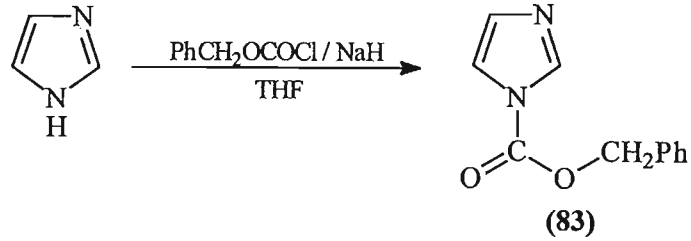
Scheme 29

TLC analysis of the first stage showed that a reaction had occurred in good yield and the second equivalent of NaH was added. Analysis of the reaction products showed an incomplete cyclisation, there being both the N-benzyloxycarbonylephidrine **(81)** and the required 3,4-dimethyl-5-phenyl-2-oxazolidone **(82)** present, the oxazolidone in the greatest yield.

Our methodology proved to be effective in a general case. (It was decided not to attempt to increase the yield of the monocyclic oxazolidone by a two pot reaction as the one pot reaction had furnished the desired result).

The occurrence of bicyclic oxazolidones, particularly those with nitrogen at the bridgehead position, is not extensively reported in the literature[76] (see **1.4.1 &.3**). It was decided to see what further examples could be prepared in this class, investigating whether the reaction went in preference when the alkyl ring, containing the N, was saturated or unsaturated (therefore being flexible or rigid), or when it was composed of five or six (or more) member atoms and if it was possible to place a hetero-atom close to the bridge position. The cyclic portion containing the carbamate linkage is already known to be five membered in preference[79].

Due to the ready availability of imidazole further investigations were to begin at this point. The preparation of the carbamate **(83)** from imidazole was readily achieved by reaction of imidazole with benzyl chloroformate in the presence of NaH **(Scheme 30)**.



(83)

Scheme 30

Substitution of an aldehyde group at the 2-position, on which a Grignard reaction was to be carried out to produce the alcohol for cyclisation, did not readily occur using DMF and BuLi. At this stage these studies were abandoned in favour of the carbamate to alcohol rearrangement reaction.

2.2.3 CONCLUSION

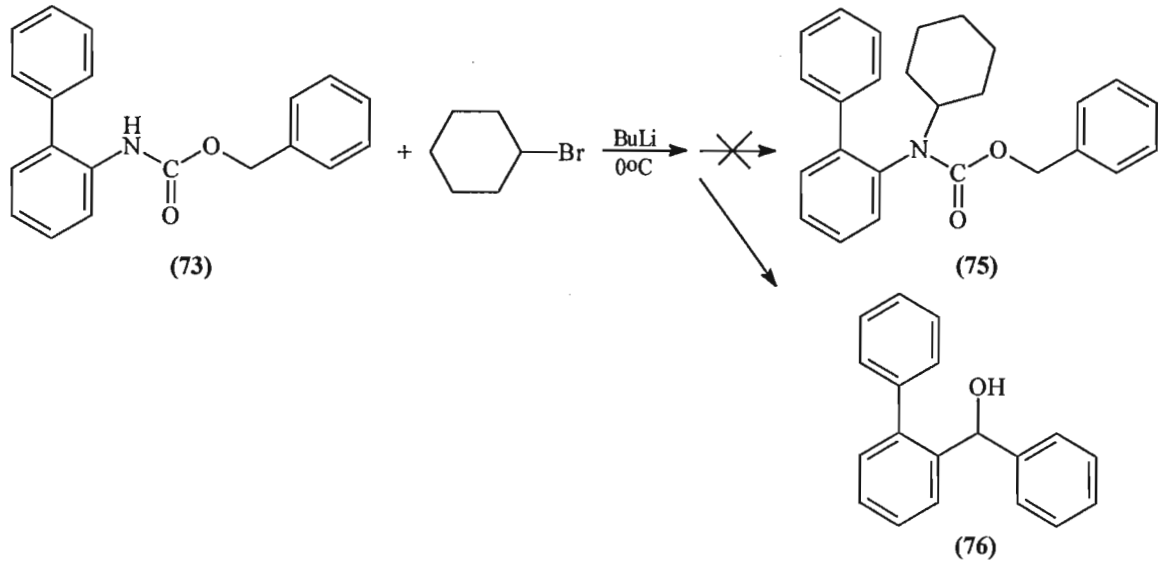
Initial studies show that induced cyclisation of N-carbamate protected β-amino alcohols with sodium hydride (NaH) is successful and should prove to be general. Studies also indicate that the ease of cyclisation and the stability of the product may depend on the substituents attached to the carbon to which the alcohol is attached. The scope of products would, of course, also depend on the ease with which the β-aminoalcohol could be formed.

2.3 REARRANGEMENT OF N-MONOSUBSTITUTED CARBAMATES TO ALCOHOLS

2.3.1 INITIAL DISCOVERY

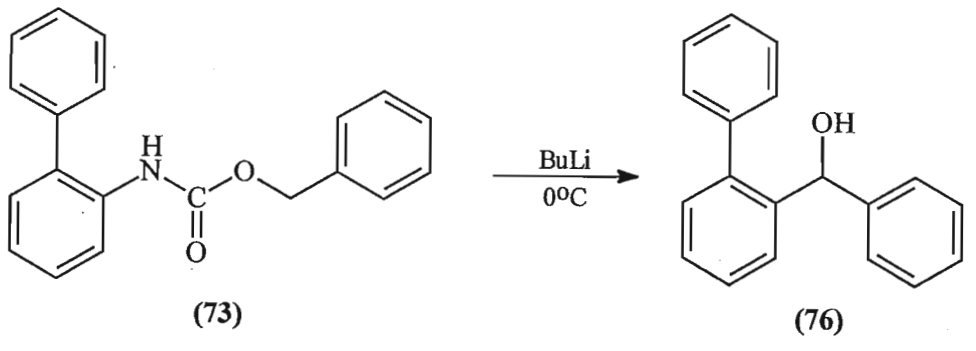
As mentioned previously, this surprise rearrangement and elimination reaction came to light when attempting to substitute the last hydrogen on the nitrogen of N-(2-biphenyl) benzyl carbamate **(73)** (page 54). The reaction was carried out at 0°C, using one equivalent of BuLi to abstract this last proton. However, instead of the desired substitution reaction taking place to give **(75)**, a good yield (64%) of an unknown product **(76)**, with molecular mass shown to be 260 by GC-MS, was obtained **(Scheme 31)**. Careful analysis of the mass spectrum showed that this compound could have the structure of 1'-phenyldiphenylmethanol **(76)**. NMR and IR analysis supported this conclusion. The ^{1}H NMR spectrum consisted of the peaks in the phenyl region, as expected, and only two

other peaks - one at δ5.89 and one much further upfield at approximately δ2.2, both with integral of one proton. The ^{13}C NMR spectrum consisted of only the aromatic carbons and one additional peak at δ72, which was indicated to be a methine carbon. Analysis of the proton spectrum after deuterated water exchange showed exchange with the peak at δ2.2, suggesting this peak to be due to an alcohol. The IR spectrum showed a broad absorption band in the alcohol region at 3420 cm^{-1}.



Scheme 31

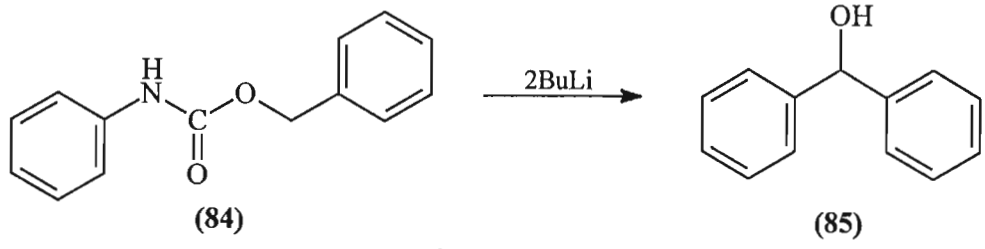
As this rearrangement reaction had taken place in the presence of bromocyclohexane, the substituent we had hoped would be substituted on the nitrogen, it was decided to repeat the reaction with only BuLi being added **(Scheme 32)**. Once again the secondary alcohol, 1'-phenyldiphenylmethanol (1'-phenylbenzhydrol or (2-biphenyl)phenylmethanol) **(76)**, was obtained in the same yield as that previously obtained.



Scheme 32

As it was unknown to which position on the biphenyl system the rearrangement was occurring, and to determine if this reaction was more general, it was decided to attempt the reaction using the carbamate derivative of aniline (N-phenyl benzyl carbamate **(84)**). Once again the rearrangement and elimination reaction occurred, the yield of diphenylmethanol **(85)** (56% by GC peak integration) being in the same region as that obtained for the N-2-biphenyl benzyl carbamate **(73)**.

In an attempt to increase the yield of this rearrangement reaction the reaction was repeated, using N-phenyl benzyl carbamate **(84)**, using two equivalents of BuLi, and not one as previously used **(Scheme 33)**. The yield increased to approximately 95% (by GC peak integration), the recovered yield being 71%. From this increase in yield it was deduced that the rearrangement reaction mechanism obviously required two equivalents of BuLi. All subsequent reactions were therefore carried out using two equivalents of BuLi.



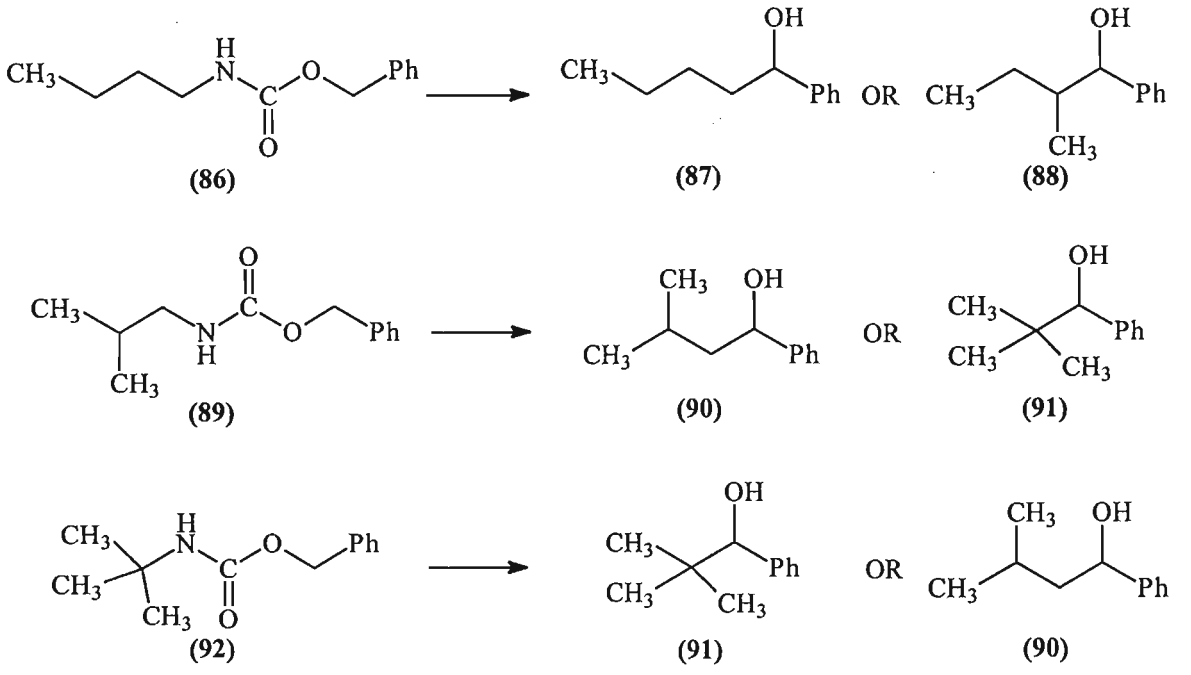
(84) **(85)**

Scheme 33

2.3.2 MECHANISTIC CONSIDERATIONS

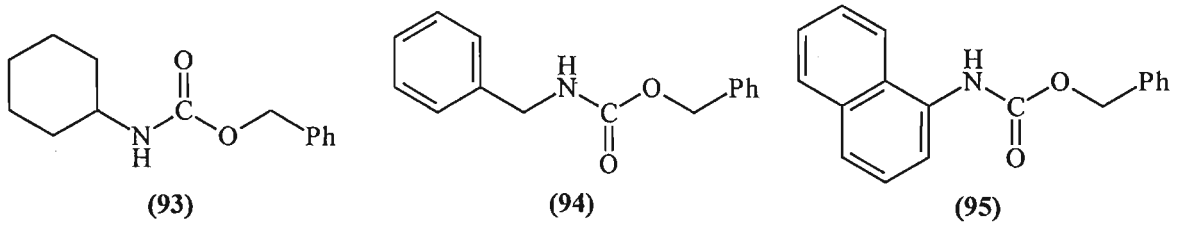
As the mechanism, and the generality, of this rearrangement and elimination reaction were not known it was decided to prepare a range of N-monosubstituted carbamates, including both aromatic and alkyl substituents attached to the nitrogen (N-carbamates). The butyl series, **(86)**, **(89)** and **(92)**, was chosen to determine (a) if the reaction occurred with alkyl substituents and (b) how many members/atoms the presumed cyclic reaction intermediate contained. This was to be determined by which position was substituted, the NMR spectra of the potential products being sufficiently unique to distinguish this fact **(Scheme 34)**. If

the reaction intermediate was a five membered cyclic structure then compounds **(87)**, **(90)** and **(91)** would be expected. If the reaction intermediate was six membered then compounds **(88)**, **(91)** and **(90)** would be obtained.

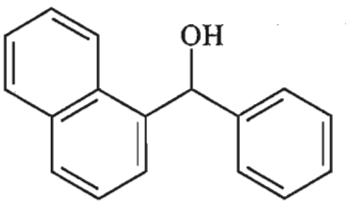


Scheme 34

The cyclohexyl derivative, N-cyclohexyl benzyl carbamate **(93)**, was chosen due to its alkyl, yet cyclic, character. The benzyl derivative, N-benzyl benzyl carbamate **(94)**, was chosen due to its more alkyl than aromatic nature and to determine the reaction intermediate, if the reaction occurred, by the product formed. The naphthalene derivative, N-α-naphthyl benzyl carbamate **(95)** was used as another aromatic example.

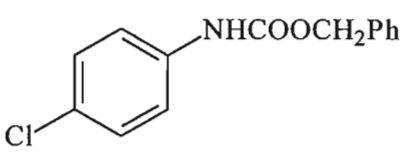


None of the reactions of the N-alkyl derivatives was successful, a number of unidentifiable products being produced and not the desired rearrangement product. The reaction with naphthalene was successful, the yield of (α-naphthyl)phenylmethanol **(96)** being on a par to those of the other aromatic compounds (62%).

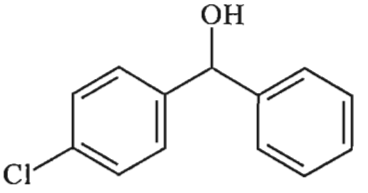


(96)

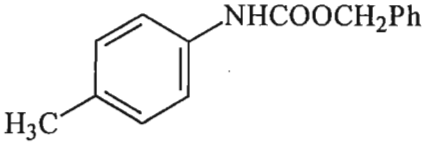
As none of the reactions involving the substituents that were to have given clues to the reaction mechanism and intermediate were successful, an aromatic compound containing a marker was chosen, namely the benzyl carbamate derivative of *p*-chloroaniline **(97)**. The position of the rearrangement would be readily recognisable due to the NMR splitting pattern in the phenyl region. In this compound the chlorine has a weak electron-withdrawing effect. To determine if the reaction went in preference when there was an electron-withdrawing or an electron-donating effect the benzyl carbamate derivative of *p*-toluidine **(99)** was also prepared.



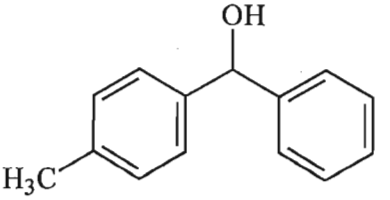
(97)



(98)



(99)



(100)

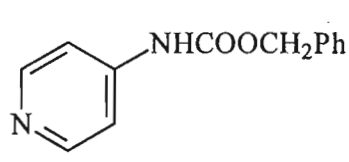
The rearrangement reactions for the above compounds were successful, producing (*p*-chlorophenyl)phenylmethanol **(98)** and (*p*-methylphenyl)phenylmethanol **(100)**. However the reactions were not as clean as those involving unsubstituted aromatic carbamates, there being numerous other unidentifiable products formed. As a result the yields of required product were low (approximately 14% for the methyl substituted **(100)** and approximately 10% for the chlorine substituted **(98)**). A reason for the drastic decrease in yield, except that of side reactions occurring at the substituent, could not be found and it appeared that electron-donating or withdrawing effects made little difference in comparison with one another. It may be possible to suggest that the *para*-substitution, or the substitution itself, caused the decrease in yield, but then the good yield obtained for the *ortho*-phenyl substituted compound **(76)** cannot be explained (unless the position is of particular importance). It has been shown in the Smiles aromatic rearrangement that bulky groups in the *ortho*-position decrease the number of transition state structures and enhance the close proximity of the three important rearrangement participants, thus enhancing reaction probability and rate (see **1.5.1**)[100,103]. These results may be analogous in this rearrangement reaction.

Analysis of the products, by NMR, showed that the rearrangement substitution had taken place in the *para* position, in relation to the marker, *i.e.* onto the same position as the nitrogen had been attached. This suggested a five membered cyclic reaction intermediate. (Mechanistic details will be discussed at a later stage in **2.3.8**)

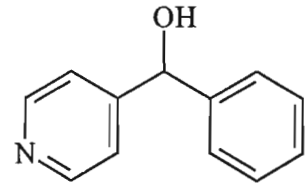
2.3.3 INTRODUCING A HETERO-ATOM

The studies were extended to aromatic systems containing a hetero-atom to determine if the rearrangement still occurred in these examples and if the hetero-atom had any effect on the reaction. First N-4-pyridyl benzyl carbamate **(101)** was prepared, from 4-aminopyridine, and the rearrangement reaction attempted. The reaction occurred successfully with a moderate yield (35%) of (4-pyridyl)phenylmethanol **(102)** being produced. As this reaction had been successful it was decided to change the position of the

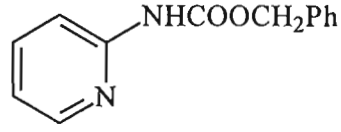
hetero-atom and determine the effect, if any. The benzyl carbamate derivative of 2-aminopyridine, N-2-pyridyl benzyl carbamate **(103)** was prepared and once again the reaction was successful, (2-pyridyl)phenylmethanol **(104)** being formed. In the case of the N-4-pyridyl benzyl carbamate **(101)** the yield of secondary alcohol **(102)** was approximately 10% greater than in the case of the N-2-pyridyl benzyl carbamate **(103)**. Unfortunately, due to the lack of ready availability of 3-aminopyridine, the effects of the hetero-atom in the *meta* position could not be ascertained.



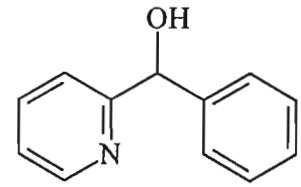
(101)



(102)



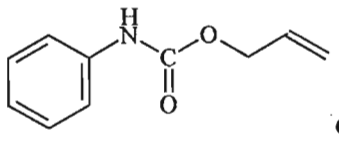
(103)



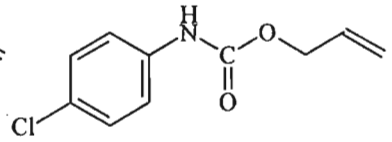
(104)

2.3.4 OTHER CARBAMATE DERIVATIVES

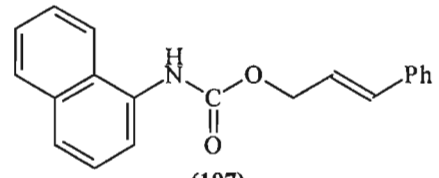
Thus far in the studies only the benzyl carbamate had been used and it was decided to determine if this rearrangement reaction would occur with other O-carbamate moieties. The allyl carbamates of aniline and *p*-chloroaniline, N-phenyl allyl carbamate **(105)** and N-*p*-chlorophenyl allyl carbamate **(106)** respectively, were prepared. N-naphthyl cinnamyl carbamate **(107)** was also prepared, by the reaction of naphthylisocyanate with cinnamyl alcohol.



(105)



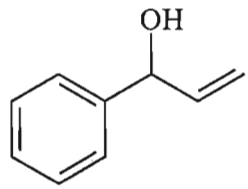
(106)



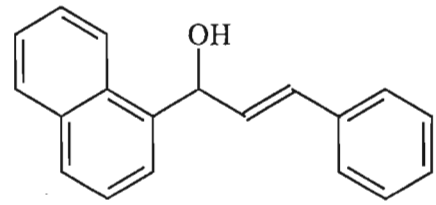
(107)

The rearrangement was successful in the case of N-phenyl allyl carbamate **(105)**, giving 1-phenylprop-2-en-1-ol **(108)**. However the yield was very low, as could be seen by GC-MS analysis, and no product could actually be isolated. The reaction was not a clean one and numerous side reactions on the allyl portion obviously occurred. The reaction involving the N-*p*-chlorophenyl allyl carbamate **(106)** was not successful.

The rearrangement of the N-naphthyl cinnamyl carbamate **(107)** was far more successful with the required product, 1-(α-naphthyl)-3-phenylprop-2-en-1-ol **(109)**, being formed in 40% yield.



(108)



(109)

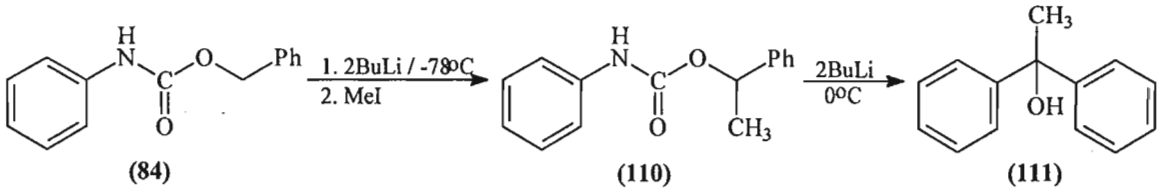
2.3.5 ATTEMPTS TO OBTAIN REARRANGEMENT TO A TERTIARY ALCOHOL

As the above reactions had shown some success it was decided to expand the study further to a compound that was substituted at the point of rearrangement in the carbamate portion of the molecule, namely N-phenyl 1-phenylethyl carbamate **(110)**. This compound was prepared by reaction of two equivalents of BuLi with N-phenyl benzyl carbamate **(84)** at -78°C, with subsequent addition of iodomethane (see 1st half of **Scheme 35**). Unfortunately

the product **(110)** could not be successfully separated from the starting material **(84)** and this mixture had to be used when attempting the rearrangement reaction.

The rearrangement (2nd half **Scheme 35**) was successful but occurred in low yield (10%). The tertiary alcohol product, 1,1-diphenylethanol **(111)**, was easily separated from other products and the secondary alcohol (diphenylmethanol **(85)** formed from the starting material).

Attempts to prepare the tertiary alcohol by a two stage one pot reaction **(Scheme 35)** from N-phenyl benzyl carbamate **(84)** gave a mixture of products and a lower yield of the tertiary alcohol, as evidenced by GC-MS results.



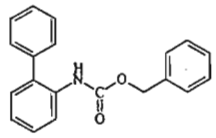
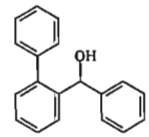
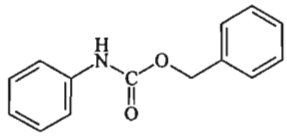
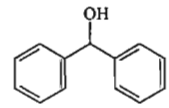
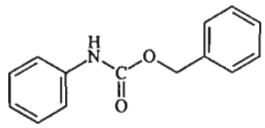
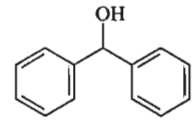
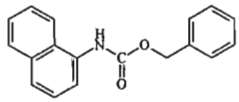
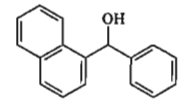
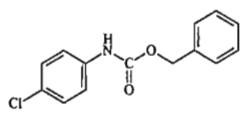
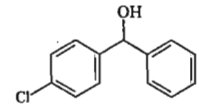
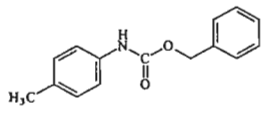
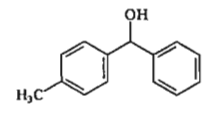
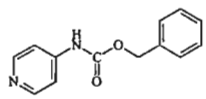
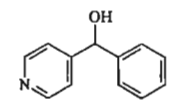
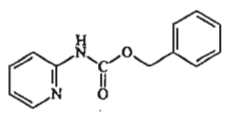
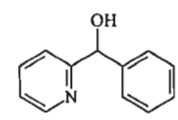
(84) **(110)** **(111)**

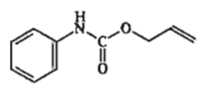
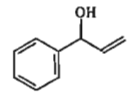
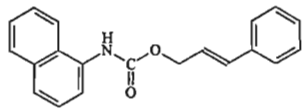
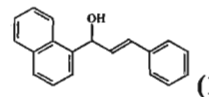
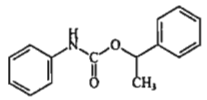
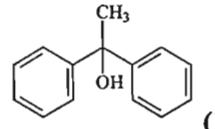
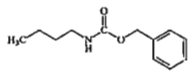
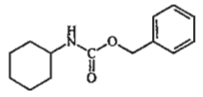
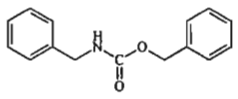
Scheme 35

2.3.6 SUMMARY OF RESULTS

The results of all the studies into this rearrangement reaction of N-monosubstituted carbamates to substituted alcohols, with presumed concomitant loss of cyanic acid (HNCO), are summarised in **TABLE 2**.

TABLE 2: Products and yields for attempted alcohol formation from carbamates.

CARBAMATE	Eq. BuLi	ANION COLOUR[1]	PRODUCT	YIELD (%)
N-(2-biphenyl) benzyl carbamate  **(73)**	1	yellow / light orange	1'-phenyldiphenylmethanol  **(76)**	64
N-phenyl benzyl carbamate  **(84)**	1	deep yellow	diphenylmethanol (benzhydrol)  **(85)**	(58)[2]
N-phenyl benzyl carbamate  **(84)**	2	very dark orange	diphenylmethanol  **(85)**	71 (94.5)[2]
N-α-naphthyl benzyl carbamate  **(95)**	2	red (very deep yellow)	α-naphthylphenylmethanol  **(96)**	62
N-*p*-chlorophenyl benzyl carbamate  **(97)**	2	deep orange / red	*p*-chlorodiphenylmethanol  **(98)**	10
N-*p*-methylphenyl benzyl carbamate  **(99)**	2	deep orange / red	*p*-methyldiphenylmethanol  **(100)**	14
N-(4-pyridyl) benzyl carbamate  **(101)**	2	deep red	(4-pyridyl)phenylmethanol  **(102)**	35
N-(2-pyridyl) benzyl carbamate  **(103)**	2	deep red	(2-pyridyl)phenylmethanol  **(104)**	23

CARBAMATE	Eq. BuLi	ANION COLOUR[1]	PRODUCT	YIELD (%)
N-phenyl allyl carbamate  **(105)**	2	orange	1-phenylprop-2-en-1-ol  **(108)**	v.v. low[2]
N-*p*-chlorophenyl allyl carbamate **(106)**	2	orange		0
N-α-naphthyl cinnamyl carbamate  **(107)**	2	deep olive green to black	1-(α-naphthyl)-3-phenylprop-2-en-1-ol  **(109)**	40
N-phenyl (1-phenyl)ethyl carbamate  **(110)**	2	light orange	1,1-diphenylethanol  **(111)**	10
N-*n*-butyl benzyl carbamate  **(86)**	2	deep bright orange		0
N-*i*-butyl benzyl carbamate **(89)**	2	deep yellow		0
N-*t*-butyl benzyl carbamate **(92)**	2	light bright orange		0
N-cyclohexyl benzyl carbamate  **(93)**	2	deep yellow / orange		0
N-benzyl benzyl carbamate  **(94)**	2	red		0

1-Anion colour is dependant on concentration. 2-Yields based on GC peak integration.

2.3.7 GENERAL DISCUSSION

All the carbamates, with the exception of N-naphthyl cinnamyl carbamate **(107)**, were prepared by the reaction of the primary amine with the chloroformate, using NaH as base **(Eqn 27)**. This method proved to be a simple and general route to the N-monosubstituted carbamates, with yields being good.

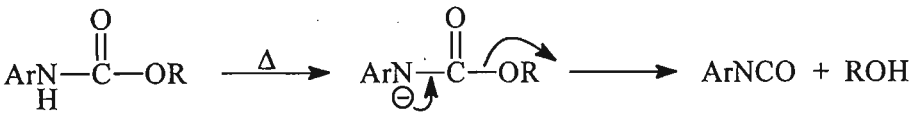
$$RCH_2OCOCl + R'NH_2 \xrightarrow[THF,\ R.T.,\ 18h]{NaH} RCH_2OCONHR' \qquad \textbf{(Eqn 27)}$$

R = CH_2=CH_2, Ph
R' = Ph, naphthyl, butyl, benzyl, pyridyl, cyclohexyl, *p*-ClPh, *p*-MePh

The above reactions for the formation of the carbamate could be seen to have occurred by the increase in R_f in TLC analysis using an ethyl acetate in hexane mixture and by the downfield shift of the benzylic protons. These protons in the chloroformate are found at δ4.8 and move to δ5.0 - δ5.25 in the carbamate. The allyl system showed a similar downfield shift of all protons in the system.

From an inspection of the analytical data of the starting carbamates and the rearrangement results an interesting correlation comes to the fore. In the examples where good yields of the secondary alcohol rearrangement product were obtained, the GC analysis of the parent carbamate, even when pure, produces peaks representing the carbamate and two degradation products, namely the aromatic isocyanate and the alcohol of the remaining portion (usually benzyl alcohol). The examples where this feature occurred are N-(2-biphenyl) benzyl carbamate **(73)**, N-phenyl benzyl carbamate **(84)**, N-naphthyl benzyl carbamate **(95)**, N-naphthyl cinnamyl carbamate **(107)** and to a lesser extent N-*p*-chlorophenyl benzyl carbamate **(97)** and N-*p*-methylphenyl benzyl carbamate **(99)**. The degradation of N-monosubstituted carbamates, particularly those with good leaving groups such as aryloxy or benzyloxy, to isocyanates is a common occurrence[129] **(Scheme 36)**. In the case of N-aryl carbamates the formation of the aromatic isocyanate is further enhanced

as the electrons are delocalised over the entire molecule and thus the aromatic nature of the ring stabilises the attached isocyanate portion. The formation of alkyl isocyanates did not occur under the conditions used to obtain the gas chromatographs, the formation of alkyl isocyanates not occurring as readily as aryl isocyanates.

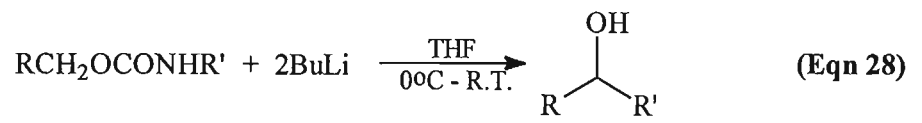


Scheme 36

GC-MS analysis of the reaction mixture for the formation of the N-pyridyl benzyl carbamates, **(101)** and **(103)**, showed only starting materials and side reaction by-products, suggesting that the carbamate formation had not occurred. However, NMR analysis showed that the reaction had occurred, as could be seen from the benzylic proton shift from approximately δ4.8 in the chloroformate to approximately δ5.2 in the carbamate. In the instance of these compounds the rearrangement to secondary alcohol also did occur.

It may be possible to suggest that the above mentioned GC-MS results of the parent carbamate may act as an indication, in as yet untested molecules, that the rearrangement reaction to substituted alcohol could possibly occur.

The rearrangement reaction of carbamate to alcohol was carried out by addition of two equivalents of BuLi to the carbamate, dissolved in THF **(Eqn 28)** (except in the origional reaction involving **(73)**).



(Eqn 28)

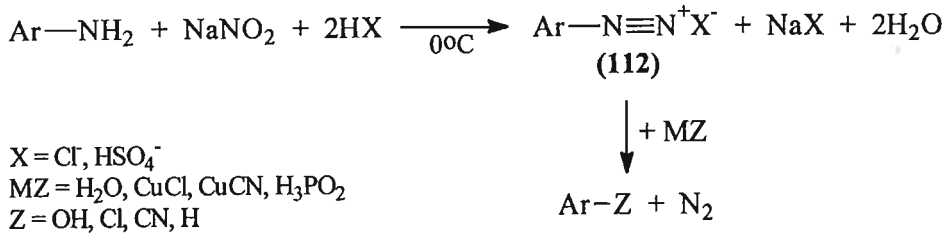
R = Ph, CH_2=CH_2, $PhCH_2$=CH_2
R' = Ar, pyridyl

Analysis of the products by NMR shows a downfield shift of the original benzylic protons from approximately δ5.1 to approximately δ5.6 - δ5.9, with the exception of naphthyl-phenylmethanol **(96)** and (2-pyridyl)phenylmethanol **(104)**, and a decrease in the integral. There is also the appearance of a slightly broader peak upfield in the δ2.2- δ2.65 region for the alcohol. This peak is found further downfield in the pyridyl examples. That this peak was due to the alcohol was further confirmed by its loss on exchange with deuterated water, this fact being determined for benzhydrol **(85)** and 1'-phenyldiphenylmethanol **(76)**.

Addition of the butyllithium to the carbamates produced a wide range of anion colours, generally ranging from deep yellow to red. These anion colours are dependent on concentration, as well as on the compound itself. As the reaction progressed the anion colour faded, as expected, and this feature aided in the monitoring of the reaction progress.

The rearrangement and elimination reaction is begun at 0°C, with the reaction mixture being allowed to slowly warm to room temperature as the reaction progressed. The reaction was attempted where the BuLi was added at room temperature; however these conditions were not favourable with a decrease in yield and numerous by-products being observed, although the reaction was over more rapidly, as could be seen by the loss of anion colour. Too rapid an increase in the reaction temperature from 0°C to room temperature had a similar effect.

One of the most difficult functionalities to remove in synthetic organic chemistry is the amine, and related, functionalities, *i.e.* the breaking of the C-N bond. The most common method of achieving this, which is generally only successful in the case of aromatic amines, is the formation of the diazonium salt **(112)** and then replacement of this group[130] **(Scheme 37)**. The reaction is only applicable to primary amines and all amine derived functionalities must therefore be reduced to the primary amine. The diazonium salt is prepared by the reaction of nitrous acid (HNO_2), which is prepared *in situ* by the reaction of a mineral acid on sodium nitrite ($NaNO_2$), with the amine. The diazonium salt may then be replaced by a number of functionalities, with loss of the nitrogen as N_2. However, the only reaction to replace the C-N bond with a C-C bond is the replacement of the diazonium



Scheme 37

salt with the cyanide group, to form the nitrile, from which further synthetic steps may be achieved. The diazotization reaction is in some cases a difficult reaction due to the instability and reactivity of the salt, which must also be used immediately upon its formation. The replacement reaction to give the nitrile is further complicated as the diazonium salt reaction mixture must first be neutralised before reaction with the cuprous cyanide, to prevent the formation and loss of HCN. After obtaining the nitrile numerous additional steps are needed to build up the desired molecule. The replacement of the amine functionality by this traditional method is therefore a lengthy and complicated procedure. The rearrangement reaction of the N-monosubstituted carbamate to the substituted benzyl alcohol achieves the same result as the diazotisation reaction as it removes the amine functionality and replaces it with a C-C bond, with the presence of the alcohol function on which further synthesis may be achieved. This rearrangement reaction is a simple reaction, readily carried out, which allows for the replacement of the amine in two steps. It also gives in the two steps a more complicated, or built-up, compound without the need for numerous synthetic steps to achieve this, although the reactions scope in this field has not been fully evaluated. It involves the use of, comparatively, non dangerous reagents and the "intermediate" N-monosubstituted carbamate formed from the primary amine need not be used immediately and may be stored, if pure, for a few weeks.

The most common literature method for the preparation of the secondary alcohols formed from the rearrangement of the carbamates has been the reduction of the corresponding ketones and by other more traditional methods [131, 132, 133, 134, 135, 136]. These ketones may not always be readily prepared and this rearrangement reaction provides a simple two step procedure to the secondary alcohol.

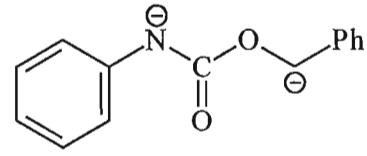
2.3.8 MECHANISTIC DISCUSSION

No literature precedent was found relating to a potential mechanism for this rearrangement reaction of N-monosubstituted carbamate to alcohol. Those that were found that may resemble a potential mechanism are discussed in **1.5**, the Smiles aromatic heteroatom migration rearrangement being the most significant.

From these initial results obtained for the attempted rearrangement reactions of N-monosubstituted carbamates to substituted alcohols the following generalised conclusions can be drawn:

(a) The rearrangement reaction occurs in the case of aromatic carbamate derivatives and not in the case of alkyl carbamates.

(b) The reaction requires two equivalents of BuLi as can be seen by the increased yield from one to two equivalents (in the case of N-phenyl benzyl carbamate **(84)**). This suggests two anions in the reaction intermediate, one at the nitrogen and one at the benzylic carbon **(113)**.



(113)

(c) The reaction may occur with a variety of carbamate moieties, so long as the carbon adjacent to the oxygen of the carbamate linkage has a position available for substitution / anion formation.

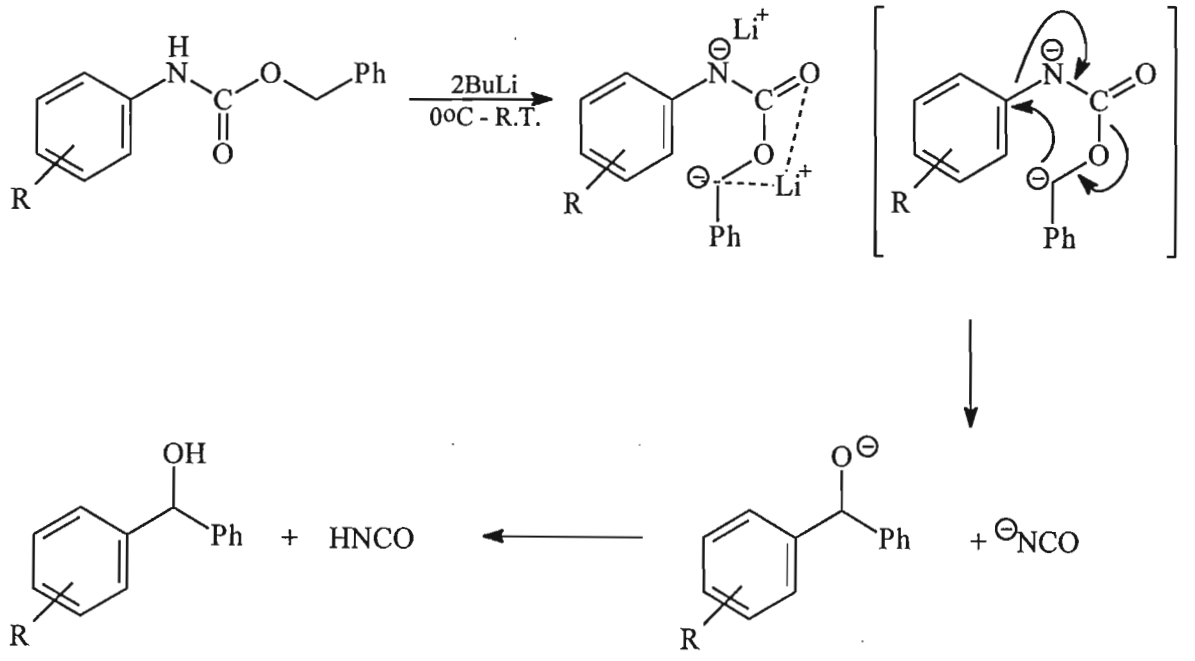
(d) The rearrangement occurs to the same position on the aromatic ring that the nitrogen of the carbamate linkage was attached to. This suggests a five membered reaction intermediate consisting of the carbamate linkage, the adjacent carbon and the position of substitution. This cyclic transition state complex would in essence be an oxazolidone[79].

(e) Substituents in the *para* position to the point of attachment of the carbamate on the phenyl ring appear to decrease the yield of alcohol. There appears to be little difference between the effects of electron-withdrawing or donating groups with electron-withdrawing

groups having fractionally more negative influence on the reaction yield. Electron-donating groups, or simply substitution, in the *ortho* position appear to have a positive effect on the reaction as can be seen by the good yield obtained in the case of N-(2-biphenyl) benzyl carbamate **(73)**, even with only one equivalent of BuLi.

(f) Hetero atoms in the aromatic ring do not appear to hinder the reaction occurring, so long as the aromatic character of the ring is maintained, although yields are slightly lower.

From the above generalised conclusions the following reaction mechanism can be tentatively proposed **(Scheme 38)**.



Scheme 38

The formation of cyanic acid (HNCO) as a by-product in this reaction was not confirmed, although it seems the most likely compound to be formed. Cyanic acid would be difficult to detect as it has the potential to polymerise at temperatures above 0°C; however no solid material was observed to form during the rearrangement reaction. Cyanic acid is also volatile and in aqueous environments is hydrolysed to NH_3, CO_2 and H_2O, making detection difficult[137]. The possible detection of an ammonia odour is overpowered by the residual odour of the THF and BuLi in the reaction mixture, after quenching.

The rearrangement and elimination reaction of a N-monosubstituted carbamate to the substituted alcohol is an unusual and novel reaction, as is the mechanism proposed.

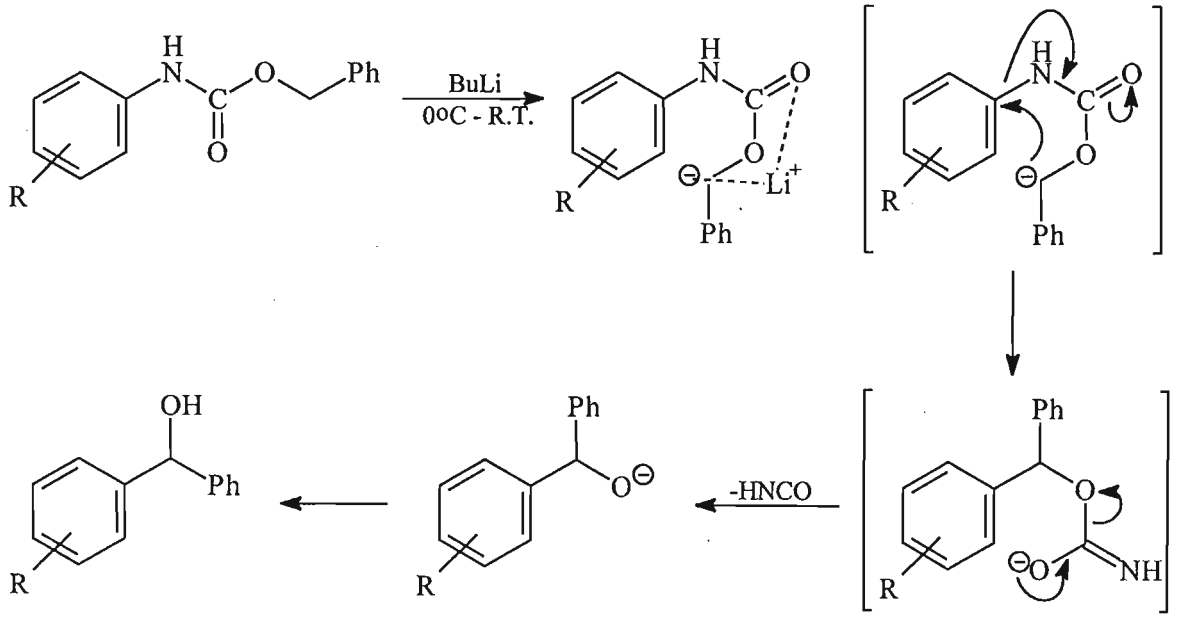
In the mechanism **(Scheme 38)** the attack of the benzylic anion on the point of attachment of the nitrogen on the aromatic ring is electronically not favoured as there is already a high electron density in the area creating a nucleophilic and not electrophilic environment. However, if the mechanism of attack is of a S_N1-type substitution, with the aromatic-nitrogen bond being broken before substitution of the benzylic anion, then a fractionally positive (δ+ve) charge would exist at that point on the aromatic ring, favouring attack by a nucleophile to a slightly greater degree. In the first instance (S_N2-type) an electron-withdrawing substituent in the *ortho* or *para* position would favour progression of the reaction as this would minimise the negative charge/greater electron density at the point of rearrangement. On the other hand an electron-donating group at either of these positions would help stabilise the positive charge created in the S_N1 scenario and thus favour progression of the reaction. Initially, from the results obtained, it appears that this is the more likely option, *i.e.* that of a concerted S_N1-type mechanism. However, in this scenario the ready cleavage of the aromatic-nitrogen bond is not readily explained, this usually being difficult to achieve. If the mechanism is of the S_N1 type then the question arises as to whether the rearrangement reaction occurs inter- or intra-molecularly. No studies to determine which option actually occurs were undertaken. For steric reasons, from modelling studies and a knowledge of the ready formation of the oxazolidone into a five membered ring, the intra-molecular case seems the more plausible. However, in the case of the S_N2 scenario the formation of a benzenonium type transition state is possible. The formation of the benzenonium ion **(56)** is reported for aromatic migration/rearrangement in the Hofmann and Pinacol rearrangements (see **1.5**). Here the aromatic ring is attached to a three membered ring transition state with some of the electron density from the aromatic system being transferred to an electron deficient centre, and this positive charge therefore being spread over the aromatic ring. In the case of the Hofmann rearrangement the loss of the halide ion creates an electron deficiency on the nitrogen and the aromatic migration is believed to occur simultaneously, each fact aiding the occurrence of the other. If, in the reaction mechanism above (**Scheme 38**), the formation of the isocyanate ion is a driving

force in the reaction then a small electron deficiency may exist at the nitrogen, allowing for formation of a benzenonium type ion **(56)** and nucleophilic attack on the ring. In this case electron-donating effects on the ring would stabilise the positive charge over the ring and favour the reaction occurring. Electron-withdrawing effects would have the opposite effect. The results obtained for reactions with such electronic features are concurrent with this theory. The Smiles aromatic rearrangement is well known and involves nucleophilic attack on the aromatic system, with the formation of a *spiro*-transition state **(50)**. In this case electron-withdrawing effects on the aromatic ring enhance the reaction favourability as the excess negative charge can be distributed over the whole system. However, reactions for non-activated systems have been reported[104], where the aromatic ring holds the excess electron density. The aromatic system also takes on a negative charge if one of the hetero-atoms, usually a nitrogen, is positively charged. It has also been shown in the Smiles rearrangement that substituents in the *ortho* position enhance the reaction rate and yield due to the formation of a "V" shaped transition state **(51)** with the *ortho* substituent forcing the reacting components into favourable alignment for the rearrangement to occur. The results obtained are therefore also able to be fitted to, and are more likely attributable to, a transition state and reaction mechanism of the S_N2-type, resembling that of the Smiles rearrangement.

In the case of the pyridyl systems reaction to the point of attachment is more likely due to the existence of resonance structures in the aromatic ring. The nitrogen is able to be negatively charged and therefore the *ortho*- and *para*-positions carry a positive charge[100], aiding progression of the reaction and possibly a five-membered *spiro*-reaction intermediate. Pyridyl systems are known to undergo the Smiles rearrangement[103].

The evidence for the need for two equivalents of BuLi in the reaction, and therefore the presence of two anions in the intermediate complexes in the mechanism, is not totally conclusive. In the original reaction involving N-(2-biphenyl) benzyl carbamate **(73)** only one equivalent of BuLi was used and a yield in excess of 50% was obtained. However, in the case of the N-phenyl benzyl carbamate **(84)** doubling the equivalents of BuLi led to an almost two-fold increase in the yield of the alcohol product. However, this increased yield

is only slightly greater than that obtained in the original reaction scenario. If in fact the reaction does not require the addition of two equivalents of BuLi, but only an excess, then the rearrangement reaction would occur *via* a different reaction mechanism. In this mechanism **(Scheme 39)** there is the formation of only one anion, found at the benzylic position. The rearrangement step takes place *via* a S_N2 mechanism, with subsequent loss of the cyanic acid occurring to give the alcohol.



Scheme 39

Unfortunately the studies undertaken were not extensive enough to reach any binding conclusions and thus no definite reaction mechanism can be proposed. Furthermore no rate studies were carried out.

2.3.9 CONCLUSION

A novel and apparently unique rearrangement reaction of an aromatic N-monosubstituted carbamate ($ArNHCOOCHR^1R^2$) to a secondary (if R^1 = H) or tertiary alcohol, with elimination of cyanic acid, was discovered when the carbamate is reacted with two equivalents of butyllithium at 0°C (in THF). The rearrangement occurs when the substituent attached to the nitrogen of the carbamate linkage is aromatic in nature, which may contain a hetero-atom, but appears not to occur when this substituent is alkyl in nature. The *O*-carbamate moiety may be varied, so long as the carbon adjacent to the oxygen has a hydrogen available for abstraction and formation of an anion. The reaction mechanism may be tentatively proposed to be of an intra-molecular S_N2-type concerted mechanism with concomitant elimination. This reaction resembles, and may be an extension of, the Smiles rearrangement, with a carbon replacing a nitrogen on the aromatic ring.

The two reactions involved in obtaining the substituted benzyl alcohol from the primary amine are simple and readily carried out. At present the yields for both the carbamate formation reaction and the rearrangement reaction are, unexplainably, variable, although generally good.

This rearrangement reaction of N-monosubstituted carbamate to secondary, or tertiary, alcohol of the substituted methanol type, but usually thus far the substituted benzyl alcohol type, provides a simple route to replacing an amine functionality with a more complex carbon based functionality. Previously this has been difficult to achieve, the most common route being *via* the diazonium salt. This rearrangement reaction should therefore prove to be very useful in synthetic organic chemistry; however the full scope and therefore the utility of the rearrangement still needs to be discovered.

3. CONCLUSION and FUTURE PROPOSALS

Due to the time constraints inherent in a Masters project (one year of practical work) many facets of this research were not completed and many desired reactions could not be attempted. This fact only served to augment the number of questions that research proposes and to answer few.

The initial aim of this Masters project was to obtain chiral induction across the carbamate linkage, from chiral amines to the benzylic position of benzyl carbamate. This goal was never achieved; however, in the course of this investigation an extension of existing oxazolidone work and a novel rearrangement reaction were exposed. The new bicyclic oxazolidone with nitrogen at the bridgehead position, 3-oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one **(77)**, was formed by a trans-carbamation type reaction from benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** by both thermal and chemical means, using sodium hydride (NaH) which has as yet not been used to achieve such a reaction. Further investigation into this reaction proved unsuccessful on the whole, with many proposed questions remaining unanswered. A novel rearrangement reaction where N-monosubstituted carbamates rearrange to give substituted methanol products, on treatment with butyllithium, was discovered in attempts to substitute the nitrogen of the carbamate. Thus far it has been determined that this reaction appears to occur within the following generalisations:

(a) The nitrogen substituent must be aromatic in nature. It may contain a hetero-atom and may be substituted.

(b) The O-carbamate moiety may be varied, so long as a position on the carbon adjacent to the oxygen is available for substitution.

(c) The transition state is a five membered cyclic one and rearrangement occurs to the position to which the nitrogen was attached.

Some of the questions that remained unanswered in the oxazolidone work were:

(a) Could the trans-carbamation cyclisation reaction occur with other sized cyclic structures containing the nitrogen and could these structures be unsaturated?

(b) What effect does the alcohol being either primary, secondary or tertiary have on the reaction?

(c) What effect do the characteristics of the substituents on the alcohol have on the cyclisation reaction?

When looking at future proposals for the carbamate to alcohol rearrangement reaction it becomes obvious that only the initial studies have thus far been completed. Future work entails:

(a) investigations into the effects of substituents on the N-aryl group, both electronically and structurally

(b) whether altered reaction conditions could allow the reaction to occur with N-alkyl substituents

(c) determination of the true reaction mechanism

(d) investigations into altering the O-carbamate moiety. Must this moiety contain an aryl or unsaturated component or can the rearrangement occur with simple alkyl groups? What effects do substituents on the carbon adjacent to the oxygen have on the rearrangement to a tertiary alcohol?

(e) optimising reaction conditions - trying different solvents.

4. EXPERIMENTAL

4.1 INSTRUMENTATION and CHEMICALS

NMR spectra (^{1}H 200 MHz and ^{13}C 50 MHz) were recorded on a Varian Gemini 200 NMR spectrometer and ^{1}H 60MHz spectra recorded on a Varian T60 instrument. Unless otherwise stated, spectra were run using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. All values are reported in ppm downfield of TMS and all *J* values are reported in Hz. Mass spectra were recorded on a Hewlett-Packard (HP5988A) mass spectrometer or a Varian high resolution mass spectrometer, linked to a gas chromatograph. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyser. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infra-red spectra were obtained on a Shimadzu FTIR-4300 instrument using KBr disks. Optical rotations were determined on a Perkin-Elmer 241 digital polarimeter.

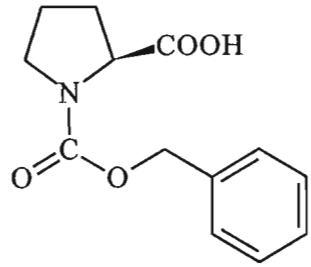
For thin layer chromatography, precoated Kieselgel 60 F_{254} Merck plastic sheets were used. Unless otherwise specified all thin layer chromatography was run using 20% ethyl acetate in hexane for ease of comparison. All chromatography solvent system ratios were then adjusted accordingly. Purification of compounds was achieved by centrifugal chromatography on a Harrison Research Chromatotron Model 7924T, on glass plates coated with Merck silica gel (200-400 mesh), 2-4 mm thick.

All commercially obtained chemicals were used as is, unless indicated otherwise, and all solvents were dried using standard literature procedures[138]. Low reaction temperatures were maintained using dry ice/solvent baths[139].

4.2 PREPARATIONS

4.2.1 *PREPARATION OF BENZYL 2-(HYDROXYDIPHENYLMETHYL)PYRROLIDINE-1-CARBOXYLATE (64)*

N-Benzyloxycarbonyl-L-proline **(65)**



$C_{13}H_{15}NO_4$
MM 249.26 g/mol

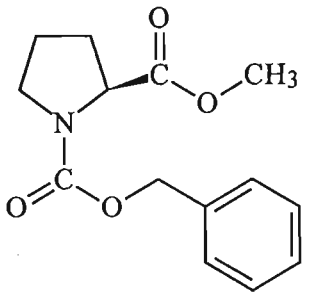
(65)

L-Proline (5.00 g, 49 mmol) was dissolved in 4N NaOH (10 ml) and the stirred solution cooled in an ice bath. Benzyl chloroformate (6.5 ml, 45 mmol) was added dropwise and the solution then allowed to stir for 2 h. The cooled solution was acidified (Congo red indicator) using approximately 1M HCl and the product separated out as an oil. The product was extracted into ethyl acetate and the extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed to yield a very viscous, colourless oil in almost quantitative yield, which was used without further purification[117].

Yield: 10.78 g (99%). δ_H (200 MHz) 7.57 (1H, s, COO*H*), 7.24-7.38 (5H, m, Ar-*H*), 5.08-5.22 (2H, m, CH_2Ph), 4.33-4.44 (1H, m, NC*H*COOH), 3.43-3.65 (2H, m, NCH_2CH_2), 2.00-2.24 (2H, m, CHCH_2), 1.85-2.00 (2H, m, $CH_2CH_2CH_2$); δ_C (50 MHz) 177.34 and 176.30 (s, *C*OOH)[a] [a], 155.54 and 154.59 (s, *C*=O)[a], 136.39 (s, Ar-*C*), 128.47, 128.38, 128.06, 127.88 and 127.62 (d, Ar-*C*H), 67.40 and 67.17 (t, PhCH_2)[a], 59.19 and 58.68 (d, NCH)[a], 46.92 and 46.58 (t, NCH_2)[a], 30.84 and 29.61 (t, CHCH_2)[a], 24.24 and 23.42 (t, $CH_2CH_2CH_2$)[a]; *m/z* 204 (M^+ -COOH, 3.4%), 160 (9.0), 114 (25.0), 91 (100), 70 (7.6), 65 (8.9), 44 (7.9).

[a] due to the occurance of rotamers (see page 49)

N-benzyloxycarbonyl-L-proline methyl ester **(63)**



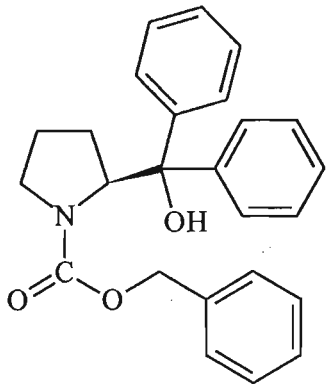
(63)

$C_{14}H_{17}NO_4$
MM 263.29 g/mol

N-methyl-N-nitrosourea[119] (10 g, 97 mmol) was added to an ice-cooled, well stirred system of diethyl ether (75 ml) above a 50% solution of KOH, in water (50 ml), to generate an excess of diazomethane[118]. The diethyl ether layer was decanted and dried three times, at 0°C, over potassium hydroxide pellets. N-Benzyloxycarbonyl-L-proline **(65)** (2.5 g, 10 mmol) was dissolved in diethyl ether and slowly added to the diazomethane solution. The mixed solution was stirred and the excess diazomethane allowed to evaporate off overnight before the diethyl ether was removed to yield the methyl ester as a very viscous colourless oil. The product was used without further purification for the next step. Yield: 2.45 g (93%). (Found: C, 64.07; H, 6.70; N, 5.28; $C_{14}H_{17}NO_4$ requires C, 63.86; H, 6.51; N, 5.32%). δ_H (200 MHz)[116] 7.23-7.37 (5H, m, Ar-*H*), 4.97-5.21 (2H, m, PhCH_2), 4.28-4.39 (1H, m, C*H*COOMe), 3.69 and 3.55 (3H, 2x s, COOCH_3,)[a] , 3.41-3.64 (2H, m, NCH_2), 2.10-2.21 (1H, m, CHC*H*H), 1.81-2.00 (3H, m, CHCH*H*CH_2); δ_C (50 MHz) 173.17 and 173.0 (s, *C*OOMe)[a], 154.75 and 154.15 (s, N*C*=O)[a], 136.72 and 136.64 (s, Ar-*C*)[a], 128.41, 128.35, 127.91, 127.87, 127.79 and 127.68 (d, Ar-*C*H), 66.87 and 66.80 (t, *C*H_2Ph)[a], 59.15 and 58.78 (d, N*C*HCOOMe)[a], 52.10 and 51.96 (q, O*C*H_3)[a], 46.89 and 46.38 (t, N*C*H_2)[a], 30.85 and 29.84 (t, CH*C*H_2)[a], 24.28 and 23.48 (t, $CH_2CH_2CH_2$)[a]; *m/z* 263 (M^+, 3.5%), 204 (17.8), 160 (22.9), 128 (6.4), 91 (100).

[a] due to the occurance of rotamers (see page 49)

Benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)**[116]



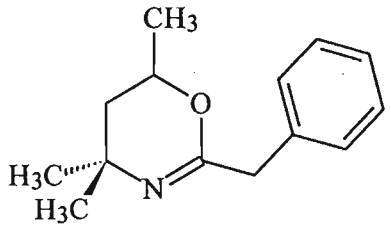
$C_{25}H_{25}NO_3$
MM 387.47 g/mol

(64)

Phenyl magnesium bromide (40 mmol) was prepared by adding bromobenzene (6.28 g, 4.2 ml, 40 mmol) to magnesium turnings (1.94 g, 80 mmol) in THF (40 ml), under nitrogen, in a 100 ml flask fitted with a reflux condenser. The reaction was initiated by applying a small amount of heat to the flask and the reaction mixture allowed to stir for 30 min. The PhMgBr was transferred by syringe to an ice cooled solution of N-benzyloxycarbonyl-L-proline methyl ester **(63)** (2.63 g, 10 mmol) in THF (20 ml), under nitrogen. The reaction mixture was allowed to stir for 3 h before being quenched with approximately 7 ml of a saturated NH_4Cl solution. The organic layer was extracted into chloroform and the extracts were washed with brine and dried over anhydrous $MgSO_4$ before the solvent was removed. The product was purified using centrifugal chromatography (10% ethyl acetate in hexane). Yield 2.70 g (70%). δ_H (200 MHz) 7.20-7.40 (15H, m, Ar-*H*), 6.0 (1H, s, O*H*), 5.10-5.17 (2H, d, C*H*$_2$Ph, *J*=6.2), 4.89-4.95 (1H, m, NC*H*CPh$_2$OH), 3.40-3.45 and 3.0 (1H, m, NCH*H*), 1.87-2.07 (2H, m, CHCH$_2$C*H*$_2$), 1.39-1.45 and 0.85 (1H, m, NCHCH*H*); δ_C (50 MHz) 157.95 (s, *C*=O), 146.16, 143.54 and 136.40 (s, Ar-*C*), 128.39, 127.99, 127.93, 127.75, 127.65, 127.50, 127.34, 127.21 and 127.06 (d, Ar-*C*H), 81.52 (s, *C*Ph$_2$OH), 67.30 (t, PhCH$_2$), 66.09 (d, NCH), 47.73 (t, NCH$_2$), 29.51 (t, CH$_2$CH$_2$CH$_2$), 22.87 (t, NCHCH$_2$); *m/z* Only peaks in GCMS with m/z of 279 and 108 due to rearrangement and decomposition products.

4.2.2 *PREPARATION OF 2-(1-PHENYLCYCLOPENTYL)-4,4,6-TRIMETHYL-TETRAHYDRO-1,3-OXAZINE* (72)[127]

2-Benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine (70)

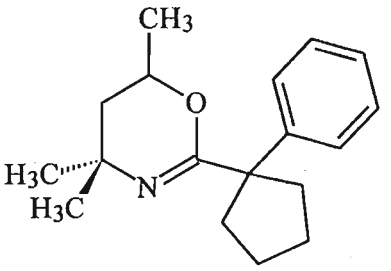


(70)

$C_{14}H_{19}NO$
MM 217.31 g/mol

Concentrated sulfuric acid (17 ml), in a flask fitted with an overhead stirrer, was cooled to between 0°C and 5°C in an ice bath. To this was added phenyl acetonitrile[140] (9.9 g, 85 mmol) from a dropping funnel at such a rate so as to keep the temperature near 0°C. On completion of this addition 2-methyl-2,4-pentanediol (9.08 g, 76.8 mmol) was added dropwise at a rate to maintain a temperature of 0-5°C. The reaction mixture was stirred for 1 h before 54 g of crushed ice was added and the reaction mixture stirred until this had melted. The reaction mixture was made just alkaline with 40% NaOH, with ice being added when necessary to keep the temperature below 35°C. This aqueous solution was extracted with chloroform (3x 50 ml) and the extracts dried over anhydrous $MgSO_4$ before the solvent was removed. The product was obtained by distillation under reduced pressure (320°C/760 mmHg, 180°C/0.4 mmHg). Yield: 3.35 g (19%). (Found: C, 77.33; H, 8.93; N, 6.21; $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45%). δ_H (200 MHz) 7.18-7.34 (5H, m, Ar-*H*), 4.02-4.11 (1H, m, OC*H*CH_3), 3.44 (2H, s, CH_2Ph), 1.72 and 1.65 (2H, dd, Me_2CCH_2CHMe, *J*=1.4, *J*=6.8), 1.22, 1.21, 1.18 and 1.71 (6H, 2x s, $(CH_3)_2C$ and 3H, d, OCHCH_3); δ_C (50 MHz) 157.14 (s, N=*C*O), 137.15 (s, Ar-*C*), 129.02, 128.59, 128.17, 127.80 and 126.30 (d, Ar-*C*H), 67.87 (d, O*C*HMe), 49.81 (s, N*C*Me_2), 42.40 (t, *C*H_2Ph), 41.70 (t, C*C*H_2CH), 31.78 and 29.52 (q, $(CH_3)_2C$), 21.28 (q, OCH*C*H_3); *m/z* 217 (M^+, 21.8%), 202 (2.9), 118 (10.8), 91 (69.4), 84 (100).

2-(1-Phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine **(71)**

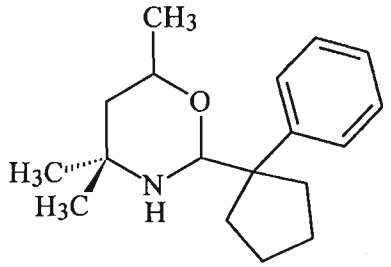


$C_{18}H_{25}NO$
MM 271.40 g/mol

(71)

To a solution of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine **(70)** (0.3 g, 1.4 mmol) in THF (10 ml), under nitrogen and anhydrous conditions, at -78°C, was added BuLi (1.1 ml, 1.1 eq., 1.37 M) over 10 min and the resultant dark orange solution allowed to stir for 30 min. Freshly distilled 1,4-dibromobutane (0.279 g, 0.16 ml, 1.5 mmol, 1.1 eq.) was then added over 10 min and the reaction mixture allowed to stir for a further 45 min, still at -78°C, before a further portion of BuLi (1.11 ml, 1.1 eq., 1.37 M) was added over 10 min. The deep emerald green solution was allowed to stir for 1 h before being stored overnight at -20°C. The reaction mixture was poured into 5 ml ice water and acidified to pH 2-3 with a 9N HCl solution. It was then washed 3 times with small portions of diethyl ether before being basified with a 40% NaOH solution. The resulting solution was extracted into diethyl ether and the extracts dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporator to yield the pure 2-(1-phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine **(71)** as a yellow oil. Yield: 0.33 g (88%). δ_H (200 MHz) 7.11-7.41 (5H, m, Ar-*H*), 3.88-3.98 (1H, m, C*H*CH_3), 2.48-2.60 (2H, m, cyclopentyl), 1.6-1.9 (7H, m, CCH_2CH, cyclopentyl), 1.07-1.27 (1H, m, cyclopentyl), 1.18 (3H, OCHCH_3), 1.13 and 1.10 (6H, 2x s, C(CH_3)$_2$); δ_C (50 MHz) 159.78 (s, N=*C*(C)O), 146.09 (s, Ar-*C*), 127.68, 126.51 and 125.66 (d, Ar-*C*H), 67.47 (d, O*C*HCH_3), 57.16 (s, *C*$(CH_2)_4$Ph), 49.68 (s, N*C*$(CH_3)_2$), 42.07 (t, CCH_2CH), 36.58 and 35.97 (t, -C$CH_2$$(CH_2)_2$$CH_2$-), 31.99 and 29.26 (q, C$(CH_3)_2$), 23.36 and 23.31 (t, -C$CH_2$$(CH_2)_2$$CH_2$-), 21.29 (q, CH$CH_3$); *m/z* 271 ($M^+$, 78.4%), 243 (56.6), 230 (73.3), 194 (27.1), 167 (16.1), 145 (55.2), 128 (25.9), 115 (34.5), 103 (29.3), 91 (100), 58 (25.8).

2-(1-Phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine **(72)**



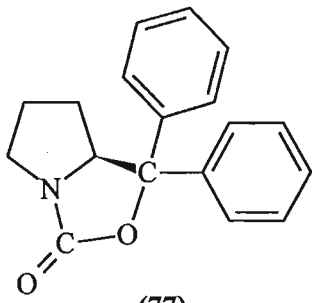
$C_{18}H_{27}NO$
MM 273.41 g/mol

(72)

2-(1-Phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine **(71)** (0.3 g, 1.1 mmol) was dissolved in a mixture of 5 ml THF and 5 ml 95% EtOH and cooled to 0°C. One drop of conc. HCl was added. A solution of $NaBH_4$ (0.06 g, 1.5 mmol, 1.4 eq.) in 0.5 ml water was prepared, to which 2 drops of 4N NaOH were added. This solution was added dropwise to the first and the pH tested to determine that the solution was just alkaline. The reaction mixture was allowed to stir for 2 h before being stored at -20°C overnight. The solution was basified and extracted into diethyl ether, the extracts dried over anhydrous $MgSO_4$, and the solvent removed by distillation on a rotary evaporator to yield a fine yellow powder. The product was purified by centrifugal chromatography (ethyl acetate in hexane). Yield: 0.23 g (75%). δ_H (200 MHz) 7.18-7.45 (5H, m, Ar-*H*), 4.11 (1H, s, N*H*), 3.6-3.8 (1H, m, C*H*CH_3), 1.1-2.4 (10H, m, cyclopentyl & CHCH_2C), 1.10, 1.09, 1.07 and 0.88 (6H, 2x s, C(CH_3)$_2$ and 3H, d, OCHCH_3); δ_C (50 MHz) 144.01 (s, Ar-*C*), 128.99, 127.23 and 125.77 (d, Ar-*C*H), 86.88 (d, NHCHOCH), 68.57 (d, O*C*HCH$_3$), 55.02 (s, NC(CH$_3$)$_2$), 48.53 (s, *C*(CH$_2$)$_4$Ph), 45.36 (t, CCH$_2$CH), 36.17 and 34.94 (t, -C*C*H$_2$(CH$_2$)$_2$*C*H$_2$-), 32.72 and 23.91 (q, C(*C*H$_3$)$_2$), 23.59 and 23.50 (t, -CCH$_2$(*C*H$_2$)$_2$CH$_2$-), 22.34 (q, CH*C*H$_3$); *m/z* 273 (M^+, 0.06%), 258 (0.3), 174 (0.9), 145 (3.2), 128 (100), 115 (3.3), 91 (12.9), 86 (19.8), 83 (15.8), 77 (1.8), 58 (6.2), 46 (4.4).

4.2.3 PREPARATION OF 2-OXAZOLIDONES

3-Oxa-1-aza-4,4-diphenylbicyclo[3.3.0]octan-2-one **(77)**



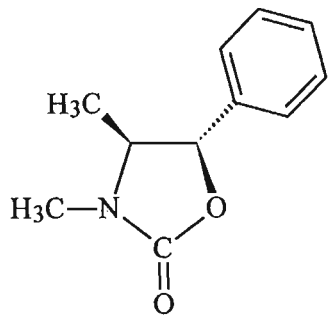
(77)

$C_{18}H_{17}NO_2$

MM 279.33 g/mol

To a stirred suspension of NaH (0.037 g, 1 mmol, 2 eq., 80%) in dry THF (2 ml) was added dropwise a solution of benzyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate **(64)** (0.2 g, 0.5 mmol) in THF (2 ml) and the reaction mixture allowed to stir for 1 h. The reaction was quenched with water (1 ml) and the product was extracted into chloroform, the extracts dried and the solvent removed. The crystalline product was purified using centrifugal chromatography (10% ethyl acetate in hexane) Yield: 90%. Melting Point: 123-124°C; (Found: C, 77.59; H, 6.21; N, 4.89; $C_{18}H_{17}NO_2$ requires C, 77.40; H, 6.13; N, 5.02%). δ_H (200 MHz) 7.53 (1H, t, Ph, *J*=1.0), 7.49 (1H, m, Ar-*H*), 7.19-7.40 (8H, m, Ar-*H*), 4.49-4.57 (1H, q, NC*H*CPh_2, *J*=2.6), 3.62-3.75 (1H, dt, NC*H*HCH_2, *J*=4.0, *J*=5.6), 3.13-3.25 (1H, dq, NCH*H*CH_2, *J*=2.1), 1.78-1.95 (2H, m, $CH_2CH_2CH_2$), 1.62-1.76 (1H, m, NCHC*H*HCH_2), 0.97-1.19 (1H, m, NCHCH*H*CH_2); δ_C (50 MHz) 160.26 (s, *C*=O), 143.06 and 140.01 (s, Ar-*C*), 128.31, 128.06 127.45, 125.68 and 125.19 (d, Ar-CH), 85.63 (s, CPh_2), 68.95 (d, $NCHCPh_2$), 45.77 (t, NCH_2), 28.73 (t, $CH_2CH_2CH_2$), 24.62 (t, $CHCH_2CH_2$); IR (cm^{-1}) 1757 (C=O); *m/z* 279 (M^+, 44.3%), 182 (67.7), 165 (67.0), 146 (70.8), 105 (100), 77 (29.9), 69 (25.7); $[\alpha]_D^{27}$: -215.1° (0.5058g/100 ml in $CHCl_3$).

3,4-Dimethyl-5-phenyl-2-oxazolidone **(82)**



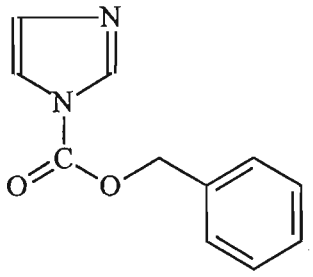
(82)

$C_{11}H_{13}NO_2$

MM 191.22 g/mol

NaH (0.133 g, 1.1 eq., 50%) was added to a solution of (-)-ephedrine (0.5 g, 3 mmol) in dry THF (10 ml) at room temperature. The solution was allowed to stir for 5 min before benzyl chloroformate (0.516 g, 0.44 ml, 3 mmol, 1 eq.) was added dropwise. The reaction mixture was allowed to stir for 1 h before another 1.1 equivalents of NaH (0.133 g, 50%) were added. The reaction mixture was left to stir for 3 h before being slowly quenched with water. The THF was removed and the reaction mixture extracted into chloroform, the extracts dried and the solvent removed under vacuum. The pale yellow oil that was obtained was purified by centrifugal chromatography (10% ethyl acetate in hexane). The oxazolidone **(81)** was obtained as a colourless oil which crystallised out in off-white needles. Yield: 0.296 g (52%). δ_H (200 MHz)[128c] 7.22-7.40 (5H, m, Ar-*H*), 5.557 (1H, d, OC*H*Ph, *J*=4.1), 3.94-4.08 (1H, dq, NC*H*CH_3, *J*=3.3, *J*=4.1), 2.84 (3H, s, NCH_3), 0.75 (3H, d, NCHCH_3, *J*=3.3); δ_C (50 MHz) 158.04 (s, *C*=O), 135.17 (s, Ar-*C*), 128.41 and 126.08 (d, Ar-*C*H), 78.28 (d, OCHPh), 56.91 (d, N*C*HCH_3), 28.88 (q, NCH_3), 14.21 (q, CH*C*H_3); *m/z* 191 (M^+, 12.4%), 176 (2.5), 147 (1.6), 132 (3.3), 117 (5.0), 105 (3.8), 91 (5.4), 77 (6.1), 58 (30.3), 57 (100), 51 (5.8), 42 (53.9).

Imidazole benzyl carbamate **(83)**



(83)

$C_{11}H_{10}N_2O_2$

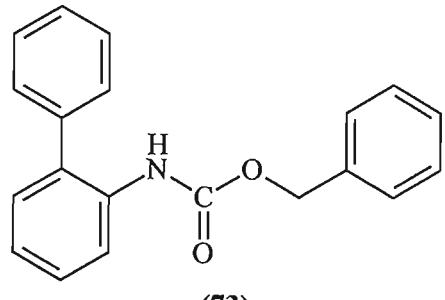
MM 202.21 g/mol

To a solution of imidazole (1.0 g, 15 mmol) in dry THF (40 ml), at room temperature, was added NaH (0.648 g, 16 mmol, 1.1 eq., 50%). The solution was stirred for 5 min before benzyl chloroformate (2.75 g, 2.3 ml, 16 mmol, 1.1 eq.) was added dropwise. The reaction mixture was allowed to stir for 2 d before being quenched with water. The solvent was removed and the product was extracted into chloroform. The extracts were dried over anhydrous $MgSO_4$, and the solvent removed to yield a yellow oil which was purified by centrifugal chromatography (20% ethyl acetate in hexane). Yield: 1.93 g (65%). δ_H (200 MHz) 8.11 (1H, t, NC*H*N, *J*=0.55), 7.34-7.42 (6H, m, Ar-*H* and (OC)NC*H*), 7.02 (1H, q, NC*H*CHN(CO), *J*=0.4), 5.36 (2H, s, PhCH_2); δ_C (50 MHz) 148.09 (s, *C*=O), 136.68 (d, NCHN), 133.59 (s, Ar-*C*), 130.14 (d, (OC)NCH), 128.65, 128.36 and 128.23 (d, Ar-CH), 116.69 (d, NCHCHN(CO)), 69.31 (t, PhCH_2); *m/z* 202 (M^+, 5.7%), 158 (6.7), 126 (0.7), 105 (0.7), 91 (100), 77 (4.9), 65 (18), 63 (4.4).

4.2.4 GENERAL PROCEDURE FOR THE PREPARATION OF BENZYL CARBAMATES

To a stirred solution of the primary amine (aryl or alkyl) (0.25-1.0 g) in dry THF, at room temperature, NaH (1.2 eq.) was added. To this solution benzyl chloroformate (1.1 eq.) was slowly added dropwise, as the reaction is exothermic and may be vigorous. The reaction mixture was allowed to stir for approximately 18 hours before water was added to destroy any excess NaH. The THF was removed under reduced pressure and the product was extracted into chloroform. The extracts were dried over $MgSO_4$ before the solvent was removed *in vacuo*. The carbamates were purified by centrifugal chromatography (ethyl acetate in hexane) to yield the (usually crystalline) benzyl carbamates.

N-(2-Biphenyl) benzyl carbamate **(73)**



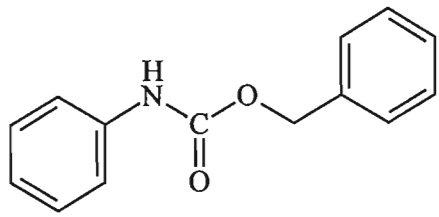
(73)

$C_{20}H_{17}NO_2$

MM 303.36 g/mol

Yield: 61% (oil) (Found: C, 79.36; H, 5.72; N, 4.53; $C_{20}H_{17}NO_2$ requires C, 79.18; H, 5.65; N, 4.62%). δ_H (200 MHz) 8.153 (1H, d, Ar-*H*, *J*=4.0), 7.03-7.51 (13H, m, Ar-*H*), 6.77 (1H, s, N*H*), 5.09 (2H, s, PhCH_2); δ_C (50 MHz) 153.31 (s, *C*=O), 137.95, 136.03, 134.66 and 119.86 (s, Ar-*C*), 130.12, 129.14, 129.03, 128.47, 128.39, 128.22, 127.82 and 123.46 (d, Ar-CH), 66.81 (t, $PhCH_2$); *m/z* 303 (M^+, 8.6%), 258 (4.1), 195 (5.7), 167 (14.3), 106 (3.3), 91 (100); IR (cm^{-1}) 3420 (NH), 1738 (C=O).

N-phenyl benzyl carbamate **(84)**



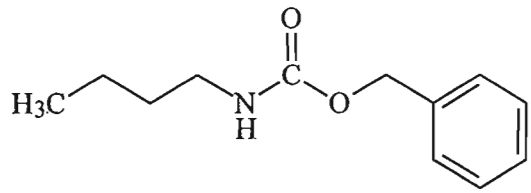
(84)

$C_{14}H_{13}NO_2$

MM 227.26 g/mol

Yield: 56%. Melting Point: 63-64°C (Found: C, 74.35; H, 5.97; N, 6.15 $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%). δ_H (200 MHz) 7.35-7.44 (3H, m, Ar-*H*), 7.10-7.25 (7H, m, Ar-*H*), 6.89-6.98 (1H, m, N*H*), 5.05 (2H, s, PhCH_2); δ_C (50 MHz) 153.5 (s, *C*=O), 137.65 and 135.74 (s, Ar-*C*), 128.82, 128.40, 128.08, 123.29 and 118.92 (d, Ar-*C*H), 66.72 (t, Ph*C*H_2); *m/z* 227 (M^+, 4.6%), 183 (3.4), 119 (9.2), 107 (4.2), 91 (100).

N-butyl benzyl carbamate **(86)**



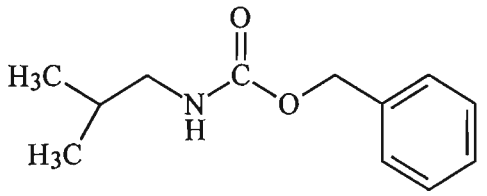
(86)

$C_{12}H_{17}NO_2$

MM 207.27 g/mol

Yield: 57% (oil) (Found: C, 69.31; H, 8.03; N, 6.77; $C_{12}H_{17}NO_2$ requires C, 69.53; H, 8.27; N, 6.76%). δ_H (200 MHz) 7.24-7.31 (5H, m, Ar-*H*), 5.29 (1H, s, N*H*), 5.05 (2H, s, PhCH_2O), 3.08-3.17 (2H, q, CH_2N, *J*=3.2), 1.23-1.46 (4H, m, $CH_3CH_2CH_2$), 0.88 (3H, t, CH_3CH_2, *J*=3.5); δ_C (50 MHz) 156.59 (s, *C*=O), 136.79 (s, Ar-*C*), 128.42, 128.00 and 127.94 (d, Ar-*C*H), 66.39 (t, Ph*C*H_2), 40.76 (t, *C*H_2N), 31.98 (t, *C*H_2CH_2N), 19.88 (t, CH_3CH_2), 13.74 (q, *C*H_3); *m/z* 207 (M^+, 1.9%), 108 (81.2), 91 (100), 77 (6.3), 57 (2.1).

N-(2-methylpropyl) benzyl carbamate **(89)**



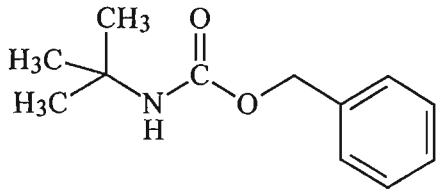
(89)

$C_{12}H_{17}NO_2$

MM 207.27 g/mol

Yield: 59% Melting Point: 29-30°C (Found: C, 69.54; H, 7.83; N, 6.70; $C_{12}H_{17}NO_2$ requires C, 69.53; H, 8.27; N, 6.76%). δ_H (200 MHz) 7.19-7.27 (5H, m, Ar-*H*), 5.65 (1H, m, N*H*), 5.03 (2H, s, PhCH_2), 2.90-2.97 (2H, t, CHCH_2N, *J*=3.2), 1.63-1.73 (1H, m, $(CH_3)_2CHCH_2$), 0.84 (6H, d, $(CH_3)_2CH$, *J*=3.4); δ_C (50 MHz) 156.26 (s, *C*=O), 136.34 (s, Ar-*C*), 127.80, 127.36 and 127.3 (d, Ar-*C*H), 65.72 (t, PhCH_2), 47.92 (t, CH_2N), 28.17 (d, $CHCH_2$), 19.37 (q, $(CH_3)_2CH$); *m/z* 207 (M^+, 2.1%), 108 (49.9), 91 (100), 77 (6.6), 41 (7.5).

N-tert-*butyl benzyl carbamate* **(92)**



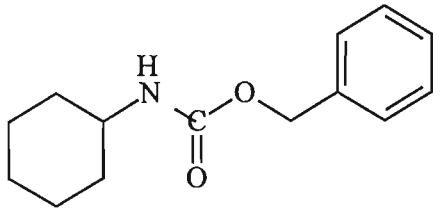
(92)

$C_{12}H_{17}NO_2$

MM 207.27 g/mol

Yield: 58% (oil). δ_H (200 MHz) 7.24-7.36 (5H, m, Ar-*H*), 5.04 (2H, s, PhCH_2), 4.75 (1H, s, N*H*), 1.32 (9H, s, $(CH_3)_3C$); δ_C (50 MHz) *ca.* 155 (s, *C*=O), 136.72 (s, Ar-*C*), 128.48, 128.05 and 127.99 (d, Ar-*C*H), 65.96 (t, PhCH_2), 50.35 (s, $(CH_3)_3C$), 28.90 (q, $(CH_3)_3C$); *m/z* 207 (M^+, 0.7%), 191 (2.0), 148 (8.1), 108 (41.4), 91 (100), 77 (8.5), 57 (7.6), 42 (13).

N-cyclohexyl benzyl carbamate **(93)**



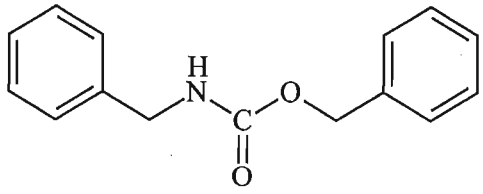
(93)

$C_{14}H_{19}NO_2$

MM 233.31 g/mol

Yield: 58%. Melting Point: 76-80°C (Found: C, 72.49; H, 8.08; N, 5.95; $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%). δ_H (200 MHz) 7.26-7.38 (5H, m, Ar-*H*), 5.10 (2H, s, PhCH_2), 4.65 (1H, s, N*H*), 3.47-3.53 (1H, m, C*H*N), 1.08-1.97 (10H, m, cyclohexyl); δ_C (50 MHz) 156 (s, *C*=O), 136.66 (s, Ar-*C*), 128.50, 128.13 and 128.05 (d, Ar-*C*H), 66.47 (t, Ph*C*H_2), 49.87 (d, *C*HN), 33.42 (t, -*C*H_2C*H*CH_2-), 25.48 (t, -(CH_2)$_2$*C*H_2(CH_2)$_2$-), 24.77 (t, -CH*C*H_2*C*H_2*C*H_2-); *m/z* 233 (M^+, 2.0%), 126 (3.3), 108 (100), 107 (85.6), 99 (8.9), 83 (46.8), 79 (50.0), 77 (30.3), 55 (26.9).

N-benzyl benzyl carbamate **(94)**



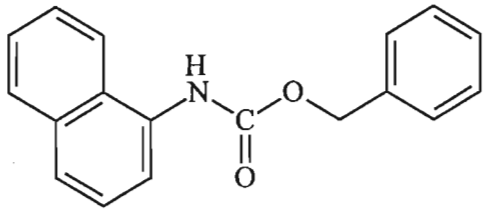
(94)

$C_{15}H_{15}NO_2$

MM 241.28 g/mol

Yield: 60%. Melting Point: 50-52°C (Found: C, 75.03; H, 6.46; N, 5.67; $C_{15}H_{15}NO_2$ requires C, 74.66; H, 6.27; N, 5.81%). δ_H (200 MHz) 7.24-7.37 (10H, m, Ar-*H*), 5.12 (3H, s, PhCH_2O, N*H*), 4.36 (2H, d, PhCH_2N, *J*=3.0); δ_C (50 MHz) 155.94 (s, *C*=O), 138.38 and 136.45 (s, Ar-*C*), 128.65, 128.51,128.12 and 127.48 (d, Ar-*C*H), 66.85 (t, *C*H_2O), 45.12 (t, *C*H_2N); *m/z* 241 (M^+, 0.7%), 150 (57.4), 107 (30.9), 91 (100), 79 (27.5).

N-α-*naphthyl benzyl carbamate* **(95)**



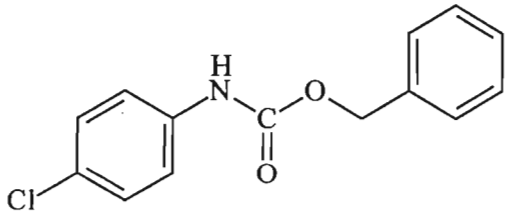
(95)

$C_{18}H_{15}NO_2$

MM 277.32 g/mol

Yield: 12%. Melting Point: 114-115°C (Found: C, 77.70; H, 5.56; N, 5.06; $C_{18}H_{15}NO_2$ requires C, 77.96; H, 5.45; N, 5.05%). δ_H (200 MHz) 7.33-7.90 (12H, m, Ar-*H*), 7.03 (1H, s, N*H*), 5.25 (2H, s, PhCH_2); δ_C (50 MHz) 136.06, 134.05 and 132.37 (s, Ar-*C*), 128.73, 128.62, 128.39, 126.23, 125.99, 125.79, 125.11 and 120.43 (d, Ar-*C*H), 67.30 (t, PhCH_2); *m/z* 277 (M^+, 11.7%), 233(7.2), 169 (26.2), 140 (12.2), 115 (15.5), 108 (10.9), 91 (100), 79 (13.8), 77 (10.7).

N-p-*chlorophenyl benzyl carbamate* **(97)**



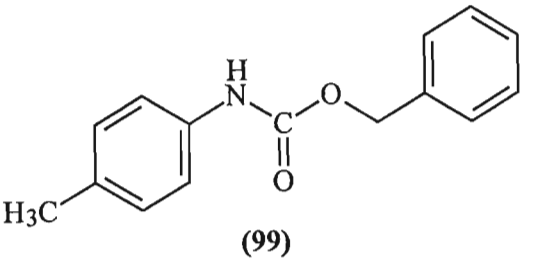
(97)

$C_{14}H_{12}NO_2Cl$

MM 261.70 g/mol

Yield: 49%. Melting Point: 96-98°C (Found: C, 64.16; H, 4.42; N, 5.31; $C_{14}H_{12}ClNO_2$ requires C, 64.24; H, 4.62; N, 5.35%; δ_H (200 MHz) 7.22-7.37 (9H, m, Ar-*H*), 6.75 (1H, s, N*H*), 5.18 (2H, s, PhCH_2); δ_C (50 MHz) 153.18 (s, *C*=O), 136.33 and 135.78 (s, Ar-*C*), 129.04, 128.64, 128.46 and 128.35 (d, Ar-*C*H), 119.86 (s, Ar-*C*-Cl), 67.19 (t, PhCH_2); *m/z* 261 (M^+, 10.3%), 217 (4.1), 153 (10.4), 127 (8.8), 91 (100).

N-p-*methylphenyl benzyl carbamate* **(99)**



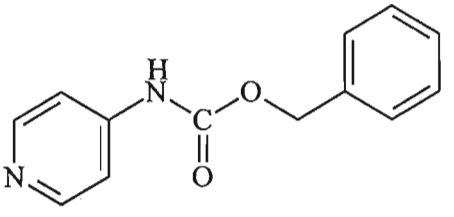
(99)

$C_{15}H_{15}NO_2$

MM 241.28 g/mol

Yield: 75%. Melting Point: 70-72°C (Found: C, 74.49; H, 5.91; N, 5.59; $C_{15}H_{15}NO_2$ requires C, 74.66; H, 6.27; N, 5.81%; δ_H (200 MHz) 7.33-7.40 (5H, m, CH_2Ar-*H*), 7.07-7.28 (4H, m, MeAr-*H*), 6.65 (1H, s, N*H*), 5.18 (2H, s, PhCH_2), 2.29 (3H, s, CH_3); δ_C (50 MHz) 153 (s, *C*=O), 136.09, 135.12 and 133.08 (s, Ar-*C*), 129.53, 128.59 and 128.3 (d, Ar-*C*H), 66.92 (t, PhCH_2), 20.75 (q, CH_3); *m/z* 241 (M^+, 11.1%), 197 (7.99), 133 (6.1), 91 (100), 77 (7.5).

N-(4-pyridyl) benzyl carbamate **(101)**



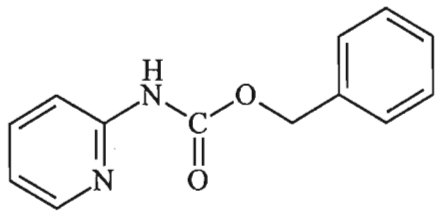
(101)

$C_{13}H_{12}N_2O_2$

MM 228.25 g/mol

Yield: 23%. Melting Point: 141-142°C (Found: C, 68.12; H, 5.17; N, 12.15; $C_{13}H_{12}N_2O_2$ requires C, 68.40; H, 5.30; N, 12.28%). δ_H (200 MHz) (Acetone d_6) 9.37 (1H, s, N*H*), 8.43 (2x 1H, d, NC*H*CH, *J*=1.6), 7.56 (2x 1H, d, NCHC*H*, *J*=1.6), 7.33-7.47 (5H, m, Ar-*H*), 5.22 (2H, s, CH_2Ph); δ_C (50 MHz) 153.91 (s, *C*=O), 151.10 (d, NCHCH), 147.21 (s, pyCNH), 137.24 (s, Ar-*C*), 129.23 and 128.98 (d, Ar-*C*H), 112.94 (d, NCHCH), 67.36 (t, CH_2Ph); *m/z* 228, (M^+, 10.8%), 210 (2.6), 184 (1.8), 120 (2.3), 108 (2.7), 91 (100), 77 (3.9).

N-(2-pyridyl) benzyl carbamate **(103)**



(103)

$C_{13}H_{12}N_2O_2$

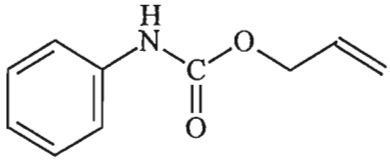
MM 228.25 g/mol

Yield: 50%. Melting point: 114°C. δ_H (200 MHz) 10.39 (1H, s, N*H*), 8.13-8.17 (1H, m, NC*H*), 8.04 (1H, d, N(CH)$_2$C*H*, *J*=4.2), 7.60-7.69 (1H, m, NCHC*H*), 7.32-7.42 (5H, m, Ar-*H*), 6.76-6.83 (1H, m, NCC*H*), 5.23 (2H, s, PhCH_2); δ_C (50 MHz) 153.52 (s, *C*=O), 152.37 (s, py*C*), 147.63 (d, N*C*H), 138.48 (d, NCHCH*C*H), 135.88 (s, Ar-*C*), 128.59, 128.43 and 128.37 (d, Ar-*C*H), 118.37 (d, NC*C*H), 112.50 (d, NCH*C*H), 67.09 (t, Ph*C*H$_2$); *m/z* 228 (M^+, 9.0%), 183 (3.9), 122 (9.0), 106 (7.6), 94 (16.3), 91 (100), 79 (7.9), 78 (7.9), 77 (6.0).

4.2.5 GENERAL PROCEDURE FOR THE PREPARATION OF ALLYL CARBAMATES

To a solution of the (aryl) primary amine (0.25-1.0 g), in dry THF and at room temperature, was slowly added one equivalent of allyl chloroformate. The reaction mixture was allowed to stir for 8 hrs (or overnight) and the solvent and unreacted chloroformate removed by vacuum distillation. The products were purified, where necessary, by centrifugal chromatography (ethyl acetate in hexane) to yield the crystalline allyl carbamates.

N-phenyl allyl carbamate **(105)**



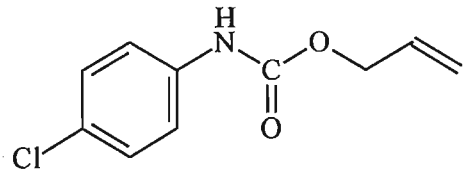
(105)

$C_{10}H_{11}NO_2$

MM 177.20 g/mol

Yield: 66%. Melting Point: 56-58°C. (Found: C, 68.19; H, 6.44; N, 7.93; $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.91%). δ_H (200 MHz) 7.26-7.42 (4H, m, Ar-*H*), 7.02-7.11 (1H, m, Ar-*H*), 6.68 (1H, s, N*H*), 5.88-6.07 (1H, m, C*H*=CH_2), 5.23-5.42 (2H, m, CH=CH_2), 4.65-4.69 (2H, dt, OCH_2CH, *J*=2.8, *J*=0.7); δ_C (50 MHz) 153.19 (s, *C*=O), 137.75 (s, Ar-*C*), 132.41 (d, CH_2*C*H=CH_2), 129.06, 123.51 and 118.66 (d, Ar-*C*H), 118.27 (t, CH=CH_2), 65.85 (t, OCH_2CH); *m/z* 177 (M^+, 33.9%), 132 (29.5), 106 (36.3), 92 (29.3), 77 (16.0), 41 (100).

N-p-*chlorophenyl allyl carbamate* **(106)**



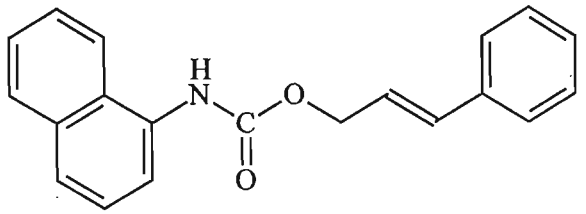
(106)

$C_{10}H_{11}NO_2Cl$

MM 211.64 g/mol

Yield: 95%. Melting Point: 43-45°C. (Found: C, 57.11; H, 5.01; N, 6.49; $C_{10}H_{10}ClNO_2$ requires C, 56.73; H, 4.76; N, 6.62%). δ_H (200 MHz) 7.22-7.36 (4H, m, Ar-*H*), 6.9 (1H, s, N*H*), 5.85-6.04 (1H, m, C*H*=CH_2), 5.22-5.40 (2H, m, CH=CH_2), 4.63-4.67 (2H, dt, OCH_2CH, *J*=2.9, *J*=0.7); δ_C (50 MHz) 153.23 (s, *C*=O), 136.41 (s, Ar-*C*), 132.21 (d, *C*H=CH_2), 129.00 and 119.99 (d, Ar-*C*H), 118.43 (t, CH=*C*H_2), 66.02 (t, O*C*H_2CH); *m/z* 211 (M^+, 37.8%), 153 (20.5), 126 (48.9), 99 (32.0), 90 (17.1), 41 (100).

4.3.6 PREPARATION OF N-α-NAPHTHYL CINNAMYL CARBAMATE (107)



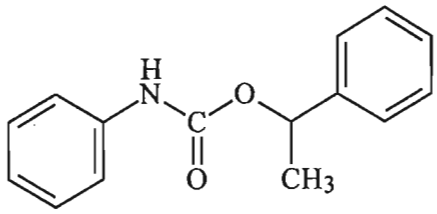
(107)

$C_{20}H_{17}NO_2$

MM 303.36 g/mol

Naphthyl-1-isocyanate (0.5 g, 2.96 mmol) and cinnamyl alcohol (0.397 g, 2.96 mmol) were dissolved in dry THF (10 ml) and then 4 drops triethylamine (Et_3N) were added to the stirred solution as catalyst. The now slightly red solution was allowed to stir for 6 h during which time precipitation of the product began. The solvent was removed *in vacuo* and the product purified by centrifugal chromatography (30% ethyl acetate in hexane) to yield the pale yellow crystalline carbamate. Yield *ca.* 0.5 g (56%). Melting Point: 99-100°C. (Found: C, 78.95; H, 5.83; N, 4.64; $C_{20}H_{17}NO_2$ requires C, 79.18; H, 5.65; N, 4.62%). δ_H (200 MHz) 7.42-7.90 (12H, m, Ar-*H*), 7.06 (1H, s, N*H*), 6.69 (1H, d, CH=C*H*Ph, *J*=7.9), 6.31-6.42 (1H, dt, CH_2CH=CH, *J*=3.2, *J*=8.0), 4.87 (2H, dd, OCH_2CH, *J*=3.2, *J*=0.7); δ_C (50 MHz) 136.15, 134.02 and 132.36 (s, Ar-*C*), 134.27 (d, CH=CHPh), 128.70, 128.60, 128.08, 126.63, 126.24, 125.99 and 125.77 (d, Ar-CH), 123.32 (d, CH=CHPh), 66.04 (t, OCH_2CH); *m/z* 303 (M^+, 0.5%), 259 (6.5), 169 (36.3), 140 (12.5), 134 (7.3), 117 (100), 115 (34.7), 105 (6.6), 91 (19.4), 77 (8.8).

4.2.7 PREPARATION OF N-PHENYL (1-PHENYL)ETHYL CARBAMATE (110)



(110)

$C_{15}H_{15}NO_2$

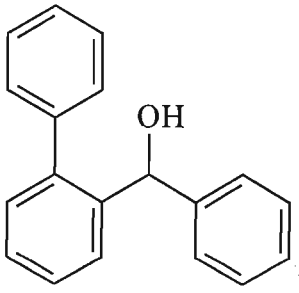
MM 241.28 g/mol

BuLi (1.82 ml, 1.33 M, 2 eq.) was added to a solution of N-phenyl benzyl carbamate **(84)** (0.25 g, 1 mmol) in THF (5 ml), under nitrogen and anhydrous conditions, at -78°C. The solution was allowed to stir for 40 min before iodomethane (0.08 ml, 0.17 g, 1 eq.) was added and the reaction mixture allowed to stir for a further 1.5 h. The reaction was quenched with water (2 ml) and the solvent removed. The organics were extracted into chloroform, the extracts dried and the solvent removed. The product was purified by centrifugal chromatography (10% ethyl acetate in hexane) to yield a very pale yellow oil. This was determined to be a mixture of starting material and product, which were inseparable. Yield: 0.142 g (54%) (based on product mass and NMR integral ratios). δ_H (200 MHz) 6.97-7.39 (10H, m, Ar-*H*), 5.88 (1H, q, C*H*Ph, *J*=3.3), 1.56 (3H, d, CH_3, *J*=3.3); δ_C (50 MHz) *ca.* 153 (*C*=O), 141.55 (s, NAr-*C*), 137.83 (s, Ar-*C*), 66.83 (d, *C*HPh), 22.21 (q, CH_3); *m/z* 241 (M^+, 1.5%), 197 (1.0), 182 (3.9), 119 (3.3), 105 (100), 93 (19.3), 91 (6.9), 77 (14.7).

4.2.8 *GENERAL PROCEDURE FOR THE REARRANGEMENT OF CARBAMATES TO SECONDARY AND TERTIARY ALCOHOLS*

To a stirred solution of the aryl benzyl carbamate or the N-naphthyl cinnamyl carbamate in dry THF, under nitrogen and at 0°C, was added 2.2 equivalents of *n*-butyllithium (in hexane). The reaction mixture was allowed to stir for 6-8 h, during which time it was allowed to warm up to room temperature. (Except in the case of N-(4-pyridyl) benzyl carbamate where the reaction mixture was allowed to stir at 0°C for 3.5 h.) The reaction was quenched by adding 5 ml water. The solvent was partially removed before the reaction mixture was extracted into chloroform, the extracts dried over anhydrous $MgSO_4$ and the solvent removed on a rotary evaporator. The products were purified by centrifugal chromatography (ethyl acetate in hexane) to yield the crystalline products in varying yields

(2-Biphenyl)phenylmethanol [1'-phenylbenzhydrol / 1'-phenyldiphenylmethanol] **(76)**

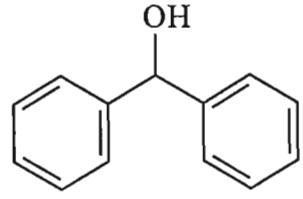


(76)

$C_{19}H_{16}O$
MM 260.33 g/mol

Yield: 64% (1eq. BuLi). Melting point: 61°C (Lit[133]: 66°C). (Found: C, 87.25; H, 6.35; $C_{19}H_{16}O$ requires C, 87.66; H, 6.20%). δ_H (200 MHz) 7.51-7.55 (1H, m, Ar-*H*), 7.10-7.39 (13H, m, Ar-*H*), 5.89 (1H, s, C*H*OH), 2.2 (1H, s, CHO*H*); δ_C (50 MHz) 143.77, 141.25, 140.97 and 140.76 (s, Ar-*C*), 129.96, 129.33, 128.15, 128.09, 127.84, 127.35, 127.14 and 126.59 (d, Ar-*C*H), 72.20 (d, *C*HOH); IR (cm^{-1}) 3420 (OH); *m/z* 260 (M^+, 64.4%), 242 (100), 181 (82.1), 165 (96.2), 152 (88.5), 105 (70.5), 77 (89.8).

Diphenylmethanol [benzhydrol] **(85)**



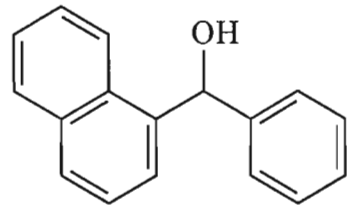
(85)

$C_{13}H_{12}O$

MM 184.23 g/mol

Yield: 71%. Melting point: 60°C (Lit[141]: 65-67°C). δ_H (200 MHz) 7.18-7.29 (10H, m, Ar-*H*), 5.62 (1H, s, C*H*OH), 2.95 (1H, s, CHO*H*); δ_C (50 MHz) 143.72 (s, Ar-*C*), 128.34, 127.37 and 126.50 (d, Ar-*C*H), 75.95 (d, *C*HOH); IR (cm^{-1}) 3228 (OH); *m/z* 184 (M^+, 36.8%), 165 (8.3), 105 (100), 77 (49.4).

(α-Naphthyl)phenylmethanol **(96)**



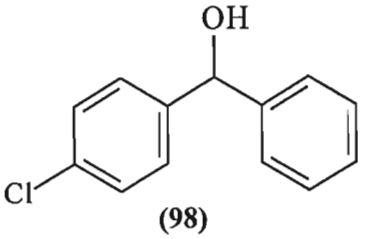
(96)

$C_{17}H_{14}O$

MM 234.29 g/mol

Yield: 62%. (Found: C, 86.84; H, 6.24; $C_{17}H_{14}O$ requires C, 87.15; H, 6.02%). δ_H (200 MHz) 7.22-8.03 (12H, m, Ar-*H*), 6.495 (1H, s, naphC*H*(OH)Ph), 2.42 (1H, s, O*H*); δ_C (50 MHz) 143.06, 138.74, 133.88 and 130.64 (s, Ar-*C*), 128.74, 128.50, 128.45, 127.64, 127.02, 126.12, 125.57, 125.30, 124.58 and 123.95 (d, Ar-*C*H), 73.60 (d, naph*C*H(OH)Ph); *m/z* 234 (M^+, 64.6%), 215 (23.9), 155 (21.7), 128 (88.7), 105 (100), 77 (42.9).

(p-Chlorophenyl)phenylmethanol [p-chlorobenzhydrol / p-chlorodiphenylmethanol] **(98)**



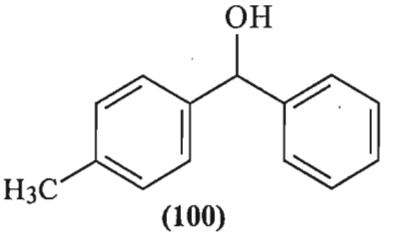
(98)

$C_{13}H_{11}OCl$

MM 218.68 g/mol

Yield: 10%. Melting point: 55-56°C (Lit[134, 135]: 50-56°C). (Found: C, 71.63; H, 5.02; $C_{13}H_{11}ClO$ requires C, 71.38; H, 5.07%). δ_H (200 MHz) 7.25-7.36 (9H, m, Ar-*H*), 5.79 (1H, s, C*H*OH), 2.32 (1H, s, CHO*H*); δ_C (50 MHz) 143.41 and 142.18 (s, Ar-*C*), 133.25 (s, Ar-*C*-Cl)[142], 128.64, 128.58, 127.85 and 126.50 (d, Ar-*C*H), 75.60 (d, *C*HOH); *m/z* 218 (M^+, 52.2%), 139 (47.3), 111 (11.1), 105 (100), 77 (39.2).

(p-Methylphenyl)phenylmethanol [p-methylbenzhydrol / p-methyldiphenylmethanol] **(100)**



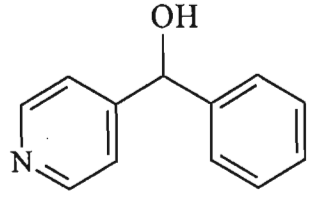
(100)

$C_{14}H_{14}O$

MM 198.68 g/mol

Yield: 14%. Melting point: 50-54°C (Lit[143]: 52-53°C). δ_H (200 MHz) 7.30-7.36 (5H, m, Ar-*H*), 7.10-7.30 (4H, m, CH_3Ar-*H*), 5.77 (1H, s, C*H*(OH)), 2.32 (s, CH_3), 2.32 (1H, s, O*H*); δ_C (50 MHz) 143.94 and 140.95 (s, Ar-*C*), 137.23 (s, Ar-*C*-Me)[142], 128.97, 128.23, 127.23, 126.32 and 126.25 (d, Ar-*C*H), 75.85 (d, *C*H(OH)), 20.92 (q, CH_3); *m/z* 198 (M^+, 45.8%), 183 (23.0), 119 (79.6), 105 (100), 92 (55.8), 77 (58.1).

(4-Pyridyl)phenylmethanol **(102)**

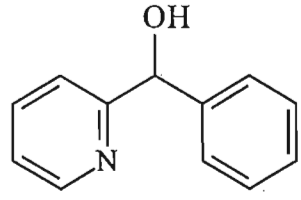


(102)

$C_{12}H_{12}NO$
MM 185.22 g/mol

Yield: 35%. δ_H (200 MHz) 8.33 (2x 1H, dd, NC*H*, *J*=2.3, *J*=0.7), 7.24-7.38 (7H, m, Ar-*H* and 2x NCHC*H*), 5.74 (1H, s, C*H*(OH)), 5.6-5.8 (1H, s, O*H*); δ_C (50 MHz) 153.98 (s, py*C*), 148.98 (d, N*C*HCH), 143.23 (s, Ar-*C*), 128.63, 128.57, 128.18 and 126.84 (d, Ar-*C*H), 121.53 (d, NCH*C*H), 74.48 (d, *C*H(OH)); *m/z* 185 (M^+, 58.1%), 167 (4.5), 107 (25.4), 79 (100), 77 (30.7).

(2-Pyridyl)phenylmethanol **(104)**

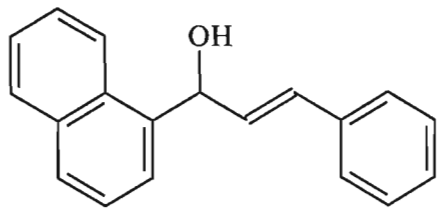


(104)

$C_{12}H_{12}NO$
MM 185.22 g/mol

Yield: 23%. δ_H (200 MHz) 9.84 (1H, s, O*H*), 8.20 and 8.24 (1H, d, NC*H*, *J*=0.4), 7.95-7.98 (1H, dd, NCC*H*, *J*=2.4, *J*=0.4), 761-769 and 6.93-7.00 (2x 1H, m, NCHC*HCH*), 7.50-7.59 (3H, m, *m* & *p*-Ar-*H*), 7.25-7.39(2H, m, *o*- Ar-*H*), 5.30 (1H, s, C*H*(OH)); δ_C (50 MHz) 150.60 (s, py*C*), 146.88 (d, N*C*H), 139.17 (s, Ar-*C*), 138.93 (d, NCHCH*C*H), 128.60, 128.44 and 126.72 (d, Ar-*C*H), 119.92 (d, NC*C*H), 114.24 (d, NCH*C*H), 74.51 (d, *C*H(OH)); *m/z* 185 (M^+, 84.0%), 167 (9.0), 108 (48.0), 105 (12.6), 79 (100), 77 (40.0), 51 (29.6).

1-(α-Naphthyl)-3-phenylprop-2-en-1-ol **(109)**

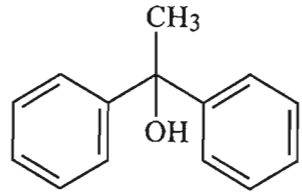


(109)

$C_{19}H_{16}O$
MM 260.33 g/mol

Yield: 40%. (oil that crystallises out exceptionally slowly) δ_H (200 MHz) 7.05-8.14 (12H, m, Ar-*H*), 6.34-6.72 (1H, dd, CH=C*H*Ph, *J*=8.0, *J*=0.4), 6.42-6.53 (1H, dd, C*H*=CHPh, *J*=8.0, *J*=2.8), 5.95 (1H, d, C*H*(OH), *J*=2.8), 2.65 (1H, s, O*H*); δ_C (50 MHz) 138.22, 136.49 and 133.83 (s, Ar-*C*), 130.99 (d, *C*H=CHPh), 130.74, 128.75, 128.46, 128.42, 127.64, 126.54, 126.11, 125.60, 125.41 and 123.93 (d, Ar-*C*H), 123.70 (d, CH=*C*HPh), 71.88 (d, *C*H(OH)); *m/z* 260 (M^+, 21.4%), 181 (3.0), 169 (11.5), 155 (100), 141 (25.7), 127 (34.1), 115 (8.8), 105 (10.7), 77 (17.4).

1,1-Diphenylethanol [α-methylbenzhydrol] **(111)**

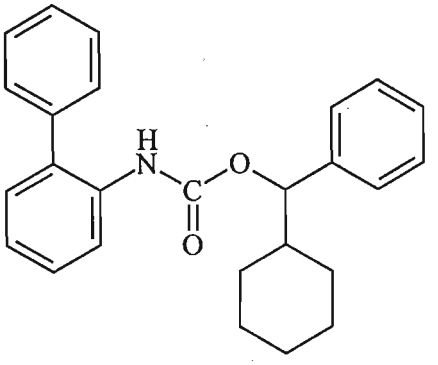


(111)

$C_{14}H_{14}O$
MM 198.26 g/mol

Yield: 10%. Melting point: 78-82°C (Lit[144]: 77-81°C). δ_H (200 MHz) 7.05-7.72 (10H, m, Ar-*H*), 3.28 (1H, s, O*H*), 1.89 (3H, s, C*H*$_3$); δ_C (50 MHz) 142.83 and 137.38 (s, Ar-*C*), 130.93, 128.96, 128.54, 128.03, 125.28, 124.42 and 119.64 (d, Ar-*C*H), 76.92 (s, $Ph_2C(CH_3)OH$), 27.28 (q, CH_3); *m/z* 198 (M^+, 5.7%), 183 (69.4), 165 (9.1), 155 (5.2), 120 (15.6), 105 (100), 77 (55.4), 51 (19.6), 43 (60.9).

4.2.9 *PREPARATION OF N-(2-BIPHENYL) (CYCLOHEXYLPHENYL)METHYL CARBAMATE* (75)



(75)

$C_{26}H_{27}NO_2$

MM 385.50 g/mo

BuLi (0.4 ml, 1.1 eq., 2.35M) was added dropwise to a solution of N-(2-biphenyl) benzyl carbamate **(73)** (0.25 g, 0.8 mmol) in dry THF (5 ml) at -78°C. The slightly orange solution was allowed to stir for 0.5 h before bromocyclohexane[145] (0.148 g, 0.115 ml, 1.1 eq.) was added. After a few minutes the solution turned a deep emerald green and this solution was stirred for 3 h before the reaction was quenched with water (2 ml). The THF was removed and the residue extracted into chloroform and the extracts dried over anhydrous $MgSO_4$. The solvent was removed to yield a pale yellow, milky oil which was purified using centrifugal chromatography (5% ethyl acetate in haxane). Yield: 27% δ_H (200 MHz) 8.026 (1H, d, Ar-*H*, *J*=3.8), 7.04-7.49 (13H, m, Ar-*H*), 6.63 (1H, s, N*H*), 5.446 (1H, d, OC*H*(C_6H_{11})Ph, *J*=4), 0.88-1.76 (11H, m, cyclohexyl); δ_C (50 MHz) 153.31 (s, *C*=O), 139.74, 138.13, 134.71 and 120.46 (s, Ar-*C*), 130.07, 129.29, 128.98, 128.34, 128.14, 127.81, 127.68, 127.03 and 123.53 (d, Ar-*C*H), 81.30 (d, O*C*H(C_6H_{11})Ph), 42.88 (d, OCH(*C*H)-Ph), 28.98 (t, -*C*H_2C*H*C_2H$_2$-), 26.24 (t, -(CH_2)$_2$*C*H_2(CH_2)$_2$-), 25.82 and 25.75 (t, -CH_2*C*H2CH2-); *m/z* 385 (M^+, 0.5%), 258 (10.9), 207 (6.3), 173 (11.9), 167 (8.6), 107 (21.6), 91 (100), 81 (11.2), 79 (9.1).

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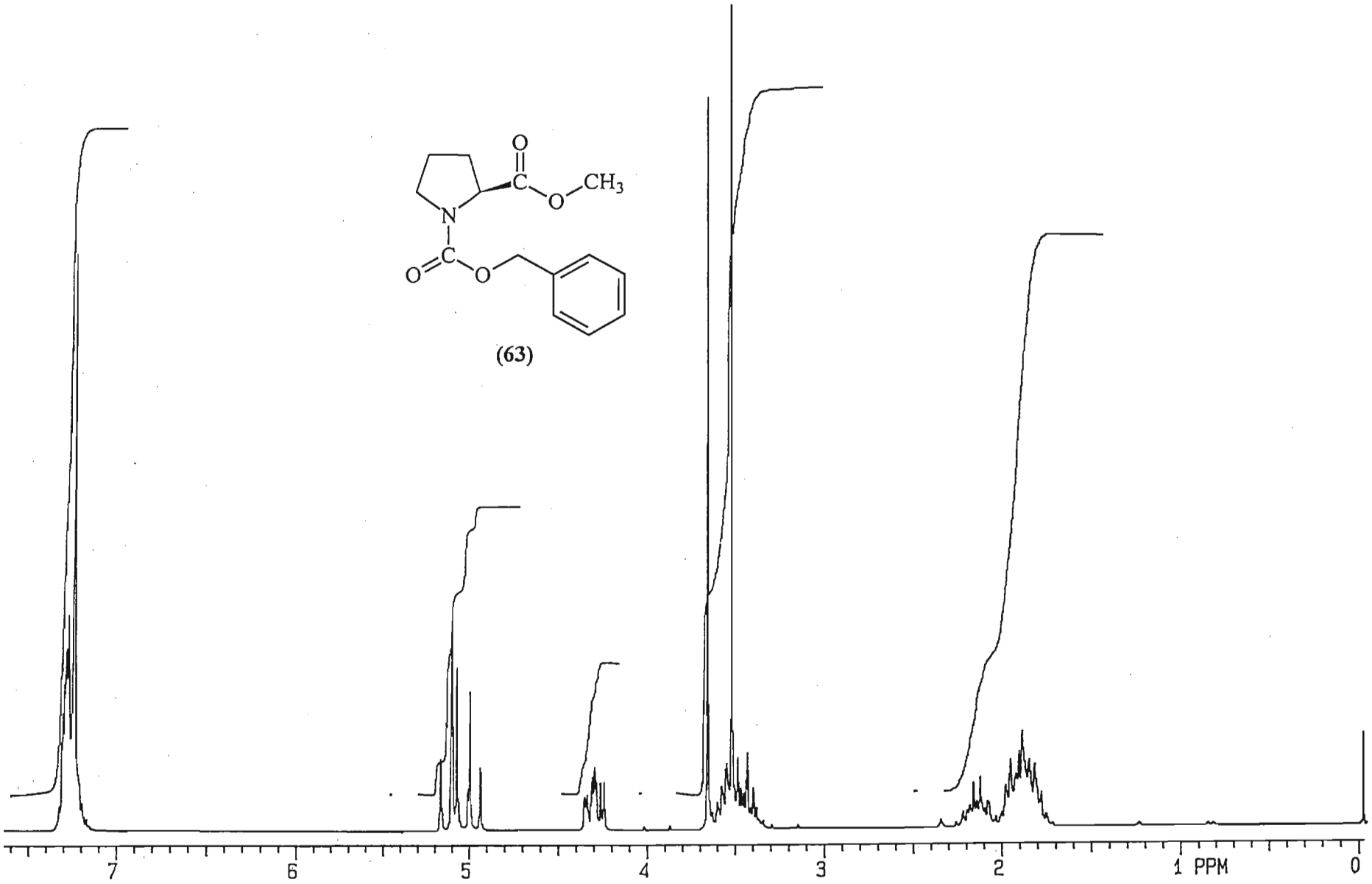
6. APPENDIX

^{1}H and ^{13}C NMR Spectra

and

IR Spectra



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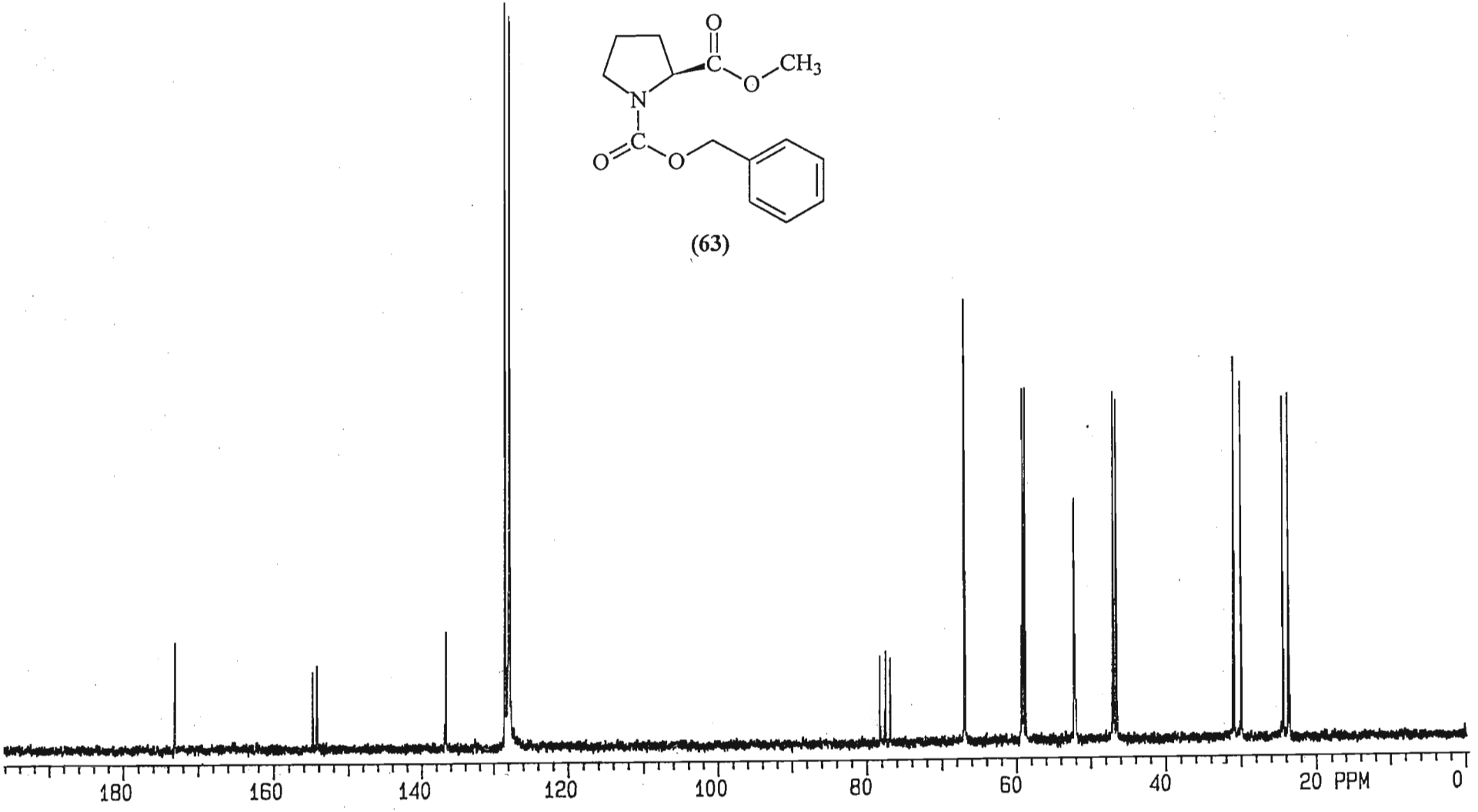

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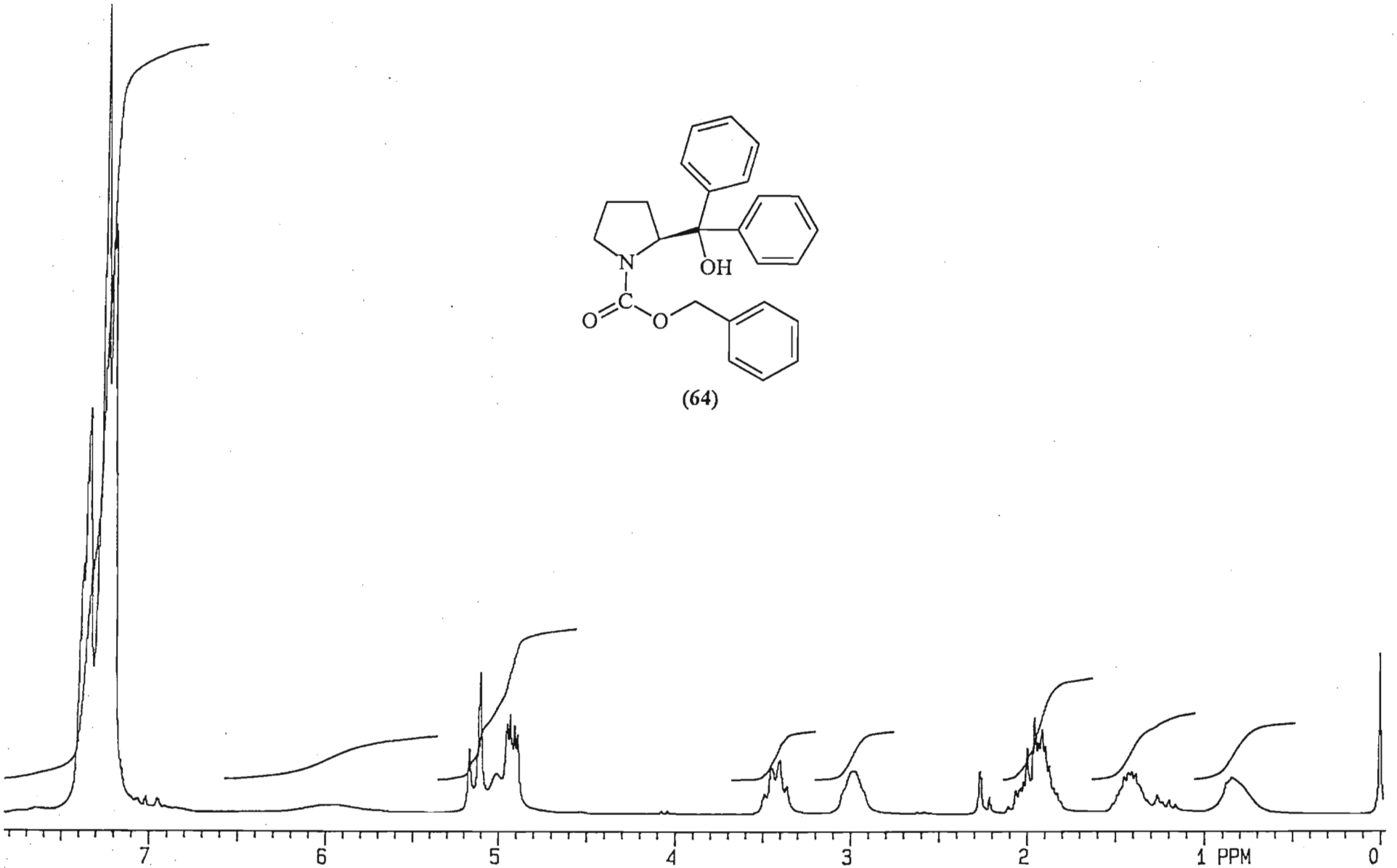

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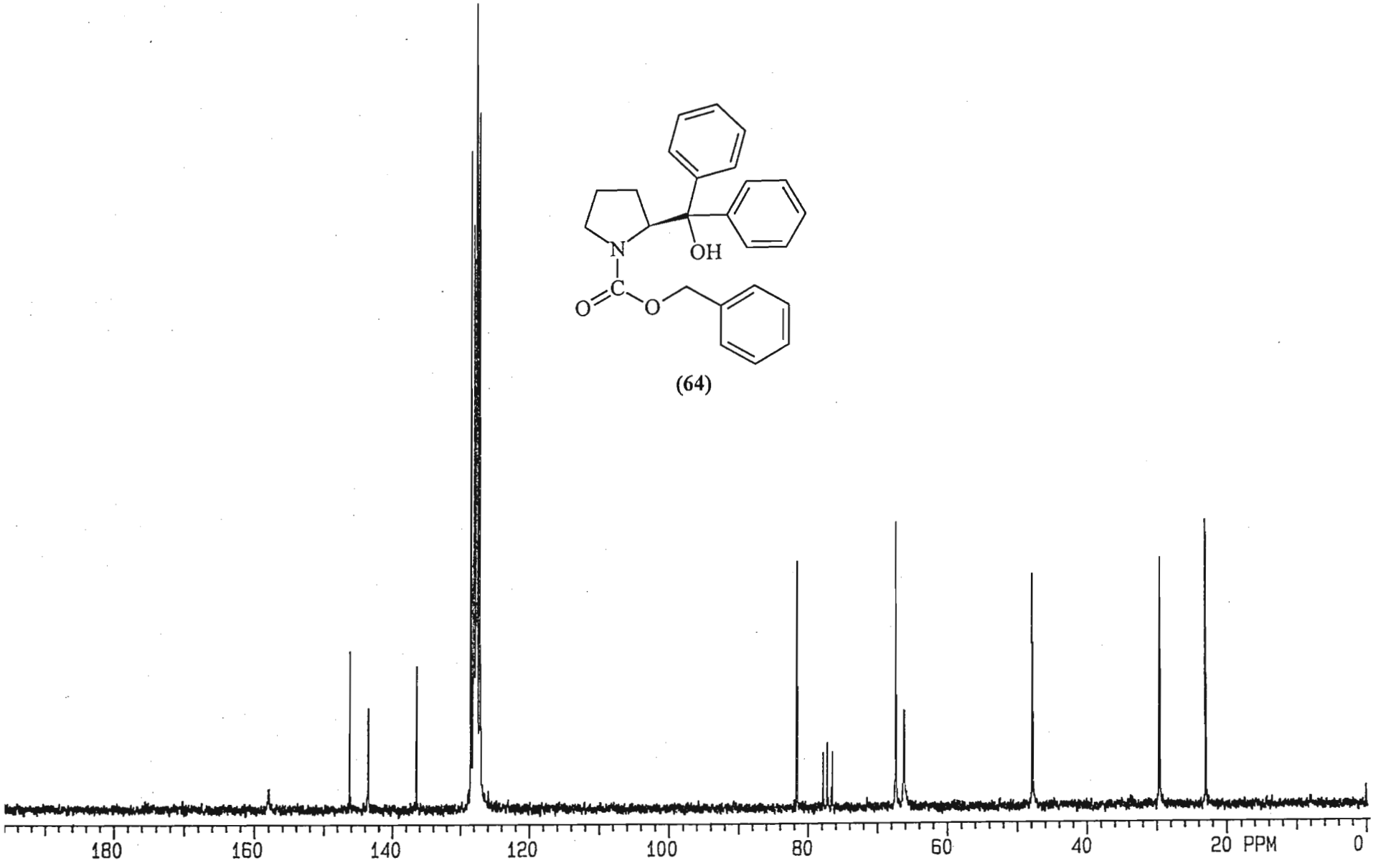

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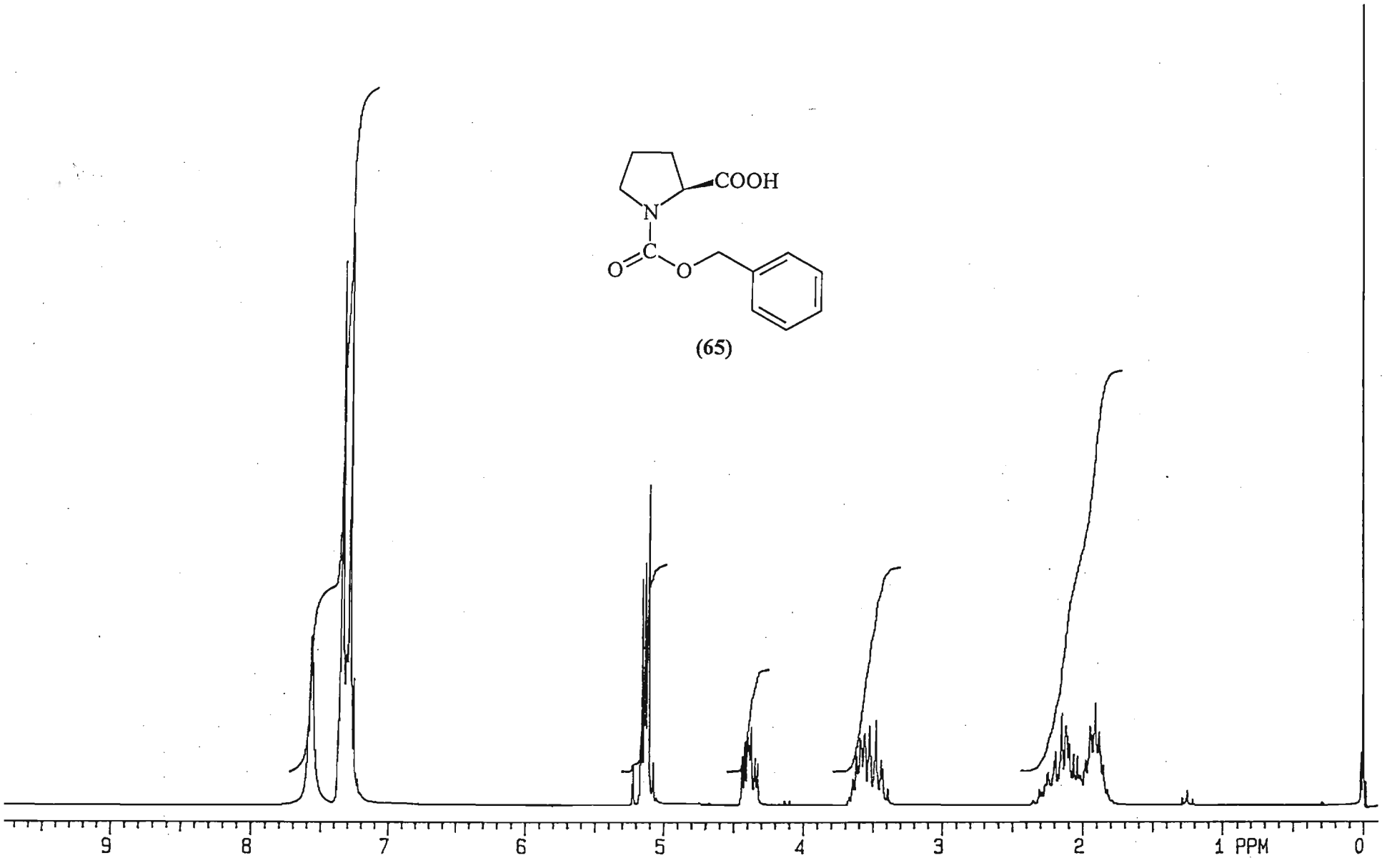

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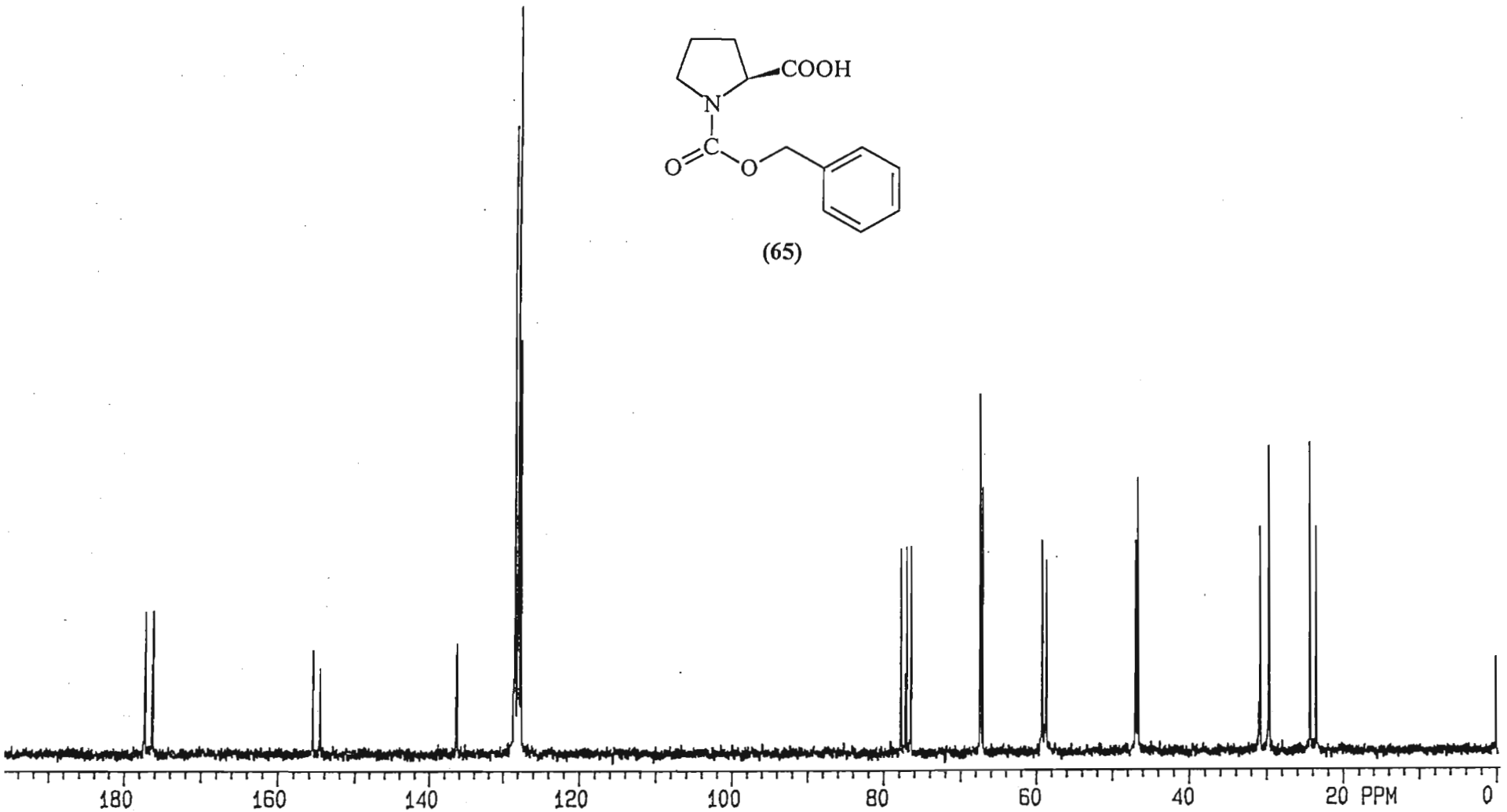

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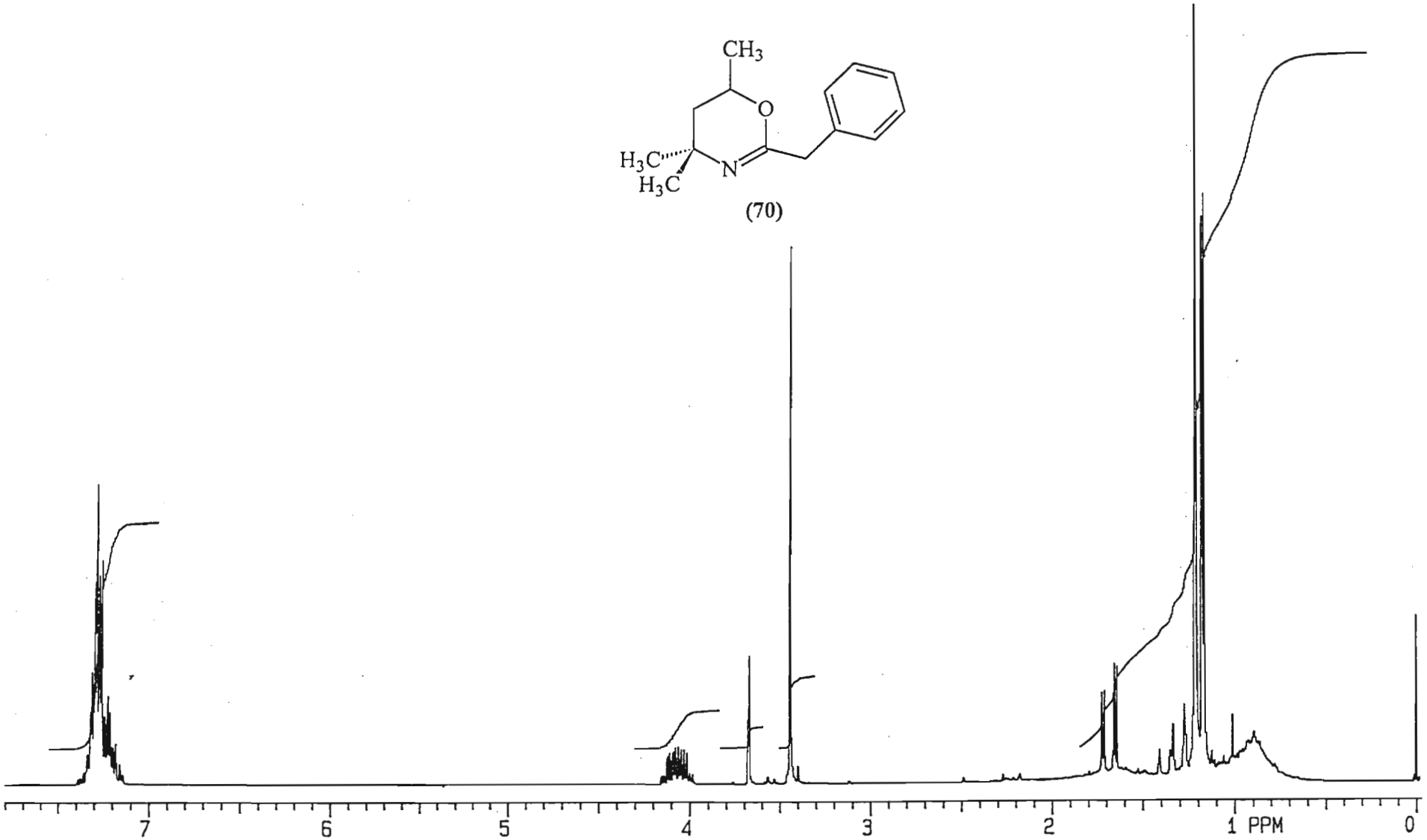

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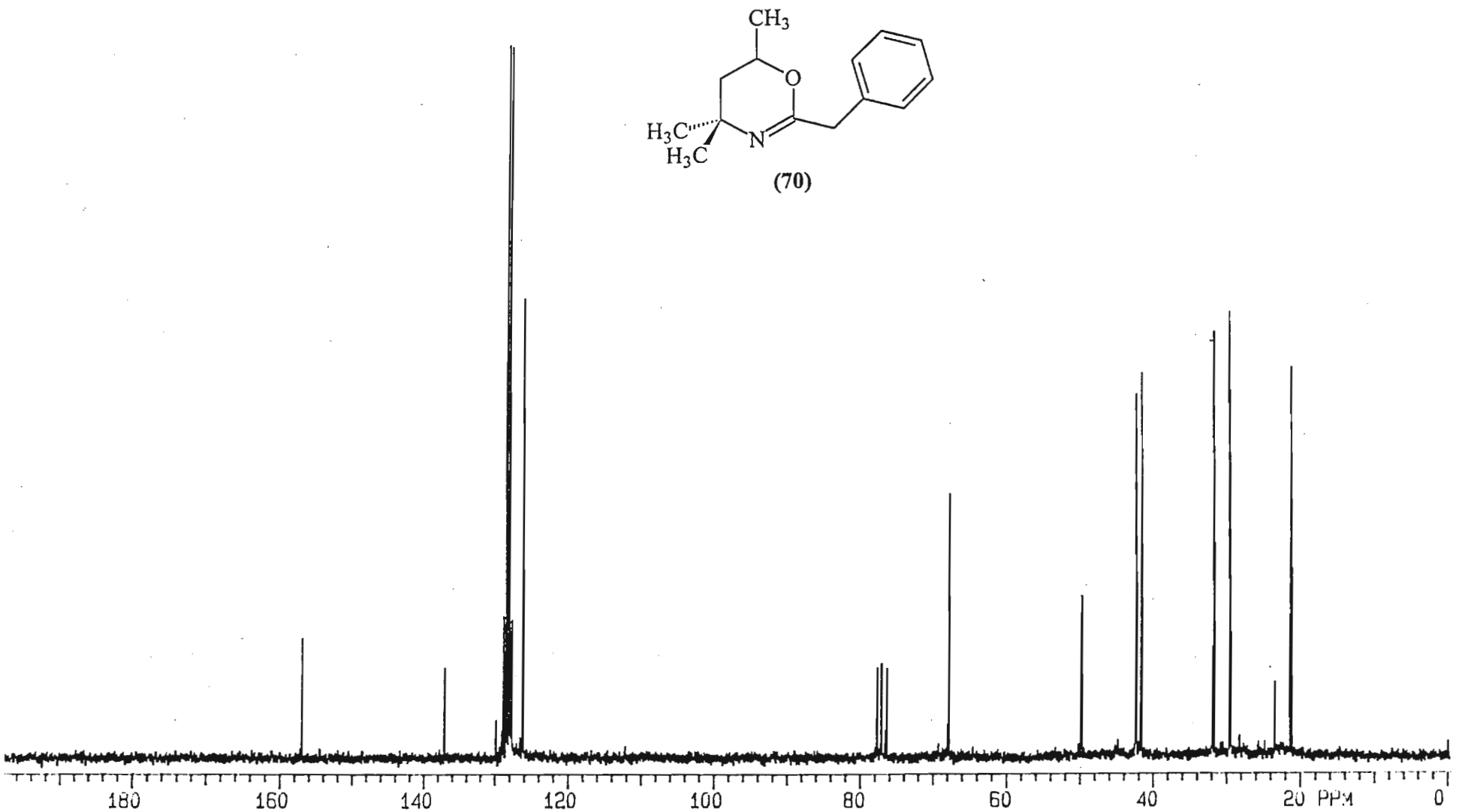

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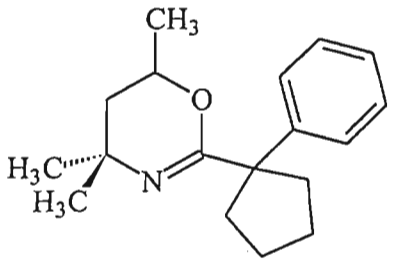

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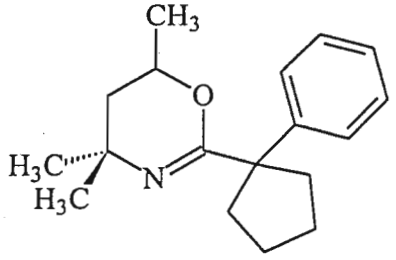

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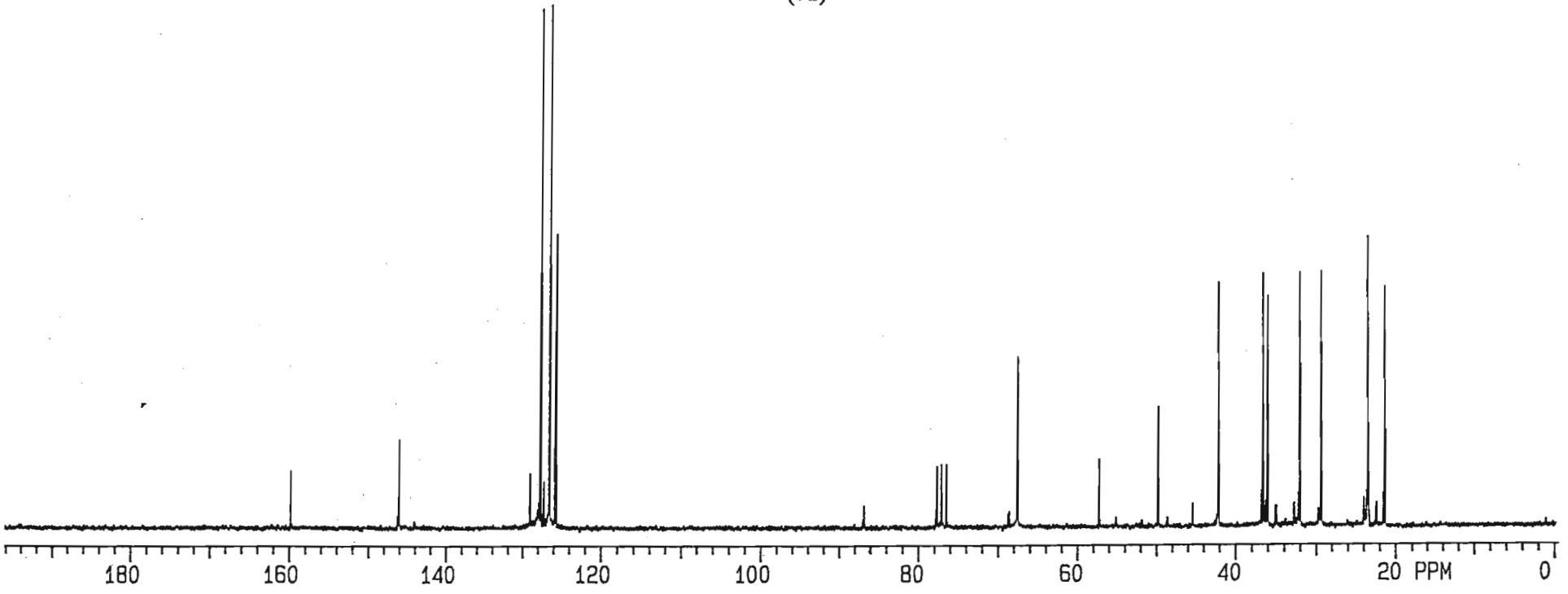

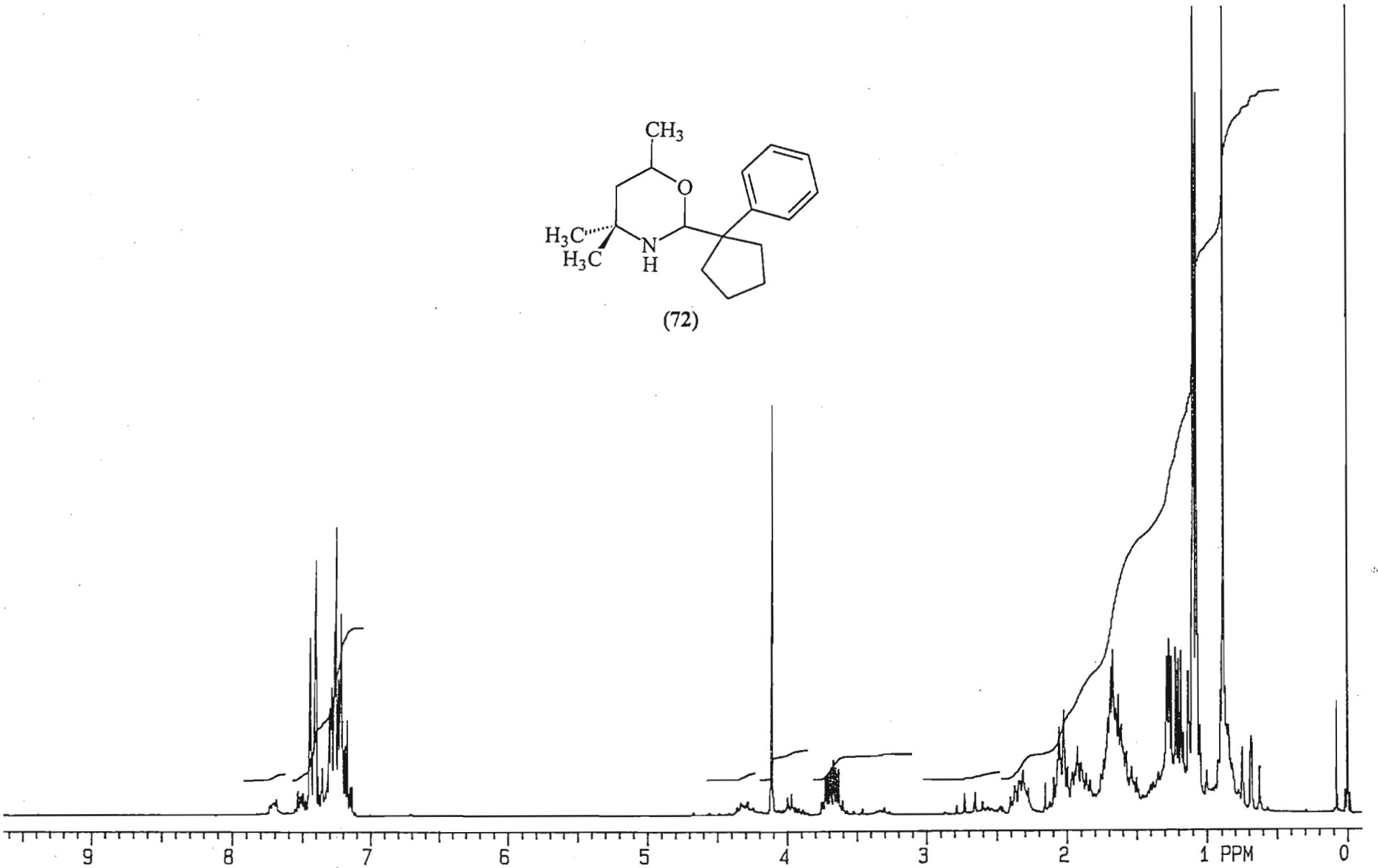

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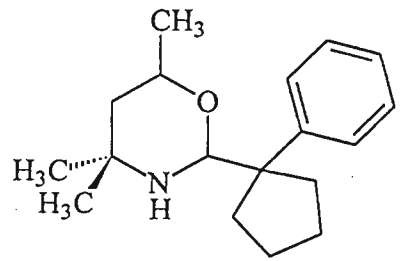

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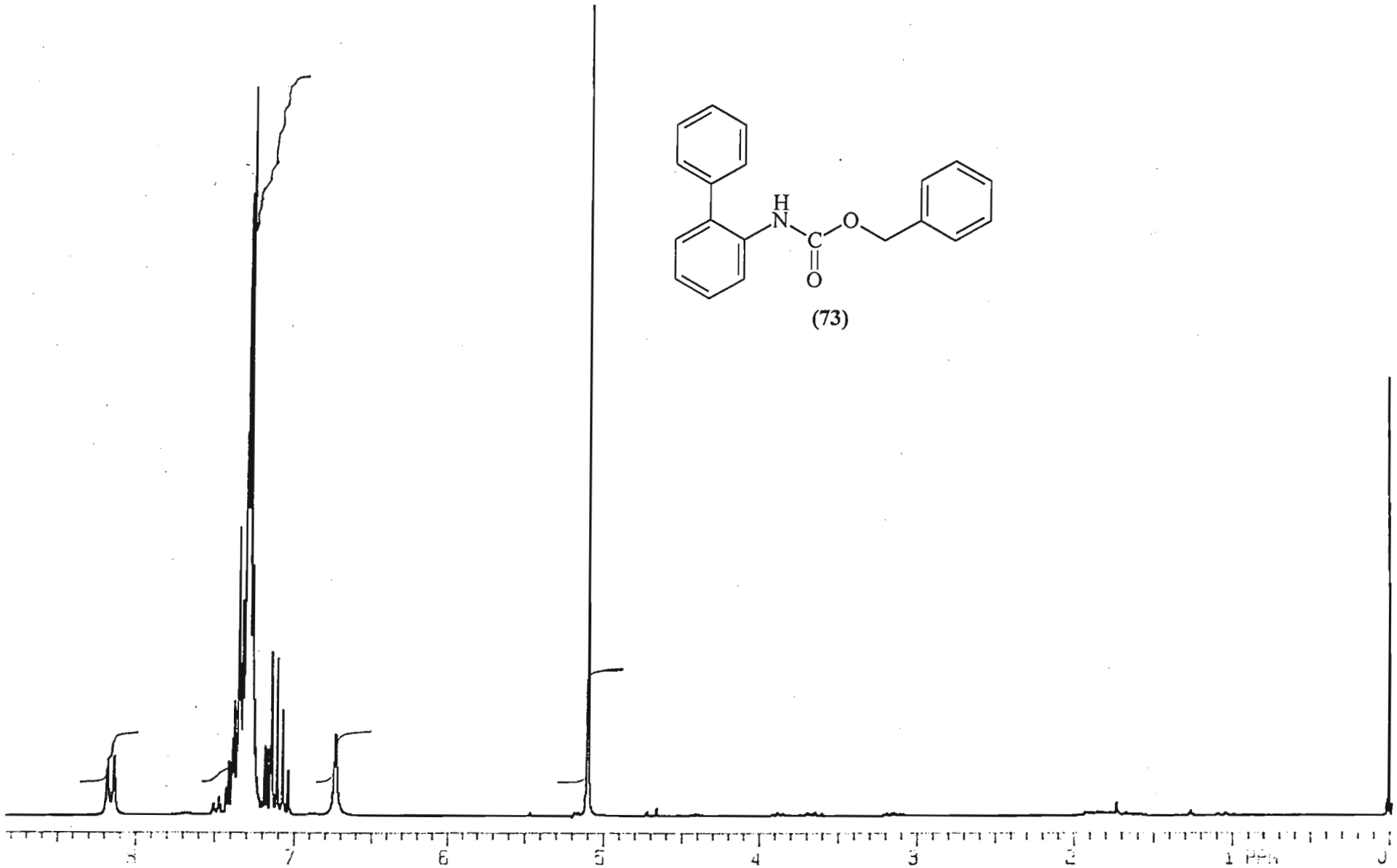

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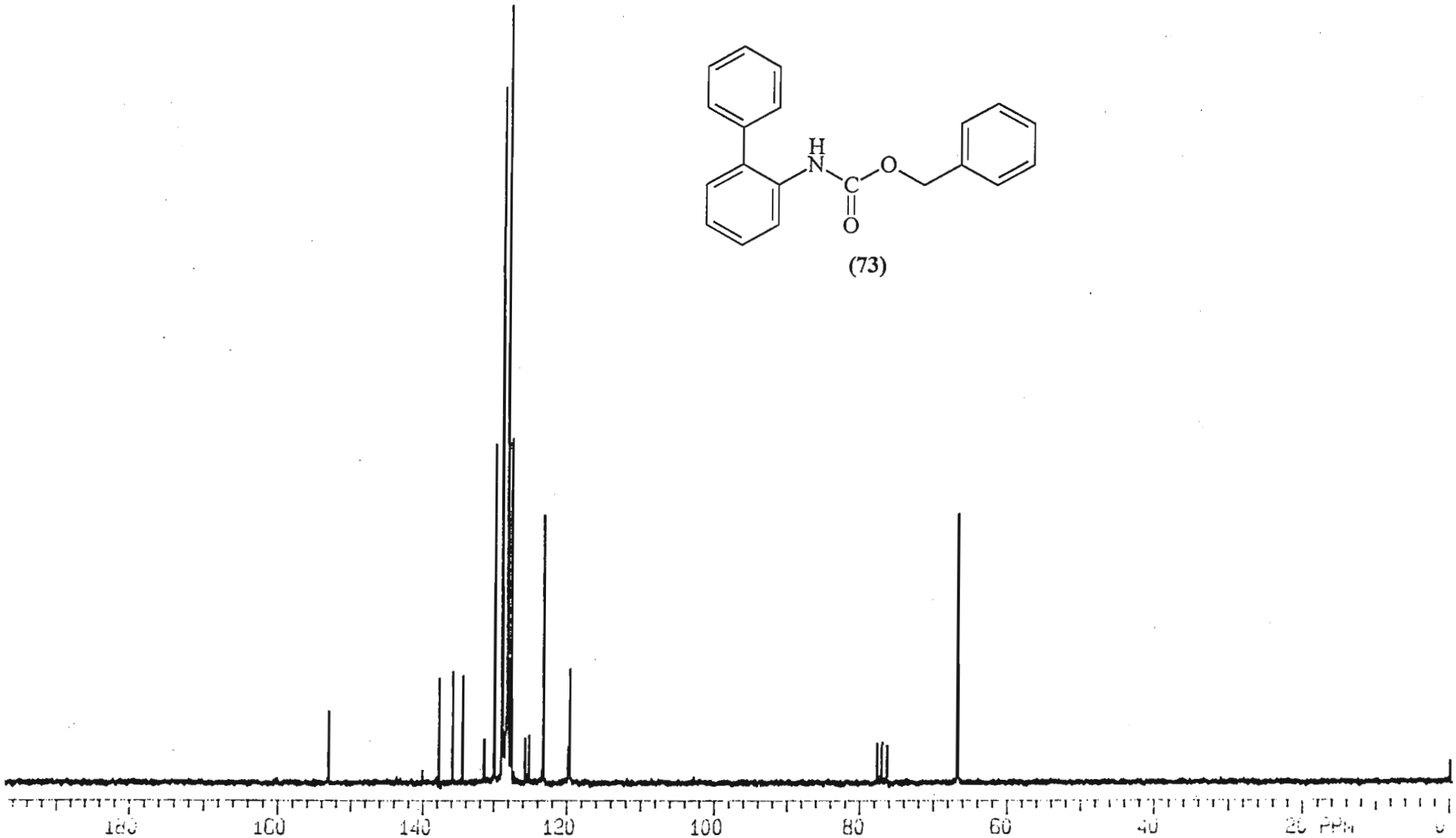

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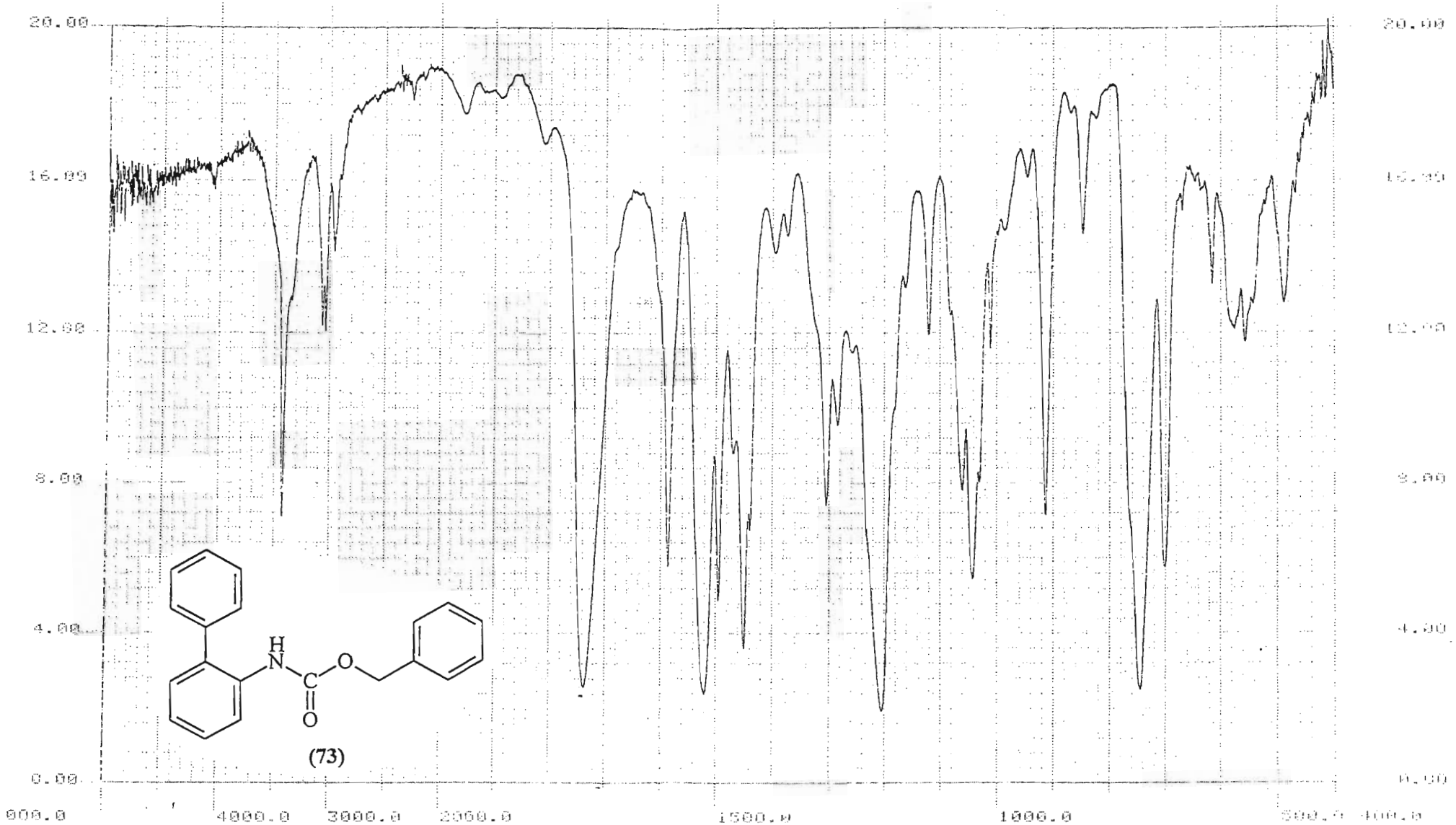
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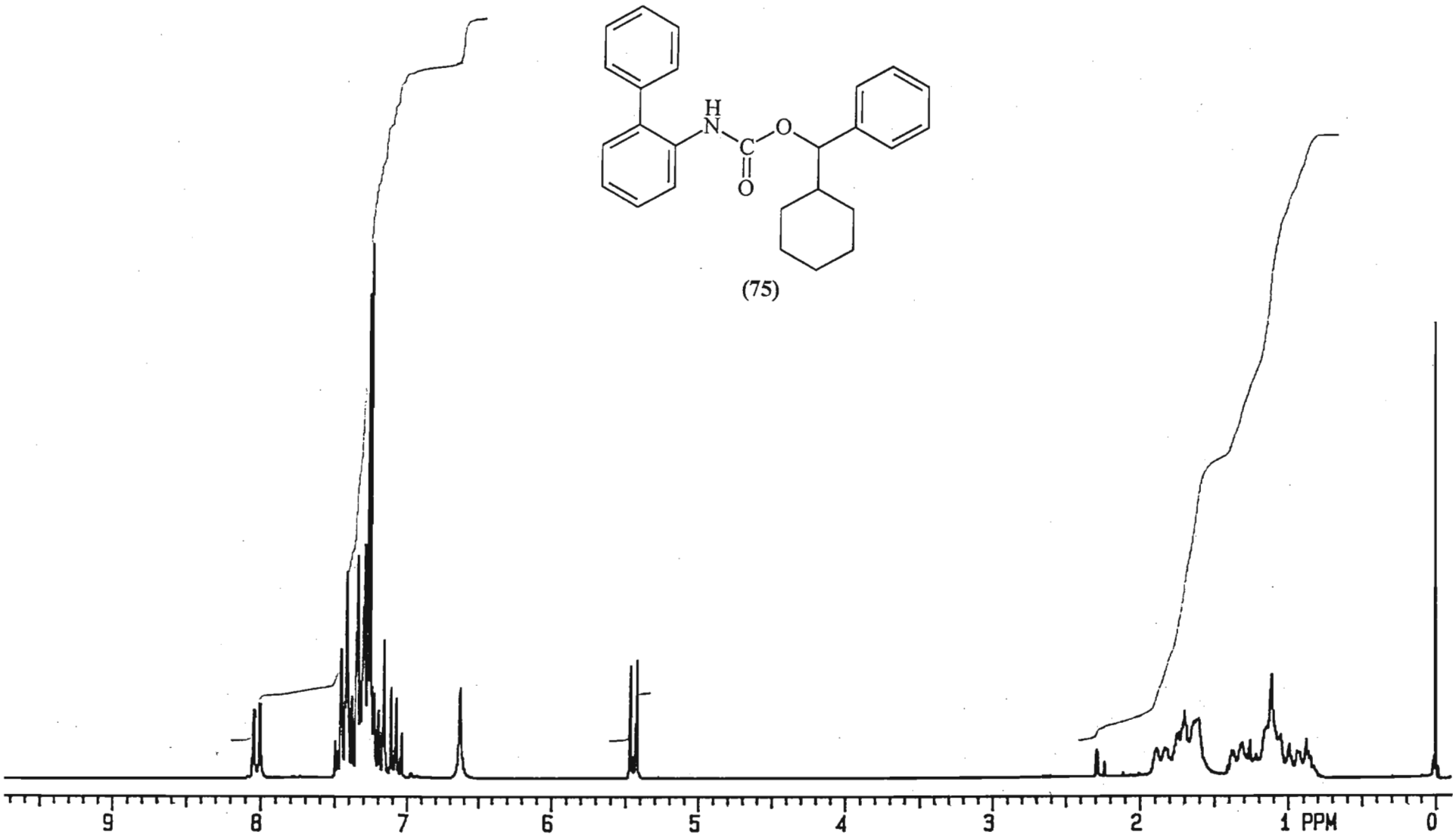
N
C
O
O

(73)



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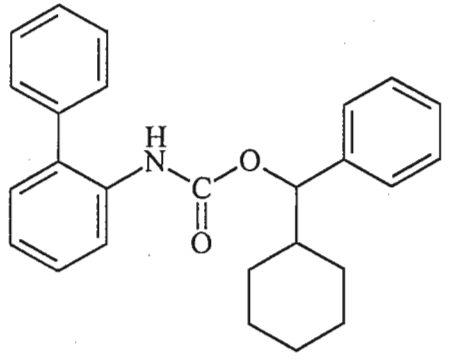

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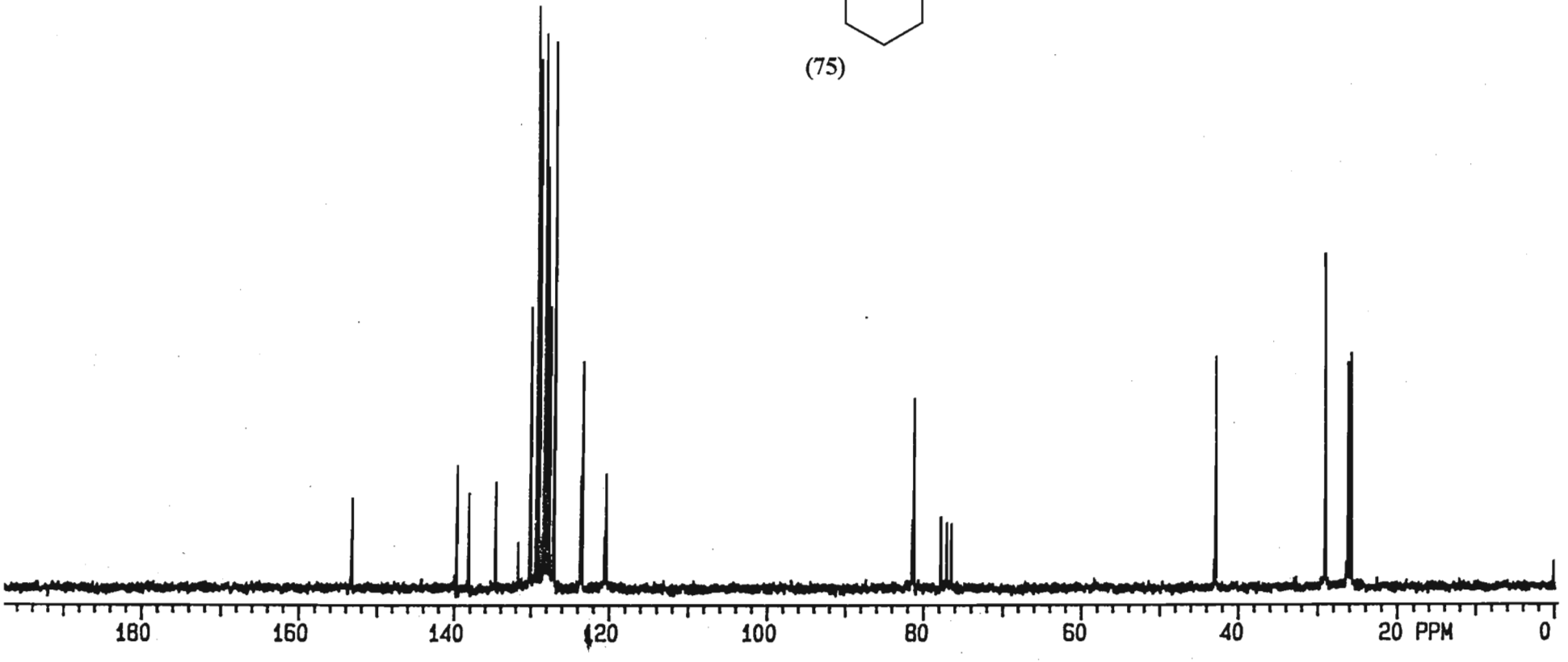

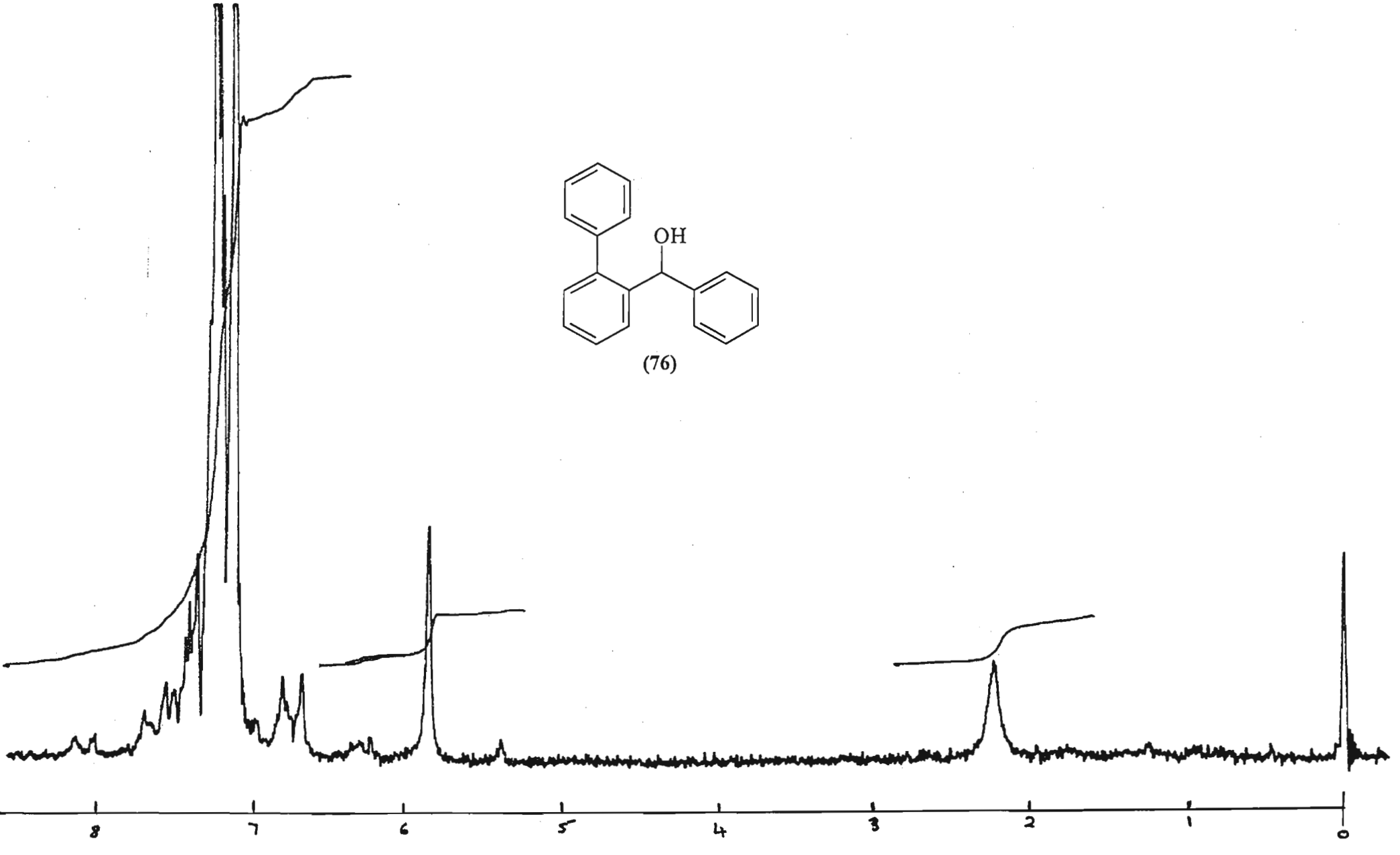

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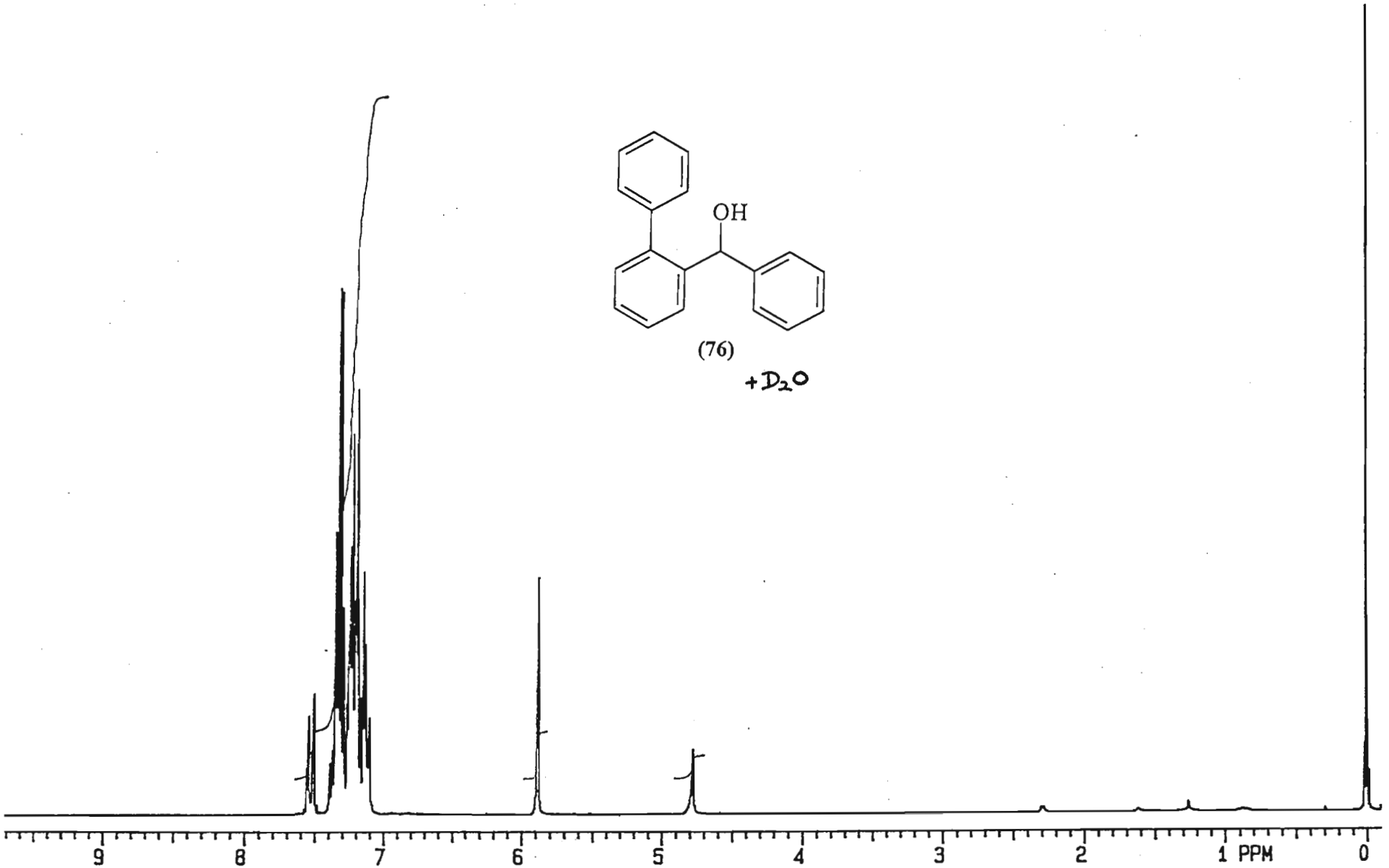

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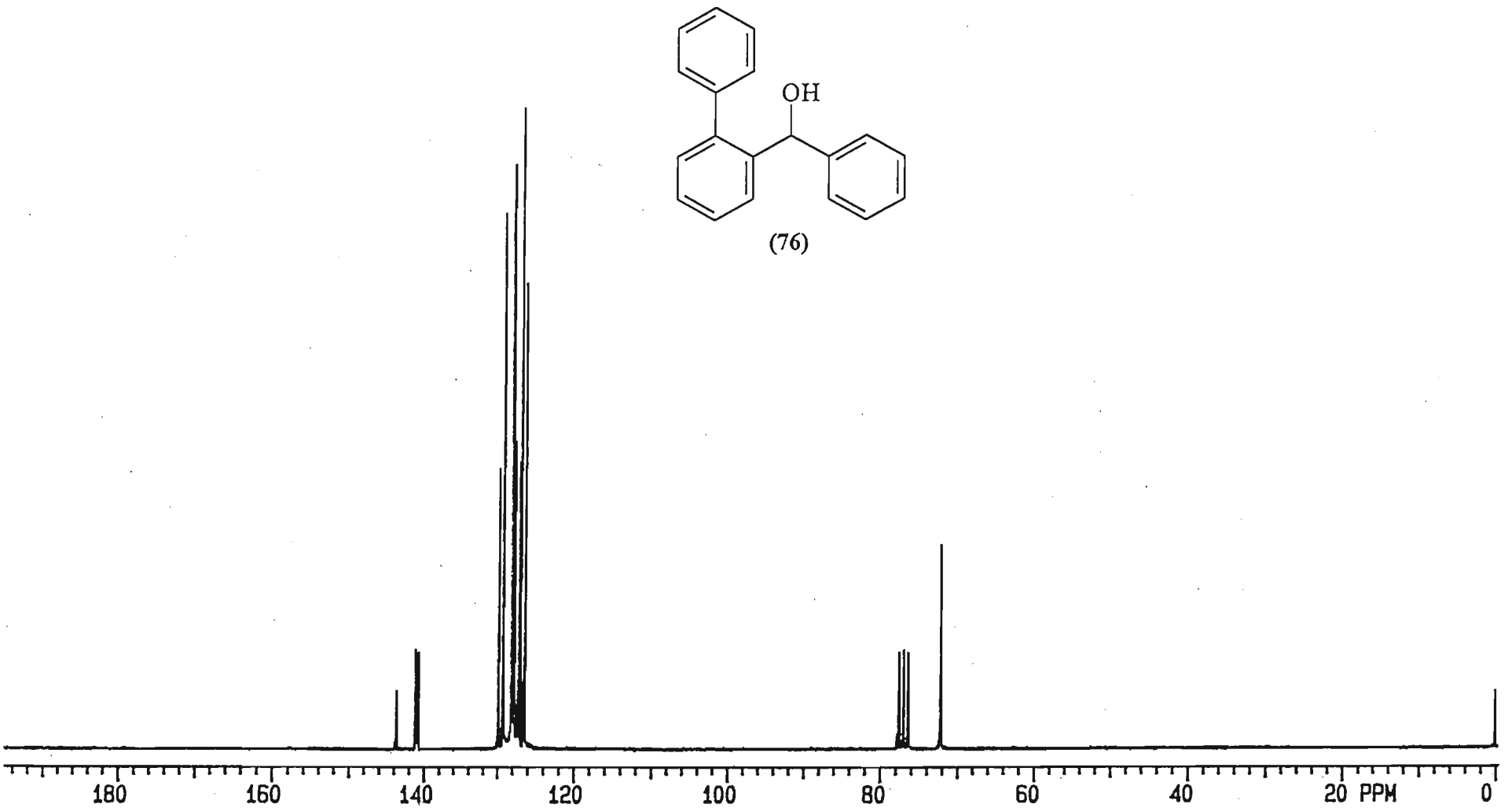

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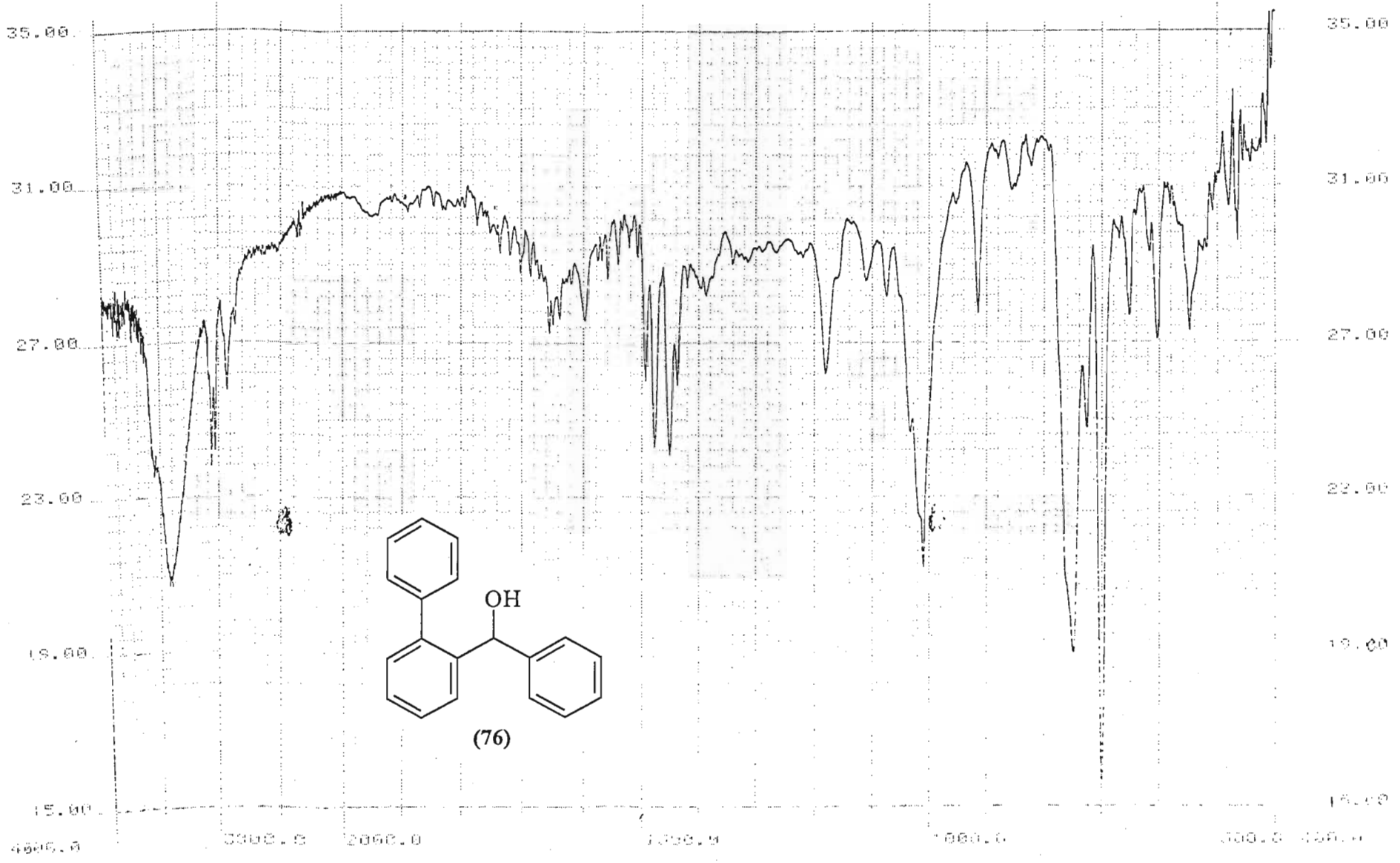

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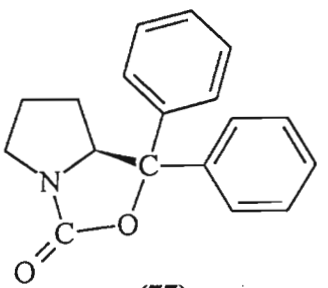

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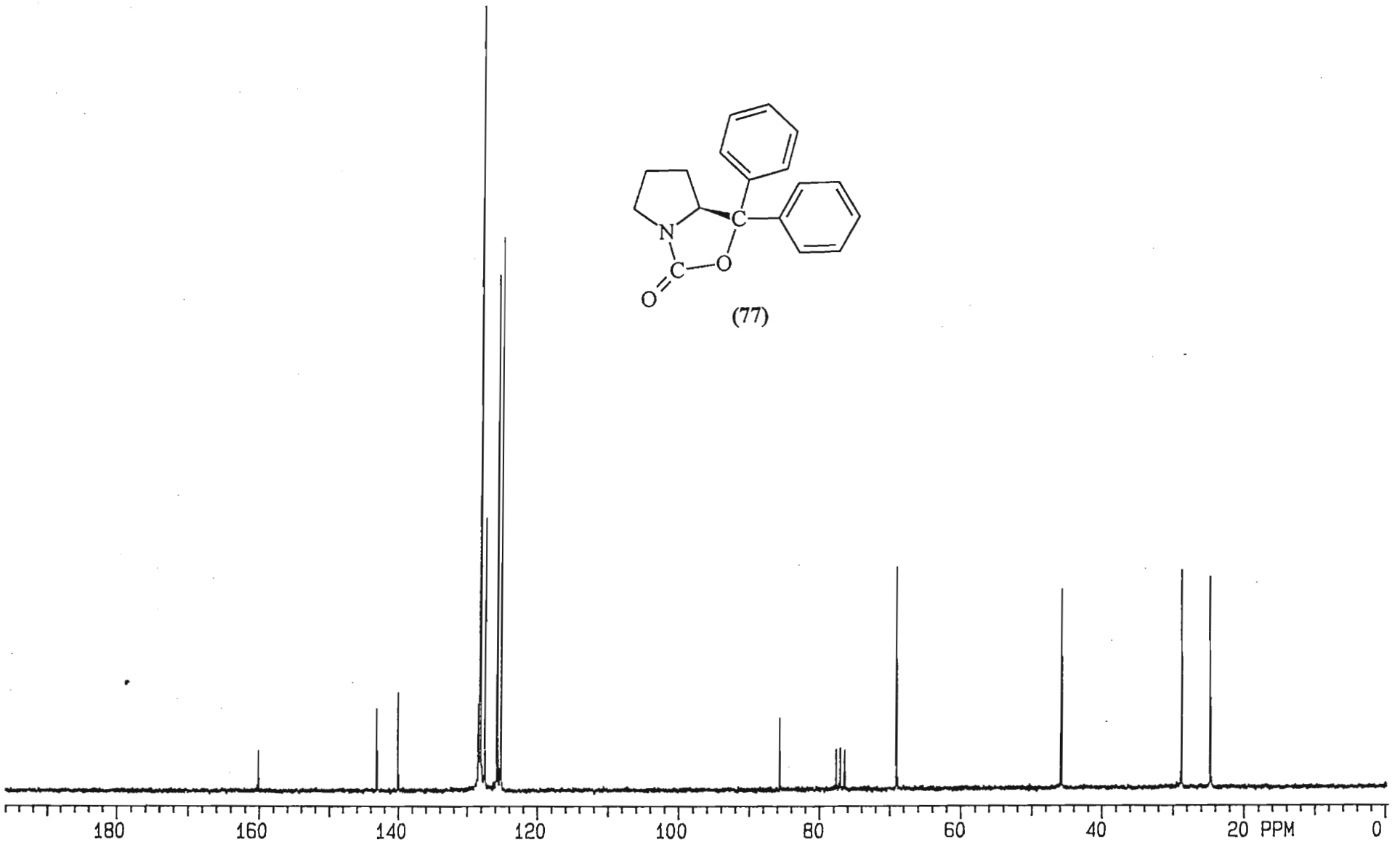

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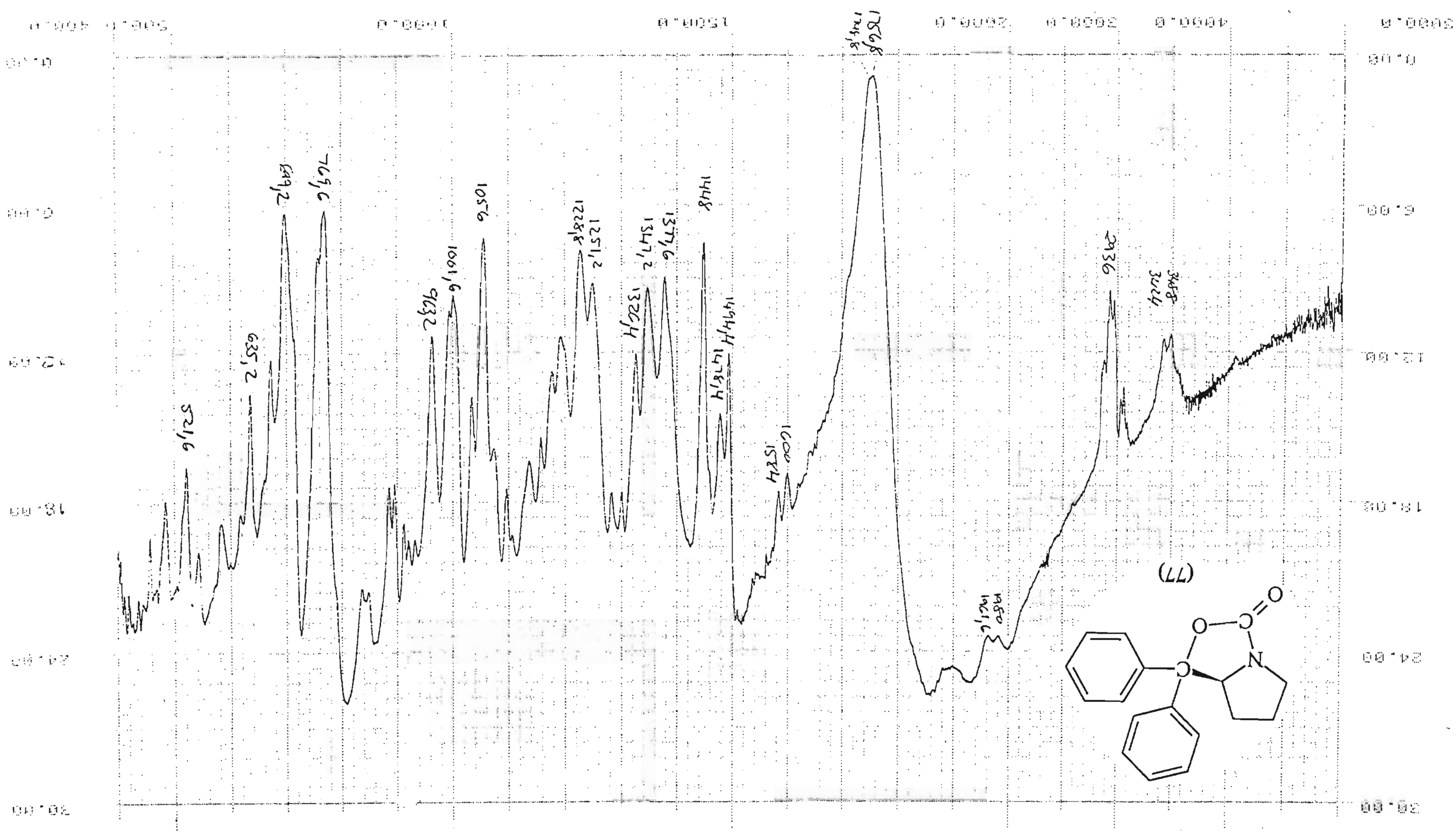
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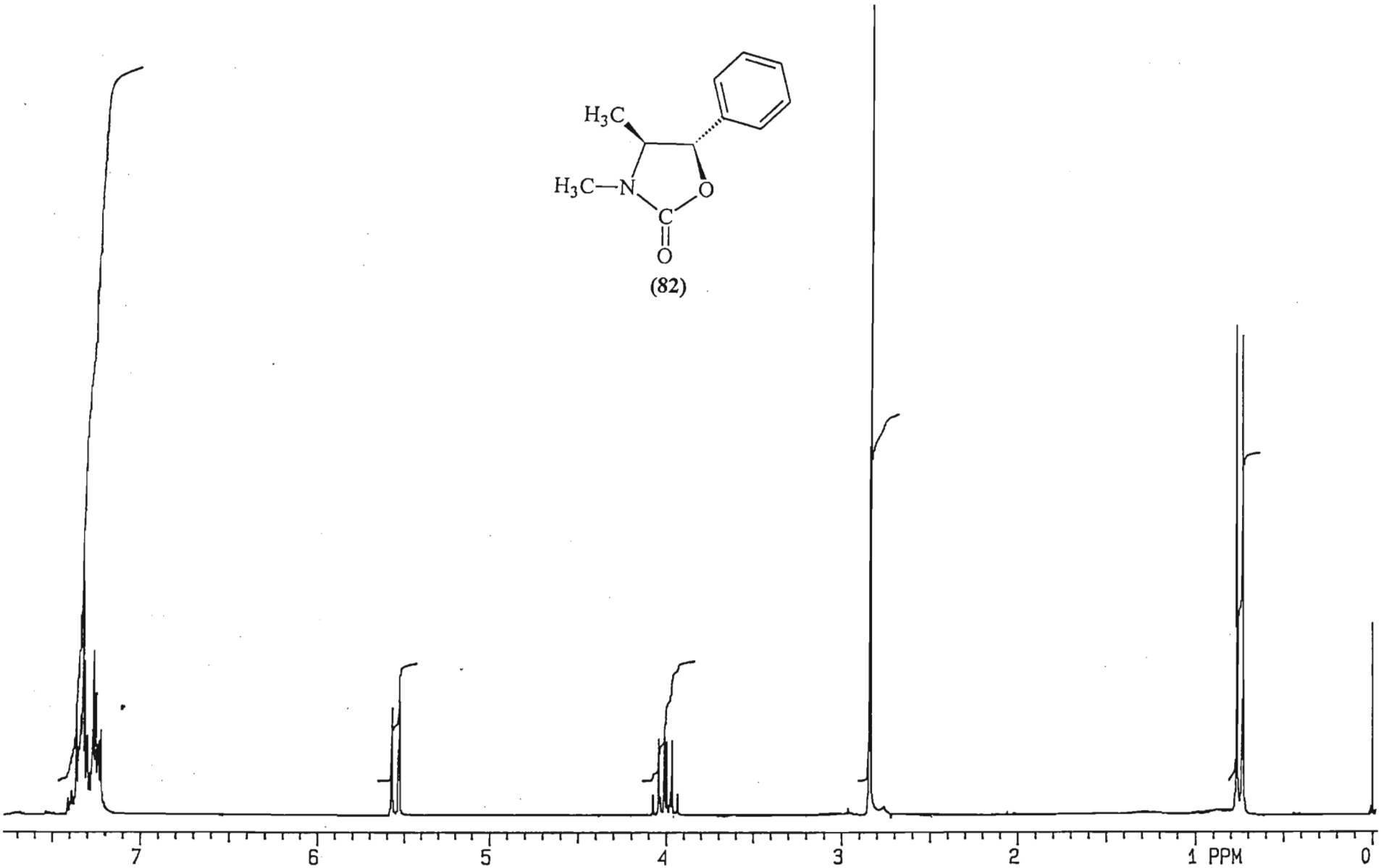

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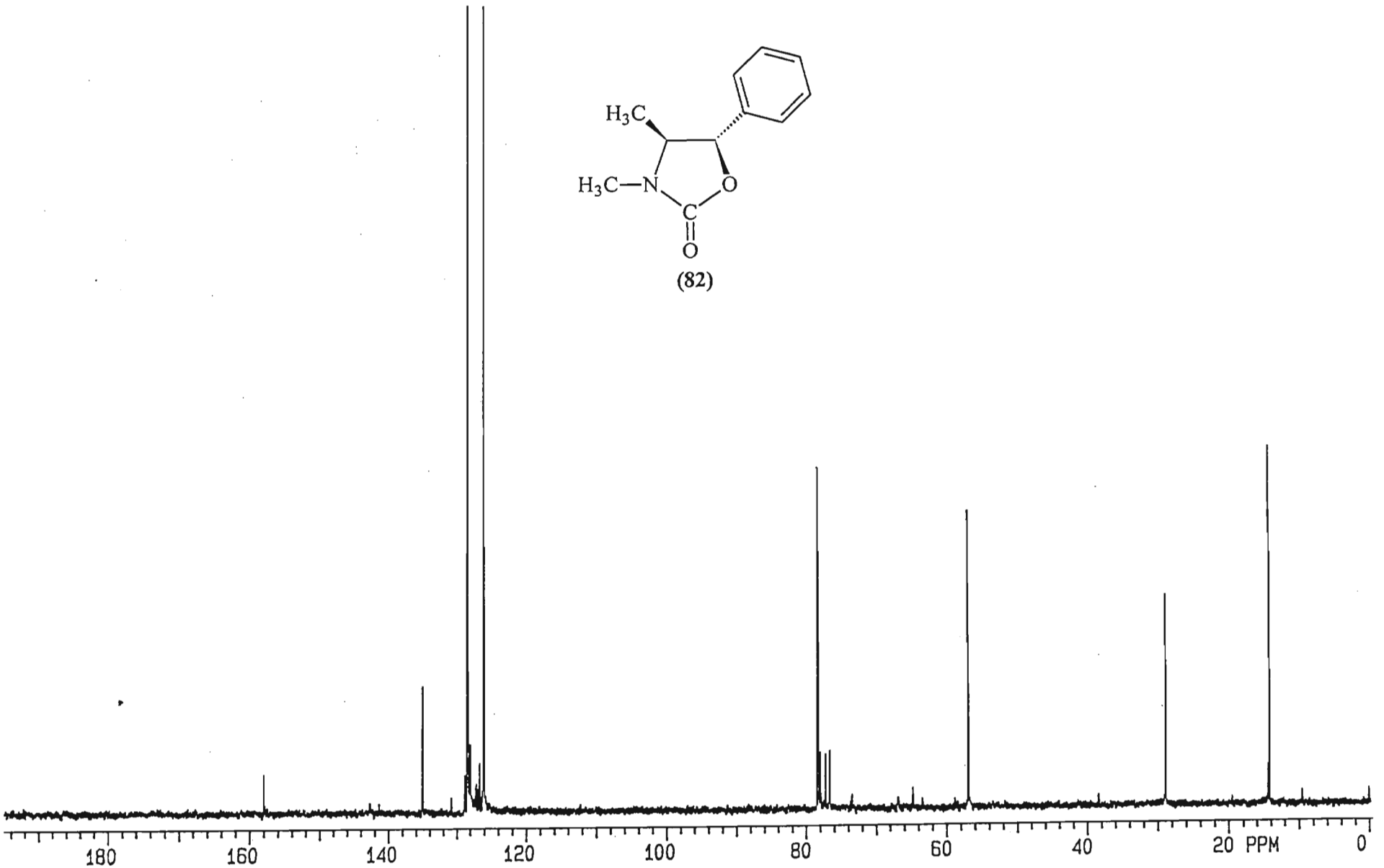

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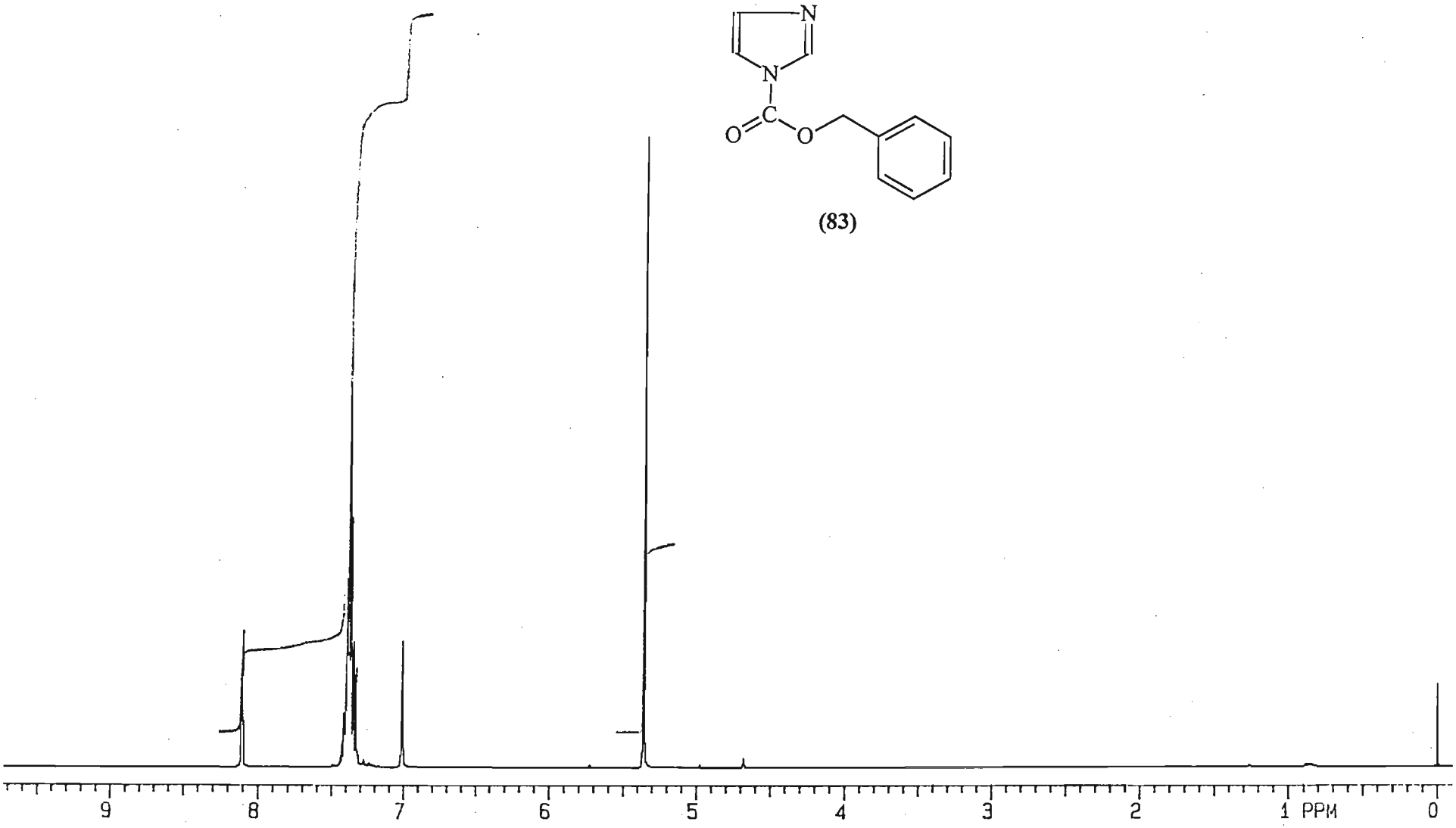

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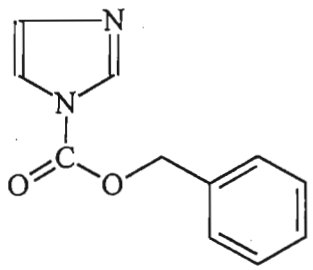

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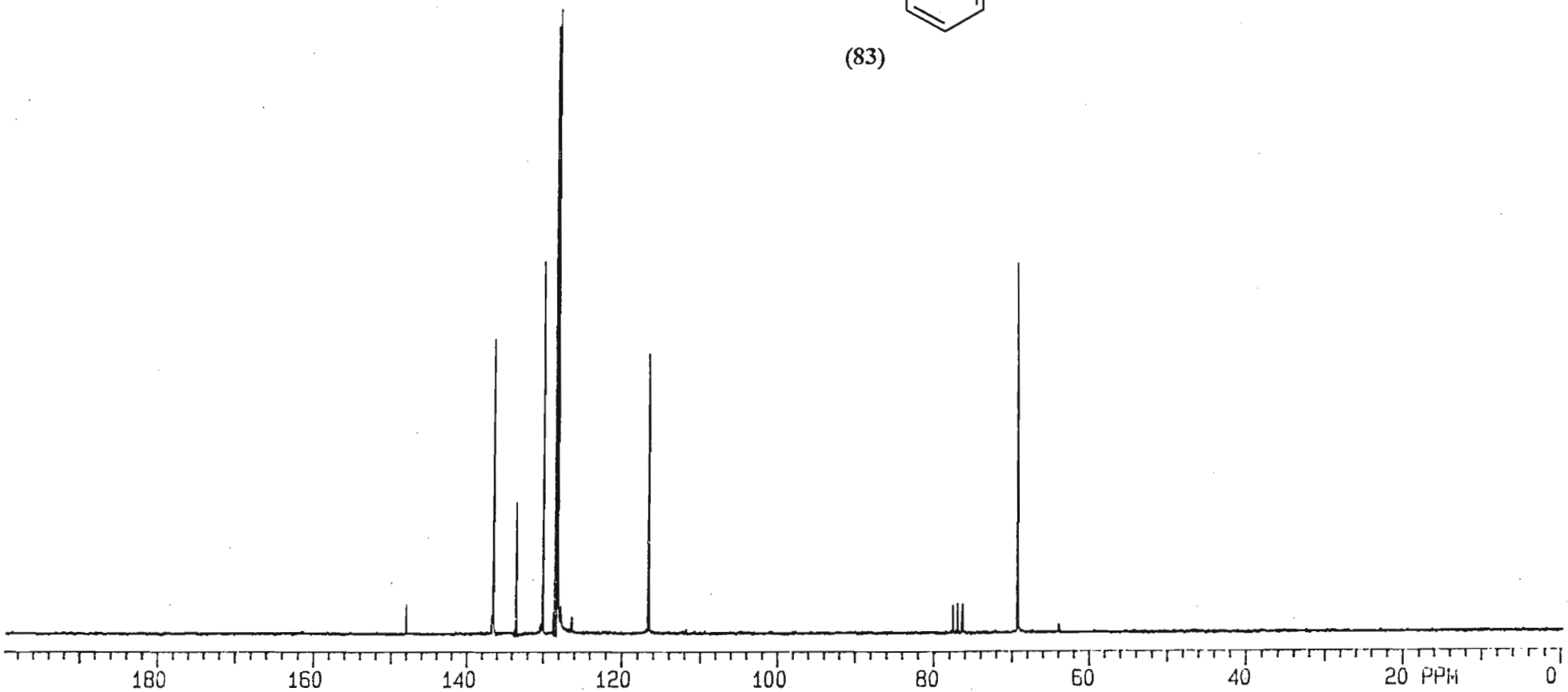

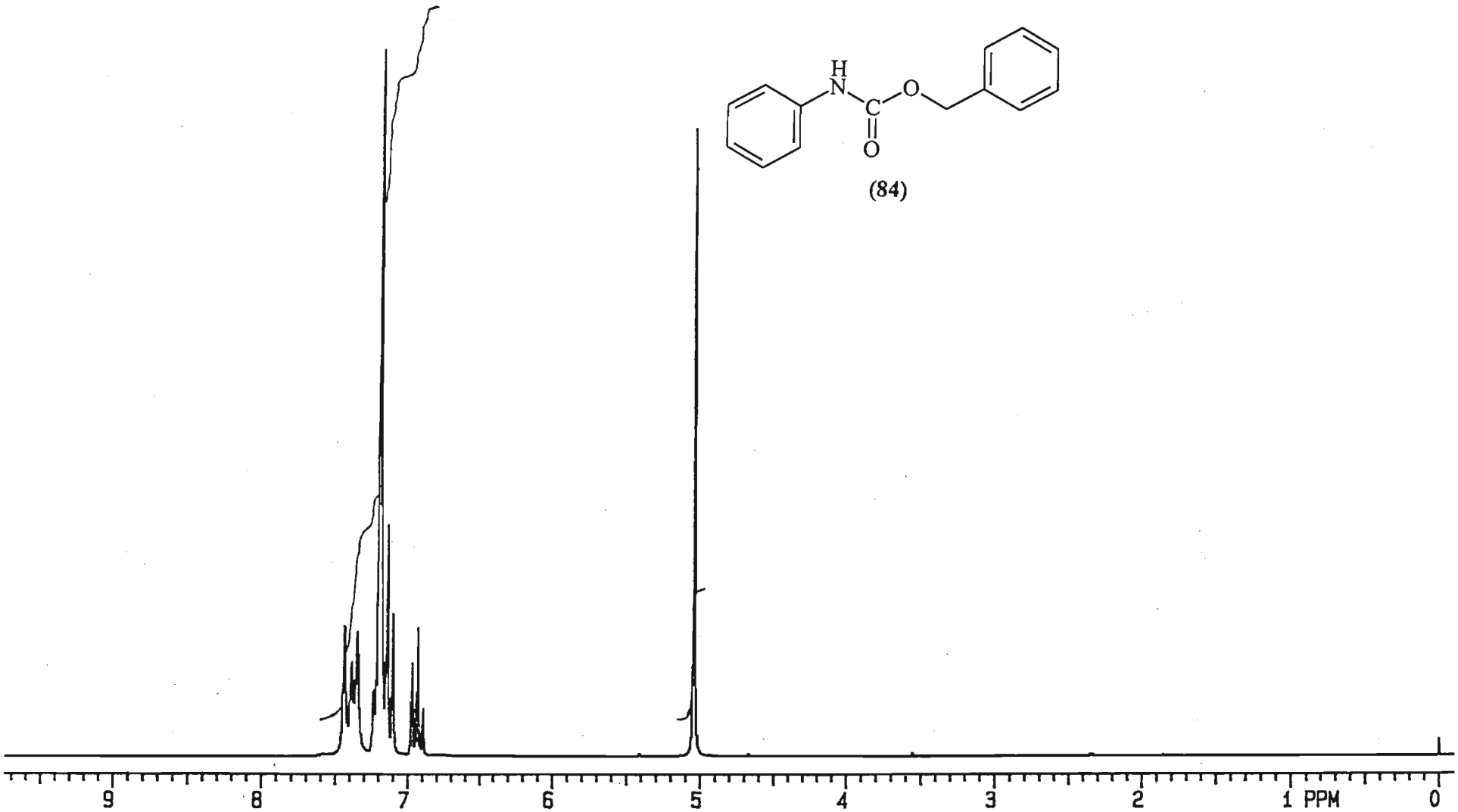

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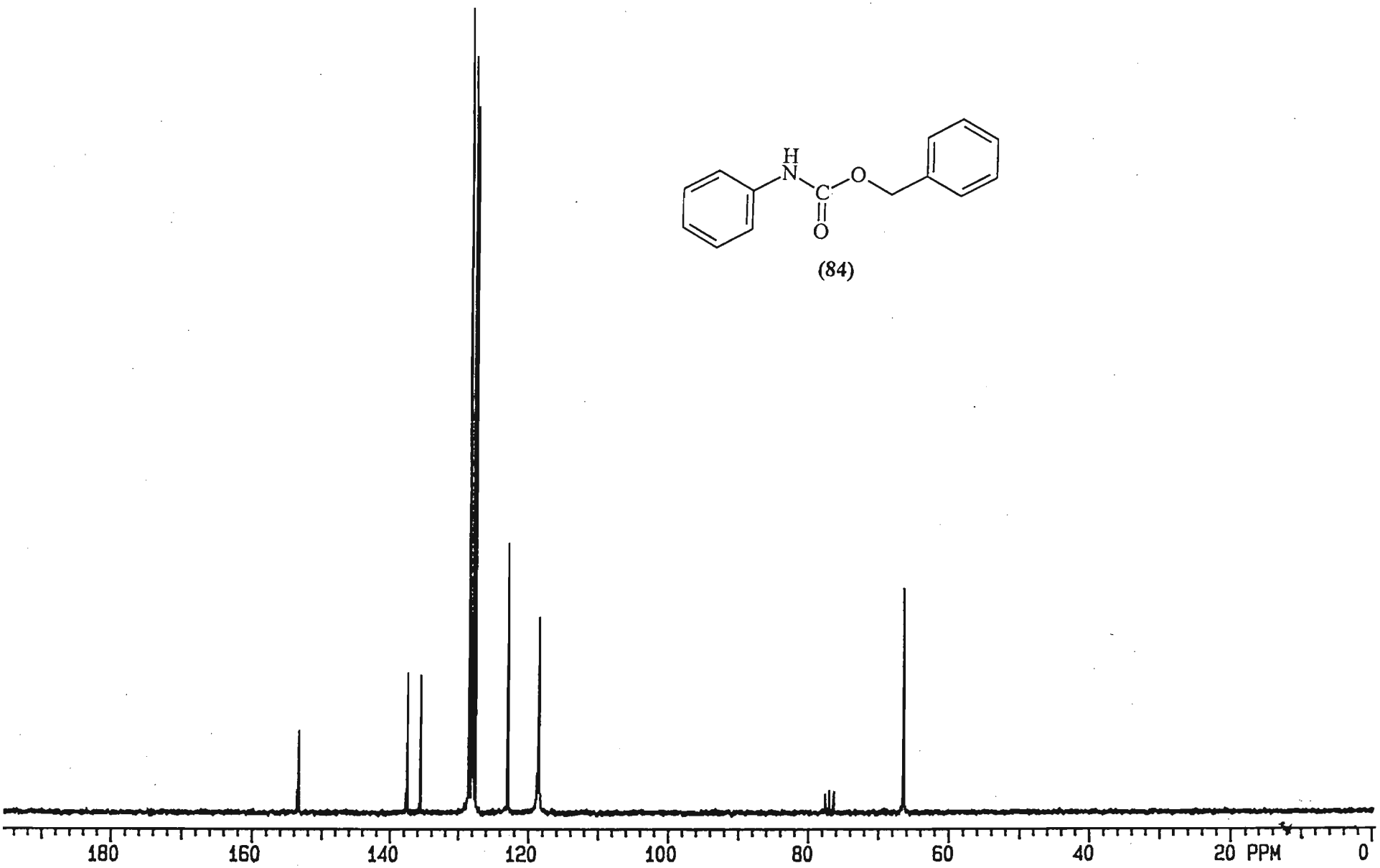

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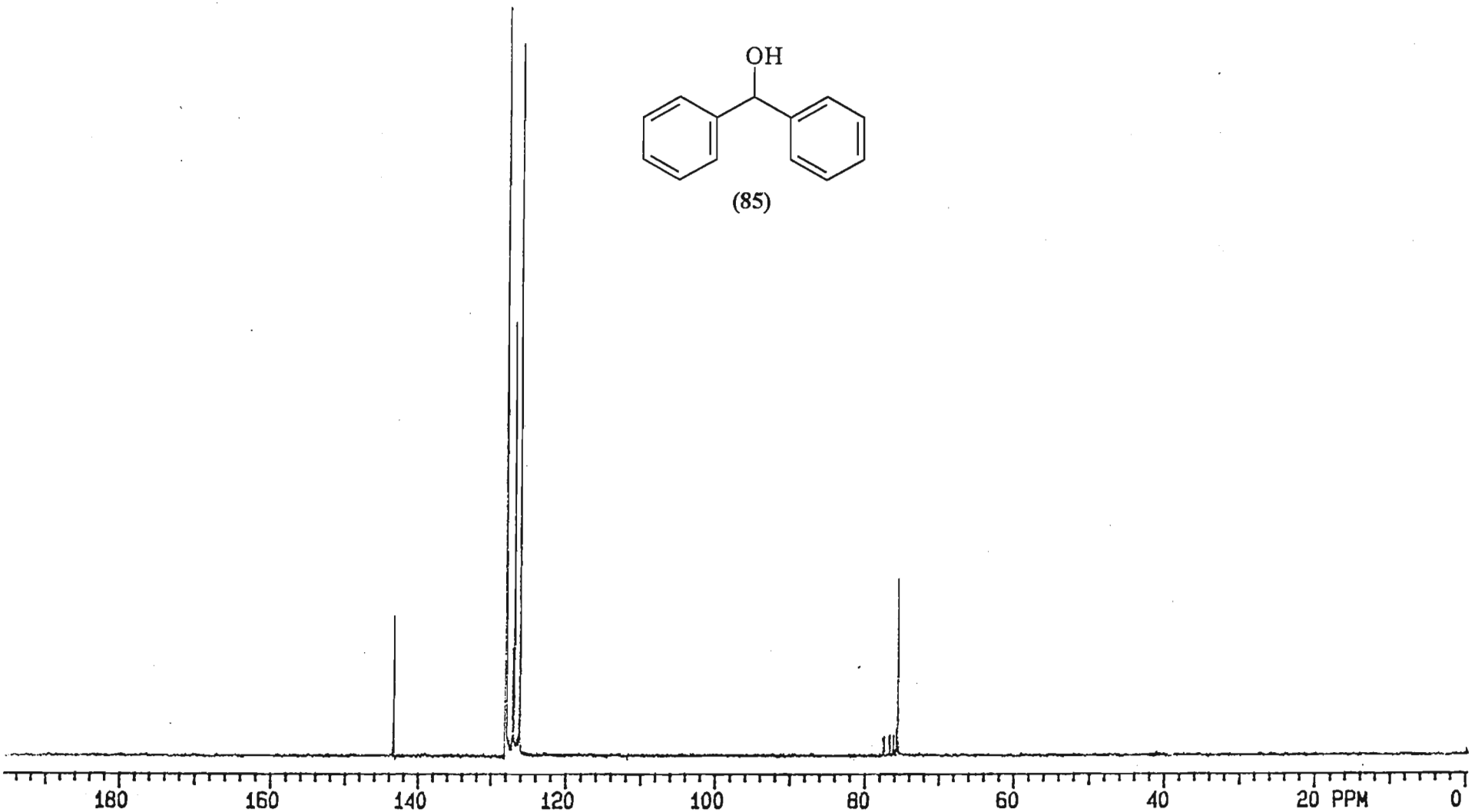

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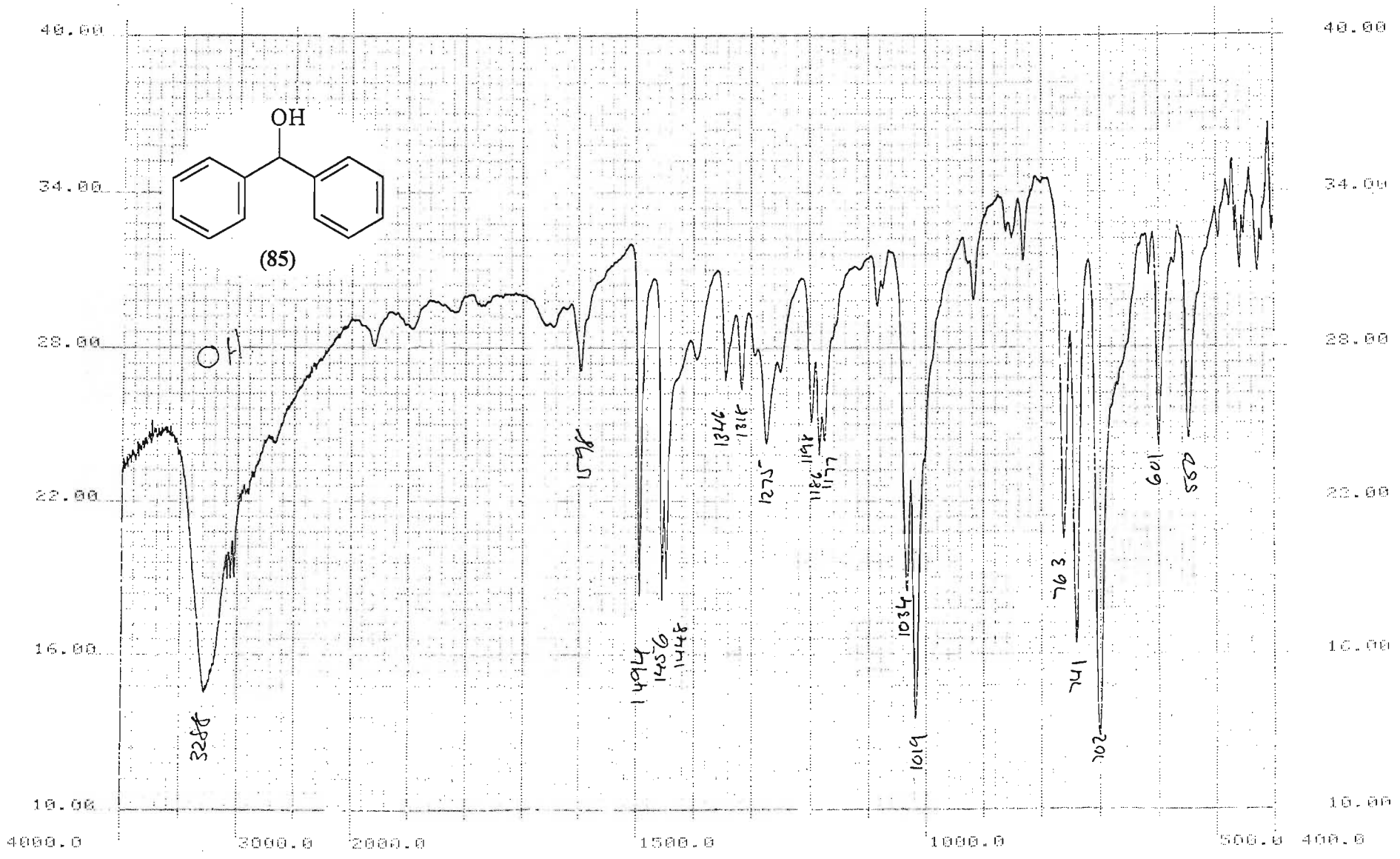
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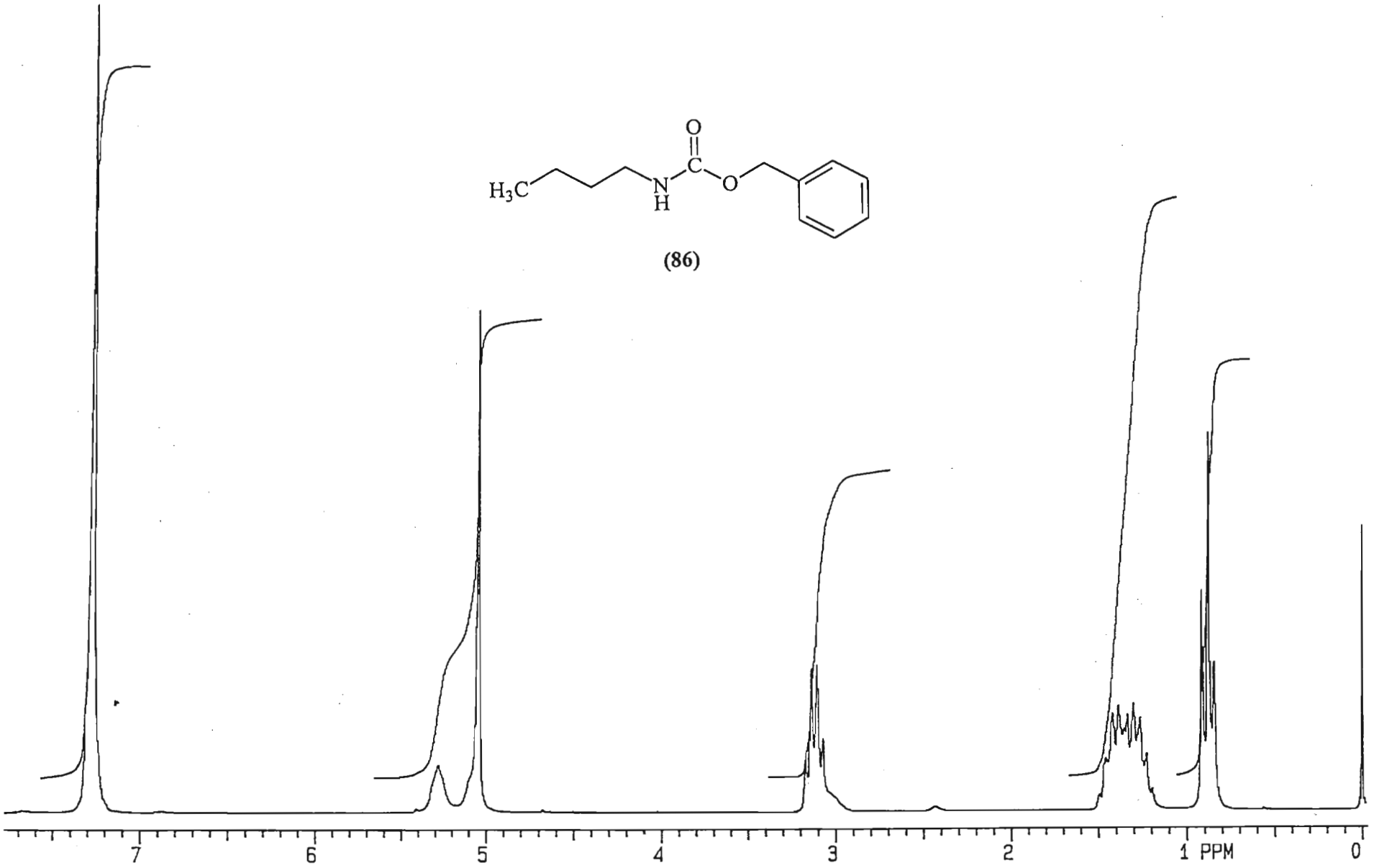

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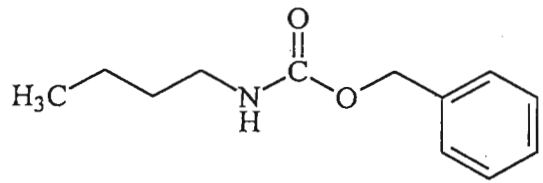

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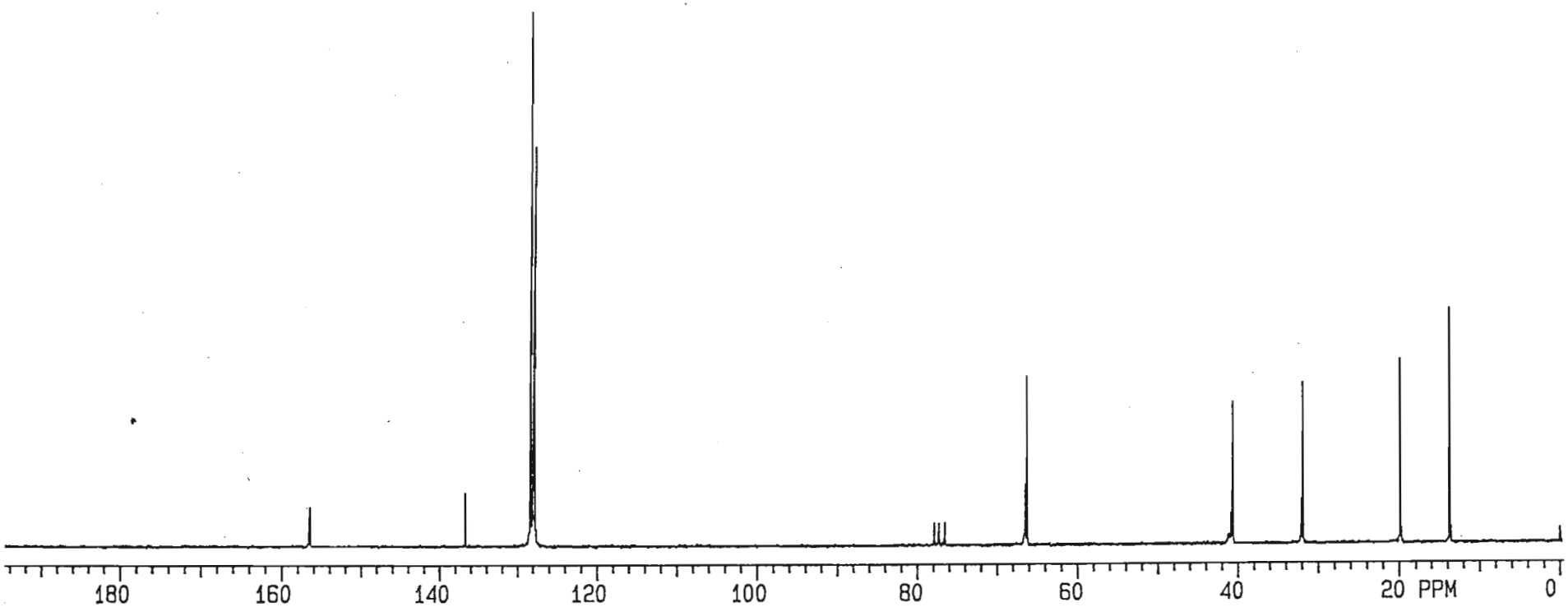

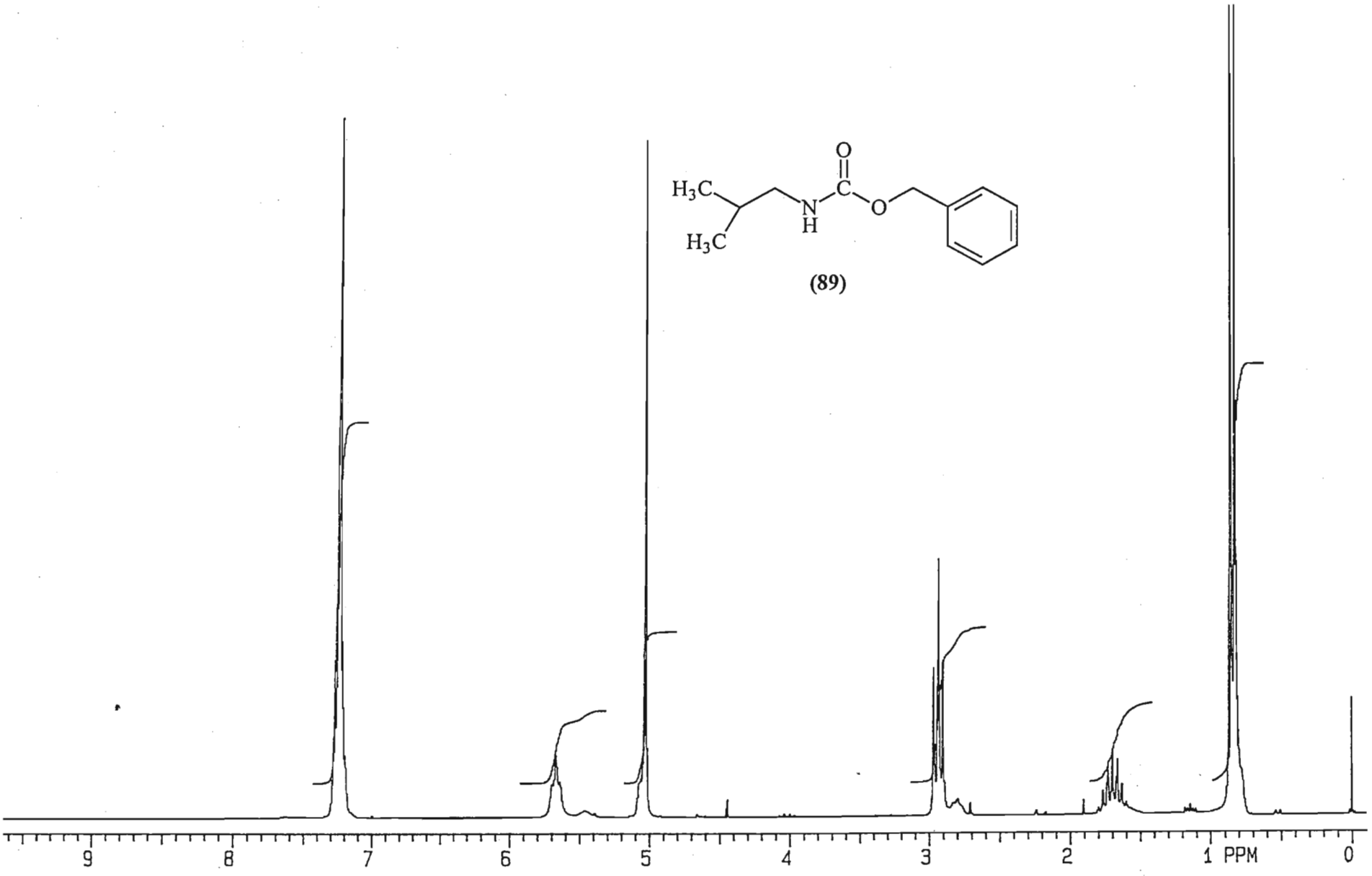

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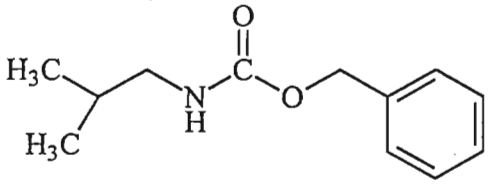

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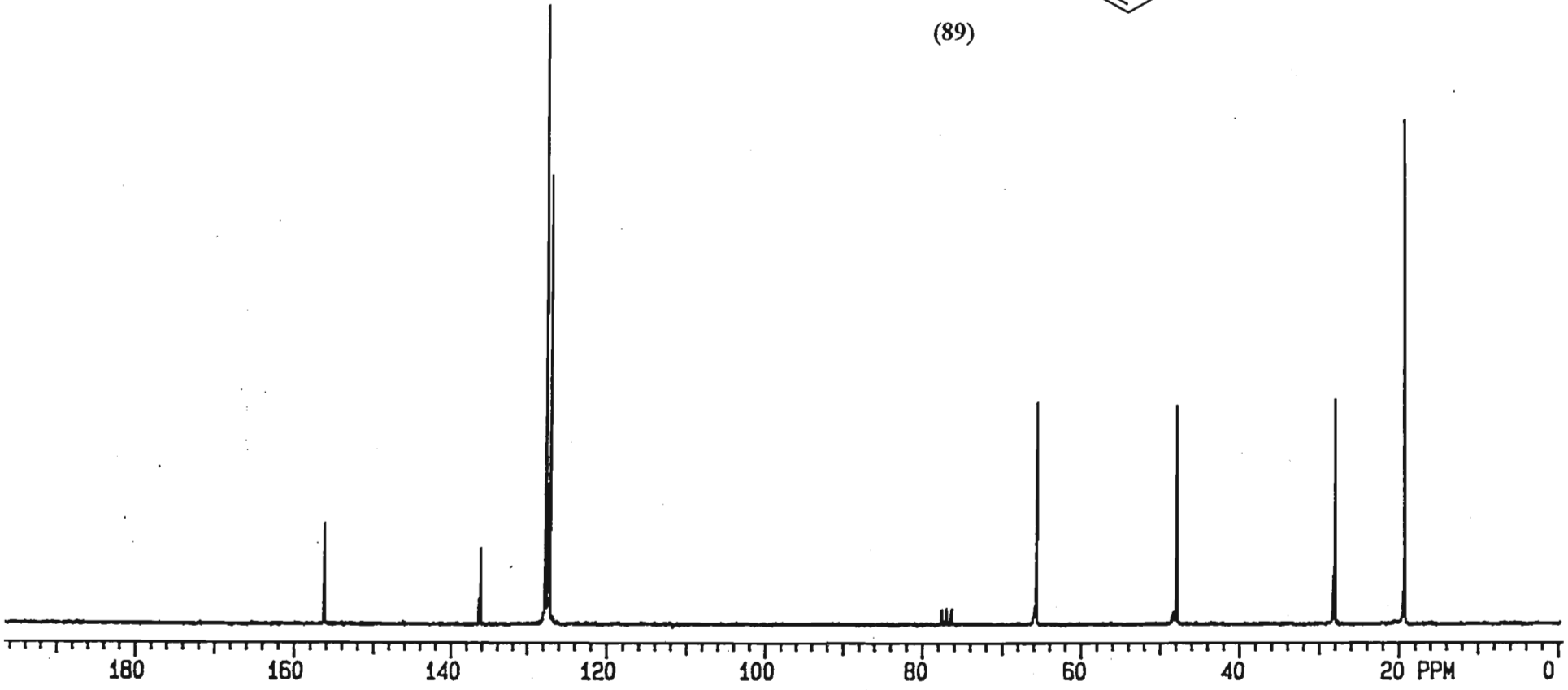

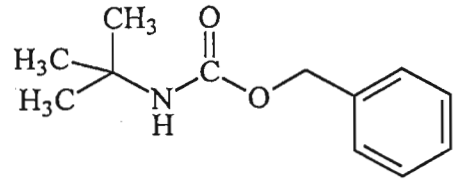

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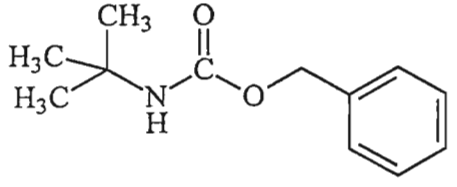

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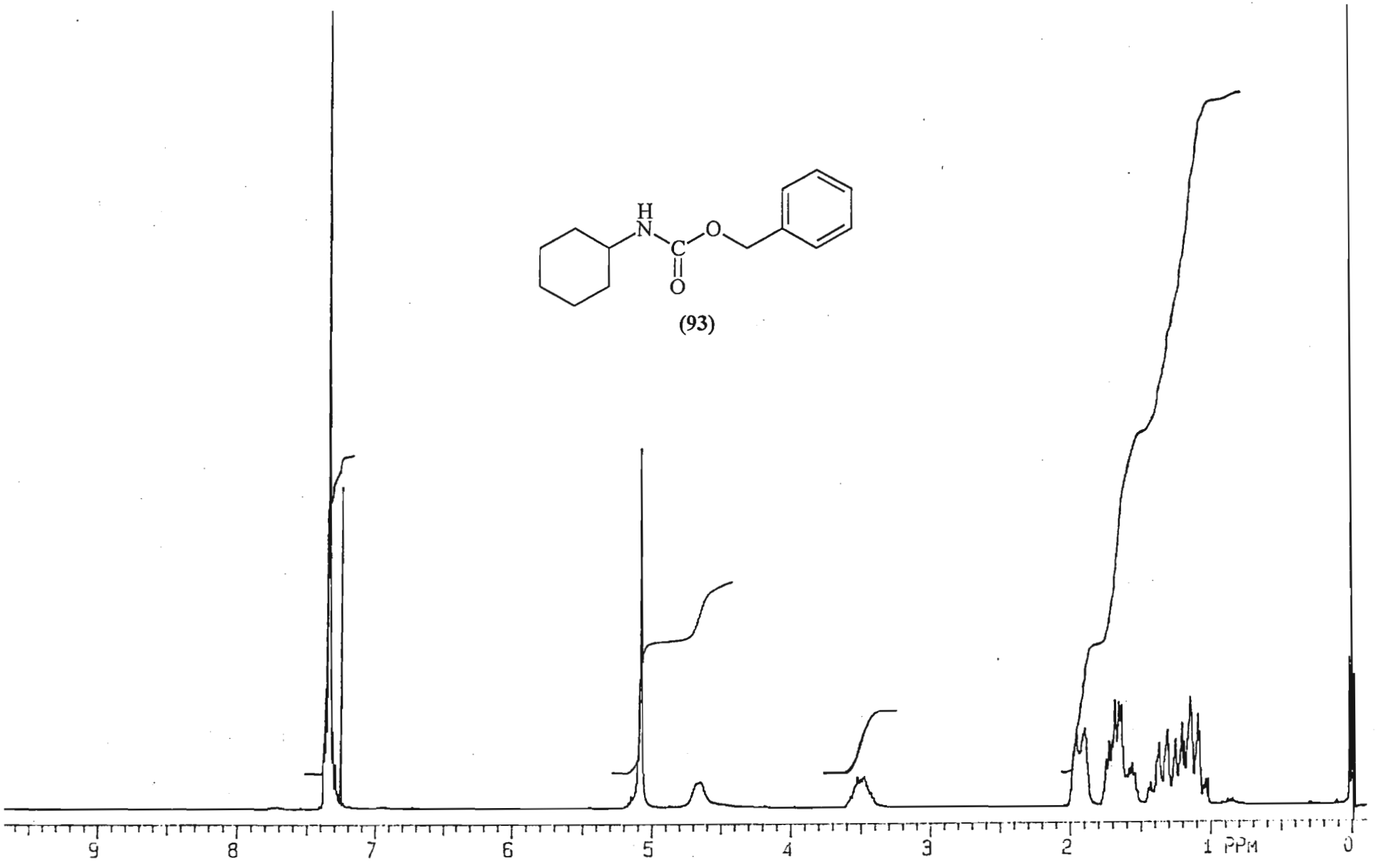

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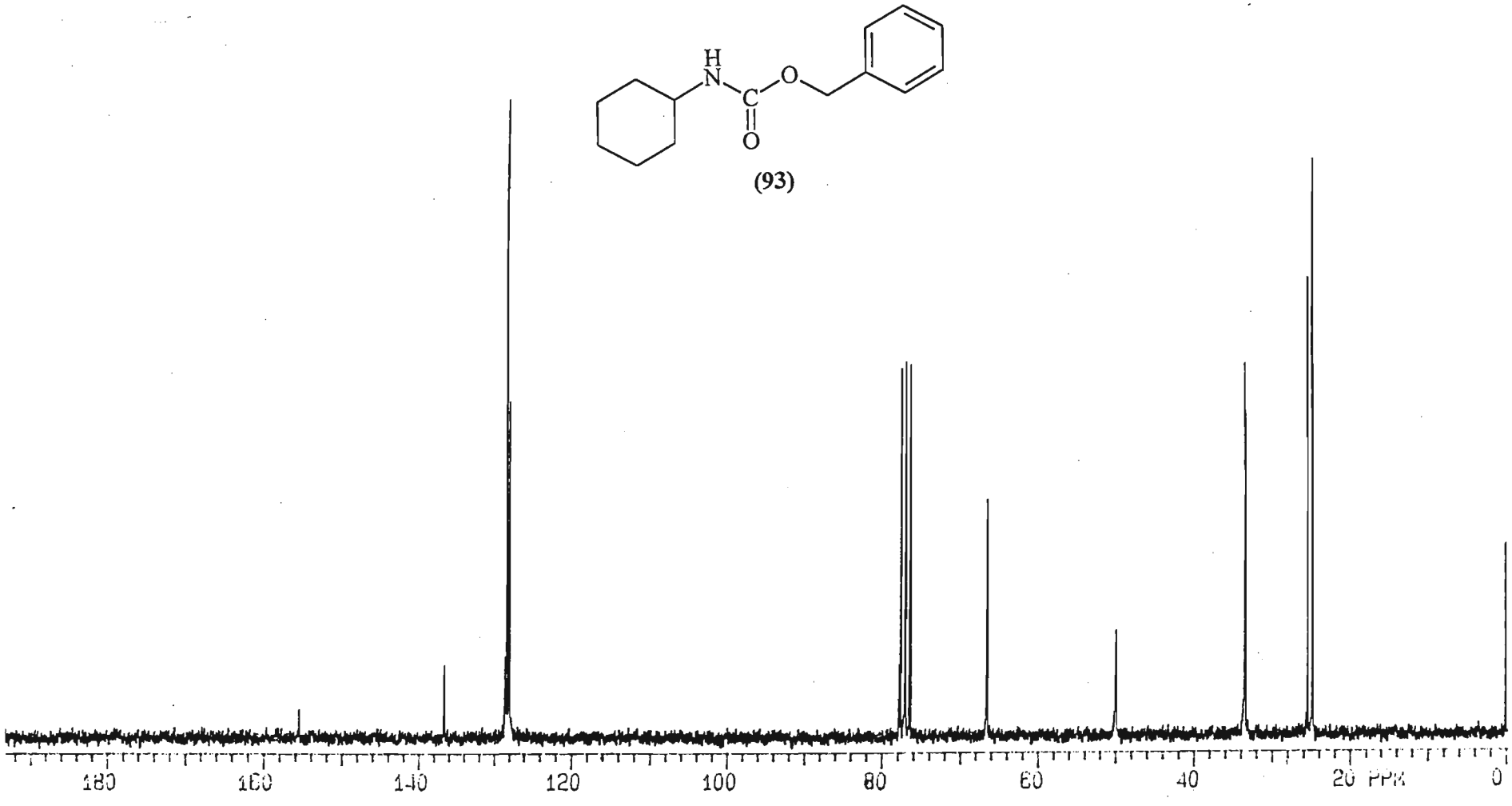

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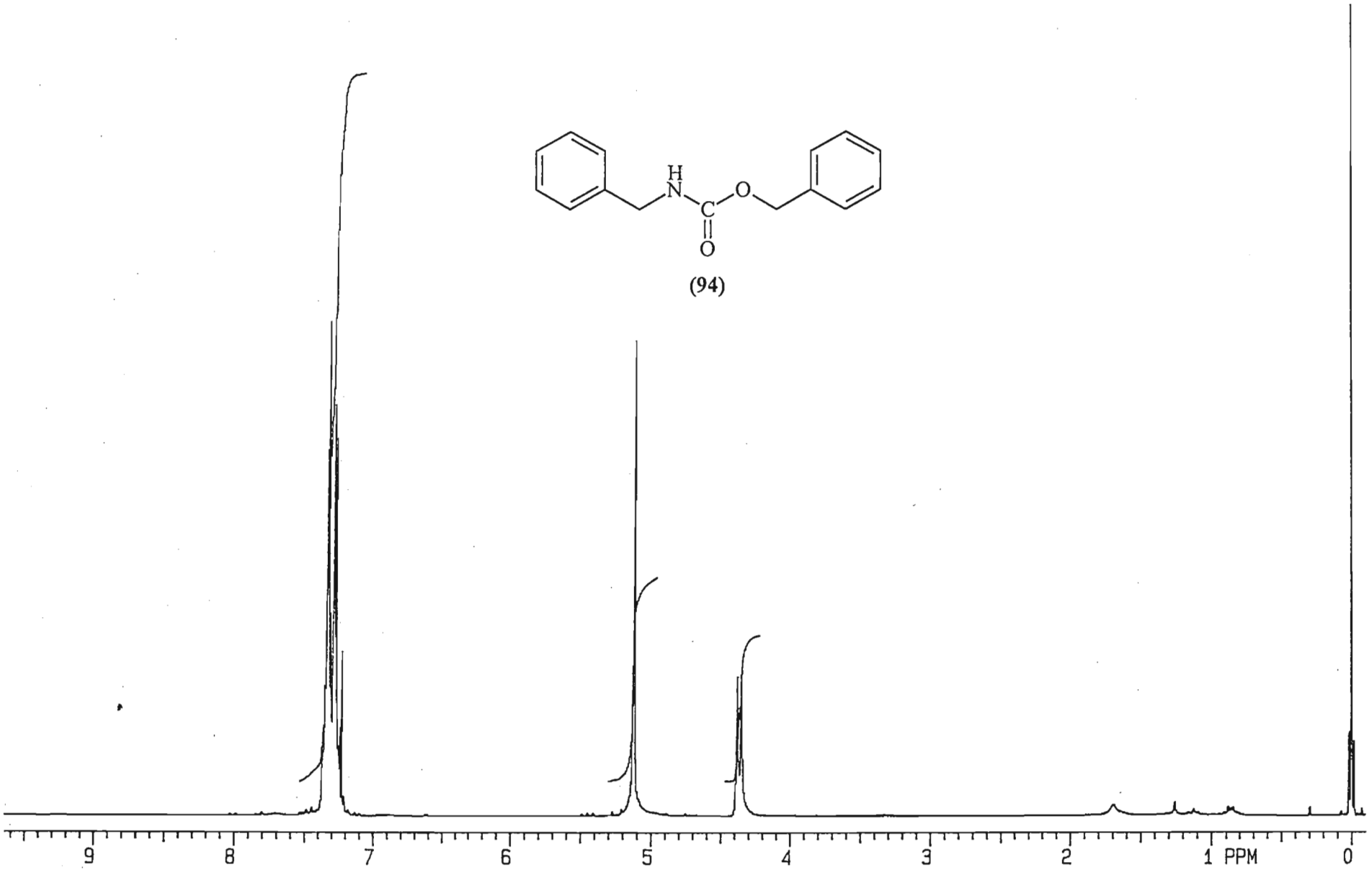

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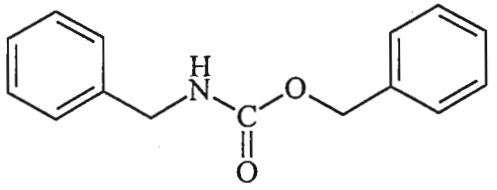

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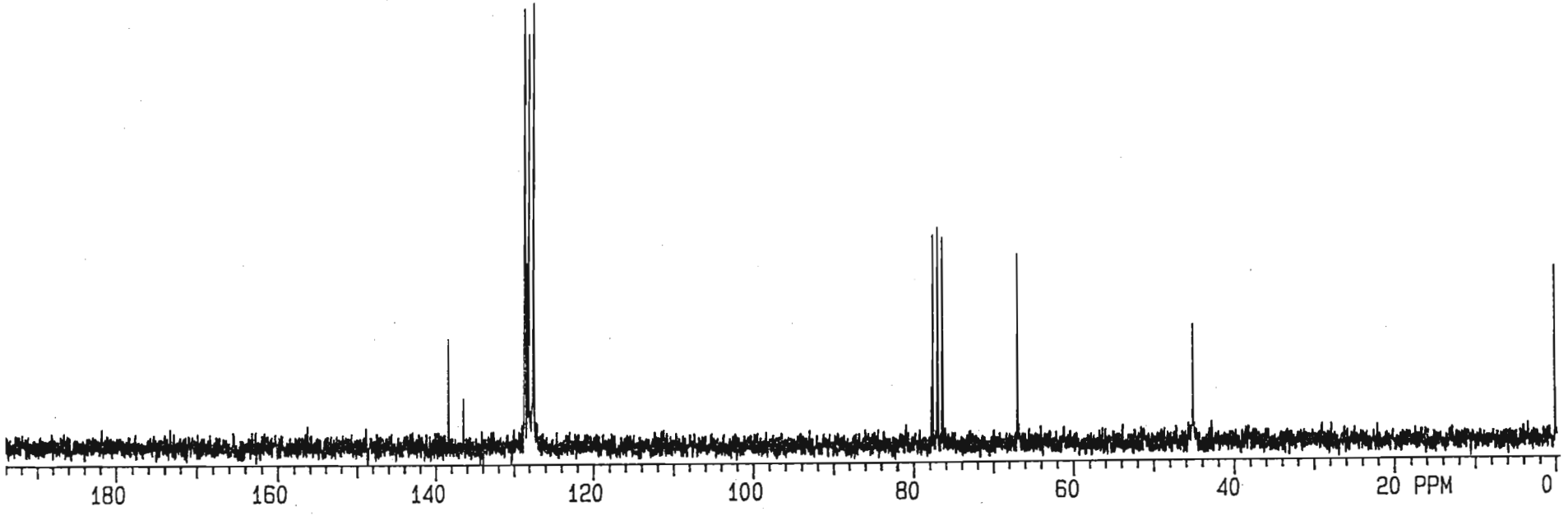

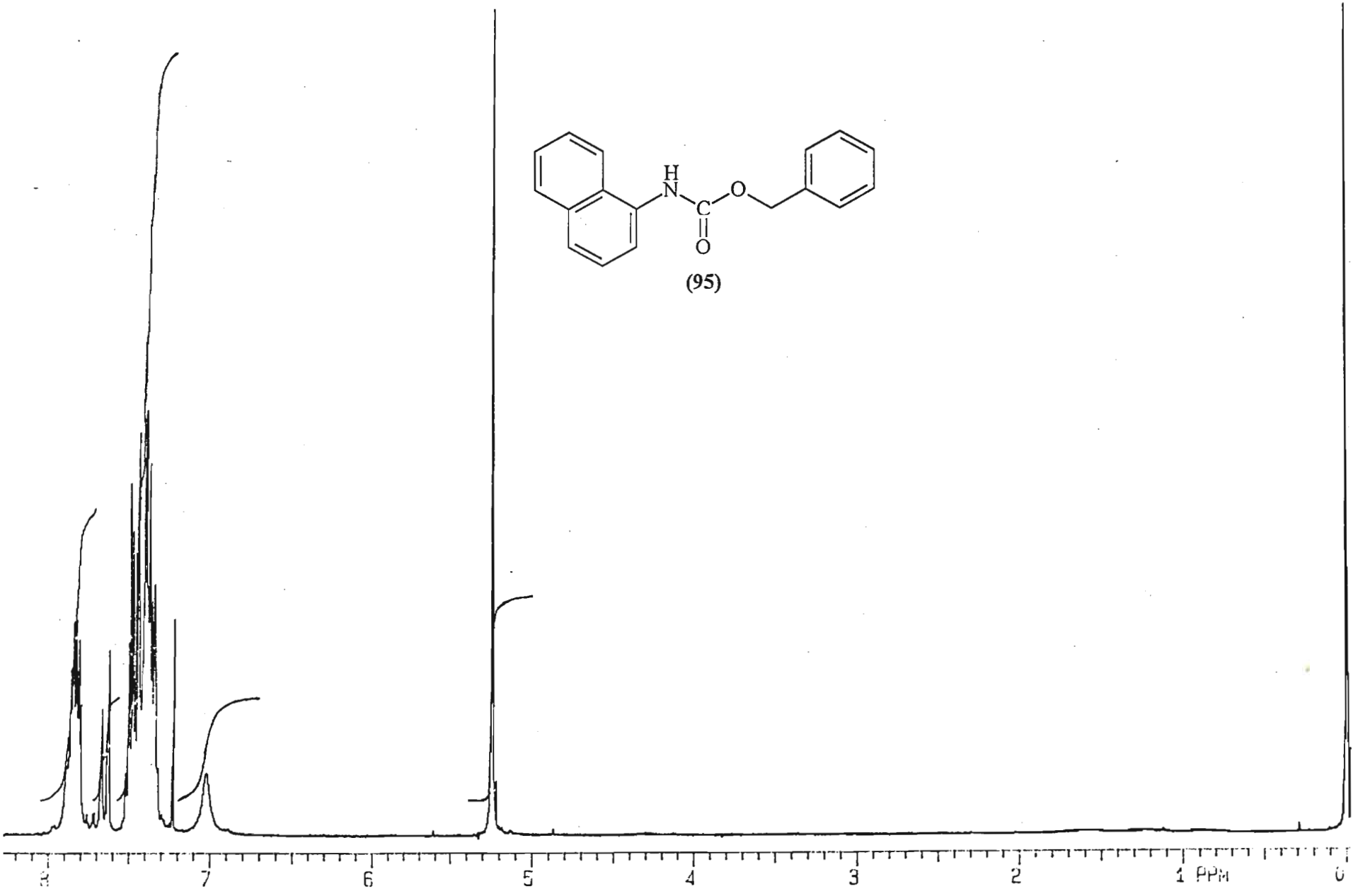

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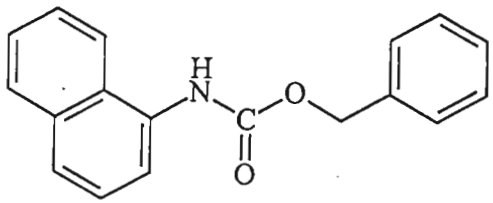

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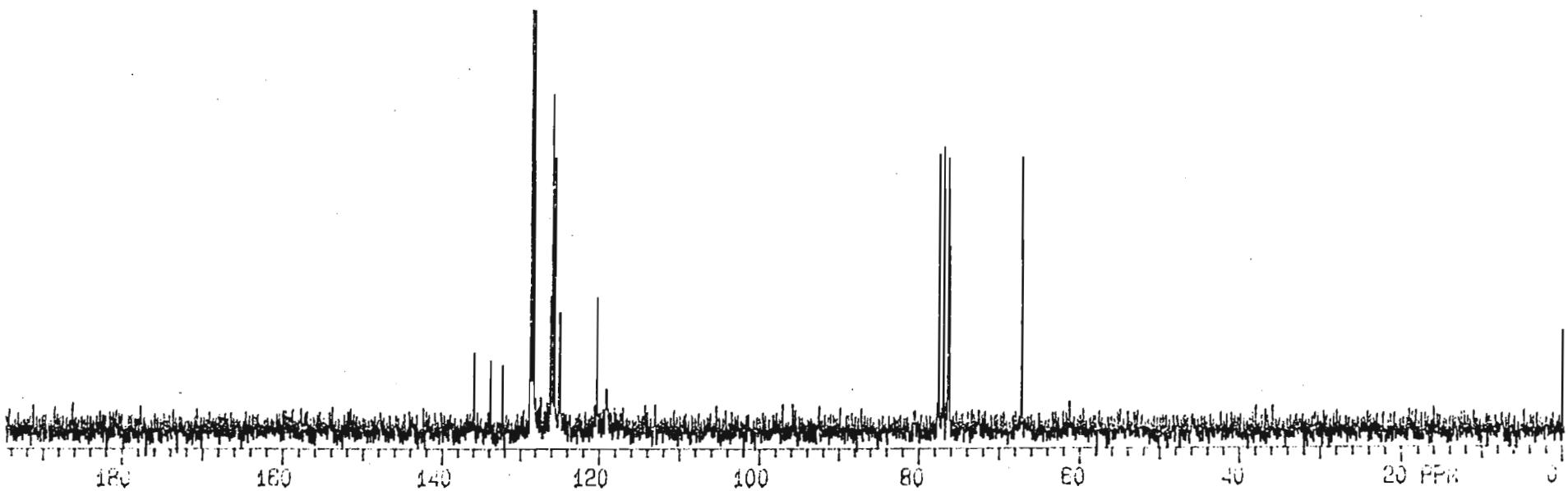

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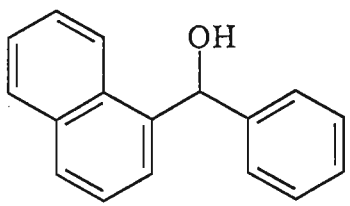

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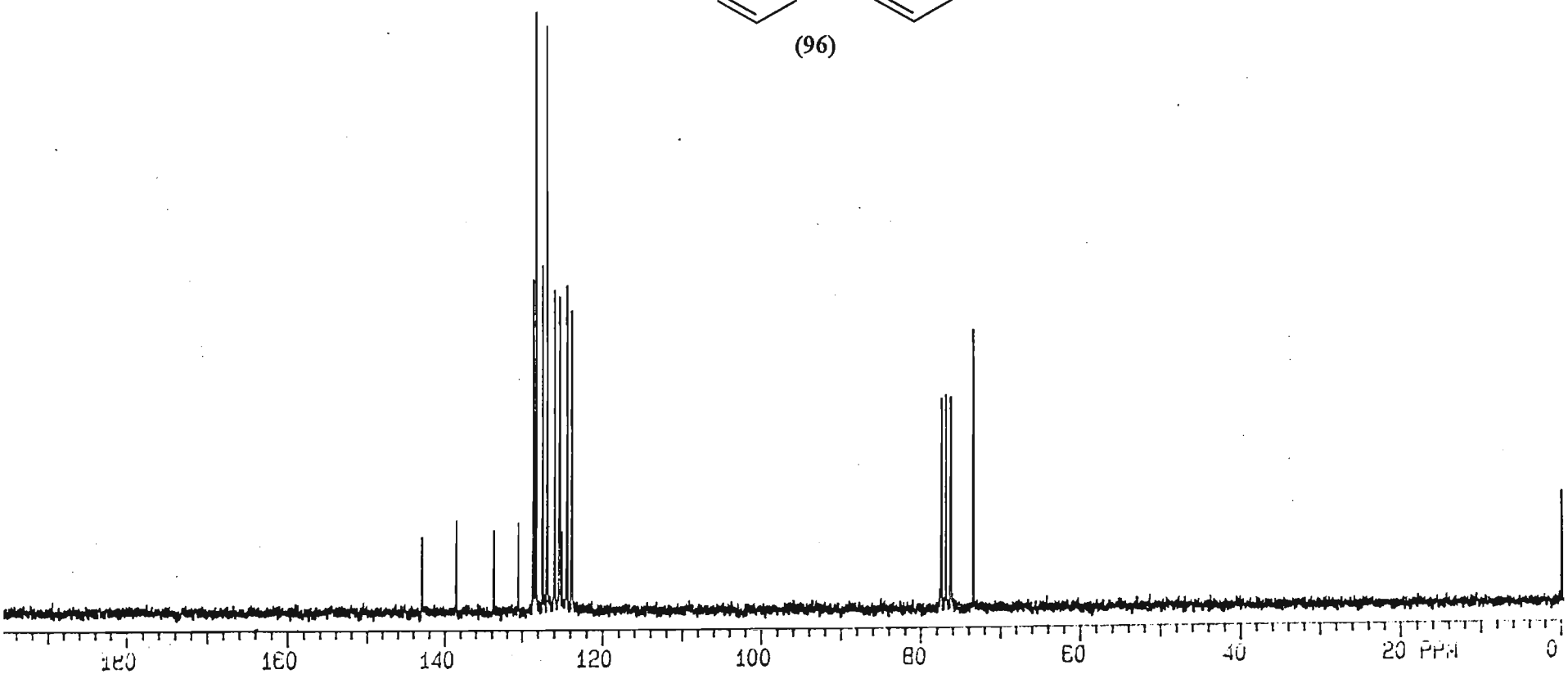

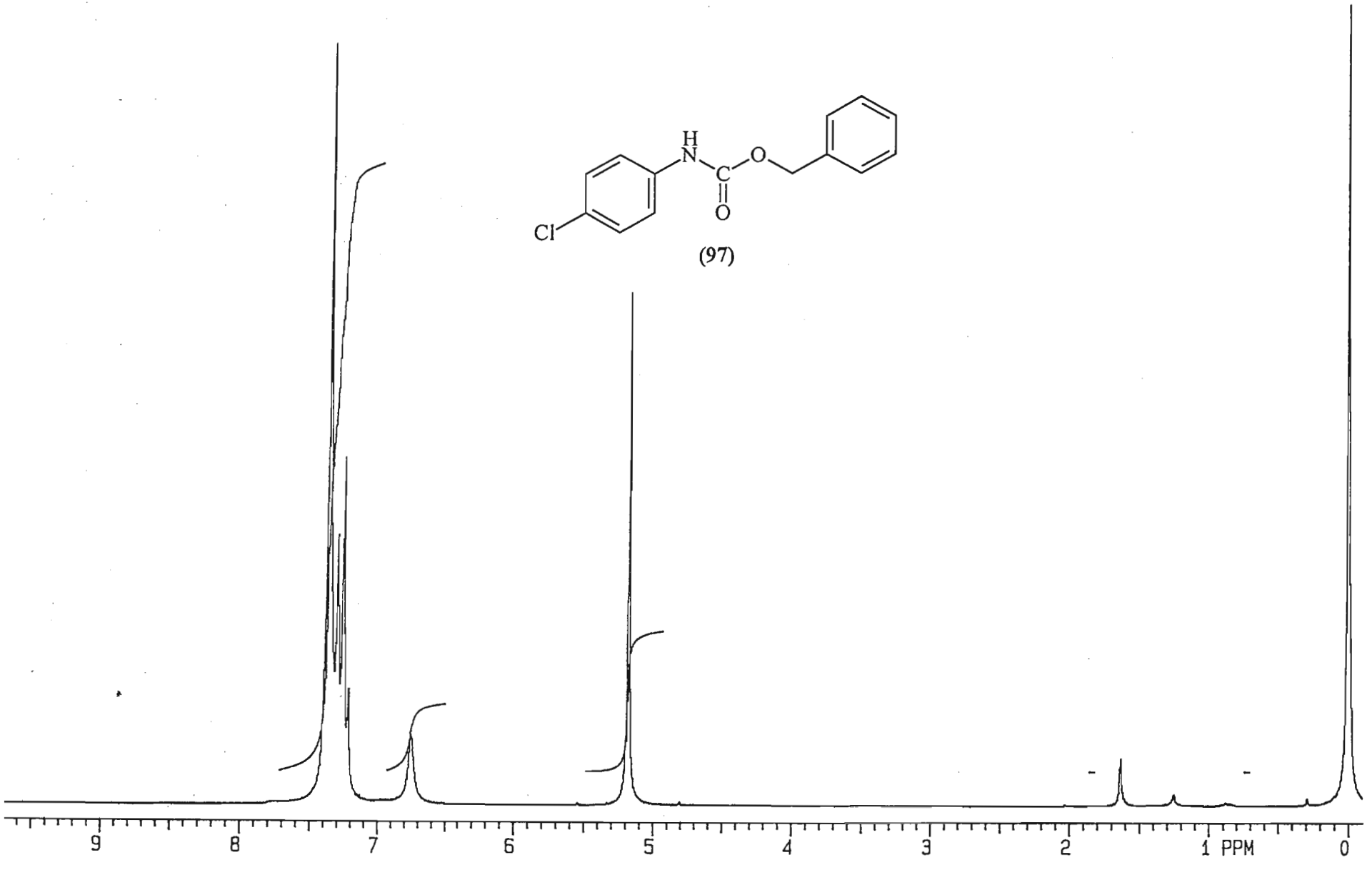

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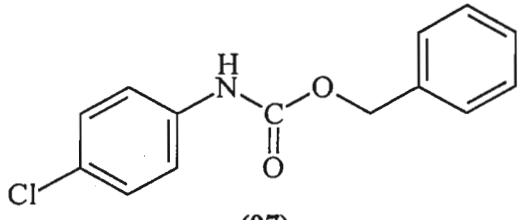

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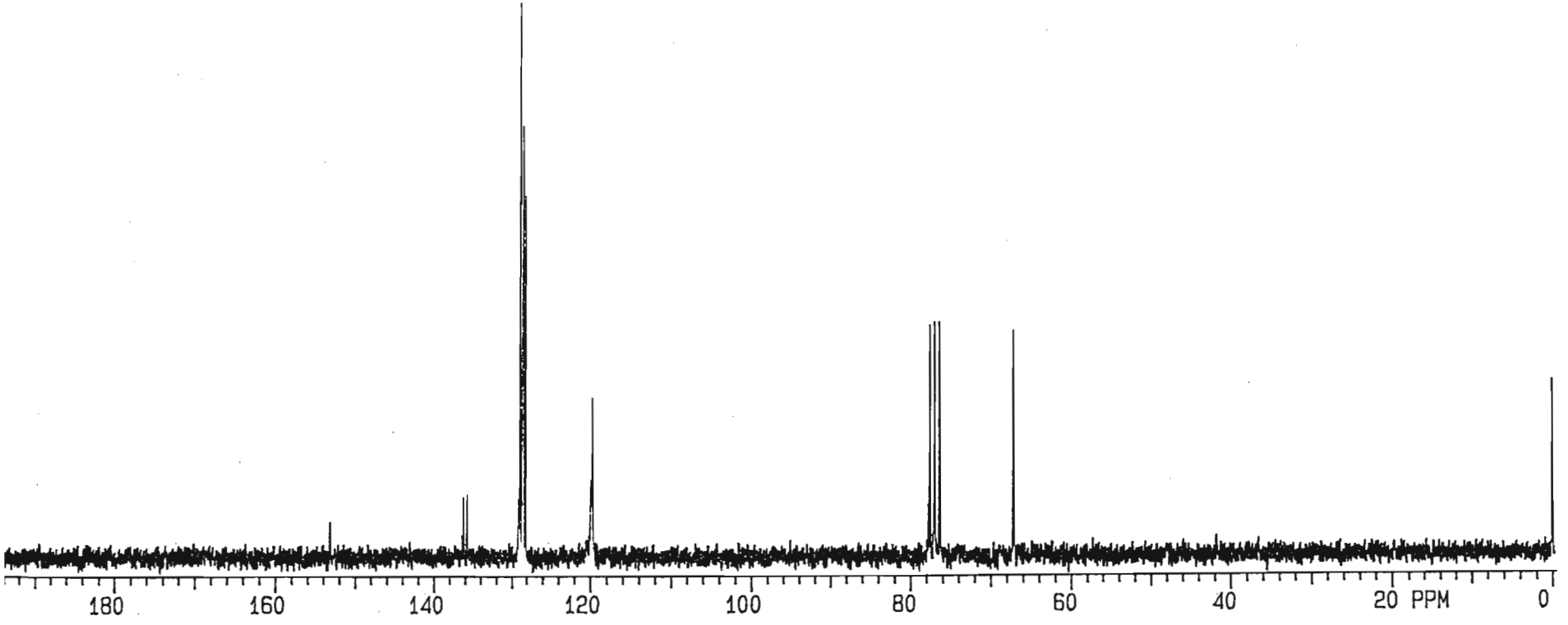

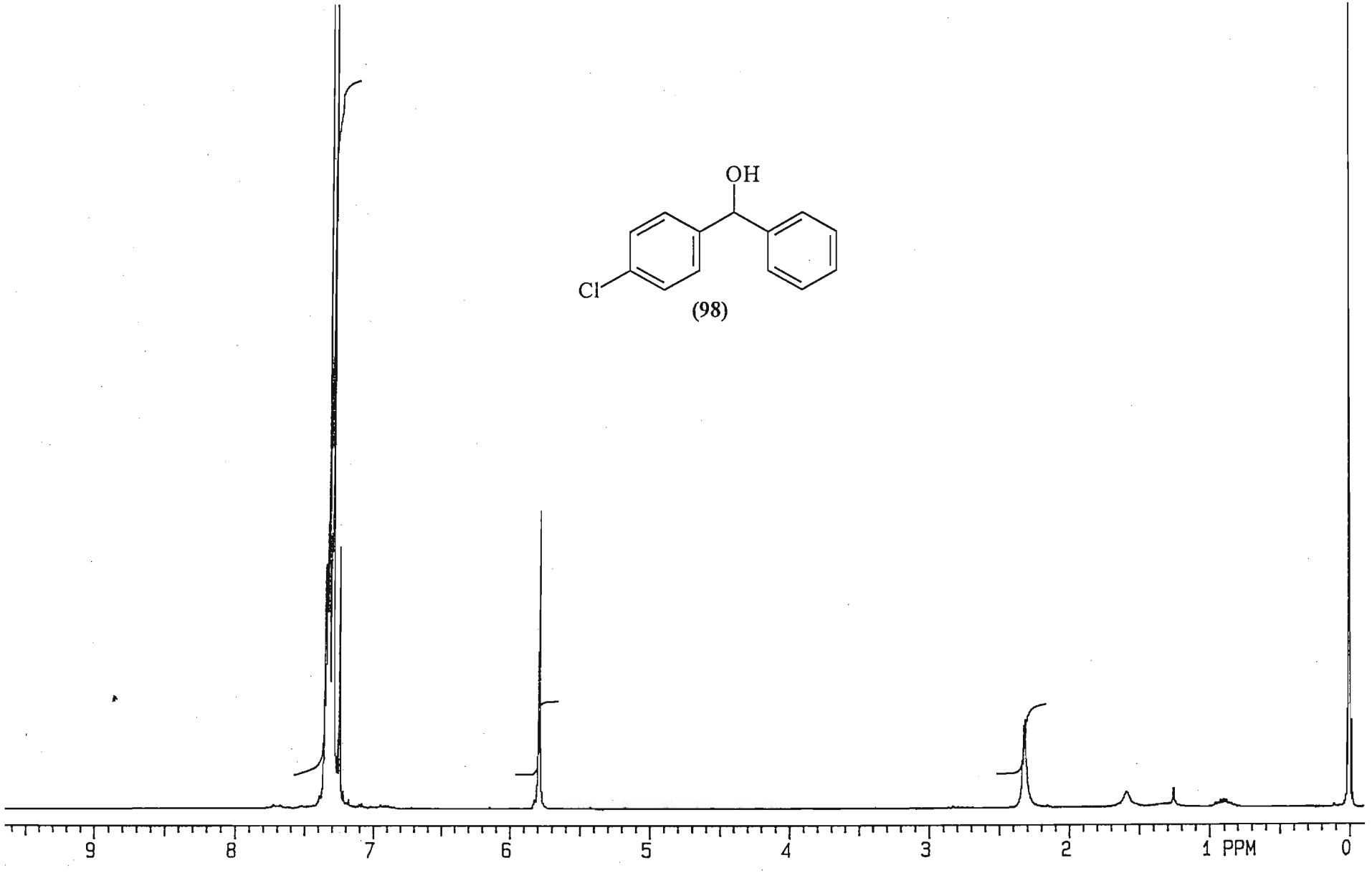

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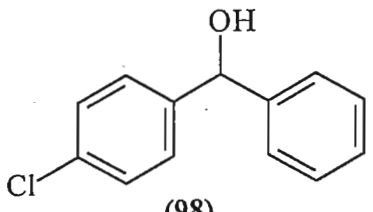

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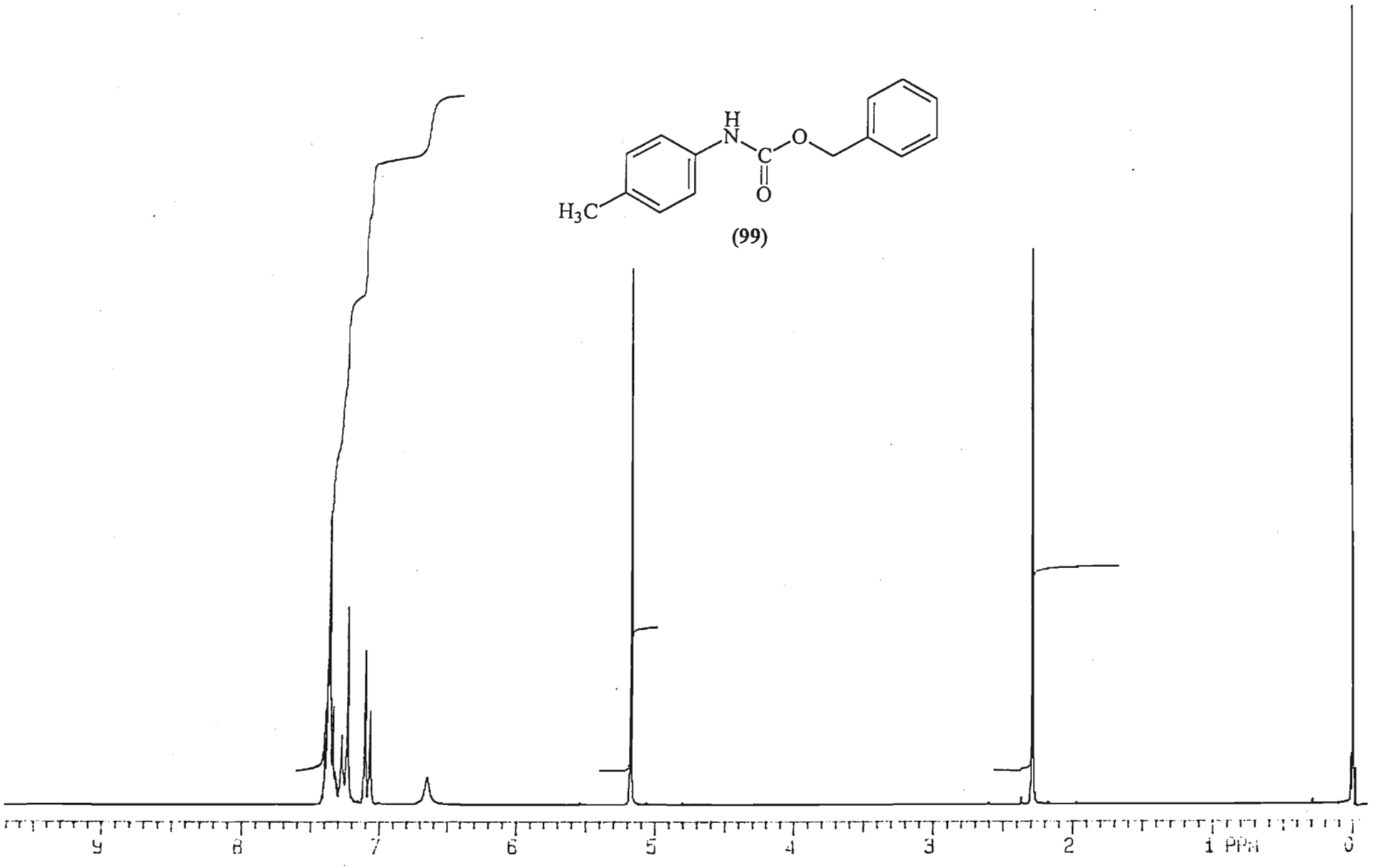

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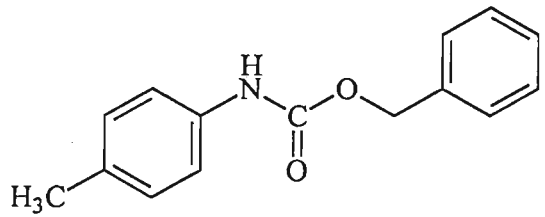

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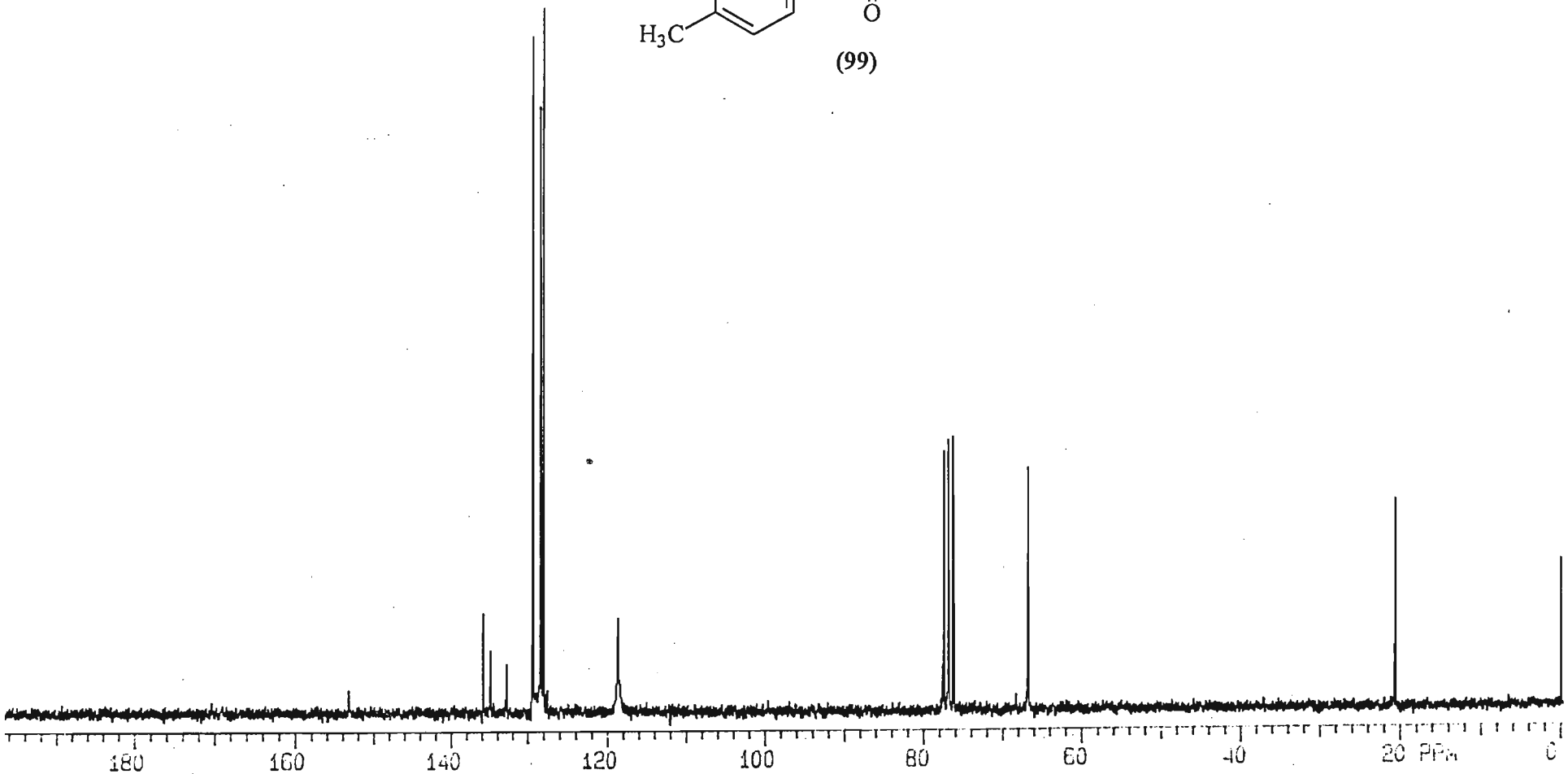

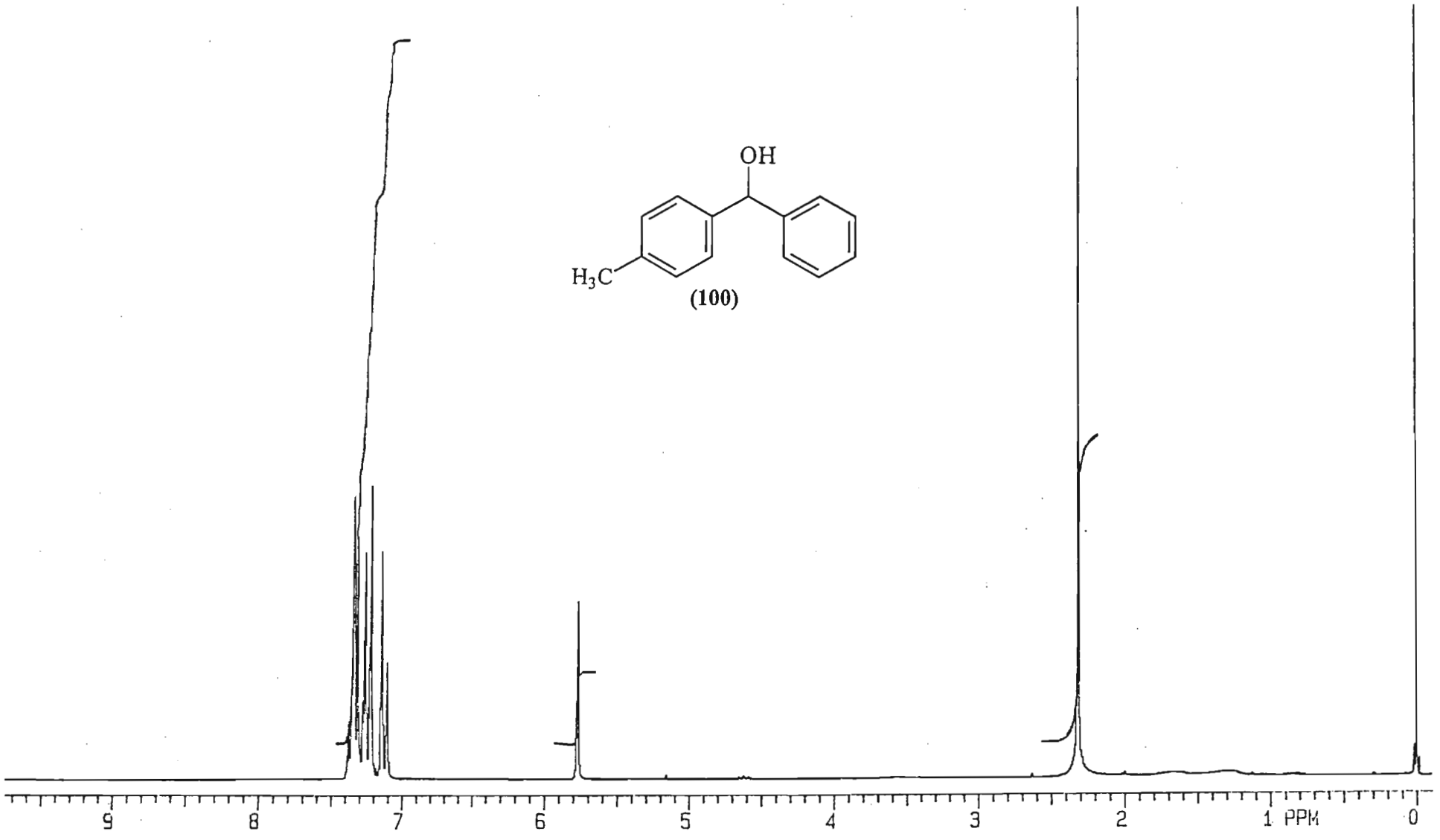

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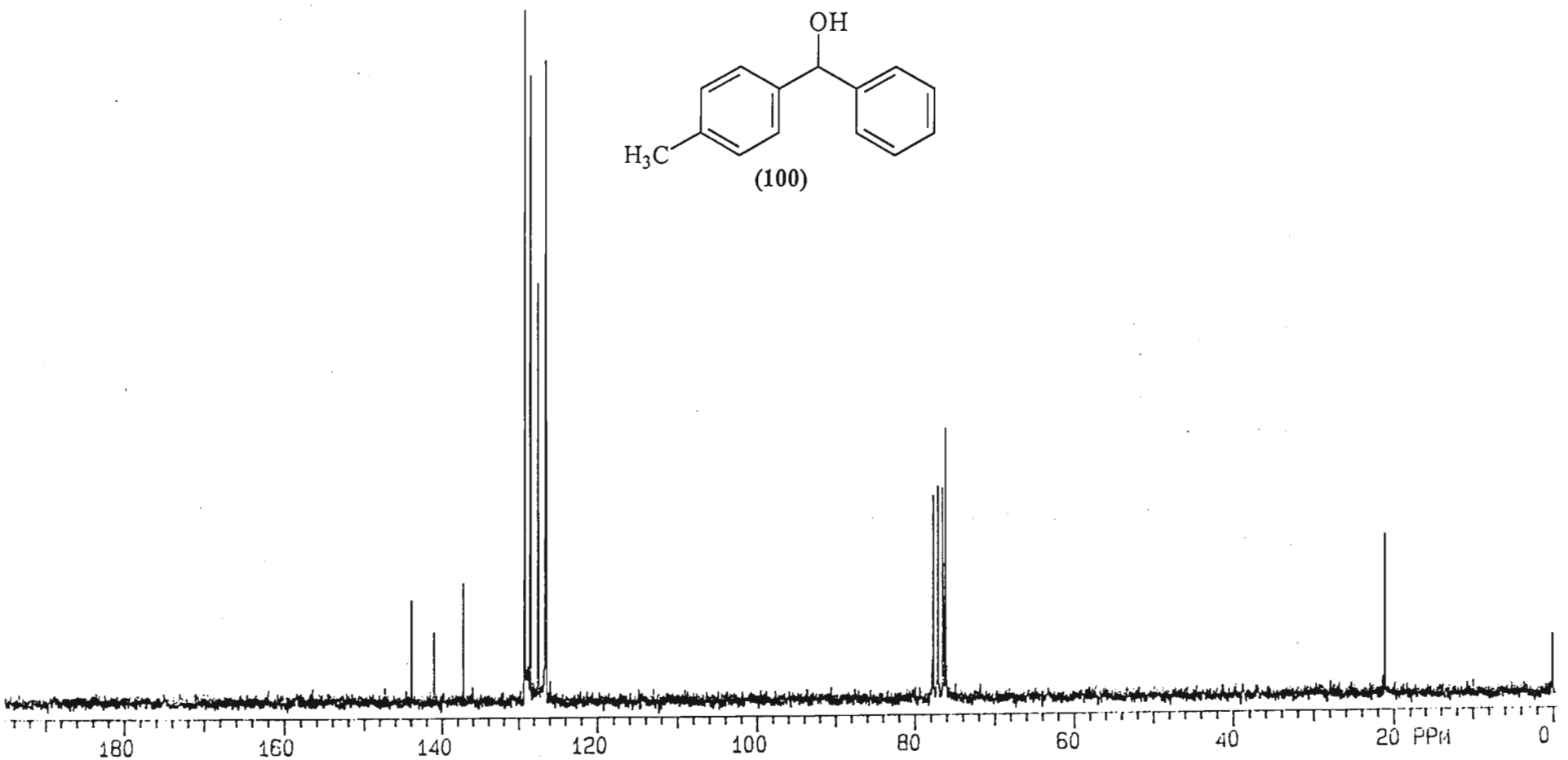

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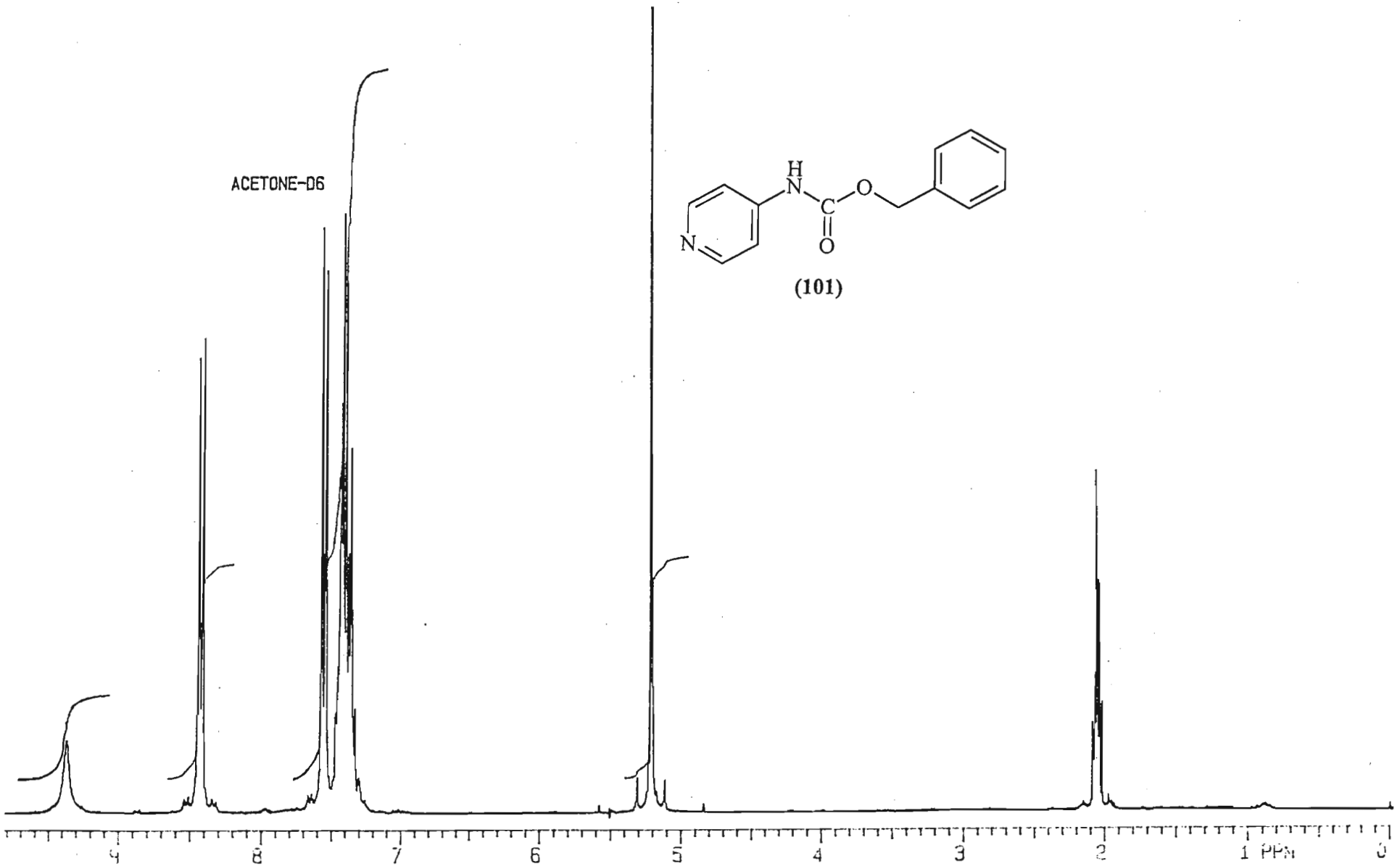

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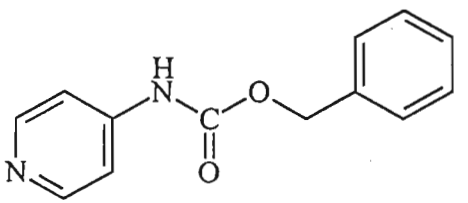

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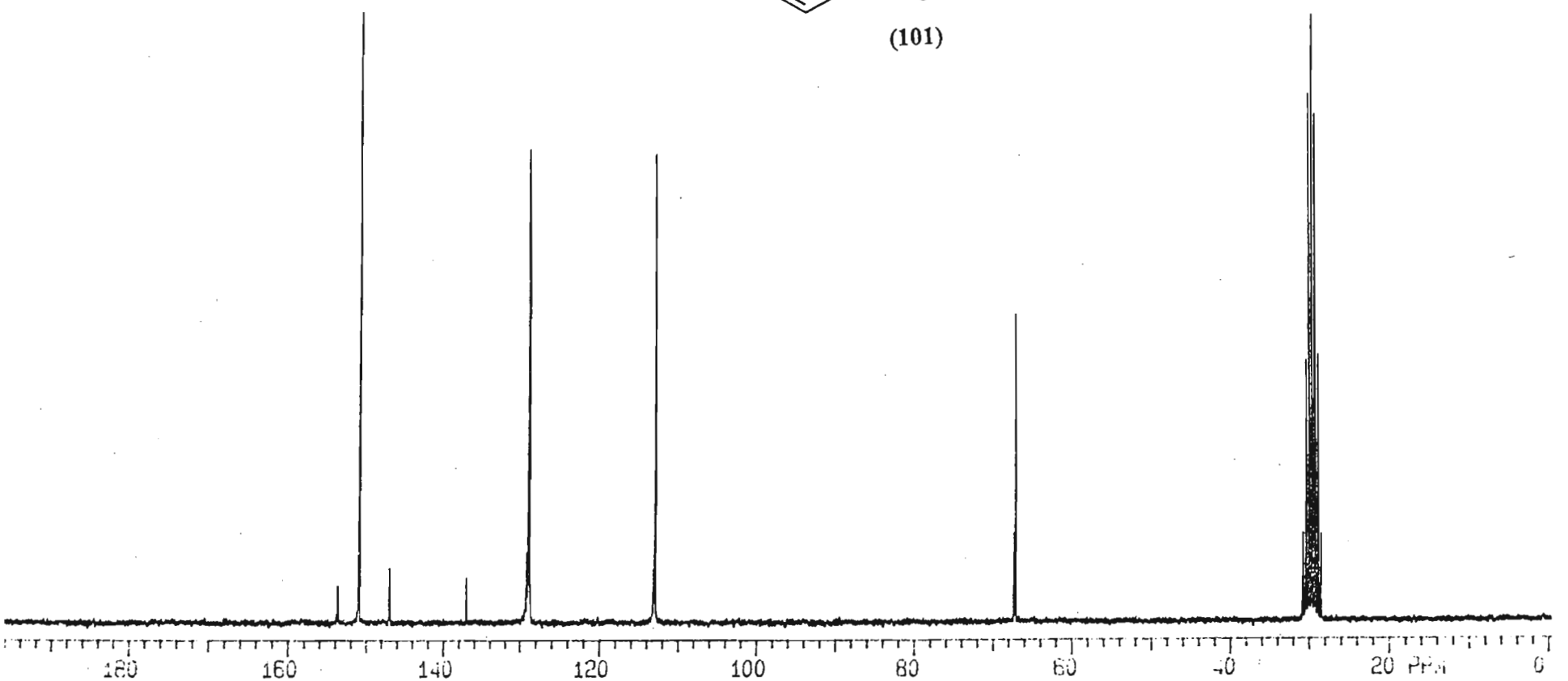
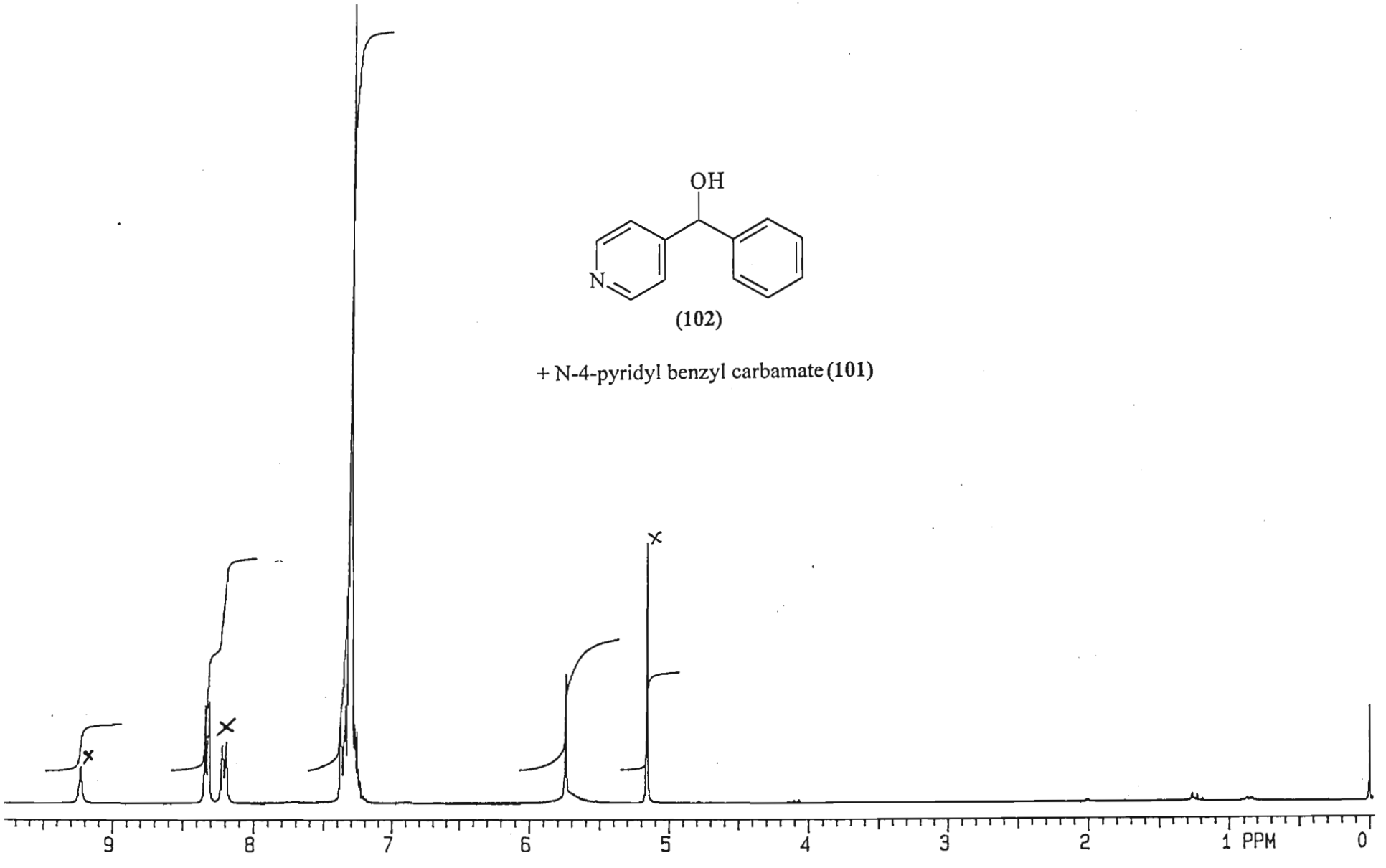
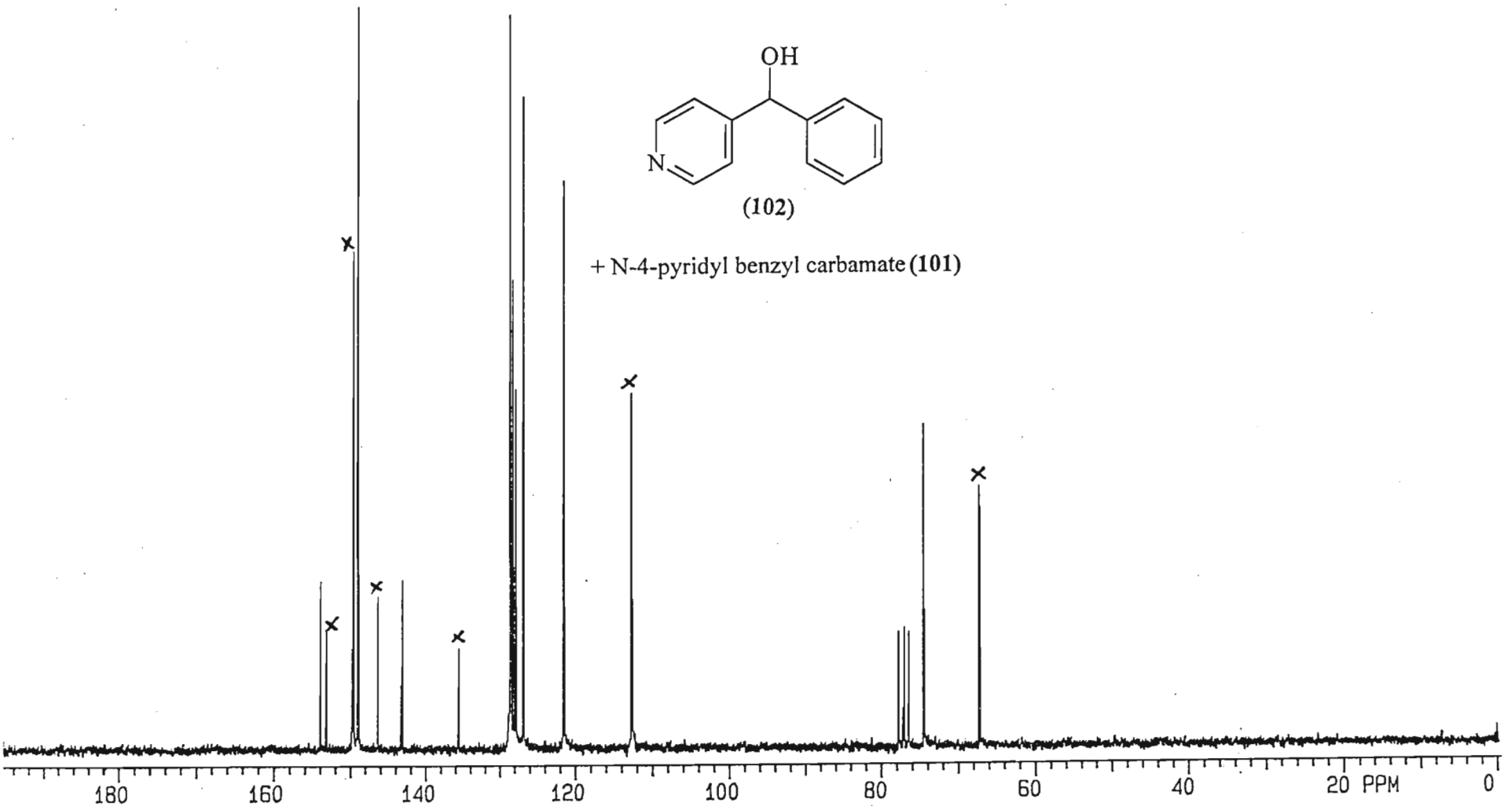




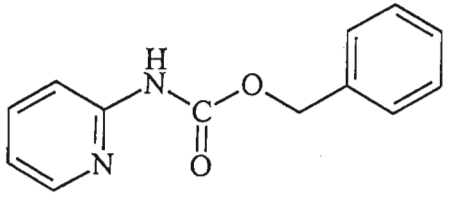
(102)

+ N-4-pyridyl benzyl carbamate **(101)**



(102)

+ N-4-pyridyl benzyl carbamate **(101)**



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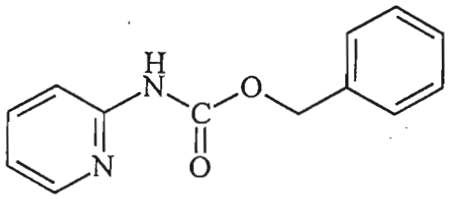

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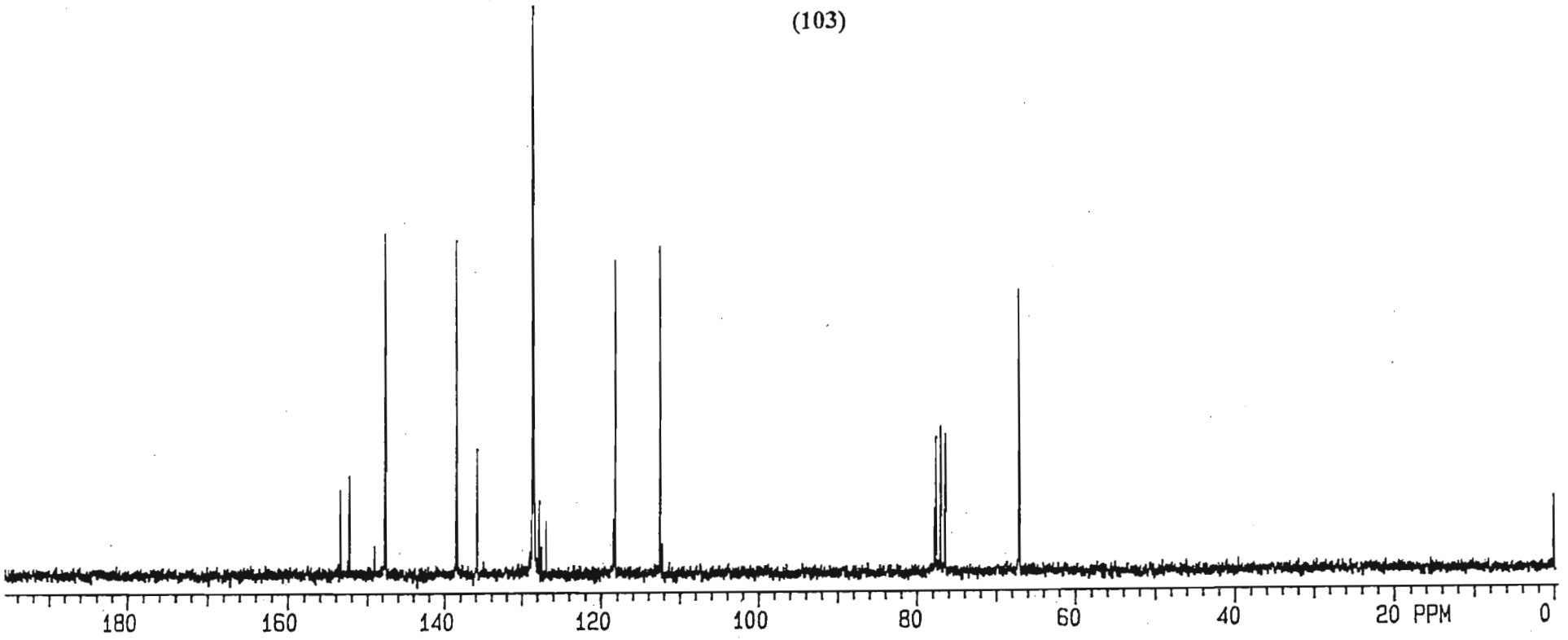

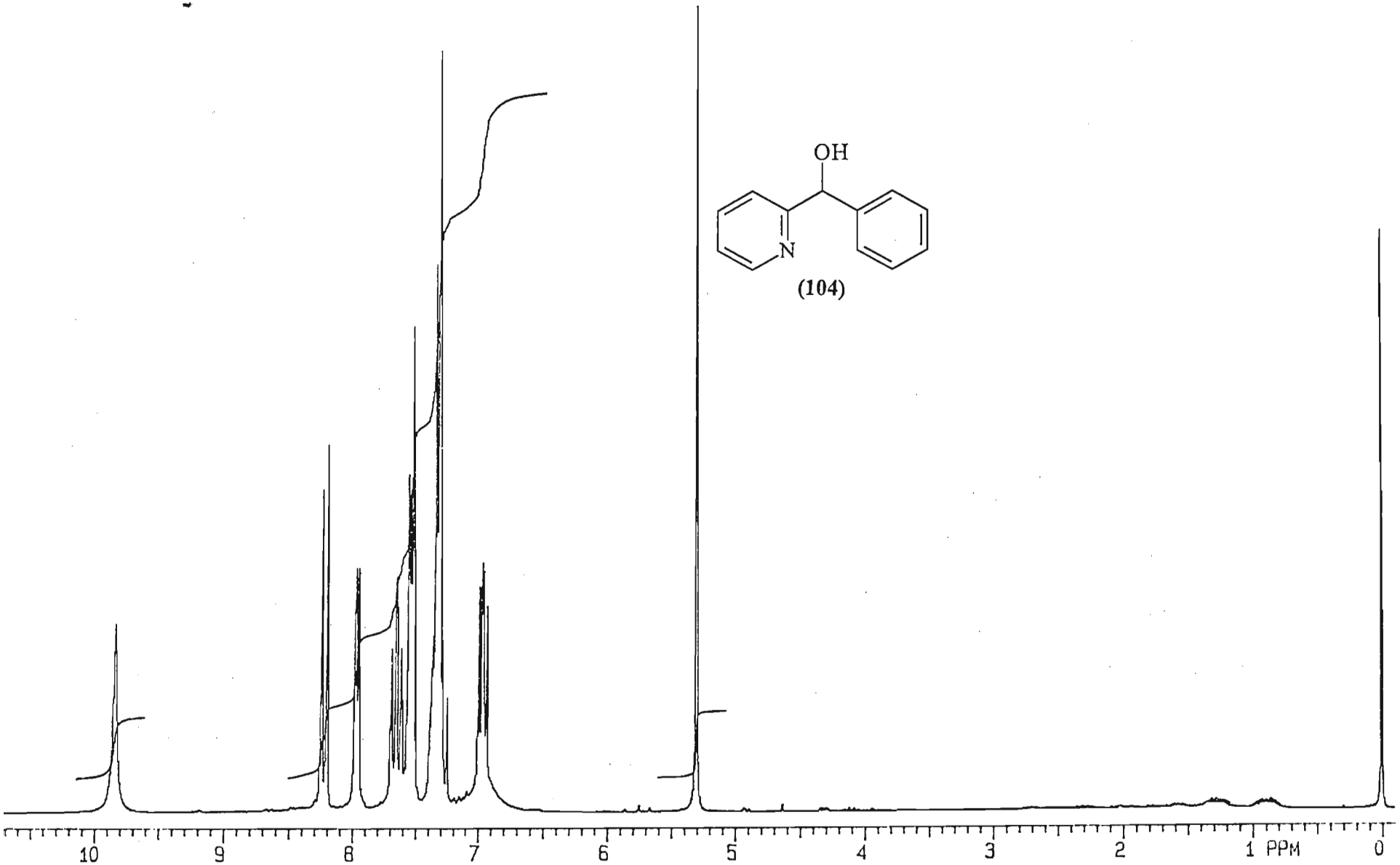

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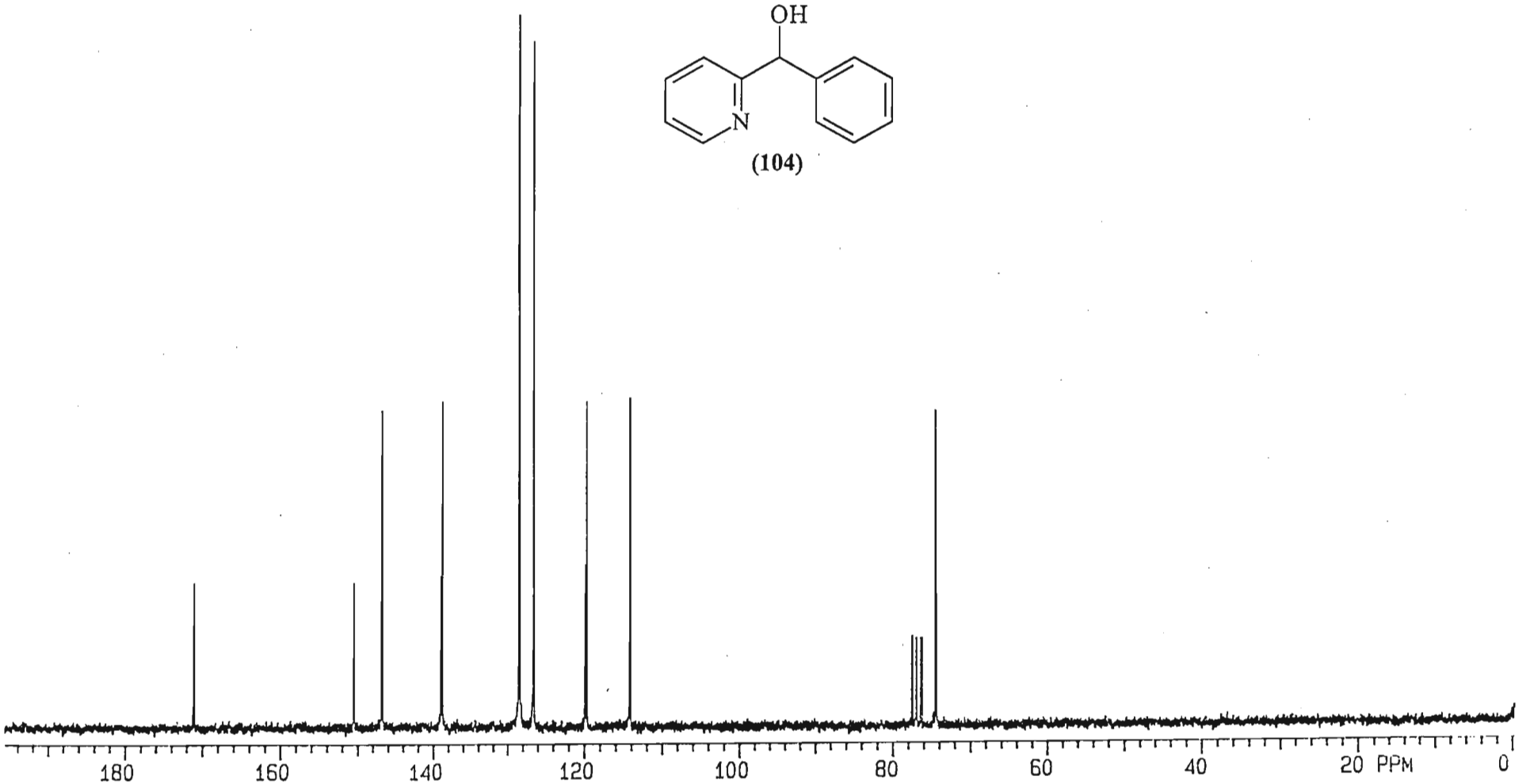

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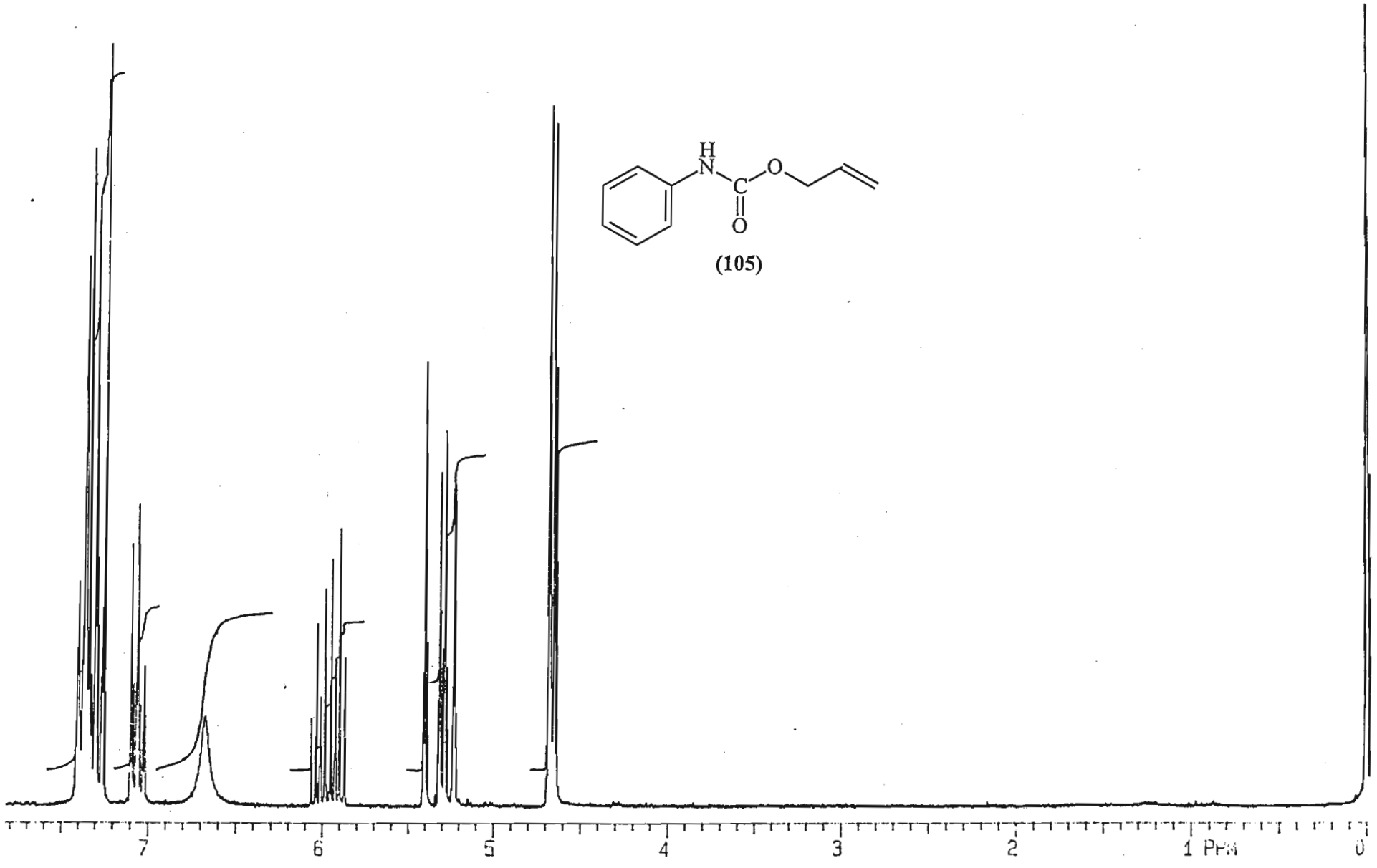

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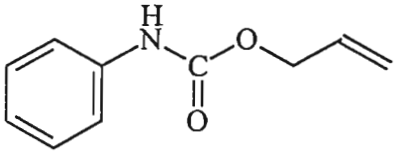

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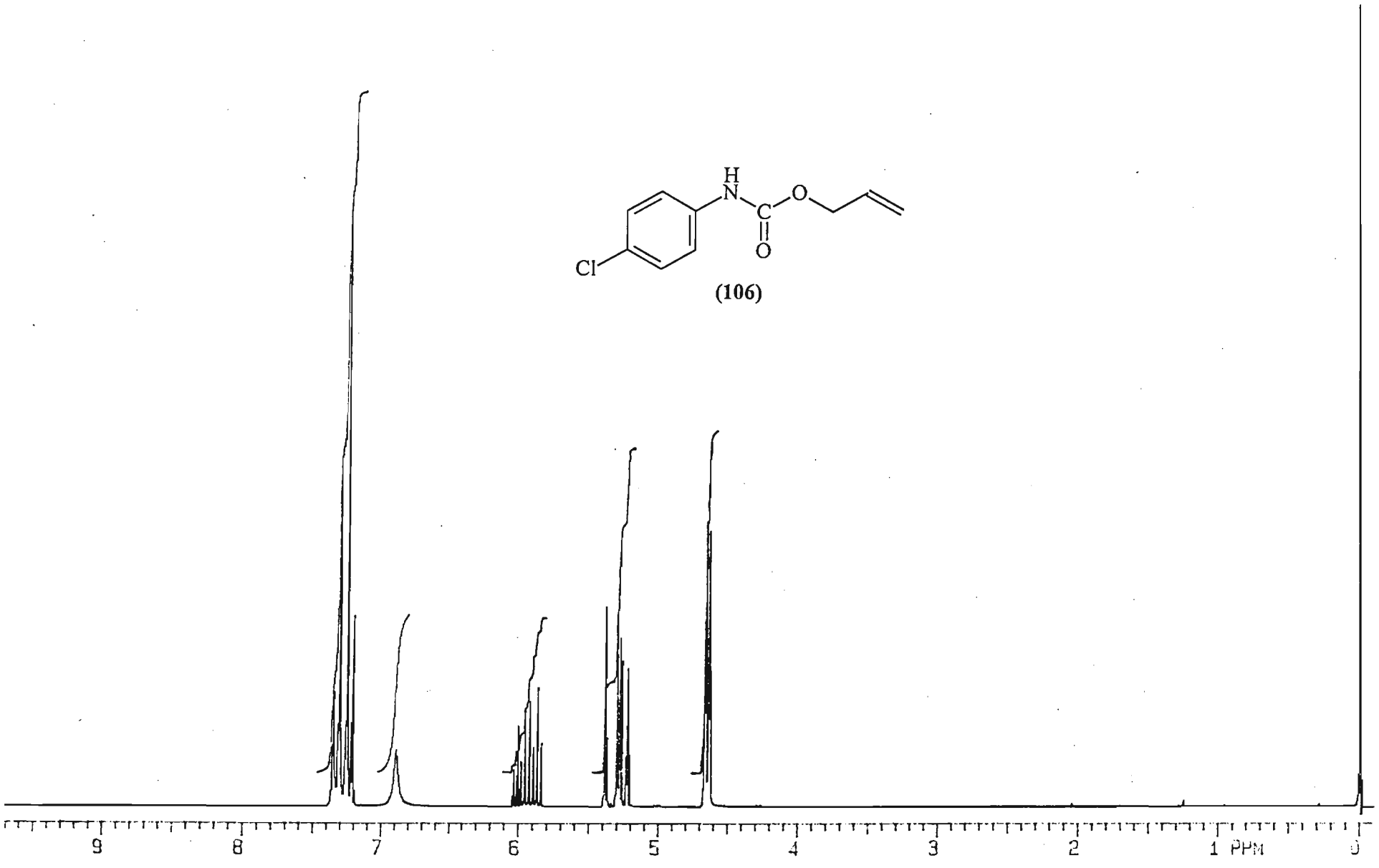

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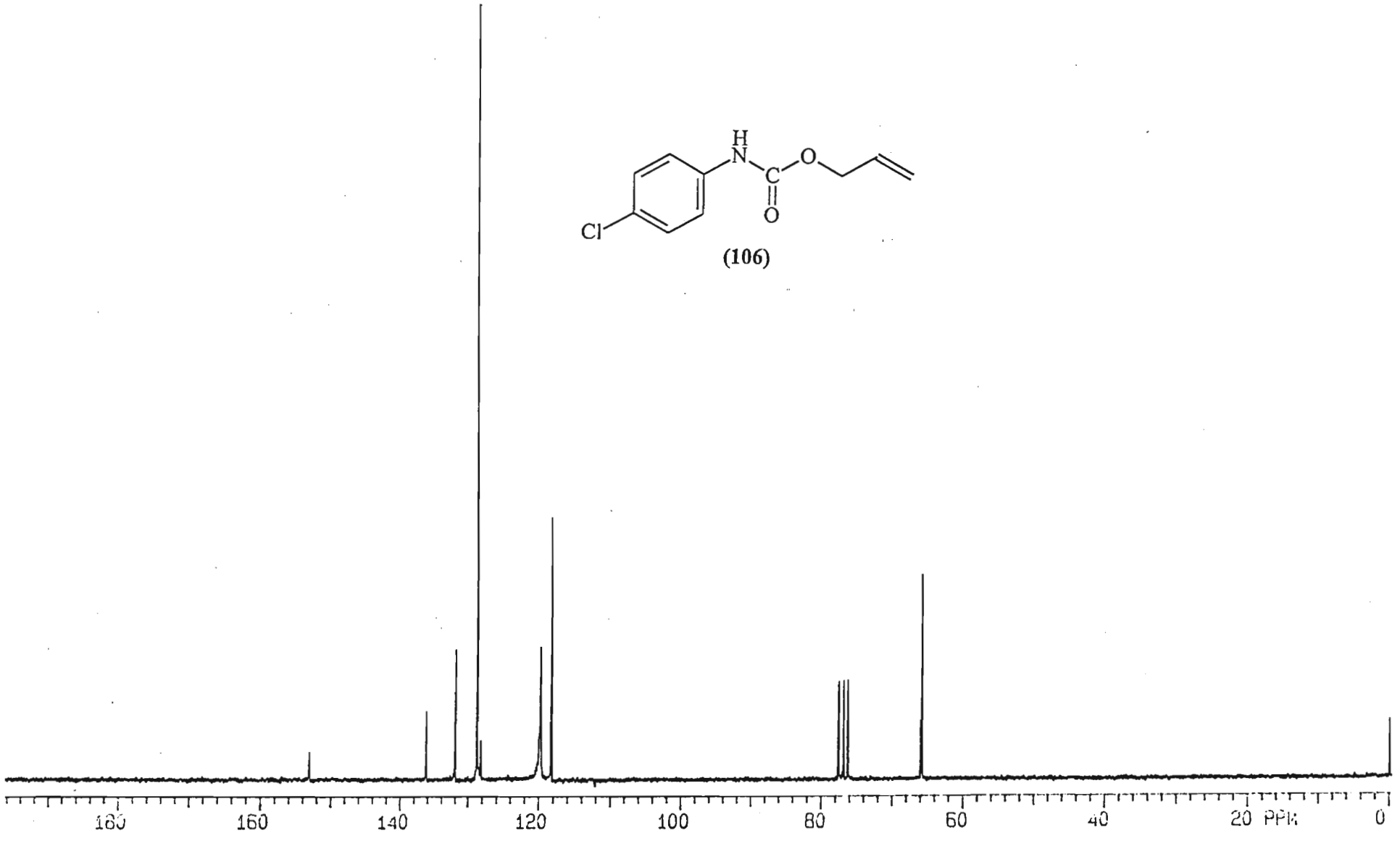

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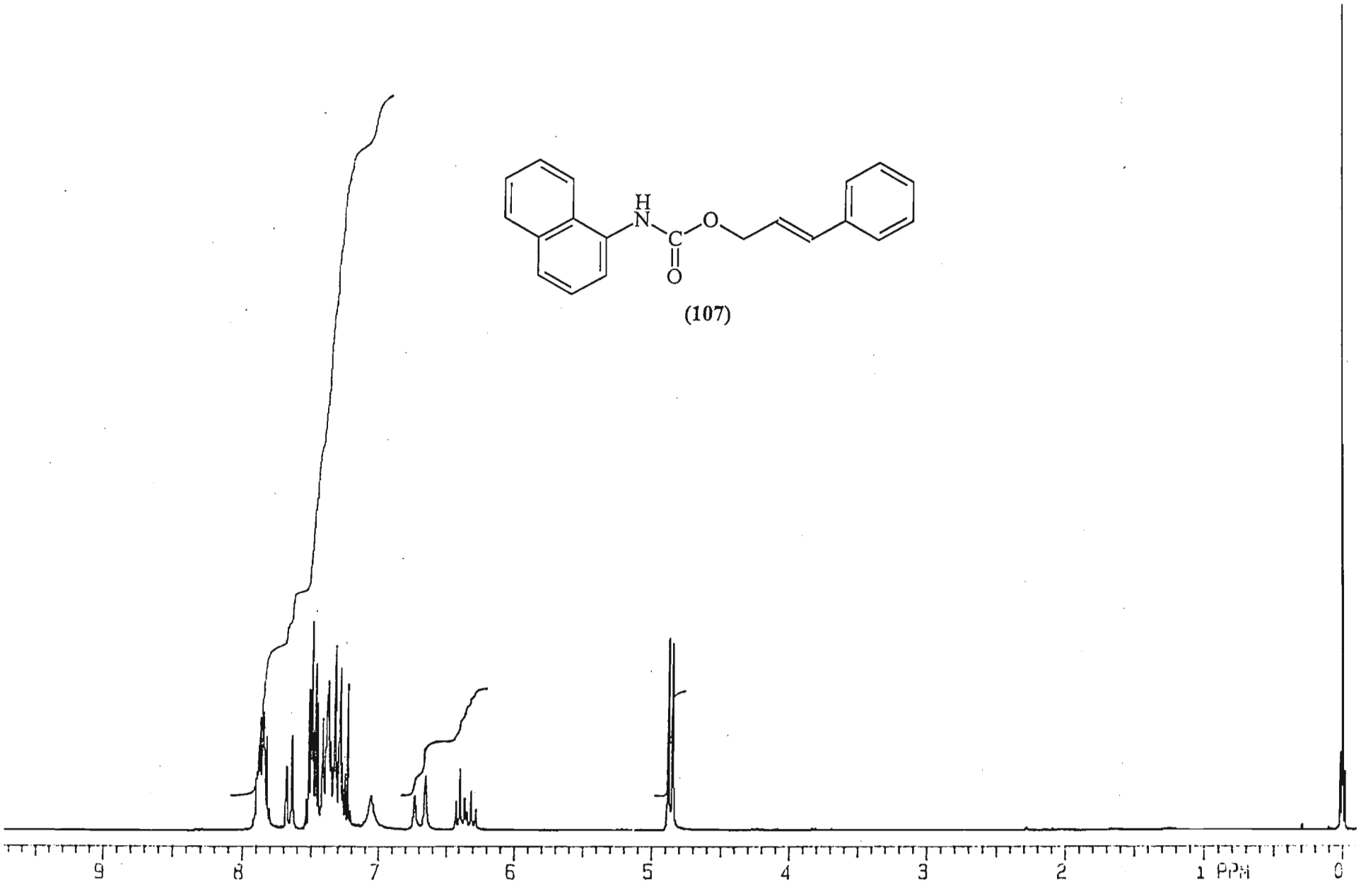

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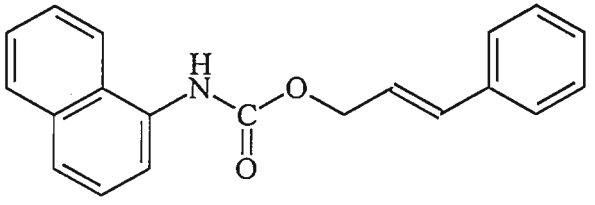

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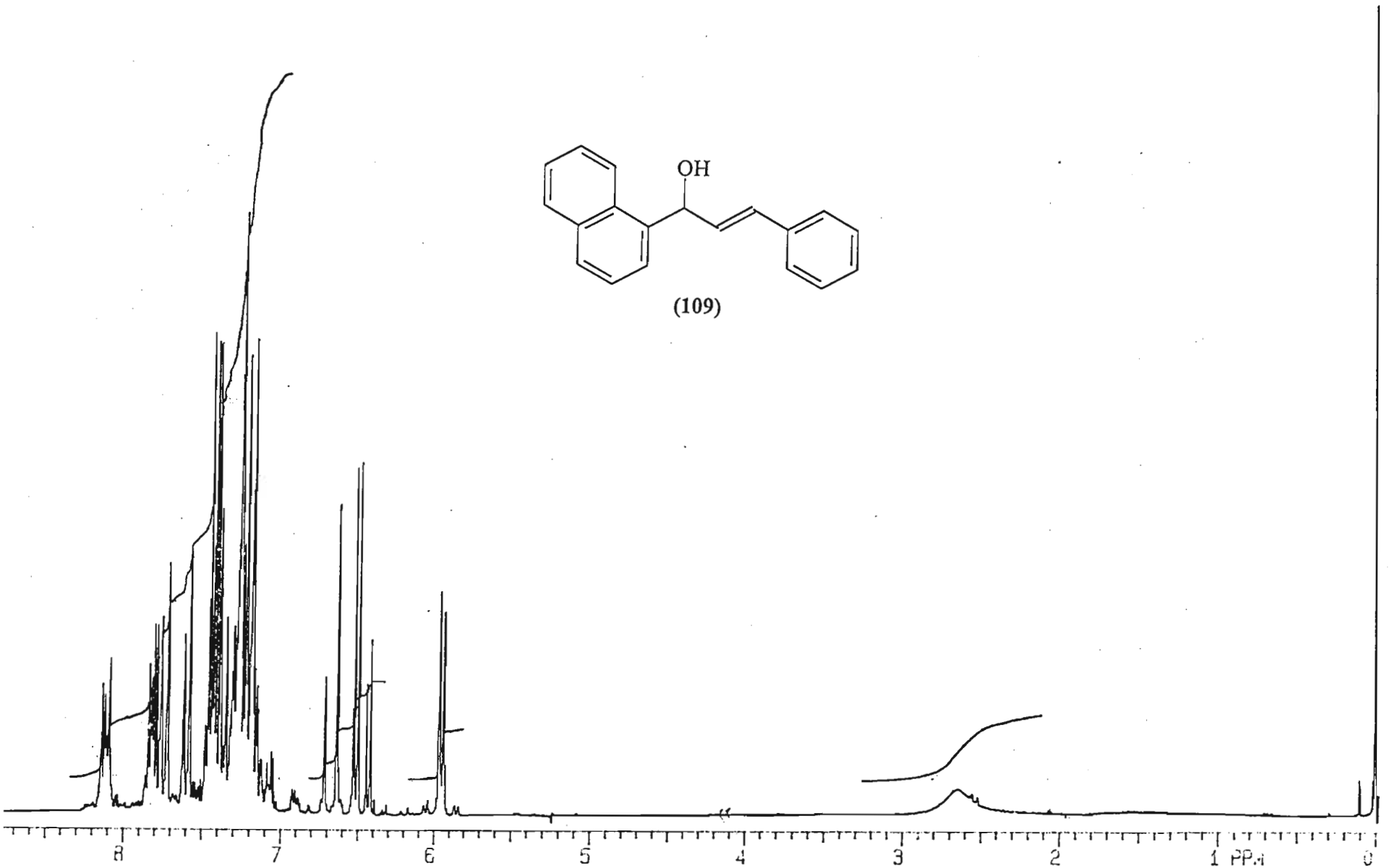

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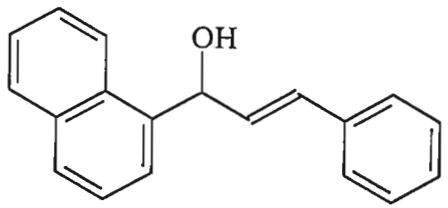

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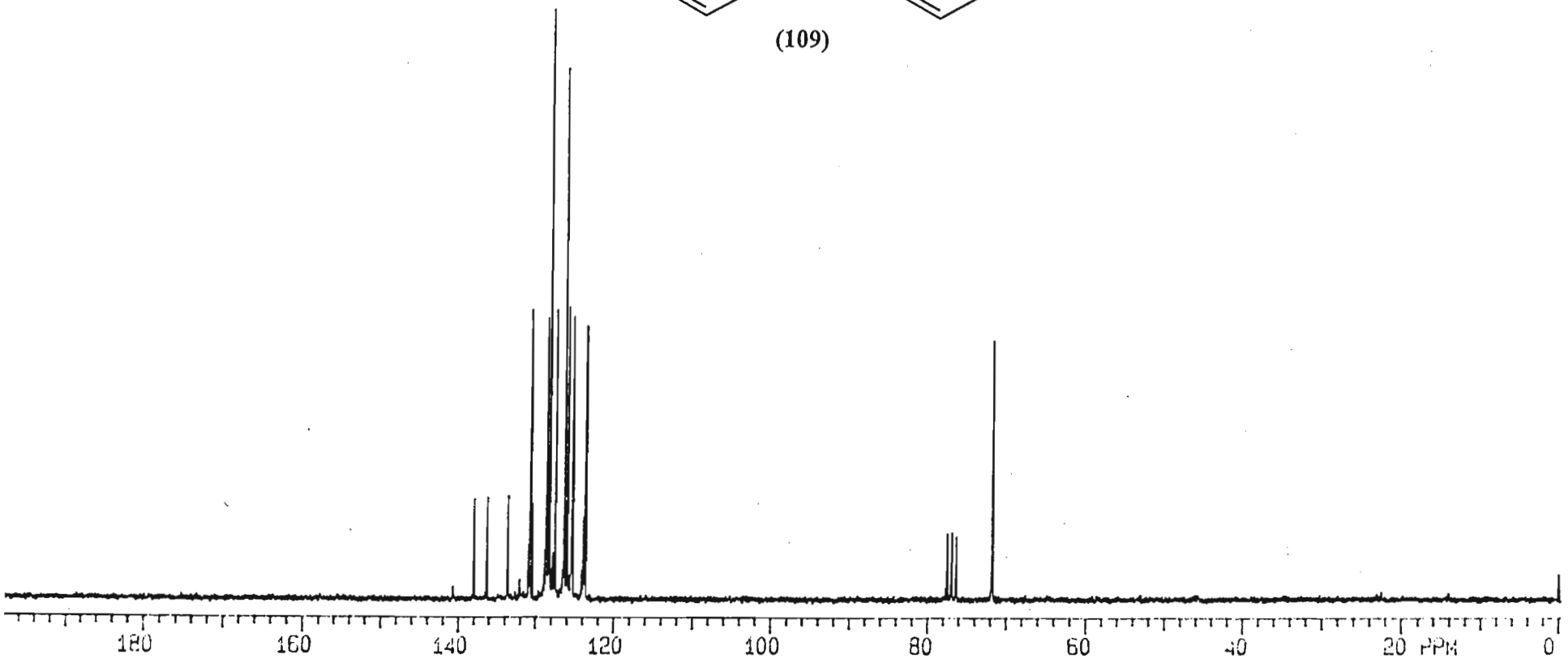
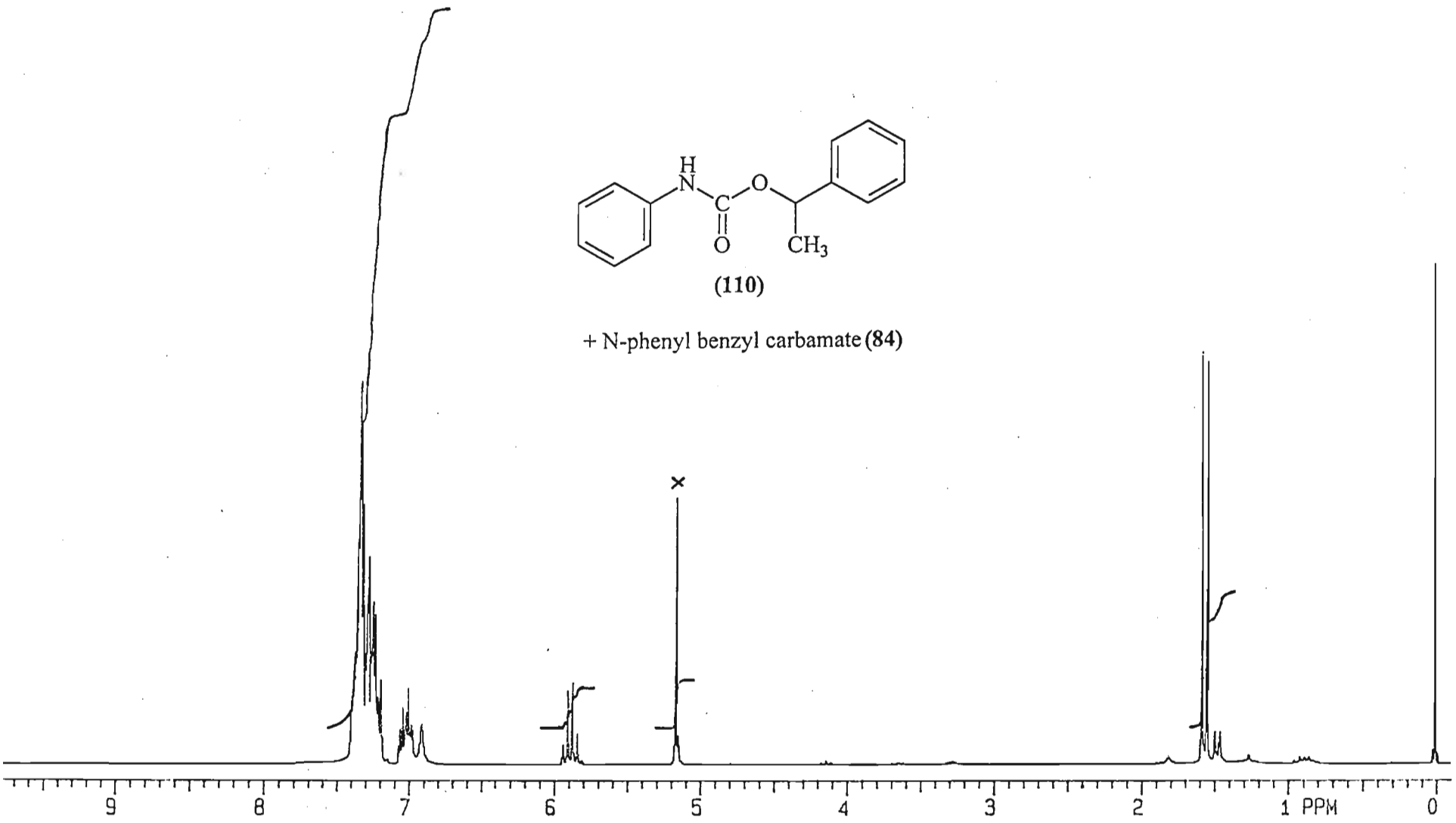
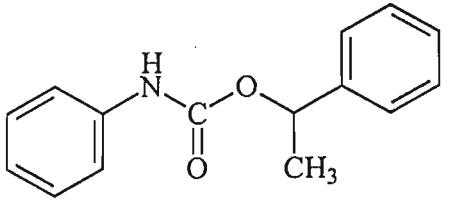




(110)

+ N-phenyl benzyl carbamate **(84)**



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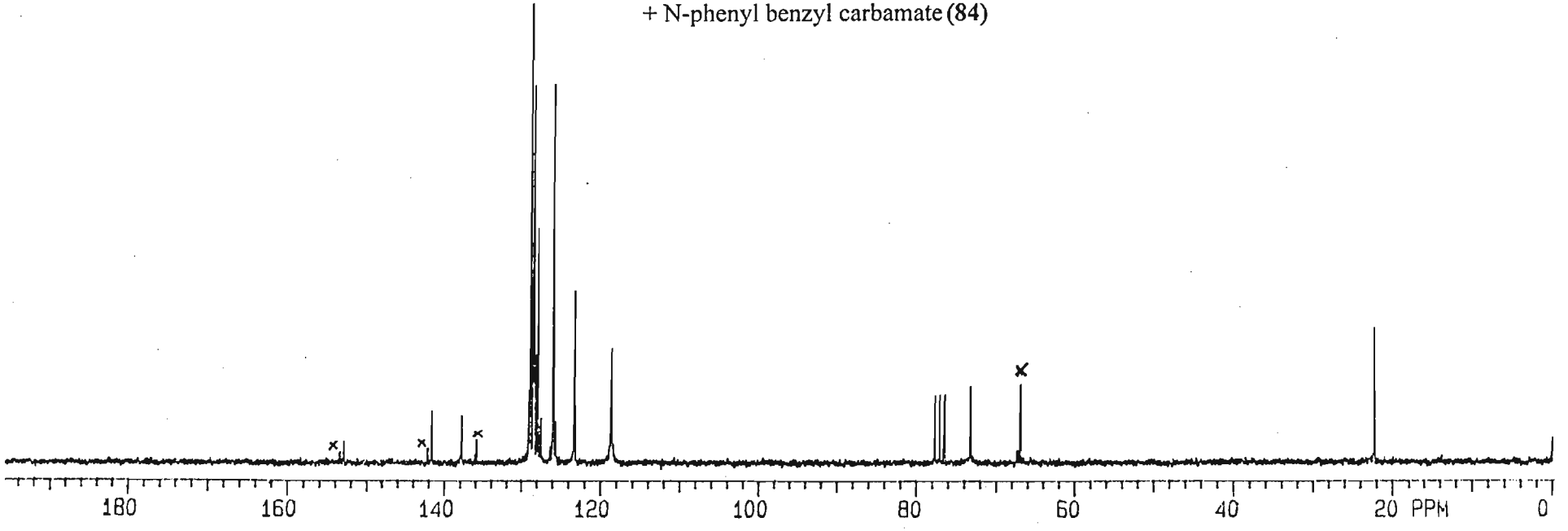
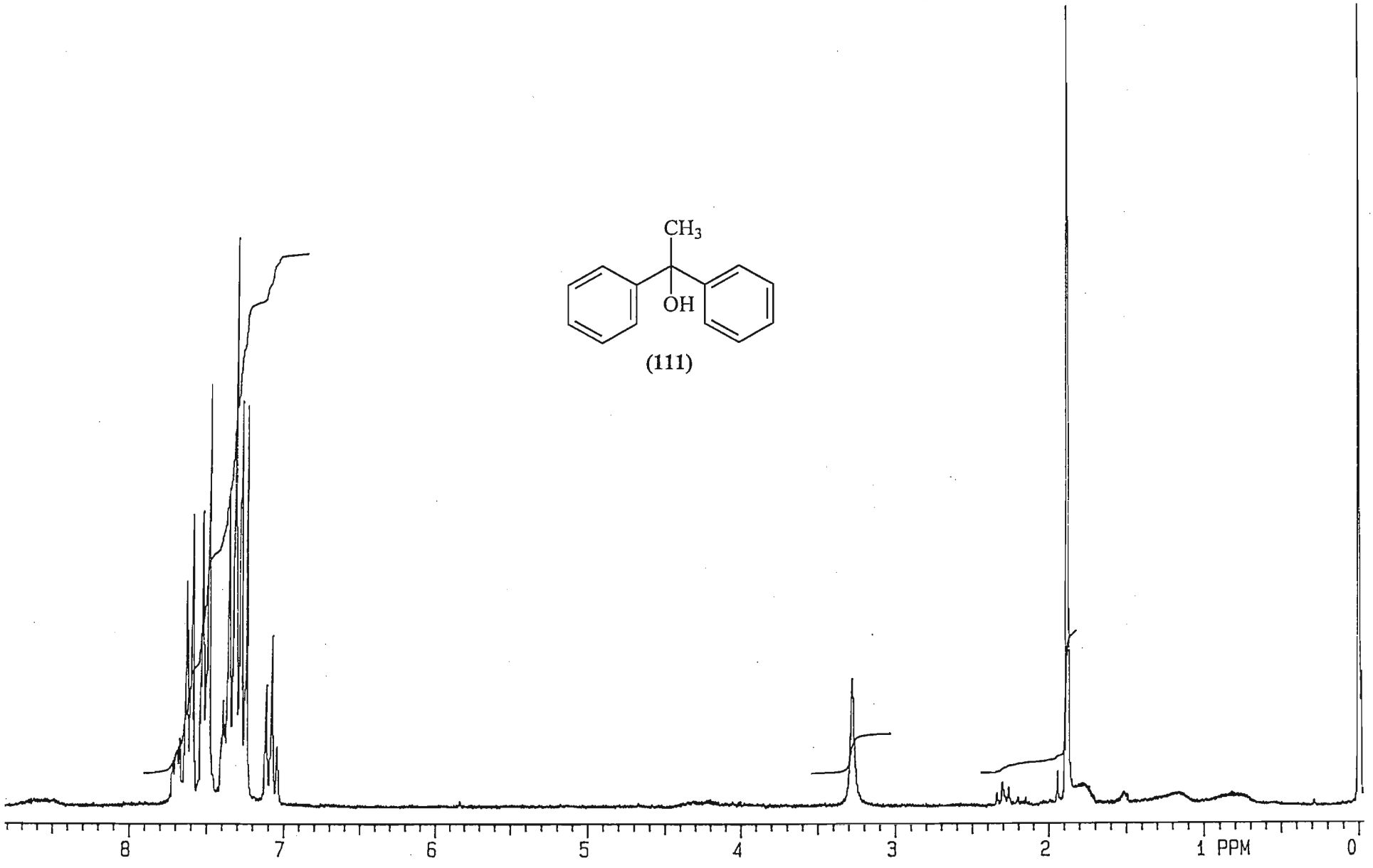
+ N-phenyl benzyl carbamate **(84)**





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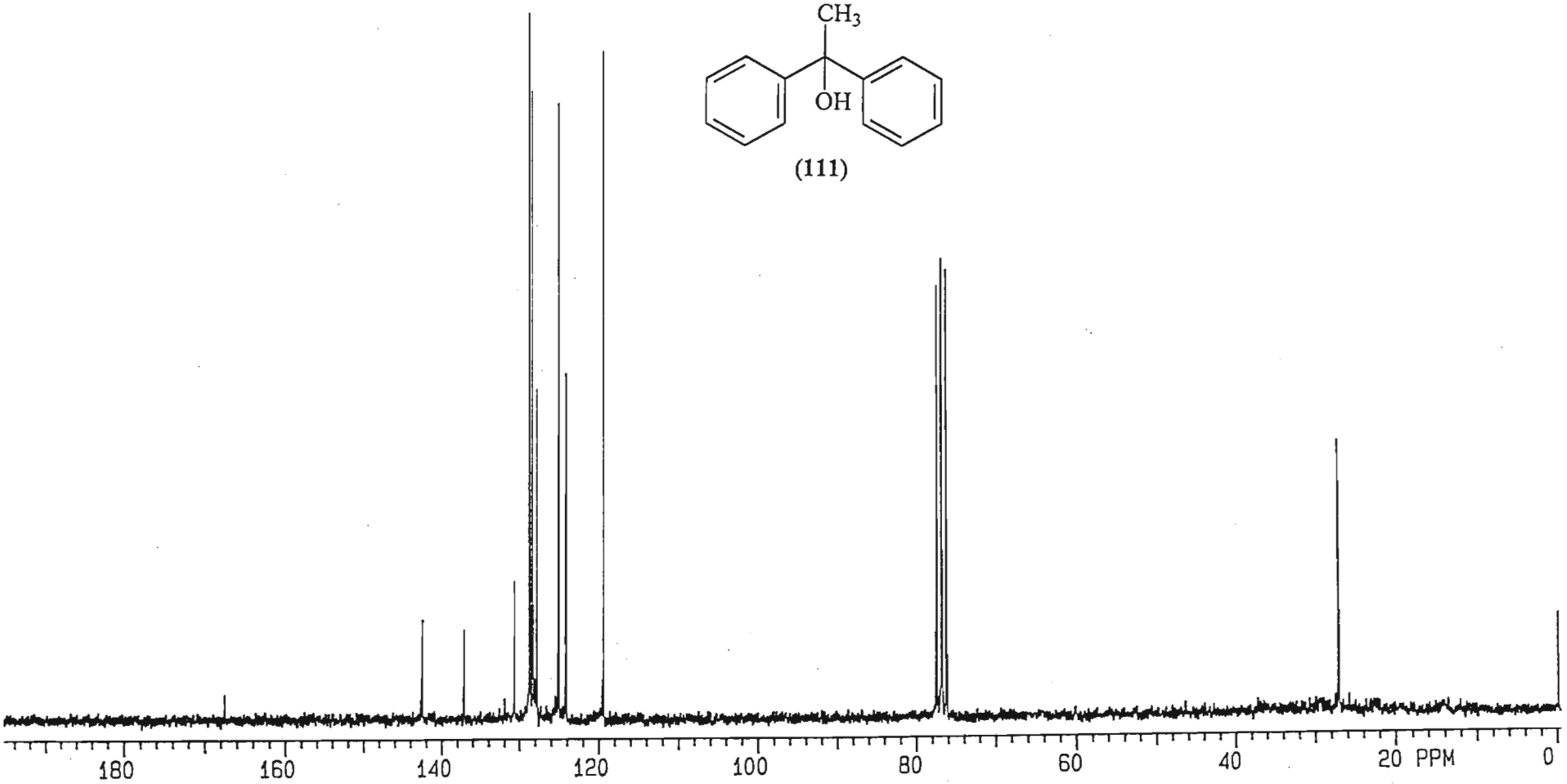

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