

The Functionalisation of Thenyl Carbamates

by

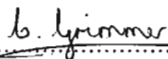
Craig Douglas Grimmer

B.Sc.Hons (Natal)

A thesis submitted in partial fulfilment
of the requirements for the degree of
Master of Science, University of Natal.

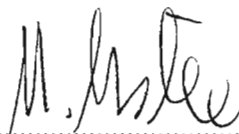
Declaration

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



Craig D. Grimmer

We, the undersigned, hereby certify that the above statement is true and correct.



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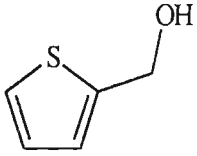
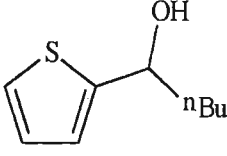
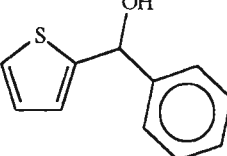
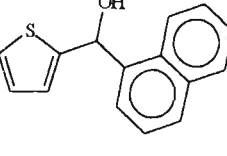
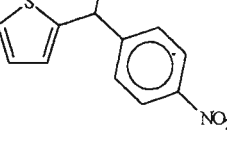
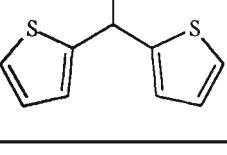
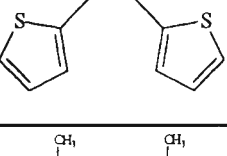
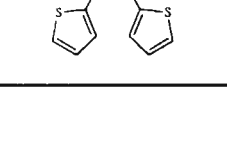
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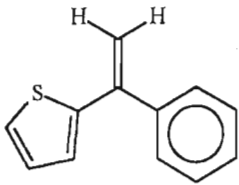
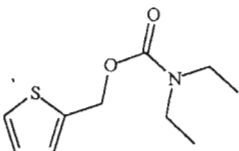
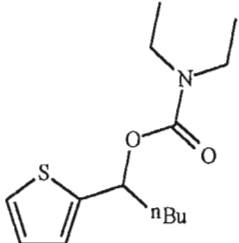
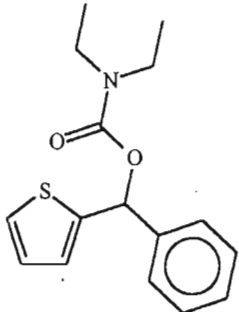
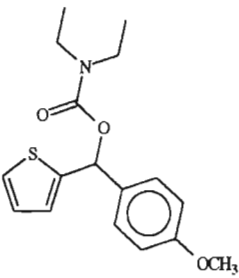
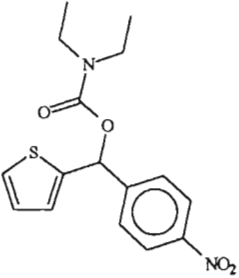
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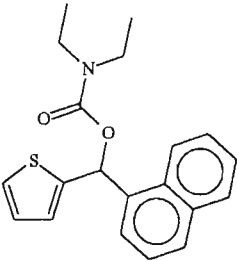
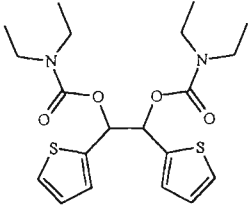
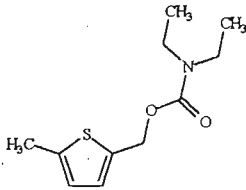
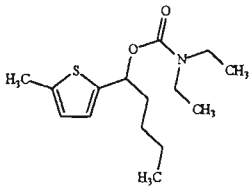
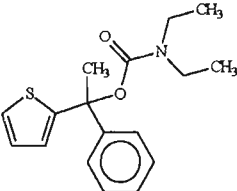
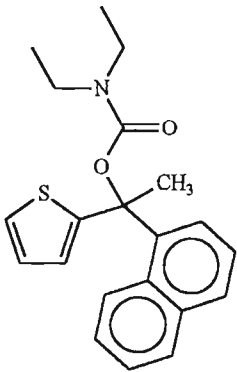
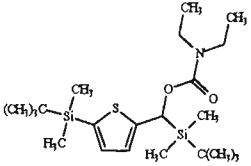
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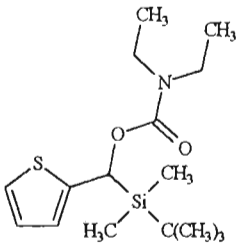
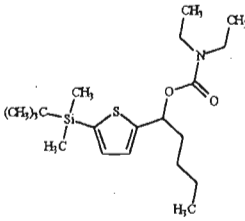
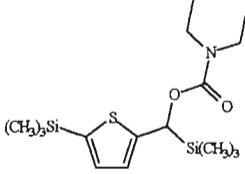
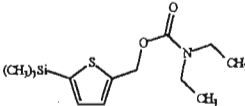
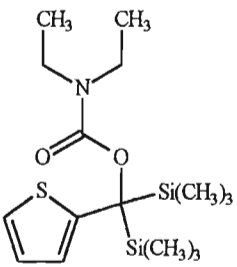
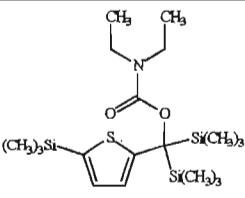
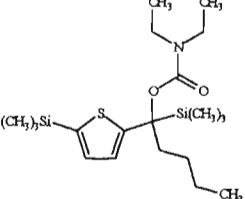
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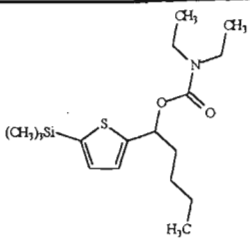
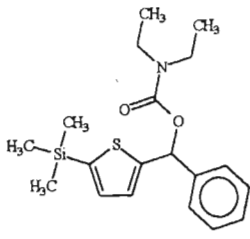
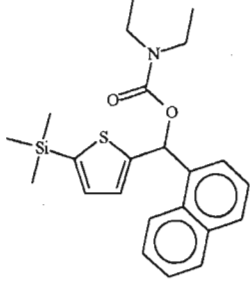
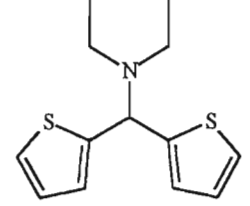
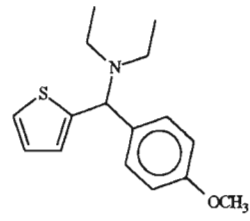
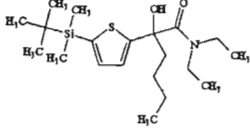
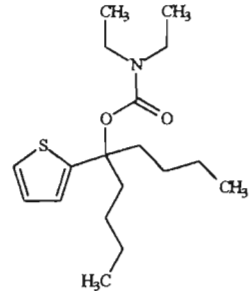
Index of Compounds

Number	Structure	Spectra (pg)	Preparation (pg)
37		134	92
38		136	93
39		138	94
40		142	95
42		145	96
43		151	97
44		154	98
45		156 (solvent CCl ₄)	99

51	 <chem>O=CC(=Cc1ccccc1)c2ccsc2</chem>	159	100
52	 <chem>CCN(CC)C(=O)OCCc1ccsc1</chem>	164	101
53	 <chem>CCN(CC)C(=O)OC(C)c1ccsc1</chem>	166	102
54	 <chem>CCN(CC)C(=O)OC(Cc1ccccc1)c2ccsc2</chem>	168	103
55	 <chem>CCN(CC)C(=O)OC(Cc1ccc(OC)cc1)c2ccsc2</chem>	n/a	104
56	 <chem>CCN(CC)C(=O)OC(Cc1ccc([N+](=O)[O-])cc1)c2ccsc2</chem>	170	105

57		173	106
58		176	107
61		178	108
63		183	109
64		185	110
65		187	111
66		189	112

67		194	113
70		196	114
71		198	115
73		201	116
74		203	117
75		206	118
76		210	119

78		212	120
80		215	121
82		218	122
83		222	123
84		n/a	124
86		226 (CDCl ₃ / D ₂ O)	125
87		229	126

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Abbreviations

Ac	<u>a</u> cetate, <u>a</u> cetyl
aq.	<u>a</u> queous
Ar	<u>a</u> ryl, <u>a</u> romatic
*	asterisk (superscript) - chiral centre, chiral substituent
b.p.	<u>b</u> oiling <u>p</u> oint
Bu	<u>b</u> utyl
ⁿ Bu	<u>b</u> utyl (primary or straight chain)
^s Bu	<u>b</u> utyl (<u>s</u> econdary)
^t Bu	<u>b</u> utyl (<u>t</u> ertiary)
BuLi	<u>b</u> utyl <u>l</u> ithium (primary, secondary or tertiary denoted as above)
°C	degrees <u>C</u> entigrade (<u>C</u> elsius)
CI	<u>c</u> hemical <u>i</u> onisation
COSY	<u>c</u> orrelation <u>s</u> pectroscopy
d	<u>d</u> ays, <u>d</u> oublet
DEPT	<u>d</u> istortionless <u>e</u> nhancement by polarisation <u>t</u> ransfer
DIPT	<u>d</u> i- <u>i</u> so-propyl <u>t</u> artrate
DMG	<u>d</u> irecting <u>m</u> etalation group
DoM	<u>d</u> irected <u>o</u> rtho <u>m</u> etalation
E ⁺	<u>e</u> lectrophile
Ed.	<u>e</u> ditor or <u>e</u> ditors
ed.	<u>e</u> dition
EI	<u>e</u> lectronic <u>i</u> onisation
Et	<u>e</u> thyl (CH ₂ CH ₃)
ether	diethyl <u>e</u> ther (d.e.), petroleum <u>e</u> ther (p.e.)
Fr.	<u>F</u> rench
GC/MS	gas <u>c</u> hromatography/ <u>m</u> ass <u>s</u> pectrometry
Ger.	<u>G</u> erman
h	<u>h</u> our
HETCOR	<u>h</u> eteronuclear chemical shift <u>c</u> orrelation
hex	ⁿ <u>h</u> exane (straight chain)
HRMS	<u>h</u> igh <u>r</u> esolution <u>m</u> ass <u>s</u> pectrometry
K	degrees <u>K</u> elvin

LDA	<u>l</u> ithium <u>d</u> i- <u>i</u> so-propyl <u>a</u> mid <u>e</u>
m	<u>m</u> ultiplet
MCPBA	<u>m</u> eta- <u>c</u> hloro- <u>p</u> er <u>b</u> enzoic <u>a</u> cid
Me	<u>m</u> ethyl (CH ₃)
MeI	<u>m</u> ethyl <u>i</u> odide (iodomethane)
min	<u>m</u> inute
m.p.	<u>m</u> elting <u>p</u> oint
Nap	<u>n</u> aphthalenyl, <u>n</u> aphthyl (C ₁₀ H ₇)
NMR	<u>n</u> uclear <u>m</u> agnetic <u>r</u> esonance
Nu ⁻	<u>n</u> ucleophile
Ph	<u>p</u> henyl (C ₆ H ₅)
PND	<u>p</u> roton <u>n</u> oise <u>d</u> ecoupled spectrum
Pr	<u>p</u> ropyl
ⁱ Pr	<u>i</u> so- <u>p</u> ropyl
q	<u>q</u> uartet, <u>q</u> uaternary (unprotonated carbon - NMR spectra)
R	alkyl, aryl
rt	<u>r</u> oom <u>t</u> emperature
Russ.	<u>R</u> ussian
s	<u>s</u> inglet
sat.	<u>s</u> aturated
t	<u>t</u> riplet
TBDMS	<u>t</u> ertiary- <u>b</u> utyl- <u>d</u> imethylsilyl- (TBDMS = TBS)
TBDMSCl	<u>t</u> ertiary- <u>b</u> utyl- <u>d</u> imethylsilyl <u>c</u> hloride
TBHP	<u>t</u> ertiary- <u>b</u> utyl- <u>h</u> ydro- <u>p</u> eroxide ('BuOOH)
'BOC, 'Boc	<u>t</u> ertiary-butoxycarbonyl
TBS	<u>t</u> ertiary- <u>b</u> utyl-dimethylsilyl- (TBS = TBDMS)
TCHO	2- <u>t</u> hiophenecarboxaldehyde
TFA	<u>t</u> ri <u>f</u> luoroacetic <u>a</u> cid
THF	<u>t</u> etra <u>h</u> ydro <u>f</u> uran
TLC	<u>t</u> hin <u>l</u> ayer <u>c</u> hromatography
TMS	<u>t</u> etra <u>m</u> ethylsilane
TMS	<u>t</u> ri <u>m</u> ethylsilyl-
TMSCl	<u>t</u> ri <u>m</u> ethylsilyl <u>c</u> hloride

Summary

The carbamate functionality has always been associated with a major class of biocides because of its ability to function as an inhibitor of the enzyme acetylcholinesterase. However, carbamates are not limited to pesticidal applications, they have also shown potential as intermediates in organic synthesis. Research has shown that amongst its other properties, the carbamate group has the ability to migrate, function as a leaving group and participate in rearrangement reactions. As part of ongoing research at this department on the synthetic utility of the carbamate group, this project has been primarily concerned with the chemistry of carbamates in conjunction with thiophene, an aromatic heterocycle.

The thiophenes also represent an important class of organic compounds. They are found in natural products, biologically and pharmacologically active systems (both naturally occurring and synthetic), synthetic precursors and more recently, organic conductors and electro-optical devices. In exploring the chemistry of thiophene carbamates, the unique nature of the thiophene ring has been shown to affect the synthesis and reactions of these compounds; the often peculiar character of thiophene imparts properties which make these carbamates remarkable and distinct from carbamates of other aromatic and conjugated systems such as benzene and conjugated polyenes.

With a wide range of potential applications, the purpose of this project has been to study the synthesis and reactions of thiophene carbamates, in particular, the reaction of deprotonated thenyl carbamates with electrophiles, using the electrophile as a means of studying the charge delocalisation in such systems.

A series of thenyl carbamates has been synthesised from thenyl alcohols and their reactions with electrophiles have been studied. The electrophilic substitution reactions illustrate the possibilities for the functionalisation of these compounds, particularly remote functionalisation *via* anionic charge migration; the charge has been found to migrate across five carbon atoms, a phenomenon not observed in this department's studies of other carbamate systems. The substitution products which form in these reactions depend on the nature of both the carbamate and the electrophile. In addition, three rearrangements (carbamate to amine, substituted carbamate to alkene, and substituted carbamate to α -hydroxyamide) have been observed which may find application in organic synthesis. The potential uses for these carbamates range from biologically active applications as carbamates

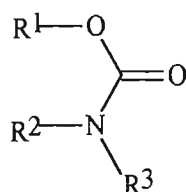
or as derivatives (amines or alkenes *via* rearrangement or alcohols *via* deprotection); many contain a chiral centre and thus may be used in enantioselective or diastereoselective processes in the synthesis of other products, as well as the industrial applications in the fields of non-linear optics and conducting polymers.

CHAPTER 1

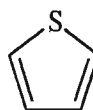
AN INTRODUCTION TO CARBAMATE CHEMISTRY

1.1 *The Carbamate Functional Group*

The primary goal of this project was to study the synthesis and reactions of the carbamate group (1), particularly in conjunction with the thiophene system (2).



(1)



(2)

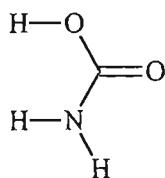
R^1 = alkyl or aryl

R^2, R^3 = alkyl, aryl or H

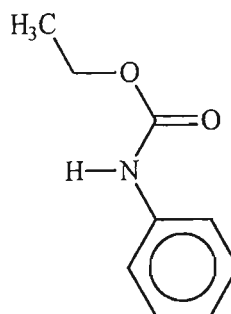
This investigation was motivated by recent work that has shown that the carbamate functionality can be used as an intermediate in organic synthesis, in addition to its applications as a final product.

1.2 *Nomenclature of Carbamates*

The nomenclature of carbamates is based upon carbamic acid (3), which is unstable but has many stable derivatives. Esters of carbamic acid (*O*-substituted) are termed carbamates. In the term “alkyl” or “aryl carbamate”, the alkyl or aryl refers to the oxygen substituent. Nitrogen substituents are termed “*N*-alkyl” or “*N*-aryl” and are named according to *IUPAC* conventions. As an example to illustrate the naming of such compounds, (4) bears the name ethyl-*N*-phenylcarbamate.



(3)

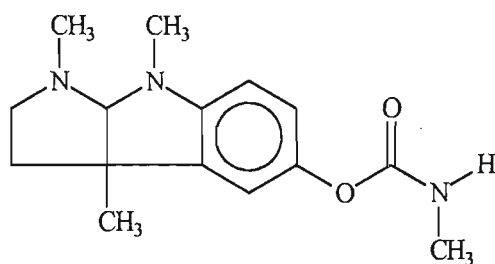


(4)

1.3 Pharmacological Applications

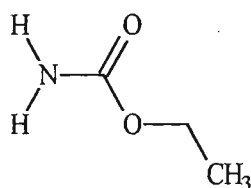
Perhaps the most well-known application of carbamates has been their use as biocides. This important class of agrochemicals is known as the “organocarbamates”¹. Certain carbamates are biologically active in that they act as inhibitors of the enzyme cholinesterase by transferring a carbamoyl group to the active hydroxyl group on the enzyme. Cholinesterase is responsible for the hydrolysis of acetylcholine after the transmission of a nerve impulse across a synapse. The slow hydrolysis of the carbamoylated enzyme causes an accumulation of acetylcholine in the brain, since cholinesterase is no longer able to perform its required function. This increase in the concentration of acetylcholine exacerbates Parkinson’s syndrome (a disorder of the nervous system as a result of degenerative changes in the brain), eventually leading to the death of the affected organism². The ability to function in this way has led to the use of carbamates in both the pest control and medicinal fields.

An early application of the above-mentioned property of carbamates was in witchcraft trials in West-Africa³. The accused was forced to drink a potion made from the calabar bean, in which the active component is a colourless or pale yellow crystalline alkaloid known as physostigmine². The uses of physostigmine (5) are however not limited to a poison in witchcraft. It is precisely because of its powerful inhibition of cholinesterase that it has recently been investigated as a potential treatment of Alzheimer’s disease⁴. It was found to be unsuitable because of a variety of side-effects but a variation of the carbamate group has provided an alternative for further testing⁴. Physostigmine also functions as a miotic (causing contraction of the pupil of the eye) and has therefore been used in ophthalmic surgery². Other uses for this compound include treatment of glaucoma (a disease of the eye), the relief of the symptoms of the muscular disease *myasthenia gravis* and as an antidote for *curare* poisoning⁵.



(5)

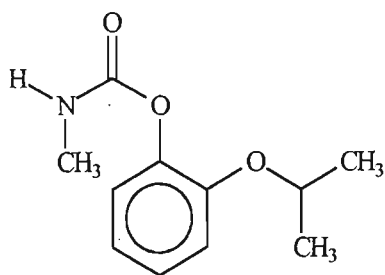
Ethyl carbamate (6) functions as a depressant of the central nervous system and has been used as an antidote for nervous system stimulants such as strychnine. It also inhibits cellular growth and this has led to its use in the treatment of leukaemia⁶.



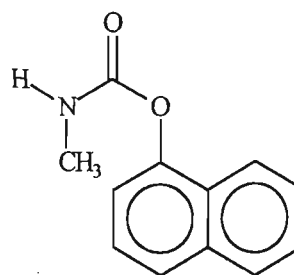
(6)

Other medicinal applications of carbamates include antiseptics, anaesthetics, anticonvulsants, antipyretics, hypnotics, sedatives and muscle relaxants⁶, as well as insect repellents⁵.

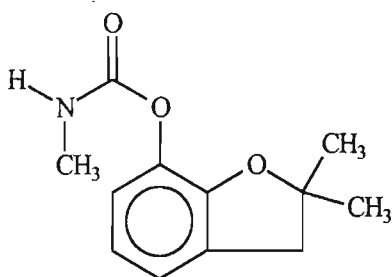
As mentioned before, the most widely known application of the carbamate is as a biocide. The development of the organocarbamates as a class of pesticides was prompted by the hazards to non-target organisms and environmental persistence of the organochlorine and organophosphorus compounds. Carbamates are generally more biodegradable and less toxic to non-target organisms and function effectively as insecticides, herbicides and fungicides. Some well-known examples are propoxur (7), carbaryl (8) and carbofuran (9). Carbaryl and carbofuran are the most widely used commercial carbamate insecticides.



(7)



(8)



(9)

The above examples show an important characteristic of most insecticidal carbamates; they are mono-methyl or di-methyl substituted. Herbicidal or fungicidal carbamates are, however, usually not *N*-methyl derivatives and are, for the most part, thiocarbamates or dithiocarbamates⁵.

1.4 Other Applications

Carbamates have been found to be useful in other fields beside that of the biocidal application; these include a crease resistant fabric finish, hair conditioner, fuel additives, softeners and plasticisers, flavour-enhancing food additives and solvents⁵.

1.5 Synthesis of Carbamates

1.5.1 Reaction of Alcohols with Urea

The early methods for the production of carbamates by the reaction of an alcohol with urea required heat, pressure and long reaction times⁶. The use of heavy metal salts as catalysts were found to be effective in reducing the reaction times and improving reaction yields but this has not led to the reaction being generally applicable to carbamate synthesis since it is limited to the formation of certain carbamates only. It is, however, the preferred commercial route to methyl and ethyl carbamates (Scheme 1).

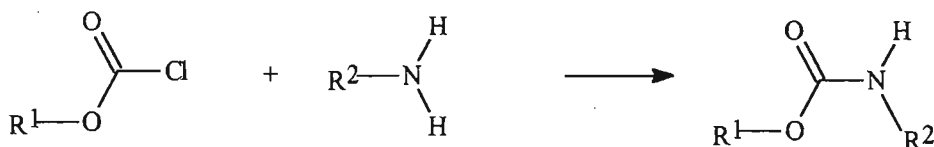


R = Me, Et

Scheme 1

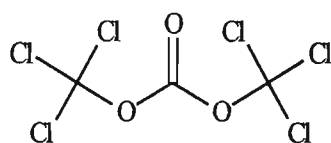
1.5.2 Reaction of Alkyl Chloroformates with Amines

This method has found general application in laboratory synthesis of carbamates⁶. The alkyl chloroformate, or chloroformic ester, is prepared by treatment of an alcohol with phosgene (carbonyl dichloride, carbonyl chloride) in the presence of a base and then allowed to react with an amine (Scheme 2).



Scheme 2

Although this method is a good procedure for laboratory use, a disadvantage of the reaction is the use of phosgene (COCl_2) in the preparation of the chloroformate. The primary disadvantage is the toxicity of the gas, but there is also the problem of handling a gaseous reagent. The latter often means using an excess of phosgene in a laboratory preparation. In a recent publication⁷, an alternative to the use of phosgene has been proposed. "Triphosgene" or bis(trichloromethyl) carbonate (10) is reported to react with nucleophiles in a manner similar to that of phosgene, but since it is both crystalline and stable, it provides an alternative to phosgene in carbamate synthesis. It is easier to handle, less toxic⁸ and can be used in equivalent amounts.

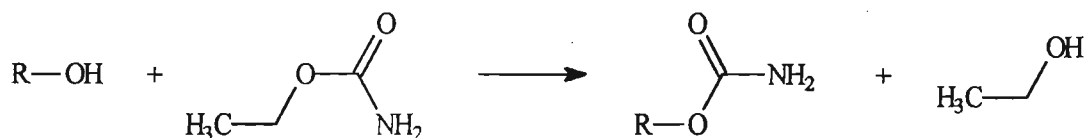


(10)

"Triphosgene"

1.5.3 Transesterification

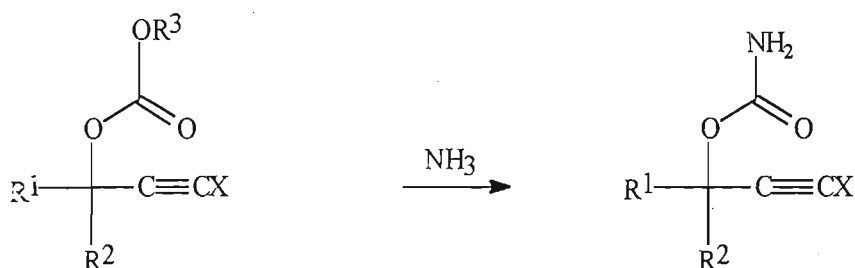
Simple carbamates (methyl or ethyl) and a higher boiling alcohol can be used to prepare more complex carbamates *via* an interchange reaction in which an acid or base catalyst is used⁶. The reaction (Scheme 3) can be used to prepare unsubstituted or *N*-substituted carbamates from primary and secondary alcohols and diols, but not tertiary alcohols or phenols.



Scheme 3

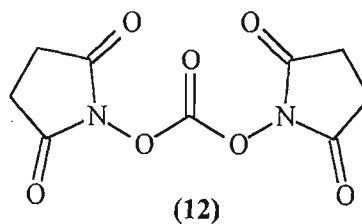
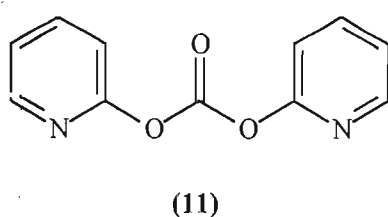
1.5.4 Reaction of Amines with Carbonates

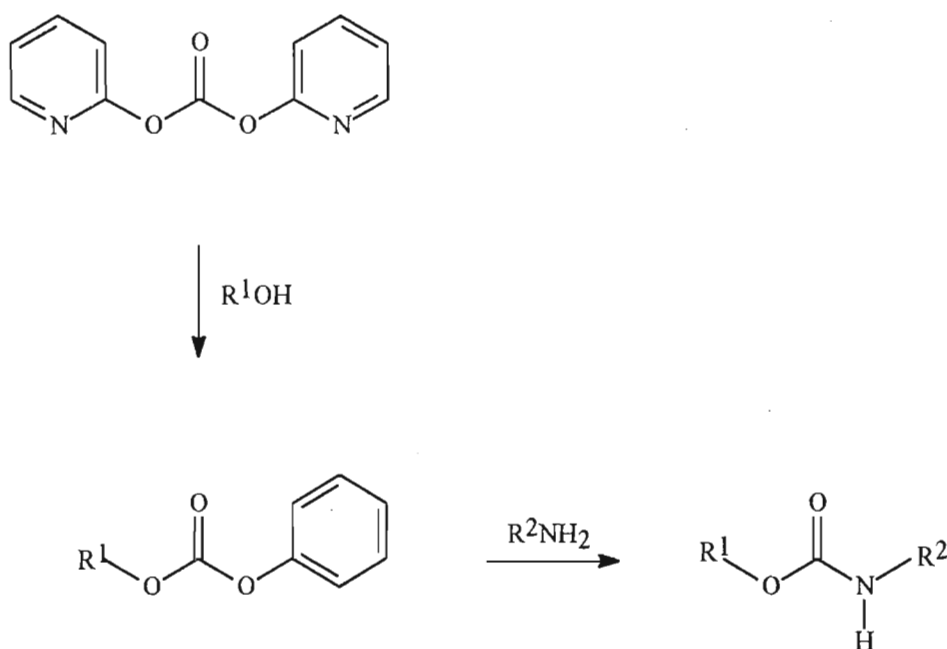
The use of the carbonate as a protecting group in organic synthesis is well established⁹. In 1955 it was shown that tertiary acetylenic carbinols, protected as carbonates, react with amines to form carbamates¹⁰ (Scheme 4).



Scheme 4

Recently, the versatility of this technique has been shown in the synthesis of carbamates from a variety of alcohols, including sterically hindered secondary and tertiary alcohols, as well as protected glycols^{11,12}. Di-(2-pyridyl)-carbonate (11) or *N,N*-disuccinimidyl carbonate (12) is used in the synthesis of a non-symmetrical carbonate, which is then treated with an amine, yielding a carbamate (Scheme 5).

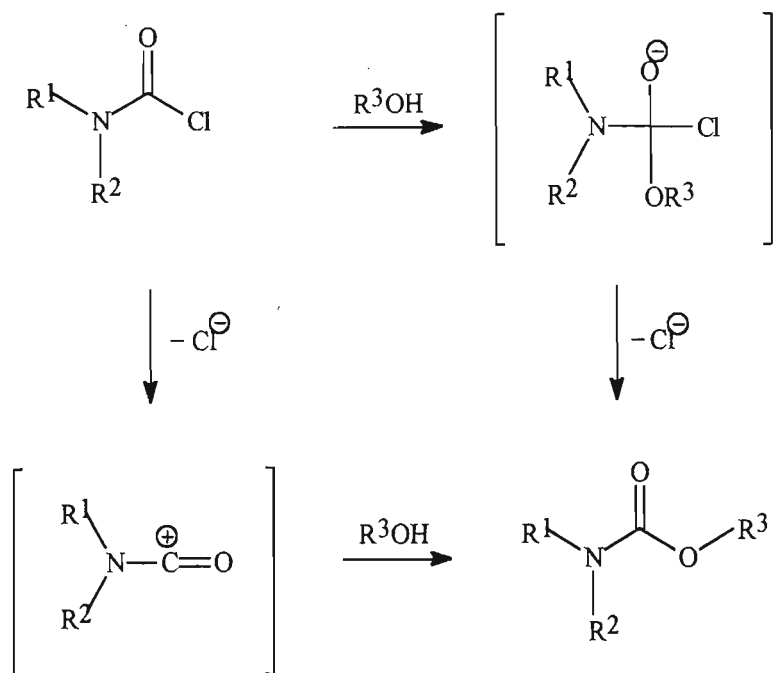




Scheme 5

1.5.5 Reaction of Carbamoyl Chlorides with Alcohols

This method can be used to prepare *N,N*-disubstituted carbamates from *N,N*-disubstituted carbamoyl chlorides³. The preparation of the carbamoyl chloride requires the use of phosgene; the problems associated with this are discussed in section 1.5.2. There are two proposed reaction pathways: displacement of the chloride ion by the hydroxyl nucleophile, or unimolecular loss of the chloride ion followed by nucleophilic addition of the alcohol. The two mechanisms are shown in Scheme 6.

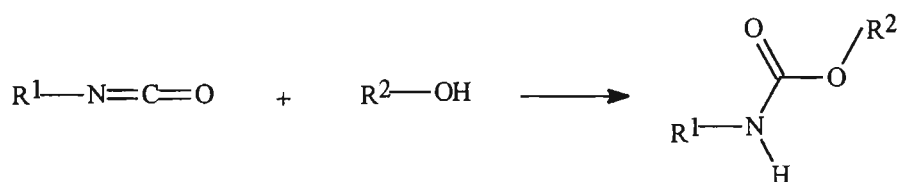


$\text{R}^1, \text{R}^2, \text{R}^3 = \text{alkyl or aryl}$

Scheme 6

1.5.6 Reaction of Isocyanates with Alcohols

The reaction between isocyanates and alcohols is a good method of producing mono-*N*-substituted carbamates (Scheme 7). It is extremely general in that a wide variety of alcohols may be used resulting in a range of *N*-substituted carbamates^{13,14}.

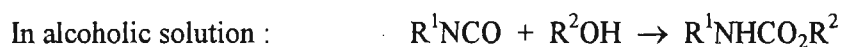
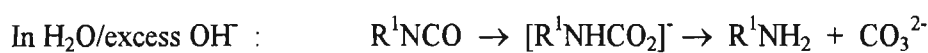
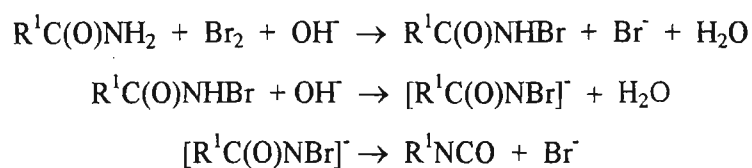


Scheme 7

The isocyanate can be prepared in a number of different ways¹³: the use of phosgene and the salt of a primary amine is disadvantageous because of the hazards associated with phosgene⁸.

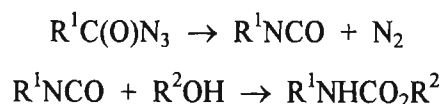
but there are the Hofmann, Curtius and Lossen rearrangements, all of which give an isocyanate product.

The Hofmann rearrangement (Hofmann degradation, Hofmann hypobromite reaction) takes place between a primary amide and bromine in the presence of a base (Scheme 8).



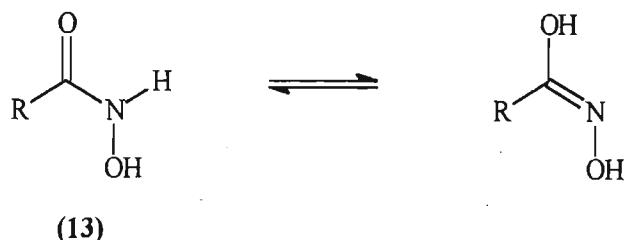
Scheme 8

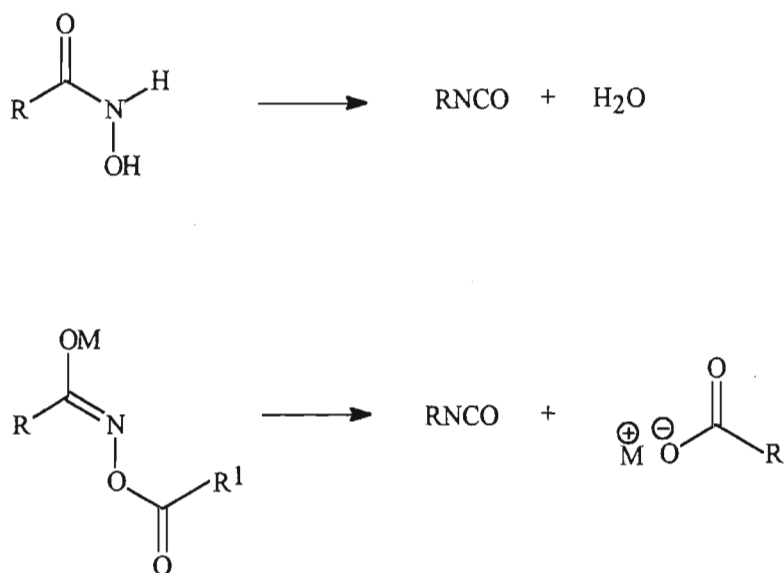
A similar reaction takes place in the Curtius rearrangement when an acyl azide is heated. Loss of nitrogen results in the formation of the isocyanate. In the presence of an alcohol a carbamate ester is produced¹⁵ (Scheme 9).



Scheme 9

The less well-known Lossen rearrangement^{13, 18}, the thermal decomposition of hydroxamic acids (13) or derivatives, is shown in Scheme 10.

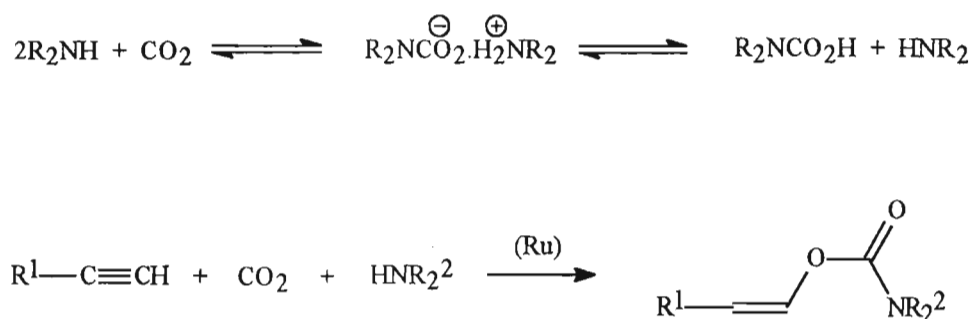




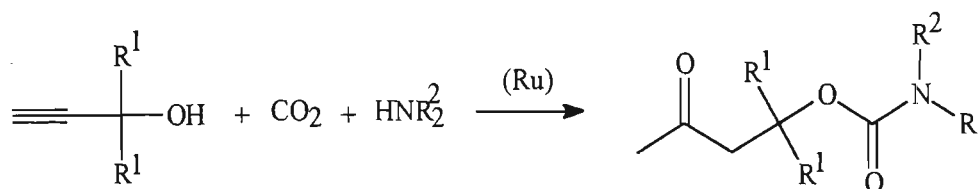
Scheme 10

1.5.7 Preparation of Vinyl Carbamates

Vinyl carbamates (enol carbamates) cannot be obtained directly from the usual procedures for the preparation of alkyl carbamates¹⁷. Such procedures usually involve more than one step and require the use of phosgene⁸. This has led to the development of a synthesis for these compounds using terminal alkynes, CO₂ and an amine in the presence of a variety of ruthenium-based catalysts¹⁷. The reaction (Scheme 11) exploits the CO₂/amine - ammonium carbamate - carbamic acid equilibrium and is advantageous in that it is a one-step synthesis. It has recently been adapted to the synthesis of *O*-β-oxoalkylcarbamates (Scheme 12).



Scheme 11



Scheme 12

1.5.8 Other Syntheses

Recent research in the field of carbamate preparation has been to move away from the use of often unstable chloroformates or toxic phosgene. This has led to the development of preparative methods using CO_2 , an amine and an electrophile¹⁹ and the catalytic use of CO_2 in a method using an amine and dimethyl carbonate²⁰.

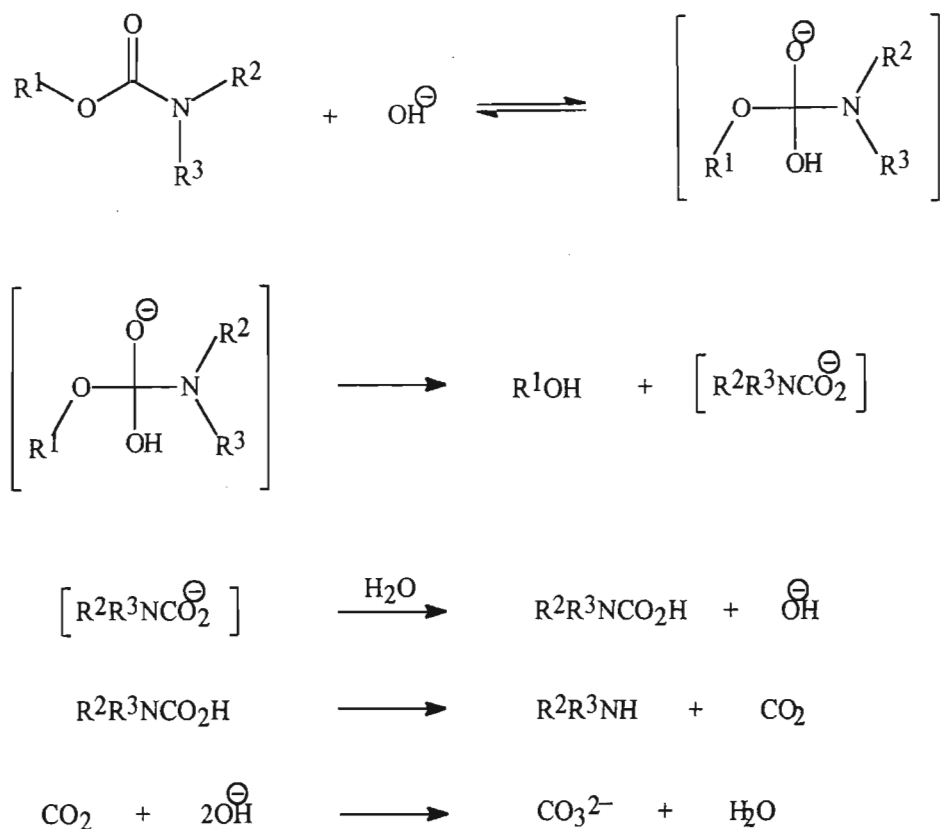
1.6 Reactions of Carbamates

1.6.1 Thermal Decomposition

The degree of *N*-substitution of carbamates has a large influence over the thermal stability and the decomposition products of these compounds. *N,N*-disubstituted carbamates are the most stable and rarely decompose cleanly; *N*-unsubstituted carbamates are the least stable and decompose to allophanates, cyanuric acid and alcohol; *N*-monosubstituted carbamates are of intermediate stability and the decomposition products include isocyanates, alcohols, olefins, ureas, carbodiimides and carbon dioxide. The rate of thermal decomposition is greatly enhanced by the presence of trace amounts of metal salts⁶.

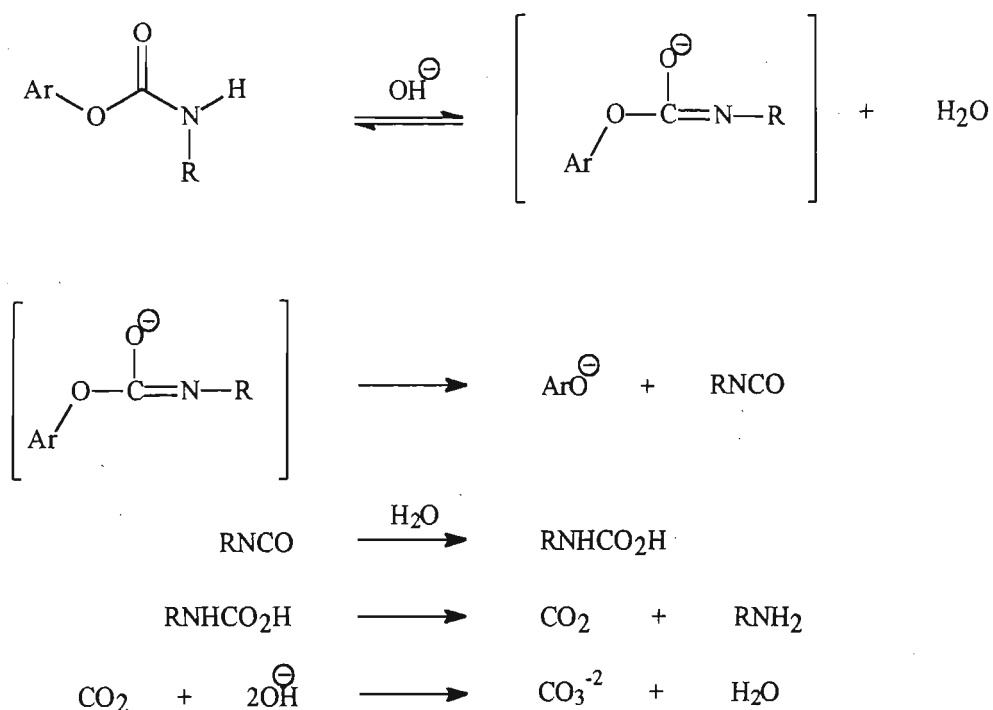
1.6.2 Alkaline Hydrolysis

The hydrolysis of *N,N*-disubstituted, *N*-monosubstituted and *N*-unsubstituted carbamates of aliphatic alcohols takes place by the mechanism shown in Scheme 13.



Scheme 13

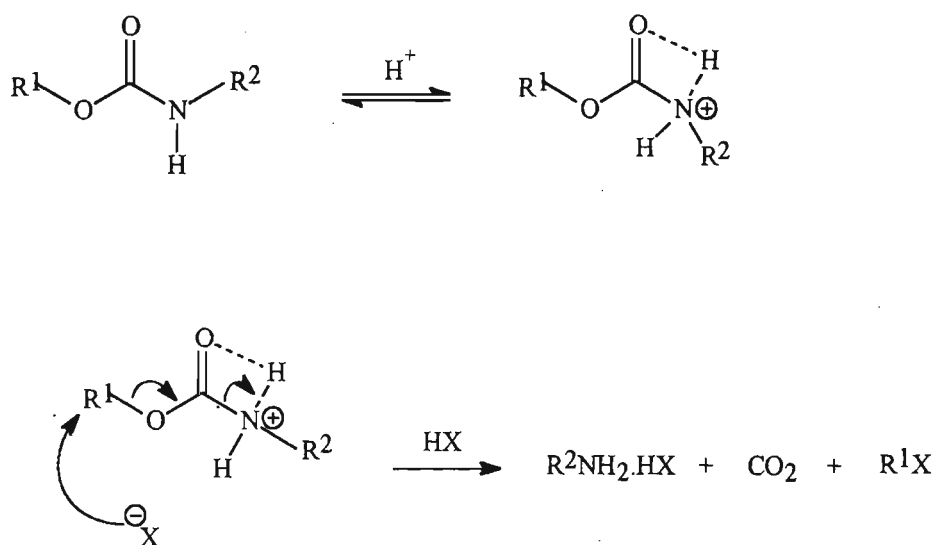
Phenolic ($\text{R}^1 = \text{Ar}$) carbamates hydrolyse more rapidly than the aliphatic carbamates by a different mechanism, due to the elimination of the phenoxide anion to form an isocyanate intermediate (Scheme 14). However, *N,N*-disubstituted aromatic carbamates follow the decomposition mechanism shown in Scheme 13 because of the inability of these compounds to form the isocyanate species.



Scheme 14

1.6.3 Acidic Hydrolysis

The treatment of carbamates with HCl or HBr in glacial acetic acid results in the protonation of the carbamate followed by halide attack on the alkoxy group. This leads to an alkyl halide, an ammonium halide salt, and CO₂ (Scheme 15).

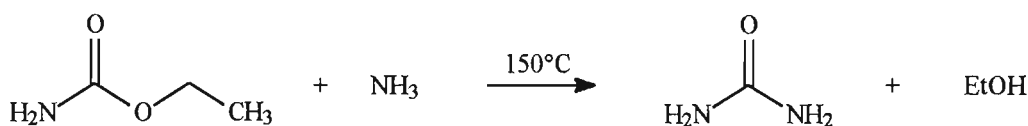


Scheme 15

Under other conditions, carbamates are quite stable to acids, for example, anhydrous HCl or BF_3 do not decompose carbamates⁶.

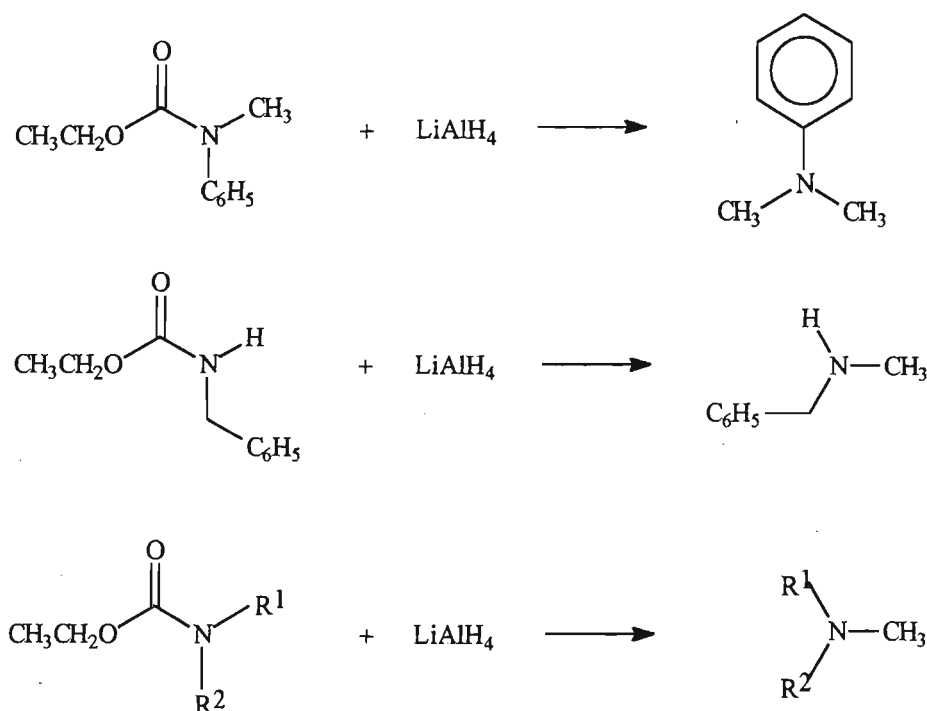
1.6.4 Reactions at the Ester Group

The discovery by Werner²¹ in 1918 that heating (150°C) ethyl carbamate and ammonia produced urea and ethanol (Scheme 16) has been exploited in the preparation of *N,N'*-dialkylureas from *N*-alkylcarbamates²².



Scheme 16

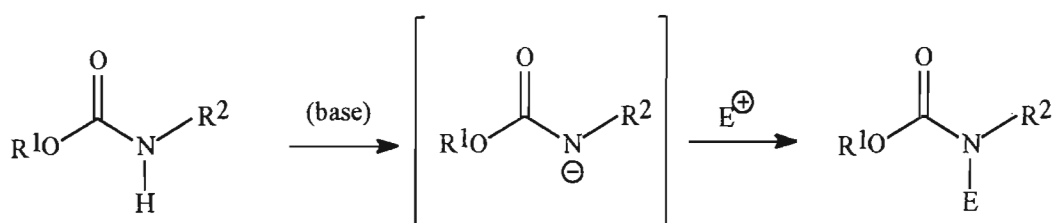
The reduction of carbamate esters by lithium aluminium hydride (LiAlH_4)^{23,24} has been found to be a useful preparation of secondary and tertiary methyl amines (Scheme 17). The reactions proceed rapidly (reflux 1 hour) and the products are produced in good yields.



Scheme 17

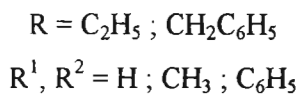
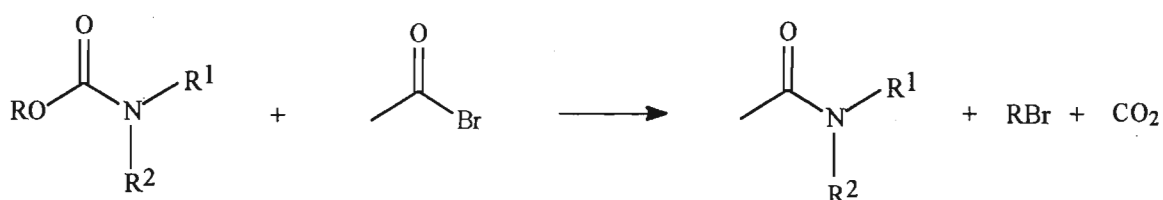
1.6.5 Reactions at the Amido Group

Substitution of *N*-monosubstituted or *N*-unsubstituted carbamates can be achieved by the generation of a nucleophile from the carbamate by treatment with a base. Subsequent treatment of this intermediate with an electrophile yields an *N*-disubstituted or *N*-monosubstituted carbamate (Scheme 18).



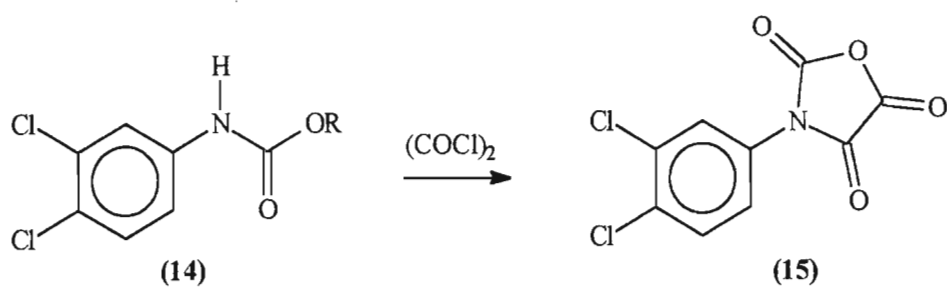
Scheme 18

N-substituted acetamides can be prepared by the reaction of a carbamate with acetyl bromide, producing the substituted acetamide, an alkyl bromide and carbon dioxide (Scheme 19). Under the same conditions, acetyl chloride does not react with *N,N*-disubstituted or *N*-phenyl carbamates²⁵.

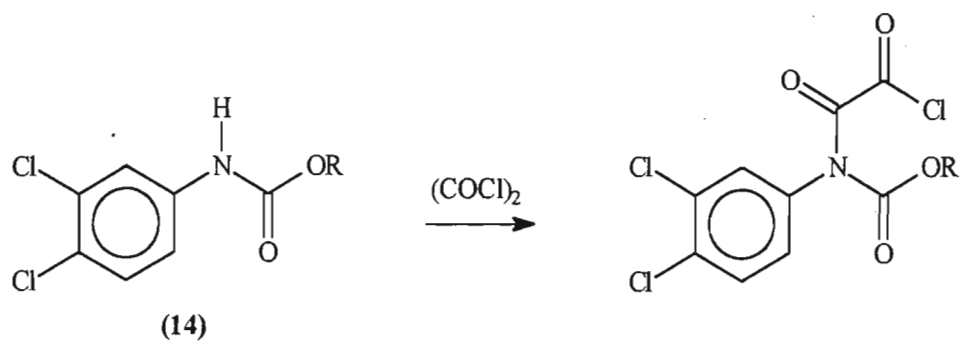


Scheme 19

3-(3,4-Dichlorophenyl)oxazolidinetrione (15), a cyclic anhydride, has been prepared by the treatment of isopropyl 3,4-dichlorocarbanilate (14) with oxalyl chloride (Scheme 20). The reaction produces propylene as a by-product²⁶.



$\text{R} = {}^i\text{Pr} ; {}^s\text{Bu} ; {}^t\text{Bu} ; \text{C}_6\text{H}_{11}$

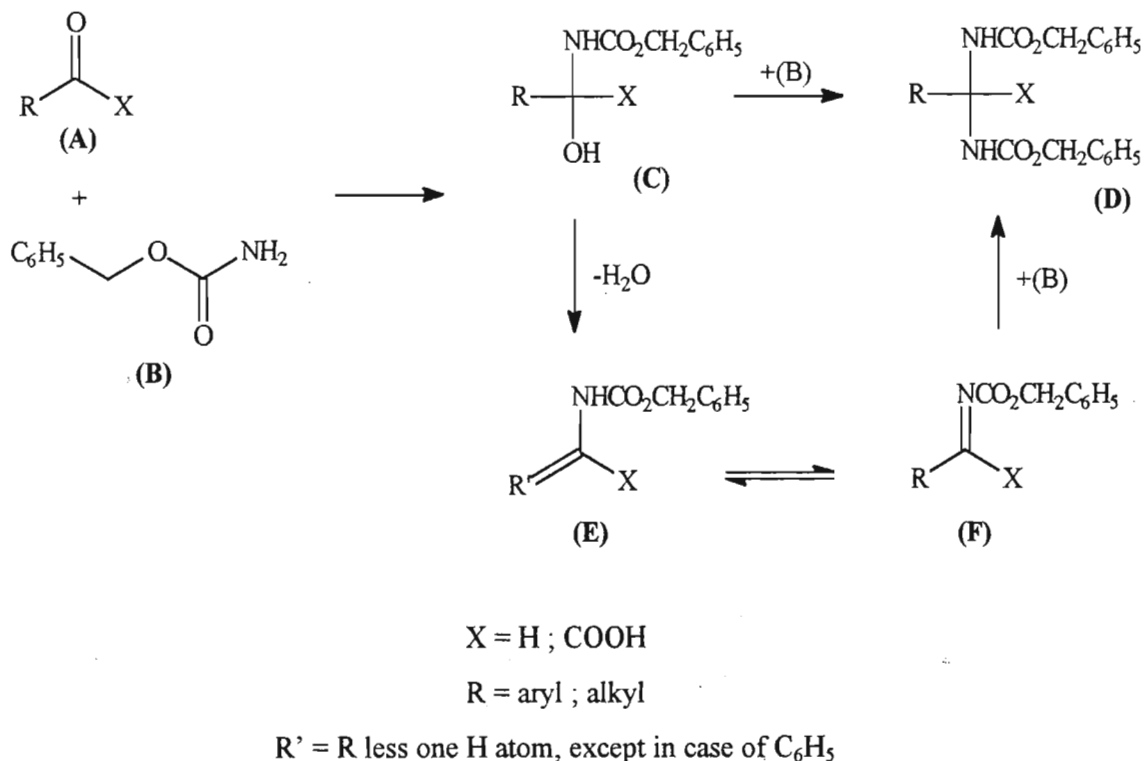


$\text{R} = \text{CH}_3 ; \text{CH}_2\text{CH}_3 ; {}^n\text{Pr}$ (no cyclization)

Scheme 20

1.6.6 Reactions with Carbonyl Groups

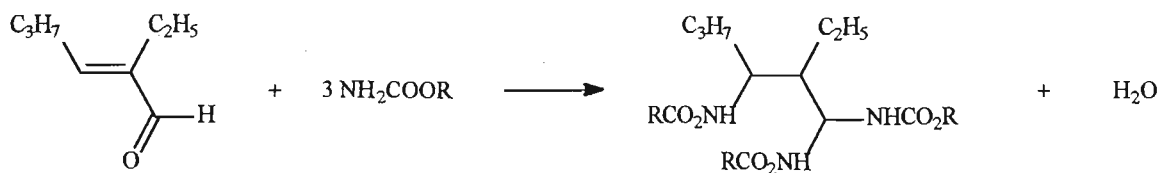
Benzyl carbamates have been found to condense in a 2:1 ratio with both aromatic and aliphatic aldehydes or α -keto acids (Scheme 21)^{27, 28}



Scheme 21

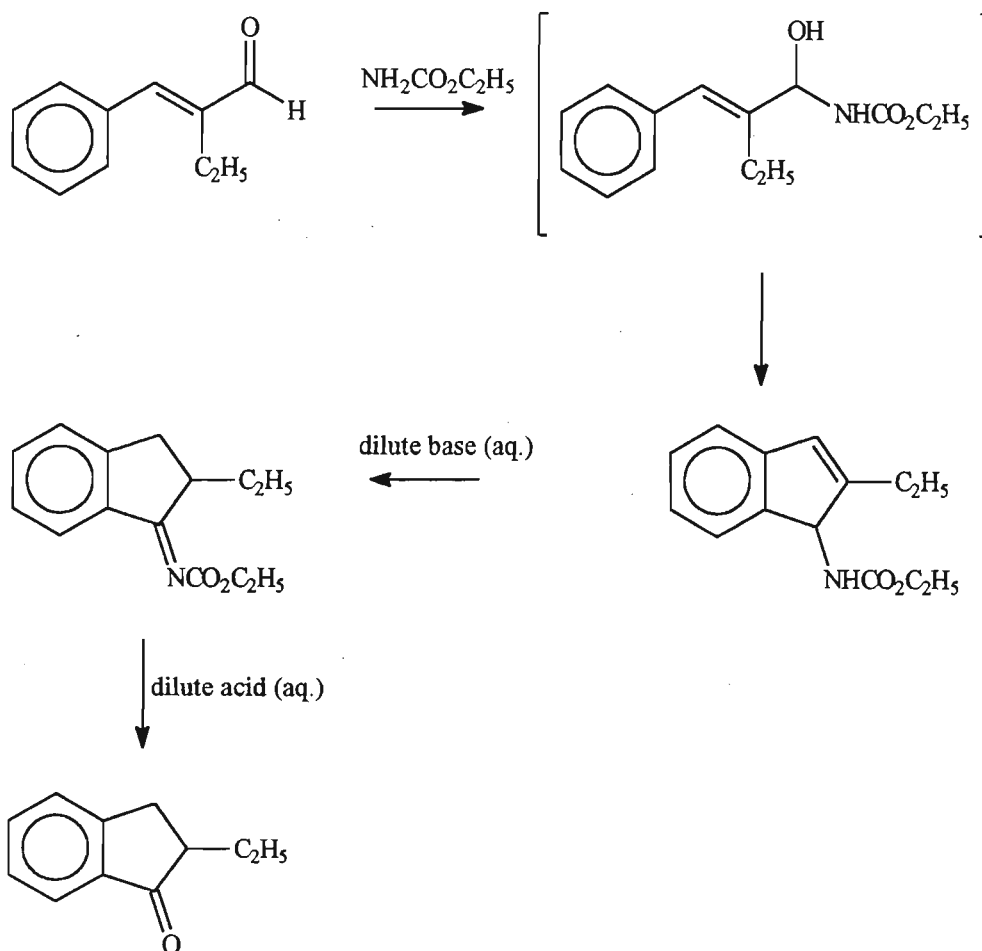
Hydrolysis of species E or species D by boiling in dilute aqueous HCl reverses the reaction yielding species A and B. Catalytic hydrogenation of aldehyde-derived products afford primary amines, while α -keto acid-derived products produce α -amino acids.

In a similar reaction, three moles of carbamate have been found to add to α,β -unsaturated aldehydes. Two moles add to the carbonyl and one mole to the C=C double bond²⁹ (Scheme 22).



Scheme 22

The addition of carbamates to aromatic aldehydes has been exploited as a route to substituted indanone derivatives from readily available aldehydes³⁰. α -Ethylcinnamaldehyde reacts with ethyl carbamate in a 1:1 addition yielding the indanone derivative (Scheme 23).

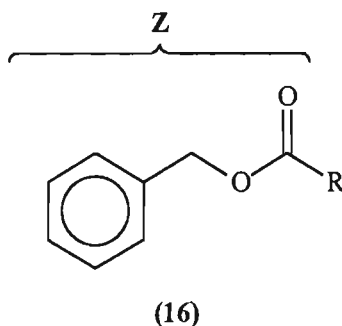


Scheme 23

1.7 Carbamates as Synthetic Intermediates

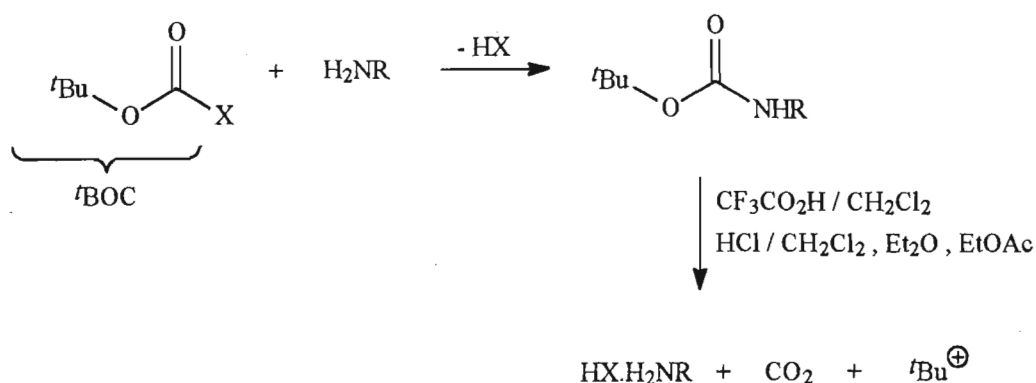
1.7.1 Protecting Group Abilities of Carbamates

The importance of protecting groups in organic synthesis was first realised by E. Fisher in 1895. Both the chloroacetyl and urethane (carbamate) groups were used as *N*-terminal protecting groups in peptide synthesis. This was, however, an unreliable method for addressing the problems in peptide synthesis. 37 Years later, Bergman and Zervas introduced the benzyloxycarbonyl (16) group as an easily and selectively removable protecting group in peptide synthesis⁹.



The benzyloxycarbonyl group can be removed under a variety of conditions. By substitution of the benzyl system, the stability can be varied to give a range of benzyl-type carbamate (urethane) protecting groups of different degrees of stability, depending on the required properties.

Alkyl urethanes are also widely used as blocking groups in organic synthesis. The *tertiary*-butoxy carbonyl group ('BOC) is frequently used as an amino-protecting function in peptide synthesis. The 'BOC group^{9, 31} is easily introduced in good yields and removed in quantitative yields by trifluoroacetic acid/dichloromethane or hydrochloric acid in dichloromethane, ether or ethyl acetate (Scheme 24). Under these conditions of cleavage, the "Z" group remains unaffected. However, undesirable side products can form during the cleavage due to the generation of the 'Bu cation, which is readily attacked by nucleophiles. In the absence of a nucleophile, the cation eliminates a proton to form isobutene.

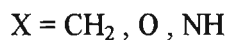
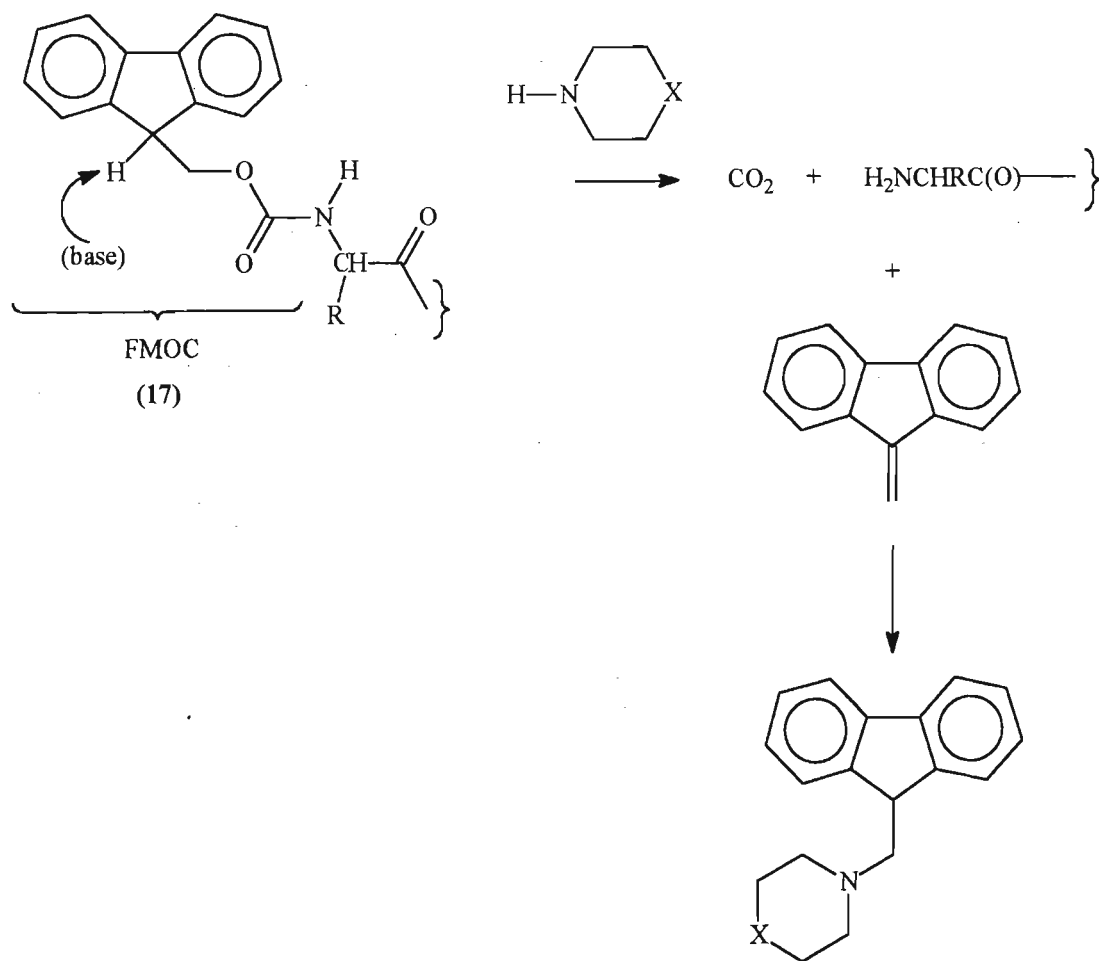


$\text{HX} = \text{HN}_3$ (azide), HOCO_2^tBu (pyrocarbonate), HONCPhCH_3 (oxime)

Scheme 24

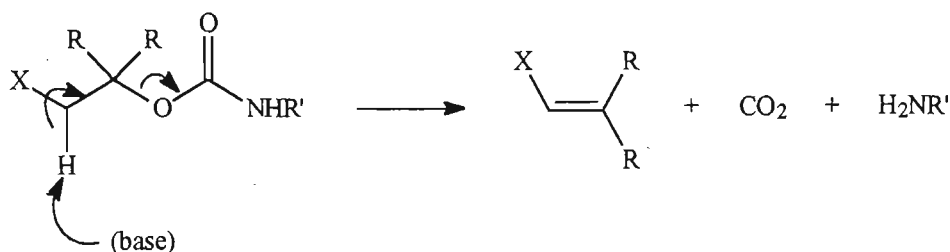
As in the case of the “Z” groups, a series of alkyl carbamate-type protecting groups has been synthesised with different degrees of stability. A major advantage of the ^tBOC group is the stabilisation of the cationic intermediate formed during deprotection by the positive inductive effect of the methyl groups in the ^tbutyl substituent. By the introduction of substituents on the blocking group, varied acid sensitivity can be obtained by choosing substituents with different inductive effects.

In both of the above cases, the urethane-type protecting groups are acid sensitive. In 1970, base-sensitive urethane-type blocking groups^{9, 32} such as Fmoc (17) were introduced (Scheme 25).



Scheme 25

Such groups are stable to HBr/HOAc and TFA . One disadvantage of these species is that some are not easily dissolved in organic solvents. Another disadvantage is that the deprotected amine can react with the dibenzofulvalene. This has been countered by the use of cyclic amines in the deprotection reaction. The initial step in the deprotection of the acid stable urethanes is shown in **Scheme 26**. As in the case of "Z" and 'BOC type groups, variation of the substituent (X) greatly influences the reactivity of the base X.

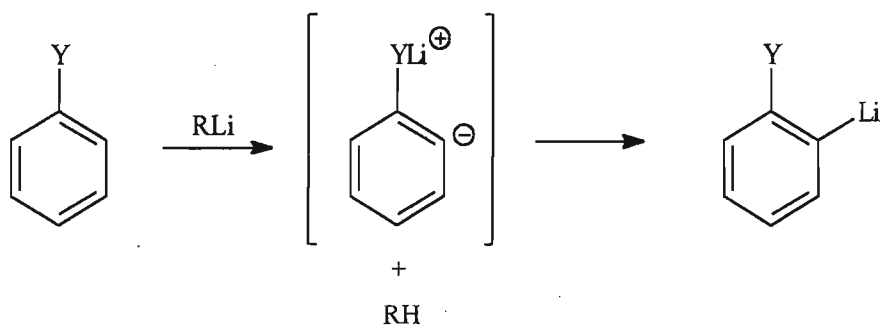


Scheme 26

1.7.2 Activating-Stabilising Abilities of Carbamates

1.7.2.1 Directed *ortho*-Metalation or β -Metalation

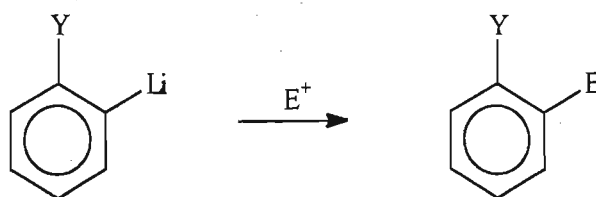
Directed *ortho*-metalation (DoM) was discovered independently by Gilman and Bebb³³, and Wittig and Fuhrmann³⁴ when anisole was deprotonated in the *ortho*-position using $n\text{BuLi}$ ³⁵. Studies have shown that in the metalation of substituted aromatics, the incoming metal atom tends to replace a hydrogen atom *ortho* to the heteroatom-containing substituent³⁶ (Scheme 27).



Y = directing metalation group (DMG)

Scheme 27

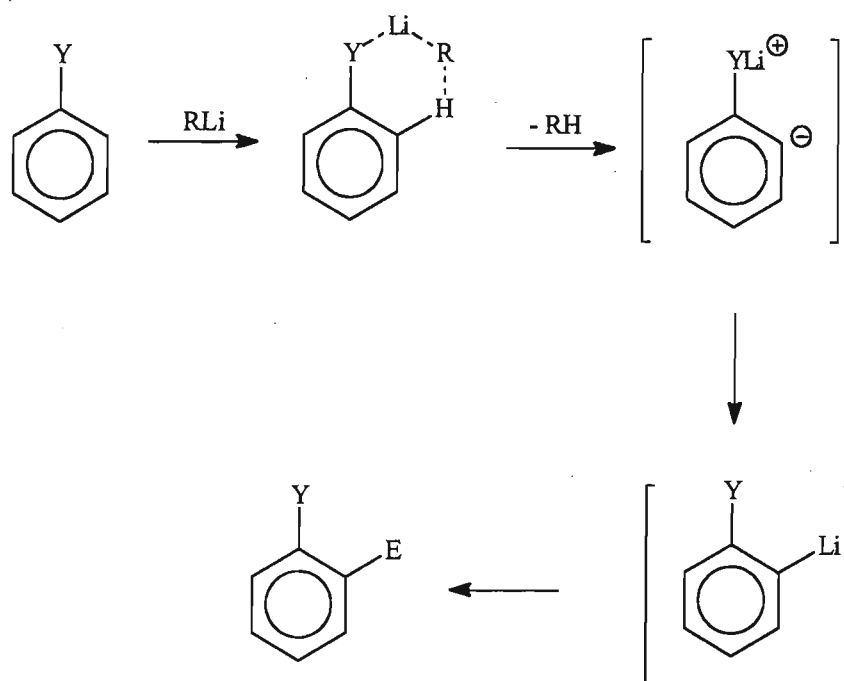
Subsequent treatment of the organolithium species with a suitable electrophile yields an *ortho*- or 1,2-disubstituted product (Scheme 28).



Scheme 28

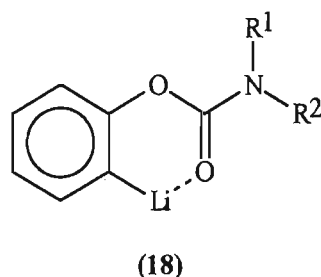
Many DMG's have been identified and evaluated for their potential use in organic synthesis. They have been roughly divided into strong, moderate, and weak directing groups since the different groups have different activating effects^{35, 36}.

The substitution reaction can be viewed as a three step process: co-ordination of the alkyllithium species to the heteroatom of the directing group; following this (or at the same time), the carbanionic portion of the alkyllithium base removes an adjacent hydrogen atom as a proton generating the *o*-lithiated product; reaction of the organolithium species with an electrophile resulting in a 1,2-disubstituted product^{35, 36, 37} (Scheme 29).



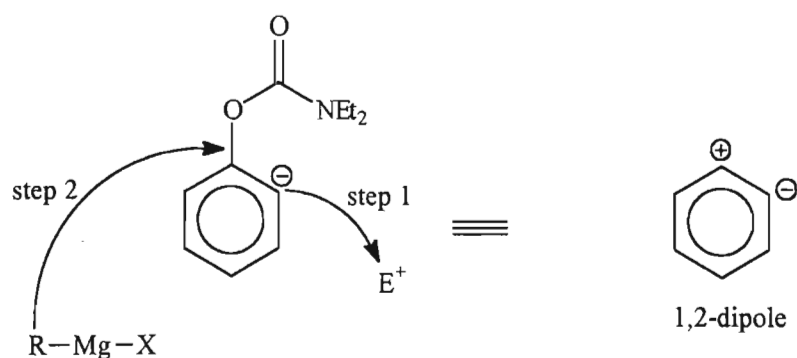
Scheme 29

In order for the deprotonation to be successful, the DMG must function as a good co-ordination site for the alkyl-lithium base and as a poor electrophile in order to prevent nucleophilic attack by the base³⁵. The carbamate (18) possesses both of these qualities and has been shown to be a powerful DMG^{35, 38}. Additionally, the carbamate has the ability to function as a “carrier” of an amide, another powerful DMG, transferring the amide portion of the carbamate to the *ortho*-position from where it can also influence metalation of aromatic systems. The abilities of the carbamate and amide DMG’s are not limited to phenyl carbamates and have successfully been extended to other aromatic systems³⁵.



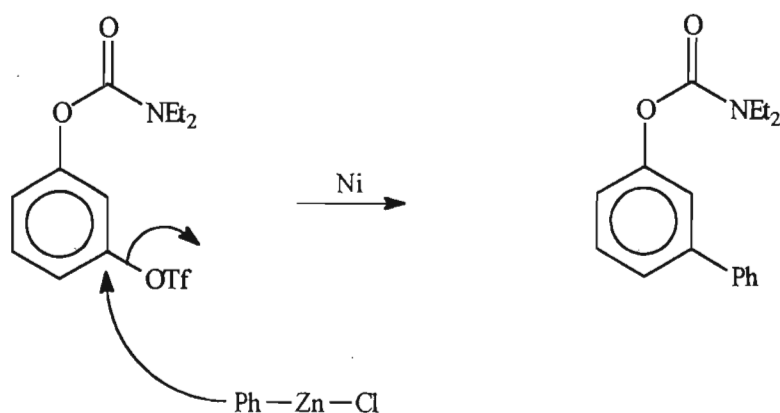
Following *ortho*-substitution with an electrophile, the carbamate can be removed in high yields by either reduction (LiAlH_4 / THF / reflux ; H^+) or hydrolysis (NaOH / aq. CH_3OH or $\text{HO}(\text{CH}_2)_2\text{OH}$ / reflux), depending on the sensitivity of the introduced substituent³⁸, yielding an *ortho*-substituted phenol.

Recent developments have shown that it is possible to synthesise polysubstituted aromatics *via* nucleophilic substitution of carbamates derived from phenols by a Grignard reagent, in the presence of a nickel catalyst³⁹. The combination of the directed *ortho*-metalation using the carbamate and the nucleophilic substitution of the carbamate establishes an aromatic equivalent of a 1,2-dipole (Scheme 30).



Scheme 30

An extension of this work, using triflate substituted aryl carbamates, introduces the use of organozinc reagents (RZnX) as nucleophiles. This has considerable value in synthetic procedures because of the chemoselectivity of the zinc-based nucleophile, being unreactive towards aldehydes (CHO), COR, nitriles (CN), carboxylic esters (CO₂R), in contrast to the Grignard reagent (RMgX)⁴⁰. This has been used in the synthesis of functionalised biaryls (Scheme 31).

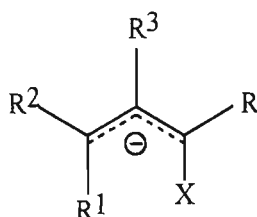


Scheme 31

1.7.2.2 α -Metalation

The α -metalation reaction is the deprotonation of a site α to a heteroatom. The organometallic product is usually a heteroatom-stabilised nucleophilic lithium complex which can be reacted with electrophiles⁴¹.

The heteroatom substituted allylic anion (19) has the ability to function as a homoenolate anion equivalent⁴².



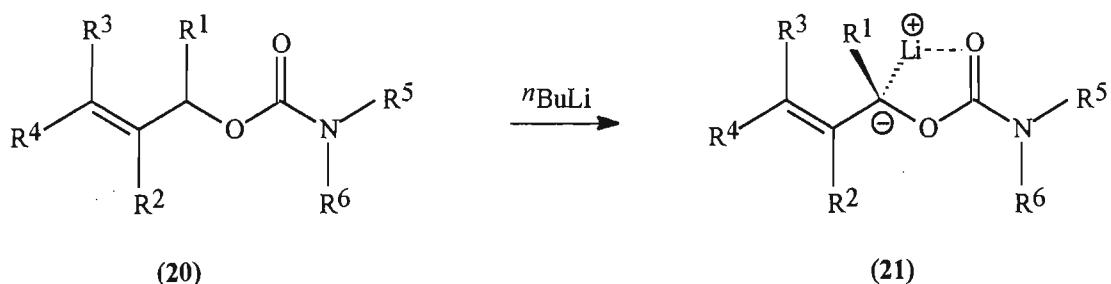
(19)

Reaction of such a species with an electrophile presents a regioselectivity problem in that substitution can occur at either the α - or γ -position. It has been determined that a number of factors influence the selectivity of the reaction^{42, 43}:

- size and nature of the group(s) attached to the heteroatom
- counterion
- solvent and additives
- reaction temperature
- reaction time
- nature of the incoming electrophile

The allyl anions (19) are generated from allyl ethers by deprotonation with a strong base. Anions of allyl ethers have been used in organic synthesis but, due to the selectivity problem, the stability of the anionic species, and the difficulty in generating the anion (particularly in the case of allyl alkyl or allyl trialkylsilyl ethers^{44,45}), their use as homoenolates has been limited. Another problem associated with homoenolates is the tendency to undergo a Wittig rearrangement at higher temperatures^{43, 45}.

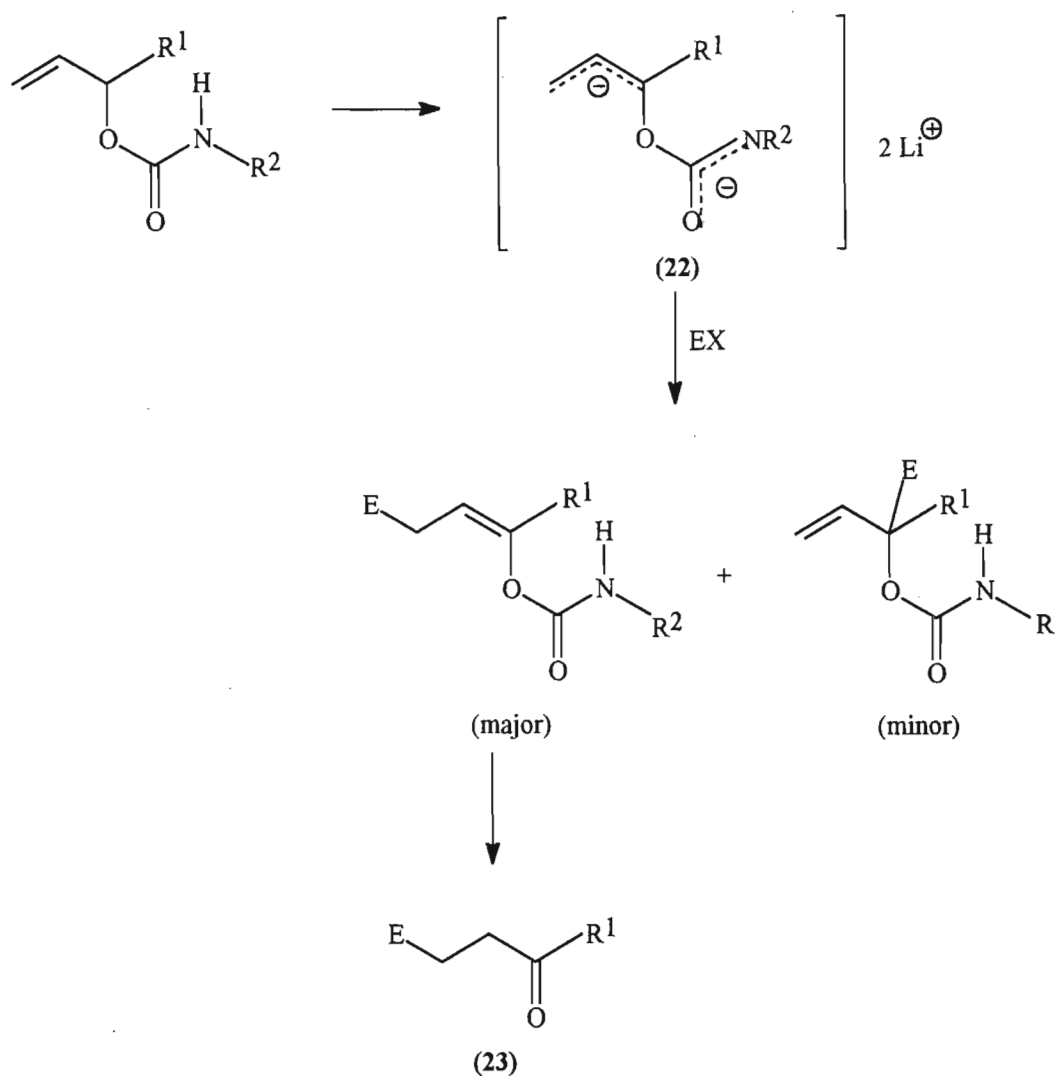
In 1980, it was discovered that the presence of an *N,N*-dialkylcarbamoyl group in the allylic ester (20) afforded highly stabilised allylic carbamate lithium complexes (21) which were not subject to the above limitations^{44, 45}.



The organometallic species (21) has been termed a “tight ion pair” in which the lithium cation is held at the α-carbon atom by complexation with the (carbonyl) oxygen of the ester⁴⁵. (21) is stable up to ~ -50°C (in contrast to other allylic anions) because of this complexation, resulting in increased thermodynamic stability and enhanced acidity of the α-hydrogen atom. Thus allylic carbamates (20) can be readily deprotonated, even with electron donating substituents at positions R¹ and R⁴ (R³).

Regiochemistry of alkylation and silylation is controlled by the position of the substituents present and by the nature of the incoming electrophile⁴⁶.

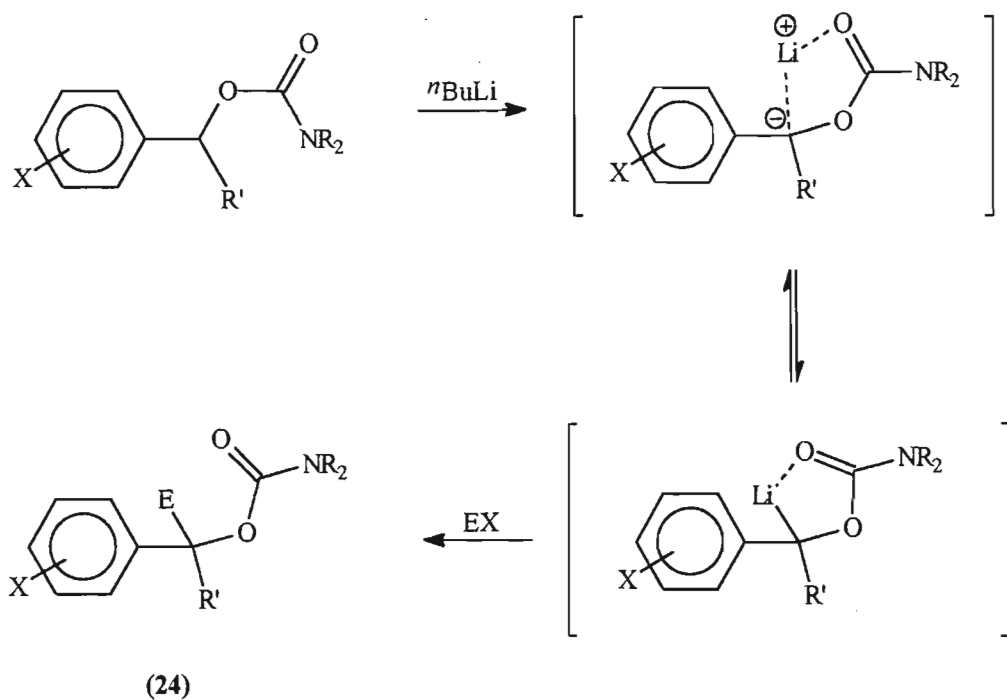
Protection of the carbonyl group of the carbamate from nucleophilic attack is achieved by shielding the carbonyl by sterically-demanding *N*-alkyl groups or by reduction of the electrophilic nature of the carbonyl by the use of lithium salts (Scheme 32). In order to produce the lithium salt, the carbamate is doubly deprotonated by an alkyllithium base and introduces the double lithium salt of a carbamate dianion (22)⁴⁷.



Scheme 32

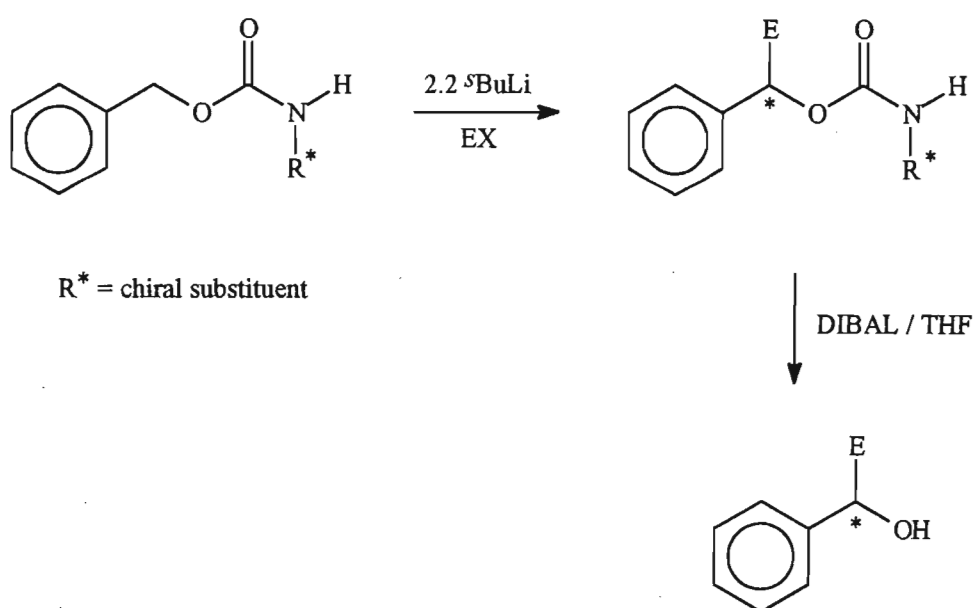
Hydrolysis of the major product yields β -substituted carbonyl compounds (23).

α -substituted benzyl carbamates (24) have been synthesised (Scheme 33) from benzylic *N,N*-dialkylcarbamates⁴⁸. The carbamate group stabilises the anionic intermediate and prevents Wittig-type rearrangements. The intermediate is stable in solution and generally reacts with electrophiles with good yields. Carbamates of secondary benzylic-type alcohols and of benzyl alcohols possessing electron-withdrawing substituents on the ring are also readily deprotonated.



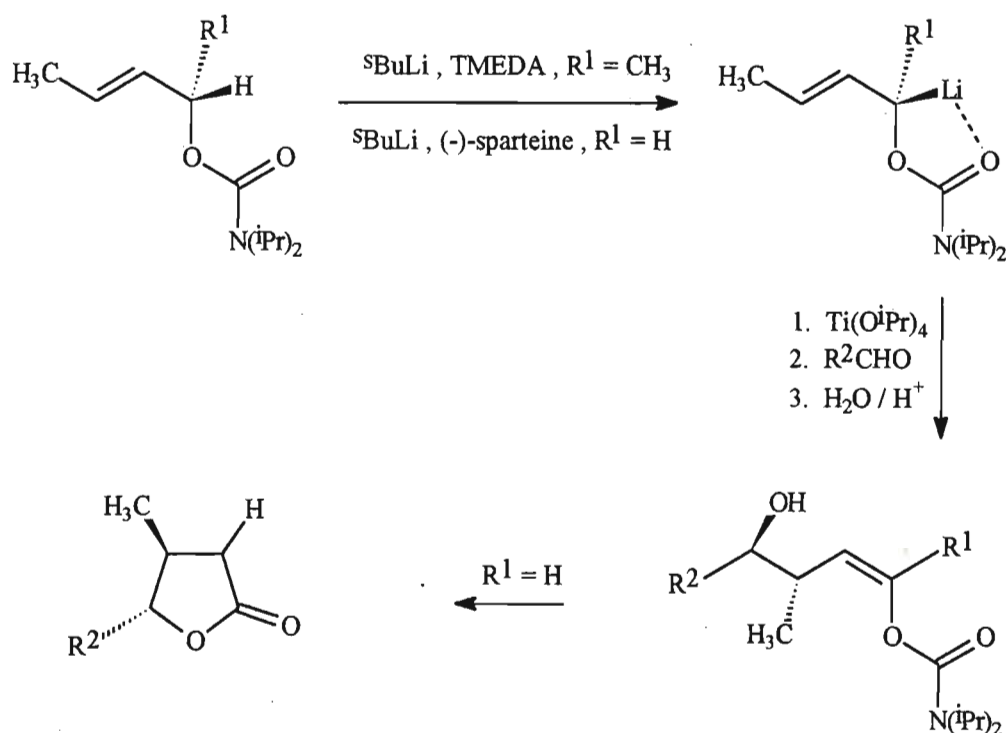
Scheme 33

Secondary and tertiary benzylic alcohols have been prepared in high yields by the deprotection of *N*-alkyl benzyl carbamates using DIBAL in THF⁴⁹. A possible application of this reaction is the synthesis of chiral secondary and tertiary benzyl alcohols by the inclusion of a chiral *N*-substituent (R^*) on the carbamate (Scheme 34).



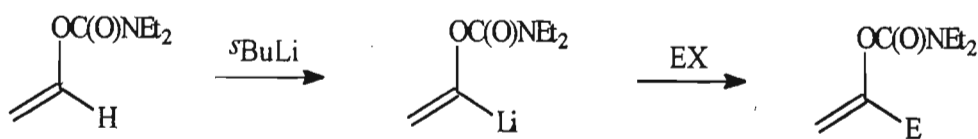
Scheme 34

α -Metalation using alkyllithium bases has been extended to 1,3-chirality transfers in the reaction of α -chiral-2-alkenylcarbamate with aldehydes using lithium-titanium exchange, since deprotonation occurs with retention of configuration and racemization is slow at low temperatures⁵⁰. The further development of this reaction using enantiomerically-pure lithium diamine complexes for deprotonation, followed by lithium-titanium exchange has been used in the synthesis of optically-active lactones (Scheme 35)⁵¹.

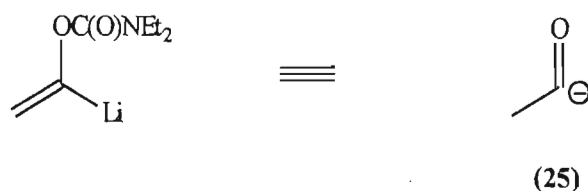


Scheme 35

In addition to being able to function as a homoenolate anion equivalent, the α -metalated enol carbamate ion can be regarded as an equivalent of the acyl anion (25), a valuable “umpolung” synthon for the preparation of α -hydroxyl and α -amino methyl ketones, which can be used as building blocks in organic synthesis⁵² (Scheme 36a & 36b).



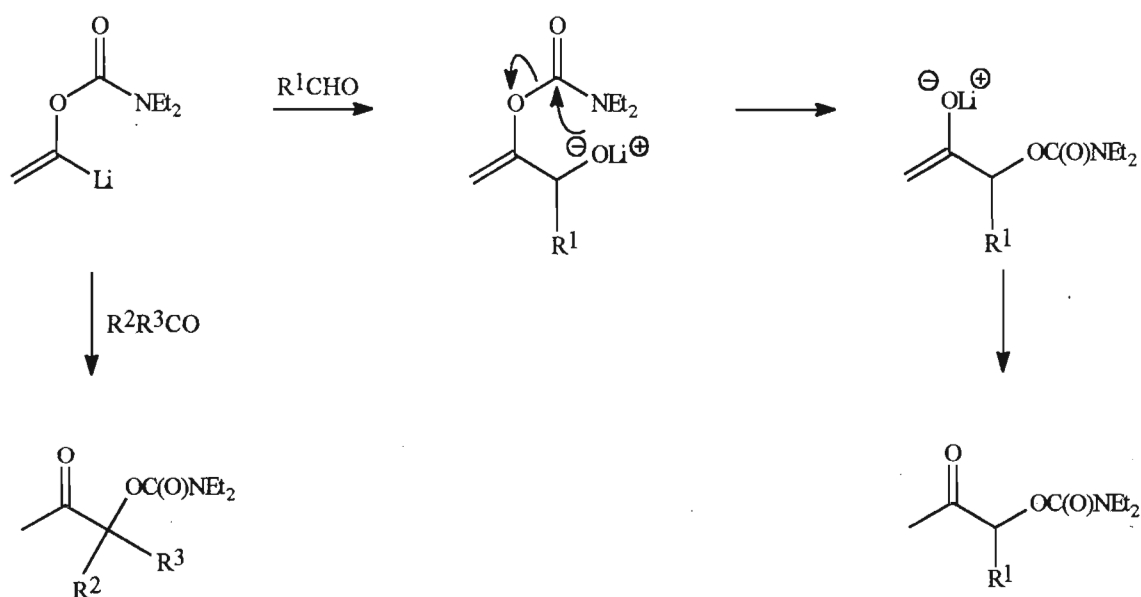
Scheme 36a



Scheme 36b

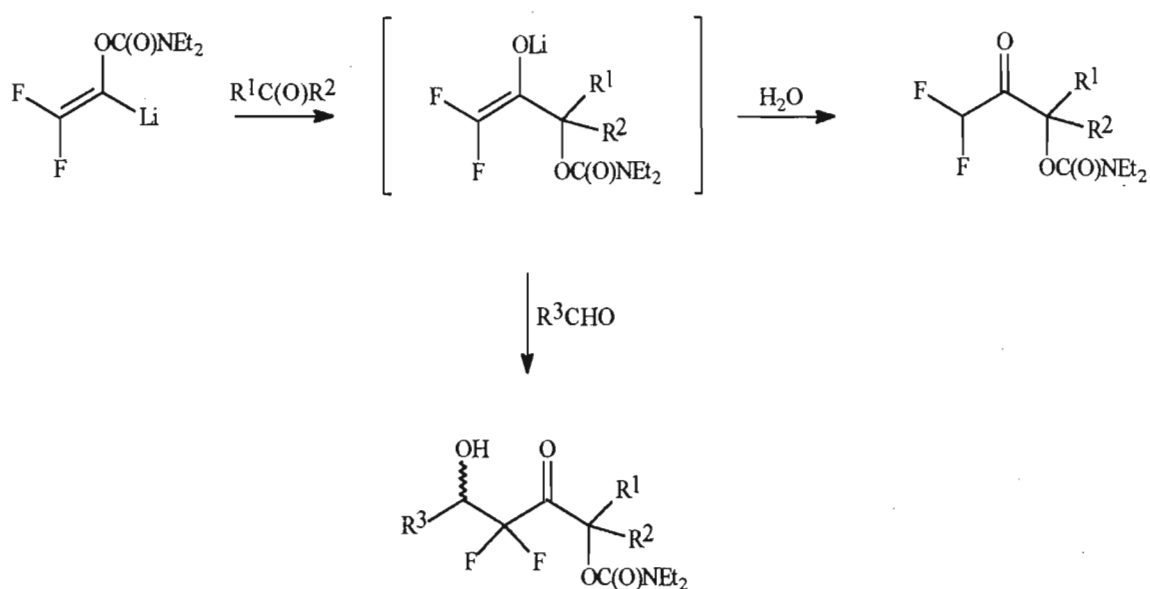
1.7.3 Migratory / Leaving group Abilities of Carbamates

In studying the properties of α -metalated enol carbamates⁵², it was found that when the α -metalated enol carbamate reacted with an aldehyde or ketone, migration of the carbamoyl portion of the carbamate took place (Scheme 37). Reaction with alkyl halides yields the expected α -substituted products.



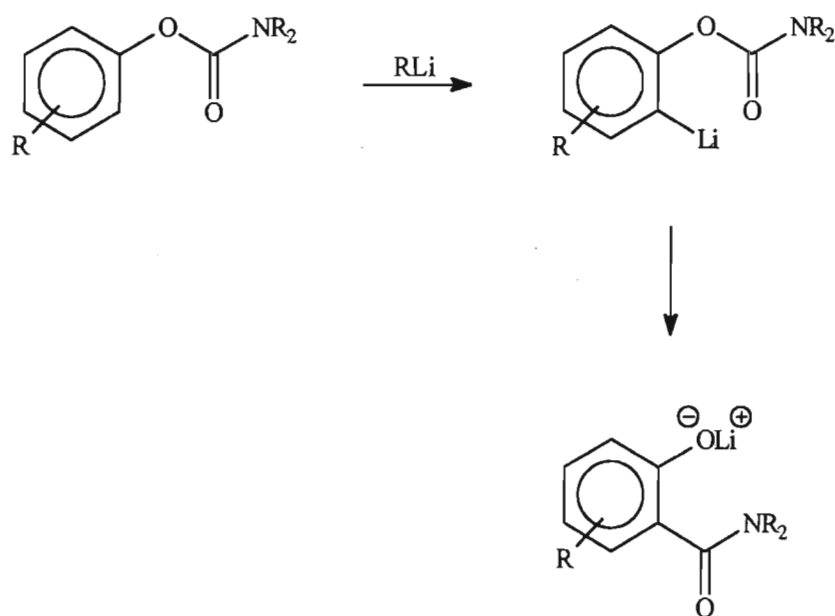
Scheme 37

More recently, metalated difluoroenol carbamates have been found to add to carbonyl electrophiles providing a method for the synthesis of complex fluoroketones from relatively inexpensive and readily available trifluoroethanol. Aqueous work-up of the initial addition product yields difluoromethylketones (*via* carbamoyl transfer), but addition of a second electrophile can be used for the preparation of difluoroaldol type products (Scheme 38)⁵³.



Scheme 38

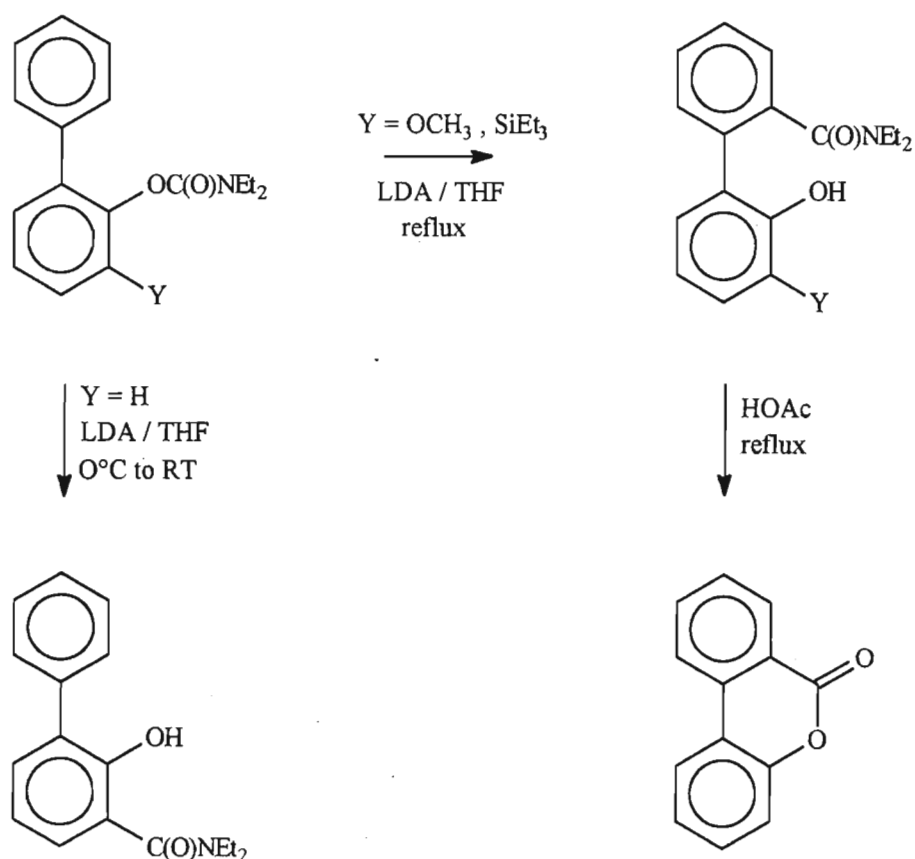
Other work in the field of directed *ortho*-metalation on the substitution of carbamate protected phenols has also shown migration of the amide portion of the carbamate from the oxygen to the *ortho* carbon atom of the aromatic ring³⁵ (Scheme 39).



Scheme 39

This migration has been termed an anionic equivalent of the *ortho*-Fries rearrangement. The migration also takes place in naphthyl, phenanthryl, pyridyl, and quinolinyll carbamates. The rate of rearrangement has been found to depend upon the degree of *N*-substitution and reaction temperature, and it is thought to proceed *via* an intramolecular mechanism³⁵. The carbamate functions as a carrier of the amide and, after protection of the phenol, the amide can participate in further substitution reactions since it is also a powerful DMG.

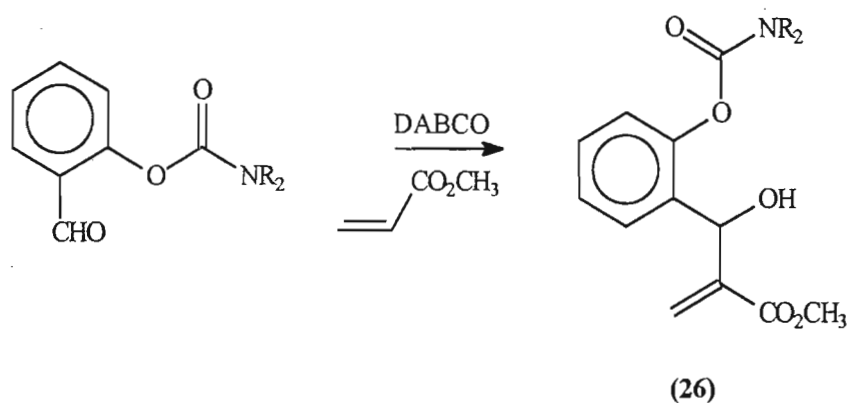
Development of this migration to more remote centres on biaryl *ortho* carbamates has been utilised in the synthesis of hindered biaryls, fluorenones and dibenzo[b,d]pyranones⁵⁴ (Scheme 40).



Scheme 40

Research at this department has shown that the migratory and leaving group abilities of the carbamate can be utilised in the synthesis of substituted chromenes and coumarins^{3b}. The

N,N-dialkylcarbamate ester of salicylaldehyde reacted with methyl acrylate afforded the precursor (26) to both the chromene and coumarin systems *via* a DABCO-catalysed Baylis-Hillman Reaction^{3b} (Scheme 41).

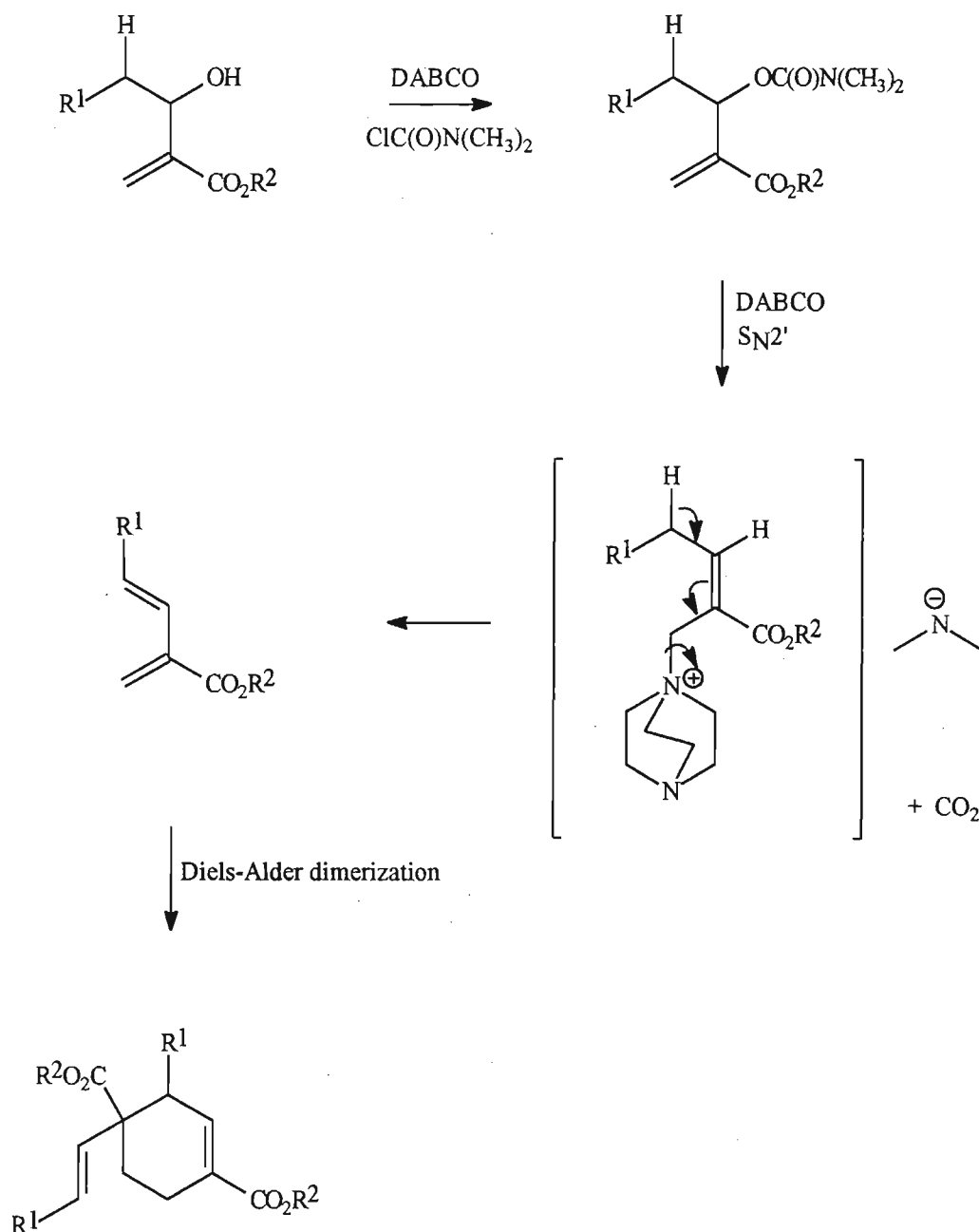


Scheme 41

Subsequent abstraction of the hydroxyl proton using a suitable base and manipulation of the reaction conditions gives the chromene (27) and coumarin (28) in varying yields (Scheme 42).

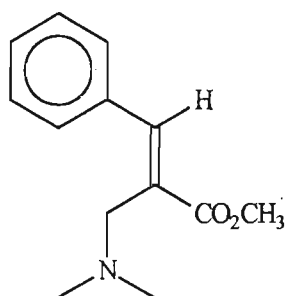
equivalent; the higher yield is attributed to the lower susceptibility to attack by $^t\text{BuLi}$ of the *N,N*-diethylcarbamate, due to the reduced electrophilic character of the ester as a result of a larger inductive effect (ethyl vs methyl)^{3b, 45, 46}.

Substituted cyclohexenes were prepared *via* a DABCO-catalysed Diels-Alder Reaction following the *in situ* generation of a carbamate ester from an allylic alcohol^{3b} (Scheme 43).



Scheme 43

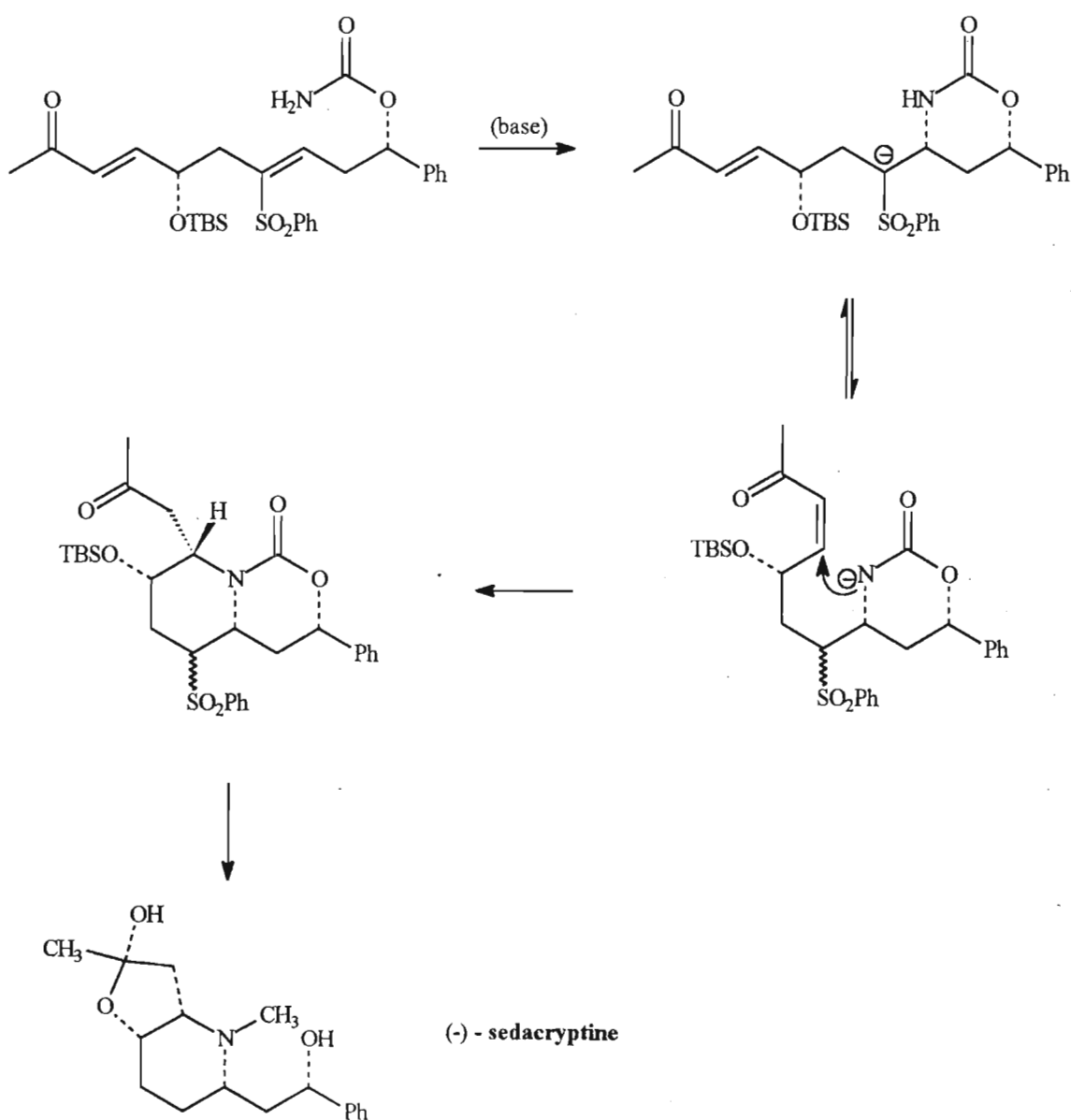
In aromatic allyl alcohols and carbamates, the above mechanism cannot take place. Instead, nucleophilic attack by the amine anion on the carbon atom of the carbon-nitrogen (DABCO) bond replaces DABCO, affording β -amino esters (29) which are important precursors to β -lactam antibiotics^{3b}.



(29)

1.7.4 Other Abilities of Carbamates as Intermediates

Intramolecular conjugate additions of carbamates and amides have recently been used in the synthesis of piperidine and indolizidine alkaloids. In a multistep synthesis of (-)-sedacryptine (Scheme 44), a double intramolecular conjugate addition of the carbamate has been used. Akiyama and Hirama⁵⁵ have proposed that this type of reaction can be utilised in the preparation of other related alkaloid systems.

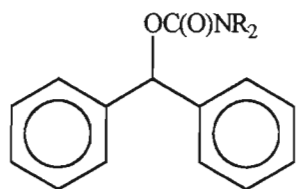


Scheme 44

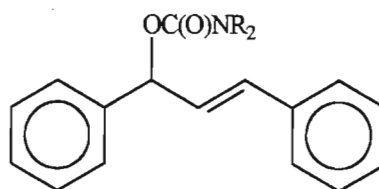
1.7.5 Recent work at these laboratories

1.7.5.1 Biphenyl allylic carbamates

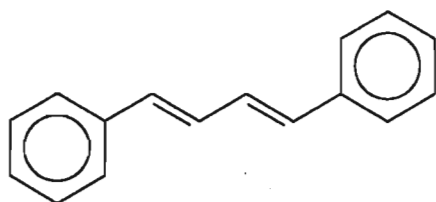
Work at this department on the functionalisation of diphenylmethyl carbamate (**30**) and α,γ -diphenylallyl carbamate (**31**) by electrophilic substitution has shown that the success and the regioselectivity of these reactions (for these compounds) is determined by the steric hindrance of the alkyl substituents on the carbamate, the bulk of the incoming electrophile, and the proximity of the phenyl rings to the abstracted proton. Substitution was found to occur at the α - or γ -position (where available) and hence it was concluded that anionic charge delocalisation did not take place beyond the γ -position. Studies on the nucleophilic displacement of the carbamate ester led to the conclusion that the carbamate is eliminated *via* an S_N2' mechanism, since nucleophilic substitution reactions were successful with species (**31**) but not with species (**30**). Nucleophilic substitution was found to take place at the γ -position of the allylic system^{3a}. It is hoped that the study of these reactions will introduce the possibility of functionalisation of conjugated polyenes (**32**) by the introduction of a carbamate (**33**) to promote reaction with other species, since such polyenes are known to be relatively unreactive^{3a}.



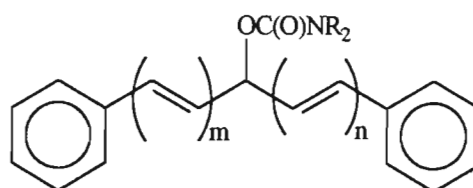
(30)



(31)



(32)



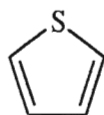
(33)

CHAPTER 2

AN INTRODUCTION TO THIOPHENE CHEMISTRY

2.1 Introduction

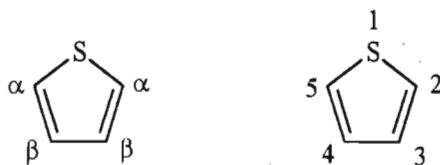
The discovery of thiophene by Viktor Meyer is reported to have been accidental^{56,57}. The indophenine test for aromatic (benzene) compounds, when performed on a sample of pure benzene, did not give the expected blue colour normally produced with benzene obtained from coal-tar. Meyer concluded that the coal-tar benzene contained an impurity responsible for the colour produced during the indophenine test. The impurity was isolated, purified and characterised and subsequently named thiophene (2) in order to indicate its similarity to benzene and to acknowledge the presence of the sulphur heteroatom. It is a colourless, water-insoluble liquid and has (when pure) an odour not unlike that of benzene⁵⁶. It has been stated that thiophene and benzene ought to be compared as one would compare a tortoise and a boa-constrictor; in the same class, but of widely different species, and thiophene is the boa-constrictor⁵⁸.



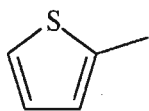
(2)

2.2 Nomenclature

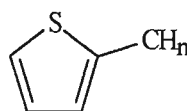
Due to the similarity of thiophene and benzene, in certain physical and chemical properties, the nomenclature of thiophene radicals and derivatives follows the corresponding compounds in the benzene series⁵⁶ (for example, "benzoin" and "thenoin", "benzyl" and "thenyl"). Positions on the ring are denoted by either Greek or numeric characters:



Labelling nuclear positions on the thiophene ring



2-thienyl or α -thienyl

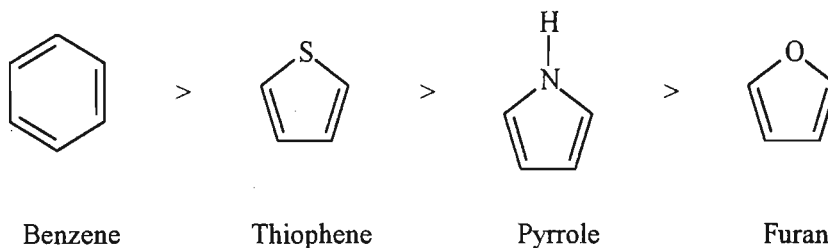


thienyl

The former system of labelling is generally used when referring to either position 2 or 5 (in the case of α) or position 3 or 4 (in the case of β). “Thienyl” is the thiophene equivalent of “benzyl”; although not widely known, the term represents correct nomenclature and there are numerous examples of its use in the chemical literature⁵⁹.

2.3 Aromaticity

Although the relative aromaticity of thiophene has been the subject of much debate, the following series of decreasing aromatic character, based on twelve criteria, has been proposed⁶⁰:



2.4 Reactivity

2.4.1 Electrophilic Substitution Reactions of Thiophenes

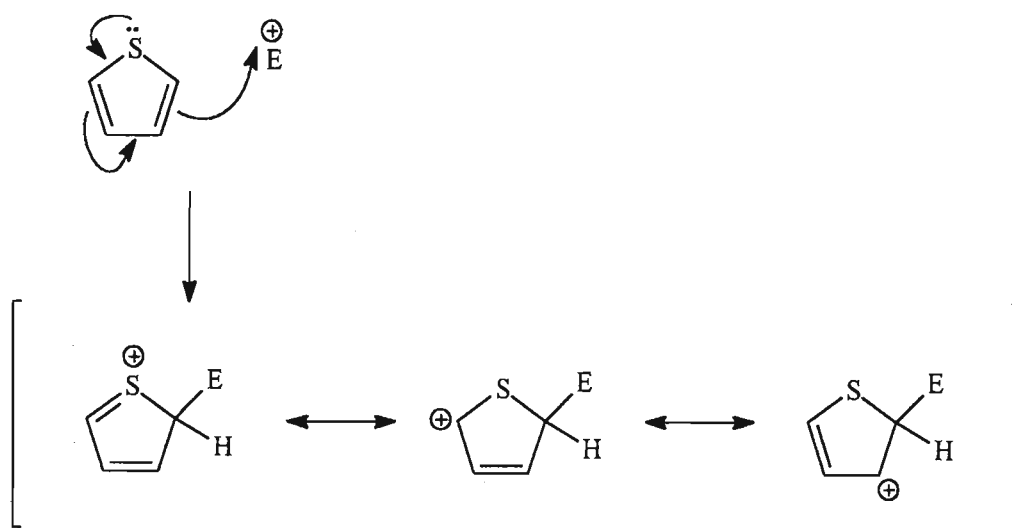
In electrophilic substitution reactions of thiophenes, the following generalisations can be stated⁶⁰:

- Thiophene is much more reactive toward electrophilic substitution than benzene, although the mechanism of substitution is usually the same.
- α -substitution is preferred over β -substitution to the extent that existing substituents can be rearranged or expelled altogether. This α -selectivity decreases with increasing temperature and extreme conditions/vigorous reagents (for example, nitration).

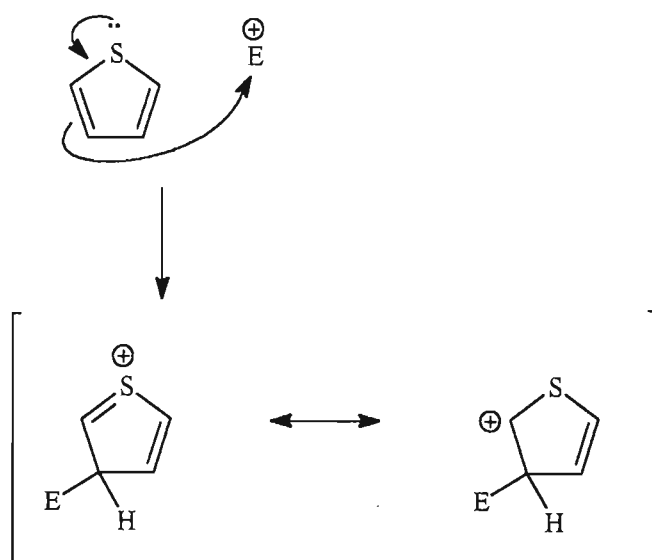
- The more favourable geometry of thiophene (compared with benzene) means that steric effects are less severe in thiophenes than in their benzene analogues.
- Substituents in the α -position have a much greater influence in the further substitution of thiophenes than in benzene; deactivating groups strongly resist *ortho*-substitution, even when the other positions are blocked.
- The nature and course of an electrophilic substitution reaction, with thiophene as substrate, is influenced considerably by the reaction conditions, thus permitting the use of a greater variety of reagents and conditions.

2.4.2 Directing Effects in Electrophilic Substitution

Electrophilic attack on the thiophene ring takes place preferentially at the α -position due to the directing effect of the sulphur atom. The α : β ratio is dependent upon the nature of the electrophile; milder electrophiles are generally more selective⁶¹. The Wheland intermediates (Scheme 45) illustrate the limiting resonance structures for α - and β -attack; three in the α -case (Scheme 45a) and only two in the β -case (Scheme 45b), hence the dominance of α -substitution^{60,61}.



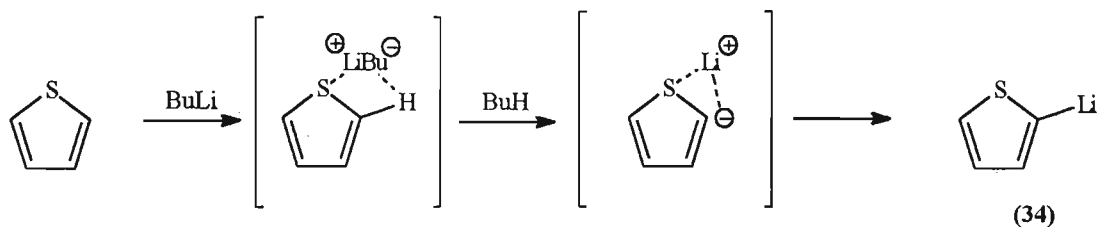
Scheme 45a (α -substitution)



Scheme 45b (β-substitution)

2.4.3 Metalation

In most cases the metalation of thiophene is carried out with organolithium bases in ether as solvent, but magnesium, sodium and mercury derivatives are also widely used⁶⁰. The reaction is rapid, quantitative and in most cases regiospecific. Metalation by butyllithium involves co-ordination of the metal in the metal alkyl to the sulphur in the ring, removal of the neighbouring hydrogen atom as a proton by the butyl anion, and substitution by the metal (Scheme 46).



Scheme 46

The thienyllithium species (34) is one of the most versatile synthetic intermediates. It allows the introduction of a variety of substituents regiospecifically at either the α- or β-position,

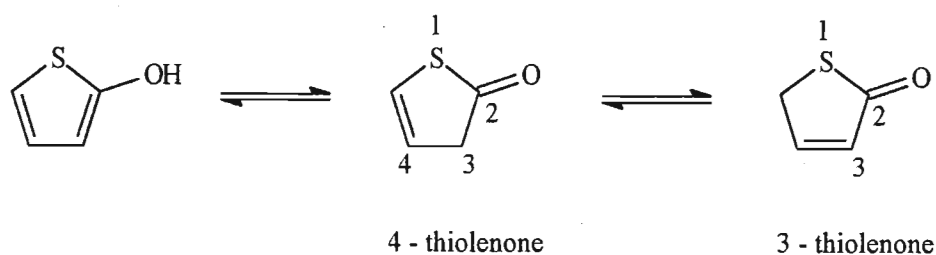
depending on the extent of ring substitution and the steric demands of any existing substituents.

2.4.4 Tautomerism of Thiophenes

In contrast to benzenoid chemistry, in which phenols, anilines and thiophenols are valuable synthetic intermediates, hydroxy-, amino- and mercapto-thiophenes are often unstable, difficult to synthesise and exist in tautomeric form^{60,62}.

2.4.4.1 Hydroxythiophenes

2- And 3-hydroxythiophene have been successfully prepared by the action of oxygen on 2- or 3-thienylmagnesium bromide in the presence of isopropylmagnesium bromide^{63a}, albeit in low yield. A better yield is obtained in the synthesis of 2-hydroxythiophene by the action of *tertiary*-butyl perbenzoate on 2-thienylmagnesium bromide, followed by acidic decomposition of the resulting ether^{63b}. 2-Thienol (2-hydroxythiophene) has three tautomeric forms (**Scheme 47a**). Generally, the non-aromatic, γ -thiolactones are preferred over the hydroxy form, the 3-thiolenone being more prevalent than the 4-thiolenone. In the case of 3-hydroxythiophenes (**Scheme 47b**), only two tautomers are possible and generally the hydroxy form is favoured. The equilibria between the different forms are affected by the nature of the other substituents (if any) and on the nature of the solvent⁶⁰. Both 2- and 3-hydroxythiophenes are unstable⁶² and decompose rapidly even at low temperature⁵⁶.



Scheme 47a



Scheme 47b

2.4.5 Side Chain Reactivity of Thiophenes

Many of the characteristics of benzene are obvious in the substitution chemistry of thiophene and similarities are also observable in the reactions of thienyl substituents. However, as in the case of hydroxy derivatives (also amino- and mercapto-), the thienyl ring bestows some unique properties upon its substituents. Generally, the thienyl ring exerts a negative inductive effect on attached groups, but it has the ability to stabilise both positive and negative charges on a substituent much more effectively than the phenyl group. Thus the thiophene ring can function as either an electron donor or an electron acceptor⁶⁰.

2.5 NMR Spectroscopy

Proton NMR has been described as a valuable tool for structure determination of thiophenes since chemical shifts are well documented and the aromatic ring protons show characteristic coupling constants. In thiophene itself, all four ring protons are coupled to each other and often long range coupling occurs between the ring protons and substituents in substituted thiophenes. This property can be used in the characterisation of complex systems⁶⁰.

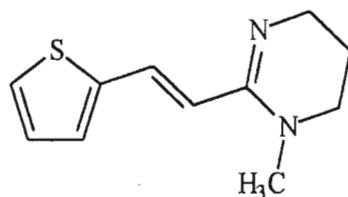
2.6 Odour

One of the characteristics attributed to organosulphur chemistry is that of disagreeable odours. Unquestionably, there are organosulphur compounds that have such properties, but most higher molecular weight divalent organosulphur compounds have little or no smell. The availability, reasonable cost, and synthetic utility of low molecular weight organosulphur compounds suggest that research involving the organosulphurs will at some stage produce fragrances that are less than pleasant⁶⁴.

2.7 Applications of Thiophenes

2.7.1 Biological Applications

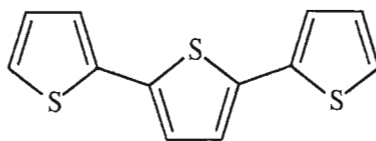
Substituted thiophenes have been and are used in the fields of medicine (choleretics* and antihistamines⁶⁵, anti-inflammatory drugs⁶⁶), agrochemicals (growth inhibitors⁶⁷ and pesticides), flavouring agents⁶⁸, and veterinary products (anthelmintics⁶⁹ - drugs for destroying or expelling worms). In several cases, where a physiologically active compound contains a phenyl group, research has shown that replacement of the phenyl group by an α -thienyl substituent produces an analogue with comparable characteristics⁷⁰; indeed, it is often customary when preparing a new compound (containing a phenyl group) for such an application to synthesise the thiophene derivative to compare activities. Examples of drugs based on thiophene are Ticarcilline® (β -substituted)⁷¹, a semi-synthetic penicillin, and Banminth® (α -substituted)⁶², an anthelmintic also used in chemotherapy.



Banminth

In the field of agrochemistry, α -terthienyl (35) is the most outstanding example. It is naturally-occurring (isolated from the common marigold⁷²) and has been shown to be a potent phototoxin, exhibiting considerable toxicity towards several organisms, because of its efficiency in generating singlet oxygen^{73,74}. Many other naturally-occurring and synthetic thiophenes possess this property and as a result also exhibit phototoxicity (toxic to algae, bacteria, insect eggs, fish, fungi, insect larvae, nematodes, mosquitoes *Aedes aegypti*, *Aedes intrudens*, *Aedes atropalpus*)^{73,75,76}. Besides its pesticidal applications, α -terthienyl has also shown ultraviolet light mediated antibiotic activity⁷⁷. Thus the substituted thiophenes represent an important class of biologically active and naturally-occurring compounds⁷⁸.

* Choleretic, *n.* - An agent that stimulates the secretion of bile by the liver.



(35)

2.7.2 Technological Applications

Conjugated polyenes are widely distributed in Nature (the most obvious examples are the carotenoids⁷⁹). Investigation of such compounds has included studying optical and electrical properties since their conjugated structure confers characteristics that can be exploited in technological applications such as non-linear optics and conductivity studies. According to the soliton theory, electrical conductivity in conjugated polyenes is a consequence of “solitons” or mobile charge defects. One prediction of this theory is that delocalisation along such a conjugated chain is limited. Theoretical and ¹³C NMR studies of neutral and anionic α,ω -diphenylpolyenes of increasing length indicate that the point at which the magnetic properties of the neutral and anionic species converge occurs at approximately 15 CH units, that is, a conjugation length of approximately 30 CH units (charge density was found to be greatest at the centre of the polyenyl anion, diminishing with increasing distance from the chain centre)⁸⁰.

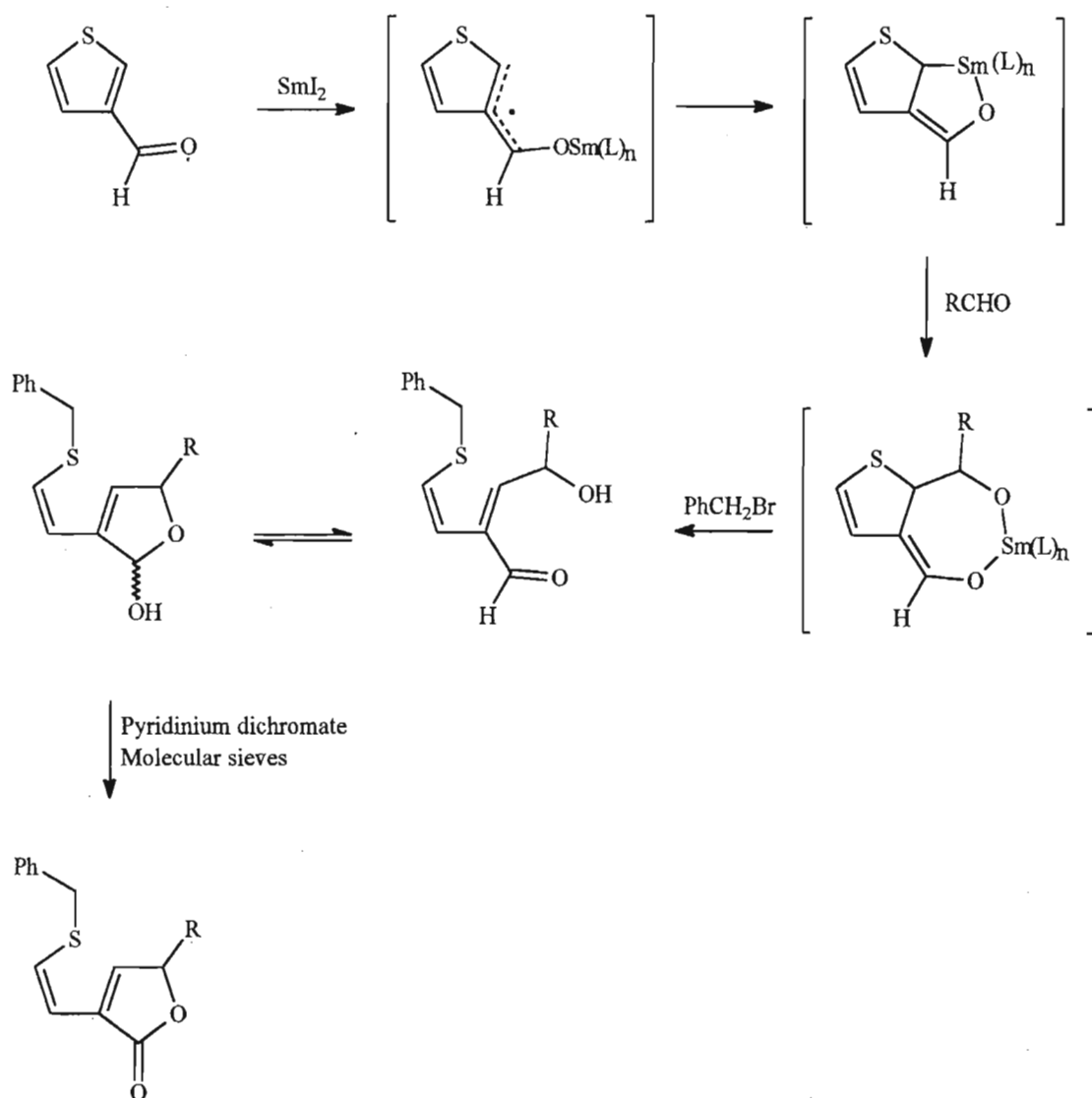
The study of the interaction of the electromagnetic field of light with non-linear optical materials has been termed “non-linear optics” or NLO. The interaction as light passes through such a species causes the light beam to be altered in phase, frequency, amplitude or polarisation. Such non-linear optical materials have been used in the construction of optical devices for commercial application in the fields of laser experimentation, telecommunications, computers and optical signal processing. Much interest has been shown in the NLO properties of thiophenes, particularly because of the lower delocalisation energy (117 kJ/mol) of thiophene over that of benzene (151 kJ/mol), which is the primary conjugated linking group used in NLO materials. Thus thiophene offers better effective conjugation and better π -electron delocalisation than benzene. It has been recognised that thiophene and polythiophene materials are an important category of NLO materials and by variation of the substituents on the thiophene ring and the incorporation of metallic components these compounds have the potential to improve the NLO properties of many previously prepared benzenoid compounds⁸¹.

The polythiophenes also find application as conducting polymers for use in electrochromic devices⁸². Polythiophenes can be engineered to have structures with a wide range of conductivities, ranging from insulator to semiconductor to metal, for application in the field of molecular electronics⁸³ (α,ω -dihexylsexithiophene is the principal component in a fully organic transistor). One major disadvantage to the use of these compounds is their very poor solubility. This has been attributed to strong π - π intermolecular and hydrophobic interactions between the thiophene-based molecules. Improved solubility has been achieved by the inclusion of alkyl substituents in the β -position of the thiophene rings but this lowers the effective conjugation and carrier mobility. Unsubstituted oligothiophenes are reported to be unstable due to the high reactivity of the α -carbon atoms of the terminal thiophene rings⁸³.

2.7.3 Other Applications

2.7.3.1 Synthetic Applications

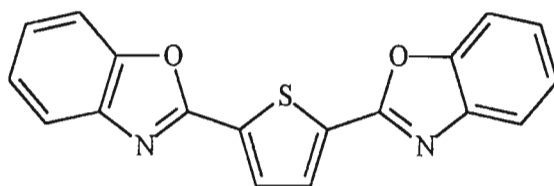
In addition to the biological and technological applications, thiophenes are also potentially useful as precursors in synthetic organic chemistry by the use of ring opening reactions; either desulphurisation in which the ring is opened by sulphur removal, or bond cleavage with the sulphur atom retained in the product (for example, the SmI_2 promoted coupling of thiophenecarboxaldehydes⁸⁴, Scheme 48).



Scheme 48

2.7.3.2 Optical applications

It has been observed that thiophene analogues of coloured benzenoid compounds show a bathochromic shift leading to commercial interest in the use of such compounds as dyes and optical brighteners⁶⁰. These are mainly non-scientific applications - brilliantly coloured paints, textile dyes, paper and washing powder additives. The so-called “whiter-than-white” washing powders contain an optical brightener or optical bleach. Such a substance absorbs radiation in the ultra-violet part of the electromagnetic spectrum and emits in the visible region so that the washed item appears to reflect more light than is incident upon it. 2,5-Dibenzoxazolyl-thiophenes (**36**) are used as brighteners for hydrophobic fibres (for example, polyamides, polyesters, and acrylic fibres)⁸⁵.



(36)

CHAPTER 3

DISCUSSION

3.1 Introduction

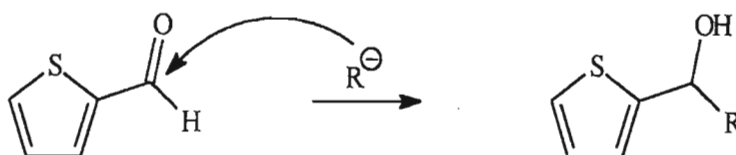
The purpose of this project has been to study the synthesis and functionalisation of thenyl carbamates, in particular their preparation from thenyl alcohols and their substitution with a variety of electrophiles. The aromatic and conjugated nature of the thiophene ring allows negative charge delocalisation in electrophilic substitution reactions and this leads to several different products. Three electrophiles have been used to study the regioselectivity in such systems.

The discussion of the results follows the synthetic route from alcohol through to substituted carbamate. The anomalous results that are especially significant have been discussed separately (3.5 - Other Reactions), while the remainder are included as part of the general discussion.

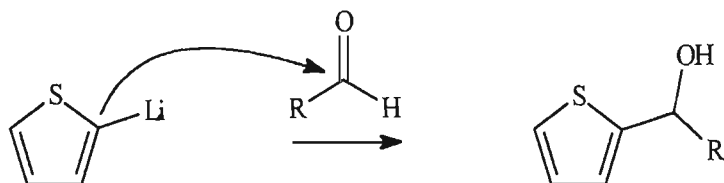
3.2 Preparation of Alcohols

Two readily available starting materials, thiophene and 2-thiophenecarboxaldehyde (Merck[®] and Acros[®] respectively), suggested the following routes to thenyl alcohols:

- nucleophilic attack on the carbonyl of 2-thiophenecarboxaldehyde (**Scheme 49**);
- the use of 2-thienyllithium (2-lithiothiophene) as a nucleophilic reagent for reaction with aldehydes (**Scheme 50**).



Scheme 49



Scheme 50

These reaction routes provide thenyl alcohol and a range of substituted derivatives. The existence of the hydroxy group in each species provides a means of synthesising the carbamates *via* commercially available carbamoyl chlorides (see chapter 1, section 1.5.5 and this chapter, section 3.3). A range of thenyl alcohols was prepared, including both alkyl- and aryl-substituents. These ultimately provide alkyl- and aryl-substituted carbamates. The results are shown in Table 1.

Table 1: Yields of Alcohol Preparations

Alcohol substituent (R)	Thenyl Alcohol	Method of preparation	Yield
H	(37)	Scheme 49 (H)	73%
ⁿ Bu	(38)	Scheme 49 (ⁿ Bu)	64%
Ph	(39)	Scheme 49 (PhMgBr)	77%
1-Naphthyl	(40)	Scheme 49 (NapMgBr)	75%
<i>p</i> -Ph(OCH ₃)	(41)	Scheme 50	60%
<i>p</i> -Ph(NO ₂)	(42)	Scheme 50	85%(crude)
2-Thienyl	(43)	Scheme 50	80%
(2-Thienyl)CHOH	(44)	n/a	2.4%

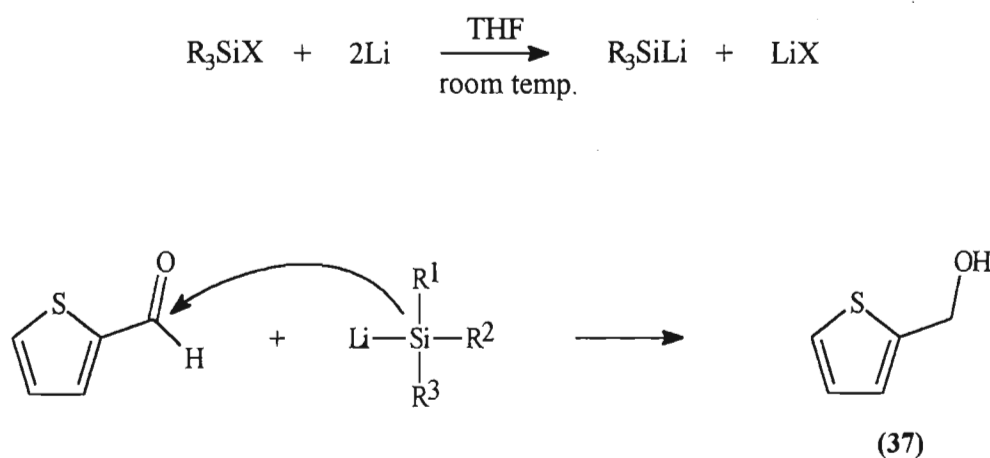
Table 1

3.2.1 Nucleophilic Attack on the Carbonyl of 2-Thiophenecarboxaldehyde

3.2.1.1 Reduction of 2-Thiophenecarboxaldehyde to 2-Thiophenemethanol

Several methods were evaluated for the preparation of 2-thiophenemethanol (37). Initially, since one of the proposed uses of the thenyl carbamates was the electrophilic substitution reaction using silicon-based electrophiles, an attempt was made to reduce 2-

thiophenecarboxaldehyde using a silicon-based nucleophile (**Scheme 51**), prepared by the action of metallic lithium on trialkylsilyl halides⁸⁶. The lithium derivative of the silyl halides is nucleophilic and has been found to add to multiple bonds, a property exploited in the synthesis of α -silylcarbinols⁸⁷.



Scheme 51

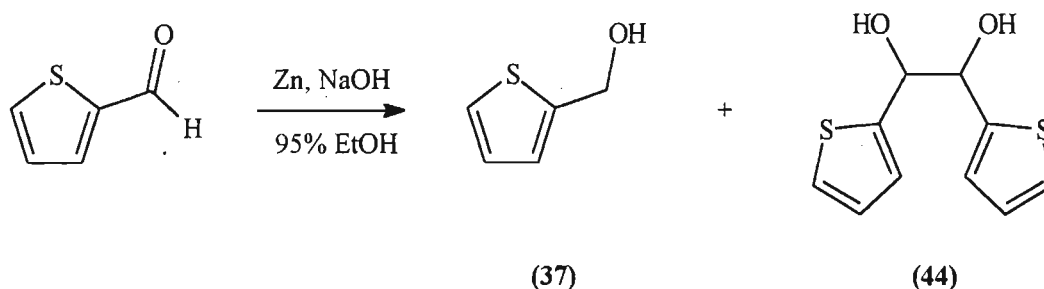
The product (37) results from normal addition of the silyllithium nucleophile to the ketone. The Brook Rearrangement⁸⁷, in which the silicon substituent migrates onto the oxygen of the alcohol functional group, was found to take place. On aqueous work-up, this rearrangement leaves unsubstituted 2-thiophenemethanol (37) as the reaction product (**Scheme 51**), through cleavage of the silyl ether. This method, although providing the required alcohol, was discarded on the basis of long reaction times and the poor reaction yields. After several days, much of the aldehyde remained unreacted. This has been attributed to the difficulty experienced in reliable and efficient preparation of the silyllithium nucleophile. In a more recent publication (1996), in which lithium metal is used, the use of a drybox and an argon atmosphere is recommended for handling such air-sensitive reagents⁸⁸. This technique would undoubtedly improve the yield and reproducibility of this reaction.

Zinc metal, in the presence of aqueous base behaves in a manner similar to that of metallic zinc in aqueous acid. This property means that zinc, in an aqueous alkaline solution, can function as a reducing agent by generating nascent hydrogen and sodium zincate (**Scheme 52**).



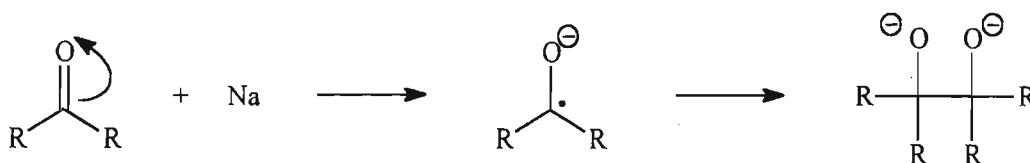
Scheme 52

This method of reduction with zinc has been previously exploited for the reduction of 2-thiophenecarboxaldehyde to thenyl alcohol (37). Using the details published in the *abstract*⁸⁹ (a patent application), this reduction was attempted (Scheme 53) as an alternative to the silyllithium reduction.



Scheme 53

Although the reaction time was considerably less than the silyllithium reduction, the reaction yields were unsatisfactory and another method was sought for the reduction. An interesting by-product, which is not mentioned in the *abstract*⁸⁹, is the pinacol-type coupling product (44) of 2-thiophenecarboxaldehyde, albeit in very low yield. This product is not altogether unexpected, since the bimolecular reduction of aldehydes and ketones (particularly aromatic ketones) by active metals is well-known. A proposed mechanism is that of direct electron transfer, producing a ketyl species which dimerises⁹⁰ (Scheme 54).



Scheme 54

Figure 1 shows the NMR spectrum (¹H) of the 1,2-diol product (44) produced via the zinc/aq. hydroxide method shown in Scheme 53. Two sets of signals are visible suggesting

either a non-symmetrical molecule or a mixture of diastereomers. The latter is more likely since there is no coupling between the thenyl protons and the integral is not the same for the two thenyl signals. If this were the spectrum of a non-symmetrical molecule, one would expect coupling between the non-equivalent thenyl protons (and others) and the integrals for these signals to be the same.

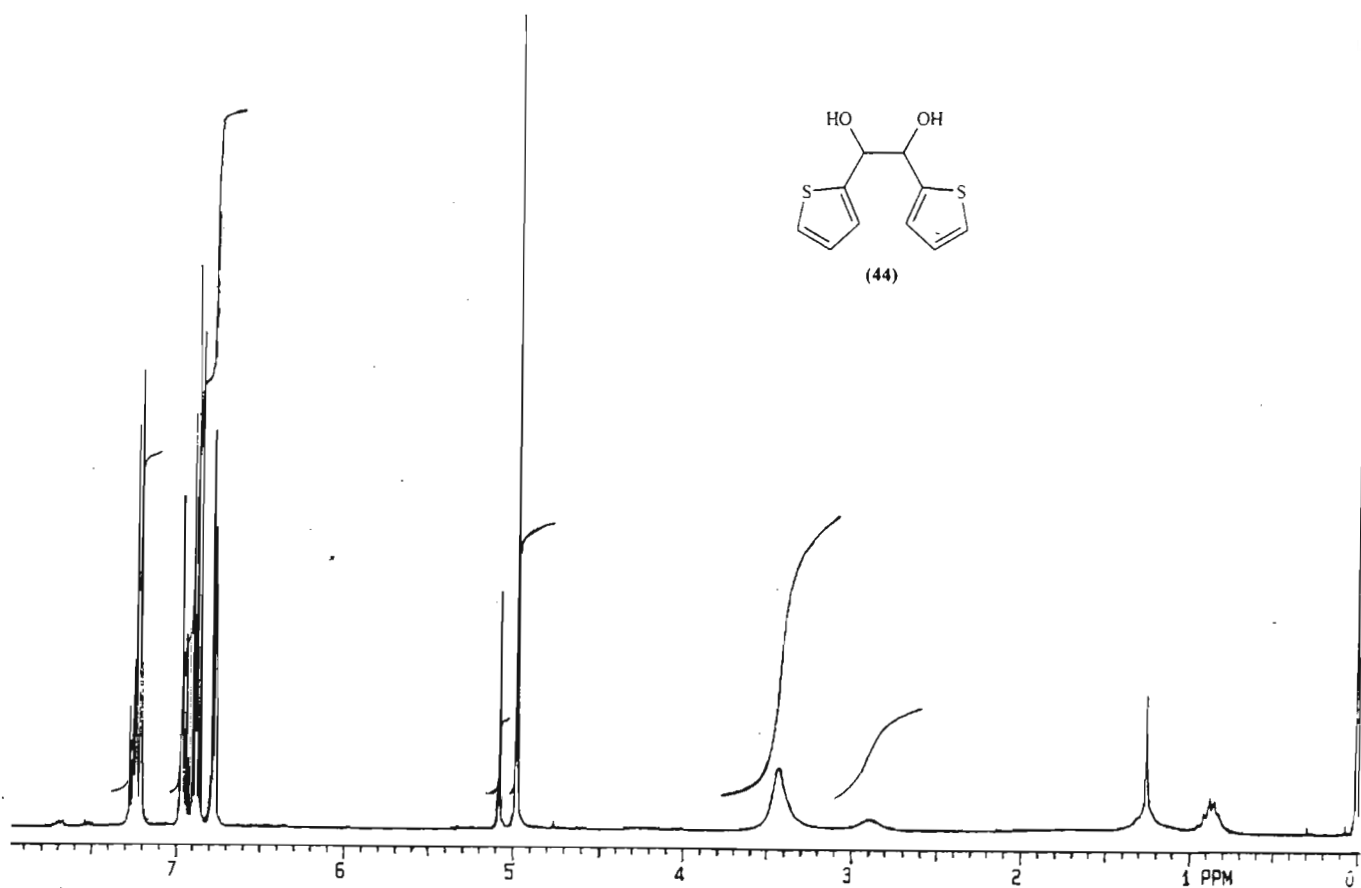
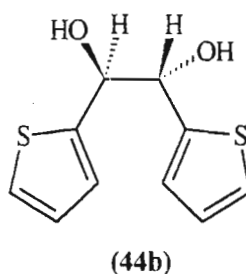
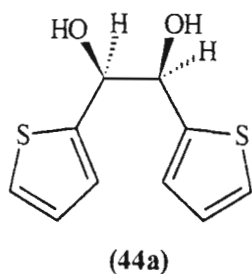
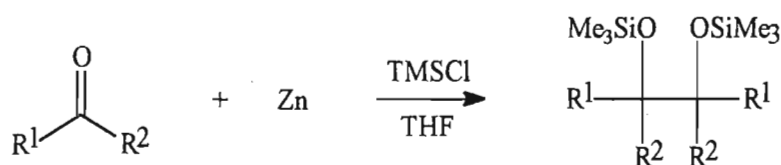


Figure 1

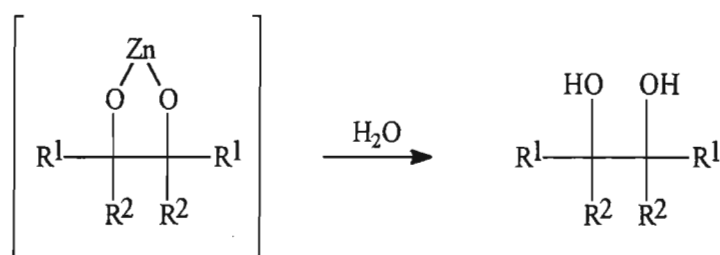
The formation of this by-product (44) led to a side study of two similar reactions, the Pinacol Coupling and the Acyloin Condensation (see chapter 2, section 2.2).

The Pinacol Coupling Reaction has been called the classic metal transfer reaction and provides a method for the synthesis of 1,2-diols⁹¹ from aldehydes and ketones in the presence of an active metal. A variation of this reaction by So and co-workers⁹² (using zinc as the reducing agent), traps the coupling product as a bis-trimethylsilyl ether (Scheme 55). The silyl ether product can be hydrolysed using tetrabutylammonium fluoride giving the pinacol product.



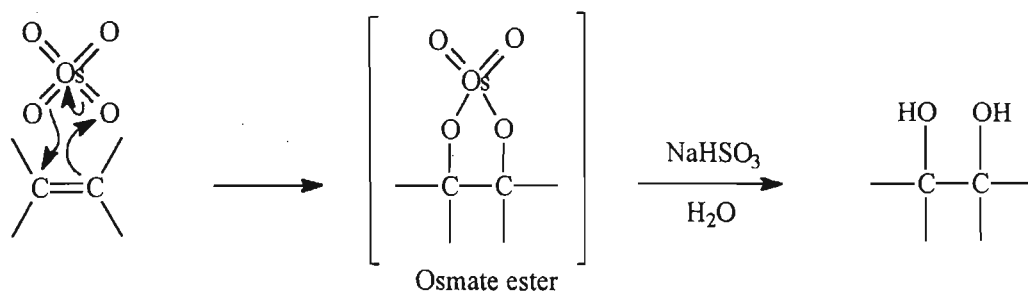
Scheme 55

The report states that small quantities of the 1,2-diol product were observed in all reactions, attributed to the hydrolysis of the intermediate coupling product by “adventitious water” (Scheme 56).



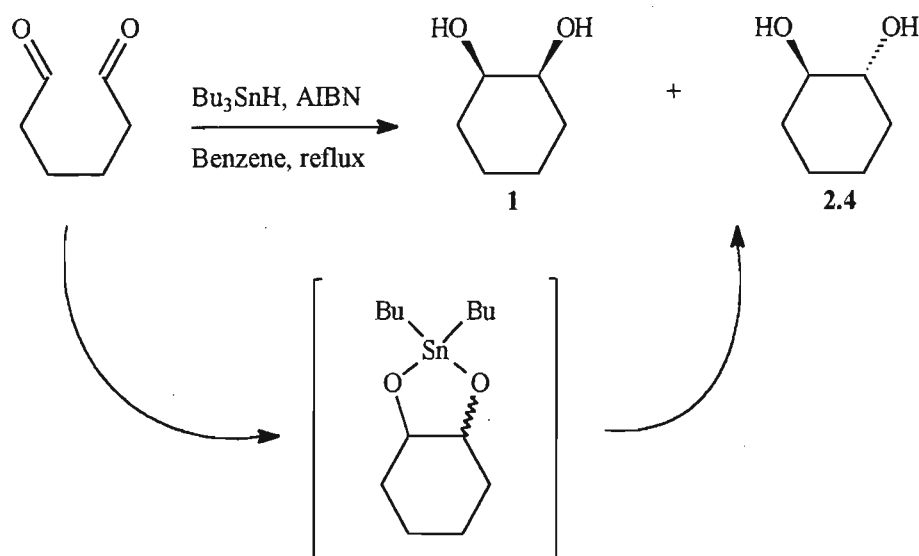
Scheme 56

The intermediate presented in Scheme 56 is similar to the cyclic ester intermediate formed during dihydroxy addition to alkenes by OsO₄ or alkaline KMnO₄. These oxidising reagents give a *syn* addition product, from the sterically less-hindered side of the alkene double bond⁹⁰ (Scheme 57).



Scheme 57

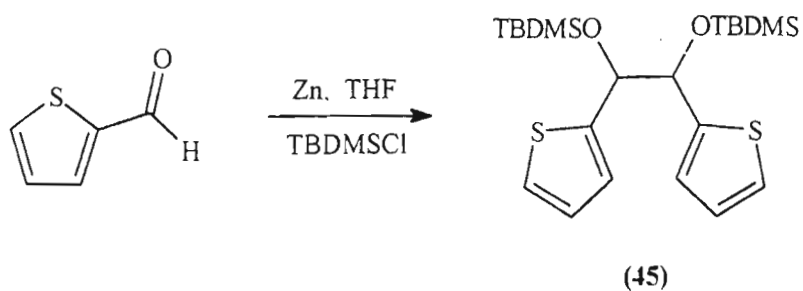
In a recent publication (1995), Hays and Fu⁹³ describe the use of tributyltinhydride as a reagent in a pinacol coupling reaction, in which a degree of diastereoselectivity has been observed (**Scheme 58**).



Scheme 58

The above schemes illustrate the mechanism for the formation of the diastereomers. Whatever the metal involved (Zn, Os or Sn), it can either co-ordinate to the oxygen atoms from one side of the carbon-carbon bond or co-ordinate as a bridge over the C-C bond. Hydrolysis of these two organometallic species gives the diols.

In addition to the synthesis of the 1,2-diol coupling product of 2-thiophenecarboxaldehyde, the bis-*tertiary*-butyldimethylsilylether of the coupling product (**45**) was also prepared by the treatment of 2-thiophenecarboxaldehyde with TBDMSCl in the presence of zinc dust (**Scheme 58**).



Scheme 58

The ^1H NMR spectrum (Figure 2) of compound (45) also shows two sets of signals, as before, indicating a mixture of diastereomers. An interesting observation is that they are present in approximately equal amounts which is not the case with the alcohol (44).

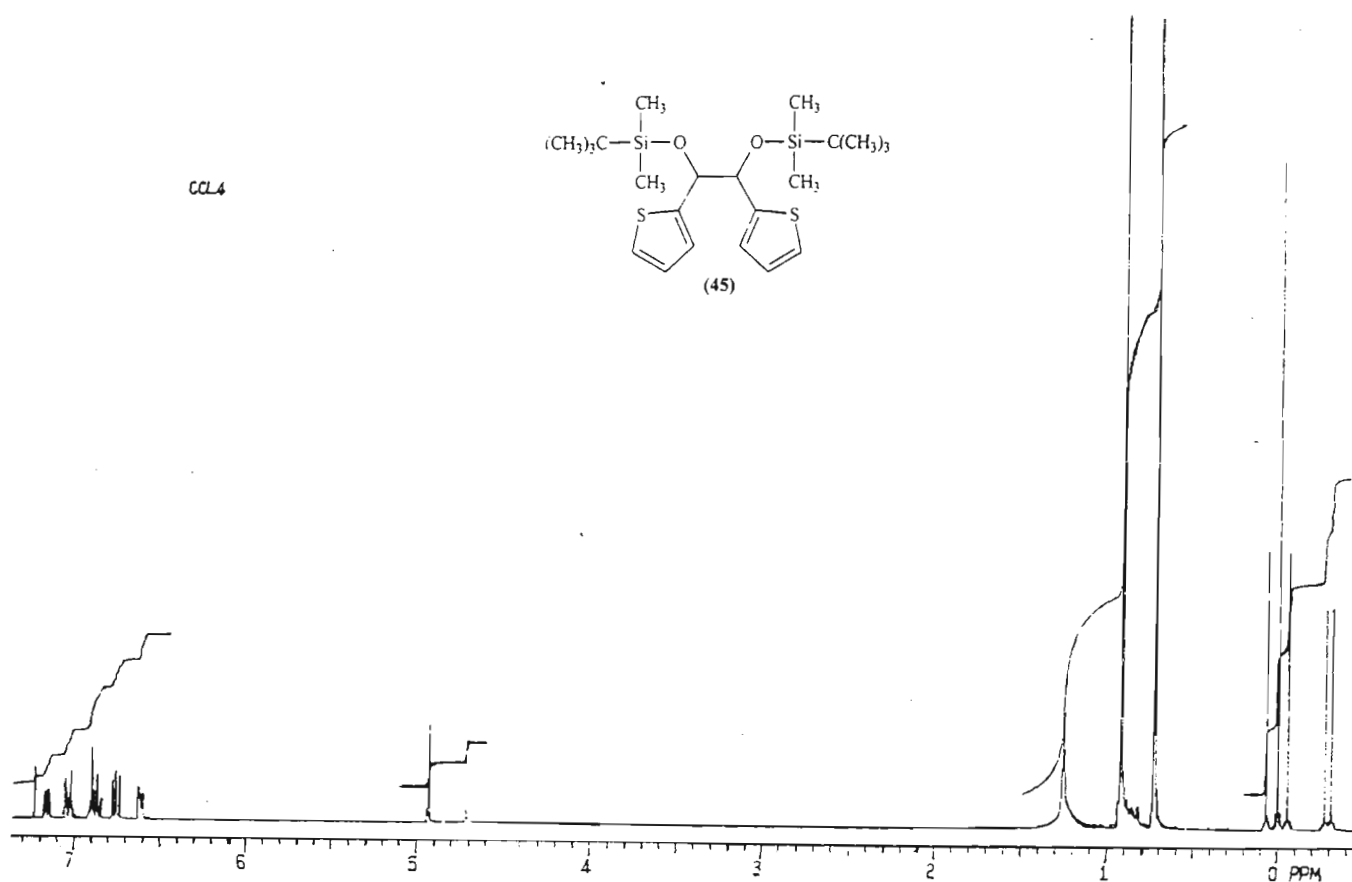
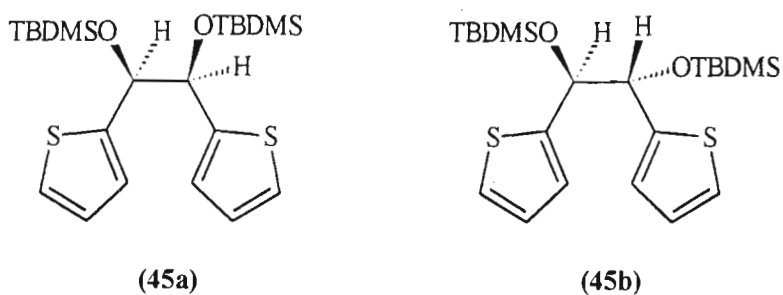
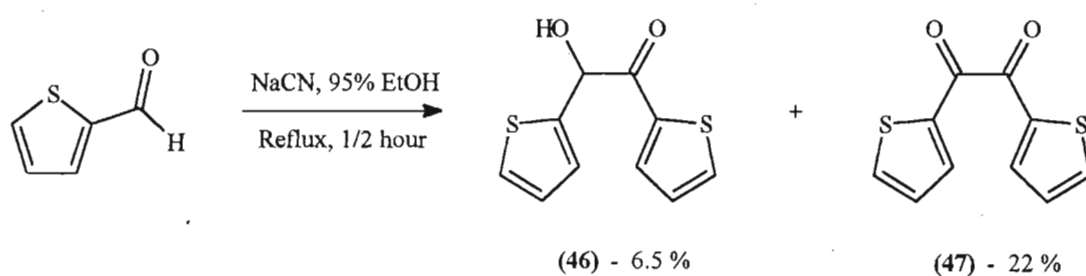


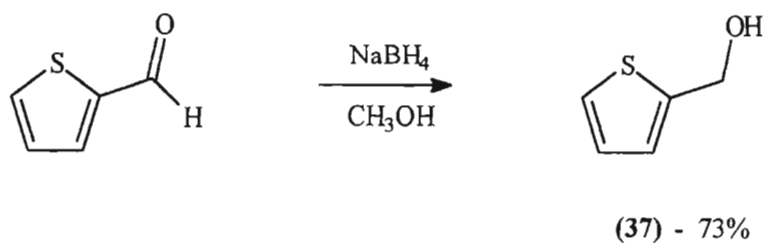
Figure 2

The Acyloin Condensation is the condensation of two molecules of an aromatic aldehyde in the presence of sodium or potassium cyanide in aqueous ethanol^{90,94}. One molecule of aldehyde loses the hydrogen of the C-H bond and is termed the “donor”; the other molecule gains this hydrogen atom and is termed the “acceptor”. Certain aldehydes, such as cinnamyl aldehyde do not undergo this reaction⁹⁴. 2-Thiophenecarboxaldehyde can act as both donor and acceptor and thus can be “self-condensed”. Two products were isolated from the reaction (Scheme 59), thenoin (46) and thenil (47), consistent with previous studies of this reaction⁹⁴.



Scheme 59

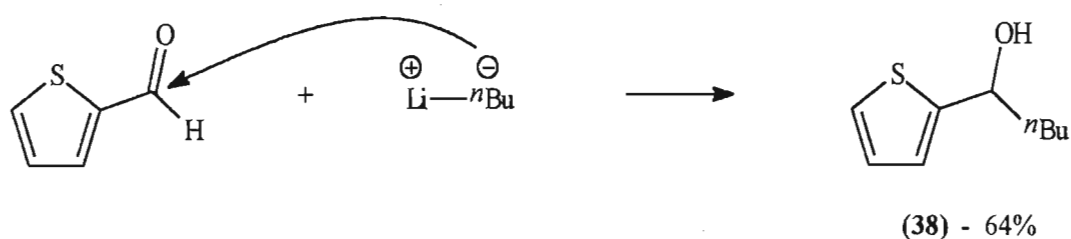
The most successful method for the reduction of 2-thiophenecarboxaldehyde to thenyl alcohol (37) was found to be treatment of the aldehyde with sodium borohydride (NaBH_4). This method (Scheme 60), adapted from that used by Longley^{3a}, is quick, simple, the yield is high and the product can be used without further purification.



Scheme 60

3.2.1.2 Reduction of 2-Thiophenecarboxaldehyde using Lithium-Based Nucleophiles

Buu-Hoi, Xuong, and Diêp^{65a} have prepared 1-(2-thienyl)-1-pentanol (**38**) by the nucleophilic action of butylmagnesium bromide on 2-thiophenecarboxaldehyde. In this work, the compound has been prepared in a similar reaction by exploiting the nucleophilic nature of butyllithium (ⁿBuLi) (Scheme 61).

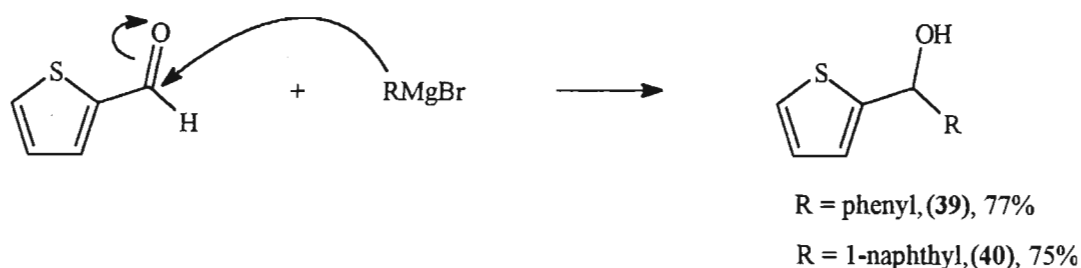


Scheme 61

This reaction was found to take place during the synthesis of di-(2-thienyl)methanol (**43**) but the conditions and reagents can be varied to give one or the other product (see this chapter, section 3.2.2).

3.2.1.3 Reduction of 2-Thiophenecarboxaldehyde using Grignard reagents

Two readily available aryl-bromides, bromobenzene (Merck[®]) and 1-bromonaphthalene (Hopkin and Williams[®]), were used to prepare the aryl-substituted thenyl alcohols (Scheme 62) using a suitably modified Grignard procedure⁹⁵.

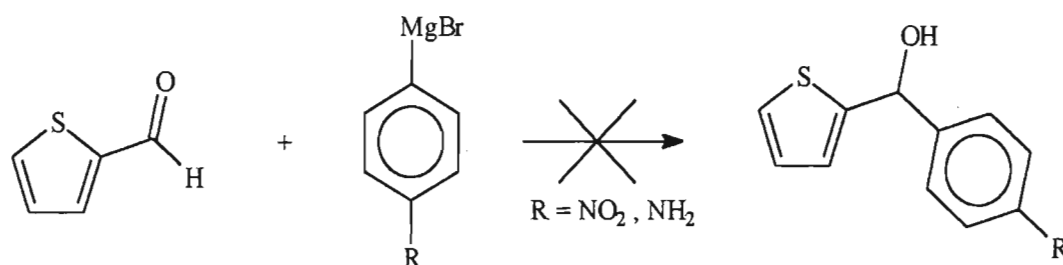


Scheme 62

Ben-Hassine and co-workers⁹⁶ have prepared the 1-naphthyl derivative previously by Grignard reaction in THF. The phenyl derivative has also been previously prepared by

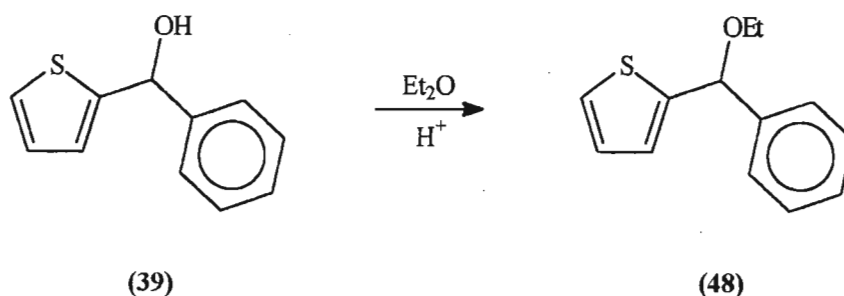
Grignard reaction^{65b}, as well as by reduction of phenyl thienyl ketone. In one case, this reduction has been done by Krishnaswamy and co-workers⁹⁷ with NaBH₄ and in another case by Minnis⁹⁸ with an aluminium amalgam in alcoholic hydroxide solution.

The attempted syntheses of (4-nitrophenyl)-(2-thienyl)methanol and (4-aminophenyl)-(2-thienyl)methanol by Grignard reaction using *p*-bromonitrobenzene and *p*-bromoaniline, respectively, with 2-thiophenecarboxaldehyde were unsuccessful (**Scheme 63**) due to the inability of the Grignard reagent to tolerate the presence of the nitro (NO₂) and amino (NH₂) functional groups⁹⁹. The oxidising power of the nitro group and the (relatively) acidic protons of the amino group rapidly destroy the Grignard reagent.



Scheme 63

The use of diethyl ether as the solvent in the Grignard reaction led to the formation of an ethereal by-product (**48**) in the case of the phenyl-substituted alcohol (**39**). The quantity of this by-product was influenced greatly by the use of HCl_(aq) in the reaction work-up (**Scheme 64**).

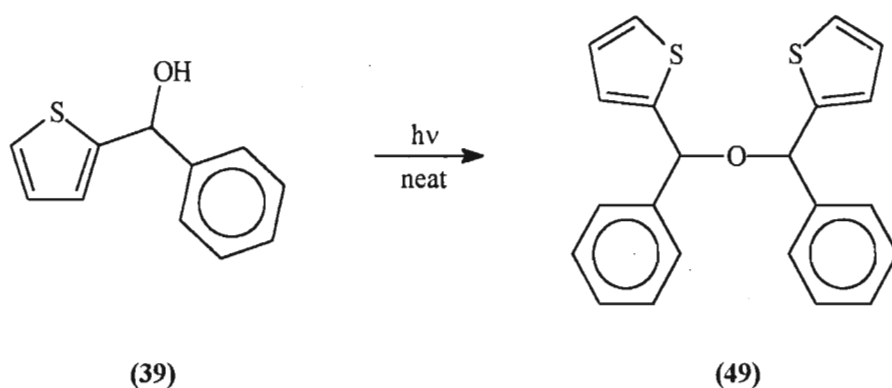


Scheme 64

It was found that the by-product formation could be eliminated by either omitting the use of acid to dissolve solid materials formed during reaction, or by using THF as the reaction solvent, with CHCl₃ as extraction solvent. The latter method (*i.e.* THF/CHCl₃) allows the

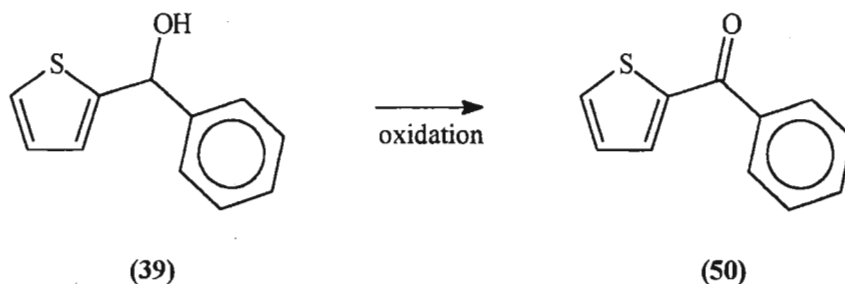
use of concentrated HCl in the reaction work-up, considerably reducing the amount of acid necessary to dissolve the solid material in the reaction vessel.

This type of compound (39) has been found to undergo photochemical (bright sunlight) ether formation, in the neat state, producing a symmetrical ether (49), or a methyl ether in methanolic solution (Scheme 65)⁹⁷.



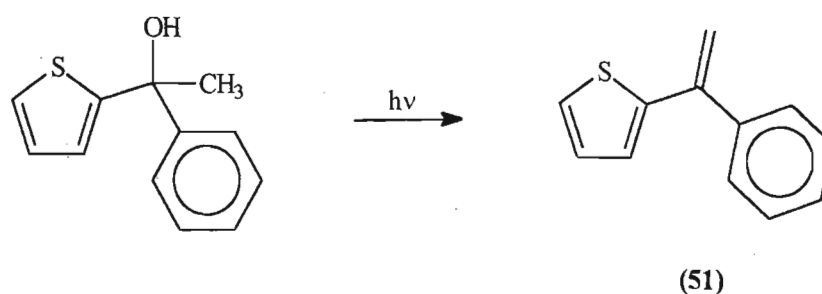
Scheme 65

The ethereal product (49) was isolated in 34% yield from a Grignard preparation of phenyl thienyl methanol (39) when no steps were taken to protect the reaction mixture from sunlight during purification. Another by-product (50), isolated in low yield (3%) from a similar reaction mixture, was identified as phenyl thienyl ketone, resulting from oxidation of the substituted methanol (Scheme 66).



Scheme 66

Krishnaswamy and co-workers also observed another photochemical reaction of interest, that presented in Scheme 67, leading to the vinyl species (51). This will be discussed further in section 3.5.2 (Dehydration to Vinylic Systems).

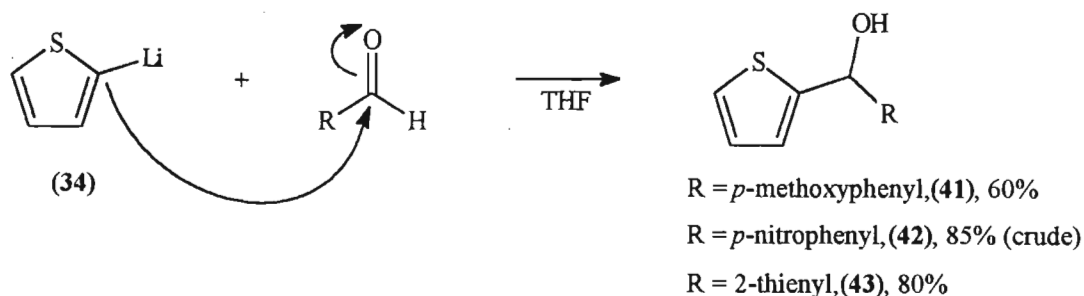


Scheme 67

It is important to note that Krishnaswamy and co-workers found that both oxygen and light were necessary for the photochemical reactions to take place and that the reactions were inhibited by the presence of β -carotene, a singlet oxygen quencher, but not by radical quenchers like hydroquinone, indicating that singlet oxygen is involved in the oxidation⁹⁷ (see chapter 2, section 2.7.1).

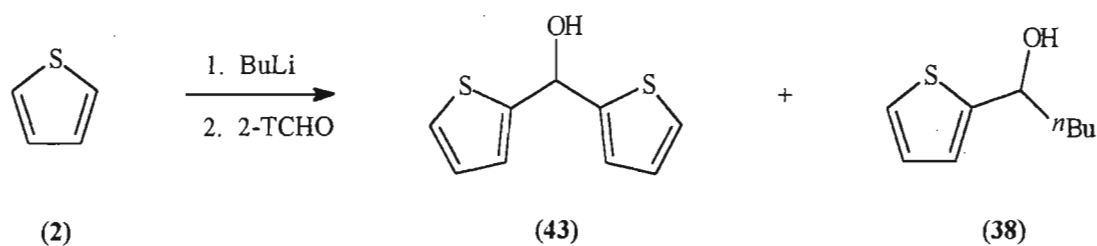
3.2.2 The Use of 2-Thienyllithium as a Nucleophilic Reagent

2-Thienyllithium or 2-lithiothiophene (**34**) (see chapter 2, section 2.4.3) is a versatile synthetic reagent. It has been prepared in good yield from thiophene with *n*-butyllithium¹⁰⁰, and also with *t*-butyllithium⁶², at room temperature. As in the case of furans and *N*-alkylpyrroles, thiophene only reacts with the strongest bases and deprotonation occurs at the α -carbon atom. This species was used as a nucleophile in the synthesis of substituted thenyl alcohols by reaction with suitable aldehydes (Scheme 68).



Scheme 68

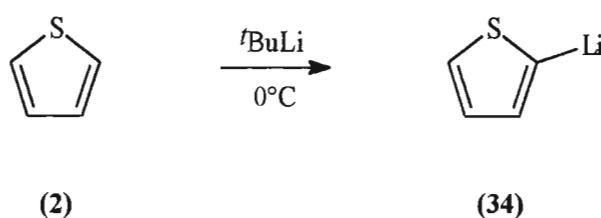
Several methods for the preparation of 2-thienyllithium (**34**) were evaluated in the synthesis of di-(2-thienyl)methanol (**43**), from thiophene and 2-thiophenecarboxaldehyde, using both *n*-butyllithium and *t*-butyllithium at room temperature and at -78°C (Scheme 69).



2-TCHO = 2-thiophenecarboxaldehyde

Scheme 69

The use of n butyllithium at room temperature gave a mixture of products, 1-(2-thienyl)-1-pentanol (38) resulting from nucleophilic addition of the base to the aldehyde, and di-(2-thienyl)methanol (43) resulting from nucleophilic addition of 2-thienyllithium to the aldehyde. Using n BuLi at -78°C resulted in exclusive formation of the n butyl addition product (38), even in the presence of thiophene, indicating that increased temperature favours the generation of the 2-thienyllithium species, while decreased temperature favours the nucleophilic addition of the base. It was decided that to prevent the nucleophilic addition, it would be necessary to use the more basic and less nucleophilic t butyllithium to form the thienyllithium species, prior to addition of the aldehyde. Using the temperature results of the n BuLi reactions as a guide, the best method found was treatment of thiophene with t BuLi at 0°C (Scheme 70), resulting in 2-thienyllithium, which was then added to electrophiles at -78°C .

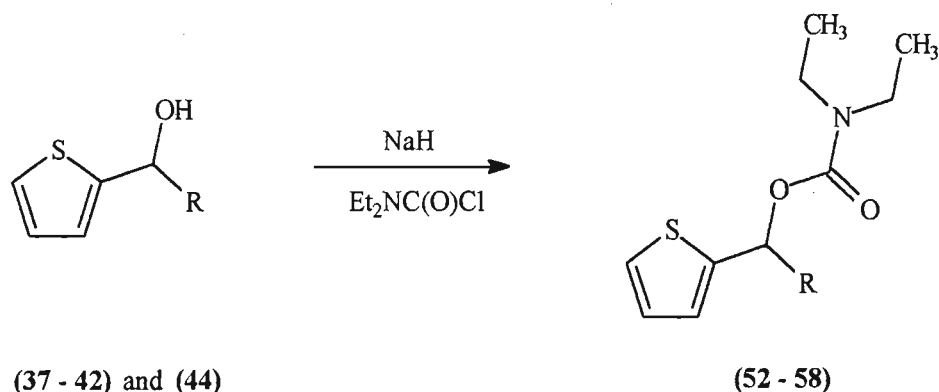


Scheme 70

In a recent communication, Tye, Eldred, and Wills¹⁰¹ describe overcoming the problem of nucleophilic addition of n BuLi by the use of t BuLi at 0°C or s BuLi in combination with TMEDA.

3.3 Preparation of Carbamates

The general method for the preparation of the carbamates studied in this work is the reaction of an alcohol with a commercially available carbamoyl chloride (Janssen[®]) after abstraction of the alcoholic proton with sodium hydride. The availability of the carbamoyl chloride and the simplicity of the reaction technique provides a quick and efficient means for carbamate preparation (Scheme 71). Only *N,N*-diethylcarbamates have been studied in this work.



Scheme 71

Table 2: Yields of Carbamate Preparations

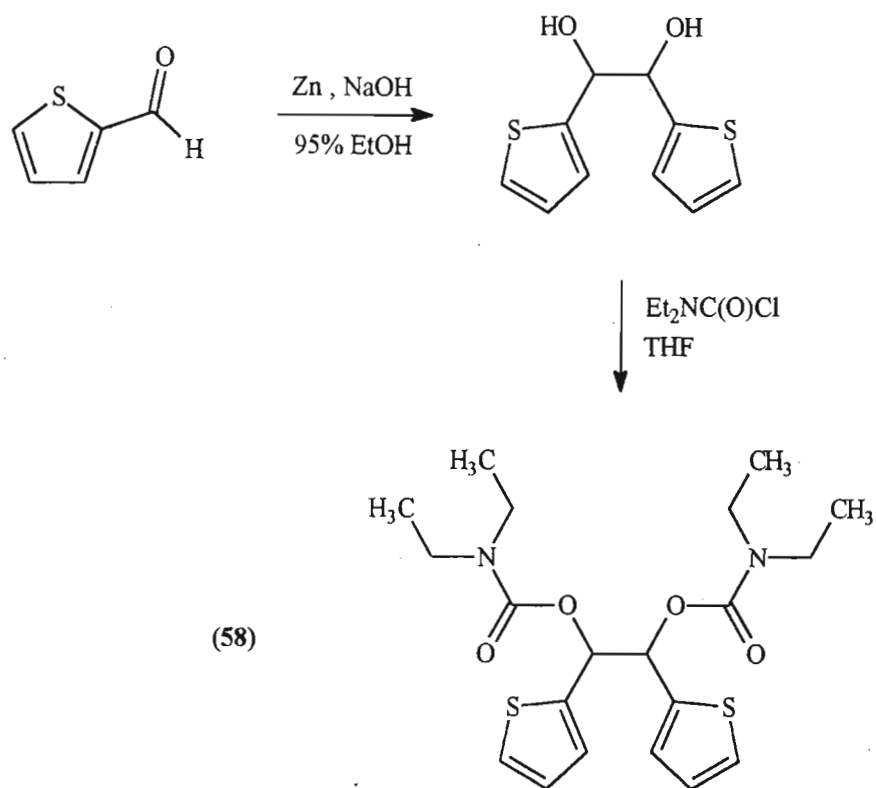
Carbamate substituent (R)	Carbamate	Yield (Carbamate) [†]	Yield (Overall) [‡]
H	(52)	89%	65%
ⁿ Bu	(53)	75%	48%
Ph	(54)	70%	53%
<i>p</i> -Ph(OCH ₃)	(55)	-	21%
<i>p</i> -Ph(NO ₂)	(56)	50%	33%
1-Naphthyl	(57)	85%	64%
2-Thienyl	-	trace (GC/MS)	n/a

Table 2

[†] Yield for alcohol to carbamate reaction (one step - scheme 71)

[‡] Overall yield calculated from thiophene/2-thiophenecarboxaldehyde (two steps - scheme 49/50, scheme 71).

In addition to the above carbamates, 1,2-di-(*N,N*-diethylcarbamoyloxy)-1,2-di-(2-thienyl)ethane (**58**) was also prepared, in low yield (Scheme 72). This is the carbamate of the pinacol coupling product of 2-thiophenecarboxaldehyde (**44**).



Scheme 72

The identity of compound (**58**) was confirmed by X-ray crystallographic analysis (see chapter 7: X-ray Crystallographic Data, page 234).

An interesting contrast between this compound (**58**) and the alcohols (**44**) and the *bis*-TBDMS ethers (**45**) can be seen in the ^1H NMR spectrum (**Figure 3**). Compounds (**44**) and (**45**) consist of differing amounts of racemates and mesomers which have different NMR spectra, hence the complexity of the spectra shown in **Figures 1** and **2**. The spectrum of (**58**), shown in **Figure 3**, indicates that only one of these two types of compound is present, that is, the racemate, as can be seen from the crystal structure (see pages 235 and 236). The unit cell contains two molecules of each enantiomer, a total of four molecules, with each member of an enantiomeric pair related by a crystallographic centre of symmetry. The crystal structure on page 235 shows one of the enantiomers. In addition to the symmetry of the unit cell, each molecule has a C_2 axis through the middle of the $C_5 - C_5'$ bond. It is unlikely that the mesomeric compound does not react (selective acylation) therefore it is either lost in the isolation process (selective crystallisation) or it isomerises to the racemate during the preparation of the carbamate from the alcohol.

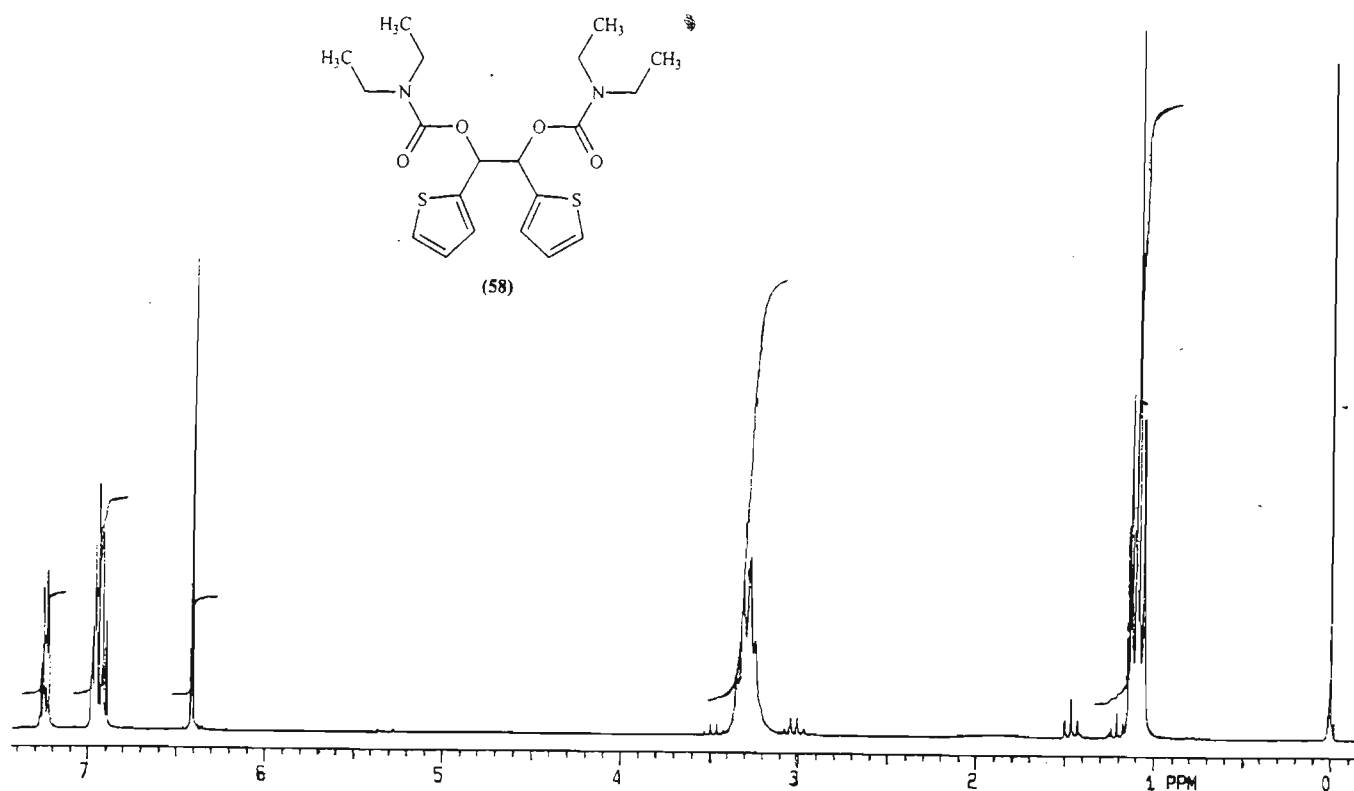
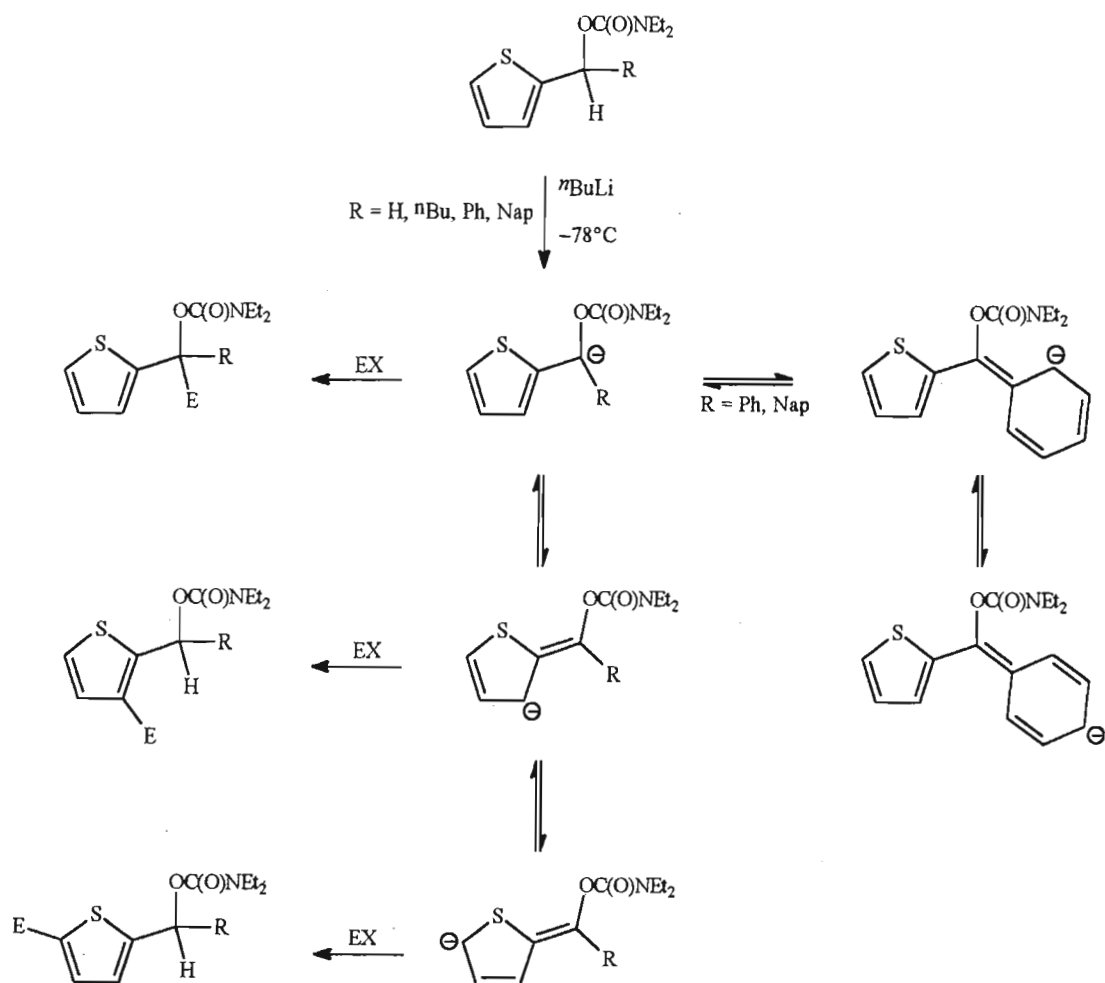


Figure 3

3.4 Electrophilic Substitution Reactions

Four of the carbamates were chosen for electrophilic substitution studies. If the mechanism of the substitution reaction is considered, it can be seen that numerous products are possible depending on the extent to which the anion can delocalise - this depends on both electronic and steric factors (Scheme 73).



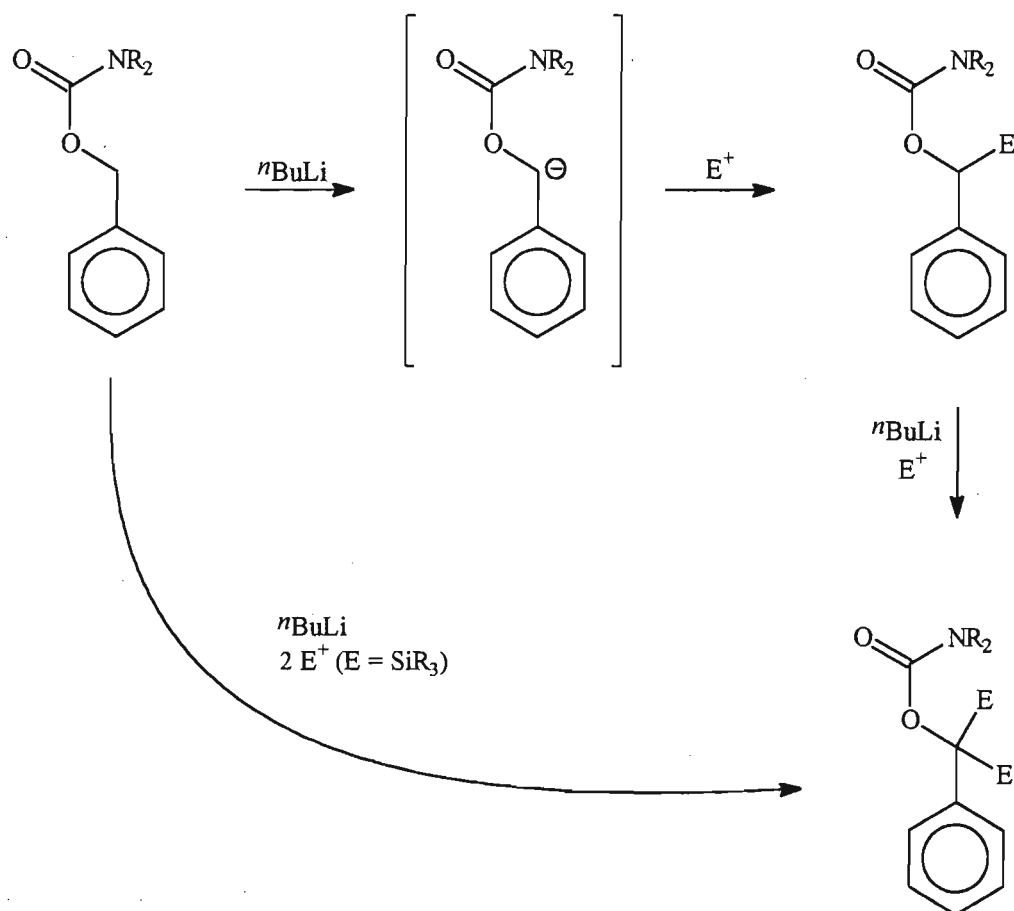
Scheme 73

The following products are possible:

- The presence of the carbamate stabilises the anion at the site of deprotonation (this is one of the reasons for the acidity of the proton(s) at this position), leading to α -substitution.

- Delocalisation of the anion across the thiophene ring (present in all of the carbamates) could lead to either 3- or 5-substituted products. Although possible, 3-substitution is unlikely for reasons discussed earlier (chapter 2, section 2.4.2).
- The presence of an aromatic substituent (phenyl or 1-naphthyl) at the thenyl position introduces more possible products since delocalisation can also occur across this ring.

Studies at this department on benzylic and cinnamyl carbamate systems¹⁰² have shown that (with one exception) anion delocalisation does not occur in benzylic systems; substitution - irrespective of the type of electrophile - usually takes place at the benzylic position where the anion is generated. It has been shown that silicon-based electrophiles have an interesting electronic property, that is, they have the ability to stabilise an anion in the α -position. This is attributed to low lying d-orbitals on the silicon atom which can, to an extent, delocalise the charge of the anion, enhancing its stability. In systems where (initially) two protons are available at the α -position, and a silicon-based electrophile has been trapped at this site, the silicon effect has been found to lead to bis-substitution, since the stabilising effect of the silicon atom makes the second proton more acidic than the first (Scheme 74).

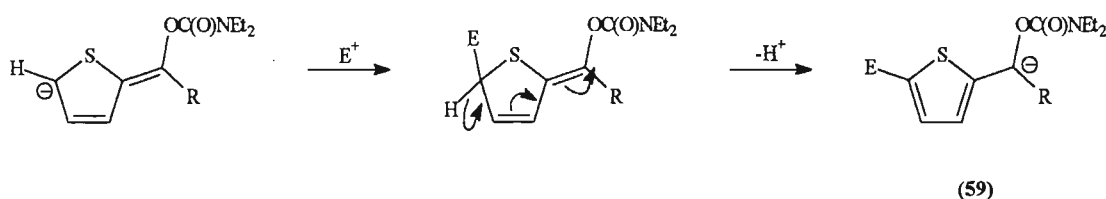


Scheme 74

Three electrophiles were chosen for the electrophilic substitution reactions on thenyl carbamates, to illustrate both the steric effect and the electronic effect:

- Methyl iodide (CH_3I) - small and therefore not sterically demanding
- Trimethylsilylchloride (TMSCl) - larger than methyl iodide, introducing a steric factor into the substitution reaction; silicon based, introducing an electronic factor which may lead to multiple substitution in the thenyl position
- *tertiary*-Butyldimethylsilylchloride (TBDMSCl) - considerable steric bulk (larger than TMSCl), possibly forcing delocalisation, and also silicon based, possibly leading to multiple substitution in the thenyl position

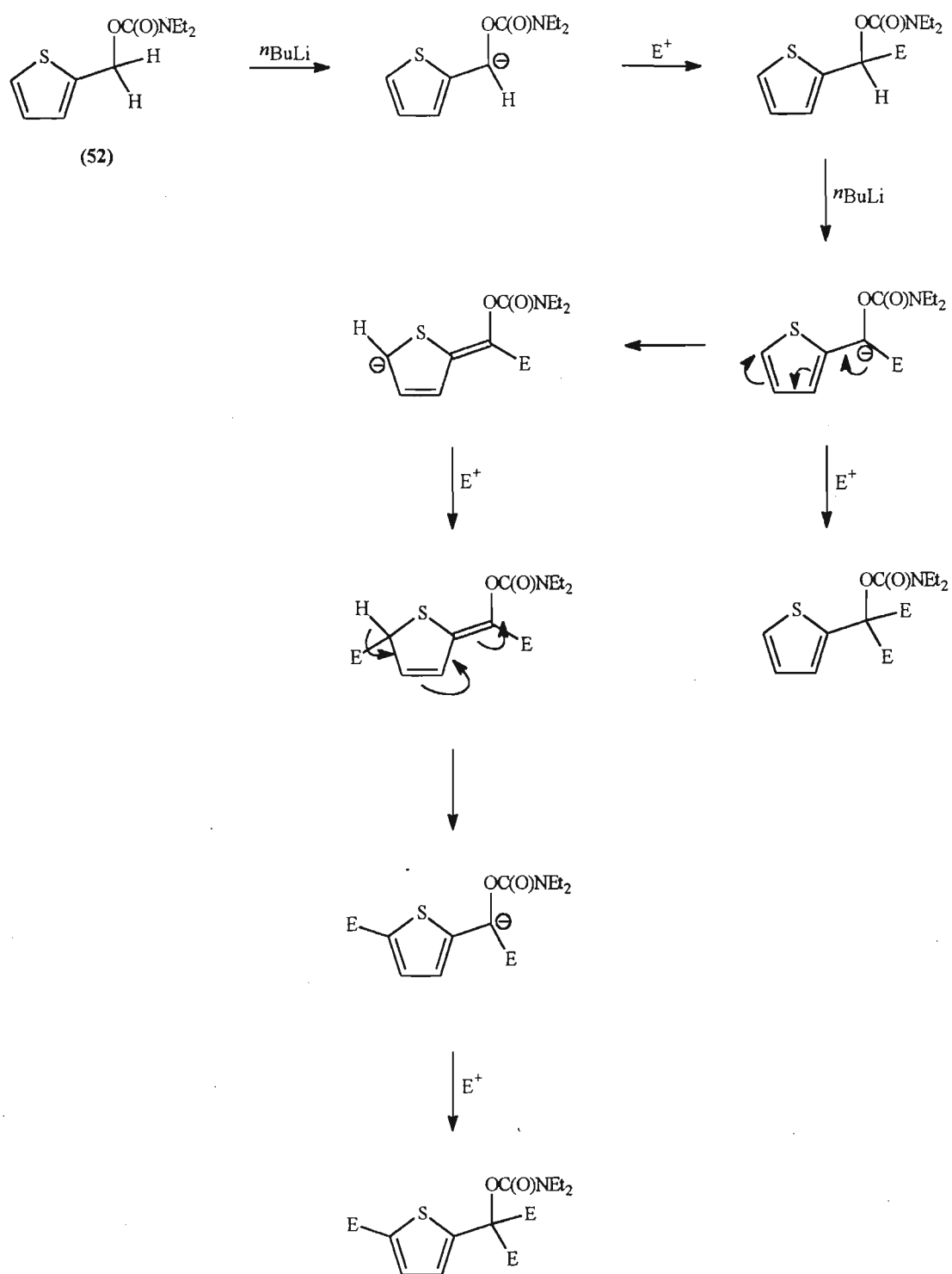
Two important aspects of the substitution mechanism shown in **Scheme 73** are the consequences of delocalisation. It can be seen that in order to regain the aromatic structure of the thiophene ring, it is necessary for one proton to be expelled (**Scheme 75**) leading to anionic species (**59**).



Scheme 75

The expulsion of one proton per molecule of delocalised product is important because this proton will quench either one carbamate anion or one molecule of unreacted base ($n\text{BuLi}$). **Scheme 75** also illustrates the second consequence of a delocalised substitution - multiple substitution can occur since the species (**59**) can capture a second electrophile.

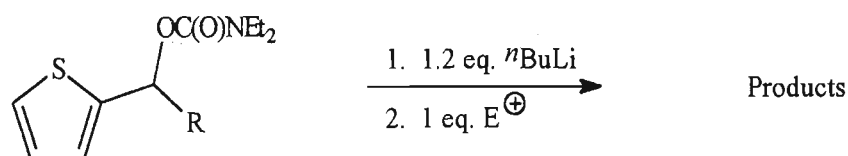
This is particularly true for *N,N*-diethylcarbamoyloxy-(2-thienyl)methane (**52**) (*N,N*-diethyl-thenylcarbamate) as presented in **Scheme 76**. Delocalisation can occur leading to multiple substitution, that is, up to three electrophiles can be captured by a single molecule of this carbamate (assuming that the 3-position of the thiophene ring does not capture an electrophile).



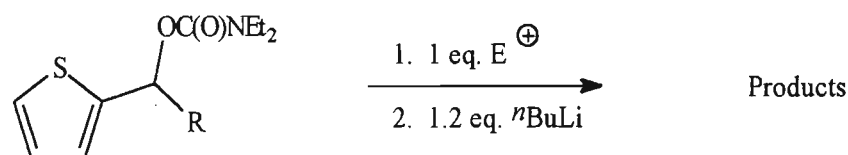
Scheme 76

It was found that the desired electrophile determined the method used to achieve substitution. The procedures used are summarised as follows:

- Treatment of the carbamate with approximately 1.2 equivalents of $n\text{BuLi}$ at -78°C ; this solution is stirred for 30 minutes and then a solution of 1 equivalent of electrophile is added; this solution is stirred for 1 hour at -78°C and then allowed to warm to room temperature with stirring for 2 more hours (**Scheme 77**).
- Treatment of a mixture of the carbamate and the electrophile with approximately 1.2 equivalents of $n\text{BuLi}$; this solution is stirred at -78°C for 1 hour and then allowed to warm to room temperature with stirring for 2 more hours (**Scheme 78**).



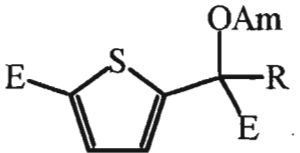
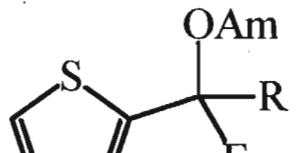
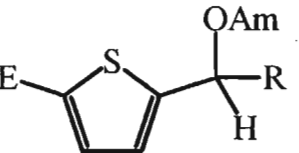
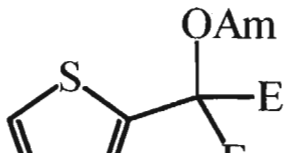
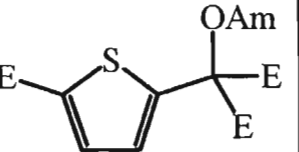
Scheme 77



Scheme 78

The results of the substitution reactions are shown in **Table 3**. Only successful substitution reactions are shown. The following general observations can be made:

- The use of TBDMSCl as an electrophile is limited to the method shown in **Scheme 78**. Addition of this electrophile after the base did not give any substituted products. Also, reactions with the more sterically-hindered carbamates (phenyl- and naphthyl-substituted) were unsuccessful in the preparation of substituted carbamates.
- The use of CH_3I as an electrophile is limited to the method shown in **Scheme 77**. Addition of this electrophile prior to the base did not yield methyl-substituted products (see this chapter, section 3.5.4).
- Substitution takes place at only two sites, the site of deprotonation (α to the carbamate) and/or at the 5-position of the thiophene ring, even in the presence of a second aromatic substituent (phenyl or 1-naphthyl).
- Multiple substitution occurs when silicon-based electrophiles are used.

R	E					
H ^a	TBS ^d	29%	15%	2% ^b	-	-
ⁿ Bu ^a	TBS ^d	-	15% ^b	18% ^b	-	-
H ^a	TMS	minor	7% ^b	2% ^b	47% ^b	6%
H ^c	TMS	40% ^b	7% ^b	28% ^b	-	minor
ⁿ Bu ^c	TMS	26% ^b	3% ^b	30% ^b	-	-
Ph ^c	TMS	-	7% ^b	42% ^b	-	-
Nap ^c	TMS	-	7% ^b	38% ^b	-	-
H ^c	CH ₃	-	12% ^b	54% ^b	-	-
ⁿ Bu ^c	CH ₃	-	7% ^b	66% ^b	-	-
Ph ^c	CH ₃	-	52%	-	-	-
Nap ^c	CH ₃	-	45%	-	-	-

a. Carbamate + electrophile; ⁿBuLi

b. Yield obtained from GC or NMR analysis

c. Carbamate + ⁿBuLi; electrophile

d. TBS = TBDMS (necessary to size table according to page width)

Table 3 - Results of Electrophilic Substitutions

One issue must be raised before discussing the substitution results in detail - is it not likely that the so-called delocalised product (5-substitution on the thiophene ring) has arisen from deprotonation at this position by *n*-butyllithium? The answer to this question is no!

In studying the preparation of 2-thienyllithium (**34**) in the preparation of thenyl alcohols, it was found that *n*-butyllithium was sufficiently basic to deprotonate thiophene at room temperature but not at -78°C, the temperature at which the *n*-BuLi solution is added during the substitution reactions (see this chapter, section 3.2.2). In addition, the most acidic proton on the carbamate species is that α to the carbamate, at the thenylic position, not the proton at the 5-position of the thiophene ring. Also, the exclusive substitution of the thenyl proton by a methyl group in the sterically-hindered carbamates (phenyl and 1-naphthyl) indicates that the base is not sterically prevented from accessing the thenyl position (which may lead to deprotonation at another site). Thus it has been concluded that 5-substituted products have arisen from delocalisation of an anion from the thenyl position.

The results show that both steric and electronic effects influence the course of the substitution reaction. In the absence of an electrophile (**Scheme 77**), the generated anion would assume the energetically most favourable position, either at the site of proton abstraction, or delocalised across the thiophene ring. Upon addition of the electrophile, it would be captured at this most favoured position. In the presence of an electrophile (**Scheme 78**), it would be expected that the anion would be captured as generated, at the site of deprotonation, unless delocalisation of the negative charge takes place prior to electrophile capture, despite the presence of the electrophile.

3.4.1 Methyl Iodide Substitutions

Table 4: Methyl Iodide Substitution Results

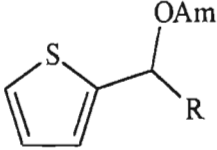
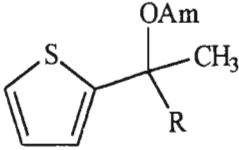
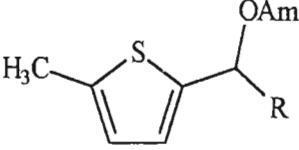
		
R = H - (52)	(60) - 12%	(61) - 54%
R = ⁿ Bu - (53)	(62) - 7%	(63) - 66%
R = Ph - (54)	(64) - 52%	-
R = 1-Nap - (57)	(65) - 45%	-

Table 4

It appears that the delocalised product is favoured in the absence of an aromatic substituent in the thenyl position. Substitution is achieved at both the α -position (products (60) and (62)) and at the 5-position of the thiophene ring, with the 5-product dominating (products (61) and (63)). It is possible that the inductive effect of the ⁿbutyl-substituent forces delocalisation, but the “tight ion pair” described earlier (see chapter 1, section 1.7.2.2) reportedly tolerates electron donating substituents at the α -position. The delocalised product (61) also dominates in the case of unsubstituted *N,N*-diethyl-thenylcarbamate (52), although to a lesser degree than in the case of the ⁿbutyl-substituted carbamate (63). This is expected as a consequence of the increased steric bulk of the ⁿbutyl group (*cf* H). These observations suggests that the delocalisation effect is stronger than the carbamate stabilising effect. However, this is clearly not the case in the phenyl and 1-naphthyl substituted thenyl carbamates. Here substitution occurs exclusively at the α -position. Since the methyl iodide is added after the ⁿbutyllithium solution this indicates an enhanced stability of the α -anion in the aromatic ring substituted thenyl carbamates, but the ⁿbutyl and H substituted carbamate results show that the delocalisation effect is greater than the carbamate stabilising effect. This suggests a degree of delocalisation across this second ring, obviously insufficient to capture an electrophile, but enough to lock the anion in the α -position leading to exclusive substitution at this site, giving products (64) and (65).

3.4.2 TBDMSCl Substitutions

Table 5: TBDMSCl Substitution Results

R = H - (52)	(66) - 29%	(67) - 15%	(68) - 2%
R = ⁿ Bu - (53)	-	(69) - 15%	(70) - 18%

Table 5

Substitution was only achieved in the case of the sterically less hindered carbamates (R = H, ⁿBu). Since the electrophile is immediately available (Scheme 78), one would expect the dominant product to be substituted at the α -position. Where R = H, almost no mono-5-substituted product (68) forms (this product is detectable by GC/MS). However, the dominant species is not the mono- α -substituted product (67), but the bis substituted product (66) displaying the silicon stabilising effect discussed earlier in this section. This bis substituted species (66) could be formed from the mono- α -substituted product (67), since there is a second proton of enhanced acidity available at the thenylic position due to the presence of the silicon atom. The steric interaction of the TBDMS groups would force the second TBDMS group to delocalise. The second possibility is that species (66) forms from species (68), that is, the first electrophile is captured after delocalisation of the negative charge, and the second electrophile is captured at the thenyl position. Where R = ⁿBu, only mono-substitution occurs giving products (69) and (70) in approximately equal yields. This indicates a steric effect, that is, the interaction between the more bulky ⁿBu group (*cf* H) and the sterically-demanding TBDMS group appears to force the anion to delocalise to relieve a steric problem at the thenyl position.

A possible future series of experiments would be to study a thenyl carbamate with a more bulky substituent in the thenyl position (for example, an *iso*-propyl group instead of H or ⁿBu). This would perhaps prevent the TBDMS electrophile from accessing the α -position altogether and thus force exclusive formation of the delocalised product.

The reactions of the phenyl and 1-naphthyl substituted carbamates with TBDMSCl did not yield any substituted products. The other reaction procedure (**Scheme 77**) was attempted on the basis that perhaps the anion would delocalise giving a 5-substituted product if a steric problem prevented the formation of an α -substituted product, but this was also unsuccessful. The methyl iodide substitution results indicate that the aryl-substituted thenyl carbamates prefer to keep the anion in the α -position, and thus the steric strain introduced by attempting to force a TBDMS group into the thenyl position may explain the lack of success in preparing the substituted carbamates.

3.4.3 TMSCl Substitutions

Table 6: TMSCl Substitution Results

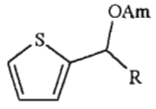
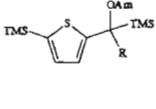
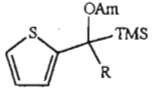
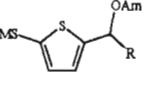
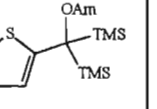
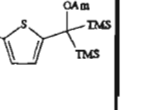
					
R = H [§] - (52)	(71) - minor	(72) - 7%	(73) - 2%	(74) - 47%	(75) - 6%
R = H ^{**} - (52)	(71) - 40%	(72) - 7%	(73) - 28%	-	(75) - minor
R = ⁿ Bu - (53)	(76) - 26%	(77) - 3%	(78) - 30%	-	-
R = Ph - (54)	-	(79) - 7%	(80) - 42%	-	-
R = 1-Nap (57)	-	(81) - 7%	(82) - 38%	-	-

Table 6

Generally, the reactions with TMS as electrophile (**Scheme 77**) show that delocalisation is favoured. As was observed in the case of TBDMSCl, multiple substitution occurs, but to a greater degree with TMS as a result of the smaller size of this electrophile (*cf* TBDMS).

In the aryl-substituted thenyl carbamates, mono-substitution occurs with the 5-substituted products (80) and (82) dominating, a small amount of the non-delocalised α -substituted products (79) and (81) forming. The thenyl substituted products (79) and (81) have not been isolated separately; their existence is confirmed by the presence of a second TMS signal in the NMR spectrum of the major (delocalised) products. The yields of (79) and (81) have been calculated from the ¹H NMR spectra of (80) and (82), respectively. Considering the

[§] Carbamate + electrophile; ⁿBuLi (**Scheme 78**)

^{**} Carbamate + ⁿBuLi; electrophile (**Scheme 77**)

methyl iodide substitution results on the carbamates, the increased bulk of the incoming electrophile forces delocalisation, but it also raises the question as to why the TBDMSCl substitutions were unsuccessful.

In the alkyl-substituted thenyl carbamates, multiple substitution occurs to a greater degree than in the case of the TBDMS electrophile, indicating that the smaller carbamates can accommodate multiple substitution of a smaller silicon-based electrophile. As seen in the mechanism presented earlier, the consequence of the ability to delocalise the anion is the formation of several products in the reaction, up to three electrophiles can be captured, as is observed in the case of *N,N*-diethyl-thenylcarbamate (**52**), leading to product (**75**). An interesting comparison is the reaction of *N,N*-diethyl-thenylcarbamate with TMSCl according to **Scheme 78**. The instantly available TMSCl leads, as expected, to the bis thenyl-substituted carbamate (**74**) - the anion captures the electrophile immediately rather than delocalising across the ring. Delaying the introduction of the electrophile leads to delocalisation (two products, (**71**) and (**73**)), and the bis thenyl-substituted product (**74**) is not observed.

3.5 Other Reactions

3.5.1 Carbamate to Amine Rearrangement

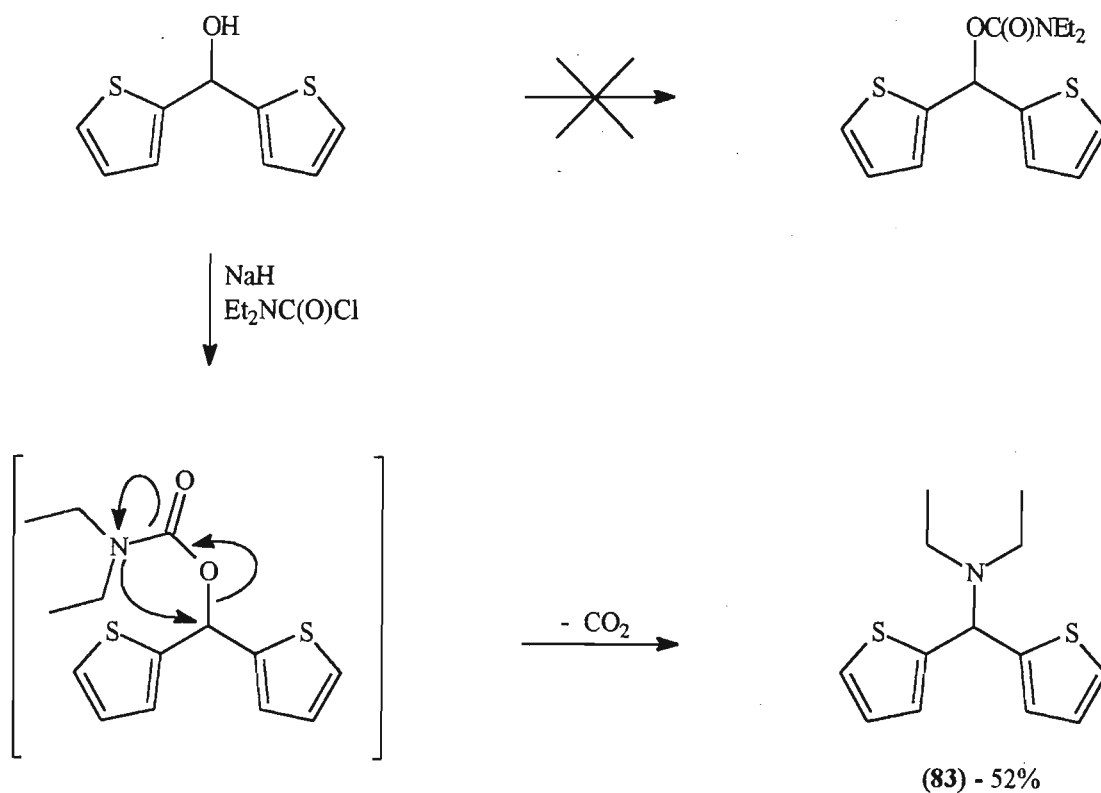
In the attempted synthesis of *N,N*-diethylcarbamoyloxy-di-(2-thienyl)-methane (**Scheme 79**), an interesting rearrangement was observed. The desired carbamate product was only detected in low yield by GC/MS analysis of the crude reaction mixture. Purification yielded *N,N*-diethylamino-di-(2-thienyl)-methane (**83**), in sufficient yield to be regarded as the only product of the reaction under the conditions used. This carbamate-to-amine reaction was noted to take place only in the aryl-substituted thenyl carbamates, to a greater or lesser degree (**Table 7**).

Table 7: Yields for Carbamate to Amine Rearrangement

Substituent (R)	Carbamate (overall yield)	Amine (overall yield)
2-Thienyl	trace (GC/MS)	(83) - 44%
<i>p</i> -Ph(OCH ₃)	21%	(84) - 23%
Ph	53%	5% ^{††}
1-Naphthyl	64%	trace (GC/MS)
Ph(NO ₂)	33%	0%

Table 7

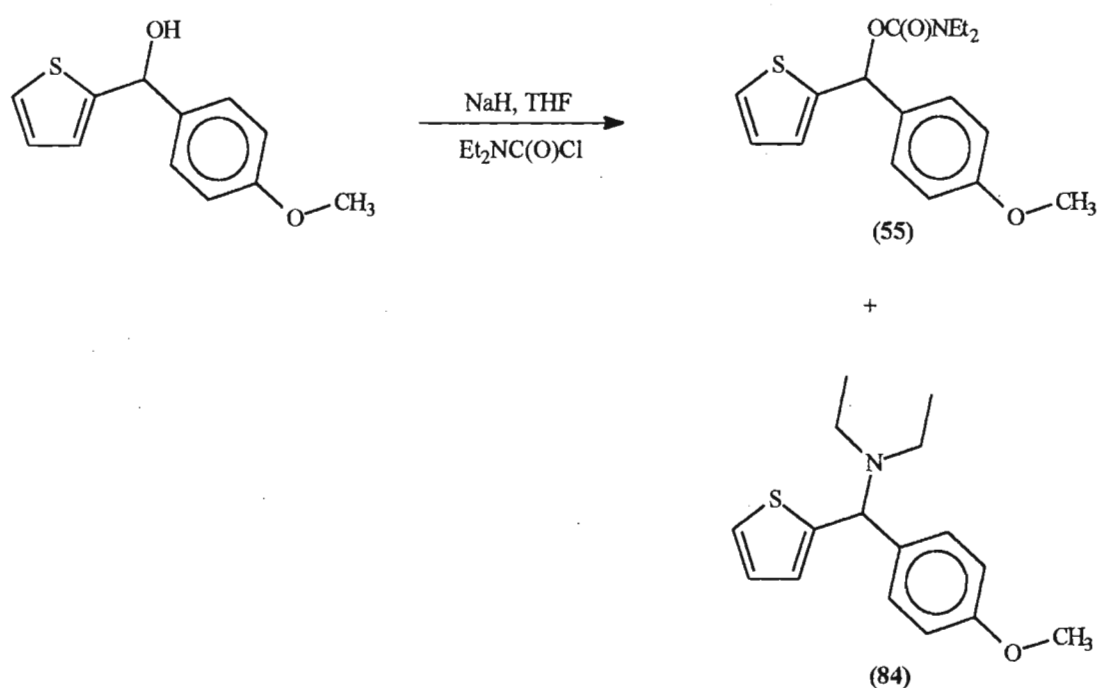
This rearrangement was observed previously by Longley^{3a}, but only in the case of *N,N*-dimethyl carbamates. Based on that study, it was concluded that the rearrangement was initiated by heat. Unsuccessful attempts to rearrange *N,N*-diethylcarbamates led Longley to conclude that the *N,N*-diethyl carbamates were unable to rearrange due to the increased steric bulk of the ethyl group (*cf* methyl group). However, this conclusion appears to be invalid for *N,N*-diethyl-thenylcarbamates.



Scheme 79

^{††} Yield calculated from GC integration; product not yet isolated.

The mechanism of the rearrangement is unclear, but the process depicted in **scheme 79** is proposed on the basis that the amine forms from the carbamate reaction product *via* loss of CO₂. It is also unclear as to when the rearrangement takes place - immediately after formation of the carbamate at 0°C, on warming to room temperature, or during the work-up procedure (*i.e.* due to heat applied during solvent removal). TLC does not provide any indication, since the carbamate and amine have very similar *R_f* values, hence the difficulty experienced in the as yet unsuccessful attempts to separate the carbamate (**55**) and amine (**84**) of the *p*-methoxyphenyl-(2-thienyl)-species (**Scheme 80**).

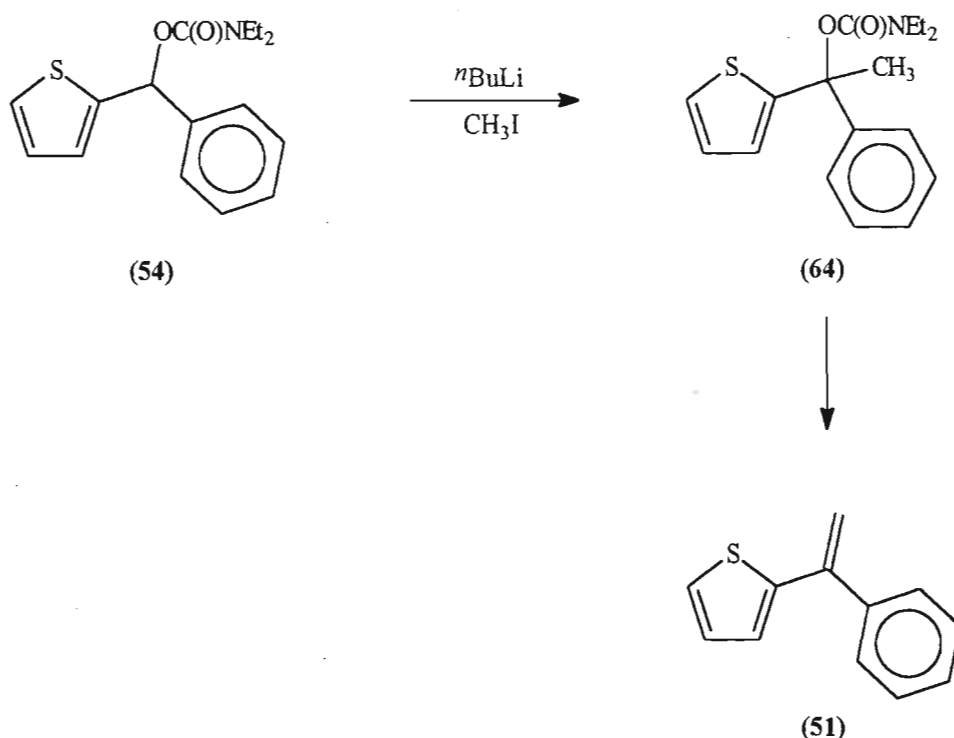


Scheme 80

The formation of products (**83**) and (**84**), together with the detection of the two other amines, means that the rearrangement of *N,N*-diethyl carbamates is not prevented by steric factors.

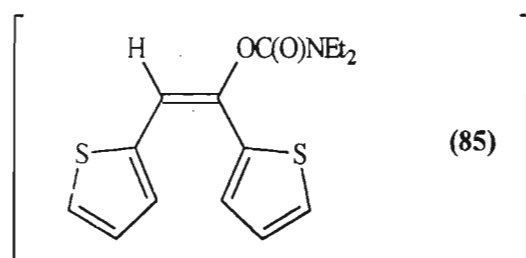
3.5.2 Decomposition Reactions producing Vinyl Systems

Evidence for this decomposition was obtained in the isolation of 1-phenyl-1-(2-thienyl)-ethene (**51**) during the purification of 1-(*N,N*-diethylcarbamoyloxy)-1-(phenyl)-1-(2-thienyl)-ethane (**64**), synthesised from the reaction of *N,N*-diethylcarbamoyloxy-phenyl-(2-thienyl)-methane (**54**) with ^{*n*}BuLi and CH₃I (**Scheme 81**).

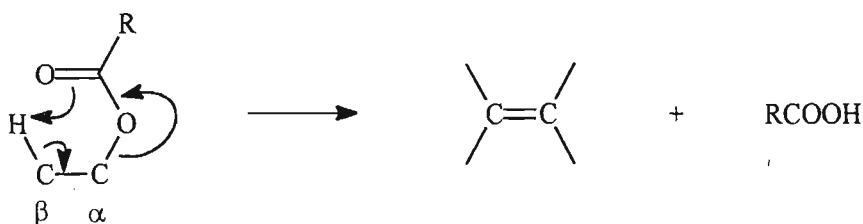


Scheme 81

In two other cases a similar decomposition has been found; that of 1-(N,N -diethylcarbamoyloxy)-1-(1-naphthyl)-1-(2-thienyl)-ethane, (65) and 1,2-di-(N,N -diethylcarbamoyloxy)-1,2-di-(2-thienyl)-ethane, (58). In the former case, the carbamate (65) is not detected by low resolution GC/MS analysis, but the mass corresponding to the vinyl species is detected. The NMR spectrum product (65) shows the vinylic hydrogen atoms as an impurity, indicating that the decomposition is not simply a McLafferty rearrangement initiated by GC/MS conditions. In the latter case, neither low nor high resolution mass spectrometry produces a molecular ion for the compound 1,2-di-(N,N -diethylcarbamoyloxy)-1,2-di-(2-thienyl)-ethane (58, molecular formula $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2$). The base peak in the high resolution mass spectrum corresponds to the formula $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{S}_2$. This represents the loss of a fragment corresponding to N,N -diethylcarbamic acid, leading to species 85, via a McLafferty fragmentation only under GC/MS conditions.



Mechanistically, this is a hydro-acyloxy-elimination⁹⁰. A carboxylic ester which has a β -hydrogen atom can undergo this elimination yielding a carbon-carbon double bond. The reaction is assisted by the presence of an electron-withdrawing group in the β -position (Scheme 82).

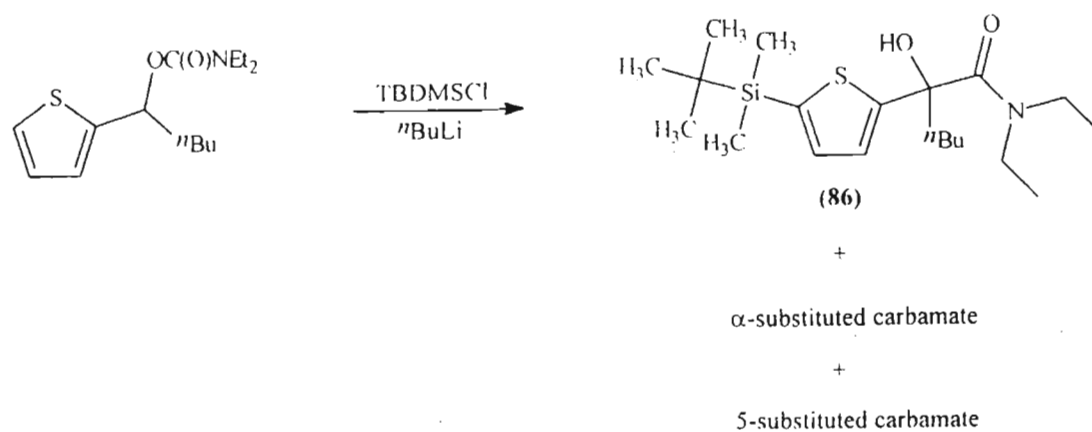


Scheme 82

This is the rearrangement (dehydration) observed by Krishnaswamy and co-workers during their study of photochemical reactions of thienyl methanols⁹⁷ (Scheme 67) indicating that the expulsion of the carbamate leading to the vinyl species may be a photochemical reaction. However, the fact that only the vinyl species and not the carbamate is detected by GC/MS indicates that the reaction may also be initiated by heat.

3.5.3 α -Hydroxyamides from Carbamates (1,2-Wittig Shift)

This rearrangement was observed during one attempt at the preparation of TBDMS substituted carbamates (Scheme 83). The amide portion of the carbamate migrates to the α -position and hydrolysis produces an α -hydroxy amide (86). The identity of this compound was confirmed by deuterium (D_2O) exchange of the hydroxy proton (Figure 4). Unfortunately, this product has only been isolated once and it has not yet been possible to reproduce this result by repeating the substitution reaction under the same conditions or under different conditions (-78°C , no warm-up and 0°C , warm to room temperature).



Scheme 83

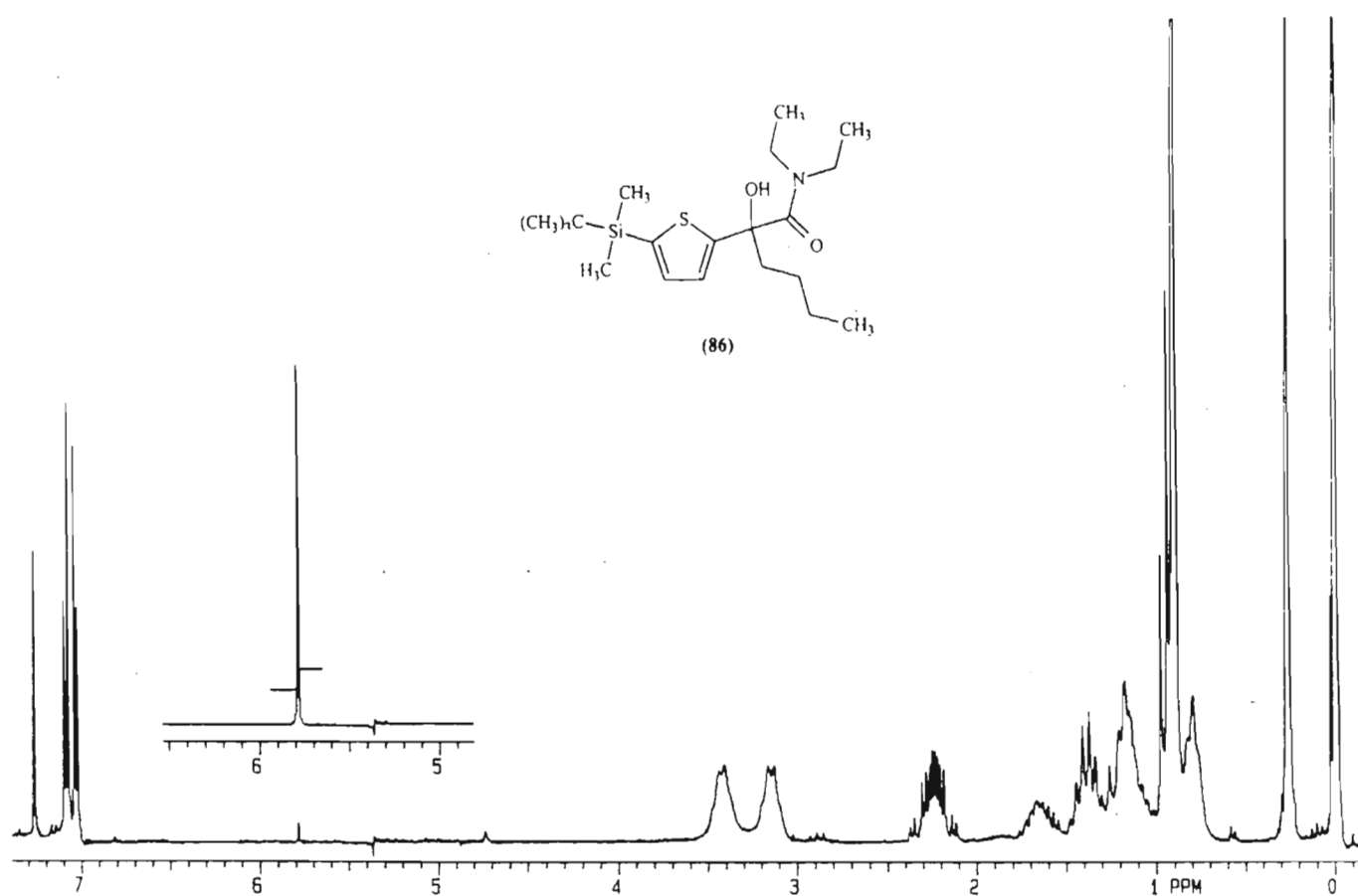
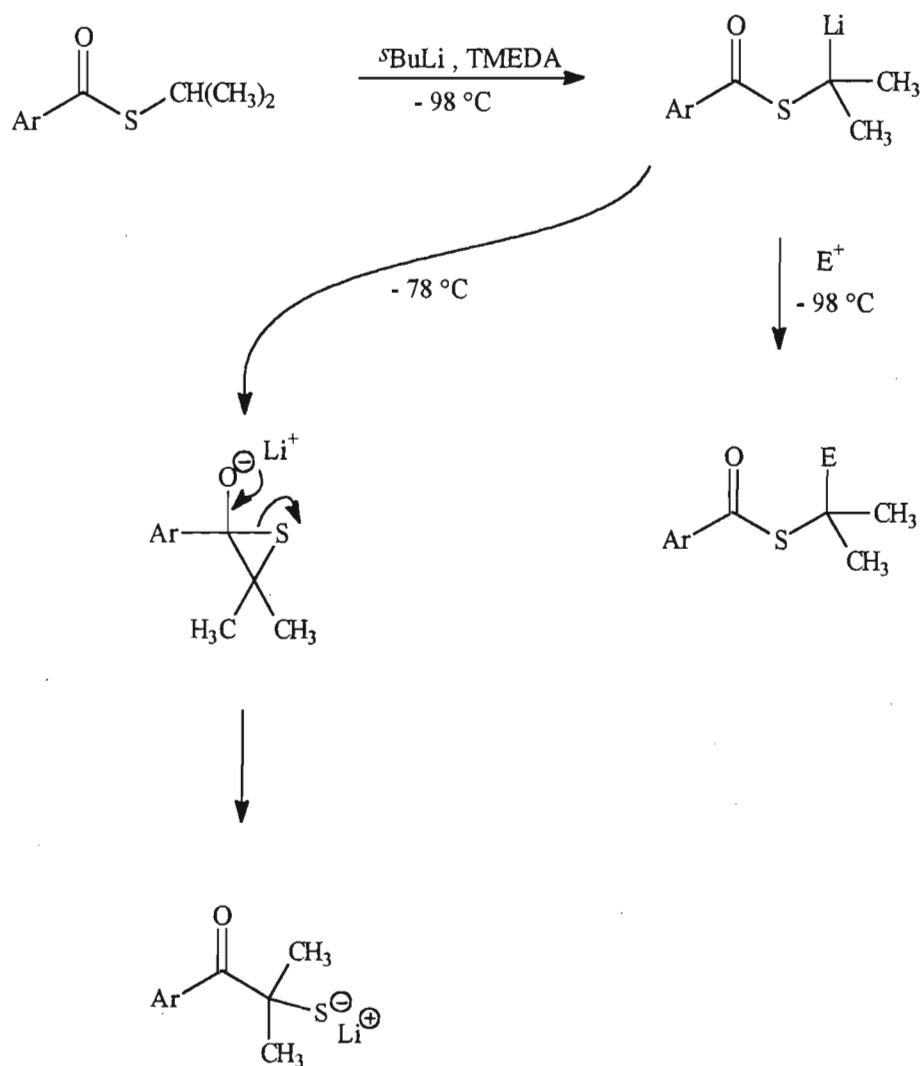


Figure 4

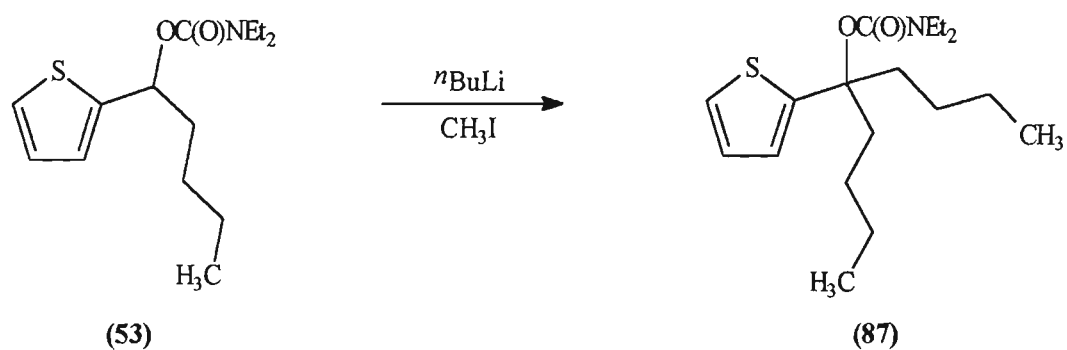
This rearrangement has been previously observed by Beak and co-workers¹⁰³. It has been found to be temperature dependent (the rearrangement takes place on warming to -78°C or if the lithiation is done at -78°C), as shown in **Scheme 84**.



Scheme 84

3.5.4 Methyl Iodide / Butyllithium Exchange

The following reaction (Scheme 85) was observed when attempting the substitution of 1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)-pentane (**53**) by using methyl iodide as electrophile.



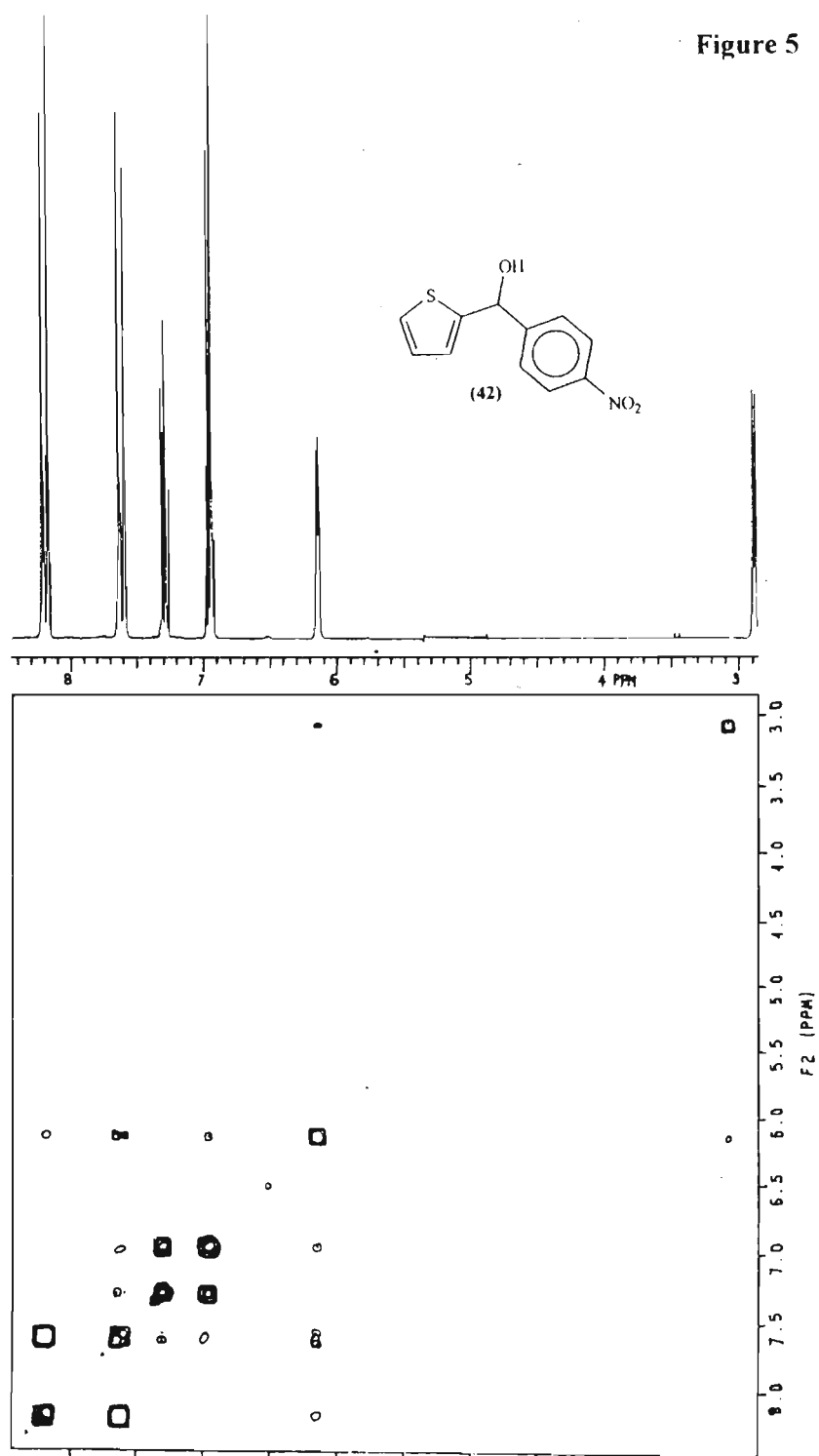
Scheme 85

The mechanism of this reaction is not known. It is suggested that an exchange takes place between the n butyllithium and the methyl iodide forming butyl iodide and methyllithium. The new base (methyllithium) abstracts a proton from the carbamate and the resultant anion reacts with the new alkyl halide (butyl iodide) giving the species **87**.

3.6 Proton NMR Spectra

Some general observations can be made from the NMR spectra of compounds prepared during this work:

Long range coupling occurs between ^1H nuclei - this is best illustrated by the COSY spectrum shown in **Figure 5**.



Allylic coupling often occurs between the proton at the 3-position of the thiophene ring and the proton at the thenyl position (**Figure 6**).

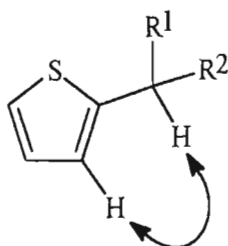
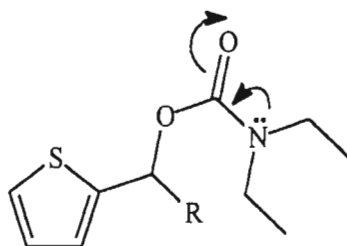


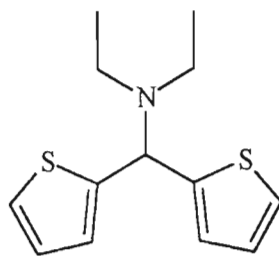
Figure 6

The ^{13}C spectra of the carbamates show that the ethyl groups in the *N,N*-diethyl carbamates are not equivalent. Two CH_3 peaks and two CH_2 peaks are visible in the carbamate spectrum. This has been attributed to a partial delocalisation of the lone pair of electrons from the nitrogen atom in the carbamate, leading to restricted rotation about the carbon-nitrogen bond (**Scheme 86**).



Scheme 86

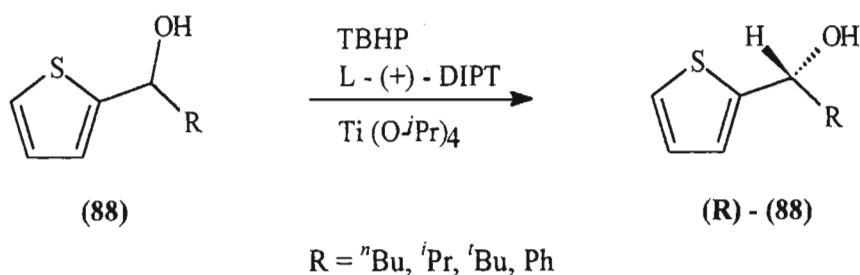
As a consequence of this resonance, the ethyl groups do not experience the same shielding effect and thus appear differently on the NMR spectrum (this difference in magnetic environment can sometimes also be seen in the proton spectra where the thenyl position is sterically crowded). In the spectrum of the diethyl amine (**83**), both ethyl groups are equivalent and only one signal (one CH_3 and one CH_2) can be seen.



(83)

3.7 Proposed Future Work

Kitano and co-workers¹⁰⁴ have reported a method for the preparation of optically-active 2-thienylcarbinols from racemic alcohols (Scheme 87).



Scheme 87

The ability to resolve thenyl alcohols provides a means for the preparation of chiral thenyl carbamates. These carbamates can then be used for the preparation of chiral amines *via* the carbamate-to-amine rearrangement or chiral α -hydroxyamides *via* the Beak rearrangement, once an investigation has been made to determine the conditions under which these reactions take place.

It is necessary to develop methods for increasing the selectivity of the electrophilic substitution reactions, particularly in the case of the complex substitution patterns found when using silicon-based electrophiles and the less sterically crowded carbamates. Not only does the variety of products reduce the yield of any one desired product, it also complicates the purification of the desired product. This has been found to be the case in this work,

especially with the TMSCl and CH₃I substitution products. Many of the products have similar R_f values and distillation has been found to be an unsatisfactory method for the purification of such compounds. Thus it would be desirable to find methods which allow selective preparation. It may be possible to control the selectivity using bulky substituents (ⁱPr, ^tBu) at the appropriate position(s). Control of the selectivity of the reaction would permit the preparation of chiral substituted products using a chiral starting carbamate.

Another possible extension of this work is to lengthen the conjugated chain. The compounds used in this project have only one aromatic ring, substitution takes place at position 1 or position 5 (four carbons from the site of anion generation). How far would a negative charge migrate along a system containing two rings - is it possible to achieve electrophilic substitution eight carbons from the site of proton abstraction, or would substitution take place only at position 1?

CHAPTER 4

EXPERIMENTAL

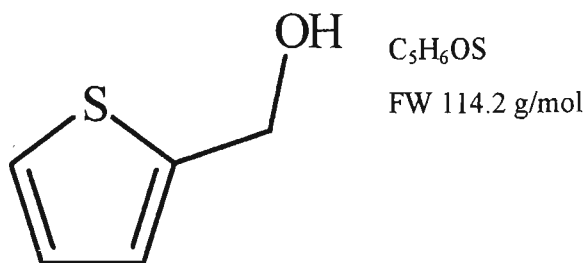
General:

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed using a Perkin-Elmer CHN Elemental Analyser. Accurate masses were determined using a Varian high resolution mass spectrometer. ^1H spectra (200 MHz) and ^{13}C (PND and DEPT) spectra (50 MHz) were recorded using a Varian Gemini 200 Spectrometer. All NMR spectra were recorded using CDCl_3 as solvent and TMS as internal standard, unless stated otherwise. All proton and carbon shifts are quoted relative to the TMS signal at $\delta = 0$. Proton-proton coupling constants are reported in Hertz (Hz). Low resolution mass spectra were recorded using a Hewlett-Packard HP5988A coupled gas chromatograph/mass spectrometer. Merck plastic sheets, pre-coated with silica gel 60 F₂₅₄, were used for thin layer chromatography. Column ("flash") chromatography was performed using Merck silica gel 60 F₂₅₄ (also Merck Basic Alumina (activity stage 1), where applicable) according to the method of Still, Kahn and Mitra¹⁰⁵; centrifugal chromatography was carried out on a Harrison Research chromatotron. Dry solvents were prepared according to standard laboratory practice. Reduced temperatures were maintained using solid CO_2 /solvent cooling baths according to the established procedure of Phipps and Hume¹⁰⁶.

Where applicable, in NMR characterisation, a subscripted "q" denotes a quaternary carbon atom. Where a spectrum shows a mixture of compounds, the signals for both proton and carbon atoms are presented in numerical order, the signals from the second compound listed in square "[]" brackets.

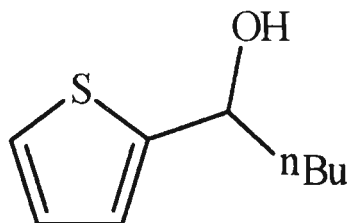
In the absence of COSY and HETCOR experiments, ambiguous quaternary and tertiary carbon signals have been intuitively assigned with the aid of ACD/CNMR[®], a software package published by Advanced Chemistry Development Inc., 141 Adelaide Street West, Suite 1501, Toronto, Canada, M5H 3L5.

2-Thiophenemethanol (37)



2-Thiophenecarboxaldehyde (1.13 g, 10.08 mmol) was stirred in methanol (20 ml) while immersed in an ice/salt cooling bath. $NaBH_4$ (0.47 g, 12.42 mmol) was added in small portions over 15 minutes. The reaction mixture was stirred for 15 minutes, the cooling bath was removed and stirring was continued for 15 minutes. $NaOH$ (20 ml, approximately 1 M) was added slowly. The solution was saturated with $NaCl_{(s)}$ and extracted with diethyl ether. The ethereal solution was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure, to give the product (0.84 g, 7.36 mmol, 73%) as a pale yellow liquid. 1H NMR ($CDCl_3$): δ 3.07 (br.s, 1 H, OH); 4.70 (s, 2 H, CH_2 - O); 6.91-6.96 (m, 2 H, CH - CH); 7.21-7.25 (m, 1 H, CH - S). ^{13}C NMR ($CDCl_3$): δ 59.6 (t, CH_2 - O); 125.40 (d, CH - C_q); 125.44 (d, CH - CH - CH); 126.79 (d, CH - S); 143.9 (s, C_q - S). m/z 114 (100%, M^+), 113 (41%), 97 (70%), 85 (91%), 81 (33%).

1-(2-thienyl)-1-pentanol (38)

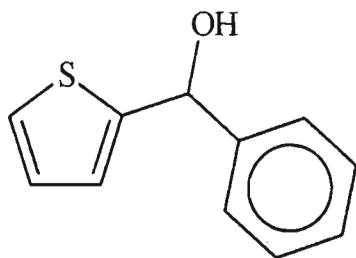


C₉H₁₄OS

FW 170.3 g/mol

Thiophene (3.04 g, 36.2 mmol), stirred in dry diethyl ether (50 ml) under N₂, was cooled to -78 °C in a CO₂/acetone cooling bath. ⁿBuLi solution (25.0 ml, 1.74 M, 43.5 mmol) was added dropwise. The mixture was stirred for 30 minutes, then 2-thiophenecarboxaldehyde (4.06 g, 36.3 mmol) was added dropwise. The solution was stirred for 90 minutes, quenched with sat. NH₄Cl, allowed to warm to room temperature and extracted with diethyl ether. The ethereal solution was dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. 6.35 g of yellow liquid remained. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product (3.92 g, 23.0 mmol, 64%) as a pale yellow liquid. ¹H NMR (CDCl₃): δ 0.89 (t, *J* = 6.78 Hz, 3 H, CH₃); 1.26-1.45 (m, 4 H, 2x CH₂); 1.76-1.90 (m, 2 H, CH₂ - CH); 2.37 (br.s, 1 H, OH); 4.87 (t, *J* = 6.53 Hz, 1 H, CH - O); 6.92-6.97 (m, 2 H, CH - CH); 7.21-7.25 (m, 1 H, CH - S). ¹³C NMR (CDCl₃): δ 14.0 (q, CH₃); 22.5 (t, CH₂ - CH₃); 27.9 (t, CH₂ - CH₂ - CH₂); 39.0 (t, CH₂ - CH); 70.3 (d, CH - O); 123.7 (d, CH - C_q); 124.4 (d, CH - CH - CH); 126.5 (d, CH - S); 149.0 (s, C_q - S). *m/z* 170 (14%, M⁺), 113 (100%), 97 (5%), 85 (49%).

Phenyl-(2-thienyl)methanol (39)

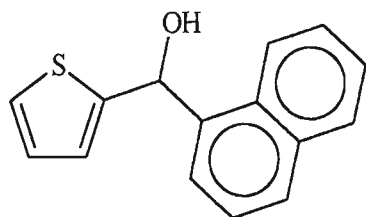


$C_{11}H_{10}OS$

FW 190.3 g/mol

Magnesium turnings (1.43 g, 58.8 mmol) and a crystal of iodine were placed in dry THF (20 ml) under N_2 . A solution of bromobenzene (8.40 g, 53.5 mmol) in THF (20 ml) was added at a rate so as to maintain (spontaneous) reflux. The mixture was stirred for 10 minutes then cooled to 0 °C in an ice bath. 2-Thiophenecarboxaldehyde (3.00 g, 26.8 mmol) in dry THF (10 ml) was added dropwise with stirring. The cooling bath was removed and stirring was continued for 30 minutes then ice water (20 ml) was added dropwise. Concentrated $HCl_{(aq)}$ was added dropwise with stirring until the solid material dissolved, then the mixture was extracted with $CHCl_3$. The organic solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving 6.58 g yellow liquid. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a white solid (3.92 g, 20.6 mmol, 77%), m.p. 56-57 °C (lit.¹⁰⁷ 57-58 °C). 1H NMR ($CDCl_3$): δ 2.26 (d, $J = 3.96$ Hz, 1 H, OH); 5.90 (d, $J = 3.90$ Hz, 1 H, CH - O); 6.72 (ddd, $J = 0.89$ Hz, $J = 1.30$ Hz, $J = 3.52$ Hz, 1 H, CH - C_q (thiophene)); 6.78 (dd, $J = 3.52$ Hz, $J = 5.01$ Hz, 1 H, CH - CH - CH (thiophene)); 7.10 (dd, $J = 1.41$ Hz, $J = 4.88$ Hz, 1 H, CH - S); 7.14-7.32 (m, 5 H, 5x CH (phenyl)). ^{13}C NMR ($CDCl_3$): δ 72.4 (d, CH - O); 124.9 (d, CH - CH - CH (thiophene)); 125.4 (d, CH - S); 126.3 (d, 2x CH (*m*-phenyl)); 126.6 (d, CH (*p*-phenyl)); 128.0 (d, CH - C_q (thiophene)); 128.5 (d, 2x CH (*o*-phenyl)); 143.1 (s, C_q (phenyl)); 148.1 (s, C_q - S). m/z 190 (25%, M^+), 157 (17%), 128 (16%), 111 (45%), 105 (100%), 85 (62%), 77 (49%).

(1-naphthyl)-(2-thienyl)methanol (40)

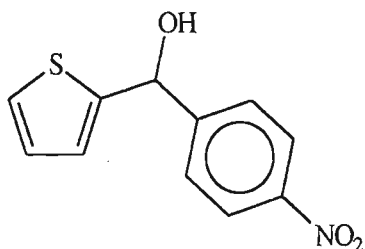


$C_{15}H_{12}OS$

FW 240.3 g/mol

A solution of 1-bromonaphthalene (4.44 g, 21.4 mmol) in dry diethyl ether (20 ml) was added dropwise to magnesium turnings (0.60 g, 24.7 mmol) in dry diethyl ether (20 ml) at a rate so as to maintain (spontaneous) reflux. The solution was heated to reflux for 10 minutes then cooled to 0 °C in an ice bath. 2-Thiophenecarboxaldehyde (2.00 g, 17.9 mmol) in dry diethyl ether (10 ml) was added dropwise with stirring. The cooling bath was removed and stirring was continued for 30 minutes then ice water (20 ml) was added slowly. Concentrated $HCl_{(aq)}$ was added dropwise with stirring until the solid material dissolved, and the mixture was extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving 4.99 g of yellow liquid. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a viscous yellow liquid (3.22 g, 13.4 mmol, 75%) (lit.⁹⁶ m.p. 30-31 °C). 1H NMR ($CDCl_3$): δ 2.81 (d, J = 0.54 Hz, 1 H, OH); 6.47 (s, 1 H, CH - O); 6.62-6.65 (m, 1 H, CH (thiophene)); 6.70 (dd, J = 3.56 Hz, J = 5.03 Hz, 1 H, CH - CH - CH (thiophene)); 7.03-7.06 (m, 1 H, CH - S); 7.22-7.34 (m, 3 H, 3x CH (naphthyl)); 7.54-7.84 (m, 4 H, 4x CH (naphthyl)). ^{13}C NMR ($CDCl_3$): δ 69.4 (d, CH - O); 123.6 (d, CH (7'-naphthyl)); 123.7 (d, CH (6'-naphthyl)); 125.27 (d, CH (5'-naphthyl)); 125.33 (d, CH - CH - CH (thiophene) and 2'-naphthyl); 125.5 (d, CH - S); 126.1 (d, CH (4'-naphthyl)); 126.6 (d, CH (8'-naphthyl)); 128.6 (d, CH (3'-naphthyl)); 128.7 (d, CH - C_q (thiophene)); 130.2 (s, C_q (8a'-naphthyl)); 133.7 (s, C_q (4a'-naphthyl)); 138.3 (s, C_q (1'-naphthyl)); 147.4 (s, C_q - S). m/z 240 (59%, M^+), 155 (100%), 128 (66%), 111 (71%), 85 (22%).

(4-nitrophenyl)-(2-thienyl)methanol (42)



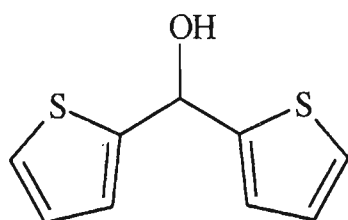
$C_{11}H_9NO_3S$

FW 235.3 g/mol

Thiophene (1.00 g, 0.012 mol) was stirred in dry THF (5 ml) under N_2 at 0 °C (ice bath). t BuLi solution (9.0 ml, 1.55 M, 14.0 mmol) was added dropwise and the mixture was stirred at 0 °C for 20 minutes. The temperature was lowered to -78 °C using a CO_2 /acetone cooling bath and 4-nitrobenzaldehyde (1.80 g, 11.9 mmol) in dry THF (20 ml) was added dropwise. The reaction mixture was stirred at -78 °C for 2 hours then quenched with sat. NH_4Cl . The mixture was allowed to warm to room temperature and was extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving a dark liquid (2.38 g, 85% - crude) which crystallised on standing. The crude solid was purified by dissolving in diethyl ether and adsorbing on silica gel (some product lost due to bumping during solvent removal). Column chromatography (60% hexane, 40% chloroform) yielded the product as a pale coloured crystalline solid (1.26 g, 5.4 mmol, 45%), m.p. 80-81 °C. 1H NMR ($CDCl_3$): δ 2.89 (d, J = 3.65 Hz, 1 H, OH); 6.14 (d, J = 3.34 Hz, 1 H, CH - O); 6.92-6.98 (m, 2 H, CH - CH (thiophene)); 7.29 (dd, J = 1.66 Hz, J = 4.67 Hz, 1 H, CH - S); 7.57-7.65 (m, 2 H, 2x CH - C_q CH (phenyl)); 8.15-8.22 (m, 2 H, 2x CH - C_qNO_2). ^{13}C NMR ($CDCl_3$): δ 71.2 (d, CH - O); 123.7 (d, 2x CH - C_qNO_2); 125.5 (d, CH - CH - CH (thiophene)); 126.3 (d, CH - S); 126.89 (d, CH - C_q (thiophene)); 126.94 (d, 2x CH - C_q CH (phenyl)); 146.4 (s, C_q - CH (phenyl)); 147.3 (s, C_q - NO_2); 150.0 (s, C_q - S). m/z 235 (19%, M^+), 202 (10%), 151 (19%), 113 (22%), 111 (30%), 85 (100%).

HRMS: $C_{11}H_9NO_3S$ calc. 235.0303, found 235.0311.

Di-(2-thienyl)methanol (43)

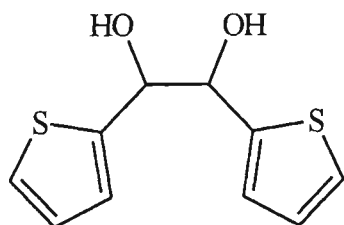


$C_9H_8OS_2$

FW 196.3 g/mol

Thiophene (2.00 g, 23.8 mmol) was stirred in dry THF (15 ml) under N_2 at 0 °C (ice bath). t -BuLi solution (23.2 ml, 1.20 M, 27.8 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 minutes then the temperature was lowered to -78 °C using a CO_2 /acetone cooling bath. 2-Thiophenecarboxaldehyde (2.67 g, 23.8 mmol) was added dropwise. The solution was stirred at -78 °C for 2 hours then quenched by the addition of sat. NH_4Cl . The mixture was allowed to warm to room temperature and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving 4.52 g of yellow liquid. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a yellow solid (3.73 g, 19.0 mmol, 80%), m.p. 53-56 °C (lit.¹⁰⁸ 51-52 °C). 1H NMR ($CDCl_3$): δ 2.68 (d, J = 4.14 Hz, 1 H, OH); 6.29 (d, J = 3.75 Hz, 1 H, CH - O); 6.96 (dd, J = 3.54 Hz, J = 4.92 Hz, 2 H, 2x CH - CH - CH); 7.01 (ddd, J = 0.83 Hz, J = 1.40 Hz, 3.52 Hz, 2 H, 2x CH - C_q); 7.28 (dd, J = 1.41 Hz, J = 4.93 Hz, 2 H, 2x CH - S). ^{13}C NMR ($CDCl_3$): δ 68.6 (d, CH - O); 125.0 (d, 2x CH - CH - CH); 125.5 (d, 2x CH - C_q); 126.7 (d, 2x CH - S); 147.1 (s, 2x C_q - S). m/z 196 (33%, M^+), 179 (22%), 163 (18%), 111 (100%), 85 (78%). HRMS: $C_9H_8OS_2$ calc. 196.0017, found 196.0006.

1,2-dihydroxy-1,2-di-(2-thienyl)ethane (44)

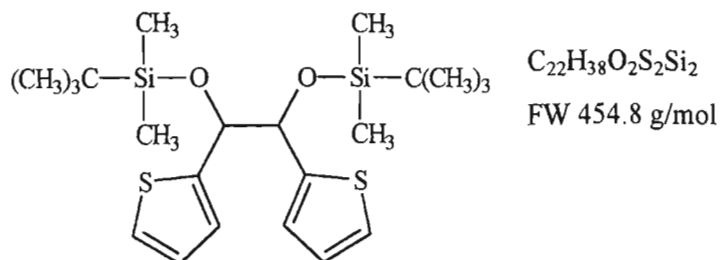


$C_{10}H_{10}O_2S_2$

FW 226.3 g/mol

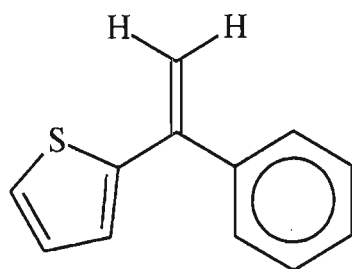
NaOH granules (0.77 g, 19 mmol) and Zn turnings (0.74 g, 11 mmol) were stirred in 95% ethanol (5.4 ml) until NaOH dissolved. 2-Thiophenecarboxaldehyde (1.06 g, 9 mmol) was added dropwise. The mixture was heated to reflux (~80 °C) for 3 hours, then allowed to cool to room temperature. The solution was filtered to remove solids, the solid material was washed with distilled water and then with diethyl ether. The layers were separated, the aqueous layer was saturated with $NaCl_{(s)}$ and extracted with diethyl ether. The organic solution was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure leaving 0.42 g yellow liquid. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded 0.026 g (0.115 mmol, 2.4%) of the product. 1H NMR ($CDCl_3$): δ 2.88 (br. s, 2 H, 2x OH); [3.43 (br. s, 2 H, 2x OH)]; 4.98 (s, 2 H, 2x CH - O); [5.08 (s, 2 H, 2x CH - O)]; 6.76-6.98 (m, 8 H, 8x CH - C_q); 7.21-7.28 (m, 4 H, 4x CH - S). ^{13}C NMR ($CDCl_3$): δ 74.3 (d, 2x CH - O); [74.8 (d, 2x CH - O)]; [125.4 (d, 2x CH)]; [125.6 (d, 2x CH)]; 125.8 (d, 2x CH); 126.0 (d, 2x CH); 126.5 (d, 2x CH); [126.6 (d, 2x CH)]; 142.4 (s, 2x C_q); [142.8 (s, 2x C_q)].

1,2-di-(*tertiary*-butyldimethylsilyloxy)-1,2-di-(2-thienyl)ethane (45)



Zinc dust (3.27 g, 50.0 mmol) was stirred in dry THF (10 ml) under N_2 . A solution of *tert*-butyldimethylsilylchloride (1.51 g, 10.0 mmol) and 2-thiophenecarboxaldehyde (1.12 g, 10.0 mmol) in dry THF (15 ml) was added slowly and the mixture was heated to reflux with stirring for 24 hours. The mixture was allowed to cool to room temperature and filtered. The solids were washed with petroleum ether (40/60) and the filtered solution was dried over Na_2SO_4 . The drying agent was removed by filtration and the solvent was removed under reduced pressure leaving 2.54 g dark liquid. Column chromatography (Basic Alumina - activity stage 1, hexane) yielded the product (0.22 g, 0.48 mmol, 10%) as white crystals. 1H NMR (CCl_4): δ -0.31 (s, 3 H, CH_3 - Si); -0.28 (s, 3 H, CH_3 - Si); -0.06 (s, 3 H, CH_3 - Si); 0.07 (s, 3 H, CH_3 - Si); 0.73 (s, 8 H, 3x CH_3 (*tert*-butyl)); 0.92 (s, 10 H, 3x CH_3 (*tert*-butyl)); 4.72 (s, 1 H, CH - O); 4.93 (s, 1 H, CH - O); 6.61 (dd, $J = 1.23$ Hz, $J = 3.52$ Hz, 1 H, CH - C_q); 6.75 (dd, $J = 3.56$ Hz, $J = 5.04$ Hz, 1 H, CH - CH - CH); 6.85-6.92 (m, 2 H, 2x CH); 7.03 (dd, $J = 1.25$ Hz, $J = 5.02$ Hz, 1 H, CH - S); 7.16 (dd, $J = 1.50$ Hz, $J = 4.80$ Hz, 1 H, CH - S). ^{13}C NMR (CCl_4): δ -5.4 (q, CH_3 - Si); -4.9 (q, CH_3 - Si); -4.61 (q, CH_3 - Si); -4.56 (q, CH_3 - Si); 18.3 (s, C_q (*tert*-butyl)); 18.5 (s, C_q (*tert*-butyl)); 26.0 (q, 3x CH_3 (*tert*-butyl)); 26.2 (q, 3x CH_3 (*tert*-butyl)); 76.2 (d, CH - O); 76.8 (d, CH - O); 124.32 (d, CH); 124.42 (d, CH); 124.49 (d, CH); 125.37 (d, CH); 125.85 (d, CH); 125.95 (d, CH); 144.4 (s, C_q - S); 147.0 (s, C_q - S). m/z 397 (0.3%, M-57), 323 (0.1%), 227 (100%), 147 (16%), 73 (64%), **no molecular ion under electronic ionisation**. HRMS: $C_{22}H_{38}O_2S_2Si_2$ calc. 454.1852, found 454.1858.

1-phenyl-1-(2-thienyl)ethene (51)

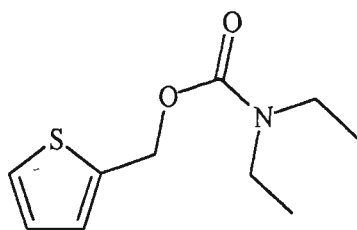


$C_{12}H_{10}S$

FW 186.3 g/mol

N,N-diethylcarbamoyloxy-phenyl-(2-thienyl)methane (0.50 g, 1.73 mmol) was stirred in dry THF (10 ml) under N_2 at $-78\text{ }^{\circ}\text{C}$. $n\text{-BuLi}$ solution (1.4 ml, 1.58 M, 2.21 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH_3I (0.25 g, 1.76 mmol) in dry THF (3 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^{\circ}\text{C}$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO_3 and extracted with diethyl ether. The ethereal solution was dried (MgSO_4), filtered and the solvent was removed under reduced pressure. 0.486 g of dark liquid remained. Silica gel chromatography (90% hexane; 10% diethyl ether) yielded the product as a pale yellow liquid (0.039 g, 0.21 mmol, 12%). ^1H NMR (CDCl_3): δ 5.246 (d, $J = 0.64\text{ Hz}$, 1 H, CH (vinyl)); 5.585 (d, $J = 0.73\text{ Hz}$, 1 H, CH (vinyl)); 6.91 (dd, $J = 1.19\text{ Hz}$, $J = 3.59\text{ Hz}$, 1 H, CH - C_q (thiophene)); 6.98 (dd, $J = 3.62\text{ Hz}$, $J = 5.09\text{ Hz}$, 1 H, CH - CH - CH (thiophene)); 7.22-7.26 (dd, $J = 1.14\text{ Hz}$, 1 H, CH - S); 7.34-7.47 (m, 5 H, 5x CH (phenyl)). ^{13}C NMR (CDCl_3): δ 113.6 (t, CH_2); 125.0 (d, CH - CH - CH (thiophene)); 126.5 (d, CH (*p*-phenyl)); 127.3 (d, CH - S); 128.0 (d, CH - C_qS); 128.2 (d, 2x CH (*m*-phenyl)); 128.3 (d, 2x CH (*o*-phenyl)); 141.0 (s, C_q (phenyl)); 143.3 (s, C_q - S); 144.7 (s, C_q - CH_2). m/z 186 (100%, M^+), 185 (68%), 171 (47%), 152 (21%), 115 (15%).

***N,N*-diethylcarbamoyloxy-(2-thienyl)methane (52)**

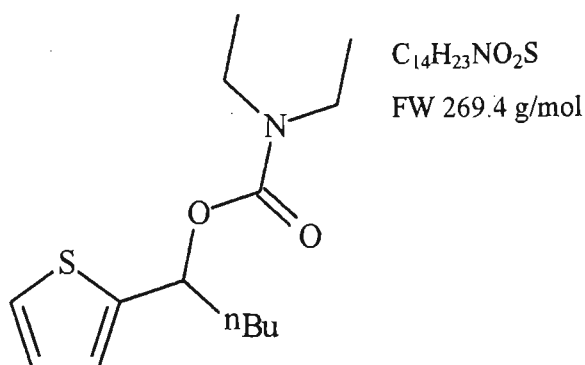


$C_{10}H_{15}NO_2S$

FW 213.3 g/mol

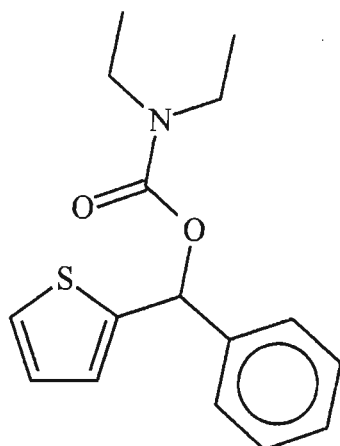
2-Thiophenemethanol (3.45 g, 30.2 mmol) in dry THF (20 ml) was added dropwise to a stirred suspension of NaH (1.45 g, 36.3 mmol, 60% suspension in mineral oil) in dry THF (20 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes and then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (4.10 g, 30.2 mmol) was added dropwise. The cooling bath was removed, the mixture was stirred for 2 hours, quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a pale yellow liquid (5.75 g, 27.0 mmol, 89%). 1H NMR ($CDCl_3$): δ 1.11 (t, J = 6.85 Hz, 6 H, 2x CH_3 - CH_2N); 3.27 (br. s, 4 H, 2x CH_2 - N); 5.26 (d, J = 0.64 Hz, 2 H, CH_2 - O); 6.96 (dd, J = 3.49 Hz, J = 5.12 Hz, 1 H, CH - CH - CH); 7.05-7.07 (m, 1 H, CH - C_q); 7.28 (dd, J = 1.27 Hz, J = 5.05 Hz, 1 H, CH - S). ^{13}C NMR ($CDCl_3$): δ 13.5 (q, CH_3 - CH_2N); 14.0 (q, CH_3 - CH_2N); 41.3 (t, CH_2 - N); 41.9 (t, CH_2 - N); 61.2 (t, CH_2 - O); 126.3 (d, CH - CH - CH); 126.6 (d, CH - S); 127.2 (d, CH - C_q); 139.4 (s, C_q - S); 155.5 (s, C_q = O). m/z 213 (0.2%, M^+), 154 (2.7%), 97 (100%), 72 (6%). HRMS: $C_{10}H_{15}NO_2S$ calc. 213.0824, found 213.0828.

1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (53)



1-(2-thienyl)-1-pentanol (3.80 g, 22.3 mmol) was added dropwise to a stirred suspension of NaH (0.84 g, 21.0 mmol, 60% suspension in mineral oil) in dry THF (25 ml) under N₂ while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (4.00 g, 29.5 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2 hours then quenched with sat. NH₄Cl and extracted with diethyl ether. The ethereal solution was dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a pale yellow liquid (4.50 g, 16.7 mmol, 75%). ¹H NMR (CDCl₃): δ 0.89 (t, *J* = 6.65 Hz, 3 H, CH₃ ("pentane)); 1.11 (t, *J* = 7.11 Hz, 6 H, 2x CH₃ - CH₂N); 1.27-1.38 (m, 4 H, 2x CH₂ ("pentane)); 1.87-2.00 (m, 2 H, CH₂ ("pentane)); 3.27 (q, *J* = 7.05 Hz, 4 H, 2x CH₂ - N); 5.96 (t, *J* = 6.95 Hz, 1 H, CH - O); 6.92-7.03 (m, 2 H, CH - CH); 7.22 (dd, *J* = 1.28 Hz, *J* = 5.02 Hz, CH - S). ¹³C NMR (CDCl₃): δ 13.5 (q, CH₃ - CH₂N); 14.0 (q, CH₃ ("pentane)); 14.2 (q, CH₃ - CH₂N); 22.4 (t, CH₂ - CH₃ ("pentane)); 27.7 (t, CH₂ - CH₂ - CH₂ ("pentane)); 36.7 (t, CH₂ - CH ("pentane)); 41.3 (t, CH₂ - N); 41.8 (t, CH₂ - N); 72.0 (d, CH - O); 124.6 (d, CH - CH - CH); 125.0 (d, CH - S); 126.4 (d, CH - C_q); 145.0 (s, C_q - S); 155.2 (s, C_q = O). *m/z* 269 (1.6%, M⁺), 168 (7%), 153 (38%), 97 (100%), 72 (12%). HRMS: C₁₄H₂₃NO₂S calc. 269.1450, found 269.1438.

***N,N*-diethylcarbamoyloxy-phenyl-(2-thienyl)methane (54)**

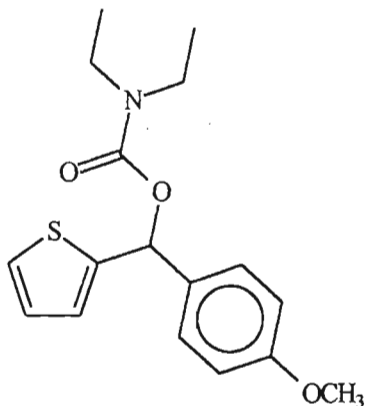


$C_{16}H_{19}NO_2S$

FW 289.4 g/mol

Phenyl-(2-thienyl)methanol (4.90 g, 25.7 mmol) in dry THF (30 ml) was added dropwise to a stirred suspension of NaH (1.24 g, 31.0 mmol, 60% suspension in mineral oil) in dry THF (20 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes, then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (3.50 g, 25.8 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2 hours, quenched with sat. NH_4Cl , and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a viscous yellow liquid (5.21 g, 18.0 mmol; 70%). 1H NMR ($CDCl_3$): δ 1.09-1.19 (br. m, 6 H, 2x CH_3 - CH_2N); 3.26-3.40 (br. m, 4 H, 2x CH_2 - N); 6.87 (ddd, J = 0.84 Hz, J = 1.39 Hz, J = 3.55 Hz, 1 H, CH - C_q (thiophene)); 6.92 (dd, J = 3.58 Hz, J = 4.95 Hz, 1 H, CH - CH - CH (thiophene)); 7.03 (s, 1 H, CH - O); 7.25 (dd, J = 1.38 Hz, J = 4.94 Hz, 1 H, CH - S); 7.29-7.46 (m, 5 H, 5x CH (phenyl)). ^{13}C NMR ($CDCl_3$): δ 13.4 (q, CH_3 - CH_2N); 14.2 (q, CH_3 - CH_2N); 41.4 (t, CH_2 - N); 41.9 (t, CH_2 - N); 73.6 (d, CH - O); 125.7 (d, CH - CH - CH (thiophene)); 126.0 (d, CH - S); 126.5 (d, CH (*p*-phenyl)); 126.7 (d, 2x CH (*m*-phenyl)); 128.0 (d, CH - C_qS); 128.4 (d, 2x CH (*o*-phenyl)); 140.5 (s, C_q (phenyl)); 144.8 (s, C_q (thiophene)); 154.7 (s, C_q = O). m/z 289 (2.5%, M^+), 173 (100%), 129 (15%), 100 (6.5%). HRMS: $C_{16}H_{19}NO_2S$ calc. 289.1137, found 289.1135.

***N,N*-diethylcarbamoyloxy-(4-methoxyphenyl)-(2-thienyl)methane (55)**

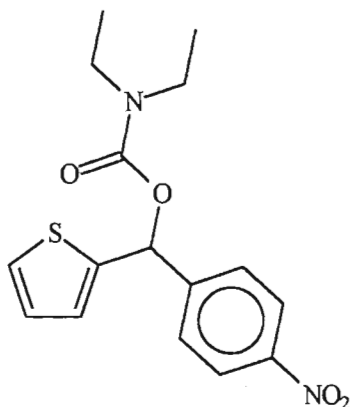


$C_{17}H_{21}NO_3S$

FW 319.4 g/mol

Thiophene (1.50 g, 17.9 mmol) was stirred in dry THF (5 ml) under N_2 while immersed in an ice bath (0 °C). t -BuLi solution (8.3 ml, 2.58 M, 21.4 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 minutes then the temperature was lowered to -78 °C using a CO_2 /acetone cooling bath. *p*-Anisaldehyde (2.43 g, 17.8 mmol) was added dropwise. The mixture was stirred for 2 hours, quenched with sat. NH_4Cl , allowed to warm to room temperature and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure leaving 3.23 g cloudy yellow liquid containing (4-methoxyphenyl)-(2-thienyl)methanol. m/z (alcohol) 220 (42%, M^+), 202 (21%), 135 (100%), 109 (37%), 77 (23%). 2.30 g of the aforementioned yellow liquid in dry THF (10 ml) was added dropwise to a stirred suspension of NaH (0.52 g, 13.0 mmol, 60% suspension in mineral oil) in dry THF (10 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (1.42 g, 10.5 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2.5 hours, quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving 3.18 g yellow liquid, purified using silica gel chromatography (90% hexane, 10% diethyl ether). Calculated overall yield of carbamate 21%. m/z 319 (0.6%, M^+), 275 (1%), 203 (100%), 160 (10%), 115 (14%), 72 (13%). HRMS: $C_{17}H_{21}NO_3S$ calc. 319.1242, found 319.1230.

***N,N*-diethylcarbamoyloxy-(4-nitrophenyl)-(2-thienyl)methane (56)**

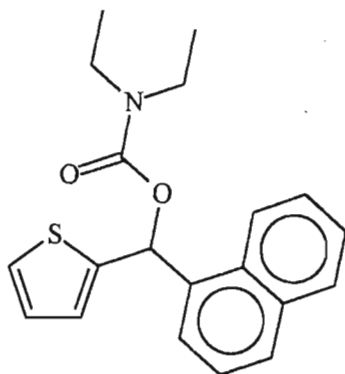


$C_{16}H_{18}N_2O_4S$

FW 334.4 g/mol

(4-nitrophenyl)-(2-thienyl)methanol (0.95 g, 4.0 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of NaH (0.20 g, 5.0 mmol, 60% suspension in mineral oil) in dry THF (5 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (0.58 g, 4.3 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2 hours, quenched with sat. NH_4Cl , and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (chloroform) yielded the product as a moist red/orange solid (0.7 g, 2.1 mmol, 50%). 1H NMR ($CDCl_3$): δ 1.14-1.20 (m, 6 H, 2x CH_3 - CH_2N); 3.31-3.40 (m, 4 H, 2x CH_2 - N); 6.92-7.01 (m, 2 H, 2x CH (thiophene)); 7.09 (s, 1 H, CH - O); 7.19-7.32 (m, 1 H, CH (thiophene)); 7.58-8.38 (m, 4 H, 4x CH (phenyl)). ^{13}C NMR ($CDCl_3$): δ 13.4 (q, CH_3 - CH_2N); 14.3 (q, CH_3 - CH_2N); 41.5 (t, CH_2 - N); 42.2 (t, CH_2 - N); 72.7 (d, CH - O); 123.8 (d, 2x CH - C_qNO_2); 126.4 (d, CH - CH - CH (thiophene)); 126.6 (d, CH - S); 126.8 (d, CH - C_q (thiophene)); 127.4 (d, 2x CH - C_qCH (phenyl)); 142.9 (s, C_q - CH (phenyl)); 147.5 (s, C_q - S); 147.7 (s, C_q - NO_2); 154.3 (s, C_q = O). m/z 334 (3%, M^+), 275 (2.8%), 218 (100%), 171 (27%), 160 (3.3%), 100 (9%), 72 (3.6%). HRMS: $C_{16}H_{18}N_2O_4S$ calc. 334.0987, found 334.0975.

***N,N*-diethylcarbamoyloxy-(1-naphthyl)-(2-thienyl)methane (57)**

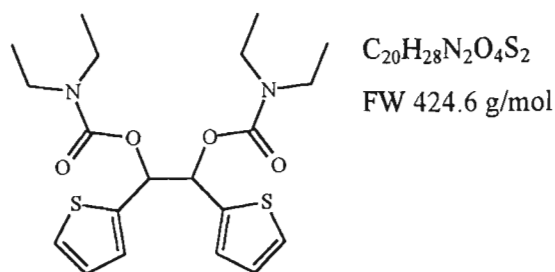


$C_{20}H_{21}NO_2S$

FW 339.5 g/mol

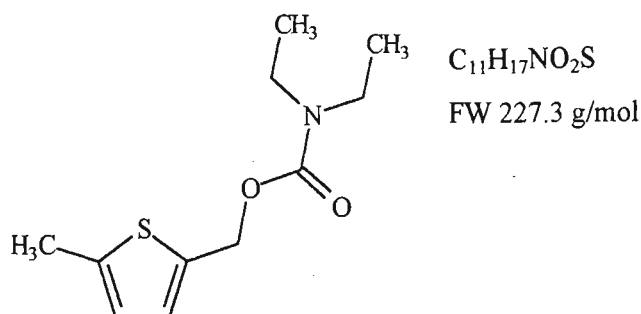
(1-naphthyl)-(2-thienyl)methanol (2.60 g, 10.8 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of NaH (0.52 g, 13.0 mmol, 60% suspension in mineral oil) in dry THF (10 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (1.47 g, 10.8 mmol) was added dropwise. The cooling bath was removed, the mixture was stirred for 2 hours, quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a pale solid (3.11 g, 9.2 mmol, 85%, recrystallised from 95% ethanol), m.p. 78-80 °C. 1H NMR ($CDCl_3$): δ 1.17 (br. s, 6 H, 2x CH_3 - CH_2N); 3.29-3.41 (br. m, 4 H, 2x CH_2 - N); 6.83-6.85 (m, 1 H, CH (thiophene)); 6.90 (dd, $J = 3.57$ Hz, $J = 5.01$ Hz, 1 H, CH - CH - CH (thiophene)); 7.25-7.28 (dd, $J = 1.31$ Hz, 1 H, CH (thiophene)); 7.45-7.56 (m, 3 H, 3x CH (naphthyl)); 7.71-7.76 (m, 1 H, CH (naphthyl)); 7.73 (s, 1 H, CH - O); 7.85-7.91 (m, 2 H, 2x CH (naphthyl)); 8.09-8.14 (m, 1 H, CH (naphthyl)). ^{13}C NMR ($CDCl_3$): δ 13.5 (q, CH_3 - CH_2N); 14.2 (q, CH_3 - CH_2N); 41.4 (t, CH_2 - N); 42.0 (t, CH_2 - N); 71.5 (d, CH - O); 124.1 (d, CH (7'-naphthyl)); 124.8 (d, CH (6'-naphthyl)); 125.2 (d, CH (2'-naphthyl)); 125.62 (d, CH (8'-naphthyl)); 125.66 (d, CH (5'-naphthyl)); 126.2 (d, CH (4'-naphthyl)); 126.4 (d, CH - CH - CH (thiophene)); 126.6 (d, CH - S); 128.7 (d, CH (3'-naphthyl)); 128.9 (d, CH - C_qS); 130.5 (s, C_q (4a'-naphthyl)); 133.9 (s, C_q (8a'-naphthyl)); 135.9 (s, C_q (1'-naphthyl)); 144.5 (s, C_q - S); 154.8 (s, C_q = O). m/z 339 (1.7%, M^+), 295 (0.7%), 223 (100%), 189 (22%), 111 (36%), 72 (20%). HRMS: $C_{20}H_{21}NO_2S$ calc. 339.1293, found 339.1303.

1,2-di-(*N,N*-diethylcarbamoyloxy)-1,2-di-(2-thienyl)ethane (58)



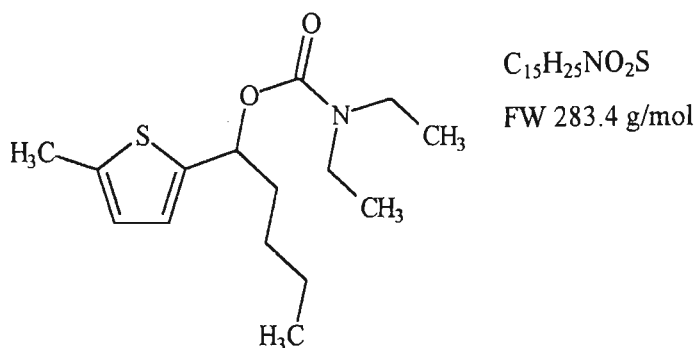
NaOH granules (7.19 g, 179.8 mmol) and Zn dust (7.00 g, 107.0 mmol) were stirred in 95% ethanol (54 ml) until the NaOH dissolved. 2-Thiophenecarboxaldehyde (10.03 g, 89.6 mmol) was added dropwise and the reaction mixture was heated to $\sim 80^\circ\text{C}$, refluxed for 3 hours, then allowed to cool to room temperature. The mixture was filtered to remove excess Zn dust and the solvent was removed under reduced pressure leaving 7.07 g yellow/orange liquid. A solution of 4.20 g of the aforementioned yellow/orange liquid in dry THF (20 ml) was added dropwise to a stirred suspension of NaH (1.30 g, 32.5 mmol, 60% suspension in mineral oil) in dry THF (20 ml) under N_2 while at 0°C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes, then cooled again to 0°C (ice bath). *N,N*-diethylcarbamoylchloride (5.21 g, 38.4 mmol) was added dropwise. The cooling bath was removed, the mixture was stirred for 2 hours, then quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure leaving a yellow liquid from which crystals were obtained on standing. The crystals were removed by filtration and washed with cold diethyl ether. The liquid was allowed to stand in the fridge and further crystallisation occurred. 0.61 g (1.4 mmol, 5%) white crystals (m.p. $150\text{--}151^\circ\text{C}$) were obtained. ^1H NMR ($CDCl_3$): δ 1.10 (t, $J = 7.13$ Hz, 12 H, 4x $CH_3 - CH_2N$); 3.30 (q, $J = 6.65$ Hz, 8 H, 4x $CH_2 - N$); 6.41 (s, 2 H, 2x $CH - O$); 6.92 (dd, $J = 3.51$ Hz, $J = 4.94$ Hz, 2 H, 2x $CH - CH - CH$); 6.97 (dd, $J = 1.37$ Hz, $J = 3.49$ Hz, 2 H, 2x $CH - C_q$); 7.24 (dd, $J = 1.36$ Hz, $J = 4.93$ Hz, 2 H, 2x $CH - S$). ^{13}C NMR ($CDCl_3$): δ 13.4 (q, 2x $CH_3 - CH_2N$); 14.1 (q, 2x $CH_3 - CH_2N$); 41.3 (t, 2x $CH_2 - N$); 42.1 (t, 2x $CH_2 - N$); 73.5 (d, 2x $CH - O$); 125.8 (d, 2x CH); 126.2 (d, 2x CH); 127.1 (d, 2x CH); 139.2 (s, 2x $C_q - S$); 154.3 (s, 2x $C_q = O$). m/z 307 (3%), 239 (1%), 147 (4%), 100 (100%), 72 (28%), **no molecular ion under electronic ionisation**. Chemical ionisation (CH_4) mass spectrum: m/z 453 ($M+29$; 1.7%), 348 (2%), 308 (100%), 233 (0.4%), 193 (8%). $C_{20}H_{28}N_2O_4S_2$: required 56.58% C, 6.65% H, 6.60% N; found 56.57% C, 6.56% H, 6.66% N. HRMS: $C_{20}H_{28}N_2O_4S_2$ calc. 424.1491, found 307.0717 ($M - C_5H_{11}NO_2$, McLafferty rearrangement).

***N,N*-diethylcarbamoyloxy-(2-(5-methyl)-thienyl)methane (61)**



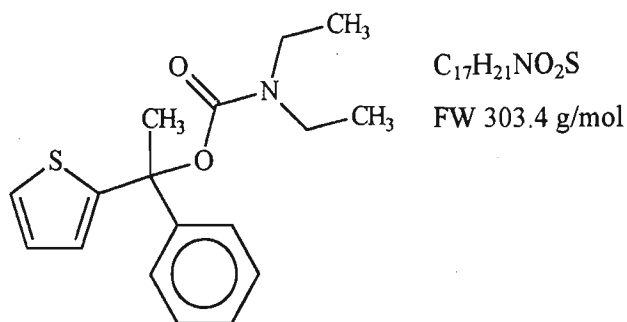
N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.50 g, 2.34 mmol) was stirred in dry THF (5 ml) under N_2 at $-78^\circ C$. $nBuLi$ solution (1.90 ml, 1.40 M, 2.66 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH_3I (0.33 g, 2.32 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78^\circ C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. 0.40g of dark yellow liquid remained, which was purified by silica gel chromatography (80% hexane, 20% diethyl ether), giving the product mixture (calculated yield for this isomer 0.29 g, 1.28 mmol, 54%; other isomer 0.062 g, 0.27 mmol, 12%) as a pale yellow liquid. 1H NMR ($CDCl_3$): δ 1.11 (t, 8 H, 2x $CH_3 - CH_2N$); [1.64 (d, $J = 6.53$ Hz, $CH_3 - CH_2N$); 2.46 (s, 3 H, $CH_3 - C_q$); 3.26-3.28 (m, 6 H, 2x $CH_2 - N$); 5.17 (s, 2 H, $CH_2 - O$); [6.09 (q, $J = 6.66$ Hz, $CH - O$); 6.59-6.61 (m, 1 H, $CH - C_qCH_3$); 6.85 (d, $J = 3.39$ Hz, 1 H, $CH - C_qCH$). ^{13}C NMR ($CDCl_3$): δ 13.5 (q, $CH_3 - CH_2N$); 14.0 (q, $CH_3 - CH_2N$); 15.4 (q, $CH_3 - C_q$); [22.3 (q, $CH_3 - CH$); 41.3 (t, $CH_2 - N$); 41.8 (t, $CH_2 - N$); 61.6 (t, $CH_2 - O$); [68.3 (d, $CH - O$); 124.6 (d, $CH - C_qCH_3$); 127.3 (d, $CH - C_qCH_2$); 137.0 (s, $C_q - CH_2$); 141.1 (s, $C_q - CH_3$); 155.6 (s, $C_q = O$). m/z (major) 227 (4%, M^+), 168 (6%), 127 (2%), 111 (100%), 77 (8%). m/z (minor) 227 (5%, M^+), 168 (11%), 111 (100%), 100 (6%), 72 (4%). HRMS: $C_{11}H_{17}NO_2S$ calc. 227.0980, found 227.0982.

1-(*N,N*-diethylcarbamoyloxy)-1-(2-(5-methyl)-thienyl)pentane (63)



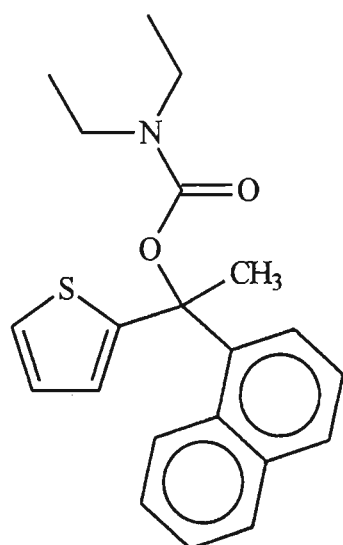
1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.9 mmol) was stirred in dry THF (5 ml) under N₂ at -78 °C. ⁿBuLi solution (1.40 ml, 1.58 M, 2.2 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH₃I (0.27 g, 1.9 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at -78 °C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO₃ and extracted with diethyl ether. The ethereal solution was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. 0.47 g of yellow liquid remained, which was purified using silica gel chromatography (90% hexane, 10% diethyl ether), containing two isomers, calculated yield for this isomer (0.35 g, 1.22 mmol, 66%), [other isomer (0.039 g, 0.14 mmol; 7%)]. ¹H NMR (CDCl₃): δ 0.83-0.95 (m, 7 H, CH₃ ("pentane)); 1.11 (m, 8 H, 2x CH₃ - CH₂N); 1.20-1.36 (m, 9 H, 2x CH₂ ("pentane)); 1.83-1.98 (m, 7 H, CH₂ ("pentane)); 2.44 (d, *J* = 0.99 Hz, 4 H, CH₃ - C_q); 3.22-3.29 (m, 10 H, 2x CH₂ - N); 5.85 (t, *J* = 6.96 Hz, 1 H, CH - O); 6.57-6.59 (m, 1 H, CH - CH); 6.79 (d, *J* = 3.39 Hz, 1 H, CH - CH). ¹³C NMR (CDCl₃): δ 13.6 (q, CH₃ - CH₂N); 13.9 (q, CH₃ - CH₂N); 14.0 ((q, CH₃ ("pentane)); 15.4 (q, CH₃ - C_q); 22.4 (t, CH₂ - CH₃ ("pentane)); 27.8 (t, CH₂ - CH₂ - CH₂ ("pentane)); 36.5 (t, CH₂ - CH ("pentane)); 41.5 (t, 2x CH₂ - N); 72.3 (d, CH - O); 124.5 (d, CH - C_qCH₃); 125.1 (d, CH - C_qCH); 139.2 (s, C_q - CH₃); 142.5 (s, C_q - CH); 155.3 (s, C_q = O). *m/z* (major isomer) 283 (6%, M⁺), 167 (97%), 137 (31%), 111 (100%), 100 (22%). *m/z* 283 (minor isomer) (2%, M⁺), 167 (100%), 137 (27%), 111 (98%), 100 (13%). HRMS: C₁₅H₂₅NO₂S calc. 283.1606, found 283.1616.

1-(*N,N*-diethylcarbamoyloxy)-1-(phenyl)-1-(2-thienyl)ethane (64)



N,N-diethylcarbamoyloxy-phenyl-(2-thienyl)methane (0.50 g, 1.73 mmol) was stirred in dry THF (10 ml) under N₂ at -78 °C. ⁿBuLi solution (1.4 ml, 1.58 M, 2.21 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH₃I (0.25 g, 1.76 mmol) in dry THF (3 ml) was added dropwise. Stirring was continued for 1 hour at -78 °C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO₃ and extracted with diethyl ether. The ethereal solution was dried (MgSO₄), filtered and the solvent was removed under reduced pressure. 0.486 g of dark liquid remained. Silica gel chromatography (90% hexane; 10% diethyl ether) yielded the product as a pale yellow liquid (0.274 g, 0.90 mmol, 52%). ¹H NMR (CDCl₃): δ 1.04 (t, *J* = 7.01 Hz, 3 H, CH₃ - CH₂N); 1.23 (t, *J* = 7.03 Hz, 3 H, CH₃ - CH₂N); 2.30 (s, 3 H, CH₃ - C_q); 3.18-3.38 (m, 2 H, CH₂ - N); 3.40-3.42 (m, 2 H, CH₂ - N); 6.74 (dd, *J* = 1.24 Hz, *J* = 3.60 Hz, 1 H, CH - C_q (thiophene)); 6.84 (dd, *J* = 3.60 Hz, *J* = 5.08 Hz, 1 H, CH - CH - CH (thiophene)); 7.14 (dd, *J* = 1.25 Hz, *J* = 5.07 Hz, 1 H, CH - S); 7.16-7.40 (m, 5 H, 5x CH (phenyl)). ¹³C NMR (CDCl₃): δ 13.5 (q, CH₃ - CH₂N); 14.4 (q, CH₃ - CH₂N); 28.6 (q, CH₃ - C_q); 41.6 (t, 2x CH₂ - N); 82.2 (s, C_q - O); 124.2 (d, CH - CH - CH (thiophene)); 124.5 (d, CH - S); 125.2 (d, 2x CH (*m*-phenyl)); 126.2 (d, CH (*p*-phenyl)); 127.1 (d, CH - C_qS); 128.1 (d, 2x CH (*o*-phenyl)); 145.6 (s, C_q (phenyl)); 151.1 (s, C_q - S); 153.7 (s, C_q = O). *m/z* 186 (100%), 185 (62%), 171 (51%), 115 (15%), **no molecular ion under electronic ionisation**. HRMS: C₁₇H₂₁NO₂S calc. 303.1293, found 303.1281.

1-(*N,N*-diethylcarbamoyloxy)-1-(1-naphthyl)-1-(2-thienyl)ethane (65)

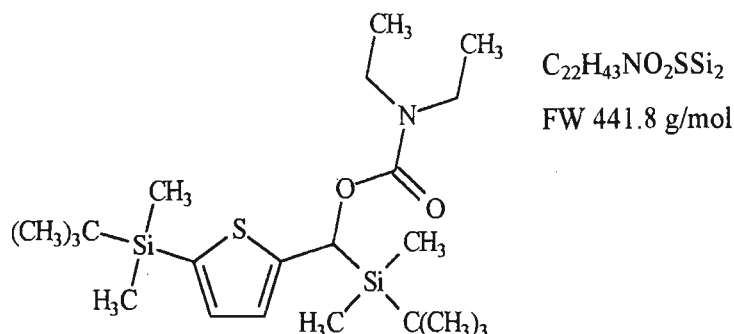


$C_{21}H_{23}NO_2S$

FW 353.1 g/mol

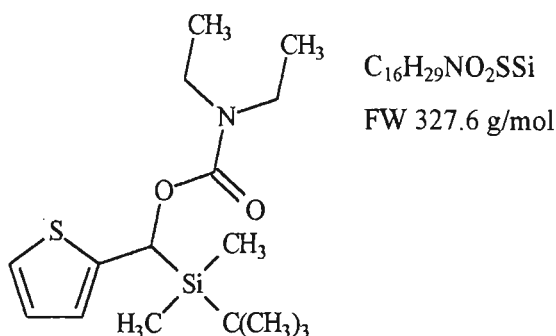
N,N-diethylcarbamoyloxy-(1-naphthyl)-(2-thienyl)methane (0.60 g, 1.8 mmol) was stirred in dry THF (10 ml) under N_2 at $-78\text{ }^{\circ}C$. $nBuLi$ solution (1.60 ml, 1.40 M, 2.24 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH_3I (0.25 g, 1.76 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^{\circ}C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Silica gel chromatography (90% hexane, 10% diethyl ether) of the resultant dark yellow liquid yielded the product as pale yellow crystals (0.28 g, 0.8 mmol, 45%) which decolourised within days. 1H NMR ($CDCl_3$): δ 0.88 (t, $J = 6.89$ Hz, 3 H, $CH_3 - CH_2N$); 1.26 (t, $J = 6.82$ Hz, 3 H, $CH_3 - CH_2N$); 2.43 (s, 3 H, $CH_3 - C_q$); 2.99-3.12 (m, 2 H, $CH_2 - N$); 3.39-3.46 (m, 2 H, $CH_2 - N$); 6.40 (dd, $J = 1.21$ Hz, $J = 3.57$ Hz, 1 H, CH - C_q (thiophene)); 6.71 (dd, $J = 3.60$ Hz, $J = 5.09$ Hz, 1 H, CH - CH - CH (thiophene)); 7.14 (dd, $J = 1.23$ Hz, $J = 5.10$ Hz, 1 H, CH - S); 7.17-7.50 (m, 3 H, 3x CH (naphthyl)); 7.76-7.86 (m, 3 H, 3x CH (naphthyl)); 8.08-8.13 (m, 1 H, CH (naphthyl)). ^{13}C NMR ($CDCl_3$): δ 13.2 (q, $CH_3 - CH_2N$); 14.3 (q, $CH_3 - CH_2N$); 31.2 (q, $CH_3 - C_q$); 41.2 (t, $CH_2 - N$); 41.4 (t, $CH_2 - N$); 83.4 (s, $C_q - O$); 123.6 (d, CH (7'-naphthyl)); 123.9 (d, CH (2'-naphthyl)); 124.6 (d, CH (6'-naphthyl)); 124.9 (d, 2x CH (5'- and 8'-naphthyl)); 125.1 (d, CH - CH - CH (thiophene)); 126.4 (d, CH - S); 126.5 (d, CH (4'-naphthyl)); 128.8 (d, CH (3'-naphthyl)); 129.3 (d, CH - C_qS); 130.6 (s, C_q (4a'-naphthyl)); 134.5 (s, C_q (8a'-naphthyl)); 139.0 (s, C_q (1'-naphthyl)); 151.9 (s, $C_q - S$); 153.3 (s, $C_q = O$). m/z 236 (100%), 203 (91%), 189 (22%), 152 (50%), 117 (17%), **no molecular ion under electronic ionisation**. HRMS: $C_{21}H_{23}NO_2S$ calc. 353.1450, found 353.1446.

***t*-butyldimethylsilyl-*N,N*-diethylcarbamoyloxy-(2-(5-*t*-butyldimethylsilyl)-thienyl)-methane (66)**



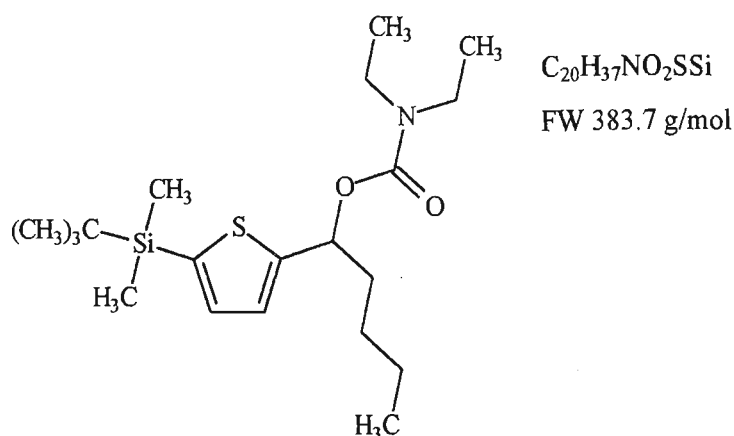
N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.49 g, 2.30 mmol) and TBDMSCl (0.38 g, 2.52 mmol) were stirred in dry THF (10 ml) under N_2 at $-78^\circ C$. n -BuLi solution (1.70 ml, 1.74 M, 2.96 mmol) was added dropwise. The mixture was stirred for 1 hour at $-78^\circ C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. 0.74 g of dark yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.16 g, 0.36 mmol, 29%) as a dark viscous liquid. 1H NMR ($CDCl_3$): δ -0.06 (s, 3 H, CH_3 - Si); 0.14 (s, 3 H, CH_3 - Si); 0.25 (s, 3 H, CH_3 - Si); 0.26 (s, 3 H, CH_3 - Si); 0.87 (s, 9 H, 3x CH_3 (*t*-butyl)); 0.88 (s, 9 H, 3x CH_3 (*t*-butyl)); 1.09-1.18 (m, 7 H, 2x CH_3 - CH_2N); 3.30-3.33 (m, 4 H, 2x CH_2 - N); 6.03 (d, $J = 0.64$ Hz, CH - O); 6.90 (dd, $J = 0.68$ Hz, $J = 3.36$ Hz, 1 H, CH - C_qCH); 7.05 (d, $J = 3.30$ Hz, 1 H, CH - C_qSi). ^{13}C NMR ($CDCl_3$): δ - 8.08 (q, CH_3 - Si); -7.48 (q, CH_3 - Si); -5.09 (q, CH_3 - Si); -5.06 (q, CH_3 - Si); 13.5 (q, CH_3 - CH_2N); 14.2 (q, CH_3 - CH_2N); 16.8 (s, C_q (*t*-butyl)); 17.0 (s, C_q (*t*-butyl)); 26.3 (q, 3x CH_3 (*t*-butyl)); 26.6 (q, 3x CH_3 (*t*-butyl)); 41.2 (t, CH_2 - N); 41.9 (t, CH_2 - N); 65.5 (d, CH - O); 124.7 (d, CH - C_qCH); 134.8 (d, CH - C_qSi); 135.1 (s, C_q - CH); 150.0 (s, C_q - Si); 155.6 (s, C_q = O). m/z 441 (3%, M^+), 384 (14%), 341 (8%), 230 (85%), 186 (100%), 115 (28%). HRMS: $C_{22}H_{43}NO_2SSi_2$ calc. 441.2553, found 441.2538.

***t*-butyldimethylsilyl-*N,N*-diethylcarbamoyloxy-(2-thienyl)methane (67)**



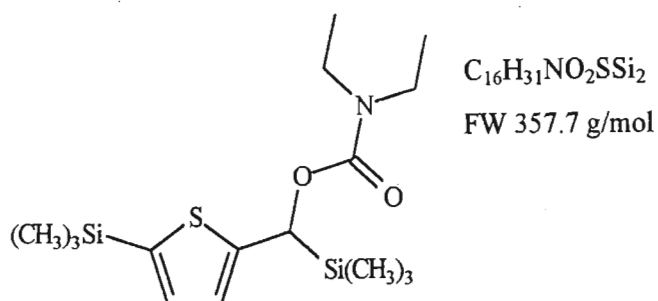
N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.49 g, 2.30 mmol) and TBDMSCl (0.38 g, 2.52 mmol) were stirred in dry THF (10 ml) under N₂ at -78 °C. *n*-BuLi solution (1.70 ml, 1.74 M, 2.96 mmol) was added dropwise. The mixture was stirred for 1 hour at -78 °C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NH₄Cl and extracted with diethyl ether. The ethereal solution was dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure. 0.74 g of dark yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.12 g, 0.37 mmol, 15%) as a dark viscous liquid. ¹H NMR (CDCl₃): δ -0.05 (s, 3 H, CH₃ - Si); 0.16 (s, 4 H, CH₃ - Si); 0.89 (s, 11 H, 3x CH₃ (*t*-butyl)); 1.13 (t, *J* = 7.26 Hz, 7 H, 2x CH₃ - CH₂N); 3.31 (q, *J* = 7.09 Hz, 5 H, 2x CH₂ - N); 6.00 (s, 1 H, CH - O); 6.85 (ddd, *J* = 0.72 Hz, *J* = 1.21 Hz, *J* = 3.50 Hz, 1 H, CH - C_q); 6.92 (dd, *J* = 3.48 Hz, *J* = 5.04 Hz, 1 H, CH - CH - CH); 7.12-7.15 (m, 1 H, CH - S). ¹³C NMR (CDCl₃): δ -8.1 (q, CH₃ - Si); -7.4 (q, CH₃ - Si); 13.5 (q, CH₃ - CH₂N); 14.1 (q, CH₃ - CH₂N); 16.9 (s, C_q (*t*-butyl)); 26.7 (q, 3x CH₃ (*t*-butyl)); 41.2 (t, CH₂ - N); 42.0 (t, CH₂ - N); 65.4 (d, CH - O); 123.57 (d, CH - CH - CH); 123.65 (d, CH - C_q); 126.6 (d, CH - S); 144.6 (s, C_q - S); 155.6 (s, C_q = O). *m/z* 327 (1%, M⁺), 230 (29%), 186 (34%), 100 (39%), 73 (100%). HRMS: C₁₆H₂₉NO₂SSi calc. 327.1688, found 327.1699.

1-(*N,N*-diethylcarbamoyloxy)-1-(2-(5-*t*-butyldimethylsilyl)-thienyl)pentane (70)



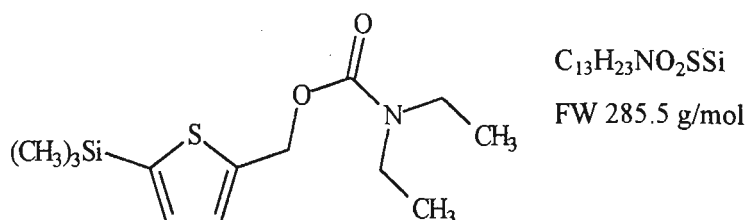
1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.86 mmol) and TBDMSCl (0.28 g, 1.86 mmol) were stirred in dry THF (15 ml) under N₂ at -78 °C. ⁿBuLi solution (1.40 ml, 1.58 M, 2.21 mmol) was added dropwise. The mixture was stirred for 1 hour at -78 °C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO₃ and extracted with diethyl ether. The ethereal solution was dried (MgSO₄), filtered and the solvent was removed under reduced pressure. 0.57 g of yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.13 g, 0.34 mmol, 18%) as a pale yellow liquid. ¹H NMR (CDCl₃): δ 0.27 (s, 6 H, 2x CH₃ - Si); 0.84-0.94 (m, 12 H, CH₃ (ⁿpentane) and 3x CH₃ (^tbutyl)); 1.11 (t, *J* = 7.10 Hz, 6 H, 2x CH₃ - CH₂N); 1.28-1.40 (m, 4 H, 2x CH₂ (ⁿpentane)); 1.89-1.98 (m, 2 H, CH₂ (ⁿpentane)); 3.28 (q, *J* = 7.05 Hz, 4 H, 2x CH₂ - N); 5.99 (t, *J* = 6.87 Hz, 1 H, CH - O); 7.05-7.09 (m, 2 H, CH - CH). ¹³C NMR (CDCl₃): δ -5.0 (q, CH₃ - Si); -4.9 (q, CH₃ - Si); 13.7 (q, CH₃ - CH₂N); 13.9 (q, CH₃ - CH₂N); 14.0 (q, CH₃ (ⁿpentane)); 16.9 (s, C_q (^tbutyl)); 22.4 (t, CH₂ - CH₃ (ⁿpentane)); 26.3 (q, 3x CH₃ (^tbutyl)); 27.7 (t, CH₂ - CH₂ - CH₂ (ⁿpentane)); 36.7 (t, CH₂ - CH (ⁿpentane)); 41.4 (t, CH₂ - N); 41.7 (t, CH₂ - N); 72.0 (d, CH - O); 126.1 (d, CH - C_qSi); 134.7 (d, CH - C_qCH); 136.4 (s, C_q - CH); 150.4 (s, C_q - Si); 155.3 (s, C_q = O). *m/z* 383 (7%, M⁺), 326 (3%), 267 (100%), 209 (26%), 167 (11%). HRMS: C₂₀H₃₇NO₂SSi calc. 383.2314, found 383.2311.

N,N-diethylcarbamoyloxy-(2-(5-trimethylsilyl)-thienyl)-trimethylsilylmethane (71)



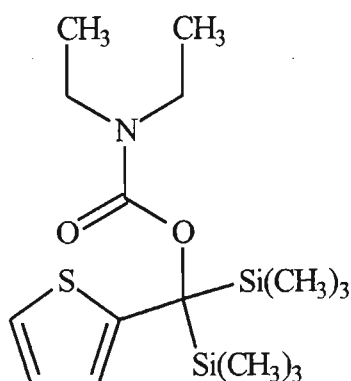
N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.50 g, 2.34 mmol) was stirred in dry THF (5 ml) under N_2 at $-78\text{ }^{\circ}C$. n BuLi solution (1.8 ml, 1.58 M, 2.84 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of TMSCl (0.26 g, 2.39 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^{\circ}C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. 0.51 g of dark yellow liquid remained, which was purified using silica gel chromatography (90% hexane, 10% diethyl ether), giving the product (calculated yield 0.17 g, 0.48 mmol, 40%) as a pale yellow liquid. 1H NMR ($CDCl_3$): δ 0.09 (s, 7 H, 3x CH_3 - Si); 0.28 (s, 8 H, 3x CH_3 - Si); 1.15 (br. s, 14 H, 2x CH_3 - CH_2N); 3.28-3.32 (m, 4 H, 2x CH_2 - N); 5.85 (d, $J = 0.71$ Hz, 1 H, CH - O); 6.85 (dd, $J = 0.79$ Hz, $J = 3.34$ Hz, 1 H, CH - CH); 7.05 (d, $J = 3.30$ Hz, 1 H, CH - CH). ^{13}C NMR ($CDCl_3$): δ -3.62 (q, CH_3 - Si); 0.00 (q, 3x CH_3 - Si); 13.6 (q, CH_3 - CH_2N); 14.1 (q, CH_3 - CH_2N); 41.5 (t, CH_2 - N); 42.0 (t, CH_2 - N); 67.8 (d, CH - O); 124.2 (d, CH - CqCH); 133.8 (d, CH - CqSi); 137.9 (s, C_q - CH); 149.3 (s, C_q - Si); 155.8 (s, C_q = O). m/z 357 (1%, M^+), 342 (2%), 188 (26%), 144 (68%), 100 (39%), 73 (100%). HRMS: $C_{16}H_{31}NO_2SSi_2$ calc. 357.1614, found 357.1626.

***N,N*-diethylcarbamoyloxy-(2-(5-trimethylsilyl)-thienyl)methane (73)**



N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.50 g, 2.34 mmol) was stirred in dry THF (5 ml) under N_2 at -78°C . $n\text{-BuLi}$ solution (1.8 ml, 1.58 M, 2.84 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of TMSCl (0.26 g, 2.39 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at -78°C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO_3 and extracted with diethyl ether. The ethereal solution was dried (MgSO_4), filtered and the solvent was removed under reduced pressure. 0.51 g of dark yellow liquid remained, which was purified using silica gel chromatography (90% hexane, 10% diethyl ether), giving the product mixture (calculated yield 0.19 g, 0.66 mmol, 28%; other isomer 0.04 g, 0.16 mmol, 7%) as a pale yellow liquid. ^1H NMR (CDCl_3): δ 0.31 (s, 8 H, 3x CH_3 - Si); 1.12 (t, $J = 7.01$ Hz, 6 H, 2x CH_3 - CH_2N); 3.20-3.40 (m, 4 H, 2x CH_2 - N); 5.28 (s, 2 H, CH_2 - O); 7.11 (s, 2 H, CH - CH). ^{13}C NMR (CDCl_3): δ -3.57 (q, 3x CH_3 - Si); 13.6 (q, CH_3 - CH_2N); 14.1 (q, CH_3 - CH_2N); 41.4 (t, CH_2 - N); 41.9 (t, CH_2 - N); 61.3 (t, CH_2 - O); 128.4 (d, CH - C_qCH_2); 133.8 (d, CH - C_qSi); 141.6 (s, C_q - CH_2); 144.7 (s, C_q - Si); 155.6 (s, $\text{C}_q = \text{O}$). m/z (major isomer) 285 (5%, M^+), 226 (4%), 169 (100%), 127 (23%), 100 (9%). HRMS: $\text{C}_{13}\text{H}_{23}\text{NO}_2\text{SSi}$ calc. 285.1219, found 285.1228.

***N,N*-diethylcarbamoyloxy-(2-thienyl)-di-(trimethylsilyl)methane (74)**

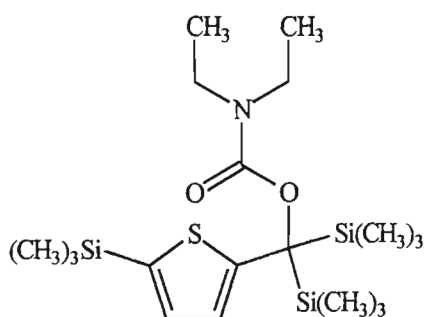


$C_{16}H_{31}NO_2SSi_2$

FW 357.7 g/mol

N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.50 g, 2.34 mmol) and TMSCl (0.26 g, 2.39 mmol) were stirred in dry THF (10 ml) under N_2 at $-78\text{ }^{\circ}C$. $n\text{-BuLi}$ solution (2.00 ml, 1.40 M, 2.80 mmol) was added dropwise. The mixture was stirred for 1 hour at $-78\text{ }^{\circ}C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. 0.51 g of dark yellow liquid remained, which was purified by silica gel chromatography (90% hexane, 10% diethyl ether) giving the product (calculated yield 0.20 g, 0.56 mmol, 47%) as a pale yellow liquid. 1H NMR ($CDCl_3$): δ 0.16 (s, 15 H, 6x CH_3 - Si); 1.14 (t, $J = 7.10$ Hz, 3 H, CH_3 - CH_2N); 1.24 (t, $J = 7.08$ Hz, 3 H, CH_3 - CH_2N); 3.26-3.40 (m, 4 H, 2x CH_2 - N); 6.46 (dd, $J = 1.18$ Hz, $J = 3.56$ Hz, 1 H, CH - CH - C_q); 6.91 (dd, $J = 3.58$ Hz, $J = 5.13$ Hz, 1 H, CH - CH - CH); 7.00 (dd, $J = 1.16$ Hz, $J = 5.10$ Hz, 1 H, CH - S). ^{13}C NMR ($CDCl_3$): δ 0.24 (q, 6x CH_3 - Si); 13.9 (q, CH_3 - CH_2N); 14.7 (q, CH_3 - CH_2N); 41.9 (t, CH_2 - N); 42.4 (t, CH_2 - N); 76.4 (s, C_q - O); 118.5 (d, CH - CH - CH); 120.0 (d, CH - C_q); 126.5 (d, CH - S); 149.0 (s, C_q - S); 156.1 (s, C_q = O). m/z 357 (0.1%, M^+), 342 (1%), 174 (100%), 130 (7%), 100 (9%). HRMS: $C_{16}H_{31}NO_2SSi_2$ calc. 357.1614, found 357.1626.

***N,N*-diethylcarbamoyloxy-(2-(5-trimethylsilyl)-thienyl)-di-(trimethylsilyl)methane (75)**

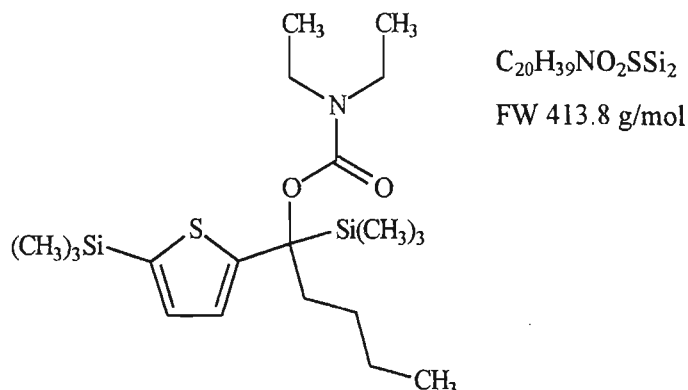


$C_{19}H_{39}NO_2SSi_3$

FW 429.8 g/mol

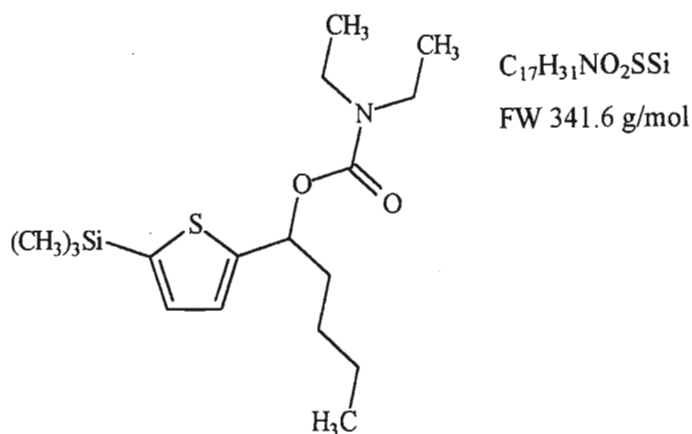
N,N-diethylcarbamoyloxy-(2-thienyl)methane (0.50 g, 2.34 mmol) and TMSCl (0.26 g, 2.39 mmol) were stirred in dry THF (10 ml) under N_2 at $-78\text{ }^{\circ}C$. n BuLi solution (2.00 ml, 1.40M, 2.80 mmol) was added dropwise. The mixture was stirred for 1 hour at $-78\text{ }^{\circ}C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. 0.51 g of dark yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product as pale yellow liquid, (0.021 g, 0.049 mmol, 6%). 1H NMR ($CDCl_3$): δ 0.15 (s, 15 H, 6x CH_3 - Si); 0.26 (s, 8 H, 3x CH_3 - Si); 1.14 (t, $J = 7.10$ Hz, 3 H, CH_3 - CH_2N); 1.24 (t, $J = 7.09$ Hz, 3 H, CH_3 - CH_2N); 3.29-3.40 (m, 4 H, 2x CH_2 - N); 6.50 (d, $J = 3.46$ Hz, 1 H, CH - CH); 7.01 (d, $J = 3.46$ Hz, 1 H, CH - CH). ^{13}C NMR ($CDCl_3$): δ 0.2 (q, 6x CH_3 - Si); 0.3 (q, 3x CH_3 - Si); 13.8 (q, CH_3 - CH_2N); 14.6 (q, CH_3 - CH_2N); 41.8 (t, CH_2 - N); 42.4 (t, CH_2 - N); 76.7 (s, C_q - O); 119.9 (d, CH - C_qC_q); 133.5 (d, CH - C_qSi); 154.1 (s, C_q - Si); 156.1 (s, $C_q = O$). m/z 429 (6%, M^+), 415 (100%). HRMS: $C_{19}H_{39}NO_2SSi_3$ calc. 429.2009, found 429.2001.

1-(*N,N*-diethylcarbamoyloxy)-1-(2-(5-trimethylsilyl)-thienyl)-1-(trimethylsilyl)pentane
(76)



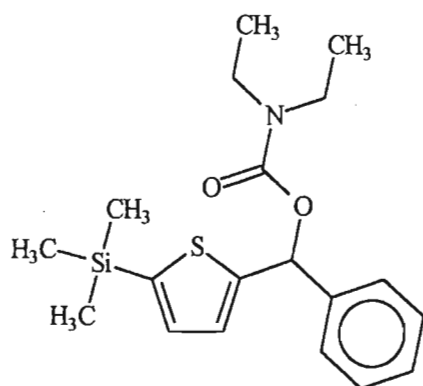
1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.86 mmol) was stirred in dry THF (5 ml) under N_2 at $-78\text{ }^\circ\text{C}$. $n\text{-BuLi}$ solution (1.73 ml, 1.40 M, 2.42 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of TMSCl (0.20 g, 1.84 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^\circ\text{C}$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO_3 and extracted with diethyl ether. The ethereal solution was dried (MgSO_4), filtered and the solvent was removed under reduced pressure. 0.51 g of yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.10 g, 0.24 mmol, 26%) as a pale yellow liquid. ^1H NMR (CDCl_3): δ 0.01 (s, 12 H, 3x CH_3 - Si); 0.29 (s, 7 H, 3x CH_3 - Si); 0.81-1.09 (m, 5 H, CH_3 ("pentane)); 1.18-1.27 (m, 5 H, 2x CH_3 - CH_2N); 1.27-1.62 (m, 5 H, 2x CH_2 ("pentane)); 1.65-2.10 (m, 3 H, CH_2 ("pentane)); 3.27-3.37 (m, 4 H, 2x CH_2 - N); 6.67 (d, $J = 3.46\text{ Hz}$, 1 H, CH - CH); 7.06 (d, $J = 3.39\text{ Hz}$, 1 H, CH - CH). ^{13}C NMR (CDCl_3): δ -1.4 (q, 3x CH_3 - Si); 0.04 (q, 3x CH_3 - Si); 13.7 (q, CH_3 - CH_2N); 14.1 (q, CH_3 ("pentane)); 14.3 (q, CH_3 - CH_2N); 23.0 (t, CH_2 - CH_3 ("pentane)); 25.6 (t, CH_2 - CH_2 - CH_2 ("pentane)); 35.8 (t, CH_2 - C_q ("pentane)); 41.7 (t, 2x CH_2 - N); 72.7 (s, C_q - O); 122.6 (d, CH - C_qSi); 133.5 (d, CH - C_qC_q); 154.4 (s, C_q - Si); 155.2 (s, $\text{C}_q = \text{O}$). m/z 414 (6%, M^+), 296 (4%), 281 (1%), 174 (100%), 73 (15%). HRMS: $C_{20}H_{39}NO_2SSi_2$ calc. 413.2240, found 413.2233.

1-(*N,N*-diethylcarbamoyloxy)-1-(2-(5-trimethylsilyl)-thienyl)pentane (78)



1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.86 mmol) was stirred in dry THF (5 ml) under N₂ at -78 °C. ⁿBuLi solution (1.73 ml, 1.40 M, 2.42 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of TMSCl (0.20 g, 1.84 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at -78 °C then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO₃ and extracted with diethyl ether. The ethereal solution was dried (MgSO₄), filtered and the solvent was removed under reduced pressure. 0.51 g of yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.20 g, 0.56 mmol, 30%) as a pale yellow liquid. ¹H NMR (CDCl₃): δ 0.30 (s, 8 H, 3x CH₃ - Si); 0.89 (t, *J* = 6.78 Hz, 3 H, CH₃ ("pentane)); 1.12 (t, *J* = 7.10 Hz, 6 H, 2x CH₃ - CH₂N); 1.26-1.37 (m, 4 H, 2x CH₂ ("pentane)); 1.89-1.98 (m, 2 H, CH₂ ("pentane)); 3.29 (q, *J* = 7.03 Hz, 4 H, 2x CH₂ - N); 5.99 (t, *J* = 6.88 Hz, 1 H, CH - O); 7.05 (d, *J* = 3.39 Hz, 1 H, CH - CH); 7.08 (d, *J* = 3.32 Hz, 1 H, CH - CH). ¹³C NMR (CDCl₃): δ 0.0 (q, 3x CH₃ - Si); 13.6 (q, CH₃ - CH₂N); 14.0 (q, CH₃ ("pentane)); 14.2 (q, CH₃ - CH₂N); 22.5 (t, CH₂ - CH₃ ("pentane)); 27.8 (t, CH₂ - CH₂ - CH₂ ("pentane)); 36.8 (t, CH₂ - CH ("pentane)); 41.3 (t, CH₂ - N); 41.8 (t, CH₂ - N); 72.1 (d, CH - O); 126.2 (d, CH - C_qSi); 133.6 (d, CH - C_qCH); 139.5 (s, C_q - Si); 150.4 (s, C_q - CH); 155.3 (s, C_q = O). *m/z* 341 (5%, M⁺), 240 (7%), 225 (100%), 169 (70%), 100 (29%). HRMS: C₁₇H₃₁NO₂SSi calc. 341.1845, found 341.1833.

N,N-diethylcarbamoyloxy-phenyl-(2-(5-trimethylsilyl)-thienyl)methane (80)

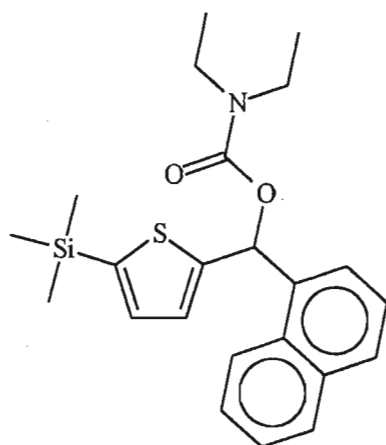


$C_{19}H_{27}NO_2SSi$

FW 361.6 g/mol

N,N-diethylcarbamoyloxy-phenyl-(2-thienyl)methane (0.50 g, 1.73 mmol) was stirred in dry THF (5 ml) under N_2 at $-78^\circ C$. $nBuLi$ solution (1.6 ml, 1.40 M, 2.24 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of $TMSCl$ (0.19 g, 1.75 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78^\circ C$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. 0.60 g of dark yellow liquid remained, which was purified by silica gel chromatography (90% hexane, 10% diethyl ether), giving the product mixture (calculated yield for this isomer 0.26 g, 0.72 mmol, 42%; [other isomer 0.042 g, 0.12 mmol, 7%]) as a pale yellow liquid. 1H NMR ($CDCl_3$): δ 0.28 (s, 7 H, 3x CH_3 - Si); 1.10-1.16 (br. m, 6 H, 2x CH_3 - CH_2N); 3.28-3.37 (br. m, 4 H, 2x CH_2 - N); 6.91-6.94 (dd, $J = 0.85$ Hz, $J = 3.57$ Hz, 1 H, CH - CH); 7.03 (s, 1 H, CH - O); 7.03-7.06 (m, $J = 3.39$ Hz, 1 H, CH - CH); 7.23-7.47 (m, 5 H, 5x CH (phenyl)). ^{13}C NMR ($CDCl_3$): δ 0.1 (q, 3x CH_3 - Si); 13.6 (q, CH_3 - CH_2N); 14.3 (q, CH_3 - CH_2N); 41.5 (t, CH_2 - N); 42.0 (t, CH_2 - N); 73.8 (d, CH - O); 126.9 (d, 2x CH (*m*-phenyl)); 127.3 (d, CH - C_qSi); 128.0 (d, CH (*p*-phenyl)); 128.5 (d, 2x CH (*o*-phenyl)); 133.7 (d, CH - C_qCH); 140.7 (s, C_q (phenyl)); 140.8 (s, C_q - Si); 150.1 (s, CH - C_q - S); 154.9 (s, $C_q = O$). m/z 361 (10%, M^+), 245 (100%), 115 (4%), 73 (10%). HRMS: $C_{19}H_{27}NO_2SSi$ calc. 361.1532, found 361.1525.

***N,N*-diethylcarbamoyloxy-(1-naphthyl)-(2-thienyl-(5-trimethylsilyl))methane (82)**

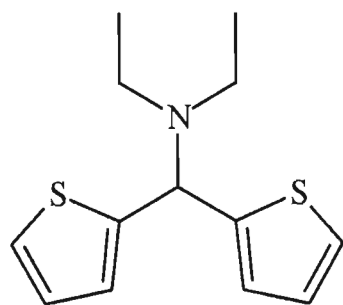


$C_{23}H_{29}NO_2SSi$

FW 411.6 g/mol

N,N-diethylcarbamoyloxy-(1-naphthyl)-(2-thienyl)methane (0.55 g, 1.6 mmol) was stirred in dry THF (5 ml) under N_2 at $-78\text{ }^\circ\text{C}$. $n\text{-BuLi}$ solution (1.30 ml, 1.58 M, 2.1 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of TMSCl (0.18 g, 1.7 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^\circ\text{C}$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO_3 and extracted with diethyl ether. The ethereal solution was dried (MgSO_4), filtered, and the solvent was removed under reduced pressure. 0.59 g of dark yellow viscous liquid remained. Silica gel chromatography (90% hexane; 10% diethyl ether) yielded a pale yellow liquid (0.17 g, 0.413 mmol, 45%) containing two substituted products, this isomer (0.14 g, 0.35 mmol, 38%), [other isomer (0.03 g, 0.07 mmol, 7%)]. ^1H NMR (CDCl_3): δ 0.26 (s, 7 H, 3x CH_3 - Si); [0.34 (s, 1 H, 3x CH_3 - Si)]; 1.13 (br. s, 6 H, 2x CH_3 - CH_2N); 3.26-3.33 (m, 4 H, 2x CH_2 - N); 6.86 (d, $J = 3.39$ Hz, 1 H, CH - CH (thiophene)); 7.00 (d, $J = 3.39$ Hz, 1 H, CH - CH (thiophene)); 7.41-7.52 (m, 3 H, 3x CH (naphthyl)); 7.68-7.86 (m, 3 H, 3x CH (naphthyl)); 7.72 (s, 1 H, CH - O); 8.10-8.15 (m, 1 H, CH (naphthyl)). ^{13}C NMR (CDCl_3): δ 0.0 (q, 3x CH_3 - Si); 13.5 (q, CH_3 - CH_2N); 14.2 (q, CH_3 - CH_2N); 41.4 (t, CH_2 - N); 42.0 (t, CH_2 - N); 71.5 (d, CH - O); 124.2 (d, CH (2'-naphthyl)); 124.9 (d, CH (7'-naphthyl)); 125.3 (d, CH (6'-naphthyl)); 125.7 (d, CH (8'-naphthyl)); 126.3 (d, CH (5'-naphthyl)); 127.7 (d, CH (4'-naphthyl)); 128.7 (d, CH - C_qSi); 128.9 (d, CH (3'-naphthyl)); 133.7 (d, CH - C_qS); 130.5 (s, C_q (4a'-naphthyl)); 133.8 (s, C_q (8a'-naphthyl)); 136.2 (s, C_q (1'-naphthyl)); 140.6 (s, C_q - Si); 149.6 (s, C_q - S); 154.8 (s, $\text{C}_q = \text{O}$). m/z (major isomer) 411 (4%, M^+), 295 (44%), 221 (29%), 189 (22%), 73 (100%). HRMS: $\text{C}_{23}\text{H}_{29}\text{NO}_2\text{SSi}$ calc. 411.1688, found 411.1697.

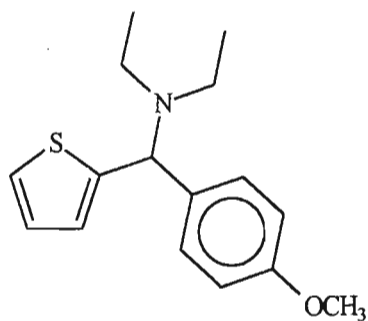
***N,N*-diethylamino-di-(2-thienyl)methane (83)**



$C_{13}H_{17}NS_2$
FW 251.4 g/mol

Di-(2-thienyl)methanol (4.50 g, 22.9 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of NaH (1.10 g, 27.5 mmol, 60% suspension in mineral oil) in dry THF (40 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (3.11 g, 22.9 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2 hours, quenched with sat. NH_4Cl , and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (80% hexane, 20% diethyl ether) yielded the product as a pale yellow liquid (3.01 g, 12.0 mmol; 52%). 1H NMR ($CDCl_3$): δ 1.10 (t, $J = 7.06$ Hz, 6 H, 2x $CH_3 - CH_2N$); 2.50 (q, $J = 7.10$ Hz, 4 H, 2x $CH_2 - N$); 5.486 (t, $J = 0.87$ Hz, 1 H, CH - N); 6.88-6.91 (m, $J = 1.10$ Hz, $J = 3.48$ Hz, 2 H, 2x CH - C_q); 6.96 (dd, $J = 3.56$ Hz, $J = 5.04$ Hz, 2 H, 2x CH - CH - CH); 7.25 (dd, $J = 1.28$ Hz, $J = 4.99$ Hz, 2 H, 2x CH - S). ^{13}C NMR ($CDCl_3$): δ 13.4 (q, 2x $CH_3 - CH_2N$); 44.0 (t, 2x $CH_2 - N$); 59.9 (d, CH - N); 124.9 (d, 2x CH - C_qS); 126.2 (d, 2x CH - CH - CH); 126.4 (d, 2x CH - S); 145.1 (s, 2x $C_q - S$). m/z 251 (3%, M^+), 179 (100%), 135 (6%), 110 (3.5%), 91 (3.5%). HRMS: $C_{13}H_{17}NS_2$ calc. 251.0802, found 251.0808.

***N,N*-diethylamino-(4-methoxyphenyl)-(2-thienyl)methane (84)**

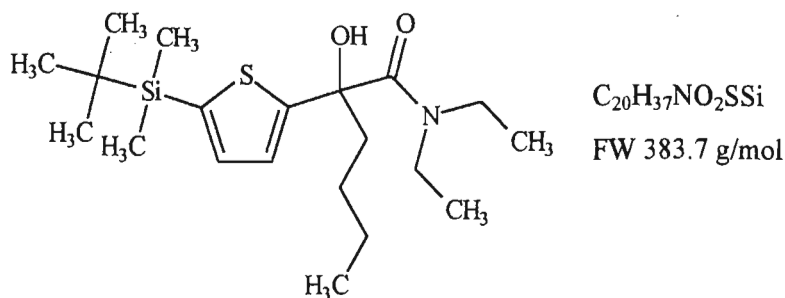


$C_{16}H_{21}NOS$

FW 275.4 g/mol

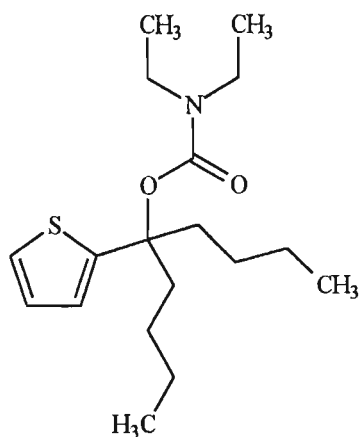
Thiophene (1.50 g, 17.9 mmol) was stirred in dry THF (5 ml) under N_2 while immersed in an ice bath (0 °C). t -BuLi solution (8.3 ml, 2.58 M, 21.4 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 minutes then the temperature was lowered to -78 °C using a CO_2 /acetone cooling bath. *p*-Anisaldehyde (2.43 g, 17.8 mmol) was added dropwise. The mixture was stirred for 2 hours, quenched with sat. NH_4Cl , allowed to warm to room temperature and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure leaving 3.23 g cloudy yellow liquid containing (4-methoxyphenyl)-(2-thienyl)methanol. m/z (alcohol) 220 (42%, M^+), 202 (21%), 135 (100%), 109 (37%), 77 (23%). 2.30 g of the aforementioned yellow liquid in dry THF (10 ml) was added dropwise to a stirred suspension of NaH (0.52 g, 13.0 mmol, 60% suspension in mineral oil) in dry THF (10 ml) under N_2 while at 0 °C (ice bath). The cooling bath was removed, the mixture was stirred for 30 minutes then cooled again to 0 °C (ice bath). *N,N*-diethylcarbamoylchloride (1.42 g, 10.5 mmol) was added dropwise and the cooling bath was removed. The mixture was stirred for 2.5 hours, quenched with sat. NH_4Cl and extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure leaving 3.18 g yellow liquid, purified using silica gel chromatography (90% hexane, 10% diethyl ether). Calculated overall yield of amine 23%. m/z (amine) 275 (6%, M^+), 246 (0.6%), 203 (100%), 160 (4%), 115 (4%), 97 (2%). HRMS: $C_{16}H_{21}NOS$ calc. 275.1344, found 275.1337.

2-hydroxy-2-(2-(5-^tbutyldimethylsilyl)-thienyl)-*N,N*-diethylhexanamide (86)



1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.86 mmol) and TBDMSCl (0.29 g, 1.90 mmol) were stirred in dry THF (15 ml) under N₂ at -78 °C. ⁿBuLi solution (1.40 ml, 1.74 M, 2.43 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 hour then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NH₄Cl and extracted with diethyl ether. The ethereal solution was dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure leaving 0.46 g dark liquid. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.05 g, 0.13 mmol, 7%) as a pale yellow liquid. ¹H NMR (CDCl₃): δ 0.26 (s, 6 H, 2x CH₃ - Si); 0.76-0.86 (m, 3 H, CH₃ - CH₂N); 0.86-0.98 (m, 12 H, 3x CH₃ (^tbutyl) and CH₃ (ⁿhexane)); 1.05-1.21 (m, 3 H, CH₃ - CH₂N); 1.30-1.47 (m, 3 H, CH₂ (ⁿhexane)); 1.51-1.74 (m, 2 H, CH₂ (ⁿhexane)); 2.18-2.31 (m, 2 H, CH₂ (ⁿhexane)); 3.11-3.19 (m, 2 H, CH₂ - N); 3.37-3.44 (m, 2 H, CH₂ - N); 5.78 (s, 1 H, OH (exchangeable D₂O)); 7.03 (d, *J* = 3.44 Hz, 1 H, CH - CH); 7.09 (d, *J* = 3.45 Hz, 1 H, CH - CH). ¹³C NMR (CDCl₃): δ -5.1 (q, CH₃ - Si); -5.0 (q, CH₃ - Si); 12.1 (q, CH₃ - CH₂N); 12.7 (q, CH₃ - CH₂N); 14.0 (q, CH₃ - CH₂ (ⁿhexane)); 16.7 (s, C_q (^tbutyl)); 22.8 (t, CH₂ - CH₃ (ⁿhexane)); 25.7 (t, CH₂ - CH₂ - CH₂ (ⁿhexane)); 26.2 (q, 3x CH₃ (^tbutyl)); 38.3 (t, CH₂ - C_q (ⁿhexane)); 41.5 (t, CH₂ - N); 42.3 (t, CH₂ - N); 74.3 (s, C_q - O); 125.3 (d, CH - C_qC_q); 134.7 (d, CH - C_qSi); 137.0 (s, C_q - Si); 153.4 (s, C_q - C_q); 172.3 (s, C_q = O). *m/z* 383 (0.4%, M⁺), 326 (1%), 283 (100%), 225 (9%), 183 (13%). HRMS: C₂₀H₃₇NO₂SSi calc. 383.2314, found 383.2310.

5-(*N,N*-diethylcarbamoyloxy)-5-(2-thienyl)nonane (87)



$C_{18}H_{31}NO_2S$

FW 325.5 g/mol

1-(*N,N*-diethylcarbamoyloxy)-1-(2-thienyl)pentane (0.50 g, 1.86 mmol) was stirred in dry THF (5 ml) under N_2 at $-78\text{ }^{\circ}\text{C}$. $n\text{-BuLi}$ solution (1.75 ml, 1.40 M, 2.45 mmol) was added dropwise. The mixture was stirred for 30 minutes then a solution of CH_3I (0.26 g, 1.83 mmol) in dry THF (5 ml) was added dropwise. Stirring was continued for 1 hour at $-78\text{ }^{\circ}\text{C}$ then the cooling bath was removed and stirring was continued for 2 hours. The reaction was quenched with sat. NaHCO_3 and extracted with diethyl ether. The ethereal solution was dried (MgSO_4), filtered and the solvent was removed under reduced pressure. 0.46 g of yellow liquid remained. Silica gel chromatography (90% hexane, 10% diethyl ether) yielded the product (0.041 g, 0.126 mmol, 7%) as a pale yellow liquid. ^1H NMR (CDCl_3): δ 0.83 (t, $J = 6.97\text{ Hz}$, 6 H, $2\times \text{CH}_3$ ("nonane")); 1.12-1.27 (m, 14 H, $2\times \text{CH}_3 - \text{CH}_2\text{N}$, $4\times \text{CH}_2$ ("nonane")); 1.94-2.09 (m, 2 H, CH_2 ("nonane")); 2.44-2.59 (m, 2 H, CH_2 ("nonane")); 3.22-3.39 (m, 4 H, $2\times \text{CH}_2 - \text{N}$); 6.84 (dd, $J = 1.19\text{ Hz}$, $J = 3.57\text{ Hz}$, $\text{CH} - \text{C}_q$); 6.97 (dd, $J = 3.60\text{ Hz}$, $J = 5.08\text{ Hz}$, $\text{CH} - \text{CH} - \text{CH}$); 7.18 (dd, $J = 1.19\text{ Hz}$, $J = 5.06\text{ Hz}$, $\text{CH} - \text{S}$). ^{13}C NMR (CDCl_3): δ 13.5 (q, $\text{CH}_3 - \text{CH}_2\text{N}$); 14.0 (q, $2\times \text{CH}_3$ ("nonane")); 14.3 (q, $\text{CH}_3 - \text{CH}_2\text{N}$); 22.7 (t, $2\times \text{CH}_2 - \text{CH}_3$ ("nonane")); 25.6 (t, $2\times \text{CH}_2 - \text{CH}_2 - \text{CH}_2$ ("nonane")); 39.8 (t, $2\times \text{CH}_2 - \text{C}_q$ ("nonane")); 41.6 (t, $2\times \text{CH}_2 - \text{N}$); 86.1 (s, $\text{C}_q - \text{O}$); 122.0 (d, $\text{CH} - \text{C}_q$); 123.2 (d, $\text{CH} - \text{S}$); 126.5 (d, $\text{CH} - \text{CH} - \text{CH}$); 149.8 (s, $\text{C}_q - \text{S}$); 153.8 (s, $\text{C}_q = \text{O}$). m/z 325 (0.8%, M^+), 224 (4%), 209 (100%), 178 (9%), 97 (6%). HRMS: $C_{18}H_{31}NO_2S$ calc. 325.2076, found 325.2070.

CHAPTER 5

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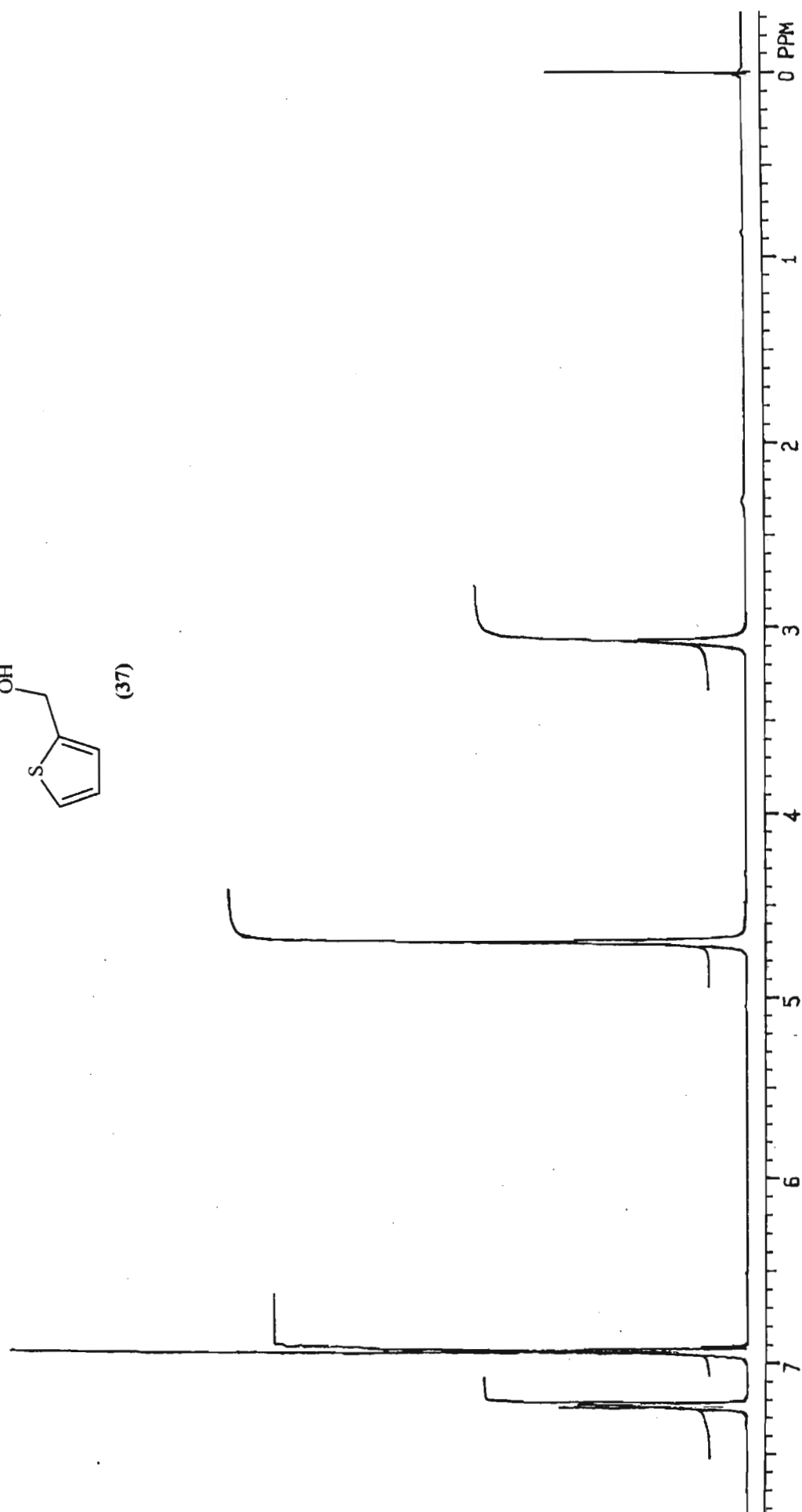
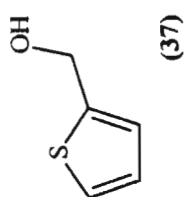
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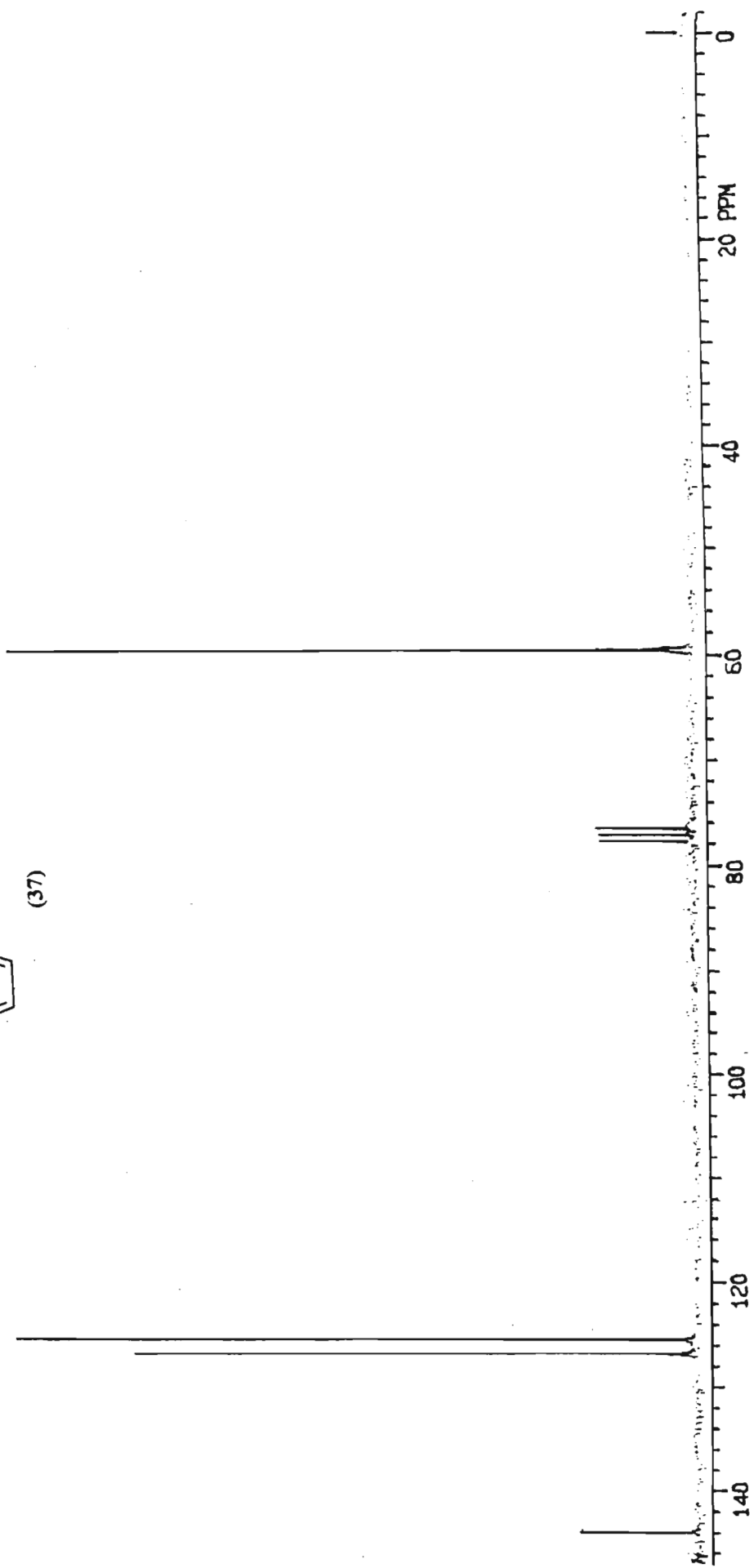
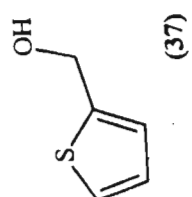
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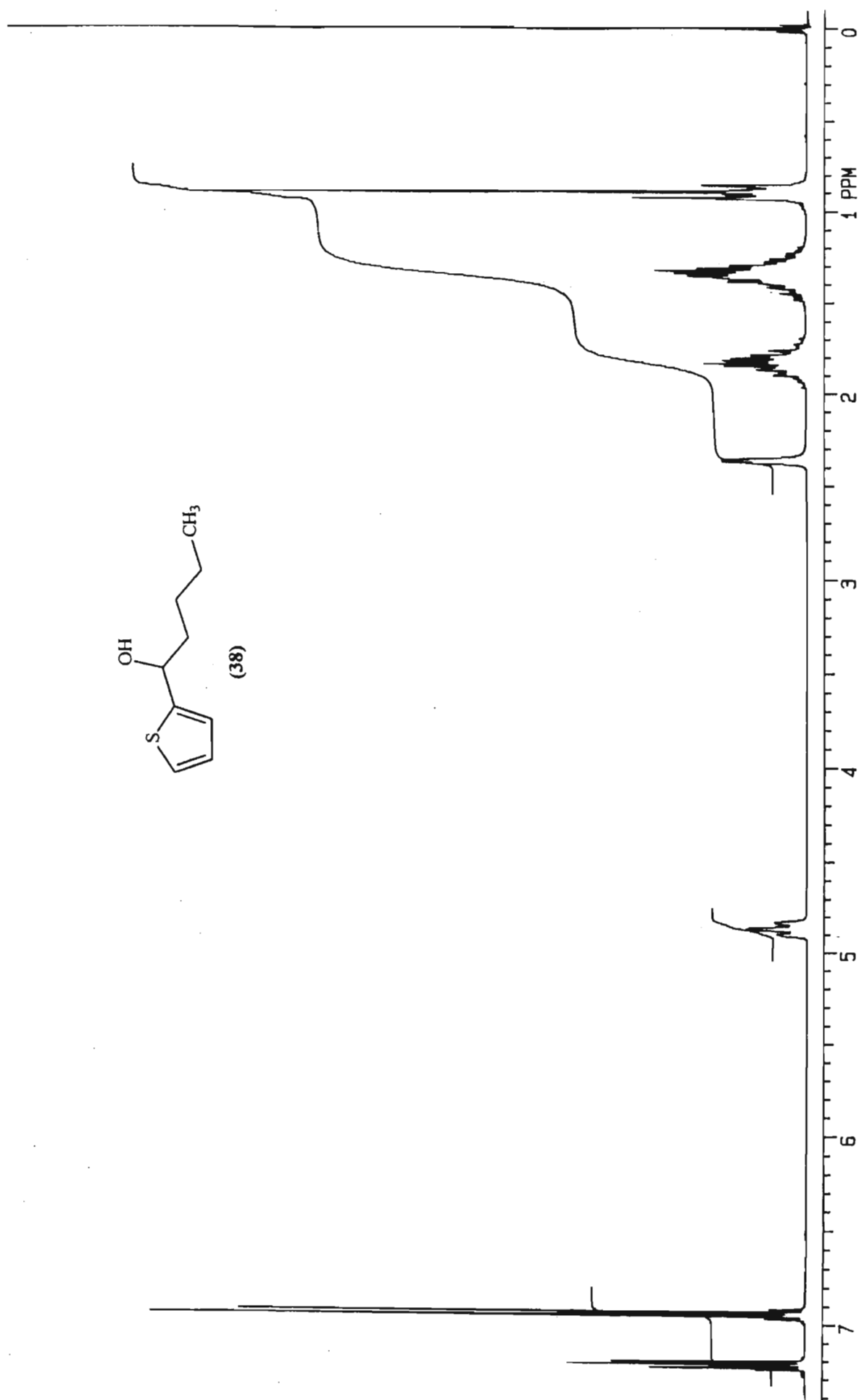
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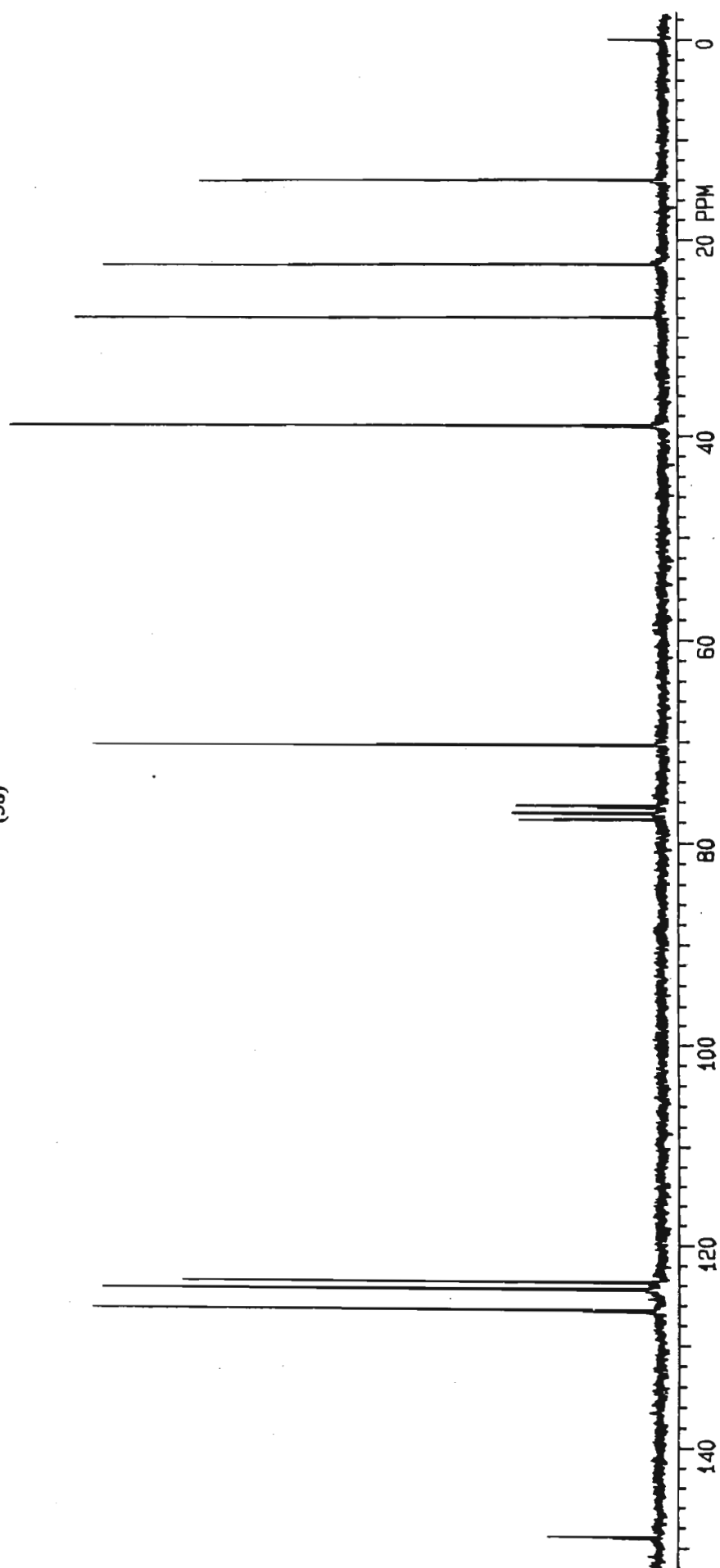
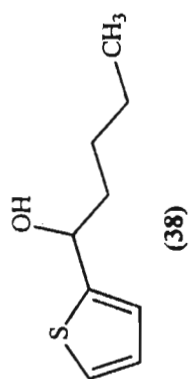
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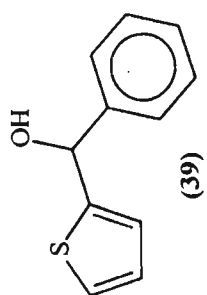
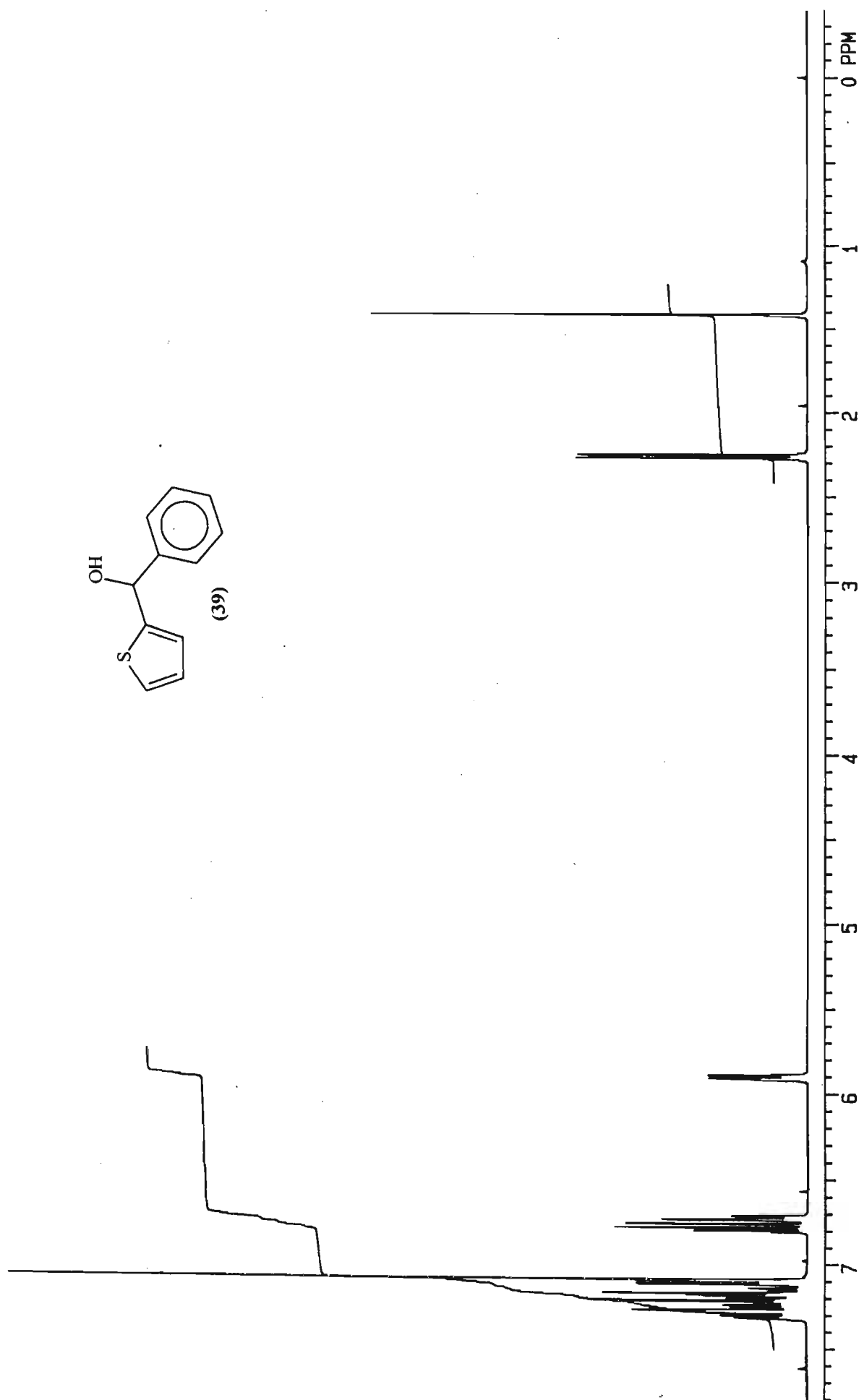
CHAPTER 6
 ^1H AND ^{13}C NMR SPECTRA

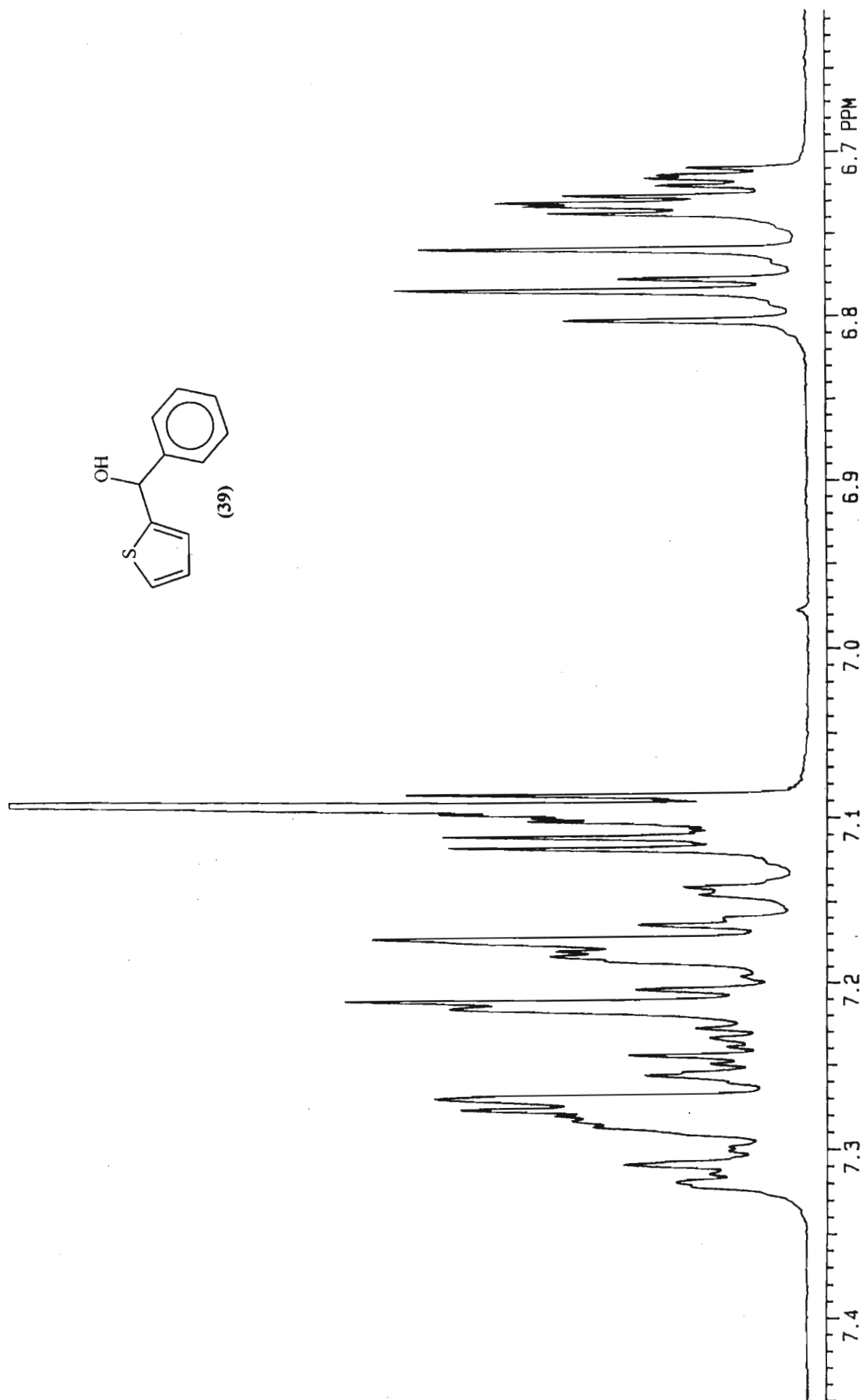


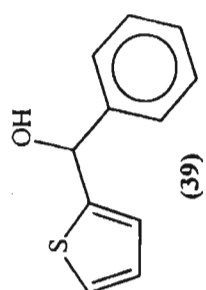


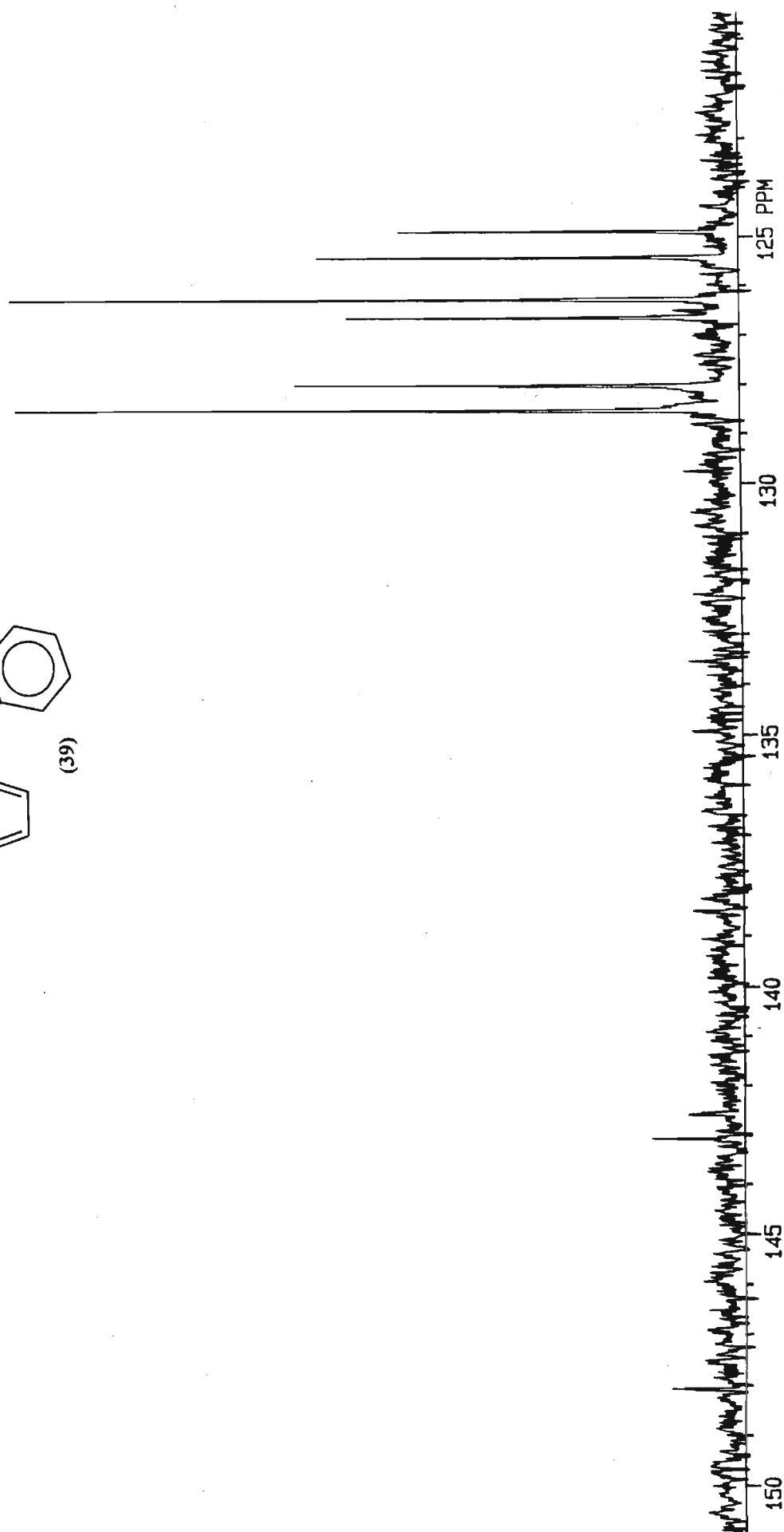
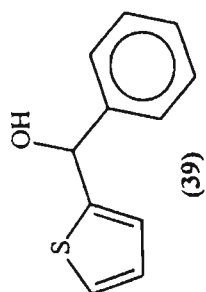


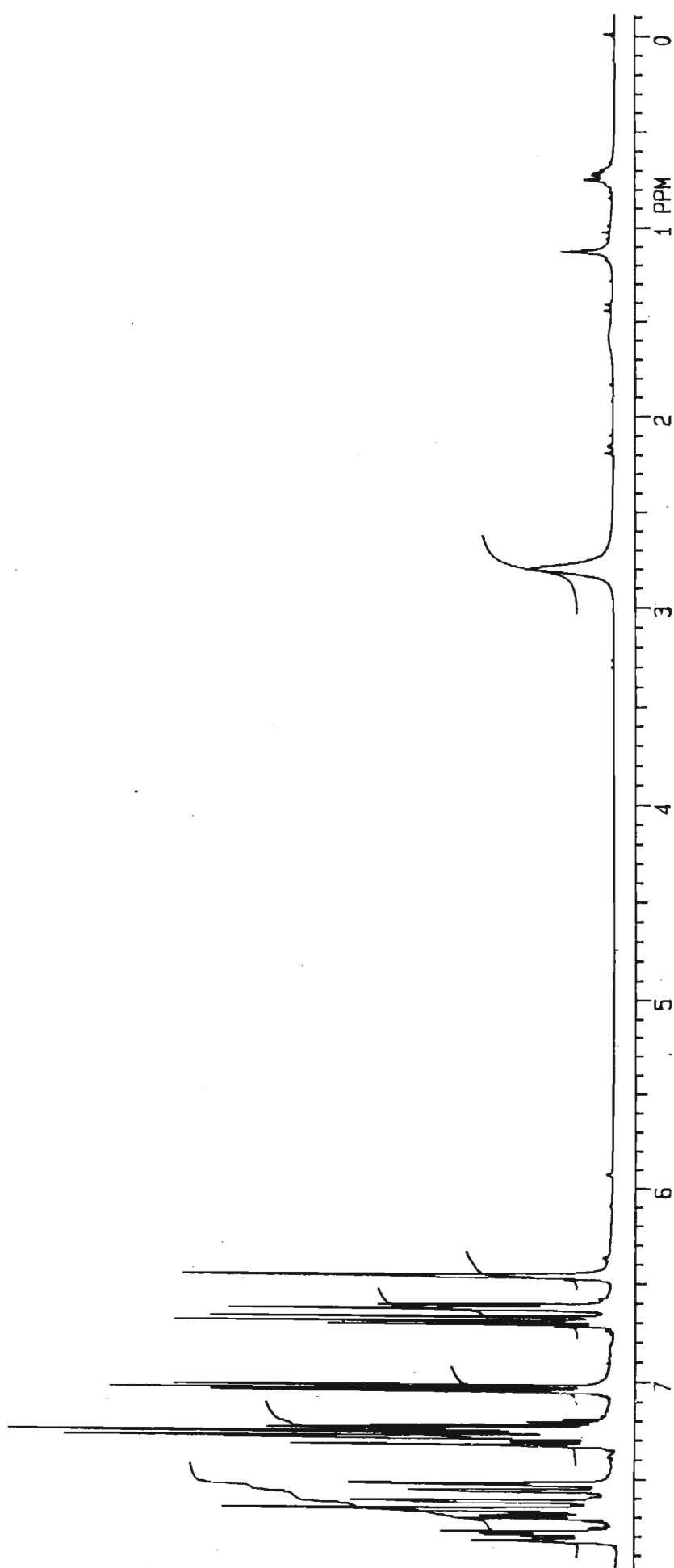
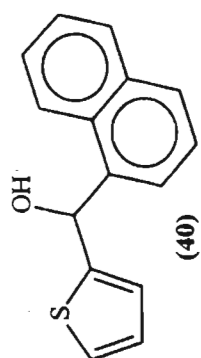


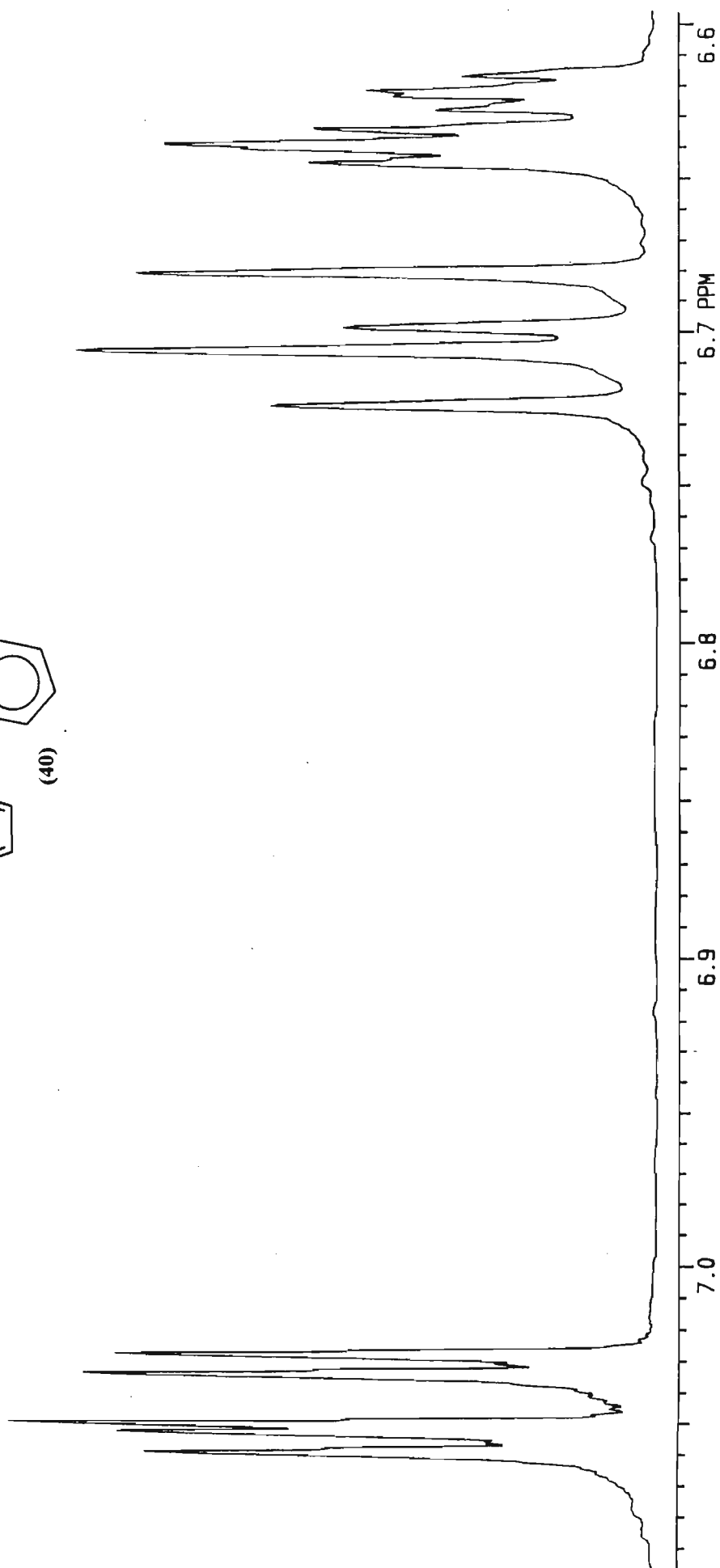
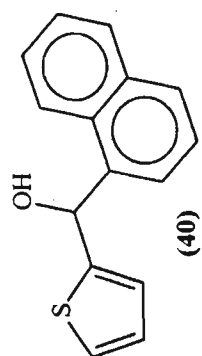


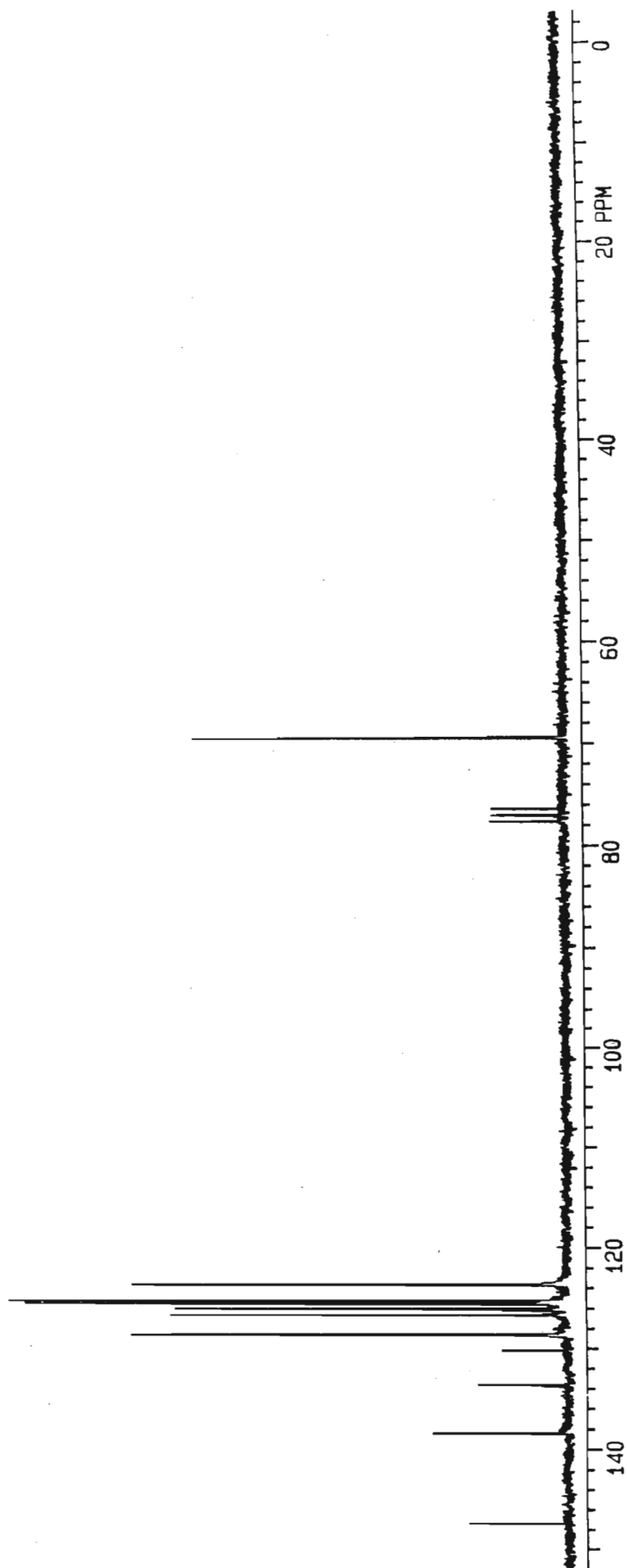
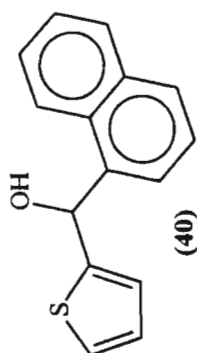


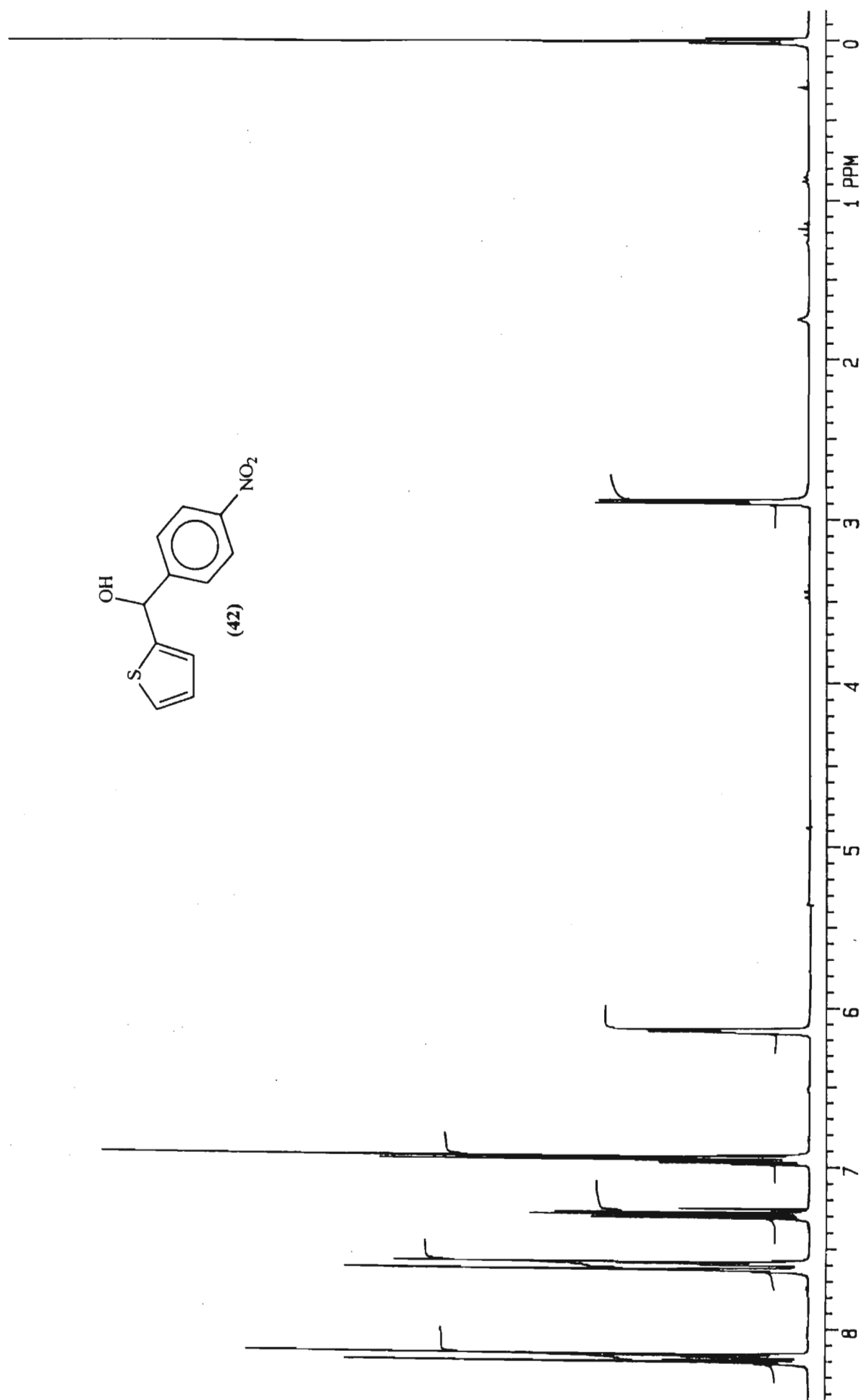
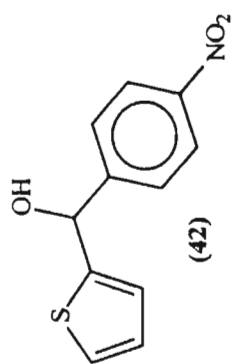


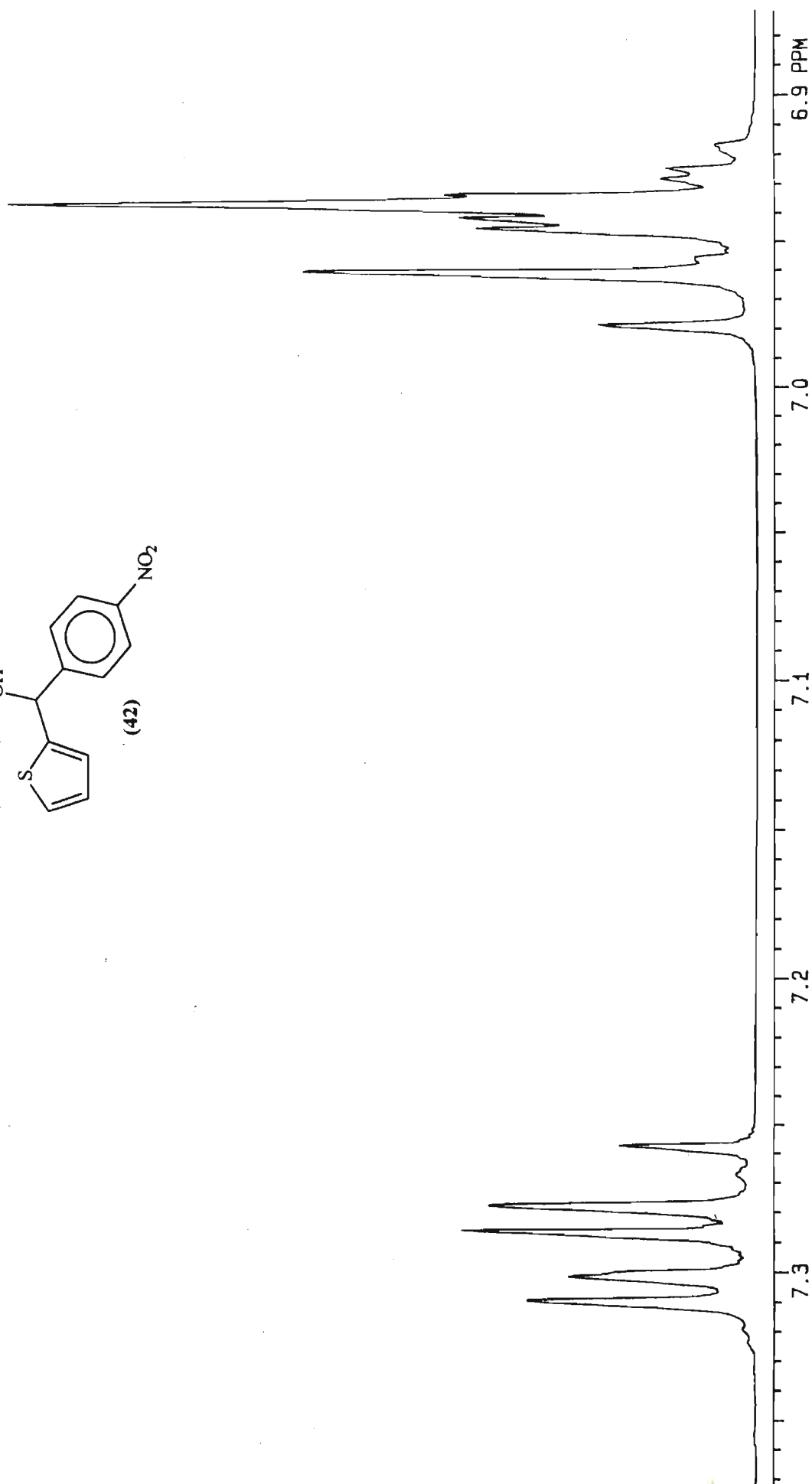
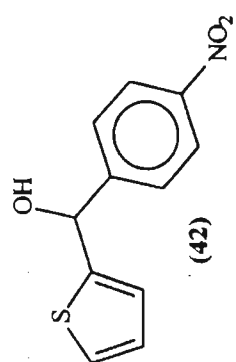


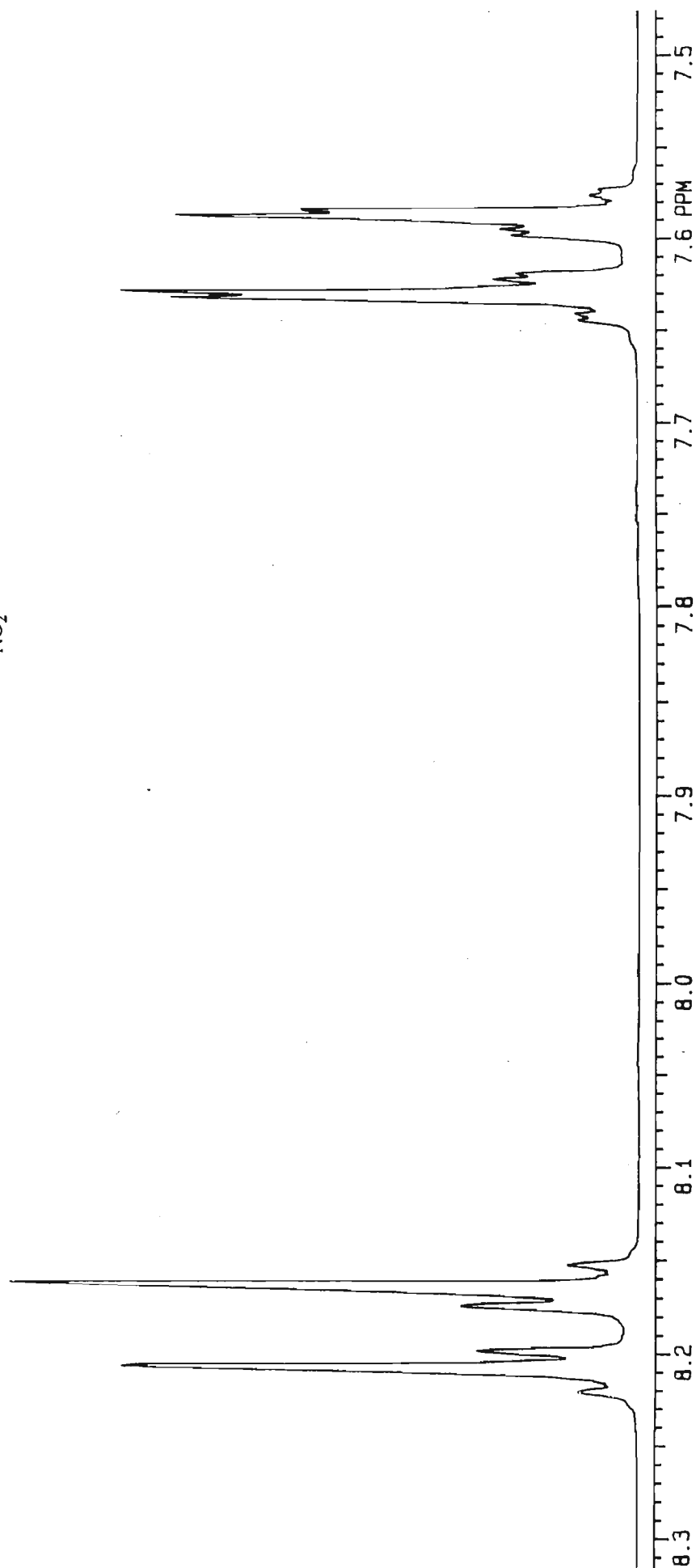
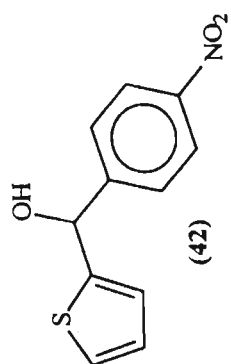


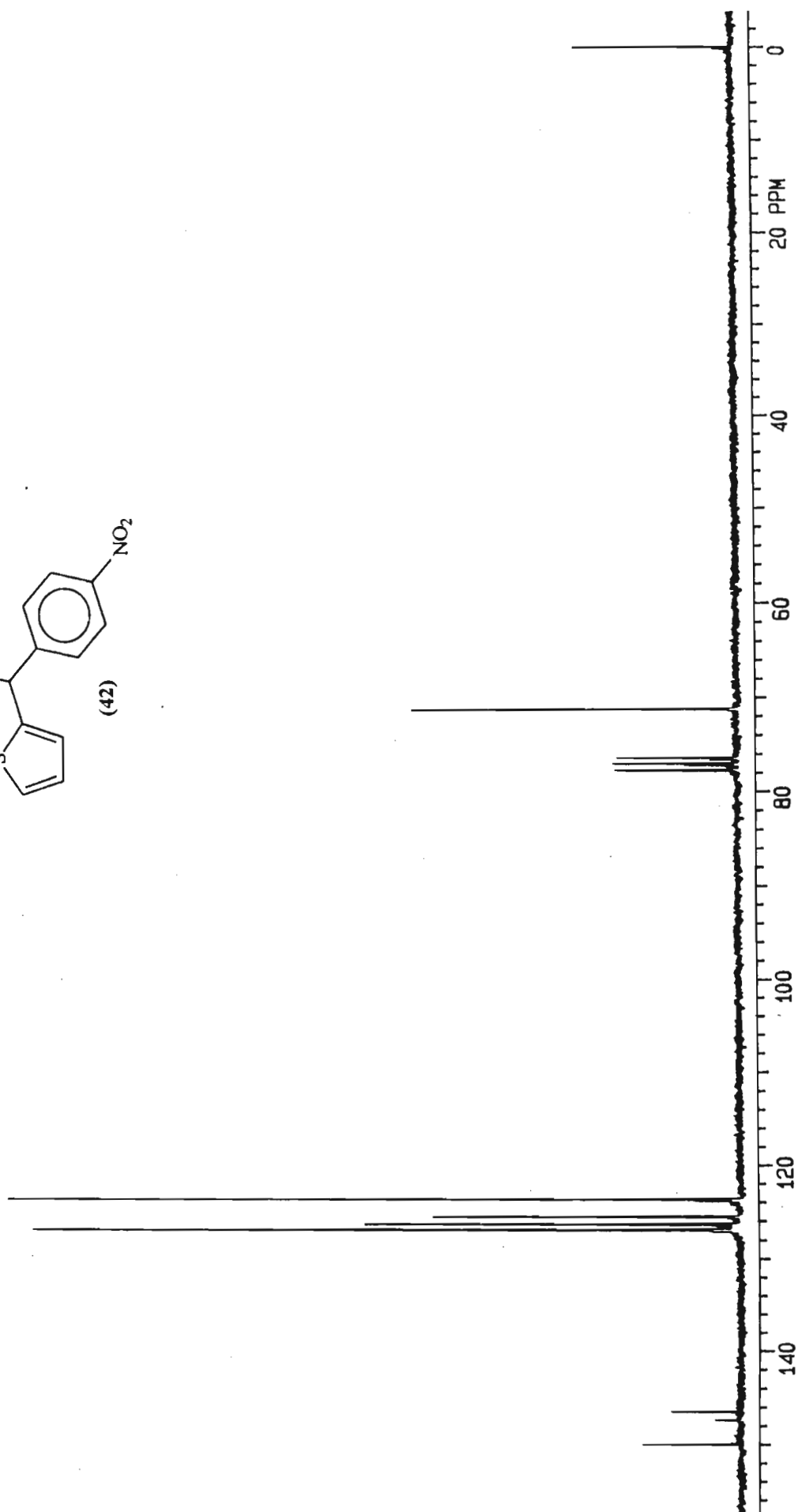
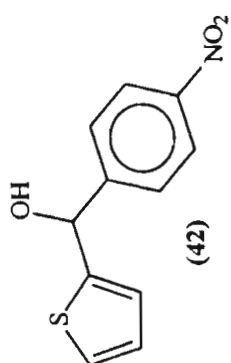


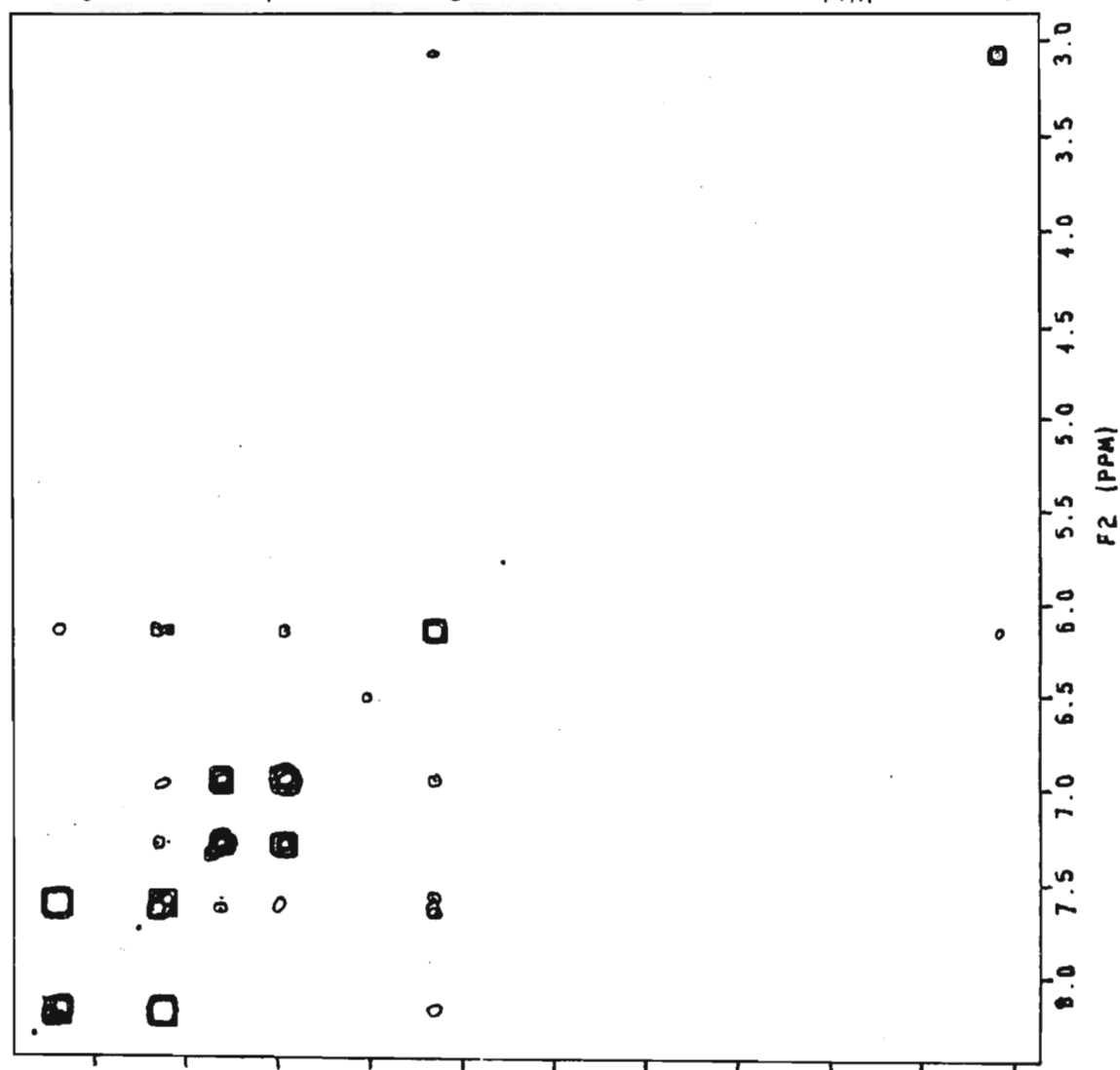
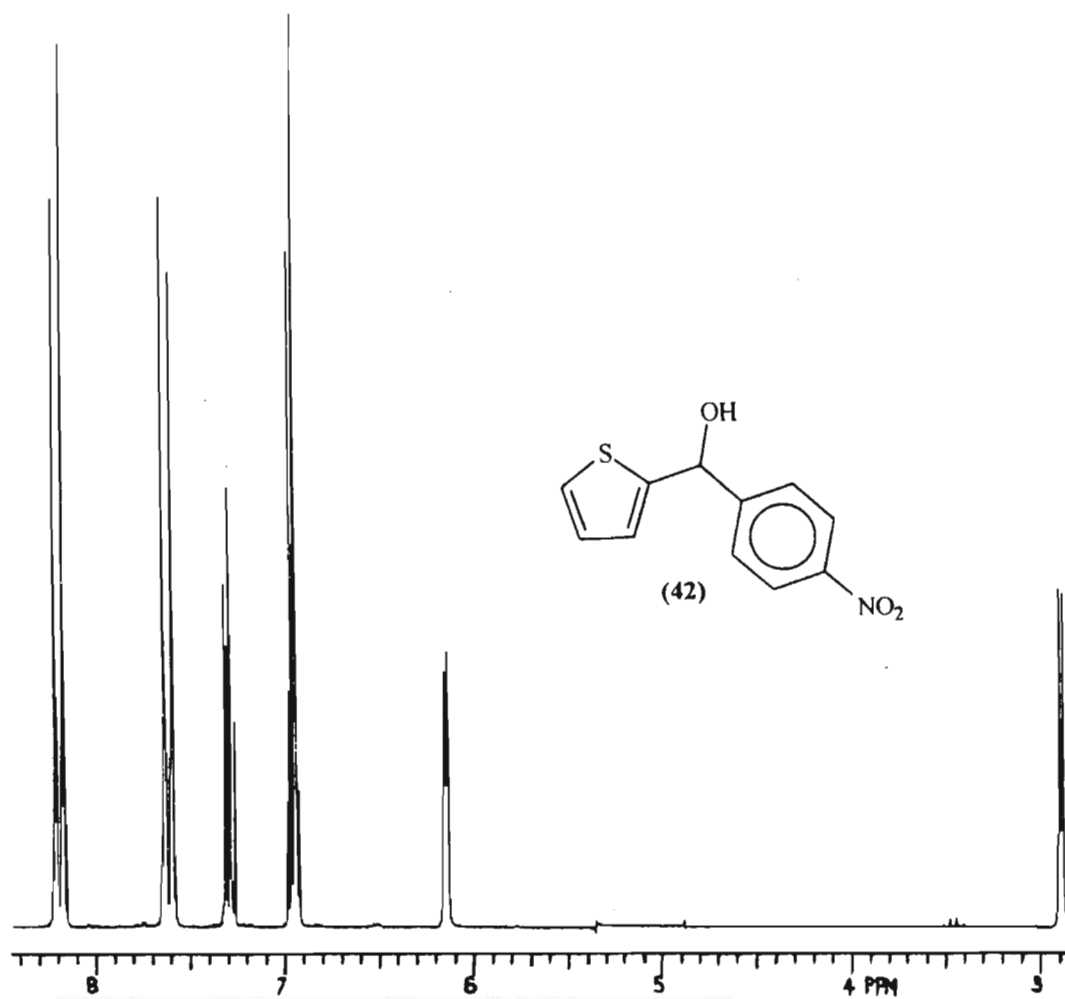


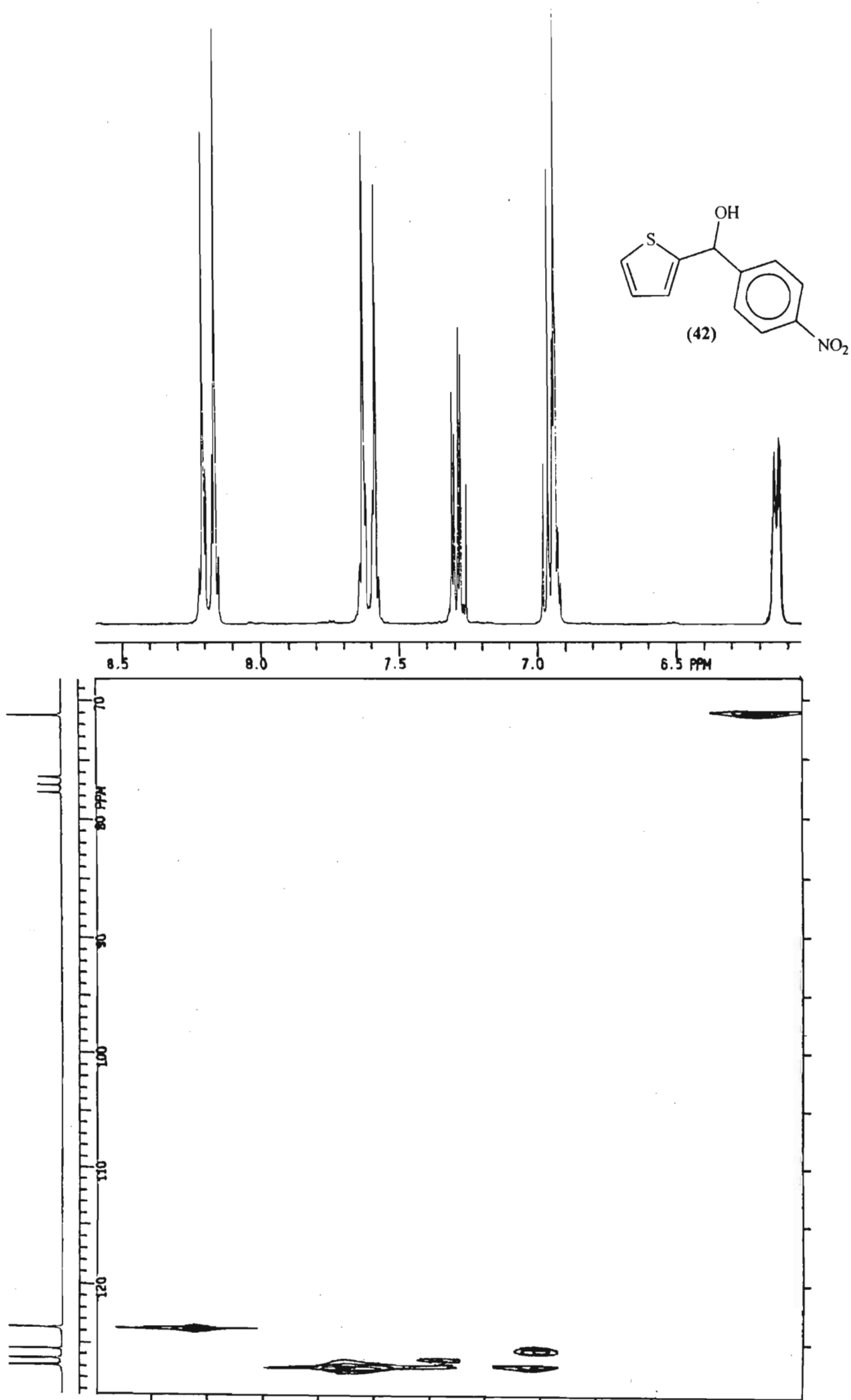


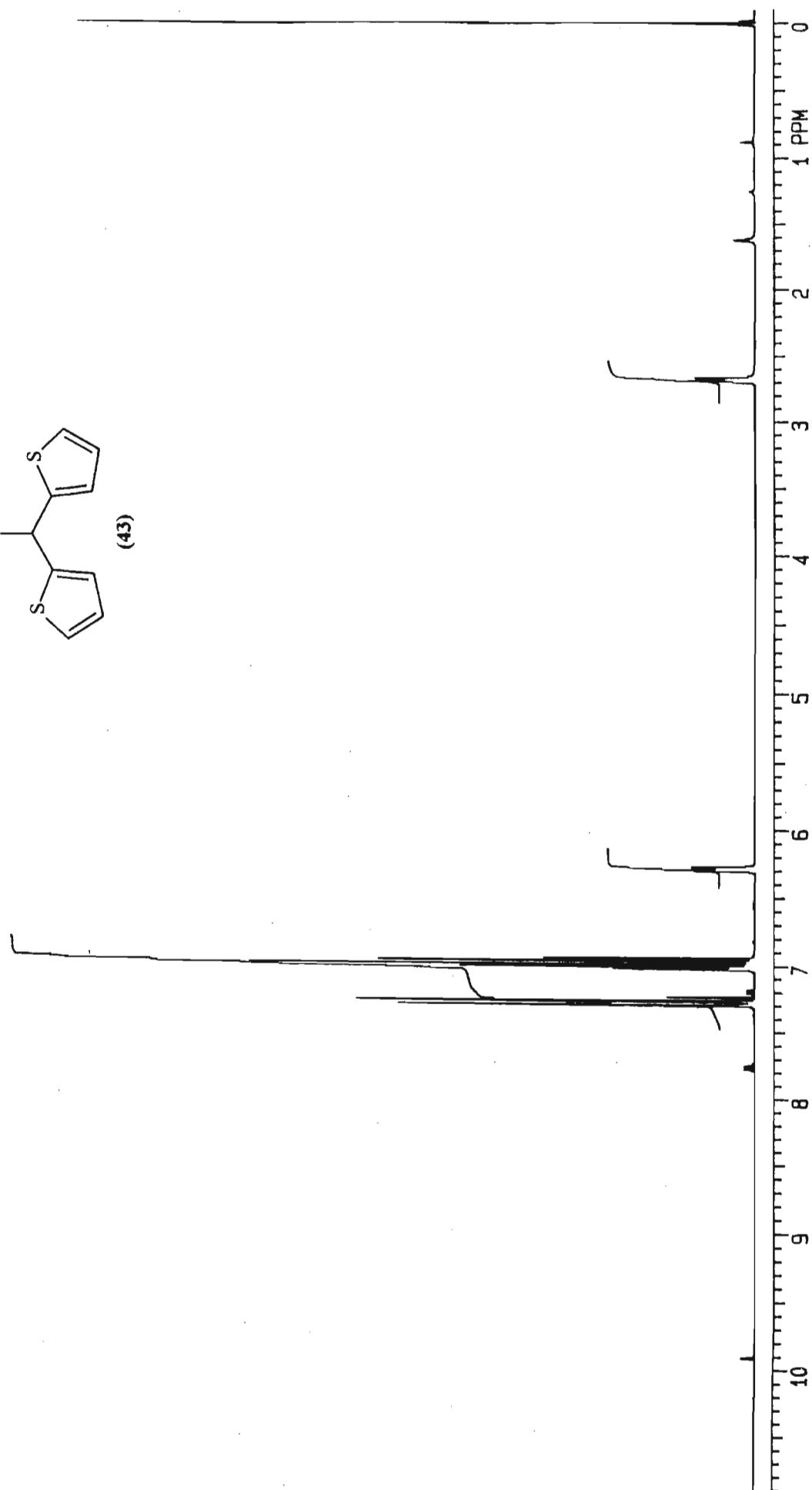
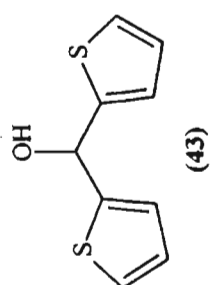


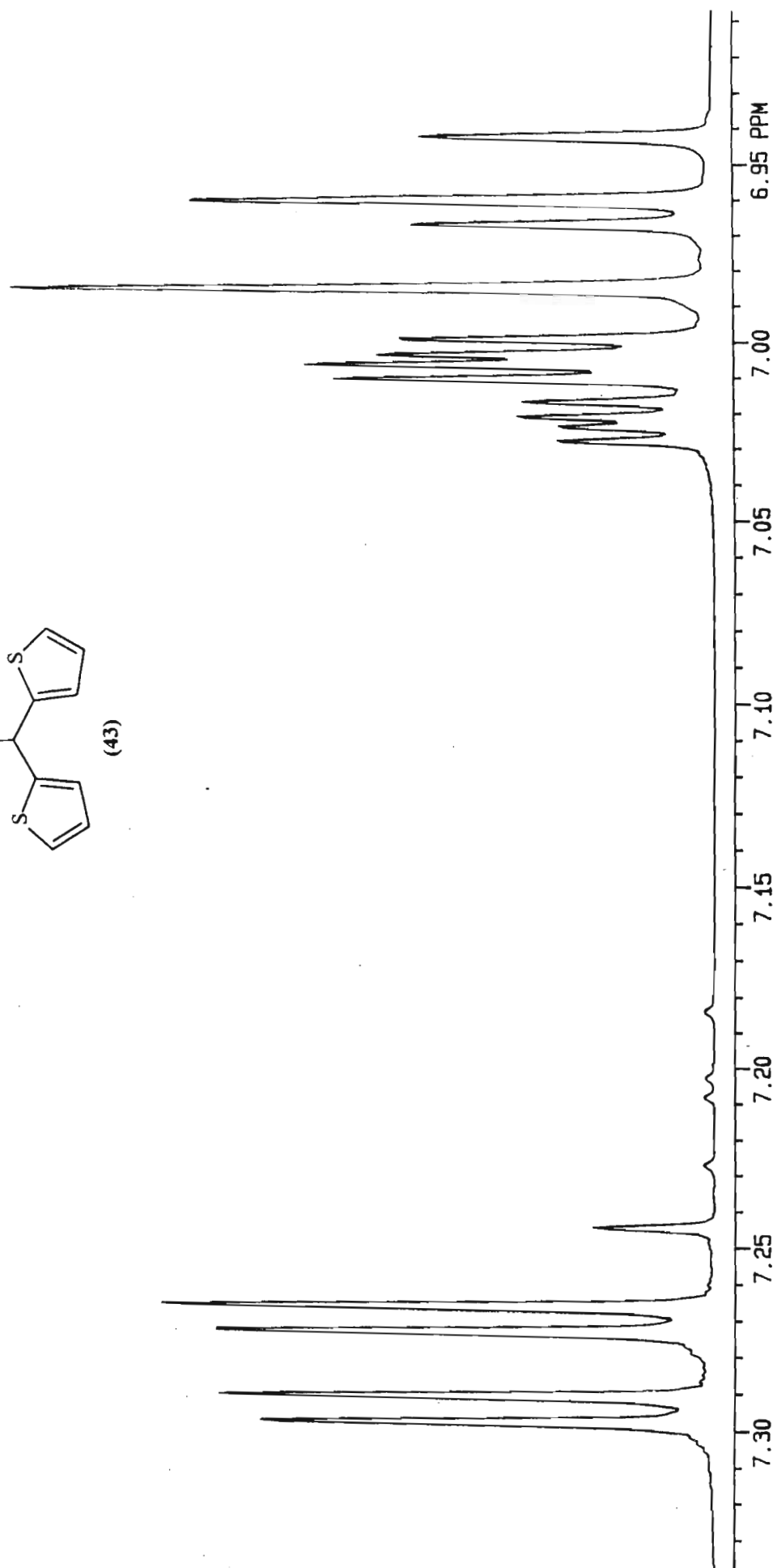
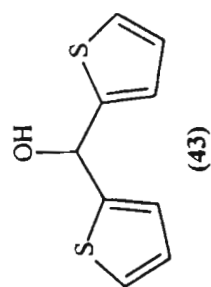


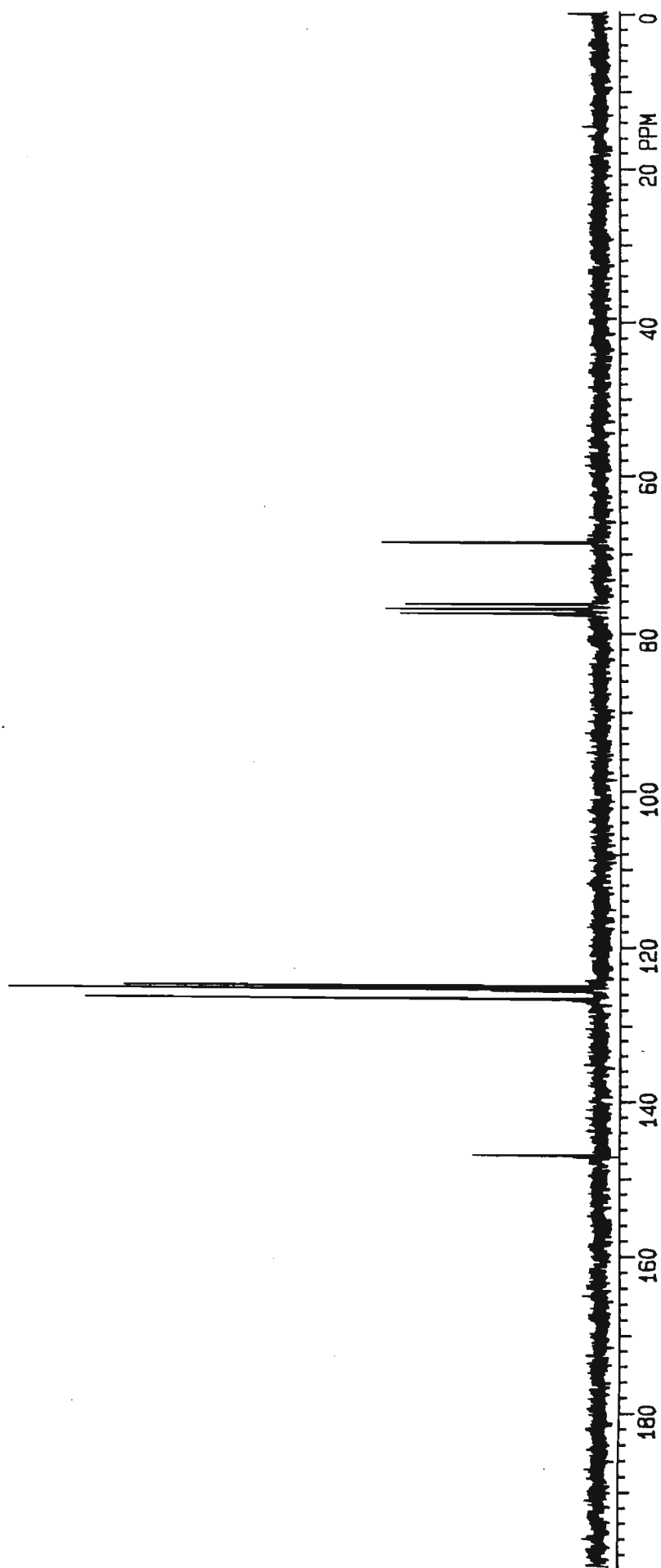
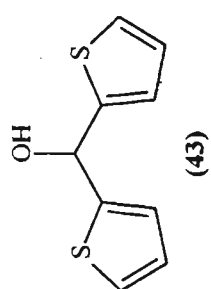




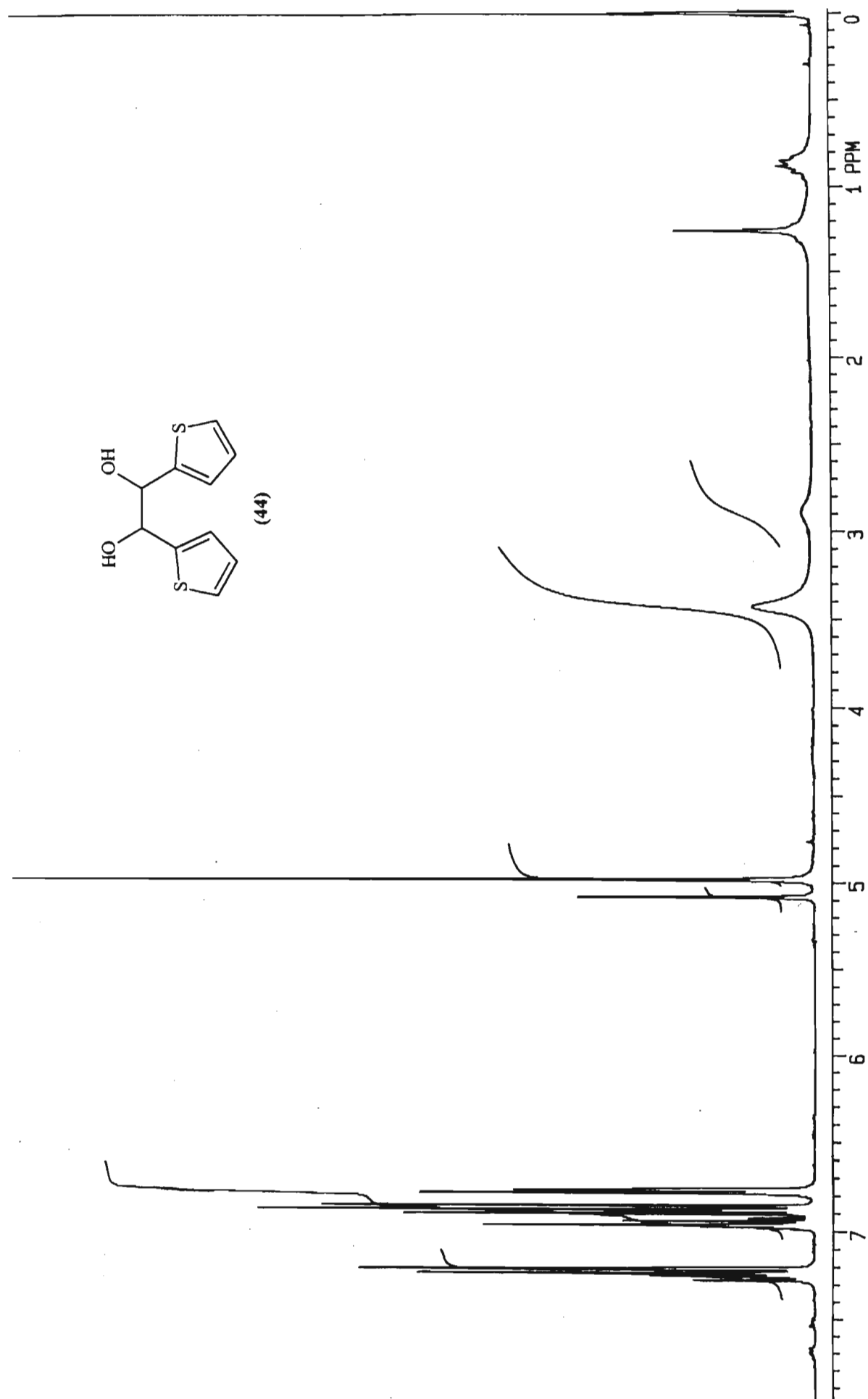


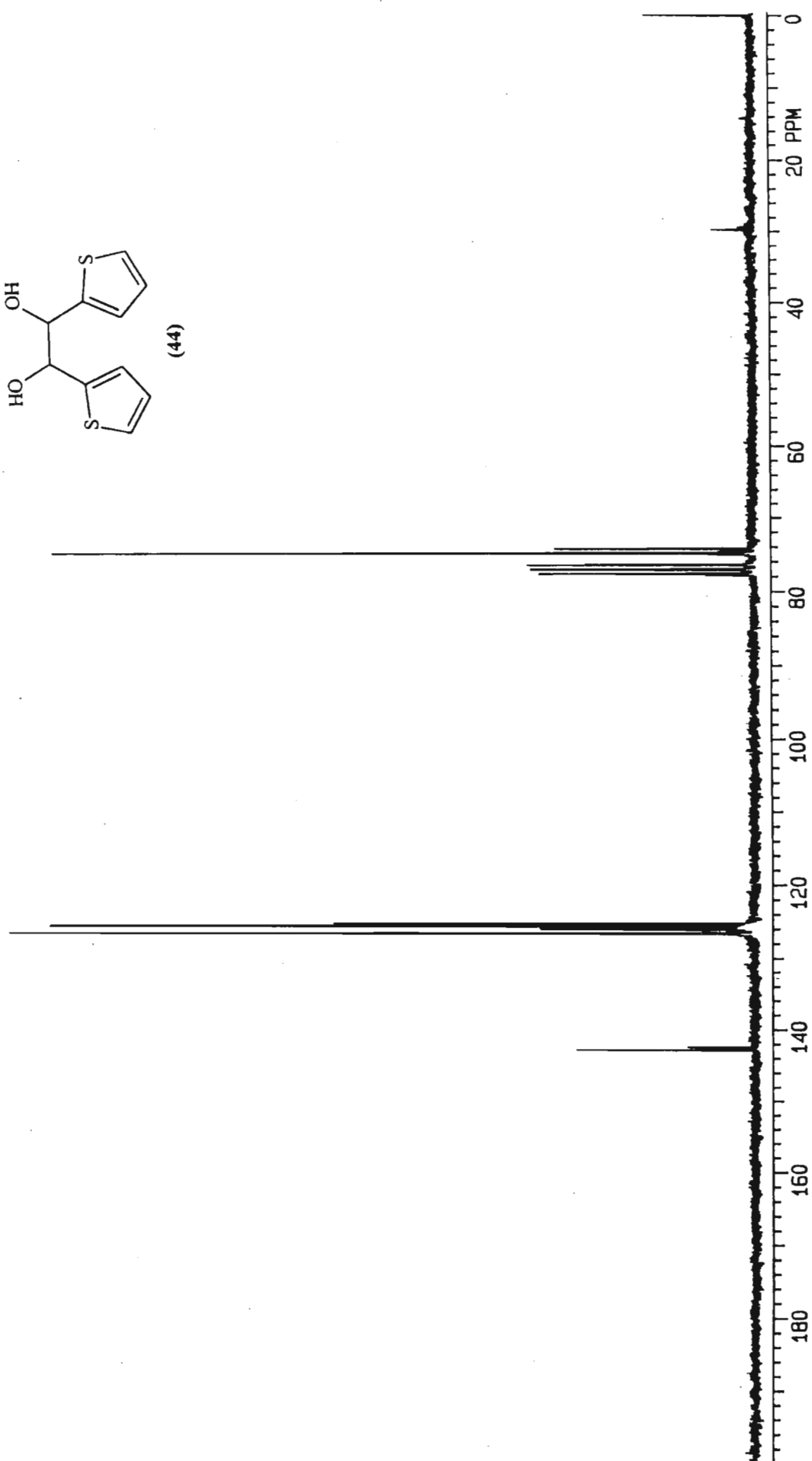
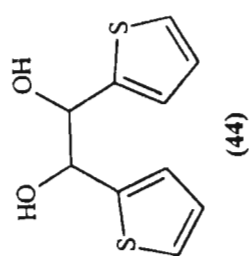


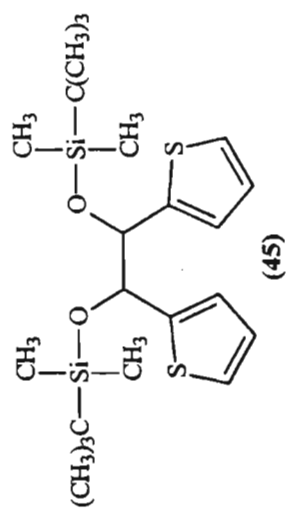
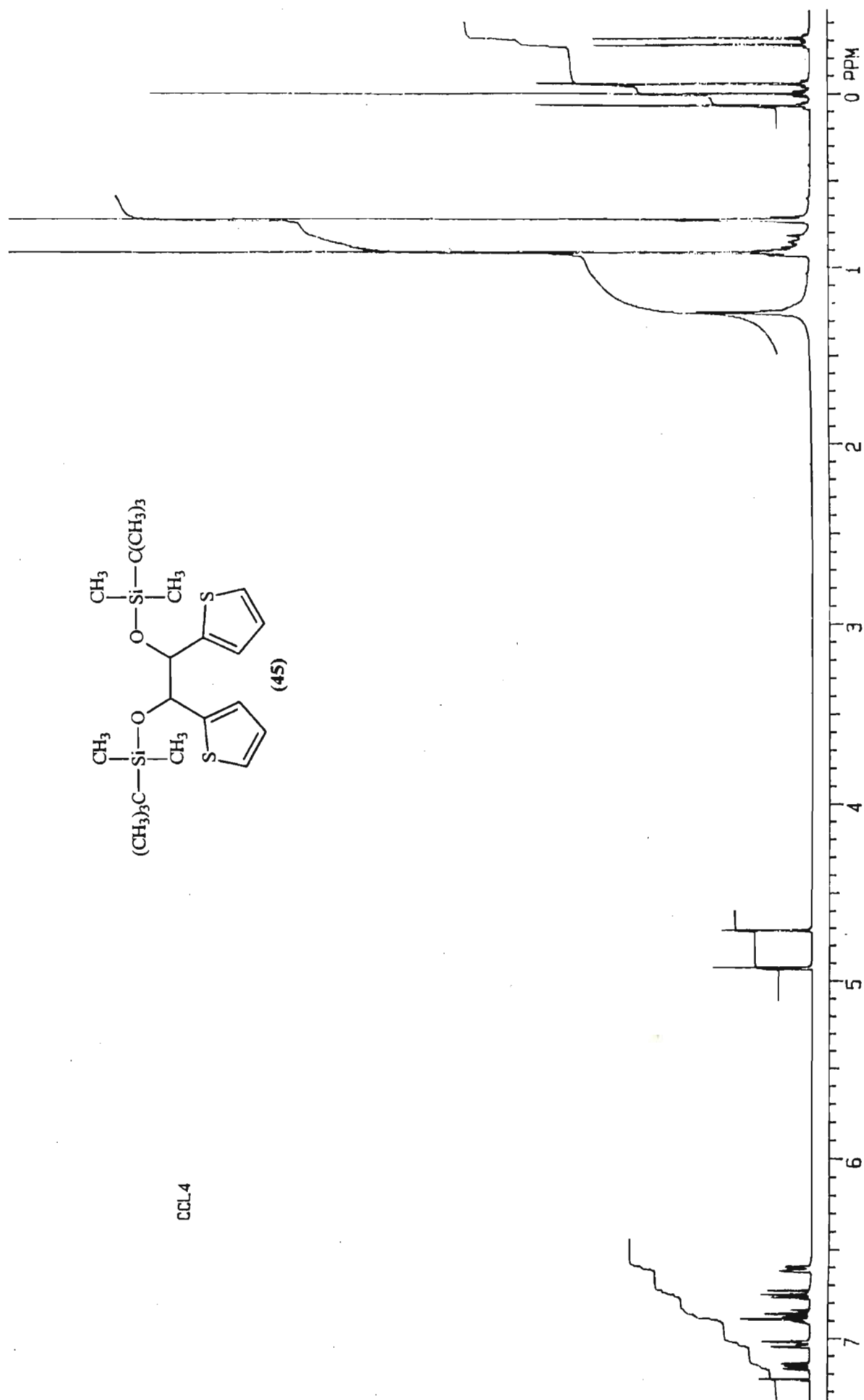




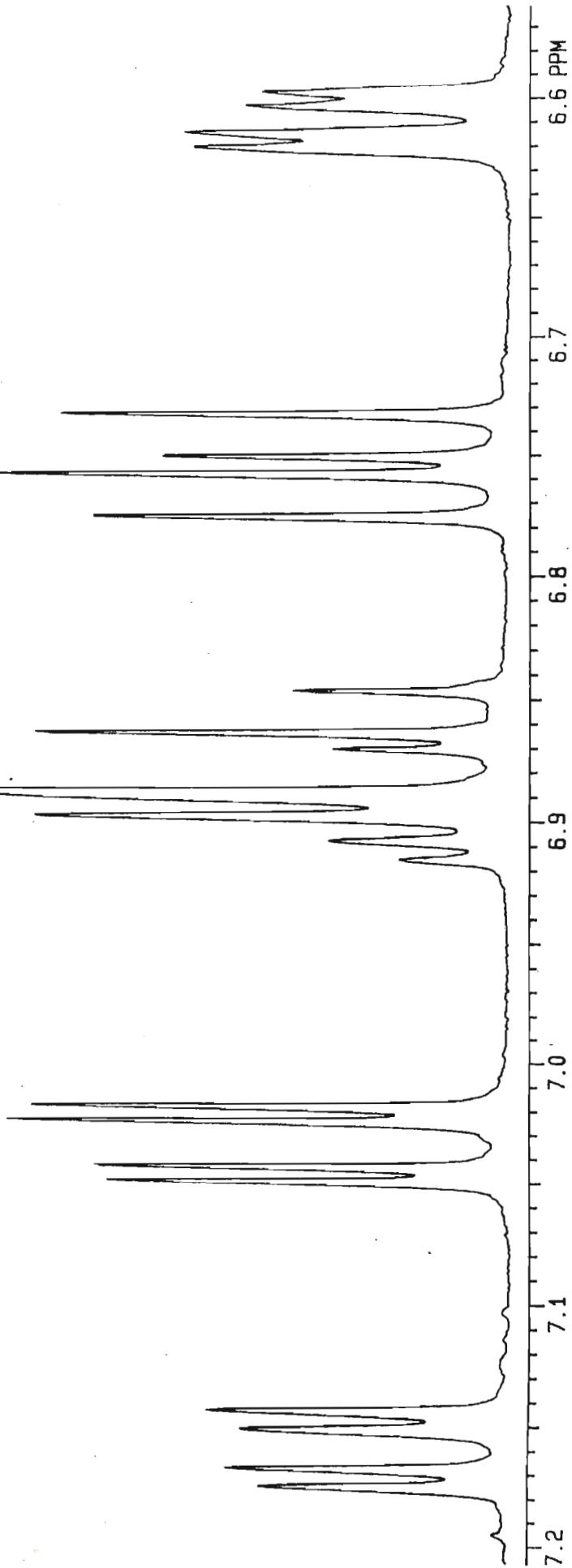
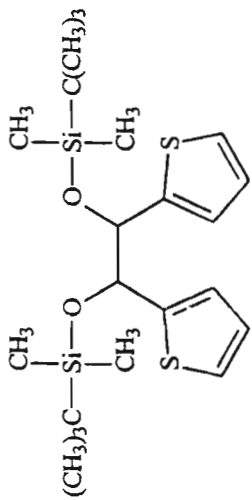
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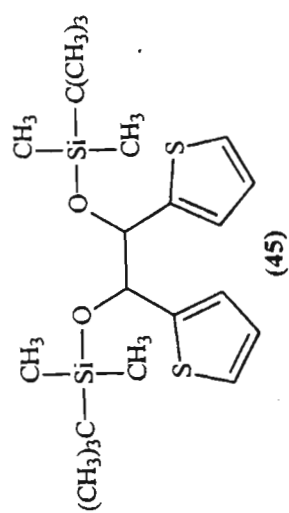




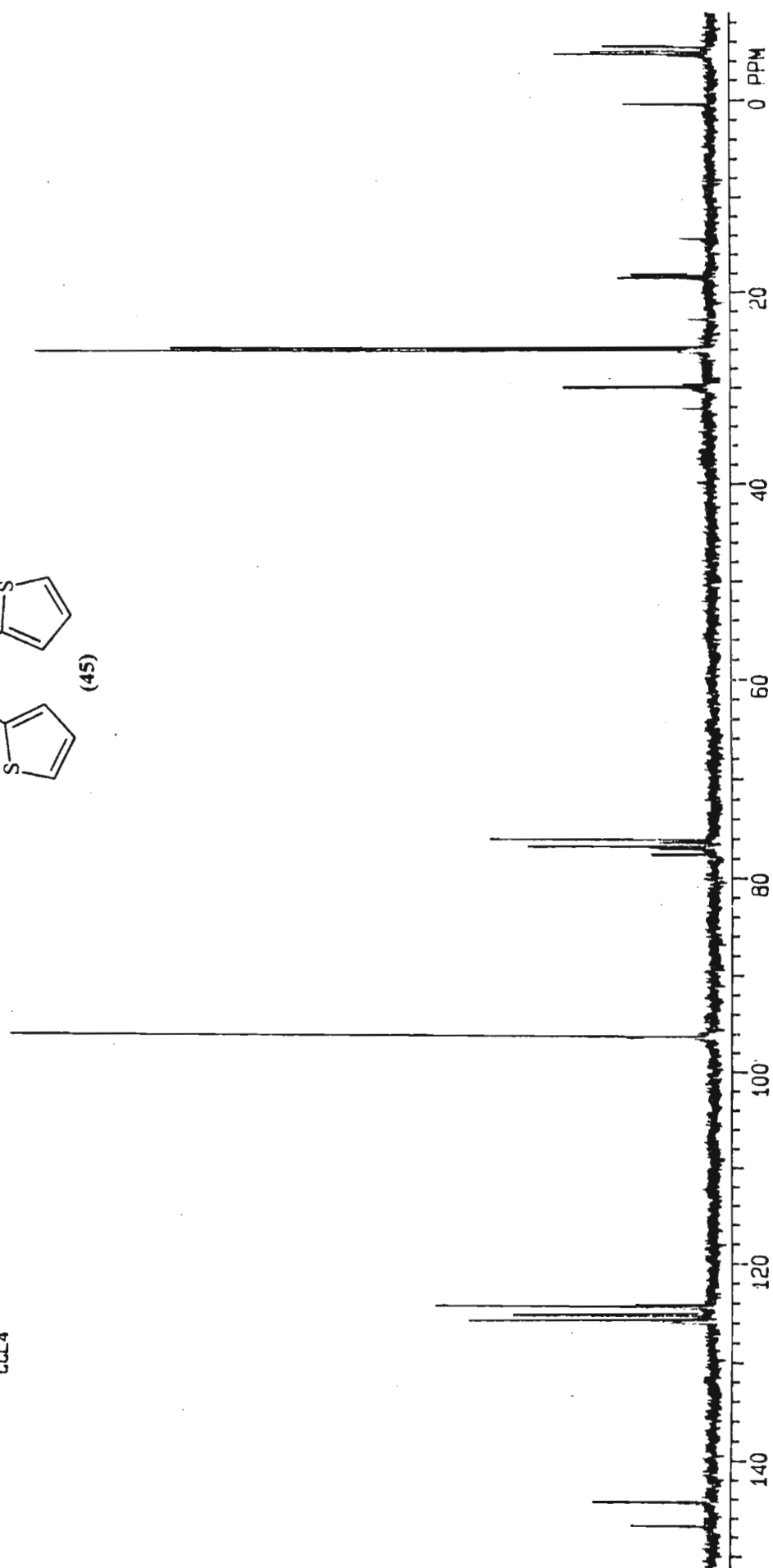


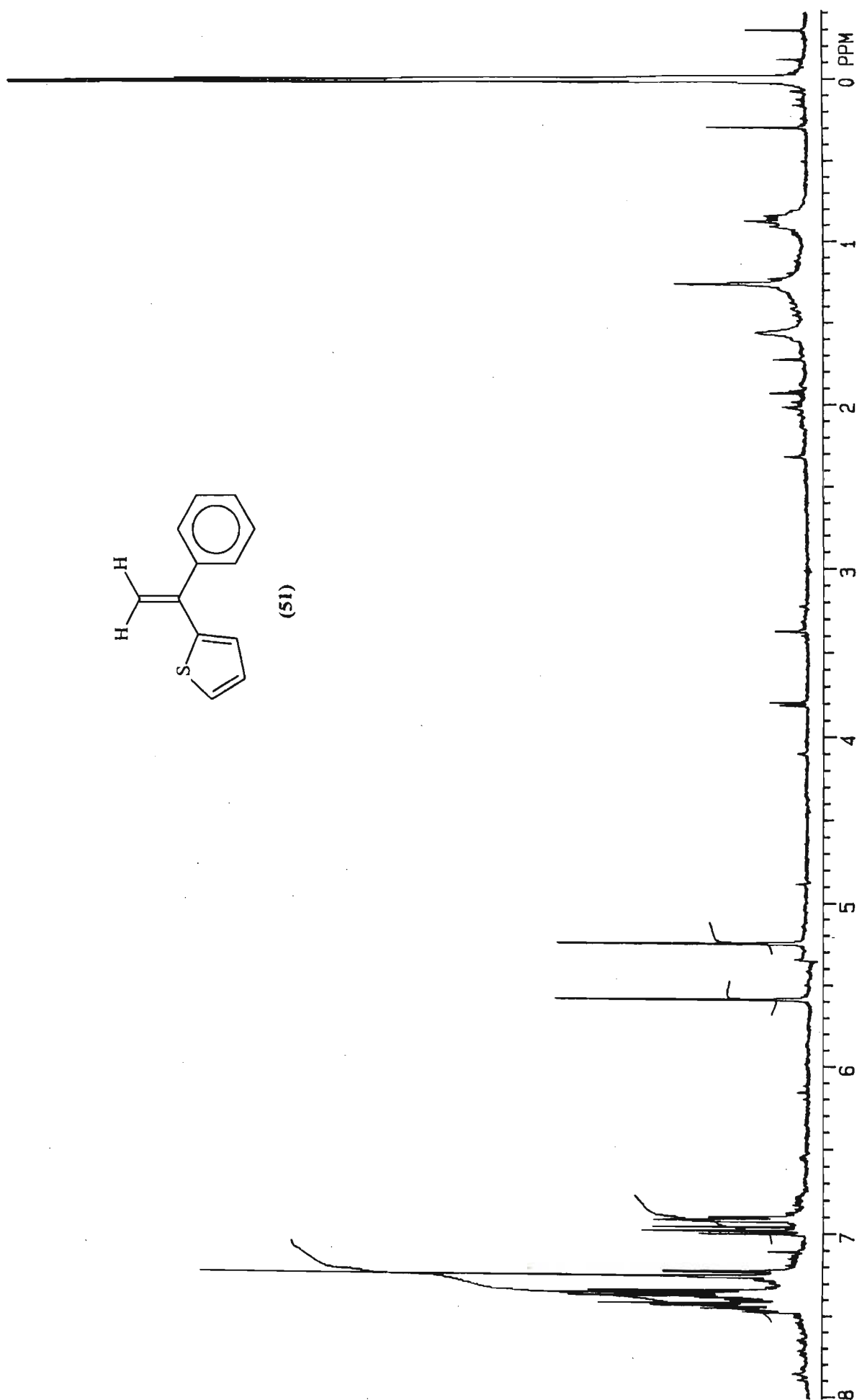
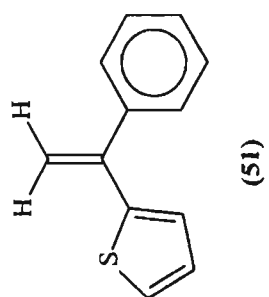
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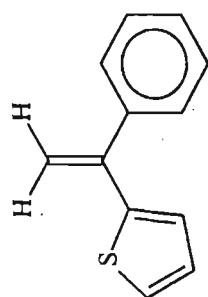




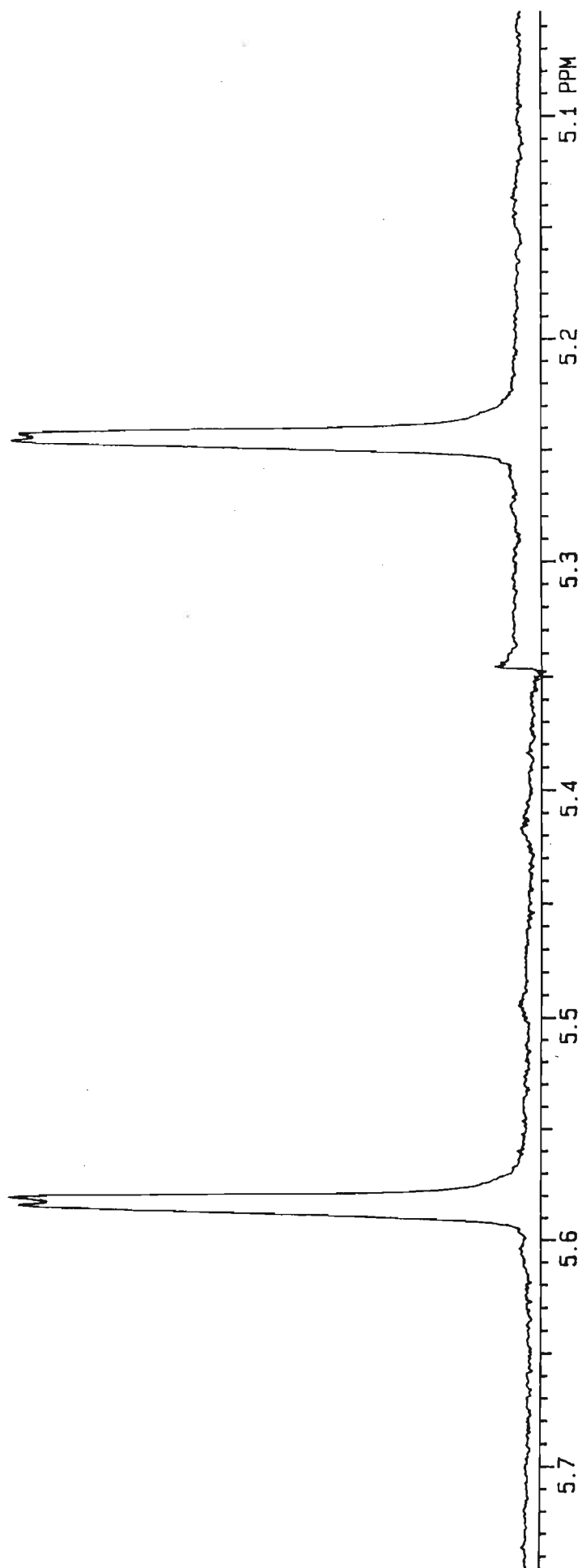
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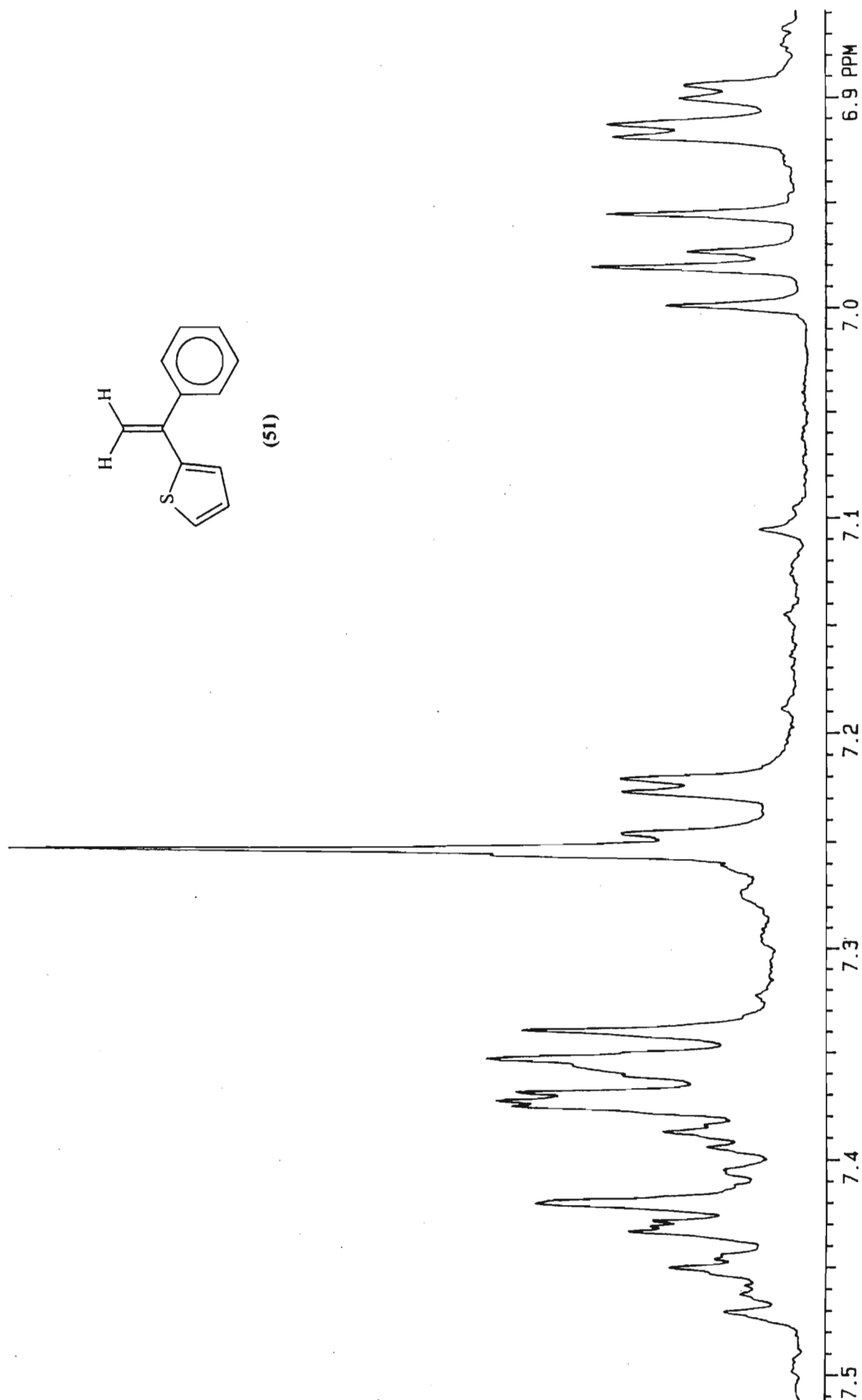
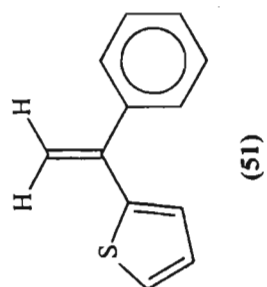


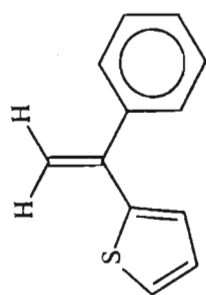




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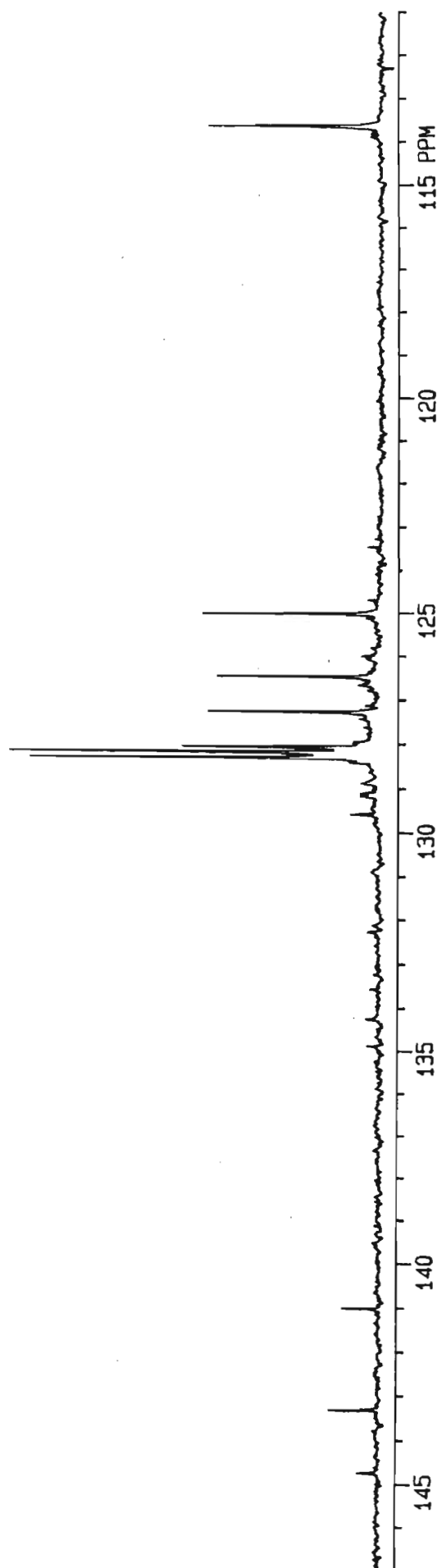
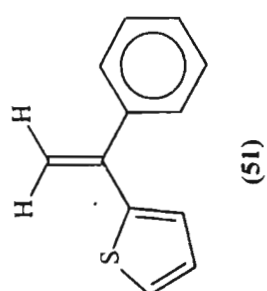


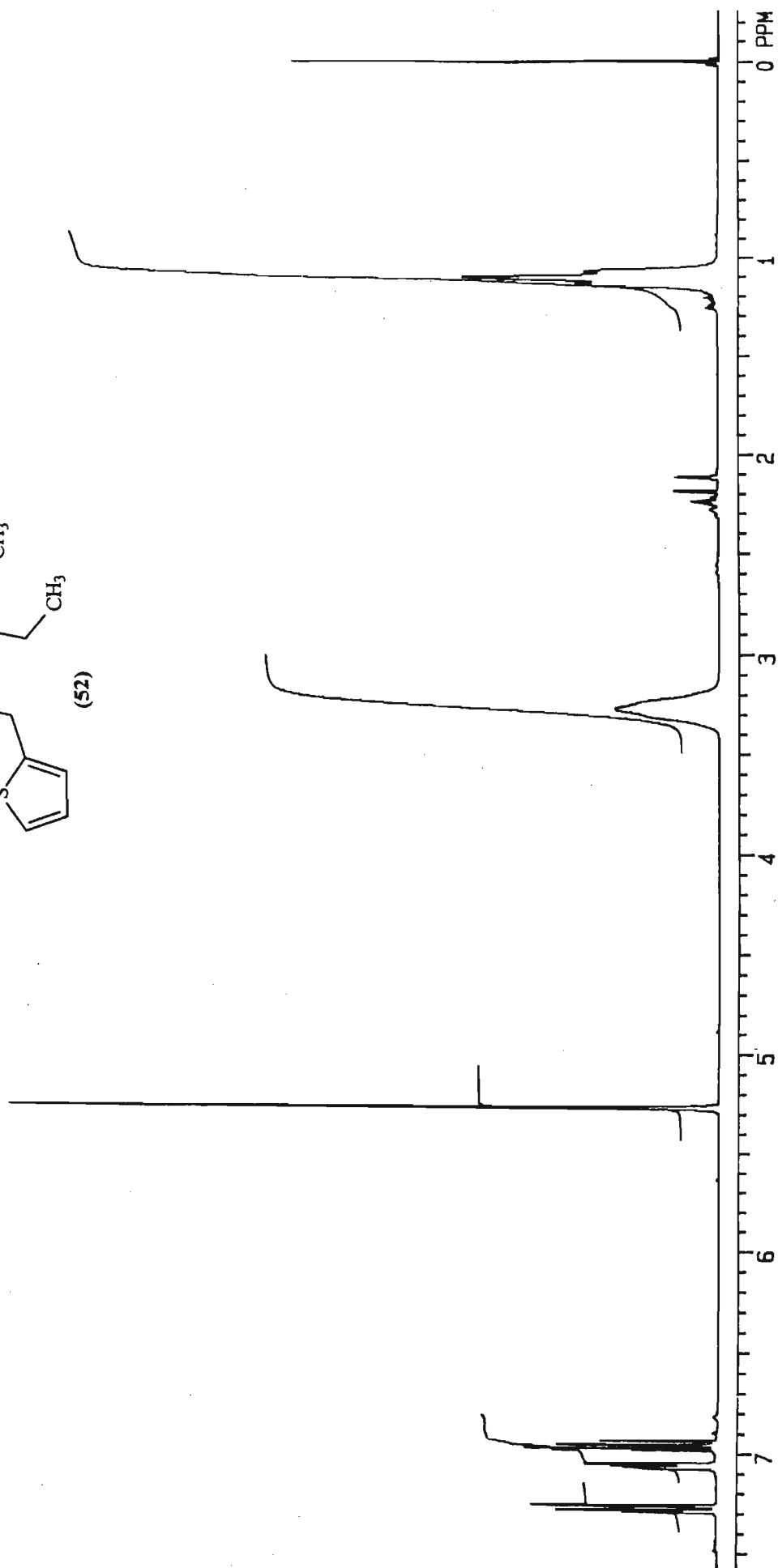
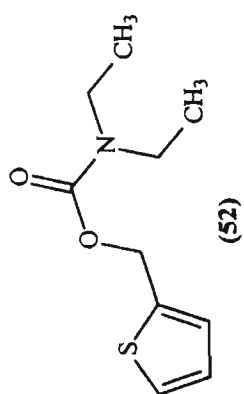


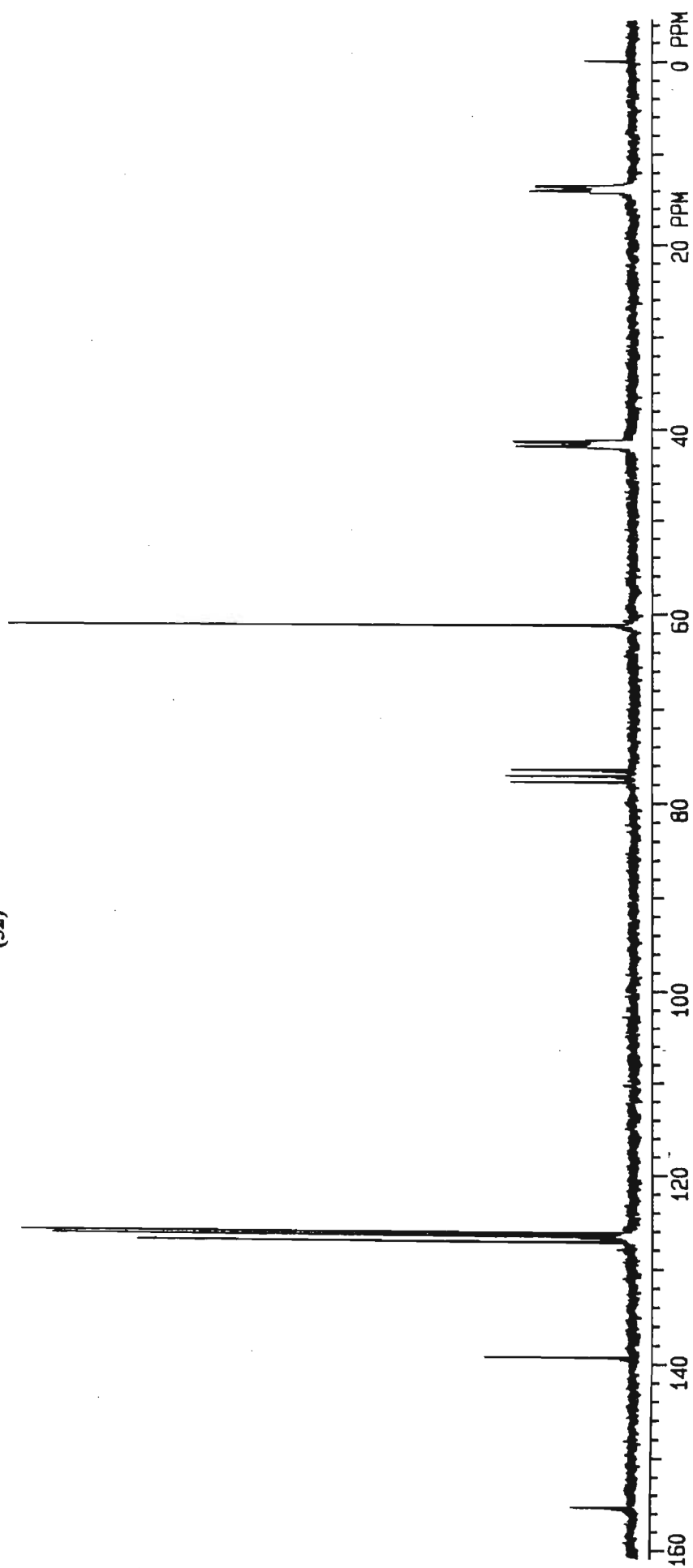
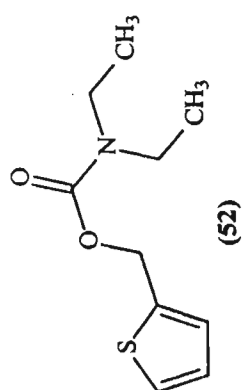


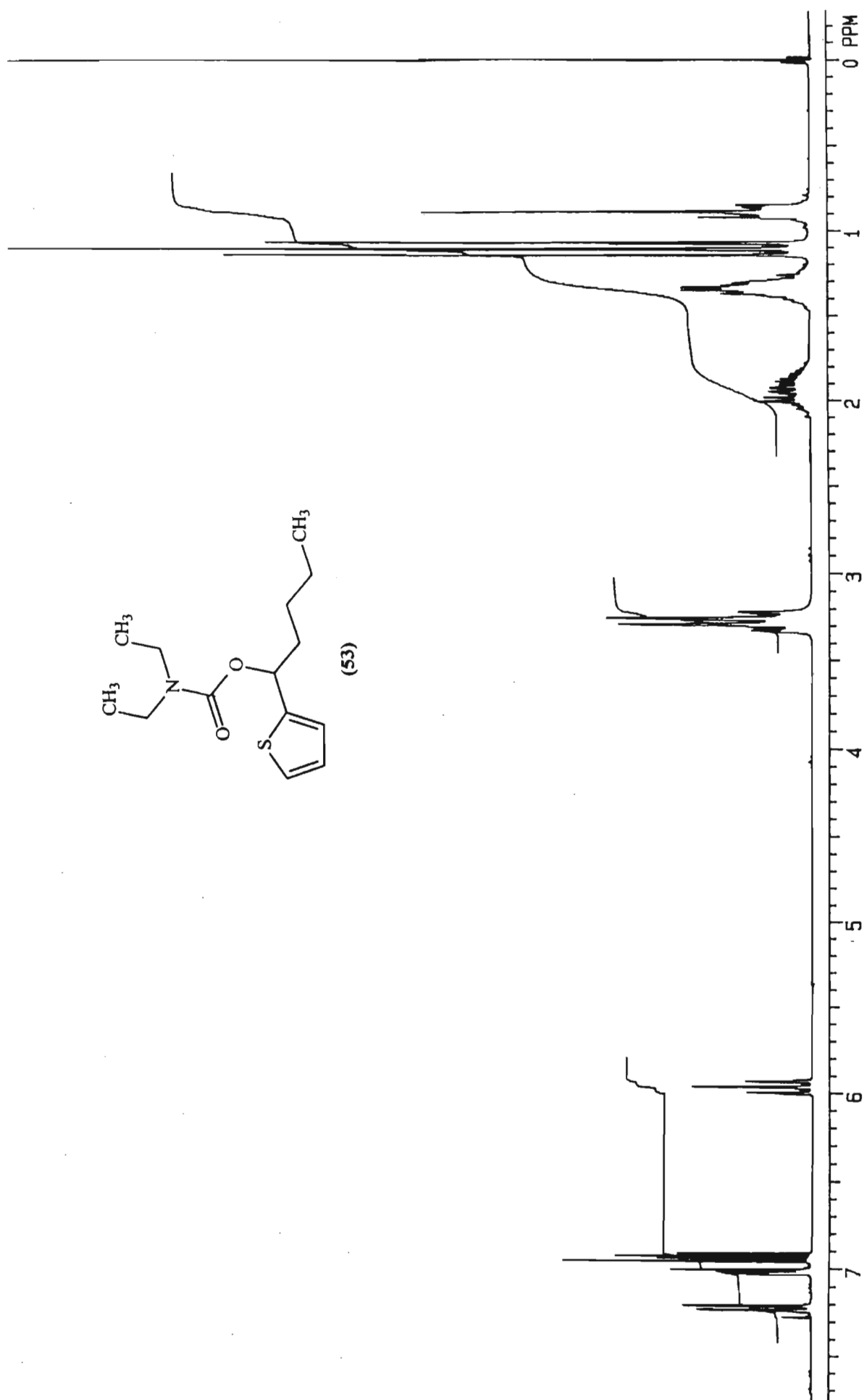
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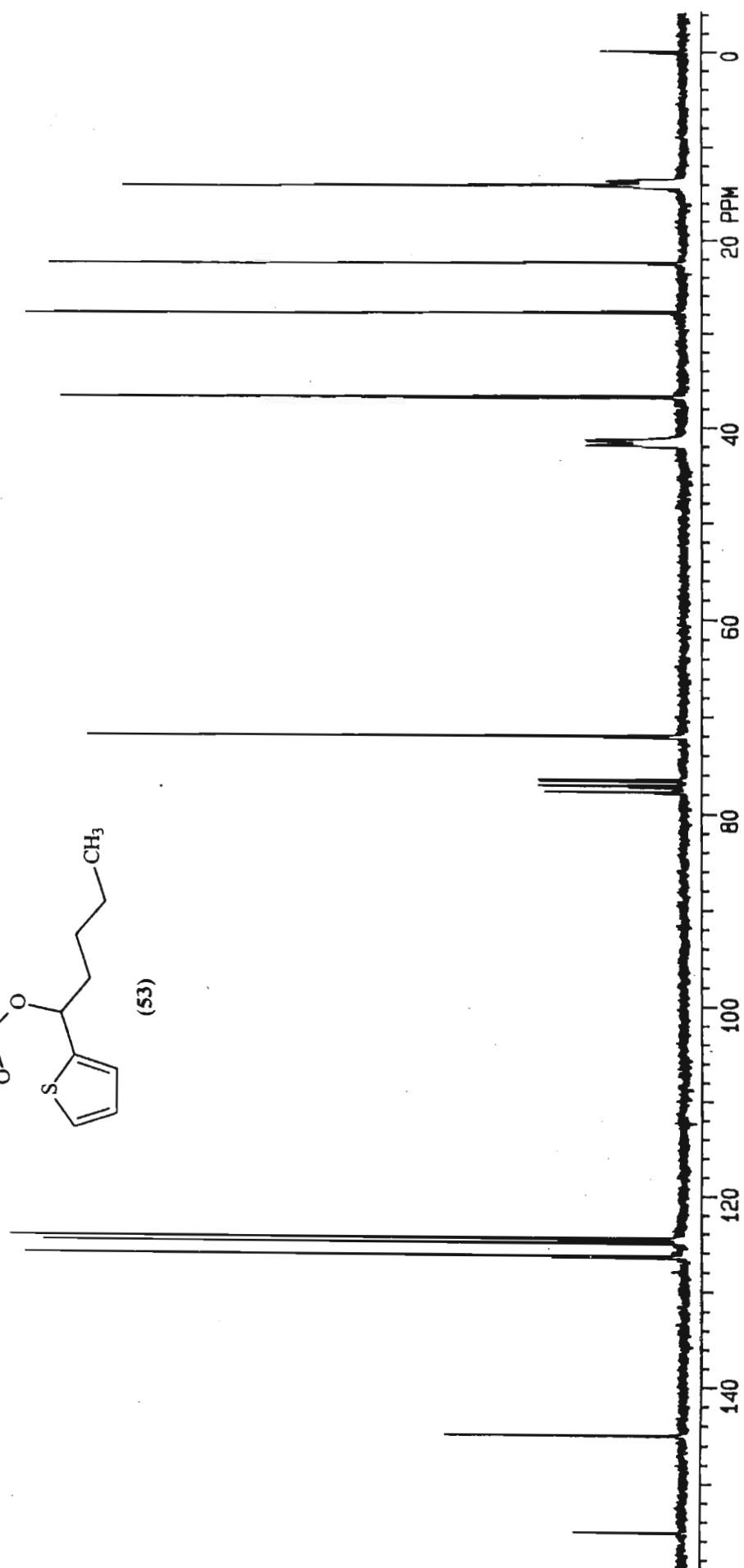
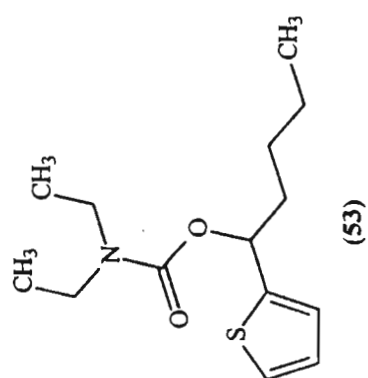


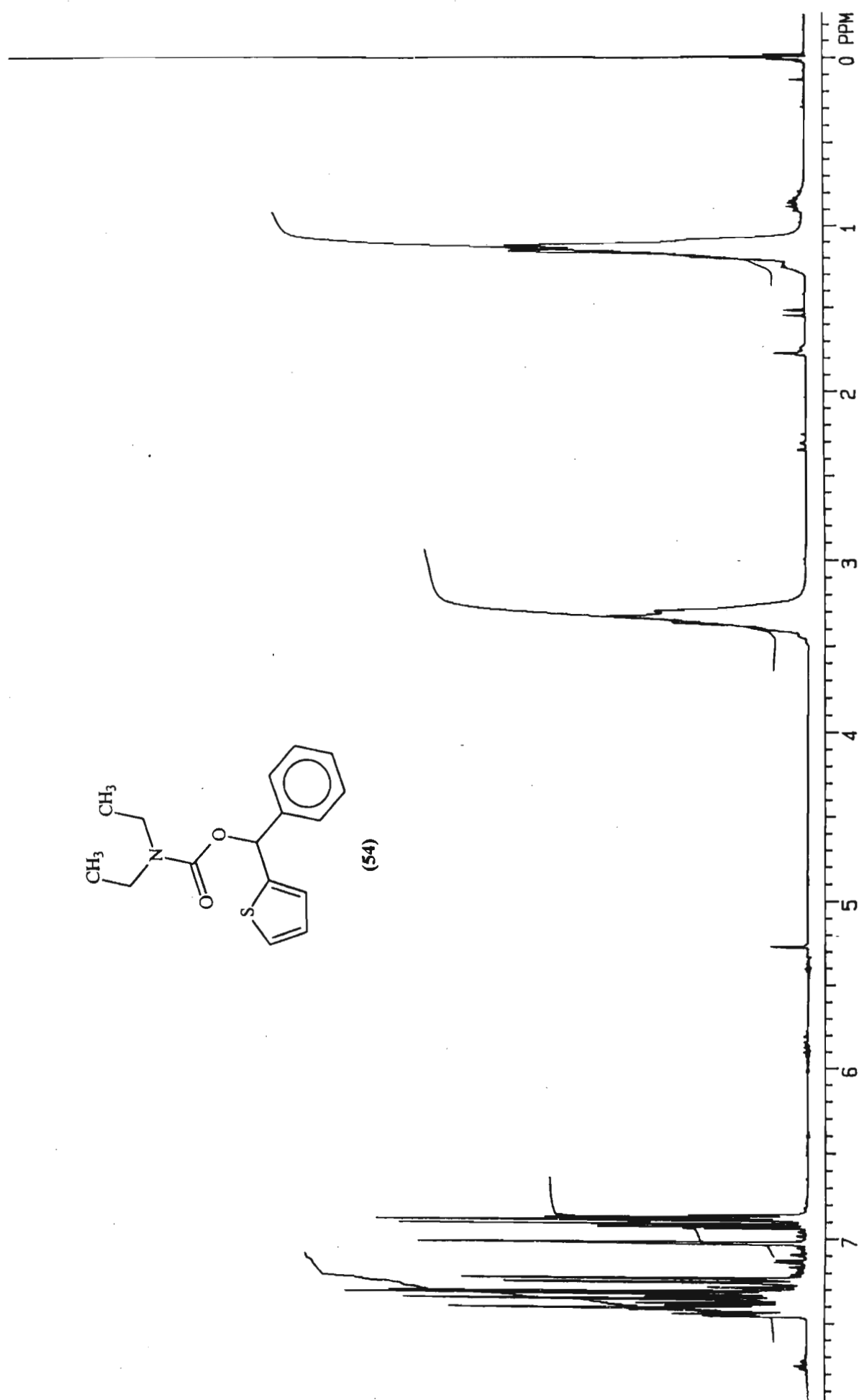


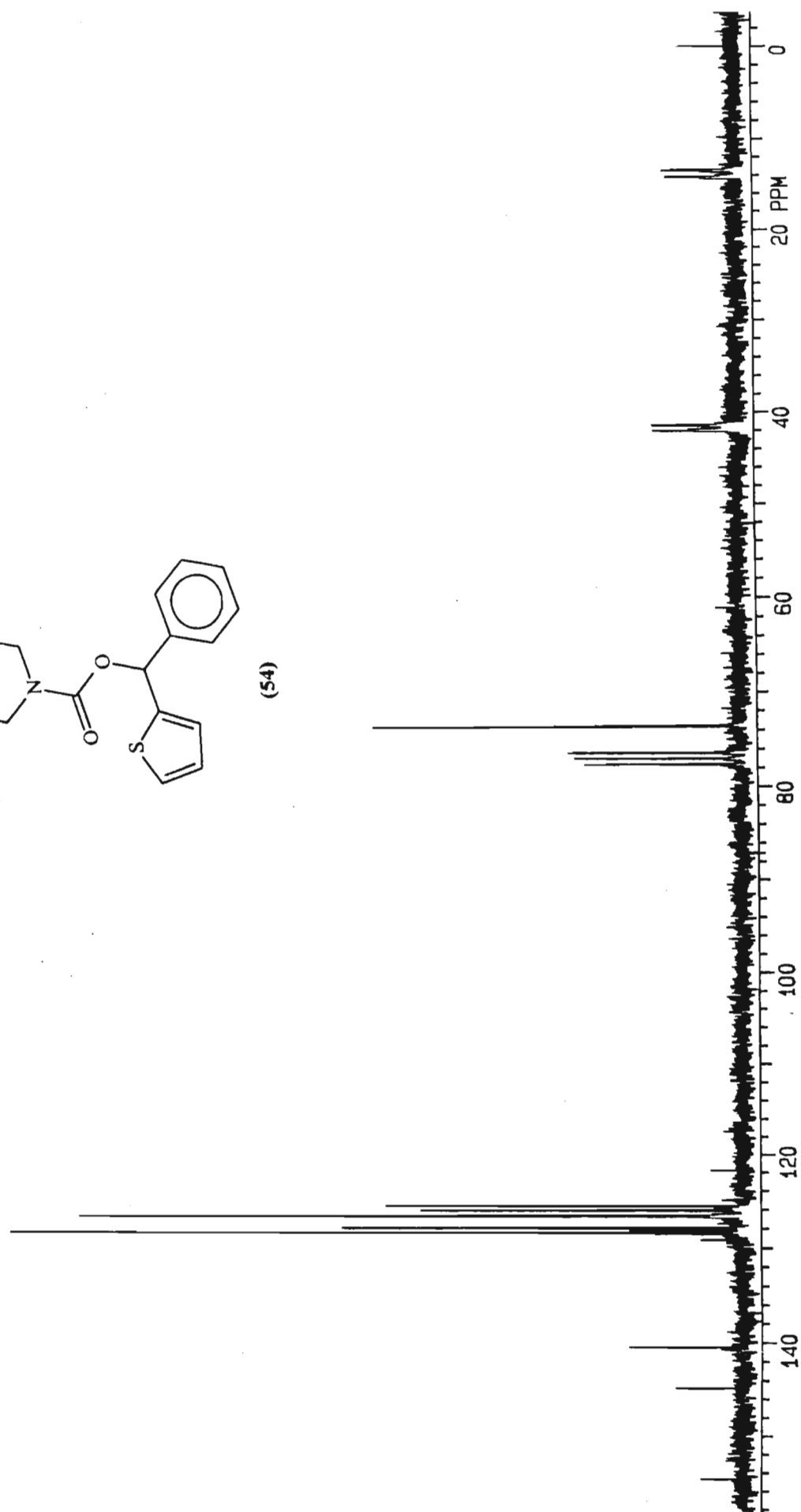
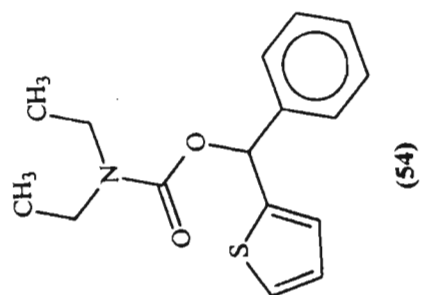


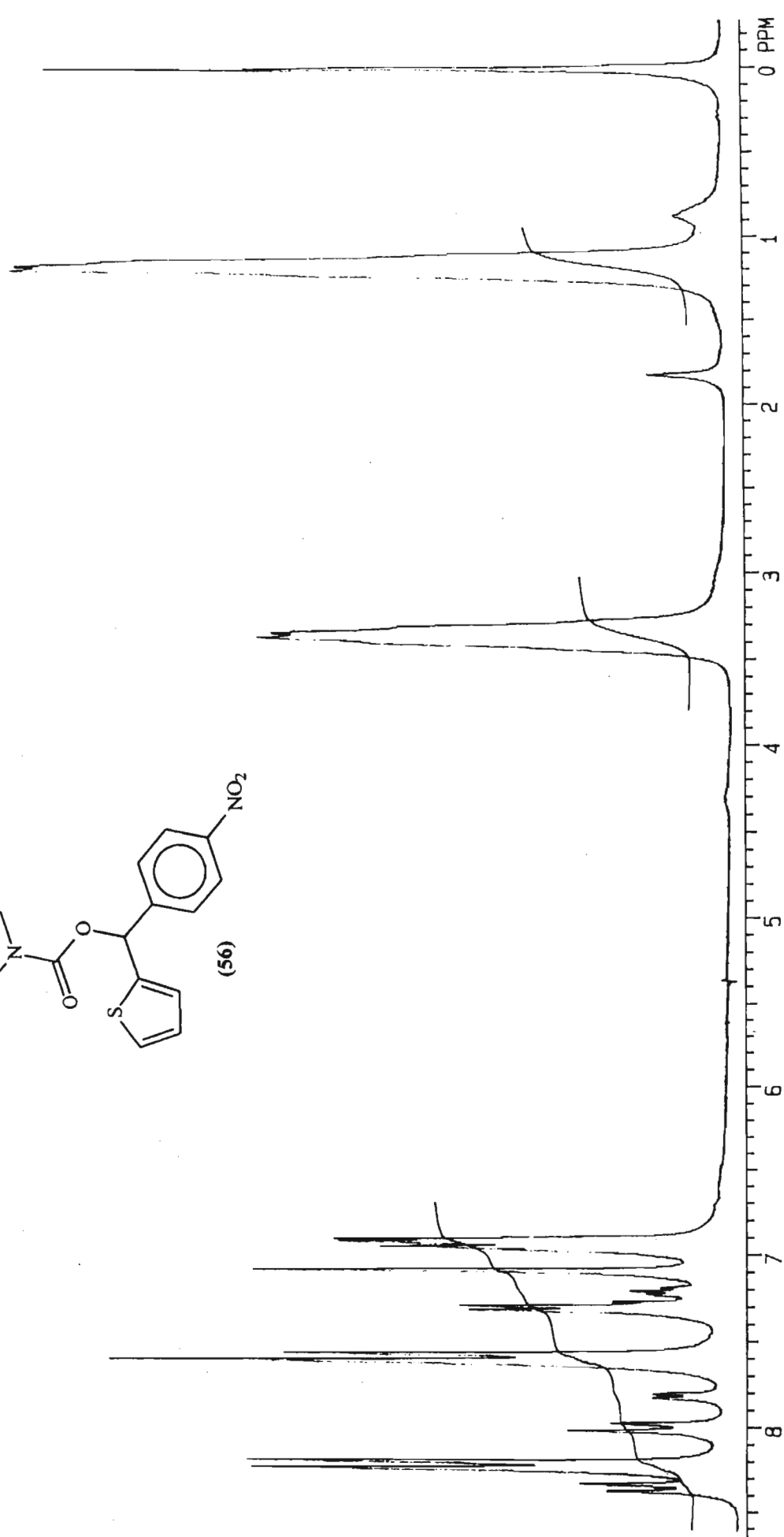
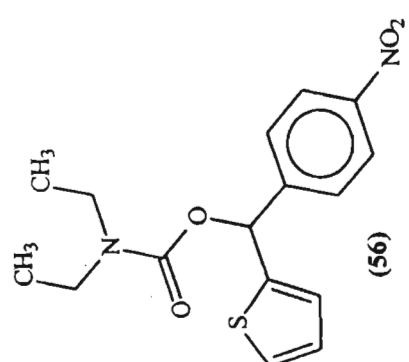


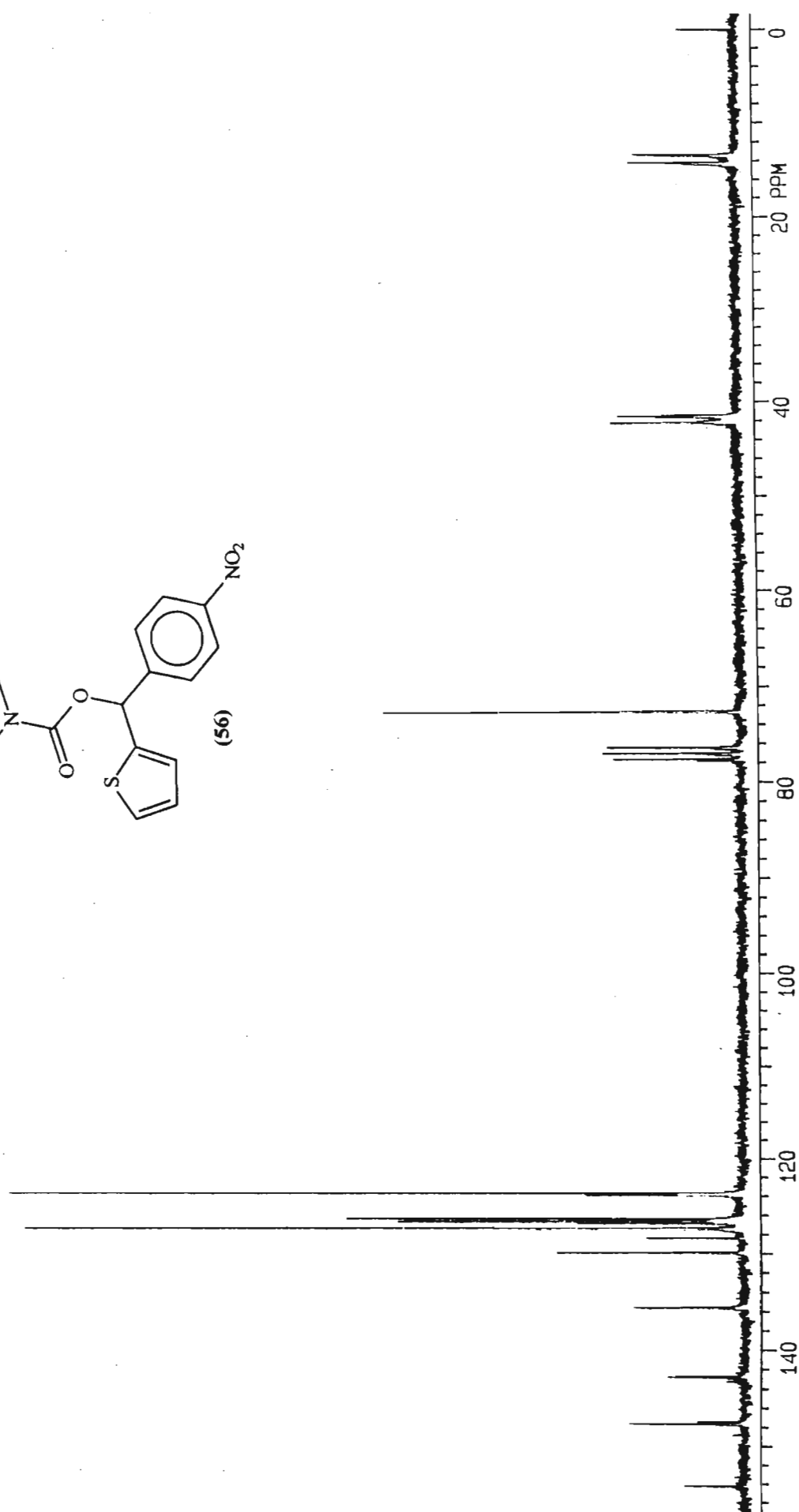
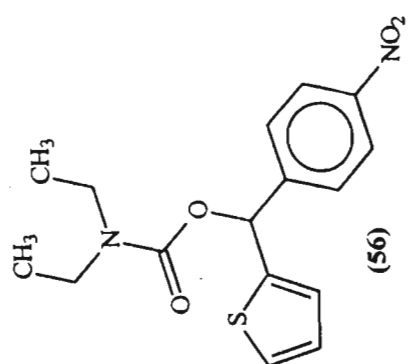


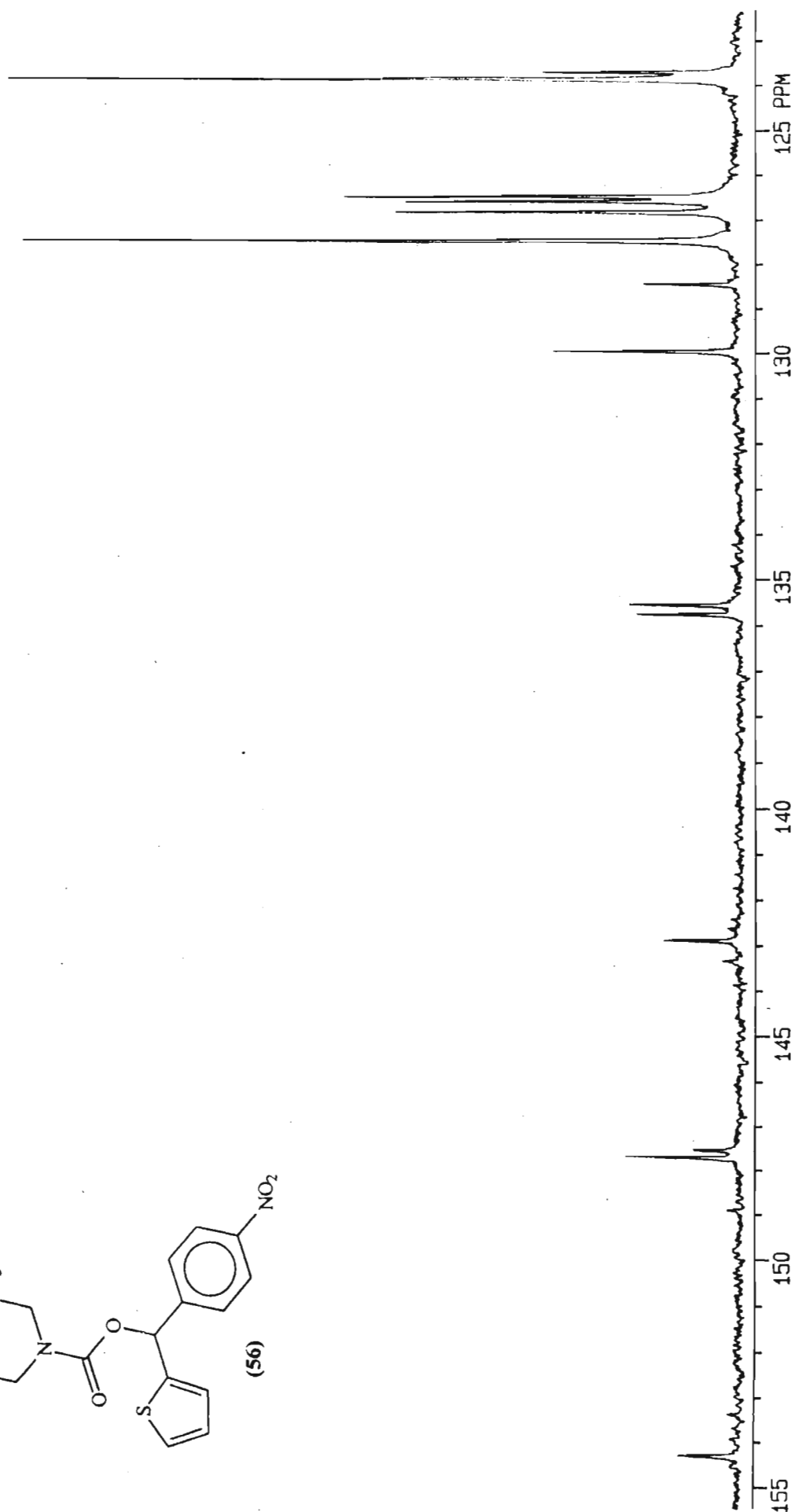
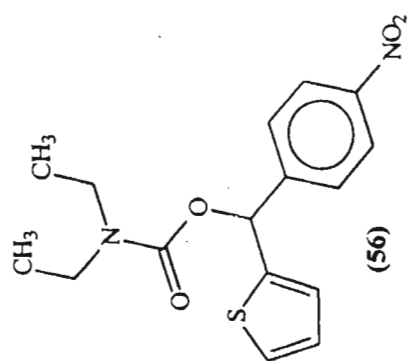
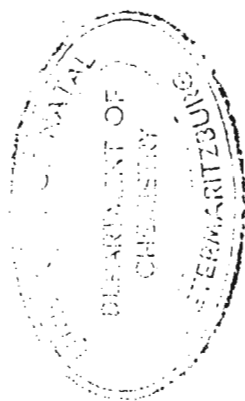


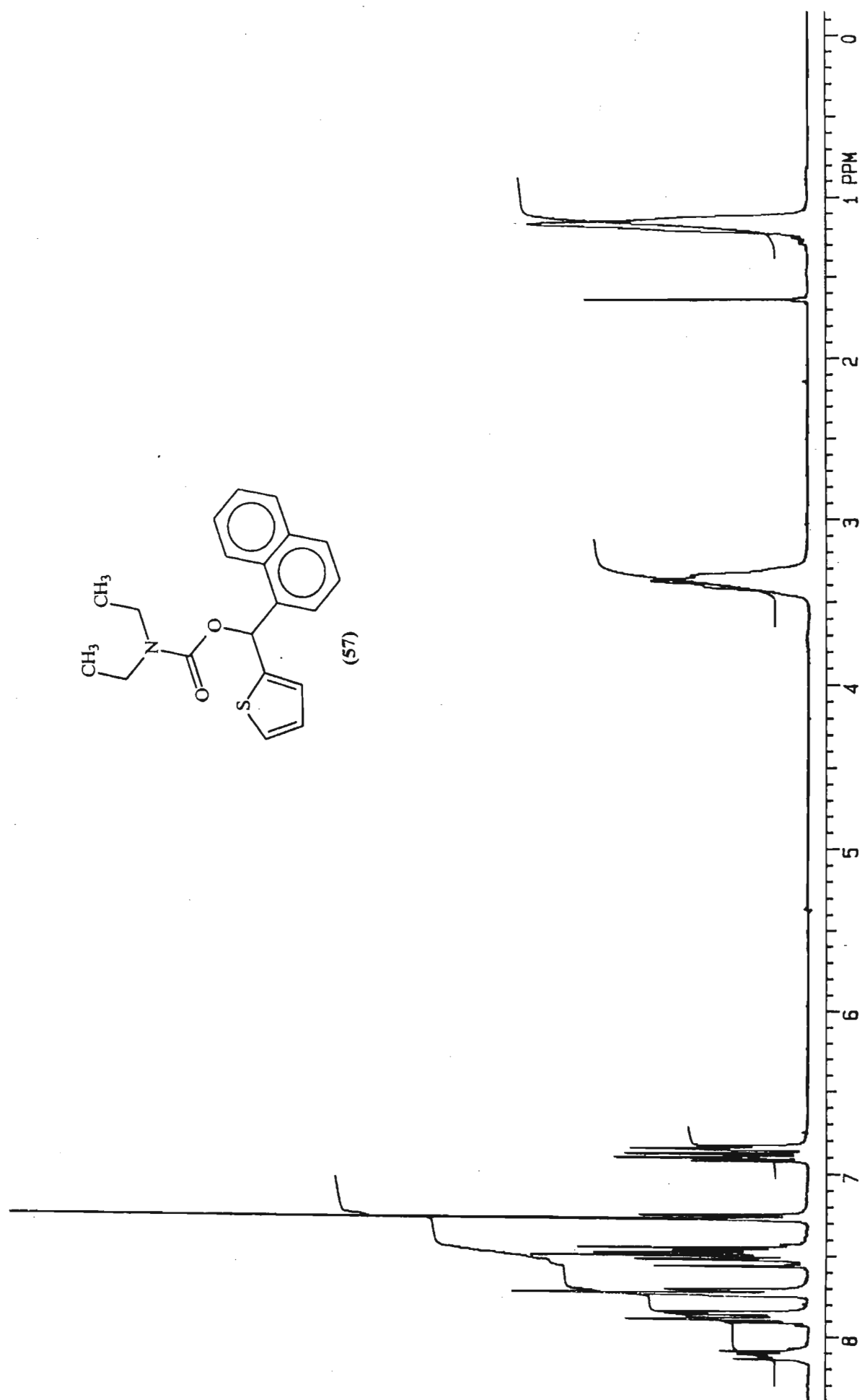


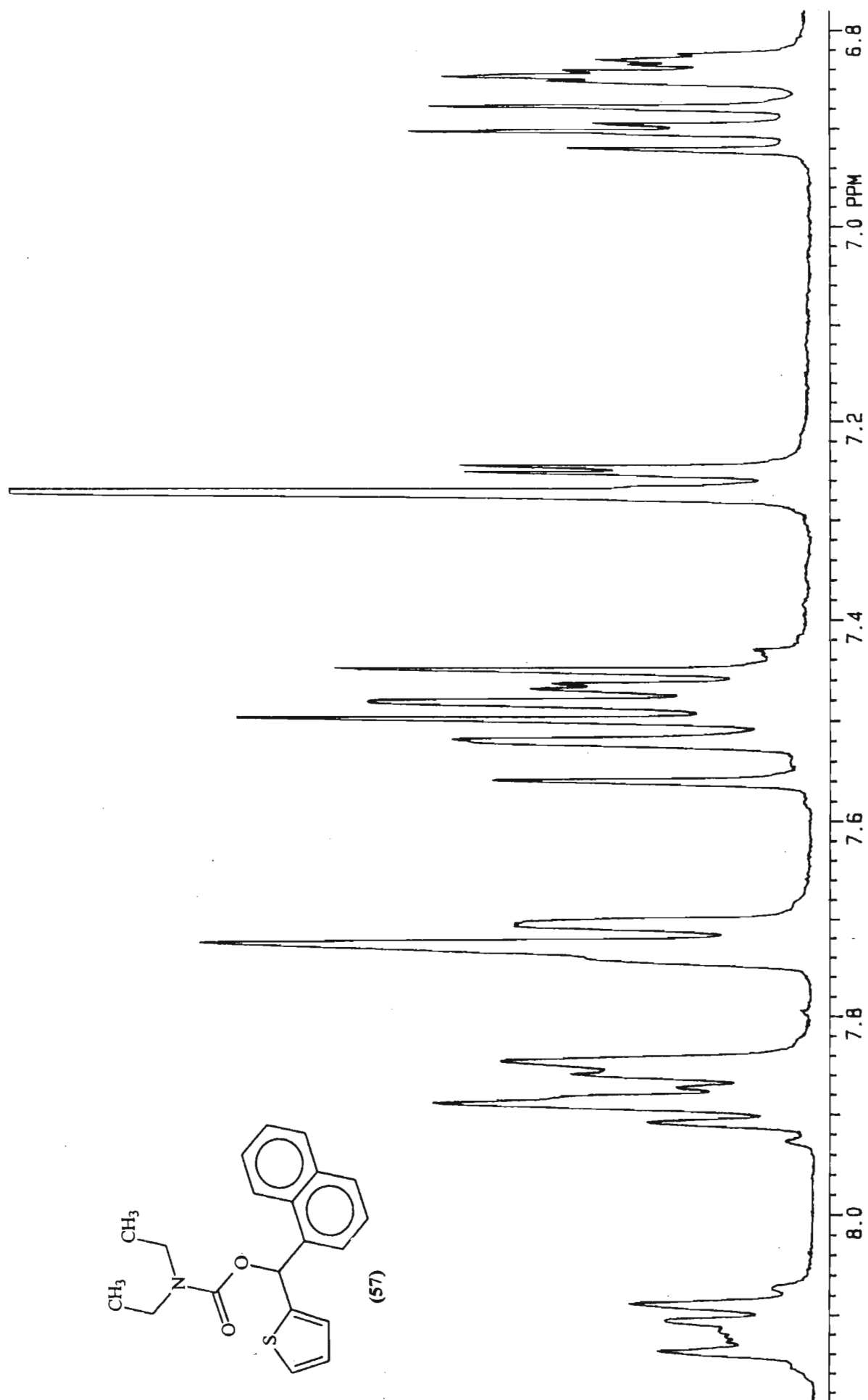


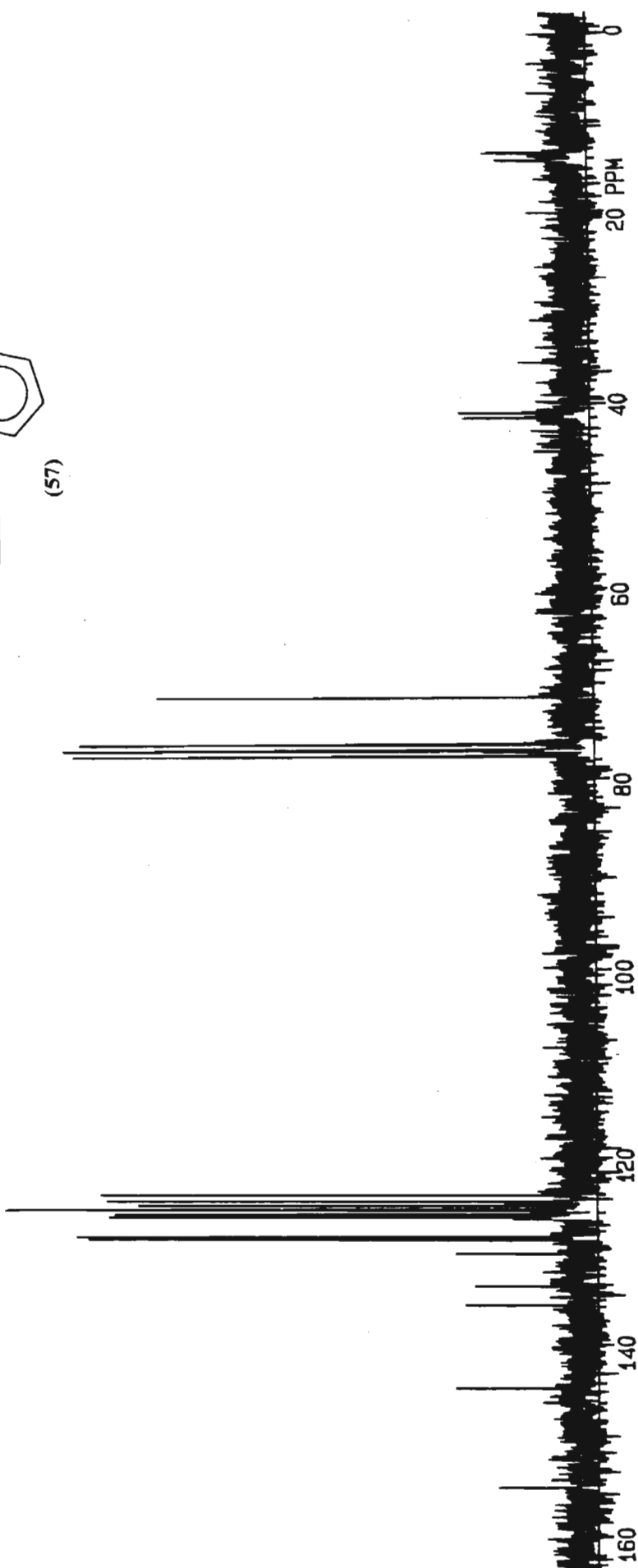
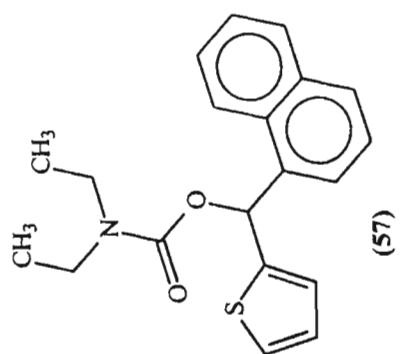


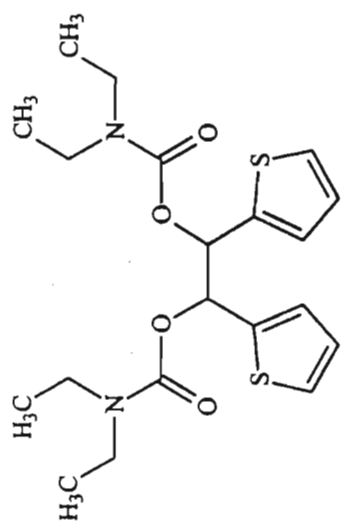




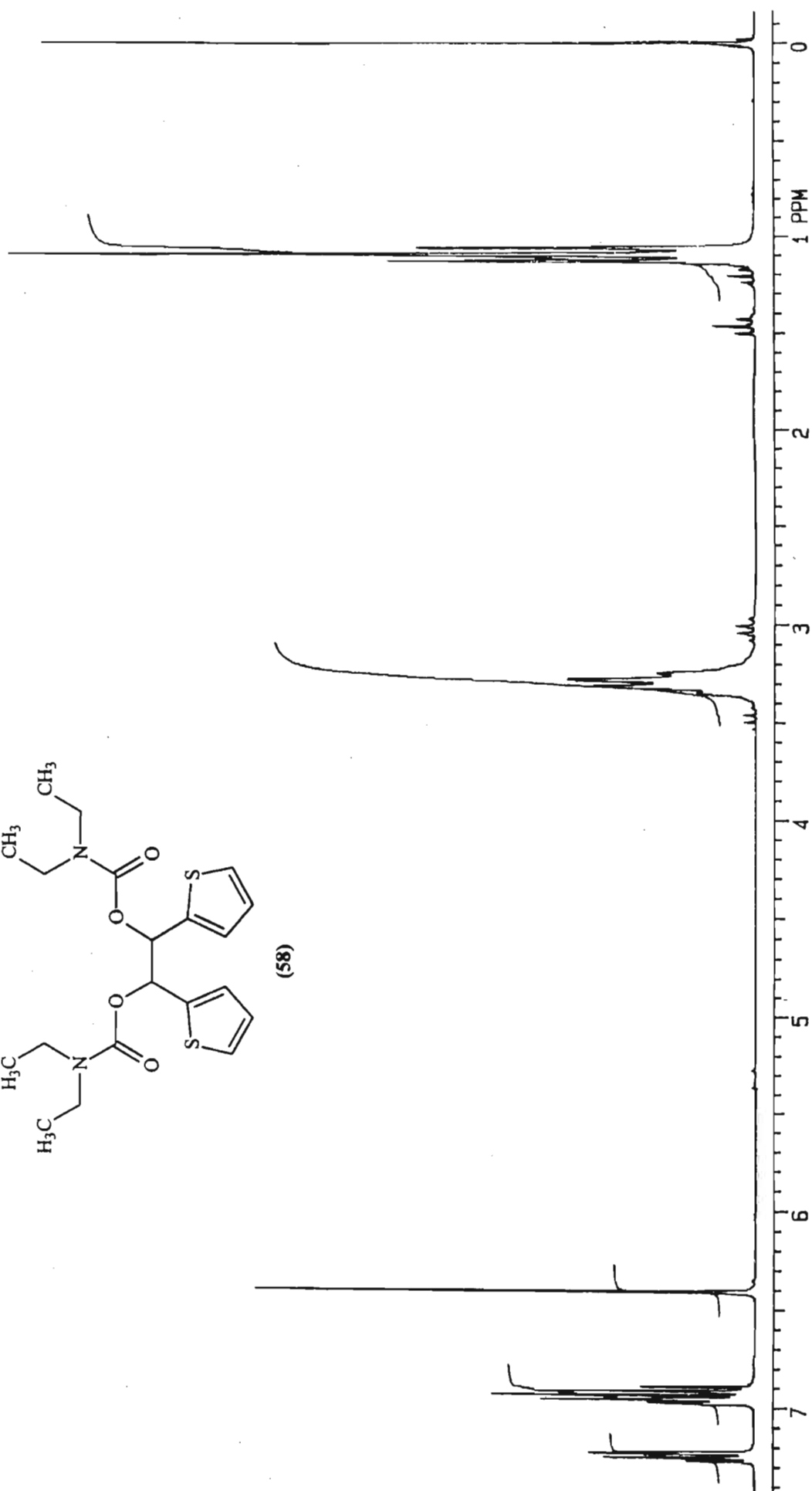


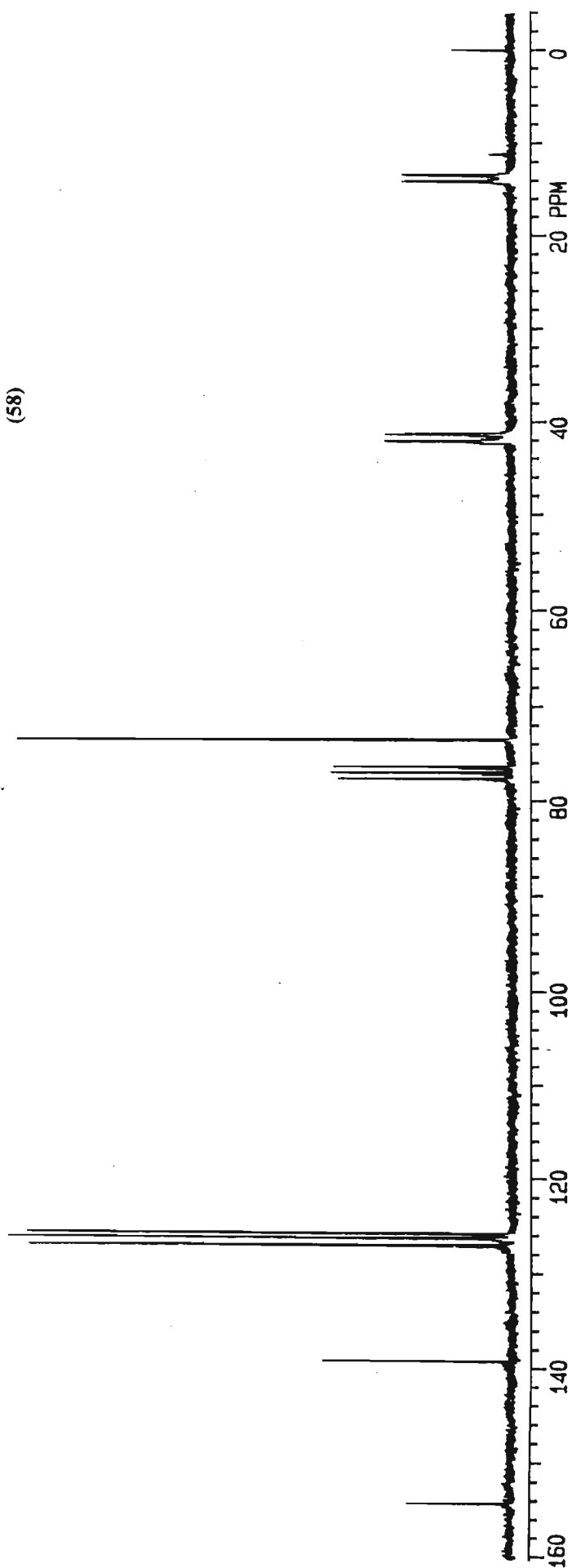
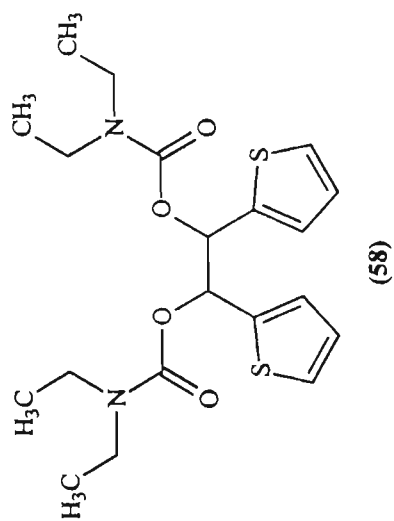


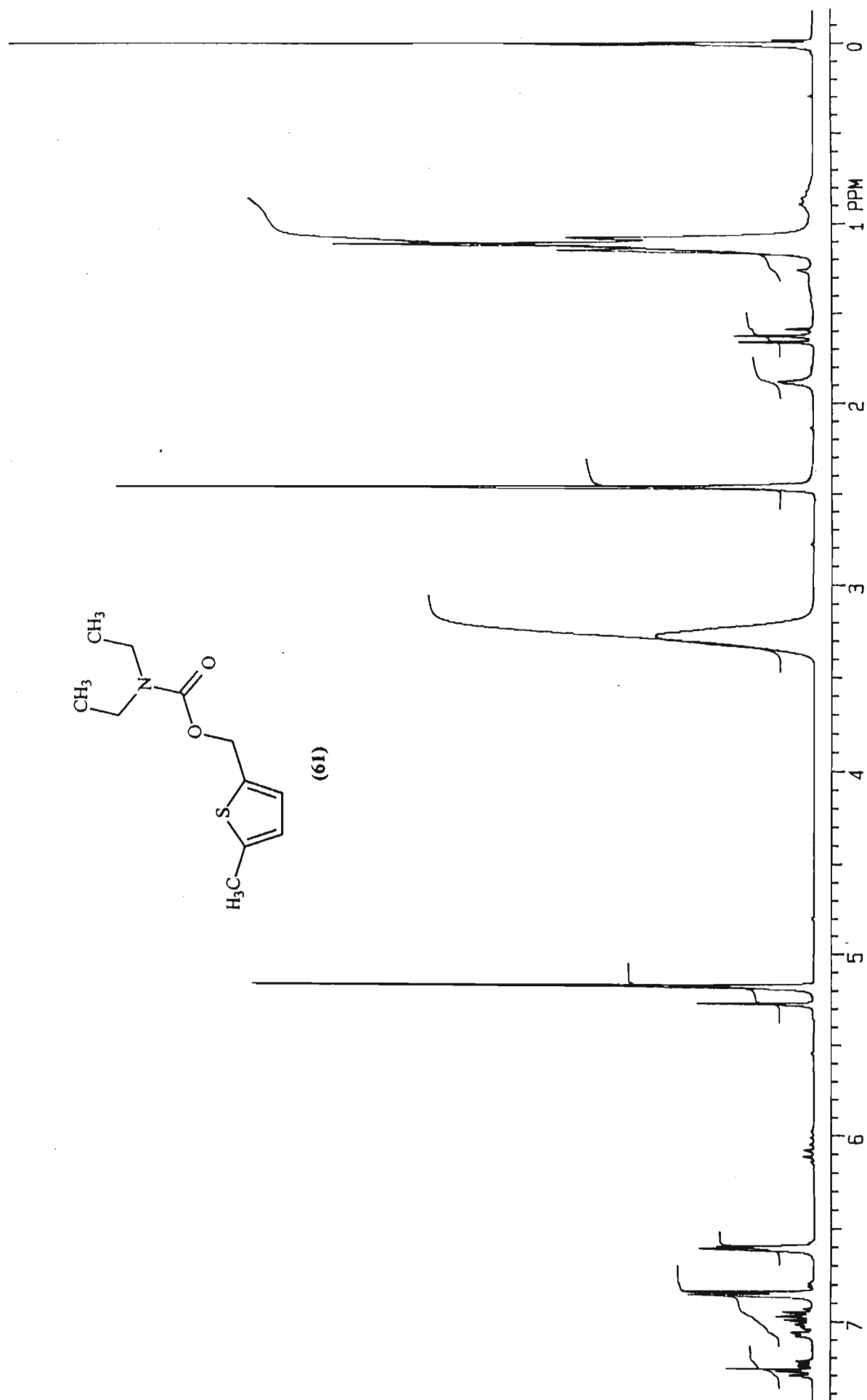


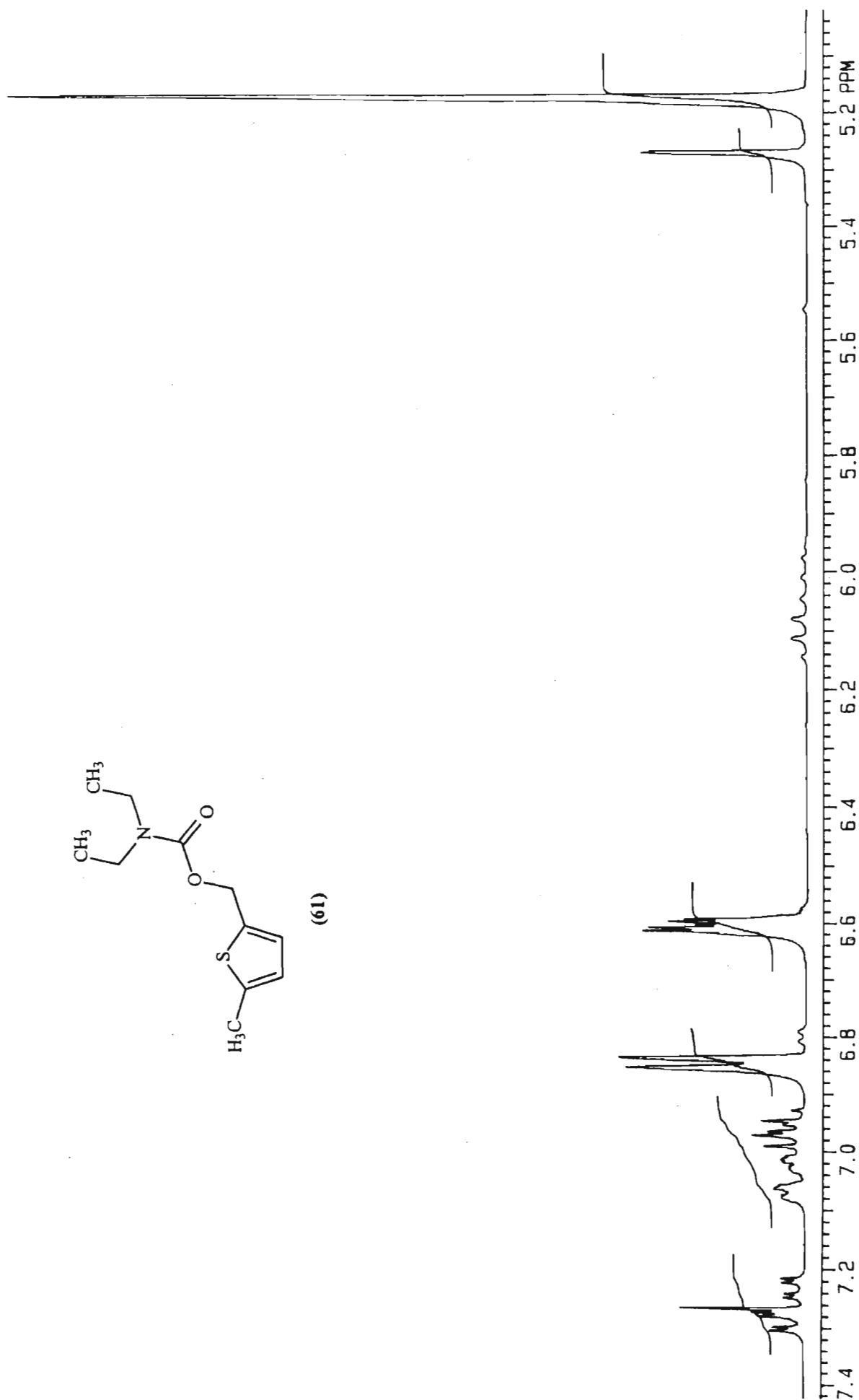
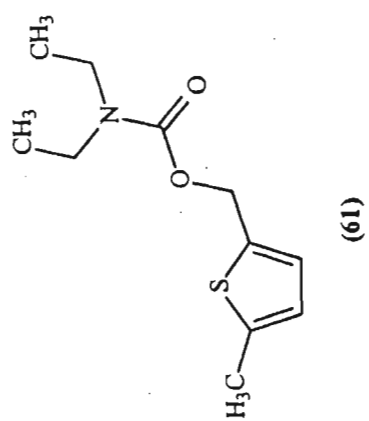


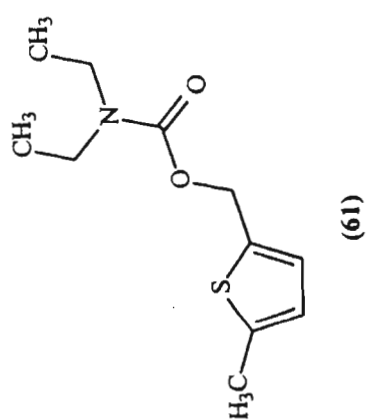
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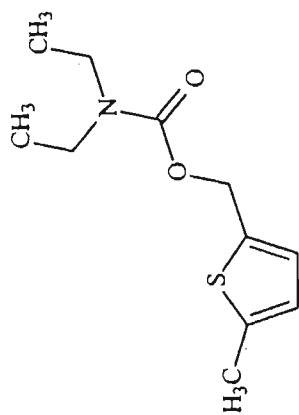




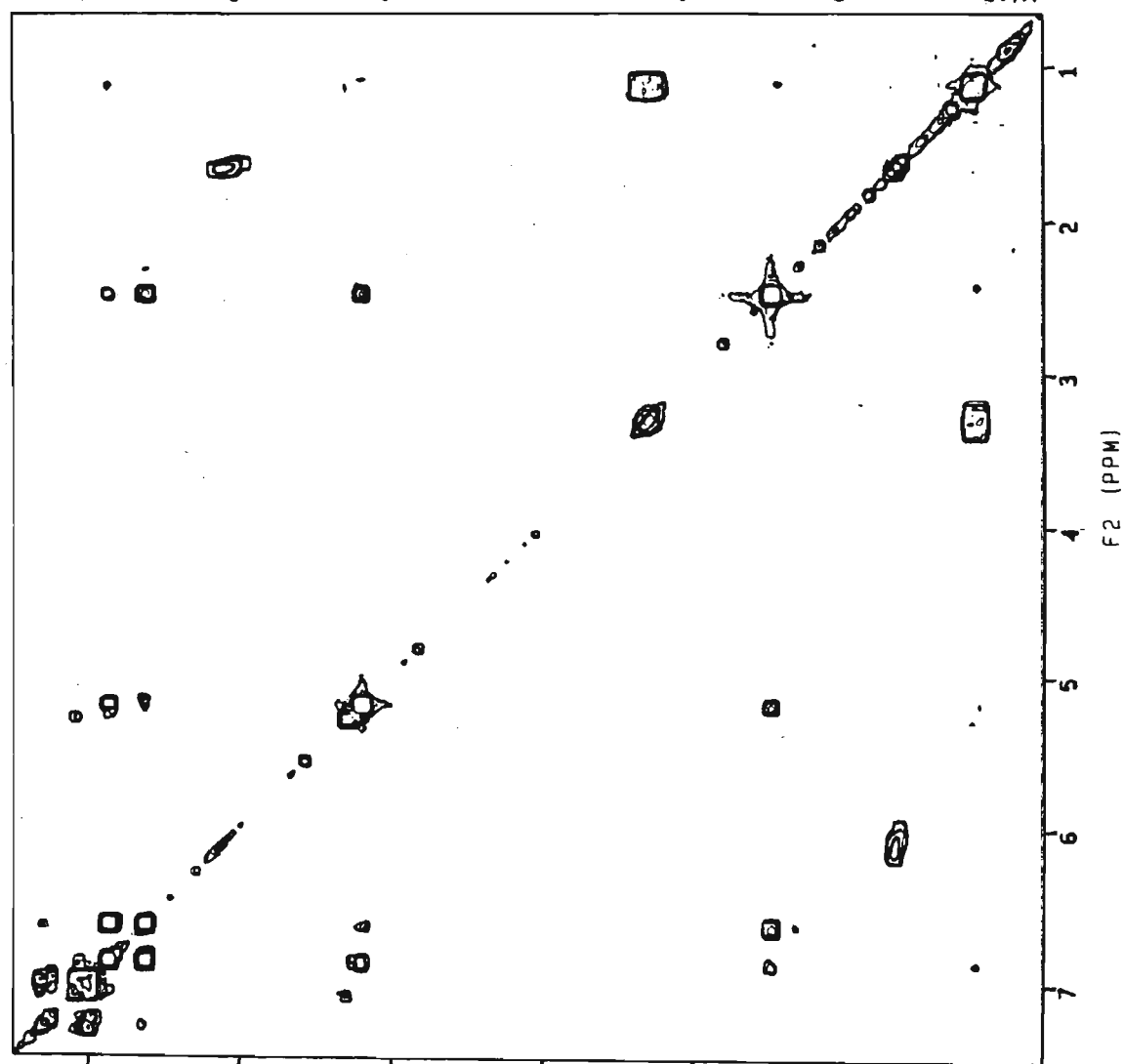
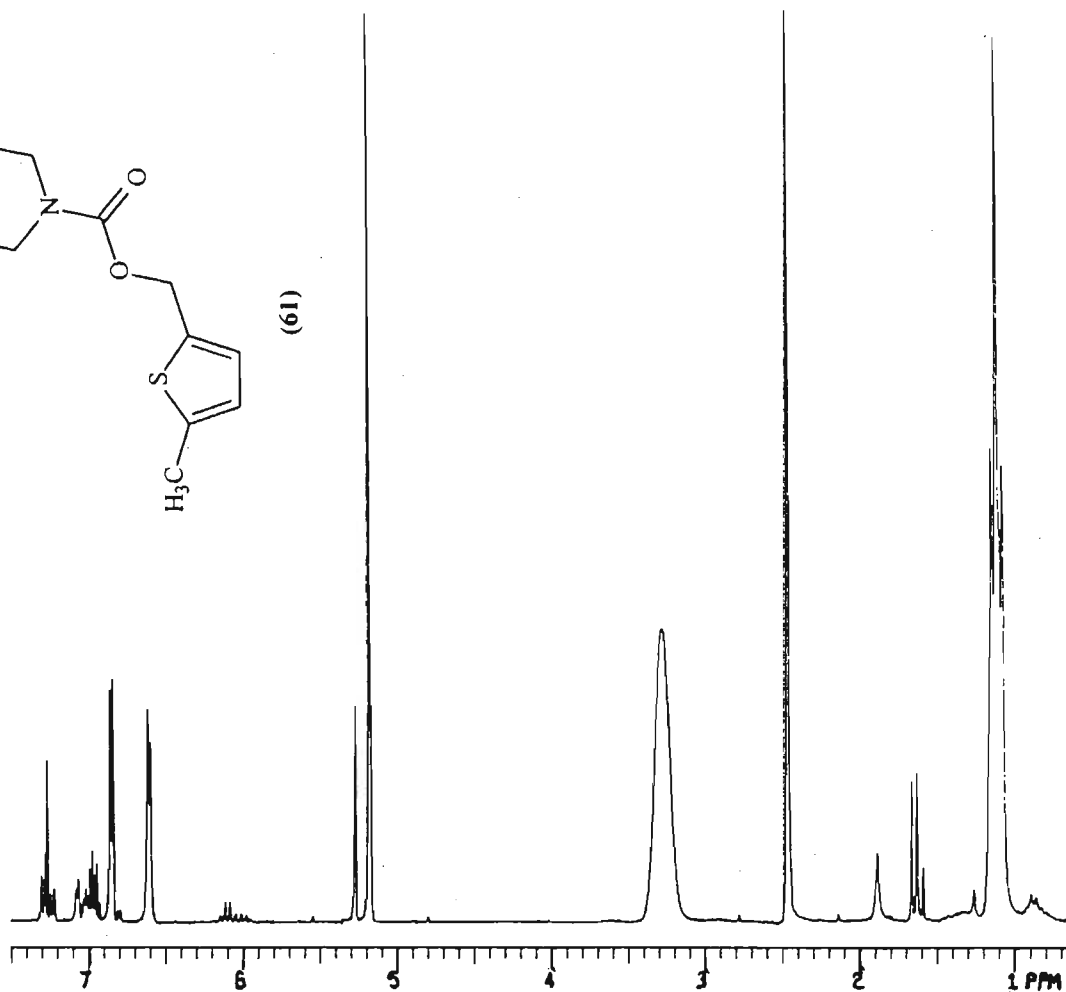


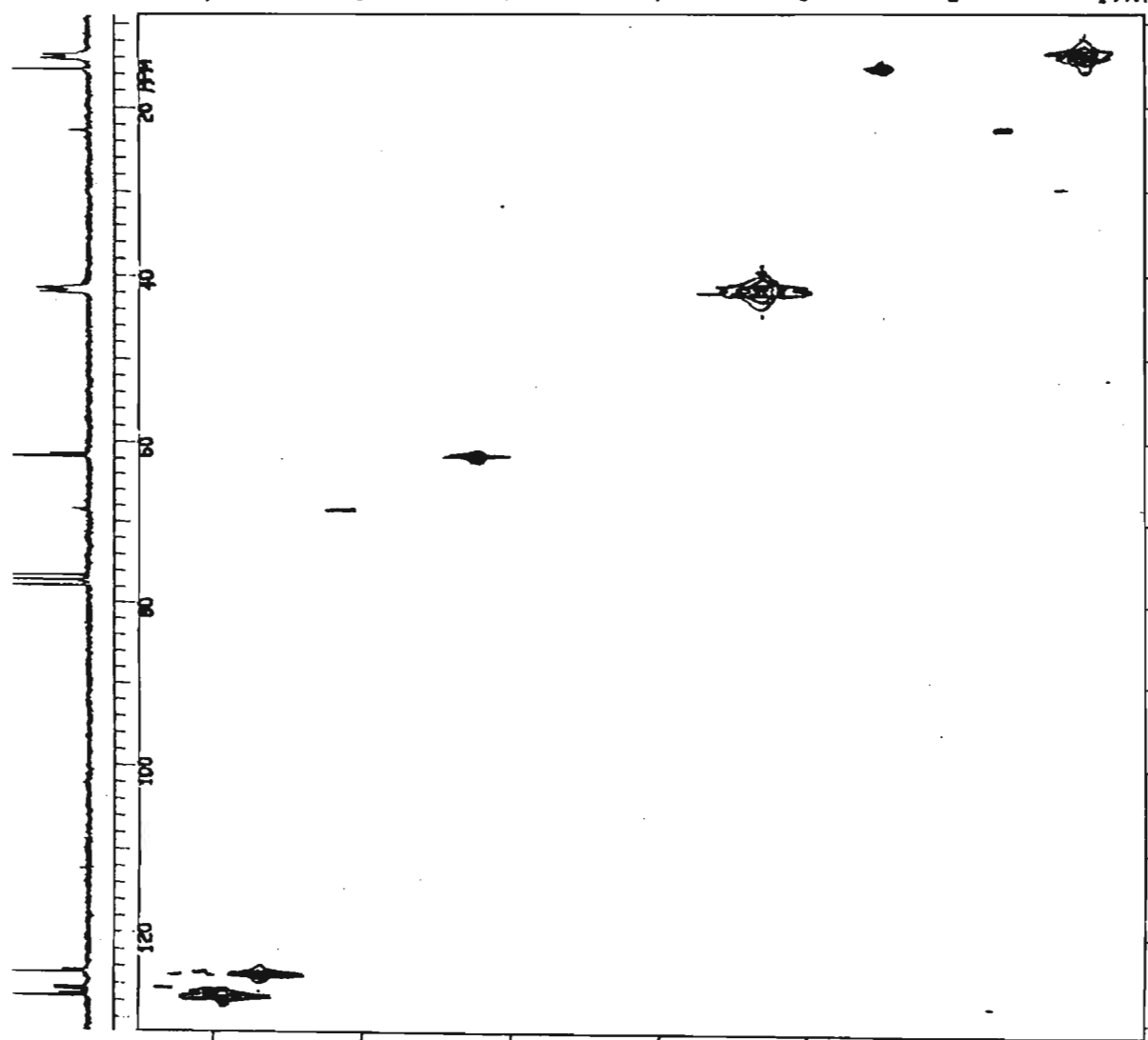
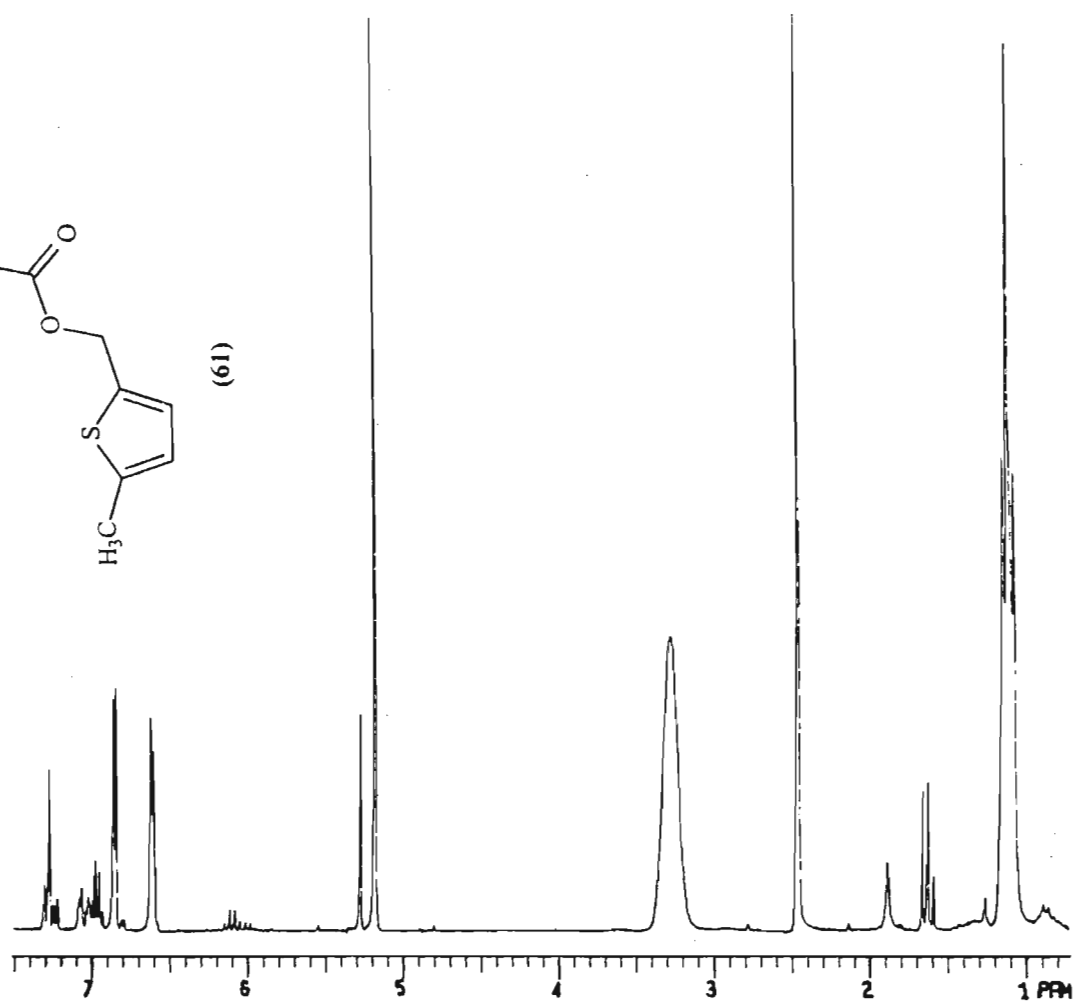
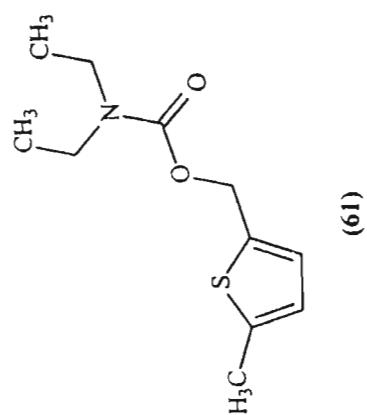


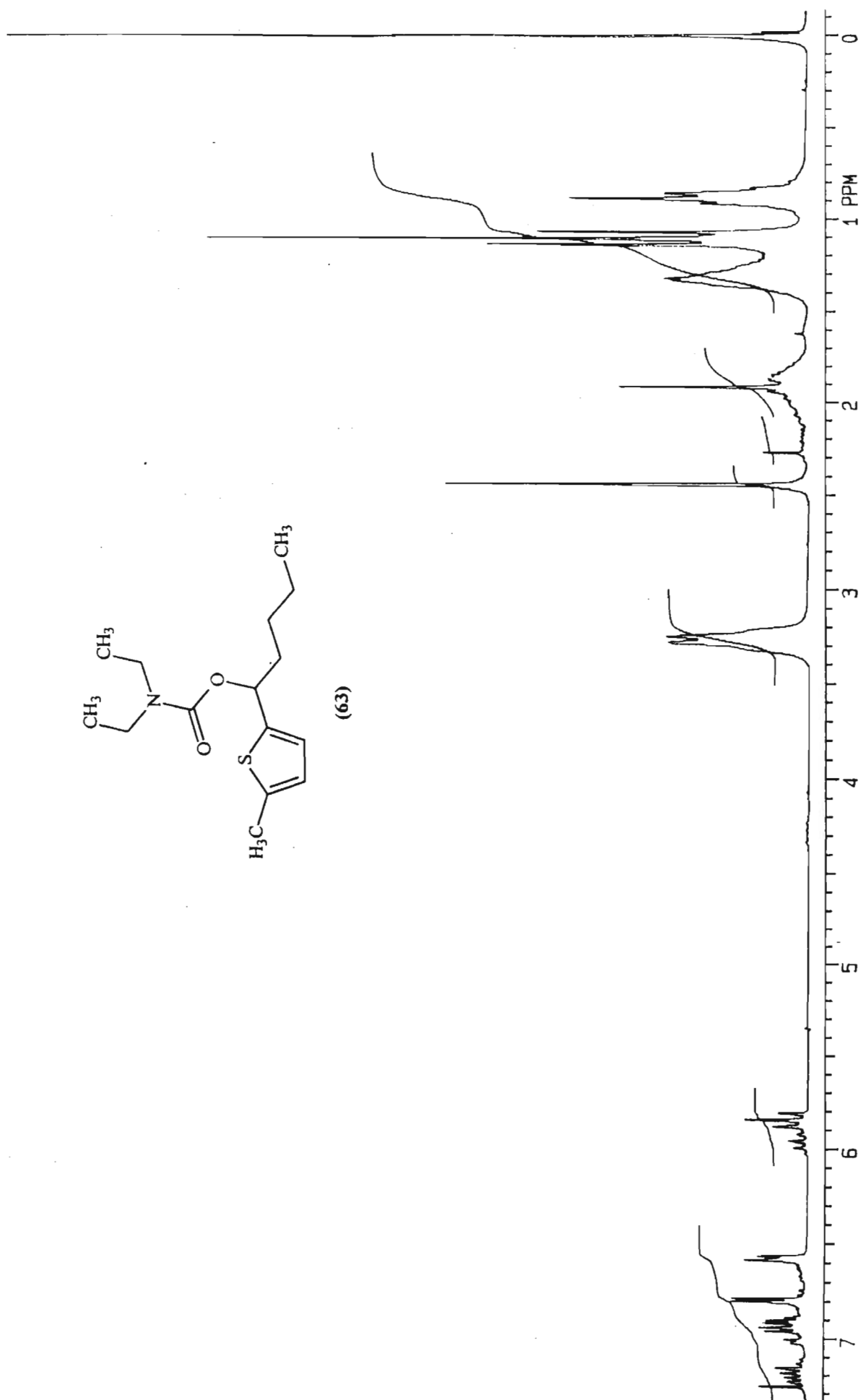


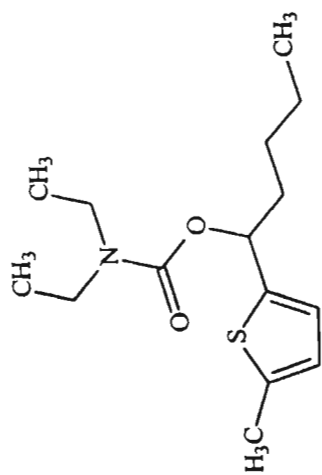


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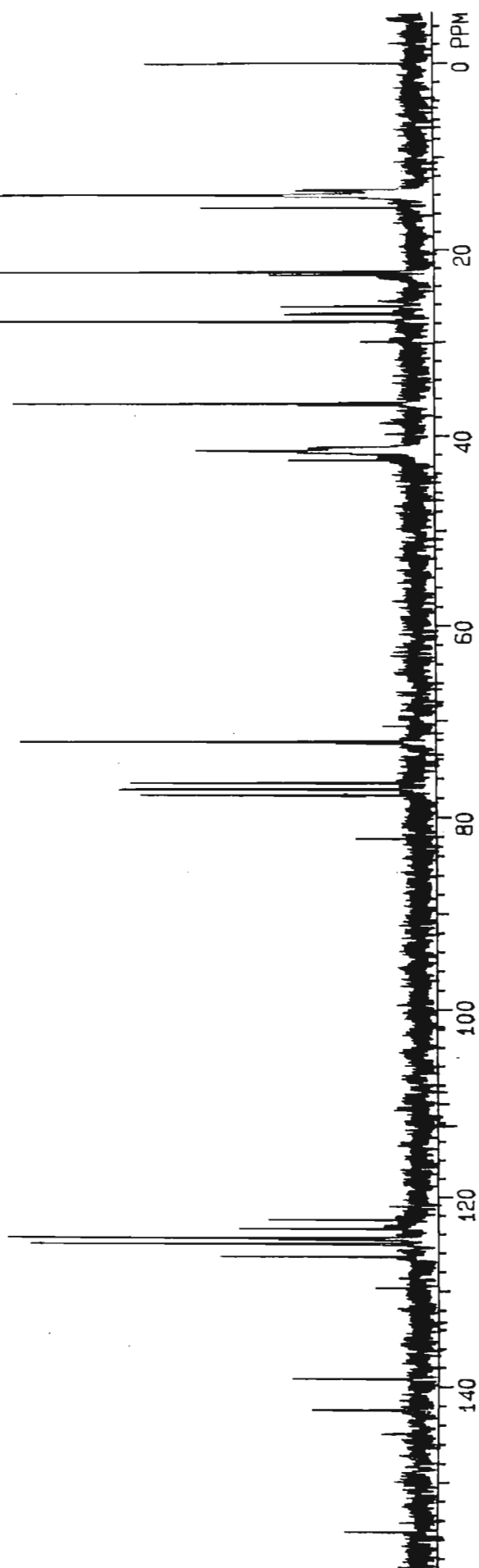


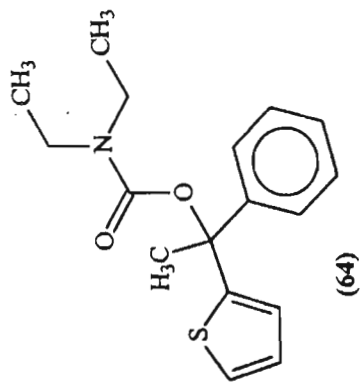


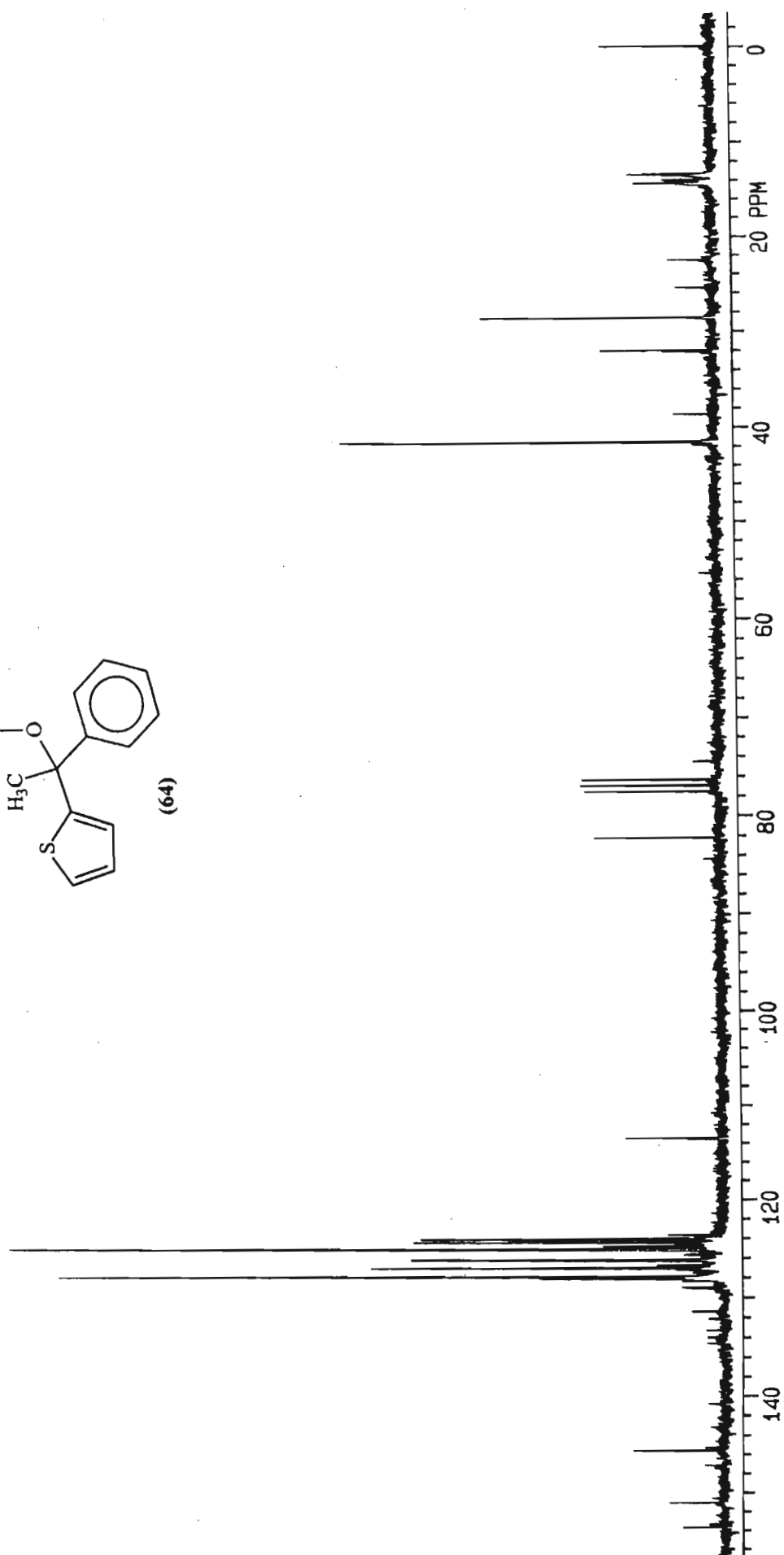
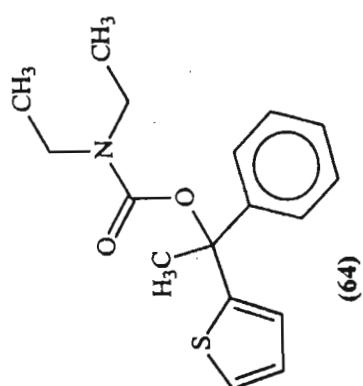




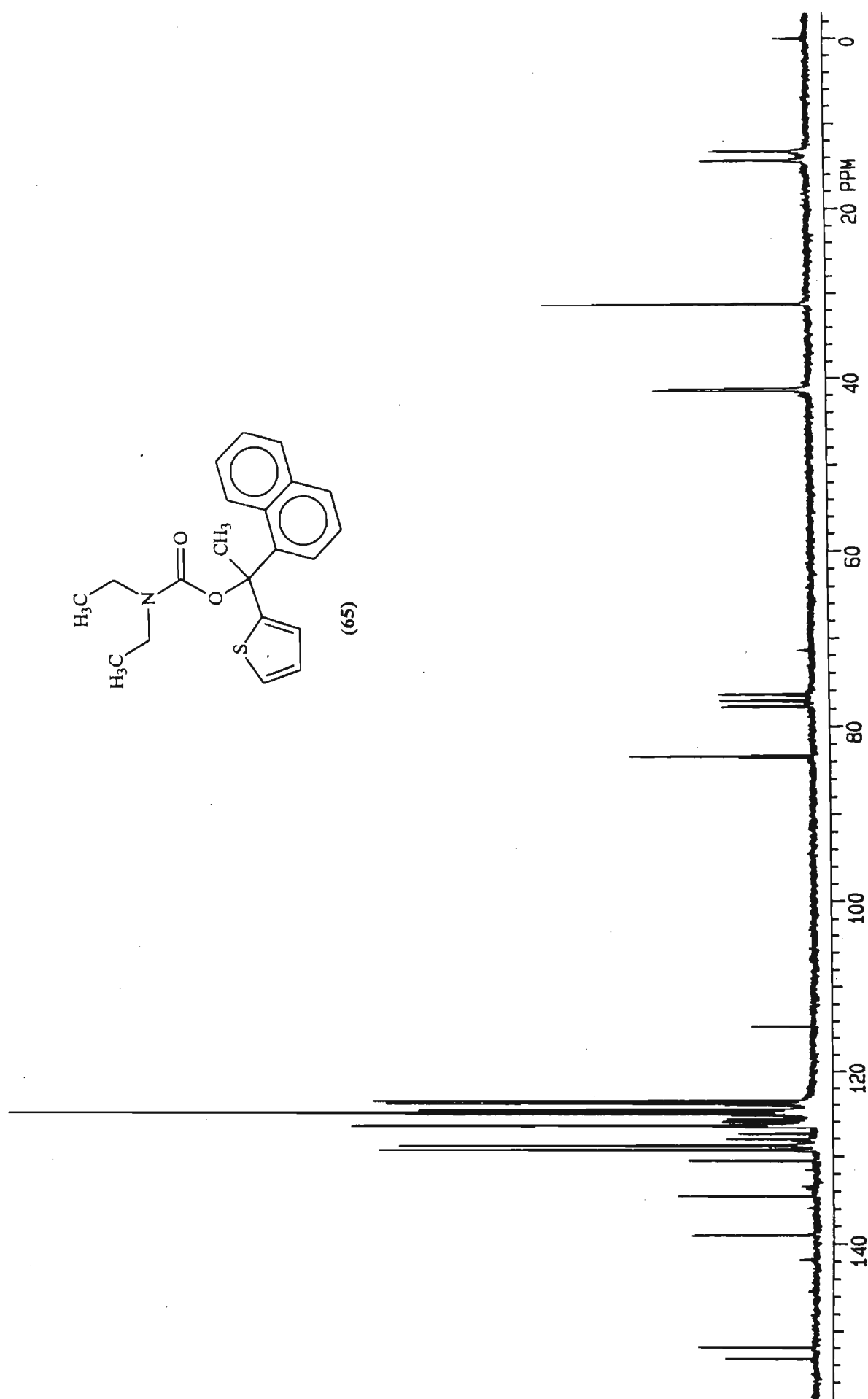
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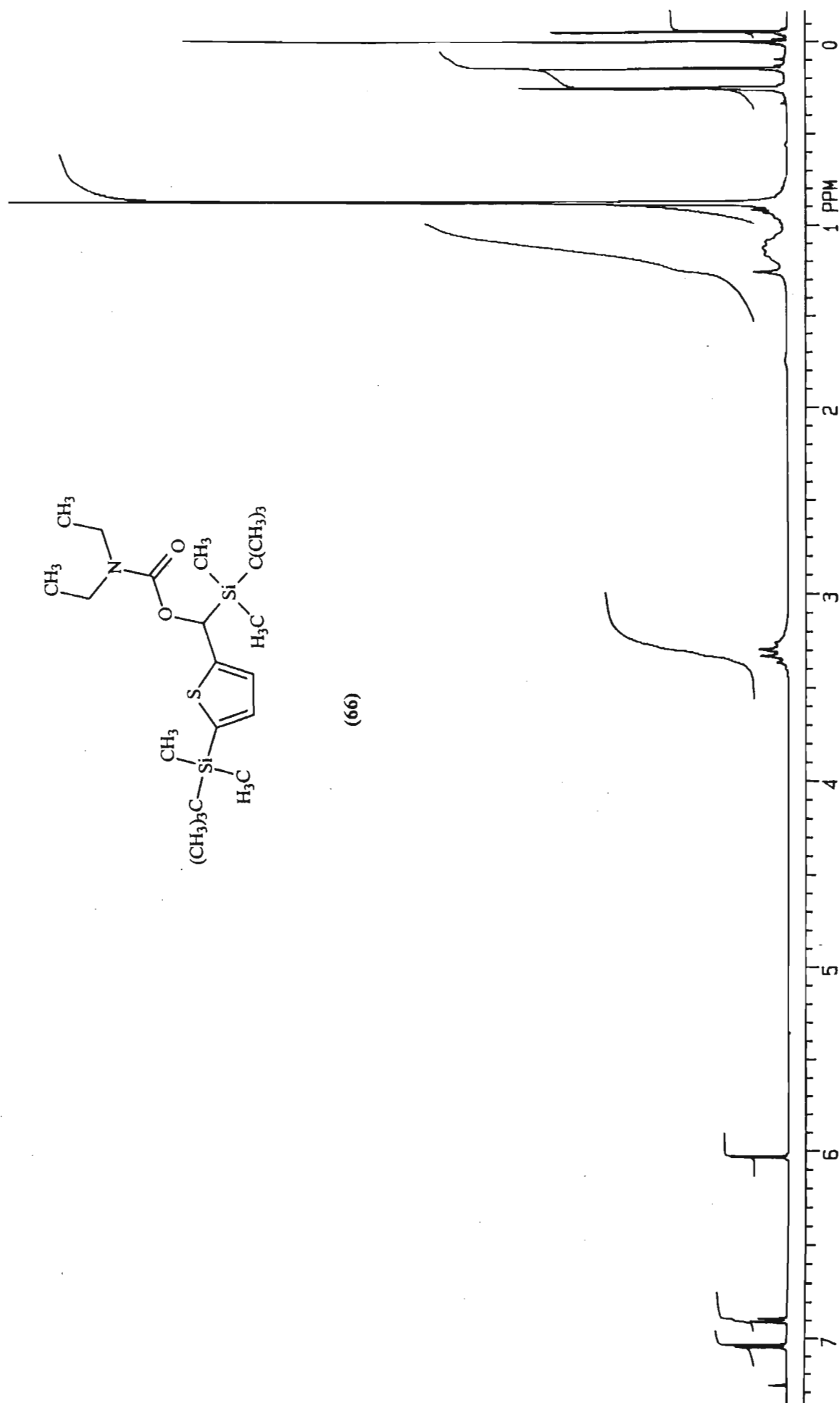


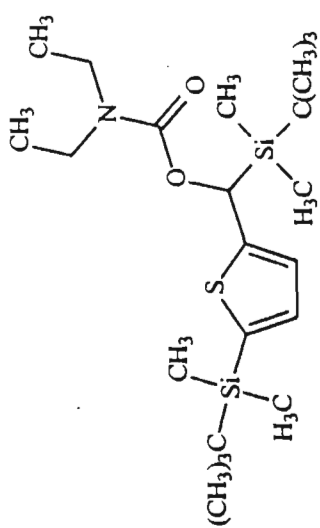




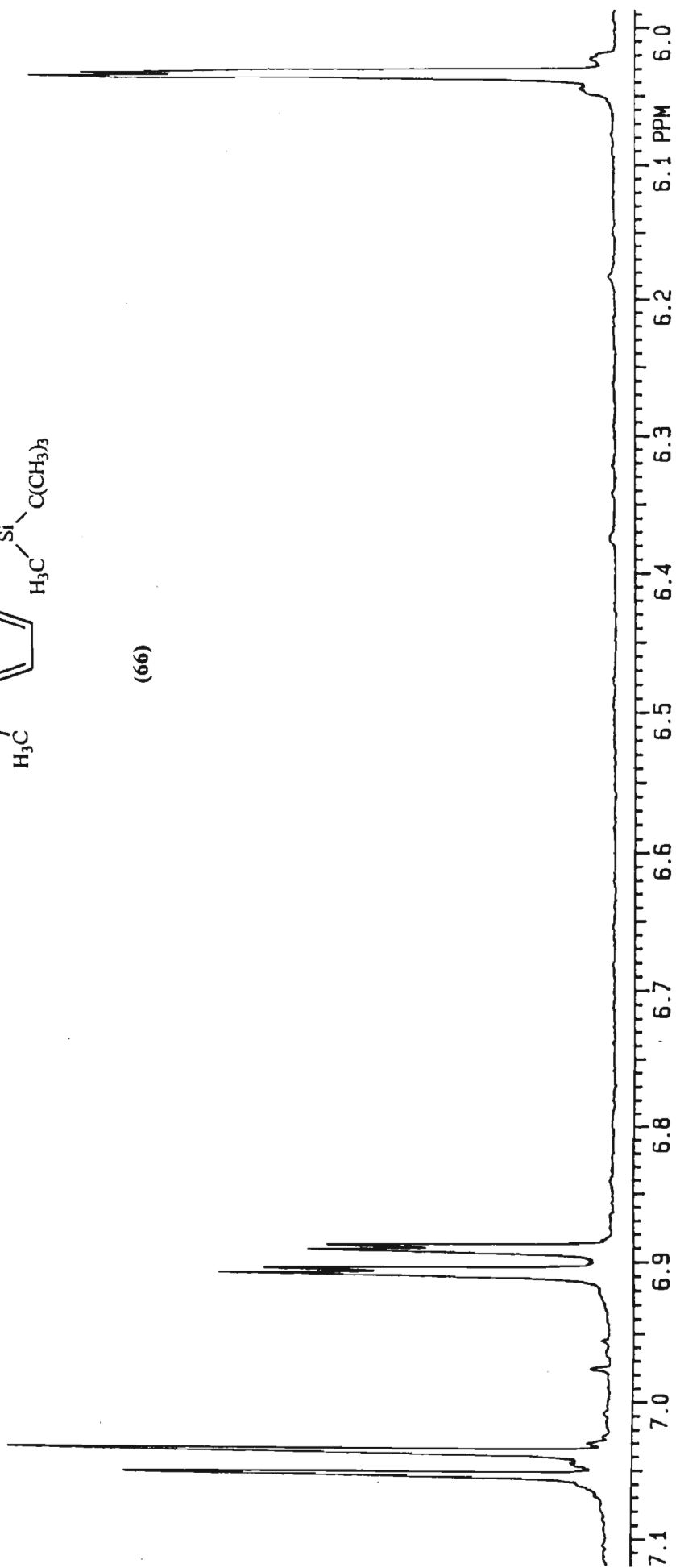


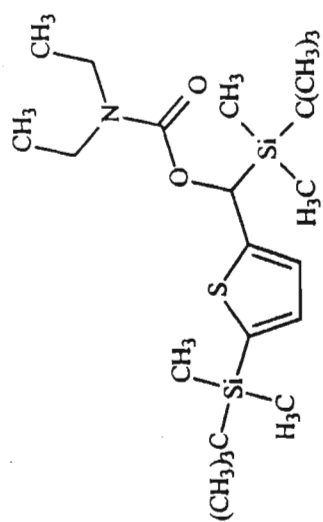




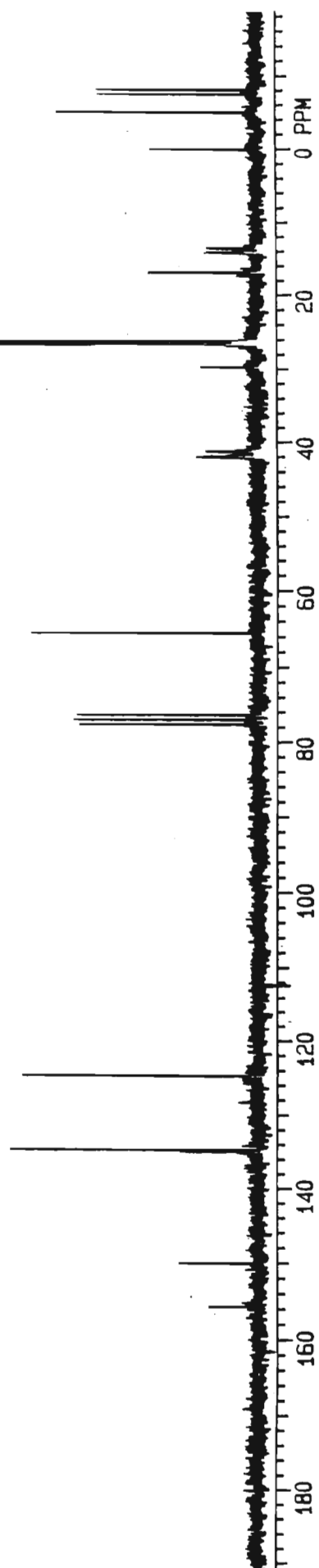


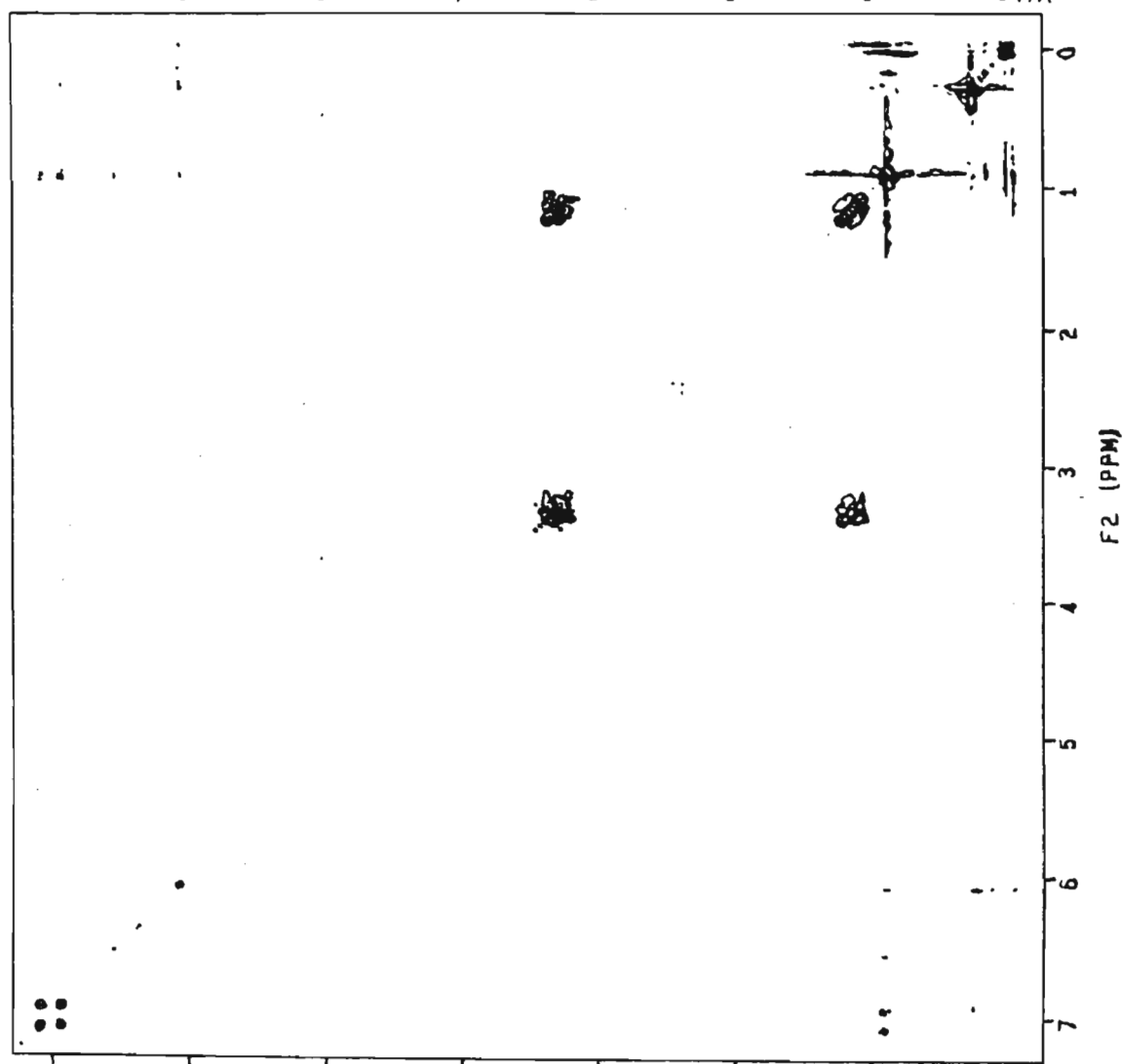
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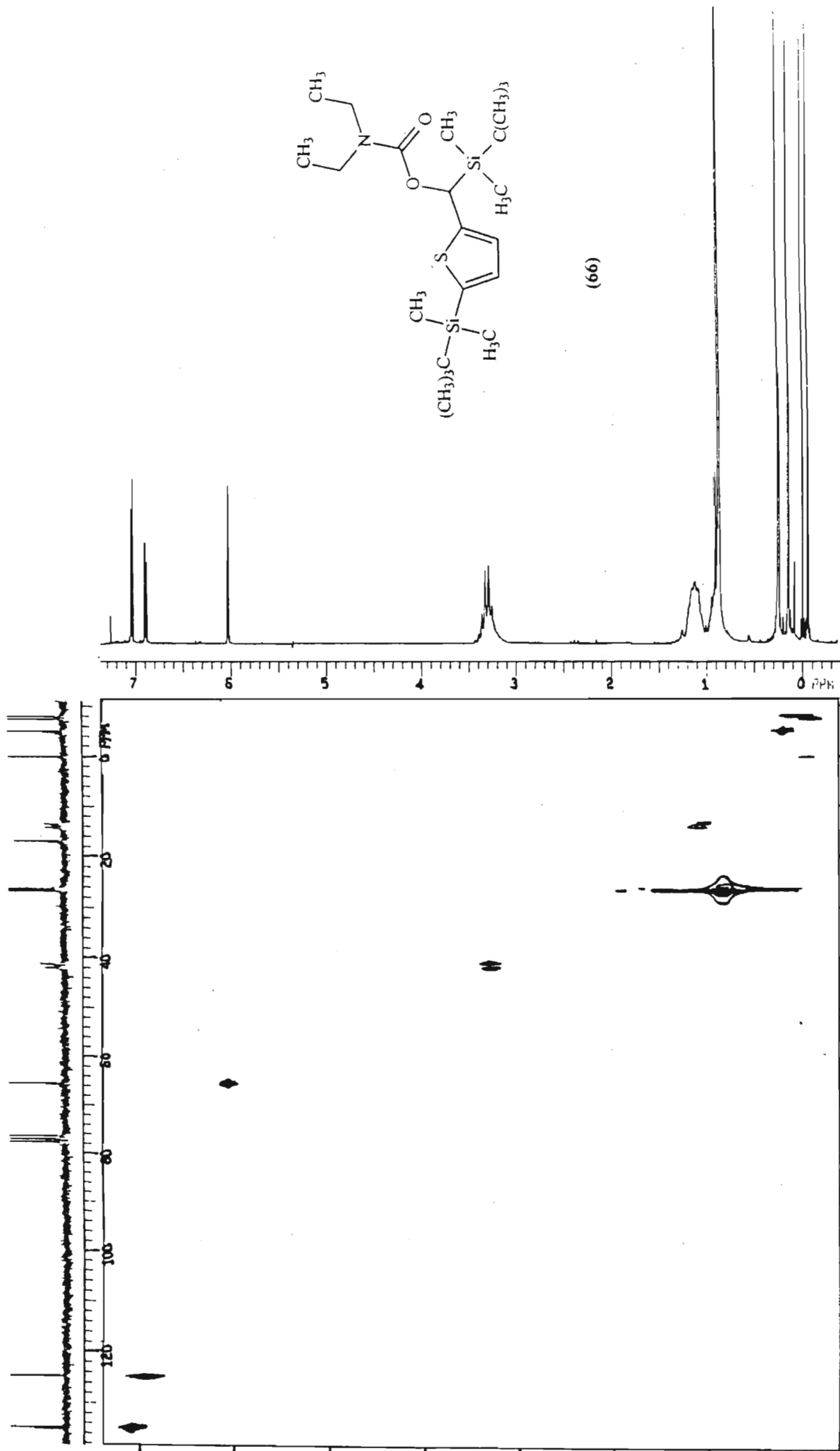
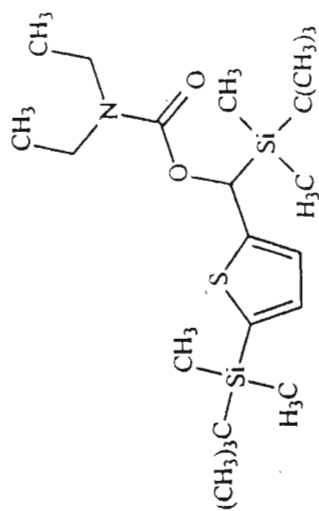


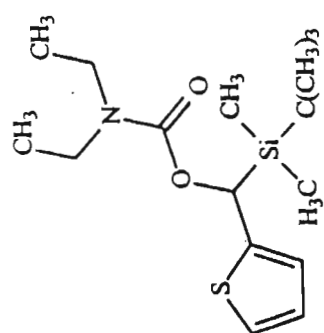


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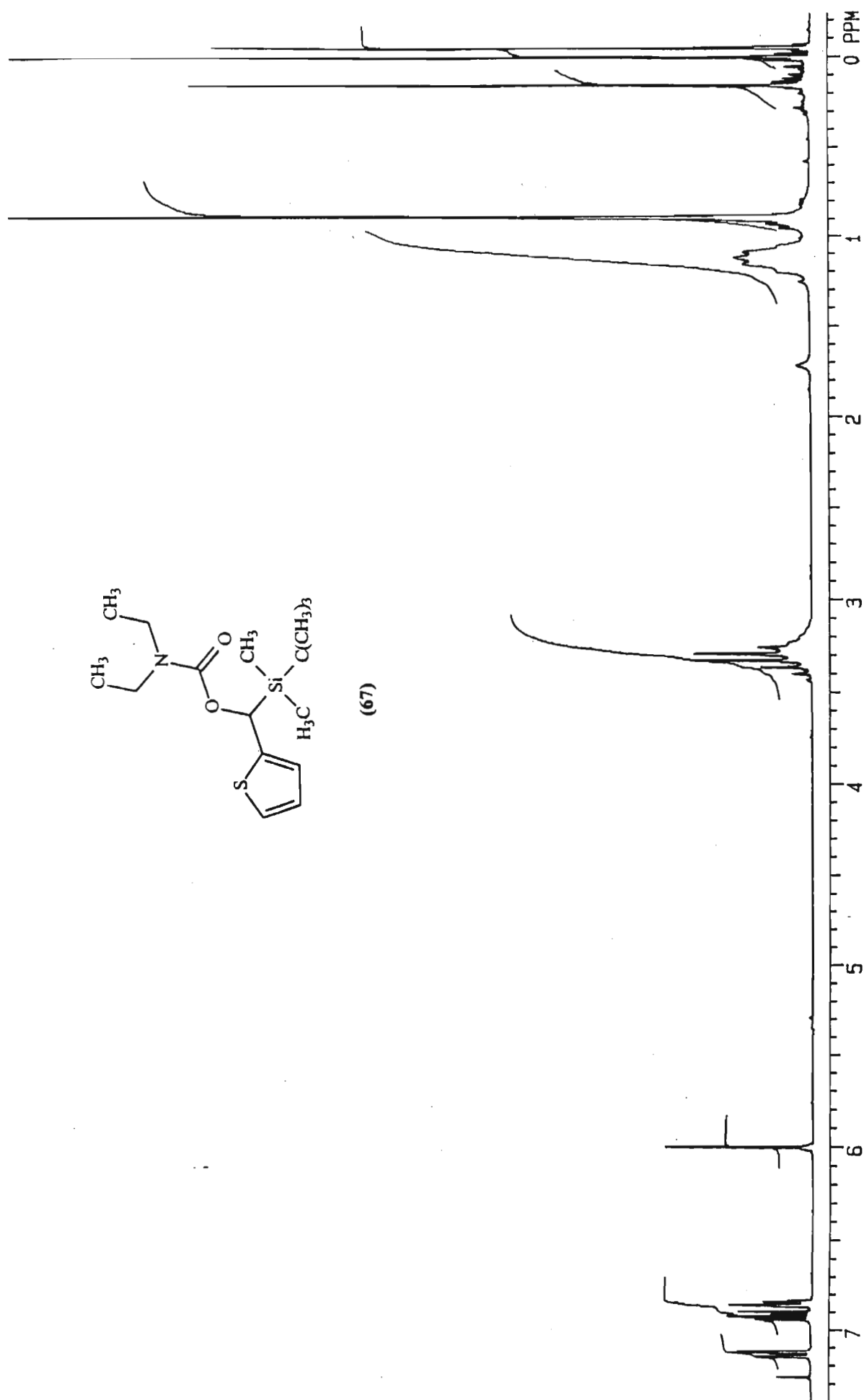


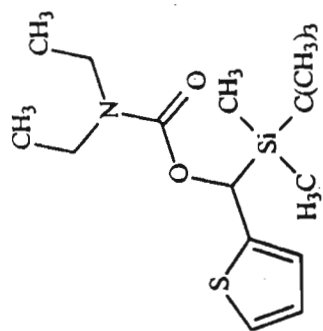




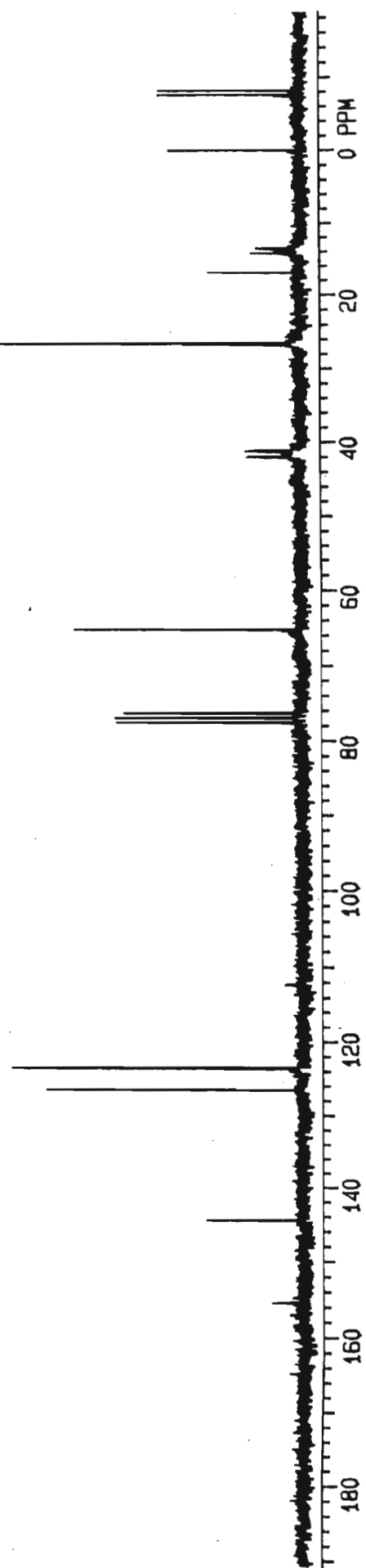


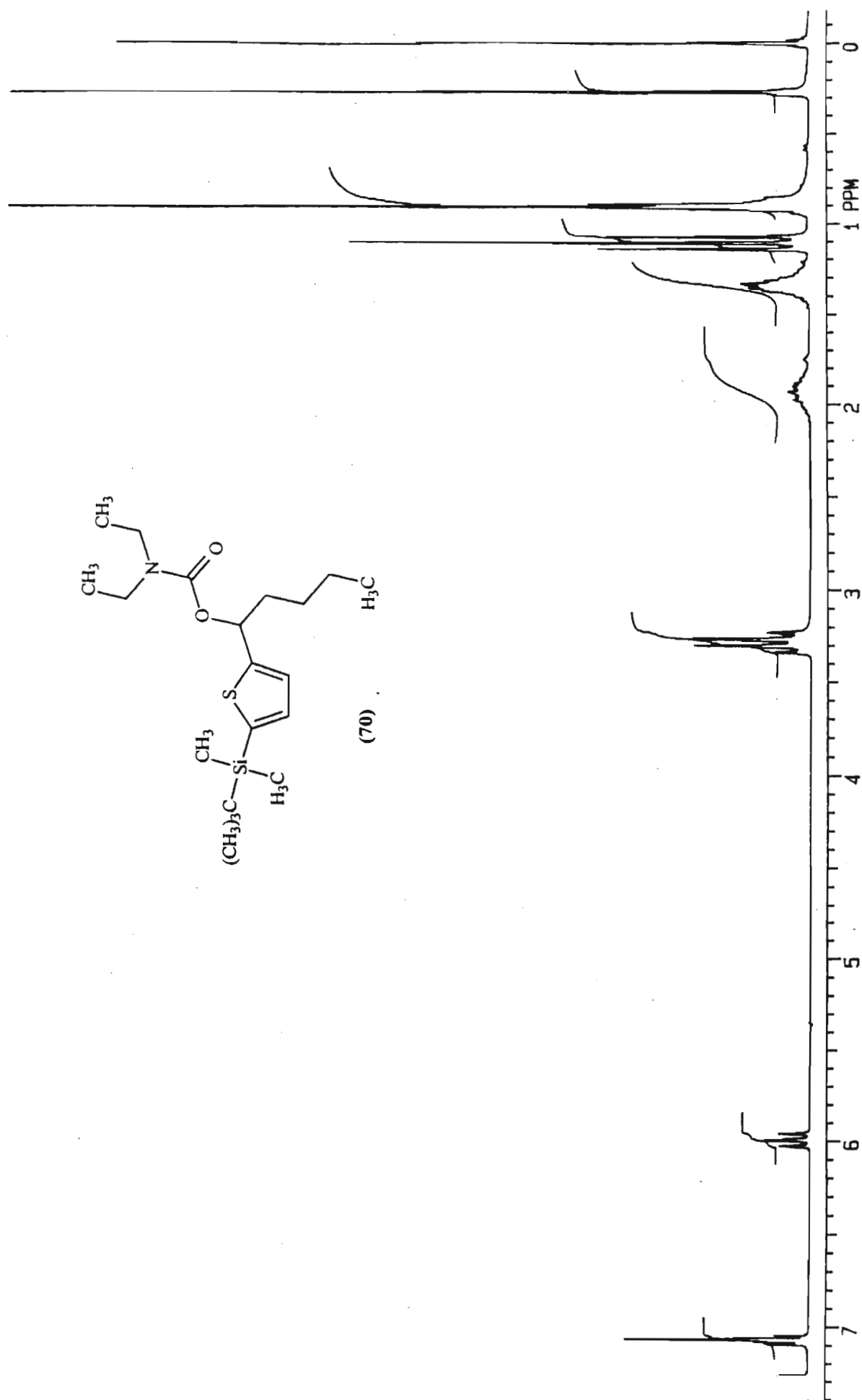
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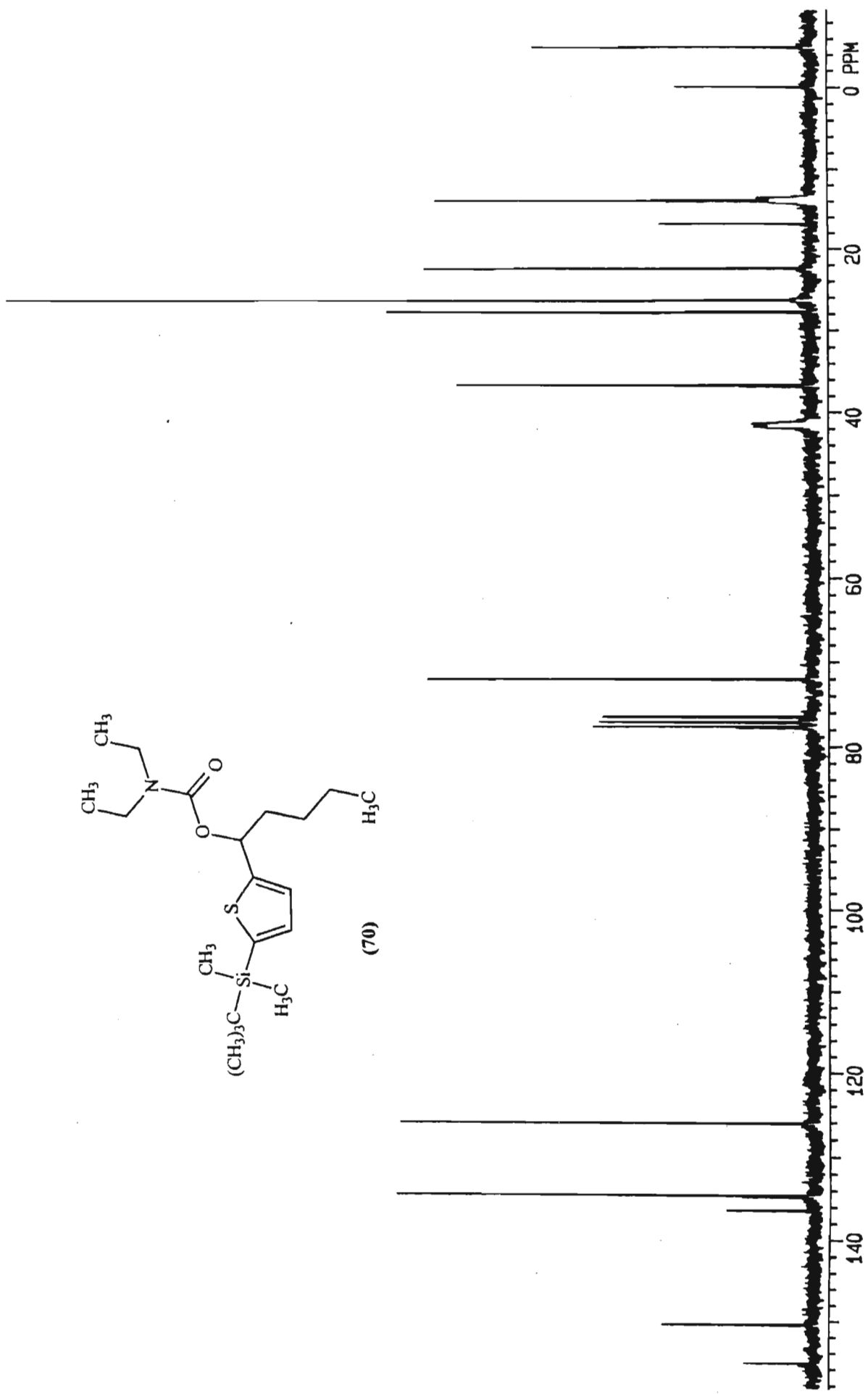


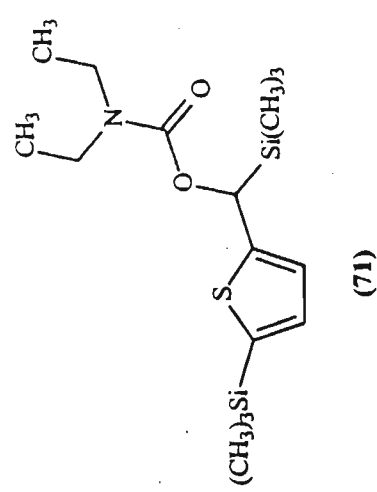
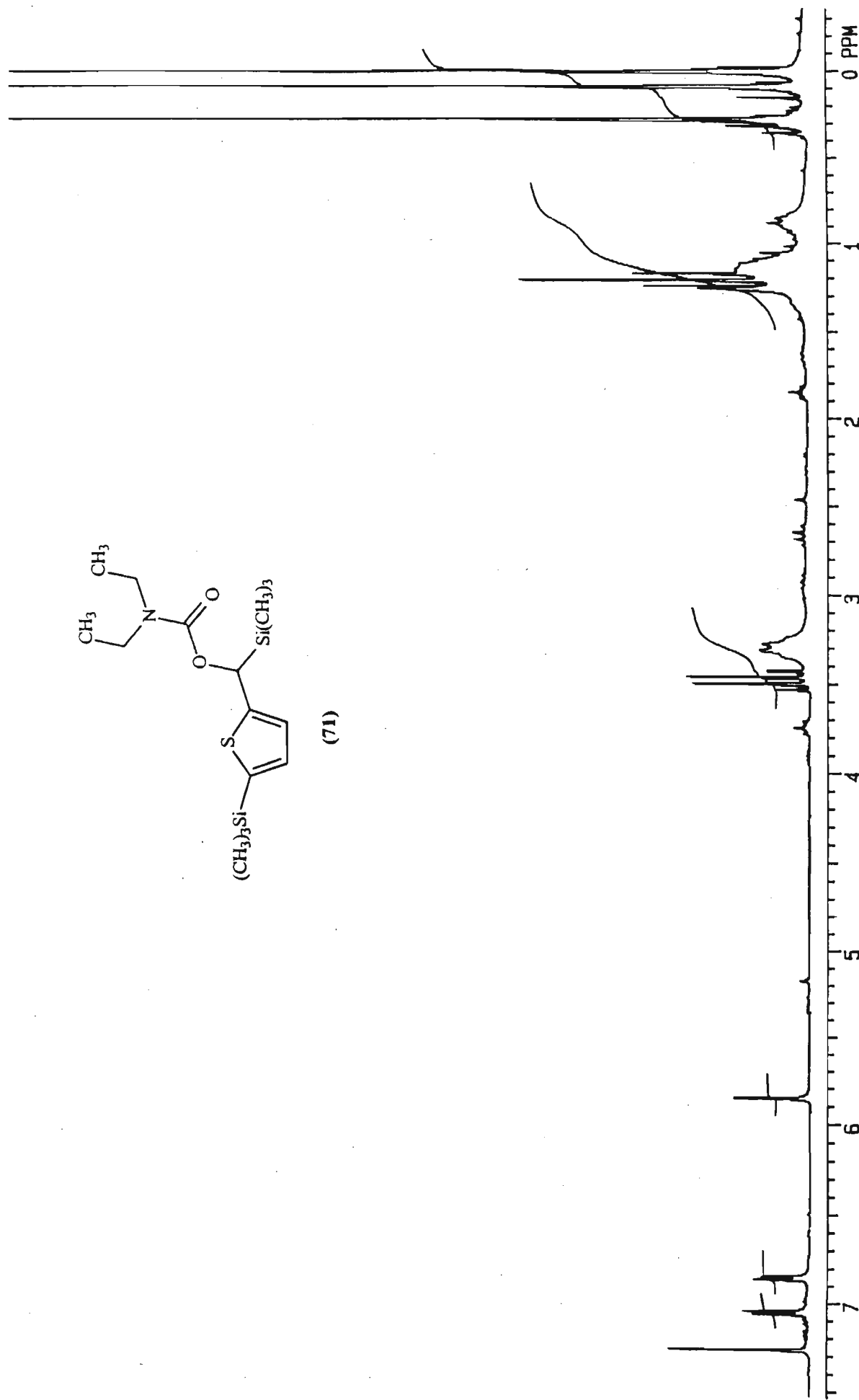


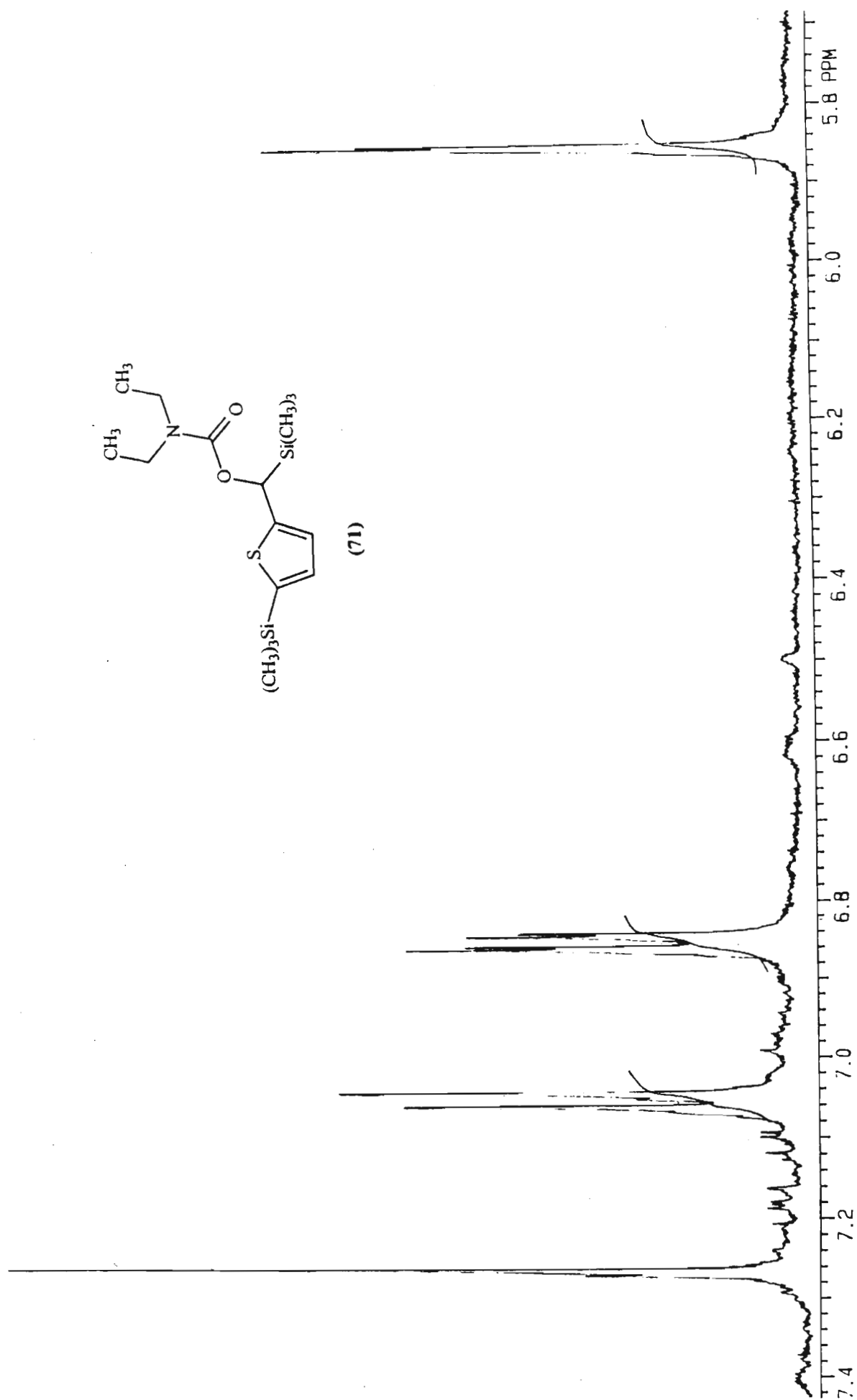
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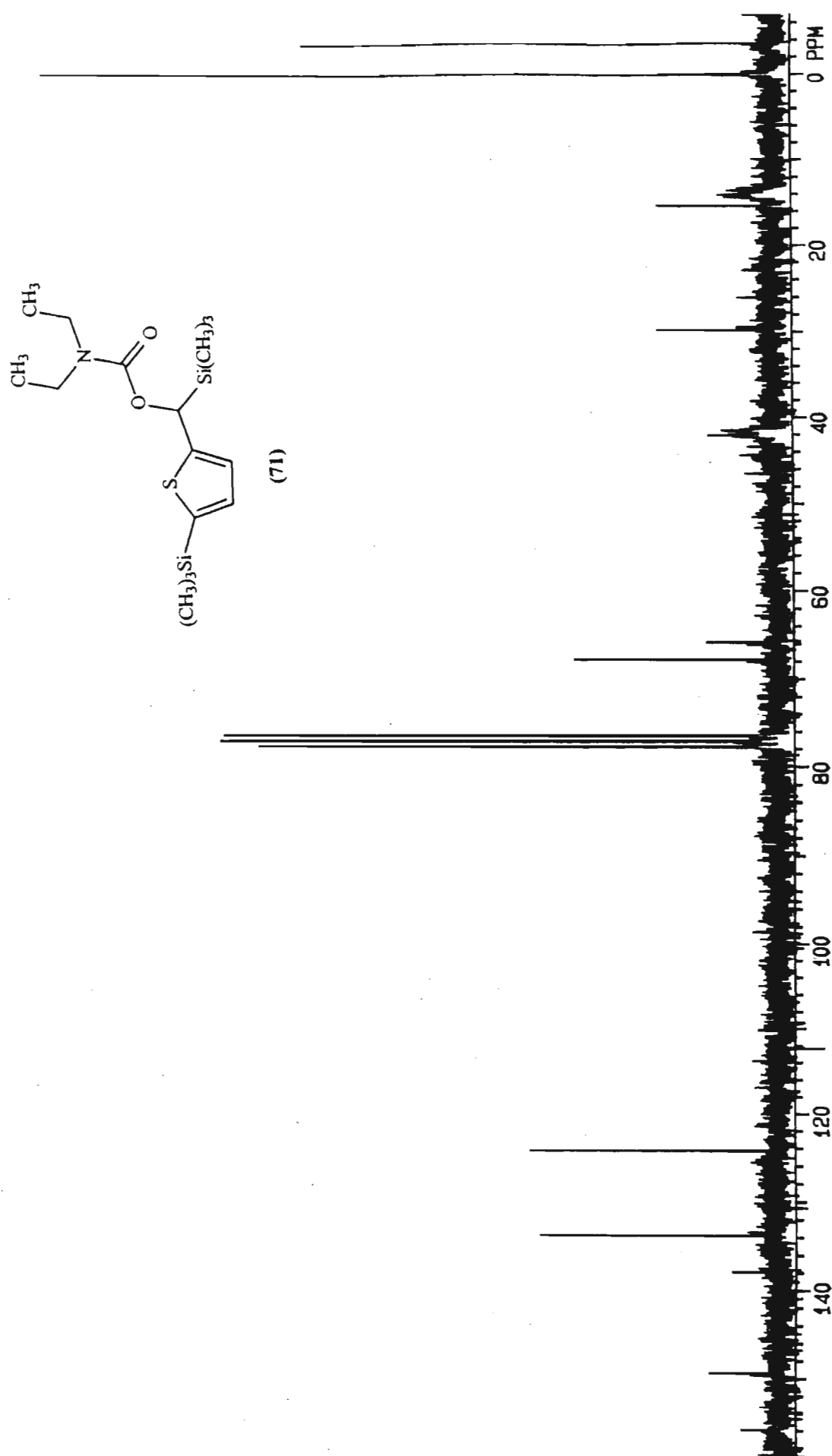


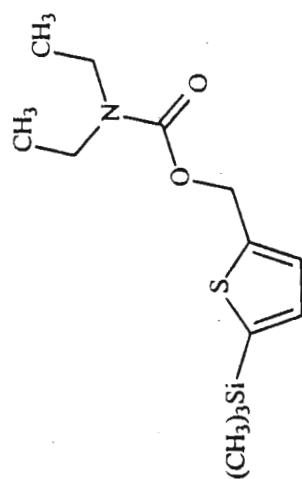




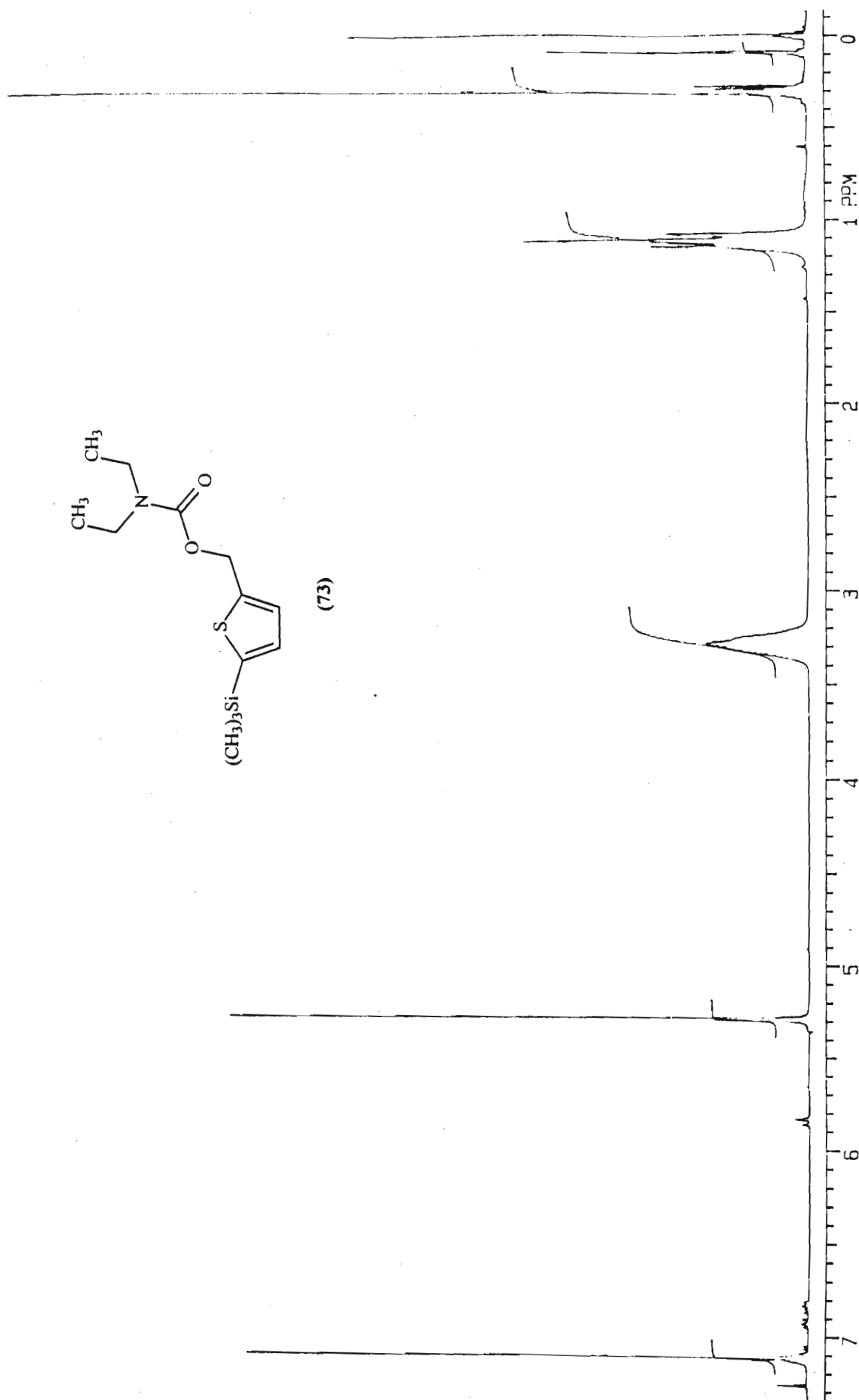


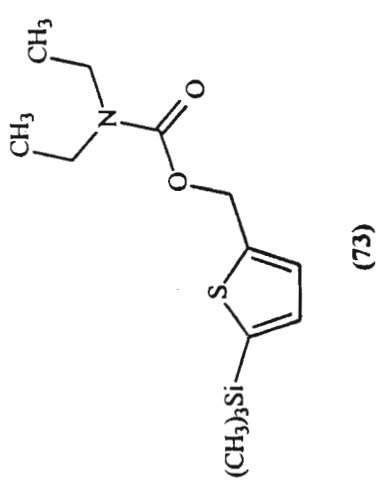
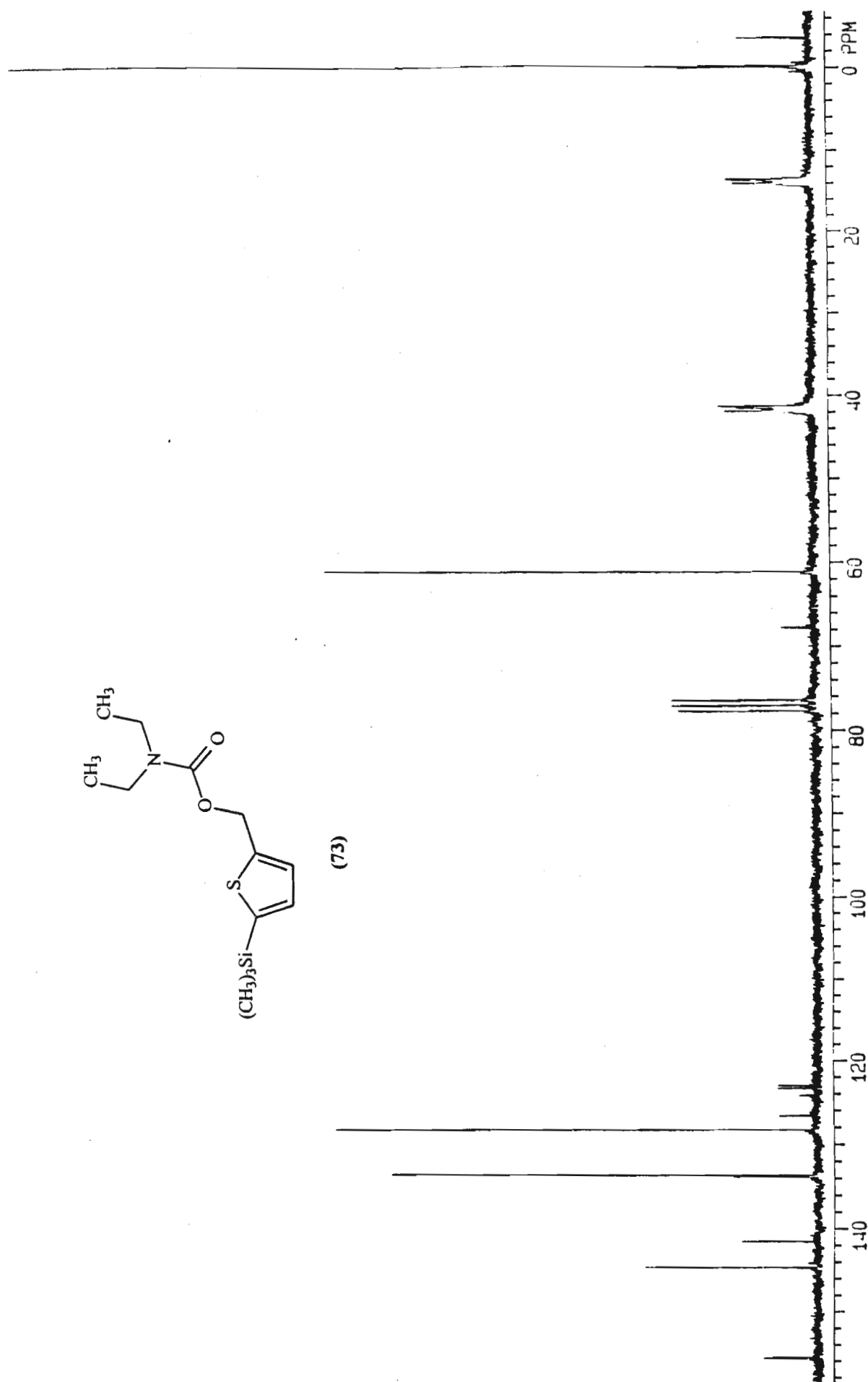


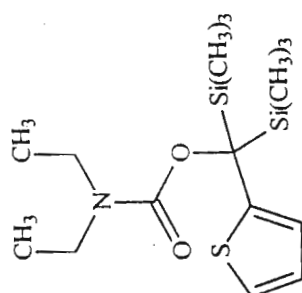




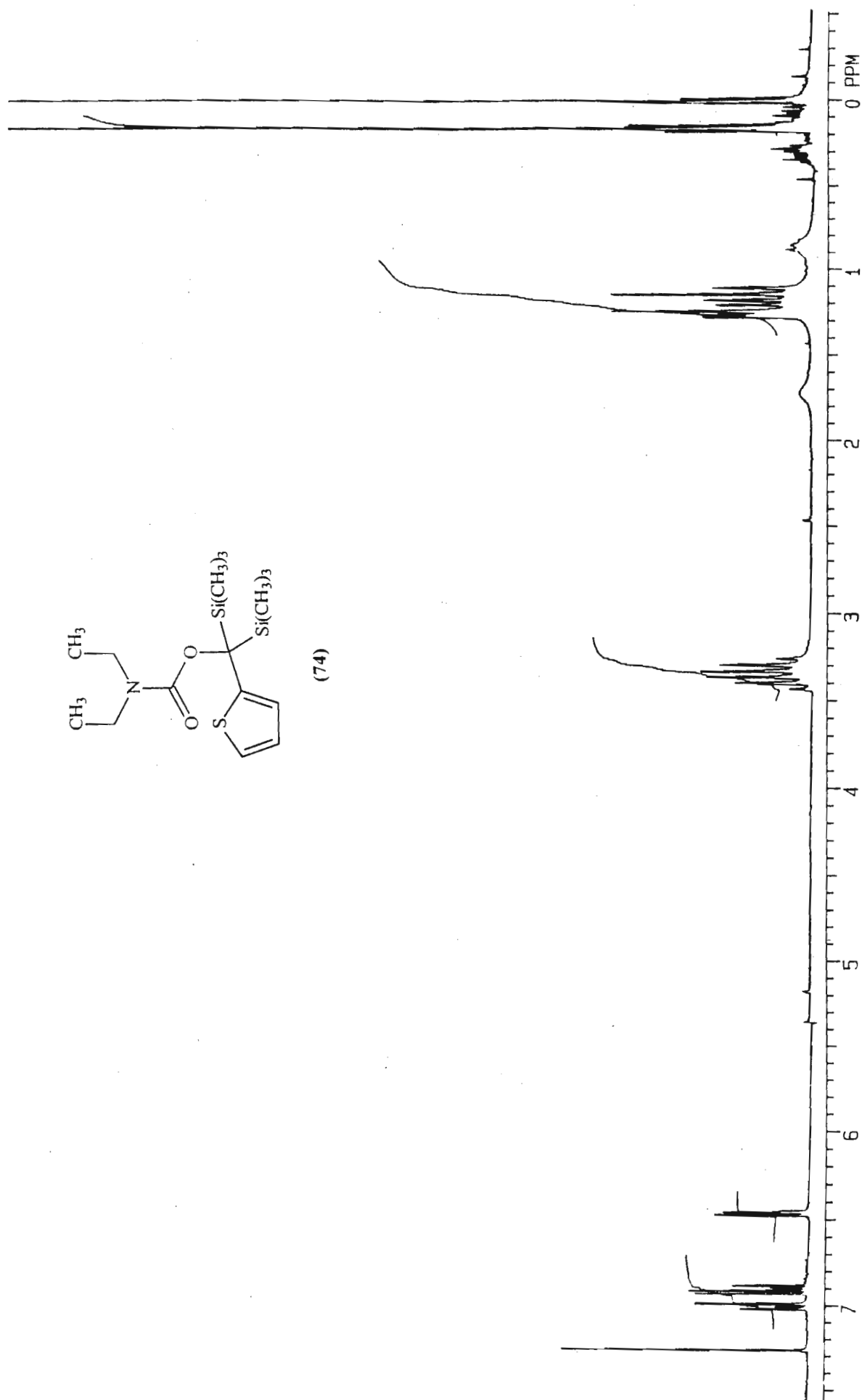
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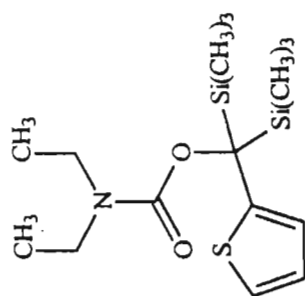




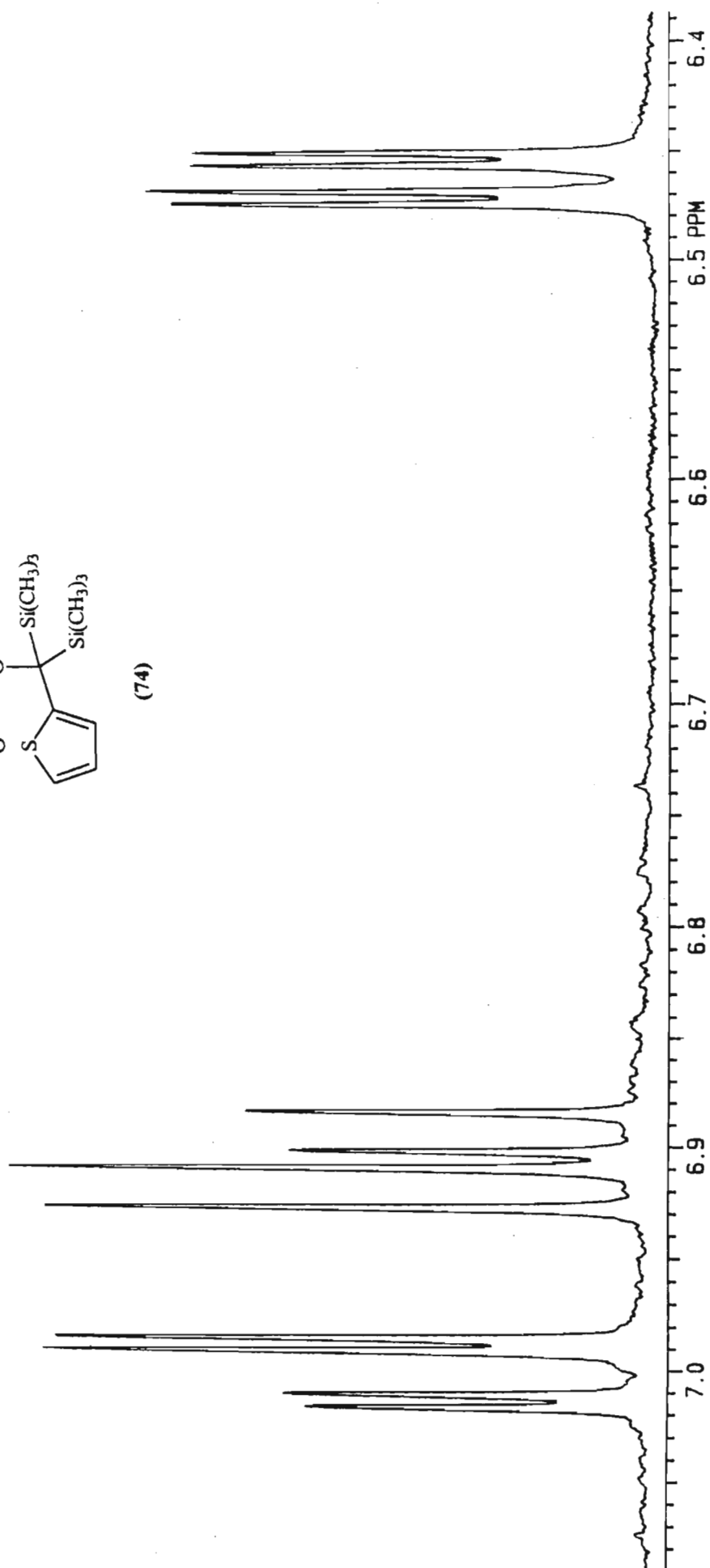


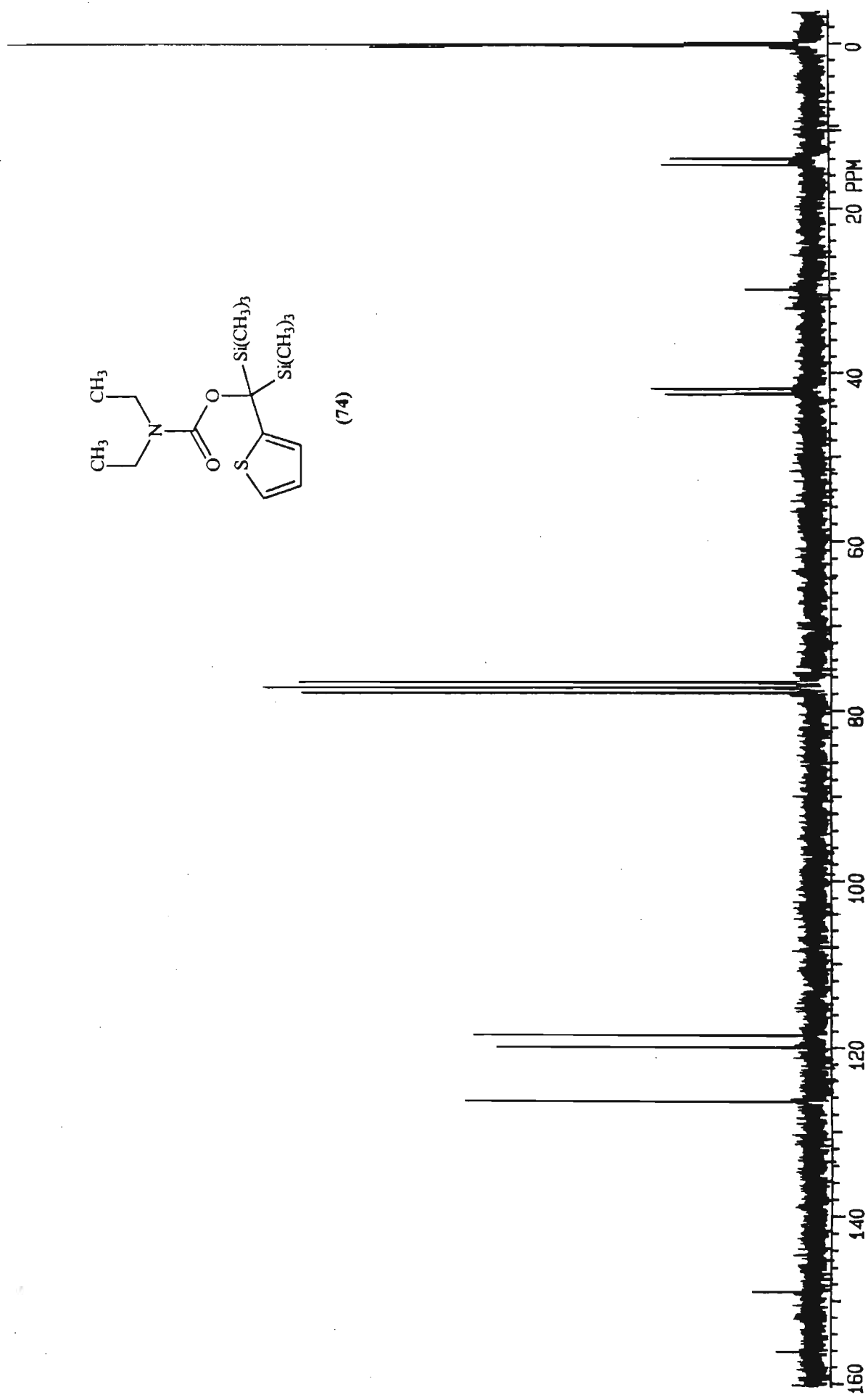
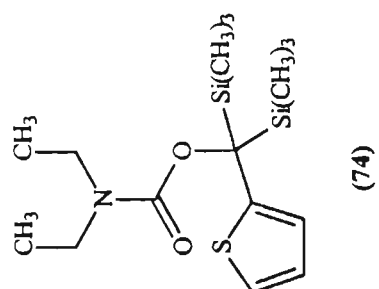
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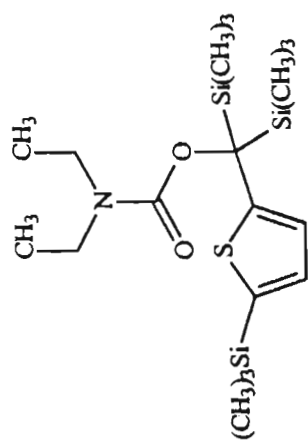




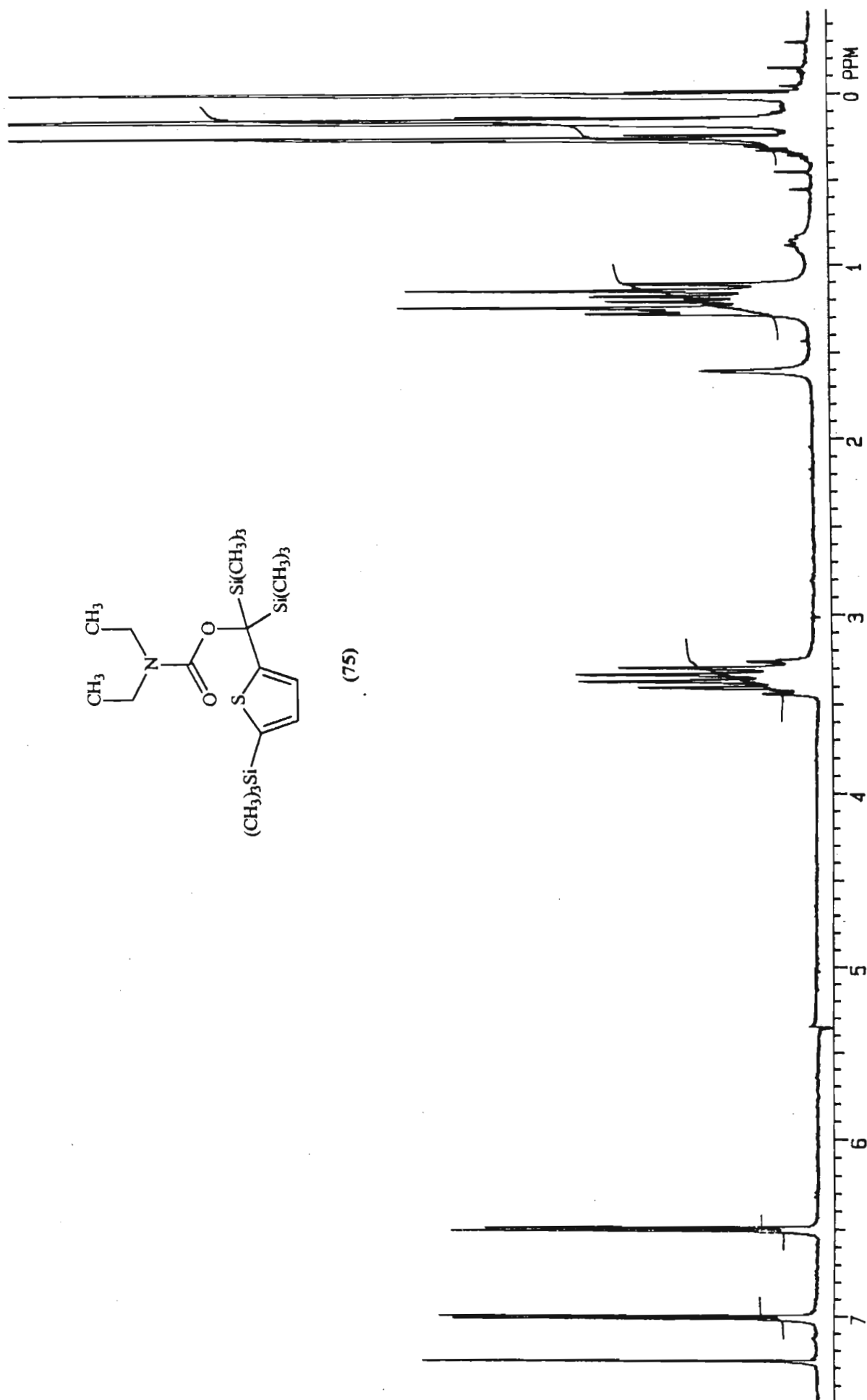
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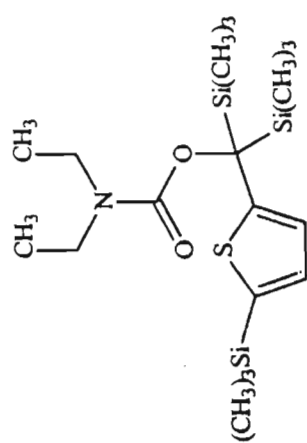




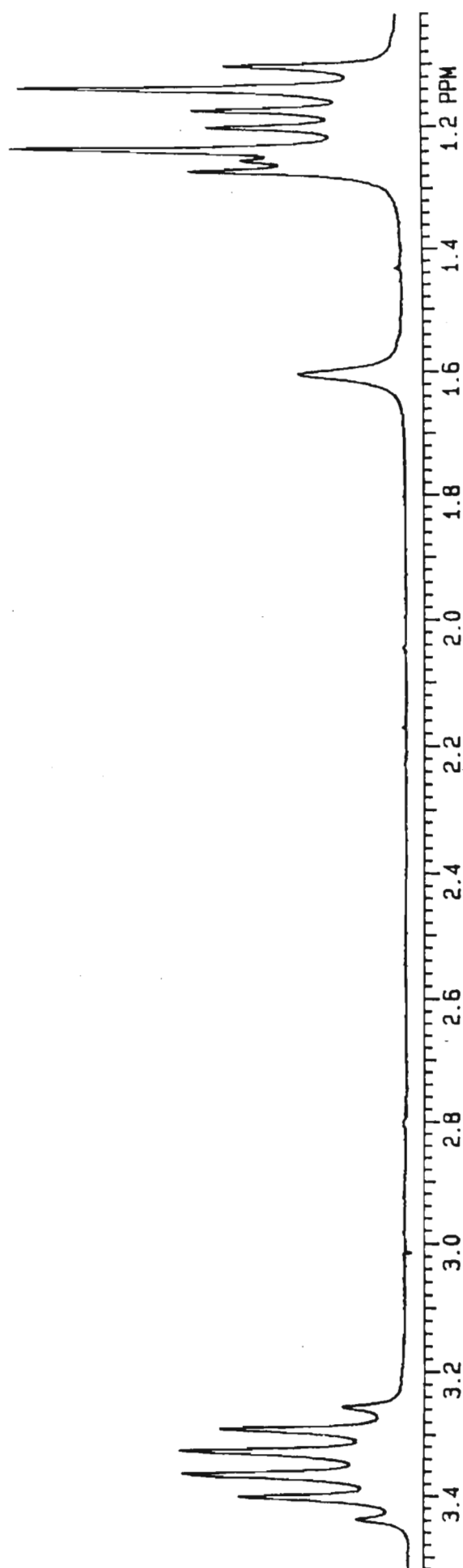


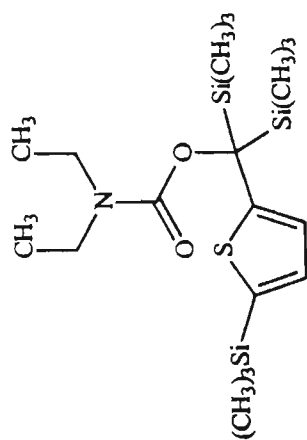
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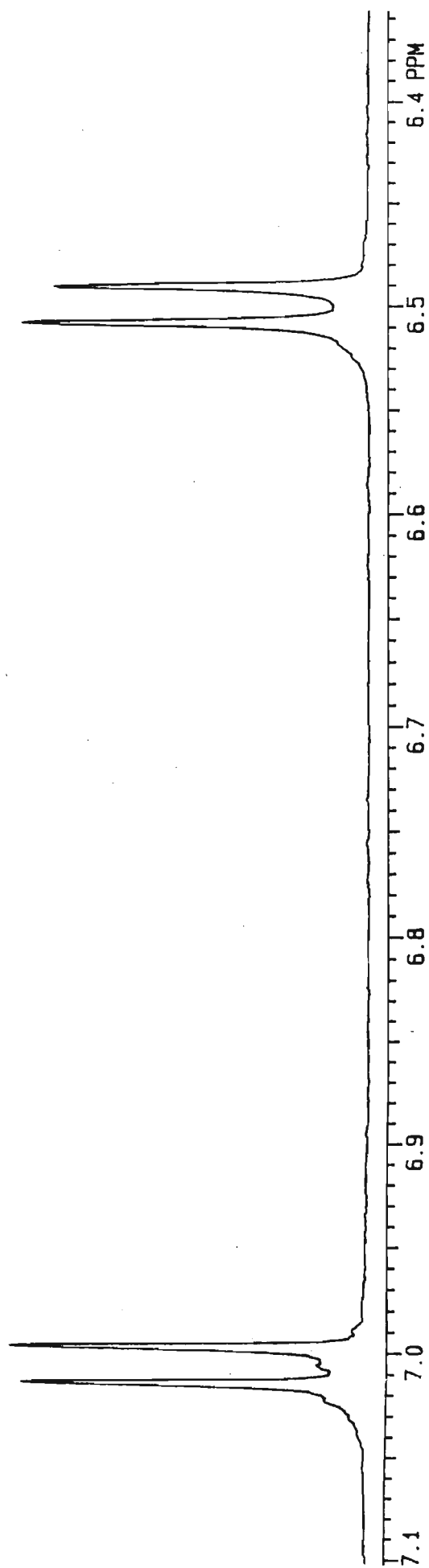


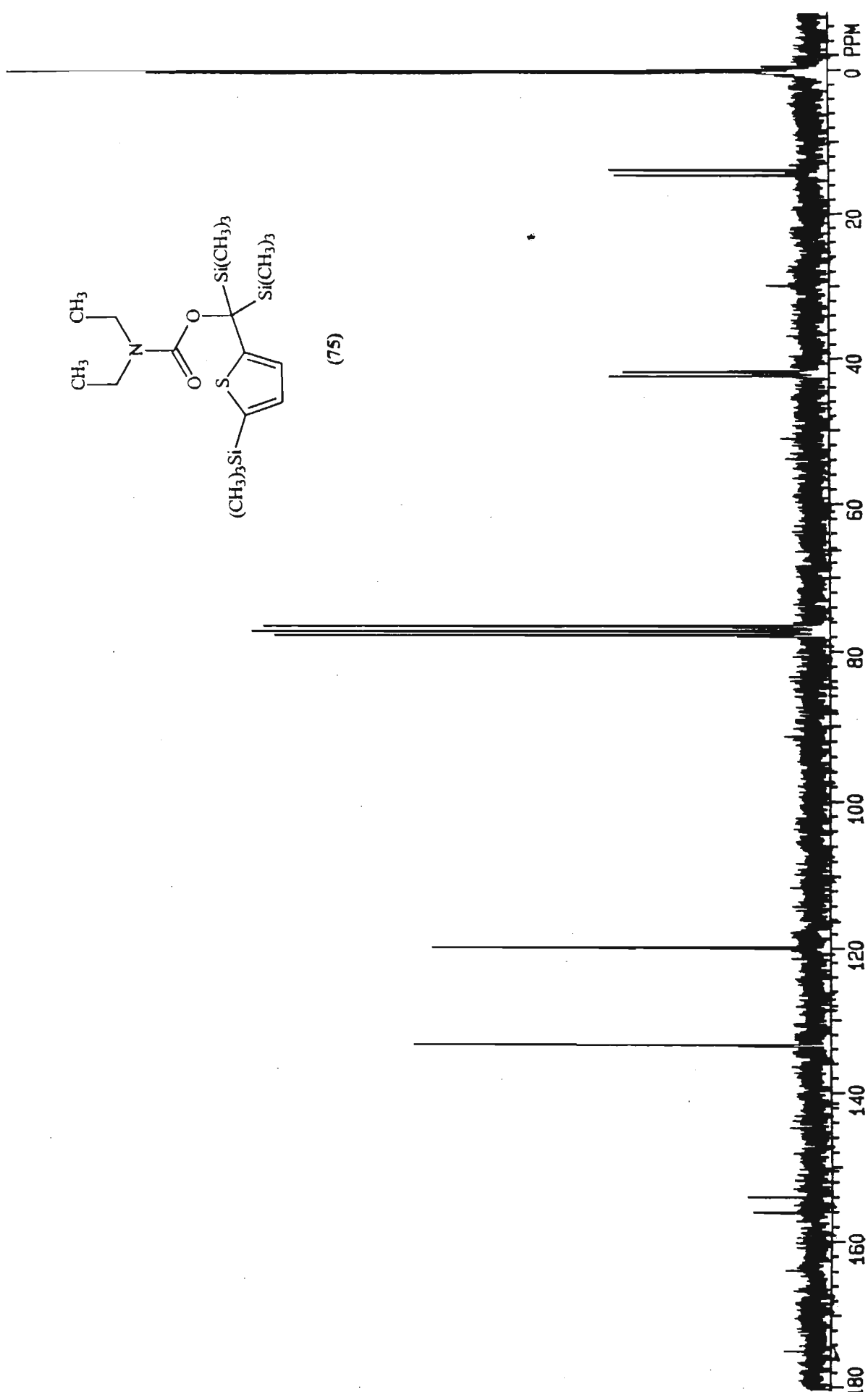
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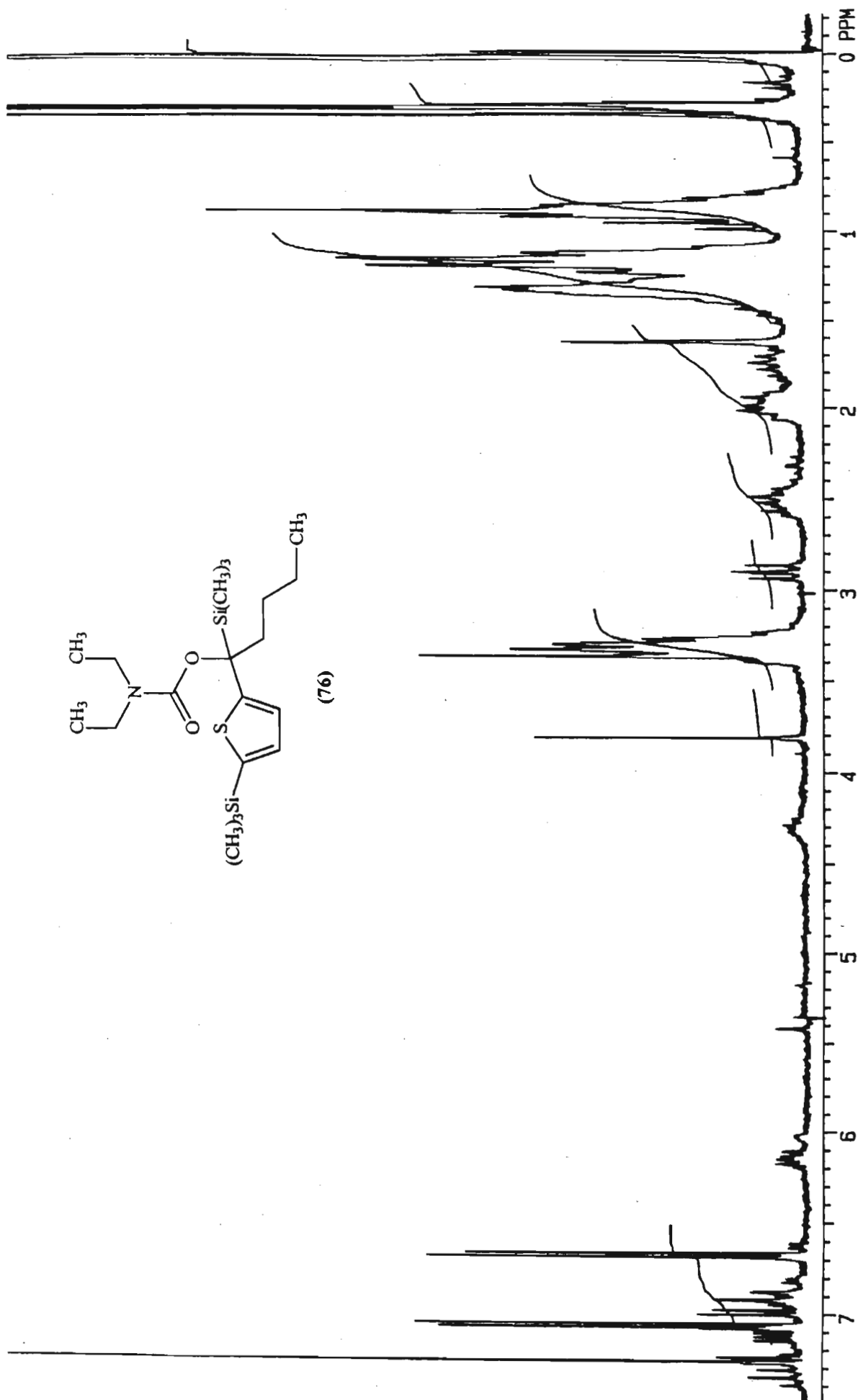


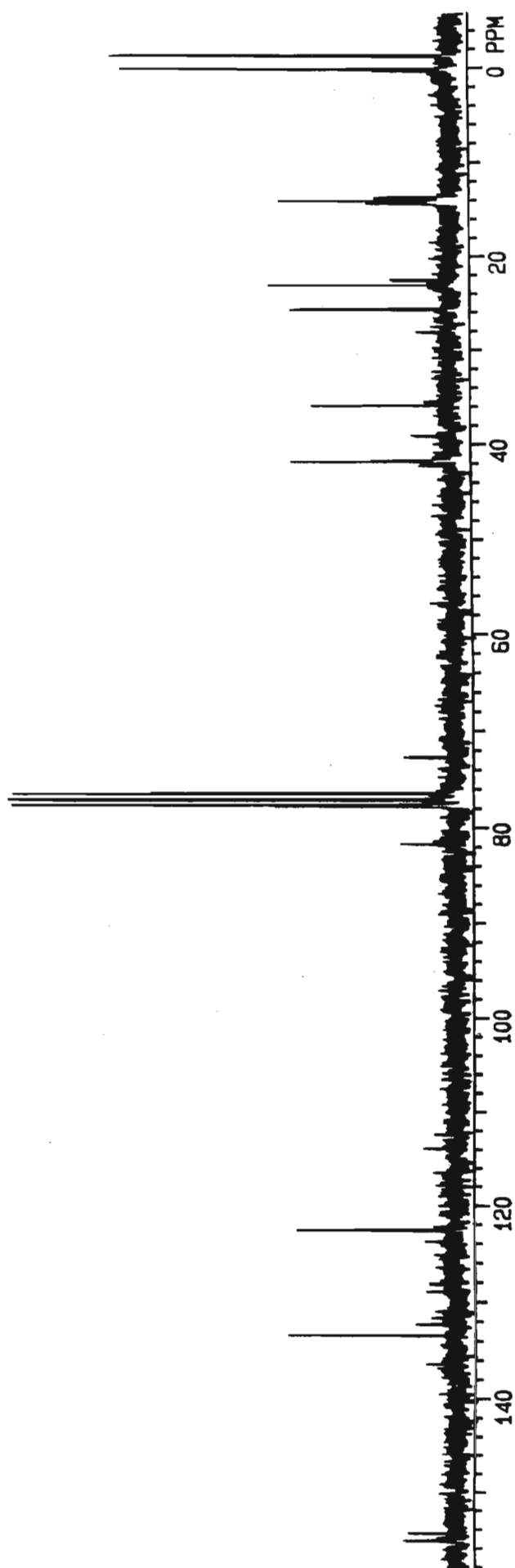
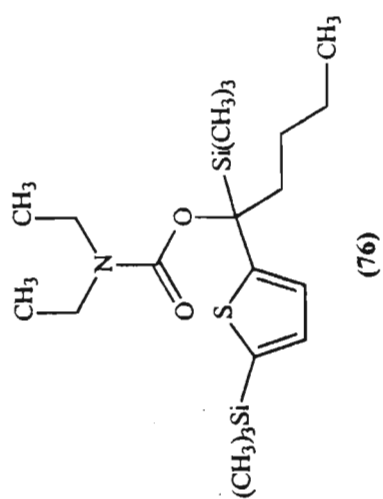


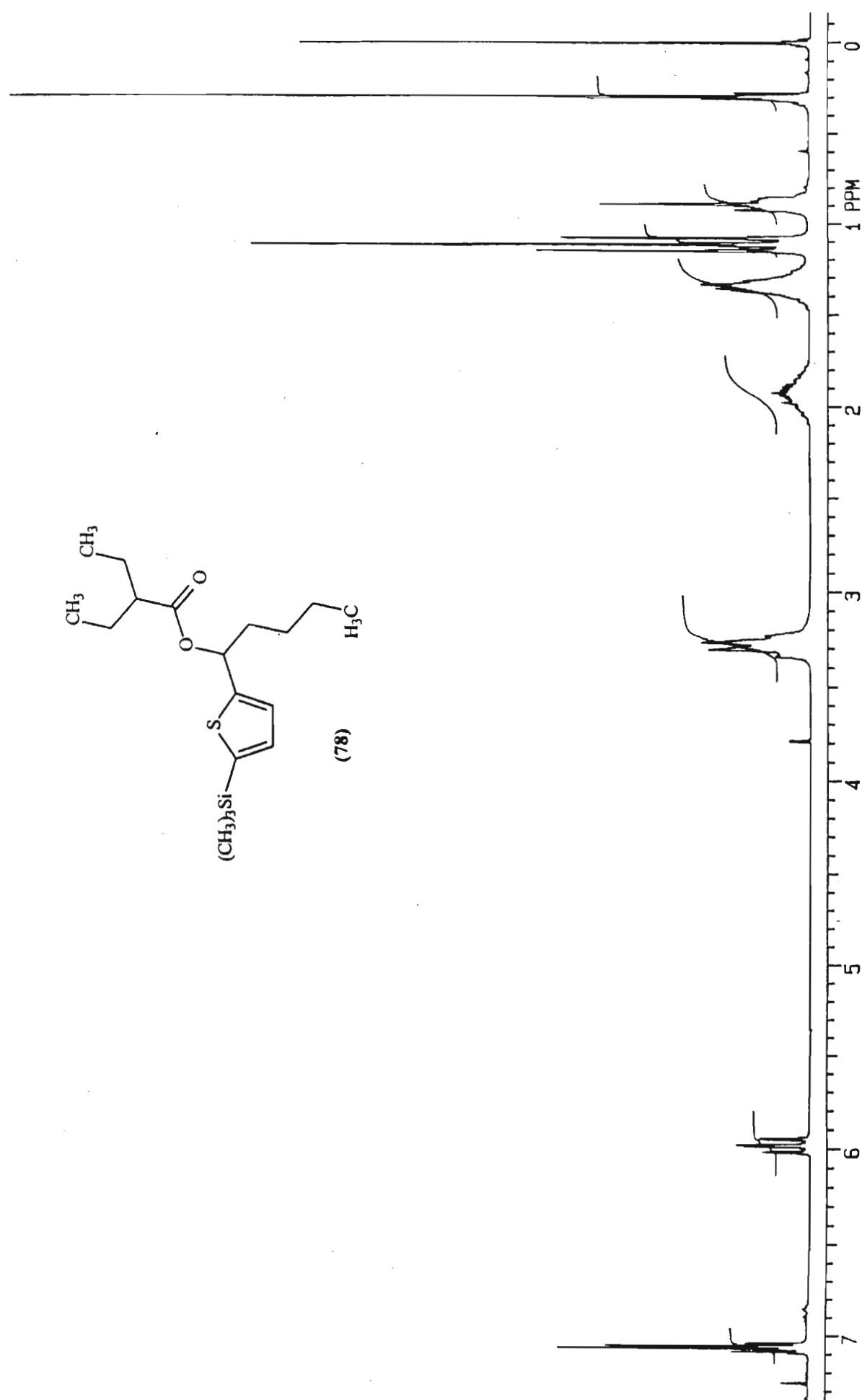
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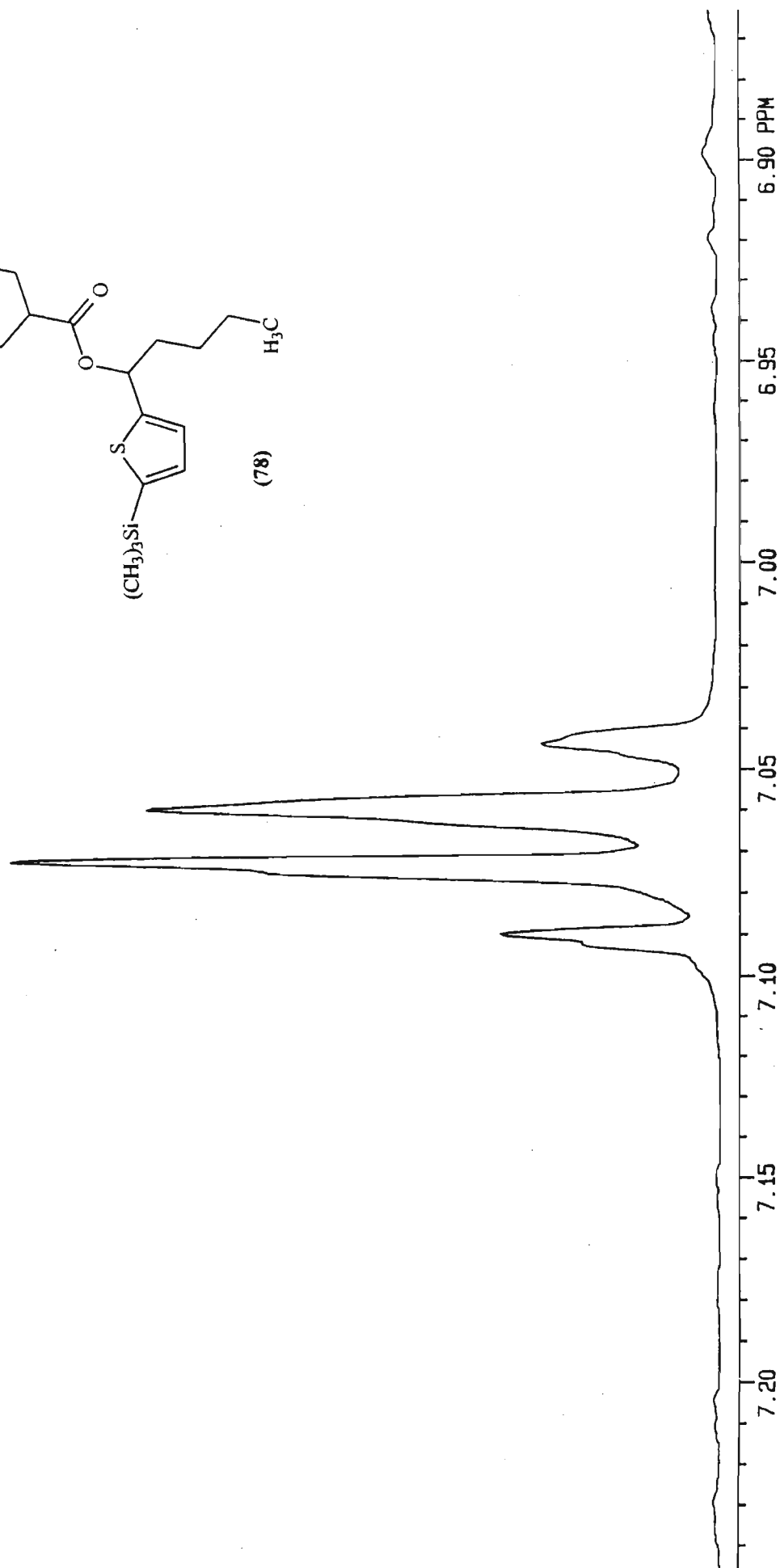
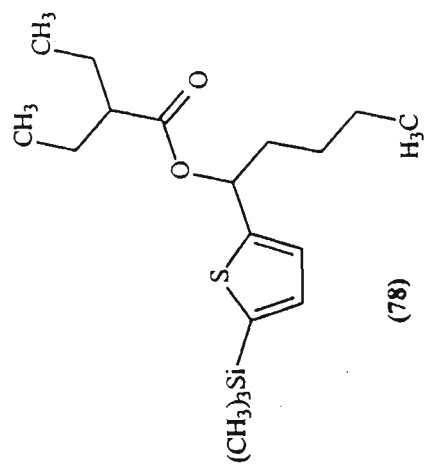


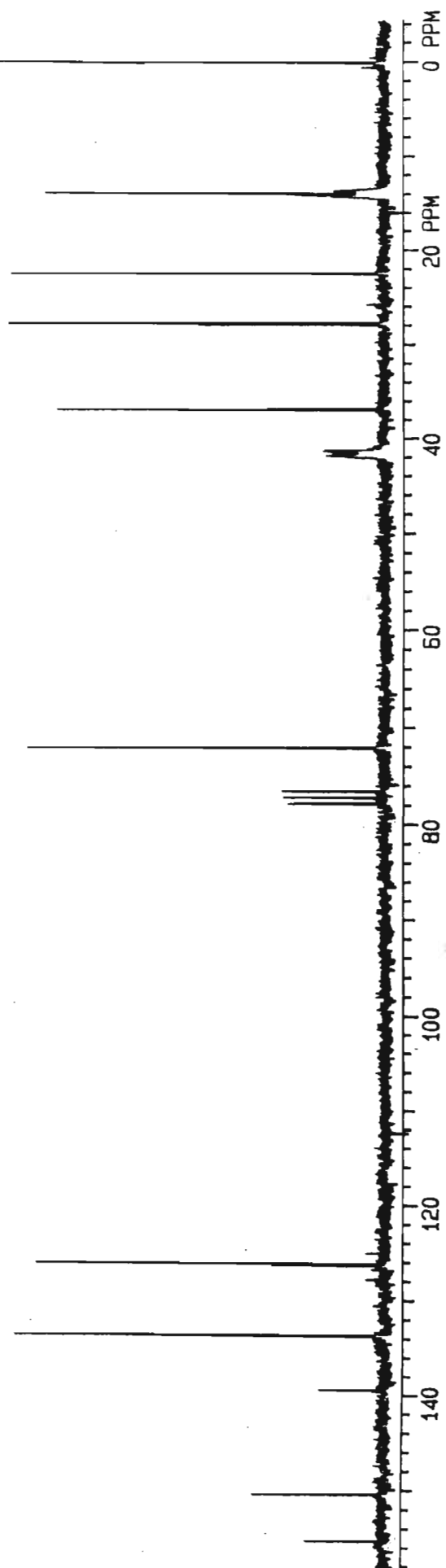
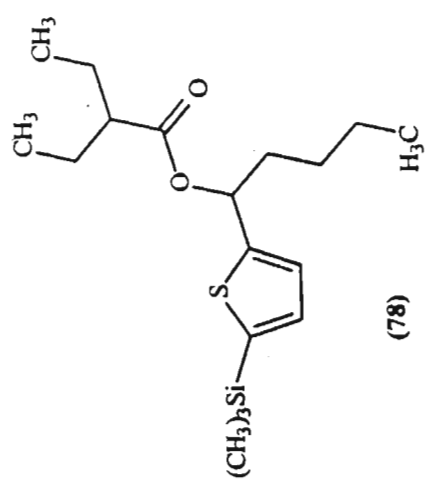


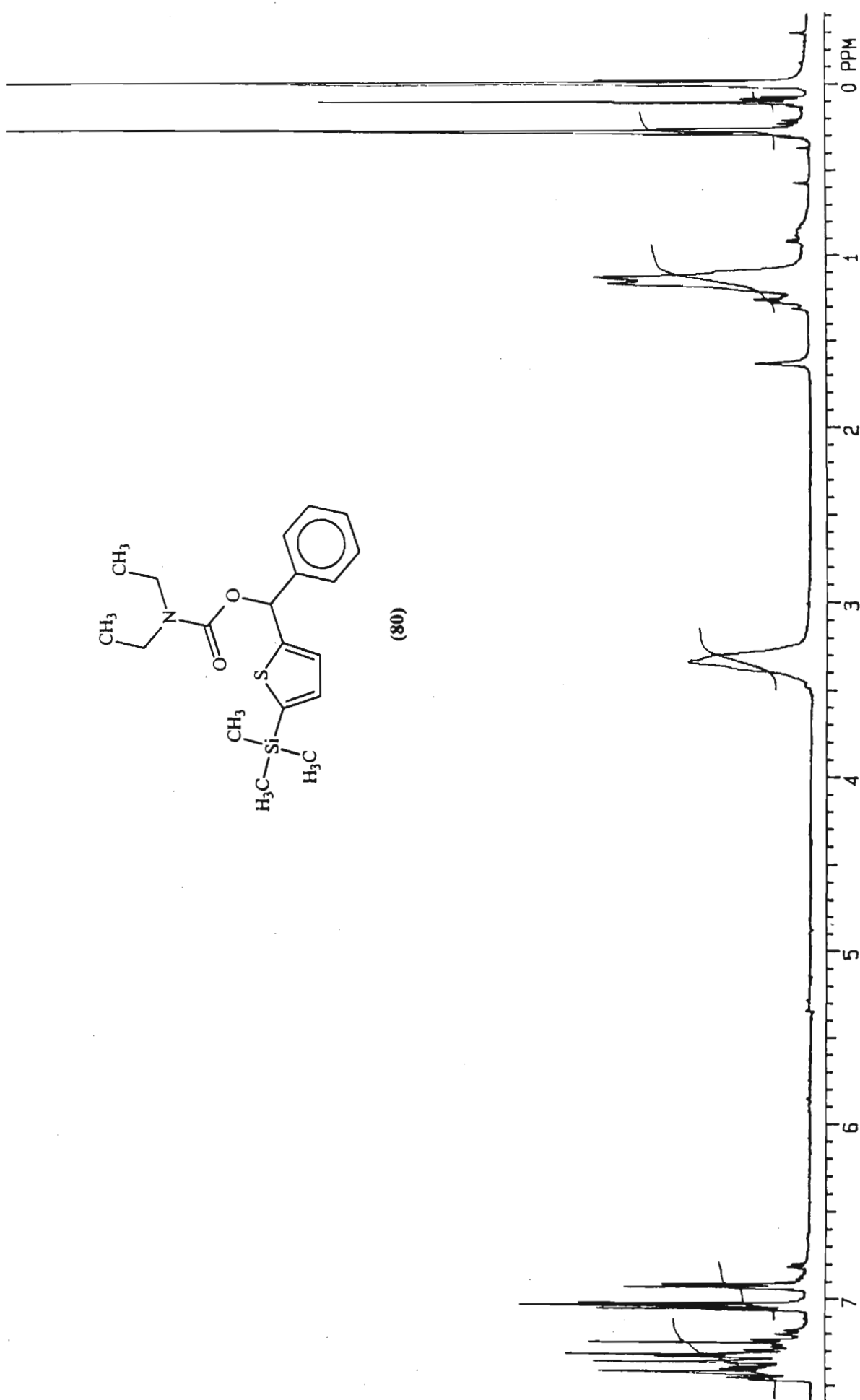
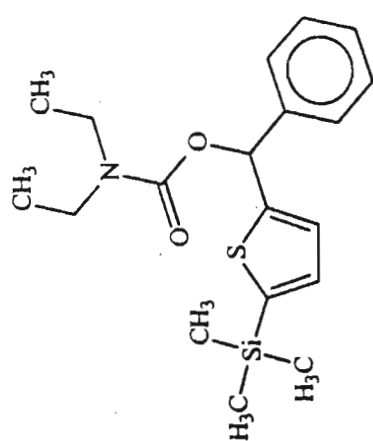


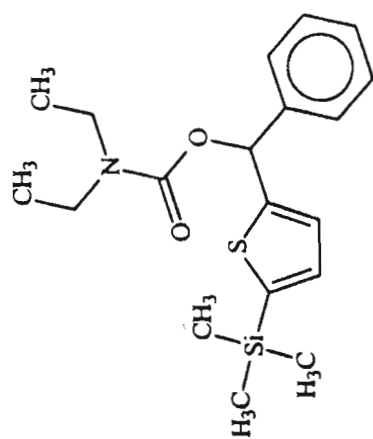




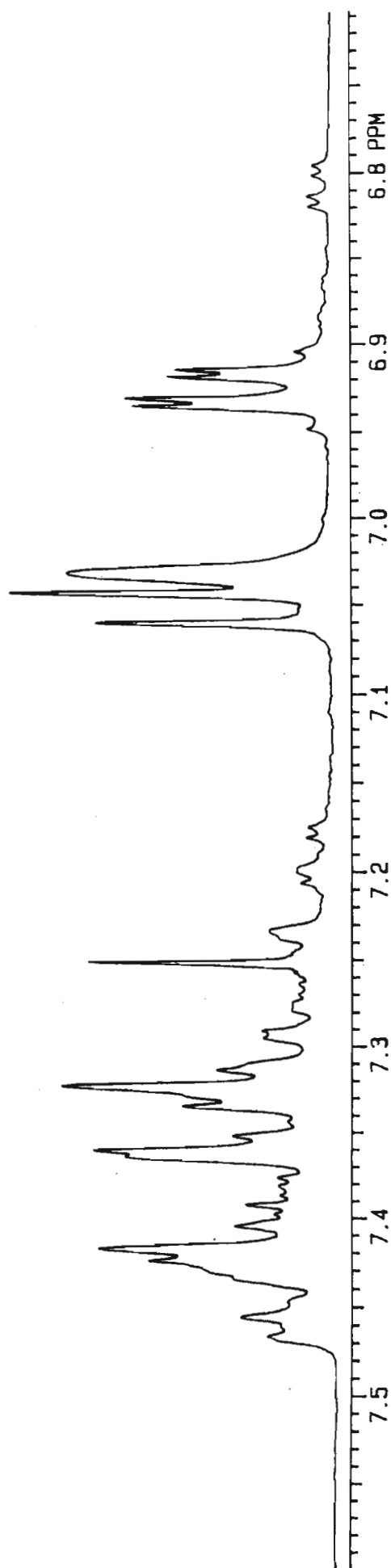


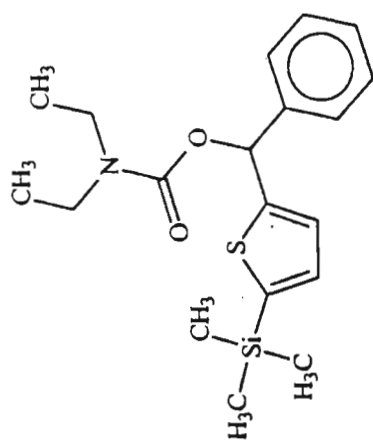




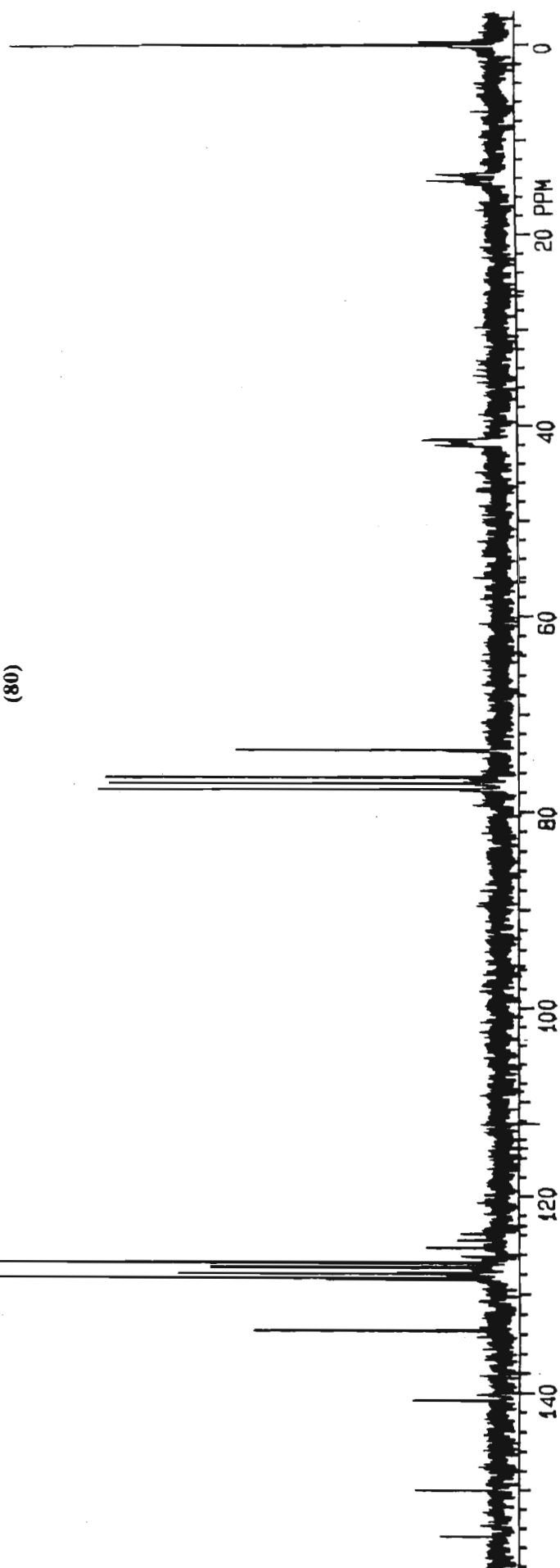


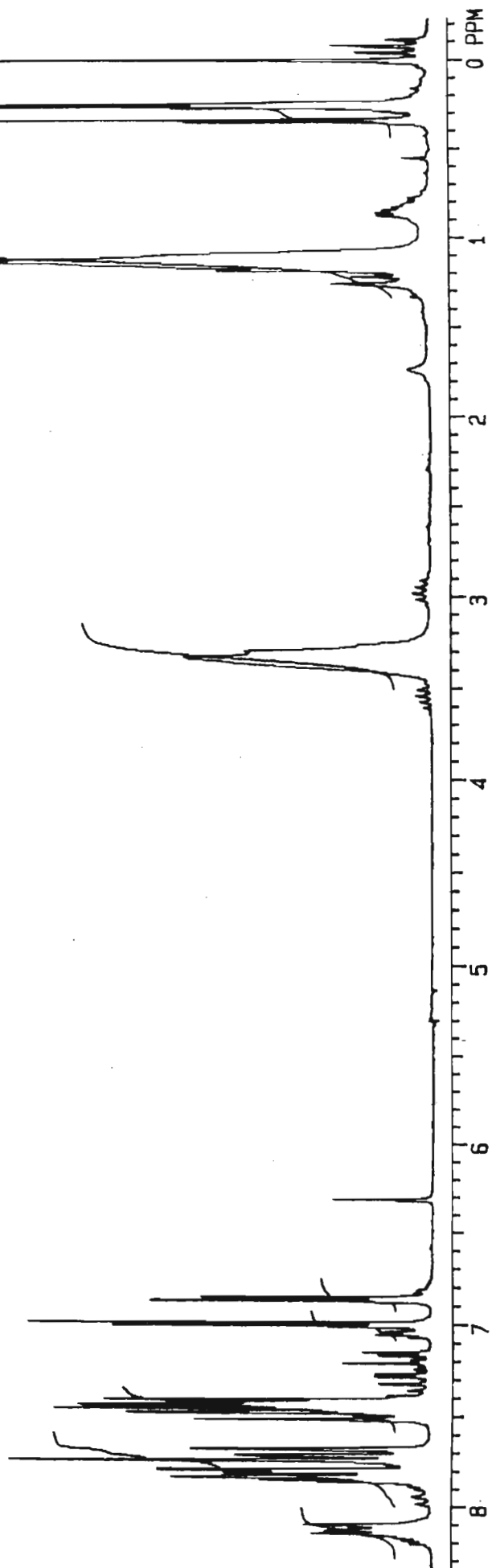
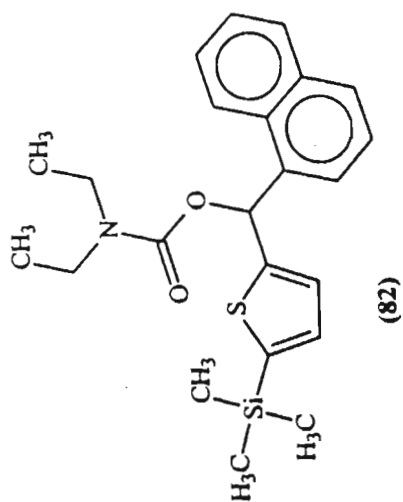
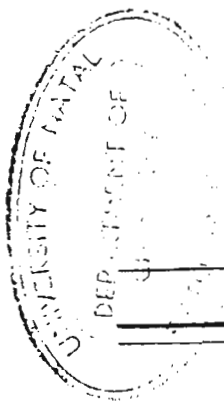
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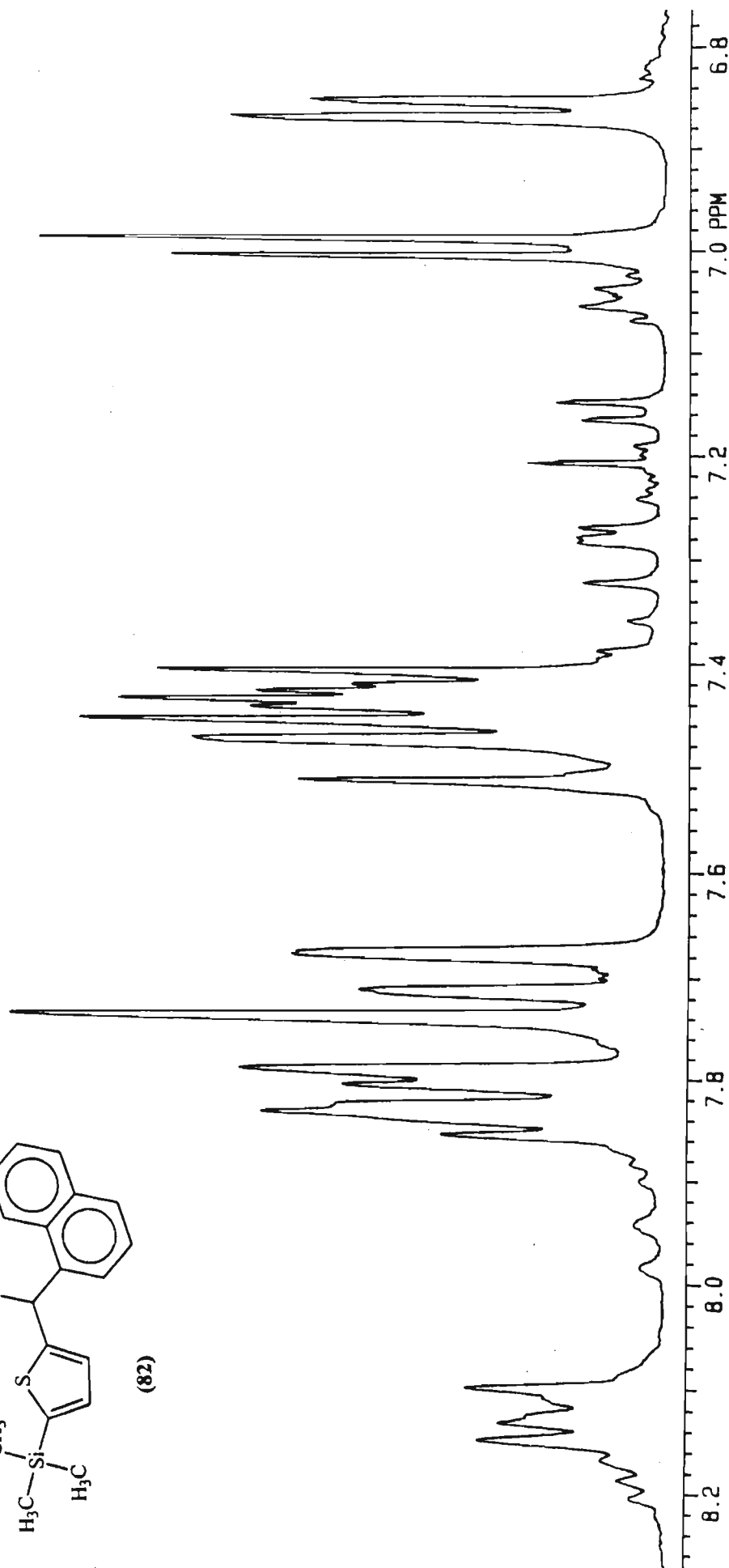
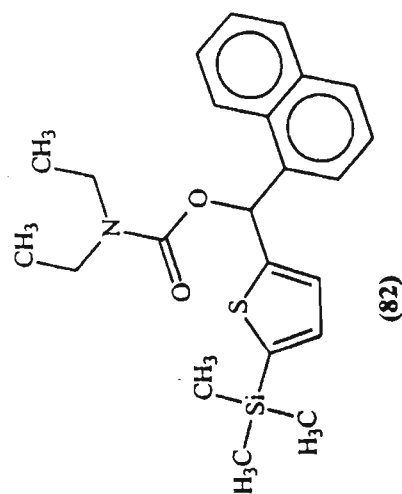




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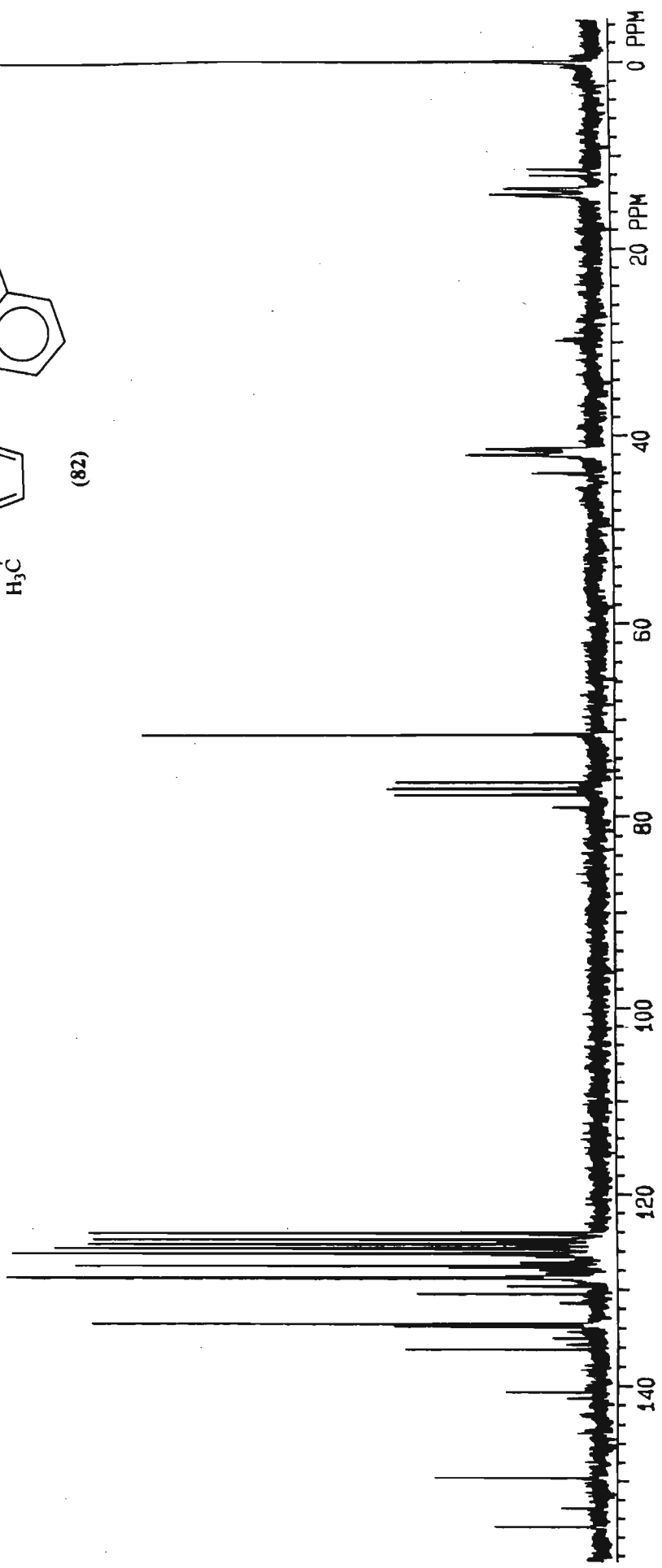
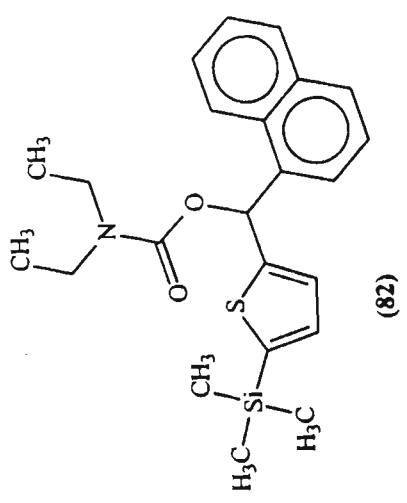


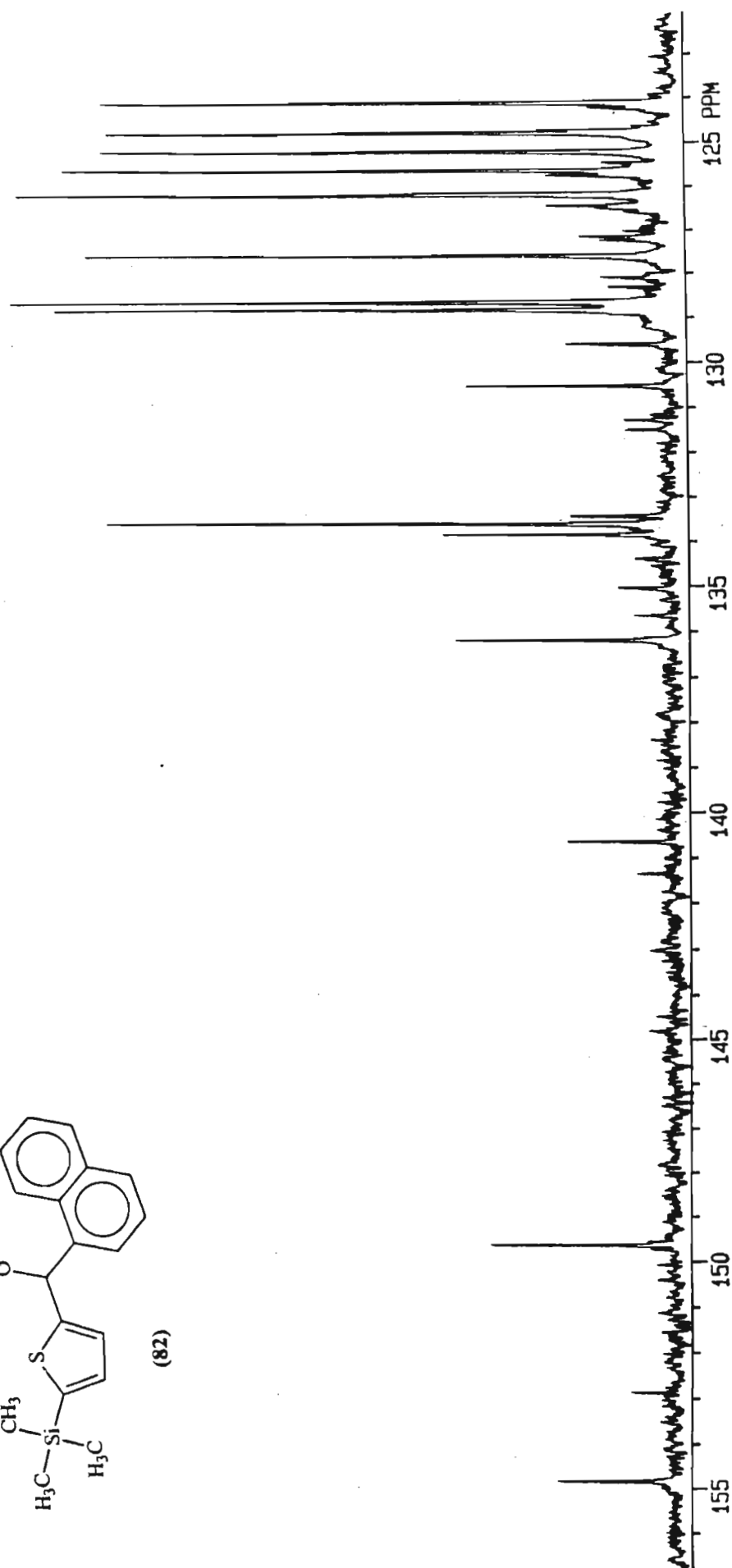
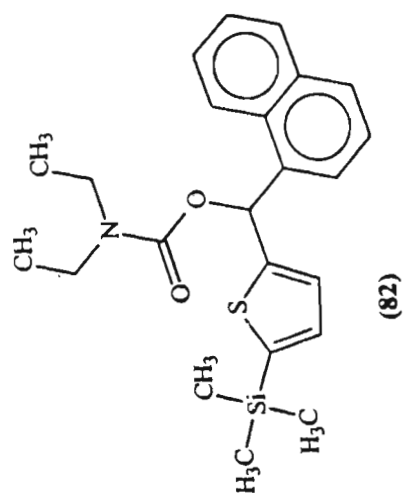


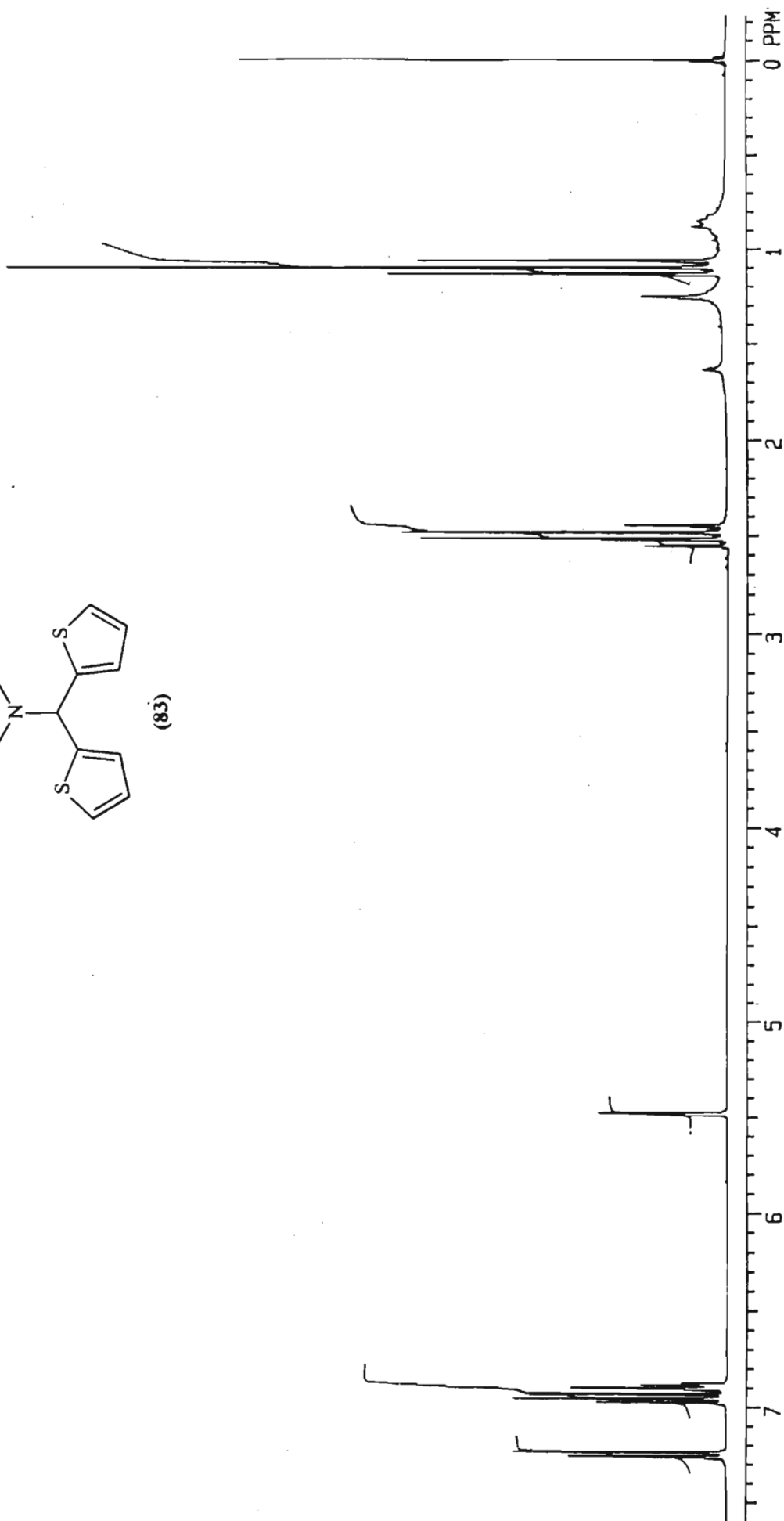
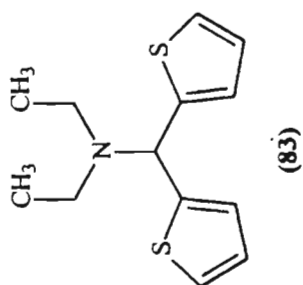


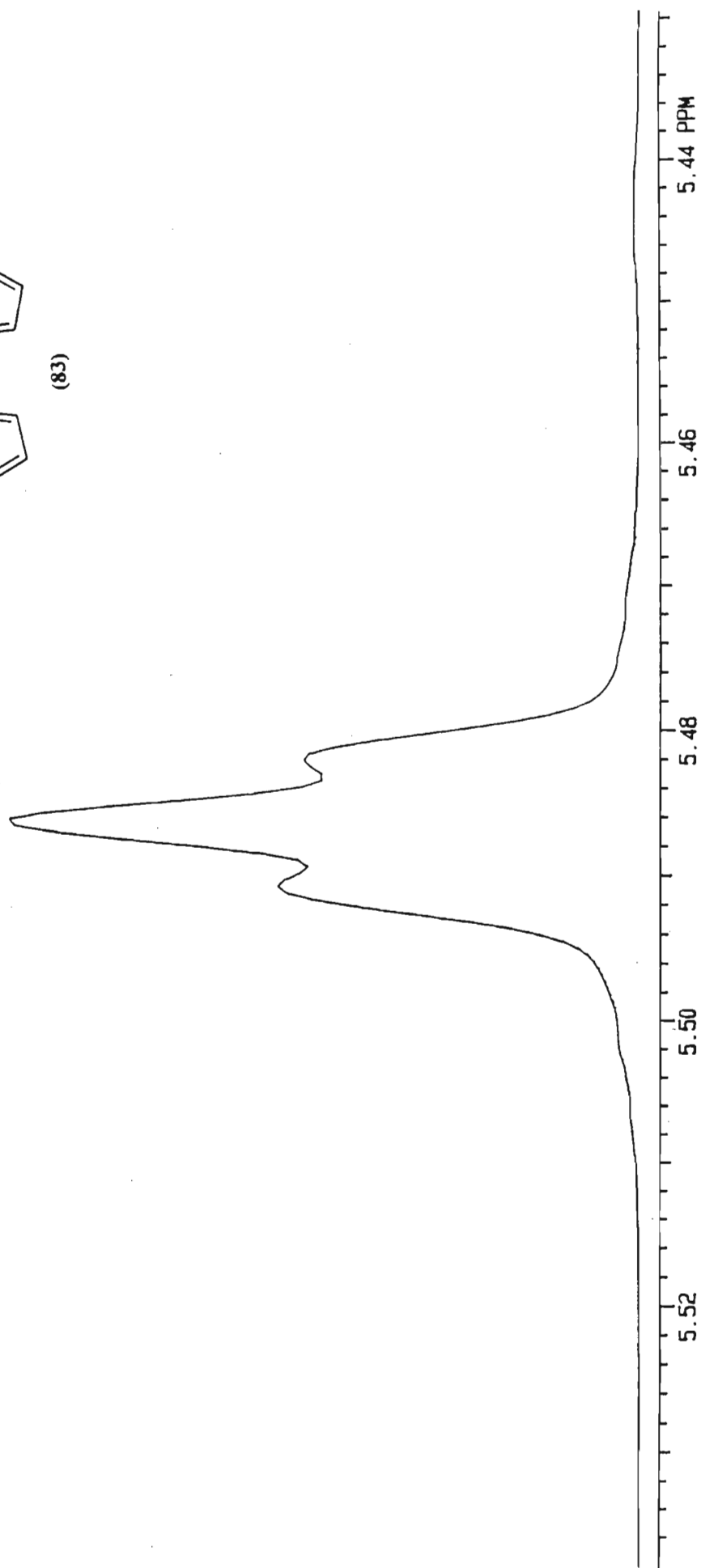
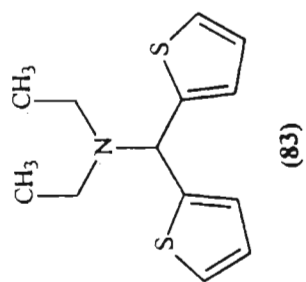
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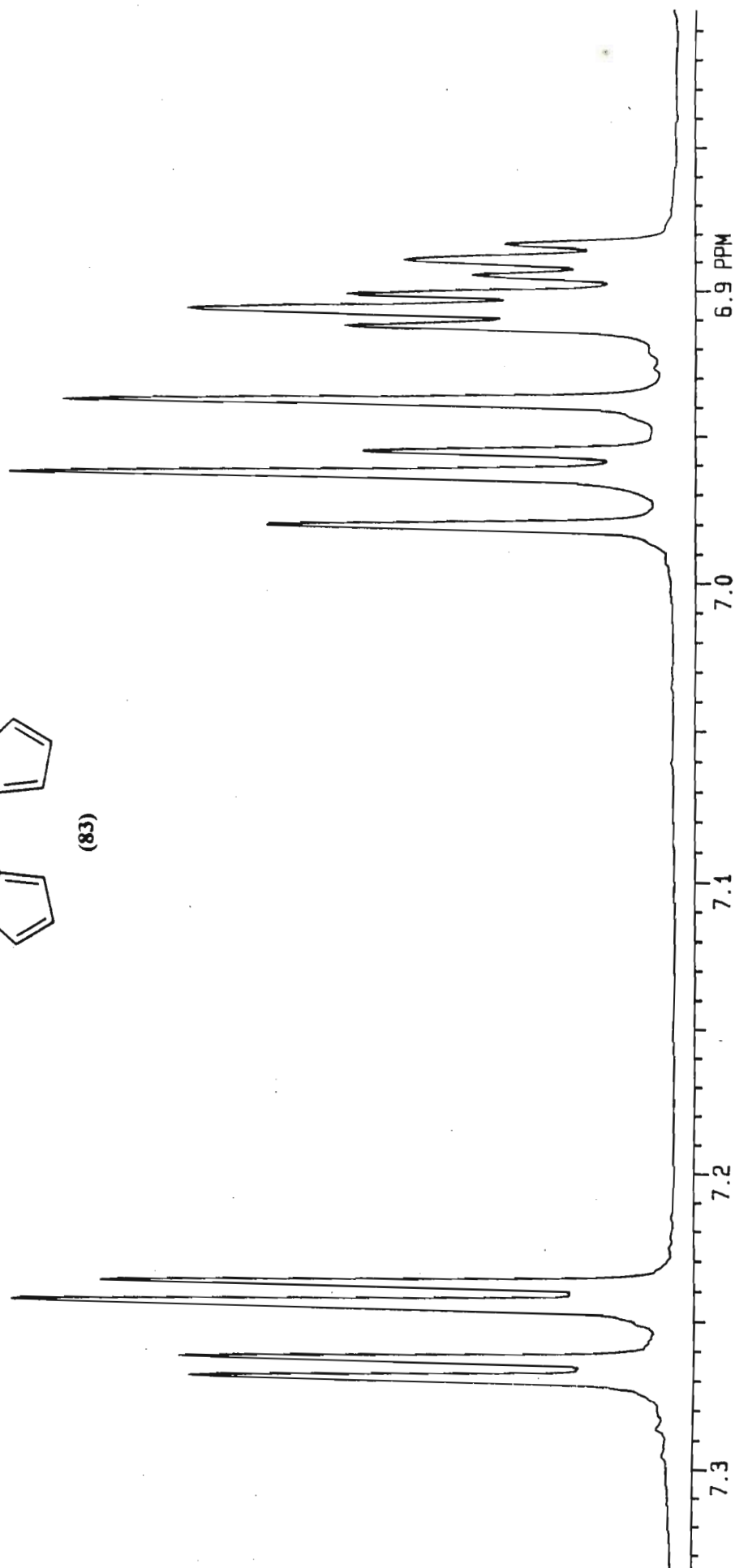
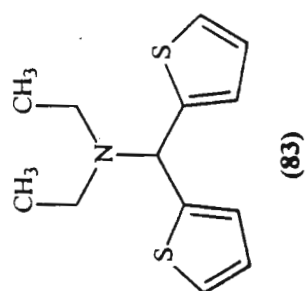
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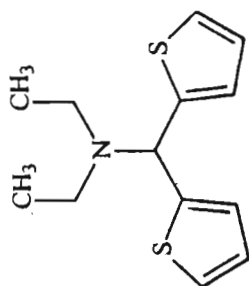
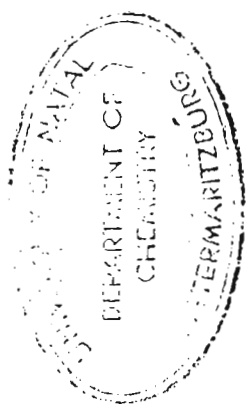




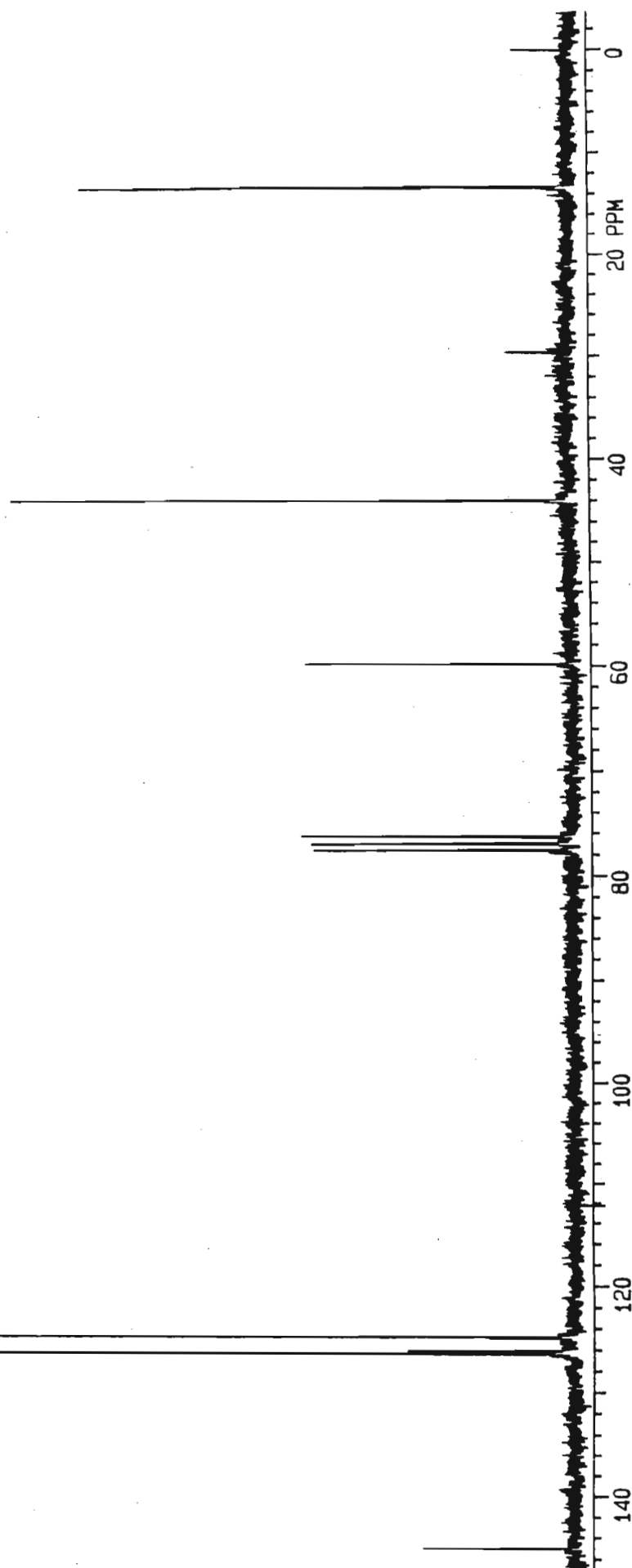


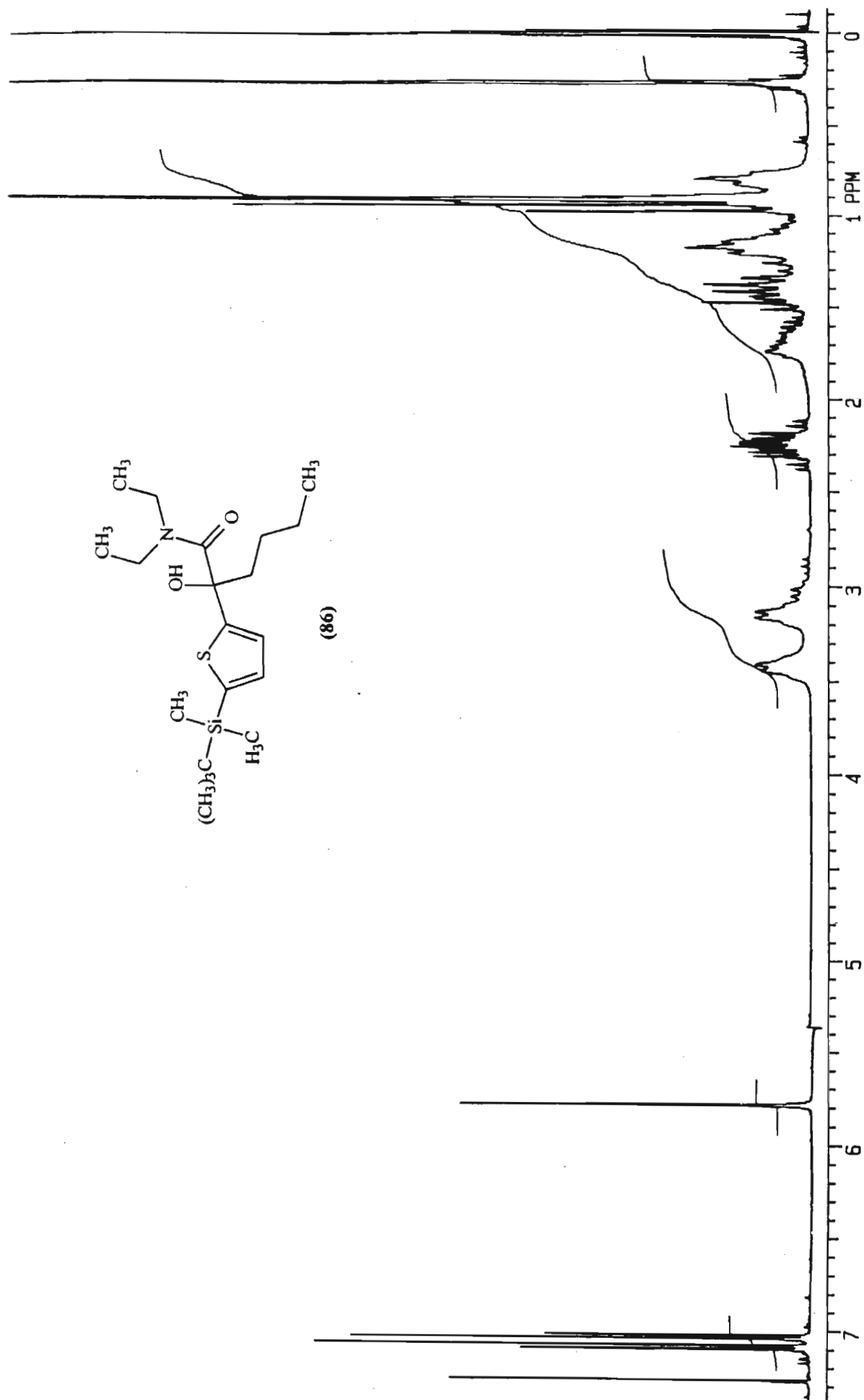


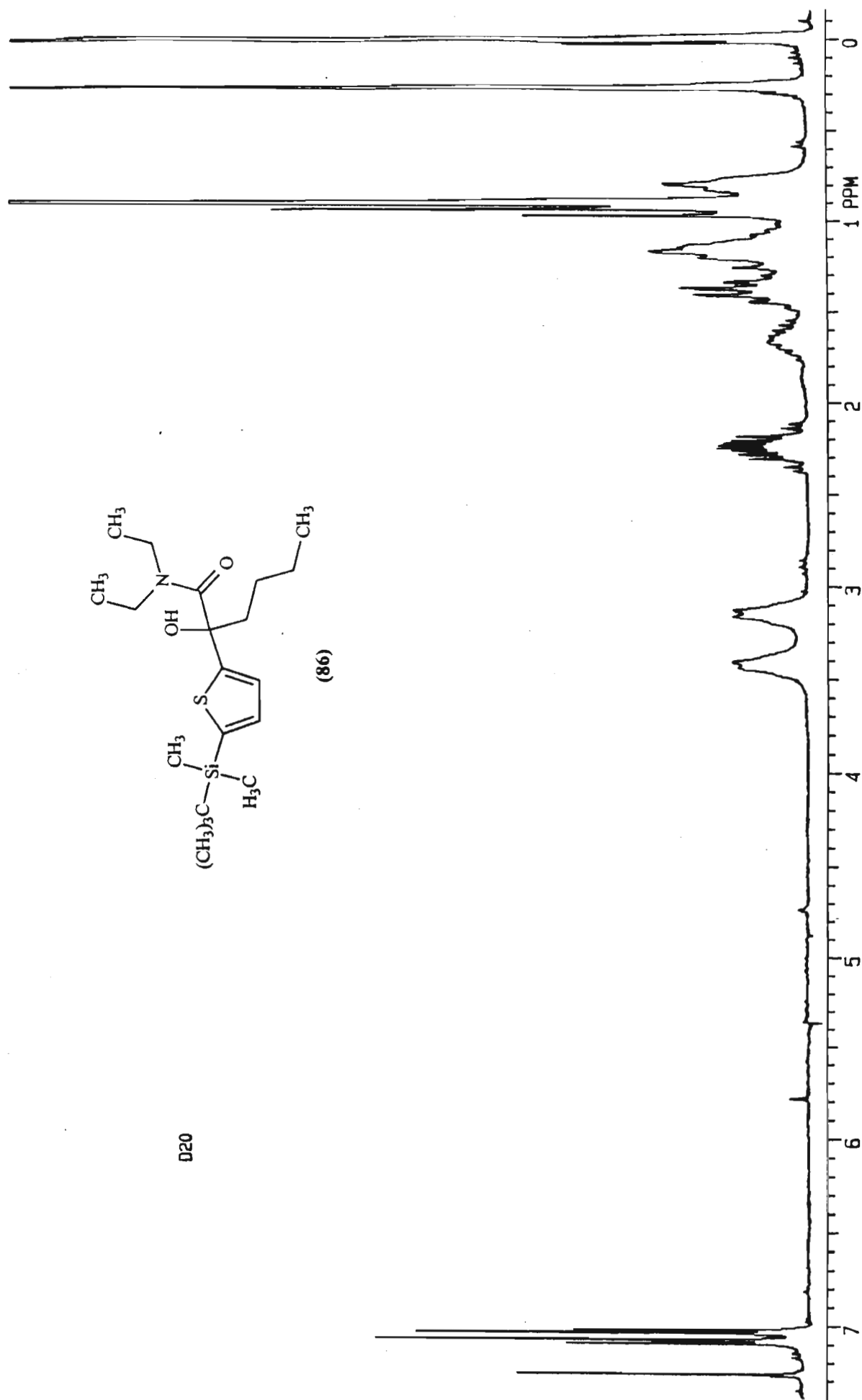




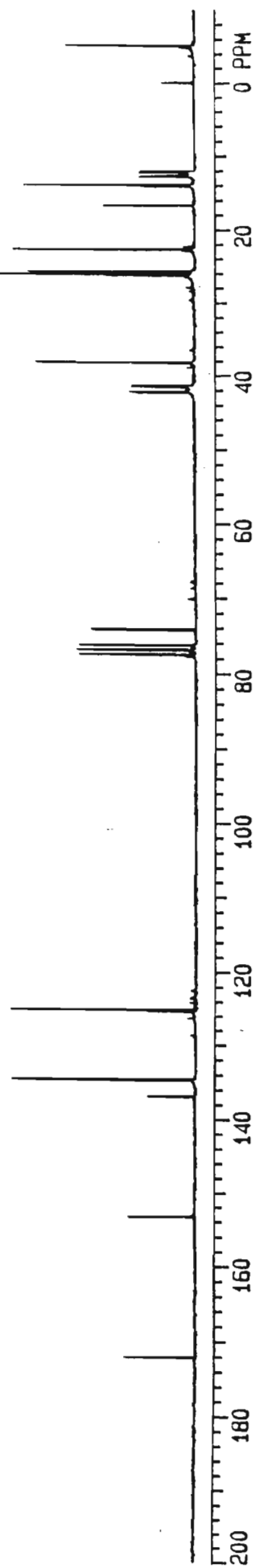
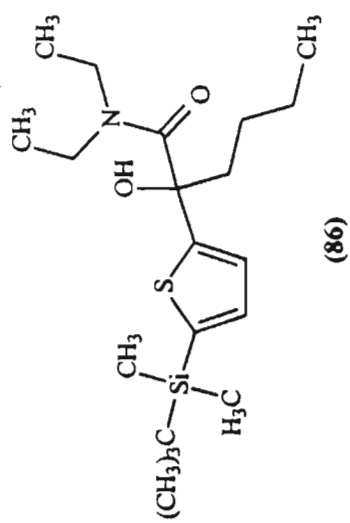
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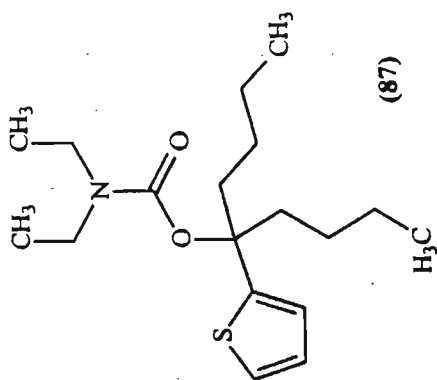
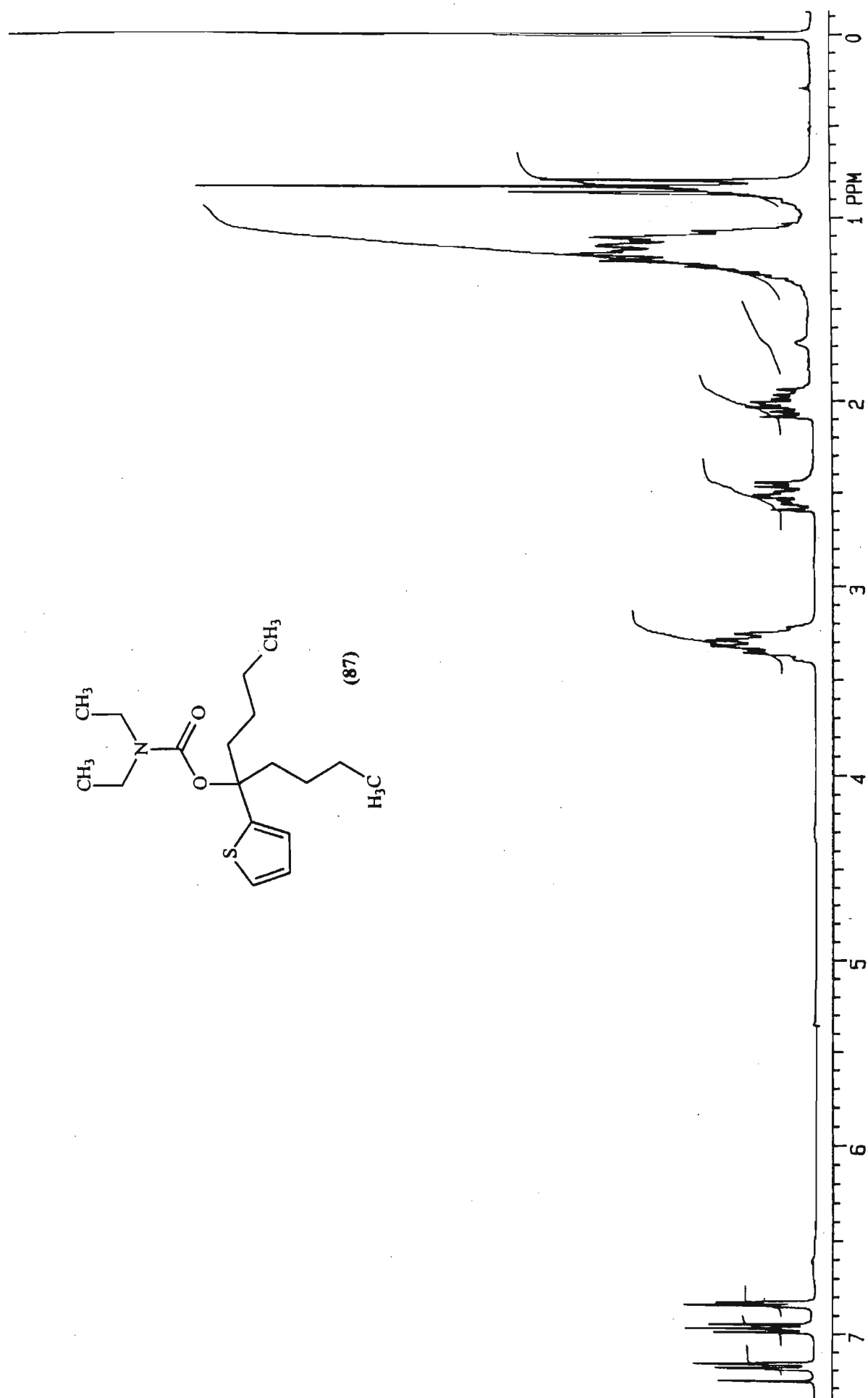


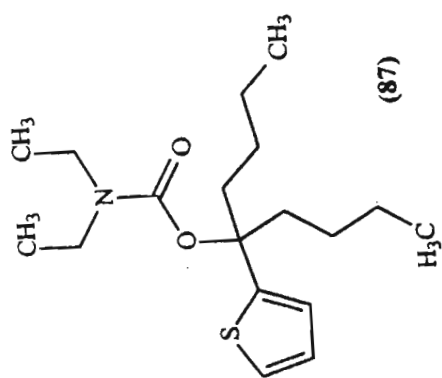




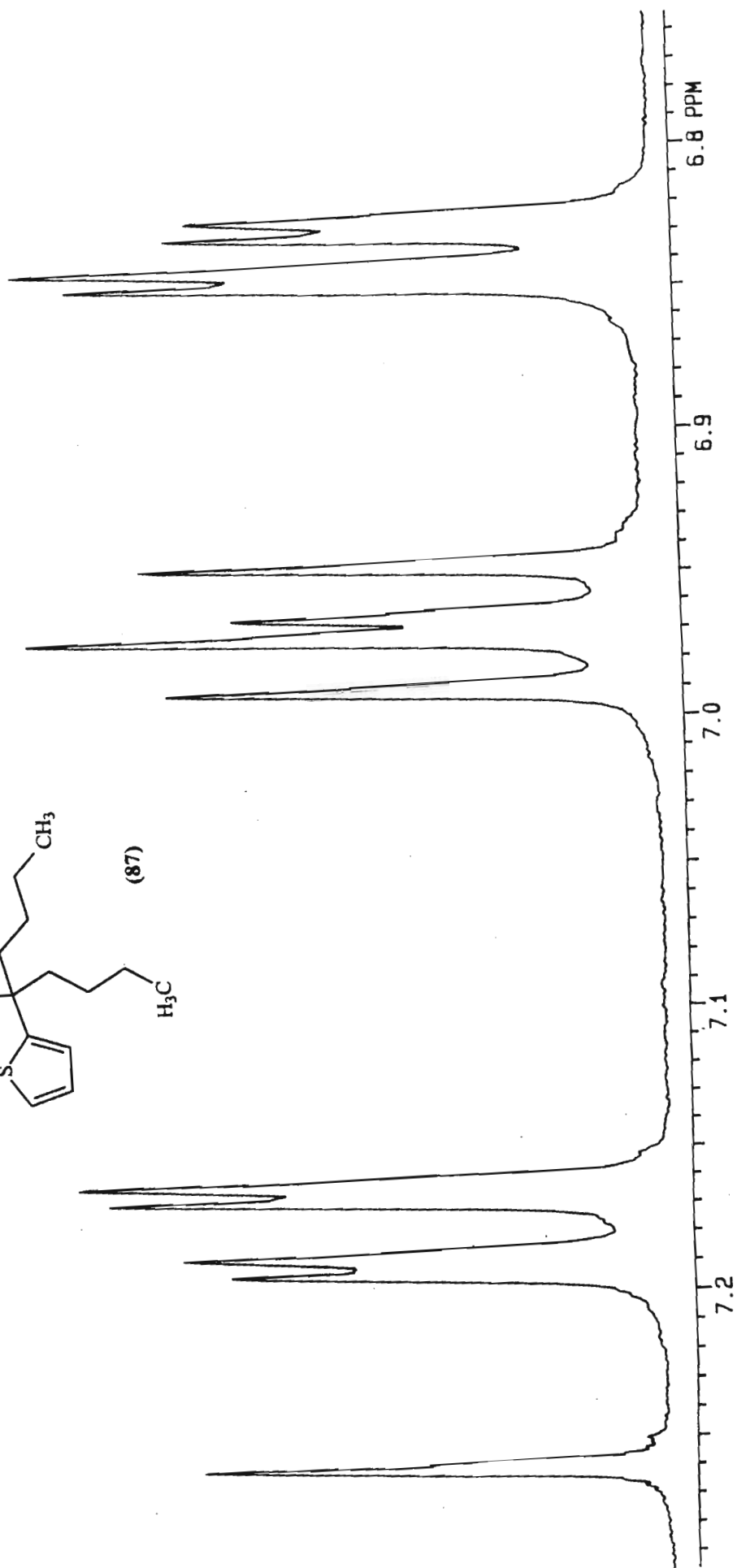
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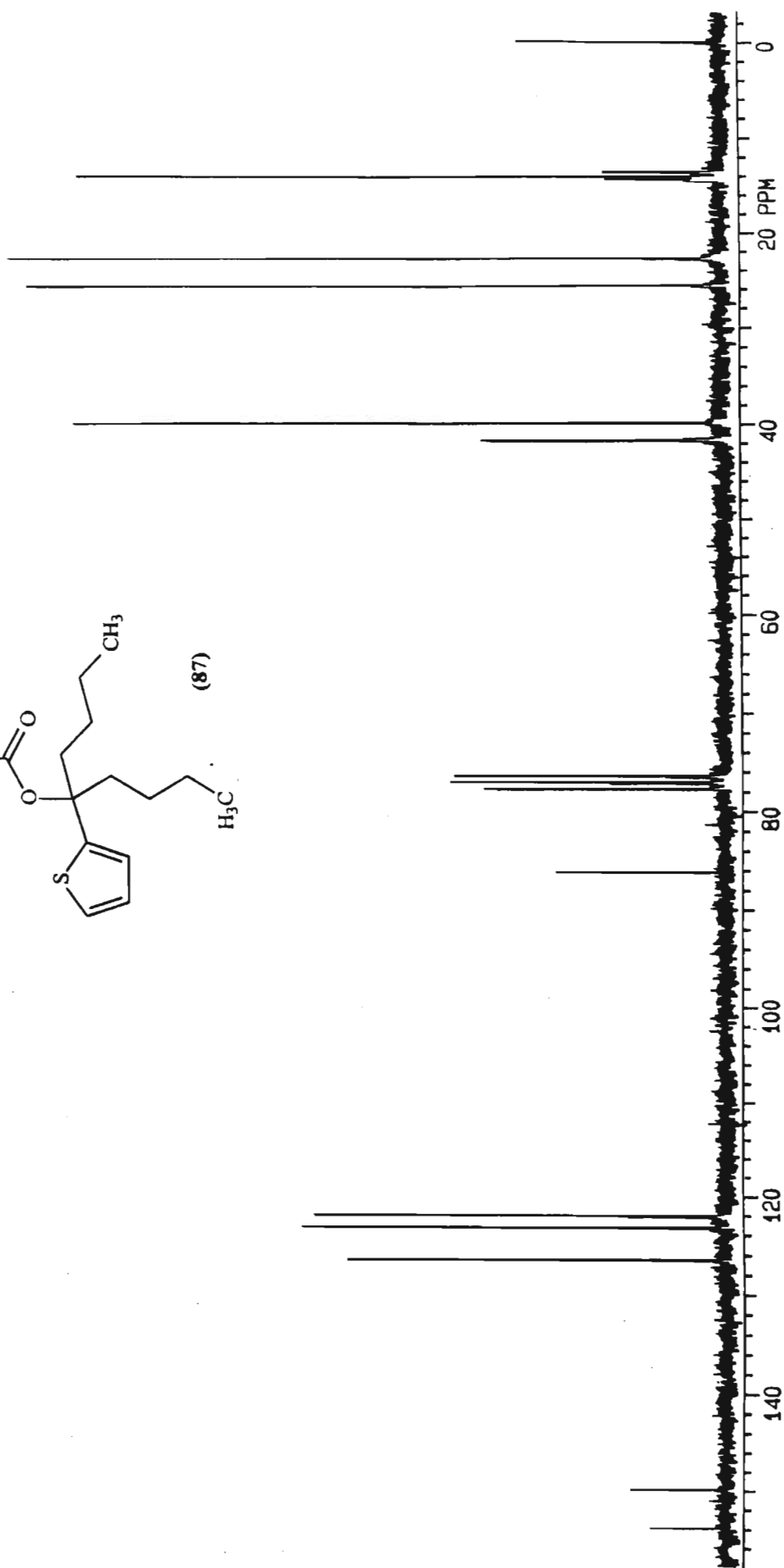
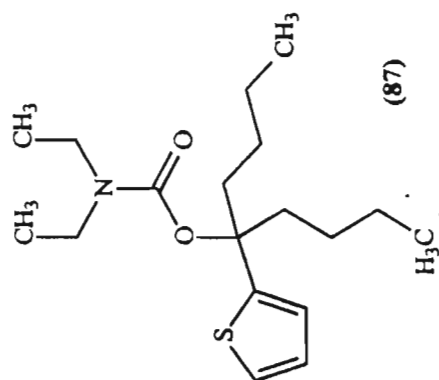


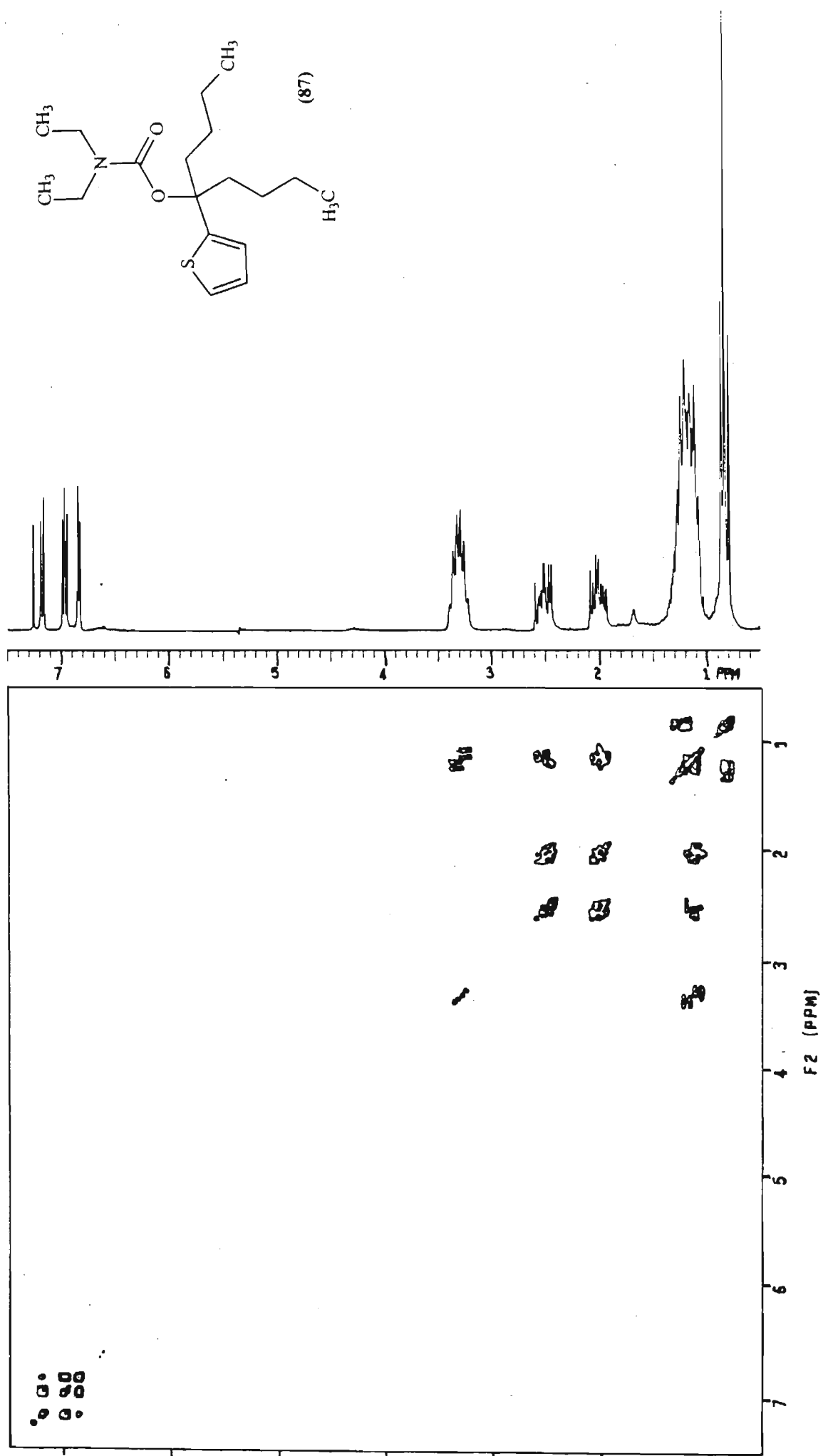


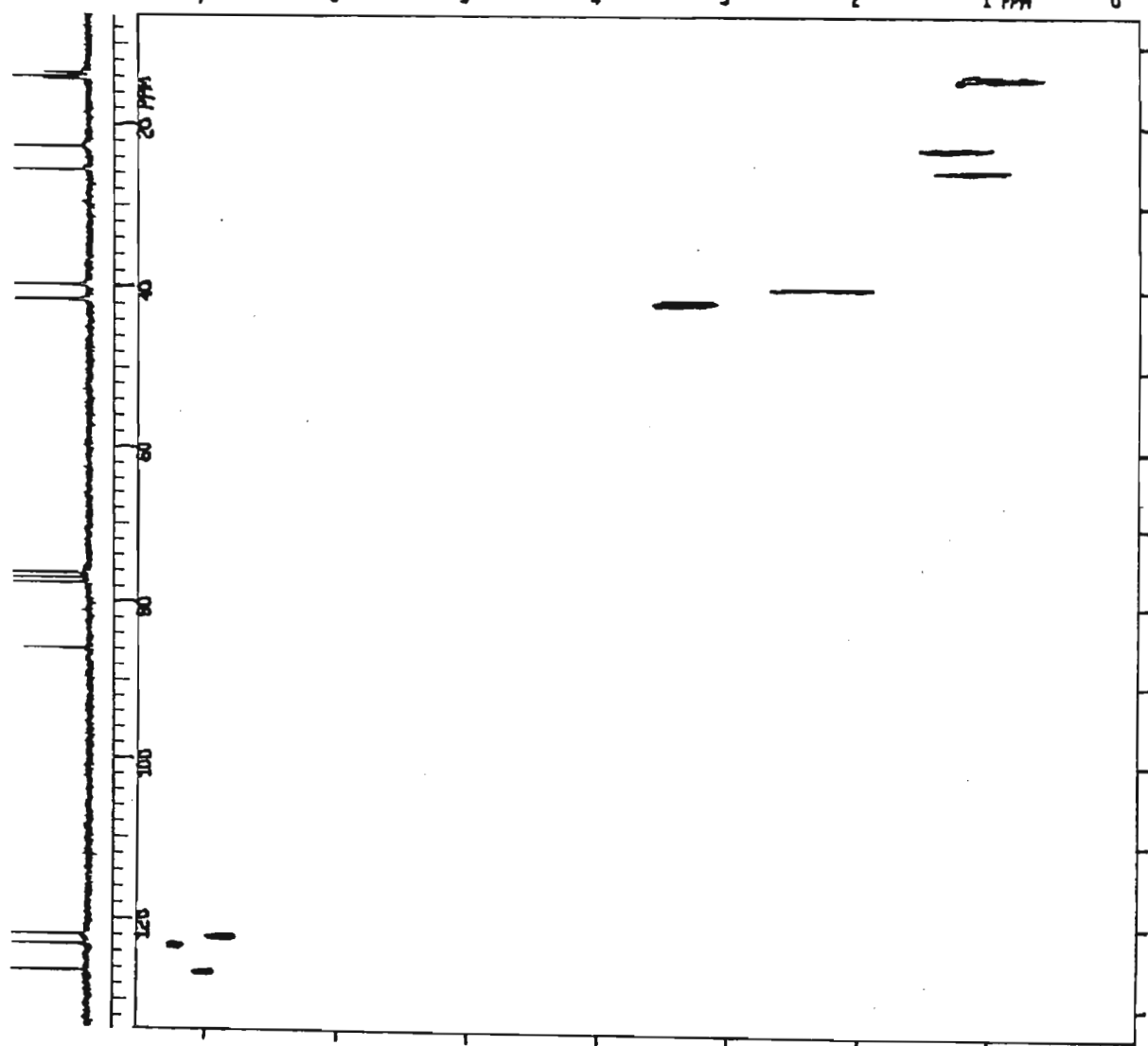
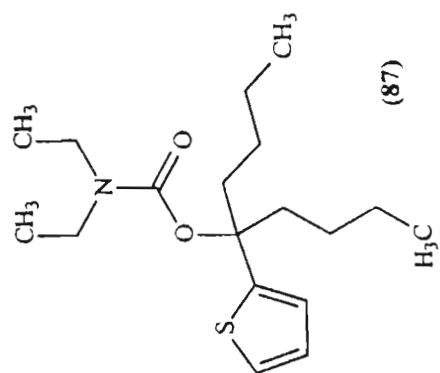


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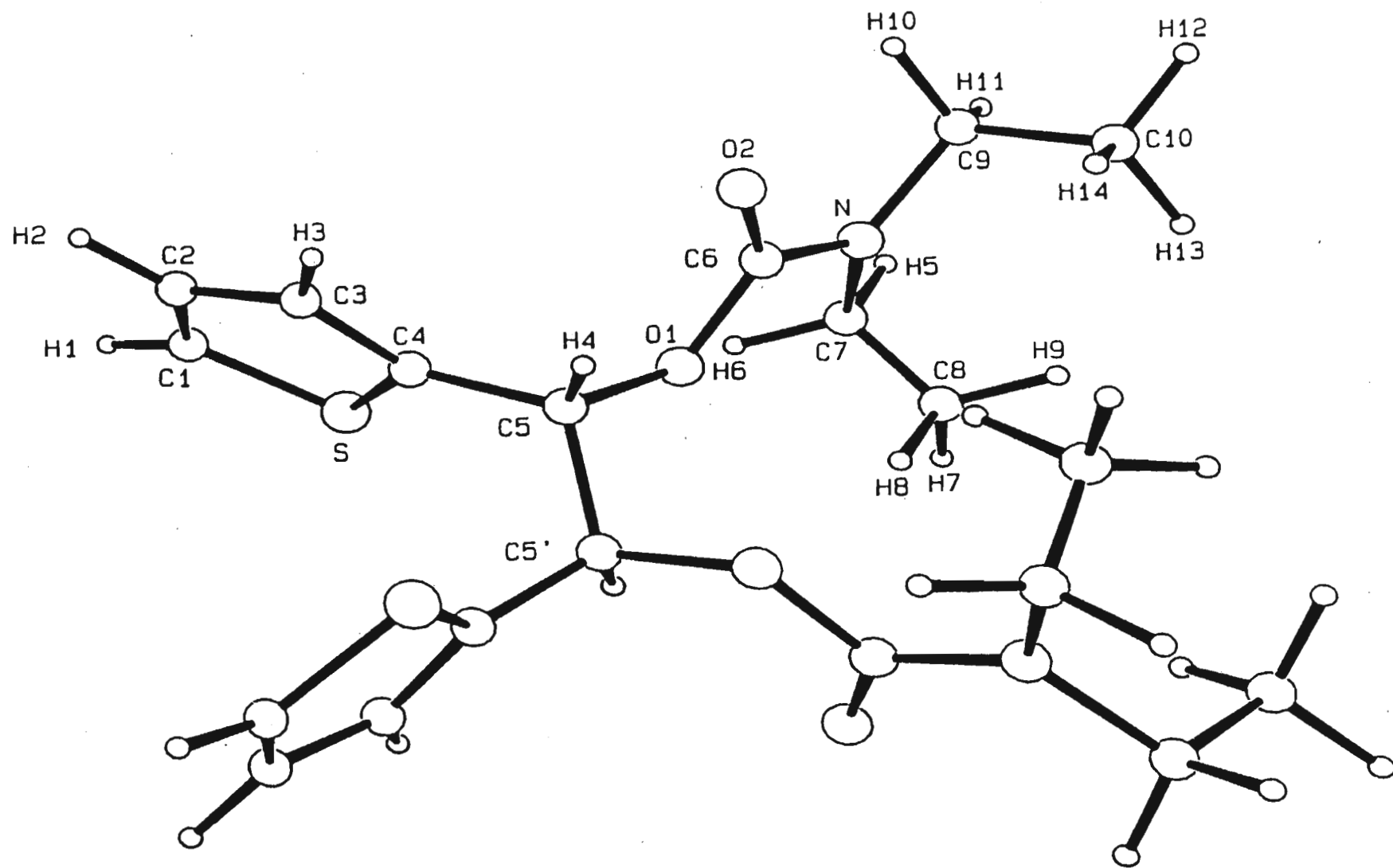








CHAPTER 7
X-RAY CRYSTALLOGRAPHIC DATA



1,2-di-(*N,N*-diethylcarbamoyloxy)-1,2-di-(2-thienyl)ethane (58)

Table 8: Crystallographic Data for 1,2-di-(*N,N*-diethylcarbamoyloxy)-1,2-di-(2-thienyl)ethane (58)¹⁰⁹

Formula	C ₂₀ H ₂₈ N ₂ O ₄ S ₂
Molecular mass (g/mol)	424.57
Cell type	Monoclinic
Space group	C2/c
a (angstroms)	16.9730 (42)
b (angstroms)	12.3776 (24)
c (angstroms)	11.7553 (23)
α (°)	90
β (°)	109.699 (17)
γ (°)	90
V (angstroms ³)	2325.07 (89)
Z	4
R factor	0.0671