Part I : Polymeric Covalently-Linked Sustained Release Dosage Forms of Aspirin

Part II : Investigation of the Synthesis of Some Novel 5-Fused Heterocyclic Ring Systems and Their Potential Application in Medicinal Chemistry

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A Thesis
Presented to
The Faculty of the College of Pharmacy
University of Houston

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Pharmacy

---

by
Richard Foster Miller
December, 1976

DEDICATION

This thesis is dedicated to those people who, through the years, have provided the inspiration, the encouragement, and the means whereby this end might be realized.

To my dear grandparents, Mr. and Mrs. Glenn B. Porter

To my parents, Mr. and Mrs. Richard R. Miller

To Marray and Marisa

And to Judy, my future wife, who has shown me patience, courage, and a side of life which no man can synthesize in a lab.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to Dr. Louis Williams and Dr. Gary E. Martin for their guidance, assistance, immense patience, and time, which made my research and preparation of this thesis possible.

I would also like to thank the other members of my committee, Dr. Lindley Cates, Dr. Kenneth Euler, and Dr. James Benbrook for their guidance and helpful suggestions.

Thanks to Dr. James Hudson of Rice University for his expert work in obtaining the GC/Mass Spectrograms which are presented in this thesis.

For the many hours he spent in the lab as an undergraduate assistant, I thank Jim Turley, for all graduate students need at least two sets of hands.

A special thanks to Dave Feuerbacher, Ken Grantham, and Stan Alford of Dresser Magcobar.

Also, I would like to acknowledge Karen Yost for she typed, corrected, and tolerated the changes in this thesis.

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An Abstract of a Thesis: Part I

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ABSTRACT

Solid phase peptide synthesis, reported by Merrifield in 1964, revolutionized the field of peptide synthesis. The advantages inherent to the solid phase procedure have since been applied to the synthesis of a wide variety of biologically important molecules.

The unique aspects of polymeric supports have also been exploited to permit the conduct of a wide variety of synthetic reactions which take advantage of the resin support. Recently, these applications have led to the development of a variety of polymeric reagents where the reactive moiety is carried by the resin via a labile covalent linkage.

A logical extension of these synthetic procedures was the utilization of labile covalent linkages, of varying hydrolytic susceptibility, as a means for attaching drugs to a polymeric backbone. The preparation of a series of aspirin containing polymers, the aspirin attached by linkages of varying hydrolytic susceptibility, and their subsequent evaluation as potential sustained release dosage forms has been described. It was also shown that linkages of intermediary stability may provide the best potential sustained release polymeric carriers.

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December, 1976

ABSTRACT

A number of syntheses of diaryl sulfides have appeared in the chemical literature of the last seventy years. Generally, these procedures have required harsh reaction conditions. The reaction of halonitro-, halodinitro-, and nitrodihalobenzenes to yield a variety of sulfides has been explored by a number of authors. The displacement of nitro groups from a variety of substrates has also been investigated. Specifically, several of these procedures have generated sulfides either as synthetic intermediates or as intended final products.

The intermediate upon which this research was focused, 1,3-bis(thiophenyl)-4-nitrobenzene, was synthesized by means of a halo- displacement from halodinitrobenzene and a subsequent nitro- displacement to yield the desired bisulfide.

The preferential and sequential displacement of halo- and nitro- substituents from aromatic rings was further explored as a means of providing a general synthetic route to dissymmetric bisulfides. Positional isomers were studied to determine their effects upon nucleophilic substituent displacement. Further, a plausible synthesis of the desired 5-fused heterocyclic ring system is discussed.

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Part I: Polymeric Covalently-Linked Sustained Release Dosage Forms of Aspirin

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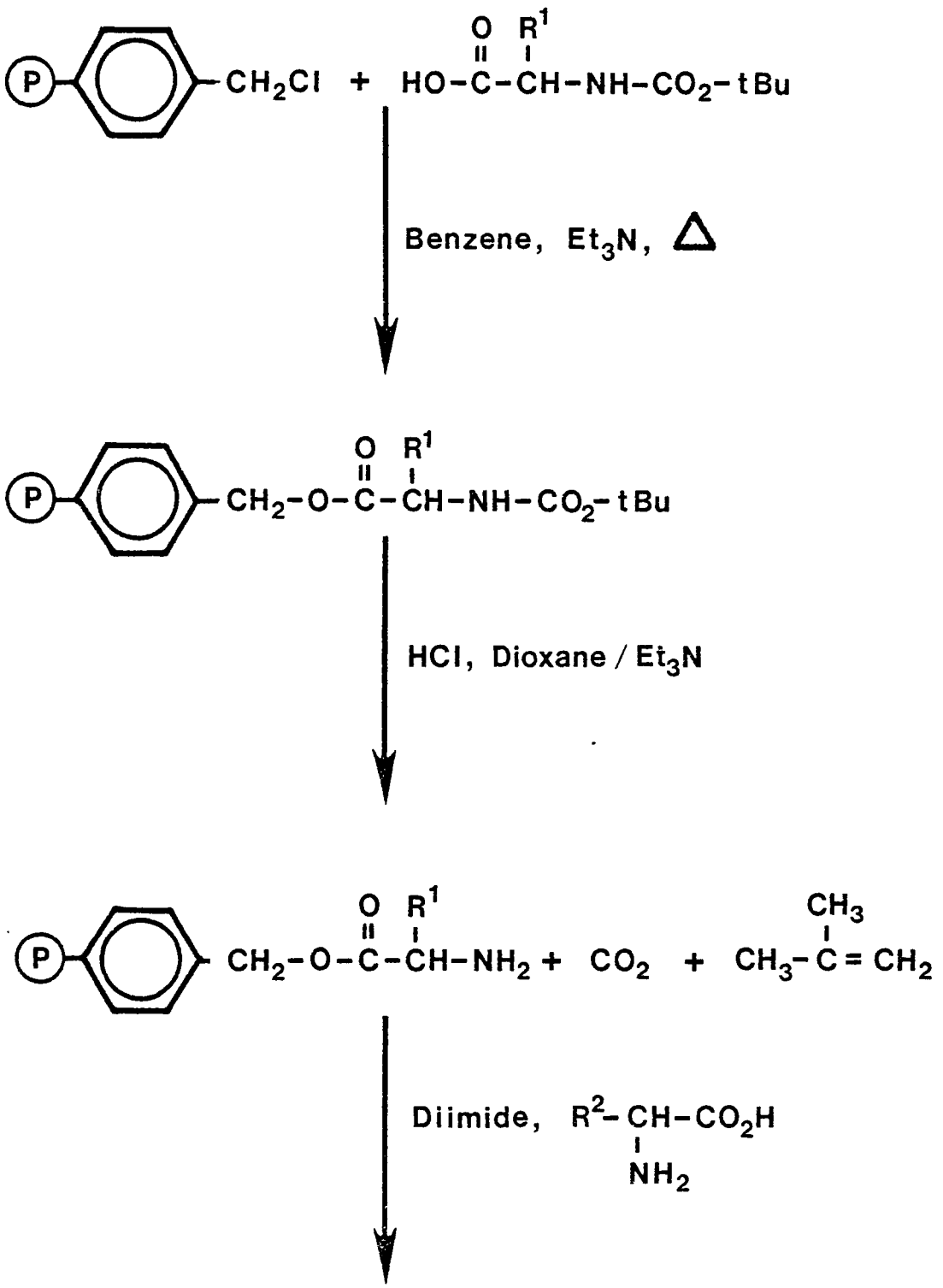
INTRODUCTION

Considerable effort has been spent on the development of synthetic reagents to facilitate the execution of chemical reactions under mild conditions. Substantial and significant advances have been made in the adaptation of polymers in such applications since insoluble resin techniques offer several advantages in preparative procedures. Polymeric resins can be used as centers upon which large molecules can be grown; provide pseudo-high dilution conditions to hold reagents from other reagents during a preparative procedure; and can be used to support catalysts during chemical transformations.

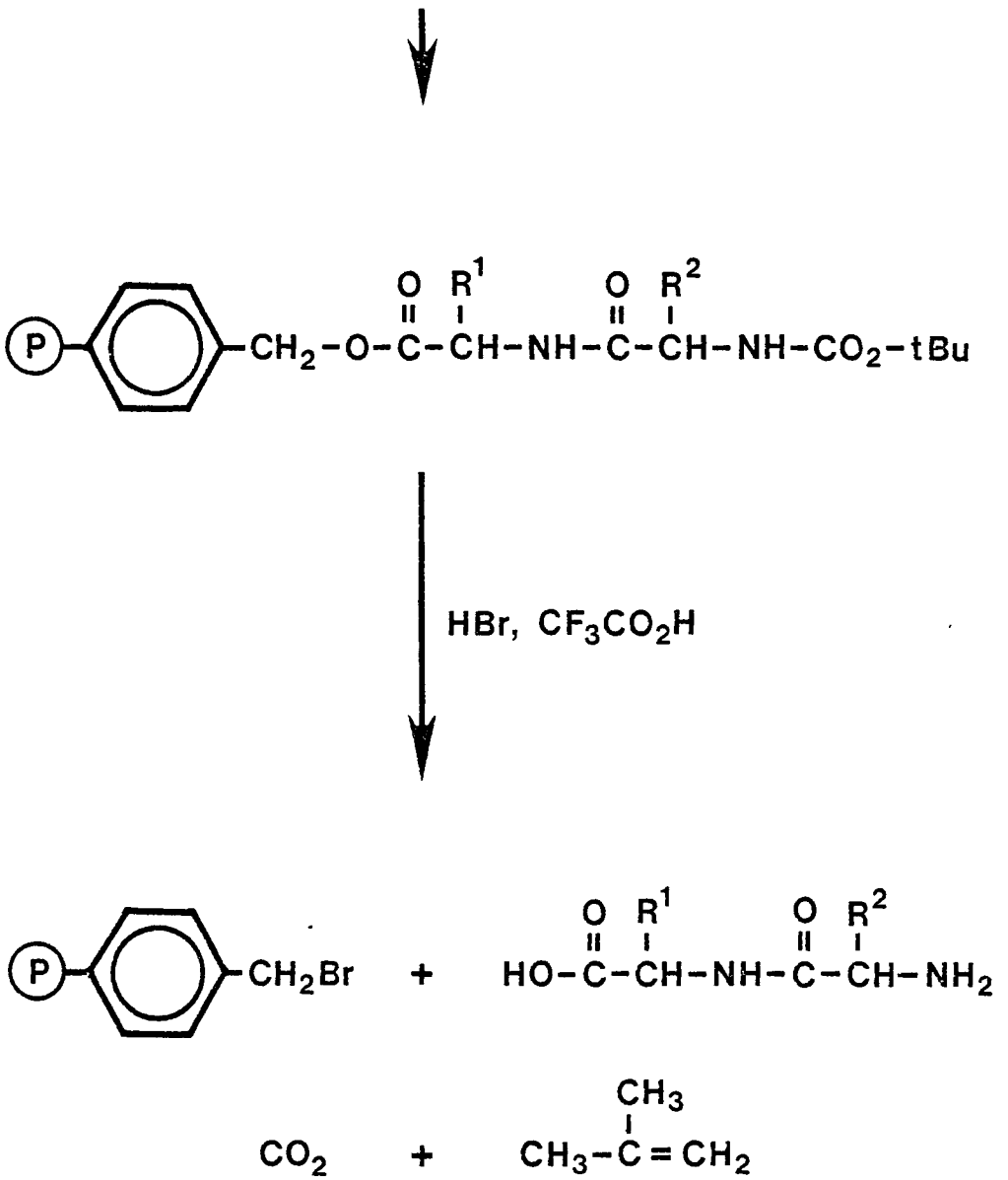
Early synthetic applications utilized polymers as insoluble solid supports on which the substrate could be covalently linked following suitable chemical functionalization of the resin. The covalently linked substrate was then subjected to the desired chemical reaction and the product subsequently cleaved from the polymer hydrolytically following completion of the desired reaction.

The earliest demonstrated application of the suitability of polymers in synthetic techniques was that of Merrifield (1) in 1963. The preparation of polypeptides, utilizing a solid insoluble polymeric resin, is illustrated in Scheme I. The advantage of the solid phase synthetic method lies in the nearly quantitative yields which may be obtained and the avoidance of the cumbersome purification procedures utilized in conventional synthetic procedures. The advantages gained in solid phase syntheses have also been applied to the syntheses

Scheme I


P
CH2Cl
+
HO-C-CH-NH-CO2-tBu
O
R1
Benzene, Et3N, Δ
CH2-O-C-CH-NH-CO2-tBu
HCl, Dioxane / Et3N
CH2-O-C-CH-NH2
+ CO2 +
CH3-C=CH2
CH3
Diimide,
R2-CH-CO2H
NH2

Scheme I (Cont.)



P— = Polystyrene Backbone

of polynucleotides by Letsinger (2-4) and Hayatsu (5, 6), as well as polysaccharides by Frechet and Schuerch (7-9) and Yip (10). In addition, other high molecular weight biopolymers as well as macrocyclic peptides (11), as shown in Scheme II, have been prepared by similar procedures.

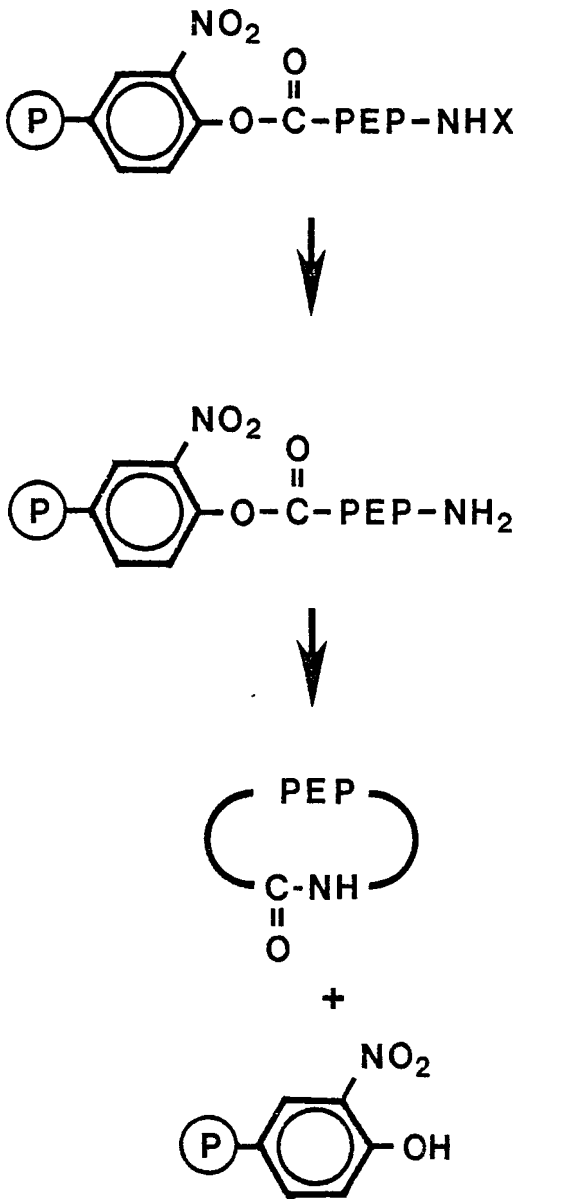
In the procedures discussed thus far, the reaction is conducted sequentially; i.e., a series of specific steps repeated in sequence. Following the final step, the product is cleaved from the resin followed by removal of the resin by filtration.

Variations of the sequential reactions discussed above have been adapted to include a variety of specific synthetic reactions. An early example of an application demonstrating the unique advantages of a polymer assisted reaction was the mixed Dieckmann cyclization of esters reported by Crowley and Rapoport (12). The complicated purification procedure, which would have been necessitated by conventional synthetic procedures was avoided since only one product was released from the resin upon cyclization.

These reactions are illustrated in Scheme III. The second product, formed by cyclization in the other possible direction, remained attached to the resin and was subsequently recovered by hydrolysis from the resin.

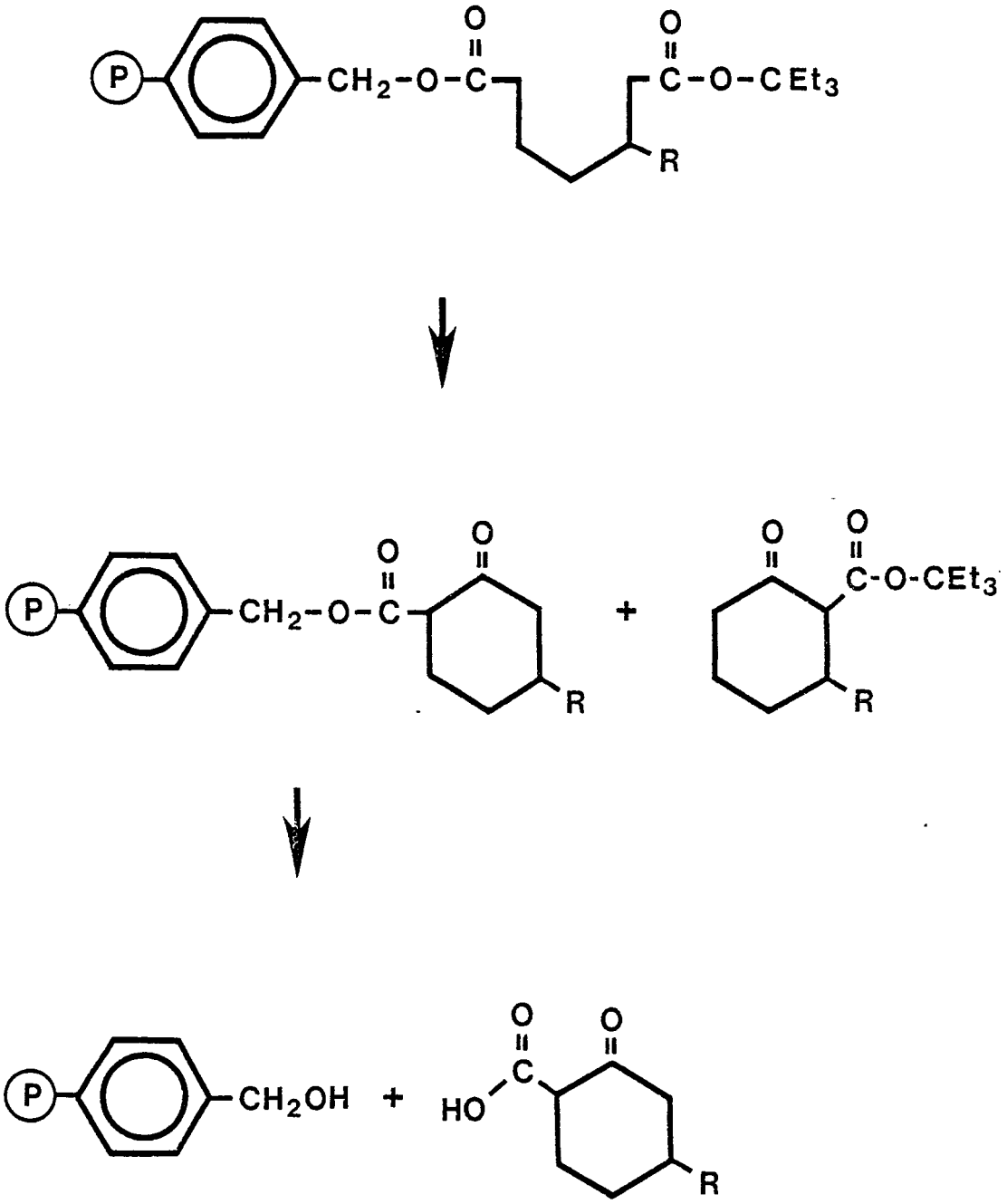
Solid phase synthesis has also been used to advantage in the monoacylation and the monoalkylation of esters (13, 14). After immobilization of the ester on a solid polymeric support, self-condensation of the ester was unlikely under the conditions of the subsequent reaction which paralleled conventional high dilution techniques. When the immobilized ester was treated with one equivalent of base, the desired

Scheme II



PEP = $-O-\left(\underset{\underset{R}{|}}{\overset{\overset{O}{\|}}{C}-CH-NH}\right)_n X$

Scheme III



monoacylated or monoalkylated product was obtained on treatment with the appropriate acyl or alkyl halide. These related reactions are illustrated in Scheme IV.

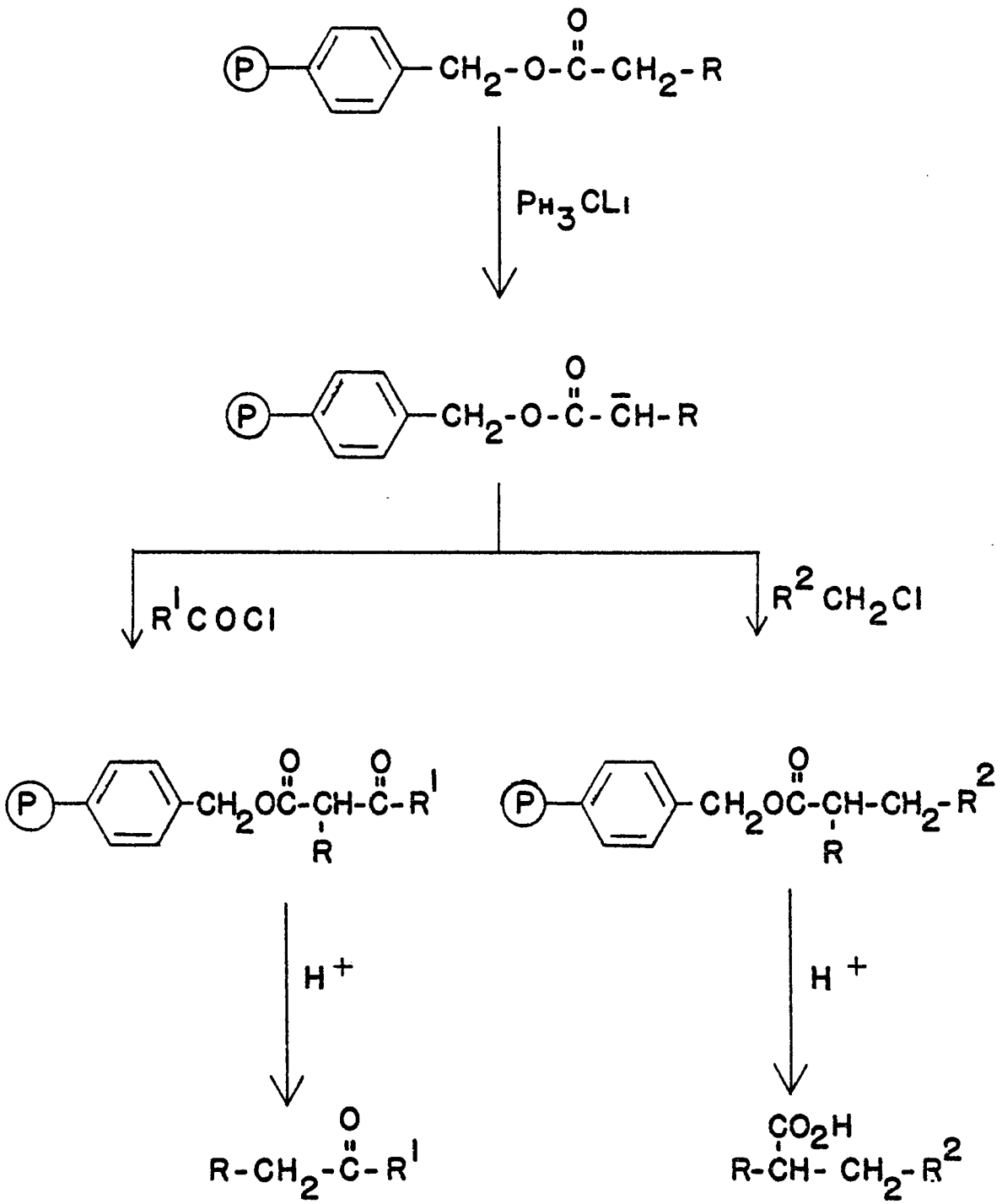
Solid insoluble polymeric supports have also been used to facilitate the mono-reaction of symmetrical bifunctional compounds. An acid chloride-containing polymer was shown to react exclusively at one hydroxyl function in the presence of a large excess of diols to give the mono-blocked diol. Subsequent reaction with trityl chloride (15) or tetrahydropyran (16) gave the corresponding monoethers which were then cleaved from the resin by base hydrolysis. The general reaction employed is shown in Scheme V.

A similar novel procedure for the mono-blocking of symmetrical dialdehydes has also been recently developed by Leznoff (17). An insoluble resin containing a diol functional group was prepared and used to selectively block one function of a series of symmetrical dialdehydes, as illustrated in Scheme VI. The free aldehyde was then used to prepare a variety of previously unreported formyl-substituted compounds.

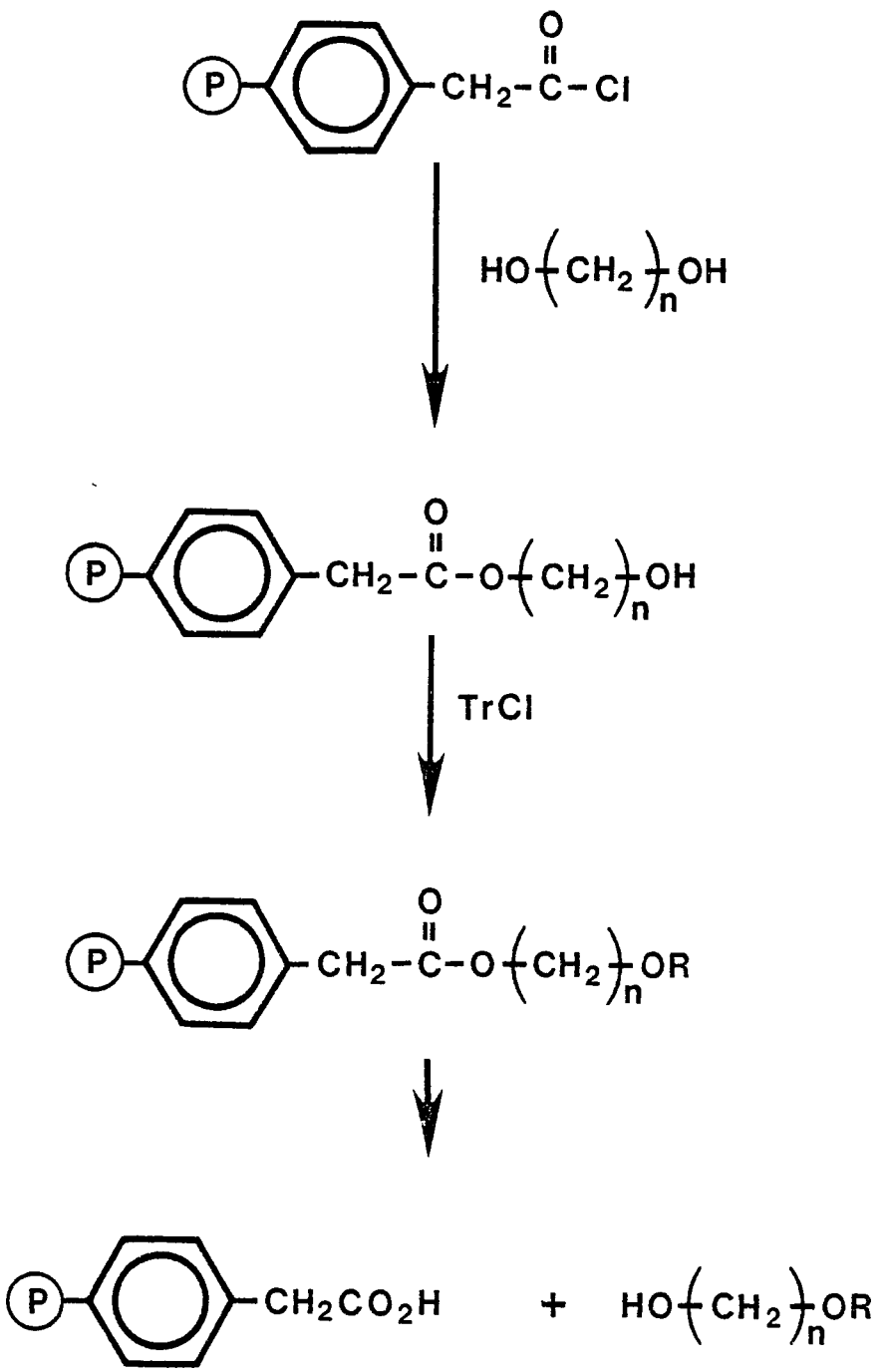
The possibility of adjacent sites coming into close proximity when mounted on polystyrene resins led to studies dealing with intraresin reactions (18-21). Depending upon the synthetic goal of the reaction, this effect may be used to advantage or may be responsible for an undesirable side reaction such as "chain-doubling" observed during polymer assisted peptide synthesis (22), illustrated in Scheme VII

It is possible to induce intrapolymeric reactions by using resins which are highly loaded with the synthetic materials. Kraus and Patchornick (23) have demonstrated the feasibility of using polymeric resins for such reactions by

Scheme IV

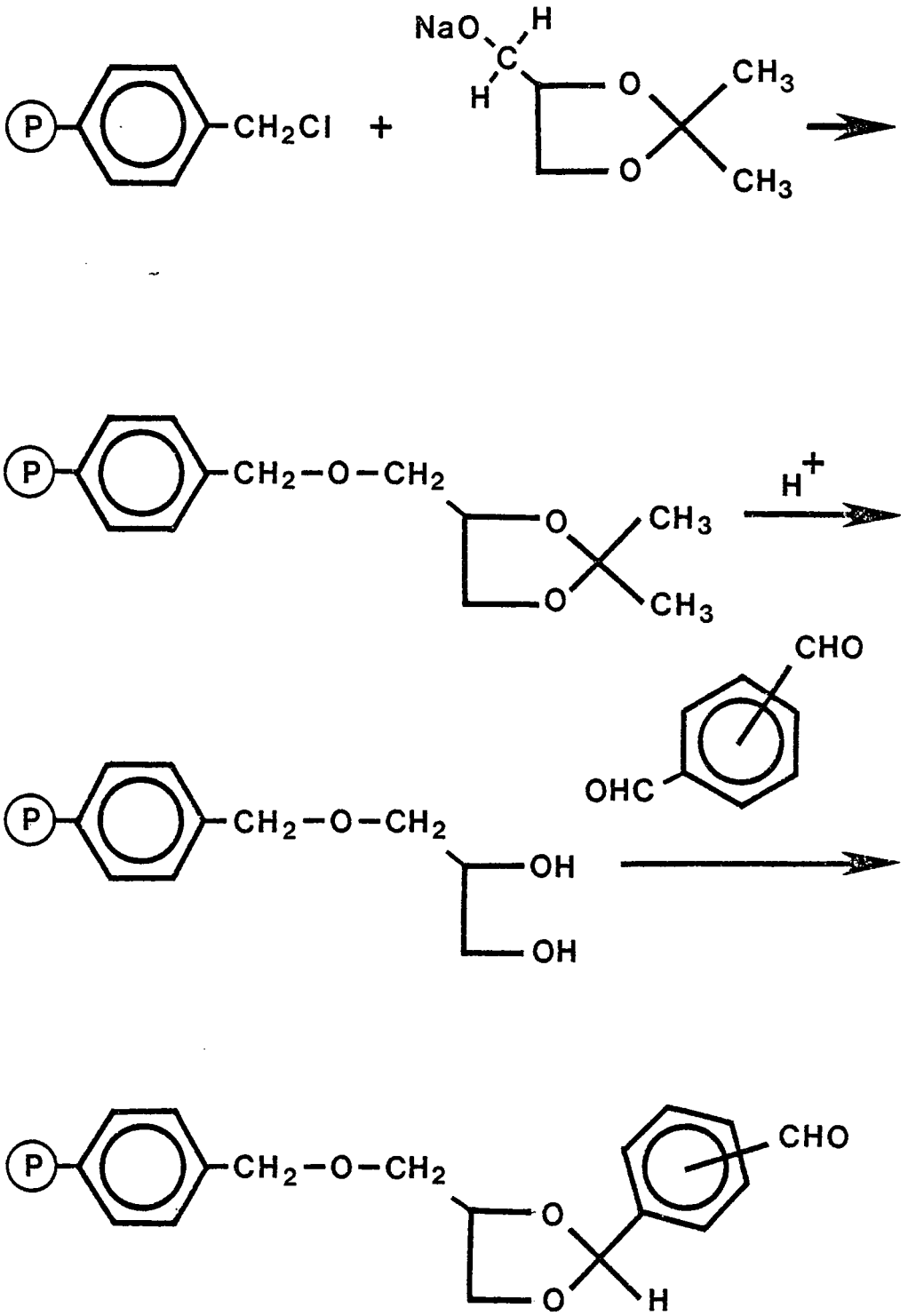

P
CH2-O-C-CH2-R
O
PH3CLi
CH2-O-C-CH-R
R1COCl
R2CH2Cl
CH2OC-CH-C-R1
CH2OC-CH-CH2-R2
H+
R-CH2-C-R1
CO2H
R-CH-CH2-R2

Scheme V

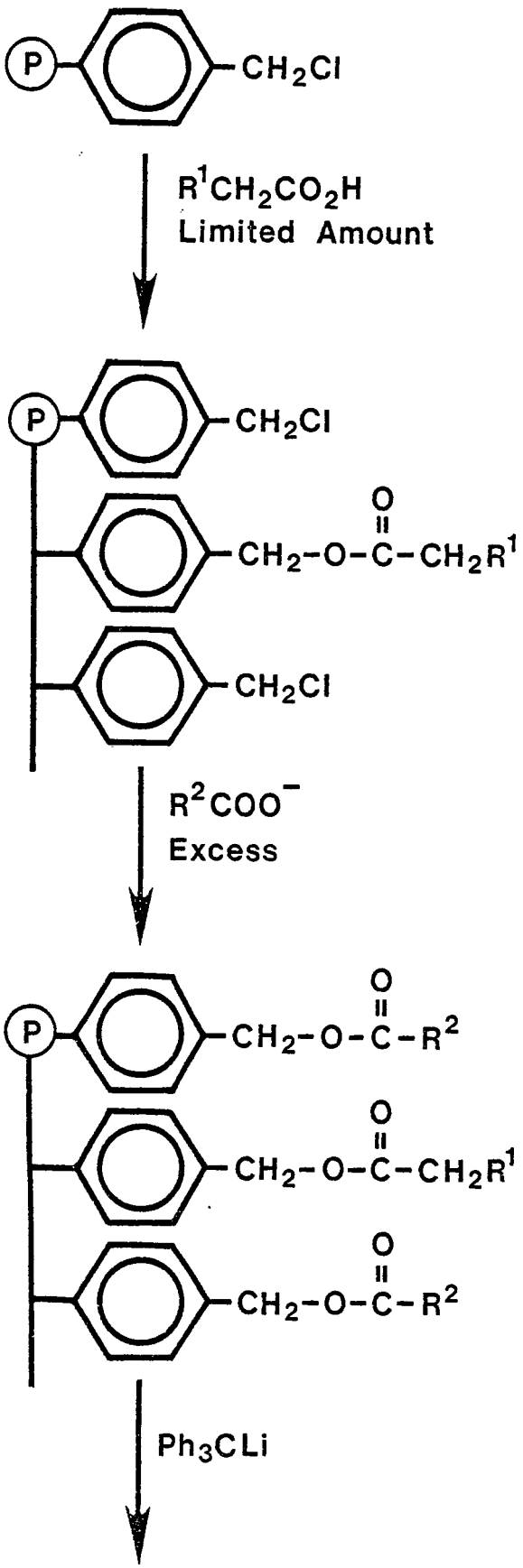


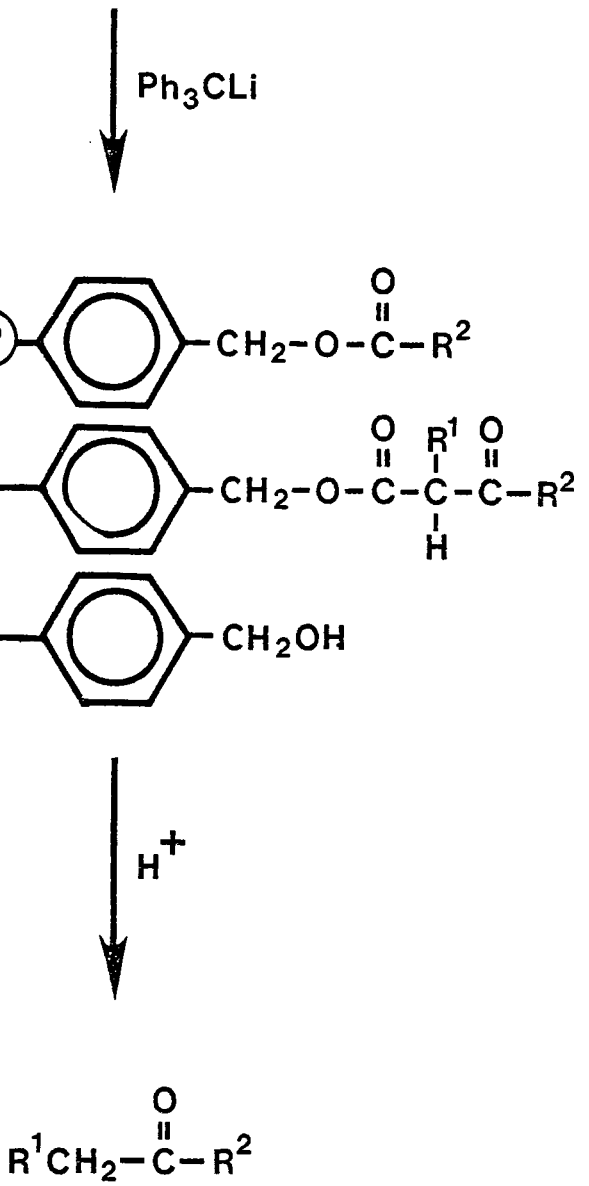
n = 1, 2, 3, etc.
Tr = Trityl

Scheme VI



Scheme VII


P
CH2Cl
R1CH2CO2H
Limited Amount
P
CH2Cl
O
CH2-O-C-CH2R1
CH2Cl
R2COO−
Excess
P
O
CH2-O-C-R2
O
CH2-O-C-CH2R1
O
CH2-O-C-R2
Ph3CLi



$$R^1CH_2-\overset{O}{\overset{\|}{C}}-R^2$$

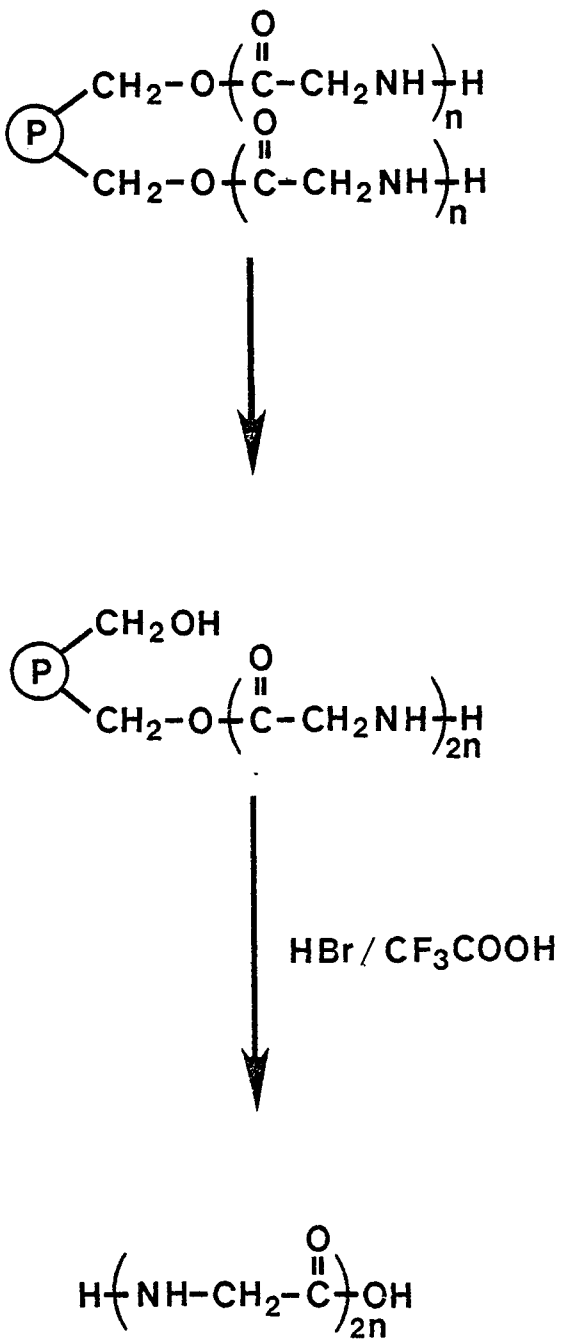
condensation of an enolizable or a nonenolizable ester bound to the same resin as shown in Scheme VIII.

As a result of the widely varied nature of functional groups attached to the resins used, numerous chemical procedures for the attachment of molecules to polymeric resins have resulted. Neckers et.al. (24) prepared polymer-protected Lewis acids such as aluminum trichloride. The complex in which the aluminum trichloride is entrapped results in a shelf-stable catalyst which when required for a preparative procedure is released by simply swelling the polymer in an appropriate solvent.

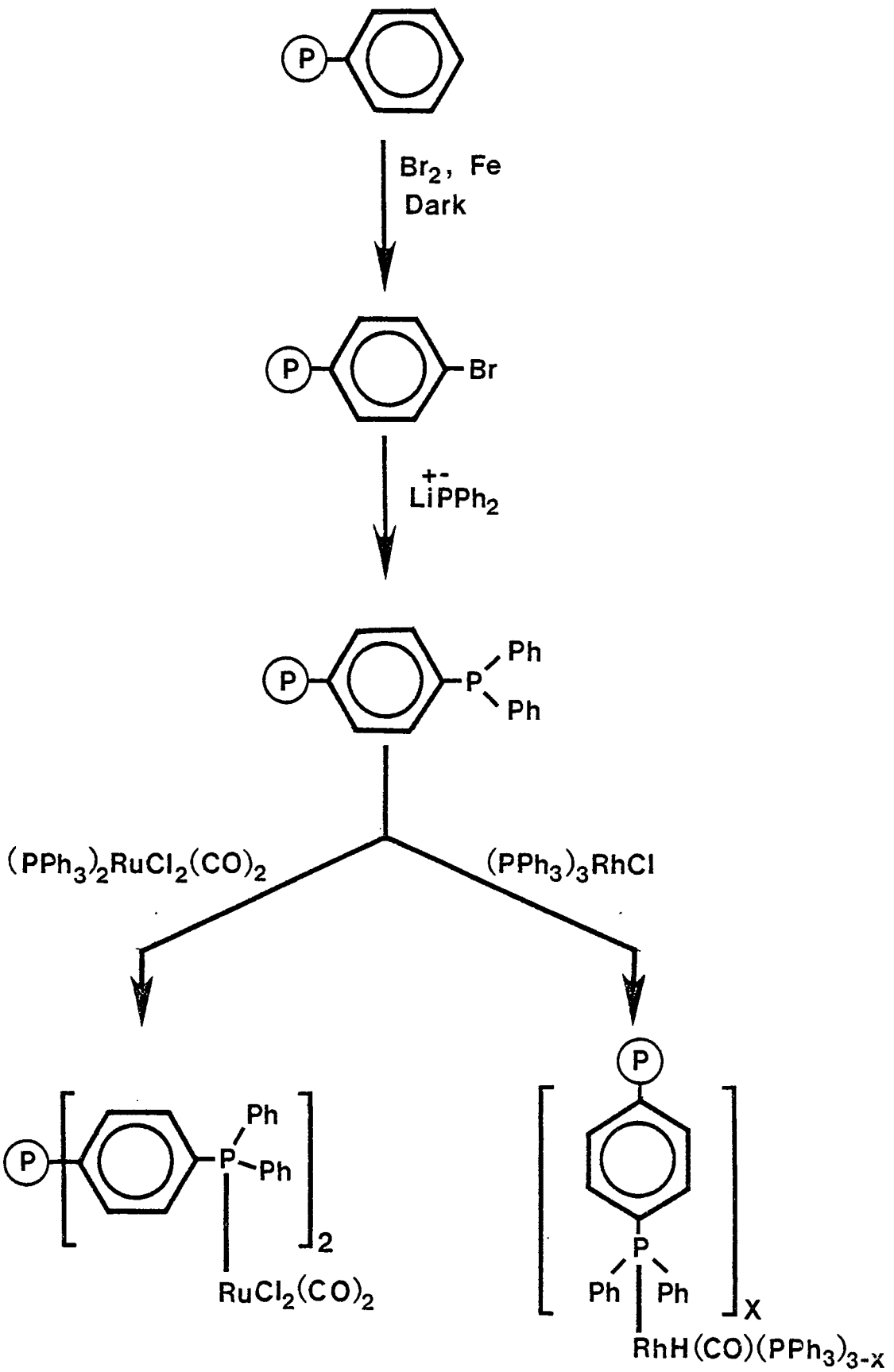
Pittman et.al. (25) later undertook the study of catalytic reactions using polymer-bound complexes of nickel, rhodium, and ruthenium and compared these to homogeneous complexes of the same metals. Cyclooligomerizations when carried out with the homogeneous complexes and then the resin-bound complexes were shown to give the same product distribution. An example of such a polymer-bound complex is shown in Scheme IX.

Hydrogenations carried out using the same two systems showed that resin-bound catalysts could selectively hydrogenate small olefins in the presence of larger ones. Such size selectivity could be modified by varying solvent, which in turn, varied the degree of polymeric swelling. Hydroformylations could be catalyzed by resin-bound catalysts which gave high yields of both straight-chain and branched aldehydes. The catalyst could be repeatedly recycled, as in the case of the cyclooligomerizations and hydrogenations, and in this case even exposed to water without drastic loss in activity which is seen in the homogeneous complexes. Pittman

Scheme VIII


P
CH2-O-C-CH2NH-H
n
CH2-O-C-CH2NH-H
n
CH2OH
P
CH2-O-C-CH2NH-H
2n
HBr / CF3COOH
H-NH-CH2-C-OH
2n

Scheme IX


P
Br2, Fe
Dark
P
Br
+-
LiPPh2
P
P
Ph
Ph
(PPh3)2RuCl2(CO)2
(PPh3)3RhCl
P
Ph
P
Ph
2
RuCl2(CO)2
P
P
Ph
Ph
X
RhH(CO)(PPh3)3-x

and Smith (26) further developed these procedures by using polymer-bound homogeneous catalysts in sequential multistep reactions as shown in Scheme X.

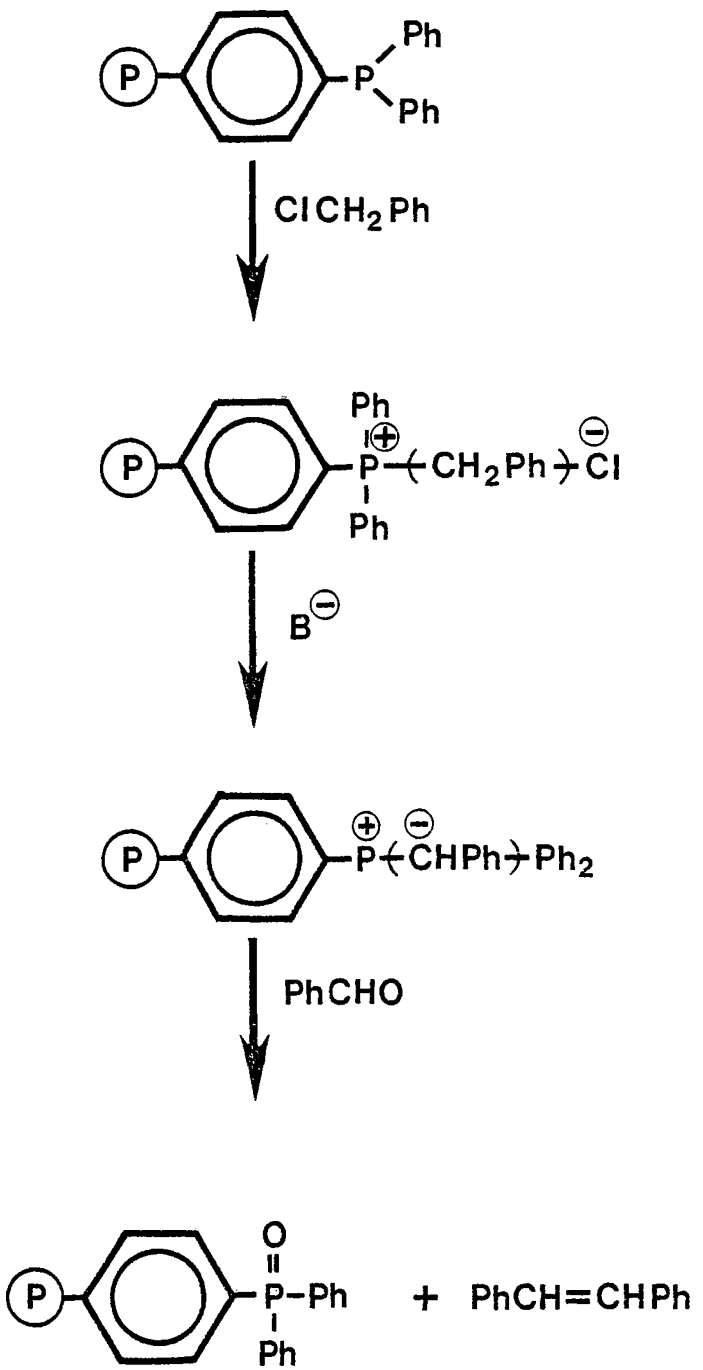
Camps et.al. (27), Collman et.al. (28), and Michels and Henz (29) further showed the diversity of such polymer-bound reagents in their applications of the Wittig reaction. Triphenylphosphine was bound to cross-linked polystyrene. Letsinger and Hamilton (30) synthesized several substituted styrene compounds possessing boron functional groups and subjected these compounds to polymerization conditions. The resulting polymer could readily absorb amino alcohols from solution.

In the synthetic procedures thus far illustrated which have employed polymers, the resin has served primarily as a support for a simpler molecule attached to the resin which underwent the desired reaction. A necessary consideration of the procedures described is that the covalent linkage, through which the small molecule is attached to the resin, be stable under the conditions of the reaction. Following the reaction, the product was cleaved from the resin which was removed from the reaction mixture by filtration.

An alternate approach was the attachment of a small molecule to the insoluble resin through a highly reactive and labile linkage. A resin which had been functionalized in this manner could then be used as a true reagent in synthetic applications rather than merely as a support on which the reaction is conducted. This concept differs considerably from the many reported applications of polymer assisted synthesis which have used the resin solely as a support.

Polymeric reagents capable of performing N-acylations and O-acylations with the acylating moiety attached to the resin

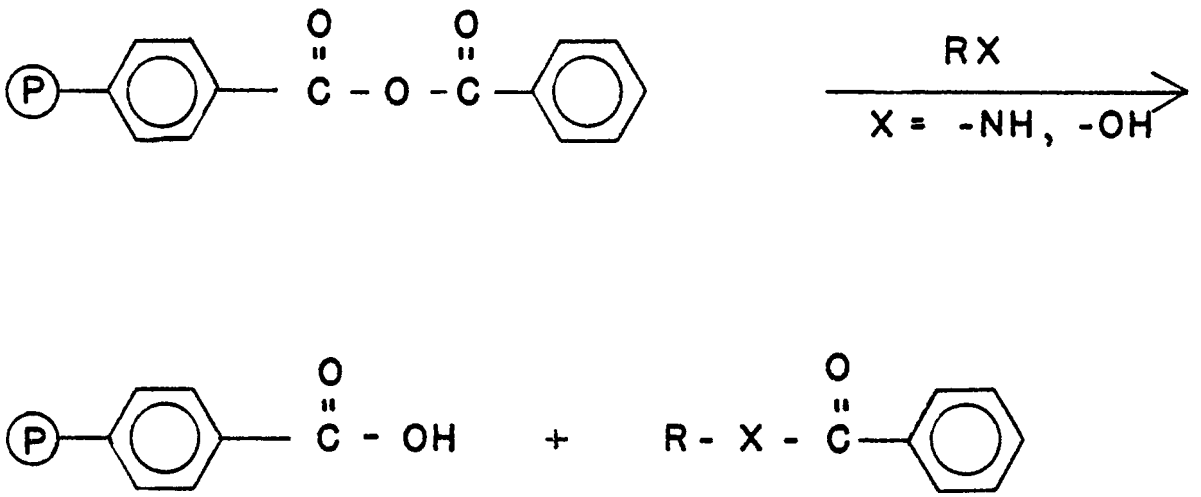
Scheme X


P
Ph
P
Ph
ClCH2Ph
P
Ph
P
CH2Ph
Cl
Ph
B
P
P
CHPh
Ph2
PhCHO
P
O
P-Ph
Ph
+
PhCH=CHPh

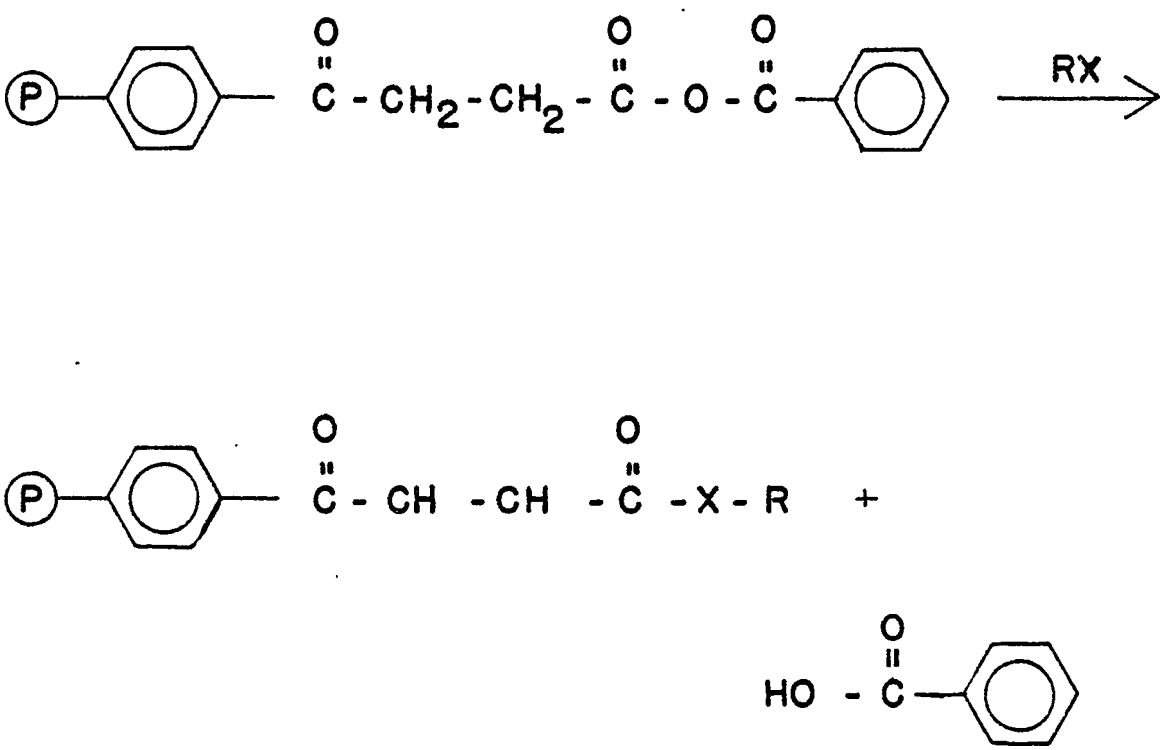
through an anhydride linkage have been reported by Shambhu and Digenis (31). Although the anhydride linkages contained in these polymeric reagents have two potential sites of nucleophilic attack, the products obtained when they were treated with an amine or alcohol demonstrated a preferential attack at only one site. Interestingly, the site differed depending on which anhydride linkage the polymeric reagent contained as shown in Schemes XI and XII.

A related report of a polymeric reagent by Shambhu and Digenis (32), with acylating capabilities, employed a mixed carbonic-carboxylic anhydride linkage similar to the monomeric counterparts of Vaughan (33) and Boissonnas (34) for the attachment of the acylating moiety. Treatment of this polymeric reagent with a variety of amines resulted in the production of the corresponding amides in good yield, although reaction at both potential sites of nucleophilic attack was observed. In addition, the generation of symmetrical anhydrides with these reagents on treatment with the tertiary amine salts of various carboxylic acids was reported (32). These reactions are illustrated in Scheme XIII.

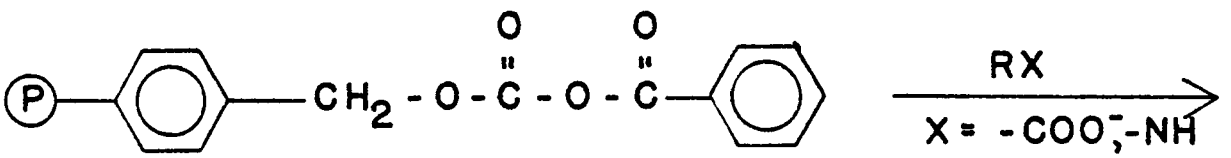
Scheme XI

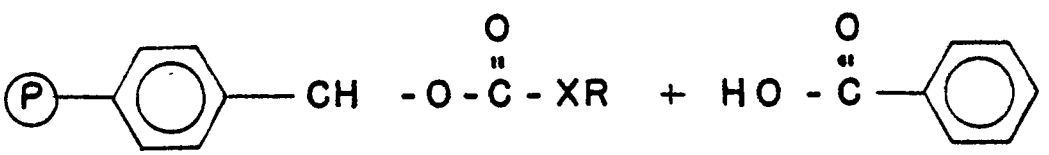


Scheme XII

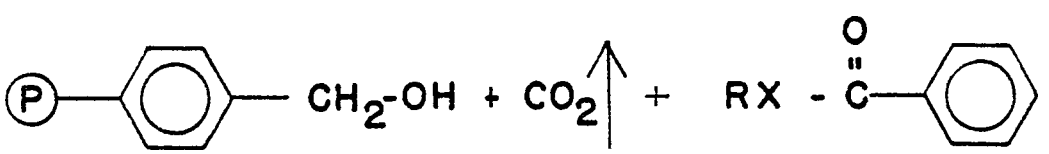


Scheme XIII





AND



OBJECTIVE

True polymeric reagents in which the reacting molecule is linked to the resin through a labile covalent linkage offer advantages in synthetic applications, depending on the lability of the covalent linkage for reactivity. By virtue of this lability, resins of this type could also offer significant advantages in the development of sustained release dosage forms when compared to the stable ester or ether covalent linkages.

DISCUSSION

The basic concept of sustained release dosage form is relatively simple; to release a fraction of the total dose initially, followed by some type of release of the balance of the dose at some later time. Ideally, sustained release dosage forms fall into two main categories: those which give a "repeat-action," where the initial dose is released in its entirety; the second type is the "continuous-release" variety, in which a fraction is initially released, followed by a gradual release of the remainder (35).

Numerous theoretical papers have been published which have laid the basic ground work for sustained release dosage forms. Studies involving analog computer models have included those of Kruger-Thiemer and Eriksen (36) and Rowland and Beckett (37). Prior to the use of mathematical models, a mechanism for sustained release from homogeneous and granular matrix preparations was proposed by Higuchi (38). Studies on theoretical formulations for sustained release dosage forms have also been published (39).

Polymers have long been employed in sustained release dosage forms in three main ways: first, as a solid inert matrix from which the entrapped drug is gradually released by diffusion; second, in polymeric microencapsulations; and third, as a film coating through which the drug diffuses, much as in the case of the solid matrix dosage forms, through a polymeric film which has been placed around the surface of the dosage form.

Polymeric matrix sustained release dosage forms have been extensively studied. Chiou and Smith (40) were the first to

apply the solid dispersion approach to the formulation of organic drugs using polyethylene glycol 6000 as a carrier. Puffer and Crowell (41) later conducted studies on the release characteristics of salicylate in polyethylene glycol suppositories. This work was followed by stability studies of aspirin in liquid and semi-liquid bases by Jun (42) and Whitworth et.al. (43, 44).

The studies conducted by Whitworth et.al. (43, 44) led to investigations by Desai et.al. (45-48) and Singh et.al. (49, 50) in which the matrix materials were varied to include polyvinylchloride and polyethylene. Brandstrom et.al. (51) conducted "in vivo" studies of these aforementioned sustained release dosage forms.

More recently, other sustained release dosage forms have been studied. These studies include the investigation of hydroxypropylmethylcellusolve matrices by Lapidus and Lordi (52), methylvinylether-maleic anhydride copolymers by Powell and Banker (53) and a methylacrylate-methylmethacrylate copolymer by Farhadieh et.al. (54). D'Arcy et.al. (55) reexamined polyvinylchloride as a matrix for sustained release preparations and Borodkin and Tucker (56) investigated the use of hydroxypropyl cellulose-polyvinyl acetate copolymers. In general, the drug is slowly released from all of the previously mentioned sustained release dosage forms as long as the matrix material remains in the dissolution medium.

Microencapsulation of drugs for the purpose of sustained release was first studied by Bauer and Lauth (57). In general terms, molecular entrapment occurs in such a manner that the drug molecule serves as a nucleus around which the polymer bead or microcapsule forms. Various papers have described this concept under a wide variety of descriptive names. Khanna and

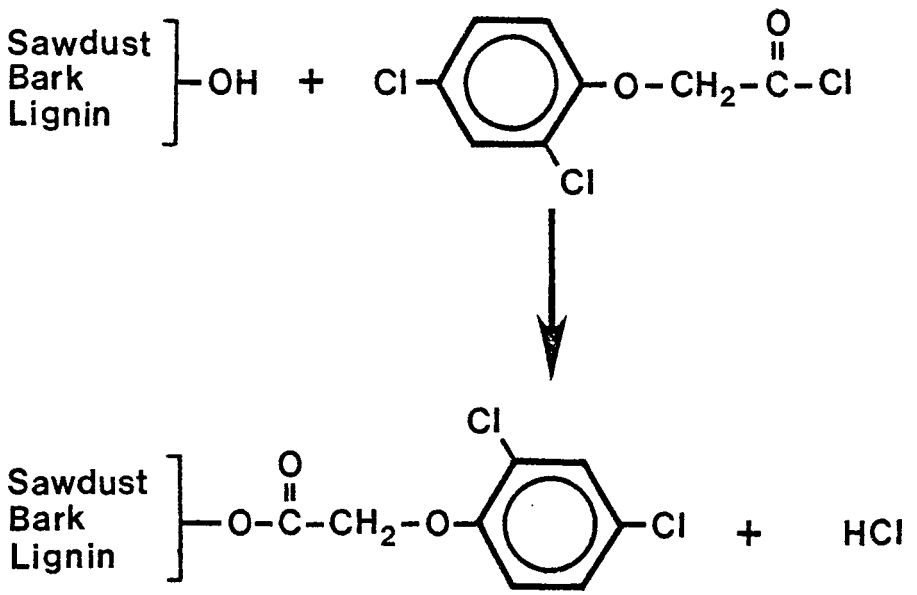
Speiser (58-61) in a series of papers refer to their work dealing with microencapsulation as bead polymerization. Molecular scale entrapments were investigated by Goodman and Banker (62) in which polymeric flocculation was employed. Polymeric gelation was studied by Boylan and Banker (63) and Heyd (64). Most recently, suspension polymerization was investigated by Croswell and Becker (65).

Allan et.al. (66) investigated the use of solid forest waste materials, which were lignocellulosic in nature, to obtain a controlled action pesticide after chemical combination with 2,4-dichlorophenoxy acetic acid (2,4-D) as shown in Scheme XIV. Shakhashir (67) further investigated the use of sustained release pesticides by attaching 2,4-D to functionalized polystyrene through a mixed anhydride linkage.

While the evolution of polymers in synthetic procedures has become progressively more sophisticated, there has been a corresponding development of polymers in sustained release dosage forms. The most recent literature reports the use of poly(lactic acid) as a matrix for the sustained release of a potent anti-cancer agent, cyclophosphamide, which was investigated by Yolles et.al. (68).

The gastric absorption of aspirin, salicylate or acetic acid can result in damage to the gastrointestinal mucosa (69-71); therefore, studies were undertaken to find a drug delivery system which might eliminate such undesired side effects. Investigations with carbonate derivatives of various drugs by Swintosky et.al. (72) suggest that both salicylic acid and acetylsalicylic acid (aspirin) might lend themselves to prodrug formation, with retention of antipyretic, analgesic and anti-inflammatory activity. Of special interest

Scheme XIV



is the hexyl carbonate derivative (73). However, the major drawback in prodrug formation is that in most cases altered physio-chemical properties are observed.

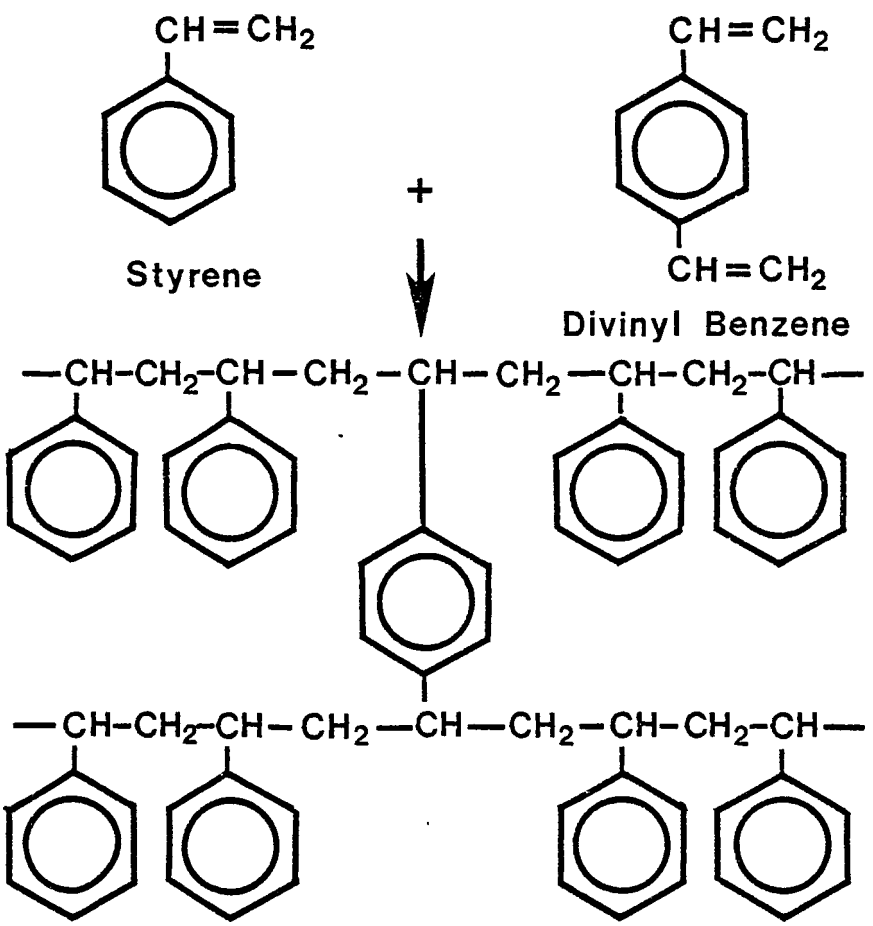
Weiner et.al. (74-76) recently reported the synthesis of polymeric salicylic acid derivatives, with the salicylate attached through either an ester or carbonate linkage to polyethylene oxide, starch, or methacrylates.

In the present study, the effect of various linkages of aspirin to polystyrene have been examined in terms of their ability to permit release of the drug from the resin support. Subsequent studies are anticipated to examine the utility of these resins as sustained release dosage forms.

RESULTS

Divinylbenzene was used in the preparation of the polystyrene polymer (1) as a cross-linking agent to produce an insoluble copolymer of the former with styrene (Scheme XV).

Scheme XV

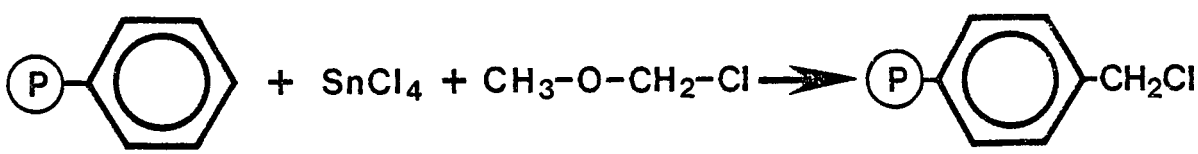


Polystyrene Polymer Backbone

The polymer (1) was found to be fully inert toward all the reagents used in the chemical syntheses and release studies performed (1). The amount of divinylbenzene, and thus the extent of cross-linking, is inversely proportional to the degree of swelling of the solid polymer in various organic solvents. Thus, a polymer with low degree of cross-linking (0.2% concentration of divinylbenzene in styrene) was used in this present study. The polymer (1) was found to swell extensively in organic solvents (73).

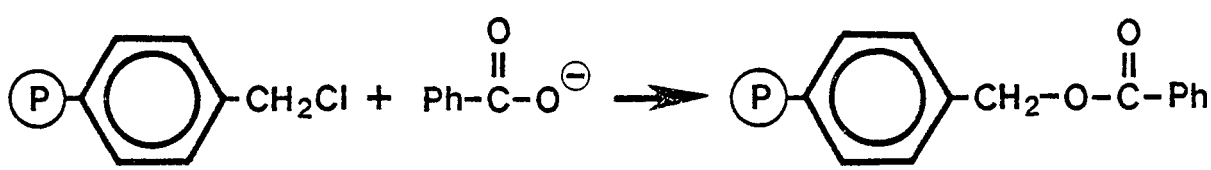
Polystyrene polymers with two kinds of functional groups were prepared, one having a free carboxylic acid and the other a highly reactive chloromethyl function.

A chemically active polymer was produced by chloromethylation (2) in a Friedel-Crafts reaction with chloromethyl methyl ether and stannic chloride according to the method of Merrifield (1).



1 2 (Eq. 1)

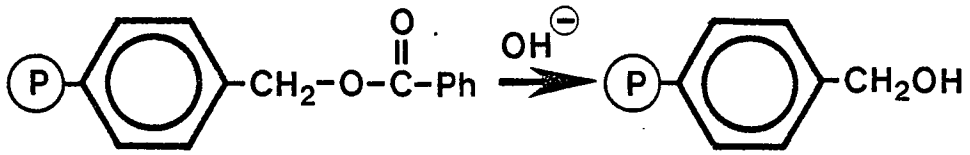
The halogen introduced was a reactive chloromethyl moiety and was susceptible to facile nucleophilic displacement. Benzoate effectively gave displacement of the halogen resulting in the resin ester linkage (3) as shown in equation 2.



2 3 (Eq. 2)

Proof of the displacement was seen by the typical ester absorption at 1710 cm^{-1} in the resin's ir spectrum.

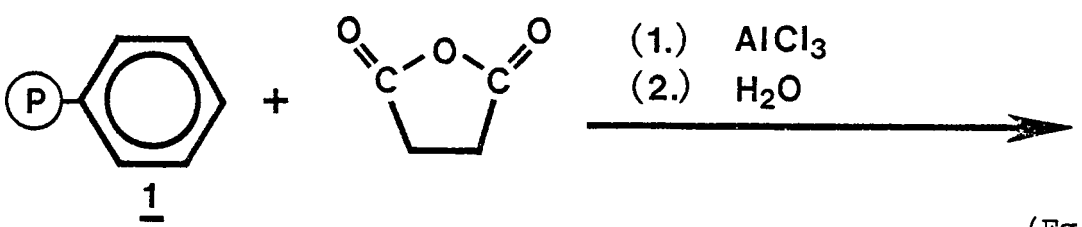
The hydrolysis of the polystyrene benzoate ester (3) in potassium hydroxide solution resulted in the formation of the hydroxymethyl derivative (4) which was subsequently used as a precursor for the synthesis of the mixed carbonic-carboxylic anhydride.



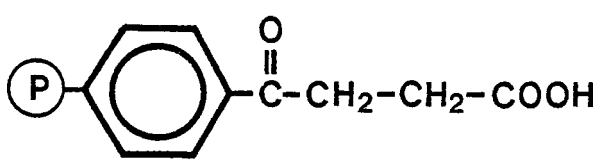
3 4 (Eq. 3)

The infrared spectrum of the benzyl alcohol derivative (4) showed the complete loss of the carbonyl peak of the ester at 1710 cm^{-1} with appearance of the hydroxyl peak at 3300 cm^{-1}.

Reaction of succinic anhydride with the polymer (1) in the presence of aluminum trichloride followed by water, resulted in the formation of succinylated polystyrene (6) (10).



1 (Eq. 4)



6

The infrared spectrum of the product exhibited bands of a hydroxyl group (3300 cm^{-1}) and that of a carbonyl function (1680 cm^{-1}), confirming the formation of the desired product.

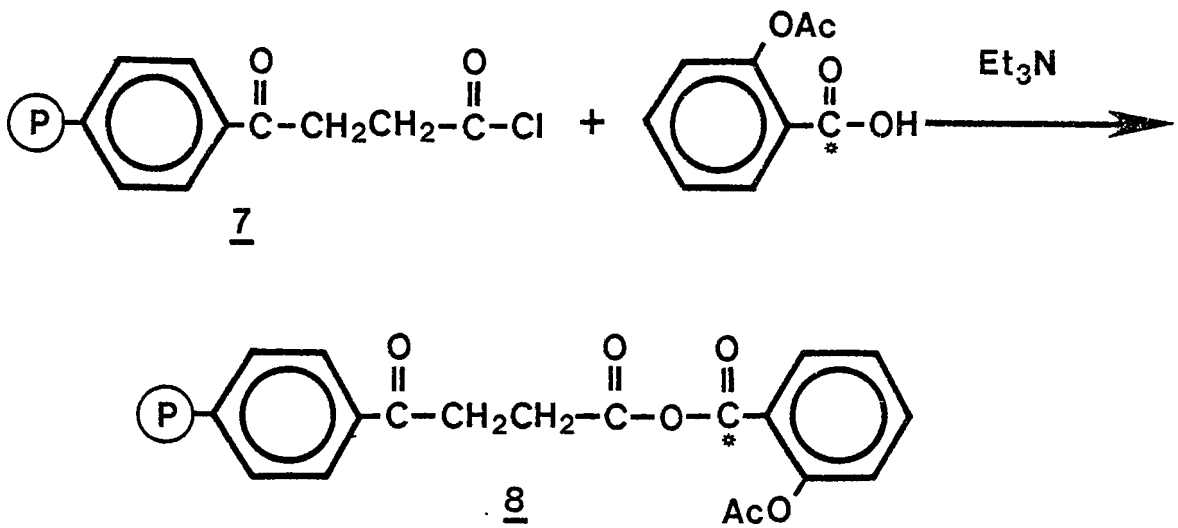
Three different chemical bonds were prepared for the attachment of radioactive ^{14}C-acetylsalicyclic acid on the

polymer: carboxylic anhydride, mixed carbonic-carboxylic anhydride and ester bond.

The carboxylic anhydride bond was prepared by the following method: Succinylated polystyrene (6) was reacted with oxalyl chloride or thionyl chloride to form the acyl chloride derivative (7) according to the method of Szmuszkovicz (78) or Kusama and Hayatsu (79).

The infrared spectrum of the acyl chloride derivative exhibited a new peak at 1790 cm^{-1} and reduction of the hydroxyl peak intensity at 3300 cm^{-1} which was indicative of the formation of the acyl halide (7).

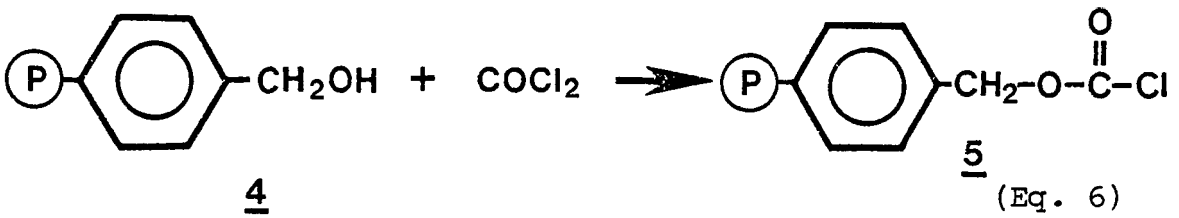
Reaction of ^{14}C-acetylsalicyclic acid, in the presence of triethylamine with the polystyrene acyl chloride derivative (7) resulted in the formation of the acetylsalicyloyl anhydride (8)(Eq. 5).



(Eq. 5)

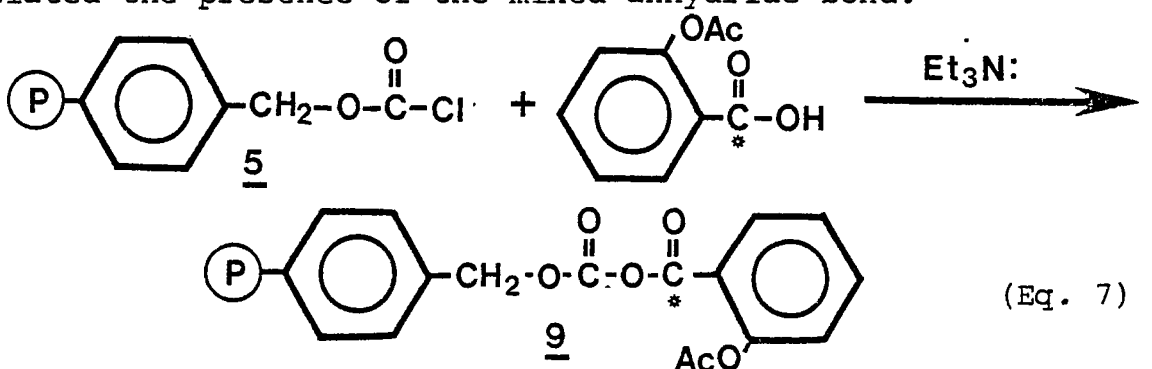
The infrared spectrum of the anhydride (13) exhibited peaks at 1750 cm^{-1} and 1715 cm^{-1} and a loss of the acyl chloride carbonyl at 1790 cm^{-1}.

The mixed carbonic-carboxylic anhydride bond was prepared by first reacting the hydroxymethyl polystyrene derivative (4) with phosgene to produce the chloroformate (5) (Eq. 6).



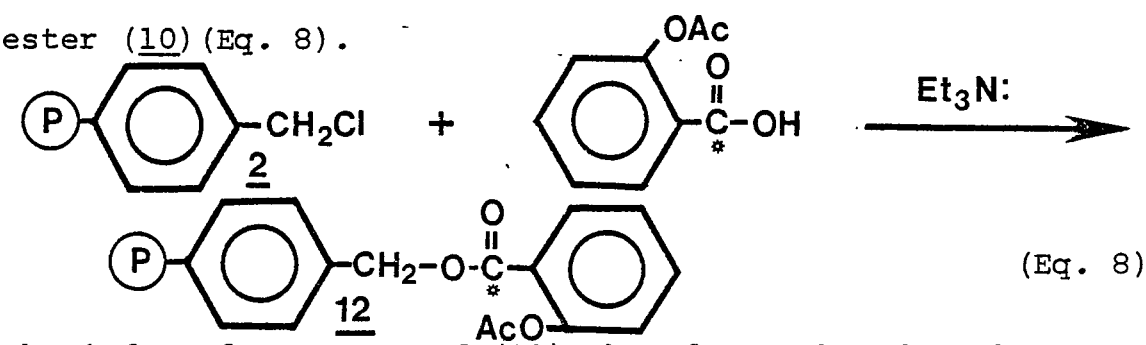
4 5 (Eq. 6)

Subsequent reaction of the chloroformate (5) with ^{14}C-acetylsalicylic acid in presence of triethylamine (Eq. 7) resulted in the formation of the ^{14}C-labelled mixed carbonic-carboxylic anhydride polystyrene derivative (9). A doublet at 1740 cm^{-1} and 1795 cm^{-1} in the infrared spectrum substantiated the presence of the mixed anhydride bond.



5 9 (Eq. 7)

Reaction of the chloromethylated polystyrene (2) with ^{14}C-acetylsalicylic acid, in the presence of triethylamine as a catalyst, produced the polystyrene acetylsalicyloyl ester (10) (Eq. 8).



2 12 (Eq. 8)

The infrared spectrum of (12) showed a carbonyl peak at 1710 cm^{-1}.

Polymeric covalently-linked sustained release dosage forms of aspirin, such as the models investigated, provide a drug delivery system which could eliminate the undesired side effects of aspirin.

In the presence of water, polystyrene polymers are known to "shrink" considerably (77). Consequently, it was assumed that the release of polymer-bound drug would be slowed when subjected to hydrolysis by an aqueous buffer.

Shakhashir (67) showed that the release of the mixed carbonic-carboxylic anhydride, the most reactive linkage investigated, proceeded at different rates and degrees of completion in dioxane containing various amounts of water. In 100% dioxane, 78% of the ^{14}C-benzoate, used in his model studies, was released from the polymeric anhydride within the first 30 min. In constrast, however, in 50% H_2O/50% dioxane only 55% of the ^{14}C-benzoate was released and in 100% water only 30% release was detected within the first 30 min.

The polystyrene ^{14}C-acetylsalicyloyl ester form failed to release any appreciable quantities of ^{14}C-acetylsalicylic acid over a 12 hr period (Figure 11). This observation led to the conclusion that shrinking of the resin by water did decrease the ability of the buffer to enter the matrix of the polymer and thus the extent of release.

Polystyrene succinic ^{14}C-acetylsalicyloyl anhydride, however, released 60% of the resin-bound ^{14}C-acetylsalicylic acid within 1 hr (Figure 12). This was unexpected when considering the results reported by Shakhashir (67). The polystyrene mixed carbonic ^{14}C-acetylsalicyloyl anhydride form released 80% of the resin-bound drug within the first hour (Figure 13). Release was so rapid that microcrystalline formation occurred and was

undesired considering the possible side effects of gastric irritation.

Since the release studies depicted in Figure 14 were performed in the same aqueous buffer, it must be concluded that the observed differences in the rate of release of ^{14}C-acetylsalicylic acid from the polymers are a result of differences in susceptibilities toward base hydrolysis. An important fact which also must be considered is that the acetate group ortho to the covalent polymer-drug linkage will aid in increasing the rate of release.

Thus, the slow step of the release of ^{14}C-acetylsalicylic acid from the polymer appears not to be dependent upon the diffusion process but rather on the hydrolytic susceptibility to be of the anhydrides and ester bonds.

EXPERIMENTAL

A. Materials and Reagents

Phosgene in benzene (12.5%) was purchased from Matheson Coleman and Bell, Norwalk, Ohio.

Scintanalyzed POP (2,5-diphenyloxazole) and POPOP (1,4-Bis(2-(-phenyloxazoyl))benzene) and scintillation grade toluene and dioxane were purchased from Fisher Scientific Company, Fair Lawn, New Jersey.

Triton X-100 (Scintillation grade) was purchased from Research Products International Corporation, Elk Grove Village, Illinois.

Labelled ^{14}C-Acetylsalicylic acid was purchased from New England Nuclear Company, Boston, Massachusetts.

Preparation of Liquid Scintillation Cocktail: POPOP (1,4-Bis-(2-(5-phenyloxazoyl))benzene), 1.2 g and POP (2,5-diphenyloxazole), 6.0 g were dissolved in 1 l of scintillation grade toluene. The solution was thoroughly stirred mechanically to insure complete dissolution and homogeniety. Triton X-100, 500 ml, was then added and the solution was again stirred thoroughly to insure homogeneity. The scintillation cocktail was stored in the dark in an amber bottle wrapped in aluminum foil.

B. Instrumentation

All sample shaking was done in a Aquatherm Water Bath Shaker, Model G-86, New Brunswick Scientific Company, Inc., New Brunswick, New Jersey.

Radioactive samples were counted in a Hewlett-Packard Liquid Scintillation Counter, Tricarb Model 3330, Hewlett-

Packard Corporation, Cupertino, California.

Infrared spectra were recorded on a Perkin-Elmer Model 700 infrared spectrometer, Perkin-Elmer Co., Norwalk, Connecticut. All infrared spectra were run as 3% KBr pellets.

C. Preparation and Reactions of Polymer Derivatives

Preparation of Crosslinked "Popcorn" Polystyrene (1). Crosslinked polystyrene resin (1) (containing 0.2% divinylbenzene w/w) was prepared by a modification of the procedure of Letsinger et.al. (77). In a 3 l flask was placed styrene (200 g, 1.92 M) which had been freshly distilled under reduced pressure at 55-60°; and divinylbenzene (0.4 g, 3.08 mM) which had also been freshly distilled under reduced pressure at 90-95°. To this was added "popcorn" polystyrene seeds (1 g/75 g styrene monomer), after which the co-polymerization was thermally initiated by heating on a steam bath for 10 min while the flask was purged with nitrogen. The flask which was ground glass stoppered was then immediately sealed and transferred to a stirred oil bath maintained at 55-60°. After about 2 days, polymerization became evident by the appearance of a white, insoluble polymer which protruded above the surface of the liquid. The polymerization proceeded to completion within 24-48 hrs. The product was thoroughly washed in 3 l of chloroform to remove any free styrene monomer and then air dried for several days. The yields of resin were essentially quantitative and the infrared spectrum was identical to that of polystyrene (Figure 1).

Preparation of Polystyrene Beads from "Popcorn" Polystyrene (1). Following preparation of the "popcorn" polystyrene resin (1), the large pieces of resin were reduced to synthetically workable particle size by grinding in a Waring

Blender. The reduced particles were sifted through standard sieves, with the portion of beads ranging in size from 40-100 mesh retained for subsequent chemical functionalization. Those larger than 40 mesh were ground further to suitable size. The beads smaller than 100 mesh were discarded.

Preparation of Chloromethyl Polystyrene (2). Preparation of chloromethyl polystyrene was by a modification of the Merrifield procedure (1). To a 1 l flask containing "popcorn" polystyrene (1) (70 g, 40-100 mesh) was added 750 ml of chloroform and the resulting suspension stirred for 1 hr to allow the polymer beads to swell. After 1 hr the mixture was cooled to 0° and a solution containing 35 ml of anhydrous stannic chloride in 100 ml of chloromethyl methyl ether was added dropwise over a 30 min time period. The suspension was stirred for an additional hr at 0°, allowed to warm to 25° and then stirred for 2 hrs at 25°. The dark reddish-brown polymer suspension was filtered through a coarse sintered glass funnel and then washed with successive 750 ml portions of chloroform (2x), dioxane, dioxane/water (1:1), 10% hydrochloric acid, dioxane and finally anhydrous ethyl ether. The resulting pale yellow resin was dried overnight at 60° under reduced pressure. Final weight of the dried polymer was 80.5 g. Chlorine content of the resin, as determined by microanalysis (80) was found to be 9.8%, representing chloromethylation of approximately 1.85 mEq/g of resin (81). The infrared spectrum is presented as Figure (2).

Preparation of Polystyrene Benzyl Benzoate Ester (3). Chloromethyl polystyrene (2) (10 g, 40-100 mesh) was placed in a reaction flask to which was added a solution containing benzoic acid (3.66 g, 0.03 M), potassium hydroxide (1.47 g, 0.026 M), and 1 ml triethylamine in 100 ml of methylcellusolve, according to the procedure of Shakhashir (67). The mixture

was refluxed for 6 hrs and filtered hot through a coarse sintered glass funnel. The resultant resin was washed with successive 300 ml portions of hot methyl cellusolve, hot dioxane, dioxane/water (1:1), dioxane and finally anhydrous ethyl ether. The polymer was dried overnight at 60° under reduced pressure. Final weight of the dried polymer was 11.9 g. Examination of the infrared spectrum of the resin showed a carbonyl absorption at 1710 cm^{-1} corresponding to the ester linkage on the polymer. Figure (3).

Preparation of Polystyrene Benzyl Alcohol (4). Chloromethylated polystyrene (2) was converted to the corresponding polystyrene benzyl alcohol according to the procedure of Martin (82). Chloromethyl polystyrene (10 g, 40-100 mesh) was added to a solution of sodium benzoate (6 g, 0.042 M) and 2 ml of triethylamine in 100 ml of methyl cellusolve and the mixture refluxed for 4 hrs. The solvent was decanted and the still hot resin was washed with 200 ml of hot methyl cellusolve by decantation. Polystyrene benzyl benzoate ester (3) was an intermediate but was not isolated. A solution containing potassium hydroxide (6 g, 0.107 M) in 100 ml of methyl cellusolve was added to the resin and subsequently refluxed for 4 hrs. The solvent was again decanted and the resin washed thoroughly with hot methyl cellusolve. The polymer was then filtered through a coarse sintered glass funnel and washed with successive 200 ml portions of hot methyl cellusolve, dioxane, hot dioxane/water (1:1), hot water, dioxane, dry benzene and finally anhydrous ethyl ether. The pale yellow polymer was dried overnight at 60° under reduced pressure. Final weight of the dried polymer was 8.2 g. Examination of the infrared spectrum showed a typical hydroxyl absorption at 3300 cm^{-1} and a complete absence of the ester absorption formerly

at 1710 cm^{-1}. Microanalysis for chlorine showed 0.00% chlorine remaining on the resin, indicating a quantitative conversion of the chloromethyl functions to their benzyl alcohol counterparts (Figure 4).

Preparation of Polystyrene Benzyl Chloroformate (5). Polystyrene benzyl chloroformate (5) was prepared from the corresponding alcohol (4) by reaction with 12.5% phosgene in benzene to give the desired chloroformate, according to the procedure of Shambhu and Digenis (32). To a flask, fitted with a $CaCl_2$ drying tube, containing 50 ml of 12.5% solution of phosgene in benzene was added 5.0 g of polystyrene benzyl alcohol (4). The mixture was maintained at 25° for 6 hrs with intermittant shaking. The resin was filtered through a sintered glass funnel, with the excess phosgene entering a methanol scrubber. The resin was then washed with 2 100 ml portions of dry, distilled benzene and anhydrous ethyl ether. The polymer was dried overnight at room temperature under reduced pressure. Final weight of the dried polymer was 6.1 g. The chlorine content, as determined by microanalysis on 2 successive reactions, was 9.7-9.8%. Examination of the infrared spectrum showed a strong carbonyl absorption at 1765 cm^{-1} corresponding to the chloroformate linkage and an absence of the benzyl alcohol absorption previously observed at 3300 cm^{-1} (Figure 5).

Preparation of Succinylated Polystyrene (6). "Popcorn" polystyrene (1) was succinylated by reaction with succinic anhydride and aluminum trichloride in a Friedel-Crafts reaction, according to the general procedure of Yip and Tsou (10). Resin (1) (20 g, 40-100 mesh) was added to 100 ml of s-tetrachloroethane and stirred for 5 min. Succinic anhydride (20 g, 0.20 M) was added while stirring was continued. The mixture

was maintained at room temperature. Anhydrous aluminum trichloride (40 g, 0.3 M) was dissolved in 100 ml of nitrobenzene and 100 ml of s-tetrachloroethane and then added dropwise over a 10 min period from a pressure equalizing addition funnel. An additional 200 ml of s-tetrachloroethane and 100 ml of nitrobenzene were also added. The reaction was heated, while mechanically stirred, for 4 hrs at 85-95°. The reaction was then quenched by adding 1.5 l of ice water over a 20 min period. The resultant aqueous mixture was allowed to stir for 8 hrs, after which it was allowed to stand for 4 hrs. The biphasic mixture was transferred to a 3 l separatory funnel and the aqueous layer discarded. The wet resin was then washed into a büchner funnel and the remaining water removed by vacuum filtration. The resin was washed with successive 1 l portions of methanol, 10% hydrochloric acid, hot water (2x), hot dioxane and finally hot methanol. The light yellow resin was dried overnight at 60° under reduced pressure. Final weight of the dried polymer was 24.8 g. Examination of the infrared spectrum showed characteristic absorptions at 820, 1680 and 1710 cm^{-1} (Figure 6).

Conversion of Succinylated Polystyrene (6) to Polystyrene Succinoyl Chloride (7). Succinylated polystyrene (6) was converted to the corresponding succinoyl chloride according to the procedure of Southard et.al. (83). Succinylated polystyrene resin (6) (5 g, 40-100 mesh) was placed in a reaction flask and suspended in a solution of 150 ml of dry, distilled benzene and the mixture was brought to reflux. At reflux, oxalyl chloride (12 ml) was added dropwise and the resulting solution was refluxed for an additional 2 hrs. The mixture was filtered hot through a sintered glass funnel and washed with successive 500 ml portions of hot benzene and finally

anhydrous ethyl ether. The polymer was dried overnight at room temperature under reduced pressure. Final weight of the dried polymer was 5.4 g. Microanalysis for chlorine showed 5.09% had been incorporated into the resin and examination of the infrared spectrum showed complete interconversion to the acyl chloride with absorptions at 1710 and 1790 cm^{-1} (Figure 7).

Preparation of Polystyrene Mixed Carbonic ^{14}C-Acetylsalicyloyl Anhydride (8). The procedure followed for the synthesis of (8) was that of Shambhu and Digenis (32). Polystyrene benzyl chloroformate resin (5), 3 g, was suspended in 30 ml of dry distilled benzene and cooled to 0°. To the polymer slurry, a cold solution containing 1.80 g (10 mEq) acetylsalicylic acid (50 uCi ^{14}C-acetylsalicylic acid) and 1.01 g triethylamine (10 mEq) in 20 ml of dry distilled benzene was added. The reaction was allowed to proceed for 30 min with constant vigorous shaking. The polymer was filtered through a sintered glass filter and washed with successive 50 ml portions of cold, dry, distilled benzene, dioxane, dioxane/water (1:1), dioxane, benzene, and finally anhydrous ethyl ether. The resin was dried overnight at room temperature under reduced pressure. Final weight of the dried polymer was 3.69.

Examination of the infrared spectrum showed a strong doublet at 1740 and 1795 cm^{-1} characteristic of the mixed anhydride linkage (84, 85) (Figure 8).

Total radioactivity of the resin was determined by refluxing 0.25 g of (8), following drying, in 100 ml of 0.1 N potassium hydroxide in a dioxane/water (90:10) mixture. Radioactivity was measured by counting five 0.1 ml aliquots of the hydrolysis solution added to 15 ml of the liquid scintillation cocktail and taking the average. The polymer, by this method, was calculated to contain 6.6×10^6 cpm g^{-1}.

Preparation of Polystyrene ^{14}C-Acetylsalicyloyl Ester (9). Chloromethylated polystyrene (2) (10.0 g, 40-100 mesh) was placed in a flask which contained 5.4 g of acetylsalicylic acid (30 mM) (50 uCi ^{14}C-acetylsalicylic acid) and 1.0 ml of triethylamine in 100 ml of methylcellusolve according to the procedure of Shakhashir (67). The mixture was refluxed for 3.5 hrs and filtered hot through a sintered glass funnel. The resultant resin was washed 3 times with successive 100 ml portions of hot methylcellusolve, hot dioxane, dioxane:water (1:1), dioxane, and finally anhydrous ethyl ether. The polymer was dried overnight at 60° under reduced pressure. Final weight of the dried polymer was 11.6 g. Examination of the infrared spectrum showed a carbonyl absorption at 1710 cm^{-1} corresponding to the ester linkage of the resin (Figure 9).

Preparation of Polystyrene Succinic ^{14}C-Acetylsalicyloyl Anhydride (10). Polystyrene succinoyl chloride (7) (10.0 g, 40-100 mesh) was placed in a flask which contained 6.1 g of sodium acetylsalicylate (30 mM) (50 uCi ^{14}C-acetylsalicylic acid) and 1 ml of triethylamine in 100 ml of dried, distilled benzene. The reaction was heated for 2 hrs at 50° and filtered hot through a sintered glass funnel. The resultant resin was washed with successive 250 ml portions of benzene, distilled water, dioxane, benzene, and finally ether. The resin was dried overnight at room temperature under reduced pressure. Examination of the infrared spectrum showed decrease in intensity of the absorption at 1790 cm^{-1} and additional absorptions at 1750 cm^{-1} and 1715 cm^{-1} (Figure 10).

Release of ^{14}C-Label from Polystyrene Resin. A sample of the appropriate resin (0.25 g, 40-100 mesh) was placed in exactly 50 ml of pH = 9.0 buffer in a 125 ml erlenmeyer flask

fitted with a ground glass stopper. The flask was then placed in a gyratory water bath shaker operating at 37°, 240 rpm for 12 hrs. Periodic 0.1 ml samples of the buffer solution were taken, added to 15 ml of liquid scintillation cocktail and counted for radioactivity.

Background radiation levels were determined by placing a sample (0.25 g, 40-100 mesh) of the appropriate resin in exactly 50 ml of scintillation grade dioxane in a 125 ml erlenmeyer flask fitted with a ground glass stopper. The flask, as before, was placed in a gyratory water bath shaker operating at 37°, 240 rpm for 2 hrs. Again, periodic 0.1 ml samples of the dioxane solution were taken, added to 15 ml of liquid scintillation cocktail, and counted for radioactivity.

Total radiation levels were determined by placing a sample (0.25 g, 40-100 mesh) of resin in exactly 50 ml of dioxane:water solution (70:30) made basic with sodium hydroxide. The suspension was then refluxed for 4 hrs. Six 0.1 ml samples of the dioxane:water solution were taken, added to 15 ml of liquid scintillation cocktail, and counted for radioactivity.

Figure 1. Infrared Spectrum of Polystyrene

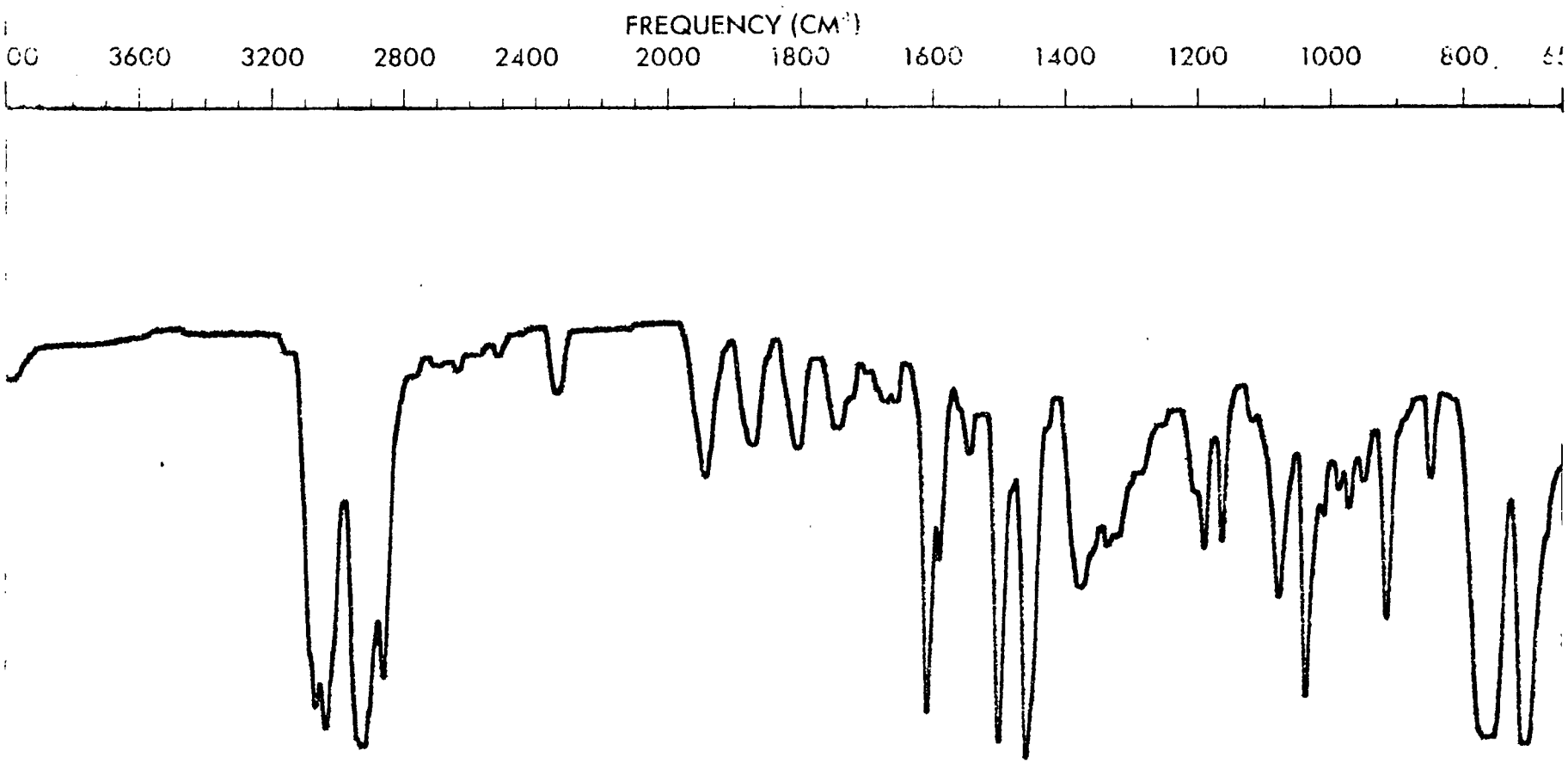


Figure 2. Infrared Spectrum of Chloromethyl Polystyrene

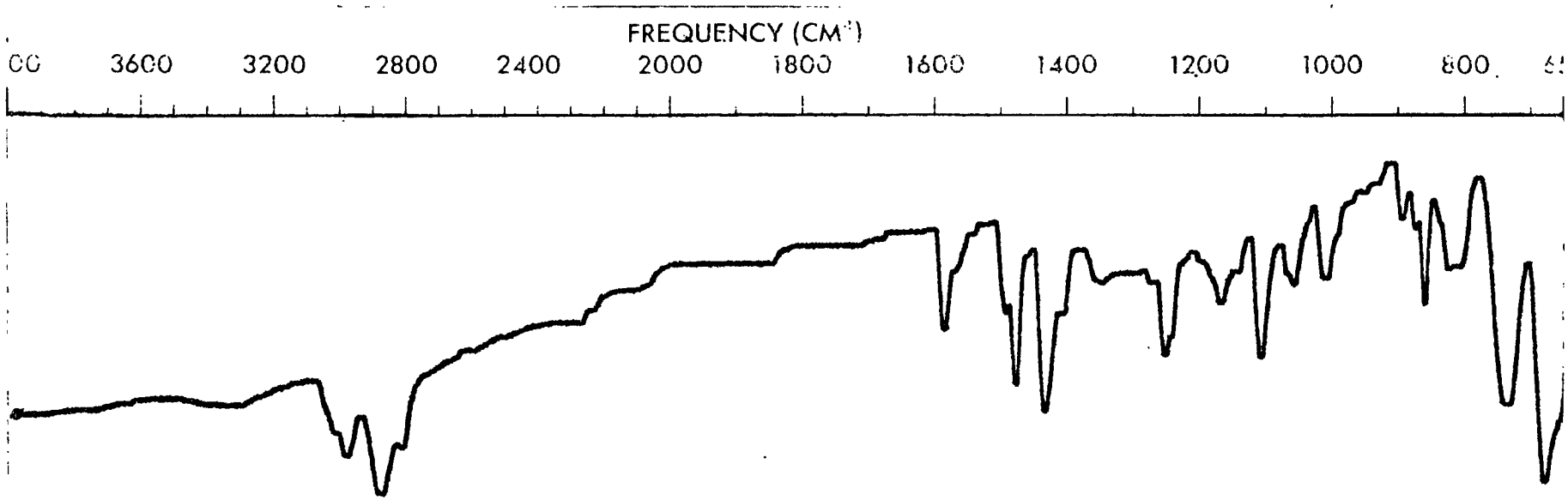


Figure 3. Infrared Spectrum of Polystyrene Benzyl Benzoate Ester

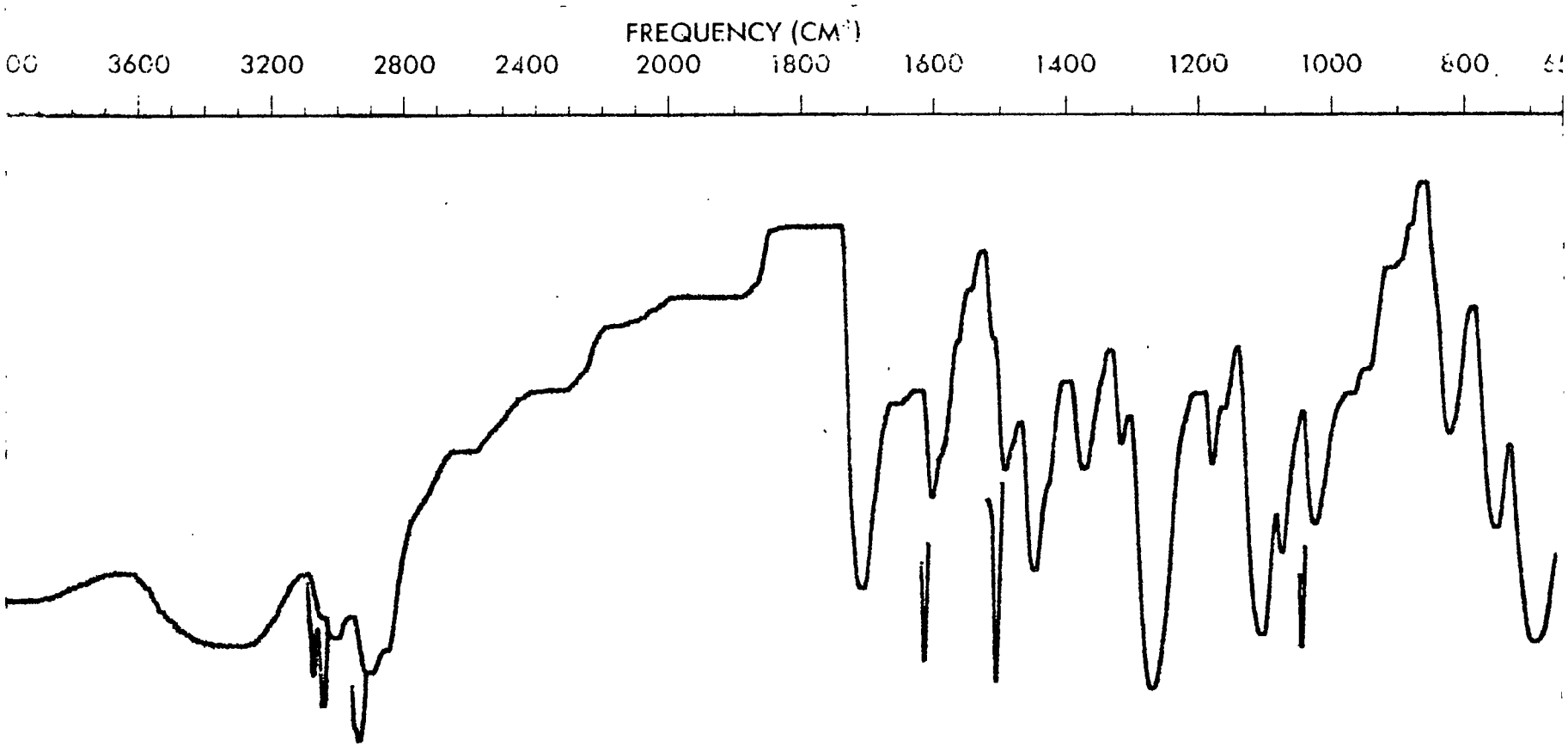


Figure 4. Infrared Spectrum of Polystyrene Benzyl Alcohol

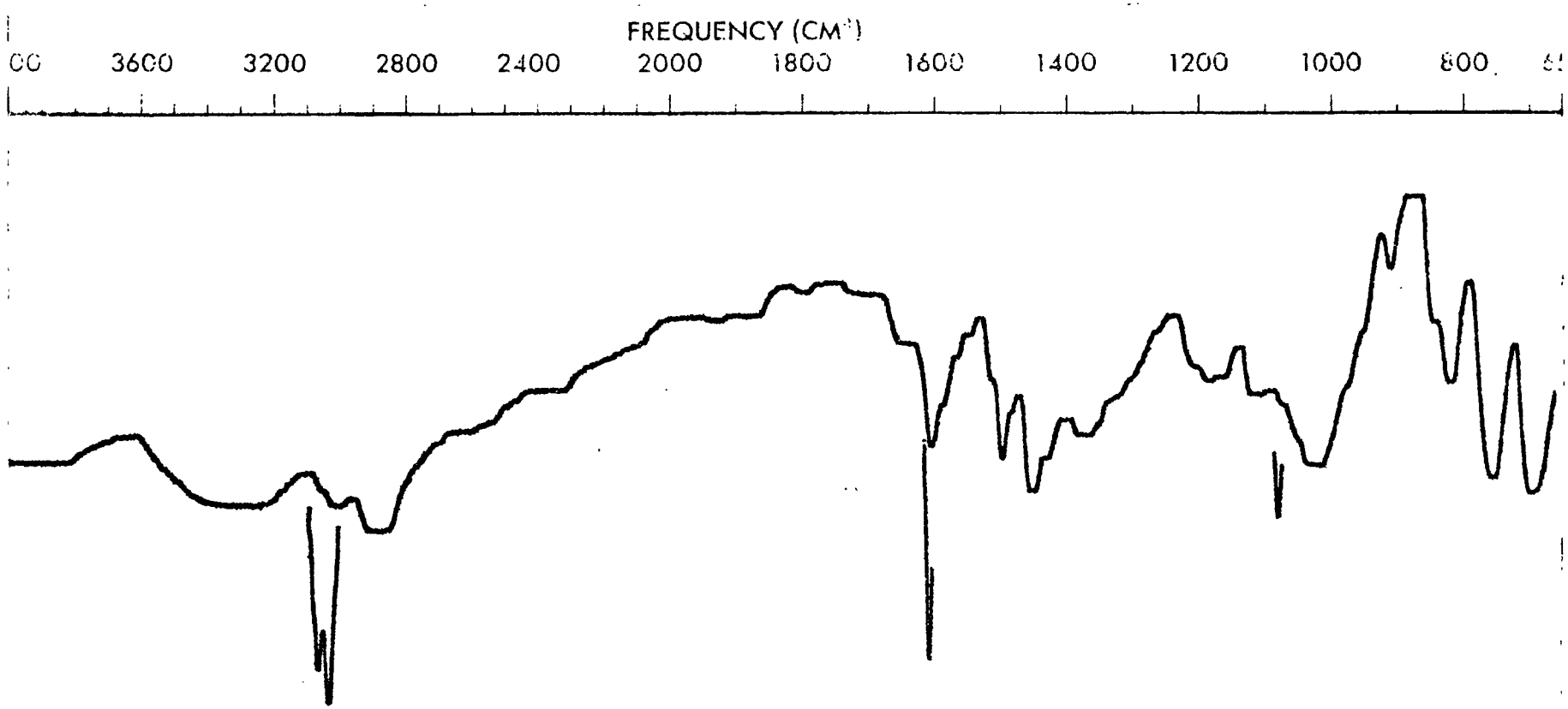


Figure 5. Infrared Spectrum of Polystyrene Benzyl Chloroformate

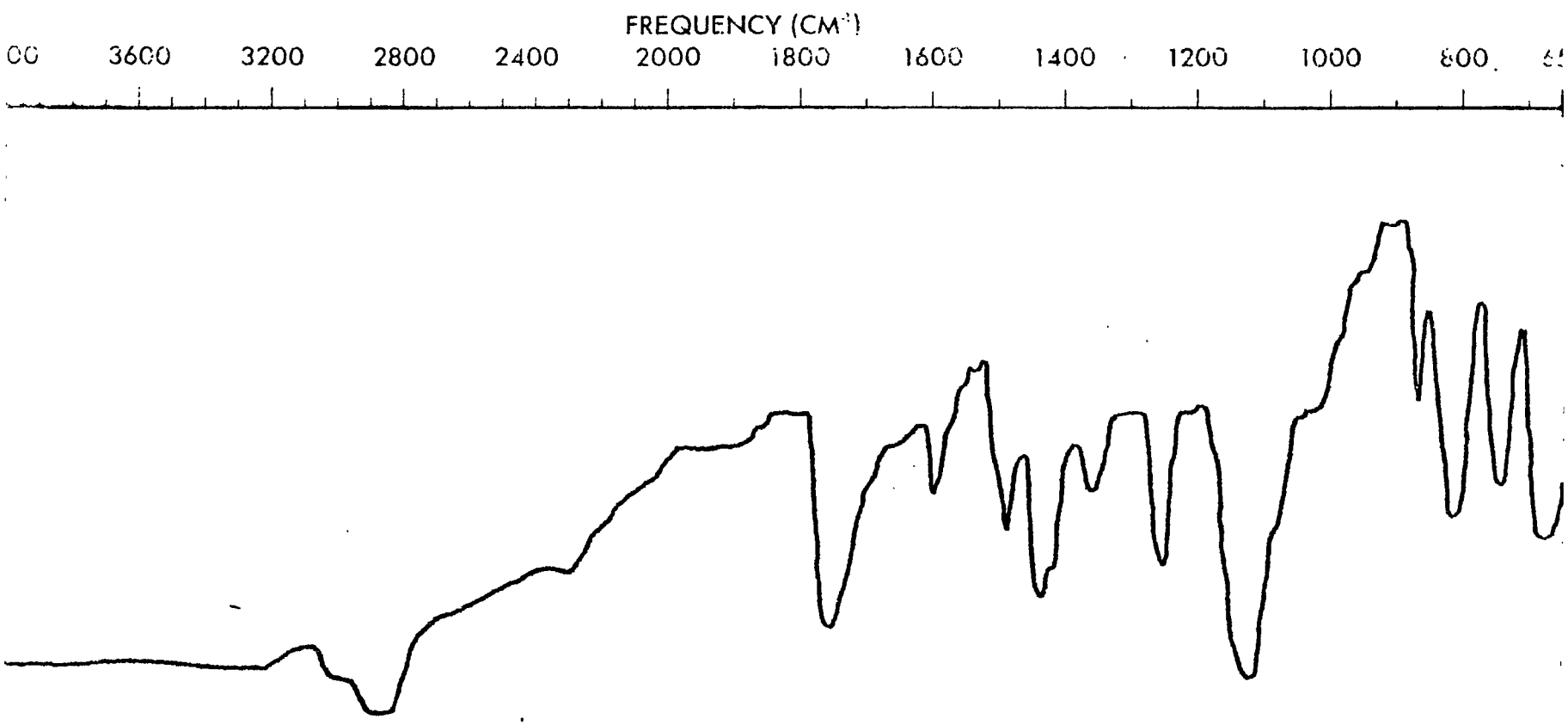


Figure 6. Infrared Spectrum of Succinylated Polystyrene

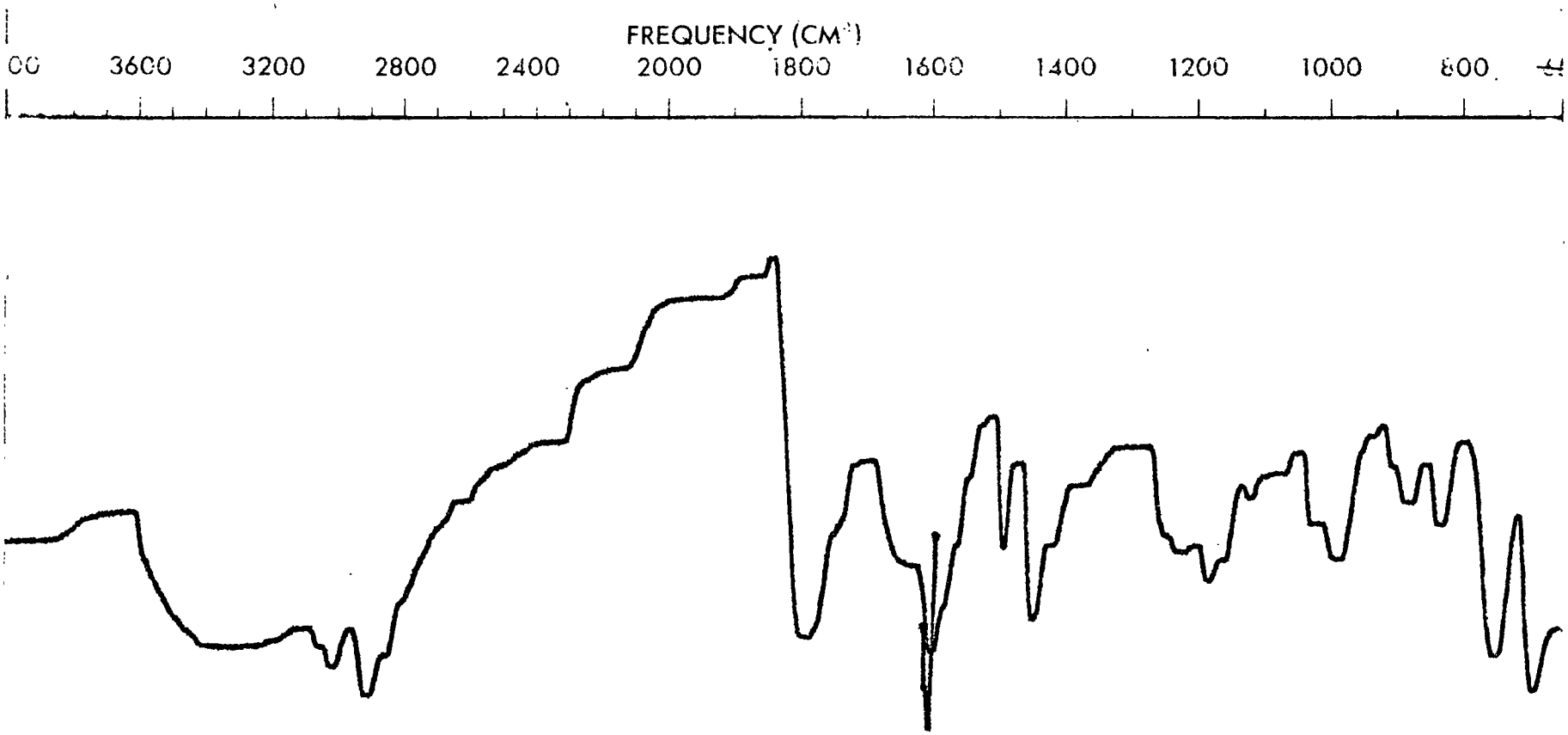


Figure 7. Infrared Spectrum of Polystyrene Succinoyl Chloride

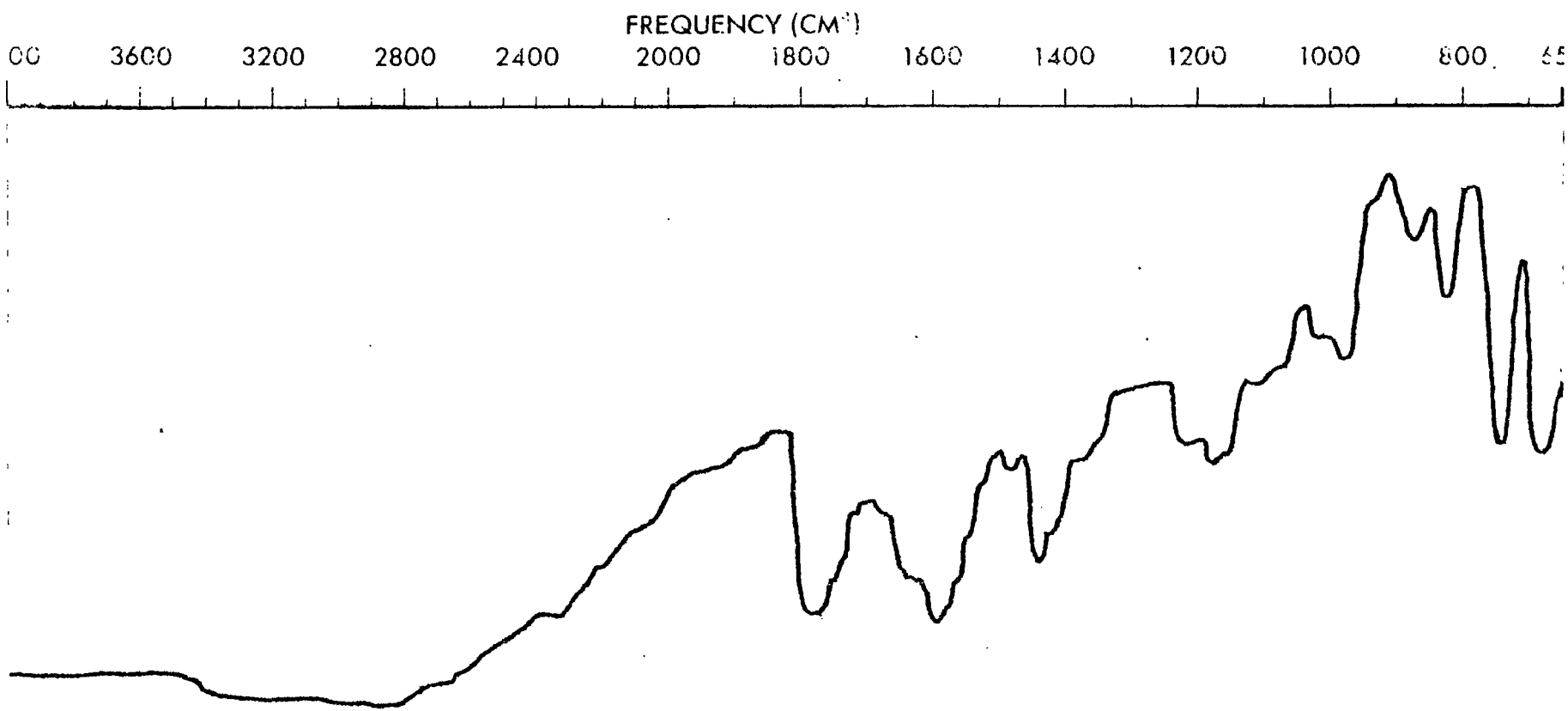


Figure 8. Infrared Spectrum of Polystyrene Mixed Carbonic ^{14}C-Acetylsalicyloyl Anhydride

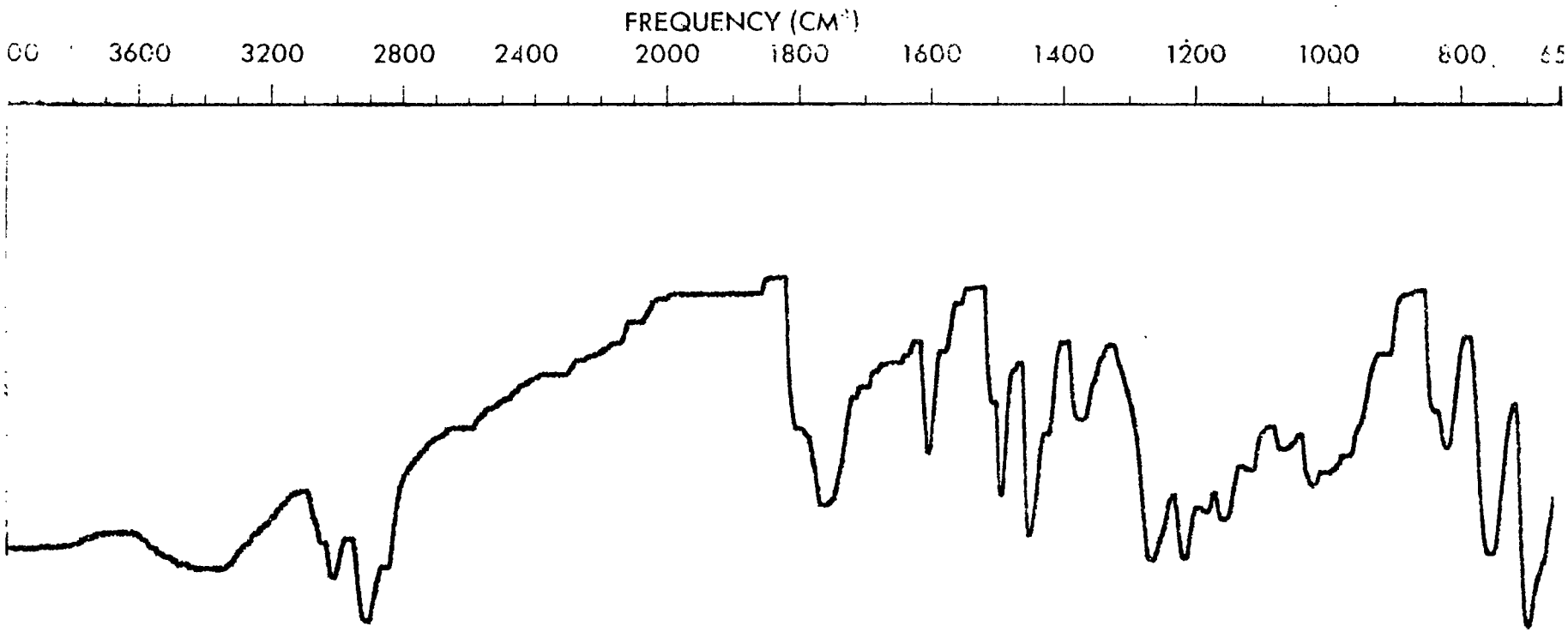


Figure 9. Infrared Spectrum of Polystyrene ^{14}C-Acetylsalicyloyl Ester

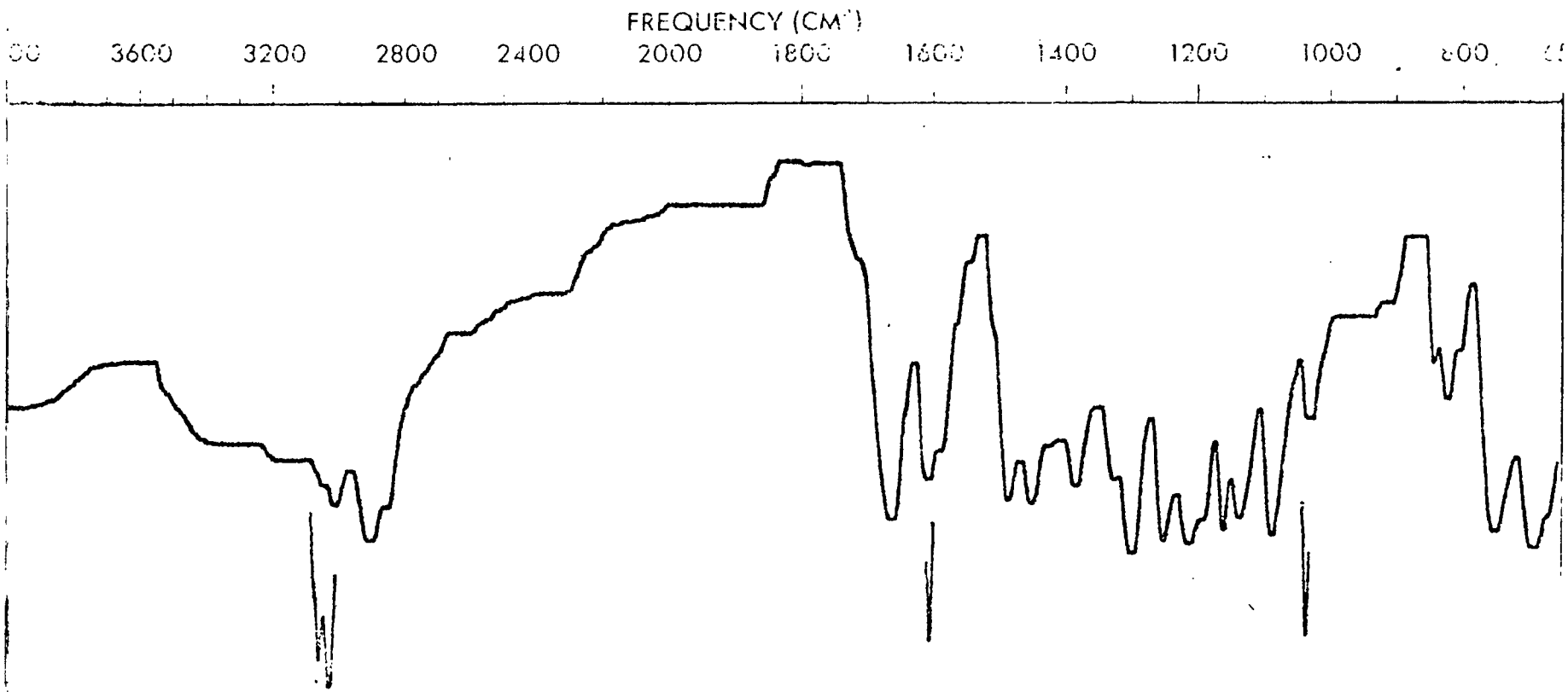


Figure 10. Infrared Spectrum of Polystyrene Succinic ^{14}C-Acetylsalicyloyl Anhydride

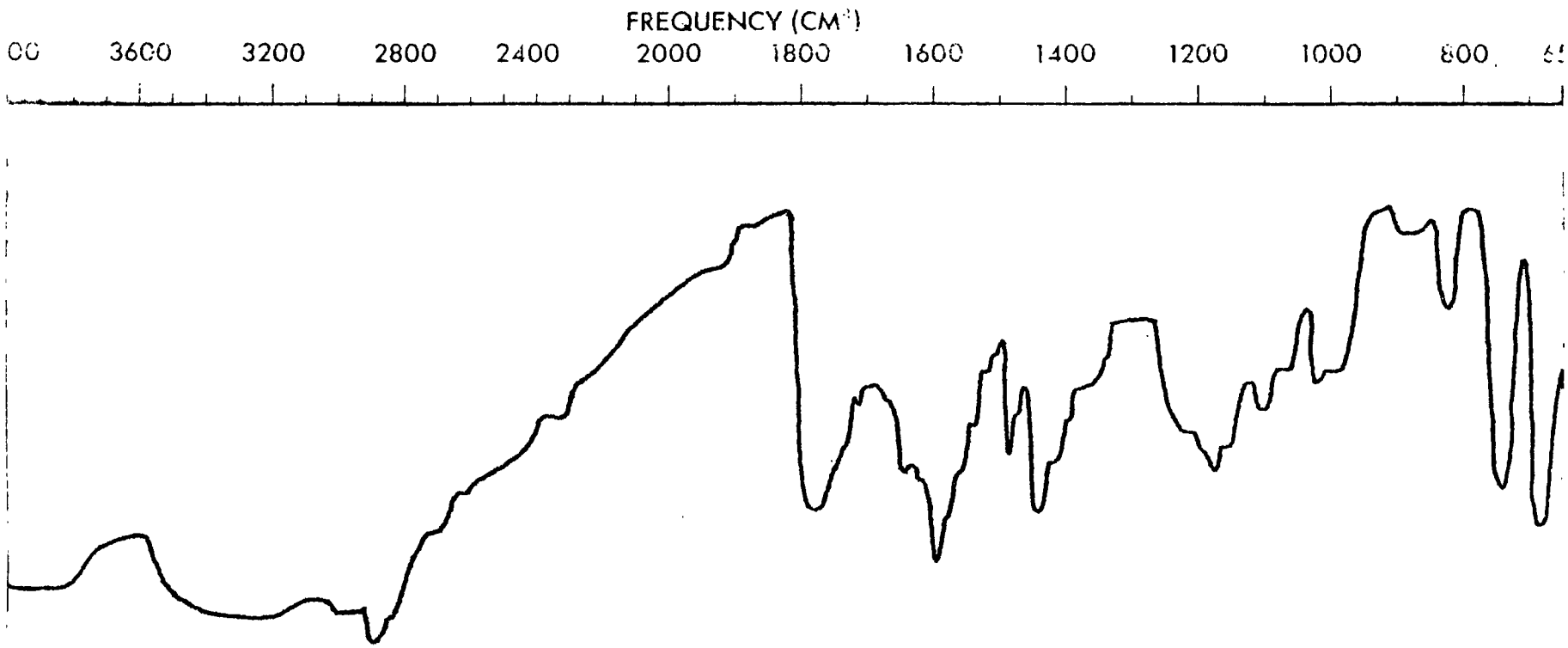


Figure 11. Release Studies: Polystyrene ^{14}C-Acetylsalicyloyl Ester in pH 9.0 Buffer

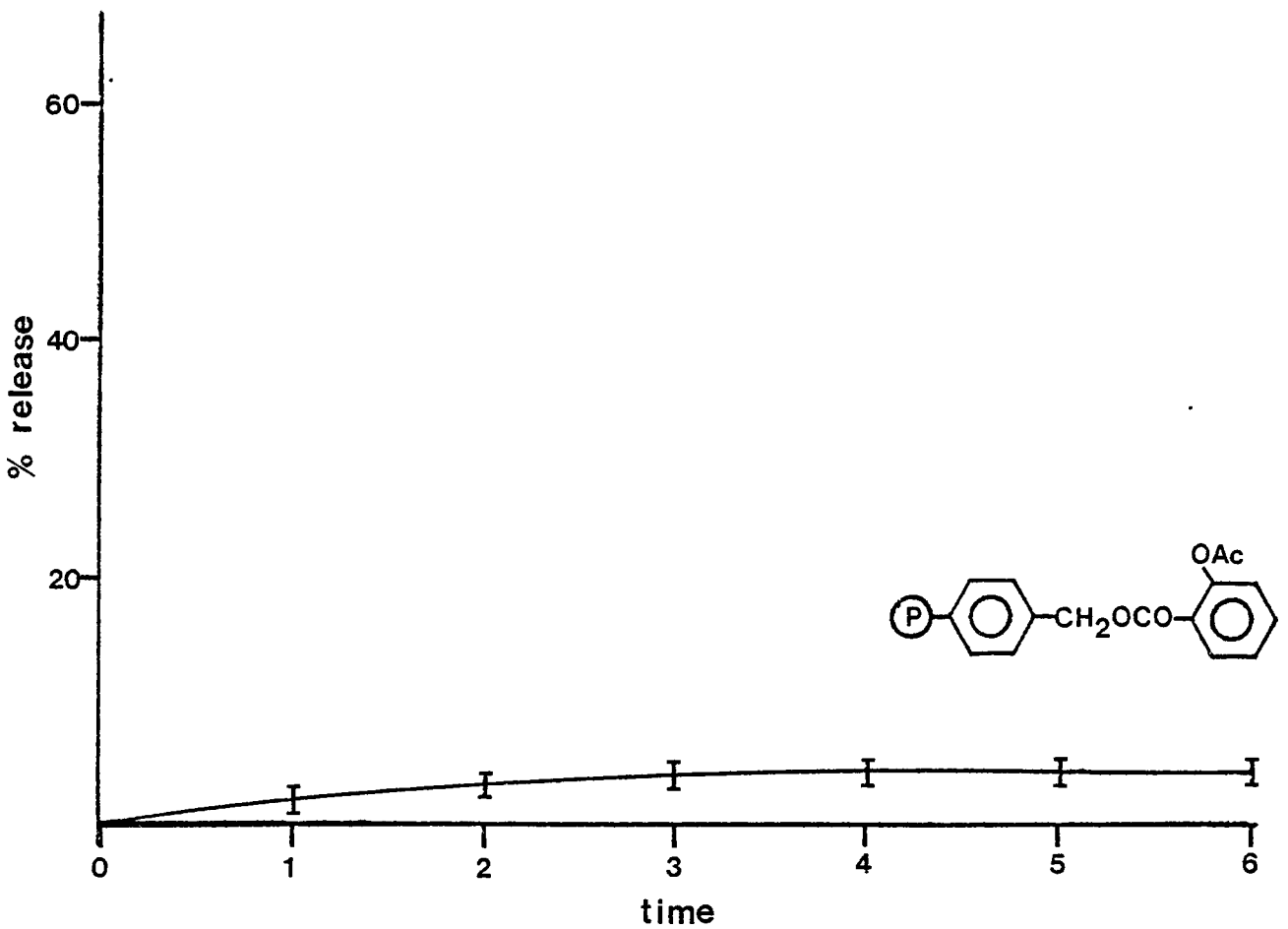


Figure 12. Release Studies: Polystyrene Succinic ^{14}C-Acetylsalicyloyl Anhydride in pH 9.0 Buffer

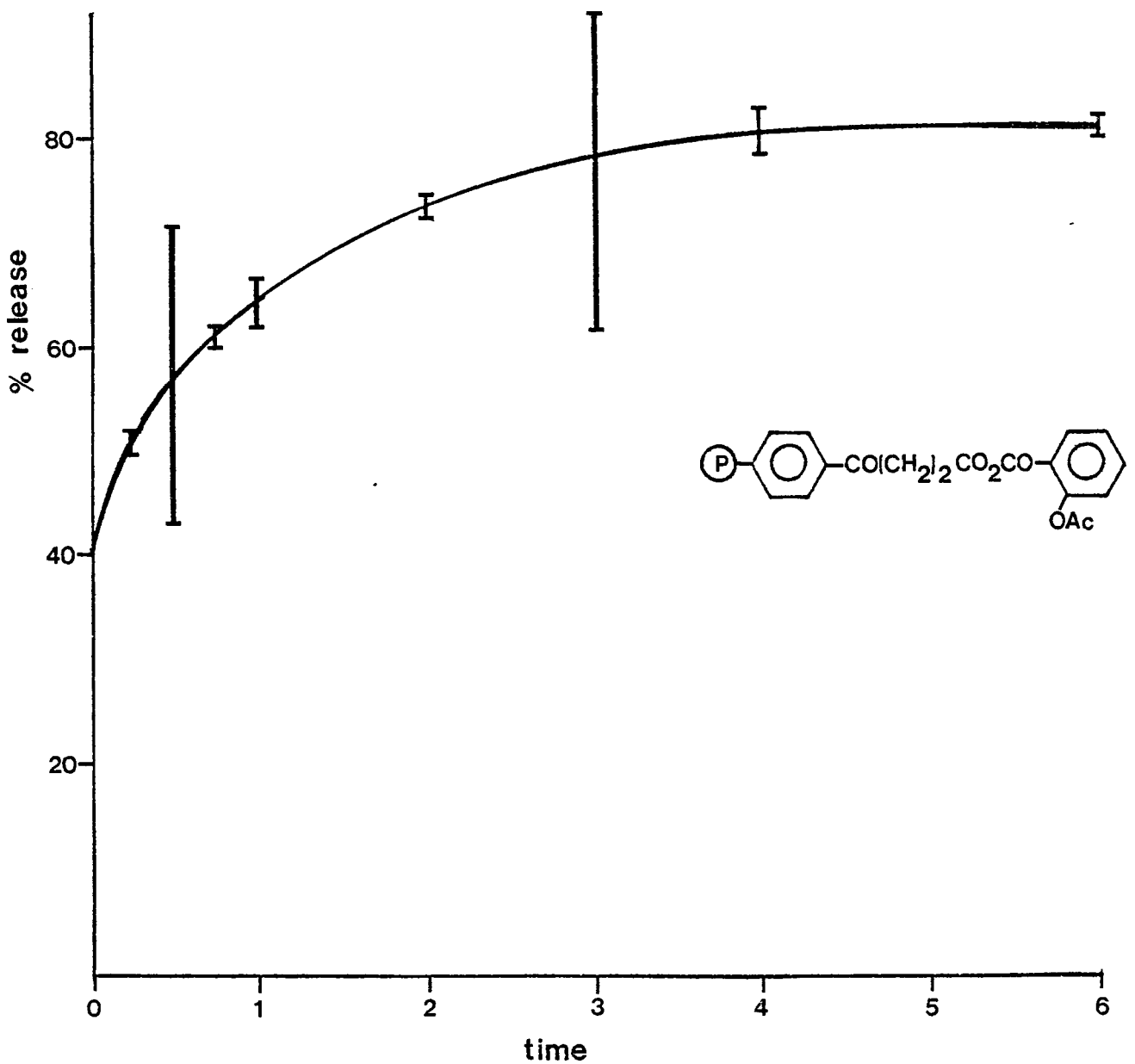


Figure 13. Release Studies: Polystyrene Mixed Carbonic ^{14}C-Acetylsalicyloyl Anhydride in pH 9.0 Buffer

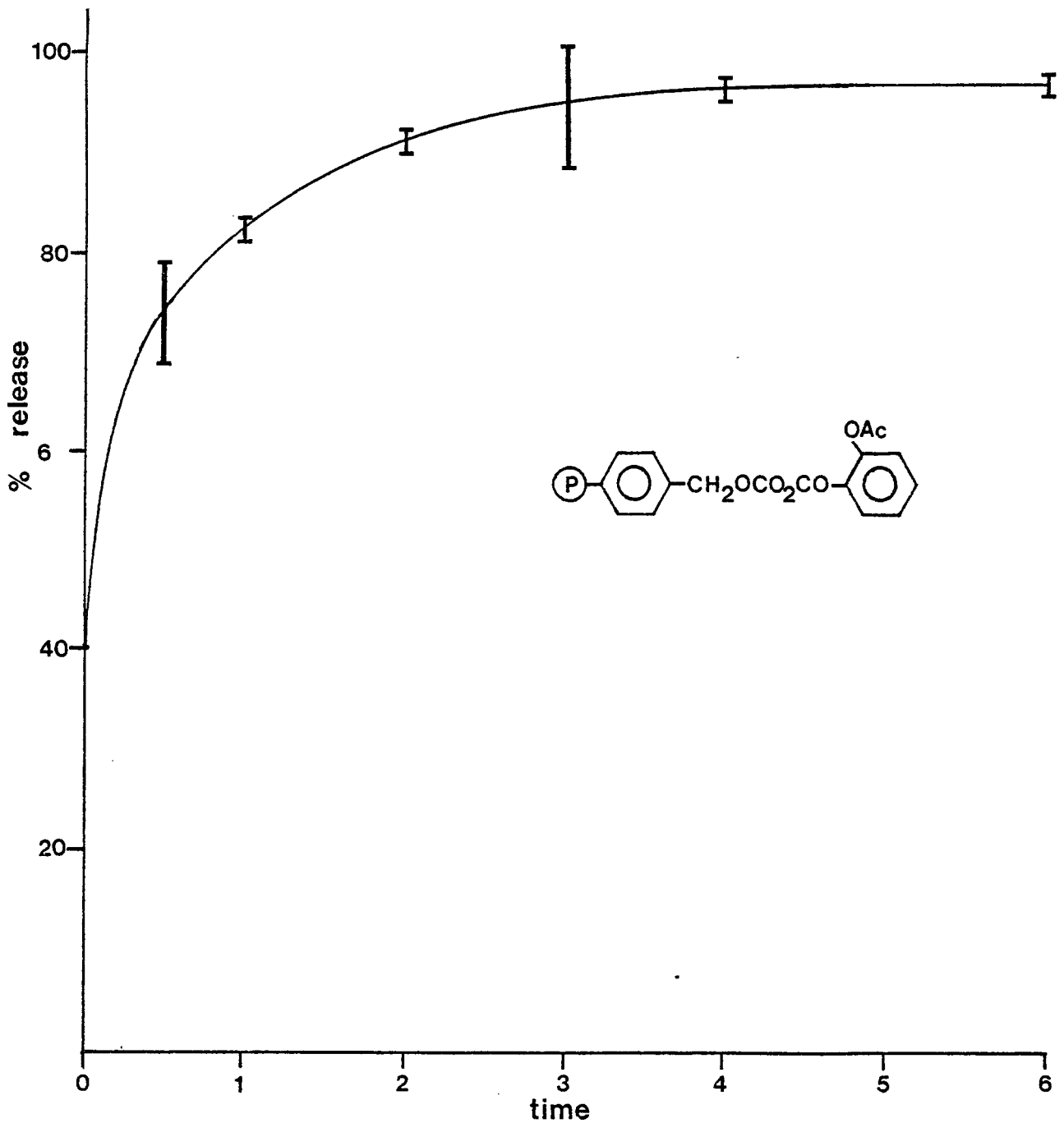
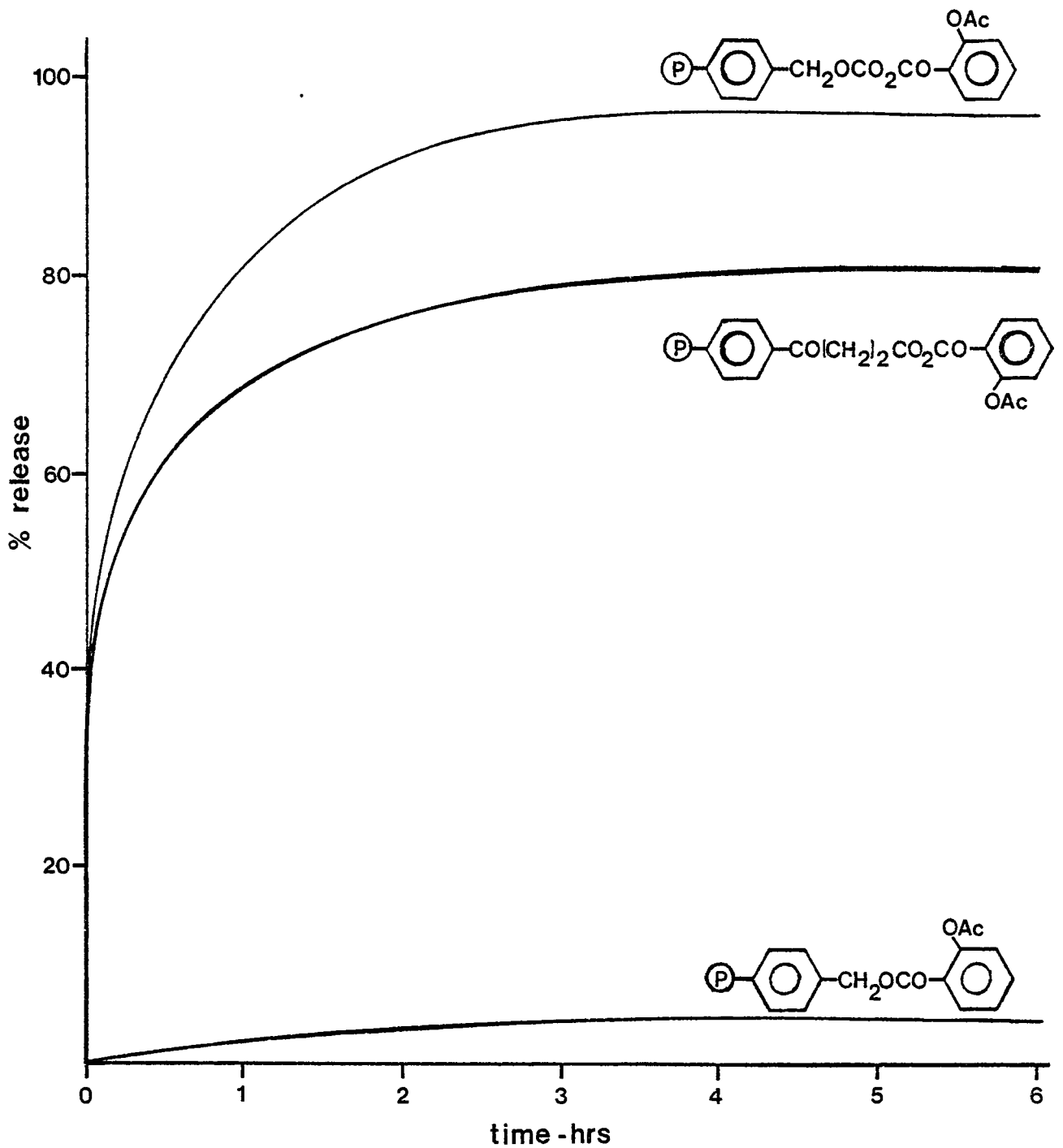


Figure 14. Comparison of ^{14}C-Acetylsalicyloyl Release Rates



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APPENDIX

```
LIST
10 DIM X[100],X1[100],X2[100]
20 INPUT "\215\NUMBER OF X VALUES ?"N
30 LET S=0
40 LET S1=0
50 LET S2=0
60 LET S3=0
70 PRINT
80 IF N=0 STOP
90 IF N<=100 GOTO 130
100 PRINT "MAX OF 100 POINTS"
110 PRINT
120 GOTO  20
130 FOR J=1 TO N
140   INPUT "\215\"X[J]
150   LET S=S+X[J]
160 NEXT J
170 LET M=S/N
180 FOR J=1 TO N
190   LET X1[J]=X[J]-M
200   LET X2[J]=X1[J]*X1[J]
210   LET S1=S1+X2[J]
220 NEXT J
230 LET S2= SQR (S1)
240 LET S3=S2/M
250 PRINT
260 FOR J=1 TO N
270   PRINT X[J];X1[J];X2[J]
280 NEXT J
290 PRINT "MEAN = ";M;" SUM OF DELTA\X = ";S1
300 PRINT "SQUARE ROOT OF S1 = ";S2
310 PRINT "% ERROR  = ";S3*100
320 PRINT
330 GOTO  20
```

```
NUMBER OF X VALUES ?


2

474
461
 474  6.5  42.25
 461 -6.5  42.25
MEAN =  467.5  SUM OF DELTA X =  84.5
SQUARE ROOT OF S1 =  9.19238
% ERROR  =  1.96628


NUMBER OF X VALUES ?2

321
316
 321  2.5  6.25
 316 -2.5  6.25
MEAN =  318.5  SUM OF DELTA X =  12.5
SQUARE ROOT OF S1 =  3.53553
% ERROR  =  1.11005


NUMBER OF X VALUES ?0

STOP AT 80
```

```
RUN

NUMBER OF X VALUES ?3

1600
1577
1597
 1600  8.67  75.1689
 1577 -14.33  205.348
 1597  5.67  32.1489
MEAN =  1591.33  SUM OF DELTA X =  312.664
SQUARE ROOT OF S1 =  17.6823
% ERROR  =  1.11116


NUMBER OF X VALUES ?3

1196
1187
1642
 1196 -145.66  21216.8
 1187 -154.66  23919.7
 1642  300.34  90204.1
MEAN =  1341.66  SUM OF DELTA X =  135340
SQUARE ROOT OF S1 =  367.885
% ERROR  =  27.4201


NUMBER OF X VALUES ?2

1196
1187
 1196  4.5  20.25
 1187 -4.5  20.25
MEAN =  1191.5  SUM OF DELTA X =  40.5
SQUARE ROOT OF S1 =  6.36396
% ERROR  =  .534113


NUMBER OF X VALUES ?3

1714
1710
1746
 1714 -9.33  87.0489
 1710 -13.33  177.688
 1746  22.67  513.928
MEAN =  1723.33  SUM OF DELTA X =  778.664
SQUARE ROOT OF S1 =  27.9045
% ERROR  =  1.61921
```

```
NUMBER OF X VALUES ?3

1638
1665
1728
 1638 -39  1521
 1665 -12  144
 1728  51  2601
MEAN =  1677  SUM OF DELTA X =  4266
SQUARE ROOT OF S1 =  65.3146
% ERROR  =  3.89472


NUMBER OF X VALUES ?3

1494
1515
2054
 1494 -193.66  37504.1
 1515 -172.66  29811.4
 2054  366.34  134204
MEAN =  1687.66  SUM OF DELTA X =  201519
SQUARE ROOT OF S1 =  448.908
% ERROR  =  26.5994


NUMBER OF X VALUES ?2

1494
1515
 1494 -10.5  110.25
 1515  10.5  110.25
MEAN =  1504.5  SUM OF DELTA X =  220.5
SQUARE ROOT OF S1 =  14.8492
% ERROR  =  .986985


NUMBER OF X VALUES ?3

1532
1557
2196
 1532 -229.66  52743.7
 1557 -204.66  41885.7
 2196  434.34  188651
MEAN =  1761.66  SUM OF DELTA X =  283280
SQUARE ROOT OF S1 =  532.24
% ERROR  =  30.2124
```

```
NUMBER OF X VALUES ?165225613

165332
1682
1768
 1652 -48.66  2367.79
 1682 -18.66  348.195
 1768  67.34  4534.67
MEAN =  1700.66  SUM OF DELTA X =  7250.65
SQUARE ROOT OF S1 =  85.1507
% ERROR  =  5.00692
```

```
NUMBER OF X VALUES ?2

1863
2132
 1863 -134.5  18090.2
 2132  134.5  18090.2
MEAN =  1997.5  SUM OF DELTA X =  36180.4
SQUARE ROOT OF S1 =  190.211
% ERROR  =  9.52245
```

```
#BASIC
LOAD RICK.
RUN

NUMBER OF X VALUES ?3

1814
1807
1828
 1814 -2.33  5.4289
 1807 -9.33  87.0489
 1828  11.67  136.188
MEAN =  1816.33  SUM OF DELTA X =  228.665
SQUARE ROOT OF S1 =  15.1216
% ERROR  =  .832535


NUMBER OF X VALUES ?3

1378
1354
1554
 1378 -50.66  2566.43
 1354 -74.66  5574.11
 1554  125.34  15710.1
MEAN =  1428.66  SUM OF DELTA X =  23850.6
SQUARE ROOT OF S1 =  154.436
% ERROR  =  10.8098


NUMBER OF X VALUES ?3

1840
1870
1856
 1840 -15.33  235.008
 1870  14.67  215.208
 1856  .67  .4489
MEAN =  1855.33  SUM OF DELTA X =  450.664
SQUARE ROOT OF S1 =  21.2288
% ERROR  =  1.1442


NUMBER OF X VALUES ?3

1901
1868
1953
 1901 -6.33  40.0689
 1868 -39.33  1546.84
 1953  45.67  2085.74
MEAN =  1907.33  SUM OF DELTA X =  3672.64
SQUARE ROOT OF S1 =  60.6023
% ERROR  =  3.17733
```

```
NUMBER OF X VALUES ?3

1940
2054
1912
 1940 -28.66  821.395
 2054  85.34  7282.91
 1912 -56.66  3210.35
MEAN =  1968.66  SUM OF DELTA X =  11314.6
SQUARE ROOT OF S1 =  106.37
% ERROR  =  5.40316


NUMBER OF X VALUES ?0

STOP AT 40

*BYE
```

PART II: Investigation of the Synthesis of Some Novel 5-Fused Heterocyclic Ring Systems and Their Potential Application in Medicinal Chemistry

LIST OF TABLES

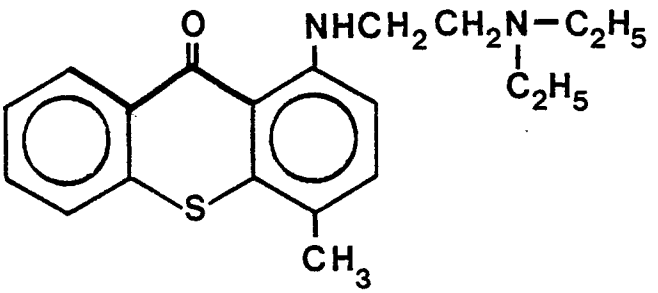
LIST OF FIGURES

INTRODUCTION

One can site various literature references which include a wide spectrum of pharmacological activities associated with heteroaromatic systems. There has been considerable interest of late in heterocyclic compounds, including those systems containing phosphorous as a heteroatom. Mann (1), reported about 150 different ring systems containing phosphorous in the 1970 edition of his text.

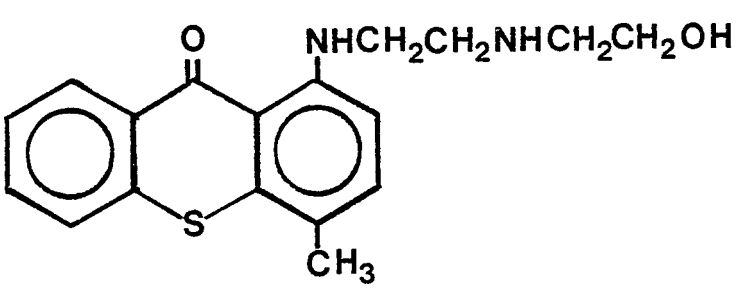
Despite the great activity in this area, particularly in the past three years, there still remain basic structures which have yet to be investigated. To deal with the heteroaromatic systems as a specific area of interest, one observes the following compounds and their major activities.

Ullman and von Glenck (2) in 1916 first synthesized some seventy compounds which were derivatives of thioxanthen-9-ones, however, only the structure of Miracil D (1) was reported. It was not until many years later that it was reported to be an orally effective schistosomicidal. Mauss (3) in 1948 was the first to author a paper which reported in detail the chemistry of Miracil D and its congeners. Hawking (4), Kikuth (5), Vogel (6), and Alves (7) described the toxicological and chemotherapeutic properties of Miracil D. However, it appeared from these works, the toxic dose of this drug was so close to the curative dose that the compound could not be considered more than a promising lead in the oral treatment of schistosomiasis.

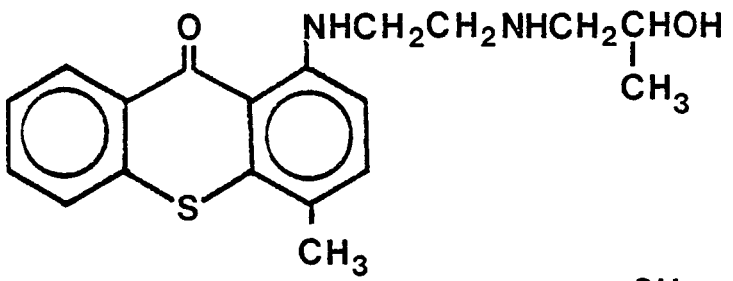


(1)

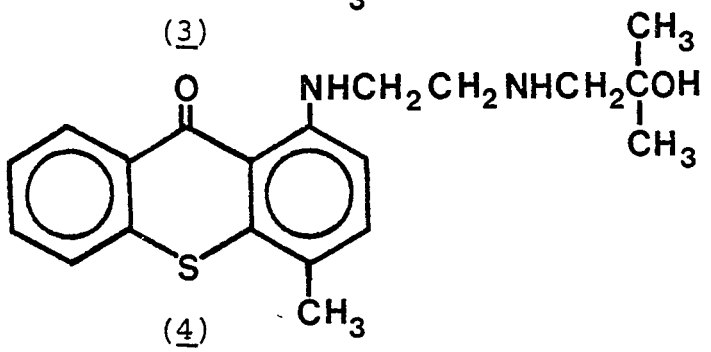
Archer and Suter (8) in 1952, prepared compounds having varying structures and evaluated their schistosomicidal activity. In their research they employed the synthetic method of thiocondensation published by Smiles (9, 10). It was observed that the thioxanthone shown below (2) was weakly active but that homologs (3) and (4) were about as active as Miracil D.



(2)



(3)



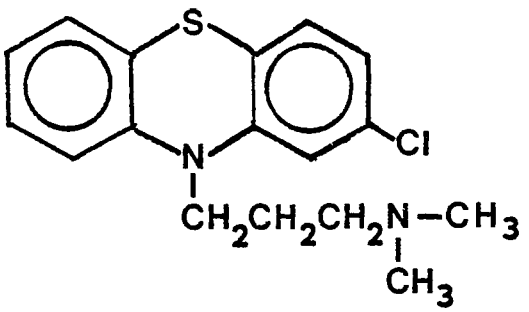
(4)

The observations of Archer and Suter (8) prompted the preparation of a series of 4-methylthioxanthones substituted in the 7-position with either chlorine, methyl or methoxy groups and in the 1-position with N-alkyl-N-hydroxyalkylaminoethylamino groups. A marked increase in activity and a decrease in toxicity was achieved with the therapeutic indices about ten times greater than that of Miracil D.

At the same time Archer and Suter (8) were preparing the above mentioned series of basic thioxanthones for evaluation as schistosomicidal drugs, they also synthesized three groups of compounds in which the sulfur atom of the thioxanthone nucleus was replaced by oxygen, imino, and carbonyl functions to furnish the corresponding xanthones, acridones, and anthraquinones (11). They had prepared the acridone and anthraquinone nuclei before they discovered that structurally a side chain was required for high activity.

Such an example of a pseudo-isosteric replacement of the atom at either the 9- or 10-position was first explored by

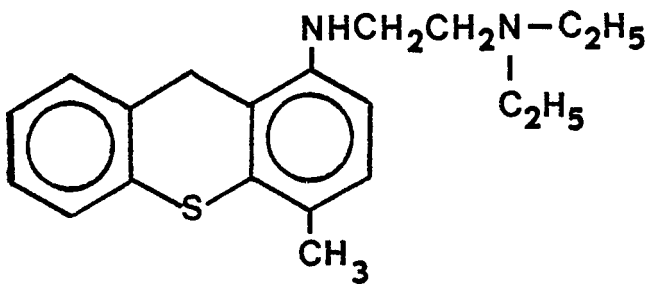
Charpentier (12), in the preparation of chloropromazine (5), a drug which was to be used to treat schizophrenia (13).



(5)

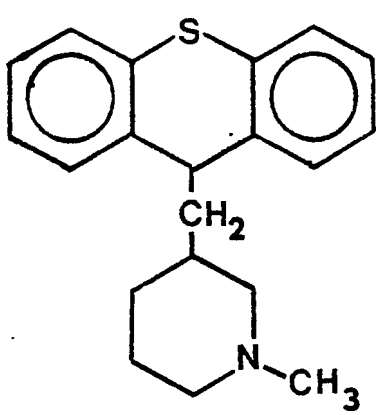
Charpentier not only included a pseudo-isosteric replacement for the carbonyl group in Miracil D but also included a side chain and a chlorine group at the 7-position which at that point in time was rather unique because it was unknown to him that such substitutions were required for high activity.

The basic groundwork was laid by Charpentier (12) for the use of pseudo-isosteric replacements and the initial observation that a side chain was required for high activity by Archer et.al. (11). Considerable effort was then spent on the development of compounds modeled after Miracil D in which similar modifications were achieved. Kikuth and Connert (14) who had previously studied the toxicological and chemotherapeutic properties of Miracil D reported the synthesis of a derivative Lucanthone (6) which proved to be an active anti-helmintic. Here again, a simple isosteric replacement was performed.



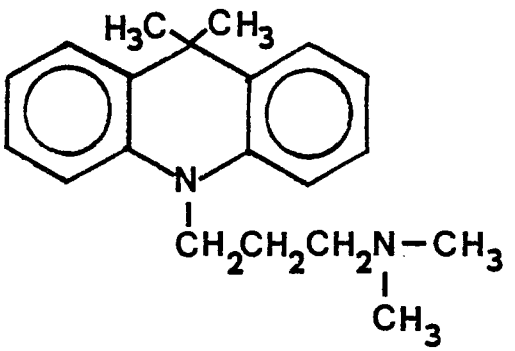
(6)

In 1961, Wander (15) reported the synthesis of Trest (7) which proved to be an active anticholinergic drug. Employed in this synthesis was a simple modification of the side chain.



(7)

In 1966, Guth and Hoffman (16) reported the synthesis of Dimethacrin (8)which proved to be an effective antidepressant.



(8)

Many more examples could be cited which would further exemplify the basic work of Charpentier (12). Modification at either the 9- or 10-position in the basic Miracil D nucleus retained activity, a side chain was required for high activity and substitution of an electron withdrawing substituent at C-7 enhanced activity. The question still arises, however, how does a simple central ring modification, a substitution on the side chain, or the addition of an electron withdrawing group so vary the pharmacological activity of the basic model molecule which was synthesized in 1916 and for all purposes forgotten until 1948.

In an attempt to answer some of the questions posed, Blanz and French (17) in 1963 reported the synthesis of some fifty-seven analogs of Miracil D in which limited isosteric replacement was studied with a major emphasis placed upon modification of the amino side chain for by this time, Miracil D was found to be active against such tumor test systems as

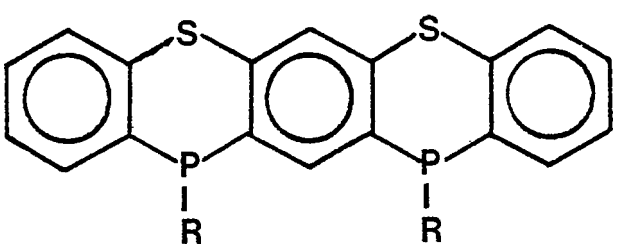
Leukemia L-1210, Adenocarcinoma 755, and Sarcoma 180 (18). As a result of this investigation, the following structure-activity relationship was reported: (a) the carbon side chain must be two carbon atoms in length, (b) the terminal alkyl group(s) must be small, (c) the ring attached nitrogen must bear one free hydrogen atom, (d) the ring must have an unsubstituted sulfur atom in position 10, (e) there must be a carbonyl in the 9-position of the basic nucleus, and (f) there must be a compact, fairly durable substituent in the ring position 4. The authors proposed that such a molecule has metal chelating ability and consequently this is the reason for the carbonyl and the dialkylaminoethylamino side chain being essential for carcinostatic activity.

This eloquent work explains the possible mechanism of action for one specific case of this general class but still does not shed any light upon the diverse pharmacological activities which are seen with simple pseudo-isosteric replacement.

Conformational studies of xanthene, thioxanthene, and acridan were reported by Aizenshtat et.al. (19) in 1972. Until this time, the conformation of such tricyclic ring systems as discussed previously was thought to be planar. The measurement of dipole moments and the use of some rather sophisticated ultra-violet absorption data pointed to the fact that these molecules are in fact not planar. Nuclear magnetic resonance data reported by Ternay (20) supported this evidence. Digenis et.al. (21) investigated the relationship between conformation and pharmacological activity of acridan derivatives, however, to date no strong conclusions are reported.

OBJECTIVE

Doak, Levy, and Freedman (22) have reported the synthesis of heterocyclic organophosphorous compounds which very well may serve as valuable precursors of other phosphorous compounds. Relatively few procedures are available for the preparation of phosphinic acid derivatives in which the phosphorous atom is a member of the ring system. Therefore, the synthesis of a series of phosphorous containing ring systems of the types shown below (9) will be investigated and tested for their potential application in medicinal chemistry.

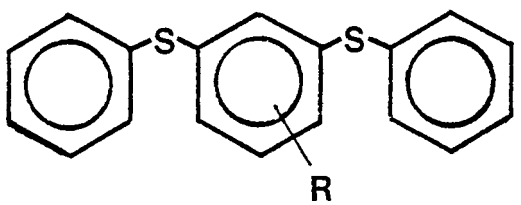


R = -Cl, $-C_6H_5$

(9)

DISCUSSION

The point at which the synthesis must focus is directly related to the formation of a substituted dimeric species as shown (10).



R= -Cl, $-NO_2$

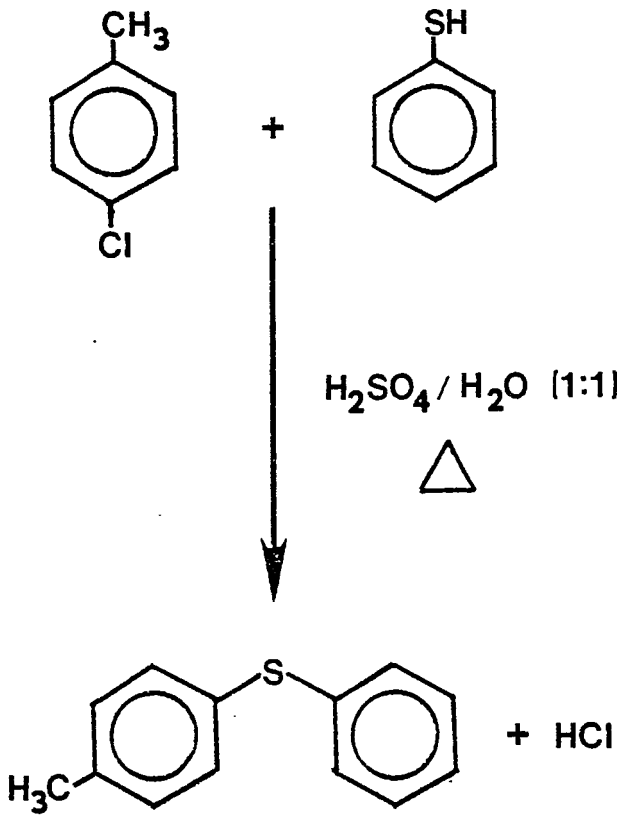
(10)

Synthesis of such a dimeric intermediate could result from modifications of a variety of synthetic procedures. Ullman and von Glenck (2) first effected the condensation of p-chlorotoluene with thiophenols under acidic conditions as shown in Scheme I. Archer and Suter (8) later reported the condensation of potassium o-chlorobenzoates with thiophenols in basic media at elevated temperatures, both with and without copper catalysts as shown in Scheme II.

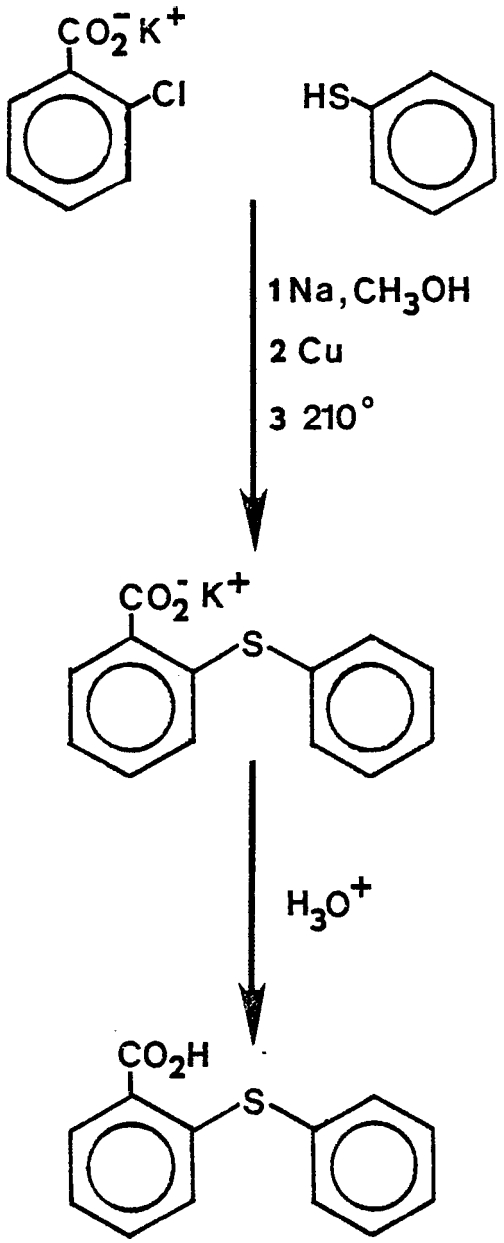
Beck and Yahner (23) have shown that when a dipolar aprotic solvent (DMF) is employed, the displacement of a nitro group by mercaptide ions occurs readily at room temperature and that such processes are synthetically valuable. An example is shown in Scheme III. Kornblum et.al. (24) investigated the condensation of thiophenoxide ions with various dinitrated benzenes as illustrated in Scheme IV. The authors

found that the solvent played a major role in both the length of the reaction and the yield. The solvents used were dimethylsulfoxide (DMSO), dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPA) with HMPA being better than DMSO which was better than DMF.

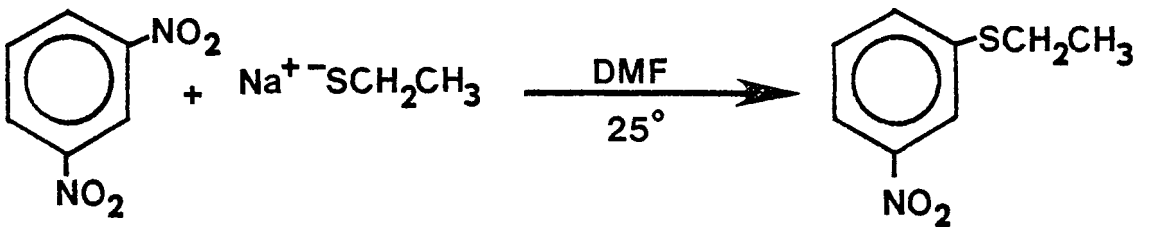
Scheme I



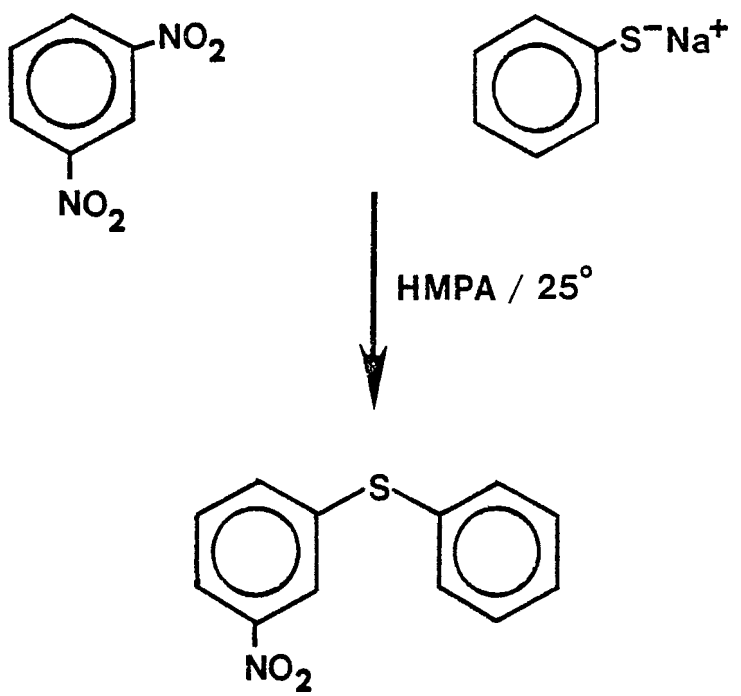
Scheme II



Scheme III

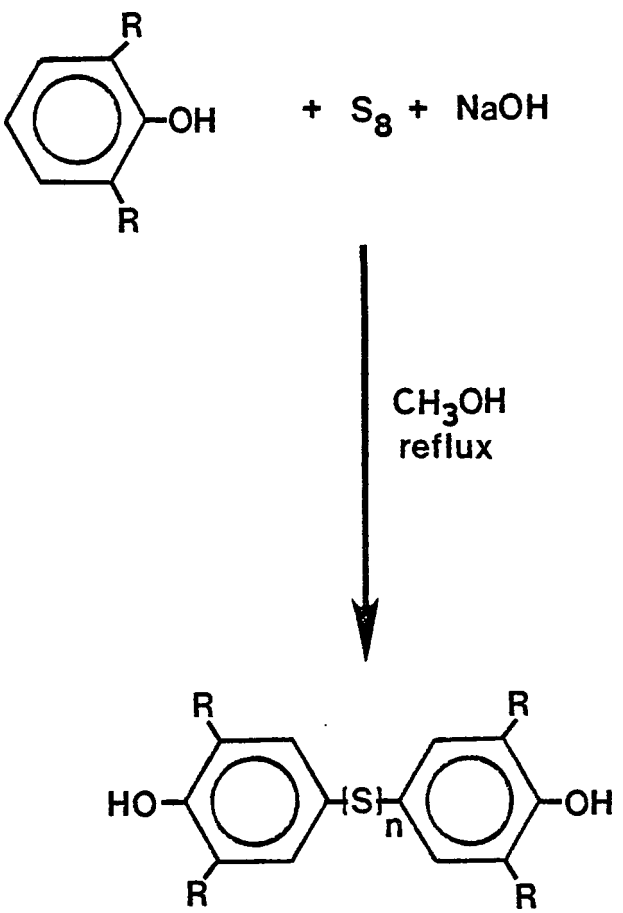


Scheme IV



Fujisawa et.al. (25) in recent literature reported the sulfurization of sterically hindered phenols using elemental sulfur as shown in Scheme V.

Scheme V



R = Me, Et, t-Bu
n = 1,2,3,...

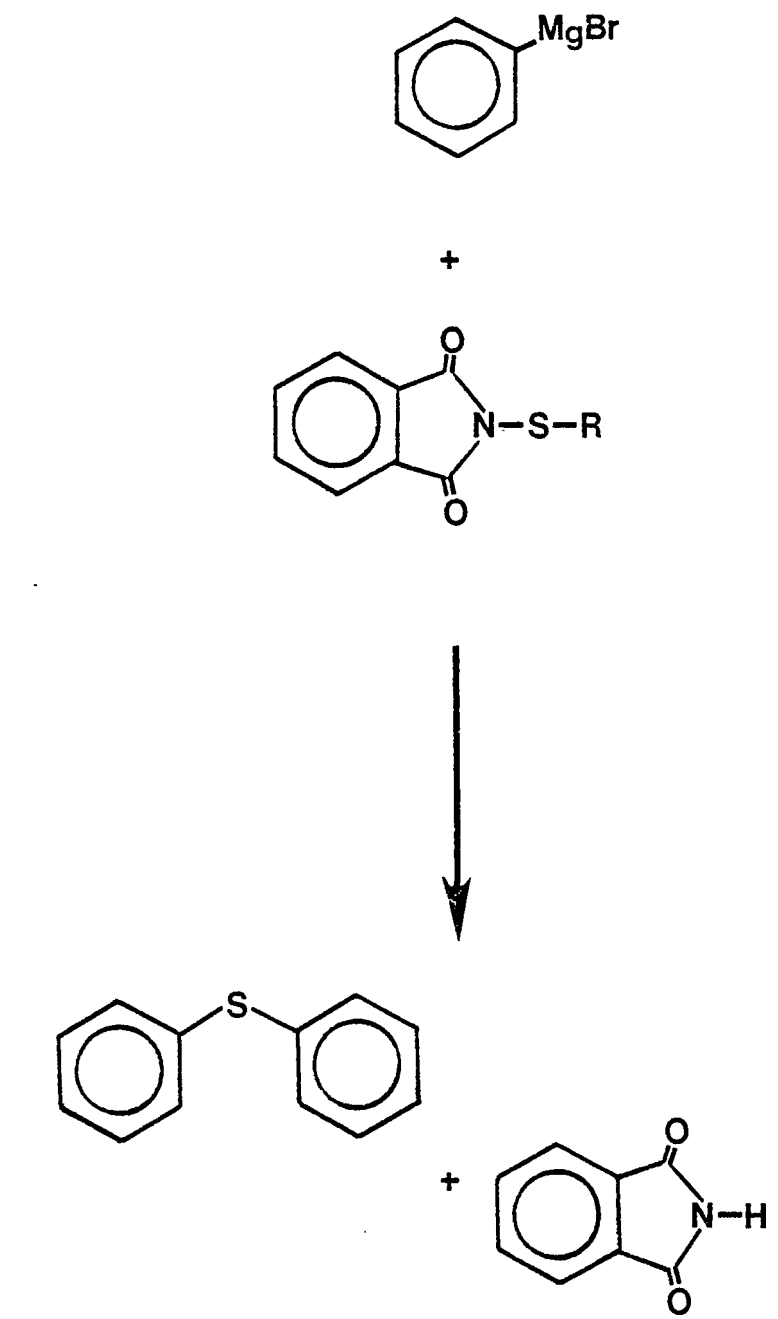
This investigation was the result of studies done by Neale et.al. (26, 27) on the rearrangements and decompositions of thiobisphenols. However, Hay and Boulette (28) reported that no reaction occurs between 2,6-disubstituted phenols and sulfur unless epoxides or activated olefins such as acetonitrile are continuously added to the reaction mixture.

Lau (29) in 1975 reported that thioimides are a useful class of sulfur-transfer reagents as shown in Scheme VI. This work was a continuation of an investigation by Behforonz and Kerwood (30) into the synthesis of alkyl- and arylsulfenimides.

Another approach to the synthesis of the dimeric intermediate previously mentioned could include the generation of aryl Grignard reagents, which upon reaction with sulfur and subsequent acidification yield aryl thiols (31), as shown in Scheme VII. This approach, however, is not a common one because the yields are generally unpredictable and by-product formation may be significant. Finally, the reaction of a Grignard reagent with a diaryl disulfide, a process which involves a nucleophilic displacement by a carbanion on the sulfur of the disulfide bond, could be a useful synthetic reaction as illustrated in Scheme VIII. Closure of the proposed intermediate could be effected by various routes.

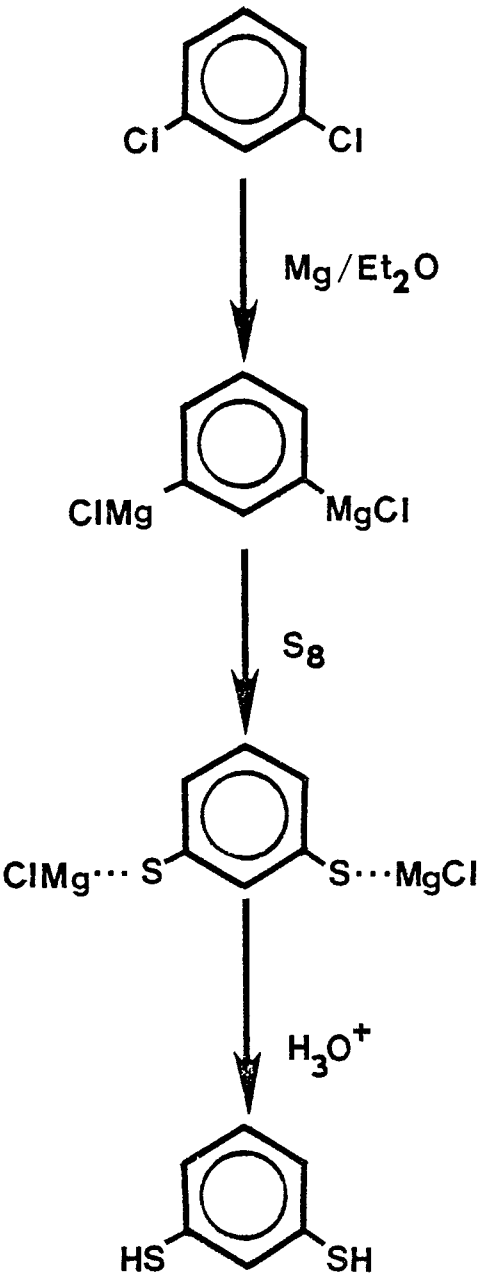
Doak and Freedman (32, 33) have reported a series of syntheses involving the use of diazonium salts such as diazonium fluoborates in organic solvents and either arsenic or substituted phosphorous chlorides as shown in Scheme IX. Several methods had been previously used for the preparation of aryl phosphinic acids (34, 35), but none had been found convenient for preparing a wide variety of such compounds, like the Doak, Levy, and Freedman procedure, in nonaqueous

Scheme VI

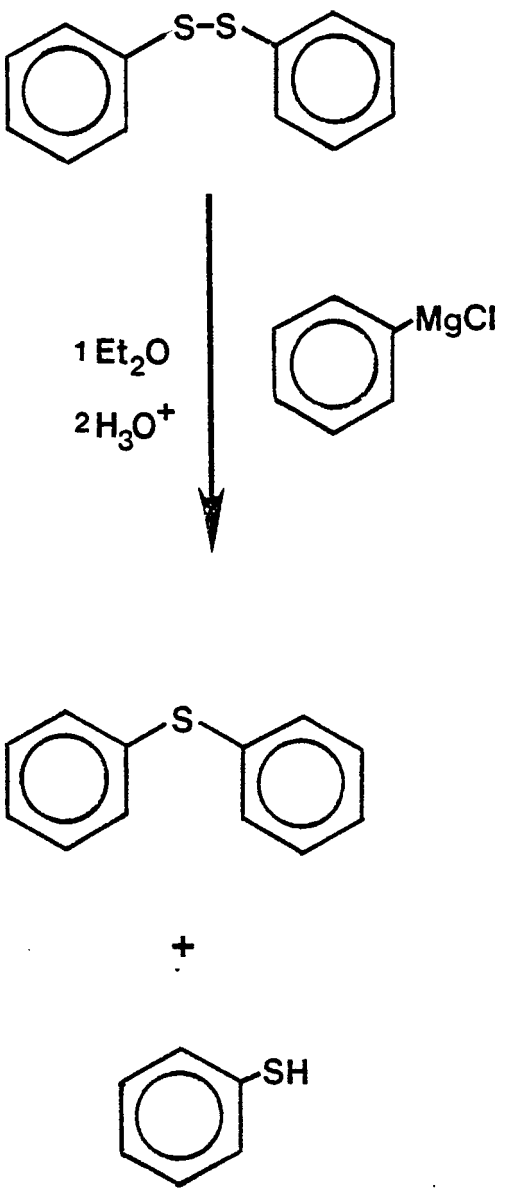


R = $-C_6H_5$

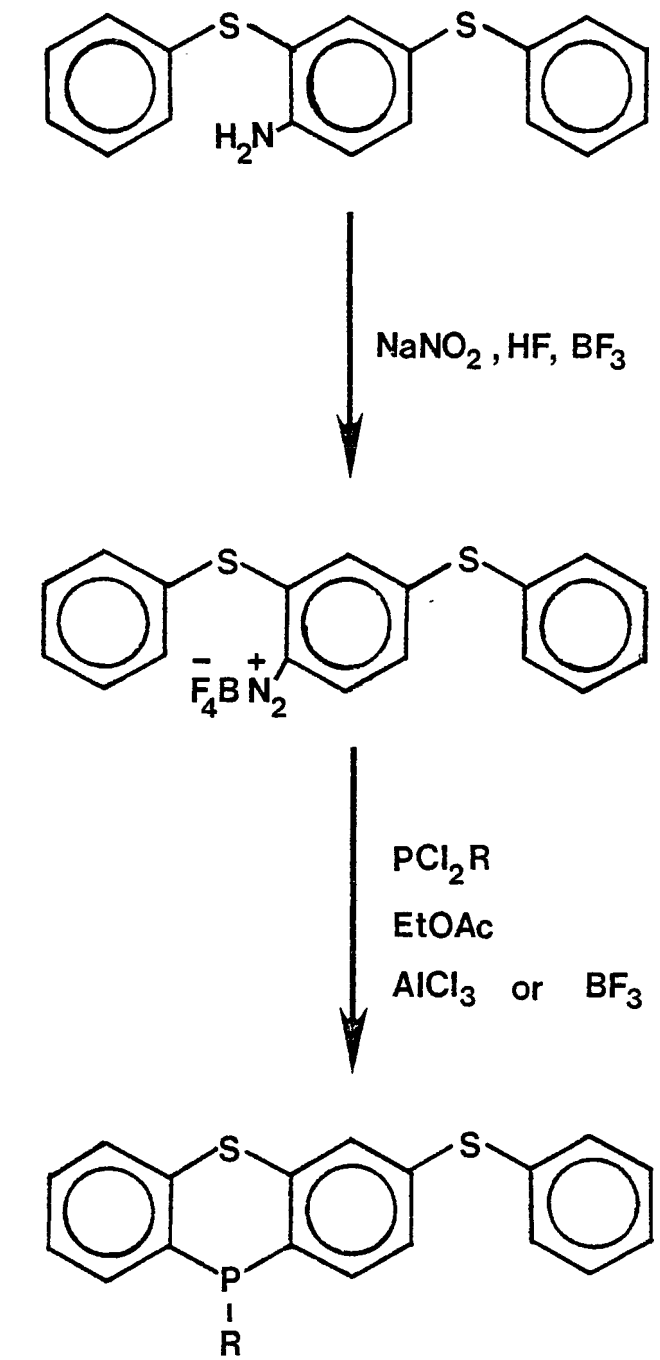
Scheme VII



Scheme VIII



Scheme IX

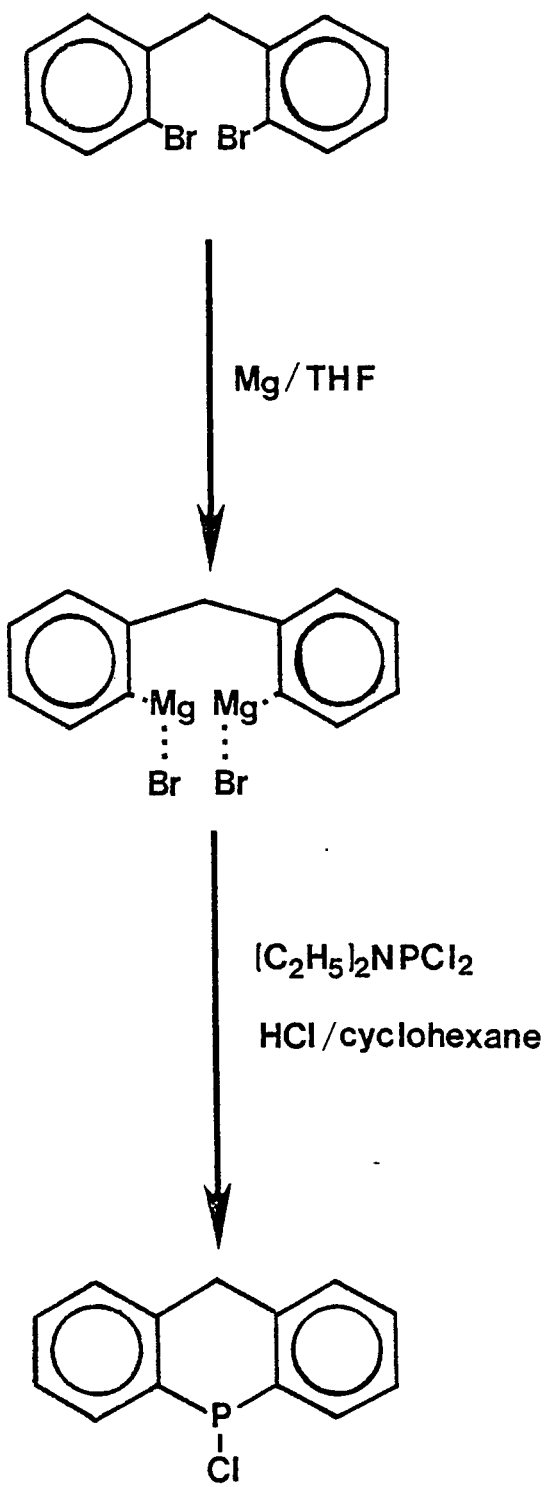


R= -Cl, C_6H_5

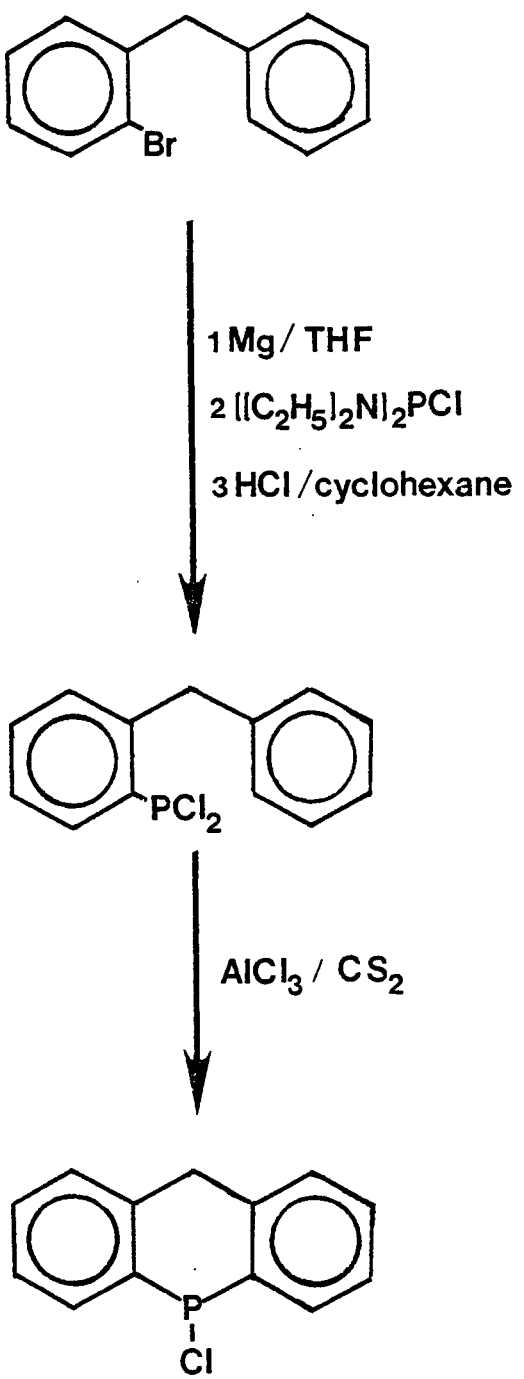
solvents. Most of the phosphinic acids were extremely soluble in water and many organic solvents, therefore, purification was achieved by converting the corresponding acids to their hemi-sodium or potassium salts.

Haring (36) and Doak and Freedman (37) have also reported the synthesis of a series of phenoxaphosphinic, phenazaphosphinic, and phenothiaphosphinic acid derivative ring systems using the same procedure. deKoe and Bickelhaupt (38) have reported the synthesis of 5-chloro-5,10-dihydrodibenzo(b,e)-phosphorin via a Grignard procedure from bis(o-bromophenyl) methane and also from (o-bromophenyl) phenyl methane. In both cases, dichlorodiethylaminophosphine derivative was used but in the latter case, condensation was achieved with aluminum chloride in carbon disulfide as shown in Scheme X. Doak, Levy, and Freedman (39) also have reported the preparation of a series of phenoxaphosphines via Friedel-Crafts and diazo reactions as illustrated in Scheme XI.

Scheme X



Scheme XI



RESULTS

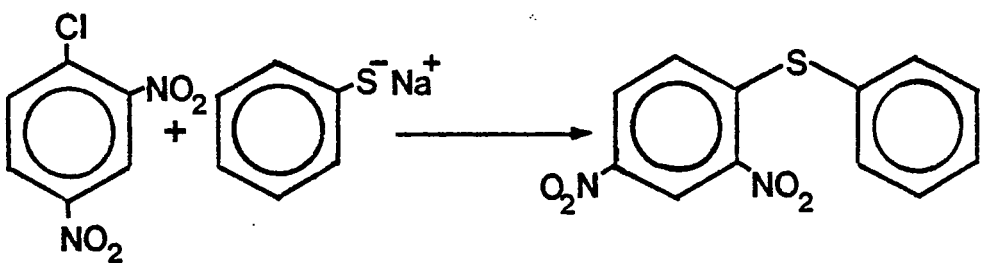
In the investigation of some novel 5-fused heterocyclic ring systems containing sulfur and phosphorous, the synthesis of the 1,5-bis(thiophenyl)-2-nitrobenzene intermediate upon which the total synthesis was focused led to several important observations. These observations consequently resulted in the elucidation of a selective displacement reaction in addition to other data of significance which will be discussed in this section.

Kornblum et.al. (24) stated that the use of hexamethylphosphorictriamide (HMPA) was of importance because of the need to solvate the attacking ion, thiophenoxide. It was reported that the relative rates of reaction and the yields were higher when using HMPA than when using either dimethylsulfoxide (DMSO) or dimethylformamide (DMF). This perhaps is the case when undertaking a nucleophilic nitro displacement; however, when using a halonitrobenzene, DMF was found to be a suitable solvent. Campbell (40, 41) reported that, in fact, DMF acted as a catalyst for nucleophilic substitutions of similar nature. Further, DMF appears to be the least toxic/carcinogenic of the two solvents of choice (42).

Kornblum (43) suggested that an acid-alumina column be used to purify the reaction mixture when HMPA was used as the solvent. However, it was observed that an acid-alumina column was unsatisfactory; the resolution achieved on silica gel tlc plates was not realized on an alumina column, even with the step-wise elution procedure outlined in the previous section. When purification was attempted using a silica gel column, the resolution was good and the tedious task of step-wise elution eliminated, for the only solvent required was

chloroform. The desired reaction product separated cleanly from the solvent (DMF) and was the first to be eluted from the column.

Most significant of all observations made was the fact that nucleophilic displacement when using a halonitroaromatic system occurred in a selective manner. This phenomenon was observed when an exothermic reaction occurred in the solid state, using 1-chloro-2,4-dinitrobenzene and sodium thiophenoxide. Upon further investigation, it was found that the major product of this reaction was 1-thiophenyl-2,4-dinitrobenzene as seen in Equation 1.

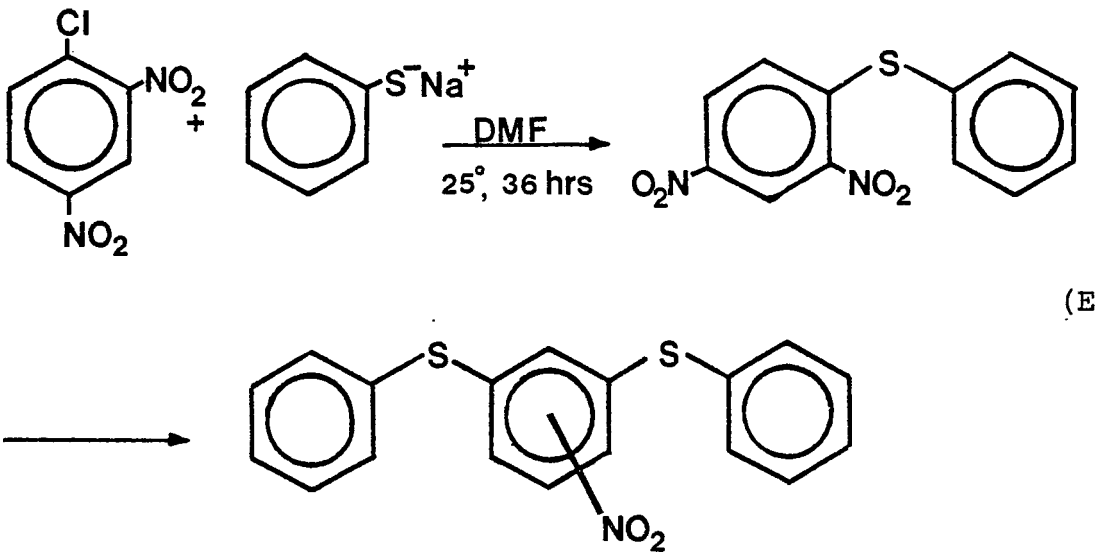


(Eq. 1)

(1) (3)

However, when solvating the halodinitrobenzene in DMF under nitrogen purge at room temperature, adding the sodium thiophenoxide (2:1 molar ratio), and allowing the mixture to react for as long as 36 hours, the formation of isomeric bis (thiophenyl)nitrobenzenes was observed as seen in Equation 2.

From these observations, it was concluded that not only a halogen but also a nitro group was being displaced, probably in the position para to the initial halogen displacement.



(Eq. 2)

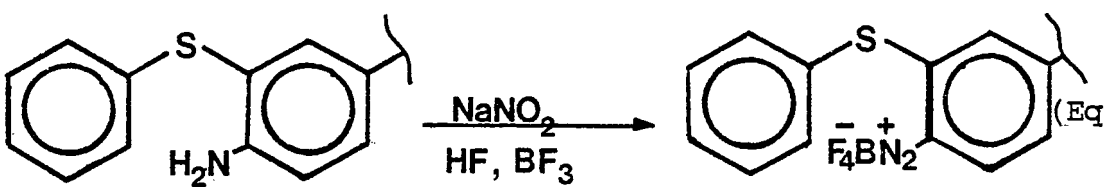
Several syntheses were consequently conducted to prove this hypothesis. 1-nitro-2,4-dichlorobenzene, 1-nitro-3,4-dichlorobenzene, and 2-nitro-1,4-dichlorobenzene were subsequently used to synthesize their respective bis(thiophenyl)-nitrobenzene derivatives by means of a dihalogen displacement.

It was assumed that the 1,2- isomer of the desired compound would not be formed because of steric hinderance. However, all isomers were prepared (Table 1). With this observation, it was decided to attempt the synthesis of the desired intermediate using 1-fluoro-2,4-dinitrobenzene. The displacement of fluorine occurred at even a faster rate and with a greater exothermic nature. Again, the selective displacement of the halogen followed by a slower displacement of the nitro group was observed. Parker (44) had earlier studied the relative rates of displacement using 2,4-dinitrohalobenzenes as a model system. Further, he noted that the particular nucleophilic reagent used, thiophenoxide ion, had a direct effect on the relative rate of the reaction. A necessary requirement in the successful syntheses was that the sodium thiophenoxide

be isolated according to the procedure of Kornblum et.al. (45).

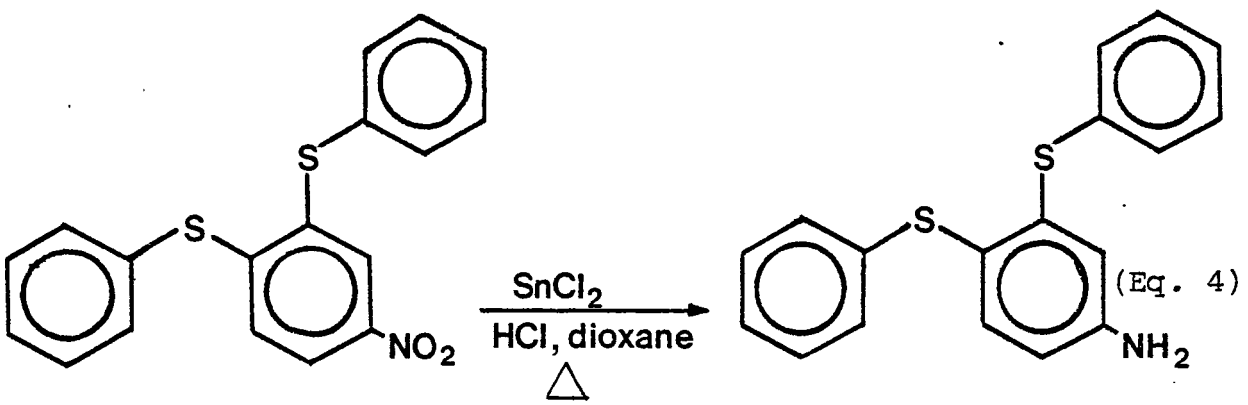
The data obtained from the elucidation of the above mentioned reaction showed the product ratio to be 1,4-bis(thiophenyl)-2-nitrobenzene (75%) and 1,2-bis(thiophenyl)-4-nitrobenzene (25%). This reaction could be further applied in the novel synthesis of mixed ethers (46).

The 1,5-bis(thiophenyl)-2-nitrobenzene intermediate consequently became of greater importance when considering the total synthesis of the heterocyclic organophosphorous compound stated as the objective. According to the general procedure of Doak, Levy, and Freedman (32, 33), a diazonium salt such as diazonium fluoroborate could be used in the synthesis of the desired phosphinic acid derivative in which the phosphorous atom is a member of the ring system. The synthesis requires that an amine be treated with sodium nitrate, boron trifluoride, and hydrofluoric acid to yield the diazonium fluoroborate as seen in Equation 3.



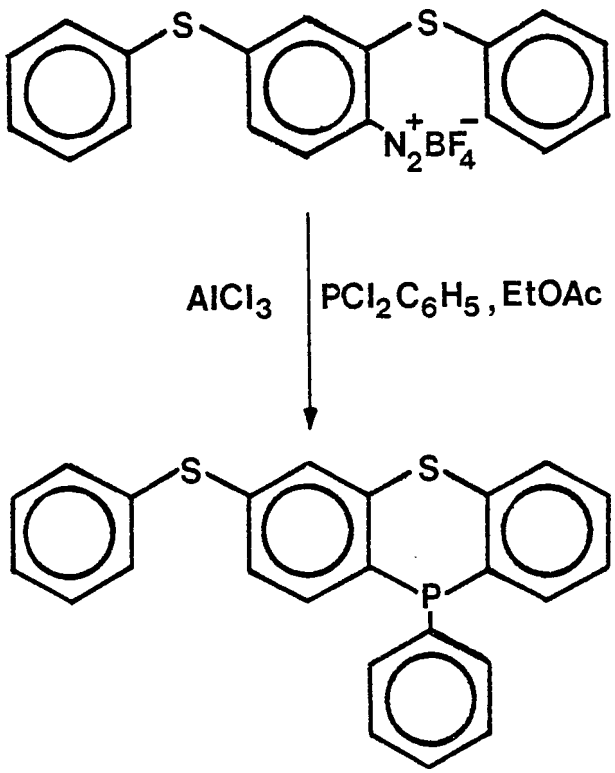
(Eq. 3)

Consequently, the nitro group of 1,2-bis(thiophenyl)-4-nitrobenzene was subjected to reduction conditions using stannous chloride, according to the general procedure of Bergstrom and Patterson (47), as seen in Equation 4. The reduction product was 1,2-bis(thiophenyl)-4-aminobenzene and was characterized by NMR (Figure 65), ^{13}C NMR (Figure 66), and ir (Figure 67), and Mass Spectra (Figure 68). In an attempt to reduce the remaining isomers which were available, it was observed that the same reaction conditions were inadequate. Stronger reducing conditions will need to be employed because of assumed steric hinderance problems encountered with the meta and para isomers.



(Eq. 4)

A promising synthetic route which can be attempted would employ the diazonium intermediate previously mentioned. After synthesis of the diazonium intermediate, the diazonium bis(thiophenyl) benzene derivatives will be reacted with dichlorophenylphosphine, using ethyl acetate as a solvent, according to the established procedure of Doak, Levy, and Freedman (32, 33), as seen in Equation 5.

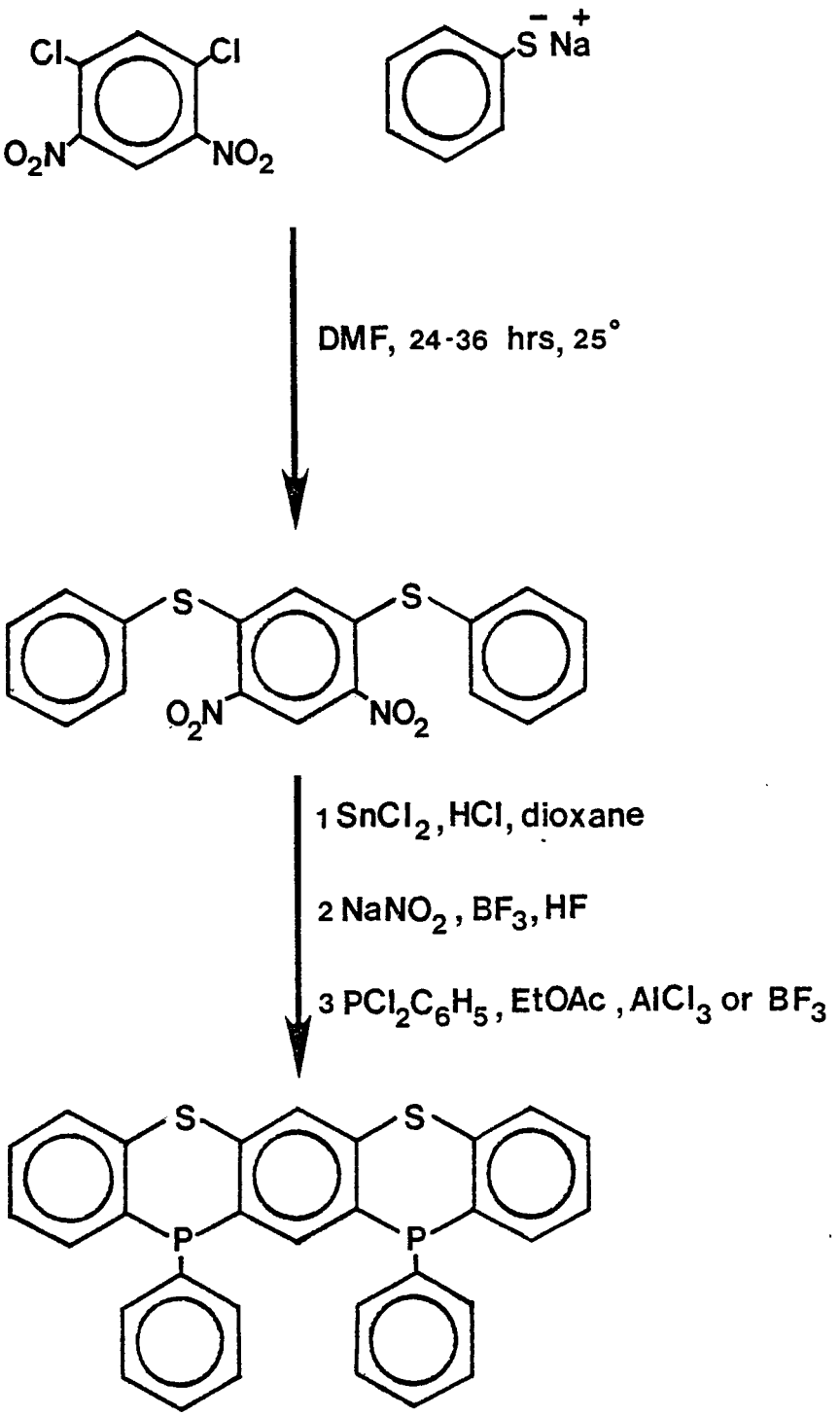


(Eq. 5)

In this particular case, ring closure will occur in only one ring.

The total synthesis of the desired 5-fused heterocyclic ring system can be realized by employing 1,3-dichloro-4,6-dinitrobenzene as shown in Scheme XII.

Scheme XII


Cl
Cl
O_2N
NO_2
S Na
DMF, 24-36 hrs, 25°
S
S
O_2N
NO_2
1 $SnCl_2$, HCl, dioxane
2 $NaNO_2$, BF_3, HF
3 $PCl_2C_6H_5$, EtOAc, $AlCl_3$ or BF_3
S
S
P
P

EXPERIMENTAL

A. Materials and Reagents

All synthetic precursors used were reagent grade or better obtained from either Aldrich Chemical Company, Inc., Milwaukee, Wisconsin; Eastman Organic Chemicals, Rochester, New York; or from Fisher Scientific Company, Fair Lawn, New Jersey, and used without further purification.

All solvents, unless otherwise noted, were reagent grade or better, obtained from the above sources and used without further purification.

Silica gel (70-230 mesh ASTM) was obtained from EM Laboratories, Inc., Elmsford, New York.

Alumina (acid, Brockman Activity 1, 80-200 mesh) was obtained from Fisher Scientific Company, Fair Lawn, New Jersey.

3,4-dichloronitrobenzene was obtained in very generous supply from Crystal Chemical Company, Inc., Houston, Texas.

B. Instrumentation

Infrared spectra were recorded on a Perkin-Elmer Model 700 infrared spectrometer, Perkin-Elmer Company, Norwalk, Connecticut.

^{1}H NMR spectra were recorded on a Varian Model EM-360 nuclear magnetic resonance spectrometer, Varian Associates, Inc., Walnut Creek, California.

^{13}C NMR spectra were recorded on a Varian Model XL-100 carbon-13 nuclear magnetic resonance spectrometer, Varian Associates, Inc., Walnut Creek, California. The fixed instrument parameters were:

pulse width: 10 microseconds
pulse delay: 5 seconds
acquisition time: 1.63840 seconds
sweep width: 5000 Hz

The instrument was equipped with a Nicolet Data System.

Mass spectra were obtained on a Finnigan Model 3300 GC/Mass Spectrometer equipped with a 6100 Data Process System, Finnigan Corporation, Sunnyville, California.

C. Syntheses and Attempted Syntheses of 1,5-bis(thiophenyl)-2-nitrobenzene Derivatives.

Attempted Synthesis of 1-thiophenyl-3-chlorobenzene. Sodium metal (0.92 g, 0.04 M) was added to 20 ml of methanol and the resulting solution of sodium methoxide was then heated to 90° to remove excess methanol. At this point, thiophenol (11 g, 0.1 M), m-dichlorobenzene (5.88 g, 0.04 M) and copper dust (0.197 g) were added according to the general procedure of Archer and Suter (8). The temperature of the reaction mixture was then raised to 215° for 20 min. The reaction mixture solidified, was cooled to 100°, and dilute sodium carbonate added. The resultant suspension was boiled, filtered, and the supernate extracted with ethyl ether. The ether layer was dried over anhydrous sodium sulfate and then concentrated. The resultant yellow oil was distilled to remove any excess thiophenol (bp 115°, 19 mm). The reaction product was characterized by NMR (Figure 1), ir (Figure 2), and Mass Spectra (M^+ = 218, Figure 3). mp = 53-55°. Analysis calculated for $C_{12}H_9ClS$: C 65.31, H 4.08, Cl 16.10, and S 14.51; found C 66.06, H 4.66, Cl 0.00, and S 29.22. The above analysis and spectral data supported the conclusion that diphenyl disulfide was formed, which was not the desired product.

Attempted Synthesis of 1,3-bis(thiophenyl)benzene. m-Dichlorobenzene (14.7 g, 0.1 M) and thiophenol (55 g, 0.5 M) were placed into a solution containing 250 ml of concentrated sulfuric acid (98%) and 250 ml of distilled water according to the general procedure of Ullman and von Glenck (2). The reaction was allowed to react at room temperature for 14-16 hrs and then heated at 60° for 6 hrs. The organic layer was separated from the acid layer, washed with 2 l of distilled water, 500 ml of sodium carbonate solution, and then tested to insure neutrality. The organic material was solubilized in benzene, dried over anhydrous sodium sulfate, concentrated, and placed in the refrigerator overnight. Crystallization occurred and the material was then recrystallized from n-hexane. The reaction product was characterized by NMR (Figure 4), ir (Figure 5), and Mass Spectra (M^+ = 218, Figure 6). mp = 53-55°. Analysis calculated for $C_{18}H_{14}S_2$: C 73.47, H 4.76, and S 21.77; found C 66.20, H 4.64, and S 29.21. The analysis and spectral data, as before, supported the conclusion that diphenyl disulfide was formed (yield 90.4%).

Attempted Synthesis of 1,3-bis(thiophenyl)benzene. To a 100 ml 3-neck reaction flask, containing 25 ml of concentrated sulfuric acid (98%) and 25 ml distilled water, was added diphenyl disulfide (5 g, 0.04 M) according to the general procedure of Smiles (48). To this reaction mixture was added benzene (3.12 g, 0.04 M) and then refluxed for 24 hrs. The organic layer was separated from the acid layer, washed with 2 l of distilled water, 500 ml of dilute sodium carbonate solution, and tested to insure neutrality. The organic layer was dried over anhydrous sodium sulfate and concentrated. Preliminary thin layer chromatography data showed the product had an equivalent R_f value when compared

to diphenyl disulfide, when using a silica gel/chloroform system. The reaction product was characterized by NMR (Figure 7), ir (Figure 8), and Mass Spectra (M^+ = 218, Figure 9). mp (wet) = 46-48°. The product was diphenyl disulfide.

Attempted Synthesis of 1,3-bis(thiophenyl)-4-nitrobenzene. To a 100 ml reaction flask was added sodium ethoxide (0.204 g, 0.003 M), p-nitrothiophenol (0.05 g, 0.003 M), and m-dichlorobenzene (0.238 g, 0.0016 M) without copper catalyst. The mixture was allowed to mix at room temperature for 2.5 hrs after which the solution turned a dark red color. The reaction mixture was then heated at 135° for 1 hr to insure completion. The reaction product was characterized by NMR (Figure 10), ir (Figure 11), and Mass Spectra (M^+ = 308, Figure 12). mp = 177-178°. A sodium fusion test proved positive for both chlorine and sulfur. Analysis calculated for $C_{12}H_8ClNO_2S$: C 54.24, H 3.01, S 12.05, Cl 13.37, and the remainder NO_2 17.33; found C 44.31, H 3.49, S 19.68, Cl 0.00, and the remainder for NO_2 32.52. The analysis and spectral data supported the conclusion that 4,4'-dinitrodiphenyl disulfide had formed.

Attempted Synthesis of 1,3-bis(thiophenyl)benzene. Sodium methoxide (20 g, 0.294 M) was placed in a reaction flask containing 40 ml of nitrobenzene. To this reaction mixture was added thiophenol (32.34 g, 0.294 M) and m-dichlorobenzene (21.6 g, 0.147 M). The resultant mixture was then heated to reflux. After 3 hrs a sample was taken of the reaction mixture and spotted on a tlc plate (silica gel) against nitrobenzene, m-dichlorobenzene, and thiophenol using a petroleum ether solvent. The product remained at the origin. The reaction product was then filtered, washed with successive 100 ml portions of cold n-hexane (6x) and finally anhydrous

ethyl ether (6x) until the washings were free of nitrobenzene. The reaction was characterized by ir (Figure 13) and Mass Spectra (M^+ = 503, Figure 14). The compound was not soluble in common NMR solvents including hot d_6 DMSO. mp = 300° without any apparent decomposition. Analysis calculated for $C_{18}H_{14}S_2$: C 73.47, H 4.76, and S 21.77; found by microanalysis S 0.00. This compound, to date, is still unknown.

Synthesis of Sodium Thiophenoxide (1). Sodium metal (2.3 g, 0.1 M) was added to 150 ml of dry methanol which had previously been purged with nitrogen to remove any oxygen in solution. To this sodium methoxide solution was added thiophenol (11.55 g, 0.105 M) while still being purged with nitrogen, according to the general procedure of Kornblum et.al. (45). The reaction mixture was then heated under vacuum to remove the excess methanol. The resultant slurry was washed with successive 100 ml portions of dry cyclohexane, which had previously been distilled over calcium hydride, and then dried for 24 hrs on a rotary evaporator at 1 mm. The resultant white crystalline material was examined by ir (Figure 15). mp = 280°.

Attempted Synthesis of 1,3-bis(thiophenyl)benzene. To a reaction flask containing 60 ml of hexamethylphosphoric-triamide (HMPA) was added 1-chloro-2,4-dinitrobenzene (1.215 g, 0.006 M) and sodium thiophenoxide (1.584 g, 0.012 M), according to the general procedure of Kornblum et.al. (24). The resultant reaction mixture was then allowed to react for 24 hrs at room temperature under nitrogen purge. The reaction mixture was then chromatographed on an acid-washed alumina column with the 100 ml fractions being collected as described in Table 2 (43).

TABLE 2

Fraction	Solvent
1	n-hexane
2	n-hexane
3	n-hexane
4	20% benzene/80% n-hexane
5	20% benzene/80% n-hexane
6	30% benzene/70% n-hexane
7	30% benzene/70% n-hexane
8	40% benzene/60% n-hexane
9	50% benzene/50% n-hexane
10	60% benzene/40% n-hexane
11	80% benzene/20% n-hexane
12	80% benzene/20% n-hexane
13	benzene
14	benzene

Fractions 1-3 contained only HMPA. Fractions 4-10 contained organic material of aromatic nature while the remainder of the fractions contained no other traces of desired compound. Fractions 4-10 were combined and characterized by NMR (Figure 16). The combined fractions were still contaminated by HMPA which proved to be a great hinderance during separation. In an attempt to re-run this particular reaction, the starting materials were combined in a reaction flask which had previously been flamed-dried and purged with nitrogen. Before the HMPA was added, a spontaneous reaction occurred and the product was characterized by NMR (Figure 17), ir (Figure 18), and Mass Spectra (M^+ = 276, Figure 19). The reaction product was 1-thiophenyl-2,4-dinitrobenzene.

Attempted Sulfurization of Phenol. The sulfurization of phenol was carried out according to the general procedure of Fujisawa et.al. (25). Into 15 ml of absolute ethanol was introduced elemental sulfur (1.9 g, 0.06 M), phenol (1.87 g 0.02 M) and sodium hydroxide (1.7 g, 0.0425 M). The reaction mixture was refluxed for 30 min, at which point the reaction mixture went from a heterogeneous yellow suspension to a homogeneous dark brown mixture. Zinc dust (5.0 g, 0.078 M), 100 ml of benzene, and 80 ml of 3 N hydrochloric acid were then added. Upon addition, copious amounts of a white gas (hydrogen sulfide) were evolved and this reaction mixture was allowed to stir at room temperature for 1 hr. The resultant product was then chromatographed on an acid alumina column and three major fractions were collected which were assumed to be the mono-, di-, and polysulfides. Each fraction was characterized by ir (Figures 20-22), and Mass Spectra (Figures 23-25). Due to limited solubility, fraction 1 was the only fraction further investigated by NMR (Figure 26). These compounds remain unidentified.

Attempted Synthesis of 1,3-bis(thiophenyl)benzene. To a reaction flask was added 1-chloro-2,4-dinitrobenzene (1.215 g, 0.006 M) and sodium thiophenoxide (1.584 g, 0.012 M) while purging the flask with nitrogen. The crystalline reaction mixture was then heated gently for 1 min at which point, a spontaneous exothermic reaction occurred. Copious amounts of gas were evolved and the reaction proceeded to completion within 30 sec. The dark brown solid reaction product was extracted with n-hexane. The reaction material, which was soluble in n-hexane, was concentrated and characterized by NMR (Figure 27), ir (Figure 28), and Mass Spectra (M^+ = 276, Figure 29). The reaction material which was insoluble in n-hexane was then extracted with chloroform, treated with decolorizing charcoal, concentrated, and characterized by NMR (Figure 30), ir (Figure 31), and Mass Spectra (M^+ = 276, Figure 32). mp = 73-76°. The remaining residue was inorganic as determined by micro-analysis. The reaction product was 1-thiophenyl-2,4-dinitro-benzene.

Synthesis of 1,4-bis(thiophenyl)-2-nitrobenzene (2). In an attempt to remedy the problems of solvent contamination experienced with the use of HMPA, the following procedure was investigated. To a reaction flask was added 60 ml of dimethyl-formamide (DMF) while being purged with nitrogen. To the solvent was added 1-chloro-2,4-dinitrobenzene (1.215 g, 0.006 M) and sodium thiophenoxide (1.584 g, 0.012 M). The reaction was allowed to stir at room temperature for 36 hrs. The reaction mixture was partitioned between benzene and water. The organic layer was then dried over anhydrous sodium sulfate. This procedure was wholly unsatisfactory because in partitioning the DMF reaction mixture between benzene and water, the separation was by no means complete. Therefore, a sample was

taken and a GC/Mass Spectrogram obtained. A major portion of the reaction material was thought to be the desired product (M^+ = 339, Figure 33), 1,4-bis(thiophenyl)-2-nitrobenzene. This material was then chromatographed on an acid-alumina column. Separation was poor for the fraction containing organic material which was aromatic in nature was still contaminated with DMF as shown by the NMR Spectrum (Figure 34).

Synthesis of 1-thiophenyl-2,4-dinitrobenzene (3). To a reaction flask being purged with nitrogen was added 60 ml DMF, 1-fluoro-2,4-dinitrobenzene (1.12 g, 0.006 M) and sodium thiophenoxide (1.584 g, 0.012 M). The resultant mixture was allowed to react for 2.5 hrs at 0° and then chromatographed on an acid-alumina column eluted with chloroform. A total of thirteen 100 ml fractions were collected and each fraction then spotted on a thin layer chromatography (tlc) plate. Fractions 1-10 when spotted showed a mixture of three compounds. These fractions were combined and concentrated to a yellow oil. The resultant yellow oil was then chromatographed on a four foot column which had been packed with silica gel 60 (70-230 mesh ASTM). The column was eluted with chloroform. Twelve 100 ml fractions were collected and each fraction spotted on a tlc plate. Fractions 1, 6, and 7 showed no compound. Fractions 2-5 each showed only one spot having the same R_f values. These fractions were then combined, concentrated, and recrystallized from cold n-hexane. The resultant yellow crystals were characterized by NMR (Figure 35), ir (Figure 36), and Mass Spectra (M^+ = 276, Figure 37). mp = 111-114°. Yield 87%.

Synthesis of 1-nitro-2,4-dichlorobenzene (4). To a reaction flask which contained 66 ml of 70% nitric acid and 66 ml of concentrated sulfuric acid (98%) at ice bath temperature was added m-dichlorobenzene (50 g, 0.34 M), according to

the general procedure of Kuhn (49). The reaction was allowed to stir 2-3 hrs while slowly equilibrated to room temperature. After 3 hrs the reaction mixture was spotted on a tlc plate and developed with a petroleum ether/ethyl ether (90:10) solvent system. Two isomers were noted, with the complete consumption of starting material being apparent. However, only one isomer, 1-nitro-2,4-dichlorobenzene was isolated. The organic layer was separated from the acid layer, washed with 2 1 of distilled water, and neutralized with aqueous sodium bicarbonate. The organic layer was then extracted with benzene and dried over anhydrous sodium sulfate. The resultant product was concentrated and crystallized to be used in a later synthesis. The product was characterized by NMR (Figure 38), ^{13}C NMR (Figure 39), and ir (Figure 40).

Synthesis and Purification of 1,5-bis(thiophenyl)-2-nitrobenzene (5). The synthetic procedure followed was as previously mentioned (2) except in the purification of the reaction product. The reaction mixture was chromatographed on a 4 x 117 cm column packed with silica gel (70-230 mesh) and eluted with chloroform. Fourteen 100 ml fractions were collected and spotted on tlc plates. Fractions 1-4 contained no compound while fractions 5-7 contained reaction material which had the same R_f values. Fractions 8-14 contained only DMF. Fractions 5-7 were combined, concentrated, and recrystallized from n-hexane. The bright yellow crystals were characterized by NMR (Figure 41), ^{13}C NMR (Figure 42), ir (Figure 43), and Mass Spectra (M^+ = 339, Figure 44). mp = 106-110°. Yield 72%. Analysis calculated for $C_{18}H_{13}NO_2S_2$: C 63.72, H 3.83, N 4.13, and S 18.88; found C 63.46, H 3.91, N 4.01, and S 19.00.

Synthesis of 1-nitro-2,4-difluorobenzene (6). The synthetic procedure followed was the same as used in the synthetic

procedure followed was the same as used in the synthesis of 1-nitro-2,4-dichlorobenzene (4); m-difluorobenzene (50 g, 0.438 M). The reaction product was characterized by NMR (Figure 45), ^{13}C NMR (Figure 46), and ir spectra (Figure 47).

Synthesis of 1,5-bis(thiophenyl)-2-nitrobenzene (7). The synthetic procedure was as previously mentioned for the synthesis and purification of (5); 1-nitro-2,4-difluorobenzene (0.95 g, 0.006 M). The reaction product was characterized by NMR (Figure 48), ir (Figure 49), and Mass Spectra (M^+ = 339, Figure 50). mp = 111-112.5°. Yield 41%.

Synthesis of 1,2-bis(thiophenyl)-4-nitrobenzene (8). The procedure was as previously mentioned (5); 1-nitro-3,4-dichlorobenzene (10 g, 0.052 M); sodium thiophenoxide (13.75 g, 0.104 M). mp = 97-101°. Yield 31%. The reaction product was characterized by NMR (Figure 51), ^{13}C NMR (Figure 52), ir (Figure 53), and Mass Spectra (M^+ = 339, Figure 54).

Attempted Synthesis of 1,3-bis(thiophenyl)-5-nitrobenzene. To a reaction flask, which was being purged with nitrogen, was added 60 ml of DMF and 1,3,5-trinitrobenzene (0.050 g, 2 x 10^{-4} M). This reaction mixture was then cooled to -70° with a dry ice acetone bath. Sodium thiophenoxide (0.052 g, 4 x 10^{-4} M) was then added and the previously red solution turned a deep purple as the highly exothermic reaction proceeded. The temperature increased from -70° to +10° within 30 sec. The reaction was allowed to stir for 2.5 hrs. The reaction product was characterized by ir (Figure 55) and Mass Spectra (M^+ = 213, Figure 56). The only reaction product isolated was 1,3,5-trinitrobenzene.

Synthesis of 2-nitro-1,4-dichlorobenzene (9). The synthetic procedure was as previously mentioned (4); 1,4-dichloro-

benzene (50 g, 0.34 M). The reaction product was characterized by NMR (Figure 57), ^{13}C NMR (Figure 58), and ir (Figure 59).

Synthesis of 1,4-bis(thiophenyl)-2-nitrobenzene (10). The synthetic procedure used was as previously mentioned (5); 2-nitro-1,4-dichlorobenzene (1.152 g, 0.006 M), sodium thiophenoxide (1.584 g, 0.012 M). The reaction product was characterized by NMR (Figure 60), ^{13}C NMR (Figure 61), ir (Figure 62), and Mass Spectra (M^+ = 339, Figure 63), mp = 111-112°. Yield 27%.

TABLE 1: Isomeric Derivatives of bis(thiophenyl)nitrobenzenes

HALONITROBENZENE	MOLES SODIUM THIOPHENOXIDE	PRODUCT	YIELD (%)	M.P. (°C)
1-fluoro-2,4-dinitrobenzene	1	1-thiophenyl-2,4-dinitrobenzene	87	111-114
1-nitro-2,4-difluorobenzene	2	1,5-bis(thiophenyl)-2-nitrobenzene	41	111-112.5
1-chloro-2,4-dinitrobenzene	1	1-thiophenyl-2,4-dinitrobenzene	42	111-114
1-nitro-3,4-dichlorobenzene	2	1,2-bis(thiophenyl)-4-nitrobenzene	31	97-101
2-nitro-1,4-dichlorobenzene	2	1,4-bis(thiophenyl)-2-nitrobenzene	27	111-112
1-chloro-2,4-dinitrobenzene	2	Mixture of 1,4-bis(thiophenyl)-2-nitrobenzene (75%) and 1,2-bis(thiophenyl)-4-nitrobenzene (25%) isomers	22	97-112
1-nitro-2,4-dichlorobenzene	2	1,5-bis(thiophenyl)-2-nitrobenzene	72	106-110

Figure 1. ^{1}H NMR Spectrum of Diphenyl disulfide

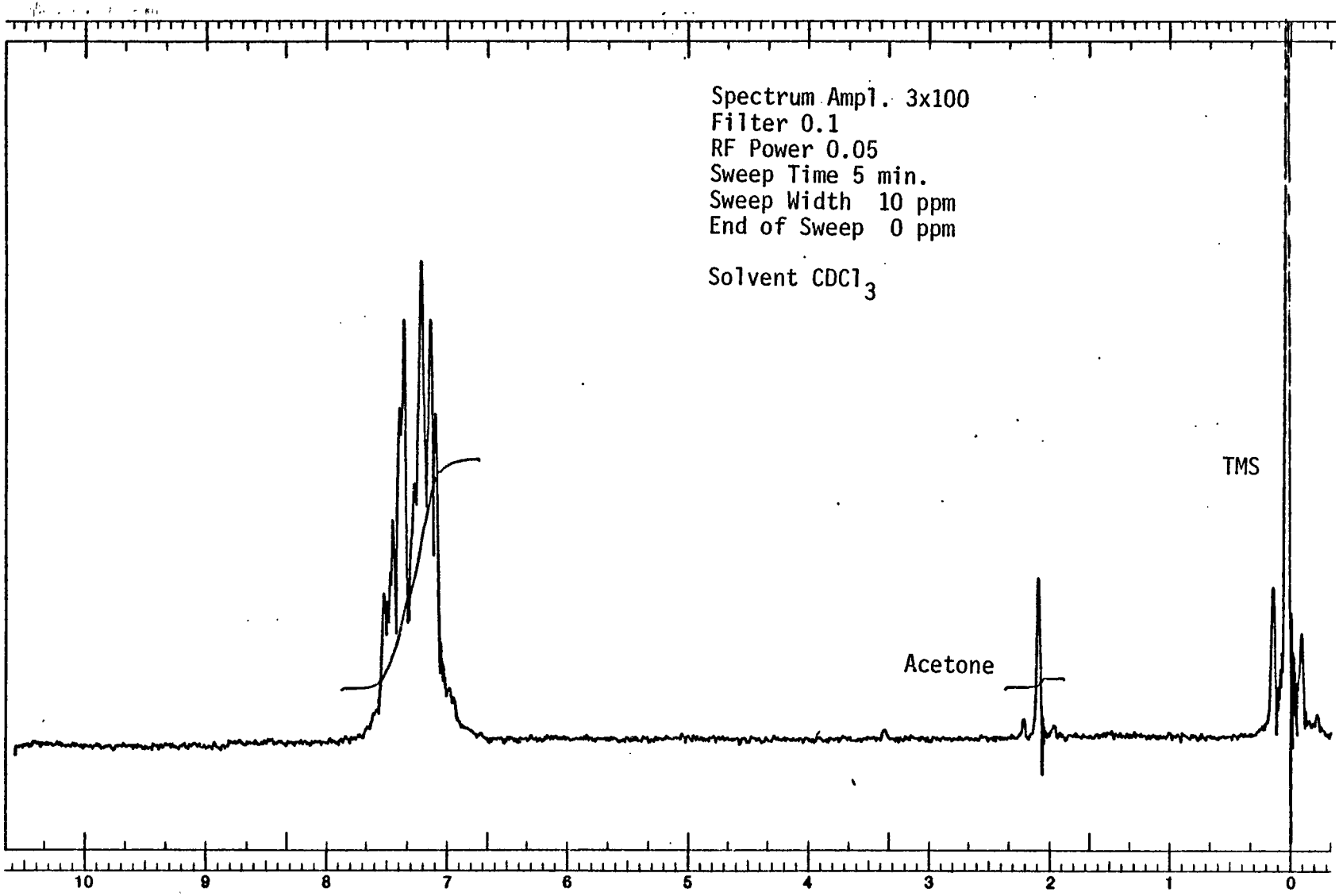


Figure 2. Infrared Spectrum of Diphenyl disulfide

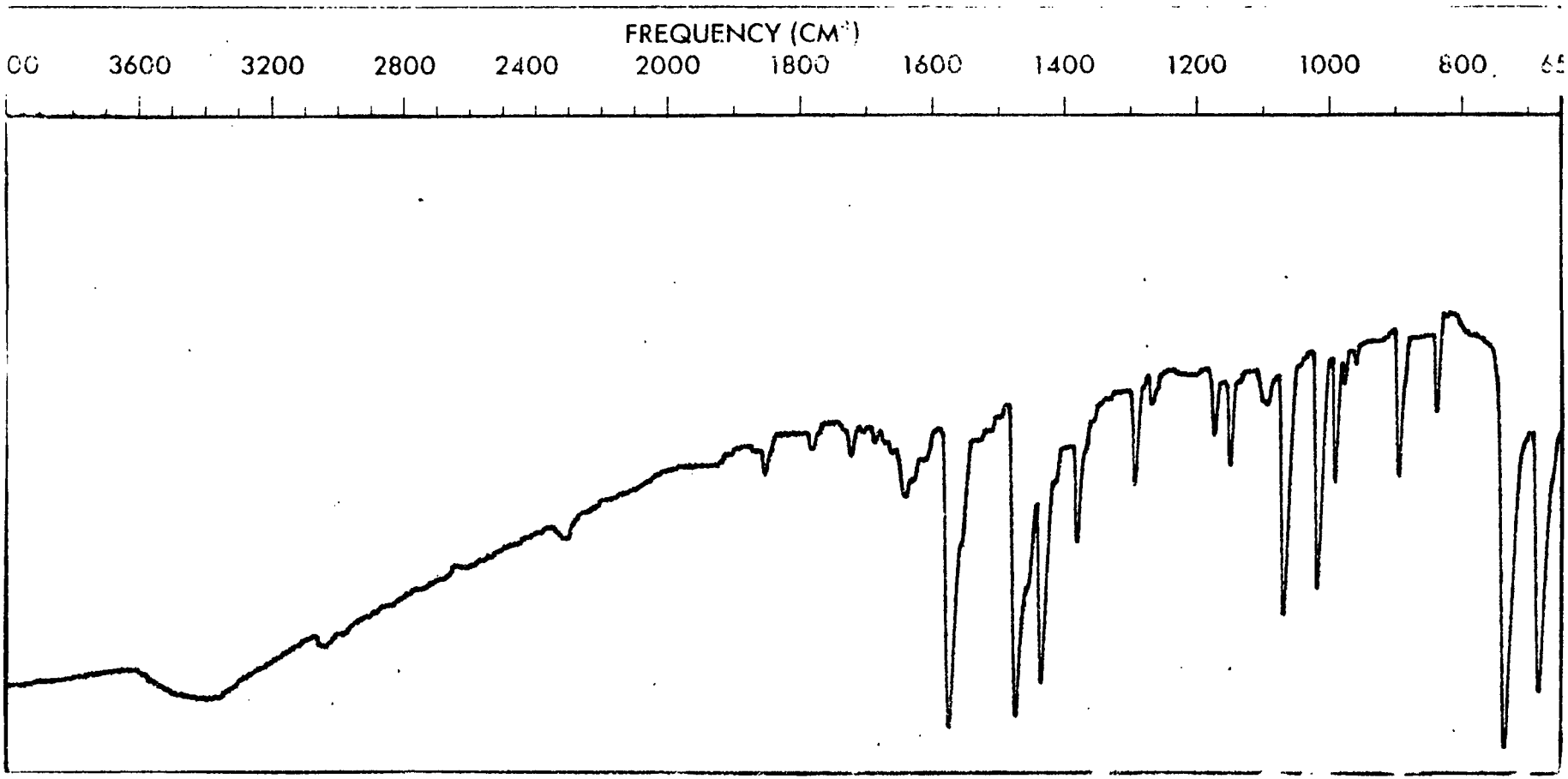


Figure 3. Mass Spectrum of Diphenyl disulfide

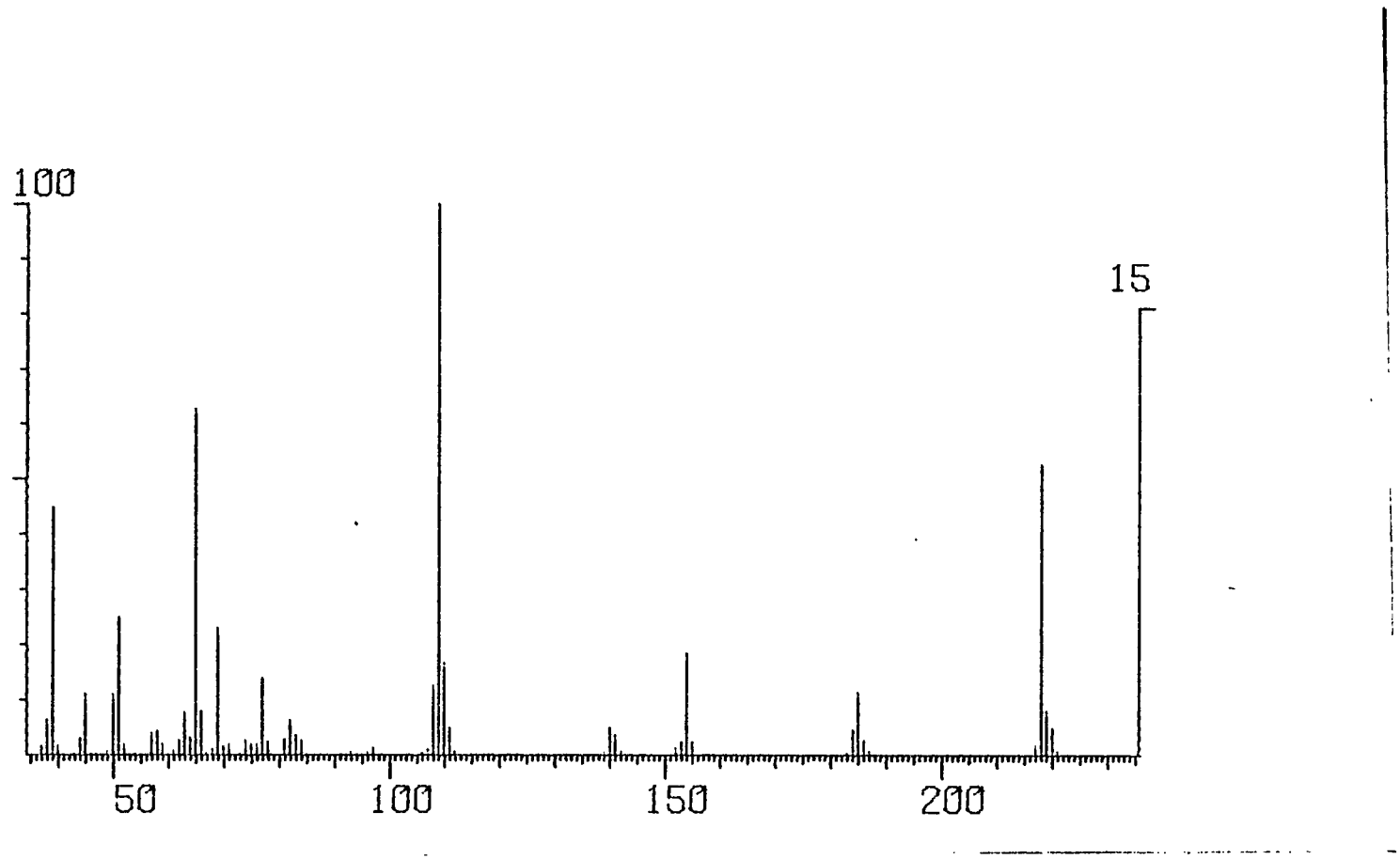


Figure 4. ^{1}H NMR Spectrum of Diphenyl disulfide

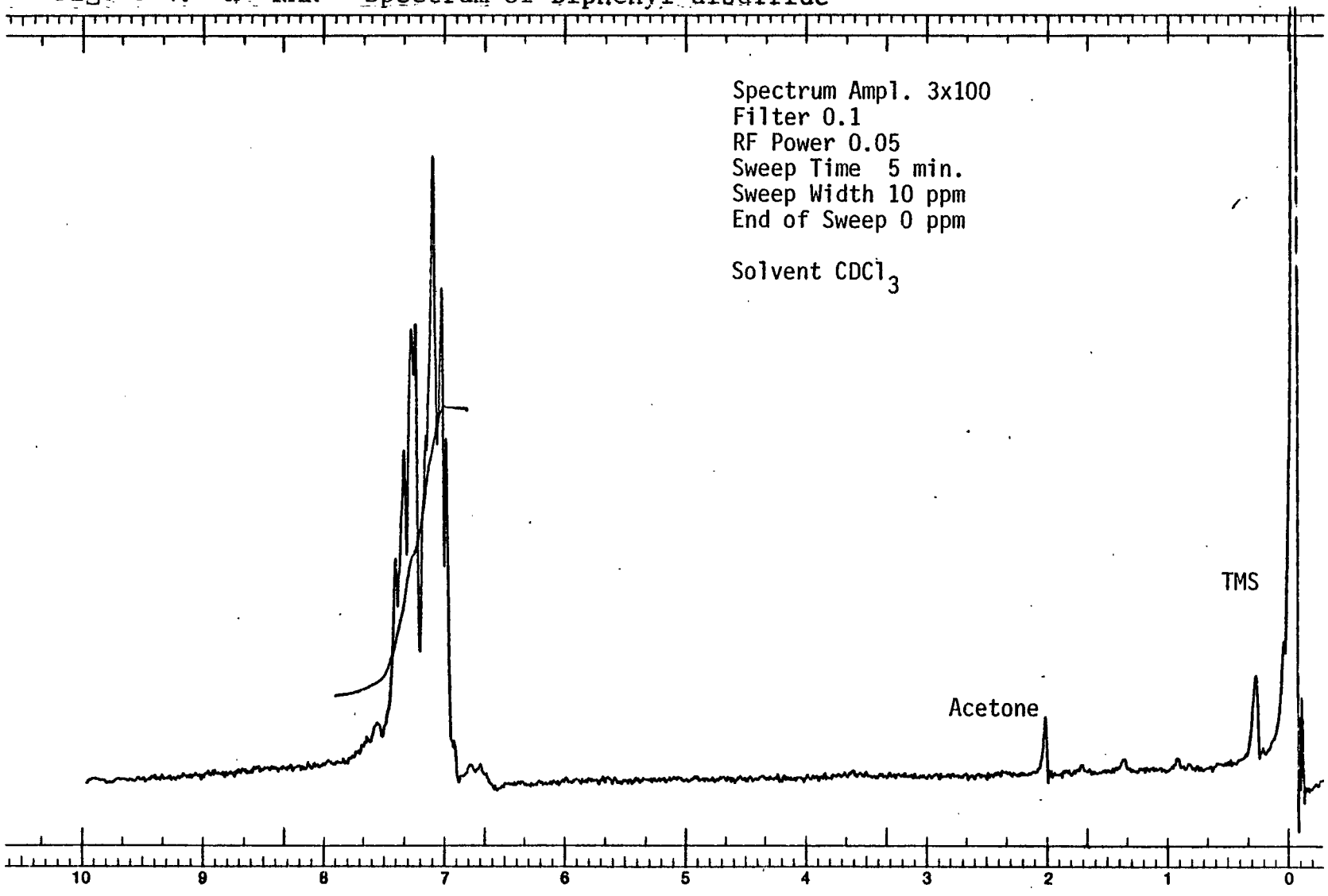


Figure 5. Infrared Spectrum of Diphenyl disulfide

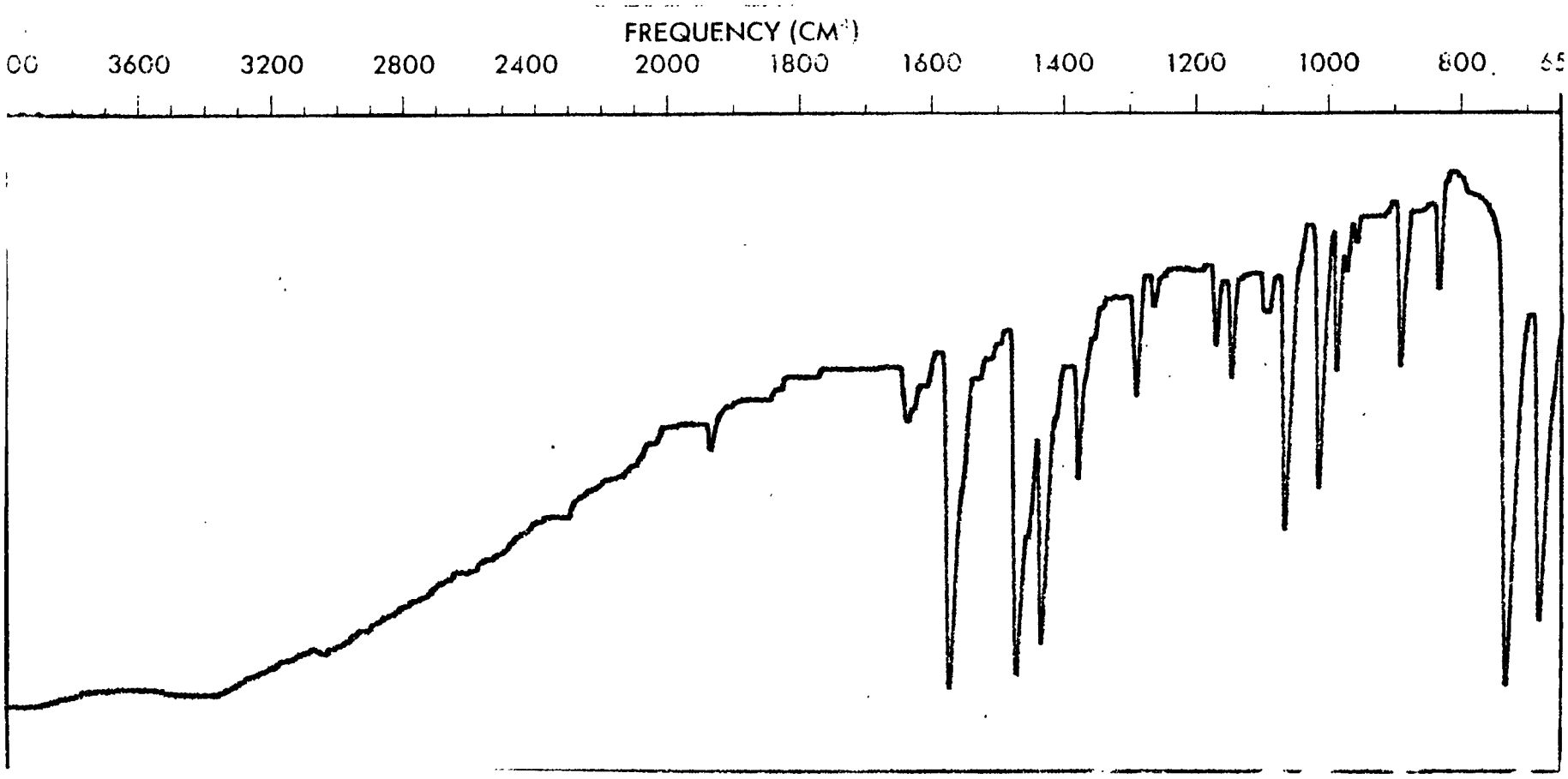


Figure 6. Mass Spectrum of Diphenyl disulfide

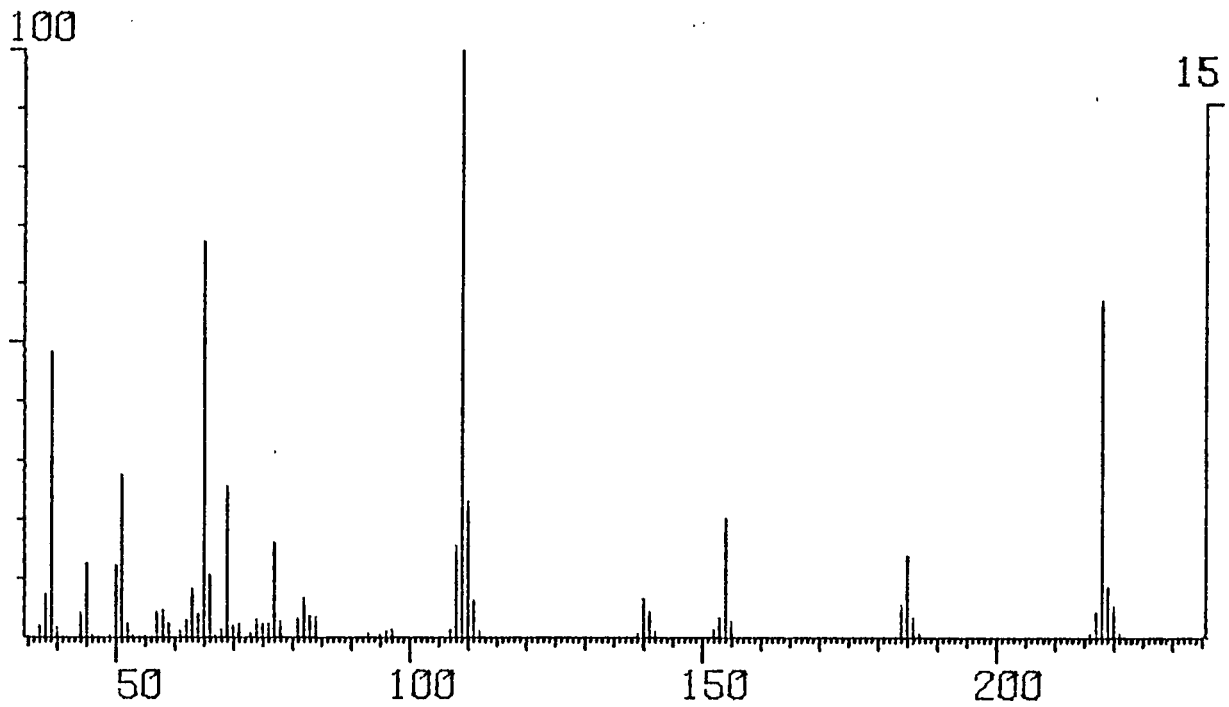


Figure 7. ^{1}H NMR Spectrum of Diphenyl disulfide

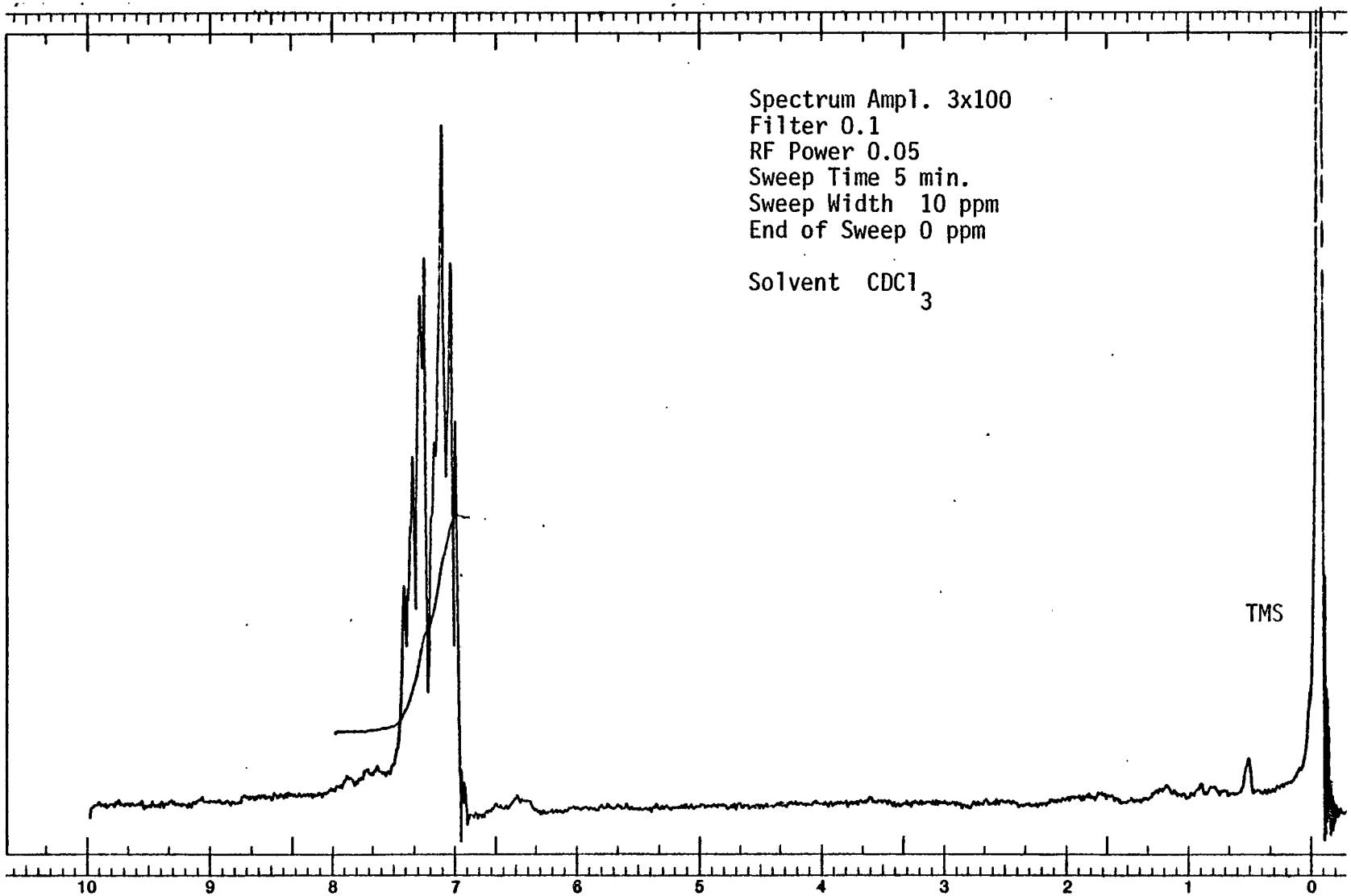


Figure 8. Infrared Spectrum of Diphenyl disulfide

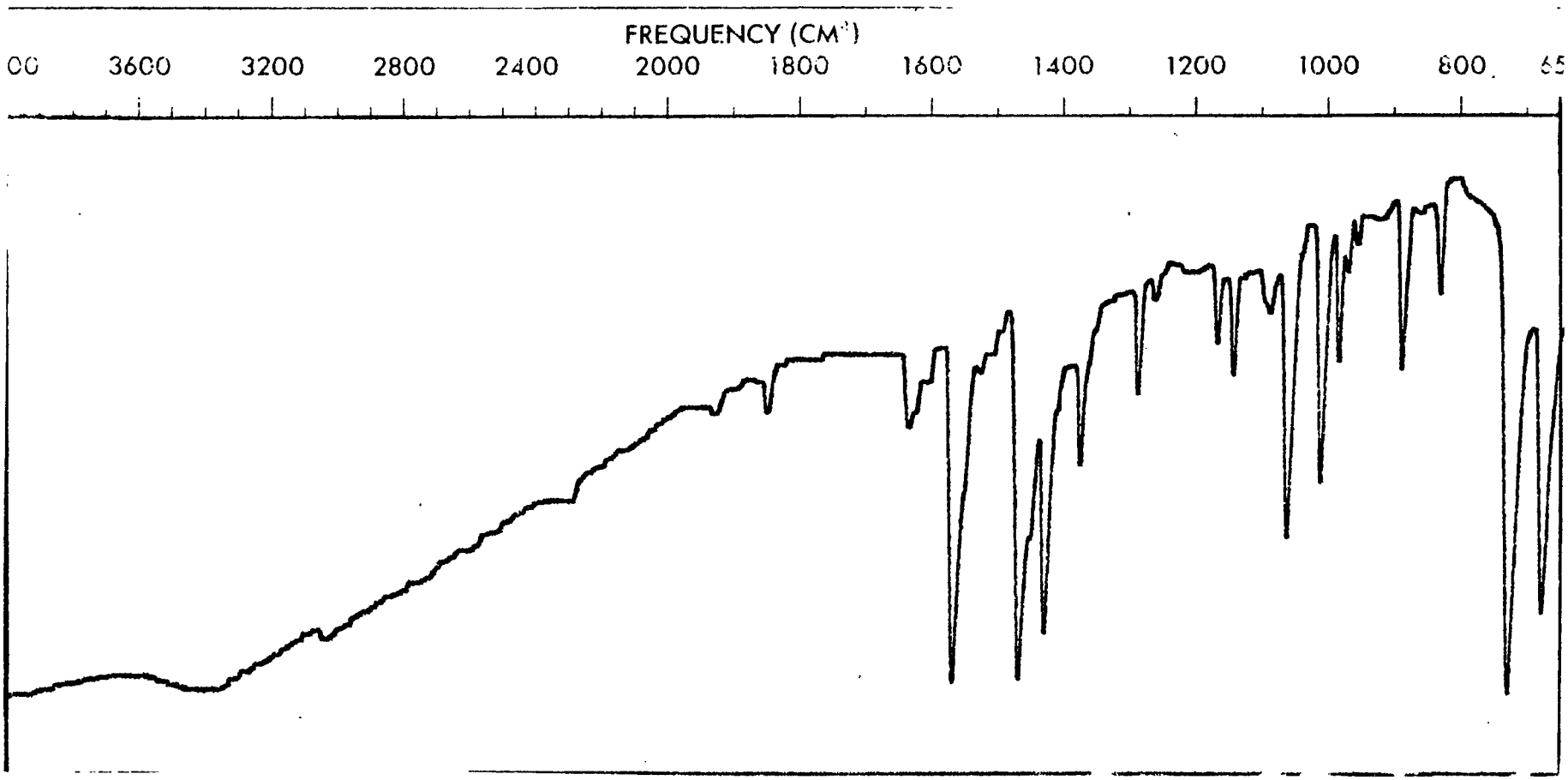


Figure 9. Mass Spectrum of Diphenyl disulfide

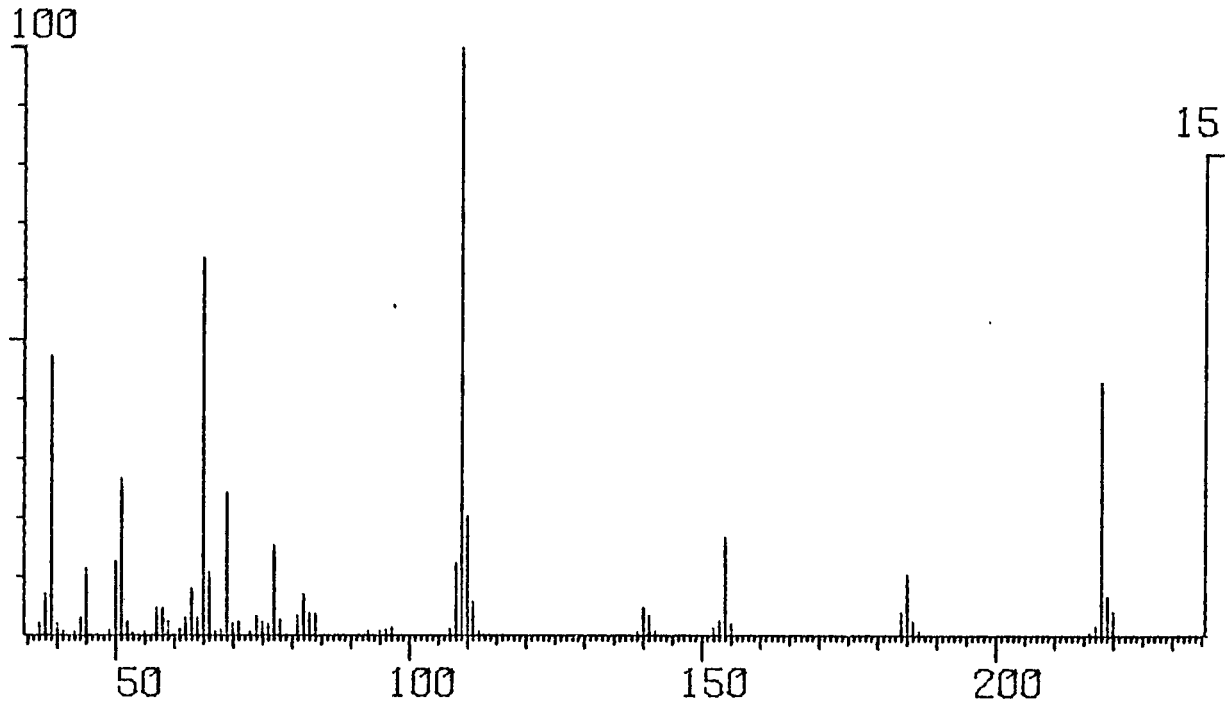


Figure 10. ^{1}H NMR Spectrum of 4,4'-dinitrodiphenyl disulfide

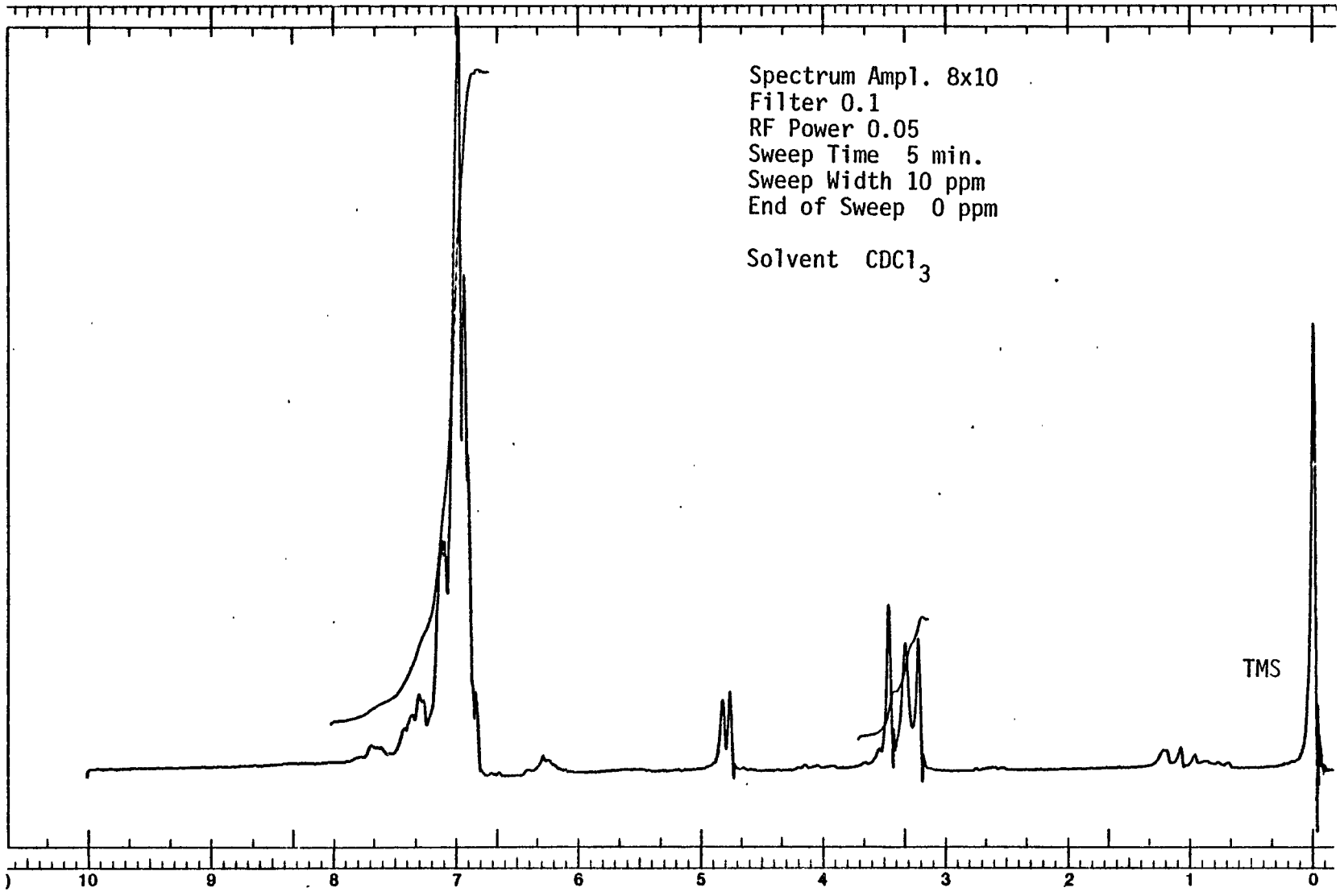


Figure 11. Infrared Spectrum of 4,4'-dinitrodiphenyl disulfide

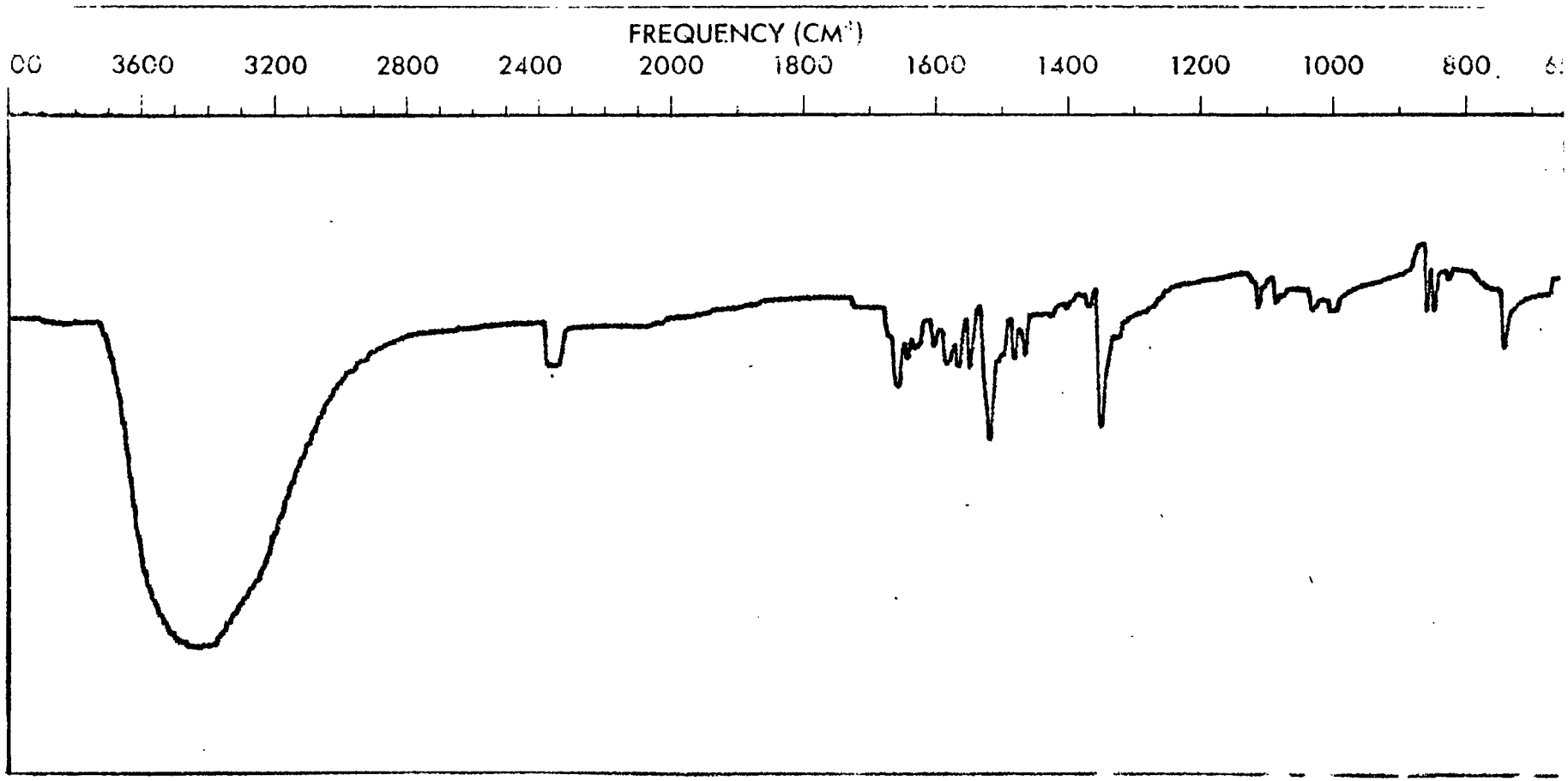


Figure 12. Mass Spectrum of 4,4'-dinitrodiphenyl disulfide

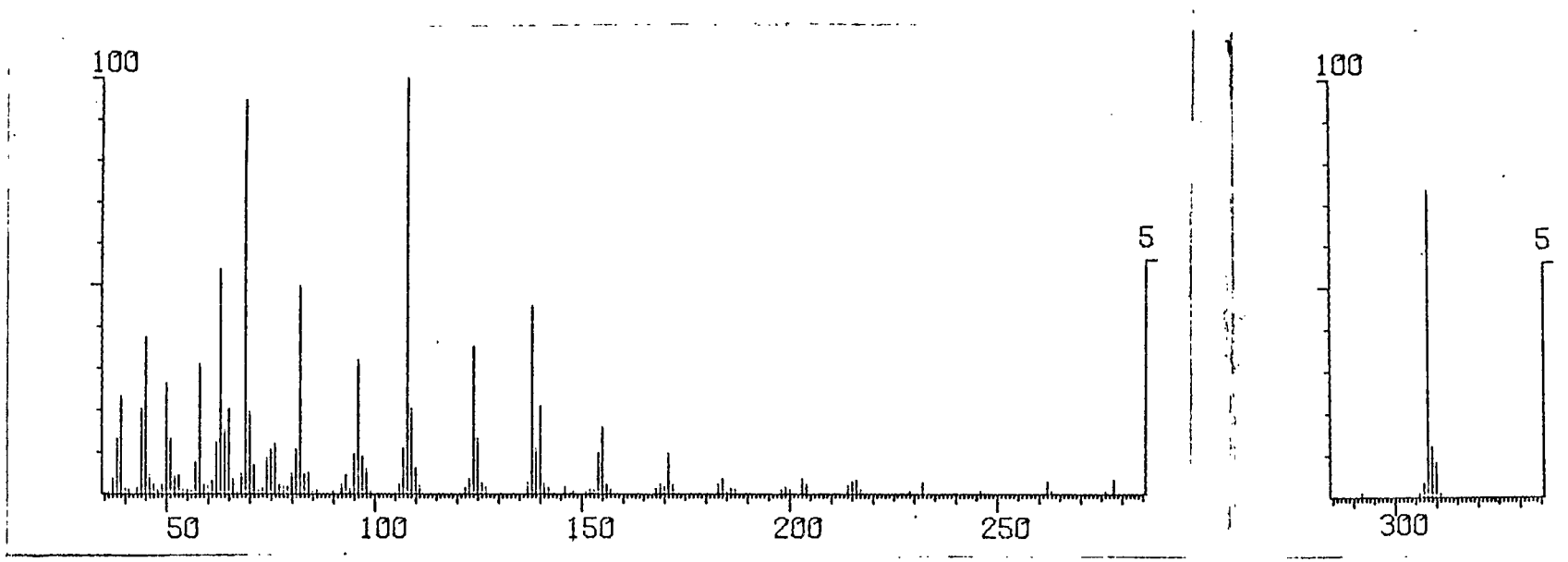


Figure 13. Infrared Spectrum of Unidentified Compound

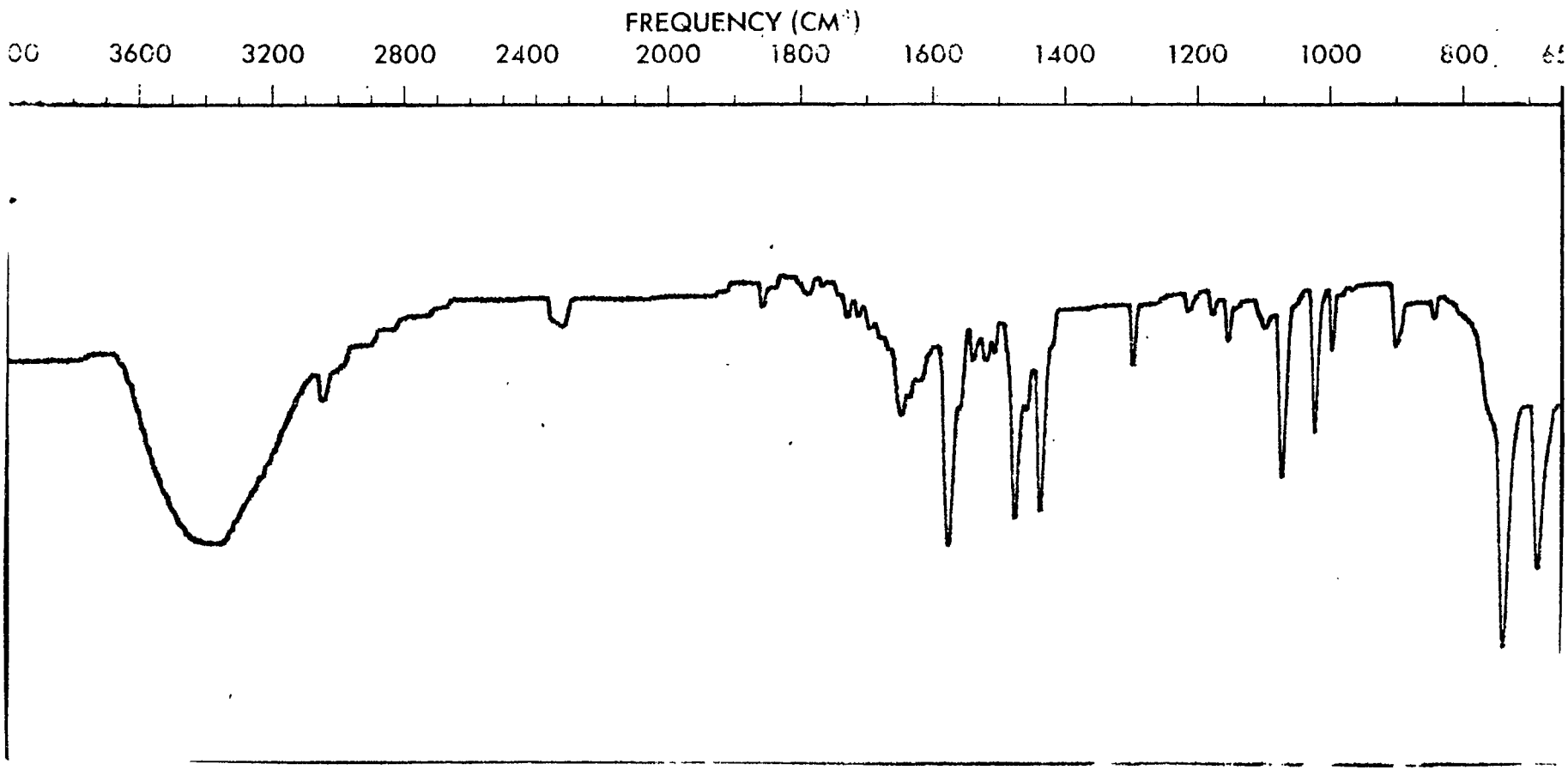
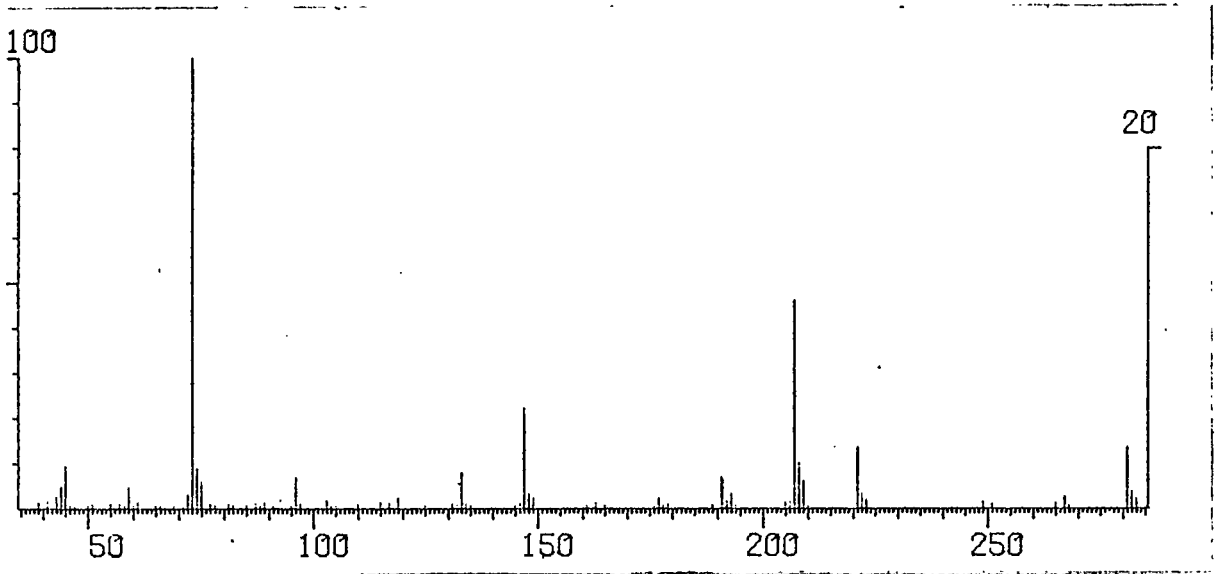


Figure 14. Mass Spectrum of Unidentified Compound (M^+=503)


100
20
50
100
150
200
250

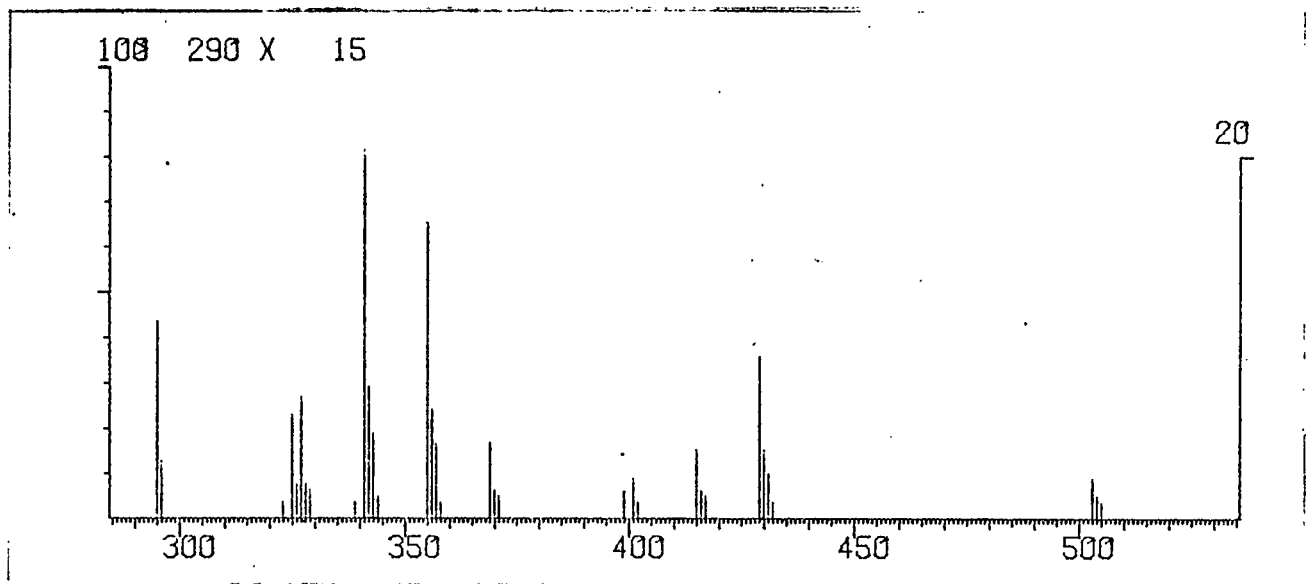

100
290 X
15
20
300
350
400
450
500

Figure 15. Infrared Spectrum of Sodium Thiophenoxide

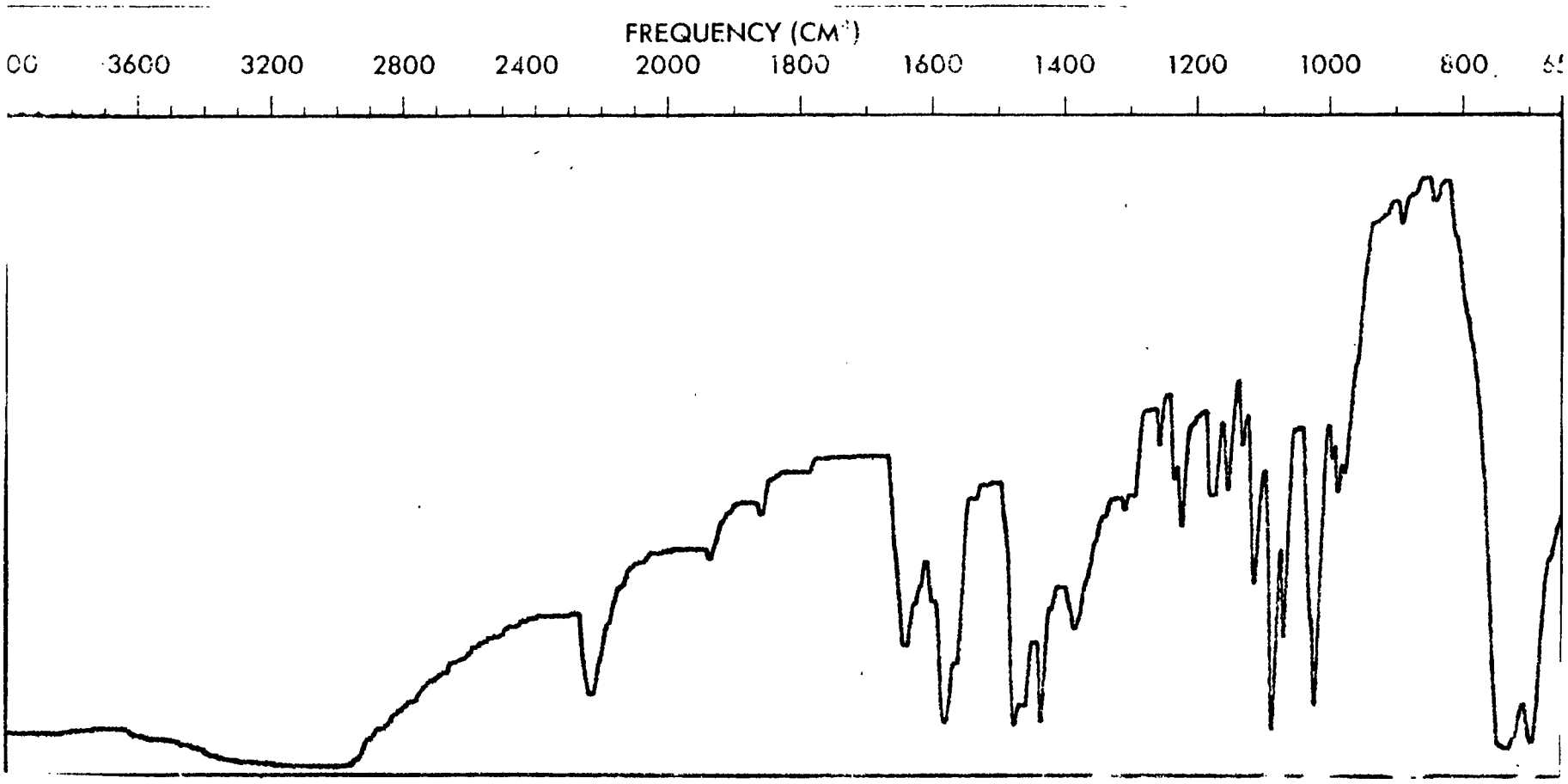


Figure 16. ^{1}H NMR Spectrum of thiophenyl-2,4-dinitrobenzene contaminated with HMPA

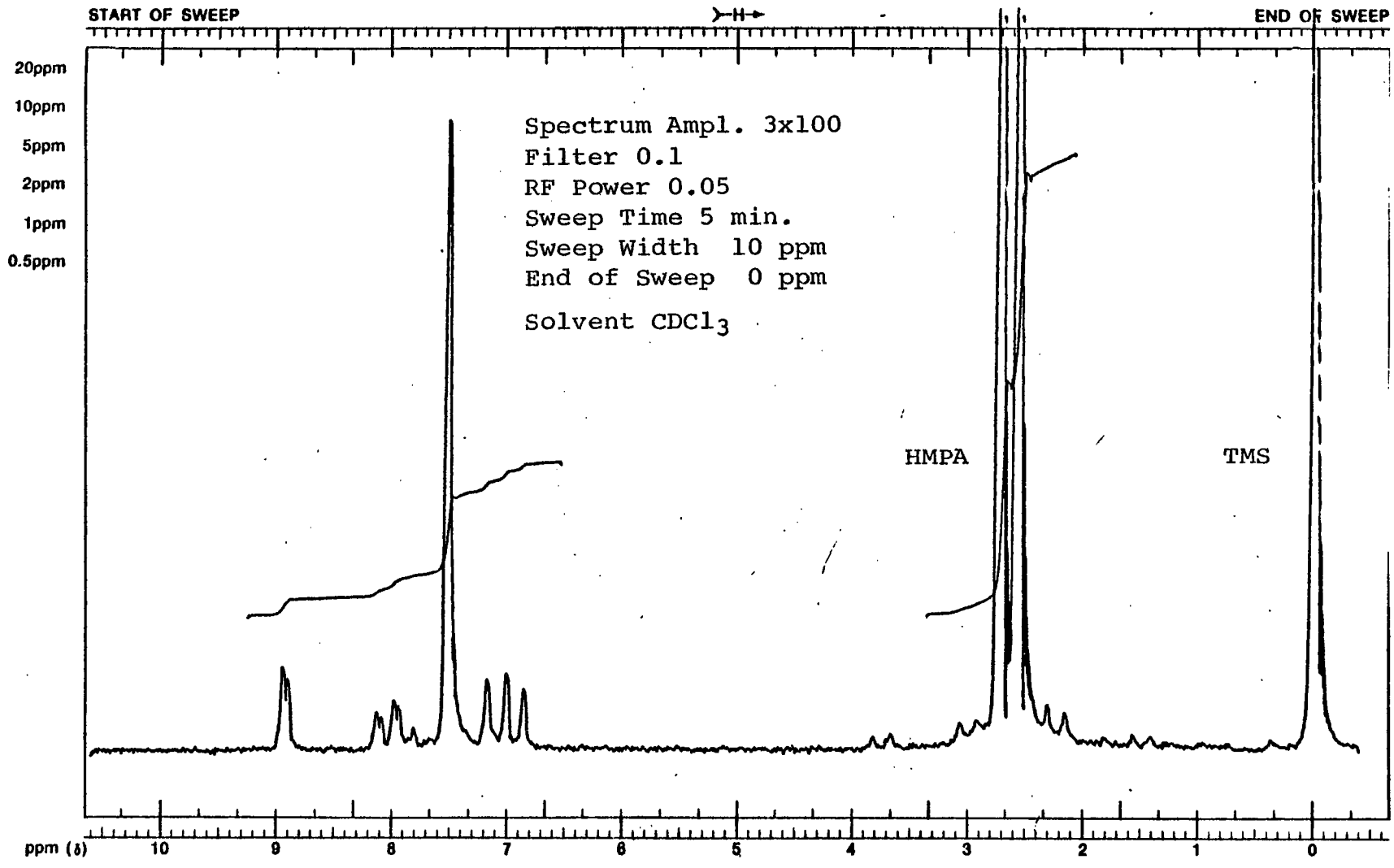


Figure 17. ^{1}H NMR Spectrum of thiophenyl-2,4-dinitrobenzene

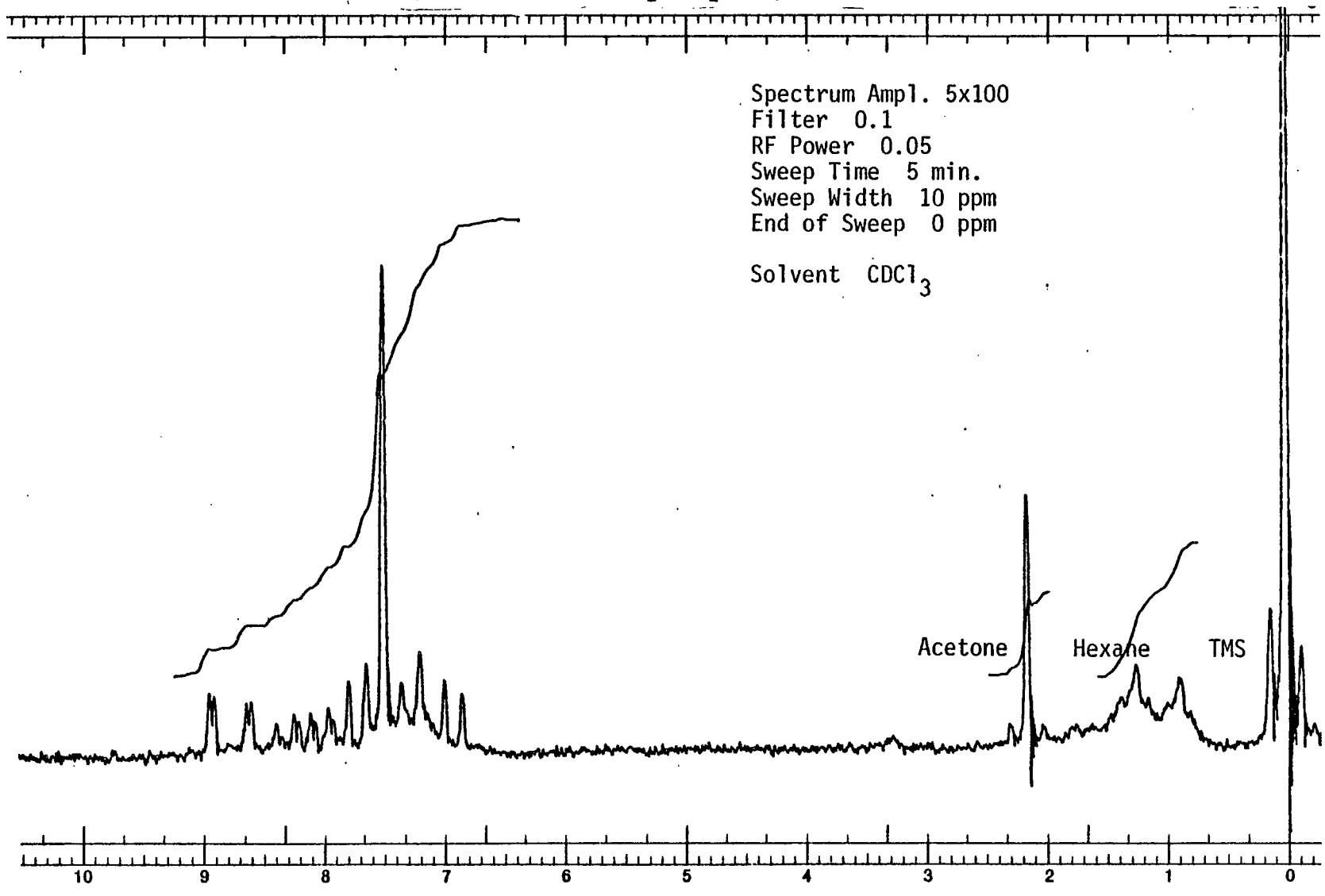


Figure 18. Infrared Spectrum of thiophenyl-2,4-dinitrobenzene

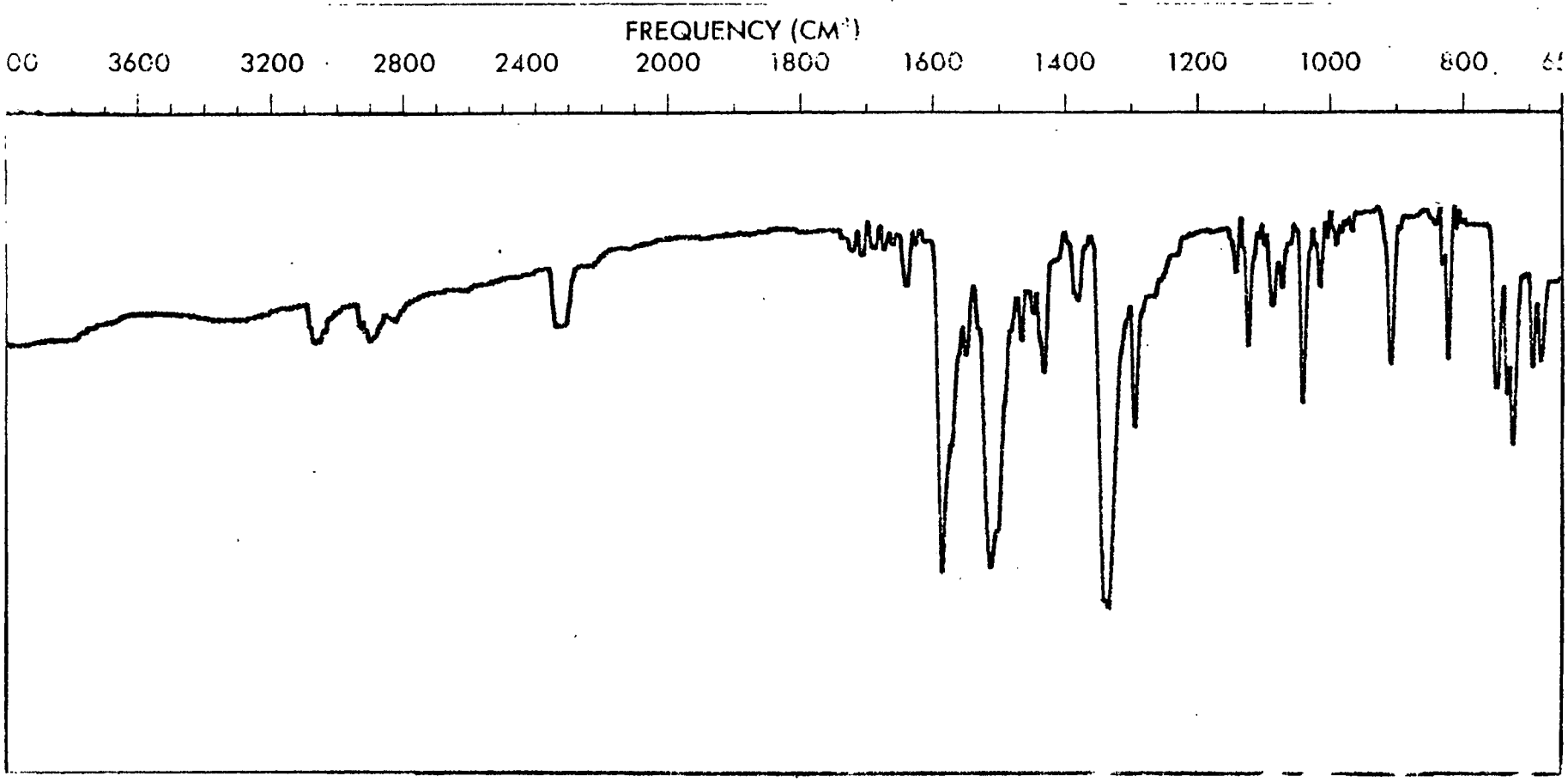


Figure 19. Mass Spectrum of thiophenyl-2,4-dinitrobenzene

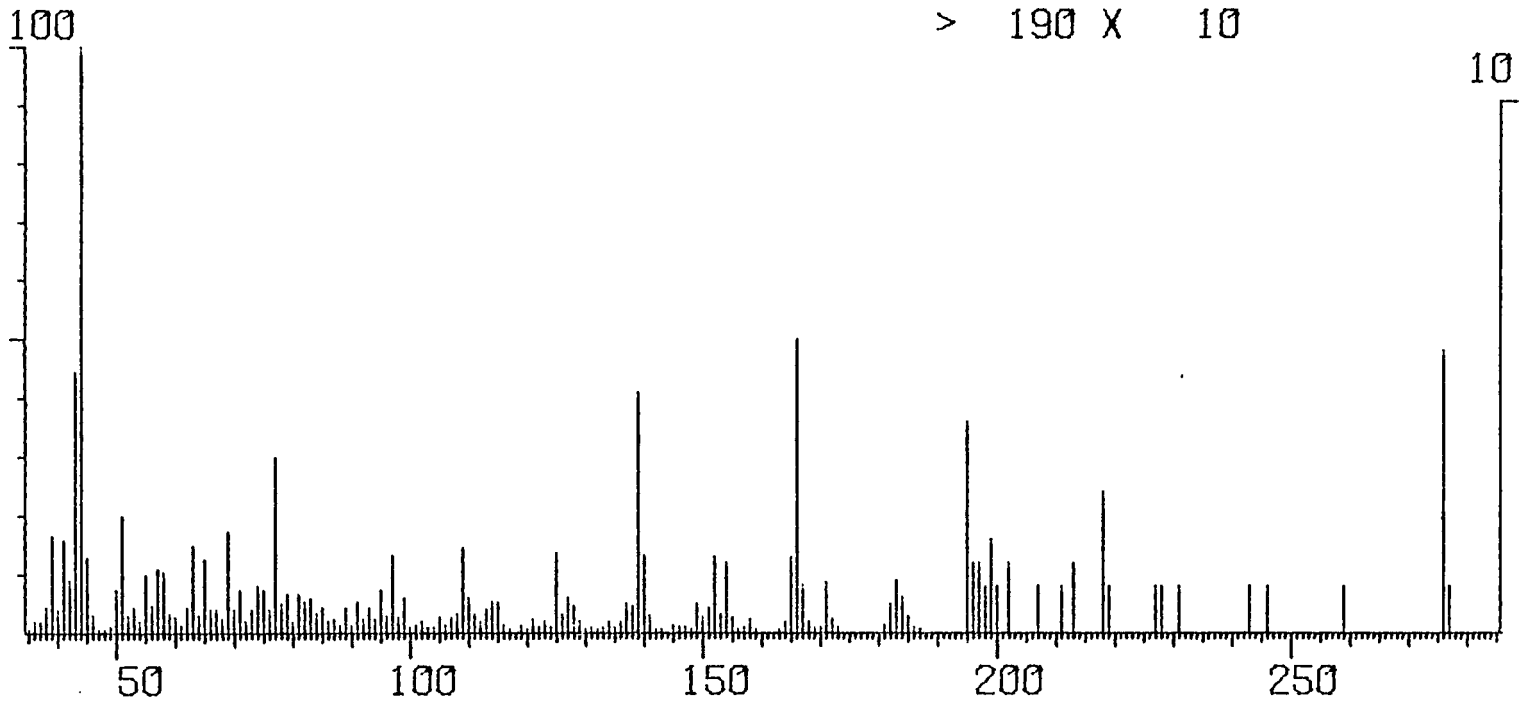


Figure 20. Infrared Spectrum of Unidentified Compound

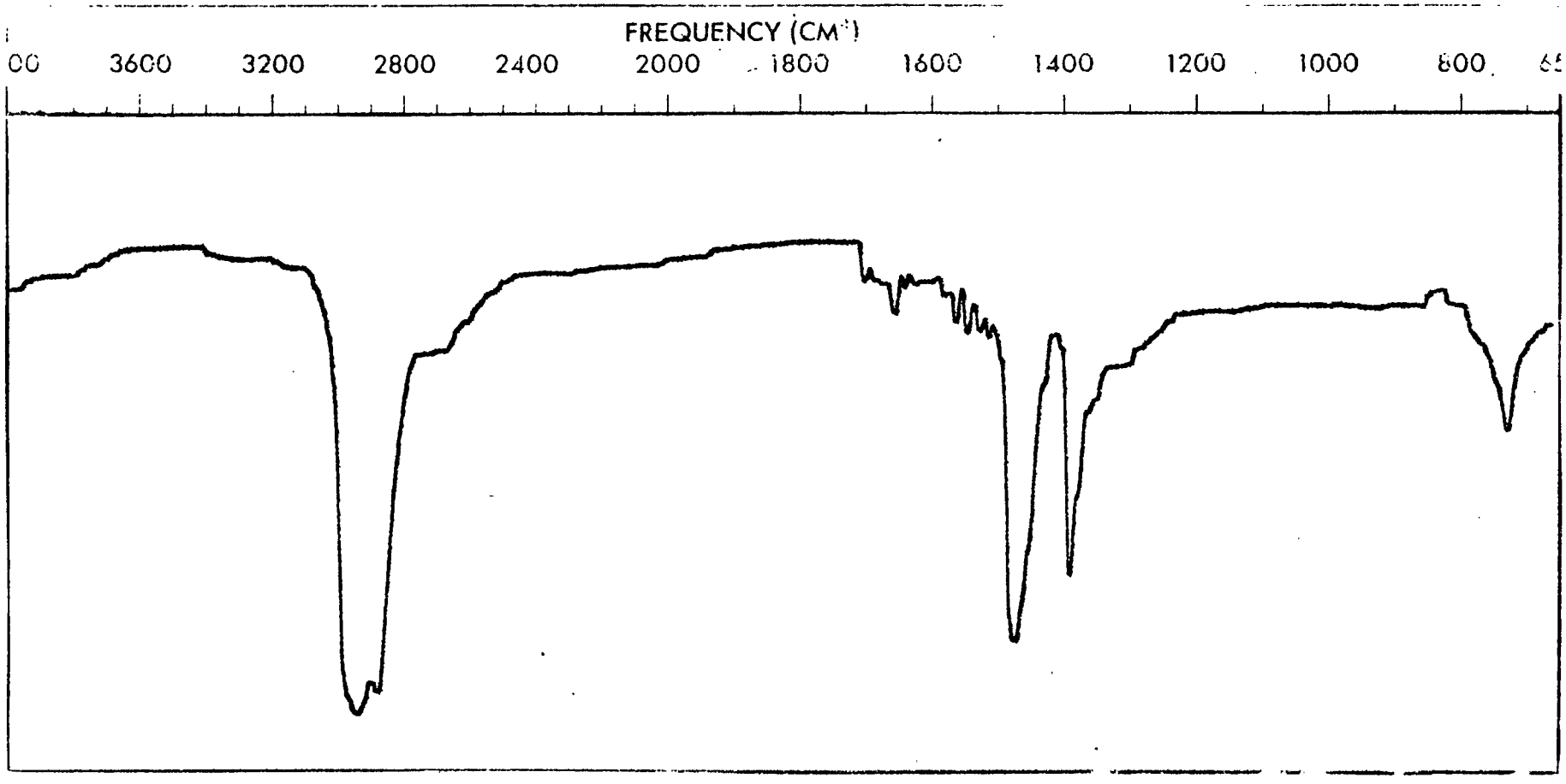


Figure 21. Infrared Spectrum of Unidentified Compound

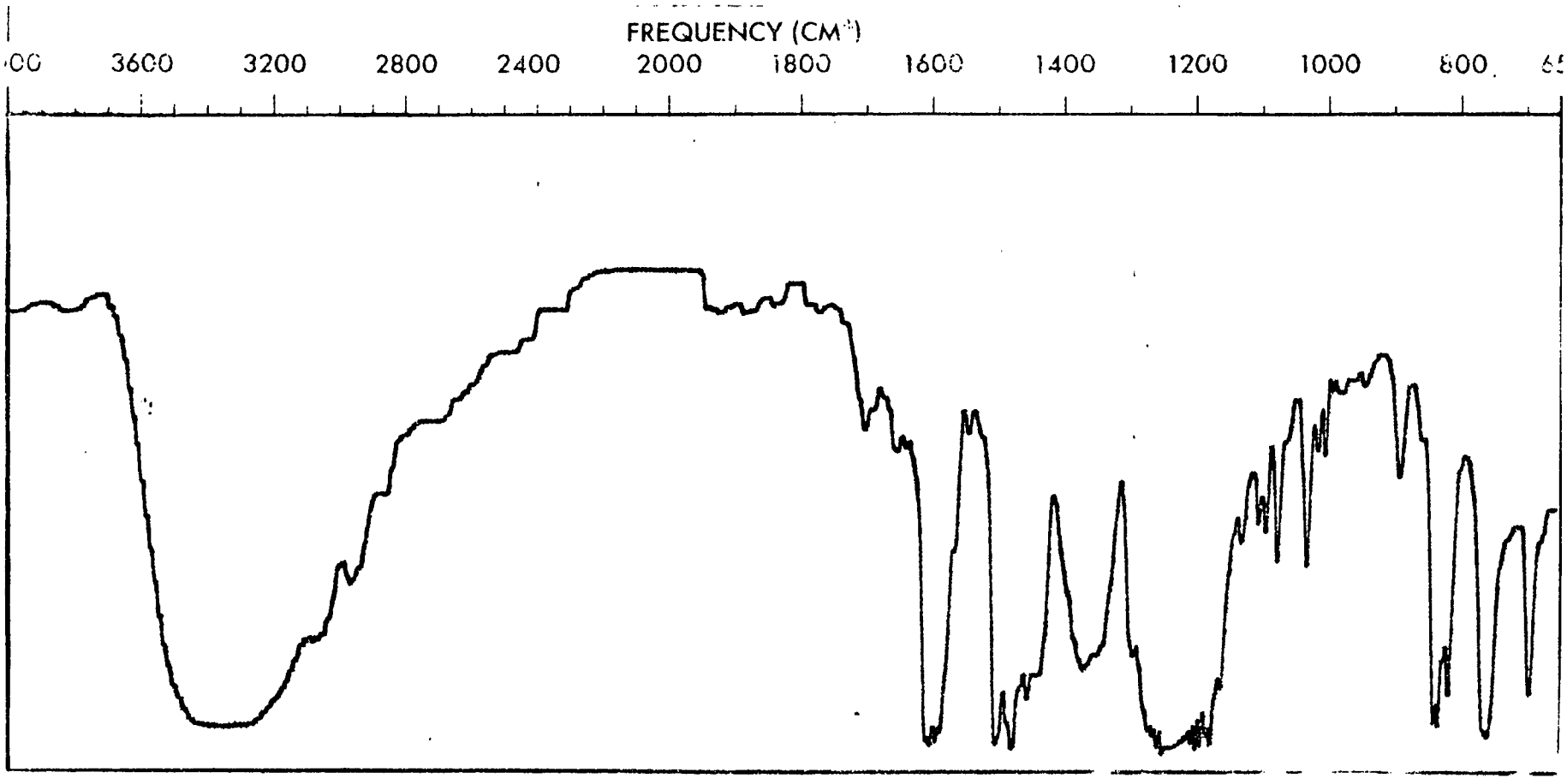


Figure 22. Infrared Spectrum of Unidentified Compound

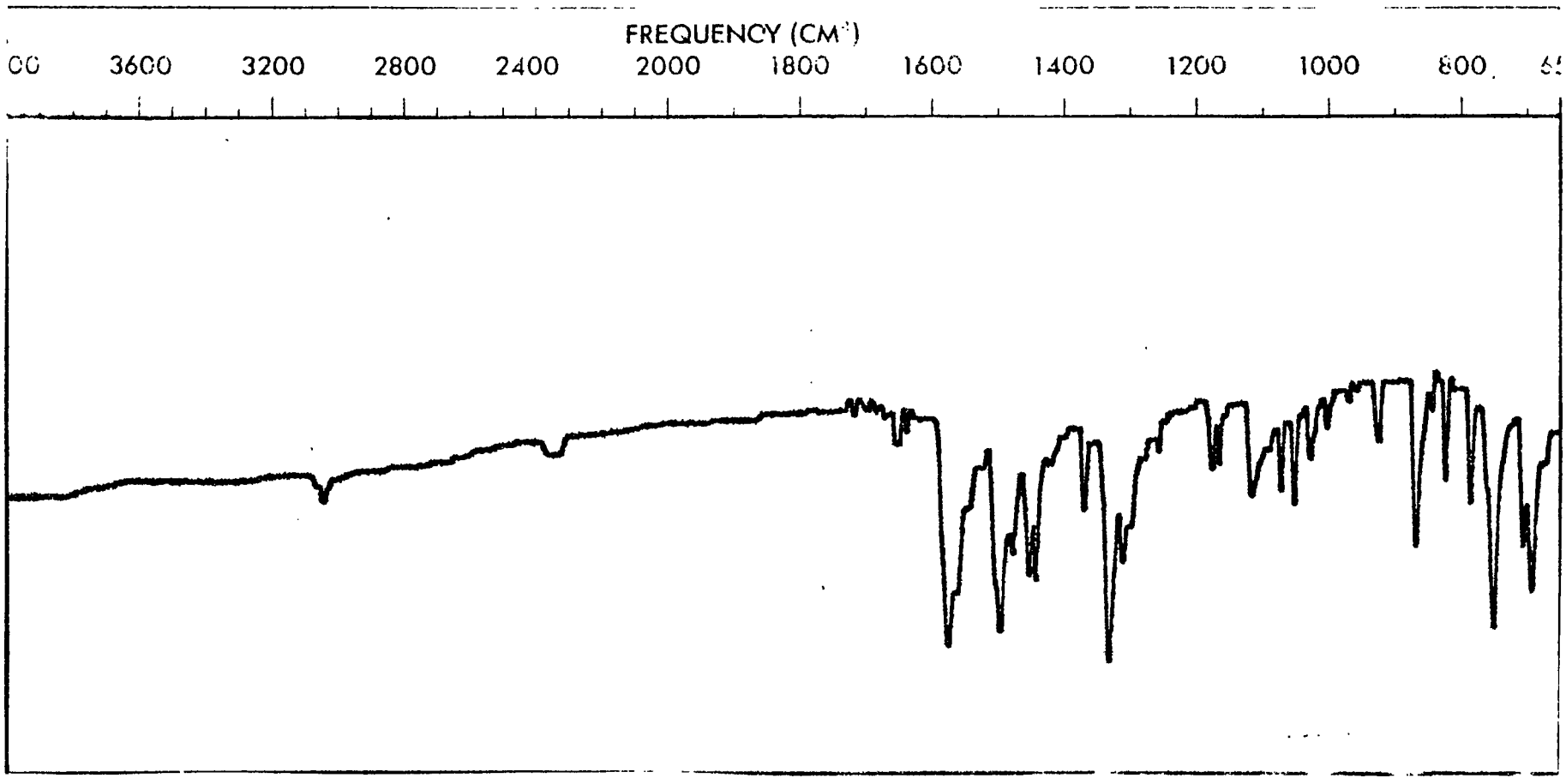


Figure 23. Mass Spectrum of Fraction 1 (M^+= 258)

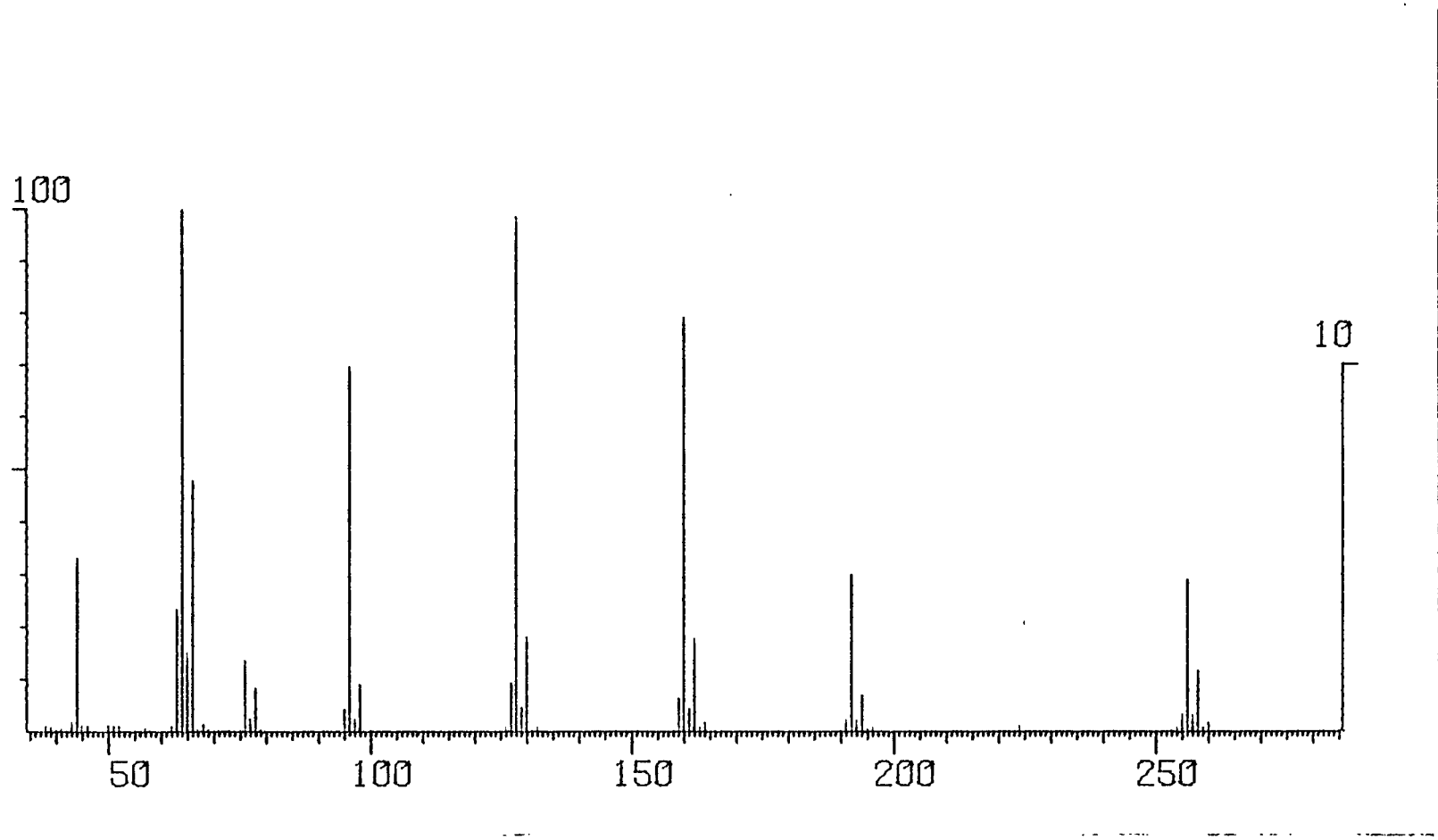


Figure 24. Mass Spectrum of Fraction 2 (M^+=309)

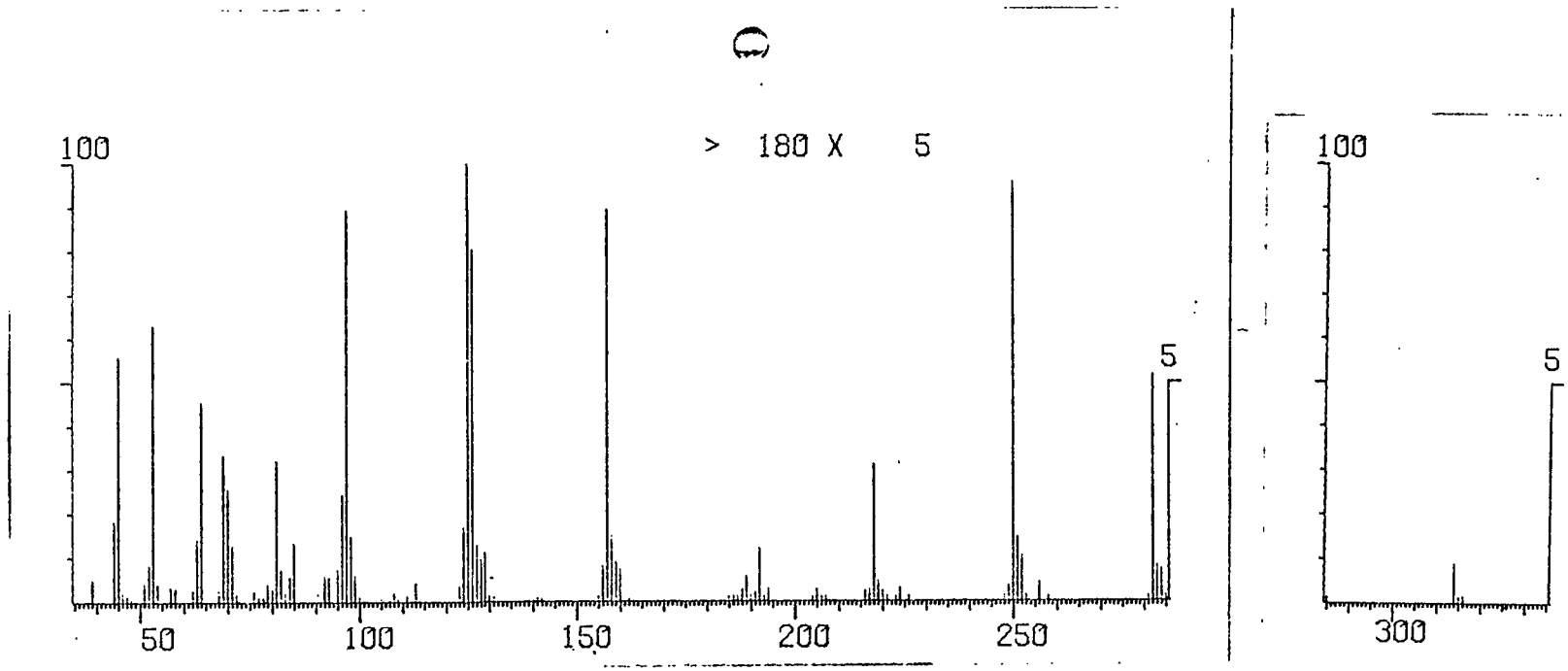


Figure 25. Mass Spectrum of Fraction 3 (M^+=408)

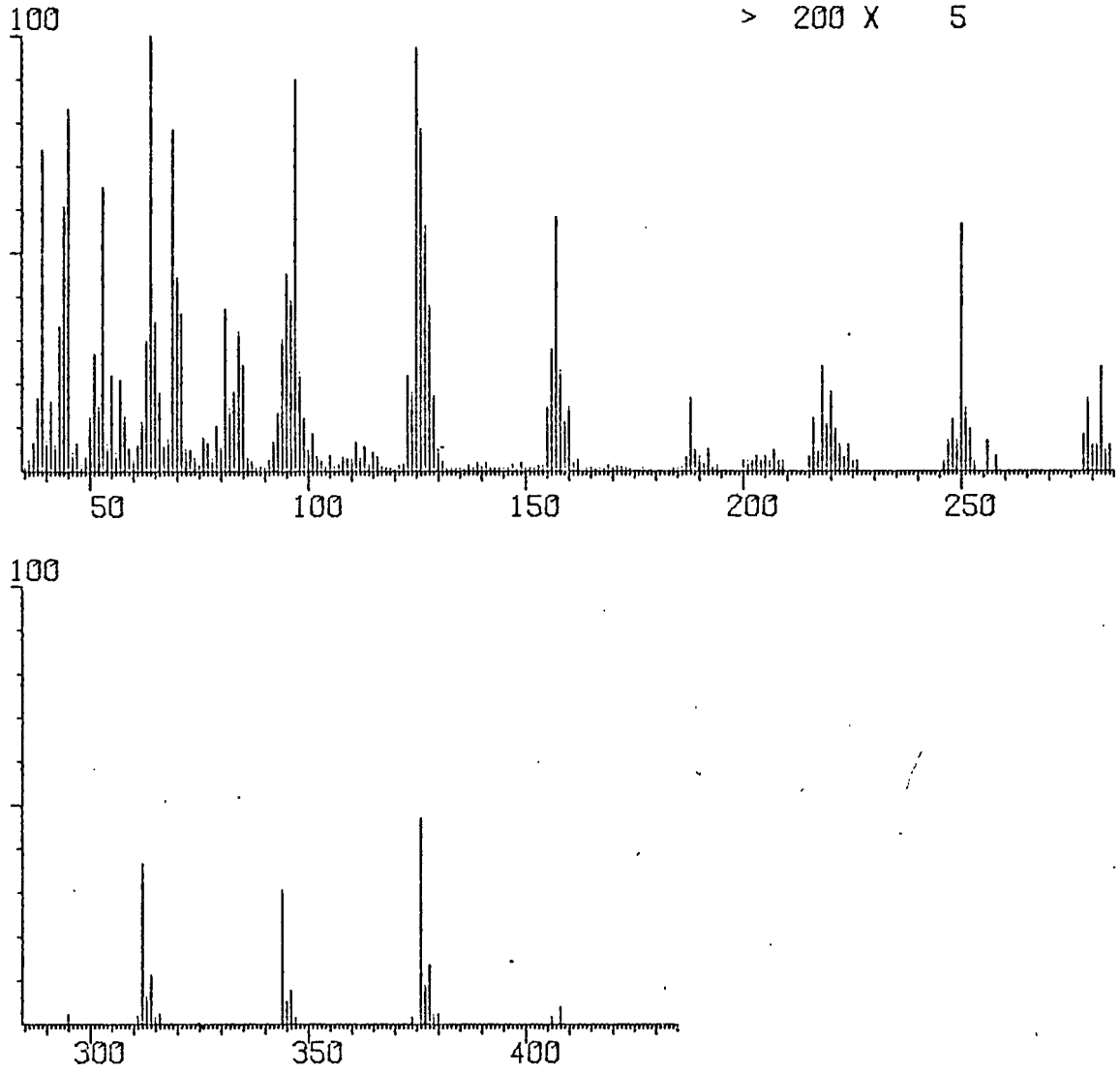

100
> 200 X 5
50
100
150
200
250
100
300
350
400

Figure 26. ^{1}H NMR Spectrum of Fraction 1 (M^{+}=258) Unidentified

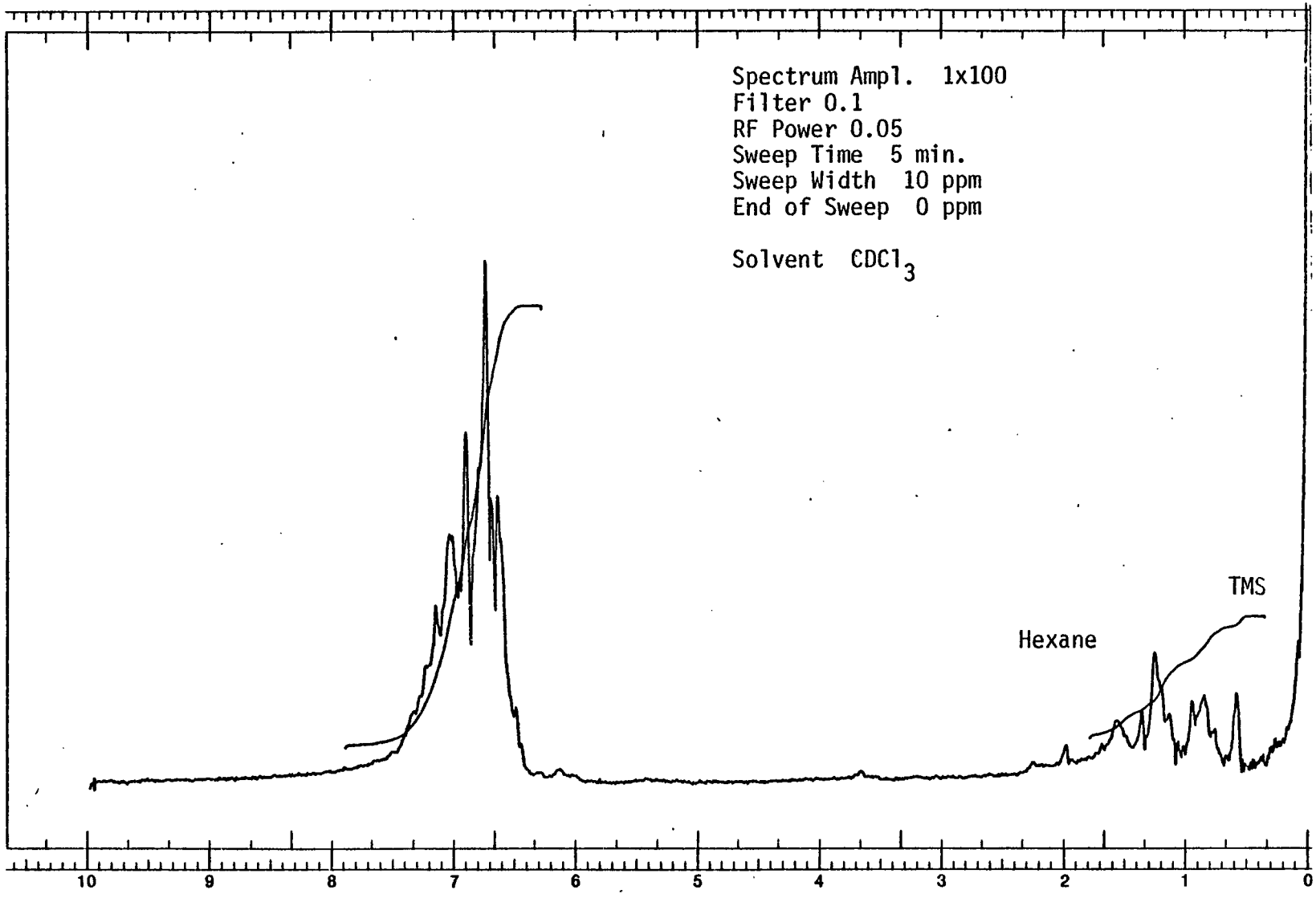


Figure 27. ^{1}H NMR Spectrum of thiophenyl-2,4-dinitrobenzene

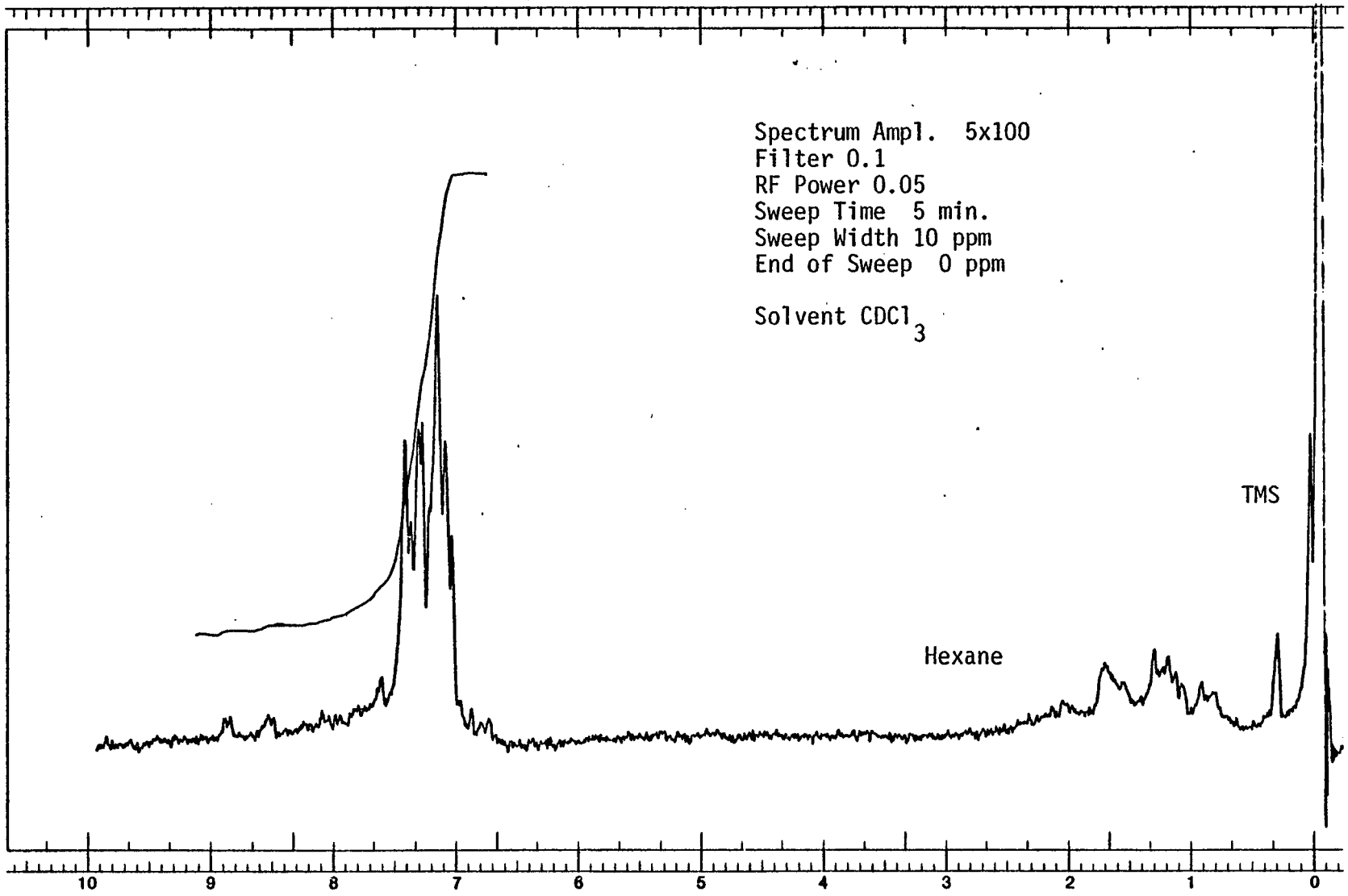


Figure 28. Infrared Spectrum of thiophenyl-2,4-dinitrobenzene

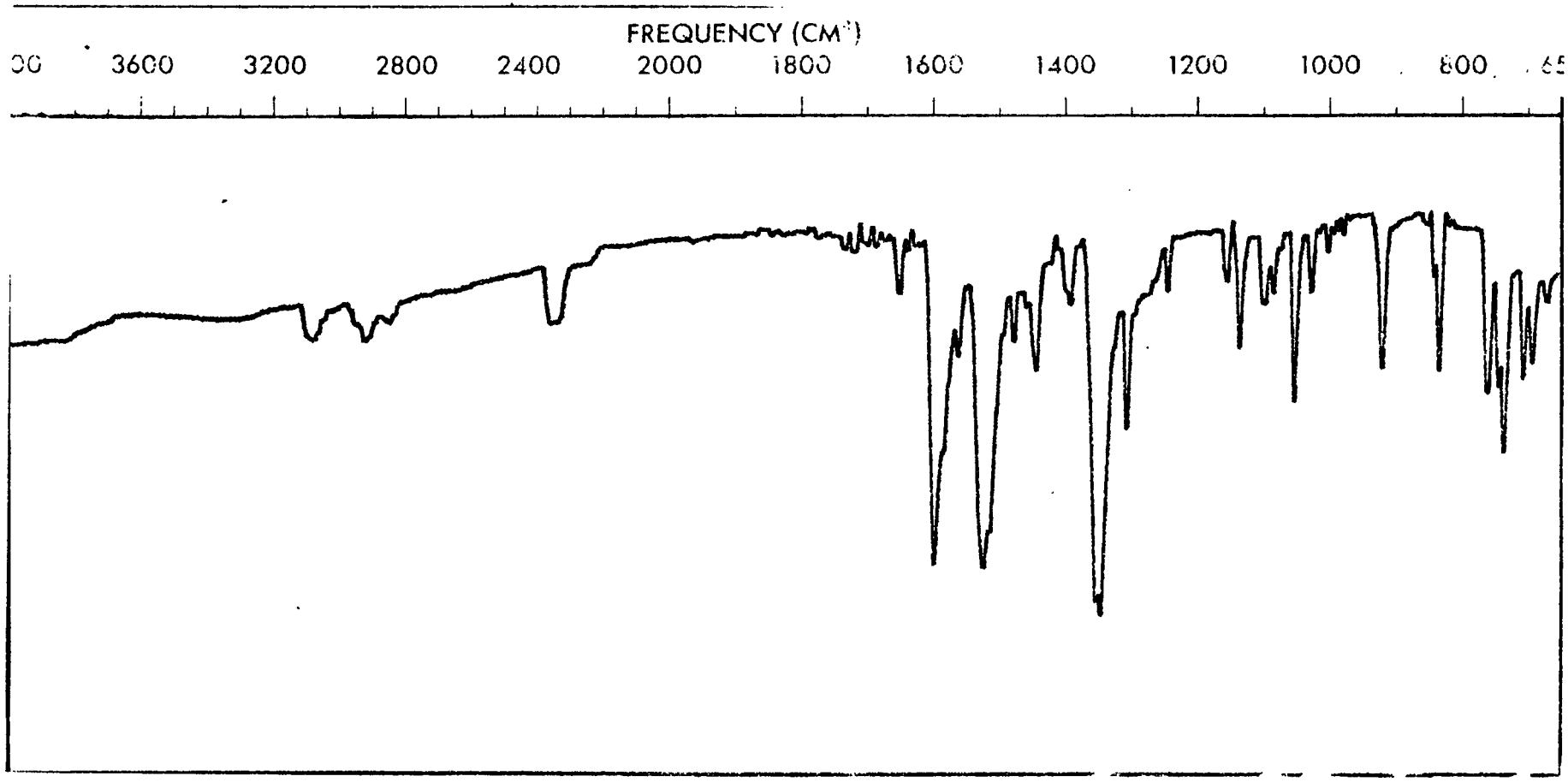


Figure 29. Mass Spectrum of thiophenyl-2,4-dinitrobenzene

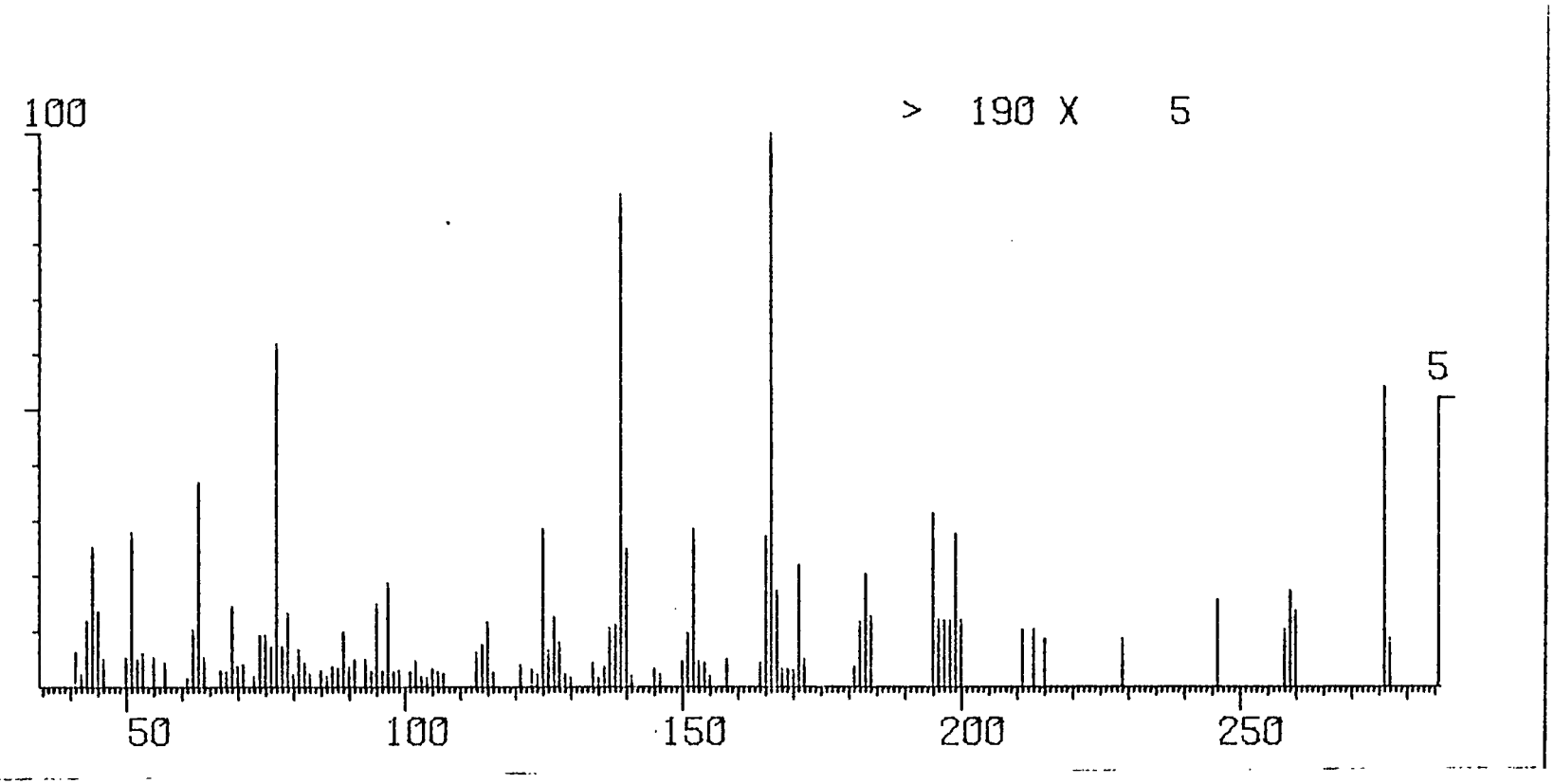


Figure 30. ^{1}H NMR Spectrum of thiophenyl-2,4-dinitrobenzene

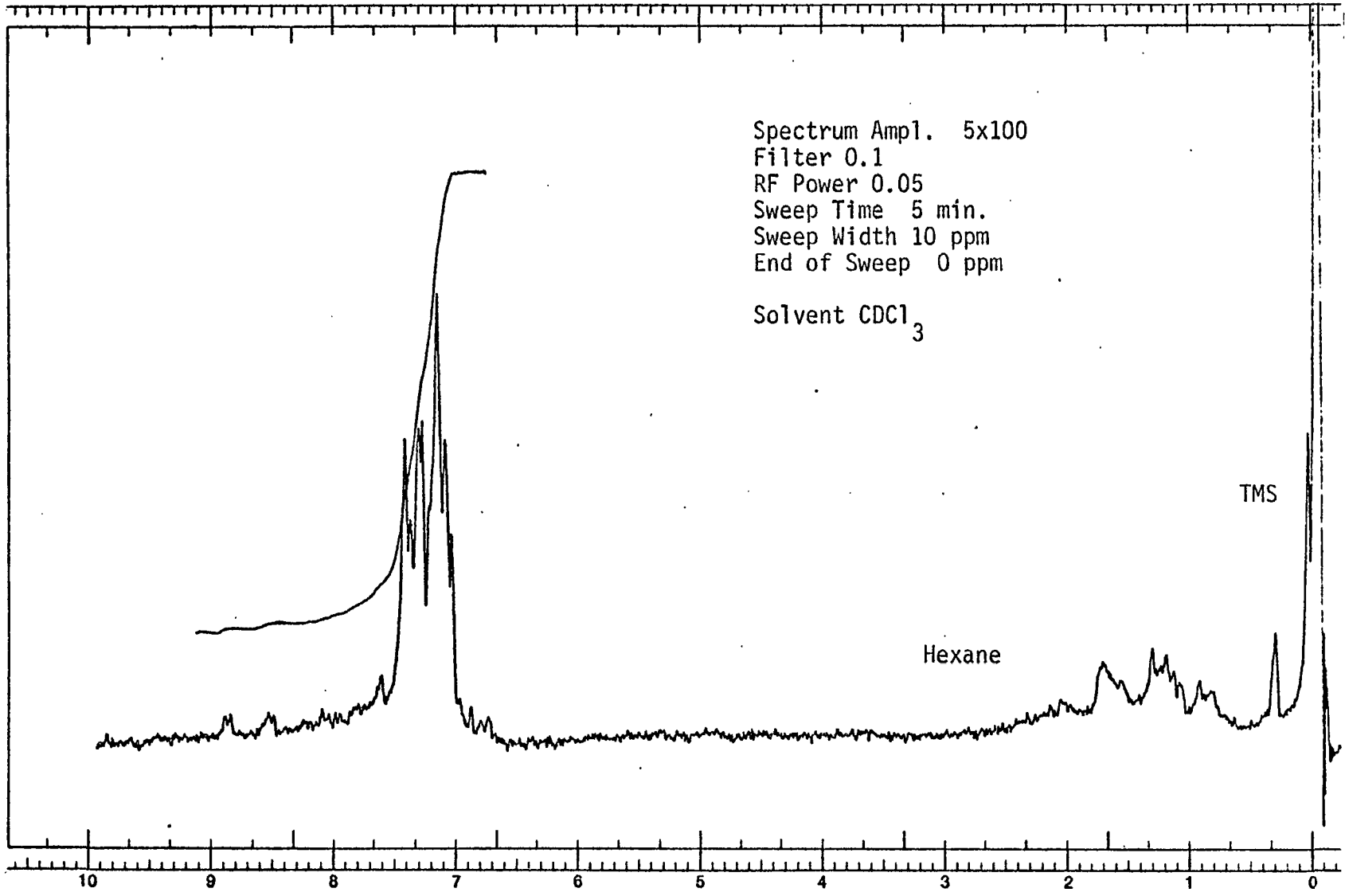


Figure 31. Infrared Spectrum of thiophenyl-2,4-dinitrobenzene

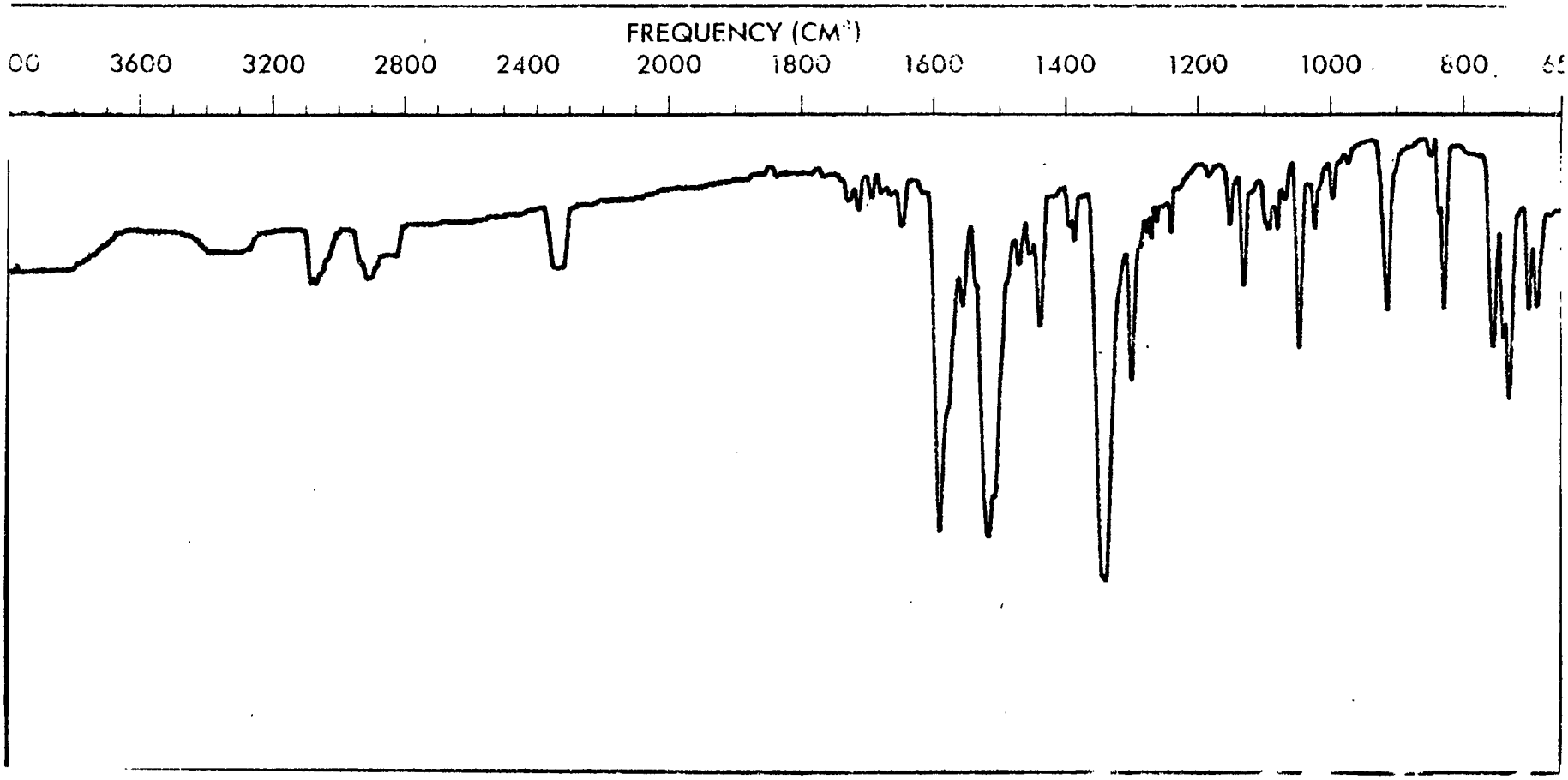


Figure 32. Mass Spectrum of thiophenyl-2,4-dinitrobenzene

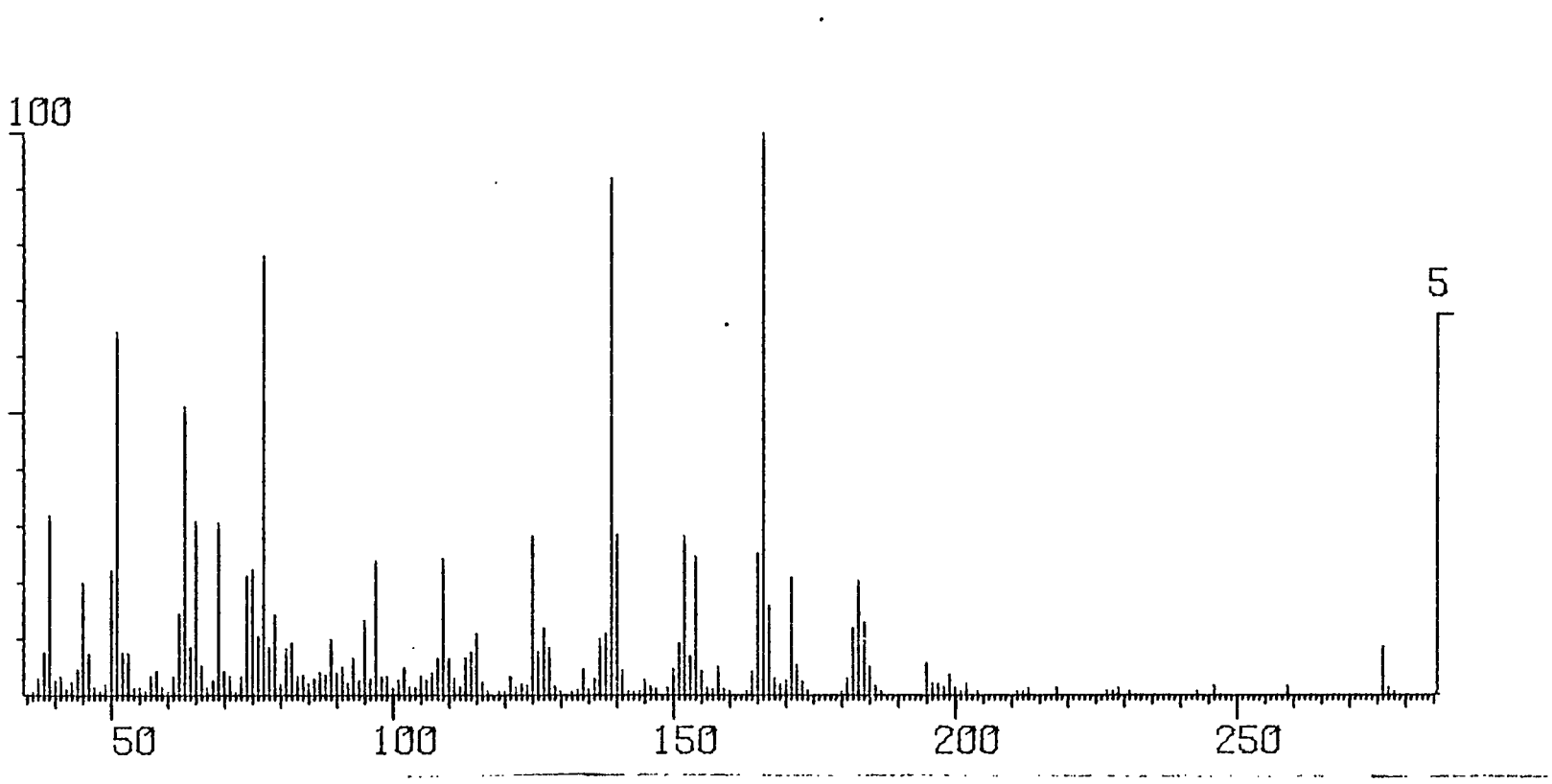
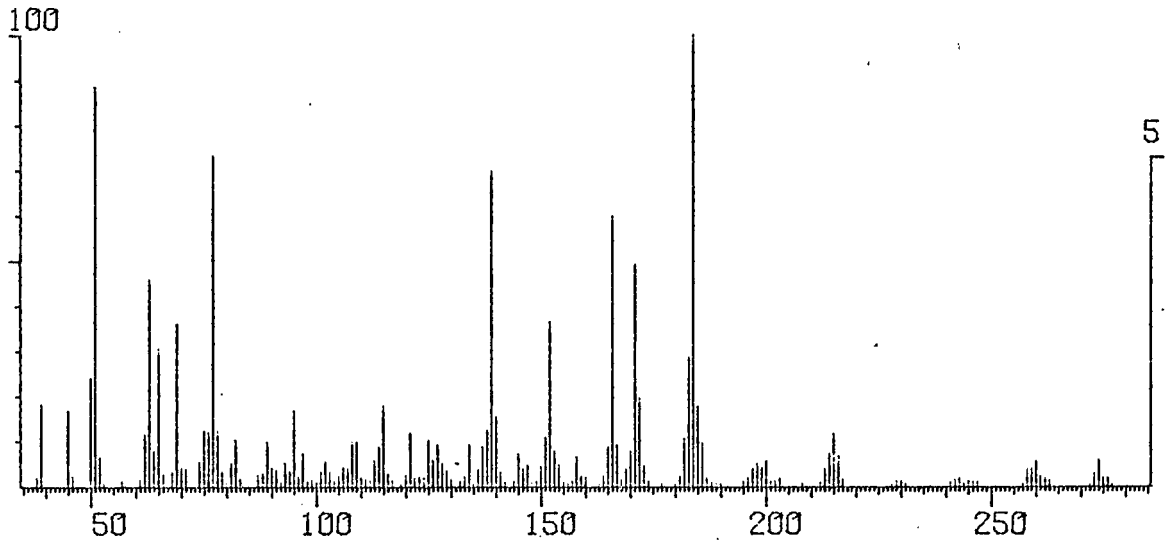


Figure 33. Mass Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene


100
5
50
100
150
200
250

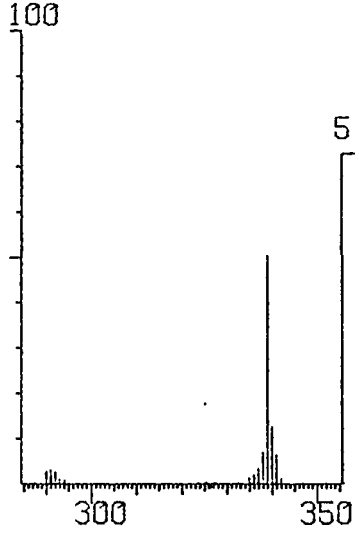

100
5
300
350

Figure 34. ^{1}H NMR Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

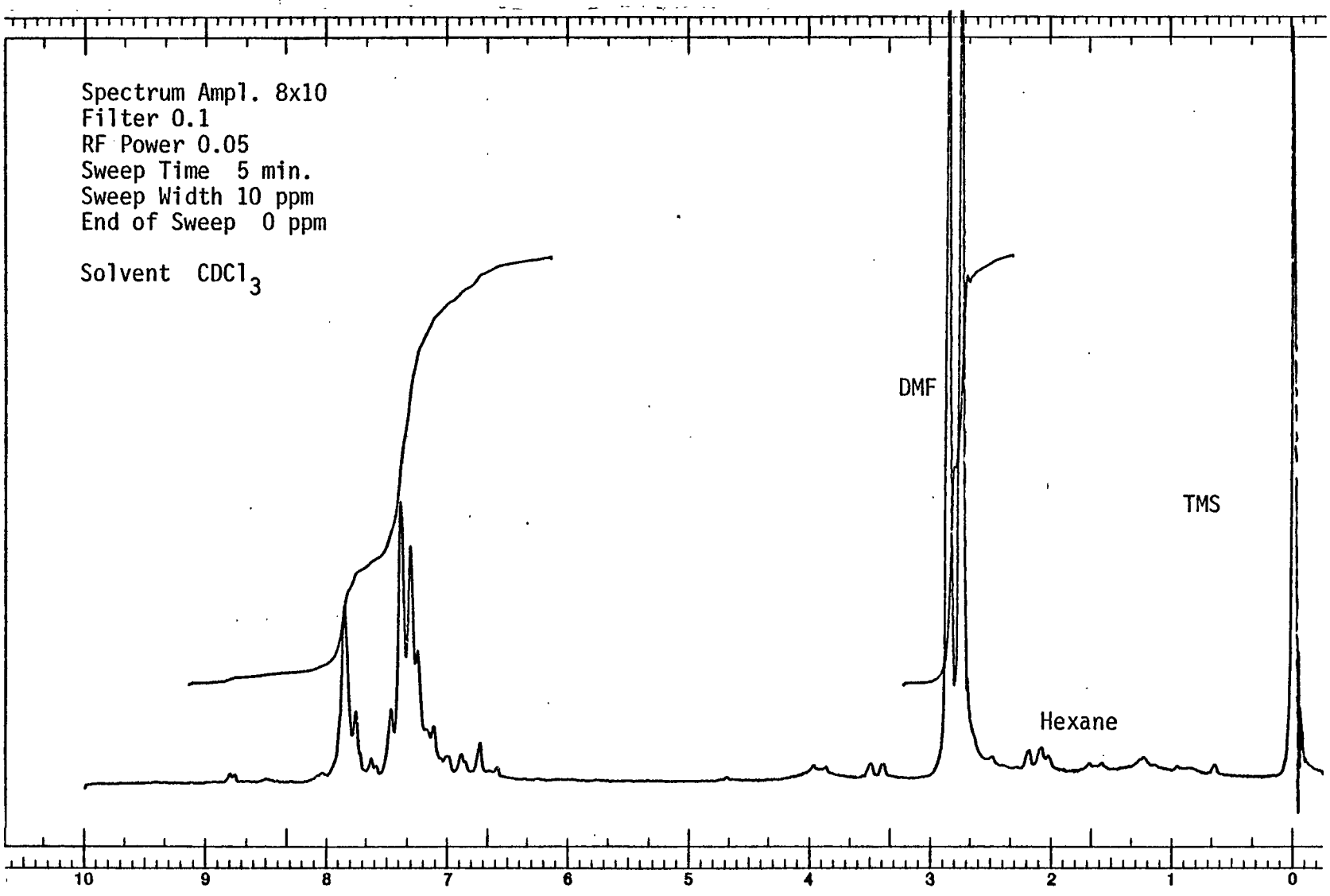


Figure 35. ^{1}H NMR Spectrum of thiophenyl-2,4-dinitrobenzene

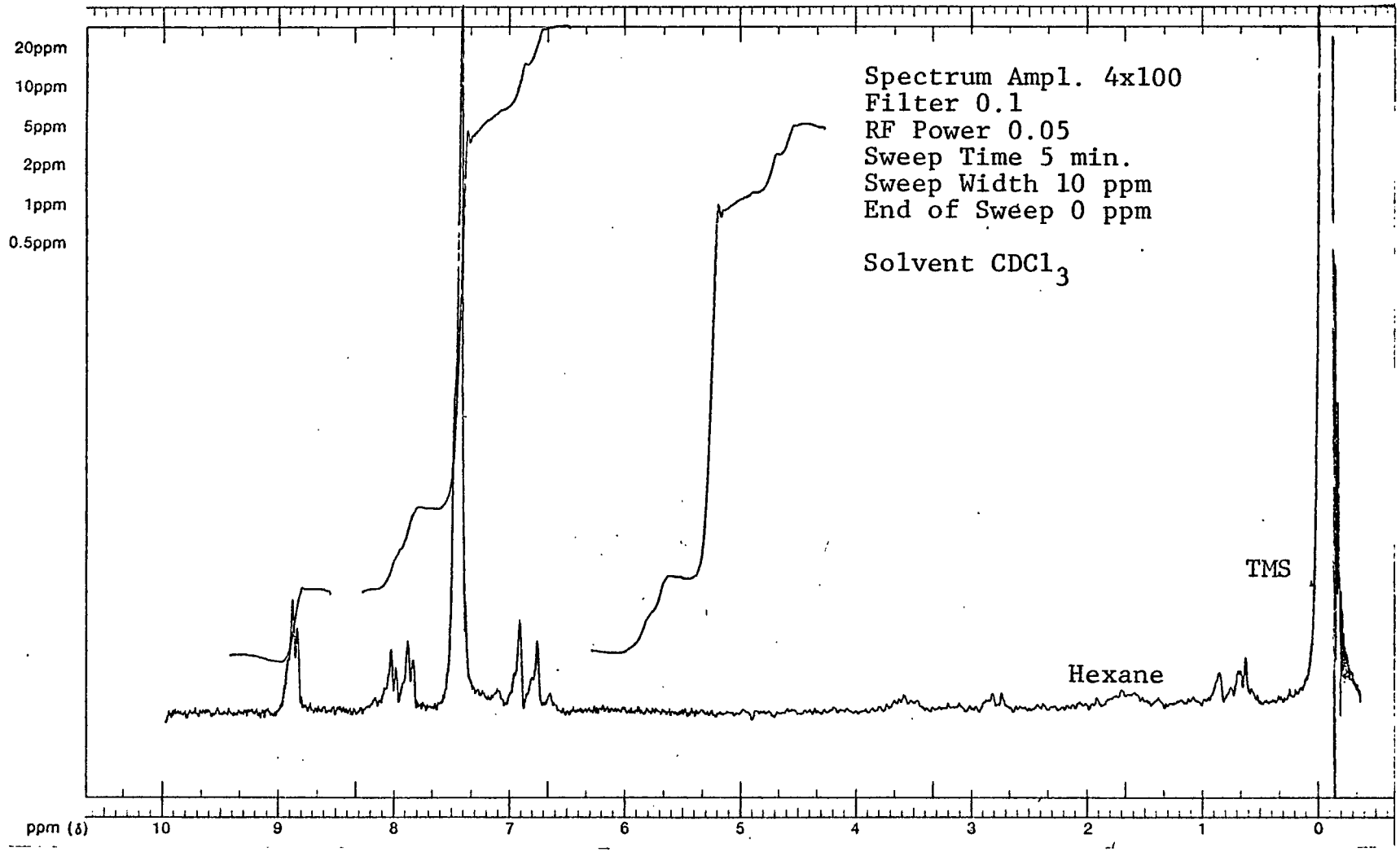


Figure 36. Infrared Spectrum of thiophenyl-2,4-dinitrobenzene

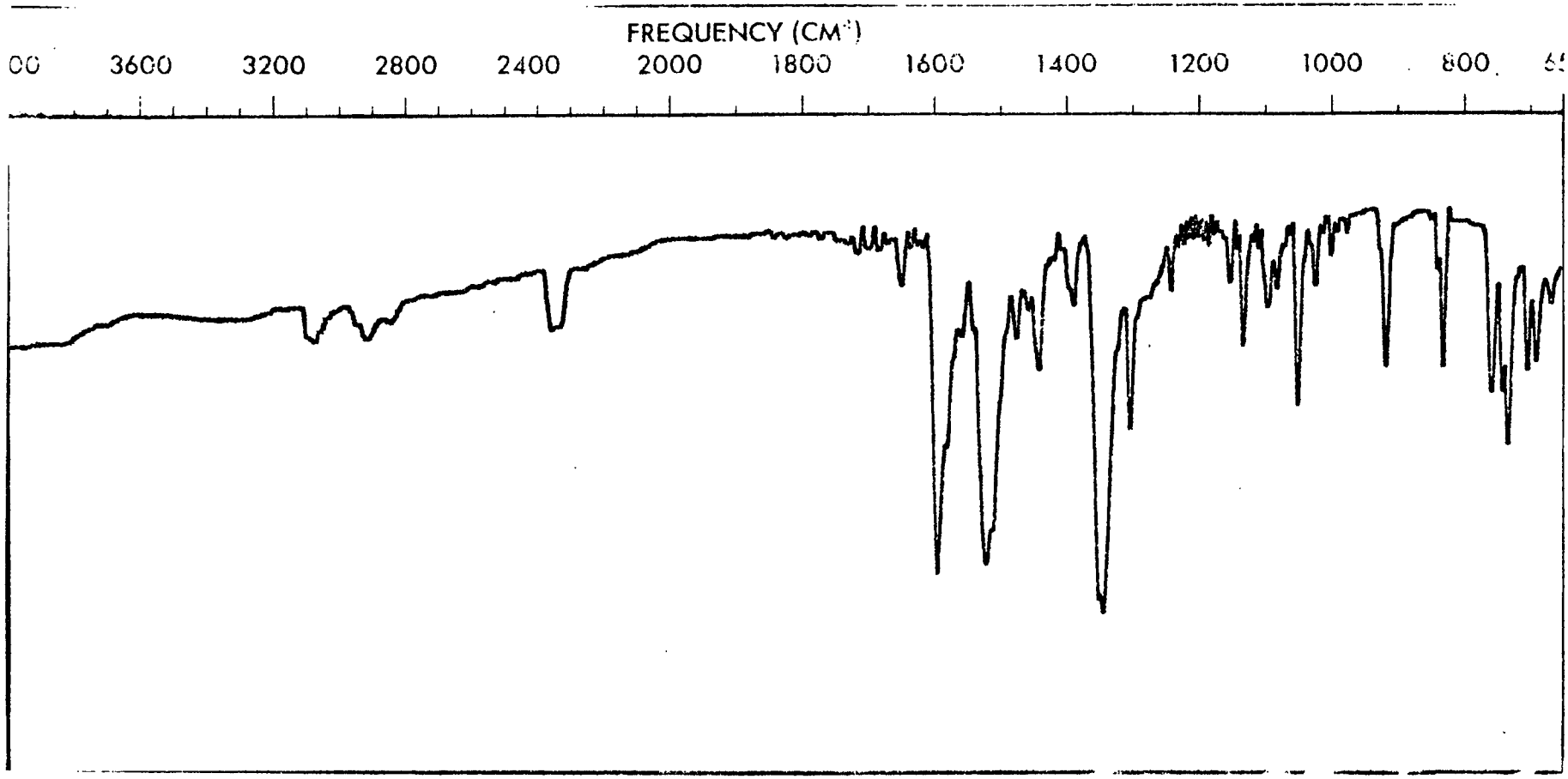
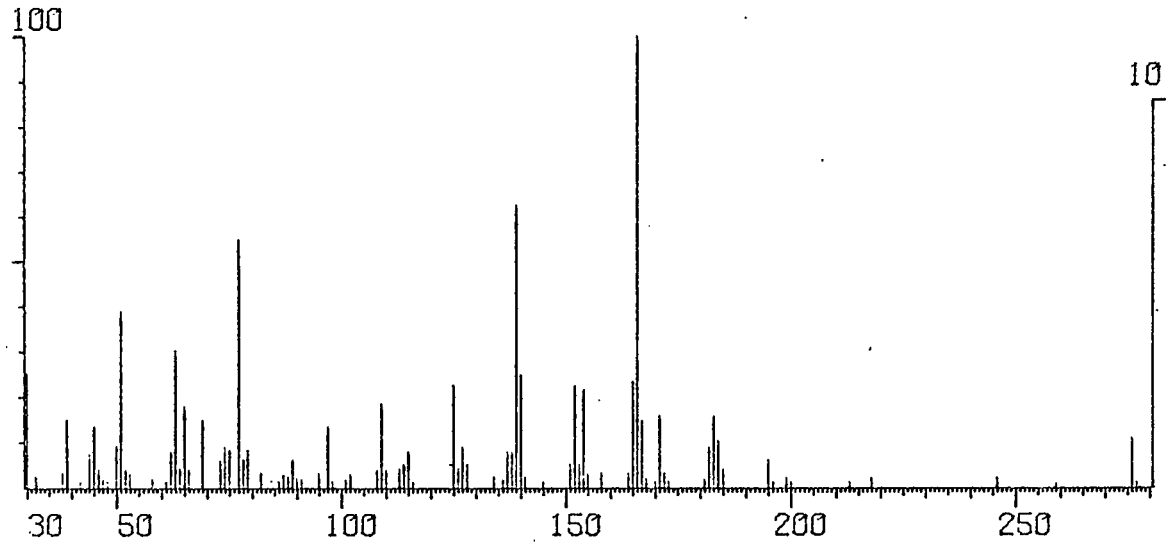


Figure 37. Mass Spectrum of thiophenyl-2,4-dinitrobenzene


100
10
30
50
100
150
200
250

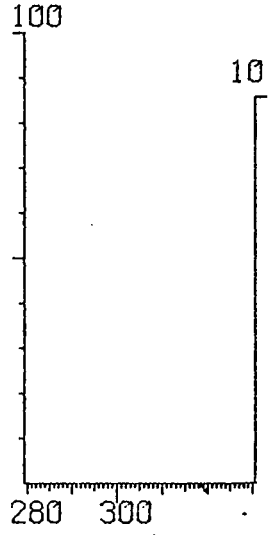

100
10
280
300

Figure 38. ^{1}H NMR Spectrum of 1-nitro-2,4-dichlorobenzene

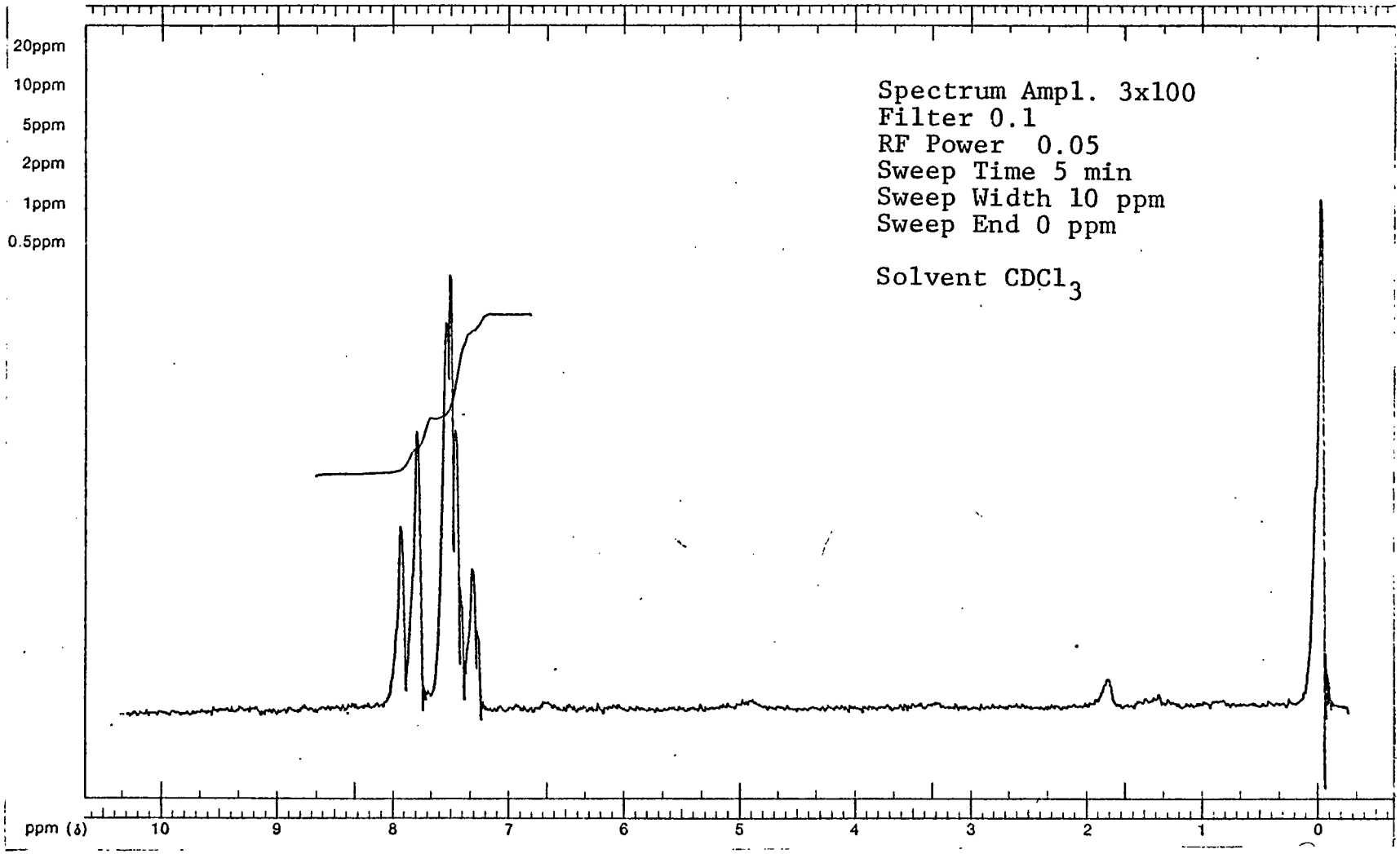


Figure 39. ^{13}C NMR Spectrum of 1-nitro-2,4-dichloro-benzene

Line	Freq. (Hz)	PPM
1	3671.50	145.926
2	3496.72	138.979
3	3305.66	131.385
4	3221.61	128.045
5	3212.99	127.702
6	3181.27	126.441
7	1966.66	78.1663
8	1934.80	76.8998
9	1902.56	75.6184

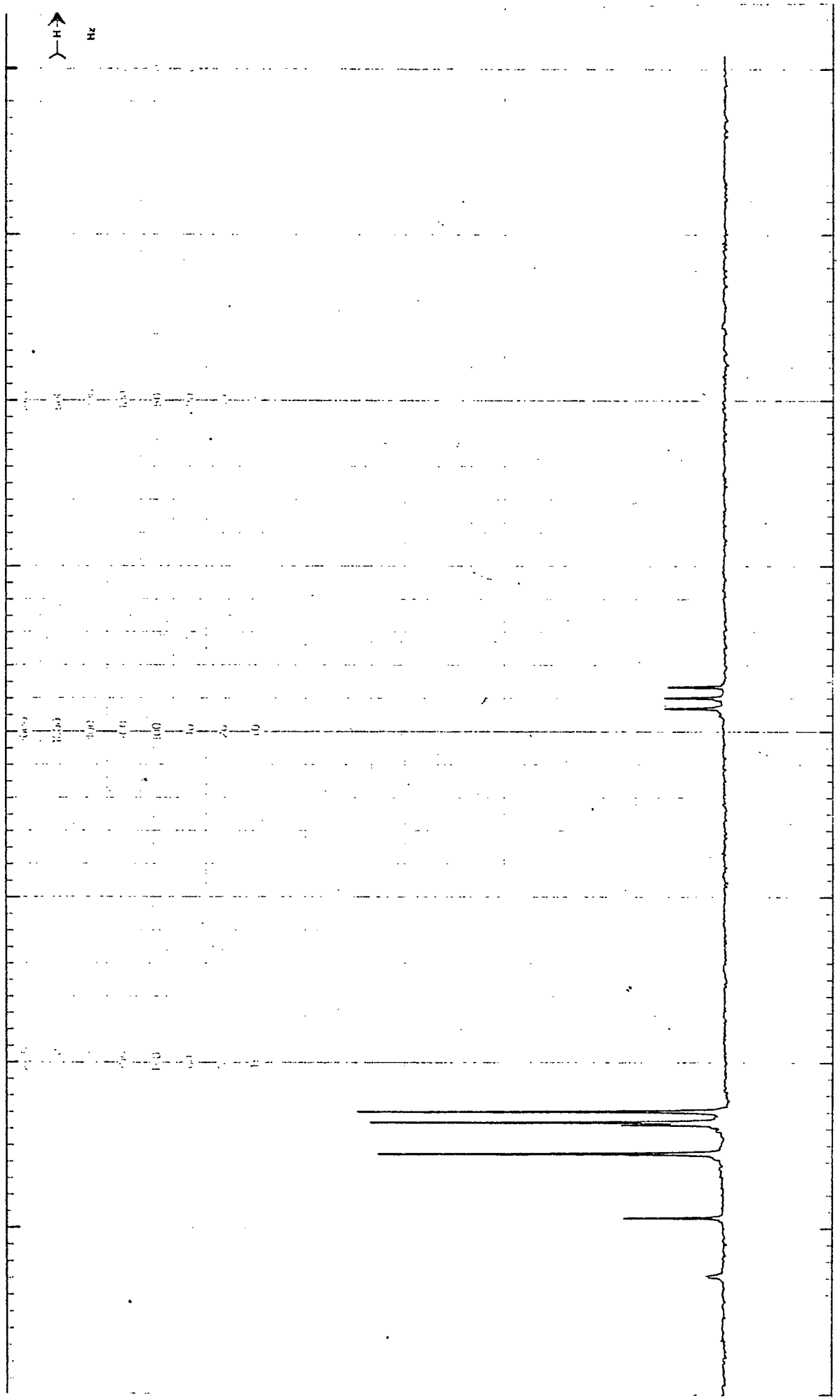

H
Hz

Figure 40. Infrared Spectrum of 1-nitro-2,4-dichlorobenzene

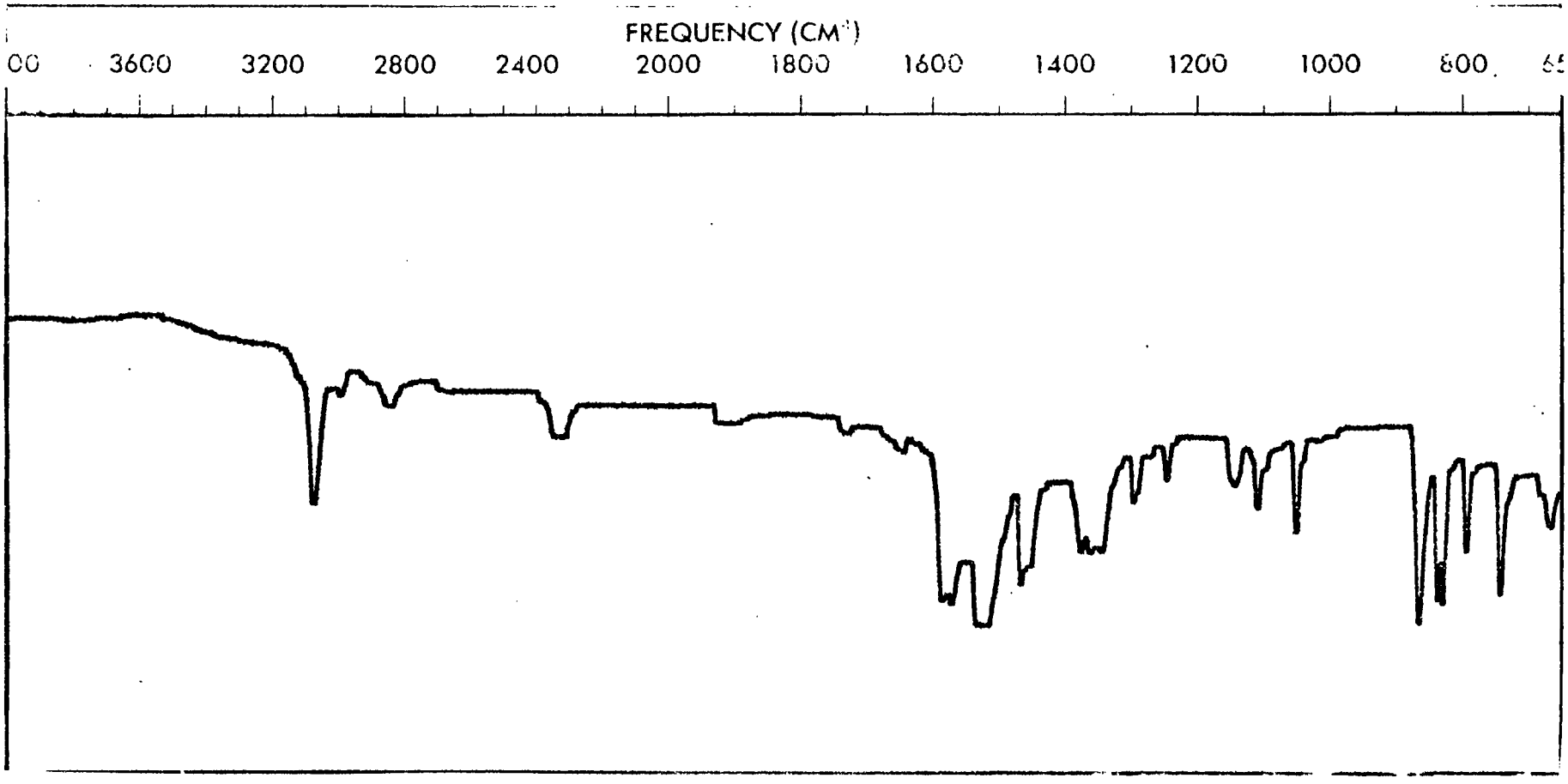


Figure 41. ^{1}H NMR Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

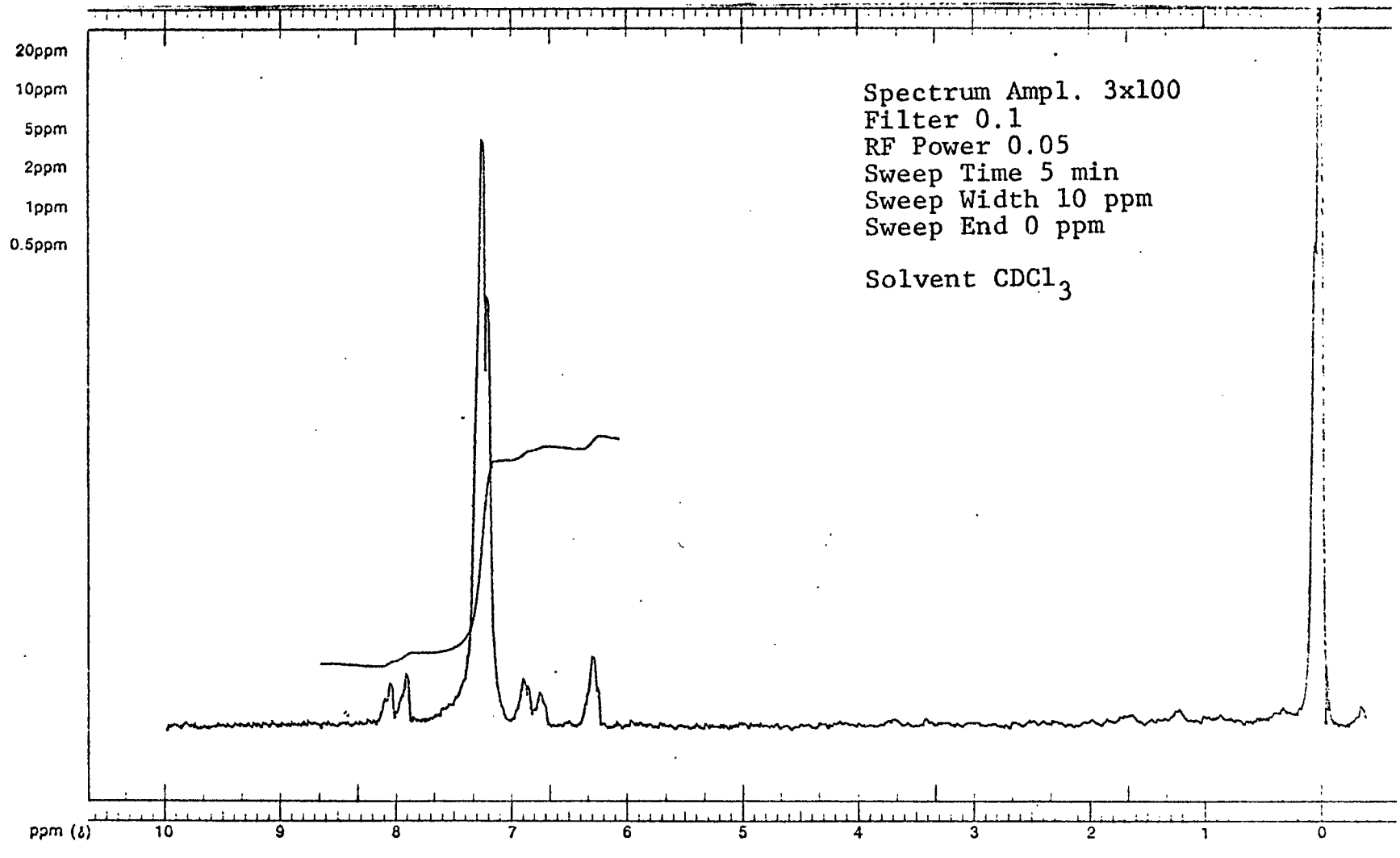


Figure 42. ^{13}C NMR Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

Line	Freq. (Hz)	PPM
1	3797.44	150.69
2	3631.77	144.11
3	3608.93	143.21
4	3482.02	138.17
5	3455.47	137.12
6	3326.97	132.02
7	3257.94	129.28
8	3215.46	127.59
9	3170.33	125.80
10	1966.20	78.1559
11	1934.80	76.8999
12	1902.62	75.6208

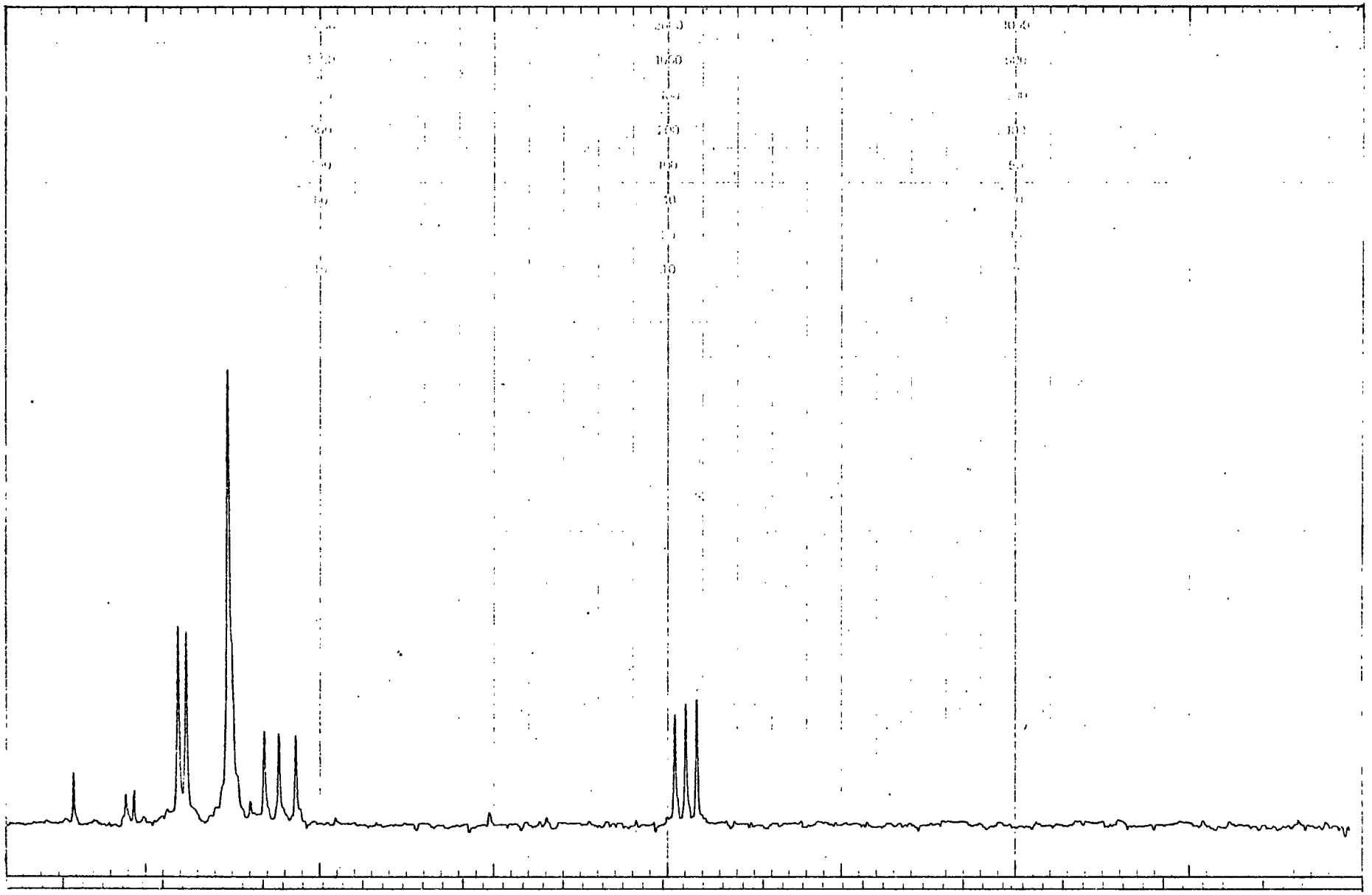


Figure 43. Infrared Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

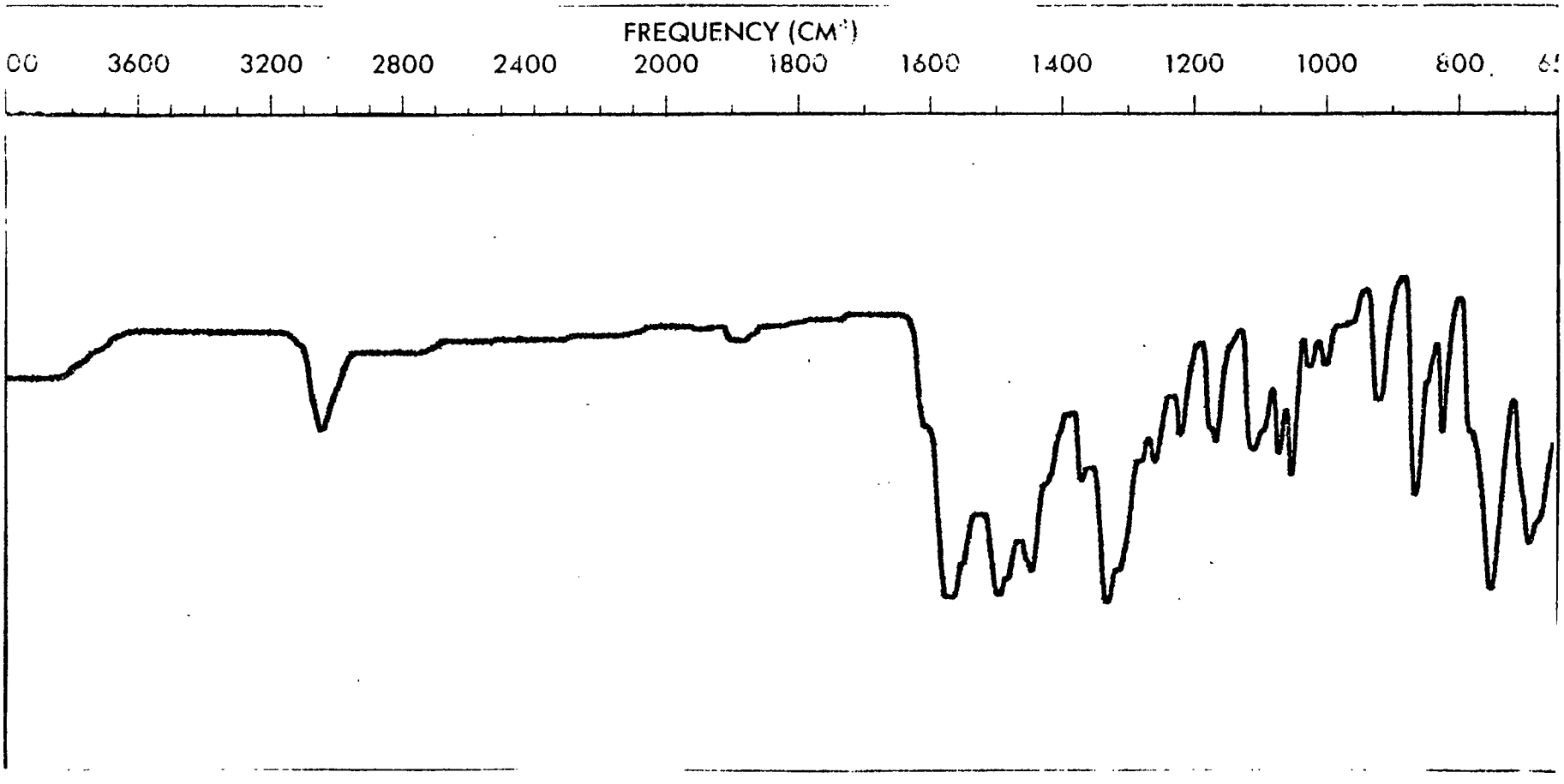


Figure 44. Mass Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

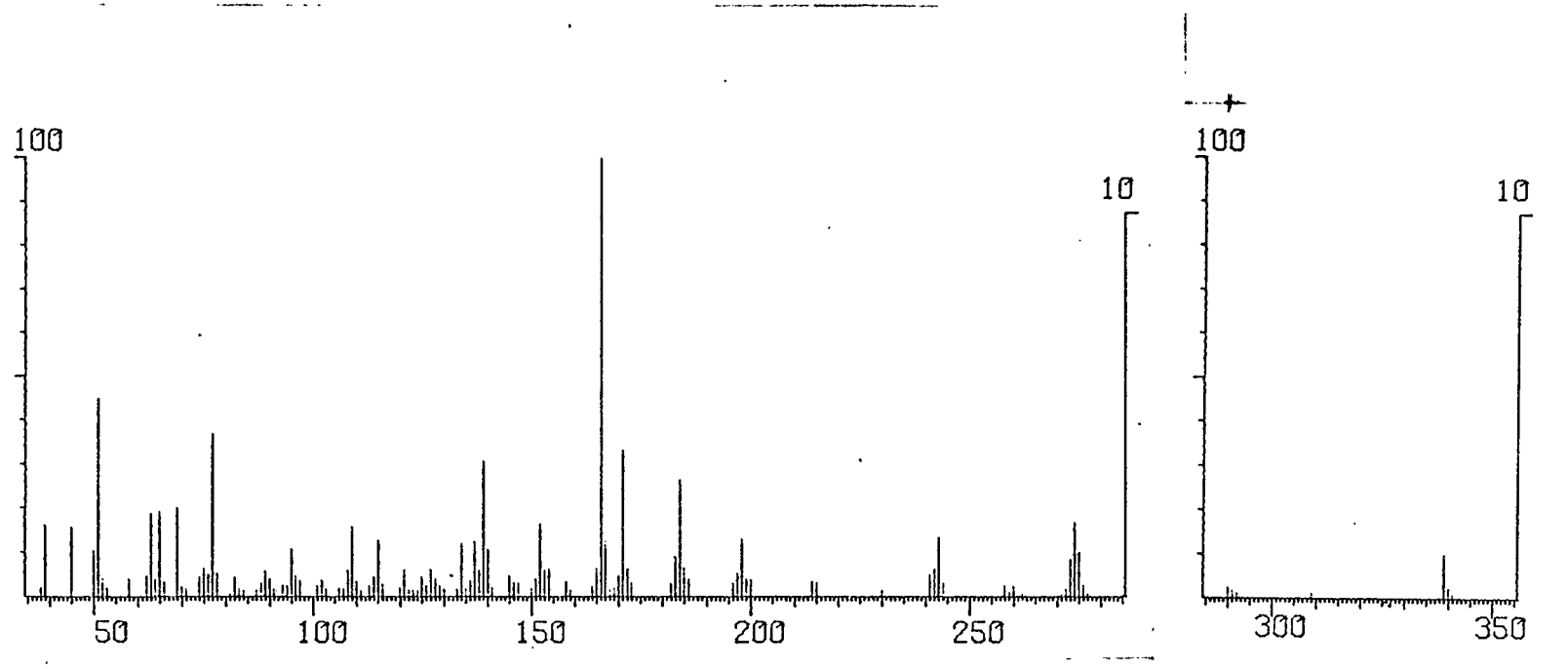


Figure 45. ^{1}H NMR Spectrum of 1-nitro-2,4-difluorobenzene

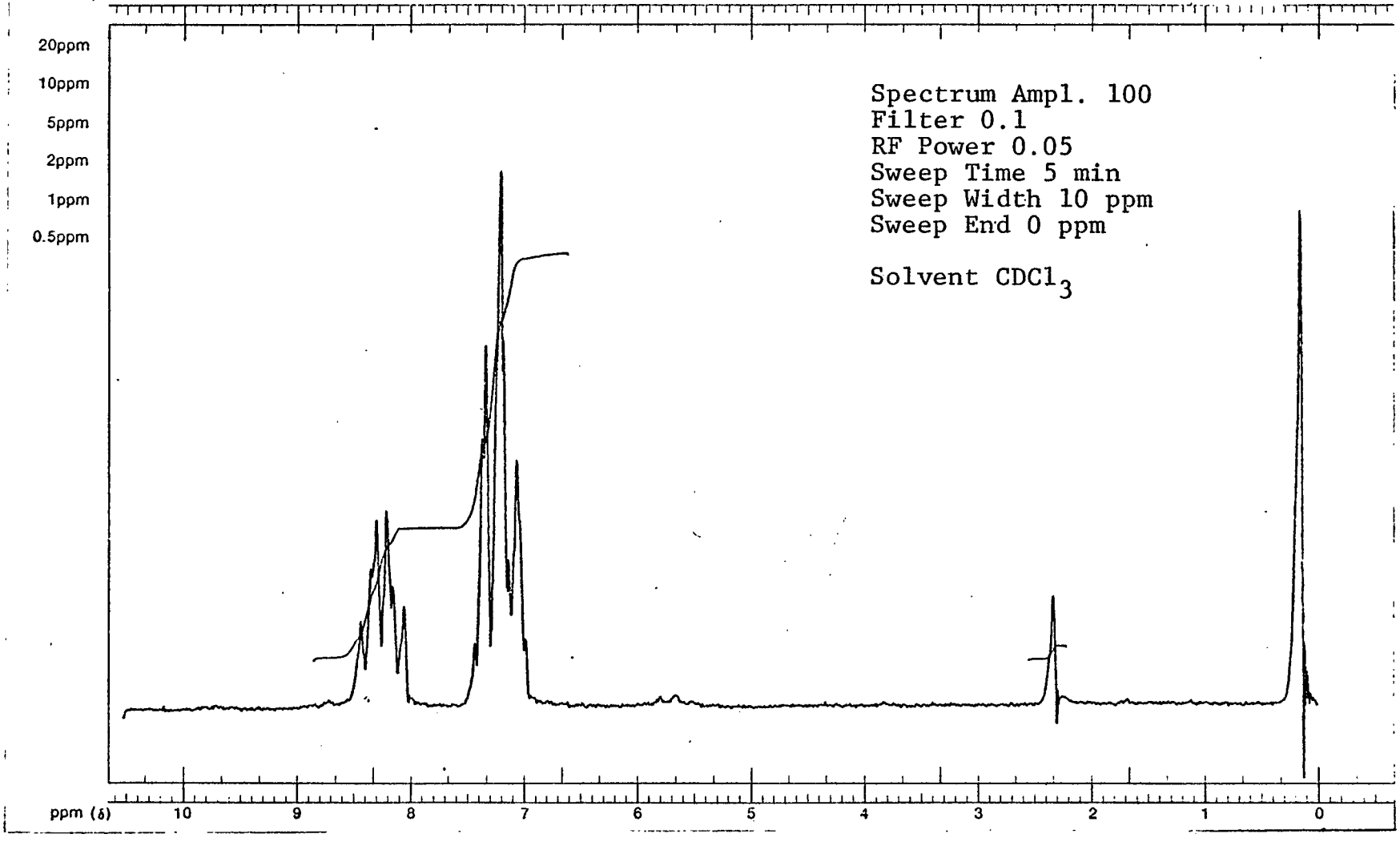


Figure 46. ^{13}C NMR Spectrum of 1-nitro-2,4-difluoro-benzene

Line	Freq. (Hz)	PPM
1	4298.83	170.859
2	4287.70	170.417
3	4075.49	161.982
4	4062.44	161.464
5	4038.88	160.528
6	4027.76	160.086
7	3808.15	151.357
8	3795.14	150.840
9	3370.95	133.980
10	3225.13	128.185
11	3224.06	128.142
12	3214.13	127.747
13	2830.18	112.487
14	2826.05	112.323
15	2806.92	111.562
16	2802.88	111.402
17	2697.24	107.203
18	2691.78	106.986
19	2672.70	106.228
20	2670.89	106.156
21	2646.07	105.169
22	1966.75	78.1698
23	1934.80	76.8998
24	1902.59	75.6196

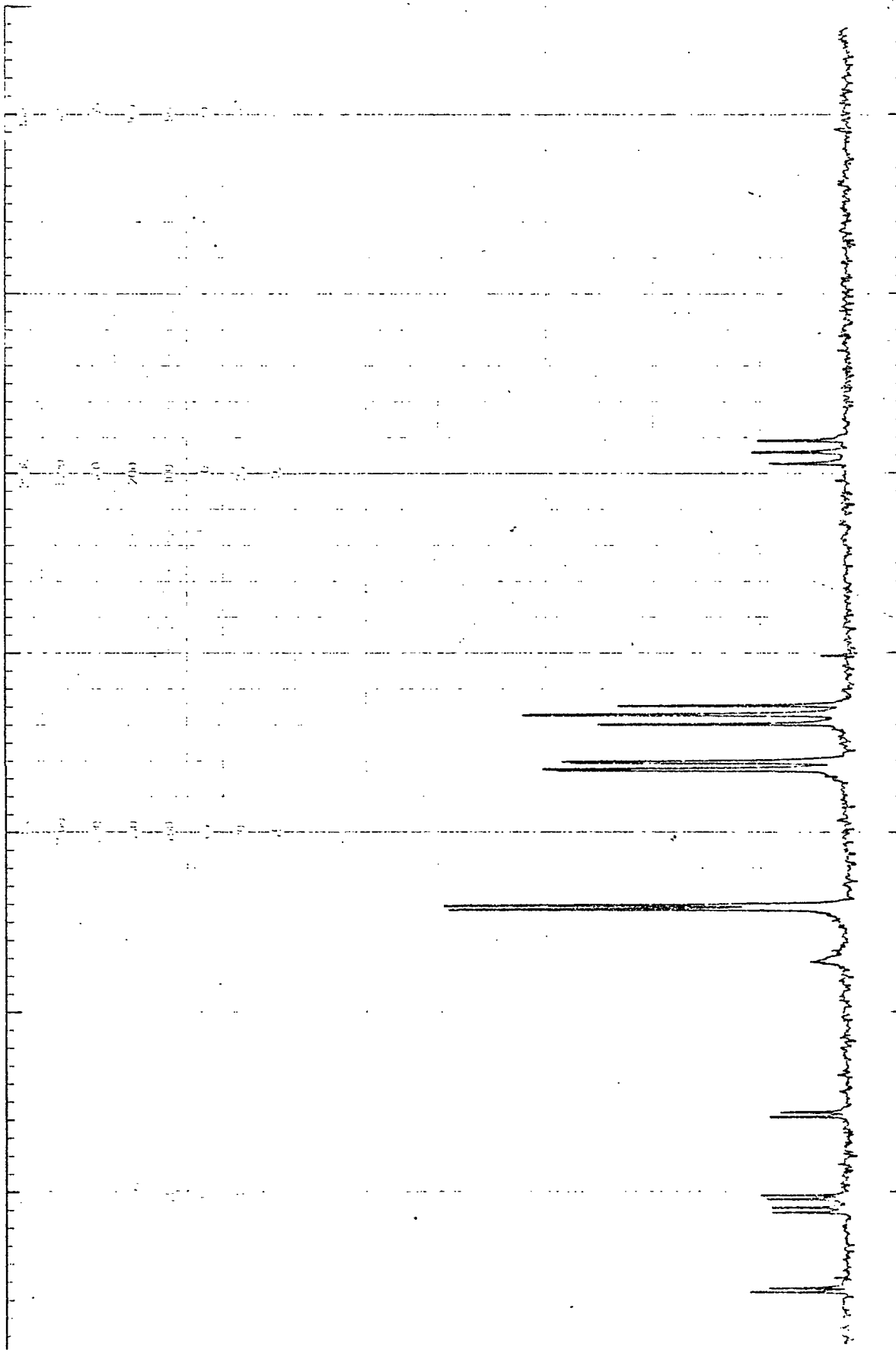


Figure 47. Infrared Spectrum of 1-nitro-2,4-difluorobenzene

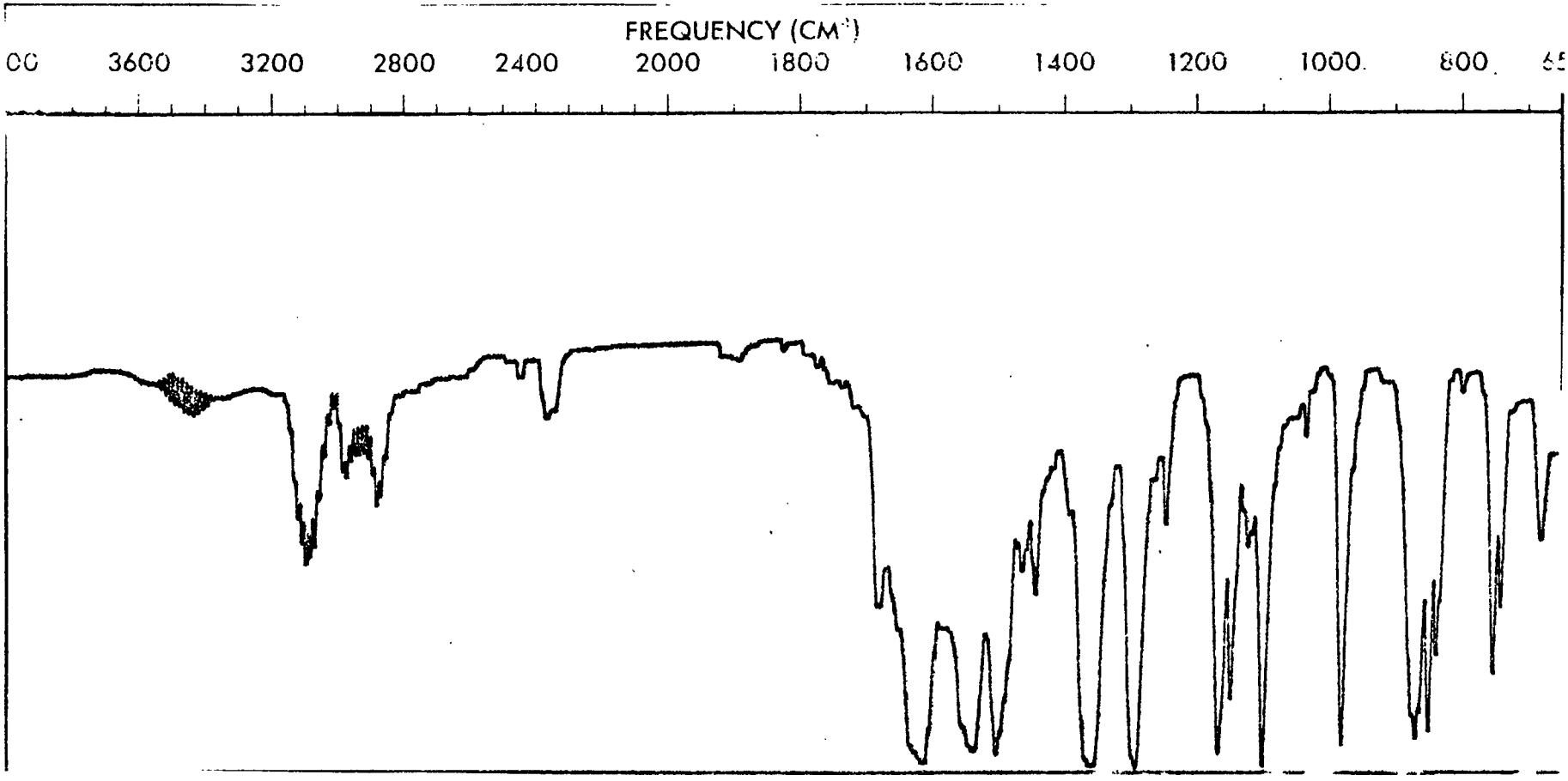


Figure 48. ^{1}H NMR Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

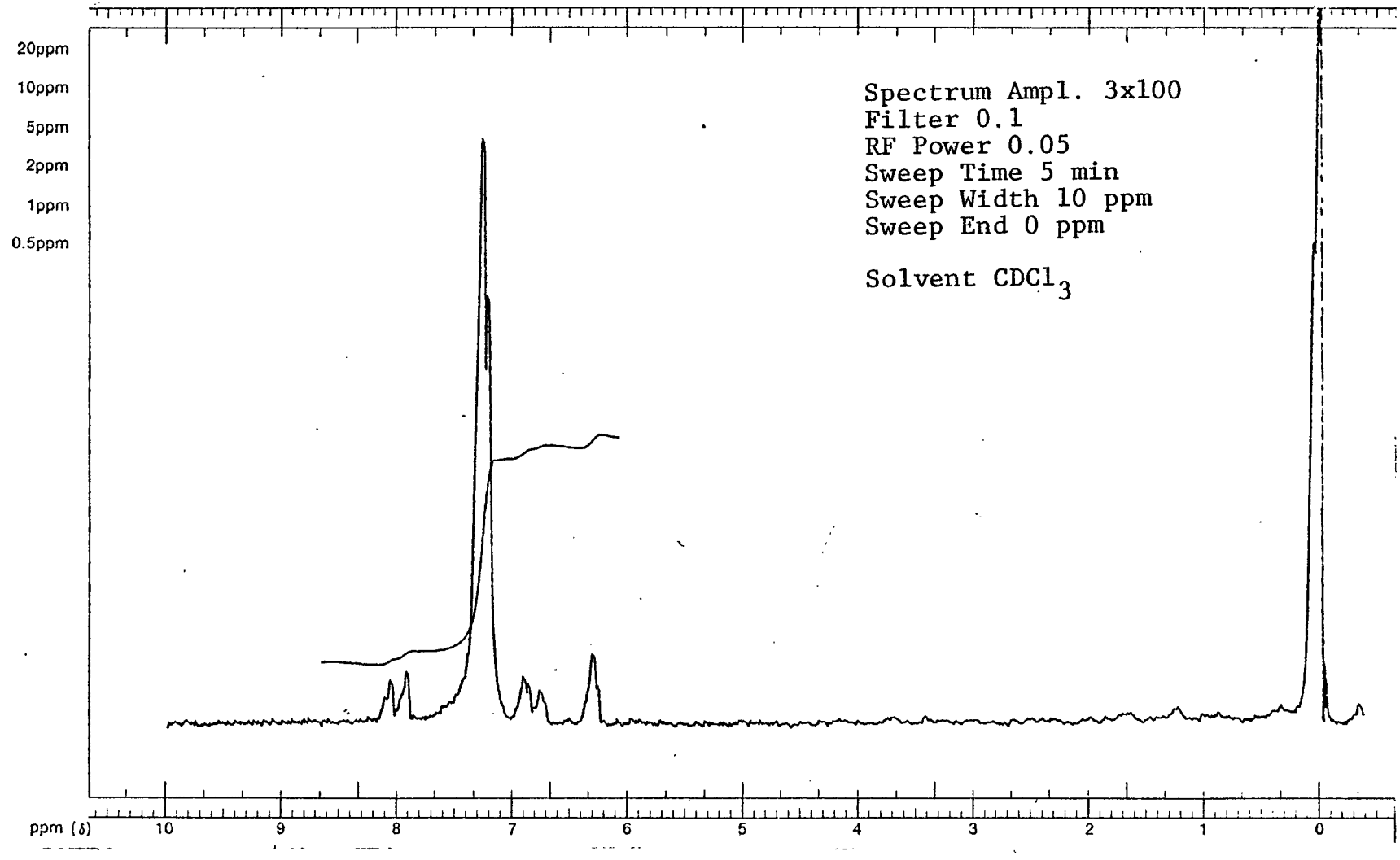


Figure 49. Infrared Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

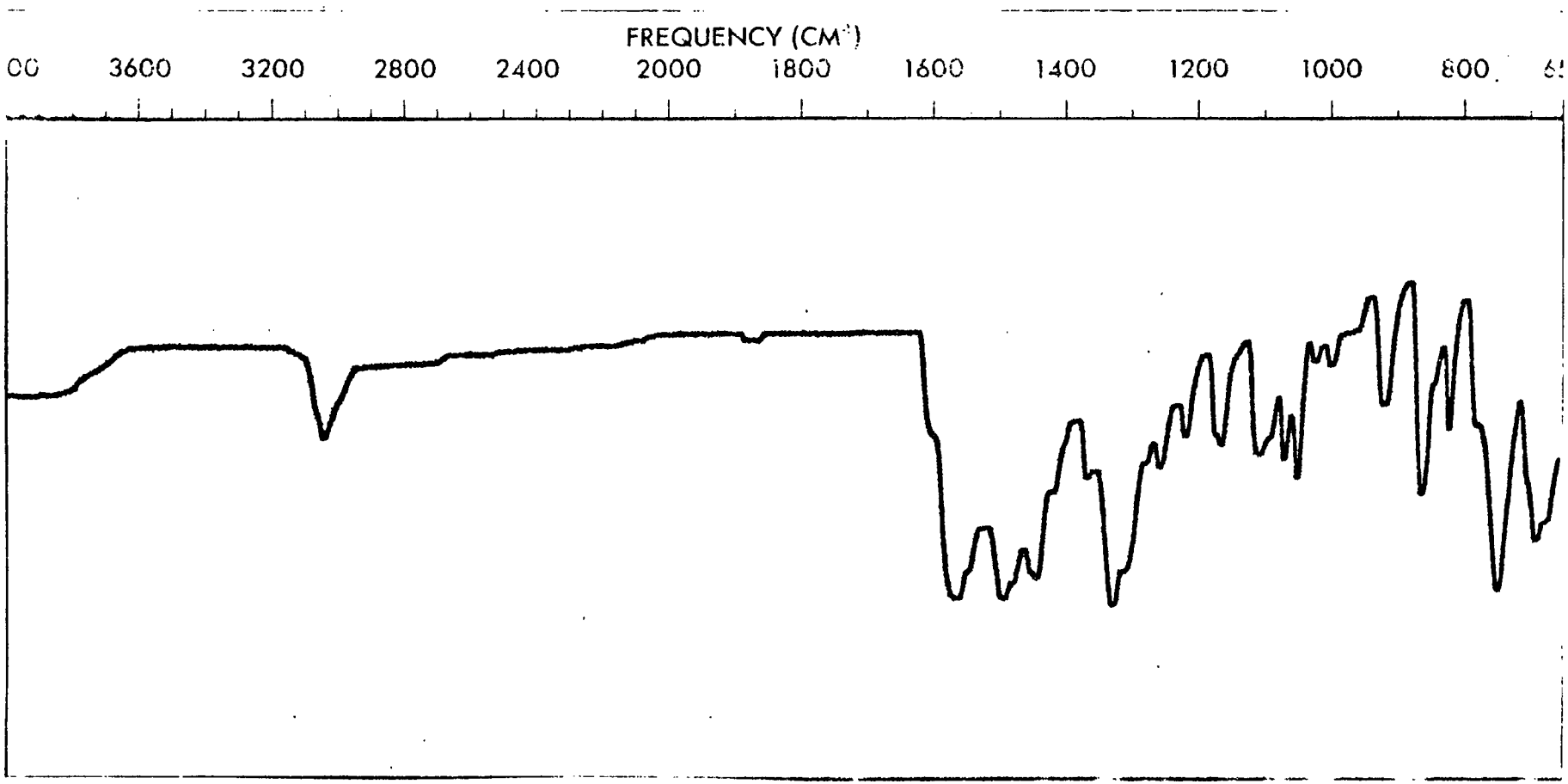


Figure 50. Mass Spectrum of 1,3-bis(thiophenyl)-4-nitrobenzene

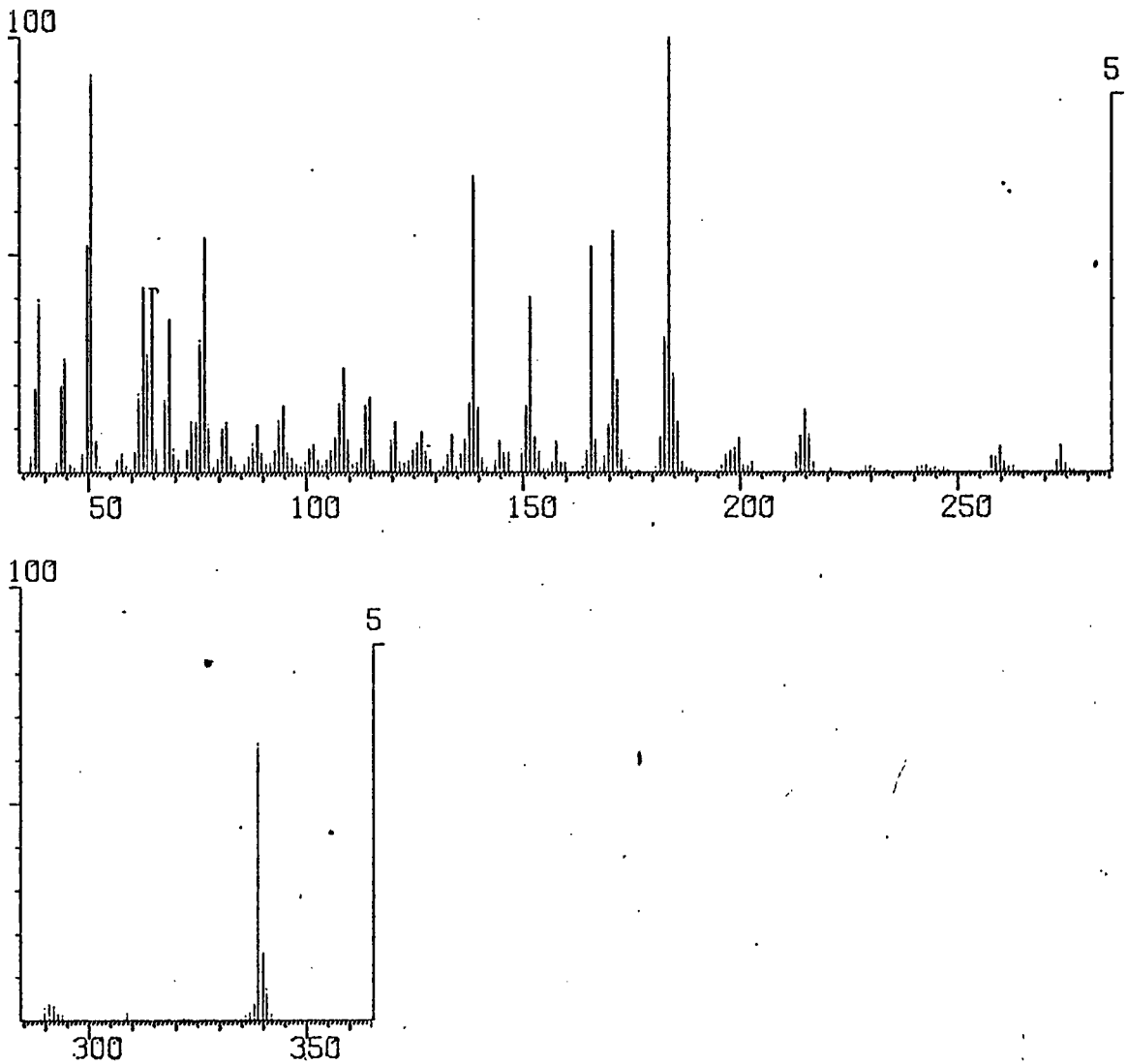


Figure 51. ^{1}H NMR Spectrum of 3,4-bis(thiophenyl)-1-nitrobenzene

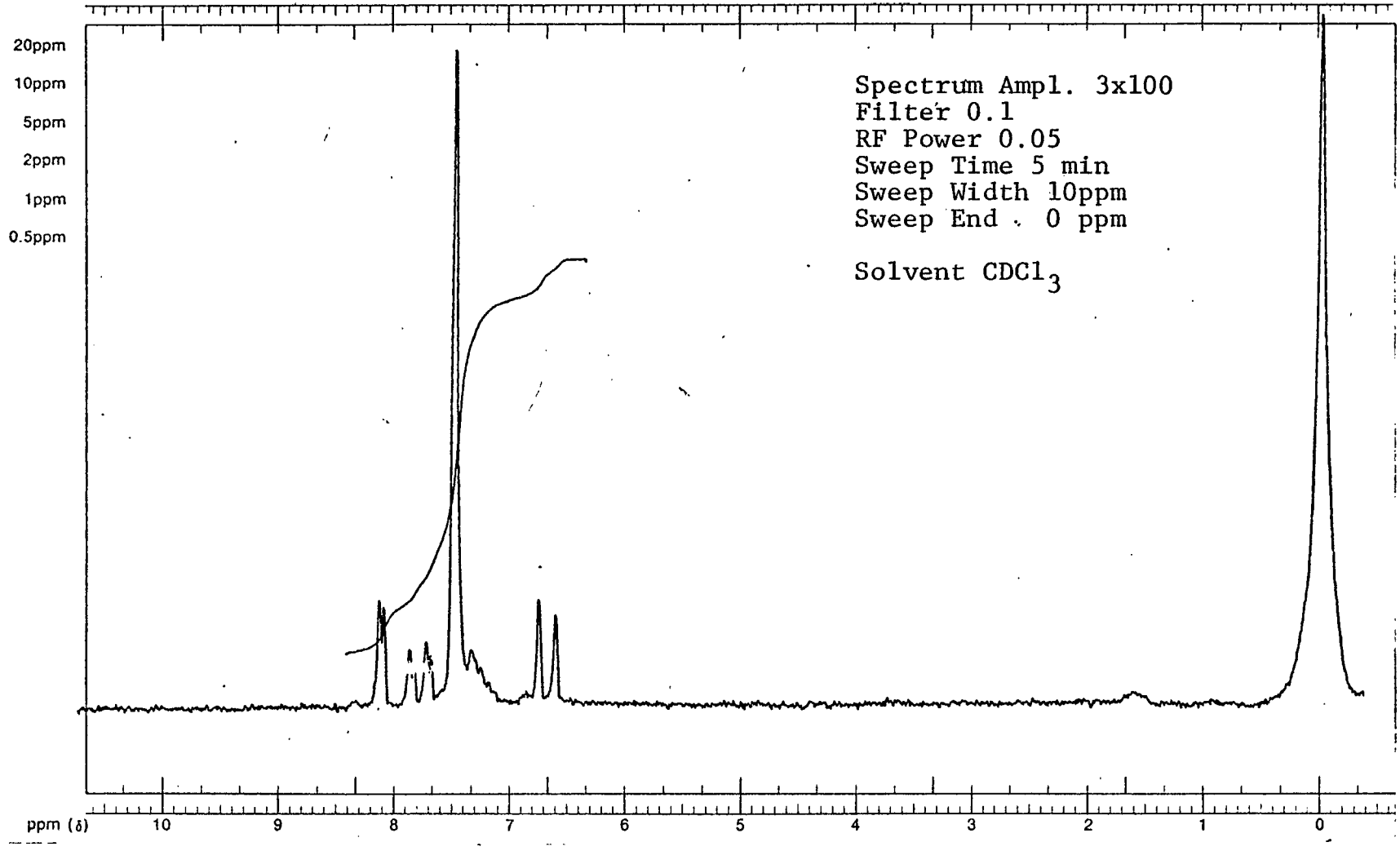


Figure 52. ^{13}C NMR Spectrum of 3,4-bis(thiophenyl)-1-nitrobenzene

Line	Freq. (Hz)	PPM
1	3728.58	148.195
2	3649.95	145.069
3	3409.37	135.507
4	3280.44	130.383
5	3276.40	130.222
6	3243.25	128.905
7	3176.20	126.240
8	3126.73	124.274
9	3062.09	121.704
10	1966.98	78.1789
11	1934.80	76.8999
12	1902.97	75.6348

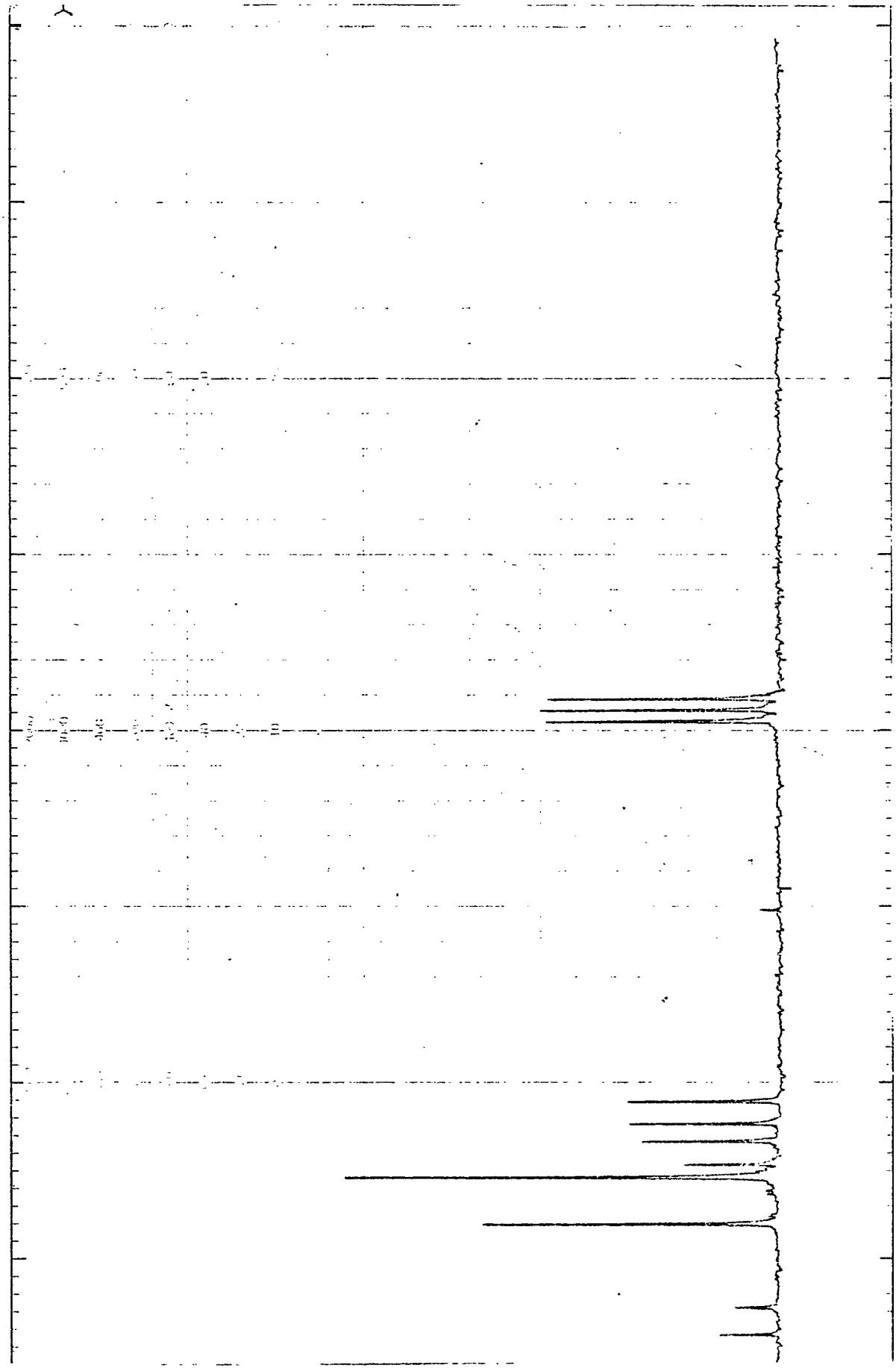


Figure 53. Infrared Spectrum of 3,4-bis(thiophenyl)-1-nitrobenzene

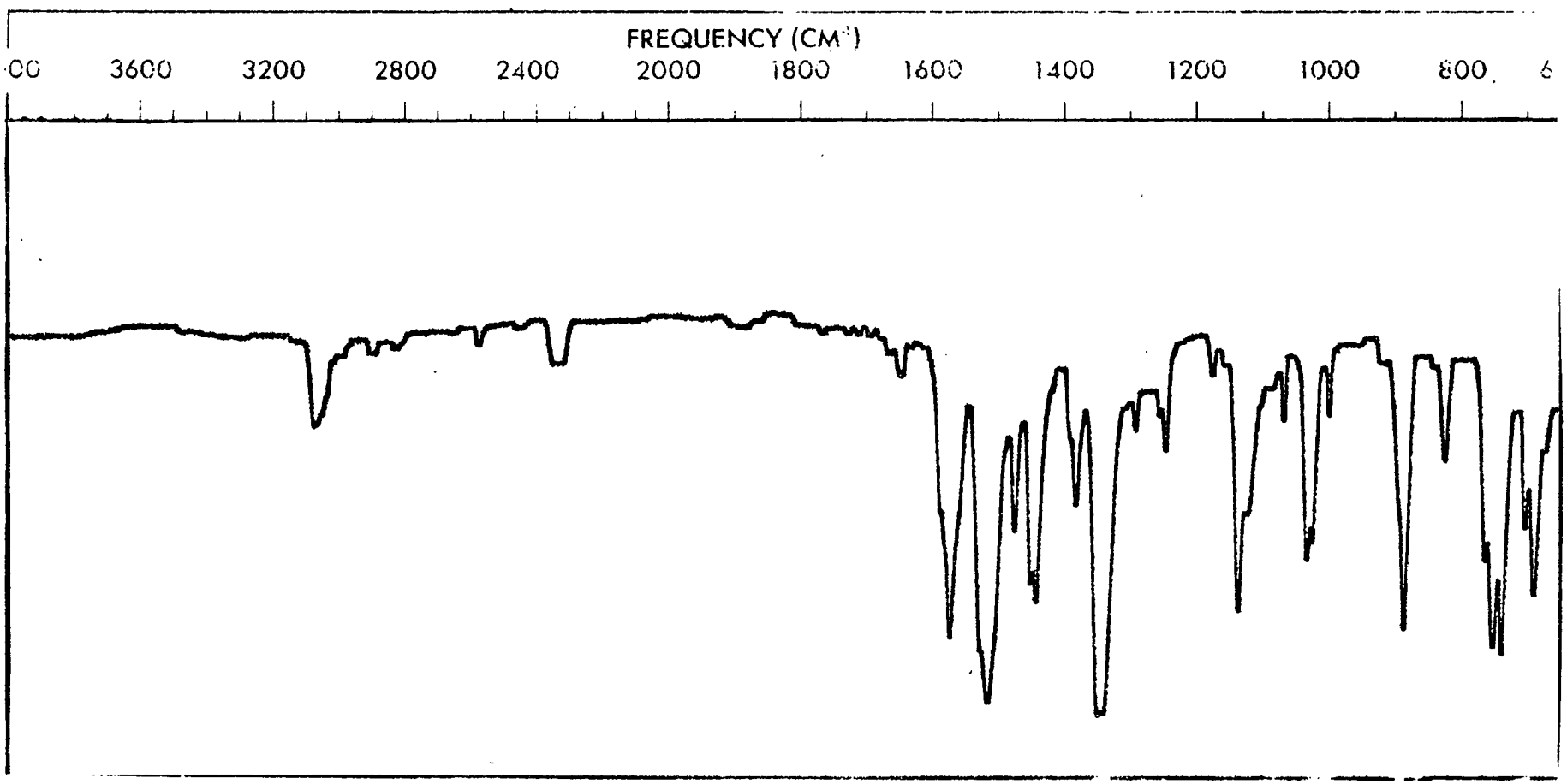


Figure 54. Mass Spectrum of 3,4-bis(thiophenyl)-1-nitrobenzene

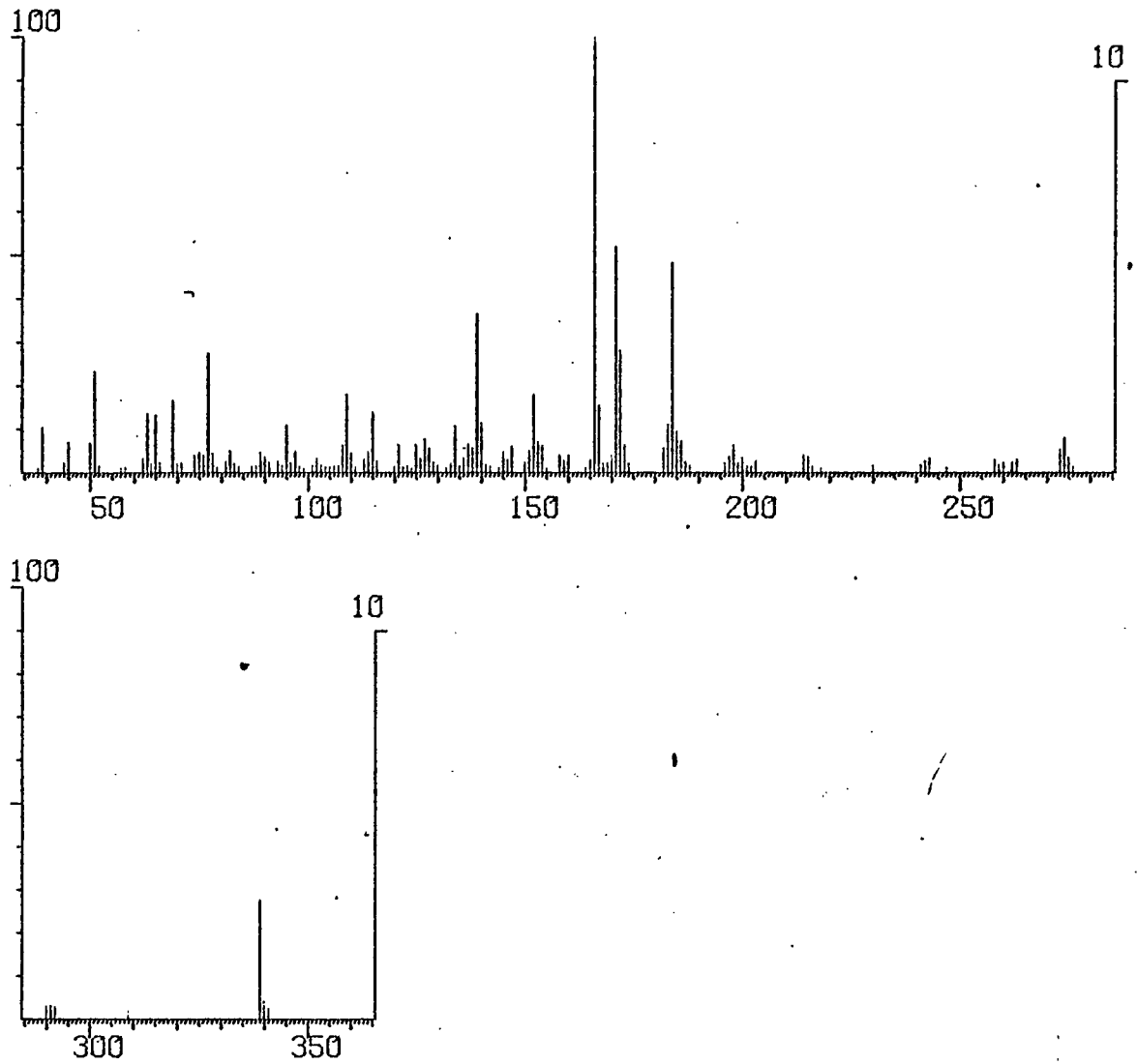


Figure 55. Infrared Spectrum of Trinitrobenzene

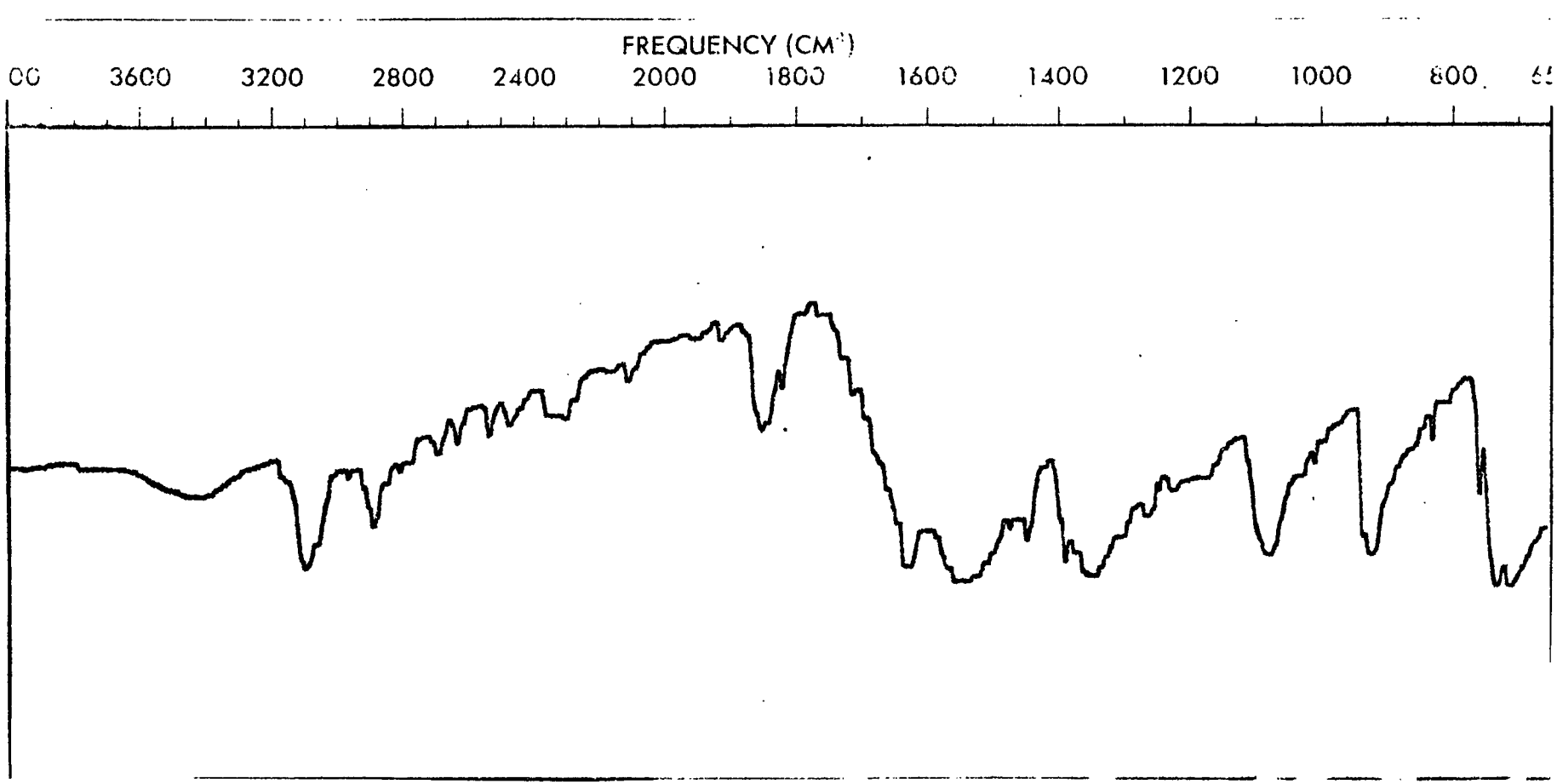


Figure 56. Mass Spectrum of Trinitrobenzene

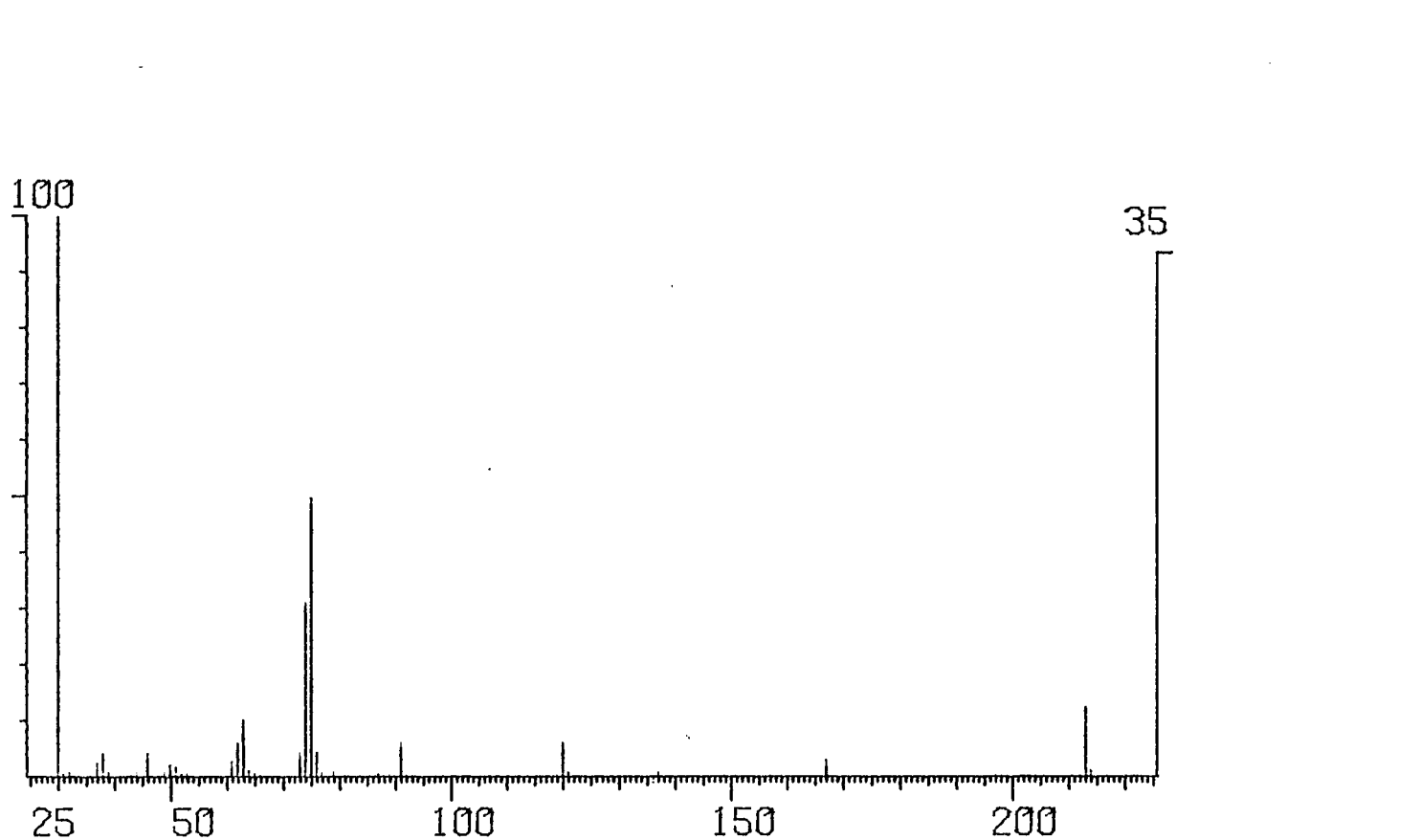


Figure 57. ^{1}H NMR Spectrum of 2-nitro-1,4-dichlorobenzene

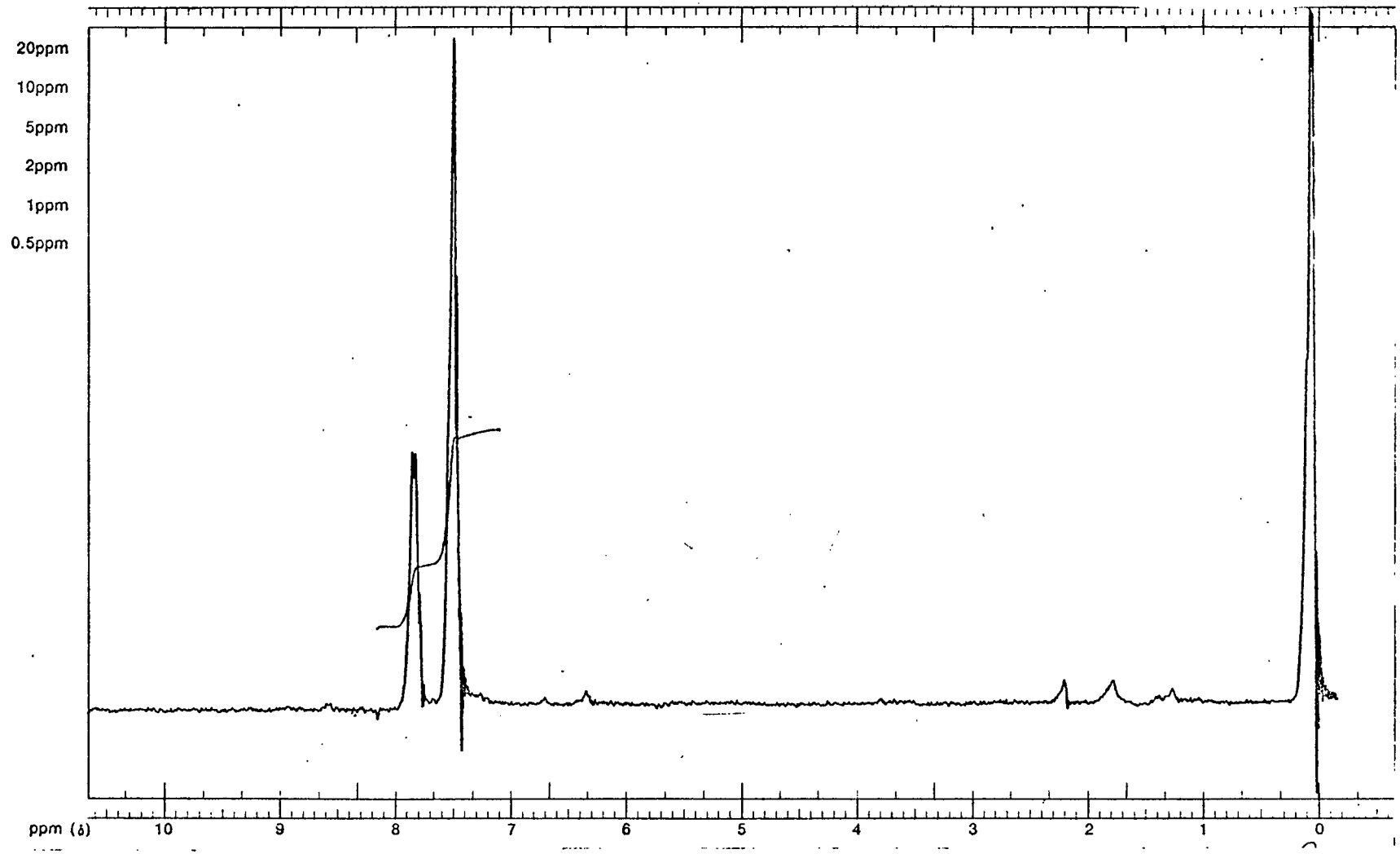


Figure 58. ^{13}C NMR Spectrum of 2-nitro-1,4-dichloro-benzene

Line	Freq. (Hz)	PPM
1	3717.06	147.737
2	3351.33	133.201
3	3347.68	133.055
4	3335.36	132.566
5	3152.42	125.295
6	3148.77	125.150
7	1967.02	78.1807
8	1934.80	76.8998
9	1902.92	75.6330

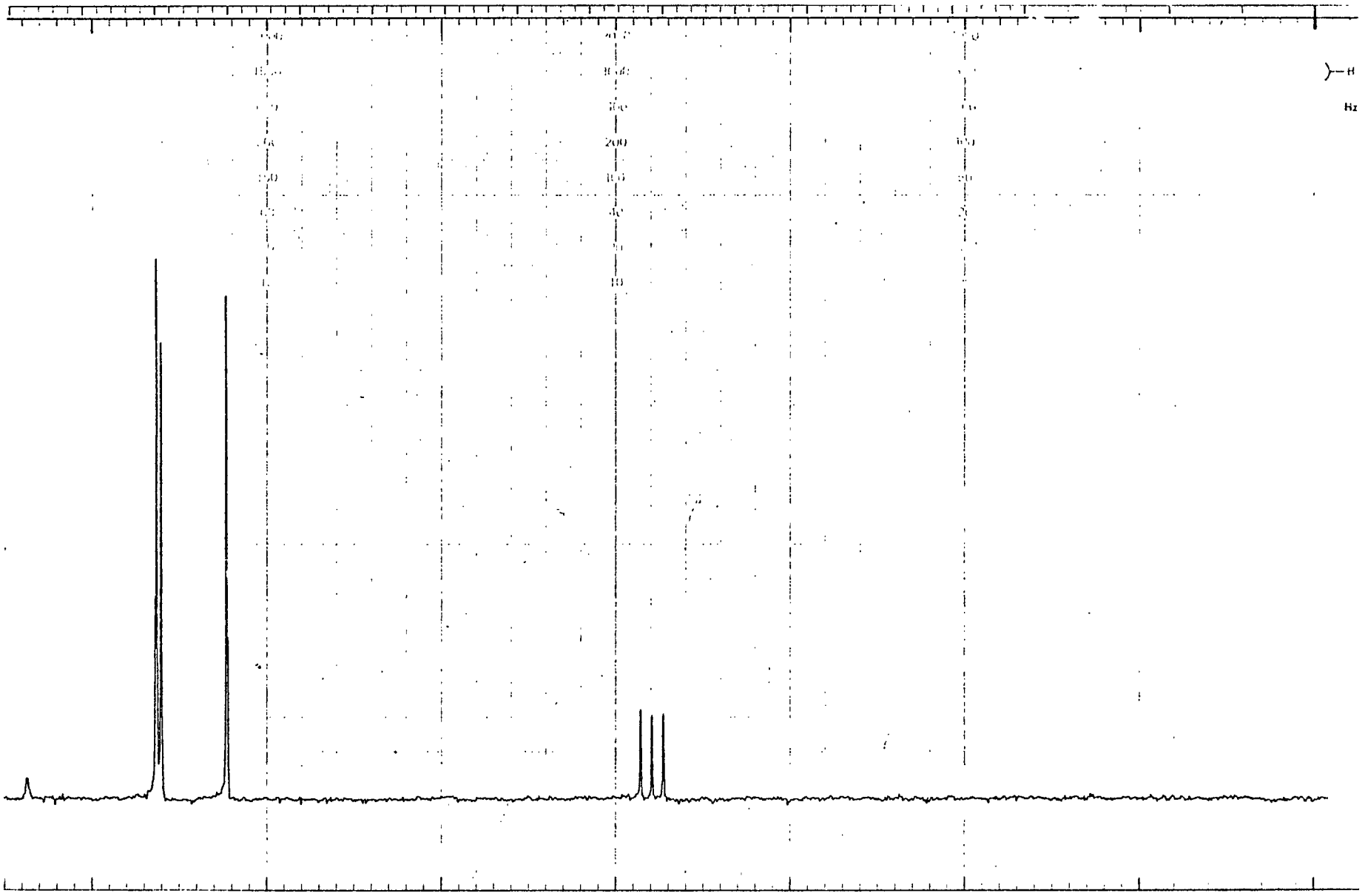

Hz

Figure 59. Infrared Spectrum of 2-nitro-1,4-dichlorobenzene

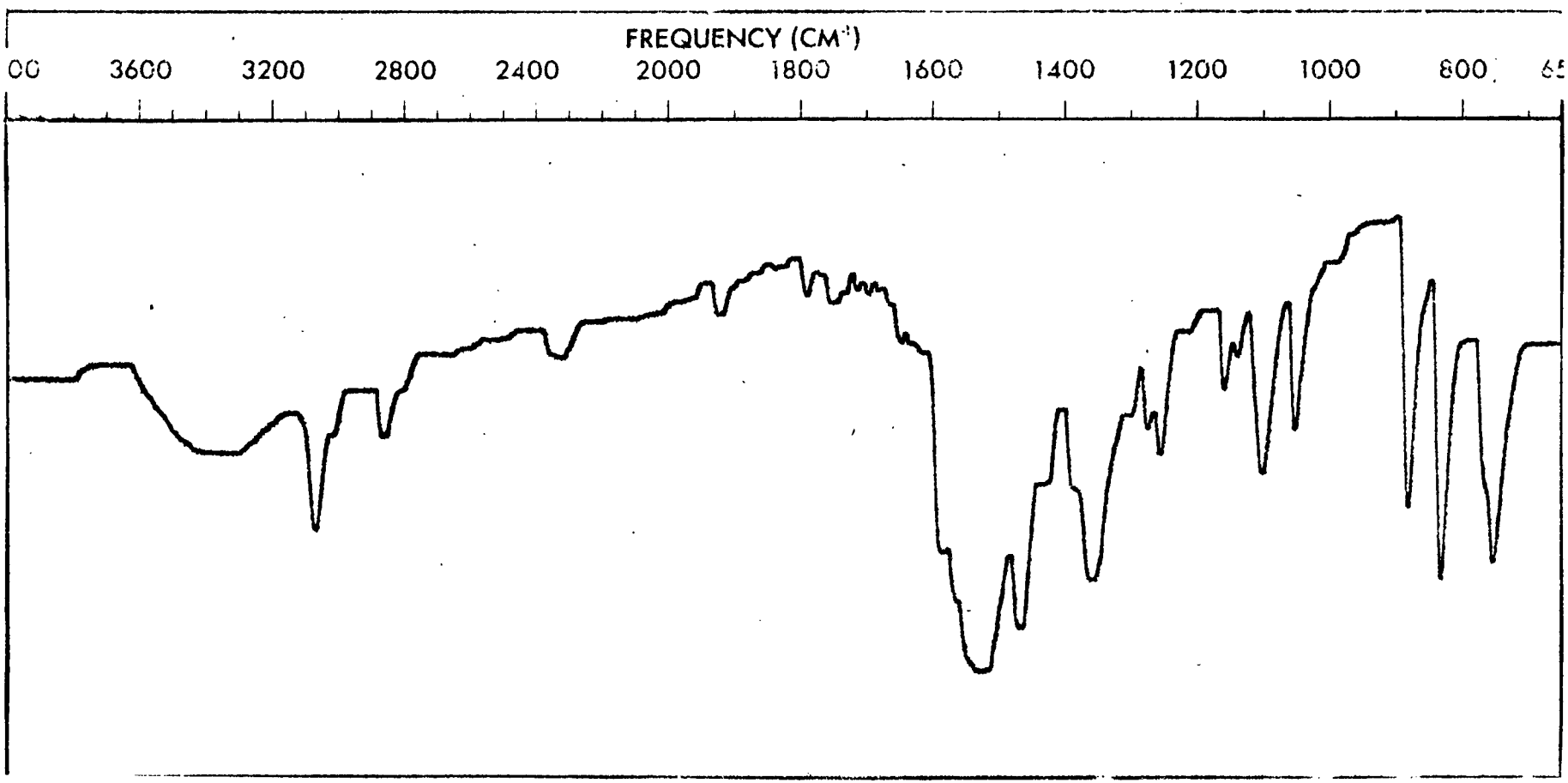


Figure 60. ^{1}H NMR Spectrum of 1,4-bis(thiophenyl)-2-nitrobenzene

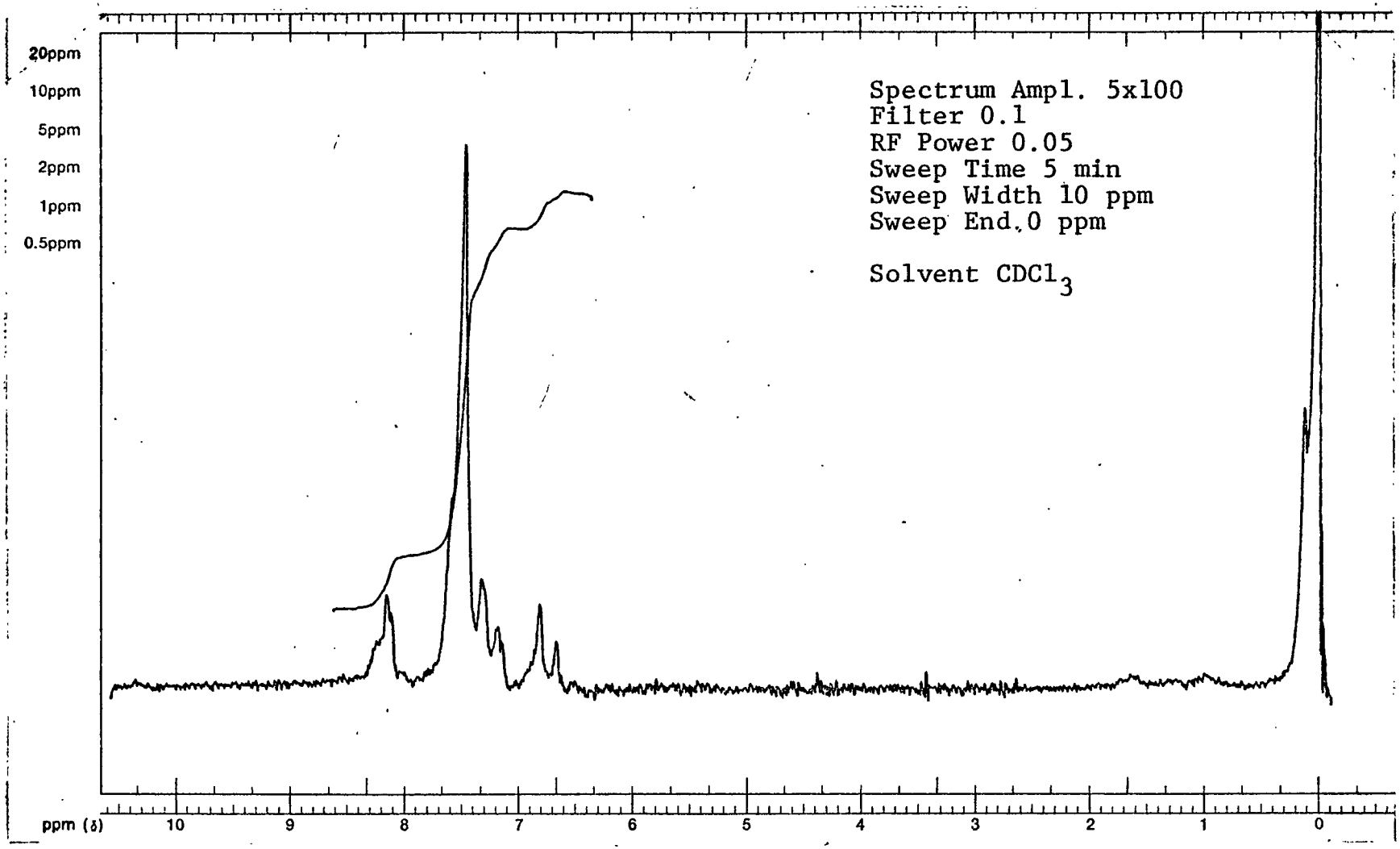


Figure 61. ^{13}C NMR Spectrum of 1,4-bis(thiophenyl)-2-nitrobenzene

Line	Freq. (Hz)	PPM
1	3649.35	145.045
2	3470.68	137.944
3	3413.23	135.661
4	3354.48	133.326
5	3351.04	133.189
6	3332.73	132.461
7	3286.73	130.633
8	3281.39	130.421
9	3273.54	130.109
10	3258.86	129.525
11	3255.06	129.374
12	3152.61	125.302
13	2509.90	99.7577
14	1980.57	78.7192
15	1973.37	78.4330
16	1966.62	78.1646
17	1943.33	77.2389
18	1941.62	77.1710
19	1934.80	76.8998
20	1902.65	75.6220

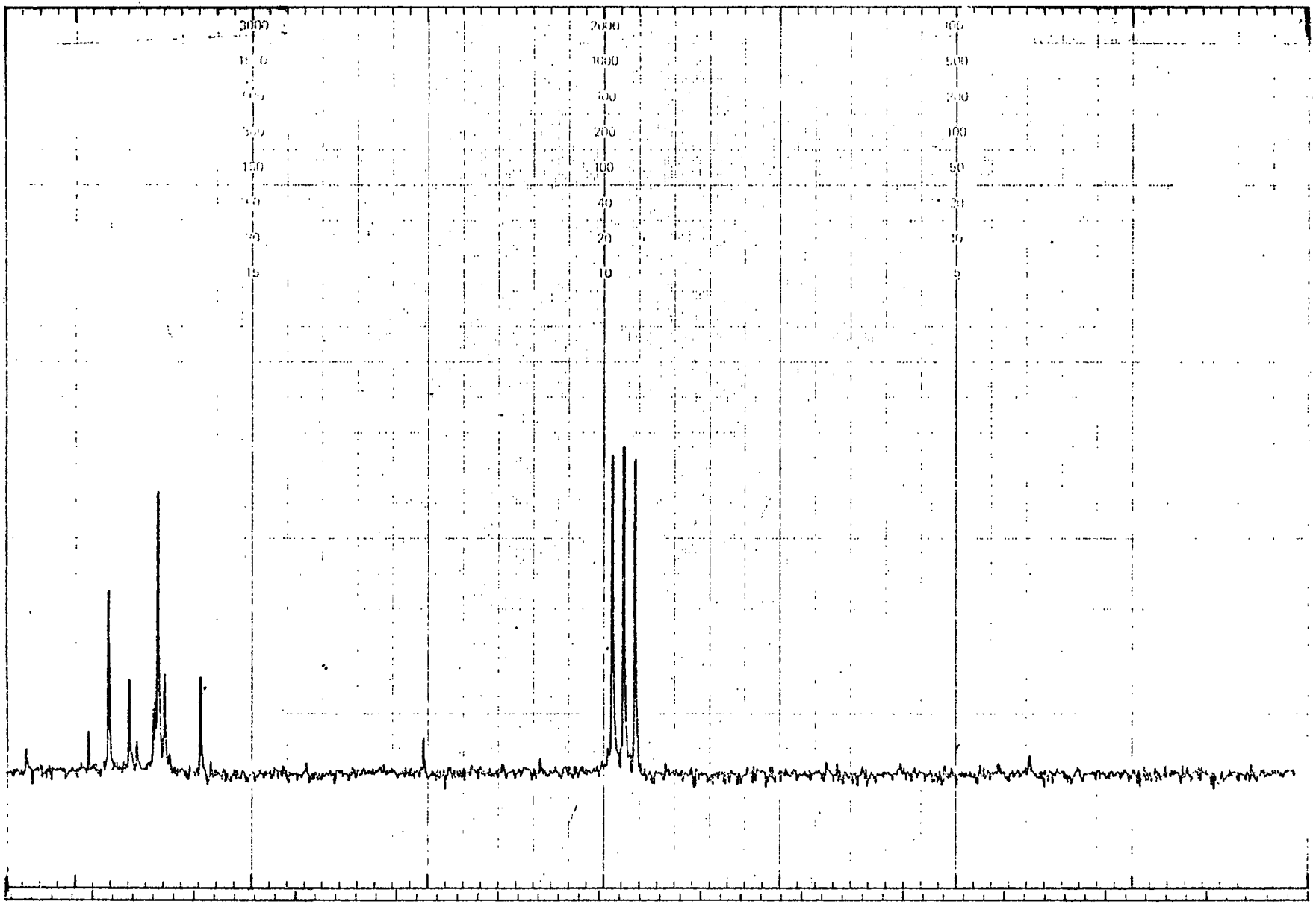

3000
2500
1000
500
200
100
100
50
40
20
20
10
10
5

Figure 62. Infrared Spectrum of 1,4-bis(thiophenyl)-2-nitrobenzene

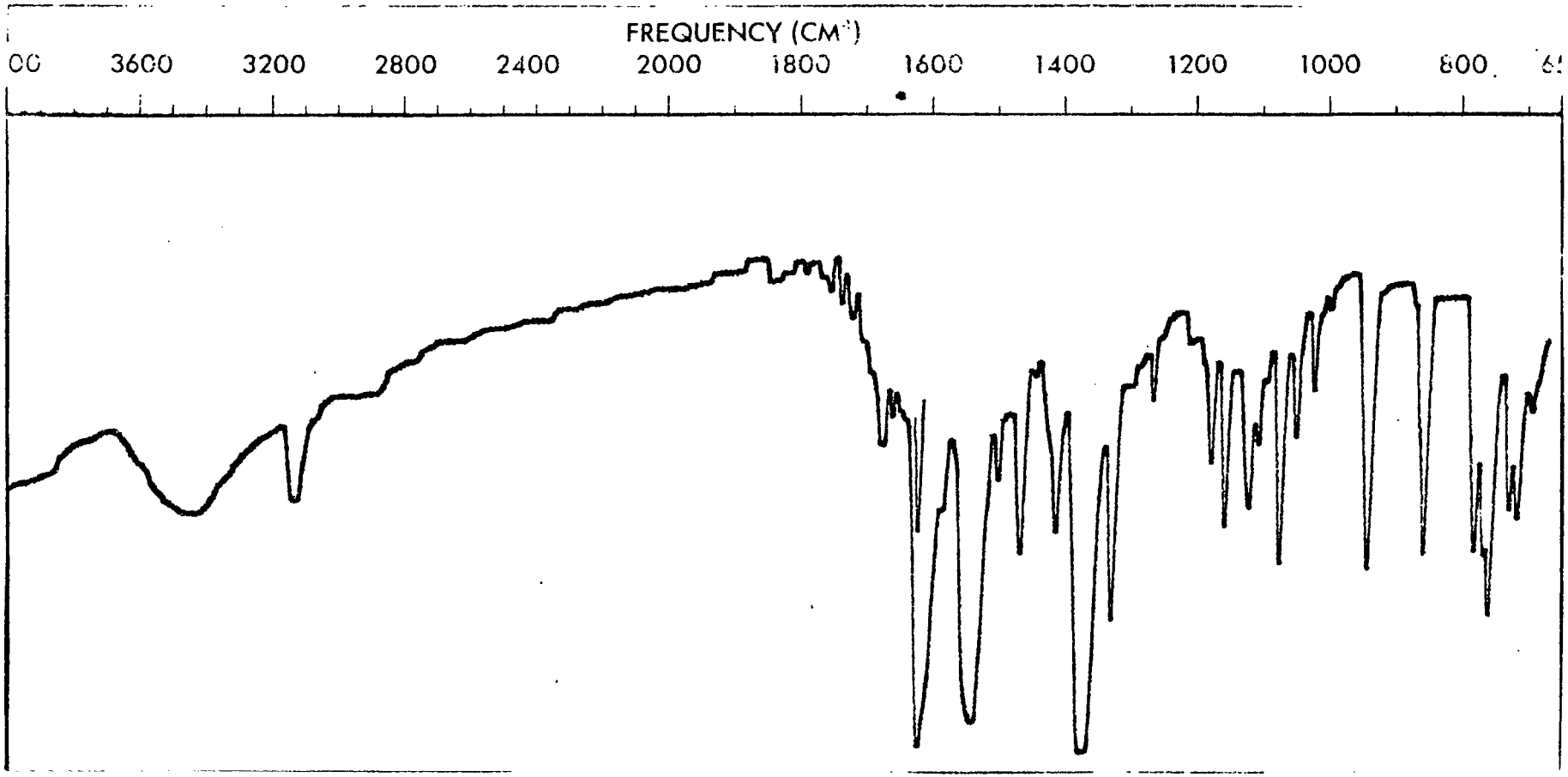


Figure 63. Mass Spectrum of 1,4-bis(thiophenyl)-2-nitrobenzene

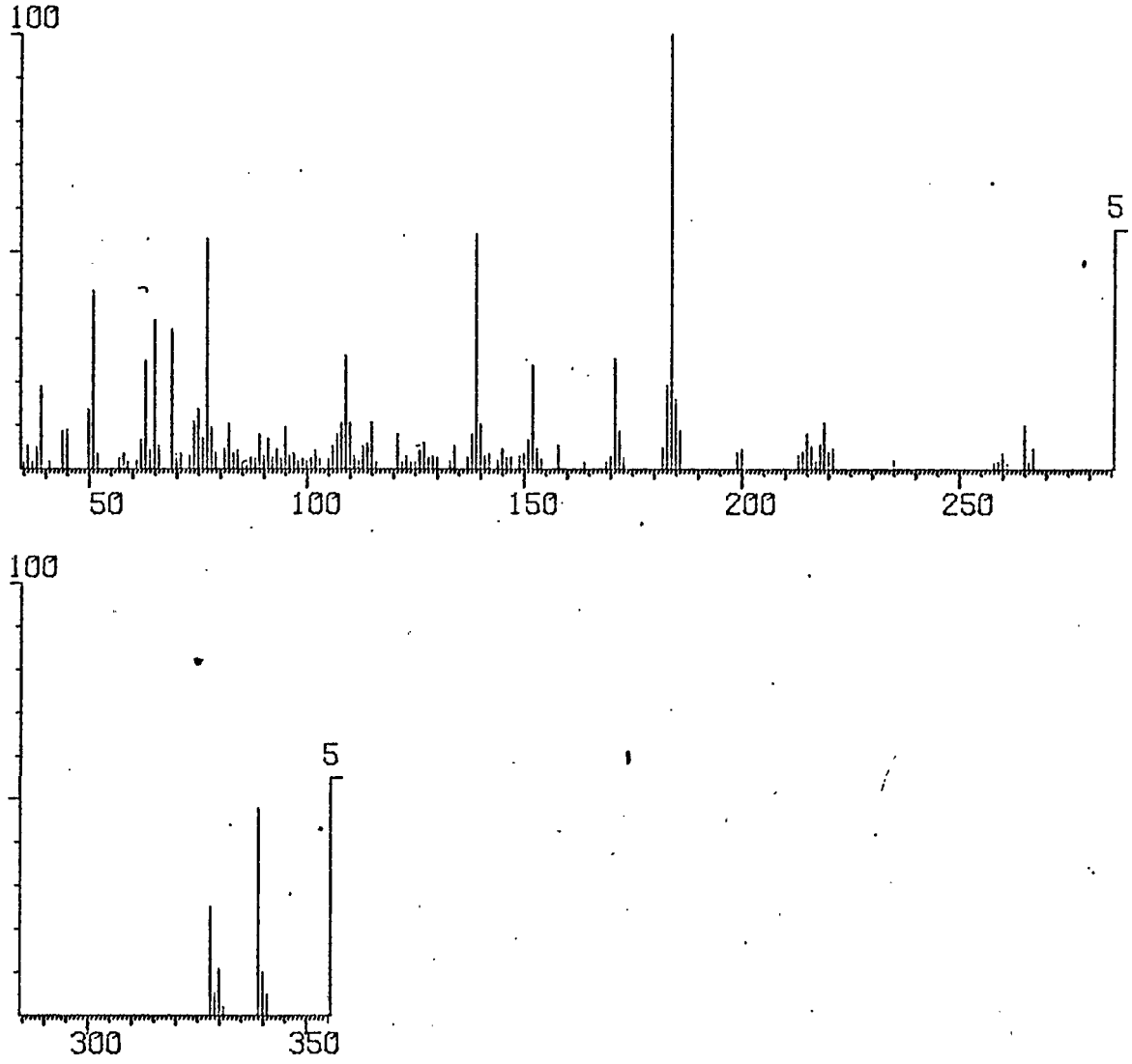


Figure 64. ^{1}H NMR Spectrum of 1,2-bis(thiophenyl)-4-aminobenzene

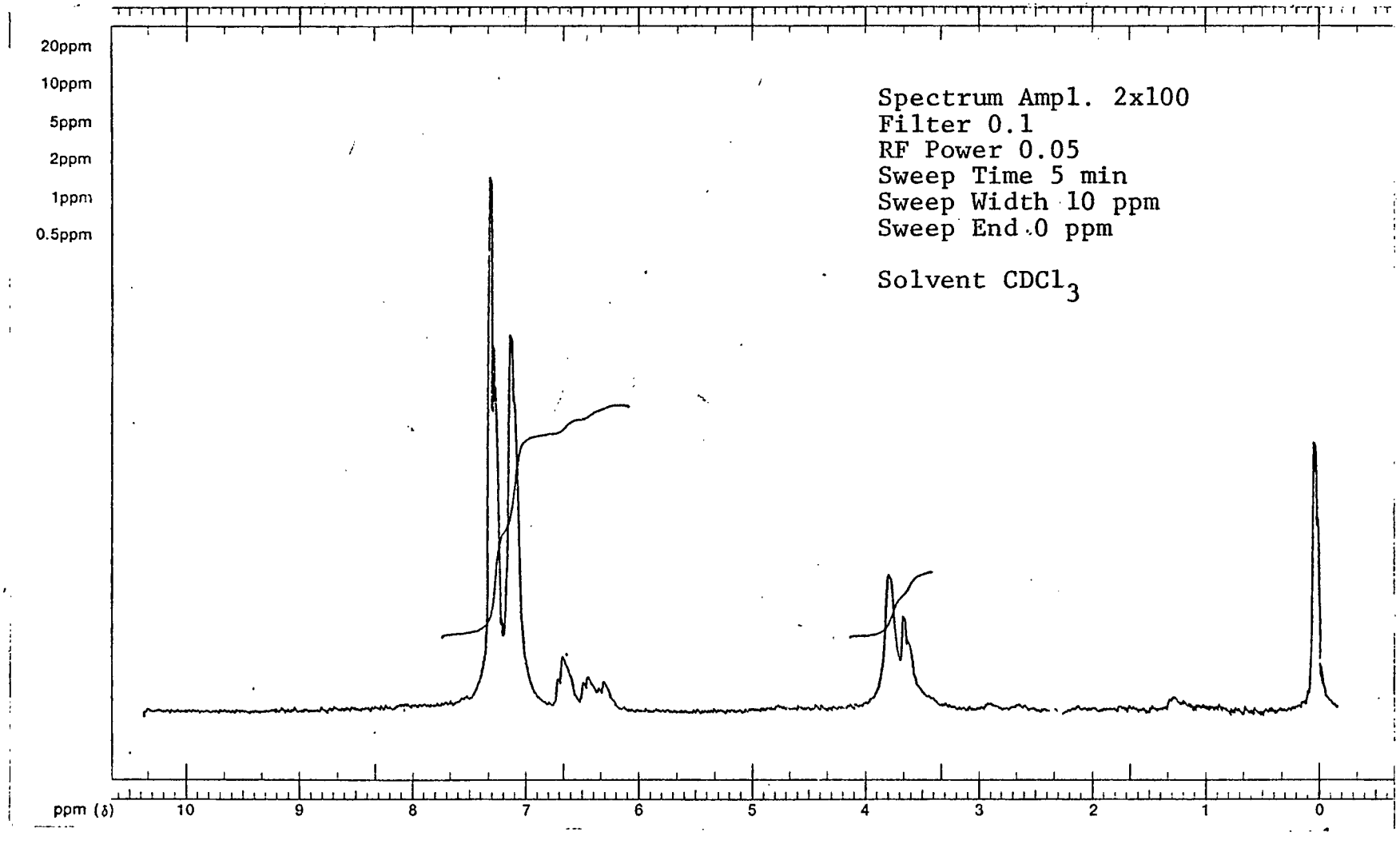


Figure 65. ^{13}C NMR Spectrum of 1,2-bis(thiophenyl)-4-aminobenzene

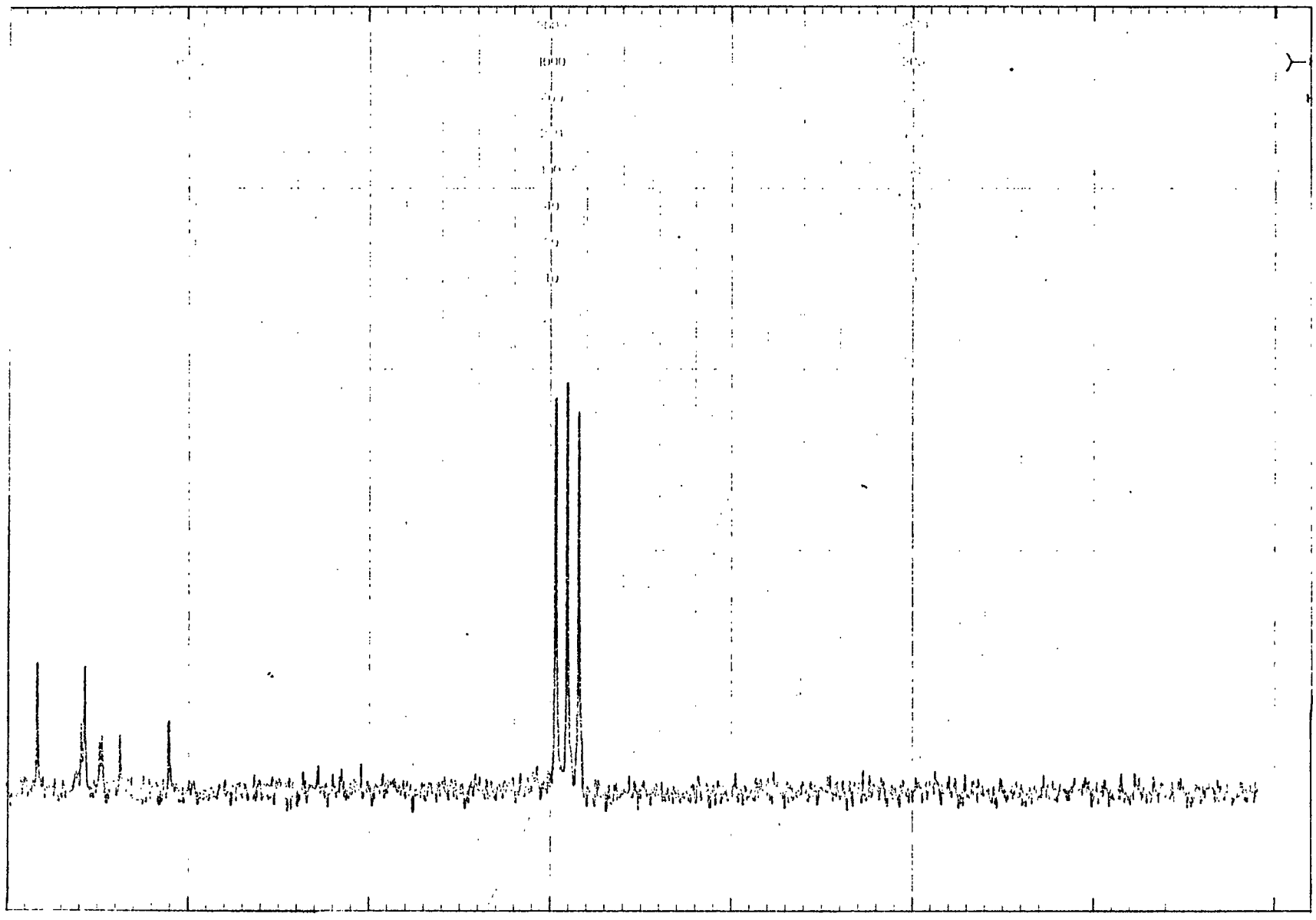
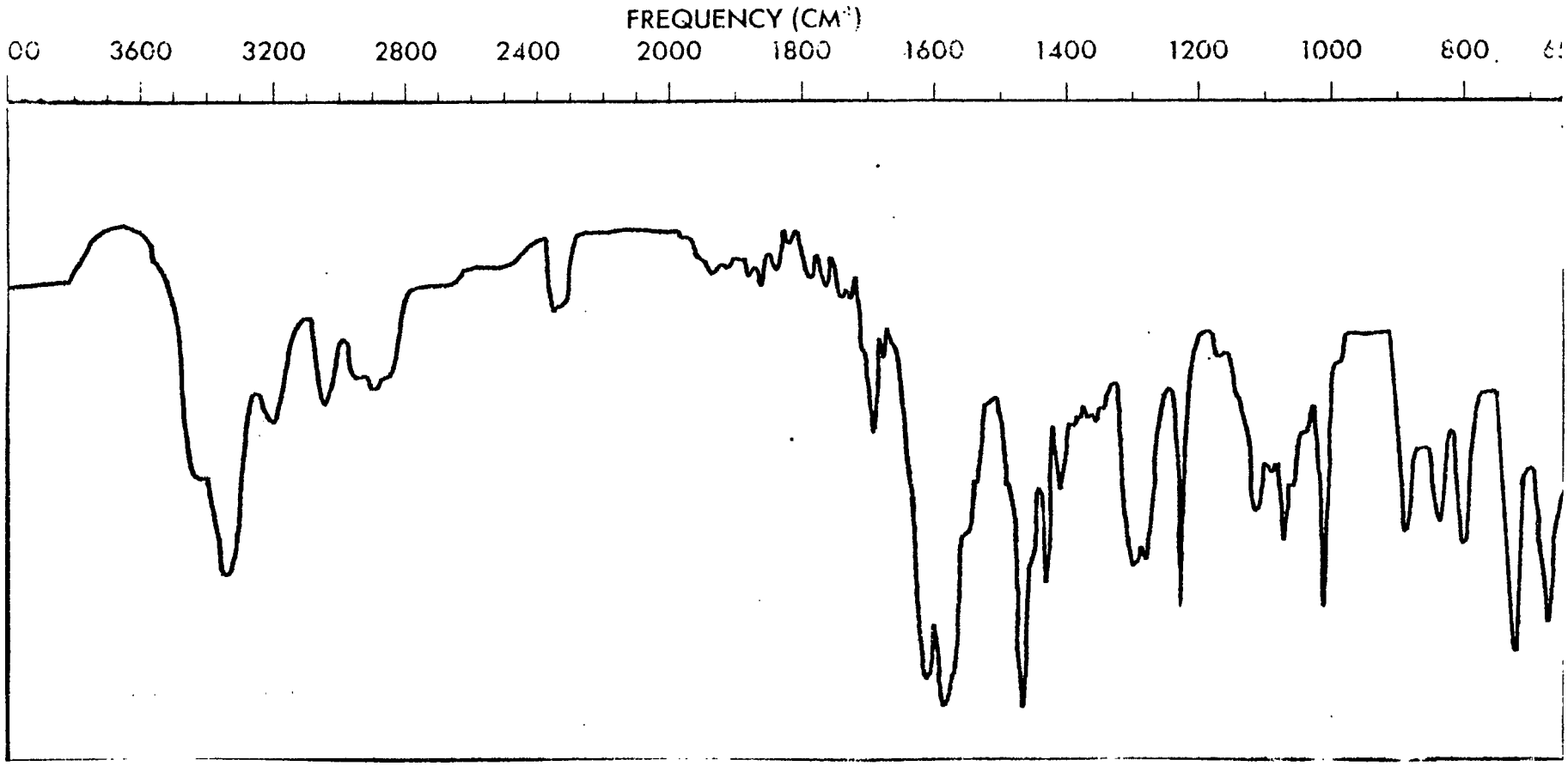


Figure 66. Infrared Spectrum of 1,2-bis(thiophenyl)-4-aminobenzene



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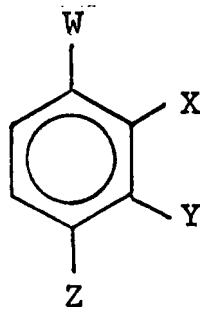
APPENDIX



SUBSTITUENT

W	X	Y	Z		1	2	3	4	5	6
Cl	NO_2	H	NO_2	Calc.	135.8	149.9	120.3	147.6	130.6	130.8
				Obs.	133.6	147.5	120.8	146.1	127.1*	133.1*
F	NO_2	H	NO_2	Calc.	164.4	136.6	120.4	145.0	131.0	117.5
				Obs.	158.5	136.6	121.8	143.3	130.7	119.7
Cl	NO_2	H	Cl	Calc.	128.1	150.3	125.5	133.8	136.1	131.2
				Obs.	125.5	147.7	125.3	133.2	133.1	132.6
NO_2	Cl	H	Cl	Calc.	147.1	131.3	130.3	141.9	128.0	126.4
				Obs.	145.9	128.0	131.3	138.9	127.7	126.4
NO_2	F	H	F	Calc.	131.2	160.0	103.7	170.6	112.1	126.6
				Obs.	134.0	156.4	106.2	165.5	111.9	128.0
NO_2	H	Cl	Cl	Calc.	148.0	125.5	136.1	141.0	131.2	123.2
				Obs.	146.5	125.3	133.7	139.6	130.9	122.4

* Unequivocable assignment not possible

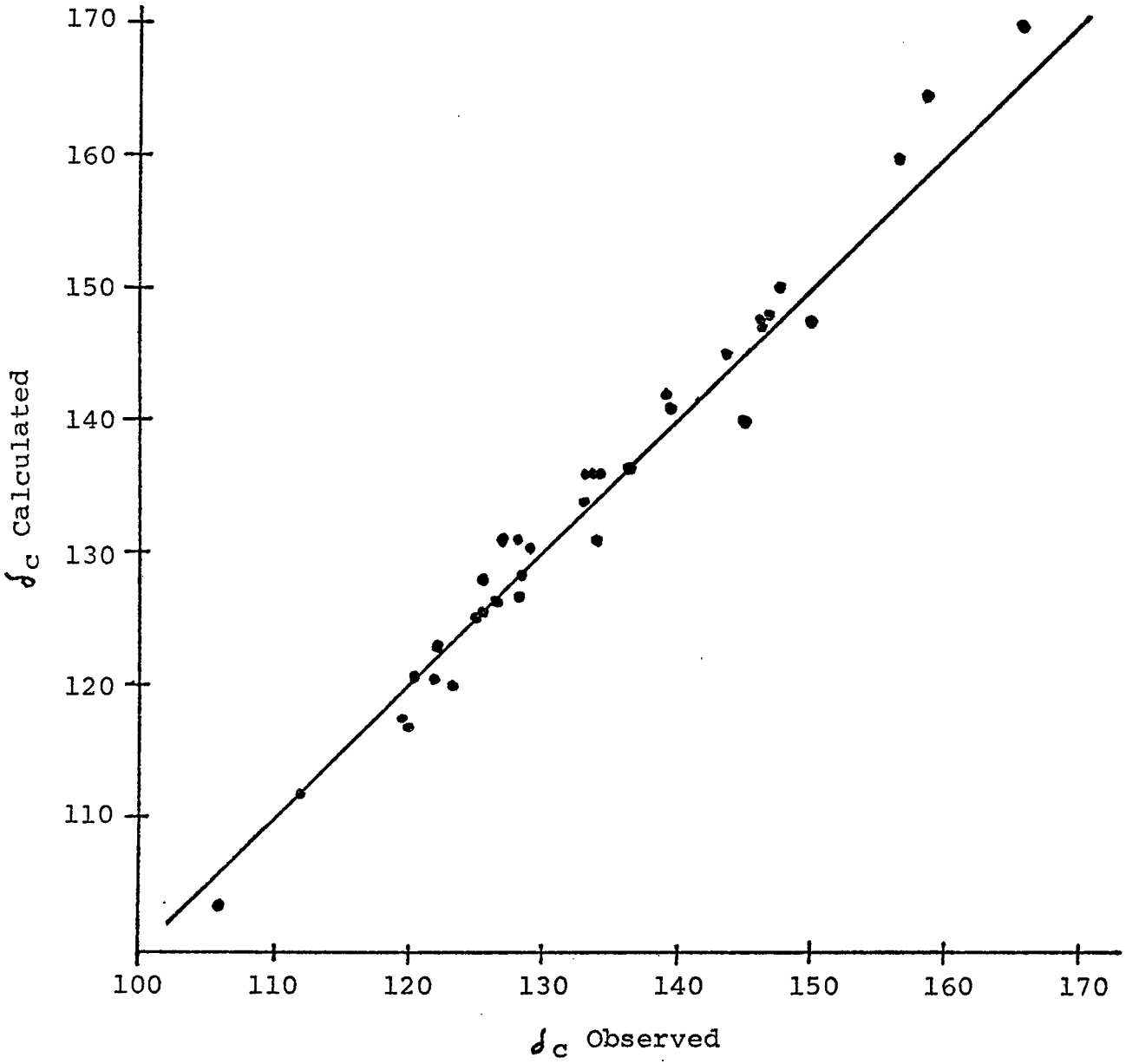

170
160
150
140
130
120
110
δ_c Calculated
100
110
120
130
140
150
160
170
δ_c Observed

Table of Crude Toxicity Data for
1,5-bis(thiophenyl)-2-nitrobenzene

Test Animal*	Dose (mg/kg in DMSD)	Survival** Time (Days)
1	500	0
2	250	0
3	125	0
4	75	0
5	50	14
6	25	2
7	Control	14

* All mice were tail-coded

** Sacrificed at the end of 14 days