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SYNTHESES OF THIENYLAMPHETAMINE DERIVATIVES
VIA
BORANE CHEMISTRY

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Ronald C. Marks

August 1988

To my Companion, Lover, and Life-friend -
our foundation is more precious than gold.
and to my precious daughter -
the inheritance of that foundation is yours.

This humble work is greatfully dedicated to you.

ACKNOWLEDGEMENTS

My thanks and gratitude belong to many, from professors to friends. Special thanks, though, must be expressed to a few:

First to my parents; thank-you for the continued encouragement from the earliest days. I love you.

Dr. Mark Goodman; thank-you for allowing me to use your ideas. Thank-you for your careful, thoughtful guidance and selfless concern, and for assistance in radioiodination synthesis.

Dr. Laila Guindi; for your special friendship and the excellent violin concerts, for the first aid to my ego, and for freely giving of your knowledge of thiophene.

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Chuck, Betty, and Amanda Anderson; for your empathy and friendship.

To the remainder of the "Group"; for your concern and friendship.

Dr. George Kabalka; for graciously providing a laboratory and guidance. Thank-you for allowing me to also use your ideas, for your assistance in radioiodination, and freely supplying financical support.

A-1

ABSTRACT

Single Photon Emission Computed Tomography (SPECT) is a medical imaging technique which provides three dimensional images of living systems after infusion of radiolabeled chemical compounds. Iodine-123 labeled N-isopropyl *p*-iodoamphetamine (IMP) has been evaluated in humans as an imaging agent for use with SPECT and shows a high brain uptake coupled with slow washout. The current synthesis of IMP has limitations which include an inefficient labeling exchange reaction and the presence of high concentrations of unlabeled material in the final product. The substitution of thiophene for the benzene ring in the amphetamine could provide a more straightforward approach to halogenated amphetamines due to the greater reactivity of heterocycles to electrophilic ring substitutions with halogens.

Iodine-131 labeled N-isopropyl 2-(2-aminopropyl)-5-iodothiophene was prepared via borane chemistry for studies as a potential substitute for the labeled N-isopropyl *p*-iodoamphetamine. [illegible]

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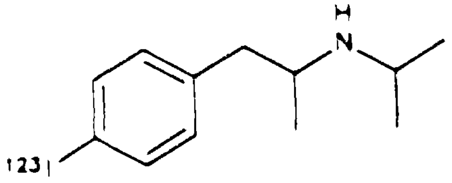
CHAPTER I

INTRODUCTION

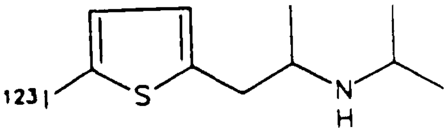
A. CLINICAL [illegible]

Medical imaging techniques provide today's health care provider with diagnostic information that was unavailable until recently. As a special branch of medicine, nuclear medicine has developed diagnostic tools that provide information on physiological processes unobtainable by any other means. Nuclear medicine imaging techniques are distinguished from radiographic and computed tomographic procedures by the use of radionuclides which emit radiation from radiopharmaceuticals previously administered to the patient.[1]

Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) are two nuclear imaging techniques that have recently become accepted as diagnostic tools. N-isopropyl p-iodoamphetamine (IA-1), labeled with iodine-123, has been approved for use in humans as a radiopharmaceutical for use with SPECT. It has been used in clinical studies of stroke, epilepsy, and dementia.[2,3,4]



IA-1



IA-2

Previous syntheses of N-isopropyl p-iodoamphetamine (IMP) have failed to prove adaptable to routine clinical use, preventing the widespread use of the compound for brain imaging. These syntheses generally required preparation of a halogenated precursor which was then labeled by isotopic exchange. Work by Mathis *et al.*[5] and Kabalka *et al.*[6] show that iodometallation occurs at low temperatures with high radiochemical yield. The high reactivity of thiophene and halogenated thiophenes in metallation reactions compared to benzene make thiophene an attractive substitute for the benzene ring in IMP. We propose to develop an analogue of IMP using thiophene (IA-2) to synthesize a new imaging agent that may be valuable for clinical use.

B. BACKGROUND

Emission Computed Tomography

Medical imaging may be classified into two broad catagories based on the source of radiated energy. In radiography and computed tomography (CT), the target is bombarded from an external x-ray source, with the target absorbing some of the radiation. The transmitted radiation is then reconstructed into an image or collected onto film for diagnosis. An external transmitter is also used in sonography (ultrasound). In contrast, nuclear imaging techniques use emitted radiation from radiopharmaceuticals that originate from within a body to produce an image. The two techniques provided substantially different information to the medical technologist. While radiography excels in providing structural and anatomic information due to its superior spatial resolution, nuclear medicine imaging provides detailed information on physiological function. The use of organ- or system-specific radiopharmaceuticals in nuclear medicine imaging provides information concerning blood flow, metabolism, and other physiological functions.[1]

Although a detailed discussion of nuclear imaging theory is beyond the scope of this thesis, a basic statement of PET and SPECT theory is essential in understanding the incentives and requirements in the development of new imaging agents. Common to both PET and SPECT, and at the foundation of nuclear imaging, is the phenomenon of nuclear instability. It is known that for a given element only certain neutron to proton ratios will result in stable nuclei. If the ratio is above or below the "stable" ratio, the nucleus is classified as unstable or radioactive. Two types of instability are recognized based on the path followed to regain stability: dynamic, which leads to alpha-decay and fission; and beta, which leads to beta-decay and electron capture. Alpha-decay is characterized by the breaking-up of the nucleus into two distinct fractions, while beta-decay is characterized by a spontaneous change of the nucleus without fragmentation. As most isotopes used in nuclear imaging are limited to those which decay via beta-decay, we will limit our discussion to beta type radiation.

Beta-decay occurs via two routes depending on the neutron to proton ratio. If the ratio lies above that classified as stable, decay occurs by a neutron transforming to a proton with emission of an electron (sometimes referred to as negatron emission):

$$n \longrightarrow p + e^- + \nu$$

where n, p, e^-, and ν stand for neutron, proton, electron, and neutrino respectively.[7] Conversely, if the neutron to proton ratio lies below that considered stable, increasing the neutron to proton ratio occurs in one of two ways. The first involves the emission of a positron, e^+, (the second form of beta-decay), while in the second, electron capture occurs:

$$p \longrightarrow n + e^+ + v$$

$$p + e^- \longrightarrow n + v$$

The captured electron, most often from the 1s orbital, leaves an empty orbital which is filled by an electron from a higher energy level. The orbital change is accompanied by release of a photon of energy. PET imaging takes advantage of positron emission, while SPECT utilizes photons emitted via electron capture.

The positron emitted via beta-decay travels a very short distance (in about 10^{-10} seconds) before encountering an electron. The positron and electron undergo annihilation with subsequent creation of two photons, each having energy of 0.511 MeV. These two photons travel at an angle of $180^\circ \pm 0.3^\circ$.[8] These photons are "counted" by two detectors arranged in a parallel plane. The photons must reach both detectors within a specified window of time to be classified as occurring from a single annihilation, and thus subject to mathematical reconstruction to produce an image.

The single photon emitted via electron capture is similarly detected, but by a single detector with no time relationship between photon emission.[9]

Radiopharmaceuticals Used in Emission Computed Tomography

The development of radiopharmaceuticals for emission computed tomography (ECT) of the brain is an active area of research. Initial attempts at nuclear imaging utilized radionuclides attached to carrier molecules with little retention in the brain. Experiments were then conducted on radiopharmaceuticals that crossed an intact blood-brain barrier, showing that this crossing was proportional to blood flow.[illegible]

Three classes of compounds have emerged after extensive development for use in ECT. Amines are the most diverse class due to the broad range of compounds that are either intermediates in the biosynthesis of neurotransmitters or are themselves neurotransmitters.[10] The central role of amines in the function of the brain allows for observation of normal and pathological brain states, such as schizophrenia and manic-depressive psychoses, as manifestations of abnormal amine metabolism or kinetics.[11] Other brain imaging agents include radiolabeled deoxyglucose, water, and gases such as oxygen, carbon monoxide, and carbon dioxide.

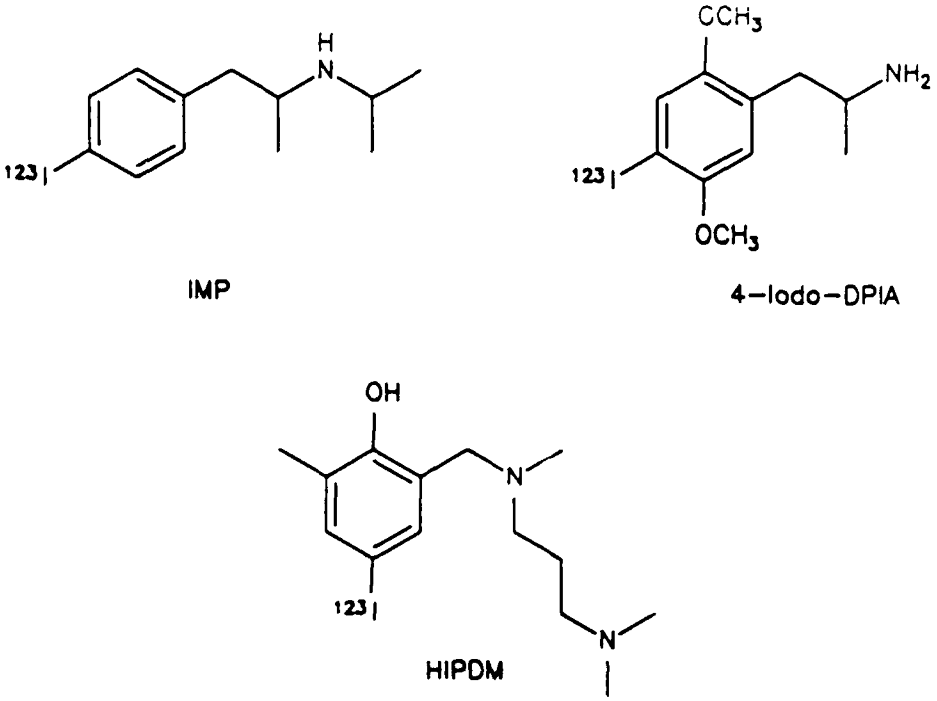
The metabolic or physiologic activity of the carrier molecule is thought to be the same as for a corresponding non-labelled counterpart,[12] allowing for introduction of radiolabels into a wide variety of compounds. Positron emitters such as ^{11}C, ^{13}N, and ^{15}O have been incorporated directly into the naturally occurring molecules. Examples include dopamine, norepinephrine, and numerous amino acids with ^{11}C and ^{13}N labels; oxy- and carboxyhemoglobin, water, carbon monoxide and carbon dioxide labelled with ^{15}O. Other radionuclides used clinically include ^{18}F labelled deoxyglucose, ethanol, and spiroperidol, and ^{68}Gd complexed with ligands such as ethylenediaminetetraaceticacid.[13]

Amines have been evaluated with the radiolabel introduced into the molecular backbone via synthesis utilizing an isotope of nitrogen or carbon, and with labelling introduced as a radionuclide substituent. To date, most agents have been labeled with single-photon emitters. The emphasis on using labeled amines stems from their ability to cross the blood brain barrier allowing for use in diagnosing disease that exhibit altered amine metabolism

Radioiodinated Amines

The first radiohalogen-labeled compound that exhibited reasonably long retention in the normal human brain was synthesized and evaluated by Sargent, et al.[14] The agent, 4-bromo-2,5-dimethoxyphenylisopropylamine (4-Br-DPIA), was labeled with ^{77}Br and ^{82}Br This work was followed up by the synthesis of 4-I-DPIA using ^{131}I, which was proposed as a useful brain imaging agent due to its first pass extraction from blood to brain in monkeys.[15] Additional research lead to the development of many radiolabeled amines. Winchell, et al.,[11] synthesized and studied forty iodophenylalkylamines labeled with ^{123}I in attempt to develop labeled amines that would be useful for brain studies. The study encompassed derivatives of aniline, benzylamines, and phenylethylamines. Their work showed that, for ring-iodinated phenylalkylamines, brain uptake, retention, and blood-to-brain ratios are greatest when the alkyl group is alpha-methylated, and N-alkylated with a single lipophilic group such as an isopropyl group. α-Methyl-N-(1-methylethyl)-benzeneethaneamine (N-isopropyl amphetamine) meets all three of these conditions.

There are currently three iodo-amino compounds which predominate research of nuclear imaging; N-isopropyl p-iodoamphetamine (IMP), 4-iodo-2,5-dimethoxyphenylisopropylamine (4-I-DPIA), and N,N,N'-trimethyl-N'-(2-hydroxy-3-methyl-5-iodobenzyl)1,3-propanediamine (HIPDM) (Figure I.B.1). Holman, et al.,[16] compared iodine-123 IMP with iodine-123 HIPDM noting that both compounds produce similar tomographic images. For long term imaging, they rated iodine-123 IMP as superior due to its higher brain uptake.



IMP

4–Iodo–DPIA

HIPDM

Figure I.B.1

Radioiodinated Amines Used for Medical Imaging

CHAPTER II

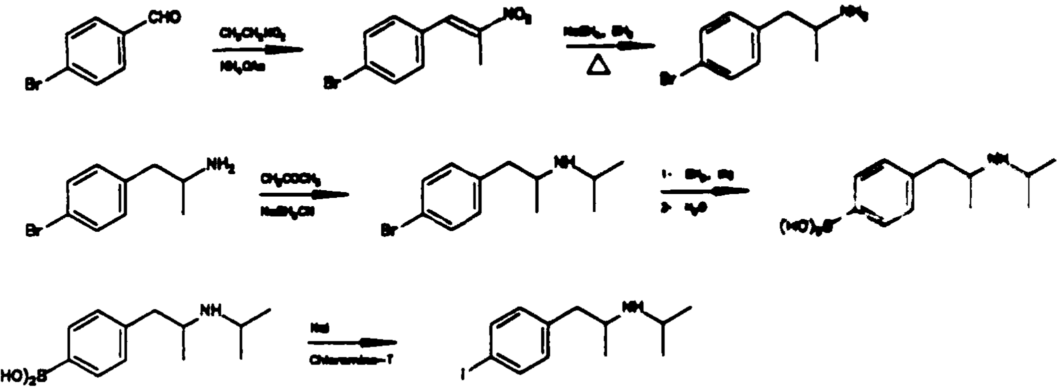
APPROACH TO THE STUDY

A. PREVIOUS SYNTHETIC WORK ON N-ISOPROPYL p-IODOAMPHETAMINE

Following the identification of N-isopropyl p-iodoamphetamine (IMP) as a primary candidate for emission computed tomography applications by Winchell, et al.,[11] new synthetic methods were developed for IMP. Carlsen and Andresen[17] reported a new synthetic method for IMP in 1982. Phenylacetic acid was first iodinated with sodium nitrate/iodine in sulfuric acid and acetic acid. The resulting p-iodophenylacetic acid was converted to p-iodophenylpropanone by acetylation followed by decarboxylation. A modified Leukart Reaction was then used to form the IMP.

The ability to radioiodinate the aromatic ring and obtain a sufficiently high yield of radioactive material remained a synthetic barrier. Decomposition of triazine precursors[18] and halogen exchange[19] both resulted in formation of chemically similar byproducts which diluted the amount of the desired radiolabeled compound produced.

To overcome this loss of product purity, a more efficient means of radioiodinating the aromatic ring was required. Kabalka, et al.,[20] expanded on their previous work in the synthesis of arylboronic acids to overcome this barrier TO ring iodination. They synthesized IMP through an entirely different chemical approach[6] (equation II-1). Beginning with the base catalyzed condensation of p-bromobenzaldehyde with nitroethane they produced p-bromo-β,β-methylnitrostyrene. Reduction of this styrene with borane gave the amphetamine which was used in a reductive amination reaction with acetone to yield the N-isopropyl p-bromoamphetamine. Sonication in the presence of magnesium metal and borane complex gave the



II-1

p-boronic acid. A transmetallation reaction was then used to obtain IMP. They reported that only trace quantities (less than four percent) of other iodinated organic products were formed.

B. THIOPHENE ANALOGUE

Preparation of a thiophene analogue to a known metabolite provides additional pathways into research of biological activity as well as chemical reactivity. Thiophene analogues of known metabolites are reasonably expected to intensify, mimic, or oppose the biological effect of the metabolite depending on the analogue's affinity for the receptor site and its intrinsic activity.[21] It was the similarity of physical properties of thiophene and benzene, and the occurrence of thiophene in benzene prepared from coal tar that lead to consideration of thiophene as an analogue of benzene. Replacement of thiophene for benzene in serological reactions led to studies on the bioisosteric relationship of the two compounds. Drug analogue studies in which benzene was replaced by thiophene became commonplace.[22] One of the earliest of these studies was the comparison of phenylethylamine with 2-thienylethylamine. Although the isologue showed vasopressor activity in the cat, it was only one-tenth as potent.[23] Alles and Feigen[24] followed with an analysis of thienyl- and furyl-analogues of amphetamine. They found no discernable difference in the drug effect in dogs and on isolated rabbit intestinal strips. The thienylamphetamine was found to be less toxic in mice, but when administered to humans, amphetamine showed much more central nervous system stimulation and circulatory stimulation.

The aromatic (or heteroaromatic) nature of thiophene is a well established phenomena. Resonance consideration of thiophene may be represented by the structures shown in Figure II.B.1. Analysis of these structures indicates that thiophene should have a dipole moment in the direction of the heteroatom, in contrast to benzene, which does not possess a dipole. Thiophene's dipole has been measured as 0.52 debye; 1.35 debye less than the corresponding non-aromatic analogue, tetrahydrothiophene.[25] This may be due to the contribution of s and d orbitals to the resonance energy.[26]

Resonance structures have also been useful in predicting the reactivity of different positions on thiophene to electrophilic attack. By considering the Wheland intermediates, attack at the 2-position yields three resonance structures while attack at the 3-position gives only

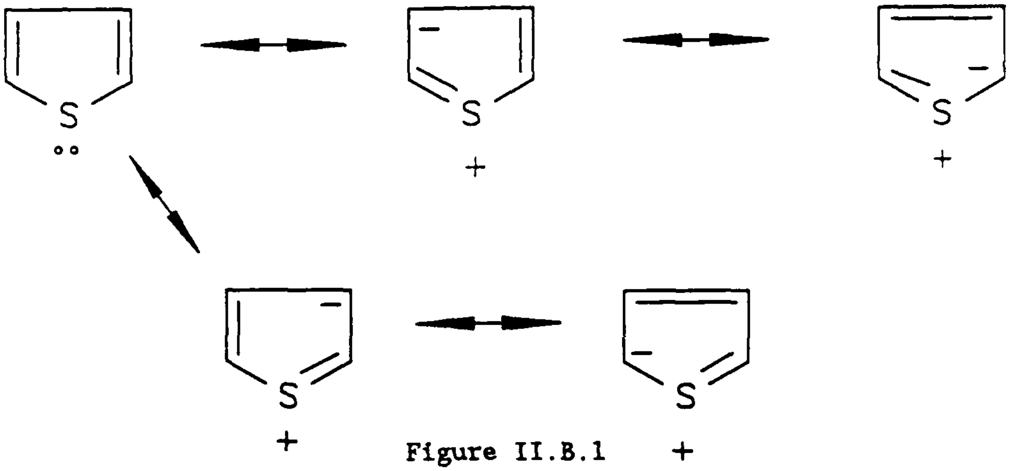


Figure II.B.1

Resonance Structures of Thiophene

two (Figure II.B.2). The 2-position is known to be the more reactive, and substitution takes place much more easily than in benzene. A measure of the ratio of rates of nitration between the two analogues has been reported as 850:1.[27]

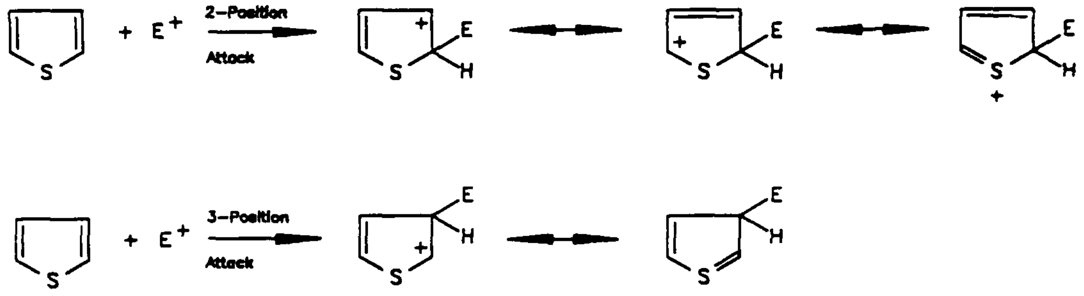


Figure II.B.2

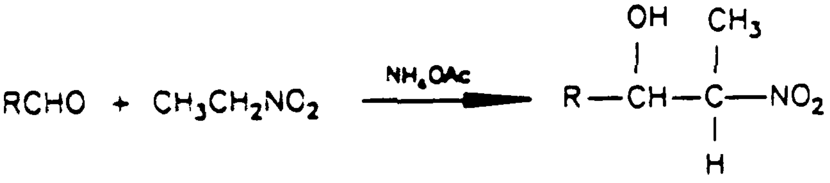
Wheland Intermediates of Electrophilic Attack on Thiophene

C. BACKGROUND

Synthesis of the thienyl analogue of IMP could theoretically be accomplished via the IMP synthesis using thienyl analogues of the chemical precursors. The following synthetic steps were used: nitroalkane condensation, reduction of the resulting nitroalkene with borane, reductive amination of a ketone to give the N-alkyl compound, formation of the boronic acid, and a transmetallation reaction with iodine to yield the final product.

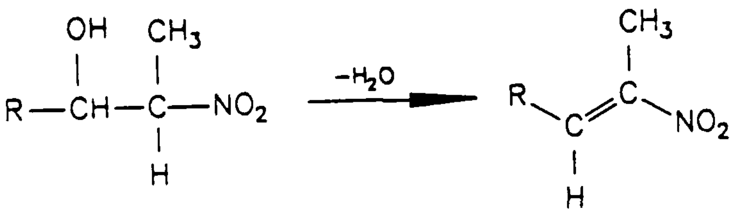
Nitroalkane Condensation

The condensation of aldehydes with nitroethane is a reaction closely related to the aldol condensation. When nitroalkyl compounds are used in this condensation, the reaction is sometimes referred to as the Henry reaction or nitroaldol condensation.[28] Like the aldol condensation, a carbanion attacks the carbonyl group, resulting in a nitroalkanol intermediate (equation II-2). Nitroethane readily deprotonates in the presence of a strong base to form the nitronate carbanion[29]. The aldol condensation, in contrast, forms the carbanion by loss of an α-hydrogen. Elimination of water from the nitroalkanol allows for formation of the nitroalkene (equation II-3).



$$RCHO + CH_3CH_2NO_2 \xrightarrow{NH_4OAc} R{-}CH(OH){-}C(CH_3)(H){-}NO_2$$

II-2



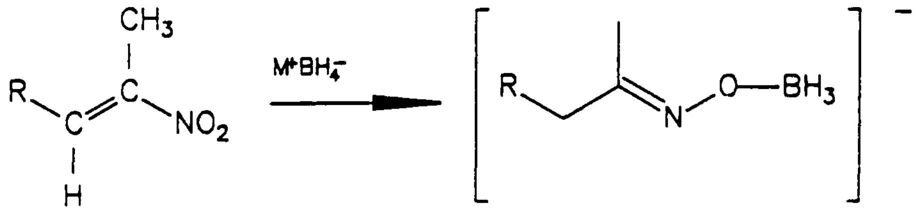
II-3

Reduction With Borane

Reduction of conjugated nitroalkenes to the corresponding alkylamines has been accomplished using lithium aluminum hydride. The use of the aluminum hydride resulted in reports of mixtures of products with modest yields.[30,31] Mourad et al.[31] reported the reduction of nitro compounds with boron hydrides. They noted that the work of Shechter et al.[32] showed that using sodium borohydride to reduce α,β-unsaturated nitroalkenes would produce the corresponding nitroalkane, and also that nitro salts are reduced by borane complexes to the hydroxylamine. Mourad postulated that both reactions proceed through a common nitronate intermediate. Hydroxylamines were then prepared by reducing conjugated nitroalkenes with borane complexes.

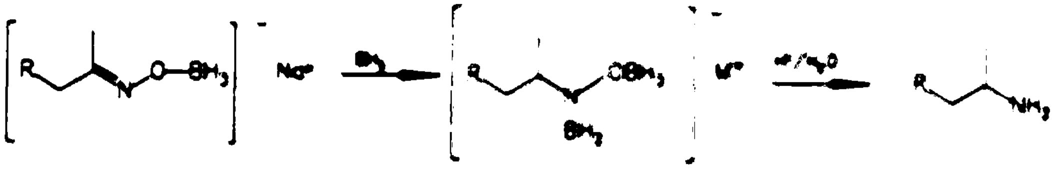
This opened the door for direct synthesis of amines from conjugated nitroalkenes. Feuer and Braunstein[33] had previously demonstrated that hydroxylamines may be reduced with borane at elevated temperatures to produce amines. Mourad et al.[31] reported the reduction of α,β-unsaturated nitroalkenes to alkylamines in borane-tetrahydrofuran is catalyzed by sodium borohydride at room temperature.

An acinitro salt of a nitroalkene is formed using a metal borohydride (equation II-4). Borane-tetrahydrofuran complex will then reduce the



II-4

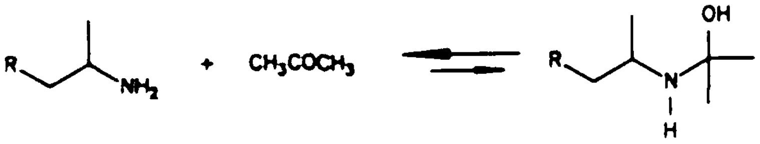
salt to the corresponding borinic ester. After acid catalyzed hydrolysis, the amine is obtained (equation II-5). This reaction was also utilized to prepare the hydroxylamine under similar [illegible] shorter reaction times.[14]



II-5

Reductive Amination

Amines may be N-alkylated via reductive amination of a ketone. Borch, Bernstein, and Durst[15] studied the reducing chemistry of sodium cyanoborohydride and determined that it reduced a wide variety of compounds selectively. They note that the cyanoborohydride reduction of ketones is pH dependent, being negligible at neutral pH. Although the reaction is unfavorable, formation of the imminium moiety (equation II-6) is optimized at pH=6, where reduction with the cyanoborohydride (equation II-7) is rapid. Kabalka et al.[6] applied this discovery to N-alkylate amphetamine.



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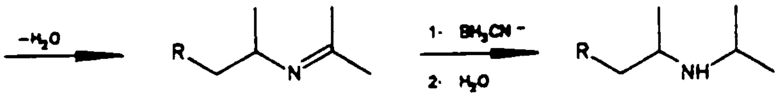


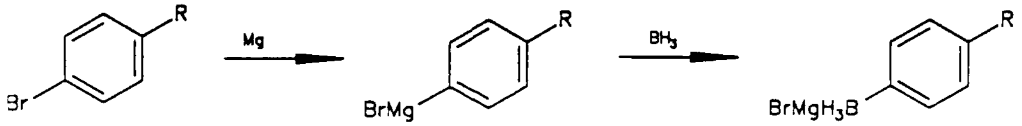
II-7

Borch and co-workers used an excess of amine to prevent formation of the tertiary amine.

Preparation of the Boronic Acid

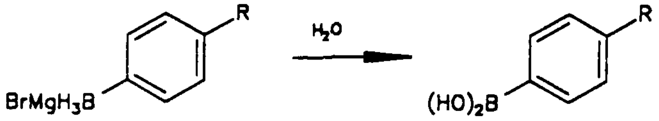
The first preparation of organoboron compounds was reported by Frankland in 1862,[36] who isolated ethaneboronic acid by hydrolysis of its diethyl ester. Other investigations into the properties and synthesis of boron compounds followed. It was inevitable that the Grignard reagent would be used in the synthesis of boronic acids, and this was done by Khotinsky and Melamed in 1909.[37] They used the Grignard reagent on alkyl esters of boric acid. Snyder, Kuck, and Johnson[38] built upon the work of both Frankland and Khotinsky and Melamed to study the reactivities of aliphatic boronic acids. An externally prepared Grignard reagent was used on alkyl borates followed by acid hydrolysis to yield the crude boronic acid. They noted that anhydrous boronic acids are subject to autooxidation in air, and the presence of water inhibits the autooxidation. The autooxidation yields the boron oxides of the formula R-BO, which exists as trimers.

Ainley and Challenger[39], along with Johnson and co-workers[40], detailed the properties and synthesis of aromatic boronic acids. Both research groups used the externally prepared Grignard reagent to synthesis the boron compounds. Their results showed that aromatic boronic acids react with aqueous metallic salts to cleave the carbon-boron bond, and also with hydrogen peroxide and bromine water. Kabalka *et al*.[41] reacted borane complexes with arylmagnesium halides in a single-pot synthesis to produce the corresponding arylborohydrides (equation II-8).



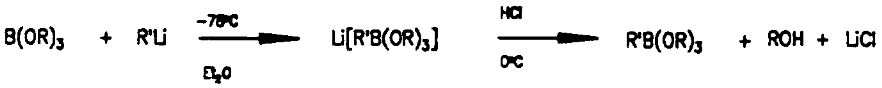
II-8

The arylborohydrides were hydrolyzed with water and an acid catalyst to the corresponding boronic acids (equation II-9).



II-9

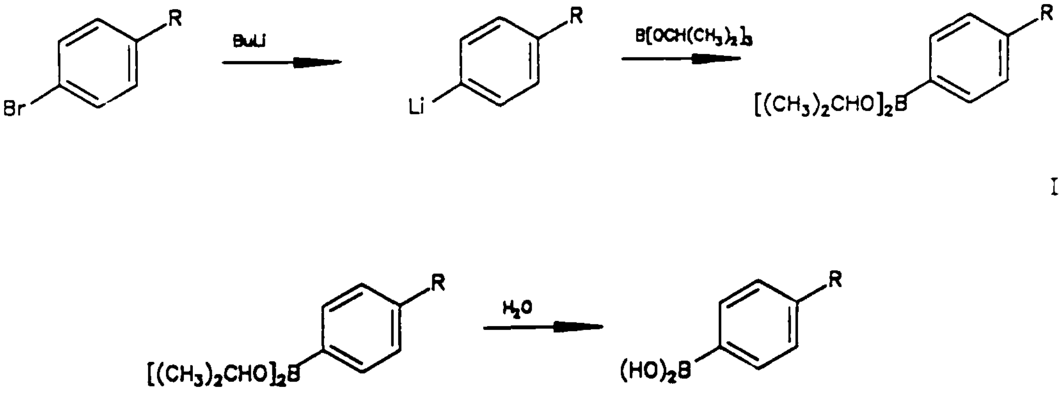
Brown and Cole[42] described a method for preparation of borinic esters from organolithium reagents and trialkoxyboranes. They reacted an alkyllithium with a trialkoxyborane (equation II-10) at -78°C in dry ether,



$$B(OR)_3 + R'Li \xrightarrow[Et_2O]{-78^\circ C} Li[R'B(OR)_3] \xrightarrow[0^\circ C]{HCl} R'B(OR)_3 + ROH + LiCl$$

II-10

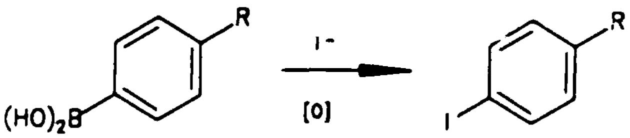
forming the alkyltrialkoxyborate complexes, which were destroyed by protonation with anhydrous hydrogen chloride. This protonation produced the corresponding alkylboranes. Gai[43] modified this method and applied it to aryllithium compounds. After lithiation of the aryl compound, addition of triisopropylborate gave the boronic ester. Hydrolysis of the ester resulted in the aryl boronic acid (equation II-11).



II-11

Iodination

Direct iodination using molecular iodine is the least complex method of placing iodine on the aromatic ring. This method has been used to iodinate thiophene in good yield[44], and is an example of the very reactive nature of the 2-position of thiophene to halogenation. Many other methods of iodination are available, including acid catalyzed reactions of iodine with HIO_3 and iodination using a mercury(II)oxide catalyst.[45] Kabalka and Gooch[46] reported a method for incorporating iodine into organic molecules using organoboranes with sodium iodide in the presence of an oxidizing agent. The reaction was rapid, stereospecific, and proceeded in the presence of a variety of functional groups. They applied this same procedure to preparation of aromatic iodides using arylboronic acids (equation II-1.).[47]



II-12

Chloramine-T was used as the oxidant by Kabalka and Gooch, but other oxidants have also been successfully used, such as N-chlorosuccinamide [48]

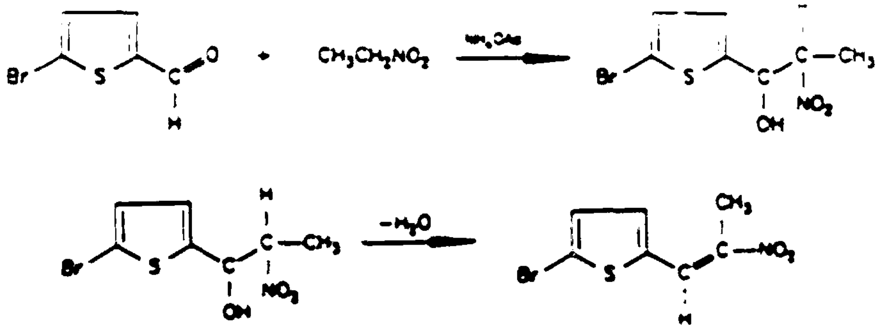
CHAPTER III

DISCUSSION AND RESULTS

We followed the synthetic pathway developed by Kabalka, Varma, [illegible] and Baldwin^6 for N-isopropyl-p-iodoamphetamine. A major deviation was required as we attempted synthesis of the boronic acid due to the greater reactivity of the 5-position on thiophene versus the para position of benzene. Three previously unknown compounds were synthesized: N-isopropyl-2-(2-aminopropyl)thiophene, the N-isopropyl-2-(2-aminopropyl)-5-thiopheneboronic acid, and N-isopropyl-2-(2-aminopropyl)-5-iodothiophene. The N-isopropyl-2-(2-aminopropyl)-5-iodoamphetamine is an analogue of N-isopropyl-p-iodoamphetamine, used in the radiolabeled form with iodine-123 as an imaging agent in nuclear medicine.

Two parallel paths of synthesis were followed. They differ only in the presence of a bromine substituent on the thiophene ring. The purpose of this dual synthesis was to produce the non-bromo compounds for use as references, and as starting material for a separate synthesis of the N-isopropyl-2-(2-aminopropyl)-5-iodothiophene via a trimethylstannyl intermediate. The primary path, though, was through the bromo compounds. Discussion, therefore, will focus on the synthesis of the bromo compounds with notation of any important procedural differences or observations encountered during synthesis of the non-bromo analogues.

Two separate procedures were used in the preparation of 2-(2-nitropropenyl)-5-bromothiophene. Both are nitroaldol condensations of 5-bromo-2-thiophene carboxaldehyde (equation III-1). The first was based on the method of Gairaud and Lappin[49] for the synthesis of 1-nitrostyrenes. Glacial acetic acid was used as the solvent with an alkylaldehyde and



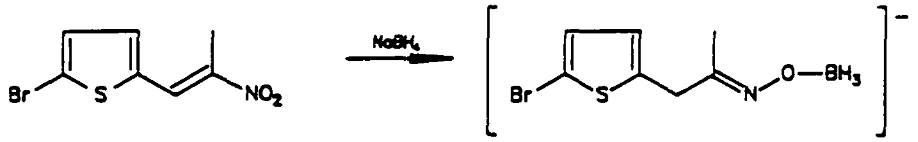
III-1

nitroethane refluxed with ammonium acetate for two hours. Pouring the solution into water precipitated a yellow solid which was collected by filtration and recrystallized to give the product. Generally yields averaged fifty percent.

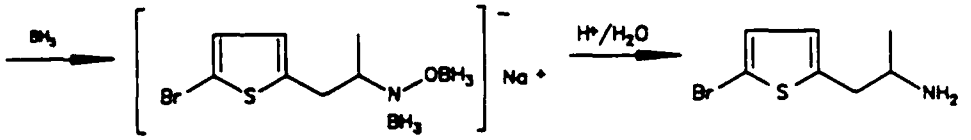
The second method utilized nitroethane as both solvent and reactant, and was based on a method outlined by Ho *et al*[50]. Removal of the solvent left the crude product with excess ammonium acetate. The ammonium acetate was removed by dissolving the solid in ether and tedious washing with copious amounts of water. This additional work was rewarded with yields of greater than eighty percent.

Methanol was used initially for recrystallizations, but was replaced by ethanol due to better solubility of the solid in ethanol, allowing for handling of smaller volumes during the purification. Yellow needle crystals that melted cleanly at 147-149°C were obtained. Nuclear magnetic resonance (NMR) spectra, both carbon-13 (page 37) and proton (page38), were obtained. Carbon-13 peak assignments are shown on page 25.

Preparation of the 2-(2-aminopropyl)-5-bromothiophene was based on the method of Mourad, Varma, and Kabalka[51] for reduction of a,b-unsaturated nitroalkenes using borohydrides. Addition of sodium borohydride to the nitropropene forms the sodium salt (equation III-2). This reaction is initially very exothermic. Reduction of the non-bromo compound occurred more vigorously than the corresponding bromo compound. Borane then reduces the salt to the borinic ester (equation III-3). The reaction normally required reflux for twenty-four hours to go to completion. Shorter reaction periods produced a mixture of the amine and hydroxylamine following hydrolysis.



III-2

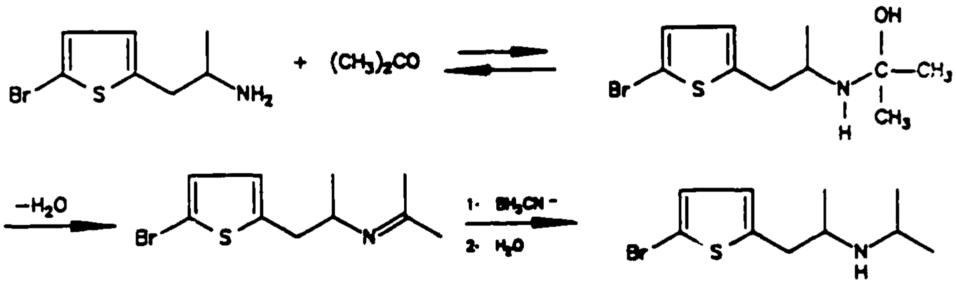


III-3

The 2-(2-aminopropyl)-5-bromothiophene was found to be unstable, turning burnt orange within eight hours. If not used immediately, it was protected as the hydrochloride salt.

Following hydrolysis, the aqueous solution was first washed with ether to remove organic impurities, and taken to approximately pH=8. At this pH, any hydroxylamine formed during the reaction is released and extracted into the ether. Further basification to approximately pH=10 released the amine into ether. A yellow liquid was the product as shown by carbon-13 (page 39) and proton (page 40) NMR spectroscopy. Carbon-13 peak assignments are given on page 25.

The primary amine was N-alkylated using the method of Borch, Bernstein, and Durst.[35] The 2-(2-aminopropyl)-5-bromothiophene, glacial acetic acid, and sodium cyanoborohydride were used in a ratio of 1 : 6 : 1.2 : 0.6. This ratio was developed by Gai[43] as optimum. Although Borch and co-workers used an excess of amine to inhibit formation of secondary and tertiary amines, we encountered no formation of the tertiary amine with the six-fold excess of ketone. Presumably, this is due to steric interactions that shield the amine from additional substitution. Formation of the imminium moiety (equation III-4) is known to be an unfavorable step in the reaction sequence[52], and may also contribute to our findings.



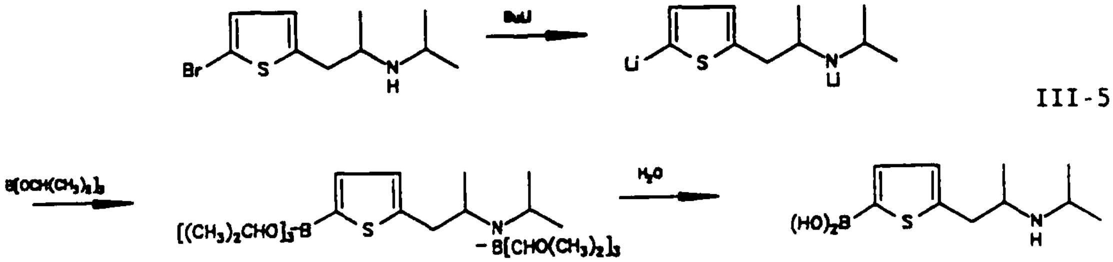
III-4

The structure of the N-isopropyl 2-(2-aminopropyl)-5-bromothiophene, a clear liquid, was confirmed by carbon-13 (page 41) and proton NMR spectroscopy (page 42). Carbon-13 peak assignments are made on page 25.

In anticipation of follow on work to develop a spectrum of medical imaging agents, N-ethyl 2-(2-aminopropyl)-5-bromothiophene was also synthesized. The reaction conditions and ratio of reactants are the same as in the synthesis of the N-isopropyl 2-(2-aminopropyl)-5-bromothiophene with the exception of a lower reaction temperature for addition of the acetaldehyde. A clear liquid was obtained which was characterized by carbon-13 (page 43) and proton NMR spectroscopy (page 44).

Initial attempts to synthesize the boronic acid using a Grignard reagent in borane-tetrahydrofuran after the method of Kabalka et al.[41] were unsuccessful. By monitoring the reaction with boron-11 NMR spectroscopy, we determined that the expected intermediate was forming (page 26). After addition of water and hydrochloric acid (solution at approximately pH=6), boron-11 NMR spectroscopy showed apparent hydrolysis to the boronic acid (page 27). After stirring for twenty-four hours at room temperature at approximately pH=2, only one peak on the boron-11 spectrum (page 28) indicated complete hydrolysis had ocurred, but carbon-13 NMR showed that the intermediate had undergone destructive proto-deboronation (page 29) to give N-isopropyl 2-(2-aminopropyl)thiophene. Comparison with the NMR spectrum of N-isopropyl 2-(2-aminopropyl)thiophene showed them to be identical. Apparently, the greater reactivity of the thiophene five-position makes this compound susceptible to protonation under acidic conditions. The benzyl analogue did not show a similar susceptibility. Attempts to hydrolyze the boron intermediate to the boronic acid without acid catalyst were also unsuccessful.

A different route to the boronic acid was available by first forming the borinic ester after the method of Brown and Cole.[42] Lithiation of N-isopropyl 2-(2-aminopropyl)-5-bromothiophene with butyllithium, followed by reaction with triisopropoxyborane (equation III-5), produces the desired



III-5

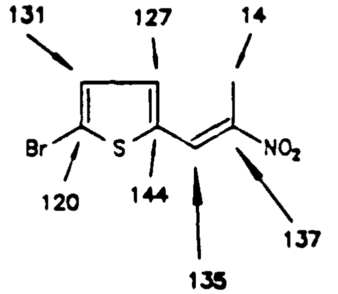
borinic ester. Diisopropyl boronic esters and dimethyl esters were previously used by Gai[43] to yield the boronic acids of benzyl compounds following hydrolysis without acid catalyst. Hydrolysis resulted in formation of the N-isopropyl 2-(2-aminopropyl)thiophene-5-boronic acid as indicated by carbon-13 (page 45), proton (page 46), and boron-11 NMR spectroscopy (page 47). Burning the compound in air gave a green flame, indicating the presence of boron. Thin layer chromatography on silica gel plates eluted with dichloromethane and methanol (4:1) showed a single spot at the origin as would be expected with a highly polar compound.

A sample submitted for high resolution mass spectrometry gave a molecular ion peak (page 48) at 284.1485 mass units, 0.0002 percent difference from the calculated value of 284.1492 for the glyme derivative of N-isopropyl 2-(2-aminopropyl)thiophene-5-boronic acid. The ion fragmentation spectrum of the boronic acid is shown on page 49.

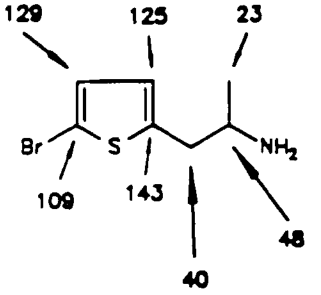
Iodination of the thiophene ring was based on the procedure of Kabalka, et al.[53] Two oxidizing agents were used separately to produce N-isopropyl 2-(2-aminopropyl)-5-iodothiophene. N-Chlorosuccinamide and chloramine-T gave similar yields. The iodo compound was purified on a silica gel column eluted with dichloromethane and ethanol (8:1). The product was indicated by carbon-13 (page 50) and proton NMR spectroscopy (page 51), as well as high resolution mass spectrometry (page 52). The molecular ion peak of the mass spectra at 310.0131 differs by 0.0002 percent from the calculated molar mass of 310.0126. The ion fragmentation spectrum of the N-isopropyl 2-(2-aminopropyl)-5-iodothiophene is shown on page 53.

Radioiodination of the boronic acid using iodine-131 showed yield of

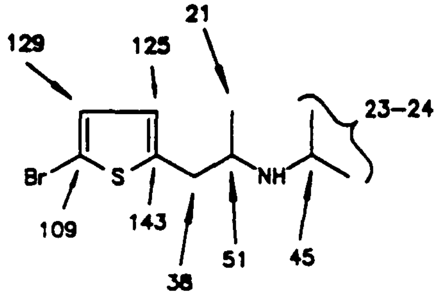
98 percent radiolabeled compound. This higher yield may be explained by the use of 1 M hydrochloric acid as a solvent in the radioiodination compared to neutral conditions for the synthesis of the unlabeled compound. Observation of protodeboronation in acid catalyzed hydrolysis in synthesis of the boronic acid prompted the neutral conditions for iodination. Acidic condition in the radioiodination increased the yield of desired product by 200 percent.



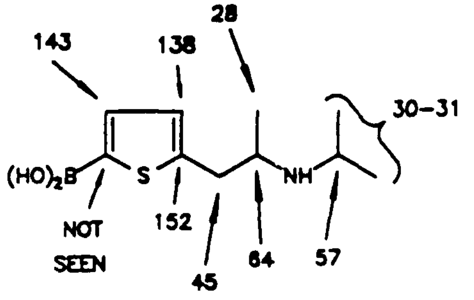
2-(2-nitropropenyl)-5-bromothiophene



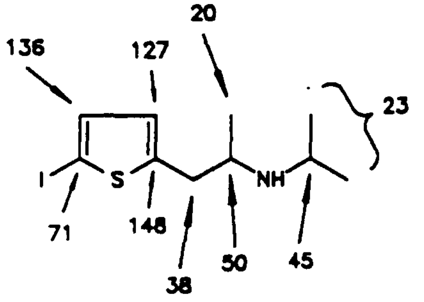
2-(2-Aminopropyl)-5-bromothiophene



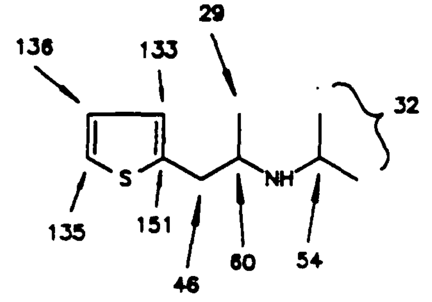
N-isopropyl 2-(2-aminopropyl)-5-bromothiophene



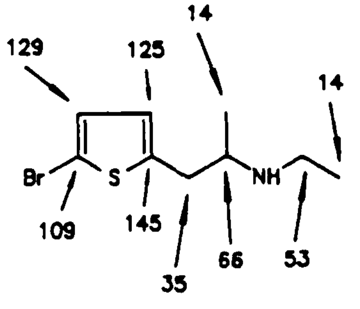
N-isopropyl 2-(2-aminopropyl)thiophene-5-boronic acid



N-isopropyl 2(2-Aminopropyl)-5-iodothiophene



N-isopropyl 2-(2-aminopropyl)thiophene



N-Ethyl 2-(2-aminopropyl)-5-bromothiophene

Figure III.A.1

Carbon-13 Nuclear Magnetic Resonance Spectrum
Peak Assignments.

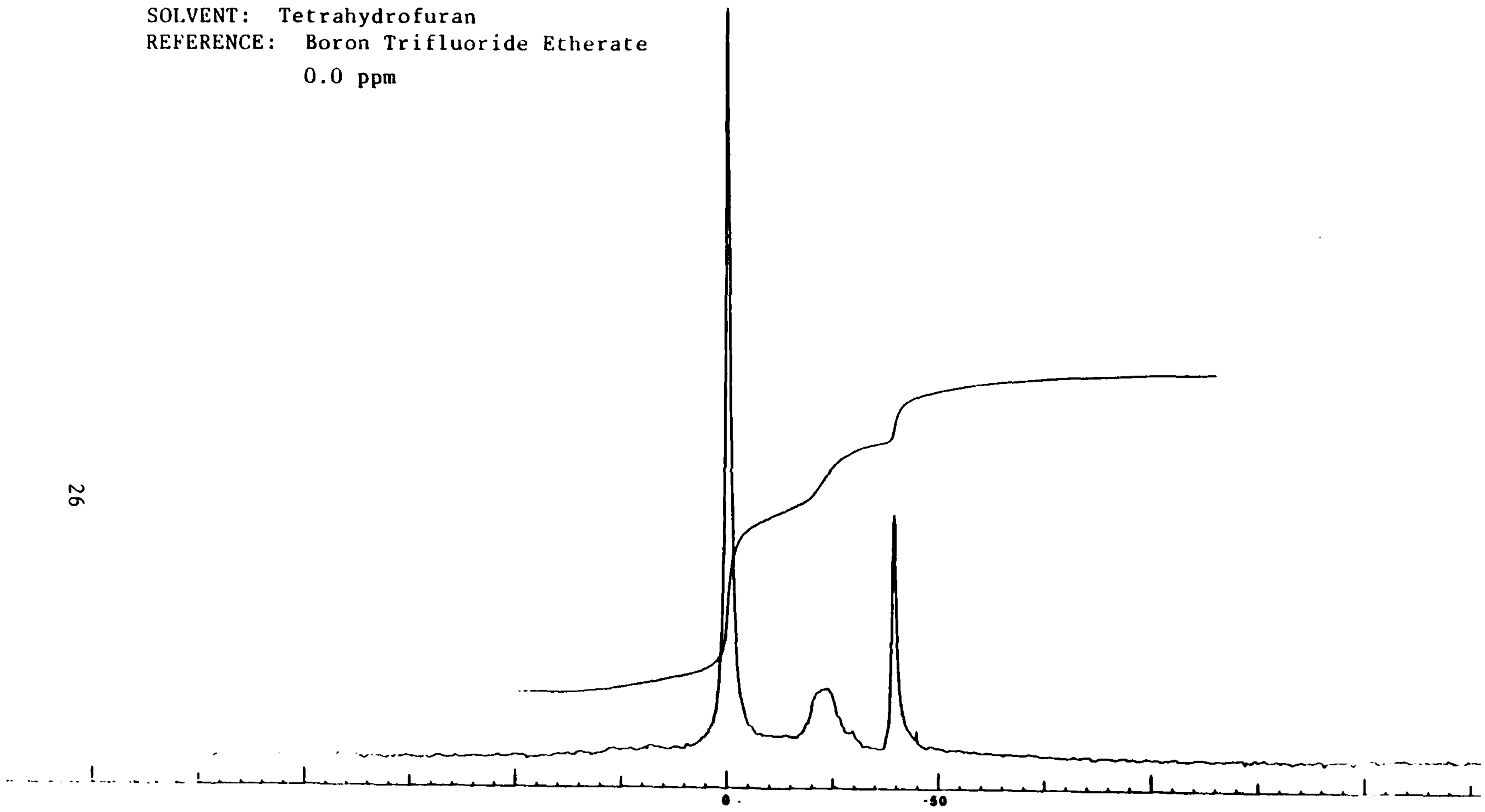

SOLVENT: Tetrahydrofuran
REFERENCE: Boron Trifluoride Etherate
0.0 ppm

Figure III.A.2

Boron-11 Nuclear Magnetic Resonance Spectrum of Grignard Synthesis of Boronic Acid Prior to Acid Catalyzed Hydrolysis.

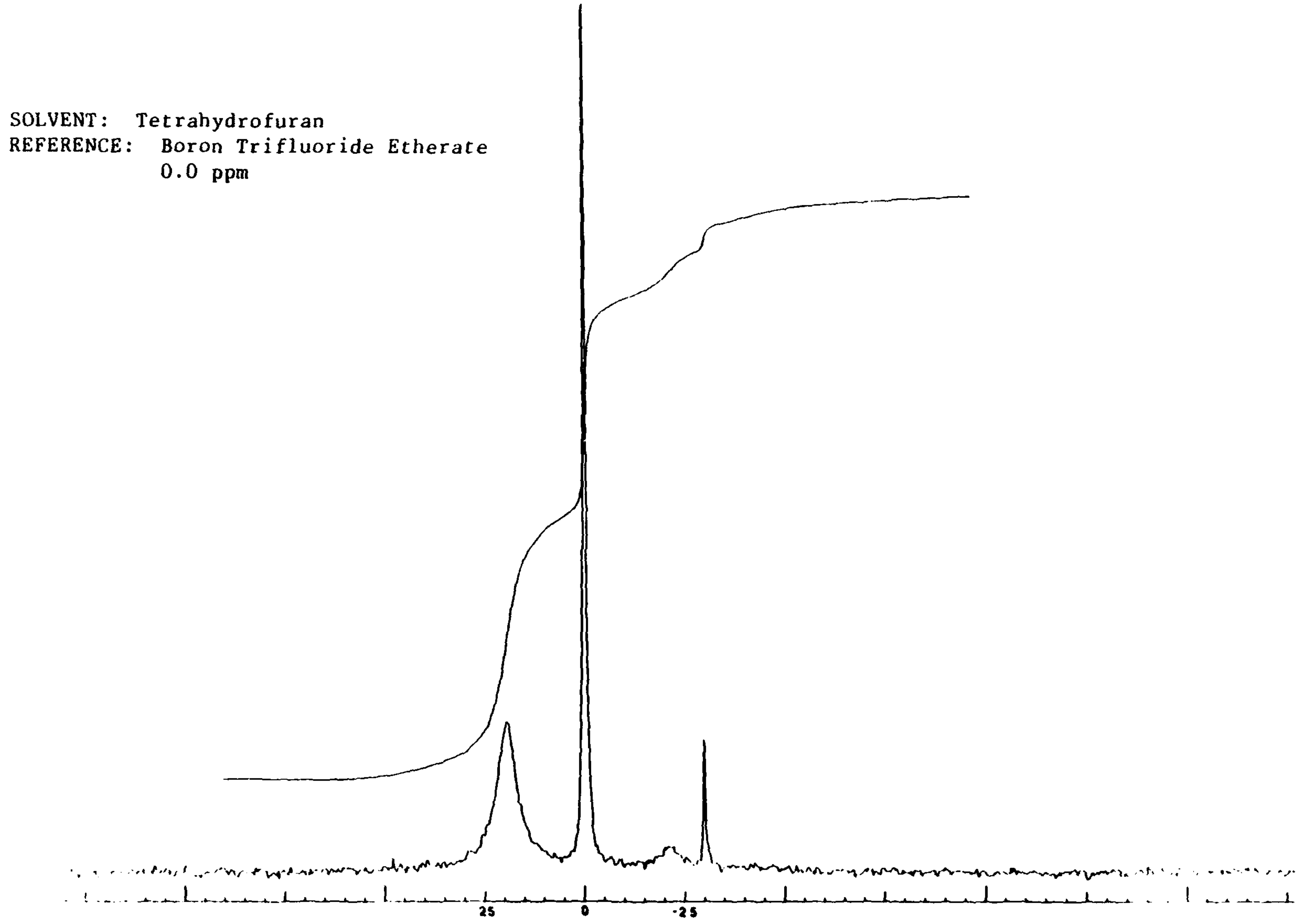
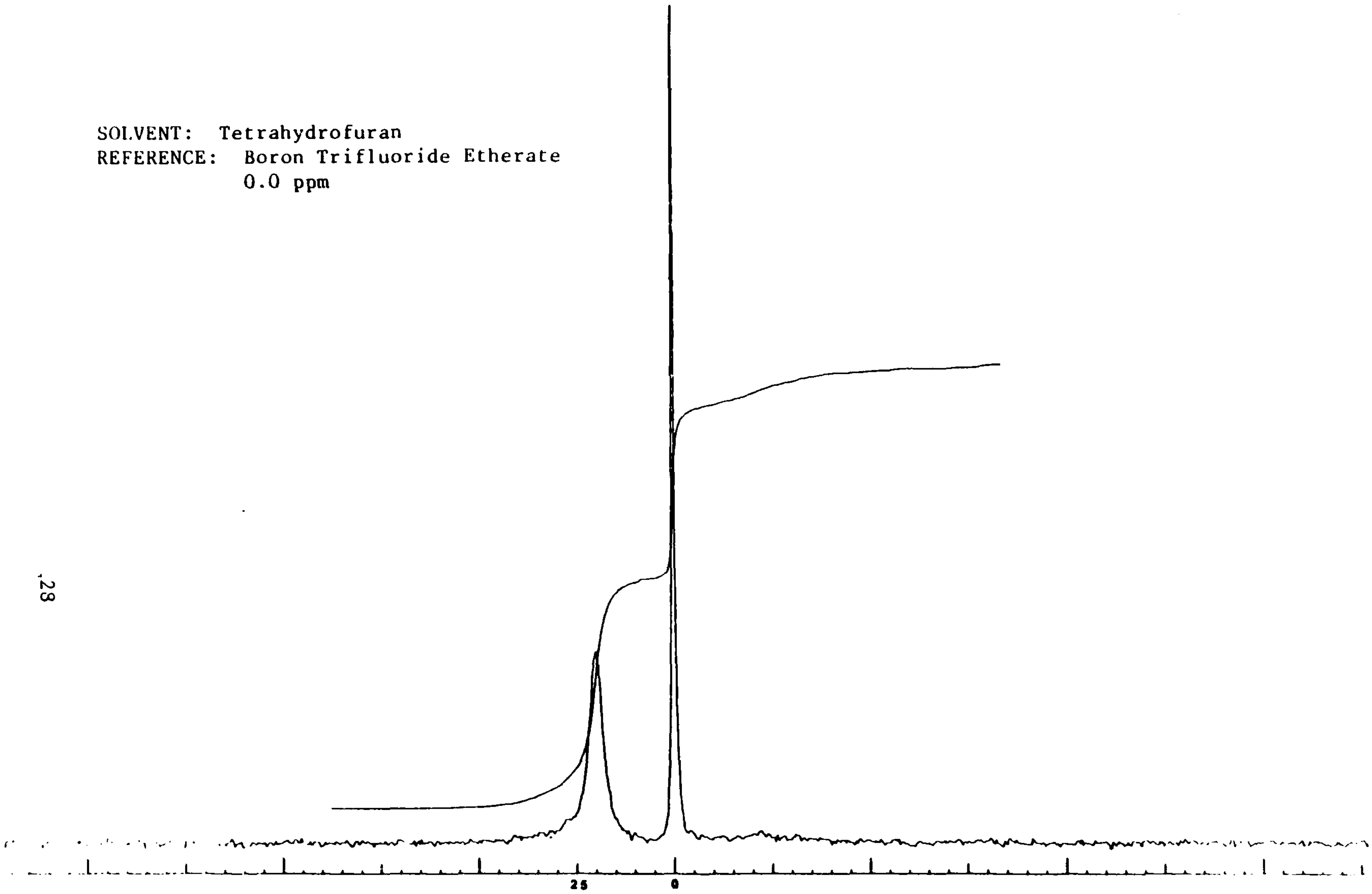


Figure III.A.3

Boron-11 Nuclear Magnetic Resonance Spectrum of Grignard Synthesis of Boronic Acid Immediately After Addition of Water and Acid.



SOLVENT: Tetrahydrofuran
REFERENCE: Boron Trifluoride Etherate
0.0 ppm

Figure III.A.4

Boron-11 Nuclear Magnetic Resonance Spectrum of Grignard Synthesis of Boronic Acid After Twenty-four Hours at pH2.

SOLVENT: Methyl-$\underline{d}_3$ Alcohol-$\underline{d}$; 99.5 atom% D
REFERNECE: Methyl Alcohol; 49.0 ppm

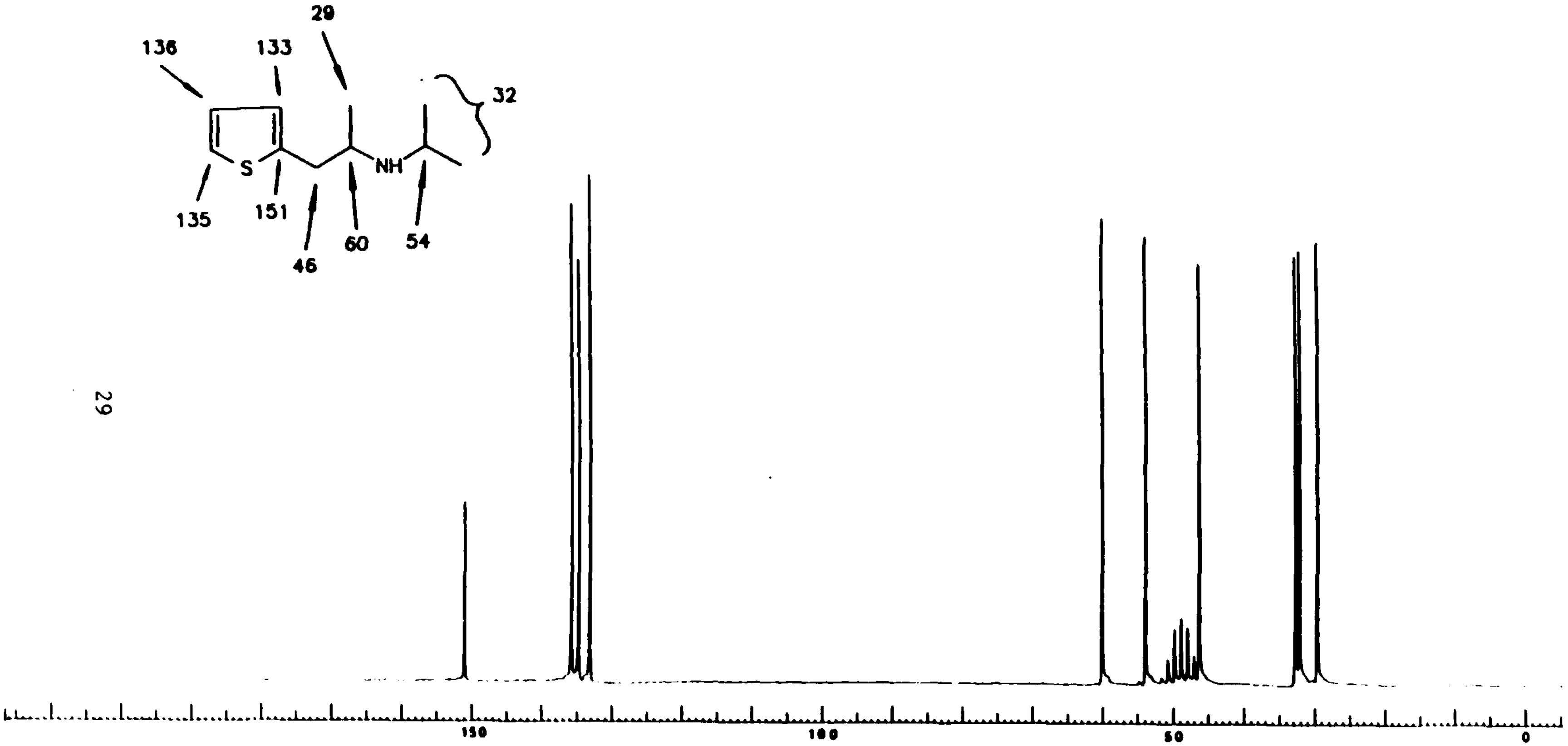


Figure III.A.5

Carbon-13 Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)thiophene.

CHAPTER IV

EXPERIMENTAL

A. GENERAL

Melting points are uncorrected. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Joel FX-90Q Spectrometer. All glassware was thoroughly oven dried and cooled under dry nitrogen just before use. Dry tetrahydrofuran (THF) and dry ether were prepared over sodium with benzophenone and collected by fractional distillation. Commercially available (Aldrich) 1.0 M borane in THF ($BH_3 \cdot THF$) and 2-carboxaldehyde-5-bromothiophene were used as received.

B. PROCEDURES

Preparation of 2-(2-Nitropropenyl)-5-bromothiophene

In a typical experiment, 4.14 g (22 mmol) of 2-carboxaldehyde-5-bromothiophene was dissolved in 75 mL of nitroethane in a 250 mL round bottom flask with stirring bar and reflux condenser. To this was added 2 [illegible] g of ammonium acetate, and the solution refluxed for five hours. The remaining solvent was then removed under reduced pressure to leave a yellow-orange solid which was dissolved in ether and washed with distilled water. The aqueous washing was extracted with ether. After combining the ether layers and drying over anhydrous sodium sulfate, removal of solvent and recrystallization from ethanol yielded 4.53 g (18 mmol, 82% yield) of yellow needle crystals, melting point 147-149°C. Carbon-13 and proton NMR spectra were obtained and are reproduced on pages 37 and 38

Preparation of 2-(2-Aminopropyl)-5-bromothiophene

A 100 mL three neck round bottom flask equipped with a magnetic stirring bar, gas inlet adapter, and reflux condenser was assembled. The third neck of the flask was covered with a rubber septum and a second gas inlet adapter placed on top of the condenser. Both gas inlet adapters were closed with 8mm septa. After beginning the nitrogen flush, the apparatus was flame dried and allowed to cool to room temperature, and then further cooled in an ice bath. A second oven dried 50 mL round bottom flask was charged with 1.93 g (7.8 mmol) of 2-(2-nitropropenyl)-5-bromothiophene, sealed with a septum, and flushed with dry nitrogen. Using a syringe, 25 mL of tetrahydrofuran was added, dissolving the yellow crystals. To the cooled 100 mL three neck flask was added 50 mL (50.0 mmol) of borane-tetrahydrofuran solution (1.0 M). The 2-(2-nitropropenyl)-5-bromothiophene in tetrahydrofuran was slowly transferred to the reaction vessel via double ended needle. After the addition was complete, the ice bath was removed, the septum from the third neck was removed, and while maintaining high nitrogen flow to minimize atmospheric contamination, 0.20 g of sodium borohydride was added. A ground glass stopper was then placed in the opening. A slight reaction ensued. A heating mantle was placed under the reaction vessel and the solution refluxed for 26 hours. The solution was then slowly poured into 100 mL ice-water and acidified to approximately pH=2 with ten percent hydrochloric acid and stirred for two hours in an oil bath at 65-70°C. The solution was then allowed to cool to room temperature. The solution was placed in a separatory funnel and washed three times with 50 mL ether. The aqueous layer was then basified to pH=7-8 with solid sodium hydroxide, washed with ether, and further basified to pH=10 and extracted with three, 100 mL portions of ether. These extracts were combined and dried over sodium sulfate. After filtering to remove the drying agent, the solvent was removed under reduced pressure to yield 1.312 g (6.0 mmol, 77% yield) of yellow liquid. Carbon-13 and proton NMR spectra were obtained and are reproduced on page 39 and page 40, respectively. The amine, if not used immediately, was protected by forming the hydrochloride salt. This was formed by taking the oil up in anhydrous ethyl ether followed by saturation with hydrogen chloride gas. The white precipitate was then collected by filtration.

Preparation of N-Isopropyl 2-(2-Aminopropyl)-5-bromothiophene

2.50 g (11.4 mmol) of 2-(2-aminopropyl)-5-bromothiophene was dissolved under nitrogen atmosphere in 25 mL of absolute methanol in a 100 mL round bottom flask. 0.43 g of sodium cyanohydridoborate, 0.8 mL (13.7 mmol) of glacial acetic acid, and 5.1 mL (68.4 mmol) of absolute acetone were added and the solution stirred for 24 hours at 25°C. Concentrated hydrochloric acid was added to approximately pH=2 and the solvent removed under reduced pressure. The residue was taken up in 25 mL distilled water and washed three times with 30 mL portions of ether. The aqueous portion was then taken to pH=7-8 with solid sodium hydroxide, washed with ether, and then further basified to pH=10 and extracted with four portions of 30 mL ether. The extracts were combined and dried over anhydrous sodium sulfate. After filtering to remove the drying agent and removal of the solvent under reduced pressure, 2.58 g (9.8 mmol, 86% yield) of a clear liquid remained.

Carbon-13 and proton NMR spectra were obtained and are reproduced on page 41 and page 42, respectively.

Synthesis of N-Ethyl 2-(2-Aminopropyl)-5-bromothiophene

A 100 mL round bottom flask with stirring bar was charged with 0.31 g (4.9 mmol) of sodium cyanohydridoborate, closed with a rubber septa, and flushed with dry nitrogen while cooled in an ice-NaCl bath to approximately -15°C. 2.04 g (8.2 mmol) of 2-(2-aminopropyl)-5-bromothiophene was dissolved in 20 mL of absolute methanol and added to the flask. To this was added 0.6 mL (9.8 mmol) of glacial acetic acid followed by 2.8 mL (49.2 mmol) of acetaldehyde via syringe. The solution was allowed to come slowly to room temperature and stirred for 24 hours.

Upon completion of reaction, concentrated hydrochloric acid was added to bring the solution to approximately pH=2 and the solvent removed under reduced pressure. Remaining residue was then transferred into a separatory funnel with 10 mL of distilled water and washed two times with 25 mL of ether. After adding solid sodium hydroxide to bring the aqueous layer to pH=7-8 and washing again with ether, the aqueous layer was further basified to approximately pH=10 with solid sodium hydroxide and extracted three times with 25 mL portions of ether. These extracts were combined and dried over anhydrous sodium sulfate.

Filtering of the extracts and removal of the solvent under reduced pressure yielded 1.99 g of aclear liquid (8.0 mmol, 98% yield). A carbon-13 NMR spectrum was obtained and is reproduced in page 43, proton NMR spectrum is reproduced on page 44.

Synthesis of N-Isopropyl 2-(2-Aminopropyl)thiophene-5-boronic Acid

A 50 mL round bottom flask was cooled under nitrogen in an acetone-dry ice bath. The flask was charged with 50 mL of dry ether followed by 0.52 g (2.0 mmol) of N-isopropyl 2-(2-aminopropyl)-5-bromothiophene. After the solution had cooled, 1.6 mL (4.0 mmol) of 2.5 M butyllithium in hexanes was added and the solution stirred at -78°C for one hour. 9.2 mL (20.0 mmol) of triisopropoxyborane was then added and the solution stirred for an additional hour at -78°C, allowed to come slowly to room temperature, and then stirred for three additional hours at room temperature.

The solution was then poured into an equal volume of water and stirred until clear. The clear solution was transferred to a separatory funnel and extracted three times with 20 mL of ethyl acetate. These extracts were combined and dried over anhydrous magnesium sulfate for approximately five minutes, filtered, and the solvent removed under reduced pressure, leaving a white solid. After titurating the solid with ether, 0.39 g (1.7 mmol, 86% yield) of a white powder remained. Carbon-13, proton, and boron-11 NMR spectra were obtained and are reproduced in on pages 45, 46, and 47, respectively. High resolution mass spectrum was obtained and is reproduced on page 48, while the ion fragmentation spectrum is shown on page 49.

Synthesis of N-Isopropyl 2-(2-Aminopropyl)-5-iodothiophene

In a dry 50 mL round bottom flask with stirring bar was placed 0.454 g (2.0 mmol) of N-isopropyl 2-(2-aminopropyl)thiophene-5-boronic acid. 10 mL of water was added, dissolving the solid boronic acid. The reaction flask was then shielded from light and stirring begun as 2.0 mL (2.0 mmol) of 1.0 M sodium iodine solution was added. This was followed by addition of 0.455

g of (2.0 mmol) chloramine-T. The solution turned dark brown upon addition of the chloramine-T and immediately turned milky. After stirring for thirty minutes, the solution was clear. The solution was transferred to a separatory funnel and extracted with three, 10 mL portions of ether. These ether extracts were combined and dried over sodium sulfate, after which the drying agent was filtered out and the remaining solvent removed under reduced pressure to leave 0.17 g of a clear liquid (0.6 mmol, 30 % yield). Carbon-13 and proton NMR spectra were obtained and are reproduced on pages 50 and 51. High resolution mass spectrum was also obtained and is reproduced on page 52, with the fragmentation pattern shown on page 53.

Radioiodination of N-Isopropyl 2-(2-Aminopropyl)thiophene-5-boronic Acid

All handling of radioactive isotopes were in accordance with standard safety procedures using approved hoods and shielding, including use of lead pigs for movement of solutions assumed to contain radioactive material.

In a dry 25 mL round bottom flask with stirring bar was placed 0.0056 g (0.02 mmol) of N-Isopropyl 2-(2-aminopropyl)thiophene-5-boronic acid. 1 mL of 1 M hydrochloric acid was added, dissolving the solid boronic acid. Aqueous sodium iodide-131 (0.02 mmol, 0.02 mL of a 1.0 M solution, 7 mCi/mL) was added, followed by 0.02 mL of 1.0 M aqueous chloramine-T. Upon addition of the chloramine-T, the solution became red. The reaction stirred at room temperature for forty minutes, during which time the color slowly faded. After transferring to a separatory funnel, 0.3 mL of 5 M potassium hydroxide was added and the aqueous layer extracted with 5 mL ether. Separation of the layers and assay of the ether layer showed 406 mCi of activity. Another 0.5 mL potassium hydroxide was added to the aqueous layer, followed by a second extraction with 5 mL ether. Separation and assay gave a total of 686 mCi of activity in the ether layers.

Radiochemical purity was analyzed using thin-layer chromatography on silica gel eluted with dichloromethane:methanol (8.5 : 1). Proportion of iodine-131 present was checked by counting the radiotracer. A single spot with an Rf value comparable to an authentic unradiolabeled sample was shown. 98 percent yield of radiolabeled compound was obtained.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Chloroform; 77.0 ppm

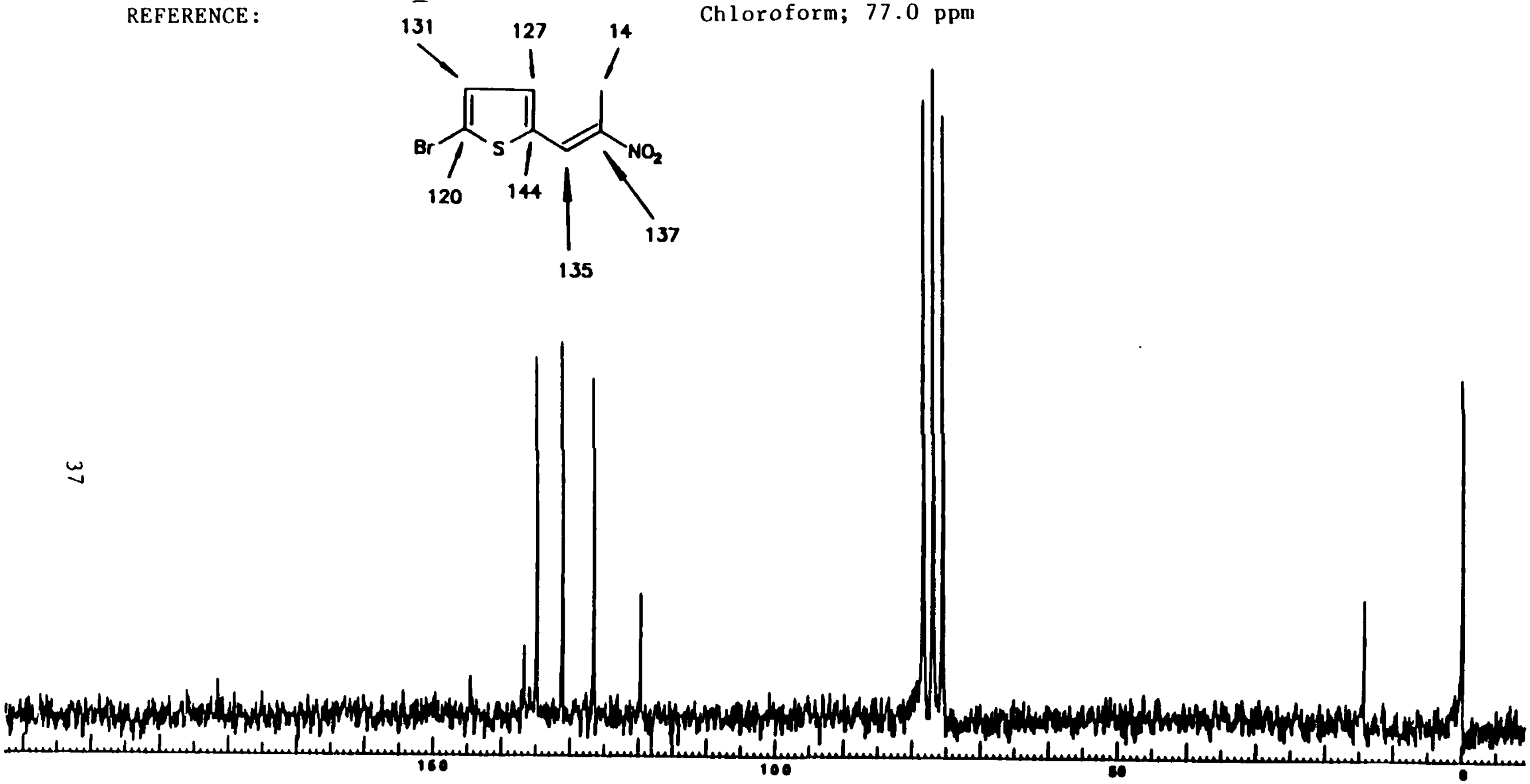


Figure IV.B.1.a

Carbon-13 Nuclear Magnetic Resonance Spectrum of 2-(2-Nitropropenyl)-5-bromothiophene.

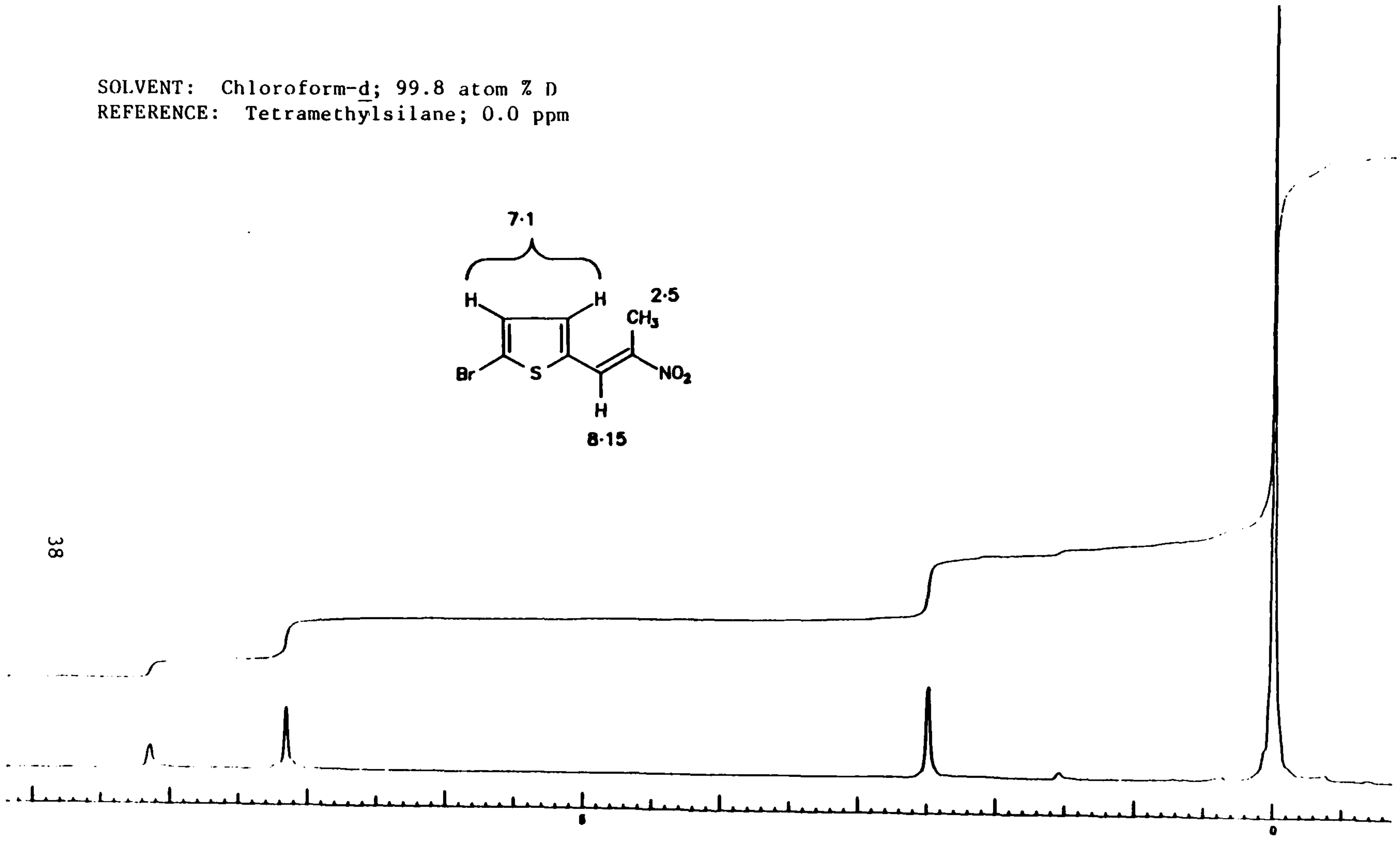

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

Figure IV.B.1.b

Proton Nuclear Magnetic Resonance Spectrum of 2-(2-Nitropropenyl)-5-bromothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Chloroform; 77.0 ppm

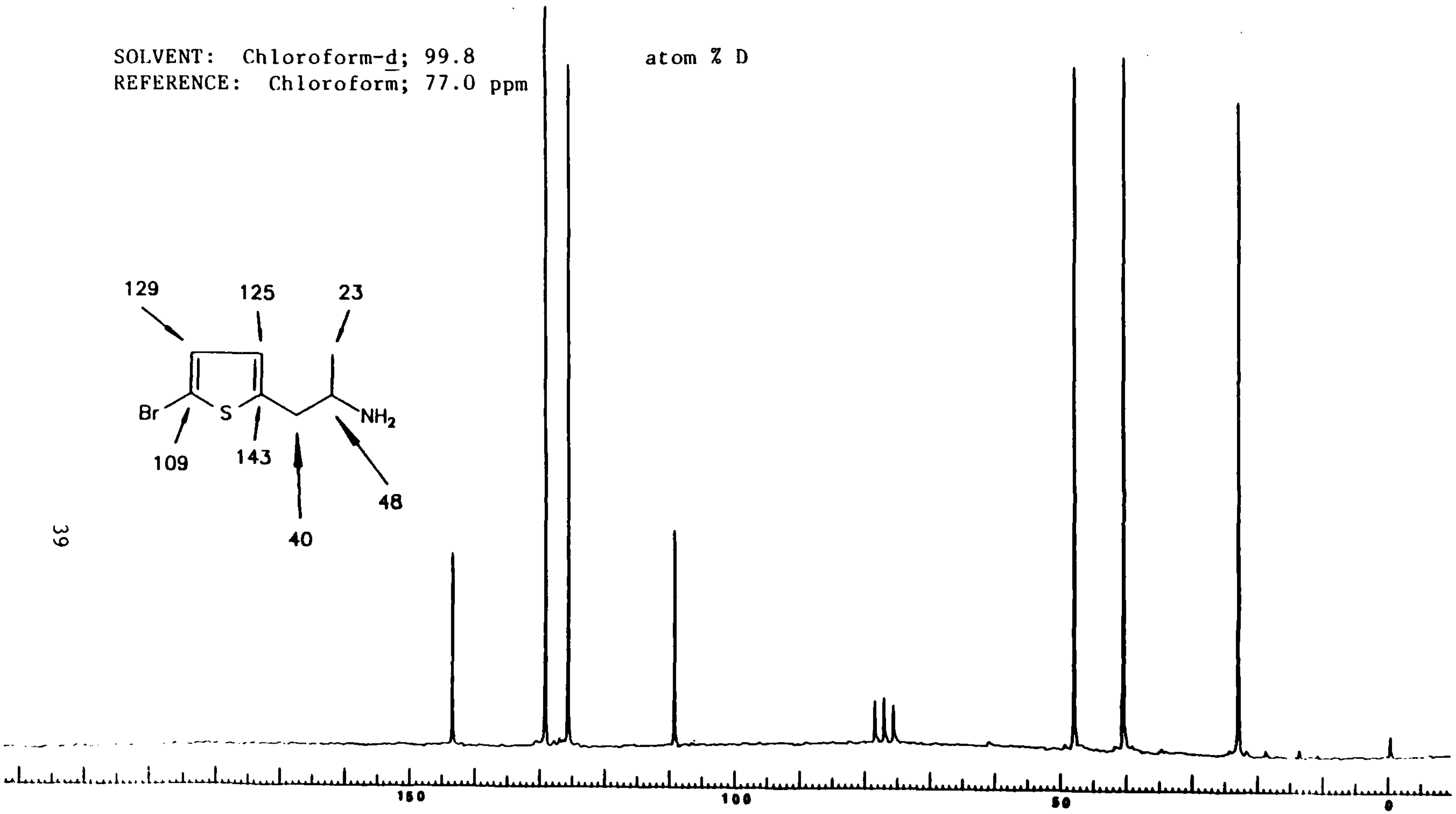


Figure IV.B.2.a

Carbon-13 Nuclear Magnetic Resonance Spectrum of 2-(2-Aminopropyl)-5-bromothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

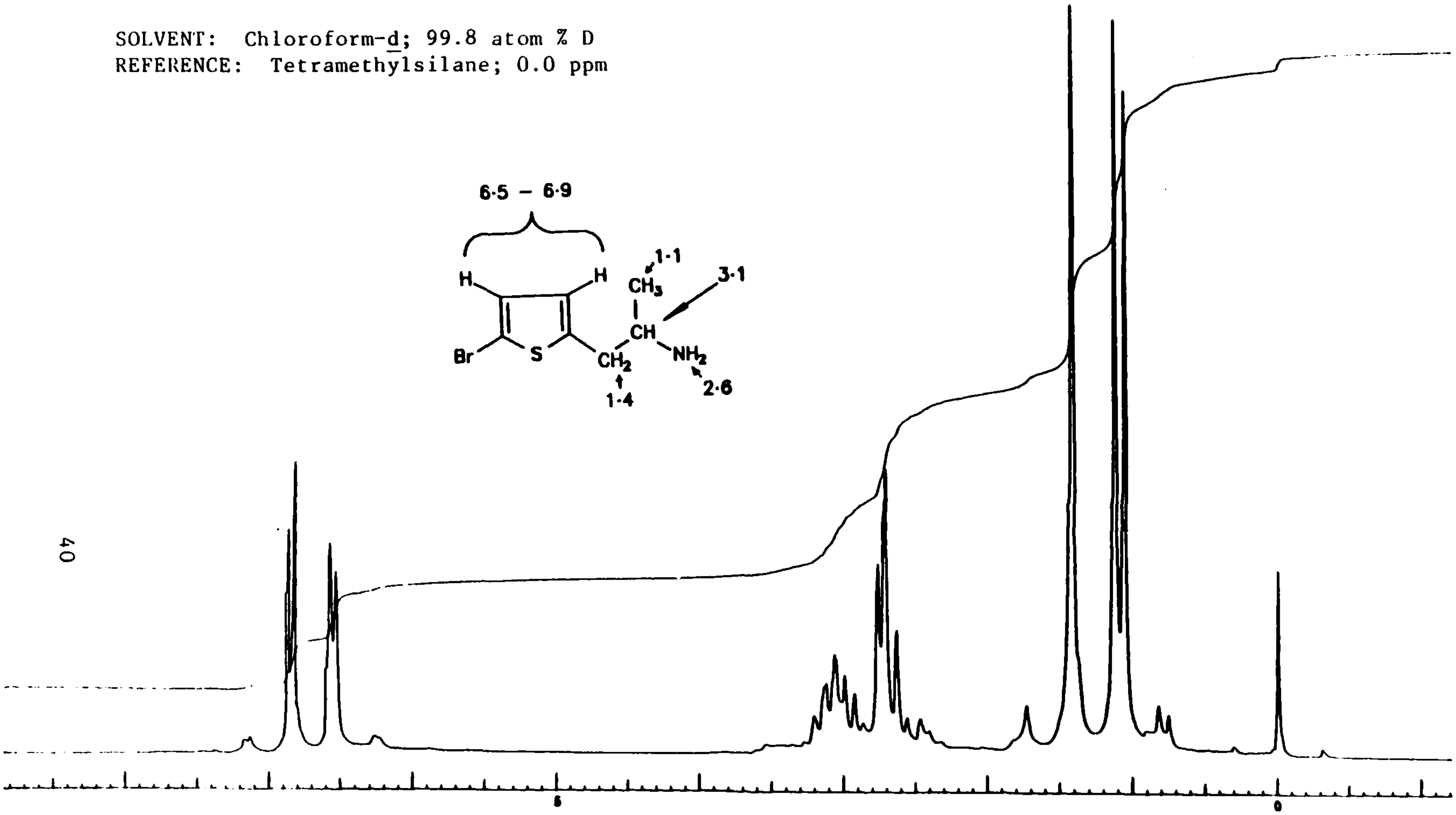


Figure IV.B.2.b

Proton Nuclear Magnetic Resonance Spectrum of 2-(2-Aminopropyl)-5-bromothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Chloroform; 77.0 ppm

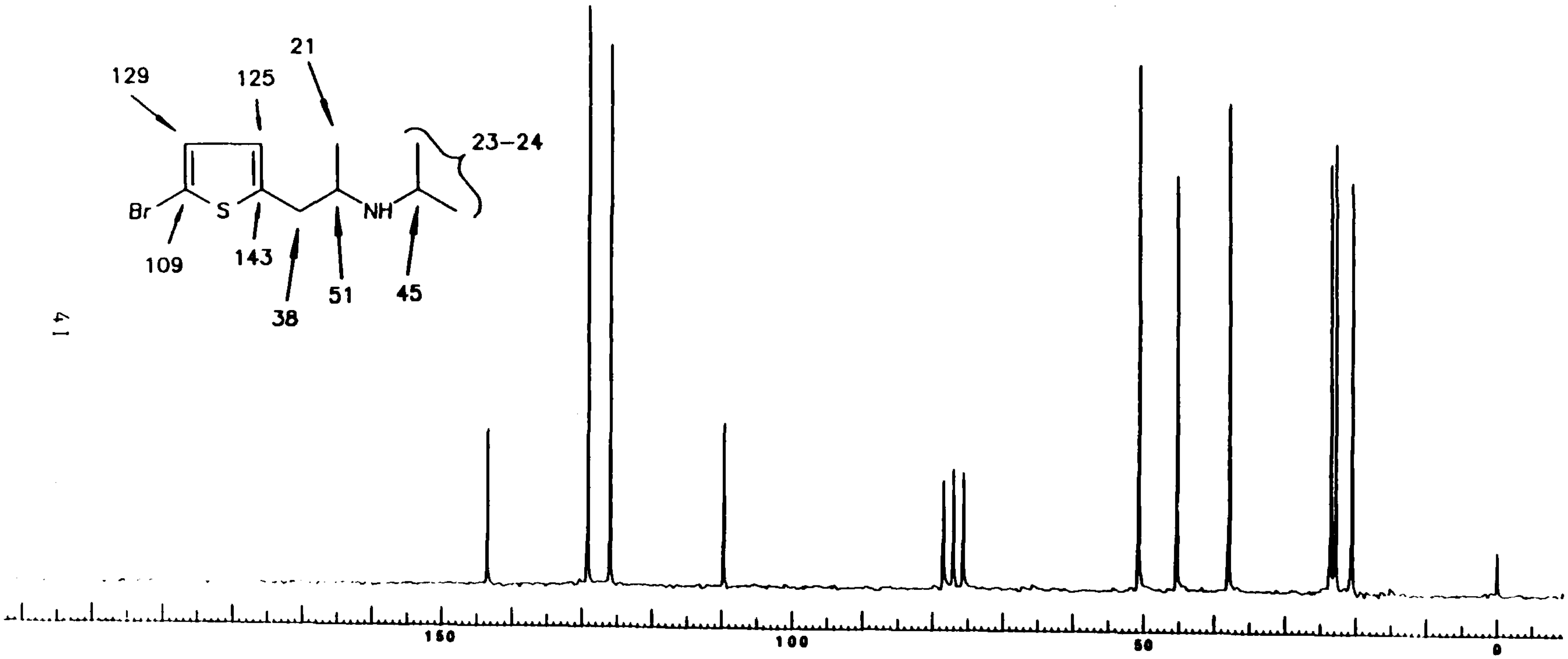


Figure IV.B.3.a

Carbon-13 Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-bromothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

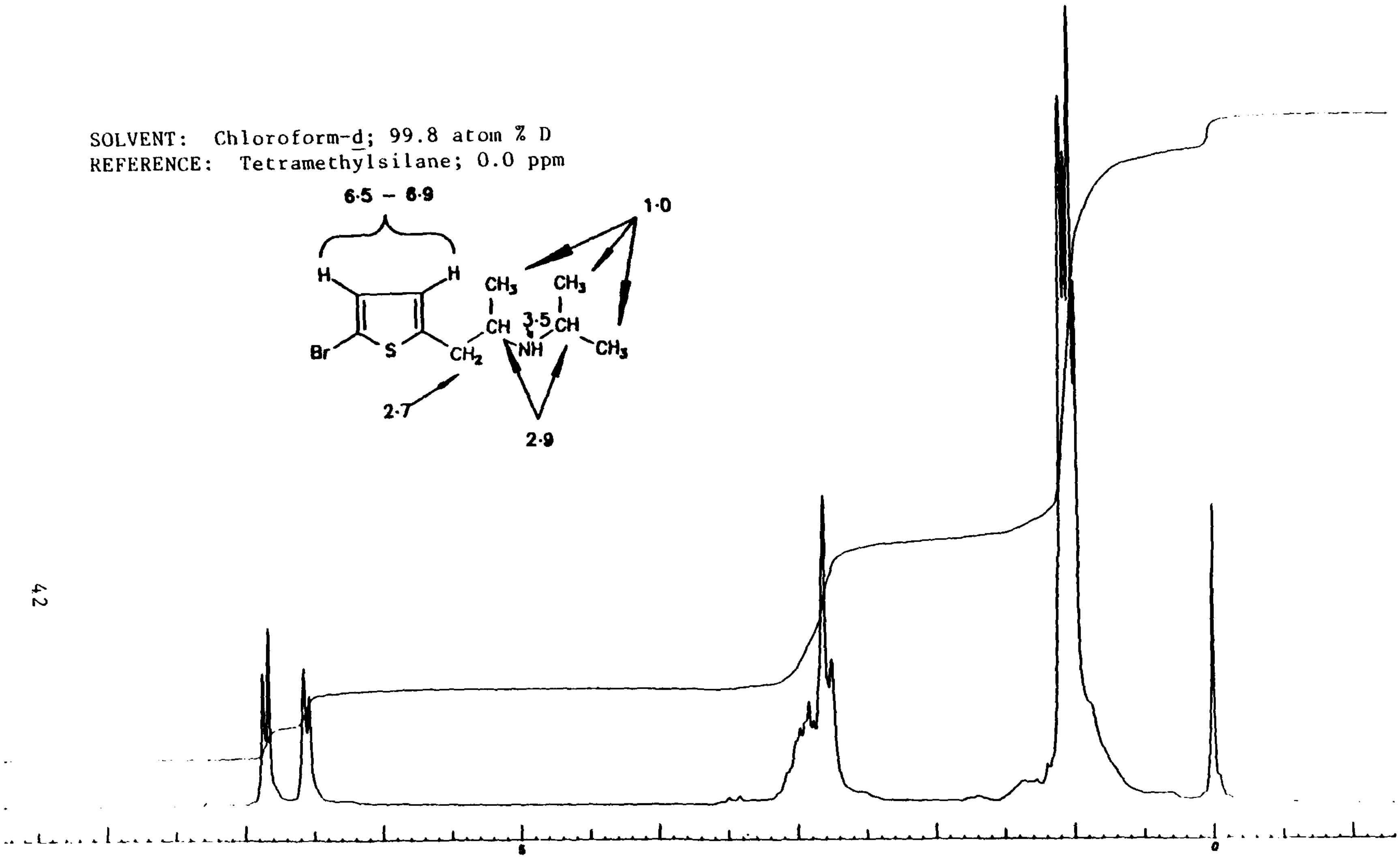


Figure IV.B.3.b

Proton Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-bromothiophene.

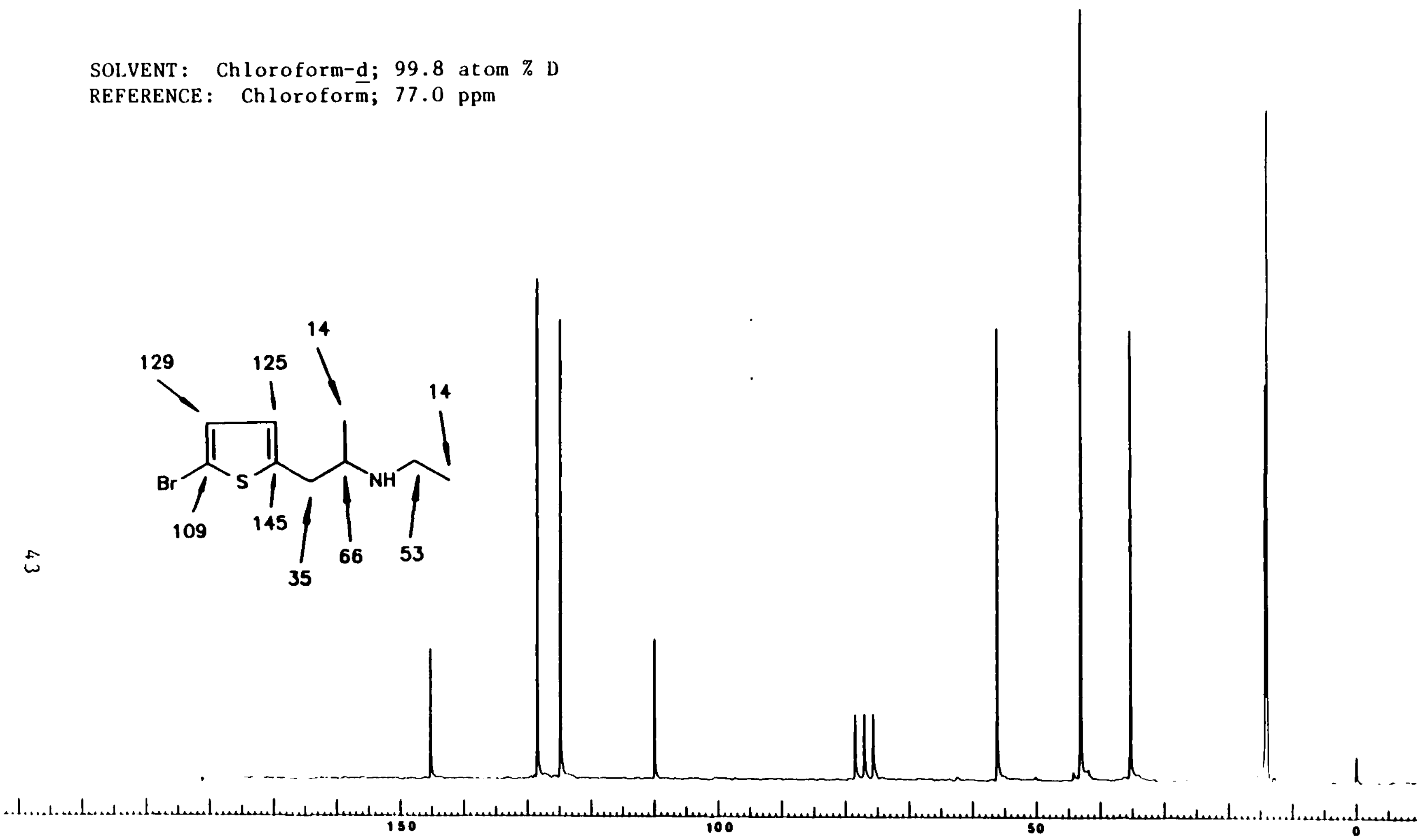

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Chloroform; 77.0 ppm

Figure IV.B.4.a

Carbon-13 Nuclear Magnetic Resonance Spectrum of N-Ethyl 2-(2-Aminopropyl)-5-bromothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

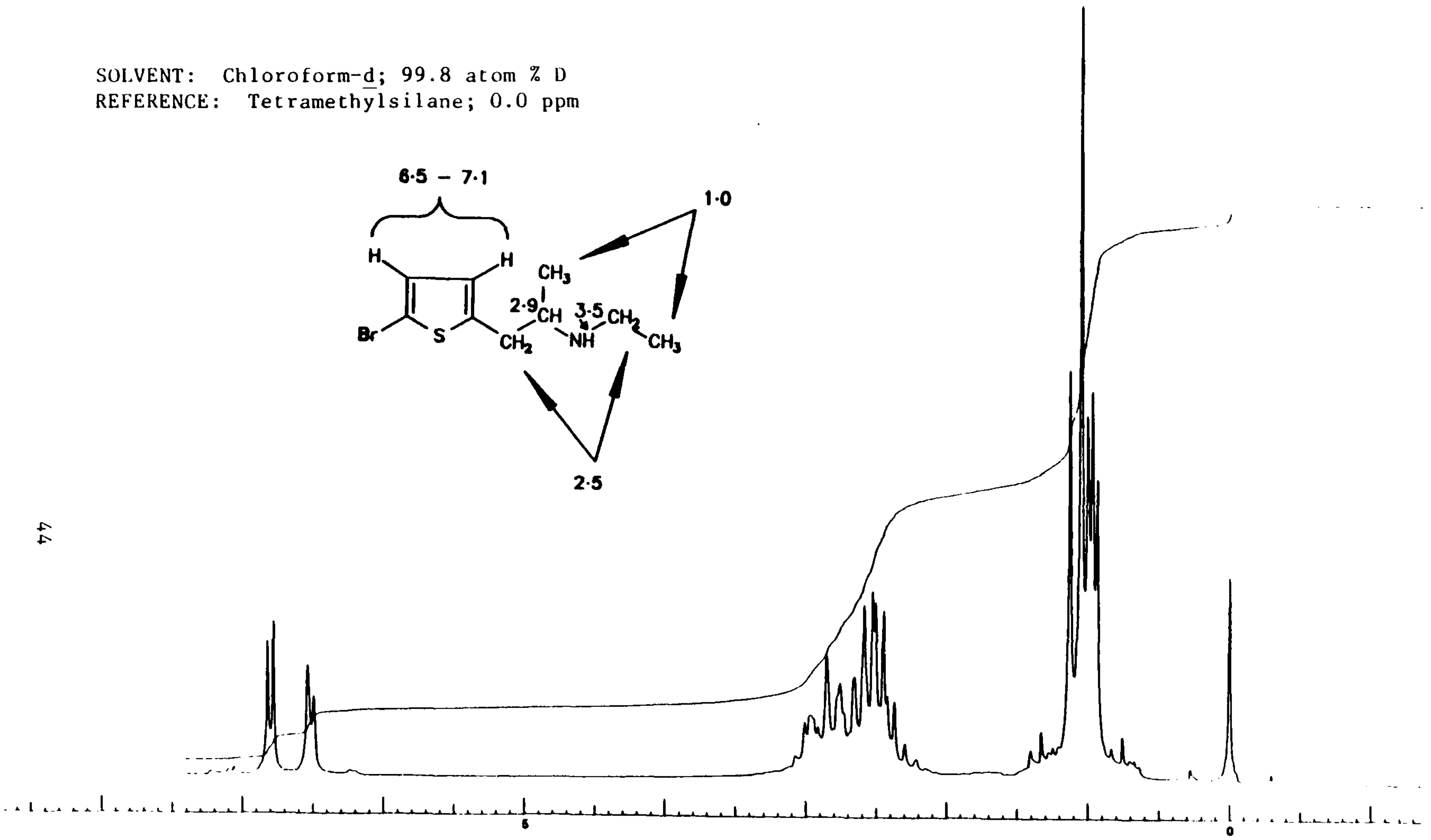


Figure IV.B.4.b

Proton Nuclear Magnetic Resonance Spectrum of N-Ethyl 2-(2-Aminopropyl)-5-bromothiophene.

SOLVENT: Methyl-d_3 Alcohol-$\underline{d}$; 99.5 atom % D
REFERENCE: Methyl Alcohol; 49.0 ppm

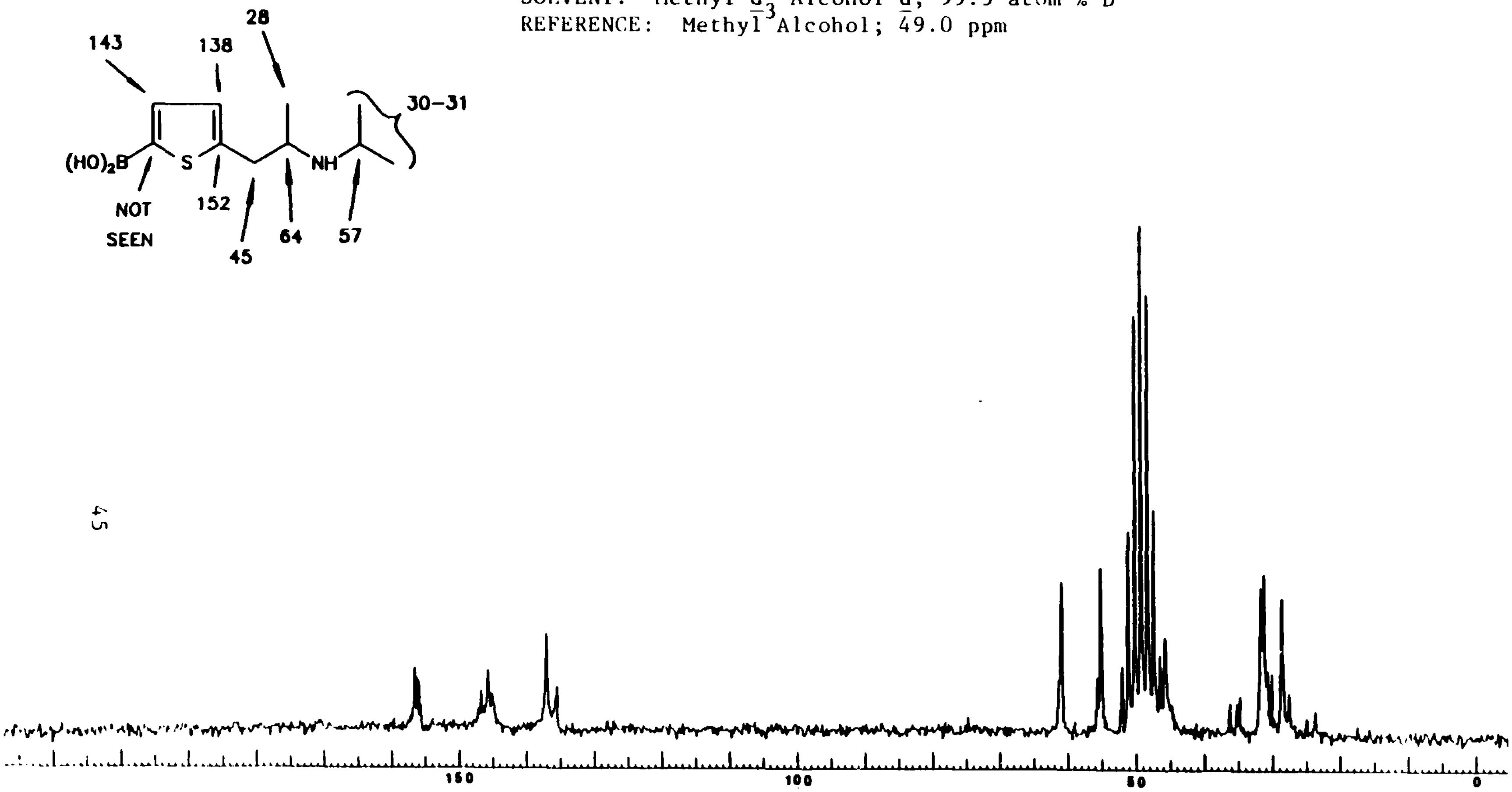
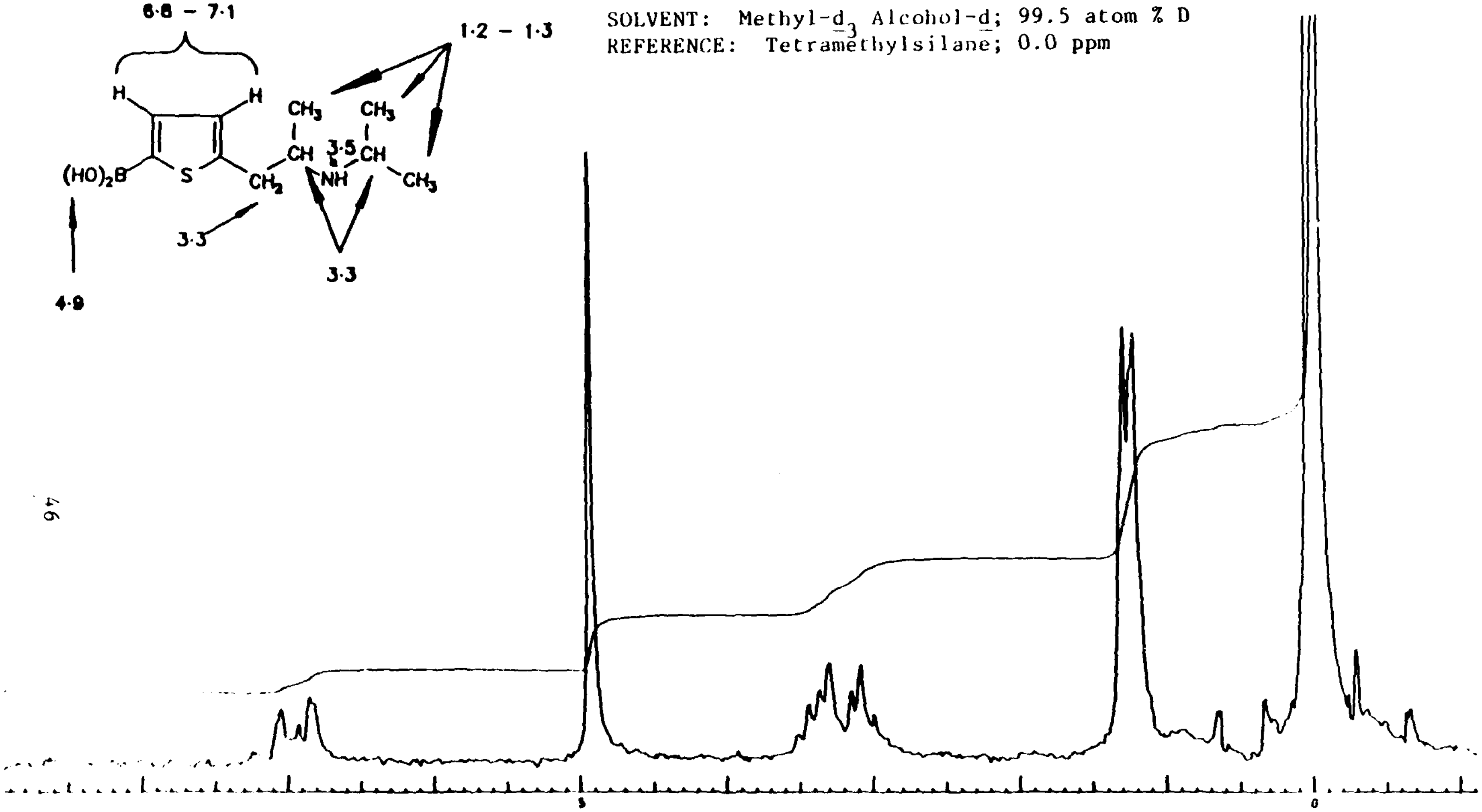


Figure IV.B.5.a

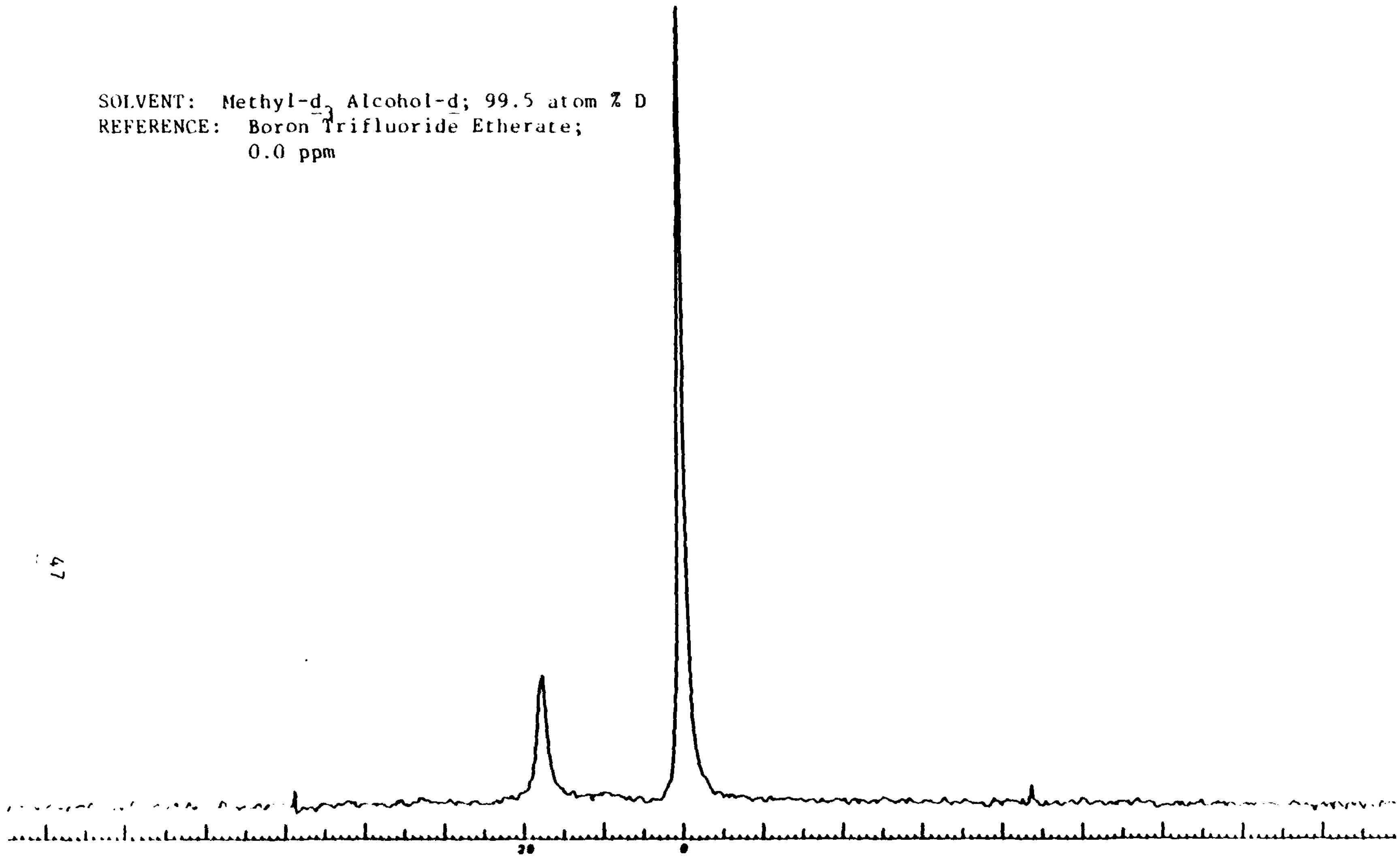
Carbon-13 Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)thiophene-5-boronic Acid.



SOLVENT: Methyl-$\underline{d}_3$ Alcohol-$\underline{d}$; 99.5 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

Figure IV.B.5.b

Proton Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)thiophene-5-boronic Acid.



SOLVENT: Methyl-d_3 Alcohol-$\underline{d}$; 99.5 atom % D
REFERENCE: Boron Trifluoride Etherate;
0.0 ppm

Figure IV.B.5.c

Boron-11 Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)thiophene-5-boronic Acid.

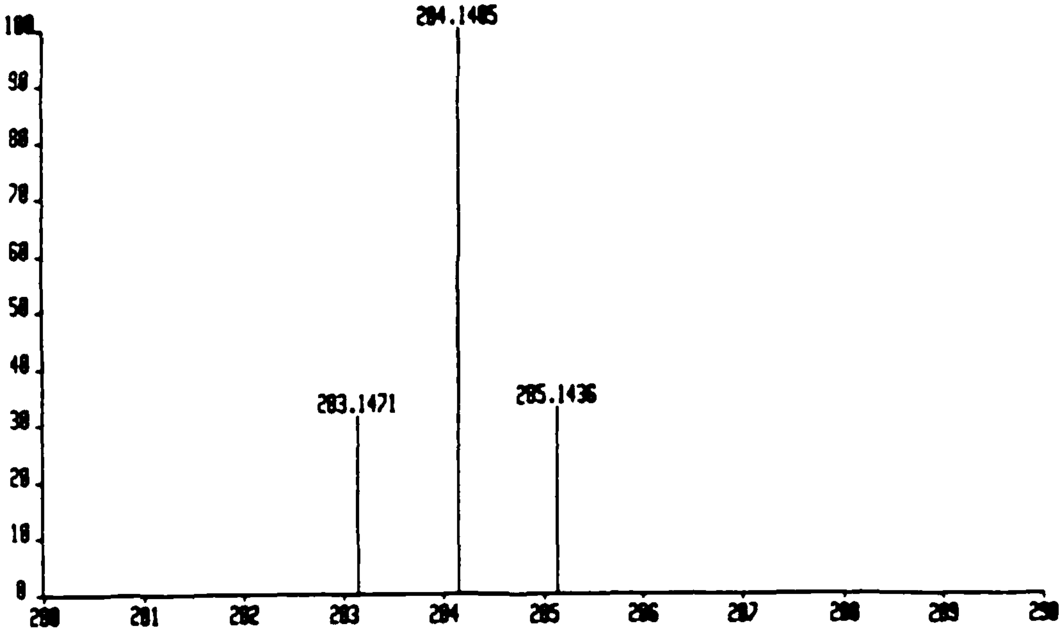


Figure IV.B.5.d

High Resolution Mass Spectrum of N-Isopropyl 2-(2-Aminopropyl)-thiophene-5-boronic Acid.

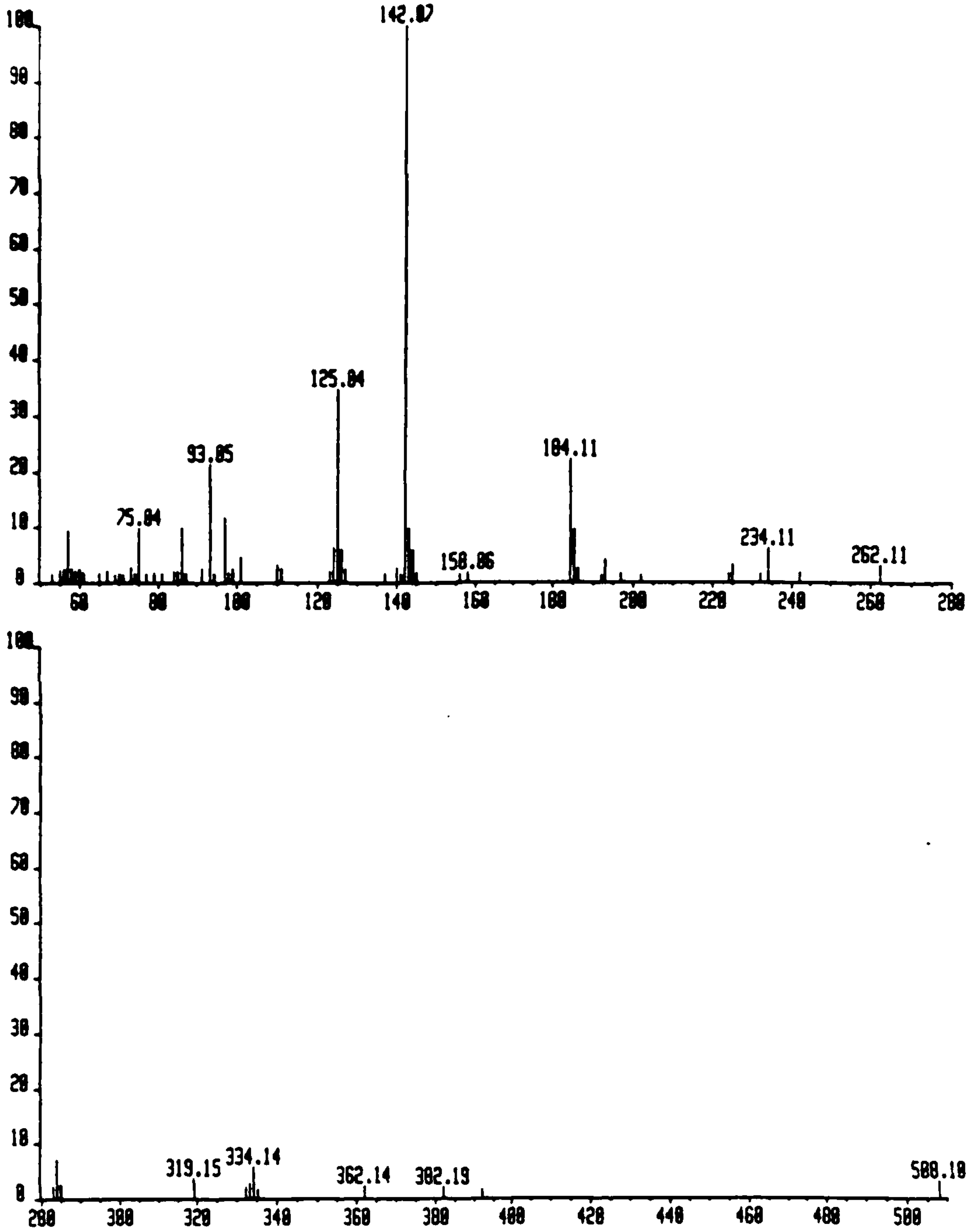


Figure IV.B.5.e
Ion Fragmentation Spectrum of N-Isopropyl 2-(2-Aminopropyl)-thiophene-5-boronic Acid

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Chloroform; 77.0 ppm

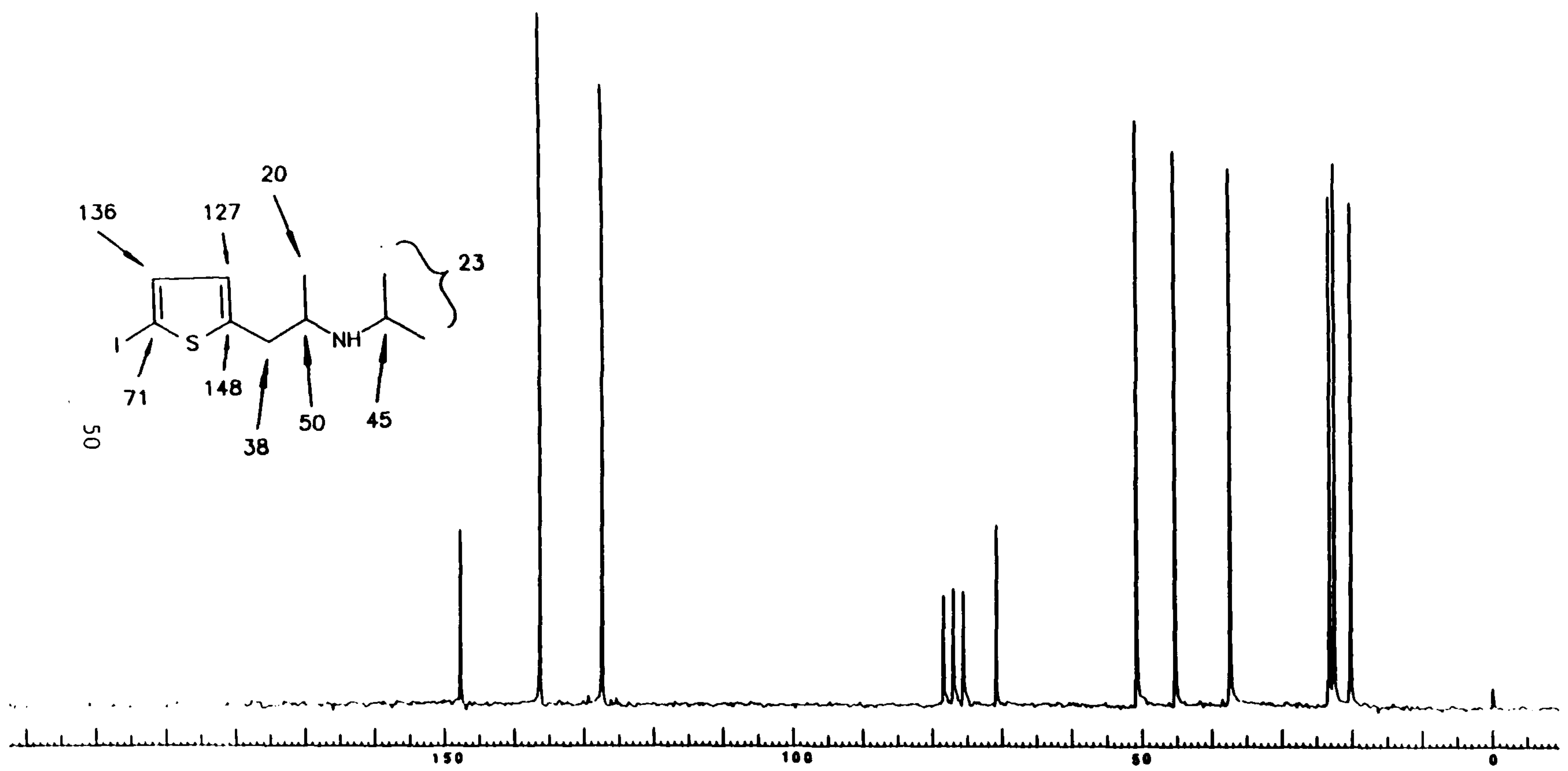


Figure IV.B.6.a

Carbon-13 Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-iodothiophene.

SOLVENT: Chloroform-d; 99.8 atom % D
REFERENCE: Tetramethylsilane; 0.0 ppm

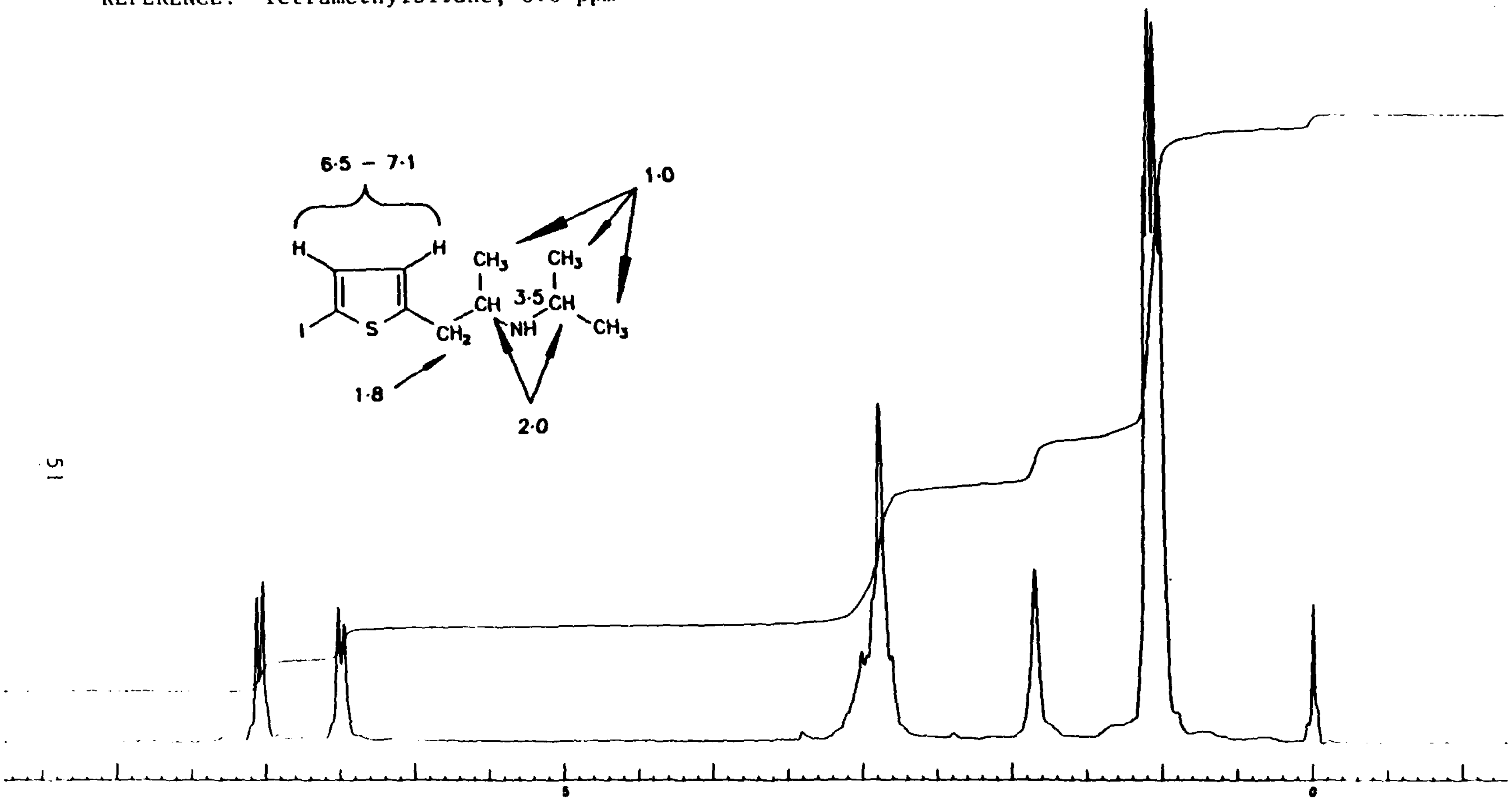


Figure IV.B.6.b

Proton Nuclear Magnetic Resonance Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-iodothiophene.

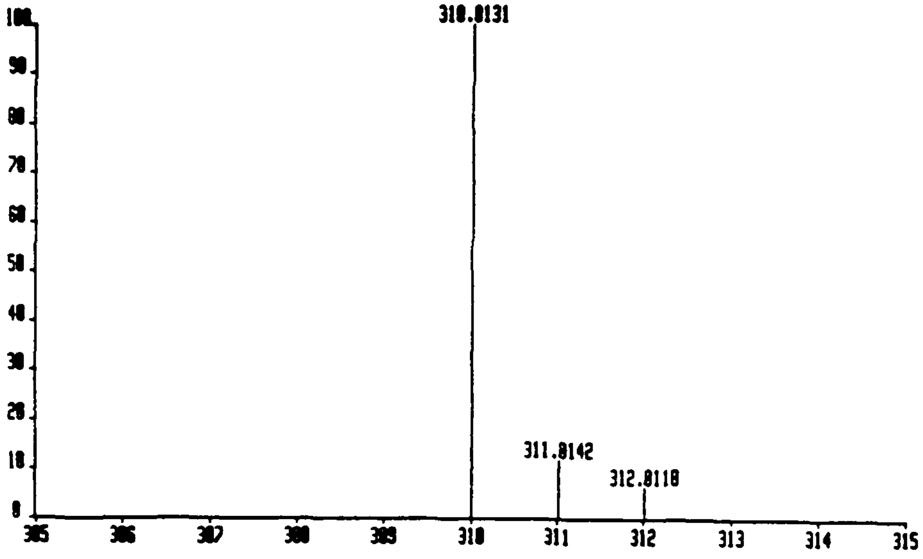


Figure IV.B.6.c

High Resolution Mass Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-iodothiophene.

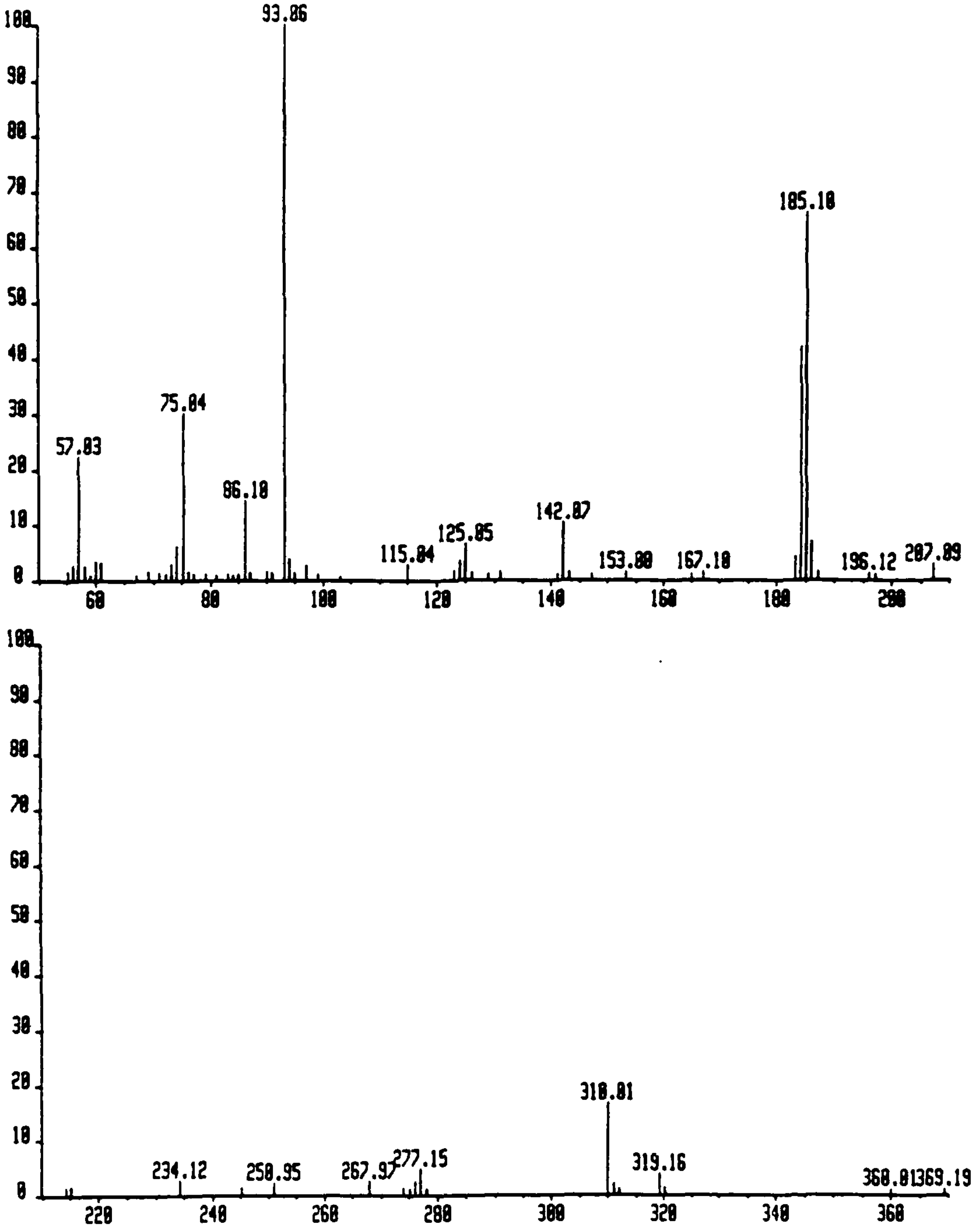


Figure IV.B.6.d

Ion Fragmentation Spectrum of N-Isopropyl 2-(2-Aminopropyl)-5-iodothiophene.

CHAPTER V

CONCLUSIONS

N-Isopropyl 2-(2-aminopropyl)-5-iodothiophene labeled with iodine-131 was sucessfully synthesized. The synthetic pathway for this synthesis parallels that developed by Kabalka _et al_.[6] for the synthesis of iodine-123 labeled N-isopropyl _p_-iodoamphetamine. Further studies with other thienyl analogues will benefit the medical imaging field as well as comparison of synthetic techniques.

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VITA

Ronald Curtis Marks [redacted] [redacted]. He graduated from Montezuma Cortez High School, Cortez, Colorado, in June of 1977. After attending Grand Canyon College in Phoenix, Arizona from September 1977 through June of 1980, he entered The University of Tennessee, Knoxville, in September of 1980. In July of 1981, Ron and Joann Williams were married. Ron graduated from The University of Tennessee with honors in June of 1982 with a Bachelor of Arts Degree in Chemistry. At graduation he was commissioned as a Second Lieutenant in the United States Air Force and designated a Distinguished Graduate of the Reserve Officers Training Corps.

While stationed at Wright-Patterson Air Force Base, Dayton, Ohio, Ron and Joann had a beautiful daughter, [redacted] While at Wright-Patterson, Ron was awarded the Air Force Commendation Medal. He was then assigned to Naval Air Systems Command in Washington, DC, from 1984 through 1986. He was promoted to First Lieutenant in July 1984, and then to Captain in 1986. The Joint Service Commendation Medal was awarded to Ron in 1986. Selection to be a chemistry instructor at the United States Air Force Academy led to graduate school at The University of Tennessee, Knoxville, in January 1987. In March of 1987 Ron began research under the direction of Dr. G. W. Kabalka.