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APPLICATION OF PALLADIUM NANOPARTICLES FOR THE REDUCTION OF NITROGEN CONTAINING FUNCTIONAL GROUPS

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Paramita Mukherjee

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Major Professor's Signature

12-14-2009

Date

APPLICATION OF PALLADIUM NANOPARTICLES FOR THE REDUCTION OF NITROGEN CONTAINING FUNCTIONAL GROUPS.

By

Paramita Mukherjee

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ABSTRACT

APPLICATION OF PALLADIUM NANOPARTICLES FOR THE REDUCTION OF NITROGEN CONTAINING FUNCTIONAL GROUPS.

By

Paramita Mukherjee

We started to look at the catalytic nature of the palladium acetate/ aqueous potassium fluoride/ polymethylhydrosiloxane system with the aim of developing better catalysts that would facilitate reductions of nitrogen-containing functional groups under mild conditions and short reaction times. We observed that this catalytic system forms palladium nanoparticles that act as the active catalyst. With the true nature of the active catalyst being characterized by advanced microscopic techniques (transmission electron microscopy), we were able to perform the reductions of aromatic and aliphatic imines under mild conditions such as low catalyst loading and performing the reaction at room temperature and short time. Our desire to further expand the scope of this catalyst system to reduce aliphatic nitroketones to undergo stepwise reduction and cyclization revealed that palladium acetate with triethylsilane acts as a better reducing combination. Therefore, we used this catalyst system to develop a facile method to reduce different nitroketones to nitrones, also at room temperature and with short reaction times.

ACKNOWLEDGEMENTS

I would like to thank Professor Robert E. Maleczka Jr. for giving me this opportunity to work in his lab. His guidance, advice and encouragement throughout my studies at Michigan State University are priceless to me. I would also like to thank Dr. William Wulff, Dr. Babak Borhan and Dr. Merlin Bruening for serving on my guidance committee.

I would also have this opportunity to thank my parents and my family back in India. My studies here in USA would not have been possible without their support. I am thankful to my husband, Pravas Deria who has supported me and guided me in all my work. I thank all my group members of the Maleczka lab for their friendship and help. I always enjoyed working with them in the lab.

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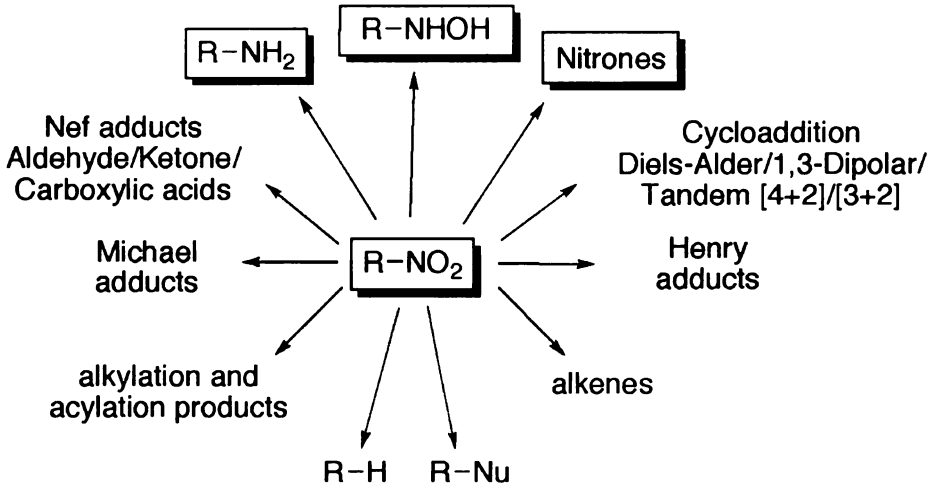
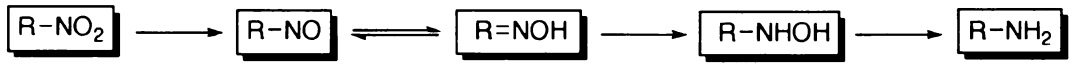
Chapter 1. Introduction.

Nitrogen containing functional groups are prevalent in a range of organic molecules. Literature survey shows that nitro compounds have served as versatile building blocks for synthesis of complex target molecules.[1] This is primarily because nitro compounds are commercially available or can be easily prepared. Moreover stereodefined aliphatic nitro compounds are now accessible through several asymmetric catalytic reactions.[1-3] The nitro group has been described in the past as a "synthetic chameleon";[1c] because once in hand, the nitro group can undergo several transformations.[1,2,4,5] It can undergo a Nef reaction to produce aldehydes, ketones, or carboxylic acids, Michael additions, alkylations, acylations, nucleophilic substitutions, eliminations, generation of nitro-aldol adducts (Henry reaction), participation in cycloaddition reactions and can be effectively reduced to amines, hydroxylamines, nitrones (Scheme 1.1).



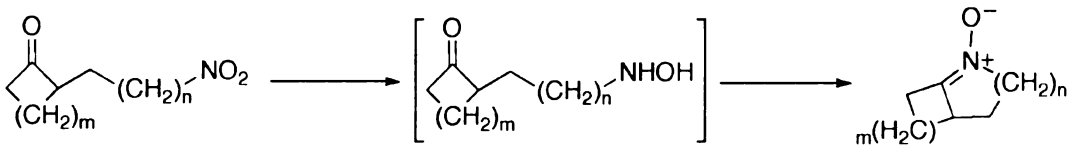
Scheme 1.1. Reactions of nitro compounds.

Reductions have always been an important method for functional group interconversion in organic chemistry. Reduction methodology can allow for the conversion of nitro compounds in steps to nitroso, oxime, hydroxylamine and finally to amine compounds (**Scheme 1.2**).



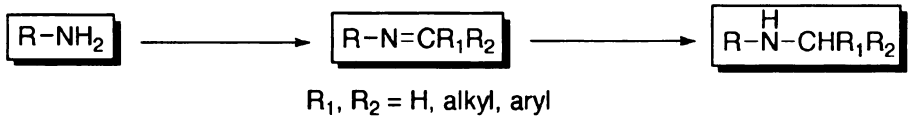
Scheme 1.2. Stepwise reduction of nitro compounds.

In this process of stepwise reduction, an intermediate stage can be trapped by reaction with another functional group existent in the same or a different molecule. For example, a chemoselective reduction of a nitroketone to the hydroxylamine ketone can be followed by intramolecular condensation with the ketone to generate a nitrone. Such a pathway provides a facile route to formation of *N*-heterocycles (**Scheme 1.3**).



Scheme 1.3. Possible formation of nitrones from functionalized nitroketones.

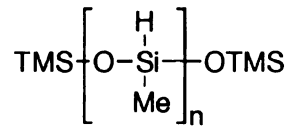
Again, reduction methods can analogously be applied for interconversion between different amines. A primary amine, produced from the reduction of nitro compound, can then be converted to a secondary amine via an imine reduction as part of a reductive amination (**Scheme 1.4**).



Scheme 1.4. Reactions of amine.

There have been several methods developed in the past that involve such transformations (**Schemes 1.1 through 1.4**). In spite of these methods being widely used, there remain a need for new milder reaction conditions, room temperature reactions, shorter reaction times using reagents that are environmentally friendly and chemoselective reaction that would improve functional group tolerance. A reagent that might meet these needs is polymethyhydrosiloxane (PMHS).

Polymethylhydrosiloxane (PMHS) is an air-stable, nontoxic polymeric byproduct of the silicone industry. It acts as an effective reducing agent when combined with catalysts of metals like Pd, Sn, Zn, Cu. In addition, it is inexpensive, readily available, environmentally friendly and non-toxic. It can be stored on the bench for years with no detrimental effect as it is stable to air and moisture. All of this makes PMHS an attractive reagent. Also a moderate polymer length (degree of polymerization equals 32 to 35) makes its viscosity low and soluble in common organic solvents. A literature survey over the past few years shows that the use of PMHS has increased dramatically with over 150 citations every year.



n = ~32-35

PMHS

Previously Maleczka and coworkers have seen that $Pd(OAc)_2$/PMHS in presence of aqueous KF is capable of facile hydride transfer and transfer hydrogenation processes.[6] Fluoride activation of PMHS makes it a more effective hydride transfer agent via the

involvement of the polycoordinating silicon hydride species. Maleczka and Terstiege found that the combination of PMHS and aqueous potassium fluoride (KF) can efficiently reduce the trialkyltin halides to trialkyltin hydrides.[6] Utilizing this method, Pd-catalyzed reductions using PMHS in presence of aqueous KF was successfully applied to one-pot Pd-catalyzed hydrostannation/Stille couplings,[7] hydrodehalogenation of arylhalides,[8] 1,4-reduction of enones,[9] and the reductive cleavage of benzylic C-O bonds,[10] all at room temperature.

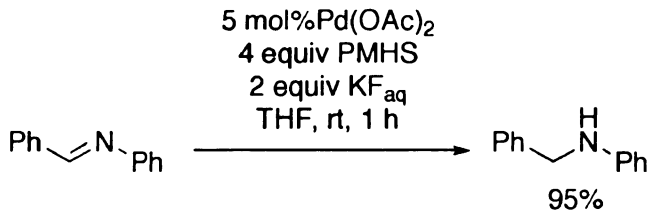
The scope of this thesis lies in finding methods to obtain several aromatic and aliphatic secondary amines from their corresponding imines using $Pd(OAc)_2$/PMHS/KF_{aq} reductions, conversion of aliphatic nitro compounds to their amines and facile reduction/cyclization of nitroketones to nitrones. Progress and success obtained in each of the above mentioned projects is detailed in the following chapters of this thesis.

Chapter 2: Application of palladium nanoparticles for the reduction of imines under milder conditions.

The most widely used methods to obtain amines by reduction of imines include $NaBH_4$,[11] $LiAlH_4$,[12] NH_3/Ra-Ni,[13] iPr-OH/aluminum isopropoxide/Ra-Ni,[14] CH_3COONH_4/Ra-Ni,[15] NH_4Cl/PtO_2,[16] BH_3.DMA.[17] Another much commendable method to obtain amines is by reductive amination of carbonyl compounds.[18] There have also been protocols developed for the catalytic enantioselective reduction of imines.[19] In this myriad of methods to obtain amines by imine reduction, there is still opportunity to develop new methods that involve inexpensive reagents, milder and catalytic conditions. PMHS is one such inexpensive reagent. It had been used in the past for the reduction of imines in combination with Zn catalyst.[20] Asymmetric reductions were also achieved using PMHS along with Zn, Ti, Sn and other metal catalysts.[19]

In the process of investigating several functional group transformations, we observed that PMHS, in the presence of catalytic $Pd(OAc)_2$, can efficiently reduce aromatic and/or aliphatic imines to their corresponding secondary amines at room temperature in short reaction times. To the best of our knowledge there has been no reports yet of using PMHS combining with Pd in the reduction of imines.

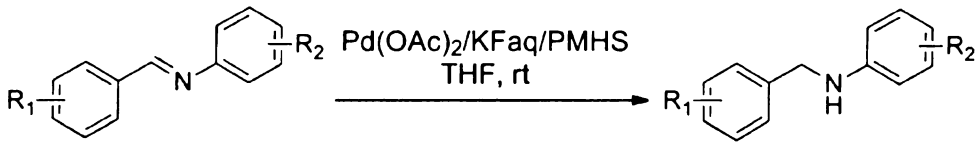
Upon treatment of *N*-benzylideneaniline to the reduction conditions of aromatic nitro compounds with catalytic $Pd(OAc)_2$ (5 mol%), PMHS (2 equiv) and aqueous KF (2 equiv), *N*-benzylaniline was obtained in 95% yield at room temperature in 1 h (**Scheme 2.1**).



Scheme 2.1. Reduction of aromatic imine with PMHS/KF_{aq} and catalytic $Pd(OAc)_2$.

Optimizing the reaction conditions revealed that catalytic $Pd(OAc)_2$ was absolutely essential for the reduction as in its absence there was no reaction after 1 day. Reducing the $Pd(OAc)_2$ concentration lower than 5 mol% required longer reaction time for complete conversion. Two equivalents of PMHS were sufficient to effectively reduce while aqueous KF could be used in catalytic amounts (10 mol%). In absence of PMHS, there was no reaction showing that the reduction mechanism is possibly through transfer hydrogenation from PMHS. However the presence of aqueous KF allowed these imine reductions to be complete in shorter reaction time such as 1 h indicating its involvement in activating the PMHS. In absence of aqueous KF, a 12 h reaction time was required for complete reduction and the isolated yield of the product amine was low (**Table 2.1**).

Applying the optimized reaction conditions, several functionalized aromatic imines underwent reductions to produce the corresponding secondary amines in moderate to good yields. Electron-withdrawing as well as electron-donating substituents on either of the phenyl rings were tolerated. With a chloride substitution on the phenyl ring bearing the imine, reduction to the amine took place but it was accompanied with some amount of hydrodehalogenated product. This is in accordance to what have been observed previously in our group that $Pd(OAc)_2/KF_{aq}$/PMHS system is capable of doing hydrodehalogenations of aromatic chlorides.[21]

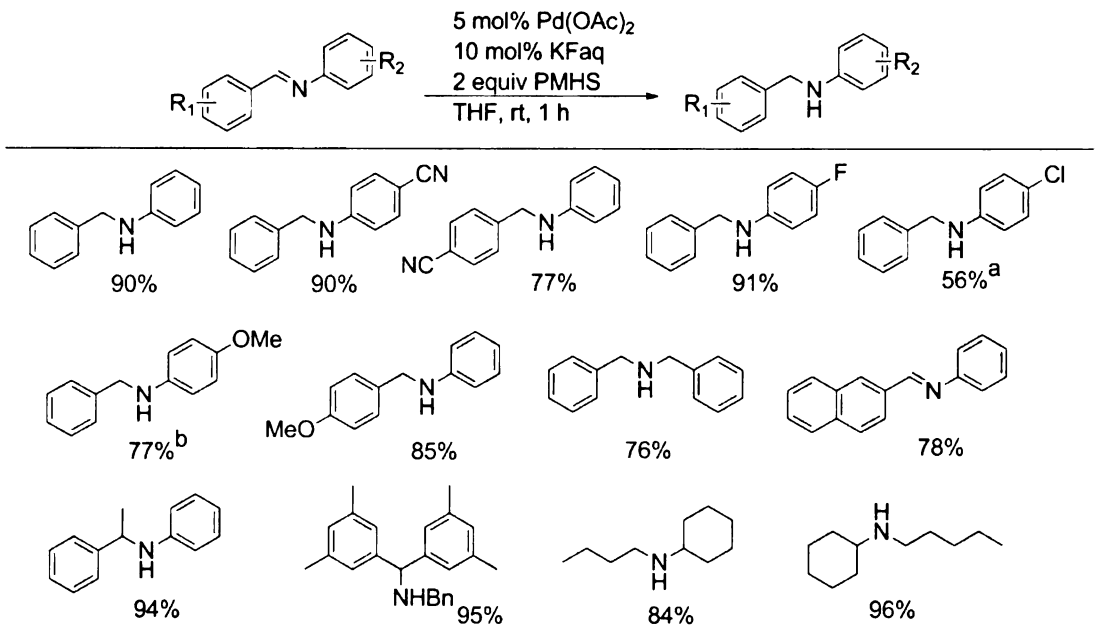


Entry	Substrate	$Pd(OAc)_2$	KFaq	PMHS	Time	Yield[a]
1	R_1=R_2=H	—	2 equiv	4 equiv	24 h	No reaction
2	R_1=R_2=H	5 mol%	2 equiv	—	12 h	No reaction
3	R_1=R_2=H	5 mol%	2 equiv	4 equiv	1 h	95%
4	R_1=R_2=H	5 mol%	50 mol%	2 equiv	1 h	93%
5	R_1=R_2=H	5 mol%	10 mol%	2 equiv	1 h	90%
6	R_1=R_2=H	5 mol%		4 equiv	12 h	69%
7	R_1=H, R_2=OMe	5 mol%		4 equiv	12 h	77%

Table 2.1. Optimization of the imine reduction conditions. [a] All reactions were performed on a 1mmol scale. Yields are isolated yields after purification by FCC.

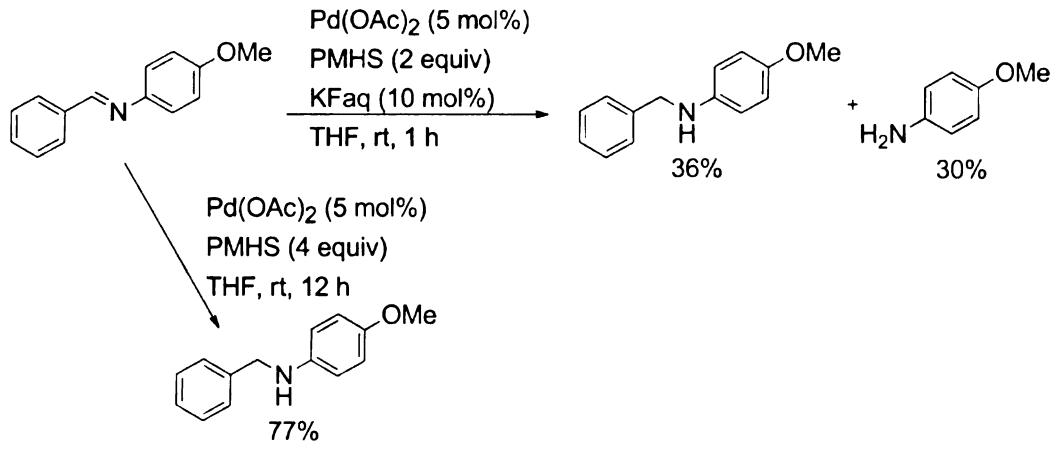
With an electron-donating substituent such as OMe on the *para* position of the nitrogen-containing phenyl ring, partial over-reduction of the product secondary amine to the corresponding primary amine was observed (**Scheme 2.3**). This was however not the case of electron-withdrawing substituents on either of the phenyl rings. The reason for such behavior could be due to more electron density on the N atom of the resulting secondary amine, when there is an electron-donating group present at the para-position, that leads to further coordination of the product to the active catalyst leading to overreduction. So the only possible way to overcome such reductions when the imine is more reactive is by reducing the activity of the catalyst. Indeed, such was observed. Reduction of *N*-benzylidene-4-methoxyaniline with 5 mol% $Pd(OAc)_2$/10 mol% KF_{aq}/2 equiv PMHS gave a mixture of the secondary amine and primary amine. Removing the KF_{aq} from the reaction conditions gave only the desired secondary amine, however all the

starting material was reduced over a period of 12 h. This is probably due to absence of KF_{aq} that makes PMHS less reactive (**Scheme 2.3**).



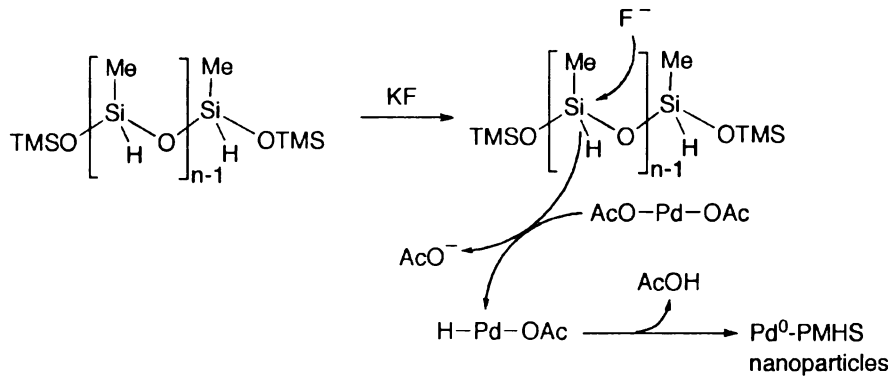
Scheme 2.2. Reduction of several functionalized imines with $Pd(OAc)_2/KF_{aq}$/PMHS. [a] This product was accompanied with some hydrodehalogenated amine in accordance with hydrodehalogenation observed previously under such conditions. [b] Reaction conditions are: 5 mol% $Pd(OAc)_2$, 4 equiv PMHS, 12 h.

Dibenzylic imines and imines formed from naphthaldehyde were successfully reduced under the conditions to give the product amines in good yield (77%). The scope of these reaction conditions extends to the reduction of aromatic ketoimines and aliphatic aldimines and ketoimines. The ketoimine derived from acetophenone was reduced to give a high yield of the product amine. Both the aliphatic aldimine derived from butyraldehyde and hexylamine, and the ketoimine derived from cyclohexanone and pentylamine respectively, were reduced to their corresponding secondary amines.

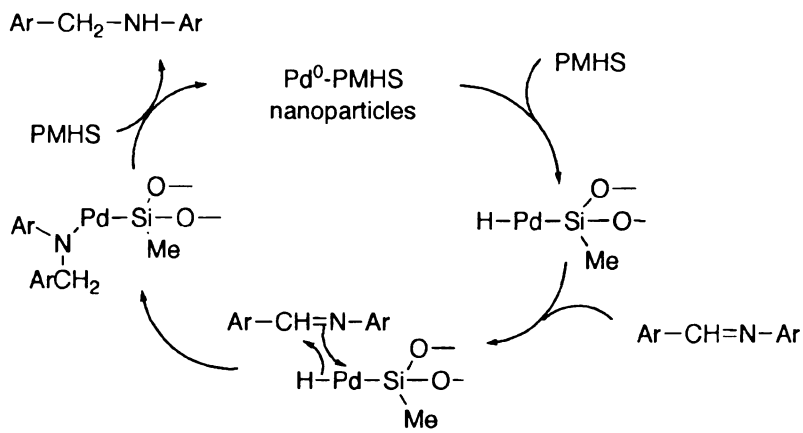


Scheme 2.3. Reduction of PhCH=NPh(*p*-OMe) in presence and absence of catalytic KF_{aq}.

To investigate the mechanism of the Pd-PMHS catalyzed reductions, it was speculated that the Si center of the polymeric PMHS is being activated by fluoride from KF to form a hypervalent Si species that initiates an effective hydride transfer. $Pd(OAc)_2$ in presence of $PMHS/KF_{aq}$ forms Pd-PMHS nanoparticles (similar observation made previously by Chauhan)[22] that acts as the active catalyst in the catalytic cycle to reduce the imines (Schemes 2.4 and 2.5).



Scheme 2.4. Activation of PMHS by KF and formation of Pd-PMHS nanoparticles.



Scheme 2.5. Catalytic cycle for imine reductions.

In order to gain more information about the nature of the catalyst we sought to observe the morphology of the active catalyst. So the same reaction conditions were followed, only in absence of the substrate, to generate the catalyst and transmission electron microscopy (TEM) was employed as a tool to observe the nature of the catalyst. TEM images of the catalyst show the presence of Pd nanoparticles of sizes between 2 to 10 nm with a large population of particles of 5 nm size (**Figure 2.1**).

X-Ray electron dispersion spectroscopic (EDS) data analysis showed the presence of Si and O on the copper grid around the Pd nanoparticles. This suggests that the PMHS is involved in dispersing the Pd particles and stabilizing then by wrapping around with high active surface area and hence prevent them from further aggregation and precipitation, thus loosing the catalyst activity.

To conclude, it was possible to develop an efficient method to reduce both aliphatic and aromatic imines to their corresponding amines in high yields under mild reaction conditions that involves low catalyst loading, short reaction time and room temperature.

An insight into the mechanism of these reaction and the nature of the precatalyst formed from $Pd(OAc)_2$ and $PMHS/KF_{aq}$ revealed the formation of Pd-PMHS nanoparticles under these conditions that act as active catalyst.

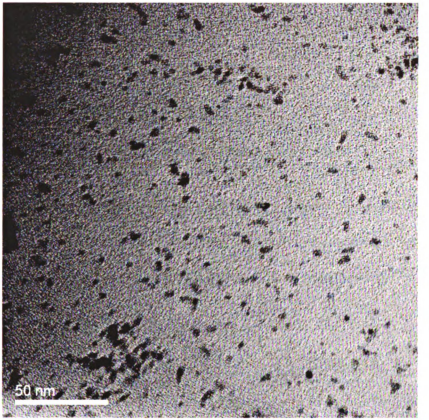
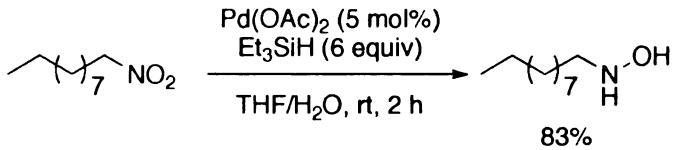


Figure 2.1. Transmission electron microscope (TEM) images of Pd nanoparticles.

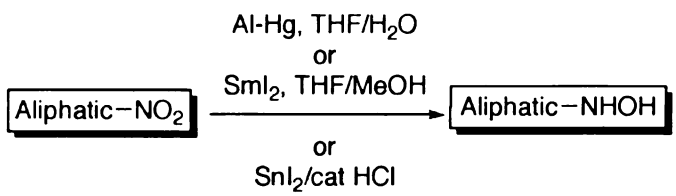
Chapter 3: Pd-catalyzed formation of nitrones from nitroketones

A facile reduction of aliphatic nitro compounds have been obtained in the past by Maleczka and coworkers using $Pd(OAc)_2$ with a non-polymeric silyl hydride, triethylsilane (**Scheme 3.1**).[23-24]



Scheme 3.1. Reduction conditions developed by Maleczka and Rahaim.

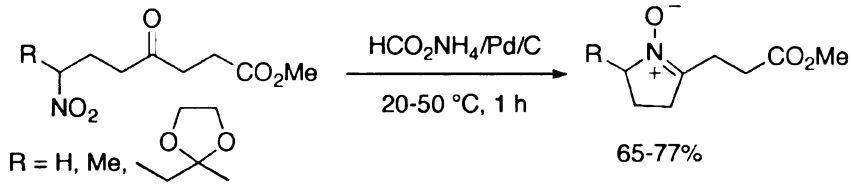
Hydroxylamines are generally obtained from oxidation of amines. Examples of generating hydroxylamines via the reduction of aliphatic nitro compounds have been few owing in part to the problem of overreduction to the amines (**Scheme 3.2**). [25]



Scheme 3.2. Some methods of aliphatic nitro reductions to hydroxylamines.

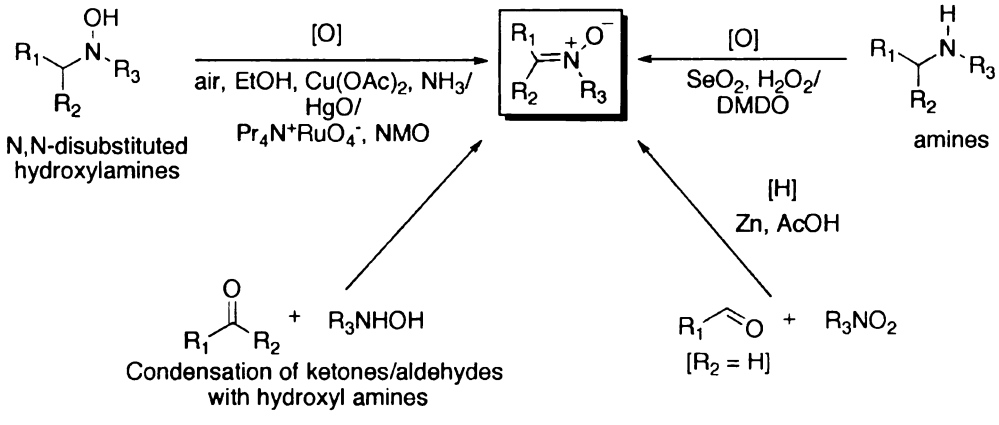
So the formation of hydroxylamine from aliphatic nitrocompounds under such milder reaction conditions was an interesting reaction that was explored. When looking at the scope of such a reaction, the primary and secondary nitro groups responded favorably to these reaction conditions. A range of functional groups were tolerated. The selective reduction of the nitro functionality in presence of a ketone produced a cyclic nitrone. This transformation was envisaged to have gone through the initial reduction to the hydroxylamine that subsequently cyclized with the ketone to produce the cyclic nitrone.

This transformation was worth exploring further because it can potentially be a new avenue towards nitrone synthesis. In the past there had been only one example reported of such cyclic nitrone formation from a γ-nitroketone by Reissig and coworkers (**Scheme 3.3**).[26]



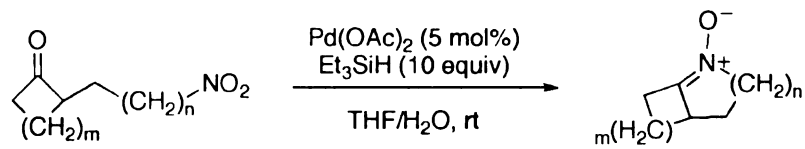
Scheme 3.3. Reissig's synthesis of five-membered cyclic nitrone.

Nitrones (or azomethine oxides), first prepared by Beckman in 1890, exist in *(E)*- and *(Z)*- forms that may interconvert.[27-28] They are generally stable, hence isolable. To date, nitrones have been mainly obtained by oxidation of amines and hydroxylamines (Scheme 3.4).[4,27-30] Compared to these methods, there are few examples of obtaining nitrones by the reduction of nitro compounds.[1,4-5,30]



Scheme 3.4. Methods to generate nitrones.

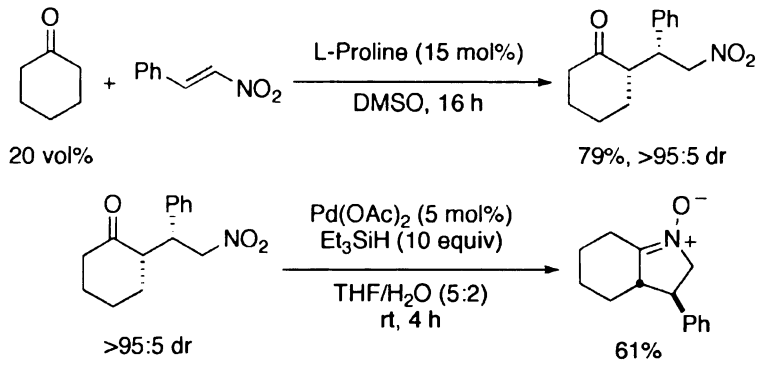
Cyclic nitrones, unlike acyclics, do not have the issue of nitrone isomerization and thus permit only a single geometry across the C=N bond. Also, cyclic nitrones due to their facial selectivity can allow predictable asymmetric induction when acting as 1,3-dipoles in cycloaddition reactions. Therefore nitrones serve as a powerful tool to modern synthetic discovery and are due further exploration with respect to our methodology (**Scheme 3.5**).



Scheme 3.5. General scheme for the nitroketone reduction.

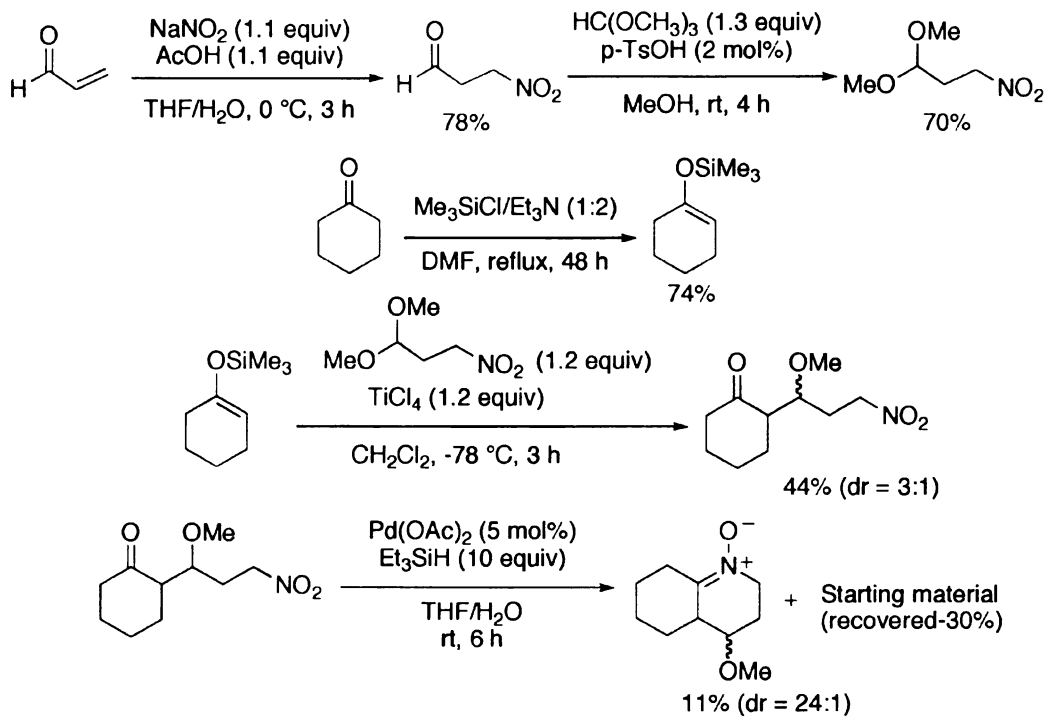
With the target synthesis of several cyclic nitrones in mind, the synthesis of their corresponding nitroketones was initiated. The nitroketones were selected such that the scope of the reduction lies in variations of ring size of the product nitrones. The reaction conditions were optimized on the cyclization of the γ-nitroketone, that had been observed by a previous group member.[23] The nitroketone was synthesized by a known literature procedure (**Scheme 3.6**).[31]

We next sought to increase the ring size of the nitrone ring from a 5-membered cyclic nitrone to a 6-membered species. The corresponding δ-nitroketone was synthesized in several steps as a mixture of diastereomers (diastereomeric ratio of 3:1 determined from ^{1}H-NMR analysis). On subjecting the nitroketone to the reduction conditions, cyclization to the corresponding nitrone did occur however the reaction yield was poor.



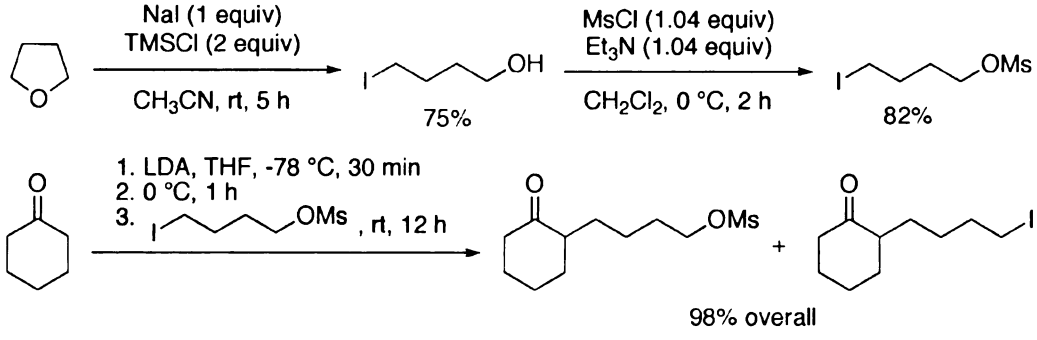
Scheme 3.6. Synthesis of the γ-nitroketone and then subjecting it to the reduction conditions.

After 6 h of stirring at room temperature with starting material recovered from the reaction mixture and only 11% of the product could be isolated (**Scheme 3.7**). The product had a high diastereomeric ratio of 24:1 that indicated one isomer cyclizing preferentially over the other.

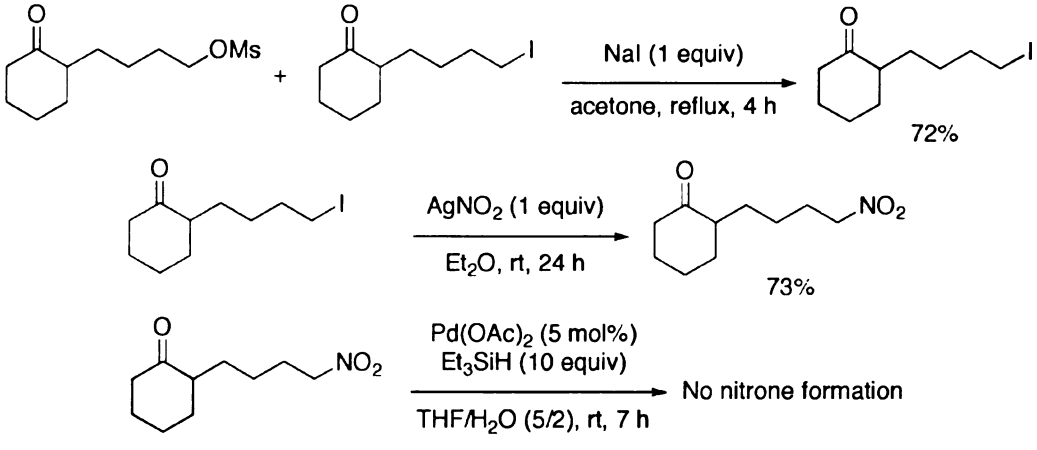


Scheme 3.7. Synthesis of the δ-nitroketone and then subjecting it to the reduction conditions.

Further synthesis of the next higher homologue was ventured to see if the trend continues that with increase in ring size the cyclization gets more difficult. The nitroketone was synthesized by C-alkylation at the α-position of cyclohexanone, followed by functional group interconversion. Subjecting the compound to the reaction conditions for 7 h gave no product nitrone (**Scheme 3.8 and 3.9**).



Scheme 3.8. Synthesis of the δ-nitroketone.

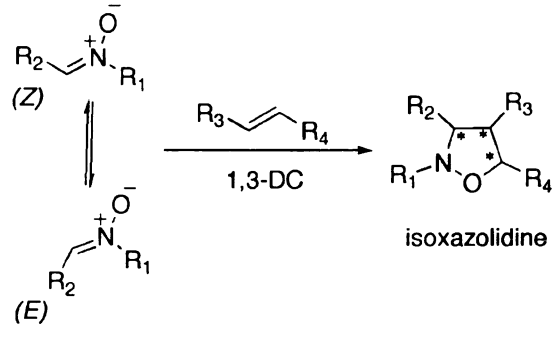


Scheme 3.9. Synthesis of the δ-nitroketone and then subjecting it to the reduction conditions.

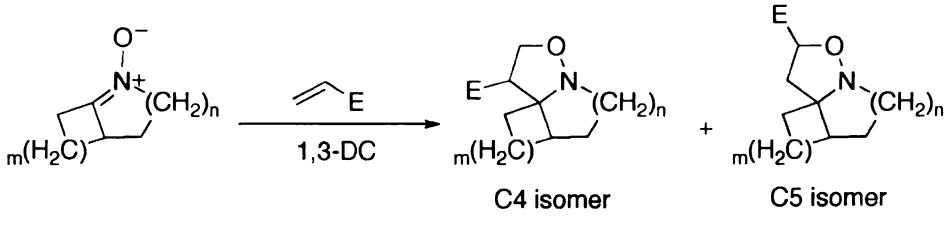
Therefore in terms of ring size, the scope of this reaction is limited to the six-membered cyclic nitrone. Improvements in reaction yield might be achieved under

rigorous conditions (such as high temperature and/or longer reaction time). The possibility of variations in the ring size of the other carbocycle still remains unexplored.

The chemistry of nitrones is dominated by their application as 1,3-dipoles for cycloaddition reactions (**Scheme 3.11**).[1,4,27-28] The importance of these 1,3-dipolar cycloaddition products is evident from the large number of targets with N and O heteroatoms that can be prepared via this route. Nitrones are good 1,3-dipoles for all electron deficient, electron rich and normal olefins thus providing a wide scope of 1,3-dipolar cycloadditions. Cyclic nitrones due to their facial selectivity can allow predictable asymmetric induction when acting as 1,3-dipoles in cycloaddition reactions. Therefore it is worth exploring the application of these nitrones in the 1,3-dipolar cycloaddition chemistry (**Scheme 3.10 and 3.11**).

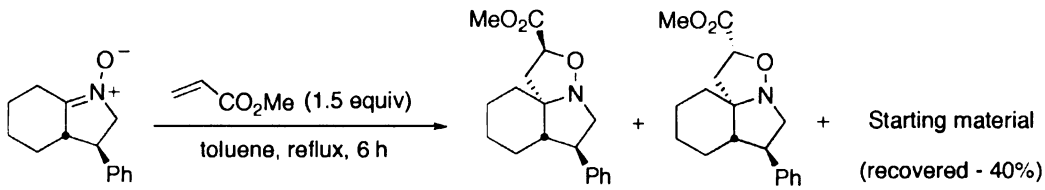


Scheme 3.10. 1,3-Dipolar cycloaddition of nitrones to dipolarophiles.



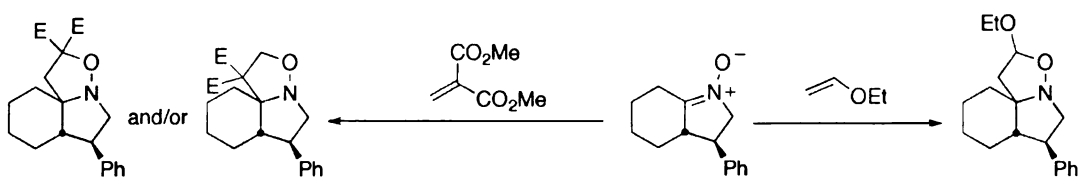
Scheme 3.11. 1,3-Dipolar cycloaddition of cyclic nitrones to dipolarophiles.

A 1,3-dipolar cycloaddition was attempted on the product cyclic nitrone (from **Scheme 3.6**) with methyl acrylate using known reaction conditions for a similar substrate.[32] The product isoxazolidine was obtained as an 1.3:1.0 inseparable diastereomeric mixture of epimers at C-5. The regiochemistry of the mode of addition of methyl acrylate to give the C5 isomer was confirmed from DEPT analysis of the product (**Scheme 3.12**). With further optimization of the reaction condition, a better conversion of the reaction is expected.



Scheme 3.12. 1,3-Dipolar cycloaddition of the nitrone with methyl acrylate.

There still remains a wide scope of reactions that might be ventured. The ring size of the cyclic nitroketone could be altered to get a series of fused nitrone rings as well as the potential for the acyclic nitrones to undergo cyclization under these conditions remain unexplored. Once the nitrones are formed, their potential to undergo 1,3-dipolar cycloaddition with stereochemically and electronically different alkenes might be thought as an application towards natural product synthesis (**Scheme 3.13**).



Scheme 3.13. 1,3-Dipolar cycloaddition of the nitrone with dipolarophiles.

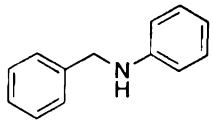
Experimental Section

Materials and Methods: All reactions were performed in dry glasswares under an atmosphere of nitrogen, with magnetic stirring, and monitored by ^{1}H-NMR (taken in a 500 MHz spectrometer) of aliquots from the reaction mixture. THF was freshly distilled from sodium/benzophenone under nitrogen. Palladium (II) acetate, anhydrous A.C.S. grade potassium fluoride and polymethylhydrosiloxane (PMHS) were purchased from Sigma-Aldrich and used without purification. The aromatic and aliphatic imines for palladium-polymethylhydrosiloxane reduction were prepared following literature procedures.[33]

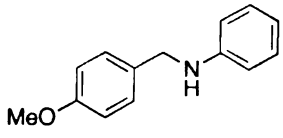
General Procedure for the Reduction of Aromatic and/or Aliphatic Imines to Amines: A round bottomed flask was charged with the imine (1 mmol), $Pd(OAc)_2$ (0.05 mmol, 11 mg) and 5mL of freshly distilled THF. The flask was sealed and its contents were stirred and purged with N_2. While purging the flask with nitrogen, KF_{aq} solution (0.1 mmol, 0.1 mL) was added via syringe (prepared separartely in a round bottomed flask using solid KF and degassed H_2O). The nitrogen purging was replaced with a balloon filled with N_2 followed by dropwise addition of PMHS (2 mmol, 0.12 mL, 1 mmol is equal to 0.06 mL) with a syringe (PMHS is added slowly dropwise to prevent rapid evolution of H_2 gas). The reaction was stirred at rt for 1 h or until completion as judged by NMR. At that time the reaction flask was opened, 5 mL of ether added and stirred for further 5 minutes. Excess anhydrous Na_2SO_4 was added to remove the catalytic amounts of water, filtered and the organics concentrated.

The crude amine thus obtained was purified by flash chromatography using silica gel or celite/basic alumina and eluting with gradients of hexanes/ethyl acetate (50:1 then 4:1).

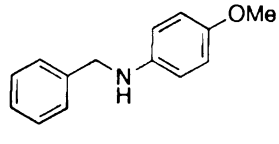
Experimental Details and Spectroscopic Data:



***N*-benzylaniline:** Subjecting *N*-benzylideneaniline to the general reduction conditions produced 0.165 g (90%) of *N*-benzylaniline as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.32 (m, 4H), 7.27 (t, J = 7.0 Hz, 1H), 7.17 (t, J = 7.5 Hz, 2H), 6.71 (t, J = 7.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 2H), 4.32 (s, 3H), 4.07 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.6, 112.8, 48.3. Spectral data were consistent with previously reported material.[34]

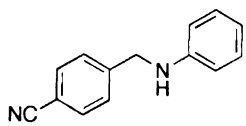


***N*-(4-methoxybenzyl)aniline:** Subjecting *N*-(4-methoxybenzylidene)aniline to the general reduction conditions produced 0.181 g (85%) of *N*-(4-methoxybenzyl)aniline as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.0 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.73 (t, J = 7.0 Hz, 1H), 6.65 (d, J = 7.5 Hz, 2H), 4.26 (s, 2H), 3.95 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 148.2, 131.4, 129.2, 128.7, 117.4, 113.9, 112.8, 55.2, 47.7. Spectral data were consistent with commercially available material.

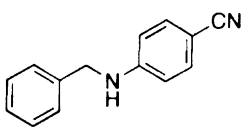


***N*-benzyl-4-methoxyaniline:** Subjecting *N*-benzylidene-4-methoxyaniline to the general reduction conditions in presence of PMHS (4 mmol, 0.24 mL, 1 mmol is equal to 0.06 mL) and no KF_{aq} for a reaction time of 12 h produced 0.164 g (77%) of *N*-benzyl-4-methoxyaniline as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.32 (m, 4H), 7.27 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 7.0

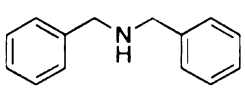
Hz, 2H), 6.61 (d, J = 7.0 Hz, 2H), 4.28 (s, 2H), 3.74 (s, 3H), 3.13 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 142.2, 139.4, 128.3, 127.3, 126.9, 114.6, 113.8, 55.5, 48.9. Spectral data were consistent with commercially available material.



4-(Phenylaminomethyl)benzonitrile: Subjecting 4-(phenyliminomethyl)benzonitrile to the general reduction conditions produced 0.16 g (77%) of 4-(phenylaminomethyl)benzonitrile as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.15 (t, J = 7.5 Hz, 2H), 6.73 (t, J = 7.0 Hz, 1H), 6.55 (d, J = 7.5 Hz, 2H), 4.41 (s, 2H), 4.18 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 145.4, 132.5, 129.5, 128.2, 127.7, 118.2, 112.9, 47.9. Spectral data were consistent with previously reported material.[35]

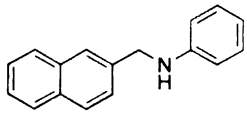


4-(Benzylamino)benzonitrile: Subjecting 4-(benzylideneamino)benzonitrile to the general reduction conditions produced 0.187 g (90%) of 4-(benzylamino)benzonitrile as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 7H), 6.57 (d, J = 8.5 Hz, 2H), 4.68 (s, 1H), 4.36 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.1, 137.8, 133.6,128.8, 127.6, 127.2, 120.3, 112.4, 98.9, 47.4. Spectral data were consistent with previously reported material.[36]

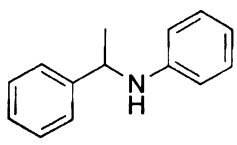


***N,N*-dibenzylamine:** Subjecting *N*-benzylidene-1-phenylmethanamine to the general reduction conditions produced 0.15 g (76%) of dibenzylamine as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.34 (m, 8H), 7.29-7.26 (m, 2H), 3.84 (s, 4H), 1.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$):

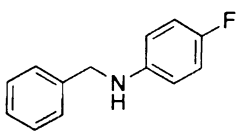
δ 140.3, 128.3, 128.1, 126.9, 53.1. Spectral data were consistent with commercially available material.



***N*-(naphthalen-2-ylmethyl)aniline:** Subjecting *N*-(naphthalen-2-ylmethylene)aniline to the general reduction conditions produced 0.182 g (78%) of *N*-(naphthalen-2-ylmethyl)aniline as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84-7.79 (m, 4H), 7.50-7.44 (m, 3H), 7.18 (t, J = 7.5 Hz, 2H), 6.73 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 7.5 Hz, 2H), 4.49 (s, 2H), 4.12 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 136.9, 133.5, 132.8, 129.3, 128.4, 127.7, 127.6, 126.1, 125.9, 125.7, 125.6, 117.6, 112.9, 48.5. Spectral data were consistent with previously reported material.[37]

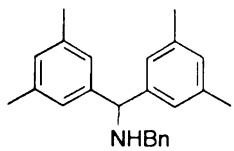


***N*-(1-phenylethyl)aniline:** Subjecting *N*-(1-phenylethylidene)aniline to the general reduction conditions produced 0.185 g (94%) of *N*-(1-phenylethyl)aniline as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 7.0 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.08 (dd, J = 7.5, 8.5 Hz, 2H), 6.64 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 7.5 Hz, 2H), 4.49-4.47 (m, 1H), 4.01 (s, 1H), 1.51 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 145.2, 129.1, 128.6, 126.8, 125.8, 117.2, 113.3, 53.4, 24.9. Spectral data were consistent with previously reported material.[38]

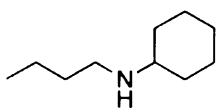


***N*-benzyl-4-fluoroaniline:** Subjecting *N*-benzylidene-4-fluoroaniline to the general reduction conditions produced 0.183 g (91%) of *N*-benzyl-4-fluoroaniline as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.32 (m, 4H), 7.29-7.26 (m, 1H), 6.87 (t, J = 8.5 Hz, 2H), 6.56-6.54 (m, 2H), 4.28

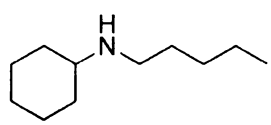
(s, 2H), 3.91 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 154.9, 144.5, 139.2, 128.6, 127.4 (d, J_{C-F} = 22.0 Hz), 115.6 (d, J_{C-F} = 22.0 Hz), 113.6 (d, J_{C-F} = 7.0 Hz), 48.9. Spectral data were consistent with previously reported material.[39]



***N*-benzyl-1,1-bis(3,5-dimethylphenyl)methanamine:** The corresponding imine, *N*-(bis(3,5-dimethylphenyl)methylene)-1-phenylmethanamine, was obtained from a friendly lab member in Dr. William Wulff's group. Subjecting *N*-(bis(3,5-dimethylphenyl)methylene)-1-phenylmethanamine to the general reduction conditions produced 0.313 g (95%) of *N*-benzyl-1,1-bis(3,5-dimethylphenyl)methanamine as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 4H), 7.25-7.22 (m, 1H), 7.02 (s, 4H), 6.83 (s, 2H), 4.70 (s, 1H), 3.72 (s, 2H), 2.27 (s, 12H), 1.70 (bs, 1H).



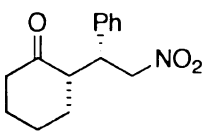
***N*-butylcyclohexanamine:** Subjecting *N*-butylidenecyclohexanamine to the general reduction conditions produced 0.13 g (84%) of *N*-butylcyclohexanamine as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 2.54 (t, J = 7.0 Hz, 2H), 2.35-2.31 (m, 1H), 1.82-1.79 (m, 2H), 1.67-1.63 (m, 2H), 1.55-1.52 (m, 1H), 1.40-1.36 (m, 2H), 1.29-0.97 (m, 8H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.8, 46.6, 33.6, 32.6, 26.1, 25.0, 20.5, 13.9. Spectral data were consistent with commercially available material.



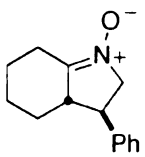
***N*-Pentylcyclohexanamine:** Subjecting *N*-cyclohexyl-idenepentan-1-amine to the general reduction conditions produced 0.163 g (96%) of *N*-pentylcyclohexanamine as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 2.56 (t, J = 7.0 Hz, 2H), 2.37-2.32 (m, 1H), 1.85-1.81 (m, 2H), 1.70-1.66

(m, 2H), 1.59-1.55 (m, 1H), 1.46-1.40 (m, 2H), 1.31-0.97 (m, 10H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.9, 47.1, 33.7, 30.2, 29.6, 26.2, 25.1, 22.6, 13.9. Spectral data were consistent with commercially available material.

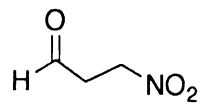
General Procedure for the Synthesis of Nitroketones and their Reduction to Nitrones:



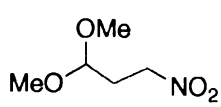
2-(2-Nitro-1-phenylethyl)-cyclohexanone:[31] A flame-dried 50 mL round-bottomed flask was charged with L-proline (0.15 mmol, 0.017 g), the nitroolefin, *trans*-β-nitrostyrene (1.0 mmol, 0.149 g), 8 mL of DMSO and cyclohexanone (20 vol%, 19.3 mmol, 10.0 mL) respectively. The reaction mixture was stirred at room temperature for 16 h under nitrogen atmosphere. At that time, ethyl acetate (10 mL) and saturated NH_4Cl solution (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried using $MgSO_4$, filtered and concentrated. Flash chromatography with hexanes/ethyl acetate (90:10, 80:20-compound eluted, R_f = 0.18) furnished the desired compound (79%, dr>95:5) as a white solid (mp = 101-102 °C, lit.[40] = 104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.28 (m, 2H), 7.26-7.22 (m, 1H), 7.16-7.14 (m, 2H), 4.91 (dd, J = 4.5 Hz, 12.5 Hz, 1H), 4.62 (dd, J = 9.5 Hz, 12.5 Hz, 1H), 3.77-3.72 (m, 1H), 2.70-2.64 (m, 1H), 2.48-2.44 (m, 1H), 2.40-2.33 (m, 1H), 2.08-2.04 (m, 1H), 1.78-1.64 (m, 3H), 1.59-1.50 (m, 1H), 1.26-1.17 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 137.8, 128.9, 128.2, 127.8, 78.9, 52.6, 43.9, 42.7, 33.2, 28.5, 25.0.



3-Phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indole-1-oxide:[23] To a flame-dried 25 mL round-bottomed flask, palladium acetate (0.05 mmol, 0.011 g), 2-(2-nitro-1-phenylethyl)-cyclohexanone (1.0 mmol, 0.247 g) and freshly distilled THF (5 mL) were added successively. The flask was then sealed and purged with nitrogen. At that time, 2 mL of degassed H_2O was added via syringe. After purging nitrogen for about 5 minutes, the nitrogen inlet was replaced with a balloon filled with nitrogen. Then triethylsilane (10.0 mmol, 1.6 mL) was added dropwise via syringe over a period of time (to avoid rapid evolution of gas, probably hydrogen). The reaction was stirred under nitrogen for 4 h and the progress was monitored by TLC. After that, the reaction flask was opened to the air, diluted with 5-10mL of diethyl ether, and stirred for 5 minutes. The layers were separated and the aqueous layer was back extracted with diethyl ether. The combined organics were concentrated and subjected to flash chromatography using gradients of hexanes/ethyl acetate (50:50, 0:100) and ethyl acetate/methanol (90:10, 80:20-compound eluted, R_f = 0.26 in 80:20 ethyl acetate/methanol) to obtain the compound as a white solid (0.131 g, 61%, mp = 97-99 °C) and stored under nitrogen in the fridge (2-8 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H), 7.29-7.25 (m, 1H), 7.24-7.22 (m, 2H), 4.29-4.23 (m, 1H), 4.19-4.13 (m, 1H), 3.23-3.18 (m, 2H), 2.82-2.75 (m, 1H), 2.13-1.93 (m, 3H), 1.85-1.82 (m, 1H), 1.43-1.19 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 139.9, 129.0, 127.4, 127.3, 68.3, 50.6, 46.0, 32.5, 24.3, 23.9, 23.6. IR (neat): 2932, 2856, 2361, 2336, 1653, 1616, 1558, 1456, 1255, 1232, 702, 662 cm^{-1}. HRMS (ESI$^+$) calculated for [$C_{14}H_{17}NONa^+$] requires *m/z* 238.1208, found *m/z* 238.1200. Spectral data were matched with the reported nitrone.[23,41]

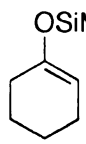


3-Nitropropanal:[42a] A flame-dried 1 L round-bottomed flask was charged with sodium nitrite (0.63 mol, 43.5 g), 125 mL of H_2O and 200 mL of distilled THF. The flask was purged with nitrogen, stirred and the temperature maintained at 0 °C. To this solution, 2-propenal (0.5 mol, 33.4 mL) was added (2-propenal was distilled) followed by addition of acetic acid (0.55 mol, 31.5 mL) over a period of 30-45 minutes. The whole reaction was carried out in dark to avoid decomposition and side reactions. The reaction mixture was then stirred under nitrogen at 0 °C for another 3 h. At that time, 250 mL of ethyl acetate was added and 100 mL of aqueous saturated $NaHCO_3$ for complete neutralization. The aqueous phase is separated and extracted with ethyl acetate (3×50 mL). The organic layers were combined and washed with brine (3×20 mL), dried using $MgSO_4$ with stirring for 2 h, filtered and concentrated. The oil obtained was mixed with toluene (3×50 mL) and concentrated by rotary evaporation to remove residual water and acetic acid to yield 40.25 g (78%) of the compound. This material was used without further purification for further reaction.

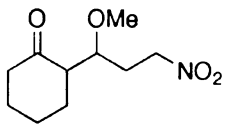


3-Nitropropanal dimethyl acetal:[42a] A flame-dried 1 L round-bottomed flask was charged with 3-nitropropanal (0.4 mol, 40.25 g), 150 mL of methanol and trimethyl orthoformate (0.5 mol, 54.7 mL, distilled). The solution was stirred under nitrogen and cooled to 0 °C, then p-toluenesulfonic acid monohydrate (0.01 mol, 1.8 g) was added and the mixture was stirred at room temperature for 4 h. At that time, the reaction flask was opened and concentrated by rotary evaporation; the remaining dark liquid was neutralized with aqueous saturated sodium bicarbonate (30 mL) and diluted with ethyl acetate (50 mL). The aqueous layer was separated and extracted with ethyl acetate (3×50 mL). The combined organic layers

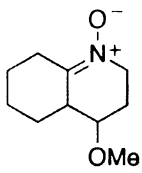
were washed with brine (2×20 mL), treated with $MgSO_4$ and charcoal (0.5 g, charcoal was added to decolorize), filtered and concentrated. The residual dark-yellow oil was purified by distillation under vacuum (P = 4 Torr, distill at 55 °C), the product collected by cooling in ice as a colorless oil (41.0 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.32–4.29 (m, 3H), 3.19 (s, 6H), 2.15-2.11 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 101.6, 70.8, 53.5, 30.1.



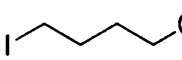
1-Trimethylsiloxycyclohexene:[42b] A flame-dried 500 mL round-bottomed flask, fitted with a reflux condensor and flushed with nitrogen, was charged with 80 mL of dry distilled dimethylformamide and distilled triethylamine (0.3 mol, 40.5 mL). Chlorotrimethylsilane (0.14 mol, 18.2 mL, distilled) was added via syringe. Cyclohexanone (0.11 mol, 11.3 mL) was added via syringe and the mixture was refluxed with stirring for 48 h. At that time the flask was cooled to room temperature and the contents poured in 150 mL of pentane. The resulting mixture was washed with cold aqueous sodium bicarbonate solution (3×125 mL). The organic layer was then washed rapidly in succession with 50 mL of cold 1.5N hydrochloric acid and 50 mL of cold aqueous sodium bicarbonate. The pentane solution was dried over sodium sulfate, filtered and concentrated. The crude product was distilled through a short Vigruex column (distilled at 75 °C, P = 20 Torr) to provide 13.8 g (74%) of the product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85-4.82 (m, 1H), 2.01-1.93 (m, 4H), 1.67-1.59 (m, 2H), 1.52-1.44 (m, 2H), 0.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 150.3, 104.2, 29.9, 23.8, 23.1, 22.3, 0.3.

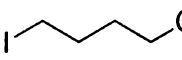


2-(1-Methoxy-3-nitro)-cyclohexanone:[43] A flame-dried 100 mL two-neck round-bottomed flask was flame dried in vacuum and cooled under nitrogen, this process being repeated a couple of times to make it completely moisture free and then charged with 3-nitropropanal dimethyl acetal (2.5 mmol, 0.367 g) and 25 mL of dry distilled CH_2Cl_2. The flask was purged with nitrogen and cooled down to -78 °C using dry ice and acetone. Titanium(IV) chloride (2.5 mmol, 0.466 g) was added via syringe and the resulting yellow solution was stirred for about 10 minutes. Then, 1-trimethylsiloxycyclohexene (2.0 mmol, 0.341 g) was added to the solution via syringe and the reaction mixture was stirred for 2 h at -78 °C. At that time, the reaction flask was opened and the reaction quenched by addition of 40 mL of cold aqueous potassium bicarbonate. The layers were separated and the aqueous layer was back extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$) and concentrated. Flash chromatography with hexanes/ethyl acetate (99:1, 95:5-compound eluted, R_f = 0.31) produced the desired compound as a light amber oil (0.19 g, 44%, based on 100% product formation). The compound was not completely pure as judged by NMR and was carried over as such for the next step. ^{1}H NMR (500 MHz, $CDCl_3$) of the major diastereomer: δ 4.51-4.41 (m, 2H), 3.72-3.69 (m, 1H), 3.32 (s, 3H), 2.41-2.37 (m, 1H), 2.26-2.19 (m, 2H), 2.08-2.04 (m, 2H), 1.94-1.91 (m, 2H), 1.69-1.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) of the major diastereomer: δ 210.9, 75.8, 72.5, 59.1, 54.6, 42.4, 30.7, 28.7, 27.5, 24.7.

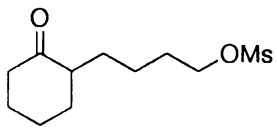


4-Methoxy-2,3,4,4a,5,6,7,8-octahydroquinoline-1-oxide: A flame-dried 25 mL round-bottomed flask was charged with palladium acetate (0.03 mmol, 0.007 g), 2-(1-Methoxy-3-nitro)-cyclohexanone (0.62 mmol, 0.134 g) and freshly distilled dry THF (4 mL). The flask was sealed and purged with nitrogen. While purging the flask with nitrogen, 1.5 mL of degassed H_2O was added via syringe. After purging nitrogen for about 5 minutes, the nitrogen inlet was replaced with a balloon filled with nitrogen. Triethylsilane (6.2 mmol, 1.0 mL) was slowly added dropwise via syringe over a period of time (to avoid rapid evolution of gas, probably hydrogen). The reaction was stirred for 6 h and progress was monitored by TLC. At that time, the reaction flask was opened to the air, diluted with 5-10mL of diethyl ether, and stirred for 5 minutes. The layers were separated and the aqueous layer was back extracted with diethyl ether. The combined organics were concentrated and subjected to flash chromatography using gradients of hexanes/ethyl acetate (50:50, 0:100) and ethyl acetate/methanol (90:10, 80:20-compound eluted, R_f = 0.18, 80:20 ethyl acetate/methanol) to obtain the compound as a dark brown oil (0.012 g, 11%) and stored under nitrogen in the fridge (2-8 °C). ^{1}H NMR (500 MHz, $CDCl_3$) of the major diastereomer: δ 3.98-3.91 (m, 1H), 3.84-3.78 (m, 1H), 3.64 (d, J = 15.0 Hz, 1H), 3.35 (s, 3H), 3.18-3.14 (m, 1H), 2.35-2.31 (m, 1H), 2.17-2.10 (m, 2H), 1.92-1.74 (m, 4H), 1.48-1.36 (m, 2H), 1.20-1.12 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) of the major diastereomer: δ 148.8, 56.4, 55.7, 44.1, 31.3, 26.4, 25.6, 24.8, 24.7. IR (neat): 3204, 2936, 2361, 2336, 1655, 1553, 1456, 1095, 970 cm^{-1}. HRMS (ESI$^+$) calculated for [$C_{10}H_{18}NO_2^+$] requires *m/z* 184.1338, found *m/z* 184.1343. Spectral data were similar to those previously reported for a related nitrone.[29e]

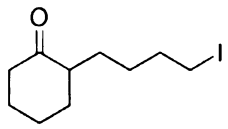
 **4-Iodobutan-1-ol:**[44] A 50 mL round-bottomed flask, fitted with a reflux condensor and purged under nitrogen was charged with 10 mL acetonitrile and sodium iodide (10.0 mmol, 1.498 g). THF (10.0 mmol, 0.721 g) was added via syringe followed by slow addition of trimethylsilylchloride (20.0 mmol, 2.52 mL). After complete addition of TMSCl, the reaction mixture was stirred at rt for 5 h. At that time, the reaction flask was opened and quenched with water. The organic layer was extracted with ether. The aqueous layer was washed with ether and the combined organic layers were washed successively with 10% sodium thiosulfate and brine. The organic layers were dried over anhydrous sodium sulfate and concentrated to give the 4-iodobutan-1-ol in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.59 (t, J = 6.5 Hz, 2H), 3.40 (bs, 1H), 3.17 (t, J = 7.0 Hz, 2H), 1.95-1.84 (m, 2H), 1.75-1.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 61.3, 33.2, 29.8, 6.7.

 **4-Iodobutyl methanesulfonate:**[45] A 250 mL round-bottomed flask, purged under nitrogen was charged with 4-iodobutan-1-ol (52.8 mmol, 10.56 g) and 50 mL of dichloromethane. The temperature of the solution was maintained at 0 °C using an ice-salt mixture. Triethylamine (54.9 mmol, 7.65 mL) is added to the reaction flask followed by dropwise addition of mesyl chloride (54.9 mmol, 4.25 mL). After completion of addition of mesyl chloride, the reaction mixture was stirred for 2 h at 0 °C. At this point, the reaction flask was opened and 50 mL of water added. The layers were separated and the aqueous layer was back-extracted with dichloromethane (3×20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to give the product in 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (t, J =

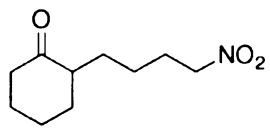
6.5 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H), 3.00 (s, 3H), 1.95-1.93 (m, 2H), 1.91-1.84 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 68.5, 37.5, 29.9, 29.2, 5.2.



4-(2-Oxocyclohexyl)butyl methanesulfonate:[46] A 500 mL round-bottomed flask, purged under nitrogen was charged with 40 mL of distilled THF. The temperature was lowered to a -78 °C and diisopropylamine (50.0 mmol, 7.01 mL) added. n-Butyllithium (1.6 M solution in hexane, 33.87 mL) was added dropwise at -78 °C, over a period of 30 minutes. The temperature slowly raised to 0 °C and stirred at this temperature for 1 h. 200 mL of distilled THF is taken in another 500 mL round-bottomed flask and maintained at -78 °C. To this, cyclohexanone (50.0 mmol, 5.18 mL) was added and the solution of cyclohexanone in THF is then transferred to the LDA solution, now maintained at -78 °C. The addition is controlled such that complete addition is over a period of 30 minutes. The reaction mixture is stirred at 0 °C using an ice-salt mixture for an hour. The temperature is then lowered to -78 °C and 4-iodobutyl methanesulfonate (50.0 mmol, 13.906 g) is added slowly over a period of time. Complete transfer is ensured with use of some more THF. The acetone-dry ice bath is then removed and the reaction stirred overnight. At that time, 100 mL of water is added to the flask and the aqueous layer is extracted with ether. The combined organic layers are washed with brine and the combined aqueous layers back extracted with ether. The organic layers are combined, dried over anhydrous magnesium sulfate and concentrated. Crude NMR taken shows the presence of both 4-(2-oxocyclohexyl)butyl methanesulfonate and 2-(4-iodobutyl)cyclohexanone. The crude is taken as such to the next step.

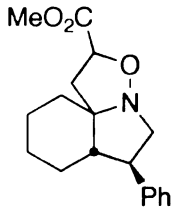


2-(4-Iodobutyl)cyclohexanone:[47] A 100 mL round-bottomed flask, purged under nitrogen was charged with 25 mL acetone (dried overnight over calcium sulfate), the crude mixture from the previous step and sodium iodide (20.0 mmol, 2.998 g) and fitted with a Friedrichs condensor. The reaction mixture was heated to mild reflux for 4 h. At that time, the reaction flask was open and the solvent remved by rotavap. The orange solid was then extracted with 25 mL pentane and 25 mL 10% sodium thiosulfate solution. The layers were separated and the organic layer extracted with 15 mL of brine. The combined aqueous layers were washed with pentane. The organics were combined and dried over anhydrous magnesium sulfate, filetered and solvent evaporated to give product in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.20-3.12 (m, 2H), 2.38-2.24 (m, 2H), 1.94-1.72 (m, 7H), 1.70-1.64 (m, 2H), 1.58-1.49 (m, 2H), 1.4-1.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.6, 41.9, 39.8, 35.3, 33.7, 27.2, 26.9, 25.2, 22.7, 4.9.



2-(4-Nitrobutyl)cyclohexanone:[48] A 25 mL round-bottomed flask, purged under nitrogen was charged with silver nitrite (14 mmol, 2.153 g) and 6 mL of ether. The solution was stirred in an ice bath under dark. 2-(4-Iodobutyl)cyclohexanone (14 mmol, 3.92 g) was added slowly to the reaction flask over a period of 30 minutes. 4 mL of ether was used to rinse the entire substrate into the reaction vessel. The solution was flushed with nitrogen all this time and now was replaced with a balloon filled with nitrogen. The reaction mixture was stirred at 0 °C for 2 h and then slowly brought to room temperature by allowing the ice bath to melt. The reaction was continued for 24 h. At that time, the reaction mixture was filtered and the

silver iodide precipitate was washed repeatedly with benzene. The combined organic layers were concentrated to give the desired product in 73% yield (based on crude NMR).



Methyl 6-phenyloctahydro-1*H*-isoxazolo[2,3-*i*]indole-2-carboxylate: A 10 mL round-bottomed flask, fitted with a reflux condensor and purged under nitrogen was charged with 3-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indole-1-oxide (0.5 mmol, 0.108 g), methyl acrylate (0.75 mmol, 68 μL) and dry distilled toluene (3 mL). The reaction mixture stirred at 0 °C for 1 h and at room temperature for 2 h showed no product formation. The reaction mixture was then refluxed for 6 h when it showed product formation. The reaction was monitored from time to time with TLC and GC-FID. At that time, the reaction flask was opened and concentrated. Flash chromatography with the crude material using gradients of hexanes/ethyl acetate (90:10, 80:20-compound eluted, R_f = 0.6 in 50:50 hexanes/ethyl acetate, 50:50) and ethyl acetate/methanol (100:0, 80:20-starting material recovered) gave 0.04 g (27%) of the C-5 isomer as an inseparable mixture of diastereomers in the ratio 1.3:1.0. ^{1}H NMR (500 MHz, $CDCl_3$) of the major diastereomer: δ 7.36-7.34 (m, 2H), 7.31-7.25 (m, 2H), 7.20-7.16 (m, 1H), 4.72-4.66 (m, 1H), 3.77 (s, 3H), 3.76-3.68 (m, 1H), 3.49 (dd, J = 2.0 Hz, 7.0 Hz, 1H), 3.32-3.26 (m, 2H), 2.41-2.36 (m, 1H), 2.30 (dd, J = 5.0 Hz, 11.5 Hz, 1H), 1.64 – 1.61(m, 2H), 1.57-1.30 (m, 4H), 1.25-1.16 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 143.3, 128.6, 128.1, 126.4, 75.1, 74.6, 52.3, 50.7, 49.4, 43.7, 31.3, 23.9, 22.3, 20.3.

^{1}H NMR (500 MHz, $CDCl_3$) of the minor diastereomer: δ 7.31-7.25 (m, 4H), 7.20-7.16 (m, 1H), 4.72-4.66 (m, 1H), 3.79 (s, 3H), 3.76-3.68 (m, 1H), 3.46 (dd, J = 2.0 Hz, 7.0 Hz,

1H), 2.71 (dd, J = 9.5 Hz, 12.5 Hz, 1H), 2.41-2.36 (m, 1H), 2.15 (dd, J = 4.5 Hz, 11.0 Hz, 1H), 1.80-1.77 (m, 2H), 1.57-1.30 (m, 5H), 1.25-1.16 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 143.5, 128.6, 127.9, 126.4, 74.9, 74.4, 52.5, 51.2, 49.3, 42.8, 30.9, 24.0, 22.4, 20.4. DEPT analysis: Methyne (CH) peaks at δ 128.6, 128.1, 127.9, 126.4, 74.9, 74.4, 51.2, 50.7, 49.4, 49.3. Methylene (CH_2) peaks at δ 43.7, 42.8, 31.3, 30.9, 24.0, 23.9, 22.3, 22.4, 20.4, 20.3. Methyl (CH_3) peaks at δ 52.5, 52.3. Hence quaternary carbons are at δ 173.2, 171.4, 143.5, 143.3, 75.1, 74.6. IR (neat): 3026, 2932, 2856, 1736, 1603, 1495, 1448, 1363, 1277, 1207, 1142, 1089, 1043, 893, 831, 761, 702 cm^{-1}. HRMS (ESI^+) calculated for [$C_{18}H_{24}NO_3^+$] requires *m/z* 302.1756, found *m/z* 302.1745. Spectral data were matched to a similar reported isoxazolidine.[49]

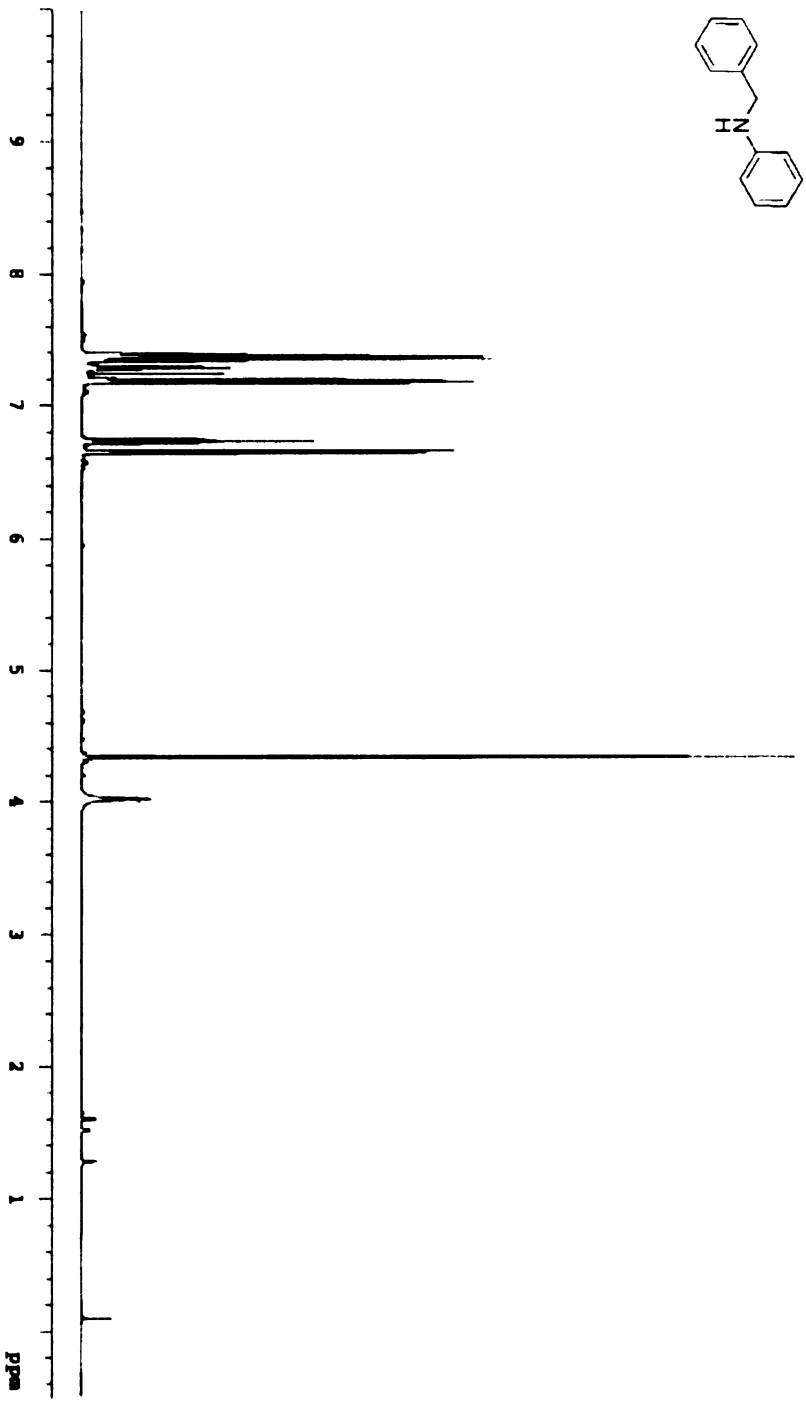


Figure 4.1. ^{1}H NMR of *N*-benzylaniline.

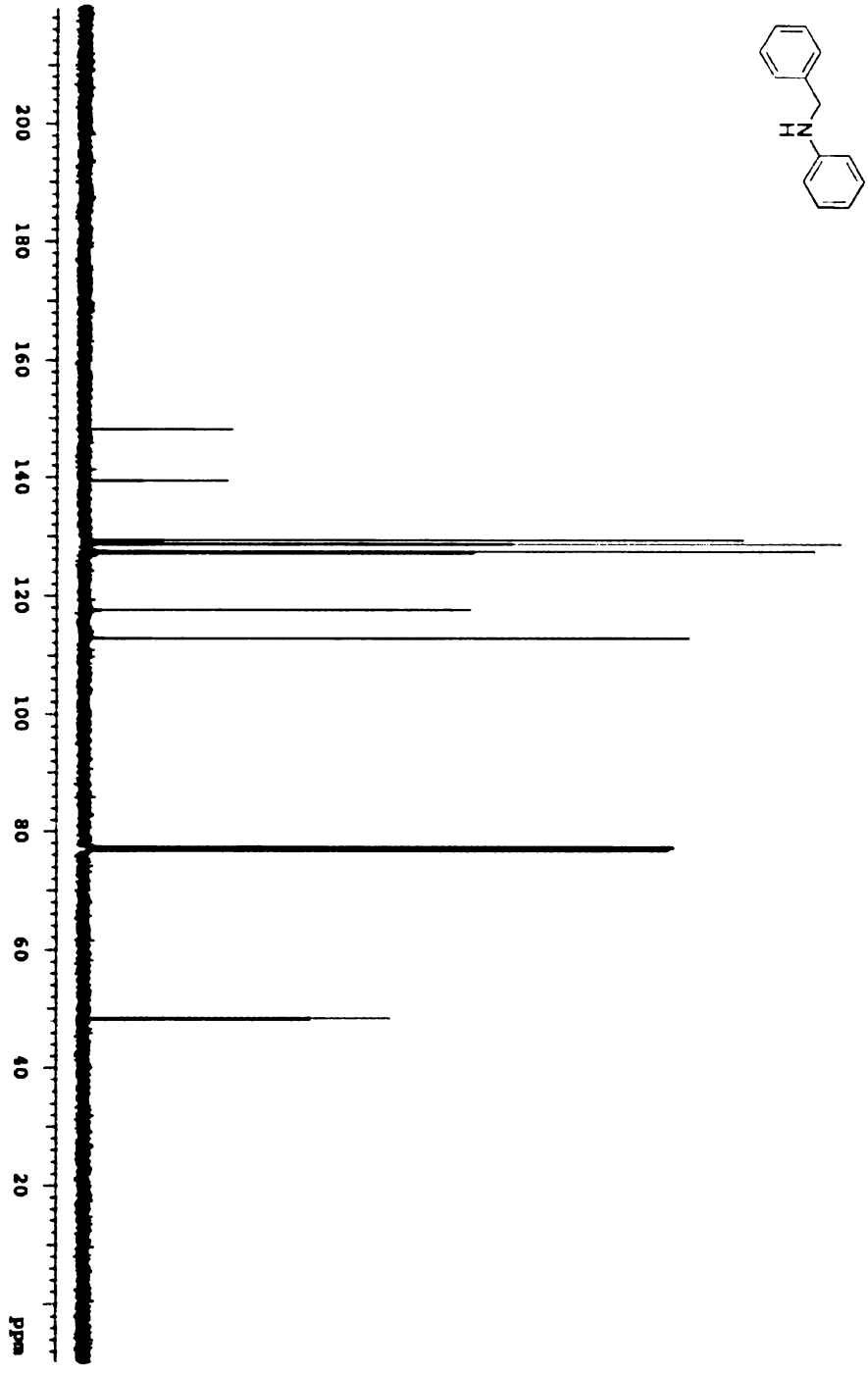


Figure 4.2. ^{13}C NMR of *N*-benzylaniline.

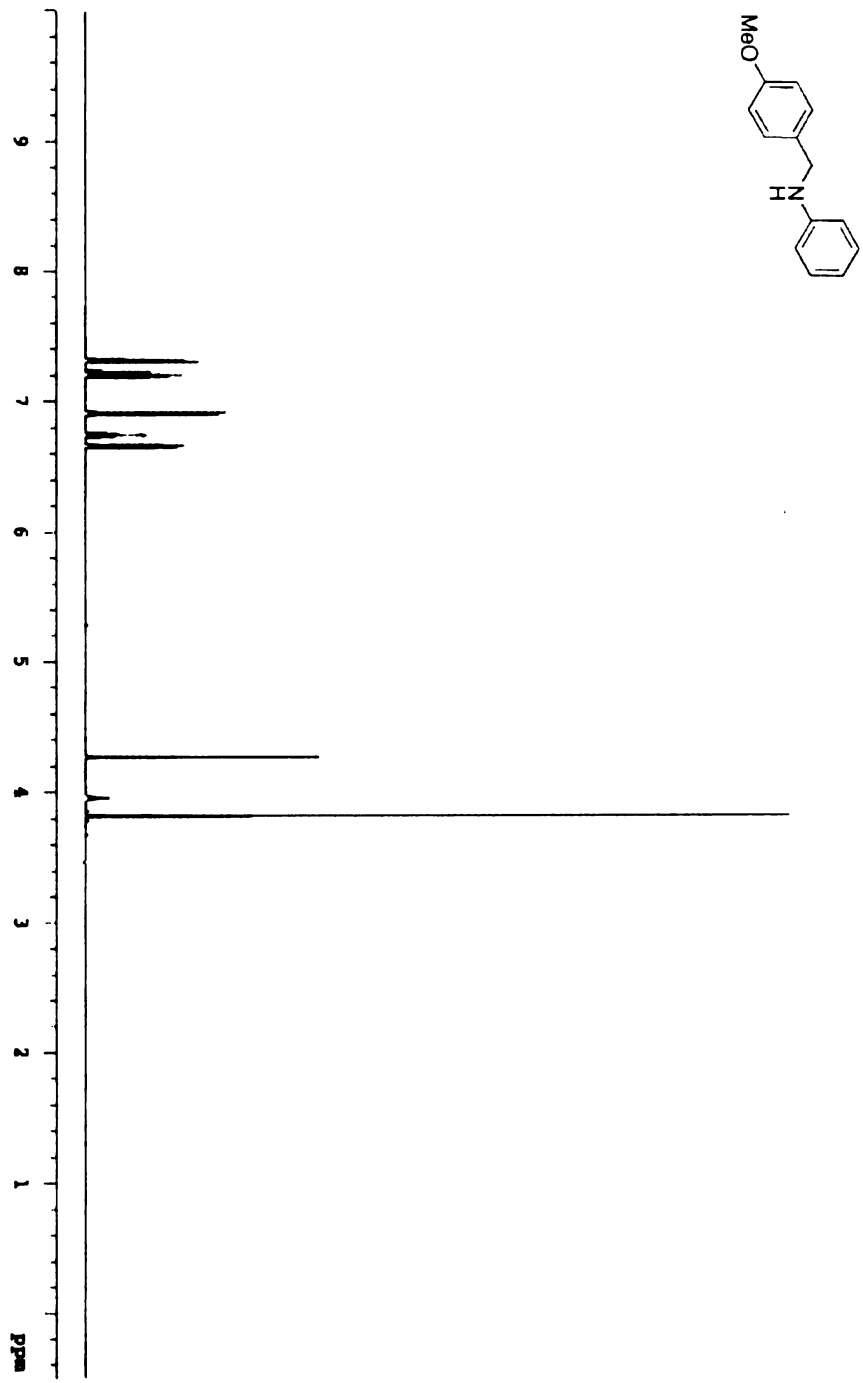


Figure 4.3. ^{1}H NMR of *N*-(4-methoxybenzyl)aniline.

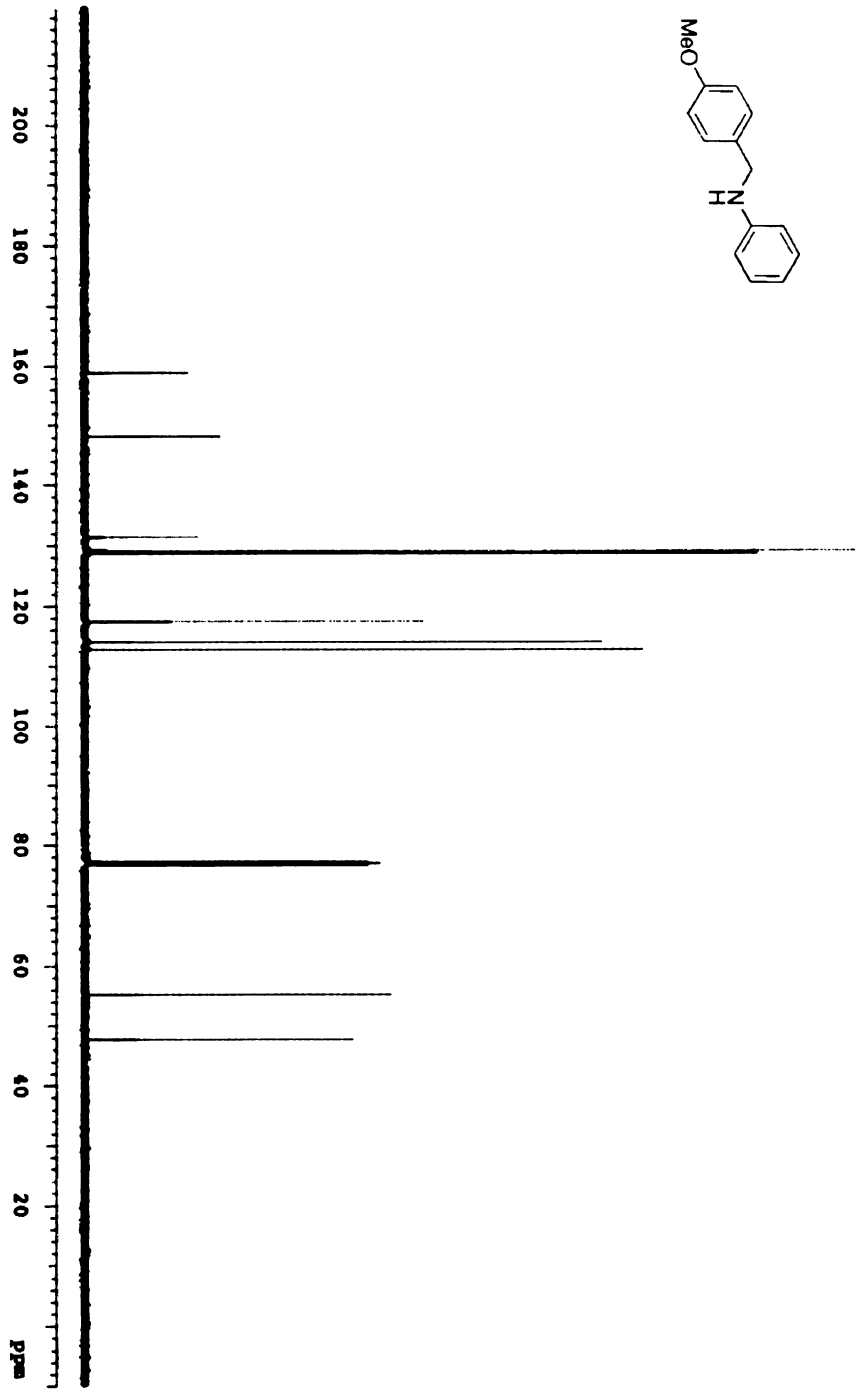


Figure 4.4. ^{13}C NMR of *N*-(4-methoxybenzyl)aniline.

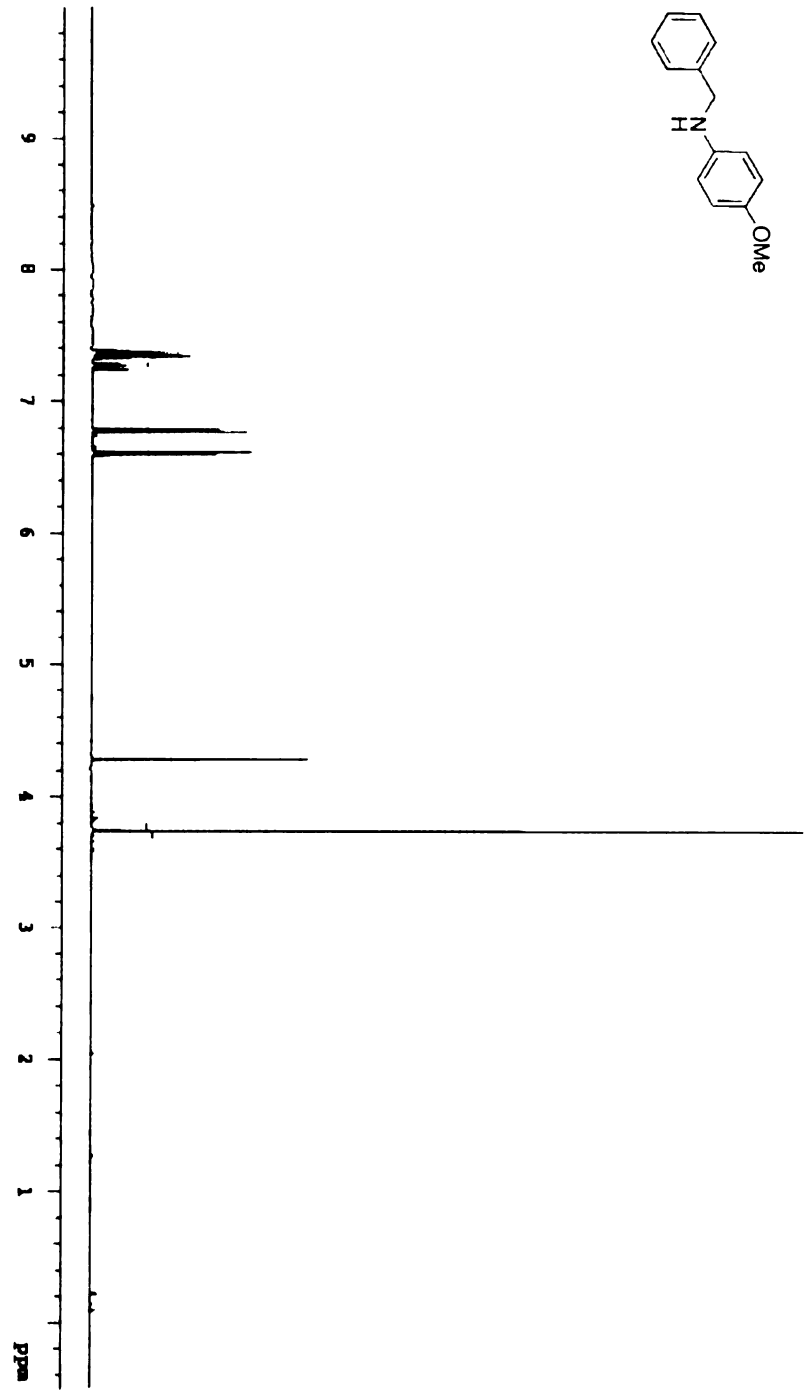


Figure 4.5. ^{1}H NMR of *N*-benzyl-4-methoxyaniline.

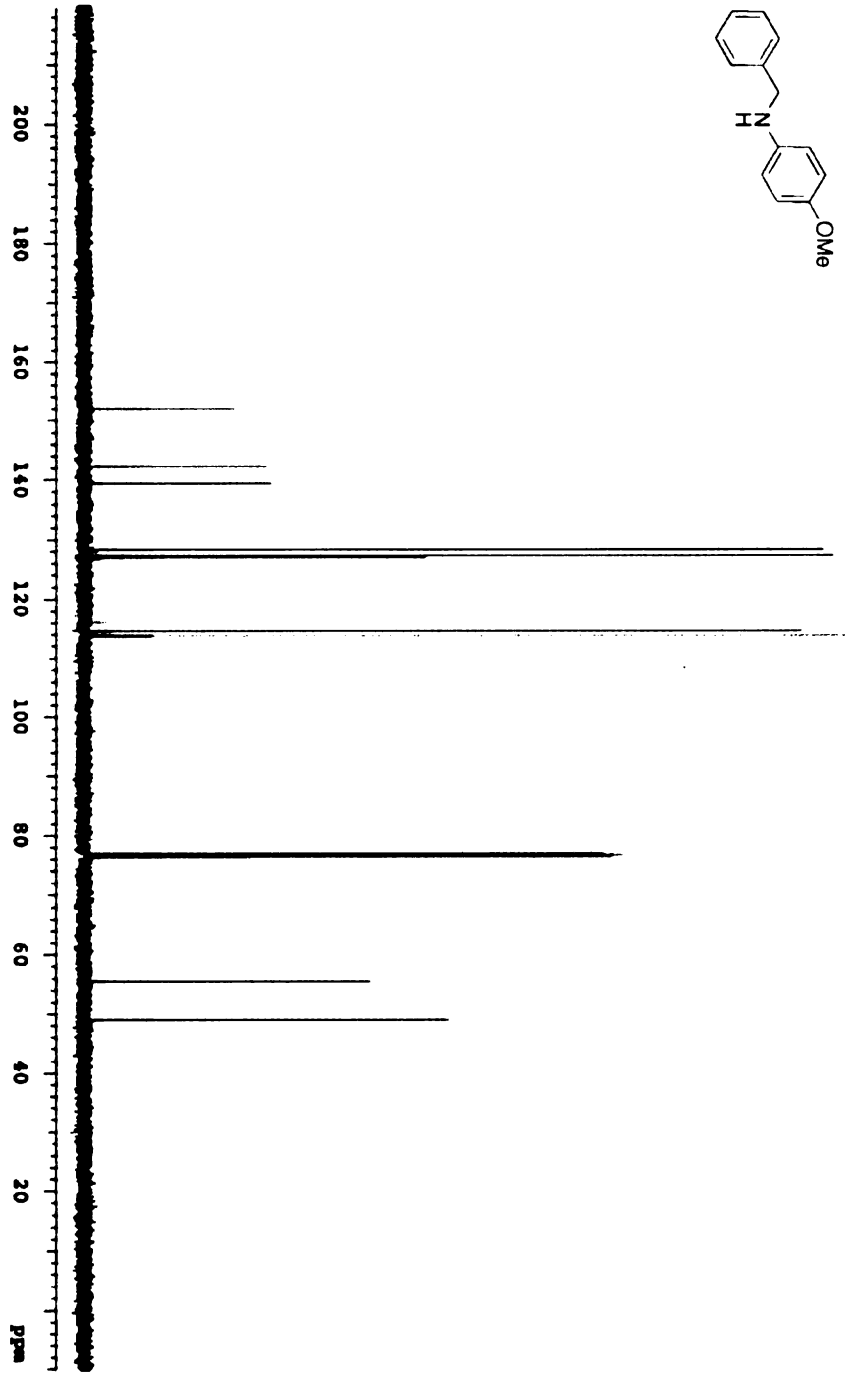


Figure 4.6. ^{13}C NMR of *N*-benzyl-4-methoxyaniline.

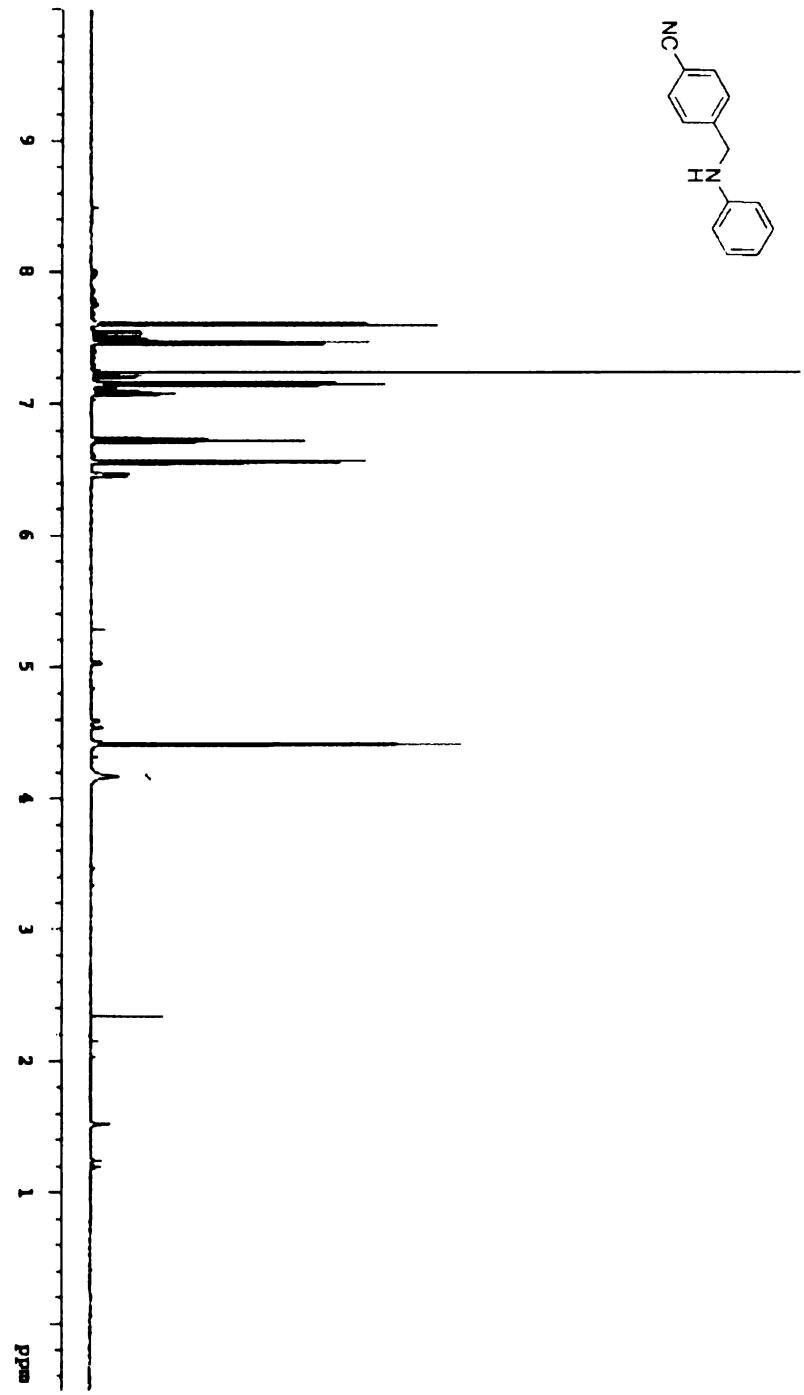


Figure 4.7. ^{1}H NMR of 4-(phenylaminomethyl)benzoaniline.

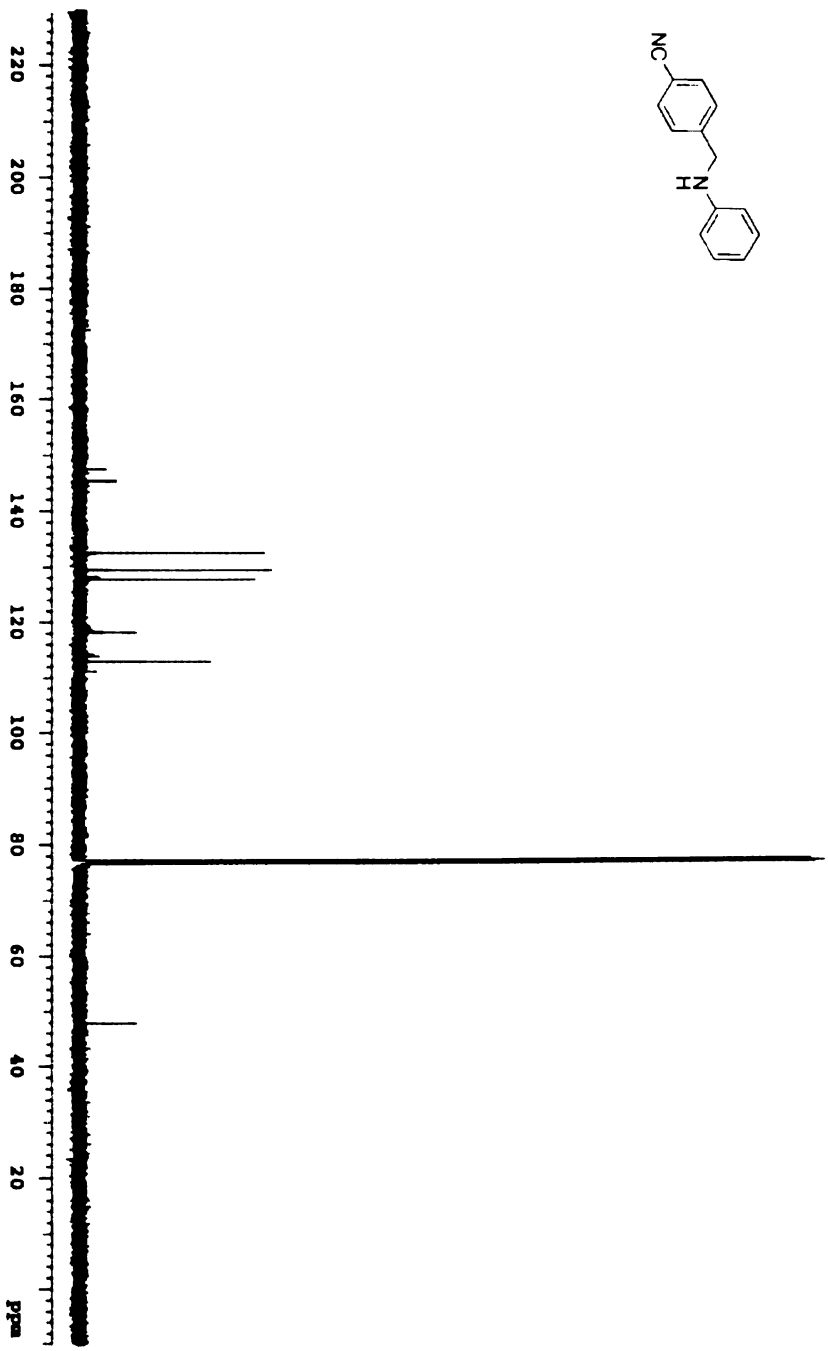


Figure 4.8. ^{13}C NMR of 4-(phenylaminomethyl)benzoaniline.

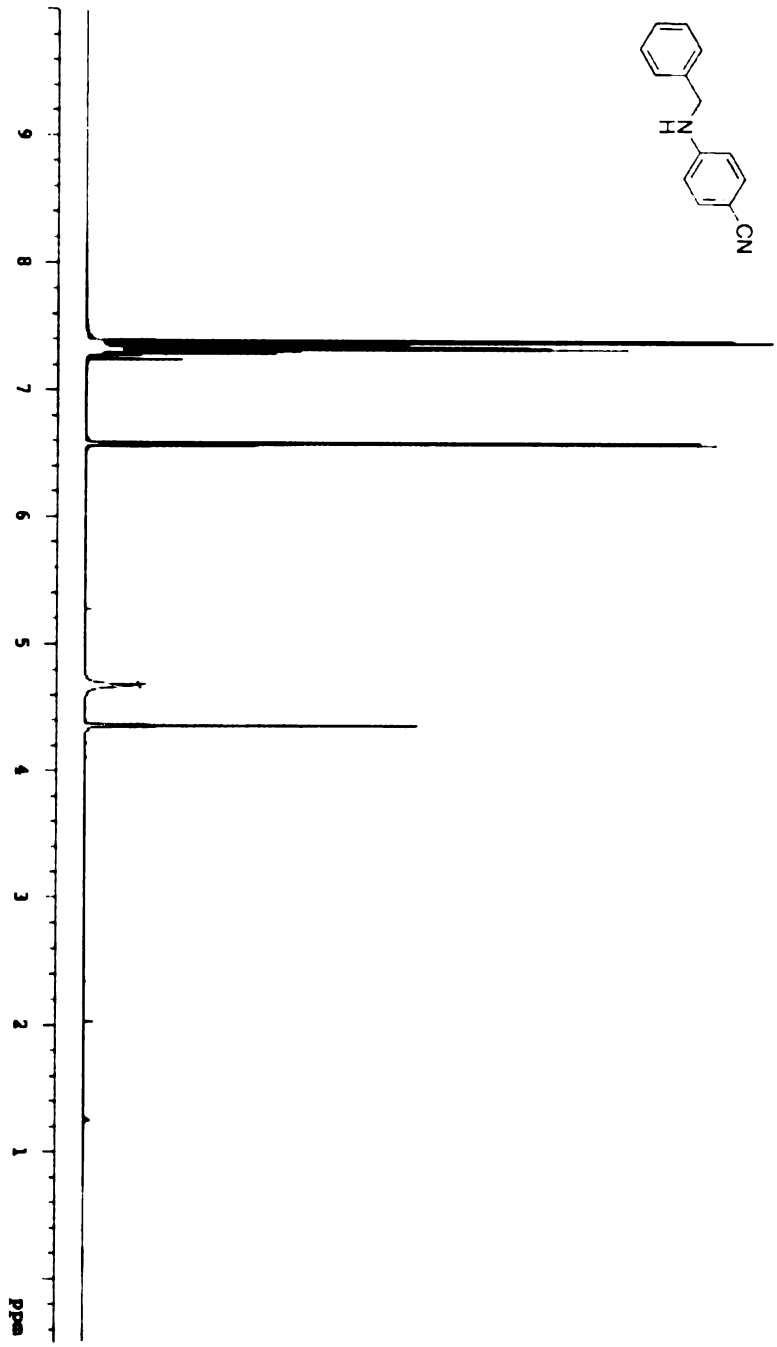


Figure 4.9. ^{1}H NMR of 4-(benzylamino)benzonitrile.

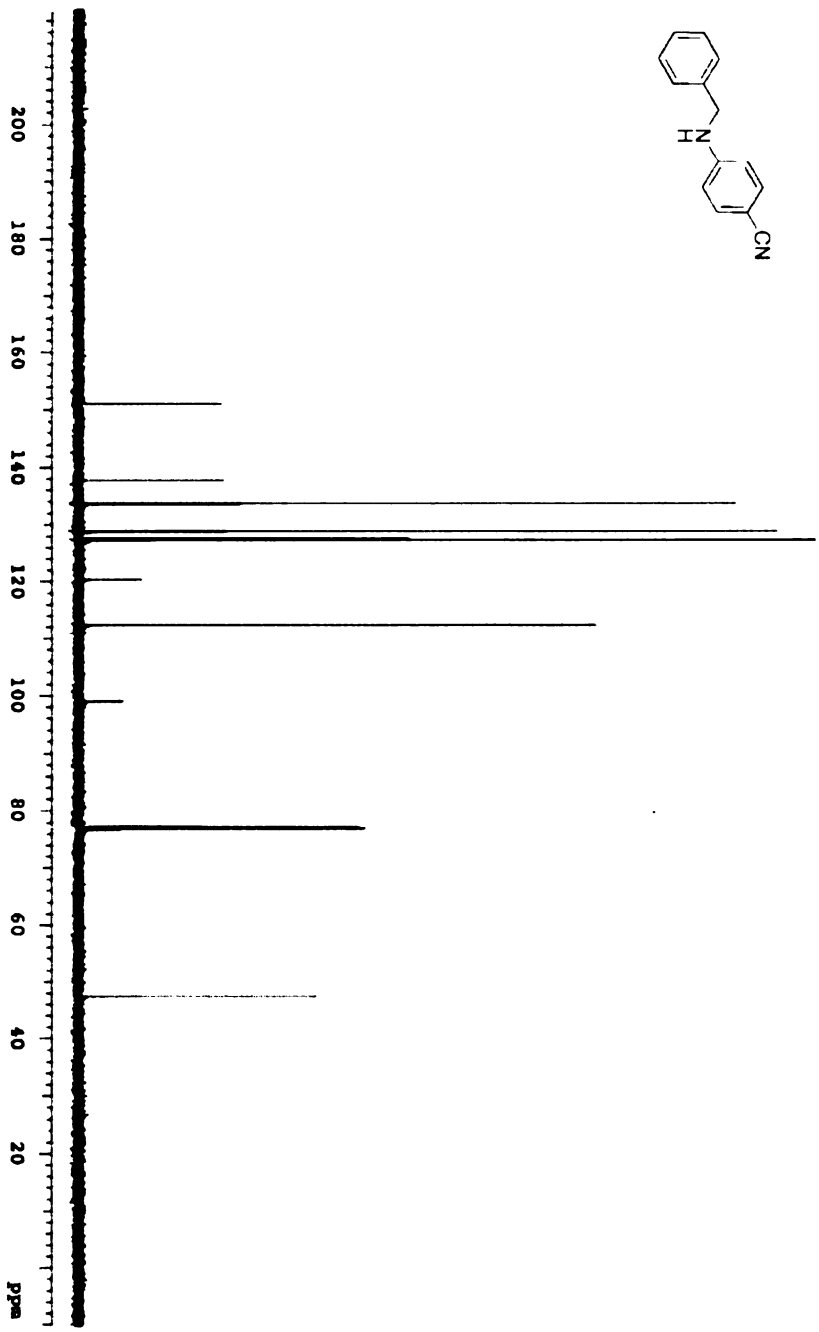


Figure 4.10. ^{13}C NMR of 4-(benzylamino)benzonitrile.

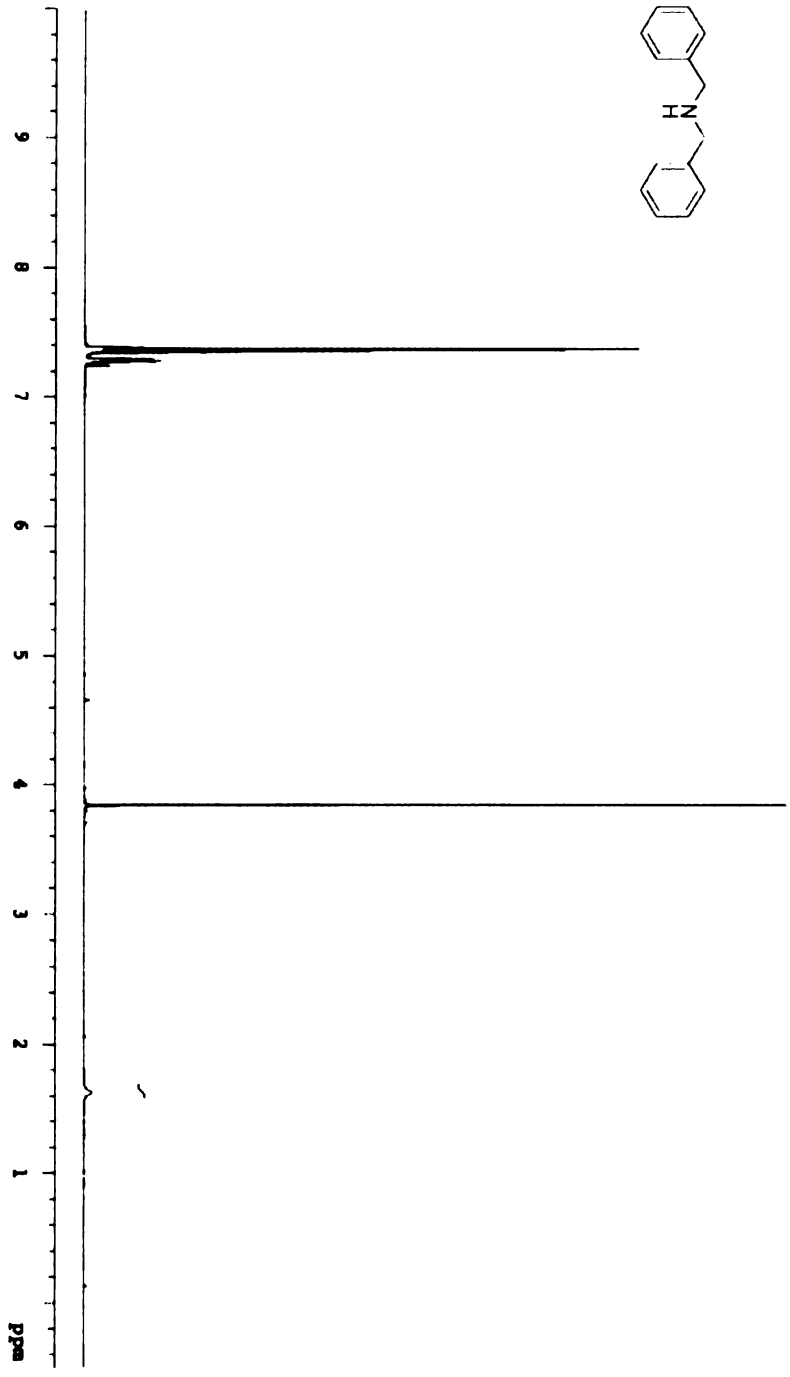


Figure 4.11. ^{1}H NMR of *N,N*-dibenzylamine.

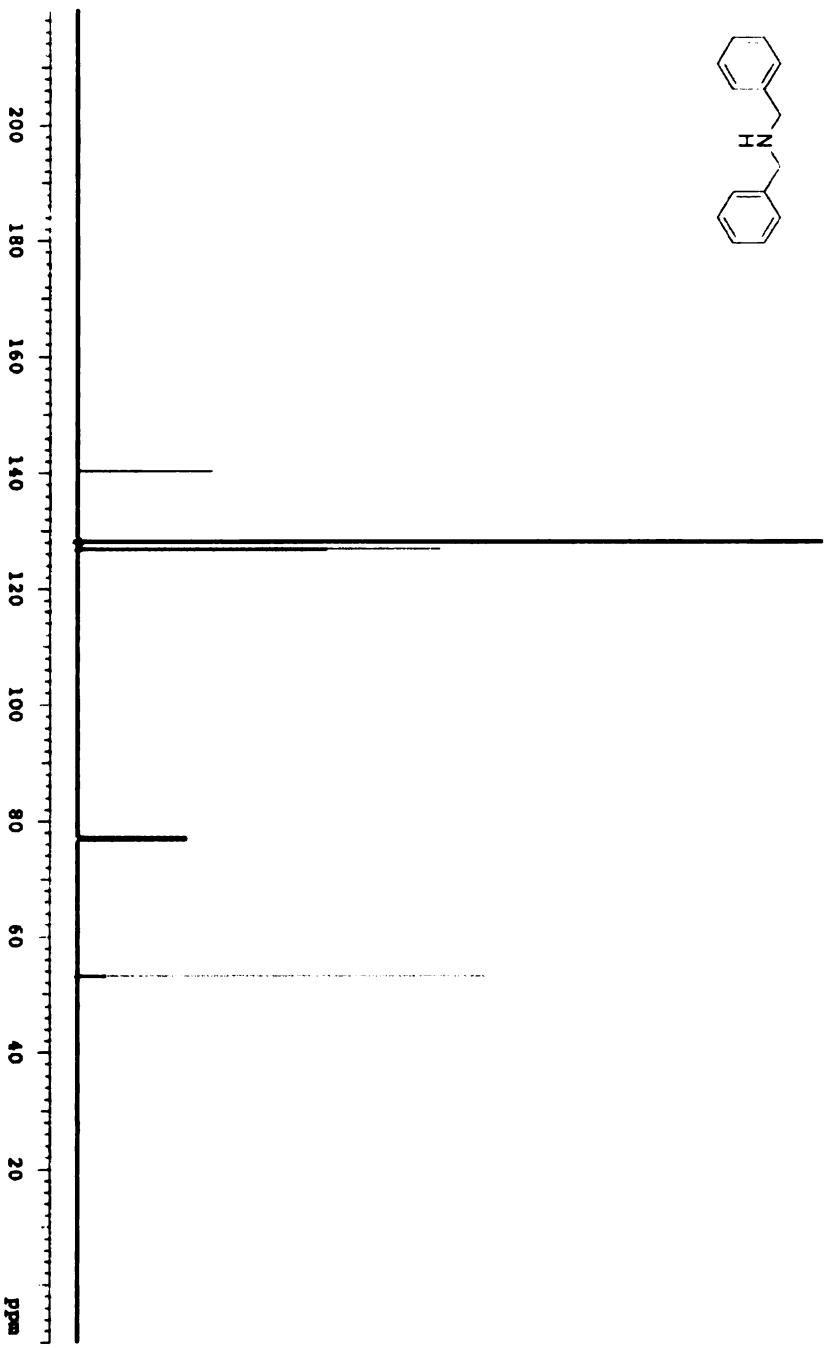


Figure 4.12. ^{13}C NMR of *N,N*-dibenzylamine.

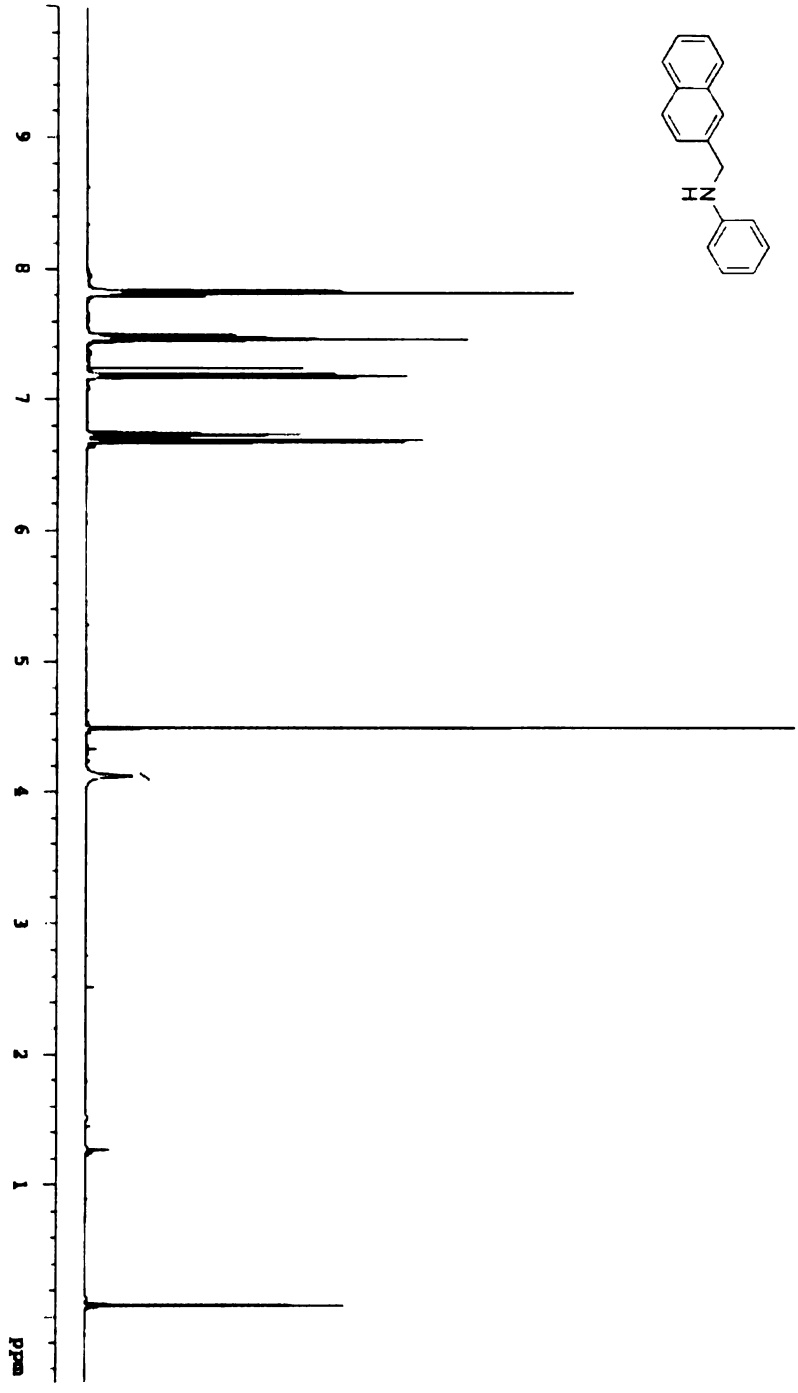


Figure 4.13. ^{1}H NMR of *N*-(naphthalen-2-ylmethyl)aniline.

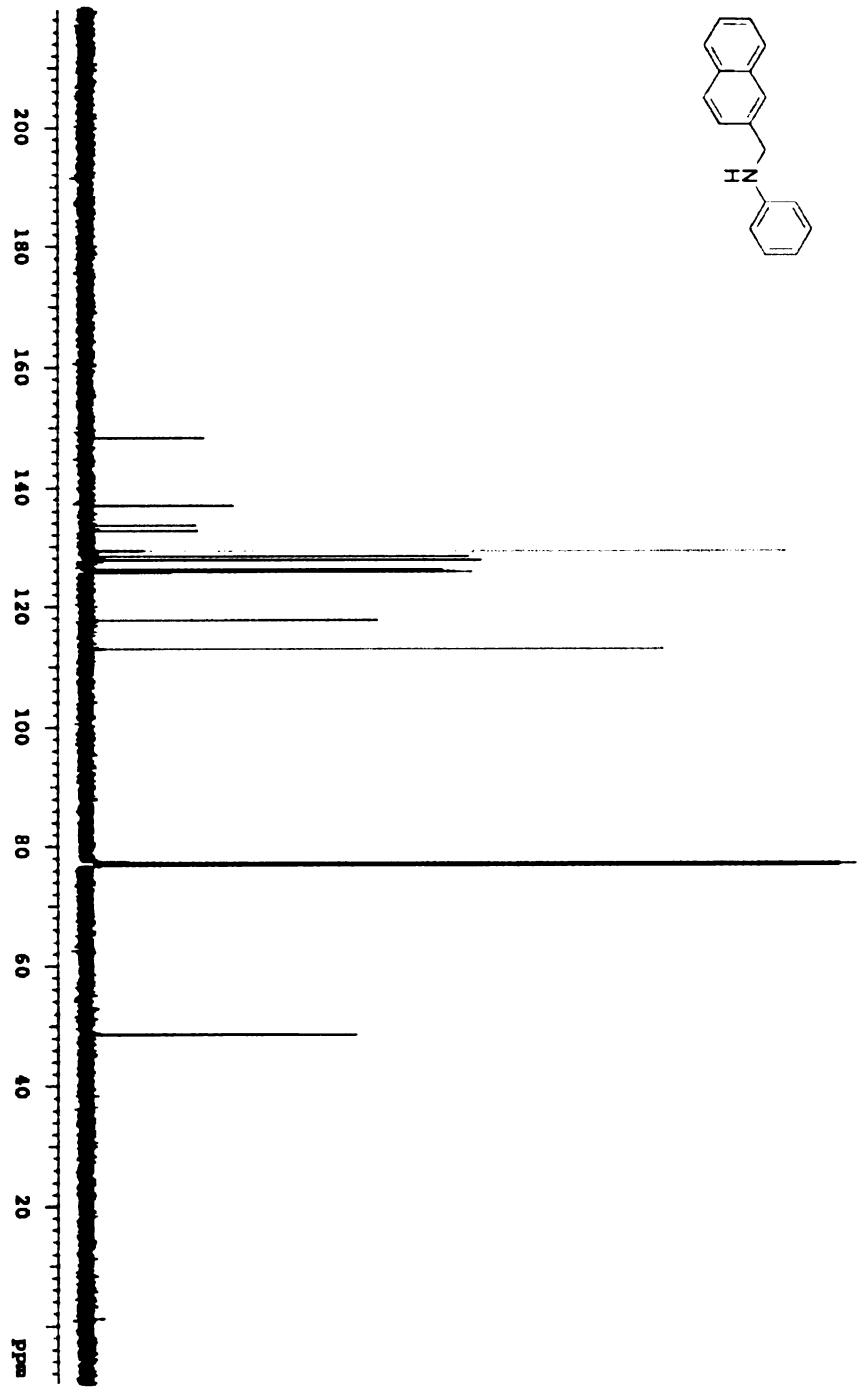


Figure 4.14. ^{13}C NMR of *N*-(naphthalen-2-ylmethyl)aniline.

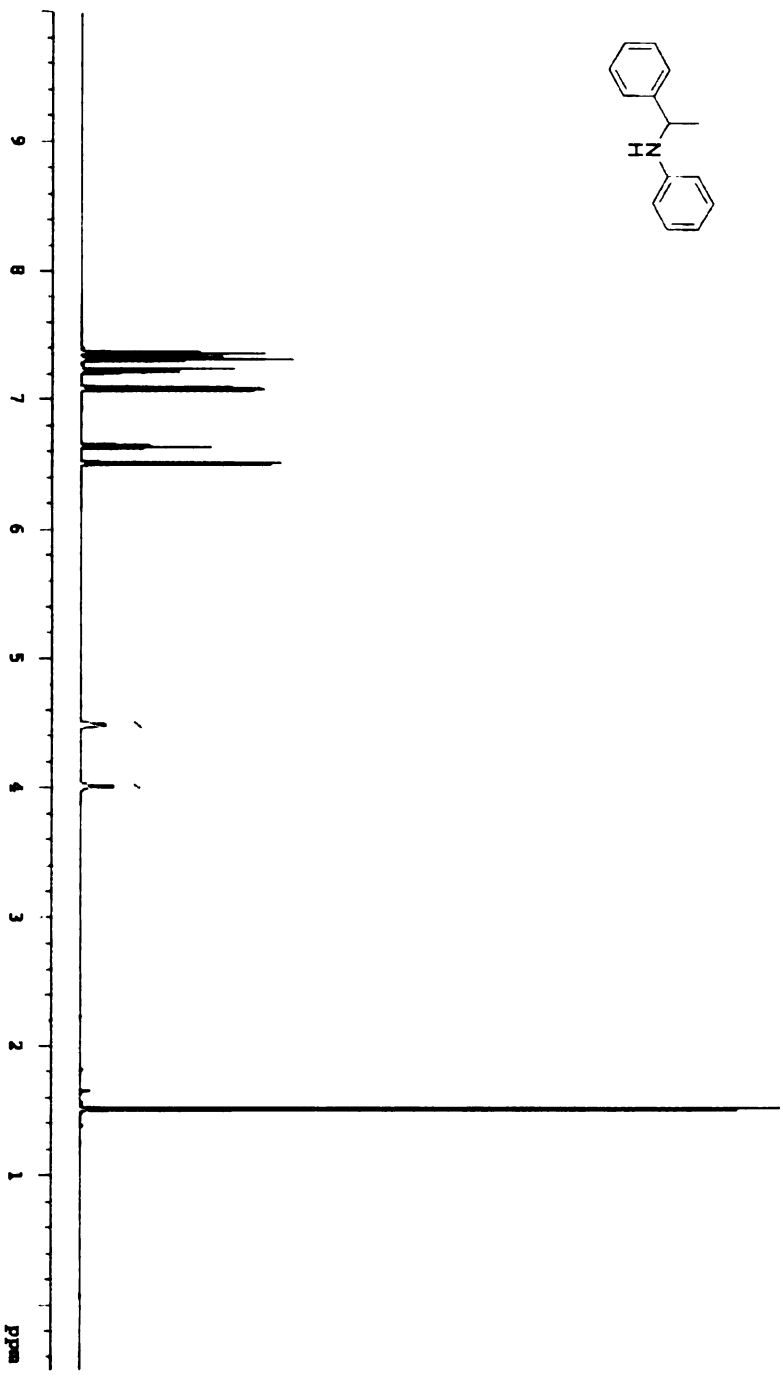


Figure 4.15. ^{1}H NMR of *N*-(1-phenylethyl)aniline.

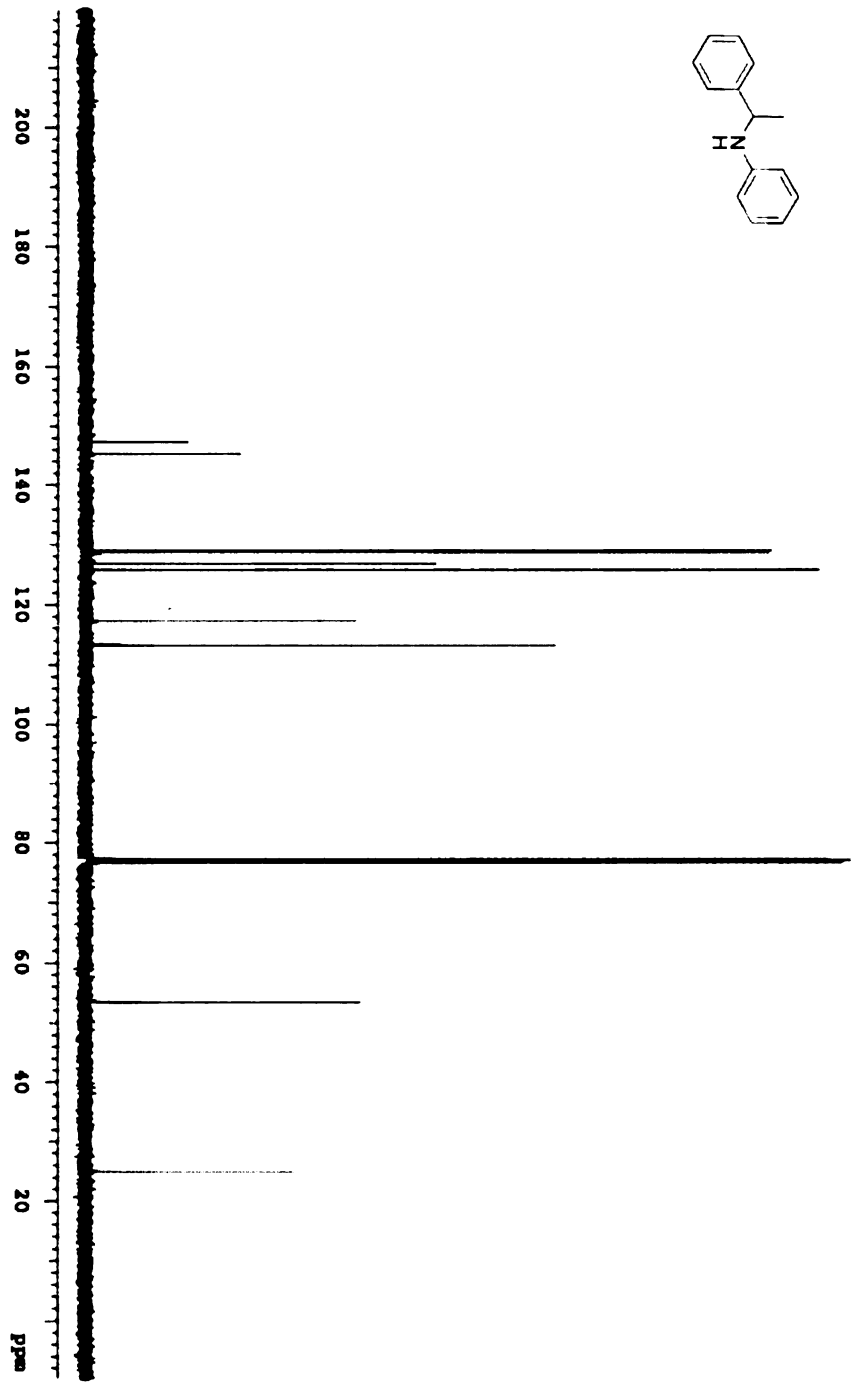


Figure 4.16. ^{13}C NMR of *N*-(1-phenylethyl)aniline.

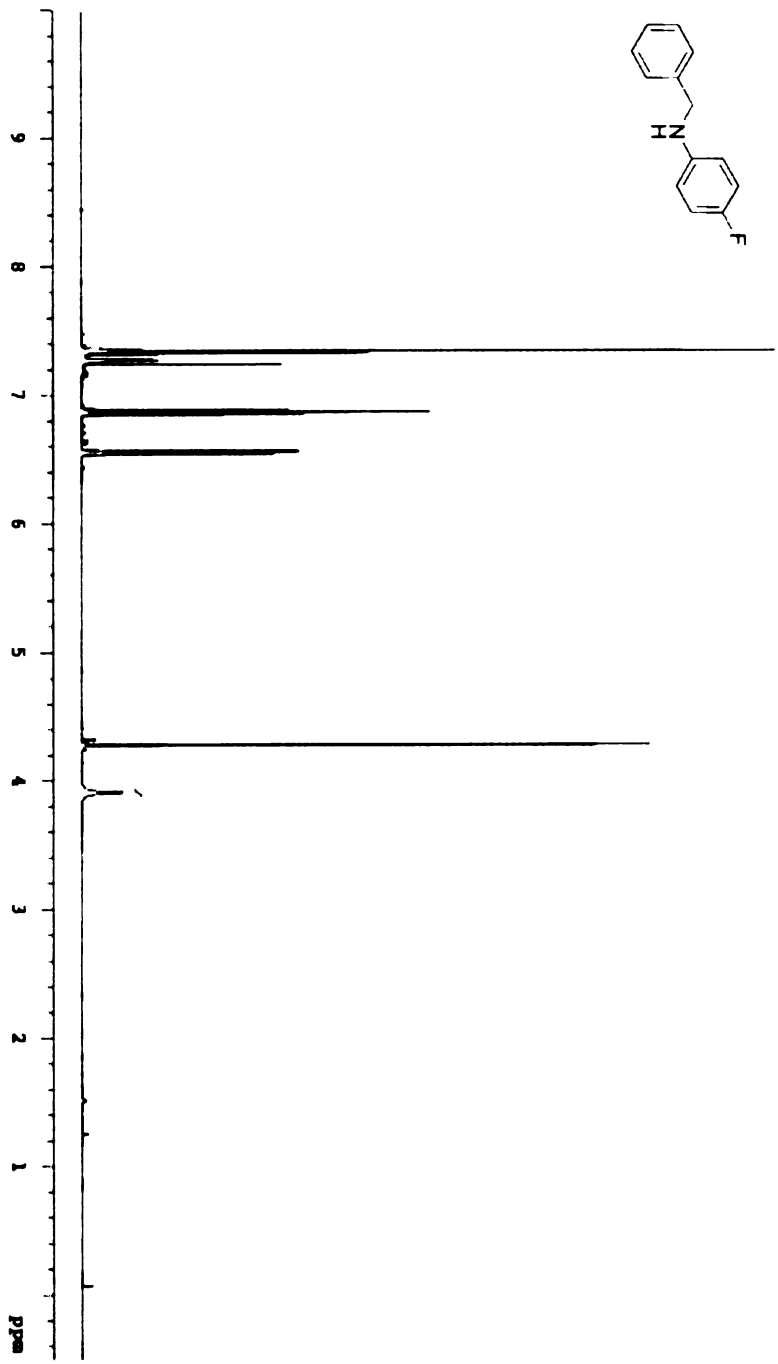


Figure 4.17. ^{1}H NMR of *N*-benzyl-4-fluoroaniline.

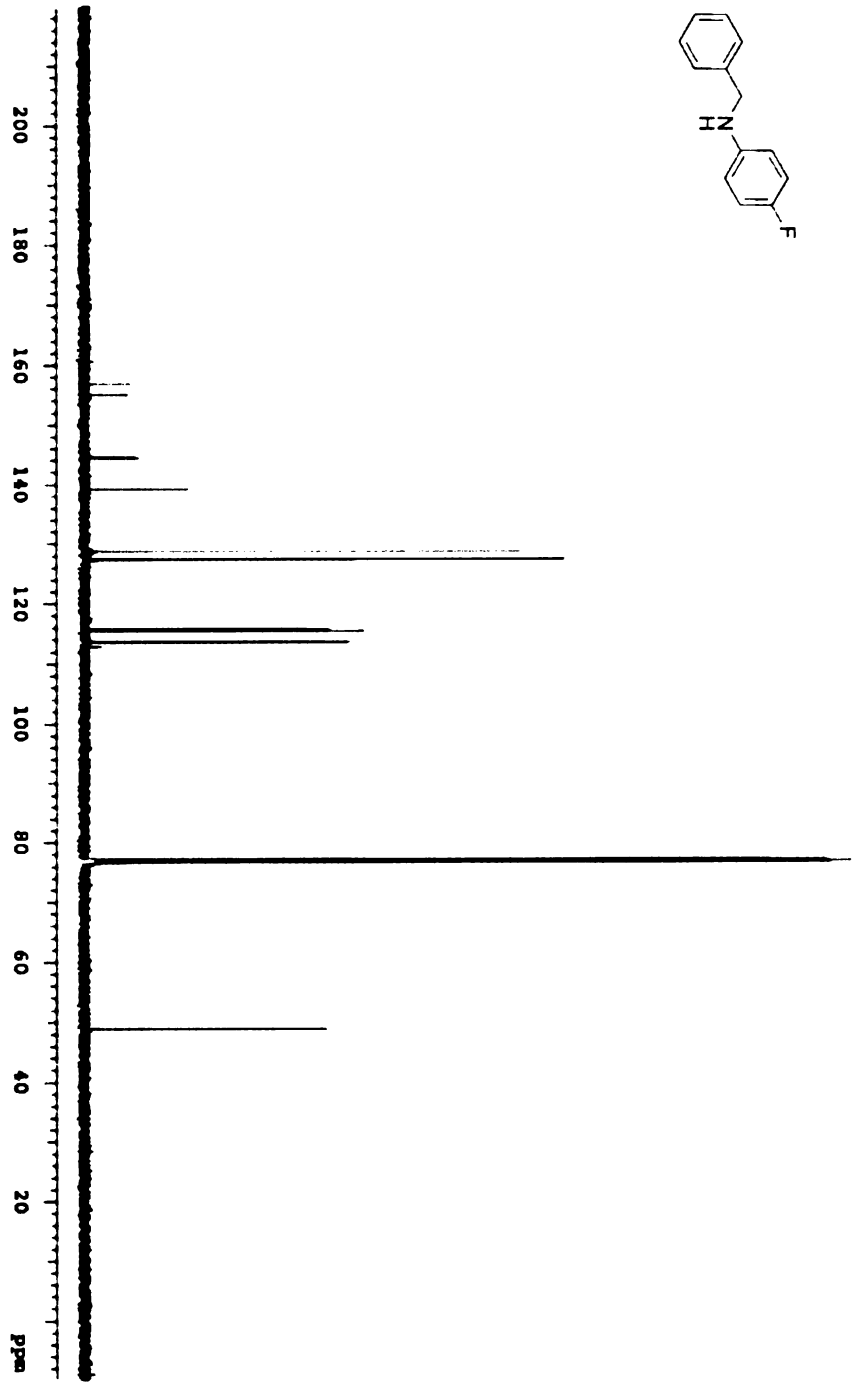


Figure 4.18. ^{13}C NMR of *N*-benzyl-4-fluoroaniline.

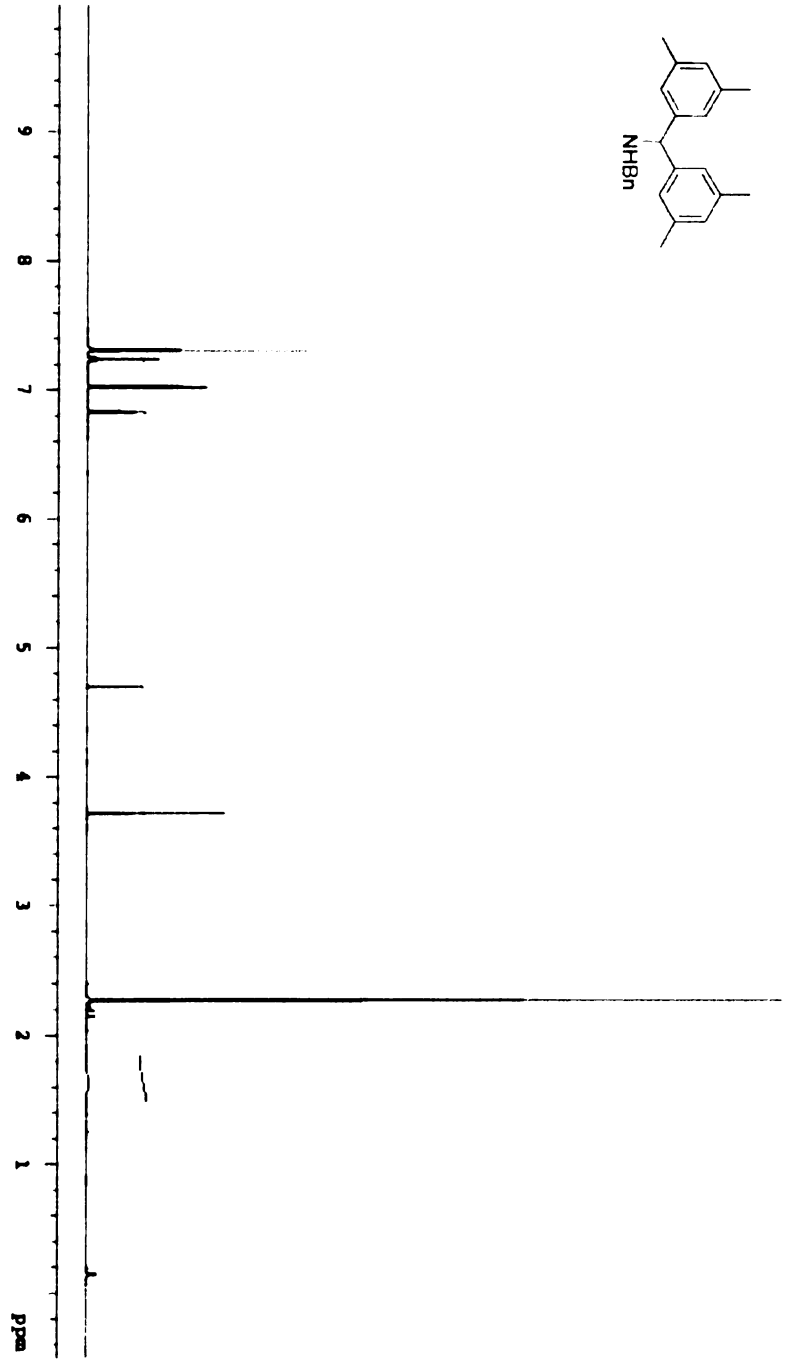


Figure 4.19. ^{1}H NMR of *N*-benzyl-1,1-bis(3,5-dimethylphenyl)methanamine.

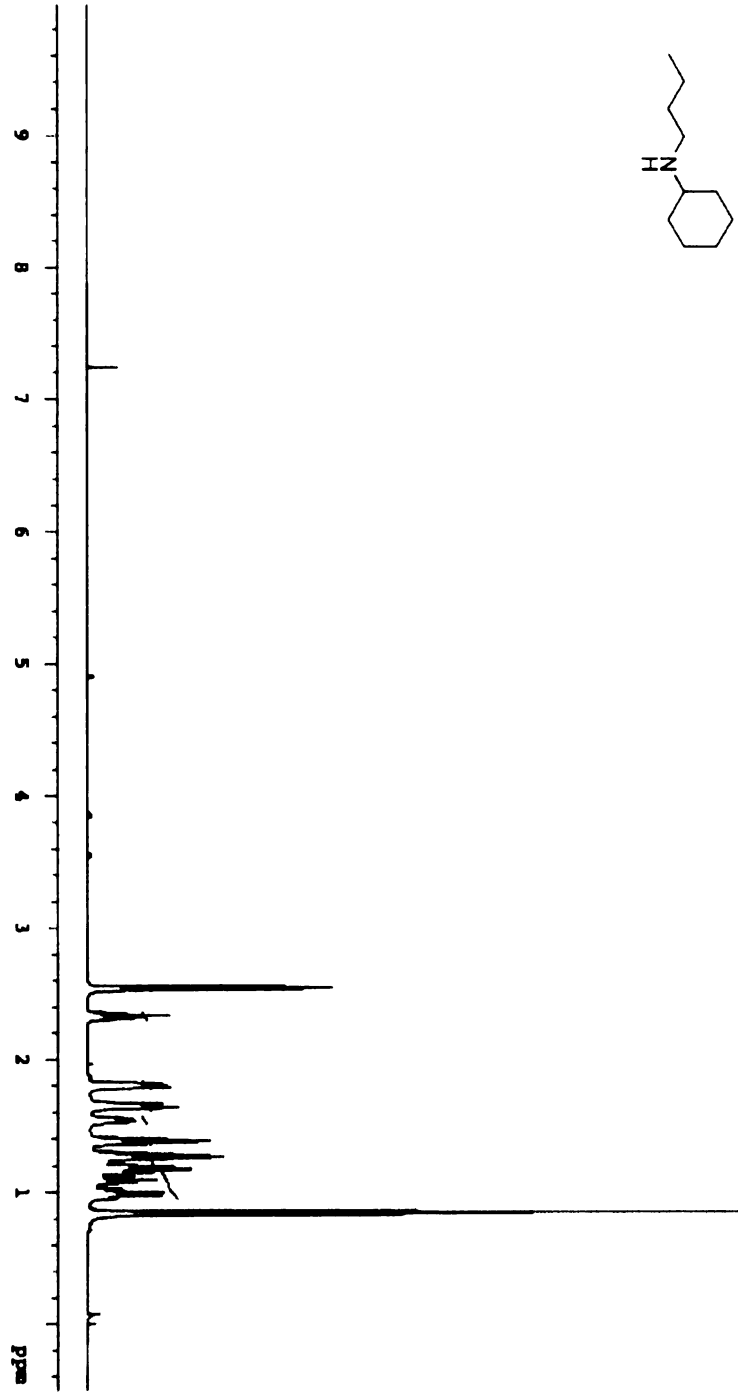


Figure 4.20. ^{1}H NMR of *N*-butylcyclohexanamine.

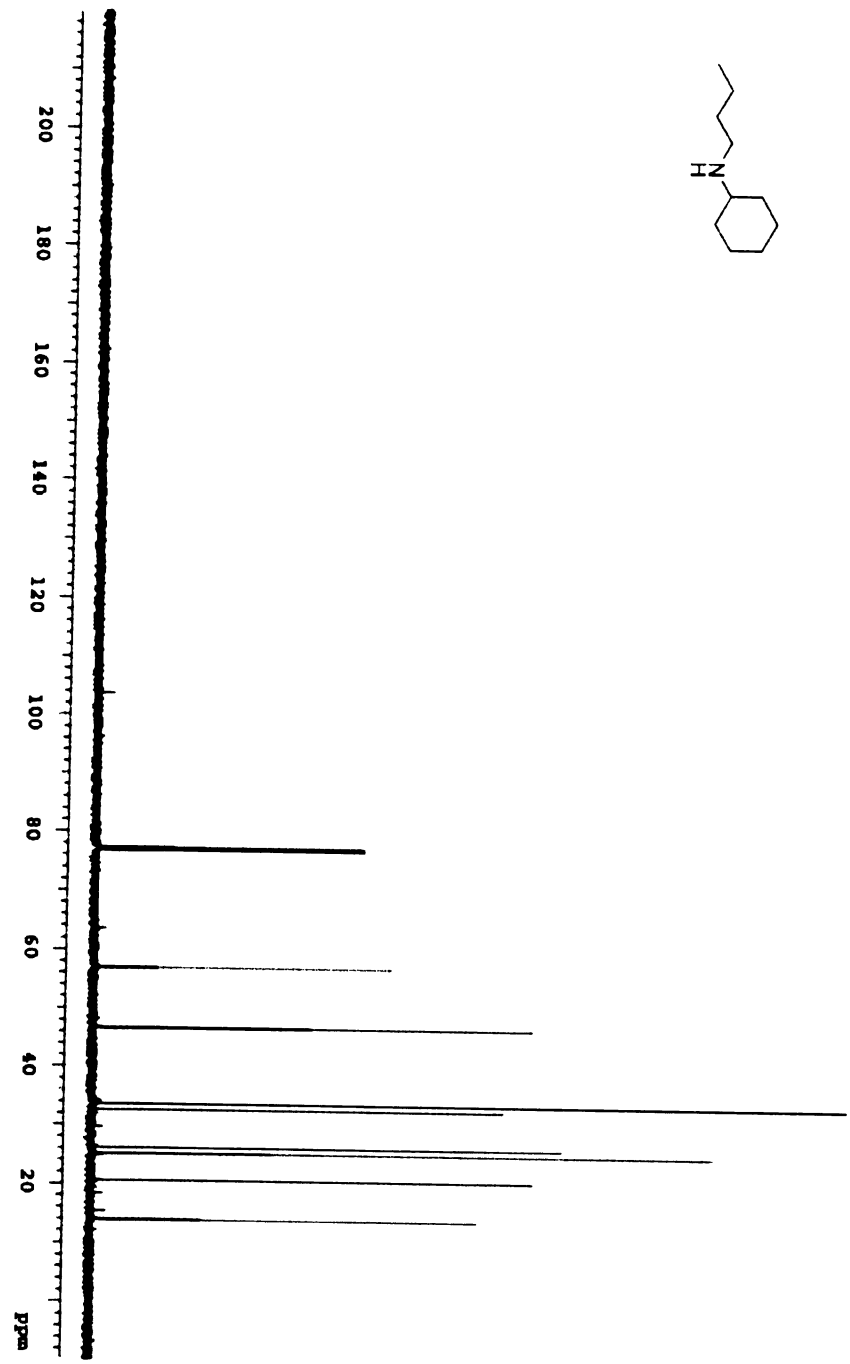


Figure 4.21. ^{13}C NMR of *N*-butylcyclohexanamine.

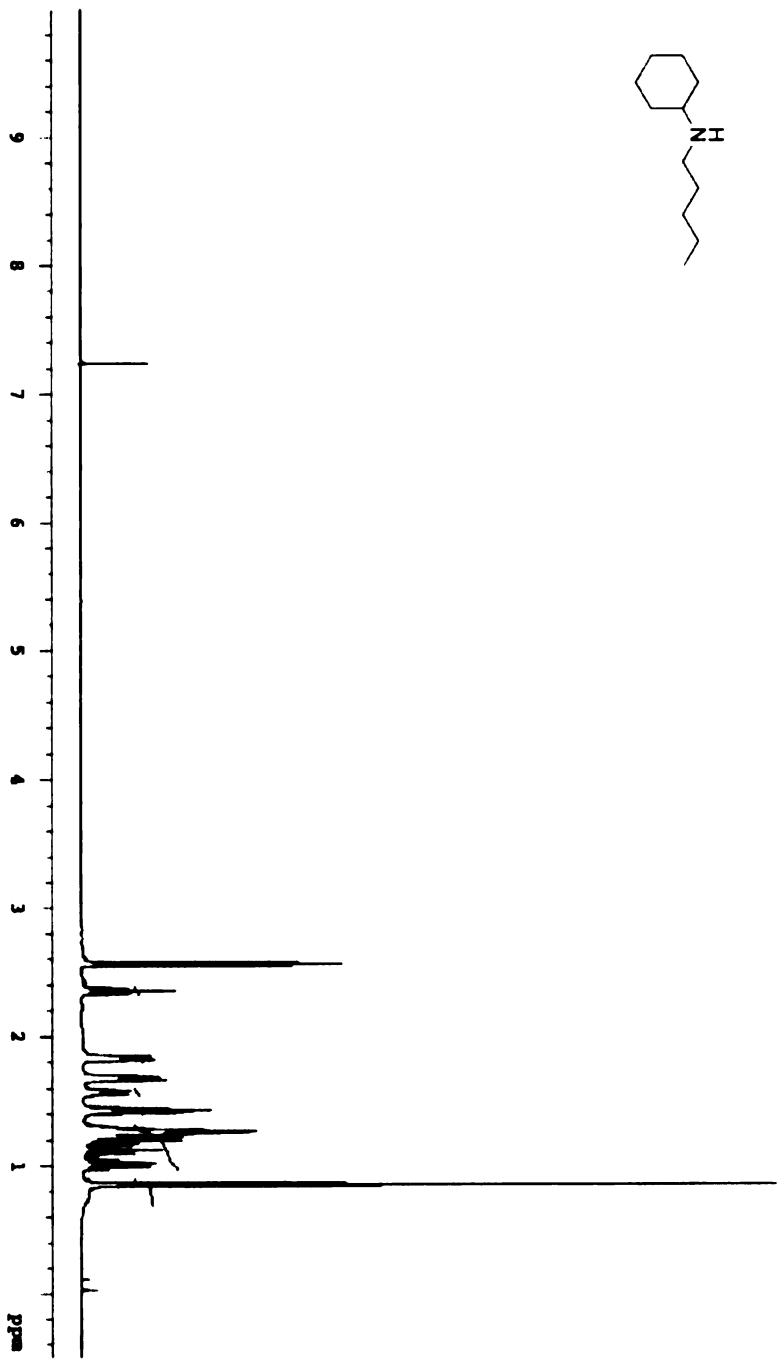


Figure 4.22. ^{1}H NMR of *N*-pentylcyclohexanamine.

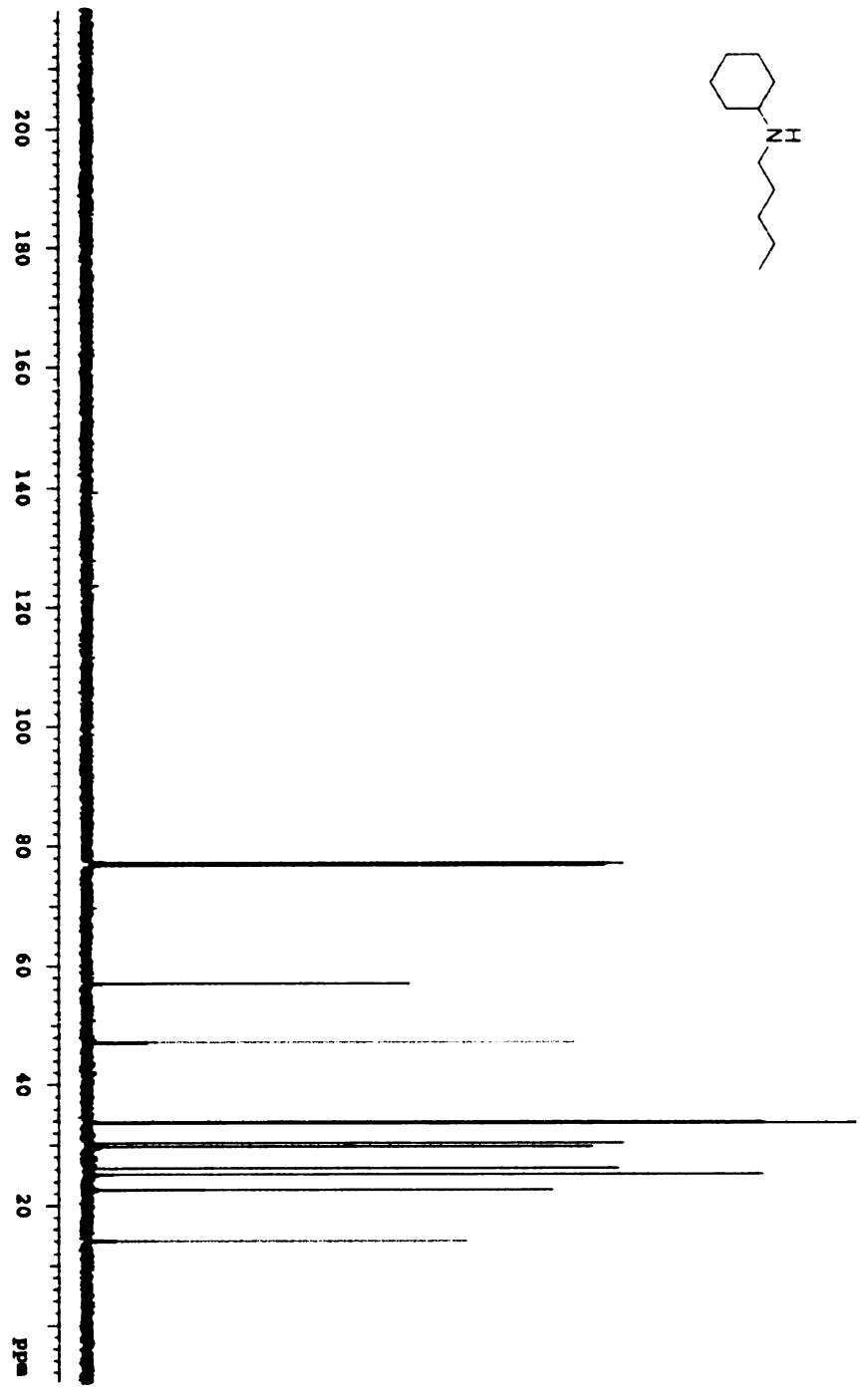


Figure 4.23. ^{13}C NMR of *N*-pentylcyclohexanamine.

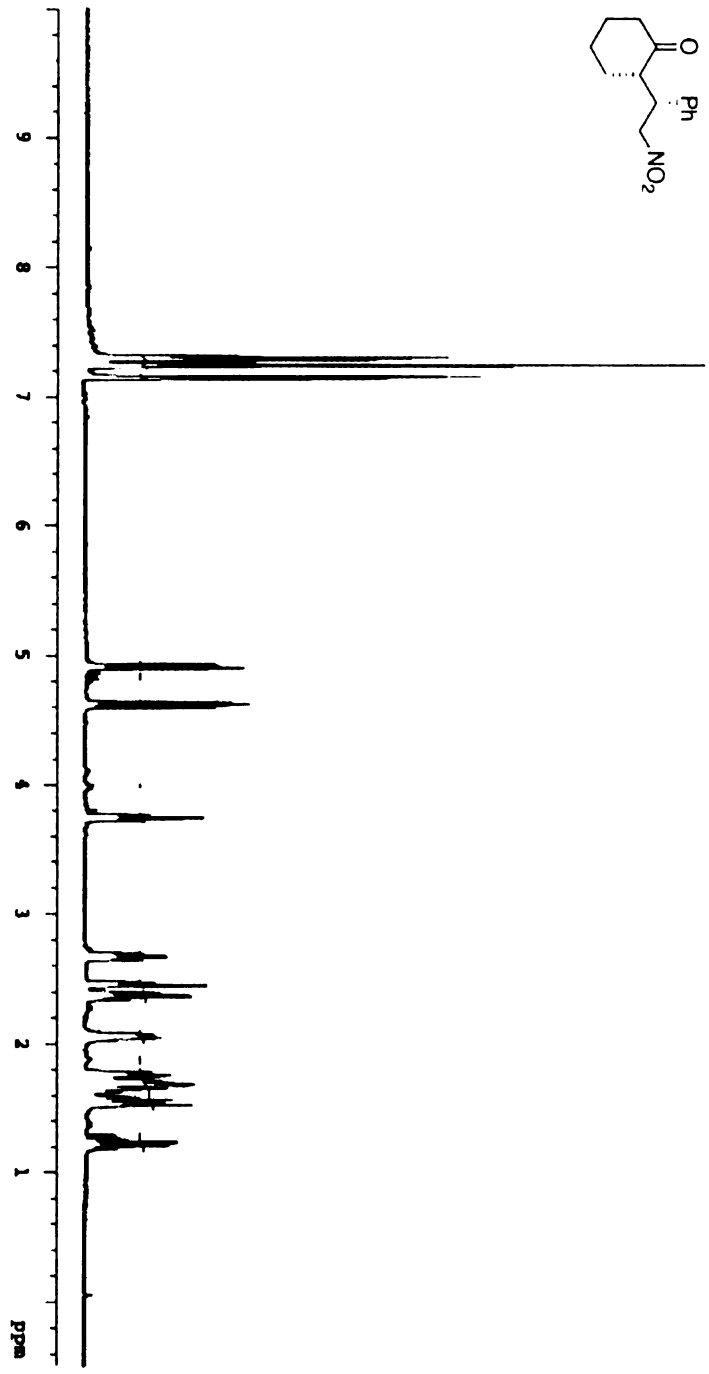


Figure 4.24. ^{1}H NMR of 2-(2-Nitro-1-phenylethyl)-cyclohexanone.

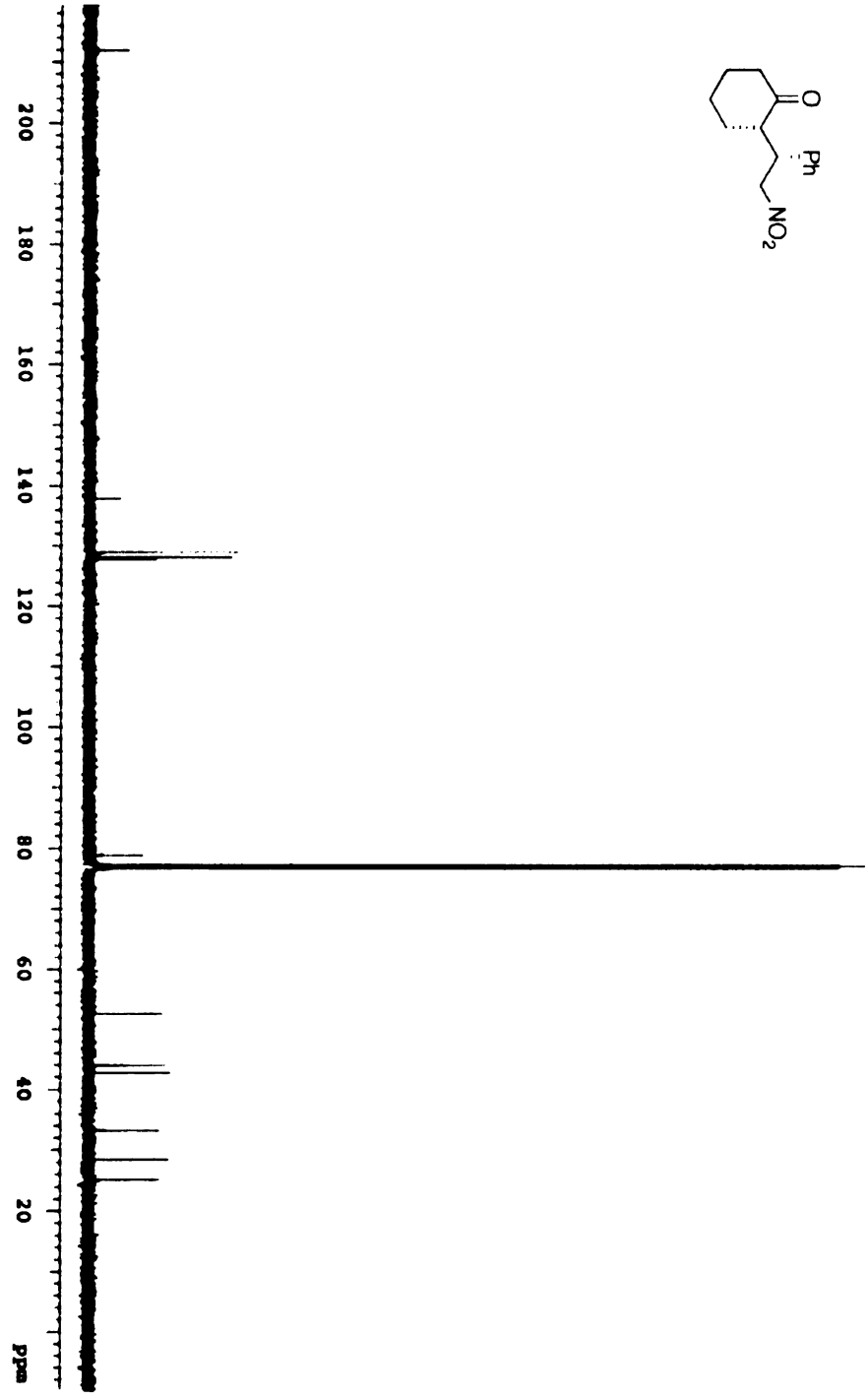


Figure 4.25. ^{13}C NMR of 2-(2-Nitro-1-phenylethyl)-cyclohexanone.

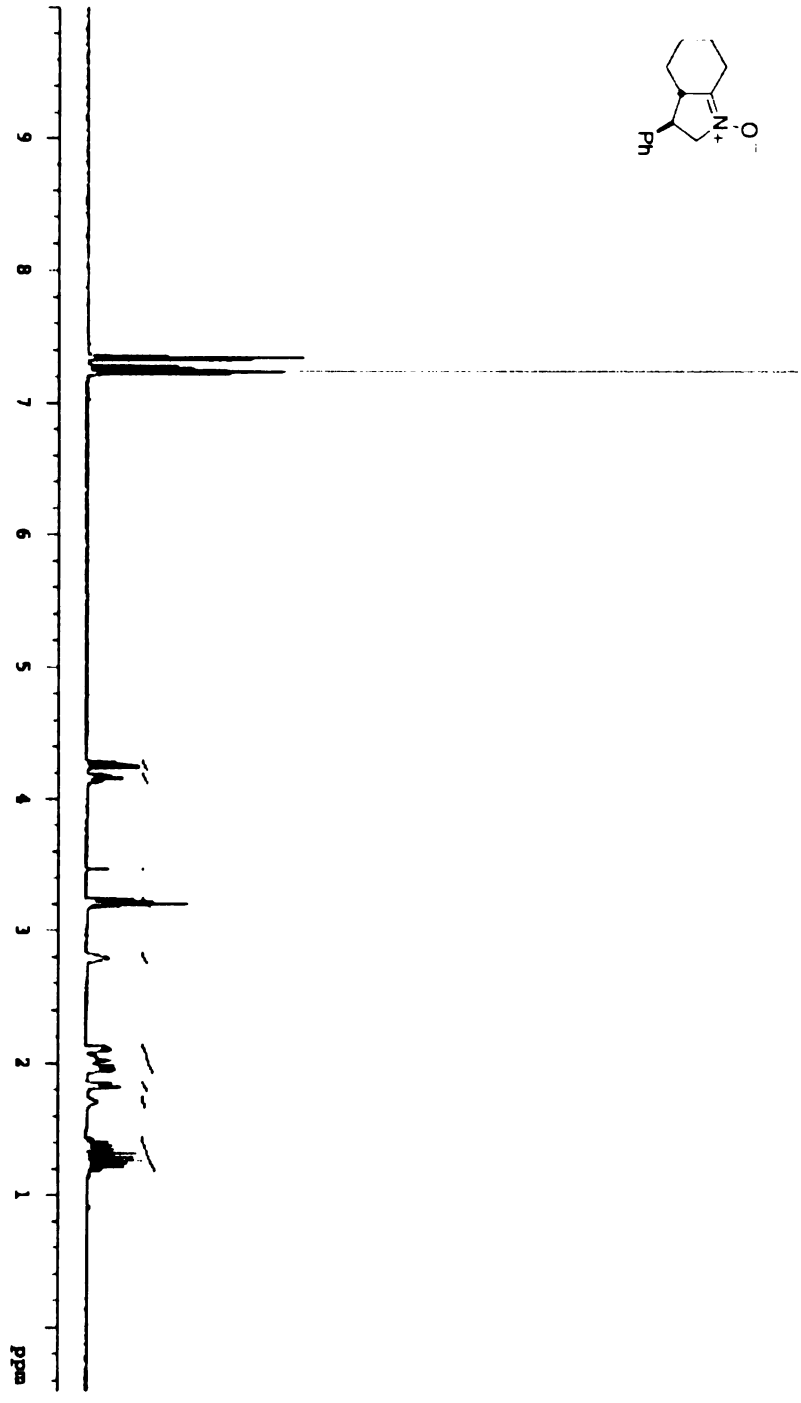


Figure 4.26. ^{1}H NMR of 3-Phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indole-1-oxide.

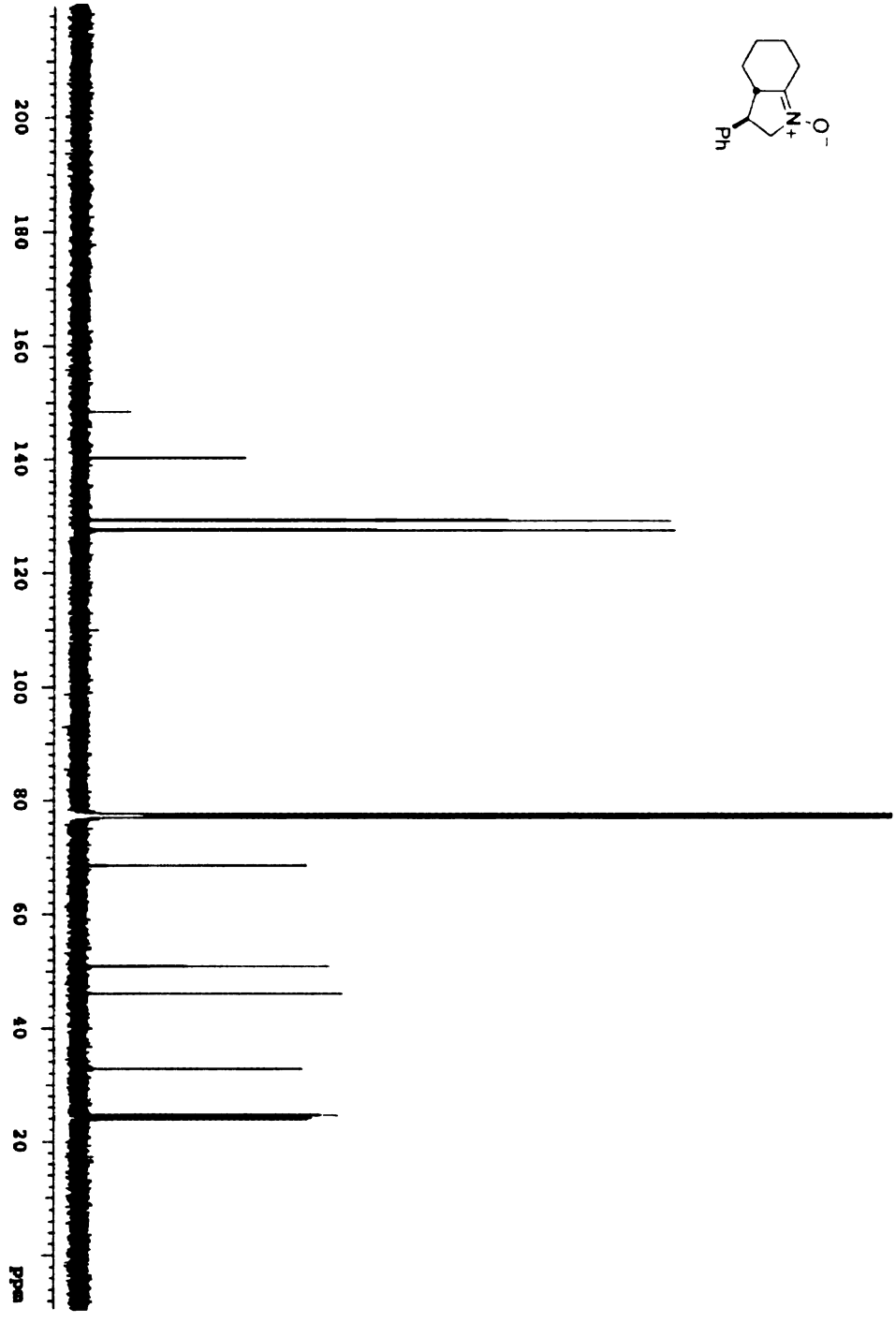


Figure 4.27. ^{13}C NMR of 3-Phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indole-1-oxide.

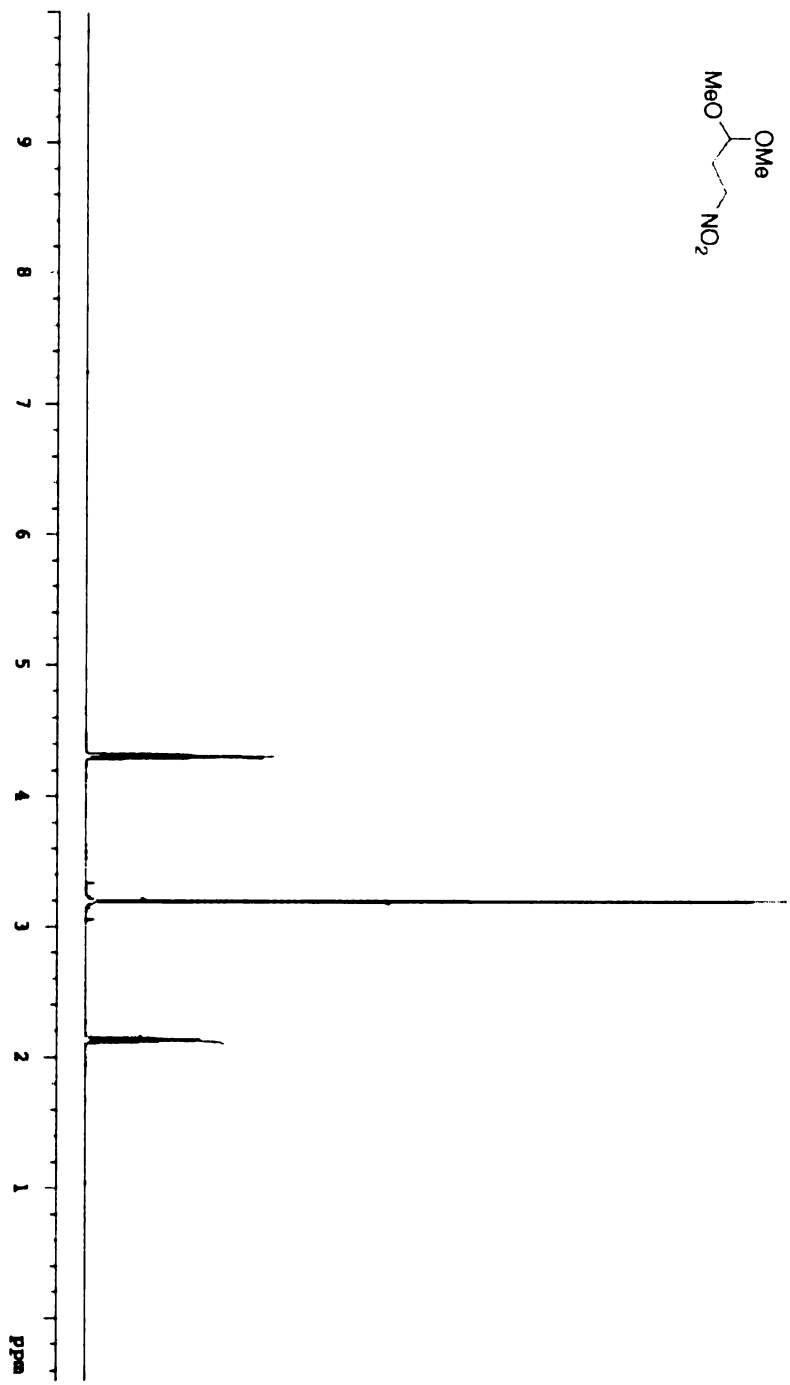


Figure 4.28. ^{1}H NMR of 3-Nitropropanal dimethyl acetal.

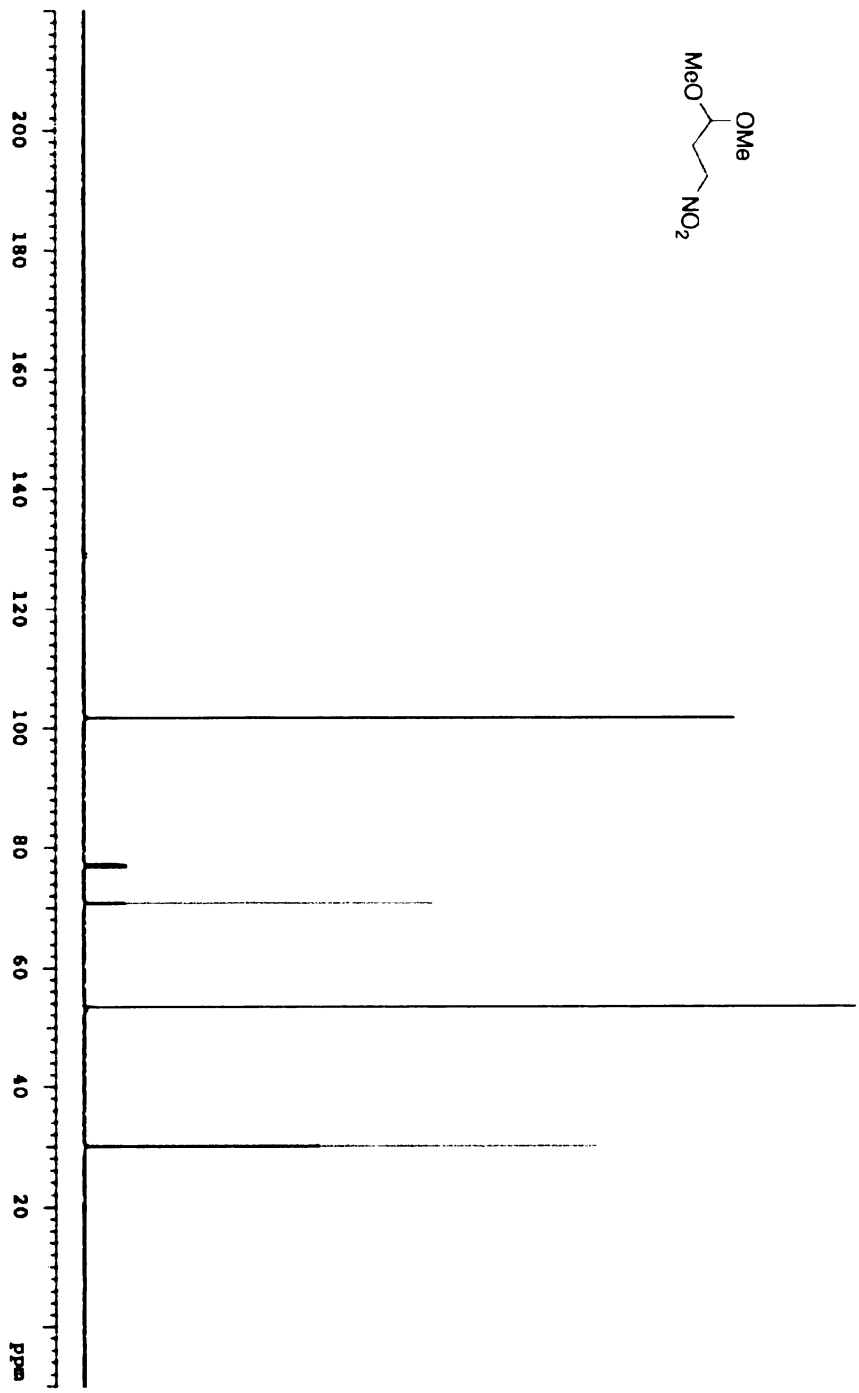


Figure 4.29. ^{13}C NMR of 3-Nitropropanal dimethyl acetal.

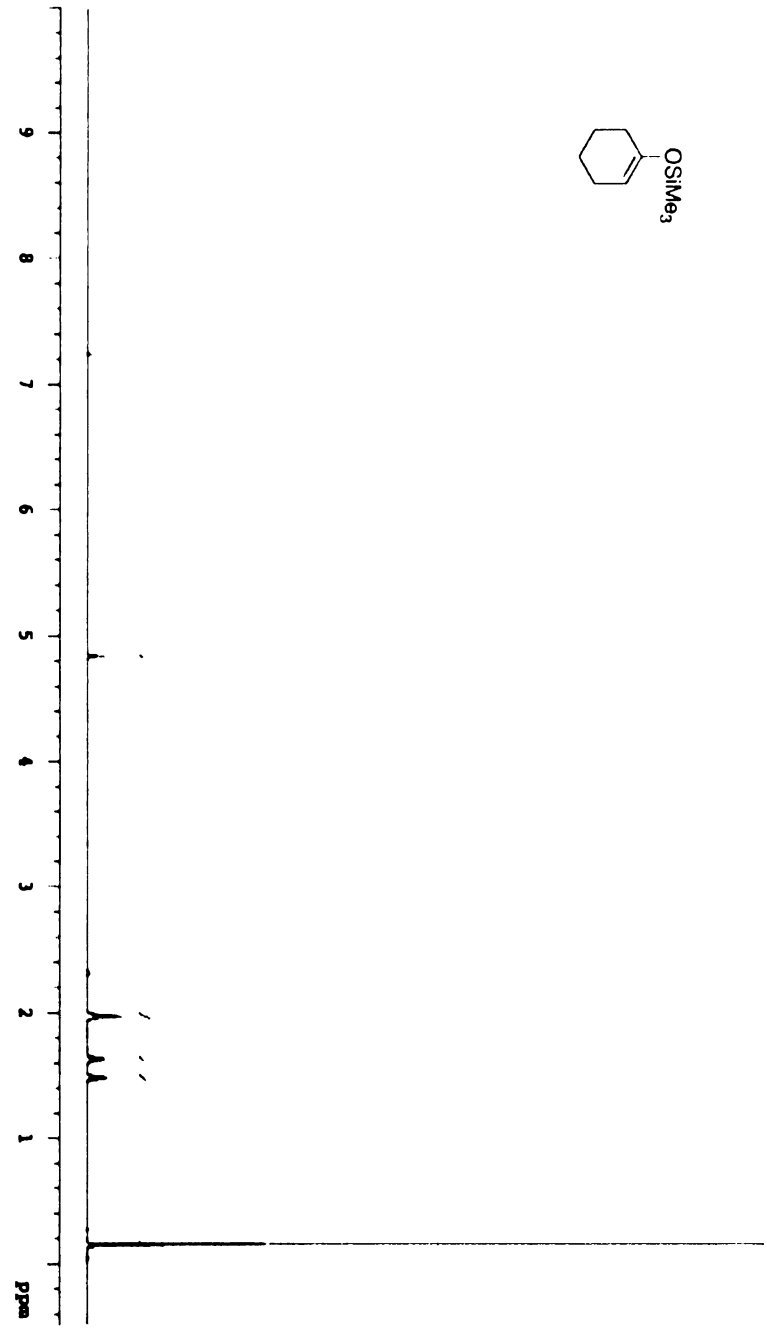


Figure 4.30. ^{1}H NMR of 1-Trimethylsiloxycyclohexene.

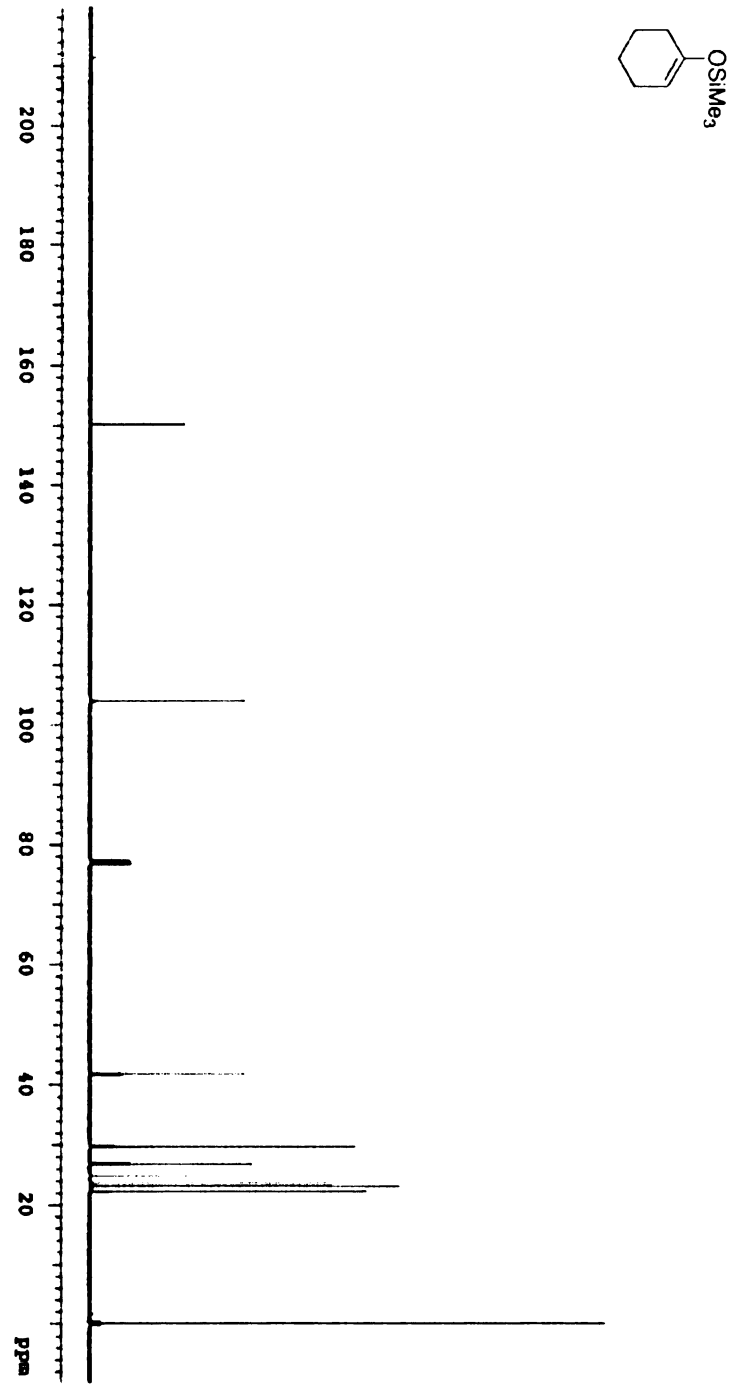


Figure 4.31. ^{13}C NMR of 1-Trimethylsiloxycyclohexene.

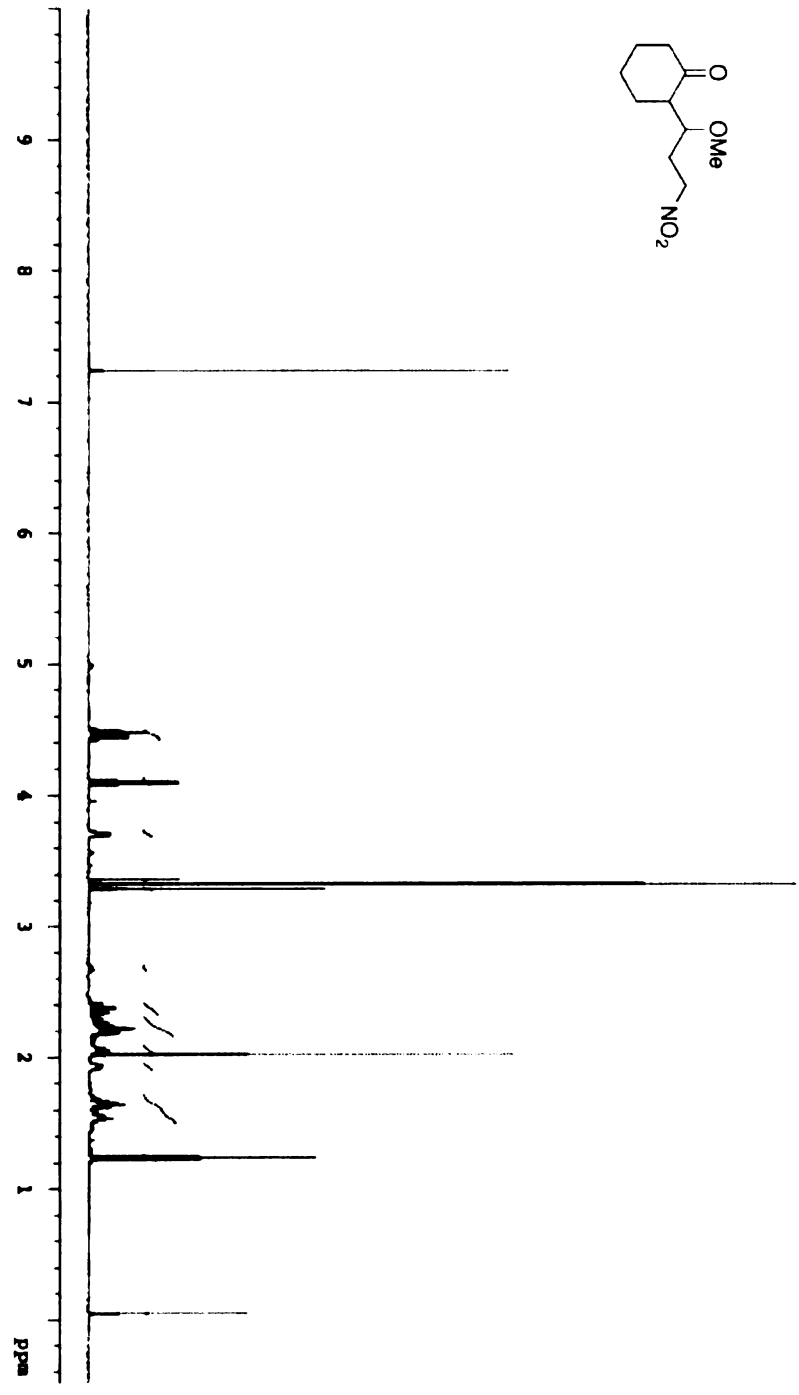


Figure 4.32. ^{1}H NMR of 2-(1-Methoxy-3-nitro)-cyclohexanone.

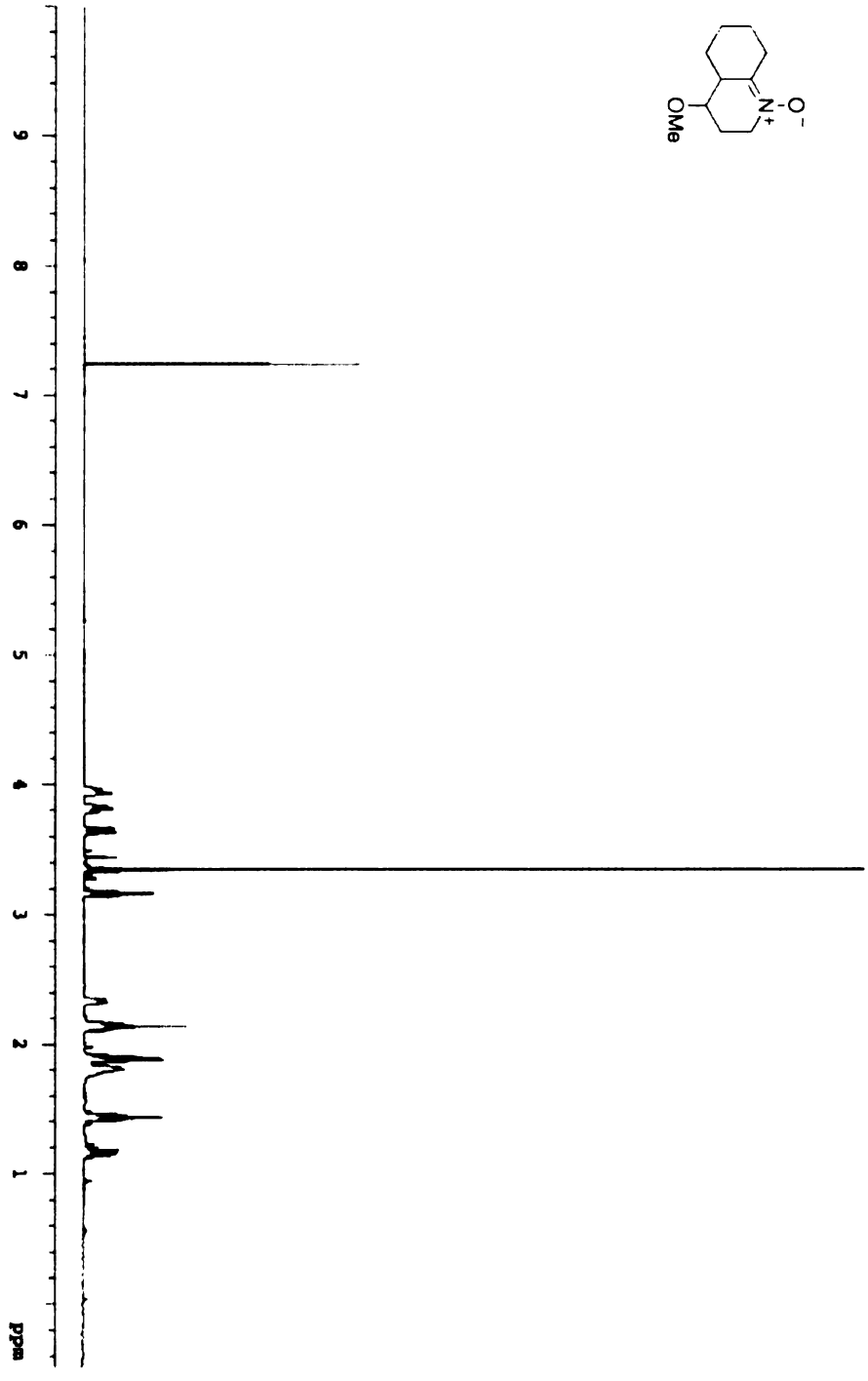


Figure 4.33. ^{1}H NMR of 4-Methoxy-2,3,4,4a,5,6,7,8-octahydroquinoline-1-oxide.

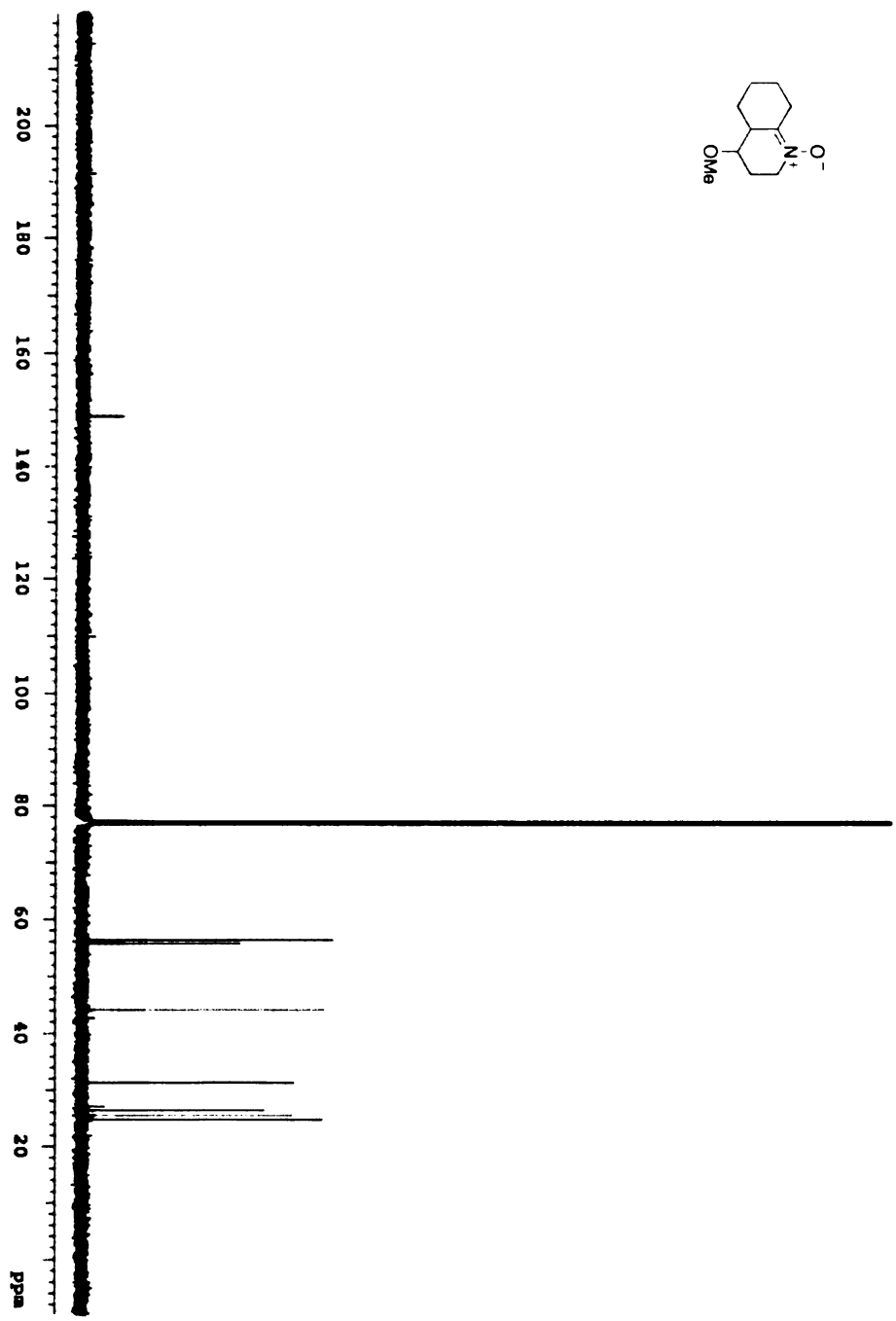


Figure 4.34. ^{13}C NMR of 4-Methoxy-2,3,4,4a,5,6,7,8-octahydroquinoline-1-oxide.

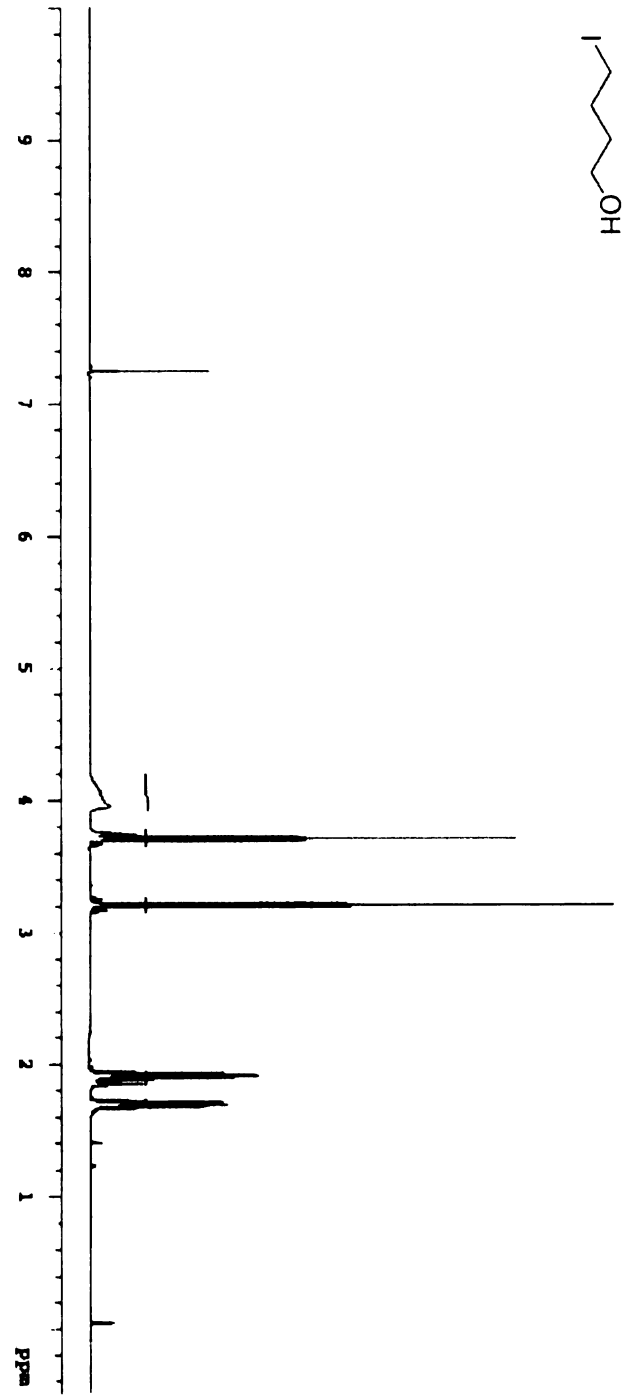


Figure 4.35. ^{1}H NMR of 4-Iodobutan-1-ol.

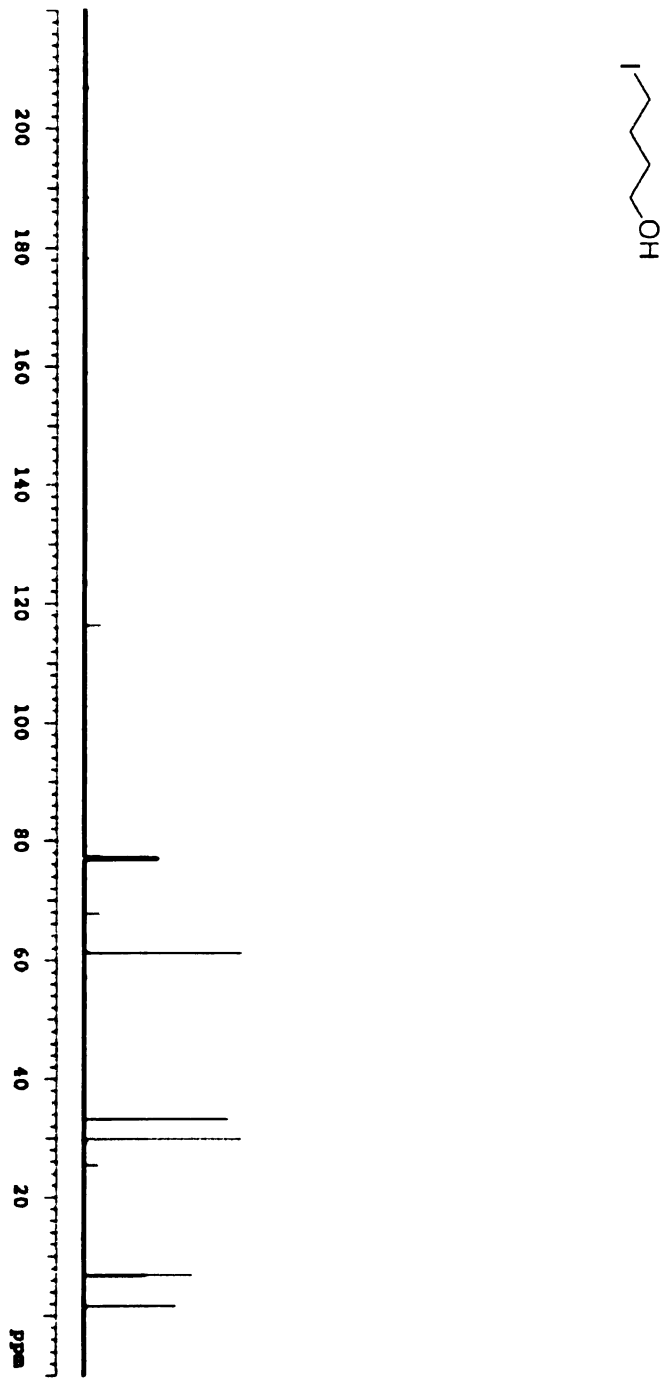


Figure 4.36. ^{13}C NMR of 4-Iodobutan-1-ol.

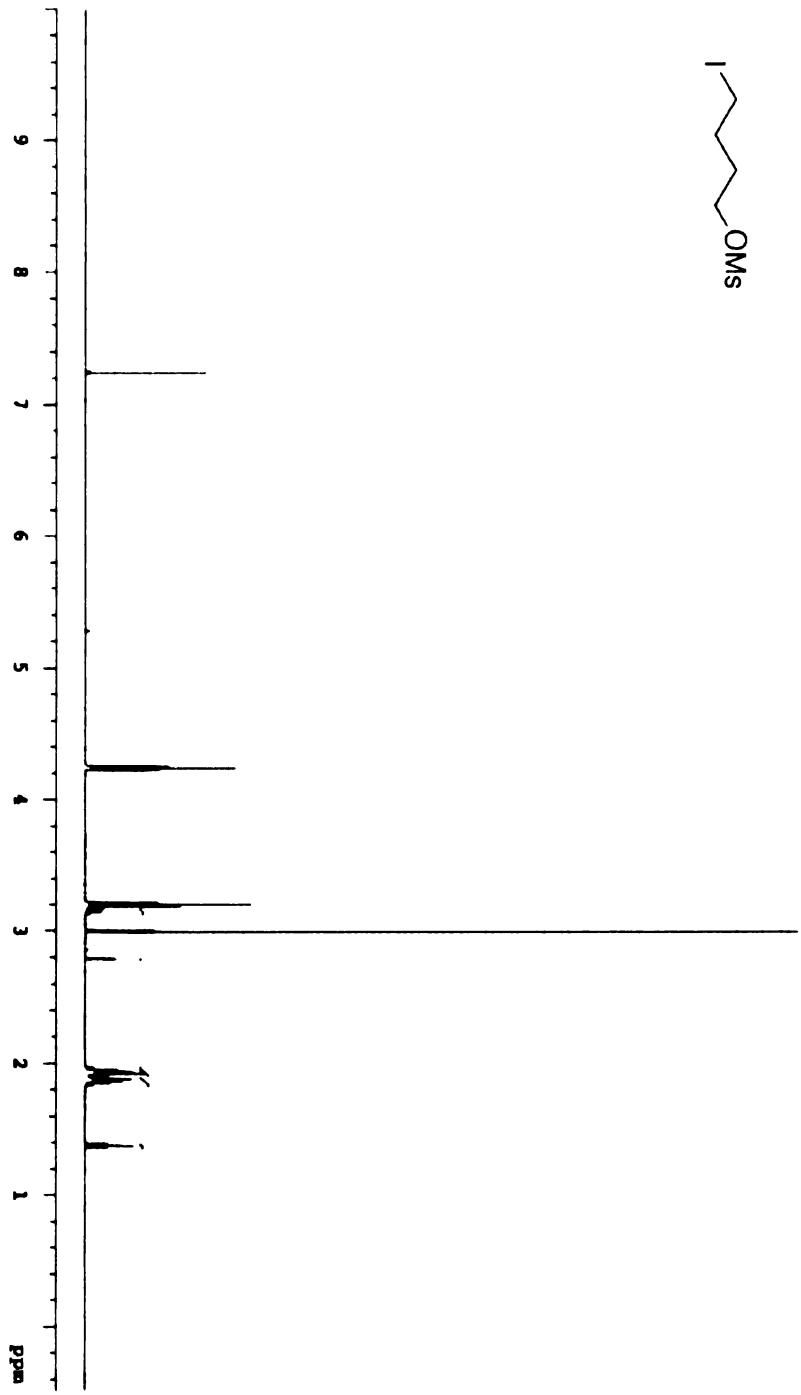


Figure 4.37. ^{1}H NMR of 4-Iodobutyl methanesulfonate.

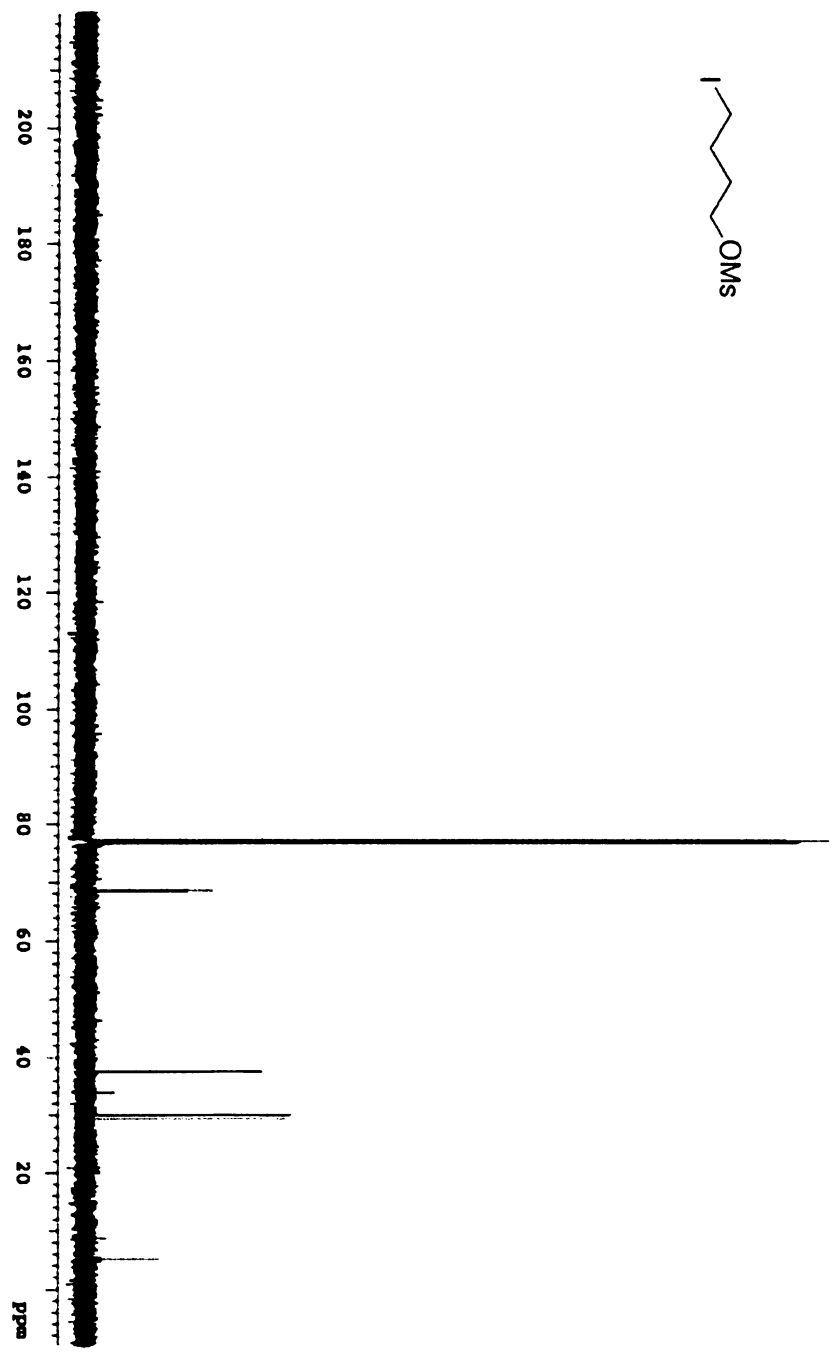


Figure 4.38. ^{13}C NMR of 4-Iodobutyl methanesulfonate.

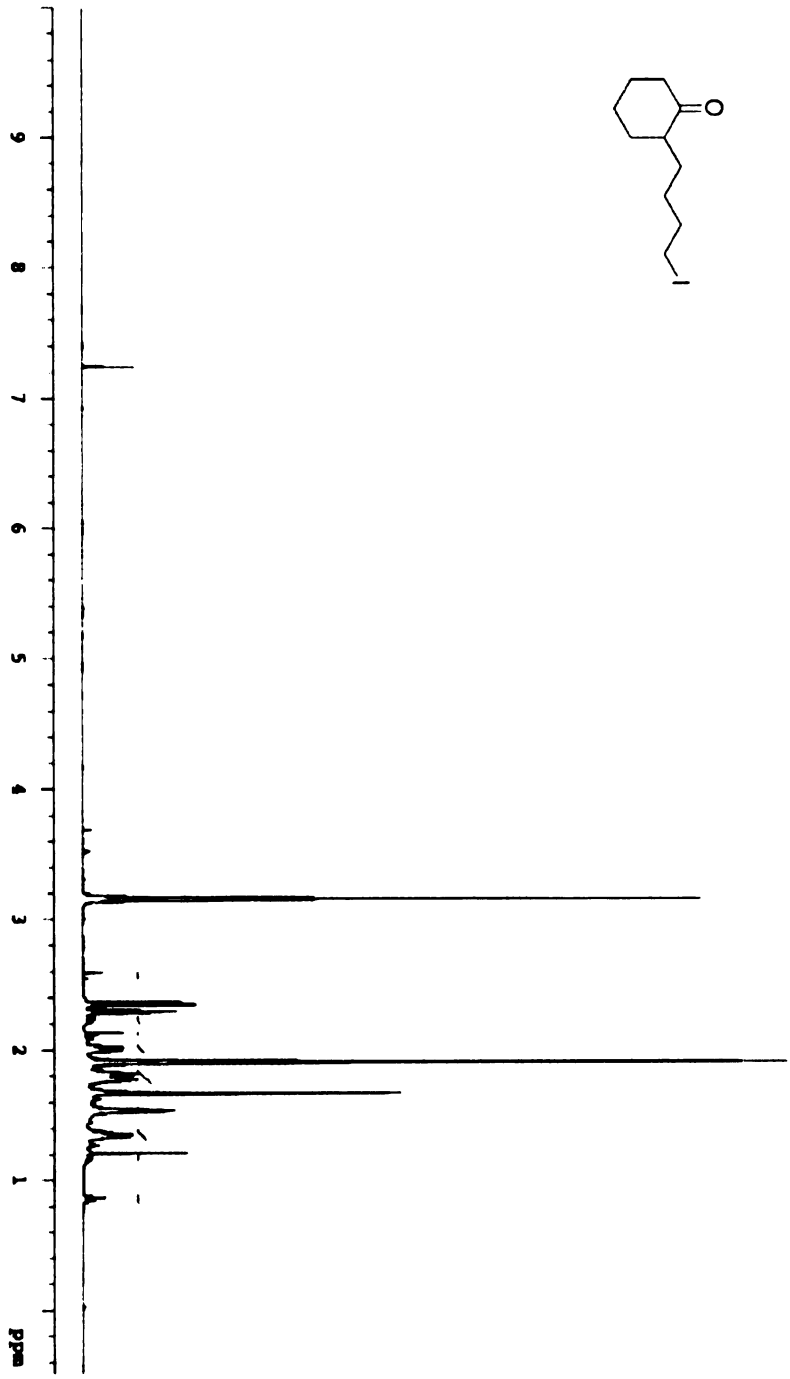


Figure 4.39. ^{1}H NMR of 2-(4-Iodobutyl)cyclohexanone.

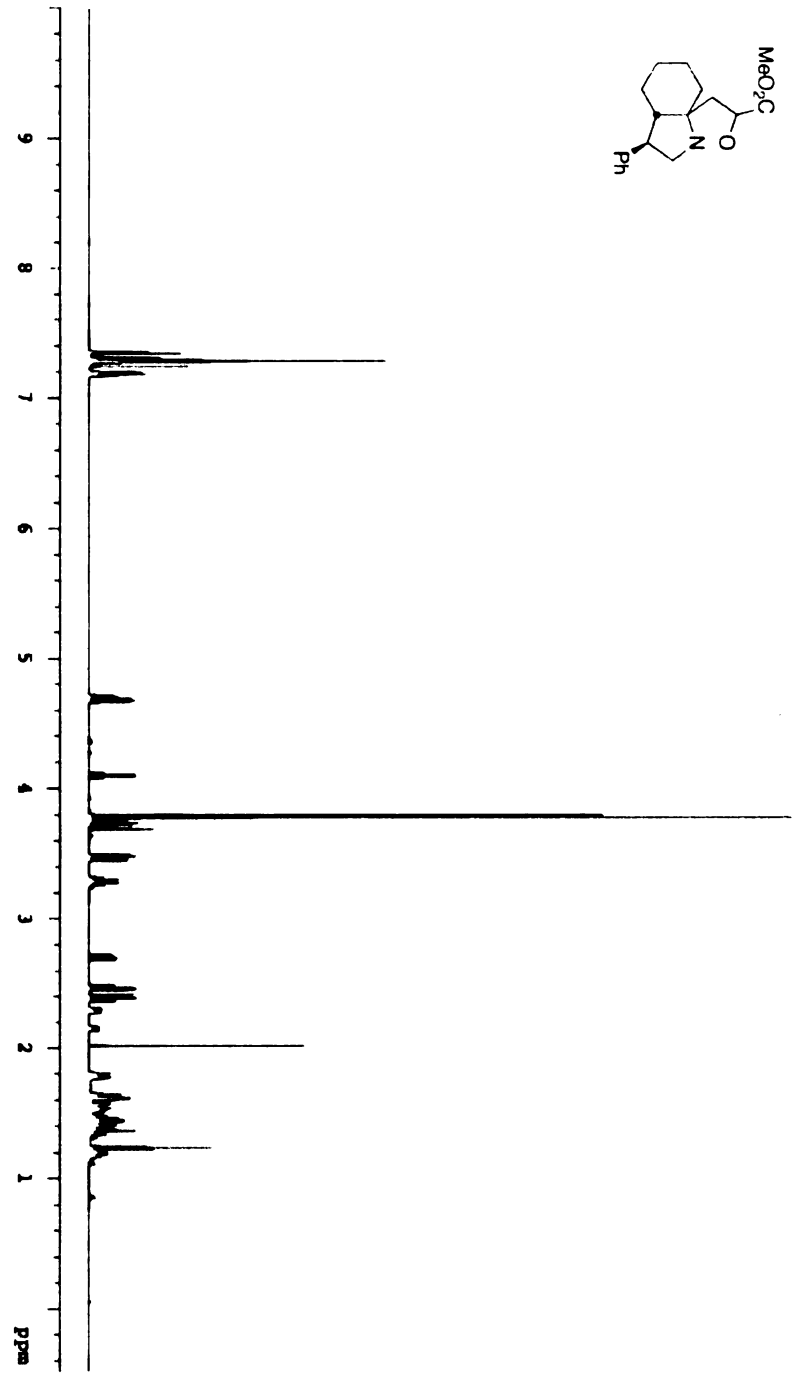


Figure 4.40. ^{1}H NMR of Methyl 6-phenyloctahydro-1*H*-isoxazolo[2,3-*i*]indole-2-carboxylate.

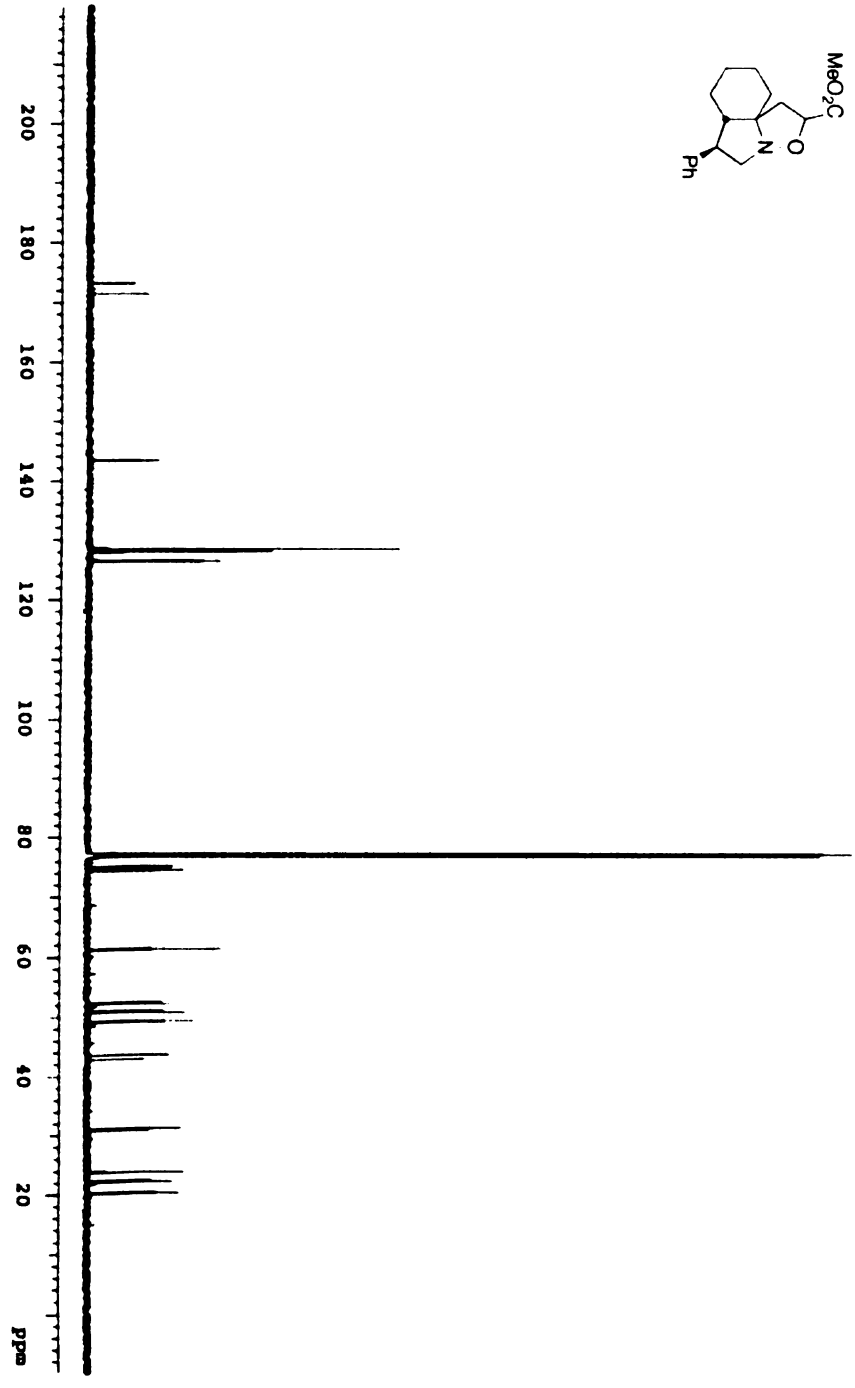


Figure 4.41. ^{13}C NMR of Methyl 6-phenyloctahydro-1*H*-isoxazolo[2,3-*i*]indole-2-carboxylate.

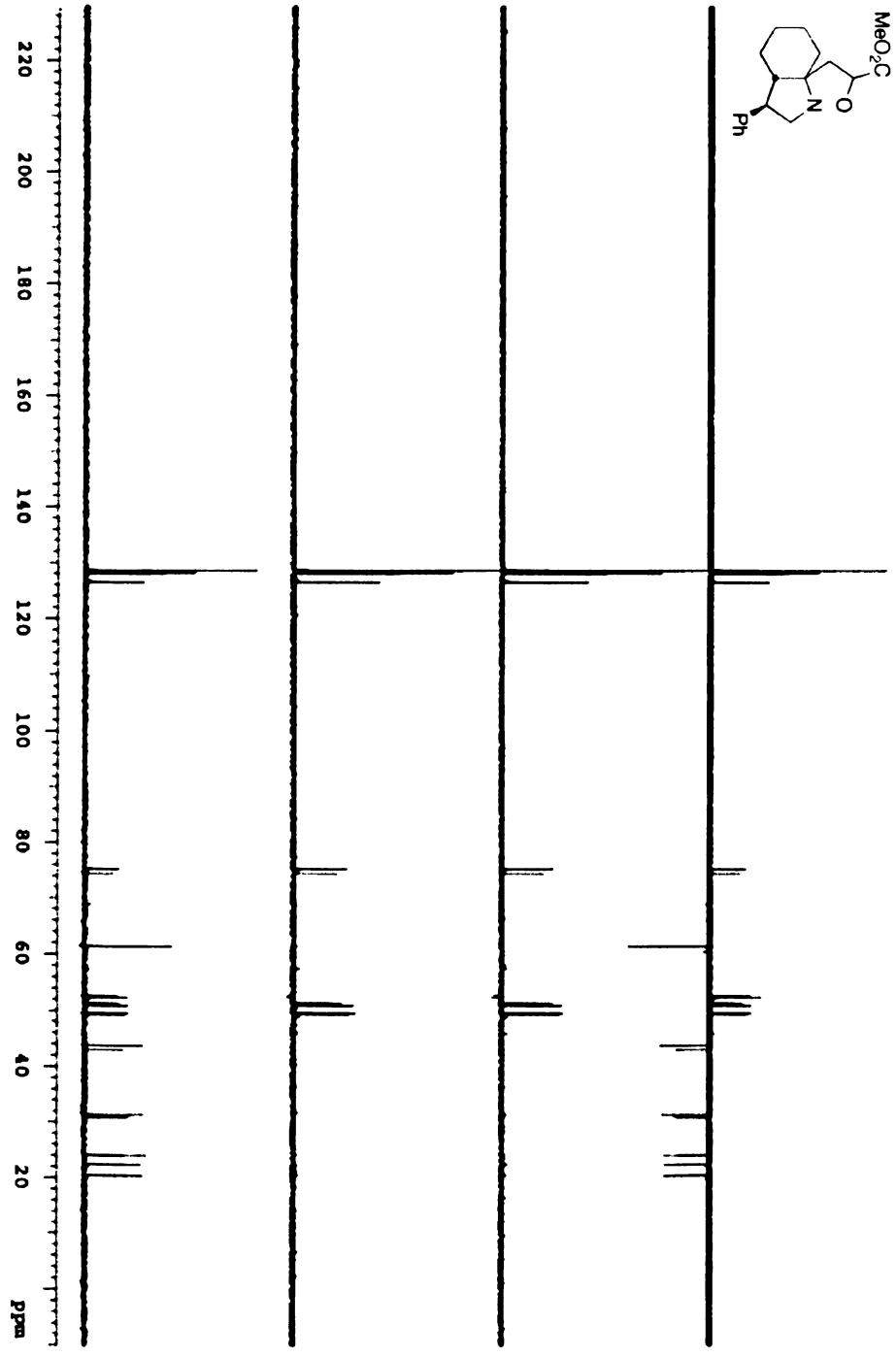


Figure 4.42. DEPT analysis of Methyl 6-phenyloctahydro-1*H*-isoxazolo[2,3-*i*]indole-2-carboxylate.

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