To the Graduate Council:

I am submitting herewith a dissertation written by John Paul Carter entitled "Carbon Alkylation of Aliphatic N-Sulfinylamines." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Fred M. Schell, Major Professor

We have read this dissertation
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# CARBON ALKYLATION OF ALIPHATIC N-SULFINYLAMINES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

John Paul Carter

December 1978

13[illegible]29

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ABSTRACT

The use of N-sulfinylamines in attempts to create the synthetic equivalent of a carbon-based anion under the nitrogen atom of a primary aliphatic amine has been explored. As N-sulfinylamines are made from primary amines by treatment with thionyl chloride and are transformed back into the parent amine by addition of water, the deprotonation and alkylation of such compounds constitutes a formal umpolung.

Treatment of a number of aliphatic N-sulfinylamines with strong base followed by simple saturated electrophiles did not provide the carbon alkylated amine after aqueous work-up. However, use of allylic halides as the alkylating agents did result in the isolation of the desired material in good yield.

A mechanism involving sulfur alkylation of the anion of the aliphatic N-sulfinylamine, followed by a [3,3] sigmatropic shift is proposed to explain the failure of saturated electrophiles to react and the structures of certain products. Support of this mechanism was obtained by independent synthesis of a key intermediate which underwent the postulated rearrangement.

Anions of N-sulfinylamines undergo reaction with methyl vinyl ketone to yield δ-aminoketones in modest yields. However, secondary N-sulfinylamines, such as cyclohexyl-N-sulfinylamine fail to add to this unsaturated ketone.

Alkylation of the N-sulfinylamine derived from trans-4-tert-butylcyclohexylamine with allyl bromide gave trans-1-allyl-4-tert-butylcyclohexylamine, following addition of water.

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# CHAPTER I

## HISTORICAL

### A. UMPOLUNG OF AMINES

Nature places certain constraints on the organic chemist. For example, many of the Lewis acid-base reactions on which synthetic organic chemistry depends tend to be dominated by carbon-heteroatom bonds which are polarized as indicated below.

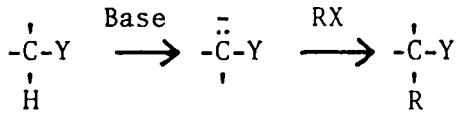
$$\overset{\delta^+}{\underset{|}{-C-}}\overset{\delta^-}{\underset{|}{X}} \qquad (1)$$

This is true because most of the synthetically useful elements (oxygen, nitrogen, and the halogens) are more electronegative than carbon and possess unshared pairs of electrons which are capable of stabilizing an adjacent positive charge. However, recently a great deal of research has been conducted[1,2,3] in an attempt to create new functional groups which reverse this polarity. This reversal has been termed symmetrization,[1] charge affinity inversion,[2] and umpolung.[3]

Conceptually such an umpolung should consist of three steps:[4] first, a synthetic reaction to create the functional group which will induce the charge affinity inversion; secondly, the reaction

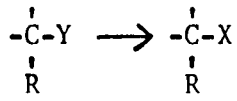
$$\overset{\delta^+}{\underset{|}{-C-}}\overset{\delta^-}{\underset{|}{X}} \longrightarrow \overset{\delta^-}{\underset{|}{-C-}}\overset{\delta^+}{\underset{|}{Y}} \qquad (2)$$

itself, for example, an alkylation; and finally, a reaction to unmask



(3)

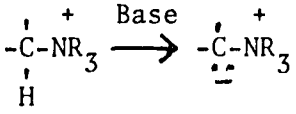
the functionality. Each of these steps should be experimentally



(4)

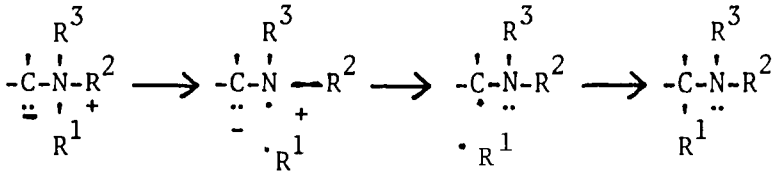
simple, high-yielding, and inexpensive to perform.

In the case of amines, perhaps the most obvious attempt at umpolung would be the generation of the ylide derived by removal of a proton from a quarternary ammonium salt. However, such ylides are found to be



(5)

unstable and undergo the Stevens rearrangement,[5] which can be rationalized as follows,[6] although the exact nature of the mechanism is in question.



(6)

The first useful umpolung of amines was reported by Schöllkopf and Gerhart in 1968.[7] They demonstrated that isocyanides, which may be generated from primary amines by formylation and dehydration,[8] are deprotonated by strong bases, such as n-butyllithium.

$$-\overset{H}{\overset{|}{C}}-NH_2 \longrightarrow -\overset{H}{\overset{|}{C}}-N{\equiv}C \xrightarrow{BuLi} -\overset{\ddot{-}}{C}-N{\equiv}C \equiv \text{"}-\overset{\ddot{-}}{C}-\overset{\cdot\cdot}{NH_2}\text{"} \qquad (7)$$

As isocyanides may be reconverted to the primary amines by treatment with acid, this series of reactions constitutes a formal umpolung. However, there are certain limitations of this method.[9] No secondary isocyanide is deprotonated unless it possesses an additional stabilizing functional group, such as an olefin, benzene ring, ester, cyanide, etc., on the α carbon, although cyclopropyl and cyclobutyl isocyanide are exceptions to this rule. Also, isocyanides which have donor functionality at the δ position to chelate the metal are lithiated. Thus compounds such as those containing oxygen or nitrogen at the δ position are metalated in contrast to the hydrocarbon.[10]

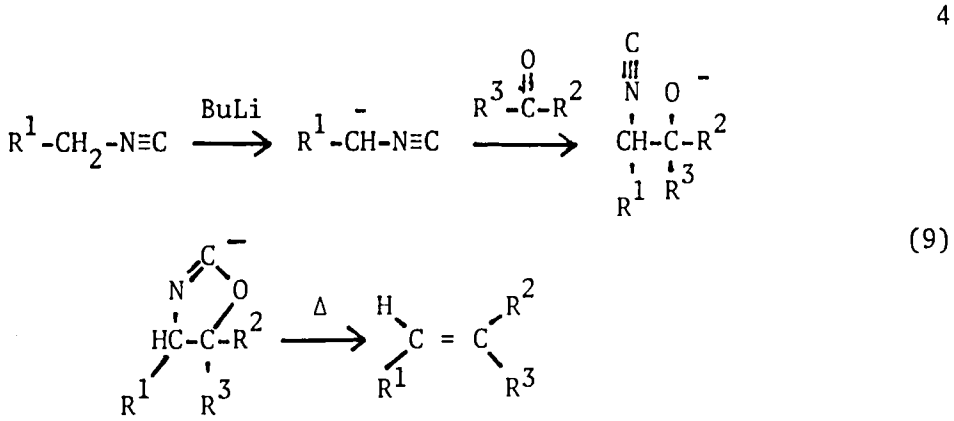
$$X\text{-}CH_2CH_2CH_2\text{-}N{\equiv}C \xrightarrow{BuLi} \begin{array}{l} CH_2\text{-}X \\ | \quad\quad Li \\ CH_2 \quad | \\ \quad\diagdown\quad | \\ \quad\quad CH\text{-}N{\equiv}C \end{array} \qquad (8)$$

$X = -OCH_3$

$X = -N(CH_3)_2$

$X = -H$

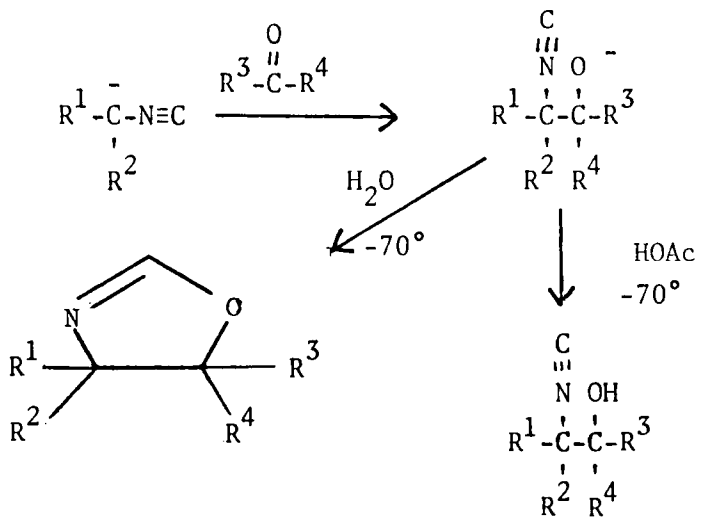
The first reported reactions of metalated isocyanides involved their addition to carbonyl compounds.[7] Addition of the isocyanide anion to the carbon-oxygen double bond is normally followed by a ring closure reaction as shown below. When heated, the cyclic product loses cyanate to provide an olefin in yields ranging from 28% ($R^1 = R^3 = -H$, $R^2 = -CH{=}CH\text{-}C_6H_5$) to 74% ($R^1 = R^2 = R^3 = -C_6H_5$).



(9)

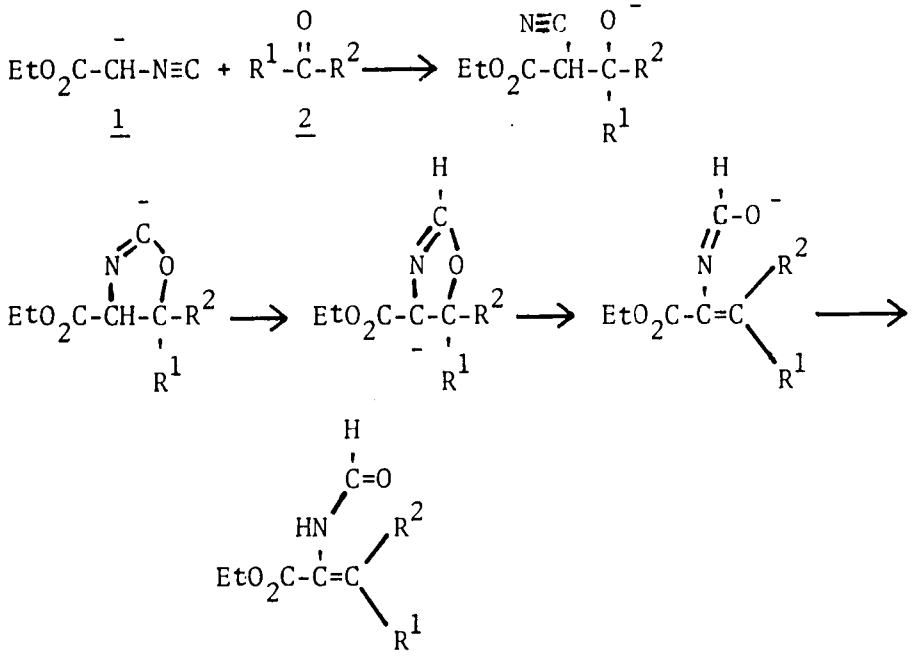
This reaction complements the Wittig reaction, which is somewhat sensitive to steric hindrance. Thus, α-lithiobenzhydryl isocyanide adds to benzaldehyde at -70°,[7] while the corresponding Wittig reagent, diphenylmethylene triphenylphosphorane, is inert towards aldehydes and ketones.[11,12]

If this isocyanide addition reaction is quenched with water or methanol at -70°, instead of heated to drive off cyanate, the 2-oxazoline is isolated.[13] Or, if glacial acetic acid is added to the reaction mixture at low temperatures, the isocyanoalcohol is obtained.[10] A typical yield for the oxazoline is 87% ($R^1 = R^3 = -C_6H_5$, $R^2 = R^4 = -CH_3$) and for the isocyanoalcohol 80% ($R^1 = R^2 = R^3 = -H$, $R^4 = -C_6H_5$).



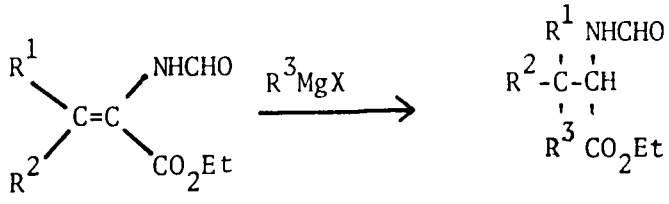
(10)

The reaction of more stabilized carbanions, such as those derived from isocyanoacetic esters, with ketones and aldehydes follows a different course[14] (Equation 11). Condensation of 1 and 2 is followed by ring closure and a series of molecular reorganizations to give, after addition of acetic acid, the α-(formylamino)acrylic ester, in yields of 13% ($R^1$ = $-CH_3$, $R^2$ = -H) to 87% ($R^1$, $R^2$ = $-(CH_2)_5-$).



(11)

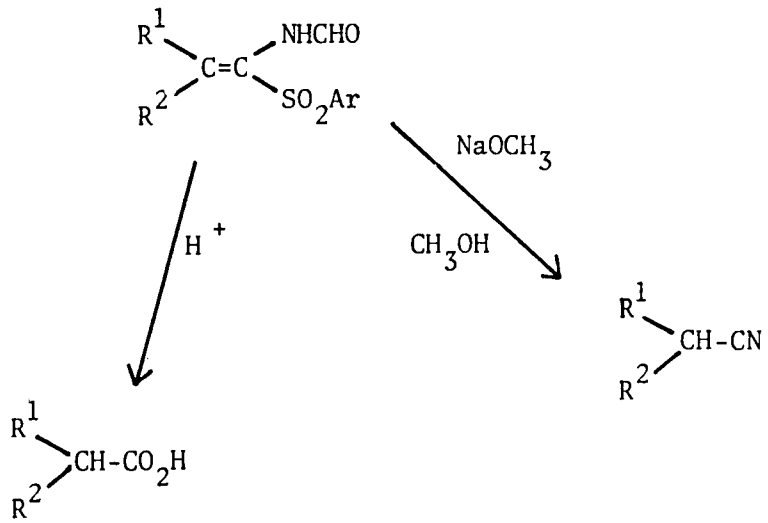
These acrylic esters undergo conjugate addition of Grignard reagents, in the absence of copper ion, to provide tertiary substituted glycines.[15] A typical yield is 76% ($R^1$ = $R^2$ = $R^3$ = $-CH_2CH_3$).



(12)

In a variation of this synthetic scheme, Schöllkopf reported[16] that arenesulfonylmethyl isocyanides, which are obtained by the alkylation of lithium isocyanomethane, undergo reaction with carbonyl compounds to give intermediates suitable for transformation into carboxylic acids and nitriles (Equation 13). Typical yields are 65% for the acid ($R^1$= $-C_6H_5$, $R^2$ = -H, Ar = $-C_6H_5$) and 58% for the nitrile ($R^1$ = Ar = $-C_6H_5$, $R^2$ = -H).

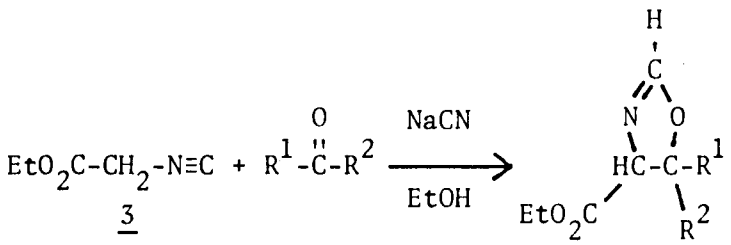
$$Li\text{-}CH_2\text{-}N{\equiv}C + ArSO_2F \longrightarrow ArSO_2\text{-}CH_2\text{-}N{\equiv}C \xrightarrow[2)\ R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-}R^2]{1)\ Base} \qquad (13)$$




The overall effect of these transformations is to convert an aldehyde or ketone into the next higher carboxylic acid or nitrile.

In order to add activated isocyanides, such as those with adjacent esters, nitriles, or sulfonyl groups, to carbonyl compounds, the reaction medium must be both protic and weakly basic.[17,18] Thus treatment of ethyl isocyanoacetate, 3, with the appropriate carbonyl compound

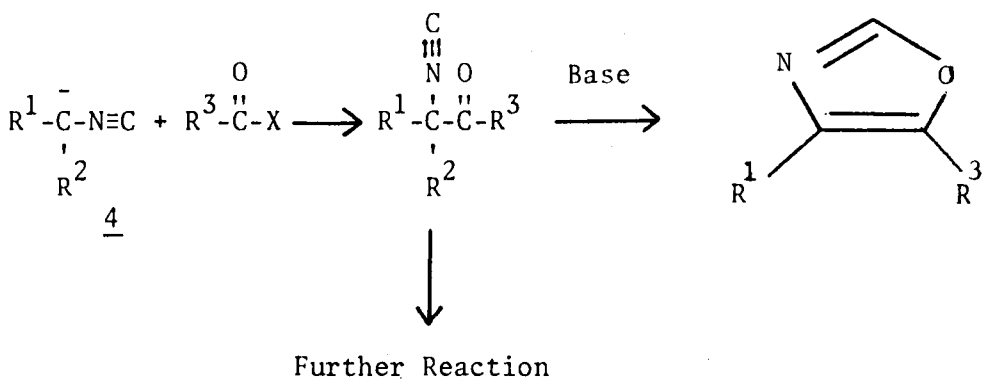
in absolute ethanol containing a catalytic amount of sodium cyanide leads to the isolation of the oxazoline in 15% ($R^1$ = -CH=CH-$CH_3$, $R^2$ = -H) to 72% yield ($R^1$ = -$C_6H_5$, $R^2$ = -H).




(14)

Similar results are obtained with arylsulfonylmethyl isocyanide and isocyanoalkyl cyanides.

Reactions of metalated isocyanides with acylating agents are complicated by the acidity of the reaction product.[19] If $R^2$ = -H (4, Equation 15) removal of this proton by base in the reaction mixture (perhaps by the unreacted isocyanide) leads either to further alkylation or cyclization to the oxazolyl anion.

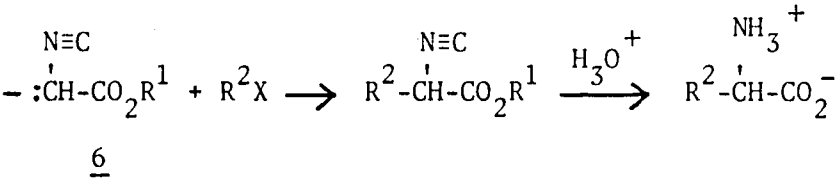



(15)

Therefore, in the synthesis of oxazoles, two equivalents of the metalated isocyanide are employed, and the oxazoles are isolated[20] in modest

[44%, $R^1 = -C_6H_5$, $R^2 = -H$, $R^3 = -CH(CH_3)_2$, $X = -OCH_3$] to good yields [83%, $R^1 = -CO_2Et$, $R^2 = -H$, $R^3 = -CH(CH_3)_2$, $X = -Cl$].

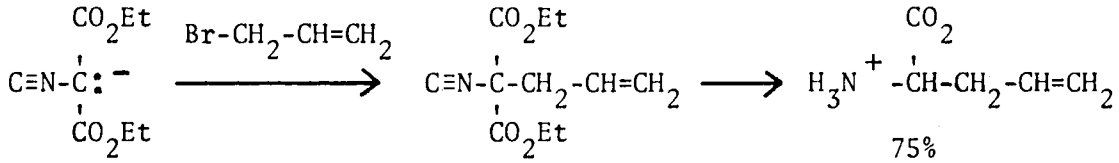
Substituted amino acids are prepared by the alkylation of isocyanoacetic esters,[21] followed by hydrolysis of the isocyanide and the ester (Equation 16). With tertiary esters, the reaction gives monoalkylation in 30% ($R^1 = -C(CH_3)_3$, $R^2 = -CH_2-C_6H_5$) to 76% yields ($R^1 = -C(CH_3)_3$, $R^2 = -CH_2-CH=CH_2$). However, for the ethyl esters (6, $R^1 = -CH_2CH_3$) mixtures of mono-, di-, and non-alkylated materials are produced. Analogous results are obtained by the use of



(16)

6

isocyanomalonic esters (Equation 17).[9]



(17)

Matsumoto[22] achieves the same goal by a slightly different route. He reported the carboxylation of benzylic isocyanides mediated by sodium hydride in 55% (Ar = -p-$CH_3O-C_6H_5$, X = -OEt, R = -Et) to 70% yield (Ar = $-C_6H_5$, $X = -OCH_3$, $R = -CH_3$).

$$Ar\text{-}CH_2\text{-}N{\equiv}C \xrightarrow[2)\ XCO_2R]{1)\ NaH} Ar\text{-}\underset{\displaystyle N{\equiv}C}{\underset{|}{C}}H\text{-}CO_2R \longrightarrow Ar\text{-}\underset{\displaystyle NH_3^+}{\underset{|}{C}}H\text{-}CO_2^- \qquad (18)$$

Furthermore, use of very mild bases, such as triethylamine enhanced the efficiency of this acylation process[23,24] (Equation 19), and therefore α-aminoketones and α-acylaminoesters are produced in high yields, 50% ($R^1$ = $-CH_3$, $R^2$ = $-C_6H_5$) to 87% ($R^1$ = $-CH_2CH_2CH_2CO_2CH_3$, $R^2$ = $-OCH_3$).

$$R^1\text{-}CH_2\text{-}N{\equiv}C + R^2\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl \xrightarrow{Et_3N} R^1\text{-}\underset{\displaystyle N{\equiv}C}{\underset{|}{C}}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}R^2 \qquad (19)$$

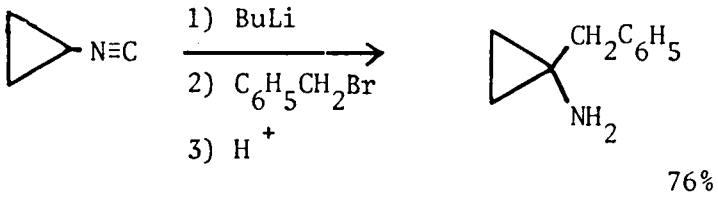
$$R^1\text{-}\underset{\displaystyle NH_2}{\underset{|}{C}}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}R^2$$

Schöllkopf[25] reports the carbon alkylation of primary amines by treatment of methyl, benzyl, and allyl isocyanides with an appropriate base (n-butyllithium or potassium t-butoxide) followed by an alkylating agent (Equation 20). Yields are from 27% ($R^1$ = -H, $R^2$ = $-CH_2CH{=}CH_2$) to 89% ($R^1$ = $-C_6H_5$, $R^2$ = $-CH_2\text{-}CH{=}CHCH_3$).

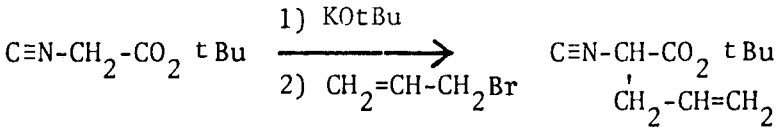
$$R^1\text{-}CH_2\text{-}N{\equiv}C \xrightarrow[2)\ R^2X]{1)\ Base} R^1\text{-}\underset{\displaystyle R^2}{\underset{|}{C}}H\text{-}N{\equiv}C \qquad (20)$$

$$\xrightarrow{H^+} R^1\text{-}\underset{\displaystyle R^2}{\underset{|}{C}}H\text{-}NH_2$$

This method is also useful for the creation of tertiary cyclopropylamines,[9] as in Equation 21, and for the alkylation of isocyano acetic esters, as in Equation 22.[21]

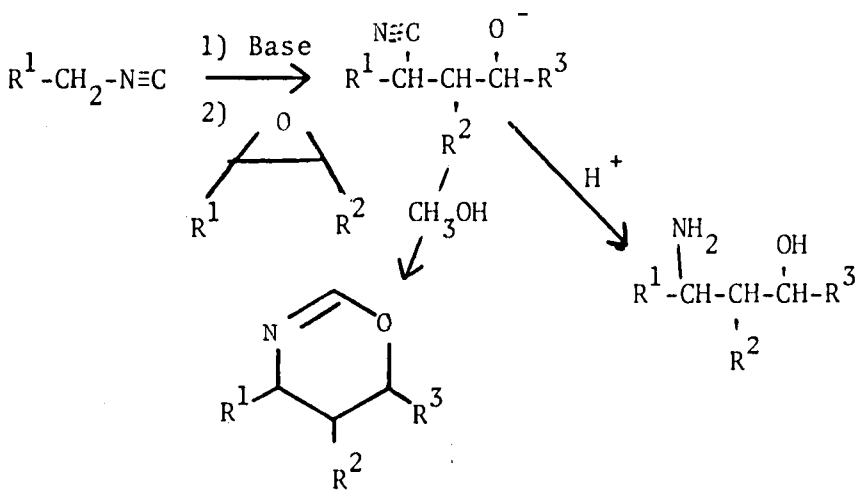



(21)



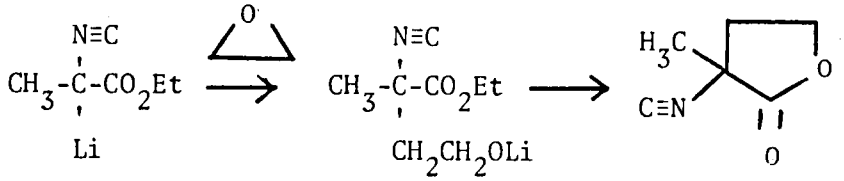

(22)

The reaction of metalated isocyanides with epoxides[26] leads to the formation of α-amino-alcohols after aqueous work-up, or to 5,6-dihydro-4-H-1,3-oxazines after treatment with methanol. In the case of unsymmetrical epoxides, attack occurs almost exclusively at the less hindered carbon. The transformation provides between 48% ($R^1$ = -H, $R^2$ = $R^3$ = $-CH_3$) and 80% yields ($R^1$ = $-C_6H_5$, $R^2$ = $R^3$ = -H).



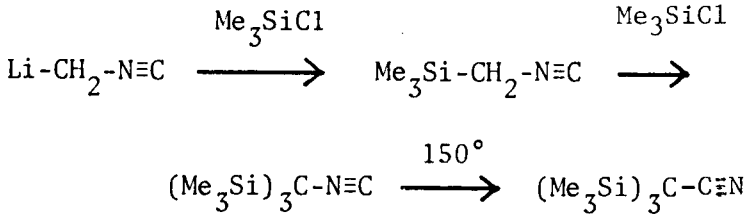

(23)

Ethyl isocyanoacetate fails to react with epoxides at high temperatures due to internal condensations; however, lithiated α-isocyanopropionate condenses with ethylene oxide to give a 51% yield of 2-isocyanobutyrolactone (Equation 24).[26]



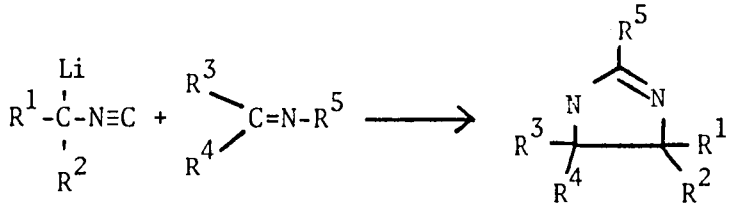
(24)

West and Gornowiez[27] observed that metalated methyl isocyanide reacts with trimethylsilyl chloride at -70° to provide tris-(trimethylsilyl)-methyl isocyanide, which when heated rearranges to the corresponding substituted acetonitrile (Equation 25).

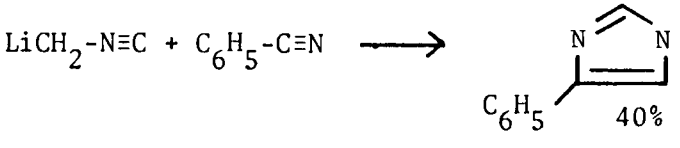


(25)

Lithiomethyl and lithiobenzyl isocyanide were reported to react with Schiff bases to produce substituted 2-imidazoline in good yield[28] (77%, Equation 26, $R^1 = R^2 = R^3 = -H$, $R^4$, $R^5 = -(CH_2)_6-$). Reaction with benzonitrile proceeds in a similar manner (Equation 27).[29]

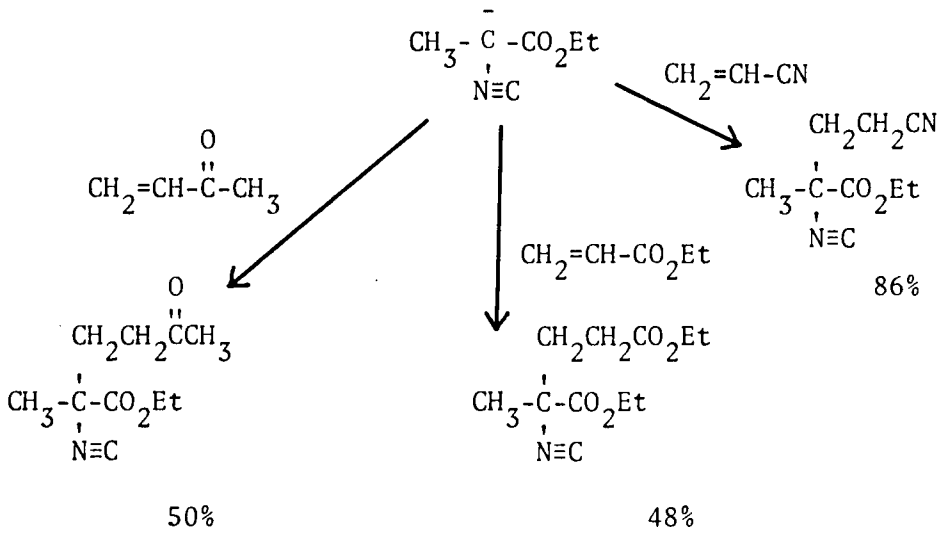


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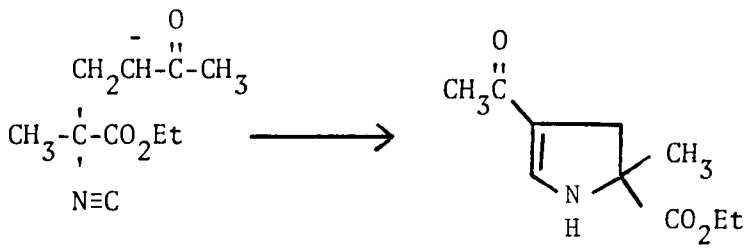
(27)

Metalated isocyanoesters attack activated olefins in a conjugate manner. Such olefins as acrylonitrile,[30] methyl acrylate,[31,32] and methyl vinyl ketone[31] have been employed. Representative cases are illustrated below.



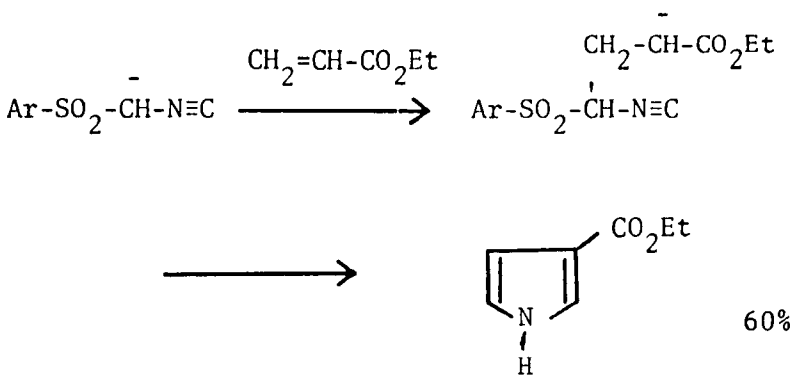

(28)

Heating the methyl vinyl ketone adduct[31] prior to addition of water leads to cyclization to the pyrroline (Equation 29).



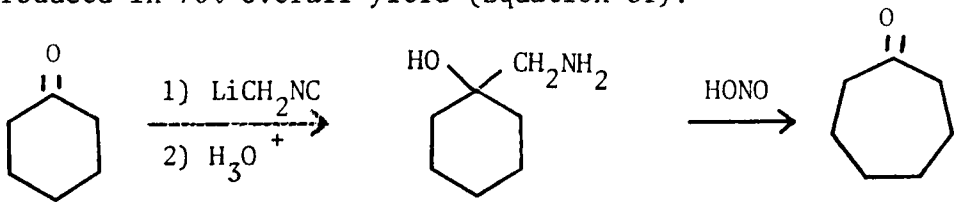

(29)

Also van Leusen[33] noted the formation of substituted pyrroles upon addition of the sodium salt of p-toluenesulfonylmethyl isocyanide to Michael acceptors (Equation 30).



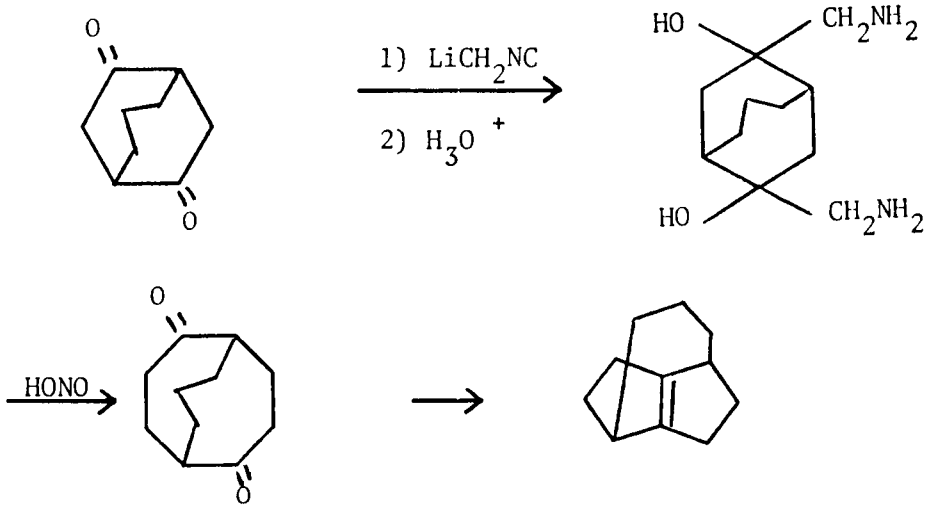

(30)

Further use of the alkylation process was discovered by Schöllkopf[34] in the ring enlargement of cyclic ketones. For example, when cyclohexanone is treated with isocyanomethyllithium, followed by hydrolysis and deamination of the resulting amino-alcohol, cycloheptanone is produced in 70% overall yield (Equation 31).



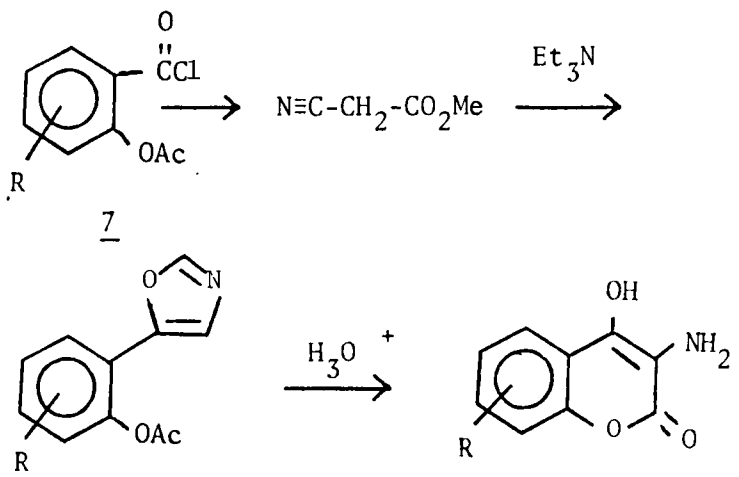

(31)

A similar sequence of reactions was used in the synthesis of tricyclo(3.3.3.$0^{2,6}$)undec-2(6)-ene as reported by Borden.[35]




(32)

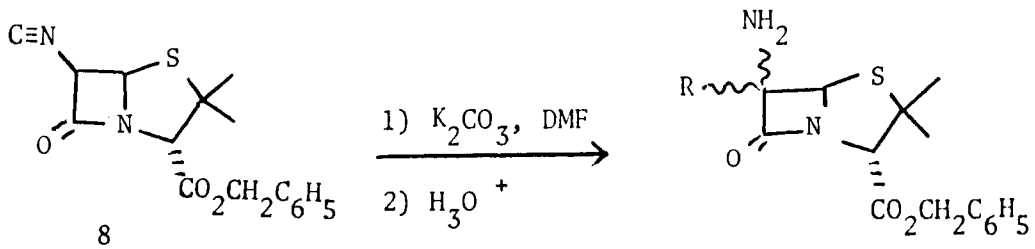
In other synthetic applications, Matsumoto[36] was able to prepare a number of substituted 3-amino-4-hydroxycoumarin derivatives in good yields by treating 7 (Equation 33) with methyl isocyanoacetate and triethylamine, followed by acid hydrolysis.



(33)

7

Also Bentley[37] synthesized substituted penicillins for pharmaceutical testing by the alkylation of 8 in Equation 34. A typical yield is 54% (R = $-SCH_3$, X = $-S-\overset{O}{\overset{\|}{C}}-OCH_3$).

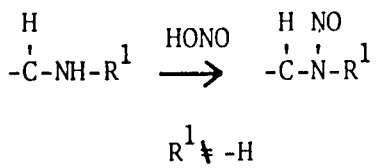


(34)

8

In conclusion, Schöllkopf's isocyanide procedure for the umpolung of primary amines has been shown to be of general synthetic utility, although the failure of unactivated secondary isocyanides to undergo reaction constitutes a major drawback in this method.

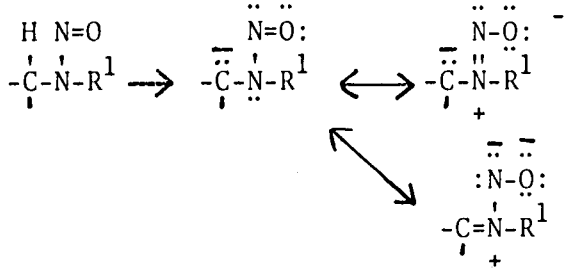
The umpolung of secondary amines has been achieved by Seebach[4] through the use of the nitrosoamine. Conceptually the umpolung proceeds as follows. A secondary amine can be converted into the nitroso compound by treatment with nitrous acid,[38] as in Equation 35.



(35)

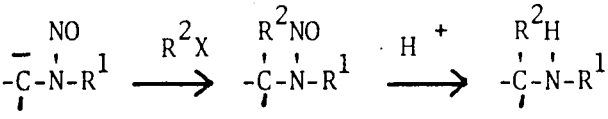
$R^1 \neq -H$

Deprotonation results in a resonance stabilized anion, as shown below.



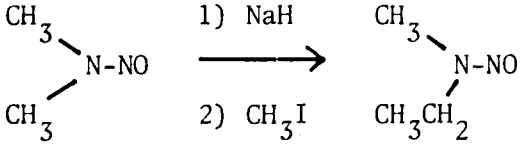
(36)

Alkylation of this anion, followed by removal of the activating nitroso group by treatment with anhydrous acid[38] completes the umpolung.



(37)

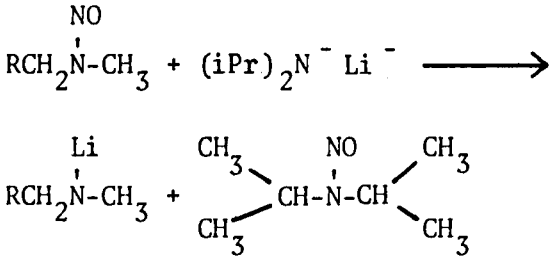
Keefer and Fodor[39] found that the attempted methylation of N,N-dimethylnitrosoamine did indeed provide N-methyl-N-ethylnitrosoamine in the rather low yield of 15% (Equation 38). Seebach and Enders[40] dramatically improved the efficiency of this process through the use of



(38)

lithium diisopropylamide (LDA) at -78°. Under these conditions the yield of the alkylated nitrosoamine is greater than 99% (Equation 38, LDA instead of NaH).

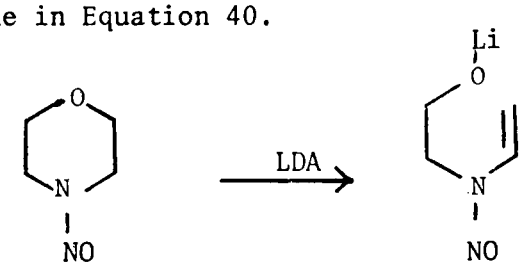
Contrary to isocyanide chemistry, nitrosoamines which possess adjacent activating functionality do not undergo metalation.[4] Instead transnitrosation becomes the principal reaction as in Equation 39.



(39)

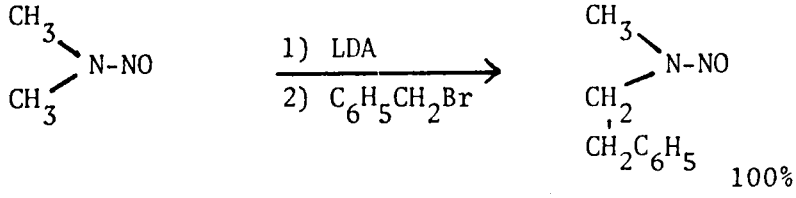
R = -Ar, $-COR^1$, $-CO_2R^1$, $-SO_2-C_6H_5-CH_3$, etc.

Also elimination reactions are observed,[4] as in the case of N-nitrosomorpholine in Equation 40.



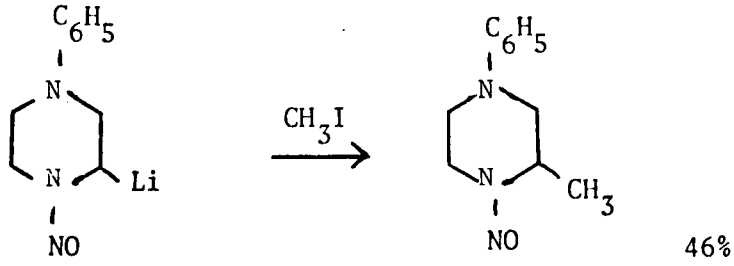
(40)

Reaction of lithiated nitrosoamines with alkyl halides[40,41,42,43] proceeds in a straightforward manner, with yields ranging from 46% to 100% as shown in Equations 41 and 42.



(41)

100%

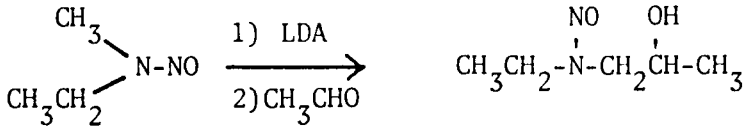


(42)

46%

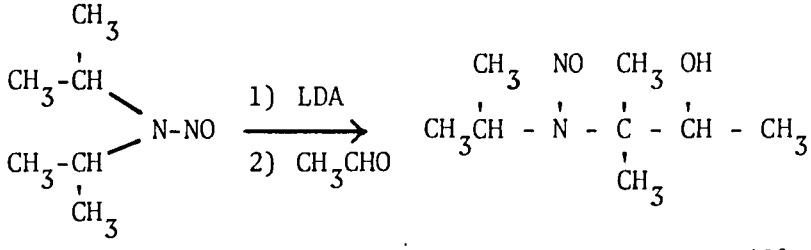
These types of anions also added smoothly to carbonyl compounds,[40,41,43] even to those which contain rather acidic protons, such as acetaldehyde.[41]

Representative examples are given below.



(43)

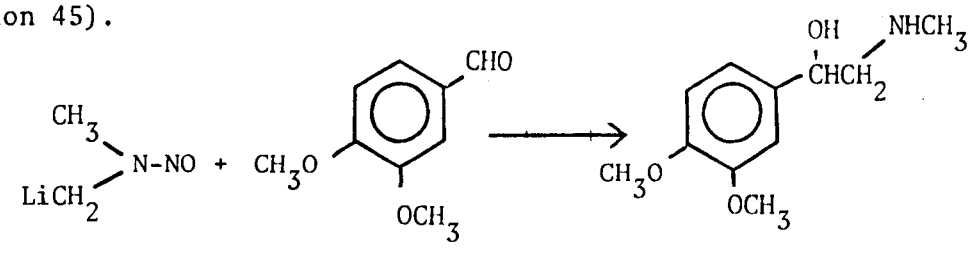
75%



(44)

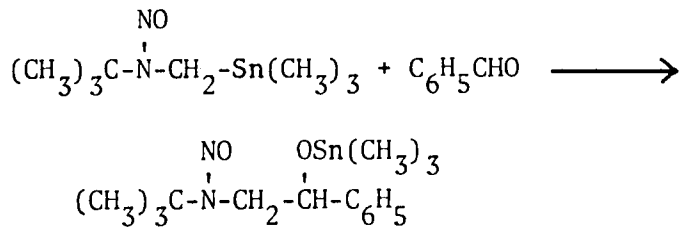
40%

The reaction between metalated nitrosoamines and substituted benzaldehydes assumes special importance, for the products, 2-amino-1-arylethanols, have been shown to possess significant physiological activity.[44] For example, condensation of lithiated N,N-dimethylnitrosoamine with 3,4-dimethoxybenzaldehyde, followed by acid hydrolysis, leads to the isolation of the dimethylether of d,l-epinephrine in 66% yield[4] (Equation 45).



(45)

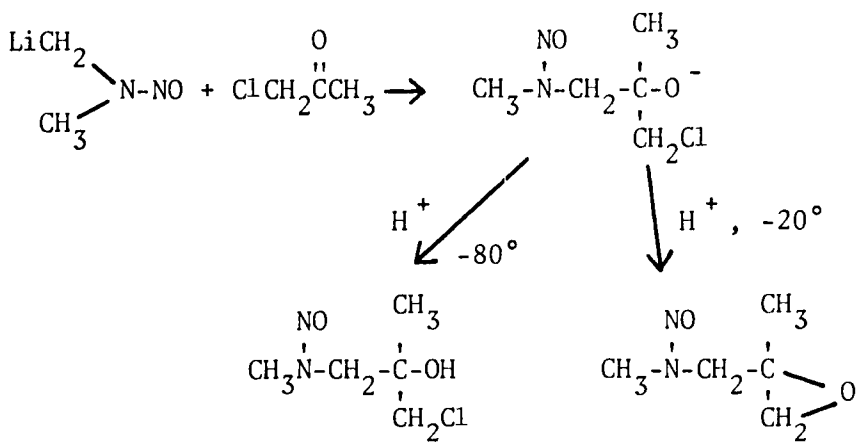
A somewhat different approach to carbonyl addition is the mere mixing and heating of benzaldehyde and the α-stannyl derivative of t-butylmethyl nitrosoamine to produce 8[45] (Equation 46) in 72% yield. This route was explored in hope that it would allow reaction between nitrosoamines and very base sensitive compounds, although no further use of it has been reported.



(46)

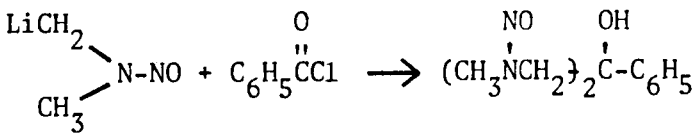
8

If an α-haloketone, such as chloroacetone, is employed as the electrophile,[43] attack by the nitrosoamine anion occurs exclusively at the carbonyl carbon. If protonation is carried out at low temperatures (-80°), the chlorohydrin is produced, but if the temperature of the reaction is allowed to rise (to -20°) before quenching, the appropriate epoxide is isolated (Equation 47).



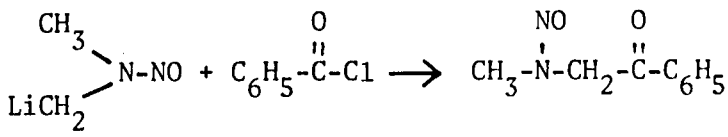
(47)

This preferential attack on carbonyls by lithiated nitrosoamines leads to complications when acylation of these anions is attempted.[40,43] Thus, reaction between lithiodimethylnitrosoamine and benzoyl chloride leads to the isolation of the bis adduct in 80% yield (Equation 48).



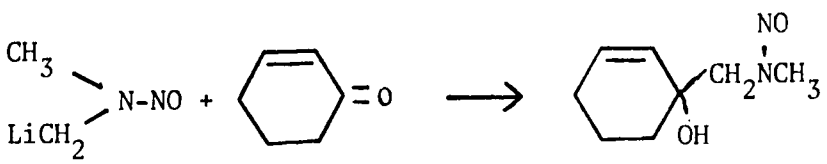
(48)

However, judicious alterations in the reaction conditions, such as inverse addition and an excess of acylating agent, leads to the production of the acylated material in reasonable yields as in Equation 49.[43]

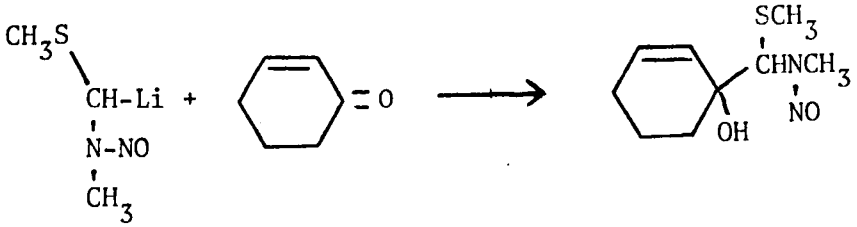


(49)

Further illustration of this preferred mode of attack is illustrated in the following reactions of 2-cyclohexen-1-one.[40,46]

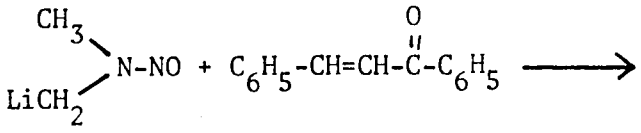


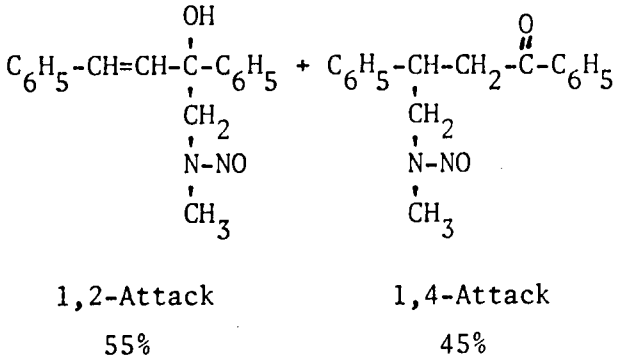
(50)



(51)

However, use of 1,3-diphenyl-2-propen-1-one as the electrophile leads to a mixture of both 1,2- and 1,4-addition products (Equation 52).[43]



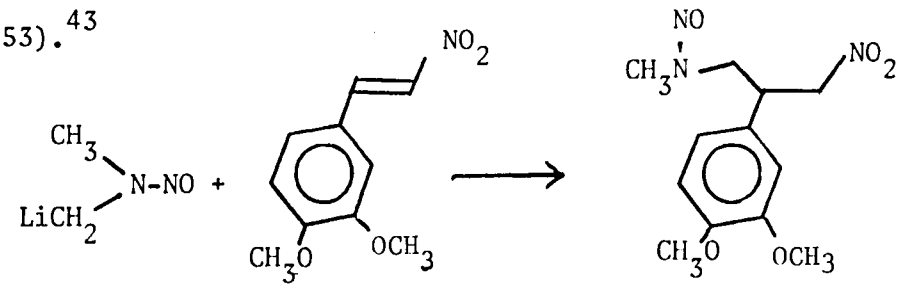


(52)

1,2-Attack 55%

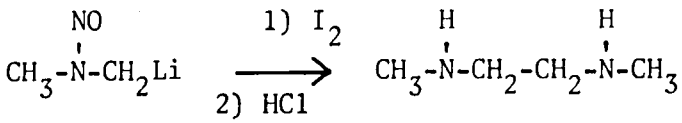
1,4-Attack 45%

And, lastly, unsaturated nitro compounds, such as β-nitro-3,4-dimethoxystyrene, are found to undergo Michael addition in high yield (Equation 53).[43]



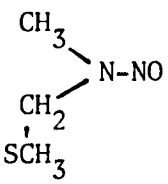
(53)

Metalated nitrosoamines fail to react with either chlorine or bromine, but treatment with iodine leads to coupling reactions in very high yield (95%, Equation 54).[40] Treatment of lithiodimethylnitrosoamine with more esoteric alkylating agents, such as diphenyl and dimethyl



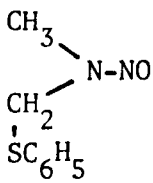
(54)

disulfide, diphenyl diselenide, trimethyltin chloride, and trimethylsilyl chloride, all proceed in a straightforward manner to give 9, 10, 11, 12, and 13 respectively in the yields indicated.[46]



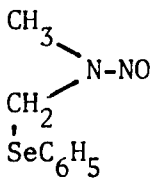
85%

9



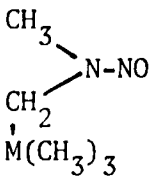
83%

10



67%

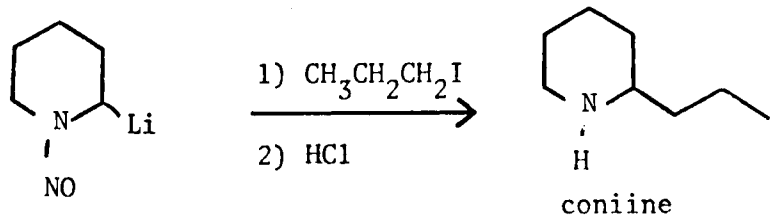
11



12 M = Sn, 95%

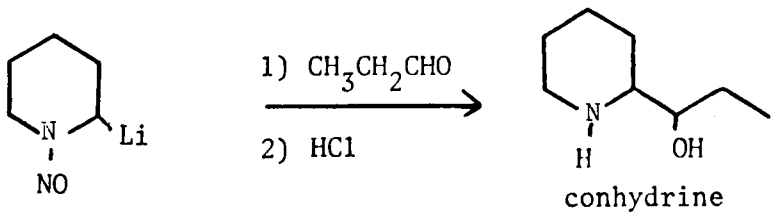
13 M = Si, 80%

Several simple alkaloids are prepared by the use of nitrosoamines as outlined below.[45,47]



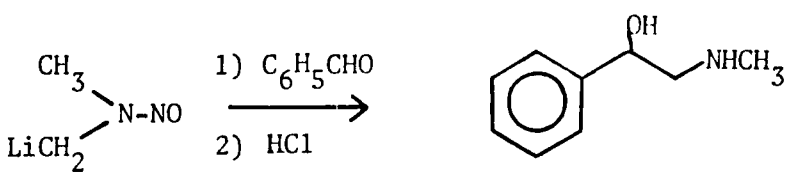
coniine

(55)



conhydrine

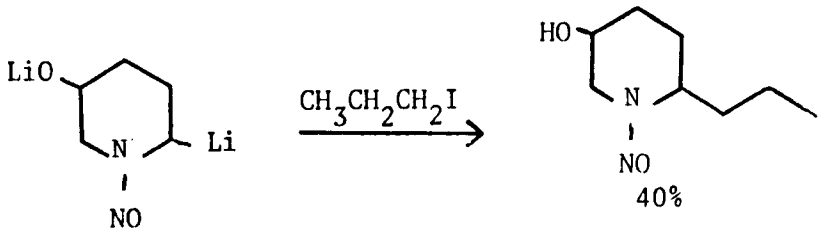
(56)



halostachine

(57)

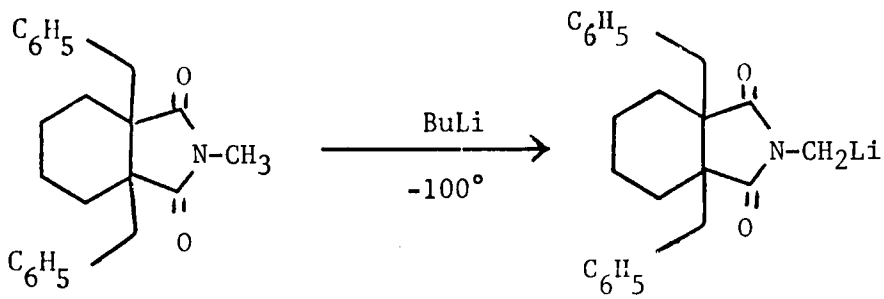
Furthermore, the anion derived from a nitrosoamine was selectively alkylated in the presence of an alkoxide, as illustrated in Equation 58, in the synthesis of ψ-conhydrine.[45,47]



(58)

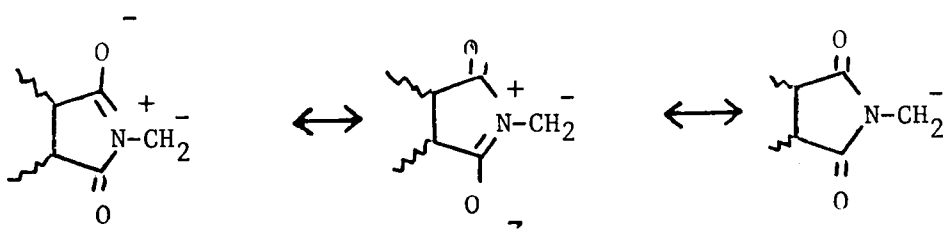
In summation, the Seebach metalated nitrosoamine umpolung of secondary amines has been shown to be of great utility in the synthesis of nitrogenous compounds. The only striking disadvantage of this method is the toxicity of the nitrosoamines themselves, which are known to be highly carcinogenic and mutagenic.[48]

A different approach to the umpolung of primary amines has also been reported by Seebach.[49] Metalation of the highly substituted succinimide proves to be successful at low temperatures.



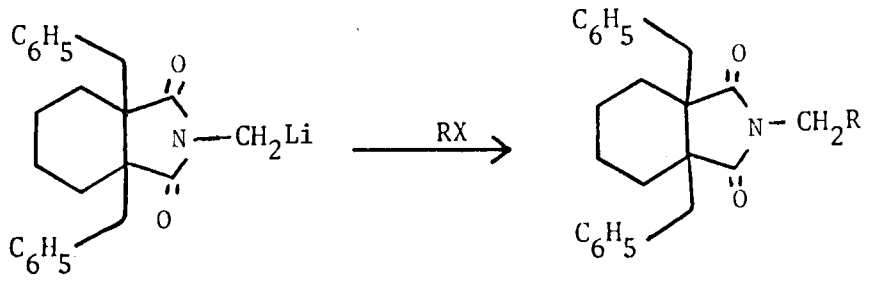

(59)

Although no resonance delocalization of the anion is possible, apparently the electron withdrawing effect of the amide group is sufficient to permit deprotonation, as shown below. This anion undergoes a variety of reactions (Equation 61), such as deuteration (80%), alkylation with



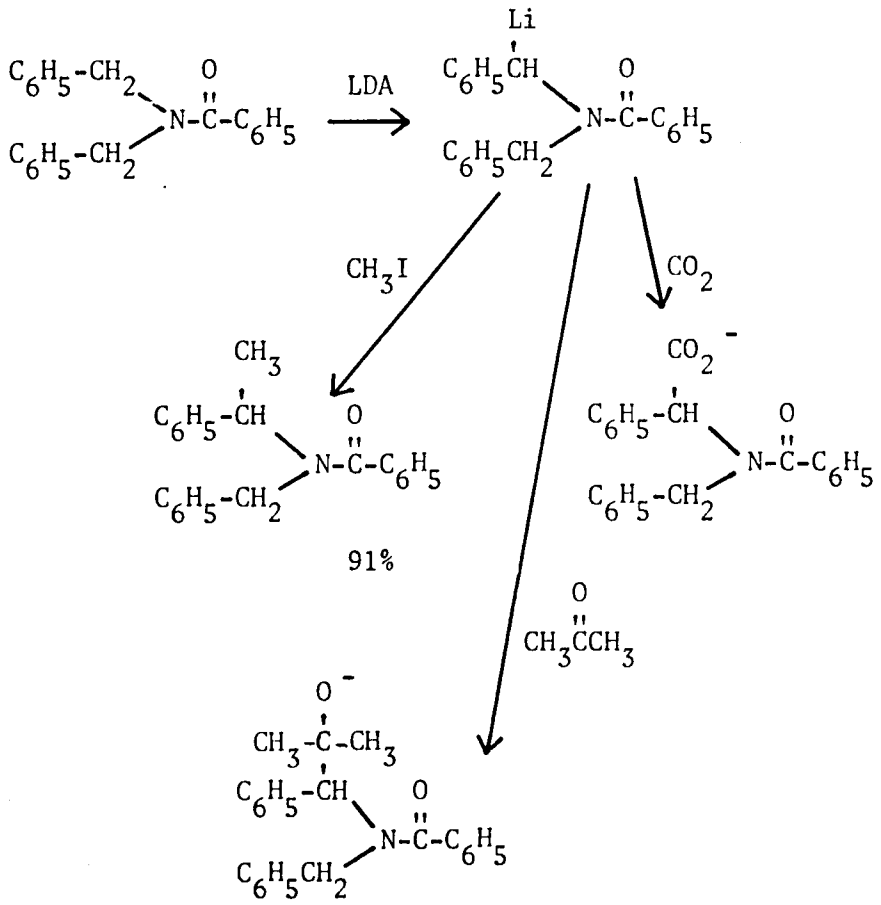

(60)

with iodomethane (70%), addition to aldehydes (benzaldehyde, 68%), and ketones (cyclohexanone, 91%), and acylation (methyl benzoate, 53%).



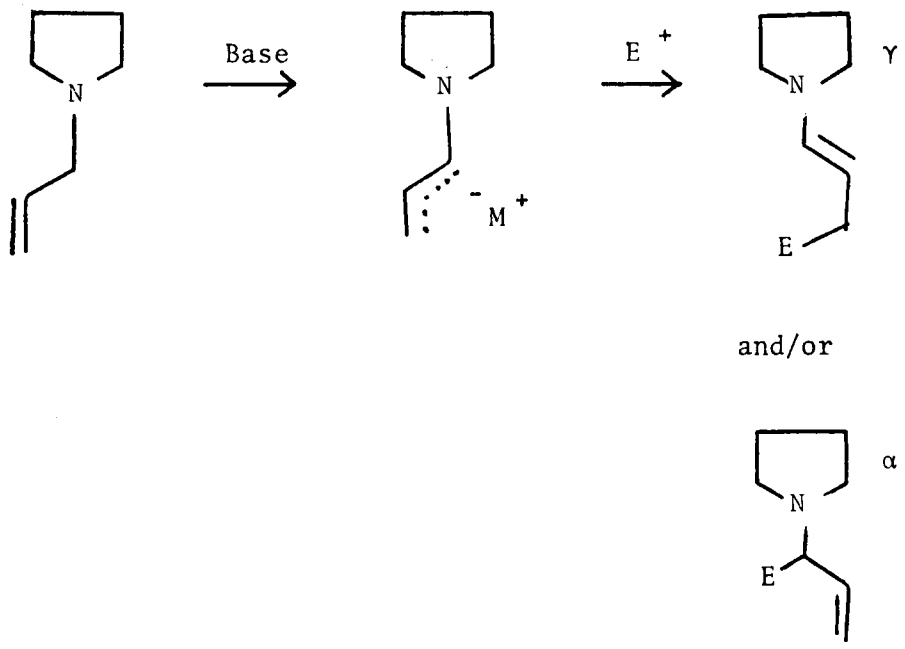
(61)

Similar results were obtained by Fraser[42] using tertiary amides as shown below (Equation 62).



(62)

A search of the chemical literature reveals several cases in which an amine was α-metalated without the introduction of an activating group. Martin and Dupriest[50] found that treatment of N-allylpyrrolidine with strong base leads to the formation of an allylic anion, which undergoes reaction with electrophiles such as n-butyl bromide, benzaldehyde, and other ketones and aldehydes in reasonable yields (Equation 63). The position of substitution was found to be strongly dependent on the

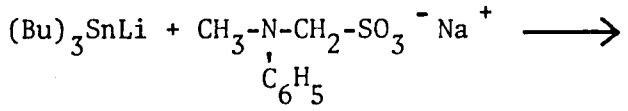



(63)

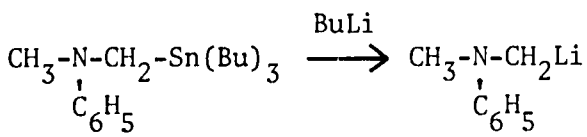
counterion. For example, if sec-butyllithium is employed as the deprotonating agent (M = $Li^+$ in Equation 63) alkylation occurs in both positions (α and γ) in approximately equal amounts. When zinc is exchanged for lithium (M = $Zn^{+2}$) reactions occurs almost totally in the α position.

Peterson[51] was able to lithiate the methyl group of a variety of tertiary amines by a transmetalation procedure. For example, reaction occurs

of tri-n-butyltinlithium and sodium N-methyl-N-phenylaminomethane sulfonate leads to the formation of 14 which upon treatment with butyllithium undergoes the transmetalation reaction.

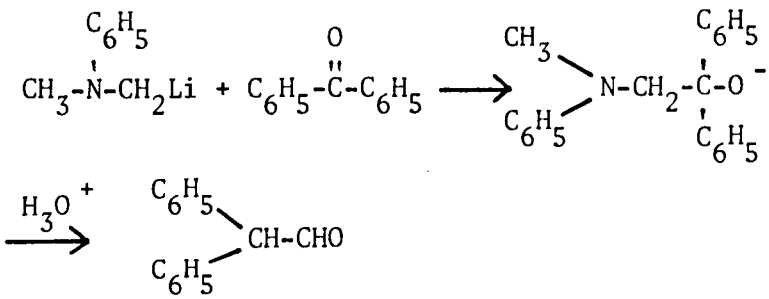


(64)



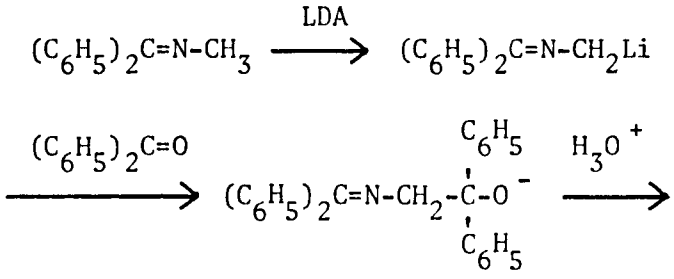
14

The utility of this reaction is illustrated by treatment of the anion with benzophenone to provide, after protonation, dehydration, and hydrolysis of the imine, a 44% yield of diphenylacetaldehyde (Equation 65).

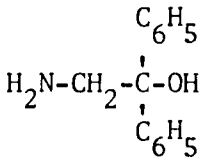


(65)

Lastly, the deprotonation of an N,N-diphenylimine was reported by Kaufmann.[52] Reaction of N,N-dibenzylmethylamine with lithium diisopropylamide at low temperatures results in the formation of an anion which is capable of reaction with electrophiles. This sequence was employed in the aminomethylation of a number of ketones, unfortunately in low yield. A typical example is given in Equation 66.



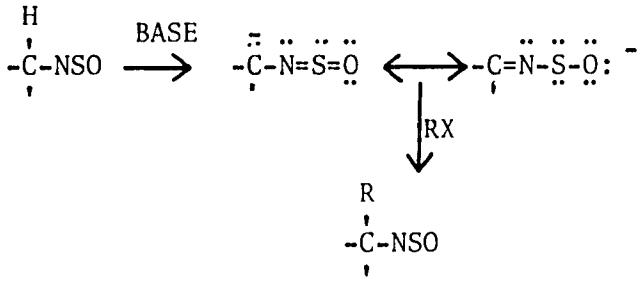
(66)



26%

## B. ALIPHATIC N-SULFINYLAMINES

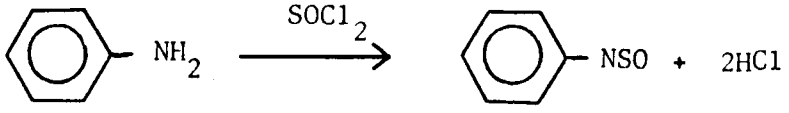
As no known activating group will allow for the umpolung of primary amines without severe restrictions, consideration was given to N-sulfinylamines (R-N=S=O) as a possible solution to this problem. Deprotonation of the carbon adjacent to the N-sulfinyl group should lead to the production of a resonance stabilized anion, which hopefully could be coerced into undergoing alkylation (Equation 67).



(67)

However, prior to the discussion of these experimental results, the previously reported chemistry of aliphatic N-sulfinylamines should be presented.

N-Sulfinylamines have been known since the late nineteenth century when Michaelis and Herz[53] reported the generation of N-sulfinylaniline




(68)

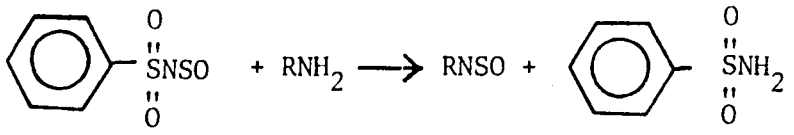
This functional group may be generated from almost any primary amine[54] through treatment of the amine with thionyl chloride. This reaction (Equation 69) is also applicable to primary amides,[55] primary urethanes,[56] unsubstituted sulfonamides,[54] and hydrazines.[54]

$$3R\text{-}NH_2 + SOCl_2 \longrightarrow R\text{-}NSO + 2R\text{-}NH_3^{+}\,Cl^{-} \qquad (69)$$

$$R = R^1,\ -Ar,\ -\overset{O}{\overset{\|}{C}}\text{-}R^1,\ -\overset{O}{\overset{\|}{S}}\text{-}R^1,\ -\overset{O}{\overset{\|}{C}}\text{-}O\text{-}R^1,\ -NH\text{-}R^1,\ \text{etc.}$$

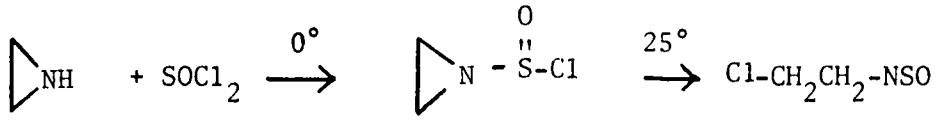
However, the reaction fails for benzylic amines,[57] due to an oxidation-reduction process which leads to the production of benzaldehyde in the case of benzylamine. If conservation of the amine is required, two equivalents of some tertiary amine may be added to the reaction mixture to absorb the liberated hydrogen chloride.[54] Preparation of sensitive N-sulfinylamines can be achieved by a "transsulfinylation" reaction. Transfer of the sulfinyl group occurs from the less basic to the more basic nitrogen. N-Sulfinylbenzenesulfonamide is an especially good transsulfinylating agent when benzene is employed as the reaction

solvent. The low basicity of the sulfonamide and its insolubility in benzene are apparently responsible for driving the equilibrium to the right, as outlined in Equation 70.[54,58]

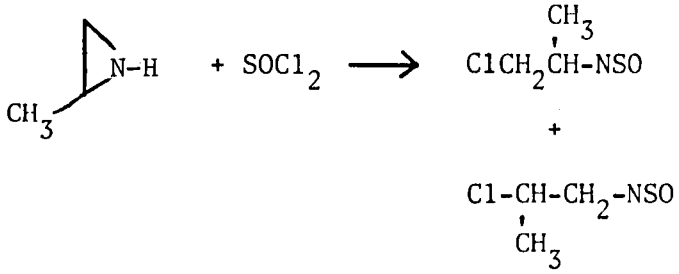


(70)

The reaction between aziridines and thionyl chloride has been studied by Tomalia.[59] Interaction between $SOCl_2$ and the nitrogen atom apparently provides 15, which undergoes rearrangement on warming (Equation 71). Similar reactions occur with substituted aziridines (Equation 72).

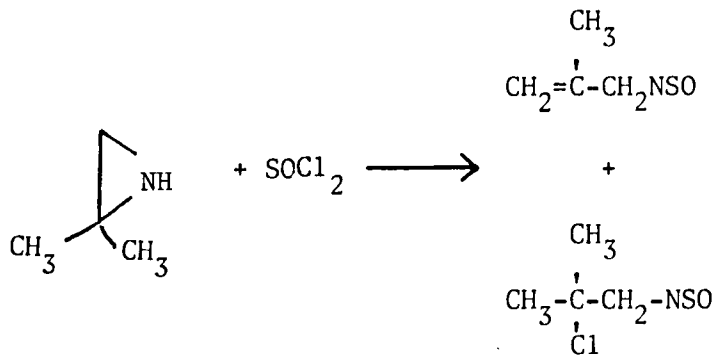


(71)



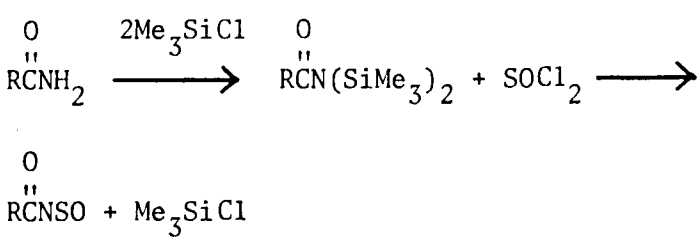
(72)

2,2-Dimethylaziridine under these conditions gives a mixture of 2-chloro-2-methylpropyl N-sulfinylamine and N-sulfinyl-2-methallylamine, which has not been prepared by other methods (Equation 73).



(73)

Scherer[55] found that the N-sulfinyl derivative of less basic nitrogenous materials, such as primary amides, are generated by the action of thionyl chloride on the bis(trimethylsilyl) derivative of the parent amide. This method permits the isolation of highly purified N-sulfinylbenzamide and N-sulfinylacetamide, which are difficult to prepare by conventional means.



(74)

Infrared and Raman spectra of a series of aliphatic N-sulfinylamines were analyzed by Glass and Pullen.[60] Based on their interpretation, an angled structure, similar to that of sulfur dioxide, was assigned to the NSO group, with an angle of about 120° between the nitrogen-sulfur and the sulfur-oxygen bonds. Similar results were obtained by Grunwald in a CNDO/2 calculation of N-methyl-N-sulfinylamine.[61]

One of the most prominent transformations of N-sulfinylamines is the addition of the elements of water to the sulfinyl group (Equation 75).

This reaction unveils the parent amine in a very rapid and quantitative fashion,[54] and therefore, N-sulfinylamines must be handled in the total absence of moisture.

$$R\text{-}NSO + H_2O \longrightarrow RNH_2 + SO_2 \qquad (75)$$

An addition reaction also occurs with alcohols[62,63] (Equation 76). However, this transformation proceeds at a much lower rate, and hindered compounds, such as N-sulfinyl-t-butylamine, show little or no reaction.[62]

$$RNSO + R^1OH \longrightarrow RNH_2 + R^1O\text{-}\overset{\overset{O}{\|}}{S}\text{-}OR^1 \qquad (76)$$

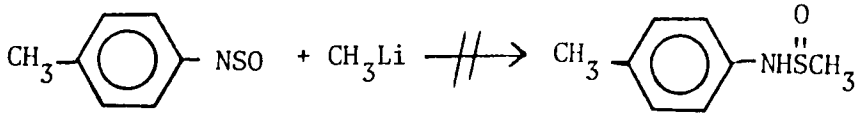
Grignard reagents have been shown to add across the nitrogen-sulfur double bond to provide N-substituted sulfinamides on aqueous work-up[64,65,66] (Equation 77). This reaction proceeds in yields from 54% ($R^1$ = $-CH_2-CH=CH_2$, $R^2$ = $-p-CH_3-C_6H_4$) to 90% [$R^1$ = $-CH(CH_3)_2$, $R^2$ = $-p-CH_3-C_6H_4$].

$$R^1MgX + R^2NSO \longrightarrow R^2\text{-}NH\text{-}\overset{\overset{O}{\|}}{S}\text{-}R^1 \qquad (77)$$

It would appear that there is some controversy concerning a similar reaction with organolithium compounds. Schönberg[66] reported that N-sulfinylaniline is attacked by phenyllithium and α-naphthyllithium to provide, after aqueous work-up, the sulfinamide, although no yields were given (Equation 78). However, Katzenellenbogen[65] found that no reaction occurs between methyllithium and N-sulfinyl-p-toluidine, since

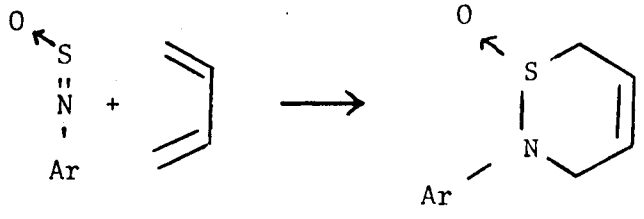
$$C_6H_5\text{-NSO} + RLi \longrightarrow C_6H_5\text{-NH-}\overset{\overset{O}{\|}}{S}\text{-R} \qquad (78)$$

only p-toluidine the expected product of hydrolysis of the starting material, is isolated from the reaction mixture (Equation 79).

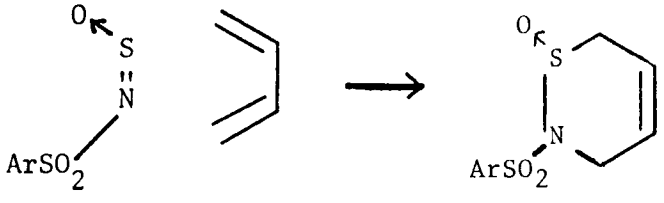



(79)

The area of N-sulfinylamine chemistry most thoroughly explored has been the Diels-Alder type reactions of aromatic N-sulfinylamines and N-sulfinylsulfonamides[67,68] (Equations 80 and 81).

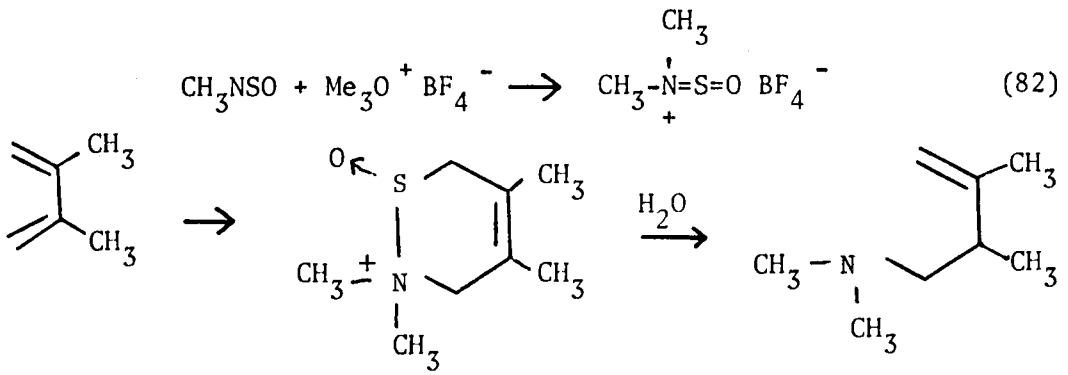



(80)



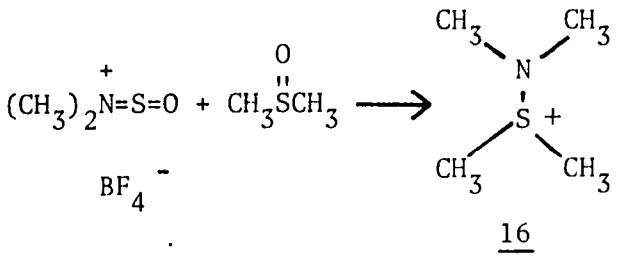

(81)

Unactivated aliphatic N-sulfinylamines, however, do not undergo such reactions. Sufficient activation is provided by nitrogen alkylation[69] of aliphatic N-sulfinylamines by trialkyloxonium tetrafluoroborates. Exposure of imonium salts produced in this fashion to dienes result in cycloadditions analogous to the aromatic N-sulfinylamines (Equation 82).



(82)

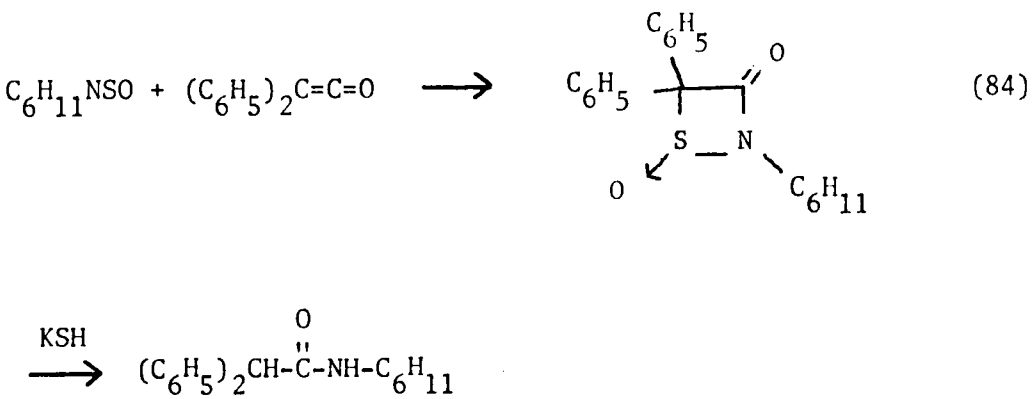
Upon further study of these activated species, Kresze[70] found that their interaction with sulfoxides provides sulfimides. Thus reaction between N-sulfinyldimethylimonium tetrafluoroborate and dimethylsulfoxide gives a 46% yield of compound 16.



(83)

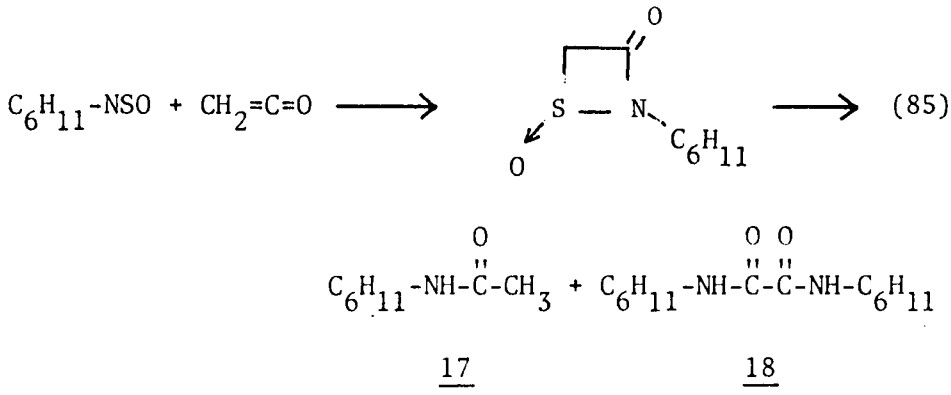
16

Cyclohexyl-N-sulfinylamine has been shown[71] to undergo an addition reaction with diphenylketene in rather high yield (99.8%) as shown in Equation 84. The adduct is decomposed with potassium hydrogen sulfide



(84)

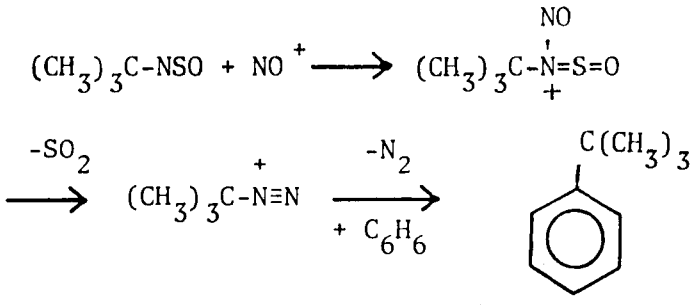
to provide the appropriate amide. The reaction between ketene and N-sulfinylcyclohexylamine was deduced from the thermal decomposition products (17 and 18) of the cycloadduct.



(85)

17 18

Olah has studied[72] the reaction between aliphatic N-sulfinylamines and nitrosonium salts in order to observe under anhydrous conditions the chemistry of carbocations derived from amines. For example, N-t-butylsulfinylamine interacts with $NO^+$ $SbF_6^-$ and benzene, as indicated in Equation 86, to produce a 25% yield of t-butylbenzene.



(86)

## CHAPTER II

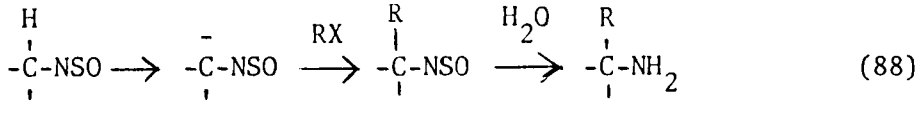
## RESULTS AND DISCUSSION

The previously described pathways directed at the umpolung of amines suffer from several disadvantages. The isocyanide method does not allow for the alkylation of unactivated secondary amines, and even the alkylation of unactivated primary isocyanides, other than methyl, proceeds in low yield. Thus the search for other acidifying functional groups should be continued.

The N-sulfinylamine functionality was selected as a possible answer to this problem. Although the known chemistry of N-sulfinylamines and strong bases was limited to nucleophilic attack (cf. p 30), formation of an anion on the carbon adjacent to the nitrogen atom should be favored by resonance stabilization (Equation 67, p 26). As N-sulfinylamines can be generated from primary amines and can be transformed back into the amines by addition of water, the deprotonation and alkylation of these types of molecules would be a formal umpolung (Equation 88).



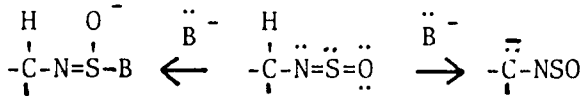
(87)



(88)

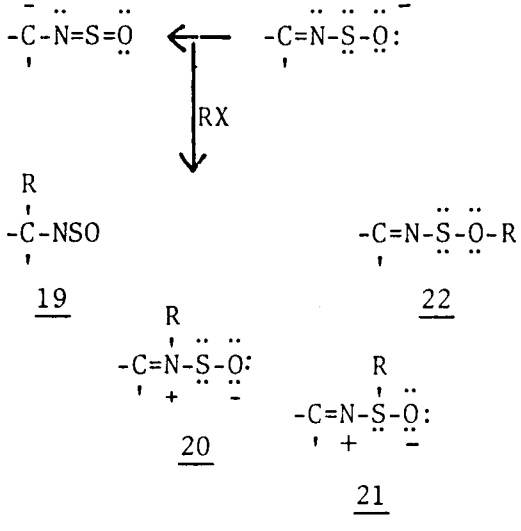
A priori, several difficulties were foreseen. First, the base used to remove the acidic proton must be non-nucleophilic, to favor

deprotonation rather than addition, as illustrated in Equation 89.



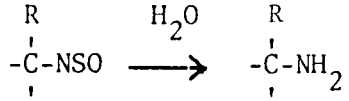
(89)

Second, there are several sites of possible interaction between the anion and the electrophile, namely, all three heteroatoms of the N-sulfinylamine and the carbon atom as shown in Equation 90.

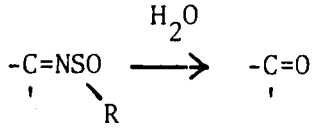


(90)

The product of carbon alkylation, 19, should, upon the addition of water, provide a new primary amine. The products of heteroatom alkylation, 20, 21, and 22, as they contain a carbon-nitrogen double bond, should hydrolyze to the corresponding carbonyl compound (Equations 91 and 92).



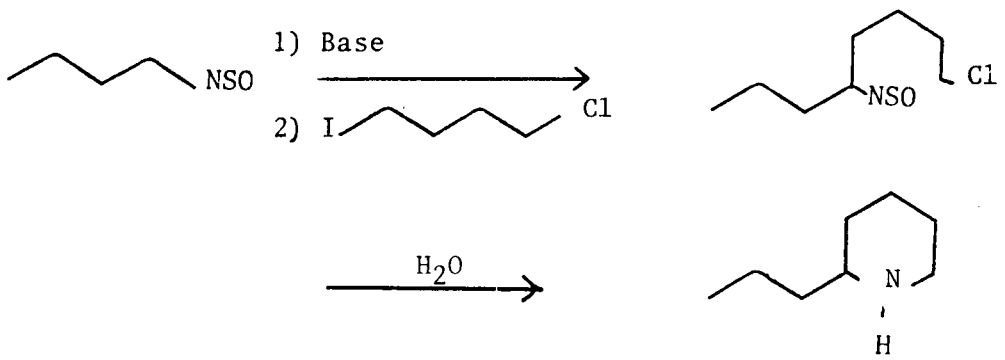
(91)



(92)

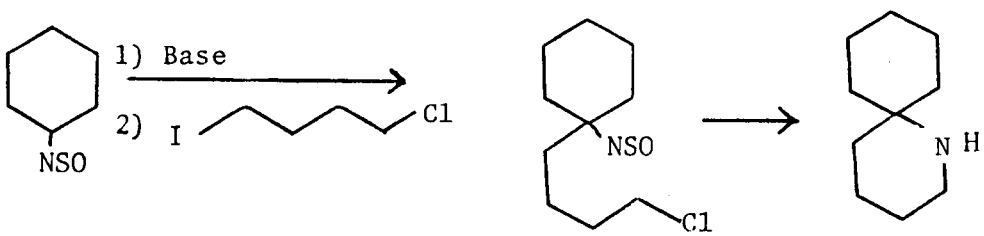
Since at least some understanding of the experimental conditions affecting the site of alkylation in ambient anions is available,[73] as are a rather large number of non-nucleophilic bases,[74] these difficulties were believed surmountable.

If this type of umpolung proved successful, the straightforward and experimentally simple synthesis of a number of natural products could be envisaged. For example, d,l-coniine, a poisonous constituent of hemlock, could be obtained in a two-step scheme, as outlined in Equation 93. And the synthesis of azaspirocycles should be easily




(93)

obtained through the use of difunctional alkylating agents (Equation 94). These types of compounds could be precursors to any number of



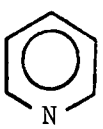
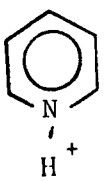

(94)

interesting substances and are not easily made by conventional organic chemistry.

Prior to the research on the alkylation reaction, efficient methods of synthesis of N-sulfinylamines from the primary amines were sought. One of the literature procedures[75] for the generation of this type of compound involves the addition of thionyl chloride to a solution of three equivalents of the primary amine (Equation 95). Under these conditions, the stoichiometry of the reaction does not allow for the conversion of more than one-third of the amine into the desired N-sulfinyl compound. This type of disregard for the conservation of the

$$3\ RNH_2 + SOCl_2 \longrightarrow RNSO + 2\ RNH_3^+\ Cl^- \qquad (95)$$

amine is undesirable, particularly if the amine is the result of several synthetic transformations. Another procedure[75] calls for the addition of pyridine to the reaction mixture to absorb the liberated hydrogen chloride (Equation 96).

$$RNH_2 + SOCl_2 + 2\ \text{} \longrightarrow RNSO + 2\ \text{} \qquad (96)$$

Although the stoichiometry here allows for complete reaction of the amine, the typical yield is about 40%. This represents only a slight improvement over the first method.

When this method was used, a perplexing problem was encountered on distillation of the crude product. A white solid (presumably pyridine hydrochloride) "co-distilled" with the N-sulfinylamine, and even repeated distillation did not provide an uncontaminated sample. Since the literature procedure[75] calls for ether to be used as the solvent,

all the pyridine hydrochloride was apparently not removed by filtration, and it "co-distilled" due to thermal dissociation and recombination. This difficulty was overcome by substitution of the less volatile base, quinoline, for pyridine, and by addition of ligroin to the reaction mixture prior to work-up to insure the total precipitation of hydrochloride salt. These changes, together with lowering the reaction temperature to -20° and the complete exclusion of moisture, led to routine yields of 80% for spectroscopically pure N-sulfinylamines. It should be noted that all the compounds made by this method are golden yellow, and repeated distillation removed this coloration. The color, however, appeared to have no effect on subsequent reactions.

This method was found to be quite general for nonfunctionalized amines and allowed for the synthesis of a number of different aliphatic N-sulfinylamines. However, distillation at too high a temperature (greater than 150°) or to dryness resulted in vigorous decomposition and release of a noxious and uncharacterized yellow gas.

The method failed in the case of N-allylamine, which was not unexpected. Michaelis[57] reported that the reaction between thionyl chloride and benzylamine does not give the N-sulfinylamine, but instead an oxidation-reduction process occurs to provide benzaldehyde. The method also failed to produce the N-sulfinylamine derived from ethyl glycinate, which apparently polymerized before it could undergo transformation into the desired material.

As this procedure allowed for the facile synthesis of N-sulfinyl compounds, alkylation studies were begun. Preliminary results

supported the proposed acidity of the protons on the carbon adjacent to the NSO group. Addition of 1.0 equivalent of N-cyclohexylsulfinylamine to a solution of lithium triphenylmethide in tetrahydrofuran (THF) resulted in the instantaneous disappearance of the red color characteristic of the base. After addition of aqueous acid and work-up, cyclohexylamine was isolated in good (90%) yield.

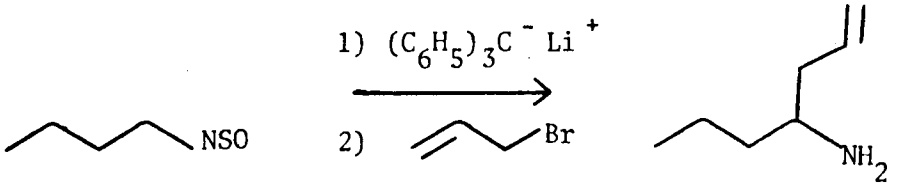
Attempts to alkylate the presumed anion with methylating agents failed under all conditions. These included changes in concentration, temperature, reaction time, solvent, base, methylating agent, and work-up (see Experimental Section, p 61). No product of methyl alkylation was obtained in any of the experiments. In the case of N-butylsulfinylamine, the expected product, 2-aminopentane, was purchased, and gas chromatographic analysis of the reaction mixtures indicated its complete absence. If the reaction conditions were mild (-78° for 3 hours) the principal product was the parent amine, while under forcing conditions (greater than 0° for more than 3 hours), polymeric mixtures were isolated.

In a further attempt to prove the existence of this elusive anion, deuteration studies were undertaken (Equation 97). These reactions were singularly unsuccessful. The experimental conditions employed

$$\text{-}\overset{\text{H}}{\overset{|}{\text{C}}}\text{-NSO} \xrightarrow[2)\,D_2O]{1)\ \text{Base}} \not\longrightarrow \text{-}\overset{\text{D}}{\overset{|}{\text{C}}}\text{-}NH_2 \qquad (97)$$

were approximately the same as those used for the methylation study, except that the electrophile was deuterium.

During the course of the alkylation experiments, allyl bromide was substituted for the methylating agent because rapid analysis of the crude reaction mixtures would be possible. The proton nuclear magnetic resonance (pmr) spectrum of the desired product should be readily discernible due to the absorption of the olefinic hydrogens. Reaction of N-butylsulfinylamine and allyl bromide under normal conditions (lithium triphenylmethide in THF at -78° for 3 hours) was quenched with aqueous acid. And, following an acid-base shake-out to remove the triphenylmethane, the carbon alkylated amine was obtained in 65% yield (Equation 98). Here, as in most cases, the amine was isolated as




(98)

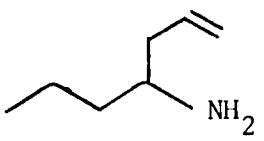
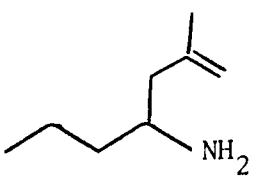
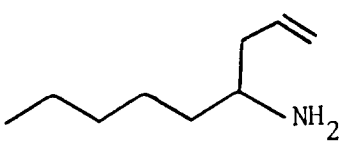
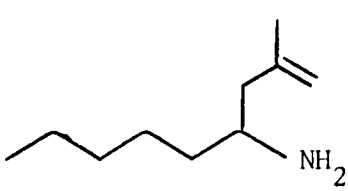
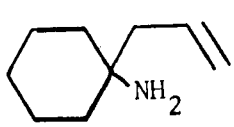
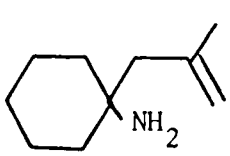
23

its N-benzamide for ease in handling and purification. Also, as in most cases, the crude benzamide is crystalline, lightly colored, and contains only small amounts of impurities. However, the yield is based on chromatographically and spectroscopically pure material.

A host of other alkylating agents including ethyl bromide, ethyl iodide, 1,2-dibromoethane, ethyl tosylate, 1,3-dibromobutane, and benzyl bromide were tried. No product of the desired alkylation process was found, although this series of reactions was run under conditions identical to those above. However, reactions of other N-sulfinylamines with allyl bromide were successful, and results obtained with them are listed in Table I. These yields are highly reproducible so long as

TABLE I

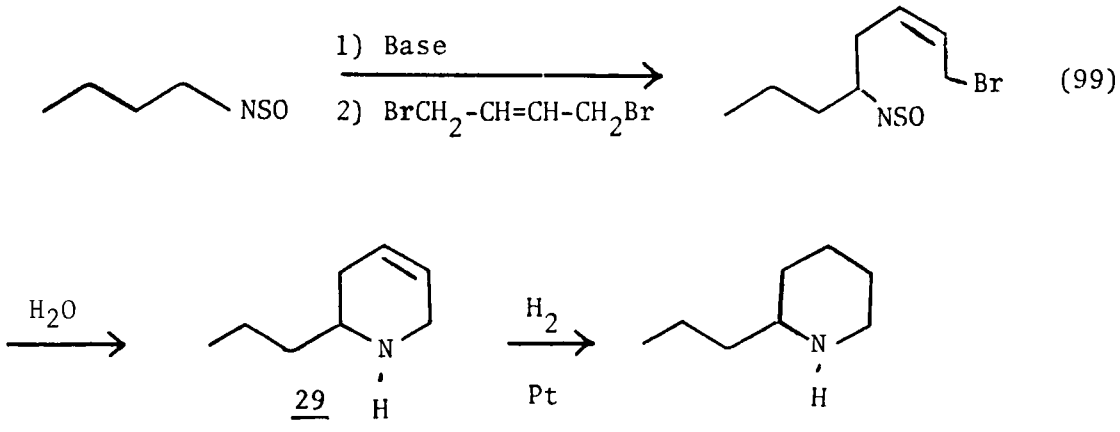
YIELDS OF ALKYLATED AMINES USING LITHIUM TRIPHENYLMETHIDE AS THE BASE

| N-Sulfinyl-amine | Alkylating Agent | Yield[a] | Structure of Product | |
|---|---|---|---|---|
| n-butyl | allyl bromide | 65% |  | 23 |
| n-butyl | methallyl chloride | 40% |  | 24 |
| n-hexyl | allyl bromide | 32% |  | 25 |
| n-hexyl | methallyl chloride | 31% |  | 26 |
| cyclohexyl | allyl bromide | 32% |  | 27 |
| cyclohexyl | methallyl chloride | 23% |  | 28 |

[a]Yields are based on the N-sulfinylamine and refer to chromatographically pure benzoylated material.

extreme care is taken to exclude even the smallest traces of moisture. Thus the reactions are best run under argon and with scrupulously dried solvents, alkylating agents, and glassware.

Since saturated but highly active alkylating agents did not prove useful, attention was focused on other allylic halides. For example, use of 1-chloro-2-methyl-2-propene (methallyl chloride) led to the generation of the desired product in modest yields, as outlined in Table I. In an effort to synthesize d,l-coniine (p 22), N-sulfinyl-butylamine was treated with 1,4-dibromo-2-butene under normal conditions. It was hoped that mono-alkylation would occur, followed by ring closure upon release of the free amine during aqueous work-up, to provide compound 29, Equation 99. Catalytic hydrogenation could then be used to produce the natural product as its racemate. Unfortunately, the only basic material isolated in several attempts was n-butylamine,




(99)

while the nonbasic fraction consisted of an ill-defined polymeric mixture. Variations in the reaction conditions, such as inverse addition and greater dilution, led to similar results, as did the use of other N-sulfinylamines.

Attempts were made to increase the yields of those alkylations that did work. Increased reaction times and temperatures (for example, overnight at room temperature rather than 3 hours at -78°) did not result in an improvement of the yields. Rather a white uncharacterizable precipitate, which was insoluble in common organic and inorganic solvents, was isolated. Perhaps, under these more vigorous conditions, the reactivity of the triphenylmethyl anion is not limited to proton removal. For example, more nucleophilic organolithium compounds, such as phenyllithium, have been reported to add to N-sulfinylamines (p 30). If this type of process was occurring, then use of a weaker base might allow for better reactions. Potassium t-butoxide was selected as such a base.

When N-sulfinylhexylamine was added to a solution of potassium t-butoxide in THF at 0°, an immediate color change was noted. When exactly one equivalent of N-sulfinylamine was added, a deep brown color persisted. This disappeared on addition of allyl bromide. The reaction mixture was worked-up in the usual manner after stirring at 0° for thirty minutes, to provide a 37% yield of N-benzoyl-4-amino-1-nonene after benzoylation and column chromatography. An increase in the reaction time, from thirty minutes to 12 hours, led to the isolation of the desired product in a 51% yield. Further increases in reaction time did not furnish greater yields.

Solvent effects were briefly investigated. When the reaction was run in pentane, no color change was noted. After standard work-up, no alkylation product could be isolated. When the reaction was performed

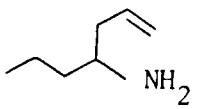
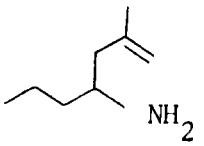
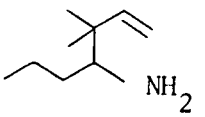
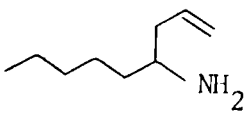
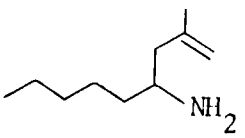
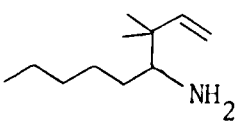
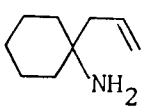
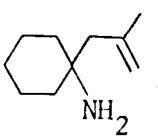
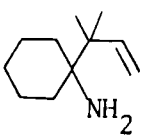
in N,N-dimethylformamide, a decrease in the yield (from 51% to 15%) was observed. However, use of the highly polar 1,2-dimethoxyethane (DME) did result in an improved yield (from 51% to 56%). This increase was noted with other N-sulfinylamines and other electrophiles as outlined in Table II.

N-Hexylsulfinylamine failed to react with 3-methyl-1-chloro-2-butene (γ,γ-dimethylallyl chloride) under mild conditions (lithium triphenylmethide at -78° for 3 hours). However, under more forcing conditions (potassium t-butoxide at 0° for 12 hours) a low yield (less than 15%) of the alkylated material was obtained. Moreover, when the reaction mixture was refluxed for one hour after stirring for 12 hours at 0°, a good yield of the product was realized (47%). Similar results were obtained with other N-sulfinyl compounds (Table II).

Two features of this reaction should be noted. First, in the cyclohexyl case (the last entry in Table II), the net result of this transformation has been the formation of a bond between two nonprotonated carbon atoms, a nontrivial process in synthetic organic chemistry. And second, the structures of the alkylated materials as deduced from their proton and carbon-13 nuclear magnetic resonance spectra proved highly interesting. These compounds appear to be produced by an $S_N2'$ reaction between the anion of the N-sulfinylamine and the electrophile. However, there is no precedent for such reactivity in the literature. Typically, γ,γ-dimethylallyl bromide undergoes the $S_N2$ reaction exclusively.[76-82] Apparently the $S_N2'$ process is very sensitive to steric hindrance at the carbon γ to the halogen. For example, DeWolfe and Young state that this reaction is unknown for γ,γ-disubstituted allylic halides.[83]

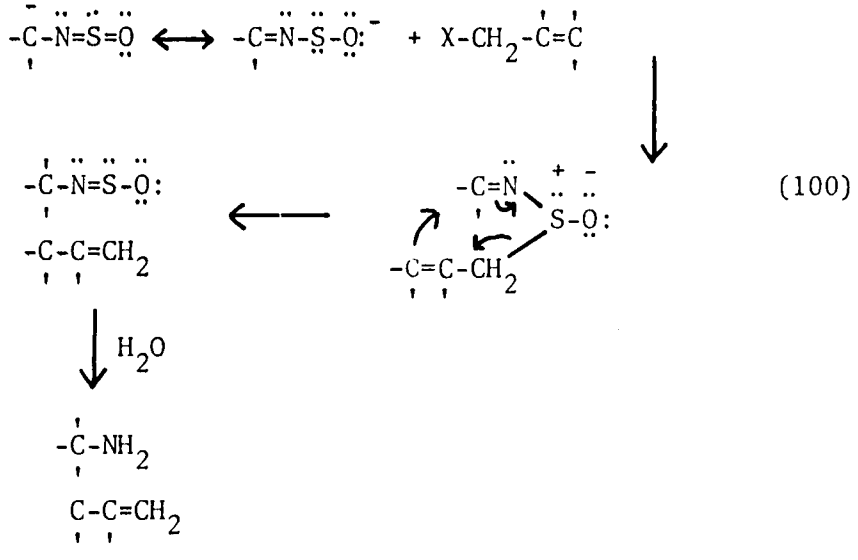
TABLE II

YIELDS OF ALKYLATED AMINES USING POTASSIUM t-BUTOXIDE AS THE BASE

| N-Sulfinyl-Amine | Alkylating Agent | Yields[a] | Structure of Product | | |
|---|---|---|---|---|---|
| n-butyl | allyl bromide | 46% |  | 23 | (p 41) |
| n-butyl | methallyl chloride | 58% |  | 24 | (p 41) |
| n-butyl | γ,γ-dimethylallyl chloride | 47% |  | 30 | |
| n-hexyl | allyl bromide | 56% |  | 25 | (p 41) |
| n-hexyl | methylallyl chloride | 42% |  | 26 | (p 41) |
| n-hexyl | γ,γ-dimethylallyl chloride | 50% |  | 31 | |
| cyclohexyl | allyl bromide | 53% |  | 27 | (p 41) |
| cyclohexyl | methallyl chloride | 56% |  | 28 | (p 41) |
| cyclohexyl | γ,γ-dimethylallyl chloride | 28% |  | 32 | |

[a]Yields are based on the N-sulfinylamine and refer to chromatographically pure benzoylated materials.

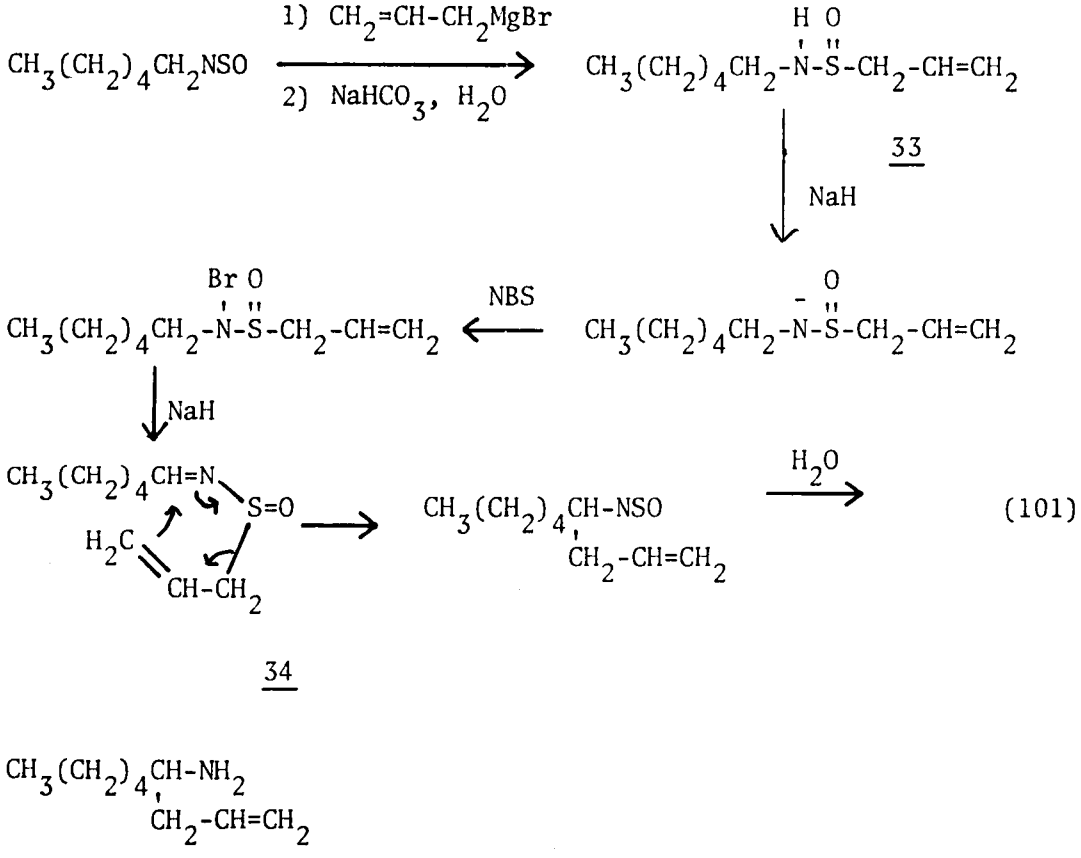
This unexpected product, together with the failure of highly active saturated alkylating agents to react, raises interesting mechanistic questions. A priori, simple activation of the carbon center was expected, and reaction with symmetrical electrophiles provided products readily explained by simple carbon alkylation. However, a reasonable alternative which accounts for the products obtained on the reaction with the γ,γ-dimethylallyl chloride is available. Alkylation of the sulfur atom of the N-sulfinylamine anion would give a product which might rearrange through a [3,3] sigmatropic shift to regenerate the N-sulfinylamine. Thus, for the disubstituted electrophile, sulfur displaces the chloride in an $S_N2$ reaction and it is the sigmatropic shift that makes the reaction appear to have proceeded by the $S_N2'$ pathway, as illustrated in Equation 100.



(100)

Although this mechanism does answer a number of questions, further experimentation was called for, in order to test its validity. Slow

addition of allylmagnesium bromide to an ethereal solution of N-sulfinylhexylamine, followed by gentle basic work-up, gave compound 33. Oxidation of this substance should provide an intermediate virtually identical to the intermediate (Equation 100) in the sulfur alkylation mechanism. Treatment of 33, Equation 101, with sodium hydride was accompanied by gas evolution to give its anion. Addition of N-bromosuccinimide (NBS) to this reaction mixture, followed by another equivalent of sodium hydride, gave what is believed to be 34. This apparently underwent the proposed [3,3] sigmatropic shift, for after the standard work-up procedure, a low yield (less than 5%) of 3-amino-1-nonene (p 41) was isolated.




(101)

The rearrangement of intermediate 34, together with the unusual product obtained in the reaction with γ,γ-dimethylallyl chloride and the failure of saturated electrophiles to react strongly support the sulfur alkylation mechanism. It should also be noted that the reaction provides the best yields when run under conditions that are reported to favor heteroatom alkylation in other ambient anions,[73] which is to say, in dilute solution, in polar solvents, and with a highly electropositive counterion.

In an effort to define other synthetically useful alkylating agents, a study of the interaction between the anions of aliphatic N-sulfinylamines and carbonyl compounds was undertaken. Addition of acetone to a solution of N-sulfinylbutylamine and lithium triphenylmethide led to the isolation of butylamine together with a small amount of polymeric material after the usual work-up. Alterations of the reaction conditions provided no more useful result.

Attempted alkylation of N-sulfinylhexylamine with benzaldehyde did not yield any of the desired amino-alcohol. The only product of interaction between the N-sulfinylamine and the aldehyde that was isolated was imine 35. Alterations in reaction conditions did not

$$CH_3(CH_2)_4CH_2\text{-}N{=}CH\text{-}C_6H_5$$

35

furnish any better results.

More encouraging data were obtained from the reaction of N-sulfinylamines and methyl vinyl ketone (MVK). Addition of the unsaturated

ketone to a mixture of N-butylsulfinylamine and lithium triphenylmethide gave at least some of the desired adduct, although it was contaminated with large quantities of other ill-defined materials. Use of potassium t-butoxide led to an improved yield of the desired products, 36 and 37.

$$CH_3(CH_2)_2CH_2NSO \xrightarrow[2)\ MVK]{1)\ KOtBu,\ DME} CH_3(CH_2)_2\underset{\underset{NHBz}{|}}{CH}CH_2CH_2\overset{\overset{O}{||}}{C}CH_3 \qquad (102)$$

36

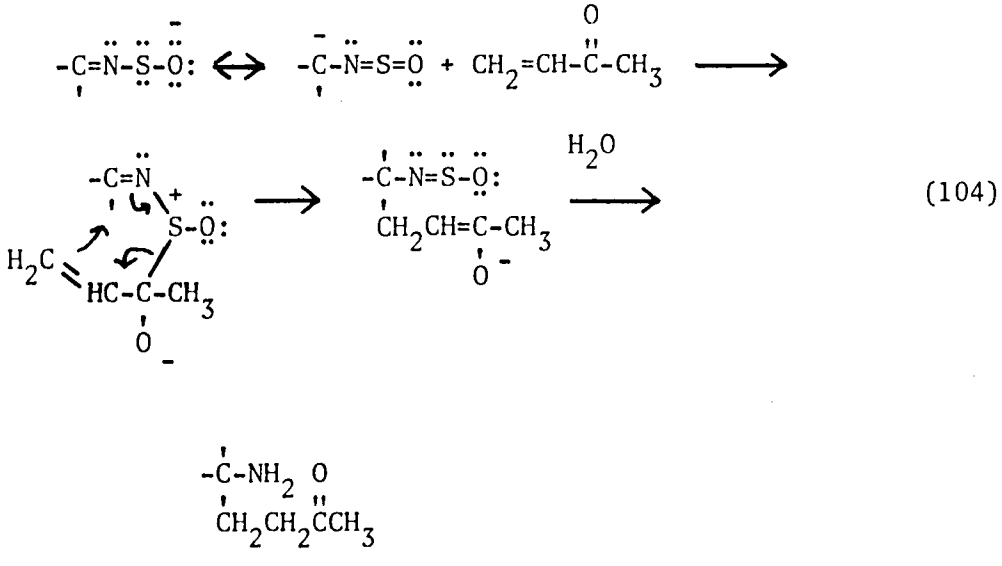
38%

$$CH_3(CH_2)_4CH_2NSO \xrightarrow[2)\ MVK]{1)\ KOtBu,\ DME} CH_3(CH_2)_4\underset{\underset{NHBz}{|}}{CH}CH_2CH_2\overset{\overset{O}{||}}{C}CH_3 \qquad (103)$$

37

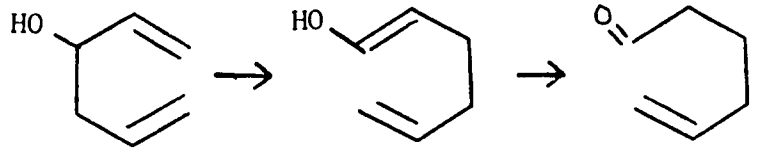
42%

The mechanism of this process is unknown and there are two reasonable possibilities; first, a mechanism similar to that involved in the reaction of allylic halides, with sulfur attacking the carbonyl carbon, followed by sigmatropic shift (Equation 104). This conjecture is

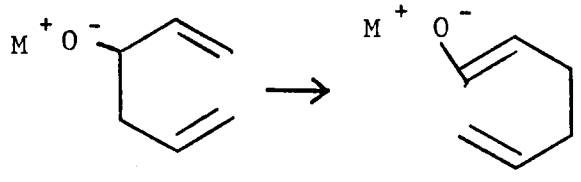


(104)

supported by an observation by Evans[84] that another [3,3] sigmatropic shift, the oxy-Cope rearrangement, is vastly accelerated on generation of the alkoxide, as indicated in Equations 105 and 106.

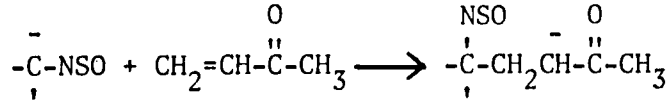


Relative Rate 1.0 (105)



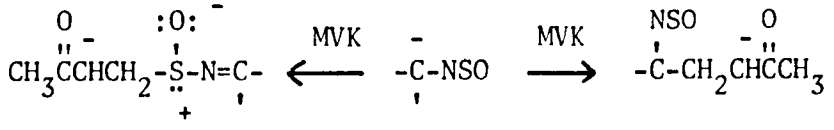
$10^{10}$ to $10^{17}$ (106)

The other reasonable possibility is the addition of the carbon centered anion to the unsaturated ketone in a Michael fashion (Equation 107).



(107)

This pathway may be favored over sulfur alkylation as sulfur interaction with the double bond does not give an intermediate capable of undergoing the sigmatropic shift. Thus an equilibrium may be occurring that is drained to the side of carbon-carbon bond formation as in Equation 108.

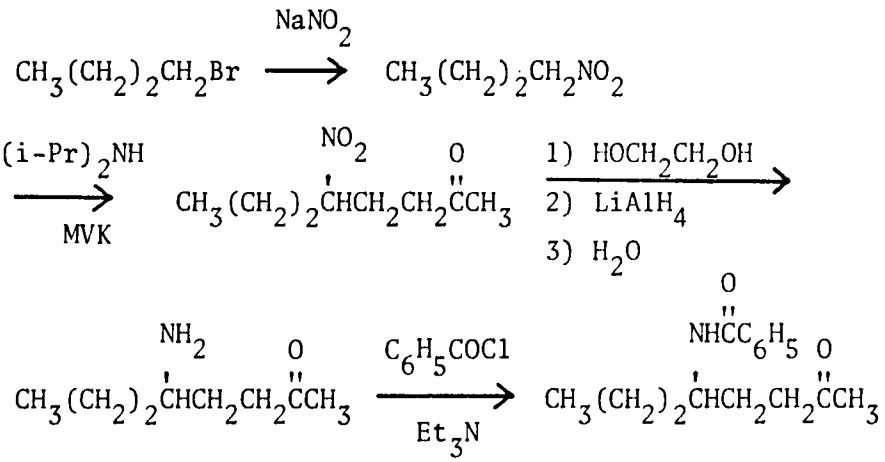


(108)

The alkylation products obtained by this reaction were isolated as benzamides, and attempts to isolate either the amino-ketone or the imine

resulted in decreased yields. This was especially true if distillation of the reaction mixture was attempted, and an independent synthesis of the supposed product was undertaken.

The reaction between n-butyl bromide and sodium nitrite under conditions reported by Kornblum[85] led to the production of 1-nitrobutane. Addition of this compound to methyl vinyl ketone, catalyzed by diisopropylamine, as described by McMurray,[86] gave a 45% yield of



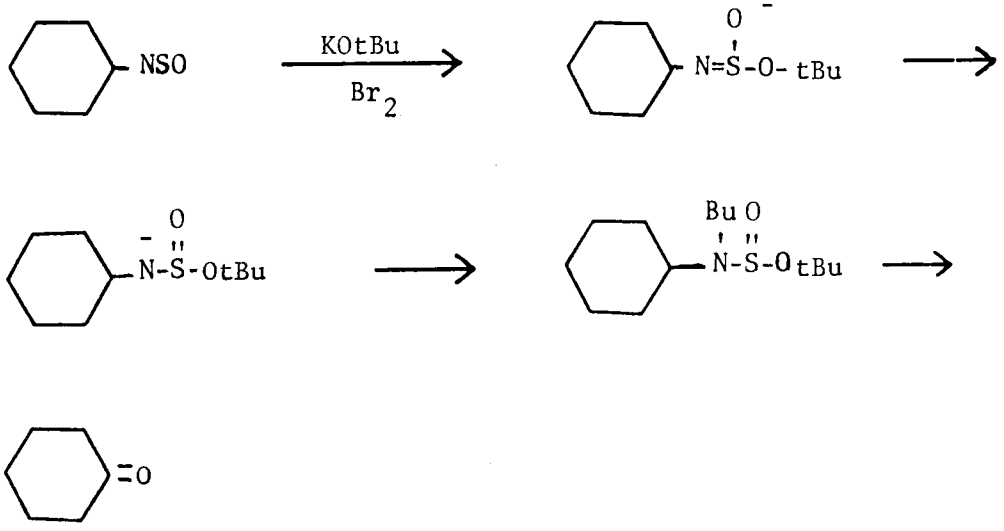
(109)

5-nitrooctan-2-one. This was ketalized, reduced with lithium aluminum hydride, and deketalized to provide 5-aminooctan-2-one. Benzoylation of this compound furnished a material spectroscopically identical to that produced by reaction of the N-sulfinylamine.

A number of attempts to add methyl vinyl ketone to N-sulfinylcyclohexylamine resulted in failure. Under those conditions which worked for the butyl and hexyl compounds, only cyclohexylamine was isolated. The acid insoluble material isolated was polymeric. Apparently the rate of alkylation of this secondary N-sulfinylamine is

approximately the same as the rate of polymerization of methyl vinyl ketone.

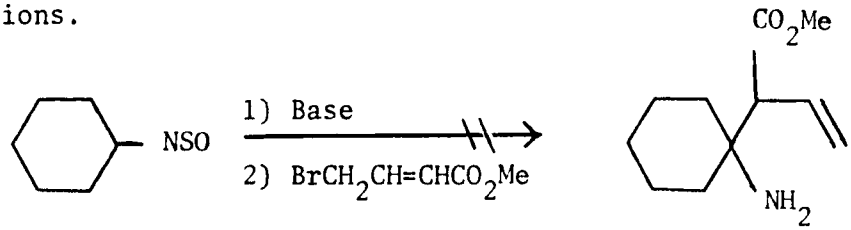
Other types of electrophiles have been tested. For example, addition of bromine to a solution of N-cyclohexylsulfinylamine and lithium triphenylmethide provided the parent amine or intractable mixtures on work-up. However, use of potassium t-butoxide as the base lead to the isolation of a mixture which contained at least some cyclohexanone, as indicated by gas chromatography. A rationale of this oxidation is that the butoxide anion is attacking the N-sulfinylamine to yield a nitrogen anion, which adds bromine. Acid hydrolysis gives an N-bromoamine which loses hydrogen bromide to form an imine, which is hydrolyzed to the ketone, as in Equation 110. However, this is



(110)

apparently not the only process that occurs, for the carbonyl compound is contaminated with large amounts of other ill-defined materials. As this reaction is neither clean nor high-yielding, further investigation was not pursued.

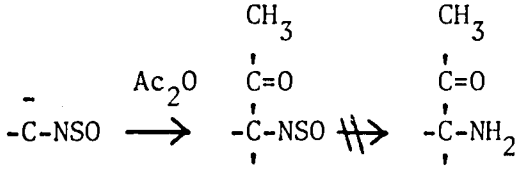
Also methyl 4-bromocrotonate (methyl 4-bromo-2-butenoate) was used as a possible electrophile (Equation 111). However, no olefinic materials other than the starting unsaturated ester could be isolated in any reactions of this compound with any N-sulfinylamine under a variety of conditions.



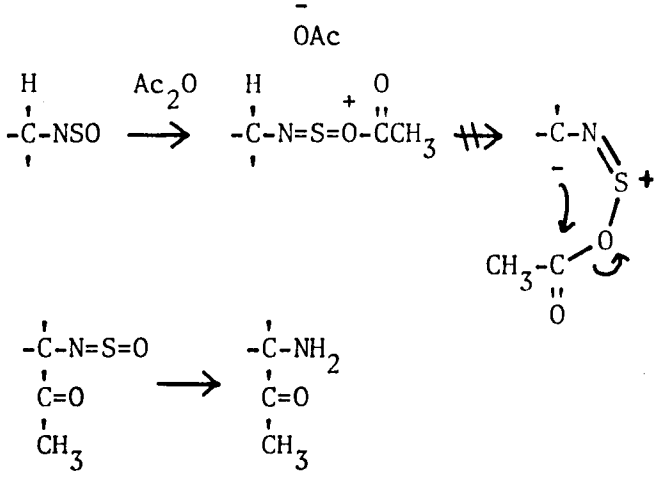

(111)

38

In another study, acetic anhydride was employed as the alkylating agent in reactions both with the preformed anion and with the N-sulfinylamine itself. These efforts were aimed at producing α-aminoketones, as in Equations 112 and 113. However, in all cases only the acetamide of the parent amine was isolated.



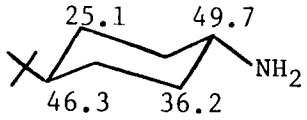

(112)



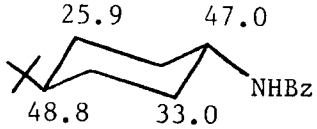

(113)

As a prelude to the possible synthesis of complex nitrogenous materials, a study of the stereochemistry of the alkylation reaction with allylic halides was undertaken. For this purpose, N-sulfinyl-4-t-butylcyclohexylamine was chosen as a typical rigid system. The parent amine[87] was prepared by catalytic hydrogenation[88] of the oxime, which gave an 85:15 mixture of cis and trans isomers, as judged by proton magnetic resonance spectroscopy. Treatment of the amine with thionyl chloride produced the N-sulfinylamine in 80% yield. Alkylation of this substance was achieved by reaction with potassium t-butoxide and allyl bromide. The carbon alkylated amine 43 was isolated in 32% yield.

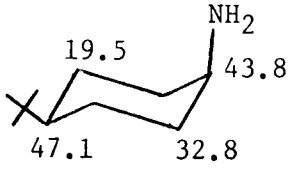
Study of the carbon-13 nuclear magnetic resonance spectra of this amine, together with those of the parent amine and their benzamides led to the conclusion that alkylation had occurred in an equatorial manner. First, the chemical shift of the allylic methylene carbon in is quite similar to that of a very similar carbon in compound 45 as reported by House.[89] Further similarities were noted between the chemical shifts of the $\gamma$ carbon of both the alkylated amine 43 (22.1 ppm) and its



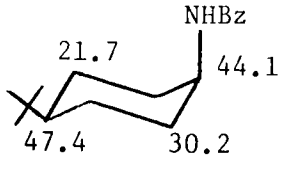

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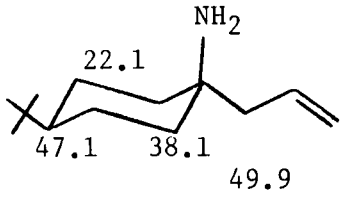

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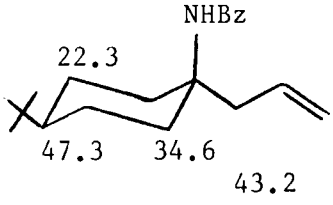

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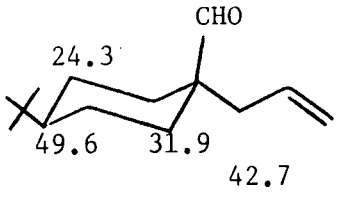

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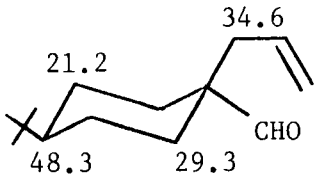

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44




45

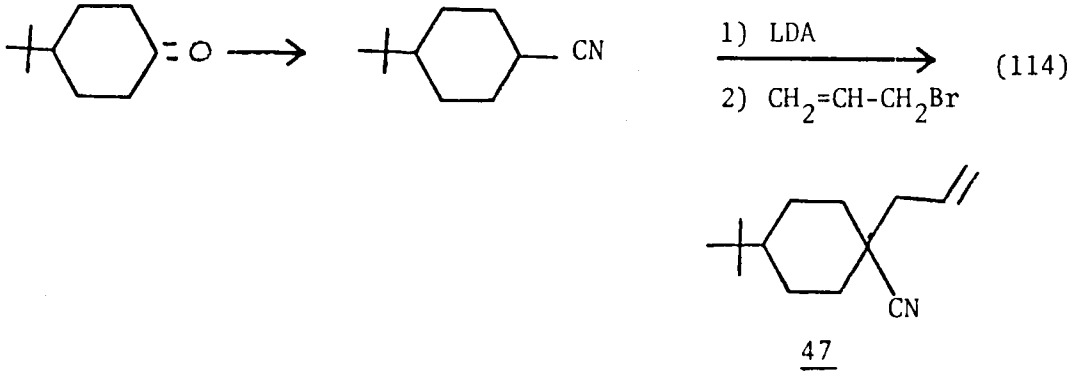



46

benzamide 44 (22.3 ppm) and the axial amine 41 (19.5 ppm) and its benzamide 42 (21.7 ppm). These values are somewhat less than equatorial amine 39 (25.1 ppm) and its benzamide 40 (25.9 ppm). It should be noted that the change in the gamma effect[90] in going from amine to benzamide is rather small for all of these compounds, even though the change of the substituent electronics is rather large. This slight difference in chemical shifts (the largest is less than 2 ppm) is rather surprising.

In further support of this stereochemical assignment, an independent synthesis of the compound in question was undertaken. 4-t-Butylcyclohexanone was converted into its cyanohydrin by treatment with potassium cyanide and hydrochloric acid.[91] This was dehydrated by phosphorous oxychloride[91] and hydrogenated to give 4-t-butyl-1-cyanocyclohexane.[89] This substance was then alkylated with allyl

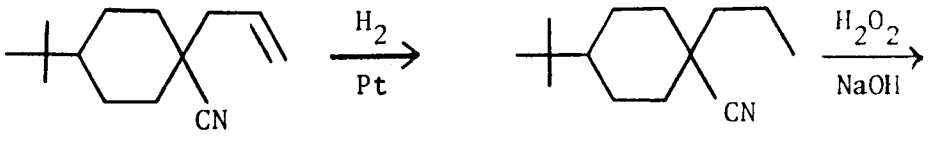
bromide to provide compound 47 in a 12:88 cis:trans mixture as described by House.[89]



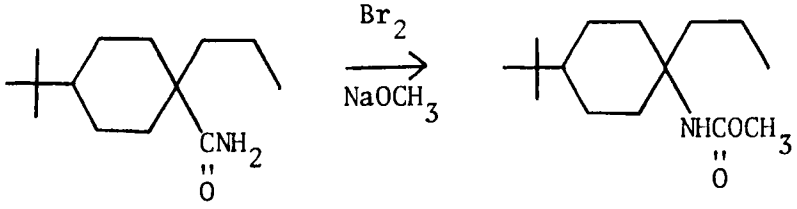

(114)

47

Hydrolysis of this cyanide under either acidic or basic conditions could not be achieved without affecting the olefin. Therefore, the double bond was hydrogenated, and the cyanide converted to the amide by the method of Noller[92] using 30% hydrogen peroxide and sodium hydroxide. The amide was submitted to the Hoffmann rearrangement in methanol by the excellent procedure of Radlick.[93]

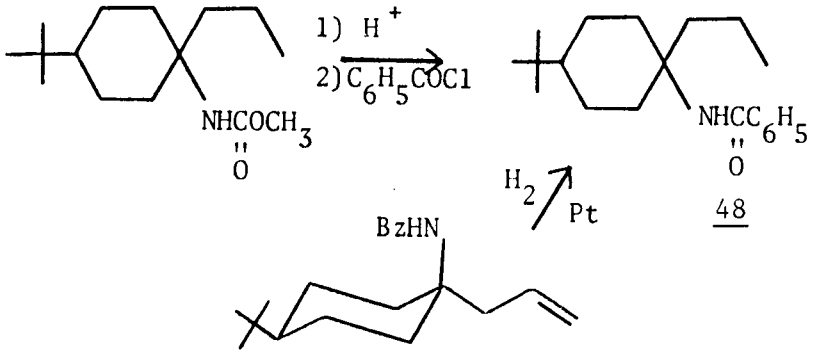



(115)




(116)

The resulting urethane was hydrolyzed to the corresponding amine and treated with benzoyl chloride to provide compound 48, Equation 117. This substance was found to be spectroscopically identical to the reduced alkylated t-butylcyclohexylamine, thus confirming the stereochemical assignment.




(117)

# CHAPTER III

## EXPERIMENTAL SECTION

Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Beckman IR-5A or a Perkin Elmer 257 infrared spectrophotometer using reagent grade carbon tetrachloride as a solvent. The infrared absorptions are reported in microns and standardized using a polystyrene film. Proton magnetic resonance (pmr) spectra were recorded on a Varian T-60A spectrometer. The spectra were run as deuteriochloroform solutions, unless otherwise specified, with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Proton splitting patterns are designated as s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; and m, multiplet. Carbon magnetic resonance (cmr) spectra were recorded on a Nicolet TT-14 spectrometer using deuteriochloroform as the solvent and the internal standard. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

All experiments requiring anhydrous conditions were carried out under an atmosphere of dry argon and in glassware that had been flame-dried in a dry argon stream. Dry tetrahydrofuran and 1,2-dimethoxyethane were distilled from lithium aluminum hydride immediately prior to use.

Preparative layer chromatography was performed using EM-brand aluminum oxide F-254 precoated plates. Thin layer chromatographic analyses were made using plates coated with Woelm alumina G and column chromatography was carried out using Fisher-brand neutral alumina (Brockman activity I).

## A. ALIPHATIC N-SULFINYLAMINES

All aliphatic N-sulfinylamines were prepared in the same manner. A solution of 1 mole of the appropriate amine and 258 g (2 moles) of freshly distilled quinoline in 750 ml of anhydrous ether was added to a 2-l round-bottomed flask equipped with an overhead stirrer, a calcium chloride drying tube, and a pressure equalizing addition funnel. After cooling the reaction mixture to -20° (Dry Ice, $H_2O$:$CH_3OH$, 1:4), a solution of 119 ml (1 mole) of thionyl chloride in 100 ml of anhydrous ether was added to it over a period of 3 hours. After stirring overnight at -20°, the solution was allowed to warm to room temperature, and to it was added 500 ml of ligroin. The solution was then filtered in the absence of moisture. Evaporation of the solvent and distillation of the residue at reduced pressure (0.05 mm Hg) provided the N-sulfinylamine as a golden yellow liquid. Yields were typically 80%. It should be noted that distillation should not be attempted at temperatures greater than 150° or be allowed to go to dryness. Boiling points are, for N-sulfinyl-butylamine, 45°-50°; for n-hexyl-N-sulfinylamine, 55°-60°; for cyclohexyl-N-sulfinylamine, 55°-60°; and for 4-t-butylcyclohexyl-N-sulfinylamine, 90°-95°.

## B. ATTEMPTED METHYLATION OF N-SULFINYLAMINES

As a rather large number of reactions were run in an attempt to alkylate several N-sulfinylamines with "$CH_3X$," and as none of these experiments was successful, no detailed experimental information will be given for each. Instead, a general outline of the reaction conditions will be presented, as will Table III.

Into a 250-ml three-necked flask, equipped with a magnetic stirrer and an argon inlet and outlet was placed the base and solvent. The temperature of the reaction mixture was adjusted, and 1.0 g of N-sulfinylamine was added dropwise, followed by the methylating agent. After stirring for various amounts of time, the reaction was quenched. The solution was then adjusted to pH 1 by addition of sufficient 5% hydrochloric acid. This was extracted twice with 50 ml of ligroin. The aqueous layer was then made basic with 10% sodium hydroxide and extracted with anhydrous ether. To the ether layer was added one equivalent of benzoyl chloride and one equivalent of triethylamine. After stirring for one hour, the mixture was extracted with 50 ml of 5% hydrochloric acid, with 50 ml of water and with 50 ml of saturated salt water. The ether layer was dried with magnesium sulfate, and the solvent removed by rotatory evaporation. The residue was then chromatographed on alumina.

## C. ATTEMPTS TO DEUTERATE N-SULFINYLAMINES

Also in this case the number of experiments is quite large. A general experimental outline is provided, together with Table IV.

TABLE III

REACTION CONDITIONS EMPLOYED IN THE ATTEMPTED METHYLATION OF N-SULFINYLAMINES

| Temp. | Conc. of N-Sulfinylamine (M) | Solvent | Time (hr) | Methylating Agent | Base[a] | Quenching Agent | N-Sulfinylamine |
|---|---|---|---|---|---|---|---|
| -78° | 0.01 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex, CHex |
| -78° | 0.05 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex |
| -78° | 0.1 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex, CHex |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex, CHex |
| -78° | 0.5 | THF | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 0.75 | THF | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 1.0 | THF | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -23° | 0.2 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex |
| -23° | 1.0 | THF | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -100° | 0.2 | THF | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| 0° | 0.2 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex |
| RT | 0.2 | THF | 3 | methyl iodide | LTPM | 5% HCl | Bu, Hex |
| 66° | 0.2 | THF | 1 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | KOtBu | 5% HCl | Bu |
| -23° | 0.2 | THF | 3 | methyl iodide | KOtBu | 5% HCl | Bu, Hex |
| 0° | 0.2 | THF | 3 | methyl iodide | KOtBu | 5% HCl | Bu, Hex, CHex |
| 0° | 0.2 | THF | 12 | methyl iodide | KOtBu | 5% HCl | Bu, Hex, CHex |
| -78° | 0.01 | pentane | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 0.2 | ether | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| 5° | 0.01 | benzene | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -23° | 0.2 | dimethyl-ether | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -23° | 0.2 | DME | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -23° | 0.2 | diglyme | 3 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | LDA | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM + HMPA | 5% HCl | Bu |

TABLE III (continued)

| Temp. | Conc. of N-Sulfinylamine (M) | Solvent | Time (hr) | Methylating Agent | Base[a] | Quenching Agent | N-Sulfinylamine |
|---|---|---|---|---|---|---|---|
| -78° | 0.2 | THF | 3 | methyl iodide | KTPM | 5% HCl | Bu, Hex |
| RT | > 1 | THF | 3 | methyl iodide | NaH | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | radical anion of napthalene | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | nBuLi | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | tBuLi | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | MeLi | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | TMP | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | HMDS | 5% HCl | Hex |
| -78° | 0.2 | DMF | 3 | methyl iodide | $K_2CO_3$ | 5% HCl | Bu |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | $H_2O$ | Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | 5% NaOH | Bu, Hex |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | glacial HOAc | Bu |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | satd. $NaHCO_3$ | Bu |
| -78° | 0.2 | THF | 3 | methyl iodide | LTPM | $CH_3OH$ | Hex |
| -78° | 0.2 | THF | 3 | methyl chloride | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | dimethyl sulfate | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | 3 | trimethyloxonium tetrafluoroborate | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | < 30 sec | methyl iodide | LTPM | 5% HCl | Bu |
| -78° | 0.2 | THF | 1/4 | methyl iodide | LTPM | 5% HCl | Bu |
| -78° | 0.2 | THF | 1 | methyl iodide | LTPM | 5% HCl | Hex |
| -78° | 0.2 | THF | 12 | methyl iodide | LTPM | 5% HCl | Hex, CHex |
| RT | 0.2 | THF | 24 | methyl iodide | LTPM | 5% HCl | Hex |
| RT | -- | neat | > 3 weeks | methyl iodide | none | none (observed by pmr) | Bu |

[a]Abbreviations are: LTPM, lithium triphenylmethide; HMPA, hexamethylphosphoramide; TMP, N-lithio-2,2,6,6-tetramethylpiperidine; HMDS, sodium 1,1,1,3,3,3-hexamethyldisilazane; KTPM, potassium triphenylmethide; LDA, lithium diisopropylamide; $KO_tBu$, potassium t-butoxide.

TABLE IV

REACTION CONDITIONS EMPLOYED IN THE ATTEMPTED DEUTERATION OF N-SULFINYLAMINES

| Temp. | Solvent | Source of Deuterium | Base[a] | N-Sulfinylamine |
|---|---|---|---|---|
| -78° | THF | deuterium oxide | LTPM | Hex, Bu, CHex |
| -23° | DME | deuterium oxide | LTPM | Hex, Bu, CHex |
| -23° | diglyme | deuterium oxide | LTPM | Hex, Bu, CHex |
| -23° | THF | deuterium oxide | LTPM | Hex, Bu, CHex |
| 0° | THF | deuterium oxide | LTPM | CHex |
| -23° | THF | deuterium oxide | KOtBu | CHex |
| 0° | THF | deuterium oxide | KOtBu | CHex |
| 0° | THF | deuterium oxide | KOtBu | CHex, Hex |
| 66° | THF | deuterium oxide | KOtBu | Hex |
| 0° | DME | deuterium oxide | KOtBu | Hex |
| -78° | THF | deuterium oxide | LTPM + HMPA | Hex |
| RT | THF | deuterium oxide | NaH | Hex |
| -78° | THF | deuterium oxide | radical anion of napthalene | Hex |
| -78° | THF | deuterium oxide | KTPM | Hex |
| -78° | THF | deuterium oxide | tBuLi | Bu |
| -78° | THF | deuterium oxide | LDA | Hex |
| -78° | THF | DOAc | LTPM | Hex, CHex, Bu |
| -78° | THF | $CH_3OD$ | LTPM | Hex, CHex |
| -78° | THF | $D_2SO_4$ | LTPM | Hex |
| 0° | diglyme | pryidine deuteriosulfate | KOtBu | Hex |
| 0° | DME | DOAc | KOtBu | Hex |
| 0° | DME | $CH_3OD$ | KOtBu | Hex |
| 0° | DME | $D_2SO_4$ | KOtBu | Hex |
| -78° | THF | $DOAc/D_2O$ | LTPM | Hex |
| -78° | THF | $D_2SO_4/D_2O$ | LTPM | Hex |
| 0° | DME | $DOAc/D_2O$ | KOtBu | Hex |
| 0° | DME | $D_2SO_4/D_2O$ | KOtBu | Hex |

[a]Abbreviations are: LTPM, lithium triphenylmethide; HMPA, hexamethylphosphoramide; KTPM, potassium triphenylmethide; KOtBu, potassium t-butoxide.

In a 250-ml round-bottomed flask equipped with a magnetic stirrer and an argon inlet and outlet was placed 0.01 mole of the base in 50 ml of solvent. The temperature of the solution was adjusted, and 0.01 mole of the N-sulfinylamine was added dropwise. One ml of a deuterium source was added dropwise and the mixture stirred for 30 minutes. The reaction was quenched by addition of 50 ml of 5% hydrochloric acid and extracted with 50 ml of ligroin. The aqueous layer was made basic (pH greater than 10) with 10% sodium hydroxide and extracted three times with 50 ml of anhydrous ether. To the combined ether layers was added 1.2 ml (0.01 mole) of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring for 1 hour, the mixture was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water, and with 50 ml of saturated salt water. The organic layer was dried with magnesium sulfate, and the solvent was removed by rotatory evaporation. The residue was then chromatographed on alumina.

## D. ATTEMPTS TO ALKYLATE N-SULFINYLAMINES WITH SATURATED ALKYLATING AGENTS

The attempts to alkylate N-sulfinylamines with saturated electrophiles resulted in total failure. The conditions employed were not as numerous as those used in the methylation experiments, and only two general experimental descriptions will be given. The alkylating agents used included ethyl bromide, ethyl iodide, ethyl tosylate, propyl iodide, butyl bromide, benzyl bromide, benzyl chloride, 1,3-dibromopropane, and 1,4-dibromobutane.

Method A

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer and argon inlet and outlet, was placed 2.54 g (0.01 mole) of triphenylmethane. Following addition of 50 ml of dry THF, the solution was cooled to 0° and 6.2 ml of a 1.6 M solution of butyllithium in hexane was added dropwise. After stirring at 0° for 1 hour, the solution was cooled to -78°, and 0.01 mole of the N-sulfinylamine was added. After 10 minutes, 0.01 mole of the electrophile was added.

After 3 hours at -78°, the cold bath was removed and 50 ml of 5% hydrochloric acid was added. The acidic solution was extracted with 50 ml of ligroin and made basic (pH greater than 10) with 10% sodium hydroxide. This solution was extracted three times with 50 ml of anhydrous ether. To the combined organic layers was added 1.2 ml (0.01 mole) of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring for 1 hour, the mixture was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water, and 50 ml of saturated salt water. The organic layer was dried with magnesium sulfate, and the solvent was removed by rotatory evaporation. The residue was then chromatographed on alumina.

Method B

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer and an argon inlet and outlet, was placed 1.19 g (0.01 mole) of potassium t-butoxide and 50 ml of dry DME. The mixture was cooled to 0° and 0.01 mole of the N-sulfinylamine was added dropwise. Then

0.01 mole of the electrophile was added. After stirring for 12 hours at 0°, the reaction was worked-up in the manner previously described.

## E. ALKYLATIONS OF ALIPHATIC N-SULFINYLAMINES

As only four general methods were used, only these procedures will be described. For the method used, see Table V.

### Method A

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer and an argon inlet and outlet, was placed 2.57 g (0.01 mole) of triphenylmethane and 50 ml of dry THF. After cooling the solution to 0°, 6.25 ml of a 1.6 M solution of n-butyllithium was added. The mixture was cooled to -78° and to it was added 0.01 mole of the N-sulfinylamine. Ten minutes later, 0.01 mole of the electrophile was added dropwise. Stirring at -78° was continued for three hours, after which 50 ml of 5% hydrochloric acid was added. The acidic layer was extracted with 50 ml of ligroin and made basic (pH greater than 10) with 10% sodium hydroxide. The aqueous layer was extracted three times with 50 ml of anhydrous ether. To the combined organic layers was added 1.2 ml (0.01 mole) of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring at room temperature for 1 hour, the reaction was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water, and 50 ml of saturated brine. The organic layer was dried with magnesium sulfate, and the solvent removed by rotatory evaporation. The residue was then chromatographed on alumina using benzene as the eluent.

TABLE V

METHODS OF SYNTHESIS OF ALKYLATED N-SULFINYLAMINES

| N-Sulfinylamine | Electrophile | Method | Yield |
|---|---|---|---|
| butyl | allyl bromide | A | 65% |
| butyl | methallyl chloride | A | 40% |
| butyl | allyl bromide | B | 46% |
| butyl | methallyl chloride | B | 58% |
| butyl | γ,γ-dimethylallyl chloride | C | 47% |
| butyl | methyl vinyl ketone | D | 38% |
| hexyl | allyl bromide | A | 32% |
| hexyl | methallyl chloride | A | 31% |
| hexyl | allyl bromide | B | 56% |
| hexyl | methallyl chloride | B | 42% |
| hexyl | γ,γ-dimethylallyl chloride | C | 50% |
| hexyl | methyl vinyl ketone | D | 42% |
| cyclohexyl | allyl bromide | A | 33% |
| cyclohexyl | methallyl chloride | A | 23% |
| cyclohexyl | allyl bromide | B | 53% |
| cyclohexyl | methallyl chloride | B | 56% |
| cyclohexyl | γ,γ-dimethylallyl chloride | C | 28% |
| 4-t-butyl cyclohexyl | allyl bromide | B | 41% |

Method B

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer and an argon inlet and outlet, was placed 1.19 g (0.01 mole) of potassium t-butoxide and 50 ml of dry DME. After cooling the solution to 0°, 0.01 mole of the N-sulfinylamine was added dropwise, followed by addition of 0.01 mole of the electrophile. The reaction was quenched by addition of 50 ml of 5% hydrochloric acid after stirring at 0° for 12 hours. The acidic solution was extracted with 50 ml of ligroin and then made basic (pH greater than 10) with 10% sodium hydroxide. The aqueous layer was extracted three times with 50 ml of anhydrous ether. To the combined organic layers was added 1.2 ml (0.01 mole) of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring at room temperature for one hour, the reaction mixture was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water, and 50 ml of saturated brine. The organic layer was dried with magnesium sulfate and the solvent removed by rotatory evaporation. The residue was chromatographed on alumina with benzene as the eluent.

Method C

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser, and an argon inlet and outlet was placed 1.19 g (0.01 mole) of potassium t-butoxide and 50 ml of dry DME. After cooling the solution to 0°, 0.01 mole of the N-sulfinylamine was added dropwise, followed by 1.05 g (0.01 mole) of 1-chloro-3-methyl-2-butene. After stirring for 12 hours at 0°, the reaction mixture was refluxed

for 1 hour and then cooled to room temperature prior to the addition of 50 ml of 5% hydrochloric acid. The acidic solution was extracted with 50 ml of ligroin and made basic (pH greater than 10) with 10% sodium hydroxide. The aqueous layer was extracted three times with anhydrous ether and to the combined organic layers was added 1.2 ml (0.01 mole) of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring the solution for one hour at room temperature, it was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water and 50 ml of saturated brine. The organic layer was dried with magnesium sulfate and the solvent removed by rotatory evaporation. The residue was chromatographed on alumina with benzene as the eluent.

Method D

Into a 250-ml round-bottomed flask, equipped with a magnetic stirrer, an argon inlet and outlet, and a pressure equalizing addition funnel with a varibor stopcock, was placed 1.19 g (0.01 mole) of potassium t-butoxide and 50 ml of dry DME. After the solution was cooled to 0°, 0.01 mole of the N-sulfinylamine was added. A solution of freshly distilled methyl vinyl ketone in 15 ml of dry DME was added very slowly (approximately one drop every 3 seconds) to the reaction mixture. After stirring for 12 hours at 0°, the reaction was quenched with 50 ml of 2.5% hydrochloric acid and extracted with 50 ml of ligroin. The acid layer was carefully made barely basic by addition of potassium carbonate and was extracted three times with 50 ml of anhydrous ether. To the combined organic layers was added 1.2 ml of benzoyl chloride and 1.4 ml (0.01 mole) of triethylamine. After stirring for 1 hour at room

temperature, the solution was extracted with 50 ml of water and 50 ml of saturated brine. The organic layer was dried with magnesium sulfate, and the solvent was removed by rotatory evaporation. The residue was chromatographed on alumina with 1:9, ether:benzene as the eluent.

Analytical Data

1. N-benzoyl-4-amino-1-heptene (p 41) (from N-butylsulfinylamine and allyl bromide) melting point: 83.8°-84.2°; pmr ($CDCl_3$)δ 0.8-1.9 (complex multiplet, 7H), 2.3 (t, 2H, allylic -$CH_2$-), 4.1 (m, 1H, CH-N), 4.9-6.2 (3H, complex multiplet, olefinic CH), 6.4 (d, 1H, -NH), 7.5 (complex multiplet, 5H, aromatic); Ir ($CCl_4$)μ 3.0 (strong, NH), 5.95 (strong, amide).

Anal. Calcd. for $C_{14}H_{19}NO$: C 77.38; H 8.81; N 6.45. Found: C 77.56; H 9.09; N 6.24.

2. N-benzoyl-4-amino-2-methyl-1-heptene (p 41) (from N-butylsulfinylamine and methallyl chloride) melting point: 70°-71°; pmr ($CDCl_3$)δ 0.8-2.0 (complex multiplet, 7H), 1.9 (s, $CH_3$), 2.4 (d, allylic $CH_2$), 4.4 (m, 1H, CH-N), 4.9 (s, 2H, olefinic $CH_2$), 6.6 (d, 1H, NH), 7.5 (complex multiplet, 5H, aromatic; Ir ($CCl_4$)μ 3.0 (strong, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{15}H_{21}NO$: C 77.88; H 9.15; N 6.05. Found: C 77.64; H 9.40; N 6.03.

3. N-benzoyl-4-amino-3,3-dimethyl-1-heptene (p 45) (from N-butylsulfinylamine and 1-chloro-3-methyl-2-butene) melting point: 119°-120°; pmr ($CDCl_3$)δ 0.8-1.9 (complex multiplet including singlet, 13H), 4.1 (m, 1H, -CH-N), 4.9-6.2 (complex multiplet, olefinic and NH),

4H, 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{16}H_{23}NO$: C 78.32; H 9.45; N 5.71. Found: C 78.68; H 9.46; N 5.71.

4. N-benzoyl-5-amino-2-octanone (p 49) (from N-butylsulfinylamine and methyl vinyl ketone) melting point: 89.5°-90.0°; pmr ($CDCl_3$)δ 0.8-1.9 (complex multiplet, 7H), 1.9 (t, 2H), 2.6 (t, 2H), 4.1 (m, 1H, -CH-N), 6.4 (d, 1H, -NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium, NH), 5.9 (medium, C=O), 6.05 (strong, amide).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C 72.84; H 8.63; N 5.66. Found: C 72.90; H 8.63; N 5.68.

5. N-benzoyl-4-amino-1-octene (p 41) (from N-hexylsulfinylamine and allyl bromide) melting point: 66°-67°; pmr ($CDCl_3$)δ 0.8-1.9 (complex multiplet, 11H), 2.3 (t, 2H, allylic $CH_2$), 4.1 (m, 1H, -CH-N), 4.9-6.4 (complex multiplet and a doublet, 4H, olefin and NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium), 6.05 (strong, amide).

Anal. Calcd. for $C_{16}H_{23}NO$: C 78.32; H 9.45; N 5.71. Found: C 78.49; H 9.68; N 5.52.

N-hexylsulfinylamine and methallyl chloride) melting point: 59°-60°; pmr ($CDCl_3$)δ 0.8-1.9 (complex multiplet, 11H), 1.9 (s, 3H, $CH_3$), 2.4 (d, 2H, allylic $CH_2$), 4.4 (m, 1H, CH-N), 4.9 (s, 2H, olefinic), 6.1 (d, 1H, NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium, NH), 5.9 (strong, amide).

Anal. Calcd. for $C_{17}H_{25}NO$: C 78.72; H 9.71; N 5.40. Found: C 78.87; H 9.82; N 5.35.

7. N-benzoyl-4-amino-2,2-dimethyl-1-octene (p 45) (from N-hexylsulfinylamine and 1-chloro-3-methyl-2-butene) melting point: 96.0°-96.5°; pmr ($CDCl_3$)δ 0.6-2.0 (complex multiplet including a singlet, 17H), 4.2 (m, 1H, CH-N), 4.9-6.3 (complex multiplet, 3H, olefinic), 6.5 (d, 1H, NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{18}H_{27}NO$: C 79.07; H 9.95; N 5.12. Found: C 78.95; H 10.09; N 4.82.

8. N-benzoyl-4-amino-2-decanone (p 49) (from N-hexylsulfinylamine and methyl vinyl ketone) melting point: 98.0°-98.5°; pmr ($CDCl_3$)δ 0.8-1.8 (complex multiplet, 11H), 2.0 (t, 2H, $CH_2$-C-N), 2.1 (s, 3H, $CH_3$), 2.6 (t, 2H, $CH_2$-C=O), 4.1 (m, 1H, CH-N), 6.4 (d, 1H, NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (weak, NH), 5.8 (medium, C=O), 6.0 (strong, amide).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C 74.14; H 9.15; N 5.09. Found: C 74.13; H 9.28; N 5.00.

9. N-benzoyl-1-amino-1-(2-propenyl)cyclohexane (p 41) (from N-sulfinylcyclohexylamine and allyl bromide) melting point: 84.5°-85.5°; pmr ($CDCl_3$)δ 1.3-2.6 (complex multiplet, 10H), 2.9 (d, 2H, allylic $CH_2$), 4.9-6.2 (complex multiplet, 4H, olefinic and NH), 7.4 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (weak, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{16}H_{21}NO$: C 78.97; H 8.70; N 5.76. Found: C 79.12; H 8.67; N 5.58.

10. N-benzoyl-1-amino-1-(2-methyl-2-propenyl)cyclohexane (p 41) (from N-sulfinylcyclohexylamine and methallyl chloride) melting point: 118.8°-119.5°; pmr ($CDCl_3$)δ 1.4-2.6 (complex multiplet including singlet at 1.9, 13H), 2.9 (s, 2H, allylic $CH_2$), 4.9 (d, 2H, olefinic), 6.0 (s, 1H, NH), 7.6 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (medium, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{17}H_{23}NO$: C 79.33; H 9.01; N 5.44. Found: C 79.35; H 9.06; N 5.43.

11. N-benzoyl-1-amino-1-(2,2-dimethyl-2-propenyl)cyclohexane (p 45) (from N-cyclohexylsulfinylamine and 1-chloro-3-methyl-2-butene) melting point: 83.5°-85.0°; pmr ($CDCl_3$)δ 1.0-2.8 (complex multiplet containing singlet at 1.0, 16H), 4.9-6.4 (complex multiplet including singlet at 5.5, 5H, olefinic and NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (weak, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{18}H_{25}NO$: C 79.66; H 9.28; N 5.16. Found: C 79.83; H 9.62; N 5.06.

12. N-benzoyl-1-amino-1-(2-propenyl)-4-(1,1-dimethylethyl)-cyclohexane (p 54) (from 4-t-butylcyclohexyl-N-sulfinylamine and allyl bromide) melting point: 104.5°-106.0°; pmr ($CDCl_3$)δ 0.9 (s, 9H, t-butyl), 1.0-2.9 (complex multiplet, 9H), 4.9-6.2 (complex multiplet, 4H, olefinic and NH), 7.5 (complex multiplet, 5H, aromatic): Ir ($CCl_4$)μ 3.0 (weak, NH), 6.0 (strong, amide).

Anal. Calcd. for $C_{20}H_{29}NO$: C 80.22; H 9.76; N 4.68. Found C 79.97; H 9.80; N 4.52.

## F. 1-AMINO-4-(1,1-DIMETHYLETHYL)-CYCLOHEXANE (39 and 41) (p 54)

A mixture of 50 g of 4-t-butylcyclohexanone,[94] 50 g of hydroxylamine hydrochloride, 250 ml of pyridine, and 250 ml of ethanol was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and the solvents were removed by rotatory evaporation. The residue was recrystallized from 95% ethanol to yield the oxime (47 g, 88%). The oxime was dissolved in 125 ml of methanol, and to this solution was added 6.3 g of 5% rhodium-on-alumina. This mixture was subjected to atmospheric pressure hydrogenation, to give after filtration, removal of the solvent, and distillation, 18 g (0.11 mole) of 4-t-butylcyclohexylamine; bp 80°-85° (0.05 mm Hg).

## G. ALTERNATE PREPARATION OF N-BENZOYL-5-AMINO-2-OCTANONE (36) (p 49)[86]

To a solution of 19 g (0.186 mole) of 1-nitrobutane[85] and 10 ml of diisopropylamine in 200 ml of chloroform was added dropwise 7 g of methyl vinyl ketone. After three hours, another portion of the ketone (7 g) was added, and the reaction mixture stirred for 24 hours. The solution was washed with 100 ml of water, 100 ml of 10% hydrochloric acid, 100 ml of saturated sodium bicarbonate, and 50 ml of saturated brine. The organic layer was dried with magnesium sulfate, and the solvent was removed by rotatory evaporation. The residue was dissolved in 50 ml of benzene, to which was added 11.5 g (0.186 mole) of ethylene glycol and a trace of p-toluenesulfonic acid. This mixture was refluxed overnight

in a flask equipped with a Dean-Stark trap. After cooling the solution to room temperature, the solvent was removed by rotatory evaporation. The residue was dissolved in 50 ml of dry THF, and this solution was added very slowly to a mixture of 5 g of lithium aluminum hydride in 50 ml of dry THF. Excess hydride was destroyed by the addition of saturated potassium hydroxide to the reaction mixture, after the reaction was stirred for one hour. The reaction mixture was filtered, made slightly acidic and then slightly basic. It was extracted three times with anhydrous ether, benzoylated and chromatographed in the usual manner to give 3 g (0.012 mole) of N-benzoyl-5-amino-2-octanone. This material was spectroscopically and chromatographically identical with that prepared by alkylation of the N-sulfinylamine.

## H. PREPARATION OF INTERMEDIATE BY AN ALTERNATE METHOD

To a cooled (0°) solution of 11.8 g (0.082 mole) of allylmagnesium bromide in 50 ml of ether was added dropwise 11.9 g (0.082 mole) of N-hexylsulfinylamine. After stirring at 0° for thirty minutes, the reaction mixture was refluxed for one hour. After cooling it to room temperature, the reaction was quenched with ice cold half-saturated sodium bicarbonate. After extraction of the aqueous layer with two portions of 50 ml of methylene chloride, the combined organic layers were dried with potassium carbonate and the solvent removed by rotatory evaporation to yield 6.03 g (0.037 mole, 45%) of the sulfinamide. This substance was dissolved in 10 ml of THF, to which was added 1.54 g (0.037 mole) of a 54% dispersion-in-oil of sodium hydride. When the gas

evolution ceased, another 35 ml of THF was added, followed by 6.5 g (0.037 mole) of N-bromosuccinimide. After stirring the solution for 30 minutes, another equivalent of N-bromosuccinimide was added. After the reaction had proceeded for one hour at room temperature, it was quenched by the addition of 50 ml of 5% hydrochloric acid. After extraction of the aqueous layer with 50 ml of ligroin, it was made basic (pH greater than 10) with 10% sodium hydroxide and extracted three times with anhydrous ether. The organic layer was dried with magnesium sulfate, and to it was added 4.4 ml of benzoyl chloride and 5.1 ml of triethylamine. After stirring this solution for 1 hour at room temperature, it was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water and 50 ml of saturated brine. The solution was dried with magnesium sulfate, and the solvent was removed by rotatory evaporation. The residue was chromatographed on alumina with benzene as the eluent to provide 300 mg (0.0013 mole, 4%) of N-benzoyl-4-amino-1-nonene.

### I. 1-CYANO-1-(2-PROPENYL)-4-(1,1-DIMETHYLETHYL)-CYCLOHEXANE (47) (p 56)[89]

To a solution of 45 g (0.28 mole) of 4-t-butyl-1-cyano-1-cyclohexene, prepared according to the method of Abramovitch,[91] in 500 ml of methanol was added 3 g of 5% palladium-on-carbon. Hydrogenation of this mixture at atmospheric pressure was followed by filtration and removal of the solvent by rotatory evaporation. Distillation of the residue provided 39 g (0.23 mole, 82%) of 4-t-butyl-1-cyanocyclohexane (bp 80°-85° at 0.5 mm Hg).

To a cold (-30°) solution of lithium diisopropylamide in 100 ml of DME, from 11.4 grams of diisopropylamine and 0.12 moles of butyllithium, was added a solution of 15 g (0.09 mole) of the cyano compound in 30 ml of DME. The resulting mixture was stirred for 20 hours, after which 14.5 g (0.12 mole) of allyl bromide was added. After the reaction mixture had been stirred at room temperature for 24 hours, it was partitioned between ether and water. The organic layer was dried with magnesium sulfate, concentrated, and distilled to give 13.0 g (70%) of the alkylated nitrile (bp 85°-90°, 0.5 mm Hg).

## J. 1-AMINO-1-PROPYL-4-(1,1-DIMETHYLETHYL)-CYCLOHEXANE

To a solution of 10 g (0.046 mole) of 1-allyl-1-cyano-4-t-butylcyclohexane in 75 ml of methanol was added 1 g of 5% palladium-on-carbon. Atmospheric hydrogenation of this mixture, followed by filtration, removal of the solvent and distillation gave 8.8 g (0.040 mole, 87%) of 1-propyl-1-cyano-4-t-butylcyclohexane.

A solution of 8 g (0.037 mole) of the nitrile in 30 ml of 95% ethanol was added to a mixture of 15 ml of 30% hydrogen peroxide and 1.5 ml of 6 M sodium hydroxide.[95] This mixture was heated at 50° for five hours. Removal of most of the solvent by rotatory evaporation was followed by extraction of the residue with two 50 ml portions of ether. The organic layer was dried with magnesium sulfate and concentrated. Column chromatography of the residue on alumina with ether as the eluent gave 6.2 g (0.026 mole, 70%) of the amide.

To a solution of 0.23 g (0.01 mole) of sodium in 50 ml of methanol at -78° was added 0.8 g (0.005 mole) of bromine. After disappearance of the brown color, a solution of 1.12 g (0.005 mole) of the amide was added dropwise. After stirring at -78° for 30 minutes, the cold bath was removed and the reaction mixture was heated to about 50° with a water bath. After one hour, 5 ml of glacial acetic acid was added to the mixture and the solvent removed by rotatory evaporation. The residue was dissolved in 50 ml of ether and extracted with 50 ml of water and 50 ml of saturated brine. The solution was dried with magnesium sulfate and the solvent removed to provide 0.97 g (0.004 mole, 80%) of 1-carbamoyl-1-propyl-4-(1,1-dimethylethyl)-cyclohexane.

This was dissolved in 50 ml of ethylene glycol and 5 ml of concentrated hydrochloric acid. The mixture was heated to 100° for 2 days. After cooling the solution, the solvent was removed under reduced pressure. The residue was dissolved in 50 ml of water. After making the aqueous layer basic (pH greater than 10), it was extracted three times with 50 ml of anhydrous ether. The ether layers were combined and dried with magnesium sulfate, and to the solution was added 0.004 mole of benzoyl chloride and triethylamine. After the reaction mixture was stirred for 1 hour, it was extracted with 50 ml of 5% hydrochloric acid, 50 ml of water, and 50 ml of saturated brine. The organic layer was dried and the solvent removed to give 0.73 g (0.0027 mole, 67%) of N-benzoyl-1-propyl-4-(1,1-dimethylethyl)-cyclohexane. This substance was identical to the material prepared by atmospheric pressure hydrogenation of the alkylated 4-t-butylcyclohexylamine.

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# APPENDIXES

# APPENDIX I

## PROTON MAGNETIC SPECTRA

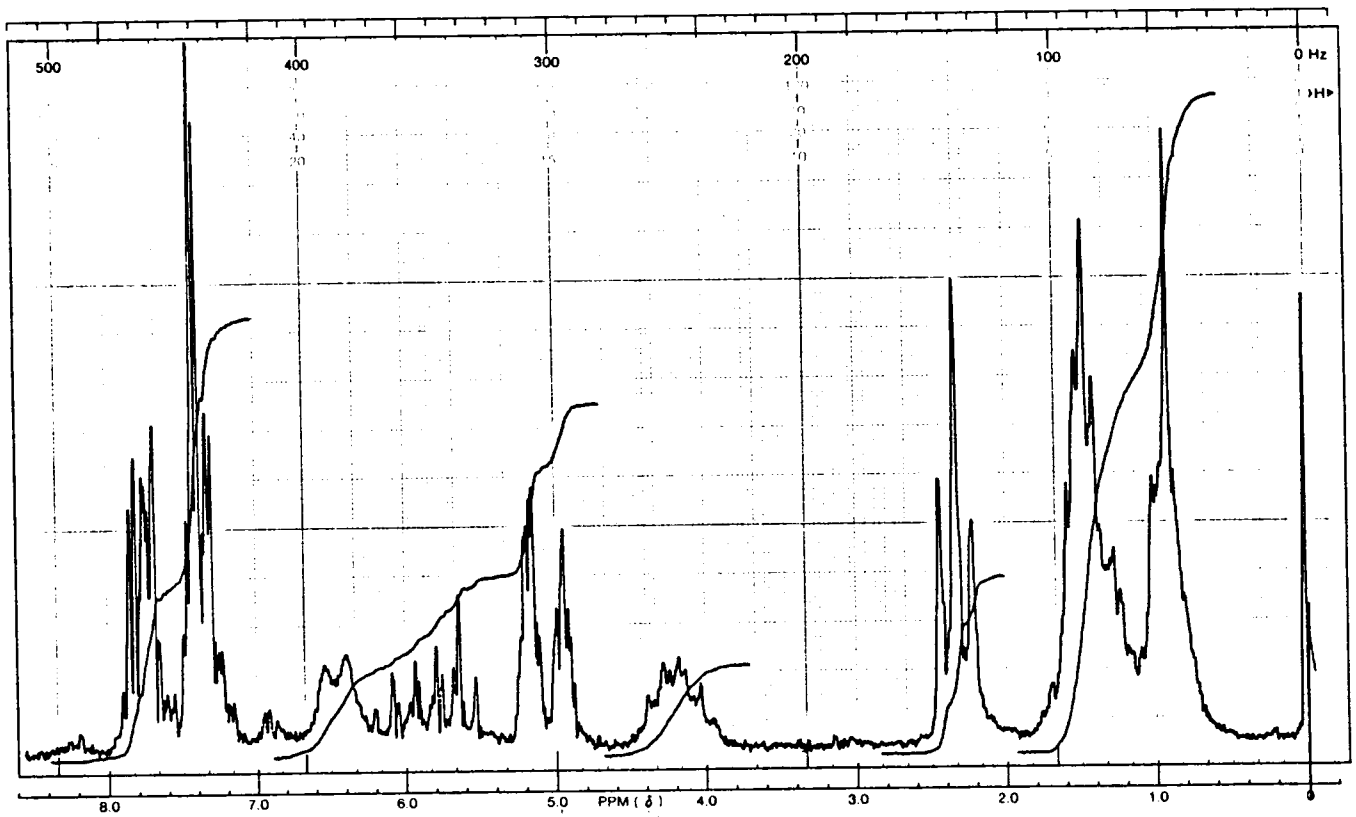



Figure 1. Proton magnetic resonance spectrum of N-benzoyl-4-amino-1-heptene, compound 23.

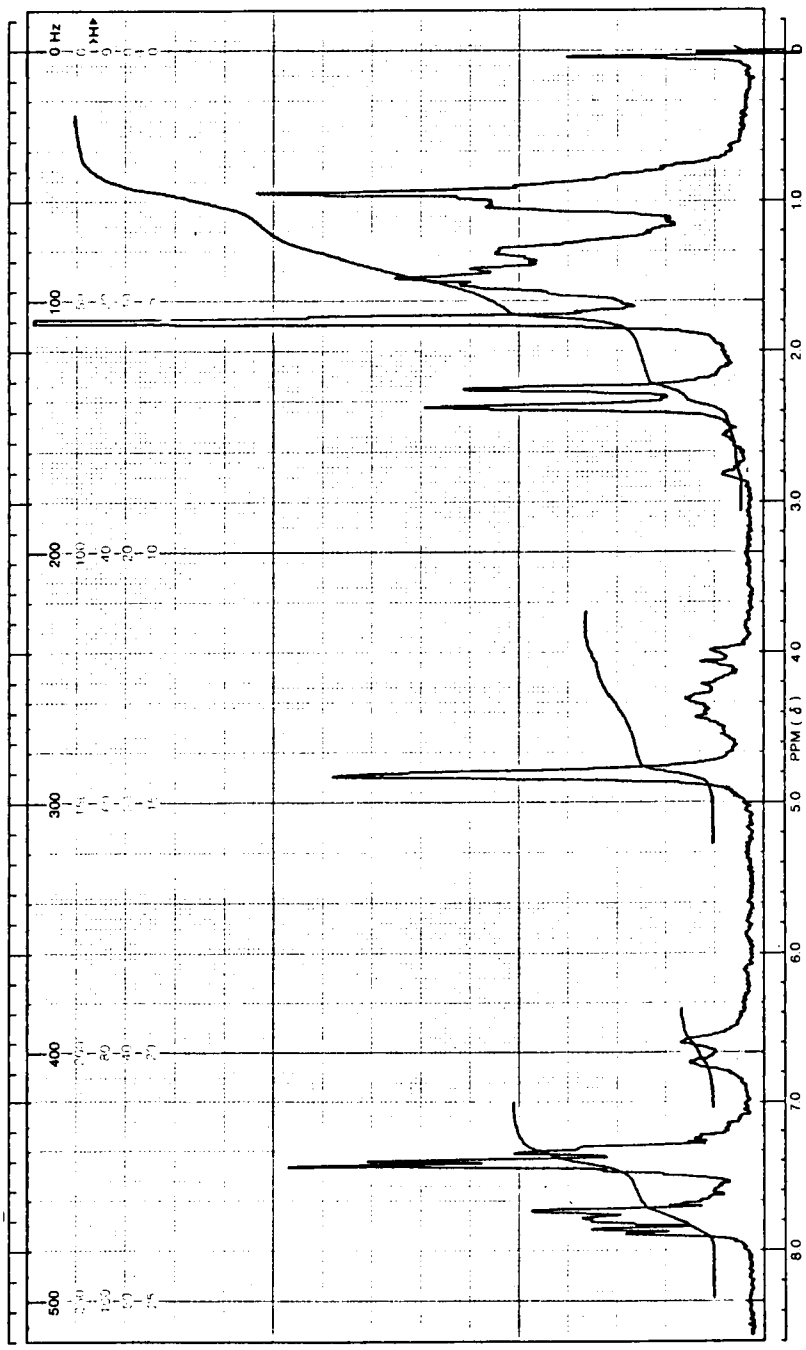



Figure 2. Proton magnetic resonance spectrum of N-benzoyl-4-amino-2-methyl-1-heptene, compound 24.

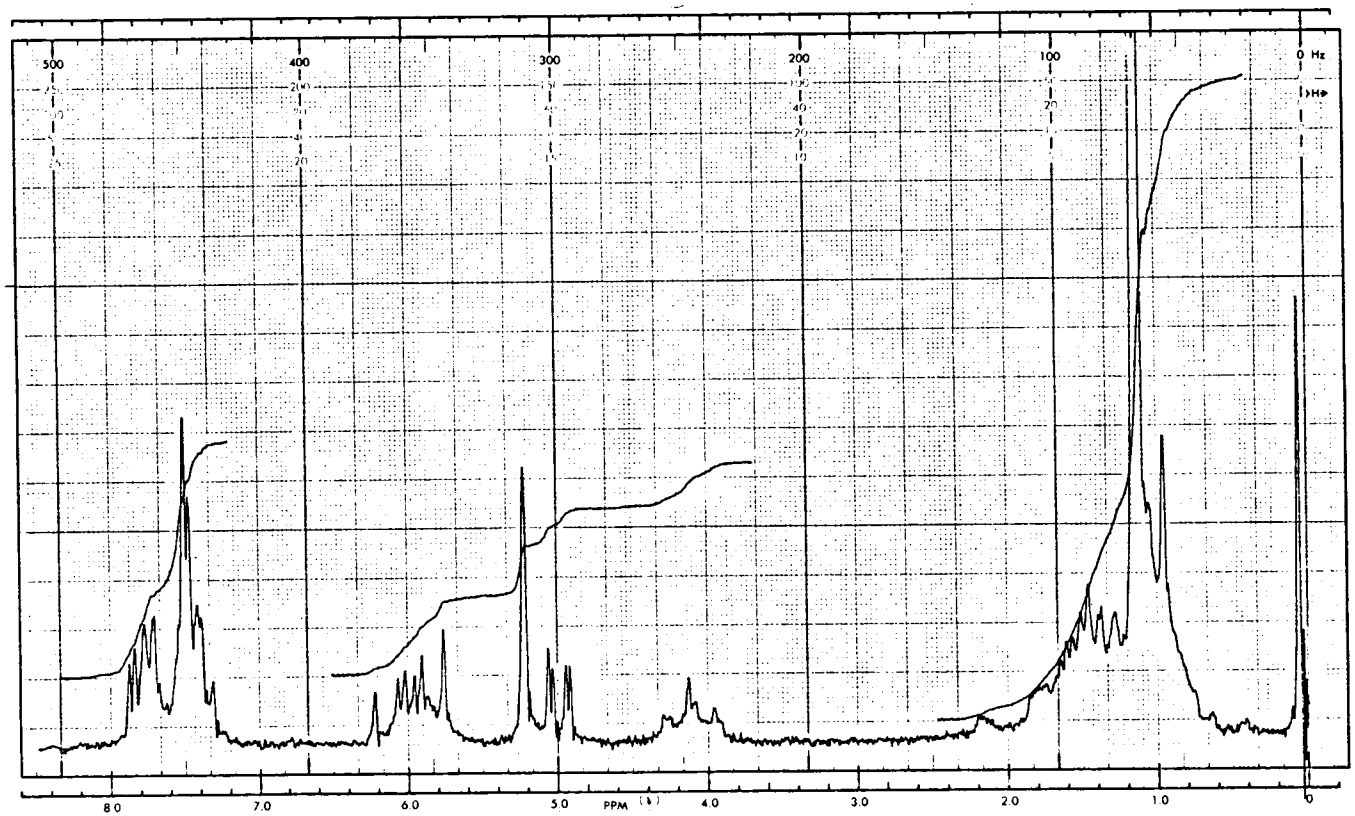



Figure 3. Proton magnetic resonance spectrum of N-benzoyl-4-amino-2,2-dimethyl-1-heptene, compound 30.

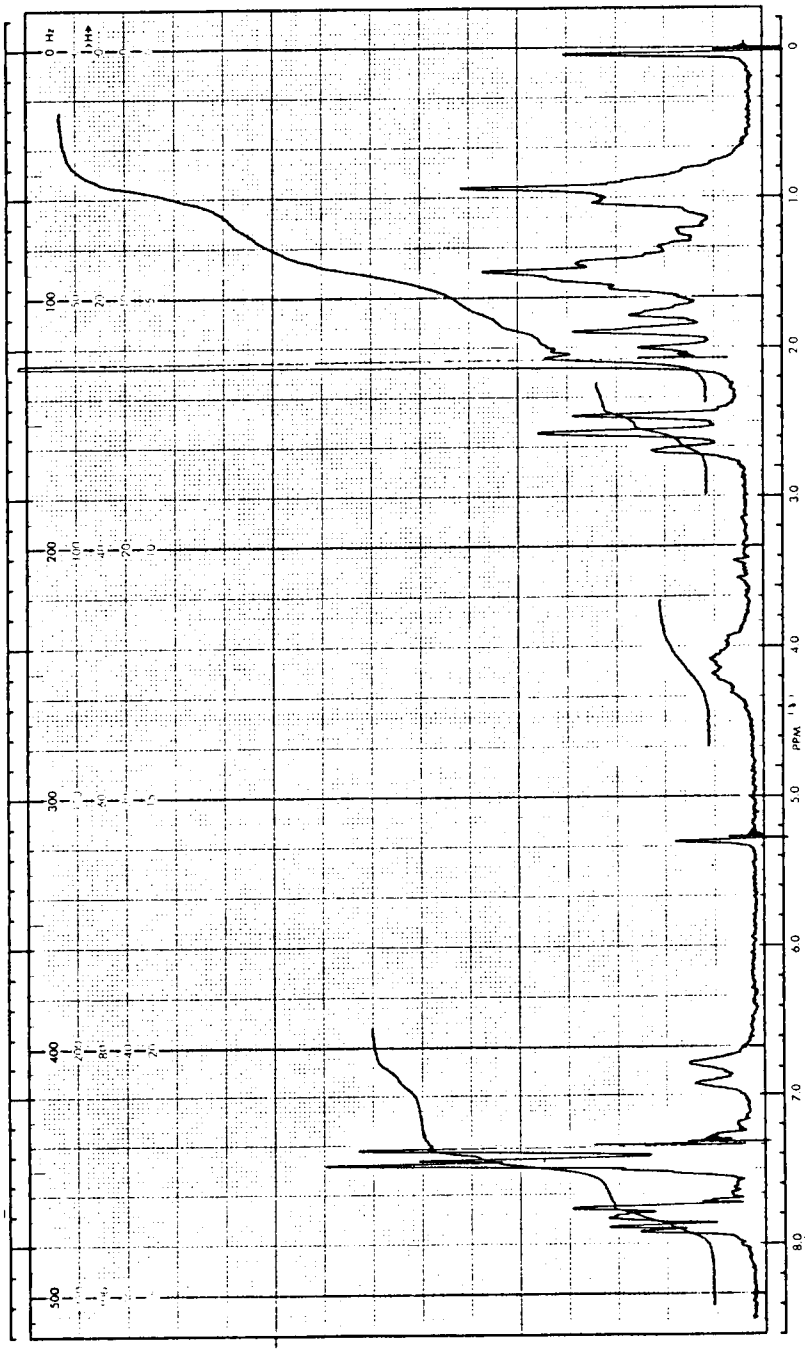



Figure 4. Proton magnetic resonance spectrum of N-benzoyl-5-amino-2-octanone, compound 36.

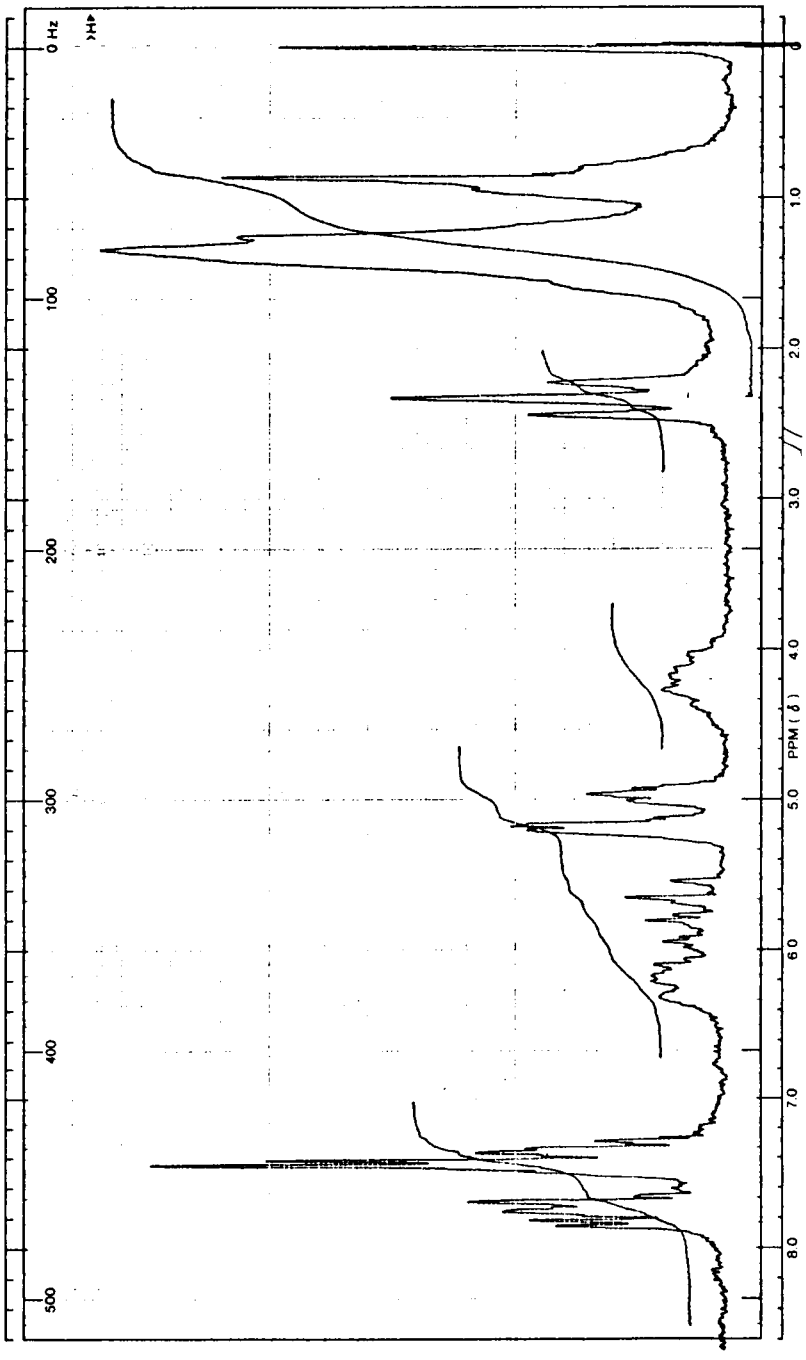



Figure 5. Proton magnetic resonance spectrum of N-benzoyl-4-amino-1-nonene, compound 25.

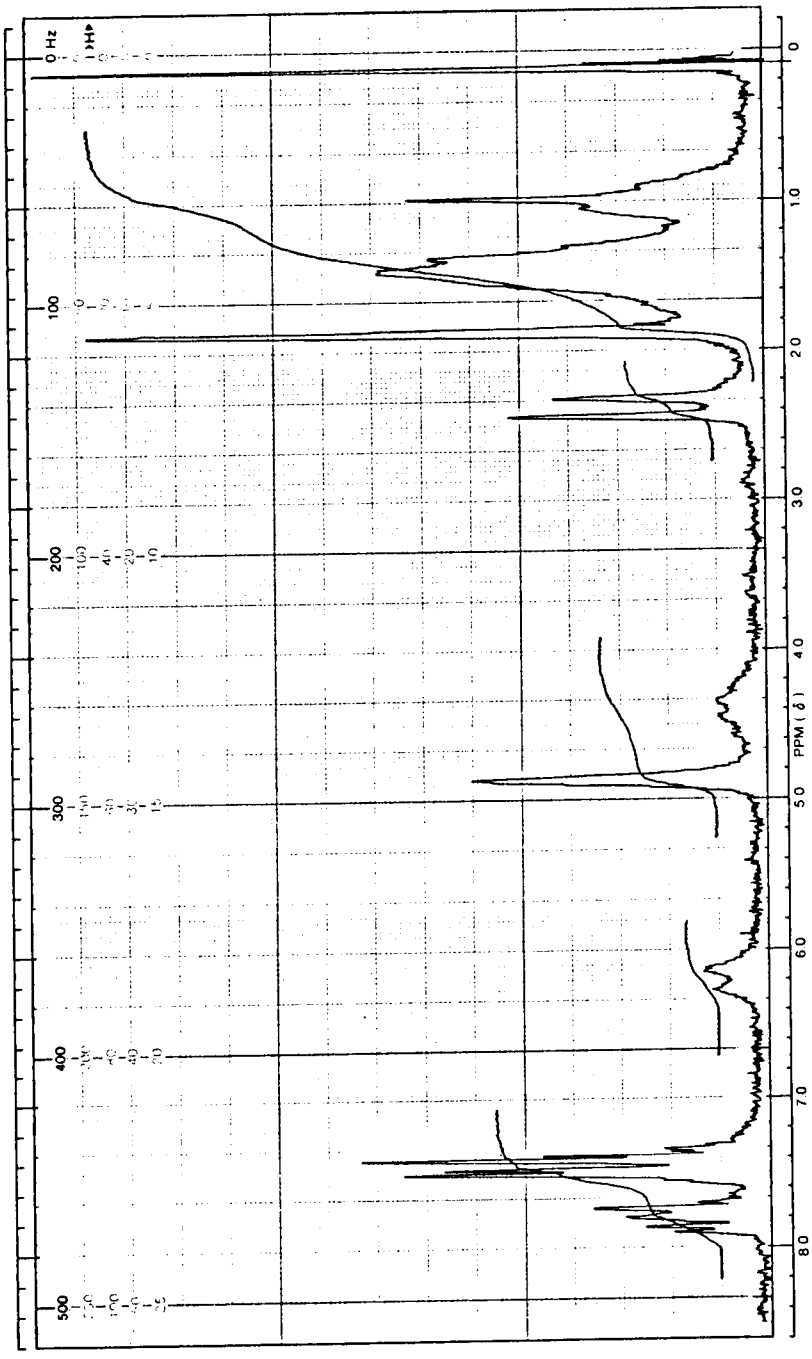



Figure 6. Proton magnetic resonance spectrum of N-benzoyl-4-amino-2-methyl-1-nonene, compound 26.

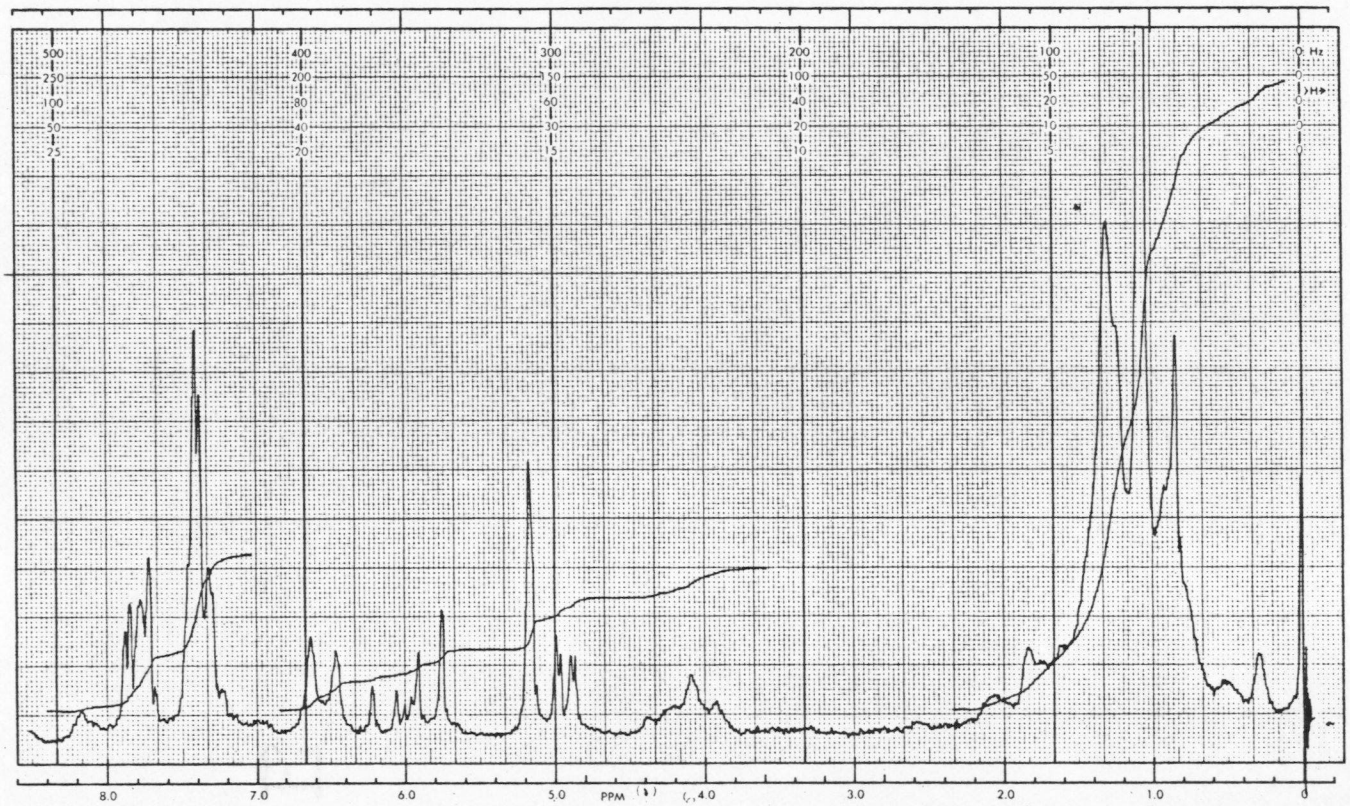



Figure 7. Proton magnetic resonance spectrum of N-benzoyl-4-amino-3,3-dimethyl-1-nonene, compound 31.

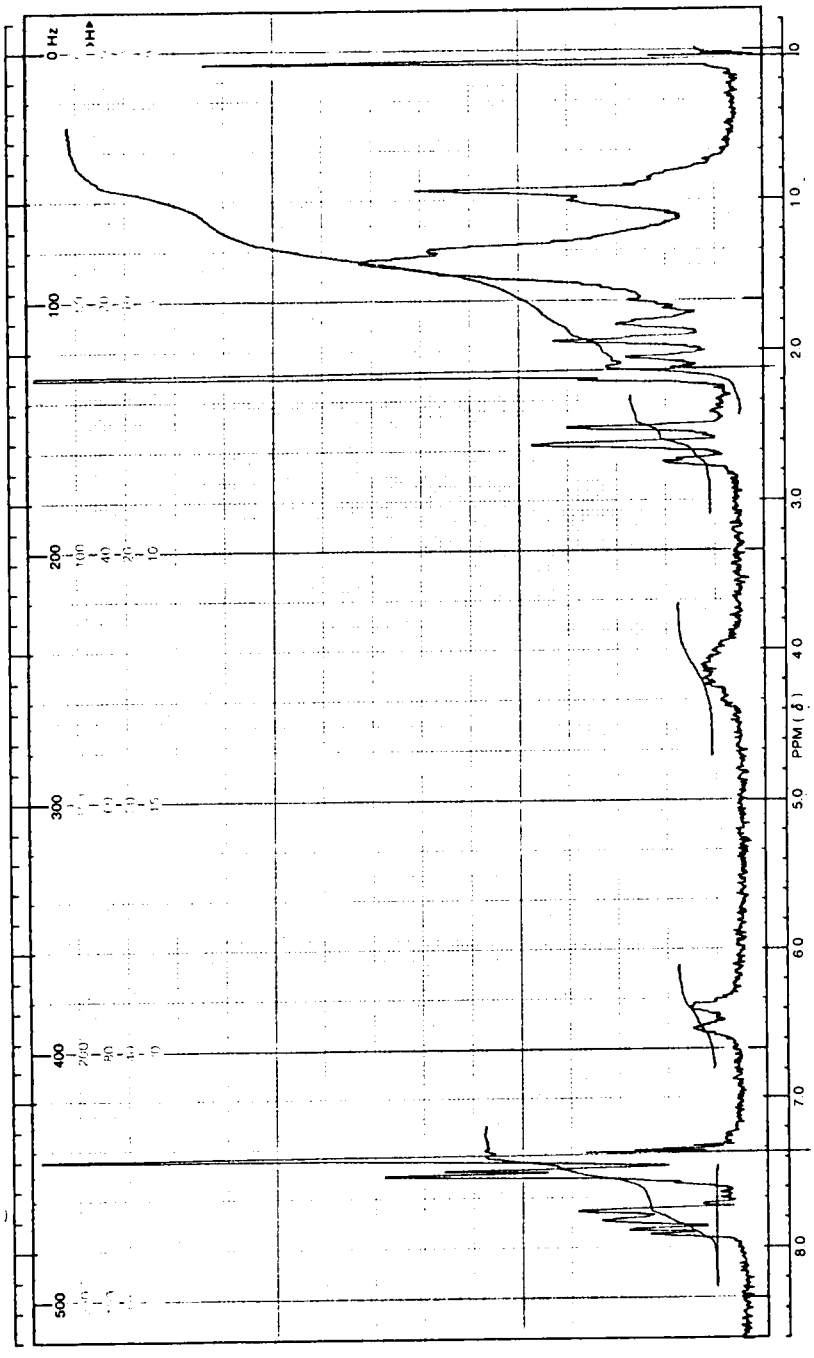



Figure 8. Proton magnetic resonance spectrum of N-benzoyl-5-amino-2-decanone, compound 37.

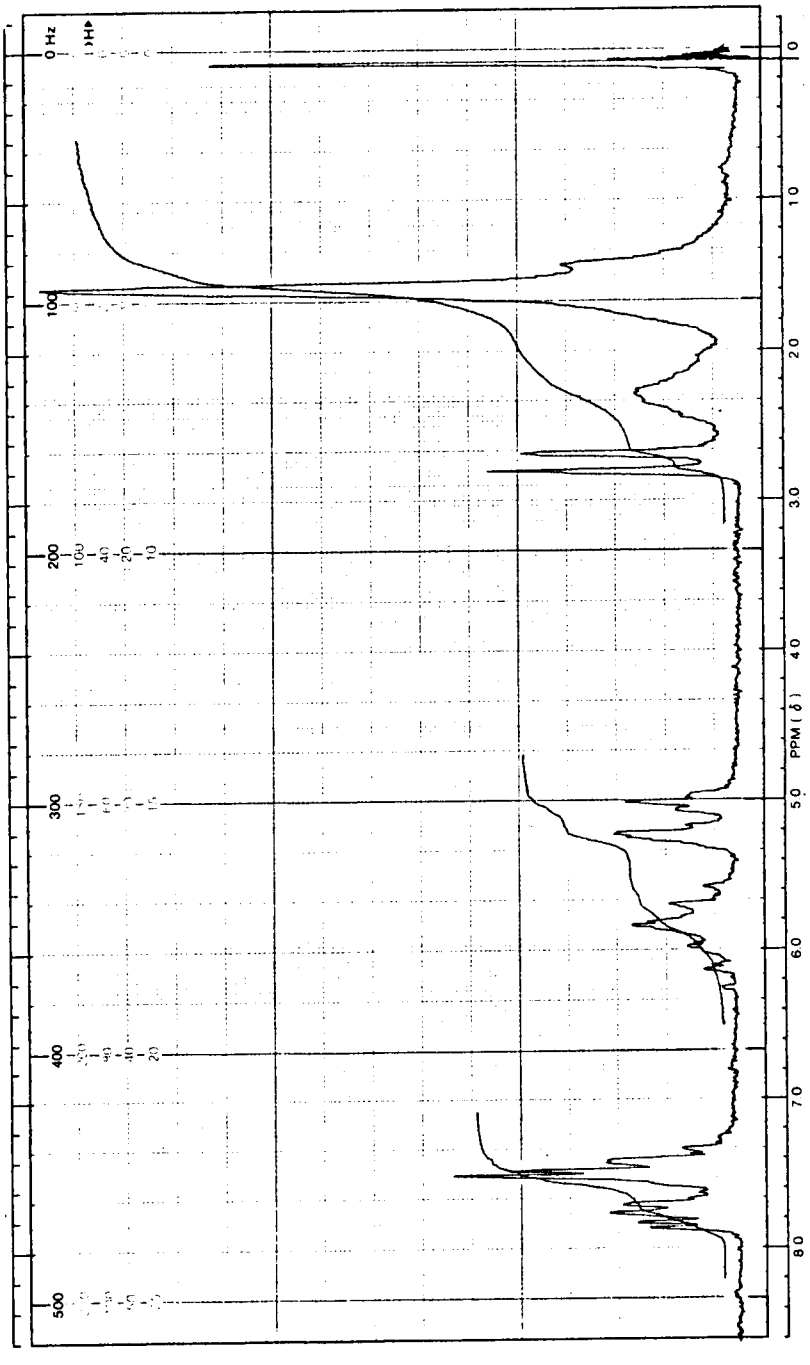



Figure 9. Proton magnetic resonance spectrum of N-benzoyl-1-amino-1-(2-propenyl)-cyclohexane, compound 27.

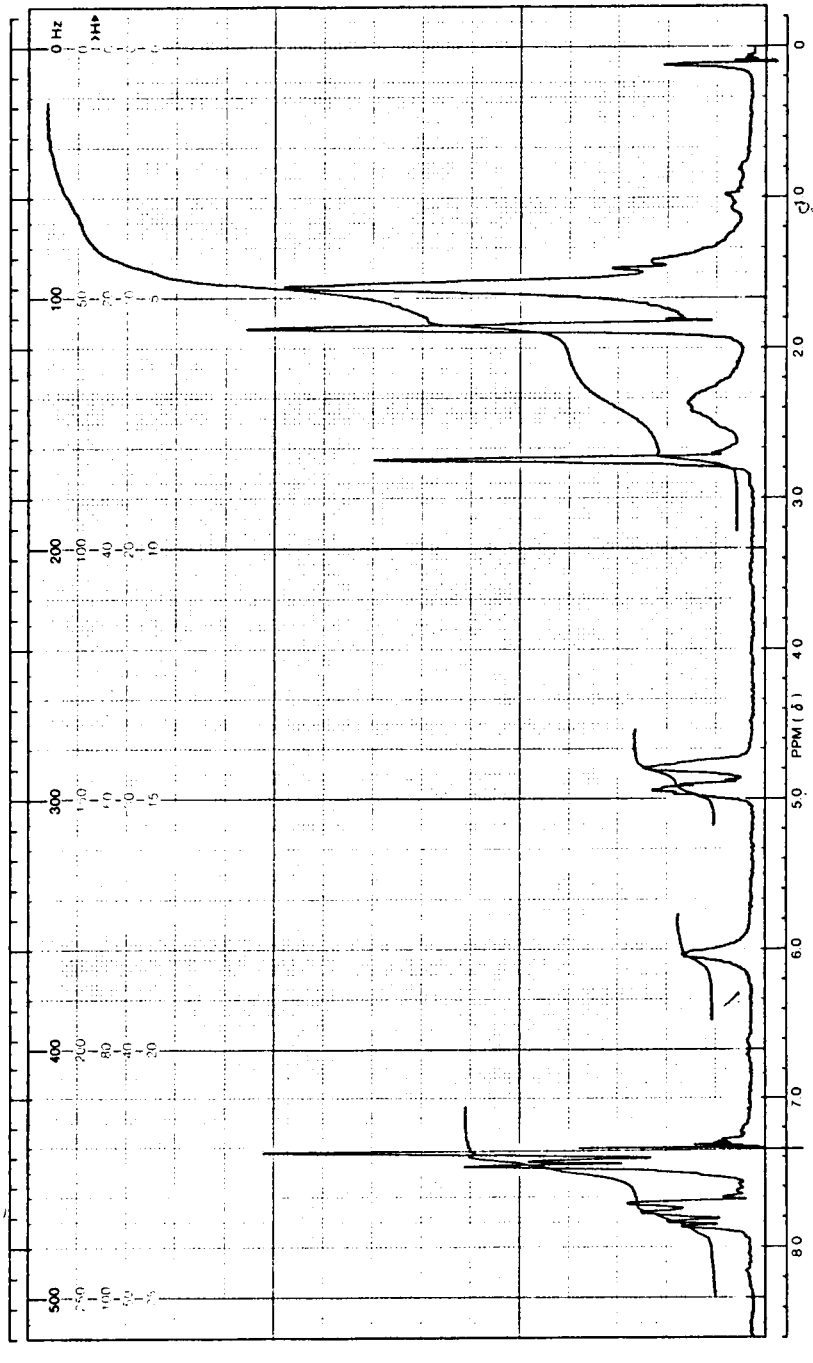



Figure 10. Proton magnetic resonance spectrum of N-benzoyl-1-amino-1-(2-methyl-2-propenyl)-cyclohexane, compound 28.

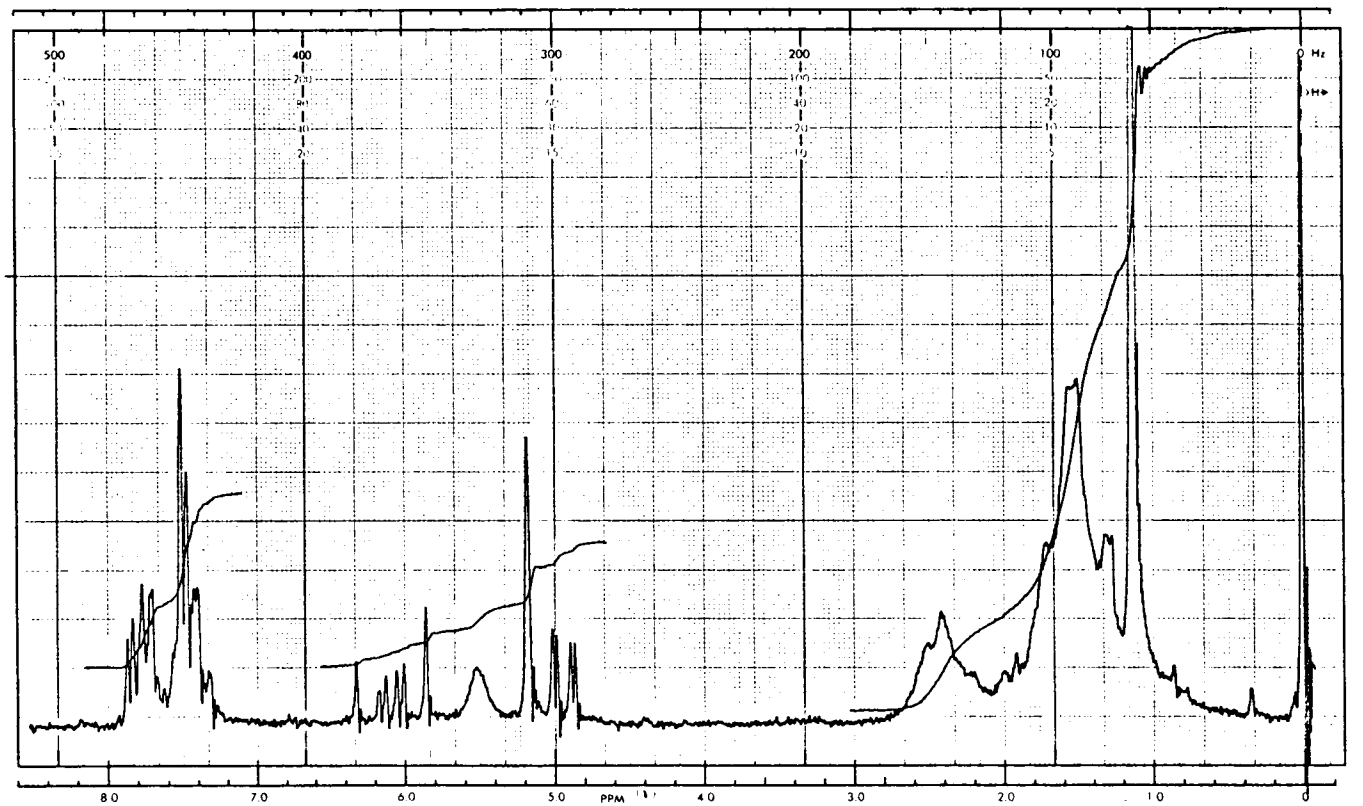



Figure 11. Proton magnetic resonance spectrum of N-benzoyl-1-amino-1-(1,1-dimethyl-2-propenyl)-cyclohexane, compound 32.

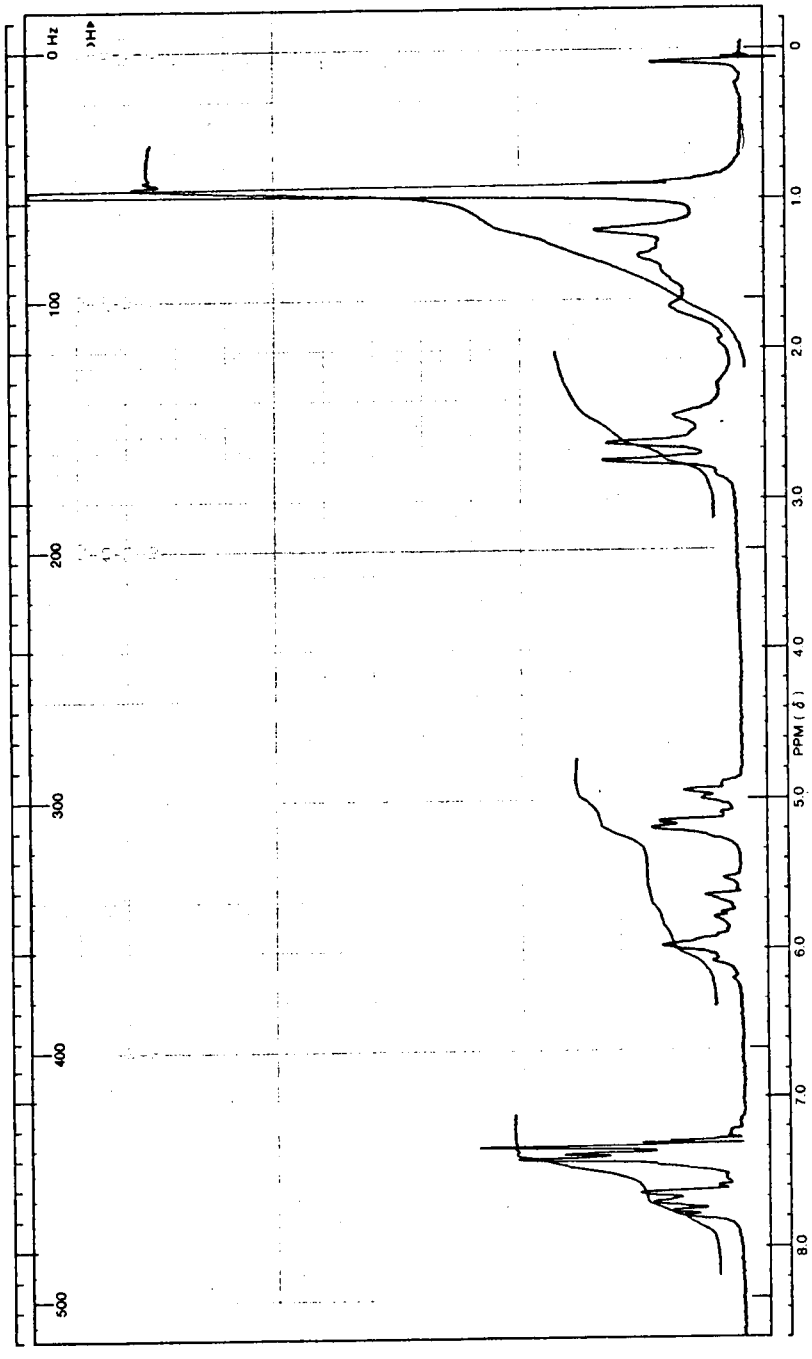
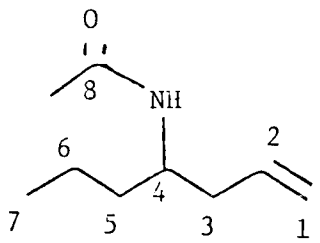



Figure 12. Proton magnetic resonance spectrum of N-benzoyl-1-amino-1-(2-propenyl)-4-(1,1-dimethylethyl)-cyclohexane, compound 44.

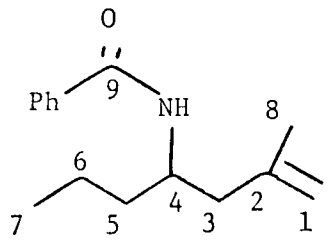
# APPENDIX II

## CARBON-13 MAGNETIC RESONANCE SPECTRA

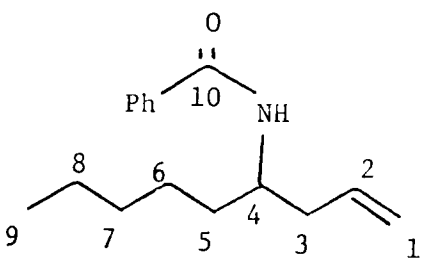
The carbon-13 magnetic resonance spectral assignments can be obtained by referring to the numbered structures below and to Table VI, p 103.



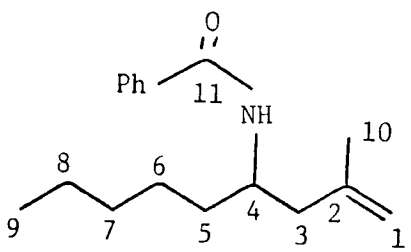

Compound 23



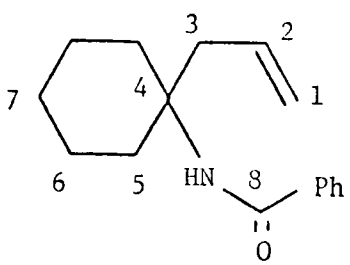

Compound 24



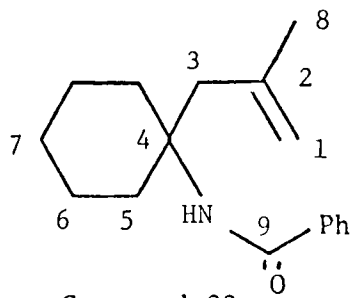

Compound 25



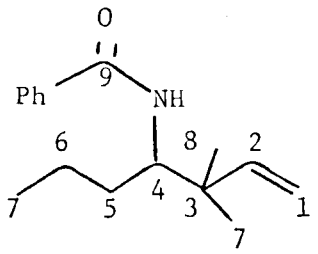

Compound 26



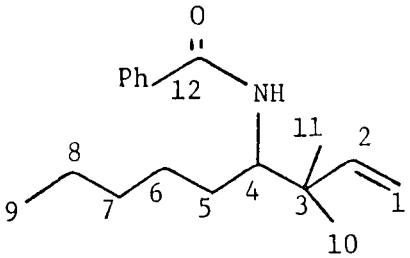

Compound 27



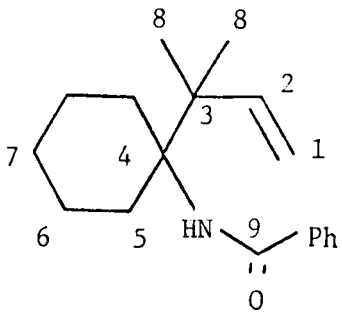

Compound 28



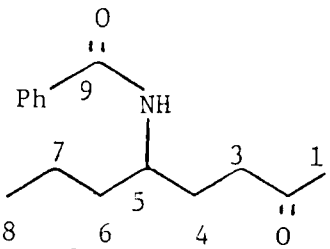

Compound 30



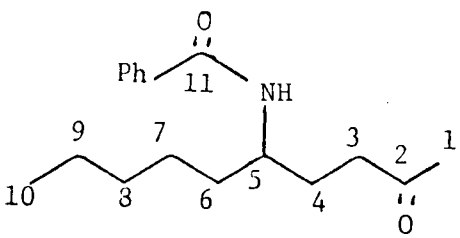

Compound 31



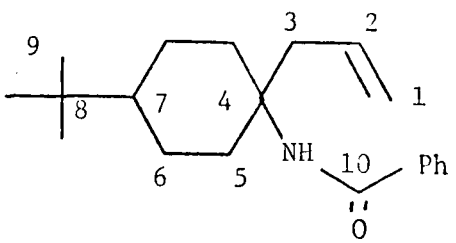

Compound 32




Compound 36




Compound 37




Compound 44

TABLE VI

CARBON-13 MAGNETIC RESONANCE SPECTRAL DATA

| Compound Number | Carbon-13 Shift[a] for Carbon Number | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Aromatic |
| 23 | 117.5 | 134.3 | 39.1 | 48.7 | 36.2 | 19.1 | 13.8 | 166.9 | | | | | 126.7, 128.3, 130.9, 134.4 |
| 24 | 112.0 | 142.1 | 43.0 | 47.1 | 36.5 | 18.7 | 13.3 | 21.6 | 166.7 | | | | 126.6, 127.4, 130.1, 134.6 |
| 30 | 112.7 | 144.6 | 40.9 | 56.3 | 32.4 | 19.7 | 13.6 | 24.7 | 22.6 | 167.1 | | | 126.5, 128.1, 130.7, 134.8 |
| 36 | 29.6 | 208.7 | 40.0 | 37.4 | 49.1 | 28.3 | 18.3 | 13.6 | 166.6 | | | | 126.6, 128.0 130.9, 134.4 |
| 23 | 117.3 | 134.4 | 38.9 | 48.9 | 31.4 | 25.4 | 29.4 | 22.2 | 13.7 | 166.8 | | | 126.7, 128.1, 130.8, 134.8 |
| 26 | 112.8 | 142.6 | 43.6 | 47.6 | 35.0 | 25.4 | 31.6 | 21.0 | 13.7 | 21.3 | nob | | 126.6, 128.3, 130.9, nob |
| 31 | 112.4 | 144.6 | 40.9 | 56.5 | 31.3 | 26.1 | 30.0 | 27.1 | 13.6 | 22.5 | 24.6 | 167.2 | 125.5, 127.9, 130.6, 134.8 |
| 37 | 29.8 | 208.9 | 40.2 | 35.4 | 49.6 | 31.5 | 25.4 | 28.4 | 22.2 | 13.7 | 167.0 | | 126.6, 128.2, 131.0, 134.5 |
| 27 | 118.1 | 133.9 | 42.2 | 56.2 | 38.4 | 22.0 | 25.8 | 167.1 | | | | | 126.7, 128.5, 130.9, 136.4 |
| 28 | 114.8 | 142.0 | 45.0 | 56.1 | 35.1 | 21.8 | 25.6 | 24.8 | 166.9 | | | | 126.5, 128.4, 130.9, 136.2 |

TABLE VI (continued)

| Compound Number | Carbon-13 Shift[a] for Carbon Number | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Aromatic |
| 32 | 112.9 | 144.9 | 45.2 | 62.4 | 30.1 | 22.3 | 25.3 | 22.6 | 167.1 | | | | 126.3, 128.3, 130.7, 136.7 |
| 44 | 117.6 | 133.6 | 43.2 | 55.4 | 34.6 | 22.3 | 47.3 | 32.0 | 27.1 | 166.8 | | | 126.4, 128.0, 130.5, 136.0 |

[a]In parts per million downfield from tetramethylsilane.

nob: not observed.

# VITA

John Paul Carter was born in Charlottesville, Virginia, on July 23, 1951. With his parents, he moved to Chattanooga, Tennessee, three years later. There he attended elementary school and McCallie School. After graduation he entered Hamilton College and remained there for three years until the death of his father in 1972. He returned to Chattanooga, and in 1973 he was graduated from the University of Tennessee at Chattanooga.

He entered graduate school at the University of Tennessee in June, 1973, and remained there for a number of years. During this time, he was educated as a scientist and in other areas. In March, 1977, he took his first wife, the former Pamela Reid.

His future occupation and location are unknown as of this time.