DILITHIATION REACTIONS OF N-SUBSTITUTED BENZYLAMINES

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DILITHIATION REACTIONS OF N-SUBSTITUTED BENZYLAMINES

Thesis
Submitted in Partial Fulfillment
for Honors in Chemistry

by
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ABSTRACT

N-Cyclohexyl-2-methylbenzylamine was metalated with two equivalents of \(\gamma\)-butyllithium activated with one equivalent of tetramethylethylenediamine (T.M.E.D.A.), and the solvent system, time, and temperature were varied to establish a maximum yield. It was experimentally found that a thirty minute ice-water bath metalation in diethyl ether, followed by a fifteen minute condensation with benzophenone in refluxing diethyl ether gave the best yield with the benzophenone electrophile. The product was characterized by N.M.R. and found to be 2-(cyclohexylamino)-2-(2-toluyl)-1,1-diphenylethanol (the benzylic adduct) in a 29% yield.

When N-cyclohexyl-2-methylbenzylamine was metalated for three hours in an ice-water bath using diethyl ether as the solvent, then condensed with excess dry ice, two products were isolated with near quantitative total yield. While the products were not amiable to characterization by melt point or N.M.R. it was assumed that they are amino acids. It is also possible that the two products are different salts of the same amino acid.

N-(2-toluyl)-benzylamine was metalated with two equivalents of \(\gamma\)-butyllithium activated with one equivalent of T.M.E.D.A. and the solvent system, temperature, and time were varied to give the maximum yield of the benzophenone adduct. It was experimentally found that maximum yield occurred in diethyl ether with a thirty minute metalation in an ice-water bath, and fifteen minute condensation with benzophenone in refluxing diethyl ether. A
maximum yield of 69.2% of ether N-(2-tolyl-6-diphenyl-hydroxymethyl)-benzylamine, or N-(2-tolyl)-2-diphenyl-hydroxymethylbenzylamine, the (ortho-adducts) were obtained.

N-(2-tolyl)-benzylamine was metalated in hexane with two equivalents of o-butyllithium activated with one equivalent of T.M.E.D.A. for thirty minutes in an ice-water bath, then condensed with benzophenone at reflux for fifteen minutes. Two products were obtained that were not fully characterized, but 33% of the product appeared to be the ortho-adduct(s) and 67% of the product appeared to be 2-(2-amino-N-benzylphenyl)-1,1-diphenylethanol, the (side-chain adduct). With a combined overall yield of 32.8% of theoretical.
INTRODUCTION

The bonding of a metal atom to carbon has been an important route in producing carbanions [Fig-1]. In 1928, Gilman reported the first use of an organolithium compound to act as a metalating reagent. Gilman also reported the use of \( n \)-butyllithium [Fig-2] to metalate an aromatic ring in 1934.

\[
\begin{align*}
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Li}^+ \\
\end{align*}
\]

[Fig-2]

One of the earliest reports of the use of \( N,N,N',N' \)-tetramethylethylenediamine (T.M.E.D.A.) [Fig-3] as a catalyst for \( n \)-butyllithium was reported by Eberhardt and
Butte in 1964. Slocum and Jennings reported that n-butyllithium in solution existed as a hexamer or tetramer [Fig-4]. They reported that T.M.E.D.A. activated n-butyllithium existed as a monomer and proposed the following complex [Fig-5]. By the late sixties most investigators lithiating heterocyclic aromatics with n-butyllithium were testing their systems with T.M.E.D.A. activated n-butyllithium. Ludt, Slocum, and others reported both acceleration of the rate of metalation and changes in the regiospecificity.

Heterocyclic aromatic compounds are of interest because they show a high degree of regiospecific lithiation. In these systems, the aromatic carbon alpha to the hetero-atom is generally metalated. This is also true for phenyl systems, ferrocenes, and thiophenes with a hetero-atom.
substituent attached to the ring.

In the late sixties, Ludt found that he could synthesize the isoindolins by the following scheme [Fig-6]. From the results of the above reaction it was hypothesized that a similar method could be used to convert the ortho-methylbenzylamines to isoquindolines [Fig-7].

Since the side-chain hydrogens are 100 times more acidic than the ring hydrogens, it was believed that they would be the preferential reaction site. Experimentation showed that only when the methyl was ortho to the hetero-atom chain did the side-chain meta late. When the ortho-methylbenzylamine was N-substituted with benzene something unexpected happened. N-Phenyl-2-methylbenzylamine directed to the ortho-position instead of the side-chain at 0 to 5°C [Fig-8]. This
prompted a study of other "heavy" N-substituents to determine the nature of the change in directionality.

N-Cyclonexyl-2-methylbenzylamine [Fig-9a] and N-tertbutyl-2-methylbenzylamine [Fig-9b] were chosen for the above study.
2-methylbenzylamine [Fig-9b] were chosen for the above study because of their bulk and steric hinderance. Initially it was found that with T.M.E.D.A. activated n-butyllithium both compounds metalated on the side-chain [Fig. 10]. It was also found that N-phenyl-2-methylbenzylamine would metalate to the side-chain at 68°C [Fig. 11]. It was then believed that the
nature of change in directionality was caused by the aromaticity of the substituent. Ludt proposed that this change in the N-phenyl system was due to thermodynamic control vs kinetic control.

It was believed that T.M.E.D.A. activated n-butyllithium complexed with the hetero-atom and then reacted in an acid base controlled fashion. The exception to the rule was when the N-substituent was phenyl that the ortho position was then kinetically favored; and that it took higher temperatures to get the thermodynamically favored side-chain metalation. It was believed by some that the aromatic nature of N-phenyl substituent was the responsible factor in the exception. It was from this point that synthetic work in this project began.
DISCUSSION

Currently the main question in dilithiations is what are the controlling factors in regiospecificity? There are six factors which seem to hold the answers: acidities of the various hydrogens, the distance from the hetero-atom, the angle of the incoming lithium, the number of nuclei in the transition ring, inductive effect of each group, and steric considerations. None of these is the sole factor in regiospecificity but acts in cooperation with one or more of the other factors.

The relative acidities of the various potential reactive hydrogens are considered the main factor in regiospecificity. In benzylamine systems the hydrogen attached to the nitrogen atom has a pKa of 31, the next in acidity is on the side-chain with a pKa of 35, a factor of 10,000 times less acidic. Even if the acidity was a small factor in regiospecificity this magnitude would and does control the site of lithiation. However, when a second equivalent of lithium is introduced acidity is not always the sole directing factor. When phenyl and toluic substituted benzylamines are lithiated one can obtain side chain and/or ortho- metalation.

The pKa’s for the side-chain and ortho- hydrogens are 35 and 37 respectively. This is a difference in acidity of 100 fold. If acidity were the sole factor then the second equivalent of lithium would add to the side-chain exclusively. It has been found that this is not the case. Furthermore, when N-cyclohexyl-2-methyl-benzylamine is dilithiated the second lithium adds to the benzylic position. Clearly other factors are at work.
Postulations that the lithium in "butyllithium complexes with the hetero-atom before substitution were found in the literature in 1946. If this is the case, then how far from the hetero-atom can lithiation take place? Model studies of known lithiations were used to determine the following distances.

From a nitrogen hetero-atom the maximum distance that lithium is known to add is 3.7 Angstroms in the meta- addition to N,N-dimethylaniline [Fig. 12]. With the discovery of the benzylic addition in N-cyclohexyl-2-methylbenzylamine the minimum distance for lithiation becomes 1.4 Angstroms from the nitrogen atom [Fig. 13].

The angle at which the lithium ion is presented to the carbon with which it will eventually bond seems to have a small effect upon addition. Note the two cases above where the angle that a bond normally takes from the meta- position to its hydrogen is 150° from the angle that is inline with hetero-atom. For the benzylic adduct the angle is 109°. It is probable that there
is some spacing between the complexed lithium and the hetero-atom thereby reducing this angle. However, for positions such as meta- in aniline this would still create a heavy discrepancy [Fig. 14].

![Diagram of complexed lithium and hetero-atom](image1.png)

[Fig-14]

It has been postulated by Ludt\textsuperscript{27} and Maxwell\textsuperscript{28} that the number of atoms in the transition ring plays a role in determining the addition site [Fig. 15]. In part, this is believed to produce the proper bond angle when a six membered ring is formed, and there is a preference for six membered rings. It has been found experimentally that rings of 3, 4, 5, and 6 members are all found to occur in lithiations of nitro- substituted aromatics [Fig. 16]. The five membered ring formed in the
addition of lithium to the meta- position of dimethylaniline does not lead to a better bond angle that the four membered ring of the ortho- position. In the phenyl substituted benzylamines there is the possibility of six membered ring formation vs five membered ring formation in side-chain adduct vs ortho- adduct formation.

If the addition occurred on the ortho- position of the phenyl ring
the transition ring would be four membered. It was found that by varying the reaction conditions either the ortho-adduct or the side-chain adduct could be selectively synthesized. This indicates that the size of the transition ring is not a major factor in this reaction.

An inductive effect is established when ever electron donating or withdrawing groups are bound to benzene. When benzene is benzylamine substituted there is an increase in electron density ortho- and para- to the side-chain with a decrease in electron density meta- to the side chain [Fig. 17]. There is also a resonance stabilization effect that helps addition ortho- and para- to the side-chain. The activated lithium in n-butyllithium exists with a very strong positive character and would be drawn to the negative character. This could produce a competition between acid-base reaction and electrophilic substitution. One strong argument for this hypothesis is the regiospecificity reversal seen in lithiating N,N-dimethyl-4-methoxybenzylamine.

Slocum, Eook, and Jennings\textsuperscript{29} reported in 1970 that without T.M.E.D.A. N,N-dimethyl-4-methoxybenzylamine underwent metalation in predominately the ortho- position to the amine
side-chain. They found that when n-butyllithium was T.M.E.D.A. activated that metalation was predominately ortho- to the methoxy group. One possible explanation is that n-butyllithium activated with T.M.E.D.A. needs to find only one pair of electrons to complete an octet [Fig. 18]. The two non-bonded pairs of electrons associated with the oxygen in anisole could donate one pair for complexing with the lithium while the other could be involved in electron enrichment of the aromatic ring [Fig. 19].

With unactivated n-butyllithium all four electrons on the oxygen could be bound to the lithium leaving none to interact with the aromatic ring. This effect is also seen in ortho-tert-
butylanisole where without T.M.E.D.A. there is a radical reduction of product yield.\(^3\)

One of the most promising factors to explain changes in regiospecificity is steric hinderance. Regiospecific changes in N-substituted 2-methylbenzylamines show a high degree of correlation to the N-substituent. So far three sites have been identified as sites of lithiation, side-chain methyl, aromatic ring ortho, and benzylic [Fig-20]. When R is H, one can add

![Chemical structure](image)

[Fig-20]

lithium to any one of the three above mentioned sites by altering R'.

It has been well apparent that without T.M.E.D.A. lithiation of benzylamine substrates with n-butyllithium is a very slow process. With T.M.E.D.A. there is an acceleration, but it still must take time to complex, remove hydrogen, and add. During this time the molecule will move through a number of conformers. As the conformation changes it may alter or destroy the complex. To help visualize what might occur, model studies were
The model study of N-cyclohexyl-2-methylbenzylamine was quite revealing. Both the side-chain methyl and the ortho- carbon are frequently and grossly crowded [Fig-21]. There is a large number of conformers that will produce crowding in these two positions. The benzylic carbon on the other hand does not undergo this severe crowding. Only in one conformation does the benzylic carbon show any degree of crowding [Fig-22]. As can clearly be
seen there is still plenty of room for complexation and addition.

Steric model studies of N-phenyl-2-methylbenzylamine and N-(2-toluyl)-benzylamine were less revealing. In both cases the methyl side-chain undergoes severe crowding. The ortho- position is heavily crowded as well, but not to the same extent or frequency. However, the ortho- position on the ring which carries the side-chain is subjected to less steric crowding than the ortho- positions on the opposite ring.

The metallations followed by condensation and quenching of the N-(2-toluyl)-benzylamine was shown by N.M.R. to give the ortho- adduct A or B. It was not discernible if the site of reaction was on the substituent ortho or the benzylic ortho. The reaction times for metatation varied between thirty minutes and twenty-four hours. The solvents tested were diethyl ether, tetrahydrofuran, and hexanes. The temperatures ran 0°C to 5°C or 68°C [hexane or T.H.F. reflux]. The
condensations were run in diethyl ether, T.H.F., or hexanes as the solvent. The temperatures tested at condensation were 0° to 5°C, 38°C [diethyl ether reflux] or 68°C [T.H.F. reflux]. The quenchings were done with 200 grams of chipped ice and approximately 5 grams of ammonium chloride. The use of the ammonium salt was to reduce the likelihood of cyclizing the product.

It was found experimentally that a thirty minute, ice cold metalation and a fifteen minute refluxing condensation all in diethyl ether gave the best yields. T.L.C.s of the mother liquors showed that in no case was all of metalation product recovered. All mother liquors were reduced and chilled in ice with seed crystals until no further crystallization occurred.

The metalations ran at reflux [T.H.F. and hexanes] gave products that could not be isolated or characterized. Some crystals formed from the refluxing hexanes metalation after 5 weeks but time did not allow an analysis and yield was low. The crystal shape and color indicate that they may have been ammonium chloride. The metalation run in cold hexanes did give a small amount of two different products. Their nature was not fully investigated as they were not recovered until the last day of the research program. The products are believed to be the side-chain adduct C and the ortho- adduct A or B.

The metalations done in T.H.F. produced no recoverable product. A metalation was done without T.M.E.D.A. and also gave no recoverable product. Only a trace of product [less than milligrams] was obtained when 3 equivalents of p-butyllithium was
The two products formed by the CO₂ condensation had a combined yield of near theoretical weight. The N.M.R. of the two products was not clear as to their structure.
CONCLUSIONS

The discovery of benzylic lithiation in N-cyclohexyl-2-methylbenzylamine expands the possibilities of benzylamine lithiations. It is no longer a question of "side-chain vs. ortho-" metalation alone; clearly other possibilities exist. Of the six factors that may control regiospecificity pKa, ring inductance, and steric hinderance seem the most promising. A major degree of doubt will be cleared up when the exact site of ortho- lithiation is determined. Steric hinderance favors the ortho- position on the methyl substituted ring. Ring inductance favors the unsubstituted ring.

One experiment that would help resolve the relative strength of steric hinderance vs. ring induction would be to dilithiate N-methyl-2-methoxy-benzylamine [Fig 23]. Steric hinderance would

![Chemical Structure](image)

[Fig-23]

favor lithiation at the ortho- position to the benzylamine group. Ring induction would favor the ortho- position next to the benzylamine group without T.M.E.D.A. With T.M.E.D.A. the ortho-
position next to the methoxy group would be favored.

Another question that needs to be answered is, what is the exact nature of isomerization in the jump from the side-chain to ortho- position seen in N-phenyl-2-methylbenzylamine. There is clearly a temperature dependent factor; but if the third product of the N-(2-tolyl)-benzylamine is as suspected the side-chain adduct, then the apolar solvent hexane is also most likely a factor. If the lithium in the N-phenyl-2-methylbenzylamine system is isomerizing then it is important to know to which ortho-position is it isomerizing to. Does the lithium jump from one side of the ring to the other. Or does lithium jump to the other ring? It may be that the lithium does not move at all but is delocalized between the side-chain and one of the ortho-positions. Cleavage of the reaction product at the nitrogen followed by characterization of the products would help clear this up.

The appearance of two products in the metalation of the N-(2-tolyl)-benzylamine in cold hexane leads to more questions. This experiment needs to be repeated to establish whether there are two products formed. Much could be learned if the molecule was cleaved at the nitrogen and the fragments characterized. This experiment as well as metalations in hexane is called for.

The benzylic addition has produced two new compounds [Fig 24]. The first, N-cyclohexyl, alpha-phenyl, alpha-hydroxy, beta-ortho-toluic, beta-phenethylamine is an alpha, beta, N-substituted
phenethylamine. This class of compounds is well known for their neurological activity. The second compound, N-cyclohexyl, alpha-amino-\textit{ortho}-methyl, beta-phenethyl-acid is an aromatic alpha-aminoacid. Both are being tested for their pharmacological properties.

The benzylic lithiation of N-cyclohexyl-1-methylbenzylamine substrate opens a new synthetic pathway to two classes of pharmaceuticals, betaphenethylamines, [Fig 25] and phencyclidines [Fig 26]. By condensing the dilithioamine with benzaldehyde, one can obtain an ephedrin like compound [Fig 27]. If this product is then oxidized by chromic acid then a proprion like compound should result [Fig 28]. The benzaldehyde adduct could also be reduced with lithium aluminum hydride to produce the amphetamine like compound [Fig 29].
The N-cyclohexyl-1-methylbenzylamine dilithioamine can also be used to produce the N-cyclohexyl-1-methyl quaternary salt analog of phenethylpiperidene. If the dilithiation can be done without the methyl side-chain then the quaternary salt would result. At the condensation phase one equivalent of ethylhalide would give the benzylic ethyl [Fig 30]. If this is followed by alkylation with 1,5-dihalopentane in dilute solution one should obtain the P.E.P. (phenethylpiperidine) analog [Fig 31]. By the use of the Hofmann degradation one should obtain P.E.P. By varying the condensate and or removing the cyclohexyl group many new analogs of this drug could be created. Possibilities in this area are limited only by imagination.
The commercial value of this synthetic process is linked to its economy. One of the main questions of this project is: to what extent does benzylic lithiation take place? This question can be easily answered by condensing the dilithioamine with D$_2$O followed by N.M.R. analysis.
EXPERIMENTAL

Equipment: Melting points were taken on a Thomas Hoover Melting Point Apparatus. N.M.R.s were run on a EM 360. Starting materials were tested on a Glow Mac 550 as were characterizations of the reaction products. The stationary phase was carbowax. The H.P.L.C.s were run on a Beckman 110A the stationary phase was alumina normal phase. The eluting solvent was a mixture of hexanes, ethyl acetate and iso-propanol.

Treatment Of Starting Materials: The N-tert-2-methylbenzylamine and the N-cyclohexyl-2-methylbenzylamine were stored over molecular sieves. The N-(2-tolyl)-benzylamine and the benzophenone were dried in a drying pistol just prior to use. The T.M.E.D.A. was redistilled once a month and stored over molecular sieves. The diethyl ether and the hexanes were distilled from a sodium metal and benzophenone ketal mixture just prior to use. The T.H.F. was distilled from lithium aluminum hydride just before use. The n-butyllithium was Aldrich 2.3 molar.

Synthesis of the starting materials: Three techniques were used to make the starting materials. Method one was to react the appropriate substrate amine with the corresponding aldehyde to give the imine. This was then reduced to the amine by reacting it with sodium borohydride. The product was then purified by vacuum distillation or recrystalization. This route was in effective for the N-cyclohexyl-2-methylbenzylamine, and N-tert-butyl-2-methylbenzylamine substrates. This method was also unpredictable due to climatic factors [humidity].

The second method was to react the substrate amine with the
appropriate acid chloride to give the amide. The amide was then reduced with lithium aluminum hydride. This route produced very low yields.

The third method was to react the substrate amine with the appropriate alkyl chloride. This produced the best results.

Synthesis of N-(2-tolyl)-benzylamine: In a five hundred milliliter round bottom flask was placed: 35 grams of sodium bicarbonate, 32 milliliters of HzO, and 107 grams of ortho-toluidine. Into the flask was then introduced 42 grams of benzyl chloride in a slow dropwise fashion with vigorous mechanical stirring. The mixture was then refluxed overnight. The next morning 100 milliliters of HzO was added to the mixture. The organic layer was removed in a separatory funnel. The water layer was extracted with three portions of diethyl ether. The ether layers and the organic layer were combined and washed twice with 100 milliliters of sodium chloride saturated HzO, dried with magnesium sulfate and rotary evaporated. The excess o-toluidine was removed by vacuum distillation at 100°C and 20 millimeters of mercury. To the remaining solution was added an equal amount of methanol, after crystallization the mixture was vacuum filtered. The filtrate was condensed, seeded, crystallized and then refiltered. Total yield 48.8 grams, 74% of theoretical. The product was recrystallized to a melt point of 53°C to 60°C with 33% methanol, 66% iso-propanol.

Synthesis of N-cyclohexyl-2-methylbenzylamine: The synthesis of this substrate is the same as above with the exception of 100
grams of cyclohexylamine was used for the amine and 50 milliliters of alpha-chloro-\textit{ortho}-xylene was used for the alkylhalide. The addition of the alkylhalide was done over a ten minute time period. After the product was separated, extracted, washed, dried, and rotary evaporated, it was vacuum distilled under a pressure of six millimeters of mercury at a temperature of 136\degree C. The product had to be redistilled due to pressure flux in the original distillation.

\textbf{Synthesis of \textit{N-t}t\textit{e}rt-butyl-2-methylbenzylamine:} In a 500 milliliter round bottom flask was placed 50 grams of \textit{ortho}-tolualdehyde, 26 milliliters of \textit{t}t\textit{e}rt-butylamine and 25 milliliters of cyclohexane. The flask was fitted with a Dean-Stark trap and a condenser. The mixture was refluxed until 7 milliliters of H\textsubscript{2}O was in the trap. The H\textsubscript{2}O was let out and the mixture was left at reflux until 24 milliliters of cyclohexane had been recovered. 12 grams of sodium borohydride was suspended in 120 milliliters of iso-propanol and was added to the flask. The mixture was refluxed for 28 hours and then quenched with 500 grams of chipped ice. The organic layer was recovered with a separatory funnel and dried with magnesium sulfate and stored for 5 days over potassium hydroxide pellets. The mixture was then vacuum distilled at 20 millimeters of mercury. [note: this route produces a thermal decomposition product on distillation which is soluble in the product]

\textbf{Metalation of \textit{N-(2}toluyl\textit{)-}benzylamine in diethyl ether condensed with benzophenone:} The metalator [see appendix] was charged with 0.024 moles (4.75 grams) of \textit{N-(2}toluyl\textit{)-}benzylamine,
0.024 moles (2.79 grams) of T.M.E.D.A., and 100 milliliters of dry diethyl ether. The flask was cooled in an ice-water bath and 22 milliliters of 2.3 molar n-butyllithium was added slowly through the septum with a hypodermic syringe with continuous magnetic stirring. The entire process was done under N₂ gas.

The addition of the first 11 milliliters of n-butyllithium produced an opaque white solution. The second 11 milliliters turned the mixture transparent red. After 20 minutes the solution started turning a milky yellow. After 30 minutes had passed from the addition of n-butyllithium 4.59 grams of benzophenone in 50 milliliters of diethyl ether was added dropwise through the side-arm funnel. The mixture initially turned blue and was heated to reflux for 15 minutes. At the point of reflux the mixture had turned green. The contents of the flask were poured over 200 grams of chipped ice and 5 grams of ammonium chloride. The organic layer became yellow and after stirring quickly became lime green. This was stirred until the ether evaporated, and excess ammonium chloride was added to the saturation point. A solid layer formed of an off white waxy substance which was washed with 30 milliliters of methanol and gave 4.63 grams of very pure crystals. The mother liquor was condensed and gave 1.67 grams more. The product was characterized by N.M.R. and found to be ether N-(2-tolyl)-6-diphenylhydroxymethyl)-benzylamine or N-(2-tolyl)-2-diphenylhydroxymethylbenzylamine the ortho-adducts. Melting point was 133-134°C with a total yield of 6.30 grams (69.2% of theoretical). ¹H N.M.R. (60 MHz, CDCl₃) 7.50 to 6.30 (18H, multiplet), 4.05 (2H, singlet),
2.15 (3H, singlet).

Metalation of N-(2-toluyl)-benzylamine condensed with benzophenone in cold hexane: This run was performed as above except the solvent system was hexane during the metalation phase. 150 milliliters of anhydrous hexane was needed to dissolve the starting materials. Some of the starting materials condensed out of solution when the mixture was chilled to 0°C. On addition of the first 11 milliliters of n-butyllithium the mixture turned yellow, as the second equivalent of lithium was added a large mass of a highly viscous material coagulated on the stirring bar. The stirring bar stopped and the mixture turned red. On addition of the benzophenone the mixture turned green then slowly to red. On quenching the solution turned bright yellow and the color persisted for an unusually long time but slowly became transparent. There were some undissolved clumps of red solid in the mixture and flask and these were added to the quenching mixture; which with stirring slowly turned yellow and dissolved.

The mixture was gently heated and stirred until the solvents were driven off. A viscous yellow oil was left behind which was decanted off. The oil was dissolved in 30 milliliters of methanol. Crystalization was effected in acetonitrile. This crop was quite small and was vacuum filtered and washed twice with 30 milliliters of acetonitrile. The flask slowly filled with crystals on standing. After refiltering a third crop of crystals formed when the flask was chilled in ice. The crystals from the first two crops had a melting point of 110 to 115°C. The third crop of crystals had a melting point of 126°C. The
mixed melting point of crystal crop one and three was a split melting with initial melting at 110 to 118°C and then continuing at 125 to 128°C. Most of the crystals were mixed before it was realized that they were not the same product. All the crystals were an off white color. The first crop was gummy, the second grainy, and the third fluffy. Approximately one gram was isolated in each crop. ¹H N.M.R. crystal crop #2 (60 MHz, CDCl₃) 6.75 to 5.65 (multiplet with spike @ 6.65), 3.30 (singlet tailing to 2.80), 1.40 (singlet). ¹H N.M.R. crystal crop #3 (integration indiscernible), 7.50 to 6.35 (multiplet with spike @ 7.45), 4.10 to 3.95 (singlet), 3.80 to 3.40 (multiplet), 2.25 (doublet), 2.10 (singlet).

Metalation of N-cyclohexyl-2-methylbenzylamine condensed with benzophenone: To the metalator was added 0.024 mole (4.87 grams) of N-cyclohexyl-2-methylbenzylamine, 0.024 mole (2.79 grams) of T.M.E.D.A. and 100 milliliters of anhydrous diethyl ether. The flask was cooled in an ice-water bath and 22 milliliters of 2.3 molar η-butyllithium were added through the septum with a hypodermic syringe. The entire process was done under N₂ gas with continuous magnetic stirring.

On addition of the η-butyllithium the mixture turned green, then rapidly to opaque red, and then slowly to a milky yellow. After 30 minutes, 4.59 grams of benzophenone in 50 milliliters of diethyl ether was added slowly through the side-arm funnel, and the reaction mixture turned an initial bright green, then slowly turned maroon. The mixture was brought to reflux and turned dark as tars developed on the flask. Gentle swirling of the metalator
dissolved the tars; and after 15 minutes, the mixture was quenched over 200 grams of chipped ice and 5 grams of ammonium chloride. The mixture turned green and rapidly became transparent. The flask was placed on a heat and stir plate, and the solution was saturated with ammonium chloride. This was heated gently until the ether evaporated. The surface oil was decanted off and dissolved in 30 milliliters of methanol. This slowly afforded a white crystalline product. The mother liquor was condensed and chilled to yield a second crop of crystals. A total of 2.59 grams was obtained. Furthermore, it was found that by condensing and redissolving the filtrate in acetonitrile the hydrochloride salt of the unchanged substrate (1.53 grams) was recovered. The reaction product was characterized by N.M.R. and found to be 2-(2-amino-N-benzylphenyl)-1,1-diphenylethinol the benzylic adduct. Melting Point 117-120°. Total yield 2.59 grams (28.0% of theoretical). ¹H N.M.R. (60 MHz. CDCl₃) 7.75 to 7.15 (11 H, multiplet), 6.35 (1 H, singlet), 2.50 (3 H, singlet), 2.20 to 0.60 (11 H, multiplet).

Metalation of N-cyclohexyl-2-methylbenzylamine condensed with CO₂: This metalation was run the same as above until the 30 minute metalation period had passed. However, after 30 minutes the dry ice [CO₂] was as yet not available. The metalation period was extended to 3 hours until the dry ice was available. The solution became opaque yellow with the extinction of the metalation time. Just prior to the end of the 3 hour metalation period 50 grams of dry ice was suspended in 100 milliliters of hexane in a 500 milliliter flask. The flask was placed on a stir...
plate and stirred at a fast rate. At 3 hours the reaction mixture was dumped into the CO$_2$ mixture all at once. The mixture evolved a large amount of gas and then became milky white. This was left on the stir plate overnight. The mixture was then vacuum filtered and was found to behave in an unorthodox way in most all of the solvents tested. It was eventually dissolved in water, the organic layer extracted with water. The combined extracts were basified with sodium hydroxide pellets to a pH of $>$12 and extracted with diethyl ether. The aqueous layer was then acidified with hydrochloric acid to a pH of $<$1 and extracted with diethyl ether. The basic extract was crystalized by rotary evaporating it to a slurry then mixing it with iso-propanol. This gave 1.79 grams of crystals.

The acid extract was evaporated to a slurry and crystalized with acetonitrile. The mother liquor was re-evaporated and crystalized with acetonitrile. These crystals were very hygroscopic and had to be removed from the funnel quickly and placed in a drying pistol. The pistol was heated with refluxing hexane for 4 hours to give a total of 4.06 grams.

Both products decomposed before melting. The N.M.R.'s had to be run in D$_2$O. The spectra are not conclusive as to the structure of the products. The crystals N.M.R.'s contained a water peak. The combined yields were near quantitative. $^1$H N.M.R. Base crystals (60 MHz D$_2$O) 7.30 (4 H, singlet), 4.85 (water peak), 2.45 (3 H, singlet), 2.20 to 0.80 (11 H, multiplet). Acid crystals (60 MHz, H$_2$O) 7.55 (singlet), 5.00 (water peak), 4.15 to 3.80 (quartet of multiplets), 2.65 to 0.85
(multiplet). [Determination of the number of hydrogens at delta
7.55 was not possible due to the lack of clarity in the other
peaks]
APPENDIX-A (THE METALATOR)
END NOTE REFERENCES


2. Ibid.


5. Ibid.


8. Ibid.


14. Ibid.

15. Ludt, R. E., Dissertation.

16. Ibid.

17. Unpublished data, Summer Undergraduate Research Program, under the direction of R. E. Ludt, Virginia Military Institute, Lexington, Virginia. (See ADDITIONAL REFERENCES items 1 through 7)


23. Ludt, R. E., Unpublished communication.
27. Ludt, R. E., Unpublished communication.
29. Slocum, Book, and Jennings.
31. Dreiding Stereomodels.
ADDITIONAL REFERENCES


