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## Side-Chain Metalations of Certain Dimethylpyridines by Means of Organoalkali Metal Reagents

Stephen Bendzunas

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SIDE-CHAIN METALATIONS OF CERTAIN DIMETHYLPYRIDINES  
BY MEANS OF ORGANOALKALI METAL REAGENTS

by

Stephen Bendzunas

A Thesis  
Submitted to the  
Faculty of The Graduate College  
in partial fulfillment  
of the  
Degree of Master Arts

Western Michigan University  
Kalamazoo, Michigan  
April 1977

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Stephen George Bendzunas

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## INTRODUCTION

It is well known that the hydrogen atoms of a methyl group directly attached to a pyridine nucleus are sufficiently acidic to be abstracted by a suitable base to generate the corresponding  $\alpha$ -anion. These monoanions have frequently served as intermediates in the preparation of a large number of substituted pyridines. On the other hand, all attempts to form  $\alpha,\alpha'$ -dianions on dimethylpyridines have met with failure.

The purpose of the present study was to investigate new and efficient methods for the possible generation of  $\alpha,\alpha'$ -dianions of various dimethylpyridines, namely 2,3-, 2,4-, and 2,6'-lutidine, and to investigate the reaction of these  $\alpha,\alpha'$ -dianions with a variety of electrophilic reagents.

Although it may be unlikely that the organometallic compounds in the following investigation are completely dissociated into free anions and cations, the term anions will be taken to mean any organometallic compound containing a highly polarized carbon metal bond in which at least a partial negative charge resides on the carbon atom.



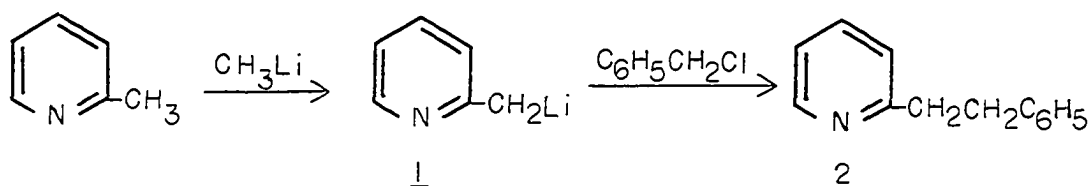
## II. HISTORICAL

It is known that hydrogens on an alkyl group attached to an aromatic ring can be removed if a sufficiently strong base is used. Thus toluene treated with n-amylsodium results in the formation of benzyl anions. Protons attached to an alkyl group on a pyridine ring are much more acidic than those of toluene and are easily removed with weaker bases such as sodium amide and phenyllithium.

In the following sections, a literature review of the methods used for chain metalation and subsequent functionalization of certain picolines and lutidines is presented.

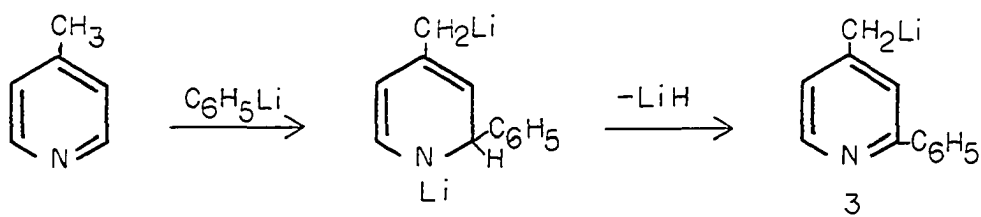
### A. Metalation of Alkylpyridines

Ziegler and Zeiser<sup>1</sup> were the first to observe that 2-picoline could be metalated. They used an ether solution of methyllithium to treat 2-picoline and obtained 2-picolylithium (1). Subsequent reaction with benzyl chloride gave 2-phenethylpyridine (2).

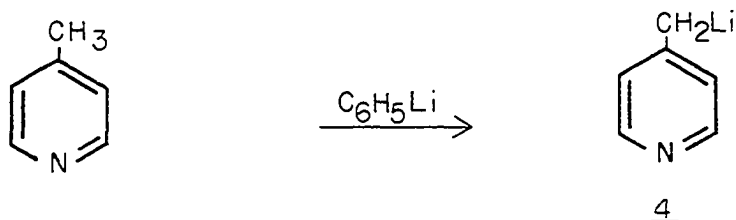


Kloppenborg and Wibaut<sup>2</sup> used phenyllithium in ether solution to obtain 1.

It was later found that 4-picoline reacted with phenyllithium to give a product in which metalation of the methyl group and addition of phenyllithium across the azomethine bond had occurred.

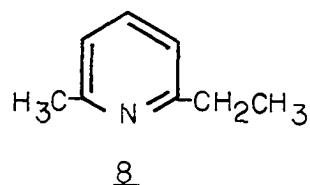
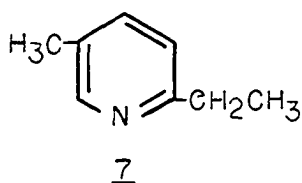
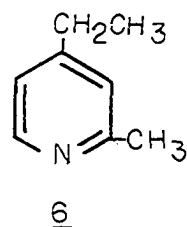
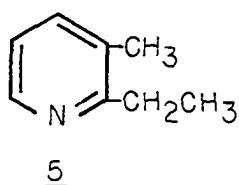


By the slow addition of an ether solution of phenyllithium to an ether solution of 4-picoline, Wibaut and Hey<sup>4</sup> avoided the formation of 3 and obtained good yields of 4-picolylithium (4).



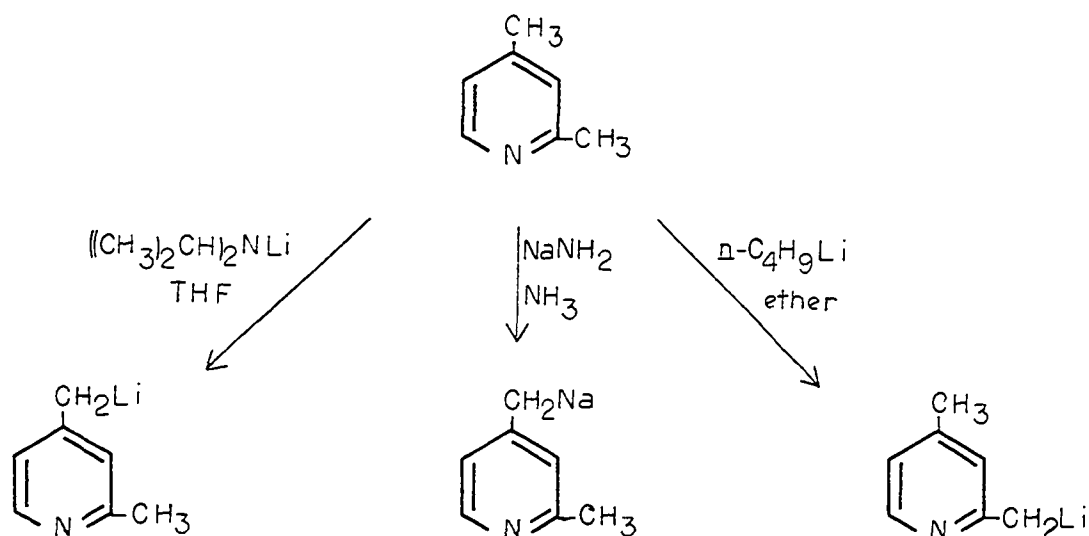
Although there have been many attempts to metalate 3-picoline with organoalkali reagents, there have been no reported instances where this has been accomplished. Only addition to the azomethine bond occurs.

Sodium amide in liquid ammonia has also been used to metalate alkylpyridines in high yields. Lochte and Cheavens<sup>5</sup> treated 2,3-, 2,4-, 2,5-, and 2,6-lutidine with sodium amide in liquid ammonia followed by reaction with methyl iodide. As products they received 2-ethyl-3-methylpyridine (5), 2-methyl-4-ethylpyridine (6), 2-ethyl-5-methylpyridine (7), and 2-ethyl-6-methylpyridine (8), respectively.



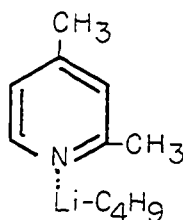
These results point out that the protons of the 4-methyl group were the most acidic followed by those of the 2-methyl group. Those on the 3- and 5-methyl groups failed to react.

An interesting study concerning the relative ease of metalation of the 2-methyl vs the 4-methyl position of certain dimethylpyridines and quinolines has been recently reported by Kaiser and his co-workers.<sup>6</sup> In order to ascertain the site of metalation as a function of base, these workers allowed 2,4-lutidine to react with three different base systems and the resulting carbanions were subsequently identified by treatment with methyl iodide. It was found that when sodium amide in liquid ammonia or lithium diisopropylamide in tetrahydrofuran (THF) was used, metalation of the 4-methyl group results; whereas when n-butyllithium in ether was used, metalation occurred on the 2-methyl group.



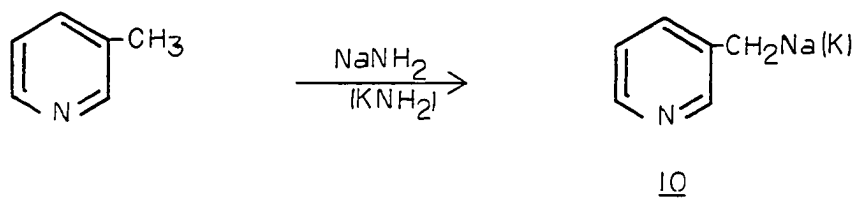
This selectivity of the metalation as a function of base is surprising especially in view of the higher acidity of the 4-methyl

group. Metalation at the 2-methyl group by n-butyllithium was attributed to prior complexation of the lithium species with the nitrogen of the pyridine ring.



Thus, because of the close proximity of the basic butyl group to the 2-methyl group, the proton was abstracted from the 2-methyl group. On the other hand, when either lithium diisopropylamide or sodium amide was used, prior complexation of the metal took place with the solvent and in the case with lithium diisopropylamide, complexation also took place with the diisopropyl amine as it was formed during the reaction. Consequently, the lithium or sodium species could not complex effectively with the nitrogen on the pyridine ring and attack occurred at the most acidic position, the 4-methyl group.

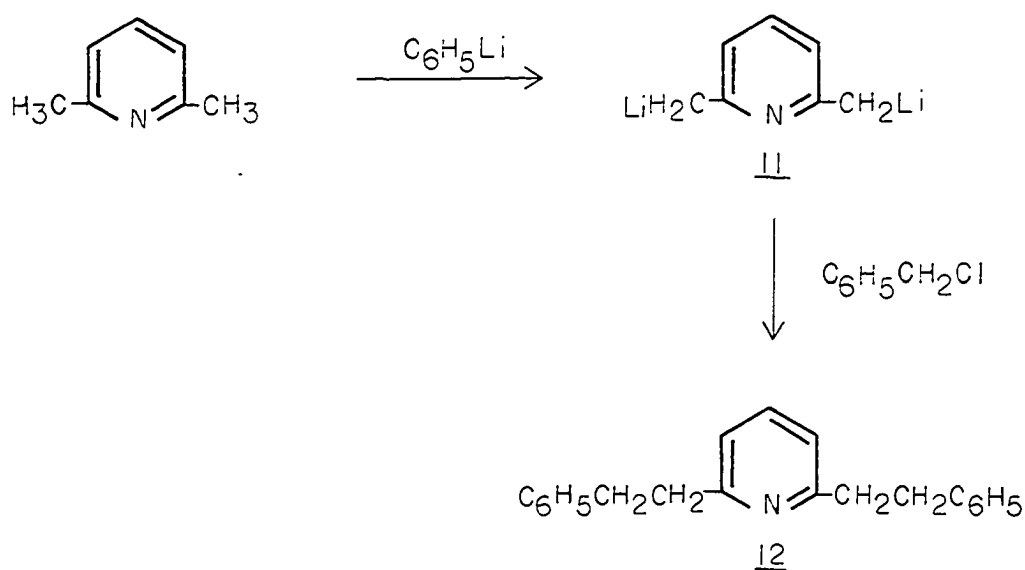
Not only have the protons of the 2- and 4-methyl groups been shown to be reactive towards sodium amide in liquid ammonia, but also the protons of the 3-methyl group have been shown to react.<sup>5</sup> Upon treatment with sodium or potassium amide in liquid ammonia, 3-picoline was metalated to give good yields of the 3-picolyllalkali metal compound 10.



### B. Attempted Dimetalation of 2,6-Lutidine

There has been sporadic evidence<sup>7,8</sup> for the formation of a dianion of 2,6-lutidine. This evidence has been inconclusive and based on the formation of minor side products of reactions.

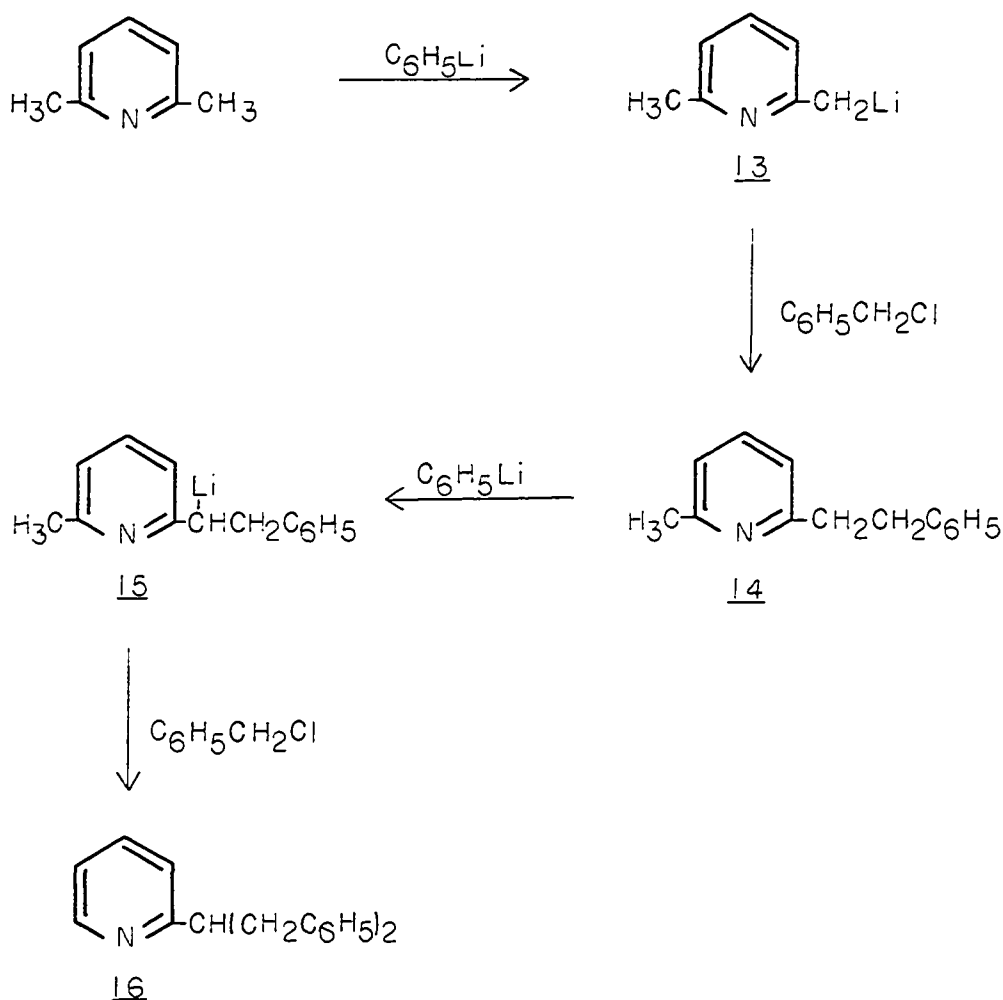
Bergmann and Rosenthal<sup>9</sup> were the first to attempt to form a dianion with 2,6-lutidine. They treated 2,6-lutidine with two equivalents of phenyllithium followed by two equivalents of benzyl chloride. A product was obtained in which two benzyl groups had been incorporated onto the 2,6-lutidine. To explain these results, they proposed a dianion intermediate 11 which reacted with two equivalents of benzyl chloride to give 2,6-diphenethylpyridine (12).



They reported the picrate of 12 as having a melting point of  $138^\circ$ .

Later DeJong and Wibaut<sup>10</sup> reinvestigated this reaction by preparing all possible products by other routes. They were able to determine that 12 was not the product but rather 16. The formation of 16 took place through a two step sequence as shown in Scheme I.

Scheme I.



First 2,6-lutidine was metalated to give 13 which reacted with one equivalent of benzyl chloride to give 14. Compound 14 was next



metalated by another equivalent of phenyllithium to produce 15 which subsequently reacted with another equivalent of benzyl chloride to give the final product 16. Thus, a compound is formed in which two benzyl groups have been incorporated onto the 2,6-lutidine.

DeJong and Wibaut also determined that the picrate of Bergmann and Rosenthal's product was actually a mixture of 16 along with some other side product. This mixture had an eutectic point of 137°. The contaminating side product was thought to be a compound in which the benzyl groups had been substituted on the alkyl group and the ring of 2,6-lutidine.

DeJong and Wibaut prepared 2,6-diphenethylpyridine (12) by the hydrogenation of 2,6-distyrylpyridine. The melting point of the picrate of Bergmann and Rosenthal's product and that of 12 prepared in this manner was lower than the melting point of 12.

Recently, 2,6-lutidine was treated with two equivalents of n-butyllithium and a nmr taken of the anion.<sup>13</sup> It was shown conclusively that only the monoanion was formed and that no dianions were present in the reaction mixture.

Other than 2,6-lutidine, no other isomeric lutidine has been used for the attempted formation of dianions.

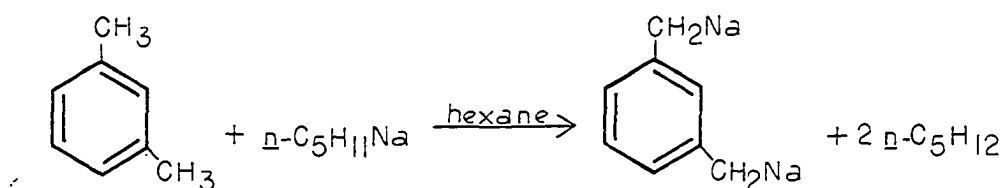
### III. STATEMENT OF PROBLEM

As outlined in the previous section, several excellent methods have been reported in the literature for the formation of  $\alpha$ -monoanions of methylpyridines. These anions have been shown to be of substantial practical utility in the synthesis of functionalized pyridines and related systems. On the other hand, all attempted preparations of  $\alpha, \alpha'$ -dianions have been unsuccessful. In view of the expectation that these dianions should be at least as useful as the pyridine monoanions, the present study was initiated in order to develop efficient methods for their formation and to explore their reactions with a variety of electrophilic reagents.

#### IV. RESULTS AND DISCUSSION

##### A. Metalation of Lutidines with n-Amylsodium in the Presence of N,N,N',N'-Tetramethylethylenediamine

Although methyl substituents on a pyridine nucleus are known to be more acidic than alkanes, their acidity is still quite low and it was anticipated that only very strong bases would be able to convert dimethylpyridines to their dianions. Very recently, Trimitsis and co-workers<sup>14</sup> have shown that n-amylsodium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) could convert m-xylene to its  $\alpha,\alpha'$ -dianion in quantitative yields at room temperature in two hours.



Since the pyridyl methyl groups are known to be more acidic than those attached to a phenyl ring, it was felt that the above base-catalyst system would be ideally suited for the  $\alpha,\alpha'$ -diionization of dimethylpyridines.

Reaction of 2,3-lutidine with 3.5 equivalents of n-amylsodium-TMEDA for two hours at room temperature followed by deuteration of the reaction mixture with deuterium oxide afforded 2,3-lutidine (17) containing an average of 2.5 deuterium atoms per molecule as shown by nuclear magnetic resonance (nmr) and mass spectroscopic analysis of

Table I

Results of Deuteration of Lutidine Anions as Determined by Mass Spectroscopy

-13-	Lutidine Used	Equiv of Base	Reaction Time	Total D Incorporated <sup>a</sup>	0	1	Deuterium Atoms 2	3	(Percent) 4	5	6
	2,3-	3.5	1 hr	2.5	2.5	17.1	29.7	27.7	11.6	1.4	---
	2,3-	3.5	2 hrs	2.5	1.8	11.5	28.6	36.3	18.7	2.6	---
	2,3-	3.5	3 hrs	2.5	4.2	12.1	29.5	35.9	16.0	2.2	---
	2,4-	3.5	1 hr	2.2	2.5	27.1	37.13	19.6	12.4	2.7	---
	2,4-	3.5	2 hrs	2.7	2.1	19.5	27.2	22.4	17.8	9.1	---
	2,5-	3.5	1 hr	2.3	3.0	15.2	37.4	37.2	6.5	---	---
	2,5-	3.5	2 hrs	2.6	1.7	9.7	32.0	44.3	12.0	1.7	---
	2,5-	3.5	3 hrs	3.0	1.1	3.8	22.0	46.3	22.4	4.4	---
	2,6-	3.5	2 hrs	3.1	2.0	10.7	23.5	24.8	20.1	12.8	6.1

<sup>a</sup>Based on the calculation procedure as presented by Biemann<sup>19</sup>

Table II

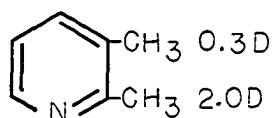
Results of Deuteration of Lutidine Anions as Determined by Nuclear Magnetic Resonance

Lutidine Used	Equiv of Base	Reaction Time	Total Deuterium Incorporated <sup>a</sup>	Position							
				3	4	5	6	2-me	3-me	4-me	5-me
2,3-	3.5	1 hr	2.5	---	0.1 <sup>b</sup>	0.0	0.1	2.0	0.3	----	----
2,3-	3.5	2 hrs	2.5	---	0.1	0.0	0.1	2.0	0.3	----	----
2,4-	3.5	2 hrs	2.7	0.0	---	0.0	0.1	1.6	---	1.0	----
2,5-	3.5	2 hrs	2.4	0.0	0.0	---	0.1	2.3	---	----	0.0
2,6-	3.5	2 hrs	3.0	0.0	0.0	0.0	---	3.0 <sup>c</sup>	---	----	----

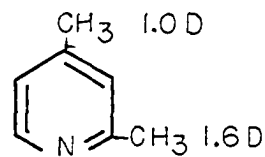
<sup>a</sup>Based on one integration on a typical product mixture<sup>b</sup>0.1 is approaching the limits of sensitivity of the instrument<sup>c</sup>Includes both the 2-methyl and 6-methyl since both are magnetically equivalent

the reaction product (Tables I and II). Nmr analysis was performed on the methiodide salt of the product, the N-methyl group serving as a convenient internal standard.

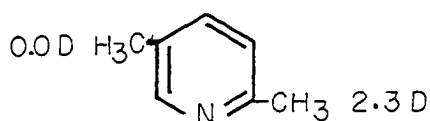
Similar experiments were also performed with 2,4-, 2,5-, and 2,6-lutidine, the methiodide salt again formed and an nmr taken of the derivative. A mass spectrum was also taken of the deuterated sample. These results are given in Tables I and II. The deuterium distribution within each lutidine as determined by nmr is outlined below.



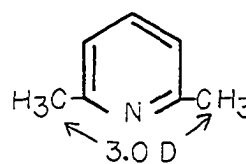
17



18



19



20

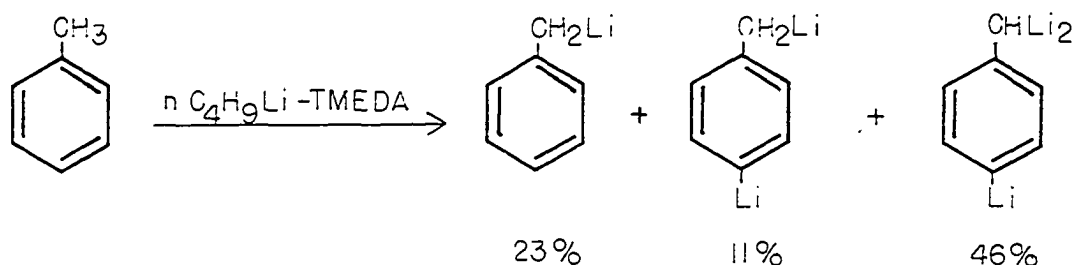
Fractional deuterium incorporation of the various positions in the lutidines can be explained by taking into account the mass spectral data which show that the number obtained by nmr analysis is actually an average of a variety of deuterated species ranging from those with only one deuterium atom to those with as many as six deuterium atoms per molecule.

Variation of time influenced the results as seen in Table I. Increasing the time of reaction with n-amylsodium-TMEDA from one to

three hours had no effect on 2,3-lutidine; however, with 2,4- and 2,5-lutidine, the average deuterium content of the sample increased.

It can be seen from the results as shown in Table I and II, that n-amylsodium-TMEDA is much too strong a base to affect clean dimetalation of dialkylpyridines. Nevertheless, these results contain a number of interesting observations that merit discussion.

It is clearly seen that there is very little ring metalation. This is surprising since West and his co-workers<sup>13</sup> have found that treatment of toluene with excess n-butyllithium-TMEDA leads to a high percentage of ring metalation.



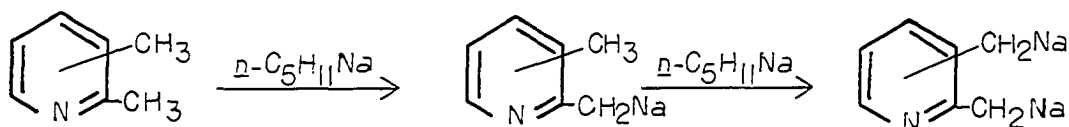
The low amount of ring metalation in the case of the lutidines can be ascribed to the much higher acidity of the methyl hydrogens relative to the ring hydrogens. Thus,  $\alpha$ -metalation will be highly favored and subsequent ring metalation of an  $\alpha$ -monoanion will not occur since the partial negative charge delocalized in the ring will undoubtedly deactivate the ring hydrogens. Calculations<sup>11</sup> based on the nmr of the 2-picolyll anion taken in THF show the relative charge distribution in the carbanion of -0.15, -0.15, -0.22, and -0.15 for the positions 3-C, 4-C, 5-C, 6-C, respectively. This large amount of delocalization would greatly hinder the abstraction of one of the

ring protons to form a ring metalated species.

It is evident from the deuteration studies that in all the above lutidines, the 2-methyl group is very reactive, generally losing more than one proton. Also it is seen that in the case of 2,5-lutidine, the 5-methyl group is totally unreactive. The 3-methyl and 4-methyl groups are intermediate between these extremes.

These results can be explained by means of a two step sequence as shown in Scheme II.

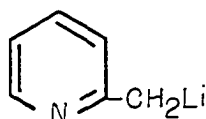
Scheme II



According to this sequence, the lutidine first reacts with one equivalent of base to produce the lutidyl monoanion 21 which in turn reacts with another equivalent of base to form the dianion 22. The negative charge of the monoanion 21 would undoubtedly make the ionization of the second methyl group much more difficult. Moreover, the ease of proton abstraction from the second methyl group would not be expected to be the same for all isomers of lutidine, but should depend on the charge accumulation on the carbon bearing the methyl group. Carbon-13 nmr<sup>11</sup> in which chemical shifts relative to 2-picoline of 5.2, 7.8, 4.4, 23.7, and 1.0 ppm for C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub>, respectively for 2-picolylolithium 23, along with theoretical



calculations<sup>14</sup> show that the charge accumulation increases in the order  $C_6 < C_4 < C_2 < C_3 < C_5$ .



23

On the basis of these results, it can be expected that the ease of abstraction of a proton from the second methyl group would decrease in the order 6-methyl > 4-methyl > 3-methyl > 5-methyl. These predictions are verified by the experimental results of the present study.

The fact that abstraction of a proton from 2,4-lutidine occurs at the 2-methyl group and not the more acidic 4-methyl group bears out Kaiser's theory that prior complexation takes place; that is, the sodium may coordinate with the nitrogen of the pyridine ring bringing the amyl group closer to the 2-methyl group which then preferentially gives up a proton to form the anion.

There appears to be large amounts of tri- and higher polyanions formed when the lutidines are treated with a 3.5 molar excess of n-amylsodium-TMEDA as is evident from the mass spectra data in Table I. If one plots the number of deuterium atoms incorporated vs its percent composition of the reaction product, it is seen that there is a maximum at three deuterium atoms per molecule as shown in Figure I.

It is seen that the maxima for 2,5- and 2,3-lutidine are sharper than those for 2,4- and 2,6-lutidine. This is expected if one looks

-61-

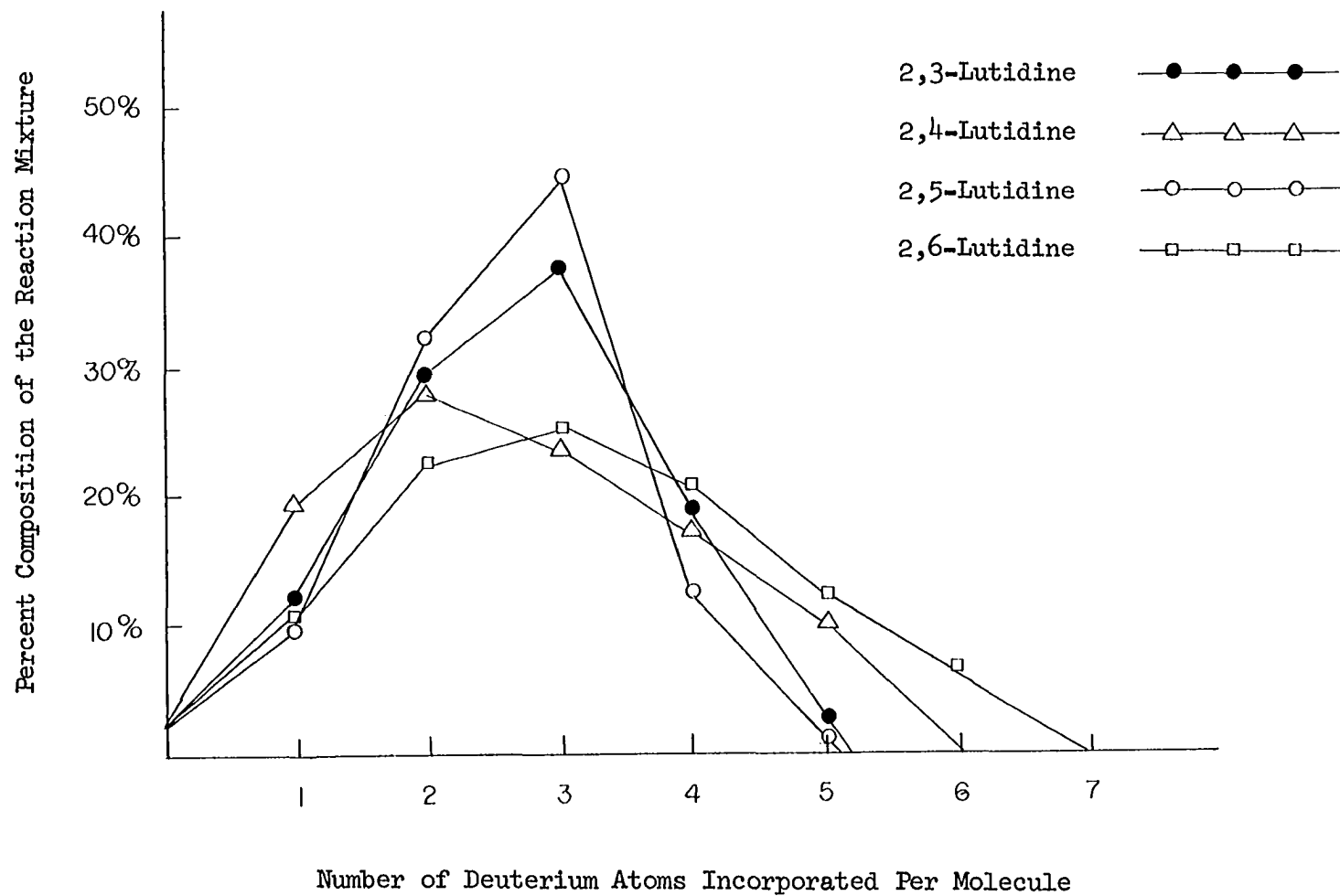
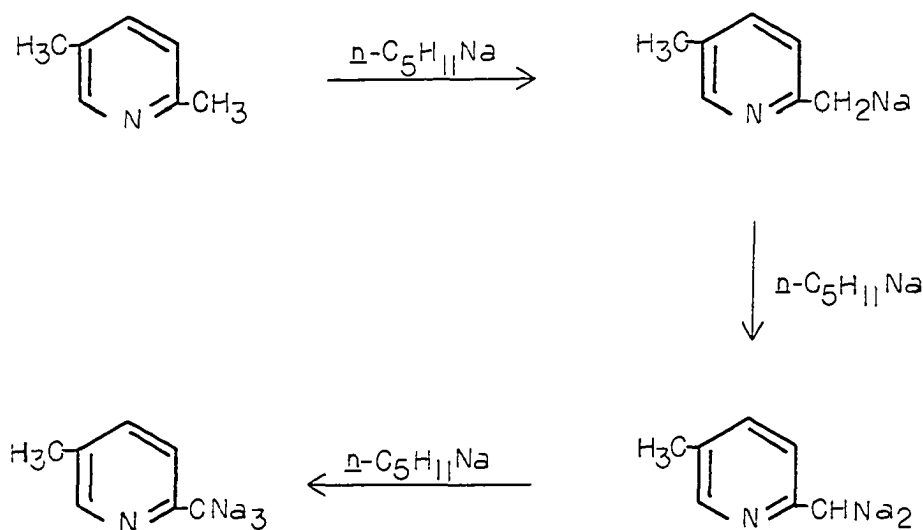


Figure I. Distribution of deuterated species obtained when the various lutidines are treated with 3.5 equivalents of n-amylsodium-TMEDA for two hours at room temperature.

at the reactivities of the methyl groups that each lutidine contains. 2,5-Lutidine has only one reactive methyl group and has a sharp maximum at three deuterium atoms per molecule. 2,3-Lutidine has one very reactive methyl group and one weakly reactive methyl group resulting in a maximum that is not quite as sharp as that for 2,5-lutidine. On the other hand, 2,4- and 2,6-lutidine contain two reactive methyl groups and thus the maxima at three deuterium atoms per molecule are broad. The sharpness of the maxima are therefore dependent on the number of reactive methyl groups present in the lutidine molecule.

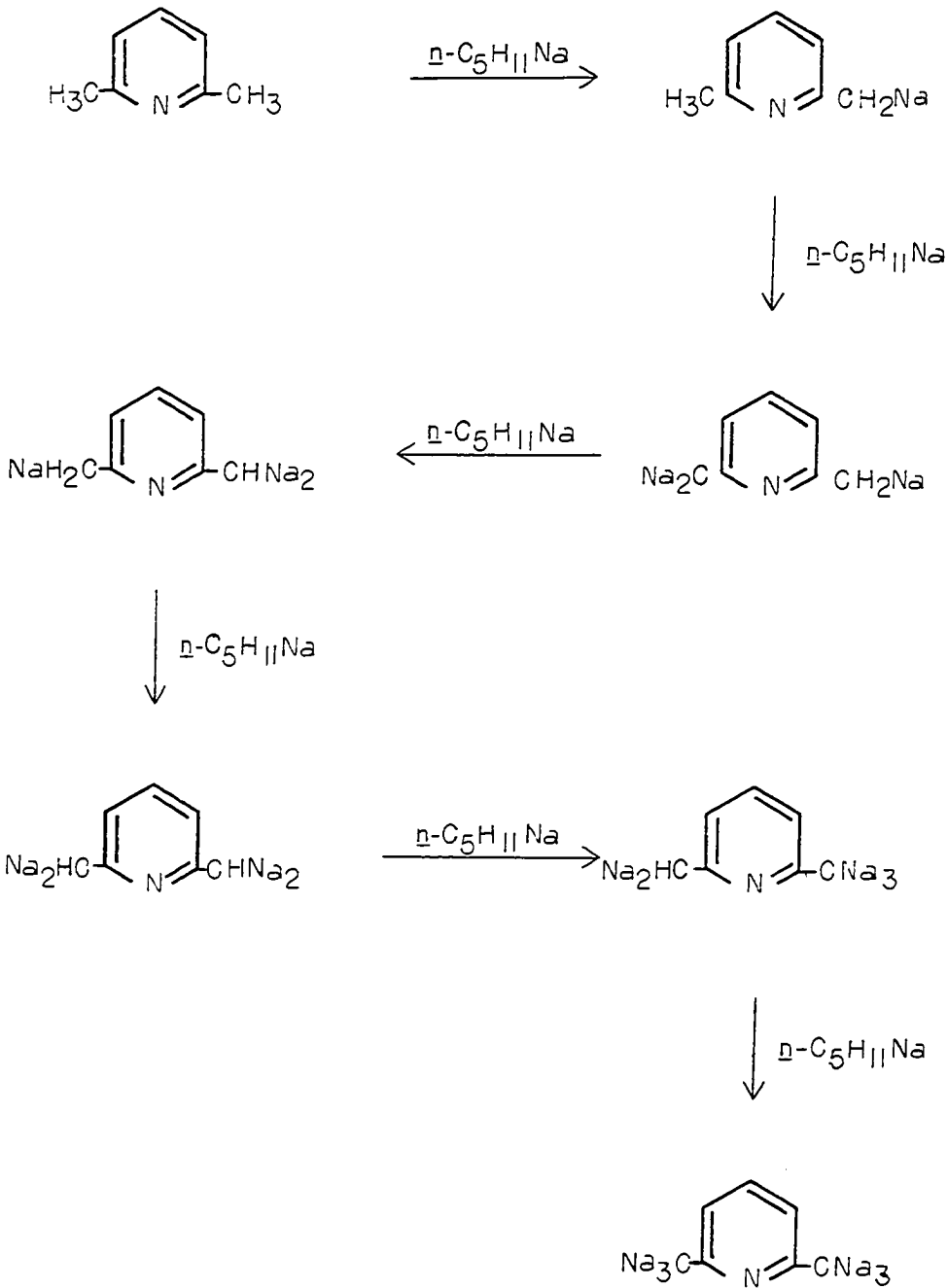
To explain how polyanionic species may be formed in the reaction mixture, a general reaction sequence can be written. This sequence takes place with a stepwise abstraction of a proton by base. For 2,5-lutidine, a reaction sequence such as that in Scheme III can be written based on nmr and mass spectral data.

Scheme III



A similar sequence can be written for 2,6-lutidine as presented in Scheme IV.

Scheme IV



As can be seen from these proposed sequences, there is a stepwise removal of a proton by n-amylsodium. Apparent anionic species may be seen in the reaction product due to an exchange reaction during the quenching of the reaction intermediates. However, this is probably not of great importance since the formation of anionic species is time dependent. Although some of the higher polydeuterated species may be produced in this manner, much of the lower polydeuterated species are not.

In the case of 2,5-lutidine, only the reactive 2-methyl protons are removed leaving the 5-methyl hydrogens untouched. With 2,6-lutidine, both methyl groups react to give large amounts of polydeuterated species. There is a stepwise abstraction of a proton from each methyl group as seen in Scheme IV; this distinction is supported by nmr data.

Similar sequences can be written for 2,4- and 2,3-lutidine; however, insufficient data negate the proposing of them. Nevertheless, stepwise abstractions similar to those above can be expected.

B. Metalation of the Lutidines with n-Butyllithium in the Presence of N,N,N',N'-Tetramethylethylenediamine

As shown in the previous section, n-amylsodium-TMEDA did not effect clean dianion formation under the conditions employed. It was demonstrated that n-amylsodium-TMEDA tri-, tetra- and penta-metalated the various lutidines. A different base was therefore needed to cleanly dimetalate the various lutidines.

n-Butyllithium, the most commonly used organolithium reagent, had been previously shown to convert 2,6-lutidine only to its monoanion, so the use of a catalyst in conjunction with this organolithium base seemed necessary. As with n-amylsodium, N,N,N',N'-tetramethylethylenediamine (TMEDA) was chosen for the present study.

Treatment of 2,4-lutidine with two equivalents of n-butyllithium-TMEDA for two hours at room temperature and subsequent deuteration with deuterium oxide, resulted in the incorporation of 1.4 deuterium atoms per molecule as shown by quantitative nmr analysis of the methiodide of the reaction product. As can be seen in Table III, nmr analysis showed that no deuterium was incorporated into the ring.

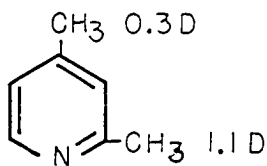


Table III

Results of Deuteration of Lutidine Anions Formed with n-Butyllithium-TMEDA with a Reaction Time of 2 hours at Room Temperature as Determined by Nuclear Magnetic Resonance

Lutidine Used	Total D Incorporated <sup>a</sup>	3	4	5	6	Position 2-me	3-me	4-me	5-me
2,3-	1.9 <sup>b</sup>	---	0.0	0.0	0.0	1.9	0.0	---	---
2,4-	1.4 <sup>c</sup>	0.0	---	0.0	0.0	1.1	---	0.3	---
2,5-	1.5 <sup>b</sup>	0.0	0.0	---	0.0	1.5	---	---	0.0
2,6-	2.0 <sup>c</sup>	0.0	0.0	0.0	---	2.0 <sup>d</sup>	---	---	---

<sup>a</sup>Based on one intergration on a typical product

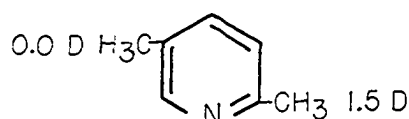
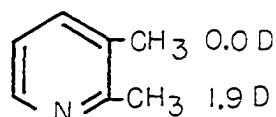
<sup>b</sup>3.5 equiv of n-C<sub>4</sub>H<sub>9</sub>Li-TMEDA was used

<sup>c</sup>2.0 equip of n-C<sub>4</sub>H<sub>9</sub>Li-TMEDA was used

<sup>d</sup>Includes both the 2-methyl and 6-methyl since both are magnetically equivalent

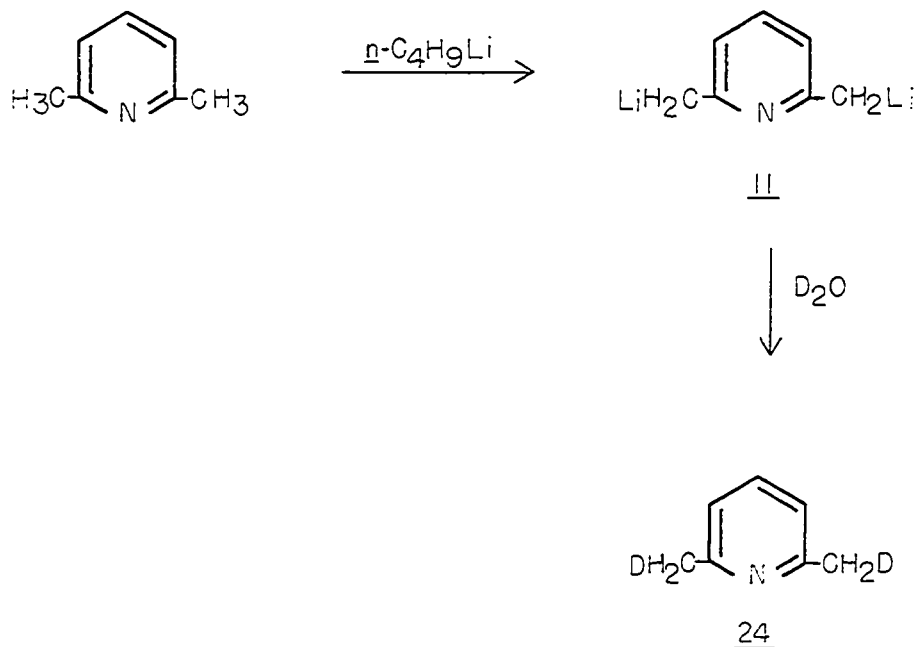
Inspection of the manner in which deuterium has been incorporated in the 2,4-lutidine when this molecule was treated with two equivalents of n-butyllithium-TMEDA at room temperature for two hours, clearly indicates that increasing the amount of base or the temperature would not lead to clean  $\alpha,\alpha'$ -dianion formation. Even under these conditions, polymetalation of the 2-methyl group was evident.

Treatment of 2,3- and 2,5-lutidine with 3.5-equivalents of n-butyllithium-TMEDA resulted in the incorporation of 1.9 and 1.5 deuterium atoms per molecule, respectively. In both cases all the deuterium was found on the 2-methyl position, indicating that in both of the above substrates  $\alpha,\alpha$ - rather than  $\alpha,\alpha'$ -dimetalation had taken place.



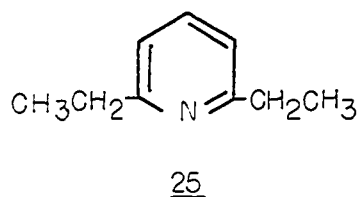
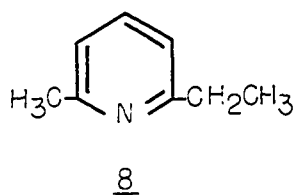
Unlike the three isomeric lutidines mentioned above, reaction of 2,6-lutidine with two equivalents of n-butyllithium-TMEDA for two hours at room temperature resulted in a complete conversion of 2,6-lutidine to its  $\alpha,\alpha'$ -dianion as shown by deuteration with  $D_2O$  followed by quantitative nmr analysis of the methiodide of the reaction product.





In order to investigate the synthetic utility of dianion 11, its reactions with a number of alkyl halides under a variety of experimental conditions were next studied.

When 2,6-lutidine was treated with two equivalents of n-butyllithium-TMEDA for two hours in hexane at room temperature followed by treatment with methyl iodide, a mixture of two products resulted. Using vapor phase chromatography (vpc) and comparison with authentic samples, these products were shown to be 2-ethyl-6-methylpyridine (8) and 2,6-diethylpyridine (25).



The mixture consisted of 33% of 8 and 67% of 25.

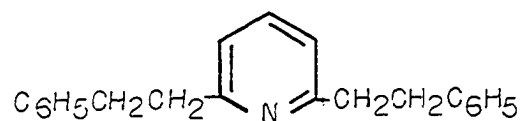
Varying the time of reaction showed best results are obtained after at least two hours. With a reaction time of 0.5 hours, only 55% of 25 was formed. Increasing the time to 4 hours increased the amount of 25 formed to 71% while a reaction time of 20 hours yielded 25 in 73%. It is evident that after about two hours reaction time, the reaction is essentially complete.

In order to optimize the yield of 25, the methylation of dianion 11 was performed in a number of solvents other than hexane. It was anticipated that a change to a polar solvent would aid the reaction. Indeed, when ether was used as a solvent, dimethylation of dianion 11 produced 2,6-diethylpyridine (25) in 82% yield. The use of tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) as solvents for the above reaction afforded 25 in only 39% and 10% yields, respectively. Ethyl ether, therefore, appears as the solvent of choice for the dimethylation of 2,6-lutidine.

The low yields of dialkyl product formed when either THF or DME were used as solvents can best be explained by taking into account the fact that n-butyllithium reacts with both of these solvents much faster than it reacts with ether. Thus, unless the metalation of the carbon acid can compete favorably with the metalation of the solvent, dianion formation will be severely curtailed. Evidently, dimetalation of 2,6-lutidine does not compete favorably with the metalation of THF and DME.

Dianion 11 was also alkylated with benzyl chloride. When 2,6-lutidine was treated with two equivalents of n-butyllithium-TMEDA for

two hours at room temperature with hexane as the solvent followed by treatment with benzyl chloride, 40% of 2,6-diphenethylpyridine (12) was formed.



12

Compound 12 was found to have a picrate which melted at  $154^{\circ}$ , in close agreement with the literature value.<sup>10</sup> Nmr analysis showed the proper structure for 12.

## V. EXPERIMENTAL

### A. General

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes.

Gas chromatograms were run on a Varian Aerograph, series 2700 gas chromatograph equipped with a thermal conductivity detector and using helium as the carrier gas. A 5' x 1/4" SE-30 on Varaport 30 column was used. The composition of mixtures were determined directly from the ratios of the measured areas of the individual peaks.

Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to tetramethylsilane, were measured to the center of a singlet or multiplet. Signals are represented by s for a singlet, d for a doublet, t for a triplet, q for a quartet, and m for a multiplet.

Mass spectra were obtained on as AEI MS-902 mass spectrometer.

All chemicals were dried and distilled prior to use. Octane and hexane were distilled from metallic sodium. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from sodium hydride. The lutidines and N,N,N',N'-tetramethylethylenediamine (TMEDA) were distilled from barium oxide.

All reactions were carried out under an atmosphere of nitrogen.

## B. The Metalation and Subsequent Functionalization of the Various Lutidines

### Preparation of sodium dispersion

Sodium dispersions were prepared by stirring molten sodium in a hydrocarbon solvent at high speed (12,000-15,000 rpm).

In a typical experiment, a 500 ml Morton flask equipped with a high speed stirrer, was fitted with a reflux condenser and a septum. The system was connected to a nitrogen tank via a T-tube leading into the reflux condenser. Into the flask was introduced 5.76 g (0.250 mol) of sodium metal and 150 ml of dry octane. The octane-sodium mixture was refluxed for ten minutes while stirring at 12,000-15,000 rpm. The mixture was cooled to room temperature and most of the octane was removed with a syringe. The sodium dispersion was employed as described below.

### Preparation of n-amylsodium

n-Amylsodium was prepared by the slow addition of n-amyl chloride to a stirred solution of dispersed sodium metal. The sodium dispersion, prepared as described above, was covered with 150 ml of hexane. The solution was cooled to  $-15^{\circ}$  to  $-20^{\circ}$  and 12.26 g (0.125 mol) of n-amyl chloride was added dropwise over a period of 45 minutes with high speed stirring (12,000-15,000 rpm). After the n-amyl chloride was added, the blue suspension was stirred for an additional 0.5 hours and used as described below. A 70% conversion to n-amylsodium was assumed.<sup>12</sup>

Deuteration of 2,3-, 2,4-, 2,5-, and 2,6-lutidine using n-amylsodium and TMEDA

Deuteration of 2,3-, 2,4-, 2,5-, and 2,6-lutidine was performed by treatment of the lutidines with n-amylsodium-TMEDA and subsequent reaction with  $D_2O$ . In a typical experiment, 2.68 g (0.025 mol) of lutidine and 10.15 g (0.088 mol) of TMEDA were added dropwise with high speed stirring (12,000-15,000 rpm) to 0.088 mol of n-amylsodium dispersion described in the previous section at  $-15^{\circ}$ . After the addition was completed, the cooling bath was removed and the mixture was stirred for two hours at room temperature. The solution was then cooled in an ice bath and 10 ml of  $D_2O$  (0.56 mol) was added dropwise. After all the  $D_2O$  was added, 30 ml of water was added to dissolve the salts formed in the reaction.

The organic layer was separated from the water layer and extracted three times with 8 M HCl. The acid layer was combined with the water layer above and the pH checked to make sure it was acidic. The excess acid was neutralized and the lutidine liberated by the addition of excess solid sodium bicarbonate with vigorous stirring and gentle heating. After the evolution of carbon dioxide had moderated, a large excess of sodium bicarbonate was added and the solution stirred for 0.5 hr. The solids were removed by filtration and the lutidines were extracted with three 25 ml portions of ethyl ether or until the ether layer had no noticeable yellow color. The ether was removed by distillation at atmospheric pressure and the residue was distilled at aspirator pressure. Quantitative recovery of 2,3-, 2,4-, and 2,5-lutidine was realized with a 70% recovery of 2,6-lutidine. Mass

spectra were taken of the deuterated lutidines and the results are summarized in Table I (page 13).

Next the methiodide salts of the lutidines were prepared and the melting points and nmr spectra recorded as summarized in Table II (page 14).

The following are all deuterated samples:

2,3-Lutidine, methiodide 203.5° (lit<sup>16</sup> 205°), nmr; (D<sub>2</sub>O), δ 2.57 (s, 2.7H, 3-CH<sub>3</sub>), δ 2.78 (s, 1.0H, 2-CH<sub>3</sub>), δ 4.30 (s, 3.0H, N-CH<sub>3</sub>), δ 7.78 (m, 1.0H, H<sub>5</sub>), δ 8.30 (m, 0.9H, H<sub>4</sub>), δ 8.57 (m, 0.9H, H<sub>6</sub>).

2,4-Lutidine, methiodide 112° (lit<sup>17</sup> 113°), nmr; (D<sub>2</sub>O), δ 2.62 (s, 2.0H, 4-CH<sub>3</sub>), δ 2.78 (s, 1.4H, 2-CH<sub>3</sub>), δ 4.20 (s, 3.0H, N-CH<sub>3</sub>), δ 7.72 (m, 2.0H, H<sub>3</sub> and H<sub>5</sub>), δ 8.57 (m, 0.9H, H<sub>6</sub>).

2,5-Lutidine, methiodide 178° (lit<sup>18</sup> 180°), nmr; (D<sub>2</sub>O) δ 2.52 (s, 3.0H, 5-CH<sub>3</sub>), δ 2.80 (s, 0.7H, 2-CH<sub>3</sub>), δ 4.26 (s, 0H, N-CH<sub>3</sub>), δ 8.07 (m, 1.0H, H<sub>3</sub>), δ 8.24 (m, 1.0H, H<sub>4</sub>), δ 8.63 (m, 0.9H, H<sub>6</sub>).

2,6-Lutidine, methiodide 233.5° (lit<sup>17</sup> 233°), nmr; (D<sub>2</sub>O) δ 2.55 (s, 3.0H, 2- and 6-CH<sub>3</sub>), δ 4.25 (s, 3.0H, N-CH<sub>3</sub>), δ 8.07 (m, 2.0H, H<sub>3</sub> and H<sub>5</sub>), δ 8.41 (m, 1.0H, H<sub>4</sub>).

Formation of 2,6-lutidine dianion 11 by means of n-butyllithium-TMEDA in hexane

A 250 ml three neck flask was fitted with a reflux condenser and an addition funnel with a septum connected to the top. The system was connected to a nitrogen tank by means of a T-tube leading into the reflux condenser. Into the flask was placed a stirring bar, 2.68 g (0.025 mol) of 2,6-lutidine and 5.80 g (0.055 mol) of TMEDA, and 60 ml of hexane. n-Butyllithium, 26 ml of 2.117 (0.055 mol) in hexane

was added dropwise over a period of 10 min. The reaction was allowed to proceed for 2 hours. After this length of time, the reaction was cooled to ca. 0° in an ice bath and used as described below.

#### Deuteration of dianion 11

Dianion 11 (0.025 mol), prepared as described above, was stirred at ca. 0° as 10 ml of D<sub>2</sub>O was added dropwise. After all the D<sub>2</sub>O was added, the ice bath was removed and 30 ml of water was added to dissolve the salts formed during the reaction.

The organic layer was separated from the water layer and extracted three times with 8M HCl. The acid layer was combined with the above water layer and the pH checked to make sure it was acidic. The 2,6-lutidine was liberated with excess sodium bicarbonate added with vigorous stirring and gentle heating. After the evolution of carbon dioxide became moderate, a larger excess of sodium bicarbonate was added and the solution stirred for 0.5 hours. The solids were removed by filtration and the 2,6-lutidine was extracted three times with 25 ml portions of ethyl ether or until no noticeable yellow color was in the ether layer. The ether was distilled at aspirator pressure to give 2.03 g (75%) 2,6-lutidine-d<sub>2</sub> (24) as shown by vpc and quantitative nmr analysis of the methiodide derivative.

#### Alkylation of dianion 11 with methyl iodide

To a stirred solution of 0.025 mol of dianion 11 in 85 ml of hexane at ca. 0°, was added 15.96 g (0.112 mol) of methyl iodide.



The reaction was allowed to proceed for 1 hr. at room temperature after which time the solution was cooled and 30 ml of water was added to dissolve the salts formed. Following the separation procedure in the deuteration of dianion 11, 2.70 g of distillate (25-40°, 0.2 mm) was collected. This was shown by vpc to consist of 33% 2-ethyl-6-methylpyridine and 67% 2,6-diethylpyridine as compared to authentic samples.

#### Alkylation of dianion 11 with benzyl chloride

To a stirred solution of 0.025 mol of dianion 11 in 85 ml of hexane at 0°, was added dropwise 13.00 g (0.10 mol) of benzyl chloride. The reaction was allowed to proceed for 2 hrs. at room temperature after which time the solution was cooled and 30 ml of water was added to dissolve the salts formed.

The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed by distillation at atmospheric pressure and the residue was distilled under vacuum. The fraction which distilled at 170° - 190° and 0.2 mm afforded 11.50 g (40%) of 2,6-diphenethylpyridine (12); picrate 154° (lit<sup>11</sup> 155°); nmr (CDCl<sub>3</sub>),  $\delta$  3.06 (s, 4H, CH<sub>2</sub>),  $\delta$  6.72 (m, 2H, pyridyl),  $\delta$  7.13 (s, 10 H, phenyl),  $\delta$  7.19 (m, 1H, pyridyl).

#### Metalation of 2,6-lutidine by means of n-butyllithium-TMEDA in solvents other than hexane and subsequent alkylation with methyl iodide

The same procedure as that used in the formation of 2,6-lutidine dianion 11 by means of n-butyllithium-TMEDA was used except that

instead of hexane, 60 ml of ether, THF, or DME were used. Methylation of 0.025 mol of dianion 11 with 15.96 g (0.112 mol) of methyl iodide followed by vpc analysis of the reaction mixture gave the results summarized in Table IV.

Table IV.

Results of Alkylation of 2,6-Lutidine Dianion 11 with Methyl Iodide in Various Solvents

Equiv of Base	Reaction Time	Solvent Used	Product Distribution	
			2-ethyl- 6-methyl- pyridine	2,6-diethyl- pyridine
2.0	0.5 hr	hexane	45%	55%
2.0	2.0 hr	hexane	33%	67%
2.0	4.0 hr.	hexane	29%	71%
2.0	20.0 hr	hexane	26%	74%
2.0	2.0 hr	ether	18%	82%
2.0	2.0 hr	THF	61%	39%
2.0	2.0 hr	DME	90%	10%

Metalation of 2,3-, 2,4-, and 2,5-lutidine and subsequent deuteration with deuterium oxide

Treatment of 2,3-, 2,4-, and 2,5-lutidine with n-butyllithium-TMEDA followed by deuteration with deuterium oxide using the same procedure as for the deuteration of 2,6-lutidine dianion, afforded 2,3-, 2,4-, and 2,5-lutidine containing an average of 1.9, 1.4, and 1.5 deuterium atoms per molecule, respectively, as shown by nmr of their methiodides. The specific deuterium content of the various positions within each molecule are given in Table III.

Preparation of authentic sample of 2-ethyl-6-methylpyridine

In a 250 ml three neck flask fitted with a reflux condenser and an addition funnel, was placed a stirring bar, 60 ml ether, and 4.28 g (0.040 mol) of 2,6-lutidine. 20 ml of 2.1 M (0.042 mol) n-butyllithium was added dropwise with stirring. After all the n-butyllithium was added, the reaction was allowed to proceed for 2 hrs. at room temperature after which time the reaction was cooled in an ice bath and 9.12 (0.064 mol) of methyl iodide was added dropwise. After stirring at room temperature for 45 min., the reaction was cooled at ca. 0° and 30 ml of water was added.

The water layer was separated and the organic layer was extracted with three 25 ml portions of 8 M HCl which were combined with the water solution. The product was liberated by the addition of an excess of solid sodium bicarbonate. The 2-ethyl-6-methylpyridine (8) was extracted with three 25 ml portions of ethyl ether and dried over

anhydrous sodium sulfate. The ether was distilled at atmospheric pressure. Distillation of the residue afforded 1.3 g (27%) of pure 2-ethyl-6-methylpyridine (25.5°, 0.2 mm).

Picrate; 130° (lit<sup>5</sup> 130°); nmr (CDCl<sub>3</sub>), δ 1.27 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), δ 2.50 (s, 3H, 6-CH<sub>3</sub>), δ 2.80 (q, 2H, CH<sub>2</sub>), δ 6.88 (m, 2H, H<sub>3</sub> and H<sub>5</sub>), δ 7.41 (m, 1H, C<sub>4</sub>).

## VI. SUMMARY

It was found that treatment of 2,3-, 2,4-, 2,5-, and 2,6-lutidine with 3.5 equivalents of n-amylsodium-TMEDA for two hours at room temperature did not result in quantitative dianion formation but rather the generation of a mixture of polyanionic species ranging from monoanions up to hexaanions. Quenching the reaction mixture with deuterium oxide resulted in a mixture of deuterated species with those which had three deuterium atoms per molecule constituting the highest percent composition of the mixture.

The reactivities of the various methyl groups were determined and found to follow the order 5-methyl < 3-methyl < 4-methyl < 2-methyl. It was also found that in the 2-methyl group, more than one deuterium atom per molecule was incorporated.

There was also a lack of ring metalation compared to chain metalation.

On the other hand, treatment of 2,6-lutidine with two equivalents of n-butyllithium-TMEDA for two hours at room temperature resulted in the formation of its  $\alpha, \alpha'$ -dianion as determined by its reaction with deuterium oxide and subsequent nmr analysis of the methiodide derivative. The  $\alpha, \alpha'$ -dianion of 2,6-lutidine was also alkylated with methyl iodide and benzyl chloride. Moreover, it was found in the case of methylation with hexane as the solvent that a reaction time of at least two hours is needed for maximum dialkylation; however, yields are not significantly improved if longer reaction

times are employed. Also ether was found to be the best solvent of those studied for the formation and subsequent methylation of the 2,6-lutidine dianion. The efficiency of the solvents in respect to the dianion formation was found to follow the order ether > hexane > THF > DME.

When 2,4-lutidine was treated with two equivalents of n-butyllithium-TMEDA for two hours at room temperature, incomplete  $\alpha,\alpha'$ -dianion formation resulted. There was, however, polymetalation of the 2-methyl group even under these conditions.

Treatment of 2,3- and 2,5-lutidine with 3.5 equivalents of n-butyllithium for two hours at room temperature resulted in the incomplete formation of an  $\alpha,\alpha'$ -dianion rather than an  $\alpha,\alpha'$  dianion.

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