PREPARATION AND CHARACTERIZATION
OF SOME 1,2-DIHYDROPYRIDINES

A Thesis
Presented in Partial Fulfillment of the Requirements
for the Degree Master of Science

by
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Approved by

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Dedication

This thesis is dedicated to my husband, Ed, who unfinkingly lent his patient support.
Acknowledgements

The scientific guidance of my advisor, Professor Gideon Fraenkel, and the assistance of Dr. G. Joseph Ray, who performed the decoupling experiments, and Dr. James W. Cooper are gratefully acknowledged.
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I. INTRODUCTION

It is known that acylquinolinium salts undergo nucleophilic attack by bases to produce 1,2-dihydroquinolines.\(^4,5,15\) An example of such a reaction is the production of Reissert compounds such as 1.

\[
\begin{align*}
\text{N-H} + \text{O} & \quad \text{OCCl} \quad \text{KCN} \\
\end{align*}
\]

Acylpyridinium salts should, by analogy, undergo similar reactions. Agawa and Miller found that reaction of certain halides, pyridine, and silver acetylides yielded N-acyl-2-alkynyl-1,2-dihydropyridines, \(^2,11\)

\[
\begin{align*}
\text{N-H} + \text{AgC} \equiv \text{CR} & \quad \text{OCCl} \\
\end{align*}
\]

However, most of the work on this class of compounds has been carried out with acylquinolinium salts.

In an investigation of homoconjugation in spirocyclopropyl anions, the reaction of 3 with ethyl chloroformate was found to give 4.

\[
\begin{align*}
\text{N-H} + \text{CH}_2\text{MgBr} & \quad \text{EtOOCl} \\
\end{align*}
\]
In order to determine the mechanism of this cyclization reaction, a competition reaction involving ethyl chloroformate, \( \text{4-}t\text{-butylpyridine} \), and \( \text{n-butylmagnesium bromide} \) was carried out. If the ethyl chloroformate reacted faster with the Grignard reagent than with the pyridine, most of the charge in \( \text{3} \) must be on the pyridine nitrogen by homoconjugation. If the reaction with the pyridine occurred fastest, then the cyclization reaction must proceed through attack of the Grignard reagent on the pyridinium salt. However, what was found to occur was reaction of all three reagents to produce what was thought to be the \( 1,4\text{-dihydropyridine} \) \( \text{5} \).

\[
\text{EtOCCl} + \text{[Npy]+n-BuMgBr} \rightarrow \text{EtOCN}^\text{O} \text{XnBu}
\]

Such compounds, as well as the \( 1,2 \) isomers, have been prepared by various routes and often isolated in low yield, \( \text{7-11,21-24} \), but few nuclear magnetic resonance (nmr) studies have been undertaken. Only a small number of dihydropyridines have been isolated when prepared by reaction of a Grignard reagent on a pyridinium salt and only the \( 4\)-substituted-\( 1,4\text{-dihydropyridines} \) have been obtained from \( 1\text{-acylpyridinium salts} \), in low yield. \( \text{16} \) It was of interest, then, to prepare and isolate a number of these compounds using different acyl halides, Grignard reagents, and pyridines, to study their nmr spectra, and to determine whether they are the \( 1,2 \) or the \( 1,4 \) isomer.

The expected cleavage reaction,
where MR is a magnesium or lithium organometallic reagent, and the
spectrum of anion 6 were also to be investigated.

The purpose of this research, then, was to prepare, isolate,
and study by means of nmr and other spectroscopic techniques several
dihydropyridines in order to determine their structure and to in-
vestigate the cleavage reactions which they are expected to undergo.
II. HISTORICAL REVIEW

Although the reduction reactions of 1-acyl and 1-arylpyridinium and quinolinium salts yielding dihydro- or tetrahydro-derivatives have been investigated by many researchers, the structures of the products of these reactions have seldom been unambiguously determined. It is known that a variety of anions react with the pyridinium or quinolinium ring systems, but the site of reaction is often uncertain.¹

It has been shown that 1-alkyl and 1-acylquinolinium salts react with Grignard reagents, aqueous base, or aqueous potassium cyanide to produce 1,2-dihydroquinolines.³⁻⁶ Other polycyclic nitrogen heterocycles undergo similar reactions.²

Dihydropyridines have been investigated as intermediates in the reduction of pyridinium ions to tetrahydropyridines. Reduction with sodium or potassium borohydride, Grignard reagents, lithium aluminum hydride, or sodium hydrosulfite was reported to give 1,2-dihydropyridines¹⁻⁷⁻¹⁰, while reduction with sodium amalgam gave the 1,4 isomers.⁸ Sodium borohydride was also reported to give a 1,2,3,6-tetrahydropyridine.¹⁰ The preparation of 1,2,5,6-tetrahydropyridine has also been reported.¹¹ In only one case was appreciable work done to confirm the structure of the product. Saunders and Gold used ultraviolet and nmr spectra for this study.⁹

The condensation reactions of 1-acylpyridinium salts with nucleophilic reagents to form substituted pyridines or dihydropyridines have also been investigated. Usually, 1-acylpyridinium
salts yielded 1,4-dihydropyridines or 4-substituted pyridines in these condensation reactions while 1-acylquinolinium salts gave the 1,2 isomers.5,6,11,13

According to Kosower, attack at the 4-position of pyridinium salts is characteristic of those electron donors which readily form charge-transfer complexes, while others substitute at the 2-position.27 However, Mosher states that addition to 1-acyl or 1-alkylpyridinium salts usually occurs at the 2-position.12 Also, the reaction between certain acid halides, pyridine, and silver acetylides led to 1-acyl-2-alkynyl-1,2-dihydropyridines.11

Acetophenone, pyridine, and benzoyl chloride when reacted over a long period of time at room temperature gave a compound which was either 1-benzoyl-4-phenacyl-1,4-dihydropyridine or the 1,2 isomer. Propiophenone or cyclohexanone gave similar products.5 N-alkyl anilines were reacted with benzoyl chloride and pyridine to give 1-benzoyl-4-(4-N,N-di-alkylaminophenyl)-1,4-dihydropyridines. These decomposed almost immediately, however, to the corresponding 4-substituted pyridine and benzaldehyde.5,6 Benzoyl chloride, pyridine, and phenylmagnesium bromide were found to react to give 1-benzoyl-4-phenyl-1,4-dihydropyridine which was isolable in very low yield and decomposed to 4-phenylpyridine and benzaldehyde.5

Grignard reagents have been shown to react with pyridine itself to give 2- and 4- substituted pyridines in low yields after pro-

 prolonged reaction.15-18 The reaction is believed to proceed through a 1,2 or 1,4-dihydropyridine intermediate.15 Similar reactions with organolithium compounds have also been investigated.19,20 In these
reactions the product is the 2-substituted pyridine. Grignard reagents also add to pyridine N-oxide to give the hydroxy-2-alkyl-1,2-dihydropyridine. 21

Nmr spectroscopy has been used in only a few cases to elucidate the structure of dihydropyridines. 9,22,23 Thus, although reactions involving dihydropyridines either as intermediates or as products have been carried out, few of these compounds have been isolated and the structures of fewer have been unambiguously determined.
III. RESULTS AND DISCUSSION

On combination at 0°C, ethyl chloroformate, n-butylmagnesium bromide, and 4-t-butylpyridine gave what appeared to be 1-carboethoxy-4-t-butyl-1,1-dihydropyridine, 5, as shown by an upfield shift of the ring proton resonances of 1.5 to 2 ppm above those for the aromatic ring protons. 26 Similar reactions were then carried out using various pyridines, Grignard reagents and halides.

A reaction mixture containing ethyl iodide, 4-t-butylpyridine and n-butylmagnesium bromide showed no change in the ring proton resonances from those of pyridine even after several hours of stirring at room temperature. When methyl chloroformate was used in place of ethyl iodide, the aromatic ring proton resonances disappeared, but the spectrum that was obtained consisted of very broad signals and no spectral parameters could be determined. When ethyl chloroformate was used as the halide, reaction was immediate.

The reaction most likely proceeds by nucleophilic attack of the Grignard reagent on a pyridinium salt. The fact that no reaction occurs when ethyl iodide is used as the quaternizing reagent but does occur in the presence of the alkyl chloroformates would tend to support such a mechanism. The carbonyl group in the acylpyridinium salts is very effective in reducing the electron density of the pyridine ring as illustrated by resonance structures 7-11.

\[
\begin{align*}
\text{7} & \quad \text{8} & \quad \text{9} & \quad \text{10} & \quad \text{11} \\
\end{align*}
\]
Attack by the nucleophile at the 2- or 4- positions would then be favored.

The usual order of reaction followed was combination of the pyridine and the Grignard reagent followed by dropwise addition of ethyl chloroformate at 0° C. An immediate change of the grey-green solution to pale yellow took place on addition of the ethyl chloroformate.

The same reaction also occurs when the pyridine and the acylating agent are combined and the Grignard reagent then added, but stirring for several hours is required. The pyridinium salt, \( 7 \), which is formed first is quite insoluble in tetrahydrofuran of diethyl ether, the usual solvents, and vigorous stirring is required to keep enough of the salt in solution to allow attack by the Grignard reagent. When ethyl chloroformate is added to a mixture of the Grignard reagent and the pyridine, however, the salt can undergo nucleophilic attack as fast as it is formed.

On studying the nmr spectra of several of these compounds it became apparent that the spectra were not of the \( A_2B_2 \) type which would be expected for compound \( 5 \). Instead, they were closer to being two different AB spectra. Figure 1 shows the spectrum of the product of the reaction of ethyl chloroformate, \( n \)-butylmagnesium and 4-picoline.

The existence of two conformational isomers was postulated to explain the appearance of four doublets in the spectrum. Differences in conformation could result through inversion at nitrogen or from restricted rotation of the carbonyl group. If such isomers did
exist, the spectrum at elevated temperatures should show a coalescence of the four doublets into two as the rate of conversion from one isomer to the other increased. This was not evident in the spectrum. The signals sharpened because of a decrease in viscosity of the sample, but the chemical shifts did not change. (Figure 2)

This spectrum (Figure 1) would, however, agree with structure 12, 1-carboethoxy-2-n-butyl-4-methyl-1,2-dihydropyridine.

The upfield doublet at 5.36 ppm is attributed to the proton on the saturated ring carbon. This proton is bonded to an allylic carbon, is affected by the high diamagnetic anisotropy of the carbonyl group, and is subject to the electron withdrawing influence of the nitrogen. Thus, the shift is lower than normally expected for a proton on a saturated carbon. The center doublets at 4.97 and 4.75 ppm are due to the protons in the 3 and 5 positions, respectively. The far downfield resonance is that of the olefinic proton on the carbon atom to nitrogen.

Nmr parameters for several 1,2-dihydropyridines are given in Table 1. Of these, 12,13,14, and 15 have been isolated. The colorless, viscous liquids are stable in air and distillable under vacuum at about 100°C.

1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine, 13.
FIGURE 1  Nmr Spectrum, 60 MHz, of 12 in CCl₄
FIGURE 2  Nmr Spectrum, 80 MHz, of $^{13}$ in CCl$_4$ at Elevated Temperatures.
gives the nmr spectrum in Figure 3. In order to ascertain that
the doublet at 4.70 ppm was actually due to the overlapping resonances
of hydrogens in the 3 and 5 positions, the spectrum was determined
at 100 MHz at low temperatures (Figure 4). Nmr parameters are
given in Table 2.

The central signal is indeed more than a doublet and, at -51°C,
it is distinctly two doublets of equal intensity. Thus, the
spectrum consists of four doublets of equal intensity—the spectrum
expected for structure 13. The small signals at 3.16, 4.43, and
5.57 ppm may be due to the type of conformational isomer previously
expected. The magnitude of these differences in chemical shift is
much closer to what would be expected for such isomers.

Decoupling experiments performed on a sample of 13 also support,
but do not definitively prove correct, the assignment of this
structure to the product. On irradiation of the H2 resonance, the
doublet at 4.62 ppm collapses to a singlet, indicating that this doublet
is due to the H3 resonance (Figure 5). When the signal at 3.19 ppm,
attributed to H6, is irradiated, the H5 doublet becomes a singlet.
When the center signal, due to overlap of the H3 and H5 doublets is
irradiated, both H2 and H6 doublets collapse to singlets.

It was still conceivable that these spectra could be due to
1,4-dihydropyridines existing in two isomeric forms. A series of
cleavage reactions and an nmr study of the anions produced was used
### Table 1

**Nmr Parameters of 1-carboethoxy-2,4-disubstituted-1,2-dihydropyridines**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>R'</th>
<th>solvent</th>
<th>H₂</th>
<th>H₃</th>
<th>H₅</th>
<th>H₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>n-Bu</td>
<td>CH₃</td>
<td>CCl₄</td>
<td>5.36</td>
<td>4.97</td>
<td>4.75</td>
<td>3.28</td>
</tr>
<tr>
<td>13</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>CCl₄</td>
<td>5.43</td>
<td>4.70</td>
<td>4.70</td>
<td>3.27</td>
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<tr>
<td>14</td>
<td>Ø</td>
<td>CH₃</td>
<td>CCl₄</td>
<td>a</td>
<td>4.82</td>
<td>4.32</td>
<td>3.25²</td>
</tr>
<tr>
<td>15</td>
<td>n-Bu</td>
<td>Et</td>
<td>CCl₄</td>
<td>5.32</td>
<td>4.90</td>
<td>4.73</td>
<td>3.33</td>
</tr>
<tr>
<td>16</td>
<td>n-Bu</td>
<td>H</td>
<td>THF³</td>
<td>a</td>
<td>4.51</td>
<td>4.34</td>
<td>3.42</td>
</tr>
<tr>
<td>17</td>
<td>CH₃</td>
<td>CH₃</td>
<td>Et₂O</td>
<td>5.59</td>
<td>4.75</td>
<td>4.75</td>
<td>a</td>
</tr>
<tr>
<td>18</td>
<td>CH₃</td>
<td>t-Bu</td>
<td>Et₂O</td>
<td>5.65</td>
<td>4.74</td>
<td>4.74</td>
<td>3.57³</td>
</tr>
<tr>
<td>19</td>
<td>Ø</td>
<td>t-Bu</td>
<td>THF</td>
<td>a</td>
<td>4.70</td>
<td>4.33</td>
<td>3.23</td>
</tr>
<tr>
<td>20</td>
<td>n-Bu</td>
<td>t-Bu</td>
<td>THF</td>
<td>5.37</td>
<td>4.72</td>
<td>4.72</td>
<td>3.37</td>
</tr>
<tr>
<td>21</td>
<td>CH₃</td>
<td>CH₃</td>
<td>THF</td>
<td>5.29</td>
<td>4.99</td>
<td>4.99</td>
<td>3.37</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>J₂₃</th>
<th>J₅₆</th>
<th>accuracy</th>
<th>No.</th>
<th>J₂₃</th>
<th>J₅₆</th>
<th>accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>7.0</td>
<td>7.0</td>
<td>±1.0</td>
<td>17</td>
<td>6.5</td>
<td>a</td>
<td>±1.0</td>
</tr>
<tr>
<td>13</td>
<td>6.0</td>
<td>7.0</td>
<td>1.0</td>
<td>18</td>
<td>7.0</td>
<td>8.0</td>
<td>1.0</td>
</tr>
<tr>
<td>14</td>
<td>6.0</td>
<td>5.0 ²</td>
<td>1.0</td>
<td>19</td>
<td>7.0</td>
<td>7.0</td>
<td>1.0</td>
</tr>
<tr>
<td>15</td>
<td>7.0</td>
<td>6.5</td>
<td>1.0</td>
<td>20</td>
<td>7.0</td>
<td>8.0</td>
<td>1.0</td>
</tr>
<tr>
<td>16</td>
<td>5.0</td>
<td>7.0</td>
<td>1.0</td>
<td>21</td>
<td>7.0</td>
<td>8.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- a— line too broad to assign parameter  
- b— broad doublet, value approximate  
- d— two small, broad doublets  
- e— prepared with CH₃₂Mg  
- c— tetrahydrofuran
FIGURE 3  Nmr Spectrum, 60 MHz, of $\text{^{13}}\text{C}_4$
FIGURE 4  Nmr Spectrum, 100 MHz, of 13 in Acetone at Low Temperature
TABLE 2
Nmr Parameters for 13, 100 MHz in Acetone

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>H2</th>
<th>H3</th>
<th>H5</th>
<th>H6</th>
<th>J23</th>
<th>J56</th>
</tr>
</thead>
<tbody>
<tr>
<td>+25</td>
<td>5.40</td>
<td>4.62</td>
<td>4.56</td>
<td>3.19</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>-30</td>
<td>5.44</td>
<td>4.68</td>
<td>4.58</td>
<td>3.24</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>-51</td>
<td>5.48</td>
<td>4.69</td>
<td>4.53</td>
<td>3.24</td>
<td>6.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

all values measured from acetone
to further prove that these compounds are, in fact, the 1,2-dihydropyridines.

\[ 13 \text{ was found to undergo cleavage with organometallic reagents to form anion } 22a, \text{ which is stable for approximately one hour at } 0^\circ C. \text{ The general upfield shift of the ring proton resonances is taken as evidence for the formation of the anion. Nmr parameters are given in Table 3. On addition of 0.06 milliliters of ethyl chloroformate, a spectrum identical to that of 13 is produced.} \]

It is known that the \( n \)-butyllithium adduct of pyridine has structure \( 23. 19, 20 \)

Addition of \( t \)-butyllithium to \( 4 \)-\( t \)-butylpyridine, then, should yield \( 22b \).

\[ (\text{CH}_3)_3\text{C Li} + \text{Py} \rightarrow \text{Li}^+\text{N} \text{Py} \]

The nmr spectrum of this anion was identical to that of \( 22a \). On addition of the anion capturing reagent ethyl chloroformate, the spectrum of 1-carboethoxy-2,4-di-\( t \)-butyl-1,2-dihydropyridine was produced. Table 3 summarizes the nmr parameters of these anions and the dihydropyridines produced when they are captured. The
FIGURE 5. Decoupling Experiments, 100 MHz
chemical shifts of the protons in anions 22a, 22b, and 23 are very similar, indicating that these are the anions of the corresponding 1,2-dihydropyridines. Addition of ethyl chloroformate to both 22a and 22b produces spectra identical to that of the originally isolated 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine 13.

The nmr parameters can also be compared to those determined for N-phenyl-1,2-dihydropyridine, 24, and N-phenyl-1,4-dihydropyridine, 25, by Saunders and Gold. The position of the resonance of H2 in each of these can be compared to that of H2 in 13. In 24, this signal is found at 5.74 ppm; in 25 at 3.73 ppm. The resonance of the corresponding proton in 13 lies at 5.40 ppm, indicating a structure similar to that of 24.

If 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine is refluxed for three hours with two equivalents of n-butyllithium, a reddish-brown solution and whitish precipitate are obtained. The nmr spectrum of the solution is characteristic of 26. (Figure 6), or of the 2-n-buty derivative.

The solution was hydrolyzed, the product isolated, and the nmr parameters determined. The chemical shifts for the ring protons
TABLE 3
Nmr Parameters for Cleavage Reactions

\[ \text{Diagram of molecular structure} \]

<table>
<thead>
<tr>
<th>X</th>
<th>COMPOUND</th>
<th>SOLVENT</th>
<th>H₂</th>
<th>H₃</th>
<th>H₅</th>
<th>H₆</th>
<th>J₂₃</th>
<th>J₅₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Et₂O-pentane</td>
<td></td>
<td>5.40</td>
<td>4.69</td>
<td>4.69</td>
<td>3.22</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td></td>
<td>5.32</td>
<td>4.62</td>
<td>4.62</td>
<td>3.16</td>
<td>4.5</td>
<td>7.5</td>
</tr>
<tr>
<td>&quot;</td>
<td>22a+</td>
<td></td>
<td>5.32</td>
<td>4.60</td>
<td>4.60</td>
<td>3.22</td>
<td>7.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Li</td>
<td>22b</td>
<td></td>
<td>6.30</td>
<td>5.44</td>
<td>5.44</td>
<td>3.24</td>
<td>4.5</td>
<td>6.0</td>
</tr>
<tr>
<td>Li</td>
<td>22a</td>
<td></td>
<td>6.36</td>
<td>5.66</td>
<td>5.38</td>
<td>3.32</td>
<td>4.19</td>
<td>5.83</td>
</tr>
</tbody>
</table>
are 2.80 τ for H₃, 3.08 τ for H₅, and 1.67 τ for H₆. These can be compared with those for the ring protons in pyridine itself. (H = 1.50 τ, H = 2.64 τ, H = 3.0 τ) 30 2,4-di-t-butylpyridine would thus be produced by loss of lithium hydride from 22a.

Thus, the product of the reaction of n-butylmagnesium bromide, 4-t-butyldipyridine and ethyl chloroformate, originally thought to be 1-carboethoxy-4-n-butyl-4-t-butyl-1,4-dihydropyridine, 2, is actually 1-carboethoxy-2-n-butyl-4-t-butyl-1,2-dihydropyridine.

A cleavage reaction with alcoholic potassium hydroxide was also attempted. No reaction occurred even after refluxing for 48 hours.

Ozonolysis of 13 yielded a white gum, the nmr spectrum of which showed one singlet at 8.80 τ, most likely due to the t-butyl group.

The major mass spectral fragments of compounds 12, 13, 14, and 15 also support the 1,2-dihydropyridine structure. Compounds 12, 13, and 15 show extremely similar fragmentation patterns. (Tables 4, 5, 6) Cleavage of the bond β to the nitrogen atom is a very important fragmentation process in the mass spectra of amines and is favored if a carbon–carbon bond is involved. 29 Thus, the alkyl group in the 2-position is easily lost as a radical. The phenyl group in 1h would not form a very stable radical and, therefore, is not easily lost as such. (Table 7)

Esters typically lose alkoxy radicals and, thus, fragments of mass 220, 192, and 178 are found for 12, 13, and 15, corresponding to loss of ethoxy radical. Esters can also rearrange and lose an olefin, in this case ethylene, giving fragments of mass 180, 152, 138, and, for 1h, 214. Complete loss of the ester function
FIGURE 6. Nmr Spectrum, 60 MHz, of 25 in CCl₄.
accompanied by rearrangement of a hydrogen atom to nitrogen occurs in all cases, followed by loss of this hydrogen. Loss of hydrogen from the group in the 4 position is also seen in the spectra of all four compounds.
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**TABLE 5**

Major Mass Spectral Fragments of 13
**TABLE 6**

Major Mass Spectral Fragments of 15

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IV. SUMMARY AND CONCLUSIONS

The reaction of acyl halides, Grignard reagents, and pyridines yielded products which were assumed to be 1,4-dihydropyridines. Further study of the nmr spectra of these products indicated that they were most likely not the 1,4-isomer. Decoupling experiments, nmr spectra at elevated temperatures, cleavage and recapturing experiments and mass spectra were used to determine the structure of these products.

The behavior of the proton resonances when irradiated, the lack of coalescence of the signals at elevated temperatures, the mass spectral fragmentation patterns, and, particularly, the similarities of the nmr spectra of the anions of these products with that of the adduct of t-butyllithium and 4-tert-butylpyridine indicate that 1-carboethoxy-2,4-disubstituted-1,2-dihydropyridines, and not the 1,4-isomers, are the products of the reaction of ethyl chloroformate, Grignard reagents, and pyridines.
V. EXPERIMENTAL

1. Instruments

Nmr spectra, other than those for decoupling experiments, were obtained using a Varian A-60-A spectrometer. Decoupling experiments were undertaken with a model HA-100 Varian spectrometer. A Carey model 14 spectrophotometer was used to determine ultaviolet spectra and a Perkin-Elmer Infracord Spectrophotometer for inrared spectra. Mass spectra were obtained with an AEI model MS-9 instrument.

2. Reagents

A list of reagents and their suppliers follows.

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<td>pyridine</td>
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<td>4-picoline</td>
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<tr>
<td>4-ethylpyridine</td>
<td>Reilly Tar and Chemical Corp.</td>
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<tr>
<td>4-t-butylpyridine</td>
<td>K and K Laboratories, Inc.</td>
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<tr>
<td>magnesium turnings</td>
<td>Mallinckrodt Chemical Works</td>
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<td>1-buty1bromide</td>
<td>Eastman Organic Chemicals</td>
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<td>methyl iodide</td>
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<td>bromobenzene</td>
<td>Matheson, Coleman and Bell</td>
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<td>di-n-butylmercury</td>
<td>Orgmet, Inc.</td>
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<td>J.T. Baker Chemical Co.</td>
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<tr>
<td>n-butyllithium</td>
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29
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<td>diethyl ether</td>
<td>Allied Chemical Corp.</td>
</tr>
<tr>
<td>tetrahydofuran</td>
<td>E.I. DuPont De Nemours &amp; Co., Inc.</td>
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</table>

4-picoline was distilled from calcium hydride and stored over potassium hydroxide pellets. All other pyridines were used without purification. Diethyl ether and tetrahydofuran were distilled from lithium aluminum hydride immediately before use.

3. Preparation of Grignard Reagents

Preparation of n-butylmagnesium bromide. A three necked $\frac{24}{40} 250$ ml. round bottomed flask containing a magnetic stirring bar was fitted with a reflux condenser topped with a straight $\frac{24}{40}$ inner joint filled with Drierite and two $\frac{24}{40}$ inner joints attached to stopcocks. The outside stopcock openings were closed with rubber serum caps. The apparatus was flushed with argon and flamed for five minutes. Magnesium turnings (8.0 g, 0.33 mole) were introduced by quickly removing and then replacing one stopcock and joint and the flask was flushed with argon for five minutes longer. The magnesium was washed with two 15 ml. portions of freshly dried THF and then 70 ml. of dry THF was added to the flask with a syringe. Stirring was begun and approximately 5 ml. of a solution of n-butyl bromide (27.24 g, 0.2 mole) in 30 ml. of dry THF was introduced dropwise by syringe. Reaction began immediately. The
solution was cooled in an ice bath and addition of the halide was completed at a rate of sufficient to maintain the reaction. The solution was then refluxed for several minutes, cooled, and transferred to a 5 24/40 flask fitted with a 5 24/40 inner joint attached to a stopcock and closed with a serum cap.

The concentration of the solution was determined by adding one milliliter of it to 10 ml. of distilled water. Three drops of methyl orange solution were added and the solution was titrated with 0.1007 N hydrochloric acid. It was found to have a titer of 2.85 M and was diluted with dry THF to yield a solution 1.65 M in butylmagnesium bromide.

Preparation of phenylmagnesium bromide and t-butyilmagnesium chloride. Preparation of these Grignard reagents was carried out in a manner similar to that for n-butyilmagnesium bromide, but on a smaller scale. In both cases, magnesium turnings (1.2 g, 0.05 mole), 0.025 mole of the halide, and a total of 25 ml. of THF were used. The titer of the t-butyilmagnesium chloride solution was 0.78 M; of the phenylmagnesium bromide solution 1.4 M.

Preparation of methylmagnesium iodide. This Grignard reagent was prepared in a 5 24/40 100 ml. three-necked, round bottom flask prepared the same way as the larger flask in the above procedure. Magnesium turnings (1.92 g, 0.08 mole) were washed with two 10 ml. portions of freshly dried diethyl ether and then 40 ml. of dry diethyl ether were added to the flask. Approximately 2 ml. of a solution of methyl iodide (2.3 g, 0.04 mole) in 10 ml. of dry diethyl ether were added, with stirring. Once the reaction was
initiated, the remainder of the halide solution was added slowly. When addition was complete, the solution was refluxed for several minutes, transferred to a $24/40$ flask with a stopcock for storage, and titrated. The concentration was $1.09$ M.

4. Preparation of 1-carboethoxy-2,4-disubstituted-1,2-dihydropyridines.

Initial preparation of these compounds was carried out in a $24/40$ vial, containing a magnetic stirring bar and fitted with a stopcock and serum cap (Figure 7), yielding enough solution for preparation of an nmr sample. The vial was flamed and flushed with argon and a positive pressure of argon was maintained during the reaction.

Preparation of 1-carboethoxy-2-n-butyl-4-t-butyl-1,2-dihydopyridine. To the prepared vial was added 4-t-butylpyridine (1.35 g, 0.01 mole). The vial was placed in an ice bath, stirring was begun, and butylmagnesium bromide was added (12.1 ml, 1.65 M solution, 0.02 mole) was added. Then ethyl chloroformate (1.08 g, 0.01 mole) was added dropwise. Reaction took place immediately, as seen by the change of the grey-green color of the Grignard solution to a pale yellow. An aliquot of solution was withdrawn by syringe and injected into a flamed and argon-flushed nmr tube.

Preparation of other 1,2-dihydropyridines. The other 1-carboethoxy-2,4-disubstituted-1,2-dihydropyridines were prepared in exactly the same manner as above but on different scales. Each compound is listed below along with the amounts of each reagents used.
--rubber serum cap

--glass stopcock, 2mm, straight bore

--324/40 inner joint

--324/40 outer joint

--magnetic stirring bar

FIGURE 7 Stopcock Vial
1-carboethoxy-2-n-butyl-4-ethyl-1,2-dihydropyridine. 4-ethylpyridine (0.53 g, 5x10^{-3} mole), n-butylmagnesium bromide (8.7 ml, 1.15 M solution, 1x10^{-2} mole), and ethyl chloroformate (0.54 g, 5x10^{-3} mole).

1-carboethoxy-2-n-butyl-4-methyl-1,2-dihydropyridine. 4-picoline (0.47 g, 5x10^{-3} mole), n-butylmagnesium bromide (8.7 ml, 1.15 M solution, 1x10^{-3} mole), and ethyl chloroformate (0.54 g, 5x10^{-3} mole).

1-carboethoxy-2-n-butyl-1,2-dihydropyridine. Pyridine (0.1 g, 1.25 x 10^{-3} mole), n-butylmagnesium bromide (1.6 ml, 1.65 M solution, 2.5 x 10^{-3} mole), and ethyl chloroformate (0.13 g, 1.25 x 10^{-3} mole).

1-carboethoxy-2-phenyl-4-methyl-1,2-dihydropyridine. 4-picoline (0.12 g, 1.25 x 10^{-3} mole), phenyl magnesium bromide (1.8 ml, 1.4 M solution, 2.5 x 10^{-3} mole), and ethyl chloroformate (0.13 g, 1.25 x 10^{-3} mole).

1-carboethoxy-2-phenyl-4-t-butyl-1,2-dihydropyridine. 4-t-butylpyridine (0.17 g, 1.25 x 10^{-3} mole), phenylmagnesium bromide (1.8 ml, 1.4 M solution, 2.5 x 10^{-3} mole), and ethyl chloroformate (0.13 g, 1.25 x 10^{-3} mole).

1-carboethoxy-2-methyl-4-t-butyl-1,2-dihydropyridine. 4-t-butylpyridine (0.17 g, 1.25 x 10^{-3} mole), methylmagnesium iodide (2.3 ml, 1.09 M solution, 2.5 x 10^{-3} mole), and ethyl chloroformate (0.13 g, 1.25 x 10^{-3} mole).

1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine. 4-t-butylpyridine (0.08 g, 6.2 x 10^{-4} mole), t-butylmagnesium chloride (1.6 ml, 0.78 M solution, 1.25 x 10^{-3} mole), and ethyl chloroformate (0.066 g, 6.2 x 10^{-4} mole).
Nmr data for these compounds is listed in Table 1.

**Isolation of 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine.**

In order to prepare these compounds on a larger scale and isolate them, a $\frac{14}{20}$ 100 ml. round bottom flask, fitted with a reflux condenser topped by a serum cap and two stopcocks closed with serum caps and attached to $\frac{14}{20}$ inner joints was flamed in a current of dry argon. (Figure 8)

As described above, 4-t-butylpyridine (1.01 g, 7.5 x $10^{-3}$ mole), t-butylmagnesium chloride (20 ml, 0.78 M solution, 1.56 x $10^{-2}$ mole), and ethyl chloroformate (0.81 g, 7.5 x $10^{-3}$ mole) were reacted at 0°C and stirred for 30 minutes at room temperature. The reaction mixture was hydrolyzed at 0°C with approximately 1 ml. of water and the resulting slurry was filtered. The white precipitate was washed with a few milliliters of THF and the washings added to the solution. This was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed on a rotary evaporator. The resulting viscous substance was placed in one arm of the apparatus pictured in Figure 9 and distilled on a vacuum line by heating the crude material with an air gun and immersing the receiving arm in liquid nitrogen. A yield of 55% was obtained, b.p., ca. $110^\circ\text{C}/0.001$ mm, max 2921 $\tilde{\nu}$, IR : 3000 cm$^{-1}$ (s), 1700 cm$^{-1}$ (s), 1365 cm$^{-1}$ (s), 1300-1275 cm$^{-1}$ (s), 1110-1090 cm$^{-1}$ (s), and 975 cm$^{-1}$ (m). (Figure 10)

**Isolation of 1-carboethoxy-2-n-butyl-4-ethyl-1,2-dihydropyridine.**

By means of the previous procedure, 4-ethyl-pyridine (0.83 g, 7.5 x $10^{-3}$ mole), n-butylmagnesium bromide (10 ml, 1.56 M solution, 1.56 x $10^{-2}$ mole), and ethyl chloroformate (0.81 g, 7.2 x $10^{-3}$ mole) were
--- rubber serum cap

--- condenser

--- rubber serum cap

--- glass stopcock 2mm, straight bore

--- 314/20 joints --inner

--- outer

--- magnetic stirring bar

FIGURE 8 Preparation Apparatus
FIGURE 9 Distillation Apparatus

- $\frac{3}{12}/30$ inner joint
- Glass vacuum stopcock
- $\frac{3}{14}/20$ joints
  - Outer
  - Inner
- Magnetic stirring bar
reacted. The product on workup had a b.p., ca. 85°/0.004 mm, max 2690 \( \tilde{\nu} \), IR; 3000 cm\(^{-1}\) (s), 1699 cm\(^{-1}\) (s), 1475 cm\(^{-1}\) (m), 1310-1270 cm\(^{-1}\) (m), 1190 cm\(^{-1}\) (w), 1110-1090 cm\(^{-1}\) (m), 1040 cm\(^{-1}\) (w). (Figure 11)

**Isolation of 1-carboethoxy-2-n-butyl-4-methyl-1,2-dihydropyridine.**

Again, the same procedure was followed, using 4-picoline (0.7 g, 7.5 x 10\(^{-3}\) mole), \( n \)-butylmagnesium bromide (10 ml, 1.0 M solution, 1.5 x 10\(^{-2}\) mole), and ethyl chloroformate (0.81 g, 7.5 x 10\(^{-3}\) mole). max 2910 \( \tilde{\nu} \), IR: 3000 cm\(^{-1}\) (s), 1700 cm\(^{-1}\) (s), 1380 cm\(^{-1}\) (m), 1310-1275 cm\(^{-1}\) (s), 1160 cm\(^{-1}\) (s), 1110-1090 cm\(^{-1}\) (m). (Figure 12)

**Isolation of 1-carboethoxy-2-phenyl-4-methyl-1,2-dihydropyridine.**

The same procedure and molar ratios were used in the preparation of this compound; 4-picoline (0.72 g, 7.5 x 10\(^{-3}\) mole), phenylmagnesium bromide (1.5 ml, 1.03 M solution, 1.5 x 10\(^{-2}\) mole), and ethyl chloroformate (0.81 g, 7.5 x 10\(^{-3}\) mole). max 2682 \( \tilde{\nu} \), IR: 3000 cm\(^{-1}\) (s), 1700 cm\(^{-1}\) (s), 1360 cm\(^{-1}\) (m), 1310-1275 cm\(^{-1}\) (s), 1120-1095 cm\(^{-1}\) (m), and 1165 cm\(^{-1}\) (m). (Figure 13)

1-carboethoxy-2,4-dimethyl-1,2-dihydropyridine was also prepared by the reaction of 4-picoline (0.12 g, 1.25 x 10\(^{-3}\) mole), dimethylmagnesium (0.8 ml, 3M solution in THF, 2.5 x 10\(^{-3}\) mole), and ethyl chloroformate (0.13 g, 1.25 x 10\(^{-3}\) mole) in the general manner used above. The nmr data for this compound is compared with that for the compound produced using methylmagnesium iodide in Table 1.

**Attempted preparation of 1-carbomethoxy-2-n-butyl-4-methyl-1,2-dihydropyridine.** In an apparatus identical to that used for the preparation of the 1-carboethoxydihydropyridines, 4-picoline (0.47
FIGURE 11 IR Spectrum of 15
g, $5 \times 10^{-3}$ mole) and $n$-butylmagnesium bromide (10 ml, 1.65 M solution, $1.5 \times 10^{-2}$ mole) were mixed and placed in an ice bath. Methyl chloroformate ($0.47$ g, $5 \times 10^{-3}$ mole) was added dropwise, with stirring. After standing at room temperature for one day only a very small amount of the dihydropyridine was produced, as seen in the nmr spectrum. The reaction was not investigated further.

**Attempted preparation of 1-ethyl-2-n-butyl-4-t-butyl-1,2-dihydropyridine.** 4-t-butyl bromide ($0.07$ g, $5 \times 10^{-4}$ mole), $n$-butylmagnesium bromide ($0.3$ ml, 1.65 M solution, $5 \times 10^{-4}$ mole), and ethyl iodide ($0.078$ g, $5 \times 10^{-3}$ mole) were combined in the manner described above. A white precipitate was obtained, but no dihydropyridine was produced.

5. **Attempted reaction of organomercury compounds with the acylpyridinium salt.**

**Reaction of di-$n$-butylmercury with 1-carboethoxy-4-t-butylpyridinium chloride.** To a 2$\frac{1}{2}$/40 vial, flamed and flushed with argon, and fitted with a stopcock and serum cap, was added 4-t-butylpyridine ($0.17$ g, $1.25 \times 10^{-3}$ mole), di-$n$-butyl-mercury ($0.39$ g, $1.25 \times 10^{-3}$ mole), and 1.25 ml of THF. The vial was placed in an ice bath and ethyl chloroformate ($0.13$ g, $1.25 \times 10^{-3}$ mole) was added slowly by syringe. The reaction mixture was refluxed for 10 hours. A similar reaction using $D_2O$ as the solvent was also carried out. In neither case did a reaction occur.

**Reaction of $n$-butylmercuric chloride with 1-carboethoxy-4-t-butylpyridinium chloride.** $N$-butylmercuric chloride was prepared by heating di-$n$-butylmercury ($5.3$ g, $1.7 \times 10^{-2}$ mole) and mercuric
chloride (4.6 g, 1.7 x 10^{-2} mole) in 20 ml. of methanol at 36° for 30 minutes and at 46° for 30 minutes. The white, crystalline precipitate was filtered, washed with cold methanol, and dried by suction. It was used without further purification.

N-butylmercuric chloride (0.37 g, 1.25 x 10^{-3} mole) was dissolved in 1 ml. of D₂O and placed in a vial in an ice bath. To this was added 4-t-butylpyridine (0.17 g, 1.25 x 10^{-3} mole) and ethyl chloroformate (0.13 g, 1.25 x 10^{-3} mole), the mixture was stirred and brought to room temperature. Nmr samples were taken over several days. The reaction was also attempted, in the same manner, using dimethyl formamide as the solvent. In neither case did a reaction occur, even after one week at room temperature.

Reaction of n-butylmercuric chloride with 1-methyl-4-t-butylpyridinium chloride. The reaction of n-butylmercuric chloride (0.37 g, 1.25 x 10^{-3} mole), 4-t-butylpyridine (0.17 g, 1.25 x 10^{-3} mole), and methyl iodide (0.178 g, 1.25 x 10^{-3} mole) in 1 ml. of D₂O was carried out in the manner described above. After refluxing overnight no reaction had occurred.

6. Cleavage reactions of 1-carboethoxy-2,4-disubstituted-1,2-dihydropyridines.

Cleavage of 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine with n-butyllithium. Into a flamed and argon-flushed % 24/40 vial fitted with a teflon stopcock on a % 24/40 inner joint and closed with a serum cap, 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine (0.2 g, 7.4 x 10^{-4} mole) was injected with a 1 c.c. syringe. The vial was placed in an ice bath and n-butyllithium (1.0 ml, 1.5 M
solution in hexane, \(1.48 \times 10^{-3}\) mole) was added slowly, with stirring. The nmr spectrum of the resulting yellow solution indicated the presence of the anion 22a. (Table 3). On addition of ethyl chloroformate (0.079 g, \(7.4 \times 10^{-3}\) mole), the starting material was formed again, as seen in the nmr spectrum.

Also in a vial which had been flamed in a current of dry argon, 1-carboethoxy-2,\(^4\)-di-t-butyl-1,2-dihydropyridine (0.8 g, \(2.9 \times 10^{-3}\) mole) and \(n\)-butyllithium (4.0 ml, 1.5 M solution, \(5.8 \times 10^{-3}\) mole) were combined in the same manner as above. After addition of the \(n\)-butyllithium, the solution was refluxed for three hours. The resulting deep red solution was found to contain 2,\(^4\)-di-t-butylpyridine, 26. In order to isolate this material, the solution was hydrolyzed at \(0^\circ\), giving a pale yellow solution and a white precipitate. The solution was extracted with three 5 ml. portions of 1 M aqueous sulfuric acid. The aqueous extracts were combined, made basic with 10% sodium hydroxide, and this was extracted with three 10 ml. portions of diethyl ether. The ether was removed on a rotary evaporator and the product was identified by nmr spectroscopy.

Cleavage of 1-carboethoxy-2,\(^4\)-di-t-butyl-1,2-dihydropyridine with \(n\)-butylmagnesium bromide. A \(\$14/20\) 25 ml. round bottom flask, equipped with a reflux condenser topped with a serum cap and a stopcock on a \(\$14/20\) inner joint, was flamed in a current of argon. 1-carboethoxy-2,\(^4\)-di-t-butyl-1,2-dihydropyridine (0.2 g, \(7.4 \times 10^{-4}\) mole), \(n\)-butyl-magnesium bromide (1.32 ml, 1.04 M solution, \(1.48 \times 10^{-3}\) mole) and 1 ml. of dry THF were added and the mixture was refluxed for 42 hours. An nmr spectrum characteristic of 2,\(^4\)-
di-t-butylypyridine, 26, was obtained. Addition of ethyl chloroformate produced no change in the spectrum.

**Attempted cleavage of 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine with alcoholic potassium hydroxide.** In an argon-flushed 24/40 vial fitted with a stopcock and serum cap, a solution of potassium hydroxide in ethanol (0.4 ml, 5 M solution, 1.8 x 10^{-3} mole) was degassed by means of argon ebullitions for five minutes. 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine was added and the solution was refluxed for four days. No evidence of reaction was found in the nmr spectrum.

**Reaction of 4-t-butylypyridine with t-butyllithium.** A flame, argon-flushed vial was placed in a dry ice-acetone bath (-78°) and 4-t-butylypyridine (0.52 g, 3.88 x 10^{-3} mole) was added. Dropwise, t-butyllithium (2.0 ml, 1.9 M solution in pentane, 3.88 x 10^{-3} mole) was introduced. After addition of approximately half the t-butyllithium, the solution turned deep red. The addition was continued and an aliquot of solution was withdrawn and injected into an nmr tube. A spectrum characteristic of anion 22b was obtained. Also at -78°, ethyl chloroformate (0.42 g, 3.88 x 10^{-3} mole) was added to the reaction mixture dropwise. A spectrum characteristic of 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine was obtained.

7. **Ozonolysis of 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine.**

A bubbler with a fritted glass disc on the delivery tube was placed in a dry ice-isopropanol bath. Enough methanol was added to immerse the disc and 1-carboethoxy-2,4-di-t-butyl-1,2-dihydropyridine
(1.3 g, 5.0 x 10^-3 mole) was added and ozonized until the solution seemed definitely blue (approximately 10 minutes). The ozonizer current was shut off and oxygen was bubbled through the solution for 15 minutes. The solution was transferred to a 24/40 three-necked, round bottom flask and placed in an ice bath. Dropwise, 65 ml. of glacial acetic acid and then 10 ml. of 30% hydrogen peroxide which had been acidified with 0.75 ml. of concentrated sulfuric acid were added. The flask was fitted with a reflux condenser, a mechanical stirrer, and a 24/40 stopper. The solution was refluxed for two hours, cooled, and transferred to a 500 ml. separatory funnel. Approximately 30 ml. of diethyl ether were added and the solution was extracted with three 125 ml. portions of 10% sodium hydroxide. The combined extracts were acidified with concentrated hydrochloric acid and extracted with three 70 ml. portions of diethyl ether. The solvent was removed on a rotary evaporator, leaving a white gum and some excess acetic acid. This was filtered, the gum washed with water and dissolved in 15 ml. of diethyl ether. This solution was dried over anhydrous magnesium sulfate, filtered, and the ether was removed by evaporation. The product was dissolved in carbon tetrachloride and this solution was placed in an nmr sample tube.
Bibliography


4. a. A. Reissert, ibid., 38, 1603 (1905).
   b. A. Reissert, ibid., 38, 3415 (1905).


