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REDUCTION OF KETOXIMES BY LITHIUM ALUMINUM HYDRIDE

ANTHONY EDWARD PETRARCA

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REDUCTION OF KETOXIMES BY LITHIUM ALUMINUM HYDRIDE

Keywords
Chemistry, Organic

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University of New Hampshire, Ph.D., 1959

Chemistry, organic
REDUCTION OF KETOXIMES

BY

LITHIUM ALUMINUM HYDRIDE

BY

ANTHONY EDWARD PETRARCA

B. Ed., Rhode Island College of Education, 1953
M. S., University of Rhode Island, 1955

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

Doctor of Philosophy

Graduate School

Department of Chemistry

June, 1959
This thesis has been examined and approved.

Stuart Dunn  
Paul R. James  
Henry S. Krivila  
Hedda Hilla  

May 28, 1957
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The author is also indebted to Dr. ... for his guidance and direction that research problem was carried out.

[Signature]

[U. S. Army]
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INTRODUCTION
INTRODUCTION

The use of lithium aluminum hydride as a reducing agent has been encouraged by the very few anomalous reactions which have been observed on reduction of a wide variety of functional groups. One of the interesting rearrangements attending its use, however, occurs in the reduction of aromatic ketoximes and some of their derivatives (I), where, in addition to the expected primary amine (II), an isomeric secondary amine (III) is formed. It has been suggested that this rearrangement, which was first reported by Larsson¹,² from the reduction of acetophenone oxime, and which has since been found to occur from the reduction of other aromatic ketoximes and some of their derivatives³⁻⁹, probably was due to a preliminary Beckmann-type rearrangement of the oxime, under the reaction conditions, to an amide which was then reduced, as usual, to a secondary amine¹⁰. That this rearrangement is, indeed, in many respects similar to the Beckmann rearrangement, was shown by the fact that electron-releasing substituents in the para-position of acetophenone oxime facilitate the rearrangement⁶. However, it is not as general as the Beckmann rearrangement, for, until very recently¹¹, only oximes of aromatic ketones have been found to undergo rearrangement on reduction with lithium aluminum hydride.
A number of aliphatic ketoximes, on reduction with lithium aluminum hydride, have been reported to give the expected primary amines in low yields\(^1\)\(^2\). Since these low yields may have been due to the formation of other isomers which were not detected by the methods used for isolation of the amines, analysis of the products by acidimetric techniques\(^3\)\(^-\)\(^6\) might reveal whether or not some reductive rearrangement occurs with these oximes as well. Reductions of several aliphatic and aromatic ketoximes were repeated in this investigation and the analytical results reported were obtained by the use of such techniques.

Because of the greater reliability of the analytical results obtained by potentiometric titration, it was possible not only to determine with a higher degree of certainty the effect of structural features of aromatic ketoximes on the course of the reduction with lithium aluminum hydride, but also to study the reaction kinetically. The results of such studies are reported herein. Briefly, they include (1) a more quantitative study of the effect of para-substituents, together with a study of the effect of ortho-substituents on the reduction of acetophenone oximes; (2) a comparative study...
of the reduction of several acetophenone oximes and their O-methyl ethers; (3) a study of the stereochemistry of the reductive rearrangement by reduction of the syn- and anti-phenyl isomers of isobutyrophenone oxime; and (4) a partial kinetic study. A mechanism for the reaction is suggested which is consistent with the results obtained from these studies.
DISCUSSION

The reductive rearrangement of oximes with lithium aluminum hydride was first discovered by Larsson\textsuperscript{1,2}, who reported the isolation of N-ethylaniline as well as \( \alpha \)-phenyl-ethylamine from the reduction of acetophenone-oxide. Smith and coworkers\textsuperscript{3} later obtained the same results, and also reported that a similar mixture of products, \( N \)-propylaniline and \( \alpha \)-phenylpropylamine, was obtained from the reduction of propiophenone-oxide. Although this rearrangement appears to be related to the Beckmann rearrangement, apparently it is not as general, for many oximes have been reduced without rearrangement with lithium aluminum hydride,\textsuperscript{5,17-19}. Aliphatic and aromatic aldoximes and a number of acyclic and cyclic aliphatic ketoximes apparently undergo reduction with little or no rearrangement, since the expected primary amines have been reported as the only isolable products.*

On the other hand, several examples of the reductive rearrangement of aromatic ketoximes and their derivatives have been reported. In the reduction of a series of para-substituted acetophenone oximes, Lyle and Troscianiec\textsuperscript{6} found that the yield of the product of reductive rearrangement

*Complete balance of material was lacking in these cases; hence, some rearrangement may have occurred but may not have been detected.
increases with an increase in the electron-releasing capacity of the \textit{para}-substituent, another striking similarity to the Beckmann rearrangement. However, although \textit{o}-methoxyacetophenone oxime was found to undergo reduction at a faster rate than \textit{p}-methoxyacetophenone oxime\textsuperscript{7}, the percentage of rearranged product obtained from the former was less than that obtained from the latter. This was in contrast to the results obtained by Pearson and Cole\textsuperscript{20} in their study of the Beckmann rearrangement; they found that \textit{o}-methyl-, \textit{o}-chloro-, and \textit{o}-nitro-substituted acetophenone oximes underwent rearrangement much more readily than the corresponding \textit{para}-substituted compounds.

Recently, Harfenist and Wagner\textsuperscript{9} reported that reduction of the 4-piperidone oxime IV with lithium aluminum hydride gave only the homopiperazine V with ring enlargement. Similarly, they found that reduction of the piperidinedione monoxime VI and 2-acetylphenothiazine oxime (VIII) gave the homopiperazine VII and 2-ethylaminophenothiazine (IX), respectively, as the only detectable bases.

\[ \text{IV} \xrightarrow{\text{LiAlH}_4} \text{V} \]
\[ \text{VI} \xrightarrow{\text{LiAlH}_4} \text{VII} \]
Reductions of some acetyl, benzoyl and benzyl derivatives of aromatic ketoximes have been reported by Exner. With a limited amount of lithium aluminum hydride in refluxing ether, O-acetylbenzophenone oxime (I, Ar=H=Ph, R=COCH₃) underwent hydrogenolysis to the parent oxime; but with an excess of the hydride in refluxing tetrahydrofuran, the same compound was reduced to a mixture of benzhydrylamine and α-benzylaniline. Reduction of O-benzoylbenzophenone oxime under the latter conditions also led to the formation of the same mixture of amines but in different relative amounts. O-Benzyl-aceto-phenone oxime, however, was reduced to α-phenylethylamine and benzyl alcohol; no product resulting from reductive rearrangement of this compound was isolated.

Cyclodecanone oxime is the first aliphatic ketoxime which has been reported to undergo reductive rearrangement with lithium aluminum hydride. Slomquist and coworkers reported that, in addition to the expected cyclohexylamine, azacycloheptadecane was obtained as a secondary product, in low yield, from this reaction. The latter product was not detected as such, but its presence was deduced from the fact that N,N-
dimethyl-9-decenylamine was identified as an accessory product in the preparation of cyclodecene by pyrolysis of trimethyl-cyclo-decylammonium hydroxide. The authors concluded that formation of this accessory product could best be explained on the basis of the formation of azacyclohendecane during the reduction of cyclodecanone oxime by lithium aluminum hydride, followed by Hofmann degradation of the mixture of the two amines.

The results of the reduction of a number of other ketoximes and derivatives of ketoximes with lithium aluminum hydride are reported in this investigation. From these results and the results of a simple kinetic study a plausible mechanism is suggested for the reaction.

**Preparation of oximes and oxime ethers**

The compounds chosen for study in this investigation were acetophenone oxime and its p-methoxy-, p-methyl-, p-chloro-, p-bromo-, o-methoxy-, o-methyl, and o-chloro-derivatives; the o-methyl ethers of p-methoxy-, o-methoxy- and p-chloroacetophenone oxime; the syn- and anti-phenyl isomers of isobutyrophenone oxime; and cyclohexanone oxime. With the exception of the ortho-substituted acetophenones, all of the ketones required for the preparation of the above oximes were obtained commercially. o-Chloro- and o-methyl-acetophenones were prepared by the reaction of dimethylcadmium with the corresponding acid chlorides according to the methods of Caso22 and Gilman23, respectively. o-Methoxyacetophenone was prepared by methylation of the o-hydroxy compound with methyl sulfate24.
Except for the two isomers of isobutyrophenone oxime, which were prepared and separated by the method of Kissman, all other oximes were prepared by the standard sodium hydroxide method of Shriner, Fuson and Curtin with suitable modifications. Preparation of 0-methyl-p-chloracetophenone oxime by methylation of the oxime with methyl iodide or methyl sulfate according to procedures of Brady and coworkers always gave rise to a product which was contaminated by the parent ketone, the amount of contamination being dependent upon the specific conditions used. The presence of the contaminant was detected by an absorption band at 1685 cm\(^{-1}\), characteristic of the carbonyl of p-chloracetophenone, in the infrared spectrum of the product. Since the ketone present with the oxime ether no doubt arose from hydrolysis, during the methylation of the N-methylated oxime (or nitrone) which is usually formed as a side product in this reaction, p-chloroacetophenone oxime was methylated under completely anhydrous conditions by treating its sodium salt with methyl sulfate in absolute methanol. That the desired product was obtained by this method was shown by the fact that its spectrum was superimposable on that of the product obtained from the reaction of p-chloroacetophenone with methoxyamine hydrochloride; neither spectrum contained the band at 1685 cm\(^{-1}\) mentioned above.

Because the methylation procedures for the preparation of oxime ethers were complicated by side reactions and gave low yields of the desired product, they were abandoned in favor
of the more direct and unequivocal procedure using methoxy-
amine hydrochloride. With the exception of a small amount
of O-methyl-p-chloroacetophenone oxime prepared by the
anhydrous methylation procedure described above, the oxime
ethers used for this investigation were prepared by reaction
of the ketones with methoxyamine hydrochloride.

Analytical Methods

The composition of the mixture of amines resulting
from the reduction of the oximes with lithium aluminum hydride
usually has been determined by separation and isolation of
the amines or some suitable derivative, and the percentage
yields have been based on the quantities of products actually
isolated. The data so obtained are not very suitable for a
quantitative study of the reaction, since wide variations in
results have been experienced from duplicate runs, probably
as a result of mechanical losses. The products obtained from
the reduction of aromatic ketoximes seemed especially suited
for analysis by acidimetric techniques, because of the large
difference in basicity of the two amines produced, one being
aliphatic, and the other aromatic. A number of such amine
mixtures have been differentially titrated in non-aqueous
solvent systems.

The first method employed in this study involved the
use of indicators (method A). In a procedure adapted from
that of Palit, aliquots of ethereal solutions of the
products obtained from reduction of the oximes, after dilution
with an appropriate amount of ethanol and ether, were titrated with a 0.1 normal solution of hydrochloric acid in non-aqueous solvent (a 9:1 mixture of ethanol and ethylene glycol). The aliphatic amine content was determined by titration to the end point of bromoresol green (pH range, 3.8-5.4 in water), while the amount of aromatic amine present was determined by titration to the end point of thymol blue (pH range, 1.2-2.8 in water). This method, when used with amine mixtures of known concentration, gave results which were considered to be sufficiently accurate in view of the possible sources of experimental error inherent in the method. Analyses of the product mixtures obtained from duplicate runs of the lithium aluminum hydride reduction of p-methylacetophenone oxime showed an average deviation of less than 2.5 (see Table I).

In spite of the reproducibility of results obtained by method A, it was subsequently shown that the results were not sufficiently reliable for the purpose of this investigation (see Table I). This was not completely unexpected since there were several sources of error inherent in the use of this method. First of all, because of the dilute solutions being titrated, the end points were not sharp and had to be determined by reference to color standards representative of the end point colors for each of the indicators. Secondly, the effect of different substituents on the pK's of the two amine types (II and III) was not taken into account.

These difficulties were circumvented by the use of potentiometric techniques. The potentiometric procedure of
Palit\textsuperscript{14} was found to be suitable for the titration of reduction-product mixtures containing an aromatic amine whose basicity was equal to or greater than that of aniline. A 1:1 mixture of ethylene glycol and isopropyl alcohol was used as solvent for the titration medium, and a 0.2 normal solution of hydrochloric acid in the same solvent mixture was used as titrant (method B).

For reduction-product mixtures containing an aromatic amine whose basicity was less than that of aniline, a more weakly basic solvent system consisting of a 2:1 mixture of acetonitrile and chloroform was employed as the titration medium, and the more strongly acidic perchloric acid (0.2 normal) in dioxane as titrant (method C). This combination was much more versatile than the one used in method B, for it could be used not only to differentially titrate mixtures of amine-types II and III containing very weak aromatic amines, but also to differentially titrate mixtures of primary and secondary aliphatic amines\textsuperscript{16} which might be encountered in the reduction of aliphatic ketoximes with lithium aluminum hydride if reductive rearrangement occurred. Mixtures of primary and secondary aliphatic amines, however, must first be treated with salicylaldehyde to convert the primary amine to the weaker Schiff base which can then be differentially titrated from the secondary amine whose basic strength remains unchanged. Analyses of the basic products obtained from the oximes reduced in this study are summarized in Table I.
**TABLE I**

Quantitative Determination of Products Obtained from Reduction of Ketoximes and Derivatives with Lithium-Aluminum Hydride

<table>
<thead>
<tr>
<th>Compound</th>
<th>Run</th>
<th>Reaction Time</th>
<th>Percent Reduction</th>
<th>Percent Rearr.</th>
<th>Anal. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃O⁻C=OCH₃</td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>54.8</td>
<td>79.5</td>
<td>A</td>
</tr>
<tr>
<td>CH₃⁻C=OCH₃</td>
<td>II&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>59.6</td>
<td>78.4</td>
<td>A</td>
</tr>
<tr>
<td>CH₃⁻C=OCH₃</td>
<td>III&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.5 hrs.</td>
<td>70.3</td>
<td>72.9</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>IV&lt;sup&gt;e&lt;/sup&gt;</td>
<td>24 hrs.</td>
<td>87.3</td>
<td>81.6</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>V&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>74.9</td>
<td>54.9</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.5 hrs.</td>
<td>64.9</td>
<td>50.6</td>
<td>B</td>
</tr>
<tr>
<td>CH₃⁻C=OCH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>64.3</td>
<td>33.0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>II&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>67.4</td>
<td>23.0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.5</td>
<td>29.9</td>
<td>B</td>
</tr>
<tr>
<td>ClCH₃⁻C=OCH₃</td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>66.9</td>
<td>40.7</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>II&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.5 hrs.</td>
<td>82.2</td>
<td>28.1</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>III&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>74.4</td>
<td>19.0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>77.5</td>
<td>10.9</td>
<td>C</td>
</tr>
<tr>
<td>BrCH₃⁻C=OCH₃</td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>71.7</td>
<td>17.2</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>II&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>62.0</td>
<td>17.6</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>III&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>66.2</td>
<td>14.3</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70.0</td>
<td>13.0</td>
<td>C</td>
</tr>
<tr>
<td>CH₃⁻C=OCH₃</td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>14.7</td>
<td>27.0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>II&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3.5 hrs.</td>
<td>80.8</td>
<td>51.7</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>III&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>21.8</td>
<td>31.4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>IV&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>87.5</td>
<td>17.4</td>
<td>C</td>
</tr>
<tr>
<td>ClCH₃⁻C=OCH₃</td>
<td>I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>25.4</td>
<td>47.5</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>II&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4.5 hrs.</td>
<td>75.7</td>
<td>0.0</td>
<td>C</td>
</tr>
<tr>
<td>OCH₃⁻C=OCH₃</td>
<td>III&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 hrs.</td>
<td>77.5</td>
<td>21.5</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82.7</td>
<td>27.8</td>
<td>C</td>
</tr>
<tr>
<td>Compound</td>
<td>Run</td>
<td>Reaction Time</td>
<td>Percent Reduction</td>
<td>Percent Dearr.</td>
<td>Anal. Method</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Cl-CH₃NOCH₃</td>
<td>Te</td>
<td>3 hrs.</td>
<td>5.7</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Te</td>
<td>5 da.</td>
<td>90.3</td>
<td>0.7</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Te</td>
<td>3 hrs.</td>
<td>90.0</td>
<td>0.0</td>
<td>B</td>
</tr>
<tr>
<td>CH₃COCH₃NOCH₃</td>
<td>If</td>
<td>3 hrs.</td>
<td>3.4</td>
<td>56.4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>If</td>
<td>4 da.</td>
<td>100.0</td>
<td>43.1</td>
<td>C</td>
</tr>
<tr>
<td>CH₃CON(CH₃)₂</td>
<td>If</td>
<td>3 hrs.</td>
<td>77.8</td>
<td>7.1</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>If</td>
<td>3 hrs.</td>
<td>69.2</td>
<td>10.9</td>
<td>C</td>
</tr>
<tr>
<td>CH₃CON(CH₃)₂</td>
<td>If</td>
<td>3 hrs.</td>
<td>95.0</td>
<td>67.0°</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>If</td>
<td>3 hrs.</td>
<td>83.2</td>
<td>71.9°</td>
<td>C</td>
</tr>
<tr>
<td>CH₃CON(CH₃)₂</td>
<td>If</td>
<td>2 da.</td>
<td>95.0</td>
<td>69.1°</td>
<td>C</td>
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<tr>
<td></td>
<td>If</td>
<td>3 hrs.</td>
<td>73.0</td>
<td>74.5</td>
<td>C</td>
</tr>
<tr>
<td>CH₃CON(CH₃)₂</td>
<td>If</td>
<td>3 hrs.</td>
<td>92.0</td>
<td>0.0</td>
<td>C</td>
</tr>
</tbody>
</table>

aAt reflux temp. of ether.  
b(amine II + amine III)/oxime x 100.  
c(amine III)/(amines II + III) x 100.  
d-Indicator titration;  
e-potentiometric titration using 1:1 ethylene glycolisopropyl alcohol mixture as titration medium with 0.1 M HCl in same solvent mixture as titrant;  
f-potentiometric titration using 2:1 acetonitrile-chloroform mixture as titration medium with 0.1 M HClO₄ in dioxane as titrant.  
Total reaction time, reflux time 29 hrs.  
The normal reduction product appeared to be contaminated with another aliphatic amine, but no derivative could be obtained.  
Total reaction time, reflux time 24.5 hrs.  
Total reaction time, reflux time 21 hrs.  
Total reaction time, reflux time 21 hrs.  
Amine type III from phenyl migration; about 8% of a third amine believed to be N-isopropylbenzylamine was also produced.  
Total reaction time, reflux time 5 hrs.  
Amine type III from phenyl migration; about 2% of a third amine believed to be N-isopropylbenzylamine was also produced.  
The expected primary amine was the only one shown to be present.
Effect of para-Substituents

The data in Table I support the conclusion of Lyle and Troschianiec that, in the reaction of para-substituted acetophenone oximes with lithium aluminum hydride, electron-releasing groups increase the relative amount of reductive rearrangement product which is formed. The data further reveal that electron-releasing substituents decrease the overall rate of reduction, which is not unexpected for a reaction of this type involving the nucleophilic attack of a substrate by hydride ion.

Ortho Effect

The reaction of ortho-substituted acetophenones with lithium aluminum hydride showed that the ortho substituent had a profound effect on the rate of reaction and the relative amount of reductive rearrangement product obtained. Each of the three ortho-substituted compounds studied, o-methyl-, o-chloro-, and o-methoxy-acetophenone oxime, gave a smaller percentage of rearrangement product than did the corresponding para-substituted compound. Furthermore, the o-methyl- and o-chloro-substituents retarded the rate of reaction considerably, whereas the o-methoxy substituent accelerated it. Thus, the effect of ortho substituents on this reaction appears to be quite different from that observed by Pearson and Cole in the Beckmann rearrangement in which o-methyl-, o-chloro- and o-nitro- substituted acetophenones underwent rearrangement much more readily than the corresponding para-substituted compounds.
On the assumption that the electrical effect of the groups is the same in the ortho as in the para position*, Pearson and Cole suggested that the accelerated rate of rearrangement was due to steric effects of the ortho substituents. This steric effect was believed to operate by preventing coplanarity between the benzene ring and the α-oximinoethyl grouping (–ClOHCH₃). Since evidence was presented in support of this view, it was further suggested that one of the initial steps in the rearrangement in any acetophenone oxime is the twisting of the α-oximinoethyl group out of the plane of the ring so that the nitrogen and carbon atoms pictured are equidistant above and below the plane of the ring (Fig. 1); the process of nitrogen-ring bond formation and carbon-ring bond breaking is thus facilitated. In ortho-substituted acetophenone oximes the twisting out of the plane of the ring is already accomplished, and the energy required for activation may, therefore, be diminished.

\[ \text{Fig. 1} \]

*Any difference in the electrical effect of a substituent in the ortho and para position would be due to its inductive effect and, for the α-chloro- and α-nitro-substituents, this would operate to hinder the rate of rearrangement.
Further support for this type of intermediate came from an investigation by Huisgen and coworkers on the related Chapman rearrangement of compounds of type X. The stereochemistry of the intermediate XI requires that the methylene group attached to the phenyl ring and the one attached to the three-membered ring be in the planes of these two respective rings; the rings, in turn, must be perpendicular to each other. This steric requirement can be fulfilled without straining the molecule only in compounds where \( n \geq 8 \) or more. The results obtained from a series of compounds studied, where \( n \geq 8\), are consistent with an intermediate of type XI.

![Diagram showing the transformation from compound X to XI](attachment:image.pdf)

The results obtained from the reductive rearrangement of ortho-substituted acetophenones with lithium aluminum hydride in this investigation, and the results reported by Marfenist and Magnien on compounds IV, VI, and VIII do not appear to be consistent with those observed in the Beckmann or Chapman rearrangements of the same or related compounds.
This would suggest that the reductive rearrangement proceeds by a different type of intermediate.

**Oxime Ethers**

On reaction of lithium aluminum hydride with oximes, hydrogen is evolved to an extent which corresponds to the removal of one active hydrogen per mole. On removal of this active hydrogen an ether-soluble complex is formed which is not the lithium salt of the oxime, since the latter was prepared by reaction of an oxime with phenyl-lithium and was found to be insoluble in ether.

The role of this oxime complex in the reductive rearrangement was investigated by carrying out the reduction of O-methyl ethers of p-methoxy-, o-methoxy- and p-chloro-acetophenone oxime. Each of these oxime ethers underwent reduction at a slower rate and gave a decreased amount of the rearrangement product as compared to the oximes themselves (Table I). This effect was very pronounced with regard to the p-chloro- and p-methoxy-acetophenone oxime ethers; the rate of reduction of these two compounds was diminished about ten-fold. No rearrangement product was obtained from the former while the amount obtained from the latter, even though appreciable, was significantly lower than that obtained from the oxime itself. These results are in agreement with those reported by Exner on the reduction of O-benzyl acetophenone oxime.
The fact that the oxime ethers undergo reduction at a slower rate than the corresponding oximes was a bit surprising, since one might expect that the anion formed by the preliminary reaction of an oxime with lithium aluminum hydride \((-\text{C}=\text{N}-\text{O}^-)\) would inhibit further nucleophilic attack by hydride ion; thus the oxime ethers would be expected to undergo reduction at a faster rate than the oximes themselves. The observed results are compatible only if a coordinated complex of the type \(-\text{C}=\text{N}-\text{O}\text{AlH}_3\) is a more powerful reducing agent than \(\text{AlH}_4^-\) itself, or if the oxime anion plays a part in the reduction. The oxime anion, or its coordinated complex, definitely seems to play an important part in the reductive rearrangement since the oxime ethers gave decreased relative amounts of the rearrangement product by comparison with the relative amounts obtained from the corresponding oximes.

The anomalous results observed in the reduction of \(\alpha\)-methoxy acetophenone oxime and its \(\alpha\)-methyl ether must be attributable to some special effect of the \(\alpha\)-methoxy group. One such effect would be the coordination of this group with aluminum hydride (fig. 2), whereupon the aluminum hydride moiety would be suitably placed for very facile attack by hydride ion on either the carbon or nitrogen atom of the carbenimine function.

\[
\text{CH}_3-\text{O-AlH}_3
\]

*fig. 2*
Kinetics

Previous attempts to isolate an intermediate in this reaction were unsuccessful as were those of this present investigation. From a mixture of a 4:1 molar ratio of p-methylacetophenone oxime and lithium aluminum hydride, which was heated under reflux for 10 hours, the oxime was recovered in 77% yield after hydrolysis. Since removal of active hydrogen alone was not sufficient to cause rearrangement to an amide as a possible intermediate, the experiment was repeated using a 2:1 molar ratio of the same oxime with lithium aluminum hydride. This would furnish sufficient complex hydride not only to remove the active hydrogen from the oxime, but also to furnish some additional complex hydride which might function as the Lewis acid which would be required to effect such a rearrangement. From this last experiment, 48% of the oxime was recovered unchanged and 28% had undergone reduction to the usual mixture of amines. There was no evidence of the presence of N-α-p-methylphenylethyl hydroxylamine, a second possible intermediate which might have been expected from reduction of this oxime with a limited amount of lithium aluminum hydride.

The Lewis acids which might be present in these systems are AlH₃, AlH₂OR, AlH(OR)₂, and Al(OR)₃ (OR=oxime anion). Of these, Al(OR)₃, which must have been present in the 4:1 molar mixture described above, should be the strongest Lewis acid in terms of electronic effects, but because of its large steric requirements, F-strain probably prevents it from being able to coordinate readily with other species.
Attempts to follow the course of the reduction of p-methylacetophenone oxime by recording the ultraviolet spectrum of a reaction mixture at different time intervals were also unsuccessful. It was hoped that the formation of an intermediate might be detected by the appearance, during the course of reaction, of a spectral band which was not common to any of those of the reactants or products, or that it might be possible to study the reaction kinetically by following the rate of appearance or disappearance of a particular band. However, due to the nature of the spectra (Fig. 3-6) neither of these results was achieved.

In view of the failure to isolate or detect the presence of an intermediate, attention was directed towards a kinetic study of the reduction of p-methylacetophenone oxime with lithium aluminum hydride. The choice of this oxime rested on the fact that it gives nearly equal amounts of both the normal and rearranged reduction products (Table I); hence experimental errors resulting from the quantitative determination of reduction products would be minimized.

In all of the reductions whose results are summarized in Table I, lithium aluminum hydride was used as a slurry. Since a kinetic study would require homogeneous reaction conditions so that the concentrations of lithium aluminum hydride in solution could be known with greater certainty, several trial runs were carried out using lithium aluminum hydride in solution rather than as a slurry to see what effect, if any, such a change in reaction conditions would
Fig. 3. Ultraviolet absorption spectrum of 0.56 M lithium aluminum hydride in anhydrous ether, $\lambda_{\text{max}}$ ($\varepsilon_{\text{max}}$): 216.5 ($\varepsilon_{\text{max}}$).
The shape of this curve was altered very little after the solution had stood at room temperature under nitrogen for three weeks.
Fig. 5. Ultraviolet absorption spectra: 
1.22 x 10^-3 M α-p-tolylethylamine in anhydrous ether, 
λ_max, (ε max.): 223 (1,650), 259 (303), 265 (354), 273 (310); λ_min, (ε min.): 241 (148), 261 (287), 270 (213); -----, 3.05 x 10^-4 M α-p-tolylethylamine in the presence of 0.29 M lithium aluminum hydride in anhydrous ether.*

*The shape of this curve was essentially the same after the solution had stood at room temperature under nitrogen for three weeks.
Fig. 1. Ultraviolet absorption spectra: 1.61 x 10^{-4} \text{M} \alpha\text{-ethyl-\textit{p}-toluidine in anhydrous ether,}\n\lambda_{\text{max.}} \quad (\epsilon_{\text{max.}}): \quad 217 \quad (3,920), \quad 249 \quad (10,400), \quad 305 \quad (1,800);\\n\lambda_{\text{min.}} \quad (\epsilon_{\text{min.}}): \quad 219.5 \quad (3,230), \quad 277 \quad (559); \quad ----, \quad 8.05 \times 10^{-5} \text{M} \eta\text{-ethyl-\textit{p}-toluidine in the presence of 0.29 M lithium aluminum hydride in anhydrous ether.}
have on the outcome of the reaction. A review of the data in Table II suggests that the change from heterogeneity to homogeneity alters the rate of reaction slightly for the reduction of \( p \)-methyl- and \( p \)-methoxy-acetophenone oxime. This effect may be due to impurities which are insoluble in ether, or it may be due to surface effects. The difference in the percentage of reductive rearrangement observed for \( p \)-methyl-acetophenone oxime must be due to some other factor since variations of this type were observed even in separate homogeneous reactions (Table II).

The analyses for the kinetic measurements would have been greatly facilitated if it had been possible to differentially titrate the amines in the presence of anionic bases such as lithium and aluminum isopropoxides. Then, after a sample of a reaction mixture had been quenched by the addition of acetone, which rapidly decomposes the excess lithium aluminum hydride to a mixture of isopropoxides, the whole mixture of amines and anionic bases could be titrated. Although similar types of mixtures have been differentially titrated\(^{37}\), attempts to apply such techniques in this study were not successful.

The kinetic measurements were made by withdrawing aliquot portions, at definite time intervals, from a reaction mixture which contained a large excess of lithium aluminum hydride. After each sample had been quenched with water and the insoluble lithium and aluminum hydroxides had been removed by filtration, the amount of amines present was
### Table II

Comparison of reduction of Acetophenone Oximes with Lithium Aluminum Hydride under Heterogeneous and Homogeneous Reaction Conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Run</th>
<th>Reaction Time</th>
<th>Per cent Reduction</th>
<th>Per cent Rearr.</th>
<th>Anal. Method</th>
</tr>
</thead>
</table>
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{Vf}\) | 3 hrs. | 64.3 | 7.8 | B |
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{VIIe}\) | 3 hrs. | 44.9 | 43.0 | C |
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{VIII}^u\) | 3 hrs. | 25.7 | 30.9 | C |
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{IX}^u\) | 3 hrs. | 57.9 | 43.2 | C |
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{III}^f\) | 3 hrs. | 54.0 | 77.1 | B |
| \[
  \text{CH}_3\xrightarrow{\text{NOM}}\text{CH}_3
\] | \(\text{III}^u\) | 3 hrs. | 49.4 | 76.5 | B |

\(a,b,c,d,f,\) see footnotes, Table I.  
80.021 mole of oxime, 0.043 mole of LAH (solution) in 200 ml. of ether. 
70.020 mole of oxime, 0.065 mole of LAH (solution) in 200 ml. of ether. 
70.010 mole of oxime; 0.034 mole of LAH (solution) in 100 ml. of ether.
determined by potentiometric titration; the amount of unreacted oxime was then calculated by difference.

The data so obtained were converted to the form required for determining the order of the reaction with respect to oxime (Table III). In Fig. 7, 8, and 9 are plotted the data for concentration vs. time, the \( \log \) of concentration vs. time, and the reciprocal of concentration vs. time, respectively. For the two runs, the slope is nearly constant for the first order plot but varies considerably for the second order plot. Of more significance, the observed rates for the two runs were found to vary directly with the concentration of oxime (Fig. 7). Hence the reaction appears to be first order with respect to oxime. This would seem to rule out the possibility of the coordinated complex (-C=O-\( \text{AlH}_3 \)) functioning as a more powerful reducing agent, unless the reduction by such a complex is intramolecular.

An interesting sideline of the rate studies was the observation that the ratio of products obtained from the reduction of \( p \)-methylacetophenone oxime varies with time (Table III). This suggests that the \( \text{t-amine} \) may be formed by different paths or from at least two intermediates (or transition states), for the amines are not interconverted by lithium aluminum hydride (see Fig. 5 and 6).

**Stereochemistry and Mechanism**

The stereochemistry of the reaction was studied by the reduction of the \textit{syn-} and \textit{anti-} phenyl isomers of isocitrophenone oxime. From the results obtained (Table I), it can
### Table III

**Rate of Reduction of p-Methylacetophenone Oxime with Lithium-Aluminum Hydride**

**Run I at 25.9 ± 0.1 °C**

- $a = 0.1008$, initial molar concentration of oxime
- $x = molar$ concentration of total amines produced in time $t$
- $(a-x) = molar$ concentration of oxime at time $t$

| Time (hrs.) | $10^2 x$ | $10^2(a-x)$ | $-\log(a-x)$ | $1/(a-x)$ | Per cent | Per cent
|------------|--------|------------|-------------|----------|----------|----------
| 0          | 2.77   | 10.08      | 0.996       | 9.9      | 27.5     | 48.1     |
| 1.233      | 2.15   | 7.31       | 1.135       | 13.2     | 20.0     | 48.8     |
| 2.250      | 3.51   | 6.57       | 1.183       | 15.3     | 24.8     | 47.3     |
| 3.233      | 4.03   | 6.05       | 1.219       | 16.6     | 20.0     | 49.7     |
| 4.267      | 5.15   | 4.93       | 1.308       | 20.3     | 51.1     | 49.7     |
| 5.333      | 6.06   | 4.02       | 1.394       | 24.8     | 60.1     | 47.2     |
| 6.366      | 6.46   | 3.62       | 1.444       | 27.8     | 64.1     | 47.2     |
| 7.283      | 6.95   | 3.13       | 1.506       | 32.0     | 68.9     | 46.6     |
| 8.250      | 7.21   | 2.37       | 1.540       | 34.7     | 71.5     | 46.0     |
| 9.250      | 7.52   | 2.56       | 1.592       | 39.1     | 74.5     | 45.8     |
| 10.250     | 7.82   | 2.26       | 1.650       | 44.6     | 77.5     | 45.3     |
| 12.244     | 8.12   | 1.96       | 1.707       | 51.0     | 80.5     | 44.7     |
| 24.217     | 8.70   | 1.38       | 1.854       | 71.5     | 86.2     | 43.7     |

**Run II at 26.3 ± 0.3 °C**

- $a = 0.0504$

<table>
<thead>
<tr>
<th>Time (hrs.)</th>
<th>$10^2 x$</th>
<th>$10^2(a-x)$</th>
<th>$-\log(a-x)$</th>
<th>$1/(a-x)$</th>
<th>Per cent</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.01</td>
<td>5.04</td>
<td>1.298</td>
<td>19.8</td>
<td>24.8</td>
<td>43.5</td>
</tr>
<tr>
<td>1.617</td>
<td>1.21</td>
<td>3.63</td>
<td>1.394</td>
<td>24.8</td>
<td>20.0</td>
<td>46.6</td>
</tr>
<tr>
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<td>1.93</td>
<td>3.11</td>
<td>1.440</td>
<td>27.6</td>
<td>25.0</td>
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</tr>
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<td>2.60</td>
<td>2.74</td>
<td>1.507</td>
<td>32.2</td>
<td>38.2</td>
<td>47.2</td>
</tr>
<tr>
<td>4.650</td>
<td>2.90</td>
<td>2.14</td>
<td>1.562</td>
<td>36.5</td>
<td>47.7</td>
<td>45.0</td>
</tr>
<tr>
<td>6.483</td>
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<td>1.669</td>
<td>46.7</td>
<td>57.5</td>
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</tr>
<tr>
<td>8.550</td>
<td>3.78</td>
<td>1.26</td>
<td>1.899</td>
<td>79.3</td>
<td>75.0</td>
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</tr>
<tr>
<td>12.450</td>
<td>4.08</td>
<td>0.96</td>
<td>2.018</td>
<td>102.2</td>
<td>81.0</td>
<td>40.4</td>
</tr>
<tr>
<td>24.550</td>
<td>4.40</td>
<td>0.64</td>
<td>2.194</td>
<td>156.2</td>
<td>87.3</td>
<td>37.5</td>
</tr>
</tbody>
</table>
Fig. 7. Rate of disappearance of p-methylacetophenone oxime on reduction with excess lithium aluminum hydride: ○, Run I; □, Run II.
Fig. 8. First-order plot of kinetic data from reduction of p-methylacetophenone oxime with lithium aluminum hydride: ○, Run I; □, Run II.
Fig. 9. Second-order plot of kinetic data from the reduction of p-methylacetophenone oxime with lithium aluminum hydride: ◼, Run I; □, Run II.
be seen that three products appear to be formed from the re-
duction of each isomer: α-phenylisobutyl amine (type II),
N-isobutylaniline (type III), and lesser amounts of a third
product believed to be N-benzyl isopropylamine. The product
of phenyl migration (amine type III) was the predominant one
formed in each case.

The formation of N-isobutylaniline as the major
product from the syn-phenyl isomer might be explained in terms
of a preliminary isomerization to the anti-phenyl isomer in
the presence of AHI₃ or some similar Lewis acid. Such iso-
erizations have been shown to occur with benzaldehydes in
the presence of hydrogen chloride⁴⁸ or boron trifluoride⁴⁹.
An explanation of this type was offered for the formation of
isobutyraniline from the Beckmann rearrangement of both
isomers of isobutyrophenone oxime with hydrogen chloride in
acetic acid⁵⁰.

However, it is difficult to rationalize the results
of this present study in terms of such an isomerization, since
the syn-phenyl isomer of isobutyrophenone oxime was recovered
in 72% yield in pure form after hydrolysis of a sample which
had been treated with lithium aluminum hydride for 10 minutes.
Furthermore, if reduction were preceded by a preliminary iso-
erization, unless it were instantaneous, the anti-phenyl
isomer would have been expected to undergo reduction at a
slightly faster rate than the syn-phenyl, since the former
already possesses the required conformation for Beckmann-type
rearrangement. However, the relative rates were in the reverse
order (see Table I).
The non-stereospecificity of the reduction of the two isomers of isobutyrophenone oxime suggests that reductive rearrangement probably occurs by way of a non-stereospecific intermediate or transition state; but the fact that the relative amount of rearranged product varies with time (Table III) further suggests that the products are formed by more than one reaction path. Several possible routes to the final products are outlined in Fig. 10. Assuming that rearrangement occurs simultaneously with the attack of hydride ion on the substrate in a concerted reaction, since migration without such attack would lead to the formation of a carbocation intermediate which would not be expected in such a strongly basic medium, path A would be stereospecific, but paths B and C would not.

Although path B cannot be eliminated by this investigation, there are several reasons why reaction by this path would appear to be unlikely. First of all, since hydroxylamine derivatives undergo reduction slowly, or not at all, with lithium aluminum hydride, one might expect to be able to isolate or detect such an intermediate from the reduction of oximes or their derivatives with this reagent. In this investigation, no evidence was found for the presence of such an intermediate, even when a limited amount of lithium aluminum hydride was used; however, hydroxyamine derivatives have been obtained from the reduction of alkylated oximes (nitrone) with lithium aluminum hydride.
Fig. 10: Mechanisms for the reduction of ketoximes and derivatives with lithium aluminum hydride.
raith C ($R' = H, acyl; M = Li, Al complex$):

\[ \text{I} \xrightarrow{(a)} \text{Rath C} \xrightarrow{k_c-1} \text{ArCHR} + \text{H}_2\text{O} \rightarrow \text{II} \]

\[ \xrightarrow{k_c-2} \text{ArCHR} \xrightarrow{H_2O} \xrightarrow{\text{I}} \text{II} \]

raith C' ($R' = alkyl; M = Li, Al complex$):

\[ \text{I} \xrightarrow{(a)} \text{Rath C'} \xrightarrow{k_c-1} \text{ArCHR} + \text{H}_2\text{O} \rightarrow \text{II} \]

\[ \xrightarrow{k_c-2} \text{ArCHR} \xrightarrow{H_2O} \xrightarrow{\text{I}} \text{II} \]

Fig. 10 (cont.)
A second argument against the likelihood of path B is that, in those reductions of hydroxylamines which have been reported, there has been no indication of the occurrence of reductive rearrangement similar to that which is encountered in the reduction of oximes.

A more promising explanation of the experimental results is offered by reaction path C (Fig. 10) which involves an oxazirane transition state. Oxaziranes are very reactive compounds which undergo a number of unusual reactions; on the basis of the work of Emmons, a mixture of amines of the type observed in this study might be formed from such a transition state. It is difficult to test this hypothesis because the required oxaziranes appear to be of the type which are too unstable to isolate. However, an oxazirane transition state not only would explain the non-stereospecificity of the reductive rearrangement, but would also explain the difference in reactivity between an oxime and its O-methyl ether, since the method of formation of the transition state for the latter would be different from that of the former (paths C and C', Fig. 10). But, the fact that different relative amounts of products are obtained from an oxime and its ether, or from the two isomers of isobutyrophenone oxime, once again suggests that the products must be formed by more than one reaction path. In the former case, if reduction occurred exclusively by paths C and C', although the methods of formation of the transition state (k_{C-1} and k'_{C-1}) and the transition states themselves, (c) and (e),...
would differ slightly, it would seem reasonable to assume that the same ratio of products should be obtained from both the oxime and its ether. Similarly, in the latter case, if the two isomers of isobutyrophenone oxime were reduced exclusively by path C, the only difference between the two should be the rate of formation of the transition state (c); the ratio of products should be the same for both isomers.

It is suggested that oximes and their derivatives undergo reduction with lithium aluminum hydride concurrently by paths A and C, with normal reduction occurring by both paths, and reductive rearrangement occurring predominantly by path C. Experimental evidence in support of a scheme such as that represented by path A is found in the work of Awad and Kaouf, who reported that the oxime XII underwent reduction only to the imine XIII with lithium aluminum hydride. Evidence in support of the scheme represented by reaction path C, and in support of the concurrent occurrence of two or more reaction paths, has been furnished by this investigation.

\[ \text{XII} \rightarrow \text{XIII} \]
Electron-releasing substituents in the *pera* position of acetophenone oximes cause, simultaneously, a decrease in the overall rate of reduction, and an increase in the relative amount of rearrangement product. Ortho-substituents appear to sterically inhibit both the rates of reduction and rearrangement, except in the case of the o-methoxy substituent whose acceleration of the rate of reduction was explained previously (Fig. 2). On the other hand the presence of two methyl groups on the alpha carbon atom causes acceleration of both the rate of reduction and rate of rearrangement as can be seen by a comparison of the results obtained from the reduction of acetophenone oxime and the two isobutyrophenone oxime isomers (Table I). These effects must also be steric, for examination of molecular models of the two isobutyrophenone oximes seems to indicate that a considerable amount of steric interaction exists between the phenyl and isopropyl groups due to the bulk of the latter. In acetophenone and propiophenone oximes little or no such steric interaction seems to be present. It appears that the phenyl-isopropyl interaction in the isobutyrophenone oximes would be partially relieved by the oxaziridine transition state, but would still be so great that complete relief would be offered only by migration of the phenyl or isopropyl group from carbon to nitrogen. This would account for both the increased rate of reduction and the increased amount of rearrangement observed for the isobutyrophenone oximes as compared to acetophenone oxime.
The differences observed in the reduction of the isobutyrophenone oximes can be explained in terms of the relative stability of the two isomers. The syn-phenyl isomer must be less stable, since it is obtained in lesser amounts from the mixture which is formed on preparation. Because of its decreased stability it must be a more energetic species than the anti-phenyl isomer and hence would require less energy to undergo transformation to the still more highly energetic oxazirane transition state. Thus, the syn-phenyl isomer should undergo reduction at a faster rate; the fact that it does, lends further credence to the idea that one of the reduction paths involves an oxazirane transition state.
EXPERIMENTAL
Infrared Absorption Spectra.

The infrared absorption spectra were recorded with a Perkin-Elmer Model 21, double beam infrared spectrophotometer with sodium chloride optics, using a standard scale and the following settings: response, 1; gain, 5.5; speed 4-6; suppression, 0. The spectra of solids were determined as mulls in nujol from 650-1300 cm$^{-1}$ and in Halocarbon oil from 1300-4000 cm$^{-1}$ unless otherwise specified. Spectra of solutions are indicated by naming the solvent in which the data were obtained. The location of the bands is given in wavenumbers (cm$^{-1}$), and those listed are strong unless otherwise specified as medium (m) or weak (w).

Ultraviolet and Near Infrared Absorption Spectra.

The ultraviolet and near infrared spectra were recorded with a Perkin-Elmer Spectronic Model 4000 recording spectrophotometer. The solvents used for determining the spectra are specified for the individual spectra. The wavelengths for the ultraviolet region are given in millimicrons (μm) and those for the near infrared in microns (μ).

Microanalyses.

The carbon and hydrogen microanalyses were determined by Drs. G. Weiler and F. S. Strauss of Oxford, England, and by Gelbraith Microanalytical Laboratories, Knoxvile, Tenn.
Preparation of Ketones.

All of the ketones used for this study were obtained commercially with the exception of o-chloro-, o-methyl- and o-methoxy-acetophenone. The preparations of these compounds are described below.

o-Chloroacetophenone.

A Grignard reagent, prepared by the reaction of 7.3 g. (0.3 mole) of magnesium with excess methyl bromide in 150 ml. of anhydrous ether, was converted to dimethylcadmium in the usual manner by addition of 29.3 g. (0.16 mole) of anhydrous cadmium chloride. This, on reaction with 36.7 g. (0.21 mole) of o-chloroacetyl chloride according to the method of Cason, produced 19.46 g. (60%) of o-chloroacetophenone, b.p. 97-98° at 9 mm., $n^\text{D} = 1.5404$, reported $n^\text{D} = 1.6844$.

The semicarbazone, after two recrystallizations from ethanol-water, melted at 170-177.5°, reported m.p. 160° and 178-179°. The 2,4-dinitrophenylhydrazone, after one recrystallization from ethanol-ethyl acetate, melted at 204-205°, reported m.p. 206° and 209-211°. The oxime melted at 101.5-103°, reported m.p. 104.5-105.5° and 114-115°, also 103° and 112-113°. A small quantity, on oxidation with sodium hypochlorite, gave o-chlorobenzoic acid, m.p. 138-138.5°, reported m.p. 140°.

o-Methylacetophenone.

o-Methyl chloride was first prepared by standard methods from the reaction of 50 g. (0.37 mole) of o-
toluic acid with 67 g. (0.56 mole) of thionyl chloride there
was obtained 53.1 g. (93.5\%) of o-toluyl chloride, b.p. 88-
89° at 10 mm.

The reaction of 32.4 g. (0.21 mole) of o-toluyl chloride with dimethylcadmium (prepared in the same manner,
and in the same quantity as described for the preparation of o-chloroacetophenone) following the procedure of Gilman\textsuperscript{23} gave 24.5 g. (87\%) of o-methylacetophenone, b.p. 87-88° at 9 mm,
\( n_D^{25} 1.5310 \), reported\textsuperscript{20} \( n_D^{20} 1.5303 \). The oxime melted at
62-63°, reported\textsuperscript{47} m.p. cl.5-63° and\textsuperscript{20} 64.5-65.5°.

\textit{o-Methoxyacetophenone}.

The preparation described below is adapted from \textit{Organic Syntheses}\textsuperscript{24}.

In a 500 ml. three-necked flask equipped with a
mechanical stirrer, a thermometer, and a dropping funnel,
27.2 g. (0.20 mole) of \textit{o-hydroxyacetophenone} was dissolved in
110 ml. of 2 N sodium hydroxide solution. The solution was
stirred while 25.2 g. (19 ml., 0.2 mole) of methyl sulfate
was added dropwise, and the temperature was maintained at
35-40°. When addition was complete, the mixture was stirred
for 5 minutes, after which 55 ml. of 2 N sodium hydroxide
was added in one lot, and then 12.6 g. (9.5 ml.) of methyl
sulfate was added as before, except that the temperature was
allowed to rise slightly higher, to 45°. The mixture was then
stirred for 30 minutes at 50°. After cooling the contents of
the flask, the organic layer was taken up in ether. The ether.
solution was dried over Drierite and filtered. After removal of the solvent, distillation at atmospheric pressure over a 215-243° range gave 21.3 g. (71%) of o-methoxyacetophenone, \( n_D^{24.5} 1.5398 \), reported \( n_D^{25} 1.5365 \). Redistillation at reduced pressure gave 18.6 g. of the ketone, b.p. 127-128° at 15 mm., \( n_D^{24} 1.5422 \). The oxime melted at 95.5-97°, reported \( m.p. 95-96° \) and \( 83° \).

Preparation of Oximes.

With the exception of the isomers of isobutyrophenone oxime, all of the oximes were prepared by the standard sodium hydroxide procedure using an approximate molar ratio of 2 moles of hydroxylamine hydrochloride to 1 mole of ketone. The ortho-substituted acetophenones had to be heated for longer periods of time to effect an appreciable amount of reaction.

For reaction mixtures in which the oxime separated as an oil which would not solidify after repeated attempts to induce crystallization, the ethanol was distilled from the reaction mixture, and the product was taken up in ether. After drying the ether solution with Drierite, the ether was removed, and the oxime was fractionally crystallized from petroleum ether at low temperatures.

The oximes were obtained in a relatively pure state after one recrystallization from ethanol-water or chloroform-petroleum ether, although in a few instances the pure compound was obtained only after several recrystallizations. Yields of the acetophenone oximes and cyclohexanone oxime are listed in Table IV.
The syn- and anti-phenyl isomers of isobutyrophenone oxime were prepared according to the method of Kissman. From 20 g. (0.135 mole) of isobutyrophenone were obtained 7.22 g. (32.8%) of crude syn-phenyl oxime (plates) and 11.11 g. (50.5%) of crude anti-phenyl oxime (prisms). After recrystallization from chloroform-petroleum ether, the former melted at 88.5-90°, reported m.p. 89-90°, and the latter melted at 98.5-99.5°, reported m.p. 95-96°. A mixture of the two isomers melted at 60-63°.

Preparation of O-Methyl-p-chloroacetophenone Oxime:

a. By methylation of p-chloroacetophenone oxime under aqueous conditions. In a 500 ml. three-necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel, 17 g. (0.1 mole) of crude p-chloroacetophenone oxime was dissolved in 135 ml. of 1.2 N sodium hydroxide. The solution was stirred while 12.6 g. (9.5 ml., 0.1 mole) of methyl sulfate was added dropwise, and the temperature was maintained at 40-45°. When the addition was complete, the mixture was stirred for 5 minutes. A 20 ml. portion of 10% sodium hydroxide was then added in one lot followed by the addition of 5 ml. of methyl sulfate as before except that the temperature was allowed to rise to 50°. Stirring was continued for 30 minutes at this temperature, after which the mixture was cooled, and the organic layer was taken up in petroleum ether. The petroleum ether solution was dried over Drierite, filtered, and concentrated by distillation.
Distillation of the residue at reduced pressure gave 12.5 g. of product, b.p. 117-123° at 15 mm., \( n_D^{24.5} 1.5575 \). Redistillation at reduced pressure gave, after an extensive forerun was collected, 8.3 g. of a liquid, b.p. 118-119° at 15 mm., \( n_D^{25.5} 1.5555 \).

**Anal.** Calcd. for C_{9}H_{10}ClNO: C, 58.86; H, 5.49.

Found: C, 61.24; H, 5.08.


b. by methylation of p-chloroacetophenone oxime under non-aqueous conditions. To a solution of 17 g. (0.1 mole) of crude p-chloroacetophenone oxime in 50 ml. of absolute methanol was added a solution of 6.5 g. (0.12 mole) of sodium methoxide in the same solvent. After the solutions were well mixed, a solution of 15.1 g. (11.4 ml., 0.12 mole) of methyl sulfate in 25 ml. of absolute methanol was added slowly (15 min.), and the mixture was then heated under reflux for 2.5 hrs. At the end of the reflux period, the methanol was distilled from the mixture. The pasty residue was cooled and extracted with three 50 ml. portions of petroleum ether. The petroleum ether solution was dried over anhydrous sodium sulfate, filtered, and concentrated by distillation of the solvent. After removal of the final traces of solvent by a current of dry air, 13.7 g. of a yellow oil was obtained.

On standing overnight, a small amount of solid precipitated from the oil. This solid, when removed by filtration, washed with cold petroleum ether and dried, amounted to 0.5 g. and melted at 128-133°. The oil and petroleum ether washings
were concentrated once again by removal of the solvent, and the residue was distilled at reduced pressure. Of the 7.5 g. (39%) collected over a 130-150° range at 18 mm., 3.4 g. of a middle fraction was obtained, b.p. 132-134° at 18 mm., n_D^26.5 1.5563.

IR Spectrum (Film, No. 156): 1640 (w), 1097, 1050, 895, 830.

UV Spectrum (95% Ethanol), λ_max. (ε_max.): 204 (30,900), 254 (18,580).

See IR Spectrum and analysis of compound prepared by method (c).

The solid, after two recrystallizations from chloroform-petroleum ether, melted at 140-141°. On recrystallization from water the solid melted at 94.5-95°, and the melting point was not depressed on admixture of this material with p-chloroacetophenone oxime of the same melting point. Because of the similarity of the infrared spectrum with that of p-chloroacetophenone oxime and its ease of transformation to that compound, it was speculated that the higher melting solid and the lower melting oxime might be syn and anti isomers respectively. Since this was not substantiated by the microanalytical data the identity of this compound is still unknown.*

Anal. Calc. for C_{16}H_{17}ClNO: C, 56.65; H, 4.75;
Found: C, 54.79, 55.03; H, 6.03, 6.10.

*The analytical data seem to fit the formula C_{16}H_{17}ClNO for α-(α-methoxy-α-p-chlorophenylethyl) hydroxylamine; however, no attempt was made to establish the true identity of the compound.
IR Spectrum (Nujol mull, No. 178): 3150 (m), 2760-2600, 1492, 1475, 1095, 1018°, 1012, 940, 833.

IR Spectrum (CS₂, No. 201): 3600 (m), 3260 (w), 1098, 829.

UV Spectrum (95% Ethanol), λ max. (ε max.): 205° (18,550), 250 (12,840).

b. By reaction of p-chloroacetophenone with methoxyamine hydrochloride. A solution of 0.0 g. (0.072 mole) of methoxyamine hydrochloride in 30 ml. of water was mixed with 9.3 g. (0.060 mole) of p-chloroacetophenone, 20 ml. of 10% sodium hydroxide, and sufficient 95% ethanol to produce homogeneity. The solution was heated for 15 minutes on the steam bath and then left overnight to cool. After dilution of the mixture with water and removal of most of the ethanol by distillation, the mixture was cooled and the oily layer was taken up in chloroform. The chloroform solution was dried over diatomite, and when the solvent was removed, 9.5 g. (86.2%) of crude product was obtained. On distillation at reduced pressure, 0.8 g. of forerun was collected, b.p. 123-127° at 16 mm., following which 7.6 g. (69%) of pure product, b.p. 127-129.5° at 16 mm., n_D 1.5544, D 22.5 1.1565, was obtained.

Anal. Calcd. for C₉H₁₀ClNO: C, 58.86; H, 5.49
Found: C, 58.94; H, 5.35.

IR Spectrum (Film, No. 231): 1640 (w) 1098, 1050, 896, 830.
Preparation of O-Methyl-o-methoxyacetophenone Oxime.

A solution of 6 g. (0.072 mole) of methoxyamine hydrochloride in 30 ml. of water was mixed with 5.0 g. (0.0333 mole) of o-methoxyacetophenone, 20 ml. of 10% sodium hydroxide and sufficient 95% ethanol to produce homogeneity. After the solution was heated on the steam bath for one hour, it was allowed to cool slowly to room temperature. The oily layer which separated was taken up in petroleum ether and the petroleum ether solution was dried over Drierite. On removal of the solvent, 5.55 g. (93.2%) of crude product was obtained. Distillation of this material at reduced pressure gave 4.82 g. (81%) of pure product, b.p. 122-124° at 10 mm., n_D^25 1.5389, D^28 1.0932.

Anal. Calcd. for C_{10}H_{13}NO_2: C, 67.02; H, 7.31. Found: C, 66.82; H, 7.15.

IR Spectrum (Film, No. 277) 1623 (m), 1497, 1468, 1440, 1275, 1243, 1078, 1053, 1043, 1028, 883, 755.

Preparation of O-methyl-p-methoxyacetophenone Oxime.

A solution of 6 g. (0.072 mole) of methoxyamine hydrochloride in 30 ml. of water was mixed with 9 g. (0.060 mole) of p-methoxyacetophenone, 20 ml. of 10% sodium hydroxide, and sufficient 95% ethanol to produce homogeneity. After the solution was heated on the steam bath for 10 minutes, it was allowed to cool slowly to room temperature. The product separated as an oil which solidified on standing. The solid was removed by filtration, and a second crop was obtained by dilution of the hot filtrate with water and allowing it to
cool slowly to room temperature; a total of 10.5 g. (98%) of crude product, m.p. 51-52°, was thus obtained. Recrystallization of this material from petroleum ether gave 9.5 g. (88%) of pure product, m.p. 52-52.5°, from two separate crops.

**Anal.** Calcd. for C_{10}H_{13}N_{2}O_2: C, 67.02; H, 7.31

**Found:** C, 67.19; H, 7.54.

**IR Spectrum (Mull, No. 574):** 1650 (w), 1620, 1265, 1049, 1027, 831.

**Reduction of Oximes and Their Derivatives with Lithium Aluminum Hydride.**

The oxime or its derivative, dissolved in ether, was added to a suspension (or a solution) of lithium aluminum hydride in ether in the amounts indicated in Tables I and II. After the mixture was heated under reflux for the amount of time specified for each run, it was cooled, and the excess hydride was decomposed by the addition of water. The insoluble precipitate was removed by filtration and washed well with ether. The filtrate and washings were combined and diluted volumetrically (or reduced in volume by distillation of ether) to 250 ml. of solution. A 25 ml. portion (1/10 aliquot) of the product-containing solution was then titrated by one of the methods described below to determine the amount of amines produced. For product-containing solutions low in concentration of amines, 50 ml. portions (1/5 aliquots) were titrated.
Titration of Reduction Products by the Indicator Method (Method A).

A 25 ml. portion (1/10 aliquot) of the product-containing solution was diluted to 50 ml. by the addition of 15 ml. of 95% ethanol and 10 ml. of ether. The sample was then titrated with 0.1095 N hydrochloric acid (dissolved in a 9:1 mixture of 95% ethanol and ethylene glycol) to the end point of bromcresol green indicator. Thymol blue indicator was then added and titration was continued until the end point of the latter was reached. (Because bromcresol green changes from blue to yellow and thymol blue changes from yellow to red, there seemed to be little interference from the former in determining the second end point). From the amount of acid required to reach the first end point, multiplied by the aliquot factor, the quantity of aliphatic amine, or normal reduction product, was determined. Similarly, from the additional amount of acid required to reach the second end point, multiplied by the aliquot factor, the amount of aromatic amine, or rearranged product was determined.

Potentiometric Titration of Reduction Products in Styrene Glycol-Isopropyl Alcohol (Method B).

A 25 ml. portion (1/10 aliquot) of the product-containing solution was added to 75 ml. of a 1:1 mixture of ethylene glycol and isopropyl alcohol in a 150 ml. beaker. The sample was then titrated potentiometrically with 0.2190 N hydrochloric acid dissolved in the same solvent mixture.
The titrations were performed with a 10 ml. microburet and the potentials were measured with a Beckmann model H-2 pH meter. The solutions were stirred with a magnetic stirrer during the course of titration. The end points were determined in the usual manner from the titration curves obtained by plotting potential against the volume of acid used, the end point being the volume at which the change in potential with respect to volume was greatest. From these values, the amount of amines produced was determined as above in method A.

Potentiometric Titration of Reaction Products in Acetonitrile-Chloroform (Method C).

The sample was titrated as in method B but 75 ml. of a 2:1 mixture of acetonitrile and chloroform was substituted for the 1:1 ethylene glycol-isopropyl alcohol mixture and 0.2108 N perchloric acid in dioxane was used as acid titrant instead of the 0.2190 N hydrochloric acid in 1:1 ethylene glycol-isopropyl alcohol.

To distinguish between primary and secondary aliphatic amines, a titration was performed on a second aliquot after preliminary treatment with salicylalddehyde to convert the primary amine to the weaker Schiff base. The secondary aliphatic amine, which did not react, was then differentially titrated with the standard perchloric acid solution.
Rate of Reduction of p-Methylacetophenone Oxime with Lithium Aluminum Hydride (Table III).

Run I. Into a 500 ml. wide-mouth, ground-glass stoppered bottle which was calibrated to the nearest 25 ml., and which had been flushed previously with nitrogen, was placed 250 ml. of a 0.49 molar solution (0.123 mole) of lithium aluminum hydride in ether. The bottle was sealed with a stopper which had been greased as a precaution against both a buildup of pressure and freezing of the stopper, in the event of attack on the glass by the strongly basic solution. After allowing the solution to come to room temperature over-night, the glass stopper was replaced by a two hole cork stopper, equipped with a dropping funnel and an outlet for release of hydrogen. The bottle was then immersed in a water bath at room temperature, and a solution of 6.01 g. (0.0403 mole) of p-methylacetophenone oxime in 50 ml. of anhydrous ether was added dropwise over a 15 minute period. Sufficient anhydrous ether was then added to bring the total volume of solution to 400 ml. The starting time and temperature of the reaction was recorded, and at definite intervals, a 25 ml. portion (1/16 aliquot) of the reaction mixture was withdrawn and placed in a flask, cooled in an ice-bath. The sample, while stirred with a magnetic stirrer, was rapidly quenched with 0.5 ml. of water, following which, the insoluble precipitate was removed by filtration and washed well with ether. The ethereal filtrate and washing were then kept in a numbered flask which was stoppered until titrated potentiometrically by method B above. The temperature of the reac-
tion mixture (from samples 2-11, Run I, Table III) was maintained at 25.9 ± 0.1°.

Run II. The procedure was the same as for the first run, except that a solution of 1.87 g. (0.0126 mole) of p-methylacetophenone oxime in 50 ml. of anhydrous ether was added to 160 ml. of the 0.49 molar solution (0.078 mole) of lithium aluminum hydride, and sufficient anhydrous ether was added to bring the total volume of solution to 250 ml. The temperature of this reaction mixture was maintained at 26.3 ± 0.3°.

**Attempted Isomerization of the syn-Phenyl Isomer of Isoisutyrophenone Oxime.**

A solution of 0.42 g. (0.0026 mole) of the syn-phenyl isomer of isoisutyrophenone oxime in 15 ml. of anhydrous ether was added to 10 ml. of a 0.49 molar solution (0.0049 mole) of lithium aluminum hydride. The homogeneous mixture was heated under reflux for about 10 minutes, cooled and decomposed with water, and the insoluble precipitate was removed by filtration and washed with ether. The filtrate and washings were dried over Drierite. On removal of the solvent, 0.30 g. (72%) of the syn-phenyl isomer was recovered unchanged, m.p. and mixed m.p. with a pure sample, 88.5-89.5°.

**Reaction of p-Methylacetophenone Oxime with Limited Amounts of Lithium Aluminum Hydride.**

a) To a solution of 2.98 g. (0.020 mole) of p-methylacetophenone oxime in 190 ml. of anhydrous ether was
added 12 ml. of a 0.49 molar solution (0.005 mole) of lithium aluminum hydride. The solution was heated under reflux for 10 hrs., cooled to room temperature, and then sealed under nitrogen for two days. The solution was decanted from a precipitate, which formed during the reflux period, and was hydrolyzed with the calculated amount of water. The lithium and aluminum hydrides were removed by filtration and washed with ether. From the ethereal filtrate and washings, after drying over Drierite, were isolated a total of 1.98 g. of relatively pure oxime (m.p. and mixed m.p. 85-86°), and 0.26 g. of an oil, which appeared to be impure oxime. An additional 0.08 g. of pure oxime was recovered from hydrolysis of the precipitate which settled from the reaction. Finally, by dissolving the lithium and aluminum hydroxides in dilute acid and extracting the insoluble residue with ether, 0.23 g. more of the oxime was recovered from the ether. The total amount of pure oxime recovered was 2.29 g. (77%).

b) To a solution of 1.49 g. (0.010 mole) of p-methylanisaldehyde oxime in 90 ml. of anhydrous ether was added 10 ml. of a 0.49 molar solution (0.0049 mole) of lithium aluminum hydride. After the solution was heated under reflux for 10 hrs., it was hydrolyzed with the calculated amount of water; a considerable amount of hydrogen was produced on hydrolysis. The insoluble precipitate was removed by filtration and washed with ether. The filtrate and washings were dried over Drierite and then diluted volumetrically to 250 ml. Titration of a 50 ml. portion (1/5 aliquot)
of this solution by method C revealed that 27.6% of the oxime had been reduced to a mixture of amines, of which 42.7% was rearrangement product. The products were isolated by the general procedure described below and were identified, by their hydrochlorides, as the amines usually obtained from the oxime, namely, α-p-tolyl methylamine and N-ethyl-p-toluidine. The hydrochloride of the former melted at 158-160°, reported m.p. 163-165°; while that of the latter melted at 157-158°, reported m.p. 158-160°. A mixture of the latter with an authentic specimen melted at 157-158°. Also recovered from the reaction mixture was 0.72 g. (48%) of unreacted oxime, m.p. 86-87°. (A greater amount was actually recovered, but some was accidentally lost).

Separation of Products from Reaction Mixtures.

After analysis of one or more aliquots of a solution obtained from a reduction mixture, separation of the products was achieved by extracting the remainder of the solution, first, with an equal volume of sodium acetate-acetic acid buffer (2 M with respect to the former and 0.4 M with respect to the latter), and then with an equal volume of 5% hydrochloric acid. Any unreacted oxime or oxime ether (I) was recovered from the ether. The sodium acetate-acetic acid buffer extracts and the hydrochloric acid extracts were each basified with the calculated amount of 20% sodium hydroxide, and each of the basic solutions was extracted with an equal volume of ether. After drying the ether extracts over
Drierite, the primary aliphatic amine (II) was recovered from the extracts of the former and the secondary aromatic amine (III) was recovered from the extracts of the latter. If the amines were present in low quantities, they were isolated as their hydrochlorides.
SUMMARY
The reaction of ketoximes with lithium aluminum hydride was studied quantitatively by analyzing the amines obtained from the reduction of ketoximes and their derivatives by potentiometric titration. This quantitative study made it possible to determine the effect of several structural features on the course of the reaction.

Electron-releasing substituents in the para position of acetophenone oximes caused, simultaneously, a decrease in the overall rate of reduction and an increase in the relative amount of reductive rearrangement product. No such correlation was possible for the effect of substituents in the ortho position. While each of the three ortho-substituted compounds studied gave decreased relative amounts of the rearrangement product than did the corresponding para-substituted compounds, two of them, the o-methyl- and o-chloro-substituted acetophenone oximes, exhibited a marked decrease in the rate of reduction, but the third, o-methoxyacetophenone oxime, underwent reduction at an accelerated rate. The behavior of the first two compounds was unambiguously due to steric inhibition of the reaction by the bulky o-methyl and o-chloro substituents; whereas, the anomalous behavior of the third was probably due to the formation of a coordinated complex between the o-methoxy substituent and aluminum hydride, which could thus facilitate the reaction intramolecularly.

The methyl ethers of several substituted acetophenone oximes underwent reduction at slower rates and gave smaller amounts of the rearrangement product than did the corresponding
oximes. This seemed to indicate that the anion first formed by removal of the active hydrogen from an oxime by lithium aluminum hydride plays an important part in the reaction. The possibility that the aluminum hydride coordination complex formed with this anion might function as a more powerful reducing agent was ruled out, unless it did so intramolecularly, by the kinetic study which showed that the reaction was first order in oxime. In this study, a variation in the ratio of products with time was also observed, suggesting that the products are formed by several reaction paths, or from several intermediates (or transition states).

The reduction of the two isomers of isocyanophenone oxime showed that the rearrangement accompanying the lithium aluminum hydride reduction is not stereospecific, for approximately the same product mixture was obtained from both oxime isomers. The oximes were not isomerized by treatment with lithium aluminum hydride, and the anti-phenyl isomer underwent reduction and rearrangement at a slower rate than the syn-phenyl isomer, thus precluding the possibility of preliminary isomerization and rearrangement before reduction to account for the major product, 1-isocyanalanilale.

The most promising explanation of the experimental results is offered by a reaction path which involves an oxazirane transition state. It is suggested that this is the main path by which reductive rearrangement occurs, but reduction must also occur concurrently by other reaction paths to account for the variation in the ratio of products with time.


12) Ref. 10, p. 756.


17) Ref. 10, pp. 751-757.

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(33) Ref. 10, p. 94.


(49) Ref. 26, p. 278.

(50) Ref. 26, p. 200.


(57) K. Kindler, W. Peschke, and E. Brandt, Ber., 68, 2241 (1935).


(64) J. von Braun and K. Weissbach, Ber. 62, 2416 (1929).


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<td>76%</td>
<td>86.5-87</td>
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<td>52</td>
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<td>15 min.</td>
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<td>77%</td>
<td>85.5-87</td>
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<td>53</td>
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<td>B</td>
<td>48%</td>
<td>101.5-103</td>
<td>104.5-105.5</td>
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<td>cyclohexanone</td>
<td>15 min.</td>
<td>B</td>
<td>57%</td>
<td>89-89.5</td>
<td>89-90</td>
<td>56</td>
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\(^a\) A, ethanol-water; \(^b\) B, chloroform-petroleum ether; \(^b\) Pure product.
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<td>N-ethyl-p-toluidine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>158-160</td>
<td>162</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>p-toluensulfonamide</td>
<td>69-70</td>
<td>71</td>
<td>59</td>
</tr>
<tr>
<td>α-phenylethylamine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>155-157</td>
<td>158</td>
<td>60</td>
</tr>
<tr>
<td>N-ethylaniline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>174-176</td>
<td>176</td>
<td>61</td>
</tr>
<tr>
<td>α-p-chlorophenylethylamine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>183-190</td>
<td>192-193</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>p-toluensulfonamide</td>
<td>128-129</td>
<td>c</td>
<td>--</td>
</tr>
<tr>
<td>N-ethyl-p-chloroaniline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>133-136</td>
<td>d</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>p-toluensulfonamide</td>
<td>100-102</td>
<td>102-104</td>
<td>59</td>
</tr>
<tr>
<td>α-p-bromophenylethylamine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>212-214</td>
<td>213-214</td>
<td>62</td>
</tr>
<tr>
<td>N-ethyl-p-bromoaniline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>168-171</td>
<td>e</td>
<td>--</td>
</tr>
<tr>
<td>α-o-methoxyphenylethylamine&lt;sup&gt;f&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>151.5-153.5</td>
<td>---</td>
<td>--</td>
</tr>
<tr>
<td>N-ethyl-o-methoxyaniline&lt;sup&gt;f&lt;/sup&gt;</td>
<td>hydrochloride</td>
<td>192-193</td>
<td>193</td>
<td>63</td>
</tr>
</tbody>
</table>
Amine | Derivative | m.p., °C | Lit. m.p., °C | Ref.
--- | --- | --- | --- | ---
α-α-tolylethylamine | hydrochloride | 160-168 | 173 | 63
α-ethyl-α-toluidine | hydrochloride | 155-166d. | g | --
α-α-chlorophenylethylamine | benzenesulfonamide | 126-127 | l | --
 | hydrochloride | 163-166 | --- | --
α-phenylisobutylamine | benzenesulfonamide | 103-103.5 | 1 | --
 | hydrochloride | 271-272 | 275-277d | 65
 | picrate | 184-185m, n | 166-168 | 65
α-isotutyylaniline | p-toluensulfonamide | 124-123 | 122-123 | 66
Hydrochloride | 200-201d. | --- | --- | --
   
---
aData from Lyle and Troscianiec. **These same products were obtained from the reduction of p-methoxyacetophenone oxime and its O-methyl ether. **Calcd. for C15H16ClN2O2S: m. p., 4.23. Found: m. p., 4.62, 4.41. Anal. Calcd. for C14H12ClN: Cl, 18.46. Found: Cl, 18.15.  Anal. Calcd. for C16H14ClN2: Cl, 20.68. Found: Cl, 21.10. h. p., 95-100° at 8 mm., nD20 1.5474. Anal. Calcd. for C14H14ClN2O2S: C, 46.84; H, 4.77. Found: C, 57.09; H, 4.94. These same products were obtained from the syn- and anti-isomers of isutyrophenone oxime. h. p., 150-151° at 15 mm., nD20 1.5118. Anal. Calcd. for C16H20O2S: C, 66.17; H, 4.94. Found: C, 66.66; H, 4.78. IR Spectrum (30°C, no. 620): 3300 (m), 1330, 1167, 1096, 743, 700, 687. Anal. Calcd. for C16H18O7: C, 50.79; H, 4.93. An isomeric picrate was also obtained which melted at the same temperature, but a mixture with the above melted at 194-195°. The corresponding hydrochloride of this isomer melted at 145-146°. h. p., 111-112° at 16 mm., nD20 1.5290. UV Spectrum (free base in 95% ethanol), λ max. (ε max.): 204.5 (32,400), 248 (13,000), 297 (2000). UV Spectrum (hydrochloride in 95% ethanol), λ max. (ε max.): 204.5 (12,400), 249 (514), 254 (492), 297 (140). NMR Spectrum (40% solution in DCl4): 1.48 (m), 1.06 (m), 1.07 (m), 1.98 (m), 2.02 (m), 2.13, 2.14, 2.16, 2.18 (m).
Fig. 11. Potentiometric titrations in 1:1 ethylene glycol-isopropyl alcohol (method B): O, reduction products from p-methoxyacetophenone oxime; △, reduction products from p-methylacetophenone oxime; □, reduction products from acetophenone oxime; ◊, reduction products from p-chloroacetophenone oxime (see Fig. 12).
Fig. 12. Iodometric titration of reduction products from p-chloroacetophenone oxime in 2:1 acetonitrile-chloroform (method C).
Fig. 13. Potentiometric titrations in 2:1
acetonitrile-chloroform (method C): ○, reaction
product from cyclohexanone oxime; □, reaction
product from cyclohexanone oxime after treatment
with salicylaldehyde.
BIOGRAPHICAL DATA
BIOGRAPHICAL DATA

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