THE PREPARATION AND INVESTIGATION
OF SOME DERIVATIVES OF OXIMES

DISSertation

Presented in Partial Fulfillment of the Requirements
for the Degree Doctor of Philosophy in the
Graduate School of The Ohio State
University

By

LOUIS GASS, B. S., M. S.

*****

The Ohio State University

1957

Approved by:

[Signature]

Adviser

College of Pharmacy
ACKNOWLEDGMENTS

I wish to express my sincere appreciation and gratitude to Dr. Frank W. Bope, Associate Professor of Pharmacy, for the guidance and advice which he so willingly and generously supplied during this investigation and for the many helpful suggestions in the preparation of this manuscript.

To Dr. Jack L. Beal, Associate Professor of Pharmacy, I am indebted for his aid and advice concerning the determination of optical properties undertaken in this manuscript.

To Dr. Lloyd E. Harris, Professor of Pharmacy, I express my sincere appreciation for the helpful suggestions offered in overcoming several difficulties encountered.

To Dr. John W. Nelson, Professor of Pharmacy, I express my sincere appreciation for the suggestions and advice given in the development of the pharmacological testing.

To Dr. Earl P. Guth, Professor of Pharmacy, I express my sincere thanks for the helpful suggestions offered in the writing of this manuscript.

Further, I wish to acknowledge with deepest gratitude the patience and forbearance exhibited by my wife, Sylvia, and the moral support which she gave me during my attendance at The Ohio State University.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL REVIEW</td>
<td>2</td>
</tr>
<tr>
<td>Chemistry</td>
<td>2</td>
</tr>
<tr>
<td>General</td>
<td>2</td>
</tr>
<tr>
<td>Stereoisomerism</td>
<td>8</td>
</tr>
<tr>
<td>Acylation and Hydrolysis</td>
<td>16</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>20</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>25</td>
</tr>
<tr>
<td>Discussion of Procedures and Equipment Used</td>
<td>25</td>
</tr>
<tr>
<td>Cyclohexanone Oxime</td>
<td>28</td>
</tr>
<tr>
<td>Preparation</td>
<td>28</td>
</tr>
<tr>
<td>Esters of Cyclohexanone Oxime</td>
<td>29</td>
</tr>
<tr>
<td>Cyclohexanone Oxime Para-Nitro-Benzoate</td>
<td>29</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>30</td>
</tr>
<tr>
<td>Cyclohexanone Oxime Para-Methoxy-Benzoate</td>
<td>31</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>32</td>
</tr>
<tr>
<td>Cyclohexanone Oxime Phenyl Acetate</td>
<td>32</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>33</td>
</tr>
<tr>
<td>Benzophenone Oxime</td>
<td>34</td>
</tr>
<tr>
<td>Preparation</td>
<td>34</td>
</tr>
<tr>
<td>Esters of Benzophenone Oxime</td>
<td>35</td>
</tr>
<tr>
<td>Benzophenone Oxime Para-Nitro-Benzoate</td>
<td>35</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>36</td>
</tr>
</tbody>
</table>
**TABLE OF CONTENTS (CONTINUED)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenone Oxime Para-Methoxy-Benzoate</td>
<td>37</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>38</td>
</tr>
<tr>
<td>Benzophenone Oxime Phenyl Acetate</td>
<td>38</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>39</td>
</tr>
<tr>
<td>Alpha (Syn) Benzaldoxime</td>
<td>39</td>
</tr>
<tr>
<td>Preparation</td>
<td>39</td>
</tr>
<tr>
<td>Esters of Alpha-Benzaldoxime</td>
<td>41</td>
</tr>
<tr>
<td>Alpha-Benzaldoxime Para-Nitro-Benzoate</td>
<td>41</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>41</td>
</tr>
<tr>
<td>Alpha-Benzaldoxime Para-Phenyl Acetate</td>
<td>42</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>42</td>
</tr>
<tr>
<td>Alpha (Syn) Para-Methoxy-Benzaldoxime</td>
<td>43</td>
</tr>
<tr>
<td>Preparation</td>
<td>43</td>
</tr>
<tr>
<td>Esters of Alpha-Para-Methoxy-Benzaldoxime</td>
<td>44</td>
</tr>
<tr>
<td>Alpha-Para-Methoxy-Benzaldoxime Para-Nitro-Benzoate</td>
<td>44</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>45</td>
</tr>
<tr>
<td>Alpha-Para-Methoxy-Benzaldoxime Phenyl Acetate</td>
<td>45</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>46</td>
</tr>
<tr>
<td>Alpha (Syn) Acetophenone Oxime</td>
<td>46</td>
</tr>
<tr>
<td>Preparation</td>
<td>46</td>
</tr>
<tr>
<td>Esters of Alpha-Acetophenone Oxime</td>
<td>48</td>
</tr>
<tr>
<td>Alpha-Acetophenone Oxime Benzoate</td>
<td>48</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>49</td>
</tr>
<tr>
<td>iv</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE OF CONTENTS (CONTINUED)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-Acetophenone Oxime Para-Nitro-Benzoate</td>
<td>49</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>50</td>
</tr>
<tr>
<td>Alpha-Acetophenone Oxime Para-Methoxy-Benzoate</td>
<td>50</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>51</td>
</tr>
<tr>
<td>Alpha-Acetophenone Oxime Phenyl Acetate</td>
<td>51</td>
</tr>
<tr>
<td>Optical Properties</td>
<td>52</td>
</tr>
<tr>
<td>Discussion of Experimental Results</td>
<td>53</td>
</tr>
<tr>
<td>Attempted Reductions</td>
<td>58</td>
</tr>
<tr>
<td>Sodium Hydrosulfite Methods</td>
<td>58</td>
</tr>
<tr>
<td>Sodium Sulfide Method</td>
<td>60</td>
</tr>
<tr>
<td>Catalytic Hydrogenation Method</td>
<td>60</td>
</tr>
<tr>
<td>Discussion of Reduction Results</td>
<td>64</td>
</tr>
<tr>
<td>Infrared Analyses</td>
<td>66</td>
</tr>
<tr>
<td>Discussion of Infrared Analyses</td>
<td>94</td>
</tr>
<tr>
<td>Pharmacological Studies</td>
<td>95</td>
</tr>
<tr>
<td>Procedures</td>
<td>95</td>
</tr>
<tr>
<td>Discussion of Pharmacological Results</td>
<td>96</td>
</tr>
<tr>
<td>SUMMARY AND CONCLUSIONS</td>
<td>101</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>102</td>
</tr>
<tr>
<td>AUTOBIOGRAPHY</td>
<td>107</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Catalytic Hydrogenation Experiments</td>
<td>62</td>
</tr>
<tr>
<td>II.</td>
<td>Absorption Bands Found in Cyclohexanone Oxime and Its Esters</td>
<td>74</td>
</tr>
<tr>
<td>III.</td>
<td>Absorption Bands Found in Benzophenone Oxime and Its Esters</td>
<td>79</td>
</tr>
<tr>
<td>IV.</td>
<td>Absorption Bands Found in Alpha-Para-Methoxy-Benzaldehyde and Its Esters</td>
<td>83</td>
</tr>
<tr>
<td>V.</td>
<td>Absorption Bands Found in Alpha-Benzaldehyde and Its Esters</td>
<td>87</td>
</tr>
<tr>
<td>VI.</td>
<td>Absorption Bands Found in Alpha-Acetophenone Oxime and Its Esters</td>
<td>93</td>
</tr>
<tr>
<td>VII.</td>
<td>The Approximate Toxicities of Para-Methoxy-Benzoate Esters of Several Oximes by Intraperitoneal Injection in Mice</td>
<td>97</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>I.</td>
<td>Infrared Absorption Spectrograph of Cyclohexanone Oxime</td>
<td>70</td>
</tr>
<tr>
<td>II.</td>
<td>Infrared Absorption Spectrograph of Cyclohexanone Oxime Para-Nitro-Benzoate</td>
<td>71</td>
</tr>
<tr>
<td>III.</td>
<td>Infrared Absorption Spectrograph of Cyclohexanone Oxime Para-Methoxy-Benzoate</td>
<td>72</td>
</tr>
<tr>
<td>IV.</td>
<td>Infrared Absorption Spectrograph of Cyclohexanone Oxime Phenyl Acetate</td>
<td>73</td>
</tr>
<tr>
<td>V.</td>
<td>Infrared Absorption Spectrograph of Benzophenone Oxime</td>
<td>75</td>
</tr>
<tr>
<td>VI.</td>
<td>Infrared Absorption Spectrograph of Benzophenone Oxime Para-Nitro-Benzoate</td>
<td>76</td>
</tr>
<tr>
<td>VII.</td>
<td>Infrared Absorption Spectrograph of Benzophenone Oxime Para-Methoxy-Benzoate</td>
<td>77</td>
</tr>
<tr>
<td>VIII.</td>
<td>Infrared Absorption Spectrograph of Benzophenone Oxime Phenyl Acetate</td>
<td>78</td>
</tr>
<tr>
<td>IX.</td>
<td>Infrared Absorption Spectrograph of Para-Methoxy-Benzaldoxime</td>
<td>80</td>
</tr>
<tr>
<td>X.</td>
<td>Infrared Absorption Spectrograph of Para-Methoxy-Benzaldoxime Para-Nitro-Benzoate</td>
<td>81</td>
</tr>
<tr>
<td>XI.</td>
<td>Infrared Absorption Spectrograph of Alpha-Para-Methoxy-Benzaldoxime Phenyl Acetate</td>
<td>82</td>
</tr>
<tr>
<td>XII.</td>
<td>Infrared Absorption Spectrograph of Alpha-Benzaldoxime</td>
<td>84</td>
</tr>
<tr>
<td>XIII.</td>
<td>Infrared Absorption Spectrograph of Alpha-Benzaldoxime Para-Nitro-Benzoate</td>
<td>85</td>
</tr>
<tr>
<td>XIV.</td>
<td>Infrared Absorption Spectrograph of Alpha-Benzaldoxime Phenyl Acetate</td>
<td>86</td>
</tr>
<tr>
<td>XV.</td>
<td>Infrared Absorption Spectrograph of Alpha-Acetophenone Oxime</td>
<td>88</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>XVI.</td>
<td>Infrared Absorption Spectrograph of Alpha-Acetophenone Oxime Benzoate</td>
<td>89</td>
</tr>
<tr>
<td>XVII.</td>
<td>Infrared Absorption Spectrograph of Alpha-Acetophenone Oxime Para-Nitro-Benzoate</td>
<td>90</td>
</tr>
<tr>
<td>XVIII.</td>
<td>Infrared Absorption Spectrograph of Alpha-Acetophenone Oxime Para-Methoxy-Benzoate</td>
<td>91</td>
</tr>
<tr>
<td>XIX.</td>
<td>Infrared Absorption Spectrograph of Alpha-Acetophenone Oxime Phenyl Acetate</td>
<td>92</td>
</tr>
<tr>
<td>XX.</td>
<td>Graphic Approximations of LD&lt;sub&gt;50&lt;/sub&gt; in Mice</td>
<td>98</td>
</tr>
</tbody>
</table>
INTRODUCTION

A number of oximes have been used experimentally as anticonvulsants in doses of 250 to 430 mg/Kg against electric shock (1). The protective activity of these compounds was comparable to the protection offered by diphenyl hydantoin, a well known anticonvulsant. No toxic effects from these doses were reported, although previous reports have been made in the literature that oximes and their derivatives are generally considered to be toxic.

It is possible that esters of oximes might have less toxicity than the parent compounds because esterification could block the adverse effects of the free oximino group. Therefore, it is the purpose of this investigation to prepare a series of oximino esters from the parent oximes, similar to those known to have anticonvulsant activity, using various acids that might contribute to the over-all anticonvulsant effect of the compounds.
GENERAL

Hydroxylamine (H$_2$NOH), can be considered the precursor of oximes. Oximes are compounds containing the (\(\equiv N-OH\)) group of hydroxylamine. The name oxime was introduced by Victor Mayer and implies that the structure is a contracted form of oxy-imine. According to I.U.C. rules (2), the oximes are named by adding the suffix, oxime, to the name of the corresponding aldehyde or ketone.

There are two general methods for preparing oximes. One procedure is via the action of hydroxylamine on aldehydes or ketones (3,4,5):

\[
\begin{align*}
R'\text{C}=O + H_2\text{NOH} &\rightarrow R'\text{C}=\text{NOH} + H_2O
\end{align*}
\]

The general procedure involves bringing together equal molecular quantities of the carbonyl compound and hydroxylamine hydrochloride in aqueous solution. To this is added a 25 to 50 per cent excess (of the molecular quantities) of sodium carbonate, bicarbonate, or hydroxide. The reaction proceeds to completion at room temperature with
aldehydes; but in preparing ketoximes, heat must be applied (6). The cyclic ketones react more readily than open chain ketones. If the carbonyl compound is insoluble in water, a hydroalcoholic solution is used to dissolve it.

If sodium hydroxide is employed for liberating the free hydroxylamine from the hydrochloride, it is necessary to saturate the solution with carbon dioxide at the end of the reaction to precipitate the oxime. The latter is then extracted with ether and the ether solution is dried over anhydrous sodium sulfate. The ether solution is then filtered and evaporated on a steam bath. The oxime is purified by recrystallization from a suitable solvent.

Another general method involves the action of nitrous acid or one of its esters upon a compound containing a reactive methyl or methylene group. The reaction can be written as:

\[
\begin{align*}
O & \quad \text{R-C-CH}_2\text{-R'} \quad \xrightarrow{\text{HB}} \quad \left[ \begin{array}{c} \text{OH} \\ \text{R-C-CH-R'} \end{array} \right] + \text{O=NOH} \quad \xrightarrow{\text{HB}} \quad \text{R-C-C-R'} + \text{H}_2\text{O}
\end{align*}
\]

The action of base on the ketoxime produces the enolic form of the ketone which reacts with the nitrous acid. It was by this type of reaction that Meyer and Zublin obtained the first reported oxime (7).

The reaction between carbonyl compounds and hydroxylamine is accelerated by alkali and by acids. The acceleration of oxime formation by alkali was first noticed
by Auwers (8) and was found by Barrett and Lapworth (6) to be proportional to the concentration of alkali. This acceleration of oxime formation by alkali suggests that the hydroxylamine behaves as a weak acid and reacts with the carbonyl compound in much the same manner as does hydrocyanic acid (9). Thus, to take the simplest possible ionic view, the hydroxylamine may be supposed to yield H\(^+\) and \(^-\)NHOH ions, the latter forming a complex with the carbonyl compound (10):

\[
\begin{align*}
&\text{R}^\circ\text{C}=\text{O} + \text{NHOH} \\
&\rightarrow \text{R}'\text{C}<\text{O}^-\text{NHOH}
\end{align*}
\]

This complex ion formation is relatively slow.

The acceleration of the reaction by hydrochloric acid is at a maximum at a concentration of 0.5 to 0.6 molecular equivalents of acid. The velocity here is more than fifty times as great as with free hydroxylamine alone. Above this concentration the reaction rate falls rapidly to a point at which further addition of acid causes little or no variation in reaction rate. The mechanism of acceleration of oxime formation via acids is not well defined. Since an equilibrium is attained when acids act on oximes, Acree and Johnson (11) concluded that the reaction involves the union of a hydroxylammonium ion with the carbonyl compound as the neutral constituent:
According to Barrett and Lapworth (6), this is highly improbable because of the already high electroaffinity of the hydroxylammonium ion, and because all the evidence further goes to show that only negative groups become attached to the carbon atom of the carbonyl group. A more likely suggestion is that the hydroxylammonium ion is not directly concerned, but the carbonyl compound forms a complex with hydrogen ions which are present as the result of hydrolysis of the hydroxylamine salt,

\[
\text{R}^\bullet \text{C}=\text{O} + \text{H}^+ \rightarrow \text{R}^\bullet \text{C}^+ \text{OH}
\]

and this positive ion then attacks the free hydroxylamine, forming a substituted hydroxylammonium ion:

\[
\text{R}^\bullet \text{C}^+ \text{OH} + \text{NH}_2\text{OH} \rightarrow \text{R}^\bullet \text{C}^+ \text{OH} \text{NH}_2\text{OH}
\]

In the presence of chloride ion this breaks down to give water, hydrochloric acid and the oxime as the final product.

The chemical and physical properties of oximes are described as follows:

1) Oximes are usually stable compounds, the alpha isomer being more stable than the beta.
2) With the exception of some members of the aliphatic series which are liquids at ordinary temperatures, oximes are generally crystalline solids. The lower members which are liquids such as acetoxime and benzaldoxime, distill without decomposition.

3) Some oximes are soluble in water, but can be extracted from aqueous solution with ether.

4) The oximino compounds are amphoteric in nature, yielding salts with both acids and bases (12):

$$\text{R'C=N-OH} + \text{HCl} \rightarrow \text{R'C=N-OH}^+ + \text{Cl}^-$$

$$\text{R'C=N-OH} + \text{NaOH} \rightarrow \text{R'C=N-O}^-\text{Na}^+ + \text{H}_2\text{O}$$

As bases, the oximes are very weak. Their hydrochlorides are extensively hydrolyzed in aqueous solution by mineral acids, yielding hydroxylamine and the parent aldehyde or ketone. The oximes are not decomposed or hydrolyzed by sodium or potassium hydroxides. However, in most cases oximes react as weakly acidic compounds, the alpha isomer being more acidic than the beta.

5) Oximes are soluble in aqueous sodium or potassium hydroxides, but are precipitated from this type of solution by carbon dioxide.

6) Dissociation constants of oximes range from $10^{-10}$ to $10^{-12}$, with alpha having a higher constant than beta (13).
7) In the aliphatic oximes, acidity decreases with increasing molecular weight but is enhanced by the presence of a carbonyl group adjacent to the oximino group. In the aromatic series, the degree of acidity is influenced by substituents in the aromatic ring.

8) Oximes can be reduced to hydroxylamines and to primary amines by a variety of methods, one of the more important methods consisting of hydrogenation under pressure.

9) Hydrogen bonding is exhibited by oximes, as shown by ortho-hydroxybenzaldoxime which differs in its physical and chemical properties from the meta- and para-hydroxybenzaldoximes (14,15).

10) In solution oximes are tautomeric substances in that they furnish both oximino and nitronic derivatives.

11) Coordinate compounds of oximes are formed with nickel and cobalt, as well as other metals, and these are used as a means of detecting and identifying numerous metallic ions (17,18).

12) By virtue of the hydroxyl group contained in oximes, ethers or esters can be formed. Alkylating agents, such as dimethyl sulfate in the presence of sodium hydroxide, or alkyl iodides, alone or with potassium carbonate, can be used to form oxime ethers. These methods
give rise to a mixture of two products. In one case, the alkyl group is attached to oxygen, as shown by its hydrolysis to the original ketone or aldehyde, hydroxylamine and alkyl alcohol. In the other case, the alkyl group is attached to the nitrogen. The nitrogen ether on hydrolysis yields the parent aldehyde or ketone and N-alkyl hydroxylamine. The two ethers are easily separated since the N-ether is insoluble either in cold ethyl ether or petroleum ether, whereas the O-ether is readily soluble in both solvents. The N-ethers are weakly basic, in contrast to the O-ethers. The latter show no basic properties, are usually more resistant to hydrolysis by acids, and melt at a higher temperature.

13) Esterification of the oximino group via acyl chlorides or anhydrides results in the loss of acidic or basic properties of oximes.

**Stereoisomerism**

Asymmetric oximes can exist as stereoisomeric forms due to the existence of a doubly bound nitrogen in these compounds as shown in the following configurations:

\[ \begin{align*}
R - C - R' \\
\| \\
N-OH
\end{align*} \quad \text{and} \quad \begin{align*}
R - C - R' \\
\| \\
HO-N
\end{align*} \]

Beckman (19), working with benzaldoximes, was the first to discover that two isomeric forms of this compound,
each having the formula \( \text{C}_6\text{H}_5-\text{CH}=\text{NOH} \), existed. He found that this was a property common to a large number of oximes. Considering the fact that the isomers had different properties, he assigned to them the following configurations:

\[
\begin{align*}
\geq & \text{C}=\text{NOH} \quad \text{and} \quad \geq & \text{C}--\text{NH}
\end{align*}
\]

The former is the standard oxime configuration and the latter configuration was given the name iso-oxime because Beckmann considered the possibility that the two isomeric forms of the oxime possessed different structures. However, these formulas had to be rejected when Goldschmidt (20) showed that both isomers reacted with phenylisocyanate as hydroxylic compounds, voiding the possibility of the iso-oxime configuration.

Hantzsch and Werner (21) later advanced an explanation of oxime isomerism which is still accepted. They extended the theory of Van't Hoff who showed that, although there is almost universally 'free rotation' (22) about a single bond joining two carbon atoms, 'free rotation' is not possible about a double bond between such atoms. While Van't Hoff applied his theory to fumaric and maleic acids to demonstrate geometrical isomerism, Hantzsch and Werner applied his explanation of the isomerism of such compounds to the oximes. According to the Hantzsch and Werner hypothesis, the triad nitrogen in oximes is to be considered
as directing its three affinities towards the three angles of a tetrahedron, the fourth angle of which is occupied by the nitrogen itself. In the case of symmetrical oximes where the carbon atom of the original carbonyl group is attached to two identical organic radicals, no isomerism is possible, and only one stereochemical formula can be constructed.

In the case of unsymmetrical oximes where the original carbonyl carbon atom is joined to different groups, R and R', it is possible to construct two stereochemical formulae:

These formulae gave rise to the two postulates which Hantzsch and Werner made, extending Van't Hoff's theory. The first was that there was no free rotation about the link \( \equiv \text{C} = \text{N} - \), and the second was that in a molecule containing the group \( \equiv \text{C} = \text{N} - \text{OH} \), the hydroxyl group is not symmetrically placed with respect to the carbon and nitrogen atoms, giving rise to
The possibility that oximino isomerism is structural and not geometrical, and that it arises from the position of the hydrogen atom of the oxime group, as in the forms: C=NOH, C=N=O, C-NH, was removed when it was established that isomeric pairs of O ethers and N ethers could be obtained. The only formulas that can be allotted to a series such as this are shown by the following:

\[
\begin{align*}
R & - C - R' \\
\text{N-OH} & \quad \text{and} \quad \text{HO-N} \\
R & - C - R' \\
\text{NOR}'' & \quad \text{R''N-O} \\
& \quad \text{R''ON} \\
& \quad \text{O$_{-}$N-R''}
\end{align*}
\]

If the isomerism of an oxime is geometrical, it should be possible to assign configurations to the two isomers, i.e., to discover which form is the alpha and which form is the beta. Hantzsch and Werner, in their theory of oxime isomerism, suggested methods for the determination of aldoximes and ketoximes. For aldoximes, both isomerides form acetyl derivatives with acetic anhydride at approximately 30°C. On subsequent treatment of the acetyl derivatives with dilute sodium hydroxide solution or dilute sodium bicarbonate solution, one is converted into the nitrile and the other reverts to original oxime. If the acetylated isomeride is converted into the nitrile because of the proximity of the hydrogen atom to the
acetyl group or if the loss of acetic acid involves groups lying on the same side of the double bond, then the configuration of two isomeric aldoximes are as follows:

\[
\begin{align*}
R - C - H & \overset{\text{OH}^-}{\longrightarrow} R - C - H \\
& \text{CH}_3\text{CON} \\
\text{Alpha (Anti)} & \text{R - C - H} \overset{\text{OH}^-}{\longrightarrow} \text{R-C\overset{\text{N}}{\text{N}} + \text{CH}_3\text{COOH}} \\
& \text{CH}_3\text{CHOCON} \\
\text{Beta (Syn)} & \\
\end{align*}
\]

On this basis, Hantzsch and Werner assigned configurations to the aldoximes. They called those which had the hydrogen atom attached to carbon and the hydroxyl group attached to nitrogen on the same side of the double bond, alpha-aldoximes, and those of the other configuration, beta-aldoximes, as shown above. Thus for example, alpha-benzaldoxime was an anti-oxime and beta-benzaldoxime, a syn-oxime.

The ketoximes do not undergo any reaction of this type, but do undergo a Beckmann rearrangement when treated with phosphorus pentachloride yielding different acid amides (23) as shown in equations 1 and 2:

\[
\begin{align*}
R - C - R & \rightarrow [R - C - OH] \rightarrow R - C = O \\
& \text{N-OH} \\
& \text{N-OH} \\
\end{align*}
\]

(1)
If the assumption is made that the groups which exchange places (R or R' and OH) are those in the syn position to one another, then the configurations of the ketoximes are known.

Brady and Dunn (24) pointed out that in some cases it is not possible to obtain syn-isomerides of substituted benzaldoximes. There are no definite rules governing the existence of a second isomeride. Substitutions in the para position do not hinder isomeric changes and both isomerides can be obtained with relative ease. With substitutions in the ortho and meta position, the isomeric changes are hindered and only one isomer is usually obtained. Ortho-methoxy-benzaldehyde exists in the anti form only, while meta-methoxy-benzaldehyde will produce an unstable syn form. All nitro and chloro substitutions exist in two forms. A hydroxyl group inhibits the formation of the syn isomer. However, acetylation of the hydroxyl group makes possible two isomers. This points out that the acidic nature of the substituting group has an important influence.

While the Hantzsch and Werner stereochemical hypothesis is generally accepted as providing the most
satisfactory explanation of the isomerism of the oximes, the earlier theory of Beckmann still finds some use. Thus, for the two benzaldoximes, the following formulas exist:

\[
\begin{align*}
\text{C}_6\text{H}_5-\text{C}-\text{H} & \quad \text{C}_6\text{H}_5-\text{C}-\text{H} \\
& \quad \text{C}_6\text{H}_5\text{C}=\text{NOH} \\
& \quad \text{C}_6\text{H}_5-\text{C}-\text{NH} \\
\text{NOH} & \quad \text{HON} \\
\end{align*}
\]

Hantzsch and Werner Beckmann

The existence of two methyl ethers of beta-nitro-benzaldoxime, both of which have the methyl group attached to oxygen, cannot be explained by Beckmann's formula but is readily accounted for by that of Hantzsch and Werner. On the other hand, a third methyl ether is known in which the methyl group is attached directly to nitrogen. Here the stereochemical formula of Hantzsch and Werner is at fault, and the iso-oxime structure of Beckmann has been assigned to this compound. In addition to the Hantzsch and Werner formula and the Beckmann formula, an additional structure, known as the 'nitrone' structure (25), has been assigned to the N methyl ethers involving a pentavalent nitrogen atom. The 'nitrone' structure accounts for the existence of two isomeric N ethers, namely:

\[
\begin{align*}
\text{R} - \text{C} - \text{H} & \quad \text{R} - \text{C} - \text{H} \\
\text{CH}_3=\text{N}-\text{O} & \quad \text{O} \text{N}-\text{CH}_3
\end{align*}
\]
Doubts as to the validity of the alpha and beta assignments to the configurations of the oximes arose when it was shown that the original assumption of Hantzsch and Werner was in error. However, the two reactions chosen by them, one for aldoximes and one for ketoximes still remain the crucial tests for determining configurations of oximes. Several other experiments have demonstrated that the original configurations, proposed by Hantzsch and Werner, should be reversed (26,27,28). The correct configurations are:

\[
\begin{align*}
R - C - R' & & R - C - R' \\
\| & & \| \\
N-OH & & HO-N
\end{align*}
\]

Alpha (Syn) Beta (Anti)

Isomeric oximes can be converted from one form to the other. This interconversion of the isomeric oximes can be performed in various ways. Of two isomers, usually, one is less stable than the other and tends to pass into the more stable form on heating or in the presence of catalysts. Beta oximes can usually be transformed into the isomeric alpha oximes with great ease. The reverse change can be effective via the hydrochlorides by the action of sulfuric acid and sometimes by the action of ultraviolet light (29). This latter method is a clear demonstration of the high energy content of the beta form. The beta oximino chlorides are more stable than the alpha oximino chlorides.
Acylation and Hydrolysis

If the tautomeric configuration for the aldoximes is adopted, then it can be shown that an acyl halide can add on in two ways to an oxime, either at the N=O double bond of the standard configuration or at both the C=N and N=O double bonds of the tautomeric configuration (30). However, Brady and Grayson (31) showed that oximes were acetylated through the oxygen and not the nitrogen by comparing their absorption bands with those of the O-ethers and the N-ethers.

The action of benzoyl chloride on the alpha aldoximes has been studied by Minunni and co-workers (32,33) and by Forster and Judd (34). The former prepared the benzoyl derivatives in an ethereal solution, while the latter tried to prepare the isomeric benzoyl derivatives from beta benzaldoxime and para-triazobeta-benzaldoxime by avoiding the presence of hydrochloric acid which would be likely to cause inversion. However, Forster and Judd were unsuccessful because both beta isomerides yielded the alpha isomerides as obtained by Minunni and co-workers. The action of benzoyl chloride on a solution of a number of other alpha aldoximes in excess sodium hydroxide has been investigated (35) and in every case a benzoyl derivative was obtained, which on hydrolysis with alkali, regenerated the original oxime. It was found that benzoyl chloride converted the otherwise stable beta-cinnamaldoxime and
ortho-methoxy-beta-cinnamaldoxime into the alpha benzoyl derivative from which the alpha aldoxime could be obtained by alkaline hydrolysis. This reaction is apparently a general one. Brady and McHugh (30) found that slight traces of acid present from the acylation caused conversion to the alpha form. Even with the Schotten-Baumann type of reaction, the alpha benzoate was obtained from the attempted acylation of the beta aldoximes. Similar results were obtained by benzoylating in pyridine solution with benzoyl pyridinium chloride in spite of all precautions to avoid isomeric change.

Hauser and Vermillion (36,37), repeating the experiments of Brady and McHugh using pyridine as a solvent, found that, although the benzoyl alpha aldoximes are stable in pure pyridine, they are gradually converted into nitriles and benzoic acid on standing in pyridine solution containing pyridinium chloride. This conversion is considered to involve the intermediate formation of benzoyl-beta-aldoximes, which, like acyl-beta-derivatives, would be decomposed readily by pyridine to form nitriles. The isomerization of benzoyl-alpha-aldoximes to their beta-isomers is assumed to take place through the medium of their acid salts, the precedent for this being the well known isomerization of the acid salts of alpha-aldoximes.

Hauser and Jordan (38), experimenting with the hydrolysis of alpha and beta-aldoxime acetates, found that
they undergo fundamentally the same types of reactions with alkali. Both form the oxime by hydrolysis and the nitrile by elimination of acetic acid. The isomeric oxime acetates differ primarily in the ease with which they eliminate acetic acid, the beta-isomers undergoing this reaction much more readily than the corresponding alpha-isomers.

The mechanism of alkaline hydrolysis of acyl derivatives of substituted benzaldoximes has been studied by Benger and Brady (39). They showed that the possible reactions which take place in the presence of alkali are as follows:

\[
\begin{align*}
\text{(I)} & \quad \text{OH}^- \\
R - C - H & \longrightarrow R - C^- \longrightarrow R-C\text{N} + R-CO^- \\
R'\text{CON} & \quad R'\text{CON} \\
& \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{(II)} & \quad \text{OH}^- \\
R - C - H & \longrightarrow R - C - H + \text{HOC-R}' \longrightarrow R-C-H + R'-CO^- \\
R'\text{CON} & \quad \text{ON} \quad \text{O} \\
& \quad \text{HON} \\
\end{align*}
\]

\[
\begin{align*}
\text{(IIIA)} & \quad \text{OH}^- \\
R - C - H & \longrightarrow R - C - H + R-CO^- \\
R'\text{CON} & \quad \text{N}^- \\
& \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{(IIIB)} & \quad \text{OH}^- \\
R - C - H & \longrightarrow R-C\text{N} + H^+ \\
R'\text{CON} & \quad \text{N}^- \\
& \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{(IV)} & \quad \text{OH}^- \\
R - C - H & \longrightarrow \text{R-COO}^- + R - C - H \\
R'\text{CON} & \quad \text{NOH} \\
& \quad \text{O} \\
\end{align*}
\]
Mechanism (I) consists in the removal of a proton from a methine group by a hydroxyl ion and gives the nitrile as the sole product. Mechanism (II) consists of an attack by a hydroxyl ion at the carbonyl group, corresponding to an acyl-oxygen fission in alkaline hydrolysis of esters, yielding the free oxime only. Mechanism (III) represents ionization of the acyl derivative or, in other words, escape of the acyl-oxy group with the pair of electrons binding it to nitrogen, corresponding to the unimolecular alkyl-oxygen fission in the alkaline hydrolysis of esters. The cation thus produced may behave in two ways: A) expulsion of the methine hydrogen as a proton with formation of a nitrile (III A), or B) attack by a hydroxyl ion with formation of an oxime (III B). With beta-oximes, it is unlikely that oxime formation occurs to any extent by this mechanism, because the addition of a hydroxyl ionic group to the cation would give the more stable alpha-aldoxime, whereas in practice the pure-beta-aldoxime is formed. The nitrogen cation may be more stable than an alkyl cation, so the speed of (III A) relative to (II) may be greater than in the case of esters; and consequently, ionization may play a greater part in the hydrolysis of the beta-acyl-aldoximes than in the case of esters. Mechanism (IV), i.e., attack by a hydroxyl ion at the nitrogen with the expulsion of the acyl-oxy ion leading to the oxime, is ruled out because it
involves stereoisomeric change with the production of the alpha-aldoxime. In the case of alpha-aldoximes, mechanism (III B) cannot be ruled out because the oxime obtained is the stable alpha derivative. The production of the nitrile in (III A) can be attributed to mesomeric effects of the substitution on the R group. Mechanism (I) would be involved only with substitutions on the R group (40).

Therefore, oxime formation in the presence of alkali is due to mechanism (II) mainly and possibly (I) or (III A) for beta-aldoximes, and possibly (III B) for alpha-aldoximes.

**PHARMACOLOGY**

Oximes and their derivatives have often been reported to be toxic. This may possibly be due to the fact that they stem from hydroxylamine which is known to be toxic to animal protoplasm (41,42) causing the formation of methemoglobin, an oxidation product of the normal blood pigment. As a result of this oxidation, the oxime is converted to nitrous oxide as well as nitrous acid, probably with the intermediate formation of dioxyammonia according to the following scheme:

\[
\begin{align*}
\text{NH}_2\text{OH} & \longrightarrow \text{NH(OH)}_2 \longrightarrow \text{N(OH)}_3 \\
\text{NH}_2\text{OH} & \longrightarrow \text{NHO} \longrightarrow \text{NHO}_2
\end{align*}
\]

Testoni (43) states that any toxicity of oximes is due to the oximino group (=N-OH), which is easily
transformed into free hydroxylamine. This toxicity is more apparent in aldoximes than in ketoximes.

Lio (44), working with benzaldoximes and anisaldoximes in frogs and rats, showed that these oximes caused muscular twitchings, clonic convulsions and thereafter, loss of voluntary muscular movement followed by paralysis. A decrease in the reflexes was evident accompanied by dyspnea and tachycardia. Death usually followed these symptoms. The alpha isomers were more potent than the beta isomers. No effort was made to indicate any useful pharmacological response for these drugs.

In similar experiments in rabbits using phenolphthalein oxime, Dresbach (45) found that no local irritation occurred from the dry powder in the eye, on the mucosa, or in open wounds. No antiseptic or antibacterial action was noted, although antipyretic effects were apparent. Antipyretic action was attributed to the fact that the oxime decomposed into para-amino-phenol which exerted its own toxic effects, while lowering body temperature. The oxime did produce evidence of hemolysis and cell destruction. In addition to these toxicities, oximes have been shown to inhibit blood catalase in animals (46) and catalase activity in living cells of Saccharomyces cerevisiae. However, the protease activity of bakers yeast cells were activated (47). In spite of this apparent
toxicity, oximes have been found as constituents of animal and plant cells (48). In plants, hydroxylamine and its derivatives, namely oximes, in conjunction with aminodicarboxylic acids play an important role in nitrogen metabolism.

When alpha-oximino butyric acid was supplied to wheat roots and corn plants, it was found that they both utilized the oxime (49). Corn, however, having greater utilization, was able to convert the oxime into amino acids and protein nitrogen. Oat plants are also capable of utilizing oximino acids as a source of nitrogen to form protein (50). This is dependent, however, on the concentration of the oximino acid. Some toxicities were noted on these plants and it was suggested that the effects might be due to the oxime action on the lipoid protein film of the cell surfaces.

Not only is hydroxylamine toxic to animal protoplasm but it is also toxic to bacteria (51,52). This toxicity is dependent upon the pH and the concentration of hydroxylamine. The oximino derivatives of hydroxylamine were also tested for toxicity to bacteria (53). It was found that the toxicity of the oximino derivatives was related to their structures.

Since hydroxylamine is known to be toxic to bacteria and oximino derivatives are toxic due to the release of hydroxylamine, it is essential, therefore, that the
dissociation of the oximes used as sources of nitrogen be minimized.

Of the oximino derivatives, the alpha-oximino carboxylic acids were found the least toxic and could be used by Azotobacter as a source of nitrogen in the absence of atmospheric or other sources of nitrogen.

Jensen (54) showed that several types of bacteria can decompose oximes with the formation of the nitrite ion and that bacteria can utilize oxime nitrogen for cell synthesis depending somewhat upon the supply of available carbon.

Nitrification, whereby nitrogen in the form of the ammonium ion or inorganic combination is converted to the nitrate ion, is the name of the process by which the bacteria utilize oximes (55). This nitrate formation is not an energy-yielding process like ammonia oxidation but may be regarded as a hydrolytic process as shown:

\[
R R^\prime \overset{\text{C=NOH + H}_2\text{O}}{\longrightarrow} R R^\prime \overset{\text{CH}_2 + \text{HNO}_2}{\longrightarrow}
\]

Pyruvic oxime is one of the oximes of alpha-keto acids which is readily nitrified. The enzyme oxidizing this oxime is termed pyruvic oxime oxidase (56). This enzyme is inhibited, probably competitively, by phenyl pyruvic oxime, D-arabinose, and alpha-keto-glutaric oxime which are not themselves oxidized by the oxime.

Yamafuji and Omura (57) feeding oximes to silkworms found that they developed a virus within them without any
infection being present. This virus formation was accelerated by heat or cold and usually caused their death. Upon further investigation an enzyme called "transoximase" was found in silkworms which was capable of catalyzing the transformation of the oximes into the corresponding amino compound (58,59,60).

In the three major groups of oximes, namely: A) plain oximes of the type $RR'C=\text{NOH}$, B) oximino ethers of the type $RR'C=\text{N-}R''$ or $RR'C=\text{NOR''}$ and C) oximino esters of the type $RR'C=\text{NOCOR''}$, useful products have been found. Those of group A have bacteriostatic (61), fungicidal (62,63) and mold growth inhibiting activity (64); those in group B are insecticides (65), local anesthetics (66) and compounds having fungicidal and fungistatic properties (67); and finally group C have insecticidal activity (68).

Within the past five years quaternary salts of oximes have been shown to be potent reactivators of red cell and rat brain choline esterase which have been inhibited by tetraethylpyrophosphate, sarin or diisopropylphosphorofluoridates (69). These three compounds inhibit choline esterase by a non-competitive action which is not readily reversible. However, pyridine-2, or -4-aldoxime methyl iodide has been shown to reactivate over 50 per cent of the choline esterase enzyme in one hour. This reactivation or reversal of inhibition occurred by displacement of the enzyme group from the phosphorus atom by another nucleophilic group such as pyridine-2, or -4-aldoxime methyl iodide.
EXPERIMENTAL

DISCUSSION OF PROCEDURES AND EQUIPMENT USED

The chemicals used in the synthesis of the intermediates and the final compounds were obtained from commercial sources and were purified whenever necessary.

Commercial anhydrous ether was further dried over sodium wire for forty-eight hours before use. Commercial absolute alcohol was distilled over sodium before use.

The four general procedures which were attempted in making the final esters were as follows:

\[
\begin{align*}
A. & \quad R' \text{C=N-O-H} + R'' \text{C-Cl} \xrightarrow{\text{Anhydrous Ether}} R' \text{C=N-O-C-R''} + \text{HCl} \\
B. & \quad R' \text{C=N-O-H} + R'' \text{C-Cl} \xrightarrow{\text{Anhydrous Ether}} R' \text{C=N-O-C-R''} + \text{HCl} \\
C. & \quad R' \text{C=N-O-H} + R'' \text{C-Cl} \xrightarrow{\text{DMF}} R' \text{C=N-O-C-R''} + \text{HCl} \\
D. & \quad R' \text{C=N-O-H} + R'' \text{C-Cl} \xrightarrow{\text{Anhydrous Ether}} R' \text{C=N-O-C-R''} + \text{HCl}
\end{align*}
\]

The fourth procedure was the final one which was used in making the oximino esters.
For the preparation of the final esters, one molecular equivalent of the oxime was used to one molecular equivalent of the acid chloride. It was found unnecessary to remove the hydrochloric acid which was formed in the reaction (70). The yields of the esters were calculated on the basis of the molecular quantity of oxime used. All reactions were carried out in anhydrous ether.

Melting points were determined by the use of the Fisher-Johns Melting Point Apparatus (115 V. - 50-60 cycle A.C.). The melting points given are uncorrected.

Saponification equivalent (S.E.) determinations were carried out according to the procedure of Shriner and Fuson (71) with the following modification. Sodium, 11.5 grams, was reacted with 750 ml. of ethanol and sufficient ethanol was added to make one liter of 0.5 N alcoholic sodium hydroxide.

Elemental analyses were performed by the Galbraith Laboratories, Knoxville, Tennessee.

The optical properties were studied with the use of a Spencer Polarizing Microscope. The immersion (Becke Line) method (72) was used to determine the refractive indices of the crystals. An Abbe Refractometer was used to determine the refractive index of the liquids used. The liquids used were: a) mixtures of kerosene with alpha-bromo-naphthalene, ranging from 1.448 to 1.658, b) mixtures of methylene iodide and sulfur, ranging from 1.737 to 1.78, and c) aqueous potassium mercuric iodide, ranging from 1.333 to
1.717 (73,74). The latter was made by saturating 10 ml. of distilled water with potassium iodide and adding red mercuric iodide until no more dissolved. A range of 1.658 to 1.737 could be obtained by mixtures of pure alpha-bromonaphthalene and pure methylene iodide in various proportions. Only two indicies of the crystals were determined and these were labeled alpha and gamma.

The crystals of each oximino ester respectively were crushed and then mounted on a slide with mineral oil to ascertain whether the crystals were isotropic or anisotropic, to demonstrate the type of extinction present, to obtain an interference whenever possible, and to determine the optic sign from the interference figure.

Infrared spectra of the compounds were prepared in the Spectographic Laboratories of the Department of Chemistry of The Ohio State University using a Baird Associates Infrared Recording Spectrophotometer, Model B, equipped with a sodium chloride prism. A potassium bromide pellet of each compound served as the investigated sample.
Preparation

Essentially, the procedure given by Vogel (75) was followed with slight modification.

Hydroxylamine hydrochloride, 50 grams (.72 M), and sodium monoacetate, 80 grams, were dissolved in 200 ml. of distilled water in a 500 ml. round bottom flask by shaking. Then 50 grams (.51 M) of freshly distilled cyclohexanone were added and the mixture was shaken vigorously for a few minutes during which crystallization took place. The flask was then placed in a refrigerator for 12 hours to allow complete crystallization. The resulting pure white crystals were then filtered off under suction, washed with cold distilled water and spread out on filter paper to air dry. The product weighed 54.7 grams (95% of the theoretical yield) with a melting point of 91 to 92°C. (Reported M.P. is 89 to 90°C.)

The dry crystals were taken up in the minimum amount (approximately 200 ml.) of petroleum ether (B.P. is 65 to 110°C.) necessary to dissolve them with heat. Activated charcoal, about 0.5 grams, was added to the hot solution. The solution was heated to boiling for a few minutes and then filtered rapidly with suction. The charcoal was washed
with a little hot petroleum ether which was then added to the original filtrate. This filtrate was concentrated to two-thirds its original volume and was allowed to crystallize slowly. The product was filtered under suction and air dried. The yield was 46.5 grams (80.7%) with a melting point of 92 to 93°C.

**Esters of Cyclohexanone Oxime**

**Cyclohexanone Oxime Para-Nitro-Benzoate**

\[
\text{S} = \text{N-O-C} - \text{phenyl} - \text{NO}_2
\]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 5.7 grams (.05 M) of cyclohexanone oxime and 50 ml. of anhydrous ether. Para-nitro-benzoyl chloride, 9.3 grams (.05 M), was dissolved in 25 ml. of anhydrous ether and this was added to the above cold ether solution rapidly. After a few minutes, a yellow precipitate formed. The stirring was continued for 5 minutes and the flask was removed from the ice bath. The ether was evaporated by a stream of air, and the solid which was left was added to 200 ml. of a 3 per cent sodium bicarbonate solution in a beaker and stirred for 10 minutes to decompose any excess acid chloride. The precipitate, free of acid chloride, was filtered with suction and washed with 300 ml. of cold distilled water. The washed precipitate was dissolved in 800 ml. of hot ethanol and activated charcoal
(approximately 1 gram) was added to the solution. After boiling for a few minutes, the solution was filtered hot through a fluted filter, and the filtrate was concentrated to 200 ml. after which it was allowed to crystallize slowly. When cool, the flask was placed in the refrigerator for 12 hours for further crystallization. The crystals were then filtered with suction and dried in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide. The yield was 12.5 grams (95.4%) with a melting point of 111 to 112°C.

ANALYSIS: Calculated for C₁₃H₁₄O₄N₂:

N, 10.69% Found: 10.86%
S.E., 262.2 Found: 266.1, 265.1

Optical properties.- The crystals were examined by use of the polarizing microscope. In plane polarized light, the crystals appeared as platelets. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Only two refractive indices were determined. Alpha was found to correspond to that of a liquid having a refractive index of 1.6792 and gamma to that of a liquid having a refractive index of 1.4772.
Cyclohexanone Oxime Para-Methoxy-Benzoate

\[ \text{S} = N-O-C - \text{OCH}_3 \]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 5.7 grams (.05 M) of cyclohexanone oxime and 30 ml. of anhydrous ether. To this was added 8.5 grams (.05 M) of para-methoxy-benzoyl chloride. The mixture was stirred for 5 minutes in the cold, and then the flask was removed from the ice bath. The ether was evaporated under a stream of air; and as the ether was concentrated, a white precipitate formed. The solid was then transferred into 200 ml. of a 3 per cent sodium bicarbonate solution. The solid liquified and after stirring for 5 minutes resolidified. The stirring was continued for 5 minutes longer. Then the solid was filtered with suction and washed with 300 ml. cold distilled water. It was then dissolved in 100 ml. of hot ethanol after which activated charcoal (approximately 0.5 grams) was added to the hot solution. After boiling for a few minutes, the solution was filtered hot through a fluted filter. The filtrate was heated to the boiling point, and distilled water was added until a very slight cloudiness appeared. The filtrate was then allowed to crystallize slowly. When the flask reached room temperature, it was placed in the refrigerator to allow further crystallization. The pure crystals were filtered
with suction and dried in a vacuum oven (2 mm. pressure) at 40°C. over phosphorus pentoxide. The yield was 10 grams (81.1%) with a melting point of 71 to 72°C.

ANALYSIS: Calculated for $\text{C}_{14}\text{H}_{17}\text{O}_3\text{N}$:

$\text{N} \quad 5.67\% \quad \text{Found:} \quad 5.63\%$

$\text{S.E.,} \quad 247.2 \quad \text{Found:} \quad 250.1, 247.7$

Optical Properties. - The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as elongated rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a negative optic sign. Only two refractive indices were determined. Alpha was found to correspond to that of a liquid having a refractive index of 1.4780 and gamma to that of a liquid having a refractive index of 1.6247.

\[ \text{Cyclohexanone Oxime Phenyl Acetate} \]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 5.7 grams (.05 M) of cyclohexanone oxime and 30 ml. of anhydrous ether. To this was added 7.7 grams (.05 M) of phenyl acetyl chloride. The mixture was stirred for 5 minutes and then the flask was
removed from the ice bath. The ether was evaporated under a stream of air and the liquid remaining was dissolved in 100 ml. of benzene. After washing the benzene solution twice with 100 ml. portions of 3 per cent sodium bicarbonate the benzene was separated from the aqueous solution. Activated charcoal (approximately 0.5 grams) was added to the benzene solution, stirred for 5 minutes in the cold with a magnetic stirrer and then heated to the boiling point. The solution was filtered through a fluted filter into a tared 125 ml. erlenmeyer flask and the benzene was removed under a stream of air. When the benzene was gone, the remaining oil was dried over phosphorus pentoxide in a vacuum desicator. The dry oil was weighed and the yield was found to be 7 grams (60.6%). When an attempt was made to purify the oil by distillation, the oil distilled at 80°C at (2 mm. pressure) with decomposition. In an attempt to crystallize the oil, the flask containing the oil was placed in a dry ice and ether bath. The oil solidified into a mass which could not be removed from the flask and melted over a wide range.

ANALYSIS: Calculated for \( C_{14}H_{17}O_2N \):

\[ N, \quad 6.06\% \quad \text{Found:} \quad 6.01\% \]

\[ \text{S.E.,} \quad 231.2 \quad \text{Found:} \quad 231.2, 227.3 \]

Optical Properties.- Since the product was an oil the index of refraction was taken directly by an Abbe Refractometer. The oil was found to have an index of refraction of 1.5370.
**Preparation**

The procedure given by Organic Synthesis (76) was followed with very slight modification.

In a 3 liter round bottom flask fitted with a magnetic stirrer were placed a mixture of 100 grams (.55 M) of benzophenone, 60 grams (.86 M) of hydroxylamine hydrochloride, 200 ml. of ethanol and 40 ml. of distilled water. To this stirred mixture was added 110 grams of sodium hydroxide pellets in small portions. When the reaction became too vigorous, the flask was placed in an ice bath. After all the sodium hydroxide had been added, the mixture was stirred until almost all the sodium hydroxide had reacted. A condenser was attached to the flask and the mixture was refluxed for 5 minutes on a steam bath. The solution was cooled and poured into a 4 liter beaker containing 300 ml. of hydrochloric acid, 500 grams of crushed ice and 1500 ml. of cold distilled water. This was stirred until a precipitate formed. After filtering the precipitate with suction and washing with 500 ml. cold distilled water, the product was spread out on filter paper and air dried. The yield was 107 grams (98.7%) and had a
melting point of 143°C. (Reported was 141 to 142°C.) The dried product was dissolved in hot methanol (4 ml. per gram) and activated charcoal (approximately 1 gram) was added to the hot solution. After boiling the solution for a few minutes, it was filtered through a fluted filter. The filtrate was allowed to crystallize slowly. When cold, it was placed in the refrigerator to allow further crystallization. The crystals were filtered with suction. The yield was 85 grams (78.5%) with a melting point of 144 to 145°C.

Esters of Benzophenone Oxime

![Esters of Benzophenone Oxime](image)

In a 250 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 9.9 grams (.05 M) of benzophenone oxime and 50 ml. of anhydrous ether. Para-nitro-benzoyl chloride, 9.3 gram (.05 M), was dissolved in 25 ml. of anhydrous ether and this was added rapidly to the cold ether solution of benzophenone oxime. After a few minutes, a yellow precipitate formed. The stirring was continued for 5 minutes and the flask was then removed from the ice bath. The ether was evaporated by a stream of air. The solid which remained was added to 200 ml. of a 3 per cent
sodium bicarbonate solution in a beaker and stirred for 10 minutes. After this, the precipitate was filtered with suction and washed with 300 ml. of cold distilled water. The impure product was dissolved in 800 ml. of hot ethanol to which activated charcoal (approximately 1 gram) was added. After boiling for a few minutes, the solution was filtered hot through a fluted filter and the filtrate was concentrated to 250 ml. The filtrate was allowed to crystallize slowly. When cold, the filtrate was placed in the refrigerator for further crystallization. After the crystals were filtered with suction, they were dried in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide. The yield was 13.5 grams (83.9%) with a melting point of 153 to 155°C.

**ANALYSIS:** Calculated for C₂H₁₄O₄N₂:

\[ N, \quad 8.09\% \quad \text{Found:} \quad 7.98\% \]

\[ \text{S.E.,} \quad 346.2 \quad \text{Found:} \quad 343.9, \quad 347.8 \]

**Optical Properties.**—The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. Since no interference figure was obtained, the type of anisotropism or optic sign could not be ascertained. Two refractive indices were determined. Alpha was found to correspond to that of a liquid having a refractive index of 1.6085 and gamma to that of a liquid having a refractive index of 1.7050.
Benzophenone Oxime Para-Methoxy-Benzoate

\[
\begin{array}{c}
\text{C=N-0-C-}
\end{array}
\]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 9.9 grams (.05 M) of benzophenone oxime and 30 ml. of anhydrous ether. To this cold solution was added rapidly with stirring 8.5 grams (.05 M) of para-methoxy-benzoyl chloride. The solution was allowed to stir for an additional 5 minutes, and then the flask was removed from the ice bath. The ether was evaporated under a stream of air. As the ether concentrated, a while precipitate formed. When the ether had been evaporated, the remaining solid was transferred to 200 ml. of a 3 per cent sodium bicarbonate solution. This was stirred for 10 minutes and filtered with suction. After washing with 300 ml. of cold distilled water, the impure product was dissolved in 100 ml. of hot ethanol to which activated charcoal (approximately 0.5 grams) was added. The solution was boiled for a few minutes and filtered through a fluted filter. Distilled water was added to the boiling filtrate until a slight cloudiness appeared. The filtrate was then allowed to crystallize slowly. When cool, the flask was placed in the refrigerator for further crystallization. Afterwards, the crystals were filtered with suction and
dried in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide. The yield was 13.4 grams (81.0%) with a melting point of 157 to 159°C.

ANALYSIS: Calculated for C_{21}H_{17}O_3N:

N, 4.23% Found: 4.33%
S.E., 315.2 Found: 316.9, 317.5

Optical Properties.- The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as platelets. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Only two refractive indices were attempted. Alpha could not be obtained since it had a refractive index higher than 1.78 which was the highest refractive index liquid available. Gamma was found to correspond to a liquid having a refractive index of 1.5475.

Essentially the same procedure was followed here as for benzophenone oxime para-methoxy-benzoate except that 7.7 grams (.05 M) of phenyl acetyl chloride was used
instead of benzophenone oxime. The yield was 13.5 grams (85.1%) with a melting point of 79 to 81°C.

**ANALYSIS:** Calculated for C_{21}H_{17}O_{2}N:

<table>
<thead>
<tr>
<th>Element</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4.44%</td>
<td>4.51%</td>
</tr>
<tr>
<td>S.E.</td>
<td>315.2</td>
<td>316.9, 317.5</td>
</tr>
</tbody>
</table>

**Optical Properties.** - The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Two indices of refraction were attempted but could not be obtained with the refractive index liquids available.

**ALPHA (SYN) BENZALDOXIME**

![Chemical Structure](image)

**Preparation**

The procedure given by Vogel (77) was the one essentially followed with a slight modification.

In a 1 liter round bottom flask fitted with a magnetic stirrer, 42 grams of sodium hydroxide were dissolved in one 120 ml. of distilled water and cooled. Pure benzaldehyde,
63 grams (.6 M), was added to the solution and stirred rapidly. To the stirred solution, 45 grams of hydroxylamine hydrochloride were added in small portions. Heat evolved from the mixture and the benzaldehyde dissolved upon the complete addition of the hydroxylamine hydrochloride. Upon cooling the solution, a crystalline mass formed to which sufficient distilled water was added to put the mass into solution. Carbon dioxide was bubbled into the solution until it was saturated and an emulsion formed. The emulsion was extracted with three 100 ml. portions of ether which were combined and washed with 100 ml. of distilled water. The ether extract was poured into a 500 ml. erlenmeyer flask over anhydrous sodium sulfate and allowed to dry for 24 hours. Then, the ether was filtered into a beaker and removed by distillation on a steam bath. The liquid remaining was transferred to a 100 ml. round bottom flask and distilled at 118 to 119°C./11mm. The liquid, collected in a 50 ml. round bottom flask, solidified upon cooling in an ice bath. The yield was 55 grams (75.6%) with a melting point of 33 to 34°C. (The reported yield for .2 M was 12 grams with a melting point of 35°C.)
Esters of Alpha Benzaldoxime

Alpha Benzaldoxime Para-Nitro-Benzoate

\[
\begin{align*}
\text{C}_5\text{H}_4\text{O} & \quad \text{N-O-C}^- \\
\text{H} & \quad \text{C-H} \\
\text{N} & \quad \text{NO}_2
\end{align*}
\]

The same procedure was used here as for benzophenone oxime para-nitro-benzoate except that 6.1 grams (.05 M) of alpha-benzaldoxime was used in place of benzophenone oxime. After drying in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide, the yield was found to be 11 grams (81.5%) with a melting point of 166 to 168°C.

ANALYSIS: Calculated for C_{14}H_{10}O_{4}N_{2}:  
N, 10.37%  Found: 10.37%  
S.E., 270.1  Found: 267.7, 275.7

Optical Properties.- The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared to consist of colorless needles. With crossed nicols, the needles were found to be anisotropic and displayed paralleled extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Only two refractive indices were determined. Alpha was found to correspond to that of a liquid having a refractive index of 1.6882 and gamma to that having a refractive index of 1.5470.
The same procedure was used here as for benzophenone oxime para-methoxy-benzoate except that 6.1 grams (.05 M) of benzaldoxime was used in place of benzophenone oxime. After drying in a vacuum oven (2 mm. pressure) at 40°C. over phosphorus pentoxide, the yield was 9 grams (75.3%) with a melting point of 70 to 71°C.

**ANALYSIS:** Calculated for C_{15}H_{13}O_{2}N:

- N, 5.86% Found: 6.02%
- S.E., 239.2 Found: 233.8, 234.4

**Optical Properties.** - The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Two refractive indices were attempted but could not be obtained with the refractive index liquids available.
**Preparation**

In a one liter round bottom flask fitted with a magnetic stirrer, 42 grams of sodium hydroxide were dissolved in 125 ml. of distilled water. This was cooled and 78.6 grams (.6 M) of para-methoxy-benzaldehyde was added to the solution with rapid stirring. To this stirring solution, 45 grams of hydroxylamine hydrochloride were added in small portions. At one point the solution solidified and had to be shaken vigorously to break up the solid. As more hydroxylamine hydrochloride was added, the solid liquified. When all the hydroxylamine hydrochloride had been added, the solution had to be cooled, whereupon, it solidified again. Sufficient distilled water was added to dissolve all the solid and carbon dioxide was bubbled into the solution until it was saturated. A white emulsion formed which was extracted with three 100 ml. portions of ether. The ether fractions were combined and washed with 100 ml. of distilled water. The washed ether fractions were dried over anhydrous sodium sulfate in a 500 ml. erlenmeyer flask for 24 hours. The ether was then filtered and removed by distillation. When all the ether was removed, the liquid remaining was
cooled and a white solid mass formed. The mass was dissolved in 100 ml. of hot ethanol to which activated charcoal (approximately 0.5 grams) was added. After boiling the solution for a few minutes longer, it was filtered through a fluted filter. Distilled water was added to the hot filtrate until it became cloudy, and it was allowed to crystallize slowly. When cool, the flask was put into the refrigerator for further crystallization. The crystals were filtered with suction and dried in a vacuum oven (2 mm. pressure) at 40°C. over phosphorus pentoxide. The yield was 113.3 grams (75.0%) with a melting point of 63 to 64°C. (Reported melting point is 65°C.)

Esters of Alpha Para-Methoxy-Benzaldoxime

Alpha Para-Methoxy-Benzaldoxime Para-Nitro-Benzoate

Essentially the same procedure was used here as for benzophenone oxime para-nitro-benzoate except that 7.6 grams (.05 M) of para-methoxy-benzaldoxime was used in place of the benzophenone oxime. After drying in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide, the yield was found to be 9.5 grams (63.3%) with a melting point of 161 to 163°C.
ANALYSIS: Calculated for $\text{C}_{15}\text{H}_{12}\text{O}_5\text{N}_2$:

<table>
<thead>
<tr>
<th>Element</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9.33%</td>
<td>9.34%</td>
</tr>
<tr>
<td>S.E.</td>
<td>300.2</td>
<td>300.0, 297.4</td>
</tr>
</tbody>
</table>

Optical Properties.—The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. Since no interference figures was obtained, the type of anisotropism or optic sign could not be ascertained. Two refractive indices were attempted. Alpha was found to correspond to that of a liquid having a refractive index of 1.5010. Gamma could not be obtained since it had a refractive index higher than 1.78, the highest refractive index liquid available.

**Alpha Para-Methoxy-Benzaldoxime Phenyl Acetate**

\[
\text{CH}_3\text{O} - \begin{array}{c} \text{C-H} \\ \text{N-O-C-CH}_2 - \end{array} \]

Essentially the same procedure was used here as for benzophenone oxime phenyl acetate except that 7.6 grams (0.05 M) of alpha-para-methoxy-benzaldoxime was used in place of benzophenone oxime. After drying in a vacuum oven (2 mm. pressure) at 40°C, over phosphorus pentoxide, the yield was found to be 10 grams (74.3%) with a melting point of 55 to 57°C.
ANALYSIS: Calculated for $C_{16}H_{15}O_3N$:

N, 5.20%  Found: 5.32%
S.E., 269.2  Found: 264.8, 272.2

Optical Properties.- The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as platelets. With crossed nicols, the crystals were found to be anisotropic with parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a negative optic sign. Two refractive indices were attempted but could not be obtained with the refractive index liquids available.

**ALPHA (SYN) ACETOPHENONE OXIME**

![Chemical Structure]

**Preparation**

In a one liter round bottom flask fitted with a magnetic stirrer, 42 grams of sodium hydroxide were dissolved in 120 ml. of distilled water and cooled. Pure acetophenone, 72 grams (.6 M), was added to the solution and stirred rapidly. To the stirred solution, 45 grams of hydroxylamine hydrochloride were added in small portions. After all the hydroxylamine hydrochloride was added, two layers still remained. The solution became hot with con-
continued stirring and reacted violently by boiling. It was cooled in an ice bath until a solid mass formed. Sufficient distilled water was then added to dissolve the mass, and carbon dioxide was bubbled into the solution until it was saturated. An emulsion formed which was extracted with three 100 ml. portions of ether, and the combined ether portions were washed with 100 ml. of distilled water. The ether extract was placed over anhydrous sodium sulfate in a 500 ml. erlenmeyer flask and allowed to dry for 24 hours. After this, the ether was filtered into a beaker and was evaporated under a stream of air while heating on a hot plate. The remaining liquid was solidified by cooling in an ice bath. The mass was dissolved in the minimum amount of boiling distilled water (approximately 500 ml.) and allowed to crystallize slowly. When cool, the beaker was placed in the refrigerator to allow further crystallization. The crystals were filtered with suction and dried in a vacuum oven (2 mm. pressure) at 40°C. over phosphorus pentoxide. The yield was 65.2 grams (80.5%) with a melting point of 58 to 60°C. (Reported melting point is 60°C.)
Esters of Alpha-Acetophenone Oxime

\[
\text{Alpha-Acetophenone Oxime Benzoate}
\]

\[
\begin{array}{c}
\text{C} - \text{CH}_3 \\
\text{N} - \text{O} - \text{C} \\
\end{array}
\]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 7.6 grams (0.05 M) of acetophenone oxime and 30 ml. of anhydrous ether. To this cold ether solution was added rapidly with stirring 7.0 grams (0.05 M) of benzoyl chloride, and a precipitate formed in a few minutes. The solution was stirred for an additional 5 minutes, and then the flask was removed from the ice bath. Under a stream of air the ether was evaporated, and the remaining solid was transferred to 250 ml. of a 3 per cent sodium bicarbonate solution. This was stirred for 10 minutes and filtered with suction. The product was washed with 300 ml. of cold distilled water and then dissolved in 100 ml. of hot ethanol to which activated charcoal (approximately 0.5 grams) was added. The solution was boiled for a few minutes and filtered through a fluted filter. Distilled water was added to the boiling filtrate until a slight cloudiness appeared. This was allowed to crystallize slowly. When cool, the flask was placed in the refrigerator for further crystallization. Afterwards, the crystals were
filtered with suction and dried in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide. The yield was 10 grams (83.7%) with a melting point of 100 to 102°C.

ANALYSIS: Calculated for C$_{15}$H$_{13}$O$_2$N:

N, 5.88% Found: 5.92%
S.E., 239.2 Found: 240.8, 241.4

Optical Properties. - The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as platelets. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. By partial interference figures and use of mica and quartz plates, the crystals were shown to be biaxial with a positive optic sign. Only two refractive indices were determined. Alpha was found to correspond to that of a liquid having a refractive index of 1.6958 and gamma to that of a liquid having a refractive index of 1.5008.

Alpha-Acetophenone Para-Nitro-Benzoate

The same procedure was used here as for benzophenone oxime para-nitro-benzoate except that 7.6 grams (.05 M) of acetophenone oxime was used in place of benzophenone oxime.
After drying in a vacuum oven (2 mm. pressure) at 60°C over phosphorus pentoxide, the yield was 11 grams (77.5%) with a melting point of 167 to 169°C.

ANALYSIS: Calculated for C₁₅H₁₂O₄N₂:

N, 9.86% Found: 9.86%
S.E., 284.2 Found: 280.1, 279.5

Optical Properties. - The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. Since no interference figure was obtained, the type of anisotropism or optic sign could not be ascertained. Two refractive indices were attempted. Alpha could not be obtained since it had a refractive index higher than 1.78, the highest refractive index liquid available. Gamma was found to correspond to that of a liquid having a refractive index of 1.5762.

Alpha-Acetophenone Oxime Para-Methoxy-Benzoate

The same procedure was used here as for benzophenone oxime para-methoxy-benzoate except that 7.6 grams (.05 M) of alpha-acetophenone oxime was used in place of benzophenone
oxime. After drying in a vacuum oven (2 mm. pressure) at 60°C. over phosphorus pentoxide, the yield was found to be 10 grams (74.3%) with a melting point of 90 to 92°C.

ANALYSIS: Calculated for C_{16}H_{15}O_{3}N:
  N, 5.20% Found: 5.13%
  S.E., 269.2 Found: 269.2, 270.7

Optical Properties.—The crystals were examined by the use of the polarizing microscope. In plane polarized light, the crystals appeared as rods. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. Since no interference figure was obtained, the type of anisotropism or optic sign could not be ascertained. Two refractive indices were attempted. Alpha was found to correspond to that of a liquid having a refractive index of 1.4740. Gamma could not be obtained since it had a refractive index higher than 1.78, the highest refractive index liquid available.

**Alpha-Acetophenone Oxime Phenyl Acetate**

![Chemical Structure]

In a 125 ml. erlenmeyer flask fitted with a magnetic stirrer and set in an ice bath were placed 7.6 grams (.05 M) of acetophenone oxime and 30 ml. of anhydrous ether. To this
cold solution, 7.7 grams (.05 M) of phenyl acetyl chloride was added rapidly with stirring and a precipitate formed in a few minutes. The solution was allowed to stir for 5 minutes longer; and then, the flask was removed from the ice bath. As the ether was evaporated under a stream of air, the precipitate liquified. When the ether had been evaporated, the liquid was dissolved in 100 ml. of benzene and washed twice with 100 ml. portions of 3 per cent sodium bicarbonate solution. The benzene was evaporated by heating on a steam bath under a stream of air. This was continued until no benzene or water remained. The liquid was then dissolved in 100 ml. of hot absolute alcohol to which activated charcoal (approximately 0.5 grams) was added. This solution was boiled for a few minutes longer and filtered through a fluted filter. When cool, the flask was placed in a dry ice and acetone bath. With rapid stirring, distilled water was added slowly until a precipitate formed in the solution. The crystals were filtered with suction and dried in a vacuum dessicator over phosphorus pentoxide in the cold. The yield was 4 grams (31.6%) with a melting point of 166 to 169°C.

ANALYSIS: Calculated for C_{16}H_{15}O_{2}N:

N, 5.53% Found: 5.35%
S.E., 253.2 Found: 253.2, 251.8

Optical Properties. - The crystals were examined by the use of the polarizing microscope. In plane polarized
light, the crystals appeared as small fine needles. With crossed nicols, the crystals were found to be anisotropic and displayed parallel extinction. Since no interference figure was obtained, the type of anisotropism or optic sign could not be ascertained. Two refractive indices were attempted but could not be obtained with the refractive index liquids available.

**DISCUSSION OF RESULTS**

The preparation of the esters of the five oximes studied, namely, cyclohexanone oxime, benzophenone oxime, para-methoxy-benzaldoxime benzaldoxime and acetophenone oxime, by the several routes followed, was not, in every instance, a simple reaction.

The preliminary esterifications were attempted in dimethyl formamide (DMF) with the anticipation that DMF would remove the hydrochloric acid formed and no excess base would be needed. Only two series of esters were attempted in this manner, that of cyclohexanone oxime and benzophenone oxime. The procedure used in the formation of the esters was the same as that used in ether with the exception that the DMF was not evaporated. Instead, 50 ml. of distilled water was added to precipitate the ester. However, it was noted that this method did not yield the desired results. First, the yields were 25 to 40 per cent lower for cyclohexanone oxime in DMF than in anhydrous
ether and even lower for benzophenone oxime. Second, the reaction did not proceed as anticipated, especially in the case of the esters of benzophenone oxime. The product formed from the union of the acid chloride with benzophenone oxime in DMF could not be obtained in a pure form as shown by the minimum of a 10° melting point range after several attempted recrystallizations. The DMF interfered with these reactions possibly for one of two reasons. First, the DMF may have been basic enough to cause an incomplete reaction between the acid chloride and the oxime. Second, the acid chloride may have been tied up with the DMF in such a way that the yields were lowered considerably. No explanation can be offered at this time for the possible impurity present in the ester of benzophenone oxime which prevented purification of the final product.

For the above reasons, this method was abandoned and another method attempted. This second method involved the use of pyridine in absolute ether to remove the hydrochloric acid formed. However, the results noted with this method corroborated the results obtained by others (36,37). The pyridinium chloride formed caused low yields of formation of the esters. Therefore, this method was modified to the final method used in the esterification of the oximes. When it was noted that it was unnecessary to remove the hydrochloric acid formed from esterification reactions run in absolute ether (71), the above method was used without the
presence of pyridine. For the majority of the esterification reactions, anhydrous ether gave not only higher yields but also compounds which could be purified easily. Only in two instances was it found that there was difficulty in obtaining good yields and a pure product. The two products which gave this difficulty were cyclohexanone oxime phenyl acetate and acetophenone oxime phenyl acetate. Great difficulty existed in crystallizing these two compounds. Evidently some impurity was present which could not be removed either by charcoal or by distillation. Purification by distillation proved to be futile since the product decomposed on heating even at 1 mm. pressure. However, crystallization could be accomplished by forcing the crystals out from the liquid by freezing it in dry ice and ether. The solid product contained some impurities as evidenced by the colorations present in the crystals. The crystals of cyclohexanone oxime phenyl acetate liquified at room temperature while acetophenone oxime phenyl acetate remained a solid. In order to purify the latter crystals, they had to be recrystallized in the extreme cold. This was done but the yields were considerably lower than the other esterification reactions. The cyclohexanone oxime phenyl acetate could not be purified by recrystallization but was purified as much as possible by repeated treatment with charcoal in hot benzene. The benzene was filtered each time and finally removed on a hot water bath, leaving the pure oil.
Some difficulties were encountered when saponification equivalents were run on the esters. Those esters containing the nitro group changed their color to a dark brown during the saponification. This gave rise to a slight difficulty in obtaining the end-point in neutralizing the excess base. This dark brown color was attributed to the nitro containing compound which was formed during the saponification. In those cases where a methoxy group was present, the product from the saponification solidified upon cooling, giving a white solid. This solid liquified upon the addition of acid, thus removing any difficulties here in obtaining a readable end-point. There were no difficulties encountered with the other saponifications.

The nitrogen analyses of the compounds gave a substantial proof that the compounds were the desired esters and were pure.

The optical properties of the fourteen oximino compounds were attempted. In every case with the exception of cyclohexanone oxime phenyl acetate which was an oil, the crystals were found to be anisotropic and displayed parallel extinction. Only four compounds, excluding cyclohexanone oxime phenyl acetate, of the fourteen prepared failed to show interference figures. Therefore the optic sign for these four compounds could not be determined. In all the others, a single isogyre was obtained as an interference figure and the optic sign was determined from this isogyre
with the aid of mica and quartz crystals. All the compounds having interference figures were found to have positive optic signs with the exception of cyclohexanone oxime para-methoxy-benzoate, benzophenone oxime phenyl acetate and para-methoxy-benzaldoxime phenyl acetate which had negative optic signs.

The indices of refraction were attempted via the immersion method (Becke Line). Of all the fourteen compounds synthesized, those being biaxial, as shown by the interference figures obtained, should have had three indices of refraction. However, since only partial interference figures were available, the beta-refractive index could not be determined because it is dependent upon an entire or complete interference figure. In the oximino compounds which showed no interference figures, it was not possible to determine whether they were uniaxial or biaxial and whether they should therefore have two or three refractive indices respectively. In several cases, namely, benzophenone oxime para-methoxy-benzoate, para-methoxy-benzaldoxime para-nitro-benzoate, and acetophenone oxime para-nitro-benzoate, only one refractive index could be obtained. The second index of refraction in these cases was higher than the refractive index liquids available. The refractive index of cyclohexanone oxime phenyl acetate was taken directly since it was an oil. The refractive indices of the other phenyl acetate esters could not be obtained for
two reasons: A) The crystals dissolved in the mixtures of kerosene and alpha-bromo-naphthalene and methylene iodide and sulfur which eliminated any chance of observing the Becke Line. B) The aqueous potassium mercuric iodide solutions did not dissolve the crystals. However, this liquid formed a film around the crystals, probably due to its inability to wet the crystals. This film interfered with the observance of the Becke Line so that no accurate refractive indices could be determined.

**ATTEMPTED REDUCTIONS**

Since all the esters synthesized were found to be insoluble in water, an attempt was made to solubilize several of the compounds. The para-nitro-benzoates of the oximes were chosen since reduction of the nitro group would lead to a primary amine which could be solubilized by making the hydrochloride salt. Three general methods were tried to see which would work best and give the best yields. The procedures are as follows:

**Sodium Hydrosulfite Methods**

1. In a 250 ml. flat bottom flask were placed 2.6 grams (.01 M) of cyclohexanone oxime para-nitro-benzoate, 100 ml. of ethanol, 25 ml. of distilled water and 5.2 grams (.03 M) of sodium hydrosulfite. A condenser was attached to the flask and the mixture was refluxed on a steam bath for
6 hours. After refluxing, the flask was cooled and water was added in order to precipitate the amine. A clear yellow solution formed with no precipitation. The basicity of the solution was tested with hydrion paper and found to have a pH of 11. Nothing could be isolated. The solution was evaporated and the solid which remained was tested for solubility in various solvents but found to be insoluble. When a portion of the solid was added to 10 per cent hydrochloric acid, there was a reaction and the odor of hydrogen sulfide was noted. Upon the addition of base to this acid solution, no precipitation occurred.

2. The same procedure was followed again with the exception that no water was added and absolute ethanol was used at the start of the reaction. The same results were noted again upon removal of the solvent.

3. In a 250 ml. flat bottom flask fitted with a magnetic stirrer, were placed 125 ml. of absolute alcohol, 3.5 grams (.01 M) of benzophenone oxime para-nitro-benzoate and 5.2 grams of sodium hydrosulfite. The mixture was stirred at room temperature for 24 hours. The precipitate which remained was filtered with suction and washed with 100 ml. of distilled water. Part of the precipitate dissolved upon the addition of the water. The remaining precipitate was air dried and a melting point was attempted. However, it was found that the solid did not melt. This solid was treated with 10 per cent hydrochloric acid and then filtered
after standing for 24 hours. A melting point was attempted again but it did not melt. However, when the solid was heated in a flame, it burned leaving a carbon residue. A part of the filtrate was acidified with 10 per cent hydrochloric acid to make the hydrochloride salt and a yellow precipitate formed on standing. This was filtered with suction and a melting point was attempted after it was dried. The solid did not melt but did burn when placed in a flame leaving a carbon residue. A part of the yellow precipitate was treated with 5 per cent sodium hydroxide to neutralize the acid and the precipitate turned white. This was filtered and a melting point was attempted again after drying with no success. However, it did burn when placed in a flame leaving a carbon residue.

**Sodium Sulfide Method**

A procedure similar to the sodium hydrosulfite method was followed here with the exception that 7.7 grams (.03 M) of sodium sulfide decahydrate was used in place of the sodium hydrosulfite. The same results were obtained.

**Catalytic Hydrogenation Method**

All hydrogenations were carried out on a Parr Hydrogenator equipped with a pressure gauge and automatic shaking attachment. The attempted reductions were carried out at room temperature at a pressure of approximately 30 p.s.i.g. (pounds per sq. in. gauge). At 25° C., 0.1 M moles
of hydrogen uptake was found to be equivalent to 0.83 pounds of hydrogen. The catalyst used was 10 per cent palladium on charcoal* which was added to a known amount of compound in the appropriate solvent. After placing the standard Parr reduction bottle on the hydrogenator, the air was exhausted and refilled with fresh hydrogen three times using a water aspirator. Then it was allowed to run the specified time. The results are tabulated in Table I.

A general procedure which was used in all cases is described below.

In the Parr hydrogenator flask was placed 4.3 grams (.015 M) of acetophenone oxime para-nitro-benzoate, 250 miligrams of 10 per cent palladium on charcoal, 200 ml. of absolute ethanol and 2 ml. of concentrated ammonium hydroxide. The ester was not completely soluble in the alcohol. The flask was attached to the Parr hydrogenator and evacuated by a water aspirator. The flask was filled with hydrogen and allowed to stand for three minutes. This was repeated twice. The third time the flask was filled with hydrogen the pressure on the gauge, 30.5 pounds, was noted. Then the shaker was turned on and readings were taken at 1 minute intervals for the first 5 minutes, at 5 minute intervals for the next 15 minutes and at 10 minute intervals.

---

*Baker and Company, Newark, New Jersey.
# TABLE I

## CATALYTIC HYDROGENATION EXPERIMENTS

<table>
<thead>
<tr>
<th>Experimental Amount*</th>
<th>Solvent</th>
<th>10 Per cent Pd on C Catalyst</th>
<th>Shaking Time in Minutes</th>
<th>Hydrogen Uptake, psig.</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 M Cyclohexanone oxime</td>
<td>200 ml. absolute ethanol 1 ml. conc. HCl</td>
<td>200 mg.</td>
<td>70</td>
<td>4.5</td>
<td>Crystals became completely dissolved in the solvent. The flask was slightly warm.</td>
</tr>
<tr>
<td>0.015 M Benzophenone oxime</td>
<td>200 ml. absolute ethanol 1 1/2 ml. conc. HCl</td>
<td>300 mg.</td>
<td>90</td>
<td>6.5</td>
<td>&quot;</td>
</tr>
<tr>
<td>0.01 M Acetophenone oxime</td>
<td>200 ml. absolute ethanol 1 ml. conc. HCl</td>
<td>200 mg.</td>
<td>30</td>
<td>4.5</td>
<td>&quot;</td>
</tr>
<tr>
<td>0.015 M Acetophenone oxime</td>
<td>200 ml. absolute ethanol 2 ml. conc. NH₄OH</td>
<td>250 mg.</td>
<td>60</td>
<td>6.5</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

*These were the para-nitro-benzoates of the listed oximes.*
intervals for the next 40 minutes. At the end of one hour it was noted that 6.5 pounds of hydrogen were taken up which was slightly over one and one-half times the theoretical amount which should have been taken up. The hydrogenator was stopped and the flask washed with nitrogen to remove the excess hydrogen present thus preventing any possibility of fire. The catalyst was removed by suction filtration and the filtrate evaporated in a tared evaporating dish under a stream of air. When dry, the crystals which weighed 3.8 grams (the approximate theoretical amount) were mixed with 50 ml. of 3 per cent sodium bicarbonate solution and extracted twice with 100 ml. portions of ether. After drying the combined ether extractions over anhydrous sodium sulfate for 12 hours, the ether was filtered through a fluted filter and dry hydrochloric acid was bubbled through the ether. A white semisolid mass formed which was removed from the ether by filtration. Attempts to purify the mass proved futile. The filtrate remaining after the ether extraction was decolorized with activated charcoal, made acidic with 10 per cent hydrochloric acid and evaporated to dryness. The crystals which were obtained were extracted with ether and the ether removed under a stream of air. A melting point taken of the crystals which remained was found to be 175-180°C. (Reported MP of para-amino-benzoic acid acid is 181°C.)
Discussion of Reduction Results

In the methods using sodium hydrosulfite and sodium sulfide, the basicity of the solution when tested was such that the ester link was in all probability split especially when heated. No account can be made for the fact that the solid obtained from the evaporation was not soluble in organic solvents. Assuming the products formed were the reduced products or the beginning products, they should have been soluble in ether as well as alcohol. If the reduction took place completely, then para-ami­no-benzoic acid should have been formed as well as the primary amine from the oxime. These should have been soluble in alcohol. If the reduction did not go completely, then the sodium salt of the oxime and acid should have been soluble in water. There were evidently two products formed as shown by the experiment using sodium hydrosulfite. No melting points were obtainable but both portions were evidently organic as evidenced from the carbon residue left on burning.

In any case, the product which was sought was not obtained. Therefore, another method was employed in the hope of obtaining the reduced compound without the possibility of splitting the ester linkage. Strongly acidic or basic reductions could not be used since either one might split the ester linkage.

Hydrogenation under pressure was attempted as the most likely procedure to use. The small amount of acid or
base used in this reaction was an activator of the catalyst as well as to form the hydrochloride salt of the amine in the case where hydrochloric acid was used.

The amount of hydrogen uptake proved to be slightly more than one and one-half times the theoretical amount for the reduction of the nitro group alone. On the basis that .01 M is equivalent to 0.83 pounds of hydrogen and only 3 molecular equivalents of hydrogen are needed to reduce the nitro group, then only 2.49 pounds of hydrogen should have been taken up. If the assumption is made that the ester split and the oxime formed was reduced to the primary amine as well as the nitro group to the primary amine, then 5 molecular equivalents of hydrogen were needed making a total of 4.15 pounds. This then can account for the amount of hydrogen uptake. The slight excess taken up could possibly be accounted for by the inaccuracy of the gauge readings.

The work up of the material showed that evidently complete reduction occurred including the splitting of the ester linkage giving rise to the primary amine of the oxime used and para-amino-benzoic acid as shown by the melting point obtained. Further work will have to be done along this line in order to find a suitable method which will reduce the nitro group without splitting the ester linkage.
There are four degrees of molecular motion which a molecule may have depending upon the amount of energy it possesses. The molecule may take any one or a combination of the four types of motion. This is dependent upon the amount of energy supplied to the molecule.

According to the energy requirements, the four degrees of motion are ranked as follows (78): (1) Translational, in which the molecule moves from one point in space to another. In order to initiate this motion, radiant energy of a very low order (20 microns in wavelength) is sufficient. (2) Rotational, where the molecule rotates about a central axis. This type of motion is initiated by radiation in the order of 20 $\mu$. (3) Vibrational, whereby the atoms are displaced from their normal positions and oscillate back and forth or move sidewise with a swinging motion within the molecule. The rotations involving small energies are superimposed on the atomic displacements giving rise to absorption bands in the near infrared region of the spectrum which extends from about 2 to 16 $\mu$. (4) Electronic, in which an electron is displaced to a higher energy level within the molecule. This takes place in visible and ultraviolet regions, and the only differences between the two are the greater energies and larger displacements involved in the ultraviolet absorption spectra.
Infrared absorption spectra are only concerned with molecules which are capable of rotation and vibration. In order for a vibration to appear in the infrared spectrum, it is essential that there be a change in the electrical symmetry, or the dipole moment of the system. Vibration of two similar atoms against each other, for example in nitrogen or oxygen molecules, will not result in a change in the electrical symmetry of the molecule and, therefore, such molecules do not absorb in the infrared region (79).

The most significant portion of the infrared spectrum is the region from 2 to 8 microns, for in this region the individual bands are more or less characteristic of specific pairs or groups of atoms. Above 8 microns, the bands are due to vibrations and rotations in which all of the atoms in the molecule take part.

The infrared absorption spectra of pure compounds are so highly specific, they have become accepted as "fingerprints" for these compounds (79). When a compound has undergone a reaction, the fingerprint changes to the characteristic of the new compound. However, the groups that are present in the parent compound plus those groups with which the parent compound was reacted will quite often show their characteristic absorption bands. Absorption in any particular band is dependent upon the specific group itself plus the neighboring groups which may influence its electronic and spatial configuration.
By infrared analyses, the determination of the structure of a new compound is placed on an empirical basis. Information from the infrared analyses when combined with other data such as: saponification equivalents, elemental analyses, etc., permits valid conclusions to be drawn concerning the structure of the compound.

Since all samples were prepared as potassium bromide pellets, there are no bands present which interfere with the absorption peaks of the compounds. Potassium bromide has an absorption of 10 to 20 per cent in the range from two to fourteen microns.

Due to the complex nature of the spectra of the compounds studied, only those bands which are particularly characteristic will be considered. The absorption bands of the esters were compared to the parent oximes. (See Tables II, III, IV, V, and VI.)

Palm and Werbin (80) examined the infrared spectra of some solid oximes in the range of 14.3 to 2.75 microns (700 to 3600 cm\(^{-1}\)) and found the following:

The OH stretching mode can be assigned unambiguously to 3.08 microns (3250 cm\(^{-1}\)) for isomeric oximes having the alpha configuration. The non-isomeric oximes have this stretching vibration around 3.16 microns (3150 cm\(^{-1}\)).

The C=N, the OH deformation and the N-OH vibrations are located with less certainty because of interfering bands due to C-H vibrations.
The OH deformation band appears around 7.7 microns (1300 cm\(^{-1}\)) while the N-OH stretching mode appears at 10.88 microns (920 cm\(^{-1}\)).

Aliphatic oximes have an absorption band near 6.02 microns (1670 cm\(^{-1}\)) which is attributed to the C=N vibration. A displacement of 0.2 microns (30 to 40 cm\(^{-1}\)) towards the lower frequencies is the usual concomitant of conjugation with a phenyl group.

One other important band which is the ester linkage should be noted since the compounds synthesized are esters. Ester linkages have bands which appear at 5.7 to 5.76 microns for unconjugated esters and 5.73 to 5.85 microns for conjugated esters.
THE INFRARED ABSORPTION SPECTROGRAPH OF CYCLOHEXANONE OXIME

FIGURE 1
THE INFRARED ABSORPTION SPECTROGRAPH OF CYCLOHEXANONE OXIME PARA-NITRO-BENZOATE

FIGURE II
THE INFRARED ABSORPTION SPECTROGRAPH OF CYCLOHEXANONE OXIME PARA-METHOXY-BENZOATE

FIGURE III
THE INFRARED ABSORPTION SPECTROGRAPH OF CYCLOHEXANONE OXIME PHENYL ACETATE

FIGURE IV
### TABLE II

**ABSORPTION BANDS FOUND IN CYCLOHEXANONE OXIME AND ITS ESTERS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Figure</th>
<th>Functional Group</th>
<th>Wave length in microns</th>
<th>Literature</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>I</td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-OH</td>
<td>10.88</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>3.08, 7.7</td>
<td>3.1, 7.9</td>
<td></td>
</tr>
<tr>
<td>A-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>II</td>
<td>-COO-e</td>
<td>5.73-5.85&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.1-7.5</td>
<td>7.35, 7.5</td>
<td></td>
</tr>
<tr>
<td>A-2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>III</td>
<td>-COO-e</td>
<td>5.73-5.85</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7.46-7.81</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>A-3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IV</td>
<td>-COO-e</td>
<td>5.7-5.76&lt;sup&gt;E&lt;/sup&gt;</td>
<td>5.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Cyclohexanone oxime.

<sup>b</sup>Para-nitro-benzoate of A.

<sup>c</sup>Para-methoxy benzoate of A.

<sup>d</sup>Phenyl acetate of A.

<sup>e</sup>Ester carbonyl absorption band was taken from a compilation of known groups by the Ohio State University Department of Chemistry.

<sup>f</sup>Conjugated ester.

<sup>g</sup>Unconjugated ester.
THE INFRARED ABSORPTION SPECTROGRAPH OF BENZOPHENONE OXIME

FIGURE V
THE INFRARED ABSORPTION SPECTROGRAPH OF BENZOPHENONE OXIME PARA-NITRO-BENZOATE

FIGURE VI
THE INFRARED ABSORPTION SPECTROGRAPH OF BENZOPHENONE OXIME PARA-METHOXY-BENZOATE

FIGURE VII
THE INFRARED ABSORPTION SPECTROGRAPH OF BENZOPHENONE OXIME PHENYL ACETATE

FIGURE VIII
### TABLE III

**ABSORPTION BANDS FOUND IN BENZOPHENONE OXIME AND ITS ESTERS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Figure</th>
<th>Functional Group</th>
<th>Wave length in microns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Literature</td>
</tr>
<tr>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>V</td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-OH</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>3.08, 7.7</td>
</tr>
<tr>
<td>B-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>VI</td>
<td>-COO-</td>
<td>5.73-5.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO₂</td>
<td>7.1-7.5</td>
</tr>
<tr>
<td>B-2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>VII</td>
<td>-COO-</td>
<td>5.73-5.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCH₃</td>
<td>7.46-7.81</td>
</tr>
<tr>
<td>B-3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>VIII</td>
<td>-COO-</td>
<td>5.7-5.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
</tr>
</tbody>
</table>

<sup>a</sup>Benzophenone oxime.
<sup>b</sup>Para-nitro-benzoate of B.
<sup>c</sup>Para-methoxy-benzoate of B.
<sup>d</sup>Phenylacetate of B.
<sup>e</sup>Negligible.
<sup>f</sup>Slight.
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-BENZALDOXIME

FIGURE IX
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-BENZALDOXIME PARA-NITRO-BENZOATE

FIGURE X
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-BENZALDOXIME PHENYL ACETATE

FIGURE XI
### TABLE IV

**ABSORPTION BANDS FOUND IN ALPHA BENZALDOXIME AND ITS ESTERS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Figure</th>
<th>Functional Group</th>
<th>Wave length in microns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Literature</td>
</tr>
<tr>
<td>Ca</td>
<td>IX</td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-OH</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>3.08, 7.7</td>
</tr>
<tr>
<td>C-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>-COO-</td>
<td>5.73-5.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.1-7.5</td>
</tr>
<tr>
<td>C-2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>XI</td>
<td>-COO-</td>
<td>5.7-5.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>19.88</td>
</tr>
</tbody>
</table>

<sup>a</sup>Alpha Benzaldoxime.
<sup>b</sup>Para-nitro-benzoate of C.
<sup>c</sup>Phenyl acetate of C.
<sup>d</sup>Slight.
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-PARA-METHOXY-BENZALDOXIME

FIGURE XII
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-PARA-METHOXY BENZALDOXIME PARA-NITRO-BENZOATE

FIGURE XIII
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-PARA-METHOXY-BENZALDOXIME PHENYL ACETATE

FIGURE XIV
### TABLE V

**ABSORPTION BANDS FOUND IN ALPHA-PARA-METHOXY-BENZALDOXIME AND ITS ESTERS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Figure</th>
<th>Functional Group</th>
<th>Wave length in microns</th>
<th>Literature</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>D&lt;sup&gt;a&lt;/sup&gt;</td>
<td>XII</td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-OH</td>
<td>10.88</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>3.08, 7.7</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7.46-7.81</td>
<td>7.55</td>
<td></td>
</tr>
<tr>
<td>D-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>XIII</td>
<td>-COO-</td>
<td>5.73-5.85</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>(10.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.1-7.5</td>
<td>7.35, 7.5</td>
<td></td>
</tr>
<tr>
<td>D-2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>XIV</td>
<td>-COO-</td>
<td>5.7-5.76</td>
<td>5.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>10.92</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Alpha-Para-methoxy-benzaldoxime.

<sup>b</sup>Para-nitro-benzoate of D.

<sup>c</sup>Phenyl acetate of D.
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA ACETOPHENONE OXIME

FIGURE XV
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-ACETOPHENONE OXIME BENZOATE

FIGURE XVI
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA ACETOPHENONE OXIME PARA-NITRO-BENZOATE

FIGURE XVII
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA ACETOPHENONE OXIME PARA-METHOXY-BENZOATE

FIGURE XVIII
THE INFRARED ABSORPTION SPECTROGRAPH OF ALPHA-ACETOPHENONE OXIME PHENYL ACETATE

FIGURE XIX
TABLE VI

ABSORPTION BANDS FOUND IN ALPHA-ACETOPHENONE OXIME AND ITS ESTERS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Figure</th>
<th>Functional Group</th>
<th>Wave length in microns</th>
<th>Literature</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>E(^a)</td>
<td>XV</td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>5.98(^f)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-OH</td>
<td>10.88</td>
<td></td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>3.08, 7.7</td>
<td>3.0, 7.62</td>
<td></td>
</tr>
<tr>
<td>E-1(^b)</td>
<td>XVI</td>
<td>-COO-</td>
<td>5.73-5.85</td>
<td>5.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.1, 6.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>(11.0)(^g)</td>
<td></td>
</tr>
<tr>
<td>E-2(^c)</td>
<td>XVII</td>
<td>-COO-</td>
<td>5.73-5.85</td>
<td>5.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>(10.97)(^h)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO(_2)</td>
<td>7.1-7.5</td>
<td>7.35</td>
<td></td>
</tr>
<tr>
<td>E-3(^d)</td>
<td>XVIII</td>
<td>-COO-</td>
<td>5.73-5.85</td>
<td>5.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCH(_3)</td>
<td>7.46-7.81</td>
<td>7.55</td>
<td></td>
</tr>
<tr>
<td>E-4(^e)</td>
<td>XIX</td>
<td>-COO-</td>
<td>5.7-5.76</td>
<td>5.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=N</td>
<td>6.02-6.21</td>
<td>6.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-O(H)</td>
<td>10.88</td>
<td>10.9(^i)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Alpha-acetophenone oxime.
\(^b\)Benzoate of E.
\(^c\)Para-nitro-benzoate of E.
\(^d\)Para-methoxy-benzoate of E.
\(^e\)Phenyl acetate of E.
\(^f\)very small.
\(^g\)questionable for this band.
\(^h\)moved over slightly to right.
\(^i\)small.
Discussion of Infrared Analyses

In almost all cases, the observed infrared spectroanalyses agreed with the literature values. However, there were some discrepancies in the pure oximes themselves. Benzophenone oxime, Figure V, and acetophenone oxime, Figure XV, do not show a clear characteristic C=N vibration which should be present. Cyclohexanone oxime has a C=N vibration which has shifted over slightly making it questionable as to whether it is a C=N vibration or not. All other pure oximes show this characteristic vibration which identifies the oxime type linkage.

The N-OH band does not appear in every case and in several cases it has shifted from the given value. In benzaldoxime, Figure IX, and para-methoxy-benzaldoxime, Figure XII, where the N-OH should be a characteristic of the pure oxime, it does not appear. This, however, has been explained previously as being due to the interfering C-H vibrations.

The ester linkage between the oxime and the acid has shifted toward the left in almost every case, but it still indicative of an ester linkage being present. By combining all the characteristic vibrations, it can be seen that the infrared spectroanalyses show a definite ester linkage of the acid with the hydroxyl group of the oxime. This was the main evidence sought in the infrared analyses.
PHARMACOLOGICAL STUDIES

Procedures

Two general procedures were attempted which were the same except that one used a solution (10 mg./0.1 ml.) of the esters in dimethyl sulfoxide (DMSO*) and the other a suspension (10 mg./0.1 ml.) of the esters in 0.6 per cent methyl cellulose solution. The suspension was made by wetting one gram of each of the esters individually with 2 ml. of a 3 per cent methyl cellulose solution in a mortar and triturating the individual ester to a fine state. Then 8 ml. of distilled water was added to the paste which was formed and triturated again to suspend the ester completely. Each was then transferred to a multiple dose vial individually.

In the procedures, the animals used were white male mice (20 to 30 grams). Groups of three mice were injected intraperitoneally with a specified amount of material using a Tuberculin Syringe fitted with a number 23 needle and a fourth was injected with the same amount of solvent or suspending agent as a control. This was done at several different dose levels in order to ascertain the approximate range of the toxicity. When the range was determined, 12 mice for each dose level were injected with one oximino ester and the results noted along with any other visible

*Provided through courtesy of Stepan Company, Chicago, Illinois.
reactions. This same procedure was repeated for each of the other two oximino esters.

The results are shown in Table VII and Figure XX.

Discussion of Pharmacological Results

Since the pure oximes are known to have toxic effects (44,45), an attempt was made to evaluate the toxicities of the oximino esters with the hope that the toxic effects of the pure oxime would be lowered but that the oximino esters would still retain some of the original depressant activity of the pure oximes. Three different oximes having the same ester portion were chosen. These were the para-methoxy-benzoates of cyclohexanone oxime, benzophenone oxime and alpha-acetophenone oxime.

In an attempt to find a suitable solvent for the esters, propylene glycol was used since the compounds were insoluble in water. However, it was found that although the esters dissolved in hot propylene glycol, they recrystallized as the solvent cooled. Therefore propylene glycol was abandoned as a suspending agent and another solvent sought.

It was found that the esters would dissolve in DMSO. Since it had a reported intragastric toxicity of 17.8 grams/kg. (81), this was used as a solvent and vehicle for the injection of the esters. Upon intraperitoneal injection of the esters at different dose levels to find the approximate dose range for the LD$_{50}$, it was found that all the mice
<table>
<thead>
<tr>
<th>Compound</th>
<th>Number of Animals</th>
<th>Dose mg./Kg.</th>
<th>Number of Animals Alive</th>
<th>Per cent Deaths</th>
<th>Approximate LD&lt;sub&gt;50&lt;/sub&gt; mg./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>2000</td>
<td>3</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1500</td>
<td>4</td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1000</td>
<td>8</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>500</td>
<td>12</td>
<td>0</td>
<td>0.0&lt;sup&gt;e&lt;/sup&gt; 1275</td>
</tr>
<tr>
<td>B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
<td>2000</td>
<td>2</td>
<td>83.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1500</td>
<td>10</td>
<td>2</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1000</td>
<td>11</td>
<td>8.3</td>
<td>1600</td>
</tr>
<tr>
<td>C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12</td>
<td>2500</td>
<td>6</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2000</td>
<td>9</td>
<td>25.0</td>
<td>2500</td>
</tr>
<tr>
<td>D&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12</td>
<td>(1200)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>12</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cyclohexanone Oxime Para-Methoxy-Benzoate.
<sup>b</sup>Benzophenone Oxime Para-Methoxy-Benzoate.
<sup>c</sup>Alpha acetophenone Oxime Para-Methoxy-Benzoate.
<sup>d</sup>Methyl Cellulose 0.6%.
<sup>e</sup>This point was not considered in Fig. XX since the zero point does not appear on the graph and only a rough approximation was sought.
<sup>f</sup>This dose represents approximately .6% methylcellulose used in the maximum dose in a 25 Gm. mouse.
FIGURE XX

GRAPHIC APPROXIMATIONS OF LD₅₀ IN MICE

* Refer to Table VII
died at a dose of 500 mg./Kg., the lowest dose given. Therefore the pure DMSO was injected in the quantity necessary to contain 500 mg./Kg. of the compound. Again the mice all died within 3 to 12 hours. All the mice went into convulsions before death. Upon intravenous injection, the mice died instantly by tonic convulsions. With a dose of DMSO as low as 3.6 grams/Kg. (approximately 0.1 ml.) more than 50 per cent of the mice died within 12 hours. This dose was approximately 20 per cent of the reported intragastric toxic dose. Therefore, DMSO could not be used as a solvent.

The only route open now was to suspend the esters and give it in as nearly a uniform suspension as possible. Methyl cellulose was chosen as the suspending agent because it was relatively non-toxic in the dosage used. The 0.6 per cent methyl cellulose used made a fairly uniform suspension which did not settle out very rapidly and which would resuspend the material again easily with a slight shaking. The particles were triturated fine enough to pass through a number 23 needle.

Table VII shows the results of the injection of the doses of the esters. The approximate LD$_{50}$ is listed in each case which was obtained from Figure XX. However, there were apparent visible symptoms which do not show up on the table. In all cases where the dose was more than 1000 mg./Kg., there was a marked depression noted. This was followed by
a loss of control of the hind quarters. When the animals went into a complete depression, loss of the righting reflex was noted, although the animals still maintained their pain reflexes and involuntary muscular movement. Those which died showed respiratory depression as well as some cyanosis just before death. In many cases, the animals went into clonic convulsions prior to the deep respiratory depression. At a dose of 500 mg./Kg., no deaths were noted and only a mild depression occurred.

All the observations were carried out over a 24 hour period. After this time, most of the animals which remained alive recovered completely. However, in the case of alpha-acetophenone oxime, there were some deaths noted after 24 hours. This could be attributed to a possible slower absorption of the ester and therefore a delay in the evidence of symptoms. This also is possibly evident from the larger dose that was necessary to kill 50 per cent of the animals in 24 hours.

From the apparent toxicity studies, it can be shown that the esters used have a fairly low toxicity. Whether this can be attributed to the esters themselves as being slightly toxic or to their possible slow absorption cannot be determined with the available data at this time. Further work will have to be done to ascertain the data as well as an exact LD$_{50}$ for each of the compounds.
SUMMARY AND CONCLUSIONS

1. Fourteen new esters of a series of oximes were synthesized. These consisted of the benzoates, para-nitrobenzoates, para-methoxy-benzoates and phenyl acetates of cyclohexanone oxime, benzophenone oxime, benzaldoxime, para-methoxy-benzaldoxime, and acetophenone oxime. Each ester was not made in the series as several of these had been prepared previously.

2. The esters were characterized by nitrogen analysis, saponification equivalents, infrared analyses and crystallography. Refractive indices were not obtained for the phenyl acetate series of the oximes.

3. Reductions were attempted on the nitro containing esters but in every case the desired product was not obtained. In the hydrogenation method using 10 per cent palladium on charcoal, two products were obtained showing that the ester link was split and complete reduction of the nitro as well as the oximino group was effected.

4. Pharmacological studies carried out with the para-methoxy-benzoates of three oximes showed the toxicity of the oximes to be quite low. No study was made to ascertain whether the low toxicity was due to the esters themselves or to their possible slow absorption since they were suspensions.


8. v. Auwers, K., Ber., 22, 605 (1889).


43. Testoni, P., Arch. inter. Pharmacodyn., 49, 393 (1935).


64. Fujikawa, F., Tokuoka, A., Takimura, M. and Muira, M., J. Pharm. Soc., Japan, 72, 518 (1952); [Chemical Abstracts, 46, 8779 (1952)].


I, Louis Gass, was born in Washington, D. C., May 1, 1926. I received my secondary school education in the public schools of the District of Columbia. My undergraduate training was obtained from The George Washington University, Rhode Island College of Pharmacy, and College of Pharmacy at Butler University, which granted me the Bachelor of Science degree in 1954. From Butler I also received the Master of Science degree in 1955. While in residence at The Ohio State University, where I specialized in pharmacy (pharmaceutical chemistry), I held an assistantship for two years while completing requirements for the degree Doctor of Philosophy.