I. A NEW COMMERCIAL SYNTHESIS OF THE INSECTICIDE PARATHION

II. STUDIES IN THE BENZOTRIAZOLE AND 2-AMINOPYRIDINE SERIES

by

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<td>TABLE XXX</td>
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GRAPH I: 52-53
A NEW COMMERCIAL
SYNTHESIS OF THE
INSECTICIDE PARATHION
INTRODUCTION

Since very ancient times insects generally have been pests, often times annoying, if not dangerous, and detrimental to the progress of civilization. There has been a continual struggle between man and these insect hosts. Man has used various means to keep them under control. Mechanical methods and predatory animals such as birds, reptiles, etc. have been employed. More recently the introduction of sanitation methods and resistant species of plants have helped immensely. Perhaps the most important and effective method of all has been the use of chemical insecticides.

Chemical insecticides may be classified in several ways as: 1- Stomach poisons, 2- Nerve or Contact poisons and 3- Fumigants or Respiratory poisons; or as 1- Inorganic, 2- Synthetic organic and 3- Natural products or insecticides derived from plants.

The first recorded use of insecticides was in 1681 when white arsenic (As$_2$O$_3$) was recommended against ants. Soon afterwards in 1690 the use of nicotine as an insecticide was reported. Various other natural products (tuba root, etc.) have been used as insecticides for a long time in some parts of the world. However it has only been in the last sixty years that insecticides have achieved significant commercial importance.

The inorganic insecticides led the way until about 1940. Free sulfur is the most important of all in this field with the lead arsenates as a good second. Other inorganic insecticides are the arsenic oxides; aluminum, calcium, copper, iron, magnesium and manganese arsenates; sodium, calcium, and copper arsenites and Paris Green.
[((CH₂COO)₂Cu·3Cu(AsO₂)₂). The fluorides, fluosilicates, fluoaluminates, as well as numerous miscellaneous types of lesser importance, also, have been used.

Among the insecticides derived from plants, nicotine, the pyrethrum extracts, rotenone and related compounds lead the way although over 1400 different plants have been shown to possess chemical constituents of insecticidal value.

There are the fumigant gases, hydrogen cyanide, chloropicrin, carbon bisulfide, carbon tetrachloride, dichloroethane, methyl bromide, etc., which have been known for a long time, but their use is limited by their gaseous and toxic nature.

In 1939 the field of insecticides was suddenly revolutionized by the discovery of a synthetic organic insecticide of tremendous promise. This material, DDT, 2,2-bis (p-chlorophenyl)-1,1,1-trichloroethane, had been prepared and described by Zeidler² in 1874. Its use as an insecticide was not discovered till Lägger³ at Geigy Company in Switzerland in 1939 found it to be an effective insecticide against a wide variety of insect pests. By 1943 large scale production of DDT was underway all over the world. Literally overnight DDT became the most important single insecticide known. DDT had advantages over the arsenates and other inorganic insecticides in that it was non-toxic to humans and did not cause a serious residue problem on sprayed materials. It had great advantages over natural products in its availability and cheapness. With the great success of DDT in the insecticide field, a tremendous amount of research was instituted to seek new and still better synthetic organic insecticides. The next great synthetic organic insecticide was BHC, benzene hexachloride, 1,2,3,4, 5,6-hexachlorocyclohexane. It had been synthesized by Faraday⁴ in 1825, but was rediscovered as an insecticide of merit in 1942 by Imperial Chemical Industries Ltd. in England. It was also called Gammexane, as the gamma isomer was the only active isomer of the five stereoisomers isolated.
1. Nicotine

2. Pyrethrín II
   (typical pyrethrum type product)

3. Rotenone

4. Benzene Hexachloride

5. Chlordane

6. Phenothiazine

7. DNOCHP

8. DNOCG

9. Xanthone
as yet. There are nine stereoisomers theoretically possible. Other important synthetic organic compounds used as insecticides were the chlorinated hydrocarbons such as Chlordane, Velisol 1068, Octaklor, 1,2,4,5,6,7,8,8-octa-chloro-4,7-methane-3a,4,7,7a-tetrahydroindane (C₁₀H₆Cl₈), and Toxaphene (C₁₅H₁₀Cl₂). Still other important organic synthetic insecticides are phenothiazine, the alkyl thiocyanates, 4,6-dinitro-o-cresol (DNOC) and 2,4-dinitro-6-cyclohexylphenol (DNOCHP), and xanthone.

A consideration of these insecticides mentioned above shows that almost every type of organic chemical may be employed as an insecticide against some pest.

Entomological tests have indicated and field tests have proven that DDT is effective against almost every known insect pest except the arachnids (spiders), acarids (mites), aphids, cotton boll weevil and a few others. BHOC has proven most effective against cotton pests as well as against many pests also controlled by DDT.

There remained the considerable problem of the control of mites and other arachnids which yearly cause tremendous damage to fruit orchards, etc. throughout the world. This problem was actually intensified by the increased use of DDT and other insecticides that killed off many of the natural predators of the arachnids. In nature there is normally a balance between various types of insects. If one of the insect groups is left untouched by DDT, etc., while its normal predator is destroyed, in short order the untouched group may itself become a major insect pest. This, indeed, has happened in actuality. The arachnids (not technically insects, but for practical purposes, we may consider them as such) have run wild since the widespread introduction of DDT, BHOC, etc. after the war. Prior to the introduction of the organic phosphates into the fight against these pests, the chief weapons available were some summer oils, DNOC, DNOCHP and a few related compounds. These products were unable to control the mite problem and the damage due to the arachnids mounted yearly.
In 1932 Lange and von Krueger\(^5\) discovered diisopropyl fluorophosphate (DFP). This compound was found to possess marked parasympathomimetic properties, which later investigators have found to be characteristic of all organic phosphates. In larger quantities these compounds are extremely toxic to all animals (wet-blooded as well as lower forms). Death is caused by convulsions, respiratory failure, circulatory failure and other typical parasympathetic reactions. Apparently all organic phosphates possess this type of toxicity.

In 1938 Schrader\(^6\) discovered the compound hexaethyl tetraphosphate, HETP, \(\text{Et}_6\text{P}_4\text{O}_{18}\), which was prepared by the reaction of phosphorus oxychloride and triethyl orthophosphate. Woodstock\(^7\) prepared this same material starting with triethyl orthophosphate and phosphorus pentoxide. This material was made commercially as the insecticide, Bladan. The product is a liquid with polar and non-polar properties. It is easily hydrolyzed to less toxic hydrolysis products. The compound may actually be a mixture of several phosphate esters rather than being pure HETP.

The next important phosphate insecticide prepared by Woodstock\(^7\) from triethyl orthophosphate and phosphorus pentoxide was tetraethyl pyrophosphate, TEPP, \(\text{Et}_4\text{P}_2\text{O}_7\). It is also, easily hydrolyzed to less toxic hydrolysis products. It is believed to be the ester in relatively pure form and to be the active component of the so-called hexaethyl tetraphosphate.

In 1946 Thurston\(^8\) and Martin and Shaw\(^9\) reported that the Allied authorities had found that the Germans had prepared \(0,0\)-diethyl-\(0\)-p-nitrophenyl thiophosphate. This compound has been known as Parathion, Thiophos and E-605. The great advantage of Parathion over the other organic phosphates known at that time lay in the fact that Parathion is not very soluble in water and is not easily hydrolyzed. This allowed the material to retain its toxicity and insect-
HEPP, Hexaethyl tetraphosphate, Bladan

TEPP, Tetraethyl pyrophosphate

Parathion, Thiophos, E-605
icidal potency for a much longer period of time than the
twenty-four hours or so for tetraethyl pyrophosphate etc. The German method of preparation of Parathion left much to
be desired from an industrial standpoint. Immediately
every insecticide company in America began research for new
methods that would be cheaper, easier, faster and more simpli-
fied. The German method involved the preparation of $\text{O}_2\text{C(di-}
$ethyl thiophosphoryl chloride, $(\text{EtO})_2\text{PSCl}_2$, from sodium eth-
$\text{oxide and thiophosphoryl chloride}, \text{PSCl}_3$, and its reaction
with sodium p-nitrophenoxide in chlorobenzene solvent. The
yields of these reactions are not spectacular and the cost
of these processes is commercially prohibitive.

Therefore new reactions, new starting materials, new
techniques, etc., that would give better yields were needed.
With this in mind, the research in numerous laboratories
throughout the country developed along obvious lines to the
use of cheap starting materials for the preparation of the
essential intermediate, $\text{O}_2\text{C-diethyl thiophosphoryl chloride}$. This naturally led to some duplication of work although the
work was done quite independently. The synthesis of $\text{O}_2\text{C-di-}
$ethyl thiophosphoryl chloride beginning with cheap starting
materials (absolute ethyl alcohol, phosphorus pentasulfide,
and chlorine), the mechanism and the fundamental chemistry
of this reaction were all worked out at the University of
Kansas and recorded before the American Cyanamid Company
reported essentially the same work at the San Francisco
meeting of the American Chemical Society in April 1949. However as Cyanamid announced their results first, further
work in this field did not seem too promising.

$\text{O}_2\text{C-Diethyl thiophosphoryl chloride was treated with}\n$anhydrous sodium p-nitrophenoxide in glycol solvents by a
method developed by the Niagara Chemical Division of Food
Machinery Corporation to give Parathion in excellent yields.
This process was practical and industrially feasible.

The use of water or alcohol solvent for this latter
reaction was reported by Cyanamid to give good yields of Parathion. Victor Chemical Company employed a tertiary amine like pyridine or triethylamine to catalyze the reaction of p-nitrophenol and O,O-diethyl thiophosphoryl chloride to give good yields. With the advent of this new synthesis of O,O-diethyl thiophosphoryl chloride, Parathion is no longer a chemical curiosity, but a commercial insecticide of highest value.

More recent developments in the organic phosphate insecticide field have included the preparation and use of compounds like \((\text{EtO})_2\frac{\text{P}}{\text{O}}\cdot\text{O} \cdot (\text{OEt})_2\), \((\text{EtO})_2\frac{\text{P}}{\text{O}}\cdot\text{O}\cdot\text{NO}_2\), and \(\text{Me}_2\text{N}\cdot\frac{\text{P}}{\text{O}}\cdot\text{O}\cdot\text{NMe}_2\). This work is still in the preliminary testing stage. Compounds like the last when applied topically to a growing plant like a fertilizer are absorbed into the plant. This would make the plant potentially insecticidal to any insect that bites it. The field of organic phosphates and thiophosphates has not been fully investigated by any means as yet. New and perhaps startling insecticides may be developed from this field in the future.

The insecticides have been classified above according to their sources or types. A few words are in order concerning the mode of action of the commercial insecticides.

The inorganic insecticides (arsenates, etc.) are mostly all stomach poisons. The insect eats the leaf or some other portion of the plant that has been sprayed with arsenate, etc. The insecticide once inside the stomach of the insect can then exert its toxic action.

The fumigants act by being inhaled and are thus respiratory poisons.

The insecticides derived from plants (nicotine, rotenone, pyrethrins, etc.) and the synthetic organic insecticides like DDT are almost always contact or nerve poisons. The compounds enter the insect by absorption in the lipoids of the nerves of the legs or of that part of the insect body
which were in contact with the sprayed surface. These insecticides act even more rapidly than the stomach poisons. Läuger et al. have developed an insecticide theory to explain the activity and toxicity of DDT and related compounds. Once the insecticide is absorbed into the nervous system of the insect, the poison can act by causing paralysis in the case of DDT or by some other mechanism as in the case of the organic phosphates. As it was stated before, the organic phosphates are parasympathomimetics. They exert their action by the inhibition of cholinesterase. This has been demonstrated by many investigators working in this field.
DISCUSSION

A new commercial synthesis of Parathion was the chief aim of this research.

The original German synthesis of Parathion\(^8\) employed the following reactions:

1. \(2 \text{Na} + 2 \text{EtOH} \xrightarrow{\text{excess alcohol}} 2 \text{NaOEt} + \text{H}_2\)

2. \(2 \text{NaOEt} + \text{PSCl}_3 \xrightarrow{\text{alcohol}} (\text{EtO})_2 \text{PSCl} + 2 \text{NaCl}\)

3. \((\text{EtO})_2 \text{PSCl} + \text{NaO\(\text{NO}_2\)} \xrightarrow{\text{heat}} (\text{EtO})_2 \text{PSO\(\text{NO}_2\)} + \text{NaCl}\)

The high cost of thiophosphoryl chloride and the hazard attending large scale reaction of sodium with alcohol with its copious evolution of hydrogen make the first two steps somewhat unfeasible commercially. The third step, the reaction between the sodium p-nitrophenoxide and \(\text{EtO}_2\text{PSCl}\) was carried out in the expensive solvent, chlorobenzene. Refluxing for a period of up to twenty-four hours was necessary for the reaction to take place. This long time for the reaction to come to completion is definitely undesirable from an industrial viewpoint.

A different approach was undertaken in the work done here at the University of Kansas. The preparation of dialkyl dithiophosphates, \((\text{RO})_2\text{PSH}\), had been known for some time.\(^{16,17,18,19}\) They are prepared as follows:

4. \(\text{ROH} + \text{P}_2\text{S}_3 \xrightarrow{} 2 (\text{RO})_2\text{PSH} + \text{H}_2\text{S}\)

The metal salts, zinc, etc.; of these acids have been used as additives to lubricating oils.\(^{20,21,22,23,24,25}\) Esters of the dithioacid and amine derivatives have been used as flotation agents in the treatment of ores.\(^{26,27,28}\) However the free acids, \((\text{RO})_2\text{PSH}\), have not been isolated previously in pure form with the exception of \((\text{C}_6\text{H}_5\text{O})_2\text{PSH}\).\(^{18}\) This reaction went in excellent yield with ethyl alcohol. The use of alcohols other than ethyl met with varied success. Primary aliphatic alcohols (such as \(n\)-butyl) served well. Whereas alcohols like allyl, benzyl\(^1\), the secondary and the
tertiary alcohols gave anomalous results. This reaction of phosphorus pentasulfide with various alcohols goes with results depending upon the type of alcohol (aliphatic, alicyclic, primary, secondary or tertiary), the temperature, the degree of saturation and the mutual solubility. Phosphorus pentasulfide was treated with the following alcohols: absolute ethyl, 95% ethyl, allyl, sec-butyl, n-butyl, isopropyl, β-chloroethyl, benzyl and cinnamyl. In the case of absolute ethyl alcohol, the ratio of phosphorus pentasulfide to alcohol was varied to give a large variety of products. This reaction is quite spontaneous and very exothermic. With benzyl and cinnamyl alcohols, the reaction may become explosive.

The desired intermediate, 0,0-diethyl dithiophosphate, was prepared in good yield as below:

\[ 4 \text{EtOH} + P_2S_5 \rightarrow 2 (\text{EtO})_2PSSH + H_2S \]

The 0,0-diethyl dithiophosphate can be used in the crude form or can be purified by vacuum distillation.

The second step of the new process was the difficult one. It was the reaction of 0,0-diethyl dithiophosphate in the crude or pure form with chlorine gas. The overall desired result was the replacement of -SH of \((\text{EtO})_2PSSH\) by -Cl to form \((\text{EtO})_2PSCl\). This chlorination reaction was not a simple or straightforward process, but one which needed constant care and supervision in order to prevent overchlorination. The reactions involved are of an oxidation-reduction type, with 0,0-diethylthiophosphoryl chloride being formed in several possible reactions. After considerable study and experimentation, the following reaction was decided upon as that most nearly fitting all conditions found and maintained in the reaction.

\[ 2 (\text{EtO})_2PSSH + 3\text{Cl}_2 \rightarrow 2 (\text{EtO})_2PSCl + 3\text{Cl}_2 + 2\text{HCl} \]

Experimental evidence showed that this equation could be further broken down into four steps.
1. \((\text{EtO})_2\text{PSSH} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSSCl} + \text{HCl}\)

2. \((\text{EtO})_2\text{PSSCl} + (\text{EtO})_2\text{PSSH} \rightarrow (\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{HCl}\)

3. \((\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + (\text{EtO})_2\text{PSSCl}\)

4. \((\text{EtO})_2\text{PSSCl} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2\)

The desired product, 0,0-diethyl thiophosphoryl chloride, was isolated and separated from the other products of the reaction mixture (sulfur monochloride, etc.) in pure form by vacuum distillation.

In addition to these above reactions, there are various side reactions which occur to a greater or lesser extent depending on the experimental conditions employed. Variations in conditions such as changes in temperature, concentrations of reactants, time of reaction, etc., were all tried in order to find the influences of these factors, if any, on the desired reaction. It was found that the overall reaction was relatively independent of such influences. The chlorination reactions were highly exothermic and required efficient cooling in order to prevent overheating, subsequent loss of product and the formation of tars.

The chief factor to be considered is the degree of chlorination. There is the danger of under- or over-chlorination. The degree of chlorination may be gauged from the amount of chlorine absorbed as indicated by the gain in weight of the reaction vessel.

The tremendous advantages of this series of reactions for the preparation of the intermediate, 0,0-diethyl thiophosphoryl chloride, starting with simple, cheap, easily available starting materials are very easily seen. Thus research was significant from the commercial aspect as well as from the insight afforded into fundamental organic thio-phosphate chemistry.

The Niagara Chemical Division of Food Machinery Corporation Research Laboratories developed the use of glycols (ethylene, diethylene, propylene, etc.) as solvents for the reaction of 0,0-diethyl thiophosphoryl chloride and anhydrous
sodium \( p \)-nitrophenoxide.\(^{12} \) As polar solvents, glycols permitted the reaction to go to completion in a matter of ten to fifteen minutes compared to the reaction time of about twenty-four hours with non-polar solvents like chlorobenzene.\(^{8} \) From an industrial viewpoint this was an improvement of paramount significance. The reaction was:

\[
\text{(EtO)}_2PSCl + \text{NaOClNO}_2 \xrightarrow{\text{glycol \ heat}} (\text{EtO})_2PS\text{ClNO}_2 + \text{NaCl}
\]

Parathion

After a thorough discussion of the experimental results of this research, a detailed comparison of the old and new methods for the preparation of Parathion will be made at the end of this Discussion section.

The introduction of any new insecticide or medicinal agent makes it obligatory that the material be subjected to careful pharmacological testing to ascertain its minimum lethal dose (MLD\(_{50}\)), toxicity, toxic symptoms and actions on warm-blooded animals. Under the supervision of Dr. Wenzel of the School of Pharmacy, and with the help of Messrs. Sam, Sadow, and Negredy, the MLD\(_{50}\) for oral administration of Parathion on white mice was determined. The data obtained were later corroborated by publication of other pharmacological studies on Parathion.\(^{29} \)

A number of various possible syntheses of Parathion using \( p \)-chloronitrobenzene, \( p \)-nitrophenol, C,C-diethyl di-thiophosphate, etc., were attempted. The reactions were most interesting on paper although they were not eminently successful when tried in the laboratory. They will be mentioned briefly in the experimental part of this section of the thesis.

---

The German method\(^{8} \) required the use of thiophosphoryl chloride. This material, although commercially available, is somewhat expensive. Some preliminary experiments were run on the preparation of thiophosphoryl chloride by the method of Thorpe.\(^{30,31} \)
Table I

<table>
<thead>
<tr>
<th>Moles PCl₃</th>
<th>Moles P₄S₈</th>
<th>Apparatus</th>
<th>Time</th>
<th>Temp.</th>
<th>Crude Yield</th>
<th>% Boiling</th>
<th>% Product Color</th>
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<tr>
<td>0.067</td>
<td>0.022</td>
<td>tube</td>
<td>---</td>
<td>ca. 150</td>
<td>51.3</td>
<td>85-125/1</td>
<td>45.5 yellow</td>
</tr>
<tr>
<td>1.50</td>
<td>0.50</td>
<td>pipe</td>
<td>15</td>
<td>ca. 150</td>
<td>52.0</td>
<td>118-124/1</td>
<td>45.7 colorless</td>
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<tr>
<td>1.50</td>
<td>0.50</td>
<td>bomb</td>
<td>30</td>
<td>ca. 150</td>
<td>56.5</td>
<td>118-124/1</td>
<td>63.0 colorless</td>
</tr>
<tr>
<td>1.50</td>
<td>0.50</td>
<td>bomb</td>
<td>30</td>
<td>ca. 150</td>
<td>71.0</td>
<td>118-127/1</td>
<td>63.0 colorless</td>
</tr>
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a - the reported boiling range of PCl₃ was 125°C.

There are a number of other methods for the preparation of thiophosphoryl chloride, but the Thorpe method possesses good commercial possibilities.

The next essential step in the German method was the preparation of O,O-diethyl thiophosphoryl chloride in the following manner. 8,34,35,36,37,38

1. 2 Na + 2 EtOH \( \xrightarrow{\text{excess alcohol}} \) 2 NaOEt + H₂

2. 2 NaOEt + PCl₃ \( \xrightarrow{\text{alcohol}} \) (EtO)₂PSCl + 2 NaCl

Table IIIa

<table>
<thead>
<tr>
<th>Moles Na</th>
<th>Ethanol ml.</th>
<th>PCl₃ ml.</th>
<th>Temp. °C.</th>
<th>Time min.</th>
<th>Range °C./mm.</th>
<th>Crude Yield %</th>
<th>Pure Product Yield %</th>
<th>nD²⁰</th>
<th>nD²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.59</td>
<td>250</td>
<td>0.295</td>
<td>---</td>
<td>20</td>
<td>93.5</td>
<td>---</td>
<td>---</td>
<td>69.0</td>
<td>1.469</td>
</tr>
<tr>
<td>1.18</td>
<td>520</td>
<td>0.59</td>
<td>30-78</td>
<td>10</td>
<td>94.5</td>
<td>71.2</td>
<td>1.456</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a - PCl₃ was added to the NaOEt in these two experiments. The major product seemed to be O,O-diethyl thiophosphoryl chloride, (EtO)₂PSCl. The reported b.p. of (EtO)₂PSCl was 105-106°C/20mm. 39

Table IIIb

<table>
<thead>
<tr>
<th>Moles Na</th>
<th>Ethanol ml.</th>
<th>Benzene ml.</th>
<th>PCl₃ solvent °C.</th>
<th>Time hrs.</th>
<th>range °C./mm.</th>
<th>Pure Product Yield %</th>
<th>nD²⁰</th>
<th>nD²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>350</td>
<td>0.50</td>
<td>200</td>
<td>0-25</td>
<td>84-88/14</td>
<td>69.0</td>
<td>1.469</td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>850</td>
<td>1.00</td>
<td>50</td>
<td>0-5</td>
<td>68-75/5-6</td>
<td>67.5</td>
<td>1.422</td>
<td></td>
</tr>
<tr>
<td>4.00</td>
<td>1700</td>
<td>2.00</td>
<td>100</td>
<td>0-5</td>
<td>69-73/5</td>
<td>79.3</td>
<td>1.472</td>
<td></td>
</tr>
</tbody>
</table>

a - NaOEt solution was added to the PCl₃ in these cases. The major product is O,O-diethyl thiophosphoryl chloride, (EtO)₂PSCl.

b - This product was redistilled to give some (EtO)₂PSCl in a yield of 88% (b.r. = 77.5-78.5°C/6mm.; nD²⁰ = 1.472), and some EtOPSCl₂ in a yield of 4.5% (b.r. = 57-79°C/7mm.;
n_{D}^{20} = 1.497). The reported boiling range of (EtO)_{2}PSCl was 96-99°C./25mm. 39

A slight modification was tried using absolute alcohol, pyridine (or some other tertiary amine) and thiophosphoryl chloride. 39

\[ 2 \text{EtOH} + 2 \text{PSCl}_3 \xrightarrow{\text{benzene}} (\text{EtO})_2\text{PSCl} + 2 \text{HCl} \]

<table>
<thead>
<tr>
<th>Moles</th>
<th>Ethanol</th>
<th>Absolute</th>
<th>PSCl₃</th>
<th>Benzene</th>
<th>ml.</th>
<th>Temp. °C.</th>
<th>hrs. range</th>
<th>Yield %</th>
<th>( n_{D}^{20} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.05</td>
<td>1.00</td>
<td>0.50</td>
<td>100</td>
<td>75-80</td>
<td>3</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>0.50</td>
<td>450</td>
<td>0-15</td>
<td>3</td>
<td>70-80/6-8</td>
<td>38.3</td>
<td>1.490ₐ</td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>2.00</td>
<td>1.00</td>
<td>900</td>
<td>0-10</td>
<td>4</td>
<td>64-84/6</td>
<td>55.0</td>
<td>1.491ₐ</td>
<td></td>
</tr>
<tr>
<td>4.00</td>
<td>4.00</td>
<td>2.00</td>
<td>1800</td>
<td>0-5</td>
<td>7</td>
<td>57-79/6</td>
<td>60.0</td>
<td>1.495ₐ</td>
<td></td>
</tr>
</tbody>
</table>

a - This reaction led to the formation not of the desired product, but of 0-ethyl thiophosphoryl chloride, EtOPSCl₂. The reported boiling range of EtOPSCl₂ was 68°C./20mm. 34

B - Dimethyl aniline was used instead of pyridine.

There are some other methods for the preparation of 0,0-diethyl thiophosphoryl chloride. 40,41,42,43

The yields in these reactions for the preparation of 0-ethyl thiophosphoryl chloride (EtOPSCl₂), 0,0-diethyl thiophosphoryl chloride ((EtO)₂PSCl) and 0,0,0-triethyl thiophosphate ((EtO)₃PS) are satisfactory although not spectacular.

In these reactions the matter of recovery of the solvent used is of great importance. Absolute ethyl alcohol is needed to prepare sodium ethoxide. The maximum concentration of sodium ethoxide that one can obtain as a solution in absolute alcohol is about 15%. This means that a large amount of expensive absolute alcohol must be used as a solvent in this reaction. In the isolation of the final product, water was added to the benzene-alcohol solution. The product was extracted in the non-aqueous layer. The aqueous layer contained the excess alcohol from which the alcohol, now no longer absolute, can be recovered by distillation in yields of about 85-90%. This fact, as well as the great hazard of using
metallic sodium in commercial processes, does not add to the industrial attractiveness of this method for the preparation of the product, O,O-diethyl thiophosphoryl chloride. When one considers, also, the cost of the original starting materials, sodium, thiophosphoryl chloride and absolute alcohol (in great excess), the process becomes even less promising.

In addition in this process there is the possibility of forming O,O,O-triethyl thiophosphate and O-ethyl thiophosphoryl chloride. In the case where the thiophosphoryl chloride was added to the sodium ethoxide, the major product was O,O,O-triethyl thiophosphate. When the sodium ethoxide was added to the thiophosphoryl chloride even under the most nearly ideal conditions, 5% or so of O-ethyl thiophosphoryl chloride was formed.

This process took several days to run in the laboratory. It would not be applicable to the higher molecular weight alcohols (ROH), from hexyl alcohol up, where the sodium alkoxide (RONa) was difficult or impossible to prepare. The product formed by this procedure, O,O-diethyl thiophosphoryl chloride, can be obtained in very pure form, however, by simple vacuum fractionation from its main contaminants, O-ethyl thiophosphoryl chloride and O,O,O-triethyl thiophosphate.

The second reaction, in which amines are used to take up the hydrogen chloride split out in the reaction of absolute ethyl alcohol and thiophosphoryl chloride in benzene solution, had several potential advantages. It eliminated the hazard of metallic sodium and the cost of the excess absolute alcohol. The tertiary amine could be recovered as the hydrochloride salt in yields of about 85% and regenerated as the free base with alkali. The great disadvantage of this reaction was that it did not give the desired product, O,O-diethyl thiophosphoryl chloride, but rather only the mono product, O-ethyl thiophosphoryl chloride. Were this the compound desired, this process would be a very acceptable method of preparation. The recovery of the benzene solvent
could be accomplished by distillation in yields up to 90%.

The last step in the German method for the preparation of Parathion was an $\text{S}_2^\text{N}$ reaction$	ext{8}$

$\text{(EtO)}_2\text{PSCl} + \text{NaO} \xrightarrow{\text{No}_2} \text{chlorobenzene} \rightarrow \text{(EtO)}_2\text{PSO} \xrightarrow{\text{No}_2} \text{NaCl}$

This reaction went in excellent yields of about 80-90%, but required a long reaction time (up to twenty-four hours). The preparation of O,O-diethyl thiophosphoryl chloride will be discussed in this thesis. Sodium p-nitrophenoxide can be prepared from p-nitrophenol and sodium hydroxide or commercially from p-nitrochlorobenzene and hot aqueous sodium carbonate. The sodium salt is a hydrate and should be dehydrated at 110-115°C. for several hours before reacting with O,O-diethyl thiophosphoryl chloride.

<table>
<thead>
<tr>
<th>Moles</th>
<th>Sodium Chloro-</th>
<th>Temp.</th>
<th>Time</th>
<th>$n^\text{D}$</th>
<th>Yield</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-nitro-</td>
<td>p-nitro-</td>
<td>benzene</td>
<td>ºC</td>
<td>hrs</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Phenoxide</td>
<td>(EtO)$_2$PSCl</td>
<td>Solvent</td>
<td>a</td>
<td>b</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>0.276</td>
<td>0.276</td>
<td>125</td>
<td>130-140</td>
<td>4</td>
<td>1.509</td>
<td>68.0</td>
</tr>
<tr>
<td>0.21</td>
<td>0.21</td>
<td>165</td>
<td>135-140</td>
<td>22</td>
<td>1.538</td>
<td>53.0</td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>150</td>
<td>125</td>
<td>7</td>
<td>1.528</td>
<td>85.5</td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>150</td>
<td>125</td>
<td>9.5</td>
<td>1.514</td>
<td>52.0</td>
</tr>
<tr>
<td>0.088</td>
<td>0.088</td>
<td>40</td>
<td>120-130</td>
<td>5</td>
<td>1.512</td>
<td>unsatisfactory</td>
</tr>
<tr>
<td>0.132</td>
<td>0.132</td>
<td>80</td>
<td>135-140</td>
<td>1.5</td>
<td>1.531</td>
<td>81.0</td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>150</td>
<td>125-135</td>
<td>125</td>
<td>1.532</td>
<td>90.0</td>
</tr>
</tbody>
</table>

a = Xylene was used as solvent.
b = Distilled and purified at about 200°C./0.005mm.; $n^\text{D} = 1.537$

The recovery of chlorobenzene solvent was about 80-90%. This method with the recovery of the chlorobenzene solvent is economical enough except for the long period of time needed for the reaction to go to completion.

The new synthetic method for Parathion we developed here involved first the preparation of O,O-diethyl thio- phosphate. This material had been prepared previously by several investigators using ethyl alcohol and phosphorus pentasulfide.$^{16,17,18,19}$

The pure or semi-pure product was never isolated as the free acid, but only as the metallic salts.
Some preliminary reactions were run using absolute ethyl alcohol and phosphorus pentasulfide in various proportions.

**Table IV**

<table>
<thead>
<tr>
<th>Moles $P_2S_5$</th>
<th>Moles Absolute Ethanol</th>
<th>Ratio of $P_2S_5$/EtOH</th>
<th>n(^D) of Crude Product</th>
<th>n(^D) of Distilled Product</th>
<th>Product Believed to be</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>0.60</td>
<td>1/3</td>
<td>1.515</td>
<td>1.502</td>
<td>$(EtO)_2PSSH$</td>
<td>92.5</td>
</tr>
<tr>
<td>0.15</td>
<td>0.45</td>
<td>1/3</td>
<td>1.531</td>
<td>1.518</td>
<td>$(EtO)_2PSSH$</td>
<td>95.0</td>
</tr>
<tr>
<td>0.10</td>
<td>0.40</td>
<td>1/4</td>
<td>1.504</td>
<td>1.501</td>
<td>$(EtO)_2PSSH$</td>
<td>88.0</td>
</tr>
<tr>
<td>0.15</td>
<td>0.75</td>
<td>1/5</td>
<td>1.486</td>
<td>1.490</td>
<td>$Et_2HPO_3S_2 + $Et_2PO_3S</td>
<td></td>
</tr>
<tr>
<td>0.20</td>
<td>1.20</td>
<td>1/6</td>
<td>1.473</td>
<td>1.486</td>
<td>unknown</td>
<td>---</td>
</tr>
<tr>
<td>0.10</td>
<td>0.80</td>
<td>1/6 (^a)</td>
<td>1.447</td>
<td>1.502</td>
<td>$(EtO)_2PSSH$</td>
<td>---</td>
</tr>
<tr>
<td>0.10</td>
<td>0.80</td>
<td>1/8 (^a)</td>
<td>1.452</td>
<td>1.496</td>
<td>$(EtO)_2PSSH$</td>
<td>---</td>
</tr>
<tr>
<td>0.10</td>
<td>1.00</td>
<td>1/10</td>
<td>1.436</td>
<td>1.498</td>
<td>unknown</td>
<td>---</td>
</tr>
</tbody>
</table>

$\text{a} - 0.1 \text{ mol of } P_2O_5 \text{ was also present in each of these runs.}$

0,0-Diethyl dithiophosphate was prepared in this reaction.

$$4 \text{ EtOH} + P_2S_5 \longrightarrow 2 (EtO)_2PSSH + H_2S$$

**Table V**

<table>
<thead>
<tr>
<th>Moles $P_2S_5$</th>
<th>Moles Absolute Ethanol</th>
<th>Temp. °C.</th>
<th>Time hrs.</th>
<th>% Yield</th>
<th>n(^D)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.417</td>
<td>4</td>
<td>80-105</td>
<td>1</td>
<td>95.0</td>
<td>1.504</td>
<td>distilled product recovered 0.083 m. $P_2S_5$, in steel bomb, gases formed.</td>
</tr>
<tr>
<td>0.500</td>
<td>2</td>
<td>0-30</td>
<td>4</td>
<td>100.0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>50-110</td>
<td>2</td>
<td>95.0</td>
<td>---</td>
<td>pure $(EtO)_2PSSH$, n(^D) = 1.511</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>50-115</td>
<td>2</td>
<td>97.0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>50-110</td>
<td>2</td>
<td>96.0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>8 (^a)</td>
<td>50-110</td>
<td>2</td>
<td>92.5</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>4 (^a)</td>
<td>50-110</td>
<td>2</td>
<td>92.4</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>40-100</td>
<td>3</td>
<td>97.0</td>
<td>1.513</td>
<td>pure $(EtO)_2PSSH$, n(^D) = 1.508. b.r. = 84-85°C./1mm.</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>80 up</td>
<td>unsatisfactory</td>
<td>97.4</td>
<td>---</td>
<td>insufficient cooling</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>50-105</td>
<td>2.5</td>
<td>97.4</td>
<td>---</td>
<td>good product</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>40-110</td>
<td>4.5</td>
<td>97.4</td>
<td>---</td>
<td>good product</td>
</tr>
</tbody>
</table>

$\text{a} - 95\% \text{ ethyl alcohol was used in these cases.}$

The reaction of four moles of alcohol and one mole of phosphorus pentasulfide was carried out with a number of
alcohols other than absolute ethyl with varying success. The reaction went most smoothly and successfully with low molecular weight primary aliphatic alcohols.

Table VI

<table>
<thead>
<tr>
<th>Moles P₄S₈</th>
<th>Moles ROH Used</th>
<th>Alcohol</th>
<th>Temp. °C.</th>
<th>Time hrs.</th>
<th>Yield %</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
<td>n-butyl</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>b.r.=118-138°C./1-4mm. stable</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>sec-butyl</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>unstable to vac. distillation</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>allyl</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>unstable, explosive, composition unknown</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>isopropyl</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>unstable to vac. distillation</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>benzyl</td>
<td>30-170</td>
<td>1</td>
<td>0</td>
<td>very exothermic, impossible to control over 115°C. normal behavior</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>β-chloroethyl</td>
<td>30-118</td>
<td>1</td>
<td>93</td>
<td>normal behavior</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>benzyl</td>
<td>35-135</td>
<td>2</td>
<td>74</td>
<td>products unknown composition</td>
</tr>
<tr>
<td>0.48</td>
<td>1.93</td>
<td>cinnamyl</td>
<td>70 up</td>
<td>1</td>
<td>0</td>
<td>decomposes above 100°C. normal behavior, identity of product uncertain</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>allyl</td>
<td>30-110</td>
<td>1.5</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

The crude products obtained from this reaction were quite acidic as expected. Titration of known quantities of these products with standardized alkali solution should provide the percentage acid in the crude samples. This might be used as a measure of purity and the degree of completion of the reaction. It must be assumed that hydrogen sulfide gas that was absorbed in the liquid may be ignored as a negligible quantity.

An apparent molecular weight can be calculated assuming 100% acid as a method of indicating possible impurities or the degree of purity. Approximately a 0.5 N sodium hydroxide solution was used to titrate five milliliter samples of the 0,0-dialkyl dithiophosphate, (RO)₂PSSH, solutions. The blue end-point of brom thymol blue and the red end-point of phenolphthalein were used. There was considerable fading of the end points in some cases and some difficulty in ascertaining the end points in strongly colored solutions.
The calculations employed were:

\[
\text{Percentage Acid} = \frac{\text{Normality} (\text{NaOH}) \times \text{Volume} (\text{NaOH}) \times (\text{RO})_2 \text{PSSH} \times 100}{\text{Weight sample} (\text{RO})_2 \text{PSSH}}
\]

\[
\text{Apparent Molecular Weight of Product} = \frac{\text{Weight sample} (\text{RO})_2 \text{PSSH}}{\text{Normality} (\text{NaOH}) \times \text{Volume} (\text{NaOH}) \times 1000}
\]

\[
\text{Milliequivalent}
\]

### Table VII

<table>
<thead>
<tr>
<th>(RO)_2PSSH used in sample</th>
<th>% (RO)_2PSSH in sample</th>
<th>Apparent Molecular Weight if 100% Acid</th>
<th>Expected Molecular Weight</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>absolute ethyl</td>
<td>84.1</td>
<td>221</td>
<td>186</td>
<td>vacuum distilled</td>
</tr>
<tr>
<td>absolute ethyl</td>
<td>87.4</td>
<td>213</td>
<td>186</td>
<td>crude</td>
</tr>
<tr>
<td>absolute ethyl</td>
<td>85.8</td>
<td>217</td>
<td>186</td>
<td>crude</td>
</tr>
<tr>
<td>95% ethyl</td>
<td>88.7</td>
<td>210</td>
<td>186</td>
<td>crude</td>
</tr>
<tr>
<td>allyl</td>
<td>49.5</td>
<td>425</td>
<td>210</td>
<td>not like ethyl</td>
</tr>
<tr>
<td>n-butyl</td>
<td>88.8</td>
<td>273</td>
<td>242</td>
<td>crude, like ethyl</td>
</tr>
<tr>
<td>n-butyl</td>
<td>94.4</td>
<td>257</td>
<td>242</td>
<td>crude, like ethyl</td>
</tr>
<tr>
<td>sec-butyl</td>
<td>86.6</td>
<td>280</td>
<td>242</td>
<td>crude, like ethyl</td>
</tr>
<tr>
<td>allyl</td>
<td>52.1</td>
<td>404</td>
<td>210</td>
<td>not like ethyl</td>
</tr>
<tr>
<td>isopropyl</td>
<td>85.8</td>
<td>255</td>
<td>214</td>
<td>crude, like ethyl</td>
</tr>
<tr>
<td>β-chloroethyl</td>
<td>91.6</td>
<td>279</td>
<td>255</td>
<td>crude, like ethyl</td>
</tr>
<tr>
<td>benzyl</td>
<td>18.8</td>
<td>176</td>
<td>310</td>
<td>not like ethyl at all</td>
</tr>
<tr>
<td>absolute ethyl²</td>
<td>101.5</td>
<td>183</td>
<td>186</td>
<td>as pure (EtO)_2PSSH</td>
</tr>
</tbody>
</table>

Note: 

- This product was obtained by treating the crude product with potassium hydroxide, filtering, reacidifying with 6 N hydrochloric acid, extracting with ether and evaporating the ether. \( n_D^{22} = 1.504 \)

The results of the experiments in which four moles of alcohol were treated with one mole of phosphorus pentasulfide coincide with the data obtained from the titration of the subsequent 0,0-dialkyl dithiophosphate samples with alkali. The reaction,

\[
4 \text{ROH} + \text{P}_2\text{S}_5 \rightarrow 2 (\text{RO})_2\text{PSSH} + \text{H}_2\text{S},
\]

was substantiated with the simple aliphatic primary and secondary alcohols.¹⁸ The crude products in different runs contained from 84 to 95% acid. With allyl alcohol (perhaps due to the unsaturated nature of the alcohol), the reaction went to a much lesser degree, while with cinnaamyl and benzyl alcohols, the reaction did not behave in the usual manner at
all. The aromatic nature of the cinnamyl and benzyl alcohols doubtless influences the course of the reaction profoundly.

While the preparation of the 0,0-diethyl dithiophosphate was an important beginning step, the crucial step in our method for the synthesis of Parathion was the chlorination of this material to form 0,0-diethyl thiophosphoryl chloride. The -SH group was replaced by -Cl in a four step reaction discussed previously. A large number of experiments were needed to ascertain the optimum conditions required for obtaining the best yields of the desired product, 0,0-diethyl thiophosphoryl chloride.
<table>
<thead>
<tr>
<th>Weight (EtO)2PSSH in grams</th>
<th>Gain in Weight Chlorine in grams</th>
<th>Temp. °C.</th>
<th>Time min.</th>
<th>Distillation Fractions °C./mm. Yield (g.)</th>
<th>Yield based on (EtO)2PSSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>85</td>
<td>30-50</td>
<td>—</td>
<td>28-72/3 92</td>
<td>60.5</td>
</tr>
<tr>
<td>352</td>
<td>98</td>
<td>30-100</td>
<td>60</td>
<td>30-55/7 1.564</td>
<td>42.5</td>
</tr>
<tr>
<td>343</td>
<td>186</td>
<td>30-70</td>
<td>60</td>
<td>62-73/5 2.9</td>
<td>unsuccessful</td>
</tr>
<tr>
<td>71a</td>
<td>38</td>
<td>30-50</td>
<td>—</td>
<td>75-77/6 1.456</td>
<td>unsuccessful</td>
</tr>
<tr>
<td>101</td>
<td>35</td>
<td>30-50</td>
<td>19</td>
<td>29-53/6 1.470</td>
<td>38.3</td>
</tr>
<tr>
<td>103</td>
<td>40</td>
<td>30-50</td>
<td>21</td>
<td>53-70/6 1.53b</td>
<td>34.6</td>
</tr>
<tr>
<td>101</td>
<td>36</td>
<td>30-50</td>
<td>12</td>
<td>70-75/5-6 1.470</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>30-50</td>
<td>6</td>
<td>71-78/6 1.473</td>
<td>48.5</td>
</tr>
<tr>
<td>100</td>
<td>21</td>
<td>30-50</td>
<td>9</td>
<td>55-71/7 1.470</td>
<td>71.3</td>
</tr>
<tr>
<td>100</td>
<td>23</td>
<td>30-60</td>
<td>3</td>
<td>55-70/6 1.470</td>
<td>50.5</td>
</tr>
<tr>
<td>100</td>
<td>12c</td>
<td>30-115</td>
<td>3</td>
<td>71-76/5-6 1.470</td>
<td>63.4</td>
</tr>
<tr>
<td>Weight (EtO)2PSSH in grams</td>
<td>Gain in Weight Chlorine in grams</td>
<td>Temp. °C.</td>
<td>Time min.</td>
<td>Distillation Fractions °C./mm.</td>
<td>Yield (g.)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>100</td>
<td>10°c</td>
<td>30-50</td>
<td>15</td>
<td>80-87/5-7</td>
<td>30b</td>
</tr>
<tr>
<td>200</td>
<td>61</td>
<td>25-90</td>
<td>23</td>
<td>30-50/1</td>
<td>19</td>
</tr>
<tr>
<td>200</td>
<td>61</td>
<td>25-70</td>
<td>13</td>
<td>30-50/1</td>
<td>19</td>
</tr>
<tr>
<td>200</td>
<td>61</td>
<td>20-70</td>
<td>13</td>
<td>25-50/1</td>
<td>30</td>
</tr>
<tr>
<td>200</td>
<td>61</td>
<td>25-55</td>
<td>22</td>
<td>25-50/1</td>
<td>182b</td>
</tr>
<tr>
<td>500</td>
<td>119</td>
<td>5-75</td>
<td>30</td>
<td>50-56/1</td>
<td>165b</td>
</tr>
<tr>
<td>500</td>
<td>119</td>
<td>5-75</td>
<td>30</td>
<td>61-65/1</td>
<td>308.6b</td>
</tr>
<tr>
<td>300</td>
<td>26</td>
<td>25-45</td>
<td>18</td>
<td>53-60/1</td>
<td>101b</td>
</tr>
<tr>
<td>211f</td>
<td>60</td>
<td>50-120</td>
<td>5</td>
<td>25-50/1</td>
<td>32</td>
</tr>
<tr>
<td>500</td>
<td>125</td>
<td>15-65</td>
<td>30</td>
<td>50-55/1</td>
<td>169b</td>
</tr>
<tr>
<td>500</td>
<td>125</td>
<td>210°h</td>
<td>80</td>
<td>50-55/1</td>
<td>11</td>
</tr>
<tr>
<td>200</td>
<td>41</td>
<td>25-80</td>
<td>19</td>
<td>58-62/1</td>
<td>168b</td>
</tr>
<tr>
<td>500</td>
<td>122</td>
<td>20-90</td>
<td>10h</td>
<td>30-63/2-3</td>
<td>18</td>
</tr>
</tbody>
</table>

Table VIII (cont'd)
### Table VII (cont'd)

<table>
<thead>
<tr>
<th>Weight (EtO)₂PSSH in grams</th>
<th>Gain in Weight Chlorine in grams</th>
<th>Temp. °C.</th>
<th>Time min.</th>
<th>Distillation Fractions °C./mm.</th>
<th>Yield (g.)</th>
<th>n²⁰</th>
<th>Residue Lost grams</th>
<th>Gases Lost grams</th>
<th>(EtO)₂PSCl % Yield based on (EtO)₂PSSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>107</td>
<td>25–90</td>
<td>78</td>
<td>30–60/2–3</td>
<td>21</td>
<td>1.484</td>
<td>135</td>
<td>11</td>
<td>84.3</td>
</tr>
<tr>
<td></td>
<td>60–69/2–3</td>
<td>1.477</td>
<td>8</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25–58/2</td>
<td>1.506</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57–60/2</td>
<td>1.471</td>
<td>23</td>
<td>7.5</td>
<td>90.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60–62.5/2</td>
<td>1.469</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30–57/2</td>
<td>1.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58–61/2</td>
<td>1.473</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a - Vacuum distilled (EtO)₂PSSH was used instead of the crude product.

b - This was the desired (EtO)₂PSCl product as identified by boiling range and refractive index.³⁹

c - Less chlorine was absorbed and the corresponding absence of the sulfur chlorides and the other highly chlorinated products was noted.

d - The residue was largely unchlorinated (EtO)₂PSSH.

e - % Yield based on phosphorus pentasulfide used to prepare (EtO)₂PSSH starting material.

f - The residue was rechlorinated.

g - The yield is total for both chlorinations.

h - This was the loss in weight of the chlorine tank source. It is a measure of the amount of chlorine gas used, but not totally absorbed.

i - The crude (EtO)₂PSCl product was redistilled.

j - These are the redistilled products.

### Table IX

<table>
<thead>
<tr>
<th>(RO)₂PSSH in grams</th>
<th>R</th>
<th>Gain in Weight Chlorine in grams</th>
<th>Temp. °C.</th>
<th>Time min.</th>
<th>Distillation Fractions °C./mm.</th>
<th>Yield (g.)</th>
<th>Residue Lost grams</th>
<th>Gases Lost grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>β-chloroethyl</td>
<td>8</td>
<td>30–50</td>
<td>3</td>
<td>80–135/5</td>
<td>4</td>
<td>53</td>
<td>11</td>
</tr>
<tr>
<td>100</td>
<td>allyl</td>
<td>36</td>
<td>30–60</td>
<td>23</td>
<td>unsuccessful</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the chlorination of 0,0-diethyl dithiophosphate, the optimum amount of chlorine absorption (measured by the gain in weight of the reaction flask) is approximately 20 to 30 grams per each 100 grams of 0,0-diethyl dithiophosphate. The crude product often becomes turbid at the point of optimum absorption. This is possibly due to the formation of free sulfur at this point.

The main chlorination reaction can be broken down into four distinct steps. In addition, there are numerous side reactions. The 0,0-diethyl thiophosphoryl chloride obtained in this reaction is in a semi-pure state. It is colored a light yellow due to the presence of sulfur chlorides and highly chlorinated side products. It has the same characteristic odor and reactivity as 0,0-diethyl thiophosphoryl chloride prepared from sodium ethoxide and thiophosphoryl chloride. The crude product contained a small quantity of more highly chlorinated lower boiling materials such as sulfur chlorides, 0-ethyl thiophosphoryl chloride, etc. Upon vacuum distillation of this crude product a yellow solid residue, melting at 112-124°C, after recrystallization from dioxane, remained. This material was later identified as free sulfur. The reported melting point of free sulfur was 112.8-120°C.

A number of by-products, one of which was gaseous hydrogen chloride, are formed in these reactions. The hydrogen chloride came off in copious quantities during several stages of the chlorination. In the chlorination of crude 0,0-diethyl dithiophosphate, the hydrogen chloride was accompanied by a little hydrogen sulfide. This was not the case when vacuum distilled 0,0-diethyl dithiophosphate was chlorinated. (The other side reaction products will be discussed later.)

There was some excess chlorine in the effluent gases indicating that complete absorption of the influent chlorine did not occur using laboratory techniques.
The overall chlorination reaction was discovered during our work to be:

$$2 \text{(EtO)}_2\text{PSSH} + 3 \text{Cl}_2 \longrightarrow 2 \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl}$$

There are a number of side reactions as well. Our experiments showed that this chlorination did not go in a single, simple, well-defined step, but was a several stage reaction. These stages may be illustrated as follows:

1. "Initial Step"

$$\text{(EtO)}_2\text{PSSH} + \text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSSCl} + \text{HCl}$$

The intermediate, \(\text{(EtO)}_2\text{P}^{(\text{SCl})}(\text{SH})\text{Cl}\), may be formed momentarily.

2. "Lag Step"

$$\text{(EtO)}_2\text{PSSCl} + \text{(EtO)}_2\text{PSSH} \longrightarrow \text{(EtO)}_2\text{PSS-SSp(OEt)}_2 + \text{HCl}$$

3. "Rapid Gain Steps"

$$\text{(EtO)}_2\text{PSS-SSp(OEt)}_2 + \text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSCl} + \text{(EtO)}_2\text{PSSSCl}$$

4. \(\text{(EtO)}_2\text{PSSSCl} + \text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2$$

Overall reaction then is:

$$2 \text{(EtO)}_2\text{PSSH} + 3 \text{Cl}_2 \longrightarrow 2 \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl}$$

Typical side reactions that might lead to other products such as free sulfur follow:

1. \(\text{(EtO)}_2\text{PSSH} + \text{S}_2\text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSS-SSCl} + \text{HCl}$$

2. \(\text{(EtO)}_2\text{PSS-SSCl} + \text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 + S$$

The overall reaction might be:

$$\text{(EtO)}_2\text{PSSH} + \text{Cl}_2 \quad \text{S}_2\text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSCl} + \text{HCl} + S$$

These reactions have, also, been postulated and reported by the American Cyanamid Company.\(^{11}\)

Another side reaction proposed was:

$$\text{(EtO)}_2\text{PSSCL} + \text{Cl}_2 \longrightarrow \text{(EtO)}_2\text{PSCl} + \text{SCl}_2$$

Cyanamid, also, reported using the potassium and sodium salts of \(\text{O,O-diethyl dithiophosphate}\) in the chlorination.
reaction with comparable results.11

The following table shows the possible correlation of the reactions proposed above and the experimental data observed in the laboratory.

Table X

<table>
<thead>
<tr>
<th>Period</th>
<th>Gain in Weight of</th>
<th>Loss in Weight of</th>
<th>Time</th>
<th>Temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>flask in grams</td>
<td>Cl₂ tank in grams</td>
<td>minutes</td>
<td>°C.</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>22</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>78</td>
<td>35</td>
<td>15-53</td>
</tr>
<tr>
<td>C</td>
<td>102</td>
<td>110</td>
<td>30</td>
<td>50-65</td>
</tr>
<tr>
<td>A</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>25-80</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>45</td>
<td>10</td>
<td>60-80</td>
</tr>
<tr>
<td>C</td>
<td>19</td>
<td>19</td>
<td>4</td>
<td>60-80</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>--</td>
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<td>20-40</td>
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<tr>
<td>B</td>
<td>5</td>
<td>--</td>
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</tr>
<tr>
<td>C</td>
<td>107</td>
<td>--</td>
<td>49</td>
<td>60-90</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>--</td>
<td>10</td>
<td>25-50</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>--</td>
<td>50</td>
<td>25-50</td>
</tr>
<tr>
<td>C</td>
<td>87</td>
<td>--</td>
<td>18</td>
<td>70-90</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>--</td>
<td>10</td>
<td>25-40</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>--</td>
<td>10</td>
<td>below 40</td>
</tr>
<tr>
<td>C</td>
<td>43</td>
<td>--</td>
<td>9</td>
<td>60-90</td>
</tr>
</tbody>
</table>

Period A is the "Initial Period". The reaction was

$$(\text{EtO})_2\text{PSSH} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSSCl} + \text{HCl}$$

During this period hydrogen chloride gas came off fairly rapidly and the solution became darker and more yellow.

Period B is the "Lag Period". The reaction was

$$(\text{EtO})_2\text{PSSCl} + (\text{EtO})_2\text{PSSH} \rightarrow (\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{HCl}$$

During this period hydrogen chloride was given off copiously and rapidly. Chlorine absorption during this period was very low if not negligible.

Period C is the "Rapid Gain Period". The reactions were

$$(\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + (\text{EtO})_2\text{PSSSCL}$$

$$(\text{EtO})_2\text{PSSSCL} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2$$
Hydrogen chloride was given off rapidly during the first part of this period, but the evolution fell off as the reaction progressed. The gain in weight was very rapid. The chlorination can easily be carried beyond the end-point of this reaction (see the chlorination of 0,0-diethyl thiophosphoryl chloride below). The reaction during this period was very exothermic.

It had been noted that the residues in the still pot after the 0,0-diethyl thiophosphoryl chloride had been distilled off generally solidified or became semi-solid. This solid material was originally thought to be some high molecular weight polythiophosphate, such as \((\text{EtO})_2\text{PSS-SSP(OEt)}_2\); for it contained no chlorine and was insoluble in most organic solvents.\(^{45}\) These residues were recrystallized with some difficulty from dioxane as a yellow crystalline product melting generally at about 120°C. Mixed melting points with free sulfur gave no depression in melting point as well as no difference between their individual melting points. All of these residues were readily soluble in carbon disulfide. This is strong additional evidence for their identification as free sulfur. The formation of free sulfur can be explained by the reactions\(^{11}\)

\[
(\text{EtO})_2\text{PSS-SSCl} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2 + \text{S}
\]

or\(^{46}\)

\[
2 \text{S}_2\text{Cl}_2 \rightarrow \text{S}_2 + \text{S}_2\text{Cl}_4
\]

Although it was known that the sulfur chlorides were major by-products of the reaction, even semi-pure sulfur dichloride or sulfur monochloride was never isolated from the chlorination mixture upon distillation. However, there was a great deal of indirect evidence for the formation of the sulfur chlorides in the chlorination.

It was known that the sulfur halides, sulfur dichloride and sulfur monochloride, were readily hydrolyzed in water.\(^{46}\)

\[
2 \text{S}_2\text{Cl}_2 + 2 \text{H}_2\text{O} \rightarrow \text{SO}_2 + 4 \text{HCl} + 3 \text{S} ;
\]

\[
2 \text{S}_2\text{Cl}_2 + 3 \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO}_3 + 4 \text{HCl} + 3 \text{S} ; \text{etc.}
\]
The low-boiling fractions obtained on distillation of the crude chlorination mixture were believed to contain a quantity of sulfur chlorides of some composition. These samples fumed and gave off hydrogen chloride and chlorine gases. They were deep yellow orange in color (as are pure sulfur mono- and di-chlorides) and free sulfur sublimed from these materials on standing. The following table shows the relation between forerun low-boiling fractions, pure 0,0-diethyl thiophosphoryl chloride and pure sulfur monochloride.

<table>
<thead>
<tr>
<th>Product</th>
<th>Deposition of Sulfur</th>
<th>Fuming of Chlorine</th>
<th>Acidity of Water Layer</th>
<th>Approx. time of Hydrolysis</th>
<th>Color</th>
<th>Odor</th>
</tr>
</thead>
<tbody>
<tr>
<td>foreruns</td>
<td>large amt.</td>
<td>strong</td>
<td>very acidic</td>
<td>1 hr.</td>
<td>yellow</td>
<td>unpleasant</td>
</tr>
<tr>
<td>S₂Cl₂</td>
<td>large amt.</td>
<td>strong</td>
<td>very acidic</td>
<td>instantly</td>
<td>yellow</td>
<td>unpleasant</td>
</tr>
<tr>
<td>pure (EtO)₂PSCl</td>
<td>none</td>
<td>very little</td>
<td>weakly</td>
<td>over 24</td>
<td>colorless</td>
<td>pleasant</td>
</tr>
</tbody>
</table>

These simple hydrolysis experiments indicate that the foreruns contain a great deal of sulfur chlorides of some composition.

The chlorination of pure 0,0-diethyl thiophosphoryl chloride was carried out in the same manner as that of 0,0-diethyl dithiophosphate. The pale yellow liquid absorbed chlorine very rapidly and became increasingly darker yellow. The color finally became the color of bromine or the dichromate ion. Hydrogen chloride came off during the chlorination and the reaction was extremely exothermic.

A variety of highly chlorinated products were formed, but not identified. No unchanged 0,0-diethyl thiophosphoryl chloride remained. Free sulfur was isolated from the still pot residue. In the dry ice-acetone trap a large quantity of a brownish-red liquid was found after the vacuum distillation. This material fumed violently of chlorine gas. Free sulfur sublimed from the liquid. On reaction with water it was
instantly hydrolyzed to free sulfur and an acidic water solution. Upon being warmed to room temperature, it apparently underwent further reactions (perhaps disproportions) as its index of refraction gradually shifted toward higher values. A possible reaction might be:

$$\text{SCl}_4 \xrightarrow{\text{heat}} \text{Cl}_2 + S + \text{unknown products}$$

The index of refraction changed in twenty-four hours from $n_D^{27} = 1.466$ to $1.496$ on warming to room temperature.

In briefly summarizing the conclusions obtained from the data secured in our laboratory concerning the chlorination of $\text{O,O-diethyl dithiophosphate}$, the following might be stated:

The major product is the desired $\text{O,O-diethyl thiophosphoryl chloride}$ which is obtained in yields of about 90%.

The side products are hydrogen chloride gas, free sulfur and some sulfur chlorides.

The exact stoichiometry of the reaction has not been positively determined, but all data point to the validity of the following equation as being that most closely representing the chlorination reaction:

$$2 \,(\text{EtO})_2\text{PSSH} + 3 \text{Cl}_2 \rightarrow 2 \,(\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl}$$

It is believed that no one equation can adequately describe this chlorination due to the large number of possible side reactions and due to the complex behavior of the sulfur chlorides formed. The sulfur isolated from the reaction mixture residue upon distillation resulted from some decomposition or metathetical reaction of the sulfur chlorides formed in the main reaction.

Hydrolysis studies might provide a suitable analytical method for the determination of the chemical nature of the by-products and of the amount thereof formed in the reaction. Further hydrolysis work was not carried out in this laboratory.

The chlorination of pure $\text{O,O-diethyl thiophosphoryl chloride}$ showed that the chlorination reaction did not stop.
with the formation of O,O-diethyl thiophosphoryl chloride from O,O-diethyl dithiophosphate, but rather that the chlorination of O,O-diethyl thiophosphoryl chloride went even more readily to give highly chlorinated organic compounds and some sulfur chlorides. Early chlorination experiments where the amount of chlorine absorbed was not regulated rigidly gave similar results, namely highly chlorinated products, sulfur chlorides and no O,O-diethyl thiophosphoryl chloride.

The chlorination of pure distilled O,O-diethyl dithiophosphate proceeded in the same manner as that with crude O,O-diethyl dithiophosphate. However with the pure product, it was much easier to follow the various steps proposed for the reaction and to see the formation of sulfur in the reaction mixture. This formation of sulfur to give a turbid chlorination mixture occurred at about the point of optimum chlorine absorption. It occurred probably by a reaction of the type below:

\[(\text{EtO})_2\text{PSS-SSCl} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + 3 + \text{S}_2\text{Cl}_2\]

The fourth step of the proposed reaction mechanism allowed for the formation of sulfur monochloride which could react as follows:

\[\text{S}_2\text{Cl}_2 + (\text{EtO})_2\text{PSSH} \rightarrow (\text{EtO})_2\text{PSS-SSCl} + \text{HCl}\]

The experimental data on the chlorination substantiated the four postulated steps of the chlorination mechanism.

1. \[(\text{EtO})_2\text{PSSH} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSSCl} + \text{HCl}\]
2. \[(\text{EtO})_2\text{PSSCl} + (\text{EtO})_2\text{PSSH} \rightarrow (\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{HCl}\]
3. \[(\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{Cl}_2 \rightarrow (\text{EtO})_3\text{PSCl} + (\text{EtO})_2\text{PSSSCl}\]
4. \[(\text{EtO})_2\text{PSSSCl} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2\]

overall: \[2 (\text{EtO})_2\text{PSSH} + 3 \text{Cl}_2 \rightarrow 2 (\text{EtO})_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl}\]

The final step needed for the new process for Parathion was developed by the Niagara laboratories.\(^{12}\) This work was verified in our laboratory. The new method employed the materials of the old German method\(^{8}\) except that an ionic,
polarizable solvent was used instead of inert, non-polar xylene, toluene or chlorobenzene. The new solvents employed were high boiling alcohols or better still the glycols. A typical reaction was:

\[
\text{(EtO)}_2\text{PSO} + \text{NaO}_2 \rightarrow \text{(EtO)}_2\text{PSO(OH)}_2 + \text{NaCl}
\]

Table XII

<table>
<thead>
<tr>
<th>Moles</th>
<th>Moles</th>
<th>Glycol</th>
<th>ml.</th>
<th>Time Temp.</th>
<th>n^D_20</th>
<th>Yield Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EtO)_2PSO</td>
<td>NaO2</td>
<td>Solvent</td>
<td>Solvent min.</td>
<td>°C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.255</td>
<td>0.255</td>
<td>diethylene</td>
<td>150</td>
<td>60</td>
<td>70-90</td>
<td>1.530</td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>diethylene</td>
<td>150</td>
<td>60</td>
<td>90-110</td>
<td>1.538</td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>ethylene</td>
<td>100</td>
<td>60</td>
<td>90-110</td>
<td>1.546</td>
</tr>
<tr>
<td>0.20</td>
<td>0.20</td>
<td>ethylene</td>
<td>100</td>
<td>60</td>
<td>90-110</td>
<td>1.538</td>
</tr>
<tr>
<td>0.1325</td>
<td>0.1325</td>
<td>diethylene</td>
<td>75</td>
<td>60</td>
<td>70-90</td>
<td>1.524</td>
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<tr>
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<td>0.1325</td>
<td>diethylene</td>
<td>75</td>
<td>60</td>
<td>70-120</td>
<td>1.532</td>
</tr>
<tr>
<td>0.1325</td>
<td>0.1325</td>
<td>diethylene</td>
<td>55</td>
<td>60</td>
<td>90-105</td>
<td>1.526</td>
</tr>
<tr>
<td>0.1325</td>
<td>0.1325</td>
<td>triethylene</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.265</td>
<td>0.265</td>
<td>ethylene</td>
<td>75</td>
<td>60</td>
<td>90-110</td>
<td>1.540</td>
</tr>
<tr>
<td>0.1325</td>
<td>0.1325</td>
<td>diethylene</td>
<td>75</td>
<td>60</td>
<td>80-95</td>
<td>1.534</td>
</tr>
<tr>
<td>0.147</td>
<td>0.147</td>
<td>diethylene</td>
<td>75</td>
<td>60</td>
<td>80-95</td>
<td>1.535</td>
</tr>
<tr>
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<td>0.795</td>
<td>diethylene</td>
<td>250</td>
<td>60</td>
<td>80-90</td>
<td>1.534</td>
</tr>
<tr>
<td>0.795</td>
<td>0.795</td>
<td>ethylene</td>
<td>35</td>
<td>60</td>
<td>80-90</td>
<td>1.530</td>
</tr>
</tbody>
</table>

a - The (EtO)_2PSO product used was impure.
b - This product was molecularly distilled at 110-170°C./0.005-0.01mm.; n^D_20 = 1.532.
c - The adjectives describe the nature of the Parathion product.

The reaction went in nearly quantitative yields in a very short period of time compared to the old German method. While each of the reactions was run for sixty minutes in the laboratory, the reaction actually went to completion in about ten minutes. This is, indeed, a great saving of time over the twenty-four hours needed for the German method, and also over the Cyanamide method using water or ethyl alcohol as solvent, with a reaction period of one to two hours. The course of the reaction can be followed rather closely by the color of the reaction mixture. The color changed from the brilliant carmine red of the anhydrous sodium p-nitrophenoxide to orange and finally to the turbid brown-yellow of the 0,0-diethyl-0-p-nitrophenyl thio phosphate (Parathion) with sodium chloride.
in fine suspension.

These main topics make up the fundamental part of this section of the thesis. However, in the development of these reactions a number of other experiments closely related to these were undertaken.

1. We attempted to prepare Parathion in a single experiment by an inverted German method. This experiment was unsuccessful although Cyanamid reported a successful preparation of Parathion in this manner.\(^\text{11}\)

\[
\text{FSCl}_3 + \text{NaO} \xrightarrow[\text{PCl}_3]{} \text{NO}_2 \xrightarrow[\text{OSPCl}_2]{} \text{NaCl}
\]

\[
\text{NO}_2 \xrightarrow[\text{OSPCl}_2]{} 2 \text{NaOEt} \rightarrow (\text{EtO})_2 \text{PSO} \xrightarrow[\text{NO}_2]{} 2 \text{NaCl}
\]

2. It had been reported by Niagara\(^\text{12}\) that the percentage of nitro group in Parathion as found by their analytical method was lower than that predicted from the structural formula of Parathion. It was postulated that Parathion might exist as a mixture of two tautomeric forms.

\[
\begin{align*}
\text{Normal, Benzoid} & \quad (\text{EtO})_2 = P = S \\
\text{Abnormal, Quinoid} & \quad (\text{EtO})_1 = P = S
\end{align*}
\]

It was expected that, if there were an appreciable quantity of the quinoid form present in a Parathion sample, a 2,4-dinitrophenyl hydrazone might be formed by reaction with 2,4-dinitrophenyl hydrazine. However, no such hydrazone was formed. It is not believed that much of the quinoid form, if any at all, actually exists.

3. A silane derivative, an analogue of Parathion, was prepared using O,O-diethyl thiophosphoryl chloride and p-hydroxyphenyl trichlorosilane. The p-hydroxyphenyl trichlorosilane was prepared by H. S. Sadow\(^\text{47}\) using phenol and silicon tetrachloride with a Reimer-Tiemann rearrangement. It is known that such silane compounds hydrolyze easily to form
silicon resins, plastics, films, etc. It was hoped that by coupling in one molecule the toxic components of Parathion with the trichlorosilane group (-SiCl₃) a permanent insecticidal film might be prepared. With this in mind the following compound, 0,0-diethyl-0-p-trichlorosilanophenyl thiophosphate, was prepared and sent to Niagara for testing.

\[(\text{EtO})₂\text{PSCl} + \text{HO} \overset{\text{PCL₃}}{\rightarrow} (\text{EtO})₂\text{PSCO} \overset{\text{SiCl₃}}{\rightarrow} (\text{EtO})₂\text{PSO} \overset{\text{SiCl₃}}{\rightarrow} \text{HCl}\]

4. The reaction of phosphorus pentasulfide, absolute ethyl alcohol and p-nitrophenol was run by this proposed equation.

\[\text{P₆S₈} + 2 \text{HO} \overset{\text{NO₃}}{\rightarrow} 4 \text{EtOH} \rightarrow 2 (\text{EtO})₂\text{PSCO} \overset{\text{NO₃}}{\rightarrow} 3 \text{H₃S}\]

(Note the similarity of this reaction to that employed for the preparation of 0,0-diethyl dithiophosphate.)

A black-brown liquid was obtained in a yield of 74\%. The refractive index \(n_D^{23}\) was 1.533. Some 0,0-diethyl dithiophosphate was obtained by distillation of this product. Some unreacted p-nitrophenol was recovered as well from this unsuccessful reaction.

5. The reaction of

\[(\text{EtO})₂\text{PSSH} + \text{NaO} \overset{\text{NO₃}}{\rightarrow} (\text{EtO})₂\text{PSO} \overset{\text{NO₃}}{\rightarrow} \text{NaSH}\]

for the preparation of Parathion was equally unsuccessful. It gave as the product, a turbid viscous material \(n_D^{25} = 1.582\) which finally crystallized on standing.

6. The heating of 0,0-diethyl dithiophosphate in a sealed bomb gave a black liquid and a great deal of hydrogen sulfide gas.

7. The heating of 0,0-diethyl dithiophosphate and p-nitrophenol for the attempted formation of Parathion by the following reaction was, also, tried without success.

\[(\text{EtO})₂\text{PSSH} + \text{HO} \overset{\text{heat}}{\rightarrow} (\text{EtO})₂\text{PSCO} \overset{\text{NO₃}}{\rightarrow} \text{H₃S}\]

Various conditions were used; heating in a bomb or closed vessel, in a test tube and with glycol solvent at high temperature. However, the reaction was unsuccessful in every case.
8. The reaction

\[(\text{EtO})_2\text{PSSH} + \text{Cl}_2 \overset{\text{heat}}{\rightarrow} (\text{EtO})_2\text{PSS} \overset{\text{NO}_2}{\rightarrow} + \text{HCl}\]

was unsuccessful. A black liquid which solidified on cooling was formed. The thio analogue of Parathion did not seem to be formed.

9. The treatment of crude O,O-diethyl dithiophosphate with alkali solution led to the following results and scheme:

\[\text{crude } (\text{EtO})_2\text{PSSH} \text{ } n^20 = 1.508\]

\[\downarrow \text{aqueous KOH}\]

\[
\begin{cases}
\text{(gas)} \\
\text{(gas)} \\
\text{aqueous layer} \\
\text{insol. black} \\
\text{precipitate} \\
\text{filtrate} \\
\text{wash with} \\
\text{ether} \\
\text{(black ppt)} \\
\text{extract with} \\
\text{ether twice} \\
\text{neutral liquid} \\
\text{(tan ppt)} \\
\text{water} \\
\text{extract} \\
\text{extract} \\
\text{acidify with} \\
\text{6 N HCl} \\
\text{ether soln} \\
\text{evaporate} \\
\text{orange oil} \\
\text{neutral} \\
\text{ether layer} \\
\text{discard} \\
\text{aqueous layer} \\
\text{evaporate} \\
\text{greenish} \\
\text{acidic oil} \\
\text{pure } (\text{EtO})_2\text{PSSH} \\
\text{n}^20 = 1.504 \\
\text{titrated as 101.5%} \\
(\text{EtO})_2\text{PSSH by our analytical method}
\end{cases}
\]

The total recovery of \((\text{EtO})_2\text{PSSH}\) and neutral products was 47.8%.
10. The method of Mastin\textsuperscript{39} for the preparation of 0,0-diethyl-0-potassium thiophosphate was attempted in another preparation of Parathion.

\begin{align*}
(\text{EtO})_2\text{PSCl} + 2 \text{KOH} & \xrightarrow{\text{absolute alcohol}} (\text{EtO})_2\text{PSOK} + \text{KCl} + \text{H}_2\text{O} \\
(\text{EtO})_2\text{PSOK} + \text{Cl} \equiv \text{NO}_2 & \xrightarrow{\text{alcohol glycol}} (\text{EtO})_2\text{PSO} \equiv \text{NO}_2 + \text{KCl}
\end{align*}

The first reaction went well as reported by Mastin, but the second step using p-nitrochlorobenzene was unsuccessful.

A comparison between the old German synthesis\textsuperscript{8} of Parathion and the new synthesis developed in our laboratory will show the fundamental work and importance of this project. The following table shows the relation between the various processes.

<table>
<thead>
<tr>
<th>Process</th>
<th>Starting Materials</th>
<th>Product Sought</th>
<th>Max. Time hours</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>German\textsuperscript{8}</td>
<td>Sodium Absolute Alcohol Thiophosphoryl Chloride</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>6-8</td>
<td>70-80</td>
</tr>
<tr>
<td>Our Synthesis and Cyanamid\textsuperscript{11}</td>
<td>Chlorine gas Phosphorus Penta sulfuride Absolute Alcohol</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>3</td>
<td>80-93</td>
</tr>
<tr>
<td>German\textsuperscript{8}</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>Parathion</td>
<td>24</td>
<td>80-90</td>
</tr>
<tr>
<td>Our Synthesis and Niagara\textsuperscript{11,12}</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>Parathion</td>
<td>1</td>
<td>95-100</td>
</tr>
<tr>
<td>Cyanamid\textsuperscript{11,13}</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>Parathion</td>
<td>2</td>
<td>64-75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sodium Absolute Alcohol Thiophosphoryl Chloride</th>
<th>(EtO)\textsubscript{2}PSCl</th>
<th>6-8</th>
<th>70-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td>Starting Materials</td>
<td>Product Sought</td>
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<td>German\textsuperscript{8}</td>
<td>Sodium Absolute Alcohol Thiophosphoryl Chloride</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>6-8</td>
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<td>German\textsuperscript{8}</td>
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<td>80-90</td>
</tr>
<tr>
<td>Our Synthesis and Niagara\textsuperscript{11,12}</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>Parathion</td>
<td>1</td>
<td>95-100</td>
</tr>
<tr>
<td>Cyanamid\textsuperscript{11,13}</td>
<td>(EtO)\textsubscript{2}PSCl</td>
<td>Parathion</td>
<td>2</td>
<td>64-75</td>
</tr>
</tbody>
</table>

The German processes were less feasible from the economic standpoint for many reasons including the longer time of reaction, lower yields, greater hazards in the use
of starting materials (metallic sodium) and the greater initial cost of starting materials. With all these things in mind one sees that the new synthesis we have developed for Parathion is significant commercially. In addition it has contributed to the knowledge of the fundamental chemistry of the organic thiophosphate field. It is quite certain that Cyanamid is now using this process for Parathion on an industrial scale.
EXPERIMENTAL

Thiophosphoryl chloride; \( \text{P}3\text{Cl}_4 \).

Although thiophosphoryl chloride is commercially available, some experiments were run using the method of Thorpe.\(^{30,31}\)

Phosphorus pentasulfide (Baker) (111.1 grams, 0.5 mole) and phosphorus pentachloride (Mallinckrodt) (312.5 grams, 1.5 moles), both finely powdered, were intimately mixed together in a large beaker (1000 ml.) with a stirring rod with some hydrogen chloride fuming off.

The solid mixture was added to a medium sized (ca. 2000 ml.) steel bomb fitted with a small screw opening. The bomb was completely sealed and then heated to above 150°C. using Meker and Bunsen burners for a thirty minute period.

The bomb was cooled and opened. A clear dark brown liquid remained after a small amount of solid black residue was removed by filtration. A crude yield of 300 grams (71\%) was obtained. Distillation at 118-127°C./1 atm. gave a fairly pure sample of thiophosphoryl chloride in a yield of 265 grams (63\%). The material was almost colorless. The reported boiling point was 125°C.\(^{32,33}\)

0,0-Dimethyl thiophosphoryl chloride \( \text{(EtO)}_2\text{P}3\text{Cl}_4 \).

The previous methods\(^8,34,35\) for the preparation of this compound were of this nature.

In a 5-liter 3-necked round bottomed flask fitted with a mechanical stirrer and reflux condenser was placed absolute ethyl alcohol (Commercial Gold Shield) (1700 ml.). In order to make about a 15\%(by weight) solution of sodium ethoxide in absolute alcohol, metallic sodium (92 grams, 4 moles) was added to the alcohol piecewise over a two hour period.

In another 5-liter 3-necked round bottomed flask fitted with a mechanical stirrer and a 2 liter dropping funnel were placed absolute alcohol (200 ml.), benzene (100 ml.) and thiophosphoryl chloride (Niagara or Eastman) (339 grams, 2 moles). The material was cooled in an ice-salt bath to
about 0°C. The sodium ethoxide solution (4 moles) was added dropwise to the thiophosphoryl chloride solution over a 4 1/2 hour period with the temperature being kept below 5°C throughout. The mixture was stirred for thirty minutes at 0-5°C. after all the sodium ethoxide had been added. The mixture was viscous and milky due to the sodium chloride formed during the reaction.

The mixture was extracted with three liters of ice water and a small amount of chloroform to help facilitate the separation of the product from the water layer. A heavy yellow oil, the desired product, 0,0-diethyl thiophosphoryl chloride, separated at the bottom of the separatory funnel. The oil was dried over anhydrous sodium sulfate. The oil was then vacuum distilled. A yield of 299 grams (79.3%) of 0,0-diethyl thiophosphoryl chloride was obtained distilling at 69-73°C./5mm. (nD^20 = 1.472). On redistillation 263 grams (88% yield) of this product, boiling at 77.5-78.5°C./6mm. (nD^20 = 1.472), was obtained. The reported boiling range was 96-99°C./25mm. 39 Calculated for C₄H₁₀O₂P₂Cl₂: % Cl = 18.80, % P = 16.42, % S = 17.00; found % Cl = 18.96, % P = 16.64, % S = 17.76.

0,0,0-Triethyl thiophosphate ((EtO)₃P).  
Metallic sodium (27.2 grams, 1.18 moles) was added piecewise to absolute ethyl alcohol (Commercial Gold Shield) (520 ml.) in a 1-liter 3-necked round bottomed flask fitted with a reflux condenser and a mechanical stirrer and cooled in an ice bath. The material was stirred for three to four hours in order to get all the sodium ethoxide into solution.

Thiophosphoryl chloride (Niagara or Eastman) (100 grams, 0.59 mole) was added rapidly through a dropping funnel in about ten minutes to the sodium ethoxide solution in the flask described above. 39 The flask was kept in an ice bath, but the excessive heat of reaction caused the temperature to rise to the reflux temperature (78°C.) of the alcohol solvent. After one hour of stirring at room temperature, the milky
mixture was poured into three times its volume of ice water. This dissolved the sodium chloride formed in the reaction. The product, O,O,O-triethyl thiophosphate, separated out as a yellow oil (crude yield was 105 grams). The material was dried in ether solution over calcium chloride. The product was vacuum distilled at 85-95°C./8mm. in a yield of 79 grams (71.2%). It had a refractive index (n_D) of 1.456 and gave a negative Beilstein halogen test. The reported boiling range was 105-106°C./20mm.\(^9\)

**O-Ethyl thiophosphoryl chloride (EtOPSCl\(_2\)).**

Thiophosphoryl chloride (Niagara or Eastman) (339 grams, 2 moles) was added to dry benzene solvent (1400 ml.) in a 5-liter 3-necked round bottomed flask fitted with a thermometer, mechanical stirrer and dropping funnel. The temperature was maintained below 5°C. throughout the entire reaction by immersion of the flask in an ice-salt bath.\(^9\)

Pyridine (316 grams, 4 moles), absolute ethyl alcohol (Commercial Gold Shield) (184 grams, 4 moles) and dry benzene (300 ml.) were placed in a 1-liter dropping funnel. The solution was then added dropwise to the thiophosphoryl chloride solution over a three hour period. The mixture was allowed to stir for an additional four hours.

The pyridine hydrochloride formed during the reaction was not filtered off. The batch was washed three times with 2000 ml. portions of ice water to remove the pyridine hydrochloride. The wash water was neutral (pH 6). The benzene layer was dried over anhydrous sodium sulfate overnight.

The benzene solution was then vacuum distilled to give a 92.5% recovery of the benzene solvent. The product, O-ethyl thiophosphoryl chloride, was vacuum distilled at 57-79°C./6mm. in a yield of 224 grams (60%). The refractive index (n_D) was 1.495. It gave a very strongly positive Beilstein halogen test. The reported boiling range is 68°C./20mm.\(^4\)
Sodium p-nitrophenoxide (Niagara) was yellow as the ordinary hydrate, but was a brilliant brick red when in the anhydrous state. It was necessary that the material be made anhydrous by heating for ninety minutes in an oven at 110-115°C. Anhydrous sodium p-nitrophenoxide (42.7 grams, 0.265 mole) was ground to a fine powder in a mortar. It was then placed in a 500-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, thermometer and reflux condenser with a calcium chloride drying tube. The chlorobenzene (Eastman) solvent (150 ml.) and 0,0-diethyl thiophosphoryl chloride (50 grams, 0.265 mole) were added. The mixture was refluxed for 12 1/2 hours at 125-135°C. The color changed from the red of anhydrous sodium p-nitrophenoxide to the brown of the Parathion as reaction took place.

The material was cooled and the sodium chloride formed was filtered off in a yield of 13 grams (85%). The chlorobenzene solvent was removed from the filtrate by vacuum distillation at 22-30°C./7mm. with a 82.5% recovery. The residue from this distillation was the desired Parathion product in a yield of 69 grams (90%). The refractive index ($n_D^{23}$) was 1.532. The product gave a negative Beilstein halogen test. It was medium brown in color and had a peculiarly characteristic odor. The physical properties correspond to those of commercial samples.12

The product was molecularly distilled using a Hickman still at 110-170°C./0.005-0.01mm. to give a light orange clear liquid of high purity ($n_D^{23} = 1.537$).

When the reactants were refluxed for only seven hours, the yield was 85.5%. Thus the reflux time does not seem to be too critical, although the reactants must be refluxed till all the red color of the anhydrous sodium p-nitrophenoxide has disappeared.
0,0-Diethyl dithiophosphate ((EtO)₂PSSH).

Phosphorus pentasulfide (Niagara or Baker) (1333.8 grams, 6 moles) and absolute ethyl alcohol (Commercial Gold Shield) (1104 grams, 24 moles) were placed in a 5-liter 3-necked round bottomed flask fitted with a mechanical stirrer, an efficient reflux condenser and a thermometer. The slurry was rapidly stirred and the flask was surrounded by an ice bath to maintain the temperature below 50°C, for about one hour in order to avoid too vigorous a reaction. Hydrogen sulfide gas was evolved in copious quantities with an accompanying spontaneous rise in the temperature as reaction took place. The temperature was then raised to 90-110°C, for another hour (thirty minutes were needed to raise the temperature from 50 to 100°C.) in order to assure complete reaction.

The solution became black as the hydrogen sulfide was evolved and the 0,0-diethyl dithiophosphate was formed. The materials were then cooled and filtered to remove a small quantity of unreacted phosphorus pentasulfide. The filtrate was a black liquid saturated with hydrogen sulfide.

The crude product, 0,0-diethyl dithiophosphate, was obtained in a yield of 2175 grams (97.4%). For our purposes this crude material was more than satisfactory, but it could be purified by vacuum distillation or by extraction with alkali (see page 35). The crude product could be vacuum distilled at 84-85°C./1mm. for a yield of 277 grams out of 500 grams (75.5%). The distilled product was a water-clear liquid with a refractive index (nD⁰) of 1.508.

The method described above for the preparation of 0,0-diethyl dithiophosphate could be applied to low-molecular weight aliphatic alcohols such as n-butyl, but with other types of alcohols such as benzyl and cinnamyl, the reaction above did not work in the manner described above.

0,0-Diethyl thiophosphoryl chloride ((EtO)₂PSCl).

Step I- (EtO)₂PSSH + Cl₂ → (EtO)₂PSCl + HCl
Step II- 

\[(\text{EtO})_2\text{PSSCl} + (\text{EtO})_2\text{PSSH} \rightarrow (\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{HCl}\]

Step III- 

\[(\text{EtO})_2\text{PSS-SSP(OEt)}_2 + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSSCl} + (\text{EtO})_2\text{PSSSCl}\]

Step IV- 

\[(\text{EtO})_2\text{PSSSCl} + \text{Cl}_2 \rightarrow (\text{EtO})_2\text{PSSCl} + \text{S}_2\text{Cl}_2\]

Overall- 

\[2 (\text{EtO})_2\text{PSSH} + 3 \text{Cl}_2 \rightarrow 2 (\text{EtO})_2\text{PSSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl}\]

This is a typical chlorination experiment:

0,0-Diethyl dithiophosphate (500 grams, 2.68 moles) was placed in a 500-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and chlorine gas inlet tube. The flask was kept in an ice bath to maintain the temperature below 90°C. during the very exothermic chlorination reaction. Chlorine gas was passed in at a moderate rate to chlorinate the 0,0-diethyl dithiophosphate. The progress of the chlorination reaction was followed by the rise in temperature, turbidity (free sulfur was formed as a by-product in a side reaction at about the end of the desired reaction), gaseous by-products and the gain in weight of the reactants in the flask. Chlorine was absorbed at the ratio of about 20 to 30 grams per each 100 grams of crude 0,0-diethyl dithiophosphate being chlorinated under the optimum conditions for the maximum yield of the desired product, 0,0-diethyl thiophosphoryl chloride.

<table>
<thead>
<tr>
<th>Period</th>
<th>Gain in Weight of Reactants (grams)</th>
<th>Time (Minutes)</th>
<th>Approx. Temp. Range °C</th>
<th>Gaseous Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I</td>
<td>10</td>
<td>10</td>
<td>25-50</td>
<td>little $\text{H}_2\text{S}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>much $\text{HCl}$</td>
</tr>
<tr>
<td>Step II</td>
<td>10</td>
<td>50</td>
<td>25-50</td>
<td>less $\text{H}_2\text{S}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>more $\text{HCl}$</td>
</tr>
<tr>
<td>Step III</td>
<td>57</td>
<td>15</td>
<td>70-90</td>
<td>$\text{HCl}$ off copiously</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>less $\text{HCl}$ than in Step III</td>
</tr>
<tr>
<td>Step IV</td>
<td>30</td>
<td>3</td>
<td>70-90</td>
<td></td>
</tr>
</tbody>
</table>

The reactants turned a turbid green color due to the presence of sulfur monochloride, free sulfur and related products. The green turbid liquid was filtered to give a yield of 600 grams of crude 0,0-diethyl thiophosphoryl chloride.

This material was then vacuum distilled in the usual manner through a short Vigreux column. A forerun of sulfur
chlorides and other highly chlorinated products was obtained at 30-60°C./2-3 mm. in a yield of 21 grams. Semi-pure 0,0-diethyldithiophosphoryl chloride was obtained in a yield of 425 grams (2.26 moles, 84.3%). The liquid was a pale greenish yellow with a boiling range of 60-69°C./2-3 mm. with a refractive index \(n_D^{25}\) of 1.477. This crude product was then redistilled at 2 mm. to give a little forerun (7 grams) and pure, colorless 0,0-diethyl thiophosphoryl chloride with a boiling range of 57-60°C. (106 grams) \(n_D^{25} = 1.471\) and 60-62°C. (300 grams) \(n_D^{25} = 1.469\). The total yield was 405 grams (2.16 moles, 80.5%). The reported boiling range was 96-99°C./25 mm.\(^{39}\)

**Chlorination Product of \((\text{EtO})_2\text{PSCl}\).**

0,0-Diethyl thiophosphoryl chloride (200 grams, 1.06 moles) was chlorinated in exactly the same manner as 0,0-diethyl dithiophosphate above.\(^{11}\) The weight of the reaction mixture increased 70 grams in ten minutes as the color changed from a pale yellow to a brilliant orange red (color of bromine). Considerable quantities of hydrogen chloride gas were given off during the course of the chlorination reaction. The reaction was extremely exothermic. Sulfur chlorides were formed as the resulting liquid fumed violently in the air.

The material was fractionated to give:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Boiling Range °C./mm.</th>
<th>(n_D^{27})</th>
<th>Yield grams</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35-52/1-2</td>
<td>1.493</td>
<td>52</td>
<td>orange</td>
</tr>
<tr>
<td>2</td>
<td>52-57/1-2</td>
<td>1.443</td>
<td>75</td>
<td>yellow-orange</td>
</tr>
<tr>
<td>3</td>
<td>57-65/1-2</td>
<td>1.455</td>
<td>14</td>
<td>yellow</td>
</tr>
</tbody>
</table>

Free sulfur (m.p. = (116) 120-125°C.) crystallized out of the orange liquid residue (yield 44 grams) on cooling and standing.

In the dry ice-acetone trap, a red-brown liquid (the color of bromine) with a reactive index of 1.466 \(n_D^{27}\) was isolated. The liquid fumed very strongly. When five grams of this material were added to water (25 grams), complete hydrolysis occurred almost instantaneously with the formation..
of a large amount of free sulfur, heat and a homogeneous liquid phase. In this hydrolysis, the material resembled the sulfur mono- and di-chlorides very closely. In fact it may be assumed that the material actually contains some of the sulfur chlorides.

When the material was allowed to stand in a closed vessel at room temperature overnight, sulfur sublimed from the original material; the refractive index \( n^2_D \) changed from 1.466 to 1.496; and chlorine gas was evolved. This behavior, also, resembles that of the sulfur chlorides.

0,0-Diethyl-O-nitrophenyl thiophosphate \((\text{EtO})_2\text{PSO}(\text{NO}_2)\)

Parathion; Niagara method

Anhydrous sodium \( p \)-nitrophenoxide (Niagara) (21.4 grams, 0.1325 mole) and diethylene glycol solvent (75 ml.) were placed in a 250-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and dropping funnel. 0,0-Diethyl thiophosphoryl chloride (25 grams, 0.1325 mole) was placed in the dropping funnel. The slurry of the sodium \( p \)-nitrophenoxide in the diethylene glycol was heated to 70°C. to give a clear carmine red color. The 0,0-diethyl thiophosphoryl chloride was added dropwise to the rapidly stirred slurry over a ten minute period. The dropping funnel was replaced by a thermometer and the reactants were heated and stirred at 80-90°C. for another fifty minutes. The clear initial carmine red color became orange, then orange-yellow and finally yellow and turbid, due to the precipitation of insoluble sodium chloride as the reaction proceeded. The reaction could be followed by the color changes in this case as the nitro group colored the original anhydrous sodium salt a brilliant red. The reaction was essentially complete at the end of the ten minute addition period. The total reaction time used was one hour.

The slurry was cooled to 45°C. and the product was extracted with 200 ml. of water. The water dissolved the sodium chloride and it was miscible with the glycol solvent.
The product, Parathion, separated out as a dark brown oil. The upper aqueous layer was extracted three times with 20 ml. portions of chloroform. The oil and the chloroform extracts were dried over anhydrous sodium sulfate overnight. The sodium sulfate was removed by filtration and the chloroform removed by vacuum distillation at 2mm. The residue was the product, Parathion. It was a brown, non-viscous oil with a very characteristic odor. The yield was 37.5 grams (97.5%). The product had a refractive index \( n_D^{23} \) of 1.524 and gave only a very faint Beilstein halogen test due to a trace of chloroform solvent still present. This product had the same physical properties as commercial Parathion.\(^{12}\)

**0.0-Diethyl-0-p-trichlorosilanophenyl thiophosphate (\((\text{EtO})_2\text{PCl} \equiv \text{SiCl}_3\)).**

p-Hydroxyphenyl trichlorosilane, \( \text{HOC} \equiv \text{SiCl}_3 \) (prepared by H. S. Sadow) (22.8 grams, 0.1 mole) was dissolved in 80 ml. of dry xylene solvent in a 200-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser.\(^{8}\) 0.0-Diethyl thiophosphoryl chloride (18.9 grams, 0.1 mole) and a trace of phosphorus trichloride catalyst were added quickly to the stirred solution.\(^{37}\) No apparent reaction took place at room temperature. The materials were then heated to the reflux temperature of xylene with the gentle evolution of hydrogen chloride gas occurring accompanied by a little foaming. The materials were refluxed for twenty hours with the color changing from colorless to yellow to light brown to a reddish brown finally. The solution was vacuum distilled at 1mm. to remove the xylene solvent leaving a residue of 35 grams (92.5%). The product was a non-viscous, brown liquid. It hydrolyzed instantly when it was added to water with the \(-\text{SiCl}_3\) group being converted to \(-\text{Si(OH)}_3\) or \(-\text{SiO(OH)}_2\).\(^{48}\)

**0.0-Diethyl-0-potassium thiophosphate (\((\text{EtO})_2\text{PCl} \equiv \text{K} \)).**

Potassium hydroxide (11.8 grams, 0.21 mole) was added
to absolute ethyl alcohol (Commercial Gold Shield) (150 ml.) in a 200-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser. 0,0-Diethyl thiophosphoryl chloride (18.8 grams, 0.1 mole) was added dropwise to the alcoholic potash solution. A white precipitate, potassium chloride, came down as soon as all the 0,0-diethyl thiophosphoryl chloride was added. The reaction was highly exothermic. The material was allowed to reflux for three hours during which time it became canary yellow. The material was cooled and the potassium chloride was filtered off in a yield of 7.5 grams (0.1 mole, 100%). The solution contained the desired potassium salt.

The filtrate was evaporated on a hot plate to one-fourth its volume to give a still deeper yellow turbid solution. The solution was placed in a 200-ml. 3-necked flask with ethylene glycol solvent (75 ml.) and p-chloronitrobenzene (Eastman) (15.8 grams, 0.1 mole). The materials were heated together and refluxed at 104°C. The color changed from light yellow to an orange-red in less than ten minutes.

No potassium chloride was formed in the reaction. The materials were refluxed for five hours. Some solid material crystallized out on cooling and standing. It was unreacted p-nitrochlorobenzene. No yield of the desired product was obtained.

Alkali Treatment of Crude (EtO),PSSH.

(see outline on page 48)

(A) Crude 0,0-diethyl dithiophosphate (100 grams) was placed in a 300-ml. beaker. Concentrated potassium hydroxide solution was added till the solution was strongly alkaline to Universal pH paper. This neutralization of a strong acid with the concentrated base was very exothermic. A gas was given off during the neutralization. The gas may have been hydrogen sulfide or possibly a mercaptan. The solution was allowed to cool in an ice bath for one hour after neutralization. This resulting mixture was made up of a soluble
(A) Crude \( n^2_0 = 1.508 \)
\((\text{EtO})_2\text{PSSH} \) (100 grams)
\( \text{aqueous KCl} \)

- Gas \( \text{H}_2 \text{S} \) or mercaptan
- Oil insol. black ppt.

(B) Aqueous layer
- Wash black ppt. with ether
- Aqueous layer
- Oil (C)
- Extract twice with ether
- Ether soln
- Evaporate

(C) Water
- Ether
- Water
- Ether soln + little ppt.
- Evaporate
- Orange neutral oil (I)

(D) Black ppt.
- Black (0.3 g.)
- M.p. = 114-123\(^\circ\)C.
- Free sulfur

(E) Tan ppt.
- (E) (3 g.)
- M.p. = 39-44\(^\circ\)C.

(F) Neutral Liquid (2 g.)
- \( n = 1.507 \)

(G) Alkaline
- Acidify with 6 N HCl
- Turbid emulsion

(H) Ether
- Water layer
- Discard
- Evaporate no residue
- Orange liquid residue (1 g.)

(K) Yellow liquid (2 g.)
- B.r. = 72-82\(^\circ\)C./1mm.

(L) Yellow liquid (2 g.)
- Ether layer
- Water layer
- Discard
- Evaporate

(M) Orange liquid residue (1 g.)

Total recovery of \((\text{EtO})_2\text{PSSH}\) and neutral products was 47.8%

Pure \((\text{EtO})_2\text{PSSH}\)
\( n^2_0 = 1.504 \)
Yield = 37.5 grams
37.5% recovery
aqueous alkaline layer, a small quantity of black oil and a quantity of black-brown precipitate.

The precipitate (B) was filtered off from the filtrate (C). (B) was then washed with a quantity of ether which partially dissolved the precipitate to form a yellow ether filtrate, leaving a black-gray precipitate (D) in a yield of 0.3 gram. The melting point was 114-123°C. (D) was probably free sulfur. The ether was then evaporated after the ether solution had been dried over anhydrous sodium sulfate. A deep orange liquid was formed from which tan crystals (E) of melting point 39-44°C. (yield 3 grams) crystallized. The remaining liquid (F) was neutral and had a refractive index \(n_D\) of 1.507 (yield 2 grams).

(C) was extracted twice with ether to remove neutral compounds from the potassium salt of 0,0-diethyl dithiophosphate. The aqueous layer was yellow. The light yellow ether extract containing a little precipitate (G) was separated from the aqueous solution of the potassium salt of 0,0-diethyl dithiophosphate (H).

(G) was extracted once with water. The precipitate was insoluble, but remained in the aqueous layer (J). The ether layer was dried over anhydrous sodium sulfate. It was evaporated to give an orange liquid (I) in a yield of 5 grams. It was neutral and had a refractive index \(n_D\) of 1.495.

(I) was vacuum distilled using semi-micro equipment to give the following: (K) a yellow liquid, b.r. = 72-82°C./1mm. (2 grams) \(n_D^{20} = 1.4513\); (L) a yellow liquid, b.r. = 155-165°C./1mm. (2 grams) \(n_D^{20} = 1.5086\); and (M) an orange residual liquid (1 gram) \(n_D^{20} = 1.530\).

The water layer (J) was extracted with chloroform. After drying over anhydrous sodium sulfate and evaporation of the chloroform, no residue was found.

(H) was made acidic with 6 N hydrochloric acid solution. It took much less acid to reacidify the alkaline solution than it had potassium hydroxide originally to make the 0,0-diethyl
dithiophosphate alkaline. The clear yellow solution became very turbid and white almost instantly during the acidification due to the formation of an oil emulsion. The emulsion was extracted three times with ether. This gave a clear yellow ether extract and a yellowish clear water layer. The aqueous layer was discarded. The ether solution was dried over anhydrous sodium sulfate. The ether was then evaporated to give a greenish acidic oil (N). This was pure O,O-diethyl dithiophosphate obtained in a yield of 37.5 grams (37.5%) with a refractive index \( n_D \) of 1.504. When (N) was titrated with standardized sodium hydroxide, it showed 101.5% O,O-diethyl dithiophosphate by our analytical method, compared to the 87.4% found for the crude product (A).

**Pharmacological Actions of Parathion**

The acute toxicity and MLD\( _{50} \) (minimal lethal dose) in white mice of Parathion, \((\text{EtO})_2\text{PSO}_2\text{NO}_2\), were determined under the direction of Dr. Duane Wenzel, School of Pharmacy, University of Kansas, with the cooperation of Joseph Sam, Harvey S. Sadow and Richard A. Megredy.\(^{50}\)

**Test Animals** White mice were used for these tests. Both male and female mice were employed. The compound was given orally. About halfway through the tests a new batch of younger mice were used with a resulting lowering of the MLD\( _{50} \) value as was expected.

**Technique of Preparation of Drug and Method of Administration**

Parathion is a heavy, yellow-brown oil, insoluble in water and soluble in organic solvents. In order to prevent complication factors and physiological side effects, it was believed better not to use an oil emulsion of the Parathion lost the oil, such as olive oil, cause some effect itself; hence, a water emulsion was used. Acacia was used as the emulsifying agent. The emulsion was prepared by weighing out a small calculated amount of the Parathion oil into a 50-ml. volumetric flask, adding a small amount of acacia to the oil and sufficient water to make up the volume to 50 ml. The material was well shaken, placed in a rubber stoppered
bottle, and drawn out with a large hypodermic needle (No. 20), with shaking, into a 1-ml. calibrated syringe. The needle was then replaced with an oral stomach needle for injection into the mouse's stomach.

Each mouse was weighed and held by one person while another calculated the dose to be given. The required dose was, then, administered via the stomach tube.

Complications—There was always the danger of injecting the stomach tube into the lungs. When this occurred, no damage was usually done if none of the drug was administered. However, if some of the Parathion was given, due to the very rapid absorption in the lungs, death occurred almost simultaneously, in fact before the tube could be withdrawn from the mouse.

If the mice were not fasted overnight before administration of the drug, erratic results were obtained due to the fact that the absorption of the drug depended on the contents of the mice's stomachs. Hence to get the most consistent results, it is necessary to use fasted mice. Doses averaged around 0.30 ml. in volume and the mice averaged around 25-30 grams in weight.

![Table XIV](image)

<table>
<thead>
<tr>
<th>Relative Age of Mice</th>
<th>Dose mg./Kg.</th>
<th>Number of Deaths</th>
<th>Number Injected</th>
<th>Percentage of Deaths</th>
<th>HLD&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>older</td>
<td>30</td>
<td>2</td>
<td>7</td>
<td>28.6</td>
<td>about 35 mg.</td>
</tr>
<tr>
<td>older</td>
<td>40</td>
<td>6</td>
<td>7</td>
<td>85.7</td>
<td>per Kg.</td>
</tr>
<tr>
<td>younger</td>
<td>15</td>
<td>1</td>
<td>9</td>
<td>11.1</td>
<td>about 22 mg.</td>
</tr>
<tr>
<td>younger</td>
<td>20</td>
<td>3</td>
<td>12</td>
<td>25.0</td>
<td>per Kg.</td>
</tr>
<tr>
<td>younger</td>
<td>25</td>
<td>7</td>
<td>10</td>
<td>70.0</td>
<td></td>
</tr>
</tbody>
</table>

* Data for non-fasted mice were not tabulated, for they were not particularly valid.

Symptoms—The symptoms observed were hypersensitivity, hyperirritability, rapid breathing at first, jerky breathing
later, peripheral spasms, tonic and clonic convulsions, hind leg paralysis, stimulatory threshold lowered considerably, eyes glassy and miotic, feet reflex action movement even after death, rigor mortis setting in prematurely, death due to respiratory failure and general anticholinesterase activity.

Conclusions - MLD$_{50}$ was lower for young animals as they were more susceptible to toxic effects of acetylcholine. MLD$_{50}$ for the older mice was about 33mg./Kg. MLD$_{50}$ for the younger mice was about 22mg./Kg. Total mice injected were sixty-four (64). Total fasted mice injected were fifty-two (52). Total number of fasted mice which died of oral toxic effects of Parathion was twenty (20). Total number of fasted mice which died of accidents or invalid test doses was five (5). Total number of fasted mice which recovered from the oral toxic effects was twenty-seven (27).

The results show that the insecticide, Parathion, is a potent and very toxic agent with very great physiological effects even in very low dosages. The low MLD$_{50}$'s place this drug among the most toxic known. The results from the graph (which see) for the acute oral toxicity of Parathion are:

$\text{MLD}_{50} = 22.6 \text{ mg./Kg.} \\
\text{MLD}_{50} = 33.3 \text{ mg./Kg.}$ 

DuBois$^{29}$ found MLD$_{50}$'s in this same range for Parathion in similar experiments carried out independently. The toxicity of Parathion was due to its great irreversible inhibition of cholinesterase, the enzyme regulating the de-esterification of acetylcholine. When the cholinesterase is destroyed or inhibited reversibly or irreversibly, the acetylcholine is thus allowed to exert its physiological effects in excess producing toxic symptoms. These toxic symptoms noted were those generally associated with parasympathomimetic effects.$^{51}$
ORAL MLD 50 of PARATHION (for mice)

x = young mice
MLD 50 = 22.6 mg/kg, (log = 1.355)

O = older mice
MLD 50 = 33.3 mg/kg, (log = 1.528)
SUMMARY

The chief accomplishment of this portion of the thesis was the development of a new commercial synthesis of the important industrial insecticide, Parathion.

This new synthesis consisted of three steps, all of which went in excellent yields.

1. \[ \text{P}_2\text{S}_5 \text{O} + 4 \text{EtOH} \rightarrow 2 \text{(EtO)}_2\text{PSSH} + \text{H}_2\text{S} \quad 95-97.5\% \]
2. \[ 2 \text{(EtO)}_2\text{PSSH} + 3 \text{Cl}_2 \rightarrow 2 \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl} \quad 90-94.5\% \]
3. \[ \text{(EtO)}_2\text{PSCl} + \text{NaO}\text{Cl} \rightarrow 2 \text{(EtO)}_2\text{PSCl} + \text{NaCl} \quad 95-100\% \]

Overall yields were 88-93%.

The starting materials employed were readily available and far less expensive than those used in the former process. The hazards involved in the former process were eliminated. The chemical operations were simpler and less time was needed to bring the reactions to completion than in the old process.

Table XIII (page 36) shows a comparison between the various processes developed for the synthesis of Parathion in regard to starting materials, time of reaction and percent yields.

The study of the chlorination of 0,0-diethyl dithiophosphate and the possible mechanism of this reaction was of great interest. The chlorination was found to consist of essentially four major steps:

1. \[ \text{(EtO)}_2\text{PSSH} + \text{Cl}_2 \rightarrow \text{(EtO)}_2\text{PSSCl} + \text{HCl} \]
2. \[ \text{(EtO)}_2\text{PSSCl} + \text{(EtO)}_2\text{PSSH} \rightarrow \text{(EtO)}_2\text{PSS-SPP(OEt)}_2 + \text{HCl} \]
3. \[ \text{(EtO)}_2\text{PSS-SPP(OEt)}_2 + \text{Cl}_2 \rightarrow \text{(EtO)}_2\text{PSCl} + \text{(EtO)}_2\text{PSSSCL} \]
4. \[ \text{(EtO)}_2\text{PSSSCL} + \text{Cl}_2 \rightarrow \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 \]

overall: \[ 2 \text{(EtO)}_2\text{PSSH} + 3 \text{Cl}_2 \rightarrow 2 \text{(EtO)}_2\text{PSCl} + \text{S}_2\text{Cl}_2 + 2 \text{HCl} \]

In addition to the synthesis of Parathion and intermediates by both the old German method and our new synthetic
method, the following compounds of interest were prepared in good yields: thiophosphoryl chloride, \(0,0,0\)-triethyl thiophosphate, \(0\)-ethyl thiophosphoryl chloride, \(0,0\)-dibutyl dithiophosphate, other \(0,0\)-diaryl dithiophosphates, and \(0,0\)-diethyl-\(0\)-\(p\)-trichlorosilanophenyl thiophosphate.
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18. Cambi, Chimica e industria (Italy), 26, 27 (1944); C.A., 40, 3734 (1946).
19. Malatesta and Pizzotti, Chimica e industria (Milan), 27, 6 (1945); C.A., 40, 7039 (1946).
34. Pitsuichimuka, Ber., 41, 3854 (1908).
47. Sadow, Masters Thesis, University of Kansas; August 1949.
48. Sadow, H. S., private communication.
50. Wenzel, D., private communication.
This section of the thesis deals with those reactions and experiments that were carried out during the course of the research which did not contribute directly to the solution of the major problems of the thesis. These reactions are deemed to be worthy, however, of at least passing attention in their own right. The contents of this portion of the thesis will be largely experimental with only a brief discussion of the individual reactions being made.

A- Organic Phosphates other than Parathion

The organic phosphates have found increasing use in industrial fields of almost every sort. They have been used as plasticizers, medicinals, insecticides and for many other purposes. Our chief interest has been in the insecticidal potentialities of the organic phosphates.

The neutral phosphates will be considered first, followed by the acid phosphates.

The orthophosphates, $R_3PO_4$, may be prepared by the methods of Nicolai, Evans, Noller, and Carruthers. Other syntheses are, also, available. The method of Nicolai is as follows:

$$POCl_3 + 3 \text{ROH} \rightarrow R_3PO_4 + 3 \text{HCl}$$

Several experiments were run using phosphorus oxychloride and isobutyl or n-butyl alcohol. There were difficulties encountered in attempts to isolate the product and to remove the hydrogen chloride formed in the reaction. Extraction of the hydrogen chloride with sodium carbonate or sodium hydroxide solution or removal of the hydrogen chloride under partial vacuum did not work too well.

Table XV

<table>
<thead>
<tr>
<th>Moles POCl$_3$</th>
<th>Moles Alcohol</th>
<th>Temp. (°C)</th>
<th>Time (hrs.)</th>
<th>Removal of HCl</th>
<th>Boiling Range</th>
<th>$n_D^{20}$</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 isobutyl</td>
<td>3.0</td>
<td>20-100</td>
<td>1.5 vacuum</td>
<td>135-150/10$^a$</td>
<td>1.419$^a$</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>0.5 n-butyl</td>
<td>1.5</td>
<td>100</td>
<td>1.0 NaOH</td>
<td>----$^b$</td>
<td>1.416$^c$</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>0.5 n-butyl</td>
<td>1.5</td>
<td>100</td>
<td>1.0 vacuum</td>
<td>over 1.442$^d$</td>
<td>80/15$^e$</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>
a - The reported boiling range was 264°C, and \( n^2_\text{D} = 1.417. \)
b - The material was extracted with ether without any distillation.
c - The refractive index for \( \text{n-Bu}_3\text{PO}_4 \) is 1.424. \(^1\)
d - A polyphosphate and \( \text{n-butyl chloride} \) were formed.
e - The reported boiling point was 289°C, and \( n^2_\text{D} = 1.420. \)

**Tri-isobutyl phosphate (\( \text{1-Bu}_3\text{PO}_4 \)).**

Isobutyl alcohol (Eastman) (222.4 grams, 3 moles) was placed in a 1-liter 3-necked round bottomed flask fitted with a stirrer, dropping funnel and reflux condenser. The flask was cooled in an ice bath to keep it below 20°C. Phosphorus oxychloride (Monsanto) (153.3 grams, 1 mole) was added dropwise to the isobutyl alcohol over a forty-five minute period. After all the phosphorus oxychloride had been added, the temperature was allowed to rise with a considerable evolution of hydrogen chloride gas. The flask was heated on a steam bath for thirty minutes to facilitate the reaction. After the hydrogen chloride still in the solution was removed by extraction with sodium carbonate solution and by use of a partial vacuum, the residual solution was vacuum distilled. Complete reaction was not obtained in this experiment. A yield of 65 grams (24.5%) with a boiling range of 135-150°C./10mm. was obtained. It was assumed that this was the desired product, tri-isobutyl phosphate. The reported boiling point was 264°C. \(^1\)

In the case of tri-\( \text{n-butyl phosphate} \), some decomposition occurred on vacuum distillation over 80°C./15mm. This may be explained in the following known reactions: \(^17\)

1. \( 3 \text{n-Bu}_3\text{PO}_4 + \text{POCl}_3 \rightarrow \text{n-Bu}_3\text{P}_4\text{O}_{18} + 3 \text{n-BuCl} \)
2. \( 2 \text{n-Bu}_3\text{P}_4\text{O}_{18} \xrightarrow{\text{heat\,\, vacuum}} \text{decomposition into a higher polymer; presumably n-Bu}_3\text{O} \) and \( \text{n-Bu}_1\text{O}_2\text{P}_8\text{O}_{28} \)

\( \text{n-Butyl chloride} \) was found in the dry ice \( \text{CO}_2 \) trap in this case.

The method of Evans\(^4\) employs metallic sodium to form the sodium alcolholate which then in turn reacts with phosphorus oxychloride to give the desired product.
1. \( 3 \text{Na} + 3 \text{ROH} \rightarrow 3 \text{NaOR} + \frac{3}{2} \text{R}_2 \)

2. \( 3 \text{NaOR} + \text{POCl}_3 \rightarrow \text{R}_2 \text{PO}_4 + 3 \text{NaCl} \)

In this method an excess of the alcohol (ROH) was used as solvent. A modification of this procedure employed in this laboratory was the use of inert dry benzene as a supplementary solvent. This conserved the more expensive high molecular weight alcohols.

Table XVI

<table>
<thead>
<tr>
<th>Moles POCl₃</th>
<th>Alcohol Moles</th>
<th>Moles Na</th>
<th>Moles ROH (ml.)</th>
<th>Solvent</th>
<th>Time Temp.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 n-propyl 1.5+</td>
<td>1.5</td>
<td>355</td>
<td>---</td>
<td>Benzene</td>
<td>90</td>
<td>40-60</td>
</tr>
<tr>
<td>0.5 methyl (1.5 m. NaOMe)</td>
<td>500</td>
<td>---</td>
<td>120</td>
<td>40-70</td>
<td>195-200/6</td>
<td>64b</td>
</tr>
<tr>
<td>0.5 n-hexyl 1.5+</td>
<td>1.5</td>
<td>40</td>
<td>200</td>
<td>90</td>
<td>20-80</td>
<td>128-133/65.5</td>
</tr>
<tr>
<td>0.56 1-buty1 1.68+</td>
<td>1.5</td>
<td>425g</td>
<td>500</td>
<td>90</td>
<td>10-20</td>
<td>128-133/65.5</td>
</tr>
</tbody>
</table>

a - No \(\text{Me}_2 \text{PO}_4\) was isolated due to its almost infinite solubility in water which was used to remove the sodium chloride formed.

b - The purity of this product was in doubt due to possible side-reactions.

c - The reported boiling range was 128-134°C./15mm.

d - The reported boiling range was 264°C.

**Tri-n-propyl phosphate (n-Pr₃PO₄).**

n-Propyl alcohol (Eastman) (200 ml.) was placed in a 500-ml. 3-necked round bottomed flask fitted with a stirrer and reflux condenser. Metallic sodium (34.5 grams, 1.5 moles), cut into small pieces, was added slowly piecewise to the stirred alcohol. The desired sodium n-propoxide began to crystallize out of solution, so an additional 155 ml. of n-propyl alcohol was added to keep it in solution. After several hours all of the sodium had reacted to give a dark brown solution of sodium n-propoxide. This material became a slush on cooling.

This slush was transferred to a 1-liter 3-necked round bottomed flask fitted with a dropping funnel, reflux condenser, and stirrer. Phosphorus oxychloride (Monsanto) (76.5 grams, 0.5 mole) was added dropwise to the sodium n-propoxide slush over an hour period with the formation of the desired product and sodium chloride. The reaction was highly exothermic.
and the temperature rose to 60°C. No cooling bath was used. The dark brown color of the solution became lighter as the reaction progressed. The mixture was stirred for thirty minutes after all the phosphorus oxychloride had been added.

The reaction mixture was then poured into 150 ml. of ether in a 2-liter separatory funnel and washed with 600 ml. of cold water. This removed the sodium chloride and much of the unreacted n-propyl alcohol. The ether layer was again extracted with 600 ml. of cold water and then dried over anhydrous sodium sulfate. The ether was removed by vacuum distillation by water pump and the remaining n-propyl alcohol by vacuum pump. About 300 grams of n-propyl alcohol were recovered. The desired product, tri-n-propyl phosphate, distilled at 119-125°C./5-6mm. in a yield of 78.5 grams (71%). It had a very pleasant odor and was slightly yellow. The reported boiling range was 128-134°C./15mm. Tri-isobutyl phosphate (1-Bu₃PO₄).

The modification used in this laboratory employed benzene as the solvent.

iso-Butyl alcohol (Eastman) (425 grams) was treated with metallic sodium (39 grams, 1.7 moles) in a 1-liter 3-necked flask fitted with a stirrer and reflux condenser. The sodium isobutoxide formed separated out as a waxy suspension.

The entire mass of the sodium isobutoxide was dissolved in 500 ml. of dry benzene in a 2-liter 3-necked flask (in an ice bath) fitted with a mechanical stirrer, thermometer and dropping funnel. Phosphorus oxychloride (Monsanto) (86 grams, 0.56 mole) was added over an hour period at 10-20°C. The brown solution became lighter and turbid as sodium chloride formed. The material was stirred for thirty minutes after all the phosphorus oxychloride had been added.

The cool solution was then washed twice with 1000 ml. portions of ice water to remove unreacted phosphorus oxychloride, sodium chloride and some isobutyl alcohol. The benzene solution was dried over anhydrous sodium sulfate.
After the benzene was removed under partial vacuum, some isobutyl alcohol (152 grams) was recovered. The product, tri-isobutyl phosphate, distilled at 128-132°C./5-6 mm. in a yield of 97.5 grams (65.5%). The product had a very pleasant odor and was lemon yellow in color. The reported boiling point was 264°C.¹

The use of benzene does not alter the yield of the trialkyl phosphate formed by the Evans method. It merely supplants the use of excess alcohol (ROH) as solvent.

The method of Noller⁶,⁷ and Carruthers¹⁰ is as follows:

\[ 3 \text{ROH} + \text{POCl}_3 + 3 \begin{array}{c} n \end{array} \rightarrow \begin{array}{c} R_2 \end{array} \text{PO}_4 + 3 \begin{array}{c} H \end{array} \]

Tri-n-hexyl phosphate (n-Hex₃PO₄).

n-Hexyl alcohol (Eastman) (153.3 grams, 1.5 moles), pyridine (Eastman or Reilly) (118.7 grams, 1.5 moles) and benzene (280 ml.) were placed in a 1-liter 3-necked round bottomed flask fitted with a mechanical stirrer, thermometer, and dropping funnel. The flask was kept in an ice bath while phosphorus oxychloride (Monsanto) (76.7 grams, 0.5 mole) was added dropwise over an hour period at 0-10°C. The material was then heated to 35-40°C. for two hours. The reaction material was extracted three times with 500 ml. portions of cold water to remove the pyridine hydrochloride. The benzene layer was dried over anhydrous sodium sulfate. The solvent was then removed by vacuum distillation. The product, tri-n-hexyl phosphate, distilled at 185-197°C./4-5 mm. in a yield of 78 grams (44.5%). It was a colorless liquid with an olefinic odor, similar to witch hazel. This product easily decolorized potassium permanganate solution.

The three methods all give the desired products, trialkyl orthophosphates. The Evans method using the sodium alcoklates seems to be the best way whenever the alcohol used reacts sufficiently with metallic sodium. The use of benzene as solvent allows the less reactive alcohols of higher molecular weight to be employed in the Evans method.
The method of Woodstock\textsuperscript{16} using phosphorus pentoxide and trialkyl phosphate in various proportions can lead to tetra-, pyro-, meta- or tri-phosphates according to the ratio of phosphorus pentoxide to trialkyl phosphate used. The Schrader method can, also, be used for the preparation of the tetraphosphates.\textsuperscript{17}

Tetraphosphate:

\[ 2 \text{R}_3\text{PO}_4 + \text{P}_2\text{O}_5 \rightarrow \text{R}_6\text{P}_4\text{O}_{13} \]

Pyrophosphates:

\[ 4 \text{R}_3\text{PO}_4 + \text{P}_2\text{O}_5 \rightarrow 3 \text{R}_4\text{P}_2\text{O}_7 \]

Metaphosphates:

\[ \text{R}_3\text{PO}_4 + \text{P}_2\text{O}_5 \rightarrow 3 \text{RPO}_3 \]

Triphosphates:

\[ 5 \text{R}_3\text{PO}_4 + 2\text{P}_2\text{O}_5 \rightarrow 3 \text{R}_5\text{P}_5\text{O}_{10} \]

<table>
<thead>
<tr>
<th>Moles R$\text{PO}_4$</th>
<th>Moles P$_2$O$_5$</th>
<th>R Ratio of R$\text{PO}_4$/P$_2$O$_5$ Product</th>
<th>$n_D$</th>
<th>% Yield</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.188 0.094</td>
<td>n-butyl 2/1 n-Bu$_4$P$<em>4$O$</em>{13}$</td>
<td>1.437\textsuperscript{c}</td>
<td>95</td>
<td>amber, viscous</td>
<td></td>
</tr>
<tr>
<td>0.274 0.127</td>
<td>ethyl 2/1 Et$_4$P$<em>4$O$</em>{13}$</td>
<td>1.433\textsuperscript{c}</td>
<td>95.5</td>
<td>viscous</td>
<td></td>
</tr>
<tr>
<td>0.115 0.0575</td>
<td>2-ethyl- n-hexyl 2/1 Oc$_4$P$<em>4$O$</em>{13}$a</td>
<td>--</td>
<td>94</td>
<td>amber, non-viscous</td>
<td></td>
</tr>
<tr>
<td>0.188 0.047</td>
<td>n-butyl 4/1 n-Bu$_4$P$_2$O$_7$</td>
<td>1.431\textsuperscript{c}</td>
<td>95</td>
<td>amber, non-viscous</td>
<td></td>
</tr>
<tr>
<td>0.274 0.069</td>
<td>ethyl 4/1 Et$_4$P$_2$O$_7$</td>
<td>1.418\textsuperscript{a}</td>
<td>97</td>
<td>opalescent,</td>
<td>pleasant odor</td>
</tr>
<tr>
<td>0.115 0.02875</td>
<td>2-ethyl- n-hexyl 4/1 Oc$_4$P$_2$O$_7$a</td>
<td>--</td>
<td>96</td>
<td>amber, non-viscous</td>
<td></td>
</tr>
<tr>
<td>0.188 0.047</td>
<td>n-butyl 4/1 n-Bu$_4$P$_2$O$_7$</td>
<td>1.428\textsuperscript{c}</td>
<td>97</td>
<td>amber, nonviscous</td>
<td></td>
</tr>
<tr>
<td>0.155 0.155</td>
<td>2-ethyl- n-hexyl 1/1 Oc$_2$P$_3$a</td>
<td>--</td>
<td>--</td>
<td>resin,</td>
<td>viscous\textsuperscript{b}</td>
</tr>
<tr>
<td>0.155 0.155</td>
<td>&quot; 1/1 Oc$_2$P$_3$a</td>
<td>--</td>
<td>--</td>
<td>polymerized\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>0.155 0.155</td>
<td>&quot; 1/1 Oc$_2$P$_3$a</td>
<td>--</td>
<td>--</td>
<td>very reactive\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>0.137 0.137</td>
<td>ethyl 1/1 EtPO$_3$</td>
<td>--</td>
<td>83</td>
<td>amber, turbid</td>
<td></td>
</tr>
<tr>
<td>0.094 0.094</td>
<td>n-butyl 1/1 n-BuPO$_3$</td>
<td>--</td>
<td>83.5</td>
<td>clear, viscous\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>0.094 0.094</td>
<td>n-butyl 1/1 n-BuPO$_3$</td>
<td>--</td>
<td>75.5</td>
<td>very viscous, turbid</td>
<td></td>
</tr>
</tbody>
</table>
Table XVII (cont)

<table>
<thead>
<tr>
<th>Moles R₈PO₄</th>
<th>Moles P₂O₅</th>
<th>R</th>
<th>Ratio of</th>
<th>Product</th>
<th>ν²₀</th>
<th>Yield</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.115</td>
<td>0.046</td>
<td>2-ethyl-</td>
<td>5/2</td>
<td>O₅P₂O₁₀⁺⁻</td>
<td>—</td>
<td>96</td>
<td>amber, non-viscous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n-hexyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pleasant odor</td>
</tr>
<tr>
<td>0.274</td>
<td>0.110</td>
<td>ethyl</td>
<td>5/2</td>
<td>Et₅P₂O₁₀⁺⁻</td>
<td>—</td>
<td>94</td>
<td>non-viscous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pleasant odor</td>
</tr>
<tr>
<td>0.094</td>
<td>0.0375</td>
<td>n-butyl</td>
<td>5/2</td>
<td>n-Bu₅P₂O₁₀⁺⁻</td>
<td>—</td>
<td>94</td>
<td>olefinic odor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>non-viscous tan color</td>
</tr>
</tbody>
</table>

a - O₅ = 2-ethyl-n-hexyl.
b - These products are known to be somewhat unstable.¹

c - These values of the refractive indexes check closely with values reported in the literature.¹

A typical experiment of the Woodstock¹⁶ type follows:

Tetra-n-butyl pyrophosphate (n-Bu₅P₂O₁₀⁺⁻).

Tri-n-butyl phosphate (Commercial Solvents) (50 grams, 0.188 mole) was placed in a 200-ml. 3-necked round bottomed flask fitted with a mechanical stirrer and thermometer. Phosphorus pentoxide (Mallinckrodt) (6.7 grams, 0.047 mole) was added quickly and the resulting mixture was stirred for one hour. The temperature rose to about 35°C, and most of the phosphorus pentoxide dissolved to give a slightly turbid solution. The material was filtered to give a very small amount of residue and a clear amber-tan colored liquid. The yield of this liquid product was 55 grams (97%). The material had a characteristic odor.

In the experiments for the preparation of the metaphosphates, the temperature often rose to 60-65°C, and the resulting solutions were more turbid than solutions arising with the other polyphosphates. Filtration in some cases was not easily accomplished even under vacuum. Decantation was employed with several of the metaphosphates. It is known that the metaphosphate compounds are not particularly stable, especially the higher alkyl metaphosphates.¹

The preparation of alkyl acid phosphates of the types,
RH₃PO₄ and R₂HPO₄, and their amine salts also was desired for their possible use as insecticide products. Several methods were employed for the preparation of these materials.

The method of Plimmer and Burch\textsuperscript{18} was the best. The reaction was:

\[
\text{RPO}_3 + \text{ROH} \rightarrow \text{R}_2\text{HPO}_4
\]

**Di-n-butyl acid phosphate (n-Bu₂HPO₄).**

n-Butyl metaphosphate (29 grams, 0.213 mole) and n-butyl alcohol (Eastman) (15.8 grams, 0.213 mole) were mixed and shaken together in a 100-ml Erlenmeyer flask. The solution became a lighter tan in color than that of n-butyl metaphosphate. The viscosity of the solution decreased and there was a mild evolution of heat as the exothermic reaction took place. The resulting mixture was strongly acidic (PH was 2 to 4 with Universal PH paper). The yield of the di-n-butyl acid phosphate was 44.8 grams (100%).

The method of Michelhaus\textsuperscript{19}, also, gave fairly good results.

1. POCl₃ + ROH $\rightarrow$ ROPOCl₂ + HCl
2. ROPOCl₂ + 2 H₂O $\rightarrow$ RH₂PO₄ + 2 HCl

This method was satisfactory for simple aliphatic alcohols, but as phosphorus oxychloride reacted violently with amines, the use of amino alcohols in the Michelhaus method gave undesired and unknown products.

<table>
<thead>
<tr>
<th>Moles POCl₃</th>
<th>Moles ROH</th>
<th>Alcohol</th>
<th>Moles Water</th>
<th>Time</th>
<th>Temp.</th>
<th>Yield</th>
<th>% Yield</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>ethyl</td>
<td>1.00</td>
<td>75</td>
<td>0-40</td>
<td>64</td>
<td>100</td>
<td>HCl hard to remove resin to form</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>β-dimethyl-aminooethyl</td>
<td>0.50</td>
<td>45</td>
<td>0-100</td>
<td>--</td>
<td>--</td>
<td>Be salt formed</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>ethyl</td>
<td>0.84</td>
<td>3 hrs</td>
<td>0-150</td>
<td>52</td>
<td>82</td>
<td>EtOPOCl₂ not found unsuccessful</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>β-diethyl-aminooethyl</td>
<td>1.00</td>
<td>55</td>
<td>0-180</td>
<td>--</td>
<td>--</td>
<td>Resinous identity unknown</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td>β-dibenzyl-aminooethyl</td>
<td>0.10</td>
<td>6 hrs</td>
<td>0-80</td>
<td>18</td>
<td>100</td>
<td>product identity unknown</td>
</tr>
</tbody>
</table>
Ethyl diacid phosphate ($\text{Et}_2\text{HPO}_4$).

Absolute alcohol (Commercial Gold Shield) (23 grams, 0.5 mole) was placed in a 500-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and dropping funnel. Phosphorus oxychloride (Monsanto) (76.7 grams, 0.5 mole) was added dropwise over a fifteen minute period. After all the phosphorus oxychloride had been added, the temperature was allowed to rise to room temperature while hydrogen chloride was copiously evolved.

The material was transferred to a 250-ml. 1-necked flask and heated to refluxing to facilitate the evolution of hydrogen chloride. The reflux temperature rose slowly to 150°C. At that temperature the material was very fluid and light amber yellow in color. The refluxing was continued till hydrogen chloride was no longer given off. This took about two and a half hours. The color was red-brown and the material became more viscous on cooling. The product, O-ethyl phosphorus oxychloride, boiled at 150°C. The reported boiling point was 167°C.\(^{19}\) The yield was 67 grams (82%).

Water (15 grams, 0.84 mole) was added to the warm O-ethyl phosphorus oxychloride carefully to convert it to ethyl diacid phosphate. The reaction was vigorous with hydrogen chloride being given off. The material was refluxed for one hour to give ethyl diacid phosphate in a yield of 52 grams (82%). The product was a red-brown viscous liquid, soluble in water. When it was treated with barium hydroxide, ethyl barium phosphate was formed as a heavy white insoluble precipitate.

The Wielchhaus method is not applicable to amino alcohols, but worked well with simple alcohols.

The Lossen\(^{20}\) method gave good results with aliphatic alcohols.

1. $2\text{ROH} + \text{P}_2\text{O}_5 \rightarrow \text{RH}_2\text{PO}_4 + \text{RPO}_3$
2. $\text{RPO}_3 + \text{H}_2\text{O} \rightarrow \text{RH}_2\text{PO}_4$
Ethyl diacid phosphate (EtH₂FO₄).

Absolute ethyl alcohol (Commercial Gold Shield) (23 grams, 0.5 mole) was placed in an ice-cooled 200-ml, 3-necked round bottomed flask fitted with a mechanical stirrer and reflux condenser. Phosphorus pentoxide (Nallinckrodt) (35.5 grams, 0.25 mole) was added as rapidly as possible to the stirred alcohol. Most of the phosphorus pentoxide dissolved in the alcohol to give a very turbid solution. The mixture became hot as the phosphorus pentoxide reacted. Water (4.5 grams, 0.25 mole) was added after ten minutes to complete the reaction. The contents of the flask became more fluid. After another ten minutes, the material was filtered to remove any unreacted phosphorus pentoxide. The product, ethyl diacid phosphate, was a colorless, viscous liquid of pleasant odor. The yield was 53 grams (85.5%).

A very old method for the preparation of 0-ethyl phosphorus oxychloride, EtOP0Cl₂, was attempted.²¹

\[
\text{Et}_2\text{FO}_4 + 2 \text{POCl}_3 \rightarrow 3 \text{EtOP0Cl}_2
\]

0-Ethyl phosphorus oxychloride (EtOP0Cl₂).

Triethyl phosphate (Monsanto) (91 grams, 0.5 mole) was placed in a 500-ml, 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and dropping funnel. The flask was cooled in an ice bath. Phosphorus oxychloride (Monsanto) (153 grams, 1 mole) was added dropwise to the triethyl phosphate over a fifteen minute period. The colorless starting materials turned amber brown on being mixed. The material was transferred to a 500-ml, 1-necked flask fitted with a thermometer and reflux condenser. Refluxing was carried out for ten hours at temperatures of 107-142°C. The material became much darker red-brown and very viscous. The yield was 161 grams (66%).

Another method was tried for the preparation of the acid phosphates.²²

\[
3 \text{n-BuOH} + \text{P}_2\text{O}_5 \rightarrow \text{n-Bu}_2\text{HPO}_4 + \text{n-BuH}_2\text{PO}_4
\]
The method was unsuccessful. The reaction of n-butyl alcohol and phosphorus pentoxide gave a mixture of products which were not identified.

The amine salts of monocarboxylic phosphates were prepared by the reaction of amines and di-n-butyl acid phosphate.

<table>
<thead>
<tr>
<th>Table XIX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moles Bu₄HPO₄</strong></td>
</tr>
<tr>
<td>0.0476</td>
</tr>
<tr>
<td>0.0476</td>
</tr>
</tbody>
</table>

**Diethyl amine di-n-butyl phosphate (Et₂NH-Bu₄HPO₄).**

Equimolar quantities of di-n-butyl acid phosphate (0.0476 mole) and diethyl amine (Eastman) (0.0476 mole) were mixed together in a small beaker with good stirring and cooling in an ice bath. A great deal of heat was liberated rather rapidly in spite of the ice bath. The yield was 92.5%.

**Trimethyl amine di-n-butyl phosphate (Me₃N-Bu₄HPO₄).**

Di-n-butyl acid phosphate (0.0476 mole) was placed in a small beaker in an ice bath. Trimethyl amine gas (Matheson) was passed in slowly till the solution was saturated and absorbed no more trimethyl amine. The yield was 97.5%.

The hexaethyl and hexa-n-butyl tetraphosphates and the tetraethyl and the tetra-n-butyl pyrophosphates are well known insecticides. Therefore, these other organic phosphates were prepared in the hope that they, too, might possess significant insecticidal activity.

**B-Alcoholates and Glycolates of Sodium p-nitrophenoxide**

It was stated under the preparation of Parathion by the Niagara method²³ that glycols and alcohols were substituted for chlorobenzene as the reaction solvent medium. It is known that sodium p-nitrophenoxide has several hydrated forms, a dihydrate and tetrahydrate. It was found that sodium p-nitrophenoxide will form alcoholates and glycolates with alcohols and glycols as well.
As in the case of the hydrates, the alcolholates and glycolates seemed to be fairly stable as long as the boiling point temperature of the alcohol or glycol was not exceeded. The ratio of sodium p-nitrophenoxide to alcohol (or glycol) varied with the alcohol (or glycol) used.

Sodium p-nitrophenoxide propylene glycolate

\((\text{HOCH}_2\text{CHOHCH}_3\text{-NaOCl})\text{NO}_2\).

Propylene glycol (Eastman) (15.2 grams, 0.2 mole) and sodium p-nitrophenoxide (Niagara) (32.2 grams, 0.2 mole) were mixed together in a small evaporating dish. A considerable amount of heat of reaction or association was evolved raising the temperature to a maximum of 50°C. The material became a semi-solid. It was heated in an oven for one hour at 110-115°C. The material was removed from the oven and ground in a mortar while cooling. It solidified suddenly into a very hard orange solid powder. It was dried overnight in a vacuum desiccator over phosphorus pentoxide. The yield of product, sodium p-nitrophenoxide propylene glycolate, was 47.4 grams (100%).

The formation of these glycolates and alcolholates may have something to do with the great reactivity of sodium p-nitrophenoxide with 0,0-diethyl thiophosphoryl chloride in the preparation of Parathion. The association of the polar solvent (glycol, alcohol etc.) with the sodium p-nitrophenoxide apparently makes the \(S_N^2\) reaction where the p-nitrophenoxide ion displaces the chloride ion of 0,0-di-ethyl thiophosphoryl chloride go to completion much more easily.41

Further work on the heat of formation and the other physical and chemical properties of these compounds should be done.

C– Trichloroethyl Phosphates

According to the insecticide theory of Läuger24 the CCl₃- group of DDT, etc. was very important as a lipoid solubilizing radical. This radical rendered the insecticide molecules soluble in the fatty nerve tissue of the insect.
<table>
<thead>
<tr>
<th>Moles NaO(\x28\x2b\x29)NO₂</th>
<th>Moles Alcohol or Glycol</th>
<th>Alcohol (a)</th>
<th>Consistency Product</th>
<th>Color</th>
<th>Max.°C</th>
<th>Heated in oven</th>
<th>Ratio Na salt/</th>
<th>% Yield</th>
<th>Remarks (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0186</td>
<td>excess</td>
<td>ethyl (a)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>21 days(^b)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.0186</td>
<td>excess</td>
<td>diethylene (g)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>225 hrs.(^b)</td>
<td>1/0.8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.0186</td>
<td>excess</td>
<td>propylene (g)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>225 hrs.(^b)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.0186</td>
<td>excess</td>
<td>triethylene (g)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>225 hrs.(^b)</td>
<td>1/1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
<td>triethylene (g) very hard</td>
<td>yellow</td>
<td>50</td>
<td>2h hrs.</td>
<td>1/1</td>
<td>100</td>
<td>exothermic</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>diethylene (g) soft solid</td>
<td>orange</td>
<td>45</td>
<td>1 hr.</td>
<td>1/1</td>
<td>100</td>
<td>exothermic stable</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>propylene (g) very hard</td>
<td>orange</td>
<td>50</td>
<td>1 hr.</td>
<td>1/1</td>
<td>100</td>
<td>exothermic stable</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>ethyl (a) powdery</td>
<td>orange</td>
<td>40</td>
<td>---</td>
<td>1/0.33</td>
<td>86</td>
<td>greater volatility of ROH may explain lower ratio</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>isopropyl (a) powdery</td>
<td>orange</td>
<td>35</td>
<td>---</td>
<td>1/0.33</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>n-butyl (a) soft solid</td>
<td>orange</td>
<td>37</td>
<td>---</td>
<td>1/1</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>ethylene (g) very hard</td>
<td>yellow</td>
<td>52</td>
<td>20 min.</td>
<td>1/1</td>
<td>99.5</td>
<td>exothermic</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>trimethylene (g) powdery</td>
<td>orange</td>
<td>49</td>
<td>30 min.</td>
<td>1/1</td>
<td>99.5</td>
<td>exothermic</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>carbitol (a,g) semisolid</td>
<td>orange</td>
<td>46</td>
<td>30 min.</td>
<td>1/1</td>
<td>100</td>
<td>reaction not as vigorous as with glycols</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Maximum temperature attained by the reactants due to the heat of association of the sodium p-nitrophenoxide and the alcohol or glycol is this value.

\(^b\) Material was heated in oven part of the time and kept in a vacuum desiccator the remainder of the time.

\(^c\) All odors were slight. The materials were ground in a mortar and dried overnight in a vacuum desiccator over phosphorus pentoxide.
There, the insecticide could then exert its toxic effect due to the presence of some toxiphoric group in the molecule, such as Cl in DDT.

Since the phosphates are important insecticides, although they operate by quite different mechanisms than DDT, it was desired to prepare the β,β,β-trichloroethyl (R-) derivatives of tri-R ortho-, tetra-R pyro- and hexa-R tetra-phosphates to see if the Läuger theory was valid in these cases.

Trichloroethyl alcohol was prepared from chloral by the Meerwin-Fonndorf-Verley reaction. It was then reacted with phosphorus oxychloride to form tri-β,β,β-trichloroethyl phosphate. The preparation of the β,β,β-trichloroethyl analogues of Parathion and TEPP were attempted without notable success. The trichloroethyl alcohol was a very labile alcohol being very susceptible to oxidation to chloral.

**Trichloroethyl alcohol (CCl₃CH₂OH).**

Absolute isopropyl alcohol and anhydrous chloral had to be prepared first. The absolute isopropyl alcohol was prepared by the method of Lund and Bjerrum using magnesium metal:

1. \[
    \text{Mg} + 2 \text{1-PrOH} \stackrel{\text{iodine}}{\longrightarrow} \text{H}_2 + \text{Mg(O-1Pr)}_2
\]
2. \[
    \text{Mg(O-1Pr)}_2 + 2 \text{H}_2\text{O} \longrightarrow \text{Mg(OH)}_2 + 2 \text{1-PrOH}
\]

In a 2-liter 1-necked round bottomed flask fitted with a reflux condenser was placed 100 ml. of isopropyl alcohol (99%, Eastman). The alcohol was refluxed and to the boiling alcohol was added oil free magnesium turnings (10 grams) and iodine (1 gram). When all the iodine was dissolved, another gram of iodine and more isopropyl alcohol (900 ml.) were added. The material was refluxed for thirty minutes. The red-brown color of the iodine became lighter as refluxing occurred. All color was gone at the end of the thirty minute period. The absolute isopropyl alcohol was distilled off in about 90% yield at 89.7-89.9°C.

Anhydrous chloral was prepared by a method suggested by Bradlow.
\[
\text{CCl}_3\text{CH(OH)}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{CCl}_3\text{CHO} + \text{H}_2\text{SO}_4 - \text{H}_2\text{O}
\]

Chloral hydrate (Eastman or Mallinckrodt) (330.8 grams, 2 moles) and sulfuric acid (sp. gr. 1.84) (330.8 grams) were placed in a 1-liter 1-necked flask fitted with a distilling head and condensation system. The flask was heated to the boiling point of anhydrous chloral. This material came over and was condensed in the reaction flask to be used in the next step of the reaction. The anhydrous chloral was a colorless liquid obtained in a yield of 288 grams (98%). The boiling range was 94-96°C.

The reduction of anhydrous chloral to trichloroethyl alcohol proceeded as follows:

1. \[3 \text{CCl}_3\text{CHO} + \text{Al(O 1-Pr)}_3 \xrightarrow{1-\text{PrOH}} \text{Al(OCH}_2\text{CCl}_3)_3 + 3 \text{CH}_3\text{COCH}_3\]

2. \[2 \text{Al(OCH}_2\text{CCl}_3)_3 + 3 \text{H}_2\text{SO}_4 \rightarrow \text{Al}_3(\text{SO}_4)_3 + 6 \text{CCl}_3\text{CH}_2\text{OH}\]

Absolute isopropyl alcohol (1100 ml.) was added to the anhydrous chloral (288 grams, 1.96 moles) in the 2-liter 3-necked round bottomed flask fitted with a mechanical stirrer, thermometer and a Vigreux column and distillation apparatus for the acetone and isopropyl alcohol coming over during the course of the reaction. Aluminum isopropoxide (Eastman) (140 grams, 0.687 mole) in slight excess was powdered and added to the solution in the flask. The flask was heated and the contents stirred vigorously with a mixture of acetone and isopropyl alcohol distilling over at 74-81°C. Heating and distillation were continued until no more acetone was detected in the distillate. Ketone reagent (2,4-dinitrophenyl hydrazine) was used to detect the presence of acetone. After all the acetone had distilled over, the reaction was complete. This required five hours. Another hour was needed to remove most of the remaining isopropyl alcohol solvent. The material remaining in the flask was burgundy in color. This material was treated with 20% (by volume) sulfuric acid (300 ml.). The black tarry material was then steam distilled in the usual manner. About 2500 ml. of distillate was collected
with about 160 grams of a heavy clear oil separating out as the desired product. The aqueous layer was salted with sodium sulfate and extracted three times with 200 ml. portions of ether. The ether extracts and oil were combined and dried over anhydrous sodium sulfate. The trichloroethyl alcohol distilled at 140-153°C/1 atm. in a yield of 237.5 grams (81.5%). It was redistilled at 65-75°C/50-55 mm. in a yield of 220 grams (75%). The product was slightly yellow and melted at 10-15°C. The refractive index (nD^27) was 1.478. The reported boiling range was 94-97°C/125 mm. and the melting point was 16-17°C. 25

The next steps were to prepare those trichloroethyl phosphates that might possess some insecticidal activity.

**Tri-β,β,β-trichloroethyl phosphate (\((\text{CCl}_3\text{CH}_2)_3\text{PO}_4\)).**

Trichloroethyl alcohol (155 grams, 1 mole), which was almost colorless on being freshly distilled, but dark brown on standing, was dissolved in dry benzene (1100 ml.) in a 1-liter 3-necked flask fitted with a mechanical stirrer and reflux condenser. 4 Metallic sodium (23 grams, 1 mole) was added to the solution piecewise. The color became light yellow, then dark brown again as the sodium reacted. The solution was refluxed for three hours to complete the reaction, nevertheless only part of the sodium (14 grams, 0.61 mole) reacted to give the sodium salt of the alcohol. The unreacted sodium was removed from the solution.

Two-thirds of the solution, 0.406 mole of the sodium salt, was placed in a 2-liter 3-necked flask fitted with a mechanical stirrer and reflux condenser. The flask was cooled in an ice bath. Phosphorus oxychloride (Monsanto) (20.8 grams, 0.135 mole) was added quickly to the solution at 0°C. 4 The temperature was kept at 0°C. For thirty minutes and then raised to 80°C. for one hour. The benzene solution was washed twice with 1800 ml. portions of ice water. The wash water was neutral. This indicated that all the phosphorus oxychloride had reacted to form the desired phosphate. The benzene
solution was dried over anhydrous sodium sulfate and vacuum distilled at 22-28°C./2mm. Some unreacted trichloroethyl alcohol was obtained at 22-28°C./2mm. The main portion, presumably the desired product, distilled at 50-55°C./2mm, in a yield of 20 grams (30%). It gave a positive Beilstein halogen test and was reddish purple in color. The exact identity of this product was not proved.

\[
\text{0,0-di-}\beta,\beta,\beta\text{-trichloroethyl thiophosphoryl chloride:} \quad (\text{CCl}_3\text{CH}_2\text{O})_2\text{PSCl}.
\]

The remaining third of the sodium salt of trichloroethyl alcohol (0.204 mole) prepared above was placed in a 1-liter 3-necked flask fitted with a reflux condenser and mechanical stirrer. Thiophosphoryl chloride (Eastman) (17.3 grams, 0.102 mole) was added to the solution. The solution was stirred for a short time at room temperature. The benzene solution was washed twice with 500 ml. portions of water. The benzene layer was dried over anhydrous sodium sulfate and vacuum distilled. Some unreacted trichloroethyl alcohol was recovered distilling at 22-28°C./2mm. The main portion, presumably the desired product, distilled at 40-50°C./2mm, in a yield of 13 grams (32.4%). It was light yellow in color and gave a positive Beilstein halogen test. The exact identity of this product, also, was not proved.

The German method for the preparation of Parathion failed to give the desired trichloroethyl analogue of Parathion, \( (\text{CCl}_3\text{CH}_2\text{O})_2\text{P} = \text{NO}_2 \), when 0,0-di-\( \beta,\beta,\beta \)-trichloroethyl thiophosphoryl chloride (of doubtful purity) and sodium p-nitrophenoxy were reacted together.

The Woodstock procedure for the preparation of alkyl pyrophosphates did not give the tetra-\( \beta,\beta,\beta \)-trichloroethyl pyrophosphate when phosphorus pentoxide and trichloroethyl phosphate were reacted together. Polymerization occurred to form a blue-black resin in this case.

The great reactivity of the \( \beta,\beta,\beta \)-trichloroethyl radical, especially toward oxidation reactions, makes compounds containing this group easily oxidized and labile. Certainly few
of them would be of any practical industrial importance. However, further academic and fundamental investigations into the behavior of this series of compounds might bear important theoretical fruit not only in the insecticide field, but also, in a greater insight into basic organic reactions in this field.

D- An Analogue of DDT; 1,1-Di(p-chlorophenyl)-1-hydroxy-2,2,2-trichloroethane

DDT, the well known insecticide of great importance, contains a tertiary hydrogen. Attempts to prepare the tertiary alcohol analogue by hydrogen peroxide oxidation of DDT have been unsuccessful.29

The following method was tried in our laboratory, also, without success.30 The similarity to the Zeidler31 method for DDT suggested the reaction:

\[
\text{CCl}_3\text{COOH} + 2 \text{HCl} \xrightarrow{\text{sulfuric acid}} \text{CHCl}_3 + \text{H}_2\text{O}
\]

Chlorobenzene (Eastman) (225 grams, 2 moles), trichloroacetic acid (Eastman) (164 grams, 1 mole) and sulfuric acid (sp.gr. 1.84) (300 ml.) were mixed together in a 1 liter 3-necked round bottomed flask fitted with a mechanical stirrer, thermometer and reflux condenser. The material was heated on a steam bath for one hour at 70-80°C. and then at 90-100°C. for three hours. The original milky color changed to a clear brown at the end of the reaction. The material was allowed to cool by standing overnight. It was then poured into 1000 ml. of ice water in a 2-liter separatory funnel. The small amount of chlorobenzene was separated off. The aqueous layer was neutralized using concentrated sodium hydroxide solution.

A large amount of tabular crystals was filtered off and dried. The yield of this material was 450 grams. It was soluble in water, did not melt under 270°C., contained sodium ion (as seen by a yellow flame test), gave a positive Beilstein halogen test, contained sulfate ion (as seen by precipitation of barium sulfate), and decomposed after acidification into
chloroform and carbon dioxide when heated (chloroform was identified by the resorcinol color test). The crystals were, thus, a mixture of sodium sulfate and the sodium salt of trichloroacetic acid. None of the desired DDT hydroxy analogue was found.

**E. Action of Nitrous Acid on Amides and Aliphatic Amines in Non-aqueous Solvents.**

It is known that acid amides and acid sulfonamides can be diazotized in liquid anhydrous hydrogen fluoride to give the corresponding fluoride derivative (acid fluoride or acid sulfonyl fluoride). \(32\)

\[
\text{RCNH}_2 + \text{NaNO}_2 + 2\text{HF} \rightarrow \text{RCOF} + \text{NaF} + 2\text{H}_2\text{O} + \text{N}_2
\]

\[
\text{RSO}_2\text{NH}_2 + \text{NaNO}_2 + 2\text{HF} \rightarrow \text{RSO}_2\text{F} + \text{NaF} + 2\text{H}_2\text{O} + \text{N}_2
\]

This reaction takes place by way of a carbonium ion.

\[
\text{RCNH}_2 \xrightarrow{} \text{RCNH}_2^+ \xrightarrow{\text{F}^-} \text{RCO}^+ \text{N}_2 \text{F}^-\]

This carbonium ion can then react with the base present, namely the fluoride ion, \(\text{F}^-\), to form the desired acid fluoride (or acid sulfonyl fluoride).

In the case of the \(\alpha\)-hydroxy acid amides, the carbonium ion formed would be \(\text{RCHCHO}_2^+\) or \(\text{R}_2\text{COHCO}^+\). These could lead to the corresponding \(\alpha\)-hydroxy acid fluoride, or if rearrangement of the pinacol-pinacolone type occurred, ketoaldehydes or diketones might be formed. In this reaction one of the \(R\) groups migrates in the usual manner to the carbon atom bearing the positive charge.

\[
\begin{align*}
\text{R'}\text{C} \xrightarrow{\text{co}} & \xrightarrow{\text{co}} \text{R} \xrightarrow{\text{w}} \text{C} \xrightarrow{\text{co}} \text{R'} + \text{H}^+ \\
\text{R} \xrightarrow{\text{co}} \xrightarrow{\text{co}} & \xrightarrow{\text{co}} \text{R} \xrightarrow{\text{w}} \text{C} \xrightarrow{\text{co}} \text{R} + \text{H}^+
\end{align*}
\]

With the formation of carbonium ions in this manner, the diazotization of acid amides in alcohol solvents should lead to the formation of esters if the carbonium ion behaves in the same manner in alcohol as in hydrogen fluoride.
The reaction of sodium nitrite, anhydrous hydrogen chloride and benzamide in various alcohols should give the corresponding alkyl benzoate and nitrogen according to this equation.\textsuperscript{32,33}

\[
\text{\textless\textgreater}-\text{CONH}_2 + \text{NaNO}_2 + \text{ROH} + \text{HCl} \xrightarrow{\text{ROH solvent}} \text{\textless\textgreater}-\text{COOR} + \text{NaCl} + \text{N}_2 + 2\text{H}_2\text{O}
\]

The reaction of nitrous acid on amides in alcohol solution is complicated by the fact that an alcoholysis side reaction occurs under the same experimental conditions in a yield approaching that of the desired main reaction itself.

This side reaction is:

\[
\text{\textless\textgreater}-\text{CONH}_2 + \text{ROH} + \text{HCl} \rightarrow \text{\textless\textgreater}-\text{COOR} + \text{NH}_4\text{Cl}
\]

The reverse reaction of forming amides from esters with concentrated ammonia solution is, also, known.\textsuperscript{34,35}

In several of the experiments when the insoluble salts were filtered off after the reaction had taken place, the precipitates were found to contain unreacted sodium nitrite and ammonium chloride as well as sodium chloride. This indicates that the proposed reaction did not run as expected and that the alcoholysis reaction actually was the chief reaction taking place.

Aliphatic amines were then employed in place of the amides in the hope that perhaps ethers might be formed.\textsuperscript{35} However, no ether was ever isolated. The formation of azeotropic mixtures did not facilitate the isolation of definite products. A typical reaction equation follows:

1. \(n\)-Butylamine + HCl \(\rightarrow\) \(n\)-Butylamine-HCl
2. \(n\)-Butylamine-HCl + HCl + NaNO\(_2\) \(\rightarrow\) \(n\)-Butylamine\(^+\) OH\(^-\) + NaCl + H\(_2\)O
3. \(n\)-Butylamine\(^+\) OH\(^-\) \(\rightarrow\) \(n\)-Butylamine\(^+\) + N\(_2\) + OH\(^-\)
4. \(n\)-Butylamine \(\leftrightarrow\) sec-Butylamine = \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3\) \(\leftrightarrow\) \(\text{CH}_2\text{CH}_2\text{CHCH}_3\)
5. \{Bu\(^+\) + EtOH \(\rightarrow\) BuOEt + H\(^+\) \} Bu is either normal or secondary.

A typical experimental run with the amides follows:

\(n\)-Butyl benzoate (\(\textless\textgreater\)-COOCH\(_2\text{CH}_2\text{CH}_2\text{CH}_3\)).

Benzamide (Eastman) (60.5 grams, 0.5 mole) and sodium
<table>
<thead>
<tr>
<th>Moles Benzamide</th>
<th>Alcohol</th>
<th>ml.</th>
<th>Moles ROH</th>
<th>Moles NaNO₂</th>
<th>Time hrs.</th>
<th>Temp. °C.</th>
<th>Boiling range ester °C./mm.</th>
<th>Yield</th>
<th>Ester</th>
<th>n°D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>absolute ethyl</td>
<td>450</td>
<td>0.536</td>
<td>0.507 (NaHCO₃ used to neutralize the HCl)</td>
<td>2.5</td>
<td>0-80</td>
<td>77-80/1</td>
<td>43</td>
<td>ethyl benzoate</td>
<td>1.498b</td>
</tr>
<tr>
<td>0.495</td>
<td>absolute ethyl</td>
<td>600</td>
<td>0.507</td>
<td>0.75</td>
<td>0-10</td>
<td>76-78/1</td>
<td>36</td>
<td>ethyl benzoate</td>
<td>1.500b</td>
<td></td>
</tr>
<tr>
<td>0.5a</td>
<td>n-hexyl</td>
<td>51 g. d</td>
<td>0.522</td>
<td>1.5</td>
<td>80</td>
<td>165-170/760</td>
<td>36</td>
<td>n-hexyl acetate (density was 0.89)</td>
<td>1.409</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>absolute ethyl</td>
<td>500</td>
<td>0.522</td>
<td>2.0</td>
<td>40-80</td>
<td>72-75/1</td>
<td>61.5</td>
<td>ethyl benzoate</td>
<td>1.502b</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>absolute ethyl</td>
<td>23 g. d</td>
<td>0.522</td>
<td>1.75</td>
<td>80</td>
<td>unsuccessful, benzamide recovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>400</td>
<td>0.522</td>
<td>1.5</td>
<td>117</td>
<td>93-98/1</td>
<td>79</td>
<td>n-butyl benzoate</td>
<td>1.493c (Alcoholysis occurred)</td>
<td></td>
</tr>
<tr>
<td>0.36</td>
<td>sec-butyl</td>
<td>250</td>
<td>0.37</td>
<td>2.0</td>
<td>100</td>
<td>90-100/1</td>
<td>10</td>
<td>sec-butyl benzoate</td>
<td>1.483c</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>400</td>
<td>no NaNO₂</td>
<td>1.5</td>
<td>117</td>
<td>93-98/1</td>
<td>62</td>
<td>n-butyl benzoate</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

(THIS EXPERIMENT SHOWED THE ALCOHOLYSIS SIDE REACTION TO BE VERY IMPORTANT)

0.5 tert-butyl 400 0.522 2.5 0-5 unsuccessful, no reaction

a - Acetamide was used in place of benzamide in this reaction.
b - The refractive index (n°D) for ethyl benzoate was reported as 1.507.
c - The refractive index (n°D) for (d) sec-butyl benzoate was reported as 1.493.
d - Benzene (400 ml.) solvent was used in these cases.
nitrite (Mallinckrodt) (36 grams, 0.522 mole) were finely divided and suspended in a n-butyl alcohol (Eastman) (400 ml.) in a 1-liter 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and gas inlet tube. Anhydrous hydrogen chloride (Matheson) gas was passed in at a moderate rate for one hour. After ten minutes a little nitrogen dioxide was noticed over the solution. The slurry was refluxed for thirty minutes after the hydrogen chloride was no longer added. The material was cooled and the white solid inorganic salts were filtered off. The solid was a mixture of sodium chloride, sodium nitrite and ammonium chloride. The weight of the solid was 45-50 grams. This was more than the stoichiometric theoretical amount of sodium chloride expected according to the equation originally proposed for the reaction. However, considerable alcoholysis occurred in the reaction accounting for the unreacted sodium nitrite, ammonium chloride and the greater amount of inorganic salts. The excess n-butyl alcohol was removed using a solvent stripper and the residue was vacuum distilled. The product, n-butyl benzoate, distilled at 93-98°C./1mm. in a yield of 70 grams (79%). The reported boiling point was 248.5-249.5°C. 38

With the amines the experiments were run in this manner.

Sodium nitrite (Mallinckrodt) (36 grams, 0.522 mole), n-butyl amine (Eastman) (36.5 grams, 0.5 mole) and n-butyl alcohol (Eastman) (250 ml.) were placed in a 500-ml. 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and gas inlet tube. The flask was cooled in an ice bath during part of the reaction. Dry hydrogen chloride gas (Matheson) was passed in for one hour. After five minutes some nitrogen dioxide was liberated. The ice bath was removed and still more nitrogen dioxide and hydrogen were evolved. No detectable evolution of nitrogen was noted. The material was stirred for thirty minutes after all the hydrogen chloride gas had been added. The inorganic salts present were then filtered off from the cooled solution. A yield of 33 grams was obtained consisting of sodium chloride and sodium nitrite.
Table XXII

<table>
<thead>
<tr>
<th>Moles RNH₂</th>
<th>Amine</th>
<th>Moles NaNO₂</th>
<th>ml. ROH</th>
<th>Alcohol</th>
<th>Time hrs</th>
<th>Temp. °C</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>0.522 250</td>
<td>absolute ethyl</td>
<td>1.5</td>
<td>80</td>
<td>Azeotropic mixture, no single product isolated.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>0.522 250</td>
<td>n-butyl</td>
<td>0.75</td>
<td>117</td>
<td>Some n- and sec-butyl chlorides were found as well as some n-butyl alcohol and possibly some dibutyl ether. Azeotropic mixture still present. Major products were n- and sec-butyl chlorides.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>0.522 250</td>
<td>n-butyl</td>
<td>1.5</td>
<td>0-30</td>
<td>No definite product was isolated.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>ethyl-HBr salt</td>
<td>0.522 250</td>
<td>n-butyl</td>
<td>1.25</td>
<td>0-10</td>
<td>Liquid nitrogen dioxide, ethyl chloride, n-butyl chloride and other products were found. Some n-butyl and n-amyl chlorides and azeotropic mixtures were formed. n-Butyl chloride was found.</td>
<td></td>
</tr>
<tr>
<td>1.11</td>
<td>ethyl</td>
<td>1.14 250</td>
<td>n-butyl</td>
<td>1.5</td>
<td>0-30</td>
<td>Some n-butyl and n-amyl chlorides and azeotropic mixtures were formed.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>0.522 250</td>
<td>n-amyl</td>
<td>1.5</td>
<td>138</td>
<td>n-Butyl chloride was found.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>n-butyl</td>
<td>0.522 250</td>
<td>absolute ethyl</td>
<td>1.0</td>
<td>80</td>
<td>Benzyl chloride and unreacted benzyl amine hydrochloride were isolated.</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>benzyl</td>
<td>0.522 150</td>
<td>absolute ethyl</td>
<td>1.0</td>
<td>30-80</td>
<td>Benzyl amine hydrochloride was recovered, the reaction was unsuccessful.</td>
<td></td>
</tr>
<tr>
<td>0.14</td>
<td>benzyl-HCl salt</td>
<td>-c 100</td>
<td>n-amyl</td>
<td>0.5</td>
<td>137</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a = 200 ml. of dry benzene was used as solvent.

b = n-Bu⁺ and Cl⁻ → n-BuCl The chloride ion prevents the butyl carbonium ion from reacting with the less basic ethyl alcohol, hence butyl chloride is formed in preference to ethyl butyl ether.

c = 0.15 mole of amyl nitrite was used instead of sodium nitrite.³⁷
The filtrate was still saturated with hydrogen chloride. It was fractionated through a three-foot heated packed column. The fractions obtained were:

1st. b.r. = 67.5-78°C. \( n^2_D = 1.396 \) yield 48 grams
   (This is sec-butyl chloride chiefly. \( n^2_D = 1.395 \))

2nd. b.r. = 82-100°C. \( n^2_D = 1.392 \) yield 51 grams
   (positive Beilstein halogen test)

3rd. b.r. = 100-116°C. \( n^2_D = 1.395 \) yield 126 grams
   (This is mostly n-butyl alcohol. It gave a positive
   Beilstein halogen test.)

The residue was a black solid (54 grams).

\[
\text{Benzamide} (\text{CONH}_2) \\
\text{C}_6\text{H}_5\text{COCl} + 2 \text{NH}_3 \xrightarrow{\text{NH}_4\text{OH}} \text{C}_6\text{H}_5\text{CONH}_2 + \text{NH}_4\text{Cl}
\]

Concentrated ammonium hydroxide (1000 ml.) was placed in a 2-liter 3-necked round bottomed flask fitted with a mechanical stirrer, reflux condenser and dropping funnel. Benzoyl chloride (Baker) (250 grams, 1.78 moles) was added slowly through the dropping funnel over a thirty minute period to the rapidly stirred ammonia solution. The white solid product, benzamide, began to precipitate out. A considerable amount of heat was evolved as the reaction proceeded. After all the benzoyl chloride had been added, the mixture was stirred for two hours. The reactants were then poured into 2000 ml. of cold water (in a 4-liter beaker) to dilute the ammonium hydroxide. The solid product was filtered off and washed several times with cold water. The benzamide was dried over phosphorus pentoxide in a vacuum desiccator. The white cubic crystals were obtained in a yield of 172 grams (80%). Their melting point was 90-115°C. The product should be re-crystallized in order to secure benzamide of a higher degree of purity. The reported melting point of benzamide was

130°C. 38

This general problem of the action of nitrous acid on
amides and aliphatic amines in non-aqueous solvents was dropped as being unfruitful for several important reasons. These reasons have been substantiated by experiments carried out in the laboratory.

1. - The reaction of sodium nitrite and anhydrous hydrogen chloride on amides in alcohol solvents gave the desired ester product, but the alcoholysis side reaction gave the same ester product in similar yields simultaneously.

2. - The poor solubility of sodium nitrite in organic solvents resulted in the desired diazotizations being incomplete. The unreacted sodium nitrite became coated with sodium chloride or amine hydrochloride thus preventing further reaction from taking place.

3. - The carbonium ion formed from the diazotization of aliphatic amines in alcohol in the presence of excess hydrogen chloride gas reacted to form alkyl chlorides. It had been hoped that the carbonium ion would combine with the alcohol molecule present to form an ether and a hydrogen ion. However, the chloride ion seemed to be a stronger base than the alcohol, thus only the alkyl chlorides were formed.

In addition, alcohols have long been used as means of deaminating aromatic amines by way of the diazonium salts. This fact tends to negate any further hope of success along this line. The problem of the action of alcohols on diazonium compounds seems to have been sufficiently well investigated.

4. - The use of nitrogen trioxide to form nitrous acid in alcohol solution was not feasible since alkyl nitrites were prepared in this manner.

\[
\text{N}_2\text{O}_3 + 2 \text{ROH} \rightarrow 2 \text{RONO} + \text{H}_2\text{O}
\]

5. - Alkyl nitrites did not diazotize the amine hydrochlorides satisfactorily either.

This project was generally unsuccessful and no conclusions of a positive nature were obtained except that the alcoholysis of amides went in good yield to form the corresponding ester under reasonable experimental conditions.
SUMMARY

The trialkyl ortho phosphates were prepared in three ways. The method of Evans, with and without our modification, gave the best yields (64-71%).

The alkyl tetra-, pyro-, meta- and tri-phosphates were prepared by the method of Woodstock in yields of 83 to 97%. Many of these compounds are important commercial insecticides.

The dialky1 acid phosphates were prepared in several ways. The method of Flimmer and Burch was the best giving quantitative yields. The amine salts of the dialky1 acid phosphates were, also, prepared in good yield (92.5-97.5%).

Sodium p-nitrophenoxide was found to form alcoholates and glycolates in addition to the usual hydrates. These alcoholates and glycolates were stable solid materials prepared in yields of 83 to 100%. The existence of such glycolate molecules may help explain the speed of the reaction of sodium p-nitrophenoxide and C,C-diethyl thiophosphoryl chloride in the preparation of Parathion.

Trichloroethyl alcohol was prepared in a yield of 81.5%, but when the preparation of the various trichloroethyl phosphates was attempted, products of unknown structures and resins were formed. Confirmation of the Läuger insecticide theory in the phosphate field was not realized.

An attempt to prepare 1,1-di(p-chlorophenyl)-1-hydroxy-2,2,2-trichloroethane, the hydroxy analogue of DDT, from trichloroacetic acid and chlorobenzene was unsuccessful.

The reactions of nitrous acid on amides and aliphatic amines in alcohol solvents led to no positive conclusions except that the alcoholysis of amides in the presence of excess hydrogen chloride to form esters went in excellent yields (60-80%) in a short period of time.
BIBLIOGRAPHY

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34. ibid., p. 229.
37. Knoevenagel, Ber., 23, 2995 (1890).
STUDIES IN THE
BENZOTRIAZOLE AND
2-AMINOPYRIDINE SERIES
INTRODUCTION

The work described in this section of the thesis began as a study of various types of compounds which might possess some antihistamine activity. Among these types were the benzotriazoles. The theory of resonance has not been applied expressly in the benzotriazole series. Therefore, in this work, emphasis has been placed upon a consideration of the chemical reactivity of the benzotriazoles based on the principles of resonance. Applications of the resonance theory to the benzotriazoles led us to consider how the theory would apply if the benzene ring were replaced by the pyridine nucleus, and, hence, to a consideration of the pyridotriazoles, their syntheses from the corresponding 2-aminopyridines, and related matters.

The field of antihistamine compounds is a relatively new one. Histamine is a powerful vasodilator with countless side-effects. These side-effects are those commonly associated with allergies of all types (hay fever, common cold, edema, anaphylactic shock, hives, etc.). Adrenaline (epinephrine) will counteract the action of histamine and hence alleviate the symptoms of excess histamine. It is a direct physiological antagonist protecting the animal against twice the normal lethal dose of histamine. The antihistamine compounds now on the market are stereotropically antagonists rather physiological antagonists. They work by blocking out the histamine from the sites of action in the body where the histamine exerts its toxic or undesirable effects. Antihistamines protect the animal against doses of 1500 to 2000 times the normal lethal dose of histamine. The antihistamines are often also antispasmodics.

The chemical structure of all known antihistamine materials show them to be large molecules, able to block the histamine sterically. In general all contain the β-dimethylaminooethyl group somewhere in the molecule. Many of these compounds are now on the market as common cold remedies under countless trade names. A few of the more important ones are listed on
Antergan

Benadryl

Histamine

Pyribenzamine

Thenylene

Thephoran

Neoantergan

Neohetramine

Trimeton

Tubocurarine Chloride (curare)

Myanesin
page 86 under their best known names. It is easily seen that the antihistamine field is an important one both medically and commercially.

One of the potential antihistamine compounds that was sought possessed the benzotriazole nucleus. This led to the consideration of benzotriazoles in general with special emphasis on the nature of the substitution reactions on benzotriazole nucleus by nucleophilic reagents (SN2 reactions). Interpretation of the results of these reactions, on the basis of modern resonance theory, or perhaps the uncovering of experimental data which might somewhat expand the applicability of the theory, was one of the chief aims of this section of the thesis. The benzotriazoles are weakly acidic compounds7,8 and can be alkylated in alkaline solution relatively easily. Several new benzotriazoles were prepared by means of this reaction.

Benzotriazole, itself, has been found to possess curare-like activity.9 Myanesin (Tolysorol, 2,3 dihydroxypropyl-2′-methylphenyl ether) also possesses remarkable curare-like activity. (See page 86). It was believed to be most important to prepare the hybrid of benzotriazole and Myanesin. This was done by adding the 2,3-dihydroxypropyl side chain to the benzotriazole.

The study of benzotriazoles especially in respect to the resonance theory led to the consideration of the pyridotriazoles. Although the 1- or 3-pyrido(3,4-d)-v-triazoles are much more accessible than the 1- or 3-pyrido(2,3-d)-v-triazoles,10 the latter type compounds were studied, as the starting materials for their syntheses were readily available. The substitution of a nitrogen atom for a carbon in the benzene ring of benzotriazole might impart to the pyridotriazole somewhat different physical and chemical properties. It was known that the pyridotriazoles were stronger acids than the corresponding benzotriazoles.8 This can be explained readily by means of the resonance theory. The differences between
the pyridotriazoles and the benzotriazoles are more of degree
than of essential nature.

The syntheses of the 1- or 3-pyrido(2,3-d)-v-triazoles
are not as simple as for the benzotriazoles. Whereas
2-phenylenediamine is readily available, any 2,3-diamino-
pyridine derivative can be prepared only after great difficulty
and a long series of reactions. Various 2-aminopyridines
were employed as starting materials. The nitration of the
products to the corresponding 2-nitramino-pyridines followed
by subsequent acid rearrangement to the 2-amino-3(or 5)-
nitropyridines have been reported in some cases, but the yields
and procedures have left much to be desired.11,12,13,14,15,16

The various substituted 2-aminopyridines differed remark-
ably in their behavior during nitration and subsequent re-
arrangement. 2-Aminopyridine, itself, nitrates easily17,18,19,20,21
and rearranges without much trouble to give a large amount
of the 5-nitro-2-aminopyridine and only very small quantities
(2 to 3%) of the desired 3-nitro-2-aminopyridine.17,22

The 5-methyl-2-aminopyridine on the other hand nitrates
almost violently giving 5-methyl-2-nitraminopyridine. This
material rearranges also with apparent partial decomposition
yielding 5-methyl-3-nitro-2-aminopyridine and some nitrogen
dioxide. These materials apparently were greatly activated
by the presence of the 5-methyl group.

The 5-bromo(or 5-chloro)-2-aminopyridine nitrates smoothly
giving the 5-bromo(or 5-chloro)-2-nitraminopyridine in good
yield.23,24 These products rearrange without difficulty in
fair yields to the corresponding 3-nitro-2-aminopyridines.
The 5-halogen group apparently deactivated the compound
sufficiently to allow nitration and rearrangement to occur
in the desired manner.

A study and comparison of these reactions with those
reported in the literature proved most interesting and in-
formative.

The catalytic reduction of the various 3-nitro-2-aminopy-
ridines was tried with varying success, depending apparently
on the particular compound, state of purity, impurities present, etc. Reduction to the desired 2,3-diaminopyridines using tin or stannous chloride and hydrochloric acid gave very poor yields. Numerous reduction methods have been reported in the literature.\(^2,8,10,11,12,16,25,26,27,28\) Other methods have been used to obtain the diaminopyridines as well.\(^29,30,31\)

The diazotization step to form the final desired pyridotriazole also went in poor yields. Of course, the diaminopyridine starting material was never obtained in a pure state. This doubtless accounts for the fact reported\(^10\) that 1- or 3-pyrido(2,3-d)-v-triazoles are much less readily prepared than the 1- or 3-pyrido(3,4-d)-v-triazoles.

The problem of the relative acidity of the pyridotriazoles was to be attacked by this approach. The following syntheses were run:

\[ \text{I. } \begin{align*}
\text{Cl} & \quad \text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

\[ \text{Reduction} \rightarrow \begin{align*}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*} \downarrow \text{Diazotization} \downarrow
\]

\[ \begin{align*}
\left\{ \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{array}
\right\} & \quad \begin{align*}
\text{Sodamide} \\
\text{alkylation} \quad \text{RX}
\end{align*}
\]

\[ \begin{align*}
\text{RX} & \quad \text{RX}
\end{align*}
\]

\[ \left\{ \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{array}
\right\}
\]

\[ \text{II. } \begin{align*}
\text{Cl} & \quad \text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

\[ \text{Sodamide} \quad \text{alkylation} \quad \text{RX}
\]

\[ \rightarrow \begin{align*}
\text{Cl} & \quad \text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*} \quad \text{Reduction} \quad \downarrow
\]

\[ \text{Cl} \quad \text{Cl}
\]

\[ \left\{ \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{array}
\right\}
\]

\[ \text{Diazotization} \quad \text{Cl}
\]

\[ \left\{ \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} & \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{array}
\right\}
\]
Whereas the second method (II.) led to only one product (A), the first method (I.) can lead to either (A) or (B) or both (A) and (B). If either (A) or (B) were exclusively prepared by method (I.), the influence of the nitrogen of the pyridine ring could be determined in the pyridotriazoles according to resonance theory.
DISCUSSION

As it was stated in the introduction, the effective antihistamine compounds are large molecules possessing the \( \beta \)-dimethylaminoethyl group.\(^6\) It was believed that the following compounds might possess antihistamine activity:

\[
\begin{align*}
\text{(I)} & : \quad \text{N} - \text{CO} - \text{CH}_2 - \text{N} - \text{Me}_2 \\
\text{(II)} & : \quad \text{N} - \text{CO} - \text{CH}_2 - \text{N} - \text{Me}_2 \\
\text{(III)} & : \quad \text{N} - \text{CO} - \text{CH}_2 - \text{N} - \text{Me}_2 \\
\text{(IV)} & : \quad \text{N} - \text{CO} - \text{CH}_2 - \text{N} - \text{Me}_2
\end{align*}
\]

The proposed method of preparation of (I) and (II) follow:

\[
\begin{align*}
\text{(I)} & \quad \text{N} - \text{NO}_2 + \text{C}_6\text{H}_{12} - \text{CO}_3^- \quad (\text{or} \quad \text{C}_6\text{H}_{12} - \text{CO}_2^-) \\
\text{Heat together} \quad \rightarrow \quad \text{C}_6\text{H}_{12} - \text{CO} - \text{CH}_2 \\
\quad \text{N} - \text{NO}_2 + \text{H}_2\text{O} \\
\quad \text{Catalytic reduction} \quad \rightarrow \quad \text{N} - \text{CO} - \text{CH}_2 - \text{N} - \text{Me}_2
\end{align*}
\]
Although the initial condensation of α-nitroaniline and succinic (or phthalic) anhydride progressed in the desired manner, subsequent catalytic reduction of the nitro group to the amino group did not go completely. A mixture of the amino and nitro compounds was found. As this was not the chief interest of our work, these compounds were then dropped in order to devote more time to the benzotriazoles.

The methods of Tschitschibabine, Bogert, and others for the alkylation of α-picoline using sodamide and alkyl halides did not yield any 1,1-diphenyl-2(2'-pyridyl)-ethane (III) when α-picoline, sodamide and benzhydryl bromide were heated together in dry toluene for forty-eight hours. It is known that alkyl bromides give much poorer yields in this reaction than the alkyl chlorides due to the formation of quaternary ammonium compounds (bromides). The only definitely identified products isolated from the reaction mixture were tetraphenylethane, unreacted benzhydryl bromide and unreacted α-picoline. It is possible that some of the desired product, 1,1-diphenyl-2(2'-pyridyl)-ethane, was formed, but it was never isolated and identified.

It is known that benzhydryl chloride can give tetraphenylethane when it is heated with sodium in dry benzene or with sodium in liquid ammonia. The exact mechanism for the formation of tetraphenylethane in this case has not yet been determined.

\[
\text{C}_8\text{H}_5\text{CH}_2 + \text{NaNH}_2 + \phi_2 \text{CHBr} \rightarrow \text{NaBr} + \phi_2 \text{CHCH} \phi_2 + \phi_2 \text{CHBr} + \text{C}_8\text{H}_5\text{CH}_2
\]

The product (IV) was to be prepared by two methods:

1. a. sodamide condensation

\[
\text{C}_8\text{H}_5\text{NO}_2 + \text{NaNH}_2 + \text{CHCl}_3 + \text{CH}_2\text{NHMe}_2 \rightarrow \text{C}_8\text{H}_5\text{NO}_2 + \text{CHCl}_3 + \text{CH}_2\text{NHMe}_2 + \text{NCl}
\]

b. catalytic reduction

\[
\text{C}_8\text{H}_5\text{N}^+ \text{NHCH}_2\text{CH}_2\text{NHMe}_2 \rightarrow \text{C}_8\text{H}_5\text{N}^+ \text{NHCH}_2\text{CH}_2\text{NHMe}_2 + 2 \text{HCl}
\]
c. diazotization to (IV)

\[
\begin{align*}
\text{Method 1 & has been reported in the literature,}^4 & \text{ although the} \\
\text{product of step a was prepared in a different manner. Step} \\
a & \text{showed the application of the Eisleb synthesis in the ben-} \\
zene series.}^4 & \text{Hitherto such reactions were usually carried} \\
& \text{out with an aliphatic amine and a nitrochlorobenzene mole-} \\
cule. Step b gave an impure product, which failed to react} \\
& \text{according to the Brady and Reynolds}^4 & \text{method for the pre-} \\
& \text{paration of benztrotiazoles.} \\
&& \text{Method 2 will be described below with the other benzo-} \\
& \text{triazoles.} \\
&& \text{The review article on triazoles by Benson and Savell}^1 \\
& \text{contains a great deal of information of the reactions, prop-} \\
& \text{erties and behaviors of these materials. Our special inter-} \\
& \text{est was in the benztrotiazoles and in 1-substituted benzo-} \\
& \text{triazoles. It was known that benztrotiazoles could be} \\
& \text{alkylated with alkyl halides in the presence of alkali} \\
& \text{(sodium hydroxide, sodium ethoxide, etc.).}^1,4^6,4^7,4^8,4^9,5^0 \\
& \text{In our experiments sodamide was employed as the alkaline} \\
& \text{condensing agent.}^4
\end{align*}
\]
Table XXIII

<table>
<thead>
<tr>
<th>Moles Benzo-</th>
<th>Moles Alkyl</th>
<th>Moles NaH₂</th>
<th>Alkyl Halide</th>
<th>Toluene</th>
<th>hrs.</th>
<th>Yield</th>
<th>Solvent</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>triazole</td>
<td>NaH₂</td>
<td>Halide</td>
<td>ml.</td>
<td>Time</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
<td>Ethyl Br</td>
<td>300</td>
<td>6</td>
<td>17</td>
<td>yellow oil</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.25</td>
<td>Benzyl Cl</td>
<td>250</td>
<td>7</td>
<td>12</td>
<td>white ppt.</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>8-Dimethyl-</td>
<td>250</td>
<td>14</td>
<td>83</td>
<td>yellow oil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>aminooethyl Cl</td>
<td></td>
<td></td>
<td></td>
<td>b.p. = 185-190°C.</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>Benzhydryl</td>
<td>275</td>
<td>14</td>
<td>15.9a</td>
<td>white ppt.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Br</td>
<td></td>
<td></td>
<td></td>
<td>b.p. = 87.5°C.</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>Glycerol</td>
<td>250</td>
<td>6</td>
<td>93</td>
<td>brown, viscous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-monochlorohydrin</td>
<td></td>
<td></td>
<td></td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NaOH</td>
<td>100</td>
<td>2</td>
<td>--</td>
<td>decomposed when</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H₂O</td>
<td></td>
<td></td>
<td>distilled at 1 mm.</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>&quot;</td>
<td>250</td>
<td>4</td>
<td>100b</td>
<td>very viscous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35° light brown oil</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.p. = 225-228°C.</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>at 0.06 mm.</td>
<td></td>
</tr>
</tbody>
</table>

- These yields are those based on purified product. In every case these yields could be raised by working up the residues and filtrates.
- These yields are those based on the amount of sodium chloride recovered from the reaction.
- The reported boiling point was 149.5°C./12mm.
- The reported melting point was 115-116°C.
- The reported boiling point was 115-117°C./0.3mm. and the reported melting point was 170.5-171.5°C. for the HCl salt.

The benzotriazole possesses a very acidic hydrogen which can be removed by alkaline reagents (like sodamide) to form an anion. The anion of benzotriazole is very stable for it is stabilized by a large number (10) of resonance forms. These include four major structures which are equivalent. This stable anion can then enter into typical S_N2 displacement reactions very readily. The 1-alkylation is an example of this S_N2 type reaction.
The benzotriazole anion is a very strong base. Although the fact that benzotriazole will enter into $S_N^2$ reactions has been recognized for some time,\textsuperscript{1} the application of the resonance theory to the explanation of these reactions has never been tried. The stability of the anion is easily demonstrated by its considerable resonance stabilization.

The substitution of a pyridine nucleus for the benzene nucleus and the effects on the chemical and resonance behavior of this substitution will be discussed below.

The sodamide condensation of alkyl halides and benzotriazole to form 1-alkylated benzotriazoles went in excellent yields in a short time.
The new compounds, 1-(benzhydryl) benzotriazole and 1-(2',3'-dihydroxypropyl) benzotriazole, were prepared. This latter compound is a hybrid of Myanesin and benzotriazole, both of which possess powerful curare-like activity. It was hoped that this material might be even more potent. It has been sent to Smith, Kline and French for pharmacological testing.

1-(β-Dimethylaminoethyl) benzotriazole was found to be inactive as an antihistamine compound by Upjohn.

A considerable amount of work has been done on the benzotriazole field. A large number of ring substituted and 1-substituted derivatives have been made. Some unsymmetrical ring substituted benzotriazoles have been prepared. Subsequent 1-alkylation can result in two products being formed. So far there has been no effort made to predict or to explain the preponderance of one isomer over the other. It is believed that a rigorous application of the resonance theory to this problem might do much to solve this impasse and to allow a greater degree of insight into why one isomer will be formed in preference to another. This is believed to be a most fundamental problem the results of which might be applied to all fields of organic chemistry.

Substitution of the pyridine nucleus for the benzene nucleus in benzotriazoles led to the preparation and study of 1- or 3-pyrido(2,3-d)-v-triazoles. The 1- or 3-pyrido (3,4-d)-v-triazoles have been reported rather frequently in the literature compared to the (2,3-d) triazoles. These compounds were not available commercially and had to be prepared by a long series of reactions.
The starting materials for the syntheses of the 1- or 3-pyrido(2,3-d)-ν-triazoles were 2-aminopyridine, 5-methyl-2-aminopyridine, 5-bromo-2-aminopyridine, and 5-chloro-2-aminopyridine. A typical series of reactions follow: (R will be H, CH₃, Br or Cl depending upon the starting material).

**Step A**

\[ R[N\equiv\text{N}][\text{N}_2] \xrightarrow{\text{HNO}_3} R[N\equiv\text{N}][\text{NNO}_2] \]

**Step B**

\[ R[N\equiv\text{N}][\text{NNO}_2] \xrightarrow{\text{H}_2\text{SO}_4} \]

**Step C**

Reduction (catalytic or SnCl₂, HCl) \( \text{(if R is H, NO}_2 \text{ may go to the 5 as well as the 3 position.)} \)

**Step D**

Diazoitation

\[ R[N\equiv\text{N}][\text{N}_2] \rightarrow \text{(diazo) R[N\equiv\text{N}][\text{N}_2]} \]

**Step E**

\[ \text{(R' = CH}_2\text{CH}_2\text{NMe}_2) \]

**Step F**

\[ \text{Catalytic reduction} \]

Either or both isomers are possible by this procedure.

Only one isomer is possible by this procedure.
The nitration step (see Step A on the chart on page 97) is as follows:

\[
R\begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{H}_2
\end{array}
\end{array} + \text{HNO}_3 + \text{N}_2\text{SO}_4 \xrightarrow{\text{ice bath}} 0-5^\circ\text{C.} R\begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{NNO}_2
\end{array}
\end{array}
\]

### Table XXIV

Preparation of 5-R-2-nitraminopyridines

<table>
<thead>
<tr>
<th>Moles(^a)</th>
<th>(\text{H}_2\text{SO}_4) ml.</th>
<th>(\text{HNO}_3) a</th>
<th>No. of batches</th>
<th>Temp(^d) C.</th>
<th>Time hrs.</th>
<th>Yield (%)</th>
<th>M.P. (^\circ\text{C}).</th>
<th>Prod. color</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 methyl</td>
<td>266g. 27g.</td>
<td>1</td>
<td>0-5</td>
<td>2</td>
<td>8</td>
<td>(145)152</td>
<td>yellow</td>
<td></td>
</tr>
<tr>
<td>0.25 methyl</td>
<td>266g. 27g.</td>
<td>1</td>
<td>0-5</td>
<td>2</td>
<td>31</td>
<td>152-153</td>
<td>yellow</td>
<td></td>
</tr>
<tr>
<td>0.25 methyl</td>
<td>266g. 27g.</td>
<td>4</td>
<td>0-5</td>
<td>2</td>
<td>32</td>
<td>(140)156</td>
<td>(166)175-6</td>
<td>yellow</td>
</tr>
<tr>
<td>1.00 methyl</td>
<td>1064g. 108g.</td>
<td>1</td>
<td>reaction became too hot and decomposition occurred in spite of good cooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.093 methyl</td>
<td>22 6g.(^b)</td>
<td>1</td>
<td>0-5</td>
<td>2</td>
<td>70</td>
<td>176</td>
<td>orange</td>
<td></td>
</tr>
<tr>
<td>0.28 methyl</td>
<td>66 18g.(^b)</td>
<td>1</td>
<td>0-5</td>
<td>2</td>
<td>64</td>
<td>172</td>
<td>orange</td>
<td></td>
</tr>
<tr>
<td>0.278 methyl</td>
<td>66 18g.(^b)</td>
<td>2</td>
<td>0-5</td>
<td>2</td>
<td>63.3</td>
<td>(170)180</td>
<td>orange</td>
<td></td>
</tr>
<tr>
<td>0.139 methyl</td>
<td>33 9g.(^b)</td>
<td>19</td>
<td>0-5</td>
<td>2</td>
<td>49.5</td>
<td>(175)177</td>
<td>(178)183-182.5(^g) orange</td>
<td></td>
</tr>
<tr>
<td>0.0835 methyl</td>
<td>43 5.4(^c)</td>
<td>10</td>
<td>0-30</td>
<td>1</td>
<td>44.5</td>
<td>(150)180</td>
<td>tan-orange</td>
<td></td>
</tr>
<tr>
<td>0.32 hydrogen</td>
<td>75 21g.(^b)</td>
<td>2</td>
<td>0-5</td>
<td>2</td>
<td>72.5</td>
<td>191-192.5</td>
<td>(188)191.5-192.5(^f),(^g) tan</td>
<td></td>
</tr>
<tr>
<td>0.0957 hydrogen</td>
<td>45 6.2(^c)</td>
<td>10</td>
<td>0-30</td>
<td>1</td>
<td>52</td>
<td>1845</td>
<td>tan</td>
<td></td>
</tr>
<tr>
<td>0.574 hydrogen</td>
<td>270 37.2(^c)</td>
<td>10</td>
<td>0-30</td>
<td>1</td>
<td>81.5</td>
<td>(175)184-58</td>
<td>tan</td>
<td></td>
</tr>
<tr>
<td>0.029 bromo</td>
<td>25 1.9(^c)</td>
<td>1</td>
<td>0-30</td>
<td>1</td>
<td>63.5</td>
<td>(175)177(^h) yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.058 bromo</td>
<td>50 4.3(^d)</td>
<td>7</td>
<td>0-30</td>
<td>1.5</td>
<td>62.6</td>
<td>(164)167-170(^h) yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.039 chloro</td>
<td>25 2.5</td>
<td>1</td>
<td>0-30</td>
<td>1</td>
<td>52</td>
<td>(160)162-162.5(^f),(^g) yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.078 chloro</td>
<td>50 5</td>
<td>20</td>
<td>0-30</td>
<td>1</td>
<td>78</td>
<td>165-166(^d) yellow</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
a - These amounts are per batch.
b - Fuming nitric acid (sp. gr. 1.50) was used in these cases.
c - 75% of the theoretical amount of nitric acid was used.
d - 85% of the theoretical amount of nitric acid was used.
e - All melting points were with decomposition.
f - Recrystallized three times.
g - The reported melting point was 184°C. (dec.).
h - The reported melting point was 181°C. (dec.).
i - The reported melting point was 159-160°C. (dec.).
j - The nitration was very exothermic especially in the case of the methyl. Good cooling was needed.

The application of the resonance theory to this nitration of 5-R-2-aminopyridines illustrates very nicely why the 5-R-2-nitroaminopyridines are formed as the products instead of the 5-R-3-nitro-2-aminopyridines.

In the normal state 5-R-2-aminopyridine exists in the following resonance forms:

\[
\begin{align*}
(\text{I}) & \leftrightarrow (\text{II}) & \leftrightarrow (\text{III}) \\
(\text{IV}) & \leftrightarrow (\text{V}) & \leftrightarrow (\text{VI}) \\
\end{align*}
\]

Although the first two forms (I and II) are the best by far, the other forms contribute some to the chemical behavior of the molecule. One should note that the ring is relatively more negative at the 3 and 5 positions than at the 2, 4 or 6 positions. Therefore it would be expected that an electrophilic attacking reagent would enter the ring at the 3 or 5 positions much more readily than at the 2, 4 or 6 positions. This is indeed the case. This can be seen from a consideration of the transition states that would occur after attack by the positive nitrating ion, $\text{NO}_2^+$ (this is accepted as the usual nitrating agent in such reactions). If one assumed attack of the $\text{NO}_2^+$ at the 2, 4 or 6 position, one would obtain this type of transition state.
Neither of these transition states is very favorable. Note the positive charge on the nitrogen atom.

If one assumed attack at the 3 position, one would have this transition state.

This is a better transition state from a resonance viewpoint than the ones above, but the last form with the positive charge on nitrogen is not too favorable.

One must look therefore for the most negative place in the molecule in order to find the place where the $\text{NO}_2^+$ will attack. It is not the nitrogen atom of the ring for pyridine itself cannot be directly nitrated. Therefore the most likely and in fact only place where the $\text{NO}_2^+$ attacks the molecule is at the 2-amino group, converting it to a 2-nitramino group.

In this case the resonance energy of the pyridine nucleus is retained in the transition state. This results
in a more stable transition state even though the two Kekulé structures are the only major contributing structures.

(In the benzene series (i.e. aniline), the nitration occurs in a different manner. The use of aniline with nitric acid alone results in the oxidation of aniline and none of the desired nitro products. In sulfuric acid (the same conditions as we employed in the case of 5-R-2-aminopyridines), the nitration occurs in the meta position as the $\text{-NH}_2$ group is present largely as the ionic salt group, $\text{-NH}_2\overset{+}{\text{+}}$.

Aniline without the sulfuric acid solvent has the 2, 4 and 6 positions with a higher electron density and thus the $\overset{2}{\text{NO}}_2$ ion is most likely to attack at those positions. (In the case of acetonilide, nitration does occur at the ortho and para positions.) In sulfuric acid, aniline becomes $\text{C}_6\text{H}_5\text{NH}_2\overset{+}{\text{+}}\text{HSO}_4\overset{-}{\text{-}}$. The $\text{-NH}_2\overset{+}{\text{+}}$ group by its inductive effects causes a lower electron density at the 2, 4 and 6 positions thus allowing the $\overset{2}{\text{NO}}_2$ ion to attack the relatively more negative meta positions. The product in this case is m-nitroaniline. There is considerable difference between the nitration reactions of aniline and 2-aminopyridine. These differences stem from the influences of the benzene and pyridine nuclei.)

The nitration was extremely exothermic and good cooling was needed in order to prevent the nitramino compound formed from spontaneously rearranging to the corresponding 3- (or 5) nitro-2-amino compound. The 5-methyl-2-nitraminopyridine seemed very susceptible to this arrangement. Several times it rearranged and decomposed violently when not sufficiently cooled. (Due to the limitations of laboratory equipment in the realm of extremely efficient cooling for large batches of material, numerous small batches were employed in the nitration and subsequent rearrangement steps. Doubtless with better and more efficient cooling devices, larger batches could have been used in these reactions.)

The 2-nitramino compounds were now rearranged by treat-
ment with concentrated sulfuric acid. (The nitration and rearrangement can be done in one step, but in our work the intermediate 2-nitramino compounds were isolated.) This was Step 3 on the chart on page 97.

\[
\text{R} - \text{NH}_2 \text{NO}_2 + \text{H}_2 \text{SO}_4 \rightarrow \text{R} - \text{NH}_2 \text{NO}_2
\]

(If \( \text{R} \) is \( \text{H} \), the \( \text{NO}_2 \) can migrate to the 3 or 5 positions.)

Table XXV

Rearrangement of 5-R-2-nitraminopyridines

<table>
<thead>
<tr>
<th>Moles ( \text{R} \text{NH}_2 \text{NO}_2 )</th>
<th>ml. ( \text{H}_2 \text{SO}_4 )</th>
<th>No. of Neutraliz. batches</th>
<th>Temp.</th>
<th>Time</th>
<th>% Yield</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 methyl 15 1</td>
<td>( \text{Na}_2 \text{CO}_3 )</td>
<td>20</td>
<td>12</td>
<td>50</td>
<td>185-187</td>
<td>orange</td>
</tr>
<tr>
<td>0.105 methyl 160 1</td>
<td>---</td>
<td>0-up decomposed violently</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.013 methyl 20 7</td>
<td>( \text{Na}_2 \text{CO}_3 )</td>
<td>0-20</td>
<td>12</td>
<td>25</td>
<td>190-191</td>
<td>brown</td>
</tr>
<tr>
<td>0.033 methyl 50 3</td>
<td>( \text{Na}_2 \text{CO}_3 )</td>
<td>0-20</td>
<td>12</td>
<td>20</td>
<td>188 (dec.)</td>
<td>brown</td>
</tr>
<tr>
<td>0.033 methyl 20 1</td>
<td>( \text{Na}_2 \text{CO}_3 )</td>
<td>0-20</td>
<td>8</td>
<td>20</td>
<td>188 (dec.)</td>
<td>brown</td>
</tr>
<tr>
<td>0.033 methyl 50 20</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>unsuccessful, ( \text{NO}_2 ) given off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.130 methyl 5 1</td>
<td>violent decomposition with ( \text{NO}_2 ) given off. A black tar was formed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.065 methyl 100 2</td>
<td>( \text{NaOH} )</td>
<td>0</td>
<td>4</td>
<td>22.5</td>
<td>190-2</td>
<td>orange</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>189.5-190.5 ( \text{b} )</td>
<td></td>
</tr>
<tr>
<td>0.072 hydrogen 50g. 1</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>70</td>
<td>168-187</td>
<td>brown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>189-190 ( \text{c} )</td>
<td>golden yellow</td>
</tr>
<tr>
<td>0.036 hydrogen 25 1</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>0.25</td>
<td>40</td>
<td>155-178</td>
<td>green-yellow</td>
</tr>
<tr>
<td>0.144 hydrogen 100 1</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>0.25</td>
<td>unsuccessful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.164 hydrogen 114g. 1</td>
<td>---</td>
<td>0-up decomposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.164 hydrogen 114g. 1</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>66 ( \text{d} )</td>
<td>188 ( \text{f} )</td>
<td>yellow green</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>189-190 ( \text{f} )</td>
<td>yellow</td>
</tr>
<tr>
<td>0.072 hydrogen 50 1</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>35 ( \text{a} )</td>
<td>188-8.5 ( \text{f} )</td>
<td>orange</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>158-166 ( \text{f} )</td>
<td>yellow</td>
</tr>
<tr>
<td>0.072 hydrogen 50 20</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>24 ( \text{d} )</td>
<td>188-8.5 ( \text{f} )</td>
<td>canary yellow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>158-166 ( \text{f} )</td>
<td>orange-yellow</td>
</tr>
<tr>
<td>0.072 hydrogen 50 20</td>
<td>( \text{NaOH} )</td>
<td>0-20</td>
<td>12</td>
<td>24 ( \text{d} )</td>
<td>188-8.5 ( \text{f} )</td>
<td>canary yellow</td>
</tr>
</tbody>
</table>
Table XXV (cont)

<table>
<thead>
<tr>
<th>Moles&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ml. &lt;sup&gt;a&lt;/sup&gt;R</th>
<th>No. of</th>
<th>Neutral-</th>
<th>Temp.</th>
<th>Time</th>
<th>M.P. °C.</th>
<th>Color prod.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>batches</td>
<td>izing</td>
<td>Agent °C.</td>
<td>hrs.</td>
<td>Yield %</td>
<td></td>
</tr>
<tr>
<td>0.0142 bromo</td>
<td>20</td>
<td>1</td>
<td>none</td>
<td>0-20</td>
<td>12</td>
<td>64.5</td>
<td>(195)204-7h yellow</td>
</tr>
<tr>
<td>0.023 bromo</td>
<td>35</td>
<td>10</td>
<td>none</td>
<td>0-20</td>
<td>12</td>
<td>70</td>
<td>(194)202-4h yellow</td>
</tr>
<tr>
<td>0.02 chloro</td>
<td>20</td>
<td>1</td>
<td>none</td>
<td>0-20</td>
<td>12</td>
<td>57.2</td>
<td>(205)207-8b,h golden yellow</td>
</tr>
<tr>
<td>0.0404 chloro</td>
<td>40</td>
<td>25</td>
<td>none</td>
<td>0-20</td>
<td>12</td>
<td>56.1</td>
<td>(160)192-3&lt;sup&gt;i&lt;/sup&gt; orange</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(170)191-2&lt;sup&gt;j&lt;/sup&gt; orange</td>
</tr>
</tbody>
</table>

a - These amounts were per batch.
b - Recrystallized three times.
c - This was a mixture of the 5-nitro and 3-nitro isomers.
d - This was the yield of 5-nitro-2-aminopyridine.
e - This was the yield of the 3-nitro-2-aminopyridine.
f - The reported melting point of the 5-nitro isomer was 188-189°.<sup>17</sup>
g - The reported melting point of the 3-nitro isomer was 162°.<sup>17</sup>
h - The reported melting point was 205°.<sup>23</sup>
i - The reported melting point was 195-196°.<sup>24</sup>
j - The product was vacuum sublimed at 2mm.

This rearrangement reaction was very exothermic especially in the case of the methyl compound. It may very well be that this group activates the ring sufficiently due to the inductive effects of the methyl group to cause this enhanced activity. This would increase the electron density on the pyridine ring and hence would render it more susceptible to attack by the rearranging $\text{NO}_2$ ion. The halogen groups (chloro and bromo) have exactly the opposite effects (they draw electrons away from the ring thereby inducing a lower electron density on the nucleus) and deactivate the ring to attack by the $\text{NO}_2$ ion. This can be observed qualitatively in the laboratory. The 5-methyl-2-nitraminopyridine rearranges much more vigorously and rapidly than the 2-nitraminopyridine which in turn rearranges considerably more readily than the 5-chloro (or bromo)-2-nitraminopyridine.
No definite mechanism has been postulated for this rearrangement, but the situation might be similar to this:

\[
\begin{align*}
R & \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \\
\text{N}^\ominus + R & \xrightarrow{\text{N}^\ominus} \\
\end{align*}
\]

This is followed by attack at the relatively electro-negative 3-position (or 5- if R is H).

The higher temperatures at which these rearrangements are carried out would help drive the rearrangement to completion. The 2-nitramino derivatives all are unstable at elevated temperatures. All of them melt with decomposition. Apparently the greater stability of the rearrangement product also is a factor in driving the rearrangements to completion.

The next step (Step C, see chart on page 97) was the reduction of the 5-R-3-nitro-2-aminopyridines to the corresponding 5-R-2,3-diaminopyridines. Several methods were tried in an attempt to obtain a successful reduction. They involved use of sodium hypo (or hydro) sulfite, sodium chloride and hydrochloric acid, and catalytic reduction using Adams catalyst (platinum oxide). The last two methods gave fair results.

\[
\begin{align*}
R & \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \\
\end{align*}
\]

\[
\begin{align*}
R & \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \\
\end{align*}
\]

\[
\begin{align*}
R & \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \xrightarrow{\text{N}^\ominus} \\
\end{align*}
\]
Table XXVI
Reduction of 5-R-3-nitro-2-aminopyridines

<table>
<thead>
<tr>
<th>Moles</th>
<th>Reducing Agent</th>
<th>Abs. EtOH</th>
<th>Time</th>
<th>Pressure</th>
<th>% Yield</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100 (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>--</td>
<td>unsuccessful</td>
<td>193-4 (dec.)</td>
<td>brown</td>
</tr>
<tr>
<td>0.02</td>
<td>50 ml.</td>
<td>3</td>
<td>3</td>
<td>12.5</td>
<td>194 (dec.)</td>
<td>green-brown</td>
</tr>
<tr>
<td>0.013</td>
<td>methyl H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>50</td>
<td>12</td>
<td>unsuccessful</td>
<td>195-6 (dec.)</td>
<td>brown</td>
</tr>
<tr>
<td>0.0216 hydrogen</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>50</td>
<td>8</td>
<td>5.2</td>
<td>187.3</td>
<td>diHCl salt</td>
</tr>
<tr>
<td>0.0046 bromo</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25</td>
<td>1.5</td>
<td>1.1</td>
<td>58</td>
<td>diHCl salt</td>
</tr>
<tr>
<td>0.05</td>
<td>bromo</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>125</td>
<td>2</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>0.009</td>
<td>bromo</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>5</td>
<td>2.2</td>
<td>1</td>
</tr>
<tr>
<td>0.02</td>
<td>chloro</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>150</td>
<td>2</td>
<td>4.8</td>
<td>32</td>
</tr>
<tr>
<td>0.2</td>
<td>chloro</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1200</td>
<td>15</td>
<td>42</td>
<td>47.5</td>
</tr>
<tr>
<td>0.0575</td>
<td>chloro</td>
<td>SnCl&lt;sub&gt;3&lt;/sub&gt;,HCl</td>
<td>200</td>
<td>8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.0575</td>
<td>chloro</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;,PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>200</td>
<td>6</td>
<td>14.4</td>
<td>10 ca. 70</td>
</tr>
</tbody>
</table>

a - The Parr apparatus used was calibrated at approximately at 8 lbs. drop per 0.1 mole H<sub>2</sub> used.
b - This was the free amine.
c - Recrystallized twice.
d - For the large (2-liter) Parr apparatus, the calibration was about 7 lbs. drop in pressure per 0.1 mole H<sub>2</sub> used.
e - These products were impure, but were used as such for the subsequent reactions.
f - The product was not isolated in a pure form, but was diazotized immediately.
g - This was a mixture of 3-nitro and 5-nitro-2-aminopyridine.

The sodium hydrosulfite reduction gave no product that could be isolated and identified.

The stannous chloride-hydrochloric acid reduction gave a purple solid as the free amine product. This material turned brown in hydrochloric acid solution and seemed to diazotize properly to the triazole derivative.

The catalytic hydrogenation gave erratic results.

Whether the reduction occurred or not seemed to depend on the purity of the starting material, solubility, and other
matters. Generally, however, the reduction did take place although the resulting dianinopyridine was very susceptible to oxidation and decomposition. Even the hydrochloride salts turned black and almost impossible to decolorize or further purify.

The next step of the syntheses was the diazotization to the desired 6-R-1-(or 3-)-pyrido(2,3-d)-v-triazole.\(^2\,^8\,^10\) (See Step D on chart on page 97).

\[ R \begin{array}{l} \includegraphics[width=0.2\textwidth]{diagram.png} \end{array} + \text{HCl} + \text{NaNO}_2 \rightarrow R \begin{array}{l} \includegraphics[width=0.2\textwidth]{diagram.png} \end{array} (\text{I}) \quad \text{(II)} \]

Whether the compound is the 1- (II) or the 3- pyridotriazole (I) has not been definitely established.

Table XXVII

<table>
<thead>
<tr>
<th>Molea</th>
<th>Molea ml.</th>
<th>Acid</th>
<th>Acid d</th>
<th>% Yield</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R \begin{array}{l} \includegraphics[width=0.2\textwidth]{diagram.png} \end{array} )</td>
<td>( R \begin{array}{l} \includegraphics[width=0.2\textwidth]{diagram.png} \end{array} )</td>
<td>NaNO(_2)</td>
<td>Acid</td>
<td>Yield</td>
<td></td>
</tr>
<tr>
<td>0.019 bromo 0.002 20</td>
<td>6% HCl</td>
<td>26.5</td>
<td>brown ppt., ash present</td>
<td>unsuccessfull</td>
<td></td>
</tr>
<tr>
<td>0.00035 chloro 0.0004 7</td>
<td>0.12N</td>
<td>trace</td>
<td>ash present, impure, brown ppt.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.00092 chloro 0.001 30</td>
<td>0.20N</td>
<td>( H_2\text{SO}_4)</td>
<td>---</td>
<td>ash present, impure, reddish brown ppt., unsuccessful</td>
<td></td>
</tr>
<tr>
<td>0.0046 chloro 0.005 132</td>
<td>0.20N</td>
<td>( H_2\text{SO}_4)</td>
<td>trace</td>
<td>light brown ppt., ash present, impure, no melting point found</td>
<td></td>
</tr>
<tr>
<td>0.106 chloro 0.106 860</td>
<td>0.20N</td>
<td>( H_2\text{SO}_4)</td>
<td>9.2</td>
<td>light tan ppt., c ash present</td>
<td></td>
</tr>
<tr>
<td>0.0575(^\text{b,c})</td>
<td>0.06 200</td>
<td>0.75N</td>
<td>( HCl)</td>
<td>(37^b)</td>
<td>dark brown ppt., more ash than preceding experiment</td>
</tr>
<tr>
<td>0.0575(^\text{b})</td>
<td>0.06 200</td>
<td>0.75N</td>
<td>( HCl)</td>
<td>(22.5^b)</td>
<td></td>
</tr>
</tbody>
</table>

a - These starting materials were impure.
b - These values were approximate as the preceding intermediates were not isolated as such. \(^\%\) Yield was based on 5-R-3-nitro-2-aminopyridine.
c - The stannous chloride reduction seemed to give a better starting material for this diazotization step.
d - The concentration of the acid used were approximate.

This is a normal type diazotization. In the benzene
series with ortho diamines, the two amino groups are generally practically equivalent. One uses enough nitrite to diazotize only one of the groups. This is usually done at higher temperatures (room temperature up to 100°C.) than ordinary diazonium coupling or replacement reactions (usually carried out at 0 - 5°C.). The products of these reactions are the desired benzotriazoles. Benzotriazole, itself, is prepared from o-phenylenediamine in this manner.

\[
\text{O-phenylenediamine} \rightarrow \text{benzotriazole}
\]

In the case of the pyridine series, the adjacent amino groups are not equivalent. It is known that in 2-aminopyridine the amino group is relatively not basic (in fact it is considered acidic); while in 3-aminopyridine the amino group behaves just as does the amino group of aniline. This behavior is based on the presence of the nitrogen in the ring which profoundly influences the activity and chemical properties of all pyridine derivatives. 3-Aminopyridine can be diazotized in a manner analogous to aniline, while with 2-aminopyridine, this is not so. Diazotization occurs in the latter case only with great difficulty and not in a normal manner.

With this behavior in mind, one would predict that the major, if not the only, product of the diazotization of 5-R-2,3-diaminopyridines would be 6-R-3-pyrido(2,3-d)-v-triazole, not the 6-R-1-pyrido(2,3-d)-v-triazole as reported in the literature. The latter compounds were postulated by Tschitschibabine although he gave no proof that the -1-pyrido compound actually was the one formed.
However the 3-pyrido(2,3-d)-v-triazoles and the 3-pyrido(3,4-d)-v-triazoles have been reported, but once again the structures were chosen arbitrarily without definite proof. We believe that the latter is actually the case.

\[
\begin{align*}
\text{N} & \equiv \text{C} - \text{N} \equiv \text{N} \\
\text{N} & \equiv \text{C} - \text{N} \equiv \text{N}
\end{align*}
\]

6-carboxy-3-pyrido(2,3-d)-v-triazole

It was our intention to prove conclusively which isomer or both was formed in this reaction. (See chart on page 97.) Step II, the sodamide catalyzed alkylation of the 6-chloro-1-(or 3)pyrido(2,3-d)-v-triazole with β-dimethylaminoethyl chloride, went as expected to give a dark brown product (hydrochloride salt) which had a peculiarly pleasant odor. However Step F, the sodamide catalyzed alkylation of 5-chloro-3-nitro-2-aminopyridine with β-dimethylaminoethyl chloride, failed to go as desired. Unreacted 5-chloro-3-nitro-2-aminopyridine and a tar were isolated and recovered. Thus our proposed method for identifying the pyridotriazole formed went awry. Nevertheless this study in the field of pyridotriazoles has given an insight into the complexity of the reactions and chemical behaviors of this type compound and its intermediates.

Table XXVIII

<table>
<thead>
<tr>
<th>Moles</th>
<th>Moles</th>
<th>ml.</th>
<th>Moles</th>
<th>Time</th>
<th>Temp.</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>NaNH₂</td>
<td>Benzene</td>
<td>ClCH₃CH₂NMe₃</td>
<td>hrs.</td>
<td>°C.</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>0.054</td>
<td>125</td>
<td>0.05</td>
<td>24</td>
<td>110</td>
<td>ClCH₃CH₂NMe₃, unreacted starting pyridine compd.</td>
</tr>
<tr>
<td>0.144</td>
<td>0.30</td>
<td>150</td>
<td>0.144</td>
<td>24</td>
<td>80</td>
<td>sodamide and unreacted pyridine compund</td>
</tr>
<tr>
<td>0.0575</td>
<td>0.06</td>
<td>125</td>
<td>0.06</td>
<td>13</td>
<td>30</td>
<td>same as above</td>
</tr>
</tbody>
</table>

\( ^a \)
a - Toluene was used in this case.

This method of sodamide condensation was applied by Scholtz\textsuperscript{64} to the preparation of various secondary and tertiary amines beginning with 2-aminopyridine.\textsuperscript{65,66} The presence of the 3-nitro- and 5-chloro- groups may alter the reactivity of the 2-aminopyridine so as to prevent this type of condensation from taking place. It would be expected, however, that the 3-nitro group would facilitate reaction for by its inductive and resonance states it could make the hydrogens of the 2-aminogroup even more acidic and thus more susceptible to the sodamide catalyzed alkylation.

\[
\begin{align*}
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \\
&\quad \text{Cl} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{Me} \quad \text{2} \\
&\quad \text{Na} \quad \text{N} \quad \text{H} \\
\end{align*}
\]

A more complete study of this sodamide catalyzed alkylation reaction as applied to ring-substituted 2-aminopyridines seems to be most desirable.

The alkylation (sodamide catalyzed) of pyridotriazoles went as desired. \textsuperscript{44}

\[
\begin{align*}
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \\
&\quad \text{Cl} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{Me} \quad \text{2} \\
&\quad \text{Na} \quad \text{N} \quad \text{H} \\
\end{align*}
\]

A more complete study of this sodamide catalyzed alkylation reaction as applied to ring-substituted 2-aminopyridines seems to be most desirable.

The alkylation (sodamide catalyzed) of pyridotriazoles went as desired. \textsuperscript{44}

\[
\begin{align*}
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \\
&\quad \text{Cl} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{Me} \quad \text{2} \\
&\quad \text{Na} \quad \text{N} \quad \text{H} \\
\end{align*}
\]

**Table XXIX**

Alkylation of 6-chloro-1-(or 3)pyrido(2,3-d)-v-triazole

<table>
<thead>
<tr>
<th>Moles</th>
<th>Moles</th>
<th>ml.</th>
<th>Moles</th>
<th>Time</th>
<th>Temp.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClNH2</td>
<td>C6H5NH2</td>
<td>NaNH2</td>
<td>Benzene</td>
<td>C6H5CH3NMe2</td>
<td>Solvent</td>
<td>hrs.</td>
</tr>
<tr>
<td>0.0065</td>
<td>0.0065</td>
<td>50</td>
<td>0.007</td>
<td>30</td>
<td>80</td>
<td>35 HCl salt was made, impure peculiar and pleasant odor</td>
</tr>
</tbody>
</table>

This alkylation reaction should progress even more rapidly with the pyridotriazoles than with benzotriazole,
itself, as the nitrogen in the pyridine nucleus can bear the negative charge (see structure X). This favorable resonance will help stabilize the transition ion and allow the reaction to occur still more readily in this case.

\[ \text{R} - \text{N} = \text{N} - \text{N} + \text{R} - \text{N} = \text{N} - \text{N} + \text{NaNH}_2 \rightarrow \text{Na}^+ \text{N}_3^- + \text{Na}^+ \]

Structures (I), (II), (III) and (IV) are all equivalent and are very important. Structure (X) is the most important of the remaining ones by far. It also shows why pyridotriazoles are more acidic than the corresponding benzotriazoles. This form with a negative charge on nitrogen is much more favorable than if it were on carbon.

Both the 1-pyrido and 3-pyrido compounds give the same
transition ions (see the resonance states above). Whether (XI) or (XII) is formed depends on the electronic nature of the ring and the substituent R and on the entering group R'. In all likelihood both (XI) and (XII) are formed. Unfortunately we were unable to establish exactly what occurs when the pyridotriazoles are alkylated. It is known in the benzotriazole series that when unsymmetrical benzotriazoles are alkylated in this manner that mixtures of the two possible isomers do occur. As yet no way has been found to correlate the experimental facts and the electronic character of the unsymmetrical benzotriazole being alkylated.

The field of the triazoles (especially the pyridotriazoles) has been relatively untouched. A great deal of work remains to be done, not only on the reactions of these compounds, but also in the syntheses of such materials. Considerable attention should be given to the nitration reactions on 2-aminopyridines and their subsequent rearrangements. This field, itself, may produce compounds of great significance and importance in their own right if it is systematically studied and developed.

The electronic interpretations of the nitration and rearrangement reactions on 2-aminopyridine and of the alkylation (alkaline) reaction on benzotriazole and pyridotriazoles show once again the wide applicability of the resonance theory to explain logically and correctly that which is found to be experimentally the case. Although these reactions and the resonance theory both have been known for some time, they were correlated for the first time in this thesis.

A number of compounds were prepared for the first time; among them was the hybrid of benzotriazole and Kyanesin. This material, 1-(2',3'-dihydroxypropyl)benzotriazole, should possess considerable curare-like activity if the theory of hybridization in organic chemistry is valid in this instance. The compound is now being tested at Smith, Kline and French.
**EXPERIMENTAL**

**Sodamide (NaNH₂).**

Sodium metal (161 grams, 7 moles) was cut into small pieces and kept under xylene until it was needed.

Liquid ammonia (3000 to 3500 ml.) from an inverted ammonia tank was run into a 5-liter 3-necked round bottomed flask fitted with an ammonia condenser, sealed mechanical stirrer and inlet tube. The flask was placed in a large earthen crock. Dry ice was placed in the crock around the flask to effect better cooling. The liquid ammonia had a greenish tinge due to some unknown impurity.

Ferric nitrate (Mallinckrodt) (2.1 grams) was added as a catalyst; its color immediately turned to a reddish-brown. Metallic sodium (3 grams) was added. It was almost instantly converted to sodamide in a rather violent reaction. The color became dark grey. The remainder of the metallic sodium was added over an hour period. As long as any unreacted sodium metal remained in the liquid ammonia, the color was a brilliant dark blue. About ten minutes after all the sodium had been added, the blue color disappeared to give rise to a black-grey color which persisted.

The dry ice bath was removed from around the flask and the excess liquid ammonia was allowed to escape by evaporation through a Ruesen valve overnight.

A large quantity of grey powder was encrusted around the sides of the flask after the ammonia had evaporated. It was loosened with a dry spatula and stored in a wide mouthed capped bottle under petroleum ether (b.r. = 80-100°C.).

The yield of sodamide was 269 grams (95.5%).

**β-Dimethylaminoethyl chloride hydrochloride (ClCH₂CH₂NMe₂·HCl).**

Thionyl chloride (Eastman) (580 grams, 4.88 moles) was placed in a 2-liter 3-necked round bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser. The flask was kept in an efficient ice bath throughout
the reaction.

β-Dimethy laminoethyl alcohol (Eastman) (420 grams, 4.50 moles) was added to the thionyl chloride through the dropping funnel over a period of one hour. Copious quantities of sulfur dioxide were evolved. Toward the end of the reaction the solid product began settling out of solution.

The solid material was dissolved in 2000 ml. absolute alcohol (Commercial Gold Shield) to recrystallize the hydrochloride and to eliminate the slight excess of thionyl chloride as hydrogen chloride, ethyl chloride and sulfur dioxide. The solution was filtered hot, then cooled to give some product (275 grams).

The filtrate was evaporated to a low volume and more product, β-dimethy laminoethyl chloride hydrochloride, (315 grams) was isolated. The combined yield was 590 grams (91.2%). The melting point was 199-202°C. The reported melting point was 202-203°C. 69

\[ \text{N-}(2-\text{Nitrophenyl})\text{phthalimide} \]

0-Nitroaniline (Eastman) (69 grams, 0.5 mole) and phthalic anhydride (Monsanto) (74 grams, 0.5 mole) were placed together in a finely divided state in a 250-ml. 1-necked round bottomed flask fitted with a thermometer and reflux condenser. 35 The materials were melted together at about 185°C. for one hour to form a brown-black liquid which solidified on cooling. Water was driven off during the reaction. The crude yield was quantitative.

The crude product was recrystallized from glacial acetic acid in the usual manner. The product (68 grams, 50.7%), \( N-(2-\text{nitrophenyl})\text{phthalimide} \), was a light greenish yellow crystalline powder melting at 201-203°C. The reported melting point is 202-203°C. 35

\[ \text{N-}(2-\text{Nitrophenyl})\text{succinimide} \]

0-Nitroaniline (Eastman) (69 grams, 0.5 mole) and succinic anhydride (Eastman) (50 grams, 0.5 mole) were placed together
in a finely divided state in a 250-ml. 1-necked round bottomed flask fitted with a thermometer and reflux condenser.\textsuperscript{32,33,34} The materials were melted together at about 180°C. for one hour to form a brown-black liquid which solidified on cooling. Water was driven off during the reaction. The crude yield was quantitative.

The entire batch of crude material was recrystallized in the usual manner from 95\% ethyl alcohol. The recrystallized product was yellowish-brown and had a melting point of 156-158°C. The reported melting point was 156°C.\textsuperscript{32,33,34} The yield of first crop crystals was 55 grams (50\%) and of second crop 3.5 grams (3\%).

**Attempted preparation of 1,1-Diphenyl-2-(2'-pyridyl)-ethane \( (\text{C}_8\text{H}_8\text{N}_2\text{C}_4\text{H}_4\text{O}_2) \).**

\( \text{a-Picoline (Reilly)} \) (28 grams, 0.3 mole), sodamide (12 grams, 0.3 mole), dry toluene (250 ml.) and benzhydryl bromide (redistilled Dow) (50 grams, 0.2 mole) were placed in a 500-ml. 3-necked round bottomed flask fitted with a reflux condenser and sealed mechanical stirrer.\textsuperscript{36,38} The mixture was refluxed for forty-eight hours forming a red-brown solution (color was due to the formation of the sodium salt of \( \text{a-picoline} \)) accompanied by the copious evolution of ammonia throughout the entire reaction (especially during the first portion).

The solution was cooled and a little water was added. The material was extracted with ether. The ether layer became reddish-brown. The aqueous layer was a dark brown-black. An insoluble precipitate was also present. The ether layer was separated and dried over anhydrous potassium carbonate. The aqueous layer and precipitate were discarded.

An alternative procedure involved the extraction of the ether layer with hydrochloric acid to remove the amine components of the mixture from neutral products. When this was done, a large amount of tar was formed. The amine portions consisted chiefly of recovered \( \text{a-picoline} \) and a small amount of a high boiling material which might have been the desired
product. It was never sufficiently purified for positive identification.

The ether solution was evaporated and a solid precipitated out. It was recrystallized from benzene giving a melting point of 209-211°C. This could arise from a type of Wurtz reaction on benzhydryl bromide by sodamide. This reaction seems to take precedence over the desired one in this case. This corresponds to Tschitschibabine's observation that alkyl bromides in this reaction do not give the desired products nearly as readily as the alkyl chlorides.36

The preparation of the desired product did not seem to be successful for tetraphenylethane, 70 α-picoline and benzhydryl bromide were the only products isolated from the reaction mixtures.

\[ \text{o-}(\text{β-Dimethylaminoethylamino})\text{nitrobenzene} \]

β-Dimethylaminoethyl chloride hydrochloride (144 grams, 1 mole) was placed in a 800-ml. beaker with a little ice. It was treated with a concentrated solution of sodium hydroxide (40 grams in a minimum amount of water). The free amine was liberated. It separated out as an oil. The aqueous layer was extracted twice with 50 ml. portions of toluene. The oil and the toluene extracts were then combined and dried over anhydrous potassium carbonate.

In a 1-liter 3-necked round bottomed flask fitted with a stirrer, reflux condenser and dropping funnel, α-nitroaniline (Eastman) (138 grams, 1 mole) was placed in 300 ml. of dry toluene solvent.43,44,71,72 Sodamide (39 grams, 1 mole) was added and the solution was refluxed for one hour to remove the ammonia gas given off during the reaction. The sodium salt of α-nitroaniline was a brown solid which precipitated out of the toluene solution. The toluene solution was cooled and the solution of β-dimethylaminoethyl chloride was added to the sodium salt. The mixture refluxed for three hours during which time the color became red-brown. Sodium chloride
precipitated and was filtered from the cooled solution.

The toluene solution was cooled in an ice bath and dry hydrogen chloride gas was passed in to saturate the solution. A yellow precipitate came down and was filtered off. The yellow solid was recrystallized four times from absolute alcohol. The yield was 150 grams (61%) or 118 grams (48.2%) after the first recrystallization. The melting point was (138) 140-141°C. Calculated for

\[ C_{16}H_{15}N_8O_5 \cdot HCl: \% C = 48.88; \% H = 6.56. \]

Found: \% C = 50.08; \% H = 5.76.

The analysis for this compound did not agree with the calculated values as closely as hoped, but the product is still believed to be the desired 2-(β-dimethylaminoethy lamino)-nitrobenzene in somewhat impure form. The reported boiling point of the free amine was 125-126°C./0.2mm. \(^{43}\) The refractive index (n^25\(_D\)) found was 1.637 for the free amine. The reported value was 1.615.\(^{43}\)

Benzotriazole (\( \begin{array}{c} N \\ N \end{array} \)).

2-Phenylenediamine (Eastman) (108 grams, 1 mole) was placed in glacial acetic acid (Baker) (120 grams, 115 ml., 2 moles) and water (300 ml.) in a 1000-ml. beaker.\(^{62,73,74}\) Upon gently heating, the 2-phenylenediamine dissolved in the acid solution. The material was cooled to 5-10°C. using an ice bath.

Sodium nitrite (Mallinckrodt) (75 grams, 1.09 moles) in 120 ml. of water was added all at once to the 2-phenylenediamine solution. The temperature rose rapidly (as desired to complete the reaction) from 5-10°C. to 70-80°C. with the color changing from dark brown-green to reddish brown.

The ice bath was removed and the solution was allowed to stand for one hour. On cooling the crude benzotriazole oiled out. The beaker was again cooled in an ice bath for three hours. The brown oil solidified and more white crystals came out of solution. The solid material was removed by filtra-
tion, dried and then vacuum distilled to purify the product. The product, benzotriazole, had a boiling range of 175-188°C/4-7mm. The colorless product was recrystallized from benzene in a yield of 76 grams (64%) as a fine white powder melting at 96-98°C. The reported melting point was 96-97° and 100°C. The product was recrystallized from benzene and a yield of 8 grams was obtained from the filtrate. The product remained in the filtrate and was never isolated. The product was recrystall-
lized three times from benzene. The melting point was 156-157°C. Calculated for C_{19}H_{15}N_{3}: % C = 79.97; % H = 5.30. Found: % C = 80.25; % H = 5.20. The total purified yield was 9 grams (15.8%).

1-(Ethyl)benzotriazole and 1-(benzyl)benzotriazole were prepared in the same manner in good yields.

l-(8-Dimethylaminoethyl)benzotriazole (\(N^2\) \(N^6\)-diethyl \(N^2\)-methylbenzotriazole).

Benzotriazole (Eastman) (23.8 grams, 0.2 mole) was added to 250 ml. of dry toluene contained in a 500-ml. 3-necked flask fitted with a reflux condenser, mechanical stirrer and dropping funnel. The material was warmed to about 50°C. to dissolve all the benzotriazole. Sodamide (8 grams, 0.2 mole) was then added carefully as a powder to the benzotriazole solution. Copious quantities of ammonia gas were evolved and the sodium salt of benzotriazole came down immediately as a solid gray suspension.

\(\beta\)-Dimethylaminoethyl chloride hydrochloride (29 grams, 0.2 mole) was treated with sodium hydroxide solution to liberate the free amine. The amine was extracted with toluene with the toluene solution being dried over anhydrous potassium carbonate.

The toluene solution of the \(\beta\)-dimethylaminoethyl chloride was added to the sodium salt of benzotriazole and the mixture was refluxed for fourteen hours. Sodium chloride was formed and filtered off in a yield of 11 grams (95%). The toluene was removed by distillation and the product was vacuum distilled.

1st fraction b.p. = 145-160°C./3mm. Yield 21 grams (58%) light yellow oil

2nd fraction b.p. = 160-190°C./3mm. Yield 9 grams (25%) brown-yellow oil

Total yield was 30 grams (83%).

Some of the first fraction was dissolved in absolute alcohol and dry hydrogen chloride gas was passed in to form the hydrochloride salt. The white salt was recrystallized.
three times from absolute alcohol to give a melting point of 192°C. The reported melting point was 170.5-171.5°C.\(^43\) Calculated for \(\text{C}_2\text{H}_5\text{N}_4\text{HCl}\): \(\% \text{C} = 52.98; \% \text{H} = 6.67.\) Found: \(\% \text{C} = 52.34; \% \text{H} = 6.74.\)

The melting point differs from that reported by Wright (also his compound was prepared in a different manner), but does not seem to be too far from the desired material.

Glycerol \(\alpha\)-monochlorohydrin \((\text{ClCH}_3\text{CHOHCH}_2\text{OH}).\)

Glycerol (500 grams, 402 ml., 4.9 moles) (90% solution) and glacial acetic acid (Baker) (10 grams) were mixed in a 1-liter 2-necked flask fitted with a thermometer, hydrogen chloride gas inlet tube and a short gas outlet tube.\(^7\) The material was heated to 105-110°C. on a Glascol heater. A rapid stream of dry hydrogen chloride (Matheson) gas was introduced into the glycerol solution till the gain in weight of the reactants was 190 grams. Three hours were needed for the reaction to take place. The temperature was maintained at 105-110°C. in order to get optimum yields of the product.

<table>
<thead>
<tr>
<th>Time interval minutes</th>
<th>Weight in grams</th>
<th>Gain in weight grams</th>
<th>Color of solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>976</td>
<td>0</td>
<td>water clear</td>
</tr>
<tr>
<td>40</td>
<td>1010</td>
<td>34</td>
<td>straw yellow</td>
</tr>
<tr>
<td>100</td>
<td>1118</td>
<td>142</td>
<td>darker yellow</td>
</tr>
<tr>
<td>180</td>
<td>1173</td>
<td>197</td>
<td>yellow-orange</td>
</tr>
</tbody>
</table>

If hydrogen chloride was added too rapidly, the temperature rose above 110°C.

The yellow-orange solution fumed a little of hydrogen chloride. It was vacuum distilled using a water pump. The results were:

1st fraction b.r. 30-55°C./10mm. mostly water
b.r. 55-110°C./10mm. \(\alpha,\gamma\)-dichloro compound
Yield was 157 grams.

(b.r. of \(\text{ClCH}_3\text{CHOHCH}_2\text{Cl}\) = 71-78°C./1\text{mm}.)

2nd fraction b.r. 110-125°C./10mm. desired product
\(n_\text{D}^20 = 1.479\) for product
= 1.473 for glycerol
= 1.480 for \(\text{diCl}\) product
The reported boiling range for glycerol α-monochlorohydrin was 115-118°C./11mm. and 113-136°C./20mm. The yield was 252 grams (46.5%). The product was a water clear, viscous liquid with a pleasant peculiar odor.

**1-(2',3'-Dihydroxypropyl)benzotriazole**

Benzotriazole (23.8 grams, 0.2 mole) was dissolved in warm (40°C.) toluene (250 ml.) in a 500-ml. 3-necked round bottomed flask fitted with a stirrer, dropping funnel and reflux condenser. Sodium (8 grams, 0.2 mole) was added to the toluene solution. Within a few minutes the white sodium salt of benzotriazole precipitated out of solution with accompanying copious evolution of ammonia gas. The materials were refluxed ninety minutes to assure complete reaction. Glycerol α-monochlorohydrin (22 grams, 0.2 mole) was added to the sodium salt of benzotriazole to give a heavy dark resinous oil. Refluxing was continued for three hours. The sodium salt disappeared rapidly as the reaction occurred. The oil was insoluble in toluene and separated out at the bottom of the flask.

The toluene solution was decanted and discarded. The oil product was dissolved in a minimum amount of alcohol. The crude yield was quantitative. The alcohol solution was brown with some white solid in it. This white solid was sodium chloride formed in the reaction. The yield of sodium chloride was 11.5 grams (100%).

The alcohol solution was placed in a Hickman still. The alcohol was removed by distillation under vacuum using an ordinary vacuum pump. After the solvent was removed, molecular distillation was carried out.

1st fraction b.r. = 210-217°C./0.03-0.20mm.
2nd fraction b.r. = 217-260°C./0.07-0.08mm.

The product was a medium brown, very viscous, clear semi-solid oil.

The product (18 grams of it) was again molecularly distilled to obtain as pure and as anhydrous a product as
possible using completely anhydrous equipment. The material was divided into four fractions:

1. b.r. = 205-225°C./0.05-0.06mm.
2. b.r. = 225-228°C./0.06mm.
3. b.r. = 228-244°C./0.06mm.
4. b.r. = 244-268°C./0.06-0.07mm.

The purified yield was 13.5 grams (35%). The product was light orange-brown in color and was very viscous. It would not flow. Calculated for C₉H₁₁C₂N₃: % C = 55.95; % H = 5.74. Found: % C = 55.90; % H = 5.93.

5-Bromo-2-aminopyridine \( \left( \text{C}_9\text{H}_9\text{N}_2 \right) \).

2-Aminopyridine (Reilly) (94 grams, 1 mole), glacial acetic acid (Baker) (304 ml.) and acetic anhydride (Mallinckrodt) (104 ml.) were placed in a 1000-ml. 1-necked round bottomed flask fitted with a reflux condenser. The solution was refluxed for three hours to form an orange solution of 2-acetamidopyridine.

The solution was cooled to 45-55°C. The material was placed in a 1000-ml. 3-necked round bottomed flask fitted with a dropping funnel and mechanical stirrer. Bromine (Baker) (164 grams, 54 ml., 1 mole) was added dropwise to the 2-acetamidopyridine solution over a thirty minute period. The solution was then stirred till all the bromine color had disappeared.

Most of the solvent (acetic acid, etc.) was removed by heating on a steam bath with a water pump under reduced pressure. A slurry was formed as the solvent was removed. A dilute solution of sodium bisulfite was added to remove any excess unreacted bromine.

The material was now made almost alkaline with solid sodium carbonate. A brown precipitate settled and was removed by filtration. A small portion of this material was recrystallized from absolute alcohol to give a tan powder. This product was 5-bromo-2-acetamidopyridine. The melting point was 165-170°C. The reported melting point was 175°C.58,59
The crude 5-bromo-2-acetamidopyridine was placed in a 1000 ml. 1-necked flask fitted with a reflux condenser with 95% ethyl alcohol (300 ml.) and concentrated hydrochloric acid (250 ml.). The product was refluxed for three hours, with the orange color becoming dark brown-black as deacetylation occurred. The solvent was then removed under reduced pressure on a steam bath.

Solid potassium carbonate was added to make the solution definitely alkaline. A brown precipitate was filtered off. The product, 5-bromo-2-aminopyridine, was recrystallized from benzene to give a yield of 62 grams (35.8%). The melting point was 133-135°C. The reported melting point was 137°C.25,58,59 The second crop yield was 11 grams (6.3%) with a melting point of 125-130°C. The total yield was 73 grams (42.1%).

5-Methyl-2-nitraminopyridine (\(\text{C}_6\text{H}_5\text{N}^+\text{N}_2\text{NO}_2\)).

This is a typical nitration experiment.

This experiment was run in nineteen (19) separate small batches in order to obtain better cooling and to avoid decomposition of the desired product at higher (over 50°C) temperatures.12,13,14,15

Each batch was run in this manner:

Cold concentrated sulfuric acid (Baker and Adamson) (sp.gr. 1.84) (33 ml.) was placed in a 100-ml. beaker which was in an ice bath. The use of a metal beaker did not help in this reaction. 5-Methyl-2-aminopyridine (Reilly) (15 grams, 0.139 mole) was added to the sulfuric acid with good stirring. The material fumed a little and the solution heated up strongly as the neutralization reaction occurred. The resulting solution of the amine in sulfuric acid was cooled to 0-5°C by standing for one hour in the ice bath.

Fuming nitric acid (Baker and Adamson) (sp.gr. 1.50) (9 grams) was added carefully to the solution with good stirring. (Concentrated nitric acid (sp.gr. 1.42) also can
be used as the nitrating agent with about equally successful results.) The nitrating mixture was allowed to stand for two hours in an ice bath. The color changed from a light yellow to a dark orange-brown.

The nineteen batches (total amount of product nitrated was 285 grams (2.64 moles)) were combined by pouring the total nitrating mixture onto about 1500 grams of ice in a 4-liter beaker. A yellow-orange precipitate came out of solution. The mixture was cooled and the precipitate filtered off.

The precipitate was recrystallized in the usual manner from 12 liters of water. The product, 5-methyl-2-nitraminopyridine, was obtained in a yield of 200 grams (49.5\%) with a melting point of 177°C. (dec.). The material was recrystallized three times giving a melting point of 183-183.5°C. (dec.). It was light yellow in color. Calculated for C₆H₅N₂O₂: % C = 47.05; % H = 4.61. Found: % C = 47.13; % H = 4.60.

The product prepared using concentrated nitric acid as the nitrating agent had a melting point of 175-176°C. (dec.). Found: % C = 47.38; % H = 4.60.

Also prepared by this method were the following:

2-Nitraminopyridine had a melting point of 191.5-192.5°C. (dec.). The reported melting point was 184°C. (dec.).\(^{17}\) Calculated for C₆H₅N₂O₂: % C = 43.17; % H = 3.62. Found: % C = 43.13; % H = 3.59.

5-Bromo-2-nitraminopyridine had a melting point of 177°C. (dec.). The reported melting point was 181°C. (dec.).\(^{23}\) 5-Chloro-2-nitraminopyridine had a melting point of 165-166°C. (dec.). The reported melting point of 159-160°C. (dec.).\(^{24}\)

5-Bromo-3-nitro-2-aminopyridine (\(\text{C}_6\text{H}_5\text{N} = \text{NO}_2\)).

This is a typical rearrangement experiment.

This experiment was run in ten (10) batches to get better cooling. Cold concentrated sulfuric acid (Baker and Adamson)
(sp. gr. 1.84) (35 ml.) was placed in a 100-ml. beaker in an ice bath. 5-Bromo-2-nitraminopyridine (5 grams, 0.023 mole) (total for the ten batches 50 grams, 0.229 mole) was added to the sulfuric acid. It was necessary to warm the solution to room temperature in order to get the 5-bromo-2-nitraminopyridine into solution. The solution warmed up a little as rearrangement took place. The material was allowed to stand overnight in a water bath. The color changed from light yellow to dark orange.

(In the cases of 5-methyl-2-nitraminopyridine and 2-nitraminopyridine, no warming was needed to get the compounds into sulfuric acid solution. In fact much better cooling was needed to prevent the material from getting too hot and decomposing. The materials were allowed to stand only one or two hours in these cases in an ice bath in order to secure complete rearrangement.)

The ten batches combined by pouring onto about 1700 grams of ice. A yellow precipitate came out of solution. The precipitate was filtered off and recrystallized in the usual way from absolute ethyl alcohol. The yield was 26 grams (52%) with a melting point of 202-204°C. There was a second crop of 8 grams (16%). The reported melting point was 205°C.

In the cases of 5-methyl-2-nitraminopyridine and 2-nitraminopyridine, it was necessary to neutralize the acid-ice water solution with sodium hydroxide or sodium carbonate before the desired product came out of solution. This introduced complications in the purification of the final products due to the presence of large quantities of sodium sulfate.

In the case of 2-nitraminopyridine, two isomers were formed on rearrangement. They were 5-nitro-2-aminopyridine and 3-nitro-2-aminopyridine. The 5-isomer was formed in much larger quantities than the 3-isomer. The 3-isomer was the one desired. It was separated from the 5-isomer by
exhaustive steam distillation. The 3-isomer was volatile with steam while the 5-isomer was not. The 3-isomer was also much more soluble in water than the 5-isomer.

5-Chloro-3-nitro-2-aminopyridine had a melting point of 192-193°C. The reported melting point was 195-196°C. 24

5-Methyl-3-nitro-2-aminopyridine had a melting point of 189.5-190.5°C. Calculated for C₆H₇N₂O₂: % C = 47.05; % H = 4.61. Found: % C = 47.15; % H = 4.73.

5-Nitro-2-aminopyridine had a melting point of 188°C. The reported melting point was 189°C. 17

3-Nitro-2-aminopyridine had a melting point of 166-166.5°C. The reported melting point was 162°C. 17

**Mixture of 2,5-Diaminopyridine and 2,3-Diaminopyridine.**

This is a typical catalytic reduction experiment. In most cases the products obtained were impure and defied purification even as the hydrochloride salts.

A mixture of 5-nitro-2-aminopyridine and 3-nitro-2-aminopyridine (very largely the 5-isomer) (3 grams, 0.0216 mole) was placed in a citrate of magnesia bottle with absolute ethyl alcohol solvent (50 ml.) and a trace of Adams catalyst (platinum oxide). Acetic anhydride was a possibility as a solvent for this reduction, but it was not tried in the laboratory. The bottle was placed in the Parr hydrogenator and flushed out three times with hydrogen. A heat lamp was used to facilitate solution of the material in alcohol. A pressure drop of 5.2 pounds was calculated for a theoretical use of 0.0648 moles of hydrogen. (The pressure drop of 8 pounds for each 0.1 mole of hydrogen was the calibration of the Parr apparatus used.)

The color changed from yellow to dark brown as reduction occurred. A pressure drop of 5.1 pounds was noted. The reduction took place in about two hours.

The platinum catalyst was filtered off and dry hydrogen chloride gas (Matheson) was passed into the alcohol solution
in order to form the dihydrochloride of the product. The alcohol solution was evaporated to a low volume, cooled and the dihydrochloride product was filtered off in a yield of 3.4 grams (67.3%). The product was a purple-black solid which was not pure.

5-Methyl-2,3-diaminopyridine had a melting point of (194) 195-196°C. (dec.). Calculated for C₆H₅N₂: % C = 58.51; % H = 7.37. Found: % C = 48.50; % H = 5.43. The reduction did not go to completion. Some of the 5-methyl-3-nitro-2-aminopyridine was still present.

The stannous chloride -hydrochloric acid reduction of 5-chloro-3-nitro-2-amino pyridine by the method of McKee gave as the product a purple solid which was not further purified. It was assumed to be 5-chloro-2,3-diaminopyridine.

6-Chloro-1- or 3-pyrido(2,3-d)-y-triazole

This is a typical diazotization experiment. Approximately 8.3 grams or 0.58 mole of 5-chloro-2,3-diaminopyridine (the hydrochloride salt also could be used in the diazotization reaction) was dissolved in 150 ml. of water to which 14 ml. of concentrated hydrochloric acid had been added. The purple color of 5-chloro-2,3-diaminopyridine turned to a dark brown as its hydrochloride salt was formed.

Sodium nitrite (Mallinckrodt) (4.1 grams, 0.06 mole) was dissolved in 50 ml. of water. The solution of sodium nitrite was added to the solution of 5-chloro-2,3-diaminopyridine in a large beaker. Reaction occurred immediately and a light brown precipitate was formed.

The material was allowed to stand for twenty-four hours. The solid was removed by filtration. When it was dried, it weighed 3.3 grams (37% yield based on 5-chloro-3-nitro-2-aminopyridine). The light brown solid contained some inorganic matter. The material was recrystallized from absolute alcohol. It gave a brown product which was still impure.
6-Chloro-1-or 3-(β-dimethylaminoethyl)pyrido(2,3-d)-v-triazole

\[
\text{6-Chloro-1-or 3-pyrido(2,3-d)-v-triazole (1 gram, 0.0065 mole), sodamide (0.3 gram, 0.0065 mole) and dry benzene (50 ml.) were placed in a 100-ml. 1-necked round bottomed flask fitted with a reflux condenser. The materials were refluxed for one hour.}^{44} \text{ A black solid was formed and ammonia gas was liberated.}
\]

β-Dimethylaminoethyl chloride, prepared from the hydrochloride (0.75 gram, 0.007 mole) and sodium hydroxide in benzene solution (25 ml.), was added to the reactants. Refluxing was continued for thirty hours. The solution became brown and turbid due to the formation of a little sodium chloride. Ammonia still came off during this period.

The sodium chloride was filtered off after the refluxing was stopped. A black benzene filtrate was obtained. A little absolute alcohol (20 ml.) was added to the benzene. Dry hydrogen chloride gas (Mátheson) was added to the solution to form two liquid phases. The upper benzene layer was almost colorless. It was discarded. The alcohol layer was dark brown. It was evaporated to dryness to give a soft brown solid which had a peculiarly pleasant odor. The yield was 0.6 grams (35%). There was a little inorganic matter still present in this impure product.

More work still must be done in this field in order to clear up a number of points.
Work which began as the consideration of some compounds that might possess antihistamine activity developed into a study of benzotriazoles and 1-or 3-pyrido(2,3-d)-v-triazoles.

A number of 1-substituted benzotriazoles were prepared including 1-benzhydryl benzotriazole and 1-(2',3'-dihydroxy-propyl)benzotriazole. This latter compound should possess curare-like activity for it is a hybrid of benzotriazole and Myanesin both of which are good curare-like materials.

The resonance theory was applied for the first time to the explanation of the alkaline alkylation of the benzotriazoles.

The 1-or 3-pyrido(2,3-d)-v-triazoles were synthesized starting from 5-R-2-aminopyridines. R was hydrogen, methyl, bromo and chloro. These syntheses were both long and difficult with the yields low and the reactions tedious.

The resonance theory was applied in the explanation of the reaction occurring when 2-aminopyridines were nitrated as well as the subsequent rearrangement reaction of the 2-nitramino-pyridines formed.

Our intention to prove the structure of the pyridotriazole alkylation products was unsuccessful. It is still not known whether 2,3-diaminopyridines form the 1-pyrido(2,3-d)-v-triazoles or the 3-pyrido(2,3-d)-v-triazoles or both. The literature has reported both, but without proof of structure of any of the materials reported. We believe the product formed to be the 3-pyrido(2,3-d)-v-triazole, but we were unable to confirm this idea in the laboratory.

A number of new compounds of the pyridine series were prepared. They were 5-methyl-2-nitraminopyridine, 5-methyl-3-nitro-2-aminopyridine and 5-methyl-2,3-diaminopyridine. In addition many compounds of this nature in the pyridine series that have been reported in certain obscure and unreliable literature (J. Russ. Phys.-Chem. Soc., etc.) were prepared again and their properties noted.
6-Chloro-1-or-3-pyrido(2,3-d)-v-triazole and 6-chloro-1-or-3-(β-dimethylaminoethyl)pyrido(2,3-d)-v-triazole were prepared in an impure state.

The resonance theory was applied to the explanation of the alkaline alkylation of the pyridotriazoles.

The attempted sodamide condensation of α-picoline and benzhydryl bromide did not work.
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