

THE PREPARATION OF COMPOUNDS RELATED TO THE INSECTICIDE

O,O-DIETHYL-O,p-NITROPHENYL THIOPHOSPHATE

by

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## INTRODUCTION

Since prehistoric times, man has been afflicted by insects and pests of many kinds. It was not, however, until he began to cultivate crops and to remove vegetation growing around the desired plants, thus enabling them to receive more nourishment, that he first gave attention to insect pests. With only ten plants on which to feed in place of the hundreds before removal of excess vegetation, insects could quickly destroy an entire crop. As man became increasingly civilized and built villages and towns, possibilities for social and physical contact increased. At the same time, transmittal of parasitic insects and insect borne diseases was facilitated. The over-all effect, as is often the case when man is involved, was an upsetting of "Nature's balance of life". As a result, the insect population has been ever on the increase.

Seeing and understanding the cause of his affliction, man rose to the occasion and began to rid himself of the pests. Perhaps the earliest method he used was the purely manual operation of removing and killing them by hand. This procedure has persisted up to quite recent times. Another early method of pest control was the use of insect traps.<sup>1</sup> Many ingenious devices of this type, several of which are still used to some extent, have been built.

Biological methods have been applied to pest control, with marked success in some instances, and failure in others. The encouragement of a plant or animal that preys

on the undesirable insect may bring control in some cases, whereas in others it may upset the natural balance of life with the usual ruinous results. As will be pointed out later, this may also happen when chemical means of insect control are used. Examples of cases where environmental conditions have limited the use of biological methods are numerous.

Simple sanitation techniques have often led to complete control of mosquitoes and other insect pests, but the general application of this method is limited by the fact that strict control of environmental conditions is often difficult, if not impossible.

One of the newer and more promising methods of insect control has been the development of pest resistant strains of plants and animals. This procedure has been markedly successful in the cattle industry, although it is limited by the great amount of time involved in breeding and testing new strains.

Use of insecticides on a commercial scale dates back to 1681, when the first article, recommending the use of arsenicals, was published. Undoubtedly, chemicals were used to combat pests before this date, for the Arabian Nights mentions the insecticidal use of pyrethrum flowers,<sup>2</sup> a substance employed up to the present day. Large scale production of chemicals for insecticidal purposes, however, dates back only about fifty years. At that time and continuing until about eight years ago, inorganic chemicals

were the main constituents of these preparations. Arsenic compounds have been the most popular of all inorganic insecticides. The average annual production of arsenicals during recent years has been approximately 100,000,000 pounds, most of which was consumed in this country.

The major consideration in the application of a chemical for pest control is its application in such a manner that it may come into contact with the pest and remove its powers of destruction. One of the most common methods of application is by spraying, with water as a diluent. Keeping pace with the research into new insecticides, has been the investigation of new procedures of application to the affected areas. Since many pest controlling compounds are insoluble in water, procedures for solublizing or emulsifying a number of them have been developed. Solid and liquid compounds have been mixed with dusts and applied by means of dusting machines. This procedure has been quite popular where the pest control chemical is to be applied over an extensive area. It has not, however, been used as widely as the spraying process.

Suspensions of solids and liquids in air, or aerosols, the individual particles of which are of colloidal dimensions, have been applied. They have been used extensively in orchards to give a uniform coating of insecticide over the entire tree. This method has the limitation that the preparation of the suspension requires more elaborate machinery than other procedures.

In some instances, the plants or animals themselves may be injected with a substance that is incompatible with the pest. This procedure has been almost completely limited to greenhouse plants, since most compounds that are toxic to the pest may also be poisonous to the plant or animal injected.

The use of organic chemicals as insecticides has gained most of its popularity during the last seven or eight years, since the arrival on the scene of 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane. This material, more popularly known as "DDT", was first synthesized by Zeidler<sup>3</sup> in 1874. There is no known record of his having looked for any use for the compound, and it was not until approximately fifty years later that the firm of J. R. Geigy A.-G. in Switzerland began to investigate similar compounds as moth preventive agents. Numerous active compounds were discovered during the period 1924 to 1939, most of which were of the sulfone type. Most effective of these was bis-(p-chlorophenyl) sulfone. In 1939, shortly after the discovery of the mothcidal properties of this compound, Lauger, Martin, and Muller<sup>4</sup> of the Geigy firm tested 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane and found it to be highly effective against moths as well as other species of insects. Subsequent work in 1940 and 1941 confirmed their conclusions that DDT was a highly effective insecticide. Because of barriers to international communication existing during the war it was not until late in 1942 that news of

these experiments reached the United States. A sample of DDT was immediately obtained and analyzed by Haller<sup>5</sup> of the U. S. Department of Agriculture. The analysis was confirmed and the insecticidal activity was found to be even greater than reported. Because of the wartime need of a versatile insecticide private agencies were encouraged by the government to start manufacturing it on a commercial scale. By May 1943 a pilot plant was built, and from this time on the rate of production increased steadily until the end of the war in 1945, at which time the total annual output was 32,998,587 pounds.<sup>1</sup>

Along with the increasing use of DDT during the war and since, the number of organic compounds tested for insecticidal properties has steadily increased. With the increasing number of compounds tested the preparation of new compounds that possess toxic action to insects has begun to fit a general pattern so that now new insecticides are discovered by testing compounds similar to known insecticidal substances. This pattern makes necessary a classification that will assist the chemist by pointing out the known highly active compounds. Such a classification is the following:

- I. Inorganic Compounds
  - A. Arsenicals
  - B. Fluorine Compounds
  - C. Antimony Compounds
  - D. Mercury Compounds

- E. Selenium Compounds
- F. Thallium Compounds
- G. Miscellaneous Inorganic Compounds

## II. Organic Compounds

### A. Compounds from Natural Sources

1. Pyrethrums
2. Nicotine Salts
3. Rotenone and the Fish Oil Poisons
4. Miscellaneous Insecticides Derived from Plants

### B. Synthetic Organic Compounds

1. DDT
2. Hexachlorocyclohexane
3. Chlordane
4. Parathion
5. Organic Sulfur Compounds
6. Organic Nitrogen Compounds
7. Miscellaneous Organic Compounds

In choosing the proper insecticide to be used, one must consider certain facts about the insect, the subject upon which it acts, and the use of the plant or animal. For the control of chewing insects a stomach poison is recommended. Such materials are applied on the surface of the plant or animal on which the insect feeds. The poison is thus ingested along with the food of the insect. Stomach poisons should be insoluble in water, for plant use, to prevent their being washed away by rain. They should

also be able to withstand decomposition over fairly long periods of time to maintain their effectiveness.

For non-biting or non-chewing insects substances which will kill the insect on contact must be applied. Such materials are called contact insecticides. They must be water or oil soluble since solution in the body moisture or oil of the insect is required to facilitate their absorption into its body. Stored substances may be kept free of insects by fumigation, since here the direct application of toxicant is usually impracticable.

It is often difficult to distinguish whether a substance acts as a stomach or contact poison. Frequently insecticides may function in both of these manners and also as a fumigant. Many of the newer insecticides combine all three of these functions. For this reason, and because the organic insecticides, such as DDT, can be used against so many different species of insects, they have become very popular. With their increasing popularity, many instances of misuse have arisen. As has been the case with the sulfa drugs, DDT and several other new insecticides have reached the hands of indiscriminant producers, and claims unwarranted by results of experimental testing of activity have been made. Statements that DDT would kill any and all insects, that it would control all orchard pests,<sup>6</sup> have been frequent. Even when reputable advice has been given, users have often tried their own experiments in the application of these agents, sometimes with disastrous results. When

DDT has been used in orchards, for example, the European Red Mite has become much more active,<sup>6</sup> because the Coddling Moth which feeds on the Mite is killed and the Mite, unopposed and not affected by DDT, is encouraged to much greater destruction.

Another factor to be considered in the use of insecticides, is the possible sudden development of immunity to toxic action of a given compound in a strain of a species of insect. This factor has appeared in the use of DDT as a residual poison. Although the possibility that a species might develop such a resistant strain was feared for some time, no reports of such instances were forthcoming until October 1948,<sup>7</sup> when a strain of common house fly was reported as being immune to residual doses of DDT that killed ordinary laboratory test flies. These same flies were easily killed by normal doses of other insecticides, or larger doses of DDT. Another instance of this type is the case of the high resistance of the Coddling Moth, in the Pacific Northwest, to lead arsenate.<sup>6</sup> Growers have begun to use DDT against this moth. In the citrus orchards of California, the red scale insects, within a period of twenty years, have developed almost complete immunity to hydrocyanic acid gas.

If insects may develop strains that are resistant to a given insecticide, there exists the gloomy prospect that they might become resistant to any and all insecticides. Should this occur the chemist faces a real battle--that of

producing new insecticides faster than the insects develop new resistant strains, until all insects of a harmful nature are wiped out. This is a most ambitious project, since, of the estimated three million species of insects in the world, several thousand are known to be injurious. Indeed the insect population of the world is estimated to be greater than the combined population of all other creatures.

Studies have been made of the mechanism by which contact insecticides act. Lauger, Martin and Muller<sup>4</sup> have postulated that a compound, to be active, must possess groups that help it to dissolve in the body oils and moisture, and other groups that give it a toxic action. They attribute high activity of DDT to its chloroform residue, which is both lipophylic and toxic, and therefore gives the molecule an affinity for the nerve lipoids, where it is absorbed and then exerts its toxic action. The para substituted dichlorophenyl groups of the molecule also have a toxic effect, and aid in the insecticidal action. DDT attacks the peripheral nervous system of crustacea, acting on the motor neurones to produce a multiplication of nerve impulses. At the same time the sensory neurones may also be attacked.

The postulate that the chloroform residue has a toxic action has been tested by Kirkwood and Dacey,<sup>8</sup> who prepared 2,2-bis-(p-chlorophenyl)-1,1,1-trifluoroethane and found it to be less toxic than the corresponding chlo-

rine analogue (Figure 1). This was the expected result

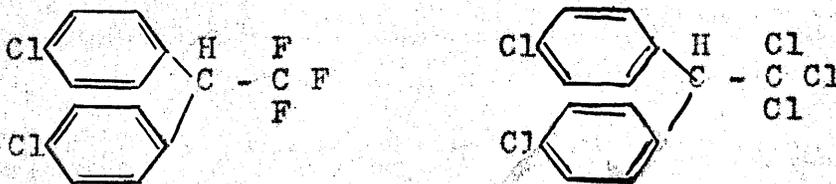


Figure 1.

since fluoroform is not toxic to animal life, whereas chloroform is.

Further studies on analogues of DDT<sup>9</sup> have shown that substitution of different halogens for the chlorine groups at the para position of the phenyl groups were more toxic for specific uses than DDT in some cases, and less toxic in others.

Slade<sup>2</sup> has studied the insecticidal action of the  $\gamma$ -isomer of hexachlorocyclohexane. This compound is more commonly known as "hexachlorobenzene", "gammexane", or "666". The  $\gamma$ -isomer, along with four other known isomers and possibly others that have not yet been isolated, is produced by the photochemical chlorination of benzene. It is an excellent insecticide, useful as a stomach, contact and respiratory poison. The  $\gamma$ -compound, Figure 2, is the only one of the five known isomers that has

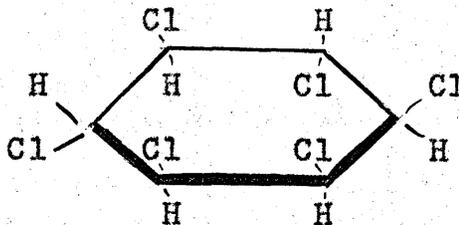


Figure 2

appreciable insecticidal activity.

Slade<sup>2</sup> states that Gammexane, itself, is the isomer that most nearly resembles meso inositol, the chlorine atoms being in positions corresponding to the hydroxyl groups. Meso inositol, however, has never been isolated in the pure state, but is supposedly the active inositol in the vitamin B complex. Slade postulates that in acting as a contact insecticide, Gammexane is absorbed from the outside of the insect and then distributed throughout some portion of the organism to the cells where it blocks a vital reaction and the organism dies.

The previously described studies of DDT and Gammexane illustrate the type of information needed by the chemist in the preparation of new and better insecticides. Even with a large body of information concerning a given insecticidal compound, there is still a considerable amount of empiricism in the investigation into newer compounds to be tested for insecticidal use. It was from these viewpoints that studies on the preparation of compounds related to O,O-diethyl-O,p-nitrophenyl thiophosphate (parathion) were started. Parathion is one of the newer insecticides to be used on a commercial scale. It is one of a group of compounds on which very little work has been reported in the literature. The first reports of parathion were made by Thurston<sup>10</sup> in 1946. At that time it was called "E-605". Since then it has been referred to as "A.A.T.P.", "3422", "thiophos", "parathion" and "niran". All of these names

refer to the commercially available compound O,O-diethyl-O,p-nitrophenyl thiophosphate (Figure 3).

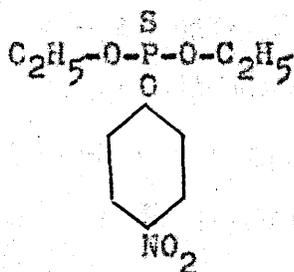
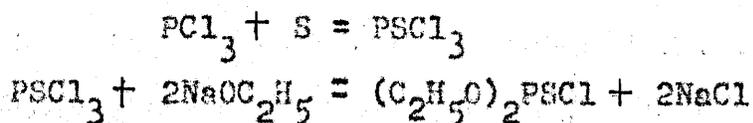
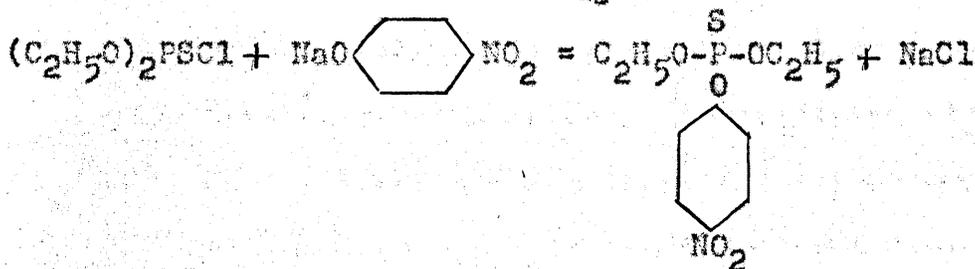


Figure 3

Thurston<sup>10</sup> reports that the Elberfield chemists of I. G. Farbenindustrie, as a result of their earlier work on phosphorus containing war gases and because of a shortage of nicotine for insecticidal purposes, prepared and tested over 300 compounds before arriving at parathion. They recommended its preparation in three steps starting with sulfur and phosphorus trichloride. These raw materials are heated to 130° to form phosphorus thiochloride in almost quantitative yield. This is then reacted with two moles of sodium ethylate in ethanol to give diethoxythiophosphorylchloride in about 80% yield. The product is isolated by extraction from water, in which it is stable up to about 80 to 90° C., with benzene and then distilled at reduced pressure. The purified compound is reacted with one mole of sodium p-nitrophenoxide in chlorobenzene at 130°C. to give O,O-diethyl-O,p-nitrophenyl thiophosphate in about 90% yield, as shown by the equations:





Marcovitch<sup>6</sup> reports that parathion acts as both a contact and stomach poison. He postulates that it acts by inhibition of the enzyme choline esterase. His reasoning is based on the fact that atropine cures cases of parathion poisoning and also inhibits the action of physostigmine and related substances known to inhibit the action of choline esterase. He then concludes that if atropine is curative in cases of parathion poisoning it must be so because of an inhibition of the action of some substance on choline esterase, and that substance must be parathion or a degradation product of it.

Parathion is very toxic to warm blooded animals. When used as a residual insecticide on plants, however, the concentrations required are so low, that no health hazard is presented. Furthermore, it is sufficiently volatile to vaporize before it is consumed, if a period of time elapses between the application and consumption. It has also been found to be quite active against the Colorado Potato Beetle, the European Red Mite, grasshoppers, flies, Plant lice on cotton, Red spider on cotton, Mexican bean beetle, Bean leaf hopper, Green peach aphid on tobacco, Tobacco hornworm, Codling moth, Woolly apple aphid, Plum curculio, Grape berry moth, Japanese beetle, Cabbage worms, European corn borer,

Ants, Mole crickets, Meally bugs, Scale insects, Thrips and several others.

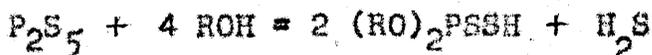
Two of the outstanding characteristics of parathion which make it of great insecticidal interest are its ovicidal action and its low phytotoxicity. Wolfenbarger<sup>11</sup> has found that parathion along with other phosphate insecticides have the further advantage of being plant nutrients.

DISCUSSION OF THE PROBLEM

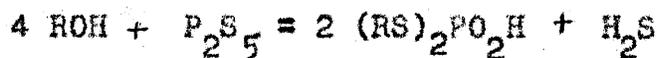
The field of thiophosphate chemistry has not been explored to any great extent; hence the problem of preparing new compounds of this type has aroused an interest that can be satisfied only by the acquisition of more knowledge of the subject through research. Organic dithiophosphates have been reported in the literature as being used for inhibition of corrosiveness of detergent additives to lubricating oils.<sup>12</sup>

In the last five or six years several patents specifying the use of the salts of thiophosphoric acid esters as detergents, corrosion inhibitors, pour point depressors and plasticizing and fire retarding agents<sup>13,14,15,16,17</sup> have been issued.

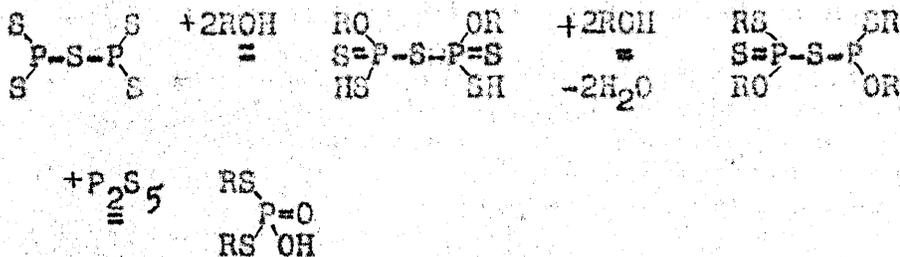
The methods of preparation of these compounds vary considerably. Cambi<sup>18</sup> and others have reported that esters of dithiophosphoric acid may be prepared by the reaction



While this is the probable reaction and is the one most often reported, Jauregg, *et. al.*<sup>19</sup> maintain that in their attempts to prepare thiocholesterol by boiling cholesterol with phosphorous pentasulfide in carbon disulfide, they obtained a substitution product in which the cholesteryl radical was connected by a sulfur atom to the phosphorous group as shown by the equation

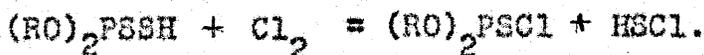


where R represents the cholesteryl radical. They state that the mechanism of their reaction is as follows.

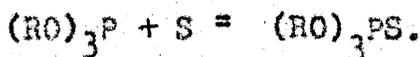


In the light of most accepted theories of organic chemistry it seems difficult to accept this report as being correct.

Dialkoxy-dithiophosphoric acid esters may be converted to dialkoxythiophosphoryl chlorides by direct chlorination<sup>20</sup> according to the equation:

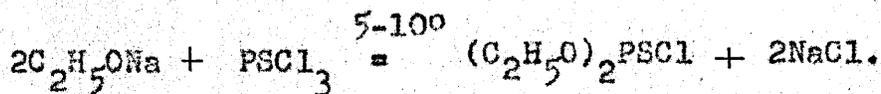


Dialkoxythiophosphoryl chlorides may then be reacted with the alkali metal salt of an alcohol or phenol in order to replace the chlorine atom with an alkoxy or aryloxy group giving a trisubstituted monothiophosphate, in the manner described by Thurston<sup>10</sup> and elaborated upon by Fletcher, et. al.<sup>21</sup>. Neutral monothiophosphoric acid esters have also been prepared from neutral phosphorous acid esters by reaction with sulfur<sup>22,23</sup> according to the equation:

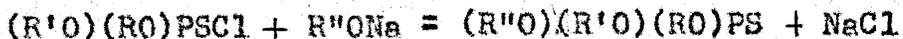
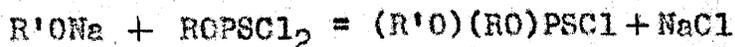
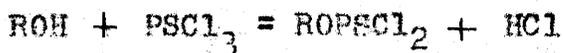


Other methods of preparation involve the reaction of thiophosphoryl chloride with the appropriate alcohol or phenol to substitute one, two or three of the chlorine atoms, depending upon the conditions used. Fletcher, et. al.<sup>21</sup> have reported a fifty percent yield of diethoxythiophosphoryl chloride from the reaction of two moles of sodium ethoxide and thiophosphoryl chloride in an alcohol-benzene solution

maintained at 5 to 10° C., as shown by the reaction:

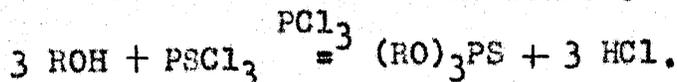


Using this reaction it is possible to prepare a mixed neutral ester containing two like aryl or alkyl groups. If all three groups are to be different the preparation is accomplished by reacting one mole of the alcohol or phenol with one mole of thiophosphoryl chloride at a low temperature, followed by reaction with one mole of the sodium salt of the second alcohol or phenol at a low temperature and then by the replacement of the third chlorine atom using the sodium salt of the alcohol or phenol at an elevated temperature. In each case it is best to use equimolar quantities of reactants. The equations for the reactions involved in such a procedure are as follows:



where R, R', and R'' refer to different alkyl or aryl radicals.

If an unmixed neutral ester of thiophosphoric acid is to be prepared from thiophosphoryl chloride the reaction may be conducted in two different ways (1) by the conventional reaction of the sodium salt of the alcohol or phenol using a polar solvent and (2) by reaction of the alcohol or phenol itself with thiophosphoryl chloride in the presence of phosphorus trichloride as a catalyst<sup>24</sup> as follows:



## SCOPE OF THE PRESENT WORK

Since the field of organic thiophosphate chemistry has been relatively untouched, the search for new compounds to be prepared becomes a matter of the experimenter's choice. In the preparation of the new compounds in this research there were two main purposes, (1) to attempt to correlate the structure with the insecticidal activity, and (2) to find better methods of preparing the monothiophosphate neutral ester type compound. In the preparation of these substances several intermediates were needed that could not be purchased from ordinary sources. These compounds were prepared, using in many cases new procedures that were applicable.

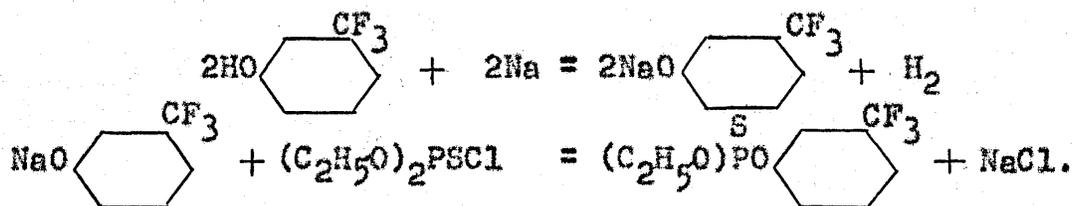
The preparation of compounds similar to O,O-diethyl-O,p-nitrophenylthiophosphate involves any one of the three methods of attack already mentioned (1) replacement of two of the chlorine groups on thiophosphoryl chloride followed by the reaction of the product with sodium phenoxide, (2) reaction of phosphorous pentasulfide with excess alcohol to form the diethoxydithiophosphate followed by chlorination and reaction of the chlorinated product with a sodium phenoxide, or (3) the preparation of the diethoxyphenoxy phosphite and the reaction of this product with sulfur to form the thiophosphate ester. Procedure one was used for the most part because of the availability of thiophosphoryl chloride and the ease of formation of the

intermediate diethoxythiophosphoryl chloride from it.

Because of the great interest in fluorine compounds and their ever increasing availability it was decided to prepare o-, m-, and p-sodiumfluorophenoxides and react these with diethoxythiophosphoryl chloride to produce compounds having the p-nitrophenyl group of 0,0-diethyl-0,p-nitrophenylthiophosphate replaced by o-fluorophenyl, m-fluorophenyl and p-fluorophenyl groups.

Since many bromine containing compounds are highly toxic, parathion analogues in which the p-nitrophenyl group is replaced by the o-bromophenyl, m-bromophenyl and p-bromophenyl groups were also prepared.

The nitro group is a strongly electron withdrawing one, as is also the trifluoromethyl group. Furthermore the trifluoromethyl group exhibits physiological activity when substituted into different compounds. An attempt was therefore made to prepare the parathion analogues having the nitro group replaced by the trifluoromethyl one. The m-trifluoromethylphenyl derivative was prepared by the following sequence of reactions:



Due to the lability of the fluorine atoms in the trifluoromethyl group when it is in the ortho and para positions of the phenol, all attempts to prepare the phenoxides of

these two phenols led to failure.

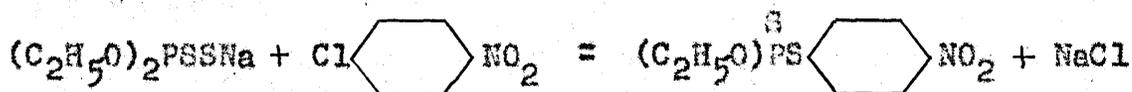
Frear and Seiferle<sup>25</sup> have reported that there may be some correlation between insecticidal activity and the number of like substituted groups in a compound. From their study they report that chlorine is the most effective group that can be substituted into a compound and that as the number of chlorine atoms in the compound is increased the activity increases. Of the compounds they tested 95.5% of those containing five chlorine atoms were active as insecticides.

Pentachlorophenyl for this reason seemed to offer bright possibilities as a group to be substituted for the p-nitrophenyl group of parathion. Since pentachlorophenol is widely used as a fungicide, it was hoped that the resulting compound might possess some fungicidal as well as insecticidal activity. O,O-Diethyl-O-pentachlorophenyl thiophosphate was therefore prepared.

The statement has been made that the insecticidal activity of Parathion is due to the carbon-oxygen-phosphorus bridge. Further statements have been made that the insecticidal activity of Parathion is due to the O,O-diethoxyphosphorus group,  $\begin{matrix} \text{C}_2\text{H}_5\text{O} \\ \diagdown \\ \text{P} \\ \diagup \\ \text{C}_2\text{H}_5\text{O} \end{matrix}$ . Also the oxygen analogue of Parathion, diethyl-p-nitrophenyl orthophosphate, is more toxic. These statements and the results of the toxicity tests of Parathion and its oxygen analogue lead one to believe that if a compound were prepared in which one of the oxygen atoms was replaced by sulfur the resulting substance should

have less toxic action than Parathion. To test this postulate attempts were made to prepare the o-, m- and p-isomers of O,O-diethyl-nitrophenyldiethiophosphate.

In searching for a new method of preparing Parathion the possibility of preparing it from the reaction of the sodium salt of O,O-diethyl-monothiophosphoric acid and p-nitrochlorobenzene was thought to be applicable because p-nitrochlorobenzene is known to give sodium p-nitrophenoxide when treated with sodium hydroxide. Attempts to prepare O,O-diethyl-p-nitrophenyldithiophosphate from sodium O,O-diethyldithiophosphate by the reaction



were unsuccessful. The product consisted of a mixture of bis-(p-nitrophenyl)-disulfide and bis-(p-nitrophenyl)-sulfide. Attempts to effect this reaction using a compound from which the halogen is more easily lost such as p-iodo-nitrobenzene and 2,4-dinitrochlorobenzene gave similar products, i.e., a mixture of mono- and di-sulfide.

DISCUSSION OF EXPERIMENTAL PROCEDURES

In the laboratory preparation of the compounds in this research two ideas were kept in mind: (1) the compounds obtained should be isolated in pure form so that reliable physical and analytical data could be obtained concerning them, and (2) since the compounds were being prepared for possible usage as insecticides it was desirable to retain all by-products in the samples tested for insecticidal activity, because of their possible synergistic activity. Because of the first reason, the intermediates employed in the final step for the preparation of each new compound were made as pure as possible, and because of the second reason only a portion of each reaction mixture was purified beyond removal of the solvents. The final purification of the new liquid compounds to be analyzed was effected by short path high vacuum distillation, all solids were purified by recrystallization. The, so called, molecular distillations were performed in a simple Hickman Molecular Still and pressures were read on a tilting McLeod Gauge. This type of gauge is subject to great error when used for such distillations since it will measure only the pressure of the residual gas in the apparatus and gives no indication of the pressure of condensable vapors. Since the temperature and pressure are both critical in distillations, the inability to measure either one accurately makes any report of the other useless. The distillation temperatures and pressures

were for this reason not reported.

In the preparation of the sodium salts of the phenols, the method found most useful involved the treatment of a solution of the appropriate phenol in the reaction solvent with an equivalent quantity of metallic sodium. Attempts to prepare anhydrous sodium phenoxides by reaction of the phenols with aqueous solutions of sodium hydroxide, followed by removal of the water, were rather unsuccessful because of the difficulty in removing water of hydration without oxidation of the products. Similarly the reaction of the phenols with sodamide was unsuitable because of the difficulty of removing ammonia formed in the reaction.

The final step in all preparations was the reaction of diethoxythiophosphoryl chloride with the appropriate sodium phenoxide. The solvent most often used for this reaction was diethylene glycol. Reaction in this solvent is immediate at temperatures of 70 to 90°C. Anhydrous m-xylene or toluene were occasionally used as solvents. With these inert solvents, reaction times were usually 8 to 16 hours at the reflux temperature of the solvent. The difference in reaction rates for the inert and polar solvents was thought to be due, at least in part, to the insolubility of sodium phenoxides in the inert solvents and their high solubility in the polar glycol solvents.

The glycol solvents were also preferred from the stand-

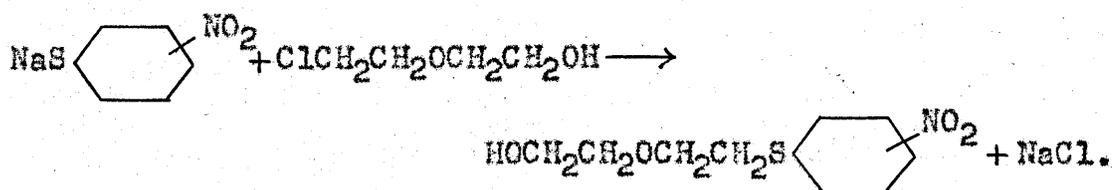
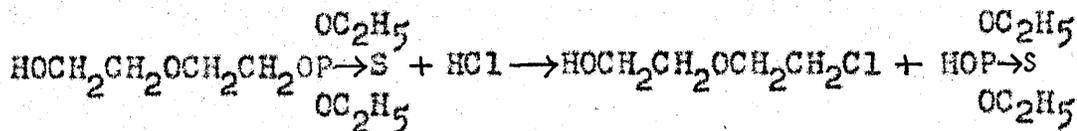
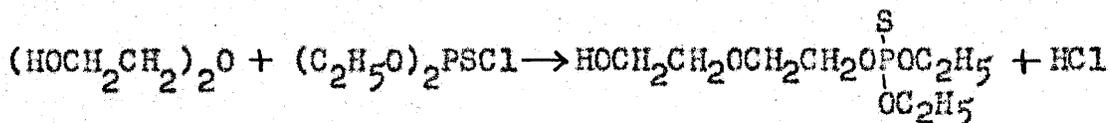
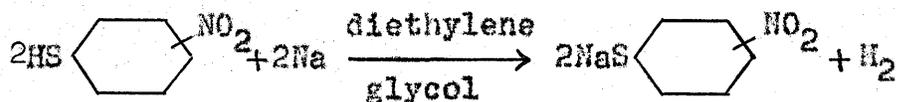
point of ease of manipulation, since at the end of the reaction they were easily removed by washing with water, while the inert solvents had to be removed by distillation. All distillations were made in vacuo to protect the new compound from excessive heating during removal of the solvent. These distillations were difficult to control because of severe bumping which could only be prevented by the addition of large amounts of glass wool to the distillation flask. When all of the solvent had been removed, the residual product was eluted from the glass wool with another solvent, usually chloroform. The chloroform was removed by distillation at atmospheric pressure.

The use of glycol solvents, although they were easier to manipulate, had the disadvantage of giving several side reactions that were not obtained with inert solvents. In some cases the glycol solvent reacted with diethoxymonothiophosphoryl chloride to give glycolthiophosphate esters or chlorosubstituted glycols. The latter compounds sometimes reacted further with the sodium phenoxides to give  $\beta$ -hydroxy- $\beta'$ -phenoxydiethyl ethers. These side reaction products made the isolation of the desired constituent from the mixture a difficult task. The overall yield using glycol solvents, however, was better than that obtained when an inert solvent was used.

The preparation of the sulfur containing analogue of Parathion from the corresponding *p*-nitrothiophenol using diethylene glycol as a solvent has not been successful,

presumably because of the slow reaction of sodium p-nitrophenyl sulfide. The product obtained in the reaction when diethylene glycol was the solvent was  $\beta$ -hydroxy- $\beta'$ -(p-nitrophenylthio)-diethyl ether.

Treatment of diethylene glycol with an excess of diethoxy-monothiophosphoryl chloride gave  $\beta, \beta'$ -dichlorodiethyl ether. The formation of this compound indicates the path through which other by-products were formed in the same type of reaction with other sodium nitrophenyl sulfides. A probable mechanism is shown below:



The nitrothiophenols used in this research were prepared from their disulfides by reduction with dextrose in alkaline solution. The o- and p-dinitrodiphenyl disulfides were obtained from the reaction of the corresponding o- and p-nitrochlorobenzenes with sodium disulfide. m-Dinitrodiphenyl disulfide was prepared by sulfonation of nitro-

benzene with chlorosulfonic acid, followed by reduction of the sulfonyl chloride group with 50% hydrogen iodide.

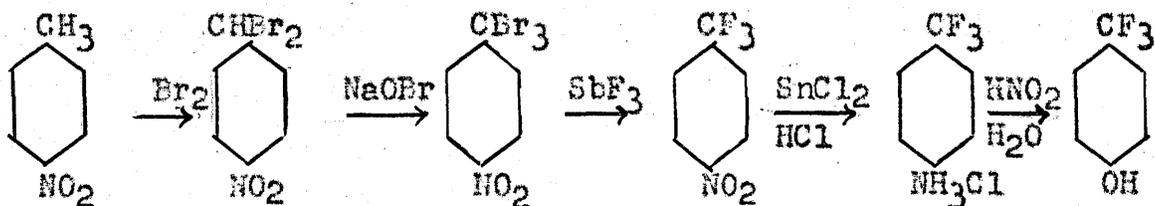
All of the nitrothiophenols are unstable in the presence of air, and for this reason were used shortly after their preparation. m-Nitrothiophenol is so unstable that it has never been isolated in the pure state. It was prepared by reduction in alcohol solution with dextrose and sodium ethoxide. This was followed by the addition of diethoxymonothiophosphoryl chloride. The final product obtained in this case, as with the o- and p-nitrothiophenols, was not the one expected, but rather, ethyl-m-nitrophenyl sulfide.

The product obtained upon treatment of p-chloronitrobenzene with sodium O,O-diethyldithiophosphate was assumed to be a mixture of bis-(p-nitrophenyl) disulfide and bis-(p-nitrophenyl) sulfide, since other similar types of reactions have been shown to give a mixture of mono- and disulfides. The reaction of 2,4-dinitrochlorobenzene with sodium O,O-diethyldithiophosphate gives a mixture of bis-(2,4-dinitrophenyl)-disulfide and bis-(2,4-dinitrophenyl)-sulfide. This was proved by the change of melting point on extraction with alcohol and by analysis of the extracted residue. This result is also in agreement with that of Twiss<sup>26</sup> who treated 2,4-dinitrochlorobenzene with sodium thiosulfate and got a mixture of mono- and disulfides and that of Talen<sup>27</sup> (in his attempts to prepare bis-(2,4-dinitrophenyl) disulfide) who used sodium ethyl xanthate,

thiourea or phenyl isothiocyanate as a source of sulfur and always obtained a mixture of the mono- and disulfide.

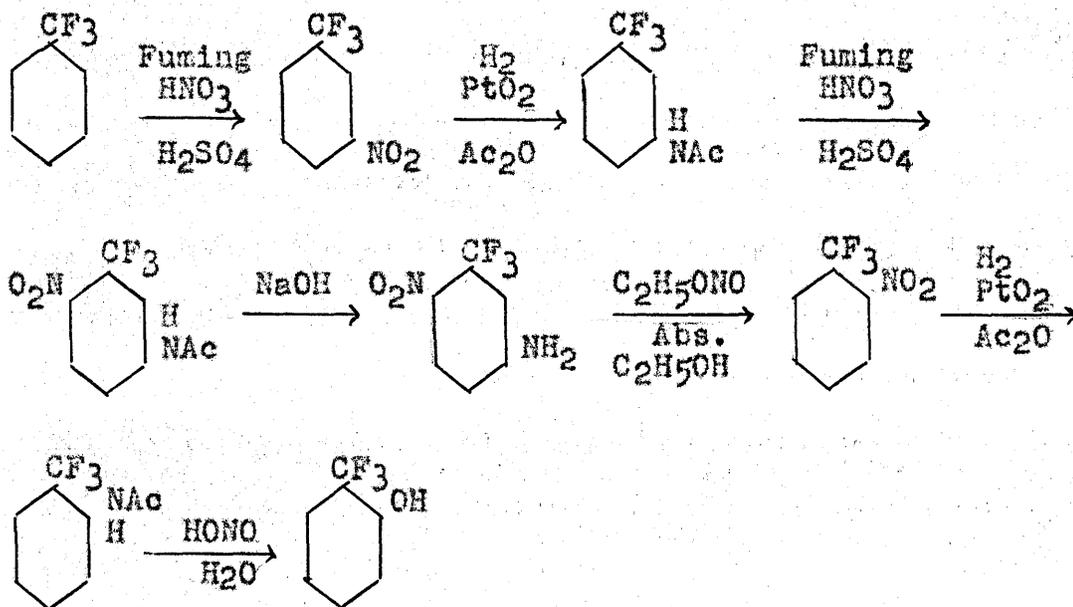
Attempts to prepare the sodium salt of *o*- and *p*-trifluoromethyl phenol failed. This was not unexpected, since Jones<sup>28</sup> had reported that in his attempts to prepare the sodium salts of these compounds using concentrated sodium hydroxide he obtained *o*- and *p*-hydroxybenzoic acids while with cold dilute alkaline solutions one mole of hydrogen fluoride was lost from the molecule to give a solid polymeric product. It was not surprising therefore that when *o*- and *p*-trifluoromethyl phenols were treated with sodium at room temperature a water-insoluble polymeric solid was obtained.

The preparation of the *o*- and *p*-trifluoromethyl phenols was comparatively difficult. The methods outlined by Jones<sup>28</sup> for the preparation of these phenols was used. *p*-Trifluoromethyl phenol was prepared by the following sequence of reactions:

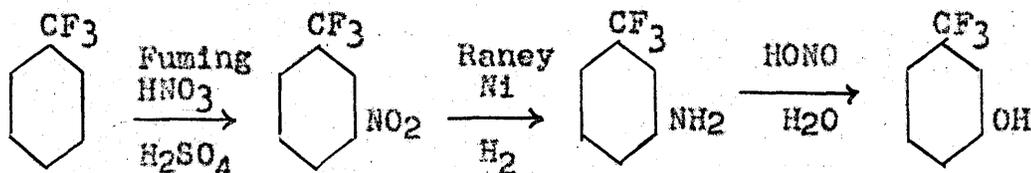


The first reaction, that of direct bromination of *p*-nitrotoluene, was quite difficult to carry out on a large scale because excessive local heating leads to oxidation and decomposition of the product. Use of 100 g. of *p*-nitrotoluene per run gave the best results. Direct chlorination

of *o*-nitrotoluene was unsuccessful. The preparation of *o*-trifluoromethyl phenol was equally difficult, because of the many steps involved in the synthesis as shown below:



The benzotrifluoride used for this latter preparation and also for the preparation of *m*-trifluoromethyl phenol was obtained from Hooker Electrochemical Company and was of practical grade, boiling over a temperature range of 3 to 4 degrees. *m*-Trifluoromethyl phenol was prepared from benzotrifluoride through the following sequence of reactions as suggested by Swartz<sup>29</sup>:



Attempts to prepare *o*-trifluoromethyl phenol from *o*-chlorobenzotrifluoride by means of the lithium derivative,

*o*-trifluoromethylphenyl lithium, were unsuccessful, no reaction taking place. Jones<sup>28</sup> had previously reported that the Grignard reagent could not be formed with this compound.

The *o*- and *p*-bromophenols used in this research were obtained from Eastman Kodak Corporation and were of reagent grade. *m*-Bromophenol, however, is not available from any of the common sources of supply and had to be prepared from *m*-bromoaniline through diazotization followed by steam distillation from an acid solution of the diazonium salt. The *m*-bromoaniline used was obtained from Eastman Kodak Corporation and was reagent grade.

The fluorophenols were all prepared in this laboratory. The *o*- and *p*-fluorophenols were readily obtained through the Schiemann reaction from the corresponding anisidine or phenetidine, followed by cleavage of the corresponding fluoroanisole or fluorophenetole with anhydrous aluminum chloride or aluminum bromide. The phenetidine and anisidine were reagent grade materials obtained from Monsanto Chemical Company.

*m*-Fluorophenol was prepared by diazotization of *m*-aminophenol in anhydrous hydrogen fluoride followed by decomposition of the diazonium salt in this same solvent, according to the procedure of Ferm<sup>30</sup>. The *m*-aminophenol used was a technical grade material obtained from Eastman Kodak Corporation.

*O,O*-Diethyl-*O*-pentachlorophenyl thiophosphate was made

using pentachlorophenol which had been sublimed in vacuo.  
The original pentachlorophenol was a technical grade supplied  
by Paragon Testing Laboratories.

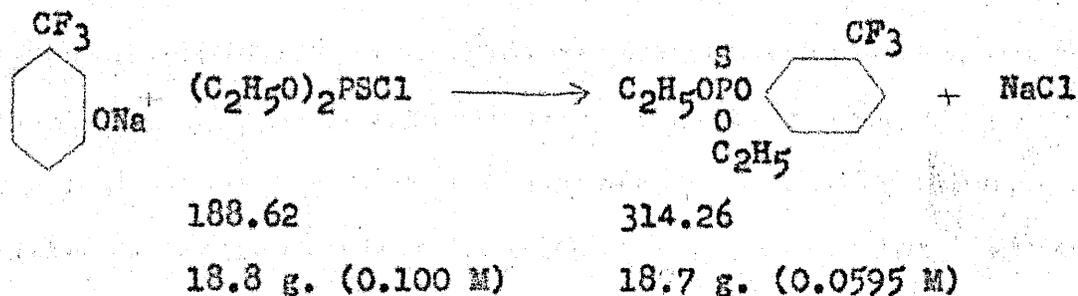
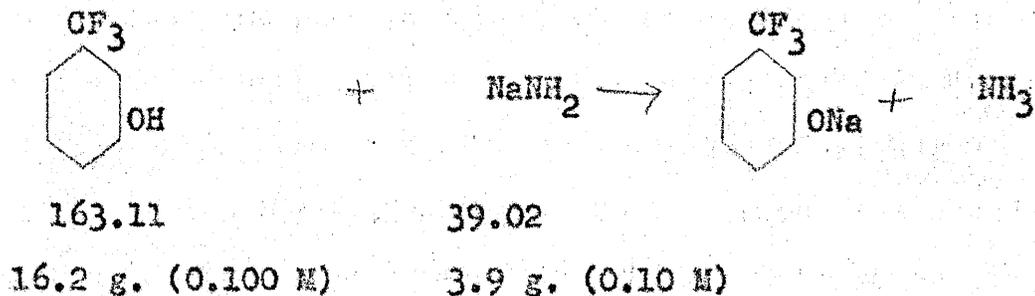
EXPERIMENTAL

A. O,O-Diethyl-O-trifluoromethylphenyl Thiophosphates

O,O-Diethyl-O,*m*-trifluoromethylphenyl thiophosphate--

A 500 ml. three neck flask fitted with a Hershberg stirrer, reflux condenser with drying tube attached, and a thermometer was charged with 100 ml. of dry *m*-xylene, 16.2 g. (0.1M) *m*-trifluoromethylphenol<sup>27</sup> and 3.9 g. (0.10 M) of sodamide. The mixture was stirred for a period of sixteen hours while a stream of dry nitrogen was passed over it to sweep out the ammonia formed. When the effluent gas no longer gave a test for ammonia with moist pink litmus, 18.8 g. (0.100 M) of diethoxymonothiophosphoryl chloride was added. This mixture was heated for twenty-four hours at the reflux temperature of *m*-xylene while being stirred. After cooling to room temperature the product was filtered. The filtrate was subjected to vacuum distillation to remove the solvent and any unreacted diethoxymonothiophosphoryl chloride. A large amount of glass wool was added to the distillation flask to prevent bumping during the distillation. The residue was washed free of the glass wool with small portions of ether, and the ether removed by distillation leaving a crude residue of O,O-diethyl-O,*m*-trifluoromethylphenyl thiophosphate weighing 18.7 g.; yield 59.5%. A portion of this material was subjected to molecular distillation;  $n_D^{27}$  1.5138.

Analysis. Calculated for  $C_{11}H_{14}O_3F_3PS$ : C, 41.96; H, 4.49; S, 10.20. Found: C, 41.95; H, 4.58; S, 10.70.



$$\frac{0.0595}{0.100} \times 100 = 59.5\% \text{ yield}$$

Attempts to prepare O,O-diethyl-O,*o*-trifluoromethyl-phenyl thiophosphate and O,O-diethyl-O,*p*-trifluoromethyl-phenyl thiophosphate were unsuccessful due to the instability of the intermediate sodium phenoxides.

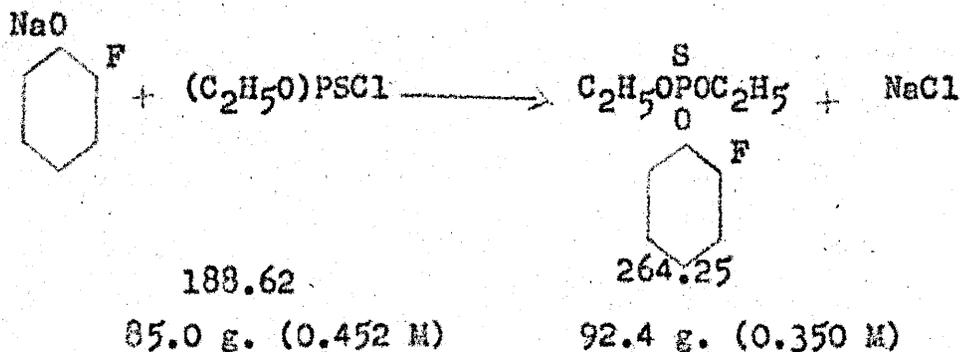
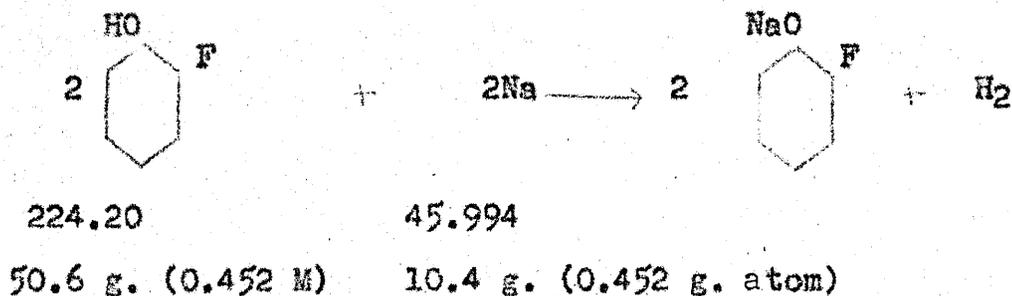
#### B. O,O-diethyl-O-fluorophenyl Thiophosphates

O,O-Diethyl-O,*o*-fluorophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with drying tube attached, a Hershberg stirrer and a thermometer was charged with 50.6 g. (0.452 M) of *o*-fluorophenol,<sup>29</sup> 200 ml. of dry diethylene glycol, and 10.4 g. (0.452 g. atom) of sodium metal cut into small chunks. The mixture was stirred while heating until reaction started at which time the mixture was cooled until all of the sodium had reacted.

After cooling to room temperature, 85.0 g. (0.452 M) of diethoxy-monothiosphoryl chloride was added and the mixture stirred for a period of two hours at a temperature of 70 to 90°. After cooling to room temperature the product was washed into 1700 ml. of water. An oil which separated was removed and added to 3-100 ml. chloroform extracts of the water layer. The chloroform solution was dried over Drierite, filtered and the chloroform and unreacted diethoxy-monothiosphoryl chloride removed by distillation, leaving 92.4 g. of crude O,O-diethyl-O,*o*-fluorophenyl thiophosphate residue; yield 77.2%. A portion subjected to two successive molecular distillations gave a pure sample;  $n_D^{26}$  1.500.

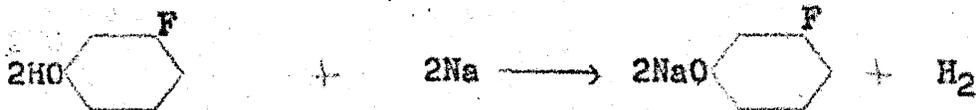
Analysis. Calculated for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>PSF: C, 45.45; H, 5.34.

Found: C, 45.73; H, 5.54.



$$\frac{0.350}{.452} \times 100 = 77.2\% \text{ yield}$$

O,O-Diethyl-O,*m*-fluorophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with drying tube attached, a Hershberg stirrer, and a thermometer was charged with 150 ml. of dry diethylene glycol, 31.6 g. (0.282 M) *m*-fluorophenol<sup>28</sup> and 6.5 g. (0.282 g. atom) sodium cut into small chunks. The mixture was stirred while heating until reaction started, at which time it was cooled until all of the sodium had reacted. After cooling to room temperature 53.2 g. (0.282 M) diethoxymonothiophosphoryl chloride was added. This mixture was stirred for a period of two hours at a temperature of 70 to 90°. After cooling to room temperature, the product was washed into 1500 ml. of water. An oil which separated was removed and added to three 100 ml. chloroform extracts of the water layer. The chloroform solution was dried over Drierite, filtered and the chloroform and unreacted diethoxymonothiophosphoryl chloride removed by distillation, leaving 61.7 g. of crude O,O-diethyl-O,*m*-fluorophenyl thiophosphate; yield 83.0%. A portion subjected to molecular distillation gave a pure sample;  $n_D^{27}$  1.4911. Analysis for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>PSF: C, 45.45; H, 5.34. Found: C, 44.91; H, 5.52.

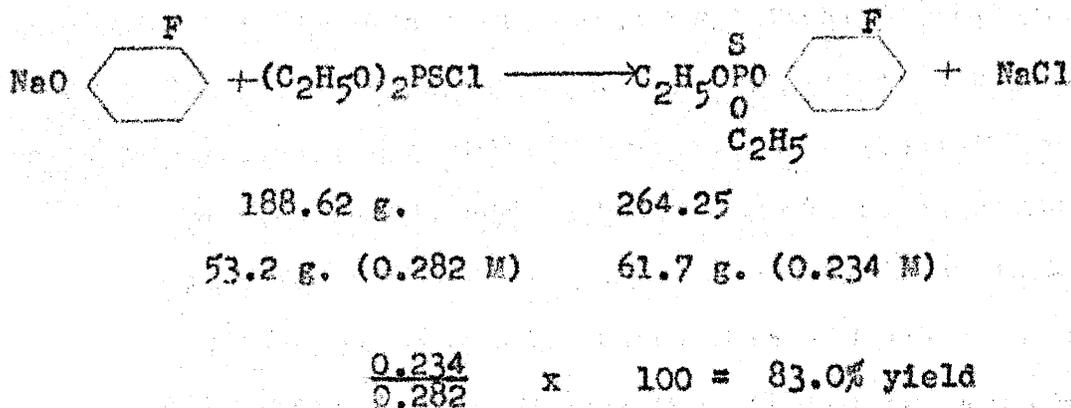


224.20

45.994

31.6 g. (0.282 M)

6.5 g. (0.282 g. atom)



O,O-Diethyl-O,p-fluorophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with drying tube attached, a Hershberg stirrer, and a thermometer was charged with 46.5 g. (0.415 M) p-fluorophenol, 200 ml. dry m-xylene and 10.0 g. (0.42 g. atom) sodium in small chunks. The mixture was stirred overnight during which time all of the sodium reacted. Exactly 78.0 g. (0.415 M) diethoxy-monothiophosphoryl chloride was then added. The mixture was heated with stirring at the reflux temperature of m-xylene for a period of five hours. After cooling to room temperature and stirring for another nineteen hours the resulting red liquid was filtered and the m-xylene removed under vacuum along with any unreacted diethoxy-monothiophosphoryl chloride using glass wool to prevent bumping. The residue was washed free of the glass wool with small portions of ether, and the ether removed by distillation leaving a crude residue of O,O-diethyl-O,p-fluorophenyl thiophosphate weighing 53.1 g.; yield 48.5%. A portion of this material was subjected to molecular distillation to give a pure sample;  $n^{24} 1.4995$ . Analysis. Calculated

for  $C_{10}H_{14}O_3PSF$ : C, 45.45; H, 5.34. Found: C, 45.33;  
H, 5.42.

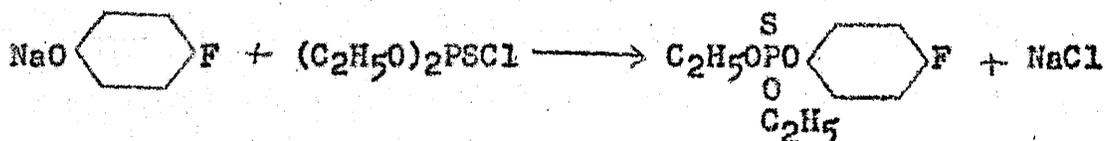


224.20

45.994

46.5 g. (0.415 M)

10.0 g. (0.42 g. atom)



188.62

264.25

78.0 g. (0.415 M)

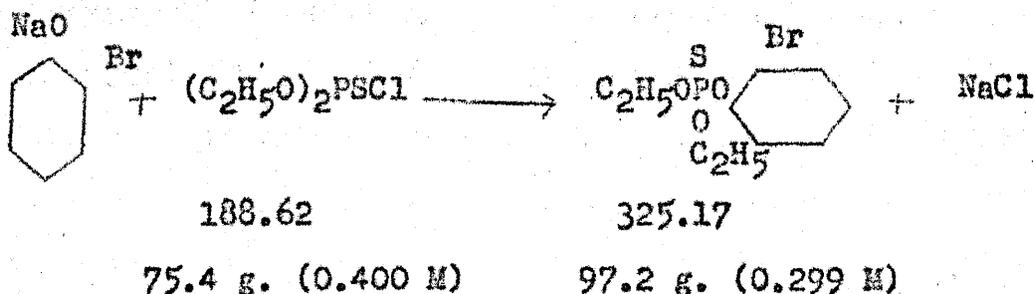
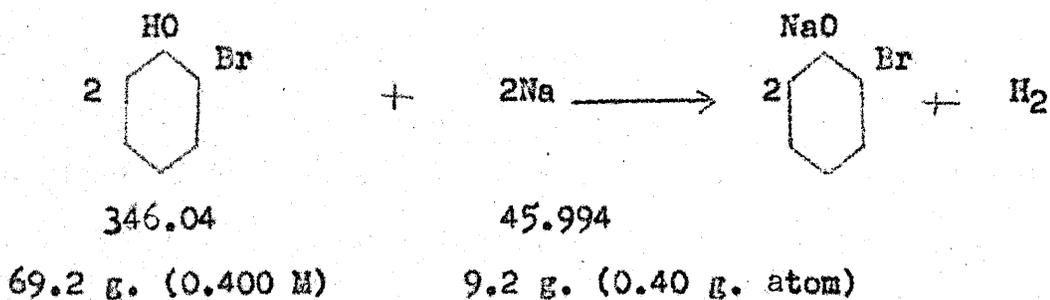
53.1 g. (0.201 M)

$$\frac{0.201}{0.415} \times 100 = 48.5\%$$

### C. Preparation of O,O-diethyl-O-bromophenyl Thiophosphates

O,O-Diethyl-O,o-bromophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with a drying tube attached, a Hershberg stirrer, and a thermometer was charged with 69.2 g. (0.400 M) o-bromophenol, 200 ml. dry diethylene glycol and 9.2 g. (0.40 g. atom) sodium metal cut into small chunks. The mixture was stirred while heating until reaction had started at which time it was cooled until all of the sodium had reacted. After cooling to room temperature, 75.4 g. (0.400 M) diethoxy-monothio-phosphoryl chloride was added. This mixture was stirred for a period of two hours at a temperature of 70 to 90°. After cooling to room temperature the product was washed

into 1500 ml. of water. The oil which separated was removed and combined with three 100 ml. chloroform extracts of the water layer. The chloroform solution was washed with 1 l. of 0.5 N. sodium hydroxide and three 100 ml. portions of water. The chloroform solution was dried over Drierite, filtered and the chloroform and unreacted diethoxy-monothiophosphoryl chloride removed by distillation, leaving 97.2 g. of crude O,O-diethyl-O,m-bromophenyl thiophosphate as a residue; yield 74.6%. A portion subjected to molecular distillation gave a pure sample;  $n_D^{26}$  1.5300. Analysis. Calculated for  $C_{10}H_{14}O_3PSBr$ : C, 36.93; H, 4.34. Found: C, 37.13; H, 4.57.

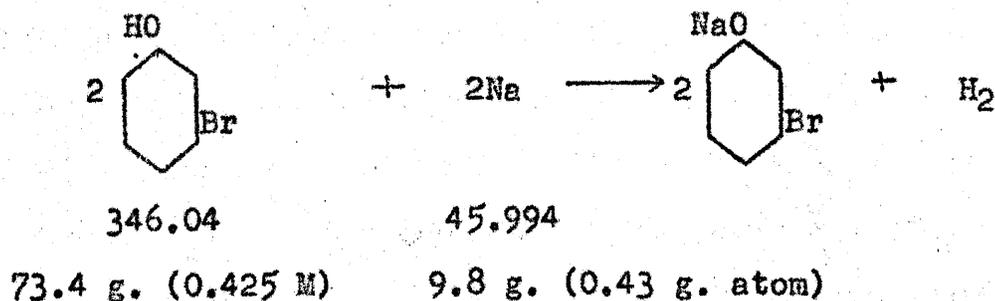


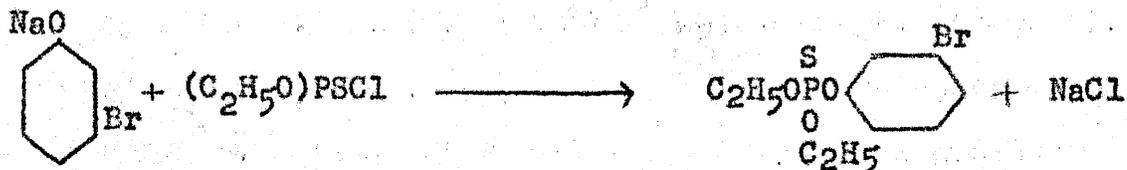
$$\frac{0.299}{0.400} \times 100 = 74.8\%$$

O,O-Diethyl-O,m-bromophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with drying tube attached, a Hershberg stirrer, and a thermometer was

charged with 73.4 g. (0.425 M) of *m*-bromophenol,<sup>31</sup> 200 ml. dry toluene and 9.8 g. (0.43 g. atom) sodium metal cut into small chunks. This mixture was warmed while being stirred until all of the sodium had reacted. After cooling to room temperature, 80.2 g. (0.425 M) diethoxymonothiophosphoryl chloride was added. This mixture was heated with stirring for a period of eight hours. A precipitate was removed by filtration and the filtrate stripped of toluene and unreacted diethoxymonothiophosphoryl chloride by distillation. A large amount of glass wool was added to the distillation flask to prevent bumping during this distillation. The residue was washed free of the glass wool with small portions of ether, and the ether removed by distillation leaving a crude residue of O,O-diethyl-O,*m*-bromophenyl thiophosphate weighing 65.8 g.; yield 47.6%. A portion subject to vacuum distillation boiled at 153.7 to 155.2° at 5 mm. ;  $n_D^{24}$  1.5352.

Analysis. Calculated for  $C_{10}H_{14}O_3PSBr$ : C, 36.93; H, 4.34. Found: C, 37.12; H, 4.24.





188.62

325.17

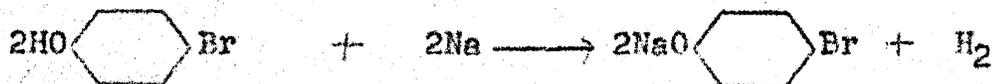
80.2 g. (0.425 M)

65.8 g. (0.203 M)

$$\frac{0.203}{0.425} \times 100 = 47.6\% \text{ yield}$$

0,0-Diethyl-0,p-bromophenyl thiophosphate--A 500 ml. three-necked flask fitted with a reflux condenser with drying tube attached, a Hershberg stirrer, and a thermometer was charged with 51.8 g. (0.300 M) of p-bromophenol, 200 ml. of dry diethylene glycol and 6.9 g. (0.30 g. atom) of sodium metal cut into small chunks. The mixture was heated with stirring until all of the sodium had reacted. Exactly 56.6 g. (0.300 M) of diethoxymonothiophosphoryl chloride was then added and the mixture stirred at a temperature of 70 to 90° for a period of 4 hours. After cooling to room temperature the product was washed into 1500 ml. of water and the oil separated and combined with 3-100 ml. of chloroform extracts of the aqueous layer. The chloroform solution was washed with 1 l. of 0.5 N sodium hydroxide solution followed by 2-200 ml. portions of water. The chloroform solution was dried over Drierite, filtered and the chloroform and unreacted diethoxymonothiophosphoryl chloride removed by distillation, leaving 58.5 g. of crude 0,0-diethyl-0,p-bromophenyl thiophosphate; yield 60.0%. A portion subjected to molecular distillation gave a pure sample;  $n_D^{28}$  1.5262. Analysis.

Calculated for  $C_{10}H_{14}O_3PBr$ ; C, 36.93; H, 4.34. Found; C, 37.01; H, 4.64.

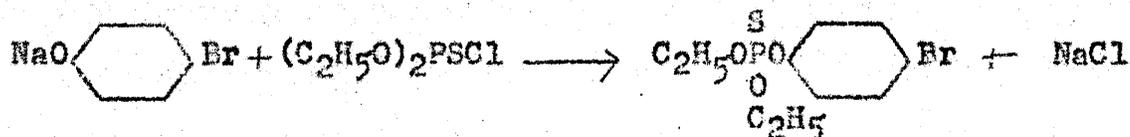


346.04

45.994

51.8 g. (0.300 M)

6.9 g. (0.30 g. atom)



188.62

325.17

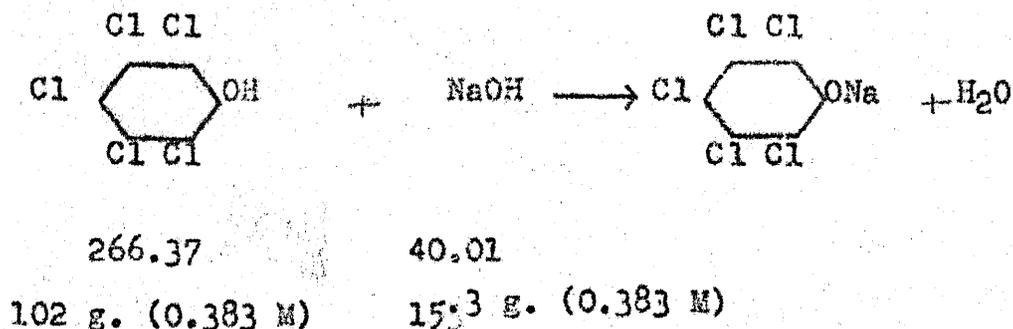
56.5 g. (0.300 M)

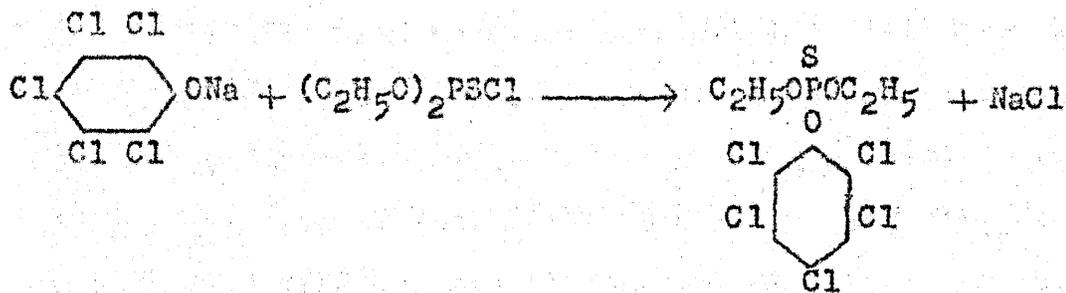
58.5 g. (0.180 M)

$$\frac{0.180}{0.300} \times 100 = 60.0\% \text{ yield}$$

D. O,O-Diethyl-O-pentachlorophenyl Thiophosphate--A 500 ml. three-necked flask fitted with a Hershberg stirrer, and a tube leading to a vacuum line was charged with 102 g. (0.383 M) of pentachlorophenol, 100 ml. of water and 15.3 g. (0.383 M) of sodium hydroxide. The mixture was stirred until it became homogeneous, at which time it was heated on a steam bath while the water was evaporated by connecting to an aspirator. The evacuation and heating continued for a period of twenty four hours. After removal of the steam bath and disconnection of the vacuum line, the flask was fitted with a thermometer and a reflux condenser with drying tube attached. Exactly 300 ml. of diethylene glycol was added and the mixture stirred

until all of the sodium pentachlorophenoxide had gone into solution. Then 72.2 g. (0.383 M) of diethoxymonothiophosphoryl chloride was added. The mixture was stirred for a period of three hours at a temperature of 70 to 90°. The product was allowed to cool to room temperature and was then washed into 1500 ml. of water. The aqueous mixture was extracted with three 100 ml. portions of chloroform. Any unreacted pentachlorophenol present at this point was removed by washing of the chloroform solution with 1 l. of 0.4 N. sodium hydroxide. This was followed by three 100 ml. water washes, and the solution was then dried over Drierite. The chloroform was removed at the water pump leaving 60.0 g. (37.3%) of white crystalline O,O-diethyl-O-pentachlorophenyl thiophosphate melting at 90.5 to 94.0°. After four successive recrystallizations of this solid from acetone, a pure product melting at 97.3 to 97.4° was obtained. Analysis. Calculated for C<sub>10</sub>H<sub>10</sub>Cl<sub>5</sub>O<sub>3</sub>PS: C, 28.70; H, 2.41; Cl, 42.36. Found; C, 28.42; H, 2.53; Cl, 42.18.





188.62

418.52

72.2 g. (0.383 M)

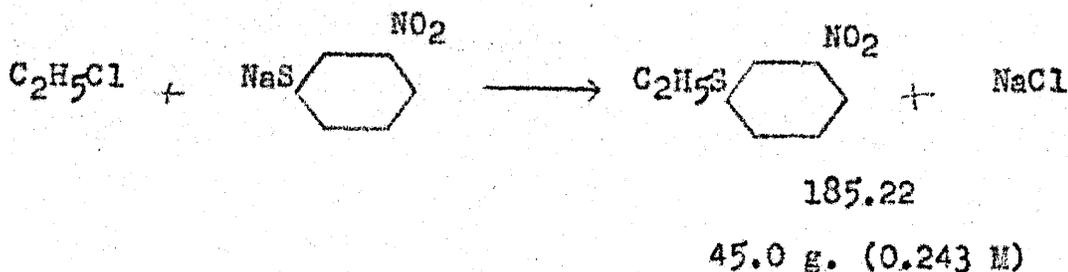
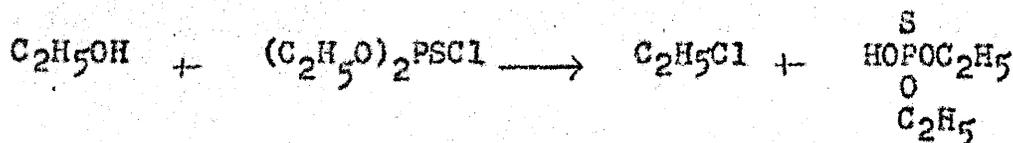
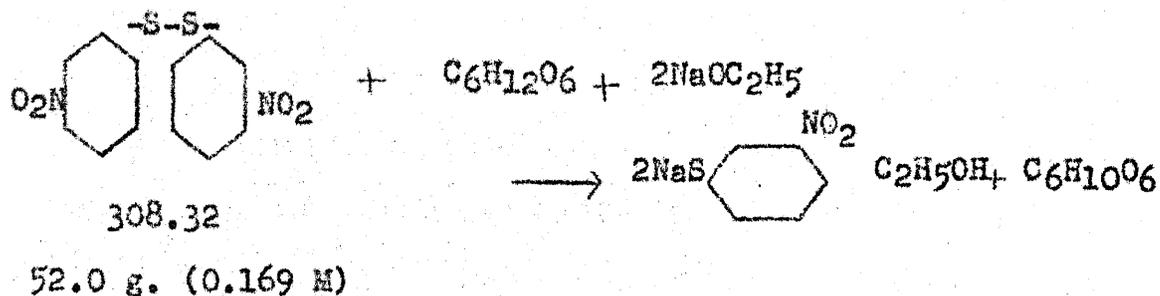
60.0 g. (0.143 M)

$$\frac{0.143}{0.383} \times 100 = 37.3\%$$

### E. Miscellaneous Products

Ethyl-m-nitrophenyl sulfide--A 1000 ml. three-necked flask, fitted with a reflux condenser with drying tube attached, a Hershberg stirrer and a dropping funnel was charged with 52.0 g. (0.178 M) of m,m'-dinitrodiphenyl disulfide, 250 ml. of absolute alcohol, and 36.4 g. of dextrose. The mixture was warmed on a steam bath while a solution of sodium ethoxide in absolute alcohol, prepared by allowing 16.4 g. sodium to react in 250 ml. of absolute alcohol, was added dropwise. After all of the sodium ethoxide had been added, the stirred mixture was warmed on the steam bath for a period of thirty minutes. Exactly 134 g. (0.718 M) of diethoxymonothiophosphoryl chloride was added and heating was continued for a period of two hours at the reflux temperature of the alcohol solution. At the end of this time the mixture was washed into 1 l. of water. The oil that separated from the water

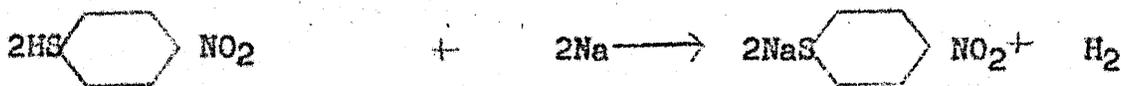
mixture was combined with three 100 ml. portions of chloroform that had been used to wash the water mixture. The resulting chloroform solution was washed with two 100 ml. portions of 0.5 N sodium hydroxide solution and finally with water and then dried over Drierite. The Drierite was removed by filtration and the solvent chloroform and unreacted diethoxymonothiophosphoryl chloride removed by distillation, leaving a residue of 45.0 g. (71.8%) of crude ethyl-*m*-nitrophenyl sulfide. A portion was molecularly distilled to give a colorless product;  $n_D^{27}$  1.5820. Analysis. Calculated for  $C_8H_9NO_2S$ : C, 52.45; H, 4.96. Found: C, 50.33; H, 4.83.



$$\frac{0.243}{2 \times 0.169} \times 100 = 71.8\% \text{ yield}$$

$\beta$ -Hydroxy- $\beta'$ -(*p*-nitrophenylthio)-diethyl ether-- A 500 ml. three-necked flask, fitted with a reflux condenser with drying tube attached, a Hershberg stirrer, and a dropping funnel was charged with 46.5 g. (0.300 M) of *p*-nitrophenyl thiophenol, 250 ml. of dry diethylene glycol and 6.9 g. (0.30 g. atom) of sodium metal cut into small pieces. The mixture was warmed until all of the sodium had reacted to give a clear solution. After cooling to 70°, 56.4 g. (0.300 M) of diethoxy-monothio-phosphoryl chloride was added and the stirred mixture was maintained at a temperature of 70 to 85° for a period of three hours. The product of this treatment was washed into 1500 ml. of water. The oil which separated was removed and the water layer washed with four 150 ml. portions of chloroform. These were combined with the oil and the resulting solution dried over anhydrous magnesium sulfate. The dried solution was filtered and the chloroform and unreacted diethoxy-monothio-phosphoryl chloride were removed by distillation, leaving a crude brown mixture of  $\beta$ -hydroxy- $\beta'$ -(*p*-nitrophenylthio)-diethyl ether and other undetermined products weighing 88.0 g. A portion subjected to molecular distillation yielded a yellow solid which after recrystallization from low boiling petroleum ether melted at 44.5 to 45.0°(Corr.).

Analysis. Calculated for  $C_{10}H_{13}NO_4S$ : C, 49.37; H, 5.38; N, 5.76; S, 13.20. Found: C, 49.13; H, 5.25; N, 6.88; S, 13.65.

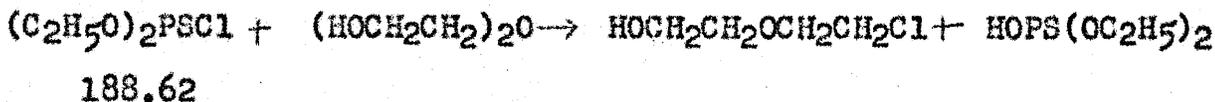


310.34

45.994

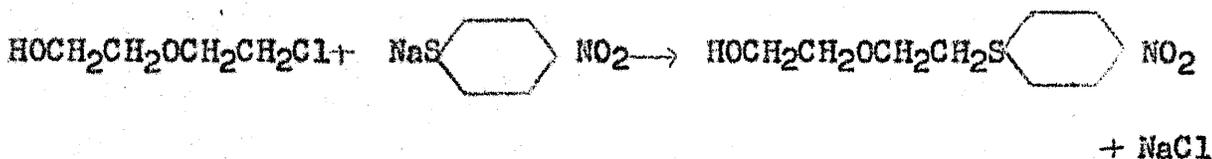
46.5 g. (0.300 M)

6.9 g. (0.30 g. atom)



188.62

56.4 g. (0.300 M)



243.27

#### F. Attempts to Prepare O,O-Diethyl-nitrophenyldithiophosphates

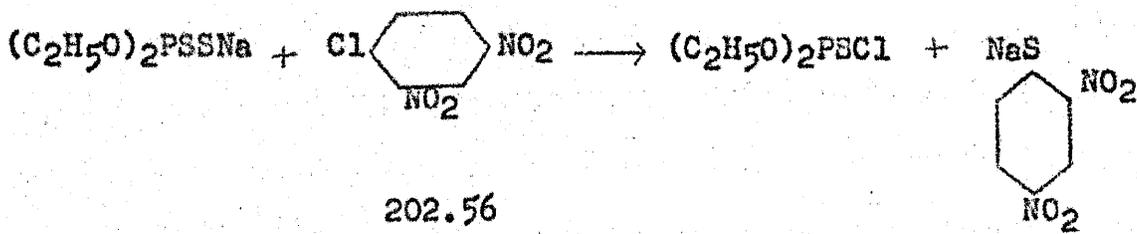
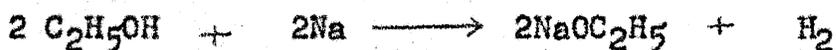
Using p-chloronitrobenzene--A 500 ml. three-necked flask, fitted with a Hershberg stirrer, a reflux condenser with a drying tube attached and a thermometer, was charged with 50 ml. of absolute alcohol and 2.3 g. (0.10 g. atom) of finely divided sodium metal. When all of the sodium had reacted, 21.9 g. (0.100 M 85% pure) of diethoxydithiophosphoric acid was added. To the resulting milky solution 15.8 g. (0.100 M) of p-chloronitrobenzene was added. The mixture was stirred under reflux for a period of twelve hours. At the end of this time the mixture was washed into 400 ml. of water. The brown precipitate, which separated was removed by filtration and recrystallized three times from 95% ethyl alcohol. A yellow solid melting at 83.0 to 83.1° was obtained. This

corresponds to the melting point ( $83.5^{\circ}$ ) of p-chloronitrobenzene.

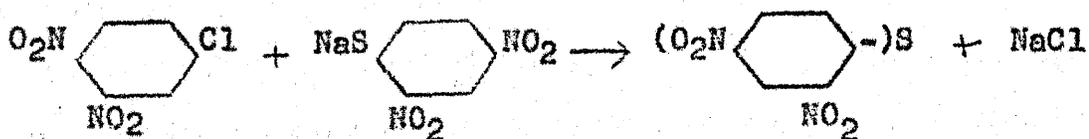
Using p-iodonitrobenzene--A 500 ml. three-necked flask, fitted with a Hershberg stirrer, a reflux condenser with a drying tube attached, and a thermometer was charged with 50 ml. of absolute alcohol and 2.3 g. (0.10 M) of finely divided sodium metal. When all of the sodium had reacted, 21.9 g. (0.100 M, 85% pure) of diethoxydithiophosphoric acid was added. To the resulting milky solution then was added 24.9 g. (0.100 M) of p-iodonitrobenzene in 30 ml. of absolute alcohol. Following a twelve hour refluxing period, the mixture was washed into 400 ml. of water from which a brown precipitate was removed by filtration. A sample of this precipitate after recrystallization from absolute alcohol melted at  $169.0$  to  $170.0^{\circ}$ . This corresponds to the melting point of p,p'-dinitrodiphenyl disulfide which is listed as  $168$  to  $170^{\circ}$ .

Using 2,4-dinitrochlorobenzene--A 500 ml. three-necked flask, fitted with a reflux condenser with a drying tube attached, a Hershberg stirrer, and a thermometer, was charged with 50 ml. of absolute alcohol and 2.24 g. (0.093 g. atom) of sodium metal cut into small pieces. After all of the sodium had reacted, 17.3 g. (0.093 M) of diethoxydithiophosphoric acid was added. A vigorous reaction ensued; when this had subsided 17.4 g. (0.093 M) of 2,4-dinitrochlorobenzene was added and the resulting mixture was warmed to the reflux temperature with stirring, during

which time a yellow solid separated out. The mixture was stirred under reflux for a period of four hours and then was washed into 300 ml. of water and filtered. The dried precipitate weighed 14.5 g., and melted with some decomposition at 200 to 204°. After a portion of the precipitate had been extracted with hot 95% alcohol, a yellow crystalline solid that melted at 197.0 to 197.2° (corresponding to bis-(2,4-dinitrophenyl)-sulfide, m.p. 193°) remained. Analysis. Calculated for C<sub>12</sub>H<sub>6</sub>N<sub>4</sub>O<sub>8</sub>S: C, 39.35; H, 1.65. Found: C, 39.32; H, 1.67.



17.4 g. (0.093 M)



366.26

14.5 g. (0.0397 M)

$$\frac{2 \times 0.0397}{0.093} \times 100 = 84.5\% \text{ yield}$$

G. Tests for Insecticidal Activity

The new compounds reported here are all being tested for possible insecticidal activity by the Niagara Chemical Division Food Machinery Corporation, Middleport, New York. No results are available at the present time.

DISCUSSION OF EXPERIMENTAL RESULTS

Preparation of Analogues of O,O-Diethyl-O,p-nitrophenyl Thiophosphate. (Experimental, p. 31-48 )--Members of this general class of compounds were prepared in higher yield from diethoxymonothiophosphoryl chloride and the desired sodium phenoxide using diethylene glycol as a solvent than when an inert solvent was used. Under the former conditions, however, greater amounts of by-products were formed, which made the isolation of the pure compound sought more difficult. When inert solvents were used these difficulties were eased, since the solvent did not react with the intermediates to any measurable extent.

O,O-Diethyl-O,m-trifluoromethylphenyl Thiophosphate (Experimental, p. 31-32)--This compound was prepared by the standard reaction of diethoxymonothiophosphoryl chloride with sodium m-trifluoromethylphenoxide in dry m-xylene. The m-trifluoromethylphenol used in this preparation was prepared from benzotrifluoride by nitration, using the method of Swartz<sup>29</sup> to give m-nitrobenzotrifluoride followed by reduction of this nitro compound and conversion to the phenol by diazotization and hydrolysis as described by Sveinbjornsson<sup>34</sup>. The conversion of the resulting phenol to sodium m-trifluoromethylphenoxide was accomplished by the reaction of sodamide with the phenol. This method of preparation of sodium phenoxides is slow due to the length of time necessary to get rid of the last traces of ammonia

formed in the reaction. No difficulty was experienced in the isolation of the pure compound by molecular distillation of the final reaction product from which the volatile components had been removed. The yield of crude material was lower than might have been expected using diethylene glycol as a solvent instead of m-xylene.

O,O-Diethyl-O,o-fluorophenyl Thiophosphate (Experimental, p. 32-33)--This compound was isolated with difficulty from the final reaction mixture of sodium o-fluorophenoxide and diethoxymonothiophosphoryl chloride in diethylene glycol by successive molecular distillations of the residue left after extraction with water and distillation of the volatile components. Attempts to obtain a pure sample by ordinary low pressure distillation were unsuccessful.

The o-fluorophenol used for the preparation of this compound was prepared from o-anisidine using the Schiemann reaction, as described by Weygand<sup>31</sup>, and subsequent hydrolysis of the resulting o-fluoroanisole with pyridine aluminum chloride, as described by Prey<sup>35</sup>. The intermediate salt o-methoxybenzenediazonium fluoroborate was isolated in excellent yield by this method, but its decomposition to give o-fluoroanisole gave lower yields than expected. Weygand had reported a yield of 57.7% and the best obtainable in this laboratory was 34.4%. Elaborate precautions made to condense any condensable vapors from the decomposition did not serve to increase the yield. Excessive localized overheating of the material being decomposed may have caused

the lower yields. Weygand<sup>31</sup> reports the decomposition of 100 g. of o-methoxybenzenediazonium fluoroborate per run, whereas 406 g. of this same material was decomposed in one batch in this laboratory. A consideration of the difference in the size of the apparatus used and the difficulty in obtaining adequate heat transfer in the larger batch of solid material provides an insight into how overheating could occur.

The hydrolysis of o-fluoroanisole with pyridine aluminum chloride gave the best yields of o-fluorophenol, namely a yield of 65.4%. Weygand had reported a yield of 82% using hydrogen iodide (density 1.96). There is no common source of this latter substance and it is difficult to prepare, so the easily prepared pyridine aluminum chloride was used.

O,O-Diethyl-O,m-fluorophenyl Thiophosphate (Experimental, p. 34-35)--This compound was prepared by the reaction of sodium m-fluorophenoxide and diethoxy-monothiophosphoryl chloride in diethylene glycol. The product was isolated in a pure state only after repeated successive molecular distillations of a portion of the residue that had been washed with water and from which the volatile constituents had been distilled.

The m-fluorophenol used in this preparations was prepared by diazotization of m-aminophenol in anhydrous hydrogen fluoride. The reaction proceeds smoothly and is quite adequate for the preparation of m-fluorophenol but not of o and p-fluorophenols.

O,O-Diethyl-O,p-fluorophenyl Thiophosphate (Experimental, p. 35-36)--This substance was prepared by the reaction of sodium p-fluorophenoxide and diethoxymonothiophosphoryl chloride in dry m-xylene. Its isolation from the reaction mixture was a bit difficult (because of the severe bumping during the removal of the solvent m-xylene) until glass wool was added to the distillation flask. When all of the solvent had been removed a sample of the pure product was obtained by a single molecular distillation.

The p-fluorophenol used in this preparation was prepared (by the method described by Suter, et. al.<sup>32</sup>) from p-fluoroanisole\* by hydrolysis with anhydrous aluminum chloride using chlorobenzene as the solvent as recommended by Weston and Suter.<sup>36</sup>

O,O-Diethyl-O,o-bromophenyl Thiophosphate (Experimental, p. 36-37)--This compound was isolated from the reaction of sodium o-bromophenoxide and diethoxymonothiophosphoryl chloride in diethylene glycol by a single molecular distillation. The o-bromophenol used in this preparation was reagent grade obtained from Eastman Kodak Corporation.

O,O-Diethyl-O,m-bromophenyl Thiophosphate (Experimental, p. 37-39)--This compound was prepared by the reaction of sodium m-bromophenoxide and diethoxymonothiophosphoryl chloride in dry m-xylene. It was isolated in the pure state by distillation through a 3-inch Vigreux column at reduced pressure. It is the only compound reported in this research

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\*Obtained through the kindness of A. F. Helin, Univ. of Kansas

that was isolated from its reaction mixture by direct distillation. Attempts to prepare the pure compound by the same reaction using diethylene glycol as the solvent were unsuccessful, even after repeated successive molecular distillations.

The m-bromophenol used in these preparations was prepared from m-bromoaniline by diazotization followed by hydrolysis. The method of Natelson and Gottfried <sup>37</sup> was used for the decomposition of the diazotized m-bromophenol.

O,O-Diethyl-O,p-bromophenyl Thiophosphate (Experimental, p. 39-40)--This compound was prepared by the reaction of sodium p-bromophenoxide and diethoxymonothiophosphoryl chloride in diethylene glycol. It was isolated in the pure state by a single molecular distillation.

O,O-Diethyl-O-pentachlorophenyl Thiophosphate (Experimental, p. 40-42)--This compound was prepared from sodium pentachlorophenoxide and diethoxymonothiophosphoryl chloride in diethylene glycol. The resulting solid was recrystallized until its melting point did not change on successive recrystallizations.

Sodium pentachlorophenoxide was prepared by the addition of a solution of an equivalent amount of sodium hydroxide to pentachlorophenol and evaporation of the resulting solution to dryness on a steam bath, under vacuum. This is the only sodium phenoxide that was prepared in this manner. The operation is rather long and tedious.

O,O-Diethylnitrophenyldithiophosphates (Experimental, p. 42-48)--Attempts to prepare these compounds from the desired sodium nitrophenylsulfide and diethoxymonothiophosphoryl chloride in diethylene glycol or in alcohol were completely unsuccessful. Attempts to prepare O,O-diethyl-o-nitrophenyldithiophosphate by this reaction gave a mixture that could not be resolved even after repeated successive molecular distillations. Part of the difficulty lies in the fact that the nitrothiophenols are so unstable that they are oxidized to disulfides and other undetermined substances on contact with air. This makes them difficult if not impossible to isolate in a pure state. When, for example, m,m'-dinitrodiphenyldisulfide is reduced with glucose and sodium hydroxide, the free thiophenol cannot be precipitated, even under an atmosphere of carbon dioxide, by the addition of acid. A dark red unresolvable tar separates instead.

Ethyl-m-nitrophenyl Sulfide (Experimental, p. 42-43)  
--This compound was isolated from the reaction mixture obtained by refluxing excess diethoxymonothiophosphoryl chloride with the solution resulting from reduction of bis-(m-nitrophenyl) disulfide with sodium ethylate and dextrose in absolute alcohol. Ethyl-m-nitrophenyl sulfide has been reported in only one previous instance. Douleavy and English<sup>38</sup> prepared it by diazotization of m-nitroaniline followed by decomposition of the diazonium salt in potassium ethyl xanthate solution. The resulting xanthate was hydro-

lyzed in a 20% potassium hydroxide solution in 70% ethyl alcohol and the hydrolyzed product alkylated by addition of diethyl sulfate. This is reported as being a general method for the preparation of m-nitrophenyl alkyl sulfides, alkyl bromides being substituted for diethyl sulfate in other instances. Their yield was 40 to 50%.

$\beta$ -Hydroxy- $\beta'$ -(p-nitrophenylthio)-diethyl ether (Experimental, p. 44-45)--This is a new compound that was isolated from the reaction of sodium p-nitrophenyl sulfide and diethoxy-monothio-phosphoryl chloride in diethylene glycol by successive molecular distillation of the residue left from removal of the water soluble and volatile materials. After two molecular distillations the compound was recrystallized to give a yellow crystalline solid.

The reaction of sodium diethoxydithiophosphate with halogenated nitrobenzenes to give O,O-diethylnitrophenyl thiophosphates was a complete failure. The reaction of 2,4-dinitrochlorobenzene with sodium diethoxydithiophosphate to give a mixture of bis-(2,4-dinitrophenyl) disulfide and bis-(2,4-dinitrophenyl) sulfide is a new reaction but is not surprising considering the results of Talen<sup>27</sup> and of Twiss<sup>26</sup> in similar reactions. They treated 2,4-dinitrochlorobenzene with sodium thiosulfate, sodium ethyl xanthate, thiourea and phenyl isothiocyanate and in each case obtained a yellow solid which decomposed a few degrees above 200° C. and which on extraction with ethyl alcohol left bis-(2,4-dinitrophenyl) sulfide. The alcohol solution in each case was found to

contain bis-(2,4-dinitrophenyl) disulfide. Their results correspond very closely with the ones reported here.

SUGGESTIONS FOR FUTURE WORK

A. Completion of Work Already Started

Proposed suggestions for extension of the present work are as follows:

I. The synthesis of O,O-diethyl-o-nitrophenyldithiophosphate. The low yield or complete lack of formation of this compound in the reaction of diethoxymonothio-phosphoryl chloride with sodium o-nitrophenyl sulfide in diethylene glycol may perhaps be remedied by the use of an inert solvent such as toluene or m-xylene in place of the glycol.

II. The synthesis of O,O-diethyl-m-nitrophenyldithiophosphate. To accomplish this synthesis it will be necessary to find a means of isolating sodium m-nitrophenyl sulfide in a dry state, after which the reaction with diethoxymonothio-phosphoryl chloride in an inert solvent such as toluene or m-xylene should give the desired compound.

III. The synthesis of O,O-diethyl-p-nitrophenyldithiophosphate. Here again as with the o- and m- analogues of this compound the use of an inert solvent should give the desired product.

B. Work Contemplated But Not Started

I. The chemistry of Parathion and its analogues has recently been reported by Cassaday and co-workers<sup>39</sup> leaving little to be investigated along these lines. However, there are a number of interesting compounds, from the standpoint of possible insecticidal activity, that could be pre-

pared, using the basic structure of Parathion and making substitutions on the benzene ring. Such compounds are O,O-diethyl-O-(2-methyl-4,6-dinitrophenyl) thiophosphate and O,O-diethyl-O-(2-cyclohexyl-4,6-dinitrophenyl) thiophosphate. These compounds are of interest because the free phenols, 4,6-dinitro-o-cresol and 2,4-dinitro-6-cyclohexyl phenol, are both good insecticides in themselves.

II. The chemistry of compounds with a phosphorus to nitrogen linkage have been studied to a lesser extent than their corresponding oxygen analogues. The preparation of O,O-diethyl-N,p-nitrophenyl thiophosphate and other similar compounds should be of interest.

III. The preparation of diethyl-p-nitrophenyl tetra-thiophosphate should be of interest in a comparison of insecticidal activity with Parathion. This compound could be prepared by the reaction of thiophosphoryl chloride with two moles of sodium ethyl sulfide in an inert solvent followed by treatment with sodium p-nitrophenyl sulfide in the same solvent.

SUMMARY

I. The synthesis of the following new organic compounds is reported:

- O,O-diethyl-O,m-trifluoromethylphenyl thiophosphate
- O,O-diethyl-O,o-fluorophenyl thiophosphate
- O,O-diethyl-O,m-fluorophenyl thiophosphate
- O,O-diethyl-O,p-fluorophenyl thiophosphate
- O,O-diethyl-O,o-bromophenyl thiophosphate
- O,O-diethyl-O,m-bromophenyl thiophosphate
- O,O-diethyl-O,p-bromophenyl thiophosphate
- O,O-diethyl-O-pentachlorophenyl thiophosphate
- $\beta$ -hydroxy- $\beta'$ -(p-nitrophenylthio) diethyl ether

All of the thiophosphates listed were prepared by the reaction of the desired sodium phenoxide with diethoxy-monothiophosphoryl chloride.

In an attempt to prepare O,O-diethyl-p-nitrophenyl dithiophosphate, the new compound  $\beta$ -hydroxy- $\beta'$ -(p-nitrophenylthio) diethyl ether was synthesized.

In addition, a new method for the preparation of ethyl-m-nitrophenyl sulfide is also reported.

The treatment of halogenated nitrobenzenes, having an active halogen atom, with sodium O,O-diethyldithiophosphate has been found unsuccessful in the preparation of O,O-diethyl-nitrophenyl dithiophosphates.

A new method for the preparation of bis-(2,4-dinitrophenyl) sulfide is reported.

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