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The Synthesis and Insecticidal Activity of Some Halogenated Aromatic Ethers.

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THE SYNTHESIS AND INSECTICIDAL ACTIVITY OF SOME HALOGENATED AROMATIC ETHERS

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by

Tien-chih Chen
B.S., National South-western Associated University, 1941
M.S., Louisiana State University, 1948
August, 1949
MANUSCRIPT THESIS

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</table>
Since man is predestined to share the earth with insects, it is desirable, and in some cases necessary, for him to control those which transmit disease, reduce the food supply, and cause human misery.

Chemical substances, both natural and synthetic, have been used in this connection for a long time. The introduction of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT) and its successful application as a contact poison against numerous species of harmful insects suggest the possibility of finding other useful insecticides among the synthetic compounds.

DDT appears to depend on its lipophilic $\text{CCl}_3$- group for penetration of the insect and its chlorinated aryl rings for its paralyzing effects. Thus it appeared worth while to obtain other compounds having lipophilic groups and appropriately situated halogen atoms for testing against harmful insects. Therefore, a series of sixteen aliphatic-aromatic ethers halogenated in either or both the alkyl and aryl group was synthesized by standard procedures. These ethers were tested individually against three types of harmful insects and one harmful Arachnida by exposing the test organisms to predetermined quantities of the compounds deposited on suitable surfaces.
An immature flying insect (mosquito larvae), a mature flying insect (house flies), and a mature crawling insect (confused flour beetles) and a harmful Arachnida (rat mites) were selected for these biological tests. DDT was used as the reference standard insecticide in all of the tests with these organisms.

Some of the compounds were inactive against the indicated organisms under the conditions of our tests. Others were quite active, and in one or two instances, their activity exceeded that of DDT. This indicates that it is possible to build an insecticide around the lipophilic ether linkage in conjunction with the presence of halogen atoms in either the aliphatic or aromatic portions of the molecule.

It is likewise obvious that these features characteristic of certain compounds found to be active must be associated with a molecular configuration of a certain degree of specificity for maximal insecticidal activity.

The 3-chlorinated allyl ethers were definitely superior to the isomeric 2-chlorinated allyl ethers as judged by the degree of mortality in the four types of test organisms. The substitution of multiple halogen atoms in the phenyl group of aliphatic-aromatic ethers failed to enhance the toxicity of the compounds toward the test organisms. The o-chlorinated benzyl ethers of the p-substituted phenols were more active than the corresponding benzyl ethers except in the case of rat mites.
INTRODUCTION

Chemical Insecticides

In the performance of their biological functions, some insects are useful to mankind while others do serious and often irreparable harm. Some insects, e.g. the house fly, the anopheline mosquito, and the body louse transmit certain communicable diseases; while others, e.g. certain beetles, moths, and weevils are responsible for economic losses of considerable proportions. In addition to the more serious aspects of the insect problem mentioned above, man and domestic animals suffer from the attacks of such pestiferous insects as bedbugs, deer flies, and salt marsh mosquitoes.

The Arachnida, including mites, ticks, spiders, and scorpions, while not true insects, present some of the problems associated with the latter. Mites (family, Trombidiidae) transmit scrub typhus, while soft ticks (family, Argasidae) transmit relapsing fever, and hard ticks (family, Ixodidae) transmit certain rickettsiae and tularemia. Some of the lesser important Arachnida, e.g. red spiders and clover mites injure vegetable crops and herbaceous plants. The venom of a few of the Arachnida are known to elicit dangerous physiological responses in warm-blooded animals.
The seriousness of the insect problem has necessitated the development of numerous methods of control which may be classified under the broad headings: a) mechanical, b) biological, and c) chemical.

Chemical agents which are used to provide protection against insects are classified as a) insecticides, b) fumigants, and c) repellents. The insecticides may be further divided into a) stomach poisons, and b) contact insecticides. The contact insecticides, the more useful type, are lipophilic compounds which, on external contact, penetrate the chitinous cuticle of the insect, bringing about paralysis or death, depending on the degree of penetration and the potency of the insecticide. When contact insecticides are used against the adult stages, they are called adulticides; and when used against the immature stages, they are called larvicides.

The source of an insecticide is an important consideration, for this frequently determines its availability and cost, and, on occasion, the degree of its chemical stability. The two main sources are discussed separately as follows:
A. Insecticides of Botanical Origin.—The principal insecti-
cidal plants listed roughly in order of their introduction into
modern usage are:

1) Atoxome and allied products (genera: Derris (41),
Lonchocarpus (21, 40), Tephrosia (39), Milletia
(21)).
2) Nicotine - Nicotiana tabacum and N. rustica (19),
3) Quassia - Quassia amara (6),
4) Pyrethrum - Chrysanthemum genus (26),
5) Yam bean - Pachyrhizus erosus (13),
6) Ryania - Ryania speciosa (36),
7) Thunder god vine - Tripterygium wilfordii (47).

The introduction of a botanical insecticide is frequently
marked by three stages in the order given: a) the use of the
dried and powdered plants as a dust, b) the preparation and use
as a spray of a more or less concentrated liquid extract of the
plant, and c) the isolation of the active principle of the plant
and its formulation as a dust, an emulsion, or some other useful
preparation. In general, the botanical insecticides have little
or no residual activity since their active principles are not
stable in the presence of light and moisture.

B. Synthetic Insecticides.—The fumigating action of
naphthalene (51) and p-dichlorobenzene (9) against insects has
been known and made use of for some time. However, no dependable
insecticide of true synthetic origin existed until fairly recently. The first organized attempts to prepare synthetic insecticides were directed toward imitating the structures which had been established for the active principles found in the botanical insecticides. These efforts met with only indifferent success, but the discovery in 1939 of the broad and powerful insecticidal activity of the earlier prepared (53) DDT (2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane) by Müller gave great impetus to the work in the field of synthetic insecticides. The simultaneous disclosure of the opportunities in the field of synthetic insecticides was no less important. Using the DDT molecule as a working model, it may be possible to synthesize one or more compounds which would meet at least some of the following requirements which could be said to represent a near perfect insecticide:

1) High activity
2) Low toxicity to man, useful animals, birds, and fish
3) Low toxicity to useful insects
4) Low phytotoxicity
5) Long action
6) Rapid knock-down activity
7) Absence of formulation difficulties
8) Easily prepared from available materials
9) Inexpensive.
I. Some Biological Activities of Ethers

The alkylation or the arylation of the hydroxyl group in the alcohols or phenols produces ethers, some of which depress the activity of certain portions of the nervous system of higher animals. This physiological activity of ethers is attributed to their strong affinity for the lipoids of nerve tissue. Thus, the central nervous system is depressed, through a systemic action, by diethyl ether (12), paraldehyde (12), N-acetylphenetidin (34), and morphine (12), all of which contain one or more ether linkages. Likewise, the sensory nerve fibers are blocked by the application or injection of local anesthetic, some of which, e.g. eugenol (20), phenacaine and Supercaine (20), have been potentiated by the introduction of an ether group.

The degree of physiological response which an ether elicits depends on at least three factors: a) its physical properties, b) the associated chemical features, and c) the arrangement of the latter.

A. Aliphatic Ethers

1) **Length of the chain.**—As the series is ascended, that is, the alkyl groups become larger, the narcotic activity and the toxicity of the ethers are
increased, probably due to the slow excretion of the compound. This increased activity is enhanced by branching in the hydrocarbon chain.

2) **Unsaturation in the molecule.**—The introduction of one or more double bonds in the alkyl chain of an ether gives it a more powerful narcotic action and increases its toxicity. Both biological effects are produced at a more rapid rate than that observed with the corresponding saturated ether. Thus, the effective blood concentration of divinyl ether is one-fourth that of diethyl ether.

3) **Alicyclic radicals.**—Cyclopropane is the most potent of the general anesthetics. Therefore, it is to be expected that an ether with at least one alicyclic group would hold considerable promise as a depressant of the central nervous system. The smaller alicyclic radicals have received the most attention in this connection. As a consequence, encouraging results have been obtained with cyclopropylmethyl ether as a surgical anesthetic (20).

4) **Introduction of halogens.**—In general, the depressant action of an ether is augmented by loading the molecule with halogen atoms, more specifically with
chlorine and bromine. Simple ethers containing β-chlorine atoms are also known to be irritating to the eyes, skin, and respiratory tract (11).

5) **Alkoxy groups**.—The ethers of the dihydric and polyhydric alcohols are more active depressants than the alcohols from which they are derived. These compounds containing multiple ether linkages separated by short hydrocarbon residues are strongly narcotic and behave much like the ethers from the monohydric alcohols (20). The simpler acetals and the glycercyl ethers are representative of this class of compounds.

B. **Aromatic Ethers**.—The aromatic ethers, that is, those containing one aryl and one alkyl group, are more active locally than the dialkyl ethers. The aromatic ethers are highly toxic orally, causing fatty degeneration of the liver and kidneys (20). Hence, both the monomethyl and the dimethyl ether of resorcinol are more toxic than resorcinol. The effects of other substituent groups in the aryl residue on the physiological activity of the resulting molecules have not been fully investigated.

These neurotoxic effects of the ethers and ether derivatives are apparently carried over in some of the lower forms of life, at least in insects. A large number of ethers have been prepared and tested for their insecticidal activity. Frear (10) lists
approximately 400 different ethers for which insecticidal activity is claimed, either as a stomach poison, a contact insecticide or a fumigant. Of the various ethers which have been tried as insecticides, about fifteen or twenty have reached the market where some of them are very well established. A number of the commercial insecticidal ethers are listed in Table I along with the number of ether linkages in each compound and the insects against which each compound is particularly active.

**TABLE I**

**SOME COMMERCIALLY IMPORTANT ETHERS AND THE INSECTS AGAINST WHICH THEY ARE ACTIVE**

<table>
<thead>
<tr>
<th>Ether</th>
<th>Susceptible Insects</th>
<th>Number of Ether Linkages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotenone (Rotenoids)</td>
<td>Mosquitoes, Flies</td>
<td>5</td>
<td>39, 40, 41</td>
</tr>
<tr>
<td>Sesamin</td>
<td>House Flies</td>
<td>6</td>
<td>22, 50</td>
</tr>
<tr>
<td>Indalone (Butyl mesityl oxide)</td>
<td>House Flies, Mosquitoes</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>Fumigant</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Cyclohexene oxide</td>
<td>Fumigant</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Dichloroethyl ether</td>
<td>Fumigant</td>
<td>1</td>
<td>42, 45</td>
</tr>
<tr>
<td>(3,4-Methylenedioxy-6-propyl benzyl) (butyl) diethylene glycol ether (Piperonyl butoxide)</td>
<td>House Flies</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>2-Butoxy-2'-thiocyanodithyl ether (Lethane 384)</td>
<td>House Flies, Aphids</td>
<td>2</td>
<td>28, 29, 30</td>
</tr>
<tr>
<td>2,2-bis(p-Methoxyphenyl)-1,1,1-trichloroethane (Methoxychlor)</td>
<td>House Flies</td>
<td>2</td>
<td>37</td>
</tr>
</tbody>
</table>
II. The Synthesis of Aromatic Ethers

Ethers are compounds which are characterized by an R-O-R linkage. The ether oxygen may occur as a unit in a chain as in the oxides of the hydrocarbon radicals, the hemiacetals, the acetals, and the ketals. It may also constitute the heteroatom in such heterocyclic compounds as the alkylene oxides, the dienes, the trioxymethylene, and the furans.

The alkyl oxides and the aryl oxides are divided into three types: a) aliphatic ethers, those composed of the same or different alkyl groups; b) aromatic ethers, those composed of the same or different aryl groups; and c) aliphatic-aromatic ethers, those composed of one alkyl group and one aryl group. The ethers occur as gases, liquids, and solids, depending upon their complexity. The lower members, unlike water and alcohols, show no association and hence have low boiling points compared to the alcohols with which they are isomeric. Ethers are excellent organic solvents especially for resins, waxes, and fats. Chemically, they are inert, even as organic compounds go, being less active than the alcohols but somewhat more active than their isosteric hydrocarbons (49).

Many publications on all three types of ethers have appeared, but only the literature of the third type (aliphatic-aromatic ethers) is pertinent to this study, and hence my efforts have been directed toward locating and reviewing the articles dealing with the preparation, isolation, and purification of the aliphatic-
aromatic ethers. Some references to true aromatic ethers are in­
cluded as complementary material.

The methods for the preparation of aliphatic-aromatic ethers
may be distributed among five types of reactions listed here in
order of their applicability in the laboratory:

1) Reaction of phenols or phenolates with alkyl salts;
2) Reaction of the diazonium salts;
3) Dehydration;
4) Addition to an unsaturated linkage;
5) Miscellaneous.

A. Reaction of Phenolates with Alkyl Salts.—This method
consists of heating metallic phenolate with an alkyl halide. It
was used by Williamson (52) in 1852 to prepare a series of ethers,
the structures of which were conclusively proved by the reaction.
This reaction provides a good yield of many ethers, usually in a
relatively pure state. Some applications of this method and its
modifications are shown in Table II.
TABLE II

SOME APPLICATIONS OF THE WILLIAMSON'S METHOD FOR THE SYNTHESIS OF AROMATIC ETHERS

<table>
<thead>
<tr>
<th>Phenolic Compounds</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOH</td>
<td>CH_2=CH-CH_2Br</td>
<td>K_2CO_3 + Acetone, Heat</td>
<td>PhOC_2CH=CH_2</td>
<td>7</td>
</tr>
<tr>
<td>PhOH</td>
<td>4-Chloro-</td>
<td>Excess PhOH, 180°</td>
<td>4-Phenoxyquinidine</td>
<td>4</td>
</tr>
<tr>
<td>2,4,6-Cl_3C_6H_2OAg</td>
<td>C_2H_5I</td>
<td>Heat</td>
<td>2,4,6-Cl_3C_6H_2OC_2H_5</td>
<td>18</td>
</tr>
<tr>
<td>PhOH</td>
<td>R_3PO_4</td>
<td>Heat</td>
<td>PhOC_6H_5</td>
<td>33</td>
</tr>
<tr>
<td>PhOH</td>
<td>C_6H_5X</td>
<td>Cu catalyst, Heat</td>
<td>PhOC_6H_5</td>
<td>2</td>
</tr>
<tr>
<td>PhOH</td>
<td>(CH_3)_2SO_4</td>
<td>Heat</td>
<td>PhOC_3</td>
<td>1</td>
</tr>
</tbody>
</table>
B. Reaction of the Diazonium Salts.—Another general method for the preparation of ethers makes use of the reactivity of the diazonium compounds. Diazo methane is very useful in methylating phenolic hydroxyls. Aryl diazonium salts react with certain alcohols to give the corresponding ethers. Some examples of this reaction are listed in more detail in Table III.

### Table III

**Some Applications of the Use of Diazonium Compounds in the Synthesis of Aromatic Ethers**

<table>
<thead>
<tr>
<th>Phenolic Compounds</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOH</td>
<td>CH₂N₂</td>
<td>Cold</td>
<td>PhOCH₃</td>
<td>35</td>
</tr>
<tr>
<td>PhOH</td>
<td>α-C₁₀H₇N₂X</td>
<td></td>
<td>PhOα-C₁₀H₇</td>
<td>17</td>
</tr>
<tr>
<td>PhN₂X</td>
<td>CH₃OH</td>
<td>Heat</td>
<td>PhOC₂H₅</td>
<td>16</td>
</tr>
<tr>
<td>PhN₂X</td>
<td>C₂H₅OH</td>
<td>Heat</td>
<td>PhOC₂H₅</td>
<td>16</td>
</tr>
<tr>
<td>PhOH</td>
<td>C₆H₅N₂X</td>
<td>Heat</td>
<td>PhOC₆H₅</td>
<td>16</td>
</tr>
</tbody>
</table>
C. Dehydration.—Methods for preparing ethers involving dehydration of alcohols and/or phenols require elevated temperatures and special catalyst. They are generally more suited to industrial installations than to the laboratory. Some of the ethers so prepared and the required conditions are listed in Table IV.

**TABLE IV**

**SOME APPLICATIONS OF REACTIONS INVOLVING DEHYDRATION IN THE SYNTHESIS OF AROMATIC ETHERS**

<table>
<thead>
<tr>
<th>Phenolic Compounds</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOH</td>
<td>CH$_2$OH-CHOH-CH$_2$OH</td>
<td>CH$_3$COONa, Heat</td>
<td>PhOCH$_2$-CHOH-CH$_2$OH</td>
<td>54</td>
</tr>
<tr>
<td>PhOH</td>
<td>C$_6$H$_5$OH</td>
<td>Th$_2$ 450º</td>
<td>PhOC$_6$H$_5$</td>
<td>5</td>
</tr>
<tr>
<td>PhOH</td>
<td>C$_6$H$_5$OH</td>
<td>AlCl$_3$ 350º</td>
<td>PhOC$_6$H$_5$</td>
<td>27</td>
</tr>
<tr>
<td>PhOH</td>
<td>C$_6$H$_5$OH</td>
<td>ZnCl$_2$ 350º</td>
<td>PhOC$_6$H$_5$</td>
<td>27</td>
</tr>
<tr>
<td>PhOH</td>
<td>CH$_3$OH</td>
<td>HF</td>
<td>PhOCH$_3$</td>
<td>44</td>
</tr>
<tr>
<td>PhOH</td>
<td>iso-C$_3$H$_7$OH</td>
<td>BF$_3$, Heat</td>
<td>PhOCH(CH$_3$)$_2$</td>
<td>14, 46</td>
</tr>
</tbody>
</table>
D. Addition to an Unsaturated Linkage.—Phenolic ethers are also obtained by a reaction between a phenol (or phenolate) and an olefin in which the phenol adds to the double or triple bond of the latter in the presence of an acid catalyst. Some reactions of this type are given in outline form in Table V.

### TABLE V

**SOME APPLICATIONS OF THE REACTION BETWEEN A PHENOL AND AN OLEFIN IN THE SYNTHESIS OF AROMATIC ETHERS**

<table>
<thead>
<tr>
<th>Phenolic Compounds</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOMe</td>
<td>PhC=CHCOOC₂H₅</td>
<td>Heat</td>
<td>PhC(OPh)=CHCOOC₂H₅</td>
<td>43</td>
</tr>
<tr>
<td>PhOH</td>
<td>Olefin</td>
<td>H₂SO₄ or H₃PO₄</td>
<td>PhOR</td>
<td>32</td>
</tr>
<tr>
<td>PhOH</td>
<td>Olefin</td>
<td>HgSO₄</td>
<td>PhOR</td>
<td>3</td>
</tr>
<tr>
<td>PhOH</td>
<td>CH₂=CH-CH₂Cl</td>
<td>BF₃(Benzene)</td>
<td>PhOCH₂CH(OH)CH₂Cl</td>
<td>24</td>
</tr>
</tbody>
</table>
E. Miscellaneous.—The reactions for the preparation of aromatic ethers which could not be classified under the foregoing types of reactions are presented in Table VI.

<table>
<thead>
<tr>
<th>Phenolic Compound</th>
<th>Reactants</th>
<th>Condition</th>
<th>Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhONa</td>
<td>C₆H₅ONa</td>
<td>Ba(OH)₂ 250-300°C</td>
<td>PhOC₆H₅</td>
<td>38</td>
</tr>
<tr>
<td>PhONa</td>
<td>ROH</td>
<td>CO atmos.</td>
<td>PhOR</td>
<td>38</td>
</tr>
<tr>
<td>PhOH</td>
<td>[(C₂H₅)₃O]BF₄</td>
<td>Heat</td>
<td>PhOC₂H₅</td>
<td>31</td>
</tr>
<tr>
<td>PhONa</td>
<td>[(C₂H₅)₃O]BF₄</td>
<td>Heat</td>
<td>PhOC₂H₅</td>
<td>31</td>
</tr>
</tbody>
</table>
DISCUSSION

A series of mixed ethers was prepared from halogenated phenols in view of the well known neurotoxic effects of aryl halides. The number and the positions of the ring halogens were varied to some degree in an attempt to determine the possibility of a correlation between these structures and their insecticidal activity. Two structural features were included in the alkyl portions of the mixed ethers, namely the introduction and location of a halogen atom.

The 3-chlorinated allyl ethers were definitely more toxic than the isomeric 2-chlorinated allyl ethers to the three species of insects and to the rat mites. The reason for this difference in activity is not apparent, but a determination of the dehydrohalogenation rates of the isomeric pairs would be the next logical step in the study of these compounds since it has been demonstrated that the insecticidal activity of certain halogenated hydrocarbons is dependent upon such a reaction.

The substitution of multiple chlorine atoms in the phenyl group of the four ethers with 3-chloroallyl, benzyl, and o-chlorobenzyl radicals, respectively, failed to enhance the toxicity of these ethers to any of the test organisms. The
increased halogen content of these compounds decreases their solubility in water, and, is probably not without some influence on their solubility in oil and fatty material. Since the oil/water distribution coefficient of many contact insecticides is highly critical with respect to their degree of activity, it is possible that an unfavorable distribution between oil and water explains the reduced activity of the ethers derived from polyhalogenated phenyl radicals.

In general, the activity of the p-halophenyl 3-chloroallyl ethers was not significantly reduced by substituting a benzyl radical for the aryl halogen atom. In view of this, the benzyl group appears to offer some promise in the field of synthetic contact insecticides. Further, it would be of some interest to compare the influence of the benzyl group and that of its open chain analogues, the heptyl groups, in at least one compound known to have a measurable degree of insecticidal activity.

With the exception of p-chlorephenyl p-chlorobenzyl ether and p-bromophenyl p-chlorobenzyl ether, which were very active against house flies, the ethers with the benzyl and the p-chlorobenzyl groups showed only moderate activity. However, the p-chlorobenzyl ethers were invariably more active toward the insect species than were the corresponding unsubstituted benzyl ethers.

The mites proved to be more resistant to these halogenated...
others than did the three species of insects. This is in keeping with the fact that only a very limited number of miticides have been discovered up to the present. Such a situation may be explained on the basis of certain fundamental biological differences between the physiology of the insects and that of the Arachnida.
EXPERIMENTAL

I. Chemical

The Williamson synthesis was modified in several respects and one or the other of these modifications was used in the preparation of the ethers included in this study. These modifications are described below under the headings: Modifications I, II, and III.

Modification I.—Six and six-tenths grams (0.1 mole) of potassium hydroxide was added to 50 ml. of ethanol contained in a 250-ml. round-bottomed flask fitted with a reflux condenser by means of a ground-glass joint. The mixture was heated to dissolve the alkali and then allowed to cool. One-tenth mole of the appropriately substituted phenol, dissolved in 50 ml. of ethanol, was added to the alcoholic alkali. To this solution was added 0.1 mole of the alkyl chloride. The resulting mixture was refluxed over a free flame for a period of four hours during which the potassium chloride separated. The salt was filtered with suction, and the filtrate was again refluxed for one hour to insure the completion of the reaction. The alcoholic solution was poured into an excess of chipped ice and allowed to stand overnight. The ethers which occur as a solid were removed.
from the water by filtration with suction and then recrystallized to maximum purity. The liquid ethers were extracted from the water with diethyl ether, and dried over anhydrous sodium sulfate. The solvent ether was removed by distillation, and the desired ether was further purified by distillation under vacuum (15).

Modification II.—In a 250-ml., round-bottomed, two-neck flask, fitted by means of ground glass joints with an upright condenser and a dropping funnel, was placed an alcoholic solution of 0.1 mole of the halogen-substituted potassium phenolate prepared by dissolving equivalent quantities of the halogenated phenol and potassium hydroxide in 80 ml. of ethanol. This solution was heated to boiling and 0.1 mole of the alkyl chloride, previously dissolved in 20 ml. of ethanol, was added dropwise over a period of two hours. The refluxing was continued for one hour or until there was no more evidence of potassium chloride formation. The insoluble potassium chloride was filtered with suction. In those cases involving poorly soluble ethers the filtrate separated into two layers. In all cases the entire filtrate was added to an excess of chipped ice. From this point the procedure followed that described in Modification I.

Modification III.—One-tenth mole of the phenol and an equivalent quantity of the alkyl chloride were dissolved in 100 ml. of acetone. To this solution was added 0.1 mole of freshly fused, powdered potassium carbonate. The resulting mixture was refluxed
on a water bath for eight hours. The mixture was filtered free of insoluble material. The filtrate was poured into an excess of ice water and the separated ether along with any unreacted alkyl chloride was extracted with 100 ml. of diethyl ether. The ether extract was washed with several portions of aqueous alkali to remove any unreacted phenol. The ether solution was dried over anhydrous sodium sulfate and the desired ether was collected by fractional distillation under reduced pressure (15).

1) \( p \)-Chlorophenyl 2-chloroallyl ether.—This ether, which is a colorless liquid, was prepared by the procedure described under Modification I in an average yield of 53% of the theoretical. It was purified to a constant refractive index by distillation in a Hickman vacuum still (15). \( n_{25}^D = 1.5426 \)

Analyses: Calculated for \( C_9H_8OCl_2 \): C, 53.23; H, 3.97.

Found: C, 52.98; H, 3.96.

2) \( p \)-Chlorophenyl 3-chloroallyl ether.—Prepared by Modification III. It occurs as a colorless liquid which at maximum purity has a refractive index of: \( n_{25}^D = 1.5541 \). The yield was 60% of the theoretical.

Analyses: Calculated for \( C_9H_8OCl_2 \): C, 53.23; H, 3.97.

Found: C, 52.84; H, 4.15.

3) \( p \)-Chlorophenyl \( \alpha \)-dichlorobenzyl ether.—Obtained by Modification II. It is a colorless liquid with a refractive index of: \( n_{25}^D = 1.5269 \) in the purified state. The yield was 62% of
the theoretical.

Analyses: Calculated for \( \text{C}_{13}\text{H}_{9}\text{OCl}_{3} \):  
\[ \text{C}, \ 54.29; \ \text{H}, \ 3.16. \]

Found:  
\[ \text{C}, \ 54.88; \ \text{H}, \ 3.62. \]

4) **p-Chlorophenyl o-chlorobenzyl ether.**—This ether was prepared, as a colorless liquid, by Modification I. It is a liquid at room temperature but crystallizes in a refrigerator. The yield was 50% of the theoretical. \( n_{25}^{\circ} = 1.5897 \).

Analyses: Calculated for \( \text{C}_{13}\text{H}_{10}\text{OCl}_{2} \):  
\[ \text{C}, \ 61.68; \ \text{H}, \ 3.98. \]

Found:  
\[ \text{C}, \ 61.52; \ \text{H}, \ 4.19. \]

5) **p-Bromophenyl 3-chloroallyl ether.**—Prepared by Modification I. It occurs as a colorless liquid which at maximum purity has a refractive index of: \( n_{25}^{\circ} = 1.5686 \). The yield was 42% of the theoretical.

Analyses: Calculated for \( \text{C}_{9}\text{H}_{8}\text{OClBr} \):  
\[ \text{C}, \ 44.94; \ \text{H}, \ 3.35. \]

Found:  
\[ \text{C}, \ 44.49; \ \text{H}, \ 3.14. \]

6) **p-Bromophenyl o-chlorobenzyl ether.**—Prepared by Modification I. It occurs as a solid in the refrigerator but melts at room temperature. The refractive index of this ether when pure is: \( n_{25}^{\circ} = 1.6072 \). The yield was 50% of the theoretical.

Analyses: Calculated for \( \text{C}_{13}\text{H}_{10}\text{OClBr} \):  
\[ \text{C}, \ 52.47; \ \text{H}, \ 3.39. \]

Found:  
\[ \text{C}, \ 52.40; \ \text{H}, \ 3.42. \]

7) **2,4-Dichlorophenyl 2-chloroallyl ether.**—Obtained by Modification I. It is a colorless liquid with a refractive
Index of: \( n_{D}^{20} = 1.5567 \). The yield was 66\% of the theoretical.

Analyses: Calculated for \( \text{C}_{9}\text{H}_{7}\text{OCl}_{3} \):

\[
\begin{align*}
\text{C,} & \quad 45.51; \quad \text{H,} \quad 2.97. \\
\text{Found:} & \quad \text{C,} \quad 45.60; \quad \text{H,} \quad 3.01.
\end{align*}
\]

8) 2,4-Dichlorophenyl 3-chloroallyl ether.—Prepared by Modification III. It occurs as a colorless liquid which at maximum purity has a refractive index of: \( n_{D}^{20} = 1.5628 \). The yield was 70\% of the theoretical.

Analyses: Calculated for \( \text{C}_{9}\text{H}_{7}\text{OCl}_{3} \):

\[
\begin{align*}
\text{C,} & \quad 45.51; \quad \text{H,} \quad 2.97. \\
\text{Found:} & \quad \text{C,} \quad 45.75; \quad \text{H,} \quad 3.19.
\end{align*}
\]

9) 2,4-Dichlorophenyl benzyl ether.—This ether, which occurs as colorless crystals, was prepared by Modification I in an average yield of 62\% of the theoretical. The crude product was recrystallized from \( \text{i-butanol} \) to a maximum melting point of 59.5 - 61.0\°.

Analyses: Calculated for \( \text{C}_{13}\text{H}_{10}\text{OCl}_{2} \):

\[
\begin{align*}
\text{C,} & \quad 61.68; \quad \text{H,} \quad 3.98. \\
\text{Found:} & \quad \text{C,} \quad 61.41; \quad \text{H,} \quad 4.08.
\end{align*}
\]

10) 2,4-Dichlorophenyl \( \alpha\alpha\)-dichlorobenzyl ether.—Obtained by Modification II. It is a colorless liquid with a refractive index of: \( n_{D}^{20} = 1.5360 \) in the pure state. The yield was 78\% of the theoretical.

Analyses: Calculated for \( \text{C}_{13}\text{H}_{8}\text{OCl}_{4} \):

\[
\begin{align*}
\text{C,} & \quad 48.48; \quad \text{H,} \quad 2.50. \\
\text{Found:} & \quad \text{C,} \quad 48.15; \quad \text{H,} \quad 2.69.
\end{align*}
\]
11) 2,4-Dichlorophenyl o-chlorobenzyl ether.—This ether, which occurs as colorless crystals, was prepared by Modification I in an average yield of 71% of the theoretical. The crude product was recrystallized from ethanol to a maximum melting point of 63.0 - 65.0°.

Analyses: Calculated for C_{13}H_9OCl_3: C, 54.29; H, 3.15.

Found: C, 54.00; H, 3.24.

12) 2,4,5-Trichlorophenyl benzyl ether.—Prepared by Modification I. It occurs as a colorless crystals. The crude product was recrystallized from ethanol to a melting point of 74.0 - 76.0°. The yield was 66% of the theoretical.

Analyses: Calculated for C_{13}H_9OCl_3: C, 54.29; H, 3.15.

Found: C, 54.48; H, 3.16.

13) 2,4,5-Trichlorophenyl o-chlorobenzyl ether.—This ether, which occurs as colorless crystals, was prepared by Modification I in a yield of 70% of the theoretical. The crude product was purified by recrystallization from ethanol to a melting point of 123.0 - 125.0°.

Analyses: Calculated for C_{13}H_9OCl_3: Cl, 44.04.

Found: Cl, 44.40.

14) 1,2,3,4,5-Pentachlorophenyl 3-chloroallyl ether.—This ether, occurring as colorless crystals, was prepared by Modification III in a yield of 66% of the theoretical. The
crude product was purified by recrystallization from petroleum ether to a maximum melting point of 133 - 135°.

Analyses: Calculated for C_{13}H_{4}OCl_{6}: Cl, 62.41.

Found: Cl, 62.42.

15) 1,2,3,4,5-Pentachlorophenyl benzyl ether. — This ether was prepared by Modification I in a yield of 60% of the theoretical. The crude product was purified by recrystallization from a mixture of ethanol and benzene (3:5) to a melting point of 164-166°.

Analyses: Calculated for C_{13}H_{7}OCl_{5}: Cl, 49.73.

Found: Cl, 49.14.

16) p-Benzylphenyl 3-chloroallyl ether. — Obtained by Modification III. It occurs as a colorless liquid which at maximum purity has a refractive index of: n_{25}D = 1.5437. The yield was 50% of the theoretical.

Analyses: Calculated for C_{16}H_{15}OCl: C, 74.27, H, 5.84.

Found: C, 74.53, H, 5.92.
II. Biological

There are several problems connected with any program designed to evaluate a series of new compounds with respect to their insecticidal activity. If too few species of insects are used, some highly specific activity may be overlooked in one of the compounds and even in the entire series. When an activity against some species is disclosed, it is difficult even for an experienced technician to appraise it since degrees of physiological responses and mortality percentages are difficult to reproduce.

One approach to this problem consists of testing each compound of a new series against one insect in the larval stage, one species of a flying insect, one species of a crawling insect, and one species of a harmful Arachnida. The qualitative and quantitative activity of the new compound against each species of test organisms should be compared with that of a standard insecticide for that species and always at the same dose level. Several dose levels should be employed and each test should include as many test organisms as conditions permit.

The others prepared in this study have been tested against mosquito larvae, confused flour beetles, house flies, and rat mites. The methods employed with each of these test organisms are described below.

1) Screening Procedure Used with Mosquito Larvae.—Each of the others and the reference standard (DDT) were dissolved
separately in acetone at the rate of 0.5 g. per 100 ml. Two milliliters of each of these solutions were diluted to 1000 ml. with water. Twenty milliliters of this dilution was further diluted in a 600 ml. beaker to 200 ml. to give a solution of 1 p.p.m. To each beaker was added ten third instar mosquito larvae (Anopheles quadrimaculatus). The mortality from each compound was determined after 4, 6, 24, and 48 hours. These tests were repeated as concentrations of 0.1 p.p.m. All tests were carried out in duplicate. The results are given in Table VII.

2. Screening Procedure Used with Flour Beetles.—Each of the ethers and the reference standard (DDT) were made into 0.5% solution in acetone. One-half milliliter of each solution was pipetted over a sheet of filter paper fitted snugly into the bottom of a Petri dish having a diameter of 10 cm. This represented a dosage of 15 μg. of the ether per sq. cm. The solvent was allowed to evaporate. Samples of approximately 20 confused flour beetles (Tribolium confusum) were introduced into each Petri dish. After twenty-four hours of exposure, the mortality of each sample of beetles was determined. The tests were repeated at dose levels of 30 μg. and 60 μg. per sq. cm. The ethers, the reference compound and a control were tested in duplicate. The results are shown in Table VIII.
<table>
<thead>
<tr>
<th>Exposure (hms)</th>
<th>0.5 P.M.</th>
<th>1 P.M.</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-dichlorophenyl benzyl ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-dichlorophenyl 3-chloroacetate ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-dichlorophenyl 2-chloroacetate ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-bromophenyl o-chlorobenzyl ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-bromophenyl 3-chloroacetate ether</td>
<td></td>
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<tr>
<td>F-bromophenyl 2-chloroacetate ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-chlorophenyl o-chlorobenzyl ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-chlorophenyl 3-chloroacetate ether</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-chlorophenyl 2-chloroacetate ether</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

TABLE VII

EXPOSURE TO TWO DILLATIONS OF THE SPREAD AND OF NOT

COMPARATIVE AVERAGE MORTALITY OF RESPECTIVE LABORATORY MICE, 6, 24, AND 48 HOURS OF CONTINUOUS
<table>
<thead>
<tr>
<th>Dilution</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 p.p.m.</td>
</tr>
<tr>
<td>Exposure (hours)</td>
<td></td>
</tr>
<tr>
<td>2,4-Dichlorophenyl α, α-dichlorobenzyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 0 0 10</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl o-chlorobenzyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 5 10 30</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenyl benzyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 5 5 20</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenyl o-chlorobenzyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 25 70 85</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl 3-chloroallyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 15 40 45</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl benzyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 10 35 55</td>
</tr>
<tr>
<td>p-Benzylphenyl 3-chloroallyl ether</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 15 75 100</td>
</tr>
<tr>
<td>DDT (Reference standard)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 35 95 100</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 0 0 5</td>
</tr>
<tr>
<td>Ethers</td>
<td>Percent Mortality (%)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>P-Chlorophenyl 2-chloroallyl ether</td>
<td>51</td>
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<tr>
<td>P-Chlorophenyl 3-chloroallyl ether</td>
<td>11</td>
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<tr>
<td>P-Chlorophenyl o-chlorobenzyl ether</td>
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<td>P-Bromophenyl 2-chloroallyl ether</td>
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</tr>
<tr>
<td>P-Bromophenyl 3-chloroallyl ether</td>
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<tr>
<td>2,4-Dichlorophenyl 2-chloroallyl ether</td>
<td>0</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl benzyl ether</td>
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*Continued on next page*
<table>
<thead>
<tr>
<th>Ethers</th>
<th>Percent Mortality</th>
<th>Dosages (ug/cm²)</th>
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<tr>
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<tr>
<td>2,4-Dichlorophenyl α,α'-dichlorobenzyl ether</td>
<td>12</td>
<td>12</td>
</tr>
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<td>2,4-Dichlorophenyl o-chlorobenzyl ether</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenyl benzyl ether</td>
<td>5</td>
<td>5</td>
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<td>2,4,5-Trichlorophenyl o-chlorobenzyl ether</td>
<td>20</td>
<td>25</td>
</tr>
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<td>1,2,3,4,5-Pentachlorophenyl 3-chloroallyl ether</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl benzyl ether</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>p-Benzylphenyl 3-chloroallyl ether</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>DDT (Reference standard)</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3. Screening Procedure Used with House Flies.—Each of the others prepared in this study and a reference standard (DDT in this case) were made into 5% solutions using one of the following common organic solvents: ethyl methyl ketone, xylene or Dechase (refined kerosene). The same solvent was always used where the solubility of the compounds permitted. One milliliter of each of the solutions was distributed over a 6" by 6" glass panel by use of a pipette. This represents an application of 50 mg. of the compound per 225 sq. cm. The treated panels were held for seven, ten, and thirty days respectively before they were tested. This was done to evaluate the residual toxicity of the compounds under test. Samples of approximately 30 adult house flies (Musca domestica) each were exposed to a 50 sq. cm. area of each treated plate. This exposure extended for 30 minutes and was accomplished by placing each sample of flies under an inverted Petri dish. Counts were made of the incapacitated flies at 5-minute intervals during the exposure periods. At the conclusion of the exposure period, all flies from each sample were transferred to holding cages made of plastic screening and supplied with food (a 10% solution of honey in water). After twenty-four hours, the mortality of each sex of flies was determined. Each compound and the reference compound were tested in quadruplicate and a control was tested in duplicate. All compounds giving promising results at the thirty-minute exposure were tested in quadruplicate at a fifteen-minute exposure. The results obtained with the
The results are shown in

Table X.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>100°C</td>
<td>30</td>
<td>Good</td>
</tr>
<tr>
<td>B</td>
<td>120°C</td>
<td>45</td>
<td>Fair</td>
</tr>
<tr>
<td>C</td>
<td>150°C</td>
<td>60</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Note: The results are based on the average of three replicate measurements.

Materials and Methods:

1. Prepare samples A, B, and C.
2. Heat each sample in a sealed container at the specified temperature for the given time.
3. Evaluate the results based on the criteria listed above.

References:


<table>
<thead>
<tr>
<th>Age of Deposit in Percent (Days)</th>
<th>Percent Mortality</th>
<th>Male Female</th>
<th>Male Female</th>
<th>Male Female</th>
<th>Male Female</th>
<th>Male Female</th>
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<tr>
<td>7</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>30</td>
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<tr>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
<td>REFERENCES TO INSECTIS OR 500 MG. PER SQ. FT. OF VARIOUS CHEMICALS OF PENTOCLASS EPAX</td>
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TABLE II
<table>
<thead>
<tr>
<th>Ethers</th>
<th>Solvents Used</th>
<th>Time of Exposure (Min.)</th>
<th>Percent Mortality Age of Deposit in Panels (Days)</th>
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<tbody>
<tr>
<td></td>
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<td>2,4-Dichlorophenyl benzyl ether</td>
<td>Deobase</td>
<td>15</td>
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</tr>
<tr>
<td></td>
<td>Deobase</td>
<td>30</td>
<td>0</td>
</tr>
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<td>2,4-Dichlorophenyl O,O-dichlorobenzyl ether</td>
<td>Deobase + Acetone</td>
<td>15</td>
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<td></td>
<td>Deobase</td>
<td>30</td>
<td>10</td>
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<td>Deobase</td>
<td>15</td>
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<td></td>
<td>Deobase</td>
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<tr>
<td></td>
<td>Benzene</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl 3-chloroallyl ether</td>
<td>Xylene</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xylene</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl benzyl ether</td>
<td>Benzene</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>p-Benzylphenyl 3-chloroallyl ether</td>
<td>Deobase</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deobase</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>DDT (Reference standard)</td>
<td>Deobase</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deobase</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>
TABLE X

FOURTY-EIGHT-HOUR MORTALITIES OF RAT MITES (LIPONYSSUS BACOTTI)
AFTER 30 MINUTES EXPOSURE TO THE INDICATED PERCENTAGES OF
VARIOUS HALOGENATED ETHERS IN PYROPHYLITE DUSTS

<table>
<thead>
<tr>
<th>Ethers</th>
<th>Percentage of Ether (%)</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Chlorophenyl 2-chloroallyl ether</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>p-Chlorophenyl 3-chloroallyl ether</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>p-Chlorophenyl (\alpha,\alpha)-dichlorobenzyl ether</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>p-Chlorophenyl o-chlorobenzyl ether</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>p-Bromophenyl 3-chloroallyl ether</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>p-Bromophenyl o-chlorobenzyl ether</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl 2-chloroallyl ether</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl 3-chloroallyl ether</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl benzyl ether</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl (\alpha,\alpha)-dichlorobenzyl ether</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl o-chlorobenzyl ether</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenyl benzyl ether</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenyl o-chlorobenzyl ether</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl 3-chloroallyl ether</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>1,2,3,4,5-Pentachlorophenyl benzyl ether</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>p-Benzylphenyl 3-chloroallyl ether</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>DBF (Reference standard)</td>
<td>6</td>
<td>56</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) The percentage concentrations of the dusts are not uniform because the concentration of the material necessarily depended in each case on the amount of diluent (pyrophyllite) which had to be added to prepare a sufficiently flowable powder. The liquid ethers required more diluent g./g. than did the solid ethers.
SUMMARY

1. Eleven new aliphatic-aromatic ethers were prepared, purified, and satisfactorily analyzed. A physical constant was determined for each of these ethers.

2. Five ethers, specifically p-chlorophenyl $\sigma$-chlorobenzyl ether, p-bromophenyl $\sigma$-chlorobenzyl ether, 2,4-dichlorophenyl benzyl ether, 2,4-dichlorophenyl $\sigma$-chlorobenzyl ether, and 1,2,3,4,5-pentachlorophenyl benzyl ether, which were described in publications appearing during the course of this investigation, were prepared, purified, and more completely characterized.

3. Of this series of sixteen ethers thirteen were tested for the first time against mosquito larvae, confused flour beetles, house flies, and rat mites.

4. Of this series of sixteen ethers three, specifically p-chlorophenyl $\sigma$-chlorobenzyl ether, p-bromophenyl $\sigma$-chlorobenzyl ether, and 1,2,3,4,5-pentachlorophenyl benzyl ether, were tested for the first time against mosquito larvae, confused flour beetles, and rat mites.
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3-

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SELECTED BIBLIOGRAPHY

1. Allmann, F., and Wenner, P.
   Ueber die Verwendung von p-Toluen sulfonsaureester
   als Alkylierungsmittel.
   Ann., 327: 120-124 (1903)

2. Allmann, F., and Sponagel, P.
   Ueber Phenylierung von Phenolen
   Ann., 350: 83-107 (1906)

3. Auerhahn, A., and Stadler, R.
   Ethers.
   German Patent 734,402. Mar. 19, 1943
   C. A., 38: 1246 (1944)

   Reaction of 4-chloroquinolines and of 2-chloro-
   lepidines with NH₃ and the preparation of the
   corresponding phenyl ethers.

5. Briner, E., Mme J. Bren-Staalat et H. Paillard
   Recherches sur la d'eshydration du phenol. Contri-
   bution a la catalyse de contact.
6. Bussey, R. L.

A bibliography of quassia.

7. Claisen, L.

Über die Umagerung von Phenolallylather in die isomerers allyl phenole.
Ann., 418: 78 (1919)

8. Cotton, R. T., and Roark, R. C.

Ethylene oxide as a fumigant.


p-Dichlorobenzene as a vapor fumigant.

10. Frear, B. E. H.

A Catalogue of Insecticides and Fungicides

11. Goldman, L., and Cullen, C. E.

Some medical aspects of chemical warfare agents.
J. Am. M. A., 114: 2200-2204 (1940)


The Pharmacological Basis of Therapeutics.

13. Hansberry, R., and Lee, C.

The yam bean Pachyrrhizus erosus Urban as a possible insecticide.
J. Econ. Entomol., 36: 351-352 (1943)

Organic reactions with boron fluoride. IV. Ether cleavage in the presence of organic acids.


15. Highman, K. C. D.

*Modern Laboratory Appliances*


16. Hirsch, R.

*Über neue synthese mittelst diazo-verbindungen. II.*

*Ber.,* 25: 1973-1975 (1892)

17. Honigschmid, O.

*Über eine neue synthese der Ather.*

*Monatshefte,* 23: 823-824 (1903)

18. Hunter, W. H., Olson, A. O., and Daniels, E. A.

A catalytic decomposition of certain phenol-silver salts.


19. Jackson, K. E.

*Alkaloids of tobacco.*

*Chemical Reviews,* 29: 123-197 (1947)

20. Jenkins, G. L., and Hartung, W. H.

*The Chemistry of Organic Medicinal Products*


21. Jones, H. A.

A list of plants reported to contain rotenone or rotenoids.


Chemical nature of the insecticidal principle in Namay seed.


Insecticidal properties of 1,3-indandiones.

_*Ind. Eng. Chem._, 34: 494-495 (1942)

24. Lefebvre, H., Levas, E., and Mae Levas

Condensation of epichlorohydrin with different phenols in the presence of BF₃.

_*Compt. rend._, 222: 1439-1440 (1946)

_C. A._ 49, 5712 (1946)


Fumigant action of cyclohexene oxide.


26. Mardzhanyan, G. M.

Toxic characteristics of different pyrethrum species.


27. Marx, V., and Weith, W.

*Über die Aetherifizierung der phenole.*

*Ber._, 14: 189-191 (1881)

28. Murphy, D. F.

Insecticidal activity of aliphatic thiocyanates. III.

Red spiders and mites.

_*J. Econ. Entomol._, 29: 606-611 (1936)
29. Murphy, D. F.

Insecticidal activity of aliphatic thiocyanates.

II. Mealy-bugs.


30. Murphy, D. F., and Pest, C. H.

Insecticidal activity of aliphatic thiocyanates.

I. Aphids.

*J. Econ. Entomol.*, 25: 123-129 (1932)


*New Methods of Preparative Organic Chemistry.*


Pp. 305-315.

32. Niederl, J. B., and Matelson, S.

The arrangement of saturated alkyl phenyl ethers.

Synthesis of isopropyl phenol and cresols.


33. Moller, C. R., and Dutton, G. R.

Note on the preparation of triallyl phosphates and their use as alkylating agents.


34. Payne, S.

Acetanilid poisoning; a clinical and experimental study.

35. Fechmann, E. V.

Uber Diazomethan

Ber., 28: 857-858 (1895)

36. Pepper, B. B., and Carruth, L. A.

A new plant insecticide for the control of the
European corn borer.

J. Econ. Entomol., 38: 59-66 (1945)


Insecticidal activity of some alkoxy analogues of DDT.

Science, 101: 464-465 (1945)

38. Richter von Victor

The Chemistry of the Carbon Compounds. III.


39. Roark, R. C.


40. Roark, R. C.

The chemical relationships between certain insecticidal
species of fabaceous plants.

J. Econ. Entomol., 26: 587-594 (1933)

41. Roark, R. C.

List of common names used for species of derris in con-
nection with insecticidal properties.

42. Roark, R. C., and Cotton, R. F.

Tests of various aliphatic compounds as fumigants.


43. Buhemann, S.

Condensation of phenols with esters of the acetylene series.

J. Chem. Soc., 79: 918; 1185 (1901)


Hydrogen fluoride as a condensing agent. XII. Reactions of methyl, ethyl, and phenyl compounds with benzene and its derivatives.


45. Snapp, O. I.

Dichloroethyl ether for the control of the plum curculio on peaches.


46. Sowa, F. L., Hemion, G. F., and Niewland, J. A.

Organic reactions with boron fluoride. IX. The alkylation of phenol with alcohols.


A Chinese insecticidal plant, Tripterygium Wilfordii, introduced into the United States.

Science, 93: 60-61 (1941)
48. Nachs, H.

Synergistic insecticides.

*Science*, 186: 530-531 (1947)

49. Whitman, F. C.

*Organic Chemistry*


50. Wilcoxen, F., et al.

Insecticidal properties of extract of male fern.


51. Wilcoxen, F., Hartwell, A., and Yonken, W. J.

Greenhouse fumigations with naphthalene solutions.

*Contrib. Boyce Thompson Inst.*, 5: 461-469 (1933)

52. Williamson, A. W.

Theory of etherification.


53. Zeidler, O.

*Verbindungen von Chloral mit Brom- und Chlorbenzol*

*Ber.*, 7: 1180-1181 (1874)

54. Zivkovic, P.

New formation of ethers of glycerol with phenol.

*Monatshefte*, 29: 951-958 (1908)

*C. A.*, 3: 906 (1909)
Tien-chih Chen was born in Chekiang, China, on July 4, 1922. His elementary schooling was received in the primary school of Chekiang. He was graduated from Shanghai High School, Shanghai, in July 1937.

The following September, he entered National South-western Associated University, from which institution he was graduated with the Bachelor of Science degree with a major in Chemistry in August 1941.

In September, 1941, he was appointed an assistant in the Department of Chemistry, National South-western Associated University and continued in this capacity until August of 1946. In May, 1946, he passed a competitive examination for a State Department Fellowship under the auspices of United States Embassy in China for advanced studies in a university of the United States of America. In September, 1946, he entered Louisiana State University as a graduate student in the College of Chemistry and Physics. In May, 1948, he received the Master of Science degree from this institution.

In September, 1948, he secured a position as an assistant to the Chemist of the Technical Development Division,
Communicable Disease Center, United States Public Health Service, at Savannah, Georgia. In February, 1949, he returned to Louisiana State University with an appointment as a research assistant in the Department of Chemistry where he continued his work leading to the Degree of Doctor of Philosophy in Chemistry.
EXAMINATION AND THESIS REPORT

Candidate: Tien-Chih Chen

Major Field: Organic Chemistry

Title of Thesis: THE SYNTHESIS AND INSECTICIDAL ACTIVITY OF SOME HALOGENATED AROMATIC ETHERS

Approved:

[Signatures of faculty members]

EXAMINING COMMITTEE:

[Signatures of committee members]

Date of Examination: July 20, 1949

[Signature of presiding officer]