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Preparation of Compounds of Potential Physiological Activity: Amino Esters of Substituted Benzilic, Glycolic and Acetic Acids and Related Compounds

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University of Tennessee - Knoxville

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To the Graduate Council:

I am submitting herewith a dissertation written by Kumbla Vittal Nayak entitled "Preparation of Compounds of Potential Physiological Activity: Amino Esters of Substituted Benzilic, Glycolic and Acetic Acids and Related Compounds." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Hilton A. Smith, Calvin A. Buehler, Major Professor

We have read this dissertation and recommend its acceptance:

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Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)
To the Graduate Council:

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[Signatures]

We have read this dissertation and recommend its acceptance:

[Signatures]

Accepted for the Council:

[Signature]

Dean of the Graduate School
PREPARATION OF COMPOUNDS OF POTENTIAL PHYSIOLOGICAL ACTIVITY:
AMINO ESTERS OF SUBSTITUTED BENZILIC, GLYCOLIC AND
ACETIC ACIDS AND RELATED COMPOUNDS

A DISSERTATION

Submitted to
The Graduate Council
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

by
Kumbla Vittal Nayak
March, 1959
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION AND HISTORY</td>
<td>1</td>
</tr>
<tr>
<td>A. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>B. History</td>
<td>5</td>
</tr>
<tr>
<td>1. Anticholinergics</td>
<td>5</td>
</tr>
<tr>
<td>2. Cholinesterases, Substrates, Anticholinesterase, and Inhibition of Anticholinesterases</td>
<td>10</td>
</tr>
<tr>
<td>3. Psychotherapeutic Drugs</td>
<td>14</td>
</tr>
<tr>
<td>C. Conclusion</td>
<td>29</td>
</tr>
<tr>
<td>II. DISCUSSION OF RESULTS</td>
<td>30</td>
</tr>
<tr>
<td>A. Esters of Substituted Benzilic Acids</td>
<td>31</td>
</tr>
<tr>
<td>1. Preparation of 2-Diethylaminoethyl Ester Hydrochlorides of Substituted Benzilic Acids</td>
<td>31</td>
</tr>
<tr>
<td>2. Attempted Preparation of 2,2'-Diethylbenzilic Acid</td>
<td>32</td>
</tr>
<tr>
<td>a. o-Ethyliodobenzene</td>
<td>32</td>
</tr>
<tr>
<td>b. o-Ethylbenzaldehyde</td>
<td>32</td>
</tr>
<tr>
<td>(1) Method I</td>
<td>35</td>
</tr>
<tr>
<td>(2) Method II</td>
<td>36</td>
</tr>
<tr>
<td>(3) Method III</td>
<td>36</td>
</tr>
<tr>
<td>c. Attempted Benzoin Condensation of o-Ethylbenzaldehyde</td>
<td>37</td>
</tr>
<tr>
<td>d. Attempted Preparation of 2,2'-Diethylbenzil</td>
<td>37</td>
</tr>
</tbody>
</table>
II. (Continued)

   e. Attempted Preparation of 2,2'-Diethylbenzilic Acid. 38

B. Esters of Substituted Phenylcyclohexylglycolic Acid 40

   1. Catalytic Half-hydrogenation 40
   2. Synthesis of the Ester Hydrochloride of 4-Methylphenylcyclohexylglycolic Acid. 42
   3. Synthesis of 2-Diethylaminoethyl 3,5-Dimethylphenylcyclohexylglycolate Hydrochloride. 49

C. The Ester Hydrochlorides of Substituted Dicycloc

   hexylglycolic Acid 55

   1. Catalytic Hydrogenation 55
   2. Attempted Catalytic Hydrogenation of Ester

      Hydrochlorides of Methoxy Substituted Benzilic

      Acids. 56

D. Attempted Preparation of Esters of 1-Mercapto-

diarylacetic Acid. 58

   1. 1-Mercaptodiarylacetic Acids 58
   2. Attempted Preparation of 2-Diethylaminoethyl

      1,1-Diphenyl-1-mercaptoacetate Hydrochloride. 61

E. Preparation of 1,1-Diphenyl-2-hydroxy-4-N,N-di-
methylbutylamine Hydrochloride 63
II. (Continued)

F. Attempted Preparation of 1,1-Diphenyl-1-N,N-dimethylamino-2-butene Hydrochloride

1. Method I .......................... 65
2. Method II .......................... 65

G. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-diethylaminoethoxy)acetate Dihydrochloride 68

H. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-thioacetoxyacetate Hydrochloride .......................... 69

I. Attempted Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetate 70

J. 2-Diethylaminoethyl 1,1-Diphenyl-1-(isopropthio)acetate Hydrochloride .......................... 71

K. Attempted Preparation of 2-N,N-Diethylaminoethyl Methyamide of Phenylcyclohexylglycolic Acid 72

1. Preparation of 2-N,N-Diethylaminoethyl Methyamide of Benzoylformic Acid 75

2. Attempted Synthesis of 2-N,N-Diethylaminoethyl Methyamide of Phenylcyclohexylglycolic Acid 76

L. Attempted Preparation of 2-Diethylaminoethyl Phenylcyclohexylthioglycolate 78

1. Method I .......................... 78
2. Method II .......................... 79
II. (Continued)

M. Preparation of 2-Diethylaminoethyl Phenyl-\(\Delta^2\)-cyclohexenylacetate Hydrochloride. .......... 80

N. Preparation of 2-Diethylaminoethyl Phenyl-\(\Delta^2\)-cyclohexenylglycolate Hydrochloride. .......... 82

O. Physiological Testing. .......................... 83
   1. Tests at the Army Chemical Center. ......... 83
   2. Tests at Parke, Davis and Company. .......... 90
   3. Tests at the National Service Center ......... 93
   4. Summary of the Test Results. ................. 93
   5. Structure and Physiological Activity of
      Compounds. ................................... 94

III. EXPERIMENTAL .................................... 96

A. Esters of Substituted Benzilic Acids .......... 96
   1. 2-Diethylaminoethyl Chloride ................. 96
   2. General Method for the Preparation of 2-Di-
      ethylaminoethyl Ester Hydrochlorides ......... 97
   3. Attempted Preparation of 2,2'-Diethylbenzilic
      Acid ........................................ 97
      a. \(o\)-Ethyliodobenzene ....................... 97
      b. \(o\)-Ethylbenzaldehyde ....................... 98
         (1) Method I ........................... 98
         (2) Method II .......................... 99
         (3) Method III ........................ 100
III. (Continued)

c. Attempted Benzoin Condensation of o-
Ethylbenzaldehyde. ....................... 101
d. Attempted Preparation of 2,2'-Diethyl-
benzil ........................................ 101
e. Attempted Preparation of 2,2'-Diethyl-
benzilic Acid. ............................... 102

B. Esters of Substituted Phenylcyclohexylgly-
colic Acids. ................................. 103

1. General Method for the Catalytic Half-
hydrogenation of the Amine Ester Hydro-
chloride of Alkyl Substituted Benzilic
Acids. ........................................ 103

2. Synthesis of the Ester Hydrochloride of
4-Methylphenylcyclohexylglycolic Acid. 104
  a. 4-Methylbenzoyl chloride ............... 104
  b. 4-Methylbenzoyl cyanide ............... 104
  c. Ethyl 4-Methylphenylglyoxylate ....... 104
  d. 4-Methylphenylcyclohexylglycolic
     Acids. .................................... 105
  e. 2-Diethylaminoethyl 4-Methylphenyl-
     cyclohexylglycolate Hydrochloride. ... 106

3. Synthesis of the Ester Hydrochloride of
3,5-Dimethylphenylcyclohexylglycolic
Acid .......................................... 107
### III. (Continued)

| a. Purification of 2,4-Dimethylaniline | 107 |
| b. 3,5-Dimethylbromobenzene | 107 |
| c. 3,5-Dimethylbenzoyl chloride | 109 |
| d. 3,5-Dimethylbenzoyl cyanide | 109 |
| e. Ethyl 3,5-Dimethylphenylglyoxylate | 110 |
| f. 3,5-Dimethylphenylcyclohexylglycolic Acid | 110 |
| g. 2-Diethylaminoethyl 3,5-Dimethylphenyl-cyclohexylglycolate Hydrochloride | 111 |

#### C. Esters of Substituted Dicyclohexylglycolic Acids

   - Attempted Preparation of Esters of Methoxy Substituted Dicyclohexylglycolic Acids.

#### D. Attempted Preparation of Esters of 1-Mercaptodiarlyl-acetic Acids

1. Diphenyloarboxymethyl N-Phenylthiocarbamate.
2. 1-Mercaptodiphenylacetic Acid.
3. Attempted Preparation of the Amino Ester of 1-Mercaptodiphenylacetic Acid.
   - Method I
III. (Continued)

b. Method II .............................................. 115

(1) 2-Diethylaminoethyl 1-Bromo diphenylacetate .............. 115

(2) Attempted Preparation of 2-Diethylaminoethyl 1-Mercaptodiphenylacetate 116

E. Preparation of 1,1-Diphenyl-2-hydroxy-N,N-di- methylbutylamine Hydrochloride .............. 117

1. 1,1-Diphenylacetone ........................................ 117
   a. 1-Bromo-1-phenylacetone ................................. 117
   b. 1,1-Diphenylacetone ...................................... 117

2. Preparation of 1,1-Diphenyl-4-N,N-dimethylamino-2-butanone Hydrochloride 119

3. 1,1-Diphenyl-2-hydroxy-4-N,N-dimethylbutylamine Hydrochloride .............. 119

F. Attempted Preparation of 1,1-Diphenyl-4-N,N-di- methylamino-2-butene Hydrochloride .............. 120

1. Method I .................................................... 120
   a. Attempted Preparation of 1,1-Diphenyl-2-acetoxy-4-N,N-dimethylbutylamine Hydrochloride .............. 120
   b. 1-Bromo-1,1-diphenyl-2-acetoxy-4-di- methylbutylamine Hydrochloride .............. 121
CHAPTER 2

2. Method II. .................................... 121
   a. 1-Bromo-1,1-diphenyl-2-propanone .... 121
   b. Hydrolysis of 1-Bromo-1,1-diphenyl-2-
      propanone. ............................ 122
   c. 1,1-Diphenyl-1-hydroxy-4-N,N-dimethyl-
      aminobutanone-2 Hydrochloride .... 122
   d. Acetylation of 1,1-Diphenyl-1-hydroxy-4-
      N,N-dimethylaminobutanone-2 Hydro-
      chloride ............................. 123

G. 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-diethyl-
    aminoethoxy)acetate Hydrochloride .... 124
   1. 1,1-Diphenyl-1-chloroacetic Acid ...... 124
   2. 1,1-Diphenyl-1-(2-diethylaminoethoxy)-
      acetic Acid ........................... 124
   3. 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-di-
      ethylaminoethoxy)acetate Dihydrochloride ... 125

H. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-
    1-thioacetoxyacetate Hydrochloride .... 125
   1. 1,1-Diphenyl-1-thioacetoxyacetic Acid ... 125
   2. 2-Diethylaminoethyl 1,1-Diphenyl-1-thio-
      acetoxyacetate Hydrochloride .......... 126

I. Attempted Preparation of 2-Diethylaminoethyl 1,1-
    Diphenyl-1-(1-mercaptoacetoxy)acetate ... 126
   1. 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetic
      Acid ................................. 126
CHAPTER III. (Continued)

2. Attempted Preparation of the Amino Ester of 1,1-Diphenyl-1-(1-mercaptoacetoxy)-acetic Acid. .......... 127

J. 2-Diethylaminoethyl 1,1-Diphenyl-1-(isopropylthio)acetate Hydrochloride. .......... 128
1. Diphenylcarboxymethyl Isopropyl Sulfide. 128
2. Esterification of Diphenylcarboxymethyl Isopropyl Sulfide. 128

K. Attempted Preparation of 2-N,N-Diethylaminoethyl Methylamide of Phenylcyclohexylglycolic Acid 129
1. Benzoyl Cyanide. .......... 129
2. Benzoylformic Acid .......... 129
3. Benzoylformyl Chloride .......... 130
4. 2-N,N-Diethylaminoethyl Methylamine. .......... 130
5. Preparation of 2-N,N-Diethylaminoethyl Methylamide of Benzoylformic Acid. .......... 131
6. Attempted Preparation of the 2-N,N-Diethylaminoethyl Methylamide of Phenylcyclohexylglycolic Acid. .......... 132

L. Attempted Preparation of 2-Diethylaminoethyl Phenylcyclohexylthioglycolate 134
1. Method I .......... 134
   a. Method A .......... 134
### III. (Continued)

<table>
<thead>
<tr>
<th>Method B</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Preparation of 2-N,N-Diethylaminoethyl Isothiouronium Chloride Hydrochloride</td>
<td>134</td>
</tr>
<tr>
<td>(2) 2-N,N-Diethylaminoethanethiol</td>
<td>135</td>
</tr>
</tbody>
</table>

c. Attempted Preparation of 2-N,N-Diethylaminoethanethiol Ester of Benzoylformic Acid | 135 |

<table>
<thead>
<tr>
<th>Method II</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. 1,1-Diphenyl-1-chloroacetyl Chloride</td>
<td>136</td>
</tr>
<tr>
<td>b. 2-N,N-Diethylaminoethyl Thiolbenzilate Hydrochloride</td>
<td>136</td>
</tr>
<tr>
<td>c. Attempted Catalytic Half-hydrogenation of 2-N,N-Diethylaminoethyl Thiolbenzilate Hydrochloride</td>
<td>137</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M. Preparation of 2-Diethylaminoethyl Phenyl-Δ²-cyclohexenylacetate Hydrochloride</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ethyl Phenyacetate</td>
<td>138</td>
</tr>
<tr>
<td>2. Ethyl Phenylmalonate</td>
<td>138</td>
</tr>
<tr>
<td>3. Preparation of 3-Bromocyclohexene</td>
<td>138</td>
</tr>
<tr>
<td>4. Diethyl Phenyl-Δ²-cyclohexenylmalonate</td>
<td>139</td>
</tr>
<tr>
<td>5. Phenyl-Δ²-cyclohexenylacetic Acid</td>
<td>139</td>
</tr>
<tr>
<td>6. Amino Ester Hydrochloride of Phenyl-Δ²-cyclohexenylacetic Acid</td>
<td>140</td>
</tr>
</tbody>
</table>
III. (Continued)

N: Preparation of 2-Diethylaminoethyl Phenyl-Δ²-
cyclohexenylglycolate Hydrochloride. ....... 142

1. Bromination of Phenyl-Δ²-cyclohexenylacetic
   Acid ............................................. 142
   a. Method I ..................................... 142
   b. Method II .................................... 143

2. Debramination of Phenyl-2,3-dibromocyclohexyl-
   glycolic Acid ................................... 143

3. Amino Ester Hydrochloride of Phenyl-Δ²-
cyclohexenylglycolic Acid ..................... 144

IV. SUMMARY ........................................... 145

BIBLIOGRAPHY ......................................... 149
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Amino Ester Hydrochlorides of Substituted Benzilic Acids</td>
<td>33</td>
</tr>
<tr>
<td>II. Comparison of Properties of Products of Oxidation of 2,2'-Diethylbenzoin With Those of o-Ethylbenzoic Acid</td>
<td>39</td>
</tr>
<tr>
<td>III. Amino Ester Hydrochlorides of Substituted Phenyl-cyclohexylglycolic Acids</td>
<td>43</td>
</tr>
<tr>
<td>IV. 2-Diethylaminoethyl 4-Methylphenylcyclohexylglycolate Hydrochloride</td>
<td>47</td>
</tr>
<tr>
<td>V. 2-Diethylaminoethyl 3,5-Dimethylphenylcyclohexylglycolate Hydrochloride</td>
<td>52</td>
</tr>
<tr>
<td>VI. Ultraviolet Absorption Data</td>
<td>54</td>
</tr>
<tr>
<td>VII. Amino Ester Hydrochlorides of Substituted Dicyclohexylglycolic Acids</td>
<td>57</td>
</tr>
<tr>
<td>VIII. 1-Mercaptodiarylacetic Acids</td>
<td>60</td>
</tr>
<tr>
<td>IX. Anticholinesterase Screening (Test No. 1)</td>
<td>85</td>
</tr>
<tr>
<td>X. Blood Pressure, Gut, and Respiration Effects (Tests 2, 3, and 4)</td>
<td>86</td>
</tr>
<tr>
<td>TABLE</td>
<td>PAGE</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>XII.</td>
<td>Eye Effects (Tests 5 and 6)</td>
</tr>
<tr>
<td>XII.</td>
<td>Tests for Cerebral Stimulation (Parke, Davis and Company)</td>
</tr>
<tr>
<td>XIII.</td>
<td>Tests for Atropine-Like Activity (Parke, Davis and Company)</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ultraviolet Absorption Spectra of 2-Diethylamino-ethyl 4-Methylphenylcyclohexylglycolate Hydrochloride in 95 Per Cent Ethanol</td>
<td>48</td>
</tr>
<tr>
<td>2. Ultraviolet Absorption Spectra of 2-Diethylamino-3,5-Dimethylphenylcyclohexylglycolate Hydrochloride in 95 Per Cent Ethanol</td>
<td>53</td>
</tr>
</tbody>
</table>
CHAPTER I

INTRODUCTION AND HISTORY

A. Introduction

Medicinal chemistry is one of the areas of scientific endeavor which has been achieving increasing importance during the last two decades. It tends to become more and more the study of the chemical reactions between therapeutic agents and living tissues. In 1940 practically nothing was known about the processes by which drugs produce their effect, how they react with protoplasm and how they are in turn modified, detoxified, metabolized, or eliminated by living organisms. Appreciable progress in this direction is now being made.

Recent advances in such a field are by no means easily defined. Countless drugs have been introduced for the specific treatment of ailments, but it is only after constant trials that the value of any compound can be accurately assessed. When the period of the last ten years is surveyed as a whole, it is apparent that certain definite advances have been made in medicinal chemistry. In addition to the use of new compounds, a better understanding has been gained of the mode of action of well-established medicaments.

An attempt will therefore be made to describe here briefly recent advances in the fields of anticholinergics, anticholinesterases, inhibitors of anticholinesterases and tranquilizers. However, the synthetic organic approach to new antispasmodic and tranquilizing drugs and their molecular
Spasm,¹ for the purpose of this discussion, may be defined as a violent, involuntary contraction due to muscular action, usually accompanied by pain and interference with function. There are two types of muscles, skeletal or striate, which is exclusively innervated by the central nervous system, and visceral or smooth, which is principally innervated by the autonomic nervous system. The therapeutic applications of antispasmodics are principally concerned with abolishing spasms of involuntary structures, that is, muscles which surround the alimentary canal, the blood vessels, and other tubes of the viscera.² A smooth muscle spasm may be caused by either direct or indirect stimulation of the muscle through the nerve endings. Antispasmodics, therefore, may be divided into two classes: (1) The direct acting or musculotropic and (2) those which interfere with nervous activation, the neurotropic. The neurotropic spasm is induced by an excess of acetylcholine and the antispasmodic reduces the concentration or effect of this compound.

Two well-known alkaloids have long been accepted as standards for the two main types of antispasmodic activity. Atropine (I-1) is effective against neurotropic type spasms and papaverine (I-2) is active toward musculotropic type spasms.
The clinical utility of both common natural antispasmodics, however, is hampered by certain limitations and undesirable side effects. Papaverine\textsuperscript{1} tends to relax all smooth muscles equally so that, when relaxation of the intestinal tract is produced, there results a prolonged and undesirable fall in arterial blood pressure. Further, all the organs activated by the autonomic nervous system are affected by atropine which causes cycloplegia, mydriasis, dryness of the mouth, occasional rise in arterial blood pressure, etc. For these reasons, as well as those of a purely economic nature, a search has been under way for a more satisfactory antispasmodic.

Much of the research in this field for the last two decades has been directed towards the preparation of a commercially competitive antispasmodic which possesses both musculotropic and neurotropic activity with selectivity and as few side effects as possible. Despite the preparation and testing of thousands of compounds for antispasmodic activity, the goal has not been achieved to date.

The evaluation of new antispasmodics is a time-consuming process. The tests must be performed both \textit{in vitro} and \textit{in vivo}. The first of these employs an isolated muscle strip in which a spasm is induced. The new compound is then compared to atropine or some other reference standard with respect to its ability to block or reduce the spasm. The \textit{in vivo} test employs live animals. The results obtained from the latter test seem to show good correlation with clinical effectiveness. These methods are discussed in greater detail in Research Today.\textsuperscript{3}
An essentially empirical approach consisting of preparing modifications and variations of the structures of naturally occurring drugs has been applied to the synthesis of antispasmodics. Due to the lack of complete understanding of physiological modes of action of drugs, no efficient theoretical concept is available to provide the basis for the synthesis of pharmaceuticals. It is imperative therefore to adopt an empirical method until suitable theories are available.

Most of the work in this field has dealt with the modifications of atropine, the tropine ester of tropic acid, rather than with the papaverine type structures. Since tropine itself has no spasmolytic activity, its bicyclic structure was assumed to be incidental and it was considered as an amino alcohol. Further, the tropic acid was viewed as a branched chain phenylacetic acid. On this basis, extensive studies have been made of derivatives of carboxylic acids in the form of esters, amides, and related types. Amines, amino alcohols, amino ethers, and other compounds which are not acid derivatives have also been investigated.

The mechanism of spasm formation involves the compound, acetylcholine:

$$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{OH}$$

Acetylcholine attached to the receptor sites on the surface of an effector organ acts as the chemical mediation of nerve impulses. Nerves that release acetylcholine at their terminals are called cholinergics. The drugs that block the effects of acetylcholine are called anticholinergics.
B. History

1. Anticholinergics

It is of interest that the majority of anticholinergics including atropine, (I-1), bear a certain degree of structural similarity. They consist of a large blocking group linked by a short connective group to strongly basic amino function as shown in I-4.

\[
\begin{align*}
\text{Large Blocking Group} & \quad \text{Connecting Group} & \quad \text{Amino Function} \\
R & \quad X & \quad Y - C - C - N \quad \ldots
\end{align*}
\]

In searching for an efficient anticholinergic, attempts have been made to vary each of the three parts of the molecule systematically or at random. The \( R \) and \( R' \) substituents essentially form an umbrella-like structure. When \( R \) is phenyl, \( R' \) may be hydroxymethyl, cyclohexyl and phenyl; however, the activity of the compound is reduced when \( R' \) is H. Several compounds have been made where \( R \) is a cycloalkyl, (cyclopentyl or cyclohexyl), group. Different modifications of the molecule have been devised by the variation of \( X \) group from among \( H, OH, CN, COOR, CONH_2, CONHR, CONR_2, \) halogen or alkyl. The connecting group, \( Y \), usually an ester or amide group, is connected to the amino function through a \(-\text{CH}_2-\text{CH}_2-\) linkage. Most of the early studies were concerned with tertiary amines. But they have the limitation that eight or nine carbon atoms (including those of the connecting group) must be present in the system for any activity.
As indicated before, the chemical mediation of the nerve impulse by acetylcholine involves the attachment of this molecule to receptor sites on the surface of the nerve. By virtue of its structural similarity, a blocking agent may presumably be attached to these sites preventing acetylcholine from reaching the nerve cells. The main point of attachment of acetylcholine and the blocking agent is probably at the amino function.

It is perhaps pertinent to discuss briefly some of the synthetic anticholinergics. Several esters of 3-diethylamino-2,2-dimethylpropanol exhibiting both neurotropic and musculotropic activity, were prepared by Fromherz. The benzilic acid ester, though potent, was found to be toxic. Halpern described a series of esters of alpha alkyl phenylacetic acids in which the alkyl group varied from ethyl to heptyl. 2-Diethylaminoethyl diphenylacetate hydrochloride (Transentin) was found to possess high activity. Blicke and Kaplan reported tests of 2-diethylaminoethyl benzilate in which it was found to be one-half as active as atropine. Buchel, Levy, and Pernot reported that the esters of type

\[
\text{I-5}
\]

had important spasmyloytic as well as other physiological properties. Several compounds of this type in which the substituent R was varied were also studied. Blicke prepared the 2-N-piperidinoethyl ester of benzilic acid and claimed that it was useful as an antispasmodic.
Buchel, Levy and Pernot\textsuperscript{9} found that acetylation of the hydroxyl group in benzilic acid esters sharply reduced the activity of the compounds. A series of compounds has been reported\textsuperscript{11} in which the alpha carbon is substituted with chlorine, bromine, ethoxyl and basic groups. The hydrogenated products of diphenylacetic and benzilic acids were generally found to be more active than their precursors.

The effect of nuclear substitution on activity has not been evaluated comprehensively. Hoffmann\textsuperscript{12} found variable effects in a series of esters of para-substituted phenylcyclohexylacetic acids. In general, esters of the para nitro acid were less potent, those of the para amino acid, more potent than the unsubstituted compounds. Introduction of a para methoxyl group in benzilic acid esters resulted in reduction of the activity.\textsuperscript{13,14} A series of alkoxyl substituted benzilates studied by Bocksthaler and Wright\textsuperscript{15} proved in general to be less active than the unsubstituted ones.

Wagner-Jouregg, Arnold, and Born\textsuperscript{16} reported several esters which possessed arylalkyl alpha substituents and in most cases a sharp drop in activity occurred with an increase in the number of carbon atoms in the alkyl portion. Protiva and Exner\textsuperscript{17} replaced quaternary nitrogen common to almost all antispasmodics with sulfur and phosphorus. It was claimed that these compounds

\[
R_1R_2CXCOOCH_2CH_2S(CH_3)_2I \quad \text{(I-6)}
\]

\[
R_1R_2CXCOOCH_2CH_2P(C_2H_5)_2 \quad \text{(I-7)}
\]

\((R_1\text{ and } R_2 \text{ were alkyl or aryl groups; } X \text{ was } H \text{ or OH})\)

were more active than the analogous nitrogen compounds.
2-Diethylaminoethyl \( \text{D-aminothiobenzoate} \) was found to be six times as active as the analogous oxygen ester and the toxicity remained relatively constant. In a series of compounds of the type
\[
\text{C}_6\text{H}_5\text{CRHCOSCH}_2\text{CH}_2\text{N}\left(\text{C}_2\text{H}_5\right)_2
\]

Dupre, Levy, and Tchoubar found that, except where \( R \) is a phenyl group, no increase in activity was observed. The replacement of one or both of the benzene rings in diphenylacetic acid with heterocyclic groups proved to be rewarding. The group of esters of phenyl-2-thienylglycolic acid prepared by Blicke and Tsao were quite active. The activity of compounds of this type in which the phenyl ring was converted to a cyclohexyl ring was found to increase even further.

Duschinsky prepared a series of esters, thio esters and amides of \( \alpha\)-aminodiphenylacetic acid. Here the amino function is in the acid portion of the molecule. These compounds were claimed to be useful as antispasmodics. Moffett and Aspergren prepared a number of \( \alpha,\alpha\)-diphenyl-\( \gamma \)-amino amides and tested the anticholinergic activity. In several cases the same tertiary groups that previously gave highly active anticholinergics in the ester series also gave active compounds when introduced into the \( \gamma \)-position of these amides. The effect of substitution or replacement of one of the phenyl groups and of the branching alkyl chain generally reduced the activity. Moffett and coworkers further observed that mono- and disubstitution on the amide nitrogen of \( \alpha,\alpha\)-diphenyl-\( \gamma \)-tertiary amino amides reduced the anticholinergic activity. Compounds of the type
were also claimed to be useful spasmolytics.

It was shown by Brender\textsuperscript{26} that 2-diethylaminoethyl α-phenyl-α-N-piperidyl acetate possessed only a small activity compared to atropine, but it had an activity twice that of papaverine.

Denton and coworkers\textsuperscript{27} described the preparation and testing of a group of amino ketones of the type

\[
\text{RCOCHR'}\text{CH}_2\text{NR}_2\text{R}_3
\]

where \( R \) is a phenyl, naphthyl, or heterocyclic group, \( R' \) is hydrogen or phenyl and \( R^2R^3 \) are alkyl or together with nitrogen form a ring. Some of these were said to be very active spasmolytics. This work has been further extended.\textsuperscript{28}

Pfanz and Jassmann\textsuperscript{29} in their search for an ideal synthetic spas­molytic substance reported the preparation of a series of tertiary amino alcohols of the type

\[
\text{HO·C(Ph)(R)CH}_2\text{CH}_2\text{NRR'}
\]

where \( R \) was alkyl, cycloalkyl, phenyl, and benzyl, and \( R' \) was a short alkyl chain or ring. However, the spasmolytic activity of these compounds was not reported.

Numerous amino alcohols and alkenes have been prepared and tested for their spasmolytic activities. For a detailed survey of these types, the reader is referred to the dissertation of Magee.\textsuperscript{30}
2. **Cholinesterases, Substrates, Anticholinesterase, and Inhibition of Anticholinesterases**

Cholinesterase is an enzyme, which can hydrolyze acetylcholine, widely distributed in the tissues. There are various classifications of cholinesterase enzymes. A substrate is any substance acted upon by an enzyme. The substrate, acetylcholine, is the one that is of interest here. An anticholinesterase drug essentially inhibits the action of the enzyme, generally cholinesterase, which hydrolyzes acetylcholine by means of attraction or reaction.

According to one school of thought, the mechanism of action of anticholinesterase drugs is based on the fact that certain parts of cholinesterase structure react specifically with the drug. A complex is formed as the drug reaches the receptor and the strength of this combination depends on the chemical character of the drug and receptor molecules. According to Bergel, the combinations may be an attraction of polar groups or a bonding of low energy, but if the drug possesses ionizable groups capable of forming cations, it is assumed that an electrovalent bond is formed with an anionic site as the receptor. Wilson and Bergman have illustrated this diagrammatically as in (I-12).

![Diagram of Cholinesterase Interaction](image-url)
When an ester is used, the possibility of hydrogen bonding at the cationic site is suggested. Some investigators believe that some types of drugs actually undergo a chemical reaction with cholinesterase with the formation of a covalent bond. The influence of substituents on the cationic and the anionic heads of the molecules on its anticholinesterase activity has been studied. It is concluded that there exists an optimum size for this cationic head.

An excess of an anticholinesterase has a definite destructive effect on the nervous system due to the fact that an extreme excess of acetylcholine is formed. Intensive investigations are being conducted in search of effective inhibitors of anticholinesterases.

Physostigmine, (I-13), the most important alkaloid derived from the calabar bean, is one of the most efficient agents for the inhibition of cholinesterase activity. In very small amounts (10^{-6} M) it protects acetylcholine from enzymic hydrolysis. It is believed that the anticholinesterase activity of physostigmine is due to the urethane group. Studies have been conducted with systematic structural variations of aromatic carbamate (ArOOCNR_{2}). Certain aryloxy amidine derivatives have shown anticholinesterase activity. Thus, N-N-dimethylthymoloxycetamidine (I-14) exhibited high activity.
A series\textsuperscript{36} of substituted phenyl methylcarbamates showed high inhibition properties toward cholinesterase. Zeller\textsuperscript{37} reported the anticholinesterase activities in p-aminobenzoic acid and the corresponding sulfonamides. Phenanthrene amino alcohols were found\textsuperscript{38} to be effective inhibitors of the cholinesterase of human blood plasma. Thompson\textsuperscript{39} investigated the action of chemical vesicants, chloroalkyl amines, mustard gas, various arsines and Lewisite on the inhibition of the enzyme. Jacob and Olomucki\textsuperscript{40} reported interesting results on the inhibition of cholinesterase by RN(CH\textsubscript{3})\textsubscript{3}I types of compounds. Many of the 3,5-di-alkyl-pyridinium halides\textsuperscript{41} have been found to be inhibitors of cholinesterase activity.

War gases prepared during World War II were found to be very potent anticholinesterases. These compounds contain phosphorus in the form of phosphates and they exert an irreversible inhibition of cholinesterase which is fatal even in extremely small doses. The first two nerve gases prepared\textsuperscript{42} by Germans were isopropyl methyl phosphonofluoridate (sarin) and ethylphosphoro dimethyl amidocyanidate (tabun). It was found that diisopropylfluorophosphate (DFP), \([\text{CH}_3\text{O}]_2\text{CHO}\)\textsubscript{2} PO\textsubscript{F}, was the most powerful inhibitor of cholinesterase yet discovered. DFP is too toxic to be useful as a
drug. Brauer studied a series of phosphate esters for their anticholinesterase activity. He observed that all active compounds contained the grouping R-O-P where R may be an alkyl or aryl radical. Hexaethyltetraphosphate and tetraethylpyrophosphate were shown to be the most active compounds of those investigated by Brauer. Besides the alteration of alkyl radicals, the effects of other structural variations on the anticholinesterase activity of phosphate have been investigated. The thioester, \((C_2H_5S)_2POF\), as well as ethyl difluorophosphate, \((C_2H_5O)POF_2\), were, however, found to be active.

Razumov, Markovich and Mukhacheva reported several alkylated amide esters and mixed esters of alkyl phosphoric acids of the type

\[ \text{EtP(O)(OCHMe}_2\text{)N(Et)}_2 \].

An especially powerful anticholinesterase was named Armin.

\[ \text{EtP(O)(OEt)OC}_6\text{H}_4\text{NO}_2\text{-p} \]

It showed mouse toxicity at 0.4-0.5 mg./kg. and anticholinesterase inhibition at \(1 \times 10^{-7}\) to \(2 \times 10^{-9}\) M. concentration. Razumov and coworkers also found several alkyl phosphorous acids and dialkyl phosphinic acids to be active inhibitors. They reported the compound

\[ \text{Pr}_2\text{PO}_2\text{C}_6\text{H}_4\text{NO}_2\text{-p} \]

to be as strong an inhibitor of cholinesterase as Armin, but twenty times less toxic to animals.
The information available on the inhibitors of anticholinesterase is quite limited. Kunkel, Wills and Monier found that N-benzyl atropinium chloride and atropine showed reasonable activity over an extended period of time.

In 1955 Wilson of Columbia University discovered hydroxylamine to be a very active inhibitor of anticholinesterase. However, the amount required to obtain 100% inhibition was too large. Wilson subsequently reported that pyridine aldoxime methiodide (I-18) was 100 per cent effective against DFP in animals. Several hydroxamine acids and oximes have been tested. The hydroxamic acids have been found to be poor inhibitors of anticholinesterase, but several oximes were very active. A detailed discussion of this subject has been presented by Glenn.

3. Psychotherapeutic Drugs

The various new drugs being studied so vigorously in mental disorders deserve an effort at classification in order to avoid confusion. They may be classified most readily, at present, on the basis of overall action on humans, as (1) hallucinogens, (2) tranquilizers, and (3) central stimulants. Chemical classification may come at a later date with the fuller understanding of structure-action relations. It is interesting, however, to note that most of the hallucinogenic drugs are indoles.
The hallucinogens break the overall nervous integration ordinarily present in a healthy person. A transitory psychotic-like state may be produced by their action, and this seems to be usually of a schizophrenic type. In general, they are depressant agents and cause muscle relaxation, lowered blood pressure, slow respiration, diminished heart action, and decreased speed of reaction time. In larger doses, they may cause delirium.

Among the typical hallucinogens are mescaline, adrenolutin, bufotenine, lysergic acid diethylamide and yohimbine. Similar effects are also caused by morphine. These drugs are related to the indoles. On the other hand, the same kind of effects can be caused by appropriate amounts of ethanol which is not chemically related to indole in any simple way. There may be different mechanisms of action for the different chemical types.

The tranquilizers are drugs which reduce anxiety, nervous and muscular tension, and acuity of awareness. They are mildly depressant, and induce muscular relaxation. They are not as intense nor as powerful in their action as the usual central depressants, like the bromides, chloralhydrate, paraldehyde and depressant barbitals. They are not anticonvulsants; neither are they very close in action to alcohol. The new tranquilizers are reserpine, chlorpromazine, meprobamate, azacyclonol and suavitil. There is little chemical similarity among these agents. Both reserpine and chlorpromazine, however, have indole-like radicals in their constitution.

The central stimulants, on the other hand, are drugs which tend to cause increased alertness, increased respiratory and pulse rates, increased blood pressure and muscle tone, and increased speed of reaction,
with exaggerated reflexes. They promote wakefulness and reduce the sense of fatigue. The common central stimulants again are a diverse chemical group. Some of them may cause convulsions in doses only slightly above those which induce increased alertness. These drugs include strychnine, metrazol, the xanthines such as caffeine, many alkyl amines, many tropines, cocaines and other local anesthetics.

A brief summary of the types of investigations which have been pursued on tranquilizing drugs will be discussed in this section.

During the past four years a number of tranquilizing agents have been used successfully in the treatment of neuroses and psychoses. The most important of these are: chlorpromazine, a phenothiazine derivative prepared as one of a series of antihistaminic and adrenolytic agents; reserpine, an alkaloid originally used as a hypotensive agent; benactyzine, a benzilic acid ester with potent anticholinergic action; and meprobamate, a simple propanediol dicarabamate derivative that is devoid of autonomic effects. It is of interest that compounds so dissimilar in chemical structure and pharmacological action should all be effective as tranquilizers.

The discovery that serotonin (I-19) occurs in the brain has stimulated considerable thought concerning its role in the central nervous
system. Speculation in this direction received impetus when Gaddeum found lysergic acid diethylamide (abbreviated LSD, I-20) to be a potent antagonist of serotonin on smooth muscle in vitro. This observation led to the hypothesis that an hallucinogenic agent produces its aberrant mental effects by interfering with a normal function of serotonin in the brain.

Serotonin, when administered parenterally to animals, is metabolized and excreted as 5-hydroxyindolacetic acid. It has been shown that the tissue catalyst responsible for this metabolism is the enzyme known as monoamine oxidase, and that this enzyme is present in the brain. It may be that monoamine oxidase regulates the action of serotonin in the same way that cholinesterase regulates the action of acetylcholine.

Serotonin in brain tissue is normally present largely in a bound form and is thus protected from the action of enzyme monoamine oxidase, the concentration of which is highest in the brainstem and lowest in the cortex; in the cerebellum there is virtually none of this enzyme. It is in the regions of the brain where serotonin levels are highest that reserpine is said to exert its central action.

The idea that serotonin plays a role in the maintenance of normal mental functions arose from studies of antimetabolites of this hormone. According to Woolley and Shaw, one can picture it (serotonin) as causing its effects by combination with specific receptor sites, designed especially to react with it and not with other hormones. The serotonin fits the receptor much as a key fits a lock, and many features of the hormonal structure are required so that the serotonin key will function in the
receptor lock. If one now makes a substance that resembles serotonin several ways, but differs in a few, one may have formed an antimetabolite of this hormone. The analog fits the receptors well enough to combine with them, much as an ill-fitting key can be thrust into a lock, but just as such a related key may not turn the lock, so also one pictures the substance resembling serotonin as being unable to fulfill the physiological role of serotonin. In short, the antimetabolites of serotonin are chemical compounds that resemble this hormone in structure. They bring about a deficiency of this hormone, specifically, because they combine with the serotonin receptors by virtue of their structural resemblance to it.

The first pharmacological property of serotonin to be discovered was that it caused smooth muscles to contract. Thus it can be used to cause the muscles of the walls of the blood vessels to contract, and possibly for this reason serotonin raises blood pressure in an animal. The uterus and intestines likewise are made to contract. These properties of serotonin were therefore the first used in an effort to find an antimetabolite.

A method has also been devised to determine whether a compound is an antagonist of serotonin. This method would give a quantitative measure of its potency.

Several structural analogs of serotonin were synthesized and were shown to act as antimetabolites of the hormone. The synthetic amino and nitro analogs (I-21, I-22) were found to be antimetabolites. Another synthetic
compound that exhibited very great antagonistic activity towards serotonin was called medamin (I-23). There are several classes of naturally occurring alkaloids which are structural analogs of serotonin. The harmala alkaloids, of which harmine, I-24, is a representative, are one such class of naturally occurring antimetabolites. Yohimbine (I-25) which can be pictured as a harmala alkaloid to which two more rings have been added is another antimetabolite of serotonin.
Woolley and Shaw\textsuperscript{59} believe that reserpine, a derivative of yohimbine (I-25), acts as an antimetabolite. The ergot alkaloids are a third class of alkaloids that have been found to be antimetabolites of serotonin. The most active of these is lysergic acid diethylamide (LSD, I-20).

Other compounds that can be shown to act as antagonists to, or to potentiate, serotonin also have been shown to influence the psychiatric state of human beings. Some of these compounds, for example, chlorpromazine (I-26) can be demonstrated to interfere with serotonin action \textit{in vitro} even though they bear no structural relationship to it and hence cannot be considered an antimetabolite of it. These compounds must exert their interference some other way.

It is of interest to know how reserpine (I-28), which acts through serotonin and chlorpromazine, (I-26), which does not, can produce similar central effects, including sedation and potentiation of hypnotics. A number of observations make it evident that reserpine, (I-28), and chlorpromazine, (I-26), induce similar effects in the brain, but do so by different mechanisms. On the one hand, the action of reserpine has been shown to be irreversible in that its effects last far beyond the time the drug has disappeared from the body. A second difference may be seen in the nature of the potentiating action of the two agents on certain
hypnotics. Both compounds have marked activity, but only that of reserpine is blocked by LSD, (I-20). Still a third difference between the action of the two substances has been shown. If a rabbit is treated with iproniazid followed by reserpine, the animal does not become sedated. On the other hand, the administration of chlorpromazine under these conditions does produce sedation.

The difference in the mode of action of reserpine and chlorpromazine may be explained by assuming that they act on physiologically antagonistic systems in the brain stems that are involved in wakefulness, regulation of temperature, control of blood pressure and other autonomic functions. Drug-induced paralysis of one system would release the opposite system and allow it to predominate as in the schematic diagram, I-27, depicting mutually antagonistic brain centers in the central autonomic nervous system. In support of this concept, it has been demonstrated that there are both parasympathetic and sympathetic areas in the brain stem. In the hypothalamus, one of the principal foci of integration of the entire autonomic system, one finds primarily parasympathetic representation in the fore and sympathetic in the posterior part. In view of the effects of
reserpine, it may be supposed that serotonin is the chemical transmitter of nerve impulses to the centers of the parasympathetic division. The fibers that innervate these centers should be termed "serotonergic nerves." By blocking serotonergic fibers, LSD, (I-20), would unmask the action of the opposing sympathetic system and produce its typical sympathetic-like responses. Reserpine could be considered to invoke its parasympathetic-like effects by presenting a low, but persistent concentration of free serotonin to activate the parasympathetic centers.

It could be postulated that chlorpromazine blocks nervous impulses activating central sympathetic centers and thus augments the activity of the parasympathetic system. This would account for the central effects of chlorpromazine and reserpine, even though they act by different mechanisms.

Chlorpromazine could be assumed to inhibit the sympathetic system by blockade of the chemical mediator that activates the sympathetic centers. Though direct evidence is lacking, norepinephrine is supposed to be the chemical mediator.

Ever since the structure of the reserpine molecule, (I-28), was proposed and proved conclusively by the synthesis of Woodward and co-
workers, it has been of interest to know which portion of the molecule is responsible for its physiological activity. Schlitter indicated that removal of the 3,4,5-trimethoxybenzoyl moiety and replacement with any other acid grouping lowered or destroyed activity.

Although much work has been done to show the relationship between serotonin and reserpine, Miller and Weinberg believe that the indole grouping is not necessarily involved in the activity of reserpine. Therefore they synthesized compounds of the type

\[
\begin{align*}
&\text{I-29} \\
&\text{I-30}
\end{align*}
\]

and subsequently a series of its modifications. Proceeding with a belief that tranquilizing activity resides in a relatively small portion of the reserpine molecule, Miller and Weinberg synthesized trimethoxybenzoate esters containing nitrogen atoms separated from another electronegative atom by two or three carbons. So far only the tertiary aminopropyl ester of trimethoxybenzoic acid has any significant activity (one-third that of reserpine). The corresponding primary aminopropyl ester is inactive as is the tertiary aminoethyl ester. Further, it is of interest to note that I-30 is composed of the parts of the reserpine molecule marked in I-28. Thus Miller and Weinberg believe that the oxygen and nitrogen
must be separated by three carbon atoms and the nitrogen atom must be tertiary. Thus the authors attempted to provide a synthetic approach to tailor-made compounds with reserpine-like activity.

Mills and coworkers\textsuperscript{68} found that many adrenergic blocking agents, when administered in near toxic doses, interfere with epinephrine action in the brain, and thereby bring on behavioral changes in laboratory animals. This group thinks that this is the way reserpine and chlorpromazine also work. From this theory, they reasoned that adrenergic blocking agents can be made to act like psychosedatives by chemically modifying them to strengthen this chemical effect. Rather than to look for an improved form of chlorpromazine, they synthesized adrenergic blocking agent derivatives and tested them for tranquilizing activity. These workers investigated several compounds including aminomethyl benzodiazepine. Many were ten to twenty times more powerful than chlorpromazine as shown by animal tests.

Mills and coworkers found that activity did not improve when the piperidino group of piperoxan, (I-31), is replaced by other tertiary amino groups. Potent and specific central depressants are obtained only when the amino function is secondary. Such depressants exist when \( R' \) (in I-32) is a

![I-31](image)

\[ I-31 \]

![I-32](image)

\[ I-32 \]

\( R = \text{CH}_3, \text{C}_2\text{H}_5 \)

\( R' = \text{C}_2\text{H}_5, \text{C}_5\text{H}_{11} \)
lower aliphatic function such as from C₂H₅ to C₅H₁₁. With substituents in the benzene ring, an 8-alkoxy function (R = CH₃, C₂H₅ in I-32) brings on the top effect.

Another type of tranquilizer developed by these workers was 1-ethyl-3-phenylpyrrolidine.

\[
\begin{align*}
\text{I-33} \\
\text{The compounds of the type I-34 and I-35 were found to be as active as chlorpromazine.}
\end{align*}
\]

\[
\begin{align*}
\text{I-34} \\
\text{I-35} \\
\text{One group of tranquilizers was made from 1-methyl-4-phenylpiperazine. When an oxygenated phenethyl side chain replaces the methyl group,}
\end{align*}
\]

\[
\begin{align*}
\text{I-36} \\
a series of central depressants of type I-37 resulted. The series included}
\end{align*}
\]
drugs with one to ten times the potency of chlorpromazine.

A "full range" product, that is one which can be used to treat mild, moderate, and severe mental disorders, has been reported. It is trilafon (perphenazine), a compound related to chlorpromazine,

and is made by condensing 10(3-chloropropyl)-2-chlorophenathiazine with 1,2-dihydroxyethyl piperazine.

Findings show it, to be five times more potent than chlorpromazine and it does not produce undesirable side effects such as dryness of the mouth, blurred vision, and hypotension. It can also be used to treat anxiety associated with organic disorders, such as tuberculosis, tension headache and asthma.

A very brief discussion of clinical uses of some important tranquilizers will be given here. For detailed discussion of this topic, the reader is referred to a review published in four parts by Bennett. Reserpine is the most extensively used Rauwolfia alkaloid in neuropsychiatry. In hospitalized psychotic patients, it is not as effective
as chlorpromazine, but is considered a safer drug, and so is preferred by some in this setting. It has been found to be slow-acting in producing change in anxiety, but it will give symptomatic improvement in anxiety, tension, psychotic excitements and acute alcoholism. However, reserpine produces several undesirable side effects. The increase in gastrointestinal activity as shown by diarrhea, aggravation or production of gastrointestinal hemorrhage has caused some concern. So serious are reactions such as gastrointestinal hemorrhage and depression that the U. S. Food and Drug Administration has recommended that patients outside of mental hospitals be limited to 0.25 mg. of reserpine daily.

Chlorpromazine (Thorazine), a phenothiazine derivative, is still the drug of choice for the hospitalized psychotic patients. It beneficially affects some 75 to 97 per cent of the acute schizophrenic and from 64 to 85 per cent of the chronic schizophrenic group. Chlorpromazine is losing favor in clinics and private practice because of the serious side effects.

Chlorpromazine has given indications of what side effects might result from the newer phenothiazine drugs, all of which must be used with caution, in spite of claims of low toxicity. Such complications from the phenothiazine derivatives now in use include drowsiness, nausea and vomiting, hypotonia with weakness and fatigue, seizures, tremors, blurred vision, dermatitis, jaundice, etc. Such side effects as dryness of the mouth, blurring of the vision, and constipation have been attributed to its atropine-like activity.
Azacyclonal (Frenquel) is comparable to chlorpromazine and reserpine in its effectiveness in diminishing mental confusion. When used in combination with these drugs, it gives responses not achieved by a single drug. Side effects including turbulence and metallic taste have been few.

The use of promazine (Sparine), a phenothiazine derivative, in acute psychotic reactions and alcoholic hallucinosis has been stressed. Convulsions have been reported with this drug as well as two cases of agranulocytosis, one being fatal. Meanwhile research with this drug is being continued in a number of hospitals and more information will soon be available.

Meprobamate (Miltown, Equanil) has three important properties: (1) It is a muscle-relaxant of voluntary muscles, (2) it is an anti-convulsant, and (3) it is effective in behavior changes. While not originally intended for use in psychotic patients, surprising results have been found in this group. The successful results in the treatment of anxiety and tension states in psychoneurotic patients seen in general practice are amazing. It has relatively few side effects.

Benactyzine (Suavitil) is a tranquilizer whose clinical use with psychotic patients has been a subject of controversy. In normal subjects 1-4 mg. produces a feeling of detachment or general apathy with every action requiring too much effort and a faraway feeling of relaxation. There is a sense of divorce between reality and the patient, a barrier between him and his emotional problems. With 4-8 mg., the sensation of detachment becomes more marked, sensibility is blunted, and feelings are retarded. There is a loss of alertness with diminished power of concen-
tration and a resulting hesitancy in speech. With larger doses there is greater retardation and some slowing and slurring of speech with impaired performance of simple mental tests.

Psychotic patients are not benefitted from this drug, according to Davies and Munkden. The potential danger in this low toxicity drug is a psychological one.

From the above brief discussion of the clinical uses of the principal presently available tranquilizers, it is evident that each one of them exhibits certain undesirable side effects. A large amount of research is presently being done in search of an ideal tranquilizer without any serious side effects. With a greater and clearer understanding of the mechanism of action of tranquilizing drugs, this goal should soon be reached. An extremely large amount of work, however, still remains to be done.

C. Conclusion

The purpose of this investigation was to synthesize compounds which offer promise as anticholinergics, inhibitors of anticholinesterases, tranquilizers, etc. The synthetic work was done in this laboratory while the pharmacological tests were conducted elsewhere (see Chapter II, Section 0).
CHAPTER II

DISCUSSION OF RESULTS

The primary aim of this research was to prepare derivatives of benzilic acid or closely related analogues which might exhibit physiological activity. A number of compounds which were derived from benzilic acid have been reported to possess such activity. The compounds prepared in the present work may be described by the general formula

\[ R_1 \, \text{X} \, \text{R}_2 \, \text{Z-CH}_2\text{CH}_2\text{N} \]  

(II-1)

Further, the present study was also directed towards an attempt to evaluate the effect of structural variations on physiological activity. With this point in mind, a series of amino ester hydrochlorides of alkyl and alkoxy substituted benzilic acids, \((R_1 \text{ and } R_2 = \text{aryl in II-1})\), was prepared. These amino ester hydrochlorides were catalytically half-hydrogenated and fully hydrogenated to study the variation, if any, in physiological activity. An effort was also made to synthesize compounds, varying the nature of the X, \((\text{H, OH, SH, -OR and SR}\) where R and R' are respectively amino alkyl and alkyl groups in II-1) and Z \((-\text{COO-}, -\text{COS-}, -\text{CH(OH)- and -CO-N- in II-1})\) components of amino esters of benzilic acid. It was hoped that such a study would provide information to permit
a correlation, if there is any, between the structural factors and physiological activity.

A discussion of preparative methods employed in the present research will be followed by the results of physiological testing which are, however, incomplete.

A. Esters of Substituted Benzilic Acids

1. Preparation of 2-Diethylaminoethyl Ester Hydrochlorides of Substituted Benzilic Acids

2-Diethylaminoethyl chloride, (II-4), was prepared by the method of Slotta and Behnisch,76 in which thionyl chloride was employed to convert 2-diethylaminoethanol (II-2) to II-3 in a 90 per cent yield. The free 2-diethylaminoethyl chloride (II-4), b.p. 147-148°, was obtained in 65 per cent yield by treatment of the amino salt with excess base by the method of Gilman and Shirley.77 II-4 was mixed with its weight of dry xylene to prevent dimerization and stored in a cold room.

The method of Blicke and Grier78 was employed for the preparation of substituted benzilic acid ester hydrochlorides. The substituted benzilic acids were obtained from previous research work.79 Equimolar quantities of the substituted benzilic acid and 2-diethylaminoethyl chloride (II-4) in dry isopropyl alcohol produced the desired product.
Table I gives the compounds thus prepared, and gives the pertinent data.

The same general procedure was used to prepare 2-diethylaminoethyl esters of the other acids investigated in this research.

2. Attempted Preparation of 2,2'-Diethylbenzilic Acid

Since 2-diethylaminoethyl 2,2'-dimethylbenzilate hydrochloride exhibited considerable physiological activity, it appeared interesting to test the activity of the corresponding ethyl substituted compound. Hence, an attempt was made to synthesize the amino ester hydrochloride of 2,2'-diethylbenzilic acid as follows.

a. o-Ethylidobenzene. Diazotization of o-ethylaniline, (II-5),

\[
\begin{align*}
\text{II-5} & \xrightarrow{\text{1}} \text{HCl} \xrightarrow{\text{2}} \text{NaNO}_2 \rightarrow \text{II-6} \\
\text{II-6} & \xrightarrow{\text{KI}} \text{II-7}
\end{align*}
\]

was performed according to the method described by Vogel\(^8\) as well as Lucas and Kennedy.\(^8\) The diazonium salt (II-6) was not isolated. On addition of a solution of potassium iodide, the o-ethylidobenzene (II-7) formed was isolated by steam distillation. The method gave a yield of 58.1 per cent, b.p. 60\(^\circ\)/1.5 mm.

b. o-Ethylbenzaldehyde. o-Ethylbenzaldehyde (II-9) has been previously prepared in 67 per cent yield by Mayer and English\(^8\) who oxidized o-ethylbenzyl alcohol (II-8) with potassium dichromate in sulfuric acid.
**TABLE I**

AMINO ESTER HYDROCHLORIDES OF SUBSTITUTED BENZILIC ACIDS

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>Melting Point °C</th>
<th>Analyses</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Calculated</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>2-CH₃C₆H₄</td>
<td>71.9</td>
<td>180-181</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅</td>
<td>3-CH₃C₆H₄</td>
<td>83.2</td>
<td>173-174</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>4-CH₃C₆H₄</td>
<td>80.7</td>
<td>175-176</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅</td>
<td>2,3-(CH₃)₂C₆H₄</td>
<td>77.9</td>
<td>191-192.5</td>
</tr>
<tr>
<td>5</td>
<td>C₆H₅</td>
<td>2,4-(CH₃)₂C₆H₄</td>
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<td>165.5-170</td>
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<td>6</td>
<td>C₆H₅</td>
<td>2,5-(CH₃)₂C₆H₄</td>
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<td>211.5-215.5 (dec.)</td>
</tr>
<tr>
<td>7</td>
<td>C₆H₅</td>
<td>2,6-(CH₃)₂C₆H₄</td>
<td>89.8</td>
<td>193-194</td>
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<td>C₆H₅</td>
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<td>69.7</td>
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<td>9</td>
<td>C₆H₅</td>
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<td>71.9</td>
<td>189.5-191</td>
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<td>10</td>
<td>C₆H₅</td>
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<td>192.5-193.5</td>
</tr>
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<td>11</td>
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<td>12</td>
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<tr>
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<td>14</td>
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<td>213-214 (dec.)</td>
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<td>17</td>
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<td>18</td>
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<td>R'</td>
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<td>Analyses</td>
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<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>21</td>
<td>2-CH₃C₆H₄</td>
<td>2-CH₃C₆H₄</td>
<td>73.6</td>
<td>175.5-176.5</td>
</tr>
<tr>
<td>22</td>
<td>2-CH₃C₆H₄</td>
<td>2-CH₃C₆H₄</td>
<td>75.5</td>
<td>190-191</td>
</tr>
<tr>
<td>23</td>
<td>4-CH₃C₆H₄</td>
<td>4-CH₃C₆H₄</td>
<td>83.4</td>
<td>172-173</td>
</tr>
<tr>
<td>24</td>
<td>3,5-(CH₃)₂C₆H₃</td>
<td>3,5-(CH₃)₂C₆H₃</td>
<td>89.2</td>
<td>199-200</td>
</tr>
<tr>
<td>25</td>
<td>4-(CH₃)₂C₆H₄</td>
<td>4-(CH₃)₂C₆H₄</td>
<td>64.6</td>
<td>181-182</td>
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<tr>
<td>26</td>
<td>2-CH₃OC₆H₄</td>
<td>2-CH₃OC₆H₄</td>
<td>65.3</td>
<td>171-172</td>
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<tr>
<td>27</td>
<td>4-CH₃OC₆H₄</td>
<td>4-CH₃OC₆H₄</td>
<td>77.4</td>
<td>167-168.5</td>
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<tr>
<td>28</td>
<td>2,3-(CH₃O)₂C₆H₃</td>
<td>2,3-(CH₃O)₂C₆H₃</td>
<td>83.7</td>
<td>184-185</td>
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<tr>
<td>29</td>
<td>3,4-(CH₃O)₂C₆H₃</td>
<td>3,4-(CH₃O)₂C₆H₃</td>
<td>78.8</td>
<td>167.5-168.5</td>
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<tr>
<td>30</td>
<td>C₆H₅</td>
<td>3,4-CH₂O₂C₆H₃</td>
<td>73.3</td>
<td>164-165.5</td>
</tr>
</tbody>
</table>

**TABLE I**

**AMINO ESTER HYDROCHLORIDES OF SUBSTITUTED BENZILIC ACIDS**

- **Produced from uncrystallizable oil of Shacklett and Smith.**
- **Crystallized from methanol.**
- **Hill and Holmes report 185-190°C.**
In this work an attempt was made to find an efficient method to prepare II-9. Among the three methods that will be described in this section, the last two methods were especially good so far as the ease and manipulation of reaction were concerned. However, the last one (Method III) gave a little higher yield.

(1) **Method I.** o-Ethylbenzaldehyde was prepared by the action of ethyl orthoformate on the Grignard reagent, o-ethylphenylmagnesium iodide by a procedure similar to that described by Smith and Nichols. These authors had prepared a series of methyl substituted benzaldehydes by this method with good yields in most of the cases. The acetal (II-10) obtained by the action of ethyl orthoformate on the Grignard reagent was decomposed by refluxing with dilute sulfuric acid. The aldehyde (II-9) was isolated first as the sodium bisulfite addition compound and subsequently this compound was decomposed by treating with sodium bicarbonate.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{OH} & \xrightarrow{\text{K}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4} \text{C}_6\text{H}_5\text{CHO} \\
\text{II-8} & \quad \text{II-9}
\end{align*}
\]
followed by distillation. The reaction gave a yield of 41 per cent of o-ethylbenzaldehyde, b.p. 210-211°.

(2) Method II. o-Ethylbenzaldehyde (II-9) was obtained by a method analogous to that of Shirley and Danzig\(^8\) by the action of n-methylformanilide on o-ethylphenyllithium which was prepared by the action of n-butyllithium on o-ethyliodobenzene by the procedure for the halogen metal interconversion reaction as described by Gilman, Laugham and Moore.\(^8\) The preparation of n-butyllithium was accomplished by the method of Gilman and coworkers.\(^8\)

\[
\begin{align*}
&\text{II-7} & \text{n-BuLi} & \text{II-11} \\
&\text{C}_{2}\text{H}_{5} & \text{I} & \text{CHO} \\
&\text{II-9}
\end{align*}
\]

n-Butyllithium was added dropwise to the ether solution of o-ethyliodobenzene (II-7) at the reflux temperature of ether. o-Ethylphenyllithium (II-11) thus formed was treated in the same flask with N-methylformanilide in ether and refluxed. The mixture was made acidic and the aldehyde obtained was purified as described in Method I (A.2.b(1)). There was obtained a yield of 50.8 per cent of o-ethylbenzaldehyde (II-9).

(3) Method III. This method is similar to Method II with a Grignard reagent (II-12) being used in the place of the organolithium compound. The method of Zaheer and Faseeh\(^8\) was adopted. N-Methylformanilide in ether was added dropwise to the Grignard reagent (II-12).
A gummy solid mass, the magnesium complex II-13, obtained after refluxing and stirring for one hour was acidified. The aldehyde liberated was subjected to the same process of purification as in Methods I and II. The method gave a yield of 61.1 per cent of II-9, b.p. 82-84°C/5.5 mm.

c. Attempted benzoin condensation of o-ethylbenzaldehyde. o-Ethylbenzaldehyde (II-9) was subjected to the standard method\textsuperscript{89} of benzoin condensation by refluxing it for two hours with a mixture of ethanol and an aqueous solution of potassium cyanide. On cooling, a little heavy dark liquid settled down. Some of the unreacted aldehyde (II-9) also was recovered. The viscous liquid obtained could not be crystallized and decomposed when subjected to distillation under reduced pressure. It was used without further purification in the next step.

d. Attempted preparation of 2,2'-diethylbenzil. The viscous liquid which was presumably 2,2'-diethylbenzoin was oxidized with copper sulfate pentahydrate in pyridine. The mixture was stirred and heated on the steam
bath. On cooling, no solid was obtained. On pouring into water, some
tarry material was liberated. Hence, a direct one-step method for con-
version of a benzoin to benzilic acid was next attempted.

e. Attempted preparation of 2,2'-diethylbenzilic acid. The method
adopted here was that of Ballard and Dehn. 90

The apparent 2,2'-diethylbenzoin (II-14) was refluxed with potassium
bromate and sodium hydroxide for seven and one-half hours. On cooling
and diluting with water, some oil separated. Even with a longer reflux-
ing period, some separation occurred. After extracting the oil with
ether, the aqueous layer was acidified. The acid thus obtained was iden-
tified as o-ethylbenzoic acid from its melting point, from the molecular
weight determination, by the neutralization equivalent and finally by its
elemental analysis. The data are shown in Table II.

A cleavage of C-O bond in the benzoin, (II-14), resulting in oxi-
dation to o-ethylbenzoic acid, might have occurred as follows:
<table>
<thead>
<tr>
<th>Property</th>
<th>o-Ethylbenzoic Acid</th>
<th>Compound Obtained in A.2.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point</td>
<td>68.91°</td>
<td>63.5-64.5°</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>150.17</td>
<td>151.7</td>
</tr>
<tr>
<td>Analysis</td>
<td>C = 72.00</td>
<td>C = 72.79</td>
</tr>
<tr>
<td></td>
<td>H = 6.72</td>
<td>H = 6.63</td>
</tr>
</tbody>
</table>
It could also be possible that benzoin condensation might have failed and the aldehyde present might have been oxidized to II-16.

It is of interest to note that Glenn\textsuperscript{92} was not successful in his attempts at benzoin condensation of 2-phenylbenzaldehyde.

Failure in both cases might be due to steric reasons.

A summary of the attempts at the preparation of 2,2'-diethyl-benzilic acid is shown on Chart I.

B. Esters of Substituted Phenylcyclohexylglycolic Acid

1. \textbf{Catalytic Half-hydrogenation}

The amino ester hydrochlorides described in A were hydrogenated using commercial Adams' platinum catalyst in a low pressure hydrogenator. The solution of the hydrochloride in glacial acetic acid and the catalyst were shaken in hydrogen under a pressure of about 64 p.s.i. until the equivalent of 3.4 moles of hydrogen was taken up for every mole of the hydrochloride. (It was expedient to allow absorption in excess of the 3 moles of hydrogen theoretically required; otherwise unchanged ester hydrochloride of the substituted benzilic acid, difficult to remove by crystallization, was present in the product. On the other hand, the fully saturated dicyclohexylglycolates were removed by crystallization, by virtue of their high solubility in organic solvents. Adamson, Barrett and Wilkinson\textsuperscript{93} report similar observations in the half-hydrogenation of diphenylcarbinols to cyclohexylphenylcarbinols.)

The time required for half-hydrogenation varied for each compound. The product obtained after hydrogenation was recrystallized from an
CHART I

PROPOSED SCHEME FOR THE SYNTHESIS OF 2,2'-DIETHYLBENZILIC ACID

II-5

1) n-BuLi
2) Ph(CH₃)NCHO
3) H₃O

II-6

II-7

1) Mg
2) HCl
3) NaNO₂

II-8

1) KI

II-9

II-10

1) Mg
2) Ph(CH₃)NCHO
3) H₃O

II-11

II-12

1) Na
2) C₂H₅OH

II-13

II-14

1) CuSO₄·5H₂O
2) Pyridine

II-15
ethanol-ether* mixture until a sharp melting substance was obtained. A summary of catalytically half-hydrogenated compounds is shown in Table III.

2. Synthesis of the Ester Hydrochloride of 4-Methylphenylcyclohexylglycolic Acid

Since the catalytically half-hydrogenated product of the ester hydrochloride of 4-methylbenzilic acid exhibited physiological activity, it was of interest to investigate which one of the two rings was reduced first during the process. It is obvious that, upon half-hydrogenation of II-17, the two possible products are 2-diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride, (II-18), and 2-diethylaminoethyl 4-methylcyclohexylphenylglycolate hydrochloride, (II-19). The analysis of the solid obtained corresponds to each of these possibilities. One solution of this problem would be in the synthesis of one of the two

*Sufficient anhydrous ether was added in all cases to the hot alcoholic solution to produce cloudiness.
TABLE III

AMINO ESTER HYDROCHLORIDES OF SUBSTITUTED PHENYL CYCLOHEXYLGlycolic ACIDS

![Chemical structure]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>Melting Point</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>°C</td>
<td>Calculated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>31</td>
<td>2-CH₃C₆H₄</td>
<td>55</td>
<td>191-193</td>
<td>65.67</td>
</tr>
<tr>
<td>32</td>
<td>3-CH₃C₆H₄</td>
<td>66</td>
<td>187-189</td>
<td>65.67</td>
</tr>
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<td>4-CH₃C₆H₄</td>
<td>75</td>
<td>200-201</td>
<td>65.67</td>
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<tr>
<td>34</td>
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<td>38</td>
<td>170-172</td>
<td>66.39</td>
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<tr>
<td>35</td>
<td>3,5-(CH₃)₂C₆H₃</td>
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<td>217-218</td>
<td>66.39</td>
</tr>
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<td>2,4,6-(CH₃)₃C₆H₂</td>
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<td>3-CH₃C₆H₄</td>
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<td>181-182</td>
<td>66.39</td>
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</table>

*HCl*
compounds, either II-18 or II-19, and checking its physical constants with those of the compound which was actually obtained by catalytic half-hydrogenation of II-17. Hence, the following attempt was made to synthesize totally II-18.

Synthesis of 2-diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride was achieved as shown in Chart II.

4-Methylbenzoic acid, (II-20) was converted to 4-methylbenzoyl chloride, (II-21), b.p. 57°/0.3 mm., by the action of thionyl chloride in 93.1 per cent yield. When II-21 was heated with cuprous cyanide, 43.5 per cent of 4-methylbenzoyl cyanide (II-22), m.p. 50-51°, was obtained. The hydrolysis and subsequent esterification of II-22 was accomplished by dissolving it in absolute alcohol saturated with hydrogen chloride and allowing it to stand for eight days in the cold room. There was obtained 50.2 per cent of II-23, b.p. 124-126°/3.5 mm. An equimolar proportion of the Grignard reagent, cyclohexylmagnesium chloride, reacted with II-23 to give 59.6 per cent of ethyl 4-methylphenylcyclohexylglycolate (II-24), b.p. 155-158°/2.8 mm. Aqueous sodium hydroxide solution was employed to saponify II-24 and upon acidification, a 65 per cent yield of 4-methylphenylcyclohexylglycolic acid (II-25), m.p. 189-190°, was realized. On refluxing II-25 with 2-diethylaminoethyl chloride in isopropyl alcohol, the amino ester hydrochloride (II-18), m.p. 202-203°, was obtained.

No depression was observed in mixed melting point of synthetic 2-diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride (II-18) with the half-hydrogenated product of 2-diethylaminoethyl 4-methyl-
SYNTHESIS OF 2-DIETHYLAMINOETHYL 4-METHYLPHENYL CYCLOHEXYLGLYCOLATE HYDROCHLORIDE.
benzilate hydrochloride (II-17). A comparison of physical constants is given in Table IV. Further, ultraviolet data in Table VI and Figure 1 substantiate the fact that the two compounds are identical. It was concluded therefore that during the course of catalytic half-hydrogenation of II-17, the unsubstituted benzene ring was reduced first. In the light of this statement, an attempt was made to synthesize the ester hydrochloride of 3,5-dimethylphenylcyclohexylglycolate hydrochloride and compare its physical constants with those of the product obtained from catalytic half-hydrogenation of the ester hydrochloride of 3,5-dimethylbenzilate hydrochloride. Here again two possible half-hydrogenated products as shown below are II-27 and II-28.
### TABLE IV

**2-DIETHYLAMINOETHYL 4-METHYLPHENYLCYCLOHEXYLGlycolate Hydrochloride**

<table>
<thead>
<tr>
<th></th>
<th>Synthetic</th>
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<tr>
<td>Melting Point</td>
<td>202-203°</td>
<td>200-201°</td>
</tr>
<tr>
<td>Analysis</td>
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<td>C, 65.67</td>
</tr>
<tr>
<td></td>
<td>H, 9.00</td>
<td>H, 9.14</td>
</tr>
</tbody>
</table>

Calcd. for C\textsubscript{21}H\textsubscript{34}NO\textsubscript{3}Cl

<p>| | |</p>
<table>
<thead>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>65.67</td>
</tr>
<tr>
<td>H</td>
<td>8.93</td>
</tr>
</tbody>
</table>

Mixed Melting Point: 202-203°
Figure 1. Ultraviolet Absorption Spectra of 2-Diethylaminoethyl 4-Methylphenylcyclohexylglycolate Hydrochloride in 95 Per Cent Ethanol.
3. **Synthesis of 2-Diethylaminoethyl 3,5-Dimethylphenylcyclohexylglycolate Hydrochloride**

The series of reactions employed for the synthesis of the ester hydrochloride of 3,5-dimethylphenylcyclohexylglycolate hydrochloride is shown in Chart III.

The purified 2,4-dimethylaniline (II-29) was brominated in the presence of hydrochloric acid in an ice bath followed by diazotization leading to deamination using stannous chloride in sodium hydroxide. 3,5-Dimethylbromobenzene (II-32), b.p. 70°/6 mm., was obtained in 56 per cent overall yield. As indicated by Fischer and Windaus, sodium stannite proved to be a more satisfactory reagent than alcohol for deamination in this reaction. These authors, as well as Fieser and Heymann, have reported the preparation of 3,5-dimethylbromobenzene by the same route.

3,5-Dimethylbenzoic acid, (II-33), m.p. 169-170°, was obtained in 67.5 per cent yield by the action of 3,5-dimethylmagnesium bromide on solid carbon dioxide in ether. Thionyl chloride was employed to prepare the acid chloride which on heating with cuprous cyanide gave 3,5-dimethylbenzoyl cyanide, II-35, m.p. 61-62°, in 61.5 per cent yield. On keeping the cyanide dissolved in ethanol and saturated with hydrogen chloride in the cold for eight days, ethyl 3,5-dimethylbenzoylformate, (II-36), b.p. 130°/4.5 mm., was formed in 46.3 per cent yield. It gave a positive test with 2,4-dinitrophenylhydrazine. The addition of cyclohexylmagnesium chloride to II-36 and acidification resulted in the formation of ethyl 3,5-dimethylphenylcyclohexylglycolate, (II-37), b.p. 175°/4.5 mm., in
SYNTHESIS OF 2-DIETHYLAminoETHYL 3,5-DIMETHYLPHENYLCYcLOhexyLGLYcolATE HYDROCHLORIDE

CHART III

II-29

II-30

II-31

II-32

II-33

II-34

II-35

II-36

II-37

II-38

II-27

50
17.8 per cent yield. The saponification of the ester, II-37, gave the corresponding acid, II-38, which on refluxing with equimolar proportions of 2-diethylaminoethyl chloride in isopropyl alcohol gave 2-diethylaminoethyl 3,5-dimethylphenylcyclohexylglycolate hydrochloride, (II-27), m.p. 217-218°, in 63.3 per cent yield. The catalytically half-hydrogenated product of 2-diethylaminoethyl 3,5-dimethylbenzilate hydrochloride, (II-26), did not show any depression in melting point when mixed with II-27. A summary of data on these two compounds is shown in Table V. Ultraviolet absorption curves (Figure 2) of both the half-hydrogenated product and II-27 indicate the identical nature of the compounds. The pertinent ultraviolet data are given in Table VI.

It has been shown that the introduction of methyl substituents into the benzene nucleus produces several effects upon the absorption spectrum of benzene. These effects may be summarized as: (a) an increase in the intensity of absorption; (b) a tendency to smooth out the benzenoid fine-structure bands; (c) displacement of the main maxima (usually to longer wavelengths).

From the Figures 1 and 2, it is evident that the catalytically half-hydrogenated products of 2-diethylaminoethyl 4-methylbenzilate hydrochloride, (II-17), and 2-diethylaminoethyl 3,5-dimethylbenzilate hydrochloride (II-26) are identical to the synthetic compounds, II-18 and II-27, respectively. Further, a comparison of Figures 1 and 2 shows that the half-hydrogenated product of II-26 (dimethyl substituted) exhibits a greater intensity of absorption at higher wavelength (269 mp) than that of mono-methyl substituted compound, II-17, (264.5 mp). It is interesting to note
### TABLE V

2-DIETHYLAMINOETHYL 3,5-DIMETHYLPHENYLCYCLOHEXYLGlyCOLATE HYDROCHLORIDE

<table>
<thead>
<tr>
<th></th>
<th>Synthetic</th>
<th>Obtained by Catalytic Half-Hydrogenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point</td>
<td>217-218°</td>
<td>217-218°</td>
</tr>
<tr>
<td>Analysis</td>
<td>C, 66.74</td>
<td>C, 66.42</td>
</tr>
<tr>
<td></td>
<td>H, 9.10</td>
<td>H, 9.21</td>
</tr>
</tbody>
</table>

Calcd. for C₂₂H₃₆NO₃Cl:

C, 66.39

H, 9.12

Mixed Melting Point: 217-218°
Figure 2. Ultraviolet Absorption Spectra of 2-Diethylaminoethyl 3,5-Dimethylphenylcyclohexylglycolate Hydrochloride in 95 Per Cent Ethanol.
<table>
<thead>
<tr>
<th>Compound (2.5 x 10^{-3} M.)</th>
<th>Wavelength ((\text{Ma}))</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Diethylaminoethyl 4-Methylphenylcyclohexylglycolate Hydrochloride (II-18)</td>
<td>264.5</td>
<td>329.3</td>
</tr>
<tr>
<td>Half-hydrogenated Product of 2-Diethylaminoethyl 4-Methylbenzilate Hydrochloride</td>
<td>264.5</td>
<td>348</td>
</tr>
<tr>
<td>2-Diethylaminoethyl 3,5-Dimethylphenylcyclohexylglycolate Hydrochloride (II-27)</td>
<td>269</td>
<td>384.1</td>
</tr>
<tr>
<td>Half-hydrogenated Product of 2-Diethylaminoethyl 3,5-Dimethylbenzilate Hydrochloride</td>
<td>269</td>
<td>388.9</td>
</tr>
</tbody>
</table>
that Shacklett\textsuperscript{97} reports an absorption maximum for phenylcyclohexyl-
glycolic acid at a wavelength of 258 \textmu m which is lower than that of
the half-hydrogenated product of II-17. In other words, a shift
towards higher wavelength occurs in absorption maxima along with a ten-
dency to smooth out the fine structure of curves with greater methyl
substitution in the compound. As described earlier, the same observa-
tions have been made as reported in the literature with methyl sub-
stituted benzenes. Hence, the shifts in absorption maxima observed in
the half-hydrogenated products of II-17 and II-26 must be due to methyl
substituted benzene rings in the compounds. The other remaining unsub-
stituted ring, therefore, must have been reduced.

Moreover, if the half-hydrogenation of compounds II-17 and II-26
had resulted in the reduction of the substituted rings, they would have
given identical absorption curves, the absorption being principally due
to only benzene rings in both the compounds.

The synthetic and ultraviolet studies, therefore, lead to the con-
clusion that the catalytic half-hydrogenation of II-17 and II-26 results
in the reduction of the unsubstituted ring.

C. The Ester Hydrochlorides of Substituted Dicyclohexylglycolic Acid

1. Catalytic Hydrogenation

The ester hydrochlorides of substituted benzilic acids were dis-
solved in pure glacial acetic acid and shaken in the presence of Adams' platinu
platinum catalyst under a hydrogen pressure of about 64 pounds per square
inch. The shaking was continued until no drop in pressure was observed
over a period of from three to four hours even after the addition of some more catalyst. The time required for full hydrogenation varied from a few hours to about a week. Generally, the greater the substitution on the benzene ring, the longer was the time required for complete hydrogenation. After evaporation of the solvent, the product obtained was recrystallized several times from an alcohol-ether mixture. The compounds thus obtained are listed in Table VII. However, the hydrogenation products of the ester hydrochlorides of 2,3,4,5-tetramethyl, 2,3,5,6-tetramethyl and 2,3,4,6-tetramethylbenzilic acids did not give correct elemental analysis. These three compounds needed five to six days of shaking until no more drop in pressure was observed for about five to six hours after addition of a fresh lot of catalyst. Even after innumerable recrystallizations, the hydrogenated products softened before melting. The hydrogenated products were presumably mixtures which resisted efforts at further purification.

2. **Attempted Catalytic Hydrogenation of Ester Hydrochlorides of Methoxy Substituted Benzilic Acids**

Attempts were made to hydrogenate ester hydrochlorides of 4-methoxy and 4,4'-dimethoxybenzilic acids using platinum catalyst by the procedure described in C.1. However the elemental analysis of the products obtained did not correspond to the completely hydrogenated products of the expected ester hydrochlorides. A cleavage of the C-O bond of the methoxyl group attached to the ring was in all probability responsible. Since Smith and Thompson had observed much smaller cleavage in hydrogenation of methoxy substituted benzenes over 5 per cent rhodium on alumina than over
<table>
<thead>
<tr>
<th>( R' )</th>
<th>( R' )</th>
<th>Yield</th>
<th>Melting Point</th>
<th>Analyses</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>76.1</td>
<td>165-166.5</td>
<td>64.67</td>
<td>10.34</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>86.4</td>
<td>181-182</td>
<td>64.67</td>
<td>10.34</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 4-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>87.4</td>
<td>190.5-192</td>
<td>64.67</td>
<td>10.34</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2,3-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>79.2</td>
<td>174-175</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2,4-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>78.9</td>
<td>155-156</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2,6-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>80.9</td>
<td>181-182</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3,4-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>80.2</td>
<td>177.5-178.5</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3,5-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>72.8</td>
<td>171-173</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2,3,5-\text{(CH}_3\text{)}_3\text{C}_6\text{H}_8 )</td>
<td>76.3</td>
<td>193-194</td>
<td>66.07</td>
<td>10.61</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2,3,6-\text{(CH}_3\text{)}_3\text{C}_6\text{H}_8 )</td>
<td>76.0</td>
<td>199-200</td>
<td>66.07</td>
<td>10.61</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3,4,5-\text{(CH}_3\text{)}_3\text{C}_6\text{H}_8 )</td>
<td>89.6</td>
<td>216.5-218</td>
<td>66.07</td>
<td>10.61</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 4-\text{C}<em>6\text{H}</em>{11}\text{C}<em>6\text{H}</em>{10} )</td>
<td>75.5</td>
<td>174.5-175.5</td>
<td>66.16</td>
<td>10.56</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 2-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>80.2</td>
<td>163.5-164.5</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>84.1</td>
<td>178.5-179.5</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 4-\text{CH}_3\text{C}<em>6\text{H}</em>{10} )</td>
<td>81.5</td>
<td>187-188</td>
<td>65.40</td>
<td>10.48</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 3,5-\text{(CH}_3\text{)}_2\text{C}_6\text{H}_9 )</td>
<td>84.4</td>
<td>183-184</td>
<td>66.71</td>
<td>10.73</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} )</td>
<td>( 4-(\text{CH}_3)_2\text{C}<em>6\text{H}</em>{10} )</td>
<td>84.4</td>
<td>185-187</td>
<td>67.86</td>
<td>10.95</td>
</tr>
</tbody>
</table>
platinum oxide, it was decided to hydrogenate the ester hydrochloride of 4-methoxybenzilic acid over 5 per cent rhodium on alumina. On termination of the hydrogenation, the resulting product was recrystallized several times from an alcohol-ether mixture. The compound, however, did not analyze for the ester hydrochloride of 4-methoxydicyclohexylglycolic acid. A quantitative analysis for the methoxy group in the hydrogenated product indicated the cleavage of 58.16 per cent of the methoxyl group. Hence further attempts at catalytic hydrogenation of methoxy substituted compounds were not made.

D. Attempted Preparation of Esters of 1-Mercaptodiarylacetic Acid

1. 1-Mercaptodiarylacetic Acids

1-Mercaptodiarylacetic acids were prepared by the method described by Becker and Bistrzycki as in Chart IV. Diphenylcarboxymethyl N-phenylthiolcarbamate (II-41) was obtained in quantitative yield by the action of phenylisothiocyanate (II-40) on benzilic acid (II-39) at room temperature for twenty hours in the presence of acetic and sulfuric acids. II-41 melted at 138-139° but did not decompose as reported by Becker and Bistrzycki. However, the analysis confirmed the identity of the compound. II-41, when hydrolyzed with 3 per cent solution of potassium hydroxide, gave 1,1-diphenyl-1-mercaptoacetic acid, (II-42), m.p. 148-149° in 88.1 per cent yield.

2,2'-Dimethoxydiphenyl-1-mercaptoacetic acid and 3,3'-dimethyl-diphenyl-1-mercaptoacetic acid were prepared by the same route. Table VIII gives a summary of the acids thus prepared.
CHART IV

SYNTHESIS OF 1,1-DIPHENYL-1-THIOLACETIC ACID

II-39

\[ \text{II-39} \]

\[ \text{II-40} \] + \[ \text{II-41} \]

\[ \text{II-42} \]

\[ \text{CH}_3\text{COOH and } \text{H}_2\text{SO}_4 \]

\[ \text{OH}^- \]
## TABLE VIII

### 1-MERCAPTODIARYLACETIC ACIDS

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>Melting Point °C</th>
<th>Analysis Calculated</th>
<th>Analysis Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>88</td>
<td>148-149</td>
<td>68.82</td>
<td>4.95</td>
</tr>
<tr>
<td>3-CH₃C₆H₄</td>
<td>3-CH₃C₆H₄</td>
<td>80</td>
<td>102-103</td>
<td>70.55</td>
<td>5.92</td>
</tr>
<tr>
<td>2-CH₃OC₆H₄</td>
<td>2-CH₃OC₆H₄</td>
<td>86</td>
<td>138-139.5</td>
<td>63.13</td>
<td>5.29</td>
</tr>
</tbody>
</table>
2. Attempted Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-mercaptoacetate Hydrochloride

When a solution of equimolar quantities of 2-diethylaminoethyl chloride and II-42 in isopropyl alcohol was refluxed, the evolution of hydrogen sulfide was indicated by the darkening of lead acetate paper. A compound isolated on addition of dry ether to the resulting deep blue solution, melted at 189-190° and its analysis (C, 42.96; H, 9.08) agreed fairly well with that of the hydrochloride of 2-diethylaminoethanethiol. The reaction might have occurred as follows:

\[
\begin{align*}
\text{II-42} & \quad + \quad \text{II-43} \\
\text{II-44} & \quad \xrightarrow{\text{HSCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\text{HCl}}
\end{align*}
\]

No attempt was made to isolate II-43 from the blue colored solution. The hydrochloride of 2-diethylaminoethanethiol, (II-44), m.p. 189-190°, according to the literature,\textsuperscript{100} melts at 170-172°.

**Anal.** Calcd. for C\textsubscript{6}H\textsubscript{14}NClS: C, 42.46; H, 9.73.

**Found:** C, 42.96; H, 9.08.
Repeated attempts with dry benzene in the place of isopropyl alcohol resulted in the evolution of hydrogen sulfide and formation of the same blue solution. This route for the preparation of the desired compound was therefore abandoned.

According to Klosa, the action of phosphorus tribromide on 2-diethylaminoethyl benzilate hydrochloride (II-45) suspended in benzene at 70-80° produced the ester hydrobromide of 1,1-diphenyl-1-bromoacetic acid (II-46).

\[
\begin{align*}
\text{II-45} & : \quad \text{C} \quad \text{OH} \\
\text{C} \quad \text{COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\cdot\text{HCl} & \quad \overset{\text{PBr}_3}{\longrightarrow} \\
\text{II-46} & : \quad \text{C} \quad \text{Br} \\
\text{C} \quad \text{COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\cdot\text{HBr}
\end{align*}
\]

The free amine from II-46 obtained by treatment with a solution of sodium bicarbonate was refluxed with sodium hydrosulfide in dry acetone. The hydrochloride isolated from this reaction melted at 172-173° which was the melting point of the hydrochloride of 2-diethylaminoethanethiol (II-44).\(^{100}\) Its mixed melting point showed no depression with an authentic sample of II-44. The saponification might have occurred as follows:

\*\*It appears that this compound has two melting points.\*\*
Some II-44 was isolated and no attempt was made to isolate the acids II-47 or II-42. This route was not explored any further.

E. Preparation of 1,1-Diphenyl-2-hydroxy-4-N,N-dimethylbutylamine Hydrochloride

The synthesis of 1,1-diphenyl-2-hydroxy-4-N,N-dimethylbutylamine hydrochloride was accomplished by the route shown in Chart V. Phenylacetone, (II-48), was brominated by the method of Schultz and Mickey\textsuperscript{102} to give 1-phenyl-1-bromopropanone, (II-49), which was subsequently reacted with benzene in the presence of anhydrous aluminum chloride to give 1,1-diphenylpropanone, (II-50). The method of Wilson and Kyi\textsuperscript{103} (modified Mannich reaction) was employed to convert II-50 to 1,1-diphenyl-4-N,N-dimethylamino-2-butanone hydrochloride (II-51). Upon catalytic hydrogenation of the carbonyl group in II-51, 1,1-diphenyl-2-hydroxy-4-N,N-dimethylbutylamine hydrochloride (II-52), m.p. 175-176°, was obtained.
SYNTHESIS OF 1,1-DIPHENYL-2-HYDROXY-4-N,N-DIMETHYLBUTYLAMINE HYDROCHLORIDE

\[
\text{II-48} \xrightarrow{\text{Br}_2} \text{II-49} \\
\text{II-49} \xrightarrow{1) \text{AlCl}_3, 2) \text{C}_6\text{H}_6} \text{II-50} \\
\text{II-50} \xrightarrow{1) (\text{CH}_3)_2\text{NH} \cdot \text{HCl}, 2) (\text{HCHO})_x, 3) \text{C}_2\text{H}_5\text{OH}} \text{II-51} \\
\text{II-51} \xrightarrow{\text{Pt, H}_2} \text{II-52}
\]
F. Attempted Preparation of 1,1-Diphenyl-4-N,N-dimethylamino-2-butene Hydrochloride

1. Method I

An attempt was made to acetylate II-52 by stirring overnight with acetyl chloride in the presence of anhydrous potassium carbonate. The acetylated compound (II-53) was brominated at -15° using dry carbon tetrachloride as solvent. The proposed sequence of reactions for the synthesis of the desired compound was as follows:

\[
\begin{align*}
\text{II-52} & \xrightarrow{1) \text{CH}_3\text{COCl}} \xrightarrow{2) \text{K}_2\text{CO}_3} \text{II-56} \\
\text{II-53} & \xrightarrow{1) \text{Br}_2, \text{CCl}_4, -15^\circ} \xrightarrow{2) \text{CCl}_4} \text{II-54} \\
\text{II-55} & \xrightarrow{1) \text{OH}^-, \text{HCl}} \xrightarrow{2) \text{HCl}} \text{II-56}
\end{align*}
\]
The bromo compound (II-54) on several recrystallizations from acetone melted at 173-174°. However, it failed to analyze correctly for II-54. The supposed bromo compound gave positive tests for unsaturation with potassium permanganate and also bromine. Its analysis conformed to the following structure:

At some stage of conversion of II-53 to II-54, dehydrobromination might have taken place. Due to the failure in obtaining the compound II-54, no further attempt was made to achieve this synthesis. Thus an alternate approach was planned.

2. Method II

A proposed series of reactions to achieve the synthesis of II-56 is shown in Chart VI.

The method of Stevens and Lenk\textsuperscript{10k} was employed in which II-50 was brominated at -15° to produce an 81.2 per cent yield of 1-bromo-1,1-diphenylpropanone (II-58), m.p. 55.5-56.5°. II-58 was hydrolyzed in a dioxane-water medium and 1-hydroxy-1,1-diphenylpropanone (II-59), m.p. 64-65°, was produced in 83 per cent yield. To obtain the aminoketone (II-60) a Mannich reaction was run on II-59 in n-octanol using dimethylamine hydrochloride and paraformaldehyde. The attempt to acetylate the tertiary hydroxyl group in II-60 according to the method of LaMer and
CHART VI

ATTEMPTED PREPARATION OF 1,1-DIPHENYL-4-N,N-DIMETHYLAMINO-2-BUTENE HYDROCHLORIDE

II-50 + Br₂ → II-58

Br₂ → -15°

1) H₂O → 2) Dioxane

II-59 → II-60

1) (CH₃)₂NH·HCl
2) (HCHO)ₓ
3) n-C₈H₁₇OH

II-60 → II-61

(CH₃CO)₂O → H₂, Pt

II-61

II-62 → II-63

1) CH₃COCl
2) K₂CO₃

II-64 → II-65

or/ and

II-64

Δ

or/ and

II-65

II-66 → II-56

1) OH⁻ → 2) HCl
Greenspan and also King and Holmes failed. A number of different reaction conditions were used in attempts at acetylation. By the action of acetyl chloride in the presence of potassium carbonate, a gummy hygroscopic substance which failed to crystallize was obtained. The details of attempts at acetylation are described in the Experimental section. No further progress was achieved in the series of reactions in Chart VI due to the failure in acetylation of II-60.

G. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-diethylaminoethoxy)acetate Hydrochloride

When a mixture of thionyl chloride and benzilic acid in carbon tetrachloride stood at room temperature for thirty hours, 1-chloro-1,1-diphenylacetic acid, (II-67), was obtained in good yield according to the method of Klosa. Etherification of II-67 was accomplished by refluxing it for thirty-six hours with 2-diethylaminoethanol and anhydrous potassium carbonate. The hydrochloride of II-68 was esterified by refluxing with 2-diethylaminoethyl chloride in isopropyl alcohol. The dihydrochloride (II-69), m.p. 212-213°, was obtained in 87.4 percent yield.
H. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-thioacetoxylacetate Hydrochloride

1-Chloro-1,1-diphenylacetic acid (II-67) described in the previous section was refluxed with thioacetic acid in benzene in an atmosphere of nitrogen. The 1,1-diphenyl-1-(thioacetoxyl)acetic acid (II-70) obtained was converted into its ester hydrochloride, (II-71), m.p. 166-167°.
I. Attempted Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetate

A benzene solution of 1-chloro-1,1-diphenylacetic acid (II-67) was added dropwise to the sodium salt of 1-mercaptoacetic acid (HSCH2COONa) and refluxed for sixteen hours. 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetic acid (II-72) was partially soluble in benzene. After
filtration of the solvent, the residue contained a mixture of sodium chloride and the acid, II-72, from which sodium chloride was removed by extraction with water. After several recrystallizations from ethyl acetate, the acid, II-72, m.p. 192-193.5°, was obtained in 80.5 per cent yield. The esterification of II-72 was achieved by refluxing with 2-diethylaminoethyl chloride in isopropyl alcohol. Since the hydrochloride and oxalate of the amine thus obtained were highly hygroscopic, the citrate, which was less hygroscopic, was prepared by the addition of citric acid in ether to the ethereal extract of the amine concerned. The citrate obtained was recrystallized successively from several solvents as described in the Experimental section. There was obtained hygroscopic white crystals, m.p. 78-79.5°, with a yield of 17 per cent. The compound, however, did not analyze correctly for II-73, due probably to its hygroscopic nature or to the presence of solvent of crystallization.

J. 2-Diethylaminoethyl 1,1-Diphenyl-1-(isopropthio)acetate Hydrochloride

2-Diethylaminoethyl 1,1-diphenyl-1-(isopropthio)acetate hydrochloride, (II-75), was obtained by the following sequence of reactions. II-67 was converted to diphenylcarboxymethyl isopropyl sulfide, (II-74), according to the method of Klosa107 by refluxing with 2-propanethiol for thirty hours in the presence of pure calcium carbonate. The amino ester hydrochloride of the acid, II-74, was obtained by the general method discussed in A.1. II-75, m.p. 138-139°, was obtained in a yield of 85.4 per cent.
Krapcho, Turk and Pribryl\textsuperscript{108} prepared their amides by the action of the acid chloride on the appropriate amine followed by hydrolysis of the \textit{alpha} chloro group as shown below:

\begin{equation}
\begin{align*}
\text{II-39} & \rightarrow \text{II-76} \\
\text{II-76} & \rightarrow \text{II-77} \\
\text{II-77} & \rightarrow \text{II-78} \\
\text{II-78} & \rightarrow \text{II-79}
\end{align*}
\end{equation}
1,1-Diphenyl-1-chloroacetyl chloride, (II-76), was prepared from benzilic acid (II-39) by the method of King and Holmes\textsuperscript{106} through the action of phosphorus pentachloride.

Magee\textsuperscript{109} in his studies of the preparation of 2-N,N-diethyl-aminocetyl methylamide of phenylcyclohexylglycolic acid by the method of Krapcho, Turk and Pribyl,\textsuperscript{107} attempted to obtain the required intermediate 1-phenyl-1-cyclohexyl-1-chloroacetyl chloride by treatment of phenylcyclohexylglycolic acid with phosphorus pentachloride and thionyl chloride. He proposed that the product obtained might be a mixture of 1-phenyl-1-cyclohexyl-1-chloroacetyl chloride, 1-phenyl-1-cyclohexylideneacetyl chloride (II-80) and 1-phenyl-1-\textsuperscript{a}-cyclohexenylacetyl chloride (II-81).

![II-80](image)

![II-81](image)

In the light of Magee’s observations, the convenient method of Krapcho, Turk and Pribyl\textsuperscript{108} for the preparation of amide was not attempted.

An alternate approach for the synthesis of the desired amide is shown in Chart VII. Benzoyl chloride, (II-82), was converted into its corresponding cyanide, (II-83), by the method of Oakwood and Weisgerber.\textsuperscript{110} Benzoylformic acid (II-84) was obtained by allowing II-83 to stand with concentrated hydrochloric acid for five days at room temperature as described by Oakwood and Weisgerber.\textsuperscript{111} By the action of phosphorus pentachloride on the acid, II-84, at the reflux temperature of benzene for
CHART VII

ATTEMPTED SYNTHESIS OF 2-N,N-DIETHYLAMINOETHYL METHYLAMIDE OF PHENYL-CYCLOHEXYLGLYCOLIC ACID

\[
\begin{align*}
\text{II-82} & \xrightarrow{\text{CuCN}} \text{II-83} & \xrightarrow{\text{HCl}} & \text{II-84} \\
& \xrightarrow{1 \text{) } \text{OH}^{-}} \xrightarrow{2 \text{) } (\text{COOH})_2} & & \text{II-86} \\
& & \rightarrow \text{II-85} \\
\end{align*}
\]

\[
\begin{align*}
\text{II-82} & \xrightarrow{\text{CuCN}} \text{II-83} & \xrightarrow{\text{HCl}} & \text{II-84} \\
& \xrightarrow{1 \text{) } \text{dil. NaOH}} \xrightarrow{2 \text{) } \text{C}_6\text{H}_8\text{MgCl}} & & \text{II-87} \\
& \xrightarrow{3 \text{) } \text{C}_6\text{H}_8\text{O}_7} & & \text{II-88} \\
& & \rightarrow \text{II-85} \\
\end{align*}
\]

\[
\begin{align*}
\text{II-82} & \xrightarrow{\text{CuCN}} \text{II-83} & \xrightarrow{\text{HCl}} & \text{II-84} \\
& \xrightarrow{1 \text{) } \text{dil. NaOH}} \xrightarrow{2 \text{) } \text{C}_6\text{H}_8\text{MgCl}} & & \text{II-87} \\
& \xrightarrow{3 \text{) } \text{C}_6\text{H}_8\text{O}_7} & & \text{II-88} \\
& & \rightarrow \text{II-85} \\
\end{align*}
\]

\[
\begin{align*}
\text{II-82} & \xrightarrow{\text{CuCN}} \text{II-83} & \xrightarrow{\text{HCl}} & \text{II-84} \\
& \xrightarrow{1 \text{) } \text{dil. NaOH}} \xrightarrow{2 \text{) } \text{C}_6\text{H}_8\text{MgCl}} & & \text{II-87} \\
& \xrightarrow{3 \text{) } \text{C}_6\text{H}_8\text{O}_7} & & \text{II-88} \\
& & \rightarrow \text{II-85} \\
\end{align*}
\]
four hours and allowing the mixture to stand overnight, there was ob-
tained benzoylformyl chloride, (II-85), b.p. 82°/4 mm., in 89.9 per-
cent yield. Several attempts to prepare the acid chloride, II-85, by
the method of Acree,112 who used thionyl chloride, were not successful
due to decarboxylation resulting in benzoyl chloride (II-82).

1. Preparation of 2-N,N-Diethylaminoethyl Methylamide of Benzoylformic
   Acid

2-N,N-Diethylaminoethylmethylamine (II-86) was obtained by shaking
2-N,N-diethylaminoethyl chloride with about a four-fold excess of 35 per-
cent aqueous methylamine solution as described by Damiens.113 The shaking
was conducted in a round-bottomed flask fitted with a two-hole rubber
stopper carrying a stopcock and a thermometer. The yields from this
procedure were in the range of 25 per cent. A large amount of high boil-
ing residue which was in all probability the tertiary amine condensation
product was formed. However, no effort was made to isolate and identify
this byproduct.

A solution of the acid chloride, II-85, in n-hexane and benzene
was treated with a benzene solution of amine, II-86, to produce the de-
sired amide (II-87). All attempts at crystallization of the hydrochlor-
ride of free amine of II-87 having failed, its oxalate was prepared by
the addition of a saturated solution of oxalic acid to the ethereal solu-
tion of free amine. The oxalate, (II-87), a white crystalline substance,
m.p. 93-94°, was obtained in a yield of 48.3 per cent.
2. **Attempted Synthesis of 2-N,N-Diethylaminoethyl Methylamide of Phenyl-cyclohexylglycolic Acid**

When cyclohexylmagnesium chloride is added to the free amine of II-87, four possible products can be formed. The most probable one is due to the addition of the Grignard reagent across the ketonic carbonyl in equimolar proportion resulting in the required amide, II-88. The other possibilities, II-89, II-90 and II-91, arise due to the action of Grignard reagent on the carbonyl of the amide linkage as described by Beis and also Maxim.

According to Beis, the Grignard reagent reacts with an amide through the following steps (no concrete evidence for the mechanism of reaction is given):

(1) \[ R\text{CONH}_2 + 2\text{Mg} \rightleftharpoons R\text{C} + \text{NHMe} + \text{R'} \text{H} \]

(2) \[ R\text{C} + 2\text{H}_2\text{O} \rightarrow R\text{C} + \text{NH}_2 + \text{MgX}_2 + \text{Mg(OH)}_2 \]

(3) \[ R\text{C} + \text{OH} \rightarrow R\text{C} + \text{NH}_2 + \text{R'} \text{H} + \text{NH}_3 \]

According to the Beis' mechanism, an N-substituted amide with a Grignard reagent can give \( RR'\text{C(OH)}\cdot\text{N(R\text{1})}_2 \). Hence the compound, II-89 is also a possible product in the present series of reactions.
Maxim\textsuperscript{115} claims that the following reactions take place between the Grignard reagent and N-substituted amides. However, this author also does not discuss any mechanism for these reactions:

\begin{align*}
(1) \quad & \text{RCO}(\text{R}_1)_2 + \text{R}'\text{MgX} \xrightarrow{\text{H}_2\text{O}} \text{RCOR}^\prime + \text{HN}(\text{R}_1)_2 + \text{Mg(OH)}\text{X} \\
(2) \quad & \text{RCO}(\text{R}_1)_2 + 2\text{R}'\text{MgX} \rightarrow \text{R}^\prime \text{N}(\text{R}_1)_2 + \text{MgO} + \text{MgX}_2
\end{align*}

On the basis of Maxims' observations, the present reaction might give either II-90 or II-91.

The action of equimolar proportions of the Grignard reagent, cyclohexylmagnesium chloride on the free amine of II-87 gave a product whose hydrochloride and oxalate were hygroscopic. However, the citrate was obtained as a white crystalline substance, m.p. 79–80\textdegree, which did possess the correct elemental composition of II-89. This substance could not be produced again in spite of several attempts. A product, m.p. 86–87\textdegree, was isolated in subsequent attempts whose elemental analysis did not agree with any of the possible four products, II-88, II-89 and II-90 or II-91. However, if three molecules of citric acid combine with two molecules of the free amine of II-89, the analytical results were found to be in fair agreement with the calculated values:

\textbf{Anal. Calcd. for C}_{60}\text{H}_{92}\text{N}_4\text{O}_{25} (two molecules of free amine of II-89 and three molecules of citric acid):

\textbf{Found:}\ C, 56.10; H, 7.41.
The citrate prepared gave a slight precipitate with 2,4-dinitrophenylhydrazine after standing over twenty-four hours. This slight precipitate and its delay in appearance might be due to steric effects. No definite conclusion could be reached as to the nature of the structure from the infrared spectrum of the citrate.

L. Attempted Preparation of 2-Diethylaminoethyl Phenylcyclohexylthiolglycolate

1. **Method I**

Benzoylformyl chloride (II-85) was prepared as indicated on Chart VII. The addition of a solution of \( \text{N,N-diethylaminoethanethiol} \) in ether to a solution of II-85 in benzene showed little indication of any reaction even on three hours refluxing. By increasing the period of refluxing to eight hours, there was obtained a compound which even after several recrystallizations softened before finally melting at 244-246°. The compound obtained did not agree in composition with II-93. It could be a mixture of sulfide and disulfide. This route was abandoned.

\[
\text{COCOCl} + \text{HSCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2 \rightarrow \text{COCO-SCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2\cdot\text{HCl}
\]

2-Diethylaminoethanethiol (II-92) was prepared by two different routes. One of them was due to Gilman and coworkers. Sodium hydrosulfide, prepared by saturating molten sodium sulfide nonahydrate with hydrogen sulfide, was refluxed with freshly prepared 2-diethylaminoethyl chloride in an inert
atmosphere to give II-92, b.p. 64-67°/23 mm., in yields ranging from 0 to 31 per cent. The more convenient method for the preparation of II-92, due to Albertson and Clinton, involved 2-diethylaminoethyl chloride hydrochloride (II-3) and thiourea (II-94).

\[
\begin{align*}
(C_2H_5)_2N\cdot CH_2CH_2Cl \cdot HCl + NH_2 \cdot S \cdot \text{NH}_2 & \xrightarrow{C_2H_5OH} (C_2H_5)_2N\cdot CH_2CH_2-S \cdot \text{NH}_2\cdot 2HCl \\
\text{II-3} & \quad \text{II-94} \\
& \quad \text{II-95} \\
& \quad \text{II-96}
\end{align*}
\]

The isothiocyanate salt (II-95) was basified and the mercaptan obtained was not isolated but was used in ether solution to lessen the amount of oxidation to the sulfide.

2. **Method II**

Another approach to the preparation of 2-diethylaminoethyl phenylcyclohexylthiolglycolate was made as follows:

\[
\begin{align*}
\text{C}_6\text{H}_5\text{H} & \xrightarrow{\text{PCl}_5} \text{C}_6\text{H}_5\text{Cl} \\
\text{II-39} & \quad \text{II-76} \\
\text{C}_6\text{H}_5\text{H} & \xrightarrow{\text{dilute HCl}} \text{C}_6\text{H}_5\text{H} \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{H} \\
\text{C}_6\text{H}_5\text{H} & \xrightarrow{\text{dilute HCl}} \text{C}_6\text{H}_5\text{H} \\
\text{II-98} & \quad \text{II-97} \\
\text{C}_6\text{H}_5\text{H} & \xrightarrow{\text{catalyst, H}_2} \text{C}_6\text{H}_5\text{H} \\
\text{II-99}
\end{align*}
\]
The procedure of Kolloff, Hunter, Woodruff and Moffett$^{117}$ was followed. The reaction of 1,1-diphenyl-1-chloroacetyl chloride, (II-76), with 2-diethylaminoethanethiol, (II-92), followed by hydrolysis of the alpha chloro group gave the compound, II-98. An attempt was made without success to half-hydrogenate II-98 in pure glacial acetic acid using platinum catalyst. Five per cent rhodium on alumina was next used without any better results.

By means of palladium on charcoal or barium sulfate, thiophene and certain of its derivatives have been reduced$^{118}$ at room temperature at 20-25 lb. per sq. in. An attempt was therefore made to half-hydrogenate II-98 using palladium on barium sulfate. It resulted in failure.

M. Preparation of 2-Diethylaminoethyl Phenyl-$\Delta^2$-cyclohexenylacetate Hydrochloride

The series of reactions adopted for the preparation of 2-diethylaminoethyl phenyl-$\Delta^2$-cyclohexenylacetate hydrochloride (II-106) is shown on Chart VIII. Ethyl phenylmalonate (II-103) was produced by the method of Levene and Meyer$^{119}$ through the action of ethyl oxalate, (II-101), on ethyl phenylacetate, (II-100), in the presence of sodium ethoxide and subsequently heating the ester (II-102) thus formed. The procedure of Kolloff, Hunter, Woodruff and Moffett$^{120}$ was followed for the preparation of phenyl-$\Delta^2$-cyclohexenylacetic acid, (II-105), from II-103. The ester hydrochloride (II-106) obtained by esterification of II-105 melted at 156-157°.
CHART VIII
PREPARATION OF 2-DIETHYLAMINOETHYL PHENYL-Δ²-CYCLOHEXYLACETATE HYDROCHLORIDE

\[
\begin{align*}
\text{C}_{6}\text{H}_5\text{CH}_2\text{COC}_2\text{H}_5 & + (\text{COC}_2\text{H}_5)_2 \quad \rightarrow \quad \text{C}_2\text{H}_5\text{ONa} \\
\text{II-100} & \quad \text{II-101}
\end{align*}
\]

\[
\begin{align*}
\text{C}_{6}\text{H}_5\text{CH(}\text{COC}_2\text{H}_5\text{)COCOC}_2\text{H}_5 & \rightarrow \Delta \\
\text{II-102} & \\
\text{C}_{6}\text{H}_5\text{OH(}\text{COC}_2\text{H}_5\text{)}_2 & + \text{CO} \\
\text{II-103} & \\
1) & \quad \text{C}_6\text{H}_5\text{Br} \\
2) & \quad \text{NaOC}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{C}_{6}\text{H}_5\text{CHCOC}_2\text{H}_5 & \rightarrow 1) \text{KOH} \\
\text{II-104} & \\
2) & \quad \text{C}_2\text{H}_5\text{OH} \\
3) & \quad \text{H}^+
\end{align*}
\]

\[
\begin{align*}
\text{C}_{6}\text{H}_5\text{CHCOOH} & \rightarrow (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{Cl} \\
\text{II-105} & \quad \text{II-106}
\end{align*}
\]
N. Preparation of 2-Diethylaminoethyl Phenyl-$\Delta^2$-cyclohexenyglycolate Hydrochloride

2-Diethylaminoethyl phenyl-$\Delta^2$-cyclohexenyglycolate hydrochloride was prepared by the following route:

\[
\begin{align*}
\text{II-107} & \rightarrow 1) \text{SOCl}_2 \\
& \rightarrow 2) \text{Br}_2 \\
& \rightarrow 3) \text{Dioxane} \\
& \rightarrow 4) 10\% \text{ NaOH}
\end{align*}
\]

Attempts to convert phenyl-$\Delta^2$-cyclohexenyacetic acid to 1-phenyl-\(1-(2,3\)-dibromocyclohexyl\)-1-bromoacetic acid were not successful by the method of Stevens and Lenk\textsuperscript{104} even at elevated temperatures. The compound isolated had the elemental analysis of phenyl-2,3-dibromocyclohexylacetic acid, a fact which indicates the failure to replace the tertiary hydrogen by a bromine atom.

The acid, II-107, was converted to phenyl-2,3-dibromocyclohexylglycolic acid (II-108) by a modification to the method of Schwenk and Papa.\textsuperscript{121} It, (II-107), was refluxed with excess of thionyl chloride followed by the addition of two moles of bromine for every mole of the
acid. On removing the solvent, the liquid was dissolved in dioxane and the alpha bromo group was hydrolyzed with 10 per cent aqueous sodium hydroxide solution to give the acid (II-108). Phenyl-Δ^2-cyclohexenylglycolic acid (II-109) was produced by a modification of the debromination method of Catravas using zinc and acetone. When the acid (II-109) was esterified, 2-diethylaminoethyl phenyl-Δ^2-cyclohexenylglycolate hydrochloride, (II-110), was obtained with a yield of 57.6 per cent.

O. Physiological Testing

1. Tests at the Army Chemical Center

Tests have been, or are being conducted, in the Physiology Division of the Directorate of Medical Research in the U. S. Army Chemical Laboratories at the Army Chemical Center, Maryland, by Drs. John F. O'Leary, Caroline Tum Suden and J. Henry Wills with the assistance of Messrs. Gerald E. Groblewski and Leonard Carlstrom. The test results on a number of compounds have not yet been received and hence the results reported here are not by any means complete.

The following tests were made:

(1) Ability to prevent mortality from a standard dose of an anticholinesterase compound which was given to six rabbits, which were then treated with the test compound. The effectiveness of the test compound is reported in terms of the mortality rate among animals treated with it as compared to those treated with atropine. The compounds are classified as less active, more active, or equal in activity to atropine.
(2) Ability to block blood pressure fall produced by a standard dose of acetylcholine. Tests were conducted on cats. A marked fall in the animal's blood pressure is produced on injecting acetylcholine. The activity of the compounds is reported in terms of their ability to block the pressure.

(3) Ability to block blood pressure fall produced by a standard dose of histamine. Tests were run on cats as in Test (2).

(4) Ability to block stimulation of gut and decrease tracheal air exchange. The test was run on animals in which a balloon had been inserted through a slit into the duodenum. The movement of the gut was then recorded by a special mechanical device. The ability of the compounds to block excitation of the gut by a standard dose of acetylcholine was recorded.

(5) Ability to produce changes in diameter of the pupil of the eye. The test was performed on rabbits and the diameter of the pupil was measured before and after administering a dose of the compound undergoing testing.

(6) Ability to produce anaesthesia of cornea. The degree of anaesthesia of cornea was determined by pressing the cornea of rabbits before and after the dose of the compound and observing how much pressure was required to produce blinking.

The results of these tests are summarized in Tables IX to XI in which the numbers are those of the compounds listed in Tables I, III, and VII. A part of these results has already been published.123,124
TABLE IX

ANTICHOLINESTERASE SCREENING (TEST NO. 1)

(Tests on Rabbits with Standard 2.0 Mg./Kg.* Unless Otherwise Stated)

<table>
<thead>
<tr>
<th>Compared to Atropine</th>
<th>More Active</th>
<th>Equally as Active</th>
<th>Less Active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1c</td>
<td>2a</td>
<td>12d</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4c</td>
<td>11a</td>
</tr>
<tr>
<td></td>
<td>21a</td>
<td>5c</td>
<td>18a</td>
</tr>
<tr>
<td></td>
<td>22a</td>
<td>6d</td>
<td>19d</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>7a</td>
<td>21a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8a</td>
<td>25c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9a</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10b</td>
<td>29a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11a</td>
<td>31a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13d</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>50a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17a</td>
<td>53a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>54a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>28a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>42a</td>
<td></td>
</tr>
</tbody>
</table>

*Compound 3 was too toxic to be tested by this dose.

a Test on rats.

b Tested at dose of 0.5 mg./kg.

c Test on rats and rabbits.

d Tested at dose of 1.0 mg./kg.
<table>
<thead>
<tr>
<th>No.</th>
<th>Dose Mg./Kg.</th>
<th>Effect on B.P. Fall in % After Acetylcholine (2.5(\mu))</th>
<th>Effect on B.P. Fall in % After Histamine (1.5(\mu))</th>
<th>Effect of Compound on Gut</th>
<th>Effect of Compound on B.P.</th>
<th>Effect of Compound on Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>- 62</td>
<td>- 47</td>
<td>None</td>
<td>None</td>
<td>- Rate</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>- 77</td>
<td>- 58</td>
<td>None</td>
<td>None</td>
<td>- Depth, + rate</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>- 25</td>
<td>- 44</td>
<td>- 100%</td>
<td>- 5%</td>
<td>- Depth, - rate</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>- 49</td>
<td>0</td>
<td>None</td>
<td>None</td>
<td>+ Depth, - rate</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>- 50</td>
<td>- 17</td>
<td>None</td>
<td>None</td>
<td>+ Depth, - rate</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>- 6</td>
<td>+ 14</td>
<td>None</td>
<td>Slight fall</td>
<td>Brief apnea</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>+ 90</td>
<td>+ 38</td>
<td>Slight fall</td>
<td>- 15%</td>
<td>Apneusis</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>- 27</td>
<td>- 16</td>
<td>Slight fall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3.5</td>
<td>- 27</td>
<td>- 33</td>
<td>None</td>
<td>Slight fall</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>- 29</td>
<td>+100</td>
<td>Slight fall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.5</td>
<td>- 45</td>
<td>- 56</td>
<td>Tonus and rate increase</td>
<td>Fall 85% then rise to 211%</td>
<td>Temporary apnea then increase</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>+ 23</td>
<td>0</td>
<td></td>
<td>-12% (coupled beats)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0.5</td>
<td>+ 10</td>
<td>+ 10</td>
<td></td>
<td>-12%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0.5</td>
<td>+ 5</td>
<td>None</td>
<td>Tonus and rate decrease</td>
<td>Temporary fall (27%)</td>
<td>- Depth then two times increase,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>temporarily</td>
<td></td>
<td>- rate</td>
</tr>
<tr>
<td>15</td>
<td>7.5</td>
<td>- 27</td>
<td>- 4</td>
<td>- 100%</td>
<td>-24%</td>
<td>- Depth, + rate</td>
</tr>
<tr>
<td>16</td>
<td>4.0</td>
<td>- 25</td>
<td>None</td>
<td>- 100%</td>
<td>-30%</td>
<td>Apneusis</td>
</tr>
<tr>
<td>17</td>
<td>0.5</td>
<td>- 6</td>
<td>- 22</td>
<td>None</td>
<td>Temporary fall (22%)</td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>0.5</td>
<td>None</td>
<td>- 8</td>
<td>Slight decrease</td>
<td>Temporary fall (100%)</td>
<td>- Depth then +,</td>
</tr>
</tbody>
</table>
# TABLE I

BLOOD PRESSURE, GUT, AND RESPIRATION EFFECTS (TESTS 2, 3, AND 4) (Continued)

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose Mg./Kg.</th>
<th>Effect on B.P. Fall in % After Acetylcholine (2.5%)</th>
<th>Effect on B.P. Fall in % After Histamine (1.5%)</th>
<th>Effect of Compound on Gut</th>
<th>Effect of Compound on B.P.</th>
<th>Effect of Compound on Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>0.5</td>
<td>+33</td>
<td>-17</td>
<td>-</td>
<td>Slight fall</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>5.5</td>
<td>-5</td>
<td>None</td>
<td>None</td>
<td>-14%</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>0.5</td>
<td>-33</td>
<td>+25</td>
<td>None</td>
<td>Moderate fall</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>2.5</td>
<td>-24</td>
<td>+9</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>23</td>
<td>7.0</td>
<td>-55</td>
<td>+5</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>25</td>
<td>0.5</td>
<td>-8</td>
<td>-59</td>
<td>Slight fall</td>
<td>-24%</td>
<td>+Rate</td>
</tr>
<tr>
<td>26</td>
<td>9.5</td>
<td>-13</td>
<td>-9</td>
<td>Slight fall</td>
<td>+Rate</td>
<td>+Depth, + rate</td>
</tr>
<tr>
<td>27</td>
<td>6.0</td>
<td>+10</td>
<td>+17</td>
<td>Immediate depressor</td>
<td>-11%</td>
<td>None</td>
</tr>
<tr>
<td>28</td>
<td>7.0</td>
<td>-30</td>
<td>-6</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>29</td>
<td>0.5</td>
<td>0</td>
<td>-20</td>
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<td>None</td>
<td>None</td>
</tr>
<tr>
<td>30</td>
<td>0.5</td>
<td>+20</td>
<td>+51</td>
<td>None</td>
<td>None</td>
<td>-Depth, + rate</td>
</tr>
<tr>
<td>31</td>
<td>0.5</td>
<td>-37</td>
<td>-21</td>
<td>Tonus decrease then</td>
<td>-18%</td>
<td>None</td>
</tr>
<tr>
<td>33</td>
<td>0.5</td>
<td>-38</td>
<td>-20</td>
<td>None</td>
<td>+25%</td>
<td>Slight fall</td>
</tr>
<tr>
<td>34</td>
<td>0.5</td>
<td>0</td>
<td>+16.7</td>
<td>None</td>
<td>-19%</td>
<td>Slight slowing of heart</td>
</tr>
</tbody>
</table>
TABLE X

BLOOD PRESSURE, GUT, AND RESPIRATION EFFECTS (TESTS 2, 3, AND 4) (Continued)

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose Mg./Kg.</th>
<th>Acetylcholine (2.5%)</th>
<th>Histamine (1.5%)</th>
<th>Effect on B.P. Fall in % After</th>
<th>Gut</th>
<th>Effect of Compound on B.P.</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.5</td>
<td>-13</td>
<td>+40</td>
<td>None</td>
<td></td>
<td>Slight depression</td>
<td>None</td>
</tr>
<tr>
<td>41</td>
<td>0.5</td>
<td>+3</td>
<td>-21</td>
<td>Tomus and rate increase greatly</td>
<td></td>
<td>Temporary fall (17%)</td>
<td>None</td>
</tr>
<tr>
<td>42</td>
<td>0.5</td>
<td>-75</td>
<td>+27</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>0.5</td>
<td>-6</td>
<td>None</td>
<td>- - -</td>
<td></td>
<td>Slight fall</td>
<td>-20%</td>
</tr>
<tr>
<td>44</td>
<td>0.5</td>
<td>+55</td>
<td>+11</td>
<td>None</td>
<td></td>
<td></td>
<td>Brief hypopnea</td>
</tr>
<tr>
<td>45</td>
<td>0.5</td>
<td>-19</td>
<td>-40</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>+ Depth, + rate</td>
</tr>
<tr>
<td>46</td>
<td>0.5</td>
<td>-20</td>
<td>-83</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>+ Rate</td>
</tr>
<tr>
<td>47</td>
<td>0.5</td>
<td>-5</td>
<td>-20</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>Slight slowing of heart</td>
</tr>
<tr>
<td>48</td>
<td>0.5</td>
<td>-15</td>
<td>-7</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>Brief hypopnea followed by hypernea</td>
</tr>
<tr>
<td>50</td>
<td>0.5</td>
<td>-36</td>
<td>-37</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>None</td>
</tr>
<tr>
<td>51</td>
<td>0.5</td>
<td>+5</td>
<td>+23</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>None</td>
</tr>
<tr>
<td>52</td>
<td>0.5</td>
<td>+4</td>
<td>0</td>
<td>None</td>
<td></td>
<td>Slight fall</td>
<td>None</td>
</tr>
<tr>
<td>53</td>
<td>0.5</td>
<td>-3</td>
<td>-7</td>
<td>Fall</td>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>54</td>
<td>0.5</td>
<td>+23</td>
<td>0</td>
<td>Slight fall</td>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>55</td>
<td>0.5</td>
<td>-13</td>
<td>0</td>
<td>Temporary fall</td>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>56</td>
<td>0.5</td>
<td>None</td>
<td>-7</td>
<td>None</td>
<td></td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
### TABLE XI

**EYE EFFECTS**<sup>a</sup> (TESTS 5 AND 6)

<table>
<thead>
<tr>
<th>Mydriasis</th>
<th>Moderate Activity</th>
<th>Least Activity</th>
<th>No Definite Effect</th>
<th>Miosis Active</th>
<th>Local Irritation Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>4</td>
<td>21</td>
<td>28</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
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<tr>
<td></td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>25</td>
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<td>8</td>
<td>14</td>
<td>19</td>
<td>19</td>
<td>19</td>
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<tr>
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<td>1</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
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<td>5</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>11</td>
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<td></td>
<td>4</td>
<td>14</td>
<td>16</td>
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<td>16</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>19</td>
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<td>19</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>21</td>
<td>21</td>
<td>42</td>
<td>42</td>
</tr>
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</tr>
<tr>
<td></td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup>No compound produced local anaesthesia.
2. **Tests at Parke, Davis and Company**

Tests were made in the laboratories of Parke, Davis and Company, Detroit, Michigan through contact with Dr. Martin L. Black. The following tests were performed:

(1) **Tests for cerebral stimulation of rats.** This test was made by the "jiggle cage" method. The compounds were administered orally or by injection, and the rat was placed in a cage suspended by a spring. The total motion of the cage was integrated over a given period of time. The results of this test were compared with that of "Suavitil," a Merck product, which is now being marketed as a tranquilizer. It is to be stressed that these are only preliminary screening tests and that a satisfactory evaluation can be done only through clinical tests.

(2) **Tests for atropine-like activity.** The test is performed on a rabbit by administering a dose of compound, and measuring the change in the diameter of the eye pupil after a definite length of time. The ideal compound from the standpoint of tranquilizing activity on humans is expected to be one which gives a high cerebral stimulation activity but a low or negligible atropine-like activity.

(3) **Tests for antibacterial activity.** None of the few compounds (Nos. 6, 10, 12, 17, 20, 23, 24, 26, 27, 28, and 30) tested exhibited any antibacterial activity.

The results of the cerebral stimulation and atropine-like activity tests are given in Tables XII and XIII in which the numbers are those of the compounds listed in I, III and VII.
**TABLE XII**

TESTS FOR CEREBRAL STIMULATION (PARKE, DAVIS AND COMPANY)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity at Indicated Dosage (Mg./Kg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4+ 4+ 4+ 4+ 4+ 4+ 1+ 1+ 0</td>
</tr>
<tr>
<td>3</td>
<td>Lethal Lethal 4+ 4+ 3+ 2+ 2+ 0</td>
</tr>
<tr>
<td>4</td>
<td>4+ 4+ 4+ 4+ 4+ 4+ 1+ 0</td>
</tr>
<tr>
<td>5</td>
<td>4+ 4+ 4+ 4+ 4+ 3+ 3+ 1+</td>
</tr>
<tr>
<td>6</td>
<td>2+ 1+</td>
</tr>
<tr>
<td>7</td>
<td>Lethal (Oral) 0</td>
</tr>
<tr>
<td>8</td>
<td>2+ 0</td>
</tr>
<tr>
<td>9</td>
<td>1+ 0</td>
</tr>
<tr>
<td>10</td>
<td>Lethal 4+ 4+ 4+ 1+ 0</td>
</tr>
<tr>
<td>11</td>
<td>2+ 0</td>
</tr>
<tr>
<td>12</td>
<td>0 0</td>
</tr>
<tr>
<td>15</td>
<td>(Oral) (Oral) 0</td>
</tr>
<tr>
<td>16</td>
<td>0 0</td>
</tr>
<tr>
<td>17</td>
<td>0 0</td>
</tr>
<tr>
<td>18</td>
<td>(Oral) (Oral) 0</td>
</tr>
<tr>
<td>19</td>
<td>0 0</td>
</tr>
<tr>
<td>20</td>
<td>0 0</td>
</tr>
<tr>
<td>21</td>
<td>0 0</td>
</tr>
<tr>
<td>22</td>
<td>1+ 0</td>
</tr>
<tr>
<td>23</td>
<td>(Lethal) 0</td>
</tr>
<tr>
<td>24</td>
<td>2+ 0</td>
</tr>
<tr>
<td>25</td>
<td>0 0</td>
</tr>
<tr>
<td>26</td>
<td>0 0</td>
</tr>
<tr>
<td>27</td>
<td>0 0</td>
</tr>
<tr>
<td>28</td>
<td>0 0</td>
</tr>
<tr>
<td>29</td>
<td>0 0</td>
</tr>
<tr>
<td>30</td>
<td>(Lethal) (Lethal) 4+ 4+ 4+ 4+ 4+ 2+ 2+ 0</td>
</tr>
<tr>
<td>31</td>
<td>4+ 4+ 4+ 4+ 4+ 4+ 4+ 4+ 0</td>
</tr>
<tr>
<td>32</td>
<td>4+ 4+ 4+ 4+ 4+ 4+ 4+ 0</td>
</tr>
<tr>
<td>**</td>
<td>(Lethal) 1+</td>
</tr>
<tr>
<td>Suavitil**</td>
<td>4+ 4+ 1+ 4+ 4+ 4+ 4+ 3+ 1+</td>
</tr>
</tbody>
</table>

*CH₂O—O—CH₂CH₂—N(C₂H₅)₂·HCl, a previously known compound.

**OCH₂CH₂N(C₂H₅)₂·HCl
TABLE XIII

TESTS FOR ATROPINE-LIKE ACTIVITY (PARKE, DAVIS AND COMPANY)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dosage (Mg./Kg.)</th>
<th>Atropine-Like Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25</td>
<td>1/250</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Convulsions 1/250</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>1/125</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1/125</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>Less than 1/500</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>Less than 1/500</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>Less than 1/500</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
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<td>1/250</td>
</tr>
<tr>
<td>31</td>
<td>25</td>
<td>1/250</td>
</tr>
</tbody>
</table>

"Suavitil"
3. **Tests at the National Service Center**

Experiments were conducted at the National Service Center, National Institutes of Health for anti-tumor tests on mice. Among the compounds (Nos. 8, 21, 24, and 28) tested on the tumor systems, sarcoma, adenocarcinoma, and leukemia, none showed any significant activity.

4. **Summary of the Test Results**

Though all compounds described in this resume have not been tested, a summary of important results will be reported here.

(1) Among the compounds tested, five (Nos. 1, 20, 21, 22 and 33) have proved "more effective than atropine" in the anticholinesterase screening tests and several more have been "equally effective" (see Table IX).

(2) Of the compounds tested for ability to antagonize the functional effects of acetylcholine and histamine, two (Nos. 2 and 42) are especially active against acetylcholine and four (Nos. 2, 11, 23 and 46) are particularly active against histamine. The compound No. 23 is of interest because it has almost no anticholinergic effect, but is moderately effective as an antihistaminic. The compound No. 42 is anticholinergic, but enhances the activity of histamine. Of these functionally active compounds, No. 11 has marked side effects on blood pressure and respiration.

(3) Several compounds were tested for effects on the eye pupil; some (see Table XI) were active in producing mydriasis; only three (Nos. 21, 28 and 33) of these also produced local irritation.
(4) Of the compounds tested for cerebral stimulation in rats, two (Nos. 4 and 30) are almost as active as the commercial product "Suavitil," and possess only 1/5 to 1/10 as great atropine-like activity. (see Table XIII).

5. **Structure and Physiological Activity of Compounds**

As mentioned earlier, the physiological tests on compounds are but partially complete. Moreover, quantitative data on these tests are not available to make thorough comparative study.

On examining Table IX it is evident that the anticholinesterase activity decreases in the order of methyl substitution: 2-methyl (compound No. 1), 3-methyl (compound No. 2) and 4-methyl (compound No. 3). The compound No. 3 is too toxic even to test by a comparable dose. However, if a phenyl group is substituted in the 4-position, the activity of the compound improves considerably (No. 20, Table IX) and becomes more active than atropine.

On half-hydrogenation of the 4-methyl compound (No. 3), the product (No. 33) becomes more active than atropine. Complete hydrogenation, however, does not increase the activity as No. 42 shows an activity equal to that of atropine. The 4,4'-dimethyl substituted compound (No. 23) is also as active as atropine.

The half-hydrogenated product (No. 31) of the 2-methyl substituted compound (No. 1) is less active than atropine. It is interesting to note that the opposite effect is observed in the case of 4-methyl substituted compounds.

The product (No. 40) obtained on hydrogenating compound (No. 1) is as active as atropine.
The 2,6-dimethyl compound (No. 7) is as active as atropine while the 2,2'-dimethyl compound (No. 21) is more active. The activity of No. 21, however, drops on hydrogenation whereas the activity of No. 7 does not.

However, no general conclusions can be drawn from these observations.
CHAPTER III

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point apparatus by means of which data could be obtained with an accuracy of 1° to 2°.

A. Esters of Substituted Benzilic Acids

1. 2-Diethylaminoethyl Chloride

2-Diethylaminoethyl chloride was obtained by the method of Slotta and Behnisch.\(^\text{76}\) 2-Diethylaminoethanol, 30 g., which was previously purified by distillation and collection of the liquid boiling at 160-161°, was added to 300 ml. of benzene. The mixture was cooled in an ice bath and 60 g. of pure thionyl chloride added dropwise with constant stirring. The mixture was refluxed on a steam bath for two hours, cooled and filtered. This gave a yield of 41.5 g. of light brownish crystals.

The chloride of 2-diethylaminoethyl chloride hydrochloride was obtained according to the method of Gilman and Shirley.\(^\text{77}\) Crude 2-diethylaminoethyl chloride hydrochloride weighing 72.0 g. was treated with 100 ml. of 40 per cent aqueous sodium hydroxide solution. The liberated chloride was extracted thrice with ether. The ether extract was dried over anhydrous magnesium sulfate and distilled. The distillate, boiling at 147-148°, was collected. The 2-diethylaminoethyl chloride thus obtained, which weighed 37 g., was mixed with an equal
amount by weight of dry xylene to prevent dimerization and kept in the cold room.

2. General Method for the Preparation of 2-Diethylaminoethyl Ester Hydrochlorides

The method described by Blicke and Grier\textsuperscript{78} was followed. Equimolar quantities of the acid and 2-diethylaminoethyl chloride were refluxed for twelve hours in isopropyl alcohol (5 l. per mole of the acid used) which was previously dried by refluxing for eight hours and subsequently distilling over calcium oxide. Cooling produced a solid which was removed by filtration and the filtrate was treated with dry ether to complete the precipitation of the hydrochloride. Recrystallization several times from ethanol-ether mixture gave the pure product which was washed with dry ether, dried, and analyzed. A summary of the ester hydrochlorides of substituted benzilic acids thus prepared is given in Table I. The substituted benzilic acids were obtained from previous research.\textsuperscript{79}

3. Attempted Preparation of 2,2'-Diethylbenzilic Acid

a. \textit{o}-Ethyliodobenzene. The method employed was analogous to that of Lucas and Kennedy.\textsuperscript{82} \textit{o}-Ethylaniline, 212 g. (1.75 m.), which was purified by distillation and collection at 213-214\textdegree, was dissolved in a mixture of 1 l. of concentrated hydrochloric acid and 1 l. of water. The mixture was placed in a 5-l. flask in an ice bath. The solution was stirred mechanically and the temperature was kept at 0\textdegree. A solution of 155 g. (2.2 m.) of sodium nitrite in 850 ml. of ice cold water was added
dropwise and the temperature of the mixture was maintained at 0°. An excess of nitrous acid as indicated by starch-iodide paper had to be present. A solution of 372 g. of potassium iodide in 600 ml. of water was added slowly with constant stirring resulting in evolution of nitrogen.

After standing overnight, the mixture was heated on a steam bath to complete the evolution of nitrogen. On cooling, the upper aqueous layer was decanted and the organic layer was rendered slightly alkaline with dilute sodium hydroxide solution. o-Ethyliodobenzene obtained on subjecting the organic layer to steam distillation was dried over magnesium sulfate and distilled in vacuo. There was obtained 236 g. of liquid, b.p. 60°/1.5 mm. (Mascarelli and Longo\textsuperscript{126} give 221°).

b. o-Ethylbenzaldehyde. (1) Method I. The procedure adopted was due to Smith and Nichols\textsuperscript{84} and also to Dornfeld and Coleman.\textsuperscript{127} Magnesium turnings, 18.25 g. (0.78 gram atoms), were suspended in 350 ml. of dry ether in a 2-l., three-necked flask fitted with a reflux condenser, mercury sealed stirrer and a dropping funnel. A solution of 175 g. (0.75 m.) of o-ethyliodobenzene in 175 ml. of dry ether was added dropwise. A tiny crystal of iodine was initially added to start the reaction. The mixture was then refluxed for two hours. At the end of this period, 186 g. of pure ethyl orthoformate was added over a period of about twenty to twenty-five minutes. The reaction mixture was refluxed again for six hours and let stand overnight.

Ether was removed by distillation on the steam bath. The mixture was cooled and treated with 600 ml. of 10 per cent hydrochloric acid with
mechanical agitation. The upper brown layer was separated and refluxed for six hours with a solution of 75 g. of concentrated sulfuric acid in 500 ml. of water. The mixture was cooled and the upper layer was isolated and subjected to steam distillation. The oily layer obtained from steam distillation was treated with a saturated solution of sodium bisulfite and stirred. The solid product obtained was subsequently treated with the solution of sodium bicarbonate until there was no evidence of any reaction. The solution was heated for about ten minutes and the oily layer was separated, washed with water, dried over anhydrous magnesium sulfate and distilled. There was obtained 41.5 g. (45.1 per cent) of \(\text{\(p\)}\)-ethylbenzaldehyde, b.p. 210-211° (Mayer and English\(^8^3\) give \(211°/749\) mm.).

(2) Method II. In this method the action of N-methylformanilide on the organolithium compound was used for the preparation of the corresponding aldehyde. The method is essentially due to Shirley and Danzig.\(^{8^5}\) \(\text{\(n\)}\)-Butyllithium was prepared according to the procedure of Gilman and coworkers.\(^{8^7}\) Into a three-necked, 1-l. flask equipped with a dropping funnel and condenser fitted with a calcium chloride tube, was placed 200 ml. of ether previously dried over sodium. While sweeping the apparatus with nitrogen, 8.6 g. (1.23 gram atoms) of lithium wire was washed with dry ether and cut into small pieces, which were directly introduced into the flask. With stirring, about 30 drops of a solution of 68.5 g. (0.5 m.) of \(\text{\(n\)}\)-butyl bromide (previously purified by distillation) in 100 ml. of dry ether was added from a dropping funnel and the reaction mixture was then cooled to about \(-10°\) with a "Dry Ice"-acetone
bath maintained at about -30° to -40°. The remainder of \(n\)-butyl bromide was added over a period of thirty minutes. Stirring was continued for two hours with the temperature of the acetone-"Dry Ice" bath being maintained at -30° to -40°. The reaction mixture was then allowed to warm up to room temperature, after which it was filtered into a dropping funnel through an adaptor plugged with glass wool.

The method of Gilman and coworkers\(^86\) was used for the halogen-metal interconversion reaction using \(n\)-butyllithium. \(\alpha\)-Ethyl iodobenzene, 23.2 g. (0.1 m.), in 100 ml. of dry ether was placed in a three-necked flask fitted with a reflux condenser, mechanical stirrer and the dropping funnel containing \(n\)-butyllithium described above. \(n\)-Butyllithium was added with stirring at a rate so that the ether refluxed. When all the \(n\)-butyllithium was added, the mixture was stirred for ten to fifteen minutes more.

A solution of 13.5 g. of N-methylformanilide in 100 ml. of dry ether was added. The mixture was allowed to stand for one-half hour before it was poured into an excess of dilute (approximately 4 N.) sulfuric acid. After separation of the organic layer, the aqueous layer was extracted twice with ether. The combined ether extracts were washed with a dilute solution of sodium carbonate, water, and then dried over anhydrous magnesium sulfate. On distillation, there was obtained 6.8 g. (50.8 per cent) of oil, b.p. 210-211° (Mayer and English\(^83\) report 210°/749 mm.).

(3) **Method III.** The method analogous to that of Zaheer and Faseeh\(^88\) was followed. \(\alpha\)-Ethyl iodobenzene, 23.2 g. (0.1 m.), in 100
ml. of dry ether was added dropwise to 2.5 g. (0.1 gram atom) of magnesium turnings in 75 ml. of dry ether. A crystal of iodine was added to initiate the reaction. After the addition was complete, the reaction mixture was refluxed for two hours, during which a solution of 13.5 g. of N-methylformanilide in ether was added dropwise. A copious white precipitate obtained in the beginning turned into a sticky solid mass. Stirring was continued for an hour more. On cooling, dilute hydrochloric acid (10 per cent) was added followed by large quantities of crushed ice. The ethereal layer was separated and the aqueous layer was extracted twice with ether. The combined ethereal solution was dried and distilled under reduced pressure. The yield was 8.2 g. (61.1 per cent) of o-ethylbenzaldehyde, b.p. 82-84°/5.5 mm. (Mayer and English give 211°/749 mm.).

c. Attempted benzoin condensation of o-ethylbenzaldehyde. In a 250-ml., round-bottomed flask, a solution of 20 g. of o-ethylbenzaldehyde, 5 g. of potassium cyanide in 40 ml. of ethanol and 40 ml. of water was refluxed for two hours. On cooling, no crystals were obtained. Upon dilution with water, an oil separated which failed to crystallize. The mixture was extracted twice with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. The ether was evaporated on a steam bath and the residual oil obtained failed to crystallize.

d. Attempted preparation of 2,2'-diethylbenzil. A mixture of 5 g. of the oil obtained in A.3.c., 15 g. of copper sulfate pentahydrate, 100 ml. of pyridine, and 30 ml. of water was refluxed for four hours. The mixture was poured into 500 ml. of water containing some ice. No
solid separated. Thus 2,2'-diethylbenzil could not be isolated. By re­
peating the experiment with an increase in the reflux period to six 
hours, the same results were obtained, although in this case, some tar was 
produced.

e. Attempted preparation of 2,2'-diethylbenzilic acid. The method 
of Ballard and Dehn$^90$ was used. In a 250-ml., three-necked flask fitted 
with a mechanical stirrer, a solution of 15 g. of sodium hydroxide, 10 g. 
of potassium bromate and 30 ml. of water was placed. Ten grams of the 
oil obtained in A.3.c. was added and the mixture was stirred while being 
heated on the steam bath. As heating continued, the mixture thickened 
and more water was added from time to time. The heating and stirring 
were continued for seven and one-half hours. A test portion of the re-
action was, however, incompletely soluble in water. The mixture was 
poured into cold water containing some crushed ice. An oil separated. 
The aqueous layer was removed and the oily layer was extracted twice 
with a cold dilute solution of sodium hydroxide. The collected alkaline 
extracts combined with the main aqueous layer was extracted with ether. 
The alkaline solution was acidified with dilute hydrochloric acid. The 
organic acid obtained on crystallization from hot water melted at 63.5–
64.5° and weighed 1 g. Its molecular weight determined through its 
neutralization equivalent was 151.7.

**Anal.** Calcd. for C$_{18}$H$_{20}$O$_3$: C, 76.05; H, 7.09.

*Found:* C, 72.79; H, 6.63.

The values found above for carbon and hydrogen are in fair agree-
ment with the calculated values for o-ethylbenzoic acid (C, 72.00; H,
6.72). Further, the melting point of o-ethylbenzoic acid (Gabriel and Michael\textsuperscript{128} report 62°; Zincke\textsuperscript{91} gives 68°) is also in agreement with the observed values of the above acid. The organic acid obtained was evidently o-ethylbenzoic acid.

In the light of these results, the experiment in A.3.e. was repeated a few times while varying the heating period from four to sixteen hours instead of seven and one-half hours. In all cases, o-ethylbenzoic acid and not the desired 2,2'-diethylbenzilic acid, was obtained.

B. Esters of Substituted Phenylcyclohexylglycolic Acids

1. \textbf{General Method for the Catalytic Half-hydrogenation of the Amino Ester Hydrochlorides of Alkyl Substituted Benzilic Acids}

To the acetic acid solutions of 2 to 3 grams of the hydrochlorides of the 2-diethylaminoethyl ester of alkyl substituted benzilic acid described in A, 0.4 g. of Adams' platinum catalyst was added. Only a minimum amount of glacial acetic acid was used to dissolve the hydrochloride. Each solution was shaken in a low pressure hydrogenator until the drop in pressure observed was equivalent to 3.4 moles which was a slight excess over that required for the half-hydrogenation of one mole of the hydrochloride. The catalyst was removed by filtration and the acetic acid was evaporated \textit{in vacuo}. The residue was digested in hot absolute ethanol, decolorized with Norit, if necessary, and filtered. On cooling, dry ether was added and the precipitate obtained was recrystallized from an alcohol-ether mixture until a sharp melting product was obtained. Data on these compounds are listed in Table III.
2. Synthesis of the Ester Hydrochloride of \(4\)-Methylphenylcyclohexyl-glycolic Acid

a. \(4\)-Methylbenzoyl chloride. \(p\)-Toluic acid, 95 g., and 70 ml. of thionyl chloride were refluxed on a steam bath for three hours. The excess of thionyl chloride was removed by distillation and the residue was distilled under reduced pressure. The liquid distilling over at 57°/0.3 mm. was collected (Hlicke and Lilienfeld\(^1\)) give 117-120°/24 mm.; McElvain and Carney\(^2\) give 106°/12 mm.). The \(4\)-methylbenzoyl chloride thus obtained weighed 100.5 g. (93.1 per cent).

b. \(4\)-Methylbenzoyl cyanide. The method is essentially that of Oakwood and Weisgerber.\(^3\) \(4\)-Methylbenzoyl chloride, 37 g. (0.24 m.), and 26.5 g. (0.25 m.) of previously dried cuprous cyanide were placed in a 250-ml., round-bottomed flask equipped with an air condenser. The two components were well mixed and heated gradually in a Wood's metal bath. The temperature of the bath was maintained at 250-260° for one and one-half hours. During the heating, the flask was frequently removed from the bath (about every fifteen minutes) and the contents were thoroughly mixed by vigorous shaking. The contents of the flask were distilled at atmospheric pressure. The fraction distilling at 222-224° was collected. The \(4\)-methylbenzoyl cyanide obtained on cooling weighed 15.1 g. (43.5 per cent), m.p. 50-51° (Soderbaum\(^4\) gives 52°).

c. Ethyl \(4\)-methylphenylglyoxylate. The method of Claisen\(^5\) was adopted here. \(4\)-Methylbenzoyl cyanide, 23 g. (0.16 m.), in 100 ml. of absolute ethanol was saturated with hydrogen chloride, during which
the temperature of the solution was maintained below 10° by keeping the
flask in an ice bath. The mixture was then allowed to stand in the
cold room for eight days. It was poured into a large quantity of water
and the ester which separated was extracted thrice with ether. The
combined ether extracts were washed with a dilute solution of sodium
bicarbonate, dried over anhydrous magnesium sulfate and distilled under
reduced pressure. There was obtained 15.3 g. (50.2 per cent) of ethyl
4-methylphenylglyoxylate, b.p. 124-126°/3.5 mm. (Auwers\textsuperscript{133}
gives 154-156°/18 mm.).

The phenylhydrazone derivative prepared from ethyl 4-methylphenyl-
glyoxylate, on crystallization from ligroin, melted at 94° (Auwers\textsuperscript{133}
gives 94°).

d. 4-Methylphenylcyclohexylglycolic Acid. A Grignard reagent,
cyclohexylmagnesium chloride, was prepared as described by Gilman and
Zoellner.\textsuperscript{134} Magnesium turnings, 1.98 g. (0.08 gram atoms) were barely
covered with sodium-dried ether. Initially pure chlorocyclohexane was
added in sufficient amount (1.5 to 2 g.) to give an optimum concentra-
tion of the chloride. On adding a tiny crystal of iodine, heat was
applied by the steam bath without stirring, and these conditions were
maintained for five to ten minutes after the iodine color had dis-
appeared. Reaction having set in, sufficient ether was added to cover
the magnesium while it was stirred, and the remainder of halide in ether
was added. Thus a total of 9.63 g. (0.08 m.) of chlorocyclohexane in
ether was added. The stirring and refluxing were continued for another
forty minutes. The Grignard reagent thus prepared was transferred into
a dropping funnel with as little exposure to the atmosphere as possible.

The Grignard reagent was added dropwise to a solution of 10.4 g. (0.054 m.) of ethyl 4-methylphenylglyoxylate in dry ether. The mixture was gently refluxed for one hour before pouring into a mixture of crushed ice and dilute sulfuric acid.

The organic layer was separated and the aqueous layer was extracted a few times with ether. The combined ether extracts were washed with a solution of sodium bicarbonate and water. They were then dried and distilled under reduced pressure. The ester obtained weighed 8.9 g. (59.6 per cent), b.p. 155-158°/2.8 mm.

Ethyl 4-methylphenylcyclohexylglycolate, 8.9 g., was refluxed overnight with 3 g. of sodium hydroxide, 25 ml. of water and 45 ml. of 95 per cent ethanol. The excess of alcohol was removed by distillation and the residual solution was poured into water. Any remaining alcohol was removed by evaporation on a steam bath. The solution was cooled and filtered to remove suspended impurities. The solution kept in the ice bath was acidified with dilute hydrochloric acid. The precipitated acid was crystallized first from benzene and then twice from drum-methanol. 4-Methylphenylcyclohexylglycolic acid, 5.2 g. (64.9 per cent), was obtained in the form of white crystals melting at 189-190°.


Found: C, 72.66; H, 8.04.

e. 2-Diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride. The general method described in A.2. was followed. The hydrochloride obtained was recrystallized a couple of times from an ethanol-
ether mixture and also from an acetonitrile-ether mixture. It melted at 206-207° and gave a yield of 93.5 per cent.

**Anal.** Calcd. for C_{21}H_{34}N_{03}Cl: C, 65.67; H, 8.93.

Found: C, 65.54; H, 9.00.

3. **Synthesis of the Ester Hydrochloride of 3,5-Dimethylphenylcyclohexylglycolic Acid**

   a. **Purification of 2,4-dimethylaniline.** The purification of technical-grade material was done as described by Shacklett.\(^{135}\) Four parts by weight of practical grade 2,4-dimethylaniline were mixed with one part by weight of glacial acetic acid and the mixture was allowed to stand overnight. The crystals were filtered off, washed with 80 per cent acetic acid, and recrystallized twice from 80 per cent acetic acid. 2,4-Dimethylaniline was regenerated from the crystals (its acetate) by use of an excess of 50 per cent sodium hydroxide solution. The amine layer was separated and distilled *in vacuo*. A colorless liquid distilling at 74-76°/3 mm. was collected.

   b. **3,5-Dimethylbromobenzene.** This bromobenzene was prepared by a modification of the method of Fieser and Heymann.\(^{95}\) 2,4-Dimethylaniline, which was purified as described above, 159 g. (1.31 m.), and 1250 ml. of concentrated hydrochloric acid were mixed in a 5-l., three-necked flask. While being stirred vigorously, the mixture was cooled in an ice bath to 5° to 10°. A solution of 70 ml. (210 g., 1.31 m.) of bromine in 125 g. of 48 per cent hydrobromic acid and 125 g. of concentrated hydrochloric acid was then added slowly. The temperature was kept below 20° and vigorous stirring was used throughout. The mixture was
then transferred to a 10-l. glass jar and heated (50-70°) until the orange color of bromine had disappeared. The mixture was then allowed to cool to room temperature and ice was added to lower the temperature below 0°. A solution of 109 g. of sodium nitrite in 300 ml. of water and ice was then added with vigorous stirring until the amine was completely diazotized, as indicated by a positive starch-potassium iodide paper test. Ice was added as needed to keep the temperature near 0-5°.

In a 12-l., three-necked flask there were mixed a cold solution of 526 g. of stannous chloride in 3 l. of water and a cold solution of 1313 g. of sodium hydroxide in 2 l. of water. The mixture was cooled to 0° with sufficient crushed ice and the diazotized solution was added slowly with vigorous stirring. Nitrogen evolved in large quantities at this step. After standing overnight, the aqueous layer was siphoned out and discarded and the organic layer was steam distilled. The organic layer of the steam distillate was separated, washed successively with dilute sulfuric acid, water, dilute solution of sodium hydroxide, and water. It was dried and distilled in vacuo. There was obtained 136 g. of 3,5-dimethylbromobenzene (56 per cent) which boiled at 70°/6 mm. (Fieser and Heymann report 88-89°/12 mm.).

A Grignard reagent was prepared with 12.16 g. (0.5 gram atom) of magnesium turnings in 250 ml. of dry ether and a solution of 85 g. (0.46 m.) of 3,5-dimethylbromobenzene in ether which was added dropwise. The reaction was initiated with a few drops of methyl iodide. After all the bromide had been added, the reaction mixture was refluxed for four and one-half hours on the steam bath. The Grignard reagent was gently poured
into a slurry of "Dry Ice" in dry ether. When the temperature of the mixture rose to that of the room, it was acidified with dilute hydrochloric acid (100 ml. of water for every 20 ml. of concentrated hydrochloric acid). Some crushed ice was also added. The organic layer was separated and the aqueous layer was extracted with ether. The combined ether layers were washed with water and then extracted with ice cold 10 per cent sodium hydroxide solution. After agitation for several minutes, the aqueous layer was kept basic to litmus. After repeating the extraction thrice, the combined aqueous layers were acidified with dilute hydrochloric acid. The precipitated 3,5-dimethylbenzoic acid weighed 46.5 g. (67.5 per cent). On recrystallization from ethanol, it melted at 169-170° (Heilbron and Bunbury136 give 170°; Fischer and Windaus91 report 166-167°).

c. 3,5-Dimethylbenzoyl chloride. A mixture of 33.5 g. of 3,5-dimethylbenzoic acid and 30 ml. of pure thionyl chloride was refluxed on a steam bath for three hours. The excess of thionyl chloride was removed by distillation and the acid chloride was distilled in vacuo. There was obtained 33.5 g. (89 per cent) of 3,5-dimethylbenzoyl chloride, b.p. 90°/3.5 mm. (Weiler137 reports 109.5°/10 mm.).

d. 3,5-Dimethylbenzoyl cyanide. The method is analogous to that described for 4-methylbenzoyl cyanide. A mixture of 10 g. (0.06 m.) of 3,5-dimethylbenzoyl chloride and 6.25 g. (0.07 m.) of previously dried cuprous cyanide was heated in a Wood's metal bath. The temperature of the bath was maintained at 270-280° for one and one-half hours. The product distilled at 244°. On cooling it formed a solid weighing 5.8 g. (61.5 per cent), m.p. 61-62°.
Anal. Calcd. for C₁₀H₉O₄N: C, 75.43; H, 5.70.
Found: C, 75.32; H, 5.70.

e. Ethyl 3,5-dimethylphenylglyoxylate. 3,5-Dimethylbenzoyl cyanide, 7 g., was dissolved in an adequate amount of absolute ethanol which was saturated with hydrogen chloride. The temperature of the mixture was maintained below 10° using an ice bath. The reaction mixture was kept in the cold room for one week. The precipitate obtained after pouring the mixture into a large quantity of water was extracted with ether. The aqueous layer was extracted twice more with ether, after which it was discarded. The combined ether extracts were washed with a dilute solution of sodium bicarbonate, water and then dried over anhydrous magnesium sulfate. Ether was removed by distillation in vacuo. The ester obtained weighed 4.2 g. and boiled at 130°/4.5 mm. It gave a positive test with 2,4-dinitrophenylhydrazine.

f. 3,5-Dimethylphenylcyclohexylglycolic acid. Magnesium turnings, 0.76 g. (0.031 m.), in dry ether were treated dropwise with 3.65 g. (0.031 m.) of chlorocyclohexane in dry ether. A crystal of iodine was added to initiate the reaction. After the addition of the chlorocyclohexane, the reaction mixture was refluxed on a steam bath for forty-five minutes until almost all of the magnesium reacted. The Grignard reagent was added slowly to a solution of 6.4 g. (0.031 m.) of ethyl 3,5-dimethylphenylglyoxylate. The reaction mixture was stirred and refluxed on a steam bath for an hour before adding it to dilute sulfuric acid and crushed ice. The ether layer was isolated and the aqueous layer was extracted several times with ether. The combined
ether extracts were successively washed with water, dilute solution of sodium bicarbonate, and water again. The extract was dried and distilled in vacuo. The method gave 1.6 g. (17.8 per cent) of ester distilling at 170°/4.5 mm.

The ester, 1.6 g., was refluxed overnight with 10 ml. of water containing 1 g. of sodium hydroxide and 15 ml. of 95 per cent ethanol. At the end, alcohol was removed by distillation. The residual solution was poured into water and boiled to evaporate any alcohol, if present. The mixture was cooled and filtered. Dilute hydrochloric acid was added slowly to the solution and cooled in an ice bath. The acid which precipitated was recrystallized from an alcohol-water mixture. It weighed 0.6 g. (41.7 per cent) and melted at 170-171°.

Anal. Calcd. for C\(_{16}\)H\(_{22}\)O\(_3\): C, 73.26; H, 8.46.
Found: C, 73.21; H, 8.66.

g. 2-Diethylaminoethyl 3,5-dimethylphenylcyclohexylglycolate hydrochloride. The general method described in A.2. was adopted. The hydrochloride thus obtained was recrystallized from an ethanol-ether mixture. 2-Diethylaminoethyl 3,5-dimethylphenylcyclohexylglycolate hydrochloride, m.p. 217-218°, was obtained in 63.3 per cent yield.

Found: C, 66.74; H, 9.10.
C. Esters of Substituted Dicyclohexylglycolic Acids

1. General Method for the Catalytic Hydrogenation of Amino Ester Hydrochlorides of Alkyl Substituted Benzilic Acids

2-Diethylaminoethyl esters of alkyl substituted benzilic acids (described in A) were dissolved in the minimum amount of pure glacial acetic acid. The solution was shaken on a low pressure hydrogenator with Adams' platinum catalyst until there was no more drop in pressure over a period of from four to five hours, even after the addition of some more catalyst. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in hot alcohol, decolorized with Norit and precipitated with ether. It was recrystallized several times from an alcohol-ether mixture until a sharp melting compound was obtained. These compounds are listed in Table VII.

An attempt was made without success to hydrogenate catalytically the ester hydrochlorides of 2,3,4,5-tetramethyl-, 2,3,5,6-tetramethyl- and 2,3,4,6-tetramethylbenzilic acids using Adams' platinum catalyst. Each of them needed shaking for about five days until no more drop in pressure was observed even after the addition of fresh catalyst. On evaporation of the solvent, the products obtained were recrystallized several times from alcohol-ether mixture. The white crystals obtained in each case softened before melting. These compounds, which were probably mixtures, defied further attempts at purification.
2. Attempted Preparation of Esters of Methoxy Substituted Dicyclohexylglycolic Acids

When the general method in C.I. was employed for the hydrogenation of 4-methoxy and 4,4'-dimethoxybenzilic acid ester hydrochlorides, the results of elemental analysis did not agree with the calculated values. Therefore an attempt was made to hydrogenate the 4-methoxy substituted compound using 5 per cent rhodium on alumina as catalyst. Again, the values of elemental analysis of the presumably hydrogenated compounds did not agree with the theoretical values. However, the analysis for the methoxy group on the presumably hydrogenated product of the ester hydrochloride of 4-methoxybenzilic acid indicated a possibility of hydrogenolysis.

Anal. Calcd. for C$_{21}$H$_4$O$_3$N$_2$O$_4$Cl$: -OCH$_3$, 7.64.

Found: -OCH$_3$, 3.68.

Further attempts to hydrogenate the methoxy substituted compounds were abandoned.

D. Attempted Preparation of Esters of 1-Mercaptodiarylacetic Acids

1-Mercaptodiphenylacetic acid, 1-mercapto-2,2'-dimethoxydiphenylacetic acid and 1-mercapto-3,3'-dimethylidiphenylacetic acid were prepared by the method analogous to that of Becker and Bistrzycki. The preparation of 1-mercaptodiphenylacetic acid is typical and hence it is described in detail.
1. Diphenylcarboxymethyl N-Phenylthiocarbamate

Benzilic acid, 22.8 g. (0.1 m.), was treated with 16.9 g. (0.125 m.), of phenylisothiocyanate in 20 ml. of glacial acetic acid. The components were mixed thoroughly and the mixture was kept in an ice bath until the temperature fell to 0°. With stirring, 10 ml. of concentrated sulfuric acid was added, after which the mixture was kept in the ice bath for three more hours and subsequently at room temperature for twenty hours. It was then introduced into ice water. The crude diphenylcarboxymethyl N-phenylthiolcarbamate obtained weighed 39.4 g., which was practically a quantitative yield. On two recrystallizations from methanol-water mixture, its melting point was 138-139° (Becker and Bistrzycki 99 give 140.5° with decomposition; Schoberl 138 reports 146-147° with decomposition).

Anal. Calcd. for C\text{21}H\text{16}N\text{O}3S: C, 69.39; H, 4.72.

Found: C, 69.52; H, 4.77.

2. l-Mercaptodiphenylacetic Acid

Diphenylcarboxymethyl N-phenylthiolcarbamate, 10 g., was refluxed for one-half hour with 350 ml. of 3 per cent potassium hydroxide solution and 75 ml. of ethanol. The reaction mixture was cooled and filtered. The filtrate was made acidic with 10 per cent hydrochloric acid. Meanwhile the mixture was kept in an ice bath and stirred regularly. The crude acid, weighing 6.6 g., precipitated out. It was recrystallized from 50 per cent acetic acid in which case beautiful crystals of l-mercaptodiphenylacetic acid, m.p. 148-149°, were obtained. The pure acid weighed 5.9 g., (88 per cent) (Becker and Bistrzycki 99
give 147-149°; Schober\textsuperscript{138} reports 150-152°).

**Anal.** Calcd. for C\textsubscript{14}H\textsubscript{12}O\textsubscript{2}S: C, 68.82; H, 4.95; S, 13.12.
Found: C, 68.92; H, 4.98; S, 13.10.

1-Mercapto-2,2'-dimethoxydiphenylacetic acid and 1-mercapto-3,3'-dimethyldiphenylacetic acid were prepared by starting with the corresponding benzilic acids by the method described in D.1. and 2. These acids are listed in Table VIII.

3. Attempted Preparation of the Amino Ester of 1-Mercaptodiphenylacetic Acid

a. **Method I.** An attempt was made to prepare the amino ester by the general method described in A.2. in which 1-mercaptodiphenylacetic acid is the starting material. The hydrochloride isolated was recrystallized from an alcohol-ether mixture several times. It melted at 189-190°. However, elemental analysis did not check with the theoretical values.

**Anal.** Calcd. for C\textsubscript{20}H\textsubscript{26}NO\textsubscript{2}SCl: C, 63.24; H, 6.90.
Found: C, 62.96; H, 6.08.

b. **Method II.** (1) 2-Diethylaminoethyl 1-bromodiphenylacetate hydrobromide. According to the method of Klosa,\textsuperscript{101} 2-diethylaminoethyl benzilate hydrochloride, 5.4 g. (0.015 m.), was suspended in 25 ml. of benzene in a 100-ml., three-necked flask equipped with a mechanical stirrer, a reflux condenser and also a thermometer. A solution of phosphorus tribromide, 10.2 g. (0.038 m.), in 20 ml. of benzene was added dropwise with stirring. During the addition, the temperature of the mixture was maintained at 70-80° for one and one-half hours on a steam bath. It was then kept at
room temperature for thirty hours with continued stirring, after which it was filtered through a sintered glass funnel, washed with benzene and recrystallized a few times from an alcohol-ether mixture. The product weighed 5.2 g. and melted at 161-162° (Kloesel reports 165-167°).

**Anal.** Calcd. for C_{20}H_{25}NO_{2}Br_{2}: C, 51.00; H, 5.35.

Found: C, 51.44; H, 5.16.

(2) Attempted preparation of 2-diethylaminoethyl 1-mercapto-
diphenylacetate. A few grams of the ester hydrobromide described above in D.J.b.(1) was treated in an ice bath with a dilute solution of sodium bicarbonate. The free amine was taken up in ether and dried. The ether extract was refluxed with an excess of commercially available dried sodium hydrosulfide (dried overnight at 110°) in dry acetone for three to sixteen hours. A deep blue solution was formed, but the product obtained in all cases was identified as the ester of benzilic acid. The same results were obtained with dry benzene as solvent.

With the use of sodium hydrosulfide which was freshly prepared by saturating molten sodium sulfide nonahydrate with hydrogen sulfide at about 130°, the same results were obtained.

It is of interest to note that in some of the above attempts, a product melting at 172-174° was isolated, which was identified as 2-N,N-diethylaminoethanethiol by determining a mixed melting point with an authentic sample.

Further attempts to prepare the ester of 1-mercaptodiphenyl-
acetic acid were abandoned.
E. Preparation of 1,1-Diphenyl-2-hydroxy-N,N-dimethylbutylamine Hydrochloride

1. 1,1-Diphenylacetone

The method described by Schultz and Mickey\textsuperscript{102} was followed.

a. 1-Bromo-1-phenylacetone. A 1-l., three-necked flask was equipped with a sealed stirrer, a dropping funnel and a water cooled reflux condenser carrying a calcium chloride drying tube. In the flask were placed 200 ml. of dry benzene and 37 g. (37 ml., 0.276 m.) of phenylacetone. The stirrer was started and 45 g. (14.4 ml., 0.28 m.) of reagent grade bromine was added dropwise during a period of one hour. The reaction mixture first became cloudy, but changed to a clear orange-red solution by the time all the bromine was added. A rapid stream of nitrogen was bubbled through the solution by means of an inlet tube which now replaced the dropping funnel. When hydrogen bromide issuing from the top of the condenser ceased, the reaction was complete. This operation required six hours and at the end, the reaction mixture became yellow. The benzene solution of 1-bromo-1-phenylacetone was then transferred to a dry 500 ml. separatory funnel.

b. 1,1-Diphenylacetone. The reaction flask used in E.l.a. above was again set up as it was originally and in it were placed 75 g. (0.56 m.) of anhydrous aluminum chloride and 150 ml. of dry benzene. The stirrer was started and the flask was heated on the steam bath so as to boil the benzene gently. The benzene solution of 1-bromo-1-phenylacetone (described above in E.l.a.) was added dropwise from a separatory funnel to the boiling mixture over a period of one hour. After the ad-
dition was complete, the almost black reaction mixture was heated to boiling for an additional hour, cooled to room temperature and poured with stirring onto 500 g. of crushed ice and 100 ml. of concentrated hydrochloric acid in a 2-l. beaker. The deeply colored benzene solution gradually became orange-yellow. When the ice had melted, the benzene layer was separated and the aqueous layer was extracted thrice with 50 ml. portions of ether. The combined ether and benzene solutions were washed with 100 ml. of water and then with 100 ml. of saturated sodium bicarbonate solution. After the solution had been dried for at least three to four hours over anhydrous magnesium sulfate, the solvents were evaporated on a steam bath until the solution no longer boiled. The dark solution was then distilled under reduced pressure. Benzene, if any, distilled first. The fraction distilling between 131-138° at 0.6 mm. pressure was collected. Most of it, however, distilled at 134-135°/0.6 mm. (Schultz and Mickey report 142-148°/2-3 mm.). The crude product that solidified in the receiver was treated with sufficient petroleum ether (b.p. 60-90°) to moisten it. It was cooled in an ice bath, collected on a filter and washed with a very small amount of petroleum ether cooled to 0-5°. The crystals became colorless. Larger amounts of petroleum ether for washings were avoided since it dissolved the substance. The product was then crystallized from petroleum ether (b.p. 60-90°) using 8 ml. of solvent per gram of crude dry solid. The hot solution was allowed to stand at room temperature until crystallization began and then kept in the cold room for twenty-four hours. The crystals were dried in air at room temperature. The yield of colorless
compound, melting at 60-61°, was 32.2 g. (Schultz and Mickey\textsuperscript{102} also report 60-61°).

2. **Preparation of 1,1-Diphenyl-4-N,N-dimethylamino-2-butane Hydrochloride**

The following procedure of Wilson and Kyi\textsuperscript{103} was adopted. A mixture of 1,1-diphenylacetone, 10.5 g., previously dried dimethylamine hydrochloride, 6.5 g., and 2.4 g. of paraformaldehyde was refluxed for sixteen hours along with 0.3 ml. of concentrated hydrochloric acid and 30 ml. of ethanol. An excess of water was added and unreacted ketone was removed by ether extraction. The aqueous solution was made alkaline with sodium hydroxide and the liberated base was removed by ether extraction. The ether extract was washed with water and dried over anhydrous magnesium sulfate. The dry ether extract was treated with absolute alcohol saturated with hydrogen chloride, until the precipitation was complete. The solid obtained was recrystallized from an ethanol-ether mixture to give white crystals weighing 6.8 g. (\textit{w}.8 per cent) and melting at 162-163° (Wilson and Kyi\textsuperscript{103} give 157-158°).

3. **1,1-Diphenyl-2-hydroxy-4-N,N-dimethylbutylamine Hydrochloride**

1,1-Diphenyl-4-N,N-dimethylamino-2-butane hydrochloride, 30 g. (0.099 m.), was dissolved in 75 ml. of absolute alcohol and was shaken with 0.4 g. of platinum oxide in a pressure bottle on a low pressure hydrogenator. When the pressure had dropped by 29.2 pounds per square inch, the hydrogenation was stopped. The mixture was filtered through a sintered glass funnel to remove the catalyst. Dry ether was added
to the filtrate until the precipitation was complete. The precipitated hydrochloride was recrystallized twice from an alcohol-ether mixture.  

1,1-Diphenyl-2-hydroxy-4-N,N-dimethylbutylamine hydrochloride thus obtained weighed 29.7 g. (99 per cent), m.p. 175-176°.  

**Anal.** Calcd. for C\textsubscript{18}H\textsubscript{24}NOCl: C, 70.71; H, 7.91.  

**Found:** C, 70.55; H, 7.57.

F. Attempted Preparation of 1,1-Diphenyl-4-N,N-dimethylamino-2-butene Hydrochloride

1. **Method I**

a. **Attempted preparation of 1,1-diphenyl-2-acetoxy-4-N,N-dimethylbutylamine hydrochloride.** A mixture of 18 g. of 1,1-diphenyl-2-hydroxy-4-dimethylbutylamine hydrochloride, 29 g. of anhydrous potassium carbonate and 15 ml. of acetyl chloride was stirred overnight in a three-necked flask equipped with a condenser carrying a drying tube.

The mixture was introduced into ice cold water. The solution was kept alkaline; a very dilute solution of sodium hydroxide was added when necessary. The free amine was extracted with two or three portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The hydrochloride, obtained by passing dry hydrogen chloride into the dried ether extract, was recrystallized a few times from an alcohol-ether mixture. The acetylated product, m.p. 145-146°, weighed 12.8 g. A depression in melting point was obtained with the starting material.
b. 1-Bromo-1,1-diphenyl-2-acetoxy-4-dimethylbutylamine hydrochloride. The acetylated compound in F.1.a. above, 10 g. (0.029 m.), was treated with dilute sodium hydroxide and the liberated amine was extracted with ether. The dried extract was evaporated and the residue dissolved in pure, dry carbon tetrachloride. The solution was cooled to -15° using an acetone—"Dry Ice" bath and 4.64 g. (0.029 m.) of bromine was added dropwise with stirring. The solution was stirred for one more hour after the addition of bromine was complete. The temperature of the mixture was then allowed to rise to that of the room. The precipitated hydrobromide was extracted and recrystallized from acetone several times. The white crystals obtained melted at 173-174° and weighed 5.3 g. The product gave positive tests for unsaturation.

**Anal.** Calcd. for H₂O₁₂SNO₂Br₂: C, 50.98; H, 5.35.

Found: C, 61.17; H, 6.60.

Another attempt gave the same product and hence this method was abandoned.

2. **Method II**

a. 1-Bromo-1,1-diphenyl-2-propanone. The method adopted here was that of Stevens and Lenk. A solution of 59 g. (0.281 m.) of 1,1-diphenylacetone (described in E.1.b.) in 420 ml. of pure carbon tetrachloride was cooled to about -15° in an acetone—"Dry Ice" bath. Bromine, 43.6 g. (15 ml., 0.273 m.) was added dropwise with vigorous stirring. When the addition was complete, the stirring was continued at about -15° for an additional one hour. The temperature then gradually rose to that of the
room. The solvent was removed under reduced pressure; the product obtained was dissolved in petroleum ether (b.p. 60-90°) and the solution was kept in the cold room for crystallization after seeding with a few crystals which were obtained by chilling a few ml. of the solution to -5° to -10°. From the solution, 79.6 g. (81.2 per cent) of 1-bromo-1,1-diphenyl-2-propanone was obtained, m.p. 55.5-56.5° (Stevens and Lenk\textsuperscript{104} report 56.5-57.5°).

b. Hydrolysis of 1-bromo-1,1-diphenyl-2-propanone. The modified method of Stevens and Lenk\textsuperscript{104} was followed. The 1-bromoketone 49 g. (0.17 m.), was dissolved in 430 ml. of dioxane and 180 ml. of water was added. The mixture was stirred and refluxed for three hours. The reaction mixture was cooled and poured into a large quantity of ice and water. Crude 1-hydroxyketone, weighing 36 g., precipitated out. Recrystallization from petroleum ether (b.p. 60-90°) gave 31.8 g. (83 per cent), which melted at 64-65° (Stevens and Lenk\textsuperscript{104} give 63-65°).

c. 1,1-Diphenyl-1-hydroxy-1-N,N-dimethylaminobutanone-2 hydrochloride. The method followed is similar to that of Zaugg, Freifelder and Horrom\textsuperscript{139} and Magee.\textsuperscript{140} A mixture of 31.8 g. (0.141 m.) of 1,1-diphenyl-1-hydroxypropanone-2, 14.4 g. (0.18 m.) of dimethylamine hydrochloride, and 9.6 g. of paraformaldehyde in 180 ml. of n-octyl alcohol was refluxed for ten minutes. Then a further 9.6 g. of paraformaldehyde was added in small portions over a period of thirty minutes with continued refluxing. After the addition was complete, 1.4 ml. of concentrated hydrochloric acid was added and refluxed for an additional five to ten minutes. The mixture was then extracted with water
and with dilute hydrochloric acid and the combined extract was made basic. The oil, which separated, was extracted with two portions of ether. These extracts were washed with water until the washings were neutral. After drying over anhydrous magnesium sulfate, the ethereal solution was saturated with hydrogen chloride while being cooled in an ice bath. Two recrystallizations from an ethanol-ether mixture gave 7.3 g. (19.3 per cent) of white crystals, m.p. 163.5-165° (Magee\textsuperscript{110} reports 163.5-165°).

d. Acetylation of 1,1-diphenyl-1-hydroxy-4-N,N-dimethylamino-
butanone-2 hydrochloride. Several unsuccessful methods which are described below were tried for the acetylation of the hydroxyl group in 1,1-diphenyl-
1-hydroxy-4-N,N-dimethylaminobutanone-2 hydrochloride.

(1) An attempt was made by the method of King and Holmes\textsuperscript{106} and LaMer and Greenspan.\textsuperscript{105} The hydroxy compound, 2 g., was heated on a steam bath with 4 ml. of acetic anhydride for ten hours. The mixture turned black. On cooling, it was poured into ether when a tar separated. This product extracted with ethanol, boiled with Norit and subsequent addition of ether gave a gum-like product. Repeated boiling with Norit and several recrystal-

tisations from an alcohol-ether mixture yielded about 50 milligrams of a substance which melted at 135-138°. The same method was repeated by varying the period of heating from two to ten hours, but the results were not improved.

(2) Another attempt was made using anhydrous zinc chloride as a catalyst. This modification also did not prove to be successful.

(3) A third attempt was made using acetyl chloride. A mixture of 2 g. of the hydroxy compound and 4 ml. of acetyl chloride was allowed to
stand at room temperature for four hours. When a clear solution was obtained, it was poured into ether. A gum-like mass, which defied all attempts at crystallization, was produced.

Finally the experiment was repeated in the presence of 2 g. of anhydrous potassium carbonate and the result obtained was the same.

Since there was no success in the attempts to acetylate the \( \alpha \)-hydroxy group, this route for the preparation of the aminoalkene was abandoned.

G. 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-diethylaminoethoxy)acetate Hydrochloride

1. 1,1-Diphenyl-1-chloroacetic Acid

The method described by Klosa\(^7\) was followed. Benzilic acid, 150 g., was suspended in 300 ml. of dry carbon tetrachloride. Thionyl chloride, 230 ml., was added to this suspension gradually over a period of twenty minutes. The mixture was stirred for two hours at room temperature and was allowed to stand for thirty more hours, at the end of which it was cooled in an ice bath to complete the separation of 98 g. of 1,1-diphenyl-1-chloroacetic acid. On recrystallization from a benzene-ligroin mixture, it melted at 120-122\(^0\) (Klosa\(^7\) gives 124-125\(^0\)).

2. 1,1-Diphenyl-1-(2-diethylaminoethoxy)acetate Acid

The method was essentially due to Klosa.\(^14\) Etherification was accomplished by refluxing 5 g. of 1,1-diphenyl-1-chloroacetic acid and 14 g. of 2-diethylaminoethanol in 30 ml. of benzene in the presence of 4 g. of
previously dried potassium carbonate for thirty-six hours with stirring. The solution was filtered and the excess of solvent was removed along with 2-diethylaminoethanol under reduced pressure. The product obtained was treated with ether. The ether extract was decolorized by boiling with Norit, after which it was treated with ethanol saturated with dry hydrogen chloride. The solid obtained was recrystallized several times from an alcohol-ether mixture. There was obtained 5.3 g. of white crystals, m.p. 176-178° (Kloss [1] gives 180-182°).

3. 2-Diethylaminoethyl 1,1-Diphenyl-1-(2-diethylaminoethoxy)acetate Dihydrochloride

The general method described in A.2. was used. The product obtained was recrystallized several times from an alcohol-ether mixture and also from an isopropyl alcohol-ether mixture. It was produced with a yield of 87.4 per cent, m.p. 212-213°.

Anal. Calcd. for C₂₆H₂₁ON₂Cl₂O₃: C, 62.52; H, 8.07.

Found: C, 62.03; H, 8.26.

H. Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-thioacetoxyacetate Hydrochloride

1. 1,1-Diphenyl-1-thioacetoxyacetic Acid

A hot solution of 9.9 g. (0.04 m.) of 1,1-diphenyl-1-chloroacetic acid (see G.1.) in 20 ml. of benzene was treated dropwise with commercially available thiolacetic acid. The mixture was mechanically stirred and a slow stream of nitrogen was introduced to sweep out the hydrogen chloride
formed during the course of the reaction. After the addition was complete, the reaction mixture was stirred and refluxed for five hours in an atmosphere of nitrogen. At the end of this period, the excess of solvent was removed by distillation under reduced pressure. The residue on recrystallization from carbon tetrachloride gave 10 g. of white crystals, m.p. 157-158°. The compound was used in the next step without further purification.

2. 2-Diethylaminoethyl 1,1-Diphenyl-1-thioacetoxyacetate Hydrochloride

The method described in A.2. was followed. The solid obtained was recrystallized from an isopropyl alcohol-ether mixture and also from a methanol-ether mixture. A yield of 59.7 per cent of white crystalline ester hydrochloride, m.p. 166-167°, was obtained.

Anal. Calcd. for C_{22}H_{28}NO_3SCl: C, 62.62; H, 6.69.
Found: C, 62.27; H, 6.77.

I. Attempted Preparation of 2-Diethylaminoethyl 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetate

1. 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetic Acid

A solution of 7.4 g. (0.003 m.) of 1,1-diphenyl-1-chloroacetic acid (described in G.1.) in benzene was added dropwise to 3.42 g. (0.003 m.) of the sodium salt of mercaptoacetic acid. The mixture was vigorously stirred and refluxed for sixteen hours, after which it was cooled and filtered. The filtrate was reduced to a small volume by evaporation on a steam bath and set aside to crystallize. Since 1,1-diphenyl-1-(1-mercaptoacetoxy)-acetic acid was partially soluble in benzene, the residue, collected on
the filter funnel, was added to water and heated. The sodium salt went into solution leaving behind 1,1-diphenyl-1-(1-mercaptoacetoxy)acetic acid. The solid thus obtained was combined with the crystals obtained from the filtrate that was set aside to crystallize. Two recrystallizations were performed with ethyl acetate when 7.3 g. (80.5 per cent) of crystalline substance, m.p. 192-193.5°, was obtained.

Anal. Calcd. for C\textsubscript{16}H\textsubscript{14}O\textsubscript{4}S: C, 63.57; H, 4.67.

Found: C, 63.63; H, 4.59.

2. **Attempted Preparation of the Amino Ester of 1,1-Diphenyl-1-(1-mercaptoacetoxy)acetic Acid**

The general method described in A.2. was used starting with 1,1-diphenyl-1-(1-mercaptoacetoxy)acetic acid. After the reaction, the solvent was removed by evaporation. The residue was dissolved in hot water. The aqueous extract, after rinsing with ether, was basified with a dilute solution of sodium carbonate. The free amine was extracted thrice with ether, washed with water and dried over anhydrous magnesium sulfate. The hydrochloride and oxalate of this amine were found to be highly hygroscopic. Hence, the citrate, which was comparatively less hygroscopic, was prepared. A saturated solution of citric acid in anhydrous ether was added to the dried ether extract of the amine. The citrate thus obtained was recrystallized from acetone, methyl alcohol-ethyl acetate mixture, ethyl alcohol-ethyl acetate mixture, isopropyl alcohol-ether mixture and finally from ethyl acetate. It gave a hygroscopic white solid weighing 0.5 g. (17 per cent) and melting at 78-79.5°. In spite of several recrystallizations and subsequent care in drying, the product obtained did not possess the
correct composition as indicated by elemental analysis, probably due to its hygroscopic nature.

Anal. Calcd. for C_{28}H_{35}O_{11}N_{S}: C, 56.65; H, 5.93.
Found: C, 58.86; H, 5.89.
C, 54.10; H, 6.29.

J. 2-Diethylaminoethyl 1,1-Diphenyl-1-(isoprophio)acetate Hydrochloride

1. Diphenylcarboxymethyl Isopropyl Sulfide

The method analogous to that of Klosa^{107} was adopted. A mixture of 10 g. (0.04 m.) of 1,1-diphenyl-1-chloroacetic acid (see G.1.), 4 g. of reagent grade calcium carbonate and 50 ml. of 2-propanethiol was refluxed for thirty hours with continuous stirring. The mixture was cooled and filtered, after which the filtrate was reduced to a small volume by evaporation under reduced pressure. When it was cooled in ice, 10.5 g. of crystals of the sulfide which separated were filtered and dried. The product melted at 118-122°. Without further purification, it was used in the next step.

2. Esterification of Diphenylcarboxymethyl Isopropyl Sulfide

The method described in A.2. was followed. The hydrochloride obtained was recrystallized several times from an alcohol-ether mixture and finally from ethyl acetate. The ester hydrochloride obtained melted at 138-139°. It was formed with a yield of 85.4 per cent.

Anal. Calcd. for C_{23}H_{32}NO_{2}SCl: C, 65.45; H, 7.65.
Found: C, 65.25; H, 7.82.
K. Attempted Preparation of 2-N,N-Diethylaminoethyl Methylamide of Phenylcyclohexylglycolic Acid

1. Benzoyl Cyanide

The method of Oakwood and Weisgerber\textsuperscript{110} was followed. In a 500-ml., round-bottomed flask fitted with an air condenser were placed 110 g. (1.2 m.) of dried cuprous cyanide and 1.43 g. (118 ml., 1.02 m.) of benzoyl chloride. The flask was placed in a Wood's metal bath which had been previously heated to 145-150°. The temperature of the bath was raised to 220-230° and maintained between these two limits for one and one-half hours. During the heating the flask was frequently removed from the bath (about every fifteen minutes) and the contents were thoroughly mixed by vigorous shaking. At the end of one and one-half hours, the contents were distilled. The temperature of the bath was slowly raised to 305-310°, and distillation was continued until no more product came over. The benzoyl cyanide, boiling at 205-208°, weighed 97 g. On cooling, it gave crystals which melted at 32-33° (Oakwood and Weisgerber\textsuperscript{110} give 32-33°).

2. Benzoylformic Acid

Again the method of Oakwood and Weisgerber\textsuperscript{111} was employed. In a 1-l. flask were placed 50 g. (0.38 moles) of benzoyl cyanide and 500 ml. of concentrated hydrochloric acid. The mixture was shaken occasionally until the solid dissolved completely and was then allowed to stand at room temperature for five days. At the end of this period, the clear yellow solution was poured into a large quantity of water and extracted thrice with ether. The ether extracts were washed with water and dried. The solvent
was removed by distillation and the residual oil crystallized on placing in the vacuum desiccator. The crude acid was recrystallized from carbon tetrachloride. The benzoylformic acid, melting at 64-66°, weighed 42 g. (73 per cent) (Oakwood and Weisgerber\textsuperscript{111} report 64-66°).

3. Benzoylformyl Chloride

In a 100-ml. three-necked flask fitted with a reflux condenser and a mechanical stirrer was placed 11.12 g. (0.0533 m.) of pure phosphorus pentachloride which was just covered with pure benzene. A solution of 8 g. (0.053 m.) of benzoylformic acid (described above in K.2.) in an adequate amount of pure benzene was added dropwise with stirring. The flask was cooled in an ice bath. When all the acid solution had been added, the reaction mixture was gently refluxed over a steam bath for four hours with stirring. It was kept overnight at room temperature. After refluxing only for a few minutes in order to complete the reaction, the solvent and phosphoryl chloride were removed by distillation under reduced pressure. The residue was distilled in vacuo to give 7 g. (89.9 per cent) of a light yellow liquid, b.p. 82°/4 mm. (Acree\textsuperscript{112} gives 125°/9 mm.).

Anal. Calcd. for C\textsubscript{8}H\textsubscript{13}O\textsubscript{2}Cl: C, 56.99; H, 2.99.

Found: C, 56.89; H, 3.04.

4. 2-N,N-Diethylaminomethylmethylamine

The method of Damiens\textsuperscript{113} was used. In a round-bottomed flask fitted with a two-hole rubber stopper carrying a thermometer and a stopcock were placed 50 g. (0.36 m.) of 2-N,N-diethylaminomethyl chloride and 270 ml. of 35 per cent aqueous methylamine solution. After the stopcock was closed,
the flask was shaken in a mechanical stirrer as the temperature rose to 50°, at which point the stopcock was opened to release the pressure. The reaction was allowed to proceed with continued shaking until the temperature had returned to that of the room. When the solution was made strongly basic, an organic layer separated. The alkaline mixture was extracted three times with ether. The ethereal extracts were washed with water, dried and fractionally distilled using a Vigreux column. The product was a colorless liquid, b.p. 152-154° (Kermack and Wight\textsuperscript{1} give 157-160°). The method gave a yield of 12.1 g. (25.2 per cent).

5. Preparation of 2-N,N-Diethylaminoethyl Methyamide of Benzoylformic Acid

A method similar to that of Krapcho, Turk and Pribyl\textsuperscript{108} was used. A solution of 2.87 g. (0.017 m.) of benzoylformyl chloride in 12 ml. of n-hexane and 8 ml. of pure benzene was maintained at 20-30° during the dropwise addition of a solution of 2.16 g. (0.017 m.) of 2-N,N-diethylaminoethylmethyamine in 4 ml. of benzene. A precipitate was formed. After all the amine had been added, the mixture was stirred for an hour more at room temperature, refluxed for an additional one hour, cooled and treated with water. After this mixture had been stirred for a few minutes with little warming, all of the solid went into solution. The aqueous layer was separated and the organic layer was extracted twice with dilute hydrochloric acid. The combined aqueous extracts were rinsed with ether and basified. The free amine liberated was extracted with ether twice. The ethereal extracts were washed with water and...
dried. Since the hydrochloride of this amine was hygroscopic, the oxalate was prepared. A saturated solution of oxalic acid in ether was added to the dried ethereal extract of the amine. The gummy substance obtained was dissolved in absolute ethanol and dry ether was added until the solution appeared cloudy. It was kept in the cold room until crystals formed. The crystals were recrystallized a few times from an ethanol-ether mixture. There was obtained 2.9 g. (48.3 per cent) of the amide, a white crystalline solid, m.p. 93-94°.

Anal. Calcd. for C_{17}H_{24}N_{2}O_{6}: C, 57.94; H, 6.86.

Found: C, 57.61; H, 6.72.

6. Attempted Preparation of the 2-N,N-Diethylaminoethyl Methylamide of Phenylcyclohexylglycolic Acid

The oxalate (described in K.5.), 8.5 g., was treated with dilute solution of sodium hydroxide, extracted with ether three or four times and the extracts were dried over anhydrous magnesium sulfate.

Meanwhile a Grignard reagent was prepared as follows: Magnesium turnings, 0.59 g. (0.024 m.) were covered with ether to which 2.83 g. (0.024 m.) of pure chlorocyclohexane in ether was added dropwise. A small piece of iodine was added, if necessary, to start the reaction. When the addition of the solution of chlorocyclohexane was complete, the mixture was gently refluxed for about forty-five minutes. The Grignard reagent thus prepared was transferred to a dropping funnel with a minimum exposure to the atmosphere.
The Grignard reagent was added dropwise with stirring to the previously dried solution of the amide. A white precipitate was obtained. After all the Grignard reagent had been added, the mixture was refluxed for seventy-five minutes on the steam bath. The reaction mixture was gently poured into water containing some crushed ice. Solid ammonium chloride was added until the magnesium hydroxide, that was present, went into solution. The ether layer was separated and the aqueous layer was extracted twice with ether. The ethereal extracts were then dried. Since the hydrochloride and the oxalate prepared were gummy and failed to crystallize, a citrate was prepared. A saturated solution of citric acid in ether was added to the dried ethereal extract of the amine. The precipitation was complete. It was recrystallized several times successively from acetone, alcohol-ether mixture, ethyl acetate and isopropyl alcohol. There was obtained 3.5 g. (27 per cent) of the citrate, a white crystalline substance, m.p. 86-87°. The product, however, did not analyze correctly for the desired compound.

**Anal. Calcd. for C\(_{27}H_{42}N_2O_9\):** C, 60.20; H, 7.86.

**Found:** C, 54.00; H, 6.87.

C, 56.23; H, 7.31.

C, 56.10; H, 7.41.
L. Attempted Preparation of 2-Diethylaminoethyl Phenylcyclohexylthioglycolate

1. Method I

a. Method A. The method described by Gilman and coworkers\textsuperscript{100} was followed. Hydrogen sulfide was bubbled through 34 g. (0.14 m.) of melted sodium sulfide nonahydrate for several hours until it was saturated. To the resulting solution was added 9 g. (0.067 m.) of freshly prepared 2-diethylaminoethyl chloride and the mixture was refluxed with vigorous stirring for one hour in an atmosphere of nitrogen. After cooling, the solution was extracted with ether and the ethereal extract was dried and distilled with minimum exposure to the air. The yield of mercaptan distilling at 64-67°/23 mm. was 2.8 g. (31.3 per cent) (Gilman and coworkers\textsuperscript{100} give 62-65°/21 mm.). The range of yields extended from 0 to 31.3 per cent.

b. Method B. (1) Preparation of 2-N,N-diethylaminoethyl isothiuronium chloride hydrochloride. The procedure of Albertson and Clinton\textsuperscript{116} was followed for the preparation of this compound.

To a refluxing solution of 15.7 g. (0.207 m.) of thiourea in 50 ml. of absolute ethanol was added over a period of one and one-half hours a slurry of 35.2 g. (0.205 m.) of 2-N,N-diethylaminoethyl chloride hydrochloride in 100 ml. of ethanol. The solution was refluxed for six hours, cooled and diluted with 200 ml. of ethyl acetate and 50 ml. of ligroin. A yield of 44 g. (86 per cent) of a white solid, m.p. 190-192° was obtained. (Albertson and Clinton\textsuperscript{116} report 194-195°.)
(2) 2-N,N-Diethylaminoethanethiol. According to Albertson and Clinton, the thiol was prepared by alkaline hydrolysis of the isothiouronium compound. To a suspension of 25 g. (0.1 m.) of 2-N,N-diethylaminoethyl isothiouronium chloride hydrochloride in 40 ml. of water was added a solution of 8.2 g. of pellets of sodium hydroxide in 30 ml. of water. There was an immediate separation of a pink oily layer. The solution was extracted three to four times with ether. The dried ethereal extract containing 2-N,N-diethylaminoethanethiol was used immediately for the preparation of the thiol ester.

c. Attempted preparation of 2-N,N-diethylaminoethanethiol ester of benzoylformic acid. The ethereal extract from the decomposition of 25 g. (0.1 m.) of 2-N,N-diethylaminoethyl isothiouronium chloride hydrochloride was added dropwise to a cooled (ice-bath) solution of 14 g. (0.083 m.) of benzoylformyl chloride (see K.3.) in 100 ml. of dry benzene. After the addition, the reaction mixture was refluxed for three hours. A little gummy substance was obtained at the bottom of the flask. On cooling, the mixture was treated with water and stirred. The water layer was separated and the benzene layer was extracted twice with water. The aqueous extracts were washed with ether, after which they were made basic and the free amine liberated was extracted with ether several times. The dried ethereal extracts were treated with absolute alcohol saturated with dry hydrogen chloride. The precipitate was recrystallized several times from an isopropyl alcohol-ether mixture. The white solid product which softened before finally melting weighed 1.1 g., m.p. 201-203°.
Anal. Calcd. for C14H20NC102S: C, 55.71; H, 6.68.

Found: C, 41.88; H, 8.09.

Repetition of the above reaction yielded a compound melting at 244-246°. This method was not further explored.

2. Method II

a. 1,1-Diphenyl-1-chloroacetyl chloride. The chloroacetyl chloride was prepared from benzilic acid and phosphorus pentachloride by the method of King and Holmes.106

In a flask which was immersed in an ice bath were placed 114 g. (0.54 m.) of phosphorus pentachloride and 60 g. (0.264 m.) of benzilic acid. The contents were mixed thoroughly. After two to three minutes, a vigorous reaction began. When this reaction had ceased, the flask was heated at 100° for fifteen minutes. Phosphoryl chloride was distilled from the flask under reduced pressure and the residue was poured into ice and water. This mixture was stirred vigorously until the organic material solidified. The water was removed quickly by filtration and the residue was dissolved in ligroin without heating. The ligroin solution was dried and evaporated to one-third of its original volume. There was obtained 34 g. (46 per cent) of the acid chloride, a white crystalline solid, m.p. 46-48° (King and Holmes106 report 48.5-49.5°; Billman and Hidy,143 50-51°).

b. 2-N,N-Diethylaminoethyl thiolbenzilate hydrochloride. The procedure of Kolloff, Hunter, Woodruff and Moffett117 was employed. The ethereal extract from the decomposition of 25 g. (0.1 m.) of 2-N,N-diethylaminoethyl isothiouronium chloride hydrochloride was added drop-
wise to an ice-cooled solution of 22 g. (0.083 m.) of 1,1-diphenyl-1-chloroacetyl chloride in 100 ml. of benzene. After the addition, the reaction mixture was refluxed for three hours. The white solid was filtered and dried. The crude 2-N,N-diethylaminoethyl 1,1-diphenyl-1-chlorothiolacetate hydrochloride weighed 13.2 g. and melted at 145-150°. The compound was recrystallized from hot methyl ethyl ketone by the addition of sufficient ether to produce cloudiness. The chilled solution gave crystals melting at 154-156° (Morrison and Königstein\textsuperscript{144} give 160°).

Twelve grams of this compound was dissolved in very dilute hydrochloric acid and heated on a steam bath for fifteen minutes to remove the alpha chloro group. The solution was cooled and crushed ice and then solid sodium carbonate were added. The free base liberated was extracted with ether three times. The combined dried ethereal extracts were treated with ethanol saturated with hydrogen chloride. On cooling, a viscous liquid which on treating with ethyl acetate became solid, was obtained. It was recrystallized from an ethanol-ether mixture. There was obtained 5.4 g. of white crystals, m.p. 138-139° (Magee\textsuperscript{145} gives 138-139°).

c. Attempted catalytic half-hydrogenation of 2-N,N-diethylaminoethyl thiolbenzilate hydrochloride. The hydrochloride was dissolved in a minimum amount of pure glacial acetic acid and shaken with Adams' platinum catalyst in a pressure bottle on a low pressure hydrogenator. There was no drop in pressure, except that due to reduction of platinum oxide, over a period of twenty-four hours. A further addition of catalyst also did not produce any drop in pressure.
Five per cent rhodium on alumina was next used as a catalyst. It also did not produce any significant drop in pressure over a period of twenty hours.

Attempts at half-hydrogenation using palladium on barium sulfate proved to be futile as only the starting material was recovered from the solvent.

This route was therefore not explored any further.

M. Preparation of 2-Diethylaminoethyl Phenyl-\(\alpha\)-2-cyclohexenyacetate Hydrochloride

1. **Ethyl Phenylacetate**

Phenylacetic acid, 204 g. (1.5 m.) was refluxed with 700 ml. of absolute alcohol and 9 ml. of concentrated sulfuric acid for eighteen hours. At the end of this period, the solution was made neutral by the addition of a few pellets of sodium hydroxide. The excess of alcohol was removed by distillation and the residue was poured into a large quantity of cold water which was then extracted with ether. The extract was dried and the solvent was evaporated on a steam bath. The residue was distilled \textit{in vacuo}. There was obtained 205 g. (83.4 per cent) of liquid, b.p. 89°/3.5 mm. (Perkin\textsuperscript{146} reports 227.1-227.6°/760 mm.).

2. **Ethyl Phenylmalonate**

The procedure described by Levene and Meyer\textsuperscript{119} was followed.

In a 2-l., three-necked flask fitted with a stirrer, reflux condenser and a dropping funnel was placed 500 ml. of absolute ethanol
(commercial absolute alcohol distilled over 5 per cent of its weight of sodium) and 23 g. of cleanly cut sodium was added in portions. When the sodium had dissolved, the solution was cooled to 60° and 146 g. (1 m.) of ethyl oxalate (purified by shaking with potassium carbonate and distilling under reduced pressure) was added with vigorous stirring in a rapid stream through the dropping funnel. This procedure was followed immediately by the addition of 175 g. (1.06 m.) of ethyl phenylacetate. Stirring was discontinued and the mixture was poured into a 2-l. beaker. A solid paste of the sodium derivative obtained was allowed to cool to room temperature, after which it was stirred with 800 ml. of dry ether and filtered. The crystals were washed with dry ether and the phenyloxaloacetic ester was liberated from the sodium salt with dilute sulfuric acid (29 ml. of concentrated sulfuric acid in 500 ml. of water). The oil obtained was separated and the aqueous layer was extracted with three 100-ml. portions of ether, which were combined with the oil. The ethereal solution was dried over magnesium sulfate and the ether distilled. The residual oil contained in the flask fitted with a modified Claisen head (with a Vigreux column as side arm) was heated under reduced pressure of about 1 mm. at about 130°. The flask was maintained at these conditions until the evolution of carbon monoxide was complete, an operation which required about five hours. If any oil distilled over, it was returned to the flask and finally ethyl phenylmalonate was distilled in vacuo. The fraction boiling at 115-120°/0.8 mm. was collected. A large portion of the liquid, however, distilled at 115-116°/0.8 mm. (Levene and Mayer119 give 158-162°/10 mm.). There
was obtained a yield of 185 g. (78.3 per cent).

3. **Preparation of 3-Bromocyclohexene**

This halide was prepared by bromination of cyclohexene using N-bromosuccinimide according to the method of Ziegler and coworkers. 147

A mixture of 304 ml. of pure cyclohexene, 300 ml. of carbon tetrachloride, and 109.8 g. of N-bromosuccinimide was placed in a 1-l., round-bottomed flask and refluxed until all the N-bromosuccinimide had reacted (one hour). The reaction mixture was cooled to room temperature and the succinimide was removed by filtration. Carbon tetrachloride and the unreacted cyclohexene were removed by distillation and the residue was distilled in vacuo to give 73 g. (57 per cent) of pure product, b.p. 72-74°/30 mm. (Crossley 148 gives 74°/28 mm.).

4. **Diethyl Phenyl-Δ²-cyclohexenylmalonate**

The method of Kolloff and coworkers 120 was used.

To a solution of 7 g. (0.305 m.) of sodium in 250 ml. of absolute ethanol was added 70.8 g. (0.3 m.) of diethyl phenylmalonate. The solution was stirred at reflux temperature during the dropwise addition of 49.1 g. (0.305 m.) of 3-bromocyclohexene. The reaction mixture was then refluxed with stirring for six hours. After cooling and making the solution acidic with acetic acid, most of the solvent was removed by distillation. Water was then added and the organic layer was separated. The aqueous layer was extracted twice with ether. The combined organic layer and ethereal extracts were dried and subsequently distilled in vacuo. They gave 55 g. (58.4 per cent) of diethyl phenyl-Δ²-cyclo-
hexenylmalonate, b.p. 158-162°/0.8 mm. A greater portion of the liquid distilled at 158-159°/0.8 mm. (Kolloff and coworkers\textsuperscript{120} give 126°/0.07 mm.).

5. Phenyl-\(\Delta^2\)-cyclohexenylacetic Acid

The method of Kolloff and coworkers\textsuperscript{120} was again employed. A solution of 55 g. (0.172 m.) of diethyl phenyl-\(\Delta^2\)-cyclohexenylmalonate and 61.3 g. (1.1 m.) of potassium hydroxide in 300 ml. of 95 per cent ethanol was refluxed for six hours. Water was added from time to time to dissolve the solid which separated. Most of the alcohol was removed by distillation. The product was dissolved in water, extracted with ether and the aqueous layer cooled and acidified. An oil, which crystallized after a few minutes, formed. There was obtained 34.5 g. (92.3 per cent) of the acid, m.p. 117-119.5° (Kolloff and coworkers\textsuperscript{120} give 120-122°).

6. Amino Ester Hydrochloride of Phenyl-\(\Delta^2\)-cyclohexenylacetic Acid

The method described in A.2. was used for the preparation of the amino ester hydrochloride. It gave a yield of 66.2 per cent of solid which was recrystallized successively from an ethanol-ether, a methanol-ether, and an isopropyl alcohol-ether mixture. There was produced a white crystalline compound, m.p. 156-157°.

**Anal.** Calcd. for C\(_{20}\)H\(_{30}\)NO\(_2\)Cl: C, 68.26; H, 8.59.

**Found:** C, 68.10; H, 8.65.
N. Preparation of 2-Diethylaminoethyl Phenyl-Δ²-cyclohexenylglycolate Hydrochloride

1. Bromination of Phenyl-Δ²-cyclohexenylacetic Acid

   a. Method I. An attempt was made to brominate phenyl-Δ²-cyclohexenylacetic acid by the method of Stevens and Lenk.\textsuperscript{104}

   To a solution of 6.48 g. (0.003 m.) of phenyl-Δ²-cyclohexenylacetic acid in 50 ml. of carbon tetrachloride maintained at -15° to -20° (acetone-"Dry-Ice" bath) 9.6 g. (0.06 m.) of bromine was added in drops. The solution was stirred for one and one-half hours after the addition of bromine was complete. The temperature of the mixture was allowed to rise to that of the room. On removing the solvent under reduced pressure, the residue was extracted with ethyl acetate. The extract was decolorized with Norit. On slow evaporation of the solvent, crystals were obtained. They were recrystallized first from benzene and then from ethyl acetate. There was obtained 4.2 g. of solid, m.p. 210-211°.


   Found: C, 45.41; H, 4.21.

   Elemental analysis agrees fairly well with the composition of phenyl-2,3-dibromocyclohexylacetic acid.

   Anal. Calcd. for C₁₄H₁₆Br₂O₂: C, 44.70; H, 4.29.

   The experiment was repeated at room temperature and also at reflux temperature of carbon tetrachloride in an effort to replace tertiary hydrogen by the bromine atom. These attempts failed as the same compound, m.p. 210-211°, was isolated.
b. Method II. The method of Schwenk and Papa\textsuperscript{121} was next used for the bromination of phenyl-\textsuperscript{2}-cyclohexenylacetic acid.

A mixture of 25.9 g. of phenyl-\textsuperscript{2}-cyclohexenylacetic acid and 60 ml. of thionyl chloride was refluxed for two hours while 38.4 g. of bromine was added dropwise over a period of two hours. The mixture was allowed to stand overnight, after which the excess of thionyl chloride was removed under reduced pressure. The residue, a brown-colored viscous liquid, was dissolved in 500 ml. of dioxane and 100 ml. of 10 per cent sodium hydroxide solution. The mixture was refluxed for three hours. Most of the dioxane was removed by distillation under reduced pressure. The residue was then poured into about 200 ml. of water containing 25 g. of sodium hydroxide and stirred vigorously. After cooling, the solution was extracted with ether. The aqueous extract was acidified with dilute hydrochloric acid in the cold to give a gummy mass. It was dissolved in dilute sodium hydroxide solution and decolorized with Norit. On acidification, it gave phenyl-2,3-dibromocyclohexylglycolic acid, a white solid, m.p. 66-70.5°, which weighed 17 g. It was used in the next debromination process without further purification.

2. Debromination of Phenyl-2,3-dibromocyclohexylglycolic Acid

A modification to the method of Catravas\textsuperscript{122} was used for the debromination process.

A mixture of 10 g. of phenyl-2,3-dibromocyclohexylglycolic acid, 10 g. of zinc dust and 60 ml. of pure acetone was refluxed for seventy-five minutes. A few drops of concentrated hydrochloric acid were added to the mixture as a catalyst, after which it was cooled and filtered.
The filtrate was evaporated to a small volume and dilute hydrochloric acid was added. The solution was extracted a few times with ether. The dried ethereal extract was evaporated and a gum-like mass was obtained. The latter was recrystallized twice from ethyl acetate. There was obtained 3.1 g. of phenyl-\(\Delta^2\)-cyclohexenylglycolic acid, m.p. 110-114\(^\circ\). The standard qualitative test for unsaturation was positive with this compound.

3. **Amino Ester Hydrochloride of Phenyl-\(\Delta^2\)-cyclohexenylglycolic Acid**

Using the method described in A.2., the ester hydrochloride was obtained in 57.6 per cent yield. On recrystallization from an alcohol-ether mixture and twice from isopropyl alcohol, it gave white crystals, m.p. 161-162\(^\circ\).

**Anal.** Calcd. for C\(_{20}\)H\(_{19}\)NO\(_3\)Cl: C, 67.87; H, 8.55.

Found: C, 67.79; H, 8.50.
CHAPTER IV

SUMMARY

Several derivatives of substituted benzilic, glycolic and acetic acids were prepared in order to investigate their physiological activity. The new compounds which were prepared in the course of this research are listed below.

Hydrochlorides of 2-diethylaminoethyl esters of:

1. 2-Methylbenzilic acid.
2. 3-Methylbenzilic acid.
3. 4-Methylbenzilic acid.
4. 2,3-Dimethylbenzilic acid.
5. 2,4-Dimethylbenzilic acid.
6. 2,5-Dimethylbenzilic acid.
7. 2,6-Dimethylbenzilic acid.
8. 3,4-Dimethylbenzilic acid.
9. 3,5-Dimethylbenzilic acid.
10. 2,3,4-Trimethylbenzilic acid.
11. 2,3,5-Trimethylbenzilic acid.
12. 2,3,6-Trimethylbenzilic acid.
13. 2,4,5-Trimethylbenzilic acid.
14. 2,4,6-Trimethylbenzilic acid.
15. 3,4,5-Trimethylbenzilic acid.
16. 2,3,4,5-Tetramethylbenzilic acid.
17. 2,3,4,6-Tetramethylbenzilic acid.
18. 2,3,5,6-Tetramethylbenzilic acid.
19. 2,3,4,5,6-Pentamethylbenzilic acid.
20. 4-Phenylbenzilic acid.
21. 2,2'-Dimethylbenzilic acid.
22. 3,3'-Dimethylbenzilic acid.
23. 4,4'-Dimethylbenzilic acid.
24. 3,5,3',5'-Tetramethylbenzilic acid.
25. 4,4'-Diisopropylbenzilic acid.
26. 2,2'-Dimethoxybenzilic acid.
27. 4,4'-Dimethoxybenzilic acid.
28. 2,3,2',3'-Tetramethoxybenzilic acid.
29. 3,4,3',4'-Tetramethoxybenzilic acid.
30. 3,4-Methylenedioxybenzilic acid.
31. 2-Methylphenylcyclohexylglycolic acid.
32. 3-Methylphenylcyclohexylglycolic acid.
33. 4-Methylphenylcyclohexylglycolic acid.
34. 2,3-Dimethylphenylcyclohexylglycolic acid.
35. 3,5-Dimethylphenylcyclohexylglycolic acid.
36. 2,4,6-Trimethylphenylcyclohexylglycolic acid.
37. 3,4,5-Trimethylphenylcyclohexylglycolic acid.
38. 2,3,5,6-Tetramethylphenylcyclohexylglycolic acid.
39. 3,3'-Dimethylphenylcyclohexylglycolic acid.
40. 2-Methylcyclohexylglycolic acid.
41. 3-Methylcyclohexylglycolic acid.
42. 4-Methylcyclohexylglycolic acid.
43. 2,3-Dimethyldicyclohexylglycolic acid.
44. 2,4-Dimethyldicyclohexylglycolic acid.
45. 2,6-Dimethyldicyclohexylglycolic acid.
46. 3,4-Dimethyldicyclohexylglycolic acid.
47. 3,5-Dimethyldicyclohexylglycolic acid.
48. 2,3,5-Trimethyldicyclohexylglycolic acid.
49. 2,3,6-Trimethyldicyclohexylglycolic acid.
50. 3,4,5-Trimethyldicyclohexylglycolic acid.
51. 4-Cyclohexylidicyclohexylglycolic acid.
52. 2,2'-Dimethyldicyclohexylglycolic acid.
53. 3,3'-Dimethyldicyclohexylglycolic acid.
54. 4,4'-Dimethyldicyclohexylglycolic acid.
55. 1,1-Diphenyl-1-thioacetoxyacetic acid.
56. 1,1-Diphenyl-1-(isopropylthio) acetic acid.
57. Phenyl-\(A^2\)-cyclohexenylacetic acid.
58. Phenyl-\(A^2\)-cyclohexenylglycolic acid.

Four other compounds prepared were:
59. 2-Diethylaminoethyl 1,1-diphenyl-1-(2-diethylaminoethoxy)-
    acetate dihydrochloride.
60. 2-Diethylaminoethyl 1,1-diphenyl-1-bromoacetate hydrobromide.
61. 1,1-Diphenyl-2-hydroxy-4-N,N-dimethylbutylamine hydrochloride.
62. Oxalate of 2-N,N-diethylaminoethyl methylamide of benzoyl-
    formic acid.

The above compounds have been or will be tested for their physiological activity. Following is the list of new compounds which were ob-
tained as intermediates or as byproducts in the preparation of the above compounds.

63. Diphenylcarboxymethyl N-phenylthiolcarbamate.
64. 1-Mercaptodiphenylacetic acid.
65. 1-Mercapto-3,3'-dimethyldiphenylacetic acid.
66. 1-Mercapto-2,2'-dimethoxydiphenylacetic acid.
67. 4-Methylphenylcyclohexylglycolic acid.
68. 3,5-Dimethylbenzoyl cyanide.
69. 3,5-Dimethylphenylcyclohexylglycolic acid.
70. Phenyl-2,3-dibromocyclohexylacetic acid.
71. 1,1-Diphenyl-1-(1-mercaptoacetoxy)-acetic acid.
72. Benzoylformyl chloride.
73. 1,1-Diphenyl-2-acetoxy-4-N,N-dimethylamino-1-butenyl bromide.

The melting points of 23, 60, 63, and 64, which have been reported before, differ from those found in the present work.
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