SYNTHESIS OF CYCLOALKYL ANALOGUES OF ANTERGAN

by

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We accept this thesis as conforming to the
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ABSTRACT

Cycloalkyl analogues of Antergan with the basic structure of N,N-dimethyl-N'-cycloalkylmethyl-N'-phenylethlenediamine have been synthesized in good yields. The alkyl group was a butyl-, pentyl-, hexyl-, or heptyl-ring structure. The compounds with the benzyl group of Antergan substituted by a hydrogen or a methyl group were also synthesized in good yields.

The general reaction sequence followed was to start with the appropriate cycloalkanecarboxylic acid and build up to a secondary amine via an acid chloride and an amide. Leung's methods (1) were followed and checked up to this step. Further reaction sequences were developed during this study. The desired amine was reacted with chloroacetyl chloride, dimethylamine and then reduced to the tertiary diamine analogues.

The preliminary antihistaminic activity of these analogues was studied and compared with that of Diphenhydramine Hydrochloride Standard Solution. The relative activity of each analogue was also determined.

Signature of Examiners
ACKNOWLEDGEMENT

My sincere gratitude is extended to my major professor, Dr. T. H. Brown, for professional guidance, understanding and encouragement during the course of this study.

I wish to express my thanks to Dr. J. E. Halliday for his guidance in pharmacological tests, and my sincere thanks to Dr. F. S. Abbott for advice and counseling.

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I am most grateful to fellow graduate students for their friendship and helpful advice.
### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Part</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>11</td>
</tr>
<tr>
<td>List of Tables</td>
<td>vi</td>
</tr>
<tr>
<td>List of Figures</td>
<td>vii</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>A. Histamine</td>
<td>1</td>
</tr>
<tr>
<td>B. Analogs of Histamine</td>
<td>7</td>
</tr>
<tr>
<td>C. Antihistamines and Relationship between Structure and Pharmacological Activity</td>
<td>9</td>
</tr>
<tr>
<td>II. STATEMENT OF PROBLEM</td>
<td>13</td>
</tr>
<tr>
<td>III. ANALYTICAL METHODS</td>
<td>14</td>
</tr>
<tr>
<td>IV. EXPERIMENTAL</td>
<td>15</td>
</tr>
<tr>
<td>A. Synthesis of N,N-Dimethyl-N'-Phenylethylene-diamine</td>
<td>15</td>
</tr>
<tr>
<td>1. α-Chloroacetanilide</td>
<td>15</td>
</tr>
<tr>
<td>2. α-Dimethylaminoacetanilide</td>
<td>16</td>
</tr>
<tr>
<td>3. N,N-Dimethyl-N'-Phenylethylenediamine</td>
<td>17</td>
</tr>
<tr>
<td>B. Synthesis of N,N-Dimethyl-N'-Methyl-N'-Phenylethylenediamine</td>
<td>18</td>
</tr>
<tr>
<td>1. α-Chloro-N-Methylacetanilide</td>
<td>18</td>
</tr>
<tr>
<td>2. α-Dimethylamino-N-Methyl-N-Phenylacetamide</td>
<td>20</td>
</tr>
<tr>
<td>3. N,N-Dimethyl-N'-Methyl-N'-Phenylethylenediamine</td>
<td>21</td>
</tr>
<tr>
<td>C. Synthesis of N,N-Dimethyl-N'-Cyclobutylmethyl-N'-Phenylethylenediamine</td>
<td>22</td>
</tr>
<tr>
<td>1. Cyclobutanecarbonyl Chloride</td>
<td>22</td>
</tr>
<tr>
<td>2. Cyclobutanecarboxanilide</td>
<td>23</td>
</tr>
<tr>
<td>Part</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>3. N-Cyclobutylmethyl-N-Phenylamine</td>
<td>23</td>
</tr>
<tr>
<td>4. α-Chloro-N-Cyclobutylmethyl-N-Phenylacetamide</td>
<td>25</td>
</tr>
<tr>
<td>5. α-Dimethylamino-N-Cyclobutylmethyl-N-Phenylacetamide</td>
<td>26</td>
</tr>
<tr>
<td>6. N,N-Dimethyl-N'-Cyclobutylmethyl-N'-Phenylethlenediamine</td>
<td>27</td>
</tr>
</tbody>
</table>

**D. Synthesis of N,N-Dimethyl-N'-Cyclopentylmethyl-N'-Phenylethlenediamine**

1. Cyclopentanecarbonyl Chloride | 29   |
2. Cyclopentanecarboxanilide | 29   |
3. N-Cyclopentylmethyl-N-Phenylamine | 30   |
4. α-Chloro-N-Cyclopentylmethyl-N-Phenylacetamide | 31   |
5. α-Dimethylamino-N-Cyclopentylmethyl-N-Phenylacetamide | 32   |
6. N,N-Dimethyl-N'-Cyclopentylmethyl-N'-Phenylethlenediamine | 33   |

**E. Synthesis of N,N-Dimethyl-N'-Cyclohexylmethyl-N'-Phenylethlenediamine**

1. Cyclohexanecarbonyl Chloride | 34   |
2. Cyclohexanecarboxanilide | 35   |
3. N-Cyclohexylmethyl-N-Phenylamine | 35   |
4. α-Chloro-N-Cyclohexylmethyl-N-Phenylacetamide | 36   |
5. α-Dimethylamino-N-Cyclohexylmethyl-N-Phenylacetamide | 37   |
6. N,N-Dimethyl-N'-Cyclohexylmethyl-N'-Phenylethlenediamine | 39   |

**F. Synthesis of N,N-Dimethyl-N'-Cycloheptylmethyl-N'-Phenylethlenediamine**

1. Cycloheptanecarboxylic Acid | 40   |
<table>
<thead>
<tr>
<th>Part</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Cycloheptanecarbonyl Chloride</td>
<td>42</td>
</tr>
<tr>
<td>3. Cycloheptanecarboxanilide</td>
<td>42</td>
</tr>
<tr>
<td>4. N-Cycloheptylmethyl-N-Phenylamine</td>
<td>43</td>
</tr>
<tr>
<td>5. α-Chloro-N-Cycloheptylmethyl-N-Phenylacetamide</td>
<td>44</td>
</tr>
<tr>
<td>6. α-Dimethylamino-N-Cycloheptylmethyl-N-Phenylacetamide</td>
<td>45</td>
</tr>
<tr>
<td>7. N,N-Dimethyl-N'-Cycloheptylmethyl-N'-Phenylethylene diamine</td>
<td>46</td>
</tr>
</tbody>
</table>

V. DISCUSSION OF CHEMISTRY | 48 |
VI. PRELIMINARY ANTIHISTAMINIC ACTIVITY STUDIES | 63 |
VII. SUMMARY | 68 |
VIII. INFRARED SPECTRA | 70 |
IX. LIST OF REFERENCES | 89 |
Biographical Information | 91 |
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Histamine Content of Tissues Compared with Heparin Content and the Relative</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mast-cell Content</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Mast Cell Number in Guinea-pig Inferior Pulmonary Lobes Before and After</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Histamine Content in Guinea-pig Inferior Pulmonary Lobes Before and After</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Cycloalkanecarbonyl Chlorides</td>
<td>49</td>
</tr>
<tr>
<td>5.</td>
<td>Cycloalkane-carboxanilides</td>
<td>50</td>
</tr>
<tr>
<td>6.</td>
<td>N-Cycloalkylmethyl-N-Phenylamines</td>
<td>52</td>
</tr>
<tr>
<td>7.</td>
<td>Cycloalkyl Analogues of Antergan</td>
<td>52</td>
</tr>
<tr>
<td>8.</td>
<td>α-Chloro-N-(R)-Acetanilides</td>
<td>59</td>
</tr>
<tr>
<td>9.</td>
<td>α-Dimethylamino-N-(R)-N-Phenylacetamide</td>
<td>60</td>
</tr>
<tr>
<td>10.</td>
<td>N,N-Dimethyl-N'-(R)-N'-Phenylethylenediamine</td>
<td>61</td>
</tr>
<tr>
<td>11.</td>
<td>Effects of Cycloalkyl Analogues of Antergan (Mono-HCl Salts) and Diphenhydramine HCl on Response of Isolated Guinea-pig Ileum</td>
<td>64</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Major Routes of Histamine Catabolism in Vivo</td>
<td>7</td>
</tr>
<tr>
<td>2.</td>
<td>$pA_2$ Value for Mono-HCl Salts of Cycloalkyl Analogues of Antergan vs. Diphenhydramine HCl</td>
<td>66</td>
</tr>
<tr>
<td>3.</td>
<td>Infrared Spectrum of $\alpha$-Chloroacetanilide</td>
<td>71</td>
</tr>
<tr>
<td>4.</td>
<td>$\alpha$-Dimethylaminoacetanilide</td>
<td>72</td>
</tr>
<tr>
<td>5.</td>
<td>$N,N$-Dimethyl-$N'$-Phenylethylenediamine</td>
<td>73</td>
</tr>
<tr>
<td>6.</td>
<td>$\alpha$-Chloro-$N$-Methylacetanilide</td>
<td>74</td>
</tr>
<tr>
<td>7.</td>
<td>$\alpha$-Dimethylamino-$N$-Methyl-$N$-Phenylacetamide</td>
<td>75</td>
</tr>
<tr>
<td>8.</td>
<td>$N,N$-Dimethyl-$N'$-Methyl-$N'$-Phenylethylenediamine</td>
<td>76</td>
</tr>
<tr>
<td>9.</td>
<td>$\alpha$-Chloro-$N$-Cyclobutylmethyl-$N$-Phenylacetamide</td>
<td>77</td>
</tr>
<tr>
<td>10.</td>
<td>$\alpha$-Dimethylamino-$N$-Cyclobutylmethyl-$N$-Phenylacetamide</td>
<td>78</td>
</tr>
<tr>
<td>11.</td>
<td>$N,N$-Dimethyl-$N'$-Cyclobutylmethyl-$N'$-Phenylethylenediamine</td>
<td>79</td>
</tr>
<tr>
<td>12.</td>
<td>$\alpha$-Chloro-$N$-Cyclopentylmethyl-$N$-Phenylacetamide</td>
<td>80</td>
</tr>
<tr>
<td>13.</td>
<td>$\alpha$-Dimethylamino-$N$-Cyclopentylmethyl-$N$-Phenylacetamide</td>
<td>81</td>
</tr>
<tr>
<td>14.</td>
<td>$N,N$-Dimethyl-$N'$-Cyclopentylmethyl-$N'$-Phenylethylenediamine</td>
<td>82</td>
</tr>
<tr>
<td>15.</td>
<td>$\alpha$-Chloro-$N$-Cyclohexylmethyl-$N$-Phenylacetamide</td>
<td>83</td>
</tr>
<tr>
<td>16.</td>
<td>$\alpha$-Dimethylamino-$N$-Cyclohexylmethyl-$N$-Phenylacetamide</td>
<td>84</td>
</tr>
<tr>
<td>17.</td>
<td>$N,N$-Dimethyl-$N'$-Cyclohexylmethyl-$N'$-Phenylethylenediamine</td>
<td>85</td>
</tr>
<tr>
<td>18.</td>
<td>$\alpha$-Chloro-$N$-Cycloheptylmethyl-$N$-Phenylacetamide</td>
<td>86</td>
</tr>
<tr>
<td>19.</td>
<td>$\alpha$-Dimethylamino-$N$-Cycloheptylmethyl-$N$-Phenylacetamide</td>
<td>87</td>
</tr>
<tr>
<td>20.</td>
<td>$N,N$-Dimethyl-$N'$-Cycloheptylmethyl-$N'$-Phenylethylenediamine</td>
<td>88</td>
</tr>
</tbody>
</table>
Leung (1) first reported "Cycloalkyl Analogues of Antergan" in 1964. The benzyl group of Antergan was replaced by a cyclopropylmethyl, a cyclobutylmethyl, a cyclopentylmethyl, a cyclohexylmethyl or a cycloheptylmethyl group, but the yield of each of these analogues was very poor. The purpose of this study was to increase the yields of four analogues (cyclobutylmethyl to cycloheptylmethyl) by new synthetic methods and make them available for pharmacological investigations into the nature of antihistaminic receptors. Two other compounds with the benzyl group of Antergan replaced by a hydrogen or a methyl group were also synthesized in order to complete the antihistaminic activity studies for a series of these compounds.

Antergan, N-benzyl-N-phenyl-N',N'-dimethylethylenediamine, was the first clinically effective antihistaminic drug produced in 1942. Although it caused a number of unpleasant side effects such as potentiating the responses to epinephrine and the stimulation of adrenergic nerves (2), the basic Antergan structure has served as a model for a number of the antihistamine drugs in use today. It was hoped in the present study that by replacing one phenyl group in the parent compound with alicyclic structures, a gradual alteration in potency and or selectivity would be found in a series of these compounds.

A. HISTAMINE

Histamine is 4(or 5)-(2'-aminoethyl)imidazole, \( C_9H_9N_3 \).
and is represented structurally by either formula I or II:

\[
\begin{align*}
\text{I} & : \quad \text{H} - \text{N} - \text{C-CH}_2-\text{CH}_2-\text{NH}_2 \\
\text{II} & : \quad \text{H} - \text{N} - \text{C-CH}_2-\text{CH}_2-\text{NH}_2
\end{align*}
\]

The imino hydrogen of the imidazole ring is mobile and can shift from one nitrogen atom to the other with a concomitant shift of the double bond. Thus, the two forms, I and II, of histamine coexist. It has little therapeutic value.

Histamine is widely distributed in mammalian tissues, but the concentration in a given organ has species variation. Much of the tissue histamine is formed in mast cells from L-histidine by enzymatic decarboxylation and it is held in the mast cell granule (3). The histamine content per mast cell is reasonably constant in normal tissue (4). The mast cells are located mainly in connective tissue in relation to blood vessels. Inspection of Table 1 indicates that as good a parallelism exists between histamine and mast cells as between heparin and mast cells in these tissues (3).

| TABLE 1 |
|---|---|---|---|
| TISSUE | HISTAMINE (mg/g) | HEPARIN (mg STANDARD HEPARIN/Kg) | MAST CELLS |
| Rat liver | 0.3 | 0 | 0 |
| Pig aorta | 0.7 | 0 | 0 |
| Ox-liver parenchyma | 4.5 | 56-75 | + |

(to be continued)
3.

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>HISTAMINE</th>
<th>HEPARIN</th>
<th>MAST CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ox aorta</td>
<td>10.0</td>
<td>5-65</td>
<td>+</td>
</tr>
<tr>
<td>Rat subcutaneous tissue</td>
<td>16.0</td>
<td>63</td>
<td>++</td>
</tr>
<tr>
<td>Ox inferior vena cava</td>
<td>20.0</td>
<td>100-120</td>
<td>++</td>
</tr>
<tr>
<td>Ox-liver capsule</td>
<td>40.0</td>
<td>540-830</td>
<td>+++</td>
</tr>
</tbody>
</table>

However, the mast cells are not the only cells containing histamine. Histamine has been found in platelets and in basophilic leukocytes; it is present in high concentration in fetal liver and in the parietal region of the stomach even though mast cells are virtually nonexistent in these sites (4).

The biological significance of histamine in mast cells is at present unknown. The release of histamine from mast cells is connected with the morphological change of the mast cell. Most of the substances known to release histamine, cause damage to the mast cells. In anaphylaxis, although each species has its own peculiarities, there is little room for doubt that most — although certainly not all — of the histamine released by antigen, comes from the mast cells. Mota (5) investigated antigen-induced mast cell damage and histamine release in the intact guinea-pig. The results of the experiment showed that anaphylaxis produced a significant reduction in the number of mast cells and in the histamine content of the lung (see Table 2 and 3) (5).
### TABLE 2

**MAST CELL NUMBER (*) IN GUINEA-PIG INFERIOR PULMONARY LOBES BEFORE AND AFTER ANAPHYLAXIS:**

<table>
<thead>
<tr>
<th>G.P.</th>
<th>BEFORE</th>
<th>AFTER</th>
<th>G.P.</th>
<th>BEFORE</th>
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<tbody>
<tr>
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<td>90</td>
<td>84</td>
<td>22</td>
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(*) The cells were counted under a magnification of 250X. Each figure was mean of 100 fields. Difference between the means of the two lobes highly significant ($P < 0.01$).

### TABLE 3

**HISTAMINE CONTENT (µg/g) IN GUINEA-PIG INFERIOR PULMONARY LOBES BEFORE AND AFTER ANAPHYLAXIS:** Difference between the means of the two lobes highly significant ($P < 0.01$).

<table>
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<td>19</td>
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<td>36</td>
<td>25</td>
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It is well known that the anaphylactic phenomenon can be considered as a sequence of reactions starting by the union of antigen with antibody and having as one of its many consequences the release of histamine. Notwithstanding a great volume of research in the field there is not yet a comprehensive explanation for the mechanism of histamine release by antigen in anaphylaxis. In the investigation of the mechanism of histamine release it was thought that the study of inhibition of histamine release by chemical compounds of known properties could possibly contribute to clear up this issue. For instance, the experiments with phenol (5) showed that the release of histamine from the mast cell by antigen was not a direct consequence of the antigen-antibody reaction but the union of antigen with antibody only triggered off a complex series of events leading to mast cell damage and histamine release. The inhibition of the anaphylactic release of histamine from the mast cells by various metabolic inhibitors (iodoacetate, chloromercuribenzoate and cyanide etc.) and its dependence on pH and temperature strongly suggested the existence of an enzymatic mechanism in this phenomenon (5). The fact that chymotrypsin inhibitors and substrates inhibited the anaphylactic release of histamine strongly implied the involvement of an enzymatic activity similar to that of alpha-chymotrypsin. Furthermore, the discovery of a heat-labile factor in the tissues, probably a pro-enzyme that required calcium for its activation and was necessary for the anaphylactic release of histamine, suggested the participation of complement in this phenomenon (5). However, in spite of observations in
favor of the participation of complement in anaphylaxis there is not yet evidence that complement is necessary for the anaphylactic release of histamine from the mast cell. Another factor necessary for the anaphylactic release of histamine is cellular integrity (5). Histamine release from intracellular particles could be demonstrated only when antigen was applied to intact cells, but not when it was added to isolated intracellular particles. Since histamine is located in the mast cell granules, the union of antigen with antibody on the mast cell membrane must trigger off an enzymatic mechanism able to release histamine from intracellular mast cell granules. Therefore, probably both membrane and intracellular enzymes were involved in the anaphylactic release of histamine from the mast cells (5).

Some of the established pharmacological actions of histamine include increase of capillary permeability, bronchiolar and other smooth muscle constriction, and stimulation of the glands of exocrine secretion (4).

Histamine is degraded either by oxidation or by methylation such that the principle excretion products are imidazoleacetic acid riboside or 1,4-methylimidazole acetic acid (6), respectively (see Figure 1).
7.

FIGURE 1

MAJOR ROUTES OF HISTAMINE CATABOLISM IN VIVO:

Diamine oxidase

Histamine

Methylation

Imidazoleacetaldehyde

1,4-Methylhistamine

Aldehyde dehydrogenase

Imidazoleacetic acid

1,4-Methylimidazole acetaldehyde

Enzymatic synthesis

Ribose

1,4-Methylimidazole acetic acid

B. ANALOGS OF HISTAMINE

Most of the compounds that have histamine-like activities contain in their structures the fragment:

\[ \begin{array}{c}
\text{N} \\
\text{C-C-C-N} \\
\text{or} \\
\text{C=C-C-N}
\end{array} \]
8.

The definition of histamine-like activity is that a compound causes contraction of smooth muscle and lowering of blood pressure, this activity is histamine-like only if it is inhibited by one of the typical antihistamine drugs. It is to be noted here, however, that, although many of the histamine analogs possess activities resembling those of histamine, none has yet been discovered that antagonizes any of the activities of histamine. The antihistamine drugs are not analogs of histamine in a chemical sense.

At first the synthetic analogs were confined to derivatives of imidazole, but in 1941 Walter, Hunt and Fosbinder (12) observed that 2-(2-aminoethyl)-pyridine exhibited typical histamine activity on smooth muscle. Since then many compounds not containing the imidazole ring have been found to have physiological activities resembling histamine. The analogs were divided into seven groups according to their chemical structures (7): I. Imidazole compounds; II. Pyrazole compounds; III. 1,2,3-Triazole compounds; IV. 1,2,4-Triazoles; V. Thiazole compounds; VI. Pyridine compounds; and VII. Miscellaneous compounds.

\[ \text{Imidazole cpds.} \quad \text{Pyrazole cpds.} \quad 1,2,3\text{-Triazole cpds.} \]
A number of the compounds mimic histamine in all of its effects while others may possess only one of histamine's activities. Generally all of the analogs are less active than the parent histamine, but there are two exceptions. N-Methylhistamine and N,N-dimethylhistamine are more active than histamine as stimulants of gastric secretion in the dog (7).

As larger numbers of compounds have been made and tested (210 analogs listed in Lit. (7)), it has become increasingly difficult to formulate any general rule relating structure to histamine-like activity. About all that can be said is that compounds possessing appreciable histamine-like activity consist of small nitrogen-heterocyclic aromatic rings to which are attached 2-aminoethyl side chains.

C. ANTIHISTAMINES AND RELATIONSHIP BETWEEN STRUCTURE AND PHARMACOLOGICAL ACTIVITY

Antihistamines are drugs with the ability to antagonize in varying degree most, but not all, of the pharmacologic actions of histamine (8). They fall into that large group of pharmacological antagonists that appear to act by occupying the "receptor site" on the effector cells to the ex-
clusion of the agonist. Apparently they bind with the histamine receptor without initiating a response. Most antihistamines act as competitive antagonists to histamine.

Antihistamines have found wide therapeutic application, chiefly for the symptomatic control of allergic diseases, due to their high degree of effectiveness after oral administration. It is evident from their mechanism of action and the etiology of allergic diseases that the antihistamine drugs in no sense achieve a cure of the patient's allergy (9). After the administration of a therapeutic dose, temporary block of the effects of histamine is obtained for periods varying from 2 to 12 hours, after which time readministration of the drug is necessary.

Antihistamines were able to inhibit the anaphylactic mast cell damage and histamine release induced by antigen. Mota (5) showed that previous contact of sensitized guinea-pig or rat tissues with antihistamines prevents histamine release and mast cell damage induced by later contact with antigen. The actual mechanism of the inhibitory effect of antihistamines on the anaphylactic mast cell damage and histamine release is not yet known. Probably the inhibition was due to the release by the antihistamine of a large proportion of the available tissue histamine, and therefore the residue left for release by antigen was considerably diminished. It is also possible that antihistamine molecules in a critical concentration near to that required for histamine release become attached to the mast cell membrane and interfere with the antigen-antibody reaction. Alternatively they may inhibit the enzymatic system
required in the anaphylactic reaction. The inhibition of hist-
amine release in anaphylaxis by antihistamines may help to ex-
plain the protective effect of these drugs in anaphylaxis. In
some cases, at least, the protection may be due more to inhibi-
tion of cellular damage than to competition at receptor site.

As most medicinals, agents used as antihistamines po-
ssess additional pharmacological activities (sedative-hypnotic,
anticholinergic, antiserotonin, antitussive, local anesthetic,
and anti-emetic) (9). The parasympatholytic action accounts
for the dryness of the mouth experienced by some patients.
Certain antihistamines can potentiate the cardiovascular action
of norepinephrine. This has been attributed to inhibition of
uptake of norepinephrine by various tissues, resulting in an
increased amount of unbound drug in the plasma reacting with
the active receptor sites (8). Thus, there may be a hazard
when antihistamines are administered to patients taking mono-
amine oxidase inhibiting drugs.

From a chemical standpoint, all of the compounds ex-
hibiting a high degree of antihistaminic activity, with only
a few exceptions, are derived from a common structural formula:

\[
\begin{align*}
& \text{R}_1 \text{X} \text{R}_3 \text{N} \text{R}_4 \\
& \text{R}_2 \text{R}_5
\end{align*}
\]

\( \text{R}_1 \) and \( \text{R}_2 \) are commonly aryl, aryl-methyl (as benzyl), hetero-
cyclic, or heterocyclic-methyl; \( \text{X} \) is =\text{N} (diamine derivative),
=\text{C-O} (aminoalkyl ether), or =\text{CH} (alkylamine); \( \text{R}_3 \) is most fre-
quently a \( -\text{CH}_2-\text{CH}_2- \) group but, in several cases, this group is
part of a cyclic ring; \( \text{R}_4 \) and \( \text{R}_5 \) are usually methyl groups, but,
considered with nitrogen, can be part of a heterocyclic ring. It is once apparent that the core of this structure is a substituted ethylamine, \(-\text{CH}_2\text{-CH}_2\text{-N}=\), also present in histamine; and it may be presumed that it is this portion of the molecule that competes with histamine for cell receptors.
PART II

STATEMENT OF PROBLEM

The yields of each of "Cycloalkyl Analogues of Antergan" reported by Leung (1) were very poor. Attempts were to be made to increase the yields of these compounds by new synthetic methods. The presence of an unsaturated ring attached to the nitrogen conforms to the required structure for antihistaminic activity.

Two related compounds with the benzyl group of Antergan substituted by a hydrogen or a methyl group were also to be synthesized.
Melting points were determined using 6406-H Thomas-Hoover Melting Point Apparatus (Arthur H. Thomas Co., Philadelphia, PA., U.S.A.). All melting points and boiling points were reported uncorrected.

A Beckman IR 10 Infrared Spectrophotometer (Beckman Instruments, Inc., Fullerton, California, U.S.A.) was used to obtain infrared spectra.

Carbon, hydrogen, nitrogen, chlorine and iodine determinations were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Im Max - Planck Institut fur Kohlenforschung, 433 Mulheim (Ruhr), West Germany.
A. Synthesis of N,N-Dimethyl-N'-Phenylethlenediamine:

1. α-Chloroacetanilide:

To a 0.5-liter three-necked flask equipped with a reflux condenser (carrying a drying tube), a side arm for setting a thermometer (range from -100 to 50°C) and a dropping funnel (125 ml.), and a mechanical stirrer was added a solution of aniline (93 g., 1 mole, A.C.S. reagent) in sodium-dried ether (250 ml.) (Note: hereafter referred as dry ether). The solution was stirred over an ice-salt bath for 30 minutes to reach -5 to -10°C. Chloroacetyl chloride (56.5 g., 0.5 mole, Aldrich Chemical Co.) was added dropwise to the vigorously stirred solution from the dropping funnel at such a rate as to keep the temperature of the reaction not higher than 0°C. After the addition was complete, stirring was continued at 0°C for another hour and the mixture was then refluxed on a heating mantle for one hour. The mixture was poured into a beaker and washed with 100 ml. of 5% HCl solution and 100 ml. of distilled water. The white product which precipitated was suction filtered and the layers were separated. The ethereal layer was dried over anhydrous sodium sulfate and reduced in volume to recover more of the anilide product in a total yield of 84.7 g. (0.5 mole, 100%). The anilide was recrystallized from 60% ethanol and melted at 134.5-135.5°C.

Infrared spectrum of the solid amide in KBr showed a strong C-O stretching band at 1675 cm.⁻¹, and the C-H vibra-
tional stretching for an aliphatic hydrocarbon at 2970 cm$^{-1}$ and 2920 cm$^{-1}$; also the absence of N-H stretching for aniline at 3370 cm$^{-1}$ and 3440 cm$^{-1}$ and the presence of C-Cl stretching at 770 cm$^{-1}$ proved the anilide structure (Figure 3).

Anal. Calcd. for C$_8$H$_6$ONCl: C, 56.64; H, 4.76; N, 8.26; Cl, 20.90. Found: C, 56.53; H, 4.85; N, 8.28; Cl, 21.10.

2. $\alpha$-Dimethylaminoacetanilide:

Dimethylamine (32 ml., approx. 0.48 mole) was trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 0.5-liter three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (500 ml.), a thermometer (range from -100 to 50° C.) and an acetone-dry ice condenser (carrying a drying tube). $\alpha$-Chloroacetanilide (40 g., 0.236 mole) was dissolved by the aid of heat in 400 ml. of absolute methanol (10) and the solution was placed in the dropping funnel. The anilide solution was then added dropwise to the vigorously stirred liquid dimethylamine at such a rate as to keep the temperature of the reaction not higher than -2° C.. After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was stirred continuously at -2 to -10° C. for at least 3 hours and then overnight at room temperature. After this time, the white aniline HCl salt was filtered off and the solvent methanol was reduced in volume by flash evaporation. In order to get rid of the dimethylamine HCl salt which had dissolved in methanol, the concentrated residue was dispersed in 200 ml. of distilled water and then extracted with two 200 ml. portions of solvent
ether. The combined ethereal extract was dried over anhydrous sodium sulfate and then reduced in volume. The residue was fractionated under reduced pressure to yield 39.5 g. (0.222 mole, 94%) \( \alpha \)-dimethylaminoacetanilide b.p. 124°C. (1.4 mm.).

Infrared spectrum indicated the presence of dimethylamino group at 2840 cm.\(^{-1}\), 2800 cm.\(^{-1}\), and 2750 cm.\(^{-1}\) (C-H stretching for R-N(CH\(_3\))\(_2\)), and the absence of C-Cl stretching band at 770 cm.\(^{-1}\) (Figure 4).

**Preparation of Methyl Iodide Derivative:**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.); if no immediate reaction occurred, it was heated on a steam-bath for 15 minutes or until the excess reagent had evaporated. The \( \alpha \)-dimethylaminoacetanilide methyl iodide salt was recrystallized from absolute methanol; m.p. 212.5-213.5°C.

**Anal.** Calcd. for C\(_{11}\)H\(_{17}\)ON\(_2\)I: C, 41.26; H, 5.36; N, 8.75; I, 39.63. Found: C, 41.44; H, 5.45; N, 8.95; I, 39.75.

**3. N.N-Dimethyl-N'-Phenylethlenediamine:**

400 ml. of dry ether was placed in a 0.5-liter three-necked flask equipped with a dropping funnel (125 ml.), a reflux condenser (drying tube), and a mechanical stirrer. Lithium aluminum hydride (10.7 g., 0.28 mole) was added to the ether, and was gently refluxed with stirring for 4 hours. A solution of \( \alpha \)-dimethylaminoacetanilide (25 g., 0.14 mole) in dry ether (50 ml.) was placed in the dropping funnel, and added to the LiAlH\(_4\) solution at such a rate as to maintain gentle
reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

After this time, the heating mantle was replaced by an ice bath and 45 ml. of water was slowly added to the vigorously stirred mixture in the flask to decompose the excess hydride. Stirring was continued for 30 minutes after the water addition was complete. Sufficient 40% NaOH solution was added to cause a clear separation of the ethereal layer. The mixture was centrifuged and the ether layer was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to yield 21 g. (0.128 mole, 91.3%) N,N-dimethyl-N' -phenylethlenediamine b.p. 81°C. (0.75 mm.).

Infrared spectrum indicated complete reduction by the absence of the carbonyl absorption band at 1690 cm.\(^{-1}\), and by the shift of the N-H stretching vibration to 3400 cm.\(^{-1}\) (Figure 5).

**Methyl Iodide Derivative:**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the \(\alpha\)-dimethylaminoacetanilide methyl iodide derivative. N,N-Dimethyl-N' -Phenylethlenediamine methyl iodide salt was recrystallized from absolute ethanol and melted at 179.7-180.5°C.

**Anal. Calcd.** for C\(_{11}\)H\(_{19}\)N\(_2\)I: C, 43.14; H, 6.27; N, 9.15; I, 41.44. Found: C, 43.07; H, 6.38; N, 9.22; I, 41.58.

**B. Synthesis of N,N-Dimethyl-N' -Methyl-N' -Phenylethlenediamine:**

1. \(\alpha\)-Chloro-N-Methylacetanilide:
To a 0.5-liter three-necked flask equipped with a reflux condenser (drying tube), a side arm for setting a thermometer (range from -100 to 50°C.) and a dropping funnel (125 ml.), and a mechanical stirrer was placed a solution of N-methylaniline (70 g., 0.65 mole, Eastman Organic Chemicals) in dry ether (300 ml.). The solution was stirred over an ice-salt bath for 30 minutes to reach -5 to -10°C. Chloroacetyl chloride (37.3 g., 0.33 mole) was added dropwise into the vigorously stirred solution from the dropping funnel at such a rate as to keep the temperature of the reaction not higher than 0°C. After the addition was complete, stirring was continued at 0°C. for 2 hours and the mixture was then refluxed on a heating mantle for one hour. After this time, 50 ml. of 5% HCl solution was added and refluxing was continued with stirring for 30 minutes. The white amine HCl salt was filtered off and the layers were separated. The ethereal layer was further washed with 50 ml. of 5% HCl solution and two 50 ml. portions of water and then dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to obtain crude solid product which was recrystallized from n-hexane (technical grade) to yield 60 g. (0.326 mole, 100%) α-chloro-N-methyl-acetanilide m.p. 67.8-68.8°C.

Infrared spectrum showed the absence of N-H stretching vibration band at 3440 cm.\(^{-1}\), and the presence of a strong carbonyl absorption at 1700 cm.\(^{-1}\) and C-Cl stretching band at 800 cm.\(^{-1}\) (Figure 6).

**Anal. Calcd.** for \(C_{9}H_{10}ONCl\): C, 58.86; H, 5.50; N,
20.

7.63; Cl, 19.30. Found: C, 59.05; H, 5.64; N, 7.76; Cl, 19.55.

2. \(\alpha\)-Dimethylamino-N-Methyl-N-Phenylacetamide:

Dimethylamine (30 ml., approx. 0.45 mole) was trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 0.5-liter three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (500 ml.), a thermometer (range from -100 to 50 °C.), and an acetone-dry ice condenser with drying tubes. A solution of \(\alpha\)-chloro-N-methylacetanilide (40.4 g., 0.22 mole) in 400 ml. of absolute methanol (10) was placed into the dropping funnel and was added dropwise to the vigorously stirred liquid dimethylamine at such a rate as to keep the temperature of the reaction not higher than -2 °C. After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was stirred continuously for at least 3 hours at -2 to -10 °C. and then overnight at room temperature. After this time, the white amine HCl salt was filtered off and the solvent methanol was reduced in volume by flash evaporation. In order to get rid of the dimethylamine HCl salt which had dissolved in methanol, the concentrated residue was dispersed in 200 ml. of distilled water and then extracted with two 200 ml. portions of solvent ether. The combined ethereal extract was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to yield 38.1 g. (0.198 mole, 90.5 %) \(\alpha\)-dimethylamino-N-methyl-N-phenylacetamide b.p. 106 °C. (0.3 mm.).

The infrared spectrum indicated the presence of a
dimethylamino group at 2880 cm\(^{-1}\), 2840 cm\(^{-1}\) and 2780 cm\(^{-1}\) (C-H stretching vibration for R-N(CH\(_3\))\(_2\)), and the absence of C-Cl stretching band at 800 cm\(^{-1}\) (Figure 7).

**Methyl Iodide Derivative:**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the \(\alpha\)-dimethylaminoacetanilide methyl iodide derivative. The \(\alpha\)-dimethylamino-N-methyl-N-phenylacetamide methyl iodide salt was recrystallized from absolute ethanol and then ethylacetate; m.p. 148.8-150.0\(^{0}\)C.

**Anal.** Calcd. for C\(_{12}\)H\(_{19}\)ON\(_2\)I: C, 43.12; H, 5.74; N, 8.38; I, 37.97. Found: C, 43.21; H, 5.80; N, 8.21; I, 38.20.

**3. N,N-Dimethyl-N'-Methyl-N'-Phenylethlenediamine:**

In a 0.5-liter three-necked flask equipped with a dropping funnel (125 ml.), a reflux condenser (drying tube), and a mechanical stirrer was placed 320 ml. of dry ether. Lithium aluminum hydride (7.9 g., 0.2 mole) was added to the ether, and was gently refluxed with stirring for 4 hours. A solution of \(\alpha\)-dimethylamino-N-methyl-N-phenylacetamide (20 g., 0.1 mole) in dry ether (50 ml.) was placed into the dropping funnel, and was added to the LiAlH\(_4\) solution at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

After this time, the heating mantle was replaced by an ice bath and 30 ml. of water was slowly added to the vigorously stirred mixture in the flask to decompose the excess hydride. Stirring was continued for 30 minutes after the water
addition was complete. Sufficient 40% NaOH solution was added to allow a clear separation of the ethereal layer. The mixture was centrifuged and the ether layer was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to yield 14.3 g. (0.08 mole, 77.3%) N,N-dimethyl-N'-methyl-N'-phenylethylenediamine b.p. 97-98°C. (1.9 mm.).

A tertiary amine was indicated by the absence of C=O absorption band at 1680 cm⁻¹ due to complete reduction of the tertiary amide carbonyl group (Figure 8).

**Methyl Iodide Derivative:**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the α-dimethylaminoacetanilide methyl iodide derivative. The N,N-dimethyl-N'-methyl-N'-phenylethylenediamine methyl iodide salt was re-crystallized from absolute ethanol and melted at 195-196°C.

*Anal.* Calcd. for C₁₂H₂₁N₂I: C, 45.00; H, 6.62; N, 8.75; I, 39.63. Found: C, 44.93; H, 7.06; N, 8.66; I, 39.68.

**C. Synthesis of N,N-Dimethyl-N'-Cyclobutylmethyl-N'-Phenylethylenediamine:**

1. **Cyclobutanecarbonyl Chloride:**

Cyclobutanecarboxylic acid (100 g., 1 mole, Aldrich Chemical Co.) was placed in a 0.5-liter three-necked flask fitted with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (250 ml.). To the stirred acid was added thionyl chloride (200 g., 1.68 mole, reagent grade-The British Drug Houses Ltd.) and the mixture was refluxed on a heating mantle for 2 hours. The product was distilled to
23.
give a forerun and cyclobutanecarbonyl chloride b.p. 130–136°C. (1 atm.). Yield: 80.8 g. (0.68 mole, 68.1%). (Lit. (1) b.p. 130–142°C., 63%; (11) b.p. 130–140°C., 70%).

2. Cyclobutanecarboxanilide:
A mixture of aniline (93 g., 1 mole), pyridine (79 g., 1 mole) and dry benzene (180 ml.) was placed in a 0.5-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (250 ml.). Cyclobutanecarbonyl chloride (80.8 g., 0.68 mole) was added dropwise from the dropping funnel into the stirred mixture. After the addition was complete, the reaction was stirred for 1 hour at room temperature, and was poured into a beaker cooled in an ice-bath. The white amide which precipitated was suction filtered and washed with water (300 ml.). The benzene layer was separated and dried with anhydrous sodium sulfate. The solvent was reduced in volume to collect more of the crude anilide with total yield of 115.4 g. (0.66 mole, 96.6%). Cyclobutanecarboxanilide was recrystallized from a benzene-petroleum ether mixture; m.p. 111–112°C. (Lit. (13) m.p. 109.0–110.6°C.; (14) m.p. 111–112°C.).

Infrared spectrum of cyclobutanecarboxanilide showed the N-H stretching vibration of a secondary amide at 3250 cm.\(^{-1}\) and 3300 cm.\(^{-1}\), and C-H stretching vibration of aromatic benzene ring at 3050 cm.\(^{-1}\) and 3080 cm.\(^{-1}\); also the C=O absorption was shifted from 1800 cm.\(^{-1}\) (carbonyl chloride) to the secondary amide carbonyl absorption at 1660 cm.\(^{-1}\) (1).

3. N-Cyclobutylmethyl-N-Phenylamine:
A 1-liter three-necked flask was equipped with a
dropping funnel (250 ml.), a mechanical stirrer and a Soxhlet
apparatus protected with a calcium chloride drying tube. Li-
thium aluminum hydride (30.4 g., 0.8 mole) in dry ether (600
ml.) was placed into the flask, and refluxed gently with stir-
ring for 4 hours. Then cyclobutanecarboxanilide (60 g., 0.34
mole) was packed into the Soxhlet extractor whose bottom was
lined with glass wool and a filter paper to prevent the bloc-
kage of the siphon arm. Three glass rods were inserted into
the powder as channels for the extracting solvent. Refluxing
was continued until all the anilide had been carried into the
flask. The reaction was then refluxed for 4 days. At the end
of this time, 100 ml. of water was added slowly to decompose
the excess hydride. The flask was cooled in an ice-bath and
stirring was continued until the mixture became white in color
(30 minutes approx.); then sufficient 40% NaOH solution was
added to allow clear separation of the ethereal layer. The
ether insoluble residue was separated by centrifugation; the
ethereal layer was dried over anhydrous sodium sulfate over-
night. The solvent was removed by flash evaporation and the
residue distilled under vacuum to yield 47.5 g. (0.295 mole,
86.5%) of the amine with b.p. range of 88-96°C. (0.8 mm.).
(Lit. (1) b.p. 150-160°C. (20 mm.), 98%).

Infrared spectrum for the reduction product showed
the absence of the carbonyl band at 1660 cm.\(^{-1}\). Due to the
absence of the oxygen-hydrogen interaction, the N-H stretching
shifted to 3420 cm.\(^{-1}\) from 3250 cm.\(^{-1}\) and 3300 cm.\(^{-1}\) (anilide)
(1).
4. α-Chloro-N-Cyclobutylmethyl-N-Phenylacetamide:

In a 0.5-liter three-necked flask equipped with a reflux condenser (drying tube), a side arm for setting a thermometer (range from -100 to 50°C.) and a dropping funnel (125 ml.), and a mechanical stirrer was placed a solution of N-cyclobutylmethyl-N-phenylamine (47 g., 0.29 mole) in dry ether (250 ml.). The solution was stirred over an ice-salt bath for 30 minutes to reach -5 to -10°C. Chloroacetyl chloride (17 g., 0.15 mole) was added from the dropping funnel to the vigorously stirred solution at such a rate as to keep the temperature of the reaction not higher than 0°C.. After the addition was complete, the reaction was continued stirring at 0°C. for 3 hours and then refluxed on a heating mantle for one hour. After this time, 50 ml. of 5% HCl solution was added and refluxing was continued with stirring for 30 minutes. The white amine HCl salt was filtered off and the ethereal layer was separated. The organic layer was further washed with 50 ml. of 5% HCl and two 50 ml. portions of distilled water and then dried with anhydrous sodium sulfate. The solvent ether was removed by flash evaporation and the residue distilled under vacuum to yield 34.6 g. (0.145 mole, 100%) α-chloro-N-cyclobutylmethyl-N-phenylacetamide b.p. 149-150°C. (1 mm.) which crystallized out after standing overnight. The compound was recrystallized from n-pentane (b.p. 35-37°C., latm.); m.p. 45.2-46.2°C..

The tertiary amide was indicated by the absence of N-H stretching band at 3420 cm.⁻¹, and by the presence of
26.

carbonyl stretching at 1675 cm.\(^{-1}\) and C-Cl stretching band at 790 cm.\(^{-1}\) (Figure 9).

**Anal. Calcd.** for C\(_{13}\)H\(_{16}\)ONCl: C, 65.67; H, 6.80; N, 5.89; Cl, 14.91. **Found:** C, 65.62; H, 7.11; N, 5.87; Cl, 15.08.

5. \(\alpha\)-Dimethylamino-N-Cyclobutylmethyl-N-Phenylacetamide:

Dimethylamine (17.5 ml., approx. 0.26 mole) was trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 0.5-liter three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (500 ml.), a thermometer (range from -100 to 50°C.), and an acetone-dry ice condenser (drying tube). A solution of \(\alpha\)-chloro-N-cyclobutylmethyl-N-phenylacetamide (30 g., 0.126 mole) in dry ether (300 ml.) was added dropwise to the vigorously stirred liquid dimethylamine in the flask at such a rate as to keep the temperature of the reaction not higher than -2°C. After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was continued stirring at -2 to -10°C. for at least 3 hours and then overnight at room temperature. After this time, the white amine HCl salt was filtered off and the solvent ether was reduced in volume by flash evaporation. The residue was fractionated under vacuum to yield 25.1 g. (80.7%) \(\alpha\)-dimethylamino-N-cyclobutylmethyl-N-phenylacetamide b.p. 134-135°C. (0.9 mm.).

The infrared spectrum showed the presence of a dimethylamino group at 2850 cm.\(^{-1}\), 2800 cm.\(^{-1}\), and 2760 cm.\(^{-1}\) (C-H stretching vibration for R-N(CH\(_3\))\(_2\)), and the absence of the C-Cl stretching band at 790 cm.\(^{-1}\) (Figure 10).

**Methyl Iodide Derivative:**
The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the α-dimethylaminoacetanilide methyl iodide derivative. The α-dimethylamino-N-cyclobutylmethyl-N-phenylacetamide methyl iodide salt was recrystallized from absolute ethanol and acetone; m.p. 147°C.

Anal. Calcd. for C_{16}H_{25}ON_{2}I: C, 49.48; H, 6.50; N, 7.22; I, 32.68. Found: C, 49.23; H, 6.75; N, 7.04; I, 32.68.

6. N,N-Dimethyl-N'-Cyclobutylmethyl-N'-Phenylethylene-diamine;

In a 0.5-liter three-necked flask equipped with a mechanical stirrer, a dropping funnel (125 ml.) and a reflux condenser (drying tube) was placed 300 ml. of dry ether. Lithium aluminum hydride (6.2 g., 0.16 mole) was added to the ether, and was gently refluxed with stirring for 4 hours. A solution of α-dimethylamino-N-cyclobutylmethyl-N-phenylacetamide (20 g., 0.08 mole) in dry ether (50 ml.) was placed in the dropping funnel, and was added to the Lithium aluminum hydride solution at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

At the end of this time, the heating mantle was replaced by an ice-bath. 20 ml. of water was slowly added to the flask to decompose the excess hydride. Stirring was continued for 30 minutes; then enough 40% NaOH solution was added to cause a clear separation of the ethereal layer. The mixture was centrifuged and the ether layer was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to yield 17.4 g. (0.075 mole, 92.1%) N,N-dimethyl-
N'-cyclobutylmethyl-N'-phenylethlenediamine b.p. 120-125°C (0.8 mm.). (Lit. (1) b.p. 168-179°C (20 mm.), 10%).

A tertiary amine was indicated by the absence of C=O absorption band at 1675 cm\(^{-1}\) due to complete reduction of the tertiary amide carbonyl group (1) (Figure 11).

**Methyl Iodide Derivative:**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the \(\alpha\)-dimethylaminoacetanilide methyl iodide derivative. The N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethlenediamine methyl iodide salt was recrystallized from reagent acetone. Observed m.p. 135-136°C.

**Anal.** Calcd. for C\(_{16}\)H\(_{27}\)N\(_2\)I: C, 51.33; H, 7.28; N, 7.48; I, 33.90. Found: C, 51.41; H, 7.64; N, 7.42; I, 34.09.

**Preparation of Hydrochloride Derivative:**

Dry hydrogen chloride was passed from a cylinder into a solution of the tertiary amine (1 g.) in dry ether (50 ml.). When precipitation was complete, the solid was suction filtered under a stream of dry nitrogen gas to prevent it from contacting air moisture and was washed with a small amount of dry ether. The white HCl salt was recrystallized from absolute ethanol (10) and dry ether. The N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethlenediamine HCl salt melted at 180.5-181.5°C.

**Anal.** Calcd. for C\(_{15}\)H\(_{25}\)N\(_2\)Cl: C, 67.00; H, 9.39; N, 10.42; Cl, 13.19. Found: C, 67.01; H, 9.25; N, 10.33; Cl, 13.11.
D. Synthesis of N,N-Dimethyl-N'-Cyclopentylmethyl-N'-Phenyl-ethylenediamine:

1. Cyclopentanecarboxyl Chloride:

In a 0.5-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (250 ml.) was placed cyclopentanecarboxylic acid (75.4 g., 0.66 mole, Aldrich Chemical Co.). To the stirred acid was added thionyl chloride (125 ml., approx. 1.72 mole) from the dropping funnel. The mixture was then refluxed for 2 hours with stirring and the excess thionyl chloride removed by co-distillation with 110 ml. of dry benzene. The residue was distilled under reduced pressure; the fraction b.p. 157-160°C. (760 mm.) was collected in 53.5 g. (0.4 mole, 61%) yield. (Lit. (1) b.p. 160-163°C., 76%; (14) b.p. 160-162°C., 86%).

2. Cyclopentanecarboxanilide:

Aniline (37.2 g., 0.4 mole) and pyridine (31.6 g., 0.4 mole) in dry benzene (100 ml.) were placed in a 0.5-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (125 ml.). Cyclopentanecarboxyl chloride (53 g., 0.4 mole) was added dropwise to the stirred and cooled mixture. After the addition was complete, the reaction was stirred for 30 minutes at room temperature. The mixture was poured into a beaker and washed with 200 ml. of water. The white product which precipitated was suction filtered and the benzene layer was reduced in volume to recover more of the anilide in a total yield of 74 g. (0.39 mole, 97.9%). The amide was recrystallized from carbon
tetrachloride; m.p. 159-161°C. (Lit. (15) m.p. 160.1-161.2°C.).

Infrared spectrum showed the N-H stretching vibration of a secondary amide at 3300 cm.\(^{-1}\) and 3260 cm.\(^{-1}\), C-H stretching vibration of aromatic benzene ring at 3040 cm.\(^{-1}\) and 3060 cm.\(^{-1}\), and the C=O absorption was shifted from 1790 cm.\(^{-1}\) (carbonyl chloride) to the secondary amide carbonyl absorption at 1660 cm.\(^{-1}\) (1).

3. N-Cyclopentylmethyl-N-Phenylamine:

To 850 ml. of dry ether in a 1-liter three-necked flask equipped with a mechanical stirrer, a dropping funnel (250 ml.) and a Soxhlet extractor protected from moisture by a calcium chloride tube was added lithium aluminum hydride (30.4 g., 0.8 mole). The mixture was stirred with gentle refluxing for 4 hours. After this time, cyclopentanecarboxanilide (73 g., 0.386 mole) was packed into the Soxhlet extractor as described for cyclobutanecarboxanilide under section PART IV C.3. Refluxing was continued until all the anilide had been dissolved. The reaction then allowed to reflux for 4 days, and was then worked up with water (100 ml.) and 40% NaOH solution. The solid was separated by centrifugation and the ethereal layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue b.p. 124°C. (2.8 mm.) was collected in 57.3 g. (0.327 mole, 84.8%) yield. (Lit. (1) b.p. 154°C. (20 mm.), 97%).

Infrared spectrum showed the absence of the C=O band at 1660 cm.\(^{-1}\) indicating complete reduction had occurred. The strong N-H vibrational band of a secondary amine was observed
at 3440 cm$^{-1}$, shifted in frequency from the same N-H for the anilide compound (1).

4. $\alpha$-Chloro-N-Cyclopentylmethyl-N-Phenylacetamide:

In a 0.5-liter three-necked flask equipped with a reflux condenser (drying tube), a side arm for setting a thermometer (range from -100 to 50°C.) and a dropping funnel (125 ml.), and a mechanical stirrer was placed a solution of N-cyclopentylmethyl-N-phenylamine (50.8 g., 0.29 mole) in dry ether (300 ml.). The solution was stirred over an ice-salt bath for 30 minutes to reach -5 to -10°C. Chloroacetyl chloride (17 g., 0.15 mole) was added to the vigorously stirred solution from the dropping funnel at such a rate as to keep the temperature of the reaction not higher than 0°C. After the addition was complete (approx. 1 hour), the reaction was stirred continuously at 0°C. for 3 hours and then refluxed on a heating mantle for one hour. After this time, 50 ml. of 5% HCl solution was added and refluxing with stirring was continued for 30 minutes. The white amine HCl salt was filtered off and the layers were separated. The ethereal layer was further washed with 50 ml. of 5% HCl solution and two 50 ml. portions of water and then dried over anhydrous sodium sulfate. The solvent ether was removed by flash evaporation and the residue crystallized when mixed with a small amount of petroleum ether (b.p. range from 30 to 60°C.) and cooled over dry ice and scratched. The crude product was recrystallized from n-pentane (b.p. 35-37°C., 1 atm.) to yield 36.5 g. (0.145 mole, 100%) $\alpha$-chloro-N-cyclopentylmethyl-N-phenylacetamide; m.p. 55-56°C.
Infrared spectrum of $\alpha$-chloro-N-cyclopentylmethyl-N-phenylacetamide was indicated by the absence of N-H stretching band at $3440\ \text{cm}^{-1}$ and by the presence of a strong carbonyl band at $1670\ \text{cm}^{-1}$ and C-Cl stretching at $800\ \text{cm}^{-1}$ (Figure 12).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{ONCl}$: C, 66.78; H, 7.22; N, 5.56; Cl, 14.08. Found: C, 66.72; H, 7.23; N, 5.61; Cl, 13.92.

5. $\alpha$-Dimethylamino-N-Cyclopentylmethyl-N-Phenylacetamide:

Dimethylamine (13.3 ml., approx. 0.2 mole) was trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 0.5-liter three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (500 ml.), a thermometer (range from -100 to $50^\circ\text{C.}$) and an acetone-dry ice condenser (drying tube). A solution of $\alpha$-chloro-N-cyclopentylmethyl-N-phenylacetamide (25.2 g., 0.1 mole) in 250 ml. of dry ether was added dropwise to the vigorously stirred liquid dimethylamine in the flask at such a rate as to keep the temperature of the reaction not higher than $-2^\circ\text{C.}$ After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was stirred continuously at $-2$ to $-10^\circ\text{C.}$ for at least 3 hours and then overnight at room temperature. After this time, the white amine HCl salt was filtered off and the solvent ether was reduced in volume by flash evaporation. The residue crystallized when mixed with a small amount of petroleum ether (b.p. range from 30 to $60^\circ\text{C.}$) and cooled over dry ice and scratched. The crude product (23.4 g., 0.09 mole, 90% yield) was recrystallized from
n-pentane (b.p. 35-37°C, 1 atm.); m.p. 45-46°C.

Infrared spectrum of α-dimethylamino-N-cyclopentylmethyl-N-phenylacetamide showed the presence of the dimethylamino group at 2830 cm.\(^{-1}\), 2780 cm.\(^{-1}\) and 2750 cm.\(^{-1}\) (C-H stretching vibration for R-N(CH\(_3\))\(_2\)), and the absence of C-Cl stretching band at 800 cm.\(^{-1}\) (Figure 13).

6. N,N-Dimethyl-N'-Cyclopentylmethyl-N'-Phenylethylene-diamine:

To a 0.5-liter three-necked flask equipped with a dropping funnel (250 ml.), a reflux condenser (drying tube) and a mechanical stirred was added 250 ml. of dry ether. Lithium aluminum hydride (6.1 g., 0.16 mole) was added to the ether, and was gently refluxed with stirring for 4 hours. A solution of α-dimethylamino-N-cyclopentylmethyl-N-phenylacetamide (20.8 g., 0.08 mole) in dry ether (100 ml.) was placed into the dropping funnel, and was added at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

The reaction was then worked up with distilled water (20 ml.) and sufficient 40% NaOH solution to give separation. The separated ethereal layer was dried over anhydrous sodium sulfate and reduced in volume to yield 17.8 g. (0.072 mole, 90.3%) N,N-dimethyl-N'-cyclopentylmethyl-N'-phenylethylene-diamine b.p. 136-138°C. (1 mm.). (Lit. (1) b.p. 185-189°C. (21 mm.), 10.2%).

The tertiary amine was shown by the absence of the C=O absorption band at 1670 cm.\(^{-1}\) due to complete reduction of the tertiary amide carbonyl group (1) (Figure 14).
Methyl Iodide Derivative:

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the α-dimethyl-amino-acetanilide methyl iodide derivative. The N,N-dimethyl-N'-cyclopentylmethyl-N'-phenylethylenediamine methyl iodide salt was recrystallized from reagent acetone; m.p. 163-164°C.

Anal. Calcd. for C_{17}H_{29}N_{2}I: C, 52.57; H, 7.54; N, 7.21; I, 32.67. Found: C, 52.39; H, 7.96; N, 7.23; I, 32.71.

Hydrochloride Derivative:

The white HCl salt was prepared as described for the N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethylenediamine HCl derivative. Observed m.p. 180-181°C.

Anal. Calcd. for C_{16}H_{27}N_{2}Cl: C, 67.92; H, 9.64; N, 9.90; Cl, 12.53. Found: C, 67.83; H, 9.46; N, 10.11; Cl, 12.39.

E. Synthesis of N,N-Dimethyl-N'-Cyclohexylmethyl-N'-Phenylethylenediamine:

1. Cyclohexanecarbonyl Chloride:

To a 1-liter three-necked flask fitted with a reflux condenser (drying tube), a dropping funnel (250 ml.) and a mechanical stirrer was placed cyclohexanecarboxylic acid (128 g., 1 mole, practical grade - Eastman Kodak). To the stirred acid was added thionyl chloride (238 g., 2 moles) from the dropping funnel. The flask was placed on a heating mantle and heated at reflux for 1.5-2 hours. After that time, the mixture was distilled, collecting the crude product from 160-185°C. This fraction was redistilled under reduced pressure collecting the fraction boiling at 82-85°C. (14-15 mm.) to yield 118 g. (0.8
35. mole, 80.5%). (Lit. (16) b.p. 67-67.5°C. (14 mm.), 81%; (17) b.p. 76°C. (17 mm.).

2. Cyclohexanecarboxanilide:

A mixture of aniline (93 g., 1 mole), pyridine (79 g., 1 mole), and dry benzene (100 ml.) was placed in a 1-liter three-necked flask fitted with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (250 ml.). To the stirred mixture in the flask (cooled in an ice-bath) was added cyclohexanecarbonyl chloride (105.5 g., 0.72 mole) drop-wise. After the addition was complete, the reaction was refluxed with stirring for 1 hour, cooled and washed with water (200 ml.). The solid which precipitated was suction filtered and the layers were separated. The aqueous phase was extracted with two 100 ml. portions of ether. The ether extracts were combined with the benzene layer, and dried with anhydrous sodium sulfate. The solvents were removed by flash evaporation to recover more of the anilide in a total yield of 126.1 g. (0.62 mole, 86.3%). The amide was recrystallized from isopropyl alcohol; m.p. 145-146°C. (Lit. (18) m.p. 143-145°C.; (19) m.p. 145-146°C.; (20) m.p. 146°C.).

3. N-Cyclohexylmethyl-N-Phenylamine:

In a 2-liter three-necked flask equipped with a mechanical stirrer, a Soxhlet extractor (drying tube) and a dropping funnel (250 ml.) was placed lithium aluminum hydride (36 g., 1 mole) in dry ether (1600 ml.). The mixture was stirred with gentle reflux on a heating mantle for 4 hours. After this time, cyclohexanecarboxanilide (101.5 g., 0.5 mole) was
packed into the Soxhlet extractor as described for cyclobutane-carboxanilide under section PART IV C.3. Refluxing with stirring was continued until all the anilide had been dissolved. The refluxing was continued with stirring for 72 hours. The reaction was then worked up with water (100 ml.) and sufficient 40% NaOH solution for complete separation. To separate the free amine from any unreduced amide, the ether solution was extracted with 5% HCl solution. The aqueous phase was separated and treated with 40% NaOH solution to reform the free amine which was then extracted with ether solvent. The combined ether extracts were dried over anhydrous sodium sulfate. The ether solvent was removed by flash evaporation to yield 80.6 g. (0.426 mole, 85.3%) N-cyclohexylmethyl-N-phenylamine b.p. 112-114°C. (1 mm.); the HCl salt of the amine melted at 220-222°C. (Lit. (1) b.p. 170-174°C. (12 mm.), 59%; (21) b.p. 168-170°C. (11 mm.), HCl salt m.p. 232°C.).

Infrared spectrum for the amine showed the absence of the C=O band at 1670 cm.\(^{-1}\) indicating complete reduction of the amide. N-H stretching vibration with one sharp peak at 3435 cm.\(^{-1}\) was characteristic of a secondary amine (1).

4. \(\alpha\)-Chloro-N-Cyclohexylmethyl-N-Phenylacetamide:

In a 0.5-liter three-necked flask equipped with a reflux condenser (drying tube), a side arm for setting a thermometer (range from -100 to 50°C.) and a dropping funnel (125 ml.), and a mechanical stirrer was placed a solution of N-cyclohexylmethyl-N-phenylamine (79.5 g., 0.42 mole) in dry ether (250 ml.). The solution was stirred over an ice-salt bath for
30 minutes to reach -5 to -10°C. Chloroacetyl chloride (24.9 g., 0.22 mole) was added from the dropping funnel to the vigorously stirred solution at such a rate as to keep the temperature of the reaction not higher than 0°C. After the addition was complete (approx. 1 hour), the reaction was continued stirring at 0°C. for 3 hours and then refluxed on a heating mantle for one hour. At the end of this time, 80 ml. of 5% HCl solution was added and refluxing was continued with stirring for 30 minutes. The white amine HCl salt was filtered off and the layers were separated. The ethereal layer was further washed with 50 ml. of 5% HCl solution and two 50 ml. portions of distilled water and then dried over anhydrous sodium sulfate. The solvent ether was removed by flash evaporation to yield 55.8 g. (0.21 mole, 100%) α-chloro-N-cyclohexylmethyl-N-phenylacetamide b.p. 170-182°C. (2.4-2.6 mm.) which crystallized after standing overnight. The compound was recrystallized from n-pentane (b.p. 35-37°C., 1 atm.) and melted at 52-53°C.

Infrared spectrum of the amide was indicated by the absence of the N-H stretching vibration band at 3435 cm.⁻¹, and by the presence of a strong carbonyl absorption at 1680 cm.⁻¹ (characteristic of tertiary amide) and C-Cl stretching at 800 cm.⁻¹ (Figure 15).

**Anal.** Calcd. for C₁₅H₂₀ONCl: C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 67.94; H, 7.40; N, 5.13; Cl, 13.44.

5. α-Dimethylamino-N-Cyclohexylmethyl-N-Phenylacetamide:

Dimethylamine (25.2 ml., approx. 0.38 mole) was
trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 0.5-liter three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (500 ml.), a thermometer (range from -100 to 50°C.), and an acetone-dry ice condenser (drying tube). A solution of α-chloro-N-cyclohexylmethyl-N-phenylacetamide (50.5 g., 0.19 mole) in dry ether (300 ml.) was added dropwise to the vigorously stirred liquid dimethylamine in the flask at such a rate as to keep the temperature of the reaction not higher than -2°C. After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was stirred continuously at -2 to -10°C. for at least 3 hours and then overnight at room temperature. The white amine HCl salt was filtered off and the solvent was removed. The residue crystallized after standing overnight at room temperature to yield 43.3 g. (0.158 mole, 83.1%). The crude product was recrystallized from n-pentane (b.p. 35-37°C., 1 atm.); m.p. 53.5-54.5°C.

The bands at 2820 cm.⁻¹, 2780 cm.⁻¹ and 2740 cm.⁻¹ (C-H stretching for R-N(CH₃)₂) and the absence of C-Cl stretching at 800 cm.⁻¹ indicated that the dimethylamino group had replaced the chlorine group of α-chloro-N-cyclohexylmethyl-N-phenylacetamide (Figure 16).


**Hydrochloride Derivative:**

The white HCl salt was prepared as described for the
39.

N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethlenediamine HCl derivative. Observed m.p. 183.5-185.0°C.

Anal. Calcd. for C_{17}H_{27}ON_{2}Cl: C, 65.68; H, 8.76; N, 9.01; Cl, 11.40. Found: C, 65.54; H, 8.72; N, 8.96; Cl, 11.57.

6. N,N-Dimethyl-N'-Cyclohexylmethyl-N'-Phenylethylene-diamine:

To a 0.5-liter three-necked flask fitted with a dropping funnel (250 ml.), a reflux condenser (drying tube) and a mechanical stirrer was placed 300 ml. of dry ether. Lithium aluminum hydride (8.4 g., 0.22 mole) was added to the ether, and the mixture was gently refluxed with stirring for 4 hours. A solution of α-dimethylamino-N-cyclohexylmethyl-N-phenylacetamide (30.2 g., 0.11 mole) in dry ether (100 ml.) was placed into the dropping funnel, and was added at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

The reaction was then worked up with distilled water (30 ml.) and sufficient 40% NaOH solution to give separation. The separated ethereal layer was dried over anhydrous sodium sulfate and reduced in volume to yield 26.7 g. (0.1 mole, 93.3%) N,N-dimethyl-N'-cyclohexylmethyl-N'-phenylethlenediamine b.p. 158-159°C. (2.2mm.). (Lit. (1) b.p. 194-195°C. (15mm.), 21.8%).

A tertiary amine was shown by the absence of C=O absorption band at 1675 cm.⁻¹ due to complete reduction of the tertiary amide carbonyl group (1) (Figure 17).

Mono-Picrate Derivative:

A sample of the tertiary amine (0.5 g.) was added to
95% ethanol (10 ml.). This solution was then added to 10 ml. of a saturated solution of picric acid in 95% ethanol, and was heated to boiling. The solution was allowed to cool slowly, and the bright yellow crystals of the picrate were isolated by suction filtration. The solid was then recrystallized from 95% ethanol; m.p. 135.5-136.5°C. 

**Anal.** Calcd. for C_{23}H_{31}O_{7}N_{5}: C, 56.43; H, 6.38; N, 14.31. Found: C, 56.41; H, 6.38; N, 14.37.

**Hydrochloride Derivative:**

The white HCl salt was prepared as described for the N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethylenediamine HCl derivative. Observed m.p. 199-200°C.

**Anal.** Calcd. for C_{17}H_{29}N_{2}Cl: C, 68.77; H, 9.85; N, 9.44; Cl, 11.94. Found: C, 68.69; H, 9.78; N, 9.31; C, 12.12.

**F. Synthesis of N,N-Dimethyl-N'-Cycloheptylmethyl-N'-Phenylethylenediamine:**

**1. Cycloheptanecarboxylic Acid:**

In a 2-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (500 ml.) was placed. 28 g. (1.15 mole) of magnesium turnings which had previously been washed with sodium-dried ether, dried at 100°C., and allowed to cool in desiccator. A small amount of cycloheptyl bromide (Aldrich Chemical Co.) and 240 ml. of dry ether was added to initiate the reaction. A solution of cycloheptyl bromide (200 g., 1.13 mole) in dry ether (600 ml.) was then added over a period of 1 hour. The reaction started readily and moderate cooling was necessary. Following
complete addition of the bromide, the mixture was stirred overnight with gentle reflux. At the end of this time, about $\frac{1}{2}$ of the original magnesium turnings remained unreacted.

In a 3-liter three-necked flask equipped with a stirrer, a reflux condenser (drying tube) and a dropping funnel (500 ml.) was placed a slurry of dry ether (1200 ml.) and powdered dry ice (2000 g.) (the dry ice was first funneled into the flask and then the dry ether was added dropwise with stirring). The Grignard solution was quickly decanted into the dropping funnel and added to the stirred dry ice slurry over a period of 15-25 minutes (22). After complete addition of the Grignard solution, another 2000 g. of dry ice was added and stirring was continued for 4 hours during which time the dry ice had evaporated. The Grignard complex then hydrolyzed by the dropwise addition of 450 ml. of 6N hydrochloric acid (cold) to the vigorously stirred mixture. The ether layer was separated and the aqueous layer was twice extracted with 400 ml. portions of ether. The combined ether solution was washed with water, dried over anhydrous sodium sulfate, and the solvent removed. The residue was fractionated under reduced pressure and the fraction boiling at 91-93 °C. (1 mm.) was collected to yield 69.3 g. (0.48 mole, 43.2%). (Lit. (1) b.p. 138-140 °C. (15 mm.), 46.7%; (23) b.p. 133-135 °C. (9 mm.), 53% and 43%; (24) b.p. 130-131 °C. (8 mm.).)

The infrared spectrum showed a strong C=O absorption band at 1710 cm.$^{-1}$ and a broad O-H band at around 3000 cm.$^{-1}$ both characteristic of carboxylic acids (1).
2. Cycloheptanecarbonyl Chloride:

Cycloheptanecarboxylic acid (60 g., 0.42 mole) was placed in a 0.5-liter three-necked flask equipped with a reflux condenser (drying tube), a dropping funnel and a mechanical stirrer. Thionyl chloride (150 g., 1.26 mole) was added dropwise to the stirred acid. After addition was complete, the mixture was stirred for 3 hours at room temperature; then the excess thionyl chloride was removed under reduced pressure by codistillation with two 90 ml. portions of dry benzene. Slight warming with a water bath was employed to aid distillation of the last traces of thionyl chloride. The red liquid residue in the flask was then fractionated under reduced pressure. After a small forerun, 54.3 g. (0.338 mole, 80%) yield of cycloheptanecarbonyl chloride b.p. 89-98°C. (14 mm.) was obtained.

3. Cycloheptanecarboxanilide:

A 0.5-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser (drying tube) and a dropping funnel (125 ml.) was placed a mixture of aniline (29.8 g., 0.32 mole), pyridine (25.3 g., 0.32 mole) and dry benzene (125 ml.). To the cooled and stirred mixture was added cycloheptanecarbonyl chloride (50 g., 0.31 mole) dropwise from the dropping funnel. After addition was complete, the reaction was stirred for 1 hour at room temperature; then poured into a beaker. The solid precipitate was suction filtered and washed with 125 ml. of water. The benzene layer was separated, dried with anhydrous sodium sulfate and reduced in volume.
to collect a further crop of anilide with 48.7 g. (0.224 mole, 72%) total yield. Cycloheptanecarboxanilide was recrystallized from a benzene-petroleum ether mixture (1:1); m.p. 137.5-139°C. (Lit. (1) m.p. 135-136°C., 74.6%).

The infrared spectrum showed similar absorption bands to other anilide analogues of this series with C=O stretching at 1660 cm.⁻¹ and N-H band at 3300 cm.⁻¹ (1).

4. N-Cycloheptylmethyl-N-phenylamine:

In a 1-liter three-necked flask equipped with a mechanical stirrer, a Soxhlet extractor (drying tube) and a dropping funnel (250 ml.) was placed lithium aluminum hydride (17.1 g., 0.45 mole) in dry ether (750 ml.). The mixture was stirred with gentle refluxing on a heating mantle for 4 hours. After this time cycloheptanecarboxanilide (46 g., 0.21 mole) was packed into the Soxhlet extractor as described for cyclobutanecarboxanilide under section PART IV C.3. Refluxing with stirring was continued until all the anilide had been dissolved. The refluxing was continued with stirring for 4 days. The reaction was then worked up with water (70 ml.) and sufficient 40% NaOH solution to give complete separation. The separated ethereal layer was dried with anhydrous sodium sulfate and reduced in volume to yield 34.4 g. (0.169 mole, 80%) N-cycloheptylmethyl-N-phenylamine b.p. 106°C. (0.1 mm.). (Lit. (1) b.p. 154°C. (17 mm.), 78.2%).

The infrared spectrum indicated complete reduction by the absence of the carbonyl absorption band at 1660 cm.⁻¹, and by the shift of the N-H stretching vibration to 3430 cm.⁻¹ (1).
5. \(\alpha\)-Chloro-\(\alpha\)-Cycloheptylmethyl-\(\alpha\)-Phenylacetamide:

In a 250 ml. three-necked flask equipped with a reflux condenser (drying tube), a side arm for setting a thermometer (range from -100 to 50°C.) and a dropping funnel (125 ml.), and a mechanical stirrer was placed a solution of \(\alpha\)-cycloheptylmethyl-\(\alpha\)-phenylamine (31 g., 0.15 mole) in dry ether (150 ml.). The solution was stirred over an ice-salt bath for 30 minutes to reach -5 to -10°C. Chloroacetyl chloride (9.1 g., 0.08 mole) was added dropwise from the dropping funnel to the vigorously stirred solution at such a rate as to keep the temperature of the reaction not higher than 0°C. After the addition was complete (approx. 1 hour), the reaction was stirred continuously at 0°C. for 3 hours and then refluxed on a heating mantle for 1 hour. At the end of this time, 25 ml. of 5% HCl solution was added and refluxing was continued with stirring for 30 minutes. The white amine HCl salt was filtered off and the layers were separated. The ethereal layer was further washed with 25 ml. of 5% HCl and two 50 ml. portions of distilled water and then dried over anhydrous sodium sulfate. The solvent ether was removed by flash evaporation to yield 21.3 g. (0.076 mole, 100%) \(\alpha\)-chloro-\(\alpha\)-cycloheptylmethyl-\(\alpha\)-phenylacetamide b.p. 170°C. (0.7 mm.). The pure liquid product crystallized when mixed with a small amount of petroleum ether (b.p. range 30-60°C.), cooled over dry ice and scratched; m.p. 27.5-28.5°C..

Infrared spectrum of the amide was indicated by a strong tertiary amide C=O absorption band at 1670 cm.\(^{-1}\), and
C-Cl stretching at 790 cm.\(^{-1}\), and by the absence of N-H stretching vibration at 3430 cm.\(^{-1}\) (Figure 18).

**Anal.** Calcd. for C\(_{16}\)H\(_{22}\)ONCl: C, 68.67; H, 7.94; N, 5.01; Cl, 12.67. Found: C, 68.91; H, 7.77; N, 4.92; Cl, 12.65.

6. \(\alpha\)-Dimethylamino-N-Cycloheptylmethyl-N-Phenylacetamide:

Dimethylamine (10 ml., approx. 0.15 mole) was trapped from a dimethylamine cylinder by an acetone-dry ice bath into a 250 ml. three-necked flask equipped with a mechanical stirrer, and two side arms for setting a dropping funnel (250 ml.), a thermometer (range from -100 to 50° C.) and an acetone-dry ice condenser (drying tube). A solution of \(\alpha\)-chloro-N-cycloheptylmethyl-N-phenylacetamide (20 g., 0.07 mole) in dry ether (200 ml.) was added dropwise to the vigorously stirred liquid dimethylamine in the flask at such a rate as to keep the temperature of the reaction not higher than -2° C. After the addition was complete, the acetone-dry ice bath was replaced by an ice-salt bath and the reaction mixture was stirred continuously at -2 to -10° C. for at least 3 hours and then overnight at room temperature. The white amine HCl salt was filtered off and the solvent ether removed. The residue was fractionated under reduced pressure to yield 16.6 g. (0.057 mole, 80.5%) \(\alpha\)-dimethylamino-N-cycloheptylmethyl-N-phenylacetamide b.p. 178-179° C. (1.7 mm.).

The infrared spectrum showed the C-H stretching vibration for dimethylamino group (R-N(CH\(_3\))\(_2\)) at 2820 cm.\(^{-1}\), 2780 cm.\(^{-1}\) and 2730 cm.\(^{-1}\), and the absence of C-Cl stretching band at 800 cm.\(^{-1}\) (Figure 19).
Methyl Iodide Derivative:

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and worked up as described for the \(\alpha\)-dimethylamino-acetanilide methyl iodide derivative. The \(\alpha\)-dimethylamino-N-cycloheptylmethyl-N-phenylacetamide methyl iodide salt was recrystallized from reagent acetone; m.p. 195-195.5°C.

**Anal.** Calcd. for \(\text{C}_{19}\text{H}_{31}\text{ON}_{2}\text{I}\): C, 53.01; H, 7.27; N, 6.51; I, 29.48. Found: C, 53.06; H, 7.35; N, 6.53; I, 29.33.

7. \(N,N\)-Dimethyl-\(N'\)-Cycloheptylmethyl-\(N'\)-Phenylethylenediamine:

To a 0.5-liter three-necked flask equipped with a dropping funnel (250 ml.), a reflux condenser (drying tube) and a mechanical stirrer was placed 200 ml. of dry ether. Lithium aluminum hydride (4.2 g., 0.11 mole) was added to the ether, and the mixture was gently refluxed with stirring for 4 hours. A solution of \(\alpha\)-dimethylamino-N-cycloheptylmethyl-N-phenylacetamide (15 g., 0.052 mole) in dry ether (100 ml.) was placed into the dropping funnel, and was added at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed for 4 days.

The reaction was then worked up with water (20 ml.) and sufficient 40% NaOH solution to give complete separation. The separated ethereal layer was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation to yield 13.6 g. (0.49 mole, 95.1%) \(N,N\)-dimethyl-\(N'\)-cycloheptylmethyl-\(N'\)-phenylethylenediamine b.p. 148-153°C. (1 mm.). (Lit. (1) b.p. 204-210°C. (17 mm.), 29%).

A tertiary amine was shown by the absence of C=O
absorption band at 1670 cm.\(^{-1}\) due to complete reduction of the tertiary amide carbonyl group (1) (Figure 20).

**Mono-Picrate Derivative:**

A sample of the tertiary amine (0.5 g.) was added to 95% ethanol (10 ml.) and was treated with a saturated solution of picric acid as for the monocyclohexyl analogue; m.p. 126.5-127.5°C.

**Anal.** Calcd. for C\(_{24}\)H\(_{33}\)O\(_7\)N\(_5\): C, 57.23; H, 6.62; N, 13.91. Found: C, 56.99; H, 6.82; N, 14.11.

**Hydrochloride Derivative:**

The white HCl salt was prepared as described for the N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethylenediamine HCl derivative; m.p. 198-199°C.

**Anal.** Calcd. for C\(_{18}\)H\(_{31}\)N\(_2\)Cl: C, 69.52; H, 10.07; N, 9.01; Cl, 11.40. Found: C, 69.65; H, 10.06; N, 8.90; Cl, 11.26.
The appropriate cycloalkanecarboxylic acid was used as the starting compound for each ethylenediamine product. Cyclobutanecarboxylic acid, cyclopentanecarboxylic acid and cyclohexanecarboxylic acid were all commercially available (Aldrich Chemicals). As cycloheptylbromide was available commercially (Aldrich Chemicals), this compound was used to prepare the Grignard reagent, and then cycloheptanecarboxylic acid by the procedure of Hussey (22) and Royals and Neal (23).

\[
\text{Br} \quad \text{Mg} \quad \text{Ether} \quad \text{MgBr} \quad \text{Dry Ice} \\
\]

\[
\text{CO}_2\text{MgBr} \quad \text{H}_2\text{O} \quad \text{COOH} \quad + \quad \text{MgOHBr} \\
\]

After obtaining the appropriate cycloalkanecarboxylic acid, the next step was to prepare the acid chloride intermediate. An acid chloride was prepared by substitution of -Cl for the -OH of a carboxylic acid. Three reagents are commonly used for this purpose: thionyl chloride, SOCl\(_2\); phosphorus trichloride, PCl\(_3\); and phosphorus pentachloride, PCl\(_5\).

\[
\text{R-CO-OH} \quad + \quad \text{SOCl}_2 \quad \rightarrow \quad \text{R-CO-Cl} \quad + \quad \text{SO}_2 \quad + \quad \text{HCl} \\
3\text{R-CO-OH} \quad + \quad \text{PCl}_3 \quad \rightarrow \quad 3\text{R-CO-Cl} \quad + \quad \text{H}_3\text{PO}_3 \\
\text{R-CO-OH} \quad + \quad \text{PCl}_5 \quad \rightarrow \quad \text{R-CO-Cl} \quad + \quad \text{HCl} \quad + \quad \text{POCl}_3
\]

Thionyl chloride was chosen as the reagent for the
preparation of the alicyclic acid chlorides not only because the products formed besides the acid chloride were gases and thus easily separated from the acid chloride, but because the acid chlorides formed were found to have higher boiling points than this reagent; any excess of the low-boiling thionyl chloride (b.p. 79°C., 1 atm.) was easily removed by distillation. Two precautions were taken for running this reaction. The first was to protect the reaction and the acid chloride from moist air; the second was to avoid high temperature by using water bath during the distillation which may cause pyrolysis of the acid chloride. The results were shown as follows (Table 4):

<table>
<thead>
<tr>
<th>CYCLOALKANECARBONYL CHLORIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>RING SIZE</td>
</tr>
<tr>
<td>Cyclobutane</td>
</tr>
<tr>
<td>Cyclopentane</td>
</tr>
<tr>
<td>Cyclohexane</td>
</tr>
<tr>
<td>Cycloheptane</td>
</tr>
</tbody>
</table>

Upon obtaining the alicyclic carbonyl chlorides, the next step in the sequence was to form the amide by reacting the chlorides with the appropriate amine. As the first series of ethylenediamine derivatives contain an N-substituted phenyl group, the primary amine, aniline was used to form the amide intermediates.

\[ 	ext{RCOCl} + \text{C}_6\text{H}_4\text{NH}_2 \xrightarrow{\text{Pyridine}} \text{R-C-N-C}_6\text{H}_4\text{OH} \to \text{RC-N-C}_6\text{H}_4\text{OH} + \text{Pyridine-HCl} \]
Separation of the amide and amine HCl depended on a difference in solubility. The cycloalkane substituted amides were found to be water-insoluble, and on completion of the reaction, water was added to extract the amine HCl. Pyridine was added to the primary amine to neutralize the hydrogen chloride formed. The anilides for cyclobutane to cycloheptane readily formed in good yields (Table 5). Cyclohexanecarboxanilide had been prepared by Schwartz and Johnson (20) from reacting the Grignard reagent and phenyl iso-cyanate:

![Chemical structure](attachment://chemical_structure.png)

TABLE 5
CYCLOALKANECARBOXANILIDES

<table>
<thead>
<tr>
<th>RING SIZE</th>
<th>MELTING POINT °C.</th>
<th>%YIELD</th>
<th>LITERATURE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutane</td>
<td>111-112</td>
<td>96.6</td>
<td>72(1)</td>
</tr>
<tr>
<td>Cyclopentane</td>
<td>159-161</td>
<td>97.9</td>
<td>95(1)</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>145-146</td>
<td>86.3</td>
<td>98(1)</td>
</tr>
<tr>
<td>Cycloheptane</td>
<td>137.5-139</td>
<td>72.0</td>
<td>74.6(1)</td>
</tr>
</tbody>
</table>

In order to obtain the cycloalkyl substituted amine, the corresponding amide was reduced with lithium aluminum hydride. The reagent discovered by Finholt, Bond and Schlesinger (25) in 1947 (4LiH + AlCl<sub>3</sub> → LiAlH<sub>4</sub> + 3LiCl) has proved to be a remarkable reducing agent for the carbonyl group in amides and similar carbonyl compounds (26). Amides are not readily
reducible to pure amines by other chemical methods. Hydrogenation with a catalyst at high temperatures and pressures can be accomplished, but usually results in a mixture of products.

Powdered LiAlH₄ is available commercially (Ventron Corp.), and if protected from moist air and carbon dioxide, it is stable indefinitely at room temperature. The hydride can be safely handled, even in very humid air, probably because of the formation of a protective coating of aluminum hydroxide (25). It is generally used in solution or suspension in dry ether (25-30 g. solid hydride dissolves in 100 g. ether at 25°C.). In the normal procedure the substance to be reduced is added to an ethereal solution or slurry of the hydride. If the substance to be reduced is a liquid or solid, ether soluble, the solution is added dropwise to produce gentle reflux. For moderately soluble materials, a Soxhlet extractor or a continuous-return type of extractor is used.

In the reduction of the amides, an excess (2- to 3-fold of the stoichiometrical quantities) of LiAlH₄ was used.

\[
2R-C-N\text{OH} + \text{LiAlH₄} \rightarrow 2R-\text{CH}_2\text{-N} + \text{LiAlO}_2
\]

Water was then added to destroy the excess hydride with the evolution of hydrogen, and the precipitation of lithium- and aluminum-hydroxide.

\[
\text{LiAlH₄} + 4\text{H}_2\text{O} \rightarrow \text{LiOH} + \text{Al(OH)}_3 + 4\text{H}_2
\]

As the amine was ether soluble, the mixture was treated with strong hydroxide solution to dissolve the precipitated alumina. This allowed a clear-cut separation of phases on centrifugation.
The resulted amine products were tabulated as follows (Table 6).

**TABLE 6**

<table>
<thead>
<tr>
<th>RING SIZE</th>
<th>BOILING POINT °C.</th>
<th>%YIELD vs. LITERATURE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutyl</td>
<td>88-96 (0.8 mm.)</td>
<td>86.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopentyl</td>
<td>124 (2.8 mm.)</td>
<td>84.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>112-114 (1 mm.)</td>
<td>85.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloheptyl</td>
<td>106 (0.1 mm.)</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Upon obtaining the N-cycloalkylmethyl-N-phenylamine, the next portion of the molecule to be attached was the β-di-methylaminoethyl chain to completely form the final tertiary diamine N,N-dimethyl-N'-cycloalkylmethyl-N' -phenylethlenediamine. Leung (1) had succeeded in obtaining the tertiary diamine by condensing the secondary amine, N-cycloalkylmethyl-N-phenylamine, with β-dimethylaminoethylbromide HBr in the presence of sodamide but the yields were very low (Table 7).

![Chemical Reaction](image)

**TABLE 7**

<table>
<thead>
<tr>
<th>R</th>
<th>BOILING POINT °C.</th>
<th>%YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutyl</td>
<td>168-179 (20 mm.)</td>
<td>10.0</td>
</tr>
<tr>
<td>Cyclopentyl</td>
<td>185-189 (21 mm.)</td>
<td>10.2</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>194-195 (15 mm.)</td>
<td>21.8</td>
</tr>
<tr>
<td>Cycloheptyl</td>
<td>204-210 (17 mm.)</td>
<td>29.0</td>
</tr>
</tbody>
</table>
The purpose of this study was mainly to develop a new synthetic method to approach the tertiary diamine with better yields. Various methods had been tried to improve the yields of the final products. Larizza (27) reported in 1964 several new derivatives of Antergan, i.e., N,N-dimethyl-N′-phenyl-N′-benzylendiamine derivatives. He used an α-substituted α-bromoacetic acid (R-CHBr-CO-OH, R=methyl, ethyl, or phenyl, 1 mole) in benzene and treated with stirring with 1 mole of Et₃N and 1 mole of the aromatic amine (PhNH₂ or PhCH₂-NHPh) in benzene (refluxed mixture) to obtain PhNH-CO-CHBr-R (I) or Ph-N-CO-CHBrCH₂Ph (II) in good yields:

\[
\text{(a) } R-\text{CH-COOH} + \text{Br} \rightarrow \begin{array}{c}
\text{Et₃N in} \\
\text{benzene, refluxed}
\end{array} \rightarrow \begin{array}{c}
\text{II} \quad \text{or}
\end{array}
\]

The latter compound (I or II, 1 mole) was added to 2.5 moles Me₂NH in benzene, the mixture heated in a closed tube at 120°C. for 16 hours to get the dimethylamino compound (III or IV) which upon lithium aluminum hydride reduction gave N,N-dimethyl-N′-phenyl-N′-benzylendiamine derivatives (V):
Similar reactions were run under the same conditions as Larizza's (equation (a) above) using α-bromoacetic acid and N-cyclohexylmethyl-N-phenylamine instead of α-substituted α-bromoacetic acid and aniline or N-benzylideneaniline respectively, but no reaction was found and the starting material, N-cyclohexylmethyl-N-phenylamine was recovered by vacuum distillation.

N-Cycloheptylmethyl-N-Phenylamine was also tried in the same reaction conditions and the result was negative.

Cyclohexanecarboxanilide was used in place of the secondary
amine to react with α-bromoacetic acid. Unfortunately, no desired product was obtained. Triethylamine seemed to be ineffective as a dehydrating agent.

Since the carbonyl chloride is usually more reactive than the corresponding acid, chloroacetyl chloride was used instead of α-bromoacetic acid and the reaction was run under the same conditions as above (equation (a)). But upon refluxing the mixture, a tarry residue resulted. There were no obvious reasons to explain why the similar reactions did not work. Triethylamine might not be suitable as a neutralizing agent in the reaction. For this reason, several commonly used neutralizing agents, such as potassium carbonate, pyridine and sodamide, were employed for the reaction. However, none of them seemed to work successfully.

Olin (28) synthesized a herbicidal derivative, α-chloro-N-t-butyl-N-cyclohexylacetamide, in 1964 by the following method: A solution of 39.5 g. (0.35 mole) chloroacetyl chloride in 50 ml. benzene was added during 33 minutes to a cold (0°C.) mixture of 46.5 g. (0.30 mole) N-t-butylcyclohexylamine, 42 g. (0.30 mole) K₂CO₃, 100 ml. H₂O, 400 g. ice, 300 ml. benzene, and 100 ml. ether to give 45 g. α-chloro-N-t-butyl-N-cyclohexylacetamide:

\[
\text{K}_2\text{CO}_3 \text{ in benzene,} \quad \text{ether and ice water mixture (0°C.)}
\]

Similar studies were undertaken using N-cyclohexylmethyl-N-phenylamine instead of N-t-butyl-cyclohexylamine to react with chloroacetyl chloride. The reaction failed again:
The failure could be due to the fact that chloroacetyl chloride reacted readily with both water and potassium carbonate before it coupled with the amine.

In view of all the above failure, the amino hydrogen of the secondary amine, N-cyclohexylmethyl-N-phenylamine, seemed to be too inert to replace in the presence of weak bases such as potassium carbonate, triethylamine or pyridine (Note: This explanation was found to be incorrect later). For this reason, equimolar sodamide was refluxed with the secondary amine in dry ether so that the sodium ion of sodamide would replace the amino hydrogen with release of gaseous ammonia. A constant dry nitrogen gas stream was bubbled through the reaction mixture so as to prevent the sodamide from reacting with atmospheric carbon dioxide and to drive away the ammonia gas formed in favor of the desired reaction. Refluxing was continued until no gaseous ammonia could be detected from the drying tube of the condenser (about 2 days). Excess chloroacetyl chloride was then added to the mixture to form the desired product (amide). However, a tarry residue soon resulted after the addition of chloroacetyl chloride:
The evidence (29, 30, 31) that amino hydrogen of primary and secondary amide reacts with sodamide made us use cyclohexanecarboxanilide for the reaction.

\[
R-\text{CO-NH}_2 + \text{NaNH}_2 \xrightarrow{\text{in benzene}} R-\text{CO-NHNa} + \text{NH}_3
\]

Cyclohexanecarboxanilide was refluxed with sodamide in benzene solution in the manner described in the previous section. Excess chloroacetyl chloride was then added to react with the sodium substituted anilide. Unfortunately, no result was obtained:

\[
\text{CO-NH} \xrightarrow{1) \text{NaNH}_2} \xrightarrow{2) \text{CH}_2\text{Cl-COCl}} \text{No Product}
\]

It was found that the secondary amine N-cyclohexylmethyl-N-phenylamine was basic enough to serve as a neutralizing agent. When chloroacetyl chloride was dropped into the amine in benzene solution at room temperature, vigorous reaction occurred with release of a large amount of heat (exothermic reaction). It was found that the rise in temperature of the reaction caused the decomposition of chloroacetyl chloride and consequently, only amine HCl salt and side products were formed with no desired amide formation. Although this reaction was a failure, yet it answered the reason why all the above reactions did not work properly. Low temperature control was essential for the desired reaction to occur and high temperature tended to decompose chloroacetyl chloride and hence a tarry residue of unknown side products resulted. At low temper
perature (-2 to -10°C.) benzene solvent solidified, therefore dry ether was used as the solvent. The ethereal solution of the amine was cooled in an ice-salt bath (-2 to -10°C.). To the cooled solution was added chloroacetyl chloride dropwise at such a rate as to keep the temperature of the reaction not higher than 0°C. Double quantities of the amine were used for the reaction. One equivalent was used to couple with chloroacetyl chloride to form the amide product while the second acted as the neutralizing agent. Chloroacetyl chloride and the reaction must be protected from moist air. 5% HCl solution was added at the end of the reaction in order to react with excess amine and to convert excess chloroacetyl chloride into more water-soluble acid. The white amine HCl salt was filtered and the original amine could be reformed from its HCl salt by the addition of strong NaOH solution and extracting with ether solvent. The resulting amides are shown in Table 8 below.

(a) \[ R-\text{NH} + \text{CH}_2\text{Cl}-\text{COCl} \xrightarrow{\text{Ether, ice-salt bath}} R-\text{N-CO-CH}_2\text{Cl} + R-\text{NH}_2-\text{Cl} \]

(b) \[ R-\text{NH}_2-\text{Cl} + \text{NaOH} \xrightarrow{} R-\text{NH} + \text{NaCl} + \text{H}_2\text{O} \]
TABLE 8

α-CHLORO-N-(R)-ACETANILIDES

<table>
<thead>
<tr>
<th>R</th>
<th>MELTING POINT °C.</th>
<th>RECRYST. SOLVENT</th>
<th>%YIELD(※)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>134.5-135.5</td>
<td>EtOH 60%</td>
<td>100</td>
</tr>
<tr>
<td>CH₃</td>
<td>67.8-68.8</td>
<td>n-hexane</td>
<td>100</td>
</tr>
<tr>
<td>Cyclobutylmethyl</td>
<td>45.2-46.2</td>
<td>n-pentane</td>
<td>100</td>
</tr>
<tr>
<td>Cyclopentylmethyl</td>
<td>55.0-56.0</td>
<td>n-pentane</td>
<td>100</td>
</tr>
<tr>
<td>Cyclohexylmethyl</td>
<td>52.0-53.0</td>
<td>n-pentane</td>
<td>100</td>
</tr>
<tr>
<td>Cycloheptylmethyl</td>
<td>27.5-28.5</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

(※) The yields were calculated on the basis of half the quantity of total amine used for the reaction, since the amine can be recovered as explained in the text.

The next step was to introduce the dimethylamino group at the α-carbon of the amides to complete the second tertiary amine end. Since the α-carbon of the amide had chlorine attached to it, the whole molecule could be assumed to be an alkyl halide and behaved accordingly. An alkyl halide undergoes nucleophilic substitution with dimethylamine to form tertiary amine:

\[
R-\text{Cl} + 2\text{HN}^\text{CH}_3 \rightarrow R-N^\text{CH}_3 + \text{Cl-}^\text{H}_2\text{N}^\text{CH}_3
\]

Dimethylamine exists in the gaseous state at room temperature and should be trapped into the flask as a liquid by an acetone-dry ice bath for the reaction. The temperature was kept at -2 to -10°C (ice-salt bath) when reaction started. Because of the low temperature of reaction, a large excess of solvent (dry ether or genuine absolute methanol (10)) was used to dissolve the amides at room temperature so that when reaction occurred
at low temperature (-2 to -10°C), the amides were still dis­solved in the solution. Double quantities of dimethylamine were used for the reaction. One equivalent was used to cou­ple with the amide to form the second tertiary amine end while the second acted as the neutralizing agent. If dry ether was the reaction solvent, the white amine HCl salt formed in the reaction was insoluble in ether and accumulated as the reaction went to completion. If absolute methanol was the reaction sol­vent, the amine HCl salt formed soon dissolved in the solvent. In order to separate the dissolved salt from the product, the reaction mixture was reduced in volume by flash evaporation. The concentrated residue dispersed in water was extracted with solvent ether. The product was found in the ethereal layer and the amine HCl salt remained in the water. The results are shown in Table 9.

\[
\text{R-N-CO-CH}_2\text{Cl} + 2\text{HN}_3\text{CH}_3 \xrightarrow{-2 \text{ to } -10\degree\text{C.}} \text{R-N-CO-CH}_2\text{N}_{\text{CH}_3} + \text{Cl-H}_2\text{N}_{\text{CH}_3}
\]

**TABLE 9**

**DIMETHYLAMINO-N-(R)-N-PHENYLACETAMIDE**

<table>
<thead>
<tr>
<th>R</th>
<th>BOILING POINT °C</th>
<th>MELTING POINT °C</th>
<th>%YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>124(1.4 mm.)</td>
<td>-</td>
<td>94.0</td>
</tr>
<tr>
<td>Methyl</td>
<td>106(0.3 mm.)</td>
<td>-</td>
<td>90.5</td>
</tr>
<tr>
<td>Cyclobutylmethyl</td>
<td>134-135(0.9 mm.)</td>
<td>-</td>
<td>80.7</td>
</tr>
<tr>
<td>Cyclopentylmethyl</td>
<td>-</td>
<td>45.0-46.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Cyclohexylmethyl</td>
<td>-</td>
<td>53.5-54.5</td>
<td>83.1</td>
</tr>
<tr>
<td>Cycloheptylmethyl</td>
<td>178-179(1.7 mm.)</td>
<td>-</td>
<td>80.5</td>
</tr>
</tbody>
</table>

The final step of the series of reactions was to re-
duce the carbonyl group of the amide to form the tertiary di-
amine compounds (Antergan analogues). Lithium aluminum hydride
was used as the reducing agent in the same manner as described
for the reduction of cycloalkanecarboxanilides into the corre-
ponding amines. The cycloalkyl analogues of Antergan readily
formed in good yields (Table 10).

\[
2R-N-CO-CH_2-N'CH_3 + LiAlH_4 \rightarrow 2R-N-CH_2-CH_2-N'CH_3 + LiAlO_2
\]

<table>
<thead>
<tr>
<th>TABLE 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N-DIMETHYL-N'-R'-PHENYLETHYLENEDIAMINE</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>H</td>
</tr>
<tr>
<td>CH₃</td>
</tr>
<tr>
<td>Cyclobutylmethyl</td>
</tr>
<tr>
<td>Cyclopentylmethyl</td>
</tr>
<tr>
<td>Cyclohexylmethyl</td>
</tr>
<tr>
<td>Cycloheptyl methyl</td>
</tr>
</tbody>
</table>

The compounds synthesized in Table 4, 5 and 6 were
repeated using Leung's method (1) while the compounds in Table
8, 9 and 10 were synthesized by the present studies. If the
compounds were solid, pure and recrystallized substances were
sent for percentage composition analysis of carbon, hydrogen,
nitrogen and halogen. No derivatives were made. For those
liquid compounds, methylidodide-, hydrochloride- or picrate-
derivatives were made for elemental microanalysis.
To supplement the analytical results of a derivative, an infrared spectrum was taken on the synthesized compound. The spectrum of a molecule in the fundamental region 2 to 15 μ shows the presence of a number of bands which can be correlated with the functional groups present in the molecule, while other bands correspond to skeletal vibrations. Because of this, infrared spectroscopy was used both to obtain information of the functional groups present in the unknown molecules and also to act as "fingerprints" for the molecule. Using this technique, it was possible to determine the completion of a reaction by the presence or absence of a particular band corresponding to a particular functional group.
PART VI
PRELIMINARY ANTIHISTAMINIC ACTIVITY STUDIES

Since the parent compound Antergan was known as the first clinically effective antihistaminic agent, its cycloalkyl analogues might be expected to have some antihistaminic activity. Therefore, quantitative comparisons of antihistaminic actions of these analogues with Diphenhydramine HCl (Benadryl HCl, Parke, Davis and Co., Ltd., Walkerville, Ontario, CANADA) were studied. The methods of Schild (32) and Reuse (33) were modified and adopted here. Histamine concentration was calculated in terms of histamine base (Histamine Dihydrochloride, Nutritional Biochemicals Corp., Cleveland, Ohio, USA) and those of other compounds tested were calculated as molar concentration of monohydrochloride salts in terms of the salts used. All drugs were freshly prepared in Tyrode solution. Strips of guinea-pig's ileum 2-3 cm. long were aerated in a 30-c.c. bath containing Tyrode solution at 37±0.5°C. and longitudinal contractions of the intestine recorded on a kymograph. The action of a single dose of histamine (0.5 ¥ of histamine base) was first tested and a number of submaximal effects (2 to 3 times, 0.5 ¥ each) obtained and the response (degree of ileum contraction in mm.) measured at the end of 15 minutes was taken as the standard mean response. The test compounds were then injected into the bath. After 1 minute contact between test compounds and guinea-pig's ileum, a double dose of histamine (i.e., 1.0 ¥ of histamine base) was then injected into the bath and the effect measured at the end of 15 minutes.
The object was to find two concentrations of the test compounds such that one would reduce the effect of a double dose of histamine to slightly less and the other to slightly more than the effect of a single dose. The pA₂ value was then obtained by interpolation on a logarithmic scale (pAₓ was defined as the negative logarithm to base 10 of the molar concentration of an antagonistic drug which would reduce the effect of a multiple dose (x) of an active drug to that of a single dose). A fresh piece of gut was used for each concentration of the test compounds. The whole experiment was repeated until the pA₂ value was found. The results of preliminary analysis were shown in Table 11 and Figure 2.

### TABLE 11

EFFECTS OF CYCLOALKYL ANALOGUES OF ANTERGAN (MONO-HCl SALTS) AND DIPHENHYDRAMINE HCl ON RESPONSE OF ISOLATED GUINEA-PIG ILEUM (15 MINUTES EXPOSURE): IV, Cyclobutylmethyl Analogue; V, Cyclopentylmethyl Analogue; VI, Cyclohexylmethyl Analogue; VII, Cycloheptylmethyl Analogue; D, Diphenhydramine. NLMC: Negative Log. Molar Concentration.

<table>
<thead>
<tr>
<th>NO. OF TEST</th>
<th>A. RESPONSE (mm.) TO HISTAMINE (0.5γ)</th>
<th>B. NLMC OF ANTAGONIST</th>
<th>C. RESPONSE (mm.) TO HISTAMINE (1.0γ) IN PRESENCE OF ANTAGONIST</th>
<th>C/A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>7.5</td>
<td>IV: 7.19</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>10.5</td>
<td>IV: 7.19</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>9.0</td>
<td>IV: 7.19</td>
<td>1.5</td>
<td>16.7</td>
</tr>
<tr>
<td>1.</td>
<td>20.5</td>
<td>IV: 7.85</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>23.0</td>
<td>IV: 7.85</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>21.8</td>
<td>IV: 7.85</td>
<td>23.5</td>
<td>107.7</td>
</tr>
<tr>
<td>1.</td>
<td>13.5</td>
<td>V: 7.54</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>24.0</td>
<td>V: 7.54</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>18.8</td>
<td>V: 7.54</td>
<td>20.5</td>
<td>109.0</td>
</tr>
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</table>

(To be continued)
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>(C/A) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>12.5</td>
<td>V: 7.23</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>23.0</td>
<td>V: 7.23</td>
<td>78.7</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>17.8</td>
<td>V: 7.23</td>
<td>14.0</td>
<td>78.7</td>
</tr>
<tr>
<td>1.</td>
<td>12.5</td>
<td>VI: 7.62</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>12.0</td>
<td>VI: 7.62</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>12.3</td>
<td>VI: 7.62</td>
<td>4.3</td>
<td>34.1</td>
</tr>
<tr>
<td>1.</td>
<td>25.0</td>
<td>VI: 8.52</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>24.0</td>
<td>VI: 8.52</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
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<td>VI: 8.52</td>
<td>20.5</td>
<td>83.7</td>
</tr>
<tr>
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<td>5.0</td>
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<td>8.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>8.5</td>
<td>VII: 7.52</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>6.8</td>
<td>VII: 7.52</td>
<td>11.0</td>
<td>161.7</td>
</tr>
<tr>
<td>1.</td>
<td>11.0</td>
<td>VII: 7.22</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>10.0</td>
<td>VII: 7.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
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<td>VII: 7.22</td>
<td>3.0</td>
<td>28.6</td>
</tr>
<tr>
<td>1.</td>
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<td>6.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>18.0</td>
<td>D: 7.62</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>15.3</td>
<td>D: 7.62</td>
<td>6.5</td>
<td>42.5</td>
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<tr>
<td>1.</td>
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<td>D: 8.62</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>17.0</td>
<td>D: 8.62</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>13.3</td>
<td>D: 8.62</td>
<td>21.3</td>
<td>160.2</td>
</tr>
<tr>
<td>1.</td>
<td>14.0</td>
<td>D: 7.62</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>11.5</td>
<td>D: 7.62</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>12.8</td>
<td>D: 7.62</td>
<td>3.3</td>
<td>25.8</td>
</tr>
<tr>
<td>1.</td>
<td>23.5</td>
<td>D: 8.44</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>23.0</td>
<td>D: 8.44</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>AVE.</td>
<td>23.3</td>
<td>D: 8.44</td>
<td>15.3</td>
<td>65.7</td>
</tr>
</tbody>
</table>
It was quite interesting to find that \( N,N \)-dimethyl-\( N' \)-cyclohexylmethyl-\( N' \)-phenylethlenediamine (i.e., cyclohexylmethyl analogue) was slightly more potent than or as potent as Diphenhydramine. The high potency order of the Antergan analogues (\( pA_2 \) value in parenthesis) was as follows:

Cyclohexylmethyl analogue (8.82) > Diphenhydramine (9.15 or 8.11) > Cyclobutylmethyl analogue (7.79) > Cyclopentylmethyl analogue (7.45) > Cycloheptylmethyl analogue (7.38)

The other two compounds tested, i.e., \( N,N \)-dimethyl-\( N' \)-phenylethlenediamine and \( N,N \)-dimethyl-\( N' \)-methyl-\( N' \)-phenylethylene-diamine were found to have no antihistaminic activity (results not shown in the Figure). The action of cyclohexylmethyl analogue was the most persistent and specific among the series of compounds tested, therefore, it was difficult to wash out and took longer duration for recovery (24 minutes). The cycloheptylmethyl analogue was the weakest in action and comparatively easy to wash out. Although the \( pA_2 \) values in the present studies were obtained from the mean of two separate determinations (in some compounds just one determination) and contributed little statistical significance, yet the validity of the method as indicated by Schild and Reuse made us believe this preliminary study gave valuable information to the finding that cyclohexylmethyl analogue of Antergan was a potent antihistaminic agent. As a result, it was suggested that this compound be submitted for more detailed pharmacological study.
The syntheses of four cycloalkyl analogues of Antergan and two related compounds have been reported in good yields. The benzyl group in Antergan was replaced by a cycloalkylmethyl group containing four to seven carbon atoms in the ring. These tertiary diamines are as follows: N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethlenediamine, N,N-dimethyl-N'-cyclopentylmethyl-N'-phenylethlenediamine, N,N-dimethyl-N'-cyclohexylmethyl-N'-phenylethlenediamine, and N,N-dimethyl-N'-cycloheptylmethyl-N'-phenylethlenediamine. The benzyl group in Antergan was also substituted by a hydrogen and or by a methyl group to become N,N-dimethyl-N'-phenylethlenediamine and N,N-dimethyl-N'-methyl-N'-phenylethlenediamine respectively.

These ethylenediamine derivatives were isolated as the free base. The hydrochloride, methyl iodide, and picrate salts of these amines were prepared for elemental microanalyses.

The general reaction sequence for the preparation of these derivatives started with the cycloalkanecarboxylic acid. The acid was reacted with thionyl chloride to form the acid chloride. Then the amide intermediate was prepared by reacting the acid chloride with aniline. Lithium aluminum hydride was used to form the desired amine. Leung's methods (1) were followed and showed good results up to this step. A new reaction sequence was used from this step on. The appropriate amine was reacted with chloroacetyl chloride, dimethyl amine,
and then reduced by lithium aluminum hydride to the ethylenediamine derivatives.

All the intermediates synthesized were characterized through their physical constants, boiling point, melting point and infrared spectra, and were verified by elemental microanalyses of intermediates themselves (for solid intermediates) or their hydrochloride or methyl iodide salt derivatives (for liquid intermediates).

The preliminary antihistaminic activity of all the six final compounds were studied by a modification of Schild's (32) and Reuse's (33) methods. It was quite interesting to find that \( \text{N,N-dimethyl-N'^}{\text{-cyclohexylmethyl-N''-phenylethylene}} \text{diamine} \) was slightly more potent or as potent as Diphenhydramine (Benadryl). The former compound was also the most potent and most specific among the series of compounds tested. The cycloheptylmethyl analogue was the least potent in action. The order of descending antihistaminic activity was as follows: Cyclohexylmethyl analogue > Diphenhydramine > Cyclobutylmethyl analogue > Cyclopentylmethyl analogue > Cycloheptylmethyl analogue. The other two related compounds, \( \text{N,N-dimethyl-N'-phenylethylenediamine} \) and \( \text{N,N-dimethyl-N'-methyl-N'-phenylethylenediamine} \), were found to have no antihistaminic activity.
PART VIII
INFRARED SPECTRA
Fig. 3. IR spectrum of α-chloroacetanilide (KBr pellet).
Fig. 4. IR spectrum of α-dimethylaminoacetanilide, liquid between NaCl plates.
Fig. 5. IR spectrum of N,N-dimethyl-N'-phenylethylene-diamine, liquid between NaCl plates.
Fig. 6. IR spectrum of α-chloro-N-methylacetanilide (KBr pellet).
Fig. 7. IR spectrum of α-dimethylamino-N-methyl-N-phenylacetamide, liquid between NaCl plates.
Fig. 8. IR spectrum of N,N-dimethyl-N'-methyl-N'-phenyl-ethylenediamine, liquid between NaCl plates.
Fig. 9. IR spectrum of α-chloro-N-cyclobutylmethyl-N-phenylacetamide, liquid between NaCl plates.
Fig. 10. IR spectrum of \( \alpha \)-dimethylamino-N-cyclobutylmethyl-N-phenylacetamide, liquid between NaCl plates.
Fig. 11. IR spectrum of N,N-dimethyl-N'-cyclobutylmethyl-N'-phenylethylene diamine, liquid between NaCl plates.

WAVENUMBER CM⁻¹
Fig. 12. IR spectrum of $\alpha$-chloro-N-cyclopentylmethyl-N-phenylacetamide (KBr pellet).
Fig. 13. IR spectrum of $\alpha$-dimethylamino-N-cyclopentylmethyl-N-phenylacetamide (KBr pellet).
Fig. 14. IR spectrum of N,N-dimethyl-N'-cyclopentylmethyl-N'-phenylethylene diamine, liquid between NaCl plates.
Fig. 15. IR spectrum of α-chloro-N-cyclohexylmethyl-N-phenylacetamide (KBr pellet).
Fig. 16. IR spectrum of α-dimethylamino-N-cyclohexylmethyl-N-phenylacetamide (KBr pellet).
Fig. 17. IR spectrum of N,N-dimethyl-N'-cyclohexylmethyl-N'-phenylethylendiamine, liquid between NaCl plates. Wavenumber cm⁻¹
Fig. 18. IR spectrum of α-chlo-N-cycloheptylmethyl-N-phenylacetamide, liquid between NaCl plates.
Fig. 19. IR spectrum of α-dimethylamino-N-cycloheptylmethyl-N-phenylacetamide, liquid between NaCl plates.

WAVENUMBER CM$^{-1}$
Fig. 20. IR spectrum of N,N-dimethyl-N'-cycloheptylmethyl-N'-phenylethlenediamine, liquid between NaCl plates.
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