SYNTHESIS OF CYCLOALKYL ANALOGUES OF ANTERGAN

by

FRED YING TOY LEUNG

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Department of Pharmacy

The University of British Columbia, Vancouver 8, Canada

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Abstract

Two series of cycloalkyl analogues of Antergan have been synthesized and analyzed. The compounds of the first series have the basic structure of N, N-dimethyl-N'-phenyl-N'--(cycloalkylmethyl)-ethylenediamine in which the alkyl group was a propyl-, butyl-, pentyl-, hexyl-, or heptyl- ring structure. The second series of dicycloalkyl analogues has the general formula of N, N-dimethyl-N'-cycloalkyl-N'-(cycloalkylmethyl)-ethylenediamine in which both alkyl groups of propyl-, pentyl-, hexyl-, or heptyl- were the same ring size. Hydrochloride, picrate, and methyl iodide salts were prepared for these diamines, and for a number of the intermediates.

In both series, the general reaction sequence followed was to start with the appropriate cycloalkyl carboxylic acid and build up to a secondary amine via an acid chloride and amide. The desired amine was then condensed with β-dimethylaminoethylbromide hydrobromide to form the tertiary diamine analogue. Two compounds, the dicyclohexyl- and dicycloheptyl-analogues, were formed by condensing the cycloalkylcarbonyl chloride with a substituted secondary ethylenediamine, and then reducing the amide with lithium aluminum hydride.

Attempts to synthesize a sufficient quantity of the cyclooctanecarboxanilide intermediate were unsuccessful. Difficulty was also encountered in preparing a stable and pure salt derivative for a number of the dicycloalkyl analogues.

Signature of Examiners
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PART I
INTRODUCTION

The purpose of this study was to prepare a number of cycloalkyl analogues of Antergan® in order to make them available for pharmacological investigations into the nature of antihistaminic receptors. It is hoped that by replacing one or both phenyl groups in the parent compound with alicyclic structures, a gradual alteration in potency and/or selectivity will be noted in a series of these compounds.

Histamine:

Before one prepares an antagonist to histamine, one should know as much as possible about the occurrence, chemistry, and pharmacodynamics of histamine in man. With such information, one is able to pattern a compound which is more likely to counter histamine at the receptor site or to alleviate some of the symptomatic states of the allergic syndrome.

Histamine or β-(4-imidazolyl)ethylamine, is formed from the amino acid histidine by decarboxylation as shown by tracer studies.

\[
\begin{align*}
\text{HC} & \equiv \text{C} - \text{CH}_2 - \text{CH} - \text{COOH} \\
\text{N} & \equiv \text{C} - \text{NH} & \text{NH}_2 \\
\text{H} & \equiv \text{H}
\end{align*}
\]

- \text{CO}_2

\[
\begin{align*}
\text{HC} & \equiv \text{C} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\
\text{N} & \equiv \text{C} - \text{NH} & \text{H}
\end{align*}
\]

Histidine decarboxylase which catalyze the biosynthesis of histamine occurs in a number of parenchymatous tissues, including the brain. The reaction occurs at different intensities with regard to different animal species and to the sites of tissues observed.
2.

Once formed, histamine may be immediately metabolized or it may be stored. Storage, which necessarily implies a more or less strong bond between histamine and cellular constituents, may be in sites different from those of its biosynthesis. Histamine storage is evidently intended to meet hypernormal local or systemic requirements for the amine, under particular physiological or pathological conditions. Impairment of storage capacity could be useful in prophylaxis of pathological manifestations, resulting from abrupt release of the amine from its body depots (1).

At the cellular level, histamine remains in an 'inactive' state in the mast cells of adult tissues (2,3). Ehrlich (4) in 1877, named the granule-containing cells in the connective tissue of animals 'Mast cells' (Mastzellen=well-fed cells) because of their overnourished nature. Asboe-Hansen (5) more recently has described mast cells as unicellular endocrine glands which react as part of the mesenchymal system in time of stress. It was observed that both heparin and histamine are released from the mast cells after anaphylactic shock (6). The number of these cells were greater when chronic inflammation or conditions characterized by increased local nutrition were present. In general, mast cells are present in large numbers in the subcutaneous connective tissue, lung pleura, mesentery, scrotum, uterus and thymus of mammals. They also occur predominantly in the loose tissue around the small blood vessels, but are absent from the central nervous system (3).
Histamine is bound to granules (7,8) held in the mast cells. About 50-80 per cent of the amine is stored in the particles which contain a membranous encasement separating the amine from the inactivating enzymes. The remaining portion, 20-50 per cent, of the amine is found in the soluble cytoplasmic fraction. It is possible that the granules in the cytoplasm of tissue mast cells are giant mitochondria as supported by their physical behavior and histochemical properties (9). The intact granules are pharmacologically inert, but after lysis they produce the depressor effect which is characteristic of histamine.

A variety of agents are capable of releasing body stores of histamine. These may be grouped under seven major headings (10).

1. Sensitizing compounds - antigens
2. Compounds which damage tissue - toxins, venoms, and traumatic agents.
4. Surface active agents - bile salts, detergents.
5. Large molecules - egg white, dextran, horse serum, and polyvinyl pyrolidone.
6. Histamine liberators - serotonin, dibasic and polybasic compounds.
7. Monobasic compounds - alkylamines and antihistamines.

Histamine release is due to changes at the particle-cytoplasm interphase, by damage resulting in a rupture or increase in permeability of a membrane enclosing the particle. A chain of enzymes called kinases and plasma proteases seem to be involved in the release of histamine by such a route (11).

The pharmacodynamic effects of released histamine
can be grouped into three categories: vascular, muscular and glandular. It produces a strong vasodilation of the capillaries and in large doses may cause an increase in their permeability, so that fluid and plasma proteins may escape from the circulation into the extracellular fluid and lead to edema. Histamine has little effect on the heart but it produces a fall in blood pressure (in higher animals) due to capillary and arteriolar dilation. Histamine contracts smooth muscle (bronchioles, small intestine, uterus, gall bladder) and stimulates the secretion of the gastric mucosa, salivary glands and also, to some extent, the mucosal glands of the intestinal tract (12). The lacrimal and nasal secretory glands also are stimulated. Another physiological role histamine appears to have is the stimulation of pain responses. Cutaneous pain mediated by histamine may be due to its release at the endings of those terminal nerves which supply the minute blood vessels to the skin (13).

A number of speculations has appeared in the recent literature on the nature of receptors relating acetylcholine and histamine activity. Edema resulting from increased capillary permeability may be related to acetylcholine (AcCh) reaction with a receptor in a cell membrane producing a change in the molecular configuration of the receptor. This change leads to widening of a membrane 'pore' and thus to greater permeability of the membrane to ions (14). Paton (15), in connection with his development of ideas on 'rate theory' and desensitization phenomena, proposed an 'ion exchange' model for recep-
tors for AcCh and histamine. On a similar idea, Rocha e Silva (16), has postulated the presence of an imidazol ring as an active center in the histamine receptor of the guinea pig ileum. Such a ring would form a hydrogen bond with a histamine molecule as a transitory complex which is reversible on pH changes. Geiger and Mandel (17), have speculated on the presence of a sulfhydryl or other type of group, in the AcCh receptor of smooth muscle, which may be trans-acetylated by AcCh when activated.

The finding that histamine actions on the isolated stomach are indirect (18), via release of acetylcholine and norepinephrine, impels caution in interpretation of data regarding histamine actions in smooth muscle until further evidence is obtained. Histamine is like acetylcholine in having relaxant actions in most blood vessels 'in vivo' and contractile actions 'in vitro' (19). Histamine differs from AcCh in having no direct stimulating action on a variety of smooth muscles 'in vivo', however.

Model experiments have been reported which support a hypothesis that histamine interacts with primary phosphate ester at the cell surface and that this effect is antagonized by calcium and antihistamines (20). Cavillito (21) has speculated about the nature of the anionic sites (carboxyl or phosphate groups) in cholinergic receptors of the muscle end-plate, and has considered how these sites might interact with cationic agonists and antagonists. Belleau (22) has proposed that
adrenergic drugs which combine with alpha receptors interact by electrostatic attraction with a surface phosphate anion, suggesting a chemical basis for certain similarities between the actions of histamine and epinephrine. He has speculated on the possibility of a single comprehensive adrenergic receptor, containing both an anionic site, for triggering responses attributed to $\alpha$-receptors, and a site which interacts with the catechol nucleus, for triggering responses attributed to $\beta$-receptors.

The stereochemical configuration required for histamine activity is shown below (23). This may indicate that the structural requirements for histamine-like activity would have bond lengths where $a = 1.36 \text{ Å}$, $b = 1.38 \text{ Å}$, and $c = 0.40 \text{ Å}$. The nitrogen atom holds the histamine molecule in a ring form through hydrogen bonding as shown.

Any histamine formed in normal physiological quantities from histidine is oxidized by the deaminase, Histaminase or diamine oxidase to imidazoleacetaldehyde, which is oxidized further to imidazoleacetic acid by xanthine oxidase. This acid is excreted as a riboside (23).
The release of excessive amounts of histamine would destroy the normal body balance and produce pathologic symptoms of the allergic state and of anaphylaxis. A number of people have produced evidence in support of the view that histamine is liberated as a result of the antigen-antibody reaction (24).

Before further discussion of the allergic condition, a few of the main terms may be defined as follows:

Antigens are substances which stimulate the formation of antibodies and react specifically with such antibodies. Such foreign agents to the body may be 'organized' as in bacteria, or 'unorganized' as egg white or serum protein.

Antibodies are globulins formed in response to, and able to react with, antigens. The antibodies formed are generally specific for the antigen which caused their production.

Anaphylaxis is an artificially-induced state of heightened reactivity to antigenic substances, conditioned by the presence on tissues of globulin antibodies.

Allergy is a naturally-occurring state of increased reactivity to antigenic substances, and is generally dependent upon the presence of antibodies formed specifically against these substances.

Both allergy and anaphylaxis depend for their appearance upon the antigen-antibody reaction.

Evidence for the release of histamine during anaphylaxis is found in many excellent reviews (25). The intracellular combination of antigen with the cellular antibody resulting in the activation of an enzyme system which catalyzes reactions leading to histamine release was postulated by Rocha e Silva in 1950 (26). Further supporting data is observed
when the temperature-concentration curve of the histamine release reaction in anaphylaxis resembles an enzyme curve, and when a heat-labile factor, probably a protein, is found to be involved (27). A scheme for the anaphylactic reaction may be represented as follows:

- Tissue + Antigen → Sensitization → Antibodies
- Challenge with Antigen

- Release of Mediators
- Bound Histamine (Mast cell granule) + Activation of Enzymes

- Free Histamine → Effects seen
- Inflammation
- Bronchoconstriction
- Muscle Contraction

It is not known whether the reaction between antigen and antibody takes place in the cells, upon the surface of the cells, or in the blood stream.

The interaction, however, produces certain pathophysiologic changes involving smooth muscle, blood vessels, glands, and connective tissues. In asthma, allergic rhinitis, urticaria, and angioedema, the basic response is local vasodilatation and increased capillary permeability leading to tissue edema in the mucosa of the respiratory tract, skin, and subcutaneous tissues.

**Antiallergenic Drugs:**

A cure of allergic symptoms may be achieved by desensitization to causative antigens. As this is a long-range and tedious process, a number of drugs have been used for the symptomatic control of allergies and anaphylaxis. Various
9.

chemicals as ascorbic acid, vitamin D, diethylstilbestrol, cortisone, cortisol, prednisone and adrenocorticotropic have been tested for antiallergic activity. These substances share this property with epinephrine and some other pressor amines, such as the alkaloid ephedrine, phenylpropanolamine and isoproterenol. The pressor amines exert their effect as bronchodilators and vasoconstrictors. Aminophylline seems to act by relaxing spastic smooth muscles, especially in the bronchies.

The number of types of effective drugs used in the symptomatic control of allergies is small although each type has many representatives. The most widely used are the antihistamine group of drugs, and these are mainly effective against those aspects of allergy concerned with the release of histamine. When these antihistaminic substances are present in the body, they compete for the active place in the sensitive cells, decreasing the amount of released histamine or H-substance formed. Because of the ability to antagonize the action of histamine on certain tissues, the antihistaminic compounds fulfill one of the requirements of competitive inhibition. The competitive aspect of this type of antagonism implies that histamine, in sufficient concentration, will overcome the effect of a given concentration of the antagonist and that the antagonist, in sufficient concentration, will overcome the effect of a given concentration of histamine. The implication of such a specific mechanism of antagonism is that both the active drug and its antagonist compete for the same
site of attachment in a tissue; the antagonist combining with this site without eliciting a response of the tissue.

By the application of mass action equations to equilibrium conditions, histamine and some antihistamines are seen to act on the same receptors in guinea pig ileum, since they give the same pAx values (28). The pAx value for a given agonist-antagonist pair is the negative log of the concentration of antagonist at which the ratio of equiactive doses of agonist in the presence and absence of antagonist is x (14).

The competitive inhibition theory to explain the activity of antihistaminics was postulated by Halpern (29) in 1942. From other workers in the field of antihistaminic agents, a number of modes of action for these drugs are known. It is found that antihistamines do not combine with histamine to neutralize its action, nor do they prevent its liberation from the cells. Also, it is generally believed that antihistaminics do not interfere with the antigen-antibody reaction (30), and that they have no effect on the production of antibodies. It is also known that these drugs do not activate histaminase to catalyze the breakdown of histamine. From the number of pharmacological activities of these antihistaminic agents, it is difficult to define these compounds as a specific group of drugs.

Loew defined antihistamine agents as "substances which are capable of diminishing or nullifying with high specificity several of the pharmacological effects of histamine,
and which do so by a mechanism other than the production of pharmacological responses diametrically opposed to those produced by histamine," (31). Judah (32) suggests that histamine and related compounds are merely trigger substances, which set into motion a general mechanism of injury in their target cells and that antagonists to such action may be labelled antihistamines. The latter worker also states that these agents are really acting directly on cellular mechanisms to inhibit the consequences of histamine attack, and not as antagonists of the primary histamine action.

Antihistamines have been seen to act at several levels of cell structure, at mitochondrial, at lysosomal and on the cell surface. Judah (33) showed that four antihistamines (diphenhydramine, promethazine, tripelennamine, and actidil—to be discussed later) greatly reduced the rate of mitochondrial swelling under a variety of different circumstances. These include 'spontaneous' swelling, and swelling induced by agents as calcium ions, phosphate, and glutathione. Histamine cause liver mitochondria to swell, and it is thus of interest that antihistamines in concentrations of $5 \times 10^{-5}$ to $5 \times 10^{-4}$ M. inhibit mitochondrial swelling. It raises the question of whether mitochondrial swelling is itself the general mechanism of injury and whether the protective effects of the antihistamines lie here. For one thing, it is related to their actions in vivo in suppressing phenomena of increased capillary permeability.
Antihistamines act on lysosomes by inhibiting their rupture. Lysosomes are subcellular bodies which contain degradative enzymes such as acid phosphatase. These enzymes could conceivably destroy the cells in which they are contained if they were not segregated. The lysosomal enzymes are ineffective unless released from the particles, and this is effected by low pH or suspension in hypotonic sucrose solution (34). The antihistamines tested showed a large reduction of enzyme release from lysosomal preparation in 0.125 M sucrose.

The antihistamine drugs are believed to make a non-specific attack on the cell membrane. Evidence is brought to show that this cannot be due to crude 'surface' effects, as the coagulation of membranes, since the effect of the drugs is reversible by dilution (34).

The mechanism of action of antihistamines appears to be in the mitochondria where they inhibit protein phosphorylation. The enzyme protein phosphokinase found in mitochondria catalyzes the reversible reaction ATP + protein ⇌ P~protein + ADP. Intact mitochondria exhibit little ATP splitting activity, but occurs when the particles swell. Antihistamines which inhibit mitochondrial swelling will be able to preserve energy supplies of damaged cells.

The protective effects of antihistamine drugs in terms of structure can be described by a complex interplay of effects, in which mitochondria, lysosomes and cell membranes
may be involved. These structural relationships are paralleled by enzymic interactions. Inhibition of mitochondrial swelling prevents the ATPase reaction from being manifest; preservation of the lysosomes keeps their degradative enzymes inactive. As the phosphoprotein turnover is inhibited by antihistaminic drugs, ion and water movement in cells and in isolated mitochondria are constrained. Upon exerting their effects, antihistamines do not interfere with normal metabolic processes, but their presence in damaged cells aid the preservation of energy supplies. It is suggested (32) that antihistamine drugs act in similar fashion in all circumstances, and that their action is directed toward intracellular events, rather than in blocking directly the attack of natural or foreign harmful agents.

**Early Antihistaminics:**

The story of the effective antihistamines starts in 1937 when Bovet (35) at the Pasteur Institute discovered that some ethers, e.g. 929F (Table 1), which antagonized adrenaline, also had some action against histamine. In 1939, Staub (36) found high activity in 1571F (Table 2), a derivative of ethylenediamine which had been synthesized in Fourneau's laboratory. None of these compounds could be used in man on account of their diverse toxic effects, such as cyanosis, prostration, and convulsions. The next advance was due to Halpern (37) who, in 1942, examined ethylenediamine derivatives synthesized by Mosnier in the Rhone-Poulenc Laboratories and found that 2325RP (Table 2)
had greater antiasthmatic activity than 1571F. The replacement of the ethyl group by benzyl, giving N-benzyl-N-phenyl-N',N'-dimethylethlenediamine (2339RP or Antergan)(Table 2), resulted in the first clinically effective antihistaminic drug. Antergan produced a number of unpleasant side effects and has been replaced by more active compounds which are better tolerated. The basic Antergan structure, however, has served as a model for a number of the antihistamine drugs in use today.

Two years after Antergan was discovered, Bovet (38) introduced the extremely potent and specific antihistamine, Neoantergan (Table 2). In 1945 Loew (39) reported tests on a series of benzhydryl alkamine ethers which has been synthesized by Rieveschhl and Huber in the United States. 2-Dimethylaminoethyl benzhydryl ether (Benadryl-Table 2) was launched from the Parke Davis Laboratories, and at about the same time the American group (40) introduced Pyribenzamine (Table 2) which has the structure of Neoantergan less the methoxy group. Benadryl and Pyribenzamine were immediately and widely used by the medical profession from that time to today. A year after these two antihistaminics were introduced in America, Halpern (41) introduced a new series of phenothiazine derivatives, e.g. Phenergan (Table 4) which appears to be even more effective than Neoantergan.

It will be seen that these earlier antihistamines fall into two main groups which are ether and ethylenediamine derivatives. A third group, based upon propylamine has also
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Chemical Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thymoxyethyldiethylamine</td>
<td>929F</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2-(Benzohydroyloxy)-N,N-dimethylethylamine</td>
<td>Benadryl</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Bromodiphenhydramine</td>
<td>2-(p-bromo-α-phenylbenzylloxy)N,N-dimethylethylamine</td>
<td>Ambrodryl</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Doxylamine</td>
<td>2-[α-(2-Dimethylaminoethoxy)-α-methylbenzyl]-pyridine</td>
<td>Decapryn</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Phenyltoloxamine</td>
<td>(2-Benzylphenyl)-β-dimethylaminoothylether</td>
<td>Bristamin</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Carbinoxamine</td>
<td>2-[p-Chloro-α-(2-dimethylaminoethoxy)benzyl]-pyridine</td>
<td>Clistin</td>
<td><img src="image" alt="Chemical Structure" /></td>
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Table 2.
ETHYLENEDIAMINE DERIVATIVES

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methaphenylene</td>
<td>N-benzyl-N-phenyl-N',N'-dimethyl-ethylenediamine</td>
<td>Antergan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>2-[2-dimethylaminoethyl-(p-methoxybenzyl) amino] pyridine</td>
<td>Neo-Antergan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tripelennamine</td>
<td>N-benzyl-N',N'-dimethyl-N2-pyridylethylenediamine</td>
<td>Pyribenzamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methapyrilene</td>
<td>2-[(β-dimethylaminoethyl)-2-thenylamino]-pyridine</td>
<td>Thenylene, Histadyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthen</td>
<td>N,N'-dimethyl-N-(2-pyridyl)-N-(5-chloro-2-thenyl)-ethylenediamine</td>
<td>Tagathen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thonzylamine</td>
<td>2-[2-dimethylaminoethyl)p-methoxybenzyl) amino] pyrimidine</td>
<td>Neohetramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N,N'-diethyl-N-ethyl-N-phenylethylenediamine</td>
<td>1571F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Chemical Name</td>
<td>Brand Name</td>
<td>Chemical Formula</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Pheniramine</td>
<td>N,N-dimethyl-3-phenyl-3-(2-pyridyl)-propylamine</td>
<td>Trimeton</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>2-[p-chloro-α(2-dimethylaminoethyl) benzyl]-pyridine</td>
<td>Chlor-Trimeton</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>Dextchlorpheniramine</td>
<td>2-[p-chloro-α(2-dimethylaminoethyl) benzyl]-pyridine</td>
<td>Polar-Trimeton</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>2-[p-bromo-α(2-dimethylaminoethyl) benzyl]-pyridine</td>
<td>Dimetane</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>Dextbrompheniramine</td>
<td>2-[p-bromo-α(2-dimethylaminoethyl) benzyl]-pyridine</td>
<td>Disomer</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>Pyrrobutamine</td>
<td>1-[4-(p-chloro-phenyl)-3-phenyl-2-butenyl]-pyrrolidine</td>
<td>Pyronil</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
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<tr>
<td>Triprolidine</td>
<td>trans-2-[3-(1-pyrrolidinyl)-1-(p-tolyl)propenyl]-pyridine</td>
<td>Actidil</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.

PHENOTHIAZINE - DERIVATIVES

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Chemical Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine</td>
<td>10-(2-dimethylamino-1-propyl)phenothiazine</td>
<td>Phenergan</td>
<td></td>
</tr>
<tr>
<td>Pyrathiazine</td>
<td>10-[2-(1-pyrrolidyl)ethyl]phenothiazine</td>
<td>Pyrrolazote</td>
<td></td>
</tr>
<tr>
<td>Trimeprazine</td>
<td>10-(3-dimethylamino-2-methylpropyl)phenothiazine</td>
<td>Temaril</td>
<td></td>
</tr>
<tr>
<td>Methdilaazine</td>
<td>10-(1-methyl-3-pyrrolidylmethyl)phenothiazine</td>
<td>Tacaryl</td>
<td></td>
</tr>
<tr>
<td>Isothipendyl</td>
<td>10-(2-dimethylaminopropyl)-9-thia-1, 10-diazaanthracene</td>
<td>Theruhistin</td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Chemical Name</td>
<td>Brand Name</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Antazoline</td>
<td>2-(N-benzylaminomethyl)-2-imidazoline</td>
<td>Antistine</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Cyclizine</td>
<td>1-diphenylmethyl-4-methylpiperazine</td>
<td>Marzine</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chlorcyclizine</td>
<td>1-(p-chlorobenzhydryl)-4-methylpiperazine</td>
<td>Perazil</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Meclizine</td>
<td>1-(p-chloro-α-phenylbenzyl)-4-(m-methylbenzyl)piperazine</td>
<td>Bonamine</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Phenindamine</td>
<td>2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene</td>
<td>Thephorin</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Dimethpyridene</td>
<td>2-{1-[2-(2-dimethylaminoethyl)-3-indenyl]ethyl}-pyridine</td>
<td>Forhistal</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
applied in 1949; an example is the potent antihistamine, Trimeton (Table 3) introduced by the Schering Corporation (42). In an attempt to produce more potent and less toxic antihistamine drugs, new derivatives of these three groups have been extensively studied. Antazoline of the ethylenediamine series may be classed as a cyclic analogue of Antergan with the dimethylamino linkage replaced by an imidazole ring. Antazoline is less active than most of the other antihistaminic drugs, but produces less local irritation. Substituted piperazine compounds were first described by Cerkovnikov (43) in 1946. Independent research were reported on these cyclizine compounds from the Abbott Research Laboratories (44) and the Wellcome Research Laboratories (45). The most effective was the p-chloro compound Chlorcyclizine (Table 5) for antihistaminic action, while the others as Meclizine and Cyclizine were primarily used as antimotion-sickness agents.

Pharmacology and Clinical Uses:

From the several thousand compounds that have been synthesized and tested for potential antihistaminic activity, about twenty-five have been found to be of particular value in the relief of certain allergic conditions. Brown (46) has divided the antihistamines into three main groups, based upon their toxic reactions, to aid the physician in selecting the antihistamine of choice which is most effective with the least toxicity to the individual patient. As different side reactions occur with the individual drug and the individual patient,
various antihistamines may have to be tested before the most effective agent with the least side effect may be found.

Group 1-These are least potent and least reactive:
   antazoline (Antistine), thonzylamine (Nechetrame),
   phenindamine (Thephorin).

Group 2-These are moderately potent and moderately reactive:
   tripelennamine (Pyribenzamine), chlorpheniramine (Chlor-Trimeton),
   pheniramine (Trimeton), methaphenilene (Diatrin),
   chlorcyclizine (Perazil), methapyrilene (Histadyl),
   pyrilamine (Neo-Antergan), chlorothen (Tagathen),
   bromodiphenhydramine (Ambo-dryl) and
carbinoxamine (Clistin).

Group 3-These are highly potent but also highly sedative:
   diphenhydramine (Benadryl), doxylamine (Decapryn)
   and promethazine (Phenergan).

The above classification lists the generic name of the drug followed by the most common brand name in brackets. Tables 1-5 contain the most popular antihistamines used today with the exception of 929F, 1571F, 2325RP, and Antergan which were included for historical background. The names of the chemical compounds are listed as available from New and Nonofficial Drugs (47) starting with the generic name, and followed by the chemical name accompanied by its chemical formula.

The principal use of antihistamine agents is for their therapeutic effect on nasal allergies particularly in seasonal hay fever and to a lesser degree in perennial vaso-motor rhinitis. Urticaria, angioneurotic edema, serum sickness and reactions from penicillin, streptomycin, sulfonamides and other drugs usually are benefited by antihistaminics. Other itching skin conditions benefited by these drugs administered internally are atopic dermatitis, contact dermatitis, pruritus
ani and vulvae, generalized pruritus and insect bites. Chronic rhinitis, asthma, and erythema nodosa-type of sensitivity reactions are rarely benefited. Pruritis is frequently relieved by the local application of antihistamines, probably to a large extent because of their local anesthetic properties. Antihistamines have no direct relief on the common cold, but benefit certain nasopharyngeal allergic conditions that stimulate the common cold.

All the antihistaminic drugs produce undesirable side reactions. The most common untoward action is sedation. This varies from mild sedation to deep sleep, depending on the particular drug, the individual response and the dose. In some persons these drugs may produce such symptoms of excitation as insomnia, tremors, nervousness, palpitation and even convulsions. Gastrointestinal disturbances as intestinal pain and diarrhea may occur. Anorexia, dryness of the mouth, throat and nose are also common. Sensitivity to one antihistamine is ordinarily not an indication that the patient is sensitive to others.

It must be remembered that antihistaminic drugs produce only symptomatic relief and do not correct the underlying disorder. The palliative effects last only as long as medication continues or until the disorder is corrected by other means.

Antihistaminics are evaluated in vitro by the Magnus procedure in which the minimum amount of the drug is used to relax histamine-induced spasm in an isolated strip of guinea
pig small intestine immersed in Tyrode solution (48). The most common 'in vivo' procedure include protection against intravenously injected or aerosolized histamine, or against anaphylactic death elicited by administration of a foreign protein to a sensitized animal. For detailed and critical reviews of these and other test methods, a number of pharmacological reports are available (49).

Structure Activity Relationships:

The presently available histamine antagonists belong to several different chemical categories—diamines, aminoalkyl ethers, and propylamines. Most of these compounds are related structurally and certain constitutional features are mutually necessary for maximum activity. The general formula relates the necessary pattern:

\[
\begin{align*}
R^1_X & \quad R^3 & \quad N_{R^4} \\
R^2 & \quad R^3 & \quad X & \quad R^5 \\
\end{align*}
\]

To have maximum activity, it is necessary that the side chain contain a tertiary amine, for secondary and primary amino derivatives are inactive. A dimethylamino or a small planar cyclic group such as the pyrrolidino or morpholino group for \( N-R^4 R^5 \) can still retain high antihistaminic value. The \( N \)-diethylalkyl group seems characteristic of antispasmodic compounds.

The basic unit for all effective agents has been the ethylamine skeleton at \( R^3 \). Essentially all the compounds contain this group, whether it be a 'straight-chain' compound such as Antergan or part of a ring compound such as Antistine. Thus
such widely structurally different compounds as Thephorin, Antistine, Perazil, Trimeton, and Phenergan show a common factor. The ethylamine skeleton also corresponds to the side chain of the histamine molecule, and to part of the imidazole chain.

The $X$ represents nitrogen, oxygen or carbon connecting the side chain to the nucleus. The nucleus of all the antihistaminic agents should have a minimum of two aryl or aralkyl groups or their equivalent in a polycyclic ring system. Thus $R^1$ and $R^2$ are aromatic (isocyclic or heterocyclic) ring systems, one of which may or may not be separated from $X$ by a methylene group. It appears that the nucleus of antihistamine agents must include an unsaturated ring structure attached to oxygen, nitrogen or carbon in such a way as to allow resonance stabilization of the active intermediate, for all compounds with saturated substituents are practically inactive. Substitution of the aromatic rings themselves which interfere with stabilization through hyperconjugation usually cause relative inactivation. It is probable that steric forces are added factors in the reduced activity of ortho-substituted compounds. The extra potency of benzyl compounds and similar methylene separations between the aromatic rings and nitrogen supports resonance ideas.

Halogenation of the para-position of one but not both groups generally increases activity. Quaternization of the $N$ diminishes activity. A minimum molecular weight of about
150 seems necessary. The molecular weights of the most active antihistaminics varies from 254 (Antergan) to 300 (Perazil). It would seem that this weight range is optimal and, perhaps is one of the requirements for effective histamine antagonism. As might be expected, the least soluble antihistaminics are among the least toxic, have the slowest onset of action, and the most prolonged effect.

Three different types of alkylenediamines (X = N) have shown outstanding antihistamine activity. In the first type replacement of the phenyl group in Antergan by the 2-pyridyl structure resulted in the compound Pyribenzamine which is twice as active as Antergan. Further substitution in the benzyl group by p-methoxy gave Neo-Antergan with fivefold the activity of the 2-pyridyl derivative. When the benzyl group in Antergan was replaced by a 2-thenyl group, Methaphenilene was obtained which has low incidence of adverse reaction as gastrointestinal irritation. The fusion of the aryl and ar-alkyl portions into a polycyclic ring formed the second main type of ethylenediamines, the thiodiphenylamine or phenothiazine series. Branching of the side chain by adding one methyl group produced Phenergan which is able to protect guinea pigs against 1500 lethal doses of histamine (50). It is reported to be as much as seven times more potent and have three times the duration of action of certain other antihistaminics. In the third type, the diamine system is enclosed in a piperazin ring. The most active member is chlorcyclizine which is four
times as active and one half as toxic as Benadryl (50). For further details regarding the ethylenediamine and other antihistaminic groups on structure activity relationships, refer to the extensive work of Idson (49) for additional references.

Based upon their chemical structure, many of the antihistamines, in addition to its antiallergic properties, have been found useful as tranquilizers, antitussives, anticonvulsants, local anesthetic agents, antispasmodic and in the treatment of motion sickness. Pharmacologically, some of these agents possess atropine-like and antiserotonin properties as well. A number of the antihistaminics have fungistatic activity, but this does not seem to be related to antihistaminic potency. These over-lapping properties suggest that the natural humoral agents as epinephrine, serotonin, acetylcholine and histamine may antagonize or increase each other effects by competing for the 'same' cell receptors. Drugs mimicking or antagonizing their actions enter into this competition and thus alter the natural equilibria of the reactions at the receptor sites. Stern (51) believes that the enzyme diamine oxidase (histaminase) really acts as the receptor for both histamine and the antihistaminics.

The main if not the only source of information on the properties of the receptors is the study of structure activity relations of drugs. This study allows us, through indirect evidence, to develop certain views and hypothesis of the drug receptors. Harms and Nauta (52) observed that rigid
structures as phenindamine (Table 5) with the side chain being fixed to one of the rings, or chlorcyclizine with the piperazine structure able to rotate around one axis possess active antihistaminic activity, while ortho-substitution on benzhydryl ether hinders the molecule from imitating these rigid or semi-rigid structures by 'curling up' the side chain. They also indicated that most of the useful antihistaminics are able to assume the spatial configuration of the rigid structures by rotation of its side chain. As with the benzhydryl ethers, the ethylenediamine group as represented by Antergan can assume this stereospecific form. The stretched chain position gives a 5 Å distance between the dimethylamino nitrogen and the methylene carbon atom. This value corresponds to the dimensions required for cholinolytic agents.

Curled Up Position - Active Antihistamine

Stretched Chain Position - Antispasmotic Form
This concept of a close fit at an antihistamine-receptor site is postulated to comprise of an anionic site to accommodate the basic centre, and a flat region at a more or less fixed distance to accommodate one of the aromatic rings which has to be approximately co-planar with the side chain. Studies as these help to explain the overlapping activities of antihistaminic and antispasmotic agents.

One can say that the forces between drugs and receptors are probably ionic, dipolar, and short range Van der Waal or London bonds. With respect to the receptor, a flat benzene ring may be expected to furnish a supporting attachment of 2 to 3 kcal. per mole to the Van der Waal bonds in reinforcing the ionic linkage between the amino group and an anionic site. Thus alicyclic structures in comparison with their aromatic prototypes show less activity and higher toxicity, because a puckered nonaromatic ring will be of much less value as a source of short-range bonds. Three factors should influence the magnitude of these forces: (a) the size of the ring; (b) the planarity of the rings; (c) the angle between the substituent chain and the ring (53).
PART II
STATEMENT OF PROBLEM

As mentioned in the introduction, the size and planarity of the ring in a drug molecule should influence its activity on a receptor site. With this thought in mind, the synthesis of a number of Antergan analogues were attempted to make them available for pharmacological screening of this nature. In the first series of compounds, the benzyl group of Antergan was to be replaced by a cyclopropylmethyl-, a cyclobutylmethyl-, a cyclopentylmethyl-, a cyclohexylmethyl-, a cycloheptylmethyl-, or a cyclooctylmethyl-group. In the second series of compounds, both phenyl groups were to be replaced by the same cycloalkyl group ranging in size from a three- to eight-membered ring.

The presence of an unsaturated ring attached to the nitrogen in the first series conforms to the required structure for antihistaminic activity. The presence of a cyclopropane structure in the molecule should increase its activity due to its size and planarity. Substitution by a larger group as a cycloheptane structure should show a lesser activity due to its bulky and puckered form.
PART III
CHEMISTRY

The appropriate cycloalkylcarboxylic acid was prepared as the starting compound for each substituted ethylene-diamine product. The formation of these alicyclic acids was dependant upon a number of factors. Ring strain, which usually means ring instability in the thermodynamic sense, was only one of the factors involved. As shown by a table in Royals (54), the highest instability was for cyclopropane (169.5 k.cal. per mole per methylene group). Strain in small rings was explained in Baeyer strain theory (55), but this theory was found not to apply to six-membered and larger rings. Another factor considered which would control the yield of cyclization reaction was the probability of the two ends of the ring-forming chain colliding. This probability is relatively high for three-membered rings, and decreases as the ring size increases.

Cyclopropanecarboxylic acid formed in good yield (50-80%) because the high probability factor outweighed the ring strain factor. An early synthetic route in forming this acid was developed by Perkin (56) who condensed ethylene dibromide with sodiomalonic ester to give diethyl cyclopropane-1,1-dicarboxylate. He then saponified the ester and by mild pyrolytic decarboxylation of the malonic acid obtained cyclopropanecarboxylic acid. This method of cyclization also gave an open-chain compound through intermolecular reaction.
The method used for the preparation of cyclopropane-carboxylic acid was via \( \gamma \)-chlorobutyronitrile with the formation of cyanocyclopropane 'in situ'. \( \gamma \)-chlorobutyronitrile was prepared from trimethylenechlorobromide according to Allen (57). Caution was required in heating up the initial reaction which became very exothermic after chlorobromide addition.

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{Br} + \text{NaCN} & \rightarrow \text{CH}_2\text{CH}_2\text{CN} + \text{NaBr} \\
\end{align*}
\]

Cyclopropanecarboxylic acid was prepared from \( \gamma \)-chlorobutyronitrile by the method of McCloskey and Coleman (58) through cyclization using sodium hydroxide flakes and then hydrolysis of the cyano-compound.

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{CN} & \xrightarrow{\text{NaOH}} \text{CH}_2\text{CH}_2\text{CN} + \text{H}_2\text{O} \\
\end{align*}
\]

Cyclobutanecarboxylic acid was prepared by hydrolysis and decarboxylation of diethyl cyclobutanedicarboxylate by the procedure of Heisig and Stodola (59) as reported in Organic Synthesis. Although the angle strain for cyclobutane formation is slightly less, its ease of formation drops sharply which may account for the low yields of the diester from condensation of trimethylene dibromide with sodiomalonic ester. A yield of about 25 per cent was reported by Heisig and coworkers, and by
Perkin (60) who first carried out this reaction in 1887.

The method of Cason and Allen (61) was employed for obtaining the cyclic diester in a 60 per cent yield by a modified procedure in condensing trimethylene dibromide with sodiomalonic ester. The best ratio of reactants appeared to be dibromide (1 mole), sodium (2 mole); diethyl malonate (1.2 mole) for intramolecular reaction (cyclization) rather than intermolecular reaction (tetraester chain).

\[
\text{Br(CH}_2\text{)}_3\text{Br} + \text{(-CH)CO}_2\text{Et} \rightarrow \text{CH}_2\text{=O(CH}_2\text{)CO}_2\text{Et} + \text{-(-CH)CO}_2\text{Et}
\]

Hydrolysis of the cyclic diester was best carried out using a basic solution (KOH) than with an acidic solution (HCl). As both carboxyl groups are attached to the same carbon atom, the dicarboxylic acid readily formed the monocarboxylic acid with the evolution of carbon dioxide upon heating.

\[
\text{CH}_2\text{-C-(CO}_2\text{Et)}_2 + \text{KOH} \rightarrow \text{CH}_2\text{-C-(CO}_2\text{H)}_2 + \text{CO}_2
\]

Three main routes are reported in the literature for the synthesis of cyclopentanecarboxylic acid. The first is a cyclization procedure in which diethyl malonate is alkylated with 1,4-dichlorobutane in the presence of sodium iodide (62) which is similar to the preparation of the three and four-membered acids. Hydrolysis and decarboxylation of the dicarboxylic
ester is reported in 85 per cent yield. Although the ends of the reactant chains are further apart than in cyclopropane chain reactants, the nearly strain-free cyclopentanane structure (due to a slight puckering which reduces eclipsing strain between adjacent hydrogen atoms) increases its ease of formation.

The second method of cyclopentanecarboxylic acid synthesis is by the use of a Grignard reagent which is prepared from cyclopentylbromide (63). The cyclic acid is then formed by reacting the Grignard reagent with Dry Ice in 80 per cent yield. (64). A third route was found by Favorsky (65) who rearranged an α-haloketone with alkali to the carboxylic acid having the same number of carbon atoms. This latter method was successfully tried following a procedure in Organic Synthesis (66) to prepare 2-chlorocyclohexanone from cyclohexanone using chlorine gas.

\[ \text{Cyclohexanone} + \text{Cl}_2 \rightarrow \text{2-Chlorocyclohexanone} + \text{HCl} \]

Ring contraction by the action of alcoholic alkali on 2-chlorocyclohexanone to cyclopentanecarboxylic acid was carried out using the general procedure of Fissekis, Skinner and Shine (67).

\[ \text{2-Chlorocyclohexanone} \rightarrow \text{Cyclopentanecarboxylic Acid} \]

One possible mechanism for the Favorski reaction is attack by a hydroxide ion (nucleophilic) at the carbonyl carbon (an electrophilic center) leading to formation of the intermediate X. This intermediate attempts to relieve the high electron density
on an oxygen atom by recreation of a carbon-oxygen double bond in Y. As this occurs, carbon atom 6 of the ring with its electron pair is released and simultaneously attacks carbon atom 2 with displacement of a chloride ion. Loftfield (68) using a radioactive tracer believes the intermediate forms a cyclopropanone structure. A similar ring contraction was carried out by Payne (69) who reacted 2-acetylcyclohexanone with hydrogen peroxide solution.

As cycloheptyl bromide was commercially available (Aldrich Chemicals), this compound was used to prepare the Grignard reagent, and then cycloheptanecarboxylic acid by the procedure of Royals and Neal (64).

\[
\begin{array}{c}
\text{Br} + \text{Mg} \rightarrow \text{MgBr}^+ + \text{CO}_2 \text{MgBr} + \text{H}_2\text{O} \rightarrow \text{CO}_2\text{H} + \text{Mg(OH)Br}
\end{array}
\]

About 7 g. of a colourless liquid with a hydrocarbon odor (b.p. 45-60°/22 mm.) was recovered, and may be a dicycloheptane compound or a ketone.

(a) \[\text{MgBr} + \text{Br} + \text{MgBr}_2\]

(b) \[\text{CO}_2\text{MgBr} + \text{MgBr} + \text{MgBr}_2 + \text{MgO}\]

Such side reactions are minimized by using higher dilutions, by adding the halide slowly, and by using an efficient stirrer. Metals such as an etched nichrome-wire stirrer promote very serious coupling, and should be avoided.
Of all the alicyclic compounds from three- to eight-membered, the latter structure is the most difficult to form from an open-chain compound. As a result, most attempts to synthesize cyclooctanecarboxylic acid have been through either a ring-enlargement or a ring contraction sequence. Stork and Landesman (70) have reported a synthesis of this acid by a reaction of the pyrrolidine enamine of cyclohexanone with acrylic and then with further reduction. An example of a ring contraction sequence was carried out by Prelog and coworkers (71) in their reaction of 1,2-cyclononanedione to form cyclooctanecarboxylic acid.

As cyclooctanol is commercially available (Aldrich Chemicals) it was possible to synthesize the corresponding ring carboxylic acid via the Grignard reagent. Little difficulty was encountered in preparing the bromide from cyclooctanol as described in the experimental section.

\[
\text{Cyclooctyl bromide was then reacted with magnesium turnings to form the Grignard reagent; then further treated with Dry Ice followed by hydrolysis with dilute acid. The yield (27\%) of cyclooctanecarboxylic acid was much lower than for the seven-membered acid prepared under similar conditions.}
\]
The lower reactivity of cyclooctane structures may be due to its larger size and stereochemistry. Cyclooctane exists in three main conformations of boat, chair, and crown with the latter the most stable (72).

After obtaining the appropriate cycloalkanecarboxylic acid, the next procedure was to prepare the acid chloride intermediate. Treatment of carboxylic acids with phosphorus pentachloride, phosphorus trichloride, or thionyl chloride replaces the hydroxyl group of the acid by chlorine.

\[
\begin{align*}
R-CO-OH + PCl_5 & \rightarrow R-CO-Cl + HCl + POCl_3 \\
3R-CO-OH + PCl_3 & \rightarrow 3R-CO-Cl + H_3PO_3 \\
R-CO-OH + SOCl_2 & \rightarrow R-CO-Cl + SO_2 + HCl
\end{align*}
\]

The choice of reagent for preparation of an acid chloride was determined largely by the relative boiling points of the acid chloride and the by-products produced in the particular reaction as distillation was the only suitable method of purification.

Another method of preparing lower aliphatic acid chlorides was by acyl exchange from another acid chloride as benzoyl chloride. This method was successfully used in the preparation of chloroacetyl chloride which was more volatile than monochloroacetic acid or benzoyl chloride. A mixture of the aliphatic acid (1 mole) and benzoyl chloride (2 mole) was
distilled through a Vigreux fractionating column in 65 percent yield.

\[
\text{CH}_2\text{-COOH} + \text{C}_9\text{H}_8\text{O} \rightarrow \text{CH}_2\text{-COOH} + \text{C}_9\text{H}_8\text{O} \]

Thionyl chloride was chosen as the reagent for the preparation of the alicyclic acid chlorides as the products were found to have a higher boiling point than this reagent, and only gaseous by-products were produced. Although side reactions in this chemical conversion were essentially nil, two precautions were taken. The first was to protect the reaction and the acid chloride from moist air; the second was to avoid high temperatures during the distillation which may cause pyrolysis of the acid chloride. The results are tabulated as follows:

Table 6.

**CYCLOALKANECARBONYL CHLORIDES**

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Boiling Points C - Refractive Index-% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopropane</td>
<td>114-116 (1 atm.) ( n^{20}_D 1.4528 ) 70</td>
</tr>
<tr>
<td>&quot; butane</td>
<td>130-142 &quot; ( n^{23}_D 1.4515 ) 63</td>
</tr>
<tr>
<td>&quot; pentane</td>
<td>160-163 &quot; ( n^{23}_D 1.4620 ) 76</td>
</tr>
<tr>
<td>&quot; hexane</td>
<td>82-85 (14-15 mm.) ( n^{15}_D 1.4710 ) 80</td>
</tr>
<tr>
<td>&quot; heptane</td>
<td>89-98 (14 mm.) ( n^{23}_D 1.4868 ) 80</td>
</tr>
<tr>
<td>&quot; octane</td>
<td>115 (22 mm.) ( n^{22}_D 1.4617 ) 73</td>
</tr>
</tbody>
</table>
Roberts and Chambers (73) prepared cyclobutane-carbonyl chloride from reacting cyclobutanecarboxylic acid and phosphorus trichloride in 92 per cent yield.

Upon obtaining the alicyclic carboxyl 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.

\[ \text{R-CO-Cl + NH}_2 \text{N} \rightarrow \text{R-CO-NH} - \text{N} + \text{N-HCl} \]

Separation of the amide and amine hydrochloride 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 hydrochloride. Pyridine was added to the primary amine to neutralize the hydrogen chloride formed.

The anilides for cyclopropane to cycloheptane readily formed in good yields. Cyclooctanecarboxanilide, however, proved to be difficult to synthesize via the acid chloride route. Anilides such as cyclohexanecarboxanilide have been prepared from the Grignard reagent upon reaction with phenyl isocyanate (74). This latter procedure was then attempted for the eight-membered ring by reacting cyclooctanemagnesium bromide with a slightly less than equivalent amount of phenyl isocyanate. Precautions were taken to avoid any hydrolysis
of the isocyanate and to insure a complete reaction. A white solid was obtained, but proved to be diphenylurea instead of the desired cyclooctanecarboxanilide. Decomposition of the isocyanate in the presence of moisture to form aniline would be the cause of this side reaction.

\[
\text{phenyl isocyanate} \quad N=\overset{\text{C=O}}{\text{C}} + \overset{\text{NH}_2}{\text{C}} \rightarrow \overset{\text{C-OH}}{\text{C}} \rightarrow \overset{\text{C=O}}{\text{C}} \text{ diphenylurea}
\]

The dicycloalkyl carboxamides for the second series did not form as readily as for the monocycloalkyl anilides. A much lower yield was noted for the synthesis of N-cyclopropyl-cyclopropanecarboxamide, than for the monocyclopropane substituted anilide. The primary amine, cyclopropylamine, was unstable at room temperature and had to be kept in the cold during storage. Cyclopropylamine was commercially available (Aldrich Chemicals), however, the next larger homologue, cyclobutylamine was not supplied commercially. One possible synthetic route for the latter amine is to form cyclobutanecarboxamide from cyclobutanecarboxylic acid via the acid chloride. The amide can then be treated with an alkaline solution of sodium hypo-bromite in a Hofmann Rearrangement to form cyclobutylamine. This method was not attempted as other workers (personal reference) had found the rearrangement did not occur as anticipated. Dicyclopentyl- and dicyclohexylamides formed in good yields of 85.6 per cent and 73 per cent respectively.
In order to obtain the cycloalkyl substituted amine, the corresponding amide was reduced with lithium aluminum hydride. This reagent discovered by Finholt, Bond, and Schlesinger in 1947 (75) has proved to be a remarkable reducing agent for the carbonyl group in amides and similar carbonyl compounds. 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.

Solid lithium aluminum hydride is available commercially (Metal Hydride Inc.) and, if protected from moist air and carbon dioxide, it is stable indefinitely at room temperature. The hydride can be safely handled, even in humid air, probably because of the formation of a protective coating of aluminum hydroxide. It is generally used in solution or suspension in anhydrous ether (25-30 g. solid dissolves in 100 g. ether at 25°). In the normal procedure the substance to be reduced is added to a 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 with a thimble to hold the substance 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 lithium aluminum hydride was used.
Water was then added to destroy the excess hydride used with the evolution of hydrogen, and the precipitation of lithium- and aluminum hydroxide.

\[
\text{LiAlH}_4 + 4\text{H}_2\text{O} \rightarrow \text{LiOH} + \text{Al(OH)}_3 + 4\text{H}_2
\]

As the amine was ether-soluble, the mixture was treated with strong sodium hydroxide solution to dissolve the precipitated alumina, and allowed a clean-cut separation of phases on centrifugation.

Table 7.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>B.Pt. C</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopropane</td>
<td>phenyl</td>
<td>111-115</td>
<td>77</td>
</tr>
<tr>
<td>cyclobutane</td>
<td>phenyl</td>
<td>150-160</td>
<td>98</td>
</tr>
<tr>
<td>cyclopentane</td>
<td>phenyl</td>
<td>154-157</td>
<td>97</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>phenyl</td>
<td>170-174</td>
<td>59</td>
</tr>
<tr>
<td>cycloheptane</td>
<td>phenyl</td>
<td>154-156</td>
<td>78</td>
</tr>
<tr>
<td>cyclopropane</td>
<td>cyclopropane</td>
<td>86-88</td>
<td>98</td>
</tr>
<tr>
<td>cyclopentane</td>
<td>cyclohexane</td>
<td>115-117</td>
<td>56</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>cyclohexane</td>
<td>142-143</td>
<td>80</td>
</tr>
</tbody>
</table>

Lithium aluminum hydride was also used to reduce free cyclohexanecarboxylic acid to yield 79 per cent of cyclohexyl-carbinol using the general procedure of Nyström and Brown (76).

\[
\text{LiAlH}_4 + 3\text{COOH} \rightarrow \text{LiAl(OCH}_2\text{)}_4 + 2\text{LiAlO}_2 + 4\text{H}_2
\]
Hydride reduction of a more hindered compound such as an ethylenediamine chain containing a carbonyl function was complete after 4 days refluxing to give 80 per cent yield.

Upon obtaining the disubstituted amine, the next portion of the molecule to be attached was the β-dimethylaminoethyl chain. β-Dimethylaminoethylbromide hydrobromide was prepared by reacting β-dimethylaminoethanol with 48 per cent hydrobromic acid according to the procedure of Cortese (77). If care was taken not to exceed the specified volume of distillate, a white product which could be used in its crude form was obtained in good yield (80%+).

\[
\text{CH}_3\text{N-CH}_2\text{CH}_2\text{OH} + 48\% \text{HBr} \rightarrow \text{CH}_3\text{N-CH}_2\text{CH}_2\text{Br}\cdot\text{HBr} + \text{H}_2\text{O}
\]

In the initial condensations of the substituted amines and the ethylamine chain in its hydrobromide salt form (potassium carbonate as condensing agent), the tertiary diamine did not form. An attempt was then made to prepare the free bromide amino-chain from its hydrobromide salt. The method of Riffken and Rubin (78) was followed in which β-dimethylaminoethylbromide hydrobromide was dissolved in water and treated with sodium...
hydroxide pellets. The mixture was mechanically shaken for 2 hours in the presence of xylene to take up the free base. A deep-red solution which resulted was used in the condensation with the substituted amine, but the results were also negative. The presence of a strong base may have caused the decomposition of $\beta$-dimethylaminoethylbromide which may explain the lack of success.

$$\text{CH}_3\text{N-CH}_2\text{CH}_2\text{Br.HBr} + \text{NaOH} \rightarrow \text{CH}_3\text{N-CH}_2\text{CH}_2\text{-Br} + \text{NaBr} + \text{H}_2\text{O}$$

$$\text{CH}_3\text{N-CH}_2\text{CH}_2\text{-Br} + \text{NaOH} \rightarrow \text{CH}_3\text{N-CH}_2\text{CH}_2\text{-OH} + \text{NaBr}$$

As alkyliodides are more reactive than the corresponding bromides, a halide exchange was carried out on $\beta$-dimethylaminoethylbromide hydrobromide. Sodium iodide was refluxed with the hydrobromide salt to readily form $\beta$-dimethylaminoethyliodide hydroiodide using the general procedure of Maréchal and Bagot (79).

$$\text{CH}_3\text{N-CH}_2\text{CH}_2\text{Br.HBr} + 2\text{NaI} \rightarrow \text{CH}_3\text{N-CH}_2\text{CH}_2\text{I.HI} + 2\text{NaBr}$$

Condensation of the iodide salt with N-cyclohexyl-N-cyclohexanemethylamine using sodium amide as the condensing agent did not form the desired tertiary diamine.

Essentially three methods have been described by Huttrer and coworkers (80) for the preparation of tertiary ethylenediamines. The first was the condensation of a dialkylaminoalkyl substituted cyclic amine with an alkyl or aralkyl
halide. A typical synthesis of this type was used for obtaining Neo-Antergan as follows:

\[
\text{H} - \text{CH}_3 \xrightarrow{N \text{-CH}_2 \text{CH}_2}\text{N} + \text{CH}_3 \text{O} - \text{CH}_2 \text{Cl} \rightarrow \text{CH}_3 \text{O} - \text{CH}_2 \text{N} \text{-CH}_2 \text{CH}_2 \text{N} - \text{CH}_3
\]

The second method used was the condensation of a cyclic halide with an asymmetrically trisubstituted alkylenediamine. A disubstituted-pyridyl ethylenediamine was prepared by Hutterer in 18 per cent yield following this procedure.

\[
\text{N} - \text{Br} + \text{N} - \text{CH}_2 \text{CH}_2 \text{N} \xrightarrow{\text{N} - \text{CH}_2 \text{CH}_2 \text{N}} \rightarrow \text{N} - \text{CH}_2 \text{CH}_2 \text{N} - \text{CH}_3
\]

The third method was the condensation of an alkyl, aralkyl or aryl disubstituted amine with a dialkylaminoethylhalide. Antergan was prepared (81) using this sequence from N-benzylaniline and dimethylaminoethyl chloride in the presence of potassium carbonate.

\[
\text{N} - \text{H} + \text{Cl} - \text{CH}_2 \text{CH}_2 \text{N} \xrightarrow{\text{K}_2 \text{CO}_3} \rightarrow \text{N} - \text{CH}_2 \text{CH}_2 \text{N} - \text{CH}_3
\]

The condensations were shown to have best results when carried out at elevated temperatures, using solvents like benzene, toluene, or xylene, and in the presence of a neutralizing agent like potassium carbonate or sodamide. In order to obtain optimal yields, it was advisable to use an excess of about 5 per cent of the halide over the secondary amine. The dialkylaminoethyl halide used in all the reaction sequences
was dimethylaminoethylbromide in its hydrobromide salt form. It was necessary, however, to use double quantities of sodamide for the reaction. One equivalent was used to form the free halide while the second acted as the neutralizing agent. In the preparation of the cycloalkyl substituted ethylenediamines, success was achieved only when the free halide was formed 'in situ' using sodium amide as the condensing agent.

The tertiary diamines, analogues of Antergan with the benzyl group replaced by a cycloalkylmethyl group, were synthesized following the third general method. Condensation of the secondary amine with β-dimethylaminoethylbromide hydrobromide was achieved by first refluxing the secondary amine with sodamide in an appropriate solvent (dry xylene or toluene) for 2 to 3 hours. The mixture was cooled and the hydrobromide salt was then added. Stirring and refluxing were continued for 20 to 48 hours depending on the size of the cycloalkyl substituent. The yellow-oil tertiary diamines of rather high boiling points were obtained by fractional distillation 'in vacuo'. A wide range of yields (low) were obtained, depending upon the character of the reactants.

Synthesis of Antergan analogues with both phenyl groups replaced by the same alkane ring structure was also attempted by the third condensation procedure. The dicyclopropyl substituted analogue formed in a low yield (5.5%), and was difficult to fractionate. A lower yield was obtained for the dicyclopentyl analogue (2.6%) using the same condensation
procedure. When the dicyclohexyl substituted diamine was attempted, the starting compounds were recovered with no yield of the desired analogue.

\[ R' \text{CH}_2N\text{CH}_2\text{CH}_2N\text{CH}_3 \]

Table 8.

<table>
<thead>
<tr>
<th>CYCLOALKYL ANALOGUES OF ANTERGAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R'</strong></td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>cyclopropyl</td>
</tr>
<tr>
<td>cyclobutyl</td>
</tr>
<tr>
<td>cyclopentyl</td>
</tr>
<tr>
<td>cyclohexyl</td>
</tr>
<tr>
<td>cycloheptyl</td>
</tr>
<tr>
<td>cyclopropyl</td>
</tr>
<tr>
<td>cyclopentyl</td>
</tr>
</tbody>
</table>

As mentioned before, various attempts to condense \(N\)-cyclohexyl-\(N\)-cyclohexylmethylamine and the hydrobromide side chain using 2,4,6-trimethylpyridine, potassium carbonate, or sodium amide were unsuccessful. Other methods of building the desired compound were considered. An attempt was made to use the chloroacetyl chloride unit to attach to the secondary amine portion, but upon refluxing, a tarry residue resulted.

A new route was then tried which was similar to the first condensation method of Huttrer. In this procedure,
Cyclohexylcarbinol was used to form hexahydrobenzyl chloride by treatment with thionyl chloride. The chloride was then reacted with N,N-dimethyl-N'-cyclohexyl-ethylenediamine which was prepared in a similar manner as for the tertiary diamines using sodium amide, cyclohexylamine, and β-dimethylaminoethylbromide hydrobromide.

\[
\text{CH}_2\text{OH} + \text{SOCl}_2 \rightarrow \text{CH}_2\text{Cl} + \text{SO}_2 + \text{HCl}
\]

\[
\text{NH}_2 + \text{HBr} \rightarrow \text{BrCH}_2\text{CH}_2\text{NCH}_3 \rightarrow \text{NaNH}_2 \rightarrow \text{NH-CH}_2\text{CH}_2\text{NCH}_3
\]

As indicated by the equation, the final condensation did not occur. Two possible explanations for the lack of reactivity may be given. The first is that hexahydrobenzylchloride is a stable compound at the reflux temperature of toluene; the second is due to steric hindrance of two bulky cyclohexane groups in close proximity.

In place of hexahydrobenzyl chloride, cyclohexylcarbonyl chloride was used to condense with N,N-dimethyl-N'-cyclohexyl-ethylenediamine to form the diamine with a carbonyl group between N' and a cyclohexyl ring. This long chain amide was then reduced with LiAlH\textsubscript{4} as discussed earlier to form the dicyclohexyl analogue of Antergan.

\[
\text{O-Cl} + \text{NH-CH}_2\text{CH}_2\text{NCH}_3 \rightarrow \text{O-N'-CH}_2\text{CH}_2\text{NCH}_3
\]
Each of the intermediates, the secondary chain amine and the following amide, and the final analogue were tested with infrared spectra to determine the completion of each stage in the reaction. Although these spectra indicated the presence of the desired compounds, the analytical results of the derivatives were not close enough to be conclusive. This latter condensation procedure was also used to form the dicycloheptyl analogue of Antergan.

N,N-dimethyl-N'-cycloheptyl-ethylenediamine was prepared by condensing cycloheptylamine (Aldrich Chemicals) and β-dimethylaminoethylbromide hydrobromide in the presence of sodamide.

The secondary amine was then treated with cycloheptylcarbonylchloride to form the amide (diamine) chain.

As shown under the discussion of lithium aluminum hydride, the reduction of this amide occurred in good yield (80%) to form N,N-dimethyl-N'-cycloheptyl-N'-(cycloheptylmethyl)ethylenediamine. Elemental microanalysis of the dipicrate derivative indicated the presence of this tertiary diamine.

For those compounds which did not have a reported literature physical constant, which were new compounds, or
which had an observed value different than the literature value, a derivative was prepared for percentage composition analysis of carbon, hydrogen and nitrogen. Some of the unknowns were identified with the aid of only one derivative as for the phenylthiourea of N-cyclohexyl-cyclohexanemethylamine. Other compounds such as the tertiary diamines required the preparation of two or more derivatives in order to find the most stable and purest product. The secondary amines readily formed a stable hydrochloride derivative in most cases. The tertiary diamines formed stable and unstable or hygroscopic hydrochlorides. In this case, the methyl iodide or picrate was formed for characterization. Depending upon the type of compounds (secondary or tertiary), the availability of the nitrogen (stereochemistry and ring size), and the procedure of preparing the derivative, a mono- or di-substituted hydrochloride or picrate was formed.

In the preparation of picrate derivatives, it was noted that some of these derivatives were unstable to heat. Recrystallization of these compounds using heat would cause the formation of two crystal structures, one yellow and the other orange in colour. These two structures possibly correspond to the mono- and dipicrate derivatives.

Some of the solid intermediates such as the amides were used in their original form (recrystallized) 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 15μ 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 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. For the identification of substances which have reference spectra, it was necessary only to compare the spectrum of the synthesized product with the known spectrum.

General regions on an infrared spectrum can be assigned to many types of linkages as for the carbon-hydrogen aliphatic stretching which occurs between the 2700 to 3000 cm.\(^{-1}\) range, and for the carbon double bonded to oxygen in aldehydes stretching between the 1720 to 1740 cm.\(^{-1}\) range. The position for a band due to a specific group may shift slightly depending on the adjoining groups. Such a shift was noted for a nitrogen-hydrogen stretching vibration when influenced by a carbonyl group of an amide. Conjugation between the cycloalkane structure and the carbonyl group would produce such an effect as noted for the cyclopropane ring.
PART IV
EXPERIMENTAL

All melting points were determined in an open capillary and are uncorrected. Infrared spectra were taken on a Unicam SP. 200 spectrophotometer. Elemental microanalyses were performed by Dr. G. Weiler and his associates, 164 Banbury Road, Oxford.

Mono-Cyclopropyl Analogue:

γ-Chlorobutyronitrile

Into a 5-liter three-necked round-bottomed flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel was placed NaCN (290 g., 6 mole) dissolved in water (approx. 500 ml.). 95% ethanol (1750 ml.) was added to the cyanide solution and heated (heating mantle) to about 60°C. 1-Bromo-3-chloropropane (trimethylenechlorobromide 790 g., 5 mole) was added through the dropping funnel cautiously (reaction heats up slowly). After addition was complete, the mixture was refluxed for 1½ hours, cooled and diluted with 2 liters of water. The product separated as an oil in the lower layer. The upper aqueous layer was extracted with chloroform (500 ml.) after separating the oily layer. The extract combined with the oil layer was washed with a saturated calcium chloride solution (800 ml.), with water (800 ml.) and then dried over anhydrous calcium chloride. The chloroform was removed by distilling under atmospheric pressure until the temperature reached 120°C. The product was fractionated and
collected between 175-200 °C (1 atm.). The pale-yellow γ-chloro-
obutyronitrile mainly distilled at 195°(760.4 mm.) to give
229 g. (44.3%) yield. (lit. (57) b.p. 194-197°(745 mm.) with
210-245 g. yield)

**Cyclopropanecarboxylic Acid**

A 2-liter, three-necked flask equipped with two
reflux condensers was set up in a fume hood to remove any
isocyanide evolved during the reaction. NaOH flakes (150 g.,
3.75 moles) and γ-chlorobutyronitrile (103.5 g., 1 mole) were
added to the flask and shaken well. It was then placed on a
steam bath and heated for about 1 hour. The reaction started
in about 30 minutes and became quite violent. (The yield was
higher if the first vigorous reaction was allowed to take place
without external cooling.) After 1 hour heating, most of the
liquid disappeared. Heating was continued on the steam bath
while water (500 ml.) was added in portions - 20 ml. to start
and then about 60-75 ml. every 10-15 minutes. After all the
water had been added (about 2 hours), the mixture was heated
for an additional 1½ hours with occasional stirring; at the
end of this time the oily layer had disappeared. The solution
was then cooled in an ice-bath and acidified by adding a mix-
ture of concentrated sulphuric acid (200 ml. sp.gr. 1.84) in
cracked ice (300 g.). After further cooling in an ice-bath,
the thick floating layer of crude acid was separated and the
cold aqueous solution extracted once with ether (1 liter).
(A mechanical stirrer was used for 15 minutes to prevent
emulsification. The ether extract combined with the crude acid was dried over anhydrous sodium sulphate. After removing the ether solvent, the residue was fractionated under reduced pressure b.p. 93-99° (26 mm.), 183-4° (1 atm.), \( n^{20}_D 1.4380 \); in 45 g. (52%) yield. (lit. b.p. 64-65° (3.8 mm.) \( n^{20}_D 1.4382 \) (82); 94-95° (26 mm.) in 75% yield (58); b.p. 182-4° (1 atm.) \( n^{20}_D 1.4390 \) (83).)

**Cyclopropanecarbonyl Chloride**

Into a 250 ml. three-necked flask equipped with a reflux condenser, a dropping funnel (125 ml.) both with drying tubes, and a mechanical stirrer was placed cyclopropane-carboxylic acid (51 g., 0.6 mole). Thionyl chloride (84 g., 0.7 mole) was slowly (1 hour) added to the stirred acid. The solution was warmed (60-70°C) and stirred for one hour. After this time the product was distilled to give 43 g. (70%) cyclopropanecarbonyl chloride b.p. 114-116° (1 atm.), \( n^{20}_D 1.4528 \). (lit. b.p. 114-119°, 95% yield (84); b.p. 46-48° (64 mm.), \( n^{20}_D 1.4475 \) (82).) Co-distillation with benzene to remove excess thionyl chloride before final distillation gave a purer product (b.p. 115-120°), but the yield was decreased by 20 per cent.

**Cyclopropanecarboxanilide**

Aniline (23.3 g., 0.25 mole), pyridine (19.8 g., 0.25 mole) and dry benzene (50 ml.) was placed into a three-necked flask (250 ml.) equipped with a dropping funnel and stirrer. Cyclopropanecarbonyl chloride (26.1 g., 0.25 mole)
was added to the cooled flask with stirring. After the drop-wise addition was complete, the reaction was stirred for 5 minutes and then poured into an ice cooled beaker. The solid which precipitated was suction filtered, water washed and dried. The benzene layer was separated, reduced in volume, and cooled to recover more of the amide. Cyclopropanecarboxanilide was obtained in 39 g. (98%) yield and melted between 111-112°. (lit. m.p. 111-12°(85); m.p. 108-109°(86).) The product was recrystallized from benzene-petroleum ether mixture.

**N-(Cyclopropylmethyl)aniline**

Into a 1-liter three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser both with calcium chloride drying tubes was placed lithium aluminum hydride (19 g., 0.5 mole) in anhydrous ether (300 ml.). The mixture was stirred with gentle reflux for 3 hours. After this time, the flask was cooled and a solution of cyclopropanecarboxanilide (40 g., 0.25 mole) in anhydrous ether (200 ml.) was slowly added from the dropping funnel. Upon complete addition of the amide solution, the reaction was refluxed for 72 hours. After refluxing, the flask was cooled in an ice-bath and water (50 ml.) was slowly added to the stirred mixture to decompose the excess lithium aluminum hydride. Stirring was continued for 30 minutes and then NaOH (100 g.) in water (250 ml.) was cautiously added. The ether layer was separated by centrifugation; dried over anhydrous sodium sulphate (overnight). The solvent was removed to yield 28 g. (77%) product
b.p. 111-115°(10 mm.). Infrared spectrum showed absence of C=O band at 1660 cm.\(^{-1}\) (present on amide spectrum), and also shift of N-H band from 3320 cm.\(^{-1}\) (amide) to 3450 cm.\(^{-1}\) (amine). N-(Cyclopropylmethyl)aniline HCl salt m.p. 171°. (lit. m.p. 173-6° (87).)

\(\beta\)-Dimethylaminoethylbromide Hydrobromide

A 2-liter three-necked flask was fitted with a dropping funnel protected by a calcium chloride drying tube, a mechanical stirrer with acid resistant blades, and a Vigreux fractionating head connected to a condenser for downward distillation. Best results were obtained when all glass fittings and stoppers were used (cork stoppers are attacked by the strong acid). Hydrobromic acid (700 ml., 48%-sp.gr. 1.42 or greater) was placed in the flask and cooled in an ice-bath. To the stirred acid in the flask was added \(\beta\)-dimethylaminoethanol (146 g., 1.64 mole) dropwise from the funnel. The reaction mixture was distilled through the fractionating column until 185 ml. of distillate was collected. It was then gently refluxed, without reversing the condenser, for 1 hour. The temperature of the reaction was then increased to collect another 70 ml. of distillate. This procedure was repeated until further 60-, 30-, 25-, 10-, and 5 ml. portions were obtained. Each fraction includes the amount of water distilled during both reflux and distillation periods. The mixture was finally refluxed for 3 hours. The process may be interrupted any time up to this point. Finally, 230 ml. of distillate was collected as crude
hydrobromic acid. In all, the volume of distillate should be about 615 to 630 ml. The final distillation was not always carried as far as stated, but was discontinued if a faint brown or violet colour appeared in the distillate, or if white fumes were given off. Further distillation causes decomposition which results in a grey coloured product of lower yield. The warm residue in the flask was poured into a 2-liter Erlenmeyer flask and allowed to cool to about 70°. Acetone (330 ml.) was slowly added and thoroughly mixed with the semi-solid product. The flask was placed in an ice chest (or refrigerator) overnight to allow further crystallization. The material was suction filtered on a Buchner funnel and washed with acetone until the yellow crystals were colourless. It was then air dried until the odor of acetone just vanished, and stored in a vacuum desiccator. The filtrate may be concentrated to about 100 ml. on a steam bath, cooled and seeded to yield another crop of product (10-20 g.). The hydrobromide salt was re-crystallized from a mixture of 5 parts of 95% ethanol and 8 parts of ethyl acetate. The total yield of β-dimethylaminoethylbromide hydrobromide was 334 g. (87.5%) m.p. 187-188°. (lit. m.p. 189°(80); 174-175°(77).)

**N, N-Dimethyl N'-phenyl N'-(cyclopropylmethyl)ethylene-diamine**

N-(Cyclopropylmethyl)aniline (13.2 g., 0.09 mole), sodium amide (7.8 g., 0.2 mole) and dry xylene (100 ml.) are placed in a three-necked flask (250 ml.) fitted with a reflux
condenser, a dropping funnel both with drying tubes, and a mechanical stirrer. The mixture was stirred with reflux for 2 hours, cooled and β-dimethylaminoethylbromide hydrobromide (23.3 g., 0.1 mole) was added. Stirring and refluxing was continued for 30 hours after which time, a red-black solution resulted. The mixture was cooled and then centrifuged to separate the liquid from the brown precipitate. Fractionation under reduced pressure yielded 3 g. of a yellow oil b.p. 162-165° (10 mm.), (15.3%). Infrared spectrum indicated a tertiary amine by the absence of the N-H band at 3400 cm.⁻¹ and the presence of bands at 1200 cm.⁻¹ and 1390 cm.⁻¹.

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 residual methyl iodide was crystallized from absolute ethanol-absolute ether mixture. Further recrystallization were carried out using either the same solvent pair or ethyl acetate. m.p. 139-140°.

**Anal. Calcd. for C₁₅H₂₅N₂I: C, 50.00; H, 6.99; N, 7.78.**
**Found: C, 49.51; H, 6.94; N, 7.14.**

Preparation of 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, anhydrous ether or benzene solution. Observed m.p. 137-138°.

Anal. Calcd. for C_{20}H_{25}N_{9}O_{7}: C, 53.68; H, 5.63; N, 15.65.
Found: C, 51.95; H, 5.57; N, 15.84.

Preparation of Di-Picrate Derivative

A sample of the compound (0.5 g.) was added to 95% ethanol (10 ml.). This solution was added to 10 ml. of a saturated solution of picric acid in 95% ethanol in the cold. A bright yellow precipitate readily formed without heating. The mixture was then placed in an ice-bath to induce further crystallization. The solid was removed by suction filtration through a Hirsch funnel, and washed thoroughly with absolute ether. A melting point was taken on this dried product; and melted between 139-141°.

Anal. Calcd. for C_{26}H_{28}N_{14}O_{14}: C, 46.16; H, 4.17; N, 16.56.
Found: C, 46.35; H, 4.13; N, 17.72.

Mono-Cyclobutyl Analogue:

Diethyl Cyclobutanedicarboxylate

A 2-liter three-necked flask was fitted with a mechanical stirrer, a reflux condenser protected by a calcium chloride tube, and a 500 ml. separatory funnel. To the stem of the separatory funnel there was attached with a rubber connection, a piece of glass tubing of such length as just to reach to the bottom of the three-necked flask. The funnel
was marked at a volume of 400 ml. A U-tube of 8-mm. glass tubing whose span was wide enough to connect a 2-liter Erlenmeyer flask to the side neck of the three-necked flask was also prepared to replace the separatory funnel. The Erlenmeyer flask was arranged for heating on a hot plate. All parts of the apparatus were dry.

The apparatus was set up with the reflux condenser in place, and with the Erlenmeyer flask in position for attachment. In the Erlenmeyer flask were placed a couple of boiling chips, absolute alcohol (1200 ml.) and sodium metal (24 g. cut into several pieces). As soon as the sodium was added, the flask was immediately attached to the three-necked flask with the U-tube. After the vigorous reaction had subsided and all the sodium had dissolved, the flask was heated on a hot plate, and about 1-liter of alcohol was distilled into the three-necked flask, most of it condensing in the reflux condenser. The alcohol was cooled with stirring for about 5 minutes; then the U-tube was removed and there was added rapidly clean sodium (2 mole, 4.6 g.) cut in pieces as large as would easily pass through the neck of the flask. The neck of the flask was immediately closed with a cork, and the mixture was stirred until all the sodium had dissolved, the cooling bath being removed if the reaction was too sluggish. After all the sodium had dissolved and the cooling bath had been removed, the stirrer was stopped and the separatory funnel with extended stem was attached. Gentle suction applied
to the top of the separatory funnel sucked up sodium ethoxide solution until the funnel was filled to the 400 ml. line. The stopcock of the separatory funnel was closed, the liquid in the stem was shaken out, the stem extension was removed, and the funnel was re-attached to the flask. The top of the funnel was fitted with the calcium chloride tube from the condenser, and a 250 ml. separatory funnel was attached to the top of the condenser by means of a channeled cork.

Diethyl malonate (192 g., 1.2 mole) was added to the stirred mixture from the funnel on top of the condenser. The stirred reaction mixture was heated to gentle boiling on a heating mantle as trimethylene dibromide (202 g., 1 mole of 1,3-dibromopropane) was placed in the top separatory funnel. The contents of the two separatory funnels were now added concurrently to the boiling reaction mixture during a period of about 1.5 hour. An effort was made to adjust the rates so that the two additions were made at a steady rate over the same period of time. (The volume of sodium ethoxide is about 4 times that of the trimethylene dibromide.)

After addition was complete, the drying tube was returned to the condenser, and the mixture was heated under reflux, with stirring, until a few drops of the reaction mixture added to about 0.5 ml. of water did not turn phenolphthalein pink. Tests were made at 30-minute intervals and the time was recorded. If the mixture had not become neutral after 90-minutes of additional heating, the work up was continued, after making the mixture
slightly acid with acetic acid. (A few drops only were needed to neutralize the slight excess of sodium used.) After the mixture was neutral, the position of the condenser was changed for distillation, and the temperature of the heating mantle was raised sufficiently to distill alcohol fairly rapidly, stirring was continued to prevent bumping. (Water may be added in small quantities to dissolve the white salt precipitation if the distillation was too sluggish.) After most of the alcohol had been distilled (800 ml. approx.) the heating mantle was removed and about 800 ml. of water was added to the flask. After the mixture had been stirred briefly, it was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with two 100 ml. portions of benzene, and the extracts were added to the main portion of product contained in a 500 ml. Claisen flask. After solvent was removed at atmospheric pressure, the residue was distilled 'in vacuo', a water pump being used. The cyclic ester was collected over a range of b.p. 110-116°(17 mm.) to yield 125 g. (60%). (lit. (88) b.p. 110°(15 mm.) in 110-130 g. (55-65%) yield; (89) b.p. 106-7°(10 mm.), n^20_D 1.4335.) Observed n^26_D 1.4320.

**Cyclobutanecarboxylic Acid**

The total yield of diethyl cyclobutanedicarboxylate was hydrolyzed by refluxing the ester for 2 hours with a solution of potassium hydroxide (112 g.) in 95% ethanol (200 ml.). Most of the ethanol was removed by distillation, and the
mixture was then evaporated to dryness on a steam bath. The residue was dissolved in the minimum amount of hot water (100 to 125 ml.), and concentrated hydrochloric acid (90-95 ml.) was added until the solution was slightly acid to litmus. After the solution had been boiled for a few minutes to remove carbon dioxide, it was made slightly alkaline with ammonia. To the boiling solution there was added a slight excess of barium chloride. The hot solution was filtered to remove the barium malonate, the filtrate was cooled, and to it was added 100 ml. of 12N hydrochloric acid. The solution was then extracted with four 250 ml. portions of ether. The extracts were combined and dried over calcium chloride; the ether was removed by distillation on a steam bath. The resulting 1,1-cyclobutanedicarboxylic acid (m.p. 156-158°) was placed into a 75 ml. distilling flask carrying a thermometer and attached to a 75 ml. Claisen flask as a receiver. The receiver was cooled with running water while the flask containing the dibasic acid was heated on an oil bath (bath temp. 160-170°) until no more carbon dioxide was evolved. Then the temperature of the bath was raised to 210-220°, and the material boiling at 189-195° was collected. The distillate was redistilled 'in vacuo', the product being collected at 114-120° (21 mm.) in 67.5 g. (54% based on crude diester) yield. Observed nD1.4400 for the colourless liquid which turns yellow in colour on standing; has an odor resembling that of butyric acid, but less repugnant than valeric acid. (lit.
(59) b.p. 191.5-193.5° (740 mm.) in 18-21% yield; (61) b.p. 104-106° (21 mm.) in 75-80% yield; (89) b.p. 88-90° (8 mm.), n\textsuperscript{20}D 1.4400; (90) b.p. 96° (15 mm.), n\textsuperscript{25}D 1.4403.

Infrared spectrum of cyclobutanecarboxylic acid shows a broad band at 3000 cm.\textsuperscript{-1} characteristic of O-H absorption of carboxylic acids; C==O stretching frequency at 1700 cm.\textsupersupt{-1} for the saturated acid.

**Cyclobutanecarbonyl Chloride**

Cyclobutanecarboxylic acid (40 g., 0.4 mole) was placed into a 250 ml. three-necked flask fitted with a mechanical stirrer, a reflux condenser and a 125 ml. dropping funnel. To the stirred acid was added thionyl chloride (80 g., 0.67 mole), and the mixture was refluxed for 1.5 to 2 hours. The product was distilled to give a forerun and cyclobutanecarbonyl chloride b.p. 130-142° (1 atm.), n\textsuperscript{23}D 1.4515. Yield: 30 g. (63%) (lit. (91) b.p. 130-140° (70%); (73) b.p. 60° (50 mm.), n\textsuperscript{25}D 1.4528)

**Cyclobutanecarboxanilide**

A mixture of aniline (18.6 g., 0.2 mole), pyridine (15.8 g., 0.2 mole) and dry benzene (50 ml.) was placed in a 250 ml. three-necked flask equipped with a mechanical stirrer. Cyclobutanecarbonyl chloride (24 g., 0.2 mole) was added drop-wise from a dropping funnel to the stirred mixture. After addition was complete, the reaction was stirred for 5 minutes 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 (100 ml.). The benzene layer
was separated and reduced in volume to collect more of the crude anilide with total yield of 30 g. (72%). Cyclobutane-carboxanilide was recrystallized from benzene-petroleum ether mixture; gave a m.p. 108-109°. (lit. (92) m.p. 109.6-110.6°; (93) m.p. 111-112°.)

Infrared spectrum of cyclobutane-carboxanilide shows a small secondary amine stretching vibration at 3300 cm.\(^{-1}\) due to N-H. C-H stretching at 3000 cm.\(^{-1}\) for the anilide is masked by the strong Nujol band at 2950 cm.\(^{-1}\). Other characteristic bands due to Nujol occur at 1460 cm.\(^{-1}\) and at 1390 cm.\(^{-1}\). A small C==O stretching vibration is noted at 1660 cm.\(^{-1}\) for the anilide. The low carbonyl frequency may be attributed to hydrogen bonding interactions.

N-Phenyl-N-Cyclobutylmethylamine

A 1-liter three-necked flask was equipped with a dropping funnel, a mechanical stirrer and a Soxhlet apparatus protected with calcium chloride drying tubes. Lithium aluminum hydride (15 g., 0.4 mole) in anhydrous ether (300 ml.) was placed into the flask, and refluxed gently with stirring for 3 hours. Then cyclobutane-carboxanilide (30 g., 0.17 mole) was placed in the thimble of the extractor in portions, and refluxing was continued until all the anilide had been carried into the flask. The reaction was then refluxed for 72 hours. At the end of this time, 50 ml. of water was added to decompose the excess hydride. Cooling in an ice-bath and stirring was continued until the mixture became white in colour (30
minutes approx.); then sufficient 4.0% sodium hydroxide solution was added to allow clear separation of the ethereal layer. The ether insoluble residue was separated by centrifugation; dried over anhydrous sodium sulphate overnight. The ether solvent was removed by flash evaporation and the residue distilled under vacuum from a water pump to yield 27 g. (98%) of the amine with b.p. range of 150-160° (20 mm.).

Infrared spectrum for the reduction product shows the absence of the carbonyl band at 1660 cm.\(^{-1}\). Due to the absence of the oxygen-hydrogen interaction, the \(\text{N-H}\) stretching frequency shifted to 3430 cm.\(^{-1}\) from 3300 cm.\(^{-1}\) (anilide). Characteristic \(\text{C-H}\) stretching vibration for cyclobutanes is noted at 2990 cm.\(^{-1}\).

**Preparation of Hydrochloride Derivative**

Dry hydrogen chloride was prepared by the addition of a few drops of concentrated sulphuric acid to sodium chloride contained in a generator, and passed into a solution of \(\text{N-phenyl N-cyclobutylmethylamine}\) (0.5 ml.) in anhydrous ether (10 ml.). When precipitation was complete, the solid was filtered off and washed with a little dry ether. The white hydrochloride salt was recrystallized from a small amount of absolute ethanol and dry ether. Observed m.p. 174-4.5\(^{\circ}\).

**Anal.** Calcd. for \(\text{C}_{14}\text{H}_{16}\text{NCl}\): \(\text{C}\), 66.82; \(\text{H}\), 8.16; \(\text{N}\), 7.08. Found: \(\text{C}\), 66.79; \(\text{H}\), 8.03; \(\text{N}\), 7.13.

\(\text{N, N-Dimethyl N'-phenyl N'-(cyclobutylmethyl)ethylene-diamine}\)
N-phenyl N-cyclobutylmethylamine (14.5 g., 0.09 mole) was added to sodium amide (7.8 g., 0.2 mole) in dry xylene (100 ml.). A 250 ml. three-necked flask fitted with a reflux condenser, protected with a calcium chloride drying tube, and a mechanical stirrer was used. The mixture was refluxed with stirring for 2 hours, cooled, and $\beta$-dimethylaminoethylbromide hydrobromide (23.3 g., 0.1 mole) was added. Stirring and refluxing was continued for 30 hours; after which time, a dark brown precipitate plus a dark red liquid layer resulted. The mixture was cooled and centrifuged to remove the solid fraction. Xylene solvent was removed from the liquid layer under reduced pressure and heat (b.p. 40°/20 mm.). The residue was fractionated to give a forerun of recovered secondary amine (11 g. approx.), and the tertiary amine b.p. 168-179° (20 mm.) in 2 g. (10%) yield.

A tertiary amine is indicated by the absence of the N-H band at 3430 cm.$^{-1}$ while characteristic amine bands at 1600 cm.$^{-1}$ and 1515 cm.$^{-1}$ are retained.

**Methyl Iodide Derivative**

The tertiary amine (0.5 g.) was mixed with methyl iodide (2 ml.) and prepared as outlined for the monocyclopropyl analogue. The melting point for the monocyclobutyl Antergan analogue was 130°.

**Anal. Calcd. for C$_{16}$H$_{27}$N$_2$I: C, 51.34; H, 7.27; N, 7.49.**

**Found: C, 51.05; H, 7.33; N, 7.39.**
Di-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 worked up as stated for the monocyclopropyl-dipicrate derivative. The melting point for the cyclobutyl analogue was 171°.

Anal. Calcd. for C_{27}H_{30}N_{2}O_{4}: C, 46.96; H, 4.38; N, 16.23.
Found: C, 46.24; H, 4.50; N, 15.85.

Mono-Cyclopentyl Analogue:

2-Chlorocyclohexanone

The preparation of this compound required the extremely toxic gas chlorine which is dangerous to inhale, and was thus performed with specially fitted apparatus in an efficient fume hood. A 3-liter three-necked flask was fitted with a gas inlet tube reaching almost to the bottom, a sealed mechanical stirrer (the propeller just below the liquid's surface to cause splashing; sealed with a glycerol-lubricated rubber tube or with a mercury seal), and a gas outlet tube connected to a trap of 125 ml. suction flask and this was further connected to a water valve (the outlet tube dipped about 7 inches into the vented container containing water).

To the flask was added cyclohexanone (294 g., 3 moles) and water (900 ml.). After the reaction vessel had been swept out with chlorine, the gas outlet tube was connected to the water valve. The flask was cooled in an ice-bath, the stirrer started, and chlorine gas (215 g. slightly more than 3 moles) was bubbled
in as rapidly as the gas was absorbed (about 45 minutes). Temperature control was not too necessary. The reaction turned brown in colour as the chloro-product was settling out. The heavier chlorocyclohexanone layer was separated and combined with three 150 ml. ether extracts of the aqueous phase, and washed with 150 ml. of water and then with 200 ml. of saturated sodium chloride solution (63.4 g. sodium chloride to 176.2 ml. of water). After gravity filtration through anhydrous sodium sulfate, the ether was removed and the residue vacuum distilled in a modified Claisen flask. The fraction (300 g. approx.) boiling below 110 (13 mm.) was collected. This material was then fractionated under reduced pressure using a Vigreux column. The yield of 2-chlorocyclohexanone boiling at 90-100°(13 mm.) was 177 g. (45%). The pale yellow solution with a $n^\text{20}_D$ 1.4870 darkens on standing. (lit. (66) b.p. 90-91°(14-15 mm.) in 240-265 g. (61-66%) yield; (94) b.p. 79°(7 mm.), $n^\text{20}_D$ 1.4825.)

Cyclopentanecarboxylic Acid

To a 2-liter three-necked flask was added sodium (61 g., 2.6 mole) in 1100 ml. of absolute ethanol (Mg-dried). A sample of 2-chlorocyclohexanone (176.5 g., 1.3 mole) was added from a dropping funnel to the well stirred solution over a 2-hour period at room temperature. After stirring an additional 10 hours (or overnight) at room temperature, the reaction mixture was placed on a heating mantle for 12 hours to remove the excess alcohol; about 800 ml. of water was added from a dropping funnel at about the same rate as the alcohol was distilled.
to maintain the original volume. After cooling, the reaction mixture was washed with ether, after which the aqueous phase was acidified, and the resulting oil which separated was taken up in ether; then dried over anhydrous sodium sulfate overnight. After removal of the solvent, the residue was fractionally distilled to yield 88 g. (59%) cyclopentanecarboxylic acid b.p. 114-117°(12 mm.), n^2_D 1.4549. (lit. (67) b.p. 120-123° (27 mm.); (62) b.p. 121.5-122°(20 mm.), n^25_D 1.4512; (95) b.p. 215-216°(760 mm.), n^20_D 1.4520.)

Infrared spectrum shows a strong carbonyl absorption band at 1700 cm.\(^{-1}\) and a broad hydroxyl absorption band at 3000 cm.\(^{-1}\). Other peaks correspond to the reference spectrum (Sadtler No. 19102) for cyclopentanecarboxylic acid as well.

**Cyclopentanecarboxylic Chloride**

Into a 200 ml. three-necked flask equipped with a mechanical stirrer, reflux condenser, and a dropping funnel (100 ml.) both with drying tubes was placed cyclopentanecarboxylic acid (30 g., 0.26 mole). To the stirred acid was added 50 ml. of thionyl chloride from the dropping funnel. The mixture was then refluxed for one hour with stirring and the excess thionyl chloride removed by co-distillation with 45 ml. of benzene. The residue was distilled under reduced pressure; the fraction b.p. 160-163°(760 mm.) was collected in 27 g. (76%) yield, n^23_D 1.4620. (lit. (93) b.p. 160-162°.)
Cyclopentanecarboxanilide

Aniline (18.6 g., 0.2 mole) and pyridine (15.8 g., 0.2 mole) in dry benzene (50 ml.) were placed in a 250 ml. reaction flask. Cyclopentanecarbonyl chloride (26.5 g., 0.2 mole) was added dropwise to the stirred mixture in the ice-bath cooled flask. After addition was complete, the reaction was stirred for 5 minutes at room temperature. The mixture was poured into a beaker and washed with 100 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 36 g. (95%). The amide was re-crystallized from carbon tetrachloride; melted at 159-161°. (lit. (96) m.p. 160.1-161.2°)

Infrared spectrum of the solid amide in Nujol shows carbonyl stretching at 1655 cm.⁻¹, and the N-H vibrational band for a secondary nitrogen at 3280 cm.⁻¹.

N-Phenyl-N-Cyclopentylmethylamine

To 400 ml. of anhydrous ether was added lithium aluminum hydride (15 g., 0.4 mole) cut into small pellets to easily be added into a 1-liter three-necked flask equipped with a mechanical stirrer and a Soxhlet extractor protected from moisture by calcium chloride tube. The mixture was stirred with gentle refluxing for 3 hours. After this time, cyclopentanecarboxanilide (37.8 g., 0.2 mole) was placed in a thimble in portions; refluxing was continued until all the anilide had been dissolved. The reaction then allowed to reflux for 72
hours, and was then worked up with water and concentrated NaOH (40%) as usual. The NaOH solution was slowly added to avoid frothing. 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. $154^\circ(20 \text{ mm.})$ was collected in 34 g. (97%) yield.

Infrared spectrum shows the absence of the C==O band indicating complete reduction had occurred. A strong N-H band is observed at 3450 cm.$^{-1}$ which is shifted in frequency from the same N-H for the anilide compound.

**Hydrochloride Derivative**

The salt was prepared as described for the cyclobutyl-amine analogue. N-phenyl-N-cyclopentylmethylamine hydrochloride melted at 188°.

**Anal. Calcd. for C$_{12}$H$_{18}$NCl: C, 68.07; H, 8.57; N, 6.62.**

**Found: C, 67.40; H, 8.49; N, 6.68.**

**N, N-Dimethyl N'-phenyl N'-{(cyclopentylmethyl)ethylene-diamine**

In a 250 ml. three-necked flask fitted with a reflux condenser (drying tube), and a mechanical stirrer (rubber sealed) were placed N-phenyl N-cyclopentylmethylamine (14 g., 0.08 mole), sodium amide (7 g., 0.18 mole) and dry toluene (100 ml.). The mixture was stirred under gentle reflux for 2 hours, cooled and $\beta$-dimethylaminoethylbromide hydrobromide was added using 21 g. (0.09 mole). Stirring and refluxing was then continued for 30 hours. After this time, the mixture was cooled; centrifuged to isolate the liquid layer. The majority of the
toluene solvent was removed by distillation from a 200 ml. round bottom flask and then the residue was fractionally distilled 'in vacuo' using a micro-distillation apparatus. The yellow oil b.p. 185-189°(21 mm.) was obtained in 2 g. (10.2%).

Infrared spectrum shows the absence of the hydrogen vibrations at 3450 cm.⁻¹ indicating a tertiary amine being present. A strong absorption at 2950 cm.⁻¹ correspond to C-H stretching vibrations for the cyclopentane structure.

**Hydrochloride Derivative**

A solution of the tertiary amine (0.5 ml.) in anhydrous ether (10 ml.) was reacted with dry hydrogen chloride from a generator until precipitation was complete. The white solid was suction filtered, washed with dry ether and recrystallized from a mixture of absolute ethanol and dry ether. The mono-hydrochloride derivative melted at 174-175°.

**Anal. Calcd. for C₁₆H₂₇N₂Cl:**
- C, 67.94;
- H, 9.62;
- N, 9.91.
**Found:**
- C, 67.51;
- H, 9.36;
- N, 10.48.

**Methyl Iodide Derivative**

The tertiary amine (0.5 g.) was mixed with methyl iodide reagent (2 ml.) and worked up as for the monocyclopropyl analogue. The melting point for the cyclopentylmethyl iodide derivative was found to be 160°.

**Anal. Calcd. for C₁₇H₂₉N₂I:**
- C, 52.58;
- H, 7.53;
- N, 7.22.
**Found:**
- C, 52.18;
- H, 7.09;
- N, 7.66.

**DiPicrate Derivative**

A sample of the tertiary amine (0.5 g.) in 95% ethanol
(10 ml.) was mixed with a saturated solution of picric acid in 95% ethanol and worked up as for the previous series. The observed melting point for the cyclopentyl dipicrate derivative was 165-6°.

Anal. Calcd. for C_{26}H_{32}O_{14}N_{8}: C, 47.77; H, 4.58; N, 15.94.
Found: C, 47.40; H, 4.57; N, 15.48.

Mono-Cyclohexyl Analogue;

**Cyclohexanecarboxyl Chloride**

To a 1-liter three-necked flask equipped with a reflux condenser, a dropping funnel (250 ml.), both carrying drying tubes, 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 a dropping funnel. The flask was placed on a heating mantle and heated at reflux for 1.5-2 hours. After this time, the mixture was distilled collecting the crude product from 160-185°. This fraction was redistilled under reduced pressure collecting the fraction boiling at 82-85° (14-15 mm.) to yield 118 g. (80.5%); n_{D}^{15} 1.4710. (lit. (97) b.p. 67-67.5°(14 mm.) (81%); (98) b.p. 76°(17 mm.), n_{D}^{15} 1.4766.)

**Cyclohexanecarboxanilide**

A mixture of aniline (93 g., 1 mole), pyridine (79 g., 1 mole), and dry benzene (100 ml.) was placed into a 1-liter three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel (drying tubes). To the mixture in the flask (cooled in an ice-bath) was added cyclohex-
anecarbonyl chloride (105 g., 0.72 mole) dropwise (stirred mixture). After addition was complete, the solution was refluxed for 1 hour, cooled and washed with water (200 ml.). The layers were separated and the aqueous phase was extracted with two 100 ml. portions of ether. The extracts were combined with the benzene layer, and dried with anhydrous sodium sulfate. The solvents were removed by distillation and the residual anilide was purified by recrystallization from isopropanol. The observed melting point for cyclohexanecarboxanilide was 143-144°; was obtained in a yield of 143 g. (98%). (lit. (99) m.p. 143-5°; (100) m.p. 145-6°.)

**N-Phenyl N-Cyclohexylmethylamine**

In a 2-liter three-necked flask equipped with a mechanical stirrer, a Soxhlet extractor and a dropping funnel (drying tubes) was placed lithium aluminum hydride (19 g., 0.5 mole) in anhydrous ether (800 ml.). The mixture was stirred with gentle refluxing on a heating mantle for 4 hours. After this time, cyclohexanecarboxanilide (67.6 g., 0.33 mole) was placed into a thimble in portions and refluxed with stirring until all the anilide had been dissolved. The refluxing was continued with stirring for 72 hours. Then the heating mantle was replaced by an ice-bath and 50 ml. of water was slowly added from the dropping funnel to the vigorously stirred mixture. Stirring was continued for 30 minutes after the water addition was complete. Sufficient 40% NaOH was added to allow a clear separation of the ethereal layer. To separate the
free amine from any unreduced amide, the ether solution was extracted with 5% hydrogen chloride solution. The aqueous phase was separated and treated with 4.0% NaOH to reform the free amine which was extracted with ether solvent. The combined ether extracts were dried over anhydrous sodium sulfate. The ether solvent was removed by flash evaporation to yield 37 g. (59%) N-phenyl-N-cyclohexylmethylamine b.p. 170-74° (12 mm.); the hydrochloride salt of the amine melted at 221-23° (lit. (101) b.p. 168-70° (11 mm.), HCl salt m.p. 232°.)

Infrared spectrum for the amine shows the absence of the C=O band at 1660 cm.
-1 indicating complete reduction of the amide. N-H stretching vibration with one sharp peak at 3425 cm.
-1 is characteristic of a secondary amine.

**N, N-Dimethyl N'-phenyl-N'-(cyclohexylmethyl)ethylene-diamine**

A mixture of N-phenyl N-cyclohexylmethylamine (10 g. 0.053 mole), sodium amide (4.7 g., 0.12 mole) and dry toluene (75 ml.) was placed into a 250 ml. three-necked flask fitted with a dropping funnel (wide bore), reflux condenser (drying tubes), and a mechanical stirrer. The mixture was stirred and refluxed for 2 hours, cooled and a slurry of β-dimethylaminoethylbromide hydrobromide (14 g., 0.06 mole) in 25 ml. of dry toluene added. Stirring and refluxing on a heating mantle were continued for 24 hours. The mixture was cooled and the liquid phase was separated from the solid phase by centrifugation. Solvent toluene was distilled from a 200 ml. flask, and
the residue fractionated under reduced pressure collecting the fraction boiling at 194-5° (15 mm.) to yield 3 g. (21.8%).

Infrared spectrum shows the absence of the N-H vibration at 3425 cm.⁻¹ indicating substitution of the hydrogen atom to form a tertiary amine. Strong absorption bands are evident at 2920 cm.⁻¹ characteristic of cyclohexane C-H stretching.

**Hydrochloride Derivative**

A solution of the tertiary amine (0.5 g.) in anhydrous ether (10 ml.) was treated with dry hydrogen chloride to form the white solid. The derivative was worked up in the usual manner as for the cyclopentyl analogue. The observed melting point for the monocyclohexyl-Antergan analogue was 199-200°.

**Anal.** Calcd. for C₁₇H₂₉N₂Cl: C, 68.77; H, 9.85; N, 9.44.
**Found:** C, 69.01; H, 9.32; N, 9.36.

**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 monocyclopropyl analogue. The mono-picrate derivative for cyclohexyl-Antergan analogue melted at 135.5°.

**Anal.** Calcd. for C₂₅H₃₁O₇N₅: C, 56.43; H, 6.38; N, 14.31.
**Found:** C, 57.10; H, 6.04; N, 14.02.

**Monocycloheptyl Analogue:**

**Cycloheptanecarboxylic Acid**

As the preparation of this acid requires a Grignard reaction, especially dry apparatus and reagents were used.
A 1-liter three-necked flask equipped with a mercury-sealed (or rubber tube) mechanical stirrer, a reflux condenser, and a 250 ml. dropping funnel protected by calcium chloride drying tubes was placed 6.1 g. (0.25 mole) of magnesium turnings. The flask was warmed on a heating mantle to displace any moisture adhering to the flask. After cooling, a small amount of the bromide and 50 ml. of dry ether was added to initiate the reaction. A solution of cycloheptyl bromide (44.4 g., 0.25 mole) in dry ether (150 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 1/4 of the original magnesium remained unreacted.

In a 2-liter three-necked flask equipped with a stirrer, a reflux condenser (drying tube), and a 500 ml. dropping funnel was placed a slurry of 300 ml. of dry ether and 500 g. of powdered Dry Ice (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 (102). After complete addition of the Grignard solution, another 500 g. of Dry Ice was added and stirring was continued for 3 hours during which time the Dry Ice had evaporated. The Grignard complex then was hydrolyzed by the dropwise addition of 100 ml. of 6N hydrochloric acid (cold) to the vigorously stirred mixture. The ether layer was separ-
ated and the aqueous layer was twice extracted with 100 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 collecting the fraction boiling at 138-140° (15 mm.) to yield 16.5 g. (46.7%), \( n^\text{23}_D \) 1.4729. (lit. (64) b.p. 133-135° (9 mm.), \( n^\text{27}_D \) 1.4730; (103) b.p. 130-131° (8 mm.), \( n^\text{20}_D \) 1.4753.). Cycloheptylbromide was available from Aldrich Chemicals.

Infrared spectrum shows a strong \( \text{C}==\text{O} \) absorption band at 1710 cm.\(^{-1}\) and a broad \( \text{O}-\text{H} \) band at 3000 cm.\(^{-1}\) both characteristic of carboxylic acids.

**Cycloheptanecarboxylic Acid**

Cycloheptanecarboxylic acid (20 g., 0.14 mole) was placed in a 250 ml. three-necked flask equipped with a reflux condenser, a dropping funnel carrying calcium chloride tubes, and a mechanical stirrer. To the stirred acid was added thionyl chloride (50 g., 0.42 mole) dropwise. After addition was complete, the mixture was stirred for 1.5 hours at room temperature; then the excess thionyl chloride was removed under reduced pressure by codistillation with two 30 ml. portions of benzene. Slight warming with a warm 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, 22.5 g. (80%) yield of cycloheptanecarbonyl chloride b.p. 89-98° (14 mm.), \( n^{23}_D \) 1.4868, was obtained.
Infrared spectrum shows a characteristic carbonyl absorption maximum at 1780-1810 cm.$^{-1}$ for the saturated-cyclic acid chloride. Complete halogenation is indicated by the absence of the O-H absorption band at 3000 cm.$^{-1}$.

**Cycloheptanecarboxanilide**

A 250 ml. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was placed a mixture of aniline (12 g., 0.124 mole), pyridine (10 g., 0.12 mole), and dry benzene (50 ml.). To the cooled flask was added cycloheptanecarbonyl chloride (20 g., 0.124 mole) dropwise from the funnel (mixture stirred). After addition was complete, the reaction was stirred for 20 minutes at room temperature; then poured into a beaker. The solid precipitate was suction filtered and washed with 50 ml. of water. The benzene layer was separated and reduced in volume to collect a further crop of anilide with 21.5 g. (74.6%) total yield. Cycloheptanecarboxanilide was recrystallized from a benzene-petroleum ether mixture, and melted between 135-136°. (Further recrystallization gave a m.p. 139°.)

The infrared spectrum shows similar absorption bands to other anilide analogues of this series with C==O stretching at 1660 cm.$^{-1}$ and N-H band at 3310 cm.$^{-1}$.

**Anal. Calcd.** for C$_{14}$H$_{19}$NO: C, 77.38; H, 8.81; N, 6.45.  
**Found:** C, 77.30; H, 8.63; N, 6.84.

**N-Phenyl N-Cycloheptylmethylamine**

To a 1-liter three-necked flask equipped with a 250 ml.
dropping funnel, a reflux condenser (drying tubes), and a mechanical stirrer was placed 200 ml. of anhydrous ether. Lithium aluminum hydride (11.4 g., 0.3 mole) was added to the ether, and was gently refluxed with stirring for 4 hours. A solution of cycloheptanecarboxanilide (30.5 g., 0.14 mole) in anhydrous ether (250 ml.) was placed into the dropping funnel, and was added at such a rate as to maintain gentle reflux. The addition required about 1 hour, after which, the mixture was stirred and refluxed for 4-5 days.

After this time, 45 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 22.3 g. (78.2%) N-phenyl-N-cycloheptylmethylamine b.p. 154° (17 mm.).

Infrared spectrum indicates 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 3460 cm.⁻¹.

Hydrochloride Derivative

The salt was prepared as described for the cyclobutylamine analogue. N-phenyl-N-cycloheptylmethylamine hydrochloride melted at 195°.

Anal. Calcd. for C₁₄H₂₂NCl: C, 70.12; H, 9.25; N, 5.84. Found: C, 70.15; H, 9.31; N, 5.88.
N, N-Dimethyl N'-phenyl N'-(cycloheptylmethyl)ethylene-diamine

N-phenyl N-cycloheptylmethylamine (10.2 g., 0.05 mole), sodium amide (5 g., 0.13 mole), and dry toluene (100 ml.) were placed in a 250 ml. three-necked flask equipped with a reflux condenser (drying tube) and a mechanical stirrer. The mixture was stirred and refluxed for 20 hours. To the cooled flask was added β-dimethylaminoethylbromide hydrobromide (14 g., 0.06 mole). Stirring and refluxing was continued for 48 hours. The mixture was then cooled and centrifuged to precipitate out the brown solid. The liquid layer was decanted and the solvent toluene was distilled from a 200 ml. flask. The residue was fractionally distilled under reduced pressure in a micro-distillation apparatus to yield 4 g. (29%) tertiary diamine b.p. 204-210° (17 mm.).

Infrared spectrum indicates a tertiary amine by the absence of the hydrogen stretching at 3460 cm.⁻¹ while absorptions at 1610 cm.⁻¹ and at 1519 cm.⁻¹ are retained.

Methyl Iodide Derivative

The tertiary amine (0.5 g.) was mixed with methyl iodide reagent (2 ml.) and worked up as for the monocyclopropyl analogue. N, N-dimethyl N'-phenyl N'-(cycloheptylmethyl)ethylene diamine methyl iodide melted at 220°.

Di-Picrate Derivative

A sample of the amine (0.5 g.) in 95% ethanol (10 ml.) was treated with a saturated solution of picric acid in the manner described for the monocyclopropyl analogue of this derivative. The observed melting point for the monocycloheptyl substituted Antergan analogue was 155°.

Anal. Calcd. for C_{30}H_{36}N_{0.14}: C, 49.18; H, 4.95; N, 15.29.
Found: C, 48.90; H, 4.74; N, 15.05.

Mono-Cyclooctyl Analogue:

Cyclooctyl Bromide

The preparation of this compound required refluxing a strong acid which readily attacks wire and rubber fittings. Best results were obtained by using all glass joints and a stirring rod with acid resistant blades. Into a 1-liter three-necked flask equipped with a mechanical stirrer, and a reflux condenser was placed cyclooctanol (50 g., 0.39 mole, available from Aldrich Chemicals) and 48% hydrobromic acid (186 ml., 1.6 mole). The mixture was allowed to stand overnight; was then refluxed 5-6 hours. (An excess of 48% HBr (200 ml.) and refluxing for about 20 hours (overnight) gave a higher yield.)

After cooling the mixture, the top black layer was separated and washed with small portions of 48% HBr until no volume change occurred. It was then washed once with water and twice with 10% sodium carbonate solution. The bromide was separated and dried over calcium chloride. The liquid was fractionated under reduced pressure to yield 60 g. (80%) cyclooctylbromide
having a b.p. 87-90°(18 mm.), n\textsuperscript{24}_D 1.4859. (lit. (104) b.p. 97°(15 mm.); (105) b.p. 104-8°(18 mm.).)

**Cyclooctanecarboxylic Acid**

A 500 ml. three-necked flask was equipped with a mechanical stirrer, a reflux condenser, and a 250 ml. separatory funnel, rubber stoppers being used for the openings. All the apparatus used was thoroughly dry. In the flask was placed 6.1 g. (0.25 mole) of magnesium turnings; 50 ml. of anhydrous ether plus a few milliliters of cyclooctyl bromide. To help initiate the reaction, a crystal of iodine was added, and the flask was warmed with a heating mantle. A solution of 47.8 g. (0.25 mole) of cyclooctyl bromide in 150 ml. of dry ether was added over a period of 1 hour from a dropping funnel. Moderate cooling with an ice-bath was needed when the reaction became more vigorous. Following complete addition of the bromide, the mixture was gently refluxed with stirring overnight. At the end of this time, about one-quarter of the original magnesium remained unreacted.

Into a 2-liter three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a 250 ml. dropping funnel was placed a slurry of 300 ml. of dry ether and 500 g. of powdered Dry Ice. The Grignard solution was quickly decanted into the dropping funnel and added to the stirred slurry over a period of 15 minutes. After complete addition of the Grignard reagent, another 500 g. of Dry Ice was added to the stirred mixture, and stirring was continued for 3 hours or until
all the Dry Ice had evaporated. The grey coloured complex was then hydrolyzed by the dropwise addition of 100 ml. of 6N HCl (cold) with vigorous stirring. The ether layer was then separated and the aqueous layer extracted with two 100 ml. portions of ether solvent. The ether layers were combined, water washed, and dried over anhydrous sodium sulfate overnight. Solvent ether was removed and the residue was fractionated 'in vacuo' to yield 10.5 g. (27%) cyclooctanecarboxylic acid with a b.p. 140-142°(14 mm.), n\textsuperscript{23}D 1.4700. (lit. (106) b.p. 150° (19 mm.), n\textsuperscript{20}D 1.4779.)

**Cyclooctanecarbonyl Chloride**

Cyclooctanecarboxylic acid (20 g., 0.13 mole) was placed into a 250 ml. three-necked flask fitted with a reflux condenser, a dropping funnel (drying tubes), and a mechanical stirrer. To the stirred acid was added thionyl chloride (50 g., 0.42 mole) dropwise. The mixture was stirred for 1.5 hours at room temperature. Then 30 ml. of dry benzene was added to the flask and codistilled with the excess thionyl chloride under reduced pressure. Warming with a water bath may be employed. After another portion of benzene (30 ml.) was added and distilled as before, the residue was fractionally distilled 'in vacuo' to yield 16 g. (73%) cyclooctane-carbonyl chloride boiling at 115°(22 mm.). (lit. (106) b.p. 110°(19 mm.).)

**Cyclooctanecarboxanilide**

A mixture of aniline (9.3 g., 0.1 mole), pyridine
(8 g., 0.1 mole) and dry benzene (50 ml.) was placed in a 250 ml. flask fitted with a mechanical stirrer and a dropping funnel. To the cooled flask was added cyclooctanecarbonyl chloride (16 g., 0.09 mole) dropwise from the funnel with stirring. After addition was complete, the reaction mixture was stirred for 20 minutes at room temperature, washed with 50 ml. of water and the solid was suction filtered. The benzene layer was separated and the solvent evaporated to recover more anilide. The yield of water insoluble product was only 1 g. and the recrystallized sample from carbon tetrachloride melted at 183-185°. (lit. (107) m.p. 129-130°.)

Infrared spectrum shows a carbonyl absorption band at 1660 cm.\(^{-1}\) and a N-H stretching band at 3330 cm.\(^{-1}\).

Cyclooctanecarboxanilide Attempted by Another Route

A solution of phenyl isocyanate (10.7 g., 0.09 mole) was dissolved in 100 ml. of anhydrous ether and added dropwise to a stirred solution of cyclooctane-magnesium-bromide (0.12 mole approx.) prepared as described for cyclooctanecarboxylic acid. The reaction mixture was stirred for 1 hour after addition was complete. Hydrolysis was effected by adding cautiously, cold water containing a little hydrochloric acid (20 ml. of ice water to 1 ml. of concentrated HCl). The solution was stirred thoroughly to obtain complete hydrolysis of the magnesium complex of the anilide. The ethereal layer was separated and dried over magnesium sulfate overnight. Solvent ether was flash evaporated to recover a crude white
product which was recrystallized from petroleum ether. A mixed melting point of this solid with diphenylurea (m.p. 238°) melted at 235°.

Di-Cyclopropyl Analogue:

**N-Cyclopropyl-Cyclopropanecarboxamide**

A mixture of 17.1 g. (0.3 mole) cyclopropylamine (Aldrich Chemicals), pyridine 23.7 g. (0.3 mole), and 60 ml. of dry benzene was placed into a 250 ml. three-necked flask equipped with a dropping funnel and a mechanical stirrer. To the cooled flask was added 31.3 g. (0.3 mole) cyclopropanecarbonyl chloride (prepared as described for the monocyclopropane series) dropwise with stirring. After addition was complete, the reaction mixture was stirred for 5 minutes, and then washed with 50 ml. of water. The white solid was suction filtered; the benzene layer was separated and evaporated to recover another crop of the amide. The total yield of crude amide, 16 g. (143%), was recrystallized from carbon tetrachloride, air dried and melted at 107°.

Infrared spectrum shows a band at 1610 cm.\(^{-1}\) for carbonyl absorption, and a band at 3320 cm.\(^{-1}\) for N-H stretching.

**Anal.** Calcd. for \(\text{C}_7\text{H}_{11}\text{NO}\): C, 66.63; H, 8.79; N, 11.10. Found: C, 66.75; H, 9.02; N, 10.82.

**N-Cyclopropyl-N-Cyclopropylmethylamine**

A 1-liter three-necked flask was fitted with a 250 ml. dropping funnel, a mechanical stirrer, and a Soxhlet extractor protected from moisture by calcium chloride drying tubes.
A slurry of lithium aluminum hydride (15 g., 0.4 mole) in anhydrous ether (250 ml.) was stirred with gentle reflux for 3 hours. Then N-cyclopropyl-N-cyclopropylcarboxamide (24 g., 0.2 mole) was added to the thimble of the extractor in portions and allowed to reflux until all the solid had been dissolved. The mixture was then refluxed for 4 days under gentle heat.

At the end of the heating time, 50 ml. of water was slowly added from the dropping funnel to the stirred mixture cooled in a water-bath. After an additional 30 minutes of stirring, just sufficient 40% NaOH solution (15-20 ml.) was added drop-wise to allow a clear separation of the ethereal layer. The mixture was centrifuged, the ether solution decanted into an Erlenmeyer flask containing sodium sulfate drying agent, and the solid residue was washed with ether solvent. The combined ether solutions were allowed to dry overnight, and the solvent removed by flash evaporation. Then the residue in a total yield of 20.8 g. (98%) was distilled 'in vacuo' at 86° (12 mm.).

Infrared spectrum showed the absence of the carbonyl band at 1640 cm.⁻¹.

**Hydrochloride Derivative**

Dry hydrogen chloride was passed into a solution of 0.5 g. of the secondary amine in anhydrous ether until precipitation was complete. The solid was filtered off, washed with a little dry ether, and recrystallized from dry ether to melt at 262°.

**Anal.** Calcd. for C₇H₁₄NCl: C, 56.94, H, 9.56; N, 9.49.
N, N-Dimethyl N'-cyclopropyl N'-(cyclopropylmethyl)-ethylenediamine

A mixture of N-cyclopropyl-N-cyclopropylmethylamine (11.1 g., 0.1 mole), sodium amide (8.6 g., 0.22 mole), and dry xylene (100 ml.) was placed into a 250 ml. three-necked flask fitted with a reflux condenser carrying a drying tube, and a mechanical stirrer. The mixture was heated to reflux temperature on a heating mantle and refluxed with stirring for 2 hours. After this initial reaction, the liquid became dark brown in colour with the formation of a dark precipitate. After cooling the flask, β-dimethylaminoethylbromide hydrobromide (25.6 g., 0.11 mole) was added. Stirring and refluxing was continued for 4 days, after which time, a bright orange solution with a dark brown precipitate formed. The mixture was cooled, centrifuged, and the xylene layer decanted into a 200 ml. distilling flask. The solvent was then removed under reduced pressure; the residue fractionated from a micro-distillation apparatus to yield 1 g. (5.5%) of a yellow oil boiling between 107-115°(19 mm.).

Infrared spectrum shows the absence of a hydrogen absorption at 31400 cm.⁻¹.

Di-Picrate Derivative

A sample of the tertiary amine (0.5 g.) was added to 95% ethanol (10 ml.), and then treated with a saturated solution of picric acid in 95% ethanol in the cold. The bright yellow precipitate was worked up in the same manner as described for the monocyclopropyl analogue. The dicycloparyl Antergan
analogue melted at 200°.

Anal. Calcd. for C_{23}H_{28}N_{6}O_{14}: C, 43.12; H, 4.41; N, 17.50.
Found: C, 42.16; H, 4.67; N, 16.98. Another analysis found: H, 4.05; N, 17.49.

Di-Cyclopentyl Analogue:

**N-Cyclopentyl-Cyclopentylcarboxamide**

Cyclopentylamine (17 g., 0.2 mole) in 50 ml. of dry benzene and pyridine (15.8 g., 0.2 mole) were placed into a 250 ml. flask. Cyclopentanecarbonyl chloride (26.5 g., 0.2 mole) was added dropwise to the stirred mixture in the cooled flask. After addition was complete, the reaction was stirred for 5 minutes; then washed with 50 ml. of water. The first crop of amide was suction filtered and the benzene layer was separated. Solvent benzene was evaporated and the residual amide recrystallized from carbon tetrachloride. The total yield of the amide was 31 g. (85.6%) and melted at 165°.

Infrared spectrum shows carbonyl absorption at 1650 cm.⁻¹ and nitrogen-hydrogen stretching at 3340 cm.⁻¹.

Anal. Calcd. for C_{14}H_{19}N_O: C, 72.88; H, 10.56; N, 7.73.
Found: C, 70.69; H, 10.27; N, 7.61.

**N-Cyclopentyl-N-Cyclopentylmethylamine**

A 1-liter three-necked flask was fitted with a mechanical stirrer, and a Soxhlet extractor protected from moisture by a calcium chloride drying tube. Into the flask was placed lithium aluminum hydride (14 g., 0.37 mole) to 300 ml. of anhydrous ether. The slurry was gently refluxed with
stirring for 3 hours. Then N-cyclopentyl-N-cyclopentylcarboxamide (30 g., 0.16 mole) was placed into the thimble in portions and allowed to dissolve by ether extraction. After all the amide had been carried into the flask, the reaction was gently refluxed for 4 days.

Water (50 ml.) was added to decompose the excess hydride; stirring was continued for 30 minutes. Then just sufficient 40% NaOH solution was added to allow clear separation of the ether layer. After decanting most of the ether solution, the remaining mixture was centrifuged and the ether layer added to the first fraction. The total ether solution was dried over anhydrous sodium sulfate, and then the solvent was removed by flash evaporation. The residue of 21.5 g. was fractionally distilled to yield 15 g. (56%) of a colourless liquid which had a b.p. 115-117° (20 mm.).

Infrared spectrum shows the absence of the carbonyl absorption band at 1650 cm.⁻¹. The cyclopentane structure shows absorption at 2950 cm.⁻¹.

Hydrochloride Derivative

The secondary amine (0.5 g.) in dry ether (10 ml.) was treated with dry hydrogen chloride until precipitation was complete. The white solid was suction filtered and washed with a little dry ether. Recrystallization of the hydrochloride salt was carried out by dissolving the solid in the minimum quantity of absolute ethanol and then adding dry ether until a cloudy solution formed. Crystals slowly formed on cooling
in an ice-bath and melted at 270° dec.

Anal. Calcd. for C_{11}H_{22}NCl: C, 64.84; H, 10.88; N, 6.87.
Found: C, 64.00; H, 10.85; N, 6.92.

N, N-Dimethyl N'-cyclopentyl-N'-(cyclopentylmethyl)-
ethylenediamine

N-Cyclopentyl-N-cyclopentylmethylamine (13.4 g., 0.08), sodium amide (7 g., 0.18 mole), and dry xylene (100 ml.) were added to a 250 ml. three-necked flask fitted with a reflux condenser (drying tubes) and a mechanical stirrer. The mixture was stirred and refluxed for 2 hours. After cooling, β-
dimethylaminoethylbromide hydrobromide (21 g., 0.09 mole) was added, and the mixture was refluxed with stirring for 48 hours. At the end of this time, the mixture was cooled, centrifuged, and the liquid layer decanted into a 200 ml. flask. Xylene solvent was removed by distillation 'in vacuo' and the dark residual liquid was fractionated in a micro-distillation apparatus to yield 0.5 g. (2.6%) of a yellow viscous oil b.p. 145-155° (10 mm.).

Infrared spectrum shows a number of bands at 1050 cm.\(^{-1}\), at 1275 cm.\(^{-1}\), and at 1635 cm.\(^{-1}\) which are different from the secondary amine absorption bands.

Di-Picrate Derivative

A sample of the tertiary amine (0.1 g.) was mixed with 95% ethanol (2 ml.) and treated with a saturated solution of picric acid as described for the preparation of the monocyclopropyl analogue di-picrate. The di-picrate salt of dicyclopentyl-Antergan analogue melted at 177°.
Anal. Calcd. for C$_{27}$H$_{36}$N$_8$O$_4$: C, 46.55; H, 5.21; N, 16.09.
Found: C, 44.44; H, 4.89; N, 15.98.

The Hydrochloride and Methyl Iodide of the above tertiary amine were unstable.

Di-Cyclohexyl Analogue:

**N-Cyclohexylhexahydrobenzamide**

A 500 ml. three-necked flask was fitted with a mechanical stirrer, a reflux condenser, and a 125 ml. dropping funnel. Cyclohexylamine (50 g., 0.5 mole), pyridine (40 g., 0.5 mole), and dry benzene (75 ml.) were placed into the flask. External cooling was applied when needed. To the stirred mixture, cyclohexanecarbonyl chloride (73 g., 0.5 mole) was added slowly from the dropping funnel (1 hour approx.). After addition was complete, the solution was stirred for 5 minutes at room temperature, and washed with 100 ml. of water. Any solid precipitate formed was suction filtered. The benzene solution of the amide was separated; the aqueous phase extracted with two 50 ml. portions of benzene. The extracts are combined and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residual amide, combined with the first crop of precipitate, was purified by recrystallization from 87% isopropanol. The melting point of N-cyclohexylhexahydrobenzamide was found to be 170-171°; gave a 76.5 g. (73%) yield. (lit. (108) m.p. 172-173°)

**N-Cyclohexyl N-Cyclohexanemethylamine**

In a 2-liter three-necked flask equipped with a
mechanical stirrer, a Soxhlet extractor and a dropping funnel (drying tubes) was placed lithium aluminum hydride (25 g., 0.66 mole) in 800 ml. of anhydrous ether. The mixture was stirred with gentle refluxing on a heating mantle for 1 h. hours. After this time, N-cyclohexylhexahydrobenzamide (69 g., 0.33 mole) was placed into a thimble in portions and refluxed with stirring until all the amide had been dissolved. The refluxing with stirring was continued for 7 days to insure complete reduction of the amide. Then the heating mantle was replaced by an ice-bath and 50 ml. of water was added dropwise to the vigorously stirred mixture. Stirring was continued for 30 minutes after the water addition was complete, and then sufficient 40% NaOH was added to precipitate the fine suspension. The ethereal layer was then worked up in the usual manner and evaporated to yield 52 g. (80%) N-cyclohexyl-cyclohexanemethylamine. A sample of the amine boiled at 142-3° (14 mm.). (lit. (109) b.p. 130-4° (1.5 mm.).)

Infrared spectrum shows reduction had been complete by the absence of the carbonyl absorption band at 1645 cm. -1.

Phenylthiourea Derivative

Due to the discrepancy between the observed boiling point and the literature value, the title derivative was prepared for analysis. Equal amounts of the amine (2 ml.) and phenylisothiocyanate (2 ml.) were mixed in a test tube and shaken for 2 minutes. If the reaction did not occur spontaneously, the mixture was heated for 3 minutes over a low flame.
The mixture was then kept in a beaker of ice until the mass solidified. The solid was powdered and washed with petroleum ether and 50% ethanol in order to remove any excess of either reactant. The residue was then recrystallized from 95% ethanol and melted at 130°.

Anal. Calcd. for C_{20}H_{30}N_2S: C, 72.67; H, 9.15; N, 8.48.
Found: C, 73.37; H, 8.98; N, 8.27.

N, N-Dimethyl N'-cyclohexyl N'-(cyclohexylmethyl)-ethylenediamine attempted by various methods

A. Condensation with the Side Chain

A 250 ml. three-necked flask was equipped with a reflux condenser (drying tube) and a mechanical stirrer. To the flask was added a mixture of N-cyclohexyl-N-cyclohexylmethylamine (a), a condensing or neutralizing agent, and a suitable solvent. The mixture was stirred and refluxed for 2 hours, cooled and β-dimethylaminoethylbromide hydrobromide (b) was added to the mixture. Refluxing with stirring was continued for (c) number of hours, and then the mixture was cooled. The liquid was decanted from the solid precipitate after centrifugation. Solvent was removed by distillation under reduced pressure, and the residue liquid was fractionated 'in vacuo' from a micro-distillation apparatus using a Vigreux column.

Table 9.

DICYCLOHEXYL ANALOGUE CONDENSATIONS ATTEMPTED
<table>
<thead>
<tr>
<th>Trial</th>
<th>(a)</th>
<th>Cond. Agent</th>
<th>Solvent Used</th>
<th>(b)</th>
<th>(c)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.6 g. (0.08 M)</td>
<td>2,4,6-tri-methylpyridine</td>
<td>toluene</td>
<td>20 g. (0.09 M)</td>
<td>30</td>
<td>Nil</td>
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<tr>
<td></td>
<td>21.9 g. (0.18 M)</td>
<td></td>
<td>75 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9.8 g. (0.05 M)</td>
<td>K₂CO₃</td>
<td>toluene</td>
<td>18.6 g. (0.08 M)</td>
<td>24</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>22.1 g. (0.16 M)</td>
<td></td>
<td>75 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9.8 g. (0.05 M)</td>
<td>Sodium Amide</td>
<td>toluene</td>
<td>28 g. (0.12 M)</td>
<td>48</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>9.5 g. (0.24 M)</td>
<td></td>
<td>75 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9.8 g. (0.05 M)</td>
<td>Sodium Amide</td>
<td>xylene</td>
<td>14 g. (0.06 M)</td>
<td>30</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>4.7 g. (0.12 M)</td>
<td></td>
<td>100 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Attempts were made to try the reactivity of a modified side chain. The free halide was isolated from its salt form, and the iodide salt was prepared by a halogen exchange.

**β-Dimethylaminoethylbromide (free halide)**

β-Dimethylaminoethylbromide hydrobromide (30 g.) was dissolved in the minimum amount of water to which was added xylene (50 ml.); followed by an excess of solid NaOH. The mixture was shaken mechanically for 2 hours where upon, the free base was dissolved in the xylene layer. The mixture was centrifuged and the xylene layer separated. It was then dried over anhydrous calcium chloride and refrigerated overnight. The solution of the free base was then used in this form (78).
The general procedure was employed using the same quantities of reactants as for trial 4, except the above solution of free base was used in place of its hydrobromide salt form. The results were negative.

\textbf{\(\beta\)-Dimethylaminoethylbromide Hydroiodide}

\(\beta\)-Dimethylaminoethylbromide hydrobromide (50 g., 0.21 mole) and sodium iodide (63 g., 0.42 mole) in absolute ethanol (200 ml.) were placed in a 500 ml. three-necked flask. The mixture was refluxed with stirring from a mechanical stirrer for 3 hours and filtered hot to remove the precipitated sodium bromide. Upon cooling the hydroiodide salt precipitated and was suction filtered to yield 65 g. (97\%) \(\beta\)-dimethylaminoethyliodide hydroiodide which melted at 132°. The product turned yellow on storage in a desiccator (79).

A condensation of the hydroiodide salt (18.8 g., 0.06 mole) with the secondary amine \(N\)-cyclohexyl-\(N\)-cyclohexylmethylamine was attempted using the general procedure and the same data as in trial 4. The results were also negative.

\textbf{B. Use of Chloroacetylchloride Unit}

Chloroacetyl chloride was prepared in a 500 ml. round bottom flask surmounted by a distillation head with a Vigreux column (10 cm.) attached to a condenser for downward distillation. In the flask was placed a mixture of monochloroacetic acid (47.3 g., 0.5 mole) and benzoyl chloride (140.6 g., 1 mole). This mixture was heated strongly until it began to boil, and then the acid chloride was distilled out of the
reaction mixture as rapidly as was consistent with good separation from the other constituents in the flask. (Distillation of the acid chloride was at such a rate that the temperature at the top of the column did not exceed the boiling point of the chloride.) The distillate was collected in a receiver immersed in an ice-bath to yield 37 g. (65%) chloroacetyl chloride with a boiling temperature range of 105-108°. The acid chloride contained a small amount of dissolved HCl, but was suitable for use in the subsequent reaction. (lit. (110) b.p. 105-107° in 76% yield.)

**N-Cyclohexyl-N-cyclohexanemethyl-chloroacetamide Attempted**

A mixture of N-cyclohexyl-N-cyclohexanemethylamine (9.8 g., 0.05 mole), pyridine (5.4 g., 0.06 mole) and benzene (50 ml.) were stirred with cooling in an ice-bath. The mixture was treated with chloroacetylchloride (6 g., 0.05 mole) in dry benzene (25 ml.) dropwise. After addition was complete, the reaction was heated under reflux for 1 hour and then cooled to room temperature. The benzene layer was separated and washed successively with water, dilute acid (some cloudy precipitate formed), and water. The solvent was removed from the separated and filtered benzene phase to yield the amide. A black tarry residue resulted which did not recrystallize from 95% ethanol.

**C. Use of a Substituted Secondary Diamine Chain**

**N, N-Dimethyl-N'-cyclohexyl-ethylenediamine**

In a 1-liter three-necked flask equipped with a reflux condenser, a dropping funnel both protected by drying
tubes, and a mechanical stirrer was placed a mixture of sodium amide (30 g., 0.75 mole, finely powdered) in dry toluene (200 ml.). The mixture was heated with stirring (to 100°C), and then a solution of cyclohexylamine (50 g., 0.5 mole) in dry toluene (50 ml.) was added from the dropping funnel. The mixture was heated for 3 hours on a heating mantle (below 100°C). After this time, \( \beta \)-dimethylaminoethylbromide hydrobromide (58.25 g., 0.25 mole) was added to the cooled mixture in the flask. More dry toluene (50-100 ml.) was used to wash the salt; then the mixture was refluxed with stirring for 24 hours. Water (75 ml.) was added to the cooled flask. The toluene layer was separated; the water layer saturated with potassium carbonate and extracted with solvent ether three times. The combined ether and toluene layers were dried over anhydrous sodium sulfate. The solvents were removed by distillation and the residual liquid fractionated under reduced pressure to yield 11 g. (26%) \( N, N \)-dimethyl-\( N' \)-cyclohexylethylenediamine with b.p. 101-103°C (14 mm.).

Infrared spectrum shows nitrogen-hydrogen stretching absorption at 3375 cm.\(^{-1}\) with one sharp peak.

**Hydrochloride Derivative**

A sample of \( N, N \)-dimethyl-\( N' \)-cyclohexyl-ethylenediamine (0.5 g.) in dry ether (10 ml.) was treated with dry HCl gas until precipitation was complete. The white solid was recrystallized from a mixture of absolute ethanol-dry ether, and the dihydrochloride derivative melted at 235-236°C.
Anal. Calcd. for C₁₀H₂₄N₂Cl₂: C, 49.38; H, 9.95; N, 11.52.
Found: C, 45.54; H, 10.14; N, 10.05.

Cyclohexylcarbinol

A 2-liter three-necked flask equipped with a 500 ml. dropping funnel, a reflux condenser, and a mechanical stirrer was placed 600 ml. of anhydrous ether. To the ether was added 34 g. (0.9 mole) of lithium aluminum hydride; the slurry was heated to gentle reflux with stirring for 2 hours. A solution of 51.3 g. (0.4 mole) of cyclohexanecarboxylic acid in 450 ml. of anhydrous ether was placed into the dropping funnel and added to the flask at such a rate as to produce gentle reflux. The mixture was then refluxed for 3 hours, after which time, the flask was cooled in an ice-bath while 50 ml. of water was added dropwise. Then 200 ml. of 10% sulfuric acid was added and the mixture stirred until a clear solution resulted. The ether layer was separated; the aqueous phase extracted with solvent ether two times. The combined ether layer was washed with aqueous sodium bicarbonate, with water, and then dried over anhydrous magnesium sulfate. Ether was removed and the oil distilled 'in vacuo' to yield 36 g. (79%) cyclohexylcarbinol b.p. 78-80° (13 mm.), n₂⁰D 1.4604. (lit. (111) b.p. 83° (14 mm.), n₂⁰D 1.4640.)

Hexahydrobenzylchloride

To a stirred solution of 36 g. (0.31 mole) cyclohexylcarbinol and 27 g. (0.34 mole) pyridine contained in a 250 ml. three-necked flask with a reflux condenser, a dropping
funnel (drying tubes), and a mechanical stirrer, there was added over a period of 2 hours, 60 g. (0.5 mole) of purified thionyl chloride. The reaction mixture was then heated at 90-105 for 20 hours, cooled to room temperature, and poured into a separatory funnel. The lower layer was drawn off, the upper (halide) layer washed twice with dilute HCl, with water, then with dilute sodium carbonate solution, and dried over anhydrous potassium carbonate. The halide was fractionally distilled at reduced pressure and the fraction boiling at 50-52°(15 mm.) retained to yield 17 g. (43%) hexahydrobenzylchloride, $n^\text{D}_{25} 1.4609$. (lit. (112) b.p. 54-55°(19 mm.), 67% yield; (113) $n^\text{D}_{25} 1.4611$.)

**Dicyclohexyl Analogue Condensation Attempted-Trial 7**

A mixture of 2.5 g. (0.06 mole) sodium amide in 100 ml. of dry toluene was placed into a 250 ml. three-necked flask equipped with a 125 ml. dropping funnel, a reflux condenser (drying tubes) and a mechanical stirrer. After warming the mixture, 9 g. (0.05 mole) N, N-dimethyl-N'-cyclohexyl-ethylenediamine was added with stirring, and then the mixture was refluxed for 2 hours. The mixture was cooled to about 50° and 10 g. (0.07 mole) of hexahydrobenzylchloride (cyclohexylmethylchloride) in an equal weight of dry toluene was added with stirring at such a rate as to keep the temperature of the reaction mixture at 60-70°. Stirring was then continued for 24 hours at 50-60°; then the mixture was cooled. The toluene solution was decanted from the solid dark precipitate after
centrifugation. Solvent toluene was removed by distillation and the residue fractionated 'in vacuo' using a Vigreux column. Infrared spectra of the fractions obtained indicated that the chloride compound was unreactive with the secondary amine chain under the above conditions.

**Cyclohexanecarbonyl Chloride and Secondary Diamine Condensation**

A 300 ml. three-necked flask was fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel. Cyclohexanecarbonyl chloride (7.3 g., 0.05 mole) was added dropwise to a stirred mixture of N, N-dimethyl-N'-cyclohexylethylenediamine (9 g., 0.05 mole), pyridine (4 g., 0.05 mole), and dry toluene (50 ml.). Upon addition of the acid chloride, an orange coloured precipitate formed with the evolution of heat (exothermic). After warming the reaction for one-half hour, the mixture was cooled and centrifuged. The solvent was removed by distillation under reduced pressure; the residue was fractionated to yield 11 g. (74.2%) of a high boiling yellow oil, b.p. 210-212° (15 mm.).

Infrared spectrum shows a strong band at 1645 cm.⁻¹ indicating the presence of a carbonyl function. The absence of a N-H absorption band at 3375 cm.⁻¹ suggests a tertiary substituted amine. The product, N, N-dimethyl-N'-cyclohexyl-N'- (cyclohexylcarbonyl)ethylenediamine, is a semi-solid at room temperature.
Found: C, 68.98; H, 11.00; N, 7.82.

N, N Dimethyl N'-cyclohexyl-N'-{(cyclohexylmethyl)-
ethylenediamine

A dry 1-liter three-necked flask was fitted with a mechanical stirrer, a reflux condenser, and 125 ml. dropping funnel protected from moisture by calcium chloride drying tubes. Lithium aluminum hydride (4 g., 0.1 mole) in 300 ml. of anhydrous ether was gently refluxed with stirring for 2 hours. A solution of N, N-dimethyl-N'-cyclohexyl-N'-(cyclohexylcarbonyl) ethylenediamine (10 g. 0.035 mole) in 75 ml. of anhydrous ether was added dropwise to the cooled hydride slurry. After addition was complete, the stirred mixture was heated to gentle reflux for 4 days.

Water (50 ml.) was added to the stirred and cooled mixture to decompose the excess hydride. Stirring was continued for 30 minutes and then the ethereal layer was separated after centrifugation. The solution was dried over anhydrous sodium sulfate; the ether solvent was removed by flash evaporation. A yellow liquid, N, N-dimethyl-N'-cyclohexyl-N'-(cyclohexylmethyl)-ethylenediamine, was obtained in 7.5 g. (79%) yield.

Infrared spectrum showed hydride reduction was complete by the absence of the carbonyl absorption band at 1645 cm⁻¹.

Di-Picrate Derivative

A sample of the compound (0.5 g.) in 95% ethanol (10ml.) was mixed with a saturated solution of picric acid in
95% ethanol (10 ml.) and worked up as usual in the cold. A melting point range of 215-216.5° was observed for N, N-dimethyl-N'-cyclohexyl-N'- (cyclohexylmethyl) ethylenediamine dipicrate.

Anal. Calcd. for C_{29}H_{40}N_8O_4: C, 48.06; H, 5.56; N, 15.46. Found: C, 35.13; H, 5.73; N, 17.95.

Di-Cycloheptyl Analogue:

N, N-Dimethyl-N'-cycloheptyl-ethylenediamine

A mixture of sodium amide (25 g., 0.6 mole) in dry toluene (200 ml.) was stirred and heated to 100 in a 1-liter three-necked flask. Then a solution of cycloheptylamine (56.6 g., 0.5 mole) in dry toluene (50 ml.) was added to the amide mixture in the flask from a 125 ml. dropping funnel. The stirred mixture was kept at a low heat for 18 to 20 hours. β-Dimethylaminoethylbromide hydrobromide (58.2 g., 0.25 mole) was then added to the cooled mixture. The mixture was refluxed with stirring for 48 hours, and then 75 ml. of water was added to the cooled reaction. The toluene layer was separated; the water layer saturated with potassium carbonate, then extracted three times with solvent ether. The combined ether and toluene layers were dried over anhydrous sodium sulfate. After removing the solvent by distillation, the residue was fractionated 'in vacuo' to yield 14.5 g. (32%) title product boiling at 116-120° (13 mm.).

Infrared spectrum shows a small N-H stretching vibration at 3350 cm.\(^{-1}\).
Hydrochloride Derivative

A solution of the secondary amine (0.5 g.) in anhydrous ether (10 ml.) was treated with dry hydrogen chloride until precipitation was complete. The recrystallized hydrochloride derivative melted at 220°. A dihydrochloride salt was formed.

Anal. Calcd. for \( \text{C}_{11}\text{H}_{26}\text{N}_{2}\text{Cl}_{2} \): C, 51.36; H, 10.19; N, 10.89.
Found: C, 47.74; H, 9.68; N, 10.81.

N, N-Dimethyl-N'-cycloheptyl-N'-(cycloheptylcarbonyl)-ethylenediamine

A 250 ml. three-necked flask was equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. A mixture of N, N-dimethyl-N'-cycloheptyl-ethylenediamine (9.3 g., 0.05 mole) pyridine (4 g., 0.05 mole), and dry toluene (50 ml.) was placed into the flask. The mixture was stirred and cycloheptylcarbonyl chloride (8.1 g., 0.05 mole) was added dropwise. After addition was complete, the mixture was warmed for one-half hour with stirring. Any residue (solid) was removed by centrifugation and the liquid layer washed with water. The toluene solution was dried over anhydrous sodium sulfate; then the solvent was removed by distillation under reduced pressure. The residue was fractionated 'in vacuo' to yield 9 g. (58%) title compound boiling at 226-229° (15 mm.). A semi-solid yellow product formed at room temperature.

Infrared spectrum shows carbonyl absorption at 1650 cm.\(^{-1}\).

Anal. Calcd. for \( \text{C}_{19}\text{H}_{36}\text{N}_{2}\text{O} \): C, 73.97; H, 11.76; N, 9.08.
Found: C, 75.62; H, 11.42.
N, N-Dimethyl-N'-cycloheptyl-N'-(cycloheptylmethyl)-ethylenediamine

A 1-liter three-necked flask was equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel (drying tubes). Lithium aluminum hydride (4 g., 0.1 mole) in anhydrous ether (300 ml.) was gently refluxed with stirring for 2 hours. A solution of N, N-dimethyl-N'-cycloheptyl-N'-(cycloheptylcarbonyl)ethylenediamine (8 g., 0.026 mole) in 75 ml. of anhydrous ether was added dropwise to the cooled hydride slurry. After addition was complete, the stirred mixture was heated at gentle reflux for 4 days.

The flask was cooled and water (50 ml.) was added to the stirred mixture. Stirring was continued for 30 minutes and the ethereal layer decanted after centrifugation. The solution was dried over anhydrous sodium sulfate; the ether solvent was removed by flash evaporation. The residual yellow oil, N, N-dimethyl N'-cycloheptyl-N'-(cycloheptylmethyl)ethylenediamine, was obtained in 6.1 g. (80%) yield.

Infrared spectrum shows a completed hydride reduction by the absence of the strong carbonyl absorption at 1650 cm\(^{-1}\).

Di-Picrate Derivative

A sample of the tertiary amine (0.5 g.) was mixed with 95% ethanol (10 ml.) and treated with a saturated solution of picric acid (10 ml.). The dipicrate salt of the di-cycloheptyl-Antergan analogue melted at 128-129°.

Anal. Calcd. for C\(_{31}\)H\(_{44}\)N\(_8\)O\(_{14}\): C, 49.46; H, 5.89; N, 14.89. Found: C, 48.95; H, 6.03; N, 14.93.
PART V

INFRARED SPECTRA
Figure 1. Infrared spectrum of cyclopropanecarboxylic acid. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 2. Infrared spectrum of cyclobutanecarboxylic acid. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 3. Infrared spectrum of cyclopentanecarboxylic acid. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 4. Infrared spectrum of cyclopropanecarboxanilide. 5 mg. solid in Nujol (mull) between sodium chloride disks.

Figure 5. Infrared spectrum of N-(cyclopropylmethyl)-aniline. Liquid between sodium chloride plates in 0.025 mm. thickness.

Figure 6. Infrared spectrum of N, N-dimethyl-N'-phenyl-N'- (cyclopropylmethyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 7. Infrared spectrum of cyclobutanecarboxanilide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 8. Infrared spectrum of N-(cyclobutylnethyl)-aniline. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 9. Infrared spectrum of N, N-dimethyl-N'-phenyl-N'- (cyclobutylnethyl)-ethylenediamine. Liquid between sodium chloride plates, 0.025 mm. thickness.
Figure 10. Infrared spectrum of cyclopentanecarboxanilide.
Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 11. Infrared spectrum of N-(cyclopentylmethyl)-aniline. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 12. Infrared spectrum of N, N-dimethyl-N'-phenyl N'-(cyclopentylmethyl)-ethylendiamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 13. Infrared spectrum of cyclohexanecarboxanilide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 14. Infrared spectrum of N-(cyclohexylmethyl)-aniline. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 15. Infrared spectrum of N, N-dimethyl-N'-phenyl-N'- (cyclohexylmethyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 16. Infrared spectrum of cycloheptanecarboxanilide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 17. Infrared spectrum of N-(cycloheptylmethyl)-aniline. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 18. Infrared spectrum of N, N-dimethyl-N'-phenyl-N'- (cycloheptylmethyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 19. Infrared spectrum of cyclooctanecarboxylic acid. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 20. Infrared spectrum of cyclooctanecarbonyl chloride. Liquid between sodium chloride plates, 0.025 mm. thickness.

Figure 21. Infrared spectrum of cyclooctanecarboxanilide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.
Figure 22. Infrared spectrum of N-cyclopropyl-N-cyclopropylcarboxamide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 23. Infrared spectrum of N-cyclopropyl-N-(cyclopropylmethyl)amine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 24. Infrared spectrum of N, N-dimethyl-N'-cyclopropyl-N'-(cyclopropylmethyl)ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 25. Infrared spectrum of N-cyclopentyl-N-cyclopentylcarboxamide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 26. Infrared spectrum of N-cyclopentyl-N-(cyclopentylmethyl)amine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 27. Infrared spectrum of N, N-dimethyl-N'-cyclopentyl-N'-(cyclopentylmethyl)ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 28. Infrared spectrum of N, N-dimethyl-N'-cyclohexylethylene diamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 29. Infrared spectrum of N, N-dimethyl-N'-cyclohexyl-N'-(cyclohexylcarbonyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 30. Infrared spectrum of N, N-dimethyl-N'-cyclohexyl-N'-(cyclohexylmethyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 31. Infrared spectrum of N, N-dimethyl-N'-cycloheptylethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 32. Infrared spectrum of N, N-dimethyl-N'-cycloheptyl-N'-(cycloheptylcarbonyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 33. Infrared spectrum of N, N-dimethyl-N'-cycloheptyl-N'-(cycloheptylmethyl)-ethylenediamine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 34. Infrared spectrum of cycloheptanecarboxylic acid. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 35. Infrared spectrum of cycloheptanecarbonyl chloride. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 36. Infrared spectrum of cyclohexylcarbinol. Liquid between sodium chloride plates, in 0.025 mm. thickness.
Figure 37. Infrared spectrum of cyclohexylmethylchloride. Liquid between sodium chloride plates, in 0.025 mm. thickness.

Figure 38. Infrared spectrum of N-cyclohexyl-N-cyclohexylcarboxamide. Solid (5 mg.) in Nujol (mull) between sodium chloride disks.

Figure 39. Infrared spectrum of N-cyclohexyl-N-(cyclohexylmethyl)amine. Liquid between sodium chloride plates, in 0.025 mm. thickness.
PART VI
SUMMARY

The synthesis of nine cycloalkyl analogues of Antergan in two series has been reported. In the first series of compounds, the benzyl group in Antergan was replaced by a cycloalkylmethyl group containing three to seven carbon atoms in the ring. This group of amines is as follows: N, N-dimethyl-N'-phenyl-N'-(cyclopropylmethyl)ethylenediamine, N, N-dimethyl-N'-phenyl-N'-(cyclobutylmethyl)ethylenediamine, N, N-dimethyl-N'-phenyl-N'-(cyclopentylmethyl)ethylenediamine, N, N-dimethyl-N'-phenyl-N'-(cyclohexylmethyl)ethylenediamine, and N, N-dimethyl-N'-phenyl-N'-(cycloheptylmethyl)ethylenediamine. In the second series of substituted Antergan analogues, both phenyl groups were replaced by the same cycloalkyl ring to form the following compounds: N, N-dimethyl-N'-cyclopropyl-N'-(cyclopropylmethyl)ethylenediamine, N, N-dimethyl-N'-cyclopentyl-N'-(cyclopentylmethyl)ethylenediamine, N, N-dimethyl-N'-cyclohexyl-N'-(cyclohexylmethyl)ethylenediamine, and N, N-dimethyl-N'-cycloheptyl-N'-(cycloheptylmethyl)ethylenediamine.

These ethylenediamine derivatives were isolated as the free base. The hydrochloride, methyl iodide, and picrate salts of these amines were prepared for elemental analyses. A number of the intermediates were prepared in their phenylthiourea or hydrochloride salt forms for microanalyses as well.
In both series, the general reaction sequence followed was to start with the cycloalkyl carboxylic acid. This acid was reacted with thionyl chloride to form the acid chloride. Then the amide intermediate was prepared by reacting the acid chloride with aniline for the first series or with a cycloalkylamine for the second series. Lithium aluminum hydride was used to form the desired amine which was then condensed with $\beta$-dimethylaminoethylbromide hydrobromide to obtain the Antergan analogue. Sodium amide was found to be the condensing agent of choice.

When the dicyclohexyl analogue did not form using the above reaction procedure, another route was used to obtain this and the dicycloheptyl analogue. Condensation of a cycloalkylcarbonyl chloride with a substituted-secondary ethylenediamine, followed by lithium aluminum hydride reduction gave the desired products.

An attempt was made to synthesize the monocyclooctyl Antergan analogue, but difficulty was encountered in forming the di-substituted amide. The preparation of this amide using phenyl isocyanate was also unsuccessful.

The first series of compounds were characterized through their physical constants as boiling points, refractive indices, and infrared spectra, and were verified by microanalyses of their salt derivatives. The second series of compounds, especially the dicyclopentyl and dicyclohexyl analogues were not as definitely characterized. In these cases, difficulty was
encountered in obtaining a pure fraction of the product, and in forming a stable salt derivative.
PART VII

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