SYNTHESIS OF CYCLOALKYL ANALOGUES OF DIPHENHYDRAMINE

by

GWENDOLYN FAYE QUEN CHAN

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We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

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Department of Pharmacy

The University of British Columbia,
Vancouver 8, Canada

Date Sept 4, 1964

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ABSTRACT

Two series of diphenhydramine analogues have been prepared. In the first series, one phenyl ring in the benzhydryl nucleus has been substituted with a cycloalkyl ring containing three to seven carbon atoms inclusive. In the second series both phenyl rings have been replaced by two rings containing three, five and six carbon atoms. The following amines have been prepared: 2-(α-cyclopropylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclobutylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclopentylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclohexylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cycloheptylbenzyloxy)-N,N-dimethylethylamine, 2-(dicyclopropylmethoxy)-N,N-dimethylethylamine, 2-(dicyclopentylmethoxy)-N,N-dimethylethylamine and 2-(dicyclohexylmethoxy)-N,N,-dimethylethylamine. These compounds have been characterized by their infrared spectra and, where possible, by elemental analyses of the chloroplatinates.

The reaction scheme involved a Grignard reaction of the cycloalkylbromide on benzaldehyde to yield the cycloalkylphenylcarbinol for the first series, and reaction on ethyl formate to yield the dicycloalkylcarbinol for the second series. Cyclobutylphenylcarbinol was obtained through a

Friedel-Crafts reaction of cyclobutanecarboxyl chloride on benzene using aluminum chloride as the catalyst and subsequent reduction of the cyclobutylphenylketone with lithium aluminum hydride. These secondary carbinols were then condensed with 2-dimethylaminoethylbromide hydrobromide in the presence of sodium amide. An alternate condensation reaction in the second series involved reaction of the dicycloalkylmethylbromide with 2-dimethylaminoethanol using sodamide as the condensing agent.

The major problems in the syntheses of the carbinols are the presence of carbonyl contaminants in some of the products, particularly in the cycloheptyl and cyclooctyl compounds, and the low yields of addition products obtained. It appears that better results would be achieved if the amount of Grignard reagent in the solution is estimated by a standard method to determine the amount of aldehyde or ester required for the reaction.

In the condensation reactions, difficulty was encountered in formation of the sodium derivative. This reaction required a finely-divided form of the condensing agent and sufficient warming time for the reaction to proceed. However, too lengthy a period of heating appears to alter the carbinol molecule so that no product could be obtained. The second phase of the condensation reaction also proceeds slowly, and a sufficient period of refluxing is necessary for the

reaction to go to completion. The alternate procedure which was also employed in the second series of compounds did not appear to improve the yields of products.

Signature of Examiners

ACKNOWLEDGEMENT

The writer expresses her sincere appreciation to Dr. T.H. Brown for the guidance and encouragement given during the course of this work.

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INTRODUCTION

A series of cycloalkyl analogues of 2-(benzhydryloxy)-N, N-dimethylethylamine, diphenhydramine, have been prepared in which one phenyl ring of the benzhydryl nucleus is replaced by a three- to seven-membered cycloalkyl ring. The synthesis of the eight-membered analogue was also attempted. Of a second series in which both phenyl rings are replaced by similar-sized cycloalkyl rings, the dicyclopropyl-, dicyclopentyl-, and dicyclohexyl-analogues have been prepared. It is hoped to correlate pharmacological activity to these changes in chemical structure and thereby obtain further knowledge concerning the antihistamine receptor site.

FORMATION AND PHARMACODYNAMIC PROPERTIES OF HISTAMINE

Histamine is present in all the main tissues and organs in the body, bound in an inactive complex to tissue proteins. The amino acid histidine, is believed to be the ultimate physiological source of all histamine, largely through the degradative action of tissue or bacterial decarboxylase (1) (2). Under the influence of certain factors, such as antigen-antibody reactions, ultraviolet rays, skin irritations (extreme heat or cold), histamine is liberated with the production of widespread physiological responses, which are summarized in Table I (3). The mechanism involved in the

inactivation and in the release of bound histamine is unknown. There are many indications that the release of histamine involves both chemical and enzymatic reactions (4).

TABLE I

SUMMARY OF PRINCIPAL ACTIONS OF HISTAMINE

Site of Action	Effect Produced	Some Important Areas Affected
Smooth muscle	Contraction	Bronchiolar, vascular, intestinal, and uterine smooth muscle
Capillaries	Dilatation and increased permeability	Skin and mucuous membranes
Glands of external secretion	Secretogogue	Lacrimal, nasal, pulmonary, and digestive glands
Cutaneous endings of pain response	Pain	Skin

ROLE OF HISTAMINE IN ANAPHYLAXIS

It was observed that anaphylaxis and allergic conditions exhibited identical symptoms regardless of the sensitizing agent in the antigen-antibody reaction. This led to the search for a common base believed to be responsible for the manifestations. The possibility that histamine plays a role in anaphylaxis was first mentioned in 1910 by Dale and Laidlaw,

who noted that the symptoms elicited by histamine injections were similar to those of anaphylactic shock. Subsequently, Dale demonstrated that histamine is normally present in the tissues, and in 1929, he proposed the theory that in anaphylaxis, histamine is released from an inert bound form in the tissues due to injury of the cell resulting from the intracellular antigen-antibody reaction (5). Further, Lewis showed that an intracutaneous injection of histamine in man causes the characteristic triple response - wheal, redness, and a flare - displayed by irritation to the skin by allergenic agents (6).

Experimental evidence from many sources supported the histamine theory. Liberation of histamine during an immunochemical reaction was demonstrated by Dragstedt and Gebauer-Fuelnegg, who found large amounts of histamine in the peripheral blood of dog after the antigen-antibody reaction. Numerous other investigators were able to show the release of histamine from sensitized organs both in vivo and in vitro, and the detection of a substance resembling histamine in the blood or perfusion liquid following the administration of antigen (4). A close quantitative relationship between the amount of histamine given and the quantity of antihistamine necessary to antagonize it, also served to substantiate the histamine theory of allergy and anaphylaxis (1).

Although the entire characteristic syndrome of anaphylactic shock could not be explained solely on the basis of histamine action, it is believed to be the main causative factor. Thus, an increase in the clotting time of blood is due to the simultaneous release of heparin (1). An unidentified "slow reacting substance" (because of its slow action on plain muscle), is another toxic substance released (7), and 5-hydroxytryptamine may also be implicated in allergic reactions (4).

As a result of all the circumstantial evidence supporting the histamine theory, Halpern postulated in 1942 that the cause of allergy and anaphylaxis may lie in a chemical action of histamine on a receptor and that possibly other structurally suitable compounds might be capable of competing with histamine for the active functional areas of the same molecular system (8). Thus began the search for agents capable of blocking or antagonizing the effects of histamine for relief of allergic conditions.

EARLY ANTIHISTAMINIC AGENTS

Early attempts were directed at using natural substances as physiological antagonists to the actions of histamine. Purified extracts of an enzyme present in the kidneys and intestinal mucosa, histaminase or diamine oxidase, which is responsible for oxidative deamination of histamine, proved too toxic for clinical use in man (9).

Certain amino acids, histidine, cysteine and arginine, were shown to inhibit the characteristic actions of histamine in animals. However, they possess such a low index of efficiency that therapeutic doses for humans would be too toxic (9).

Desensitization of the patient with gradually increasing doses of histamine proved ineffective. Preparations of Hapamine, histamine conjugated with proteins through azo linkages, were also tried. However, specificity of the antibodies so formed, were questioned (10).

Symptomatic drugs such as epinephrine, ephedrine, phenylpropanolamine and aminophylline were used. These substances initiate pharmacological actions diametrically opposed to those of histamine, that is, they were physiological antagonists. They are not true antihistamines, since they are non-specific and are capable of antagonizing the effect of many different types of drugs (10).

SYNTHETIC ANTIHISTAMINIC AGENTS

The systematic search for compounds having the specific property of counteracting the physiological effects of histamine began in the Fourneau Laboratory in Paris. In 1933, while testing the sympatholytic activity of some new antimalarials, Bovet and associates discovered that piperidinomethyl-2-benzodioxane (F 933) could protect animals from bronchial spasms caused by histamine aerosol (8). This

compound, which may be regarded as a phenolic ether, led Bovet and Staub to the investigation of a series of 21 aryl ethers containing basic side chains. The most active substance was thymoxyethyldiethylamine (F 929), which antagonized histamine action more effectively than F 933. Due to the proven antispasmodic activity of various sympathomimetic amines, Staub extended the investigation by isoteric replacement of the ether oxygen by an amine nitrogen. From the study of 17 amines in 1939, N'-phenyl-N'-ethyl-N-diethylethylenediamine (F 1571) was shown to be more active than any of the previously described histamine antagonists. However, the high toxicity of both F 929 and F 1571 precluded their use in man (10). From the results of extensive study of the properties of the aminoalkyl aryl ethers and aryl substituted ethylenediamine series, Staub concluded that the amines are more specific in their action against histamine shock, while the ethers, although less specific, gave a greater degree of protection against histamine-induced bronchial asthma (1). It was also evident that toxicity did not necessarily parallel antihistaminic potency (5).

Antihistaminic research was continued at the Rhone-Poulenc Institute by Halpern and associates. In 1940, N'-phenyl-N'-benzyl-N-dimethylethylenediamine, R.P. 2339, Antergan, was presented as the first antihistamine of low toxicity and high activity (11)(12). Subsequent variations in the ethylene diamine structure produced many useful

compounds. Particular attention was focussed on the related phenothiazine-type compounds, after Halpern introduced a number of 10-(β-dimethylaminoalkyl)-phenothiazine derivatives as potent antihistamines (1)(8).

Independent research in the United States by Rieveschl and Huber produced diphenhydramine, Benadryl, as the most effective and clinically useful compound out of a series of benzhydryl ethers. It was patterned after the general molecular shape of Trasentin, a synthetic spasmolytic agent with atropine-like properties (13). Improvement of the therapeutic index by substitution of the phenyl group in the Fourneau ether series by a benzhydryl group led to further replacement with heterocyclic groups.

From the investigations of Mayer and Yonkman, a compound related to the diamines, N'-pyridyl-N'-benzyl-N-dimethyl-ethylenediamine, tripelennamine, Pyribenzamine, was introduced as an antihistamine more effective than previous drugs (6).

Many new and useful compounds followed, modeled after the ethanolamine and ethylenediamine structures. A list of some clinically useful antihistamines and those of historical interest are included in Table II.

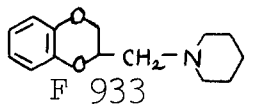
CLASSIFICATION OF ANTIHISTAMINES

With the exception of the haloalkylamines, all active antihistaminic substances could be related to a common

TABLE II

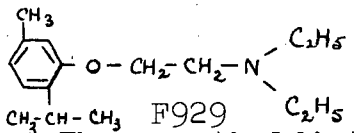
ANTIHISTAMINIC SUBSTANCES

Ethanolamine Derivatives



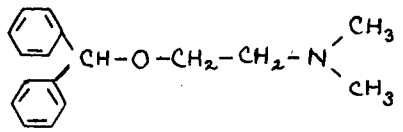
F 933

Piperidinomethyl-2-benzodioxane

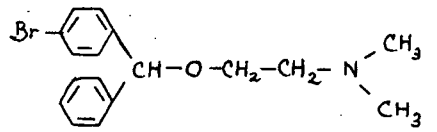


F929

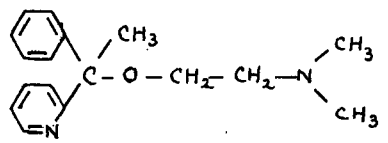
Thymoxyethyldiethylamine



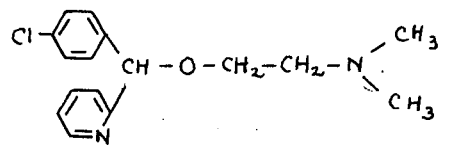
Diphenhydramine
Benadryl



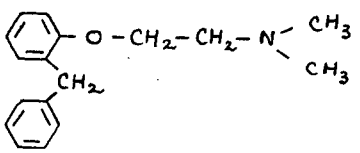
Bromodiphenhydramine
Ambodryl



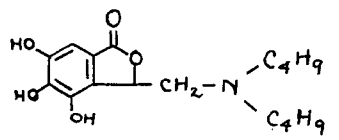
Doxylamine
Decapryn



Carbinoxamine
Clistin

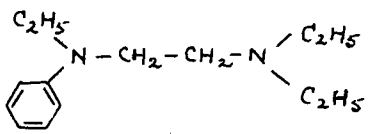


Phenyltoloxamine
Bristamin

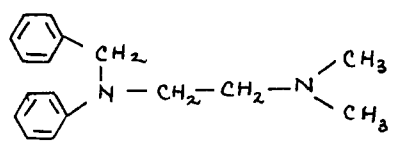


Anthallan

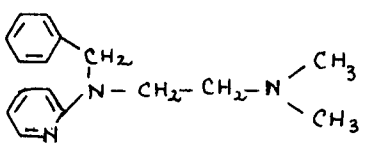
Ethylenediamine Derivatives



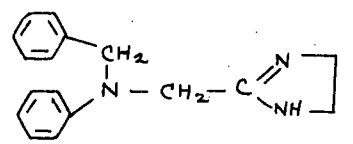
F 1571
N'-phenyl-N'-ethyl-N-diethyl-ethylenediamine



R.P. 2339
Antergan



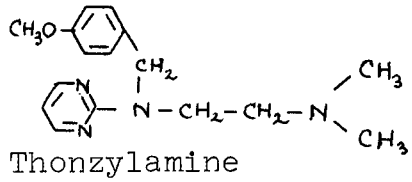
Tripelennamine
Pyribenzamine



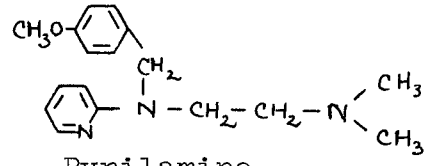
Antazoline
Antistine

TABLE II (continued)

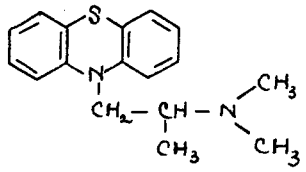
Ethylenediamine Derivatives



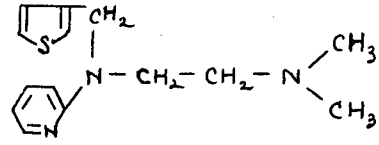
Thonzylamine
Neohetramine



Pyrilamine
Neoantergan

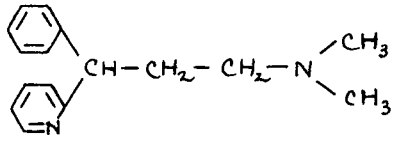


Promethazine
Phenergan

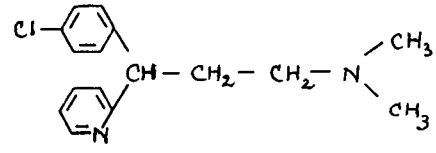


Thenyldiamine
Thenfadil

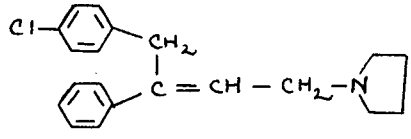
Propylamine Derivatives



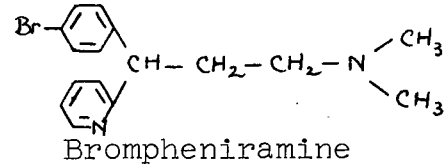
Pheniramine
Trimeton



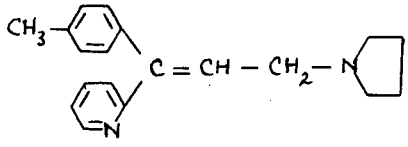
Chlorpheniramine
Chlor-Trimeton



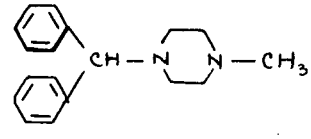
Pyrrobutamine
Pyronil



Brompheniramine
Dimetane



Triprolidine
Actidil



Cyclizine
Marezine

structural pattern(11):

$$R_2 - \underset{\displaystyle R_3}{\overset{\displaystyle |}{X}} - C - C - \underset{\displaystyle R_1}{\overset{\displaystyle |}{N}} - R_1$$

Based on differences in chemical constitution, the compounds fall into three broad classes:

1. Ethanolamines, where X = O
2. Ethylenediamines, where X = N
3. Propylamines, where X = C

GENERAL REQUIREMENTS FOR ANTIHISTIMINIC ACTIVITY

In the general formula representing active antihistamines, X may be O, N, or C, or it may be incorporated into a heterocyclic nucleus. R_2 and R_3 may be aryl, arylmethyl, heterocyclic or heterocyclic methyl. R_1 must be methyl groups for optimum activity, or it may be part of a ring.

STRUCTURE ACTIVITY RELATIONSHIPS

1. The dialkylamino group

The terminal N should be tertiary for maximum activity. Secondary and primary amines are generally much less active. Quaternization generally reduces antihistaminic activity and increases anticholinergic activity, since the structure then more closely resembles choline (4). In the benzhydryl ether series, the quaternary salts were found to be less active in vitro and in vivo than the corresponding hydrochlorides (11).

It is readily evident from Table II that the most active compounds contain a dimethylamino group. Homologs containing

higher dialkylamino groups are less active and often more toxic. Unsymmetrically substituted alkyl groups on the nitrogen function results in compounds with decreased activity. However, the dialklamino group may be incorporated into heterocyclic rings, such as pyrrolidino, piperidino, morpholino, thiomorpholino, or 2-imidazolinyl groups, without serious loss of activity. For instance, replacement of the dimethylamino group in diphenhydramine and its derivatives with pipecolino (15), piperidino and pyrrolidino (16)(17) groups had no effect on its activity, while morpholino substitution (16)(17) produced less effective compounds. Generally, substitutions on the pyrrolidino ring decreased activity as did substitution of 4-imidazolyl group for the 2-imidazolyl group (11).

Salt formation occurs at the terminal nitrogen and has primarily a solubilizing function. Sometimes, though, a difference in potency of various salts of a particular antihistamine is noticeable. The acid succinate and acid oxalate of Benadryl have a similar order of activity to the hydrochloride, but the acid succinate appears to be less toxic. Although Winder (11) suggested an anionic influence, the difference may be due to increased solubility or absorption (10).

From these considerations it would appear that substituents on the nitrogen function should preferably be symmetrical, small and planar. An approximate order of decreasing utility

of the various groups is:

dimethylamino ≧ pyrrolidino = piperidino > morpholino = thiomorpholine > diethylamino > dibutylamino > secondary amino > primary amino (11).

2. The alkylene chain

The preferred chain length is two carbon atoms. Lengthening to trimethylene or greater or branching of the chain results in a sharp drop in activity (14). An exception are the phenothiazine compounds, but this may be due to the cyclic nature of the molecule. Increase in the chain length of benzhydryl ethers by an oxygen interrupted chain also decreases activity (16).

3. The nucleus

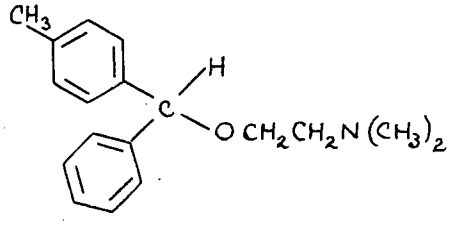
The group attached through the X atom to the basic side chain may be termed the "nucleus" of the antihistaminic substance (5).

In the benzhydryl ether series, the benzhydryl nucleus appears to be the optimum for antihistaminic activity. Replacement of one of the phenyl groups by thienyl, 1-naphthyl, or cyclohexyl diminishes activity considerably (18). Substitution of one phenyl ring with 2-pyridyl (18), or 2-furyl (19) produced effective compounds. However, 3- and 4-pyridyl, 2-imidazolinyl and substituted 2-pyrimidyl analogues are less active. Bridging of the two phenyl rings, directly or through oxygen or sulfur atoms to form the 9-fluorenyl, 9-xanthyl and 9-thioxanthyl systems, respectively,

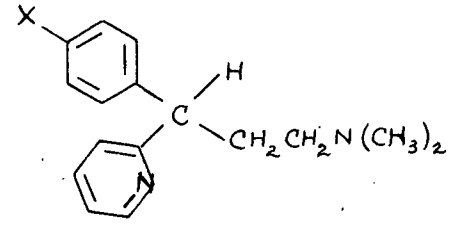
causes a loss in activity (11)(16), as does rearrangement of the rings into a naphthalene nucleus (15). Substitution of both phenyl rings with heterocyclic rings, such as pyridine, produces inactive compounds (18).

Nuclear substitution with methyl or halogen is generally an advantage, provided the substituent is in the para position (16). In diphenhydramine, p-methyl and p-ethyl substitution enhanced activity, while the o-methyl isomer showed decreased activity. As the p-alkyl substituent increases in bulk due to branching or lengthening of the chain, activity is decreased again (20). In the halogen series, maximum activity is obtained with the 4-fluoro derivative (16). When a p-methoxy group is introduced into one ring of the benzhydryl nucleus, activity is increased (3)(13). Generally, m-substitution, or substitutions into both phenyl rings reduces activity (15)(16)(20).

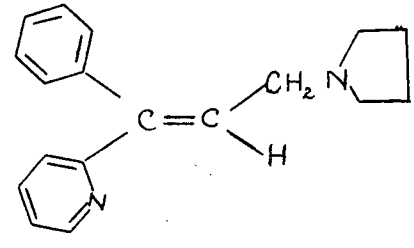
Basic ethers of tertiary alcohols have also been investigated extensively. Derivatives with the triphenyl radical in place of the diphenyl are almost inactive. This may be due to an increase in electro-negative character of the carbon adjacent to the ether linkage or more likely to a considerable increase in size of the group (14). The β-dimethylaminoethyl ethers of methyldiphenyl and methyl-(2-pyridyl)phenylmethanol are of the same order of activity as diphenhydramine and much less toxic (11). Increasing the α-hydrogen substituent to a larger alkyl group results in



(+)-isomer x 4 (-)-isomer



x = Cl or Br
Antihistaminic Activity
almost exclusively in
(+)-isomer



C_6H_5/H trans more active

I

Fig. 1. Stereoisomerism and Antihistaminic Activity

decreased activity (14) as does substitution with basic groups (18).

Hydrogenation of the aromatic rings appears to decrease activity, the greater the hydrogenation, the lower the activity:

cyclohexyl < 1-cyclohexenyl < phenyl (18).

4. Stereoisomerism

In optically active antihistamines, the activity generally resides in the (d)-isomer (Figure 1) (21). When there is very little apparent difference in activity between the enantiomorphic pair, it is usually attributed to the low order of activity, for according to Pfeiffer's rule, the lower the effective dose of the antihistamine the greater will be differences in pharmacological effect of the optical isomers (21).

In geometric isomers, invariably one isomer has high and specific antihistaminic activity, while its epimer is considerably less active (22). In compound I (Figure 1) the more potent compound is C_6H_5/H trans where there is coplanarity between the pyridyl ring and the double bond. In the C_6H_5/H cis isomer there is coplanarity between the phenyl group and the double bond.

PHYSICO-CHEMICAL REQUIREMENTS OF ANTIHISTAMINES

In addition to the structural requirements for maximum activity in antihistamines, there appears to be some

relationship between physico-chemical constants and activity. The molecular weight of the most active compounds varies from 254 (Antergan) to 300.5 (chlorcyclizine), which seems to be the range of optimal histamine antagonism. There has also been some successful correlation achieved between the dissociation constants of different chemically related compounds and their antihistaminic activity (11). Resonance and planarity are also factors in consideration of optimum activity. These physico-chemical features of the compound are primarily determined by the nucleus of the antihistaminic substance (5).

DEFINITION OF ANTIHISTAMINES

Antihistamines, according to Loew, are confined to "those drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and which do so by a mechanism other than the production of pharmacologic response diametrically opposed to those produced by histamine" (10).

MECHANISM OF ACTION OF ANTIHISTAMINES

Various investigators have shown that antihistaminic agents do not exert their effect by preventing the release of histamine from the cells nor do they affect the binding there (2). There is no indication that they activate enzymes which are known to degrade histamine (11). It is also known

that the antagonists do not combine chemically with histamine to form an inactive complex, nor do they interfere with the production or qualities of antibodies in the antigen-antibody reaction (10).

The activity of antihistaminic drugs is believed to be due to a competitive mechanism between histamine and its antagonist. They act by adsorbing onto, competing with and finally displacing histamine from its site of action into the circulatory system where it is gradually absorbed and detoxified by the cellular elements of the blood (9). Antihistaminics may alter the surface tension or once adsorbed onto the receptor site are more difficulty removed due to lesser solubility or greater Van der Waals forces (11). The attachment of the drug to the receptor produces no particular reaction, but by occupation of the same site, prevent histamine from exerting its characteristic effect.

In view of the fact that the dose-response curves are of the same form although inhibition ratios (% inhibition versus concentration of drug) are different for different biological systems, such as bronchi, intestinal strips, etc., the concept of competitive mechanism is further strengthened (12)(23).

PHARMACOLOGICAL PROPERTIES OF ANTIHISTAMINES

Although the chemical structure of antihistamines are diverse, their pharmacological properties are very similar, differing quantitatively rather than qualitatively. They

effectively antagonize the muscular actions of histamine for periods of from 4 to 24 hours. Skin reactions to histamine and allergens are reduced or prevented (11).

One of the most striking characteristics of all known antihistamines is that they have no significant influence on histamine-induced gastric secretion. This may be due to a different mechanism of action of histamine on secretory cells or that antihistamines can not gain access or have no affinity for the receptors in the secretory cell (10)(11).

Antihistaminic substances also exhibit to varying degrees other properties independent of their histamine-antagonizing effect. Most have an adrenergic potentiating effect (tripelenamine, diphenhydramine), others (pyrathiazine) are without effect, and some (F 929 and some newer antihistamines) are adrenergic blocking agents (5)(11). Anticholinergic properties as well as antispasmodic, analgesic and quinidine-like actions are exhibited by many of these compounds (7) (10). All antihistamines exert a local anesthetic action to some degree. Neoantergan, Benadryl and Antistine are 3.3, 2.5 and 1.5 times as potent as procaine (7). There is no quantitative relationship between antihistamine potency and its anesthetic effect.

Side-effects of antihistamines vary according to the individual drug and the individual patient. Sedation is the most common reaction but some drugs cause excitation. Other effects are muscular weakness, dizziness, gastric irritation,

dryness of mouth and throat, loss of appetite, palpitation and nervousness. Reactions which are serious but rare are hypersensitivity, dermatitis from topical application, leucopenia and agranulocytosis (5).

METABOLISM OF ANTIHISTAMINES

Antihistamines are readily absorbed from the gastro-intestinal tract and parenteral sites of administration. Very little is known about the metabolic fate of these drugs. The main site of degradation is in the liver, but the lungs and kidneys are also capable of metabolizing these substances (5).

THERAPEUTIC USE OF ANTIHISTAMINES

Antihistamines are generally used for symptomatic treatment of allergic conditions. They have been found to be beneficial in the treatment of the following conditions: seasonal hay fever, perennial vasomotor rhinitis, urticaris, angioneurotic edema, serum sickness, itching of pruritus vulvae and ani, atopic dermatitis, contact dermatitis, generalized pruritis and insect bites (24).

RECEPTOR MECHANISMS

Effective correlation of chemical structure to biological activity must include considerations of the interaction between the drug molecule with the receptor site, as they are interrelated.

The existence of receptors was first postulated in 1878 by Langley (25). He later referred to a "receptive substance" located in the myoneural junction which is the recipient of a sympathetic nerve stimulation (26). However, it was Ehrlich who gave chemical precision to the idea. From his work on chemotherapy in 1913 he coined the term "receptor" and stated "corpora non agunt nisi fixata" (27). His basic concepts that a receptor is a small part of a molecule (28) and that haptophoric groups in a drug molecule that are responsible for anchoring the drug are to be differentiated from toxiphoric groups that are responsible for its therapeutic effect (29) are still valid today. Since then, the term receptor has become indispensable in the reasonings of drug action.

The classical theory for drug-receptor interaction is the lock and key model of E. Fischer. A more flexible model as presented in the induced fit theory (30) is more appropriate. The dynamic nature of the drug-receptor interaction is embodied in Scheuler's definition of a receptor: "The drug-receptor is in general the pattern R of forces of diverse origin forming a part of some biological system and having roughly the same dimensions as a certain pattern M of forces presented by the drug molecule in such a way that between patterns M and R a relationship of complementarity for interaction exists" (27). Thus, the drug-receptor interaction can be seen as a mutual moulding of the shape and charge distribution of the drug and receptor.

All the knowledge of the characteristics of receptors is derived indirectly from the physico-chemical characteristics of the molecules with which they combine to initiate biological responses, since they can not be isolated and identified chemically. Although Ehrenpries has isolated a protein from the electric eel which he claims to be the acetylcholine receptor, it is not representative of the small number of receptors in various cells of other animals (31). Indirect evidence points to the existence of receptors, particularly the effects of stereoisomers and the agreement of quantitative data on drug action based upon interpretation of bond formation between drug and specific receptors.

The majority of drugs, antihistamines included, are held in close association to the receptor surface by a reversible combination of weak forces, ionic bonds, hydrogen bonds, dipole interactions and Van der Waals forces, which operate to different extents in different cases. The opposing repulsive forces which decrease stability of the combination are ionic repulsive forces, dipole-dipole interaction of like charges and steric hindrance due to electrostatic repulsion between electrons and inflexibility of bonds to binding, stretching or compression (30).

The highly specific nature of receptors is apparent by the fact that slight modifications in certain drugs produce drastic changes in responses. This specificity necessitates a high degree of complementariness between the drug and

receptor. Thus, size, shape and three-dimensional characteristics including stereoisomerism and conformation are of importance in correlating structure to biological activity (32).

However, occupation of the receptor alone does not produce a physiological effect. It is the suitable combination of a drug with its receptor which induces a biological response. Clark's classical treatment of explaining dose-response curves with the aid of the Langmuir adsorption isotherms was based on the assumptions that biological effect is an all-or-none response and is proportional to the concentration of drug-receptor complex regardless of the agonist. Subsequently, it was clearly shown that these hypotheses were not generally applicable (33). Ariens (34) introduced the terms "affinity" and "intrinsic activity," and Stephenson (35) used the term "efficacy" to explain qualitative differences in pharmacological properties of chemically related compounds. In studying homologous series of compounds they found compounds termed "partial agonists," which exhibited intermediate activity and showed a "dualism in action." The derived theoretical equations showed good agreement of curves with theory. A novel approach in explaining drug-receptor interaction is the suggestion by Paton (36) that excitatory effects depend not upon occupation of the receptor but upon the rate of drug receptor occupation.

Receptors are believed to be proteinous in nature, and can be any component of a pacemaker, that is, the bottleneck reaction in a long sequence of interdependent reactions, either as the apoenzyme or its coenzyme or substrate or a portion of any of these (8)(28). Upon union of drug with receptor, changes in the charge distribution and shape activates the receptor to induce changes in the charge distribution and shape of surrounding molecules, thus initiating the sequence of physico-chemical events leading to the effect (27).

In the complicated process of drug action, other factors must be considered, such as absorption, transport, biochemical changes or excretion of the drug, which determine the relation between the dose of the drug and its concentration in the "biophase" (27)(37). Thus the drug may be lost before reaching the effector receptor, the "site of action" (37), by being concentrated at these "sites of losses" (29), or "drug acceptors" (37).

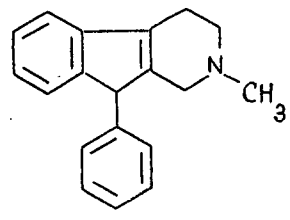
ANTIHISTAMINE RECEPTOR

A large number of antihistamines have pK_a values of about 8, which represents 16% non-ionization at physiological pH. It is suggested that these drugs penetrate as neutral molecules and act as cations (38). The generally accepted concept is that for drugs which act as cations (the ionized amine in the antihistaminics) the corresponding receptor

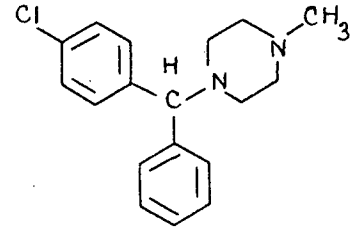
contains an anionic site so that ionic bonding is possible (33). Since the action radius of ionic groups are relatively large (the electrical field around the ions decreases with the square of the distance), it is postulated that the amino group serves as a guiding group leading the drug to its receptor site, then the relatively weak forces whose action radius decrease with the seventh power of the distance, hydrogen bonding and Van der Waals forces, come into action to stabilize the complex and to attain a close fit at the receptor surface (39).

The general composition of the antihistaminic receptor is believed to be an anionic site to accommodate the basic centre and a flat area at a more or less fixed distance to accommodate one of the aromatic rings, which must be coplanar with the side chain. The importance of the flexible side chain relative to the aromatic group is based on observations that the structure of several active antihistamines are rigid or semi-rigid, with their side chains being fixed to one of the rings as in phenindamine or able to rotate about one axis only as in chlorocyclizine (Figure 2). It is presumed that when the flexible side chain is prevented from curling up into position as in orphenadrine, an o-substituted compound, activity is weakened, in contrast to neobenodine which is in the proper spatial configuration (20).

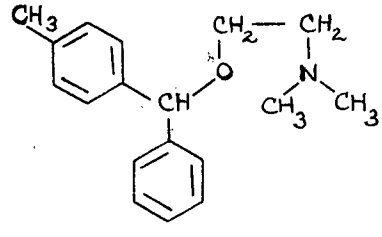
From the histamine point of view, it has been suggested that the histamine receptor contains an ionizable group



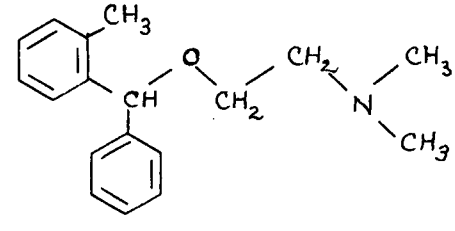
phenindamine



chlorocyclizine



neobenodine
Toladryl



orphenadrine

Fig. 2. Spatial Configuration of the Side Chain in Antihistaminic Activity

possibly an imidazole residue, with a pK_a of about 7.0 (40). Another source claims that two types of receptors exist in the guinea pig ileum and that two ionizable groups are present in the histamine receptor, the active form being that in which only one group is ionized (41).

It is known that the imino group in histamine is an anchorage point to its receptor possibly through bond formation with the polar carbonyl of a peptide. At physiological pH, histamine as a cation probably forms a chelate structure with a hydrogen bond between the receptor site and the "pyridine" nitrogen in the imidazole ring (40).

Although a drug and its antagonist act on common receptors, they do not necessarily act strictly on identical receptors. Experiments (27) with homologous series of chemically related compounds showed that by gradually increasing the length of substituents on the amino group of histamine, the compounds gradually changed from agonists to antagonists and both the intrinsic activity and affinity for the receptor strongly decreased. When larger groups, especially groups with planar rings, such as aralkyl groups, were introduced, affinity strongly increased again and highly active antagonists are obtained. It appears then that lytics are dependent for their affinity not on the original receptor of the mimetic but on adjacent receptor parts. Thus histamine probably has in common with its antagonists only the anionic site which accommodates the strongly polar group, while less

polar and more indifferent areas nearby serve as additional receptor for the nucleus of the antagonists. The great difference in chemical structures of the mimetics to the lytics and the overlapping activities of the antihistaminics, ∝-sympatholytics and anticholinergics can be accounted for on the basis of a common strongly polar group and an area adjacent to the receptor for the polar group which distinguishes the type of antagonistic activity. This is schematically represented in Table III. Spatial properties, steric factors and stereochemical features of the lytics are then important to separate these multiple biological activities. For instance, nuclear substitution on diphenhydramine could be used to separate antihistaminic activity from anti-acetylcholine activity (Table IV) (21). Introduction of ortho substituents of increasing size which tends to bring both rings out of one plane increasingly restricts rotation of the substituted phenyl group and antihistaminic activity decreases while antiacetylcholine activity increases. Para substitution, on the other hand, which does not affect the plane of the molecule, reduces anticholinergic activity and increases antihistaminic action. Stereoisomers show even greater separation of biological effects, (Table V) (21).

It is interesting to note that in comparing the structure of Benadryl and that of histamine, the 2-imidazolyl structure of histamine is replaced by the benzhydryl ether group and as the function of nitrogen changes to primary, to secondary

and to tertiary (deviates from the original function), histamine interference increases simultaneously (18).

TABLE III

MIMETICS AND DIFFERENT TYPES OF LYTICS IN RELATION TO THEIR HYPOTHETICAL RECEPTOR SURFACE

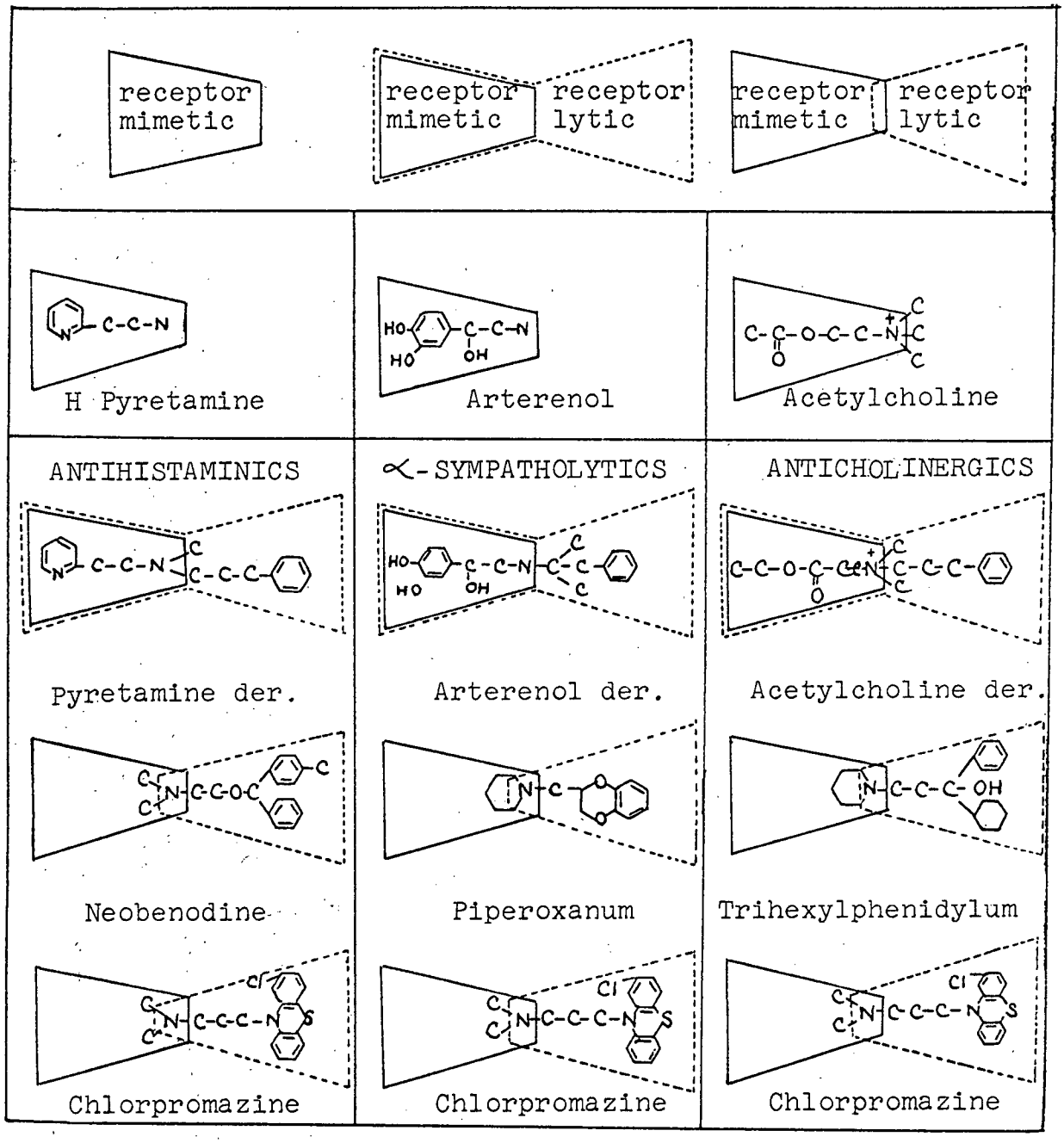
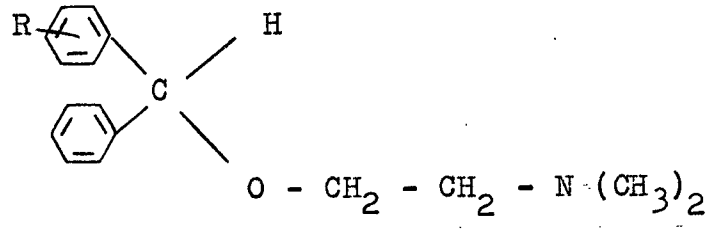


TABLE IV

USE OF SUITABLY PLACED ALKYL SUBSTITUENTS

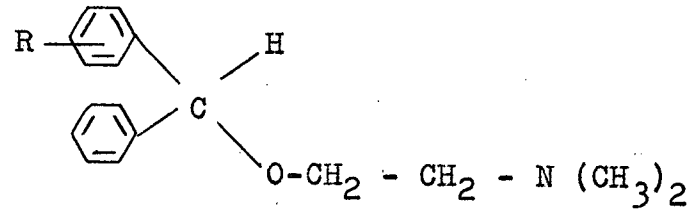
TO SEPARATE BIOLOGICAL EFFECTS



	Relative Action Against (Guinea Pig Ileum)	
R	Histamine	Acetylcholine
H	1	1
o-CH_3	0.2	2.1
o-C_2H_5	0.1	4.2
o-C_3H_7(n)	0.1	4.9
o-$CH(CH_3)_2$	0.1	6.5
o-$C(CH_3)_3$	0.05	33.0
p-CH_3	3.7	0.4

TABLE V

USE OF OPTICAL ISOMERISM TO SEPARATE BIOLOGICAL EFFECTS



R	Relative Action Against (Guinea Pig Ileum) Histamine	Acetylcholine
H	1	1
- C(CH3)(CH3)(CH3)		
(±)	0.08	26.0
(-) Isomer	0.06	50.0
(+) Isomer	0.06	00.3

PART II

STATEMENT OF PROBLEM

The purpose of this investigation is to prepare a homologous series of cycloalkyl analogues of diphenhydramine in an attempt to correlate the pharmacological activity of the analogues to the increasing strength of Van der Waals bonding of the drug molecule to the receptor site as the area beneath the cycloalkyl ring gradually increases. In this manner, it is hoped to gain some information regarding importance of dimensional requirements and the effect of Van der Waals bonding on pharmacological activity of the part of the anthistamine receptor which is complementary to the nucleus moiety of the drug molecule.

Indications of the importance of area or strength of Van der Waals bonding of the drug molecule to the antihistamine receptor is the fact that in the phenothiazine derivatives, minor structural changes of the chain attached to the heterocyclic nitrogen which causes a difference in area beneath the compound produces a change in its predominent pharmacological activity. When the dialkylamino group in phenothiazine is the essentially flat dimethylamino or pyrrolidino groups, antihistaminic activity is predominent, while puckered diethylamino and piperidino groups lead to compounds with

other properties which seem to influence acetylcholine-type transmission in the central nervous system. Similarly, dialkylaminoethyl chains are chiefly antihistaminic, some of the most potent antihistaminics belonging in this group, but in N-(3-dialkylaminopropyl) derivatives, selective central depressant activities predominate (8). It is assumed that this is due to the dialkylaminopropyl chain assuming a conformation which permit bonding to the cyclic sulfur atom (31).

Since aromatic and unsaturated heterocyclic rings can frequently be exchanged without change of fundamental quality and magnitude of biological activity, the Van der Waals forces available in such rings are of the same order of magnitude and the areas covered by these rings are similar so that the same loose and supplemental attachment to the receptor can be attained (31). Thus, although the chemical properties of the cycloalkyl derivatives will necessarily differ from those of the parent aromatic compound, the cycloalkyl homologues permit a study of the effect of variations in area beneath the ring, which is of interest here.

If area does indeed play a significant role in antihistamine receptor interactions, then a gradation in activity should be evident as the area is increased; the lowest activity should be exhibited by the cyclopropyl analogue and the highest by the cyclooctyl analogue. If both rings in the antihistaminic nucleus are utilized for bonding to the

receptor, the two rings must be coplanar. On the other hand, if only one ring is involved in bonding, then variations in area beneath the second ring should little affect the activity of the compounds. None of these compounds, however, should reach the optimum activity shown by diphenhydramine, since hydrogenation of the ring decreases activity. Although hydrogenated compounds, such as cyclohexyl analogues of diphenhydramine, have variously been reported as "inactive" or "considerably less active," this is relative to Benadryl, and does not preclude the use of the cycloalkyl analogues in the determination of area requirements. In fact, a preliminary pharmacological test of the cyclohexyl analogue prepared in this study showed considerable antihistaminic activity.

PART III

CHEMISTRY OF ALICYCLIC COMPOUNDS

As the term alicyclic implies, these substances exhibit the general behaviour of aliphatic compounds and contain a ring or cycle of carbon atoms, which influences the thermochemical stability and reactivity of the compounds.

From a consideration of the heats of combustion per CH_2 group of the alicyclic compounds (Table VI) (42), strain appears to exist in the 3- and 4-membered rings where the deviation, d, from the normal tetrahedral valence of carbon of $109^{\circ}28'$ is positive, but is negligible in 6-membered and larger rings where d is negative.

TABLE VI

HEATS OF COMBUSTION PER CH_2 GROUP OF ALICYCLICS $(CH_2)_n$

n:	3	4	5	6	7	8
molec. heat of combustion kcal/CH_2:	168.5	165.5	158.7	157.5	158.3	158.7
d:	$+24^{\circ}44'$	$+9^{\circ}44'$	$+0^{\circ}44'$	$(-5^{\circ}16')$	$(-9^{\circ}33')$	$(-12^{\circ}46')$

Cyclopropane with the highest heat of combustion per CH_2 group has the lowest thermochemical stability and is the most strained. Cyclobutane with a lower value is less strained; cyclopentane is still less strained. With medium-sized rings,

there is a rise in the heat of combustion, which then falls to the level of the 6-membered ring.

The explanation is that the 3-, 4- and 5-membered rings are planar, while the larger rings are puckered to relieve any possible strain due to departure of the bond angles from the preferred values. Evidence (43) has been presented, however, that the 4- and 5-membered rings are not exactly planar, since a slight puckering while increasing the strain, decreases the internal energy (thus increases stability) by reducing the repulsive H:H interactions (44)(45). Thus a non-planar equilibrium structure for equatorially-substituted bromocyclobutane has been obtained by microwave spectrum. Similarly, the microwave spectrum of cyclopentane shows it to have a non-planar equilibrium carbon skeleton with a dihedral angle between the two skeletal planes of 22° (46). From the combined physico-chemical data of the cyclopentane molecule, Pitzer (47)(48) has suggested that it exists in a puckered conformation, known as the envelope form.

In cyclohexane, two different strain-free conformations are possible, the boat form and the chair form, energy of the former being 5.5 kcal/mole (44) above the latter. With rings containing more than six atoms, the favored chair conformation of cyclohexane in which each carbon-carbon single bond is staggered is no longer possible, and a number of these bonds are more or less eclipsed. Mutual repulsions of hydrogen atoms arise so that the medium-sized rings of C_8 to C_{12}, though

puckered, are not entirely strainless (45). Larger rings, however, can again assume the staggered conformation.

Thus, the cyclopropane ring is easily opened by hydrogenation, while hydrogenation of cyclobutane requires a higher temperature. Cyclopentane and cyclohexane are fully resistant to hydrogenation and are as inert as the normal alkanes (42). Rings with five or more carbon atoms are characterized, as compared with the 3- and 4-membered rings, by a special stability towards splitting of the ring (49). The chemistry of cycloheptane and of cyclooctane is not as fully developed as the smaller ring compounds since their derivatives are prepared with considerably greater difficulty.

The physical and chemical properties of cycloalkyl derivatives as a function of ring size has been investigated, and on the whole, the properties show reasonably smooth gradations with ring size (50).

PART IV

DISCUSSION

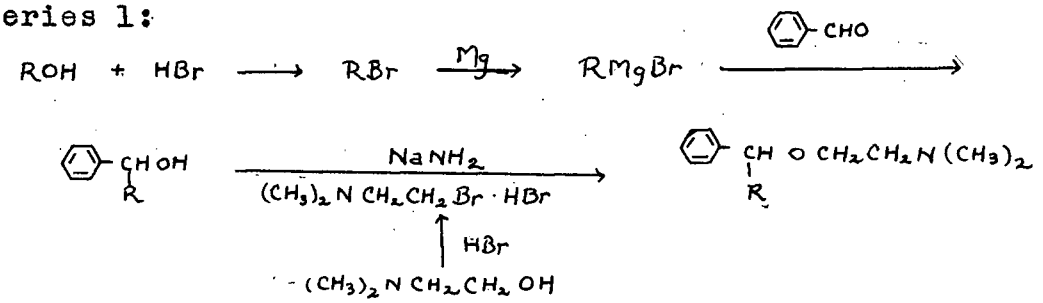
In the first series of cycloalkyl analogues, the cyclobutyl intermediate was prepared by way of a Friedel-Crafts reaction. Benzene was acylated with cyclobutylcarboxyl chloride with anhydrous aluminum chloride as catalyst to yield the ketone, which is then reduced to cyclobutylphenylcarbinol with lithium aluminum hydride. The intermediates of the other members of this series, except cyclopropylphenylcarbinol which is commercially available, were formed in a Grignard reaction of benzaldehyde on the cycloalkyl bromide. Bromination of the cycloalkanol was carried out with aqueous hydrobromic acid. The cycloalkylphenylcarbinols were then condensed with 2-dimethylaminoethylbromide hydrobromide in the presence of sodium amide.

In the second series of dicycloalkyl analogues, dicyclohexylcarbinol was prepared in a two-step process: cyclohexanecarboxaldehyde was formed through the action of ethyl orthoformate on cyclohexylmagnesium bromide, which was subsequently reacted with cyclohexylmagnesium bromide to give the carbinol. A superior method was a one-step process in which the Grignard reagent was treated with ethyl formate to yield the dicycloalkylcarbinol directly. The secondary

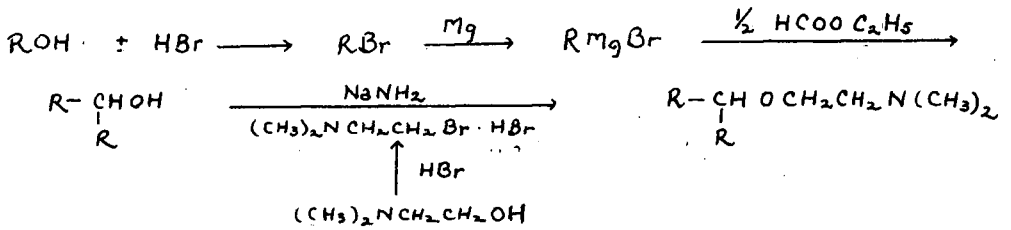
carbinols were then reacted with 2-dimethylaminoethylbromide hydrobromide with sodium amide as condensing agent. An alternate method was employed in this series, with the object of improving the yields. Dicycloalkylmethyl bromide, prepared by bromination with aqueous hydrobromic acid, was condensed with 2-dimethylaminoethanol in the presence of sodium amide.

The general routes in the syntheses of these analogues are as follow:

Series 1:

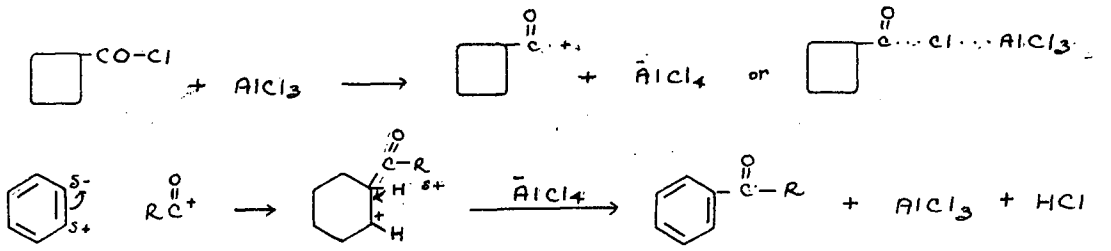


Series 2:



where R = cycloalkyl

In the Friedel-Crafts acylation of benzene, the reaction proceeds by way of an actual or potential carbonium ion, formed by interaction of the catalyst with the acylating agent. The carbonium ion then reacts with the aromatic nucleus.



The amount of catalyst required is somewhat more than a molecular equivalent since it is capable of forming rather stable complexes with carbonyl groups and the aluminum chloride is then unavailable for catalyzing the acylation reaction. Thus it is necessary to use a full molecular equivalent for each carbonyl group in the product (51). Since benzene is one of the reactants and reactions are effected in it with maximum speed, excess benzene is used as solvent. An important factor in Friedel-Crafts condensations is the purity of the catalyst. Presence of ferric chloride impurity decreases the yield and attack of moisture during storage decomposes the extremely hygroscopic powder (52). These factors probably account for a lower yield than expected (45.7%). The yields of cyclobutylphenylketone reported in the literature differ widely: 35% - 55% (53) and 81% (54).

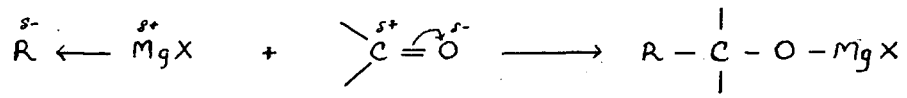
The lithium aluminum hydride reduction of cyclobutylphenylketone gave a good yield and complete reduction, as evidenced by the infrared spectrum. However, reduction of cycloheptanone was incomplete, in both methods used, that of Nystrom and Brown (55) and that of Royals and Neal (56). Since the boiling point of cycloheptanol differs by only 5.7° from that

of cycloheptanone, it could not be collected in a pure fraction and removal of the ketone by precipitation with sodium bisulfite was necessary. Perhaps a longer period of refluxing of the less reactive cycloheptanone may effect complete reduction.

Bromination of the cycloalkanols was carried out with halogen acid rather than with phosphorous halides since the latter reagent produces more impurities (57). The bromides are preferred to the cycloalkyl chlorides, since Grignard reagents are formed more rapidly from the bromides. In the Kamm and Marvel method (58), sulfuric acid is employed as a means of increasing the yield by removal of water from the equilibrium reaction. It also forms an alkylsulfuric acid which reacts with hydrobromic acid more readily in the slower reactions of high molecular weight alcohols. Although sulfuric acid tends to dehydrate secondary alcohols, the main difficulty encountered was formation of an emulsion when washing the product with sulfuric acid to remove unreacted alcohol by converting it to alkyl acid sulfate and to remove unsaturated products. To lessen the emulsion-forming tendency, it has been suggested (59) to use gaseous hydrogen bromide. Also, the product is first washed with sulfuric acid, then with methanol containing ammonia to neutralize the acid, and finally with methanol. McCullough and Cortese (60) recommended that the alcohol and hydrobromic acid reagents be mixed and left standing for 10 days in a stoppered flask.

After this period the product is washed with sodium hydroxide and sodium chloride to minimize emulsion formation. Though a product of higher purity was obtained, the yield was considerably lower than that prepared by other methods. These authors claim that halides prepared by the aid of sulfuric acid tend to spoil more easily on keeping, developing colors and free halogen acids. The best method for obtaining cycloalkyl bromides is that proposed by Norris (61) in which one mole of alcohol is reacted with four moles of acid (any greater excess is of no advantage) and hydrobromic acid is used to remove unchanged alcohol. Emulsion formation still occur using this method, but a great deal less than in the first method and the yields are substantially higher than in the second method. It appears that by allowing the mixed reagents to stand overnight in a stoppered flask before refluxing, and increasing the period of reflux, a higher yield of product is obtained.

In the Grignard reaction with carbonyl compounds, the Grignard reagent can be viewed as a source of the carbanion, $\bar{R}$, which is extremely nucleophilic. The carbanion adds to the carbonyl function:



In reality, Grignard reagents are extremely complex, many structures occurring in a solution of the reagent. The reagent may dissociate into carbanion, free radicals or

dialkylmagnesium compounds, rapidly establishing the following equilibria:

$$R^- + \bar{M}gX \rightleftharpoons R-MgX \rightleftharpoons R\cdot + \cdot MgX$$
$$\Downarrow$$
$$\tfrac{1}{2} R_2Mg + \tfrac{1}{2} MgX_2$$

It has been shown that both the anion and the cation of the Grignard reagent are complexes containing magnesium. The anions are probably complexes of the types:

$$R-\underset{R}{\bar{M}g}-X \qquad R-\underset{R}{\bar{M}g}-R \qquad X-\underset{R}{\bar{M}g}-X$$

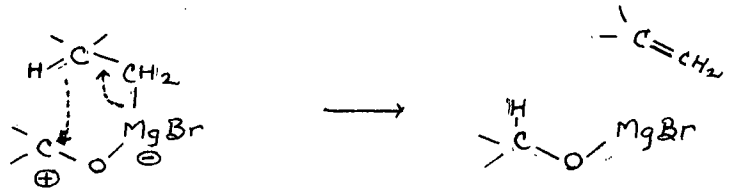
in which R^- is coordinated with RMgX, R_2Mg and MgX_2. The cations are probably complexes of MgX^+ with ether and the various halogen-containing species, such as: (62)

$$\left[\begin{array}{c} OEt_2 \\ \downarrow \\ Et_2O \rightarrow Mg - X \\ \uparrow \\ OEt_2 \end{array}\right]^+ \qquad \left[\begin{array}{ccc} OEt_2 & & OEt_2 \\ \downarrow & & \downarrow \\ R-Mg-X' & \longrightarrow & Mg-X \\ \uparrow & & \uparrow \\ OEt_2 & & OEt_2 \end{array}\right]^+$$

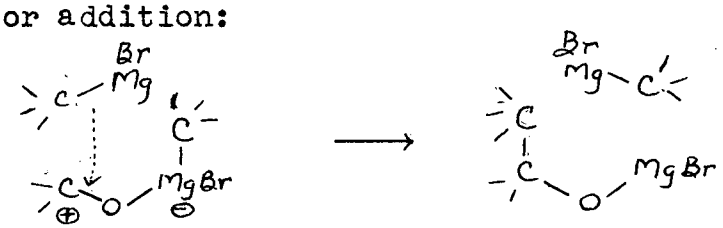
It appears probable that Grignard reagents react with carbonyl compounds by a mechanism involving coordination of the reagent with the carbonyl molecule, then intermolecular transfer of the alkyl group from a second molecule of Grignard reagent to the Grignard-ketone complex. However, an intramolecular transfer of an alkyl group within the coordination complex may also occur, depending upon the structures of the particular reactants and the experimental conditions, leading to abnormal Grignard reaction products (62). Thus steric hindrance due to increased size and complexity of the alkyl

group in the Grignard reagent and in the carbonyl may prevent the approach of a second molecule of the Grignard reagent to the carbonyl carbon and prevent the normal addition reaction, so that reduction and enolization increases at the expense of addition (63). In a study of steric effects on the reducing action of a number of Grignard reagents on benzophenone the Grignard reagent from cyclohexyl gave 7% reduction, while that from cyclopentyl gave 94% reduction (64). The cyclohexyl ring in its preferred chair conformation would have an equatorial halide which is more accessible and less hindered than a halide on the approximately planar cyclopentyl ring. Swain and Boyles (65) proposed addition of a Lewis acid, magnesium bromide, to the carbonylprior to addition of Grignard reagent to increase the yield of addition to a hindered ketone. They reasoned that since magnesium bromide is a slightly stronger Lewis acid than the Grignard reagent, it should complex preferentially with the ketone, polarizing it even more strongly than would a Grignard reagent. It would then play the role of the first molecule of Grignard reagent which complexes with the ketone in the normal addition mechanism. Since the magnesium bromide-ketone complex would be incapable of reduction by intramolecular rearrangement, it should be more susceptible to attack by an external molecule in an addition reaction. By this means, they were able to increase addition, and reduce both reduction and enolization.

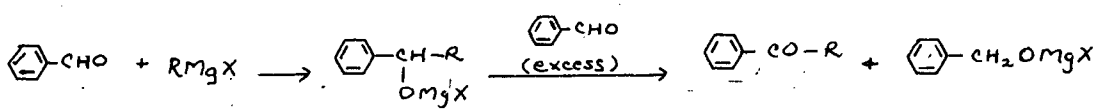
Mechanism for reduction:



Mechanism for addition:



Another important factor in Grignard reactions with an aldehyde, is that an excess of Grignard reagent must always be present in order to obtain good yields of secondary alcohols. If excess aldehyde is present, it is reduced to a primary alcohol by the halomagnesium alkoxide (I) produced by normal addition of the Grignard reagent to the aldehyde, which is itself oxidized to a carbonyl compound:



(I)

To avoid excess aldehyde the usual procedure is to carry out the reaction by a normal method of addition, that is, by adding the aldehyde to the Grignard reagent, while other sources (66) recommend avoiding any temporary excess of Grignard reagent by an inverse method of addition if there is a possibility of reduction. In these experiments, both methods of addition were tried, and the inverse addition in the original Lewis acid method was maintained, when magnesium

bromide was used. The carbonyl impurities present in some of the carbinol products synthesized in these experiments, no doubt arose from the presence of excess aldehyde since Grignard reagents are usually formed in much less than quantitative yields. A means of correcting this is to determine the amount of Grignard reagent in the solution by the generally accepted acid titration method and to adjust accordingly the amount of aldehyde necessary for the reaction.

Besides reduction, caused by steric hindrance, and the presence of excess aldehyde lowering the yields of secondary carbinols, another factor is the side reactions which occur from the formation of relatively stable cycloalkyl free radicals. These free radicals either disproportionate to cycloalkene and cycloalkane (disproportionation products) or dimerizes to dicycloalkyls (Wurtz products) (67).

The experimental conditions employed in most of the Grignard reactions in these experiments were those proposed by Gilman and Meyers (68) as optimal: a 10% excess of magnesium turnings and iodine catalysts were used. Slow rates of addition of halide were employed to prevent an increase of the Wurtz coupling side reaction (69):

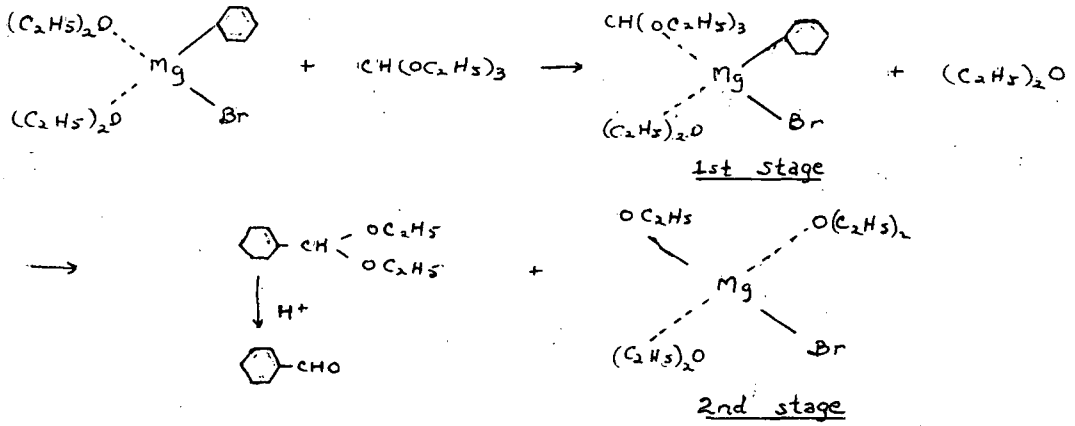
$$RMgX + R'X \longrightarrow MgX_2 + RR'$$

Phenylurethan and 3,5-dinitrobenzoate derivatives of the two carbinols which had not been previously synthesized, cycloheptylphenylcarbinol and cyclooctylphenylcarbinol, were unattainable probably due to the presence of traces of

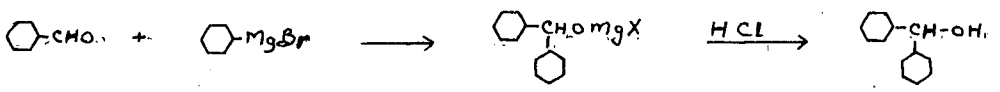
moisture in the samples. Therefore, cycloheptylphenylcarbinol itself was analyzed. In samples of cyclooctylphenylcarbinol, the carbonyl impurity could not be removed to obtain a sample of sufficient purity for analysis. Also, there is some doubt as to whether the compound formed is the desired cyclooctylphenylcarbinol or whether it is an intermediate.

Organolithium compounds are produced by very much the same procedure as is used for the preparation of a Grignard reagent. In some cases, the organolithium reactions offer advantages over the Grignard reagent either because of more satisfactory formation of the reagent from the halide or because of occurrence of fewer side reactions. Since the lithium atom is smaller than the magnesium atom, steric hindrance should be less. However, a reaction of cyclopentyllithium on benzaldehyde produced no results.

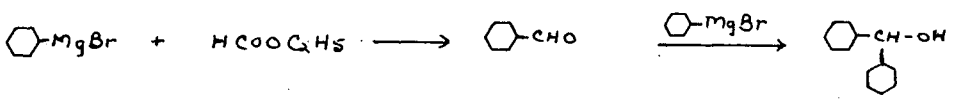
The cyclohexanecarboxaldehyde used in formation of dicyclohexylcarbinol was prepared via the acetal by reaction of ethyl orthoformate on cyclohexylmagnesium bromide. In both methods employed, poor yields resulted. This is probably because after refluxing the reaction mixture and during removal of ether a point was not arrived at in which a vigorous reaction sets in, according to a study (70) of the optimum conditions in the reaction between RMgX and $HC(OEt)_3$. It is necessary that the critical point be reached since the reaction proceeds in two-stages (71):



The cyclohexanecarboxaldehye was then reacted with cyclohexylmagnesium bromide to yield dicyclohexylcarbinol:

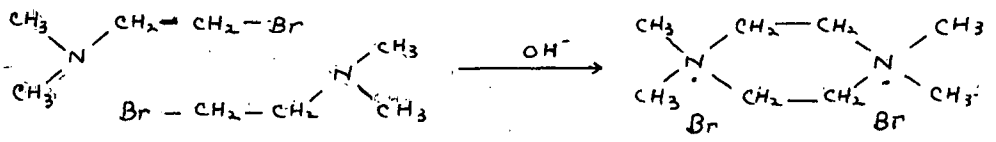


A superior method (72) of preparing dicycloalkylcarbinols is the action of ethyl formate on the Grignard reagent. The aldehyde which forms, immediately reacts with another mole of Grignard reagent to produce the dicycloalkylcarbinol:



The addition reaction of esters is analogous to that of the aldehydes (73). When excess ethyl formate relative to the Grignard reagent was used, the compound obtained was a liquid instead of a solid and the infrared spectrum showed a strong carbonyl peak and weak carbinol absorption. However, excess Grignard reagent is also to be avoided, since this leads to increased reduction (72). Attempted syntheses of dicycloheptylcarbinol employing various quantities of ethyl formate, produced the highly contaminated carbonyl product. Steric factors may be a significant factor in the synthesis of this intermediate.

In the condensation reactions of the analogues, the sodium alkoxide was first prepared by the action of a sodium dispersion in xylene on the carbinol. The sodium derivative was then reacted with the free base obtained by treating a concentrated solution of 2-dimethylaminoethylbromide hydrobromide with solid sodium hydroxide followed by extraction of the free base with xylene. However, the lack of any results by this method may be due partly to the difficulty in forming the sodium derivative. As the molecular weight of the carbinol increases, its reaction with sodium proceeds with decreasing readiness since the functional hydroxyl group is a smaller part of the whole molecule. A very finely dispersed form of sodium is therefore necessary in these reactions to make available the inherent reactivity of sodium. This could not be achieved by vigorous shaking of the flask containing molten sodium in xylene, and the particles formed were mostly coarse granules. Secondly, there is a strong tendency for 2-dimethylaminoethylbromide to dimerize in concentrated alkaline solutions leading to formation of a quaternary piperazinium salt (74):



By using sodium amide instead of a sodium dispersion as the condensing agent and the hydrobromide salt, from which the base is liberated <u>in situ</u> by an extra molecular equivalent

of sodamide, results could be obtained in most cases. Again, a very finely divided form of the amide is required for these slow reactions involving high molecular weight compounds. Sodamide is extremely hygroscopic and very susceptible to oxidation with the formation of explosive mixtures. During storage it deteriorates in time and loses much of its activity. Ideally, it should be generated in situ and simultaneously ground by a laboratory ball mill. For these reasons, an extra molecular equivalent of sodamide was added along with the hydrobromide salt in some of the condensation reactions. There appears to be considerable variability in the sodium amide condensations as evidenced by the fact that even when the same lot of intermediate was used and the reaction was run under what was believed to be the same experimental conditions, the results varied. For example, the products of four runs of cyclopropyl analogue gave different refractive indices. This may be due to a different rate of reaction from the varying particle size of the hand-ground sodamide. The slowness of the reaction is apparent from the fact that even after a period of two weeks of warming the sodamide and carbinol mixture, ammonia evolution, which should cease upon complete formation of the sodium derivative, could still be detected. When no analogue was obtained in these reactions, it was observed that a color change in the sodium derivative had occurred during the warming period. For instance, the colors in both the cycloheptyl analogue, Lot I and in the cyclopropyl analogue, Lot III, had changed overnight

from orange to yellow. In cyclopropyl analogue, Lot III, a color change from orange-brown to red had occurred overnight and although a compound was obtained, its infrared spectrum did not follow the pattern of the other analogues. The elemental analysis and the fact that this product yielded the picrate derivative while the other cyclopropyl analogues would not, indicate that Lot III is not the desired product.

In the dicycloalkyl series, sodium alkoxide formation is slower than in the first series, since these carbinols are less reactive than those containing the aromatic ring. This is believed to be the major obstacle in the extremely low yield of dicyclohexyl analogue. Even after four days of heating the sodamide and carbinol mixture, approximately half of the carbinol could be recovered, along with substantial amounts of two other fractions. The infrared spectra of the recovered carbinol compared well with that of the dicyclohexylcarbinol used in the reaction (Part VI, Figures 24 and 25).

An alternate route was then attempted, in which the sodium derivative of 2-dimethylaminoethanol was condensed with the bromide of the secondary carbinols. The electron-releasing effect of the rings in dicycloalkylcarbinols should favor the polarization of the C-O bond with formation of a carbonium ion and a hydroxyl group. A bromide ion could then be easily substituted in an SN_1 nucleophilic displacement reaction. Generally, substitution in aliphatic compounds at

a secondary carbon proceeds simultaneously by both SN_1 and SN_2 mechanisms, with SN_1 being slightly more important. However, in polar solvents and where steric hindrance may be present, an SN_1 reaction becomes predominant (62). A similar method is formation of the p-toluenesulfonate. The tosyl group like the bromide ion is a good leaving group and undergoes nucleophilic displacement reactions readily (75). The bromide of dicyclopropyl- and dicyclohexylcarbinol was condensed in this manner. In the former case, the analogue was obtained, while in the latter case, no product formed. This is probably due to the fact that the sodium derivative of 2-dimethylaminoethanol was not refluxed in the dicyclohexyl analogue condensation, while in the dicyclopropyl condensation it was refluxed 4 hours in addition to the warming period.

Derivatives of these cycloalkyl and dicycloalkyl analogues appear to be very hygroscopic so that isolation and purification of the compounds were impossible. The most suitable derivative for these compounds, with the exception of the cyclopropyl and dicyclopropyl analogues, is the chloroplatinate, which is readily recrystallized from ethanol. The derivatives of the cyclopropyl and dicyclopropyl compounds either would not form or would oil out. Therein lies the difficulty in obtaining a suitable analysis of these compounds. Although the infrared spectra of these compounds vary somewhat, with the exception of Figures 2 and 18 in Part VI, they are of the same general pattern as the analogues characterized by

analysis, and are believed to be the desired products.

The original synthesis of diphenhydramine by Rieveschl was the reaction of benzhydryl bromide (obtained by treating diphenylmethane with bromine in the presence of light and heat) with dimethylaminoethanol in the presence of anhydrous potassium carbonate:

$$(C_6H_5)_2CH_2 \xrightarrow[light]{Br_2} (C_6H_5)_2CHBr + HOCH_2CH_2N(CH_3)_2$$

$$\xrightarrow[140^\circ]{K_2CO_3} \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!>\!CHOCH_2CH_2N\!<\!\begin{matrix} CH_3 \\ CH_3 \end{matrix} + CO_2\uparrow + KBr$$

However, in view of the fact that the cycloalkylphenylcarbinols and dicycloalkylcarbinols are produced in low yields and bromination of these compounds would further decrease the amounts of reagents available for the condensation reactions, this method appeared impractical for syntheses of these analogues.

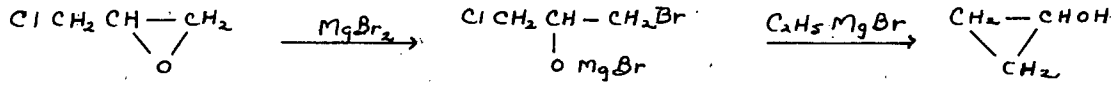
Diphenhydramine has also been reported (76) as the result of a molecular arrangement of benzhydryldimethyl-2-hydroxyethylammonium chloride in which the benzhydryl group migrated from the nitrogen atom to the oxygen atom:

$$[(C_6H_5)_2CHN(CH_3)_2CH_2CH_2OH]Cl$$

$$\downarrow \Delta$$

$$(C_6H_5)_2CHOCH_2CH_2N(CH_3)_2 \cdot HCl$$

The synthesis of cyclopropanol for use in the general reaction scheme was attempted although many experiments to prepare this compound resulted only in the formation of allyl alcohol (77). The method originated by Cottle and Magrave (78) along with the modifications proposed by Roberts and Chambers (79) were used. Epichlorohydrin was reacted with magnesium bromide to yield the propoxide (II), which is treated with ethylmagnesium bromide:



(II)

No cyclopropanol could be obtained. This is not surprising in view of the fact that Stahl and Cottle (80) reported a yield of 6% crude cyclopropanol in their experiment, and although Roberts and Chambers reported a 46% yield of cyclopropanol, their product did not give a satisfactory elemental analysis.

PART V

EXPERIMENTAL*

A. 2-DIMETHYLAMINOETHYLBROMIDE HYDROBROMIDE (81)

Aqueous 48% hydrobromic acid was distilled until 10 ml. of the distillate weighed at least 14.2 g. To 700 ml. (5.9 moles) of ice-cold redistilled 48% hydrobromic acid, 142.4 g. (1.6 moles) of 2-dimethylaminoethanol was slowly stirred in, and the rise in temperature ignored. The reaction mixture was distilled with the aid of a fractionation column until 185 ml. was collected. Without reversing the condenser, the heat was reduced so that the mixture refluxed gently for 1 hour, and then further distilled until another 70 ml. was collected. The procedure was repeated until further 60, 30, 25, 15, 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. Up to this point, the process may be interrupted at any time. Now 230 ml. of distillate was collected. The total volume of distillate collected should be between 627 and 633 ml.; if less is distilled, the yield is seriously impaired, if more, decomposition sets in.

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* Boiling points and melting points are uncorrected. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were recorded on a Unicam Sp.200 Infrared Spectrophotometer.

After the mixture had cooled to approximately 70°, the residue in the flask was thoroughly mixed with 330 ml. of acetone and the mixture refrigerated overnight. The solid which has crystallized was filtered by suction. It was washed well with acetone, air-dried until the odor of acetone just vanished and stored in a dessicator. The white crystals weigh 327.7 g. For a second crop, the filtrate was concentrated to about 100 ml. and seeded to afford another 2.5 g. of product. The total yield was 88.6%. The crude product was recrystallized from a mixture of 5 parts of 95% ethanol and 8 parts of ethyl acetate. M.p. of recrystallized product, 186-187°, lit. (82) m.p. 186-187°.

B. CYCLOPROPYL COMPOUNDS

1. Cyclopropanol

In a 3-necked flask provided with mechanical stirrer, reflux condenser and dropping funnel, with the openings protected from moisture by calcium chloride tubes, was placed 2.43 g. (0.1 g. atom) of magnesium turnings. Sufficient anhydrous ether was added to cover the metal. A few mls. of ethyl bromide was added to the flask which was immersed in an ice-salt bath. The cooling bath was removed and the mixture allowed to come to room temperature. This procedure was repeated until the reaction was initiated, as indicated by the appearance of a cloudiness. The remainder of the 10.9 g. (0.1 mole) of ethyl bromide in 12.5 ml. of

anhydrous ether was added dropwise and the mixture stirred for 15 minutes (83).

The propoxide was formed by adding 9.3 g. (0.1 mole) of epichlorohydrin to 18.4 g. (0.1 mole) of anhydrous magnesium bromide (prepared by dehydration of the hydrous salt) in anhydrous ether. It was then treated with the ethylmagnesium bromide prepared above. The reaction mixture was allowed to stand at room temperature until there was no evidence of gas evolution. The contents of the flask was poured into iced ammonium chloride solution (10%). The ether layer was separated and extracted with eight 10 ml. portions of water. The aqueous layer and extracts were combined, saturated with sodium chloride and continuously extracted with ether for 2 days. The ether extract was dried for 4 hours over calcium sulfate and then fractionally distilled. No product could be obtained (77)(78).

2. 2-(α-Cyclopropylbenzyloxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 4.9 g. (0.135 mole) of sodamide in 62 ml. of anhydrous benzene, was added a solution of 9.6 g. (0.065 mole) of cyclopropylphenylcarbinol (Aldrich Chemical Co.) in 62 ml. of anhydrous benzene. The mixture was heated with stirring in an oil-bath at 60-70° for 26 hours. When cool, 15.7 g. (0.0675 mole) of 2-dimethylaminoethyl-bromide hydrobromide was added. The mixture was refluxed with stirring for 81 hours. The cooled reaction mixture was poured into 100 ml. of water and acidified with 10% HCl. The

benzene layer was separated and extracted once with 25 ml. of water. The aqueous extract of benzene was combined with the dilute acid solution and washed once with 25 ml. of ether. Solid potassium carbonate was added to make the aqueous solution basic. The free base was extracted with six 50 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. The solvent was removed by flash evaporation and the residue distilled to give three pale-green fractions with a fish-like odour:

FRACTION	B.P.(6.5mm.)	N_D^{20}	WT.
I	126-127°	1.5195	0.4 g.
II	127-131°	1.5195	0.8 g.
III	131-135°	1.5130	1.3 g.

The infrared spectra of Fraction I and II were identical and very similar to that of Fraction III. All the spectra possessed absorption maxima at 1045 cm^{-1} assigned to C-N stretching and at 1110 cm^{-1} characteristic of the C-O-C group. The bands near 860 cm^{-1} and at 1045 cm^{-1} may be due to cyclopropyl ring deformations. All three fractions appear to be the cyclopropyl analogue, the difference being that Fraction III is of higher purity. The yield of product (three fractions) was 17.6%.

In Table VII are summarized various reaction conditions which were tried in an attempt to increase the yield of product.

TABLE VII

VARIOUS REACTION CONDITIONS IN THE SYNTHESIS OF CYCLOPROPYL ANALOGUE

LOT	SOLVENT	WARMING TIME	REFLUX TIME	% YIELD	B.P.	N_D^{20}
I	benzene	1 day	4 days	17.6	126-135(6.5mm)	1.5130-95
II	toluene	14 days	3 days	0*		
III	toluene	3 days	1 day	0		
IV	toluene	1 day	6 days	2.4	147-148(18mm)	1.4992
V	toluene	1 day	6 days	2.8	131(15mm)	1.5182

* A compound was obtained, which had a boiling point of 128-132°C(7.5mm.) and a n_D^{20} 1.5273. Analysis of the picrate, m.p. 169-170°, and the infrared spectrum of this substance indicated that it is not the cyclopropyl analogue.

Attempts at preparing various derivatives - hydrogen chloride, hydrogen sulfate, acid citric, methiodide, chloroplatinate, aurichloride, 3,5-dinitrobenzoate - of the cyclopropyl analogue were unsuccessful.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found (Lot I): C, 77.61; H, 9.30; N, 6.03. Found (Lot IV): C, 74.24; H, 9.44; N, 6.09. Found (Lot V): C, 76.56; H, 8.96; N, 5.89. Calcd. for $C_{17}H_{24}N_4O_8$: C, 49.51; H, 5.87; N, 13.58. Found (Lot II): C, 49.40; H, 4.12; N, 13.51.

C. CYCLOBUTYL COMPOUNDS

1. Cyclobutanecarboxyl Chloride (85)

A mixture of 50 g. (0.5 mole) of cyclobutanecarboxylic acid and 100 g. (0.85 mole) of thionyl chloride was refluxed for 2 hours. The excess thionyl chloride was removed by distillation and the residue distilled to give 41.2 g. (69.5%) of product, b.p. 130-140° at atmospheric pressure, n_D^{25} 1.4501, lit. (75) n_D^{25} 1.4528.

2. Cyclobutylphenylketone (54)

In a 250 ml. 3-necked flask equipped with mechanical stirrer, a dropping funnel protected with a drying tube, and a reflux condenser connected to a gas outlet which passed through a calcium chloride tube, a solution of 26.6 g. (0.2 mole) of anhydrous aluminum chloride in 200 ml. of anhydrous benzene was gently refluxed. Nineteen grams (0.16 mole) of cyclobutanecarboxyl chloride in 50 ml. of anhydrous benzene was added with stirring. The mixture was refluxed for one and three-quarter hours. It was then poured over 1 l. of chipped ice. The layers were separated and the aqueous phase was extracted with benzene. The combined benzene fractions were dried over magnesium sulfate. The solvent was evaporated and the residual oil distilled to give 11.7 g. (45.7%) of a colorless compound, b.p. 128-129°(14 mm.), n_D^{25} 1.5430, lit. (54) b.p. 116-118°(7 mm.), n_D^{25} 1.5453.

The infrared spectrum of this compound showed a strong band at 1680 cm^{-1} characteristic of aryl ketone vibration frequencies.

3. Cyclobutylphenylcarbinol (86)

In a 3-necked flask was placed a suspension of 0.83 g. (0.02 mole) of lithium aluminum hydride in 110 ml. of anhydrous ether. A solution of 11.7 g. (0.07 mole) of cyclobutylphenylketone in 11 ml. of anhydrous ether was added dropwise at 0° with stirring. After addition was complete, refluxing was continued for 1 hour. The mixture was cooled to 0° and 15 ml. of water cautiously added, followed by 36.5 ml. of 20% sulfuric acid. The layers were separated and the aqueous phase extracted several times with ether. The combined ether solutions were dried over calcium chloride. After the solvent was removed by flash evaporation, the residue was distilled to give 7.7 g. (65.3%) of product, b.p. 128°(13 mm.), n_D^{25} 1.5318, lit. (86) b.p. 120°(20 mm.).

The infrared spectrum of this compound showed a complete absence of the ketone absorption and had strong bands at 3450 cm^{-1} characteristic of OH stretching frequencies, and at 1010 cm^{-1} assigned to OH deformations of secondary carbinols.

4. 2-(α-Cyclobutylbenzyloxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 3.7 g. (0.095 mole) of sodamide in 50 ml. of anhydrous toluene, was added a solution of 7.7 g.

(0.048 mole) of cyclobutylphenylcarbinol in 50 ml. of anhydrous toluene. The mixture was warmed with stirring in an oil bath at 60-70° for 2 days. When cool, 1.9 g (0.048 mole) of sodamide and 11.1 g. (0.048 mole) of 2-dimethylaminoethylbromide hydrobromide was added. The mixture was refluxed for 6 days. The cooled reaction mixture was poured into water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with water. The aqueous extract was combined with the dilute acid solution and washed once with ether. Solid potassium carbonate was added to the aqueous solution until it was basic. The free base was extracted with six 50 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. After the solvent was removed by flash evaporation, the residue was distilled to give 2.8 g. (25%) of a pale yellow oil, collected in two fractions:

FRACTION	B.P.(16mm.)	N_D^{20}	WT.
I	153-154°	1.4991	1.8 g.
II	154-156°	1.4998	1.0 g.

The infrared spectra of both fractions show strong absorptions at 1115 cm^{-1} assigned to C-O-C vibrations and at 1070 cm^{-1} characteristic of C-N stretching frequencies.

2-(α-Cyclobutylbenzyloxy)-N,N-dimethylethylamine chloroplatinate: A solution of 0.25 g. of the amine in 5 ml. of 10% hydrochloric acid was slowly added with stirring to 5 ml. of a 25% aqueous solution of chloroplatinic acid. The

crystals began to separate at once. After standing 10 minutes in an ice-bath, the solid was separated and washed with cold water. The orange crystals were recrystallized from ethanol containing a drop of concentrated hydrochloric acid to prevent hydrolysis to yield a product melting at 145-145.5°.

Anal. Calcd. for $C_{30}H_{48}Cl_6N_2O_2Pt$: C, 41.11; H, 5.52; N, 3.20. Found: C, 41.43; H, 6.15; N, 3.22.

D. CYCLOPENTYL COMPOUNDS

1. Cyclopentyl Bromide

A mixture of 172.3 g. (2.0 moles) of cyclopentanol and 926 ml. (8.0 moles) of 48% hydrobromic acid was allowed to stand overnight in a stoppered flask and then refluxed 6 hours. The top bromide layer was separated, washed twice with 25 ml. portions of 48% hydrobromic acid, once with 25 ml. of water and twice with 25 ml. portions of 10% sodium carbonate solution. After drying the bromide over calcium chloride, it was distilled to yield 207.3 g. (69.6%) of a colorless liquid, b.p. 136.5-142°, n_D^{20} 1.4872, lit. (87) b.p. 136-138, n_D^{20} 1.4885.

2. Cyclopentylphenylcarbinol

In a 1 l. 3-necked flask equipped with mechanical stirrer, reflux condenser and dropping funnel, with the openings protected from moisture by calcium chloride tubes, was placed 33.8 g. (1.39 g. atom) of magnesium turnings

covered with anhydrous ether. A crystal of iodine and a few ml. of cyclopentyl bromide were introduced into the mixture. After the reaction was initiated as indicated by the appearance of a cloudiness, the remainder of the 183.3 g. (1.23 moles) of freshly distilled bromide in 735 ml. of anhydrous ether was added at a slow and uniform rate. The mixture was refluxed for 1 hour, after which time less than one-quarter of the magnesium remained.

To the Grignard reagent, was slowly added 130.5 g. (1.23 mole) of freshly distilled benzaldehyde in an equal volume of ether. Intermittent cooling was applied to moderate the vigorous reaction. After stirring the mixture until the reaction subsided, it was poured onto 100 ml. of ice-water and 1 l. of 10% hydrochloric acid slowly added. The layers were separated and the aqueous solution extracted with four 30 ml. portions of ether. The combined ether solution was dried over calcium chloride, the solvent was removed by flash evaporation and the residue distilled to give 8.5 g. (3.9%) of a bright-green viscous liquid, b.p. 141-148°(23 mm.) (most at 148°), n_D^{20} 1.5408, lit. (88) b.p. 142-143.5°(13 mm.), n_D^{20} 1.5412, and lit. (89), b.p. 148°(16 mm.), n_D^{20} 1.5369.

The infrared spectrum of this product has absorption maxima at 3450 cm^{-1} and 1040 cm^{-1} characteristic of OH stretching frequencies and deformations of secondary carbinols. However, the carbinol showed strong bands at 1700 cm^{-1} characteristic of carbonyl absorption. Therefore, with the object of

producing a compound free from carbonyl impurity and of increasing the yield of carbinol, alternate procedures were tried first, using lithium instead of magnesium and secondly, addition of a Lewis acid.

Lithium method: The solvent, n-hexane was washed with concentrated sulfuric acid and dried overnight over calcium chloride. A 3-necked flask was equipped with a stirrer, reflux condenser and dropping funnel with the openings protected with drying tubes, and was provided with an inlet for dry nitrogen. Seventy ml. of n-hexane was added to the flask, which was then flushed with dry nitrogen. The adhering oil on the lithium metal was wiped off and 1.39 g. (0.2 g. atom) was quickly weighed. It was pounded into a flat sheet, which was cut into small pieces and added to the reaction flask. A few ml. of a solution of 14.9 g. (0.1 mole) of freshly distilled cyclopentyl bromide in 50 ml. of n-hexane was introduced into the mixture. The flask was warmed a short period to initiate the reaction. The remainder of the bromide solution was slowly stirred in and the mixture refluxed for 1 hour. A mixture of 10.6 g. (0.1 mole) of freshly distilled benzaldehyde in 20 ml. of n-hexane was added dropwise. The reaction mixture was stirred an additional one-half hour. A small amount of water was cautiously added to hydrolyse the excess lithium. With the flask immersed in an ice-bath, 150 ml. of 5% hydrochloric acid was gradually added to dissolve the complex. The layers

were separated and the aqueous layer extracted with three 50 ml. portions of ether. The combined ether solution was dried over calcium chloride, the solvent was evaporated *in vacuo* and a tarry residue remained behind. No product could be obtained.

Lewis acid procedure: 56.5 g. (0.36 mole) of bromine was added slowly with continuous stirring to 8.6 g. (0.36 g. atom) of magnesium turnings in 105 ml. of anhydrous ether. After stirring the mixture for 2 hours, the bromine color was still evident. Freshly distilled benzaldehyde (16.7 g. 0.16 mole) was added dropwise and the mixture stirred an additional hour. Cyclopentylmagnesium bromide was prepared from 56.0 g. (0.38 mole) of bromide, 9.5 g. (0.39 g. atom) of magnesium turnings and 115 ml. of anhydrous ether. The reaction was initiated readily upon addition of a few ml. of the bromide. The Grignard reagent was stirred 2 hours, and then added at a slow and uniform rate to the Lewis acid. After the reaction mixture was stirred overnight, it was hydrolyzed by adding it slowly to 415 ml. of 10% sodium carbonate solution of 0° with good stirring. The layers were separated and the aqueous solution extracted with six 50 ml. portions of ether. The combined ether solution was dried 3 hours over sodium sulfate, the solvent was removed by flash evaporation and the brown viscous residue was distilled to give 7 g. (12.6%) of bright green viscous liquid, b.p. 134-141°(12 mm.), n_D^{20} 1.5330. A subsequent

run by this procedure where the Grignard reagent was stirred 4 1/2 hours and refluxed 2 hours, and the carbinol reaction mixture was stirred 1 hour, reduced the yield to 7.2%. In both cases the infrared spectra showed no carbonyl impurity.

3. 2-(α-Cyclopentylbenzyloxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 3.7 g. (0.094 mole) of sodamide in 50 ml. of anhydrous toluene, was added a solution of 8.0 g. (0.045 mole) of cyclopentylphenylcarbinol in 50 ml. of anhydrous toluene. The mixture was warmed in an oil-bath at 60-70° for 13 days. When cool, 1.9 g. (0.047 mole) of sodamide and 10.9 g. (0.047 mole) of 2-dimethylaminoethyl-bromide hydrobromide was added and the mixture refluxed for 3 days. The contents of the flask was then poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with water. The aqueous extract was combined with the dilute acid solution and washed once with ether. Solid potassium carbonate was added to the solution until it was basic. The free base was extracted with six 50 ml. portions of ether. After drying the ether extracts over sodium sulfate, the solvent was removed by flash evaporation, and the residue was distilled to give 5.0 g. (44.5%) of a pale green oil, b.p. 165-167°(9.5 mm.), n_D^{20} 1.5060.

The infrared spectrum of this compound has absorption maxima at 1110 cm^{-1} assigned to C-O-C vibrations and at 1070 cm^{-1} assigned to C-N stretchings.

2-(α -Cyclopentylbenzyloxy)-N,N-dimethylethylamine chloroplatinate: A solution of 0.25 g. of the amine in 5 ml. of 10% hydrochloric acid was slowly added with stirring to 5 ml. of a 25% aqueous solution of chloroplatinic acid. After standing 10 minutes in an ice-bath, the solid was separated and washed with cold water. The orange crystals were recrystallized from ethanol containing a drop of concentrated hydrochloric acid to give solid melting at 149-150°.

Anal. Calcd. for $C_{16}H_{27}Cl_6N_2O_2Pt$: C, 42.47; H, 5.79; N, 3.10. Found: C, 42.65; H, 5.84; N, 2.92.

E. CYCLOHEXYL COMPOUNDS

1. Cyclohexyl Bromide

Procedure 1 (58): In a 2 l. flask are placed 640 g. (3.8 moles) of 48% hydrobromic acid and 150 g. of concentrated sulfuric acid. To this mixture is added 200.3 g. (1.0 mole) of cyclohexanol and the mixture is refluxed 5 1/2 hours. The solution is then diluted with 100 ml. of water. The upper bromide layer is separated and washed once with 10 ml. of cold concentrated sulfuric acid, whereupon an emulsion formed which could not be cracked. Twenty ml. of 10% sodium hydroxide solution was added to the emulsion to almost neutralize it, then 10 ml. of a 10% sodium carbonate solution was added. The layers were separated by centrifuging the mixture. The bromide layer was then washed twice with 25 ml. portions of

water. After drying the organic layer over calcium chloride, it was distilled to give 228 g. (70%) of a colorless liquid, b.p. 163-168° at atmospheric pressure, n_D^{25} 1.4913-6, lit. (90) b.p. 69-71°(30 mm.), n_D^{25} 1.4917.

Procedure 2 (60): In a well-stoppered flask, 200.3 g. (2.0 moles) of cyclohexanol was mixed with seven times its volume (approximately 12 moles) of 48% hydrobromic acid and allowed to stand 12 days. The upper layer was separated, washed once with 10 ml. of 48% hydrobromic acid, once with 25 ml. of 10% sodium hydroxide solution and twice with 25 ml. portions of sodium chloride solution. After each washing, the mixture was centrifuged to effect good separation due to its emulsion-forming tendency. The organic layer was dried and distilled to yield 79 g. (24.2%) of a colorless, odorless product, b.p. 163.5-166° at atmospheric pressure, n_D^{25} 1.4920.

Procedure 3 (61): A mixture of 200.3 g. (2.0 moles) of cyclohexanol and 926 ml. (8.0 moles) of 48% hydrobromic acid was allowed to stand overnight in a stoppered flask and then refluxed for 8 hours. The bromide layer was separated, washed twice with 25 ml. portions of 48% hydrobromic acid, once with 25 ml. of water, and twice with 25 ml. portions of 10% sodium carbonate solution. The crude product was dried over calcium chloride and distilled to give 270 g. (82.8%) of a colorless liquid, b.p. 163-164° at atmospheric pressure, n_D^{25} 1.4913.

2. Cyclohexylphenylcarbinol

In a 1 l. 3-necked flask was placed 33.8 g. (1.39 g. atom) of magnesium turnings and sufficient anhydrous ether to cover the metal. A crystal of iodine and 6 ml. of cyclohexyl bromide were introduced into the mixture. The reaction was initiated after the flask was warmed for 15 minutes. The remainder of 194.7 g. (1.2 mole) of freshly distilled cyclohexyl bromide in 735 ml. of anhydrous ether was added slowly. After addition was complete, the Grignard reagent was refluxed for 2 hours. The unreacted magnesium was removed and a solution of 127.3 g. (1.2 mole) of freshly distilled benzaldehyde in an equal volume of anhydrous ether was added dropwise to the mixture. After the vigorous reaction subsided, the contents of the flask was poured onto 100 ml. of ice-water and 1 l. of 10% sulfuric acid gradually added. The aqueous layer was separated and extracted with six 75 ml. portions of ether. The ether extracts were combined with the organic layer and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue distilled to give 113.3 g. (48.4%) of a product which solidified on cooling, b.p. 192-194.5°(25 mm.).

The infrared spectrum of this compound besides showing bands at 3400 cm^{-1} characteristic of OH stretching frequencies and at 1020 cm^{-1} assigned to OH deformations of secondary alcohols, also had a strong absorption at 1700 cm^{-1} due to absorption of a carbonyl impurity. Refractionation of this product removed the contaminant.

A subsequent run under the same experimental conditions with the exception that the Grignard reagent was refluxed 1 hour instead of 2 hours, produced a compound, b.p. 173-178° (24.5 mm.) in 49.9% yield, whose infrared spectrum showed no carbonyl absorption.

3. 2-(α-Cyclohexylbenzyloxy)-N,N-dimethylethylamine Sodium Dispersion Method (91): A dispersion of sodium metal in xylene was prepared by warming a mixture of 7.5 g. of sodium in 200 ml. of anhydrous xylene until the metal became molten. The flask was then stoppered and vigorously shaken. To the dispersion was added a solution of 58.4 g. (0.31 mole) of cyclohexylphenylcarbinol dissolved in 300 ml. of anhydrous xylene. In preparation for this synthesis, 97.0 g. (0.42 mole) of 2-dimethylaminoethylbromide hydrobromide was taken the day before and dissolved in 20 ml. of water. To the salt solution was added 150 ml. of xylene, followed by an excess of sodium hydroxide pellets. The mixture was shaken mechanically for 2 hours, whereupon the free base dissolved in the xylene layer. The organic layer which tended to form an emulsion was then separated by centrifuging, dried over calcium chloride and stored in an ice-cooler overnight. This preparation was then added to the above sodium derivative in xylene and the mixture was refluxed for 7 hours. After allowing the mixture to cool, 30 ml. of 10% sodium hydroxide solution was added to dissolve the inorganic salt. The free base was extracted from the

organic layer with six 20 ml. portions of 5% hydrochloric acid. Addition of solid potassium carbonate liberated the free base, which was taken up in 125 ml. of ether. The ether extracts were dried over calcium chloride. After the solvent was removed by evaporation in vacuo, only a few drops of crude product remained. The same results were obtained when the experimental conditions were varied in subsequent runs: the reaction mixture was refluxed 6 hours with high-speed stirring; the sodium derivative was refluxed 4 1/2 hours and the reaction mixture 16 hours with high-speed stirring.

Sodium Amide Method (84): To a stirred suspension of 4.9 g. (0.14 mole) of sodamide in 62 ml. of anhydrous benzene, was added a solution of 12.4 g. (0.065 mole) of cyclohexylphenylcarbinol in 62 ml. of anhydrous benzene. The mixture was warmed in an oil-bath at 60-70° for 2 1/2 hours. When cool, 15.7 g. (0.068 mole) of 2-dimethyl-aminoethylbromide hydrobromide was added and the mixture heated at 90-95° for 19 hours. The cooled reaction mixture was poured into 100 ml. of water and acidified with 5% hydrochloric acid. The benzene layer was separated and extracted with two 25 ml. portions of water. The aqueous extracts were combined with the dilute acid solution and washed once with 25 ml. of ether. Solid potassium carbonate was added until the solution was basic. The free base was taken up with six 25 ml. portions of ether and the combined

ether extracts dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residual oil distilled to give 3.0 g. (17.7%) of a pale yellow liquid, b.p. 162°(5.5 mm.), n_D^{20} 1.5045, lit. (84) b.p. 120-125°(0.25 mm.).

Sodium Amide Method (Alternate) (92): Into a suspension of 7.8 g. (0.2 mole) of sodamide in 50 ml. of absolute toluene, was added with stirring 19.0 g. (0. 1 mole) of cyclohexylphenylcarbinol in 100 ml. of toluene. The sample was heated at 50-60° for 6 hours, after which time ammonia continued to be evolved. Then 25.6 g. (0.1 mole) of 2-dimethylaminoethylbromide hydrobromide was added and the mixture refluxed for 24 hours. After cooling the reaction mixture, the precipitate was filtered by suction and the filtrate distilled *in vacuo*. The residue was distilled to give 4.0 g. (15.3%) of a yellow oil, b.p. 171-174°(6.5 mm.), n_D^{20} 1.5069.

The infrared spectrum of the cyclohexyl analogue has absorption maxima at 1115 cm^{-1} assigned to C-O-C vibrations and 1080 cm^{-1} characteristic of C-N stretching frequencies.

2-(α-Cyclohexylbenzyloxy)-N,N-dimethylethylamine hydrochloride: An ether solution of the amine was saturated with dry hydrogen chloride. A white, flocculent solid immediately precipitated. It was recrystallized from a mixture of 20 parts of ethyl acetate and 1 part of isopropyl alcohol and stored in a dessicator. M.p. of recrystallized and vacuum-dried solid: 134.5-137°, lit. (84) m.p. 137-139°.

F. CYCLOHEPTYL COMPOUNDS

1. Cycloheptanol

Procedure 1 (55): A solution of 11.4 g (0.3 mole) of lithium aluminum hydride in 340 ml. of anhydrous ether was placed in a 1 l. flask equipped with reflux condenser, dropping funnel and mechanical stirrer, and protected from moisture by calcium chloride tubes attached to the openings. To the flask, was added 112.2 g. (1.0 mole) of cycloheptanone in an equal volume of ether at such a rate as to produce gentle reflux. Ten minutes after the last addition and with continued stirring, water was cautiously added dropwise, while the flask was cooled in an ice-bath. The mixture was then poured into 115 ml. of ice-water and 570 ml. of 10% sulfuric acid was gradually added. After separation of the layers, the aqueous phase was extracted with two 60 ml. portions of ether. The combined ether extracts were dried and the solvent evaporated. The residue was distilled to give 79.0 g. (69.2%) of product, b.p. 181-183° at atmospheric pressure, n_D^{20} 1.4682, lit. (56), b.p. 80.5(11 mm.)-79.5°(9 mm.), n_D^{20} 1.4750-1.4762.

Procedure 2 (56): Lithium aluminum hydride (18.0 g. 0.48 mole) was stirred for 1 hour with 400 ml. of anhydrous ether at reflux. A solution of 168 g. (1.5 mole) of cycloheptanone in 350 ml. of anhydrous ether was added over a period of 3 hours. The mixture was refluxed for another 3 hours and allowed to stand overnight. The excess hydride was

hydrolyzed by the addition of 300 ml. of moist ether. Addition of 35 ml. of water caused the inorganic salts to flocculate and settle. The ether solution was decanted and the solid was slurried with an additional 200 ml. of ether. The combined ether solutions were dried over sodium sulfate, the solvent evaporated and the residue distilled to give 97 g. (84.9%) of product, b.p. 183-187° at atmospheric pressure n_D^{20} 1.4701.

The infrared spectra of the products prepared by both procedures showed the presence of unreacted cycloheptanone. Repeated refractionations could not eliminate the contaminant. The unreacted ketone was then removed by precipitating it with saturated sodium bisulfite solution. The bisulfite addition product was filtered by suction and washed three times with ether. The ether washings were combined and the solvent evaporated to recover the alcohol. This was added to the alcohol layer in the filtrate and dried over sodium sulfate. After evaporating the ether, the liquid was distilled to give uncontaminated cycloheptanol, b.p. 182-184°, n_D^{20} 1.4701-1.4703.

2. Cycloheptyl Bromide

A mixture of 60 g. (0.53 mole) of cycloheptanol and 243 ml. (2.1 moles) of 48% hydrobromic acid was allowed to stand overnight and then refluxed for 7 hours. The upper layer was separated, washed once with 25 ml. 48% hydrobromic acid, once with 25 ml. of water and twice with 25 ml.

portions of 10% sodium carbonate solution. After drying the crude bromide over calcium chloride, it was distilled to give 59.5 g. (63.9%) of product, b.p. 67°(14 mm.)-72°(13 mm.), n_D^{22} 1.4952, lit. (56) b.p. 74-84°(12 mm.), n_D^{24} 1.5025.

3. Cycloheptylphenylcarbinol

In a 1 l. 3-necked flask fitted with mechanical stirrer, reflux condenser and dropping funnel, with the openings protected from moisture by calcium chloride tubes, was placed 19 g. (0.78 mole) of magnesium turnings and sufficient anhydrous ether to cover the metal. An iodine crystal and 6 g. of cycloheptylbromide was introduced into the mixture. The flask was warmed 20 minutes to initiate the reaction. The remainder of the 134.0 g. (0.75 mole) of freshly distilled bromide in 225 ml. of anhydrous ether was added dropwise. After addition was complete, the Grignard reagent was refluxed 2 1/2 hours. It was then gradually added to 33.3 g. (0.31 mole) of freshly distilled benzaldehyde in an equal volume of ether. The mixture was stirred one-half an hour and refluxed 15 1/2 hours. The contents of the flask was then poured onto 100 g. of ice and 10% hydrochloric acid added until the solution was acid. The aqueous layer was separated and extracted with five 50 ml. portions of ether. The ether extracts were combined with the organic layer and dried over calcium chloride. The solvent was removed by flash evaporation and the residue was distilled to give

8.5 g. (13.2%) of a viscous pale green liquid, b.p. 169-176° (15 mm.).

Alternate procedure employing a Lewis acid (65): 28.3 g. (0.18 mole) of bromine was added slowly with continuous stirring to 4.3 g. (0.18 mole) of magnesium turnings in 55 ml. of anhydrous ether. After stirring the mixture for 68 hours, the bromine color had not disappeared. Freshly distilled benzaldehyde (8.4 g., 0.08 mole) was added dropwise and the mixture stirred an additional hour. Cycloheptylmagnesium bromide was prepared from 67.3 g. (0.38 mole) of cycloheptyl bromide, 9.5 g. (0.39 g. atom) of magnesium turnings and 115 ml. of ether. The Grignard reagent was refluxed for 2 hours and then slowly added to the Lewis acid mixture. Stirring was continued for 1 hour. The mixture was slowly added to 210 ml. of 10% ammonium chloride solution at 0°. The layers were separated and the aqueous solution extracted with six 50 ml. portions of ether. The combined ether solutions were dried over calcium chloride. After removal of the solvent by flash evaporation, the residue was distilled to give 6.9 g. (10.8%) of a viscous brown liquid, b.p. 167-172°(15 mm.).

The infrared spectra of the compounds produced by both procedures showed the characteristic absorption bands of the secondary carbinol, at 3450 cm^{-1} and 1025 cm^{-1}. However, in some cases, an absorption at 1700 cm^{-1} indicated the presence of a carbonyl impurity. The various reaction conditions

employed in the synthesis of the carbinol and the quality of the product obtained are summarized in Table VIII.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.3; H, 9.87. Found (Lot III): C, 83.80; H, 11.76. Found (Lot IV): C, 82.75; H, 10.72. Found (Lot VI): C, 82.99; H, 11.18.

4. 2-(α-Cycloheptylbenzyloxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 2.4 g. (0.063 mole) of sodamide in 40 ml. of dry toluene, was added 6.7 g. (0.033 mole) of cycloheptylphenylcarbinol in 40 ml. of dry toluene. The mixture was warmed in an oil-bath at 60-70° for 2 days. When cool, 7.9 g. (0.034 mole) of 2-dimethylaminoethyl-bromide hydrobromide and 1.2 g. (0.032 mole) of sodamide was added. The reaction mixture was refluxed for 3 days, then poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with water. The aqueous extract was combined with the dilute acid solution and washed once with ether. Solid potassium carbonate was added to the solution until it was basic. The free base was taken up with six 50 ml. portions of ether. The combined ether solutions were dried over sodium sulfate. After the solvent was removed by flash evaporation the residue was distilled to give 0.98 g. (11.0%) of a pale, green product, b.p. 186°(10 mm.), n_D^{20} 1.5049.

A previous run in which the sodamide-carbinol mixture was warmed for 5 days instead of 2 days, while the other experimental conditions remained unchanged, yielded no

TABLE VIII

REACTION CONDITIONS IN THE SYNTHESIS OF CYCLOHEPTYLHENYLCARBINOL

MOLAR RATIO BROMIDE TO ALDEHYDE	PRESENCE OF LEWIS ACID	METHOD OF ADDITION	TREATMENT OF GRIG. REAG.	TREATMENT OF CARB-INOL MIXT.	HYDROLYSIS REAGENT	YIELD %	QUAL. OF PROD.
1:1	-	Normal	R*-1hr.	R-1hr.	10%HCI	10.5	Green, str. C=O peak
0.75:0.31	+	Inverse	R-2hr.	S*-1hr.	10%NH_4Cl	10.8	Brown, no C=O peak
0.75:0.31	+	Inverse	S-over-night	R-5hr.	10%Na_2CO_3	9.4	Brown, sm. C=O peak
0.75:0.31	+	Inverse	S-over-night	S-2hr. R-5hr.	10%HCl	10.9	Brown, sm. C=O peak
0.75:0.31	-	Inverse	S-over-night	S-2hr. R-4hr.	10%HCl	12.2	Green, sm. C=O peak
0.75:0.31	-	Inverse	R-2 1/2hr.	S-1/2hr. R-15 1/2hr.	10% HCl	13.2	Green, no C=O peak

* R is abbreviated for refluxed, S is abbreviated for stirred.

product. A change in color in the sodium derivative mixture from a deep orange to a bright yellow had occurred on the fifth day. A subsequent trial in which the sodium derivative was warmed 2 days, but the final mixture was refluxed only 1 day, gave a substance whose infrared spectrum indicated that it may be an intermediate.

2-(α-Cycloheptylbenzyloxy)-N,N-dimethylethylamine chloroplatinate: A solution of 0.25 g. of the amine in 5 ml. of 10% hydrochloric acid was added with stirring to 5 ml. of a 25% aqueous solution of chloroplatinic acid. After standing 10 minutes in an ice-bath, the solid was separated and washed with cold water. The orange crystals were recrystallized from ethanol containing a drop of concentrated hydrochloric acid to give a solid melting at 147-147.5°.

Anal. Calcd. for $C_{36}H_{60}ClN_2O_2Pt$: C, 45.00; H, 6.29; N, 2.92. Found: C, 44.99; H, 6.23; N, 2.90.

G. CYCLOOCTYL COMPOUNDS

1. Cyclooctyl Bromide

A mixture of 180.6 ml. (1.56 moles) of 48% hydrobromic acid and 50.0 g. (0.39 mole) of cyclooctanol was allowed to stand overnight in a stoppered flask. It was then refluxed for 9 hours. The upper layer was separated, washed once with 25 ml. of 48% hydrobromic acid, once with 25 ml. of water and twice with 25 ml. portions of 10% sodium carbonate solution. The crude bromide was dried over calcium chloride and

distilled to yield 48.0 g. (64.4%) of a colorless liquid, b.p. 72-77°(12 mm.), n_D^{25} 1.4848, lit. (67), b.p. 97°(15 mm.).

2. Cyclooctylphenylcarbinol

In a 500 ml. 3-necked flask, was placed 3.6 g. (0.15 g. atom) of magnesium turnings, which were covered with 25 ml. of anhydrous ether. An iodine crystal and about 15 g. of bromide was introduced into the flask. Prolonged warming of the mixture was necessary to initiate the reaction. The remainder of the 26.9 g. (0.14 mole) of freshly distilled bromide in 75 ml. of anhydrous ether was added dropwise and the mixture refluxed for 2 1/2 hours. After stirring overnight, 14.9 g. (0.14 mole) of freshly distilled benzaldehyde in an equal volume of ether was gradually added. The mixture was refluxed for 3 hours. It was then poured onto 50 gm. of ice and 10% hydrochloric acid was added until the solution was acid. After separation of the layers, the aqueous phase was extracted with three 50 ml. portions of ether. The ether extracts combined with the organic layer were dried over calcium chloride. The solvent was removed by flash evaporation and the residue distilled to give 1.8 g. (5.9%) of a bright green product, b.p. 141-142°(12 mm.).

Alternate procedure employing a Lewis acid (65): 37.3 g. (0.24 mole) of bromine was added slowly with continuous stirring to 5.7 g. (0.24 mole) of magnesium turnings in 70 ml. of anhydrous ether. After stirring the mixture overnight, 11.1 g. (0.105 mole) of freshly distilled benzaldehyde was

added dropwise. The mixture was stirred an additional one-half hour. Cyclooctylmagnesium bromide was prepared from 48.4 g. (0.25 mole) of freshly distilled cyclooctyl bromide, 6.3 g. (0.26 g. atom) of magnesium turnings, and 125 ml. of anhydrous ether. The Grignard reagent was stirred overnight. It was then slowly added to the Lewis acid mixture, and refluxed overnight. The contents of the flask was poured onto 50 g. of ice and 10% hydrochloric acid gradually added until the solution was acid. The layers were separated and the aqueous phase extracted with four 50 ml. portions of ether. The combined ether solutions were dried over calcium chloride. After evaporation of the solvent by flash evaporation, the residue was distilled to give 1.5 g. (6.6%) of a brown liquid, b.p. 167-170°(13 mm.).

The infrared spectra of the products prepared by both procedures besides showing characteristic bands of the carbinol at 3400 cm^{-1} and 1025 cm^{-1}, also had strong bands at 1700 cm^{-1} due to carbonyl absorption. An unsuccessful attempt was made to separate the impurity by passing various samples of the product through a 10 ft. x 1/4 in. column packed with Carbowax 4,000, at a temperature of 190°, and a helium pressure of 30 psig on the Beckman Gas Chromatograph. Either the samples decomposed on the column or they were not the desired product.

Various reaction conditions were tried in the preparation of cyclooctylphenylcarbinol; these are summarized in Table IX.

TABLE IX

REACTION CONDITIONS USED IN THE SYNTHESIS OF CYCLOOCTYLPHENYLCARBINOL

LOT	MOLAR RATIO BROMIDE TO BZH	METHOD OF ADDITION	TREATMENT OF GRIG. REAG.	TREATMENT OF CARB-INOL MIXT.	B.P. RANGE	YIELD %	QUAL. OF PRODUCT
I	1:1	Normal	R[a]-2 1/2 hr.	R-3hr.	141-2 (13mm.)	5.9	Green, med. C=O peak
II	1.4:1.1	Inverse	R-3 hr.	S[b]-2hr. R-3hr.	174-8 (19mm.)	8.5	Green, str. C=O peak
III	2.6:1	Inverse	S-over-night	R-5hr.	162-181 (15mm.)	0.9	Brown, str. C=O peak
IV[c]	2.5:1	Inverse	S-over-night	R-11hr.	167-170 (13mm.)	6.6	Brown, sm. C=O peak Green
V	2.5:1	Inverse	R-23 hr.	R-23hr.	158-166 (13 mm.)	8.9	str. C=O peak

(a) R is abbreviated for refluxed
(b) S is abbreviated for stirred
(c) Lewis acid procedure

3. 2-(α-Cyclooctylbenzyloxy)-N,N-dimethylethylamine (84)

Although uncertain about the products obtained in the synthesis of cyclooctylphenylcarbinol, nevertheless an attempt was made to condense it. To a stirred suspension of 4.9 g. (0.14 mole) of sodamide in 62 ml. of anhydrous toluene, was added 14.2 g. (0.065 mole) of the carbinol in 62 ml. of toluene. The mixture was warmed on the heating mantle at 60-70° for 23 hours. When cool, 2.4 g. (0.065 mole) of sodamide and 15.7 g. (0.068 mole) of 2-dimethylaminoethyl-bromide hydrobromide was added. The mixture was refluxed for 7 days, after which time ammonia evolution had ceased. The contents of the flask was poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with 25 ml. of water. The aqueous extract was combined with the dilute acid solution and washed once with 25 ml. of ether. Solid potassium carbonate was then added to the solution until it was basic. The free base was extracted with six 50 ml. portions of ether and the combined ether extracts dried over sodium sulfate. The solvent was removed by flash evaporation and the residue distilled to give 2 drops of a substance boiling at 55°(25 mm.). The infrared spectrum of this substance indicates that it may be an intermediate of the desired product.

H. DICYCLOPROPYL COMPOUNDS

1. Dicyclopropylmethyl bromide

A mixture of 34.0 g. (0.30 mole) of dicyclopropylcarbinol (Aldrich Chemical Co.) and 140 ml. (1.2 moles) of 48% hydrobromic acid was refluxed for 5 hours. After standing overnight, the bottom bromide layer was separated, washed once with 25 ml. of 48% hydrobromic acid, twice with 25 ml. of water and twice with 25 ml. of 10% sodium carbonate solution. Centrifuging was necessary to effect good separation of the layers due to an emulsion which tended to form. After the crude bromide was dried over calcium chloride, it was distilled to give 26,7 g. (50.4%) of a bright green product, which rapidly darkened on standing, b.p. 131-139°(15 mm.), n_D^{20} 1.5165.

2. 2-(Dicyclopropylmethoxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 4.9 g. (0.135 mole) of sodamide in 62 ml. of anhydrous toluene, was added 7.3 g. (0.065 mole) of dicyclopropylcarbinol (Aldrich Chemical Company). The mixture was warmed at 60-70° for 142 hours. When cool, 15.7 g. (0.0675 mole) of 2-dimethylaminoethylbromide hydrobromide was added. The mixture was refluxed for 2 days, after which time ammonia evolution had ceased. The contents of the flask was poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted with 25 ml. of water. The aqueous extract was combined with

the dilute acid solution and washed with 25 ml. of ether. Solid potassium carbonate was added to the solution until it was basic. Six 50 ml. portions of ether were used to extract the free base, and combined to dry over sodium sulfate. The solvent was removed by flash evaporation and the residue distilled to give 0.4 g. (3.4%) of a yellow oil, b.p. 91-96°(6.5 mm.), n_D^{20} 1.4513-1.4519.

A second run in which the sodium derivative was warmed at the same temperature for 2 1/2 hours and the final mixture was refluxed for 18 hours, produced a substance whose infrared spectrum indicates that it may be an intermediate. A third run in which the sodamide-carbinol mixture was warmed at the same temperature for 5 days and the final mixture refluxed for 4 days, yielded 0.8% of product, b.p. 105°(13 mm.), n_D^{20} 1.4531.

Alternate procedure: To a suspension of 5.96 g. (0.153 mole) of sodamide in 100 ml. of anhydrous toluene was added 10.8 g (0.153 mole) of 2-dimethylaminoethanol in 40 ml. of anhydrous toluene. The mixture was warmed for 18 1/2 hours and then refluxed for 4 hours. When cool, 26.7 g. (0.153 mole) of dicyclopropylmethyl bromide in 40 ml. of toluene was added. After refluxing the mixture for 5 days, it was poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with 25 ml. of water. The aqueous extract was combined with the acid solution and washed once with 25 ml. of ether.

The acid solution was made basic by addition of solid potassium carbonate. Six 50 ml. portions of ether were used to extract the base, and the combined ether extracts were dried over sodium sulfate. The solvent was removed by flash evaporation and the residue distilled to give a yellow oil with a characteristic fish-like odour, b.p. 142-153° (20 mm.), n_D^{20} 1.4761.

The infrared spectra of two products obtained by the first procedure, Lot I and III, and that synthesized by the alternate method, Lot IV, all showed absorption bands characteristic of C-O-C and C-N vibration frequencies. However, the patterns differed somewhat from each other. The major differences are that a large peak at 1700 cm^{-1} present in Lot I is absent in the spectra of the other, and a peak at 1400 cm^{-1} in the spectra of Lot I is all but absent in that of the others.

Attempts to prepare suitable derivatives of these products for analysis were unsuccessful. The various derivatives tried were: hydrochloride, chloroplatinate, aurichloride, picrate, methiodide, acid citric and 3,5-dinitrobenzoate.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.06; H, 11.55; N, 7.64. Found for Lot III: C, 69.63; H, 10.69; N, 9.11. Found for Lot IV: C, 71.14; H, 10.94; N, 7.31.

I. DICYCLOPENTYL COMPOUNDS

1. Dicyclopentyl carbinol

Cyclopentylmagnesium bromide was prepared from 149.0 g. (1.0 mole) of the bromide, 26.7 g. (1.1 g. atoms) of magnesium turnings and 600 ml. of anhydrous ether. About 5 ml. of bromide and an iodine crystal were introduced into the flask containing the magnesium covered with ether. Warming of the flask for a short period initiated the reaction. After addition of all the bromide in the remainder of the anhydrous ether, the mixture was stirred overnight. A solution of 27.8 g. (0.38 mole) of ethyl formate in 60 ml. of anhydrous ether was added dropwise during a period of 1 hour. Intermittent cooling of the flask was required to moderate the vigorous reaction. The mixture was stirred 1 hour and then refluxed for 6 hours. The contents of the flask was then poured onto 100 gm. of ice and 10% hydrochloric acid was added until the solution was acid. After separation of the layers, the aqueous phase was extracted with three 50 ml. portions of ether. The ether extracts were combined with the organic layer, washed once with 50 ml. of 10% sodium bicarbonate solution, and then dried over calcium chloride. After removing the solvent by flash evaporation the residue was distilled to give 10.6 g. (16.8%), b.p. 116-119°(12 mm.), of a green, viscous liquid, which solidified in the condenser. Lit. (93) b.p. 68°(0.2 mm.), m.p. 47.5°.

A run under identical experimental conditions with the exception that the molar ratio of bromide to ethyl formate was 2:1 produced an essentially different product. The substance was a yellow liquid instead of a pale green solid and the infrared spectrum had considerably smaller peaks at 3500 cm^{-1} and at 1020 cm^{-1}, characteristic bands of the carbinol. Also it had absorption maxima at 1725 cm^{-1} and 1185 cm^{-1} which were absent in the spectrum of the solid compound.

Anal. Calcd. for $C_{11}H_{20}O$; C, 78.49; H, 11.98. Found; C, 77.62; H, 11.80.

2. 2-(Dicyclopentylmethoxy)-N,N-dimethylethylamine

To a stirred suspension of 4.9 g. (0.135 mole) of sodamide in 62 ml. of anhydrous toluene, was added 16.9 g. (0.065 mole) of dicyclopentylcarbinol in 62 ml. of anhydrous toluene. The mixture was warmed on an oil-bath at 60-70° for 2 days. Then 15.7 g. (0.0675 mole) of 2-dimethylaminoethylbromide hydrobromide and 2.5 g. (0.068 mole) of sodamide was added. The mixture was refluxed for 5 days and then poured into 100 ml. of water and acidified with 10% hydrochloric acid. The layers were separated and the toluene layer extracted once with 25 ml. of water. The aqueous extract was combined with the dilute acid solution and washed once with 25 ml. of ether. The solution was then made basic with solid potassium carbonate and the free base extracted with six 50 ml. portions of ether. The combined ether

extracts were dried over sodium sulfate, the solvent was evaporated and the residue was distilled to give 1.3 g. (7%) of a brown oil, b.p. 152°(14 mm.), n_D^{20} 1.4679.

The infrared spectrum of the product showed absorption maxima at 1115 cm^{-1} characteristic of the C-O-C and at 1060 cm^{-1} assigned to C-N stretching frequencies.

2-(Dicyclopentylmethoxy)-N,N-dimethylethylamine chloroplatinate: A solution of 0.25 g. of the amine in 5 ml. of 10% hydrochloric acid was added with stirring to 5 ml. of a 25% aqueous solution of chloroplatinic acid. After standing 10 minutes in an ice-bath, the solid was separated and washed with cold water. The orange crystals were recrystallized from 95% ethanol containing a drop of concentrated hydrochloric acid to yield a product melting at 168-168.5° (decomp.)

Anal. Calcd. for $C_{30}H_{60}Cl_6N_2O_2Pt$: C, 40.54; H, 6.81; N, 3.15. Found: C, 40.48; H, 6.65; N, 3.48.

J. DICYCLOHEXYL COMPOUNDS

1. Cyclohexanecarboxaldehyde (71)

Two ml. of an equal mixture of cyclohexyl bromide and ether was gently warmed with 6.9 g. (0.28 g. atom) of magnesium turnings covered with anhydrous ether. The reaction was readily initiated. With the flask immersed in an ice-bath, the remainder of the 46.6 g. (0.29 mole) of cyclohexyl bromide in the balance of the 120 ml. of anhydrous ether was

added dropwise. After addition was complete, 42.5 g. (0.29 mole) of ethyl orthoformate was added gradually and the mixture was refluxed gently for 5 hours. The bulk of the ether was evaporated in vacuo. The resulting oily grey cake was added to ice water and the solution acidified with 5% hydrochloric acid. After the ethereal acetal layer was separated, the acetal was hydrolysed by refluxing the organic layer for 20 minutes with three times its volume of 5N hydrochloric acid. The ethereal aldehyde layer was then run immediately into saturated bisulfite solution. On stirring, a clumpy white precipitate separated. The bisulfite compound was filtered by suction, made into a cream with ether to remove unhydrolyzed acetal and again filtered. This procedure was repeated once more. The resulting product was white and flaky. The ether was removed from the filtrate and the recovered acetal treated with acid as before. However, the second crop of bisulfite compound which was obtained, was yellowish in colour and was not retained. The yield of bisulfite compound was 22.3 g. (33.6%).

The free aldehyde was regenerated by adding sufficient sodium carbonate to an aqueous solution of the bisulfite compound to neutralize it. The pale yellow oil which separated was taken up in ether and the solution dried over sodium sulfate. After evaporating the solvent, the residue was distilled to yield 1.9 g. of aldehyde, b.p. 160° at

atmospheric pressure, n_D^{19} 1, 4493, lit. (94), b.p. 159.3° at atmospheric pressure, n_D^{19} 1.4495. Considerable foaming of the aldehyde was encountered during its distillation. This condition was not alleviated by the use of antifoam spray.

Alternate Procedure: The Grignard reagent was prepared from 218.4 g. (1.34 moles) of cyclohexyl bromide, 32 g. (1.34 g. atoms) of magnesium turnings and 560 ml. of anhydrous ether. A small amount of the bromide and ether was gently warmed with the magnesium covered with ether until the reaction was initiated. Then the flask was immersed in ice-water and the remainder of the bromide solution in ether was dropped in. After addition was complete, 98.3 g. (0.67 mole) of ethyl orthoformate was added gradually. The mixture was refluxed for 2 hours, during which time a solid appeared. After standing overnight, the ether was distilled. Then, the reaction mixture was hydrolysed by pouring onto ice and acidified with 10% sulfuric acid. The organic layer was separated and 400 ml. of 10% sulfuric acid added. The mixture was steam-distilled, and portions of distillate which gave a bisulfite addition compound was collected and dried over sodium sulfate. The yield of crude product was 60 g. (39.9%), n_D^{19} 1.4430.

2. Dicyclohexylcarbinol

Cyclohexylmagnesium bromide was prepared from 100.9 g. (0.6 mole) of bromide, 14.7 g. (0.6 g. atom) of magnesium

turnings and 360 ml. of anhydrous ether. After addition of the bromide was complete, the Grignard reagent was refluxed for an hour. Then 60 g. (0.54 mole) of cyclohexanecarboxaldehyde was added and the mixture refluxed for 3 1/2 hours. The contents of the flask was poured onto ice and the solution acidified with 10% hydrochloric acid. After separation of the layers, the aqueous layer was extracted with three 75 ml. portions of ether. The ether extracts were combined with the organic phase and dried over calcium chloride. The solvent was removed by flash evaporation and the residue distilled to yield 39 g. (37.1%) of a substance which solidified on cooling, b.p. 146°(14 mm.)-146°(13 mm.), lit. (95), b.p. 166°(20 mm.), m.p. 63°.

Alternate Procedure: Cyclohexylmagnesium bromide was prepared from 158 g. (0.97 mole) of bromide, 24.3 g. (1.0 g. atom) of magnesium turnings and 500 ml. of anhydrous ether. The grignard reagent was stirred overnight and then refluxed an hour. A solution of 27.8 g. (0.75 mole) of ethyl formate in 30 ml. of ether was dropped in. The reaction proceeded vigorously. After stirring overnight, the mixture was refluxed for 3 hours. The contents of the flask was poured onto ice and the solution acidified with 10% hydrochloric acid. After separation of the layers, the aqueous layer was extracted with six 50 ml. portions of ether. The combined ether solution was washed once with 50 ml. of 10% sodium bicarbonate solution and then dried over

calcium chloride. The solvent was removed by flash evaporation and the viscous residue was distilled to give a substance which solidified on cooling. The yield of product was 39 g. (53%), b.p. 157.5°(20 mm.)-160°(23 mm.).

3. Dicyclohexylmethyl bromide

A mixture of 25.5 g. (0.13 mole) of dicyclohexylcarbinol and 62 ml. of 48% hydrobromic acid was refluxed gently for 17 1/2 hours. The layers were separated and the upper bromide layer was washed once with 25 ml. of 48% hydrobromic acid. once with 25 ml. of water and twice with 25 ml. of 10% sodium carbonate solution. After drying over calcium chloride, the bromide was distilled to give 2 g. (6.0%) of a pale brown liquid, b.p. 175-177°(25 mm.), n_D^{25} 1.5027.

4. 2-(Dicyclohexylmethoxy)-N,N-dimethylethylamine (84)

To a stirred suspension of 4.9 g. (0.135 mole) of sodamide in 62 ml. of dry toluene, was added 12.76 g. (0.065 mole) of dicyclohexylcarbinol in 62 ml. of dry toluene. The mixture was warmed at 60-70° on the heating mantle for 26 hours. Then 15.7 g. (0.0675 mole) of 2-dimethylaminoethyl-bromide hydrobromide was added. After refluxing the mixture for 81 hours, there was no further ammonia evolution. The contents of the flask was poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with 25 ml. of water. The aqueous extract and the dilute acid solution were washed once

with ether. Solid potassium carbonate was added to the solution to make it basic. The free base was taken up with six 50 ml. portions of ether. After drying the ether solution over sodium sulfate, the solvent was removed by flash evaporation and the residue was distilled to give 0.2 g. (1.2%) of a pale yellow oil with a characteristic fish-like odour, b.p. 153.5°(6.5 mm.), n_D^{20} 1.4775, lit. (91), b.p. 154-155°(5 mm.), n_D^{22} 1.4806.

Alternate Procedure: To a stirred suspension of 0.43 g. (0.011 mole) of sodamide in 50 ml. of dry toluene, was added 0.96 g. (0.011 mole) of 2-dimethylaminoethanol. The mixture was warmed on the heating mantle at 60-70° for 4 days. Then 2.8 g. (0.011 mole) of dicyclohexylmethyl bromide and 0.43 g. (0.011 mole) of sodamide was added. The preparation was refluxed for 4 days. The mixture was poured into 75 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with water. The aqueous extract combined with the dilute acid solution was washed once with ether. The solution was made basic by addition of solid potassium carbonate and then extracted with six 50 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. On removing the solvent by flash evaporation, there was no residue.

Various reaction conditions were tried in the synthesis of the dicyclohexyl analogue by the first procedure. These are summarized in Table X.

TABLE X

REACTION CONDITIONS IN THE PREPARATION OF DICYCLOHEXYL ANALOGUE

LOT	SOLVENT	WARMING TIME	REFLUX TIME	YIELD	B.P.	REFRACTIVE INDEX
I	Benzene	2 hr.	46 hr.	few drops	-	-
II	Xylene	2 hr.	41 1/2hr.	few drops	161-4° (6mm.)	n^{22}1.4720
III	Toluene	26 hr.	81 hr.	1.2%	153-5° (6.5mm.)	n^{20}1.4775
IV	Toluene	4 days	1 day	few drops	154° (6mm.)	n^{20}1.4735

5. Recovered Dicyclohexylcarbinol

From Lot IV of the dicyclohexyl analogue condensation reaction, the toluene layer, which was separated from the acidified solution of the final reaction mixture, was dried over calcium chloride. On distillation, five fractions were obtained:

FRACTION	B.P.
I	82-105°(760 mm.)
II	105-109°(760 mm.)
III	112-154°(19 mm.)
IV	154°(19 mm.)-162°(18 mm.)
V	162°(18 mm.)-165°(20 mm.)

Fraction II was identified as toluene. Fractions IV and V had infrared spectra identical with that of dicyclohexylcarbinol (see Figure 24 and 25, Part VI). The amount of recovered carbinol was approximately half of the quantity used in the condensation reaction.

K. MISCELLANEOUS

2-(Benzyloxy)-N,N-dimethylethylamine

When cycloheptylphenylcarbinol was first prepared, a fraction boiling between 95-105°(13 mm.) was believed to be the product; this fraction, however, turned out to be benzyl alcohol. It was condensed by adding 12.3 g. (0.114 mole) of the carbinol in 62 ml. of anhydrous toluene to 4.7 g. (0.124 mole) of a stirred suspension of sodamide in 62 ml. of anhydrous toluene. The mixture was warmed at 60-70° in an oil-bath for 2 hours. Then 14.1 g. (0.0602 mole) of 2-dimethylaminoethylbromide hydrobromide was added and the mixture refluxed for 24 hours. The contents of the flask was poured into 100 ml. of water and acidified with 10% hydrochloric acid. The toluene layer was separated and extracted once with water. The aqueous extract and the dilute acid solution were combined and washed once with ether. The free base was taken up with ether, and the ether extracts were dried over sodium sulfate. After removal of the solvent by flash evaporation, the residue was distilled to give 3 g. (25.8%) of 2-(benzyloxy)-N,N-dimethylethylamine, b.p. 105-107°(5.5 mm.), n_D^{25} 1.4941.

2-(Benzyloxy)-N,N-dimethylethylamine hydrochloride: Dry hydrogen chloride was passed through an ether solution of the product. The solid which precipitated was separated and recrystallized from a mixture of 20 parts of ethyl acetate and 1 part of isopropyl alcohol. The white, shiny needles melted at 107.5-108.5°.

Anal. Calcd. for $C_{11}H_{18}ClNO$: C, 61.20; H, 8.41; N, 6.50. Found: C, 59.90; H, 7.99; N, 6.62.

2-(Benzyloxy)-N,N-dimethylethylamine picrate: A solution of 0.3 g. of the product in 10 ml. of 95% ethanol was added to 10 ml. of a saturated solution of picric acid. The mixture was heated to boiling and then allowed to cool slowly. The yellow crystals were filtered and washed four times with 2 ml. portions of ether. The picrate melted at 126.5-127.5°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.91; H, 4.90; N, 13.68.

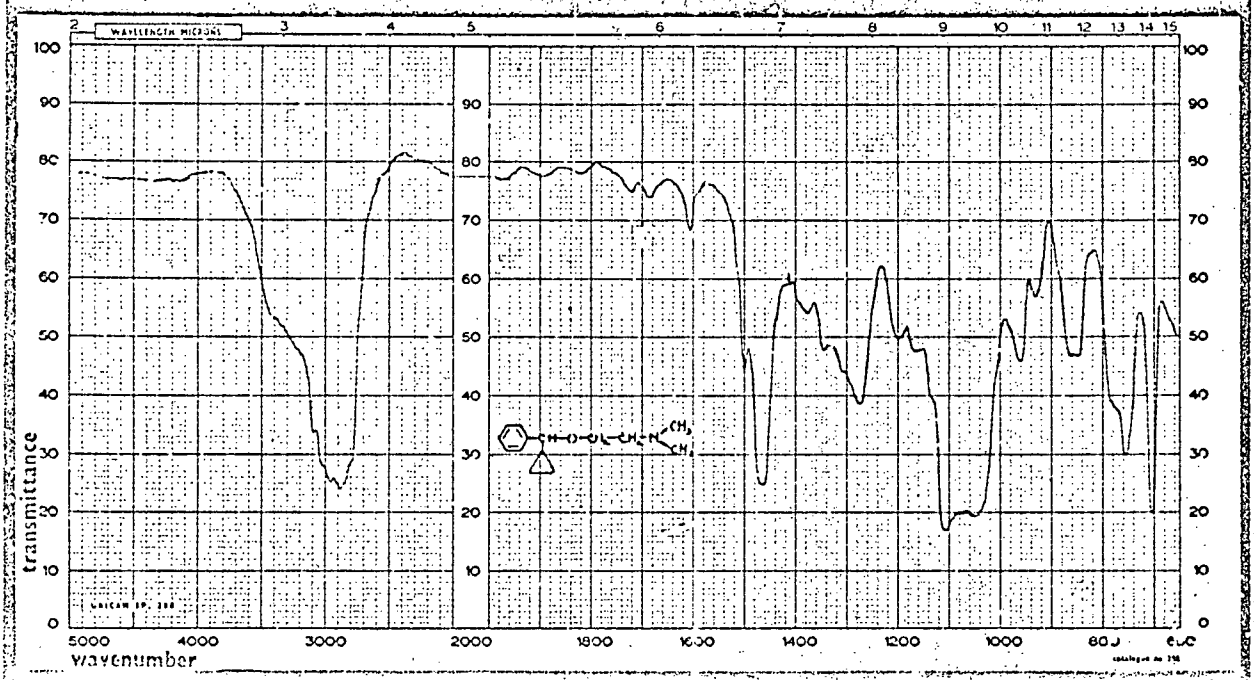
PART VI

INFRARED SPECTRA

Figure 1. Infrared Spectrum of 2-(α-Cyclopropylbenzyloxy)-N,N-dimethylethylamine, Lot. I.
Liquid film between sodium chloride plates.

Figure 2. Infrared Spectrum of 2-(α-Cyclopropylbenzyloxy)-N,N-dimethylethylamine, Lot II.
Liquid film behind sodium chloride plates.

Figure 3. Infrared Spectrum of 2-(α-Cyclopropylbenzyloxy)-N,N-dimethylethylamine, Lot IV.
Liquid film between sodium chloride plates.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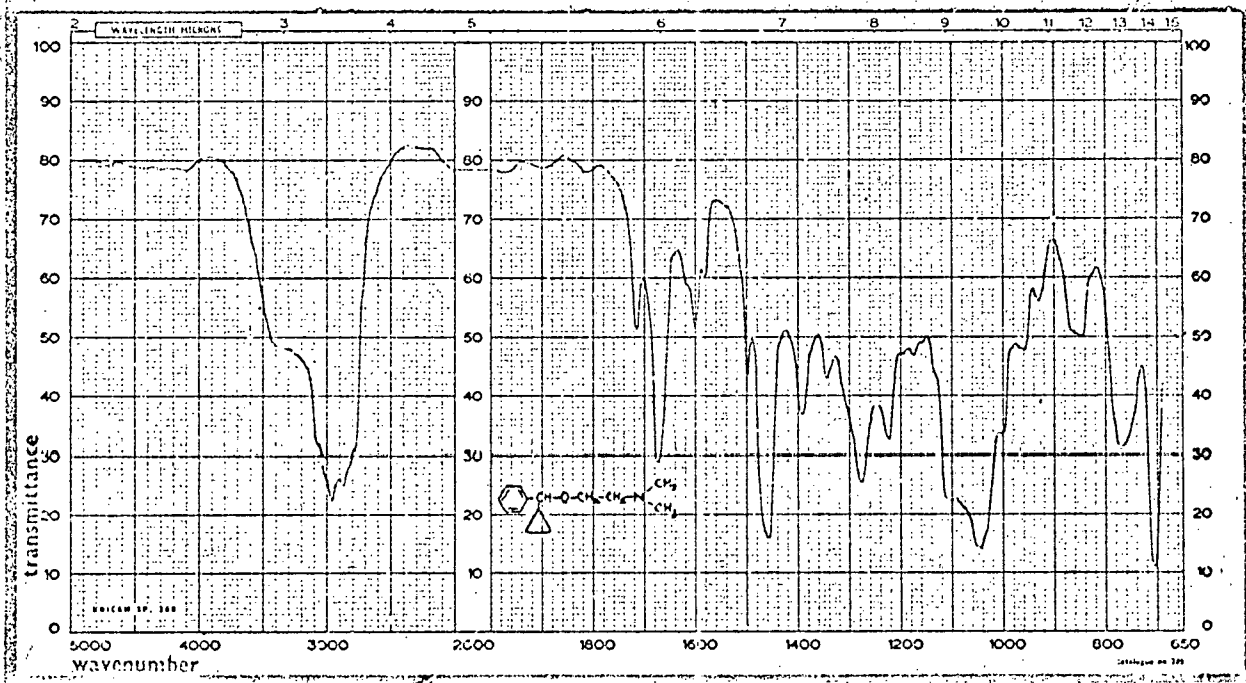
transmittance
wavenumber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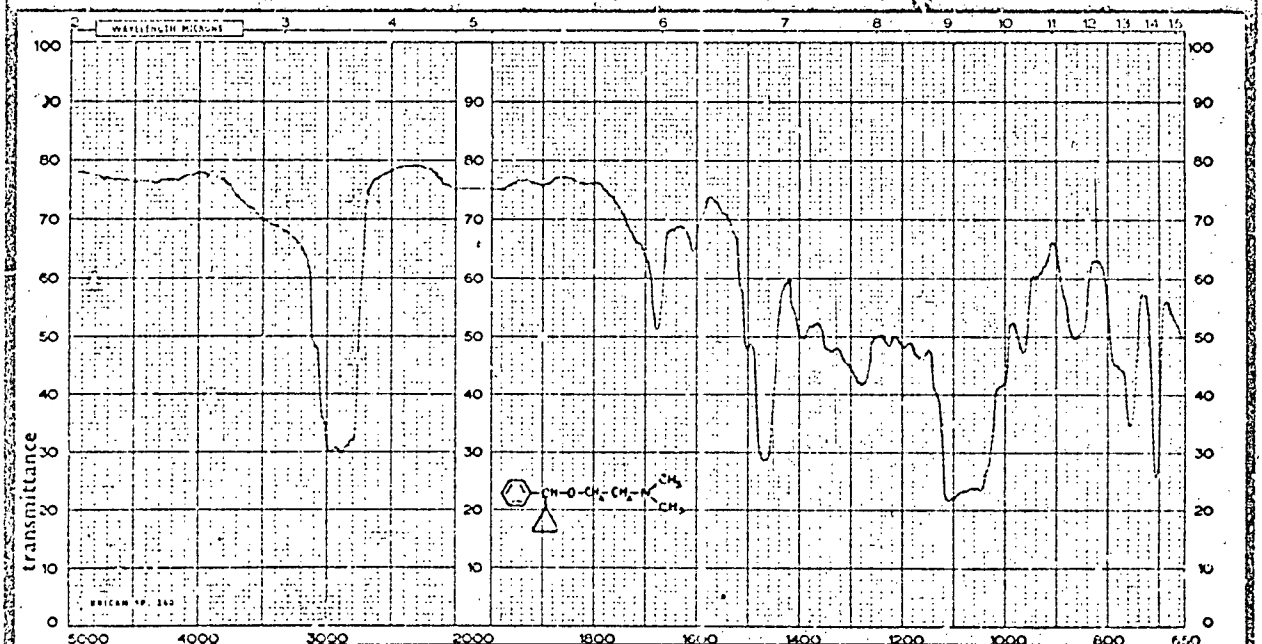
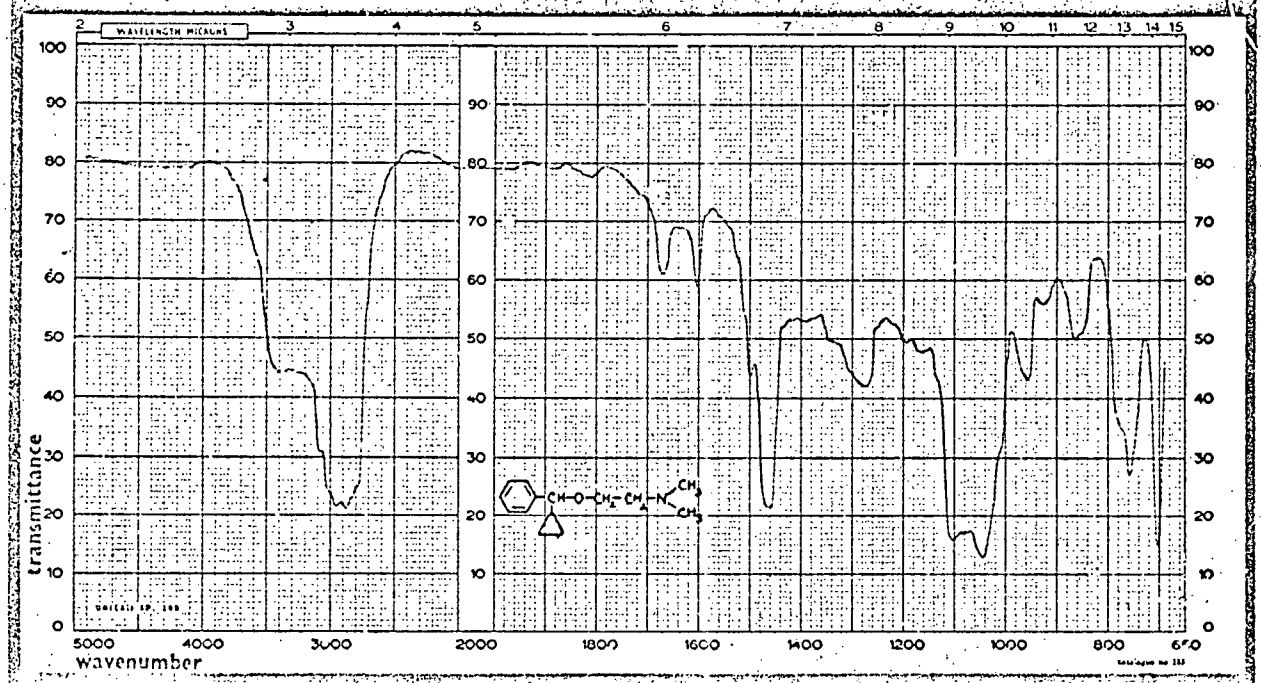

WAVELENGTH MICRONS
transmittance

Figure 4. Infrared Spectrum of 2-(∝-Cyclopropylbenzyloxy)-N,N-dimethylethylamine, Lot V.
Liquid film between sodium chloride plates.

Figure 5. Infrared Spectrum of Cyclobutylphenylketone.
Liquid film between sodium chloride plates.

Figure 6. Infrared Spectrum of Cyclobutylphenylcarbinol.
Liquid film between sodium chloride plates.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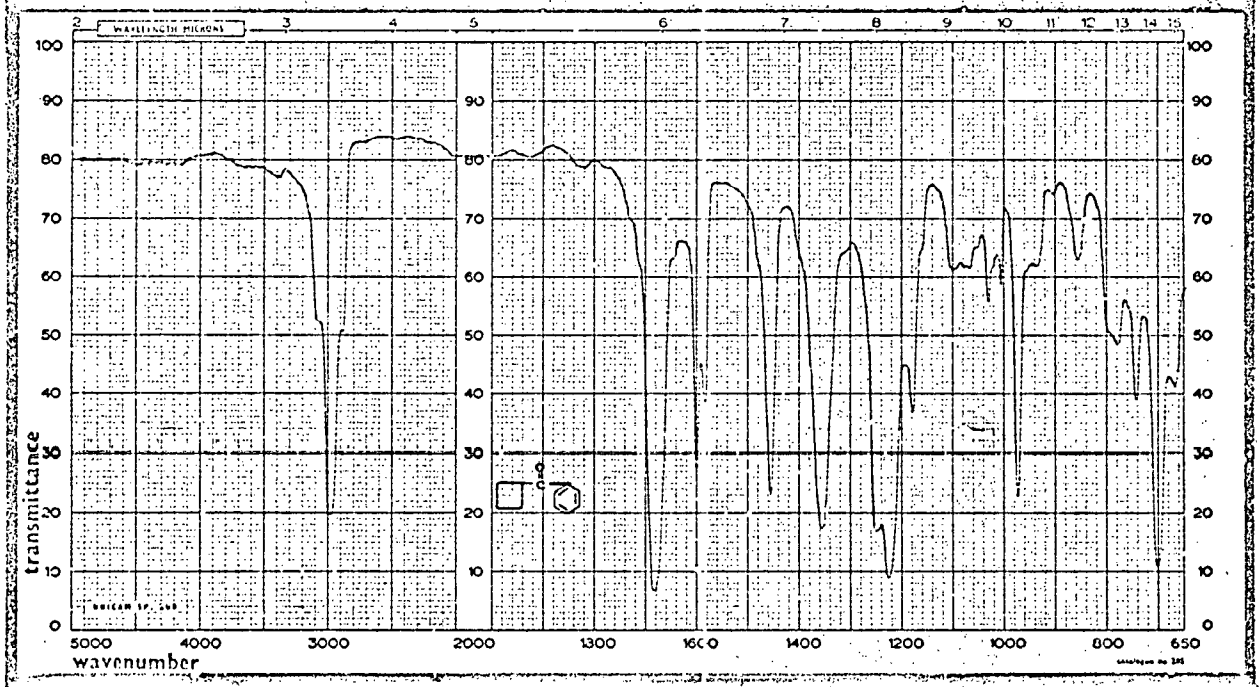
transmittance
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
wavenumber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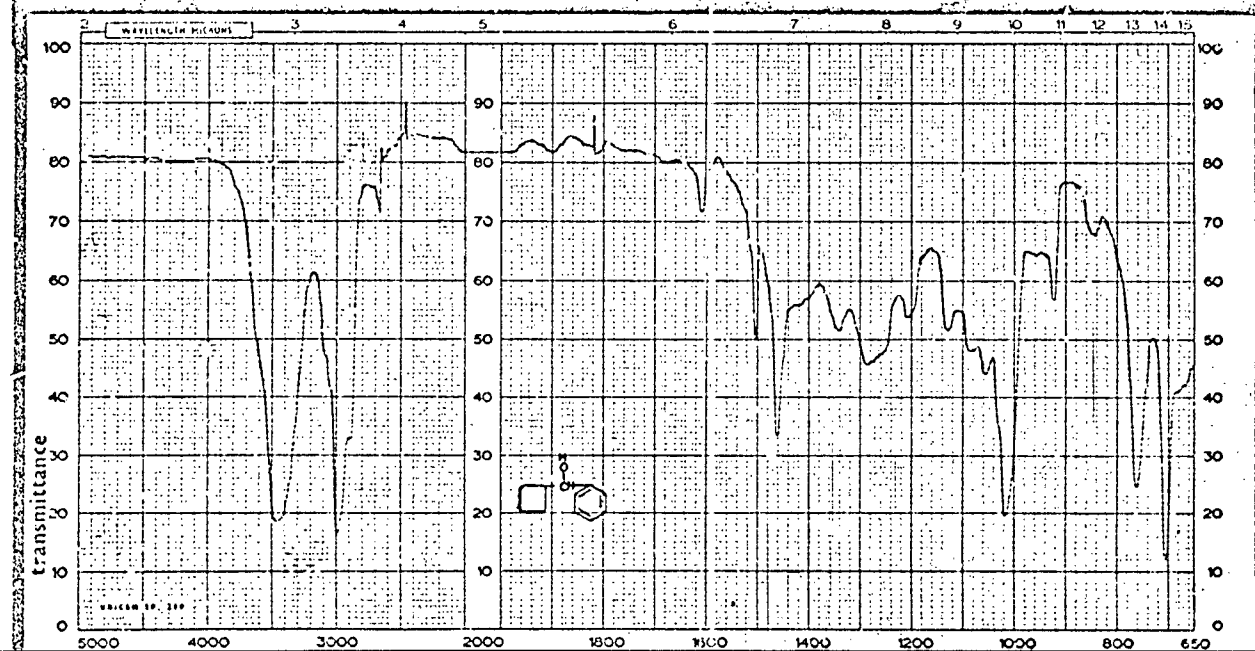
WAVELENGTH MICRONS
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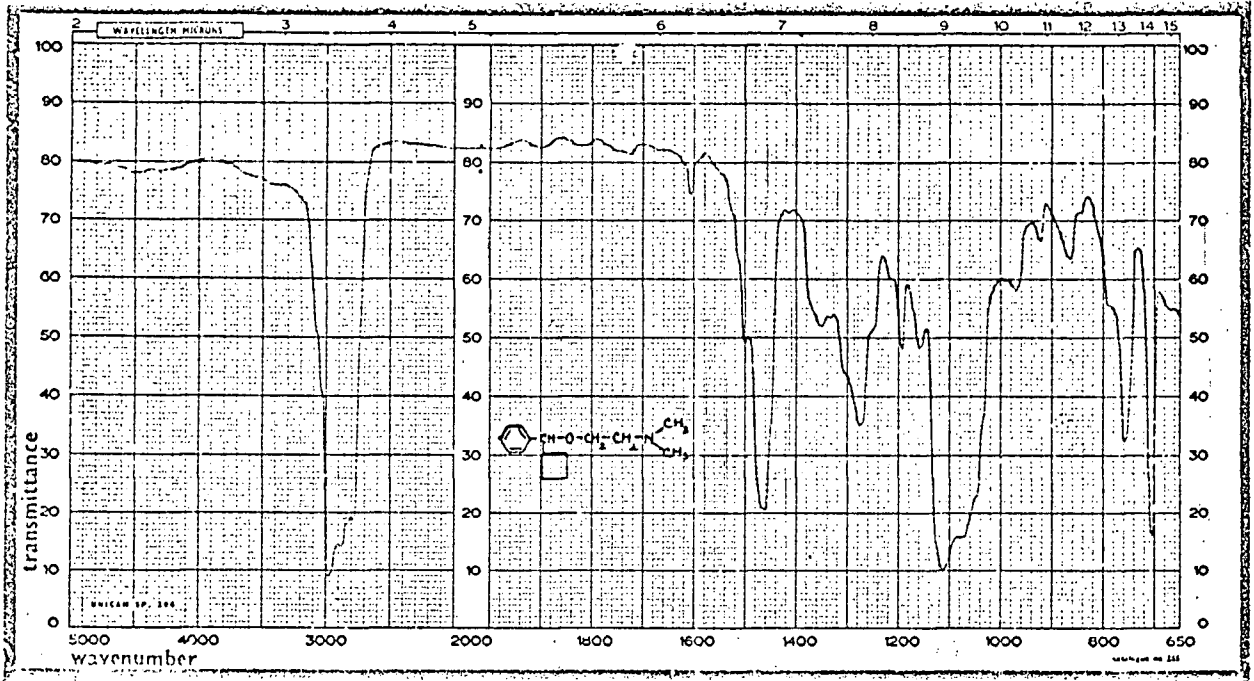
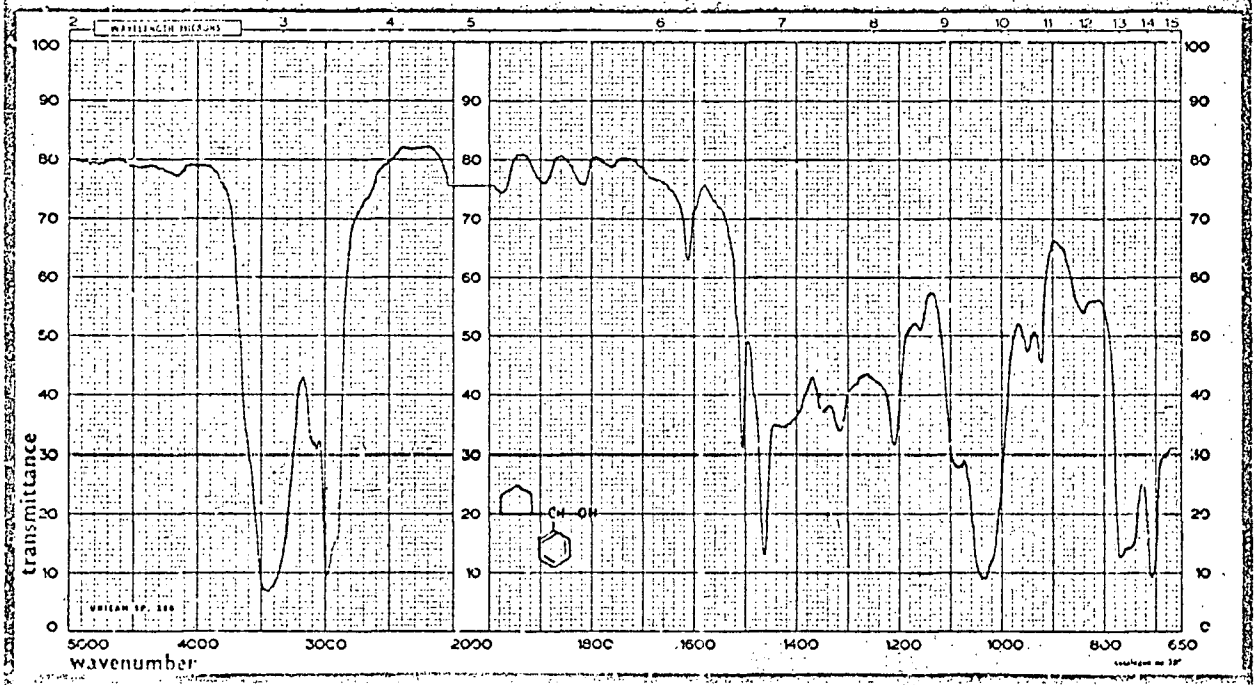
100 90 80 70 60 50 40 30 20 10 0
transmittance
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650

Figure 7. Infrared Spectrum of 2-(∝-Cyclobutylbenzyloxy)-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.

Figure 8. Infrared Spectrum of cyclopentylphenylcarbinol.
Liquid film between sodium chloride plates.

Figure 9. Infrared Spectrum of 2-(∝-Cyclopentylbenzyloxy)-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.


WAVELENGTH MICRONS
transmittance
wavenumber
UNICAM SP. 200


WAVELENGTH MICRONS
transmittance
wavenumber
UNICAM SP. 200

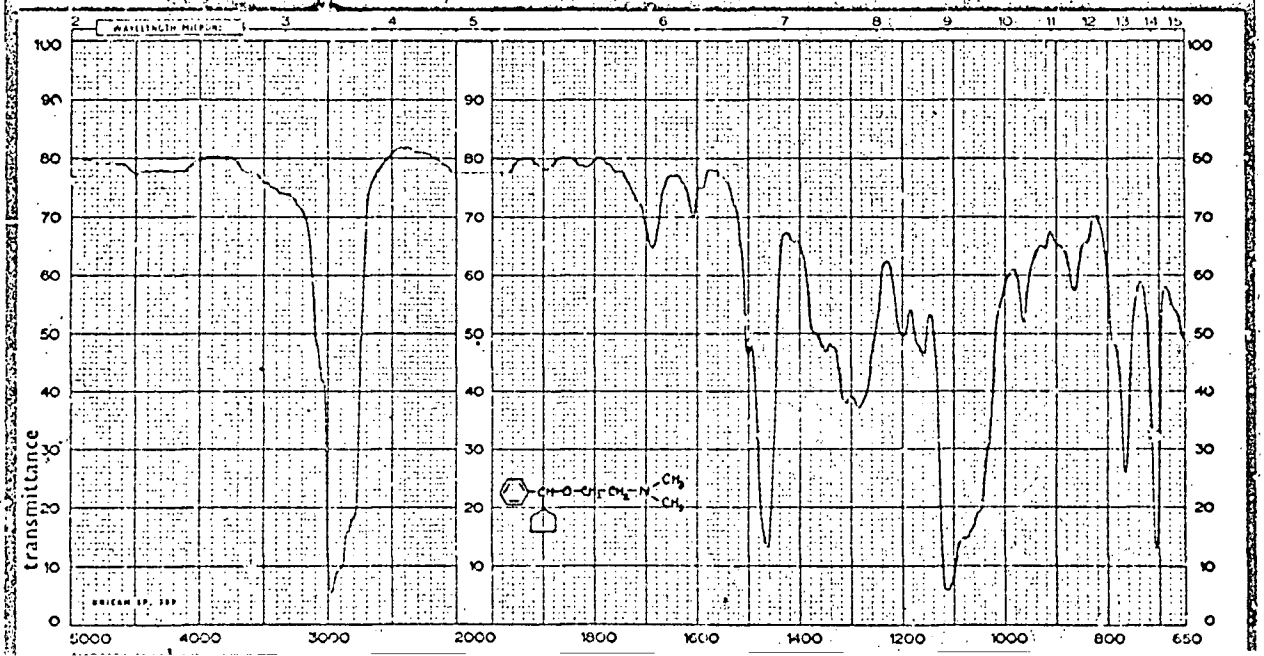
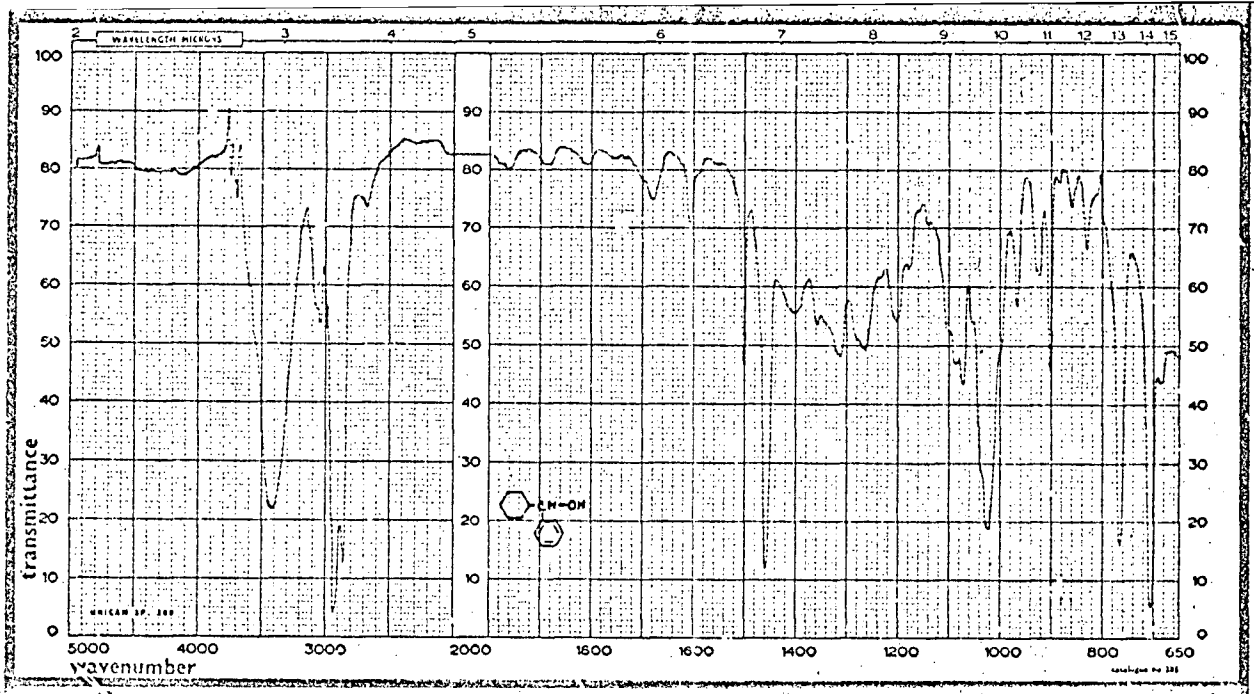
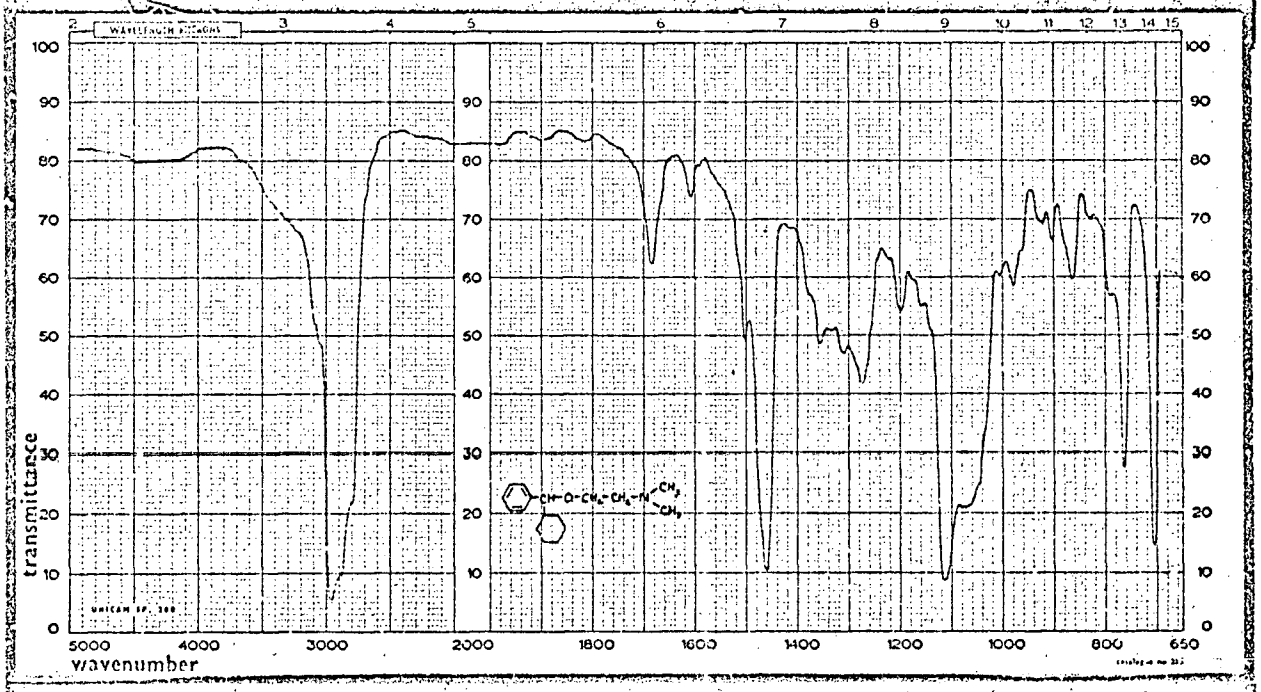

WAVELENGTH MICRONS
transmittance
UNICAM SP. 200

Figure 10. Infrared Spectrum of Cyclohexylphenylcarbinol.
Liquid film between sodium chloride plates.

Figure 11. Infrared Spectrum of 2-(∝ -Cyclohexylbenzyloxy)
-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.

Figure 12. Infrared Spectrum of Cycloheptylphenylcarbinol,
Lot IV.
Liquid film between sodium chloride plates.


WAVELENGTH MICRONS
transmittance
wavenumber
CH-OH


WAVELENGTH MICRONS
transmittance
wavenumber
CH-O-CH2-CH2-N(CH3)2

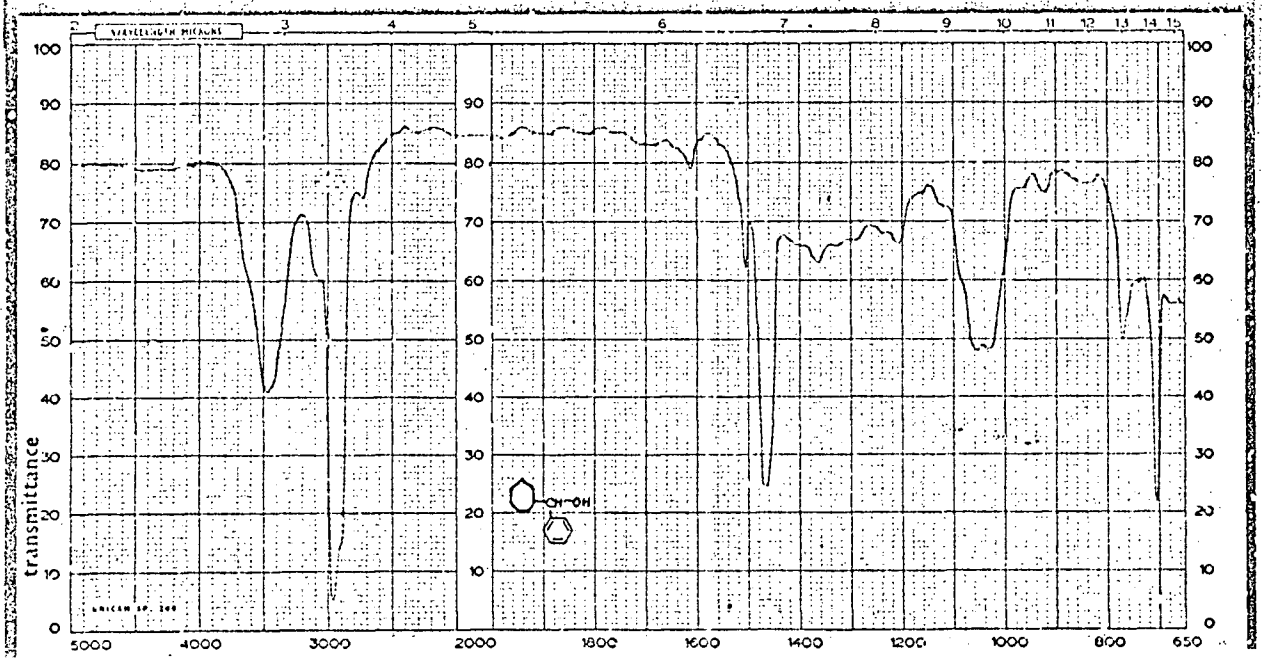
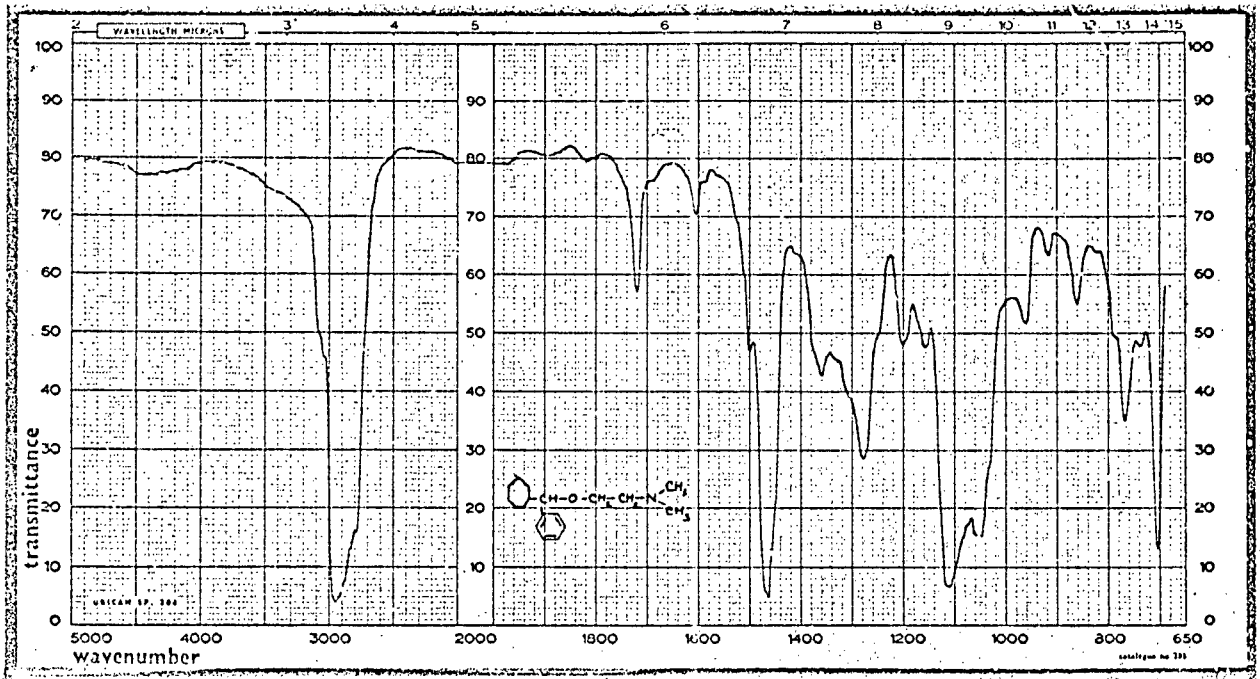
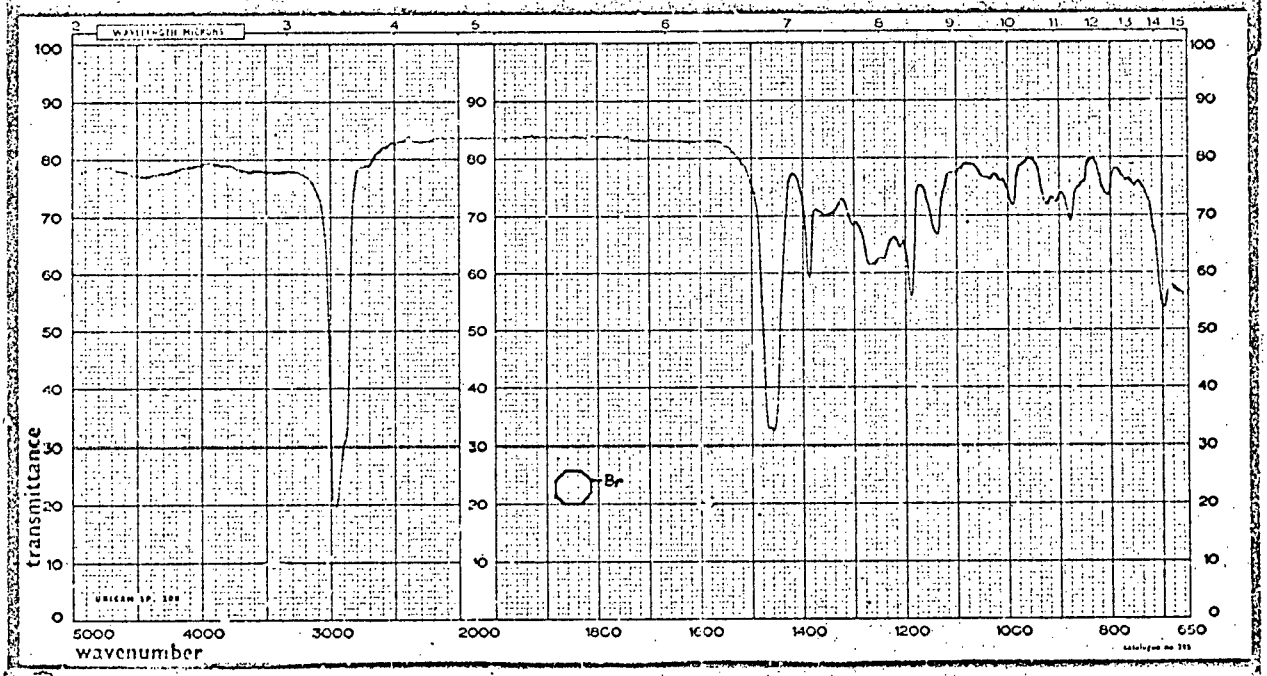

WAVELENGTH MICRONS
transmittance
CH-OH

Figure 13. Infrared Spectrum of 2-(α-Cycloheptylbenzyloxy)-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.

Figure 14. Infrared Spectrum of Cyclooctyl Bromide.
Liquid film between sodium chloride plates.

Figure 15. Infrared Spectrum of Cyclooctylphenylcarbinol.
Liquid film between sodium chloride plates.


WAVELENGTH MICRONS
transmittance
wavenumber
UNICAM SP. 200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transmittance
wavenumber
UNICAM SP. 200

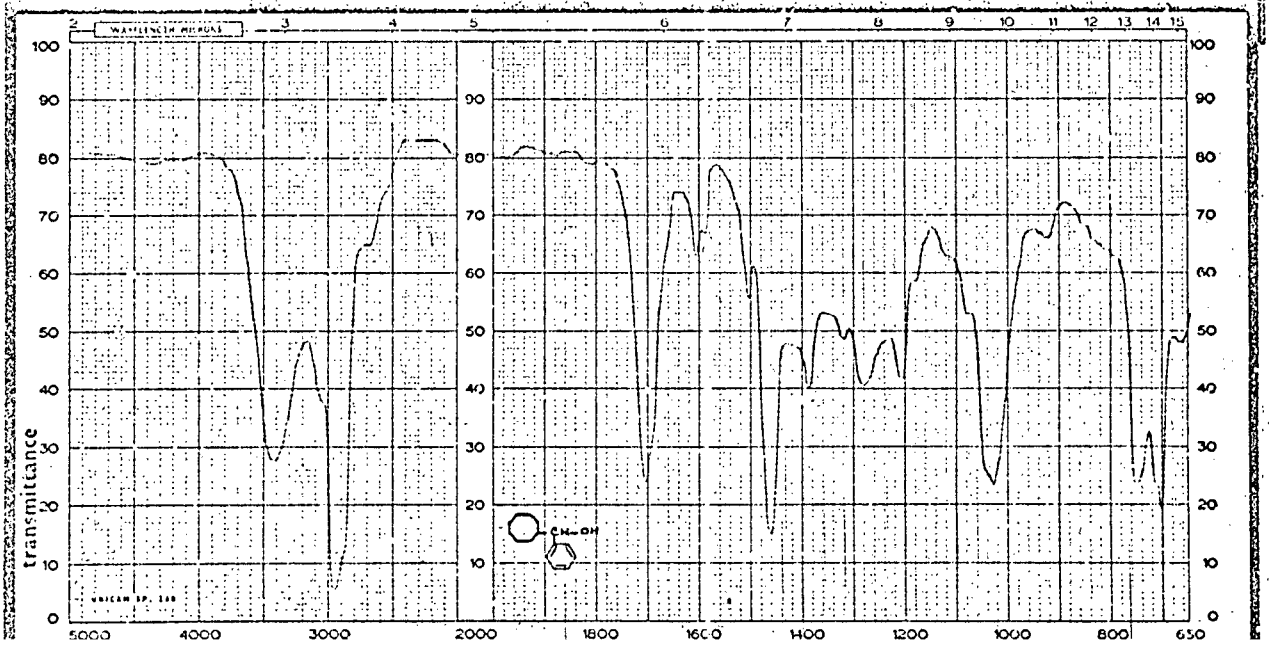
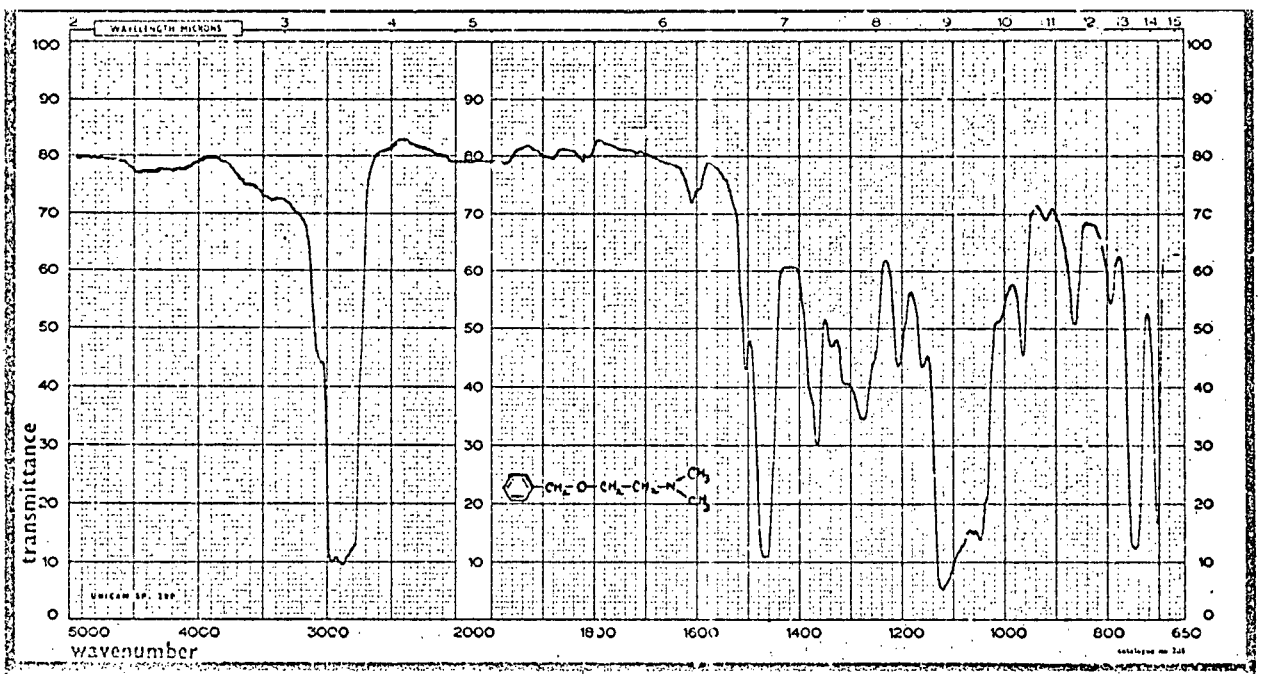

WAVELENGTH MICRONS
transmittance
UNICAM SP. 200

Figure 16. Infrared Spectrum of 2-(Benzyloxy)-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.

Figure 17. Infrared Spectrum of Dicyclopropylmethyl Bromide.
Liquid film between sodium chloride plates.

Figure 18. Infrared Spectrum of 2-(Dicyclopropylmethoxy)-N,N-dimethylethylamine, Lot I.
Liquid film between sodium chloride plates.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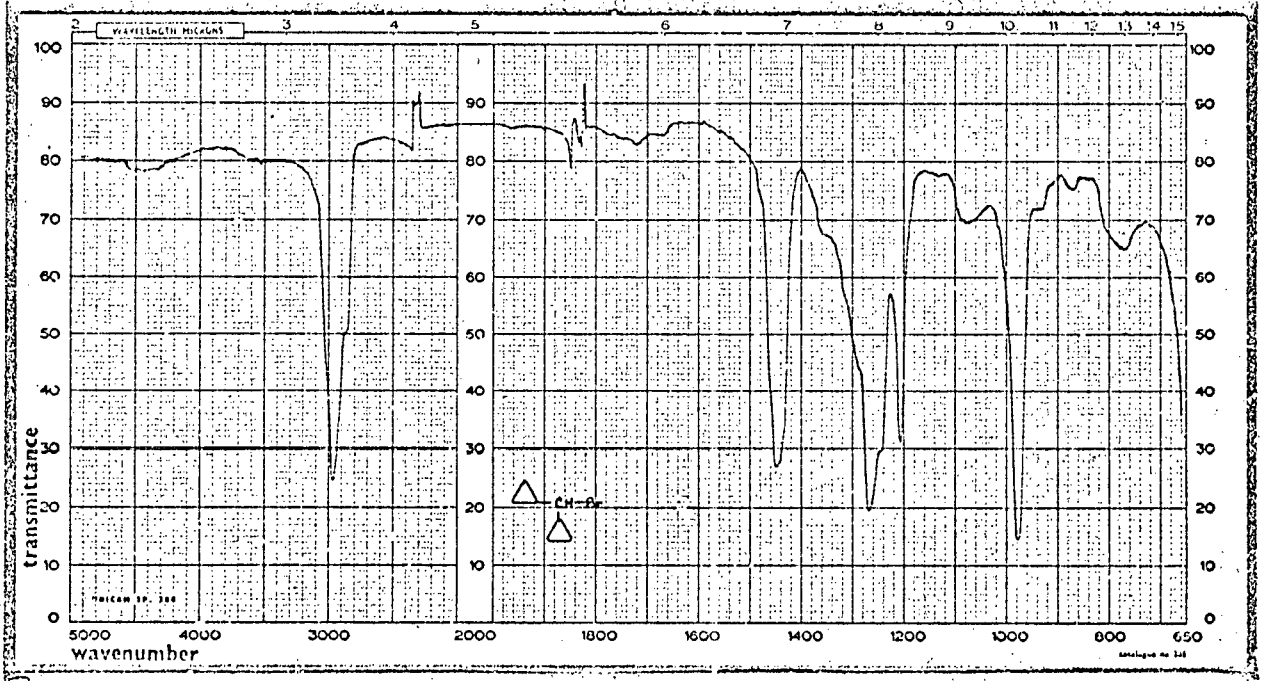
transmittance
wavenumber
UNICAM SP. 200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transmittance
wavenumber
UNICAM SP. 200

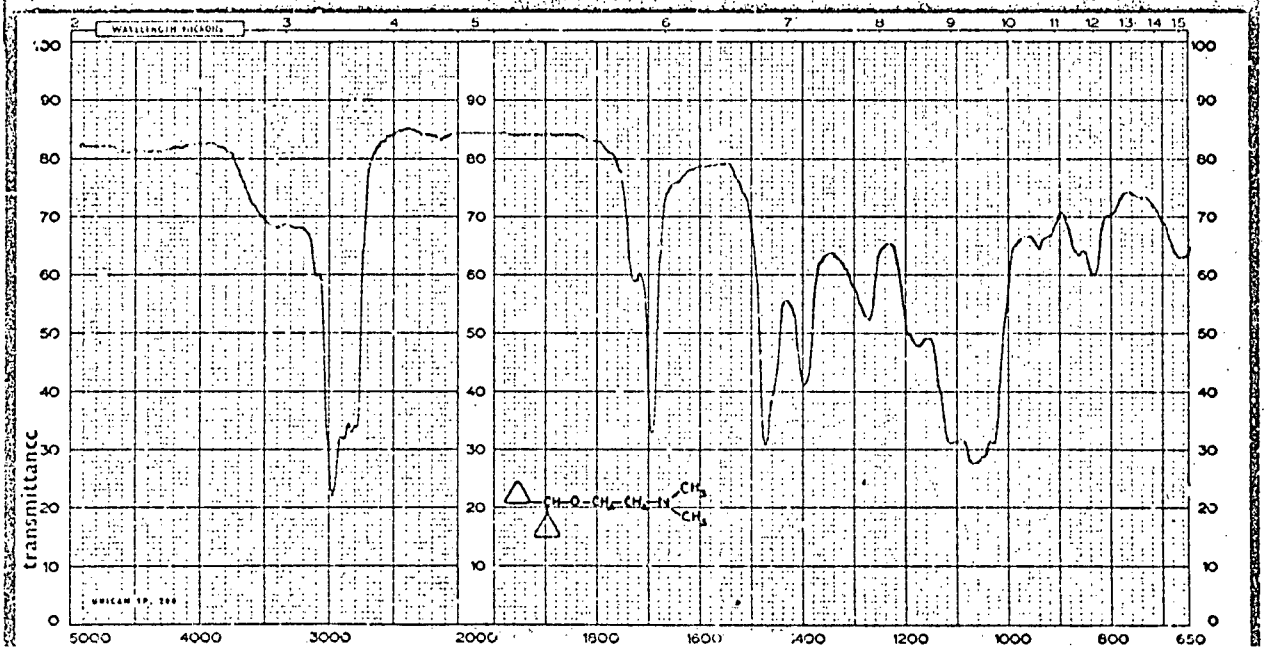
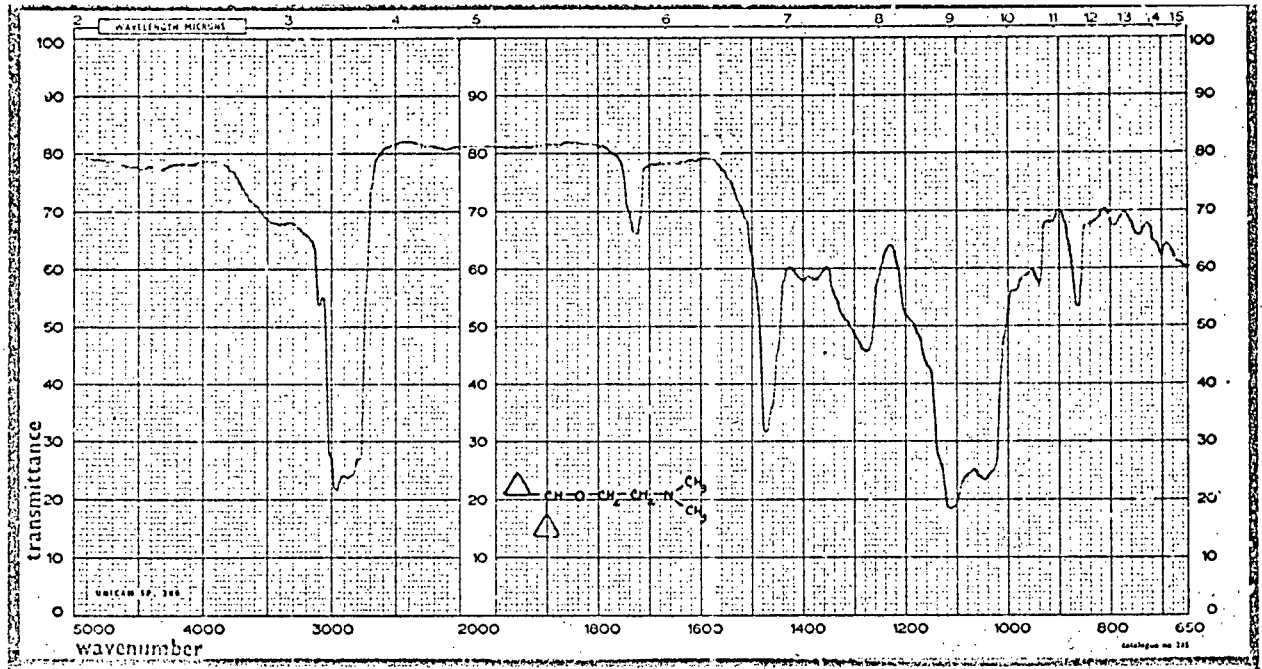
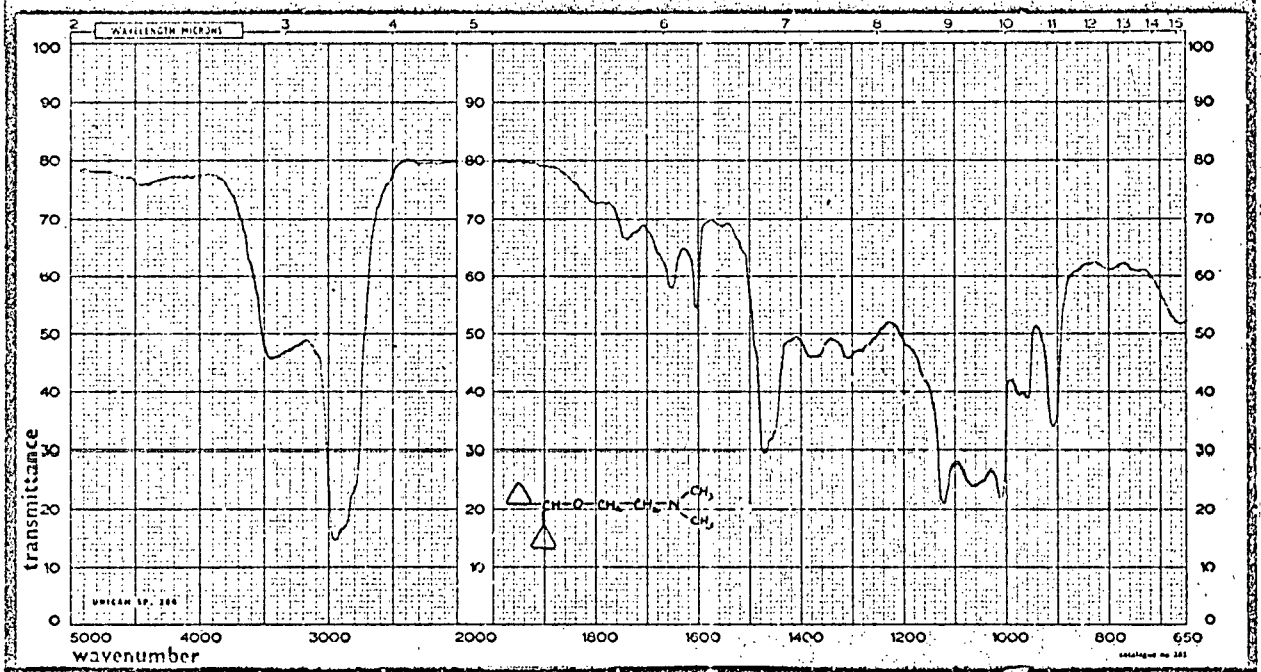

WAVELENGTH MICRONS
transmittance
UNICAM SP. 200

Figure 19. Infrared Spectrum of 2-(Dicyclopropylmethoxy) -N,N-dimethylethylamine, Lot III.
Liquid film between sodium chloride plates.

Figure 20. Infrared Spectrum of 2-(Dicyclopropylmethoxy) -N,N-dimethylethylamine, Lot IV, (Alternate Procedure).
Liquid film between sodium chloride plates.

Figure 21. Infrared Spectrum of Dicyclopentylcarbinol.
A 10% carbon tetrachloride solution in a 0.1 mm. sodium chloride cell.


WAVELENGTH MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15
100 90 80 70 60 50 40 30 20 10 0
transmittance
CH=O—CH2—CH2—N(CH3)2
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
wavenumber


WAVELENGTH MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15
100 90 80 70 60 50 40 30 20 10 0
transmittance
CH=O—CH2—CH2—N(CH3)2
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
wavenumber

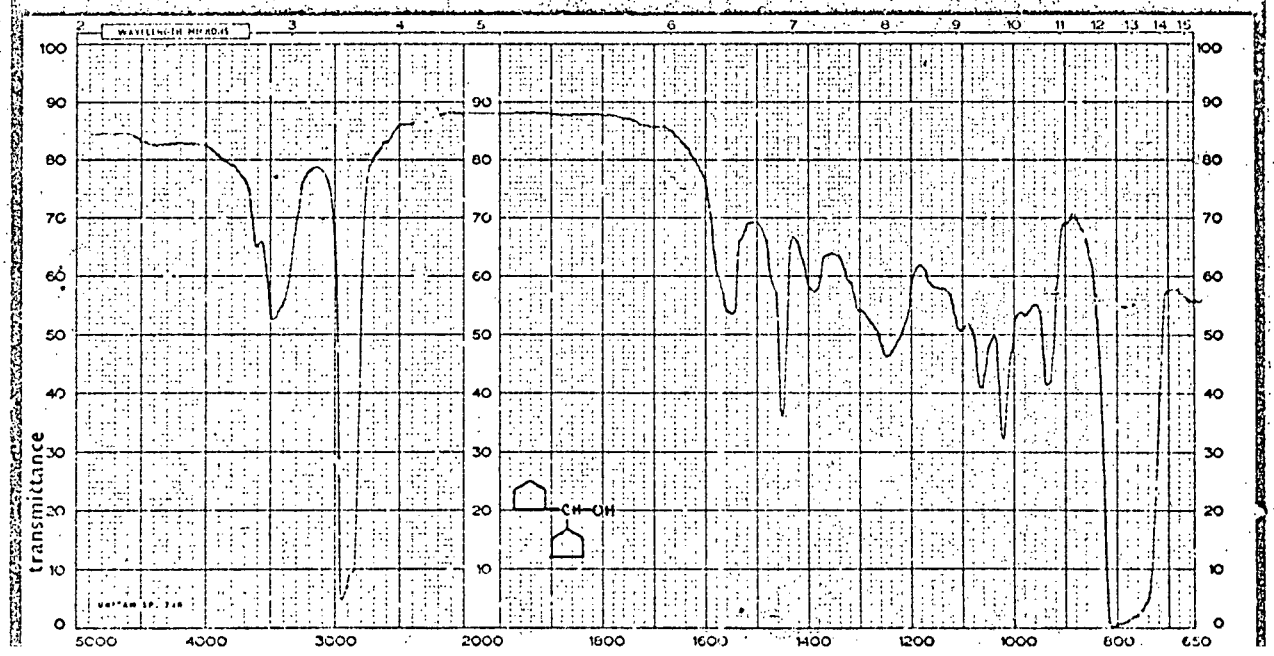
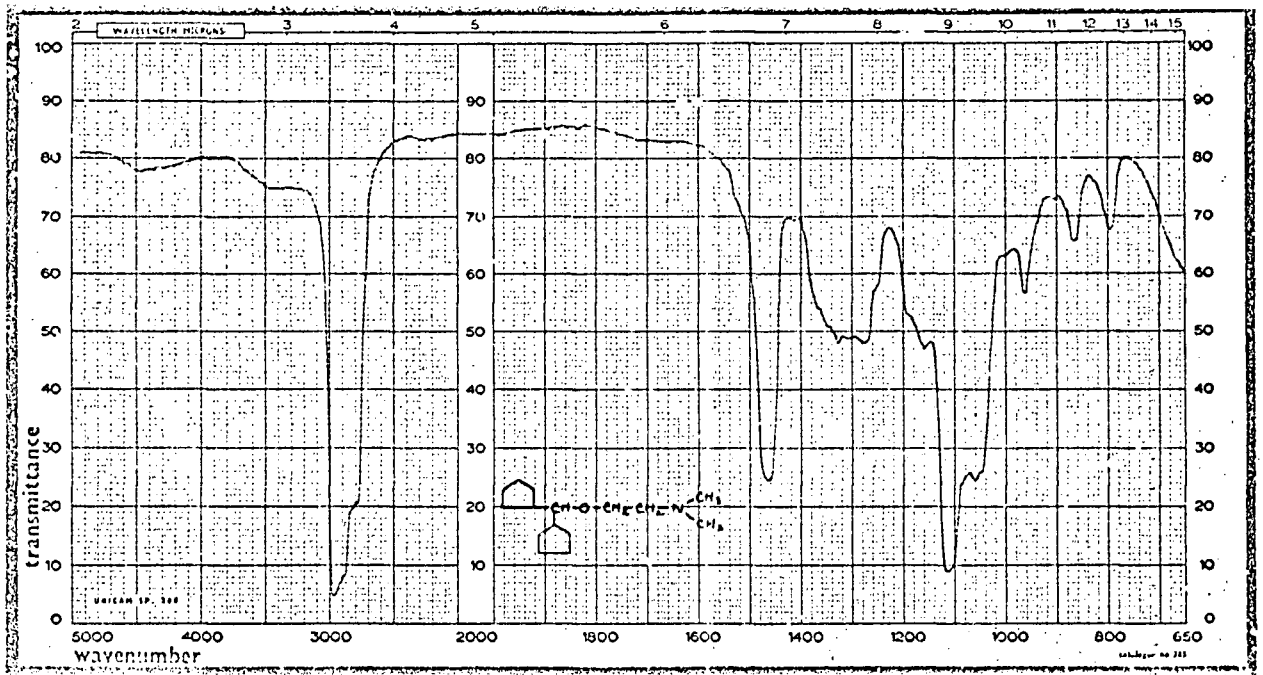

WAVELENGTH MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15
100 90 80 70 60 50 40 30 20 10 0
transmittance
CH—OH
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650

Figure 22. Infrared Spectrum of 2-(Dicyclopentylmethoxy) -N,N-dimethylethylamine.
Liquid film between sodium chloride plates.

Figure 23. Infrared Spectrum of Cyclohexanecarboxaldehyde.
Liquid film between sodium chloride plates.

Figure 24. Infrared Spectrum of Dicyclohexylcarbinol.
A 10% carbon tetrachloride solution in a 0.1 mm. sodium chloride cell.


WAVELENGTH MICRONS
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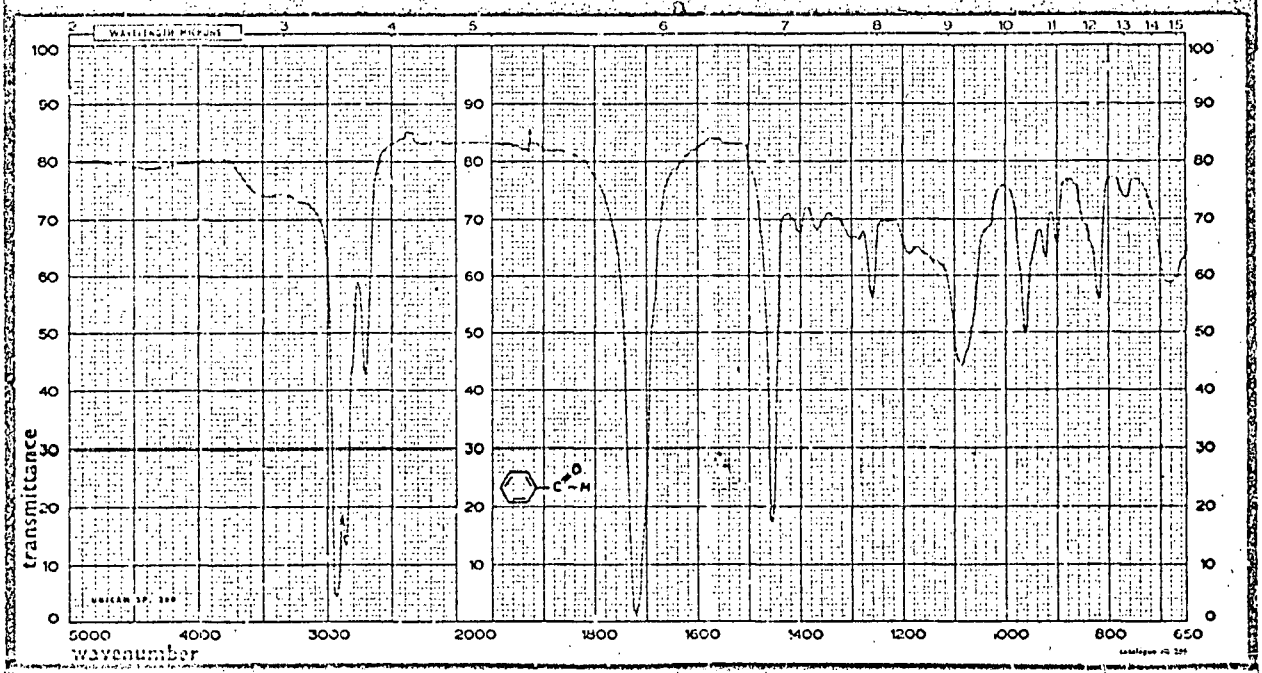
100 90 80 70 60 50 40 30 20 10 0
transmittance
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
wavenumber
UNICAM SP. 200


WAVELENGTH MICRONS
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100 90 80 70 60 50 40 30 20 10 0
transmittance
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
wavenumber
UNICAM SP. 200

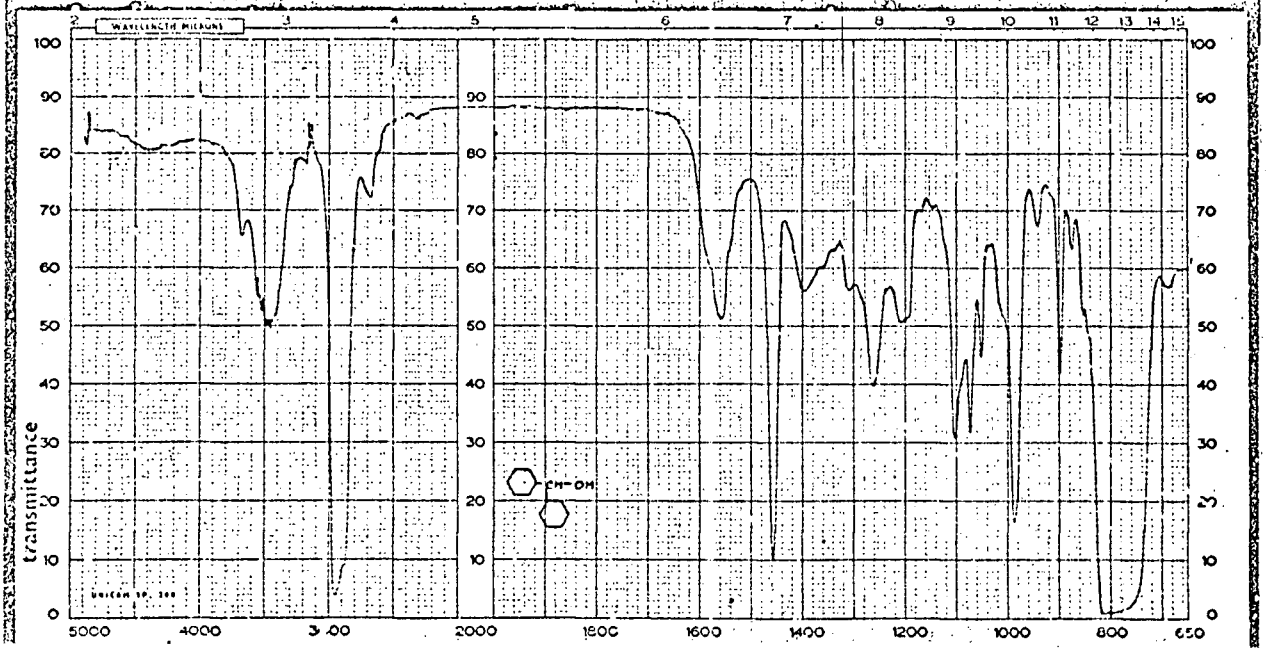
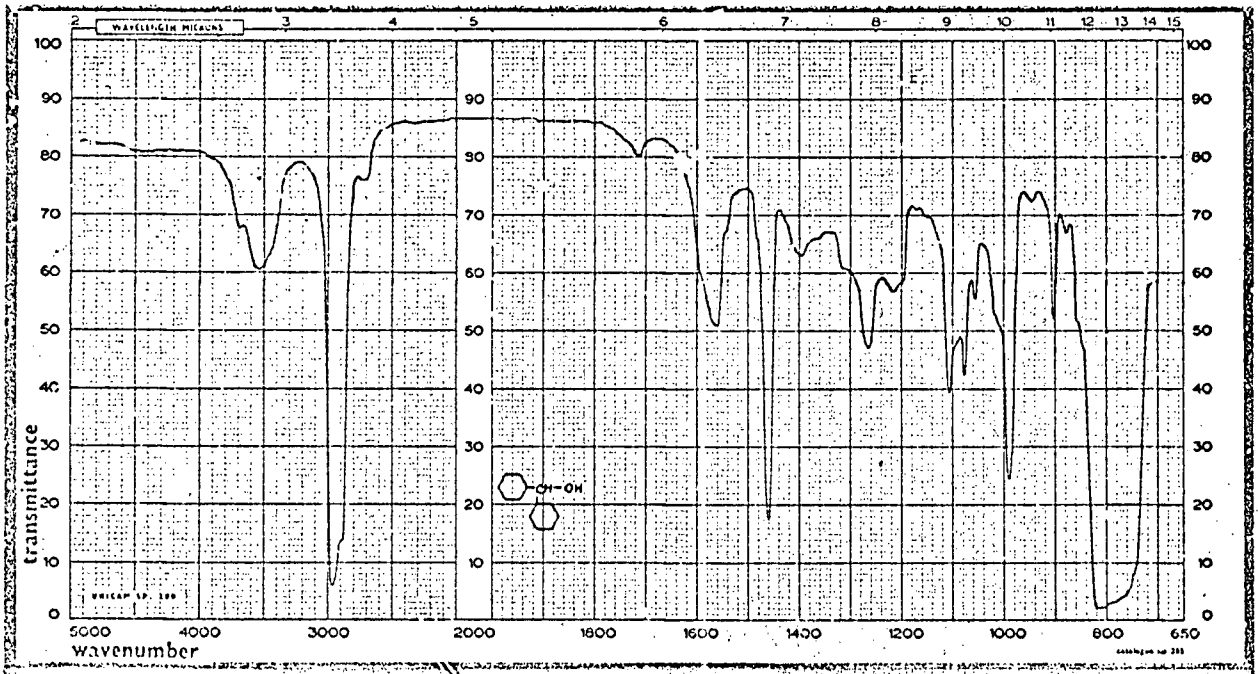
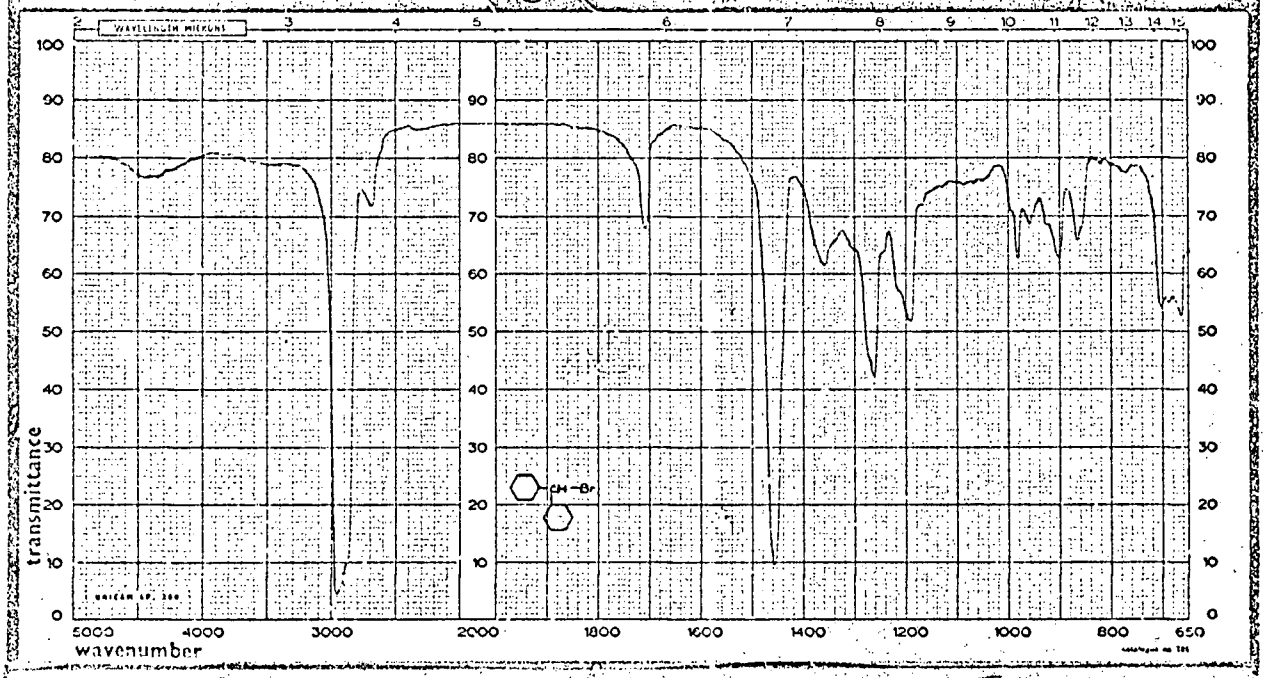

WAVELENGTH MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15
100 90 80 70 60 50 40 30 20 10 0
transmittance
5000 4000 3000 2000 1800 1600 1400 1200 1000 800 650
UNICAM SP. 200

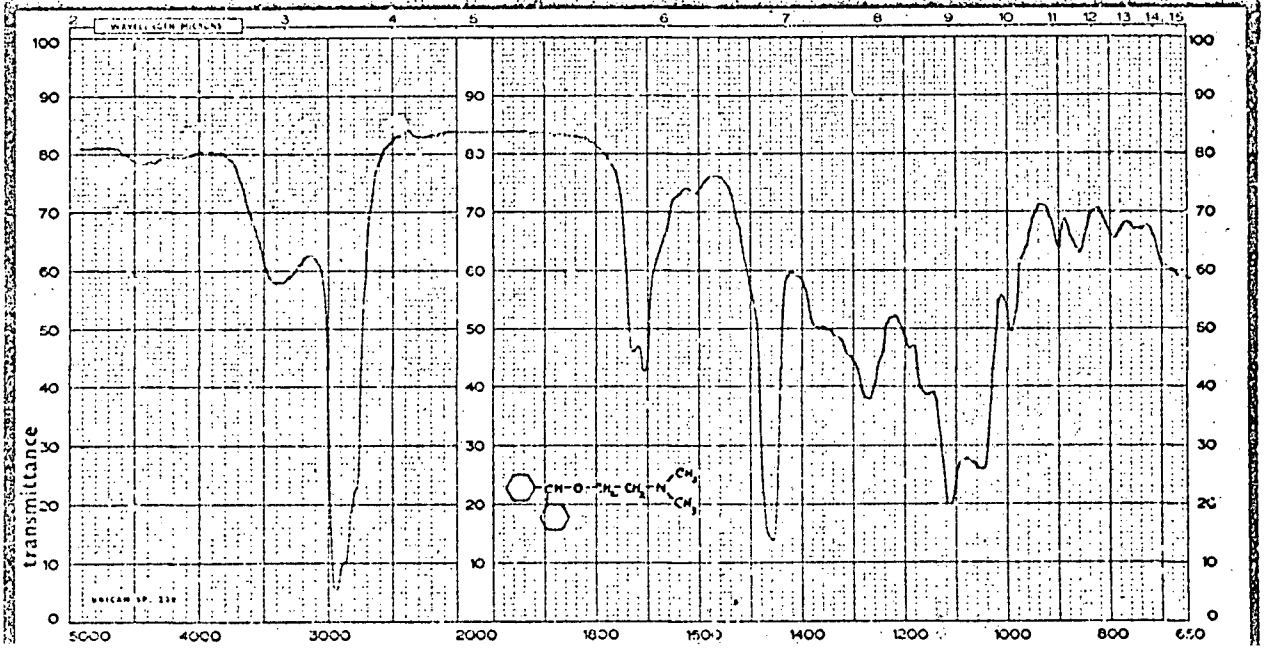
Figure 25. Infrared Spectrum of Recovered Dicyclohexylcarbinol.
A 5% carbon tetrachloride solution in a 0.1 mm. sodium chloride cell.

Figure 26. Infrared Spectrum of Dicyclohexylmethyl Bromide.
Liquid film between sodium chloride plates.

Figure 27. Infrared Spectrum of 2-(Dicyclohexylmethoxy)-N,N-dimethylethylamine.
Liquid film between sodium chloride plates.


WAVELENGTH MICRONS
transmittance
wavenumber
5000
4000
3000
2000
1800
1600
1400
1200
1000
800
650
CH-OH


WAVELENGTH MICRONS
transmittance
wavenumber
5000
4000
3000
2000
1800
1600
1400
1200
1000
800
650
CH-Br


WAVELENGTH MICRONS
transmittance
5000
4000
3000
2000
1800
1500
1400
1200
1000
800
650
CH-O-CH2-CH2-N
CH3
CH3

PART VII

SUMMARY

A series of cycloalkyl analogues of diphenhydramine containing a 3-membered to a 7-membered cycloalkyl ring, and a second series of dicycloalkyl analogues with two 3-membered, 5-membered and 6-membered rings in the nucleus of the antihistaminic molecule, have been prepared. The following compounds have been synthesized: 2-(α-cyclopropylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclobutylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclopentylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cyclohexylbenzyloxy)-N,N-dimethylethylamine, 2-(α-cycloheptylbenzyloxy)-N,N-dimethylethylamine, 2-(dicyclopropylmethoxy)-N,N-dimethylethylamine, 2-(dicyclopentylmethoxy)-N,N-dimethylethylamine and 2-(dicyclohexylmethoxy)-N,N,-dimethylethylamine. These compounds have been characterized by their infrared spectra and elemental analyses of the chloroplatinate derivatives, with the exception of the cyclopropyl and dicyclopropyl analogues, which would not yield the chloroplatinates. Other derivatives of these two compounds which were tried, either would form as oils or were too hygroscopic for recrystallization. Therefore, analyses were performed on samples of the free base, and although these results varied somewhat, the infrared spectra indicated that the products formed are the antihistaminic derivatives,

which are of slightly varying degree of purity.

The general synthetic route for the first series involved a Grignard reaction of the cycloalkyl bromide on benzaldehyde to yield the cycloalkylphenylcarbinol. The cyclobutyl secondary compound, was prepared by a Friedel-Crafts reaction of cyclobutanecarboxyl chloride on benzene with aluminum chloride as the catalyst. The cyclobutylphenylketone which resulted was then reduced to the carbinol with lithium aluminum hydride. The dicycloalkylcarbinols for the second series were obtained by a Grignard reaction of the cycloalkyl bromide on ethyl formate. These secondary carbinols were then reacted with 2-dimethylaminoethylbromide in the form of the hydrobromide salt. An extra molecular equivalent of the condensing agent, sodium amide, liberated the free base from the salt. Since the yields in the condensation reactions in the less reactive second series were particularly low, an alternate procedure was tried, in which the bromides of the dicycloalkylcarbinols were treated with 2-dimethylaminoethanol in the presence of sodium amide.

A major difficulty encountered in the preparation of the intermediates was the presence of a carbonyl contaminant in some of the prepared secondary carbinols, due to the presence of excess aldehyde or ethyl formate. The cycloheptyl- and cyclooctylmagnesium bromides form in considerably lower yields than the smaller ring compounds. Therefore, the Grignard reagent present in the solution must be estimated

by a standard method to determine the amount of aldehyde or ester required. Also, steric hindrance favored reduction, so that low yields of addition products were obtained. Both normal and inverse methods of addition were tried and the latter method appears to increase the yield of carbinol. A Lewis acid, magnesium bromide, was used in an attempt to increase addition. When the same molar ratios of bromide to benzaldehyde were used, the use of a Lewis acid appeared to yield a product with less carbonyl impurity.

The condensation reactions under the conditions employed here were slow and variable. One of the main difficulty is in the formation of the sodium alkoxide. This slow reaction necessitated the use of a finely divided form of the condensing agent, and lengthy warming of the mixture. However, too long a period of heating the carbinol and sodamide mixture appears to alter the carbinol molecule in some way so that no product could be obtained. The second phase of the condensation reaction, in which the sodium derivative is refluxed with the amine salt, also proceeded slowly, and a sufficient period of time must be allowed for the reaction to go to completion. An attempt to prepare the cyclooctyl analogue was unsuccessful. This may be due to the reagent not being the cyclooctylphenylcarbinol or to alteration of the carbinol molecule during warming with the sodamide. The alternate condensation reaction, in which a

dicycloalkylmethyl bromide was reacted with the sodium derivative of 2-dimethylaminoethanol, did not appear to improve the yields of analogue.

PART VIII

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