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A Non-Computer Method Used to Determine a Structural Analog Associated with Xerostomia Among Diverse Species of Drugs: Speculation Based on Molecular Models

Patrick J. Angelo Jr.
Loyola University Chicago

A NON-COMPUTER METHOD USED TO DETERMINE A STRUCTURAL ANALOG ASSOCIATED WITH XEROSTOMIA AMONG DIVERSE SPECIES OF DRUGS. SPECULATION BASED ON MOLECULAR MODELS

by

Patrick J. Angelo, Jr.

A Thesis Submitted to the Faculty of the Graduate School of Loyola University of Chicago in Partial Fulfillment of the Requirements for the Degree of

Master of Science

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1980

DEDICATION

To my parents, Patrick and Frances Angelo Sr., my wife Kimberly Ann (Burgess) Angelo, and inlaws Jack and Mary Burgess, for their encouragement, support and understanding.

ACKNOWLEDGMENTS

I wish to thank the members of my advisory committee Dr. Louis Blanchet, Dr. Hal D. McReynolds, and Dr. Patrick Toto. I am particularly grateful to Dr. Blanchet, and wish to express my sincere appreciation for his guidance throughout the research project.

VITA

The author, Patrick J. Angelo, Jr. is the son of Patrick J. Angelo, Sr. and Frances (Carducci) Angelo. He was born May 27, 1952, in Chicago, Illinois.

His elementary education was obtained at St. Francis Borgia, a Chicago parochial school, and secondary education at St. Patrick High School, Chicago, Illinois, where he was graduated in 1970.

In September, 1970 he entered the Triton Junior College. In September, 1972, he entered the Loyola University (Chicago) and in June, 1974 received the degree of Bachelor of Science with a major in biology.

In September, 1974, he was awarded an assistantship in Oral Biology at Loyola University Dental School.

In September, 1976, he entered the Loyola University School of Dentistry. He is presently ending his senior year. In June, 1980, he was awarded the Master of Science degree in Oral Biology.

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CHAPTER I

INTRODUCTION AND STATEMENT OF THE PROBLEM

In a little known publication, Bahn (1972) listed 17 different classes of drugs that are known to exert parasympathetic (atropinic) side effects in addition to their primary pharmacologic actions for which they are usually administered. One of these parasympathetic actions produces xerostomia ("dry mouth"), an observation which is not without great clinical significance to the dental profession since there is a preponderance of evidence relating the rate of flow of saliva, as well as its composition, to the etiology of dental caries and periodontal disease (Mandel, 1974; Mandel, 1976; Wotman, 1976; Grant, 1979). It should be of interest, certainly to medical and dental clinicians, to point out that the recommended dose-scheduling for most of these drugs is that they be administered ante-cibum (a.c., before meals), which represents a critical time associated with the exacerbation of cariogenic factors, inadvertently resulting in a form of iatrogenic medical and/or dental tooth destruction.

The drug groups which are presently known to have xerostomatic side effects are numerous and diverse in terms of their pharmacologic classification and clinical uses, are listed as follows:

Analgesics
Anorexics
Anticonvulsives
Antiemetics
Antihistamines
Antihypertensives
Antinauseants
Antiparkinsons
Antipruritics
Antispasmotics
Cold medications
Decongestants
Diuretics
Expectorants
Muscle relaxants

Psychotropic drugs:
- Central nervous system depressants
- Dibenzazepine derivatives
- Monoamine oxidase (MAO) inhibitors
- Phenothiazine derivatives
- Tranquilizers (major and minor)

In reality, only a few of those listed above are actually used to any degree in dental therapeutics, however, those used essentially include some of the analgesics, antihistamines, muscle relaxants, and the minor tranquilizers to some lesser extent. For the most part, dental clinicians who do use these aforementioned drugs are quite aware of their xerostomatic side effects and therefore employ them only when they are absolutely indicated but not before prescribing some alternate drug whenever practicable. The fact that so many pharmacologically diverse drugs should possess one single common, undesirable side effect is intriguing, and even more so are their molecular structural differences.

It has been well established that even the most subtle variations introduced into the structure of a given molecule can quite often lead to alterations in pharmacologic efficacy and potency of some specific

desirable pharmacological effect. On the other hand, certain inherent structures within a given drug, such as a substituted amide, or amidine, similar to that found in related, as well as unrelated compounds, are thought to be responsible for some of the same side effects demonstrated by these drugs, and suggests a structural-activity-relationship (SAR). Several SAR studies involving a series of narcotic analgesics have provided a wealth of material and information related to some of their common properties (Beckett, 1954). These studies, which utilized three-dimensional structural models, revealed that it was not only possible to arrange the atoms within the molecule so that they simulated those of morphine, but also demonstrated that steric factors can actually force such a structural arrangement upon a given compound (Goldstein, 1969). The narcotics, or morphine-like analgesics were at one time thought of structurally as N-methyl-Y-phenylpiperdine derivatives, and this is the group, or structural analog, that appears to be indispensable for their analgetic activity (Goth, 1978).

The conformations (originally coined by Haworth, 1929) of a molecule are the various shapes it can assume in space by rotations about its single bonds, without actually breaking them. On the other hand, rotations around double bonds are severely restricted since such rotations must break the bonds, and this requires a substantial energy input. It should be pointed out that while rotations can and do occur easily about single bonds, some rotations are not always free and unrestricted, but they do have, and exhibit favored orientation, or an average

conformation, an objective of this investigation which will be shown later.

Although conformational analysis was recognized as early as 1890 (Sachse, 1890; Sachse, 1892) when he reported that cyclohexane and other saturated six-membered rings could exist in either a "chair" or a "boat" form.

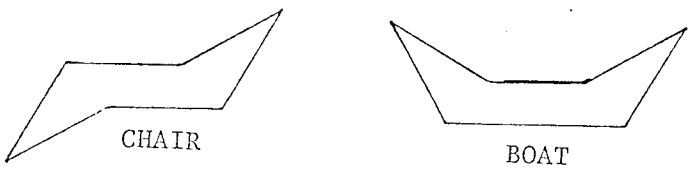


Fig. 1-1 Chair and Boat Conformations of Cyclohexane

It was not until some 60 years later that this discipline received the attention it merited. Widespread, but brief, acceptance was not to come until the pioneering paper of Barton in 1950 (Barton, 1950) in which he discussed the "puckered" cyclohexane ring under the title of "conformational analysis." However, this is not to say that conformational analysis had gone unrecognized for its worth during this time interim. A number of scientists in this country and in Europe and Asia were busy developing tools and methods for future conformational studies, while the remainder of the scientific community were not convinced of importance of this new tool. Even as late as 1948 many chemists, especially organic chemists, still viewed cyclohexane as a planar molecule which, without a doubt, was an example of "static", non-steriochemical thinking of the

times.

At the Technical University in Delft, Holland, in the 1920's, two scientists recognized conformational factors in the complexing of alicyclic and acyclic 1,2 - glycols with boric acid, and in the rate of subsequent acetonide formation (Derx 1922; Hermans, 1924). Meanwhile in this country at the California Institute of Technology at Pasadena, Dickerson and his mentor viewed the chair shape of cyclohexane through X-ray crystallography (Dickerson, 1928). Later, in the 1930's, at Graz, Austria, a team of scientists led by Kohlrausch were able to perceive, employing Raman spectroscopy, the existence of what are commonly referred to as axial and equitorial substituents in cyclohexanes:

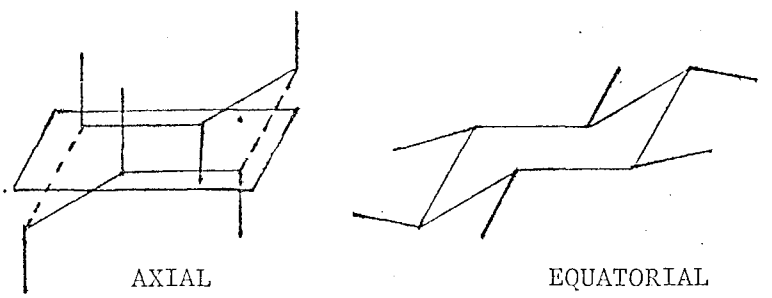


Fig. 1-2 Axial and Equitorial Bonds of Cyclohexane

While Hermans' report on the reactivity of benzoins remains an example of a classical investigation relative to the importance of molecular conformation (1924), his studies were further extended some 6 years later by Weissberger (1930) and Wolf (1930) who independently reported on the

reactivities of the corresponding chlorides. At this point, it seems noteworthy to mention the studies of Mizushima (1933; 1954; 1963) which were extended over a period of 3 decades. An excellent review of the history of conformational analysis can be perused from a German translation (Eliel, 1973; English translation, 1975), which, in addition to the formentioned investigators, mentions the works of Pitzer (1936; 1973) and Prosen, Johnson, and Rossini (1947). Over the years, many have contributed to our knowledge of conformational analysis which finally culminated in the 1969 joint award of the Nobel Prize in Chemistry to Barton and Hassel for their major works and influence in this field. From 1950 to 1965, the history of conformational analysis is well documented in several reviews (Angyal, 1952; Barton, 1956 and 1959; Orloff, 1954 and 1961) as well as textbooks and monographs (Eliel, et al., 1965; McKenna, 1966).

No division of the chemical sciences have prospered more in the last 3 decades from the numerous contributions in conformational analysis than has pharmaceutical chemistry, whose major role is that of synthesizing chemicals for medicinal use, and pharmacology which has the responsibility of describing the uses and mechanism of action of drugs as therapeutic agents in the diagnosis, prevention, alleviation of symptoms, and curative effects of those special chemical substances. In order to facilitate their work and understanding as well as their ability to visualize three-dimensional molecules, scientists over the years have created many types of structural models (Petersen, 1979). However, in a review

article Gordon (1970) felt that molecular models did have limitations, but they could be very useful and were often indispensable.

From a historical point, it seems that the first models ever constructed were those of Dalton in 1812 (Benfey, 1966, Petersen, 1970) which consisted of pins and spheres not including the tetrahedron. Dalton's models were perhaps the outgrowth of the discovery of polarized light by Malus in 1808, and Nollaston's communication (1808):

> "... when the number of particles exceeds in the proportion of four to one, a stable equilibrium may again take place if the four particles are situated at the angles of the four equilateral triangles composing a regular tetrahedron."

At the end of his paper he stated:

> "It is perhaps too much to hope that the geometrical arrangement of primary particles will ever be perfectly known."

It seems as though Wollaston had some insight into the structural representation of carbon, but there is no record of his ever constructing models.

Fifty-five years later, Kekule (1867) described and gave rough directions for the manufacture of "ball-and-stick" models, however, they were apparently never exploited, else they could have gone a long way in explaining and revealing the secret of Pasteur's (+) and (-)-tartaric acids; even Wollaston's suggestion should have given him the hint he needed. It was not until 1874 that the true significance of the tetrahedron carbon atom was provided by Van't Hoff (1874) and not LeBel as

generally believed. (Sementon, 1955). It is generally well known that Van't Hoff worked in Kekule's laboratory where he certainly must have seen the "ball-and-stick" models although the molecular models he constructed were tetrahedra joined at their apexes, sides or faces making graphic pictures:

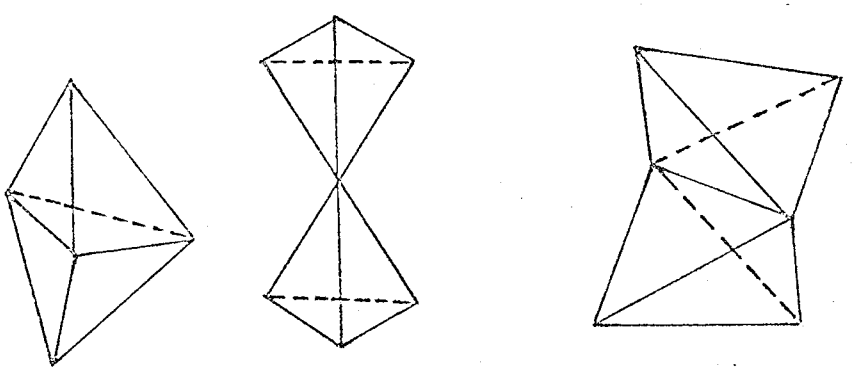


Fig. 1-3 Molecular Models used by Van't Hoff

It seems as though the use of molecular models did not truly become acceptable until around the turn of the century. According to Petersen (1970), the early models were not intended for problem solving, but rather to "express conviction with respect to the nature of things". The science world had to wait until the 1920's, with one exception, before the demand that models do something or be used to explain or predict some natural phenomena. The aformentioned exception was the remarkable work of Sachse (1890), which was ignored for 30 years, who, with the use of models proved the Baeyer strain theory in error, and cyclohexane could exist in the "chair" or "boat" forms, and that axial and equitorial substituents were

distinct and interconvertable by ring flipping. These ideas were revived by Mohr (1918), and 5 years later documented and expanded by Freudenberg (1933), and in spite of these works, they were not to be exploited until the late 1940's following World War II.

While the tetrahedra of Van't Hoff or the ball-and-stick models of Kekule made clear such concepts as asymmetry, mirror image and non-superimposability at the time Christie and Kenner (1922) reported the phenomenon of optical activity due to restricted rotation in biphenyl derivatives, they are incapable of elucidating this property. Even when the ball-and-stick models were modified, referred to as "expanded models" by Hauser (1941), they still failed whenever steric hindrance had to be demonstrated.

Since the development and use of those early molecular models of Van't Hoff and Kekule, numerous ones have been developed, some are outstanding, while others have limited applications. For an extensive review of the history of molecular models, the reader's attention is directed to the publication of Gordon (1970).

This investigation is being undertaken with a singular objective, that is, to determine a common hypothetical structural analog which probably exists in all of the pharmacologically diverse drugs reported by Bahn (1972) capable of causing xerostomia. A non-computer method will be used to determine the structure of this analog, and speculations as to its conformation will be determined by, or based on those observed in constructed molecular models.

CHAPTER II

MATERIALS AND METHODS

In order to satisfy the objectives of this investigation, 13 drugs, belonging to 4 different pharmacological groups were arbitrarily selected from Bahn's list of drugs (Bahn, 1972), including one not listed in his article. All drugs selected for this study will at first be listed according to their chemical names*, their pharmacologic or generic names, their pharmacologic or generic names, which will be underlined, and their proprietary or trade names following in brackets. For the sake of simplicity because the chemical names are so lengthy and cumbersome, and also due to the fact that some generic drugs may and do have several trade names, the only names used hereafter in this study will be generic.

The following is a list of the aforementioned drugs according to their pharmacologic classifications:

A. Anticholinergic Agents:

1. 8-N-methyl- (1,5-bicycloheptalamine)-3α-phenyl-β-hydroxypropionate; tropyl-tropate (Atropine**).

* Chemical names obtained from "Definitive Rules For The Nomenclature of Organic Chemistry" adopted by the Commission on Nomenclature and by the Council of the International Union of Pure and Applied Chemistry, 1957, and "Nomenclature of Organic Chemistry," Section D, IUPAC Information Bulletin on Tentative Nomenclature, Symbol, Units, and Standards, No. 31, August, 1973.

** The name, Atropine is used both generically and proprietarily.

2. 3-carbomoyl (3,3-diphenylpropyl)-diisopropylmethyl ammonium iodide; isopropamide (Darbid).

3. 1-bicycloheptenyl-1-phenyl-3 piperidine-propanol-1; biperiden (Akineton).

4. 3-N-triethyl-1-phenyl-hexyl propanol-1; tridihexethyl (Pathilon)

B. Sympathomimetic agents:

1. ℓ-1-(m-hydroxyphenyl)-2-methylaminoethanol; phenylephrine (Neo Synephrine).

2. d-N-methyl-β-phenylisopropylamine; methamphetamine (Desoxyn; Fetamin; Phelantin).*

3. d-N-benzyl-N,α-dimethyphenethylamine; benzphetamine (Didrex).

C. Antihistamines:

1. 2-(diphenylmethoxy)-N,N-dimethylethylamine: diphenhydramine (Benadryl).

2. 2-/ p-chlo-o- -(2-dimethylaminoethyl) benzyl/-pyridine; chlorpheniramine (Chlor-Trimeton; Teldrin).

3. 2-/ benzyl-(2-dimethylaminoethyl) amino/ pyridine; tripelennamine (Pyribenzamine).

4. N-(2'-dimethylamino-2'-methyl) ethylphenothiazine; promethazine (Phenergan).

* Not listed in Bahn's article.

D. Narcotic Analgesics:

1. N-methyl-4-phenyl-4-carbethoxypiperidine; meperidine (Demerol).
2. 6-diethylamino-4, 4-diethylamino-4, 4-diphenyl-3-heptanone; methadone (Dolophine).

These drugs were arbitrarily selected, not on the basis of the degree of xerostomia they produce, but primarily because they were the single active ingredient (exclusive of inert substances) in their proprietary preparation, as opposed to others which contained more than one active drug. All of the drugs listed in Bahn's work were listed according to their trade names as they were then listed in the 25th edition of the Physicians' Desk Reference (PDR, 1971). Since trade names give little or no information relative to the class or structure of the drug, generic names were obtained from this same PDR and cross-checked with the Merck Index (1977). The generic names were then used to obtain their true chemical names, and their structural formulae were then derived from several official drug compendia (Goodman, 1975; Goth, 1976; Aviado, 1972; Merck Index (1977).

The structural formula of each drug was first drawn on plane linear graph paper (Tops Form 3308) without regard to their stereochemical configuration, or three dimensional structure in space. Bond angles, and atomic distances were obtained from Hendrickson, et al., (1970) and were indicated in each of the drawings to be used as references although the total structures appear planar. From the semi-scaled structural formulae, ball-and-stick models were constructed in order to develop some idea

relative to their general molecular structures, and geometric relations especially where ring structures are encountered. The planar drawings were also used as a basis for the construction of the Drieding skeletal models which supplied further spatial geometric configurational information relative to strain and steric hinderances. Group structures, and their spatial configurations, which tended to be repeated in almost all of the compounds, were drawn separately and also noted on the planar drawings in heavy ink.

Scaled space-filling atomic models of Larsson and Kling, and scaled Kendrew atomic skeletal models were then fashioned from the drawings and previous models. All structures and drawings were reproduced photographically and those segments which were continually repeated, noted, and specially photographed. This structure was then drawn to scale indicating all interatomic distances (bond lengths) and bond angles Hendrickson, et al., (1970) for further comparison with photographs of Dreiding and Kendrew models. For the sake of better visualization, drawings were made of Kendrew atomic skeletal models superimposed over Larsson-Kling space-filled models.

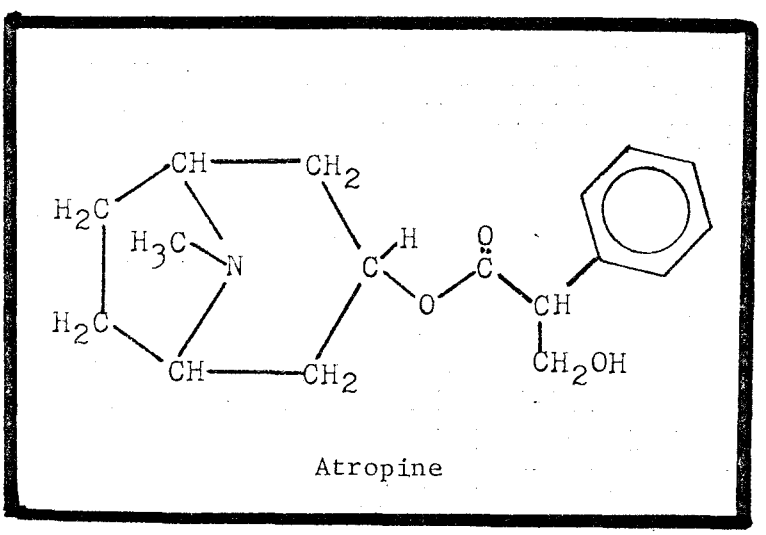
The results of these undertakings are reported in Chapter III.

CHAPTER III

RESULTS

The structural formulae of the drugs selected for this investigation are illustrated below as flat, planar structures, using the Merck Index (1977), Goodman and Gilman (1975), and Goth (1978) as major references from which each structural formula was drawn. These drawings were later used to construct all of the molecular models utilized in this study. Again, as previously stated, for the sake of simplicity, generic names of the drugs illustrated will be used in this and subsequent chapters, thus avoiding the pretentious and laborious use of lengthy, and some times cumbersome, chemical names (see Chapter II, Materials and Methods).

A. Anticholinergic Drugs



Atropine

* Atropine was not one of the drugs listed in Bahn's paper (1972), but was included in this study because it is a potent xerostomic drug.

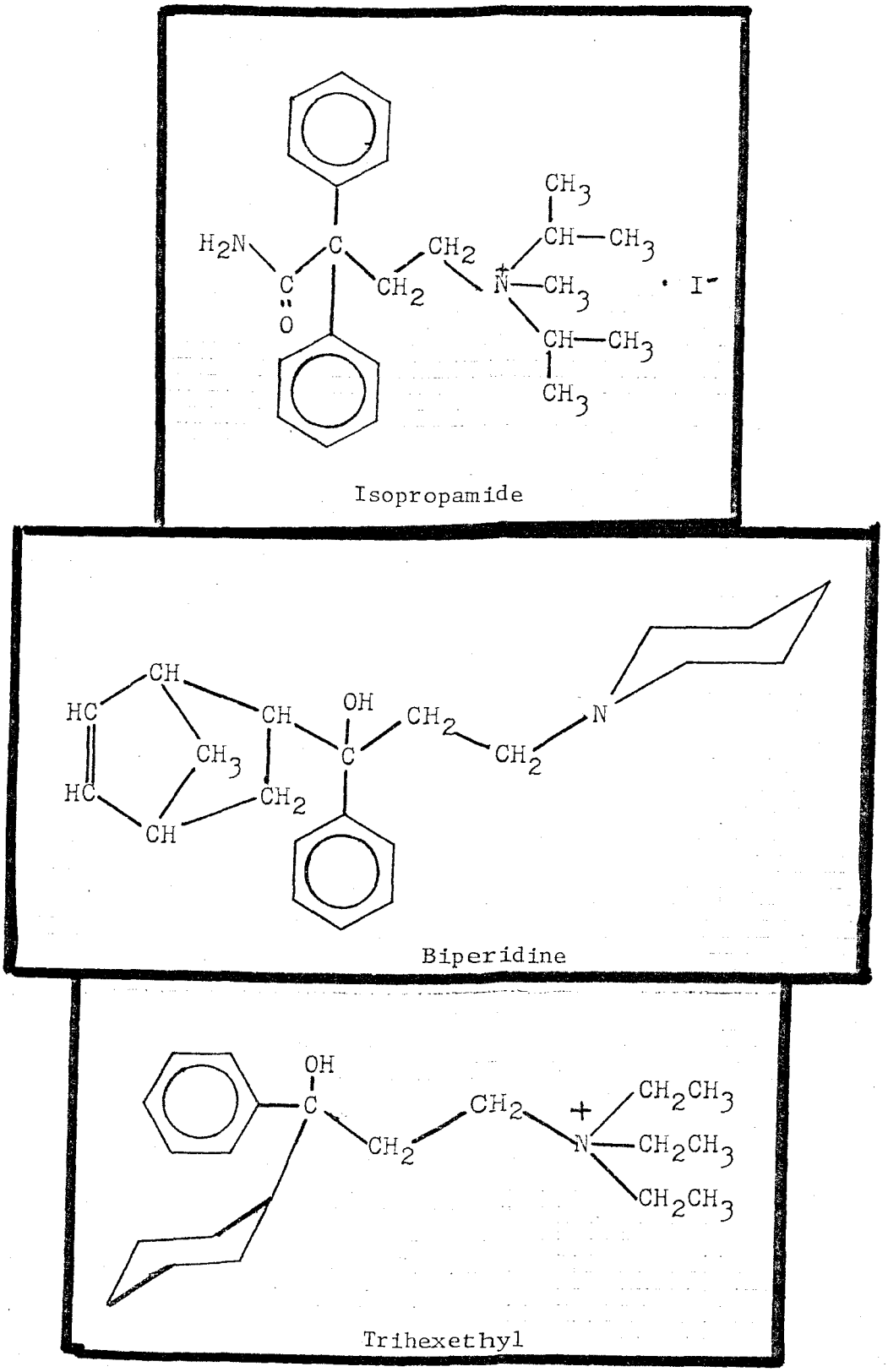
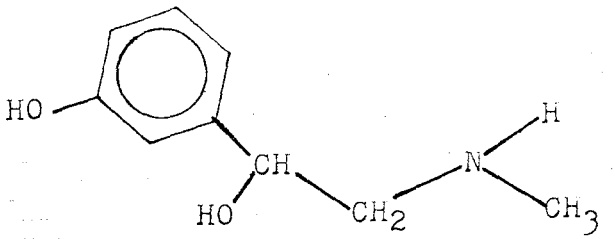
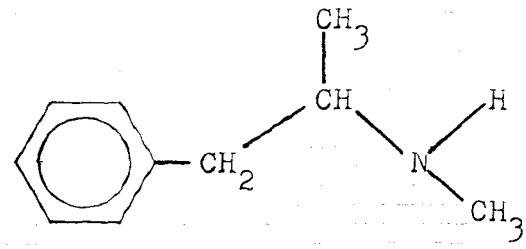


Fig. 3-1 Anticholinergic Drugs

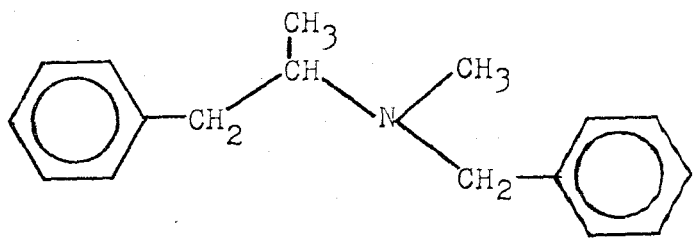
B. Sympathomimetic Agents



Phenylephrine



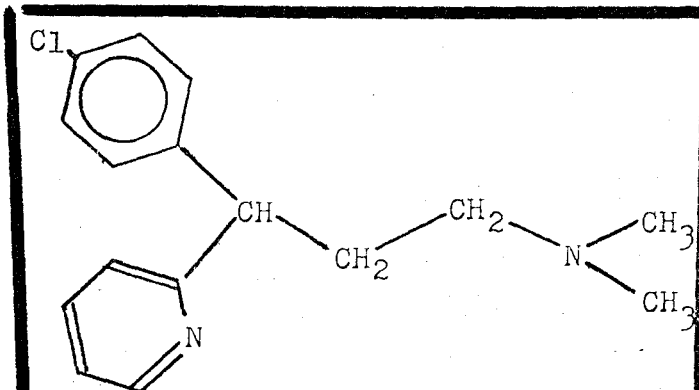
Methamphetamine



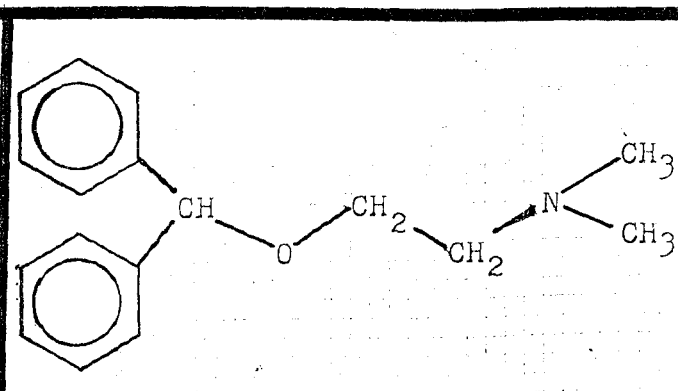
Benzphetamine

Fig. 3-2 Sympathomimetic Agents

C. Antihistamines



Chlorpheniramine



Diphenhydramine

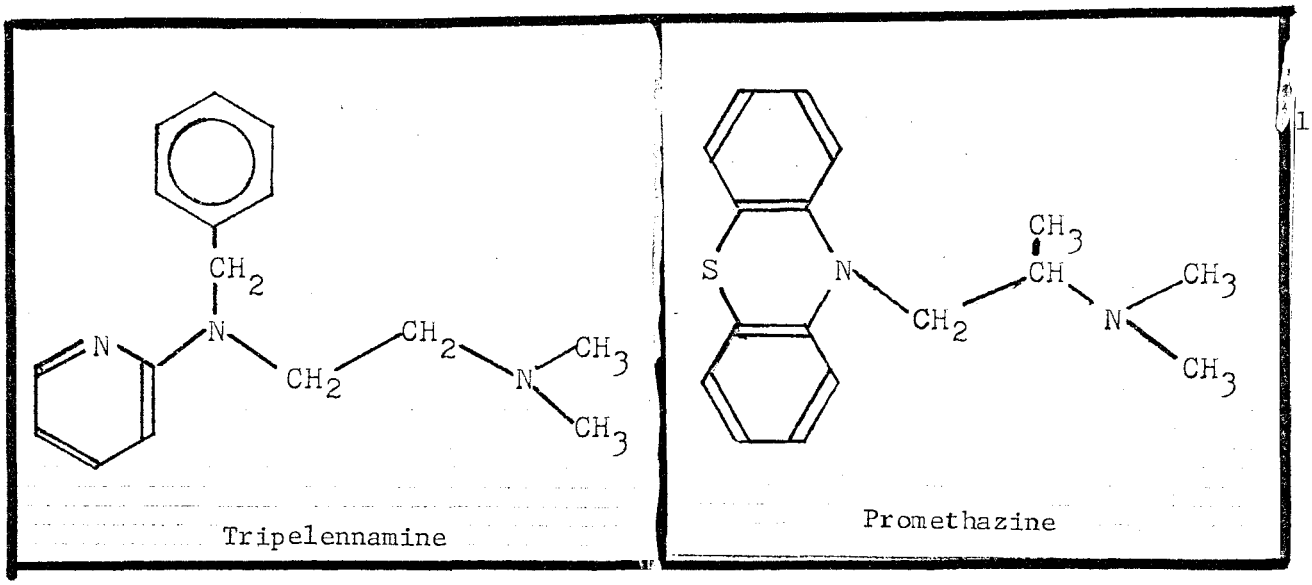


Fig. 3-3 Antihistamines

D. Narcotics

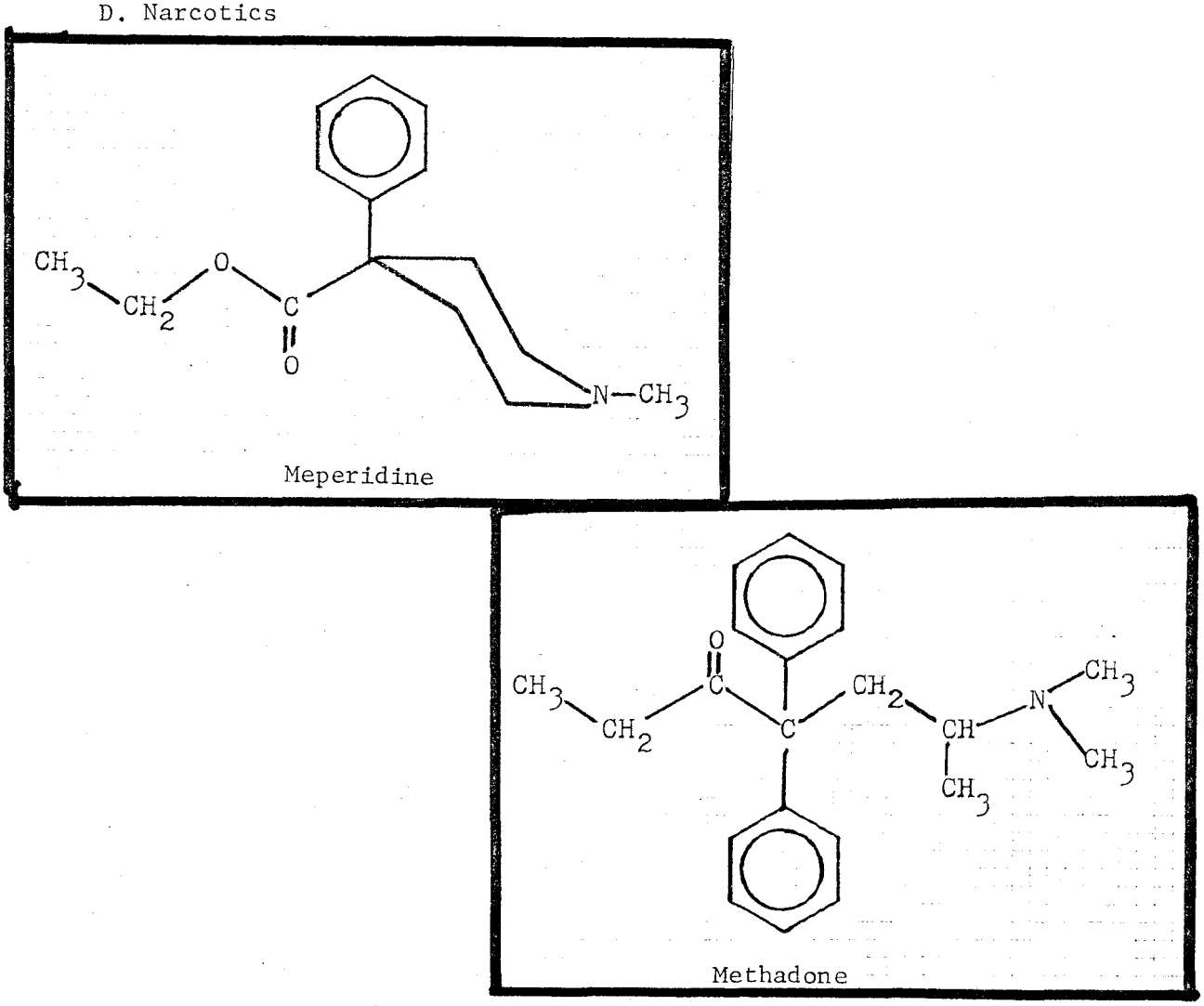
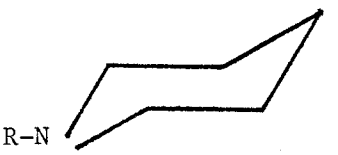


Fig. 3-4 Narcotics

Two analogous structures were consistently observed in all of the planar drawings:



Substituted Amine Substituted Piperidine

Figure 3-5 Analogous nitrogen structures (planar representations)

While one, or the other of the above structures was demonstrated in each the planar drawings gave little or no hint to molecular configuration(s) of the drugs. In order to visualize and compare configurations, especially of the analgous structures, a series of different molecular models were employed for this purpose. In all groups to follow, atropine is exhibited since it is the most potent of xerostomic drugs.

From the foregone planar drawings, "ball-and-stick" models* were constructed, photographed, and studied. For the sake of finances, and in order to conserve space, only three photographs from this group will be shown in this section of the report.

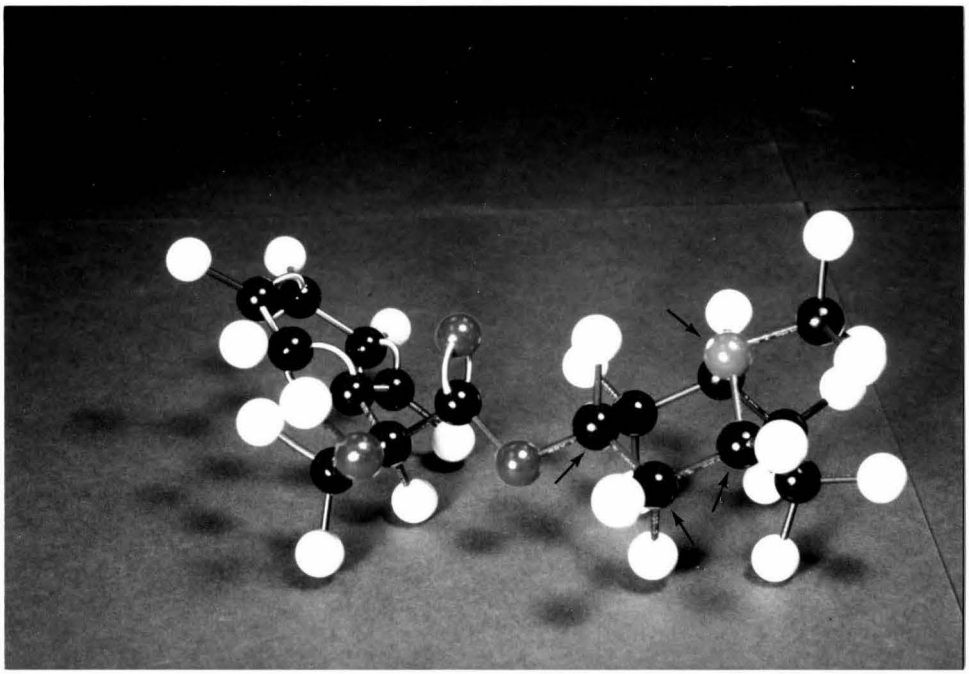


Figure 3-6 Atropine

* The Turtox Laboratories, General Biological, Inc., 8200 S. Hoyne Ave., Chicago, Ill. 60620

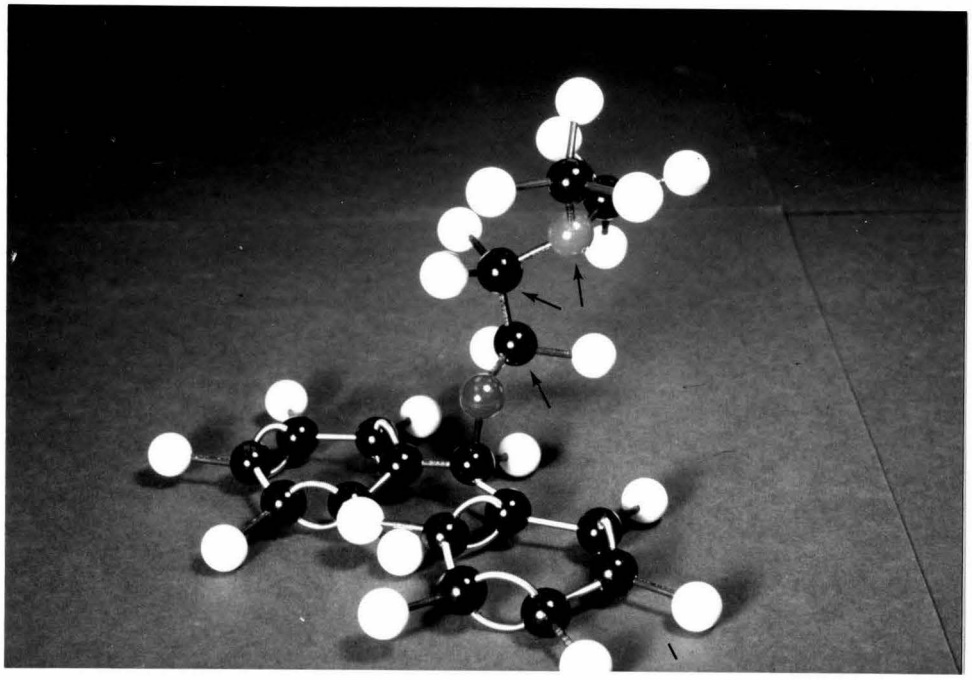


Figure 3-7 Diphenhydramine

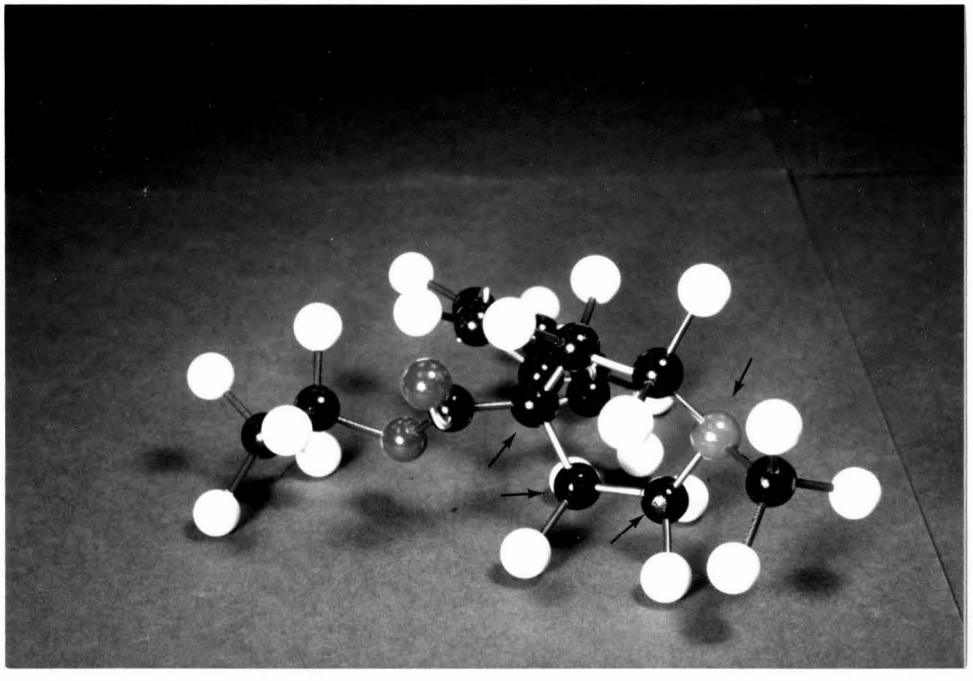


Figure 3-8 Meperidine

In all of the above photographs, the two structural moieties were observed and an effort was made to illustrate some three-dimensional relationship between them. While the "ball-and stick" models, in themselves, are not considered accurate representations, some stereochemical conformations were seen, and hence the results of these observations:

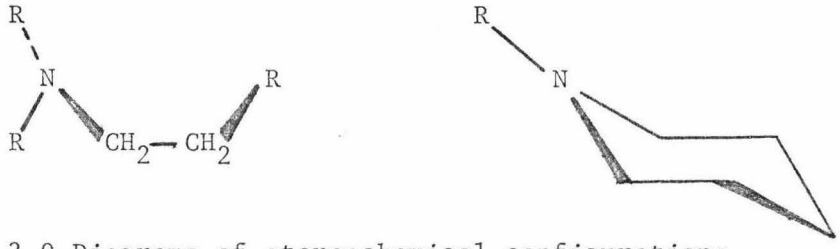


Figure 3-9 Diagrams of stereochemical configurations

In order to observe more accurate structural relationships, Dreiding Skeletal Models*, whose bond angles and lengths are more accurate, and at

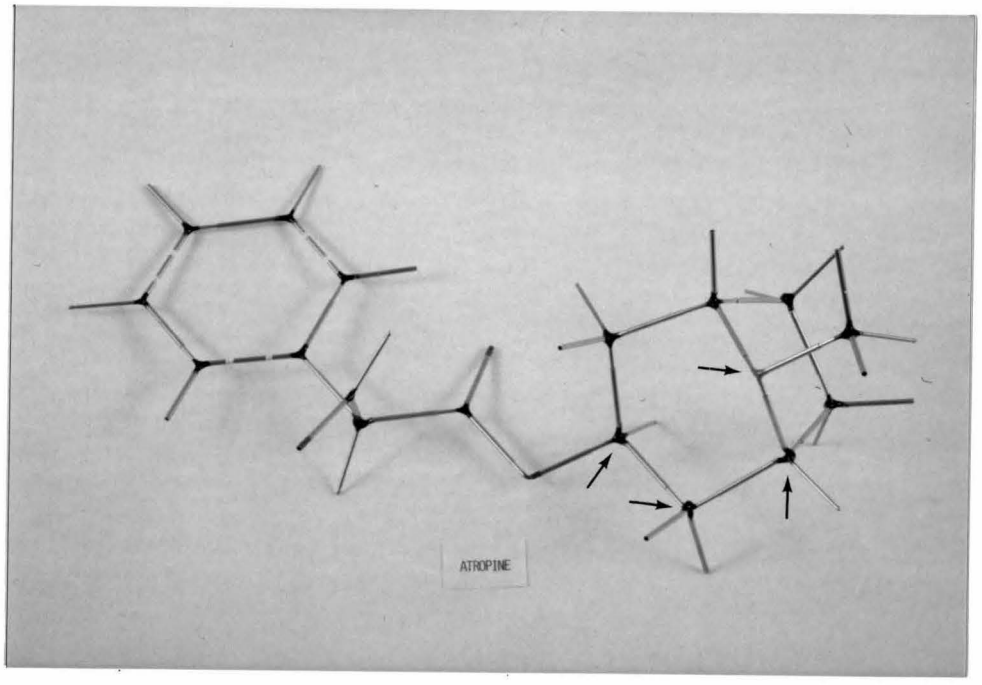


Fig. 3-9 Atropine

* Scientific Glass Apparatus Co., 735 Broad Street, Bloomfield, N.J. 07003.

least more consistent than the "ball-and-stick" models, were used for the next series of observations.

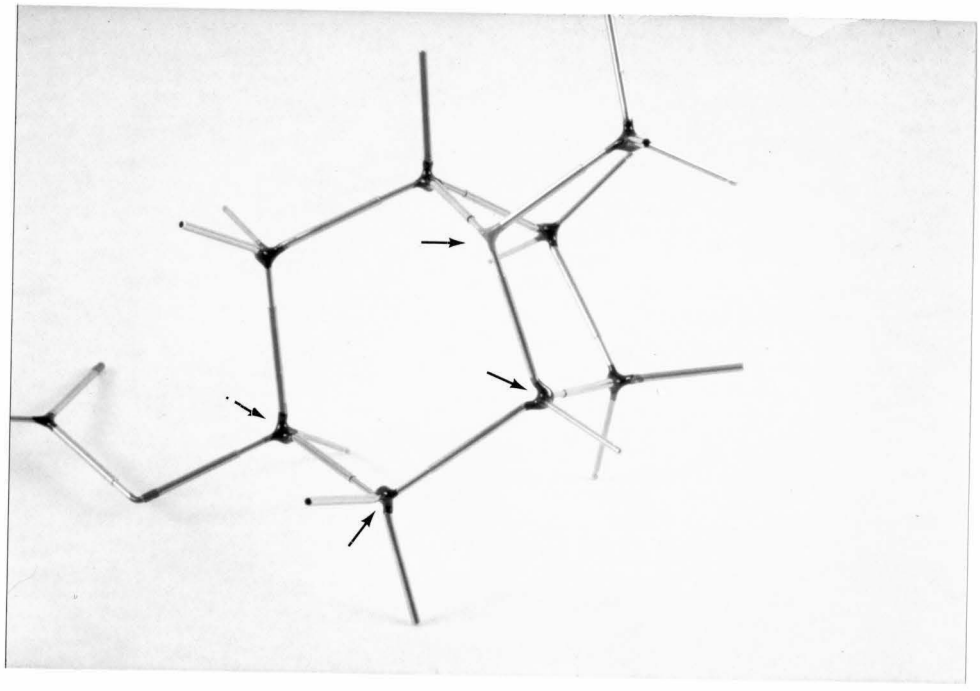


Figure 3-10 Atropine

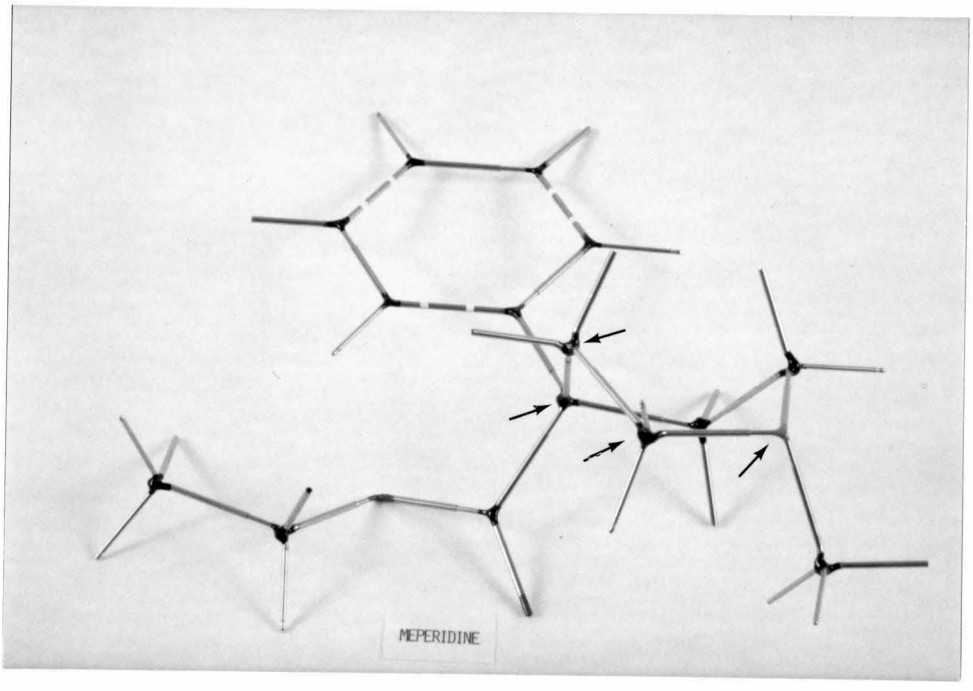


Figure 3-11 Meperidine

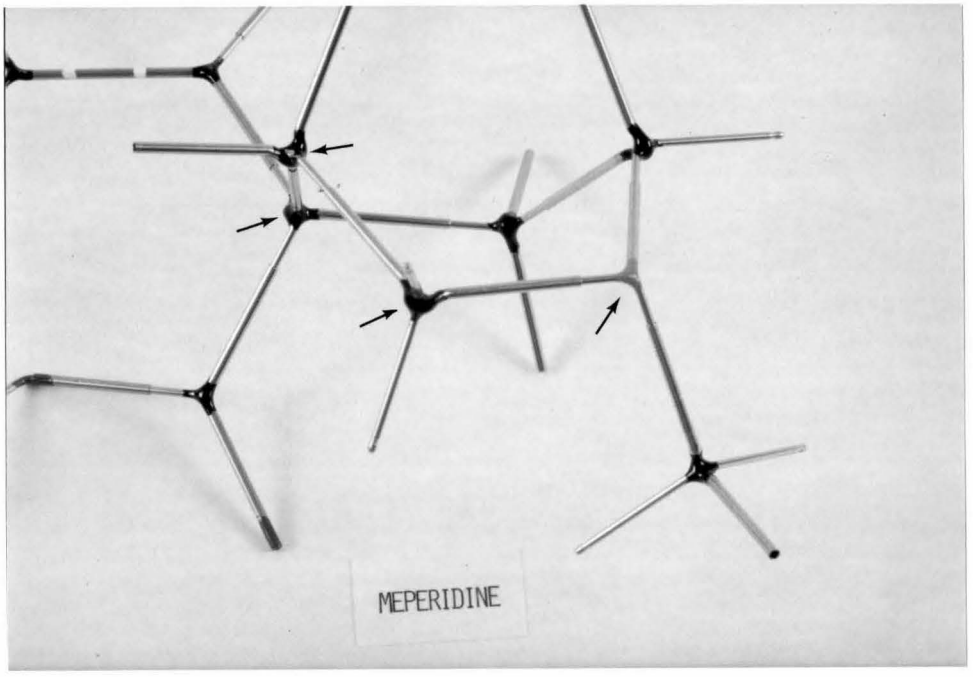


Figure 3-12 Meperidine

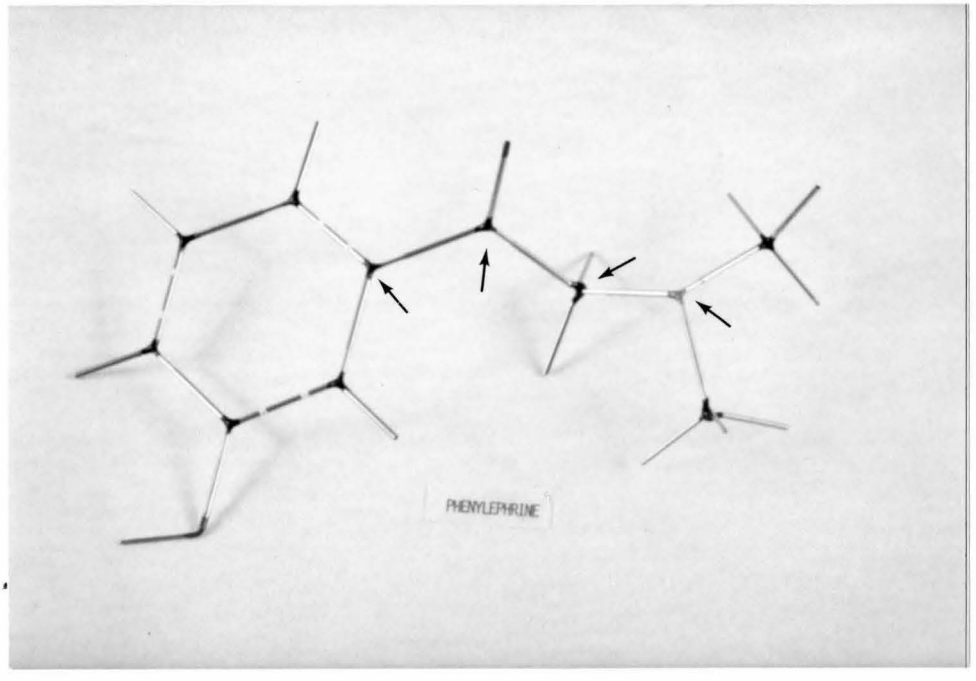


Figure 3-13 Phenylephrine

Comparisons were again conducted among the Dreiding models, which again revealed almost identical information on the stereochemical configurations of the analogous groups under investigation. The one major difference between the "ball-and-stick" models and the Dreiding skeletal models was that the latter consisted of connections by tubes and rods, they were very easily assembled, and provided an uncluttered, accurate view of dimensions of molecular skeletons (Gordon, 1970).

Space filling models of Larsson and Kling* were used next for studying the observed analogs, which are demonstrated by the following photographs:

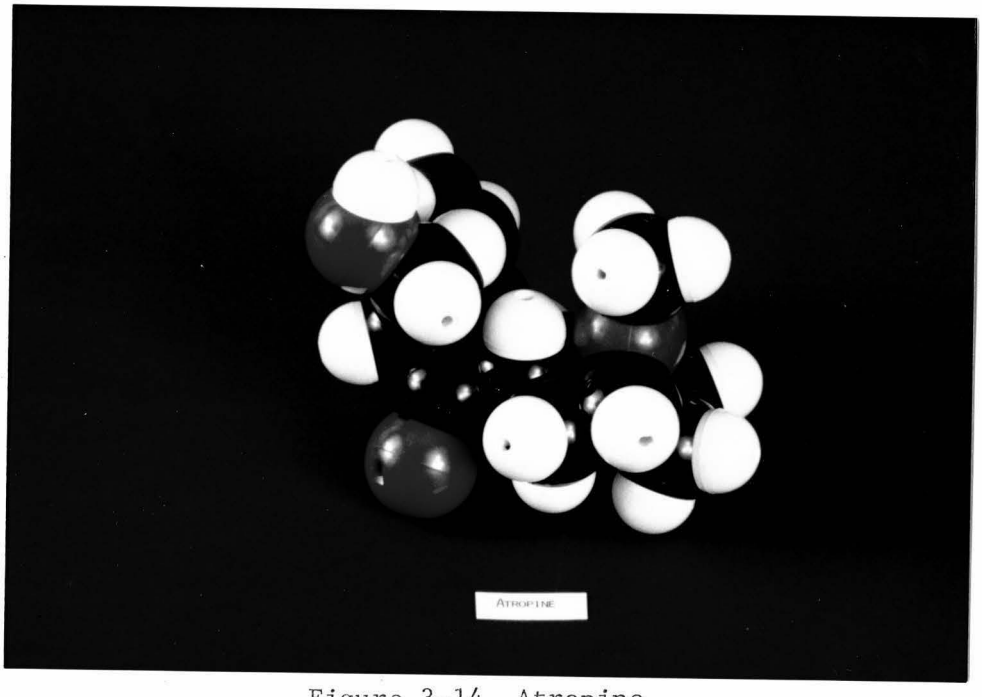


Figure 3-14 Atropine

* Blomberg and Jansson Offsettryck, Stockholm, 1975. Esselte Studium

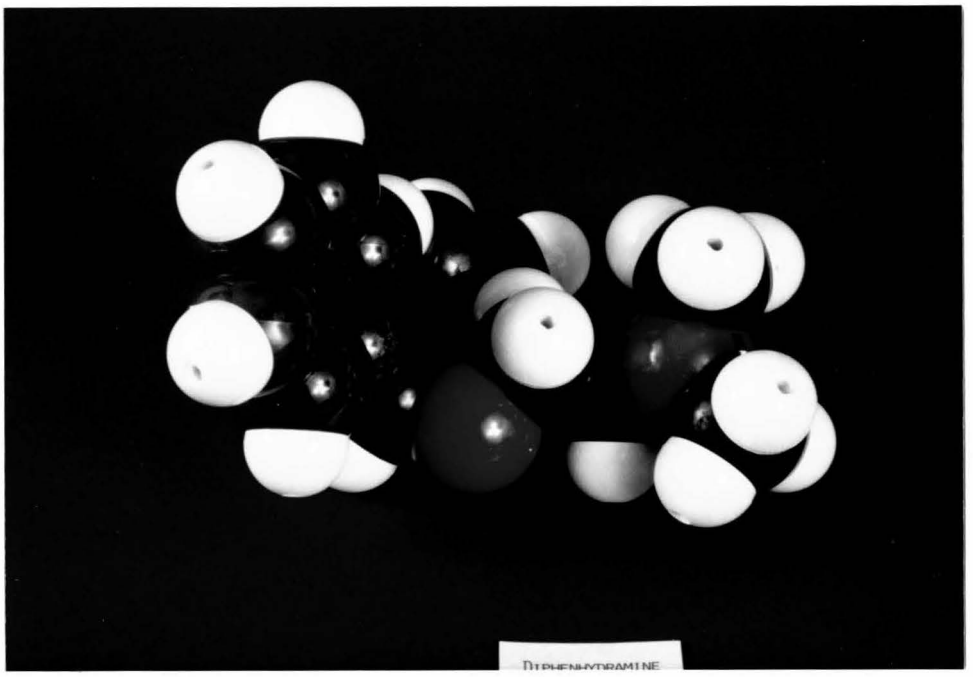


Figure 3-15 Diphenhydramine

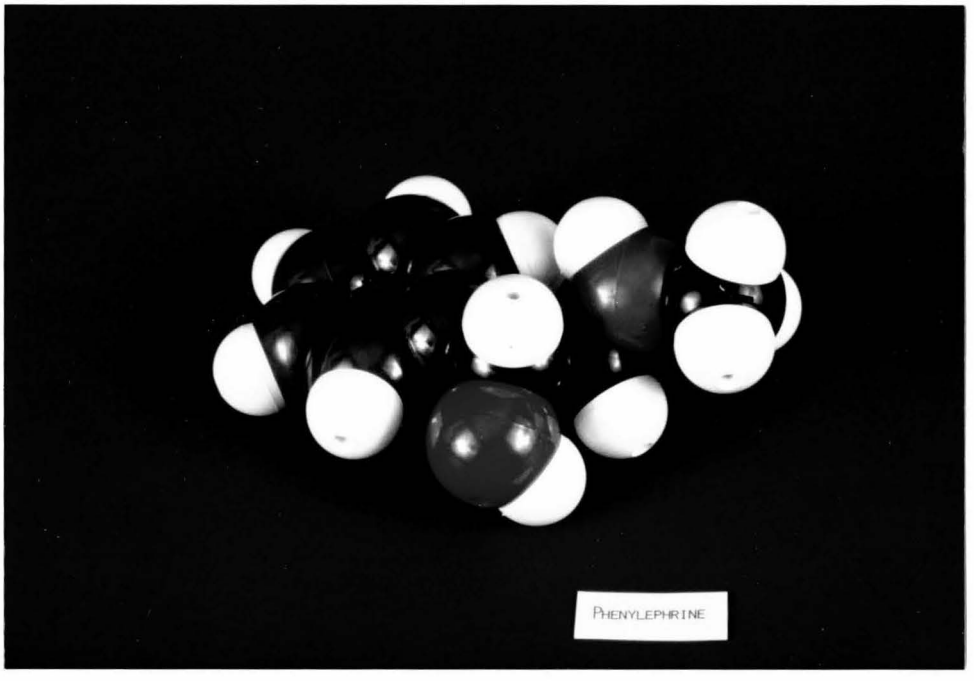


Figure 3-16 Phenylephrine

The final phase of this study utilized Kendrew skeletal models*, whose accuracy relative to bond angles and lengths is, by far, superior to those previously used in this study. The following photographs of selected drug-models demonstrate their use:

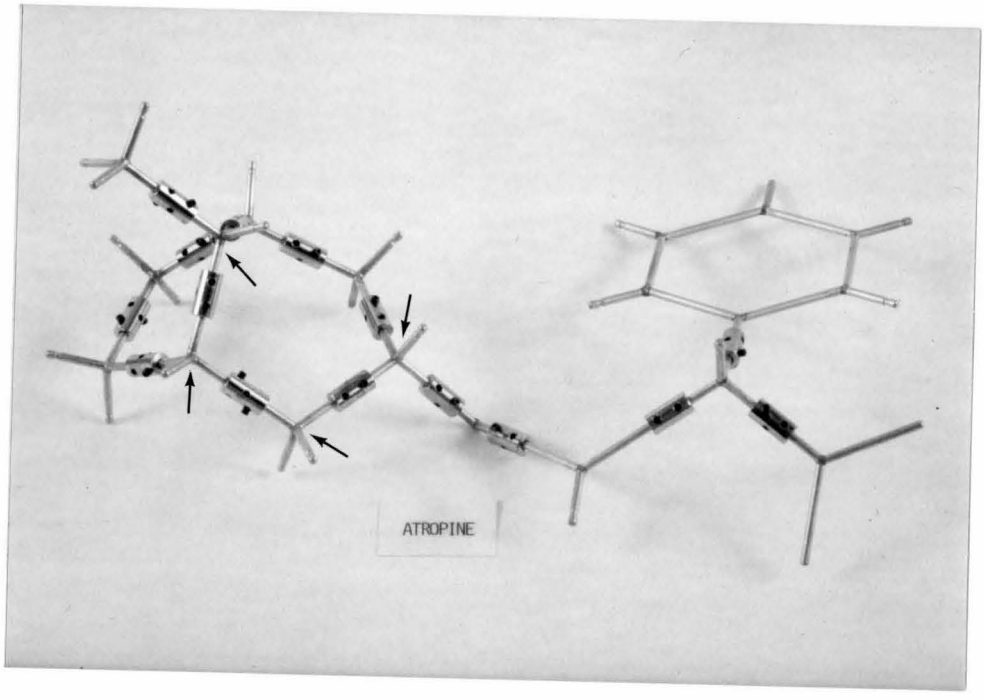


Figure 3-17 Atropine

* The Ealing Corporation, 2225 Massachusetts Ave., Cambridge, Mass. 02140.

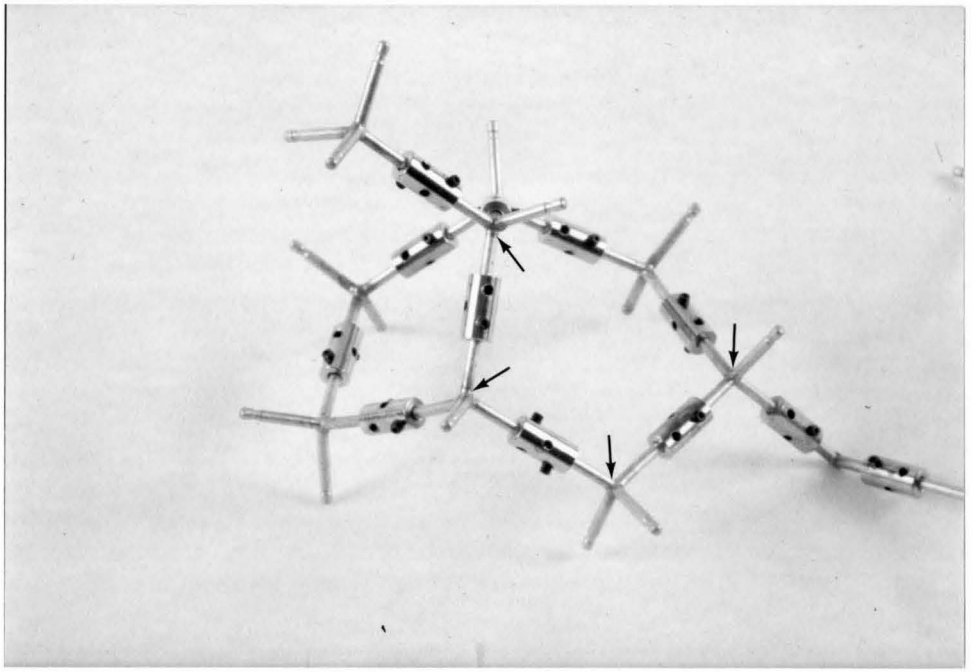


Figure 3-18 (close-up)

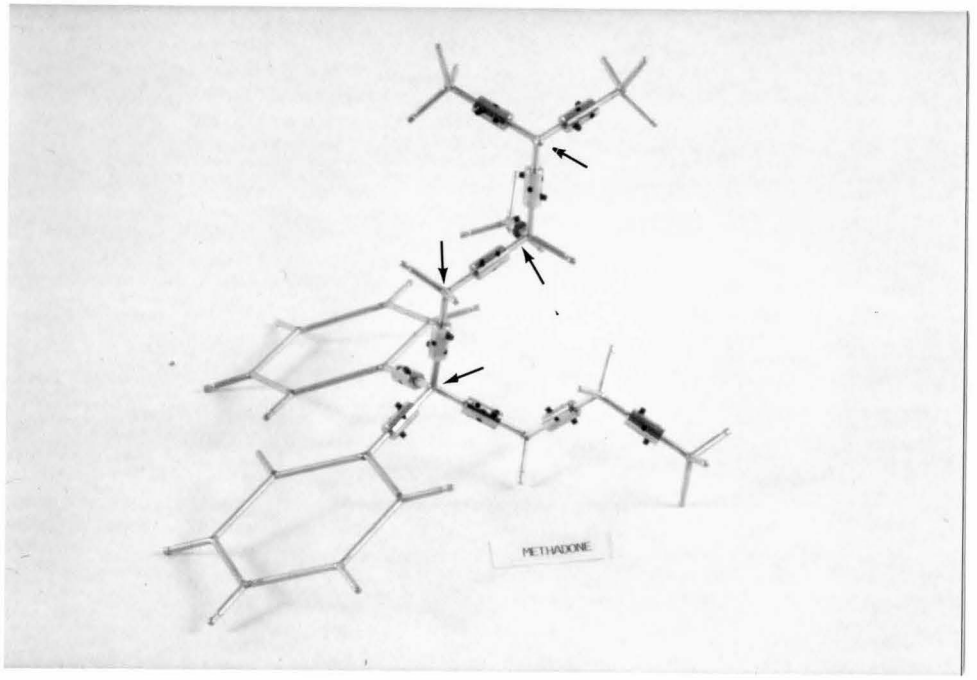


Figure 3-19 Methadone

The details of study are discussed in the chapter that follows.

CHAPTER IV

DISCUSSION

Structural formula of organic compounds, as they are depicted in most scientific and professional journals and textbooks, for the most part, are usually drawn with no intention to illustrate the detailed shapes or configurations of these molecules. The purpose of this investigation has been an attempt to examine and analyze the architectural features of several pharmacologically different drugs (Organic compounds) stereochemetrically*, in search of a possible common structural analog associated with, or responsible for their xerostomic side effect.

Organic chemists have long felt that there should exist simple relationships between the stereochemistry of organic compounds and their gross physical properties (melting and boiling points, density, and refractive index). Such properties are also referred to as bulk properties, and depend rather on an assemblage of groups, and their positions in relation to each other, as well as to their numbers in a given molecule, all of these as opposed to just the total molecule itself. While the knowledge of bulk properties and their relationship to certain predictable chemical

* Stereochemistry; "spatial chemistry": three-dimensional shapes, or configurations in space.

activity and pharmacological reactivity of some organic compounds was found to be of great value in pharmaceutical chemistry, its application has been very limited. Therefore, progress in drug research has been frustrated until recently, within the last two decades, scientists have gained a more intimate knowledge of molecular structure and its relation to the pharmacologic activity of drugs by a number of techniques, one of which makes use of the computer Sterinol Method (Hoogenstraaten, 1978), enabling them now to tailor drugs more efficiently.

One of the most fascinating paradoxes in pharmacology and pharmaceutical chemistry is that those drugs which are known for their high biological potency and selective reactivity (efficacy), are, in fact, chemically unreactive. Therefore, when studying pharmacologically active substance, it is necessary to refer to some major effect(s) of the drug, and to specific tissue components with which this substance interacts in order to produce its effect(s). These specific tissue or cellular components are known as receptors, and their existence has been deduced from structure-activity-relationship studies (SAR) in homologous or congeneric series, qualitative and quantitative studies on agonist-antagonist pairs, and selective cellular and membrane binding of radioactively labelled drugs. It is presently accepted that the presence of specific receptors not only explains how some drugs act, but also allows one to predict certain drug effects. If one, therefore, accepts this premise, then undesirable, or untoward drug actions or effects, should likewise be predictable by merely being able to identify the presence and conformation of

certain groups in the molecule.

The SAR studies of Beckett and Casy (1954), previously referred to, on a series of narcotic analgesics provided an excellent basis relative to the methodology employed in this study. They were able to deduce some information on the properties of opiate receptors that mediate their pain relieving effects, while having no idea at that time how their analgesic effect is brought about, nor the biochemical events implicated in this phenomenon. Within the last decade, endogenous opiate-like peptides with opiate-like activity have been isolated and identified from brain tissue, and are presently referred to as enkephalins and endorphins, and appear to act as neurotransmitters (Pert and Snyder, 1973; Hughes, et al., 1975; Goldstein, 1976; Snyder, 1977; Guillemin, 1977; Goth, 1978), and in some way are involved with the phenomena of pain and analgesia. The hypothetical opiate receptor, whose structural features were inferred by the aforementioned SAR studies, is presently accepted, as is the structure within the opiate molecule that interacts with it; which is coincidently similar to the group, in planar form, observed in this investigation. However, there is one exception, and that is the group commonly associated with opiate activity which is always demonstrated as part of a piperidine ring:

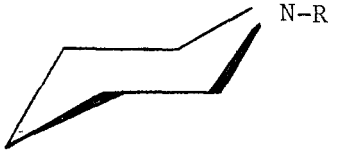
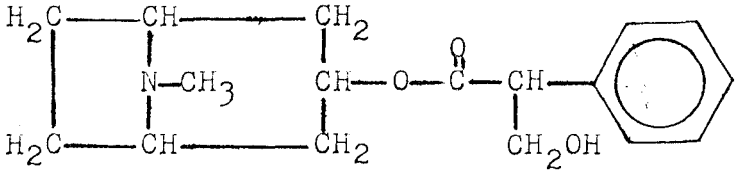
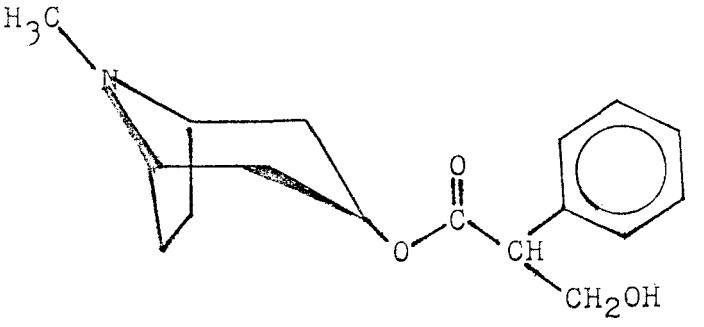


Figure 4-1 Substituted piperidine ring found in all opiates (natural and synthetic)

The planar, 13 unidimensional drawings illustrated in figures 3-1 through 3-4, as previously stated, were randomly selected from a list of some 248 drugs appearing in a publication (Bahn, 1972) that motivated this study. However, atropine and methadone, who did not appear on Bahn's list, other than the former, but only in combination with other drugs, were added by this investigator since both are considered to be potent xerostomic drugs. It is intriguing to point out that atropine, which is a potent anti-cholinergic drug, has within its structure the same substituted piperidine group as do the opiates, but it is not known for any analgesic effects, while the opiates do variously demonstrate some autonomic effects. This structure can be clearly seen when not drawn in the conventional manner as illustrated in nearly all pharmacology textbooks, and as shown in Chapter III and compared in Figure 4-2:



Atropine (conventional)



Atropine

Figure 4-2 Comparative structural drawings of atropine

Note the presence of the piperidine ring and the conformation of the specific group to which Beckett and Casy (1954) assigned opiate receptor-drug interaction. The same holds for the structure of cocaine below:

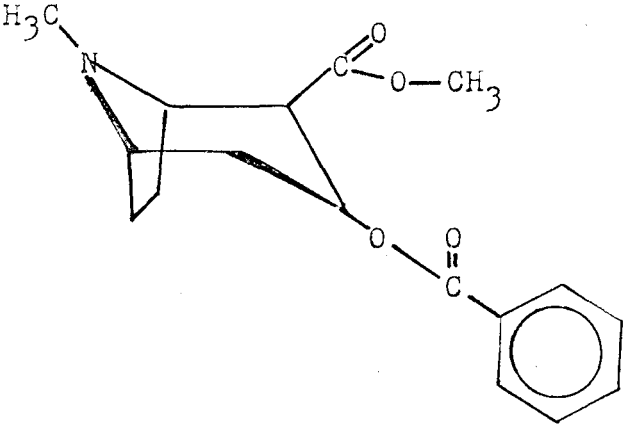


Figure 4-3 Cocaine

The "ball-and-stick" models constructed from the planar drawings appearing in Figures 3-6, 3-7, and 3-8 now began to show some dimensions, and while the least accurate relative to bond lengths and angles, would serve as a basis for the construction of future models:

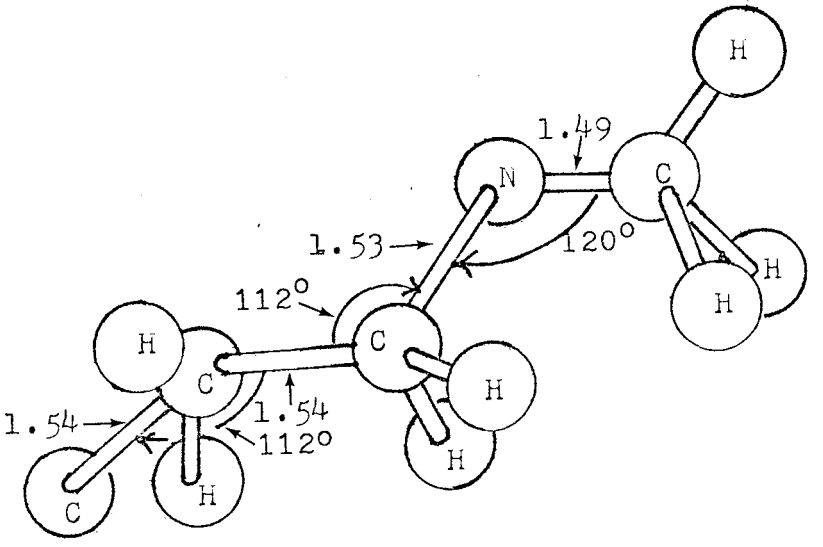


Figure 4-4 "Ball-and-stick" representation of probable xerostomic group (note numbered atoms); part of atropine structured half piperidine ring; note bond angles and lengths derived from Kendrew models.

The "ball-and-stick" models were then followed by metal skeletal models, which gave a more accurate picture of the molecular framework, uncluttered by interpositioned atoms. The Dreiding models easily reproduced the structure that kept repeating itself over and over, but contributed no more than the "ball-and-stick" models in terms of general structural configuration of the drug models selected for this study. It should be stressed at this point that the use of neither of these two model-types was intended for problem solving, that is, defining the structural analog being sought, but used rather to express a conviction relative to the nature of things sought. It should likewise be pointed out that the planar drawings, the "ball-and-stick" models, and the Dreiding skeletal models are merely caricatures of the "real things" which were illustrated

by the space-filling models of Larsson and Kling along with the more accurate Kendrew skeletal models.

To study and observe the space-filling model of a drug is almost like viewing it from some point on a cell surface, or a receptor site. In other words, one is seeing it as the cell sees it in Figures 3-14 through 3-16. On the other hand, the Kendrew skeletal models, which consist of brass rods joined by a small barrel with screws, can assume any number of angles (measured by a gauge) and lengths (2cm=1A), give accurate dimension measurements. When superimposed on each other, the two models give an accurate molecular picture of the group under investigation.

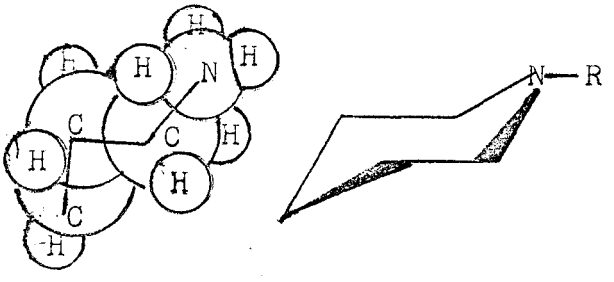


Figure 4-5 Atropine (space-filled and Kendrew superimposed), showing only xerostomic group.

It may be easy to visualize the xerostomic group which was seen in every drug model studied, in spite of the models used, may be viewed as half

of a substituted piperidine ring in the chair form, but could just as well exist in the boat form if "ring-flipping" occurred in order to satisfy the conformation of a specific xerostomic receptor.

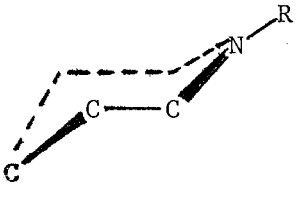
This study definitely should be expanded, in the future, to include the specific Sterimol Computer method of Hoogenstraaten (1978), which might give even more precise results compared to those invovling molecular models alone.

CHAPTER V

SUMMARY AND CONCLUSIONS

This investigation, whose purpose was an attempt to determine whether or not there existed a common structural analog among a pharmacologically diverse classification of drugs capable of causing xerostomia. This was accomplished through use of molecular models, each beneficial in its own right, to give some information relative to the intimate molecular structures of those drugs selected for this study. Planar drawings were prepared, from which "ball-and-stick", Dreiding, Larsson-Kling space filling, and Kendree models were constructed, photographed, and from these the structural analog determined.

That a single structure, with corresponding bond lengths, and bond angles, was repeatedly observed from one type of molecular model to another, finally resulted in the speculation that the analog sought consisted of the following hemi-piperidine-like confomration:



which might exist in either chair or boat form, which could occur from "ring-flipping" to conform to some specific receptor when piperidine was a part of the molecule, or rotation and bending if the structure was of the aliphatic type.

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APPROVAL SHEET

The thesis submitted by Patrick J. Angelo has been read and approved by the following committee:

Dr. Louis Blanchet, Director
Assistant Professor, Physiology/Pharmacology
Loyola

Dr. Hal McReynolds
Associate Professor, Histology,
Loyola

Dr. Patrick Toto
Professor, Oral Pathology,
Loyola

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the thesis is now given final approval by the Committee with reference to content and form.

The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science in Oral Biology

April 18, 1980
Date

Director's Signature