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Potential pharmaceutical derivatives of β-aminoethylpiperazine

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POTENTIAL PHARMACEUTICAL DERIVATIVES OF β-AMINOETHYLPIPERAZINE

BY

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HISTORY

This thesis is concerned with the design and preparation of certain organic compounds which are expected to have medicinal properties. A discussion will be given which has essentially a two-fold purpose. The first is to discuss somewhat briefly the currently accepted method of drug design,and the second to show to what extent this method has been followed in the design of the compounds prepared.

In the design of potential drugs there is in some measure a system which the designer should follow. This system, known as the method of variation, enables the designer to reduce to a minimum the degree of randomness or chance in searching for new medicinals. The usefulness of this method has increased through the years as scientific knowledge in general and the knowledge of medicinal chemistry and pharmacology in particular has increased. We must acknowledge, however, that until the fundamental chemical phenomena proceeding in living things,and the mode of drug action are fully understood, this method will not attain to that perfection which is desired.

The method of variation consists first in the selection of a compound which is known through previous investigation to elicit a certain response. This prototype as it will be referred to, may or may not be a clinically useful drug, or it may be a molecular group which is a portion of a molecule known to have medicinal properties.

Once the prototype has been selected the designer should familiarize himself with the compound. He should seek to know: "(1) the nature of the chief chemical classes to which the product

belongs, as determined by the main stem nuclei or hydrocarbon skeleton from which it derives its' name; (2) the nature and number of various functional groups that may be present, their positions, and the proximities of such groups with respect to one another; (3) the various possible degrees of rotation and extension of the structure into various spacial configurations; (4) the likelihood of steric hindrance between various portions of the molecule in different configurations in space; (5) the likelihood of electronic interactions between various portions of the molecule including such matters as inductive and mesomeric effects, hyperconjugation, ionizability, polarity, the presence of regions of relatively high or low electron density, the possibility of chelation, zwitterion formation, etc. The designer should then begin to consider the afore mentioned attributes in the light of the substance's known pharmacological properties. A knowledge of the structures and pharmacologic effects of other substances having essentially the same, or even remotely similar, sites or types of action as the prototype will also be invaluable."[1]

After the designer has familiarized himself with the properties of the prototype, he then proceeds to make variations on the prototype. The methods of approach and the variations to be made are actually peculiar to each situtation and no clear cut rules can be laid out which must be followed exactly by every designer of drugs. Rather it is important at this point to discuss orientations of approach in drug design. This approach may involve any one or more of three general main streams of thought, the method of isosteric replacement, the method of conjunction aad the method of disjunction. Again, there are actually no clear cut lines of demarcation between these three methods, but by such

classification discussion of drug design is facilitated.

Langmuir[2] defined isosteric molecules as molecules having the same number and arrangement of electrons. Based upon similar considerations the concept was extended by Huckel and Grimm to certain chemical groups. It was found that chemical groups having the same number and arrangement of electrons show great similarities in physical and chemical properties. Examples of some of these isosteres are given below:

(1) N_2 and CO

(2) N_2O and CO_2

(3) $CH_2{=}CO$ and $CH_2{=}N_2$

(4) organic compounds which possess one or the other of the isosteric pairs below and which are otherwise identical, exhibit strikingly similar physical properties:

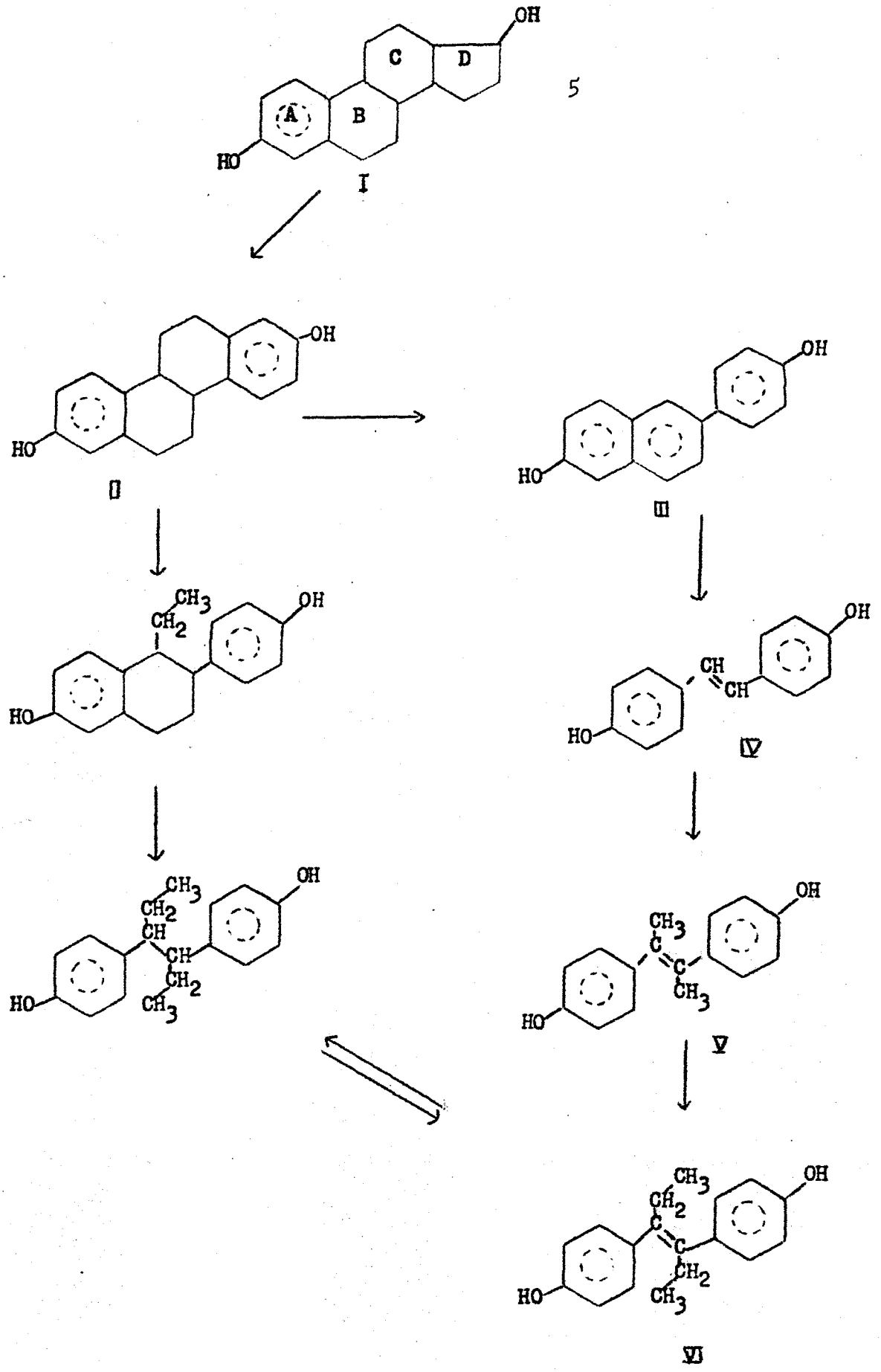
a) -N= and -CH=

b) -O-, -NH- and $-CH_2-$

c) F-, HO-, NH_2- and CH_3-

d) Ne, HF, H_2O and NH_3

Thus in designing drugs the method of isosteric replacement involves substituting isosteres into the prototype. In doing this the properties of the molecule are modified so as to enhance or diminish the desirable medicinal properties of the molecule, but not radically. Frequently, however, in practice, while employing the general approach of isosteric replacement, workers substitute groups which do not fulfill the definition of isostere as set forth by Huckel and Grimm. For example, they may substitute a cyclohexyl group for a phenyl group,or even a naphthyl group for a methyl group. Obviously, in such cases the term isostere loses


OH
C
D
A
B
HO
I
OH
HO
II
OH
HO
III
CH3
CH2
OH
HO
CH
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C
CH3
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V
CH3
CH2
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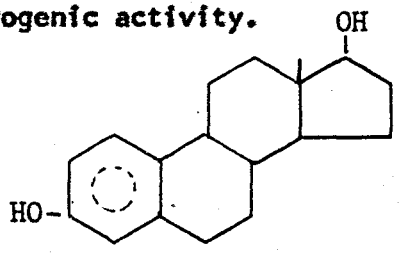
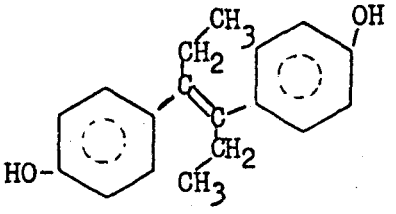
C
CH2
CH3
OH
HO
VI

its meaning, but the approach is still good. The greater the deviation of the isosteres from true isosterism the greater the expected variation in mediciaal properties of the products. Wide variation could lead to interesting compounds having new properties. In this thesis compounds have been prepared in which large groups of wide diversity of structure have been substituted into the parent nucleus. In some cases these large groups themselves have desirable medicinal properties.

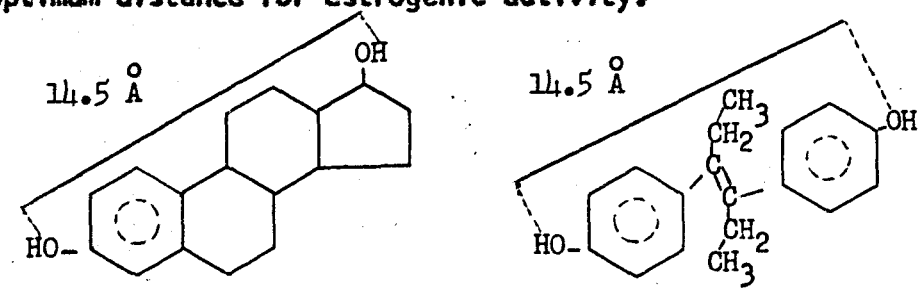
"The method of disjunction in drug design might be considered as the formulation of analogues of a prototype, toward structurally simpler products which may be viewed as partial replicas of the prototype." [3] This method of variation is clearly demonstrated by the investigations of Dodds, Cook, Robinson, and others in their work on estradiol. This compound is known to elicit certain estrogenic responses. It consists of a large and relatively planar nucleus, a phenolic hydroxyl group and the secondary alcohol group. These investigators screened a large number of phenols, ketones, hydrocarbons, etc. and came up with diethylstilbestrol as the main grouping for estrogenic activity.





The approach which these investigatore followed in this classic example of the method of disjunction is very interesting and worthy of consideration. Consider the structures given on the next page. Bearing in mind that these investigators were seeking the simpliest structure which possessed optimum estrogenic activities, they proceeded to disjoin or open the rings B and C, to substitute

aromatic rings for saturated cyclic rings and decreased the size of the hydrocarbon portions of the molecule. All of this is evidenced in structures II, III, and IV. At this point it was observed that the estrogenic activity progressively decreased in compounds II, III, and IV. Their next course of action was, however, not to reform rings B and C, but to prepare α,β-dialkyl derivatives of stilbestradiol. By plotting activity versus structure they found that maximum activity was reached in diethylstilbestriol (VI). It is interesting to note that the distance of separation of the hydroxyl groups in diethylstilbestriol is the same as in estradiol. This distance, 14.5 Å, is apparently the optimum distance for estrogenic activity.

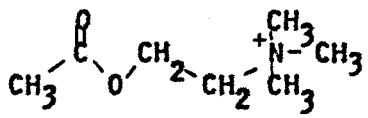


"Drug design through conjunction is defined as the systematic formulation of analogues of a prototype, in general, toward structurally more complex products, which may be viewed as structures embodying, in a general or specific way, certain or all of the features of the prototype."[4] An example of this method, given below, involves an approach which might be termed the principle of mixed moieties. A moiety is regarded as a molecular grouping which elicits a certain response. Frequently it is desirable to design a compound which has the medicinal properties possessed by two or more individual moieties. Such a compound would be prepared by uniting in a very specific way the moieties whose properties are desired.

"Future success in the use of the principle of mixed moieties depends fundamentally on how successfully pharmacologists and medicinal chemists will be able to pin down, in a relatively certain fashion, various individual moieties that activate given molecular-level processes. Thus the primary problem at present is rather like the problem that faced organic chemistry when it first became endowed with the concept of specifically characterizable functional groups. As such groups became more firmly established as a basis for classifying the reactions of organic compounds, the possibilities of predicting the character of compounds embodying two or more such groups became more and more feasible. An analogous type of development in the field of medicinal chemistry involves formalization in a specific way of the much more complex individual pharmacophoric moieties, and this would presumably lead to the possibility of predicting, with a fair degree of certainty, the effects of drugs embodying two or more moieties."[6]

The example of this method involves the preparation of a compound which has effective action on postganglionic parasympathetic neuroeffector cells and also is a ganglionic blocking agent. Most ganglionic blocking agents are bis-quaternary salts, and it seems that in the most effective ganglionic blocking agents the nitrogen atoms are separated by the same distance as in hexamethonium. Now, while compounds producing ganglionic blockade are effective in lowering the blood pressure in hypertension, they also have their undesirable side effects, for instance, decreased intestinal tone leading to constipation.[7] "Since these undesirable effects are the result of a lack of a significant degree of specificity for

sympathetic ganglia in comparison with parasympathetic ganglia, one way of increasing parasympathetic tone without decreasing ganglionic blocking activity on the sympathetic side must be sought. Fortunately, the requirements for effective action on postganglionic parasympathetic neuroeffector cells are largely independent of the requirements for ganglionic blockade. For example, acetyl-β-methylcholine is an effective postganglionic parasympathetic stimulant in doses which effect no sugnificant alteration in ganglionic function, while hexamethonium has only a slight action at postganglionic parasympthetic endings in doses that produce a high degree of ganglionic blockade. The moiety requirements for postganglionic parasympathetic stimulant action (muscarinic moiety) are summarized as shown below, referred for convenience to the structure of acetylcholine.



Acetylcholine

$(CH_3)_3-N^{\pm}\ CH_2-CH_2-CH_2-CH_2-CH_2-CH_2^{\pm}N-(CH_3)_3$

Hexamethonium

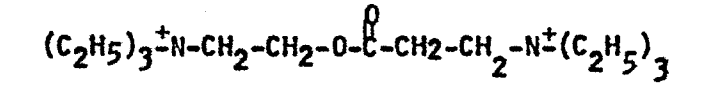
"The above generalization of the muscarinic moiety when reviewed in relation to the bisquaternary type of structure in hexamethonium, suggests the following design, embodying both the ganglionic active moiety and the muscarinic moiety.

Muscarinic Moiety

$(CH_3)_3-N^{\pm}CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-N^{\pm}(CH_3)_3$

Ganglionic Active Moiety

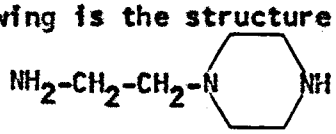
"Actual synthesis and test of this product reveals it to be, unfortunately, both a muscarinic stimulant and a ganglionic stimulant. A close homolgue,



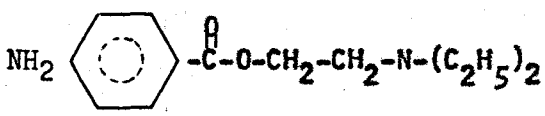
however, is a product having desired type of mixed action. It is both a ganglionic blocking agent and a weak muscarinic stimulant."[8]

Since the compounds prepared inthe present paper are all derivatives of β-aminoethylpiperazine this compound will be considered the prototype and a discussion of its chemical and stereochemical properties will be given. It should be pointed out however, that frequently large groups have been attached to β-aminoethylpiperazine, and that these large groups might just as well be considered the prototype. Therefore, following the discussion of β-aminoethylpiperazine there will be a somewhat briefer discussion on each of the compounds prepared.

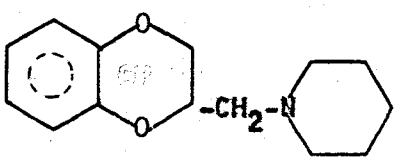
The following is the structure for β-aminoethylpiperazine:



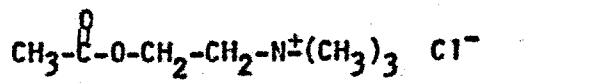
It is easily seen that this compound contains both inside and outside the ring, the $-N-CH_2-CH_2-N<$ grouping. This grouping and its isosteric analogue ($-O-CH_2-CH_2-N<$) are frequently in many different types of pharmaceutical agents, for example, local anesthetics such as procaine,



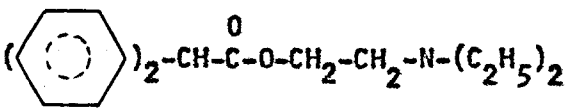
adrenergic blocking agents such as piperoxan,



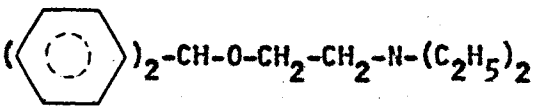
parasympathomimetic agents such as acetylcholine,



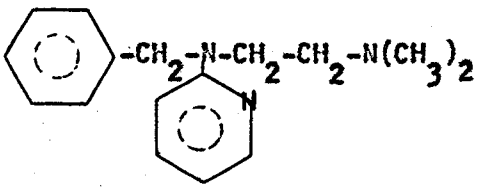
antispasmodics such as adiphenine,



and antihistaminic agents such as diphenhydramine,



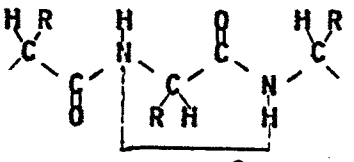
and tripelennamine.



Most of the more active antihistaminic agents contain this grouping.[9] Chlorpheninamine is an interesting example of a powerful antihistomine drug in which the isostic moiety is $-C-CH_2-CH_2-N$. This evidence alone is very striking and therefore strongly suggests that the β-aminoethylpiperazine grouping would be expectdd to have favorable properties in its compounds.

Piperazine itself is relatively non-toxic and is now used in the form of its citrate astthe agent of choice in the treatment of pinworm infestation.[8]

The nature of drug action is by no means fully understood. There is some evidence, however, that drugs combine with reception by coulombic forces at some stage during their actions and most receptors are proteins. The polypeptide nature of proteins is well understood, the bonding being explained in terms of the linking together of amino acids through their α-amino and carboxyl groups. The spacing between these polypeptide bonds is regular and this spacing is known as the identity distance. This distance is equal to 3.61 Å. A diagram illustrating this is given below:



3.61 Å

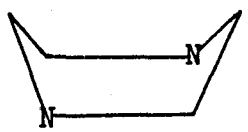
In compounds of known pharmachological activity the distance separating the functional groups frequently is found to be equal to the identity distance or some whole number multiple thereof. In a given series of compounds in which all features are the same except the distances separating the functional groups, optimum activity is frequently observed in the member of the series in which this identity distance or some whole number multiple thereof is observed. This indicates that if there is an attraction of certain groups in a drug for the nitrogen or oxygen atoms or both in a protein, the drug becomes more firmly attached if the functional groups in the drug are separated by some whole number multiple of 3.61 Å.[11]

"Many parasypathomimetic (acetyl choline like) and parasympatholytic (cholinergic blocking) agents have a peparation of 7.2 Å between the ester carboxyl group and the nitrogen. This distance is doubled between quaternary nitrogens of curarelike drugs; 14.5 Å . The preferred separation of hydrogen bonding groups in estrogenic compounds is 14.5 Å. [12]

Novel calculations of interatomic distances in β-aminoethyl-piperazine show that in the ethylendiamine moiety, planarity of N,C,C,N and lack of bond strain make the distance between nitrogens 3.75 Å. Also, calculations show that the distance between nitrogens in the piperazine moiety is 2.87 Å and the distance between terminal nitrogens is 6.60 Å. The calculations follow:

According to Aroney and Le Fevre,[13,14] piperidine and cyclohexane exist predominately in the "chair" conformation. An aryl group attached to the nitrogen atom in piperidine lies in an equatorial posttion. This apparently is due to the size of the group.rather than to any electronic interactions with the ring. Stated differently, the aryl group lies in the equational position because this position is sterically favored over the axial position. These authors also found that piperazine exists as a mixture of the "chair" and "boat" conformations. The positions of the nitrogen atoms in the rings in their two conformations are indicated by the following diagrams:

"Chair"



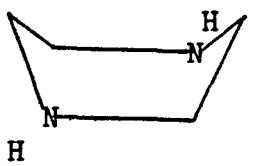
"Boat"

Unsubstituted piperazine exists as a mixture of four structures, three of which have the chair conformation and one the boat, as indicated below:

A

B

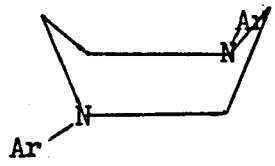
C



D

With regard to the relative abundance of each species, there is more B than A or C, and D is present in about double the amount of B. When phenyl groups are attached to the nitrogen atoms to form 1,4-diphenyl piperazine the compound consists of a mixture of the following two conformations with F predominating.

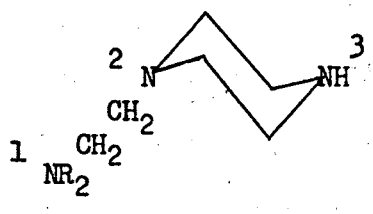
E

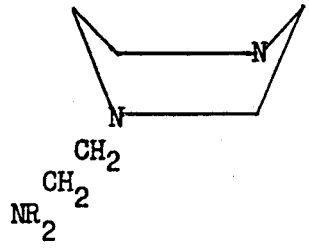


F

In order to determine the stereochemical structure of β-aminoethylpiperazine, certain conclusions,based on the evidence given above, must be made at this point. First, it seems reasonable that the compound must exist as a mixture of the "chair" and "boat" conformations with the latter predominating, since this is the case with unsubstituted and disubstituted piperazines. Secondly, from steric considerations, the aminoethyl group most probably assumes an equatorial position, even though according to Aroney and LeFevre the 1,4-dimethylpiperazine has a small amount of the axial "chair"form in the mixture. The axial methyl derivative is not nearly as sterically hindered as would be the case with the ethylenediamine with a large group attached in the β-position.

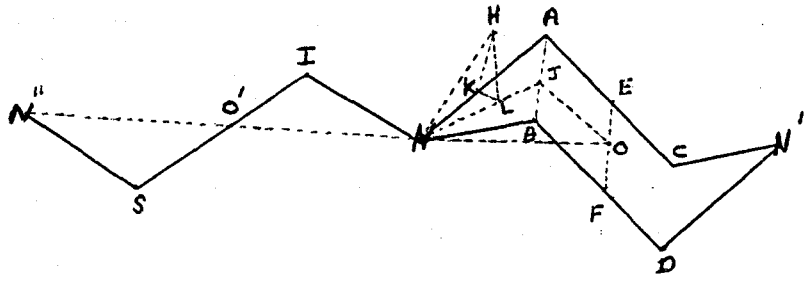
In conclusion, the β-aminoethylpiperazine grouping in the compounds prepared in this thesis is to be regarded as consisting of a mixture of the chair and boat forms.with the β-aminoethyl group attached in equatorial positions as indicated below.





It remains to determine the distances separating the nitrogen atoms,ie., the shortest distances from 1 to 2, from 2 to 3, and from 1 to 3.

A diagram of β-aminoethylpiperazine is given below:



The C-N and C-C bond distances are 1.47 Å and 1.54 Å, respectively. The NCC and CNC bond angles in the ring are tetrahedral,* 109.5°.[15-16] The CNC bond angles outside the ring are 108°.

Since the piperazine ring is symmetrical, a straight line connecting N and N' must pass through the center of plane ABCD. Therefore, the distance NO, where O is the center of the plane, must equal half the distance separating the nitrogen atoms in the ring. In determining NO, NE and EO must be known. NE is given by the following equation:

$$\cos \angle NAE = \frac{(NA)^2 + (AE)^2 - (NE)^2}{2(NA)(AE)}$$

$$\cos 109.5^\circ = \frac{(1.47)^2 + (0.77)^2 - (NE)^2}{2(1.47)(0.77)}$$

$$(NE)^2 = (1.47)^2 + (0.77)^2 - \cos 70.5^\circ (2)(1.47)(0.77)$$

$$NE = 1.87 \text{ Å}$$

*Aroney and LeFevre assume angle CNC to be tetrahedral in their work on piperazine.

The length of EO is determined as follows: Since lines AC and BD are parallel, line AB = EF, both being perpendicular to the same lines. A line drawn perpendicular from AB to N bisects ANB. Since ANB = 109.5°, ANJ = 54.75°.

$$\sin 54.8^{\circ} = \frac{AJ}{NA}$$

$$= \frac{AJ}{1.47}$$

$$AJ = (.817)(1.47) = 1.20$$

Since AJ = EO, EO is also 1.20 Å.

Therefore, $(NO)^2 = (NE)^2 - (EO)^2$

$$NO = \sqrt{(1.87)^2 - (1.20)^2}$$

$$NO = 1.437 \text{ Å}$$

The distance of separation of the nitrogen atoms in piperazine is, therefore, 2(1.437) = 2.87 Å

The distance between the nitrogen atoms in the ethylenediamine portion of the molecule will now be determined.

Since the carbon and nitrogen atoms are all considered to lie in the same plane in the ethylenediamine portion, and this portion is also symmetrical, the distance NO' is equal to half the NN'' distance. Therefore,

$$\cos\angle NIO' = \frac{(NI)^2 + (IO')^2 - (NO')^2}{2(NI)(IO')}$$

$$\cos 109.5^{\circ} = \frac{(1.47)^2 + (0.77)^2 - (NO)^2}{2(1.47)(0.77)}$$

$$NO' = 1.87 \text{ Å}$$

$$NN'' = 3.74 \text{ Å}$$

It remains now to determine angle N''NN'. This angle will be the sum of angles N''NI, INJ, and JNN'. Angle INJ is determined as follows: Angles INB and INA are 108°. For the sake of more convenient calculations, rather than determining angle INJ directly, its' supplement will be determined which is angle HNJ, where angles HNB and HNA are the supplements of angles INB and INA, and equal to 72° ($180-108^{\circ}$). Angle INJ will then simply be the supplement of angle HNJ.

By dropping lines from H to points K and L on the plane NAB where line HL is perpendicular to the plane and HK is perpendicular to line NA, angle HNJ can be determined as follows: In the right triangle HNK, line NH is equal to the nitrogen-carbon bond distance, since in this case line NH is formed by rotating line NI. Therefore:

$$\cos \angle HNA = \frac{NK}{NH}$$

$$\cos 72 = \frac{NK}{1.47}$$

$$NK = (1.47)(.309)$$

$$NK = .454 \text{ Å}$$

Since angle ANB is bisected by NJ, angle ANJ is equal to $\frac{1}{2}(109.5^{\circ})$, or 54.75°, and since HK is perpendicular to NA, KL is also perpendicular to NA. Therefore:

$$\cos \angle ANJ = \frac{NK}{NL}$$

$$\cos 54.75 = \frac{.454}{NL}$$

$$NL = \frac{.454}{.577}$$

$$NL = .786 \text{ Å}$$

NL is also the base of triangle HNL, therefore,

$$\cos \angle HNJ = \frac{NL}{NH} = \frac{.786}{1.47} = .535$$

$$\angle HNJ = 57.3^{\circ}$$

Angle INJ is therefore $(180-57.3^{\circ}) = 122.7^{\circ}$

In triangle NJO, line JO is equal to $\frac{1}{2}(1.54)$ or .77 Å, and line NO is 1.437 Å. Since triangle JNA is a right triangle, and angle ANJ is 54.75°, and line NA is 1.47 Å, it follows that:

$$\cos \angle ANJ = \frac{NJ}{NA}$$

$$\cos 54.75 = \frac{NJ}{1.47}$$

$$NJ = (.577)(1.47) = .848 \text{ Å}$$

Therefore:

$$\cos \angle JNO = \frac{(NJ)^2 + (NO)^2 - (JO)^2}{2(NJ)(NO)}$$

$$= \frac{(.848)^2 + (1.437)^2 - (.77)^2}{2(.848)(1.437)}$$

$$= .899$$

$$\angle JNN' = \angle JNO = 26^{\circ}$$

Since in triangle INO', the lines NO', NI and IO' are 1.87, 1.47 and .77 Å respectively, it follows that:

$$\cos \angle INO' = \frac{(NO')^2 + (NI)^2 - (IO')^2}{2(NO')(NI)}$$

$$= \frac{(1.87)^2 + (1.47)^2 - (.77)^2}{2(1.87)(1.47)}$$

$$= .923$$

$$\angle INN'' = \angle INO' = 22.7^{\circ}$$

Therefore, angle N''NN' is 171.4° which is the sum of angles N''NI, INJ, and JNN'.

The distance separating the terminal nitrogen atoms in β-aminoethylpiperazine, (N''N'), is determined below:

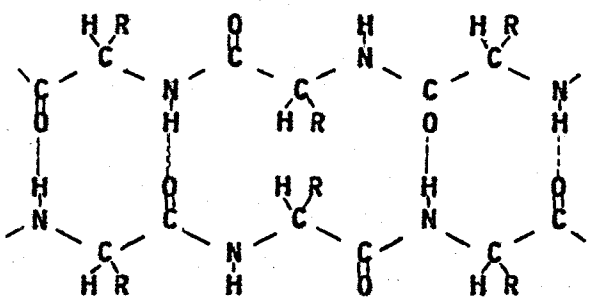
$$\cos \angle N''N' = \frac{(N''N)^2 + (NN')^2 - (N''N')^2}{2(N''N)(NN')}$$

$$\cos 171.4^\circ = \frac{(3.74)^2 + (2.87)^2 - (N''N')^2}{2(3.74)(2.87)}$$

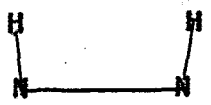
$$N''N' = 6.60 \text{ Å}$$

This distance is a little short of double the identity distance (7.2 Å).

In proteins there is hydrogen bonding between adjacent chains of polypeptides as indicated below:[17]



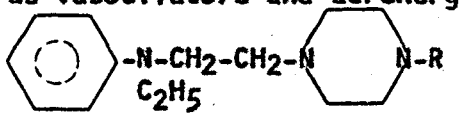
It should be pointed out that if medicinals combine with protein receptors in part through hydrogen bonding in a similar manner, then the distance separating the hydrogen atoms attached to the functional groups is also of some concern. In open chain medicinals and polypeptides the hydrogen atoms are, as indicated above, separated by the same distance as the functional groups. In aminoethylpiperazine, however, the hydrogen atoms attached to N' and N'' are not exactly perpendicular to line N''N', but rather are inclined at angles approximating 100°, as shown below:



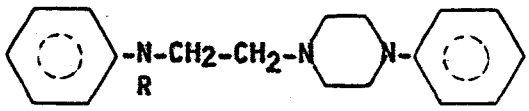
The distance separating the hydrogen atoms is, therefore, somewhat greater than 6.60 Å. The hydrogen atom at N' is here considered as axial.

There are many compounds having medicinal properties which contain the β-aminoethypiperazine moiety or some grouping very close to it. Several of these compounds will now be mentioned.

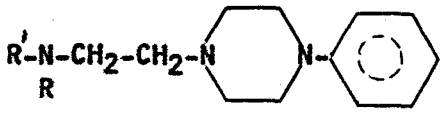
(1) The following series of compounds are known to be effective as vasodilators and adrenergic blocking agents.[18]

(A) 

R = $-CH_3$
= $-\overset{O}{\overset{\|}{C}}-CH_3$
= $-C_6H_5$
= $-C_5H_4N$

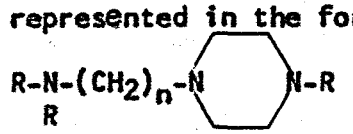
(B) 

R = $-C_2H_5$
= $-H$

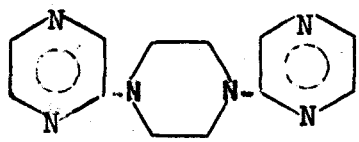
(C) 

R = $-CH_3$ $R' = -C_6H_5$
= $-CH_2-C_6H_5$ $= -CH_3$
= $-\overset{O}{\overset{\|}{C}}-CH_3$ $= -C_6H_5$

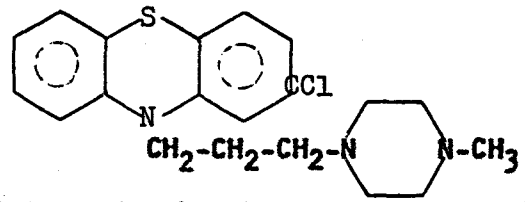
In all of these compounds the maximum activity was obtained when n=2 as represented in the formula below



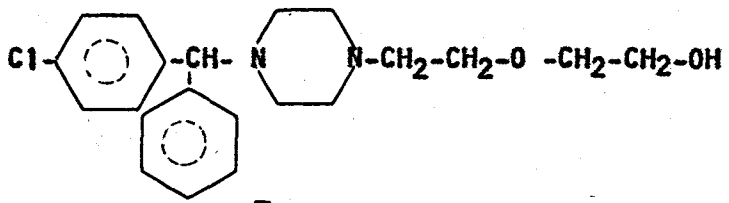
(2) The compound 1,4-di(2-pyrazyl)piperazine was prepared as a potential anticonvulsant and is a very active analgesic.[19]



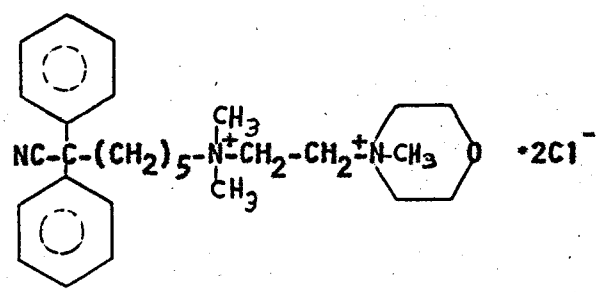
(3) Prochlorperazine is an excellent antiemetic in man and has been of value in mild neurotic disturbances.[20]



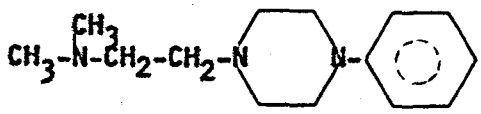
(4) Hydroxyzine has been recommended for non-hypnotic sedation of psychoneurotic individuals and for treatment of tension, anxiety, insomnia, and senile excitation.[21] It might be well to point out that, as mentioned previously, -O- and -NH- are isosteric groups and, compounds containing either of them and which are otherwise identical are expected to possess similar properties.



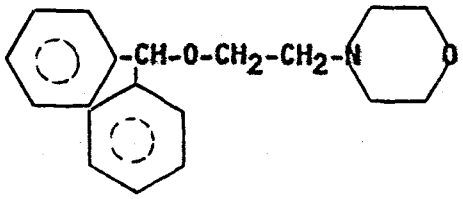
(5) The compound, 1-[N, N-dimethyl-n-(6-cyano-6,6-diphenyl-hexyl)ammonium]ethane-2-(N-methylmorpholino) dichloride, has been used with good results in the treatment of hypertension. "The spacial receptor protecting effect of the large groups may be so overpowering that the strongly polar properties of the quaternary nitrogen atom can be abandoned in favor of tertiary amino groups. This is seen in many typical antispasmodics whcih cause only a barely detectable parasympathetic ganglionic blockade." [22]



(6) The compound, 1-[β-(dimethylamino)ethyl] -4-phenylpiperazine, is a very effective antihistamine.[23]



(7) Linadryl is an effective antihistamine.[24]



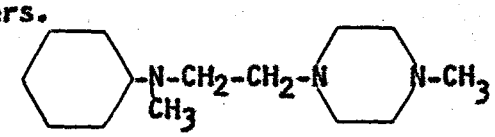
Therefore, with regard to the prototype, β-aminoethylpiperazine, it might be stated by way of summary that: (1) the compound contains the $-X-CH_2-CH_2-N$ grouping which is present in a wide variety of medicinals; local anesthetics, adrenergic blocking agents, parasympathomimetic agents, antispasmodics and nearly all of the antihistamines; (2) the distance of the terminal nitrogen atoms is close to twice the identity distance; (3) there are a number of compounds having a wide variety of medicinal properties which contain a grouping close to, if not identical to, β-aminoethylpiperazine; (4) piperazine is a relatively non-toxic substance. An additional fact of significance which has not been mentioned previously is that in many antispasmodics, groups such as pyrrolidine, piperidine and piperazine behave as anchoring groups.[25]

Rarely is a drug found which has only one action on the organism as a whole. For instance, antihistamines exhibit in some degree the properties of the local anesthetics, sympatholytic agents, antispasmodics, sympathomimetic agents, analgesics and anticholinergics.[26] This indicates that the mode of drug action for all these types of compounds is probably similar. Therefore, when a compound is designated as an analgesic, antihistamine, anticholinergic, etc., this probably means that the groups attached

to the main stem nuclei enhance its' properties as an analgesic, antihistamine, anticholinergic, etc.

The derivatives of β -aminoethylpiperazine can be expected, therefore, to have medicinal properties, and the mode of drug action can be expected to be the same as in the analgesics, antihistamines, anticholinergics, etc.

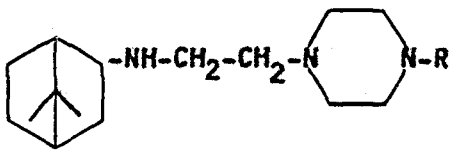
A brief discussion will now be given on each compound prepared in this thesis. In some cases large groups which themselves have certain specifically characterizable pharmacological properties have been added to the β-aminoethylpiperazine nucleus. In those instances the prepared compounds should be viewed as having properties characteristic of all their moieties. In most cases the properties of these groups added to the parent compound are harmonious with the properties expected of β -aminoethylpiperazine. In other cases where the properties of the groups added to the parent molecule are less specifically characterizable, the products should be regarded as having the same properties expected of β-aminoethylpiperazine with relatively mild variations. The compounds prepared in this study are given below and are assigned Arabic numerals. The compounds from the literature are indicated by capital letters.

(1) 

1-[β-(Cyclohexylmethylamino)ethyl]-4-methylpiperazine

This compound can be regarded as the product resulting from the replacement of compound (1)-(A) on page 19, and, therefore, is expected to have properties as a vasodilator and an adrenergic blocking agent.

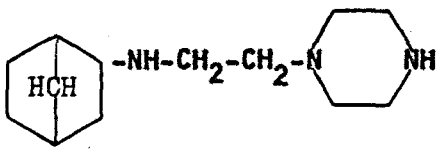
(2) Due to the close structural similarities of camphor and norcamphor, the following two compounds are discussed together and are expected to have nearly the same properties.



R= $-CH_3$

= $-H$

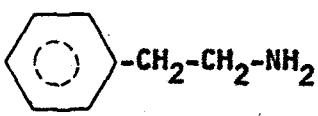
1-{β-[1,7,7-trimethyl-2-(bicyclo[2.2.1]heptyl)amino]ethyl}-4-methylpiperazine



1-{β-[2-(Bicyclo[2.2.1]heptyl)amino]ethyl}piperazine

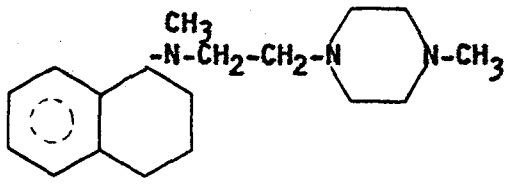
Camphor has many interesting pharmacological properties. It is an analeptic,[27] it is used as a circulatory and respiratory stimulant,[28] and locally as a mild antiseptic, analgesic and antipyretic.[29]

Compounds containing the 1-phenyl-2-aminoethane moiety are regarded as sympathomimetic amines and are classified broadly as analeptics.[30] In view of the fact that this structure resembles -

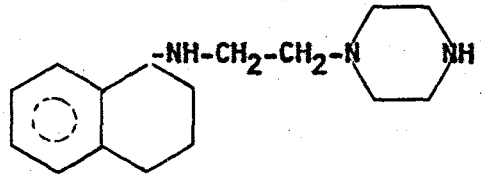


aminoethylpiperazine in certain features and that compounds of this structure and camphor are both analeptics, the camphor derivative of β-aminoethylpiperazine is expected to have analeptic properties.

One of the undesirable properties of camphor is its' water insolubility and, consequently, attempts have been made to prepare water soluble derivatives.[31] The camphor derivative of β-aminoethylpiperazine has increased water solubility over camphor.

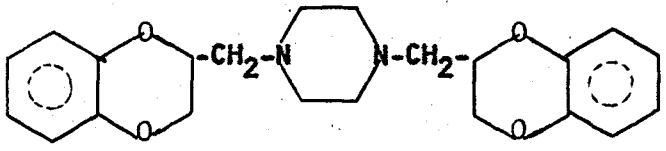
4) 

1-[β-(Methyl-1,2,3,4-tetrahydro-α-naphthylamino ethyl]-4-methylpiperazine

5) 

1-[β-(1,2,3,4-Tetrahydro-α-naphthylamino)ethyl] piperazine

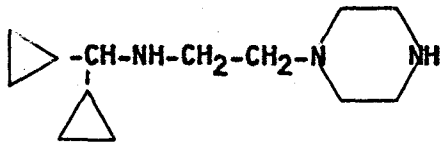
The following compound has been prepared as an antihistamine.

B) 

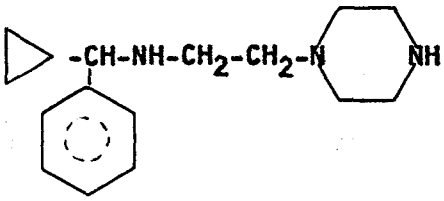
1,4-Bis(2-methyl-1,4-benzodioxane)piperazine

It is a property of the benzodioxane antihistamine drugs to cause adrenergic blockade. This compound also has considerable central nervous system depressing properties.[32] It can easily be seen that in this compound the oxygen and nitrogen atoms are separated by two carbon atoms as in most antinistamines and that this compound contains the piperazine ring. Also, the groups $-CH_2-$ and -O-, it will be recalled, are isosteres. The tetrahydronaphthyl derivatives of β-aminoethylpiperazine and the benzodioxane derivative of piperazine all contain the flat planar benzene ring attached to a non-flat, non-planar ring. This indicates that the two compounds, (4) and (5), will have antihistaminic properties.

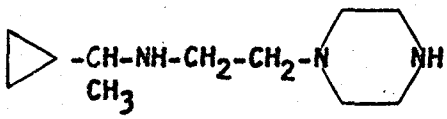
Methylation of the amino groups of a compound tends to decrease toxicity, but also tends to decrease activity.[33]

6) 

1-[β-(Dicyclopropylmethylamino)ethyl]piperazine

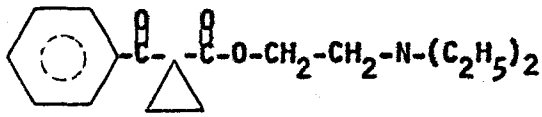
7) 

1-[β-(α-Cyclopropylbenzylamino)ethyl]piperazine

8) 

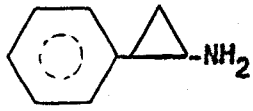
1-[β-(α-Cyclopropylethylamino)ethyl]piperazine

Few compounds related to the above structures have been prepared in which cyclopropane is used in place of a straight chain hydrocarbon. Therefore, although these compounds are expected to have properties as vasodilators and adrenergic blocking agents similar to those of the derivatives of β-amnioethylpiperazine mentioned on page 19, a prediction of any property modifications is not possible. The following two compounds are similar in some features to the above compounds, but the analogy is not too good.

C) 

β-Diethylaminoethyl-1-benzoylcyclopropanecarboxtlate

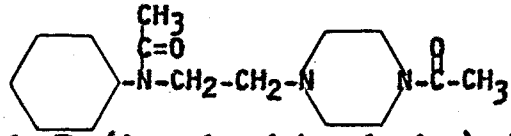
This compound is an antispasmodic and contains the $-O-CH_2-CH_2-N$ grouping characteristic of the antihistamines.[34] It also contains a phenyl and a cyclopropyl group as in compound (7).

D) 

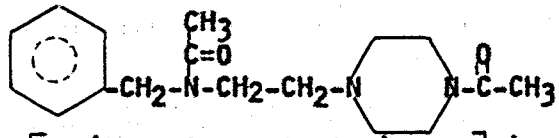
2-Phenylcyclopropylamine

Compound (D) has been used as a mood elevating drug.[35] It can be seen that this compound closely resembles the β-cyclopropylbenzylamino moiety in compound (7).

An additional fact of interest is that, cyclopropane is well known as an anesthetic of low toxicity and high therapeutic index.[36]

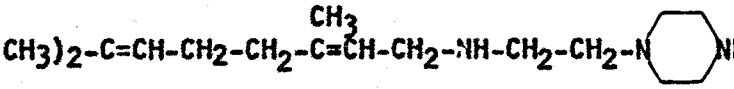
9) 

1-[β-(Acetylcyclohexylamino)ethyl]-4-acetyl piperazine

10) 

1-[β-(Acetylbenzylamino)ethyl]-4-acetylpiperazine

These compounds are also expected to possess priperties as vasodilators and adrenergic blocking agents, but again, it is difficult to assess the property modifications resulting from acetylation of the nitrogen atoms. Some compounds containing the grouping, $RCONR_2$, have anticonvulsant properties.[37]

11) 

1-[β-(3,7-Dimethyl-2,6-octadienylamino)ethyl]piperazine

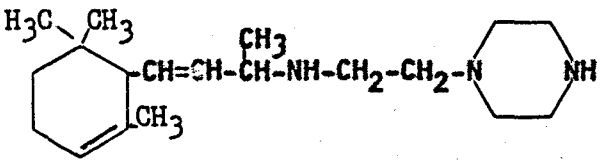
Citral, $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO$, is known to possess anti-inflammatory, antiallergic, antispasmodic and analgesic properties.[38,39]

"According to the modern mediator theory, pain arises as a result of the chemical mediators histamine and acetylcholine. Solutions of citral possess antihistamine and anticholinergic activity. The double bond in the 6-7 position does not play an important role in

antihistaminic activity. The aldehyde group is not essential for antihistaminic activity. Thus the alcohol, geraniol, is just as effective as the aldehyde, citral. The antihistaminic activity of citral and its' derivatives is not produced by a certain molecular group, but is a property of the molecule as a whole, wherein considerable changes in structure may be made without greatly affecting the activity.[40] Citral also reduces blood pressure in concentrations of 1:100,000.[41]

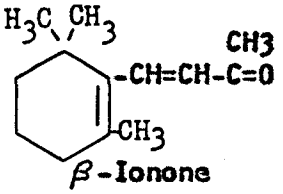
The same properties are thus possessed by citral as those expected of β-aminoethylpiperazine and the union of these two moieties should give a compound having antihistaminic, anticholinergic, and vasodilator properties.

Although this thesis is not concerned with drugs of possible use in the treatment of cancer, it is interesting that citral has inhibitory action on tumors (sarcomata) in mice,[42] and it liquefies spontaneous tumors (carcinoma of the mammary gland) in mice. Citral is non-toxic to normal cells in doses which cause regression in malignant tumors.[43]

12) 

1-{β-[3-(2,6,6-Trimethyl-2-cyclohexyl)-1-methyl-2-propenylamino]ethyl}piperazine

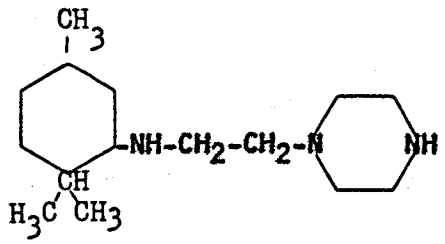
α-Ionone is a substance of very low toxicity. When injected into an animal, 2 g./kg. body weight, it is eleminated through the lungs without accident.[44] In clinical tests, β-ionone, also of low toxicity, had neurotropic, antisympathicomimetic, and antispasmodic

E) 

β-Ionone

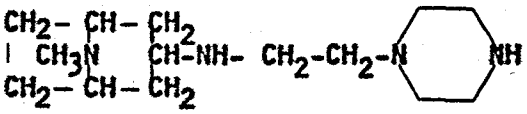
activity.[45] β-Ionone also has high anticholinergic activity.[46] In very dilute solutions, 6×10^{-6} to 6×10^{-7}, it reduces the activity of histamine by 50 - 70% in sections of guinea pig intestine.[47]

Little work has been done on the pharmacology of α-ionone however, but, due to the close structural similarities, the properties of α- ionone are at least somewhat predictable from the properties of β-ionone. If this is true, then the properties of α -ionone are harmonius with those expected of β-aminoethylpiperazine.

13) 

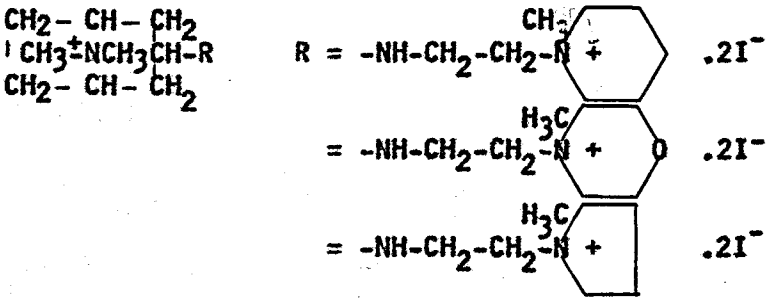
1-[β-(2-Isopropyl-5-methylcyclohexylamino) ethyl]piperazine

In one experiment, menthol depressed the isolated heart of both the frog and rabbit by dilating the coronary vessels.[48] In another experiment menthol caused a fall in blood pressure in cats and rabbits, and it blocked the vasoconstrictive action of nicotine when administered in the ratio of 1 part menthol to 2 parts nicotine.[49] In still another experiment, menthol produced vasodilation in the anesthetized dog.[50] Thus compound (13) should have strong vasodilator properties.

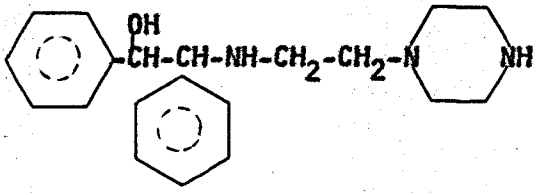
14) 

1-[β-(3-Tropylamino)ethyl]piperazine

The following compounds have been prepared and were found to have ganglionic blocking properties similar to hexamethonium.[51] These compounds also reduce the blood pressure.[52]

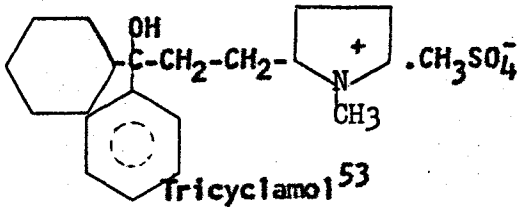
F) 

Compound (14) is not a quaternary salt, but it,also,is expected to have vasodilator and ganglionic blocking activity. It will probably be less active than compounds (F).

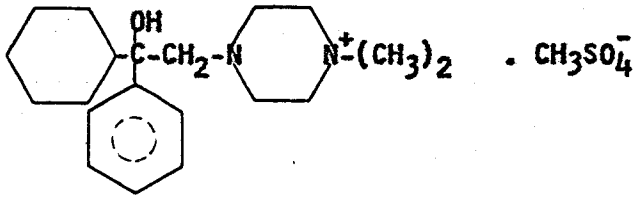
15) 

1-[β-(2-Hydroxy-1,2-diphenylethylamino)ethyl]-piperazine

The following two compounds which are structurally related to compound (15), and are used as antispasmodics.

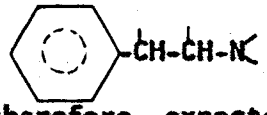
G) 

Tricyclamol[53]

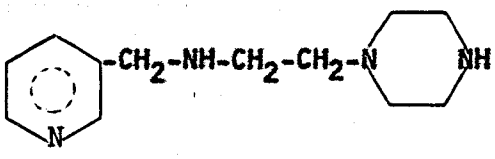
H) 

Hexocyclium[54]

Barger and Dale[55] reported that certain compounds containing the moiety shown below act as vasopressors, and are termed sympathomimetic amines. They cause a rise in blood pressure coupled with vasoconstriction.

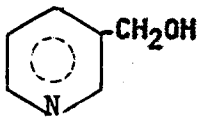
I) 

Compound (15) is, therefore, expected to have properties as an antispasmodic, and might be a vasodilator or a vasoconstrictor.

16) 

1-[β-(β-Pyridylmethylamino)ethyl]piperazine

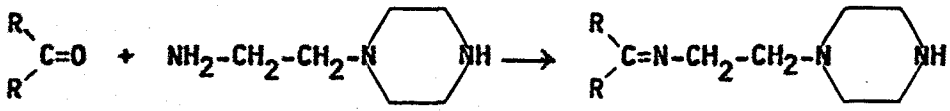
The following compound has been found to be an effective vasodilator, and is useful in overcoming cold-induced vascular spasm.[56]

J) 

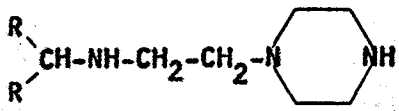
β-Pyridylmethanol

This compound can be regarded as being isosteric with the β-pyridylmethylamino grouping in compound (16). Since the two moieties in (16) have properties as vasodilators, it is expected that this compound will be a vasodilator.

The following preparations involve the condensation of a primary amine, β-aminoethylpiperazine, with aldehydes and ketones to form Schiff bases.[53] The equation for this reaction is given below:

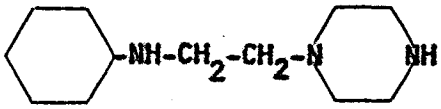


The Schiff base is then reduced using sodium borohydride ($NaBH_4$) to form the secondary amine as indicated below:



EXPERIMENTAL

1-[β-(Cyclohexylamino)ethyl]piperazine

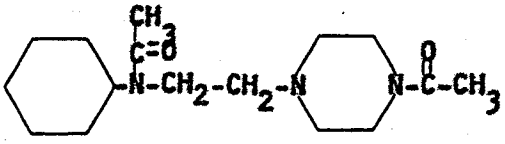


To 64.5 g. (0.5 mole) of β-aminoethylpiperazine dissolved in 100 ml. of absolute methanol was added 50 g. (0.5 mole) of cyclohexanone with shaking. The reaction took place rapidly. The resulting mixture was allowed to stand for three days. To the mixture was added 20 g. of $NaBH_4$ dissolved in absolute methanol. The methanol was evaporated and to the resulting viscous liquid was added 10 g. of NaOH dissolved in 50 ml. of water. The mixture was extracted with two 150 ml. portions of ether. The ether portions were combined and the ether evaporated. The resulting liquid was distilled.

Yield: 35.4 g. (33.5%), b.p. 148-150° @ .6mm.

Calculated for $C_{12}H_{25}N_3$: titrable N, 19.90%. Found 19.62%.

1-[β-(Acetylcyclohexylamino)ethyl]-4-acetylpiperazine

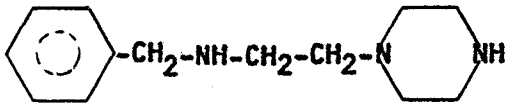


To 35.4 g. (0.17 mole) of 1-[β-(cyclohexylamino)ethyl]-piperazine, from above, dissolved in 75 ml. of anhydrous pyridine was added 32 ml. (0.34 mole) of acetic anhydride with shaking and cooling. The volatile material was distilled off under a vacuum using a water evaporator. The resulting viscous liquid was distilled.

Yield: 20.1 g. (40.0%), b.p.228-232° @ .2mm.

Calculated for $C_{16}H_{29}N_3O_2$: titrable N, 4.74%. Found 5.04%.

1- -(Benzylamino)ethyl piperazine

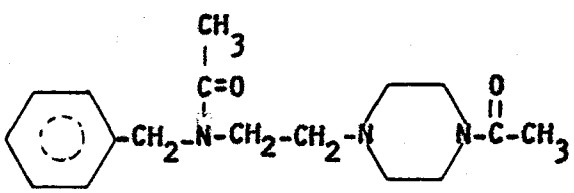


To 64.5 g. (0.5 mole) of β-aminoethylpiperazine dissolved in 100 ml. of methanol was added 53.0 g. (0.5 mole) of benzaldehyde with shaking. The resulting mixture was allowed to stand for three days. To the mixture was added 20 g. of $NaBH_4$ dissolved in 50 ml. of methanol. The methanol was evaporated using an evaporator. To the resulting viscous liquid was added 10 g. of NaOH dissolved in a minimum amount of water. This basic solution was extracted with three 100 ml. portions of ether. The ether extracts were combined and the ether evaporated. The resulting viscous liquid was distilled.

Yield: 43.2 g. (39.4%), b.p. 145-150° @ .5mm.

Calculated for $C_{13}H_{21}N_3$: titrable N, 19.17%. Found 18.98%.

1- (Acetylbenzylamino)ethyl -4-acetylpiperazine

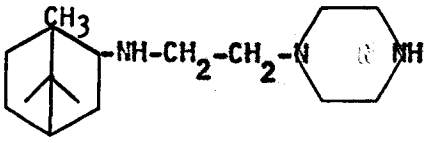


To 43.2 g. (0.2 mole) of 1-[β-(benzylamino)ethyl]piperazine, from above, dissolved in 75 ml. of pyridine was added 37.5 ml. (0.4) of acetic anhydride with shaking and cooling. The volatile material was distilled off under a vacuum using a water aspirator. The resulting viscous liquid was distilled.

Yield: 19.9 g. (32.8%), b.p. 225-230° @ .2mm.

Calculated for $C_{17}H_{25}N_3O_2$: titrable N, 4.62%. Found 5.07%.

1-{β-[1,7,7-Trimethyl-2-(bicyclo[2.2.1]heptyl)amino]ethyl}piperazine



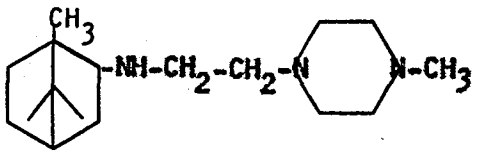
To a solution of 64.5 g. (0.50 mole) of β-aminoethylpiperazine dissolved in 100 ml. of absolute methanol was added 76 g. (0.50 mole) of camphor dissolved in 100 ml. of absolute methanol. Fifty drops of phosphorus oxychloride was added and the resulting mixture was refluxed for 48 hours.

The mixture was allowed to cool to room temperature and 20 g. of $NaBH_4$ dissolved in 200 ml. of absolute methanol was added in small portions. After hydrogen evolution had ceased the mixture was evaporated to dryness in an evaporator. The resulting viscous gum was cooled and 300 ml. of 6N HCl was added with cooling. A solid precipitate formed. The combined solid mass and solution was extracted four times with 150 ml. portions of ether. The ether portions were discarded. The acidic layer was cooled and was made basic with excess solid NaOH. A yellow oil rose to the surface. The combined oil and solution was extracted with three 150 ml. portions of ether. The ether was evaporated and the resulting oil was combined with another portion of the same oil obtained from a precedure identical to the one above. The combined portions of oil were distilled.

Yield: 52.0 g. (18.3%), b.p. 143-148° @ .3mm.

Calculated for $C_{16}H_{32}N_3$: titrable N, 15.85%. Found 15.64%.

1- {β-[1,7,7-Trimethyl-2-(bicyclo[2.2.1]heptyl)amino]ethyl} -4-methylpiperazine

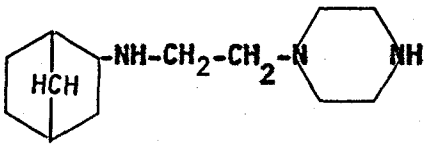


In a three-neck flask was placed 66.5 g.(0.25 mole) of 1-{β-[1,7,7-trimethyl-2-(bicyclo[2.2.1]heptyl)amino]ethyl}piperazine dissolved in 200 ml. of absolute methanol. A solution of 35.5 g. of methyl iodide in 150 ml. of absolute methanol was prepared. Half of this solution was placed in the refrigerator and the remaining half was placed in a separatory funnel attached to the three-neck flask. A reflux condenser was attached to the flask and a power stirrer was included. The methyl iodide was introduced at a slow rate into the solution being stirred. When the first portion of methyl iodide had been added the remainder from the refrigerator was placed in the separatory funnel and added slowly. The time required to introduce all of the methyl iodide was about six hours. The reaction mixture was allowed to stand overnight. The methanol was evaporated and the resulting viscous gum was dissolved in 200 ml. of 6N HCl. The acid solution was extracted with several portions of ether. The acid layer was made basic with excess solid NaOH. An oil rose to the surface. The mixture was extracted with several portions of ether, the ether layers combined and evaporated and the residue was distilled.

Yield: 9.0 g. (12.9%), b.p. 214-218° @ 30mm.

Calculated for $C_{17}H_{33}N_3$: titrable N, 15.04%. Found 14.97%.

1-{β-[2-(Bicyclo 2.2.1 heptyl)amino] ethyl} piperazine

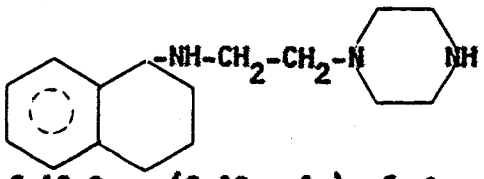


To 27.6 g. (0.25 mole) of norcamphor dissolved in approximately 75 ml. of absolute methanol was added 25.8 g. (0.2 mole) of β-aminoethylpiperazine. The mixture was allowed to stand for a few hours and then 6 g. of $NaBH_4$ was added. After the evolution of hydrogen ceased the methanol was evaporated. To the residue was added 6N HCl until the solution was acidic. The acid solution was extracted with ether and was then made basic with excess solid NaOH. This basic solution was extracted with ether. The ether extracts were combined and the ether evaporated. The resulting residue was distilled.

Yield: 10.95 g. (24.7%),

Calculated for $C_{13}H_{25}N_3$: titrable N, 18.81%. Found 18.31%.

1-[β-(1,2,3,4-Tetrahydro-α-naphthylamino)ethyl]piperazine



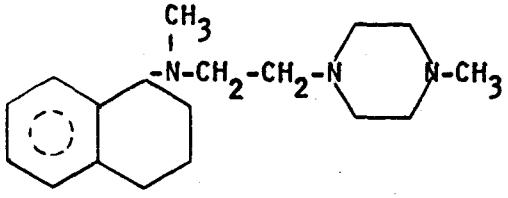
To a solution of 12.9 g. (0.10 mole) of β-aminoethylpiperazine dissolved in 100 ml. of absolute methanol cooled to 10°C was added 14.6 g. (0.10 mole) of 2,3,4-trihydronaphthone in small portions. The resulting mixture was allowed to reflux for 24 hours after 15 drops of phosphorus oxychloride had been added.

Following the refluxing the mixture was cooled in ice and 3 g. of $NaBH_4$ dissolved in 100 ml. of absolute methanol was added. After the evoltion of hydrogen ceased the methanol was evaporated in an evaporator. To this mixture was added 100 ml. of 6N HCl. and all the material went into solution. The acid solution was extracted with four 100 ml. portions of ether. The acid layer was made basic with excess solid NaOH, and an oil rose to the surface. The solution was extracted with three 100 ml. portions of ether. The ether layers were combined and evaporated, and the residue was distilled.

Yield: 31.0 g. (12.0%), b.p. 180-189° @ 1mm.

Calculated for $C_{16}H_{25}N_3$: titrable N, 16.22%. Found 16.11%.

1-[β-(Methyl-1,2,3,4-tetrahydro-α-naphthylamino)ethyl]-4-methylpiperazine

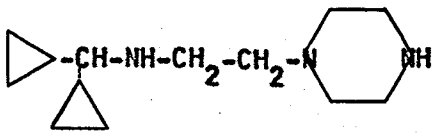


A mixture of 25.9 g. (0.1 mole) of 1-[β-(1,2,3,4-tetrahydro-α-naphthylamino)ethyl]piperazine, 19.5 g. of formaldehyde (37%) and 12.0 g. of formic acid (98+ %) was placed in a round bottom flask and heated on a steam bath for three hours. The mixture was then refluxed overnight. Concentrated hydrochloric acid (13 g.) was added and the excess formaldehyde and formic acid were removed by distillation at reduced pressure. The residue was dissolved in water and made alkaline by the addition of 40% NaOH. The oil which separated was extracted with three 50 ml. portions of ether. The ether extracts were combined and the ether evaporated. The liquid residue was distilled.

Yield: 19.9 g. (69.3%), b.p. 166-170° @ .6mm.

Calculated for $C_{18}H_{29}N_3$: titrable N, 14.62%. Found 14.36%.

1-[β-(Dicyclopropylmethylamino)ethyl]piperazine

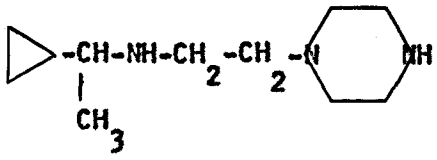


To 12.4 g. (0.13 mole) of dicyclopropyl ketone dissolved in 75 ml. of toluene was added 14.6 g. (0.11 mole) of β-aminoethyl-piperazine with shaking. An additional 50 ml. of toluene was added and the mixture was allowed to reflux with a water trap attached. Approximately 2 ml. of water was collected overnight. Most of the toluene was distilled off under reduced pressure and to the resulting residue was added a large excess of $NaBH_4$ (approximately 7 g.) dissolved in 100 ml. of methanol. The reduction took place in about four hours. The resulting solution was made more basic by the addition of 15 g. of NaOH dissolved in 50 ml. of H_2O. After cooling, the solution was extracted three times with 50 ml. portions of ether. The ether layers were combined. The remaining water-methanol layer was concentrated by evaporation and extracted with 50 ml. of ether. This ether extract was combined with the three previous ether extracts and the ether evaporated. The resulting liquid was distilled.

Yield: 3.0 g. (12.2%), b.p. 163-168° @ 8mm.

Calculated for $C_{13}H_{25}N_3$: titrable N, 18.81%. Found 18.76%.

1-[β-(α-Cyclopropylethylamino)ethyl]piperazine

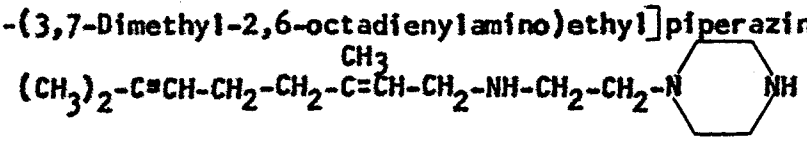


To 64.5 g. (0.5 mole) of β-aminoethylpiperazine dissolved in 50 ml of methanol was added 34 g. (0.4 mole) of methyl cyclopropyl ketone with shaking. The mixture was then allowed to reflux for one week. The mixture was treated with 15 g. of $NaBH_4$ in 50 ml. of methanol. The methanol was evaporated. The resulting viscous gum was dissolved slowly with mechanical stirring and cooling in 300 ml. of 6N HCl. The resulting acid solution was extracted three times with 50 ml. portions of ether. The ether extracts were discarded. The acid layer was then made basic with excess solid NaOH. During this process the mixture was cooled in ice. An oil rose to the surface. This mixture was then extracted three times with 100 ml. portions of ether. The ether extracts were combined and the ether evaporated. The resulting liquid was distilled.

Yield: 25.5 g. (32.3%), b.p. 153-158° @ 19.2mm.

Calculated for $C_{11}H_{23}N_3$: titrable N, 21.28%. Found 21.03%.

1-[β-(3,7-Dimethyl-2,6-octadienylamino)ethyl]piperazine

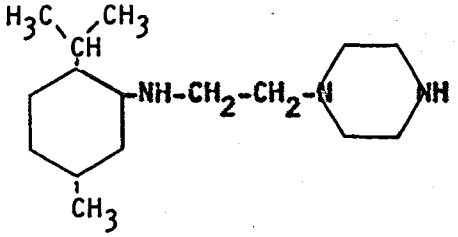


To 30.4 g. (0.2 mole) of citral dissolved in 100 ml. of toluene was added 25.8 g. (0.2 mole) of β-aminoethylpiperazine with swirling. Heat was evolved. The mixture was refluxed using a water trap. A quantitative yield of water was obtained in about 2 hours. To the mixture was added 6 g. of $NaBH_4$. No reaction was observed until a sample of methanol was added. Complete solution took place after 50 ml. of methanol had been added in small portions. The mixture was left standing overnight and a solid separated out of solution. The methanol and toluene were evaporated. The viscous gum which resulted was dissolved, with cooling, in 120 ml. of 6N HCl. This acid solution was extracted with two 100 ml. portions of ether. The ether extracts were discarded. To the acid layer was added excess solid NaOH with cooling and an oil rose to the surface. This basic solution was extracted with two 100 ml. portions and three 50 ml. portions of ether. The ether extracts were combined and the ether evaporated. The resulting viscous liquid was distilled.

Yield: 10.9 g. (20.5%), b.p. 168-172° @ .1mm.

Calculated for $C_{16}H_{31}N_3$: titrable N, 15.83%. Found 15.36%.

1-[β-(2-Isopropyl-5-methylcyclohexylamino)ethyl] piperazine

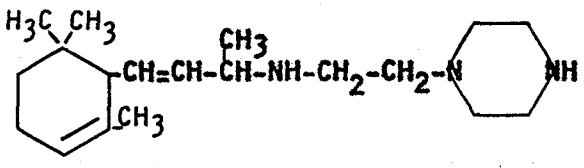


To 15.4 g. (0.1 mole) of menthone dissolved in 50 ml. of absolute methanol was added 12.9 g. (0.1 mole) of β-aminoethylpiperazine with shaking. The mixture was allowed to stand overnight. To the mixture was added 3 g. of $NaBH_4$. The mixture was allowed to stand until the evolution of hydrogen ceased, which required about 1½ hours. The methanol was evaporated and to the resulting viscous liquid was added 100 ml. of water. The liquid did not dissolve completely in the water. This mixture was then extracted with 100 ml. of ether. To the water layer was added 20 g. of solid NaOH. After cooling, this basic layer was extracted with a mixture of 100 ml. of ether and 25 ml. of butanol. The ether-butanol layer was removed and to the basic layer was added an additional 20 g. of solid NaOH. After cooling, this basic layer was extracted with 100 ml. of ether. The two ether extracts and the ether-butanol extract were combined and the volatile material was evaporated. The residue was distilled.

Yield: 4.54 g. (17.0%), b.p. 160-164° @ .02mm.

Calculated for $C_{16}H_{33}N_3$: titrable N, 15.71%. Found 15.23%.

1- {β-[3-(2,6,6-Trimethyl-2-cyclohexenyl)-1-methyl-2-propenylamino] ethyl} piperazine

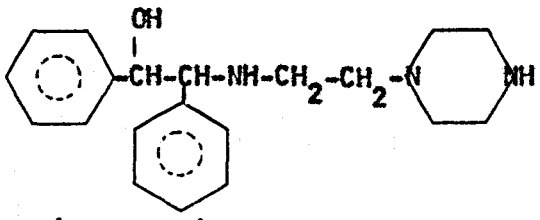


To 19.2 g. (0.1 mole) of α-ionone dissolved in 50 ml. of absolute methanol was added 12.9 g. (0.1 mole) of β-aminoethylpiperazine with shaking. The mixture was allowed to stand for about 3 hours and then 3 g. of $NaBH_4$ was added. The mixture was allowed to stand until the evolution of hydrogen ceased. The methanol was evaporated and 100 ml. of water was added to the residue. The residue was not completely soluble in the water. This mixture was extracted with two 100 ml. portions and one 50 ml. portion of ether. To the water layer was added 20 g. of solid NaOH. The resulting mixture was cooled and extracted with 75 ml. of ether. The ether extracts were combined and the ether evaporated. The liquid residue was distilled.

Yield: 7.3 g. (23.9%), b.p. 180-185° @ .05mm.

Calculated for $C_{19}H_{35}N_3$: titrable N, 15.71%. Found 15.23%.

1- [β-(2-Hydroxy-1,2-diphenylethylamino)ethyl] piperazine

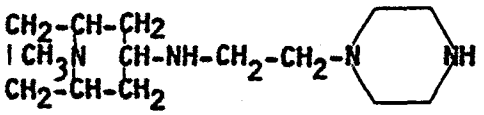


To 21.2 g. (0.1 mole) of benzoin dissolved in 100 ml. of hot toluene was added 12.9 g. (0.1 mole) of β-aminoethylpiperazine with shaking. The mixture was refluxed with a water trap attached. A quantitative yield of water was obtained within ten minutes. The refluxing was stopped and three 3 g. of $NaBH_4$ was added. Then 70 ml. of methanol was added. The addition of the methanol took the $NaBH_4$ into solution resulting in the evolution of hydrogen. Following reduction, about 1½ hours, the methanol and toluene were evaporated and the resulting viscous gum was dissolved in 70 ml. of 6N HCl with cooling in ice. The acid solution was extracted with 100 ml. and two 50ml. portions of ether. The acid layer was then made basic with excess solid NaOH while cooling. A viscous gum then rose to the surface. The basic solution and gum were extracted with one 100 ml. and two 50 ml. portions of ether. The ether was evaporated and the residue distilled.

Yield: 13.0 g. (40.0%), b.p. 233-237° @ .15mm.

Calculated for $C_{20}H_{27}N_3O$: titrable N, 12.91%. Found 12.39%.

1- [β-(3Tropylamino)ethyl]piperazine

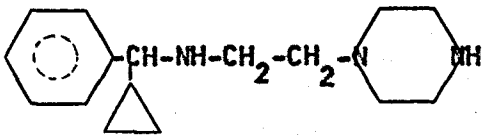


To 10 g. (0.07 mole) of tropinone dissolved in apporximately 75 ml. of absolute methanol was added 9 g. (0.07 mole) of β-amino-ethylpiperazine. The mixture was allow to stand overnight. To the mixture was added 2.8 g. of $NaBH_4$ and when the evolution of hydrogen ceased the methanol was evaporated. The resulting viscous gum was dissolved in water and solid NaOH was added until two distinct layers were formed. An attempt was made to extract the mixture with ether but the upper organic layer did not dissolve to any appreciable extent in the ether, thus forming three layers. The upper and middle layers were separated from the lower layer. The lower layer was extracted with approximately 75ml. of ether. This ether layer was added to the upper and middle layers. The lower layer was treated with solid NaOH and the upper layer thus formed was added to the ether layers already obtained. The ether was evaporated and the resulting viscous liquid was distilled.

Yield: 3.8 g. (21.5%), b.p. 160-164° @ .1mm.

Calculated for $C_{14}H_{28}N_4$: titrable N, 22.20%. Found 22.05%.

1-[β-(α-Cyclopropylbenzylamino)ethyl]piperazine

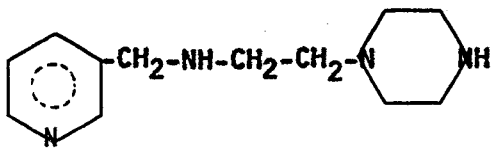


To 64.5 g. (0.5 mole) of β-aminoethyl piperazine dissolved in 50 ml. of methanol was added 73 g. (0.5 mole) of phenylcyclopropyl ketone with shaking. The mixture was allowed to reflux for one week. Part of the methanol was evaporated and 100 ml. of toluene was added and the toluene distilled. During this distillation about 5 ml. of H_2O was removed from the distilled toluene. To the resulting mixture was added 15 g. of $NaBH_4$ in absolute methanol, and the methanol evaporated. The resulting viscous gum was taken up with cooling and stirring in 300 ml. of 6N HCl. The acid solution was extracted three times with 50 ml. portions of ether. The ether extracts were discarded. The acid layer was then made basic with excess solid NaOH and extracted three times with 100 ml. portions of ether. The ether extracts were combined and the ether evaporated. The resulting liquid was distilled.

Yield: 18.35 g. (15.8%), b.p. 178-182° @ .5mm.

Calculated for $C_{14}H_{23}N_3$: titrable N, 16.20%. Found 16.37%.

1-[β-(β-Pyridylmethylamino)ethyl]piperazine

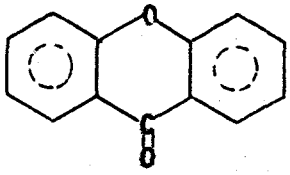


To a solution of 38.7 g. (0.30 mole) of β-aminoethylpiperazine dissolved in 25 ml. of absolute methanol was added 32.1 g. (0.30 mole) of 3-pyridinecarboxaldehyde with shaking. The mixture was allowed to stand for 15 minutes, after which 7.6 g. (0.2 mole) of $NaBH_4$ in 100 ml. of methanol was added with shaking. Upon completion of reduction the methanol was evaporated using an evaporator. Two layers appeared. To this mixture was added 200 ml. of 6N NaOH and the basic mixture was extracted with 250 ml. of ether. To the ether layer was added 100 ml. of 12N HCl and the mixture was cooled in an ice bath. An additional 200 ml. of ether was added and the entire upper layer was separated and discarded. To the lower acid solution was added 6N NaOH until it became strongly basic. All the product remained in solution. The solution was saturated with solid K_2CO_3. Two layers formed and the lower layer was discarded. The upper layer was dissolved in 300 ml. of ether and 200 ml. of ethanol. A white solid came out of solution and was filtered. The precipitate was discarded and the filtrate was dried over solid K_2CO_3. The mixture was filtered and most of the ether evaporated. The remainder of the ethanol were distilled off using the water aspirator and the resulting viscous liquid was distilled using a vacuum pump.

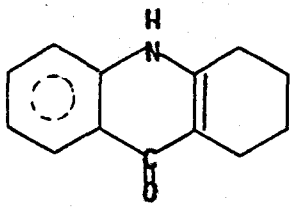
Yield: 32.0 g. (14.5%), b.p. 176-180° @ .3mm.

Calculated for $C_{12}H_{20}N_4$: titrable N, 25.43%. Found 25.57%.

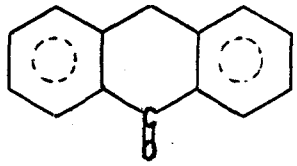
Unsuccessful attempts were made to obtain the reduced condensation products of β-aminoethylpiperazine with the following ketones:



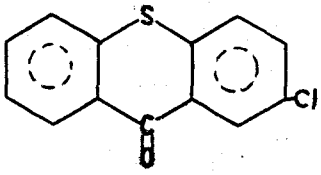
Xanthene-9-one



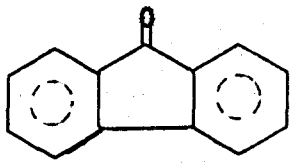
1,2,3,4-Tetrahydroacridone



Anthrone



2-Chlorothioxanthone

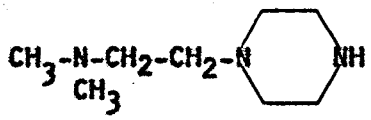


Fluorenone

These compounds were refluxed, in some cases for a week or more, with β-aminoethylpiperazine in such solvents as xylene, toluene, methanol and butanol, but in all cases following addition of $NaBH_4$ and standard purification procedures, no analyzable product was obtained.

METHOD OF ANALYSIS

The compounds prepared in this thesis were analyzed by titrating the basic nitrogen atoms. The compound shown, for example, has three titrable nitrogen atoms.



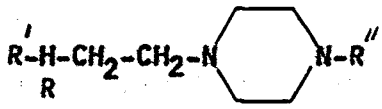
A small sample (0.05-0.15 g.) of each compound was weighed, dissolved in glacial acetic acid and titrated with standardized perchloric acid in glacial acetic acid. During the titration, the solution was stirred with a magnetic stirrer and the progress of the titration was followed using a Beckman Glass Electrode pH meter, Model H-2. The end point of the titration was determined as the point of maximum change in potential per milliliter increment of titrant added.

The method of calculation is shown below, where B is the number of titrable nitrogen atoms.

$$\frac{B \times \text{Wt. of Sample} \times 1000}{\text{ml. of Acid} \times \text{N of Acid}} = \text{Molecular Weight}$$

$$\frac{B \times 14.03 \times 100}{\text{Molecular Weight}} = \%N$$

TABLE of RESULTS



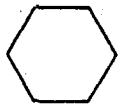
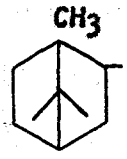
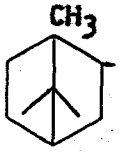
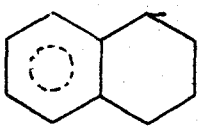
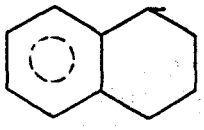
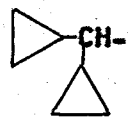
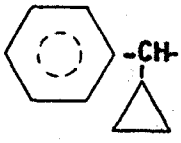
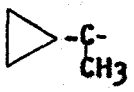
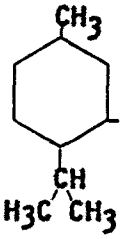
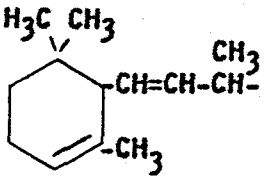
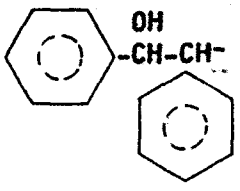
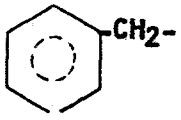
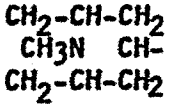
R	R′	R″	% Yield	B.P. C°	Pressure mm.	N% Calc.	N% Found
	-H	-H	33.5	148-150	0.6	19.90	19.62
	O -C-CH$_3$	O -C-CH$_3$	40.0	228-232	0.2	4.74	5.0
 -CH$_2$-	-H	-H	39.4	145-150	0.5	19.17	18.98
 -CH$_2$-	O -C-CH$_3$	O -C-CH$_3$	32.8	225-230	0.2	4.62	5.07
	-H	-H	18.3	143-148	0.3	15.85	15.64
	-H	-CH$_3$	12.9	214-218	30.	15.04	14.97
	-H	-H	24.7	192-196	38.	18.81	18.31
	-H	-H	12.0	180-189	1.0	16.22	16.11
	-H	-H	69.3	166-170	0.6	14.62	14.36
	-H	-H	12.2	163-168	8.0	18.31	18.76

TABLE of RESULTS (Cont.)

R-H-CH_2-CH_2-N N-R
R

R	R	R	% Yield	B.P. C°	Pressure mm.	N% Calc.	N% Found
	-H	-H	18.8	178-182	0.5	16.20	16.37
	-H	-H	32.3	153-158	19.2	21.28	21.03
$(CH)_3C=CHCH_2CH_2C(CH_3)=CHCH_2-$	-H	-H	20.5	168-172	0.1	15.83	15.36
	-H	-H	17.0	160-164	0.02	15.71	15.23
	-H	-H	23.9	180-185	0.05	15.71	15.23
	-H	-H	40.0	233-237	0.15	12.91	12.39
	-H	-H	14.5	176-180	0.3	25.43	25.57
	-H	-H	21.5	160-164	0.1	22.20	22.05

SUMMARY

A series of potential pharmaceutical derivatives of β-aminoethylpiperazine was prepared by condensing aldehydes and ketones with the primary amino group of β-aminoethylpiperazine to form the Schiff bases. The Schiff bases were reduced to secondary amines using sodium borohydride.

In nearly all of the compounds prepared, the groups attached to the β-aminoethylpiperazine nucleus are known to have medicinal properties which are the same as those expected of the β-aminoethylpiperazine moiety. The compounds are expected to have one or more of the following activities: antispasmodic, anticholinergic, antihistaminic, vasodilator, ganglionic blocking, analgesic, sympathomimetic and sympatholytic. The actual activities are pending the results of pharmacological testing by the A. H. Robins Co. Inc.

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AUTOBIOGRAPHY

I, Brian A. Dementi, was born in Richmond, Virginia, on March 3, 1938. I graduated from Hermitage High School in Henrico County, Virginia, in 1956; entered Hampden-Sydney College in September, 1956, and received a B. S. degree in 1961. I attended Richmond College for the session, 1960-61, and entered the Graduate School of the University of Richmond in 1961.