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DERIVATIVES OF HOMOPIPERAZINE

by
Jack Gilbert Scruggs

A dissertation submitted in partial fulfillment
of the requirements for the degree of
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University of Michigan
1956

Committee in charge:

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Professor Adam A. Christman
Professor Albert M. Mattocks
Associate Professor Peter A. S. Smith
Associate Professor Lee Worrell

DERIVATIVES OF HOMOPIPERAZINE

By Jack Gilbert Scruggs

Abstract

The object of this investigation was the synthesis of 1,4-disubstituted homopiperazines and related substances. Compounds of the former type have potential value as therapeutic agents.

A variety of 1-methyl-4-substituted homopiperazines was prepared in which the 4-substituent was (A) beta-dimethylaminoethyl, benzhydryl or para-bromobenzhydryl; (B) phenylacetyl, diphenylacetyl, diethylcarbamyl, diphenylcarbamyl or carbethoxy; (C) beta-benzhydryloxyethyl, beta-phenylacetyloxyethyl, beta-diphenylacetyloxyethyl; (D) methyl, amino, dimethylamino, gamma-phenyl-gamma-hydroxypropyl or gamma-phenyl-gamma-benzoyloxypropyl.

The products in groups (A) and (B) were obtained by interaction of 1-methylhomopiperazine with the required substituted alkyl halide or acid chloride. Compounds in group (C) were synthesized by allowing 1-methylhomopiperazine to react with ethylene bromohydrin and treatment of the resulting 1-methyl-4-(beta-hydroxyethyl)homopiperazine with benzhydryl bromide, phenylacetyl chloride or diphenylacetyl chloride. Each compound in group (D) was made by a different procedure. 1,4-Dimethylhomopiperazine was obtained by formylation of 1-methylhomopiperazine with chloral and subsequent reduction of the 1-methyl-4-formylhomopiperazine with lithium aluminum hydride. Treatment of 1-methylhomopipera-

zine with nitrous acid yielded the 4-nitroso derivative which was reduced with lithium aluminum hydride to the corresponding 4-amino compound. Methylation with formaldehyde and formic acid of 1-methyl-4-aminohomopiperazine yielded the corresponding 4-dimethylamino compound. A Mannich reaction in which 1-methylhomopiperazine dihydrochloride, formaldehyde and acetophenone were employed, produced 1-methyl-4-(beta-benzoylethyl)homopiperazine which was reduced with lithium aluminum hydride to 1-methyl-4-(gamma-phenyl-gamma-hydroxypropyl)homopiperazine [1-phenyl-3-(1-methyl-4-homopiperazinyl)propanol]. Benzoylation of the last mentioned compound with benzoyl chloride yielded the benzoyl derivative.

Two 1-benzyl-4-substituted homopiperazines were prepared in which the 4-substituent was an amino and a diethylcarbamyl group. The former derivative was prepared by nitrosation with nitrous acid of 1-benzylhomopiperazine and subsequent reduction of the nitroso group with lithium aluminum hydride. The latter derivative was formed by interaction of 1-benzylhomopiperazine with diethylcarbamyl chloride.

It was found that homopiperazine can be obtained conveniently by debenzylation of 1-benzylhomopiperazine. This process was effected in 80% yield by the use of hydrogen and a palladium-charcoal catalyst.

It was known that o-phenylenediamine condenses with acetylacetone to yield 2,3-benzo-5,7-dimethyl-1,4-diazacycloheptatriene (2,3-benzo-5,7-dimethyl-1,4-diazepine). We found that this substance can be hydrogenated, in the presence of

platinum oxide catalyst, to 2,3-benzo-5,7-dimethyl-1,4-diazacycloheptene-2.

It was also known that interaction of o-phenylenediamine with ethyl acetoacetate produces 2,3-benzo-5-methyl-1,4-diazacycloheptadiene-2,4-one-7. It was found that although this substance could not be hydrogenated with the aid of platinum oxide, reduction did take place when lithium aluminum hydride was employed. The reaction product was 2-methylbenzimidazole instead of the expected 2,3-benzo-5-methyl-1,4-diazacycloheptene-2.

It has been reported that condensation of ethylenediamine with acetylacetone yields 5,7-dimethyl-1,4-diazacycloheptadiene-4,7, and that condensation of the diamine with ethyl acetoacetate produces 5-methyl-1,4-diazacycloheptene-4-one-7. When we carried out these condensations, linear instead of cyclic reaction products were obtained: in the first instance, 4,9-dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8, and in the second instance, 1,8-dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6 was isolated.

1,5-Diazabicyclo[3.2.2]nonane, isolated as the picrate methopicrate, was synthesized by two procedures: (a) conversion of 1-methylhomopiperazine into 1-methyl-4-(beta-hydroxyethyl)homopiperazine, reaction of this compound with hydrobromic acid to form 1-methyl-4-(beta-bromoethyl)homopiperazine dihydrobromide and treatment of this salt with ammonium hydroxide whereby cyclization took place; (b) reaction of 1-methylhomopiperazine with ethylene dibromide.

To Dad, Mom and Ann

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Professor F. F. Blicke, who suggested this problem and supervised the investigation.

Grateful acknowledgement is also made for the fellowship granted to the author by The American Foundation for Pharmaceutical Education.

Jack Gilbert Scruggs

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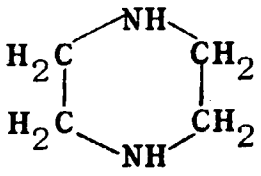
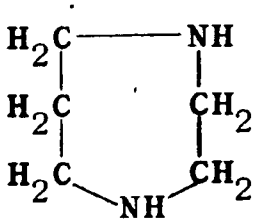
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GENERAL INTRODUCTION

During this investigation we were interested in the preparation of derivatives of the seven-membered ring homopiperazine which is the next higher ring homolog of piperazine.

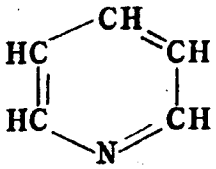
Piperazine   Homopiperazine

It seemed highly desirable to synthesize N-substituted and N,N'-disubstituted homopiperazines since hitherto only a very small number of compounds of this type has been mentioned in the literature. In fact, the total number of described substituted homopiperazines of all types is only about thirty-two.

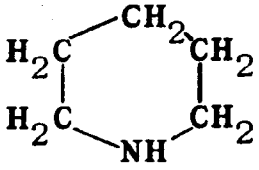
Interest in N-substituted and N,N'-disubstituted homopiperazines lies in the fact that during recent years piperazine and its derivatives have created a great deal of interest because of their activity as anthelminthics, antifilarial agents, antihistaminics, antiemetics, anticonvulsants and antimalarials.

Since seven-membered cyclic compounds which contain one or more nitrogen atoms in the ring are not common substances, formulas for a number of related ring systems are shown on the following page.

NOMENCLATURE



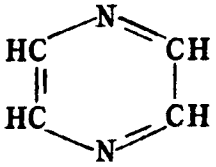
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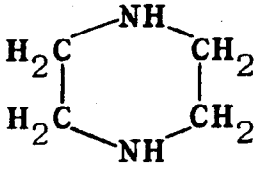
II

I Pyridine
Azacyclohexatriene

II Piperidine
Azacyclohexane
Pentamethylenimine



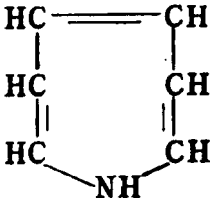
III



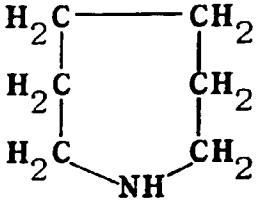
IV

III Pyrazine
1,4-Diazacyclohexatriene

IV Piperazine
1,4-Diazacyclohexane
Diethylenediamine



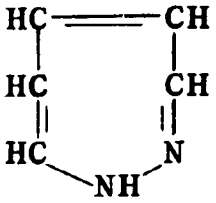
V



VI

V Azepine
Azacycloheptatriene

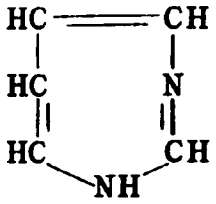
VI Homopiperidine
Azacycloheptane
Hexamethylenimine



VII

Hexahydro form unknown

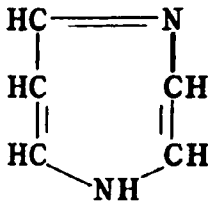
VII 1,2-Diazepine
1,2-Diaza-2,4,6-cycloheptatriene



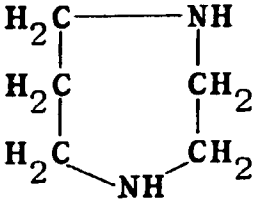
VIII

Hexahydro form unknown

VIII 1,3-Diazepine
1,3-Diaza-2,4,6-cycloheptatriene



IX



X

IX 1,4-Diazepine
1,4-Diaza-2,4,6-cycloheptatriene

X Homopiperazine
1,4-Diazacycloheptane
Trimethyleneethylenediamine

Inasmuch as information concerning piperazines is of importance in the study of homopiperazine and its derivatives, a discussion of some phases of piperazine chemistry and the pharmacological properties of piperazine derivatives has been presented in the following two sections.

Methods of Preparation of Piperazine and Substituted Piperazines

The various procedures for the preparation of piperazines have been arranged in seven groups.

I. Reaction of Two Equivalents of a Primary Amine with Two Equivalents of an Ethylene Dihalide

II. Reaction of an Ethylenediamine or Substituted Ethylenediamine with an Ethylene Dihalide or Diol

III. From a beta-Aminoalkyl Halide

IV. Catalytic Cyclodehydration (Intramolecular or Intermolecular)

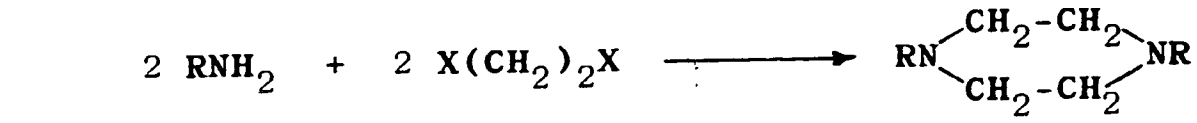
V. From 1,4-Diaza Six-membered Heterocycles

VI. Deamination of Polyamines (or Hydrochloride Salts)

VII. Miscellaneous Reactions

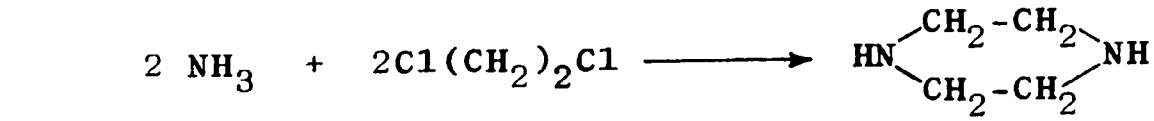
I. Reaction of Two Equivalents of a Primary Amine with Two Equivalents of an Ethylene Dihalide

General Equation:



R = Hydrogen, alkyl or aryl; X = chlorine or bromine

Examples:



(1)



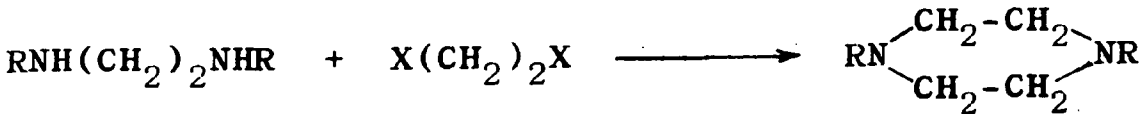
(2)



(3)

II. Reaction of an Ethylenediamine or Substituted Ethylenediamine with an Ethylene Dihalide or Diol

General Equation:

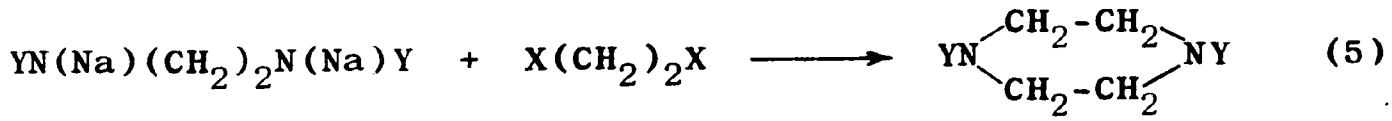


R = Hydrogen, alkyl or aryl; X = chlorine, bromine, iodine or hydroxyl

Examples:

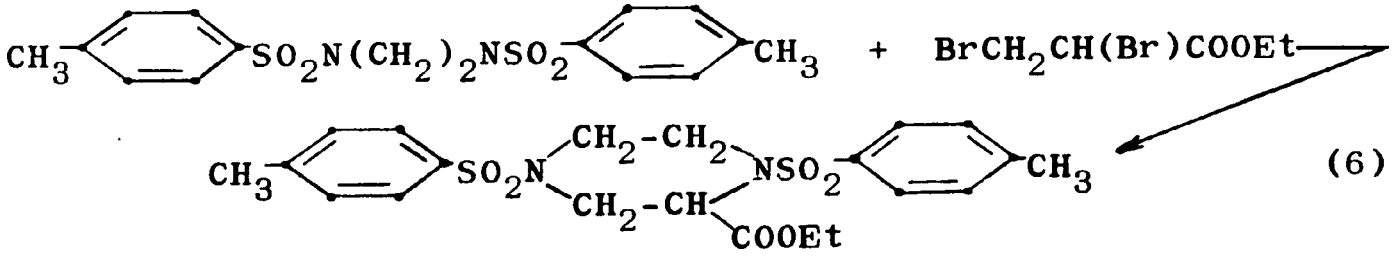


(4)



(5)

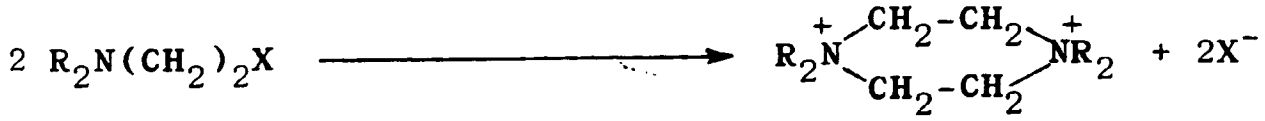
Y = Formyl, acetyl or aminoformyl; X = chlorine, bromine or hydroxyl



(6)

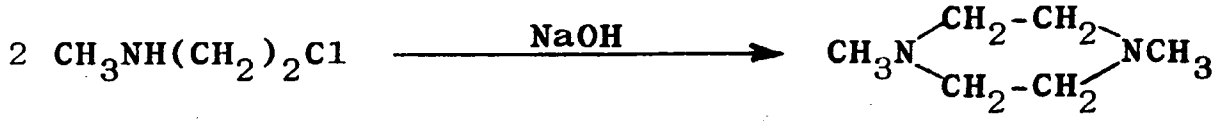
III. From a beta-Aminoalkyl Halide

General Equation:

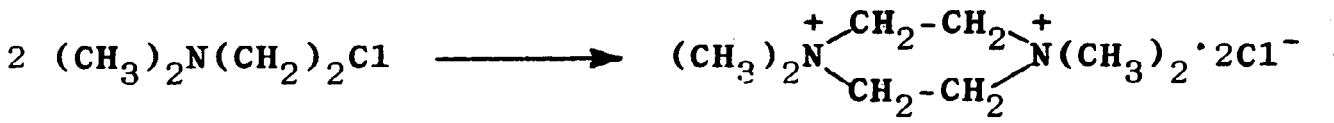


R = Hydrogen, alkyl or aryl; X = chlorine, bromine or iodine

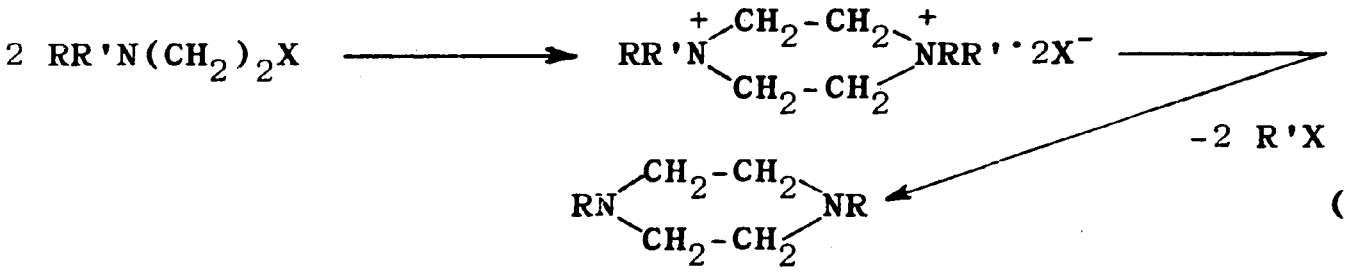
Examples:



(7)



(7)



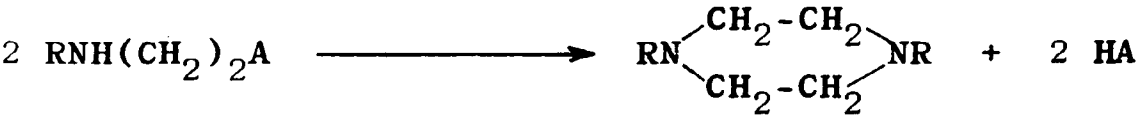
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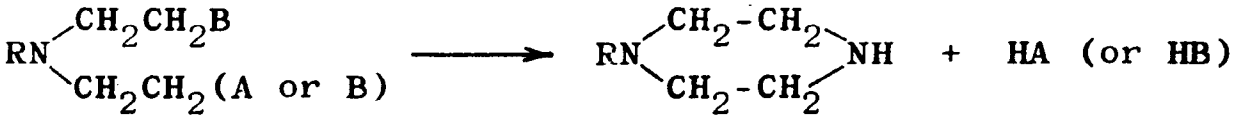
R and R' = Methyl, ethyl, propyl or butyl; X = chlorine or bromine

IV. Catalytic Cyclodehydration

(Intramolecular or Intermolecular)

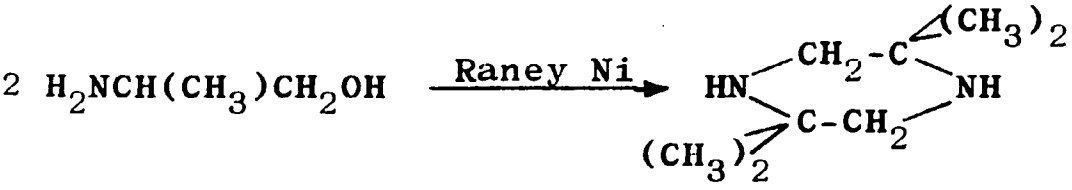
General Equations:



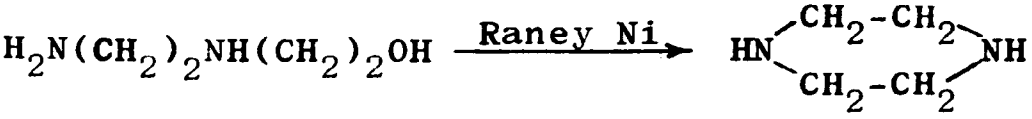


R = Hydrogen or alkyl; A = hydroxyl; B = amino

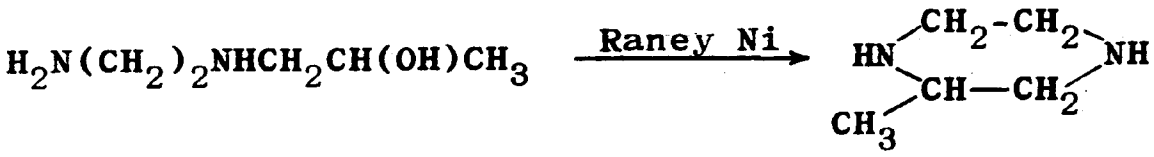
Examples:



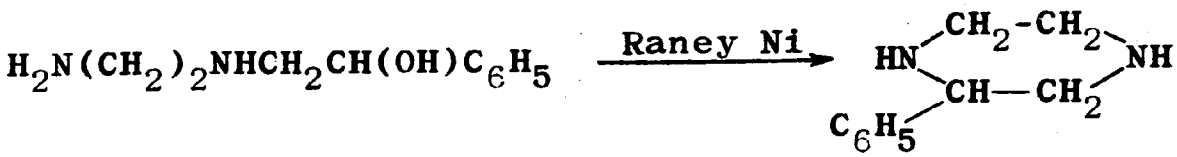
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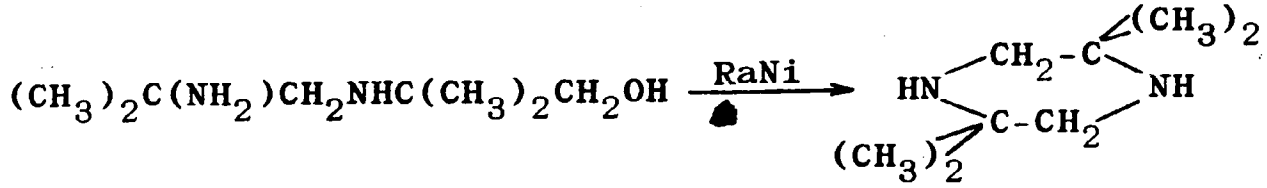
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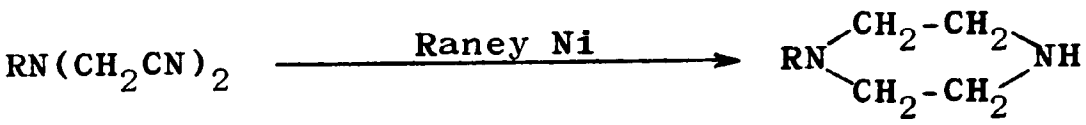
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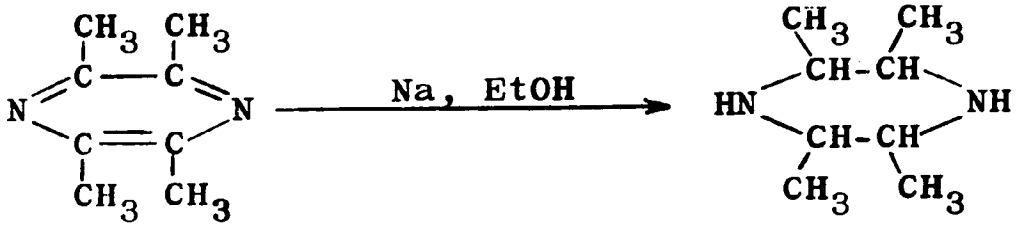


(12)

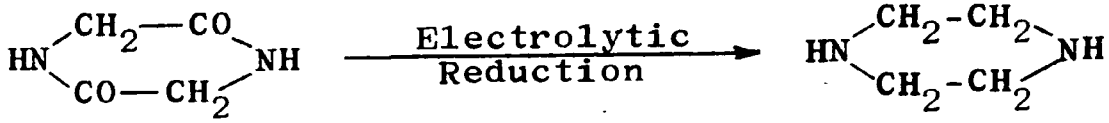
R = H, $PhCH_2$, EtOCO, EtNCO, $PhSO_2$, CH_3, Et, CH_3CO or PhCO

V. From 1,4-Diaza Six-membered Heterocycles

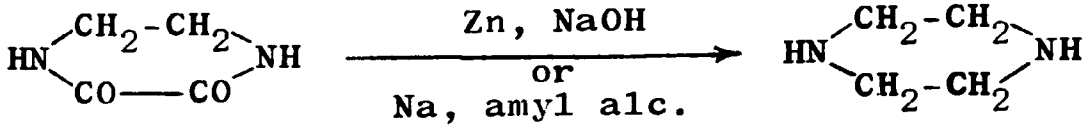
Examples:



(13)



(14)



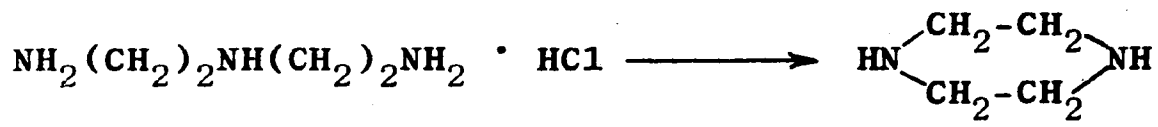
(15)

VI. Deamination of Polyamines (or Hydrochloride Salts)

Examples:



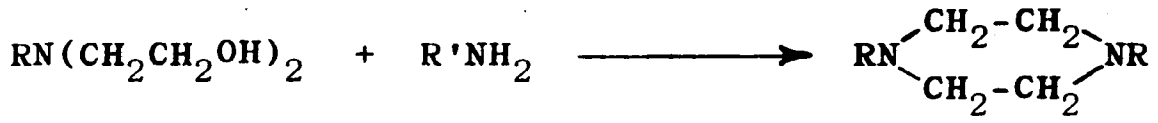
(16)



(17)

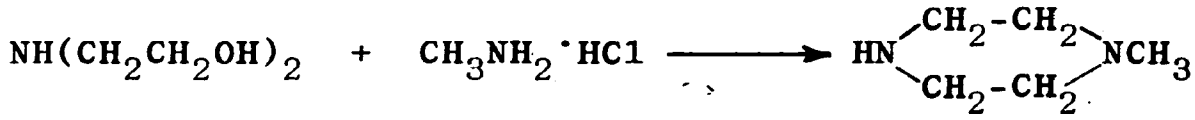
VII. Miscellaneous Reactions

Examples:

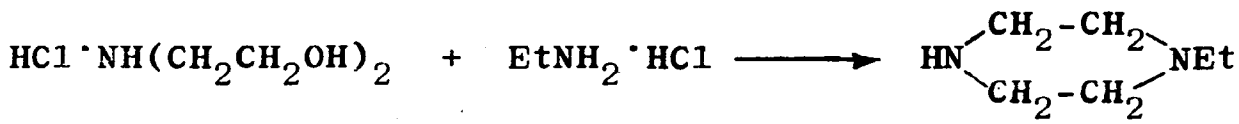


(18)

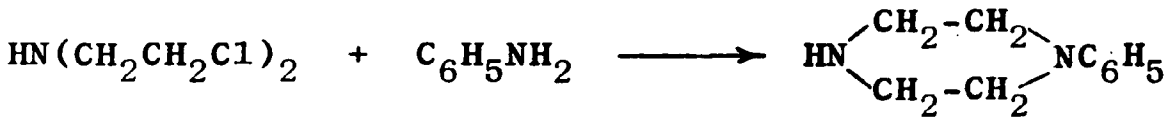
R = Me, Et, Pr or Bu; R' = H, Me or Ph



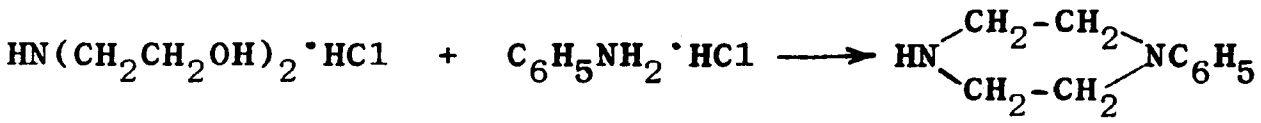
(19)



(19)



(20)

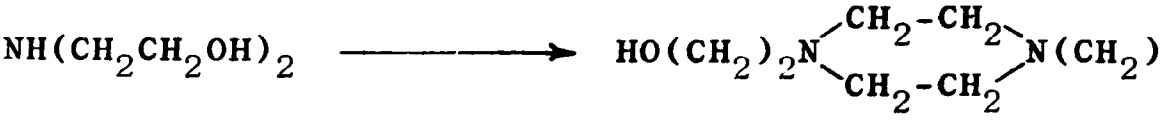


(21)



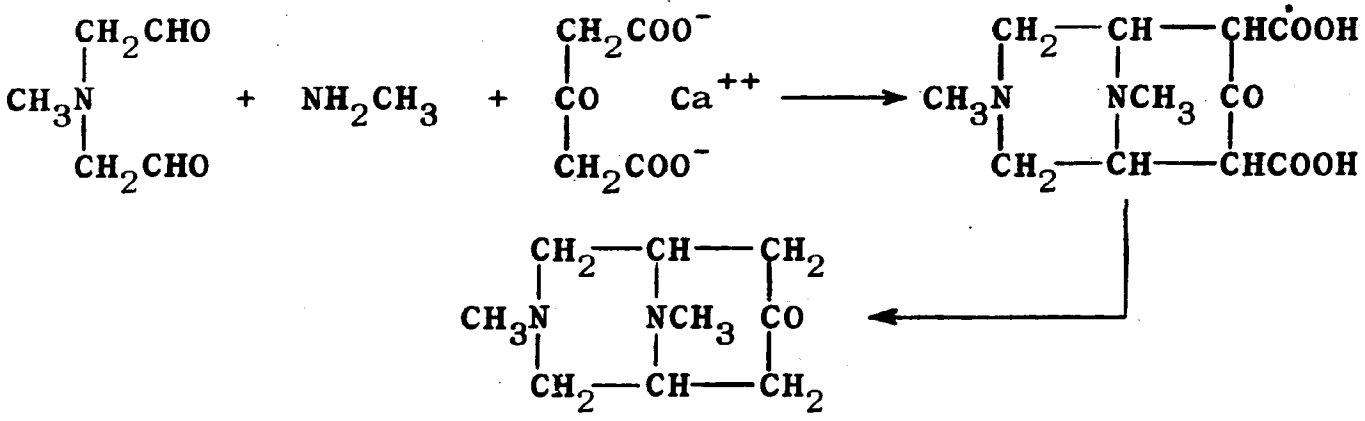
(22)

R = H, Me, Bu or Ph; R' = Ph or p-MeC_6H_4



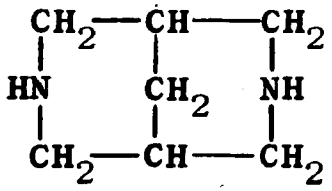
(23)

During the preparation of analogs of pseudopelletierine, Blount and Robinson (24) synthesized a compound which they called N-methylaztropinone, in the manner indicated by the following equation.



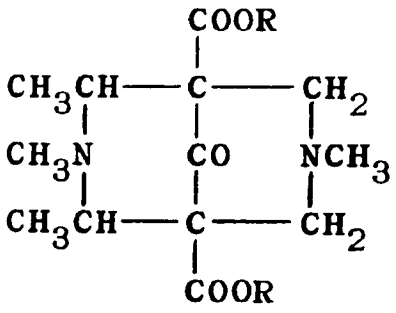
As can be seen from the formula, this compound may be considered to be a substituted piperazine. No information could be found concerning the physiological action of this compound.

A somewhat similar bicyclic ring system which consists of two fused piperidine rings is known as "bispidine" (25).

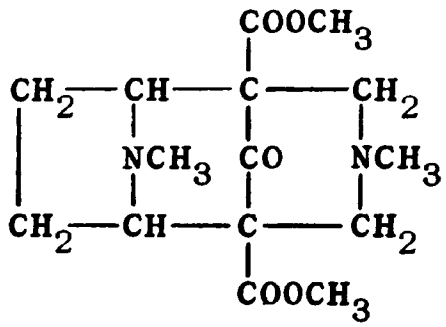


Bispidine, 3,7-diazabicyclo[3.3.1]nonane

Mannich and Veit (26) prepared two compounds which contain this ring system.



3,6,7,8-Tetramethyl-9-oxo-bispidine-1,5-dicarboxylic acid, dimethyl and diethyl esters



3,7-Dimethyl-6,8-ethylene-9-oxo-bispidine-1,5-dicarboxylic acid dimethyl ester

Although these products resemble tropinone and ecgonine in structure, and were prepared as analogs of these compounds, no information has been reported with regard to their pharmacological action.

Many of the aforementioned syntheses for N-substituted and N,N'-disubstituted piperazines may also be utilized for the preparation of piperazine itself. The manner in which certain substituents can be removed from the nitrogen atom is shown below*.

1. $C_6H_5N(C_4H_8)NC_6H_5 \xrightarrow{HNO_2} p\text{-}NOC_6H_4N(C_4H_8)NC_6H_4NO\text{-}p \xrightarrow{\text{acid}} HN(C_4H_8)NH$ (27)

2. $p\text{-}NOC_6H_4N(C_4H_8)NC_6H_4NO\text{-}p \xrightarrow{\text{alkali}} HN(C_4H_8)NH$ (28)

3. $C_6H_5CH_2N(C_4H_8)NCH_2C_6H_5 \xrightarrow{10\%\ HCl,\ 200^\circ} HN(C_4H_8)NH$ (29)

4. $ArN(C_4H_8)NAr \xrightarrow{50\%\ H_2SO_4} HN(C_4H_8)NH$ (30)
(Ar = alpha-naphthyl or beta-naphthyl)

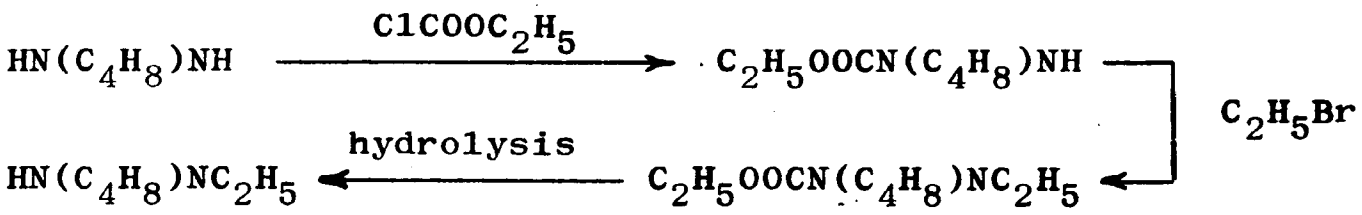
5. $C_6H_5SO_2N(C_4H_8)NSO_2C_6H_5 \xrightarrow[200^\circ]{dil.\ H_2SO_4} HN(C_4H_8)NH$ (31)

Methods for the preparation of N-substituted (monosubstituted) piperazines are of importance: occasionally, the N-substituted derivative itself is desired as a reaction product; in other instances, the N-substituted derivative is required as an intermediate. Although mono-N-substituted piperazines can be prepared by ring closure processes, no method in known whereby a product of this type can be obtained directly from piperazine without the simultaneous

*The removal of a N-carbalkoxy or a N-benzyl group is discussed later in this dissertation.

formation of more or less of the N,N'-disubstituted product.

In order to obtain 1-ethylpiperazine (32), piperazine was treated with ethyl chlorocarbonate. After isolation of the 1-carbethoxypiperazine, this product was allowed to react with ethyl bromide to form 1-carbethoxy-4-ethylpiperazine which was then hydrolyzed to yield 1-ethylpiperazine.



After the preparation of a monosubstituted piperazine by the process described above, this substance was used for the synthesis of a large number of unsymmetrically disubstituted piperazines (33).

1-Alkylpiperazines have been obtained by the use of 1-benzylpiperazine. After alkylation of this substance to produce a 1-benzyl-4-alkylpiperazine, the benzyl group may then be removed by catalytic debenzylation (34).

At one time it was believed that only a disubstitution product could be obtained by direct alkylation or acylation of piperazine. However, it was found (35) that in these instances the reaction product actually consists of a mixture of piperazine, the monosubstituted and the disubstituted piperazine. The separation of the monosubstituted product in pure form by distillation is difficult in some instances. For example, piperazine boils at 145-146°, 1-methylpiperazine at 140° and 1,4-dimethylpiperazine at

131-132°. However, when the substituent is a higher alkyl group (n-lauryl or n-decyl) separation of the monosubstitution product in pure form by distillation is a practical process (35).

An extensive study has been made to determine the factors which favor the formation of the monosubstitution product (34).

In a study of the reaction of piperazine with 2-methylpropylene oxide and with trimethylethylene oxide, the only products which could be isolated were those which represented reaction between two molecules of the alkylene oxide and one molecule of piperazine (disubstitution products) (36). However, both mono- and di-substitution products were isolated after piperazine had been allowed to react with the oxides of 2-methyl-1-butene, 3-butoxy-1-propene, 3-phenyl-1-propene and 3-phenoxy-1-propene (37). These products were described as local anesthetics (38).

1-Benzyl-, 1-p-methoxybenzyl-, 1-m-methylbenzyl- and 1-p-methylbenzylpiperazine were obtained by hydrogenation of the polymerization product prepared from an aldehyde and piperazine (39).

The synthesis of monosubstituted piperazines was also accomplished by formylation of piperazine with methyl formate or formamide, separation of the monoformyl derivative, alkylation with either an aldehyde in the presence of formic acid or an alkyl halide in the presence of sodium carbonate, then removal of the formyl group by the use of dilute hydrochloric acid (40).

Therapeutic Uses of Piperazine and Substituted Piperazines

A large number of reports have appeared in the pharmacological and medical literature which deal with the pharmacology and clinical uses of piperazine and its derivatives. The literature references pertinent to this subject from January, 1953 through August, 1956 are to be found in two tables which appear in this section. The first table deals with the use of piperazine, the second with the uses of substituted piperazines. Although piperazine, in the form of its hexahydrate or as a salt, finds clinical application only as an anthelmintic, piperazine derivatives find a wider application. The latter have been shown to be active as antihistaminics, antifilarial agents, anticonvulsants, antispasmodics, antiemetics, anthelmintics, antimalarials, fungicides, hypnotics and antihypertensive agents.

Pinworm Infections (Enterobiasis, Oxyuriasis).- Man is the only known natural host of Enterobius vermicularis (the human pinworm). However, several species of the family oxyuridae are found in mammals. For example, Oxyuris equi is found in the horse, and Aspiculuris tetraptera in the rat and mouse (41). Since the adult female pinworm, Enterobius vermicularis (8-13 mm. in length), is frequently seen in stools and in the perianal region by the patient, self-diagnosis of this infection is not uncommon. The disease is especially frequent in children from 6-18 years

of age. It is estimated that approximately 16 million persons in the United States and over 200 million people in the world (42) are infected and, unlike many intestinal helminths, pinworm is not limited to any social class since observance of the customary rules of hygiene do not prevent its transmission.

A large number of drugs have been employed in the treatment of enterobiasis with varying degrees of success; the reported efficacy of a number of them is as follows: methylrosaniline chloride (gentian violet) 60-91%; oxytetracycline (Terramycin) 85-90%, piperazine citrate 54-97%, phthalylsulfathiazole (sulfathalidine, Cremothalidine) 44-89%, tetrachlorethylene 47-55%, phenothiazine 60-82%, benzylphenylcarbamate (Diphenan, Butolan) 10-44%, thymyl N-isoamylcarbamate (Egressin) 30-52%, bacitracin 40%, and bacitracin and succinylsulfathiazole (Sulfasuxidine) 82%. Several of these agents are either too toxic, relatively therapeutically ineffective, require unrealistic quantities for successful therapy, or are too expensive; therefore, until recently, methylrosaniline has remained the drug of choice, with oxytetracycline in a secondary position (42).

Piperazine hydrate and certain piperazine salts were used for many years for the treatment of gout in the belief that they removed uric acid from the body in the form of water-soluble salts. The modern use of these compounds is limited to their application as anthelmintics.

According to a statement in the British Medical Journal (43), the first successful use of piperazine hydrate in the treatment of human pinworm was reported in 1951 by three French investigators (44) who concluded that this substance was the drug of choice for the treatment of oxyuriasis in children. The clinical trials were preceded by successful preliminary experiments on the mouse pinworm Aspiculuris or Syphacea.

The following quotation, taken from an article published in 1954 (45), seems to represent the general opinion of piperazine held at the present time: "The percentage of cures with piperazine (85%) obtained in this series compares favorably with the cures obtained with Terramycin and gentian violet. Since the syrup of piperazine used in this study was easy to take, well-tolerated, and can be made available at a reasonable cost, we are of the opinion that of the oxyuricides we have tested to date, piperazine hexahydrate (supplied as Syrup of Antepar*) comes the closest to our standards of an ideal oxyuricide".

Studies have confirmed the activity of piperazine hydrate against mouse pinworm (Aspiculuris tetraptera) (46). A good correlation of activity has been found between the chemotherapeutic agents effective against the human pinworm and those active against the mouse pinworm (47). The data obtained suggest that the mouse pinworm is useful in the study of new compounds which may be of value against Enterobius in man. This is especially important since

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* Actually Syrup of Antepar contains piperazine citrate and not piperazine hexahydrate.

Enterobius has not been transmitted successfully to an experimental host.

Ascaris Infections (Ascariasis).- Ascaris lumbricoides is a common roundworm infection of man and swine, and it is the largest of the human intestinal nematodes. The females vary in length from 20 to 25 centimeters. It is reported (48) that 3 million persons in the United States, especially inhabitants of the mountainous and hilly areas of the South, harbor the large roundworm Ascaris lumbricoides, and it is estimated that over 600 million persons in the world are hosts to this parasite. Hexylresorcinol has been the drug of choice against ascariasis for the past 25 years, and, except for local irritation and superficial burns of the buccal mucosa when the pills are chewed, there are no contraindications to its use. Santonin and oil of chenopodium have been widely employed in the treatment of ascariasis; the former is not very effective in safe doses, and the latter has caused a number of fatalities, even in the accepted dosage.

In 1949 it was reported (49) that adult humans, who had been treated with piperazine hexahydrate for Ascaris infections, were freed from large numbers of ascarides; unfortunately, an exact cure rate was not established. Five years later, it was stated (48) that by the administration of the same daily amount of piperazine citrate employed in the treatment of enterobiasis, the following cure rates were achieved in cases of ascariasis; five days' therapy, 46 of 50 cured (92%); four days' therapy, 13 of 15 cured (93%);

and three days' therapy, 14 of 15 cured (93%)."

It was found (50) that the substituted piperazine 1-diethylcarbamyl-4-methylpiperazine hydrochloride (Hetrazan), is relatively effective against Ascaris, and at the present time there is general agreement that this derivative of piperazine, when given for from 3 to 15 days, is effective against ascariasis. Its activity is somewhat irregular when given for less than 7 days.

Piperazines in the Treatment of Other Helminth Infections.- Infections caused by the following parasites do not respond or respond minimally to piperazine therapy; Necator americanus (hookworm), Trichuris trichiura (whipworm), Strongyloides stercoralis, Hymenolepis nana (dwarf tapeworm), and Giardia lamblia. Adult Trichinella spiralis organisms are removed from mice by piperazine therapy (42).

TABLE I

ACTIVITY OF PIPERAZINE AND ITS SALTS AS ANTHELMINTICS

Salt	Helminth			An.	Reference(s)
	P	R	U		
Citrate	A			H	52,53.54,57,58,61,62,63,82, 85,91,95,42
		A		H	53,54,61,62,81,83,84,85,42
			A	H	55,56
			A	Ch	59
		A		Ch	87
		A		D	86
		A		C	86
			A	Ca	59
			A	D	60,80
			A	C	60
Hydrate	A			H	67,69,70,71,93[a]
		A		H	69,94[b]
			A	H	64,68
	A			M	46,65
		A		Ch	66
		A		T	66
		A		S	66
			I	Sh	90
Tartrate	A			H	72,73,74
		A		H	74
Adipate	A	A		H	75,76,94
		A		H	96

TABLE I (cont'd)

Salt	Helminth			An.	Reference(s)
	P	R	U		
Adipate	A			H	91
			A	Ho	77
		A		Z	88
Hydrochloride	A			M	47,65
Dihydrochloride	A			M	47,65
Gluconate	A	A		H	78
Acetate	A			H	79
Carbon Disulfide Complex		A		S	89
			A	Sh	97,98
Glycolylarsanilate			I	Sh	90
Diphenylacetate			A[c]	H	92
	A			M	47
Dilaurate			A	H	92
Calcium Diacetate	A			H	51
Phosphate	A			H	42
Calcium Dicitrate	A			H	42

a cure rate 97.3%, side effects infrequent and mild.
b ineffective against trichocephalus.
c other salts prepared and tested, but not listed because they were found to possess little or no activity.

SYMBOL CODE

P, pinworms; R, roundworms; U, unspecified or other helminth
An, animal
H, humans; Ch, chickens; C, cats; T, turkeys; S, swine; M, mice; Sh, sheep; D, dogs; Ca, calves; Ho, horses; Z, zebras
A, active; I, inactive

Filarial Infections (Filariasis).- The general term "filariasis" includes several diseases in man and other vertebrates caused by slender, parasitic, nematode worms located in the circulatory and lymphatic systems, or tissues of the hosts. The adult worms range from 20 to 700 mm. in length. Intermediate hosts (mosquitoes or biting flies) are required for the completion of the life cycle.

In man, several species of filaria are known, the most important being Wuchereria bancrofti (Bancroftian filariasis, wuchereriasis), Wuchereria malayi (Malayan filariasis) and Onchocerca volvulus (onchocerciasis). The first two mentioned parasites are widely distributed in Africa, India, China, Japan, the East Indies and the West Indies. The last mentioned parasite is found only in Africa and certain parts of central America. It has been reported (99) that probably 600,000 of the 1 million natives of the Northern Gold Coast have onchocerciasis and 40,000 are blind as a result of the disease.

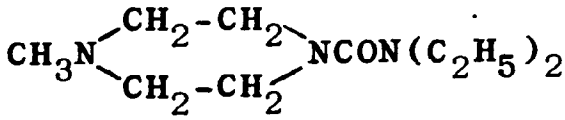
In animals filarial diseases are widespread, even in the United States, particularly in crows and English sparrows (100).

The acute stage of human filariasis is characterized by the symptoms associated with lymphatic obstruction. The chronic stage involving the extremeties, particularly the lower extremeties, the scrotum, the mammary glands and often other sites, is known as elephantiasis. Diagnosis of this disease is often difficult and there is no known effective cure (101).

There are several other less common species of filariae which are human parasites. Among these, Loa loa (eyeworm) bears mentioning because of its unusual migration within the human body. The adult worms migrate through the subcutaneous tissues at a rate of about one inch in two minutes, travelling, eventually, across the bridge of the nose to the conjunctiva of the eye, where they may be removed easily with a pointed instrument. This, in fact, is the accepted treatment of this disease, chemotherapy being unsatisfactory (102).

Though compounds which contain heavy metals, particularly antimony, and certain cyanine dyes have shown antifilarial activity in laboratory animals, their use in the treatment of human filariasis leaves much to be desired. Suramin, (Bayer 205, a complex urea derivative) has been used with some success in the treatment of onchocherciasis (99).

During the last few years, considerable work has been done in various laboratories on the development of a derivative of piperazine which would have good antifilarial activity*. Of all the many compounds of this type which have appeared in the literature during the last few years, the most promising seems to be 1-methyl-4-diethylcarbamylpiperazine



1-Methyl-4-diethylcarbamylpiperazine Hydrochloride, Hetrazan

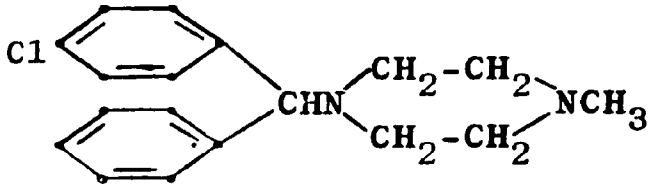
hydrochloride (Hetrazan, diethylcarbamazine) (103). The use of Hetrazan in filariasis is particularly suitable, since it

* see Table II at the end of this section.

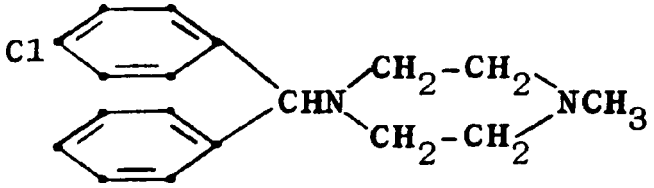
can be administered orally, and in well-tolerated amounts, rapidly inhibiting the production of microfilariae, and causing the death of the parent worm (104).

Piperazine Derivatives as Antihistaminics.- Of all the types of compounds that have been tested for antihistaminic activity, the ethylenediamines have proven to be among the most potent.

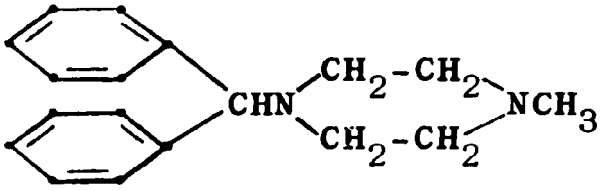
Certain piperazine derivatives, which have been shown to be very effective antihistaminics, can be considered as substituted ethylenediamines. A number of these products, which are mentioned below, appear on the market today.



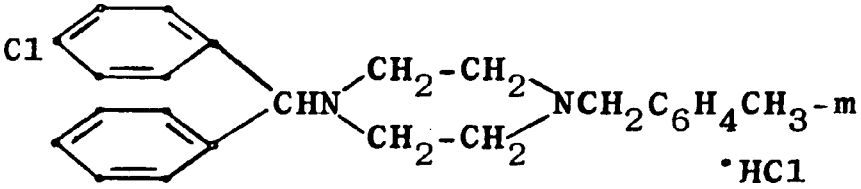
Chlorocyclizine
Perazil (B.W. & Co.)
Ref. (105)



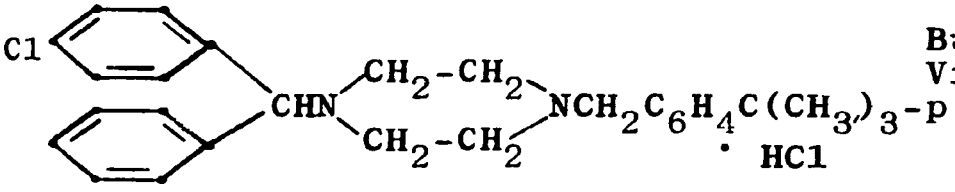
Chlorocyclizine
Diparalene (Abbott)
Ref. (106)



Cyclizinium Chloride
Marezine (B.W. & Co.)
Ref. (107)



Meclozine
Ancolan
Ref. (108)

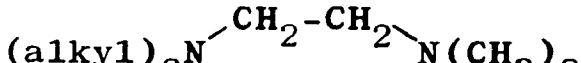


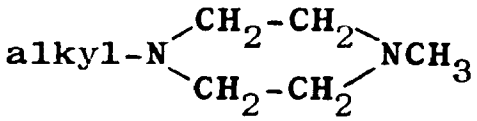
Buclizine Hydrochloride
Vibozine Hydrochloride
Ref. (109)

Piperazine Derivatives as Anticolvulsants.- A considerable number of substituted piperazines were prepared in order that they might be tested for anticonvulsant activity (110). It was reported (110) that several of these compounds had pronounced anticonvulsant activity when tested against audiogenic seizures in rats.

Piperazine Derivatives as Antispasmodics.- During the study of a number of substituted piperazines, it was found that the methiodide of 1-ethyl-4-(3-ethoxybenzhydryl)piperazine exhibited antispasmodic activity which was about one-third of that of atropine (111).

A number of potent antispasmodics and local anesthetics were found during the examination of a series of N,N-di-alkyl-N',N'-dimethylethylenediamines (112). Although these compounds are not piperazines, their relationship to the piperazine type of structure can be seen from the formulas shown below.



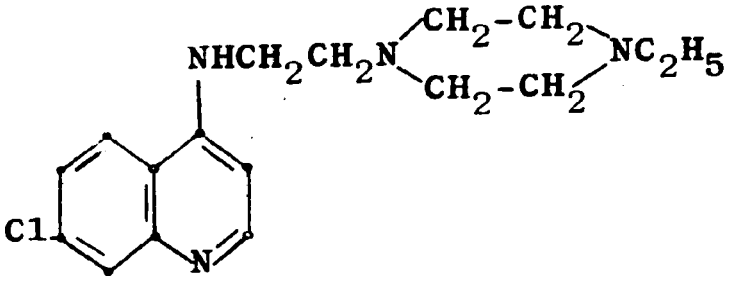


Piperazine Derivatives as Antiemetics.- Although antiemetic activity is considered to be more or less a general pharmacological function of antihistaminics (113), it is a somewhat specialized function and therefore we have chosen to separate it from this class of drugs for consideration in this discussion. It has been found (113) that cyclizine (1-methyl-4-benzhydrylpiperazine) and chlorcyclizine (1-methyl-4-p-chlorobenzhydrylpiperazine) effectively inhibit apomorphine-induced retching in dogs.

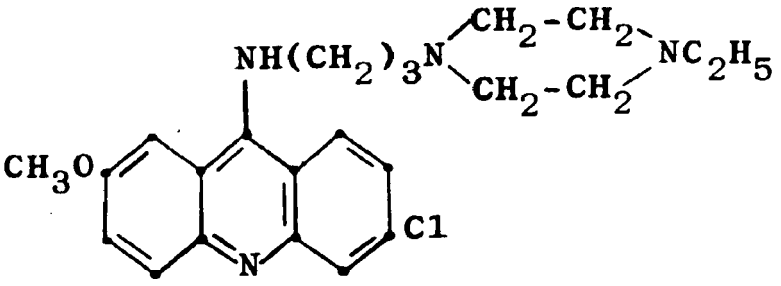
Cyclizine was found to be an effective antiemetic in humans, showing considerable activity in the prevention of seasickness, airsickness, and post-operative nausea and vomiting (114).

Piperazine Derivatives as Antimalarials.- Certain quinolines and acridines which contain a piperazinylalkylamino group have strong antimalarial activity (115). For example, two compounds which have been found to be active as antimalarials are 1-ethyl-4-[beta-(7-chloro-4-quinolylamino)-ethyl]piperazine (I) and 1-ethyl-4-[gamma-(3-chloro-7-methoxy-9-acridylamino)-propyl]piperazine (II).

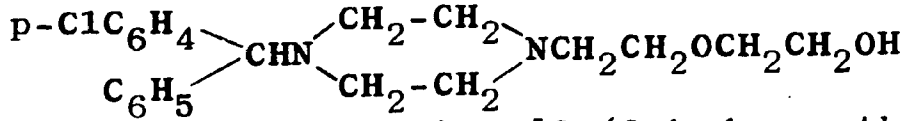
I



II



Miscellaneous Uses of Piperazine Derivatives.- One of the most recent uses of a piperazine derivative is in the treatment of mental conditions. Hydroxyzine hydrochloride (Atarax) is employed for relief of tension in certain cases.

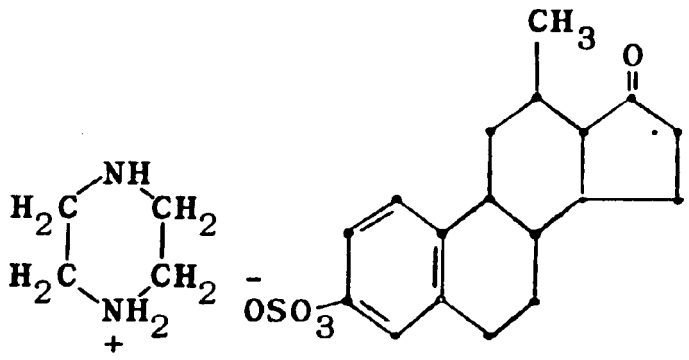


1-(p-Chlorobenzhydryl)-4-[2-(2-hydroxyethoxy)ethyl]-piperazine Dihydrochloride, Atarax

Conclusions based on subjective evaluations rate this drug as comparable in effectiveness to other tranquilizing drugs presently available(116)..

In a series of substituted piperazines, 1-methyl-4-phenylpiperazine was found to be a potent adrenergic blocking agent in animals. A number of other 1,4-disubstituted piperazines were tested for adrenolytic, antihypertensive and antihistaminic properties (117).

It should be noted that several drugs on the market today are piperazine salts but were not included in Table II because the particular activity for which they are used does not reside in the piperazinium portion of the salt, but in the anion portion. In these cases piperazine serves only the purpose of forming a salt suitable for administration of the drug and plays no significant part in its activity. An example of such a drug is Piperazine Estrone Sulfate, marketed as "Sulestrex Piperazine" (118).



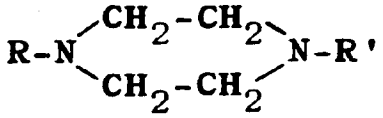
Toxicity of Piperazines.- Many of the reports on the use of piperazine in man mention the absence of side reactions. Hanzlik (119), however, in an extensive article summarized the uses of piperazine, and called attention to

undesirable side reactions such as urticaria, headache, vomiting, diarrhea, tremor, incoordination and muscular weakness. The side reactions were observed most frequently after the administration of large doses in aged or debilitated patients.

The recent extensive use of piperazine citrate in the treatment of enterobiasis has given additional information on its toxicity. When used in the recommended doses, very few side reactions have been observed except for occasional urticaria. In the few cases where other effects were noticed, such as nausea or diarrhea, these effects were mild, and recovery was rapid when therapy was stopped (42).

TABLE II

PHARMACOLOGICAL ACTIVITY OF SUBSTITUTED PIPERAZINES



R	R'	Salt	Act.*	Ref.
1-Naphthylmethyl	H	HCl	A,Sp	120
2-Naphthylmethyl	H	HCl	A,Sp	120
2-Pyridyl	H	2HCl	A,Sp	120
9-Fluorenyl	H	2HCl	A,Sp	120
Benzhydryl	H	2HCl	Sp	147
2-Pyridyl	H		F	121
2-Pyrimidyl	H		F	121
2-Pyrazinyl	H		F	121
2-Thiazolyl	H		F	121
1-(4-Me-10-thiazanthenone)	H		S	122
p-Tolyl	H		Un	123
o-Tolyl	H		Un	123
p-Cl-phenyl	H		Un	123
m-Cl-phenyl	H		Un	123
o-Cl-phenyl	H		Un	123

*Symbols used to designate the pharmacological activity (Act.) for which these compounds were tested are designated as follows: A = antihistaminic, Ac = anticonvulsant, Ad = adrenolytic, Ah = antihypertensive, An = anthelmintic, F = antifilarial, Fu = fungicidal, H = hypnotic, Se = sedative, Sp = antispasmodic, S = antischistosomiasis, Tb = antituberculosis, Un = unspecified activity.

R	R'	Salt	Act.	Ref.
$n\text{-}C_8H_{17}$	H	2HCl	Fu	35
$n\text{-}C_9H_{19}$	H	2HCl	Fu	35
$n\text{-}C_{10}H_{21}$	H	2HCl	Fu	35
$n\text{-}C_{11}H_{23}$	H	2HCl	Fu	35
$n\text{-}C_{16}H_{33}$	H	HCl, 2HCl	Fu	35
$p\text{-}BrC_6H_4CH_2$	H	HCl	H	124
$3,4\text{-}Cl_2C_6H_3CH_2$	H	HCl	H	124
Benzhydryl	H	HCl	H	124
1-Naphthylmethyl	H	HCl	H	124
Ph_2CHCO	H	CH_3Cl	Ad	125
Ph_2CHCH_2CO	H	$PhCH_2Cl$, MeCl, HCl	Ad	125
$(CH_2)_5CPhCO$	H	MeCl	Ad	125
$HOCH_2CH(OH)CH_2$	H	2HCl	An	126
$HOOCCH(CH_3)$	H		An	126
$EtOOCCH(CH_3)$	H	HCl	An	126
$Me_2NCH_2CH_2OOC$	H		Un	127
$Et_2NCH_2CH_2OOC$	H		Un	127
1,4-Benzodioxan-2-yl-methyl	H	HCl	Ad	128
C_6H_5	H		Ad	128,117
5-Ph-as-triazine-3-yl	H	HCl	A	129
5-p-MeO-phenyl-as-triazine-3-yl	H	HCl	A	129
CH_3	H	HCl	An	42,47
Et	H	HCl	An	42,47
$n\text{-}C_{12}H_{25}$	H	2HCl	An	42,47
$HOCH_2CH_2$	H	HCl	An	42,47
$HOCH_2CH(CH_3)$	H	HCl	An	42,47
EtOOC	H	HCl	An	42,47

R	R'	Salt	Act.	Ref.
CH_3	$CSNMe_2$	HCl	S	130
CH_3	$CSNEt_2$	HCl	S	130
CH_3	$CSN(i\text{-}Pr)_2$	HCl	S	130
CH_3	$CSN(n\text{-}Pr)_2$	HCl	S	130
CH_3	Benzhydryl	2HCl	A	131
CH_3	o-Cl-benzhydryl	2HCl	A	131
CH_3	m-Cl-benzhydryl	2HCl	A	131
CH_3	p-Cl-benzhydryl	2HCl	A	131
CH_3	o-Br-benzhydryl	2HCl	A	131
CH_3	p-Br-benzhydryl	2HCl	A	131
CH_3	3,4-Cl_2-benzhydryl	2HCl	A	131
CH_3	4,4'-Cl_2-benzhydryl	2HCl	A	131
CH_3	4-Cl-4'-Me-benzhydryl	2HCl	A	131
CH_3	$CONEt_2$	HCl, maleate,fumarate	F	132
CH_3	$CONMe_2$	HCl	F	132
CH_3	$CON(i\text{-}Pr)_2$	HCl	F	132
CH_3	CONHEt	HCl	F	132
CH_3	$CH_2CH_2Ph_2$	2HCl	A,Sp	120
1-Naphthylmethyl	1-Naphthylmethyl		A,Sp	120
CH_3	1-Naphthylmethyl	2HCl	A,Sp	120
2-Naphthylmethyl	2-Naphthylmethyl		A,Sp	120
CH_3	2-Naphthylmethyl	2HCl	A,Sp	120
$HOCH_2CH_2$	1-Naphthylmethyl	2HCl	A,Sp	120
$HOCH_2CH_2$	2-Naphthylmethyl	2HCl	A,Sp	120
$HOCH_2CH_2$	9-Fluorenyl	2HCl	A,Sp	120
CH_3	9-Fluorenyl	2HBr	A,Sp	120

R	R'	Salt	Act.	Ref.
CH_3	9-Phenanthryl-methyl	2HCl	A,Sp	120
CH_3	3,3-Diphenylallyl	HCl	A,Sp	120
EtOOC	9-Fluorenyl	HCl	A,Sp	120
CH_3	C_6H_5	MeI	A,Sp	120
CH_3	2-Pyridyl	2HCl	A,Sp	120
C_6H_5	2-Cyanoethyl		Un	133
C_6H_5	2-Carboxyethyl		Un	133
o-Tolyl	2-Cyanoethyl		Un	133
o-Tolyl	2-Carboxyethyl	HCl	Un	133
m-Tolyl	2-Cyanoethyl		Un	133
m-Tolyl	2-Carboxyethyl		Un	133
p-Tolyl	2-Cyanoethyl		Un	133
p-Tolyl	2-Carboxyethyl	HCl	Un	133
m-Cl-phenyl	2-Cyanoethyl		Un	133
m-Cl-phenyl	2-Carboxyethyl		Un	133
o-Tolyl	2-Carbamoylethyl		Un	133
C_6H_5	2-Carbamoylethyl		Un	133
p-Tolyl	2-Carbamoylethyl		Un	133
m-Cl-phenyl	2-Carbamoylethyl		Un	133
p-Tolyl	2-Carbethoxyethyl	2HCl	Un	133
C_6H_5	2-Carbethoxyethyl	2HCl	Un	133
o-Tolyl	2-Carbethoxyethyl	HCl	Un	133
m-Tolyl	2-Carbethoxyethyl	2HCl	Un	133
C_6H_5	2-Carbobutoxyethyl	HCl	Un	133
o-Tolyl	2-Carbobutoxyethyl	HCl	Un	133
m-Tolyl	2-Carbobutoxyethyl	HCl	Un	133

R	R'	Salt	Act.	Ref.
C_6H_5	3-Aminopropyl		Un	133
C_6H_5	3-(Phenylcarbamido)propyl		Un	133
EtOOC	$CONEt_2$		F	121
EtOOC	CSNHEt		F	121
H_2NCO	$CONEt_2$		F	121
Et_2NCO	CSNHEt		F	121
Et_2NCO	$CSNHCH_2CH=CH_2$		F	121
Et_2NCO	$C(NH)NH_2$		F	121
EtOOC	2-Pyridyl		F	121
EtOOC	2-Pyrimidyl		F	121
EtOOC	2-Cl-4-pyrimidyl		F	121
EtOOC	5-Cl-2-pyrimidyl		F	121
EtOOC	2-Pyrazinyl		F	121
EtOOC	2-Thiazolyl		F	121
$H_2NC(NH)$	2-Pyridyl		F	121
H_2NCO	2-Pyridyl		F	121
H_2NCS	2-Pyridyl		F	121
$H_2NC(NH)$	2-Pyrimidyl		F	121
H_2NCO	2-Pyrimidyl		F	121
H_2NCS	2-Pyrimidyl		F	121
$H_2NC(NH)$	2-Pyrazinyl		F	121
H_2NCO	2-Pyrazinyl		F	121
H_2NCS	2-Pyrazinyl		F	121
$H_2NC(NH)$	2-Thiazolyl		F	121
H_2NCO	2-Thiazolyl		F	121
CH_3	1-(4-Me-10-thiazanthenone)		S	122

R	R'	Salt	Act.	Ref.
CH_3CO	p-Tolyl		Un	123
CH_3CO	m-Tolyl		Un	123
CH_3CO	o-Tolyl		Un	123
CH_3CO	p-Cl-phenyl		Un	123
CH_3CO	m-Cl-phenyl		Un	123
CH_3CO	o-Cl-phenyl		Un	123
C_6H_5CO	p-Tolyl	HCl	Un	123
C_6H_5CO	m-Tolyl	HCl	Un	123
C_6H_5CO	o-Tolyl		Un	123
C_6H_5CO	p-Cl-phenyl		Un	123
C_6H_5CO	m-Cl-phenyl	HCl	Un	123
C_6H_5CO	o-Cl-phenyl		Un	123
p-Tolyl	CH_2CH_2OH		Un	123
m-Tolyl	CH_2CH_2OH		Un	123
p-Cl-phenyl	CH_2CH_2OH		Un	123
m-Cl-phenyl	CH_2CH_2OH		Un	123
o-Cl-phenyl	CH_2CH_2OH		Un	123
p-Tolyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
m-Tolyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
o-Tolyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
p-Cl-phenyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
m-Cl-phenyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
o-Cl-phenyl	$CH_2CH(OH)CH_2OCH_3$		Un	123
CH_3	CO(10-phenothiazine)	HCl	An	134
CH_3	di-Et-aminoacetyl	2HCl	An	134
CH_3	4-Me-1-piperazinyl-acetyl	3HCl	An	134

R	R'	Salt	Act.	Ref.
CH_3	Ethoxalyl	HCl	An	134
CH_3	Carbethoxyacetyl	Citrate	An	134
CH_3	N,N-di-Et-oxamoyl	HCl	An	134
2-Pyridyl	Thiocarbamoyl		Ac	135
2-Pyrazinyl	Thiocarbamoyl		Ac	135
2-Pyrimidyl	Thiocarbamoyl		Ac	135
2-Pyridyl	Ethylthiocarbamoyl		Ac	135
2-Pyrazinyl	Ethylthiocarbamoyl		Ac	135
2-Thiazolyl	Ethylthiocarbamoyl		Ac	135
2-Pyridyl	Allylthiocarbamoyl		Ac	135
2-Pyrimidyl	Allylthiocarbamoyl		Ac	135
2-Pyridyl	Phenylthiocarbamoyl		Ac	135
2-Pyrimidyl	Phenylthiocarbamoyl		Ac	135
2-Thiazolyl	Phenylthiocarbamoyl		Ac	135
2-Pyrazinyl	Allylthiocarbamoyl		Ac	135
p-Cl-phenyl	NH_2	Benzoate	Ac	136
2-Pyridyl	NH_2	Benzoate	Ac	136
2-Pyrimidyl	NH_2	HCl	Ac	136
2-Thiazolyl	NH_2	2HCl	Ac	136
CH_3	NH_2	2HCl	Ac	136
$C_6H_5CH_2$	NH_2	Benzoate	Ac	136
Et_2NCO	NH_2		Ac	136
EtOOC	NHCOOEt		Ac	137
EtOOC	$NHCOCH_3$		Ac	137
EtOOC	$NHCONHC_6H_5$		Ac	137
Et_2NCO	$NHCOC_6H_5$		Ac	137

R	R'	Salt	Act.	Ref.
EtOOC	$NHCOCH_2C_6H_5$		Ac	137
EtOOC	$NHCONHC_6H_{11}$		Ac	137
EtOOC	$NHCSNHC_6H_5$		Ac	137
EtOOC	$NHCSNHCH_2CH=CH_2$		Ac	137
Et_2NCO	$NHCOCH_3$		Ac	137
Et_2NCO	$NHCONHC_6H_5$		Ac	137
Et_2NCO	$NHCONHC_6H_{11}$		Ac	137
Et_2NCO	NHCONHEt		Ac	137
Et_2NCO	NH(p-Cl-benzene-sulfonyl		Ac	137
CH_3	NHCOOEt		Ac	137
CH_3	$NHCONHC_6H_{11}$		Ac	137
CH_3	NHCONHEt		Ac	137
$C_6H_5CH_2$	NHCOOEt		Ac	137
$C_6H_5CH_2$	$NHCOCH_3$		Ac	137
$C_6H_5CH_2$	$NHCOCH_2C_6H_5$		Ac	137
$C_6H_5CH_2$	$NHCOC_6H_5$		Ac	137
$C_6H_5CH_2$	$NHCONHC_6H_5$		Ac	137
$C_6H_5CH_2$	$NHCSNHC_6H_5$		Ac	137
p-Cl-phenyl	NHCOOEt		Ac	137
p-Cl-phenyl	$NHCOCH_3$		Ac	137
p-Cl-phenyl	$NHCONHC_6H_5$		Ac	137
p-Cl-phenyl	$NHCONHC_6H_4$-Cl-o		Ac	137
p-Cl-phenyl	$NHCONEt_2$		Ac	137
p-Cl-phenyl	$NHCSNHCH_2CH=CH_2$		Ac	137
2-Pyridyl	NHCOOEt		Ac	137
2-Pyridyl	$NHCOCH_3$		Ac	137

R	R'	Salt	Act.	Ref.
2-Pyridyl	$NHCONHC_6H_5$		Ac	137
2-Pyridyl	$NHCSNHCH_2CH=CH_2$		Ac	137
2-Pyridyl	NH(p-Cl-benzene-sulfonyl		Ac	137
2-Pyrimidyl	NHCOOEt		Ac	137
2-Pyrimidyl	$NHCOCH_3$		Ac	137
2-Pyrimidyl	$NHCONHC_6H_{11}$		Ac	137
2-Pyrimidyl	NHCSNHEt		Ac	137
2-Pyridyl	Phthalimidoacetyl		Un	138
2-Thiazolyl	Phthalimidoacetyl		Un	138
2-Pyrimidyl	Phthalimidoacetyl		Un	138
2-Pyridyl	beta-Phthalimido-propionyl		Un	138
2-Pyridyl	Succimidoacetyl		Un	138
2-Pyridyl	4-Cyclohexene-1,2-dicarboximidoacetyl		Un	138
CH_3	di-Me-sulfonyl	Maleate	An	139
CH_3	di-Et-sulfonyl	Maleate	An	139
CH_3	di-Pr-sulfonyl	Maleate	An	139
Benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-MeO-p	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-Br-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
2,5-Cl_2-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-Me-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-MeO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Me-p	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-Me-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-MeO-p	2HCl	Un	140

R	R'	Salt	Act.	Ref.
p-Me-benzhydryl	$CH_2C_6H_4$-MeO-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Me-m	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Cl-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Et-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-EtO-p	2HCl	Un	140
o-MeO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
m-Cl-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Me-o	2HCl,fumarate	Un	140
Benzhydryl	$CH_2C_6H_4$-EtO-m	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Cl-m	2HCl	Un	140
Benzhydryl	$CH_2C_6H_3$-Me_2-3,5	2HCl	Un	140
o-Br-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-Me-m	2HCl	Un	140
o-Me-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
m-EtO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p-Me-p'-MeO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
p,p'-di-MeO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
o,o'-di-MeO-benzhydryl	$CH_2C_6H_5$	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Pr-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-Bu-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-CMe_3-p	2HCl	Un	140
Benzhydryl	$CH_2C_6H_4$-CMe_3-m	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_3$-Me_2-3,5	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-Bu-p	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-CMe_3-p	2HCl	Un	140
p-Cl-benzhydryl	$CH_2C_6H_4$-CMe_3-m	2HCl	Un	140

R	R'	Salt	Act.	Ref.
CH_3	$CONEt_2$	Fumarate (monoxide)	An	141
CH_3	$CON(Et)CH_3$	Fumarate (monoxide)	An	141
CH_3	CH_2CONEt_2	Fumarate (monoxide)	An	141
CH_3	COOEt	Fumarate (monoxide)	An	141
CH_3	CONHEt	Maleate (monoxide)	An	141
CH_3	$CONMe_2$	Maleate (monoxide)	An	141
CH_3	$CH_2CH_2CONEt_2$	Maleate (monoxide)	An	141
2-Pyridyl	CSNHEt		Ac	110
2-Pyridyl	$CSNHCH_2CH=CH_2$		Ac	110
2-Pyridyl	$CONEt_2$		Ac	110
2-Pyridyl	$CONHC_6H_{13}$		Ac	110
2-Pyridyl	$CONHC_6H_{11}$		Ac	110
2-Pyridyl	$CON(Et)C_6H_5$		Ac	110
2-Pyrimidyl	CSNHEt		Ac	110
2-Pyrimidyl	$CSNHCH_2CH=CH_2$		Ac	110
2-Pyrimidyl	$CONEt_2$		Ac	110
2-Pyrimidyl	$CONHC_6H_{13}$		Ac	110
2-Pyrimidyl	$CONHC_6H_{11}$		Ac	110
2-Pyrimidyl	$CON(Et)C_6H_5$		Ac	110
5-Cl-2-pyrimidyl	$CONEt_2$		Ac	110
2-Pyraziny1	CSNHEt		Ac	110
2-Pyraziny1	$CSNHCH_2CH=CH_2$		Ac	110
2-Pyraziny1	$CONEt_2$		Ac	110
2-Pyraziny1	$CONHC_6H_{13}$		Ac	110
2-Pyraziny1	$CONHC_6H_{11}$		Ac	110
2-Thiazolyl	CSNHEt		Ac	110

R	R'	Salt	Act.	Ref.
2-Thiazolyl	$CSNHCH_2CH=CH_2$		Ac	110
2-Thiazolyl	$CONEt_2$		Ac	110
2-Thiazolyl	$CONHC_6H_{13}$		Ac	110
2-Thiazolyl	$CON(Et)C_6H_5$		Ac	110
2-Pyridyl	$CSNHC_6H_5$		Ac	142
2-Pyridyl	$CONHC_6H_5$		Ac	142
2-Pyridyl	CONH(alpha-Naphthyl)		Ac	142
2-Pyridyl	CONH(beta-Naphthyl)		Ac	142
2-Pyridyl	$CONHC_6H_4$-Cl-o		Ac	142
2-Pyridyl	$CONHC_6H_4$-EtO-o		Ac	142
2-Pyridyl	CONH(2-Biphenylyl)		Ac	142
2-Pyridyl	$CONHC_6H_4-NO_2$-o		Ac	142
2-Pyridyl	$CONHC_6H_4$-Cl-m		Ac	142
2-Pyridyl	$CONHC_6H_4NO_2$-m		Ac	142
2-Pyridyl	$CONHC_6H_4$-Br-p		Ac	142
2-Pyridyl	$CONHC_6H_4$-Me-p		Ac	142
2-Pyridyl	$CONHC_6H_4$-EtO-p		Ac	142
2-Pyridyl	$CONHC_6H_3-Cl_2$-2,5		Ac	142
2-Pyrimidyl	$CSNHC_6H_5$		Ac	142
2-Pyrimidyl	$CONHC_6H_5$		Ac	142
2-Pyrimidyl	CONH(alpha-Naphthyl)		Ac	142
2-Pyrimidyl	CONH(beta-Naphthyl)		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-Cl-o		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-EtO-o		Ac	142
2-Pyrimidyl	CONH(2-Biphenylyl)		Ac	142
2-Pyrimidyl	$CONHC_6H_4-NO_2$-o		Ac	142

R	R'	Salt	Act.	Ref.
2-Pyrimidyl	$CONHC_6H_4$-Cl-m		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-NO_2-m		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-Br-p		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-EtO-p		Ac	142
2-Pyrimidyl	$CONHC_6H_4$-Me-p		Ac	142
2-Pyrimidyl	$CONHC_6H_3$-Cl_2-2,5		Ac	142
2-Pyrazinyl	$CSNHC_6H_5$		Ac	142
2-Pyrazinyl	$CONHC_6H_5$		Ac	142
2-Thiazolyl	$CSNHC_6H_5$		Ac	142
2-Thiazolyl	$CONHC_6H_5$*		Ac	142
2-Thiazolyl	CONH(alpha-Naphthyl)		Ac	142
2-Thiazolyl	CONH(beta-Naphthyl)		Ac	142
2-Thiazolyl	$CONHC_6H_4$-Cl-o		Ac	142
2-Thiazolyl	$CONHC_6H_4$-EtO-o		Ac	142
2-Thiazolyl	CONH(2-Biphenylyl)		Ac	142
2-Thiazolyl	$CONHC_6H_4$-NO_2-o		Ac	142
2-Thiazolyl	$CONHC_6H_4$-Cl-m		Ac	142
2-Thiazolyl	$CONHC_6H_4$-NO_2-m		Ac	142
2-Thiazolyl	$CONHC_6H_4$-Br-p		Ac	142
2-Thiazolyl	$CONHC_6H_4$-EtO-p		Ac	142
2-Thiazolyl	$CONHC_6H_4$-Me-p		Ac	142
2-Thiazolyl	$CONHC_6H_3$-Cl_2-2,5		Ac	142
CH_3	$CH_2CH_2OOCCH(C_5H_{11})_2$	2HCl,MeI	Sp	143
CH_3	$CH_2CH_2OOCCH(C_6H_{13})_2$	2HCl,MeI	Sp	143
CH_3	$CH_2CH_2OOC(Ph)(CH_2)_5$	2HCl,MeI, BuI	Sp	143

*showed outstanding anticonvulsant activity

R	R'	Salt	Act.	Ref.
Et	$CH_2CH_2OOCC(Ph)(CH_2)_5$	2HCl	Sp	143
CH_3	$CH_2CH_2OOCCH(Ph)C_6H_{11}$	2HCl	Sp	143
Et	$CH_2CH_2OOCCH(Ph)C_6H_{11}$	2HCl	Sp	143
CH_3	$CH_2CH_2OOCCH(C_6H_{11})_2$	2HCl,MeI	Sp	143
CH_3	$CH_2CH_2OOCCHPh_2$	2HCl	Sp	143
$C_6H_5CH_2$	$CH_2CH_2OOCCHPh_2$	2HCl,MeI	Sp	143
CH_3	$CH_2CH_2OOCC(OH)Ph_2$	2HCl	Sp	143
p-MeO-$C_6H_4CH_2$	$CH_2CH_2OOCC(OH)Ph_2$	2HCl	Sp	143
CH_3	$CH_2CH_2OOCCH_2CHPh_2$	2HCl,MeI EtI	Sp	143
Et	CH_2CH_2OOC	2HCl	Sp	143
CH_3	CH_2CH_2OOC	2HCl,MeI	Sp	143
C_8H_{17}	COOEt	2HCl	Fu	35
C_9H_{19}	$C(NH)NH_2$	2HBr	Fu	35
$C_{10}H_{21}$	COOEt	HCl	Fu	35
$C_{11}H_{25}$	COOEt	HCl	Fu	35
$C_{16}H_{33}$	$C(NH)NH_2$	2HBr	Fu	35
$C_6H_5CH_2$	CONHEt	HCl	H	124
CH_3	$CSNHC_6H_5$		H	124
CH_3	$CSNHC_6H_5$	HCl	H	124
C_8H_{17}	$CONH_2$	HCl	H	124
$C_{11}H_{23}$	$CONH_2$	HCl	H	124
Benzhydryl	Et	MeI,EtI	Sp	111
Benzhydryl	i-Pr	MeI,EtI	Sp	111
Benzhydryl	n-Bu	MeI	Sp	111
Benzhydryl	n-Pr	EtI	Sp	111
Fluroenyl	CH_3	MeI	Sp	111

R	R'	Salt	Act.	Ref.
o-Cl-benzhydryl	CH_3	MeI	Sp	111
o-Cl-benzhydryl	Et	MeI,EtI	Sp	111
o-Cl-benzhydryl	i-Pr	MeI	Sp	111
m-Cl-benzhydryl	Et	MeI,EtI	Sp	111
p-Cl-benzhydryl	CH_3	MeI	Sp	111
p-Cl-benzhydryl	Et	MeI	Sp	111
p-Cl-benzhydryl	i-Pr	MeI	Sp	111
p-Cl-benzhydryl	n-Bu	MeI	Sp	111
p,p'-Cl_2-benzhydryl	Et	MeI	Sp	111
p,p'-Cl_2-benzhydryl	i-Pr	MeI	Sp	111
o-Br-benzhydryl	Et	MeI	Sp	111
o-Br-benzhydryl	i-Pr	MeI	Sp	111
p-NO_2-benzhydryl	Et	MeI	Sp	111
o-Me-benzhydryl	CH_3	MeI	Sp	111
o-Me-benzhydryl	Et	MeI,EtI	Sp	111
o-Me-benzhydryl	i-Pr	MeI	Sp	111
m-Me-benzhydryl	CH_3	MeI	Sp	111
m-Me-benzhydryl	Et	MeI,EtI	Sp	111
m-Me-benzhydryl	i-Pr	MeI	Sp	111
o-MeO-benzhydryl	Et	MeI	Sp	111
m-EtO-benzhydryl	Et*	MeI	Sp	111
alpha-$C_{10}H_7$CHPh	CH_3	MeI	Sp	111
beta-$C_{10}H_7$CHPh	Et	MeI	Sp	111
alpha-$C_{10}H_7$CHPh	Et	MeI	Sp	111

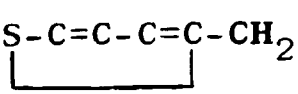
*about one-third as active as atropine

R	R'	Salt	Act.	Ref.
alpha-$C_{10}H_7CHPh$	i-Pr	MeI	Sp	111
EtOOC	COCHBrEt		Ac	144
EtOOC	COCHBr-n-Pr		Ac	144
EtOOC	COCHBr-n-Bu		Ac	144
EtOOC	COCHBr-i-Pr		Ac	144
EtOOC	$COCBrEt_2$		Ac	144
C_6H_5	Thiobutanoyl		Un	145
C_6H_5	Thioisobutanoyl		Un	145
C_6H_5	Thiopentanoyl		Un	145
C_6H_5	Thiohexanoyl		Un	145
C_6H_5	2-Et-thiobutanoyl		Un	145
C_6H_5	4-Me-thiopentanoyl		Un	145
C_6H_5	Thioheptanoyl		Un	145
C_6H_5	Thiooctanoyl		Un	145
C_6H_5	Thiononanoyl		Un	145
C_6H_5	Thiodecanoyl		Un	145
C_6H_5	Thiobenzoyl		Un	145
C_6H_5	Thio-2-thenoyl		Un	145
C_6H_5	Phenylthioacetyl		Un	145
C_6H_5	Thio-p-anisoyl		Un	145
C_6H_5	Thiopiperonyloyl		Un	145
C_6H_5	Thioveratroyl		Un	145
C_6H_5	1-Naphthylthio-acetyl		Un	145
o-Tolyl	Thiobutanoyl		Un	145
o-Tolyl	Thiobenzoyl		Un	145
o-Tolyl	Thio-2-thenoyl		Un	145

R	R'	Salt	Act.	Ref.
o-Tolyl	Phenylthioacetyl		Un	145
o-Tolyl	Thio-p-anisoyl		Un	145
o-Tolyl	Thiopiperonyloyl		Un	145
o-Tolyl	2-Naphthylthioacetyl		Un	145
m-Tolyl	Thiobenzoyl		Un	145
m-Tolyl	Phenylthioacetyl		Un	145
m-Tolyl	Thioveratroyl		Un	145
m-Tolyl	1-Naphthylthioacetyl		Un	145
p-Tolyl	Thiobenzoyl		Un	145
p-Tolyl	Thio-2-thenoyl		Un	145
p-Tolyl	Phenylthioacetyl		Un	145
p-Tolyl	Thioveratroyl		Un	145
p-Tolyl	Thiopiperonyloyl		Un	145
o-Cl-phenyl	Thiobenzoyl		Un	145
o-Cl-phenyl	Thio-2-thenoyl		Un	145
o-Cl-phenyl	Phenylthioacetyl		Un	145
o-Cl-phenyl	Thiopiperonyloyl		Un	145
o-Cl-phenyl	1-Naphthylthioacetyl		Un	145
m-Cl-phenyl	Thiobenzoyl		Un	145
m-Cl-phenyl	Thio-2-thenoyl		Un	145
m-Cl-phenyl	Thiopiperonyloyl		Un	145
m-Cl-phenyl	Thioveratroyl		Un	145
m-Cl-phenyl	1-Naphthylthioacetyl		Un	145
p-Cl-phenyl	Thiobenzoyl		Un	145
p-Cl-phenyl	Thio-2-thenoyl		Un	145
p-Cl-phenyl	Thiopiperonyloyl		Un	145

R	R'	Salt	Act.	Ref.
p-Cl-phenyl	1-Naphthylthioacetyl		Un	145
C_6H_5	CH_2CN		Un	146
C_6H_5	$CH(CH_3)CN$		Un	146
C_6H_5	$C(CH_3)_2CN$		Un	146
o-Tolyl	$CH(CH_3)CN$		Un	146
o-Tolyl	$C(CH_3)_2CN$		Un	146
m-Tolyl	$CH(CH_3)CN$		Un	146
m-Tolyl	$C(CH_3)_2CN$		Un	146
p-Tolyl	$CH(CH_3)CN$		Un	146
p-Tolyl	$C(CH_3)_2CN$		Un	146
o-Cl-phenyl	CH_2CN		Un	146
o-Cl-phenyl	$CH(CH_3)CN$		Un	146
o-Cl-phenyl	$C(CH_3)_2CN$		Un	146
m-Cl-phenyl	$CH(CH_3)CN$		Un	146
m-Cl-phenyl	$C(CH_3)_2CN$		Un	146
p-Cl-phenyl	$CH(CH_3)CN$		Un	146
p-Cl-phenyl	$C(CH_3)_2CN$		Un	146
C_6H_5	CH_2CONH_2		Un	146
C_6H_5	$CH(CH_3)CONH_2$		Un	146
C_6H_5	$C(CH_3)_2CONH_2$		Un	146
o-Tolyl	$CH(CH_3)CONH_2$		Un	146
o-Tolyl	$C(CH_3)_2CONH_2$		Un	146
m-Tolyl	$CH(CH_3)CONH_2$		Un	146
m-Tolyl	$C(CH_3)_2CONH_2$		Un	146
p-Tolyl	$CH(CH_3)CONH_2$		Un	146
p-Tolyl	$C(CH_3)_2CONH_2$		Un	146

R	R'	Salt	Act.	Ref.
o-Cl-phenyl	CH_2CONH_2		Un	146
o-Cl-phenyl	$CH(CH_3)CONH_2$		Un	146
o-Cl-phenyl	$C(CH_3)_2CONH_2$		Un	146
m-Cl-phenyl	$CH(CH_3)CONH_2$		Un	146
m-Cl-phenyl	$C(CH_3)_2CONH_2$		Un	146
p-Cl-phenyl	$CH(CH_3)CONH_2$		Un	146
p-Cl-phenyl	$C(CH_3)_2CONH_2$		Un	146
C_6H_5	$CH(CH_3)COOH$	2HCl	Un	146
p-Tolyl	$CH(CH_3)COOH$	2HCl	Un	146
o-Cl-phenyl	CH_2COOH	HCl	Un	146
o-Cl-phenyl	$CH(CH_3)COOH$	HCl	Un	146
o-Cl-phenyl	$C(CH_3)_2COOH$	HCl	Un	146
m-Cl-phenyl	$CH(CH_3)COOH$		Un	146
p-Cl-phenyl	$CH(CH_3)COOH$	2HCl	Un	146
p-Cl-phenyl	$C(CH_3)_2COOH$		Un	146
Ph_2CHO	CH_3	MeI	Ad	125
Ph_2CHO	Et	MeI	Ad	125
Ph_2CHCH_2CO	CH_3	MeI	Ad	125
Ph_2CHCH_2CO	Et	MeI,EtI	Ad	125
Ph_2CHCH_2CO	i-Pr	MeI	Ad	125
Ph_2CHCH_2CO	n-Bu	MeI	Ad	125
$(CH_3)_2CPhCO$	CH_3	MeI	Ad	125
$(CH_3)_2CPhCO$	Et	MeI	Ad	125
$(CH_3)_2CPhCO$	i-Pr	MeI	Ad	125
(9-Xantheny1)CO	Et	MeI,EtI	Ad	125
(9-Xantheny1)CO	i-Pr	MeI	Ad	125

R	R'	Salt	Act.	Ref.
CH_3	NO	HCl	An	126
CH_3	$CONH_2$		An	126
CH_3	COC_6H_5	MeI	An	126
$n\text{-}C_8H_{17}$	$COC_6H_4\text{-}NO_2\text{-}p$	HCl	An	126
$n\text{-}C_8H_{17}$	$COC_6H_4\text{-}NH_2\text{-}p$	HCl	An	126
$n\text{-}C_9H_{19}$	COOEt	HCl	An	126
$HC\equiv CCH$	COOEt	HCl	An	126
$C_6H_5CH_2$	$CH_2CH(OH)CH_2OH$	2HCl	An	126
$C_6H_5CH_2$	$CH(CH_3)COOEt$	2HCl	An	126
$EtOOCCH(CH_3)$	COOEt	HCl	An	126
	COOEt	HCl	An	126
2-Pyridyl	$CONHC_6H_{11}$		Un	147
2-Thiazolyl	$CONHC_6H_{13}$		Un	147
2-Pyrazinyl	$CONHC_6H_5$		Un	147
2-Pyrimidyl	$CONHC_6H_4\text{-}Cl\text{-}o$		Un	147
2-Pyrimidyl	$CONHC_6H_4\text{-}Br\text{-}o$		Un	147
2-Pyrimidyl	CONH(p-Tolyl)		Un	147
2-Pyrimidyl	CONH(1-Naphthyl)		Un	147
2-Pyrimidyl	$CONHC_6H_{11}$		Un	147
2-Pyrimidyl	$CONHC_6H_4\text{-}Cl\text{-}m$		Un	147
2-Pyrimidyl	CONH(Allylthio)		Un	147
2-Pyridyl	CONH(2-Naphthyl)		Un	147
2-Pyridyl	$CONHC_6H_4\text{-}Et\text{-}p$		Un	147
2-Pyridyl	$CONHC_6H_4\text{-}Cl\text{-}m$		Un	147
2-Pyridyl	$CONHC_6H_4\text{-}Cl\text{-}o$		Un	147
2-Pyridyl	CONH(Allylthio)		Un	147

R	R'	Salt	Act.	Ref.
2-Pyridyl	CONHPhS		Un	147
2-Thiazolyl	$CONHC_6H_{11}$		Un	147
2-Thiazolyl	$CONHC_6H_5$		Un	147
2-Thiazolyl	$CONHC_6H_4$-Cl-o		Un	147
2-Thiazolyl	$CONHC_6H_4$-Cl-m		Un	147
2-Thiazolyl	$CONHC_6H_4$-Br-p		Un	147
2-Thiazolyl	$CONHC_6H_4$-Et-p		Un	147
2-Thiazolyl	CONH(p-Tolyl)		Un	147
2-Thiazolyl	CONH(1-Naphthyl)		Un	147
2-Thiazolyl	CONH(2-Naphthyl)		Un	147
2-Thiazolyl	CONHPhS		Un	147
2-Pyraziny1	$CONHC_6H_5$		Un	147
2-Pyraziny1	CONHEtS		Un	147
2-Pyraziny1	CONH(Allylthio)		Un	147
$C_6H_5CH_2OOC$	$CONH_2$		Ac	148
$C_6H_5CH_2OOC$	COCl		Ac	148
$C_6H_5CH_2OOC$	$CONHCH_3$		Ac	148
$C_6H_5CH_2OOC$	$CON(CH_3)_2$		Ac	148
$C_6H_5CH_2OOC$	CONHEt		Ac	148
$C_6H_5CH_2OOC$	CONH-n-Pr		Ac	148
$C_6H_5CH_2OOC$	CONH-i-Pr		Ac	148
$C_6H_5CH_2OOC$	CONH-n-Bu		Ac	148
$C_6H_5CH_2OOC$	CONH-sec-Bu		Ac	148
$C_6H_5CH_2OOC$	$CONHC_6H_5$		Ac	148
$C_6H_5CH_2OOC$	$CONHC_6H_4$-Cl-o		Ac	148
$C_6H_5CH_2OOC$	$CONHC_6H_4$-EtO-p		Ac	148

R	R'	Salt	Act.	Ref.
$C_6H_5CH_2OOC$	CONH(m-Tolyl)		Ac	148
$C_6H_5CH_2OOC$	$CONHC_6H_{11}$		Ac	148
$C_6H_5CH_2OOC$	$CONHCH_2C_6H_5$		Ac	148
$C_6H_5CH_2OOC$	$CSNH_2$		Ac	148
$C_6H_5CH_2OOC$	Guanyl		Ac	148
$C_9H_9O_2$*	$C_9H_9O_2$		Ad	128
$C_9H_9O_2$	$C_9H_9O_2$		Ad	128
$C_6H_5OCH_2CH_2$	$CH_2CH_2OC_6H_5$		Ad	128
$C_6H_5OCH_2CH_2$	$CH_2CH_2OC_6H_5$		Ad	128
$C_6H_5O(CH_2)_3$	$CH_2(CH_2)_2OC_6H_5$		Ad	128
$C_6H_5O(CH_2)_3$	$CH_2(CH_2)_2OC_6H_5$		Ad	128
$C_{10}H_{13}O_3$**	$C_{10}H_{13}O_3$		Ad	128
$C_6H_{11}O$***	$C_6H_{11}O$		Ac	128
Tetrahydrofur-furyl	Tetrahydrofur-furyl		Ad	128
$EtOCH_2CH_2$	CH_2CH_2OEt		Ad	128
$C_6H_5CH_2$	$CH_2C_6H_5$		Ad	128
$C_9H_9O_2$	COOEt		Ad	128
$C_9H_9O_2$	C_6H_5		Ad	128
$C_9H_9O_2$	$CH_2CH_2OC_6H_5$		Ad	128
C_6H_5	$CH_2CH_2OC_6H_5$		Ad	128
CH_3CO	Et		Se	149
CH_3CO	$CH_2C_6H_5$		Se	149
EtCO	Et		Se	149
EtCO	$CH_2C_6H_5$		Se	149

*1,4-Benzodioxan-2-yl-methyl

**3,5-Dimethoxy-4-ethoxyphenyl

***Tetrahydropyran-2-yl-methyl

R	R'	Salt	Act.	Ref.
$n\text{-}C_3H_7CO$	CH_3		Se	149
$n\text{-}C_3H_7CO$	Et		Se	149
$n\text{-}C_3H_7CO$	n-Bu		Se	149
$i\text{-}C_3H_7CO$	$CH_2C_6H_5$		Se	149
$n\text{-}C_4H_9CO$	Et		Se	149
$i\text{-}C_4H_9CO$	Et		Se	149
$CH_3CH_2CH(CH_3)CO$	Et		Se	149
$n\text{-}C_6H_{13}CO$	Et		Se	149
$n\text{-}C_7H_{15}CO$	Et		Se	149
$C_4H_9CH(Et)CO$	Et		Se	149
$n\text{-}C_{11}H_{23}CO$	Et		Se	149
$n\text{-}C_{13}H_{27}CO$	Et		Se	149
C_6H_5CO	Et		Se	149
$p\text{-}NO_2\text{-}C_6H_4CO$	Et		Se	149
$o\text{-}Cl\text{-}C_6H_4CO$	Et		Se	149
$2,6\text{-}Cl_2\text{-}C_6H_3CO$	Et		Se	149
CH_3	$COCH(Ph)CH_3$	HCl	Sp	150
CH_3	$COCH(Ph)C_2H_5$	HCl	Sp	150
CH_3	$COCH(Ph)C_2H_5$	EtI	Sp	150
Et	$COCH(Ph)C_2H_5$	EtI	Sp	150
CH_3	$COCHPh_2$	HCl	Sp	150
CH_3	$COCHPh_2$	MeI	Sp	150
CH_3	$COCHPh_2$	EtI	Sp	150
CH_3	p-Tolylphenylacetyl	MeI	Sp	150
CH_3	p-Tolylphenylacetyl	EtI	Sp	150
CH_3	Mesitylphenylacetyl	EtI	Sp	150

R	R'	Salt	Act.	Ref.
CH_3	Diphenylacetoxy-acetyl	HCl	Sp	150
CH_3	Diphenylacetoxy-acetyl	MeI	Sp	150
CH_3	Biphenyleneacetyl	MeI	Sp	150
CH_3	Diphenylchloro-acetyl	HCl	Sp	150
CH_3	Diphenylhydroxy-acetyl	HCl	Sp	150
CH_3	Diphenylhydroxy-acetyl	MeI	Sp	150
CH_3	Diphenylethoxy-acetyl	HCl	Sp	150
CH_3	Diphenylpropoxy-acetyl	HCl	Sp	150
Et	Diphenylhydroxy-acetyl	HCl	Sp	150
Et	Diphenylethoxy-acetyl	HCl	Sp	150
CH_3	bis(o-Cl-phenyl)-acetyl	HCl	Sp	150
CH_3	bis(o-Cl-phenyl)-hydroxyacetyl	HCl	Sp	150
CH_3	bis(o-Cl-phenyl)-hydroxyacetyl	MeI	Sp	150
CH_3	bis(o-Cl-phenyl)-ethoxyacetyl	MeI	Sp	150
CH_3	bis(o-Cl-phenyl)-methoxyacetyl	MeI	Sp	150
CH_3	Biphenylenechloro-acetyl	HCl	Sp	150
CH_3	Biphenylenehydroxy-acetyl	HCl	Sp	150
CH_3	Biphenylenehydroxy-acetyl	MeI	Sp	150
CH_3	Biphenylenemethoxy-acetyl	MeI	Sp	150
CH_3	Biphenyleneethoxy-acetyl	MeI	Sp	150
Et	Biphenylenechloro-acetyl	HCl	Sp	150
Et	Biphenylenehydroxy-acetyl	MeI	Sp	150
Et	Biphenyleneacetyl	MeI	Sp	150
$C_6H_5CH_2$	$CH_2C_6H_4$-Am-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-Am-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4$-i-Am-p	2HCl	Un	151

R	R'	Salt	Act.	Ref.
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-i-Am-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4$-i-Hexyl-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-i-Hexyl-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4$-i-Pr-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-i-Pr-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4$-t-Bu-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-t-Bu-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4(CH_2CHEt_2)$-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4(CH_2CHEt_2)$-p	2HCl	Un	151
$C_6H_5CH_2$	$CH_2C_6H_4$-n-Heptyl-p	2HCl	Un	151
p-Cl-$C_6H_4CH_2$	$CH_2C_6H_4$-n-Heptyl-p	2HCl	Un	151
$C_6H_5CH_2OCO$	$CONHCH(CH_3)_2$		Ac	152
$C_6H_5CH_2OCO$	CONH-n-Bu		Ac	152
$C_6H_5CH_2OCO$	$CONHCH(CH_3)Et$		Ac	152
$C_6H_5CH_2OCO$	CONH-n-C_5H_{11}		Ac	152
$C_6H_5CH_2OCO$	CONH-n-C_6H_{11}		Ac	152
$C_6H_5CH_2OCO$	$CONHCH_2C_6H_5$		Ac	152
$C_6H_5CH_2OCO$	$CONHC_6H_5$		Ac	152
$C_6H_5CH_2OCO$	$CONHC_6H_4$-Cl-o		Ac	152
$C_6H_5CH_2OCO$	$CONHC_6H_4$-OEt-p		Ac	152
$C_6H_5CH_2OCO$	$CONHC_6H_4$-CH_3-m		Ac	152
$C_6H_5CH_2OCO$	$CON(CH_3)_2$		Ac	152
$C_6H_5CH_2OCO$	$CONEt_2$		Ac	152
$C_6H_5CH_2OCO$	CON(n-Pr)$_2$		Ac	152
$C_6H_5CH_2OCO$	CON(i-Bu)$_2$		Ac	152
$C_6H_5CH_2OCO$	CON(n-C_5H_{11})$_2$		Ac	152

R	R'	Salt	Act.	Ref.
$C_6H_5CH_2OCO$	$CONHCH(COOEt)_2$		Ac	152
$C_6H_5CH_2OCO$	$CONC_4H_8NCOOCH_2C_6H_5$*		Ac	152
$C_6H_5CH_2OCO$	$C(NH)NH_2$		Ac	152
PrCO	COOEt		Un	153
Et_2CHO	COOEt		Un	153
Isocaproyl	COOEt		Un	153
EtCO	COOEt		Un	153
Ac	CO_2CH_2Ph		Un	153
EtCO	CO_2CH_2Ph		Un	153
PrCO	CO_2CH_2Ph		Un	153
HCO	CO_2CH_2Ph		Un	153
PrCO	$COOCH_3$		Un	153
PrCO	COOBu		Un	153
C_6H_5	$(CH_2)_3NH_2$		Un	154
C_6H_5	$(CH_2)_3NHCHO$		Un	154
C_6H_5	$(CH_2)_3NHCOCHCl_2$		Un	154
C_6H_5	$(CH_2)_3NHSO_2CH_3$		Un	154
C_6H_5	$(CH_2)_3NHBz$		Un	154
C_6H_5	$(CH_2)_5NHCHO$		Un	154
C_6H_5	$(CH_2)_3NHAc$		Un	154
C_6H_5	$(CH_2)_3NHCOC_6H_{11}$		Un	154
C_6H_5	$(CH_2)_3NHCO(CH_2)_5C_6H_{11}$		Un	154
C_6H_5	$(CH_2)_3NHCOCH_2Ph$		Un	154
C_6H_5	CH_2CH_2NHCHO		Un	154
C_6H_5	CH_2CH_2NHAc		Un	154

*(1-Carbobenzyloxypiperazine-4-yl)carbonyl

R	R'	Salt	Act.	Ref.
C_6H_5	$(CH_2)_3NHCOOEt$		Un	154
C_6H_5	$(CH_2)_4NHAc$		Un	154
C_6H_5	$(CH_2)_5NHAc$		Un	154
C_6H_5	$(CH_2)_4NHSO_2CH_3$		Un	154
C_6H_5	$(CH_2)_5NHSO_2CH_3$		Un	154

R	R'	X*	Salt	Act.	Ref.
H	H	2-$CONH_2$		Tb	6
H	H	2-$CONHNH_2$		Tb	6
H	H	2-COOH		Tb	6
H	H	2-COOH	2HBr	Tb	6
H	H	2-COOH	2HCl	Tb	6
H	H	2-COOEt		Tb	6
H	H	2,5-Me_2	HCl	An	42,47
H	COOEt	3,5-Me_2		A,Sp	120
H	COOEt	3,4,5-Me_3		A,Sp	120
H	CH_3	3,5-Me_2		A,Sp	120
H	COOEt	2,5-Me_2		A,Sp	120
H	CH_3	2,5-Me_2		A,Sp	120
H	COOEt	2,5-Me_2		F	121
H	$CONEt_2$	2,5-Me_2		F	121
H	C_6H_5	2-Me		Un	123
H	C_6H_5	3-Et		Un	123
H	C_9H_{19}	2,5-Me_2	2HCl	F	35
H	$C_{10}H_{21}$	2,5-Me_2	HCl	F	35

*substituent on the piperazine ring (except N-substituents)

R	R'	X	Salt	Act.	Ref.
H	$C_{10}H_{21}$	2,5-Me_2	2HCl	F	35
H	$C_{11}H_{23}$	2,5-Me_2	2HCl	F	35
H	$C_{12}H_{25}$	2,5-Me_2	2HCl	F	35
H	$C_{12}H_{25}$	2,5-Me_2	2HBr	F	35
H	$C_{14}H_{29}$	2,5-Me_2	2HCl	F	35
H	$C_{16}H_{33}$	2,5-Me_2	2HCl	F	35
H	$COOCH_2CH_2NEt_2$	2,5-Me_2		Un	127
H	$COOCH_2CH_2NEt_2$	3-Me		Un	127
H	$COOCH_2CH_2NEt_2$	3 $CH_2C_6H_5$		Un	127
H	$COOCH_2CH_2NEt_2$	3 C_6H_5		Un	127
H	$C_9H_9O_2$*	2,5-Me_2	2HCl	Ad	128
H	CH_3	2,5-Me_2	HCl	An	42,47
H	Et	2,5-Me_2	HCl	An	42,47
H	n-$C_{10}H_{21}$	2,5-Me_2	2HCl	An	42,47
H	n-$C_{11}H_{23}$	2,5-Me_2	2HCl	An	42,47
H	n-$C_{12}H_{25}$	2,5-Me_2	2HCl	An	42,47
Ac	COOEt	2,5-Me_2		Un	153
CH_3	$CSNEt_2$	2,5-Me_2	HCl	S	130
CH_3	p-Cl-benzhydryl	2-Me		A,Sp	120
CH_3	p-Cl-benzhydryl	3,5-Me_2		A,Sp	120
CH_3	p-Cl-benzhydryl	2,5-Me_2		A,Sp	120
CH_3	COOEt	2-Me		A,Sp	120
CH_3	COOEt	3-Me		A,Sp	120
EtOOC	COOEt	2,5-Me_2		A,Sp	120
CH_3	COOEt	2,5-Me_2		A,Sp	120

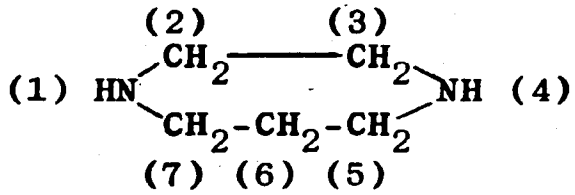
*1,4-Benzodioxan-2-ylmethyl

R	R'	X	Salt	Act.	Ref.
EtOOC	COOEt	2,5-Me_2		F	121
EtOOC	$CONH_2$	2,5-Me_2		F	121
EtOOC	$CONEt_2$	2,5-Me_2		F	121
EtOOC	CSNHEt	2,5-Me_2		F	121
$CONH_2$	$CONH_2$	2,5-Me_2		F	121
$CONH_2$	$CONEt_2$	2,5-Me_2		F	121
$CONEt_2$	$CONEt_2$	2,5-Me_2		F	121
$CONEt_2$	$C(NH)NH_2$	2,5-Me_2		F	121
$C(NH)NH_2$	$C(NH)NH_2$	2,5-Me_2		F	121
EtOOC	2-Pyridyl	2,5-Me_2		F	121
EtOOC	2-Pyrimidyl	2,5-Me_2		F	121
Ac	2-Cl-phenyl	3-Me		Un	123
C_6H_5	N-Ph-thiocarbamoyl	2-Me		Un	123
C_6H_5	N-Ph-thiocarbamoyl	3-Et		Un	123
C_6H_5	CH_2CH_2OH	2-Me		Un	123
C_6H_5	CH_2CH_2OH	3-Et		Un	123
C_6H_5	$CH_2CH(OH)CH_2OCH_3$	2-Me		Un	123
CH_3	$C_{10}H_{21}$	2,5-Me_2	2HCl	Fu	35
Et	$C_{10}H_{21}$	2,5-Me_2	2HCl	Fu	35
CH_3	Benzhydryl	2,5-Me_2	MeI	Sp	111
Et	Benzhydryl	2,5-Me_2	MeI,EtI	Sp	111
$C_9H_9O_2$	$C_9H_9O_2$	2,5-Me_2		Ad	128
$C_9H_9O_2$	$C_9H_9O_2$	2,5-Me_2		Ad	128
Et	$COCH_3$	2,5-Me_2		Se	149
CH_3	CH_3	2,5-Me_2	HCl	An	42,47
EtOOC	$COCH_3$	2,5-Me_2		Un	153

R	R'	X	Salt	Act.	Ref.
p-Tosyl	p-Tosyl	2-COOH		Tb	6
p-Tosyl	p-Tosyl	2-COOH		Tb	6
p-$NO_2C_6H_4CO$	COC_6H_4-NO_2-p	2-COOH		Tb	6

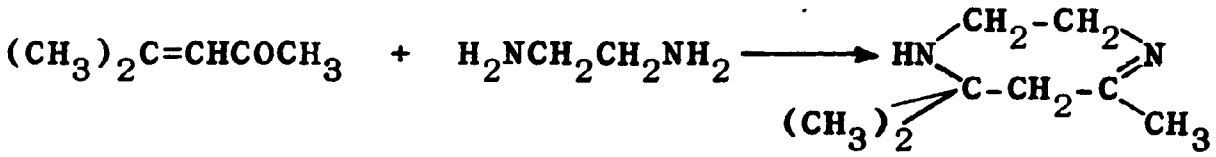
The Synthesis of 1,4-Diaza Seven-Membered Ring Compounds

In this section an attempt has been made to describe the syntheses of all compounds obtained hitherto which contain a diaza seven-membered ring in which the two nitrogen atoms are separated by two carbon atoms. The ring system of the parent compound (completely saturated) is shown below.



Homopiperazine*
1,4-Diazacycloheptane
Trimethyleneethylenediamine

The first mention of a compound which contained a ring system of this type was made by Guareschi (155) in 1894). He prepared 5,7,7-trimethyl-1,4-diaza-4-cycloheptene from ethylenediamine and phorone. It was assumed that the phorone first split into mesityl oxide and acetone, and that the former then condensed with the ethylenediamine. Guareschi also obtained



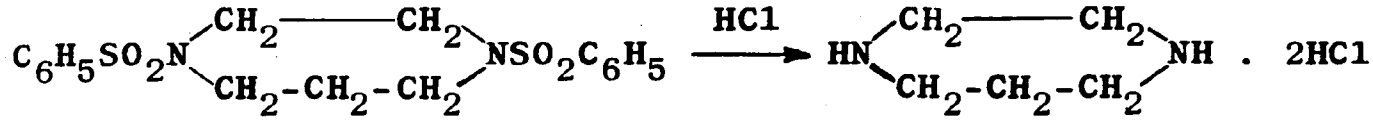
the same compound from ethylenediamine and mesityl oxide.

Bleier (156) was the first to prepare homopiperazine and some of its derivatives. From ethylenedibenzenesulfon-

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*The earliest investigators used the name trimethyleneethylenediamine; the most recent name is 1,4-diazacycloheptane. In the interest of clarity, the name homopiperazine will be used throughout this dissertation.

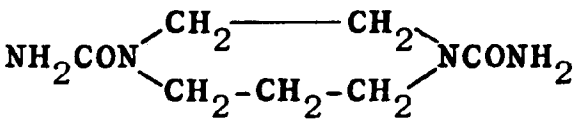
amide and trimethylenebromide, he obtained homopiperazine dibenzenesulfonamide, which was hydrolyzed with hydrochloric acid to give homopiperazine dihydrochloride; the yield and



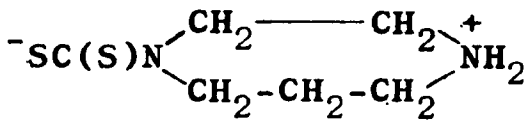
melting point were not reported. From the free base, liberated from the hydrochloride, he prepared numerous salts for characterization, e.g. hydrobromide, chloroplatinate, chloroaurate, picrate, etc.

Homopiperazine was described again by Howard and Marckwald (157), who stated that they had obtained the compound before it was reported by Bleier. Their method of preparation was essentially the same as Bleier's, but they prepared the di-p-toluenesulfonamide of ethylenediamine instead of the ethylenedibenzenesulfonamide as an intermediate. Howard and Marckwald found that homopiperazine melted at 42° and boiled at 167° (764 mm.).

Esch and Marckwald (158) prepared the **diureide** of homopiperazine from potassium cyanate and homopiperazine dihydrochloride (synthesized according to the method of Howard and Marckwald). For purposes of characterization, they also made the dithiocarbamate, which they reported to have a melting point of 216-217° (in this laboratory the melting point



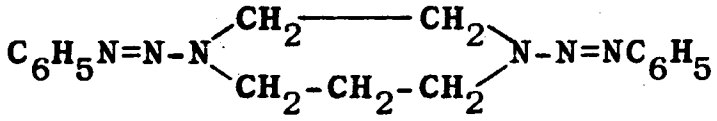
Diureide



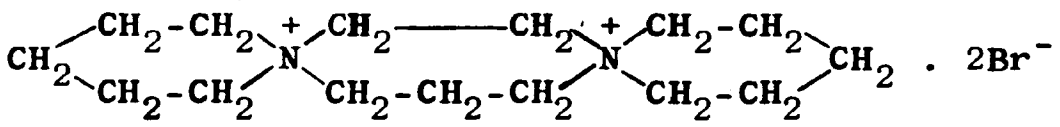
(Mono)Dithiocarbamate

was found to be 221-222°). Esch and Marckwald also showed

that homopiperazine couples with diazonium salts by preparing the yellow 1,4-di(phenylazo)homopiperazine.



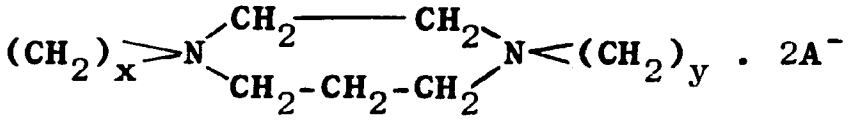
A diquaternary salt having as part of its structure the homopiperazine ring was prepared by Scholtz (159). From 1,2-dipiperidylethane and trimethylenebromide, he obtained a compound which was named "ethylene-trimethylene-dipiperidylium bromide." Aschan synthesized this compound in the same manner



as Scholtz, but also prepared it from trimethylenedipiperidyl and ethylene bromide. He synthesized many derivatives of this compound and attempted to obtain stereoisomers. His efforts to separate optically active components failed, as might be expected from present-day knowledge in this field.

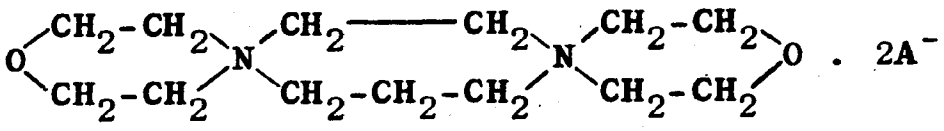
Blicke and Hotelling (160) prepared several compounds of the type mentioned above, the formulas for which are shown below, by reacting the appropriately N,N'-disubstituted diamine with trimethylene bromide.

N,N'-Ethylene-N,N'-trimethylenedi(polymethyleniminium) Salts



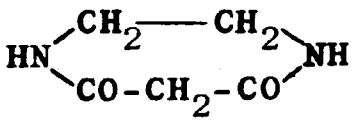
x	y	A^-
4	4	Bromide, Picrate
4	5	Bromide, Picrate
5	5	Bromide, Picrate
5	6	Bromide, Picrate
6	6	Bromide, Picrate
8	6	Bromide, Picrate

N,N'-Ethylene-N,N'-trimethylenedimorpholinium Salts



(A^- = Bromide, picrate)

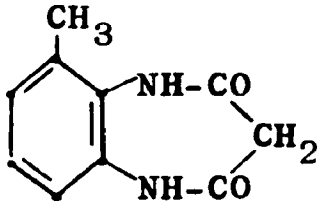
Freund, while studying various reactions of malonic acid, claimed to have prepared what he called ethylenemalonamide from ethylenediamine and ethyl malonate. However, he analyzed the product only for nitrogen, and the per cent of nitrogen found was 1.55% lower than the calculated value. Freund's



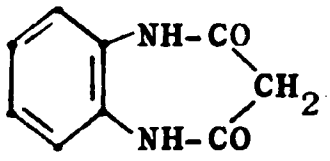
Ethylenemalonamide

procedure was later used by Lippert and Reid (162) for the preparation of eight-membered and larger rings, e.g. ethyleneadipamide, ethyleneazelamide, etc.

Meyer studied this reaction further with various phenylenediamines: interaction of malonic ester with o-phenylenediamine and with o-toluylenediamine yielded o-phenylenemalonamide and o-toluylenemalonamide, respectively. From di-

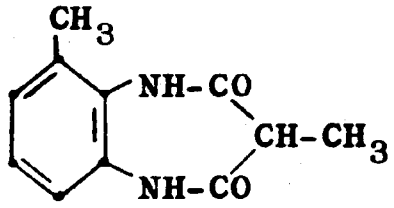


o-Toluylenemalonamide

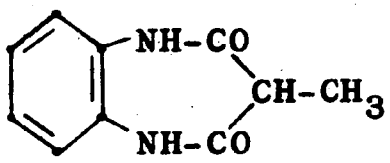


o-Phenylenemalonamide

ethyl methylmalonate with o-toluylenediamine and o-phenylenediamine, he obtained o-toluylenemethylmalonamide and o-phenylenemethylmalonamide, respectively.

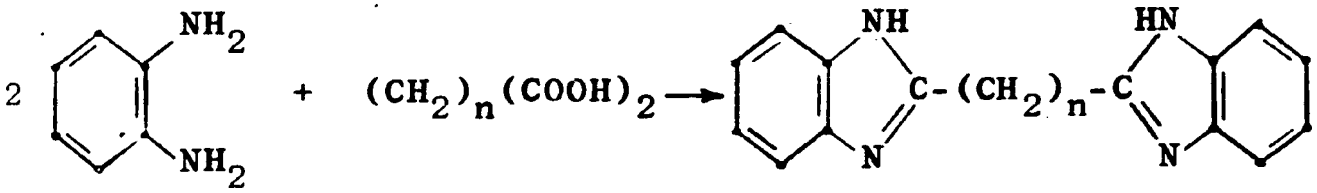


o-Toluylenemethylmalonamide



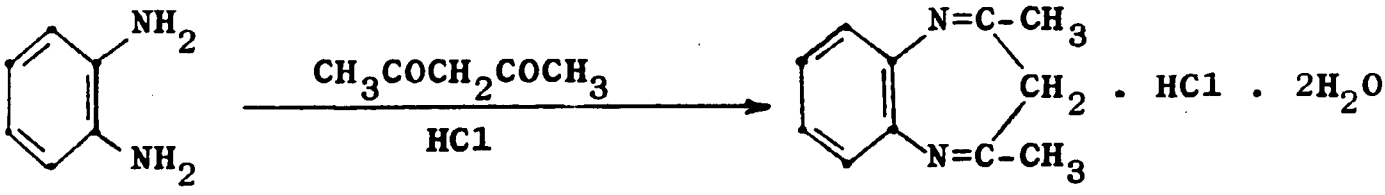
o-Phenylenemethylmalonamide

Shriner and Upson (164) prepared a series of bisbenzimidazoles by condensation of o-phenylenediamine with dibasic acids. However, Phillips (165) found that the condensation

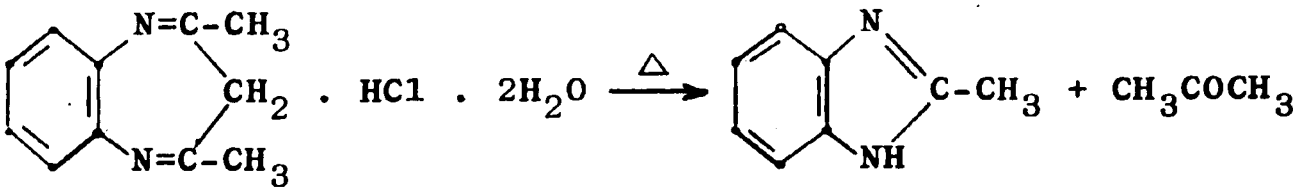


product of o-phenylenediamine and malonic acid, which had been described by Shriner and Upson, was not a bisbenzimidazole, but was o-phenylenemalonamide, a substance which he had synthesized (166) by Meyer's procedure.

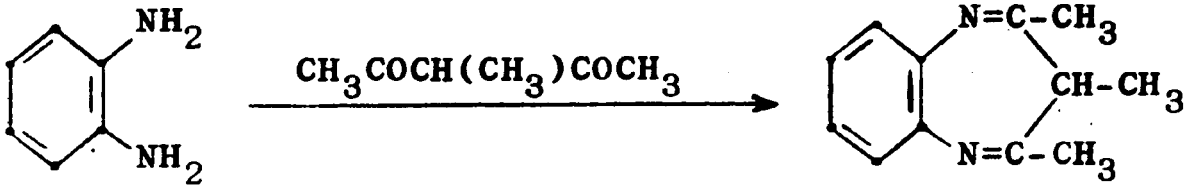
Thiele and Steimmig (167) prepared a substituted diazepine, 2,3-benzo-5,7-dimethyl-1,4-diazacycloheptatriene, in the form of the hydrochloride dihydrate, in 90-95% yield by allowing o-phenylenediamine to react with acetylacetone.

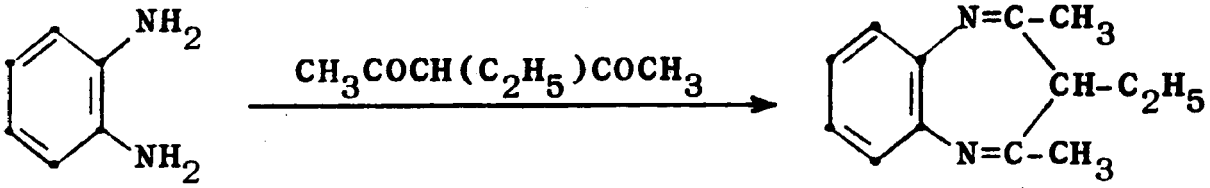


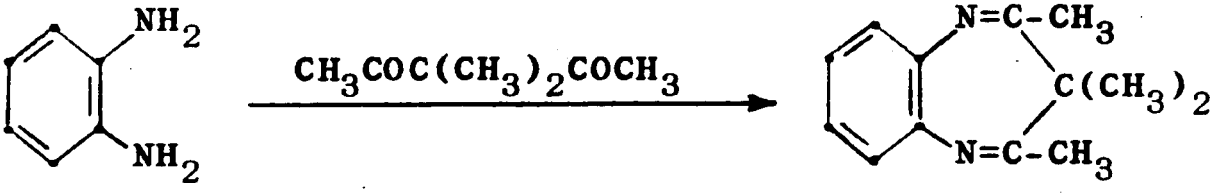
This compound dissolved in water to form a deep violet solution. When the hydrochloride dihydrate was heated it decomposed into 2-methylbenzimidazole and acetone.



Vaisman (168) claimed to have obtained 2,3-benzo-5,6,7-trimethyl-1,4-diazacycloheptatriene, 2,3-benzo-6-ethyl-5,7-dimethyl-1,4-diazacycloheptatriene and 2,3-benzo-5,6,6,7-tetramethyl-1,4-diazacycloheptatriene according to the following equations:

(1) 

(2) 

(3) 

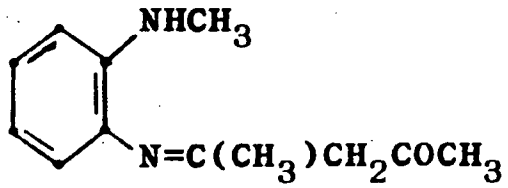
In a later article (169), however, Vaisman concluded that the tetramethyl compound (formulation (3)) was not the cycloheptatriene as he had supposed, but was some other compound which he did not specify.

In attempting to prepare the product shown in formulation (3) for use in his study of the aromaticity of seven-membered nitrogenous heterocycles, Fitch (120) also failed to obtain this compound. Although he varied the reaction conditions in about every conceivable way, he was able to obtain, besides unreacted starting material, only 2-methylbenzimidazole. From molecular models, he concluded that the two methyl groups attached to the 6 position (as we have numbered the formula) would present steric difficulties with the benzene

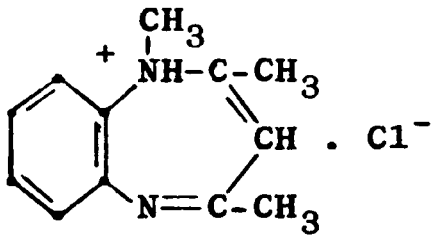
ring portion of the molecule.

Fitch was able, however, to synthesize two compounds of the 2,3-benzo-1,4-diazacycloheptatriene type. By the method of Thiele and Steimmig (167) he prepared, from 3-methylpentane-2,4-dione and o-phenylenediamine, 2,3-benzo-5,6,7-trimethyl-1,4-diazacycloheptatriene, which had also been obtained by Vaisman (168). The free amine, when exposed to air, turned from colorless to yellow in a very short time, and purification of the hydrochloride salt was very difficult.

From N-methyl-o-phenylenediamine and acetylacetone, Fitch prepared 2,3-benzo-4,5,7-trimethyl-1,4-diazacycloheptatriene, isolating first the Schiff base which was then cyclized

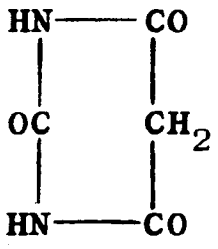


by forming its hydrochloride salt in benzene at zero degrees.

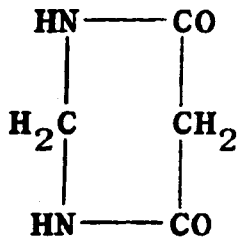


Nothing more was done with this compound, since the free amine could not be obtained and all attempts to purify the hydrochloride led to decomposition.

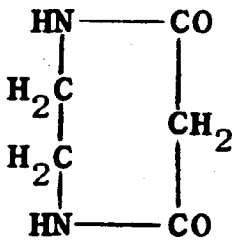
Dox (171) later confirmed the work of Freund when he prepared ethylenemalonamide or, as he called it, homodesoxybarbituric acid, from ethylenediamine and ethyl malonate. This condensation was effected by heating molecular portions of the



Barbituric Acid



Desoxybarbituric Acid



Homodesoxybarbituric Acid

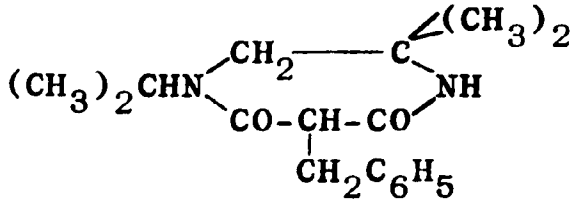
ester and the amine with sodium ethoxide. Other homodesoxybarbituric acids which were prepared from substituted diethyl malonates are listed in the following table.

Homodesoxybarbituric Acids

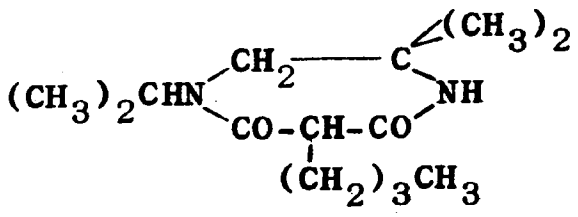
Monoalkyl	Dialkyl
Ethyl	Diethyl
Propyl	Dibutyl
sec-Butyl	Hexylethyl

These derivatives were found to be pharmacologically inert; administered orally to rabbits in doses equivalent to the hypnotic dose of barbital, no effect whatever was observed.

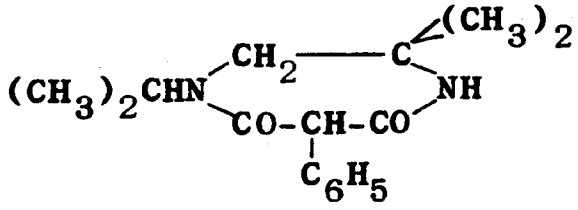
Unlike the amorphous, colloidal, high-melting products obtained by Dox, the analagous compounds prepared by Pachter and Riebsomer (172) were low-melting, crystalline solids, and could even be distilled without decomposition. The latter authors reacted N-(2-aminoisobutyl)isopropylamine with three different monosubstituted malonic esters and obtained as products diazepines, the formulas for which are shown below.



6-Benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine

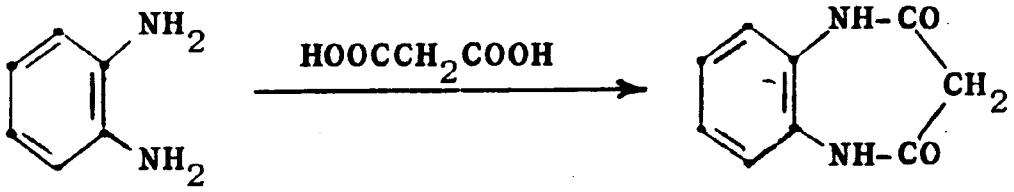


6-n-Butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine

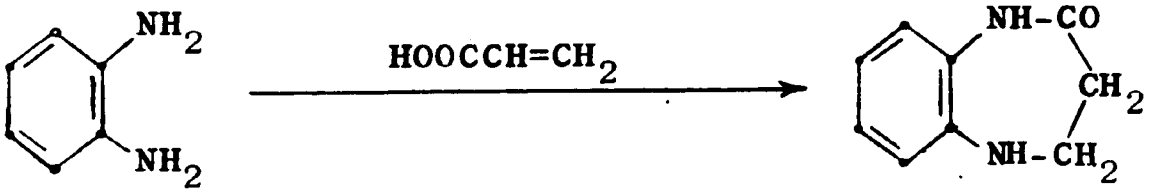


6-Phenyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine

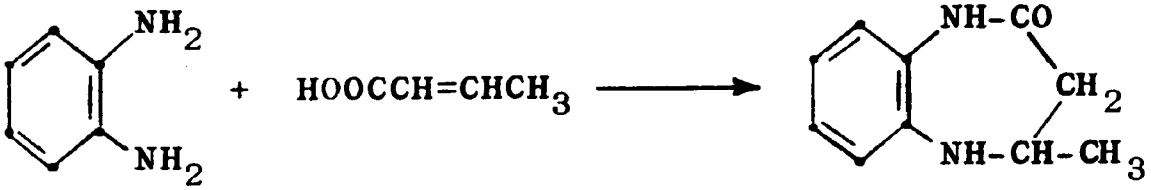
Phillips (173) showed that the reaction between o-phenylenediamine and malonic acid, in the presence of boiling dilute hydrochloric acid, gave o-phenylenemalonamide in quantitative yield.



Bachman and Heisey (174), in an attempt to prepare 2-vinylbenzimidazole from acrylic acid and o-phenylenediamine, obtained instead a compound in 67% yield which they identified and named as 2-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine.

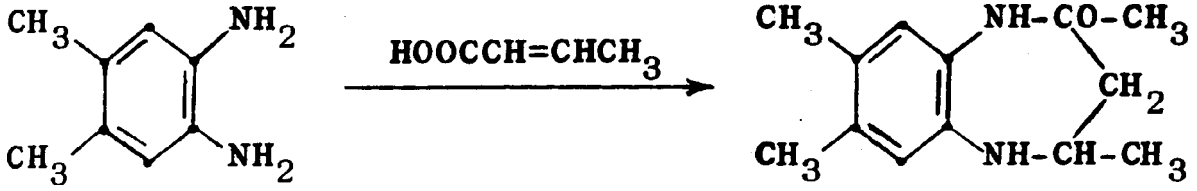


Reid and Urlass (175) extended this reaction by reacting o-phenylenediamine with crotonic acid to obtain a product in 44% yield which they named 7-methyl-2,3-benzo-1,4-diazacycloheptene-2-one-5.

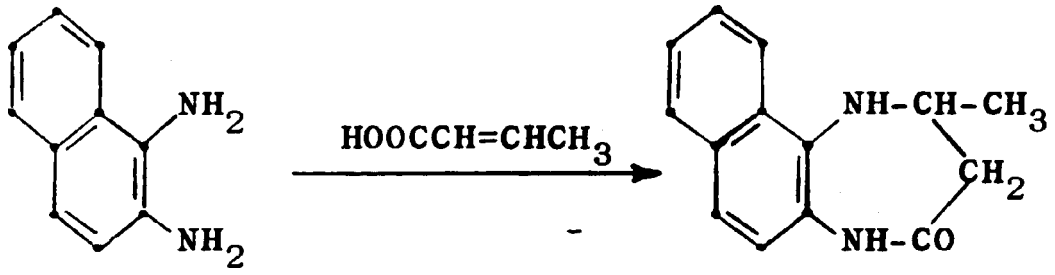


By using variously substituted diamines, Reid and Höhne

(176) obtained analagous products. From 4,5-dimethyl-1,2-diaminobenzene and crotonic acid 4',5',7-trimethyl-1,4-diaza-(benzo-1',2':2,3-cycloheptene-2-one-5) was produced in 58% yield, and from 1,2-naphthylenediamine and crotonic acid

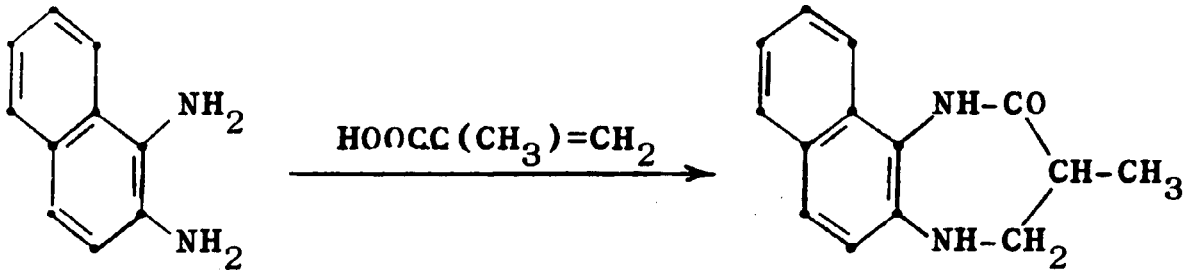


methyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptene-2-one-7) was formed in 58% yield. The formulas for other reaction

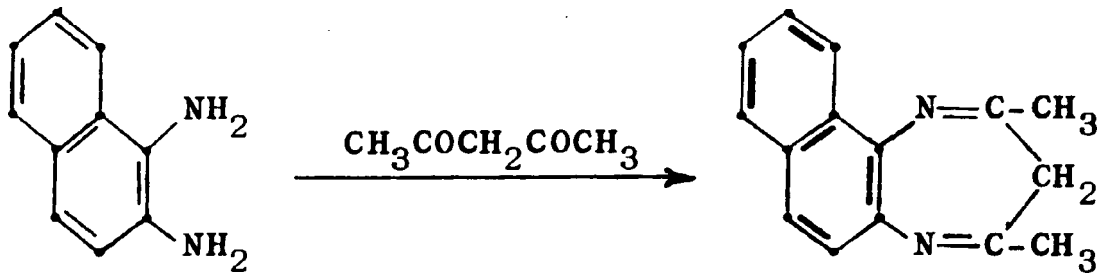


products, synthesized by the last named investigators, are shown below.

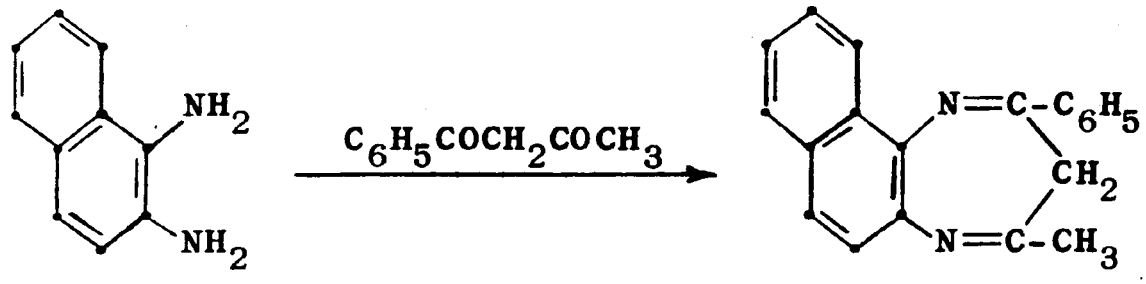
6-Methyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptene-2-one-7):



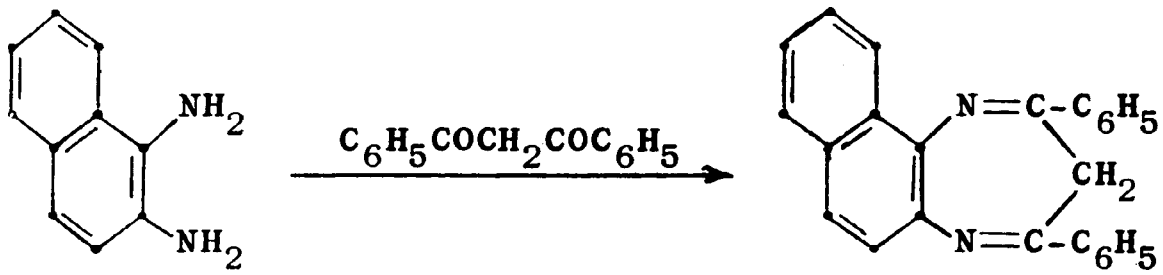
5,7-Dimethyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptatriene)



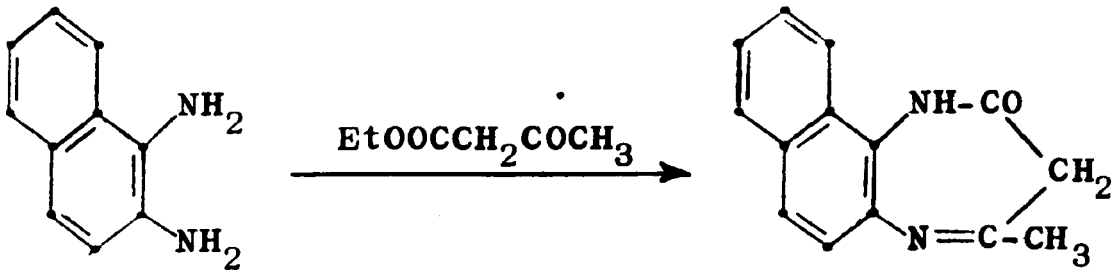
5-Methyl-7-phenyl-1,4-diaza-(naphtho-1',2': 2,3-cyclohepta-triene):



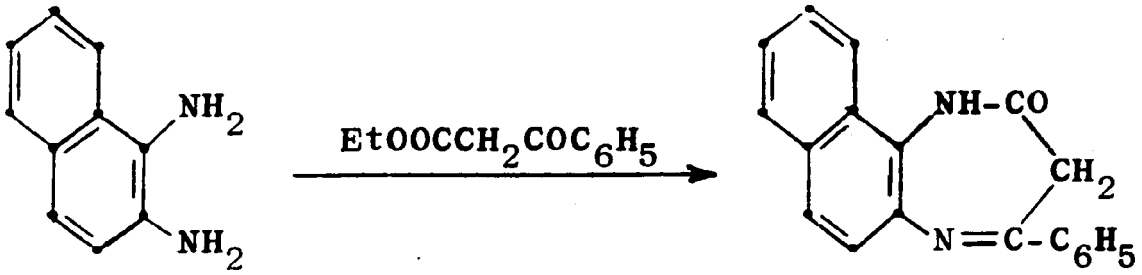
5,7-Diphenyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptatriene):



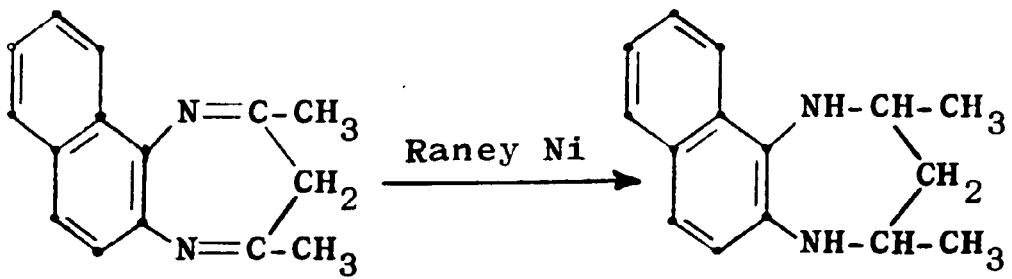
7-Methyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptadiene-one-5):



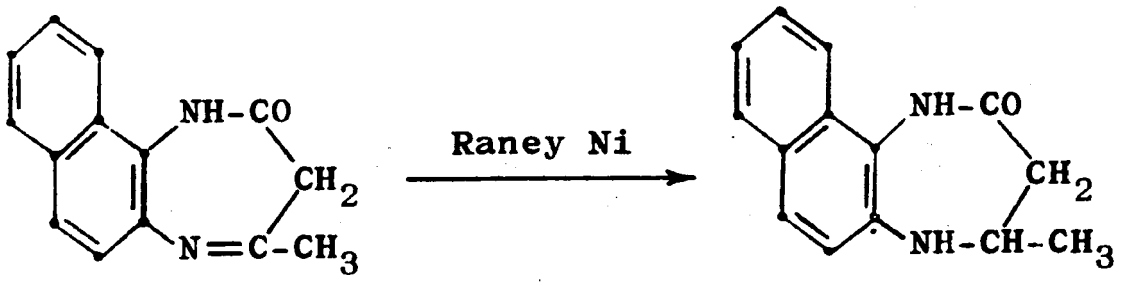
7-Phenyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptadiene-one-5):



5,7-Dimethyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptene):

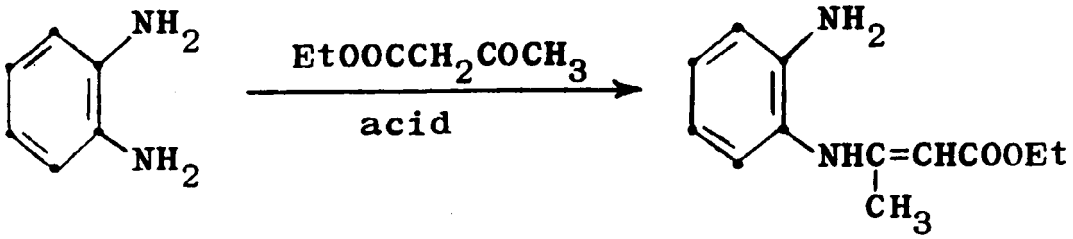


7-Methyl-1,4-diaza-(naphtho-1',2': 2,3-cycloheptene-one-5):

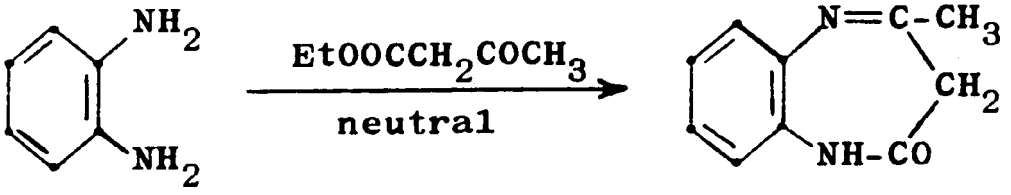


(This compound gave a depression in melting point of 20° when mixed with the compound obtained from 1,2-naphthylamine and crotonic acid.)

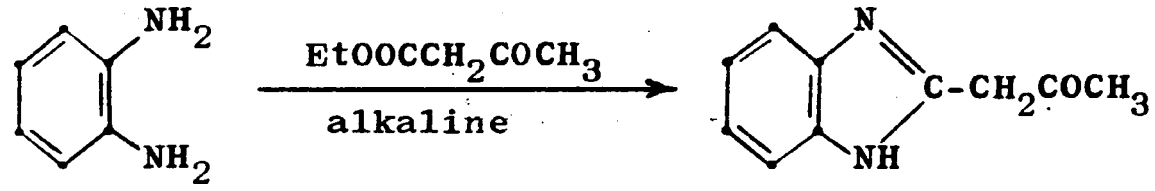
The condensation of o-phenylenediamine with ethyl acetoacetate was investigated by Sexton (177) prior to the work of Reid et al. He found that if this condensation were carried out under acid conditions, the only isolatable product was ethyl beta-2-aminoanilinocrotonate. This compound could not



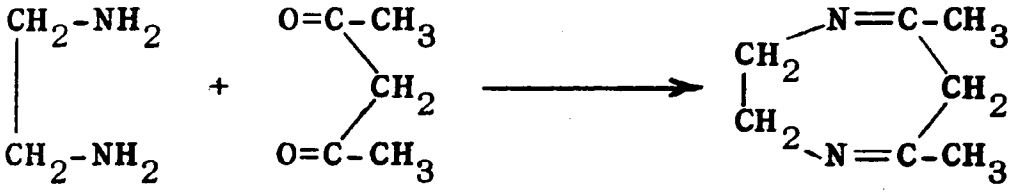
be cyclized to a 1,4-diaza compound by Sexton. Under neutral conditions, a 71.3% yield of 2,3-benzo-5-methyl-1,4-diaza-cycloheptadiene-2,4-one-7 was obtained.



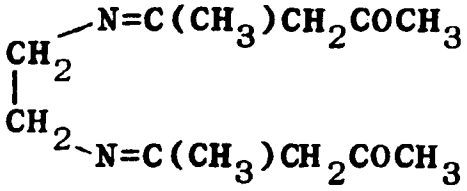
Finally, under alkaline conditions, this condensation afforded a third product, benzimidazole-2-acetone, in 63% yield.



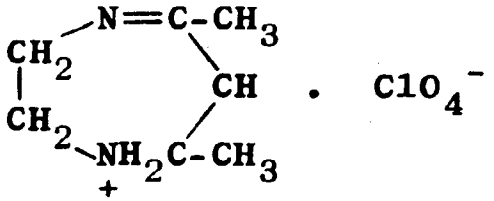
The condensation of ethylenediamine with 1,3-diketones was first described by Rosanow (178) who prepared 5,7-dimethyl-1,4-diazacycloheptadiene-4,7[1] from acetylacetone and ethylenediamine.



Schwarzenbach and Lutz (179) described the last mentioned reaction which they found to proceed predominantly with the formation of an open-chain compound unless special precautions

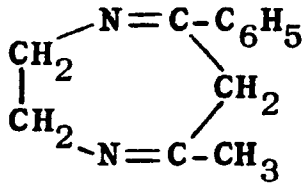


were taken. By combining acetylacetone and ethylenediamine in the proper portions with careful heating and addition of glacial acetic acid, they were able to isolate, as the perchlorate salt, a seven-membered ring compound, viz., 2,7-di-

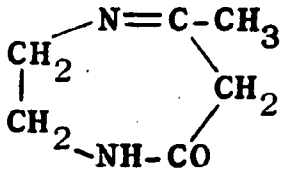


methyl-3,6-diazacycloheptadiene-1,6 perchlorate. As proof of the structure of this compound, they reported only a correct nitrogen analysis. No investigation of the free base was made.

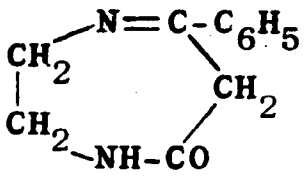
Reid and Höhne (180) also reacted ethylenediamine with 1,3-diketones; with benzoylacetone they obtained 5-methyl-7-phenyl-1,4-diazacycloheptadiene-4,7[(1)] in 88% yield.



These investigators also prepared 5-methyl-1,4-diazacycloheptene-4-one-7 from ethylenediamine and ethyl acetoacetate in 74% yield, and 5-phenyl-1,4-diazacycloheptene-4-one-7 from

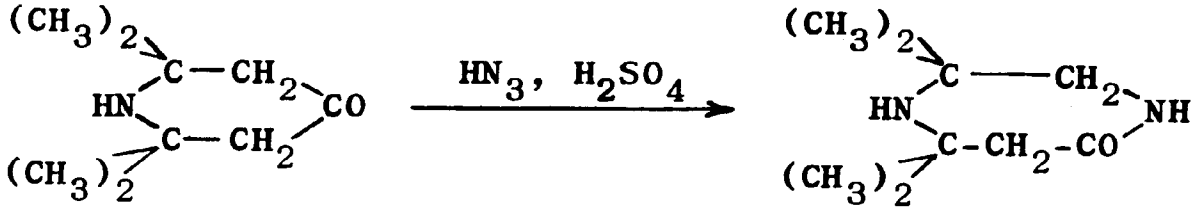


ethylenediamine and ethyl benzoylacetate in 65% yield. They



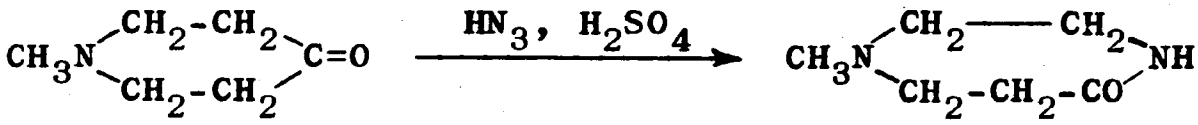
were not able to isolate a product from dibenzoylmethane and ethylenediamine.

Since the work of Reid and Höhne, 1,4-diazepine type compounds have been made only by means of the Schmidt reaction on 4-piperidones. The first reaction of this type was described by Dickerman and Lindwall (181) who treated triacetonamine with hydrazoic and sulfuric acids to obtain an 88% yield

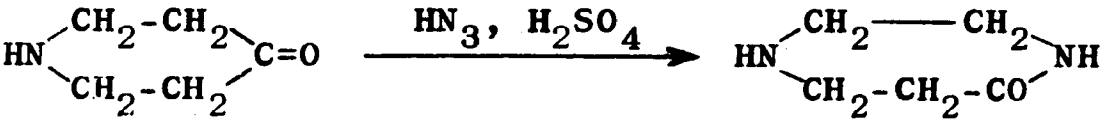


of 2,2,7,7,-tetramethyl-5-homopiperazinone. Triacetonamine

oxime was also made to undergo a Beckmann rearrangement to afford the same product, but in poor yield. 1-Methyl-4-piperidone was converted into 1-methyl-5-homopiperazinone by the Schmidt reaction in 53% yield.



By modifying the procedure of McElvain and Stork (182) somewhat, Dickerman and Lindwall (181) were able to obtain a 72% yield of 1-acetyl-3-carbethoxy-4-piperidone by a Dieckman condensation of a N-acetyldi(beta-carbethoxyethyl)amine. This substance was then hydrolyzed to 4-piperidone which, when treated with hydrazoic and sulfuric acids, was converted into 5-homopiperazinone in 51% yield.



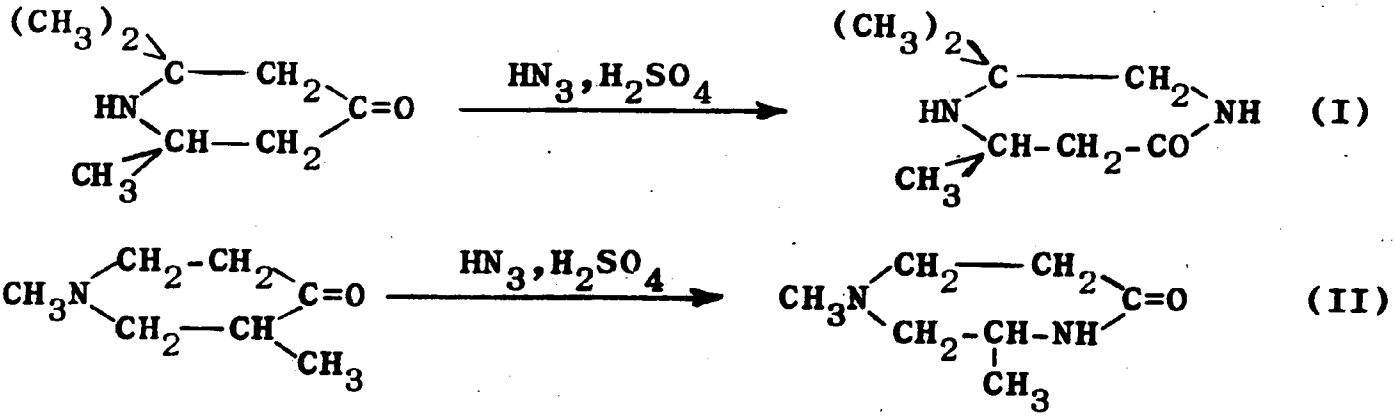
In a later paper (183) Dickerman and Besozzi reported the synthesis of six 5-homopiperazinones through the Schmidt reaction on various 4-piperidones. Their work is summarized in the following table.

5-Homopiperazinone	Yield %
1-Methyl-3-carbethoxy	29
1,3-Dimethyl-6-carbethoxy	36
1-Phenyl	71
1-Benzyl	74
1-Phenethyl	74
1-Methyl-2,7-diphenyl	95

Merely to demonstrate the use of homopiperazinones as a

source of homopiperazines, Dickerman and Besozzi (183) reduced 1-benzyl-5-homopiperazinone with lithium aluminum hydride to obtain 1-benzylhomopiperazine which they characterized as the oxalate and dipicrate salts.

Dickerman and Moriconi (184) prepared 2,7,7-trimethyl-5-homopiperazinone and 1,3-dimethyl-5-homopiperazinone by the Schmidt reaction on 2,2,6-trimethyl-4-piperidone and 1,3-dimethyl-4-piperidone, respectively.



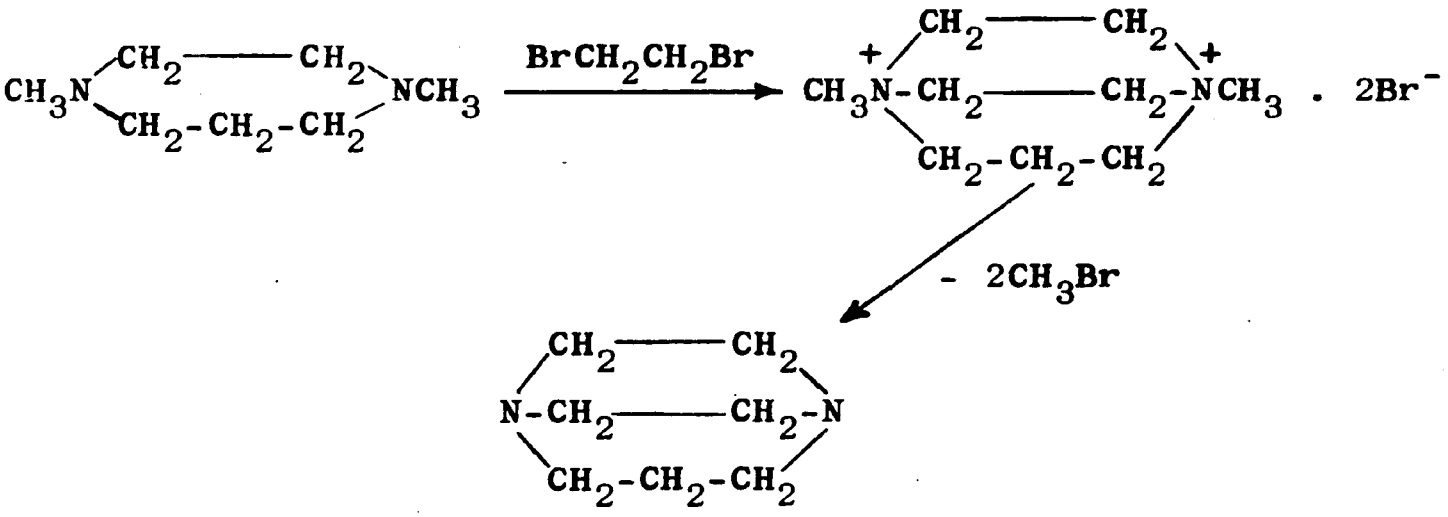
The product obtained in formulation (II) is explained on the basis of the steric effect of the methyl group, since the Schmidt reaction has been found to be subject to the same steric factors as is the Beckmann rearrangement (185). Why reaction (I) affords the product as shown rather than the isomeric 2,2,7-trimethyl-5-homopiperazinone is not understood.

Sommers, Michaels and Weston (186) used the procedure suggested by Dickerman and Besozzi (183) for the preparation of homopiperazines from homopiperazinones; from 1-methyl-5-homopiperazinone they prepared, in 49% yield, 1-methylhomopiperazine. By allowing this compound to react with benzhydryl bromide and p-chlorobenzhydryl bromide they obtained 1-benzhydryl-4-methylhomopiperazine (41% yield) and 1-(p-chloro-

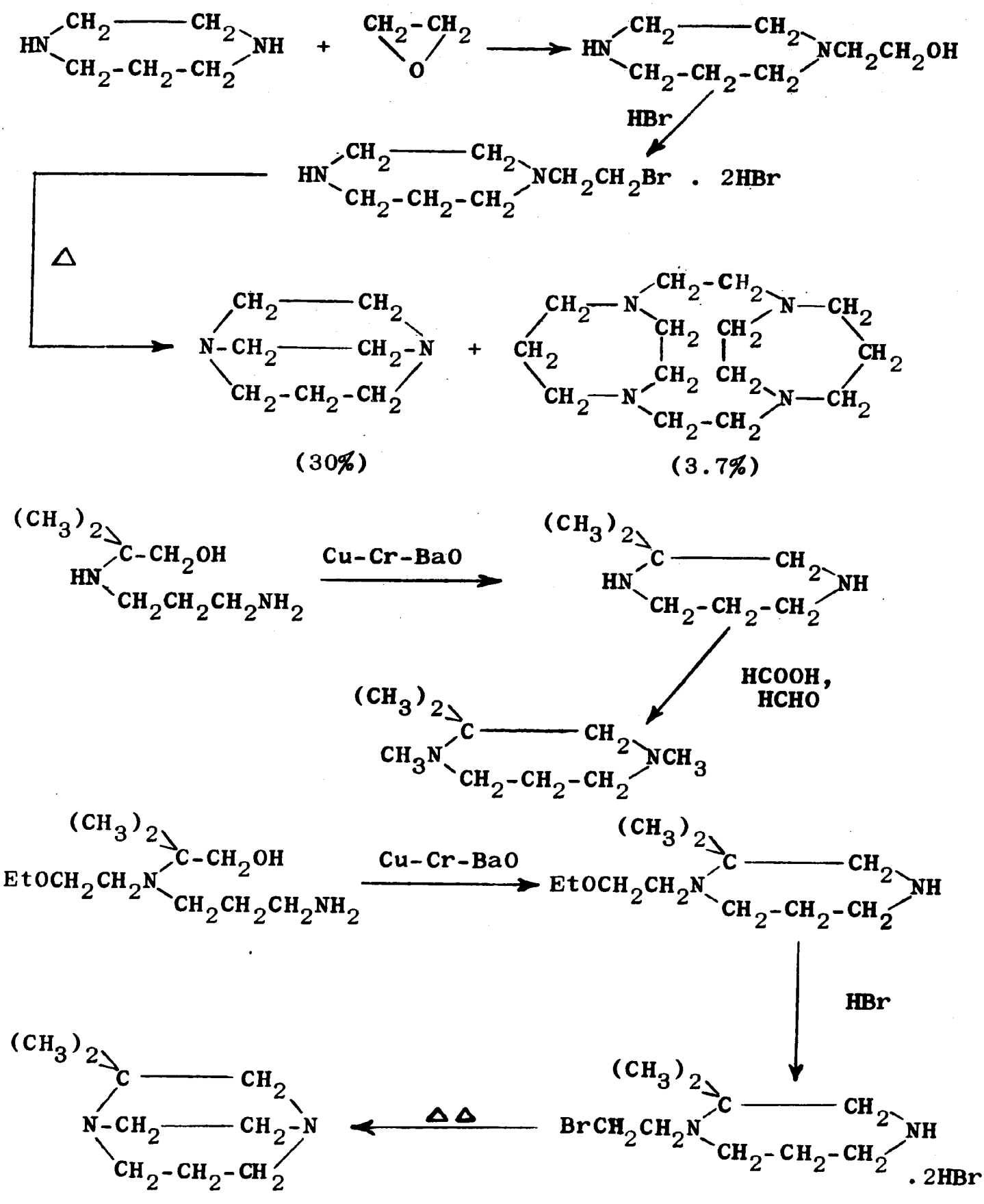
benzhydryl)-4-methylhomopiperazine (56% yield), respectively.

In preliminary animal experiments, each of these homopiperazines showed antihistaminic action greater than that of the corresponding piperazine (186).

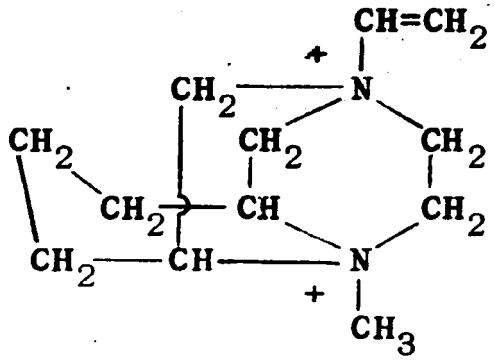
In studying the introduction of an ethylene bridge between the nitrogen atoms in piperazine and in homopiperazine, McElvain and Bannister (9) first prepared homopiperazine by the method of L. Bleier (156). This substance was methylated to give 1,4-dimethylhomopiperazine (boiling point = 158-161°, 738 mm.). The latter compound was also prepared from N,N,N',N'-tetramethylethylenediamine and trimethylenebromide; the resulting 1,4-dimethylhomopiperazine dimethobromide was then demethobrominated to give 1,4-dimethylhomopiperazine. From 1,4-dimethylhomopiperazine thus prepared and ethylene bromide, they obtained 1,5-diazabicyclo[3.2.2]nonane dimethobromide which was demethobrominated to give the free base.



The following series of equations summarize the remainder of the work done by these authors on homopiperazines and related compounds.


HBr
. 2HBr
(30%)
(3.7%)
Cu-Cr-BaO
HCOOH,
HCHO
Cu-Cr-BaO
HBr
. 2HBr
(10.6%)

A rather unique compound, which contains both a piperazine and a homopiperazine ring in its structure, was reported by Fales and Barnes (187).

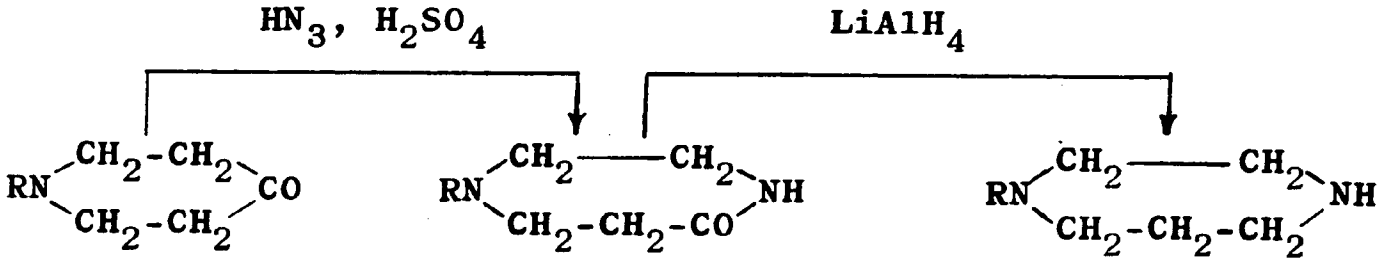


. 2 $^{-}OC_6H_2(NO_2)_3$

DISCUSSION OF THIS INVESTIGATION

This dissertation deals with the synthesis of substituted homopiperazines some of which are analagous to substituted piperazines which have proven to be therapeutically useful in recent years. As far as we are aware, only one publication has appeared which describes homopiperazines prepared because of their potential value as therapeutic agents. While this investigation was in progress, Sommers et al. (186) reported the synthesis of 1-benzhydryl- and 1-(p-chlorobenzhydryl)-4-methylhomopiperazine and stated that both of these compounds were found to be more active as antihistaminics than the corresponding piperazines.

The required intermediates for this investigation, 1-methyl-, 1-ethyl- and 1-benzyl-homopiperazine were prepared by a Schmidt reaction on 1-substituted 4-piperidones (181). The resulting 1-substituted 5-homopiperazinones were then reduced with lithium aluminum hydride to the homopiperazines*.

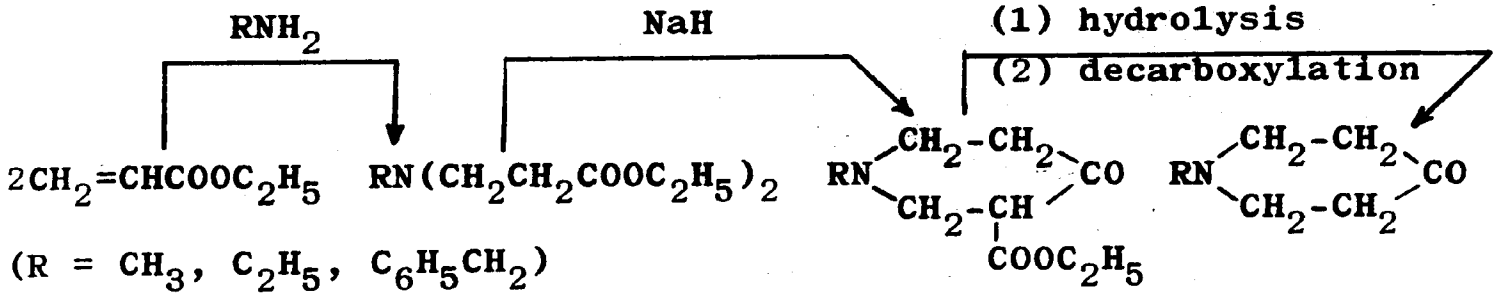


(R = CH_3, C_2H_5, $C_6H_5CH_2$)

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*Publications which describe two of these reductions appeared after they had already been carried out during this investigation. 1-Benzyl-5-homopiperazinone has been reduced with lithium aluminum hydride to 1-Benzyl-homopiperazine by S. Dickerman and A. Besozzi (183), and 1-methyl-5-homopiperazinone was reduced in the same manner to the corresponding homopiperazine by A. H. Sommers, R. J. Michaels, Jr. and A. W. Weston (186).

The substituted piperidones were prepared by methods which have been described in the literature*; these methods are outlined below.



(R = CH_3, C_2H_5, $C_6H_5CH_2$)

The 1-methyl- and 1-benzyl-homopiperazines were allowed to react with alkyl halides and acid chlorides to form 1,4-disubstituted homopiperazines.



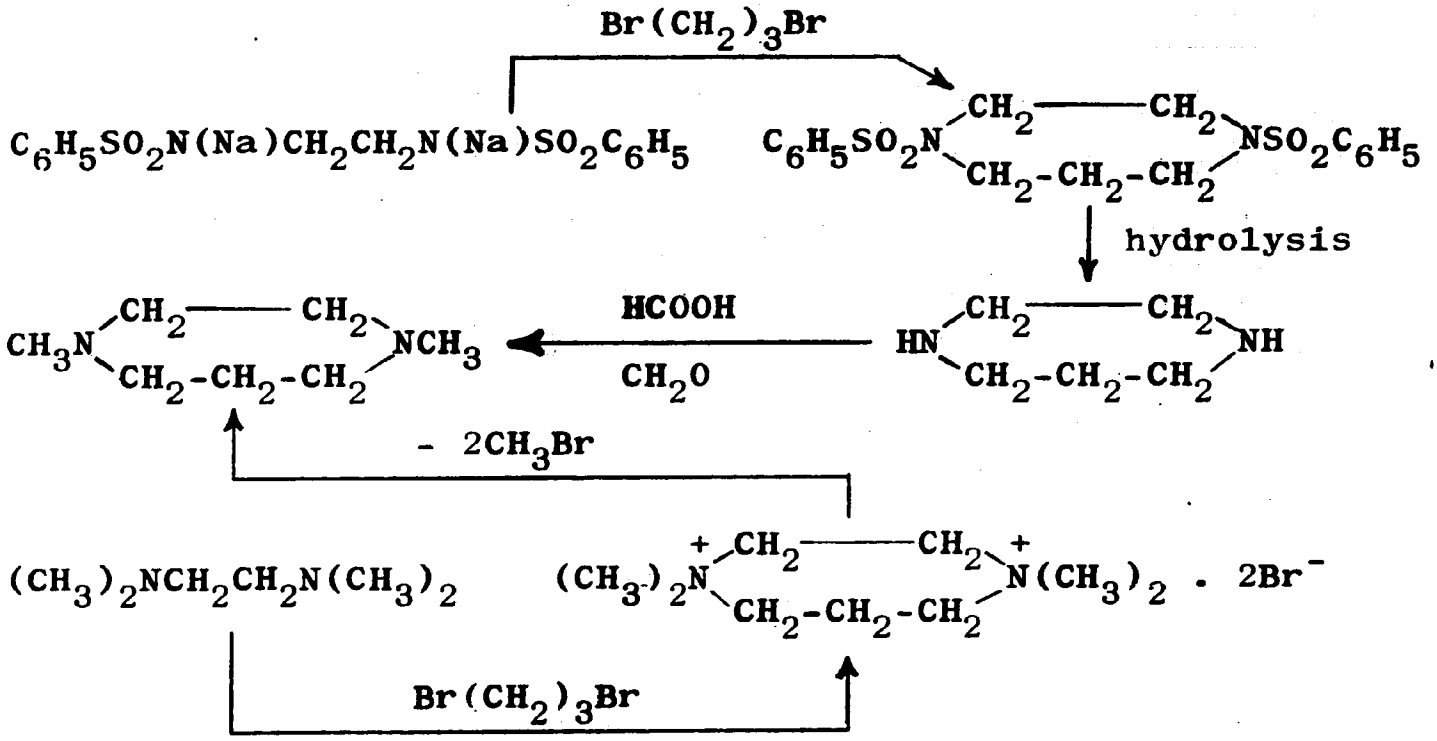
(X = Br, Cl; R = CH_3, $C_6H_5CH_2$; R' = CH_2CH_2OH, $COCH_2C_6H_5$, $COCH(C_6H_5)_2$, $CH_2CH_2N(CH_3)_2$, $CON(C_2H_5)_2$, $CON(C_6H_5)_2$, $CH(C_6H_5)_2$ $CH(C_6H_5)C_6H_4Br$-p, $COOC_2H_5$)

A number of 4-substituted 1-methylhomopiperazines were obtained in the following manner.

Formylation of 1-methylhomopiperazine with chloral (188) yielded 1-methyl-4-formylhomopiperazine which was reduced with lithium aluminum hydride to 1,4-dimethylhomopiperazine. During the course of this investigation, a publication appeared (9) which described two methods for the synthesis of 1,4-dimethylhomopiperazine which are outlined on the following page.

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*1-Methyl-4-piperidone was described by S. M. McElvain (J. Am. Chem. Soc., 70, 1822 (1948); the 1-ethyl derivative by N. W. Bolyard and S. M. McElvain (ibid., 51, 922 (1929)) and the 1-benzyl derivative by G. Stork and S. M. McElvain (182) and by S. Dickerman and A. Besozzi (183).



1-Methylhomopiperazine reacted with ethylene oxide to form 1-methyl-4-(beta-hydroxyethyl)homopiperazine*.

1-Methyl- and 1-benzyl-homopiperazine were treated with sodium nitrite and hydrochloric acid whereupon 1-methyl- and 1-benzyl-4-nitrosohomopiperazine were produced**.

By the use of lithium aluminum hydride, the nitroso derivatives were reduced to 1-methyl- and 1-benzyl-4-aminohomopiperazine, respectively.

1-Methyl-4-aminohomopiperazine was methylated with formic

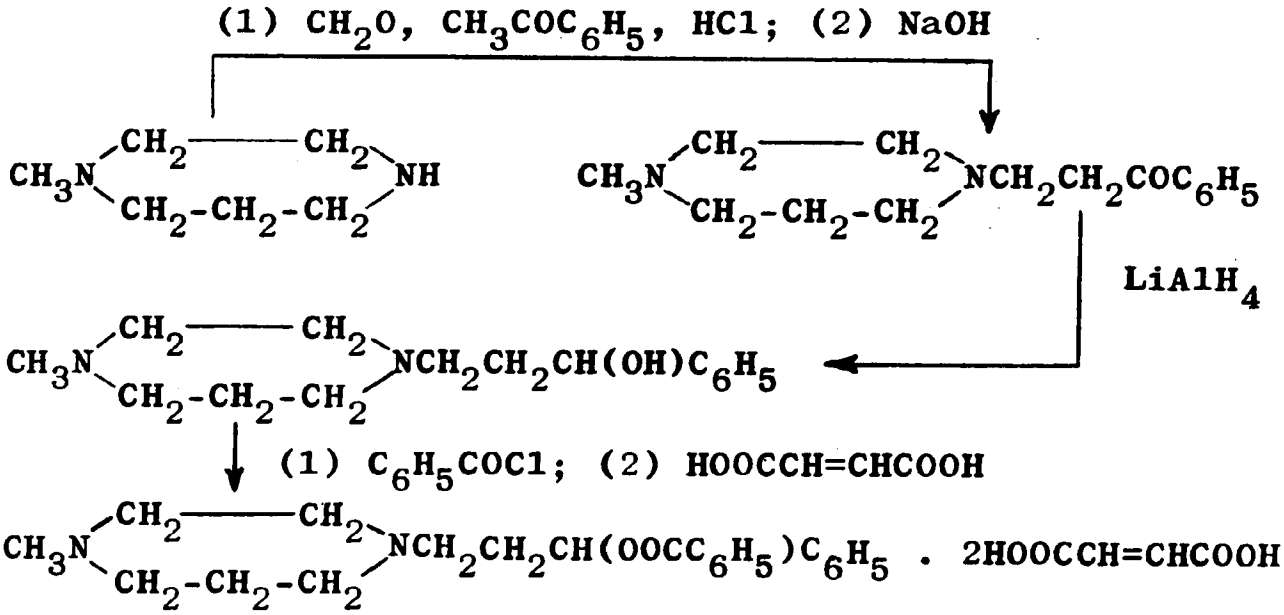
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*The method used was the same as that employed by W. H. Horne and R. L. Shriner (J. Am. Chem. Soc., 54, 2925 (1932)) to prepare diethyl-beta-hydroxyethylamine from diethylamine and ethylene oxide. By the use of this procedure, S. M. McElvain and L. W. Bannister (ibid., 76, 1126 (1954)) synthesized 1-(beta-hydroxyethyl)piperazine, 1,4-di-(beta-hydroxyethyl)piperazine and 1-(beta-hydroxyethyl)homopiperazine.

**The method followed was the same as that which had been used by E. A. Conroy (U. S. Patent 2,663,706; C. A., 49, 4730 (1955)) to obtain a series of 1-substituted 4-nitrosopiperazines.

acid and formaldehyde* to form 1-methyl-4-dimethylaminohomopiperazine.

A Mannich reaction was carried out with 1-methylhomopiperazine, formaldehyde, acetophenone and hydrochloric acid. The reaction product, 1-methyl-4-(beta-benzoylethyl)homopiperazine, in the form of the base was reduced with lithium aluminum hydride to 1-phenyl-3-(1-methyl-4-homopiperazinyl)-propanol. The last mentioned substance was treated with benzoyl chloride whereby 1-phenyl-3-(1-methyl-4-homopiperazinyl)-propyl benzoate was formed and isolated as the dimaleate.

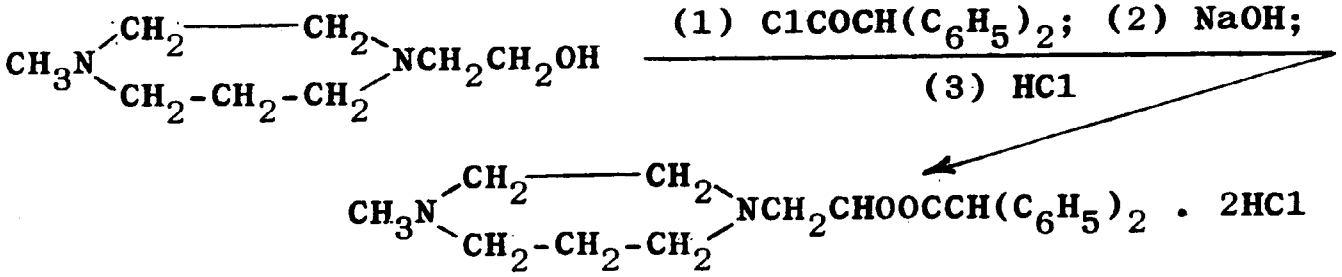


beta-(1-Methyl-4-homopiperazinyl)ethyl diphenylacetate dihydrochloride was obtained when 1-methyl-4-(beta-hydroxyethyl)homopiperazine, dissolved in benzene, was refluxed with diphenylacetyl chloride, the mixture made alkaline with sodium hydroxide solution, extracted with ether, and the ether

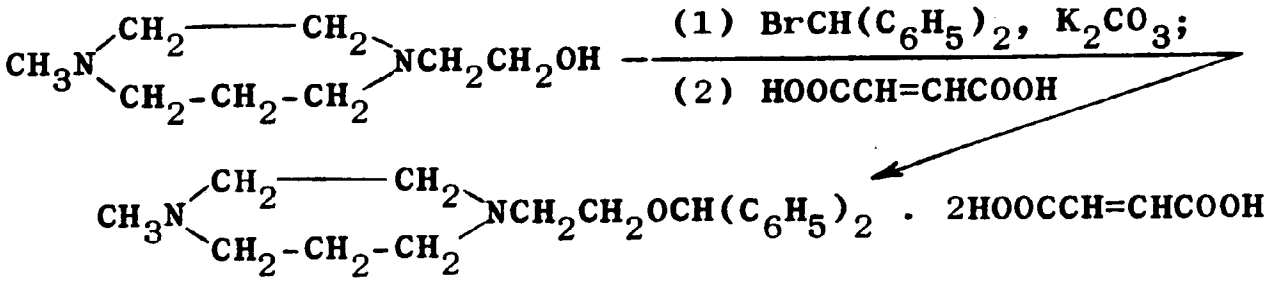
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*We used the detailed Eschweiler-Clarke procedure described by D. J. Cram (J. Am. Chem. Soc., 77, 3576 (1955)).

extracts treated with hydrogen chloride.



1-Methyl-4-(beta-benzhydryloxyethyl)homopiperazine dimaleate was synthesized by heating a mixture of 1-methyl-4-(beta-hydroxyethyl)homopiperazine, benzhydryl bromide and potassium carbonate. Since the hydrochloride obtained from this compound was an oil, the crystalline dimaleate was prepared.

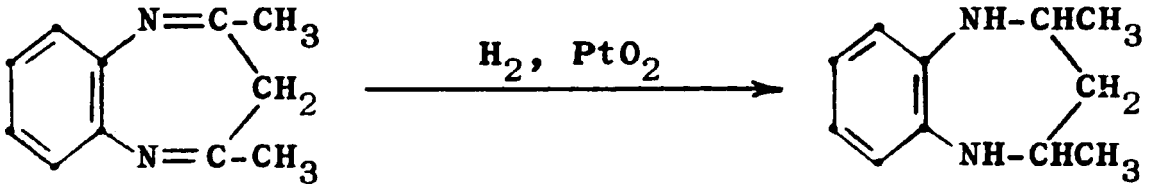


The general procedure for the debenzylation of benzyldialkylamines described by Buck and Baltzly (189) was followed in an attempt to debenzylate 1-benzylhomopiperazine. Platinum oxide catalyst was used since the authors mentioned above found this catalyst to be superior to palladized charcoal. The mixture of 1-benzylhomopiperazine, platinum oxide and glacial acetic acid was hydrogenated at 25-30° under an initial pressure of 50 pounds for 12 hours, but no hydrogen was absorbed. It was found that when the temperature was increased to 65-75° with the aid of a heating jacket, hydrogen was still not absorbed by the mixture during a 12-hour period. When

palladium-on-charcoal was used as catalyst*, the debenzylation proceeded smoothly with the formation of homopiperazine diacetate in 80% yield. The dihydrochloride and mono-dithiocarbamate derivatives of homopiperazine were also prepared.

From the discussion of the preparation of seven-membered 1,4-diaza cyclic compounds, one can conceive of several methods whereby these compounds could be utilized for the synthesis of homopiperazines. Depending upon the particular route of synthesis chosen, one could possibly arrive at a product substituted in almost any desired position.

We found that 5,7-dimethyl-2,3-benzo-1,4-diazacycloheptatriene-2,4,7** could be successfully hydrogenated to the corresponding homopiperazine:***



However, we were unable to effect hydrogenation of 5-methyl-2,3-benzo-1,4-diazacycloheptadiene-2,4-one-7**** under

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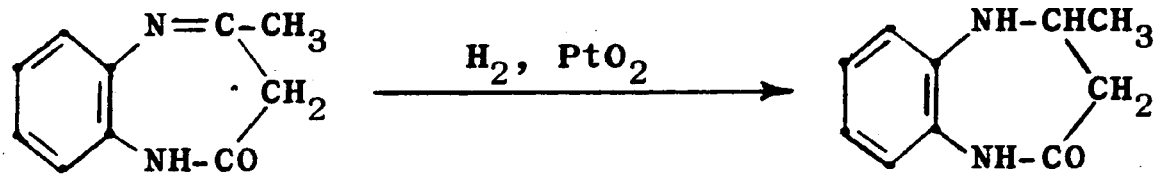
*L. Birkofer (Ber., 75, 429 (1942)), in a study of the hydrogenolysis of benzyl compounds, debenzylated 1,4-dibenzylpiperazine using palladium oxide in glacial acetic acid and obtained a 92% yield of piperazine diacetate. In a later article, R. Baltzly (J. Am. Chem. Soc., 66, 263 (1944) suggested that the debenzylation of 1-benzylpiperazine derivatives could best be accomplished by the use of palladized charcoal catalyst. W. S. Ide, E. Lorz and R. Baltzly (ibid., 77, 3142 (1955)) prepared 1-(beta-diphenylethyl)piperazine by the debenzylation of 1-(beta-diphenylethyl)-4-benzylpiperazine (no details were given).

**This compound was prepared by the method of J. Thiele and G. Steimmig, Ber., 40, 955 (1907).

***This compound was prepared according to the method of W. A. Sexton, J. Chem. Soc., 303 (1942).

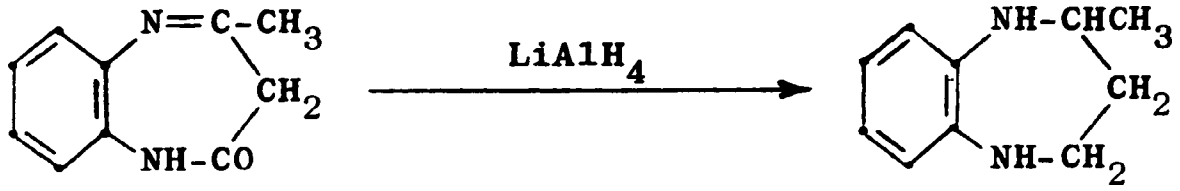
****For purposes of this discussion, this type of compound is called a homopiperazine, although in the strictest sense it is a 2,3-benzo-1,4-diazacycloheptene-2.

the same and under other conditions to the desired homopiperazinone:

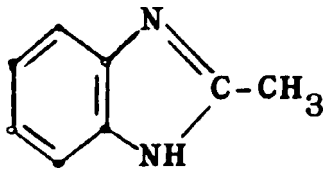


If this product had been obtained, it was our intention to reduce this homopiperazinone to the corresponding homopiperazine with lithium aluminum hydride; this reaction has been carried out successfully during this investigation with analagous products obtained from the Schmidt reaction on piperidones (see Experimental Part).

Since lithium aluminum hydride will also reduce the C=N double bond, we then attempted to reduce 5-methyl-1,4-diazacycloheptadiene-2,4-one-7 to the corresponding homopiperazine directly:



This reaction gave, however, a product which was found to be 2-methylbenzimidazole and not the expected homopiperazine.

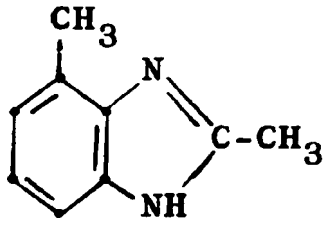


2-Methylbenzimidazole

The first mention of 2-methylbenzimidazole in the literature was made by Hübner and Rudolph (190), who prepared the compound by the action of zinc and acetic acid on o-nitro-

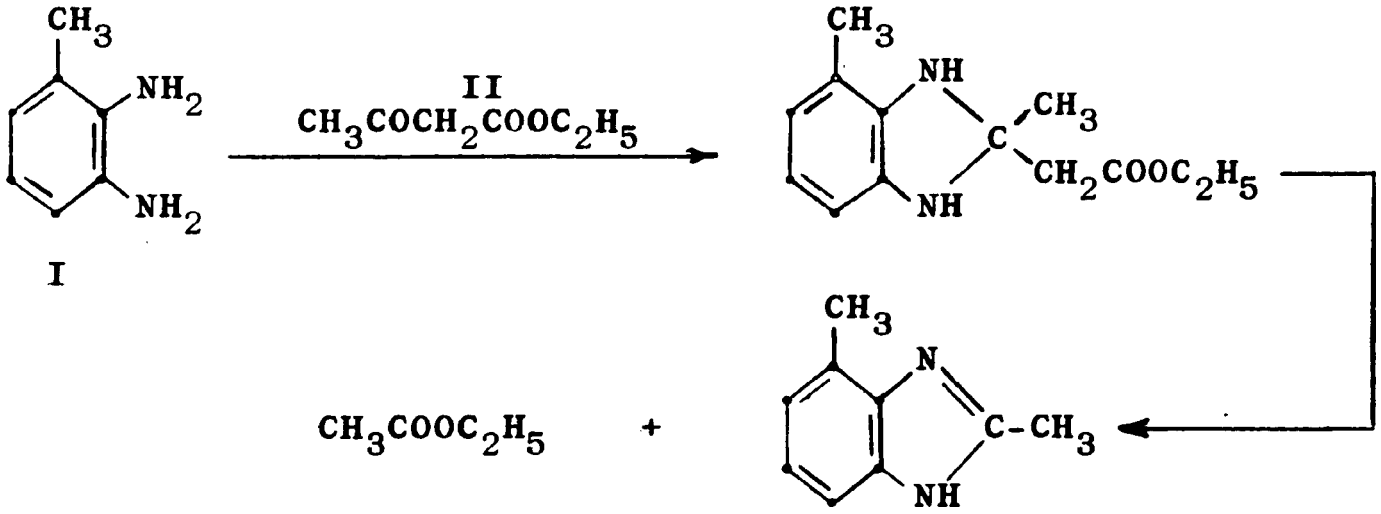
acetanilide. A more direct and simpler synthesis of 2-methylbenzimidazole, or ethenylphenylenediamine as it was also called, was described by Ladenberg (191), who prepared this compound by heating a mixture of acetic acid and o-phenylenediamine. Even today, this procedure appears to be the easiest method of preparation for 2-methylbenzimidazole.

Ladenberg continued his studies of similar reactions of diamines, and later (192) prepared what he called "aethenyltoluylenediamine", more precisely named today as 2,4-dimethylbenzimidazole.



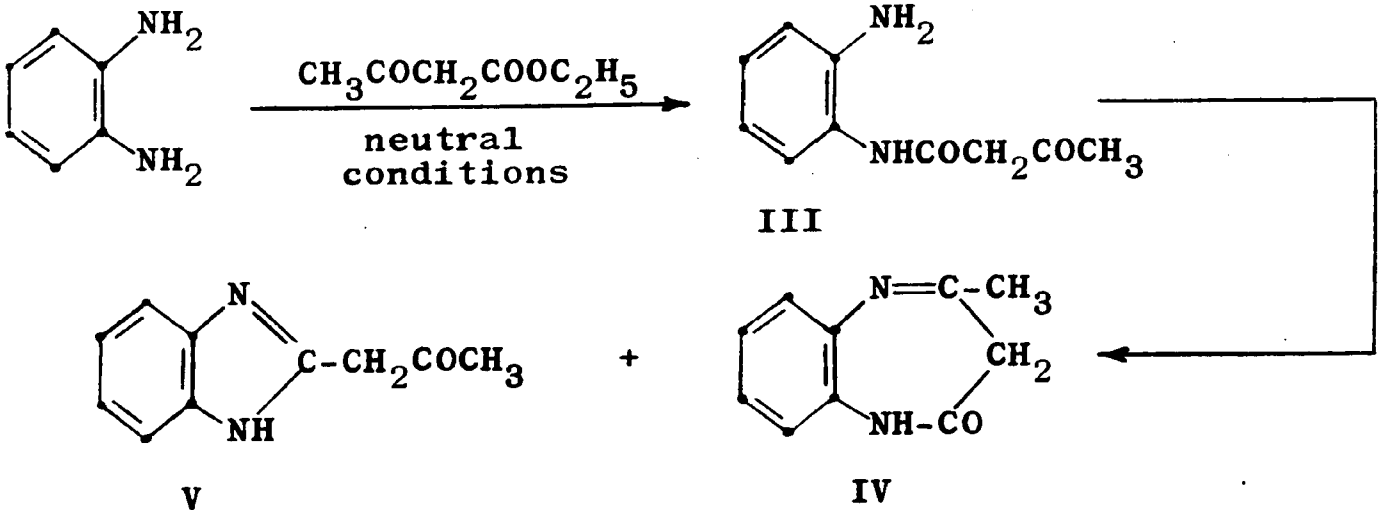
2,4-Dimethylbenzimidazole

Since he obtained this compound and ethyl acetate by heating o-toluylenediamine (I) with ethyl acetoacetate (II), he proposed the following reaction sequence:

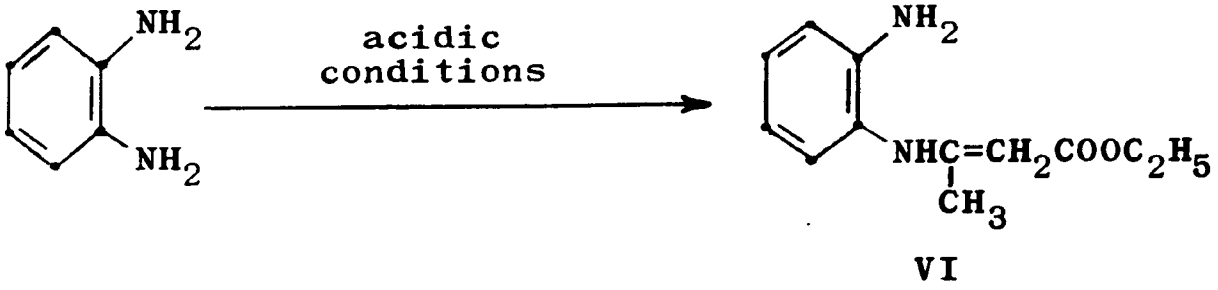


After an investigation of the same reaction, Sexton (177) proposed a somewhat different intermediate for the reaction.

In the reaction of o-phenylenediamine with ethyl acetoacetate, Sexton concluded that, under neutral conditions (i.e. without acid catalysis), the reaction proceeded through acetoacet-o-aminoanilide (III), which then cyclized under the conditions of the condensation to give a 73% yield of 5-methyl-2,3-benzo-1,4-diazacycloheptene-4-one-7 (IV) and benzimidazole-2-acetone (V) in 13% yield.



Sexton found that when the same reaction was carried out under acidic conditions, ethyl beta-2-aminoanilinocrotonate (VI) was obtained as the initial product. Attempts to cyclize

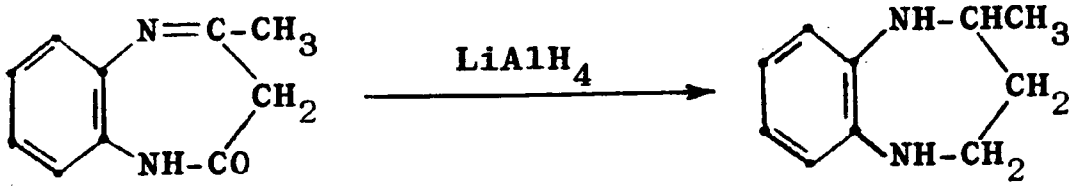


VI

VI resulted only in the formation of 2-methylbenzimidazole.

In view of the good yield of IV obtained by Sexton, we prepared compound IV by his method and found that it had the melting point which he reported. The analytical data for carbon and hydrogen which we obtained corresponded to those cal-

culated for IV. This product was then reduced with lithium aluminum hydride in the expectation that the benzohomopiperazine (VII) would be obtained. After reduction of IV, analysis



IV VII

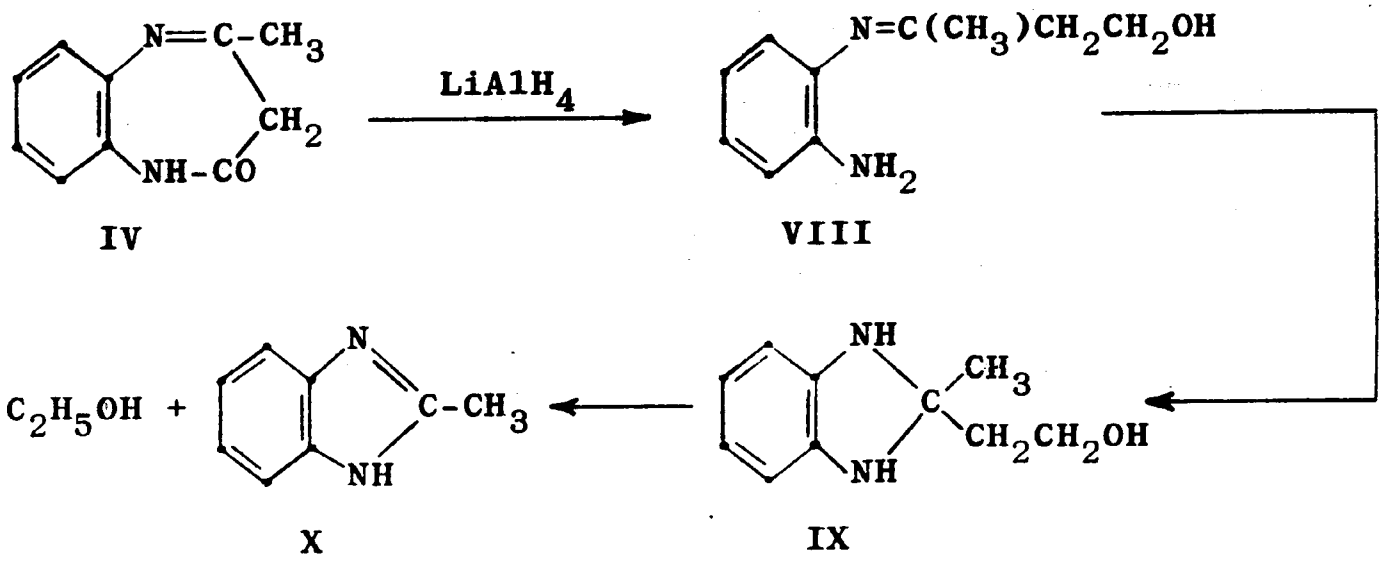
of the reaction product, which melted at 173-174°, indicated that the expected benzohomopiperazine (VII) had not been obtained. The analytical data for the product corresponded to those calculated for a methylbenzimidazole.

The reaction product was converted into a hydrochloride and a complete analysis (carbon, hydrogen, nitrogen and chlorine) was obtained for this salt. From the analytical data, the empirical formula was determined to be $C_8H_9N_2Cl$, a formula which corresponds to that of a methylbenzimidazole hydrochloride. As will be shown below, the only methylbenzimidazole which might be obtained from the reaction under discussion would be 2-methylbenzimidazole. The melting points reported in the literature for this substance range from 170° (190) to 175°, but the melting point reported most frequently is 175° (193).

Although 2-methylbenzimidazole hydrochloride has been mentioned in the literature (190), neither a melting point nor an analysis was reported. We found that the hydrochloride melted above 280°.

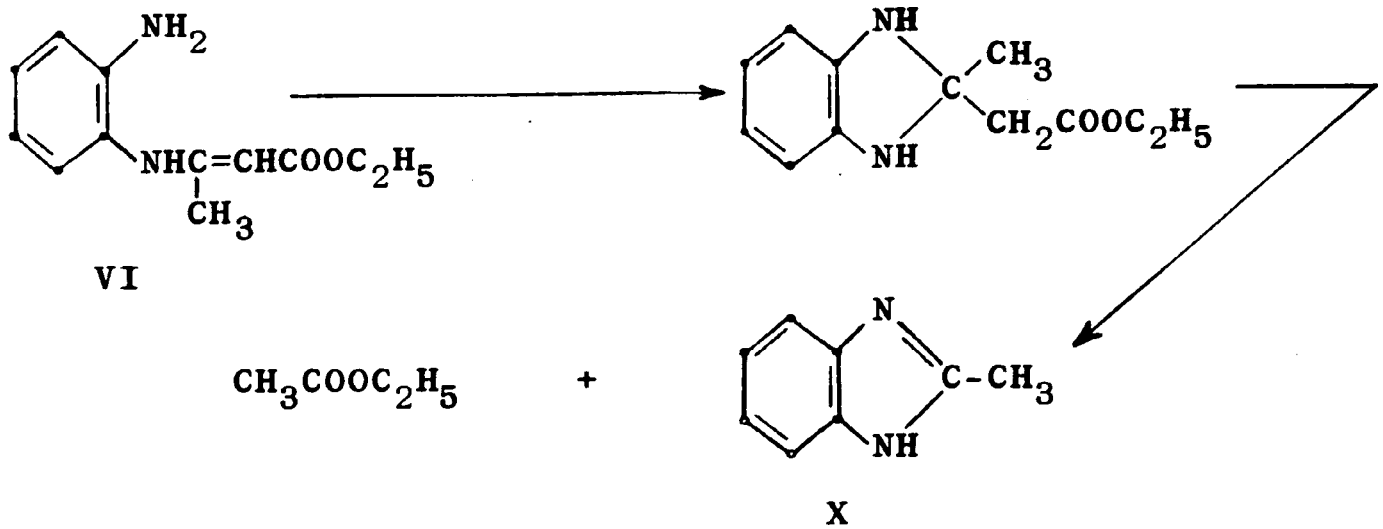
The formation of 2-methylbenzimidazole by the reaction

of IV with lithium aluminum hydride may be accounted for by the following sequence of reactions.



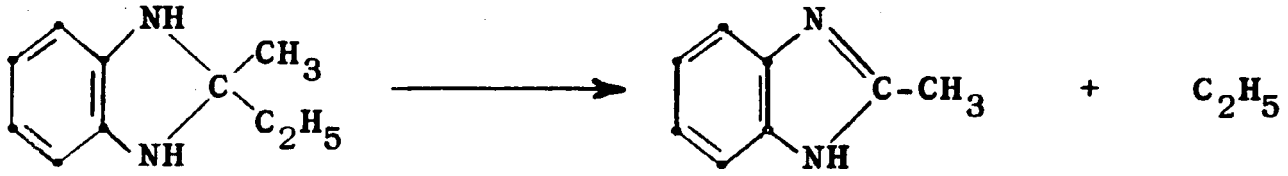
IV VIII X IX

The formation of VIII from IV is a type of reaction which has been encountered in the reduction of amides and lactams with lithium aluminum hydride (194). An example of a cyclization which is closely analagous to the cyclization of VIII to IX is shown below (177).

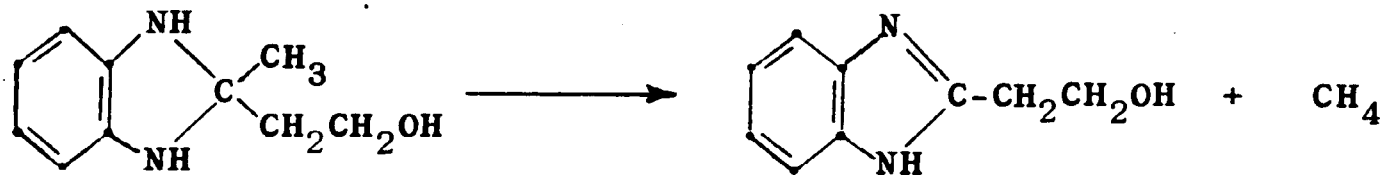


VI X

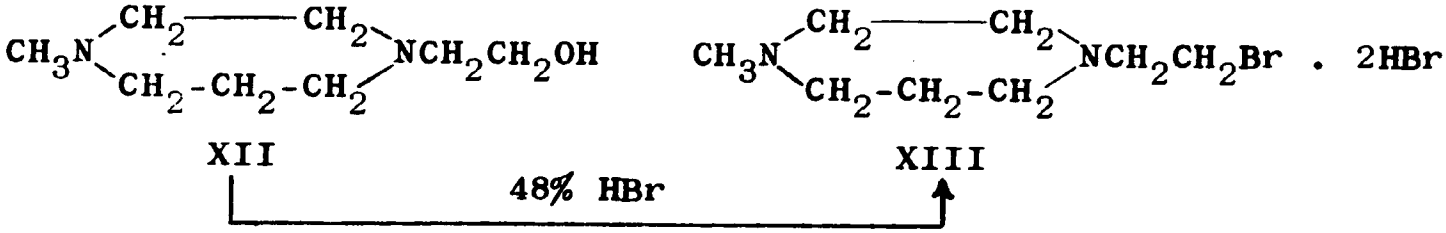
Other conversions of benzimidazolines to benzimidazoles, entirely similar to the conversion of IX into X, are to be found in the literature, for example the conversion of 2-methyl-2-ethylbenzimidazoline into 2-methylbenzimidazole and ethane (195).



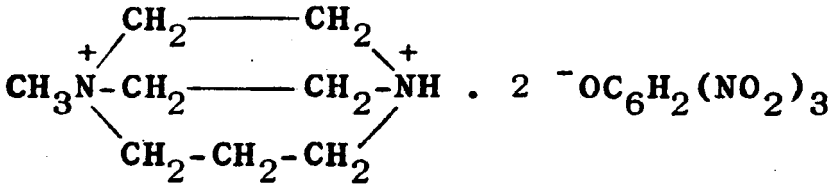
After a thorough study of reactions of this type, Elderfield and McCarthy (195) proposed the generalization that "in the elimination of a substituent from the 2 position of a 1,2-dihydro nitrogen-carbon grouping in a heterocycle to form an azomethine linkage, the carbon-carbon bond which is broken is the one proceeding from the carbon atom having the greater degree of substitution". Thus, IX would yield X and ethanol, rather than the alternative possibility as illustrated by the following equation.



1-Methyl-4-(beta-hydroxyethyl)homopiperazine (XII) was converted into 1-methyl-4-(beta-bromoethyl)homopiperazine dihydrobromide (XIII) by treatment with hydrobromic acid.

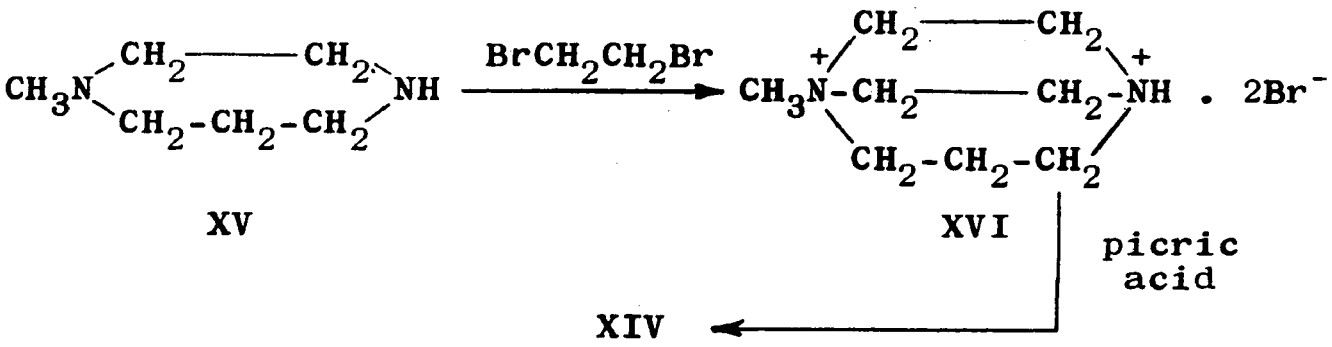


The free base was liberated from the dihydrobromide with ammonium hydroxide; when the solution of the base in ammonium hydroxide was refluxed, the base cyclized to 1,5-diazabicyclo-[3.2.2]nonane methobromide which was isolated as the picrate methopicrate (XIV). This compound was also prepared in the



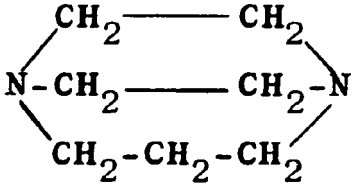
XIV

following manner. 1-Methylhomopiperazine (XV) was treated with ethylene dibromide and the reaction product, 1,5-diazabicyclo[3.2.2]nonane methobromide hydrobromide (XVI), was isolated but it could not be obtained in a pure form. After the addition of an aqueous solution of picric acid to XVI, it was found possible to isolate a sample of the picrate methopicrate (XIV) which was almost analytically pure.

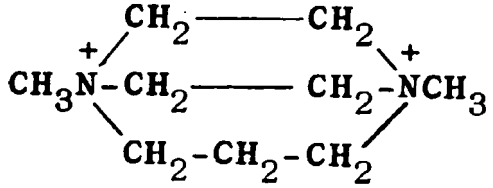


XV XVI XIV

Several syntheses, similar to those just mentioned, have been described in the literature. Pyrolysis of 1-(beta-bromoethyl)homopiperazine dihydrobromide yielded 1,5-diazabicyclo-[3.2.2]nonane dihydrobromide (XVII) which was isolated as the dihydrochloride (1,4-ethylenehomopiperazine dihydrochloride) (9), and when 1,4-dimethylhomopiperazine was heated with ethylene dibromide, 1,5-diazabicyclo[3.2.2]nonane dimethobromide



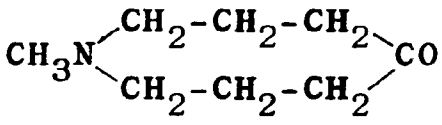
XVII



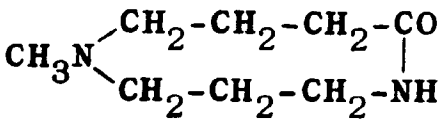
XVIII

(XVIII) was obtained (9).

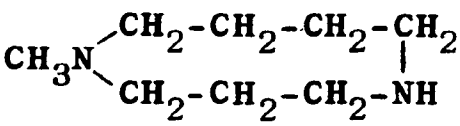
An unsuccessful attempt was made to prepare a larger ring analog of 4-piperidone, namely 5-methyl-5-azacyclooctanone (XIX). If this compound had been obtained, it was intended to subject it to a Schmidt reaction in the hope that the lactam (XX) would be formed. Reduction of this substance with lithium aluminum hydride would be expected to yield 1-methyl-1,5-diazacyclononane (XXI).



XIX

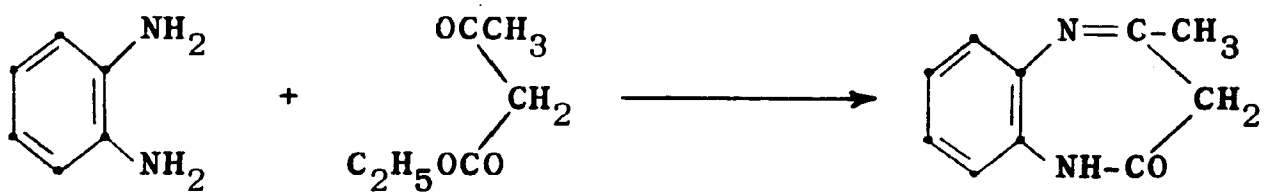


XX

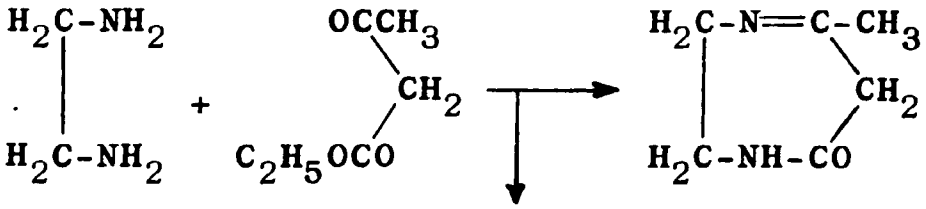


XXI

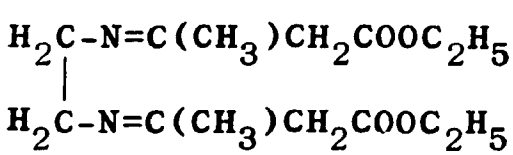
Since Sexton (177) had found that o-phenylenediamine reacted with ethyl acetoacetate to form 5-methyl-2,3-benzo-1,4-diazacycloheptadiene-2,4-one-7, we allowed ethylenediamine to react with ethyl acetoacetate, under the same conditions, in the expectation that 5-methyl-1,4-diazacycloheptene-4-one-7 would be obtained. However, instead of this product, 1,8-dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6 was isolated.



5-Methyl-2,3-benzo-1,4-diazacycloheptene-4-one-7



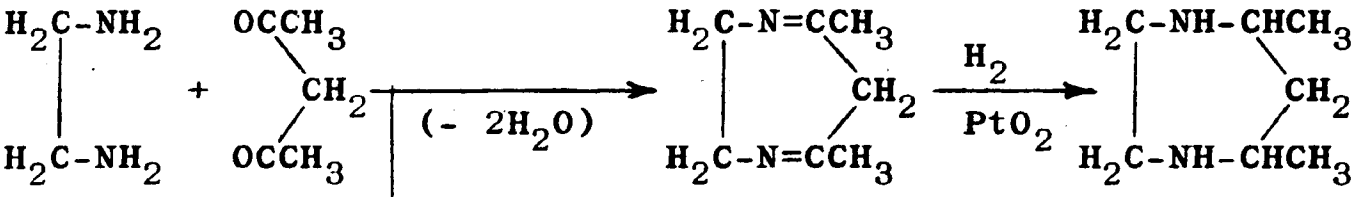
5-Methyl-1,4-diazacycloheptene-4-one-7



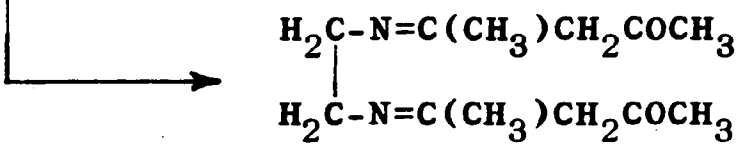
1,8-Dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6

Quite recently, Reid and Höhne (180) stated that they obtained 5-methyl-1,4-diazacycloheptene-4-one-7 in 74.5% yield by heating ethylenediamine with ethyl acetoacetate in acetic acid solution.

It was expected that acetylacetone and ethylenediamine might react to form 5,7-dimethyl-1,4-diazacycloheptadiene-4,7 which might then be hydrogenated to 5,7-dimethylhomopiperazine. However, instead of the cyclic product, 4,9-dimethyl-



5,7-Dimethyl-1,4-diazacycloheptadiene-4,7



4,9-Dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8

2,11-diketo-5,8-diazadodecadiene-4,8 was produced.

After this experiment had been completed, we found that Schwarzenbach and Lutz (179) had heated acetylacetone and ethylenediamine without removal of the water formed during the reaction, and had obtained the same compound isolated by us*. When we carried out this experiment, the acetylacetone

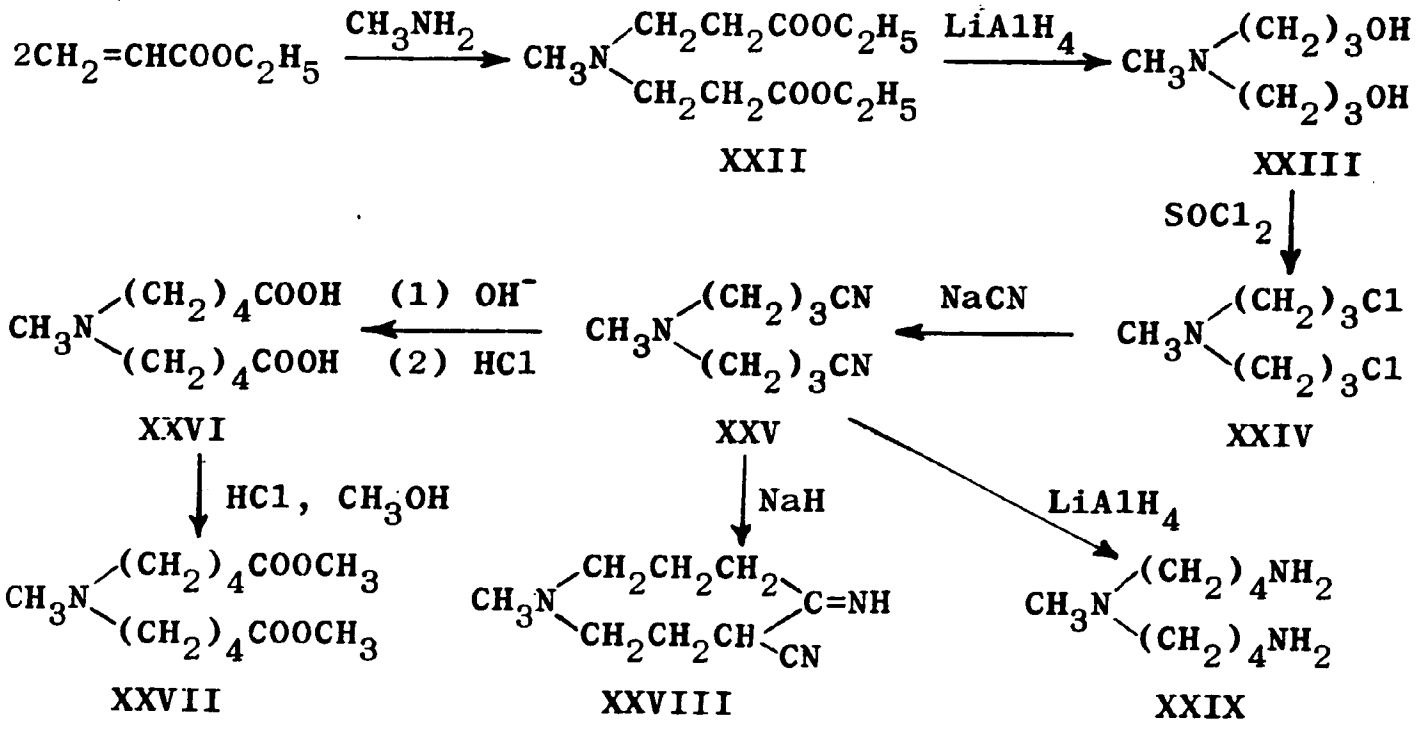
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*4,9-Dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8 was also prepared from acetylacetone and ethylenediamine by A. Entdecker and C. Combes (Compt. rend., 108, 1252 (1889)) and by L. Rügheimer (Ber., 47, 2764 (1914)). The first mentioned investigators called the reaction product beta,beta-ethylenediiminodipropyl methyl ketone.

and ethylenediamine were heated in a flask from which the water was removed as fast as it was formed and was collected in a Barrett trap (a modified Dean-Stark water trap).

By a slight change in the experimental procedure, Schwarzenbach and Lutz were able to isolate a small amount of the desired 5,7-dimethyl-1,4-diazacycloheptadiene-4,7* in the form of a perchlorate.

Ethyl acryalte and methylamine were allowed to react to form methyldi(beta-carbethoxyethyl)amine (XXII) (196). This



product was treated with lithium aluminum hydride whereupon methyldi(gamma-hydroxypropyl)amine (XXIII) was obtained**.

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*Since Schwarzenbach and Lutz (Ref. 179) numbered the ring system in a different manner, they named the product 2,7-dimethyl-3,6-diazacycloheptadiene-1,6.

**This product, although it is a known substance (J. von Braun and O. Braunsdorff, Ber., 54, 685 (1921)), had not been obtained hitherto by this process.

By the use of thionyl chloride, XXIII was converted into methyldi(gamma-chloropropyl)amine (XXIV) which reacted with sodium cyanide to form methyldi(gamma-cyanopropyl)amine (XXV). The last mentioned compound was hydrolyzed with alkali to the acid (XXVI) which, without isolation, was esterified with methanol and hydrogen chloride to form the ester XXVII. Attempts to convert the ester (XXVII), by a Dieckmann cyclization, followed by hydrolysis and decarboxylation, into the cyclic ketone (XIX) failed even though in one experiment high dilution technique (197) was employed*.

An unsuccessful effort was made next to cyclize the dinitrile (XXV) to 1-methyl-4-cyano-5-iminoheptamethylenimine (XXVIII). The attempted cyclization was carried out by the use of sodium hydride and high dilution technique (197). Many cyclizations of nitriles similar to XXV have been carried out by Ziegler and others who used as condensation agents such substances as lithium N-ethylaniline (198), sodium ethoxide (199), sodium N-ethylaniline (200), and ethyl sodiumcyanoacetate (201). As far as we are aware, no other investigator has employed sodium hydride.

The dinitrile (XXV) was reduced with lithium aluminum hydride to methyldi(delta-aminobutyl)amine (XXIX). It was hoped that the monohydrochloride of this amine could be pyrolyzed, with the evolution of ammonia, to yield 1-methyl-1,6-diazacyclodecane hydrochloride. Only products of undetermined nature were obtained from this reaction.

EXPERIMENTAL PART

Preparation of 1-Methyl-, 1-Ethyl- and 1-Benzylhomopiperazine

Methyldi(beta-carbethoxyethyl)amine.- This compound was obtained in the manner described by R. Mozingo and J. H. McCracken in Organic Syntheses, 20, 35 (1940).

1-Methyl-4-piperidone.- The process described below is the same as that used by S. M. McElvain (J. Am. Chem. Soc., 70, 1822 (1948)) except that we did not isolate the 1-methyl-3-carbethoxy-4-piperidone.

Three liters of dry benzene was placed in a 5-liter flask which was then flushed with dry nitrogen. Sodium hydride (84 g.) and 60 g. of glass beads were added and the stirred suspension was refluxed. Methyldi(beta-carbethoxyethyl)amine (25 g.) and ethanol (3 ml.) were mixed and added in one portion to initiate the reaction. After the reaction had subsided, the remainder of the diester (333 g.) was added, dropwise, at such a rate that the mixture refluxed. After the material had been refluxed for 3 hours, the mixture was cooled to 0° in an ice-bath, glacial acetic acid (210 g.) was added, and the mixture was stirred for one-half hour. Water (192 ml.) was added to precipitate sodium acetate trihydrate, and a few crystals of this salt were added to induce crystallization. The mixture was stirred for one hour, then filtered to remove the salts. The filtrate was extracted with a solution of 200 ml. of hydrochloric acid in 500 ml. of water, then 3 times with

equal portions of a solution of 150 ml. of hydrochloric acid in 250 ml. of water. To the combined extracts there was added 1500 ml. of hydrochloric acid; the mixture was refluxed until a negative test with ferric chloride solution was obtained. The water was removed on a steam-bath under reduced pressure, leaving the hydrochloride salt. The salt was dissolved in a minimum amount of water, the solution was made alkaline with 50% sodium hydroxide solution, and extracted with a total of 3 liters of chloroform. The chloroform extracts were washed with 100 ml. of water, dried over anhydrous sodium sulfate and then distilled. The product distilled at 64-120° (15 mm.); upon redistillation, the fraction which boiled at 63-73° (13 mm.) was collected; yield 420 g. (63%).

1-Methyl-5-homopiperazinone.- To 86 g. (0.75 mole) of 1-methyl-4-piperidone in a 3-liter beaker which was cooled in an ice-bath, there was added, gradually, 250 ml. of concentrated sulfuric acid. After the addition of 500 ml. of chloroform, the mixture was stirred and 75 g. (1.13 moles) of sodium azide was added, in portions, as fast as the evolution of nitrogen would permit. After addition was completed, the mixture was allowed to come to room temperature and then was stirred for an additional 4 hours. While the temperature of the mixture was kept below 40° by the use of an ice-bath, a solution of 370 g. of sodium hydroxide in 500 ml. of water was added, dropwise. The mixture was extracted with four 500 ml. portions of chloroform, the chloroform layer was separated and the water was evaporated from the aqueous layer.

The residual salts were washed thoroughly with three 200 ml. portions of chloroform, the chloroform solutions were combined with the chloroform extracts and dried over sodium sulfate. The chloroform was removed on a steam-bath; the residue weighed 91 g. (95%)*. After 4 recrystallizations from n-heptane, the product melted at 83.5-84.5°.

Anal. Calcd. for $C_6H_{12}ON_2$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.16; H, 9.30; N, 21.66.

1-Methylhomopiperazine and Dipicrate.- 1-Methyl-5-homopiperazinone (62 g.) was suspended in one liter of anhydrous ether and the suspension was added*** as rapidly as the reaction would permit to 24 g. of lithium aluminum hydride suspended in one liter of ether. The mixture was refluxed for 6 hours, stirred for 12 hours at room temperature, and then treated with 48 ml. of water. After the mixture had been stirred for an additional 2 hours, it was filtered, the filtrate was dried over anhydrous sodium sulfate, and the ether was removed on a steam-bath. The product distilled at 60-65° (30 mm.)** ; yield 41 g. (74%).

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*S. C. Dickerman and H. G. Lindwall (J. Org. Chem., 14, 534 (1949)), who used essentially the same procedure, obtained the pure product in 53% yield; m.p. 83-84°.

**After this experiment had been completed, the preparation of this compound was described by A. H. Sommers, R. J. Michaels, Jr. and A. H. Weston, J. Am. Chem. Soc., 76, 5805 (1954). They found the boiling point to be 74-75° (35 mm.); their yield was 49%.

***The 1-methyl-5-homopiperazinone was placed in a dropping funnel fitted with a wide-bore stopcock, the ether was added and the mixture swirled with a stirring rod throughout the addition to prevent clogging of the stopcock aperture.

1-Methylhomopiperazine dipicrate was made by the addition of a solution of picric acid in ether to a solution of 1-methylhomopiperazine in the same solvent. This dipicrate melted at 233-234° after two recrystallizations from water.

Anal. Calcd. for $C_{18}H_{20}O_{14}N_8$: C, 37.77; H, 3.52; N, 19.58. Found: C, 37.70; H, 3.47; N, 19.48.

1-Methylhomopiperazine Dihydrogen Citrate (JGS-113).- To 1-methylhomopiperazine (5.7 g.) dissolved in 45 ml. of acetone there was added, while the solution was stirred, 10.5 g. of citric acid dissolved in 100 ml. of acetone. After evaporation of the acetone under an air stream, the solid residue was oven-dried at 50° for 8 hours. After two recrystallizations from absolute ethanol, the dried compound melted at 164-166°.

Anal. Calcd. for $C_{12}H_{22}O_7N_2$: C, 47.05; H, 7.24; N, 9.14. Found: C, 46.80; H, 7.10; N, 9.03.

Ethyldi(beta-carbethoxyethyl)amine.- This compound was obtained by the procedure described by N. W. Bolyard and S. M. McElvain, J. Am. Chem. Soc., 51, 922 (1929).

1-Ethyl-4-piperidone.- The procedure used to obtain this compound from ethyldi(beta-carbethoxyethyl)amine was the same as that used in the preparation of 1-methyl-4-piperidone from methyldi(beta-carbethoxyethyl)amine; b.p. 66-68° (12 mm.)*; yield 41%.

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*N. W. Bolyard and S. M. McElvain (J. Am. Chem. Soc., 51, 922 (1929)) obtained 1-ethyl-4-piperidone from ethyldi-(beta-carbethoxyethyl)amine by a similar procedure; they did not report a boiling point but stated that the hydrochloride melted at 105-106°; yield 70%.

1-Ethyl-5-homopiperazinone Picrate.- 1-Ethyl-4-piperidone (67.0 g., 0.4 mole) and 240 ml. of concentrated sulfuric acid were placed in a 1-liter flask, stirred, and, during a period of 4 hours, 40.0 g. (0.6 mole) of sodium azide was added in portions. After the mixture had been stirred for 12 hours at room temperature, it was heated at 50-60° for 4 hours, cooled to 0° and made alkaline with 50% sodium hydroxide solution. The mixture was extracted four times with 300 ml. portions of chloroform, the combined extracts were dried over anhydrous sodium sulfate and the solvent was removed. The product, a dark oil, was dissolved in hot n-heptane; tan crystals separated from the cold solution which melted at 74-76°; yield 40.5 g. (57%).

The product was dissolved in water and treated with a saturated aqueous solution of picric acid; the precipitated picrate was recrystallized from methanol; m.p. 173-175°.

Anal. Calcd. for $C_{13}H_{17}O_8N_5$: C, 42.05; H, 4.62; N, 18.87. Found: C, 42.44; H, 4.76; N, 18.84.

1-Ethylhomopiperazine Dihydrochloride.- 1-Ethyl-5-homopiperazinone (40.5 g.) was placed in a modified Soxhlet extractor* which was connected to a flask which contained 12.4 g. of lithium aluminum hydride suspended in 500 ml. of ether. The mixture was stirred and refluxed for 36 hours. After the dropwise addition of 25 ml. of water to the stirred mixture, it

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*The siphon tube was removed and a new connection was made in such a manner that the liquid which dropped from the condensor could not accumulate in the extractor but dropped immediately into the reaction mixture.

was stirred for an additional hour and then filtered. The filtrate was dried over anhydrous magnesium sulfate, the ether was removed and the product was distilled; b.p. 70-76° (15 mm.); yield 29.5 g. (77%).

The product was dissolved in ether and treated with an ethereal solution of hydrogen chloride whereupon the dihydrochloride precipitated; m.p. 202-204° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_7H_{18}N_2Cl_2$: N, 13.93; Cl, 35.26. Found: N, 13.84; Cl, 35.33.

Benzyldi(beta-carbethoxyethyl)amine.- This amine was prepared by the general method used for the synthesis of methyldi(beta-carbethoxyethyl)amine. Benzyldi(beta-carbethoxy)amine has been reported in the literature (202, 203). From 366 g. of benzylamine and 740 ml. of ethyl acrylate we obtained 912 g. (95%) of product; b.p. 160-170° (0.07 mm.)*.

1-Benzyl-4-piperidone.- This compound was prepared by a Dieckmann cyclization according to the general process which has already been described. This piperidone was described previously by investigators (182) who hydrolyzed and decarboxylated 1-benzyl-3-carbethoxy-4-piperidone which had been obtained earlier by other investigators (202).

From 439 g. of benzyldi(beta-carbethoxyethyl)amine we obtained 126 g. (48%) of product; b.p. 125-130° (0.5 mm.)**

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*Ref. 202, b.p. 181-183° (2 mm.); Ref. 203, b.p. 165-172° (1 mm.); yield 84%.

**Ref. 182, b.p. 114-116° (0.3 mm.); the yield was not reported.

1-Benzyl-5-homopiperazinone.- This compound was prepared in the same manner as 1-methyl-5-homopiperazinone.

From 18.1 g. of 1-benzyl-4-piperidone, 60 ml. of concentrated sulfuric acid and 10 g. of sodium azide, 18.2 g. (89%) of product was obtained. The pale yellow crystals melted at 118-120° after recrystallization from benzene-isopropyl ether.

After this experiment had been completed, the preparation of the product, by essentially the same method, was reported by other investigators (183). They obtained the homopiperazinone in 74% yield and found the melting point to be 128-129°.

1-Benzylhomopiperazine Dihydrochloride (JGS-219).- 1-Benzyl-5-homopiperazinone (64.0 g.) was reduced with 18.0 g. of lithium aluminum hydride in 500 ml. of ether in the same manner as the 1-methyl compound. The crude product was distilled; b.p. 165-175° (15 mm.); yield 39.0 g. The dark, oily residue obtained after distillation was dissolved in 50 ml. of hot benzene and diisopropyl ether was added until the solution became cloudy. From the cold mixture, 6.4 g. of unreacted 1-benzyl-5-homopiperazinone separated. The yield of the homopiperazine, based on the amount of material which had reacted, was 89%.

The dihydrochloride precipitated when ethereal hydrogen chloride was added to the base dissolved in ether; m.p. 198-199° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{12}H_{20}N_2Cl_2$: N, 10.64; Cl, 27.37. Found: N, 10.38; Cl, 27.20.

1-Benzyl-5-homopiperazinone has been reduced by lithium

aluminum hydride with the use of tetrahydrofuran as a solvent (183). The product was obtained as a yellow oil in 94% yield. The oxalate and the picrate were prepared (183).

Preparation of 1-Methyl- and 1-Benzyl-4-substituted Homopiperazines

1-Methyl-4-formylhomopiperazine.- 1-Methylhomopiperazine (11.4 g., 0.1 mole), dissolved in 50 ml. of chloroform, was placed in a flask equipped with a stirrer, dropping funnel and a reflux condenser to which a calcium chloride tube was attached. The solution was stirred, cooled in an ice-bath and 14.7 g. (0.1 mole) of chloral*, dissolved in 50 ml. of chloroform, was added, dropwise. The mixture was refluxed for 2 hours and then distilled; yield 11.5 g. (81%); b.p. 133-135° (14 mm.).

Anal. Calcd. for $C_7H_{14}ON_2$: C, 59.12; H, 9.92. Found: C, 59.10; H, 9.64.

1,4-Dimethylhomopiperazine Dimethobromide (JGS-214).- 1-Methyl-4-formylhomopiperazine (11.5 g., 0.081 mole), dissolved in 50 ml. of ether, was added, dropwise, to 5.0 g. of lithium aluminum hydride suspended in 75 ml. of ether which had been placed in a flask equipped with a Hirschberg stirrer and a reflux condenser. After the material had been stirred and refluxed for 12 hours, 10 ml. of water was added, dropwise, and the mixture was stirred for an additional 2 hours. It

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*See F. F. Blicke and Chi-Jung Lu, J. Am. Chem. Soc., 74, 3933 (1952).

was then filtered and the filtrate was dried over anhydrous sodium sulfate. Upon distillation, 8.0 g. (80%) of product was obtained; b.p. 162-164° (745 mm.)*.

To 1.28 g. of 1,4-dimethylhomopiperazine, dissolved in 50 ml. of isopropyl alcohol, and placed in a pressure bottle, there was added a three-fold excess of methyl bromide. After 12 hours at room temperature, the precipitate was filtered and recrystallized from dilute ethanol; m.p. 277-278° (dec.)**; yield 2.9 g. (91%).

Anal. Calcd. for $C_9H_{22}N_2Br_2$: N, 8.81 Br, 50.26. Found: N, 8.89; Br, 50.24.

1-Methyl-4-(beta-dimethylaminoethyl)homopiperazine Trimaleate (JGS-130).- beta-Dimethylaminoethyl chloride was liberated (204) from its hydrochloride salt and dried over magnesium sulfate. To a stirred mixture of 4.5 g. of 1-methylhomopiperazine, 200 ml. of benzene and 3.5 g. of pyridine, there was added 4.8 g. of beta-dimethylaminoethyl chloride, dropwise. The reaction mixture was refluxed and stirred for 12 hours, filtered and the benzene was removed from the filtrate. The product boiled at 180-185° (745 mm.); yield 5.0 g. (69%). The trimaleate was prepared in ethereal solution; m.p. 155-156.5° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{22}H_{35}O_{12}N_3$: C, 49.53; H, 6.61. Found: C, 49.58; H, 6.46.

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*Ref. 9, b.p. 158-161° (738 mm.).

**Ref. 9, m.p. 286-286.5° (dec.).

1-Methyl-4-carbethoxyhomopiperazine (JGS-158) and Oxalate.- 1-Methylhomopiperazine (5.7 g., 0.05 mole) was dissolved in 20 ml. of absolute ethanol, the solution was stirred and 8.4 g. (0.1 mole) of anhydrous sodium bicarbonate was added. This was followed by the dropwise addition of 5.5 g. (0.05 mole) of ethyl chlorocarbonate at a rate such that the temperature did not exceed 50°. The mixture was refluxed for 2 hours, filtered and the ethanol was removed under reduced pressure; b.p. 130-135° (20 mm.); yield 8.0 g. (85%).

Anal. Calcd. for $C_9H_{18}O_2N_2$: C, 58.03; H, 9.74. Found: C, 57.78; H, 9.68.

The oxalate was prepared in ethereal solution and recrystallized from acetone; m.p. 97.5-98.5°.

Anal. Calcd. for $C_{11}H_{20}O_6N_2$: C, 47.82; H, 7.30. Found: C, 47.72; H, 7.08.

1-Methyl-4-diphenylcarbamylhomopiperazine Hydrochloride (JGS-108).- 1-Methylhomopiperazine (3.8 g.) was dissolved in 50 ml. of benzene and added, dropwise, to a refluxing, stirred solution of diphenylcarbamyl chloride (7.3 g.) in 50 ml. of benzene. After refluxing for one hour, the benzene was removed in vacuo, and the residue was recrystallized from acetone-ethanol; m.p. 187-189°; yield 3.8 g. (34%). Analysis showed that the product contained one-half of a molecular equivalent of ethanol of recrystallization which was not removed when the product was dried in an Abderhalden apparatus over refluxing toluene.

Anal. Calcd. for $2C_{19}H_{24}ON_3Cl \cdot C_2H_5OH$: C, 65.12; H, 7.38;

Cl, 9.61. Found: C, 65.30; H, 7.17; Cl, 9.61.

1-Methyl-4-diethylcarbamylhomopiperazine Hydrochloride (JGS-110).- 1-Methyl-4-diethylcarbamylhomopiperazine hydrochloride was prepared from 1-methylhomopiperazine (7.0 g.) and diethylcarbamyl chloride (8.4 g.) by the same procedure as was used in the preparation of 1-methyl-4-diphenylcarbamylhomopiperazine hydrochloride. The product was recrystallized from ethyl acetate, then washed with ether, and dried in an Abderhalden apparatus over refluxing toluene; m.p. 124-125°; yield 7.3 g. (60%).

Anal. Calcd. for $C_{11}H_{24}ON_3Cl$: N, 16.82; Cl, 14.20. Found: N, 16.67; Cl, 14.14.

1-Methyl-4-benzhydrylhomopiperazine Dihydrochloride (JGS-112).- Benzhydryl bromide* (5.0 g.), dissolved in 25 ml. of methyl ethyl ketone, was added, dropwise, to a solution of 1-methylhomopiperazine (4.5 g.) in 25 ml. of methyl ethyl ketone. After refluxing for 1 hour, the solvent was removed and the residue was dissolved in 25 ml. of water and the solution made alkaline with 50% sodium hydroxide solution. This solution was extracted with four 100 ml. portions of ether, the extract was dried over magnesium sulfate, and, after removal of the ether by distillation, the product was distilled. The fraction which boiled at 185-192° (40 mm.) was collected; yield 3.0 g. (55%). This compound was converted into the dihydrochloride by the addition of ethereal hydrogen chloride; the

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*Prepared according to the process described by L. Claisen, Ann., 442, 245 (1925); b.p. 172-176° (14 mm.). We found the boiling point to be 183-190° (20 mm.); yield 75%.

salt was recrystallized from absolute ethanol; m.p. 234-236°.*

Anal. Calcd. for $C_{19}H_{26}N_2Cl_2$: N, 7.93; Cl, 20.07. Found: N, 7.87; Cl, 19.89.

1-Methyl-4-(para-bromobenzhydryl)homopiperazine Dihydrochloride (JGS-115).- 1-Methyl-4-(para-bromobenzhydryl)homopiperazine dihydrochloride was prepared by the same procedure used for the preparation of 1-methyl-4-benzhydrylhomopiperazine dihydrochloride. From 5.0 g. of 1-methylhomopiperazine and 6.8 g. of p-bromobenzhydryl bromide** there was obtained a product which distilled at 169-175° (0.2 mm.). By the use of ethereal hydrogen chloride, the base was converted into the dihydrochloride; m.p. 215-216° after recrystallization from ethanol; yield 7.0 g. (81%).

Anal. Calcd. for $C_{19}H_{25}N_2BrCl_2$: N, 6.48; Cl, 16.45. Found: N, 6.32; Cl, 16.54.

1-Methyl-4-diphenylacetylhomopiperazine Hydrochloride (JGS-150).- To diphenylacetyl chloride (16.1 g.) dissolved in 50 ml. of acetone, there was added 1-methylhomopiperazine (8.0 g.) dissolved in 25 ml. of acetone. The addition was carried out over a 45 minute period while the mixture was stirred and refluxed on a steam-bath; after the addition had been completed, the mixture was stirred an additional half

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*A. H. Sommers, R. J. Michaels, Jr. and A. H. Weston (J. Am. Chem. Soc., 76, 5805 (1954)) reported a boiling point of 155° (0.3 mm.); yield 41%; m.p. 235°. This report appeared after the compound had been prepared in this laboratory.

**Prepared from p-bromobenzhydrol by the method described by L. Claisen, Ann., 442, 245 (1925).

hour at room temperature. When the mixture was cooled in ice, a copious amount of white solid precipitated; m.p. 100-102° after recrystallization from acetone-isopropyl alcohol; yield 19.4 g. (81%).

Anal. Calcd. for $C_{20}H_{25}ON_2Cl$: N, 8.12; Cl, 10.28. Found: N, 8.31; Cl, 10.23.

1-Methyl-4-phenylacetylhomopiperazine Hydrochloride (JGS-149).- 1-Methyl-4-phenylacetylhomopiperazine hydrochloride was prepared by the same procedure as 1-methyl-4-diphenylacetylhomopiperazine hydrochloride, except that benzene was used as the solvent instead of acetone. From 8.0 g. of 1-methylhomopiperazine and 10.9 g. of phenylacetyl chloride, 19.0 g. (100%) of product was obtained. After four recrystallizations from isopropyl alcohol, the hydrochloride melted at 181.5-182.5°.

Anal. Calcd. for $C_{14}H_{21}ON_2Cl$: N, 10.43; Cl, 13.19. Found: N, 10.60; Cl, 13.26.

1-Methyl-4-(beta-hydroxyethyl)homopiperazine Dipicrate, Method A.- 1-Methylhomopiperazine (22.8 g., 0.2 mole), dissolved in 250 ml. of benzene, was added to 43 g. of anhydrous sodium carbonate in a 500 ml. flask equipped with paddle stirrer, reflux condenser and dropping funnel. To the refluxing mixture, a solution of ethylene bromohydrin (25 g., 0.2 mole) in 25 ml. of benzene was added, dropwise, over a 1-hour period. After the mixture had been refluxed for 12 hours on a steam-bath, it was filtered, the benzene was removed, and the product distilled; b.p. 135-140° (17 mm.); yield 15.0 g. (48%).

The dipicrate was prepared by the addition of an aqueous solution of picric acid to an aqueous solution of the product. After two recrystallizations from water, the dried dipicrate melted at 218-219°.

Anal. Calcd. for $C_{20}H_{24}O_{15}N_8$: C, 38.96; H, 3.93; N, 18.18. Found: C, 39.16; H, 3.98; N, 18.42.

1-Methyl-4-(beta-hydroxyethyl)homopiperazine Dipicrate, Method B.- A solution of 22.8 g. (0.20 mole) of 1-methylhomopiperazine in 25 ml. of methanol was stirred and maintained at 50°. Ethylene oxide (11.5 g., 0.26 mole) was placed in a distillation flask the side arm of which was bent and introduced just below the surface of the methanol solution. The oxide was allowed to distill slowly into the solution. At least 6 hours were required for the introduction of the oxide. The mixture was stirred for several hours at room temperature and then distilled; b.p. 135-145° (18 mm.); yield 15.0 g. (48%). The dipicrate melted at 217-218° after recrystallization from water; mixed m.p. 217-218°.

1-Methyl-4-(beta-benzhydryloxyethyl)homopiperazine Dimaleate (JGS-129).- A mixture of 10.0 g. of 1-methyl-4-(beta-hydroxyethyl)homopiperazine, 18.0 g. of benzhydryl bromide (205) and 8.7 g. of anhydrous potassium carbonate was stirred and heated at about 125° for 3 hours. After the reaction had begun, the heating mantle was removed until the exothermic reaction was completed. At the end of 3 hours, the reaction mixture had become so viscous that it could no longer be stirred. After the addition of 50 ml. of water, the mixture

was refluxed and stirred for 12 hours. The mixture was extracted with four 150 ml. portions of ether and the extract was dried over sodium sulfate. The product boiled at 200-215° (2 mm.); yield 13.5 g. (55%).

Upon the addition of an ethereal solution of maleic acid to the product, dissolved in ether, the dimaleate precipitated; m.p. 150-151° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{29}H_{36}O_9N_2$: C, 62.56; H, 6.52; N, 5.03. Found: C, 62.28; H, 6.50; N, 5.18.

beta-(1-Methyl-4-homopiperazinyl)ethyl para-Nitrobenzoate Hydrochloride.- p-Nitrobenzoyl chloride (6.9 g.), dissolved in 150 ml. of benzene, was added, during a 15-minute period, to a solution of 5.3 g. of 1-methyl-4-(beta-hydroxyethyl)homopiperazine in 25 ml. of benzene. The mixture was stirred for 5 hours, refluxed for 15 minutes and the benzene was then removed. The oily product was crystallized from absolute ethanol; m.p. 179-180°; yield 8.5 g. (70%).

Anal. Calcd. for $C_{15}H_{22}O_4N_3Cl$: N, 12.22; Cl, 10.31. Found: N, 12.10; Cl, 10.45.

Attempted Preparation of beta-(1-methyl-4-homopiperazinyl)-ethyl para-Aminobenzoate Hydrochloride.- A mixture of 2.0 g. of beta-(1-methyl-4-homopiperazinyl)ethyl para-nitrobenzoate hydrochloride, 25 ml. of absolute ethanol and 0.2 g. of platinum oxide catalyst was hydrogenated under an initial pressure of 50 pounds for 24 hours. At the end of this time slightly less than the calculated amount of hydrogen had been absorbed. After filtration, the solvent was removed. It was not found

possible to convert the oily residue into crystalline material. The crude, oily hydrochloride was dissolved in water, the base was liberated by the addition of sodium hydroxide and extracted with ether. Only oily precipitates were obtained by the addition of an ethereal solution of maleic or oxalic acid. However, when picric acid, dissolved in ether, was added, a crystalline precipitate formed; m.p. 208-210° (dec.) after recrystallization from dilute ethanol. The analytical data obtained for this compound did not correspond to the calculated data.

Anal. Calcd. for $C_{33}H_{32}O_{23}N_{12}$: C, 41.09; H, 3.34. Found: C, 39.46; H, 4.11.

beta-(1-Methyl-4-homopiperazinyl)ethyl Diphenylacetate Dihydrochloride (JGS-120).- To a stirred solution of diphenylacetyl chloride (4.6 g.) in 50 ml. of benzene there was added, dropwise, a solution of 1-methyl-4-(beta-hydroxyethyl)homopiperazine in 50 ml. of benzene. The mixture was refluxed for 1 hour, cooled and the benzene removed by distillation on a steam-bath. The residual yellow oil was dissolved in 20 ml. of water, the solution was made alkaline with sodium hydroxide pellets, and extracted with ether. The extracts were dried over anhydrous sodium sulfate, and ethereal hydrogen chloride added. The ether was decanted from the precipitated salt, and the precipitate washed with ether. After recrystallization from isopropyl alcohol, the crystalline solid melted at 217-220°; yield 4.5 g. (53%). After two recrystallizations from nitromethane, the product melted at 223-225° (dec.).

Anal. Calcd. for $C_{22}H_{30}O_2N_2Cl_2$: N, 6.59; Cl, 16.67. Found: N, 6.77; Cl, 16.85.

1-Methyl-4-nitrosohomopiperazine.- 1-Methylhomopiperazine (22.8 g.) was dissolved in 75 ml. of concentrated hydrochloric acid and the solution was cooled in an ice-bath. Sodium nitrite (25 g.), dissolved in 50 ml. of water, was added while the reaction mixture was stirred and heated on a steam-bath. The addition was carried out, dropwise, over a 1-hour period. The mixture was then heated for 6 hours on a steam-bath. The solution was cooled to 0°, made alkaline with a 50% sodium hydroxide solution, and extracted with four 200 ml. portions of ether. The aqueous layer was placed in a liquid-liquid extraction apparatus (206) and extracted with ether over a 36-hour period. This ether extract was combined with the initial ether extracts and dried over anhydrous sodium sulfate. Upon distillation, 24 g. (84%) of product was obtained; b.p. 155-158° (40 mm.).

Anal. Calcd. for $C_6H_{13}ON_3$: C, 50.32; H, 9.15. Found: C, 50.30; H, 8.93.

1-Methyl-4-aminohomopiperazine.- 1-Methyl-4-nitrosohomopiperazine (810 g.) was dissolved in 50 ml. of ether and the solution was added, dropwise, to a stirred suspension of 5.0 g. of lithium aluminum hydride in 150 ml. of ether. The mixture was stirred for 12 hours, 12 ml. of water was added, dropwise, to the stirred mixture and then it was stirred for 12 hours. The solid was removed by filtration and the ethereal filtrate was dried over anhydrous sodium sulfate. Upon dis-

tillation, 7.1 g. (99%) of product was obtained; b.p. 86-90° (20 mm.).

Anal. Calcd. for $C_6H_{15}N_3$: C, 55.77; H, 11.70. Found: C, 55.95; H, 11.53.

1-Methyl-4-dimethylaminohomopiperazine Dimaleate (JGS-157).- To 58.4 g. of formic acid (90%), cooled to 0° in an ice-bath, there was added, gradually, 10.0 g. of 1-methyl-4-aminohomopiperazine; 20.6 g. of formaldehyde (37%) was added and the mixture was heated on a steam-bath for 12 hours. The mixture was cooled to room temperature, 60 ml. of 15% hydrochloric acid was added and the solvent removed on a steam-bath under reduced pressure. The black, tarry residue was dissolved in water, the solution made alkaline with 40% sodium hydroxide solution, saturated with potassium carbonate, and extracted with six 300 ml. portions of ether. Extraction was difficult because of the tendency of the aqueous solution to emulsify with ether. The ether extracts were dried over anhydrous magnesium sulfate and the product distilled; the fraction which boiled below 140° (15 mm.) was collected and redistilled; b.p. 45-50° (15 mm.); yield 3.0 g. (24%). The product was precipitated as the dimaleate from an ethereal solution; m.p. 144-146° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{16}H_{27}O_8N_3$: C, 49.35; H, 6.99. Found: C, 49.38; H, 6.93.

1-Methyl-4-(beta-benzoylethyl)homopiperazine.- A mixture of 11.4 g. (0.1 mole) of 1-methylhomopiperazine, 9.5 g. of 37% formaldehyde (0.1 mole), 60 g. (0.5 mole) of acetophenone

and about 20 ml. of concentrated hydrochloric acid was refluxed for 5 minutes, and then allowed to remain at room temperature for 12 hours. The organic layer was separated from the aqueous layer, and the latter was extracted with two 100 ml. portions of ether. The aqueous portion was cooled in an ice-bath and made distinctly alkaline by the addition of sodium carbonate. This solution was then extracted four times with 100 ml. portions of ether, the ether extracts dried over sodium sulfate, and the ether removed on a steam-bath. When an attempt was made to distill the product at 0.3 mm., considerable darkening and fuming took place, apparently due to decomposition. Therefore, the product was not distilled. The hydrochloride, hydrobromide, maleate and picrate salts were obtained only as oils. The product, in the form of the base, (13.5 g.) was obtained in 55% yield. It was not analyzed.

1-Phenyl-3-(1-methyl-4-homopiperazinyl)propanol.- 1-Methyl-4-(beta-benzoylethyl)homopiperazine (12.3 g.) was dissolved in 50 ml. of ether and added, dropwise, to a stirred mixture of lithium aluminum hydride (1.9 g.) and 200 ml. of ether. The mixture was stirred for 30 hours at room temperature and 3.8 ml. of water was added, dropwise to the stirred mixture. After the mixture had been stirred for 12 hours, it was filtered, the filtrate was dried over anhydrous magnesium sulfate, and the product was distilled; b.p. 140-155° (0.35 mm.); yield 10 g. (81%). The hydrochloride was hygroscopic. The maleate was precipitated from an ethereal solution and recrystallized from absolute ethanol; m.p. 125.5-126.5°.

Anal. Calcd. for $C_{23}H_{32}O_9N_2$: C, 57.50; H, 6.71; N, 5.83. Found: C, 57.43; H, 6.62; N, 5.88.

1-Phenyl-3-(1-methyl-4-homopiperazinyl)propyl Benzoate Dimaleate (JGS-165).- To 2.0 g. of 1-phenyl-3-(1-methyl-4-homopiperazinyl)propanol, dissolved in 50 ml. of anhydrous benzene, there was added 10.0 g. of anhydrous potassium carbonate and 4.0 g. of benzoyl chloride. The mixture was heated on a steam-bath for 1 hour, and then sufficient water was added to dissolve all of the salts. The benzene layer was removed and the aqueous layer extracted with benzene. The benzene extracts were dried over anhydrous magnesium sulfate, the benzene was removed, the oily residue was dissolved in ether and an excess of an etherealsolution of maleic acid was added. The dimaleate salt which precipitated was recrystallized from isopropyl alcohol and melted at 152-154°.

Anal. Calcd. for $C_{30}H_{36}O_{10}N_2$: C, 61.63; H, 6.21. Found: C, 61.34; H, 6.21.

1-Benzyl-4-diethylcarbamylhomopiperazine Hydrochloride (JGS-139).- To a stirred, refluxing solution of 5.5 g. (0.04 mole) of diethylcarbamyl chloride in 60 ml. of benzene there was added, dropwise, a solution of 1-benzylhomopiperazine (7.6 g., 0.04 mole) in 60 ml. of benzene. The mixture was refluxed for 1 hour, stirred for 12 hours at room temperature, the solvent was removed, and the residue recrystallized from ethyl acetate; m.p. 200-202°; yield 7.9 g. (60%).

Anal. Calcd. for $C_{17}H_{28}ON_3Cl$: N, 12.89; Cl, 10.88. Found: N, 12.75; Cl, 10.91.

1-Benzyl-4-nitrosohomopiperazine and Hydrochloride.- 1-Benzylhomopiperazine (30 g.) was dissolved in 75 ml. of ice-cold, concentrated hydrochloric acid. This solution was stirred and heated on a steam-bath while a solution of 25 g. of sodium nitrite, dissolved in 40 ml. of water, was added, dropwise, over a 2-hour period. The solution was heated on a steam-bath for 12 hours, cooled in ice, made alkaline with 50% sodium hydroxide solution, and extracted with ether. The ether was removed from the extract and the product was distilled. The fraction which boiled below 180° (1.5 mm.) was collected. The material was then redistilled; b.p. 165-175° (1.5 mm.); yield 18.0 g. (54%). Brown fumes appeared in the liquid nitrogen trap, probably nitrogen dioxide from decomposition, during the distillation.

Anal. Calcd. for $C_{12}H_{17}ON_3$: C, 65.72; H, 7.81. Found: 66.08; H, 7.60.

The hydrochloride was precipitated from an ethereal solution of the base by the addition of ethereal hydrogen chloride; it melted at 194-195° after recrystallization from ethanol-isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{18}ON_3Cl$: C, 56.35; H, 7.09; Cl, 13.86. Found: C, 56.06; H, 6.86; Cl, 14.08.

1-Benzyl-4-aminohomopiperazine and Dimaleate (JGS-175).- 1-Benzyl-4-nitrosohomopiperazine (14.0 g.), dissolved in 50 ml. of ether, was added, dropwise, to a stirred suspension of lithium aluminum hydride (5.0 g.) and 200 ml. of ether. The lithium aluminum complex precipitated on the sides of the

flask during this addition. The mixture was stirred and refluxed for 36 hours, cooled to room temperature, cautiously hydrolyzed with 15 ml. of water, and stirred and refluxed for an additional 3 hours. The hydrolyzed mixture was filtered, the ethereal filtrate dried over magnesium sulfate and distilled. The product boiled at 140-150° (4.0 mm.) with essentially no forerun or residue; yield 9.5 g. (73%).

Anal. Calcd. for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33. Found: C, 70.69; H, 9.19.

The dimaleate was precipitated from an ethereal solution of the base by the addition of a saturated solution of maleic acid in ether; m.p. 155-156° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{20}H_{23}O_8N_3$: C, 54.91; H, 6.22. Found: C, 54.90; H, 6.19.

Homopiperazine Diacetate and Dihydrochloride

Homopiperazine Diacetate (JGS-217).- A mixture of 28.5 g. of 1-benzylhomopiperazine, 30 ml. of acetic acid and 0.3 g. of palladium-charcoal catalyst (Wilkins Anderson Co.) was hydrogenated under an initial pressure of 50 pounds at 70° for 9 hours. The mixture was not filtered at this point. Acetone (100 ml.) was added whereupon a crystalline precipitate formed. After filtration of the precipitate, it was dissolved in hot isopropyl alcohol, the mixture was filtered and the filtrate was allowed to cool; the precipitate weighed 26.0 g. (80%); m.p. 160-161°.

Anal. Calcd. for $C_9H_{20}O_4N_2$: C, 49.07; H, 9.15; N, 12.72. Found: C, 49.26; H, 8.96; N, 12.83.

Homopiperazine Dihydrochloride*.- Homopiperazine diacetate (17.6 g.) was dissolved in 75 ml. of water, the solution was made alkaline with 50% sodium hydroxide solution and extracted with five 200 ml. portions of ether. The ethereal extracts were dried over anhydrous magnesium sulfate, the ether removed, and the product distilled; b.p. 65-70° (20 mm.); yield 6.1 g. (76%). The clear, colorless distillate partially solidified at room temperature to a waxy solid which fumed in air. It had a strongly ammoniacal odor. The dihydrochloride was precipitated from an ethereal solution of the base by the addition of ethereal hydrogen chloride. The dihydrochloride was recrystallized from methanol-ether; it darkened, but did not melt, below 280°.

Anal. Calcd. for $C_5H_{14}N_2Cl_2$: N, 16.19; Cl, 40.97. Found: N, 16.02; Cl, 40.64.

* * * * * *

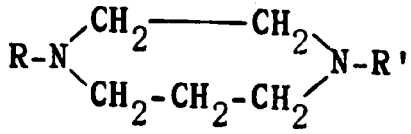
All of the homopiperazines prepared for pharmacological evaluation which have been described are listed in Table III which is found on the following page.

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*L. Bleier (Ber. 32, 1825 (1899)) prepared homopiperazine dihydrochloride by a different procedure (see General Introduction) from which he liberated the free base; b.p. 168-170°(atm. pressure).

TABLE III

1-MONOSUBSTITUTED AND 1,4-DISUBSTITUTED HOMOPIPERAZINES



No.	R	R'	Salt	M.p. or B.p.*, °C.	Code No. (JGS-)
1.	H	H	Diacetate	160-161	217
2.	H	CS_2H	Betaine Salt	221-222	233
3.	CH_3	H	Dihydrogen Citrate	164-166	113
4.	CH_3	CH_3	Dimethobromide	277-278	114
5.	CH_3	$CH_2CH_2OOCCH(C_6H_5)_2$	Dihydrochloride	223-225	120
6.	CH_3	$CH_2CH_2OOCCH_2C_6H_5$	Dimaleate	133-135	161
7.	CH_3	$CH_2CH_2OCH(C_6H_5)_2$	Dimaleate	152-153	129
8.	CH_3	$CH_2CH_2N(CH_3)_2$	Trimaleate	155-157	130
9.	CH_3	$CON(C_6H_5)_2$	Hydrochloride	187-189	108
10.	CH_3	$CON(C_2H_5)_2$	Hydrochloride	124-125	110
11.	CH_3	$CH(C_6H_5)_2$	Dihydrochloride	234-236	112
12.	CH_3	$CH(C_6H_5)C_6H_4Br$-p	Dihydrochloride	215-216	115

TABLE III (cont'd)

No.	R	R'	Salt	M.p. or B.p.*, °C.	Code No. (JGS-)
13.	CH_3	$COCH_2C_6H_5$	Hydrochloride	182-183	149
14.	CH_3	$COCH(C_6H_5)_2$	Hydrochloride	100-102	150
15.	CH_3	NH_2	.....	88 (20 mm.)*	152
16.	CH_3	$N(CH_3)_2$	Dimaleate	144-146	157
17.	CH_3	$COOC_2H_5$	.....	131 (20 mm.)*	158
18.	CH_3	$CH_2CH_2CH(C_6H_5)OOCC_6H_5$	Dimaleate	152-154	165
19.	$C_6H_5CH_2$	H	Dihydrochloride	198-199	219
20.	$C_6H_5CH_2$	$CON(C_2H_5)_2$	Hydrochloride	202-203	139
21.	$C_6H_5CH_2$	NH_2	Dimaleate	133-135	175

Analyses, %

No.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1.	$C_9H_{20}O_4N_2$	49.07	49.26	9.15	8.96	12.72	12.83		
2.	$C_6H_{12}S_2N_2$	40.86	40.74	6.86	6.84	15.89	16.23		
3.	$C_{12}H_{22}O_7N_2$	47.05	46.80	7.24	7.10	9.14	9.03		

TABLE III (cont'd)

No.	Formula	Carbon		Hydrogen		Nitrogen		Halogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4.	$C_9H_{22}N_2Br_2$					8.81	8.89	50.26	50.24
5.	$C_{22}H_{30}O_2N_2Cl_2$					6.59	6.77	16.67	16.85
6.	$C_{24}H_{32}O_{10}N_2$	56.68	56.79	6.34	6.32				
7.	$C_{29}H_{36}O_9N_2$	62.56	62.28	6.52	6.50	5.03	5.18		
8.	$C_{22}H_{35}O_{12}N_3$	49.53	49.58	6.61	6.46	7.88	8.09		
9.	$C_{19}H_{23}ON_3Cl$**	65.12	65.30	7.38	7.17			9.61	9.61
10.	$C_{11}H_{24}ON_3Cl$					16.82	16.67	14.20	14.14
11.	$C_{19}H_{26}N_2Cl_2$					7.93	7.87	20.07	19.89
12.	$C_{19}H_{25}N_2BrCl_2$					6.48	6.32	16.45	16.54
13.	$C_{14}H_{21}ON_2Cl$					10.43	10.60	13.19	13.26
14.	$C_{20}H_{25}ON_2Cl$					8.12	8.31	10.28	10.23
15.	$C_6H_{15}N_3$	55.77	55.91	11.70	11.53				
16.	$C_{16}H_{27}O_8N_3$	49.35	49.38	6.99	6.93				
17.	$C_9H_{18}O_2N_2$	58.03	57.78	9.74	9.68				
18.	$C_{30}H_{36}O_{10}N_2$	61.63	61.34	6.21	6.21				
19.	$C_{12}H_{20}N_2Cl_2$					10.64	10.38	27.37	27.20

**Analyzed as the hemi-ethanolate.

TABLE III (cont'd)

No.	Formula	Carbon		Hydrogen		Nitrogen		Halogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
20.	$C_{17}H_{28}ON_3Cl$					12.80	12.75	10.88	10.91
21.	$C_{20}H_{27}O_8N_3$	54.91	54.90	6.22	6.19				

Compounds 1, 6, 13 and 18 were recrystallized from isopropyl alcohol; compounds 3, 7, 8, 11, 12, 16, 19 and 21 from absolute ethanol; compound 2 from water; compound 14 from acetone-isopropyl alcohol; compound 4 from ethanol-water; compound 5 from nitromethane; compound 9 from ethanol-acetone; compound 10 from ethyl acetate; and compound 20 from acetone.

TABLE III (cont'd)

No.	Name	Code No.
1.	Homopiperazine Diacetate	JGS-217
2.	Homopiperazine Monodithiocarbamate	JGS-233
3.	1-Methylhomopiperazine Dihydrogen Citrate	JGS-113
4.	1,4-Dimethylhomopiperazine Dimethobromide	JGS-114
5.	beta-(1-Methyl-4-homopiperazinyl)ethyl Diphenylacetate Dihydrochloride	JGS-120
6.	beta-(1-Methyl-4-homopiperazinyl)ethyl Phenylacetate Dimaleate	JGS-161
7.	1-Methyl-4-(beta-benzhydryloxyethyl)homopiperazine Dimaleate	JGS-129
8.	1-Methyl-4-(beta-dimethylaminoethyl)homopiperazine Trimaleate	JGS-130
9.	1-Methyl-4-diphenylcarbamylhomopiperazine Hydrochloride	JGS-108
10.	1-Methyl-4-diethylcarbamylhomopiperazine Hydrochloride	JGS-110
11.	1-Methyl-4-benzhydrylhomopiperazine Dihydrochloride	JGS-112
12.	1-Methyl-4-(para-bromobenzhydryl)homopiperazine Dihydrochloride	JGS-115
13.	1-Methyl-4-phenylacetylhomopiperazine Hydrochloride	JGS-149
14.	1-Methyl-4-diphenylacetylhomopiperazine Hydrochloride	JGS-150
15.	1-Methyl-4-aminohomopiperazine	JGS-252
16.	1-Methyl-4-dimethylaminohomopiperazine Dimaleate	JGS-157
17.	1-Methyl-4-carbethoxyhomopiperazine	JGS-158
18.	1-Phenyl-3-(1-methyl-4-homopiperazinyl)-propyl Benzoate Dimaleate	JGS-165
19.	1-Benzylhomopiperazine Dihydrochloride	JGS-219
20.	1-Benzyl-4-diethylcarbamylhomopiperazine Hydrochloride	JGS-139
21.	1-Benzyl-4-aminohomopiperazine Dimaleate	JGS-175

1,5-Diazabicyclo[3.2.2]nonane and 2,3-Benzo-1,4-diazacycloheptatrienes

1-Methyl-4-(beta-bromoethyl)homopiperazine Dihydrobromide.- A mixture of 15.0 g. of 1-methyl-4-(beta-hydroxyethyl)-homopiperazine and 200 ml. of 48% hydrobromic acid was heated with a free flame until 100 ml. of distillate had been collected. The residue was then refluxed for 12 hours. The water was removed from the mixture by the use of a steam-bath and reduced pressure. In order to remove the water completely, benzene (100 ml.) was added to the residue. The benzene was then removed by distillation at ordinary pressure. The residue, a brown, viscous oil, was dissolved in hot methanol. A colorless, crystalline product separated from the cold solution; yield 28.0 g. (74%). After two more recrystallizations from methanol, the product melted at 180-182°.

Anal. Calcd. for $C_8H_{19}N_2Br_3$: C, 25.09; H, 5.00. Found: C, 25.01; H, 5.02.

1,5-Diazabicyclo[3.2.2]nonane Picrate Methopicrate, Method A.- 1-Methyl-4-(beta-bromoethyl)homopiperazine dihydrobromide (16.0 g.) was dissolved in 20 ml. of concentrated ammonium hydroxide and the solution was refluxed for one-half hour. The water was then removed on a steam-bath under reduced pressure. The last traces of water were removed by azeotropic distillation with benzene. The product in the residue could not be separated satisfactorily from the ammonium bromide by recrystallization, therefore the residue was dissolved in about 25 ml. of water and an excess of a satur-

ated aqueous solution of picric acid was added. The precipitated picrate methopicrate was washed with water, then with methanol, and dried in an Abderhalden apparatus over refluxing methanol; m.p. 184-187 (dec.).

Anal. Calcd. for $C_{20}H_{22}O_{14}N_8$: C, 40.15; H, 3.71. Found: C, 40.12; H, 3.88.

1,5-Diazabicyclo[3.2.2]nonane Picrate Methopicrate, Method B.- Although we believe that the desired product was obtained in this experiment, neither the hydrobromide methobromide nor the picrate methopicrate could be obtained in an analytically pure state.

1-Methylhomopiperazine (5.7 g.) and ethylene dibromide (9.4 g.) were added to 20 ml. of ethylene glycol, the mixture was refluxed and stirred for 4 hours and then stirred at room temperature for 12 hours. Acetone (15 ml.) and methanol (15 ml.) were added and the white crystalline product was removed by filtration of the hot mixture; yield 4.1 g. (27%); m.p. 223-225° (dec.).

Anal. Calcd. for $C_8H_{18}N_2Br_2$: C, 31.81; H, 6.00; Br, 52.91. Found: C, 29.16; H, 5.78; Br, 53.71.

A portion of the hydrobromide methobromide was dissolved in water, sodium carbonate was added to neutrality to litmus, followed by the addition of an aqueous solution of picric acid. The precipitated picrate methopicrate was filtered, washed thoroughly with water and methanol, and dried in an Abderhalden apparatus over refluxing methanol; m.p. 241-242° (dec.).

Anal. Calcd. for $C_{20}H_{22}O_{14}N_8$: C, 40.15; H, 3.71. Found: C, 39.71; H, 3.43.

2,3-Benzo-5,7-dimethyl-1,4-diazacycloheptatriene.- Although the preparation of this compound by the process described below has been reported in the literature (167), we have described the synthesis again in order to supply additional details.

A mixture of 10.0 g. of 2,4-pentanedione*, 10.8 g. of o-phenylenediamine and 250 ml. of benzene was stirred and refluxed for 6 hours in a 500-ml. flask equipped with a Barrett water trap. After 3 ml. of water had been collected, the benzene was removed. Since it was not found possible to steam distill the product, the reaction mixture was extracted with chloroform, the extract was dried over magnesium sulfate, the solvent was removed and the residue distilled; b.p. 168-180° (10 mm.); yield 7.0 g. (41%). The solidified distillate, after three recrystallizations from diisopropyl ether, melted at 88-100°**. The melting point was not raised by further recrystallization. The analytical data indicated that the product was not quite pure.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 75.79; H, 7.17.

Ethereal hydrogen chloride converted the base into a deep purple crystalline hydrochloride; m.p. 178-180°***.

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*Purchased from Distillation Products Industries, division of Eastman Kodak Co., Rochester, N. Y.

**Ref. 167, m.p. 131-132° after recrystallization from ether. We found the product was too soluble in ether to be recrystallized from this solvent.

***The hydrochloride mentioned in the literature (167) was stated to be a hydrochloride dihydrate which, when heated, decomposed into 2-methylbenzimidazole and acetone. The melting point of the hydrochloride was not reported.

2,3-Benzo-5,7-dimethyl-1,4-diazacycloheptene-2 and Maleate (JGS-162).- 5,7-Dimethyl-2,3-benzo-1,4-diazacycloheptatriene (167) (6.5 g., 0.032 mole) was dissolved in 30 ml. of absolute ethanol, 0.2 g. of platinum oxide catalyst was added and the mixture was hydrogenated for 2 hours under an initial pressure of 46 pounds. At the end of this time, hydrogen was no longer absorbed; the amount taken up was 86% of the calculated amount. The mixture was filtered, the solvent was removed from the filtrate and the residue was distilled; b.p. 160-165° (20 mm.); yield 6.0 g. (92%). The portion which boiled at 162° (20 mm.) was used for analysis.

Anal. Calcd. for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15. Found: C, 74.54; H, 8.89.

This product formed a bright pink hydrochloride with ethereal hydrogen chloride. It became white after several recrystallizations from isopropyl alcohol; m.p. 228-229°.

With an ethereal solution of maleic acid, a purple maleate was formed, which still retained a slight purple color after three recrystallizations from isopropyl alcohol; m.p. 160-161.5°.

Anal. Calcd. for $C_{15}H_{20}O_4N_2$: C, 61.63; H, 6.90. Found: C, 61.70; H, 6.89.

2,3-Benzo-5-methyl-1,4-diazacycloheptadiene-2,4-one-7.- This was prepared by the method of W. A. Sexton (177).

Attempted Preparation of 2,3-Benzo-5-methyl-1,4-diazacycloheptene-2-one-7.- All attempts to hydrogenate 2,3-benzo-5-methyl-1,4-diazacycloheptadiene-2,4-one-7 with platinum

oxide catalyst resulted only in recovery of unchanged material. Both ethanol and glacial acetic acid were employed as solvents. In each case the material obtained did not give a precipitate with ethereal hydrogen chloride and the melting point was the same as that of the original material.

Attempted Preparation of 2,3-Benzo-5-methyl-1,4-diazacycloheptene-2.- To a stirred suspension of 7.6 g. of lithium aluminum hydride and 200 ml. of ether there was added, dropwise, a solution of 15.0 g. of 2,3-benzo-5-methyl-1,4-diazacycloheptadiene-2,4-one-7 as rapidly as the reaction would permit. After refluxing for 7 hours, the mixture was stirred for 12 hours, and 15 ml. of water cautiously added, dropwise, with stirring. The mixture was filtered and the precipitate washed with hot isopropyl ether. The combined filtrate and diisopropyl ether solution was dried over magnesium sulfate. The solvent was removed on a steam-bath, leaving a light yellow, crystalline solid, which melted at 173-174°* after recrystallization from diisopropyl ether-isopropyl alcohol. This substance was 2-methylbenzimidazole.

Anal. Calcd. for $C_8H_8N_2$ (2-methylbenzimidazole): C, 72.69; H, 6.10. Found: C, 72.68; H, 6.04.

The hydrochloride (2-methylbenzimidazole hydrochloride) was precipitated from an ethereal solution of the base by the addition of excess ethereal hydrogen chloride; it decomposed

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*H. Hübner (Ann., 209, 353 (1881)) gave the melting point of 2-methylbenzimidazole as 170°; O. Hinsberg and F. Funcke (Ber., 27, 2189 (1894)), A. Ladenberg (Ber., 8, 677 (1875)), K. Brand and E. Stohr (Ber., 39, 4062 (1906)) each give the melting point as 175°.

above 280° , after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{10}H_{16}N_2Cl_2$: C, 56.96; H, 5.38; N, 16.62; Cl, 21.03. Found: C, 57.04; H, 5.22; N, 16.73; Cl, 20.87.

Attempted Preparation of 5-Methyl-1,4-diazacycloheptene-4-one-7.- To a refluxing solution of 12 g. of ethylenediamine dissolved in 100 ml. of xylene, there was added 29 ml. of ethyl acetoacetate dissolved in 200 ml. of xylene, over a 2-hour period. This operation was carried out in an apparatus fitted with a Barnett water trap which permitted the simultaneous removal of the water formed during the 2-hour period (the total amount of xylene and water collected during the 2-hour period was 150 ml.). After refluxing an additional hour, the hot mixture was filtered, cooled and rubbed to induce crystallization of the product; yield 14.5 g. After three recrystallizations from isopropyl alcohol, the product (1,8-dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6) melted at 124-126°.

Anal. Calcd. for $C_6H_{10}ON_2$(5-methyl-1,4-diazacycloheptene-4-one-7): C, 57.11; H, 7.99. Found: C, 59.14; H, 8.44.

Calcd. for $C_{14}H_{24}O_4N_2$ (1,8-dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6): C, 59.13; H, 8.51.

W. Reid and W. Höhne (180) prepared the product which was desired in this reaction, namely, 5-methyl-1,4-diazacycloheptene-4-one-7, by heating ethylenediamine with ethyl acetoacetate and acetic acid. They reported the melting point to be 129.5° and obtained a 74.5% yield.

Attempted Preparation of 5,7-Dimethyl-1,4-diazacycloheptadiene-4,7.- It seems that Reid and Höhne (176) used

2,4-pentanedione (acetylacetone) in one of their reactions, and may have obtained 5,7-dimethyl-1,4-diazacycloheptadiene-4,7, but the use of this ketone is not mentioned in the experimental part of their publication.

Ethylene diamine (24.0 g.), 10 ml. of acetic acid and 15.0 g. of 2,4-pentanedione were heated in an oil-bath at 120° (bath temperature) for 15 minutes. According to the general published directions (176), a precipitate should have been obtained after the mixture had been heated for 15 minutes. A precipitate did not form after the material had been heated for 15 or for 45 minutes.

The experiment was repeated with the use of 10 drops of concentrated sulfuric acid in place of the acetic acid. Again, a precipitate was not obtained.

In the next experiment, the same general process was employed which has been used successfully in the case of o-phenylenediamine.

A mixture of 9.0 g. of ethylenediamine, 24.3 g. of 2,4-pentanedione and 250 ml. of benzene was heated in a flask to which a Barrett water trap was attached. After 5.5 ml. of water (in addition to the benzene) had been collected in the trap, the remaining benzene in the reaction mixture was removed by distillation. The yellow, crystalline residue melted at 105-110°. After three recrystallizations from carbon tetrachloride, it melted at 110-112°. This product proved to be 4,9-dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8 instead of the desired product.

Anal. Calcd. for $C_7H_{12}N_2$ (5,7-dimethyl-1,4-diazacycloheptadiene-4,7): C, 67.70; H, 9.74; N, 22.56. Found: C, 64.13; H, 8.86; N, 12.69.

Calcd. for $C_{12}H_{22}O_2N_2$ (4,9-dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8): C, 64.26; H, 8.99; N, 12.50.

The dodecadiene has been obtained by other investigators (179, 207) by slightly different procedures from ethylenediamine and 2,4-pentanedione.

When the reaction was carried out again with the use of xylene as a solvent, and then without a solvent, the only reaction product obtained was the dodecadiene.

Attempted Preparation of 5-Methyl-5-azacyclooctanone

Methyldi(gamma-hydroxypropyl)amine.- A solution of methyldi(beta-carbethoxyethyl)amine (107 g. 0.5 mole) in 200 ml. of ether, was added dropwise to a stirred suspension of 23.0 g. (0.5 mole, 20% excess) of lithium aluminum hydride in 1 liter of ether. The mixture was stirred and refluxed for 12 hours, cooled and 50 ml. of water was added, dropwise, to the stirred mixture. After the material had been refluxed for 3 hours, it was filtered and the filtrate was dried over magnesium sulfate. After removal of the ether, the product boiled at 165-170° (20 mm.)*; yield 59.0 g. (80%).

Methyldi(gamma-chloropropyl)amine.and Hydrochloride.- The process described below is the same as that used by W. E. Hanby and H. N. Rydon (J. Chem. Soc., 516 (1947)) to

*J. von Braun and O. Braunsdorff (Ber., 54, 685 (1921)), prepared the compound by a different method, reported the boiling point to be 164-165° (13 mm.).

prepare methyldi(beta-chloroethyl)amine. They stated that this process was the "most satisfactory of many procedures tried".

Methyldi(gamma-hydroxypropyl)amine (49.0 g.) was dissolved in 60 ml. of benzene and the solution was added, dropwise, over a 2-hour period to a refluxing solution of 83.3 g. of thionyl chloride in 60 ml. of benzene. Two layers formed after the mixture had been refluxed for one-half hour on a steam-bath. The lower, oily layer, which contained the hydrochloride of the desired product, was separated and treated with 25 ml. of benzene. The tan, crystalline hydrochloride obtained was recrystallized from benzene; yield 67.0 g. (91%).

Anal. Calcd. for $C_7H_{11}NCl_3$: N, 6.35; Cl^-, 16.08. Found: N, 6.23; Cl^-, 16.32.

A solution of 62.0 g. of the hydrochloride in 200 ml. of water was added, slowly, to a stirred, cooled solution of 11.2 g. of sodium hydroxide in 30 ml. of water. After the addition of enough water to dissolve all of the material, the brown-red mixture was extracted with three 200 ml. portions of ether. The extract was dried with sodium sulfate, the solvent was removed and the residue was distilled; b.p. 113-120° (40 mm.); yield 44.0 g. (85%).

Anal. Calcd. for $C_7H_{15}NCl_2$: C, 45.66; H, 8.21. Found: C, 45.65; H, 8.23.

Methyldi(gamma-cyanopropyl)amine Picrate.- A solution of 92.0 g. of methyldi(gamma-chloropropyl)amine in 400 ml. of alcohol was added to 150 g. of sodium cyanide dissolved in

175 ml. of water. After the addition of 2.0 g. of sodium iodide, the mixture was heated on a steam-bath for 24 hours. The alcohol was removed by distillation on a steam-bath and the aqueous residue was extracted with four 200 ml. portions of ether. After the extract had been dried over sodium sulfate, the ether was removed and the residue was distilled; b.p. 110-117° (0.3 mm.); yield 53.5 g. (65%).

Upon treatment of the base, dissolved in ether, with an ethereal solution of picric acid, the picrate precipitated; m.p. 134-136° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{15}H_{18}O_7N_6$: C, 45.68; H, 4.60. Found: C, 45.78; H, 4.68.

Methyldi(delta-aminobutyl)amine Trihydrochloride.- To a stirred suspension of 5.7 g. of lithium aluminum hydride in 250 ml. of ether there was added, dropwise, a solution of 12.0 g. of methyldi(gamma-cyanopropyl)amine in 200 ml. of ether. The mixture was refluxed for 12 hours, filtered, the solvent was removed from the ethereal filtrate and the residue was distilled; b.p. 148-155° (30 mm.); yield 11.0 g. (87%).

The hydrochloride was obtained by the addition of an ethereal solution of hydrogen chloride to the base dissolved in ether; m.p. 174-175° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_9H_{26}N_3Cl_3$: N, 14.86; Cl, 37.63. Found: N, 14.78; Cl, 37.43.

Attempted Preparation of 1-Methyl-4-cyano-5-iminoheptamethylenimine.- The procedure used is essentially the same

as that employed for the preparation of cyclooctanone; a more detailed description of the required apparatus is reported in connection with this experimental procedure (197).

Sodium hydride (16.0 g.) and 2 liters of dry reagent benzene were placed in a 3-necked, 5-liter flask. After the flask had been flushed thoroughly with dry nitrogen, the mixture was stirred and refluxed, 2 ml. of methanol was added followed by the addition, at the rate of about 10 drops a minute (total time required, 80 hours), of 49.5 g. of methyldi(gamma-cyanopropyl)amine, dissolved in 950 ml. of dry benzene. After the addition had been completed, the material was refluxed for 24 hours. The mixture was cooled in an ice-bath and 39.6 g. of acetic acid was added at such a rate that the mixture did not become warm. The material was stirred for 1 hour and during this time it was allowed to warm to room temperature. Water (36 ml.) and a few crystals of sodium acetate trihydrate* were added. The mixture was stirred for 1 hour, filtered and filtrate was dried over magnesium sulfate. After removal of the solvent, the product was distilled; b.p. 114-120 (0.3 mm.);yield 42.0 g.

Since, from the boiling point, the "product" appeared to be unchanged methyldi(gamma-cyanopropyl)amine, a picrate was prepared; m.p. 134-136°. When this picrate was mixed with the picrate of methyldi(gamma-cyanopropyl)amine, the mixed melting point was found to be 134-136°.

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*This substance was added to induce crystallization of the sodium acetate trihydrate present in the reaction mixture.

Methyldi(gamma-carbomethoxypropyl)amine.- A mixture of 42 g. of methyldi(gamma-cyanopropyl)amine, 30 g. of sodium hydroxide pellets, and 500 ml. of water was refluxed (36 hours) until a negative test for ammonia vapors was obtained (moist pH paper). Concentrated hydrochloric acid was added until the mixture was distinctly acidic (about 64 ml.) and the water was removed on a steam-bath under reduced pressure. To the residue there was added 1.5 liters of absolute methanol and the solution was refluxed on a steam-bath for 12 hours. A slow stream of dry hydrogen chloride was allowed to pass into the solution during this period. The solvent was again removed on a steam-bath under reduced pressure. The residue was dissolved in water, the solution made distinctly alkaline with sodium hydroxide and then extracted with ether. The ether extracts were dried over magnesium sulfate, the ether was removed and the product was distilled; b.p. 162-172° (30 mm.); yield 25 g. (43%). The analysis of this product will be obtained at a later date.

Methyldi(gamma-carbethoxypropyl)amine has been prepared by another procedure (208).

Attempted Preparation of 2-Carbomethoxy-5-methyl-5-azacyclooctanone.- The cyclization procedure reported below is the same as that described under the heading "Attempted Preparation of 1-Methyl-4-cyano-5-iminoheptmethylenimine".

Methyldi(gamma-carbomethoxypropyl)amine (32.0 g.) was dissolved in 350 ml. of xylene, and the solution was added to 10.5 g. of sodium hydride in 1 liter of xylene by the use

of the high dilution apparatus employed in an experiment which has already been described. The addition was carried out at the rate of about 10 drops per minute. The mixture was refluxed an additional 12 hours, then 26.1 g. of acetic acid and 24.4 ml. of water were added as described previously. The mixture was filtered, the filtrate was dried over magnesium sulfate and the product was distilled. A small amount of "starting material" was recovered and a tarry residue was obtained which decomposed when an attempt was made to distill it (0.3 mm.). The residue was probably a product of a polymerization reaction.

E. A. Prill and S. M. McElvain (208) attempted the cyclization of methyldi(gamma-carbethoxypropyl)amine under various conditions. They obtained none of the cyclization product and recovered, in some experiments, a part of the "starting material".

SUMMARY

The object of this investigation was the synthesis of 1,4-disubstituted homopiperazines and related substances. Compounds of the former type have potential value as therapeutic agents.

A variety of 1-methyl-4-substituted homopiperazines was prepared in which the 4-substituent was (A) beta-dimethylaminoethyl, benzhydryl or p-bromobenzhydryl; (B) phenylacetyl, diphenylacetyl, diethylcarbamyl, diphenylcarbamyl or carbethoxy; (C) beta-benzhydryloxyethyl, beta-phenylacetyloxyethyl, beta-diphenylacetyloxyethyl; (D) methyl, amino, dimethylamino, gamma-phenyl-gamma-hydroxypropyl or gamma-phenyl-gamma-benzoyloxypropyl.

The products in groups (A) and (B) were obtained by interaction of 1-methylhomopiperazine with the required substituted alkyl halide or acid chloride. Compounds in group (C) were synthesized by allowing 1-methylhomopiperazine to react with ethylene bromohydrin and treatment of the resulting 1-methyl-4-(beta-hydroxyethyl)homopiperazine with benzhydryl bromide, phenylacetyl chloride or diphenylacetyl chloride. Each compound in group (D) was made by a different procedure. 1,4-Dimethylhomopiperazine was obtained by formylation of 1-methylhomopiperazine with chloral and subsequent reduction of the 1-methyl-4-formylhomopiperazine with lithium aluminum hydride. Treatment of 1-methylhomopiperazine with nitrous acid yielded the 4-nitroso derivative which was reduced with lithium aluminum hydride to the corresponding 4-amino compound. Methyla-

tion with formaldehyde and formic acid of 1-methyl-4-amino-homopiperazine yielded the corresponding 4-dimethylamino compound. A Mannich reaction in which 1-methylhomopiperazine dihydrochloride, formaldehyde and acetophenone were employed, produced 1-methyl-4-(beta-benzoylethyl)homopiperazine which was reduced with lithium aluminum hydride to 1-methyl-4-(gamma-phenyl-gamma-hydroxypropyl)homopiperazine [1-phenyl-3-(1-methyl-4-homopiperazinyl)propanol]. Benzoylation of the last mentioned compound with benzoyl chloride yielded the benzoyl derivative.

Two 1-benzyl-4-substituted homopiperazines were prepared in which the 4-substituent was an amino and a diethylcarbamyl group. The former derivative was prepared by nitrosation with nitrous acid of 1-benzylhomopiperazine and subsequent reduction of the nitroso group with lithium aluminum hydride. The latter derivative was formed by interaction of 1-benzyl-homopiperazine with diethylcarbamyl chloride.

It was found that homopiperazine can be obtained conveniently by debenzylation of 1-benzylhomopiperazine. This process was effected in 80% yield by the use of hydrogen and a palladium-charcoal catalyst.

It was known that o-phenylenediamine condenses with acetylacetone to yield 2,3-benzo-5,7-dimethyl-1,4-diazacycloheptatriene (2,3-benzo-5,7-dimethyl-1,4-diazepine). We found that this substance can be hydrogenated, in the presence of platinum oxide catalyst, to 2,3-benzo-5,7-dimethyl-1,4-diazacycloheptene-2.

It was also known that interaction of o-phenylenediamine with ethyl acetoacetate produces 2,3-benzo-5-methyl-1.4-diazacycloheptadiene-2,4-one-7. It was found that although this substance could not be hydrogenated with the aid of platinum oxide, reduction did take place when lithium aluminum hydride was employed. The reaction product was 2-methylbenzimidazole instead of the expected 2,3-benzo-5-methyl-1,4-diazacycloheptene-2.

It has been reported that condensation of ethylenediamine with acetylacetone yields 5,7-dimethyl-1,4-diazacycloheptadiene-4,7, and that condensation of the diamine with ethyl acetoacetate produces 5-methyl-1,4-diazacycloheptene-4-one-7. When we carried out these condensations, linear instead of cyclic reaction products were obtained: in the first instance, 4,9-dimethyl-2,11-diketo-5,8-diazadodecadiene-4,8, and in the second instance, 1,8-dicarbethoxy-2,7-dimethyl-3,6-diazaoctadiene-2,6 was isolated.

1,5-Diazabicyclo[3.2.2]nonane, isolated as the picrate methopicrate, was synthesized by two procedures: (a) conversion of 1-methylhomopiperazine into 1-methyl-4-(beta-hydroxyethyl)homopiperazine, reaction of this compound with hydrobromic acid to form 1-methyl-4-(beta-bromoethyl)homopiperazine dihydrobromide and treatment of this salt with ammonium hydroxide whereby cyclization took place; (b) reaction of 1-methylhomopiperazine with ethylene dibromide.

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