UNIVERSITY OF CINCINNATI

May 28 1943

I hereby recommend that the thesis prepared under my supervision by W. Frederick Huber *entitled* The Preparation of Some New Antispasmodics

be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

Approved by:

Hoke S. Greene

George Lucesch. Jr.

D. L. Fry.

Form 668—G. S. and Ed.—1M—7-37

THE PREPARATION OF SOME NEW ANTISPASMODICS

A dissertation submitted to the

Graduate School
of the University of Cincinnati

in partial fulfillment of the
requirements for the degree

of

DOCTOR OF PHILOSOPHY

1943

by

Wilson Frederick Huber

B.S. Lebanon Valley College 1940

M.S. University of Cincinnati 1942

ACKNOWLEDGEMENT

The author wishes to express his hearty appreciation for the many helpful suggestions and kind encouragement given by Dr. George Rieveschl Jr. under whose guidance this investigation was made.

TABLE OF CONTENTS

INTRODUCTION TO CHEMISTRY OF ANTISPASMODICS

In this introduction the author will attempt to give a survey of a field of chemotherapy which is relatively new, namely, that of antispasmodics.

Antispasmodics are drugs which depress the voluntary motion in the brain or cord, or more commonly, in both (1). They may be divided into two classes (2):

1. Neurotropic - Those which act to prevent or abolish the action of stimulation of autonomic nerves.
    a. Sympatholytic - Those whose action is on the sympathetic nervous system.
    b. Parasympatholytic - Those whose action is on the parasympathetic nervous system.
2. Musculotropic - Those which are not related to innervation.

Of greatest practical importance are the drugs belonging to the parasympatholytic group (the prototype of which is atropine) and to the group "not related to innervation" (whose chief representatives are papaverine and the nitrites) (2).

Inorganic Compounds:

Bromides have been used in medicine since about 1842 when Glover experimented on animals with potassium bromide, showing its sedative action on dogs and rabbits (3). Before this time it had been used in therapeutics as an alterative and soon after was employed in states of excitement. In recent years, other bromides have been introduced, in order to avoid the depressing action of potassium on the heart. The compounds in which the bromine is ionic, including hydrobromic acid and its salts and esters, are especially active. The bromates, hypobromites and other compounds with oxygen find little therapeutic use. The most important bromides from the medicinal standpoint are potassium bromide, ammonium bromide, strontium bromide and lithium bromide.

The action of bromides is almost wholly limited to the central nerve system and consists in an interruption of impulses between afferent and efferent centers and between afferent tracts and the centers of consciousness. Bromides have but little action on isolated tissues, it being possible to replace a large proportion of sodium chloride by the corresponding bromide, with little influence on function.

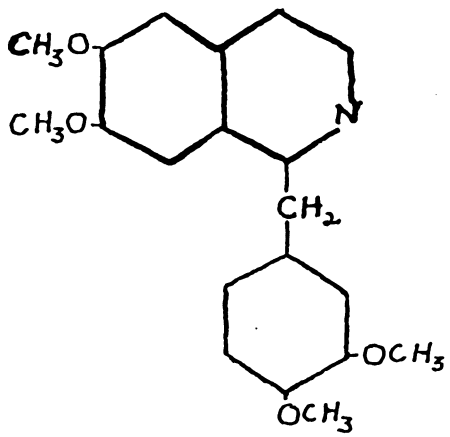
Solis-Cohen and Githens list magnesium compounds such as magnesium nitrate, magnesium chloride and magnesium sulfate under antispasmodics. Soluble magnesium salts

injected parenterally, depress or paralyze certain functions of the nerve system, both motor and sensory, loss of consciousness, anesthesia and paralysis of voluntary motion and of reflexes resulting (4). Lium claims that $MgSO_4$ relaxes the colon when given intravenously in large doses to dogs (5).

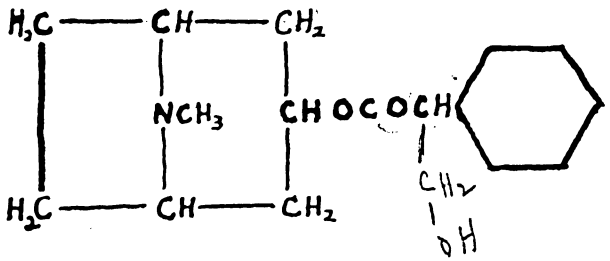
The introduction of nitrites into medicine is fairly recent. Amyl nitrite was used by Richardson in 1865, nitroglycerin soon after, and other nitrites only in recent years (6). The nitrites of chief medical importance are potassium nitrite, sodium nitrite, amyl nitrite, ethyl nitrite and several nitrates which give rise to nitrites in the body, i.e., nitroglycerin, erythrol tetranitrate, and mannitol hexanitrate. The effects of the nitrites are chiefly three: (1) A widespread action on the tissues innervated by the autonomic system, shown especially as a dilatation of the arteries; (2) a destruction of hemoglobin with formation of a mixture of methemoglobin and a little nitric-oxide-hemoglobin, and (3) an irritant topical action. The chief medical use is to bring about relaxation of smooth muscle, principally in the arterioles as in cases with high blood pressure or with localized vascular spasm, such as angina pectoris; but also in enteric, renal and gallstone colic.

Papaverine, atropine and synthetic analogs:

Before the introduction of synthetic compounds the most common antispasmodics were the naturally occuring alkaloids papaverine and atropine.



Papaverine



Atropine

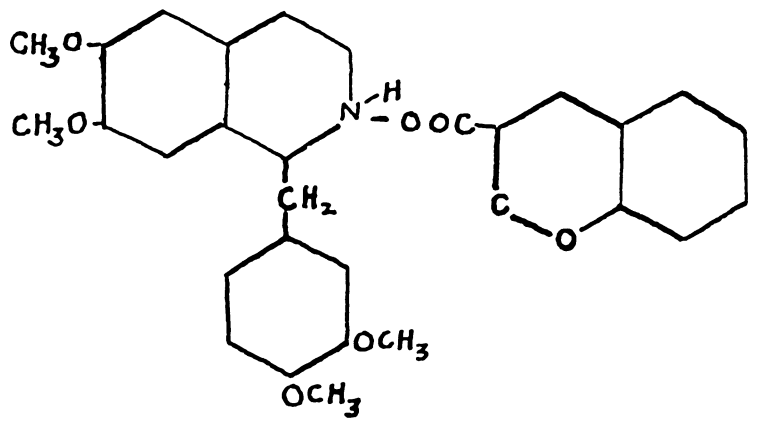
Papaverine was adopted as a therapeutic agent soon after the discovery of its antispasmodic action (7). It is obtained as a by-product of the isolation of morphine from opium. Atropine was isolated almost simultaneously by Mein and by Geiger and Hesse in 1831 from the belladonna roots, where it is found to occur with an isomer, hyoscyamine (8).

Both papaverine and atropine have a number of disadvantages (2). Papaverine has little effect in abolishing spasms induced by neural excitation, while, on the other hand, atropine is almost ineffective against spasms of entirely

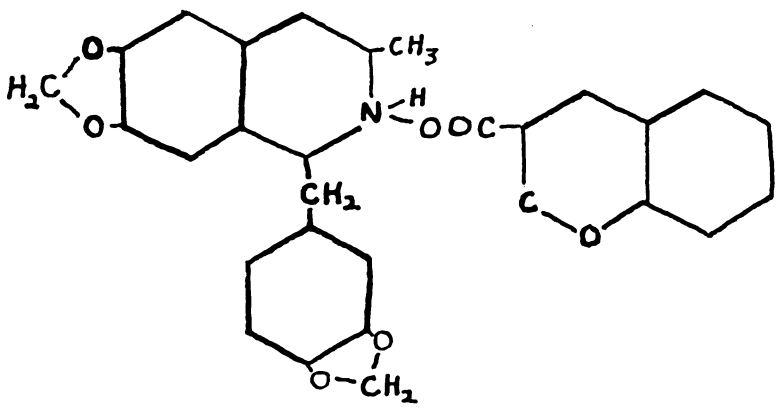
muscular origin brought about by such substances as histamine. In addition, papaverine relaxes all the smooth muscles equally, thus when relaxation of the intestinal tract is required, there results also a prolonged and undesirable fall in arterial blood pressure. Also, the parasympathetic inhibition of atropine occurs in all organs activated by nerves of the autonomic system, causing three undesired side-effects, namely, cyclopegia, dryness of the mouth, tachycardia and sometimes a rise in arterial pressure.

Papaverine can be synthesized in the laboratory, but an inexpensive commercial process has not been found to date. This and the fact that papaverine and other alkaloids with antispasmodic activity have several disadvantages as stated above has led to attempts to prepare compounds which resemble papaverine or atropine closely as well as some which do not have such an apparent relation.

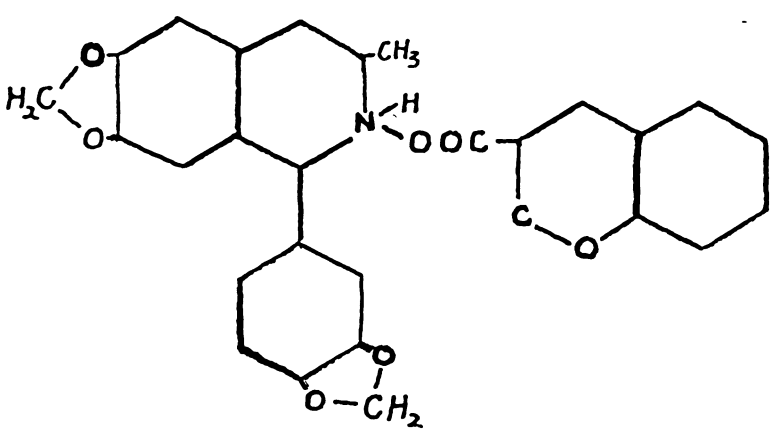
In 1935 the Merck Company in Germany took out a patent for derivatives of isoquinolines substituted in the 1-position by an aryl or aralkyl group and converted into their salts with coumarin-3-carboxylic acid (9). These compounds are claimed to have antispasmodic and sedative properties. Papaverine coumarin-3-carboxylate is an example.



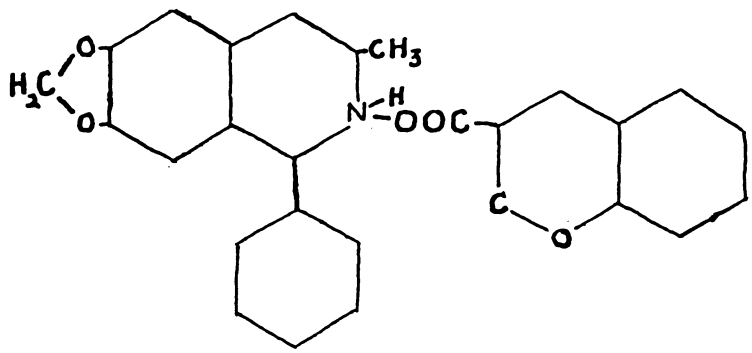
1-(3',4'-Methylenedioxybenzyl)-3-methyl-6,7-methylene-dioxy-isoquinoline coumarin-3-carboxylate,



1-(3',4'-Methylenedioxyphenyl)-3-methyl-6,7-methylene-dioxy-isoquinoline coumarin-3-carboxylate,

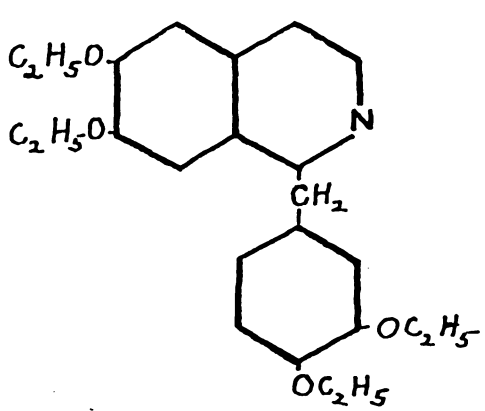


1-Phenyl-3-methyl-6,7-methylenedioxy-isoquinoline coumarin-3-carboxylate,

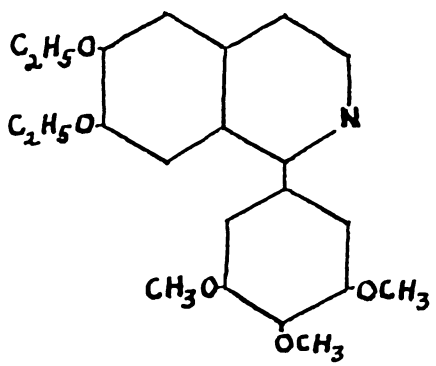


Werder also reports the 3-coumarin carboxylic acid salts of papaverine and 1-(3',4'-methylenedioxphenyl)-3-methyl-6,7-dioxymethyleneisoquinoline and claims that the latter in clinical tests has proved to have outstanding effect in the treatment of intestinal spasm in doses of .03 grams administered rectally or perorally without the constipating effect of opiates (10).

In 1934 Kottlors reported "perparin", a synthetic papaverine derivative in which ethoxy groups replace the methoxy groups, to be less toxic than papaverine and yet ten times as strong in its action (11). It is applied as an antispasmodic in gynecology.

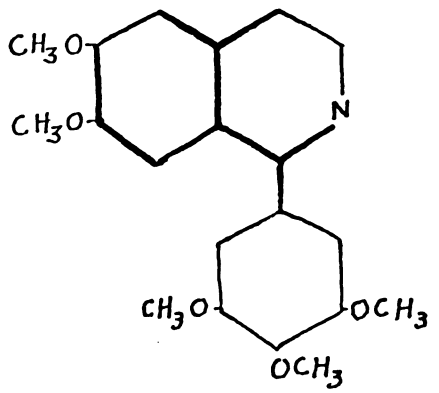


Slotta and Haberland, in 1933, reported nine 1-phenylisoquinolines which resemble papaverine in structure (12). The pharmacological tests of these compounds indicated that the size and number of the alkoxy groups in the molecule are of great importance. If five methoxyl groups are present the compound, in nontoxic quantities, has a paralyzing effect upon smooth muscle tissue. Introduction of two etnoxyl and three ethoxyl groups greatly increases the action, but a decrease occurs when five ethoxyl groups are present and the action disappears with six methoxyl groups. The most effective compound in this series was the 1-(3',4',5'-trimethoxylphenyl)-6,7-diethoxyisoquinoline

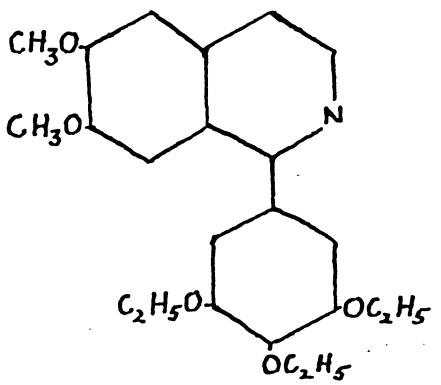


which was compared with papaverine and atropine for their action upon the stomach and the small and large intestine.

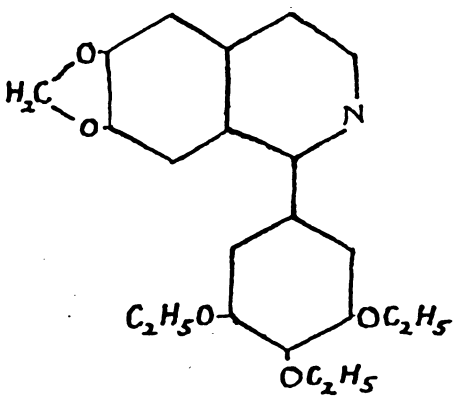
Ellinger, Koschara and Seerar also reported compounds like Slotta and Haberland's claiming they can replace papaverine as therapeutic agents (13). They prepared 1-(3',4',5'-trimethoxyphenyl)-6,7-dimethoxyisoquinoline,



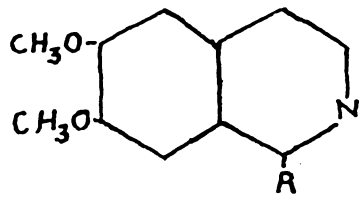
1-(3',4',5'-triethoxyphenyl)-6,7-dimethoxyisoquinoline, also known as "octaverine",



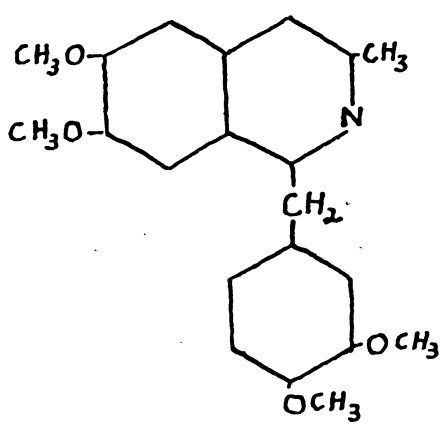
and 1-(3',4',5'-triethoxyphenyl)-6,7-methylenedioxyisoquinoline.



Fodor reports some 1-aryl- and 1-homoaryl-6,7-dimethoxyisoquinolines of the general formula

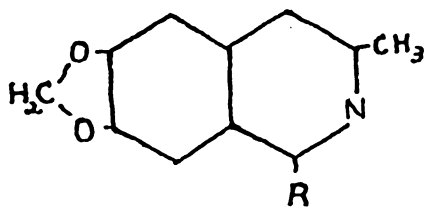


where R is either an aryl or homoaryl group (14). He prepared compounds where R is benzyl, homoveratryl, homopiperonyl, anisyl, veratryl, piperonyl, trimethylgallyl, asaryl, triethylgallyl, 3,4-dimethoxyphenylglyoxylic hydrazone, and 3,5-dioxo-6-(3',4'-dimethoxyphenyl)-2,3,4,5-tetrahydro-1,2,4-triazine. 1-Veratryl-3-methyl-6,7-dimethoxyisoquinoline

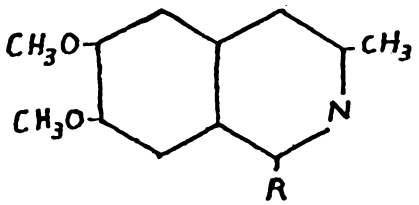


was specifically mentioned as having good spasmolytic effects. The benzyl, homoveratryl and veratryl compounds were reported previously by Darmstadt in 1931 in a patent taken out for the Merck Company (15). Darmstadt also reported the derivative where R is phenylethylmethyl as being a good antispasmodic. The homoveratryl compound is known as "eupaverine". Later, Bruckner and Fodor prepared isoquinoline

derivatives of the type



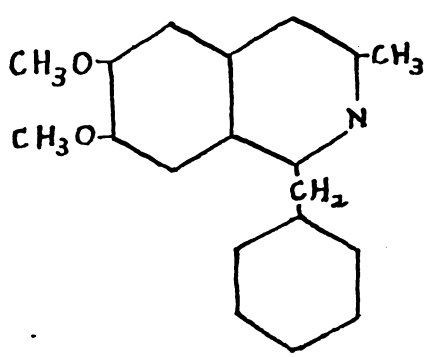
and



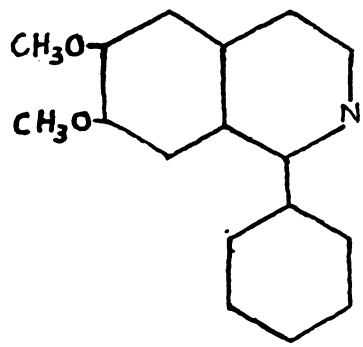
where R = p-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$ and 3,4,5-$(MeO)_3C_6H_2$ and analogous derivatives (16). All of these compounds showed on the isolated intestinal strip a spasmolytic action which in general was not only equal to that of papaverine but even surpassed it considerably. Some were also superior, as regards quality of action and toxicity, to the analogous compounds demethylated at position 3 and to papaverine. These results also indicated that the homoaryl residue (R) could be replaced by aryl residues without damage to the pharmaceutical properties of the compounds.

Darmstadt reports 1-(3',4'-dimethoxylbenzyl)-3-methyl-6,7-methylenedioxyisoquinoline as being an active antispasmodic (15).

Vinkler and Bruckner also prepared the 1-benzyl-3-methyl-6,7-dimethoxyisoquinoline



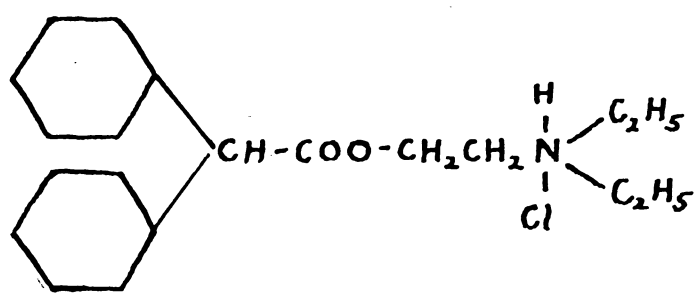
and 1-phenyl-6,7-dimethoxyisoquinoline



using some new reversible N-O acyl migr ations (17). These compounds are antispasmodics like their derivatives given above.

Alkamine Esters:

Probably most of the recent research toward the preparation of new antispasmodics has been concerned with the preparation of alkamine ester type compounds. One of the most successful compounds of this type to date is "Trasentin", β-diethylaminoethyl diphenylacetate hydrochloride, which was first reported by Meier in 1936 (18).



Meier claims that "Trasentin", like atropine, abolishes spasm through its action on the nerves and like papaverine acts directly on smooth muscle. It produces much less dilation of the pupil and dryness of the throat.

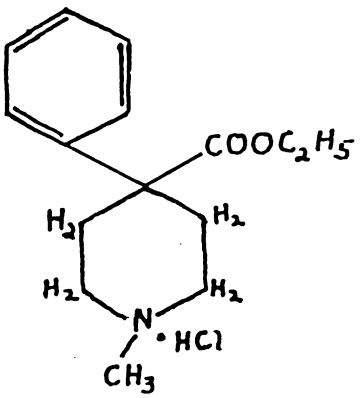
Quite a few investigators have studied the pharmacological activity of "Trasentin". Salow states that for acute pain due to spasm of smooth muscle the rectal and parenteral administration is followed in 10-30 minutes by relief which lasts four to six hours (19). Tablets taken by mouth were found to be efficacious in chronic cases.

Einhorn claims "Trasentin" has a pronounced muscular action and a neurotropic effect on parasympathetic nerve endings (20). When tested on the cat's pupil, the action of atropine is 1000 times stronger than that of the drug. After pilocarpine stimulation, the effect of the drug on salivary secretion in rabbits is much less than that of atropine. Tests on rabbits and cats indicate that the drug is moderately toxic when given intravenously, but it is not toxic except in excessive amounts when given intraperitoneally or intramuscularly.

Friedli states that "Trasentin" relieves spastic conditions of hollow viscera (21).

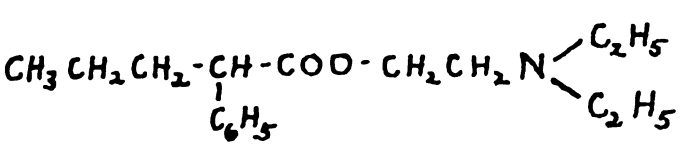
Thewlis gives an example of a woman suffering seven weeks from severe abdominal pain after eating, and although refractory to opiates she obtained relief by oral administration of 75 mg. of "Trasentin" after each meal (22).

The chemical and pharmacological properties of "Dolantin", the ethyl ester hydrochloride of 1-methyl-4-phenyl-piperidine-4-carboxylic acid,



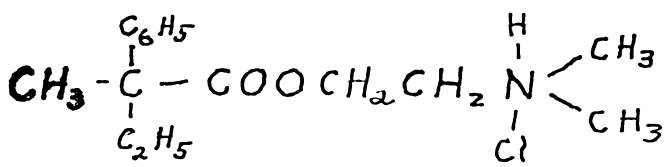
were given by Eisleb and Schaumann in 1939 (23). They claimed that this substance combined the antispasmodic action of atropine and papaverine with the analgesic action of morphine. Later, in 1940, Schaumann made a pharmacological study of Dolantin and 41 of its derivatives in various ways and found that most of the compounds have a complex neuromuscular spasmolytic action on smooth muscle and a central analgesic action somewhat like that of morphine (24). Since then Dolantin has received much study and today it is given in many clinics.

In 1938 Halpern reported the α-phenylvaleric ester of diethylaminoethanol as having antispasmodic properties resembling those of both atropine and papaverine (25).



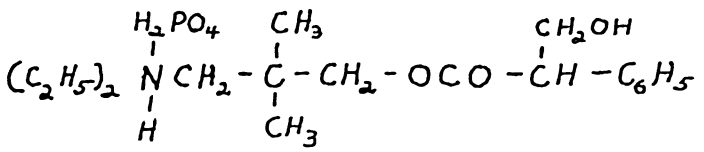
A little later he reports that many esters of the series $RCOOR'NX_2$ were studied and compared to atropine and papaverine (26). He claims that acids of the α-phenyl aliphatic series yielded the most active compounds and further that the α-phenylvalerate of diethylamino ethanol was only slightly toxic and antagonized the action of acetylcholine or $BaCl_2$ on the isolated intestine and on the intestine and bladder "in vivo". The latter ester has 1/3 the action of atropine on the isolated intestine, 1/200 on the heart and 1/5000 on the pupil. Viaud also reports the preparation of this compound by various methods and took out two patents on it in Germany and the United States respectively (27) (28).

Anna reports β-dimethylamino-α-phenyl-α-ethyl-propionate hydrochloride



as having a direct antispasmodic action on smooth muscle fibers and isolated organs (29). It is more effective than papaverine in equal concentrations, has little or no effect on the parasympathetic nervous system, produces a transient drop in blood pressure owing to vaso-dilatation and is less toxic than papaverine.

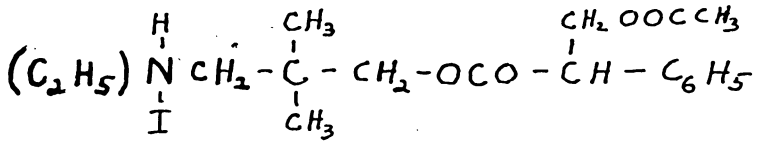
According to Pschyrembel the tropic acid ester of diethylamino-2,2-dimethyl-1-propanol in the form of a primary phosphate has been employed with considerable success to decrease spasm of the uterus during parturition (30).



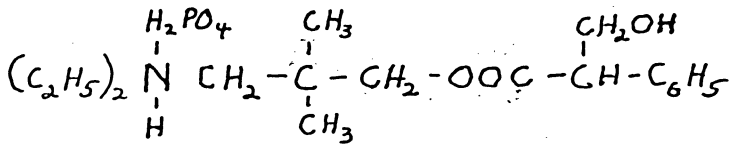
Fromherz reports the preparation and pharmacological testing of a series of esters of 3-diethylamino-2, 2-dimethyl-1-propanol (31). They were compared with atropine and papaverine on isolated small intestine to determine their relative antispasmodic activities. Their mydriatic effect on the cat was also determined. The toxicity of all the compounds was about the same and a curare effect was ascertained only in the quaternary compounds.* A table follows giving the compounds and their pharmacological data:

* Paralysis of the motor nerve ending, or "curare action", as it is called, is a condition in which the muscle contracts when a weak stimulus is applied directly to it, but fails to respond to even strong stimulation of the motor nerve, the impulse being "blocked" at the myoneural junction. Of drugs exercising the action the most important is curare, although it is often seen in poisoning by crotaline, strychnine, lathyrus, ether, brucine and certain amines, including trimethylamine, choline and muscarine; it is also shown by delphocurarine and cocaine (32).

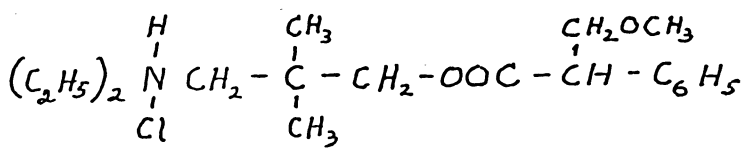
I. 3-Diethylamino-2,2-dimethyl-1-propanol acetyltropic acid ester hydroiodide.



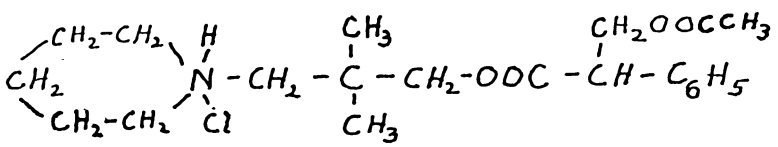
II. 3-Diethylamino-2,2-dimethyl-1-propanol tropic acid ester primary phosphate.



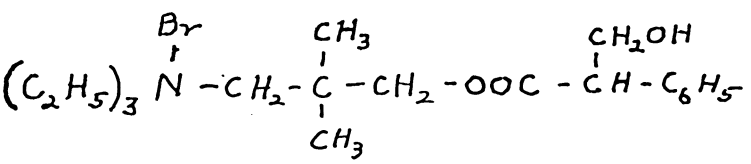
III. 3-Diethylamino-2,2-dimethyl-1-propanol methoxy-tropic acid ester hydrochloride.



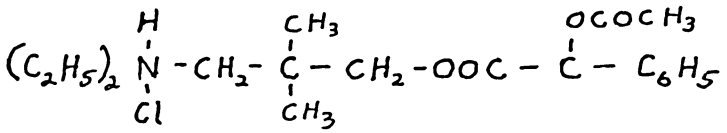
IV. 3-Piperidino-2,2-dimethyl-1-propanol acetyltropic acid ester hydrochloride.



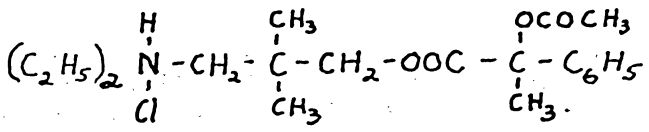
V. 3-Diethylamino-2,2-dimethyl-1-propanol tropic acid ester ethobromide.



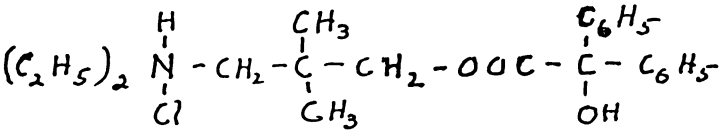
VI. 3-Diethylamino-2,2-dimethyl-1-propanol acetylmandelic acid ester hydrochloride.



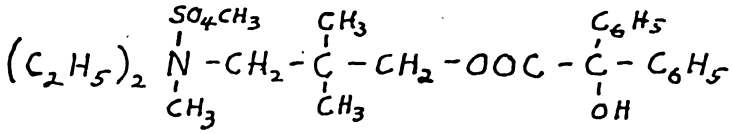
VII. 3-Diethylamino-2,2-dimethyl-1-propanol acetylatrolactinic acid ester hydrochloride.



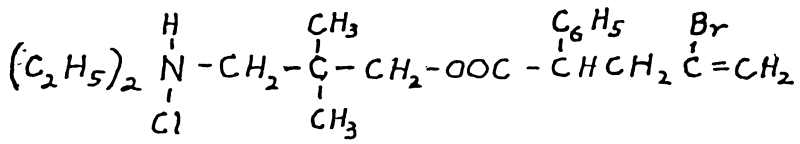
VIII. 3-Diethylamino-2,2-dimethyl-1-propanol benzilic acid ester hydrochloride.



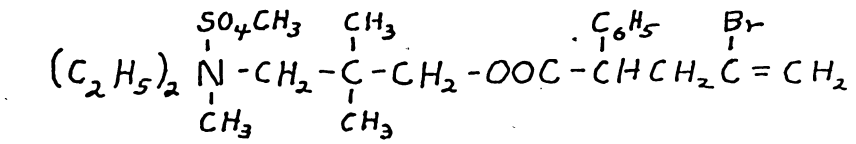
IX. 3-Diethylamino-2,2-dimethyl-1-propanol benzilic acid ester methyl sulfate.



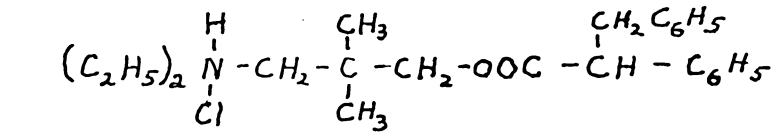
X. 3-Diethylamino-2,2-dimethyl-1-propanol phenyl-2-bromoallylacetic acid ester hydrochloride.



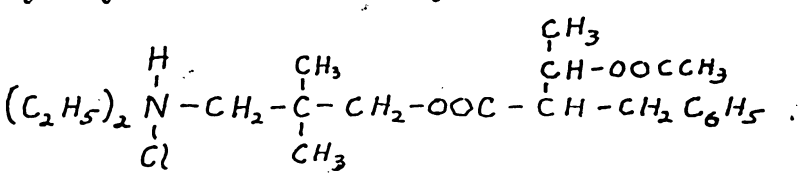
XI. 3-Diethylamino-2,2-dimethyl-1-propanol phenyl-2-bromoallylacetic acid ester methyl sulfate.



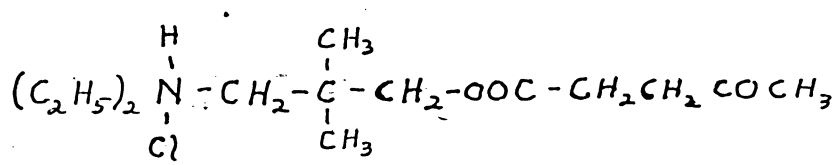
XII. 3-Diethylamino-2,2-dimethyl-1-propanol α,β-diphenyl-propionic acid ester hydrochloride.



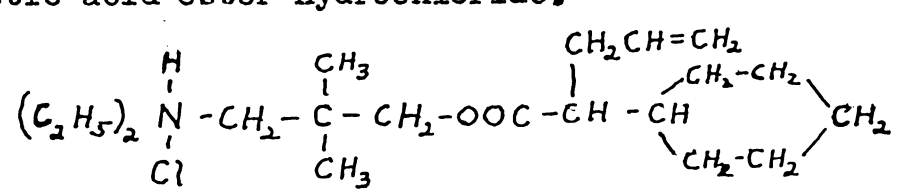
XIII. 3-Diethylamino-2,2-dimethyl-1-propanol α-benzyl-β-acetoxybutyric acid ester hydrochloride.



XIV. 3-Diethylamino-2,2-dimethyl-1-propanol levulinic acid ester hydrochloride.



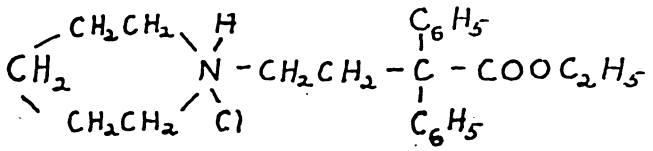
XV. 3-Diethylamino-2,2-dimethyl-1-propanol cyclohexyl-allylacetic acid ester hydrochloride.



Compd.	Dose fatal to mouse g/kg.	Parasympathetic Paralyzing Effect			Intestinal effect mg/50cc. bath fluid	
		Mydriatic effect on cat %	Isolated frog heart	Rabbit saliva mg/kg	Neural mg	Muscular mg
Atropine	.067	.001	+++	.1	.01-001	20
I	.08	1.0	++	10.0	.1-.02	5.0
I d-form	.067			20.0	.2	2.0
I l-form	.075	.05	++	2.0	.05-.01	1.0
II	.07				.1-.02	
III	.07				1-2	1-2
IV	.05	2.0	-	10.0	.2-.1	
V	.07	.5		5.0	.02	5.0
VI	.04	-	+	10.0	.2-.06	
VII	.065	.5	+	10.0	.2-.04	
VIII	.008	.2	++	1.0	.01-.002	.5
IX	.025	.1	+++	.05	.01-.001	20.0
X	.06	-		-	.02	0.5
XI	.01	.2		1.0	.01	
XII	.05	-			.04	1.0
XIII						
XIV						
XV	.01	-		-	.02	

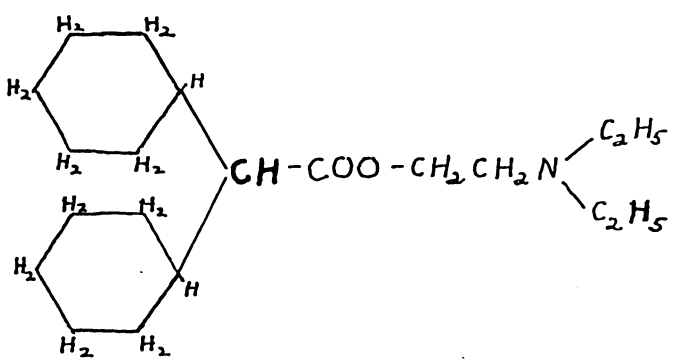
- = no effect
++ = strong effect

Bockmuhl and Ehrhart has patented the preparation of a series of basic esters of the general formula $R_1R_2R_3CCOOR_4$, which possess spasmolytic and analgetic action (33). R_1 and R_2 represent aryl radicals, R_3 a tertiary amino alkyl radical and R_4 an alkyl or aralkyl radical. Some of their preparations are: ethyl diphenylpiperidylethylacetate hydrochloride;

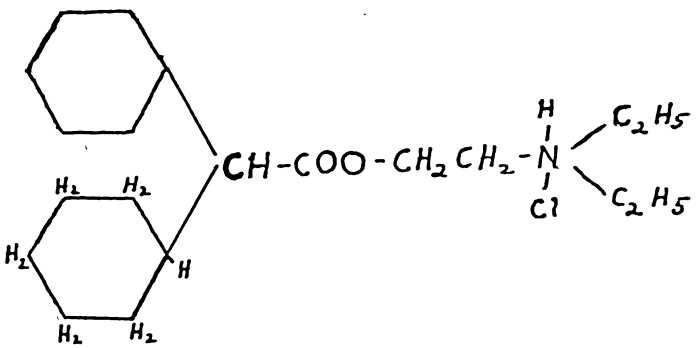


ethyl diphenyldiethylaminoethylacetate hydrochloride; isopropyl diphenylpiperidylethylacetate hydrochloride; ethyl diphenylmorpholinylethylacetate, and hydrochloride; ethyl piperidylethylfluorenecarboxylate, and hydrochloride; ethyl morpholinylethylfluorenecarboxylate, and hydrochloride; ethyl diphenyl-α-methylpyrrolidylethylacetate; and ethyl phenylveratrylacetate.

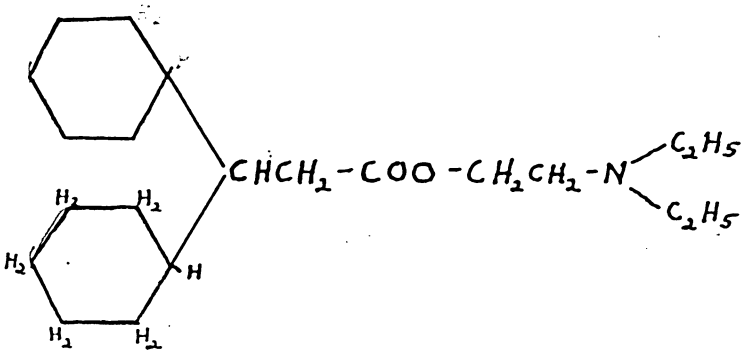
In 1942 Miescher and Hoffman secured a patent for Ciba Pharmaceutical Products Incorporated on the preparation of various basic esters with antispasmodic activity (34). These esters were produced by a process in which a di-alicyclic or aryl alicyclic lower aliphatic acid or derivative of such an acid reacts with an amino alcohol or hydrohalide or arylsulfonic ester of such an alcohol. They report the preparation of dicyclohexylacetic acid diethylaminoethanol ester and its hydrochloride,



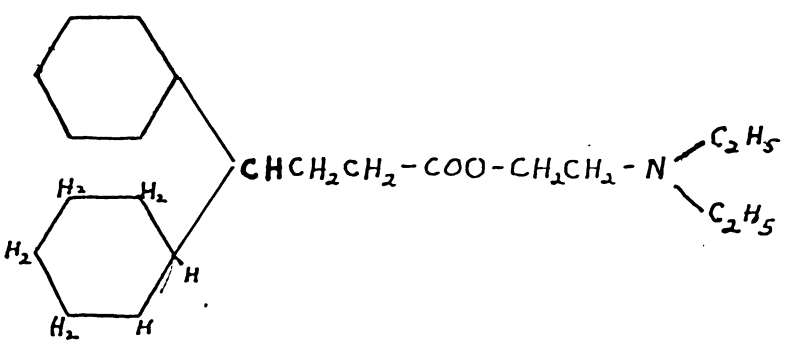
nitrate, tartrate, citrate, phosphate, oxalate, allyl bromide, methobromide, ethobromide and benzyl bromide salts; phenylcyclohexylacetic acid diethylaminoethanol ester hydrochloride (Trasentin 6H);



phenylcyclohexylpropionic acid diethylaminoethanol ester;



phenylcyclohexylbutyric acid diethylaminoethanol ester;



and basic esters of dicyclopentenylacetic acid, phenylcyclohexenylacetic acid and phenylcyclopentenylacetic acid. They also prepared the 1-piperidineethanol ester, diethylaminobutanol ester, diallylaminoethanol ester, 4-morpholineethanol ester, ethyl (acetoxyethyl) aminoethanol ester, ethyl (hydroxypropyl) aminoethanol ester, methylpropylaminoethanol ester and the dimethylaminocyclohexanol esters of phenylcyclohexylacetic acid, as well as quaternary salts of these compounds. Other antispasmodics reported in this patent are dicyclohexylacetic acid tropine ester hydrochloride, α,α-dicyclohexyl-α-hydroxyacetic acid diethylaminoethanol ester hydrochloride; α-phenyl-α-cyclohexyl-α-hydroxyacetic acid diethylaminoethanol ester hydrochloride; phenylcyclohexylacetic acid ester of ecgonine methyl ester; and phenyl (dimethylaminocyclohexyl) acetic acid diethylaminoethanol ester.

In addition to the above products Miescher and Hoffmann took out another patent for the preparation of antispasmodics by the action of a reducing agent such as H in the presence of an activated Pt or Pd catalyst on basic esters and amides of aryl-substituted lower aliphatic acids such as diphenylacetic acid diethylaminoethanol ester and the like, most of the compounds reduced being ones given in their first patent (35). Among the compounds they report are dicyclohexylacetic acid diethylaminoethanol ester hydrochloride; phenylcyclohexylacetic acid diethylamino-

ethanol ester and its hydrochloride, thiocyanide, nitrate, tartrate, phosphate, citrate, oxalate, allylbromide, methobromide, ethobromide and benzyl bromide; N-(2-diethylaminoethyl) dicyclohexylacetamide; N-(2-diethylaminoethyl) phenylcyclohexyl acetamide; phenylcyclohexylpropionic acid diethylaminoethanol ester; phenylcyclohexylbutyric acid diethylaminoethanol ester; dicyclohexylacetic acid tropine ester hydrochloride; α-cyclohexylhydracrylic acid tropine ester sulfate; α, α-dicyclohexyl-α-hydroxyacetic acid diethylaminoethanol ester hydrochloride; α-phenyl-α-cyclohexyl-α-hydroxyacetic acid diethylaminoethanol ester; α-cyclohexylhydracrylic acid scopine ester hydrochloride; α-cyclohexyl-α-propylacetic acid diethylaminoethanol ester hydrochloride; cyclohexylacetic acid diethylaminoethanol ester hydrochloride; phenylcyclohexylacetic acid ester of ecgonine methyl ester; phenyl (dimethylaminocyclohexyl) acetic acid diethylaminoethanol ester; and cyclohexyl (diethylaminoethyl) acetic acid diethylaminoethanol ester.

In February, 1943, Burtner and Cusic reported the preparation of some basic esters of some arylacetic acids (2). Their aim was to prepare a series of esters from acids which might substitute for the acid fraction of atropine and various amino alcohols corresponding to the alcoholic portion of that molecule. Since previous investigators had shown that certain basic esters of phenylalkyl- and diphenylacetic acids exhibit varying degrees of anti-

spasmodic activity they elected to study diphenylacetic acid and related types and employed basic alcohols varying in structure from those resembling tropine to the relatively simple dialkylaminoalkanols. In addition, since it was observed in previous studies on local anesthetics that cyclization of certain polynuclear carboxylic acid derivatives occasionly led to enhanced activity (36), they also studied the cyclized or bridged forms of the diarylacetic acids (fluorene, naphthalene, anthracene carboxylic acids, etc.). Lehman and Knoefel give a report on the activity of these compounds as compared to atropine, syntropan, trasentin and papaverine (37). The most promising compound appeared to be diethylaminoethylfluorene-9-carboxylate which had a potency of .14 to 20 times that of atropine, depending upon the test object. Following is a tabulation of the antispasmodics Burtner and Cusic prepared along with their reciprocal spasmolytic activities against acetyl choline and histamine induced spasm in isolated rabbit intestinal muscle referred to β-diethylaminoethyl fluorene-9-carboxylate taken as 1. The compounds are the hydrochlorides unless otherwise mentioned.

Compound	Reciprocal spasmolytic activity	
	Acetyl-choline	Hist-amine
β-Diethylaminoethanol tropic acid ester	1	20
β-Dimethyl-γ-diethylaminopropanol tropic acid ester (phosphate)	15	30
Tropine tropic acid ester (sulfate)	0.14	4
β-Diethylaminoethanol atropic acid ester	30	3
1-Methyl-4-hydroxy-piperidine atropic acid ester	30	2
β-Diethylaminoethanol α-phenyltropic acid ester	5	2
β-Diethylaminoethanol diphenylacetic acid ester	8	1.6
β-Diethylaminoethanol diphenylacetic acid ester	6	1.5
1-Methyl-4-hydroxypiperidine diphenyl-acetic acid ester	1.8	0.5
1-n-Butyl-4-hydroxypiperidine diphenyl-acetic acid ester	10	1.5
1-(β-Phenylethyl)-4-hydroxypiperidine diphenylacetic acid ester	10	3.7
1,2,6-Trimethyl-4-hydroxypiperidine diphenylacetic acid ester	4.6	2
β-Diethylaminoethanol benzilic acid ester	0.7	0.7
β-Diethylaminoethanol β-phenyl-β-hydroxypropionic acid ester	6	5
β-Diethylaminoethanol anisilic acid ester	10	6
β-Diethylaminoethanol α-chlorodiphenyl-acetic acid ester	0.7	0.7
β-Diethylaminoethanol β-diphenylacrylic acid ester	6	1.7
β-Diethylaminoethanol γ-diphenylcrotonic acid ester	10	10
β-Diethylaminoethanol diphenylmethylcar-bamic acid ester	6.5	1.5
N-β-Diethylaminoethyl diphenylacetamide. HCL	10	2.5
β-Diethylaminoethanol fluorene-9-car-boxylic acid ester	1	1
γ-Diethylaminopropanol fluorene-9-carboxylic acid ester	4	5

Compound	Reciprocal spasmolytic activity	
	Acetyl-choline	Hist-amine
γ-Diethylaminopropanol fluorene-9-carboxylic acid ester	10	4.5
β-Di-n-butylaminoethanol fluorene-9-carboxylic acid ester	12	9
β-Monoisobutylamihoethanol fluorene-9-carboxylic acid ester	5	2.5
1-Methyl-4-hydroxypiperidine fluorene-9-carboxylic acid ester	1	0.6
1-(β-Phenylethyl)-4-hydroxypiperidine fluorene-9-carboxylic acid ester	6	3.5
1,2,6-Trimethyl-4-hydroxypiperidine fluorene-9-carboxylic acid ester	2.8	1
N-β-Diethylaminoethyl fluorene-9-carboxylic acid amide. HCl	12	5
β-Diethylaminoethanol 2-aminofluorene-9-carboxylic acid ester	20	9
β-Diethylaminoethanol 9-hydroxyfluorene-9-carboxylic acid ester		
β-Diethylaminoethanol fluorene-9-acetic acid ester	11	1
β-Diethylaminoethanol γ-diphenylene-crotonic acid ester	10	10
β-Diethylaminoethanol di-1-naphthy-lacetic acid ester	50	20
β-Diethylaminoethanol di-2-naphthy-lacetic acid ester	200	40
β-Diethylaminoethanol 1-naphthilic acid ester	50	4
β-Diethylaminoethanol 2-naphthilic acid ester	100	5
β-Diethylaminoethanol α-phenyl-β-(2-furyl)-acrylic acid ester	20	4
β-Diethylaminoethanol anthracene-9-carboxylic acid ester	10	3
β-Diethylaminoethanol hydrindene-2-carboxylic acid ester	100	5
(bis)-β-Diethylaminoethanol *d, l*-camphoric	100	100

Burtner has patented the 9-fluorenecarboxylic acid esters prepared above (38).

A year previous to Burtner and Cusic's investigation into the preparation of fluorene-9-carboxylate esters as antispasmodics, Wolfes and Hromatka also took out a patent for Merck and Company, Inc. on the preparation of esters of this acid (39). They were the first to report β-diethylaminoethyl fluorene-9-carboxylate. They also patented the preparation of the hydroxyethylmorpholine ester, the tropine ester, the methylethyl (diethylaminomethyl) carbinol ester, the codeine ester, and the hydroxyethylpiperidine ester.

In April, 1942, Cheney and Bywater of the Parke, Davis and Company, reported the preparation of a large number of 4-morpholinealkyl esters and amides possessing antispasmodic activity (40). The three most active compounds in this series are β,β-dimethyl-γ-4-morpholinepropyl diphenylacetate hydrochloride.

$$(C_6H_5)_2CH-COOCH_2C(CH_3)_2CH_2NC_4H_8O\cdot HCl$$

6-(4-morpholine)hexyldiphenylacetate hydrochloride,

$$(C_6H_5)_2CH-COO(CH_2)_6NC_4H_8O\cdot HCl$$

and β-4-morpholineethyl-α-phenylcyclohexaneacetate hydrochloride.

$$C_6H_5-\underset{(cyclo)C_6H_{11}}{\overset{|}{C}}H-COOCH_2CH_2NC_4H_8O\cdot HCl$$

The pharmacological data as determined by Rowe indicated that it is essential to have a disubstituted acetic acid derivative wherein at least one group is aryl, since the mono-aryl, di- and tri-alkyl and monoalicyclic acid esters are relatively inactive (41). In general, branching of the alkyl chain and lengthening of the long straight chain in the alcohol portion of the ester lead to more active compounds within certain limits of solubility. The amides are less active antispasmodics than the corresponding esters.

Following is a table listing Cheney and Bywater's compounds along with their antispasmodic activities compared to papaverine = 100.

Compound (R = -4-morpholineethyl-)	Activity
Diphenylacetic acid R-amide	
β,β-Dimethyl-γ-4-morpholinepropyl diphenylacetate	
R N,N-diphenylcarbamate	
α-Phenylcyclohexaneacetic acid R-amide	
β,β-Dimethyl-γ-4-morpholinepropyl α-phenylcyclohexaneacetate	
β,β-Dimethyl-γ-4-morpholinepropyl benzoate	
Hydrochlorides	
α-Chlorodiphenylacetic acid R-amide	50
Diphenylacetic acid R-amide	20
α-Phenylcyclohexaneacetic acid R-amide	50
R diphenylacetate	75
Compound	**Activity**
Hydrobromide	40
R benzilate	25
R α-acetoxydiphenylacetate	25
R α-chlorodiphenylacetate	75

Compound	Activity
R β,β-diphenylpropionate	50
R dibenzylacetate	60
R α-phenylcyclohexaneacetate	100
R triphenylacetate monoalcoholate	25
R N,N-diphenylcarbamate	30
R phenylacetate monohydrate	10
R cinnamate	40
R cyclohexanecarboxylate monohydrate	10-20
R 2-camphanecarboxylate	60
R trimethylacetate picrate	5
R t-butylacetate	5-10
γ-4-Morpholinepropyl diphenylacetate	75
γ-4-Morpholinepropyl diphenylacetate bromobenzylate	50
α-Methyl-R diphenylacetate	60
δ-4-Morpholinebutyl diphenylacetate	60
β-Methyl-β-4-morpholinepropyl diphenylacetate	60
β,β-Dimethyl-γ-4-morpholinepropyl diphenylacetate	200
Sulfate	200
β,β-Dimethyl-γ-4-morpholinepropyl-phenylcyclohexaneacetate	10
β,β-Dimethyl-γ-4-morpholinepropyl benzoate	40
β,β-Dimethyl-γ-4-morpholinepropyl cinnamate	40
ω-4-Morpholinehexyl diphenylacetate	150

Benzylmethylaminoethyl dibenzylacetate is an antispasmodic according to Itikawa in a Japanese patent (42).

Amides

In 1937 Junkmann studied the antispasmodic effect of a series of alkyl substituted acetamides on the rabbit intestine in glucose-free Tyrode solution containing 0.1% of $BaCl_2$, (43) (44). It was found that generally three alkyl substitutions give stronger effects than two and that the strongest spasmolytic effect is in

the compounds with 12 to 17 carbon atoms. Still further lengthening of the substituted saturated alkyls leads rapidly to the loss of spasmolytic activity. The most active compound was tri-n-butylacetamide,

$$(n\text{-}C_4H_9)_3\,C\text{-}CONH_2$$

now known as the commercial product "jucundal". Below is a list of the acetamides reported in this article along with their spasmolytic potencies compared to that of procaine hydrochloride taken as 1 or that of papaverine hydrochloride taken as 80:

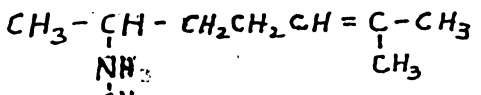
Diethyl -		methyldiethyl -	0.25
triethyl -	0.5	n-propyldiethyl -	1.5
n-butyldiethyl -	5	n-hexyldiethyl -	15
di-n-propyl -	0.85	methyl-di-n-propyl -	1.8
ethyl-di-n-propyl -	6	tri-n-propyl -	16
n-butyl-di-n-propyl -	75	ethyl-di-n-butyl -	10
n-propyl-di-n-butyl -	87	tributyl -	100
di-n-hexyl -		methyl-di-n-hexyl -	100
tri-n-hexyl -	0.0	ethyl-di-i-amyl -	150
tri-i-amyl	100	allyldiethyl -	
allyl-di-n-propyl -		allylethyl-n-propyl-	
diallyl -	0.2	methyldiallyl -	0.5
ethyldiallyl -	2	n-propyldiallyl -	6
i-propyldiallyl -	3	triallyl -	2.8
n-butyldiallyl	8		

Later, in 1940, Junkmann and Allardt took out a patent on some of Junkmann's trialkylacetamides. This patent covered compounds containing the same or different saturated alkyl groups with a total of 12 to 17 carbon atoms and in which the alkyls all contained at least 3 carbon atoms. (45).

Amines:

In 1935, Kissling reported "octinum", methyl-octenylamine, as being about ten times as active as papaverine and about twice as toxic (46). It has been tried on more than one hundred cases and has given excellent results in the treatment of convulsions, pain from spasm in stomach and intestines or pain from ulcers in these organs.

In 1936, Klavehn obtained a German patent for unsaturated amines prepared by condensing 2-methyl-2-hepten-6-one with a primary amine and subjecting the product to the action of a reducing agent (47). Examples given are 6-methylamino-2-methyl-2-heptene, known as "octin", 6-ethylamino-2-methyl-2-heptene and 6-benzylamino-2-methyl-2-heptene.



Octin

Klavehn and Wolf have patented some saturated ethylamine derivatives which have antispasmodic activity (48). These compounds have the general formula $R_2R_3NCHR_1CH_3$ where R_1 is an alkyl radical containing six carbon atoms, R_2 is H or a lower alkyl radical and R_3 is an alkyl radical containing 1, 3 or 5 carbon atoms, or a cycloalkyl radical.

Typical compounds are 2-cyclopentylaminooctane, and 2-methyl-isoamylaminooctane. They also patented some unsaturated ethylamine derivatives of the general formula $R_1CH(NR_2R_3)CH_3$, where R_1 is an alkenyl radical containing four carbon atoms, R_2 is H or a lower alkyl radical containing at least 2 carbon atoms and R_3 is a lower alkyl, lower alkenyl, cycloalkyl or phenyl-lower-alkyl radical (49). Compounds typical of the latter type are 5-benzylamino-1-hexene and 5-tert.-methyl-benzylamino-1-hexene. Still another patent was secured by Klavehn and Wolf (50). In this case, the production of compounds of the general formula $R_1CH(NHR_2)CH_3$ is claimed, where R_1 is a lower alkenyl radical from the group consisting of straight-chained alkenyl radicals having six carbon atoms and branched-chain alkenyl radicals having six carbon atoms, where the branch is upon a hydrogenated carbon atom, and R_2 is a radical from the group consisting of lower alkyl, lower alkenyl and cycloalkyl radicals. Examples of the last type of compounds are 5-methylamino-4-ethyl-1-hexene and 6-methylamino-5-methyl-1-heptane.

Subsequent to their preceeding work, Klavehn and Wolf secured a patent on saturated derivatives of ethylamine, of the general formula $CH_3CH(R_1)NHR_2$, where R_1 is an alkyl radical containing 4, 5, 6 or 7 carbon atoms in a straight or branched chain and R_2 is an alkyl radical containing 1, 3 or 5 carbon atoms or a cycloalkyl radical (51). These compounds have a favorable antispasmodic action. Some of the typical compounds prepared are 6-methylamino-

2-methylheptane, 4-methylamino-2-methylpentane, 2-methylaminoheptane, 2-methylaminononane, 6-cyclohexylamino-2-methylheptane, and 2-methylaminooctane.

It has been observed repeatedly that physiologically active compounds with hydrogenated rings retain their characteristic activity when the ring is opened (52). Tetrahydropapaverine has qualitatively the same, although quantitatively a considerably weaker, effect than papaverine. Buth, Kulz and Rosenmund wondered whether bis-β-(3,4-dimethoxyphenylethyl)amine, the product formed by opening the hetero ring, would retain this action (52). Tests showed that the mother substance, $(PhCH_2CH_2)_2NH$, weakens or completely inhibits the smooth muscle stimulating action of barium ions, although it is considerably less powerful than papaverine. Accordingly, these men synthesized a number of derivatives of $(PhCH_2CH_2)_2NH$ and obtained some with pronounced spasmolytic properties, as well as some anesthetic action. Their most active compounds and their antispasmodic activity compared to papaverine = 1, are as follows:

$C_6H_5CH_2CHEtNHCH_2C_6H_5$, 2

$C_6H_5CH_2CH(C_3H_7)NHCH_2C_6H_5$, 2

$C_6H_5CH_2CH(CH_2CHMe_2)NHCH_2CH_2C_6H_5$, 3

$C_6H_5CH_2CHC_6H_5NHCH_2CH_2C_6H_5$, 3 and higher

$C_6H_5CH_2CHC_6H_5NHCH_2CH(OMe)C_6H_5$, 3-4

$C_6H_5CH_2CH(CH_2C_6H_5)NHCHMeCH_2C_6H_5$, 4

These compounds were isolated as the hydrochlorides and the antispasmodic tests were carried out on rabbit intestine. The compounds were not very practicable, however, because of insufficient solubility.

Since the above compounds were impractical, as mentioned, Kulz, Rosenmund and Kayser continued their study along other lines (53). The introduction of alkyl residues in the side chain had been found to increase the spasmolytic activity; therefore, the effect of their introduction into other parts of the molecule was studied. Alkylation of the benzene rings resulted in a great increase in activity. The effect of alkylation on the nitrogen atom was irregular; a methyl group produced marked weakening of the activity; increasing the number of carbon atoms in the alkyl residue gradually increased the activity. A promising feature of the nitrogen alkylation was the resulting increase in solubility without the appearance of harmful secondary effects. This, in combination with a further increase in the number of carbon atoms, not by substitution but by lengthening the side chain, led to completely satisfactory results. The maximum activity was obtained with $(PhCH_2CH_2CH_2)_2NEt$ which was 2.3 times as active as papaverine and is now on the market under the name "Sestron", Kulz et al prepared 140 compounds but none were superior to "sestron". Some of the other favorable

compounds and their spasmolytic activities compared to papaverine = 1 are as follows:

(β-p-Tolylethyl)-(β-phenylethyl)amine, (1.5)

Bis(p-tolylethyl)amine, (2)

Bis(β-phenylethyl)hexylamine, (1-2)

Bis(δ-phenylbutyl)ethylamine, (2)

β-(3,4-Dimethoxyphenyl)isopropyl (γ-phenylpropyl) ethylamine, (more than 1)

(γ-Phenylpropyl)benzylamine, (1.5)

(δ-Phenylbutyl)benzylamine, (1-2)

(δ-Phenylbutyl)(β-phenylethyl)ethylamine, (1-2)

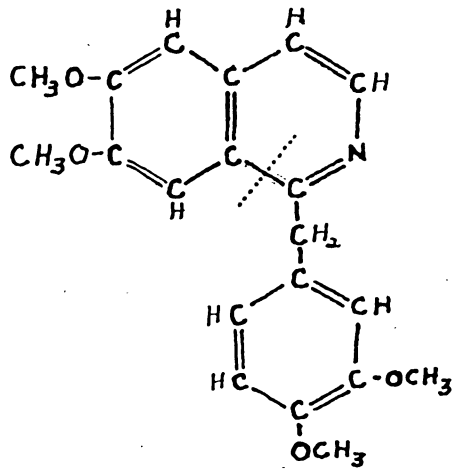
(δ-Phenylbutyl)(γ-phenylpropyl)ethylamine, (2)

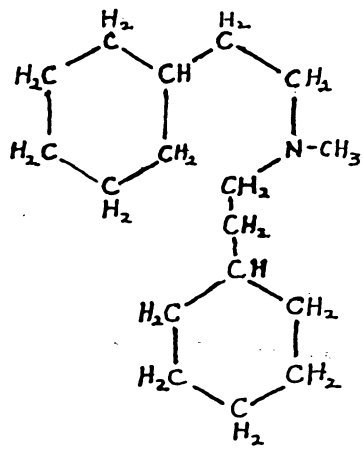
(γ-Phenylpropyl) [β-(4-methoxyphenyl)-ethyl] ethylamine, (2)

Rosenmund and Kulz have a patent on many of their more active amines (54).

In 1939 Blicke and Monroe prepared a number of secondary and tertiary amines of the general types $RN(H)(CH_2)xR'$ and $RN\left[(CH_2)xR'\right]_2$ in which R is alkyl and R' is cycloalkyl (55). Several of these compounds, especially methyldi-(β-cyclohexylethyl)amine, proved to be strong antispasmodics. Although these compounds are distinctly different from papaverine in structure, nevertheless, a relationship between some of them, for example methyldi-(β-cyclohexylethyl)-amine, and a completely hydrogenated papaverine can be

established if the isoquinoline ring is ruptured as shown in the accompanying formula.





Papaverine Methyldi-β-cyclohexylethylamine

The compounds, all isolated as the hydrochlorides, reported as active in this study were as follows:

Amine (Secondary)

Cyclohexyl-β-cyclohexylethylamine
Butyl- δ-cyclohexylbutylamine

Amine (Tertiary)

Methyldi-β-cyclohexylethylamine
Ethyldi- β-cyclohexylethylamine
Methyldi- β-phenylethylamine
Methyldi- γ-phenoxypropylamine

Other compounds were also prepared but they had weak activity or were inactive when tested on the small intestine of the rabbit according to the Magnus method (56)(57)(58).

Following the above study Blicke and Zienty

prepared a series of dicycloethyl amines of the general formula $RN(CH_2CH_2C_6H_{11})_2$ in which R is H, methyl, ethyl, propyl, isopropyl, butyl, amyl, heptyl, phenyl, β-cyclohexylethyl, allyl, cyclohexyl, benzyl or β-hydroxyethyl (59). The first five compounds were active, the butyl and amyl derivatives weakly active, the heptyl inactive, the phenyl and β-cyclohexylethyl weak, the allyl, cyclohexyl and benzyl were stimulants and β-hydroxyethyldi-β'-cyclohexylamine was inactive. They also prepared a series of secondary amines of the general formula $RN(H)(CH_2CH_2C_6H_{11})_2$ in which R = propyl, isopropyl, amyl, heptyl, phenyl, β-cyclohexylethyl or α-cyclohexylethyl; only the heptyl, β-cyclohexyl-ethyl and α-cyclohexylethyl compounds were active antispasmodics. Also, a few compounds of the type $CH_3N(CH_2CH_2R)_2$ were prepared in which R represents phenyl, phenoxymethyl, cyclopentyl or benzoyl; the first two compounds proved to be active and the last two weak.

The compounds prepared by Blicke, Monroe and Zienty (55)(59) indicated that methyldi-β-cyclohexylethylamine, $CH_3N(CH_2CH_2C_6H_{11})_2$, and certain other closely related cycloalkylalkylamines are strong antispasmodics. Since the cyclohexyl group is aliphatic rather than aromatic in character Blicke and Zienty decided to determine whether or not antispasmodic activity might be found among the saturated strictly aliphatic amines, particularly in such

a compound as methyldi-n-octylamine since this compound contains two saturated carbon chains which correspond to those formed if the cyclohexyl rings in methyldi-β-cyclohexylethylamine were ruptured between the ring carbon atoms 1 and 2 (60), Methyldi-n-octyl and methyldi-n-hexylamine were prepared and found to be weakly active as antispasmodics. However, the following compounds were found to be strong antispasmodics;

amyldi(β-cyclopentylethyl)amine

methyldi(β-3-methylcyclohexylethyl) amine

4-isomer(β-4-methylcyclohexylethyl) amine

ethyldi(β-phenylethyl) amine

propyldi(β-phenylethyl)amine

ethyl(β-cyclohexylethyl)(cyclohexylmethyl) amine

ethyl(β-cyclohexylethyl)(β-phenylethyl) amine

N,N'-dimethyl-N,N'-di(β-cyclohexylethyl)ethylenediamine

N,N'-dimethyl-N,N'-di(β-cyclohexylethyl)trimethylenediamine

Blicke and Zienty prepared still another series of antispasmodics which were mixed tertiary amines of general formula CH_3NRR' in which R represents a β-cyclohexylethyl and R' an alkyl, cycloalkylalkyl or arylalkyl group (61). The strong antispasmodics obtained were:

methylcinnamyl(β-cyclohexylethyl)amine

methylcyclohexyl(δ-cyclohexylbutyl)amine

methyl(cyclohexylmethyl)(γ-cyclohexylpropyl)amine

methyl(cyclohexylmethyl)(δ-cyclohexylbutyl)amine

methyl(β-cyclohexylethyl)octylamine

methyl(β-cyclohexylethyl)(β-phenylethyl)amine

methyl(β-cyclohexylethyl)(γ-cyclohexylpropyl)amine

methyl(β-cyclohexylethyl)(δ-cyclohexylbutyl)amine

methyldi(γ-phenylpropyl)amine

methyldi(δ-phenylbutyl)amine

In 1940, as a result of all the preceeding preparation of compounds, Blicke patented a number of his more active tertiary N,N-dicycloalkylalkylamines (62).

Hildebrandt has taken out three patents for the preparation of a series of β-(p-hydroxyphenyl)isopropyl-, β-(o-hydroxyphenyl)-isopropyl- and β-(m-hydroxyphenyl) isopropylamines all of which have a bronchoplasmolytic effect (63)(64)(65). These compounds have the general formula $HOC_6H_4CH_2CH_2MeNXY$, where X is H, alkyl or cycloalkyl, and Y is an alkyl with at least 2 carbon atoms or a cycloalkyl radical.

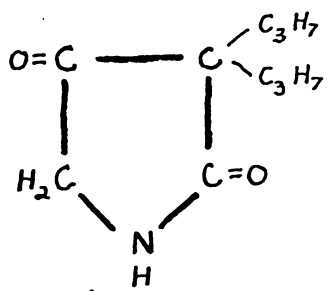
Heyn (66) in 1942 patented some antispasmodic compounds consisting of secondary and tertiary amines of the general formula YN(R)X, where R represents a cycloalkylalkyl radical, X represents a member of the group consisting of the alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, alkylcycloalkyl, and alkylcycloalkylalkyl radicals; Y represents an alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, alkylcycloalkyl; alkylcycloalkylalkyl radicals or hydrogen. The sum

of the carbon atoms in the X and Y of the tertiary amines is at least six. The patent makes specific mention of methylbis(β-cyclohexylethyl)amine and its hydrochloride.

Eisleb has reported the preparation of various compounds which have good spasmolytic activity (67). Of the many compounds given the following are specifically mentioned as being good antispasmodics: N,N,Diethyl-3, 3-diphenylpropylamine which also has local anesthetic action, 3-diethylamino-1-phenylpropylphenylketone, and 4-phenyl-pentamethylene-oxide-4-carboxylic acid 2-diethylaminoethyl ester hydrochloride.

Cerkovnikov and Prelog made a number of substituted 4-aminopiperidines claimed to have papaverine and atropine-like spasmolytic properties (68). They are of the general type, $RN(CH_2CH_2)_2NR'R''$. The compounds where R = heptyl, $R' = R''$ = methyl, and R = phenyl, $R' = R''$ = methyl, were especially powerful antispasmodics.

The preparation of 2,4-dioxo-3,3-dipropylpyrrolidine has been patented and it is claimed to be an antispasmodic capable of relaxing eleptic-type cramps (69).



Notkin and Webster claim that amidopyrine in concentrations from 1:10,000 to 1:2,500 shows antispasmodic activity when tested on muscle of isolated segments of guinea pig and rabbit intestine (70). They also describe its antispasmodic activity when given in 0.5-4.0% concentrations on dog and cat intestinal muscle (71).

Other Compounds

Seydel holds a patent for the use of calcium benzylsuccinate as an antispasmodic (72).

Dunning Jr., Dunning and Reid have prepared a number of substituted hydroxybenzyl alcohols and determined their antispasmodic activity relative to saligenin (o-hydroxybenzyl alcohol) taken as unity (73). Following is a list of the compounds and their relative activities.

Benzyl Alcohol Derivitives	Relative anesthetic efficiency	Relative antispasmodic action
3,5 diiodo-2-hydroxy-	30	50
3 iodo-5-bromo-2-hydroxy-		
3,5-Dibromo-2-hydroxy-	15	25
3-chloro-5-bromo-2-hydroxy-		
3,5 dichloro-2-hydroxy-	7.5	2.7
5-propyl-2-hydroxy-	20	10
5-iodo-2-hydroxy-	10	25
5-bromo-2-hydroxy-	5	16.5
5-chloro-2-hydroxy-	2	6
5-ethyl-2-hydroxy-	3.4	5
5-methyl-2-hydroxy-	2.5	4
2-hydroxy	1	1
6-methyl-2-hydroxy-	0.9	5.5
4-methyl-2-hydroxy-	1.8	6
6-Bromo-3-hydroxy-	2	25
3-Hydroxy-	0.2	1.1
3-Bromo-4-hydroxy-	.8	1.5
4-Hydroxy-	.03	0.75

Weider has prepared over one hundred derivatives of 3-coumarincarboxylic acid some of which he claims have antispasmodic activity (10). A number of esters and alkyl-substituted acid amides were prepared together with salts of physiologically active bases such as papaverine, mentioned on page 7 of this thesis. Compounds with simple or complex ring substituents were also synthesized and tested. Typical compounds prepared were the dl-ephedrine and l-ephedrine 3-coumarincarboxylates, l-p-aminophenyl-2-methylamino-1-propanol 3-coumarincarboxylate, quinine 3-coumarincarboxylate, and sparteine 3-coumarincarboxylate. dl-Ephedrine 3-coumarincarboxylate is a constituent of the favorably-known antiasthmatic "Epocan".

Bockmühl, Ehrhart, Stein and Hallensleben have secured a patent for the preparation of various amino alcohols which exhibit good antispasmodic action on the bronchial spasms and also on the bile ducts and intestine (74). The compounds reported are:

phenylmethylmethoxy-methylbenzylaminopropanol-HCl
methylenedioxybenzylephedrine-HCl
ethylenedioxy-benzylephedrine-HCl
3-carbethoxy-4-methoxy-benzylephedrine-HCl
m-ethoxybenzylephedrine-HCl
3-benzyloxy-4-methoxybenzylephedrine

Eisleb has patented a number of 4-aryl-4-piperidyl ketones which exhibit antispasmodic activity (75). He gives details for the preparation of

1-methyl-4-phenyl-4-piperidyl methyl ketone
1-methyl-4-phenyl-4-piperidyl ethyl ketone
1-methyl-4-phenyl-4-piperidyl phenyl ketone
1-methyl-4-phenyl-4-piperidyl benzyl ketone

1-benzyl-4-phenyl-4-piperidyl ethyl ketone
1-cyclohexyl-4-phenyl-4-piperidyl ethyl ketone

(Cf. reference (67))

Preiswerk and Mayer have patented the manufacture of 4-aralkyl-3-keto:4-dihydro-1:4benzoxazines as analgesics and antispasmodics (71). The compounds reported are the 4-benzyl-, 4-o-chlorobenzyl-, and 4-β-phenylethyl derivatives of 3-keto:4-dihydro-1:4 benzoxazine, as well as the 4-benzyl-derivatives of its 2-phenyl and 6-methyl compounds (76).

PROCEDURE AND DISCUSSION

It is evident from the introduction that there is little correlation between the chemical structure of antispasmodics and their physiological activity. Activity is found in many different types of compounds; esters, alkamine esters, amines, ketones, amides, alcohols, etc. However, when a particular type of compound is chosen it is possible to make some deductions of the relation of structure to activity. The problem here is exactly analogous to the one in the chemistry and pharmacology of local anesthetics(77).

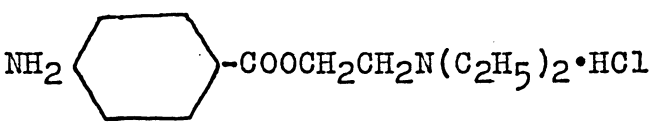
The series of alkamine esters which show antispasmodic activity provide interesting material for speculation. The compounds are of the following type:

$$R_1R_2R_3C\text{-}COO\text{-}X\text{-}NYZ$$

where R_1, R_2, R_3, Y and Z are carbon radicals and X is an alkylene chain. The work of Cheney and Bywater (40) and Burtner and Cusic (2) shows that maximum activity is obtained when $R_1R_2R_3C\text{-}COO\text{-}$ constitutes a disubstituted acetic acid wherein at least one group is aryl. Thus diphenylacetic acid, α-phenylcyclohexaneacetic acid and fluorene-9-acetic acid have led to very active compounds. Variation of the alkamine portion of the molecule (-X-NYZ) has pronounced influence on the activity as is evidenced in the lists of compounds prepared by the above workers. In a series of morpholine compounds

(NYZ= NC_4H_8O), prepared by Cheney and Bywater, branching and lengthening of X increased the activity (41). Substitution of different YZ groups in which the rest of the molecule is kept constant produces variable affects on the activity (37). Little has been done, however, concerning the connecting link between $R_1R_2R_3C$— and -X-NYZ. All the work has been centered upon carboxylic esters. A few amides, $R_1R_2R_3CONH$-X-NYZ, have been prepared, but Cheney and Bywater report them as relatively inactive.

It is important now to point out the close relationship of the structure of local anesthetics and antispasmodics of the alkamine ester type. The best known local anesthetic is procaine and has the formula



NH_2-$COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

Hudreds of compounds analogous to procaine have been prepared and it is known that local anesthetic activity can be expected in alkamine esters of an aromatic carboxylic acid,

Ar-COO-X-NYZ

The main difference between antispasmodics and local anesthetics which has been brought out by numerous researches is that the antispasmodics are esters of aliphatic acids while local anesthetics are esters of aromatic carboxylic acids.

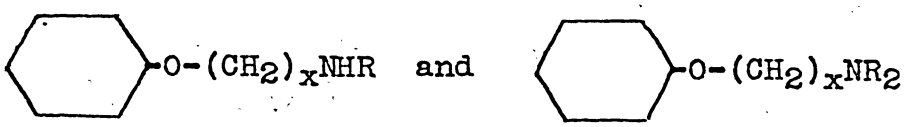
The analogy in structure is also reflected in

pharmacological action. Practically all of the antispasmodics of the alkamine ester type exhibit local anesthetic action to some degree.

In recent years much has been learned about the relationship of structure of the procaine type molecule to local anesthetic activity. Philbrook has reviewed this work extensively (78). He points out that substitution of other connecting groups for the carboxy group in

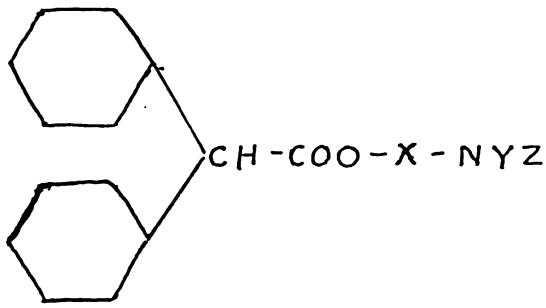
$$Ar\text{-}COO\text{-}X\text{-}NYZ$$

can be accomplished without qualitative loss of activity. Groups which can be used are -CONH-, -CO-, $-SO_3-$, -COS-, and -O-. The ether linkage was studied by Philbrook who prepared 32 compounds of the type



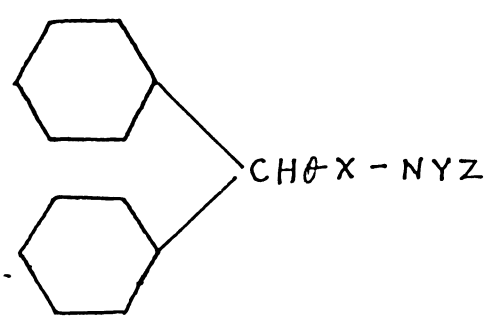
where X = 2 and 3 and R = ethyl⟶heptyl. Strong local anesthetic activity was found in the series (79). As a result of this work it may be said conclusively that the substitution of an ether group for the carboxy group did not destroy the local anesthetic activity of the procaine type molecule. In many cases the activity of the ether compounds is greater than the corresponding carboxylic acid compounds.

It is quite logical then that a study of compounds of the "Trasentin" type



be undertaken in which the carboxy is replaced by an ether group. The main objective of this research is to determine whether the ether analogs of the "Trasentin" type antispasmodic possess activity. In other words it is desired to determine whether the substitution of an ether linkage can be accomplished with the same results in antispasmodic compounds as Philbrook showed with local anesthetics.

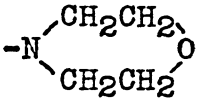
To test this hypothesis it is necessary to prepare a series of benzhydryl ethers. The desired compounds are of the following type

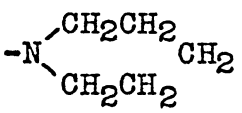
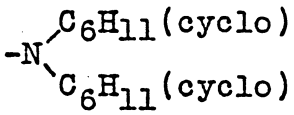


A literature survey showed that no compounds of this type have been prepared previously. In order to investigate the relation of structure and possible activity as much variation as possible in XNYZ was desirable. The following series of compounds were planned:

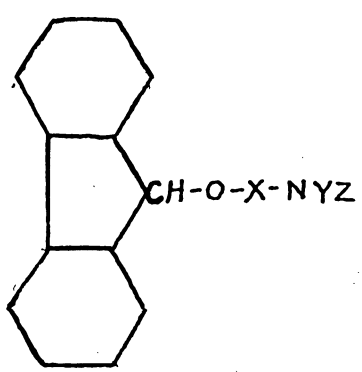
$$(C_6H_5)_2CH\text{-}O\text{-}XNYZ$$

where X = $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2-C(CH_3)_2-$, $-CH_2CH_2-O-CH_2CH_2-$

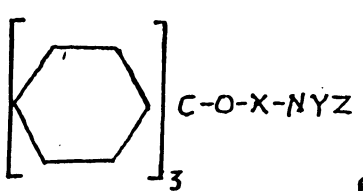
NYZ = $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(n\text{-}C_4H_9)_2$,  ,

 , 

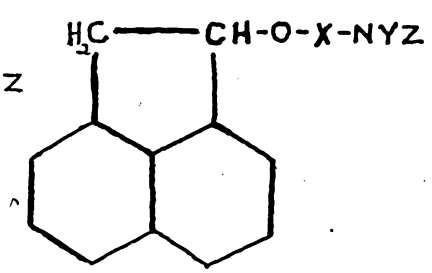
In addition it was thought worthwhile to prepare some ether compounds containing other nucleii than the benzhydryl group. The following were projected compounds:



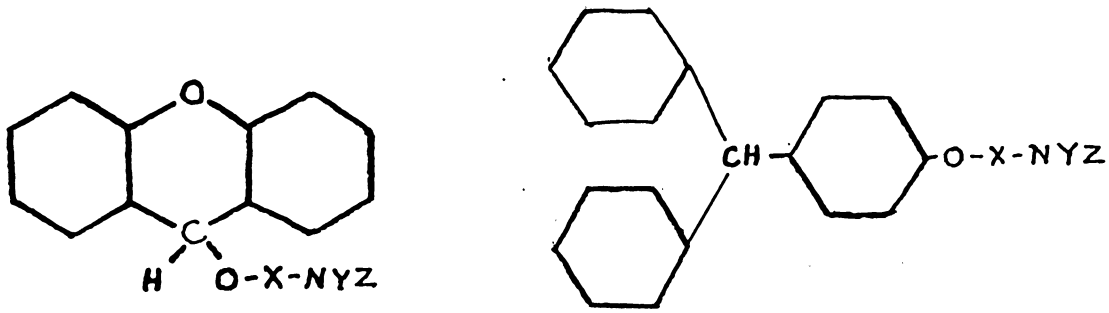
I



II

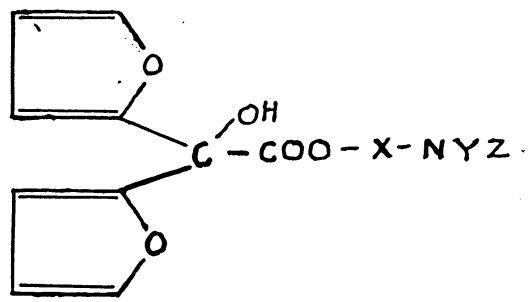


III



These are the fluorenyl, triphenyl, acenaphthyl, xanthydryl and p-benzhydrylphenyl derivatives respectively.

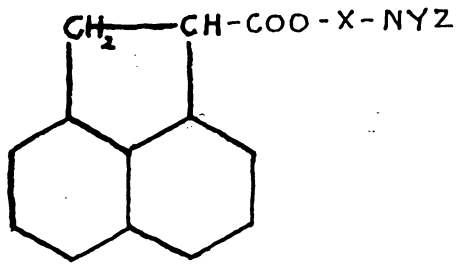
Besides the work on ether linkages attempts were made to prepare several other type compounds, namely, esters and ketones. It was decided to prepare several alkamine esters of furilic acid.



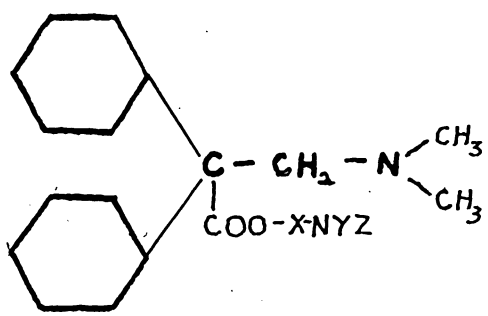
This work was under way but time has not permitted the completion of any derivatives.

An attempt to prepare 7-acenaphthylcarboxylic acid by the Grignard reaction from 7-acenaphthyl bromide was

unsuccessful. It was planned to prepare some alkamine esters of this acid in the hope that they too would exhibit antispasmodic activity.

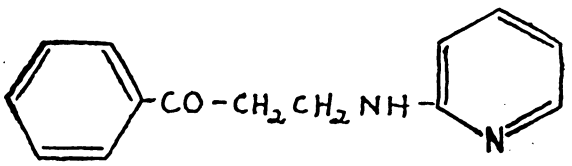


An attempt to prepare -dimethylaminomethyldiphenylacetic acid by the Mannich reaction between diphenylacetic acid, dimethylamine and formaldehyde was also unsuccessful. It was proposed to prepare several alkamine esters of this acid.



A Mannich reaction was run using 2-aminopyridine, paraformaldehyde and acetophenone to obtain β-(2-pyridylaminoethyl) phenyl ketone as this was hoped to be a new antispasmodic. A product was obtained which was isolated

both as the picrate and as the methiodide. However its structure is in doubt as the analyses of these derivatives for nitrogen were unsatisfactory.



Preparation of the compounds:

Attempted syntheses:

1. It was first decided to prepare the benzhydryl alkamine ethers by interaction between β-bromoethylbenzhydryl ether and various secondary amines. However attempts to prepare the bromo ether by reaction between the sodium salt of diphenyl carbinol and 1,2-dibromoethane in xylene as follows,

$(C_6H_5)_2CHONa + BrCH_2CH_2Br \longrightarrow (C_6H_5)_2CHOCH_2CH_2Br + NaBr$

was unsuccessful.

2. Next it was decided to prepare β-hydroxyethyl-benzhydryl ether and convert this to the bromo or chloro ether, and subsequently react the latter with secondary amines. The preparation was attempted by reaction of the sodium salt of diphenyl carbinol and ethylene chlorohydrin in xylene, as follows:

$(C_6H_5)_2CHONa + ClCH_2CH_2OH \longrightarrow (C_6H_5)_2CHOCH_2CH_2OH + NaCl$

This was also unsuccessful.

3. The preparation of the chloroether was then tried by reaction of the sodium salt of diphenyl carbinol and β-chloroethyl-p-toluenesulfonate in xylene as follows:

$$(C_6H_5)_2CHONa + p\text{-}CH_3(C_6H_4)SO_3CH_2CH_2Cl \longrightarrow$$

$$(C_6H_5)_2CHOCH_2CH_2Cl + p\text{-}CH_3(C_6H_5)SO_3Na$$

This was also considered unsuccessful, although on distillation in vacuo a small amount of product was obtained which may have been the desired compound. It was not considered practicable to continue this method any further.

4. The fourth attempt to prepare the benzhydryl alkamine ethers was carried out by heating 2 moles of the desired secondary amine, 2 moles of 1,2-dibromoethane and 1 mole of the sodium salt of diphenyl carbinol in xylene, as follows;

$$(C_6H_5)_2CHONa + BrCH_2CH_2Br \longrightarrow (C_6H_5)_2CHOCH_2CH_2NR_2HBr + NaBr$$

$$+ HNR_2$$

however, this led to no definite products.

Methods of preparation:

1. The benzhydryl alkamine ethers were then successfully prepared by reaction of 1 mole of benzhydryl bromide with 1 mole of the sodium salt of the desired amino alcohol in xylene solution as follows:

$$(C_6H_5)_2CHBr + NaOXNYZ \longrightarrow (C_6H_5)_2CHOXNYZ + NaBr$$

The free bases were isolated in approximately 25 percent yields

by distillation in vacuo.

2. The benzhydryl alkamine ethers were also prepared by the same reaction and conditions as given under 1 above except that the potassium salt of the desired amino alcohol was used. In this case the yield of free base for the example tried was 17 percent.

3. The best method of preparation for the benzhydryl alkamine ethers was found to be the reaction of one mole of benzhydryl bromide with an excess of the desired amino alcohol (0.25 to 5 moles), the latter thus serving as a reactant and solvent, and 1 mole of anhydrous potassium carbonate.

$$(C_6H_5)_2CHBr + HOXNYZ \xrightarrow{K_2CO_3} (C_6H_5)_2CH\text{-}O\text{-}XNYZ + HBr$$

The free bases were isolated in yields up to 80 percent by distillation in vacuo and were usually converted to hydrochlorides.

The acenaphthyl, fluorenyl and triphenyl alkamine ethers were also prepared by this same general method employing fluorenyl bromide, acenaphthyl bromide and triphenylmethyl bromide respectively.

Table of New Compounds Prepared

	Compound	Boiling pt. of free base	Press. mm.	Melting pt. of hydrochloride
1.	Benzhydryl β-dimethylaminoethyl ether	152-5°	2	154-8°
2.	Benzhydryl β-diethylaminoethyl ether	176°	1.5	144.5-45°
3.	Benzhydryl β-di-n-butylaminoethyl ether (methiodide)	180.5-81°	1.5	115-6°
4.	Benzhydryl β-piperidinoethyl ether	195-7°	2.5	168-9°
5.	Benzhydryl β-morpholinoethyl ether	193.5-94°	1.5	179-80°
6.	Benzhydryl β-dicyclohexylaminoethyl ether	231-2°	2	-
7.	Benzhydryl γ-diethylaminopropyl ether	176-80°	2	107-8°
8.	Benzhydryl γ-piperidinopropyl-ether (methiodide)	197.5-98°	3	116-17.5°
9.	Benzhydryl γ-morpholinopropyl ether	200-201°	1.5	185-86.5°
10.	Benzhydryl β-[β-methyl-β-4-morpholino] propyl ether	199-200°	2	174-76.5°
11.	Benzhydryl β-[β'-diethylaminoethoxy] ethyl ether	182-3°	1.5	105-6°
12.	7-Acenaphthyl-β-morpholinoethyl ether	205-6°	2.5	176-7°
13.	9-Fluorenyl-β-diethylaminoethyl ether	177.5°	3	-
14.	Triphenylmethyl β-morpholinoethyl ether	-	-	-
15.	Benzhydryl γ-diethylaminopropyl amine	174-5°	2	-

Methods of analysis;

The hydrochlorides or methiodides of the above compounds were analyzed by a Kjeldahl method in which 0.2-0.3 grams of the sample was digested with 2 grams of a 35-1 mixture of K_2SO_4-$CuSO_4$ and 6 ml. of concentrated sulfuric acid. The digested sample was then diluted, placed in an apparatus set up for steam distillation, 20 ml. of 50% NaOH added and the liberated ammonia steam distilled into 15 ml. of 2% Boric acid. The distillate was titrated with 0.05 N HCl using bromcresol green indicator and the percent nitrogen calculated.

In several cases it was found possible to determine the chloride content of the hydrochlorides by a Mohr titration. A sample of 0.2-0.3 grams was dissolved in 75 ml. of water and 1 ml. of 5% K_2CrO_4 indicator added. It was then titrated with 0.1 N $AgNO_3$ and the percentage chlorine calculated. In most cases this method was not feasable as it is very difficult to determine the endpoint.

It was also found possible to determine the chloride content of the hydrochlorides by the method of Fajan as modified by Blicke and Zienty (61). A 0.2-0.3 gram sample is dissolved in 15 ml. of water, 1 drop of phenolphthalein indicator added and the solution made alkaline with 2% chloride-free sodium hydroxide solution. Then the free base is extracted three times with 50 ml. portions of ether, the aqueous residue heated on a hot plate to expel any residual ether,

cooled and made just acid with 1:50 HNO_3. Finally, the solution is diluted to 75 ml., 10 drops of dichlorofluorescein indicator and 5 ml. of 2% dextrin are added and 0.1 N $AgNO_3$ used to titrate the chloride ion.

A potentiometric method of analysis of the free bases was developed. A 0.2-0.3 gram sample of the free base is suspended in water and titrated potentiometrically with 0.05 N HCl using a Beckmann pH meter to follow changes in pH of the solution as acid is added. A plot of pH v.s. ml. of acid added shows a deflection in the curve at the stoichimetric endpoint.

EXPERIMENTAL DETAILS

Preparation of the Amino Alcohols

The amino alcohols required in this study were:

β-Dimethylaminoethanol
β-Diethylaminoethanol
β-Di-n-butylaminoethanol
β-Piperidinoethanol
β-Morpholinoethanol
β-Dicyclohexylaminoethanol
γ-Diethylaminopropanol
γ-Piperidinopropanol
γ-Morpholinopropanol
β-Methyl-β-4-Morpholenopropanol
β-(β'-Diethylaminoethoxy)-ethanol

The β-dimethylaminoethanol, β-diethylaminoethanol, β-di-n-butylamino-ethanol and γ-diethylaminopropanol were commercial products. The preparation of the others follows:

β-Piperidinoethanol:

This alcohol was prepared according to the general method for the preparation of amino alcohols given by Burnett and Adams, with slight modifications (80). Into a three-necked round bottom flask equipped with a 500 ml. addition funnel, a water-cooled reflux condenser and a mercury-sealed wire-stirrer of the Hirschberg type was placed 202.9 gm. (2.38 moles) of piperidine. Then 95.8 gm. (1.19 moles) of ethylene chlorohydrin was added drop by drop with stirring, the mixture being warmed

gradually with a water-bath. At about 70° piperidine hydrochloride begins to precipitate and the water bath was removed. After the initial reaction subsided, the reaction mixture was refluxed for 5 hours maintaining the temperature at 180° with an oil bath. The reaction mixture was then allowed to cool, the piperidine hydrochloride removed by filtration and any traces of β-piperidinoethanol remaining in the hydrochloride recovered by washing with acetone. Finally, the filtrate and acetone extract was distilled under diminished pressure; the yield of β-piperidinoethanol was 120.3 gm. (78.2%) boiling at 66°/3.5 mm.

β-Morpholinoethanol

This compound was prepared by the same method as given for β-piperidinoethanol using 261.4 gm. (3 moles) of morpholine and 120.8 (1.5 moles) of ethylene chlorohydrin. The yield of β-morpholinoethanol boiling at 88-93°/8mm. was 147 gm. (74.7%).

β-Dicyclohexylaminoethanol

This compound was prepared according to the method of Blicke and Maxwell (81) using 362 gm. (2 moles) of technical dicyclohexylamine and 80 gm. (1 mole) of ethylene chlorohydrin. The yield of β-dicyclohexylamino ethanol boiling at 146-147°/3.5mm. was 154 gm. (67.8%).

γ-Piperidinopropanol

This amino alcohol was prepared according to the general method of Burnett and Adams (80) using 127.7 gm.

(1.5 moles) of piperidine and 70.9 gm. (.75 moles) of propylene chlorohydrin. The yield of γ-piperidinopropanol was 48.2 gm. (44.8%) boiling at 95°/3mm.

γ-Morpholinopropanol

γ-Morpholinopropanol was also prepared according to the general method of Burnett and Adams (80) for the preparation of amino alcohols, using 261.4 gm. (3 moles) of morpholine and 94.5 gm. (1.5 moles) of propylene chlorohydrin. The yield was 178 gm (82%) boiling at 91°-95°/4mm.

β-Methyl-β-4-Morpholinopropanol

The amino alcohol was prepared in accordance with Cheney and Bywater's method (40) using 178.4 gm (2 moles) of 2-amino-2-methyl-1-propanol (Eastman Kodak Co.), 300 gm (2.10 moles) of β,β'-dichlorethyl ether and 300 gm. (2.16 moles) of powdered anhydrous potassium carbonate. The yield of β-methyl-β-4-morpholinopropanol boiling at 95-97°/4 mm. was 55.8g. (35.1%). The distillate was collected as a colorless oil which solidified as a white crystalline solid on cooling.

β-(β'-Diethylaminoethoxy)-ethanol

This alcohol was prepared according to the method of Blicke, Parke and Jenner (82) using 116.0 gm. (1.6 mole) of diethylamine and 100 gm. (.8mole) of diglycol

chlorohydrin. The yield of β-(β'-diethylaminoethoxy)-ethanol was 56.5 gm. (43.8%) boiling at 96-99°/6 mm.

Preparation of Diphenyl Methane:

Diphenyl methane was prepared using Fieser's directions (83) and the proportions of reactants as given in Gilman's "Organic Syntheses" (84) with slight modifications.

A five liter round bottom flask was equipped with an addition tube and a water-cooled reflux condenser, the latter having a connection to the outdoors to permit convenient removal of the hydrogen chloride gas evolved in the reaction. Anhydrous, thiophene-free benzene (2000 gm., 2300 ml., 25.6 moles) and 500 gm. (3.96 moles) of benzyl chloride were then introduced into the flask and cooled by an ice bath to 3°C. Then 200 gm. (1.5 moles) of anhydrous aluminum chloride was added in small portions over a period of one-half hour. On addition of the first portion of aluminum chloride a vigorous reaction took place; however, after the addition of approximately one half of the aluminum chloride the reaction subsided sufficiently to permit the addition of the remainder in one portion. As the reaction continues a red oily substance (aluminum chloride addition product) separates on the bottom of the reaction flask. After all the aluminum chloride was added the ice-bath was removed and the reaction mixture

heated with a small free flame for about 15 minutes. The mixture was then permitted to cool and 1000 grams of crushed ice was cautiously added followed by 1000ml. of water in order to decompose the aluminum complex. The benzene layer was separated, washed twice with dilute hydrochloric acid to remove basic aluminum salts and then with water to remove the acid.

The benzene extract was then distilled at diminished pressure; the yield of diphenyl methane was 296.8 gm. (44.5%) boiling at 137°-140°/17 mm.

Preparation of Benzhydryl Bromide:

In a three liter, three-necked round bottom flask equipped with a water-cooled reflux condenser and a 250 ml. addition funnel was placed 405 gm. (2.41 moles) of diphenyl methane (85). It was then heated to 150°-160° by means of an oil-bath and 145 ml. (453 gm., 2.83 moles) of bromine was added drop by drop maintaining this temperature range. After all the bromine was added the mixture was warmed for another hour and then shaken with solid Na_2SO_3 to destroy any excess bromine and remove hydrogen bromide. On distillation at 6.5 mm. 456 gm. (76.8%) of benzhydryl bromide was obtained.

Preparation of the Benzhydryl β- and γ-dialkylaminoalkyl ethers:

1. Benzhydryl β-diethylaminoethyl ether:

Preparation A:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury sealed mechanical stirrer of the Hirschberg type was placed 9.20 gm. (0.40 atom) of sodium and 200 ml. of xylene. The mixture was refluxed one-half hour with stirring, cooled, 23.4 gm. (0.20 mole) of β-diethylaminoethanol added and the mixture refluxed again for four hours. Then the reaction mixture was again cooled, the excess sodium removed and 49.4 gm. (0.20 mole) of benzhydryl bromide was introduced after which the mixture was refluxed 2 more hours with stirring. Finally, the mixture was cooled, the sodium bromide which separated removed with water and the brown xylene extract dried over sodium hydroxide pellets. The extract was then distilled at reduced pressure using an eight inch column of the Vigraus type. The yield of benzhydryl β-diethylaminoethyl ether as a straw colored viscous liquid boiling at 199-202°/11.5 mm. was 16.4 gm. (28.9%).

The amine was dissolved in anhydrous ether and dry hydrogen chloride passed into it from a generator of the Fieser type (86). The white hydrochloride precipitated It melted at 142-144° but after treatment with Darco

and three recrystallizations from alcohol-ether it melted at 145° C.

Anal. Calcd. for $C_{19}H_{26}ONCl$: Cl, 11.09

Found: Cl, 11.13

Preparation B:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser, a 250 ml. addition funnel, and a mercury sealed mechanical stirrer of the Hirschberg type was placed 7.82 gm. (0.20 atom) of potassium, 23.4 gm. (0.20 mole) of β-diethylaminoethanol and 150 ml. of dry xylene. The potassium melted immediately on addition and reacted rapidly. After the initial reaction subsided somewhat the mixture was refluxed with stirring for two hours. Then 49.4 gm. (0.20 mole) of benzhydryl bromide were dissolved in 100 ml. of dry xylene and added drop by drop to the mixture with stirring. Potassium bromide separated immediately on addition of the bromide. After all the benzhydryl bromide was added the mixture was refluxed for another half hour finally becoming dark brown in color. It was then cooled, dissolved in ether, the potassium bromide filtered out, and the ether extract distilled at reduced pressure using an eight inch column of the Vigraux type. The yield of benzhydryl β-diethylaminoethyl ether was 9.7 gm. (17.1%). The hydrochloride was prepared as given under preparation A.

Preparation C:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury sealed mechanical stirrer of the Hirschberg type was placed 24.7 gm. (0.10 mole) of benzhydryl bromide, 58.6 gm. (0.5 mole) of β-diethylaminoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. Stirring was started and the mixture slowly brought up to reflux its color changing from clear through yellow to dark brown at the end of 7 hours refluxing. The mixture was then permitted to cool, dilute NaOH added, and extracted with ether. The ether extract was washed twice with water to remove the unreacted β-diethylaminoethanol which is soluble in water. Next, the ether extract was extracted three times with dilute hydrochloric acid to remove the benzhydryl β-diethylaminoethyl ether as the hydrochloride leaving any unreacted benzhydryl bromide in the ether layer. The combined hydrochloric acid extracts were then made just basic with dilute NaOH to liberate the benzhydryl β-diethylaminoethyl ether and the latter removed in ether solution. The final ether extract was dried over anhydrous sodium sulfate and then distilled at diminished pressure using an eight inch Vigraux column. The yield of benzhydryl β-diethylaminoethyl ether was 23.3 gm. (82.3%). The hydrochloride was prepared as given under preparation A.

2. Benzhydryl β-dimethylaminoethyl ether:

This compound was prepared according to the method given for benzhydryl β-diethylaminoethyl ether under preparation C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 44.6 gm. (0.5 mole) of β-dimethylaminoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base distilling as a pale blue viscous oil at 152-155°/2 mm. was 11.0 gm. (43.2%). The hydrochloride was prepared and after three recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 154-158°.

Anal. Calcd. for $C_{17}H_{22}ONCl$: N, 4.80

Found: N, 4.90

3. Benzhydryl β-di-n-butylaminoethyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 86.6 gm. (0.5 mole) of β-di-n-butylaminoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base distilling as a yellow oil at 180.5-181.0°/1 mm. was 20.5 gm. (60.3%). The hydrochloride could not be prepared conveniently as it always come down as a reddish oil which would not crystallize; therefore, the methiodide was prepared by dissolving the free base in anhydrous ether, adding an excess of methyl iodide and allowing it

to stand in the refrigator until crystallization took place. At first the methiodide come down as yellow crystals but after treatment with Darco and four recrystallizations from alcohol-ether it was white and crystalline melting at 115-116°. The methiodide was analyzed for nitrogen by the Kjeldahl-Winkler method.

Anal. Calcd. for $C_{24}H_{36}ONI$: N, 2.91

Found: N, 2.74

4. Benzhydryl β-piperidinoethyl ether:

This compound was prepared according to methods A and C respectively. In method A 9.20 gm. (0.40 mole) of sodium, 25.8 gm. (0.20 mole) of β-piperidinoethanol and 200 ml. of xylene as a solvent were used giving a yield of 7.9 gm. (26.8%) of the free base which distilled as a straw-colored oil boiling at 195-197°/2.5 mm. The hydrochloride was prepared in ether solution and after two recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 168-169°.

In method C 24.7 gm. (0.1 mole) of benzhydryl bromide, 64.6 gm. (0.5 mole) of β-piperidinoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate were used giving a yield of free base of 18.7 gm. (63.4%), distilling at 195-197°/2.5 mm. The hydrochloride was also

prepared as given above.and analyzed for chlorine by the Mohr method.

Anal. Calcd. for $C_{20}H_{26}ONCl$: Cl, 10.68

Found: Cl, 10.61

5. Benzhydryl β-morpholinoethyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 65.6 gm. (0.5 mole) of β-morpholinoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base was 18.9 gm. (63.6%) distilling as a light pink oil at 193.5-194.0°/1.5 mm. The hydrochloride was prepared in ether solution and after two recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 179-180°.

Anal. Calcd. for $C_{19}H_{24}O_2NCl$: N, 4.20

Found: N, 4.16

A second preparation of this compound employing 98.8 gm. (0.4 mole) of benzhydryl bromide, 196.8 gm. (1.5 mole) of β-morpholinoethanol and 45.2 gm. (0.4 mole) of anhydrous potassium carbonate resulted in a yield of 94.9 gm. (79.9%) of the free base.

A preparation of the sulfathiazole salt of benzhydryl β-morpholinoethyl ether was attempted. To a solution of 5.1 gm. (0.02 mole) of 2-sulfanilamidothiazole dissolved

in hot acetone was added 5.95 gm. (0.02 mole) of the free base in acetone solution. The mixture was evaporated to a small volume and diluted with dry ether, a white solid separating. This was filtered off, washed with ether and its melting point found to be 198-200°. This is the same melting point as that of 2-sulfanilamidothiazole; also a mixed melting point did not change the value so it was concluded that the desired compound wasn't formed, only 2-sulfanilamidothiazole being recovered.

6. Benzhydryl β-dicyclohexylaminoethyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 68.1 gm. (0.3 mole) of β-dicyclohexylaminoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base was 22.7 gm. (57.8%) distilling as a viscous yellow oil at 231-232°/2 mm. The hydrochloride formed as a sticky solid in ether which would not crystallize, therefore, the compound was analyzed as the free base.

Anal. Calcd. for $C_{27}H_{37}ON$: N, 3.58

Found: N, 3.70

7. Benzhydryl γ-diethylaminopropyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 34.4 gm.

(0.26 mole) of γ-diethylaminopropanol and 13.8 gm. (0.1mole) of anhydrous potassium carbonate. The yield of free base was 21.6 gm. (72.8%) distilling as a light yellow oil at 176-180°/ 1 mm. The hydrochloride was prepared in ether solution and after two recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 107-108°.

Anal. Calcd. for $C_{20}H_{28}ONCl$: N, 4.20

Found: N, 4.18

8. Benzhydryl γ-piperidinopropyl ether:

This compound was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 46.0 gm. (0.32 mole) of γ-piperidinopropanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base was 23.7 gm. (76.7%) distilling as a light yellow oil at 197.5-198.0°/3 mm. The hydrochloride formed as an oil and repeated attempts to crystallize it were unsuccessful, therefore, the methiodide was prepared in ether solution dimilarly as sone in the preparation of benzhydryl β-di-n-butylaminoethyl ether methiodide. After three recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 116-117.5°. The methiodide was analyzed for nitrogen by the Kjeldahl-Winkler method. Even though the compound was crystalline and melted sharply the analysis was low. It is believed that the iodine interfers with the determination or possibly that the wrong catalyst

was used in the Kjeldahl digestion.

Anal. Calcd. for $C_{22}H_{30}ONI$: N, 3.10

Found: N, 2.55, 2.58

9. Benzhydryl γ-morpholinopropyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 72.6 gm. (0.5 mole) of γ-morpholinopropanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base was 25.9 gm. (83.3%) distilling as a red oil at 200-201°/ 1.5 mm. The hydrochloride was prepared in ether solution and after one recrystallization from alcohol-ether it was obtained as a white crystalline solid melting at 185-186.5°.

Anal. Calcd. for $C_{20}H_{26}O_2NCl$: N, 4.03

Found: N, 4.07

10. Benzhydryl β-[β-methyl-β-4-morpholino]propyl ether:

The free base was prepared with slight modification according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 24.0 gm. (0.15 mole) of β-methyl-β-4-morpholinopropanol, 13.8 gm. (0.1 mole) of anhydrous potassium carbonate and 25 ml. of tetralin as a solvent since all the reactants are solids at room temperature. The mixture became deep red

in color and very viscous as refluxing was continued. After seven hours refluxing the reaction mixture was given the usual extraction procedure given under method C and distilled under diminished pressure. The yield of free base was 17.2 gm. (52.9%) distilling as a straw-colored oil at 199-200°/2 mm.

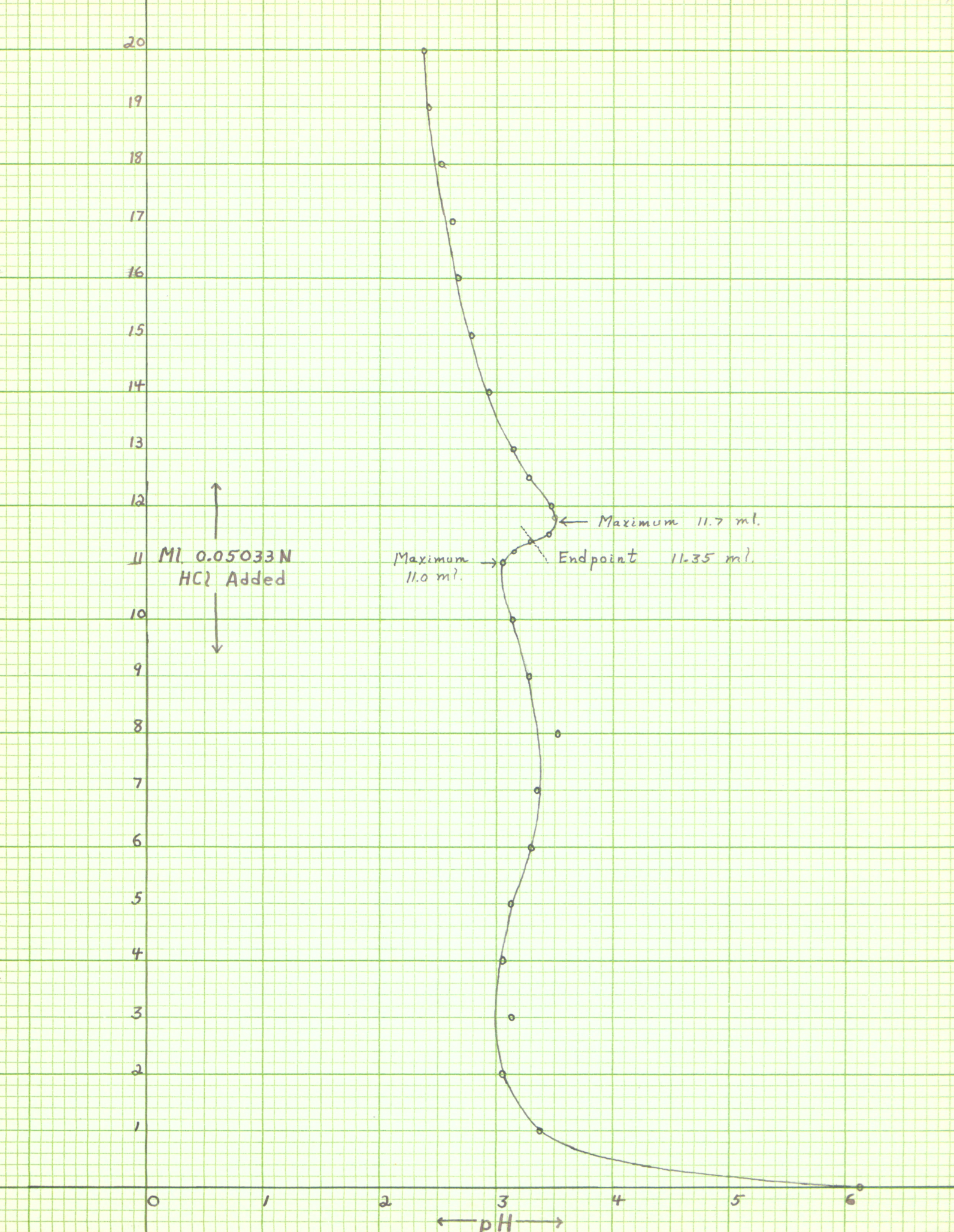
A portion of the free base was suspended in water and titrated potentiometrically with 0.05 N HCl using a Beckman pH meter. It analyzed for 10.94% HCl as compared to 10.08% theoretical. The data for the titration and a plot of this data follow:

Ml. .05033 N HCl added	pH	Ml. .05033 N HCl added	pH
0.00	6.12	11.60	3.46
1.00	3.38	11.70	3.52
2.00	3.06	11.80	3.50
3.00	3.13	11.90	3.49
4.00	3.06	12.00	3.47
5.00	3.12	12.50	3.28
6.00	3.30	13.00	3.13
7.00	3.34	14.00	2.92
8.00	3.52	15.00	2.79
9.00	3.28	16.00	2.68
10.00	3.13	17.00	2.61
11.00	3.05	18.00	2.52
11.10	3.08	19.00	2.41
11.20	3.16	20.00	2.39
11.30	3.32	25.00	2.20
11.40	3.41	30.00	2.07
11.50	3.46		

The remainder of the free base was converted into the hydrochloride in ether solution and after two recrystallizations from alcohol-ether it was obtained as a faintly pink crystalline solid melting at 174.0-176.5°.

Anal. Calcd. for $C_{21}H_{28}O_2NCl$: N, 3.87

Found: N, 3.93


20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1
2
3
4
5
6
Ml. 0.05033N HCl Added
Maximum 11.7 ml.
Endpoint 11.35 ml.
Maximum 11.0 ml.
pH

11. Benzhydryl β-(β′-diethylaminoethoxy)ethyl ether:

The free base was prepared according to method C using 24.7 gm. (0.1 mole) of benzhydryl bromide, 48.8 gm. (0.3 mole) of β-(β′-diethylaminoethoxy)ethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. The yield of free base was 24.8 gm. (68.2%) distilling as a light yellow oil at 182-183°/1.5 mm. The hydrochloride was prepared in ether solution and after two recrystallizations from alcohol-ether it was obtained as a white crystalline solid melting at 105-106°.

Anal. Calcd. for $C_{21}H_{30}O_2NCl$: N, 3.85

Found: N, 3.83

7-Bromoacenaphthene:

7-Bromoacenaphthene was prepared according to the method of Bachmann and Sheehan (87) using 18 gm. (0.106 mole) of 7-acenaphthenol (prepared by Dr. George Rieveschl Jr.) and 3.69 ml. (0.039 mole) of phosphorus tribromide. The yield of pure bromide, m.p. 70.5-71.5°, was 19.7 gm. (79.8%).

7-Acenaphthyl β-morpholinoethyl ether:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury

sealed mechanical stirrer of the Hirschberg type was placed 19.7 gm. (0.085 mole) of 7-bromoacenaphthene, 65.6 gm. (0.5 mole) of β-morpholinoethanol and 13.8 gm. (0.1 mole) of anhydrous potassium carbonate. Stirring was started and the mixture slowly brought up to reflux, the bromide dissolving when the reaction mixture got warm. Refluxing was continued eight hours, cooled, dilute sodium hydroxide added, and the mixture extracted twice with ether. The ether extract was washed twice with water to remove as much unreacted β-morpholinoethanol as possible, dried over anhydrous sodium sulfate and distilled at diminished pressure using an eight inch Vigraux column. At first a yellow liquid distilled at 110-112°/5 mm. which solidified readily to a yellow solid, m.p. 92-95°. A portion of this yellow solid was boiled with dilute nitric acid and 0.1 N silver nitrate solution in order to test for the bromide ion. The test was negative so it was concluded that the solid couldnot be unreacted 7-bromoacenaphthene. Another portion was dissolved in dry ether and anhydrous hydrogen chloride passed into it; no precipitate of hydrochloride formed so it was concluded that the solid was not the desired amino ether or any other compound with amino nitrogen. On continuing the distillation a very viscous red oil distilled at 205-206°/2.5 mm. This oil was dissolved in dry ether and anhydrous hydrogen chloride passed into it yielding 5 gm. of a white

hydrochloride, m.p. 128-132°. During three recrystallizations from alcohol-ether the melting point rapidly rose to a constant value of 176-177°. The final yield of 7-acenaphthyl β-morpholinoethyl ether hydrochloride was 3.6 gm. (12.1%).

Anal. Calcd. for $C_{18}H_{22}O_2NCl$: N, 4.38

Found: N, 4.40

Purification of Crude Fluorene:

In a two liter round bottom flask equipped with a water-cooled reflux condenser was placed 400 gm. of crude fluorene, one liter of glacial acetic acid and 60 gm. of Darco. The mixture was refluxed for two hours and then filtered hot through a hot water funnel into a two liter beaker where the fluorene separated out on cooling. Finally it was filtered on a large Buchner funnel, pressed well and washed with two 150 ml. portions of cold 95% alcohol. The yield of pure fluorene, m.p. 109-112° was 362.4 gm. (90.6%).

Preparation of Fluorenone:

Fluorenone was prepared according to the method of Huntress, Hershberg and Cliff (88) using 200 gm. of recrystalized fluorene. The yield of pure fluorenone, m.p. 82-83°, was 107.3 gm. (49.5%)

Preparation of 9-Fluorenol:

9-Fluorenol was prepared analogous to the method given for the production of benzhydrol from benzophenone in "Organic Syntheses" (89).

In a three liter three-necked round bottom flask equipped with a mercury sealed Hirschberg mechanical stirrer and a water-cooled reflux condenser were placed 150 gm. (0.83 moles) of fluorenone, 1420 ml. of absolute ethanol and 150 gm. (3.75 moles) of sodium hydroxide dissolved in 150 ml. of water. Stirring was started and the mixture heated until it became very dark in color (about 15 minutes). Then 150 gm. (2.3 moles) of technical zinc dust was added and after the mixture refluxed with stirring for seven hours it was filtered hot to remove the unreacted zinc. The zinc was washed with two 75 ml. portions of hot ethanol. The hot alcoholic filtrate was now poured with stirring into four liters of cold water; the fluorenol separated as a creamy voluminous solid which was filtered off and recrystallized from a minimum amount of 95% ethanol. The yield of recrystallized fluorenol, m.p. 151-155°, was 145gm. (96%).

Preparation of 9-Bromofluorene:

9-Bromofluorene was prepared according to the method of Levine (90) from 9-fluorenol using 30 gm. (0.165 mole) of fluorenol. The yield of 9-bromofluorene, m.p.105°, was 33.3 gm. (82.4%).

9-Fluorenyl β-diethylaminoethyl ether:

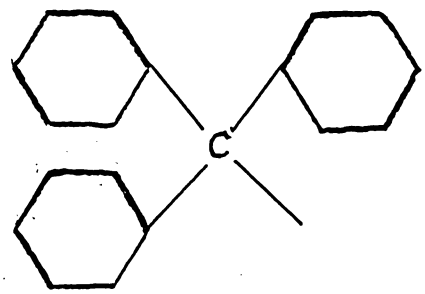
In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury sealed mechanical stirrer of the Hirschberg type was placed 6.8 gm. (0.028 mole) of 9-bromofluorene, 35 gm. (0.3 mole) of β-diethylaminoethanol and 4.0 gm. (0.028 mole) of anhydrous potassium carbonate. The mixture was refluxed seven hours and then given the usual extraction proceedure described under preparation C for benzhydryl β-diethylaminoethyl ether. The yield of free base distilling as a viscous yellow oil at 177.5°/3 mm. was 4 gm. (50.8%). This oil was dissolved in dry ether and anhydrous hydrogen chloride passed into the solution in order to form the hydrochloride. The latter formed as a white sticky solid which turned to a yellow oil on standing in the refrigerator. Repeated attempts to crystallize thia oil from various solvents such as alcohol-ether, ethyl acetate, chloroform etc. were unsuccessful. If time had permitted another preparation of the free base would have been carried out and the methiodide or some other derivative prepared.

Preparation of Triphenylmethyl Bromide:

Triphenylmethyl bromide was prepared from triphenylmethyl carbinol by Wieland's method (91) using 85 gm. (0.32 mole) of the carbinol. The yield of triphenylmethyl bromide, m.p. 151-154°, was 89.2 gm. (85.6%).

Triphenylmethyl β-morpholinoethyl ether:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury sealed mechanical stirrer of the Hirschberg type was placed 32.3 gm. (0.1 mole) of triphenylmethyl bromide and 65.6 gm. (0.5 mole) of β-morpholinoethanol. The mixture reacted immediately becoming purple in color and getting warm after which it gradually changed to a brown color. It is believed that the purple color was due to the presence of the triphenylmethyl radical.



The mixture was now heated on a water-bath with stirring for one-half hour, cooled, the precipitated β-morpholinoethanol hydrochloride filtered off and washed with ether. The filtrate, diluted with ether, had an orange color. It was washed two times with water to remove the unreacted β-morpholinoethanol, dried over anhydrous sodium sulfate, filtered, and some of the ether evaporated under diminished pressure at room temperature. As the ether extract became more concentrated a white solid separated which was presumed to be the free base of the desired compound. It melted

at 92-96°. Then, enough ether was added to again dissolve all the free base that separated and anhydrous hydrogen chloride was passed into the ethereal solution yielding 40 gm. (97.8%) of a light brown hydrochloride melting at 165-180°. One attempt to recrystallize this hydrochloride from alcohol-ether yielded only 15 gm. of product whose melting point fell to 107-111°. This product is still under study and the final results will be given when the work is completed.

Benzhydryl γ-diethylaminopropyl amine:

In a 500 ml. three-necked round bottom flask equipped with a water-cooled reflux condenser and a mercury sealed mechanical stirrer of the Hirschberg type was placed 24.7 gm. (0.1 mole) of benzhydryl bromide, 27.4 gm. (0.21 mole) of γ-diethylaminopropylamine and the mixture refluxed for 12 hours. It finally became brown in color and perfectly clear until it was allowed to cool when a brown precipitate of γ-diethylaminopropyl amine hydrochloride separated. Dilute sodium hydroxide was added to the reaction mixture and then it was extracted twice with ether. The red ether extract was washed twice with water to remove any traces of γ-diethylaminopropyl amine and dried over anhydrous sodium sulfate. On distilling the ether extract under diminished pressure there was obtained 4 gm. (13.6%) of a yellow oil boiling at 174-175°/2 mm. This oil was dissolved

in dry ether and anhydrous hydrogen chloride passed into it forming 5 Gm. of a white hydrochloride or dihydrochloride, m.p. 93-115 °. This preparation is still unfinished as time ran out beforeany more purification could be accomplished.

Attempted preparation of 7-acenaphthylcarboxylic acid:

This preparation was carried out in a manner analogous to the method used by Boord, Brode and Bossert for the preparation of benzoic acid (92).

A 500 ml. three-necked round bottom flask was equipped with a mercury sealed mechanical stirrer of the Hirschberg type, a 250 ml. addition funnel and a water-cooled condenser holding a calcium chloride tube on top to keep atmospheric moisture out of the apparatus. The entire apparatus was heated with a small free flame to drive out all adsorbed moisture possible. Then 9 gm. (18 gm; 0.077 mole in all) of 7-acenaphthyl bromide, 40 ml. of dry ether and 1.70 gm. (0.07 atom) of magnesium turnings were placed in the flask, stirring started and the reaction initiated by warming the outside of the flask with ones hands. The reaction mixture became cloudy and light greenish in color. The remainder of the bromide, 9 gm., was dissolved in dry ether and added to the reaction in 5 ml. portions over a period of one-half hour, following which the mixture was refluxed another half hour. About one-half of the magnesium appeared

to remain in the flask. The mixture was cooled and poured with stirring into a 600 ml. beaker containing 50 gm. of dry ice and 200 ml. of ether. After all the dry ice disappeared 200 gm. of ice and water was added to hydrolyze the mixture, followed by 30 ml. of dilute (1:1) HCl. A small amount of white solid material(I) remained and was removed. This white solid(I) was heated with sodium carbonate solution; it did not dissolve so it was presumed not to be the desired 7-acenaphthylcarboxylic acid. In order to determine whether any of the desired product was in the ether layer it was extracted two times with sodium carbonate solution and the combined extracts made acid with hydrochloric acid. Only a trace of a white solid(II) separated so it was discarded. The ether layer was then evaporated, a yellow viscous oil remaining. After an attempt to crystallize this oil from ethanol failed, it was crystallized by dissolving it in benzene and adding ligroin. A white solid (III) was obtained which melted at approximately 215-220°. It isn't believed that this is the desired acid as it was not removed from the ether by sodium carbonate solution. Time did not permit any further investigation of this preparation.

P H A R M A C O L O G Y

The compounds which have been prepared are being tested at the present time by Parke, Davis and Co. and Wayne University Medical School. When full details are available they will be inserted here.

SUMMARY AND CONCLUSIONS

1. A number of alkamine ethers have been prepared which have antispasmodic activity.

2. Replacement of the carboxy group in "Trasentin" by an ether group can be accomplished without essential loss of activity.

B I B L I O G R A P H Y

(1) Solis-Cohen and Githens, Pharmacotherapeutics, D. Appleton and Company, New York, 1928, p. 1710.

(2) Burtner and Cusic, J. Am. Chem. Soc. 65, 262 (1943)

(3) Solis-Cohen and Githens, Pharmacotherapeutics, D. Appleton and Company, New York, 1928, p. 1711.

(4) Solis-Cohen and Githens, Pharmacotherapeutics, D. Appleton and Company, New York, 1928, p. 1719.

(5) Lium, Surgery, 9, 538-53 (1941)

(6) Solis-Cohen and Githens, Pharmacotherapeutics, D. Appleton and Company, New York, 1928, p. 1326.

(7) Blicke, J. Am. Chem. Soc. 61, 91-3 (1939)

(8) Jenkins and Hartung, The Chemistry of Organic Medicinal Products, John S. Swift Co., Inc., St. Louis, 1941, p. 386.

(9) Firma E. Merck, German Pat., 613,005, Am. Chem. Ab. 29, 5604 (1935)

(10) Werder, E. Merck's Jahesber, 50, 88-101 (1936); Am. Chem. Ab. 31, 2742-4 (1937)

(11) Kottlors, Med. Klin. 45, 1498-9 (1934)

(12) Slotta and Haberland, Angew. Chem. 46, 766-71 (1933)

(13) Ellinger, Koschara and Seerar, Klin Wochschr., 13, 411 (1934)

(14) Fodor, Acta. Lit. Sci. Regiae Univ. Hung. Francisco-Josephinae, Sect. Chem., Mineral Phys. 6, 1-26 (1937)

(15) Darmstadt, British Pat. 348,956, Chem. Zentr. 102, II, 1196 (1931)

(16) Bruckner and Fodor, Ber. 71B, 541-9 (1938)

(17) Vinkler and Bruckner, Magyar Chem. Folyöcrat, 45, 147-55 (1939)

(18) Meier, Klin. Wochschr., 15, 1403-4 (1936)

(19) Salow, Klin. Wochschr., 15, 1405-6 (1936)

(20) Einhorn, J. Digestive Diseases Nutrition, 5, 121-5 (1938)

(21) Friedli, Schweiz. med. Wochschr., 68, 201-2 (1938)

(22) Thewlis, Med. Times, 67, 12-13 (1939)

(23) Eisleb and Schaumann, Deut. med. Wochschr., 65, 967-968 (1939)

(24) Schaumann, Arch. exptl. Path. Pharmakol., 196, 109-136 (1940)

(25) Halpern, Compt. rend. soc. biol., 126, 678-82 (1937)

(26) Halpern, Arch. intern. pharmacodynamic, 59, 149-94 (1938)

(27) Viaud, German Pat., 702,362; Am. Chem. Ab. 35, 8213 (1941)

(28) Viaud, U.S. Pat., 2,219,796; Am. Chem. Ab. 35, 1072 (1941)

(29) Unna, J. Pharmacol., 70, 179-88 (1940)

(30) Pschyrembel. Med. Klin., 48, 1599 (1934)

(31) Fromherz, Arch. exptl. Path. Pharmakol., 173, 86-128 (1933)

(32) Solis-Cohen and Githens, Pharmacotherapeutics, D. Appleton and Co., New York, 1928, p. 1551.

(33) Bockmühl and Ehrhart, U. S. Pat. 2,230,774; Am. Chem. Ab. 35, 3391 (1941)

(34) Miescher and Hoffmann, U.S. Pat. 2,265,184; Am. Chem. Ab. 36, 1737 (1942)

(35) Miescher and Hoffmann, U.S. Pat. 2,265,185; Am. Chem. Ab. 36, 1737 (1942)

(36) Burtner and Lehmann, J. Am. Chem. Soc. 62, 527 (1940)

(37) Lehmann and Knoefel, J. Pharmacol. 74, 273-83 (1942)

(38) Burtner, U.S. Pat. 2,262,754; Am. Chem. Ab. 36, 1738 (1942)

(39) Wolfes and Hromatka, U.S. Pat. 2,221,828; Am. Chem. Ab. 35, 1935 (1941)

(40) Cheney and Bywater, J. Am. Chem. Soc. 64, 970-3 (1942)

(41) Rowe, J. Am. Pharm. Assoc. 31, 57-9 (1942)

(42) Itikawa, Japan Pat. 131,529; Am. Chem. Ab. 35, 3037 (1941)

(43) Junkmann, Arch. exptl. Path. Pharmakol., 186, 552 (1937)

(44) Junkmann, Arch. exptl. Path. Pharmakol., 195, 175-83 (1940)

(45) Junkmann and Allardt, U.S. Pat. 2,186,976; Am. Chem. Ab. 34, 3450 (1940)

(46) Kissling, Med. Klin. 972 (1934)

(47) Klavehn, German Pat. 617,536; Am. Chem. Ab. 30, 731 (1936)

(48) Klavehn and Wolf, U.S. Pat. 2,230,752; Am. Chem. Ab. 35, 3390 (1941)

(49) Klavehn and Wolf, U.S. Pat. 2,230,753; Am. Chem. Ab. 35, 3391 (1941)

(50) Klavehn and Wolf, U.S. Pat. 2,230,754; Am. Chem. Ab. 35, 3391 (1941)

(51) Klavehn and Wolf, U.S. Pat. 2,256,434; Am. Chem. Ab. 36, 222 (1942)

(52) Buth, Kulz and Rosenmund, Ber. 72B, 14-28 (1939)

(53) Kulz, Rosenmund and Kayser, Ber. 72B, 2161-7 (1939)

(54) Rosenmund and Kulz, U.S. Pat. 2,006,114; Am. Chem. Ab. 29, 5602 (1935)

(55) Blicke and Monroe, J. Am. Chem. Soc. 61, 91-3 (1939)

(56) Magnus, Arch. ges. Physiol. 102, 123 (1904)

(57) Magnus, Arch. ges. Physiol. 102, 349 (1904)

(58) Magnus, Arch. ges. Physiol. 103, 515 (1904)

(59) Blicke and Zienty, J. Am. Chem. Soc. 61, 93-5 (1939)

(60) Blicke and Zienty, J. Am. Chem. Soc. 61, 771-3 (1939)

(61) Blicke and Zienty, J. Am. Chem. Soc. 61, 774-6 (1939)

(62) Blicke, U.S. Pat. 2,180,344; Am. Chem. Ab. 34, 1820 (1940)

(63) Hildebrandt, German Pat. 697,805; Am. Chem. Ab. 35, 6739 (1941)

(64) Hildebrandt, German Pat. 699,249; Am. Chem. Ab. 35, 6739 (1941)

(65) Hildebrandt, German Pat. 699,250; Am. Chem. Ab. 35, 6739 (1941)

(66) Heyn, U.S. Pat. 2,278,123; Am. Chem. Ab. 36, 4972 (1942)

(67) Eisleb, Ber. 74B, 1433-50 (1941)

(68) Cerkovnikov and Prelog, Ber. 74B, 1648-60 (1941)

(69) Swiss Pat. 213,347; Am. Chem. Ab. 36, 4974 (1942)

(70) Notkins and Webster, Rev. can. biol. 1, 660-4 (1942); Am. Chem. Ab. 36, 7142 (1942)

(71) Notkins and Webster, Rev. can. biol. 1, 665-74 (1942); Am. Chem. Ab. 36, 7142 (1942)

(72) Seydel, U.S. Pat. 1,621,757; Am. Chem. Ab. 21, 1523 (1927)

(73) Dunning Jr., Dunning and Reid, J. Am. Chem. Soc. 58, 1565-8 (1936)

(74) Bockmühl, Ehrhart, Stein and Hallensleben, U.S. Pat. 2,088,941; Am. Chem. Ab. 31, 6823 (1937)

(75) Eisleb, U.S. Patent 2,248,018; Am. Chem. Ab. 35, 6394 (1941)

(76) U.S. Patent 1,951,807; British Patent 370,350; British Chem. Ab., B, 786 (1932)

(77) Rieveschl, Ph.D. Thesis, University of Cincinnati, (1940)

(78) Philbrook, Ph.D. Thesis, University of Cincinnati, (1942)

(79) Philbrook, Unpublished work, (1942)

(80) Burnett and Adams, J. Am. Chem. Soc. 59, 2249-50 (1937)

(81) Blicke and Maxwell, J. Am. Chem. Soc. 64, 429 (1942)

(82) Blicke, Parke and Jenner, J. Am. Chem. Soc. 62, 3317 (1940)

(83) Fieser, Experiments in Organic Chemistry, p. 177-8

(84) Gilman, Organic Syntheses, Vol. XIV, p. 34.

(85) Norris, Thomas and Brown, Ber. 43, 2959 (1910)

(86) Fieser, Experiments in Organic Chemistry, p. 394.

(87) Bachmann and Sheehan, J. Am. Chem. Soc. 63, 204 (1941)

(88) Huntress, Hershberg and Cliff, J. Am. Chem. Soc. 53, 2721-2 (1931)

(89) Gilman, Organic Syntheses, Col. Vol. I, p. 84.

(90) Levine, Ph.D. Thesis, University of Cincinnati, (1937)

(91) Wieland, Ber. 42, 3024 (1909) (Footnote)

(92) Boord, Brode and Bossert, Lab. Outlines and Notebook for Organic Chemistry, p. 210.