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I hereby recommend that the thesis prepared under my supervision by George Edwin Philbrook *entitled* Structure and activity of local anesthetics: Monoalkylaminoalkylene phenyl Ethers and related compounds. *be accepted as fulfilling this part of the requirements for the degree of* Doctor of Philosophy

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STRUCTURE AND ACTIVITY OF LOCAL ANESTHETICS:

MONOALKYLAMINOALKYLENE PHENYL ETHERS

AND RELATED COMPOUNDS

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

1942

by

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The author wishes to express his deep appreciation for the untiring advice and assistance of Dr. George Rieveschl during the course of this investigation.

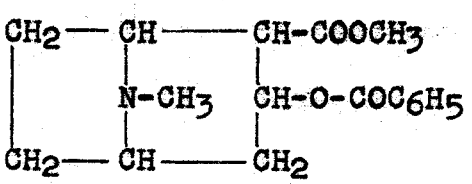
PART I

GENERAL INTRODUCTION

This introduction will attempt to give a short survey of the types of linkages commonly found in local anesthetics, and also a summary of some of the pertinent physiologically active compounds in which the ether linkage is present.

The author does not intend to give a complete survey of the literature but only to indicate in a general way the background of this work and the present trend in local anesthetic research.

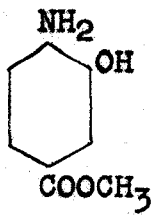
Since Koller in 1884 reported the use of cocaine in ophthalmology, the employment of local anesthetics has increased prodigiously. Willstätter (1) in 1903 brought the determination of the structure of cocaine to a successful conclusion. The structure was confirmed by synthesis in the same year. Cocaine has the following structure.



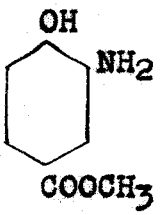
Cocaine is not completely satisfactory as a local anesthetic due to its toxicity, instability, high cost, and habit forming properties.

Einhorn (2) who had worked with Willstätter on

the chemistry of cocaine recognized the fact that all aromatic esters possess the capacity to produce anesthesia. Orthoform and New Orthoform resulted from this generalization.



Orthoform



New Orthoform

Einhorn and Uhlfelder (3) described the synthesis of Procaine (Novocaine) in 1909. This compound contains the same anesthesiophoric group as cocaine. From this has grown one of the greatest group of research programs ever seen. Hundreds of compounds, most of them based on the anesthesiophoric group,

$$Ar\text{-}CO\text{-}O\text{-}(\text{-}\dot{C}\text{-})_n\text{-}N\langle$$

have been synthesized. Recognition of this as the active grouping in cocaine grew out of the elucidation of its structure. Of the enormous number of compounds synthesized only a few have been found useful. The requirements for a good local anesthetic have been stated by Gilman (4) as follows:

1. For the same degree of anesthesia as cocaine it must be less toxic than cocaine.

2. The compound must not give rise to any

irritation or tissue damage, thus it cannot be too acid or alkaline.

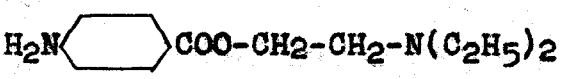
3. It must be water soluble.

4. Solutions of the compound should be sufficiently stable for sterilization by boiling.

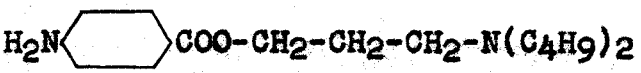
5. The compound must be compatible with adrenaline which, by its constricting action on the blood vessels, makes the area of the operation practically bloodless, and prevents too rapid absorbtion of the local anesthetic.

Of the many compounds synthesized a few of the best known are:

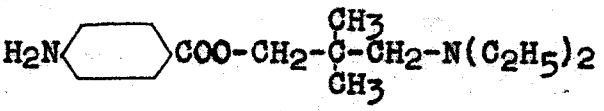
Procaine



Butyn



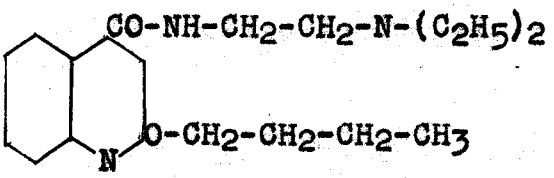
Larocaine



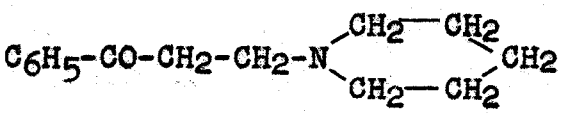
By far the largest group of local anesthetics are esters of dialkylaminoalkanols, generally with p-aminobenzoic acid.

Among the classes of compounds which have been less extensively studied are the amides. Wenker (5) found that mono-alkyl and di-alkylamides of p-aminobenzoic acid, where the alkyl groups were butyl, amyl, and piperidyl, were strong topical anesthetics. A

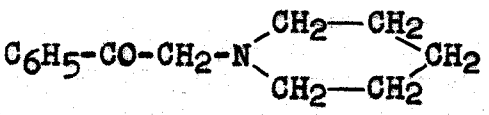
compound of this type, active both topically and on injection, is Nupercaine.



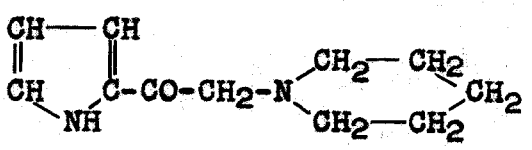
The ketones have been found to be active local anesthetics in certain cases. Mannich (6) and his co-workers have reported that β-piperidinoethyl phenyl ketone



possessed considerable action. Blicke and Blake (7) reported that piperidinomethyl phenyl ketone



was active, as was its analogue, piperidinomethyl-2-pyrryl ketone.

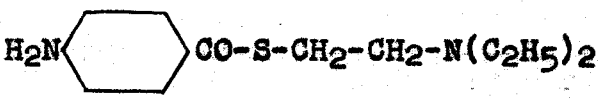


Crossen, Jenkins, and Rogers have prepared (8) compounds of the type,

and found that where R was a simple alkyl group no anesthetic action was given, and that the compounds

were toxic. Where R was diethylaminoethyl, local anesthetic activity was shown. Substitution of sulfur for carbon in the ester linkage increases the toxicity but does not destroy the activity of the compound. Unfortunately un-acetylated compounds could not be prepared. It is known that acetylation of the amino group in the p-aminobenzoic acid esters gives a marked decrease in activity.

A sulfur analogue of Procaine has been placed on the market under the name Thiocaine. It is diethylaminoethyl p-aminothiobenzoate.(9)



It is more active and more toxic than Procaine.

It is evident then that other linkages besides carboxy can be used and still maintain local anesthetic activity. There is some evidence in the literature that the ether linkage may be employed in local anesthetics and other physiologically active compounds. A German patent (10) issued to Merck covers the preparation of compounds of the type

$$R\text{-}O\text{-}(CH_2)_n\text{-}N\text{:}Y$$

for use as local anesthetics. Examples are given in which R is menthyl, p-methoxyphenyl, phenyl, and thymyl, and Y is dimethyl, camphidino, and piperidino. The

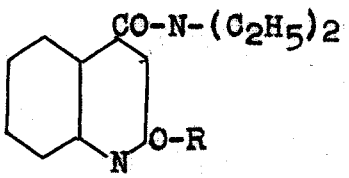
patent states that n may have any value whatsoever, but examples are given in which n is three or five.

Clemo and Perkins (11) reported that β-naphthyl-β-dimethylaminoethyl ether hydrochloride was an active local anesthetic.

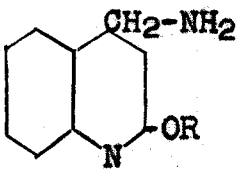
Brill (12) reported in 1925 that β-piperidinoethyl phenyl ether and γ-piperidinopropyl phenyl ether were active local anesthetics in the form of hydrochlorides and hydrobromides.

Nupercaine mentioned previously as an amide also contains an ether linkage. It is definitely established (13) that the prescence of the ether linkage is necessary for optimum physiological activity. The activity appears to be at a maximum when a n-butoxy group is substituted as in Nupercaine. It does not necessarily have to be in the 2 position for activity but is desirable from the point of view of ease of synthesis.

Wojahn (14) has shown that the diethylamides of 2-alkoxycinchoninic acids are local anesthetics.

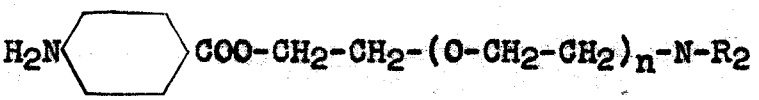


He has also shown that the 2-alkoxy-4-aminomethylquinolines are active as local anesthetics.



Thus it would appear that the aminoether linkage seemed to confer activity, at least in the quinoline derivatives.

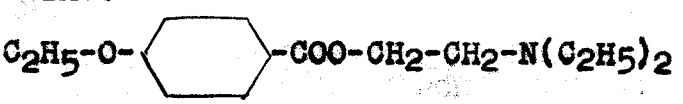
Ruberg and Shriner (15) have shown that compounds of the type



are active local anesthetics. The optimum activity occurred when n was one. Compounds in which R was longer than butyl could not be prepared. The activity increased with an increase in the length of R, but not in a regular fashion. The dimethyl compound was inactive, the diethyl compound was more active than the di-n-propyl and less active than the di-n-butyl. The compounds were tested on the rabbit cornea in 1 % water solutions.

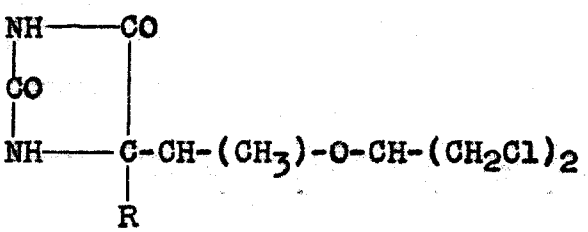
Hill and Fernald (16) have described and patented the preparation of a series of local anesthetics which are β-dialkylaminoethanol esters of 1-ethoxy-2-naphthoic acid, 2-ethoxy-1-naphthoic acid, and 1-ethoxy-4-naphthoic acid.

One of the newer local anesthetics placed on the market is Intracaine.



The free amino group of Procaine is here replaced by an ethoxy group. This compound prepared by Lott, Harris, and Christiansen (17) is the best of a large number of p-ethoxybenzoic acid esters of dialkylaminoalcohols. Sappenfield and Rovenstine (18) state that it has no special advantages over Procaine. It is used as a spinal anesthetic.

Allen and Henze (19) have described the preparation of substituted hydantoins containing an ether linkage in one of the substituted groups.



Unfortunately no pharmacological data is included in the report.

Blicke and Zienty (20) have recently described the preparation of a considerable number of di-substituted acetamides in which one substituent is an alkyl or arylalkyl group and the other is an alkoxyalkyl or aryloxyalkyl group. These compounds are shown to be active hypnotics.

The barbituric acids with ether linkages in one of the groups substituted in the 5 position have been investigated by Blicke and Zienty (21). Out of a series

of twenty two compounds they concluded from a consideration of the pharmacological data, that the 5-ethyl-5-β-butoxyethyl and 5-ethyl-5-γ-phenoxypropyl barbituric acids are the most promising.

From a consideration of the evidence stated above an investigation of local anesthetics containing an ether linkage seemed well worth while.

PART II

DISCUSSION

From the material presented in the introduction it appeared that the definition of the anesthesiophoric group should be changed to

$$Ar\text{-}X\text{-}(\dot{C})_n\text{-}N<$$

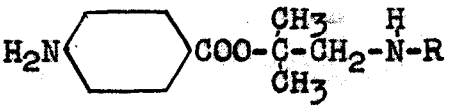
as compounds have been prepared which are active local anesthetics in which X is -COO-, -COS-, -CONH-, -CO-, $-SO_3-$, and -O-.

As a general rule an increase in the molecular weight of a compound leads to an increase in activity, and at the same time increases the toxicity and decreases the solubility.

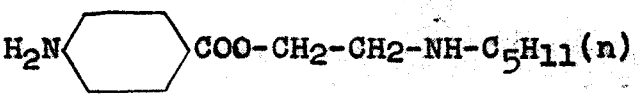
From the small number of compounds available in the literature it appeared that the ether linkage would be physiologically active and there is no evidence that it confers any abnormal toxicity. It may be possible to substitute the ether linkage in place of the ester linkage in the Procaine type of compounds, and by this means to prepare compounds of the same order of activity with a decrease in toxicity because of the lower molecular weight. It is entirely possible that the ether linkage may have an activity greater than the ester linkage.

Goldberg (22) prepared several compounds of the

type



and found that when R was n-amyl a very active topical anesthetic was obtained. Abrahamson and Goldberg (23) prepared a compound now sold under the name Amylcaine, which is a secondary amine.

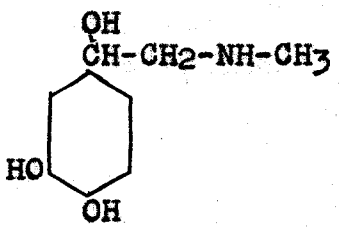


This compound is one and one half times as toxic as Procaine, but it is considered more efficient. It is used in infiltration and conduction anesthesia.

In view of the above facts it seemed that the secondary amines would be effective anesthetics. It appeared possible that the reduction in the weight of the molecule obtained by using secondary amino groups instead of the more common tertiary amino group would lead to a reduction in toxicity.

As has allready been pointed out, any local anesthetic to be useful must be compatible with adrenaline. Cocaine possesses vaso-constrictor activity and may be used alone. Almost all other local anesthetics are given with adrenaline to prevent diffusion of the anesthetic away from the site of the operation.

Adrenaline possesses the structure.

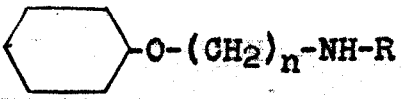


There is a possibility that a local anesthetic containing the secondary amino grouping would possess vaso-constrictor action and thus would make the simultaneous administration of adrenaline unnecessary. It is not stated in what way Amylcaine is more efficient than Procaine but this may be a possible explanation.

Long (24) has called attention to the fact that numerous workers have shown that p-aminobenzoic acid inhibits the effect of sulfanilamide. Powell, Krahl, and Clowes (25) have demonstrated that the pneumococcal therapeutic action of sulfapyridine in mice was definitely inhibited by the administration of local anesthetics derived from p-aminobenzoic acid. This effect was not observed when other local anesthetics not derived from p-aminobenzoic acid were used. This fact makes it unwise, or impossible, to use most of the valuable local anesthetics on patients who are undergoing treatment with sulfanilamide or its derivatives. For this reason a local anesthetic not derived from p-aminobenzoic acid, and as good as or better than Procaine, is very desireable. The

best compound in this class at present is probably Nupercaine.

In view of the considerations enumerated above it was decided to prepare as many compounds as possible of the type.



Previous preparations: A few compounds of this type are known. Cowan and Marvel (26) prepared compounds in which n was three and R was methyl, ethyl, n-propyl, n-butyl, and iso-butyl. They reported the following boiling points of the free bases.

R	B.P./Press.
CH_3-	133-138°/23mm.
C_2H_5-	147-148°/26mm.
n-C_3H_7-	154-155°/25mm.
n-C_4H_9-	134-135°/5mm.
iso-C_4H_9-	153-156°/20mm

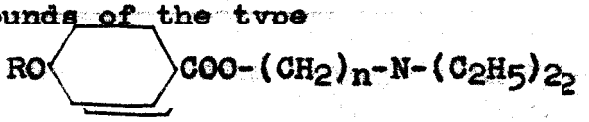
They did not investigate the compounds from a pharmacological standpoint as they were to be used as intermediates in the formation of halogenated secondary amines. Compounds of this type have been prepared by Brill (12) in which the nitrogen atom was tertiary. The patents (10) issued to Merck are also for compounds in which the nitrogen atom was tertiary. These compounds were stated to be

active but no data was given.

Since no pharmacological data was available for compounds of the type we intended to prepare, it was considered desirable to prepare as many compounds as possible to get an idea of their effectiveness in relation to variations in the alkyl group and in the length of the alkylene chain.

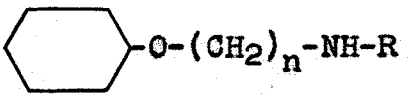
Effect of variations in alkyl groups: The effect of variations of the alkyl groups in the p-aminobenzoates has been studied by Adams and his co-workers, (27) and they came to the conclusion that an increase in the size of the alkyl group gave an increase in activity, with the normal radicals more active than the isomeric branched chain structures. The same workers (28) have studied the effect of varying the alkyl groups in the alkamine esters of p-aminobenzoic acid, and found that here also an increase in the length of the group gave an increase in the activity of the compounds and also in the toxicity. Again the normal radicals were more active than their branched isomers.

Compounds of the type



have been investigated by Rohmann and Scheurle (29) and they came to the conclusion that activity increased with an increase in the length of the alkoxy group.

In order to synthesize compounds of the type



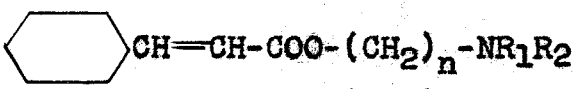
proposed in this thesis with significant variations in R it was necessary to have a large number of primary amines. These have been made available recently in experimental quantities by Sharples Chemicals Inc. We are very much indebted to this organization for the gift of a large number of primary amines. We have varied R from ethyl to n-heptyl with numerous branched chain structures in this range. The cyclohexyl and β-methoxyethyl groups were also employed. The piperidino compound was also synthesized to compare with Brill's preparation, and our results do not agree with his as we found it to be inactive on the rabbit cornea.

Variations in n: In the compounds prepared in this study n was limited to two or three. The reason for this was that the cost of the intermediates when n is greater than three would have made an extensive study prohibitive.

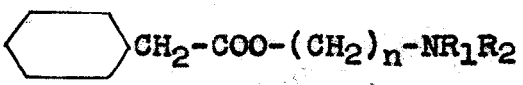
Variations of the phenyl group: A few compounds were made with a substituted phenyl group in order to determine what the effect on activity would be. An attempt was made using the β-butoxyethyl group in place of phenyl but the compound was obtained as a semi-solid

oil which could not be crystallized.

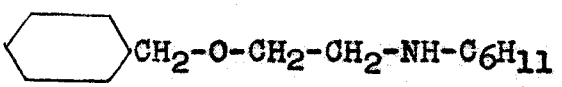
Kamm (30) has concluded that the maximum anesthetic effect is developed when the carboxy group in the ester type of local anesthetics is directly attached to an aromatic carbon atom. This type of linkage is not essential provided that the carboxy group is attached to an unsaturated carbon atom, as in the case of the dialkylaminoalkylene esters of cinnamic acid (30).



It is known that the esters of p-aminophenylacetic acid are inactive (30).



The German patent (10) states that reduced nuclei such as menthyl and thymyl gave effective local anesthetics. This is not in accord with Kamm's rule if it is extended to ethers. To test this effect in the ether series β-cyclohexylaminoethyl benzyl ether was prepared.



This compound is the ether analogue of the phenylacetic acid derivative mentioned above.

The benzyl compound may be interesting from a different standpoint. Gilman and Goodman (31) state that local anesthetics of the ester class are detoxified

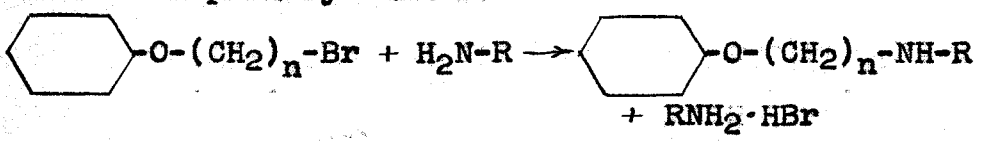
in the liver by a process of hydrolysis, and that the toxicity of a given compound is in proportion to the ratio of its rate of absorbtion to its rate of detoxification. The work of Powell, Krahl, and Clowes (25) on the inhibition of the effect of sulfapyridine by local anesthetics derived from p-aminobenzoic acid is best explained by this hydrolysis. If this holds true in the ether series, the compounds may be rather toxic as they should be very slowly hydrolyzed judging from the chemical behaviour of phenyl ethers. Butler (32) has shown that benzyl ethers are hydrolyzed by refluxing with 11 % hydrochloric acid. This is definitely unusual. The author found that β-hydroxyethyl benzyl ether was split by phosphorous tribromide at -5° to give benzyl bromide. For this reason the benzyl compound may show an appreciable reduction of toxicity because of its greater ease of hydrolysis, which should lead to more rapid detoxification.

Effect of salt formation: It has been shown by Regnier (33) and his co-workers that changing the acid used in forming the amine salt of local anesthetics may have a great effect on their activity. For example, cocaine phenylacetate is reported to be twelve times as active as cocaine hydrochloride. In view of this fact the phenylacetate and sulfamate of β-cyclohexylaminoethyl

phenyl ether have been prepared.

The picrate of n-butyl-p-aminobenzoate (Butesin) has been placed on the market in the form of an ointment for the treatment of burns. It combines the activity of Butesin as a local anesthetic with the antiseptic qualities of picric acid. With this in mind the picrate of β-cyclohexylaminoethyl phenyl ether was prepared for pharmacological study on experimental burns.

Preparation of the compounds: After a survey of the literature on the previous preparation of secondary aminoethers (10),(11),(12),(20), it was decided to prepare these compounds by condensing the appropriate bromoether with primary amines.



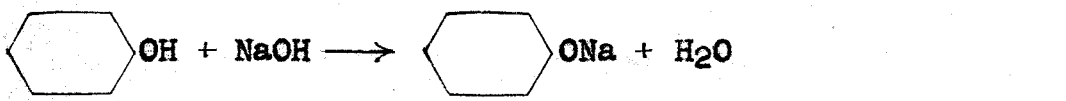
Cowan and Marvel (20) carried out the preparation by allowing an alcoholic solution of four mols of primary amine to stand in contact with the bromoether for twenty four hours. The excess amine and alcohol were removed by distillation. The free bases were then liberated with sodium hydroxide, extracted with ether, and distilled. This method is not satisfactory for the higher amines due to the large loss of amine when only small amounts were available.

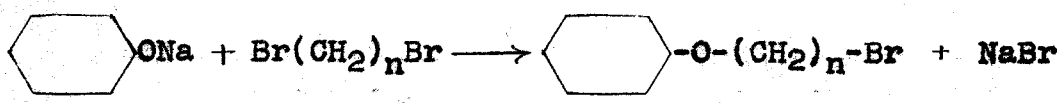
The German patent issued to Merck (10) describes a method carried out in pressure vessels for which the

equipment was not available.

Brill (12) formed the piperidine compounds by mixing piperidine and the bromoether in the cold and found the reaction in this case to be spontaneous. We adopted a modification of Brill's procedure.

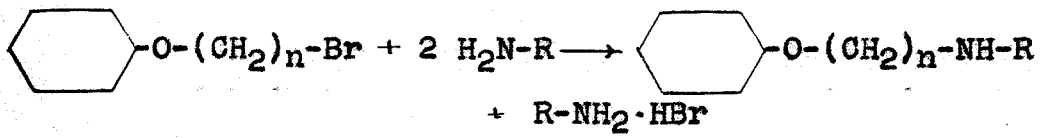
The β-bromophenetole and γ-bromopropyl phenyl ether required were prepared according to the directions of Marvel and Tanenbaum (34). The reactions are as follows:



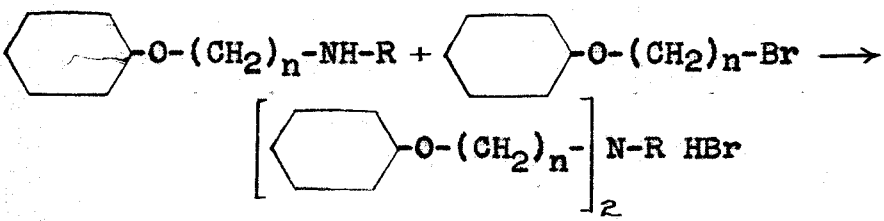


Water, trimethylene bromide (or ethylene bromide) and phenol were placed in a flask equipped with an efficient reflux condenser, a mechanical stirrer and a dropping funnel. A solution of sodium hydroxide was dropped into the boiling mixture. A large portion of the trimethylene bromide (or ethylene bromide) was recovered. The yield in the case of the γ-bromopropyl phenyl ether was 84-85% based on the unrecovered trimethylene bromide. In the case of the β-bromophenetole the yield was 55-56% based on the unrecovered ethylene bromide.

For the preparation of the secondary aminoethers the following reaction was adopted.



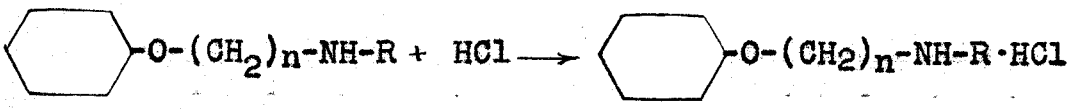
The hydrobromic acid liberated in the reaction formed salts with the amine used. The bromoether and amine in the ratio of 1.0 moles of ether to 2.1 moles of amine were heated under reflux (except in the case of ethylamine). In most cases condensation took place readily and amine hydrobromide separated out after a short period. When the reaction was complete the hydrobromides were converted to the free bases with sodium hydroxide, and extracted with ether. The ether solution was treated in two different ways. The second was an improvement of the first and reduced the risk of contamination by tertiary amine formed by the following reaction.



This reaction could have been cut down somewhat by using a large excess of primary amine. This was, however, not possible due to the limited quantities of amines available.

The first method involved drying the ether solution followed by distillation of the excess ether and primary amine. The residue from the distillation was treated

with dry hydrogen chloride in ether or ligroin solution, and the precipitated hydrochlorides were recrystallized from alcohol.



The second method involved fractional distillation of the dried ether solution and isolation of the free base of the secondary aminoether, which was then precipitated with dry hydrogen chloride and recrystallized.

After the problem was well advanced β-chlorophenetole became commercially available. The author is indebted to the Dow Chemical Co. for the gift of a large quantity of this material as well as for the gift of some β-chloroethyl o-chloro-p-tert-butylphenyl ether. For this reason the ethyl compounds made after the original supply of β-bromophenetole was exhausted were made from β-chlorophenetole.

The use of β-chlorophenetole resulted in a considerable reduction in the yield of the secondary aminoether as might be expected because of the lesser reactivity of chlorides compared to bromides. Thus, the β-iso-butylaminoethyl phenyl ether hydrochloride was obtained in a 54 % yield from β-bromophenetole and in 31 % yield from β-chlorophenetole. In general the yields of the various secondary aminoether hydrochlorides varied over wide limits between

20 % and 90 %. This can be attributed principally to losses during recrystallization which varied widely. This effect obscured any variation in yield between the ethyl and propyl compounds (based on the bromides). In terms of large scale synthesis the choice between β-chlorophenetole and β-bromophenetole would depend on the amine being used.

The phenylacetate and sulfamate of β-cyclohexylaminoethyl phenyl ether were prepared by mixing in water or alcohol solution equi-molar portions of the acid and base. The picrate was prepared by adding the free base to a cold saturated solution of picric acid in alcohol.

PART III

EXPERIMENTAL DETAILS

A - Preparation of Bromoethers

ρ-Bromoethyl phenyl ether: One kilo. (5.35 moles) of ethylene bromide, 392 g. (4.25 moles) of phenol, and one liter of water were placed in a three liter round bottomed flask fitted with an efficient reflux condenser, a mechanical stirrer, and a dropping funnel. The mixture was heated to boiling and a solution of 187 g. (4.7 moles) of sodium hydroxide in 250 ml. of water was added from the dropping funnel in the course of one hour. The mixture was refluxed five hours longer to complete the reaction, cooled, and the upper water layer separated and discarded.

The lower layer consisted of ethylene bromide, ρ-phenoxyethyl bromide, and diphenoxyethane. The mixture was distilled under reduced pressure. The first fraction collected up to 125°/18mm. consisted of water, ethylene bromide, and a little phenoxyethyl bromide. The water was separated and discarded and the ethylene bromide was recovered. The next fraction was almost pure phenoxyethyl bromide which boiled at 125-130°/18mm. The yield was 480 g. (55 % based on the unrecovered ethylene bromide). The compound was redistilled and a 1° fraction taken for use.

γ-Bromopropyl phenyl ether (34): Two liters of water, 1 kilo. (4.95 moles) of trimethylene bromide, and 370 g. (3.9 moles) of phenol were placed in a three liter round bottomed flask equipped with a mechanical stirrer, an efficient reflux condenser, and a dropping funnel. Stirring was started and the mixture was heated to boiling. A solution of 150 g. (3.75 moles) of sodium hydroxide in 500 ml. of water was added from the dropping funnel in the course of one hour. The mixture was refluxed six hours longer, cooled, and the upper water layer separated and discarded.

The lower layer consisted of trimethylene bromide, γ-phenoxypropyl bromide, and diphenoxypropane. It was distilled under reduced pressure and the first fraction boiling up to 136°/20mm. was collected. This consisted principally of water and trimethylene bromide. The water was separated and the trimethylene bromide was recovered. The second fraction boiling at 136-142° /20 mm. was almost pure γ-bromopropyl phenyl ether. The yield was 495 g. (84 % based on the unrecovered trimethylene bromide). Some diphenoxypropane was left in the distillation flask. The compound was redistilled and a 1° fraction was taken for use in synthesis.

The author is indebted to Dr. Harry W. Davis for assistance in the rather tedious preparation of large

batches of β-bromoethyl phenyl ether and γ-bromopropyl phenyl ether.

B. General Methods of Preparation of Aminoethers and Examples

The preparation of the alkylaminoalkylene ethers was carried out according to the following scheme of reactions:

$$2\ R\text{-}NH_2 + X'\text{-}(CH_2)_n\text{-}O\text{-}R' \longrightarrow R\text{-}NH\text{-}(CH_2)_n\text{-}O\text{-}R' + HX'$$

$$R\text{-}NH\text{-}(CH_2)_n\text{-}O\text{-}R' + HX \longrightarrow R\text{-}\underset{HX}{NH}\text{-}(CH_2)_n\text{-}O\text{-}R'$$

Where R = alkyl, substituted alkyl, or cyclohexyl

R' = aryl or substituted aryl

X' = chlorine or bromine

X = chloride, sulfamate, phenyl acetate or picrate

n = 2 or 3

The synthesis and purification was carried out following two different general procedures, A and B. Method B is a modification of A that was found to yield a better product.

Method A. The halo ether (0.05 mol) was placed in 250 ml. erlenmeyer flask equipped for reflux and 0.105 mol of amine was added. The mixture was heated on a water bath until solid began to separate and then 25 ml. of benzine was introduced. The mixture was refluxed one and one

one-half hours longer.

The mixture was then removed from the flask and treated with an excess of 6N sodium hydroxide solution. The benzine layer was separated and washed well with water and dried over anhydrous sodium sulfate.

The dried solution was transferred to a Claisen flask with a little dry ether and distilled at a pressure of 40 - 50 mm. until the temperature corresponded to the boiling point, at atmospheric pressure, of the amine used. The residue was removed from the flask with a little ether and treated with Darco. It was then diluted to about 200 ml. with anhydrous ether and the hydrochloride precipitated with dry hydrogen chloride. The precipitated hydrochloride was dissolved in the least possible amount of boiling absolute alcohol, cooled, diluted with dry ether and filtered on a Büchner funnel. Recrystallization was carried out until the product had a constant melting point. Three recrystallizations of the crude material were usually sufficient.

This method has the disadvantage that any tertiary amine formed will precipitate as a hydrochloride and may be incompletely removed, even by repeated recrystallizations.

Method B. The halo ether (0.1 mol) was placed in a flask with a ground glass reflux condenser and 0.21 mol of the amine was added all at once. The mixture was heated

on an oil or water bath at the boiling point of the amine for three hours. The amine hydrochloride precipitated. The contents of the flask were allowed to cool and an excess of 6N sodium hydroxide was added to liberate the free bases, which were taken up with 50 ml. of ether and washed three times with water. The ether solution, if dark, was treated with Darco and dried over anhydrous sulfate.

The ether solution contained the free base of the amine used (in cases where the amine is not water soluble), the free base of the secondary aminoether, some tertiary amine, and a small amount of the unreacted halo ether. It was placed in a round bottomed flask with a ground glass joint equipped with a 15 cm. column containing a coiled spiral of nichrome wire, and connected to a receiver for fractional vacuum distillation. The ether and a large portion of the amine, if it had a boiling point below 100° C., were removed at room temperature with a water pump. Heating was then started and the material fractionated. The portion of the aminoether collected had a boiling range of 1°. Generally a considerable residue of tertiary amine was left in the flask.

The secondary aminoether free base was diluted to 200 ml. with anhydrous ether and dry hydrogen chloride was passed in until precipitation was complete. The

hydrochloride was filtered off on a Büchner funnel, washed well with dry ether and recrystallized to a constant melting point.

The recrystallization was carried out by dissolving the compound in the least possible amount of boiling absolute alcohol, cooling and diluting with anhydrous ether or ligroin.

Melting points were taken in a Thiele melting point apparatus under such conditions that checks were obtainable.

The following four examples of preparations carried out are typical of the group as a whole.

β-Ethylaminoethyl phenyl ether hydrochloride. A mixture of 0.2 mol (20.1 g.) of β-bromophenetole and 0.42 mol (9.46 g.) of ethylamine (as a 70 % water solution) was placed in a stoppered 125 ml. erlenmeyer flask and allowed to stand for one week. In twenty-four hours the mixture had separated into two layers and at the end of the week had become a semi-solid mass.

An excess of 6N sodium hydroxide was added to the mixture followed by 50 ml. of ether. The mixture was transferred to a separatory funnel and the water layer removed. The ether layer was washed three times with 50 ml. portions of water and allowed to dry over anhydrous sodium sulfate overnight.

The ether solution was placed in an all glass vacuum fractionation apparatus and the ether was removed at room temperature with a water pump. When no more ether was given off, the flask was heated on an oil bath. The temperature rose rapidly to 127° at 16 mm.. The β-ethylaminoethyl phenyl ether was collected from 127-128° at 16 mm.

The free base was diluted with 200 ml. of anhydrous ether and dry hydrogen chloride was passed in until precipitation appeared complete. The hydrochloride was precipitated with no obvious crystalline form. It was filtered on a Büchner funnel and the mother liquor was tested for complete precipitation. The hydrochloride was washed well with dry ether.

The crude hydrochloride was dissolved in the least possible amount of boiling absolute alcohol (about 25 ml.) and allowed to cool. Large shining white plates of β-ethylaminoethyl phenyl ether hydrochloride were precipitated. Precipitation was completed by adding 75 ml. of anhydrous ether. The material was filtered on a Büchner and washed well with dry ether. The melting point was 174 - 175° and was unchanged by a second recrystallization. The yield was 4.8 g. of pure material.

Anal. Calcd. for $C_{10}H_{16}NOCl$: Cl, 17.58. Found: Cl, 17.58.

γ-Sec.hexylaminopropyl phenyl ether hydrochloride:

A mixture of 0.05 mol (10.75 g.) of γ-bromopropyl phenyl ether and 0.105 mol (10.6 g.) of sec.hexylamine was placed in a 250 ml. erlenmeyer flask equipped with a reflux condenser and heated on a water bath. After one-half hour solid began to separate. Benzene (25 ml.) was added and refluxing was continued one and one-half hours longer.

The mixture was removed from the flask and treated in a separatory funnel with an excess of 6N sodium hydroxide. The water layer was removed and the benzene layer was washed three times with water and dried over anhydrous sodium sulfate. The benzene solution was distilled under 50 mm. pressure until the temperature reached 110°.

The residue in the flask was treated with 0.5 g. of Darco and precipitated with dry hydrogen chloride. A yield of 10.35 g. of γ-sec.hexylaminopropyl phenyl ether hydrochloride was obtained. It was dissolved in the least possible amount of boiling absolute alcohol, cooled, 75 ml. of dry ether was added and the precipitated hydrochloride was filtered off. The melting point of the compound was 134-137°. After two recrystallizations the melting point was constant at 135-136.5°. Yield 7.0 g. (51.5 %)

Anal. Calcd. for $C_{15}H_{26}NOCl$: Cl, 13.05. Found: Cl, 13.09.

β-Cyclohexylaminoethyl phenyl ether: In a 500 ml. flask equipped with a reflux condenser were placed 0.547 mol (85.7 g.) of β-chlorophenetole and 1.50 mol (114.0 g.) of cyclohexylamine. The mixture was refluxed for three hours. The material in the flask was shaken with an excess of 6N sodium hydroxide and 50 ml. of ether was added. The ether layer was separated, washed three times with 100 ml. portions of water, and dried over anhydrous sodium sulfate.

The ether solution was placed in an all-glass vacuum fractionation apparatus and the ether was removed at room temperature. The flask was heated on an oil bath and the β-cyclohexylaminoethyl phenyl ether was distilled. It had a constant boiling point of 160° at 2.8 mm. The yield was 79 g. (62.7 %).

A 5.0 g. portion of the free base was converted to the hydrochloride in dry ether with dry hydrogen chloride and recrystallized to a constant melting point of 179-180°. A sample was analyzed for chlorine by the Mohr method.

Anal. Calcd. for $C_{14}H_{22}NOCl$: Cl, 13.89. Found: Cl, 13.90.

The bulk of the material was preserved in the form of the free base for use in making salts other than the hydrochlorides.

β-Cyclohexylaminoethyl benzyl ether hydrochloride: A mixture of 0.2 mol of β-chloroethyl benzyl ether was placed with 0.42 mol of cyclohexyl amine in a flask fitted with a reflux condenser. The mixture was refluxed for five hours on an oil bath. An excess of 6N sodium hydroxide and 75 ml. of ether was added. The ether layer was separated, washed three times with 100 ml. portions of water, and allowed to dry over anhydrous sodium sulfate.

The ether solution was placed in an all-glass vacuum fractionation apparatus and the ether was removed at room temperature. A fraction boiling up to 200° at 15 mm. was discarded and the β-cyclohexylaminoethyl benzyl ether was distilled. It had a boiling range of 200-201° at 15 mm. The yield was 17.4 g. (32.3 %) of the free base.

The free base was diluted with 200 ml. of dry ether and precipitated with dry hydrogen chloride. The hydrochloride was recrystallized by dissolving it in the least possible amount of boiling absolute alcohol, cooling, and diluting to 200 ml. with dry ether. After one recrystallization the melting point was constant at 174-175°. The yield of pure hydrochloride was 14.6 g. (27.1 %). The hydrochloride was analyzed by the Mohr method.

Anal. Calcd. for $C_{15}H_{24}NOCl$: Cl, 13.17. Found: Cl, 13.18 .

C Preparation of Various Salts of β-Cyclohexylaminoethyl phenyl ether

β-Cyclohexylaminoethyl phenyl ether sulfamate:

β-Cyclohexylaminoethyl phenyl ether (2.1920 g.) was weighed on the analytical balance and diluted with 60 ml. of 95 % ethanol. Sulfamic acid (0.9709 g.) was weighed on the analytical balance and dissolved in 40 ml. of distilled water. The two solutions were thoroughly mixed and allowed to evaporate at room temperature. The sulfamate was left in an amorphous solid form. The sulfamate was powdered and digested three times with anhydrous ether to remove any excess of either the ether or the sulfamic acid. It was analyzed by the Kjeldahl method for nitrogen.

Anal. Calcd. for $C_{14}H_{25}N_2O_4SCl$: N, 7.97. Found N,

β-Cyclohexylaminoethyl phenyl ether phenylacetate:

β-Cyclohexylaminoethyl phenyl ether (2.1920 g.) was weighed on the analytical balance and diluted with 50 ml. of alcohol. Phenylacetic acid (1.3614 g.) was weighed on the analytical balance and transferred quantitatively to the solution of the ether. The mixture was allowed to evaporate at room temperature to dryness. The phenylacetate was obtained in the form of large (5 mm.), transparent, colorless, rhombs and prisms with an oily surface.

The crystals were powdered, washed well with dry ether and analyzed for nitrogen by the Kjeldahl method.

Anal. Calcd. for $C_{21}H_{28}NO_3Cl$: N, 3.71. Found: N,

β-Cyclohexylaminoethyl phenyl ether picrate: A saturated solution of picric acid was prepared from 100 ml. of absolute alcohol and picric acid and cooled to room temperature. To this solution 5.0 g. of β-cyclohexylaminoethyl phenyl ether was added. On shaking for about five minutes large rhombs of the orange-yellow picrate were thrown down. The crystals were filtered and washed free from picric acid with dry ether. The compound was recrystallized from absolute alcohol by cooling a hot saturated solution. After two recrystallizations the melting point was constant at 149-150°. The compound was analyzed by the Kjeldahl method with the addition of 0.4 g. of zinc dust for each 0.1 g. of sample during the digestion to reduce the nitro groups.

Anal. Calcd. for

D Analytical Methods

Halogen Analyses: The analysis of the hydrochlorides was carried out by the Volhard and Mohr methods of halogen determination.

The Volhard method was applied as follows. A sample of the hydrochloride approximating 0.1 g. was dissolved in 75 ml. of water and 15 ml. of 0.1 N silver nitrate was added. The flask was vigorously shaken with the addition of 2 ml. of nitrobenzene and 3 ml. of ferric ammonium sulfate indicator. When the silver chloride had completely coagulated the excess silver nitrate was back titrated with 0.1 N potassium thiocyanate.

This method gave low results with the aminoether hydrochlorides and a possible explanation of this behaviour is that the compounds were somewhat surface active and prevented complete coagulation of the silver chloride, which then reacted with the potassium thiocyanate to give low results.

The Mohr method was adopted for the above reason and was applied as follows. Samples of 0.2 g. of the hydrochloride were dissolved in 50 ml. of water. Three drops of a saturated solution of potassium chromate solution were added, and the mixture titrated to a faint end point with 0.1 N silver nitrate.

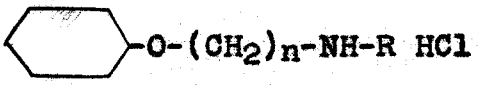
A pure sample of di-cyclohexylamine hydrochloride

when analyzed by the Mohr method gave a value of 16.45 % chlorine, as compared to a calculated value of 16.36 %. The Mohr method gave results not only of a greater precision but also of a greater accuracy. The Volhard method gave an error of 1.5 % chlorine with γ-cyclohexylaminopropyl phenyl ether hydrochloride; however the Mohr method gave an error of 0.09 % chlorine with a sample of the same material. With β-allylaminoethyl phenyl ether the Volhard method gave an error of 0.68 % chlorine and the Mohr method an error of 0.14 %. In general, the Mohr method gave results agreeing with the theoretical to less than 0.1 % and the Volhard method, where it could be used, to approximately 0.2 % or a little greater. The Volhard method was found to be useless with compounds containing more than one ether linkage, such as β-methoxyethylaminoethyl phenyl ether hydrochloride.

Nitrogen Analyses: Nitrogen was determined using a modification of the Winkler - Kjeldahl method. The compound (0.1 g.) was wrapped in filter paper and placed in a 50 ml. flask. To this were added 0.06 g. of copper sulfate as a catalyst, 2.0 g. of potassium sulfate to raise the boiling point of the mixture and 6 ml. of sulfuric acid. If nitro groups were present as in the picrate 0.4 g. of zinc dust was introduced to serve as a reducing agent. The flask was heated over a free flame

until all coloration due to organic matter had disappeared. The contents were allowed to cool and were transferred to a flask fitted with a steam generator and a condenser dipping into 10 ml. of 2 % boric acid solution. Twenty ml. of 50 % sodium hydroxide was introduced to form a layer beneath the surface of the digestion mixture. The contents were mixed and the ammonia steam distilled into the boric acid. When ammonia evolution was complete the ammonia was titrated with 0.05 N hydrochloric acid using one drop of a mixture of 10 ml. of 0.1 % brom cresol green and 2 ml. of 0.1 % methyl red as an indicator. The end point was taken at the change from a blue to a colorless solution.

E-Table of Compounds Prepared



No.	R	n	Name
1	CH_3-CH_2-	2	β-ethylaminoethyl phenyl ether hydrochloride
2.	$CH_3-CH_2-CH_2$	2	β-n-propylaminoethyl phenyl ether hydrochloride
3	$CH_3-CH_2-CH_2-CH_2$	2	β-n-butylaminoethyl phenyl ether hydrochloride
4	$CH_3-CH_2-CH_2-CH_2-CH_2-$	2	β-n-amylaminoethyl phenyl ether hydrochloride
5	$CH_3-(CH_2)_5-CH_2-$	2	β-n-heptylaminoethyl phenyl ether hydrochloride
6	$CH_3-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	2	β-sec.-amylaminoethyl phenyl ether hydrochloride
7	$CH_3-CH_2-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	2	β-sec.-hexylaminoethyl phenyl ether hydrochloride
8	$CH_3-CH_2-\underset{\displaystyle C_2H_5}{\underset{\vert}{CH}}-CH_2-$	2	β-2-ethylbutylaminoethyl phenyl ether hydrochloride
9	$(CH_3)_2CH-CH_2-$	2	β-prim.-iso-butylaminoethyl phenyl ether hydrochloride
10	$(CH_3)_2CH-CH_2-CH_2-$	2	β-iso-amylaminoethyl phenyl ether hydrochloride
11	$CH_2=CH-CH_2-$	2	β-allylaminoethyl phenyl ether hydrochloride
12	$C_6H_{11}-$	2	β-cyclohexylaminoethyl phenyl ether hydrochloride
13	$C_6H_5-CH_2-$	2	β-benzylaminoethyl phenyl ether hydrochloride
14	$CH_3-O-CH_2-CH_2-$	2	β-β-methoxyethylaminoethyl phenyl ether hydrochloride

E-Table of Compounds Prepared (Con't.)

No.	R	n	Name
15	CH_3-CH_2-	3	γ-ethylaminopropyl phenyl ether hydrochloride
16	$CH_3-CH_2-CH_2-$	3	γ-n-propylaminopropyl phenyl ether hydrochloride
17	$CH_3-CH_2-CH_2-CH_2-$	3	γ-n-butylaminopropyl phenyl ether hydrochloride
18	$CH_3-CH_2-CH_2-CH_2-CH_2-$	3	γ-n-amylaminopropyl phenyl ether hydrochloride
19	$CH_3-(CH_2)_5-CH_2-$	3	γ-n-heptylaminopropyl phenyl ether hydrochloride
20	$CH_3-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	3	γ-sec.-amylaminopropyl phenyl ether hydrochloride
21	$CH_3-CH_2-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	3	γ-sec.-hexylaminopropyl phenyl ether hydrochloride
22	$CH_3-CH_2-\underset{\displaystyle C_2H_5}{\underset{\vert}{CH}}-CH_2-$	3	γ-2-ethylbutylaminopropyl phenyl ether hydrochloride
23	$(CH_3)_2-CH-CH_2-$	3	γ-prim.-iso-butylaminopropyl phenyl ether hydrochloride
24	$(CH_3)_2CH-CH_2-CH_2-$	3	γ-iso-amylaminopropyl phenyl ether hydrochloride
25	$CH_2=CH-CH_2-$	3	γ-allylaminopropyl phenyl ether hydrochloride
26	$C_6H_{11}-$	3	γ-cyclohexylaminopropyl phenyl ether hydrochloride
27	$CH_3-O-CH_2-CH_2-$	3	γ-β-methoxyethylaminopropyl phenyl ether hydrochloride

Miscellaneous Compounds

28 γ-n-butylaminopropyl o-chloro-p-tert.-butyl-phenyl ether hydrochloride

29 β-cyclohexylaminoethyl benzyl etherhhydrochloride

30 γ-piperidinopropyl phenyl ether hydrochloride

F-Data on Compounds Prepared

No.	B.P. Free Base	M.P. HCl	Analysis %Cl Calc.	Found	% Yield	Method
1	127/16mm.	181-182	17.58	17.58		B
2		167-168	16.47	16.55		A
3		193-195	15.40	15.20		A
4	163/13mm.	128-128.5	14.55	14.61	40.3	B
5		221.5-222.5	13.04	12.99	29.9	A
6		116-117	14.55	14.44		A
7		143-144	13.78	13.53		A
8		112-113.5	13.78	13.62		A
9	142/11mm.	166-167	15.40	15.44	31.2	B
10		205-207	14.55	14.31	88.0	A
11	145/20mm.	150-151	16.62	16.76	39.4	B
12	160/2.8mm.	179-180	13.90	13.90	65.8	B
13		203-205	13.5	12.6		A
14	155/14mm.	127-128	15.33	15.29	38.9	B
15		165.5-167	16.47	16.11		A
16		169-171	15.48	15.34	57.0	A
17		182-184	14.58	14.35		A
18	175/17mm.	204-205	13.74	13.67	45.5	B
19		225-226.5	12.43	12.05		A
20		143-144	13.80	13.70		A
21		135-136.5	13.05	13.09	51.5	A
22		115-116	13.10	12.60		A
23	155/16mm.	168-169	14.54	14.52	85.3	B

F-Data on Compounds Prepared (Cont'd.)

No.	B.P. Free Base	M.P. HCl	Analysis % Cl Calc.	Found	% Yield	Method
24		190.5-191.5	13.78	13.43	47.1	A
25	153/14mm.	156-156.5	15.61	15.66	28.1	B
26		169-170	13.17	13.26	41.7	A
27	162/13mm.	131.5-132	14.46	14.44	19.9	B
28		151.5-152	11.07	10.97	21.8	A
29	200/15mm.	174-175	13.17	13.18	27.1	B
30		180-181	13.86	13.35		A

Salts of β-Cyclohexylaminoethyl phenyl ether

	M.P.	Analysis % N Calc.	Found	Form
Picrate	149-150			orange-yellow rhombs
Sulfamate				white-amorphous
Phenylacetate				transparent, colorless, rhombs

G-Pharmacological Data*

No.	Time of Onset Minutes	Duration Minutes	Irritation
2	inactive		
3	inactive		irritating
6	1	3	slight
7	1/2	7.8	slight edema
8	1	7.1	irritating
9	inactive		
10	1	11.5	irritating
12	3/4	38	irritating initially
13	1-1/4	20.5	very irritating, tears
15	inactive		
16	2	0-4	
17	1-1/5	13.8	slight
19	insoluble (this is being checked)		
20	1-1/2	16.8	slight, wears off
21	1	27,6	irritating
22	1	24.3	slight
24	1	23,6	edema
26	3/4	24.8	irritating
30	inactive		

*These compounds were tested in 1 % water solution on the rabbit cornea.

PART IV

PHARMACOLOGY

The preliminary pharmacological testing of these compounds is being carried out by the Wm. S. Merrell Co. of Cincinnati. As yet the data is very incomplete and only inferences can be drawn.

It appears that the activity of the compounds increases with increasing chain length of the N-alkyl-group and also increases with the increase in the length of the alkylene chain from two to three. This is to be expected on the basis of work carried out on the p-amino benzoic ester series. The n-propylaminoethyl and n-butyl-aminoethyl phenyl ethers showed no activity. When n was increased from two to three the activities rose to four minutes and fourteen minutes respectively.

The sec.amylaminoethyl phenyl ether hydrochloride and the sec.hexylaminoethyl phenyl ether hydrochloride showed activity but when the chain length was increased (n=3) the activities were considerably higher.

The iso-butylaminoethyl compound showed no activity; the iso-amylaminoethyl and iso-amylaminopropyl compounds both were active, with the propyl compound more active than the ethyl.

The piperidino compound reported to be active

by Brill (12) did not show any activity on the rabbit cornea, when a sample prepared by the author was tested. The melting points of the compounds agreed and Brill's directions were followed. Brill, however, did not give any details as to the methods used in testing his samples.

The cyclohexylamino compounds apparently show a reversal of the normal effect. The β-cyclohexylamino ethyl phenyl ether had a duration of action of thirty eight minutes while the propyl homologue had a duration of only twenty five minutes. These compounds are being rechecked.

There is no correlation between the irritation caused by some of the compounds and their structure.

Only one compound had its toxicity determined. The n-butylaminopropyl phenyl ether gave a minimum lethal dose for 50 % mortality of 20 mg./Kg. when injected intravenously in rabbits.

For purposes of comparison the duration of action on the rabbit cornea and the intravenous toxicity of some of the common local anesthetics are given.

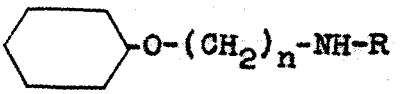
Compound	M.L.D. 50 I.V.	Duration of action Minutes
Cocaine	15 mg./Kg.	22
Procaine	55 mg./Kg.	0-2
Nupercaine	2.5 mg./Kg.	51 (0.1 % solution)

A more complete discussion of the pharmacology of these compounds will be given when the data becomes available. The results so far obtained are tabulated immediately following the tables of physical data.

PART V

SUMMARY

The synthesis of thirty compounds of the type



has been carried out and they are being tested for topical local anesthetic activity. Preliminary pharmacological data has shown that they are active.

The phenylacetate, sulfamate, and picrate of β-cyclohexylaminoethyl phenyl ether have been prepared, and they are being tested for local anesthetic activity.

The compound γ-piperidinopropyl phenyl ether reported to be an active local anesthetic by Brill has been prepared but no activity was shown by the compound on the rabbit cornea.

Preliminary pharmacological data on some of the compounds has indicated that the local anesthetic activity of these compounds increases with an increase in the length of the alkyl group and also with an increase in the length of the alkylene chain.

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THESIS RECORD

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S. Hughes Terry
E. F. Farnau

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S. Hughes Terry
Holse S. Greene

Degree Granted _____ Date _____

NOTE: List here any change in the thesis title as given above.