NOTE TO USERS

This reproduction is the best copy available.

UNIVERSITY OF CINCINNATI

May 27 1946

I hereby recommend that the thesis prepared under my supervision by George Rieveschl, Jr.
entitled New Local Anesthetics Derived from Fluorene
be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

Approved by:

Francis E. Ray

Hoke S. Greene, Chairman

Graduate Faculty of Chem. & Chem Eng.

Form 668—G. S. and Ed.—1M—7-37

NEW LOCAL ANESTHETICS DERIVED FROM FLUORENE

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

1940

by

George Rieveschl, Jr.

A.B. University of Cincinnati 1937

M.S. University of Cincinnati 1939

TABLE OF CONTENTS

ACKNOWLEDGEMENT

For the many helpful suggestions given by Dr. Francis Earl Ray, the author wishes to express his hearty appreciation.

Part I

GENERAL INTRODUCTION

TO THE CHEMISTRY OF LOCAL ANESTHETICS.

Of all the subjects in the bread field of chemotherapy none has been more thoroughly investigated than that of local anesthetics. The chief goal in most of these researches has been the elucidation of the intriguing problem of the relation of chemical constitution to local anesthetic activity and the synthesis of new compounds having distinct advantages over cocaine or synthetic local anesthetics. The amount of literature devoted to this subject is prodigious and the author has made no attempt to give an exhaustive survey, but rather a general view of the more important developments and the trend of modern research concerning local anesthetics.

Cocaine. There has always been a desire to alleviate pain almost as long as the human race has inhabited the earth. There are early records to indicate that the Egyptians and the Chinese used the juices of various plants to obtain artificial sleep and insensibility to pain (1) (2) (3) (4) *.

It is known that in the 16th century freezing of

---

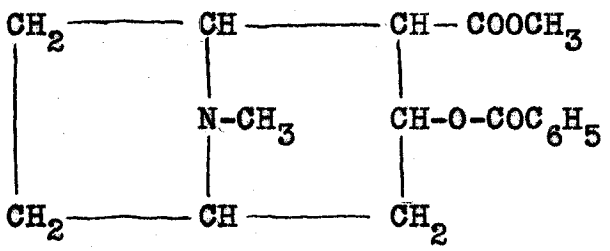
*These four references have been used as basic material for this survey, especially the excellent review (2) by Dr. Cook.

the limb with snow was used to obtain a certain degree of anesthesia for amputations. Arnot, in 1849, extended the technique somewhat by employing ice and salt. The intense cold produced by the evaporation of low boiling liquids, ether in this case, was first utilized by Richardson in 1867 for anesthetic purposes. At the present time freezing by means of ethyl chloride is used for minor surgical procedures, such as the lancing of a boil. The pain which is often felt as the frozen tissue warms is a common fault of this method.

Although it is probable that the Incas used an extract from the coca plant as an analgesic for their remarkable trephining operations, the first mention of the anesthetic properties of cocaine in scientific literature is due to Wohler in 1860. At that time Wohler had obtained a large sample of coca leaves which he gave to Niemann and asked him to endeavor to isolate the active principle. Niemann was successful and he named the crystalline substance, cocaine (5). Wohler described the unusual action of cocaine in these words: "It has a bitter taste and produces on the nerve endings of the tongue the peculiar effect that the site of application of the drug becomes as it were numb or almost anesthetic" (1). For twenty-four years no utilization of this discovery of the anesthetic properties of cocaine was made despite the fact that Moreno y Maiz (6) in 1868 again pointed out this

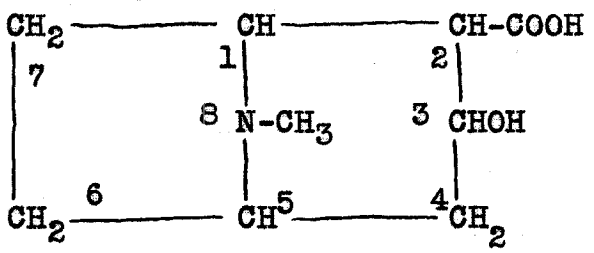
unusual property. Cocaine found its first use in ophthalmology by Koller in 1884. From that year on its use spread rapidly. By 1890 it was being used as an infiltration anesthetic (subcutaneous injection).

The next step was the determination of the structure of cocaine. The empirical formula, $C_{17}H_{21}O_4N$, was determined by Wohler, Niemann and Lossen, and also that it decomposes by hydrolysis into ecgonine (tropine-2-carboxylic acid), benzoic acid and methyl alcohol. The problem was brought to a successful close by the brilliant work of Wilstatter (7). Confirmation of the structure was obtained by synthesis. Cocaine has the following formula.

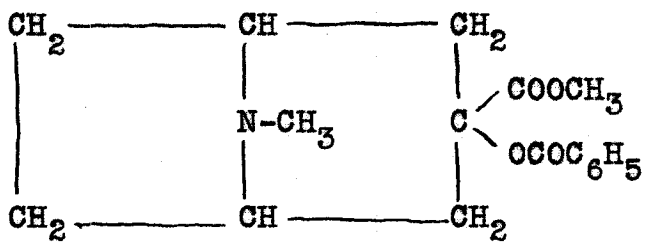


It was soon found that cocaine was not completely satisfactory as a local anesthetic, especially on injection. Not only was it habit forming, but it was expensive, difficult to purify, somewhat unstable in solution, and had a very bad effect on the blood pressure. A search was immediately begun to prepare compounds having fewer undesirable properties than those of cocaine. It was found that the cocaine molecule underwent a number of chemical trans-

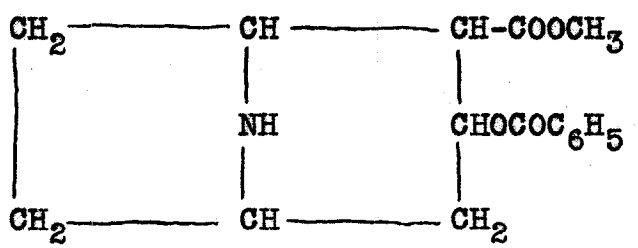
formations very easily, and soon there was a concerted attack upon the problem as to what part of the molecule was essential for the manifestation of local anesthetic activity. Investigators soon determined that ecgonine, itself,



is inactive, that the carboxy group must be esterified and that the benzoyl group is necessary for maximum action (1). Shifting the carboxy group to the 3 position gives α-cocaine (8)

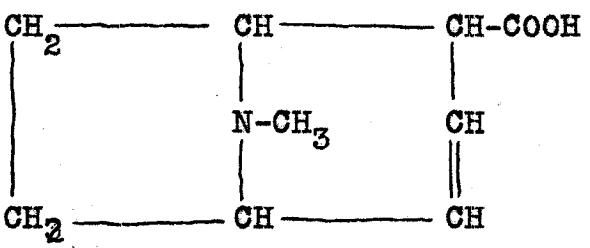


which is quite inactive. Demethylation of the amino group, giving nor-cocaine (9)

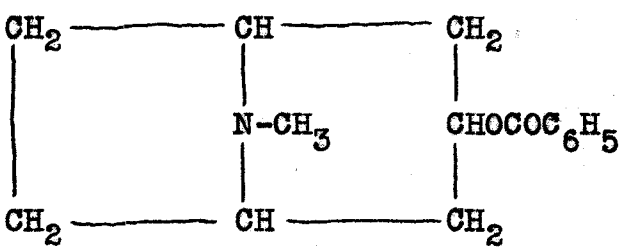


causes a slight decrease in activity but an increase in toxicity, while the formation of a quaternary ammonium salt (10) leads to the formation of curare action. If the benzene ring is substituted there is a very noticeable decrease in action. (11).

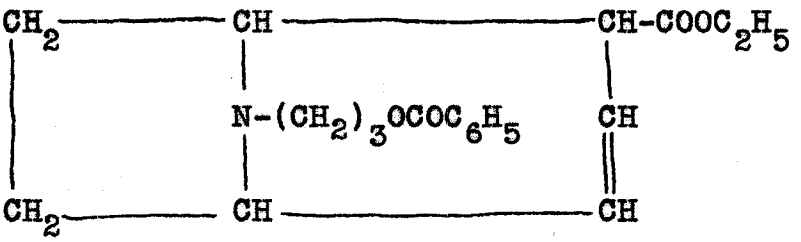
Esters of ecgonidine



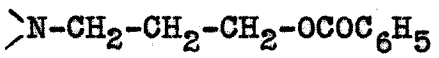
are inactive (1). The fact that tropacocaine



is as active as cocaine emphasizes the importance of the benzoyl group (12). It is interesting that tropacocaine occurs naturally in the coca plant. Attachment of the benzoate group through a trimethylene chain to the nitrogen atom of ethyl ecgonidine gives eccaine.

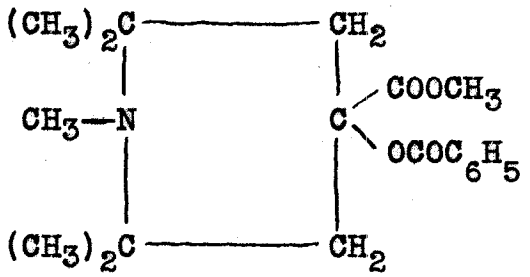


It is an improvement over cocaine both in respect to local anesthetic activity and toxicity (13). The grouping

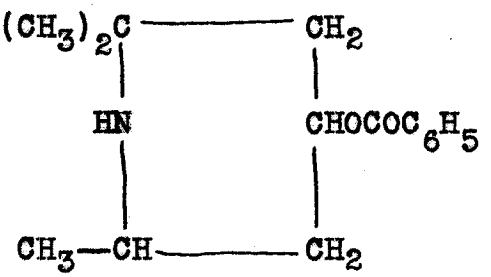


in eccaine becomes important in later synthetic work.

Steps toward the simplification of the cocaine molecule, while retaining activity, led to the eucaines. In these compounds one ring has been ruptured giving a piperidine derivative (14) (15).



α-eucaine

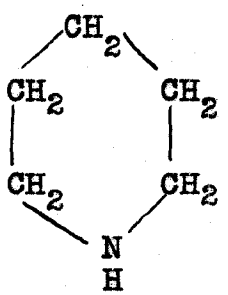


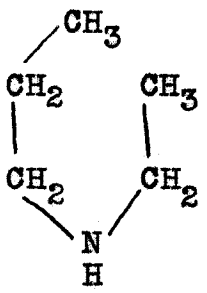
β-eucaine

β-Eucaine (16) possesses the more desirable properties although it is slightly irritating. The activity of α-eucaine is definitely unusual, since we would predict inactivity because the cocaine analogue is α-cocaine which is inactive

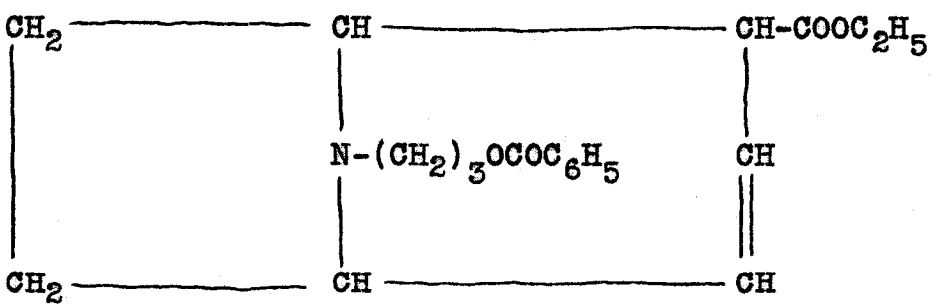
(see p. 4). The preparation of local anesthetics employing piperidine as the nucleus is still an important field of research and will be discussed later.

Simpler Cocaine Substitutes. It has been shown that simplification to a piperidine ring gives the eucaines. We may regard piperidine as analogous to ethyl-n-propyl-amine.



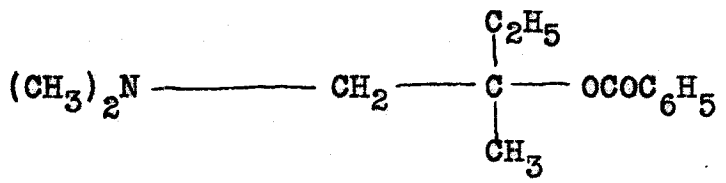


Such reasoning leads to the belief that straight chain compounds may still possess activity. In the case of the compound eccaine

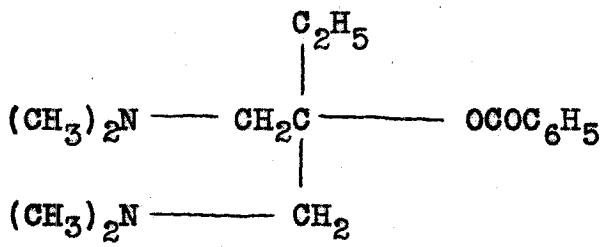


the maintenance of local anesthetic activity was thought to be due to an acylated hydroxyl group which is γ to the tertiary nitrogen atom. Fourneau took up this idea and syn-

thesized a great number of compounds in which there usually is present a tertiary hydroxy group and a secondary or tertiary amino group separated by a straight or branched carbon chain of varying length (4). This research led to Stovaine (17)



having a lower toxicity than cocaine, and it has found much favor as an anesthetic useful for spinal injection. Spinal anesthesia before the introduction of Stovaine was quite dangerous due to the toxicity of cocaine. If another dimethylamino group is substituted in Stovaine, Alypine (18)



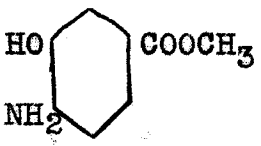
is obtained; however, it is more toxic than Stovaine.

Para-aminobenzoates. Before describing further advances in the search for a cocaine substitute it would be well to consider some of the properties which are desirable in a local anesthetic. Gilman (19) has given the following requirements for a good local anesthetic.

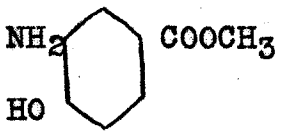
1. For the same degree of anesthesia compared to cocaine it must be less toxic than cocaine.
2. The compound must not give rise to any irritation or tissue damage, thus it cannot be too acid or alkaline.
3. It must be water soluble.
4. Solutions of the compound should be sufficiently stable for sterilization by boiling.
5. The compound must be compatible with adrenalin which, by its constricting action on the blood vessels, makes the area of operation practically bloodless and prevents too rapid absorption of the local anesthetic.

Fourneau had opened the road for the investigation of simplified molecules possessing local anesthetic action. The surprising fact that the simple ester, ethyl-p-aminobenzoate, had an anesthetic effect on the mucous membrane was discovered by Ritsert (20) in 1890; however, his observation attracted no attention for several years. In 1902 it was placed on the market and is known today as Anesthesine. The butyl ester of p-aminobenzoic acid, which is more active than the ethyl ester is marketed as Butesin. Einhorn and Uhlfelder (21) a little earlier (1896) found that the introduction of the hydroxy group into the nucleus caused an increase in activity. These com-

pounds are known under the proprietary names of Orthoform and New Orthoform.



Orthoform



New Orthoform

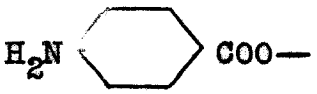
The fact that the free bases of these compounds are only very slightly soluble in water and that the hydrochlorides, although soluble, are too acid for use as local anesthetics makes them only of value as dusting powders or in ointments.

In compounds of the Stovaine type, Fourneau utilized tertiary aminoalcohols with great success. It was logical that research having as its goal the preparation of compounds involving the tertiary aminoalcohols in conjunction with the p-aminobenzoyl nucleus, whole simple esters had considerable local anesthetic action, would be worthy of immediation attention.

Einhorn (22) showed that the mono-hydrochloride of dialkylaminoethyl p-aminobenzoate

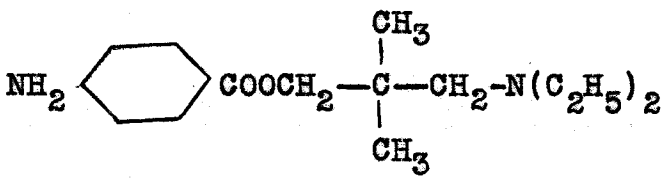
was water-soluble, practically neutral and gives, on injection, a powerful local anesthesia. Procaine, or novocaine as this compound is sometimes called, is approximately only one-sixth as toxic in mice as cocaine. It is non-irritant to subcutaneous tissues and it is exceptionally suitable for use in conjunction with adrenaline, which minimizes too rapid absorption of the local anesthetic by the tissue. The action of procaine without adrenaline is too evanescent. Procaine,however, fails as a topical anesthetic having little action on the tongue or the rabbit cornea, thus it does not displace cocaine in this particular respect.

Since procaine was introduced in 1906 it has continued to grow in favor until at the present time it is the most popular local anesthetic for injection use, chiefly because of its low toxicity and cost. Practically all of the research following the discovery of procaine has centered about the preparation of compounds which are superior to novocaine for injection purposes and compounds which are superior to cocaine for topical anesthesia. Using p-aminobenzoic acid as a foundation, many investigations have been carried out which ultimately led to the development of a number of successful local anesthetics of the procaine type. There are three methods of attacking the p-aminobenzoic acid molecule: first, variation of the aminoalcohol; second, substitution on the free amino group; and third, substitution in the aromatic nucleus.

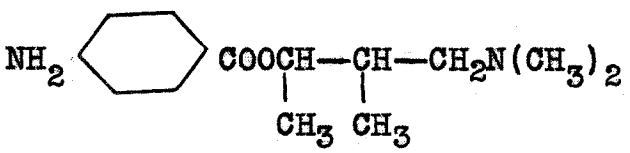


There has been much more emphasis upon the synthesis of compounds in which a more elaborate aminoalcohol is employed. Typical examples are the following compounds.

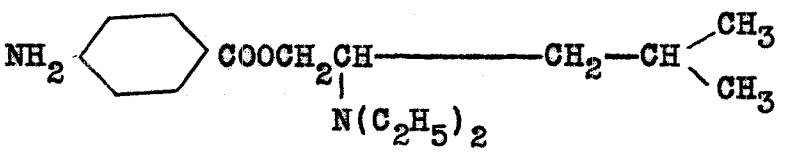
Butyn



Larocaine



Tutocaine



Panthesine

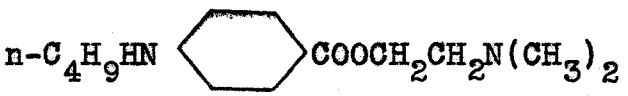
Butyn, which is the sulfate of γ-di-n-butylamino-propyl p-aminobenzoate, resulted from the investigations of Roger Adams and co-workers (23) (24). Butyn is absorbable by mucous membrane and is used extensively in the United States for eye, nose and throat operations. It is more toxic than cocaine and cannot be used for injection work. It is quite soluble in water and the solutions can be sterilized by boiling.

Tutocaine (25) is used in Europe as a topical anesthetic. It is approximately four times more toxic than procaine and is interesting from a chemical standpoint in that it is the p-aminobenzoate of a secondary alcohol.

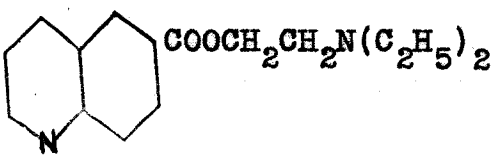
Larocaine (26) is used for spinal anesthesia.

Panthesine (27) was prepared by Karrer and has a limited use as a local anesthetic.

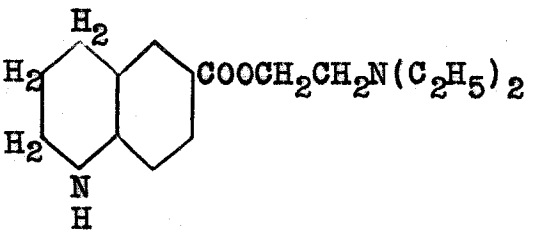
The compound pantocaine (1) (28)



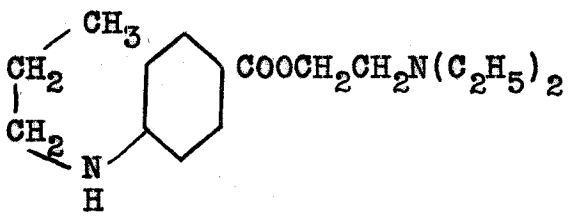
is the only local anesthetic on the market in which the free amino group has been alkylated. This compound has an interesting history (1). It was observed that the diethylamino-ethyl ester of quinoline-6-carboxylic acid



had no local anesthetic action while the same ester of the hydrogenated quinoline



was twice as active and also twice as toxic as cocaine. This led to experiments upon mono-alkylated p-aminobenzoates. It was found that the compound



was twenty times as active as cocaine, but only ten times as toxic. If the size of the alkyl group on the amino nitrogen is varied from methyl to propyl there is an increase in action which remains almost constant until octyl is reached; from then on the action decreases rapidly until dodecyl is substituted, in which case the compound has practically no action on the tongue. The compound which was finally chosen as the best of this series was pantocaine.

There are no local anesthetics in extensive use with substituents in the aromatic nucleus; however, Einhorn

found that aminoalkylbenzoic acids, aminotoluylbenzoic acids and di-aminobenzoic acids could be used for the preparation of local anesthetics, but none of the compounds which he studied were superior to procaine (1).

Chemical Constitution and Local Anesthetic Activity Of Procaine Analogues. If we start with procaine

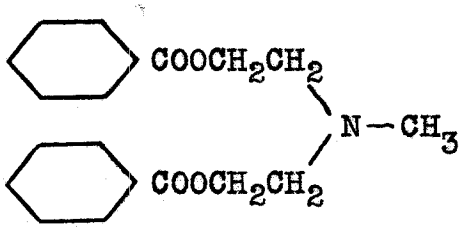
as a basic compound and vary certain parts of the molecule many interesting facts become apparent. First, let us consider simple esters of p-aminobenzoic acid. Adams and others (29) prepared a large number of alkyl aminobenzoates

and determined their local anesthetic activity. It was found that as R increases from methyl to n-butyl, there is an increase in activity, but beyond that there is not much increase probably due to the decrease in solubility as the molecular weight becomes greater. Esters containing a branches alkyl chain were less effective than straight chain esters.

Coming back to procaine it is interesting to note that elimination of the aromatic amino group in a procaine analogue does not entirely eliminate the local anesthetic

activity (3). Dimethylaminopropylbenzoate

has some activity; however, the dibenzoate of diethanolmethylamine

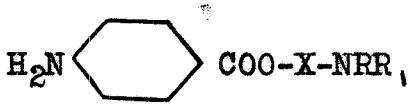


has no activity whatsoever. On the other hand, if the two ethyl groups of the alkamine portion of the procaine molecule are removed, giving β-aminoethyl p-aminobenzoate,

there is complete elimination of activity.

The synthetic work of Adams and others (23) which led to Butyn afforded some insight on the effect of variation of the alkamine portion of p-aminobenzoates on local anesthetic potency. They prepared a great number of com-

pounds of the general formula



In the first series of compounds $NH_2C_6H_4COOCH_2CH_2N=$ remained constant and $-RR_1$ was varied. Alkyl groups varying from one to five carbons, including the straight and branched chain isomers, were substituted for RR_1. It was found that an increase of the size of the alkyl groups on the nitrogen caused an increase in toxicity and an increase in anesthetic activity; however, in the compounds studied the increase in activity is usually greater than the increase in toxicity. The most interesting fact concerning this series of compounds is that the increase of the size of the alkyls greatly increases the topical anesthetic power of the compound in comparison to procaine. Unfortunately increases in the molecular weight cause a lowering of the solubility in water.

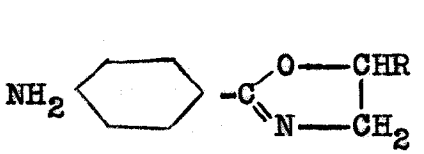
The second and third series were characterized by the $NH_2C_6H_4COOCH_2CH_2CH_2N=$ and $NH_2C_6H_4COOCH_2\underset{\displaystyle CH_3}{\underset{|}{CH}}-N=$ groups, respectively, with the RR_1 group changing. Deductions made for the first series hold in these two series also.

The effect of substitution of alkyl group on the carbon chain was studied in the fourth series of compounds of the general formula $NH_2C_6H_4COOCH_2\underset{\displaystyle R}{\underset{|}{CH}}N(C_2H_5)_2$. An increase

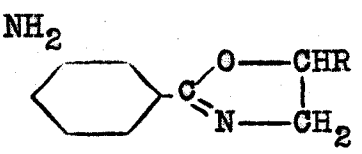
in size of the R group had approximately the same effect as increasing the size of the R groups on the nitrogen atom. The general conclusion that compounds with iso or forked chains are less toxic and less active than the analogous straight chain compounds can be drawn for all four series of derivatives.

In the last series, compounds were prepared having from two to five methylene groups between the nitrogen and the oxygen, $NH_2C_6H_4COO(CH_2)_nN(C_2H_5)_2$ where n=2,3,4,5. As the length of the chain increased both the toxicity and the local anesthetic action increased, especially with regard to topical anesthesia.

It is evident that by adhering closely to the procaine type of molecule that it is impossible to obtain a compound with a lower toxicity than procaine. Adams and Leffler (30) prepared aminophenyloxazolines, thus retaining the $-O-CH_2-CH_2-N=$ group and obtaining a 30% reduction in molecular weight. This should result in a much lower toxicity. A number of compounds of the types

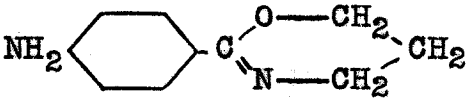


and

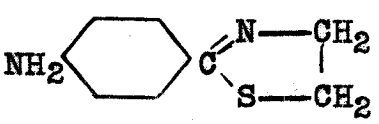


were prepared. It is true that most of the compounds were usually less active and less toxic than procaine but the free

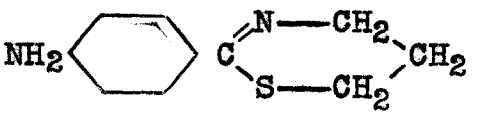
bases were too insoluble and the salts were too acid for use as anesthetics. The oxazolines were also unstable to boiling water. A similar series of aminophenyl pentoxazolines



were prepared by Novelli and Adams (31) and found to be local anesthetics, but they were more toxic than procaine and only slightly soluble in water. The sulfur analogues of these two series of compounds, aminophenylthiazolines (I) and aminophenylthiazines (II)



I



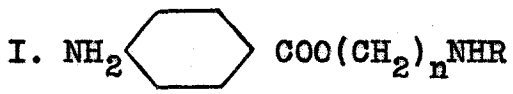
II

were synthesized by Adams and Babcock (32). They were less soluble than the corresponding oxygen compounds and the hydrochlorides were even more acid; however, they do have some local anesthetic action.

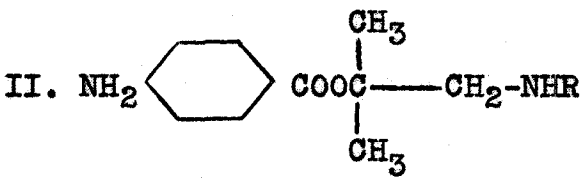
It can be stated with certainty from the work of

Adams and other investigators that any elaboration of the procaine molecules gives both increased action, especially with regard to topical anesthesia, and increased toxicity.

A recent important development in the synthesis of procaine analogues has been the use of mono-alkamine esters. Goldberg (33) prepared a number of compounds of the general formulas



I. NH_2 – C$_6$H$_4$ – $COO(CH_2)_nNHR$

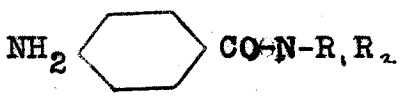


II. NH_2 – C$_6$H$_4$ – $COOC(CH_3)_2-CH_2-NHR$

In series I it was found that the mono-alkylaminopropanols were very toxic and poor anesthetics; however, the isobutylaminoethyl-p-aminobenzoate, known as Monocaine, has been recommended for dental anesthesia (34). It is a little more toxic and several times more active than procaine; furthermore, it possesses vaso-constrictor properties and the ad-

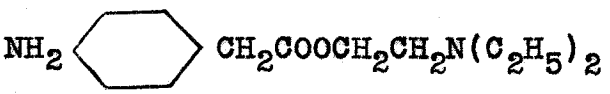
dition of adrenalin is not necessary. Compounds of type II in which R was varied from methyl to amyl were all too toxic for injection purposes; however, when R was n-amyl a very active surface anesthetic, even more active than Butyn and cocaine, was obtained. The use of secondary amino alcohols in the synthesis of local anesthetics, although very little has been done up to the present, gives indications of being a very promising modern development.

If instead of alkamine esters of p-aminobenzoic acid the mono-alkyl and di-alkylamides of p-aminobenzoic acid

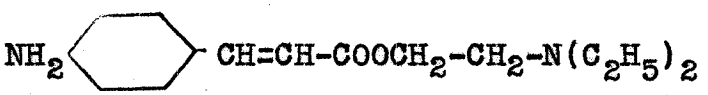


are tested for local anesthetic activity, we might expect little action due to the lower molecular weight. Wenker (35), however, found that the mono- and di-alkylamides in which the alkyl groups were small (methyl and propyl) had little action, but when the alkyl groups were larger (butyl, amyl and piperidyl) the compounds were strong surface anesthetics. These results are interesting, since they seem to indicate that the amide linkage in this particular type of molecule is associated with the development of topical anesthetic power.

Next let us consider what effect structural variation of the aromatic portion of the procaine molecule has upon local anesthetic activity. The substitution of p-aminophenylacetic acid for p-aminobenzoic acid, giving diethylaminoethyl-p-aminophenyl acetate

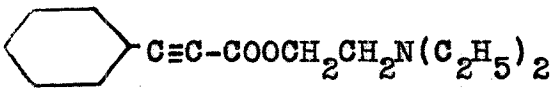


has the surprising result of removing all activity (36). On the other hand, if p-aminocinnamic acid is esterified with an alkamine ester, activity is restored (37).

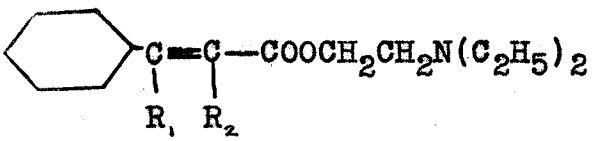


The γ-diethylaminopropyl ester of cinnamic acid is on the market under the name Apothesine (38).

We may expect greater activity in a still more unsaturated compound, such as the diethylaminoethyl ester of phenylpropiolic acid



but surprisingly, it is entirely inactive (39). Quite recently Lott and Christiansen (40) have shown that the substitution of alkyl groups in α or β positions of diethylaminoethyl cinnamate



is associated with a progressive increase in activity with lengthening of the R group.

Kamm (37) concludes that maximum anesthetic effect appears to develop when the carbonyl group is directly attached to the aromatic nucleus; however, this type of linkage is not essential provided that the carbonyl group of the ester is united to an unsaturated carbon atom, such as in the cinnamates.

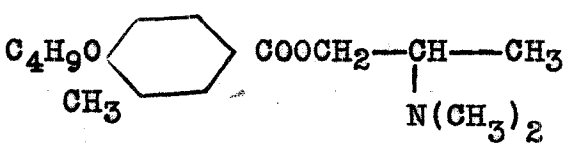
The sulfur analogue of procaine, diethylaminoethyl p-aminothiobenzoate (thiocaine)

has been prepared and it is more active and more toxic than procaine (41).

A recent important development has been the preparation of alkamine esters of alkoxybenzoic acids. There is evidence in the literature that substitution of an alkoxy group in the benzene ring (42) or even replacement of the free amino group by an alkoxy group gives an increase in activity over the corresponding amino derivative (43). Lott, Harris and Christiansen (44) have described an impressive list of alkamine esters of p-ethoxybenzoic acid and p-butoxybenzoic acid, and they reported that all of the compounds were local anesthetics. The latest local anesthetic to be placed on the market is Intracaine

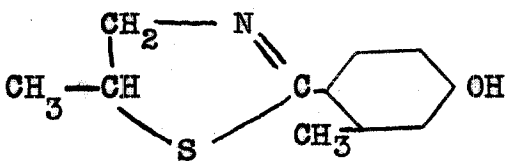
in which the free amino group of procaine has been replaced by an ethoxy group. It is recommended for spinal anesthesia, however, Sappenfield and Rovenstine (45) say that it possesses no special advantages over procaine.

A somewhat similar alkoxybenzoate, β-diethylaminopropyl 3-methyl-4-butoxybenzoate



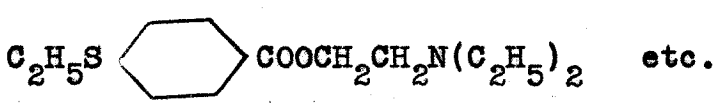
has been prepared by McIntyre and Sievers (46). Although it has excellent activity it has considerable irritating properties.

Hart and Niederl (47) found that 5-methylthiazoline-m-cresol



has approximately the same topical activity as cocaine and a lower toxicity; the methyl ether of this compound is almost three times more effective than cocaine. Although the hydrochloride of 5-methylthiazoline-m-cresol is very irritating, the tartrate is not. The activity of these compounds in view of the work of Babcock and Adams (see p.19) is another interesting example of the effect of alkoxy groups in the molecule.

Very recently a number of the sulfur analogues of alkoxybenzoic esters have been prepared by Donleavy and English (48). For example, β-diethylaminoethyl esters of the o-, m- and p-ethyl thiobenzoic acid were synthesized.



Preliminary pharmocological tests show that these compounds possess activity comparable to corresponding oxygen compounds. A very significant fact is that the substitution of sulfur for oxygen in alkoxy benzoates lowers the toxicity very remarkably to the extent that these thio compounds are less toxic than procaine. The most favorable position of the alkylthio group for maximum activity appears to be in the ortho and meta positions rather than in the para position.

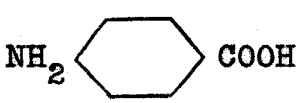
All of the alkamine esters that we have found to be local anesthetics so far in this discussion are esters of benzoic acid. It is logical to ask whether the acid need be aromatic in order to endow the compound with anesthetic activity. The use of aliphatic alkamine esters has not been investigated with much thoroughness, but it is known that alkamine esters of low molecular weight are inactive. Some activity becomes apparent only when the molecular weight is increased (49). Alkamine esters of unsaturated aliphatic acids has been shown by Bachmann (50) to possess activity which is inversely proportional to the degree of unsaturation of the acid. Shriner and Keyser (51) found that β'-diethylaminoethyl-β-aminocrotonate,

$$CH_3-\overset{NH_2}{\overset{|}{C}}=CHCOOCH_2CH_2N(C_2H_5)_2$$

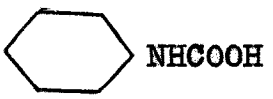
is inactive.

Aromaticity of the acidic portion of alkamine esters is generally regarded as quite necessary for the manifestation of local anesthetic activity.

Urethans. If we examine the formulas of p-amino-benzoic (I) and phenylcarbamic acid (II)

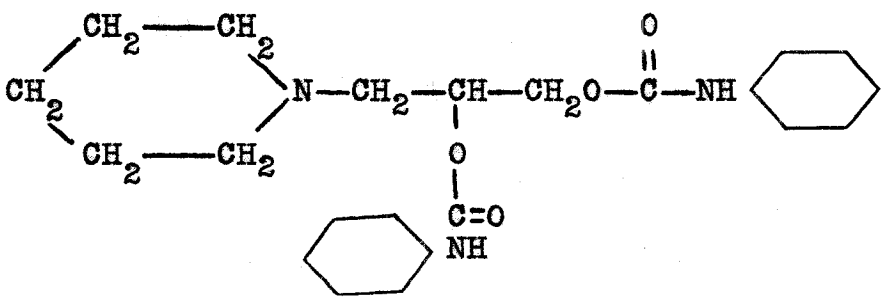


I



II

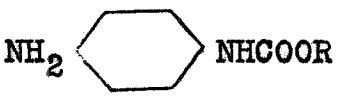
it is apparent that the two substances are isomeric. A good example of a local anesthetic derived from phenylcarbamic acid is Diothane, which is piperidinopropanedioldiphenyl-urethan (52).



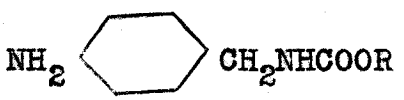
This compound is perhaps the strongest topical anesthetic known today. Cook and Rider (53) report that the phenyl urethan radical endows a compound with greater topical action

in comparison to its isomeric radical, p-aminobenzoyl.

The introduction of an amino group gives p-aminophenylcarbamate, the esters of which are active but very irritating (54).



Shriner and Cross (55) think that the irritating properties of these compounds may be due to the p-phenylenediamine linkage in the molecule. Endeavoring to avoid this particular arrangement of atoms they prepared an impressive series of alkyl-N-(p-aminobenzyl)-carbamates.



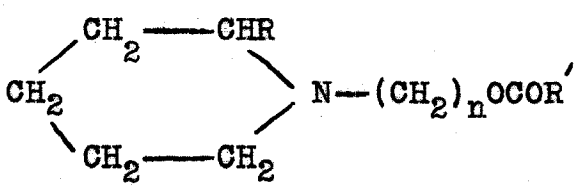
The compounds were unusually ineffective when applied topically and they were all very irritating.

Attacking the problem in a different manner Shriner and Hickey (56) synthesized alkyl- γ -diethylaminopropyl-carbamates.

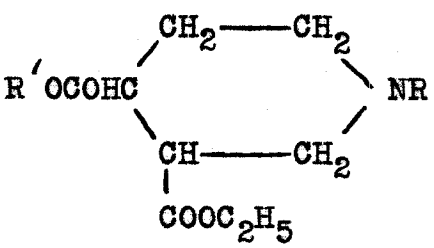
$$(C_2H_5)_2N(CH_2)_3NHCOOR$$

They were found to follow the rule that toxicity increases as the R group increases in size. The compounds exhibited no topical anesthesia until the hexyl group was substituted for R; however, the removal of any aryl groups in the molecule, as was done in this particular series of compounds, did not eliminate the severe irritation.

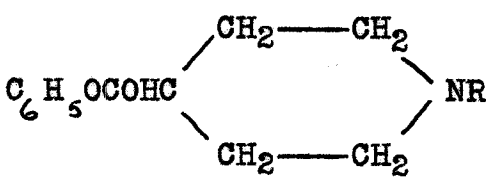
Piperidine Derivatives. It was pointed out earlier (see p.6) that in the process of simplification of the cocaine molecule by rupture of one of the rings to a piperidine compound (e.g. β -eucaine) is occasioned by the loss of little activity. A large number of piperidine derivatives have been investigated to determine their applicability as local anesthetics. McElvain and others (57) have studied three types of compounds.



I

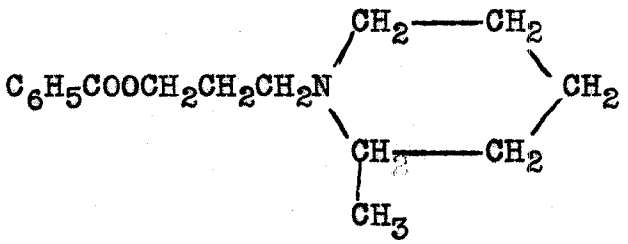


II



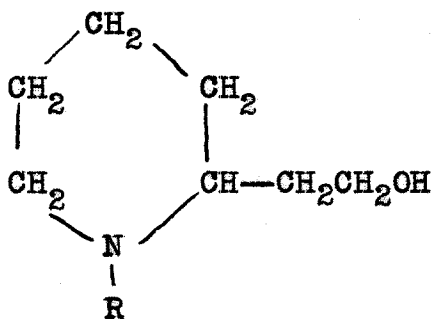
III

Usually R is alkyl and R′ is aryl, both substituted and unsubstituted. All compounds of these general types are active local anesthetics. Out of the great number of compounds which were studied, one has been placed on the market. Metycaine is the benzoate of γ-(2-methylpiperidino) propanol,

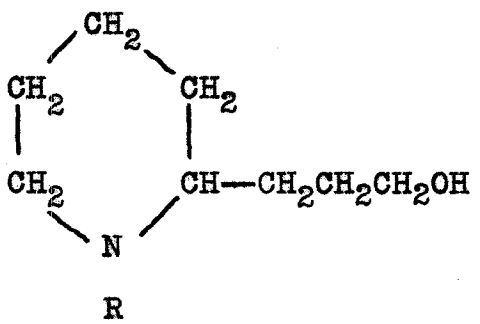


and it is well adapted to both topical and infiltration anesthesia.

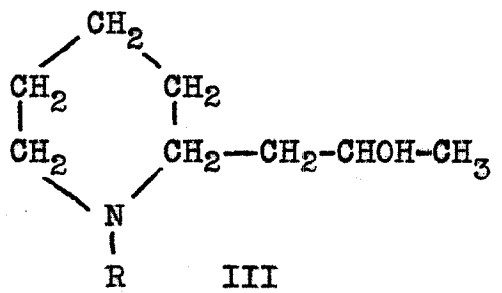
More recently Tullock and McElvain (58) have investigated benzoates of piperidyl substituted alcohols of the general formulas



I



II



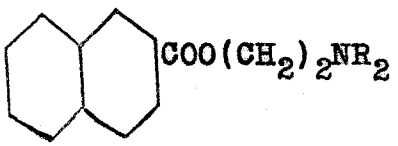
III

The R group was varied from methyl to n-butyl. Superior activity was found in all three types of compounds when R was ethyl. Ten years previously Marvel and Shelton (59) had prepared the p-aminobenzoate of N-ethyl- and N-n-propyl-2-(β -hydroxyethyl)-piperidine (I) and found the propyl derivative to be twice as active as the ethyl derivative; however, Tullock and McElvain, employing the benzoates, found the reverse to be true.

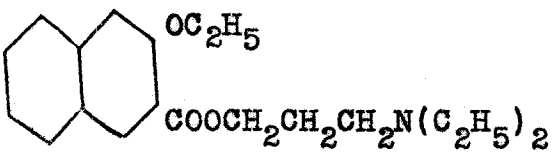
Walter and Fosbinder (60) have also prepared a number of local anesthetics from 2-(β -hydroxyethyl)-piperidine, in which the nitrogen atom is not alkylated. The piperidyl alcohol was esterified with a variety of substituted benzoic acids, e.g. o-, m-, and p-aminobenzoic acid and p-ethoxy-m-aminobenzoic acid. The o-aminobenzoate is very active, almost twice as active as the p-aminobenzoate.

Local Anesthetics from Other Compounds. Practically all of the local anesthetics which have been considered so far in this discussion have had present somewhere in their structures a benzene ring in the form of a free or substituted benzoic acid or a phenylurethan. There is no reason to suppose that other nuclei could not be employed as basic compounds in the synthesis of local anesthetics and possibly be superior. A logical course of investigation is to prepare alkamine esters of various aromatic acids and thus, by analogy, adhere to the molecular pattern of the successful benzoic esters; little work has been done along this line.

Simple alkamine esters of β -naphthoic acid are almost as active as cocaine but less toxic (61).



It should be noticed that an increase in molecular weight of the acidic part of the molecule has the same effect as increasing the size of the alkyl groups on the nitrogen, that is, an increase in topical anesthetic potency. Fisk and Underhill (62) have described other alkamine esters of naphthoic acid derivatives. One compound which had strong action was 2-ethoxy-3-(γ -diethylaminopropyl) naphthoate (63).

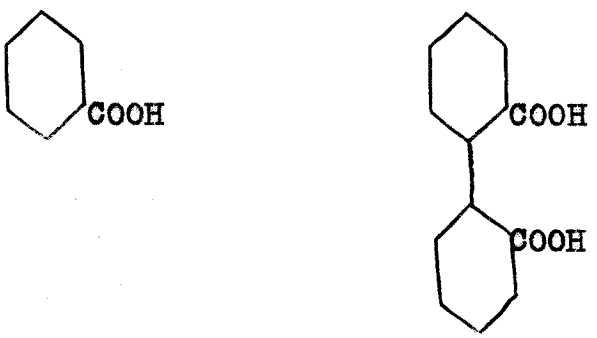


It is interesting to note again the influence of an alkoxy group.

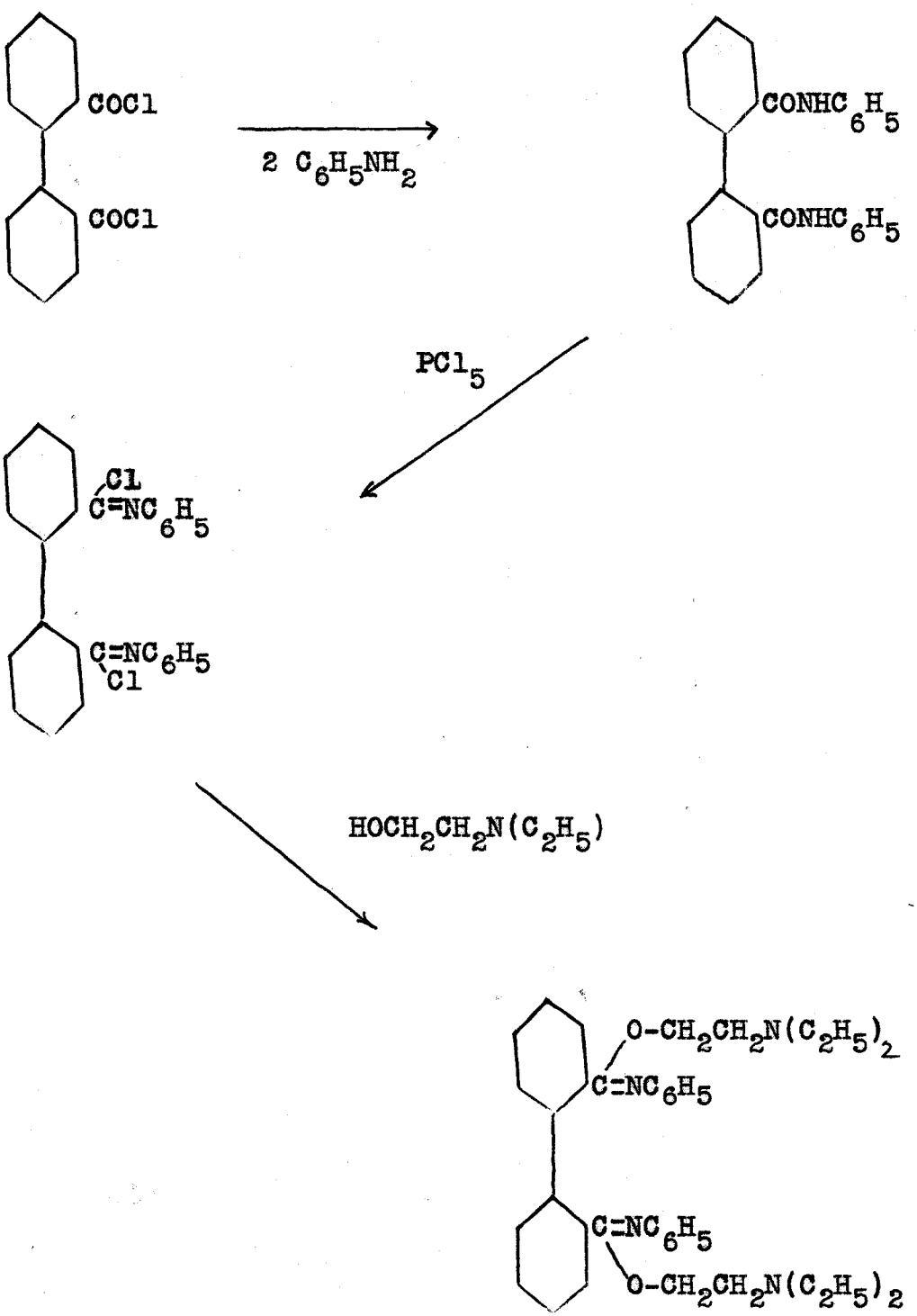
In the last few years two important papers have appeared describing local anesthetics derived from amino-naphthoic acids. Sergievskaya and Nesvad'ba (64) maintained the para relationship of the amino and carboxyl groups present in procaine and prepared various alkamine esters of 1-amino-4-naphthoic acid. They reported that the local anesthetic

action of these compounds is greater than cocaine and are less toxic than cocaine. Blicke and Parke (65) synthesized a more comprehensive list of alkamine esters, utilizing the 3-, 4-, 5- and 6-amino-1-naphthoic acids. Although a detailed pharmacological report has not appeared on these compounds, or the other compounds mentioned above, Blicke and Parke stated that all of the compounds possess definite local anesthetic action; however, a number of the hydrochlorides are irritating and also rather insoluble in water.

Roberts and Johnson (66) pointing out the fundamental similarity of benzoic and diphenic acids



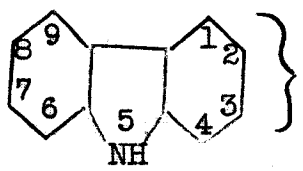
prepared diethylaminoethyl diphenate which had pronounced local anesthetic properties. They also synthesized the diethylaminoethylimido ester of diphenanilide (I) by treating diphenanilideimide chloride with diethylaminoethanol.



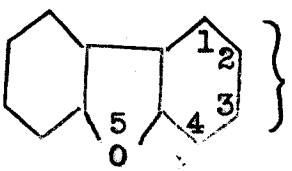
(I)

The imido ester was much more active and less irritating than the ordinary ester when tested by means of human wheals. This fact is of great importance since the imido ester grouping could be applied with facility to a vast number of other local anesthetics; however, this discovery by Roberts and Johnson has been overlooked and no investigations have been reported making use of it.

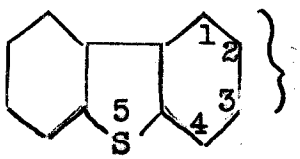
A very significant paper by Burtner and Lehmann (67) describing the use of heterocyclic acids in the synthesis of local anesthetics appeared in March, 1940. A series of alkamine esters of a number of isomeric carboxylic acids of carbazole (I), dibenzofuran (II), and dibenzothiophene (III) were prepared.



I

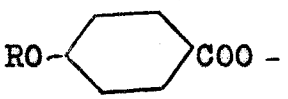


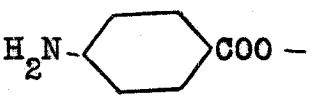
II



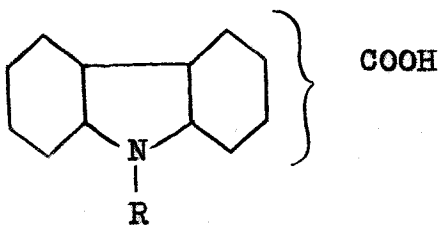
III

A detailed pharmacological report revealed that the 3-position in each series of compounds, except in the case of dibenzothiophene in which only the 2 and 4 carboxy acids were studied, was the most favorable position for the development of maximum local anesthetic action. This is unusual since it represents a meta arrangement between the carboxy group and the hetero atom, instead of the para relation between the carboxy group and nitrogen or oxygen in the procaine type of compound.

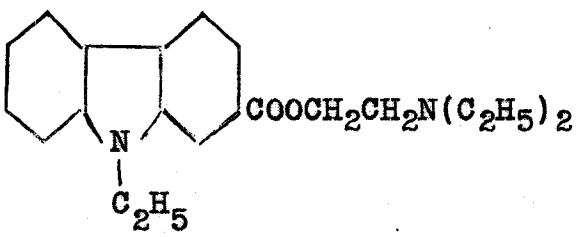




It probably is true in these heterocyclic acids that the carbon-carbon bridge to which the 3-carboxy group is para, has a more profound influence upon the activity. Several carbazole esters were prepared in which the nitrogen atom was alkylated.



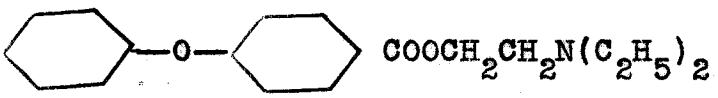
The effect of alkylation varies with the position of the carboxy group. For example, if the carboxy group is in the 3-position, an N-ethyl group causes a 100% increase in activity and no increase in toxicity; however, when the carboxy group is in the 2-position, the same substitution results in a very great loss in activity with a slight decrease in toxicity. One carbazole compound

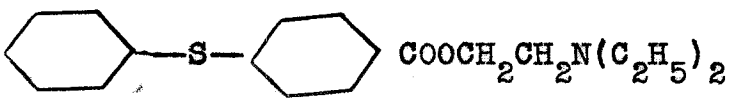


was extremely active (three times that of cocaine) and had only one-fifth the subcutaneous toxicity of cocaine. An intracutaneous injection in man gave an anesthesia lasting for 24 hours, but it was very irritating.

Analogous dibenzofuran and dibenzothiophene compounds were on the whole less active and more toxic than the carbazole derivatives. If the carbon-carbon bond in dibenzofuran and dibenzothiophene is opened to give phenoxybenzoic acid and thiophenoxybenzoic acid, respectively, we

might obtain some idea of the importance of the influence of the carbon-carbon bridge. The following two compounds were prepared

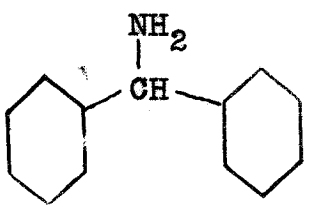




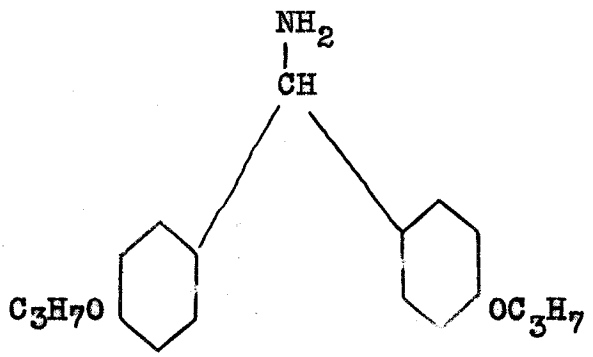
Opening the ring in the case of the dibenzofuran derivative caused a large increase in toxicity and only a slight enhancement of activity; however, the ester of thiophenoxybenzoic acid showed a substantial increase in activity and an increase in toxicity.

All of the compounds were irritating and Burtner and Lehmann consider that it is inherent to the nucleus involved.

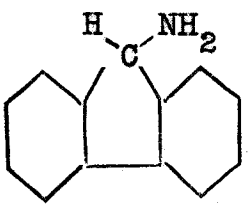
It is well known that amines of high molecular weight have local anesthetic activity. Ogata (68) found that benzhydrylamine



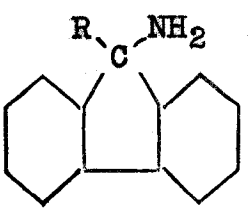
and amines of the type $C_6H_5CHRNH_2$ were active. The action is increased if alkoxy groups are substituted in the benzene rings (69). The potency of p,p′-dipropoxybenzhydrylamine



is approximately six times that of cocaine (70). It is not unusual in view of the above observations that 9-amino-fluorene

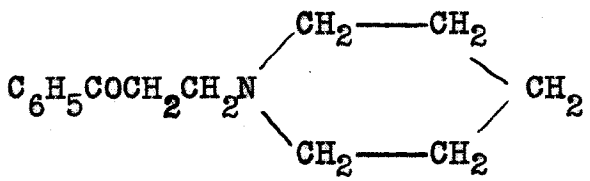


exhibits some local anesthetic properties (71). Pinck and Hilbert (72) also noticed that three compounds of the type

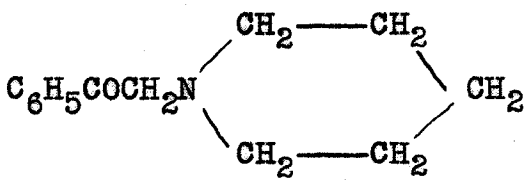


when R was methyl, phenyl, and α-naphthyl, have a numbing effect when applied to the tongue.

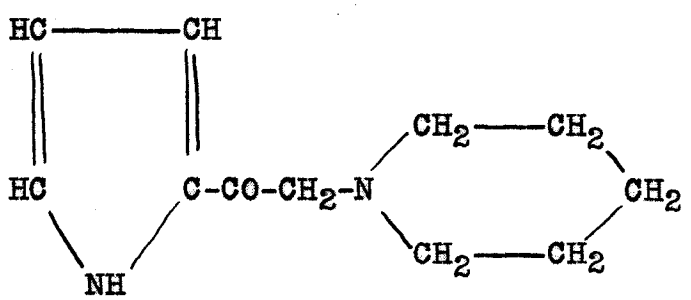
Certain ketones possess local anesthetic activity. Mannich and others (73) found that β-N-piperidinoethyl-phenyl ketone



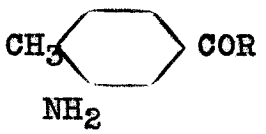
has considerable action. Blicke and Blake (74) prepared the next lower homologue, N-piperidinophenylmethyl ketone



and also the N-piperidinomethyl-2-pyrryl ketone,

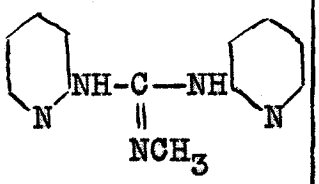
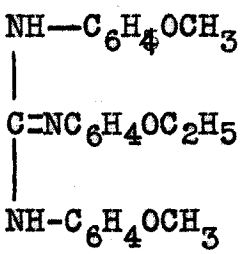
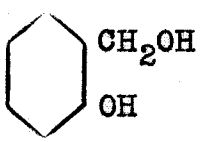


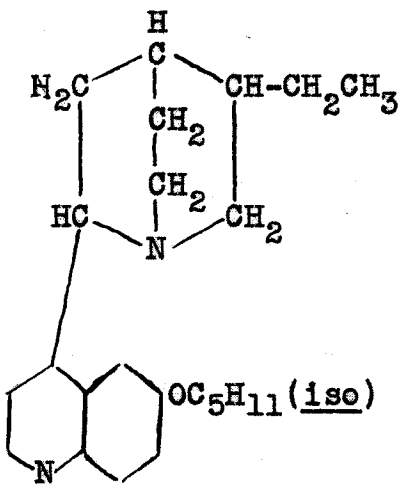
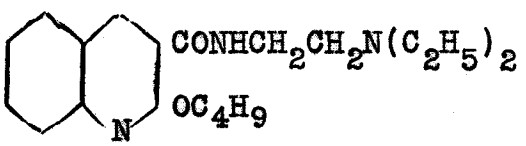
both of which were active. Hartung and Munch (75) found that acylanilines, which are closely related to the ketones just mentioned, are also active. A series of acylanilines of the general formula



were prepared. Anesthetic activity is not apparent until R is propyl; the n- butyl and iso-butyl ketones are as active as cocaine, but unfortunately, all of the compounds are irritating.

There is a vast number of other compounds of varying chemical structure which possess some degree of local anesthetic power. Rather than give any extended discussion of the better known compounds, the formulas and names of these substances are given in the following table.

Formula	Name	Literature
	α-Dipyridylmethylguanidine Protocaine	(76)
	Acoin	(77)
$C_6H_5CH_2OH$	Benzyl alcohol	(78)
	o-Hydroxybenzyl alcohol Saligenin	(79)
$C_6H_5CH_2CH_2OH$	Phenylethylalcohol	(80)

Formula	Name	Literature
$C_6H_5COCH_2OH$	Benzoylcarbinol	(81)
	Eucupine	(82)
	Nupercaine	(83)

Part II

PROCEDURE AND DISCUSSION

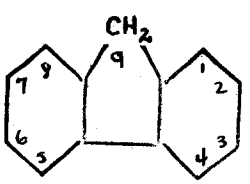
It is pointed out in the introduction that the greater part of the research upon procaine analogues concerns itself with structural variation of the alkamine portion of the molecule and little attention is paid to the acidic part of the molecule. The preparation of several alkamine esters of naphthoic and aminonaphthoic acids (see p. 32) represents the extent of the work upon the problem of using a higher aromatic hydrocarbon as the basic material for the preparation of anesthetics analogous to procaine.

There is evidence for the belief that an increase in molecular weight of a potential local anesthetic enhances the activity and particularly the topical anesthetic properties of the substance. If the increase in molecular weight is centered about the acidic moiety of the molecule it seems quite possible that a compound would have excellent local anesthetic properties, exceeding procaine, without resorting to an elaboration of the alkamine portion. The relatively low toxicity of procaine is no doubt due to the simple aminoalcohol used to esterify p-aminobenzoic acid, since there is an increase in toxicity if other aminoalcohols having a higher molecular weight are substituted. If another aromatic acid of higher molecular weight were found to replace p-aminobenzoic acid in procaine, it is not improbable that the re-

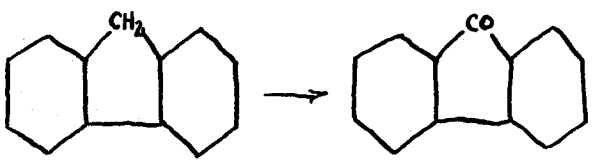
sulting substance would have greater activity and possibly the same order of toxicity as procaine, provided the new aromatic acid endowed the molecule with no additional toxicity as compared to p-aminobenzoic acid. Such speculations as these on the matter of toxicity are of little value because of the scarcity of experimental work, but the beneficial effect of increasing the molecular weight is fairly well established.

One good reason for seeking a local anesthetic containing a nucleus other than the p-aminobenzoate group lately has been supplied by the work of Goodman (84). It has long been known that many persons are extremely sensitive to procaine, which causes various skin reactions. Goodman found, by patch testing of a sensitive patient, that a relation between the structure of a number of local anesthetics and the cutaneous hypersensitivity associated with them could be demonstrated. In all cases compounds which contained the NH_2-C_6H_4COO— group caused skin reactions. From this limited study the preparation of a local anesthetic which does not contain the $NH_2C_6H_4COO$— radical may be of some practical importance.

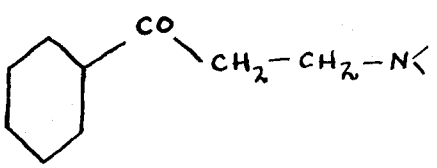
The hydrocarbon fluorene (85)



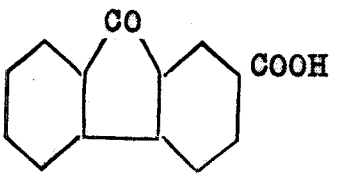
represents a cheap source of an aromatic nucleus of high molecular weight, since it is isolated easily from coal tar and purified by simple recrystallization from glacial acetic acid. This is in direct contrast to other hydrocarbons such as anthracene and phenanthrene which are very difficult to purify. All reactions, such as nitration, Friedel-Crafts, bromination, etc., give fluorene derivatives substituted in the 2 position. If we use fluorene as a starting material for the preparation of an aromatic carboxylic acid we are limited to the 2 isomer. Fluorene contains a very reactive methylene group which is easily oxidized to the ketone, fluorenone,



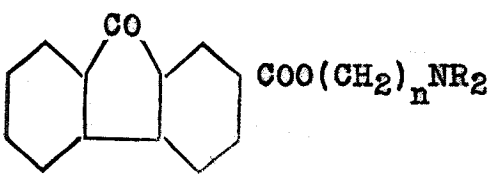
It is known that ketones (see p. 40) of the type



are active local anesthetics. By using fluorenone-2-carboxylic acid

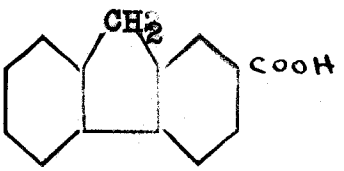


we may incorporate in one molecule both the keto and carboxy groups. The carboxy group is attached to an aromatic nucleus thus fulfilling Kamm's (37) condition for maximum local anesthetic activity (see p. 23). Alkamine esters of fluorenone-2-carboxylic acid would not be completely analogous to procaine due to the absence of the free amino group; however, since no alkamine esters of a cyclic keto acid have been prepared it would be of interest to synthesize compounds of the general formula



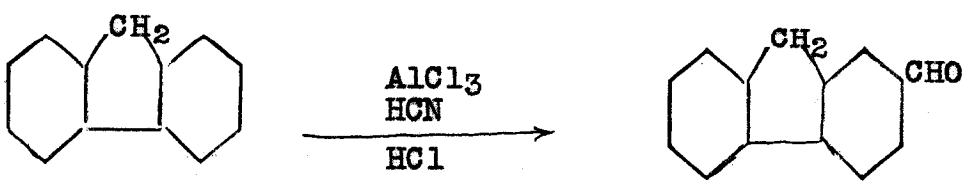
In order to synthesize compounds of this type it is necessary to have a convenient method of preparing fluorenone-2-carboxylic acid. This compound has been prepared previously

by a number of investigators. Fortner (86) obtained it by oxidizing fluorene-2-carboxylic acid



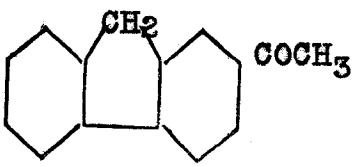
which he obtained from 2-nitrofluorene, followed by reduction, diazotization, conversion to 2-cyanofluorene, and hydrolysis. This method is rather long, (5 steps), to be of value for preparative purposes.

Hinkel, Ayling and Beynon (87), employing a modified Gatterman synthesis, reacted liquid hydrogen cyanide, aluminum chloride, hydrogen chloride, and fluorene in chlorobenzene solution and obtained a 70% yield of 2-fluorenealdehyde.



Although this would be an excellent method of preparing fluorenone-2-carboxylic acid, since the aldehyde should oxidize easily, the use of liquid hydrogen cyanide is definitely dangerous and the reaction could not be run conveniently in very large quantities.

Dziewonski and Schnayder (88) prepared 2-acetylfluorene



by a Friedel-Crafts reaction from fluorene, acetyl chloride, and aluminum chloride in carbon disulfide. 2,7-Diacetylfluorene was also formed; they reported 10% of the diacetyl compound and 8% of the monoacetyl derivative. Oxidation of 2-acetylfluorene with sodium dichromate gave fluorenone-2-carboxylic acid, but the yield was unreported. Despite the discouraging low yield in the Friedel-Crafts reaction, we thought that with possible improvements this method offered the best road to fluorenone-2-carboxylic acid.

In order for the synthesis to be of practical value the yield of 2-acetylfluorene must be considerably increased and the formation of the diacetyl derivative must be minimized. An examination of the experimental procedure of Dziewonski and Schnayder revealed that they used a 26% ex-

cess of acetylchloride over the theoretical amount needed for the formation of the monoacetyl derivative. This fact in conjunction with the high reactivity of acetyl chloride accounts for the presence of both the mono- and diacetyl derivatives.

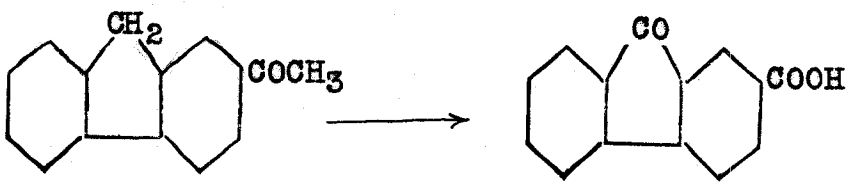
After many trials it was found by using acetic anhydride, which is much less reactive than acetyl chloride, a slight excess of fluorene and by carrying out the reaction at a higher temperature, that it was possible to obtain a quantitative yield of crude 2-acetylfluorene. The product was sufficiently pure for the next step in the synthesis.

Furthermore, it was discovered that crude, technical fluorene instead of pure, recrystallized fluorene could be used as the starting material without seriously affecting the quality of the resulting 2-acetylfluorene. This is possible because the aluminum chloride addition product separated from the reaction mixture as a semi-crystalline mass which is insoluble in carbon disulfide. The addition product may be filtered and washed free of tars with carbon disulfide. This represents a substantial improvement since the labor and cost of purification are avoided. The recrystallization of fluorene from glacial acetic acid gives a 70% yield of pure fluorene and, assuming that the crude fluorene is approximately 95% pure, the above procedure effects a saving of 25%.

After our synthesis of 2-acetylfluorene had been worked out, Ardashev, Lomovatskaya and Kacher (89) reported its preparation by a Friedel-Crafts reaction employing fluorene,

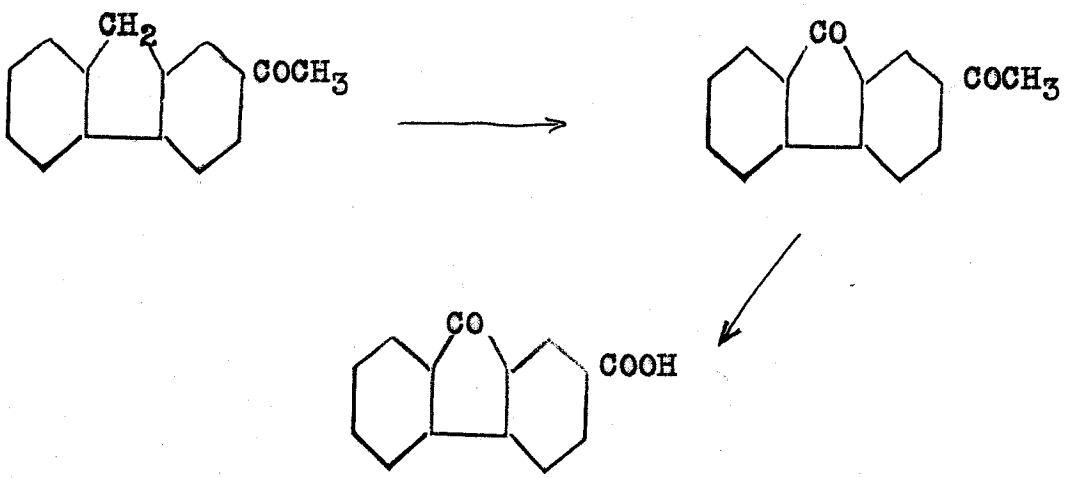
acetyl chloride and aluminum chloride in nitrobenzene solution. The yield of pure 2-acetylfluorene was 50%.

The oxidation of 2-acetylfluorene to fluorenone-2-carboxylic acid involves the oxidation of both the 9-methylene group and the 2-acetyl group.



After a number of experiments, sodium dichromate was chosen as the oxidizing agent and glacial acetic acid as the solvent. It was found that in order to obtain good yields sufficient acetic anhydride must be added to the reaction mixture to remove water arising from the oxidation of hydrogen atoms and also from the water of crystallization of the sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$). This method of oxidation results in a mixture of 2-acetylfluorenone and fluorenone-2-carboxylic acid, from which the acid is separated by extraction with potassium hydroxide. It is quite necessary that potassium hydroxide be used since the potassium salt is much more soluble than the sodium salt. The material remaining after extraction is practically pure 2-acetylfluorenone. This is a new compound and it was purified and analyzed. It may also be prepared by oxidizing

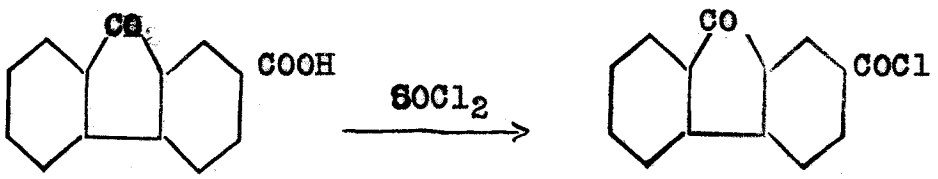
2-acetylfluorenone with the theoretical amount of sodium dichromate. This shows definitely that the oxidation takes place according to the following equations:



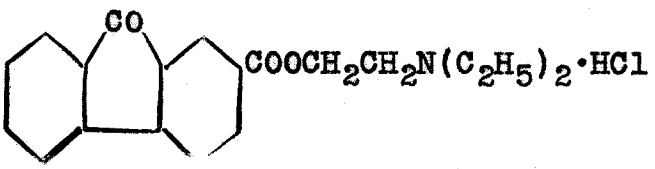
The remaining 2-acetylfluorenone may be oxidized separately to give a further quantity of the acid, or more simply, it may be added to the next batch of 2-acetylfluorene which is to be oxidized. The over-all yield of fluorenone-2-carboxylic acid, based on the acetic anhydride used in the Friedel-Crafts reaction varies from 58% to 62%. This is a good yield taking into account that crude fluorene was used and that two steps are involved in the synthesis. Furthermore, the reagents are cheap and the reactions can be carried out in large quantities.

The preparation of the acid chloride of fluorenone-

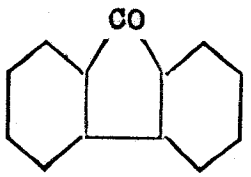
2-carboxylic acid in quantitative yields offered no difficulty provided both the fluorenone-2-carboxylic acid and the thionyl chloride were of high purity.



The alkamine esters of fluorenone-2-carboxylic acid were synthesized by condensing the acid chloride in benzene solution with the proper amino alcohol. The hydrochloride of the ester precipitated, and usually one recrystallization from methyl alcohol gave the pure compound. The following alkamine esters were prepared.

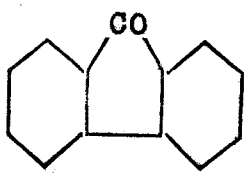


I. β -diethylaminoethyl fluorenone-2-carboxylate hydrochloride.



$COOCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$

II. γ -diethylaminopropyl fluorenone-2-carboxylate hydrochloride.



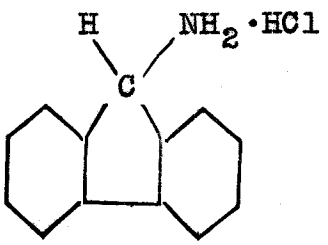
$COOCH_2CH_2N(C_4H_9)_2 \cdot HCl$

III. β -di-n-butylaminoethyl fluorenone-2-carboxylate hydrochloride.

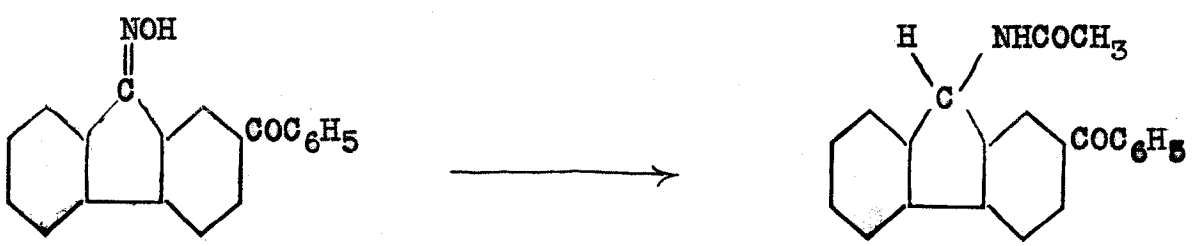
Compound I contains the same aminoalcohol as procaine. Compounds II and III were prepared to show the effect upon activity of increasing the methylene chain and the effect of increasing the size of the alkyl groups, respectively. All of the compounds when applied to the tongue had a strong local anesthetic action which lasted for an hour or more. It is evident then that the use of the high molecular weight aromatic acid has given the compound topical anesthetic properties. The molecular weight of procaine is approximately 259 while

that of I is 360, an increase of 101. Despite the high molecular weight of these compounds, they are quite soluble in water. For example, a 9% aqueous solution of II can be prepared easily.

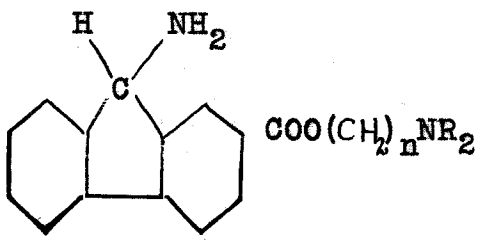
The presence of a reactive keto group in these compounds offers the opportunity of substituting other groups in the molecule. In 1930, Nakamura (71) found that 9-aminofluorene hydrochloride



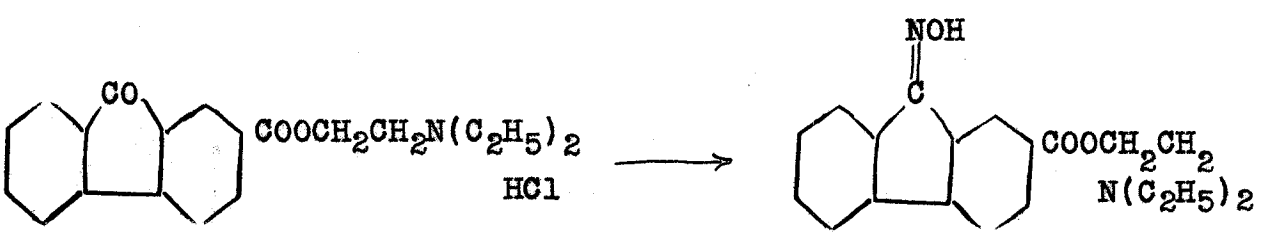
had local anesthetic action. The similarity of this compound to the active benzhydrylamines is considered in the introduction (see p. 38). We previously prepared 9-acetylamino-2-benzoylfluorene by the reduction of 9-isonitroso-2-benzoylfluorene (90)



with zinc and acetic acid. The non-acetylated amine is obtained by reduction with zinc and hydrochloric acid in ethyl alcohol. Both of these compounds as hydrochlorides are active on the tongue but they are only slightly soluble in water. Roughly compared with 9-aminofluorene they are more active, thus the benzoyl group in the 2 position gives some enhancement in potency. It was logical to attempt the preparation of alkamine esters of fluorenone-2-carboxylic acid containing an amino group in the 9 position.

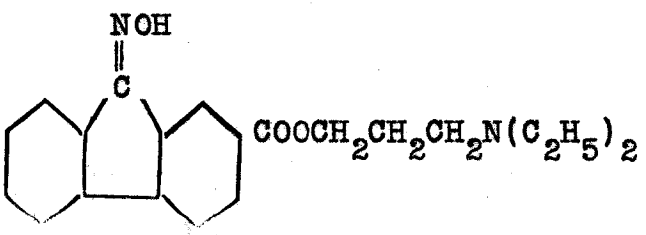


The reaction between the hydrochloride of diethylaminoethyl fluorenone-2-carboxylate, hydroxylamine hydrochloride, and barium carbonate in ethyl alcohol proceeded well giving the oxime in 60% yield.



I

The fact that I is soluble in water and insoluble in ether indicates that it is possibly the hydrochloride salt. Analysis shows it to contain 7.28% of nitrogen. The monohydrochloride of I has 7.47% of nitrogen, which is in fair agreement with the experimental value, and the dihydrochloride contains 6.81% of nitrogen. A water solution of I has an approximate P_H of 4. On addition of dilute ammonium hydroxide the free oxime is precipitated as a gum. Treatment of a solution of I with silver nitrate gives a precipitate of silver chloride followed by reduction of excess silver nitrate to free silver. All of this points to the presence of hydrogen chloride in the molecule and also indicates the presence of the =NOH radical since the silver nitrate is reduced. In the oximation reaction the barium carbonate is obviously not a strong enough base to remove hydrogen chloride from the molecule, and the analysis indicates that an equilibrium was reached between the monohydrochloride and the dihydrochloride. The oxime of γ -diethylaminopropyl fluorenone-2-carboxylate



II

is also obtained as the impure hydrochloride. The dihydrochloride of II requires 6.59% nitrogen and the monohydrochloride, 7.20% nitrogen. The nitrogen content on analysis

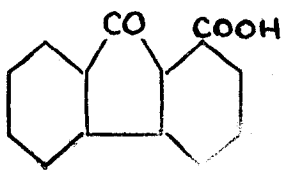
is 6.85%. Again the product is a mixture of the mono- and dihydrochlorides. Compound II when treated with ammonium hydroxide also deposits the free oxime as a gummy mass, gives distinct acid reactions when dissolved in water and produces a precipitate of silver chloride and subsequent reduction of excess silver nitrate. Both I and II are soluble in sodium and potassium hydroxide, which is further evidence that the compounds are oximes. Both of the oximes have greater local anesthetic activity than the keto esters from which they are derived. This observation is indeed interesting and the use of the oxime group in other local anesthetics has considerable possibilities.

Reduction of the oximes to the amines was attempted by several methods. Catalytic hydrogenation under pressure with Raney nickel and Adams' platinum catalyst gave evidence of reduction, but no pure compound could be isolated. Reduction with sodium amalgam and absolute alcohol gave a small amount of a substance which was thought to be the amino hydrochloride, but it was unstable and decomposed on short standing. The instability is probably due to the aliphatic nature of the amine, since the character of the 9 carbon atom in fluorene is essentially aliphatic. 9-Aminofluorene and its hydrochloride are also unstable in air.

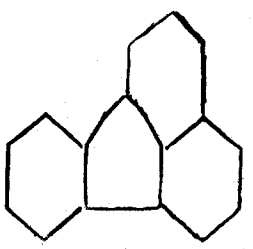
Since simple alkamine esters of fluorenone-2-carboxylic acid had strong anesthetic powers it was decided to prepare

esters of other isomeric fluorenone-carboxylic acids, and thus determine the effect of variation of the position of the carboxy group on the activity of the compound.

Fluorenone-1-carboxylic acid

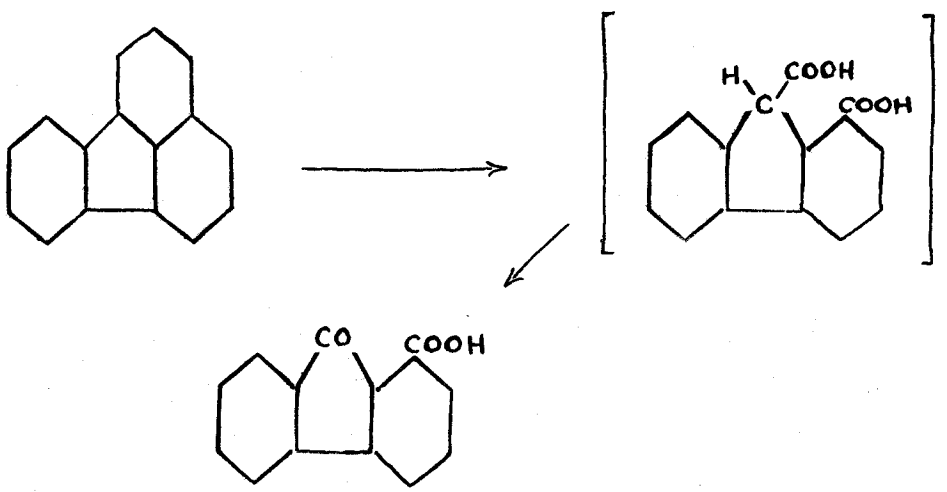


is conveniently prepared by oxidation of the rare and interesting hydrocarbon fluoranthene.



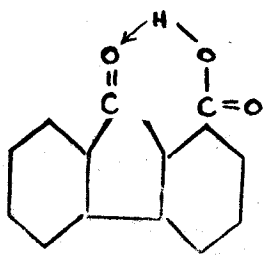
Fluoranthene is found in small amounts in the coal tar fraction which boils slightly higher than anthracene. It occurs in greater quantity in the mixture of hydrocarbons which is obtained as a residue by distilling the mercury ores found in Idria, Italy. This accounts for the name "idryl" which is often applied to fluoranthene. It is interesting to note that fluoranthene was discovered in coal tar by Fittig and Gebhard (91) in 1877 and independently in the same year, by Goldschmiedt (92) who isolated it from the Idria ores.

The oxidation of fluoranthene to fluorenone-1-carboxylic acid is best accomplished with chromic acid (93) in glacial acetic acid. The reaction probably proceeds in the following manner.



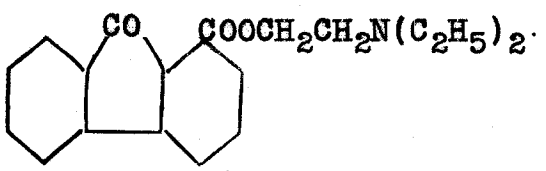
The intermediate dicarboxy compound would be immediately oxidized under the conditions of the reaction since Jeanes and Adams (94) found that fluorene-9-carboxylic acid is readily oxidized with chromic acid in hot glacial acetic acid.

Fluorenone-1-carboxylic acid is a bright red compound. This is unusual as fluorenone-2-carboxylic acid is a bright canary-yellow. The great color difference may be explained by assuming the formation of a hydrogen bond

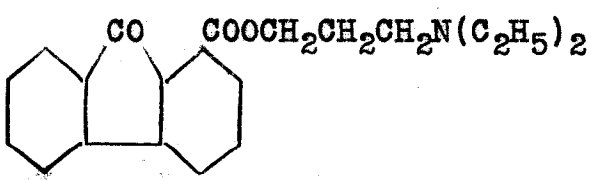


and thus enhancing the chromophoric properties of the 9-keto group. In fluorenone-2-carboxylic acid the carboxy group would seem to be too far removed from the keto group to allow hydrogen bond formation to take place. This explanation seems reasonable for the acid chloride and esters of fluorenone-1-carboxylic acid, in which hydrogen bonding is impossible, are bright yellow and not red.

The acid chloride is prepared easily using thionyl chloride and the alkamine esters are obtained by reacting the aminoalcohol and the acid chloride in either acetone or benzene. Two alkamine esters were prepared.



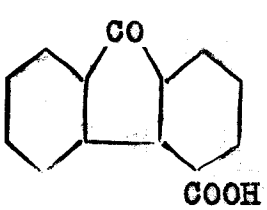
I



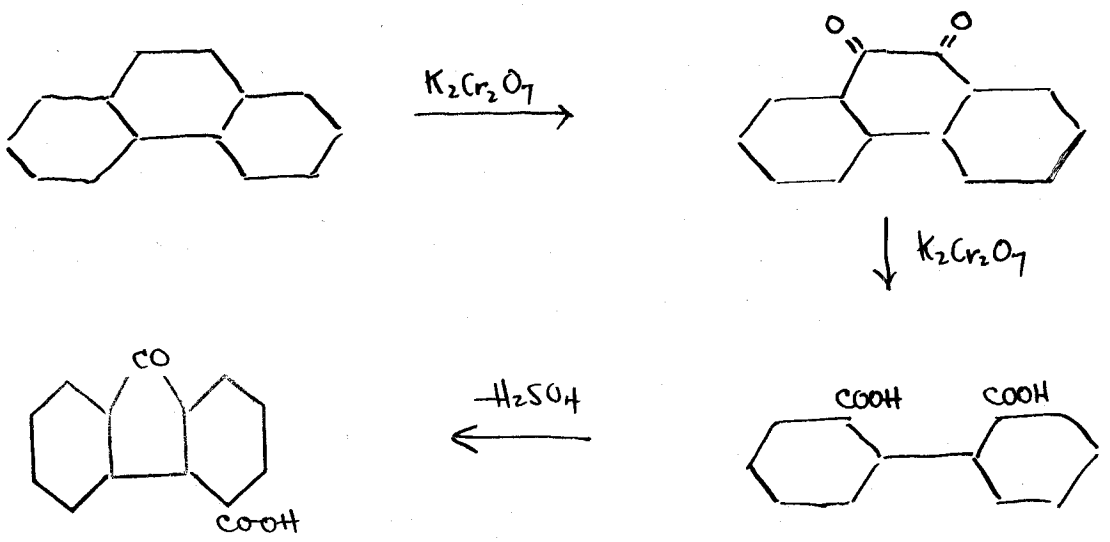
II

In the first preparation of II, using acetone as the solvent, a small amount of a substance, which was not soluble in methyl alcohol or water, was isolated. The normal ester hydrochloride (II) is readily soluble in methyl alcohol and water. Boiling the insoluble compound with dilute potassium hydroxide gave a clear solution which on acidification threw down a precipitate of fluorenone-1-carboxylic acid, identified by a mixed melting point. It was assumed that the compound was the salt of fluorenone-1-carboxylic acid and γ-diethylaminopropanol which could arise in the following manner: Aminoalcohols are strongly hygroscopic and the absorbed water hydrolyzes some of the acid chloride to the acid. The acid and the aminoalcohol then combine to give the salt. This explanation seems reasonable for Meltsner, Greenfield and Rosenzweig (95) found that mono-, di- and triethanolamine forms salts with p-nitrobenzoic acid. Furthermore when the γ-diethylaminopropanol is thoroughly dried just before condensation with the acid chloride no methyl alcohol insoluble compound is formed.

The next isomeric fluorenonecarboxylic acid studied was fluorenone-4-carboxylic acid



Its synthesis from phenanthrene is shown in the following equations:

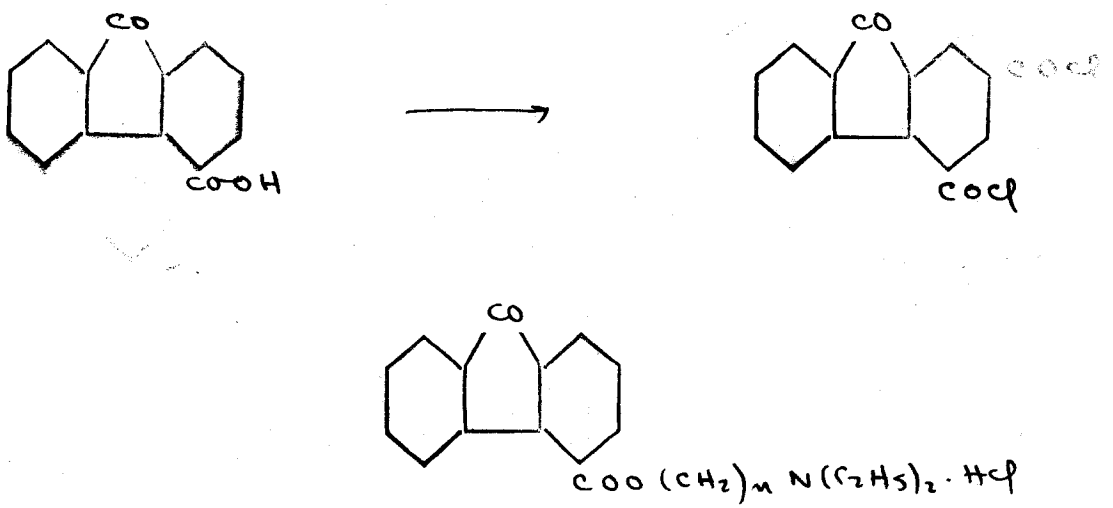


Crude phenanthrene (approximately 80% pure) is oxidized to phenanthrenequinone with potassium dichromate according to the method of Oyster and Adkins (96), with improvements given by Bischoff and Adkins (97). Further oxidation of phenanthrenequinone yielded pure diphenic acid (97).

The ring closure of diphenic acid to give fluorenone-4-carboxylic acid has been described by several workers. Underwood and Kochmann (98) heated diphenic acid with stannic chloride or zinc chloride for 7 hours, while Pick (99) and Gotz (100) used aluminum chloride in benzene or toluene solution to obtain ring closure. Graebe and Aubin (101)as well as Stobbe and Seydel (102) and Bischoff and Adkins (103) secured very rapid cyclization with concentrated sulphuric acid. In none of these methods was the yield of fluorenone-4-carboxylic acid reported, although it was implied that the yield was good.

Moore and Huntress (104) adopted Graebe and Aubin's procedure and reported an 86% yield of the acid. I found that by careful regulation of the conditions of the reaction and by using certain precautions in isolating the acid, the yield of pure fluorenone-4-carboxylic acid could be raised to 96%. The interesting property of peptization of precipitated fluorenone-4-carboxylic acid was observed when washing it on the filter with water. If a little hydrochloric acid is added to the wash water no peptization occurs.

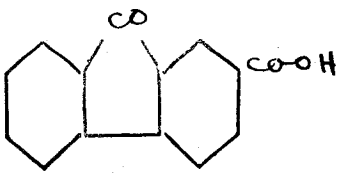
The acid chloride and alkamine esters were prepared as in the case of fluorenone-1-carboxylic acid.



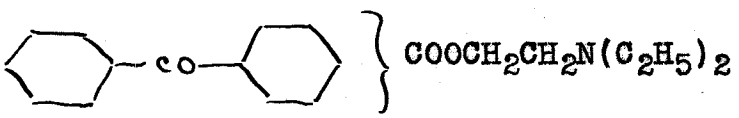
Two alkamine ester hydrochlorides were prepared (n=1,2) and both compounds were very soluble in water.

Let us consider the local anesthetic effect of the three series of isomeric alkamine esters of fluorenone-1,2- and 4-carboxylic acids. When applied to the tip of the tongue the 2 isomer gives a greater duration of numbness than 1 isomer.

The 4 isomer is the least effective of the three. In each series the γ-diethylaminopropyl ester is stronger than the diethylaminoethyl ester. The most favorable position of the carboxy group seems then to be para to the carbon-carbon bridge of the fluorene molecule.



This is in agreement with the observation of Burtner and Lehmann (see p. 36) who prepared alkamine esters of isomeric dibenzofuran-and carbazolecarboxylic acids. Sandahl and Christiansen (105) prepared the diethylaminoethyl ester of o-, m-, and p-benzoylbenzoic acid

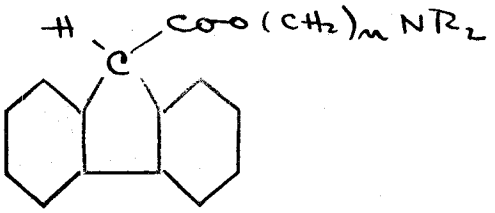


These compounds are analogous to the fluorenone derivatives in which the carbon-carbon bridge has been removed. They found that diethylaminoethyl p-benzoylbenzoate was completely inactive, while the o- and m- esters were slightly active. The profound influence of the carbon-carbon bridge on the activity is thus brought out very clearly. Opening of the

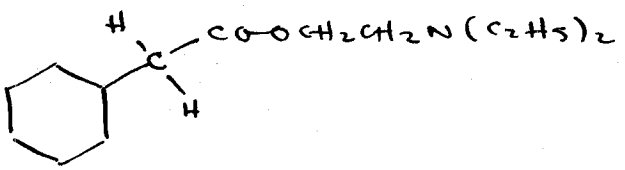
ring of the dibenzofuran and dibenzothiophene molecule was associated with no loss of activity (see p. 38). It is evident that the cyclic structure in fluorenonecarboxylic acids is much more necessary than in the analogous heterocylcic acids.

During the course of this research several foreign patents which made claim to the therapeutic use of a number of compounds derived from fluorene appeared in the literature.

In May, 1939 a Swiss patent (106) and a French patent (107) were granted for compounds of the type

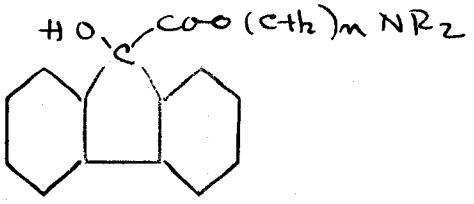


and the statement made that these substances were water-soluble and useful in therapy. If they are active local anesthetics their activity is unusual in view of the complete inactivity of the structurally analogous diethylaminoethyl phenylacetate (36).



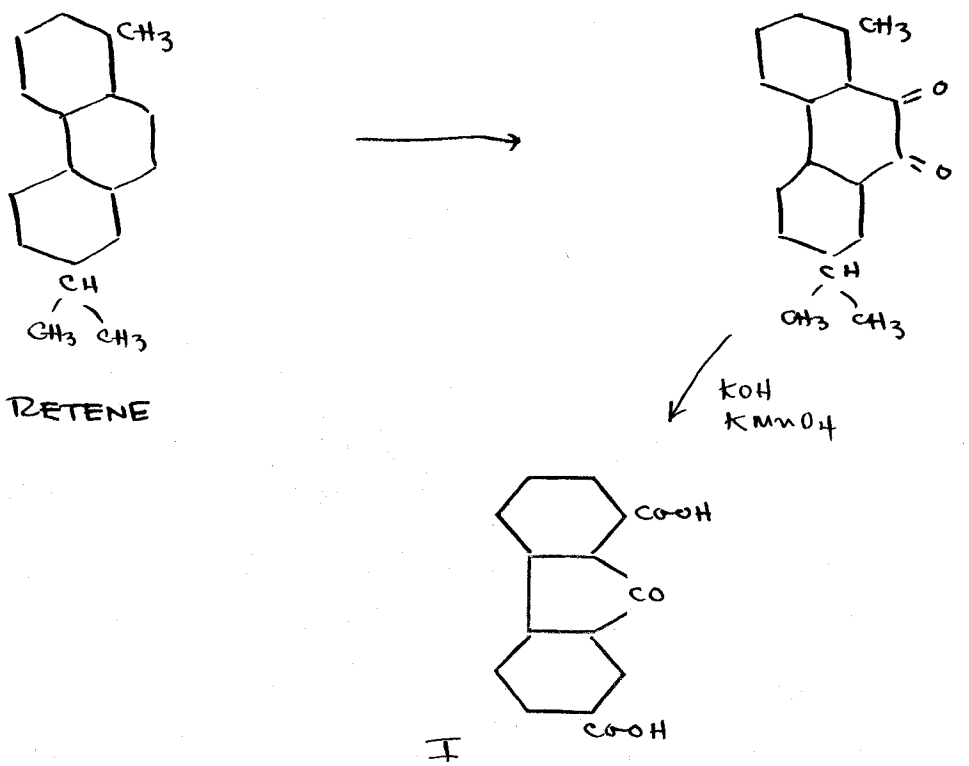
Their activity would also represent an exception to Kamm's rule (see p. 23). Two German patents (108) covering esters

of 9-hydroxyfluorene-9-carboxylic acid with alcohols containing a tertiary amino group were granted in 1938.



Again the claim of their being of therapeutic value was made. No report of the pharmacological properties of either of the two types of compounds has appeared in the literature. These substances differ widely from the new alkamine esters described in this thesis. The patented compounds are esters of <u>aliphatic</u> carboxy acids while those prepared by the author are the esters of <u>aromatic</u> acids.

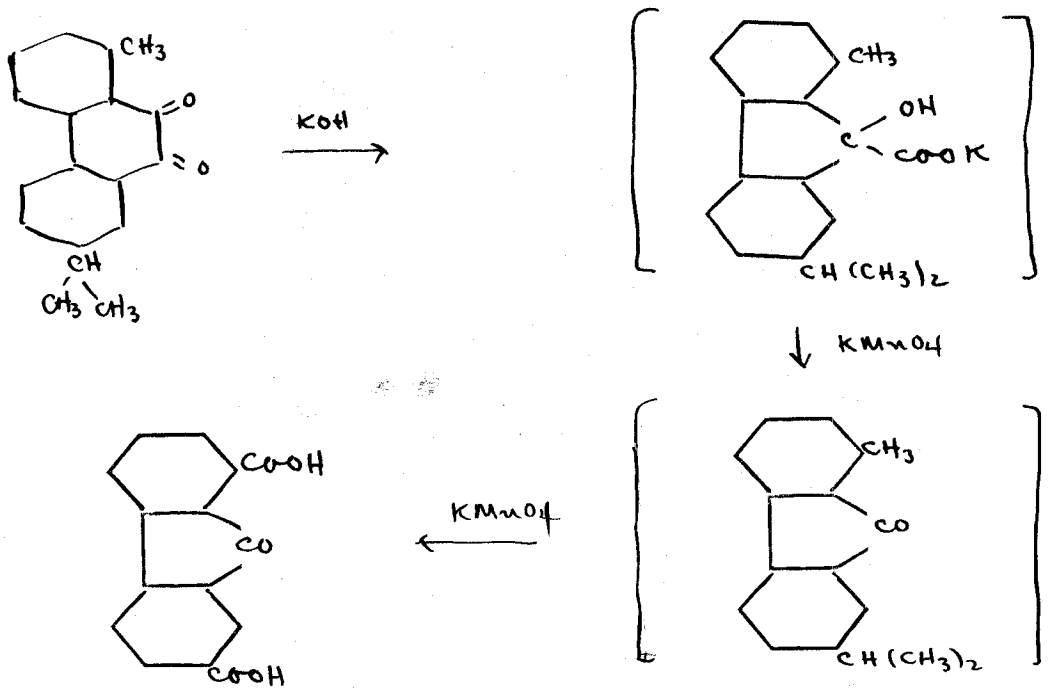
An attempt was made to synthesize the dialkamine ester of a fluorenonedicarboxylic acid, hoping to obtain an increase in local anesthetic activity. Bamberger and Hooker (109) in their work on the determination of the structure of retene carried out the following oxidation reactions.



The yield of fluorenone-1,7-dicarboxylic acid (I) resulting from the alkaline permanganate oxidation was not reported. Since retene, which occurs in pine tar, is a cheap starting material it was decided to repeat Bamberger's experiments. The original procedure of Bamberger and Hooker for the preparation of retenequinone specified pure retene which is obtained only after several recrystallizations from alcohol. A method was devised in which crude retene was used and also a large saving of glacial acetic was possible in this new procedure. Instead of isolating the retenequinone through the bisulfite addition compound as recommended by Fieser and Young (110), it was recrystallized directly glacial acetic acid.

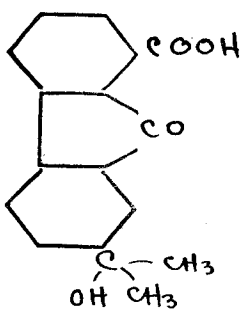
Fieser and Young, starting with pure retene, obtained a 53% yield of the qinone melting at 197°. The new procedure employing crude retene gave a 38% yield of retenequinone as beautiful reddish-orange crystals melting at 198-199°. The yield is no doubt better than 38% since this figure was calculated on the assumption that the retene was 100% pure, which certainly is not true.

The oxidation of retenequinone to fluorenone-1,7-dicarboxylic acid must be done in alkaline medium because a benzil-benzilic acid type of rearrangement must be the first step in the reaction in order to give the fluorenone on subsequent oxidation.



Much trouble is encountered in the alkaline permanganate

oxidation because of the insolubility of the qinone in the reaction medium. Bamberger and Hooker reported that the quinone may be prepared in a finely divided state by precipitation from a concentrated sulphuric acid solution. The flocculated quinone was then treated with alkaline permanganate and agitated and heated by blowing in steam. Following these directions the maximum yield of crude fluorenone-1,7-dicarboxylic acid was about 10%. The crude acid, according to Bamberger, is contaminated with 7-hydroxyisopropylfluorenone-1-carboxylic acid;



however, this is easily oxidized to the dicarboxylic acid with potassium dichromate.

Attempts were made to increase the yield by employing neutral solvents, such as acetone and dioxane, but this failed because the resulting product was very impure and darkly colored.

Stirring finely powdered retenequinone in aqueous potassium hydroxide until it was thoroughly wetted was found to be a more efficient method of obtaining the qinone in a finely divided form (thus more easily attacked by the permanganate), than the precipitation from concentrated sulfuric acid

which is recommended by Bamberger. A mechanical stirrer kept the mixture well agitated throughout the oxidation; heating was done on a hot plate. These modifications increased the yield of crude acid to 20%.

Reaction of the recrystallized acid with thionyl chloride gave the acid chloride of fluorenone-1,7-dicarboxylic acid as a dark brown solid. The identity of the acid chloride was proven by conversion to the dimethyl ester, melting at 187-188°. Bamberger reported the melting point as 188-189°. One attempt was made to prepare the di-β-diethylaminoethyl ester of fluorenone-1,7-dicarboxylic acid from the acid chloride, but only a small amount of oily material was obtained from which no solid substance could be isolated. Lack of time prevented further experimental work.

Part III

EXPERIMENTAL DETAILS

A. Preparation of 2-acetylfluorene: The crude fluorene (m.p. 100-107°) was obtained from Eastman*. The fluorene (80 grams, .48 mol) was placed in a three-necked, one liter, round-bottomed flask equipped with a dropping funnel, mercury-sealed mechanical stirrer with a strong motor and a reflux condenser connected to a hydrogen chloride trap. Dry carbon disulfide (350 cc.) was added and the fluorene dissolved with stirring. The entire content of a one-quarter pound bottle of pure aluminum chloride (approx. 113 grams, .85 mol) was added and the mixture stirred thoroughly until homogeneous. A dark red color developed. Pure, redistilled acetic anhydride (37.8 cc., .41 mol) was placed in the dropping funnel. About 1 cc. of acetic anhydride was added drop by drop. If the reaction did not start immediately, a pan of warm water was used to warm the flask and initiate the reaction. It is necessary to wait until the reaction starts before adding any more acetic anhydride, because the reaction may become violent. The further addition of acetic anhydride was adjusted to such a rate that the heat of reaction kept the carbon disulfide in

---

*The quality of crude fluorene has improved greatly in the last four years. Three kilograms of fluorene purchased in September, 1939 was exceptionally good, giving only a slight red color when dissolved in glacial acetic acid.

gentle reflux. The addition required from 45 to 55 minutes. When about one-half of the acetic anhydride had been added, a heavy precipitate of the addition product formed which made stirring very difficult; however, stirring must be maintained in order to avoid excessive local reaction at the point of introduction of the acetic anhydride. Stirring and refluxing on the water bath was continued for one hour. The heavy, dark green mass was filtered on a large Buchner funnel and sucked as dry as possible. The product was removed from the funnel, placed in a beaker, just covered with carbon disulfide, stirred mechanically for ten minutes and filtered again. The product was then washed twice with 50 cc. portions of carbon disulfide. After all the carbon disulfide had been removed the addition product was hydrolyzed by adding it in portions to a stirred mixture of 800 cc. of water and 30 cc. of concentrated hydrochloric acid. No ice should be used in hydrolyzing bath. Each portion was allowed to hydrolyze before adding more. The crude 2-acetylfluorene was filtered and washed several times with water.

The weight of partially dry ketone was about 100-110 grams. It was slightly orange in color and a dry sample melted at 113-119°. Pure 2-acetylfluorene, m.p. 132°, was obtained by two recrystallizations from alcohol, using Darco to remove the color. This melting point is the same that is reported in the literature (88) (89). The crude 2-acetylfluorene was completely soluble in carbon disulfide showing the absence of

the 2,7-diacetyl compound which is insoluble in carbon disulfide (88).

B. Preparation of fluorenone-2-carboxylic acid:

The entire yield of crude 2-acetylfluorene (preparation A) was placed in a 5 liter, round-bottomed flask and dissolved in 650 cc. of glacial acetic acid by heating.

The flask was equipped with a reflux condenser and a large hole was bored in the stopper in which a 1 inch glass cylinder (made from a large test tube) was placed. This facilitated the addition of solid sodium dichromate. The large flask was used because the addition of sodium dichromate can be accomplished without too much difficulty from escaping vapors of acetic acid.

Commercial sodium dichromate (450 grams) was ground to a coarse powder. It was added in small portions to the hot acetic acid solution of 2-acetylfluorene. The reaction was very vigorous at first (oxidation of the methylene group), but it soon moderated and the dichromate could be added at a faster rate, requiring about 45 minutes for complete addition. A dropping funnel was then fitted in the glass cylinder with a rubber stopper and 200 cc. of acetic anhydride dropped in over a course of 90 minutes, refluxing all the while. The mixture was refluxed for 6 hours more. The hot contents of the flask were poured into about 2½ gallons of hot water contained in a 4 gallon crock, stirred for 15 minutes and filtered on a large Buchner. All the chromium salts were washed out with

water containing a little sulphuric acid to prevent hydrolysis. The wet filter cake, including the paper, was transferred to a beaker containing 700 cc. of a 5% solution of potassium hydroxide. Accompanied by mechanical stirring the mixture was heated to 80° and filtered hot. The alkali insoluble material was washed with a little hot dilute potassium hydroxide. The filtrate was placed in a beaker, stirred with 15 grams of Darco for 20 minutes and again filtered and refiltered to remove all the carbon. In order to precipitate the free acid in a filterable form the acidification must be carried out at 80-90°. The solution of the potassium salt was heated with vigorous mechanical stirring to 70° and hydrochloric acid (1 to 1) was added drop by drop from a dropping funnel. When the acid began to precipitate the temperature was about 85°. The fluorenone-2-carboxylic acid was thrown down as a thick yellow mass. A slight excess of hydrochloric acid was added and the precipitate allowed to digest for 10 minutes with stirring. The acid was filtered hot and all the potassium chloride removed by 5 to 6 washings with hot water. After the acid was sucked as dry as possible it was dried in an oven at 150°. It was bright yellow and usually weighed about 30 grams.

The material which was insoluble in potassium hydroxide was re-oxidized in the same manner described above by dissolving in 500 cc. of glacial acetic acid and treating with 300 grams of sodium dichromate and 200 cc. of acetic anhydride.

The reflux time was 8 hours. The acid was isolated just as before and yielded from 23 to 27 grams of fluorenone-2-carboxylic acid. The total yield varied from 58 to 62%. The pure acid required for the synthesis of the acid chloride was prepared by recrystallization from acetic anhydride. It was a bright canary-yellow and melted with partial sublimation at 339-341° (copper block) which agreed with the literature (88).

C. Preparation of 2-acetylfluorenone: The alkali insoluble material obtained by the oxidation of 2-acetylfluorene consisted mainly of 2-acetylfluorenone. A number of recrystallizations (2 or 3) from ethyl alcohol gave the pure compound melting at 154-155°.

It may also be prepared directly by oxidation of 2-acetylfluorene. One gram of powdered sodium dichromate and 0.5 gram of 2-acetylfluorene (m.p. 130-132°) were dissolved in 20 cc. of glacial acetic acid and refluxed for 2 hours. The reaction mixture was poured into 300 cc. of water, filtered, and washed. The crude 2-acetylfluorenone was stirred with dilute potassium hydroxide to remove any fluorenone-2-carboxylic acid, filtered and washed again. Two recrystallizations (using Darco) from ethyl alcohol gave 0.3 gram of pure 2-acetylfluorenone, m.p. 154-155°.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.02; H, 4.53. Found: C, 81.30; H, 4.72.

D. Preparation of fluorenone-2-carboxychloride: The thionyl chloride for this preparation was purified by the

method of Fieser,(111).

A mixture of 250 cc. of thionyl chloride and 22.4 grams of pure fluorenone-2-carboxylic acid in a 500 cc. flask were refluxed on the water bath. The acid soon dissolved giving a clear yellow solution. If the color of the solution were dark brown or almost black it showed that the acid was impure. Refluxing was continued for 2 hours. The thionyl chloride was then distilled off as completely as possible on the water bath. The acid chloride separated in a golden yellow, crystalline cake which was broken up and placed in a Buchner funnel. The suction removed all remaining traces of thionyl chloride. The yield was 100% (24.4 grams) which melted at 174-176°. The sample for analysis was recrystallized twice from benzene, m.p. 183-184°.

Anal. Calcd. for $C_{14}H_7O_2Cl$: Cl, 14.62. Found: Cl, 14.51.

The methyl ester was prepared by reacting the acid chloride with excess methyl alcohol. Recrystallization from methyl alcohol gave long, yellow crystals melting at 185-186°; Fortner (86) reported 181°.

E. Preparation of alkamine esters of fluorenone-2-carboxylic acid: The apparatus consisted of a 500 cc., three-necked flask equipped with a dropping funnel, reflux condenser, and mechanical stirrer.

1. β-Diethylaminoethyl fluorenone-2-carboxylate hydrochloride: A stirred mixture of 200 cc. of pure, dry benzene

and 12.2 grams of fluorenone-2-carboxychloride were heated on the water bath until a clear solution resulted. From the dropping funnel 6.0 grams of β-diethylaminoethyl alcohol diluted with 45 cc. of benzene was added drop by drop. The reaction was immediate and the ester hydrochloride separated as a yellow solid. The aminoalcohol was added in 15 minutes. Refluxing and stirring were continued for 90 minutes. The yellow mass was allowed to cool, filtered, and washed several times with ether. The yield of crude ester, m.p. 212-214°, was quantitative (18.0 grams). The compound was purified by refluxing with methyl alcohol and Darco, filtering, and before crystallization took place some hydrogen chloride was passed in. The ester hydrochloride then melted at 221-222°. The sample for analysis, m.p. 223-224°, was obtained as small yellow crystals by several recrystallizations from methyl alcohol.

Anal. Calcd. for $C_{20}H_{22}O_3NCl$: Cl, 9.85. Found: 9.80.

2. γ-Diethylaminopropyl fluorenone-2-carboxylate hydrochloride: This ester hydrochloride was prepared in exactly the same manner as the β-diethylaminoethyl ester. The quantities were the same as in E1 except that 7.0 grams of γ-diethylaminopropyl alcohol were used. The crude ester hydrochloride, m.p. 215-216°, was obtained in quantitative yield (18.7) grams). Recrystallization of the compound from a methyl alcohol solution treated with Darco and hydrogen chloride gave

the pure compound, m.p. 220-221°. The sample analyzed, m.p. 221-221.5°, was recrystallized twice from methyl alcohol.

Anal. Calcd. for $C_{21}H_{24}O_3NCl$: Cl, 9.48. Found: Cl, 9.46.

3. β-Dibutylaminoethyl fluorenone-2-carboxylate hydrochloride: The preparation of this ester hydrochloride was carried out as before; however, this compound did not precipitate immediately from the reaction mixture. A hot solution of 6.32 grams of fluorenone-2-carboxychloride and 100 cc. of benzene was treated dropwise with 5.2 grams of β-dibutylaminoethyl alcohol in 25 cc. of benzene. A small amount of yellow material separated out after two hours of refluxing. After standing overnight it was filtered and 5.6 (55%) grams of light yellow solid, m.p. 162-164°, was obtained. Recrystallization from methyl or ethyl alcohol was difficult. It could best be purified by precipitating it several times from an ethyl alcohol solution with ether. The compound was obtained as a yellow powder melting at 179-180° with previous shrinking at 176°.

Anal. Calcd. for $C_{24}H_{30}O_3NCl$: Cl, 8.52. Found: Cl, 8.33.

F. Oximation of β-diethylaminoethyl fluorenone-2-carboxylate hydrochloride: Either the crude or the pure ester hydrochloride may be used as the starting material. A mixture of 14.4 grams of β-diethylaminoethyl fluorenone-2-carboxylate hydrochloride, 4.2 grams of hydroxylamine hydrochloride, 14

grams of finely powdered barium carbonate and 125 cc. of methyl alcohol were refluxed for 3 hours. The yellow color of the solution soon faded completely. The barium carbonate was removed by filtration, washing it once with a little hot methyl alcohol. The filtrate was treated with Darco, filtered again, and allowed to crystallize. About 8 grams (60%) of white fluffy oxime, m.p. 224-226° (dec.), was obtained. Dilution of the mother liquor with ether furnished an additional small amount of the oxime. Recrystallization from ethyl alcohol gave 6 grams of material melting at 231-232°.

Anal. Calcd. for $C_{20}H_{22}O_3N_2$: N, 7.28. Calcd. fof $C_{20}H_{23}O_3N_2Cl$: N, 7.47. Calcd. for $C_{20}H_{24}O_3N_2Cl_2$: N, 6.81. Found: N, 7.28.

G. Oximation of γ -diethylaminopropyl fluorenone-2-carboxylate hydrochloride: A mixture of 7.5 grams of pure γ-diethylaminopropyl fluorenone-2-carboxylate hydrochloride, 4.2 grams of hydroxylamine hydrochloride, 8 grams of barium carbonate and 100 cc. of ethyl alcohol were refluxed for 5 hours. After filtration the filtrate was evaporated down to about 25-35 cc. and the oxime allowed to crystallize. The yield of material, m.p. 216-218°, was 4.5 grams (64%). Small, almost colorless, crystals, m.p. 219-220, were obtained by recrystallization from methyl alcohol.

Anal. Calcd. for $C_{21}H_{24}O_3N_2$: N, 7.95. Calcd. for $C_{21}H_{25}O_3N_2Cl$: N, 7.20. Calcd. for $C_{21}H_{26}O_3N_2Cl_2$: N, 6.59. Found: N, 6.85.

H. Attempted reduction of alkamine ester oximes: An apparatus for catalytic reduction with hydrogen was built, following the directions of Adams and Vorhees (112). The two catalysts employed were Raney nickel (113) and Adams' platinum catalyst (114). Ethyl alcohol solutions of the oxime esters were shaken with the catalyst under a hydrogen pressure of 50 pounds. Hydrogen was absorbed very slowly and after 5 hours the solution was filtered. Evaporation of the alcohol produced a gummy green mass. This was dissolved in ether and treated with dry hydrogen chloride. No solid compound was obtained.

The oxime esters were apparently reduced very easily by 2% sodium amalgam in absolute alcohol, to which acetic acid was added at intervals to maintain neutrality. The reaction mixture was diluted with water, made alkaline, and extracted with ether. The ether solution was dried and treated with hydrogen chloride. A gum settled out and later solidified. It turned dark brown on standing in air and possessed no definite melting point.

I. Preparation of 9-amino-2-benzoylfluorene hydrochloride: The 9-isonitroso-2-benzoylfluorene was prepared from 2-benzoylfluorene (90). Approximately 1 gram of the oxime was dissolved in 15 cc. of alcohol and then 15 cc. of concentrated hydrochloric acid was added, giving a fine yellow curd. To the stirred mixture 15 grams of zinc dust was added in about 20 minutes. In a few minutes the yellow solid dissolved and

then the yellow color of the solution faded. The mixture was allowed to stand for 4 hours. The excess zinc was removed by filtration and the filtrate diluted with 300 cc. of cold concentrated hydrochloric acid. The white amine hydrochloride precipitated in a semi-colloidal state which was difficult to filter. The compound was almost impossible to recrystallize; however, a very small amount was obtained in a fairly pure state from ethyl alcohol. The compound had no definite melting point; it darkened at 185° and decomposed at 200-205°.

Anal. Calcd. for $C_{20}H_{16}NOCl$: N, 4.35. Found: N, 4.00.

J. Preparation of fluorenone-1-carboxylic acid: This synthesis followed closely the method of Fieser and Seligman (93). Twenty-five grams of fluoranthene, m.p. 107-109°, and 600 cc. of glacial acetic acid was placed in a one liter, three-necked flask equipped with an air condenser, dropping funnel and a thermometer whose bulb was immersed in the mixture. Heating with a small flame caused the fluoranthene to go into solution at 60°. The flame was removed and from the dropping funnel a solution of 85 grams of chromic anhydride (CrO_3), 75 cc. of water and 25 cc. of glacial acetic acid was added slowly. When the temperature reached 85° the rate of addition was adjusted so that the temperature did not rise above 90° at any time. The flask was swirled every 5 minutes. The addition must be slow at first; however, towards the end the oxidizing mixture may be added more rapidly and the whole operation required about 90 minutes. The reaction mixture is

allowed to stand overnight. After standing it was heated to 90°, held at that temperature for 30 minutes, and then poured with vigorous stirring into 4 liters of water. Filtration gave the crude acid which was purified by dissolving in cold 10% potassium hydroxide, stirring with charcoal, filtering again and precipitating with acid. Further purification was effected by extracting the acid with a hot, stirred suspension of barium carbonate. The extractions were repeated until the amount of acid obtained on acidification was insignificant. The total volume of barium salt solution was about 2 liters. The fluorenone-1-carboxylic acid was precipitated by adding hydrochloric acid drop by drop to the well stirred solution at 85°. After thorough cooling the acid was filtered, washed and dried in the oven at 130°. The yield of acid melting at 191-193° was 15.4 grams (52%). Fieser and Seligman (93) reported the yield as 48%.

The pure acid was obtained by recrystallization from glacial acetic acid; it formed bright orange crystals, m.p. 193-194°.

K. Preparation of alkamine esters of fluorenone-1-carboxylic acid: The acid chloride of fluorenone-1-carboxylic acid was prepared in quantitative yield by refluxing 10 grams of the pure recrystallized acid (m.p. 193-194°) and 100 cc. of pure thionyl chloride on the water bath for 2 hours, distilling off the excess thionyl chloride, and pouring the yellow oil onto a watch glass in the hood. The acid chloride crystallized

out as a bright yellow solid, m.p. 130-132°. Goldschmiedt (115) gave the melting point as 140° for recrystallized material. It was very necessary to use the pure acid, for if the crude acid (m.p. 191-193°) were used the acid chloride had a dirty greenish color and was unsuitable for the preparation of alkamine esters.

1. β-Diethylaminoethyl fluorenone-1-carboxylate hydrochloride: A solution of 2.42 grams of fluorenone-1-carboxychloride, free from thionyl chloride, in 25 cc. of acetone was treated with 1.2 grams of β-diethylaminoethyl alcohol, dried with anhydrous sodium sulphate, and refluxed for 1 hour. The yellow ester hydrochloride, which had precipitated out after 15 minutes, was filtered and weighed 3.1 grams. It was purified by dissolving in methyl alcohol, filtering, and precipitating with ether. Two such treatments gave 2.2 grams (61%) of the pure ester, m.p. 194-195°.

Anal. Calcd. for $C_{20}H_{22}O_3NCl$: Cl, 9.85. Found: Cl, 10.18.

2. γ-Diethylaminopropyl fluorenone-1-carboxylate hydrochloride: To a hot solution of 6.3 grams of the pure acid chloride in 30 cc. of dry benzene a mixture of 3.4 grams of γ-diethylaminopropyl alcohol (dried with sodium sulphate) and 10 cc. of benzene was added drop by drop. After refluxing for 2 hours it was cooled thoroughly, filtered and washed with ether. The crude ester hydrochloride weighed 9.0 grams and melted at 149-153°. It was dissolved in a small amount of

methyl alcohol, treated with Darco, filtered and precipitated with ether. This was repeated to give 6.1 grams (63%) of the pure yellow ester hydrochloride, m.p. 159-160°.

Anal. Calcd. for $C_{21}H_{24}O_3NCl$: Cl, 9.48. Found: Cl, 9.49.

L. Preparation of phenanthrenequinone (96) (97): One hundred grams of 80% phenanthrene as a fine powder was added with stirring to a cold oxidizing mixture of 1500 cc. of water, 500 cc. of 96% sulphuric acid, and 300 grams of potassium dichromate contained in a large flask. When the first brisk reaction had ceased an additional 300 grams of powdered potassium dichromate was added. After being slowly heated to the boiling point the solution was cooled, an equal volume of water added and allowed to stand for 2 hours. The crude quinone was filtered on a large Buchner funnel, washed with water until all chromium salts were removed and thoroughly dried. The dry material was suspended in 500 cc. of concentrated sulphuric acid for 12 hours in order to remove resins and acid-soluble impurities. A liter of water was then added to decrease the solubility of the phenanthrenequinone and filtered. The precipitate was washed thoroughly with water and then with 500 cc. of saturated sodium carbonate solution to remove any diphenic acid. In order to separate the phenanthrenequinone from the anthraquinone the product was placed in 2 liters of hot 20% sodium bisulfite solution and heated to boiling. The undissolved anthraquinone was filtered off and the filtrate

acidified by adding to an equal volume of dilute sulphuric acid containing 50 g. of dichromate per liter to prevent reduction of the quinone by the liberated sulphur dioxide. The finely divided yellow quinone so obtained was filtered off and washed thoroughly with water. The yield was 59 grams and it melted at 202-203°. Recrystallization from dioxane or glacial acetic acid gave bright orange needles, m.p. 205-206°.

M. Preparation of diphenic acid (97): Fifty grams of phenanthrenequinone, m.p. 202-203°, was added to a cold solution of 200 grams of potassium dichromate, 300 grams of concentrated sulphuric acid and 500 cc. of water in a 2 liter, round-bottomed flask equipped with an air condenser. The mixture was heated slowly in the course of an hour up to 105-110° at which temperature it was held for 20 hours with occasional agitation. It was cooled, filtered and washed with cold water. The crude diphenic acid was extracted with 800 cc. of saturated sodium carbonate and filtered. The free acid was precipitated with acid, cooled, filtered and washed with a little water. The diphenic acid was crystalline, had a pure white color and melted at 228-229°. The yield was 47 grams (81%).

N. Preparation of fluorenone-4-carboxylic acid: Ten grams of diphenic acid and 25 cc. of concentrated sulphuric acid were placed in a large test tube which was suspended in a glycerine bath. The mixture was stirred with a thermometer and the bath was slowly heated. At 30° the diphenic acid dissolved

giving a clear solution; at 58° the color was a light cherry red which gradually deepened until at 70° the solution was so dark that it was impossible to see through it. The temperature was raised to 130° and held there for 10 minutes with stirring. After cooling to 50° it was poured into 500 cc. of water accompanied by vigorous mechanical stirring. Any lumps were broken up and the mixture was filtered. The wet acid was then dissolved in a solution of 10 grams of potassium hydroxide in 150 cc. of water. The acid dissolved very rapidly in the cold alkali and the solution was filtered. The filtrate was heated to 85° and, with stirring, precipitated by adding hydrochloric acid slowly from a dropping funnel. After a slight excess of acid had been added the yellow suspension was allowed to cool to room temperature and then filtered. The precipitate was washed thoroughly with water acidified with a little hydrochloric acid. If pure water were used to wash it the acid peptized and passed through the filter. The acid was dried in an oven at 120°. The yield was 9.0 grams (96%). It was quite pure and melted at 224-225°. Moore and Huntress (104) reported it to melt at 223-224°. A sample recrystallized twice from ethyl alcohol melted at 227°.

O. Preparation of alkamine esters of fluorenone-4-carboxylic acid: The acid chloride was again prepared in theoretical yield by the same manner described for the acid chloride of fluorenone-1-carboxylic acid.

1. β -Diethylaminoethyl fluorenone-4-carboxylate hydrochloride: Thirty-five cc. of dry acetone and 2.4 grams of finely powdered fluorenone-4-carboxychloride, free from thionyl chloride, was heated until complete solution took place and then a mixture of 1.1 grams of dry β -diethylaminoethyl alcohol and 5 cc. of acetone was added. After refluxing for one hour the precipitated ester hydrochloride was filtered off and washed with ether. The yellow material weighed 3.3 grams and melted at 194-196° with softening at 190°. It was recrystallized from ethyl alcohol to give 2.5 grams (70%) of the pure hydrochloride, m.p. 197-198°.

Anal. Calcd. for $C_{20}H_{22}O_3NCl$: Cl, 9.85. Found: Cl, 9.97.

2. γ -Diethylaminopropyl fluorenone-4-carboxylate hydrochloride: A solution of 2.4 grams of the acid chloride in 40 cc. of dry acetone was treated with 1.4 grams of dry -diethylaminopropyl alcohol in 10 cc. of acetone. The clear solution soon turned cloudy and the ester hydrochloride precipitated. Refluxing was continued for 45 minutes. Filtration gave 3.5 grams of yellow material melting at 208-209°. This was recrystallized from ethyl alcohol giving 2.5 grams (68%) of the pure ester hydrochloride, m.p. 210-211°.

Anal. Calcd. for $C_{21}H_{24}O_3NCl$: Cl, 9.48. Found: Cl, 9.32.

P. Preparation of retenequinone: In a 5 liter, round-bottomed flask 200 grams of crude retene, m.p. 80-85°,

was dissolved with heat in 600 cc. of glacial acetic acid. An oxidizing mixture consisting of 390 grams of chromic anhydride (CrO_3), 1000 cc. of glacial acetic acid and 225 cc. of water was dropped in from the funnel very slowly. The addition was maintained at such a rate that there was little reflux; two hours were required. After standing for 20 minutes the mixture was heated slowly and refluxed for 1 hour. After standing overnight the material was filtered until all liquid had been removed. The precipitate consisted of crude retenequinone and some dark oily material which was removed completely by washing with three 50 cc. portions of acetic acid and then with water. The retenequinone was then recrystallized from about 1 liter of glacial acetic acid, using Darco and a very efficient hot water funnel. The yield was 80 grams of beautiful reddish orange crystals, m.p. 198-199°.

Q. Preparation of fluorenone-1,7-dicarboxylic acid: Five grams of retenequinone was ground into a very fine powder in a mortar and placed in a beaker with 200 cc. of 25% potassium hydroxide solution. The mixture was stirred very vigorously and heated until a fine suspension resulted. Twenty-five grams of powdered potassium permanganate was added. Stirring and heating were continued for 4 hours; the evaporated water was replaced occasionally. The excess permanganate was destroyed with ethyl alcohol and the manganese dioxide filtered off. The filtrate was neutralized with dilute sulphuric acid (1 to 3) and 100 cc. excess was added. Twenty grams of powdered

potassium dichromate was added and the mixture refluxed for 2 hours. It was cooled, filtered and washed. The crude acid weighed 1.0 gram, it darkened at 270° but did not melt. It could be recrystallized from nitrobenzene giving an orange powder not melting below 280°. The recrystallized acid reacted with thionyl chloride to give the acid chloride as a dark oil which solidified on standing to a brown powder. Reaction with excess methyl alcohol gave the dimethyl ester, m.p. 187-188°. The diethyl ester was also prepared in the same manner, m.p. 113-114°. Bamberger (109) gave 114.5°. β-Diethylaminoethanol and the acid chloride in acetone gave a dark colored oil which refused to crystallize.

Part IV

SUMMARY

1. A practical synthesis of fluorenone-2-carboxylic acid was developed.

2. It was shown that the hydrochlorides of alkamine esters of fluorenone-2-carboxylic acid are strong local anesthetics, especially in respect to topical anesthesia.

3. The most favorable position of the carboxy group in the fluorenone molecule for maximum activity is probably the 2 position.

4. The important observation that the presence of the oxime group in one series of compounds increases the local anesthetic activity in comparison to the ketonic compound from which it is derived was noted for the first time.

5. A method for the preparation of fluorenone-4-carboxylic acid in a better yield was described.

6. A more economical synthesis of retenequinone was devised, employing crude retene as the starting material.

7. The following new compounds were prepared:

2-acetylfluorenone

fluorenone-2-carboxychloride

β-diethylaminoethyl fluorenone-2-carboxylate hydrochloride

γ-diethylaminopropyl fluorenone-2-carboxylate hydrochloride

β -di-n-butylaminoethyl fluorenone-2-carboxylate hydrochloride

oxime of β -diethylaminoethyl fluorenone-2-carboxylate hydrochloride

oxime of γ -diethylaminopropyl fluorenone-2-carboxylate hydrochloride

9-amino-2-benzoylfluorene hydrochloride

β -diethylaminoethyl fluorenone-1-carboxylate hydrochloride

γ -diethylaminopropyl fluorenone-1-carboxylate hydrochloride

β -diethylaminoethyl fluorenone-4-carboxylate hydrochloride

γ -diethylaminopropyl fluorenone-4-carboxylate hydrochloride

BIBLIOGRAPHY

(1) Medicine in its Chemical Aspects. I. G. Farbenindustrie, Leverkusen, Germany, 1937, pp. 356-358.

(2) Cook, Studies of the Institum Divi Thomae 2, 63 (1938).

(3) Dyson, The Chemistry of Chemotherapy, Benn, London, 1928, pp. 147-158.

(4) Frankel, Die Arzneimittel-Synthese, Springer, Berlin, 1921, pp. 333-391.

(5) Niemann, Ann. 140, 213 (1860).

(6) Moreno y Maiz, These de Paris, 1868.

(7) Wilstatter, Wolfes and Mader, Ann. 434, 11 (1923).

(8) Wilstatter, Ber. 29, 1575, 2216 (1896).

(9) Einhorn, Ber. 21, 3029, 3411 (1888).

(10) Ehrlich, Deut. med. Wochschr. 1890, 77.

(11) Ehrlich and Einhorn, Ber. 27, 1870 (1894).

(12) Chadbourne, Brit. Med. J. 1892, 402

(13) von Braun and Muller, Ber. 51, 235 (1918).

(14) German Patent 90,069.

(15) Merling, Ber. deut. pharm. Ges. 6, 173 (1897).

(16) Vinci. Arch. path. Anat. (Virchow) 149, 201 (1897).

(17) Fourneau, Compt. rend. 138, 7661 (1904).

(18) German Patent 173,631

(19) Gilman, Ind. Eng. Chem. 14, 812 (1922).

(20) Ritsert, Pharm. Ztg. 70, 1006 (1925).

(21) Einhorn and Uhlfelder, Ann. 371, 131 (1909).

(22) Einhorn, Ann. 371, 162 (1909).

(23) Burnett, Jenkins, Peet, Dreger, and Adams, J. Am. Chem. Soc. 59, 2248 (1937).

(24) Adams, Kamm and Volwiler, U.S. Patent 1,358,751.

(25) U.S.Patent 1,474,576.

(26) Fromherz, Arch. exptl. Path. Pharmakol. 158, 368 (1930).

(27) Karrer, Helv. chim. Acta 4, 92 (1921).

(28) Fussganger and Schaumann, Arch. exptl. Path. Pharmakol 160, 53 (1931).

Ernst, Munch. med. Wochschr. 128, 9 (1931).

(29) Adams, Rideal, Burnett, Jenkins and Dreger, J. Am. Chem. Soc. 48, 1758 (1926).

(30) Adams and Leffler, J. Am. Chem. Soc. 59, 2252 (1937).

(31) Novelli and Adams, J. Am. Chem. Soc. 59, 2259 (1937).

(32) Adams and Babcock, J. Am. Chem. Soc. 59, 2260 (1937).

(33) Goldberg and Whitmore, J. Am. Chem. Soc. 59, 2280 (1937); Goldberg, Ruizk and Spoerri, J. Am. Chem. Soc. 61, 3562 (1939).

(34) Goldberg and Abrahamson, J. Pharmacol. 62, 69 (1938).

Goldberg, British Patent 482,886.

(35) Wenker, J. Am. Chem. Soc. 60, 1081 (1938).

(36) Pyman, J. Chem. Soc. 111, 167, 1119 (1917).

(37) Kamm, J. Am. Chem. Soc. 42, 1030 (1920).

(38) Wildman and Thorp, U.S. Patent 1,193,649.

(39) Gilman and Pickens, J. Am. Chem. Soc. 47, 245 (1925).

(40) Lott and Christiansen, J. Am. Pharm. Assoc. 28, 499 (1939).

(41) Hansen and Fosdick, J. Am. Chem. Soc. 55, 2872 (1933); Fosdick and Hansen, J. Am. Dental Assoc. 21, 1777 (1934); Fosdick and Hansen, J. Pharmacol. 50, 323 (1934).

(42) German Patents 512,723 and 511,467.

(43) Wildman and Thorpe, U.S. Patent 1,193,650. Rohman and Scheurle, Arch. Pharm. 274, 110 (1936).

(44) Lott, Harris and Christiansen, J. Am. Pharm. Assoc. 27, 661 (1938).

(45) Sappenfield and Rovenstine, Anesthesia and Analgesia 19, 48 (1940).

(46) McIntyre and Sievers, J. Pharmacol. 61, 107 (1937).

(47) Hart and Niederl, J. Am. Chem. Soc. 61, 1145 (1939).

(48) Donleavy and English, J. Am. Chem. Soc. 62, 220 (1940).

(49) Brill and Bulow, J. Am. Chem. Soc. 55, 2059 (1933).

(50) Bachman, J. Am. Chem. Soc. 57, 2167 (1935).

(51) Shriner and Keyser, J. Am. Chem. Soc. 60, 286 (1938).

(52) Rider and Cook, J. Pharmacol. 64, 1 (1938).

(53) Cook and Rider, J. Am. Chem. Soc. 58, 1079 (1936); Rider and Cook, ibid. 59, 1741 (1937).

(54) Horne, Cox and Shriner, J. Am. Chem. Soc. 55, 3435 (1933).

(55) Shriner and Cross, J. Am. Chem. Soc. 60, 2338 (1938).

(56) Shriner and Hickey, J. Am. Chem. Soc. 61, 888 (1939).

(57) Bailey and McElvain, J. Am. Chem. Soc. 52, 1633 (1930). This paper gives previous references.

(58) Tullock and McElvain, J. Am. Chem. Soc. 61, 961 (1939).

(59) Marvel and Shelton, J. Am. Chem. Soc. 51, 915 (1929).

(60) Walter and Fosbinder, J. Am. Chem. Soc. 61, 1713 (1939).

(61) Bjerregard and Houston, Proc. Okla. Acad. Sci. 14, 77 (1934).

(62) Fisk and Underhill, J. Pharmacol. 49, 320 (1933).

(63) Hill and Fernald, U.S. Patent 2,119,077.

(64) Sergievskaya and Nesvad'ba, J. Gen. Chem. (U.S.S.R) 8, 924 (1938).

(65) Blicke and Parke, J. Am. Chem. Soc. 61, 1200 (1939).

(66) Roberts and Johnson, J. Am. Chem. Soc. 47, 1396 (1925).

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

(68) Ogata, J. Pharm. Soc. Japan 456, 81 (1920).

(69) Valette, Bull. soc. chim. (4) 47, 289 (1930).
Bonnard and Bulif, ibid. (4) 49, 1303 (1931).

(70) Torres, Anales soc. espan. fis. quim. 24, 82 (1926).

(71) Nakamura, Sci. Papers Inst. Phys. Chem. Research (Tokyo) 14, 184 (1930).

(72) Pinck and Hilbert, J. Am. Chem. Soc. 59, 8 (1937).

(73) Mannich and Lammering, Ber. 55, 3515 (1922).
German Patent 379,950.
Mannich and Curtas, Arch. Pharm. 264, 750 (1926).

(74) Blicke and Blake, J. Am. Chem. Soc. 52, 235 (1930).

(75) Hartung and Munch, J. Am. Chem. Soc. 51, 2570 (1929).

(76) Tzobkalla, Arch. sci. biol. (U.S.S.R.) 39, 239 (1935).
Topschiew, Arch. Pharm. 272, 774 (1934).

(77) Hesse and Trolldiener, Brit. Med. J. 1, 1340 (1899).

(78) Macht, J. Pharmacol. 12, 263 (1918).

(79) Hirschfelder, J. Pharmacol. 15, 261 (1920).

(80) Hjort and Kaufmann, J. Pharmacol. 15, 129 (1920).

(81) Quigley and Hirschfelder, J. Pharmacol. 18, 326 (1921).

(82) Morganroth and Ginzberg, Berlin klin. Wochschr. 50, 343 (1913).

(83) Miescher, Helv. chim. Acta 15, 163 (1932).
Alport, Ind. Chem. 14, 187 (1938).

(84) Goodman, J. Investigative Dermatol. 2, 53 (1939).

(85) Rieveschl and Ray, Chem. Rev. 23, 287 (1938).

(86) Fortner, Monatsh. 25, 443 (1904).

(87) Hinkel, Ayling and Beynon, J. Chem. Soc. 1936, 339.

(88) Dziewonski and Schnayder, Bull. intern. acad. polon. sci., Classe sci. math. nat. 1934, 529.
Chem. Abstracts 25, 5416 (1931).

(89) Ardashev, Lomovatskaya and Kacher, J. Applied Chem. (U.S.S.R.) 11, 1344 (1938).
Chem. Abstracts 33, 5844 (1939).

(90) Rieveschl, M. Sc. Thesis, University of Cincinnati.
Rieveschl and Ray, J. Am. Chem. Soc. 60, 2675 (1938).

(91) Fittig and Gebhard, Ber. 10, 2143 (1877); Ann. 193, 142 (1878).

(92) Goldschmiedt, Ber. 10, 2022 (1877).

(93) Fieser and Seligman, 57, 2174 (1935).

(94) Jeanes and Adams, J. Am. Chem. Soc. 59, 2620 (1937).

(95) Meltsner, Greenfield and Rosenzweig, J. Am. Chem. Soc. 62, 991 (1940).

(96) Oyster and Adkins, J. Am. Chem. Soc. 43, 208 (1921).

(97) Bischoff and Adkins, J. Am. Chem. Soc. 45, 1031 (1923).

(98) Underwood and Kochmann, J. Am. Chem. Soc. 45, 3074 (1923).

(99) Pick, Monatsh. 25, 979 (1904).

(100) Gotz, Monatsh. 23, 27 (1902).

(101) Graebe and Aubin, Ann. 247, 275 (1888).

(102) Stobbe and Seydel, Ann. 370, 134 (1909).

(103) Bischoff and Adkins, J. Am. Chem. Soc. 45, 1032 (1923).

(104) Moore and Huntress, J. Am. Chem. Soc. 49, 1329 (1927).

(105) Sandahl and Christiansen, Bull. soc. chim. (5) 5, 1573 (1938).

(106) Swiss Patent 202,665.

(107) French Patent 840,824.

(108) German Patents 657,526 and 656,784.

(109) Bamberger and Hooker, Ann. 229, 102 (1885).

(110) Fieser and Young, J. Am. Chem. Soc. 53, 4127 (1931).

(111) Fieser, Experiments in Organic Chemistry, Heath, 1935, p. 339.

(112) Adams and Vorhees, Organic Syntheses, Coll. Vol. I, Wiley, New York, 1932, p. 53.

(113) Adkins and Covert, J. Am. Chem. Soc. 54, 4116 (1932).

(114) Adams, Vorhees and Shriner, Organic Syntheses, Coll. Vol. I, Wiley, New York, 1932, p. 452.

(115) Goldschmiedt, Monatsh. 23, 885 (1902).