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I hereby recommend that the thesis prepared under my supervision by Ian R. MacGregor.

entitled Non-nuclear Amino Derivatives of Fluorene

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

Approved by:

Francis E. Ray

Ralph E. Cooper

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Form 668—G. S. and Ed.—1M—7-37

NON NUCLEAR AMINO DERIVATIVES OF 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

1945

by

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ACKNOWLEDGEMENT

The author wishes to express his deep gratitude to Dr. Francis Earl Ray for his invaluable criticism and for the unfailing kindness with which he encouraged the pursuit of this investigation.

NON-NUCLEAR AMINO DERIVATIVES OF FLUORENE

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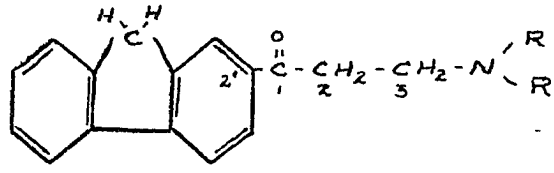

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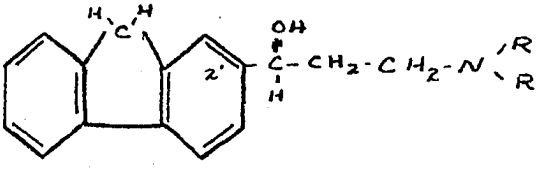

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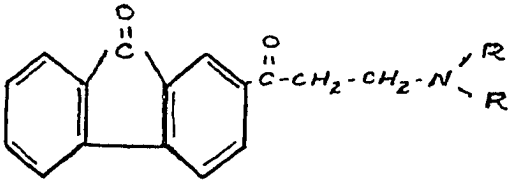

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I. GENERAL DISCUSSION OF LOCAL ANAESTHETICS ANALGESICS AND ANTISPASMODICS

Pain has followed man as closely as his shadow. Through the ages man has cried out in agony and prayed for release from physical torment. Early records show that the ancient Egyptians and Chinese had some knowledge of narcosis as they used various plant juices as well as alcohol to induce artificial sleep and insensibility to pain (1). This insensibility to pain is now divided into two classes; anaesthesia and analgesia.

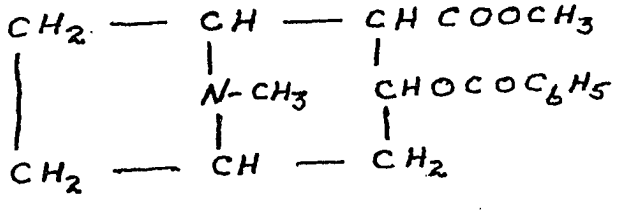
Anaesthesia is defined as the loss of feeling or sensation, especially loss of tactile sensibility although the term is often used for the loss of any other senses (2). Anaesthesia itself is divided into two classes; general and local. General anaesthesia is the loss of sensation which affects the whole body, while local anaesthesia is confined to one limited part of the body. The most important general anaesthetics include ether, chloroform, amylene, cyclopropane, nitrous oxide, ethylene and methylene dichloride. Typical local anaesthetics include cocaine, procaine, butyn, metycaine and nupercaine.

Analgesia is defined as absence of sensibility to pain and may be either general or surface. The true differentiation between anaesthesia and analgesia must lie in the depth of narcosis obtained in each case. Anaesthesia, local

and general, is apparently a much deeper or profound physiological effect causing almost complete loss of sense. Analgesia, on the other hand, is a shallower effect causing a diminution of sense perception to such a point that pain is not so easily noticed. We shall discuss briefly the question of local anaesthetics and of analgesics.

A. LOCAL ANAESTHETICS.

Probably the best known of the local anaesthetics is cocaine, which was isolated from coca leaves in 1860 by Niemann (3). It was not until 1923, however, that Wilstatter, Wolfes, and Mader (4) proved the structure of cocaine by synthesis.



Cocaine proved its worth as a strong local anaesthetic but it was soon found to have several serious disadvantages, both clinical and commercial. It is difficult to purify, can not be used safely on persons suffering from hypertension and it is habit forming. Consequently research for new and better anaesthetics was undertaken. But what are the attributes of a desirable

anaesthetic? An ideal anaesthetic should be:

1. Less toxic than cocaine for the same degree of anaesthesia.

2. Neither too acid nor too alkaline or it will give rise to irritation or tissue damage.

3. Water soluble.

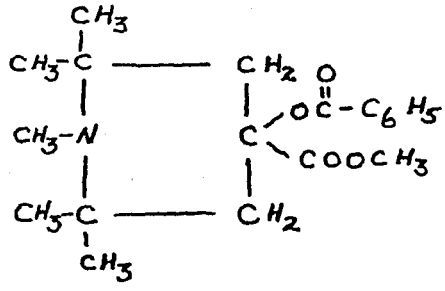
4. Stable enough to be sterilized by boiling.

5. Compatible with adrenalin, which, by its vasoconstrictive action, makes the area of operation practically bloodless and prevents too rapid absorption of the anaesthetic.

6. Non-habit forming.

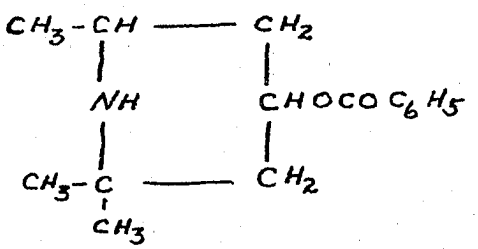
7. Absorbed slowly so that the duration of anaesthesia will be great enough to permit the completion of complicated operations.

Investigation of cocaine was begun in order to relate local anaesthetic activity and molecular structure. It was found that the anaesthetic activity was lost if either the methyl ester or the benzoyl group was removed. It was found, too, that the pyrrolidine nucleus was not necessary for activity, since the compound alpha-eucaine



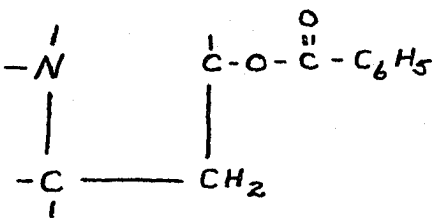
α-EUCAINE

showed as much activity as cocaine and has the additional advantage of being stable in boiling water. Since alpha-eucaine is somewhat painful and irritating on injection, it was superseded by beta-eucaine.

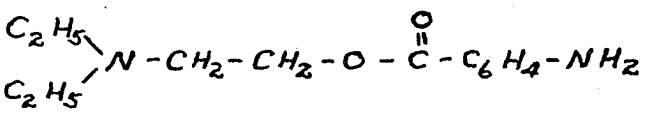


β-EUCAINE

It was noted that the grouping common to the three compounds, cocaine, alpha-eucaine, and beta-eucaine, was the following:



It was therefore proposed that the anaesthesiophoric group was $N-(C)_n-O-CO-Ar$. Working on this principle Einhorn and Uhlfelder (5) described the synthesis of procaine or novocaine which contains the same anaesthesiophoric group.



PROCAINE

Literally hundreds of compounds containing the same anaesthesiophoric arrangement were prepared in the years following the discovery of procaine. From the results of these investigations more generalizations were made relating structure and anaesthetic properties. Compounds with anaesthetic properties were prepared in which the Ar-CO-O grouping was made up of acids such as benzoic, phenyl acetic, alpha-phenyl propionic, p-tolyic, and piperonylic, to mention a few.

Few generalizations are permitted as to the effect of varying the number of carbon atoms between the ester group and the nitrogen atom. The p-aminobenzoates and cinnamates of dialkylaminomethanol

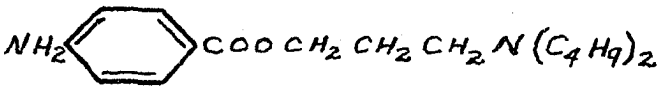
$$NR_2-CH_2-O-CO-Ar$$

in which R was ethyl, propyl, butyl and iso-amyl have been prepared. While it was found that an increase in molecular weight by increasing the size of the R group enhanced the anaesthetic potency, these compounds were not so active as the homologs of the dialkylaminoethanol type (6).

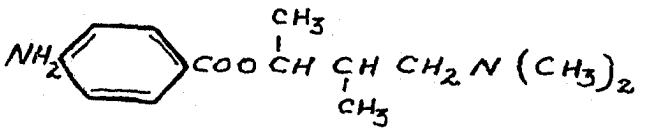
$$Ar-CO-O-CH_2-CH_2-NR_2$$

In cocaine and the eucaines the number of carbons between the acid residue and the nitrogen atom is three. A number of other compounds with three carbons in this chain have been prepared and found to be active. Among them are

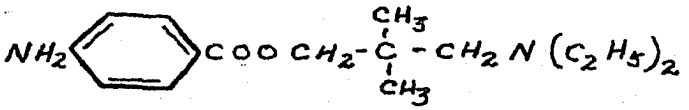
butyn, tutocaine, and larocaine..



BUTYN



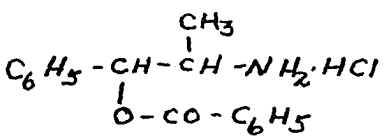
TUTOCAINE



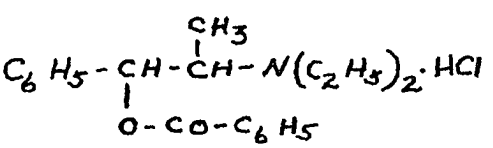
LAROCAINE

Compounds with longer connecting chains are little known. It is, therefore, impossible to state at just what point the anaesthetic activity becomes extinct (7).

The greatest structural modification in the anaesthesiophoric group have been made in the substituents on the nitrogen atom. Derivatives of primary amines have been shown to be active. The primary amine corresponding to allocaine is almost as active as cocaine and is much less toxic (8).



PRIMARY AMINE



ALLOCAINE

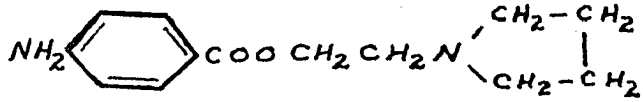
Derivatives of secondary amines should have anaesthetic activity but they, apparently, have not been tested. They may be rather unstable, as primary and secondary amine bases tend to form amides with the ester group.

Tertiary amines have been used almost universally. These may be of three types:

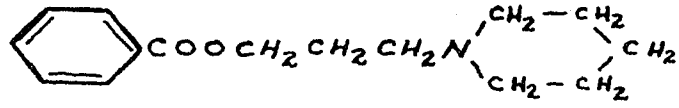
(1) Dialkylamino compounds where the alkyl groups are the same, such as dimethyl-, diethyl-, dipropyl-, etc. In members of this type the anaesthetic activity seems to increase up to a certain point with the weight of the alkyl group. In a series of p-aminobenzoates of $-CH_2CH_2NR_2$ and $-CH_2CH_2CH_2NR_2$ it was found that the activity was greatest when R was made up of three or four carbon atoms (9).

(2) Dialkylamino compounds where the alkyl groups were different. Methylethlamino- and methylpropylamino- would be examples of this type (10).

(3) The terminal carbons of the two alkyl groups may be joined, forming a heterocyclic ring with the nitrogen atom. Thus, if the terminal carbons of procaine are joined, there results an anaesthetic compound, pyrrolidinoethyl-p-aminobenzoate.



A more common type of such a cycle are the piperidino derivatives such as metycaine (11).

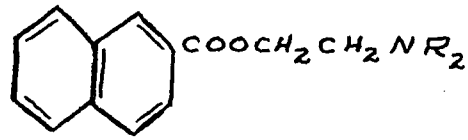


METYCAINE

As has already been indicated an impressive number of compounds containing the anaesthesiophoric grouping, NR_2-$(C)_n$O-CO-Ar, have been prepared. Unfortunately the available data do not permit the desired comparison of the relative activities, and it is therefore impossible, at the present time, to be specific about the effect of making relatively small changes in the structure.

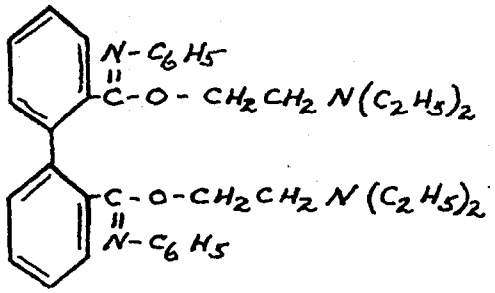
Practically all of the local anaesthetics considered in this discussion have been derivatives of benzene. There is no reason to suppose that other nuclei could not be employed as the basis of another series of local anaesthetics. Little work has been done along this line, however.

Bjerregard and Houston (12) found that alkamine esters of beta-naphthoic acid

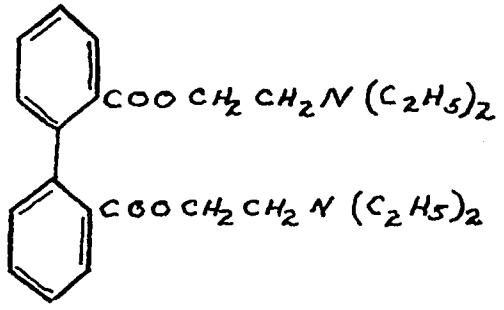


are almost as active as cocaine but are less toxic. It seems that increasing the molecular weight of the acid residue has the same effect as increasing the size of the alkyl groups on the nitrogen, that is, causes an increase in anaesthetic potency. A few other derivatives of naphthoic acids have been prepared and found to possess activity as great or greater than that of cocaine and usually of lower toxicity (13) (14) (15).

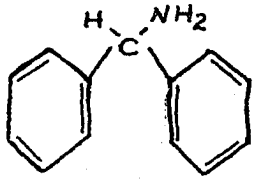
Roberts and Johnson (16) have prepared the diethylaminoethylimido ester of diphenylanilide



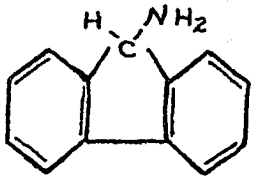
and found it much more active and much less irritating than the ordinary ester.



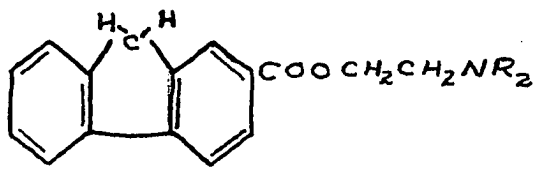
The fact that amines of high molecular weight have local anaesthetic activity is well known. Ogata (17), found, for example, that benzhydrylamine

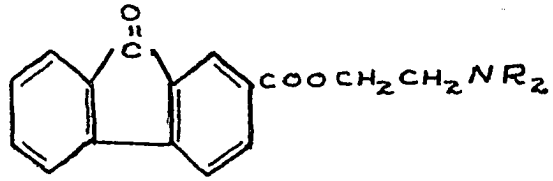


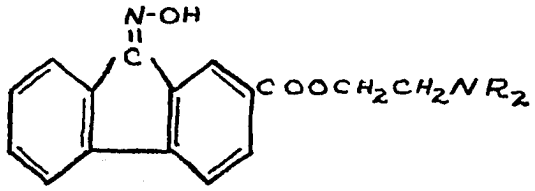
and amines of the type $C_6H_5CHRNH_2$ were active. From this consideration it is not unexpected to find that 9-amino-fluorene



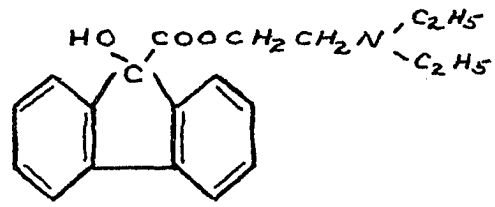
exhibits some local anaesthetic properties (18). A number of other derivatives of fluorene have been prepared by Ray and Rieveschl (19) and found to have anaesthetic properties. The compounds include derivatives of the types:



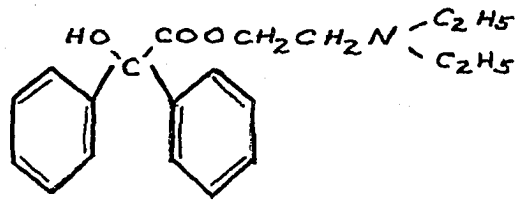




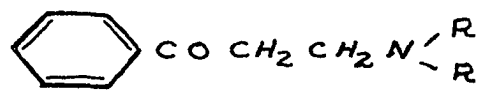
In 1942 Gilman and his co-workers (20), while investigating a number of new compounds for local anaesthetic properties, found that the fluorene derivative



was less toxic and less potent as a surface anaesthetic, but more potent as a block anaesthetic than was the corresponding benzilic acid ester.

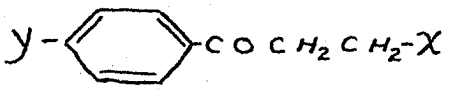


Mannich and Lammering (21), in 1922, found that the ester linkage was not essential for local anaesthetic action inasmuch as ketones of the type



had local anaesthetic activity. In the following table are listed some of the compounds that they found to be active.

KETONIC LOCAL ANAESTHETICS



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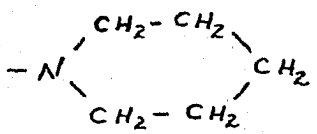
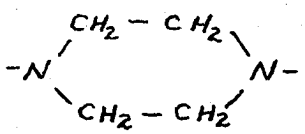
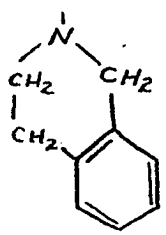
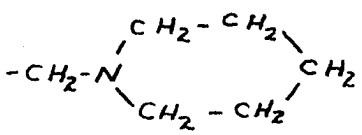
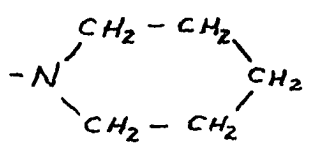
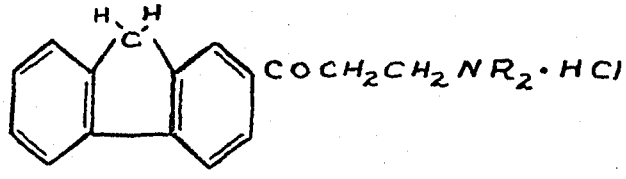
1.		H
2.		H
3.		H
4.		H
5.		-O-CH$_3$

In other words, the exchange of an ester linkage for a ketone linkage did not destroy local anaesthetic activity.

During the course of our investigation we prepared a number of ketones derived from fluorene, some of which showed local anaesthetic activity when applied topically to the tip of the tongue.



B. ANALGESIA AND ANALGESICS

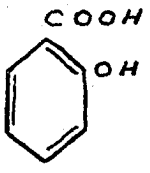
Any review of analgesia should include a discussion of the chemical and physiological properties of the following groups of analgesics: salicylates, cinchophen, neocinchophen, acetanilid, acetophenetidin, and morphine.

1. The salicylate group.

During the last third of the 19th century a search for synthetic substitutes for quinine was begun. As the result of this search, a large number of compounds were

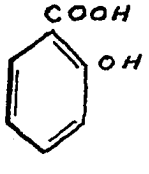
introduced into medicine and, although they showed a definite lack of antimalarial activity as well as a difference in chemical constitution, they shared with cinchona the ability to produce antipyresis and analgesia.

Salicylic acid (orthohydroxybenzoic acid)

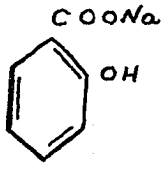


is so irritating that it should only be used externally and therefore various derivatives have been prepared for internal use. These may be divided into two classes--esters of salicylic acid, and salicylate esters of organic acids. In addition, there are simple salts of salicylic acid such as the sodium salt (sodium salicylate). By considering the following structures the relationship between the various classes may be seen:

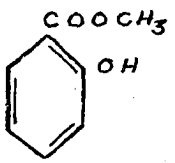
THE SALICYLATES



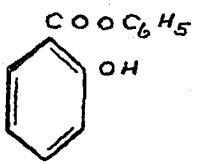
SALICYLIC ACID



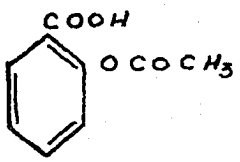
SODIUM SALICYLATE



METHYL SALICYLATE
(OIL OF WINTERGREEN)



PHENYL SALICYLATE



ACETYLSALICYLIC ACID
(ASPIRIN)

The salicylic acid content of the "salicyl" drugs is the determining factor in their physiological action. Variations in solubility and propensity to cause local irritation are the main factors which determine the degree of usefulness of these chemicals (22). Benzoic acid shares many of the actions of salicylic acid but is much weaker; this seems to indicate that the OH group has an important bearing on the action of the drugs.

The salicylates, especially salicylic acid, are weakly bacteriostatic (22); certain fermentation processes are inhibited and putrefaction of meat, urine, and other substances is delayed.

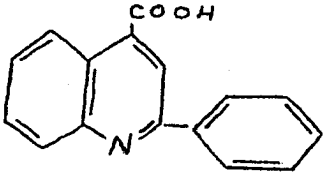
Two noticeable effects on the central nervous system are associated with the "salicyl" drugs. The lowering of body temperature, antipyresis, is usually rapid and effective in those persons with abnormally high temperatures but rarely occurs in persons with normal temperatures. There is abundant evidence that the salicylates act mainly on the central nervous system and not "peripherally on blood vessels or sweat glands" (23). If the spinal cord is cut near the brain the antipyretic drugs do not lower the temperature of fevered test animals. We generally associate sweating with the use of salicylates, but sweating does not occur unless there is fever, and the latter can be lowered by the salicylates even when sweating is prevented by the use of atropine. Barbour (24) also claims that the salicylates cause hydration of the blood, thus facilitating both sweating and radiation of heat. The same mechanisms of antipyresis given here for the salicylates likewise apply to acetanilid and acetophenetidin.

That the analgesic action of the salicylates is well known is evidenced by the tremendous quantities of

aspirin prescribed for himself each year by the layman. Goodman (22) says that the alleviation of pain is probably due to a central depressant action located in the optic thalami (nerve origins). The salicylates generally cause no mental disturbance, anaesthesia, or changes in modalities of sensation other than pain sense. In unusual cases some persons claim to note a mild hypnotic effect which may be due to psychic factors. An unusual toxic effect, called salicylism, often accompanies the excessive use of these drugs. It is characterized by headache, ringing in the ears, deafness, weak pulse and stomach derangement with nausea and vomiting. The types of pain relieved by salicylates are headache, myalgia, arthralgia, and other pains arising from integumental (external covering) structures rather than from viscera (25). The salicylates, however, are much inferior to morphine as analgesics.

2. Cinchophen and Neocinchophen.

In 1887 Doebner and Gieseke (26) reported the preparation of 2-phenylquinoline-4-carboxylic acid (Cinchophen).



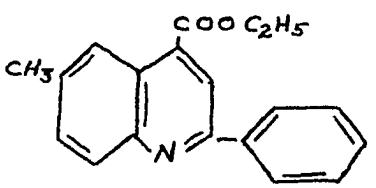
CINCHOPHEN

The compound was introduced into medicine in 1908 under the trade name Atophan, later changed to Cinchophen, and was proposed for the treatment of gout. It is a yellowish-white bitter powder which is insoluble in water.

In pharmacological action cinchophen resembles the salicylates. It has the same type and mechanism of antipyretic and analgesic action, but its ability to stimulate bile flow is said to be more pronounced.

Cinchophen is widely used in the treatment of gout despite its dangerous hepatotoxic effects. Some physicians believe that the danger of the disease is greater than that of the drug (27).

Neocinchophen (novatophan, tolysin)



NEOCINCHOPHEN

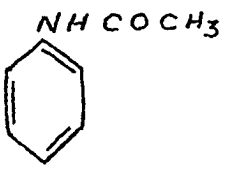
is the ethyl ester of 6-methyl-2-phenylquinoline-4-carboxylic acid and is a light yellow crystalline powder, odorless and

tasteless and nearly insoluble in water.

In its pharmacological actions neocinchophen closely resembles cinchophen and is used for the same purposes and in about the same dosages. Experiments on animals, however, seem to show that neocinchophen has a higher margin of safety than has cinchophen, probably due to slower intestinal absorption (28).

3. Acetanilid and Acetophenetidin.

In 1886 Cahn and Hepp (29) reported that aniline as well as its acetyl derivative, acetanilid, exhibited antipyretic and antineuralgic action. Aniline is, however, a highly toxic substance, destroying hemoglobin by forming methemoglobin. The substitution of an acetyl group for one of the amino hydrogens was found to reduce the toxicity to such a point that acetanilid (Antifebrin) could be introduced into medicine.



ACETANILID

Early reports on the use of acetanilid indicated that it sometimes led to serious aniline poisoning. The

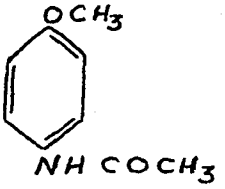
search for less toxic compounds led to p-aminophenol, since the action of acetanilid seemed to be due in part to its hydrolysis to aniline and acetic acid, the aniline being subsequently oxidized to p-aminophenol.

p-Aminophenol itself also proved to be too toxic for medicinal use but an investigation of its derivatives was undertaken with a view to finding one which would not have this undesirable toxicity. The results of the investigation may be summarized (7):

1. Replacement of an amino hydrogen by an acetyl group yields a compound of lower toxicity than p-aminophenol but still having antipyretic and analgesic properties.

2. Acetylization of both the hydroxyl and the amino groups produces compounds inferior to certain of those prepared by alkylating the hydroxyl group and acetylating the amino group.

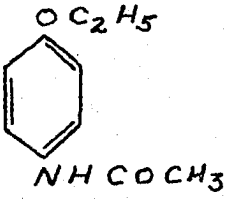
(a) Methacetin (p-methoxyacetanilid)



METHACETIN

was found to possess a higher degree of antipyretic and analgesic activity than any other member of the series.

(b) Phenacetin or Acetophenetidin



PHENACETIN

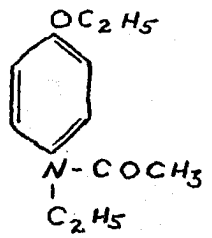
was found to be less powerful than methacetin as an antipyretic and analgesic; but it causes less hemolysis of the red blood corpuscles and is consequently more desirable as a drug.

(c) Increasing the molecular weight of the alkyl group, i.e. to propyl or butyl, brings a sharp decrease in physiological action.

3. Derivatives of p-aminophenol which contain a free hydroxyl group have no antipyretic value.

4. Substitution of an alkyl group for the amino hydrogen of phenacetin results in a compound with greater analgesic but less antipyretic action.

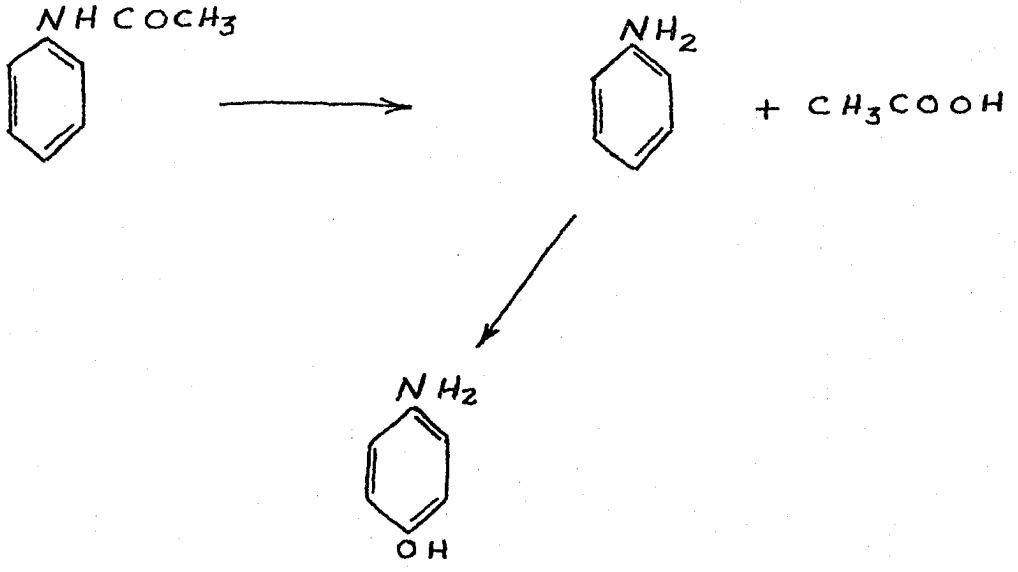
For example the ethyl derivative



is more analgesic, but less antipyretic and less toxic than phenacetin.

It is interesting to note that Phenacetin (or Acetophenetidin) was first prepared by Hinsberg (30) in 1887 while seeking a use for a quantity of p-nitrophenol which had been accumulated by the Farbwerke of F. Bayer and Company in Germany.

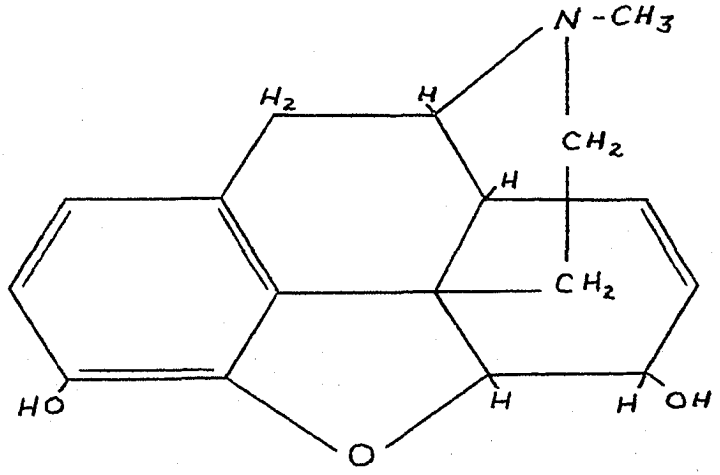
It is believed that both acetanilid and phenacetin owe their therapeutic as well as their toxic properties to conversion in the body to para-aminophenol. Michel, Bernheim and Bernheim (31) have reported that acetanilid may be hydrolyzed <u>in vitro</u> by various tissues to aniline and acetic acid, and that aniline, in the presence of these tissues, may be oxidized to p-aminophenol.



4. Morphine and its Derivatives.

Morphine, one of the many alkaloids derived from opium, is unequalled as an analgesic. It is said that if it were necessary to restrict the choice of drugs to a very few, "the great majority of physicians would place...morphine at the head of the list" (22).

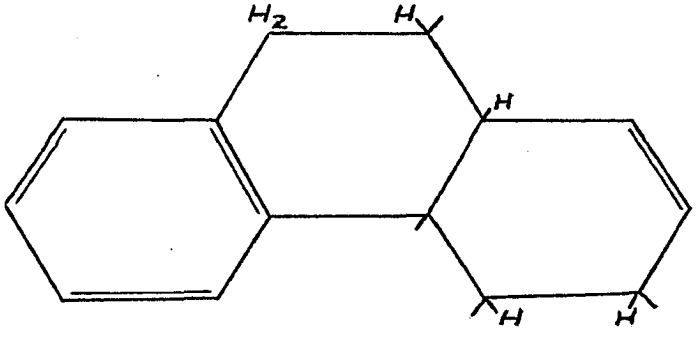
The exact structural formula of morphine has been the subject of considerable research and has not yet been entirely proved. The formula commonly accepted today is that of Gulland and Robinson (32).



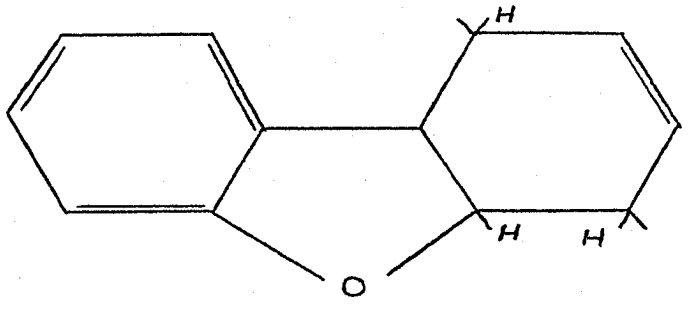
MORPHINE

Studying this proposed structure we notice the following:

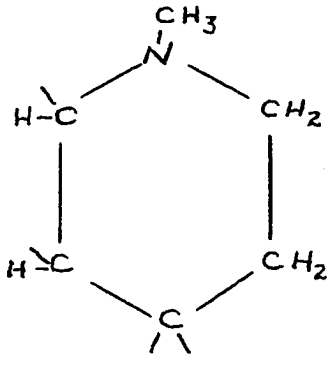
(1) A partially hydrogenated phenanthrene nucleus.



(2) An oxide bridge -- or a partially hydrogenated dibenzofuran nucleus.



(3) A nitrogen containing chain ($-CH_2-CH_2-N-(CH_3)-$) which may be considered part of a six membered heterocyclic ring.



(4) A phenolic hydroxy group.

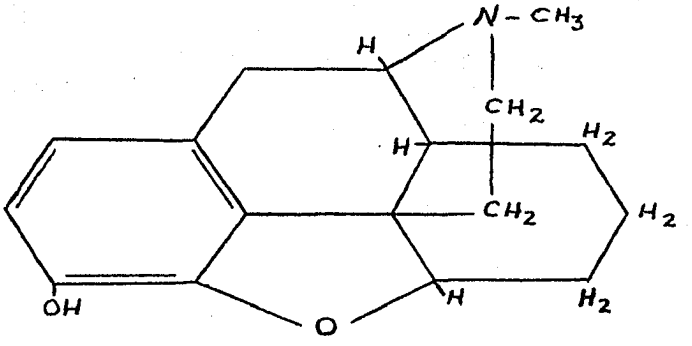
(5) An alcoholic hydroxy group.

Careful study of morphine and its derivatives has led to the assignment of definite pharmacodynamic properties to the two hydroxyl groups mentioned above. If the phenolic OH in morphine is masked by an alkyl group as in codeine ($-O-CH_3$) there is a decrease in analgesic, respiratory, depressant and intestinal spasmodic actions, but the effects on the central nervous system are enhanced (22). If, on the other hand, the alcoholic OH is masked, the narcotic and respiratory effects of morphine are exaggerated. When either of the OH groups is masked, there is an increase in convulsant action and a decrease in emetic action. These facts lead to the belief that the free phenolic OH contributes to the analgesia, hypnosis, and respiratory depression of morphine while the alcoholic OH tends to counteract these effects.

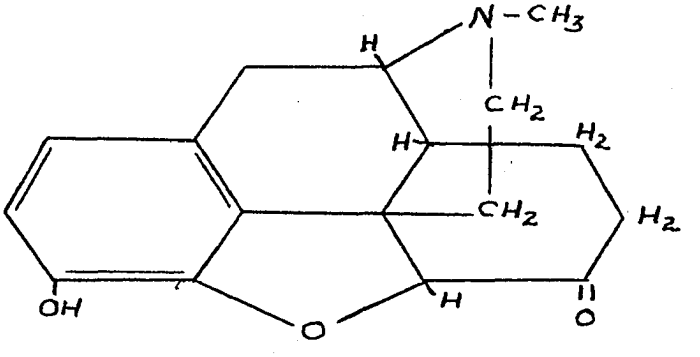
Both morphine and codeine have proved to be highly efficacious as analgesics and their importance in medicine can not be overlooked. But morphine, and codeine to a lesser degree, is an addiction drug; continual use of it by patients suffering severe pain causing stronger and stronger desire for the exhilarating drowsiness and freedom from anxiety and pain it brings about.

Much work has been done in recent years in an attempt to determine the relationship between structure and drug addiction. It was established from this work that

systematic structural changes in morphine derivatives result in changes in physiological action which are sometimes predictable. It was found that a single change did not alter all the physiological reactions to the same degree. Certain phenanthrene derivatives, particularly those with substituents in the 3-position, showed marked analgesic effect. Some of the phenanthrene derivatives obtained were found to have anti-carcinogenic properties. Two morphine derivatives, desomorphine and metopon, were discovered and found to have more powerful pain controlling properties.



DESOMORPHINE

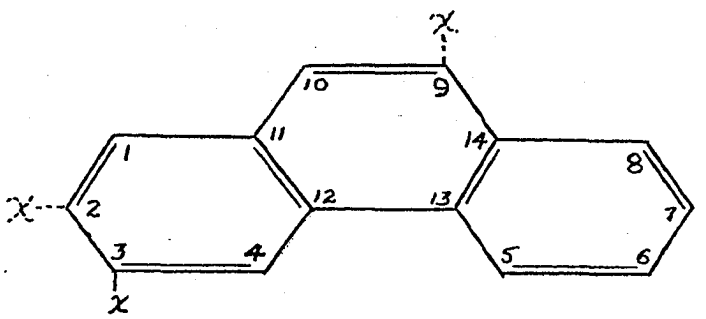


METOPON

Of these, the latter is definitely weaker in addiction liability.

(a) Phenanthrene derivatives were considered important since a phenanthrene nucleus is present in the morphine molecule. (33) (34)

Eddy (35) found that although phenanthrene itself produced a mild general depression in cats, substitution of various groups in the 2-, 3-, and 9- positions increased its depressant action.

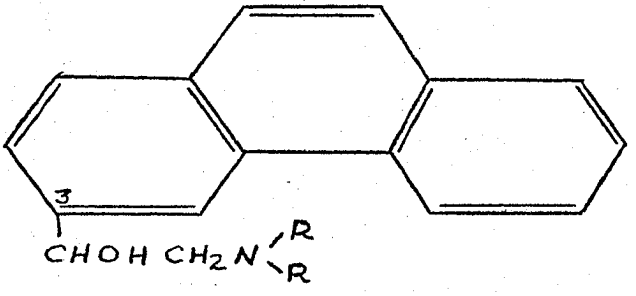


$X = -NH_2, -COOH, -OH, CH_3CO$

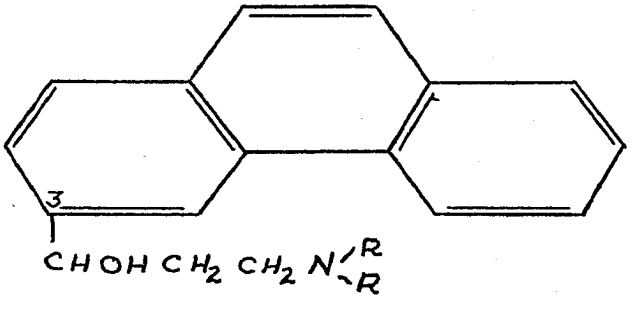
The greatest effect was found when substituents were put in the 3-position. Among those derivatives tested were compounds with the above structure where x was NH_2, COOH, OH, and CH_3CO. It was also found (36) that muzzling the OH group in the 2- or 3-position with a methyl or an acetyl group

decreased the activity in the compound just as does muzzling the phenolic OH in morphine. Eddy (37) reported, too, that introduction of two substituents in the phenanthrene nucleus resulted in decreased activity.

A series of amino alcohols of the ethanol and propanol amine type were prepared by Mosettig and his co-workers (39)



3-(2-Dialkylamino-1-hydroxy-ethyl) Phenanthrene



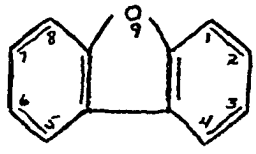
3-(2-Dialkylamino-1-hydroxy propyl) Phenanthrene

and tested by Eddy (38). The most striking of the compounds was 3(2-diethylamino-1-hydroxyethyl) phenanthrene which produced an effect remarkably like that of morphine in cats.

Each of the amino ketones produced some analgesic action, but this was much less marked than with the corresponding alcohol. Among the compounds of the propanol amine type which were tested and found to be active were the ethylamino, diethylamino, and dimethylamino derivatives. E. E. Nelson (40) has found, however, that the compound 3'-(3-diethylamino-1-hydroxypropyl) phenanthrene is less active than 3'-diethylamino-1-hydroxyethyl) phenanthrene.

These investigations on the phenanthrene derivatives have not proved that the phenanthrene nucleus is essential for morphine-like analgesia. It was apparent that other nuclei must also be considered.

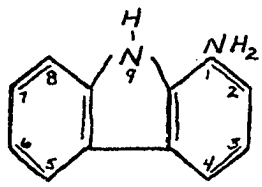
(b) Dibenzofuran derivatives were

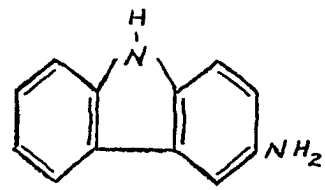


obviously the next ones to be considered as possible possessors of analgesic activity. A comparison of analogous phenanthrene and dibenzofuran derivatives was made by Eddy (41). By comparing the minimum effective doses (M.E.D.), he found

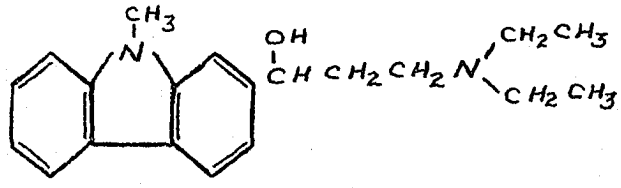
that lower doses of the dibenzofuran derivatives were required to produce analgesia but the phenanthrene derivatives were less toxic.

(c) Carbazole derivatives were prepared by Ruberg and Small (43) and tested by Eddy (42). Among the compounds tested were amines and amino alcohols of carbazole and 9-methyl-carbazole as well as amines, alcohols, and amino alcohols of tetrahydrocarbazole. It was found that, although carbazole is only slightly depressant in the cat and not analgesic, amino carbazoles are more depressant and exhibit definite analgesic action, especially when the NH_2 group is in the 1- or 3- positions.





In general the amino carbazoles had more quieting than analgesic action. The compound 9'-methyl-2'-(3-diethyl-amino-1-hydroxypropyl) carbazole



had a smaller M.E.D. and greater analgesic action than any of the phenanthrene or dibenzofuran compounds tested. It was also found to be somewhat less toxic and less convulsant in cats.

Although Mosettig and van de Kamp (44) prepared a number of propanolamines of phenanthrene, dibenzofuran and carbazole, the results of the pharmacological tests for only a few have been published. They point out that Barger and Dale (45) have carried out a systematic investigation of the amines, $Ar(CH_2)_xNH_2$ (Ar being phenyl, hydroxyphenyl, or iminazolyl). It was evident that, almost universally, the greatest physiological action is exerted by compounds in which x is 2. Compounds of this type occur frequently in nature and are probably intermediates in the photosynthesis of isoquinoline derivatives. In compounds with x less than 2 or x greater than 2, the physiological action is greatly diminished.

C. ANTISPASMODICS

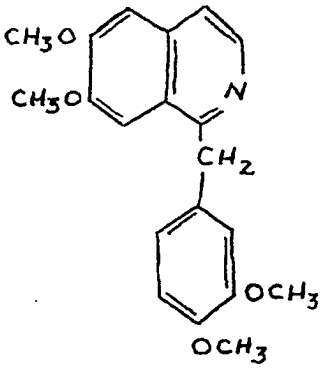
The alkaloids of opium may be divided into two distinct groups on the basis of their chemical constitution and their physiological behavior:

1. Derivatives of phenanthrene, such as morphine and codeine, which act primarily on the central nervous system as analgesics.

2. Derivatives of benzylisoquinoline, which have little effect on the nervous system but which exhibit marked antispasmodic action on smooth muscle.

We have already considered the two important members of the first group under the heading, analgesics.

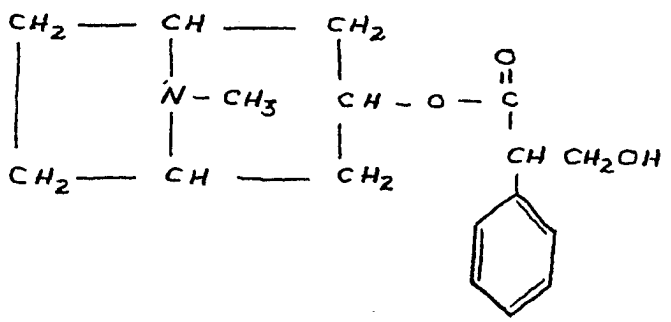
The primary member of the second group is papaverine, a derivative of isoquinoline.



PAPAVERINE

Unlike morphine, papaverine is neither analgesic nor hypnotic in therapeutic doses. Its chief use is in the treatment of pulmonary arterial embolism when it is administered in solution by intravenous injection. It is also used to relax the spasms in renal and biliary colic when it is administered orally or by injection (7).

Antispasmodics may be divided into two classes; "those which act to prevent or abolish the action of stimulation of autonomic nerves, and those which are not thus related to innervation" (46). The first of these classes, the neurotropic drugs, is further divided into sympatholytic (acting on the sympathetic system) and parasympatholytic (acting on the parasympathetic system). The drugs of greatest practical importance are those of the parasympatholytic group, such as atropine,



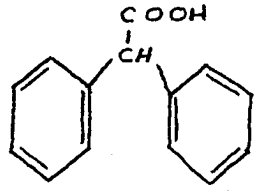
ATROPINE

and those not related to innervation, papaverine for example.

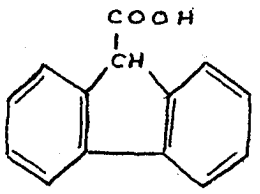
The drugs of both groups have a number of disadvantages. Papaverine has little effect against spasms of neural origin, while atropine is almost ineffective against spasms of muscular origin. In addition, papaverine relaxes all smooth muscle equally, giving rise to a prolonged fall in arterial blood pressure. Furthermore the action of atropine occurs in all organs activated by the nerves of the autonomic nervous system and causes cyclopegia, dryness in the mouth, and sometimes a rise in arterial blood pressure.

For these reasons Burtner and Cusic (46) attempted to synthesize compounds which would have a selective atropine-like action on smooth muscle and only a slight effect on the pupils, salivary glands and circulation.

Burtner and Cusic attempted to modify the structure of atropine by preparing a series of esters from acids which might substitute for the acid fraction of atropine. They chose to study esters of amino alcohols and diphenylacetic acid and related compounds such as fluorene-9-carboxylic acid.

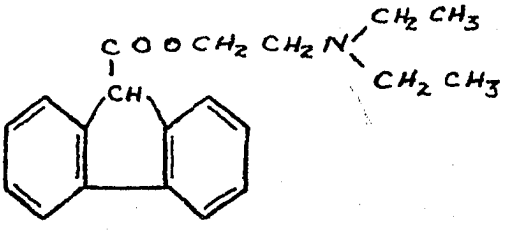


Diphenylacetic Acid

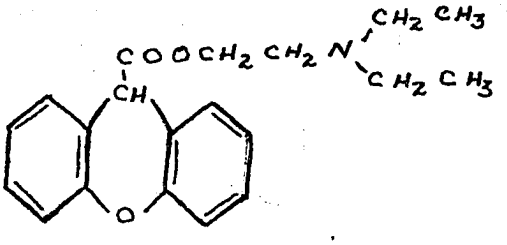


Fluorene-9-carboxylic Acid

They found that, out of sixty-two derivatives prepared, the two most promising antispasmodics were beta-diethylaminoethyl fluorene-9-carboxylate and beta-diethylaminoethyl xanthene-9-carboxylate.

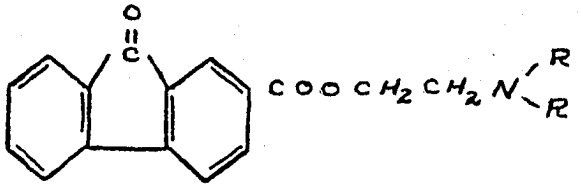


β-DIETHYLAMINOETHYL FLUORENE-9-CARBOXYLATE



β-DIETHYLAMINOETHYL XANTHENE-9-CARBOXYLATE

It should be added here that the compounds reported by Ray and Rieveschl (19) have not only been found to possess local anaesthetic action, but seem also to possess some antispasmodic action. This would mean that, as far as fluorene is concerned, the antispasmodic activity is not dependent upon substitution in the 9 position as in the compounds prepared by Burtner and Cusic (46), since compounds of the type prepared by Ray and Rieveschl (19)

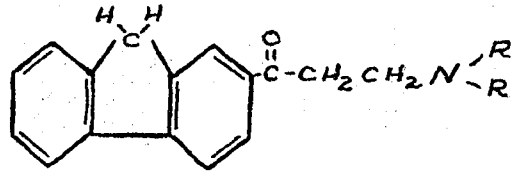


may also be antispasmodic. It should be noted that in this case the 9 carbon has been oxidized to a ketone.

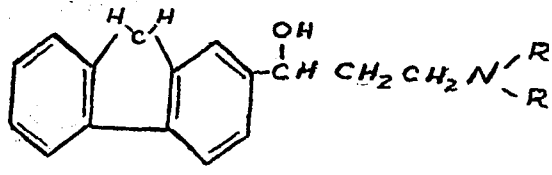
II PROCEDURE AND DISCUSSION OF THE PROBLEM

A. INTRODUCTION

In the foregoing sections we have reviewed briefly the known facts relating the physiological activity to the chemical structure of anaesthetics, analgesics, and anti-spasmodics. If a series of mono and dialkylaminopropanone and propanol derivatives of fluorene



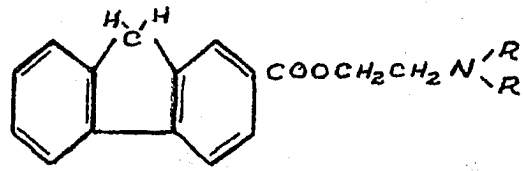
I



II

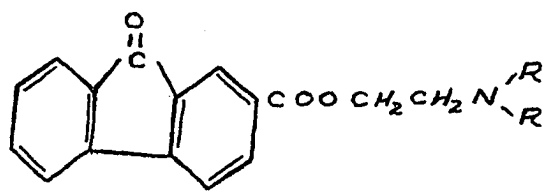
were prepared, what type of physiological activity could be expected from them?

We have already seen that the grouping $N-(C)_n-O-CO-Ar$ leads to anaesthetic activity and that the latter is especially marked when N is 2. Furthermore, we have seen that the ester linkage is not essential for anaesthetic activity (21). Reasoning by analogy we would expect the compound



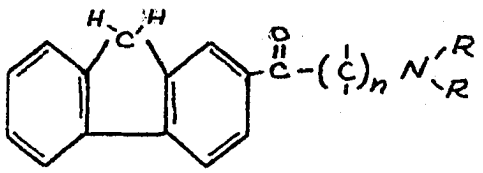
III

to exhibit anaesthetic properties, since it contains the anaesthesiophoric grouping $Ar-CO-O-(C)_nNR_2$. Since III has an acid radical of high molecular weight, it is reasonable to suppose that it would be quite active and of low toxicity (13) (14). The compounds prepared by Ray and Rieveschl (19) are similar to III except that the methylene carbon has been oxidized to a ketone.



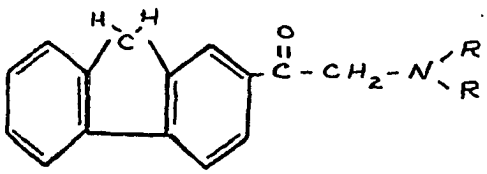
These compounds exhibit marked local anaesthetic action and, according to preliminary reports, also show antispasmodic activity corresponding to that shown by the compounds of Burtner and Cusic (46).

If, on the other hand, the ester linkage is not necessary we may say that the modified anaesthesiophoric grouping is $N-(C)_n-CO-Ar$ and we would expect compounds of the mono and dialkylaminoalkyl type to be useful as anaesthetics.

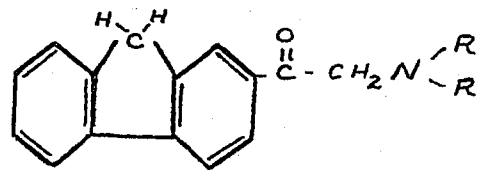


IV

The work of Barger and Dale (45) indicates that we could expect maximum physiological activity when n in the above formula is equal to 2. This would mean that the mono and dialkylaminopropanone compounds derived from fluorene would have anaesthetic properties. On the other hand, if n were one



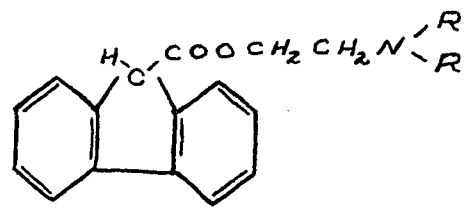
V



V

we would still expect some activity from the compounds, even though it would probably be less than that shown when n was 2. The anaesthetic activity depends to some degree upon the water solubility of the compounds. Thus, if compounds with the structure NR_2CH_2CO-Ar are much more soluble than those with the structure $NR_2CH_2CH_2CO$-Ar, we might expect the former to be more active than the latter.

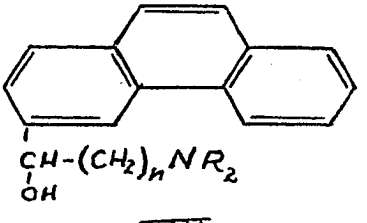
The work of Burtner and Cusic (46) with dialkylaminoethyl esters of fluorene-9-carboxylic acid



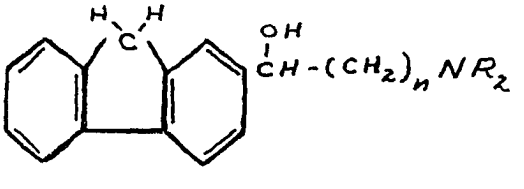
VI

gives us reason to think that compounds of the type prepared during this investigation might have antispasmodic activity. There was no report as to the local anaesthetic properties of the compounds prepared by Burtner and Cusic, although they contain the typical ester anaesthesiophoric group. If the ester linkage is not necessary for anaesthetic activity, is it not also possible that it is not required for antispasmodic activity? This would mean that dialkylaminoalkyl derivatives of fluorene (IV) might also possess antispasmodic properties.

When the keto group of a compound such as that shown above is reduced to an alcohol, we have a series of compounds analogous to those prepared by Mosettig and van de Kamp (39).

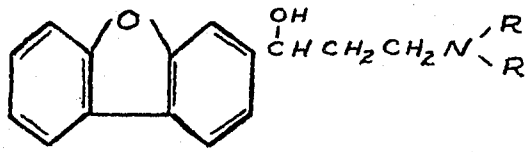


VII



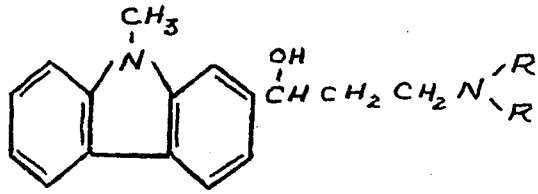
VIII

The phenanthrene derivatives were shown by Eddy (38) and Nelson (40) to produce an analgesic effect remarkably like that of morphine in cats. Furthermore, the dibenzofuran



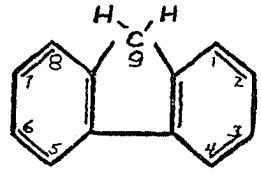
IX

and the 9-methyl-carbazole



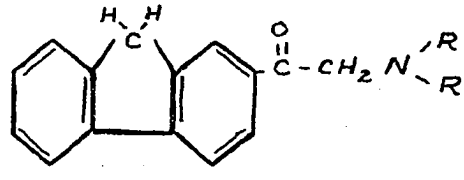
X

derivatives (40) (41) also showed analgesic activity in cats. The diethylaminopropyl derivative of 9-methyl-carbazole was more analgesic and less toxic than the corresponding phenanthrene derivative. Coming back now to the fluorene ring,



we see that it is analogous to dibenzofuran with a methylene group in place of an oxygen bridge, or analogous to carbazole with a methylene group in place of the CH_3-N group in the 9 position. These facts would lead us to suppose that compounds of the propanolamine type might have analgesic activity comparable to morphine and have little or no toxicity.

Considering the above facts, we have investigated the preparation of two series of non-nuclear amino derivatives of fluorene. The first series consisted of compounds of the dialkylaminopropanone and propanol type (I and II), while the second series included compounds of the dialkylaminoethanone type (V).



V

The former were prepared by application of the Mannich reaction to 2-acetylfluorene, while the latter were prepared by brominating acetylfluorene and reacting the bromo compound with the mono or dialkylamine.

B. THE MANNICH REACTION

1. Introduction.

In 1903 and 1906 Tollens and his co-workers (47) (48) found that when acetophenone, ammonium chloride and formaldehyde react, a tertiary amine identified as tri-3-(1-phenyl-1-oxopropyl) amine is obtained.

$$(C_6H_5\overset{O}{\overset{\|}{C}}-CH_2CH_2)_3N$$

This was the first published report of a condensation, which is now known as the Mannich reaction. Later Petrenko-Kritschenko and his students (49) studied reactions of the same type, but failed to recognize the reaction as a general one. In 1917 Mannich (50) began a detailed study of the reaction, claiming it to be a definite reaction type.

F. F. Blicke (51) has defined the Mannich reaction as a condensation of a primary or secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity.

Essentially the reaction replaces the active hydrogen by an aminomethyl or a substituted aminomethyl group. Thus, letting RH be a compound with an active hydrogen, the general equation for the Mannich reaction would be: $RH + HCHO + HNR'R'' \longrightarrow RCH_2NR'R'' + H_2O$ where R' and R'' may be the same or different alkyl, aryl, or hydrogen groups.

The end product of the reaction depends, however, upon the number of replaceable hydrogen atoms on the nitrogen atom. Ammonia, for example, may react with one, two, or three molecules of the substance carrying the reactive hydrogen to give products of the type indicated by the equations:

$$RH + HCHO + NH_3 \longrightarrow RCH_2NH_2$$

$$2RH + 2HCHO + NH_3 \longrightarrow RCH_2NHCH_2R$$

$$3RH + 3HCHO + NH_3 \longrightarrow RCH_2-\underset{\displaystyle CH_2R}{\overset{\displaystyle |}{N}}-CH_2R$$

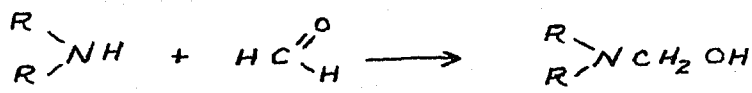
It is, therefore, clear that if a primary amine be condensed with formaldehyde and a substance having an active hydrogen atom, it may form not only the secondary amine,

$$RH + HCHO + R'NH_2 \longrightarrow RCH_2NHR'$$

but the latter may condense with another molecule of RH to form a tertiary amine.

$$RCH_2NHR' + RH + HCHO \longrightarrow R-CH_2-\underset{\displaystyle R'}{\overset{\displaystyle |}{N}}-CH_2-R$$

The mechanism of the reaction has not been established. The possibility that the primary step may be the addition of the amine to formaldehyde



has been considered; but Bodendorf and Koralewski (52) found that, in the case of antipyrene, the reaction of dimethylaminomethanol gives a poorer yield of condensation product than either formaldehyde and the amine or formaldehyde and the amine hydrochloride. The latter workers also investigated the possibility that the initial reaction might be the formation of the methylol from the ketone.

$$RCOCH_3 + HCHO \longrightarrow RCOCH_2CH_2OH$$

They found, however, that the methylol from antipyrene does not react at all with dimethyl amine (52). Apparently neither of these processes represents the primary step of the Mannich reaction. It must be pointed out, nevertheless, that the negative results obtained by Bodendorf and Koralewski are not sufficient proof. The concentration of the Schiffs base formed from an amine and formaldehyde in the normal Mannich reaction might be much lower than the concentration of the Schiffs base in the reaction of dimethylaminomethanol and antipyrene. The same would be

true for the concentrations of the methylol compound in each case.

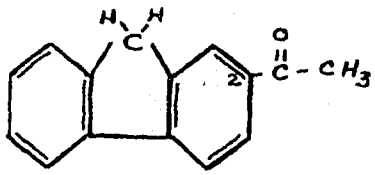
2. Starting Materials.

(a) Formaldehyde may be used in the form of a 20-40% solution or as paraformaldehyde. In a few cases it has been found that aqueous formaldehyde is superior (53). Throughout our investigation we used paraformaldehyde, because of the insolubility of 2-acetyl-fluorene in aqueous solution.

The time of reaction depends upon the nature of the ketone and the amine salt, and on the boiling point of the solvent employed. Since we used paraformaldehyde in the preparation of our compounds, it was necessary to choose an organic solvent for the reaction. Ethanol was tried first, but no reaction occurred in this solvent, the unchanged ketone being recovered. Isoamyl alcohol, having a relatively high boiling point (130°) was used by van de Kamp and Mosettig (44) in condensations involving acetylphenanthrenes and proved highly satisfactory; it so proved with 2-acetyl-fluorene. The condensations in this solvent took place with most of the amines tried, the time of reaction varying from 15 minutes to 6 hours.

(b) Compounds with a suitable active hydrogen atom may be of several types. Compounds with a hydrogen atom on a carbon alpha to a carbonyl group, such as ketones, aldehydes, acids, and esters have proved satisfactory in numerous cases (51). Phenols and acetylenes, as well as alpha-picolines and quinaldines, also have proved to be satisfactory (51).

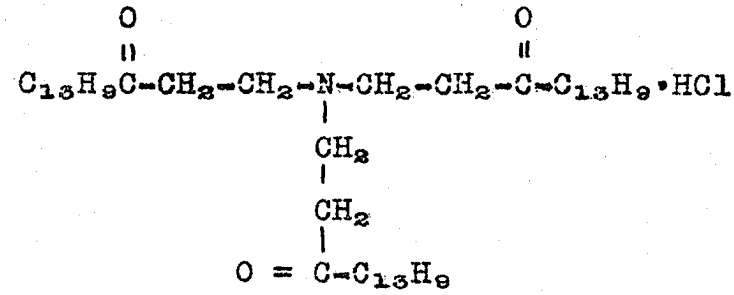
As previously mentioned, the fluorene compound used as a source of active hydrogen in this investigation was 2-acetylfluorene.



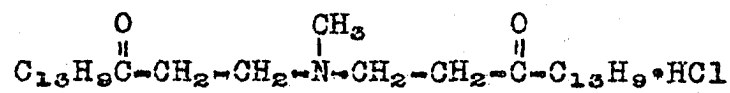
(c) Amines used in the Mannich reaction are generally in the form of the hydrochloride. Hydrogen chloride seemingly aids in the depolymerization of the paraformaldehyde.

In preparing the compounds from 2-acetylfluorene we found that ammonium chloride and the primary amine hydrochlorides used gave rather low yields of the condensation products. In some cases, namely with ammonium chloride and with monomethylamine hydrochloride, tertiary amines

were found. Thus 2-acetylfluorene, paraformaldehyde, and ammonium chloride yielded a product that was identified as tri-3-(1,2'-fluoryl-1-oxopropyl) amine hydrochloride,



while monomethyl amine hydrochloride yielded a small amount of methyl-di-(1,2'-fluoryl-1-oxopropyl) amine hydrochloride.



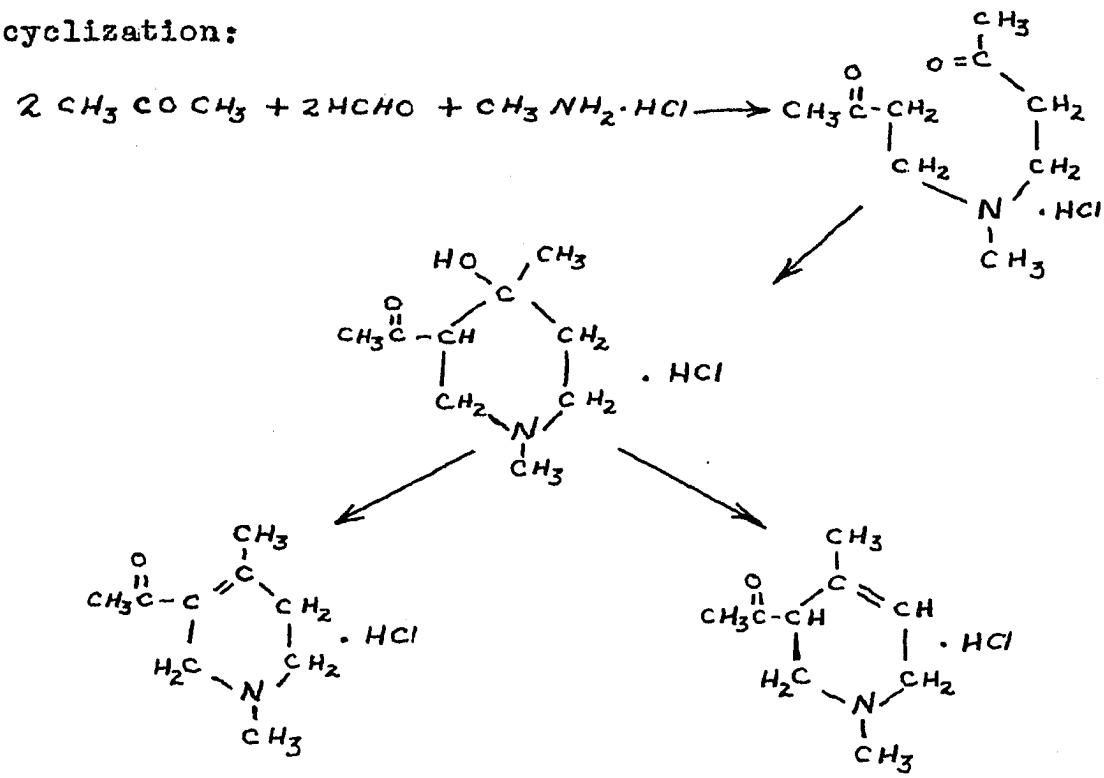
Secondary amines, in most cases, proved much more satisfactory. Diethylamine hydrochloride, however, gave no condensation product, the amine hydrochloride being recovered. This is not unusual since diethylamine seems to be less reactive than other secondary amines. Kermack and Muir (54) have reported that the condensation does not take place with diethylamine, ethylmethyl ketone, and formaldehyde. Furthermore, it has been reported that 2-acetylfuran and formaldehyde react normally with the salts of dimethylamine, dipropylamine, di-n-butylamine, and diethanolamine but <u>not</u> with the salt of diethylamine (55).

The amines which gave the best results in this investigation, with respect to yield, time of reaction,

ease of isolation of the product, and local anaesthetic activity, were the heterocyclic compounds, piperidine hydrochloride and morpholine hydrochloride.

3. Secondary Products of the Reaction.

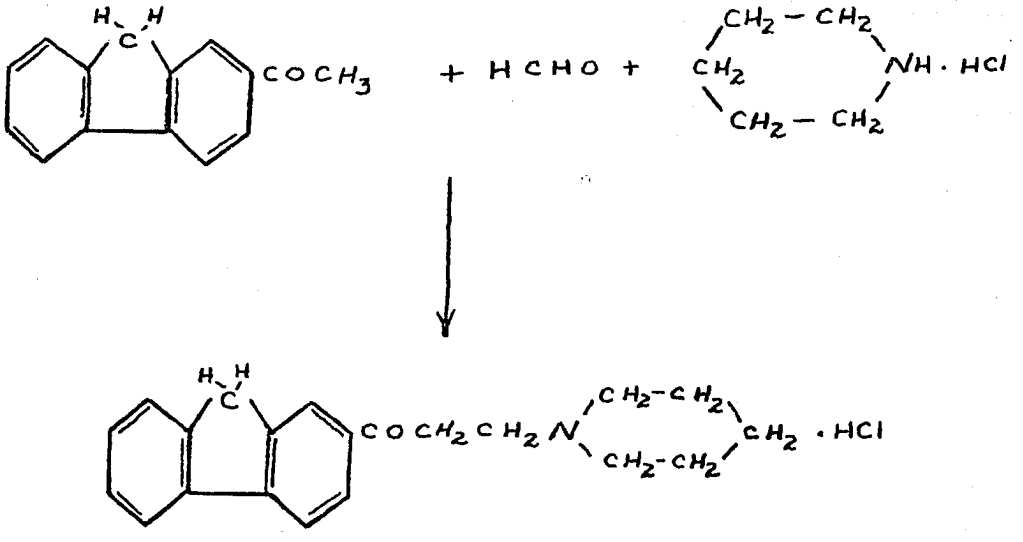
The primary products of Mannich condensations have already been described. It should be noted, however, that the primary products derived from two molecules of ketone, two molecules of formaldehyde, and one molecule of primary amine are unstable and readily undergo cyclization. Mannich and Ball (56) found, for example, that the compound obtained from acetone, formaldehyde, and methylamine underwent such cyclization:



We were unable to isolate and identify any such products from the reactions carried out in this investigation, although methyl-, ethyl-, allyl-, and benzylamines, all primary, were used.

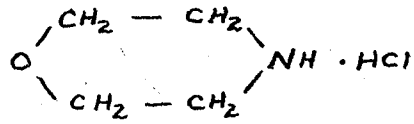
3. Mannich Condensation with 2-Acetylfluorene.

We have found in this investigation that the Mannich reaction proceeds very well with 2-acetylfluorene in most cases. Outstanding among these is the reaction with piperidine hydrochloride and with morpholine hydrochloride. For example, with piperidine hydrochloride the reaction,

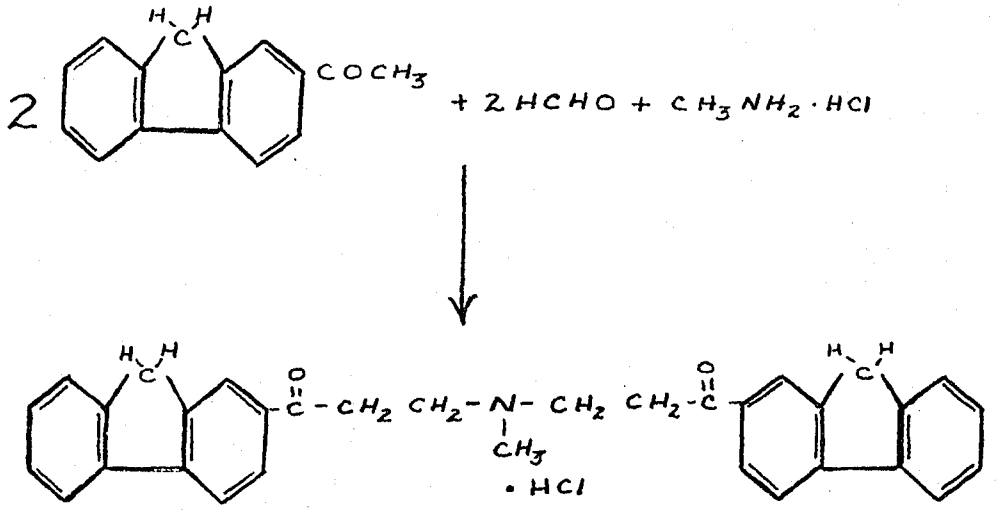


2'-(3-Piperidino-1-oxopropyl)-Fluorene Hydrochloride

proceeded very smoothly in isoamyl alcohol. The yields were high (aprox. 80%), and the product was readily recrystallized from ethyl alcohol. The compound was noticeably anaesthetic when applied to the tip of the tongue. We found the same things to be true of the reaction with morpholine hydrochloride.



Both monomethyl and dimethylamine hydrochloride condensed as was expected. The yields were rather low in both cases, probably due to the fact that both products were so very soluble in the alcohol used for recrystallization. We found, however, that part of the product from the condensation of monomethylamine hydrochloride with formaldehyde and 2-acetyl-fluorene would not dissolve in alcohol. Although no attempt was made to purify and establish the structure of this insoluble compound, we believe that it was the tertiary amine resulting from the condensation of two molecules of formaldehyde, two molecules of 2-acetyl-fluorene and one molecule of monomethylamine hydrochloride.



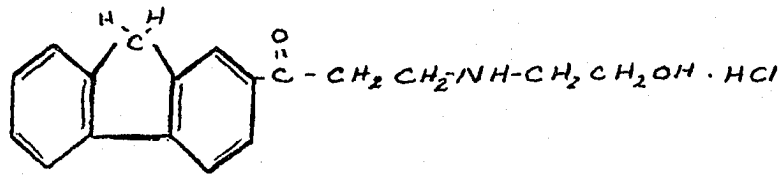
Benzylamine, when used in the Mannich reaction with 2-acetylfluorene, gave a white crystalline compound that was insoluble in alcohol. This led us to believe that a tertiary amine had been formed in this case too, since all the other primary condensation products had been soluble in alcohol. The benzylamine product, although not soluble in alcohol, was soluble in glacial acetic acid. We had previously proved that the compound isolated from the reaction with ammonium chloride was the tertiary amine, insoluble in alcohol but soluble in glacial acetic acid. Analysis proved, however, that this conclusion in regard to the benzylamine product was incorrect and that we had really obtained the secondary amine.

A condensation between 2-acetylfluorene, formaldehyde and ethylamine hydrochloride took place readily, despite the failure of diethylamine to react. The compound was very soluble in alcohol and had a strong local anaesthetic action.

Some difficulty was encountered in the attempted preparation of 2'-(3-diethanolamino-1-oxopropyl) fluorene hydrochloride. A number of trials were made before we were able to isolate a crystalline product from the condensation, the compound usually separating from the solvent as a heavy oil. In one trial we attempted the condensation using no solvent other than the diethanolamine hydrochloride itself. The 2-acetylfluorene, paraformaldehyde and diethanolamine hydrochloride were heated in a round-bottom flask placed in an oil bath heated to 120°. The condensation seemed to occur, for we noticed droplets of water collected in the neck of the flask. The product was a mass of "taffy-like" material which we were unable to purify by recrystallization.

A solid product was finally isolated using isoamyl alcohol as a solvent for the condensation, but the yield was so low that no further attempts were made to prepare the compound. When this material was analyzed, however, there appeared a discrepancy between the calculated and found values for nitrogen and chlorine. This difference could not be accounted for by impurities since a second recrystallization did not change the melting point. On the other hand, if an

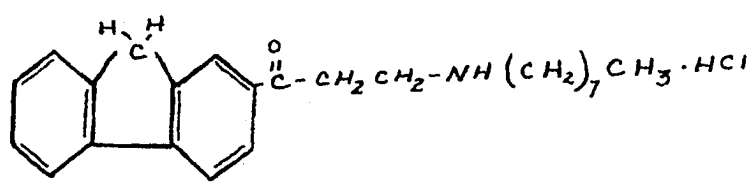
ethanol radical was replaced by a hydrogen atom during the course of the reaction 2'-(3-ethanolamino-1-oxopropyl) fluorene hydrochloride would be the final product.



The calculated values for nitrogen and chlorine for this compound agree very well with the values found.

Two other amines, di-n-propylamine and allylamine were condensed with 2-acetylfluorene and formaldehyde. Both of them yielded white crystalline products which were soluble in alcohol and which had strong local anaesthetic action on the tongue. The di-n-propylamine compound was, of the two, much more soluble in water.

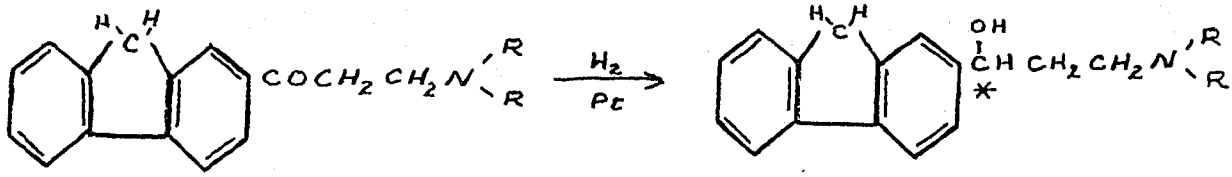
An interesting phenomenon was observed when di-n-octylamine was used. The compound isolated from the reaction proved to be a secondary amine hydrochloride rather than a tertiary amine hydrochloride, judging from the chloride and nitrogen analyses.



This indicated that during the reaction at 130°, one of the octyl groups was split off and replaced by a hydrogen atom, and helps to substantiate the replacement of an ethanol radical by hydrogen in the condensation of 2-acetylfluorene with formaldehyde and diethanolamine hydrochloride.

C. REDUCTION OF THE KETO-AMINES.

In order to prepare compounds that might have analgesic value (57) we reduced a few of the ketones derived from the Mannich condensation to secondary alcohols:



The reduction in each case was carried out with hydrogen, using platinum oxide catalyst. The reaction was slow, often taking as much as 24-36 hours. The alcohols were more soluble in ethyl alcohol than the corresponding ketones. It was necessary to add ether to the ethyl alcohol solution in order to precipitate the alcohols.

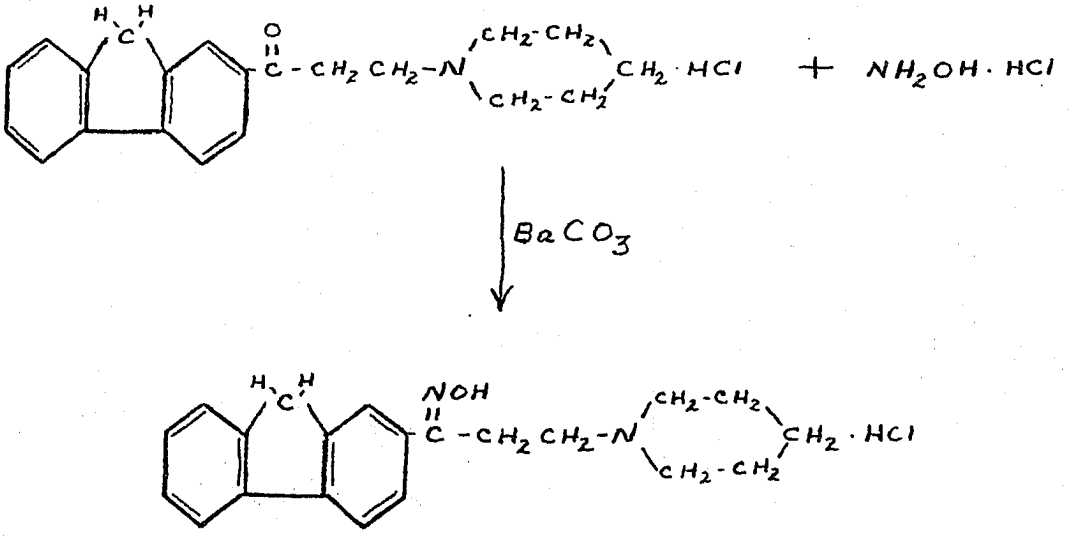
Although the alcohols have an asymmetric carbon atom (marked by an asterisk in the formula), no attempt was

made to resolve the d and l forms. If it should be found that any of these secondary alcohols has analgesic action, we believe that it would then become advisable to separate these isomers with a view to finding whether or not one form is more active than the other.

D. OTHER DERIVATIVES OF THE KETO-AMINES.

1. 2'-(3-Piperidino-1-oximidopropyl) fluorene hydrochloride.

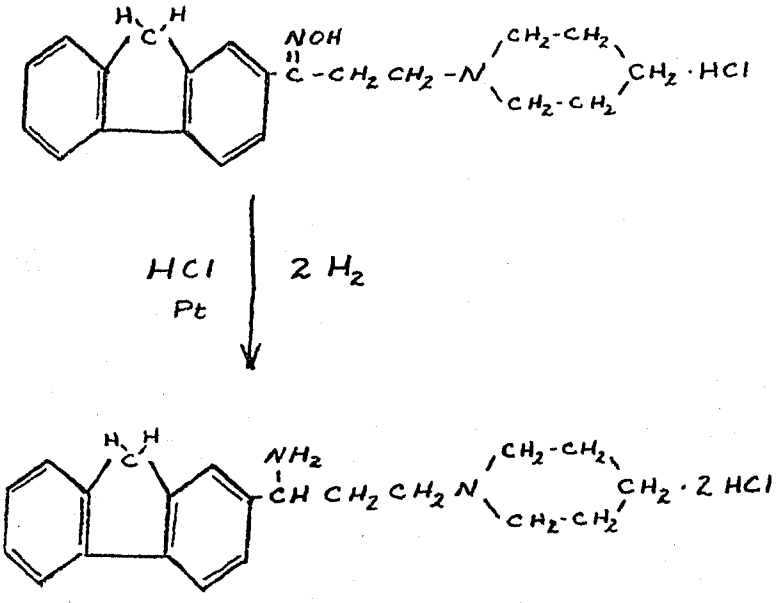
Since the keto-amines prepared by the Mannich reaction showed some local anaesthetic properties upon topical application to the tip of the tongue, and yet were not very soluble in water, it was felt that we might enhance the anaesthetic properties by converting the compounds to a more soluble form. The first method tried was to convert the ketone to a ketoxime which we expected to be more soluble in water. The piperidine derivative was used, since it was so easily prepared and showed some local anaesthetic properties. The oxime was prepared by reacting one mol. of the ketone with 1.5 mol. hydroxylamine hydrochloride, using barium carbonate to set free the hydroxylamine for the reaction:



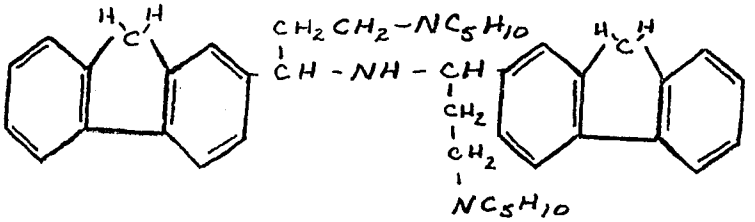
The product no longer showed any anaesthetic action on the tip of the tongue, nor were we able to notice an appreciable difference in water solubility between the ketone and the ketoxime.

2. 2'-(3-Piperidino-1-aminopropyl) fluorene dihydrochloride.

As a matter of interest we reduced a sample of the ketoxime to the corresponding amine. The reduction was carried out catalytically, using platinum oxide as a catalyst and ethyl alcohol as the solvent:



An excess of hydrochloric acid was added to the solution in order to form the dihydrochloride salt of the reduced compound and to prevent the formation of the secondary amine:

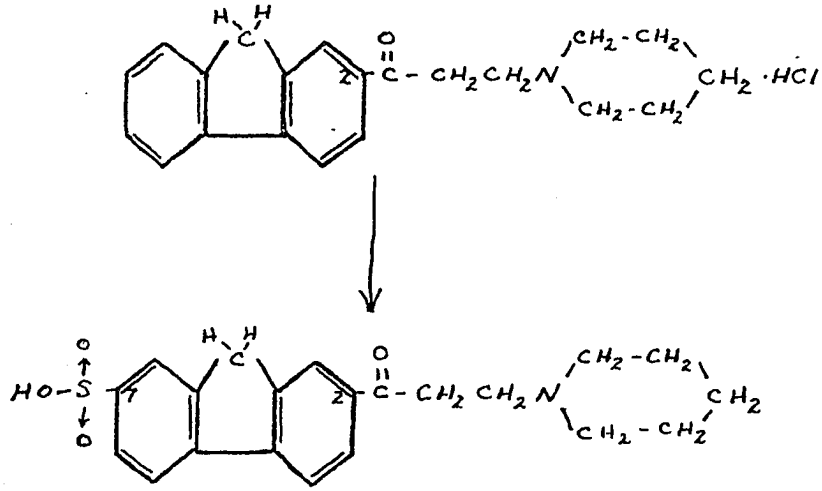


The compound that was isolated from the alcohol solution by precipitation with ether was much more soluble in alcohol, and was somewhat more soluble in water than the oxime. It had no local anaesthetic action on the tongue.

It was also found that the reduced compound could be isolated from alcohol solution as the picric acid salt by adding an excess of a saturated solution of picric acid in alcohol. The compound thus prepared was a yellow crystalline solid having a sharp melting point at 237°, but was much less water soluble than the hydrochloride had been.

3. Potassium 2'-(3-Piperidino-1-oxopropyl) fluorene-7'-sulfonate.

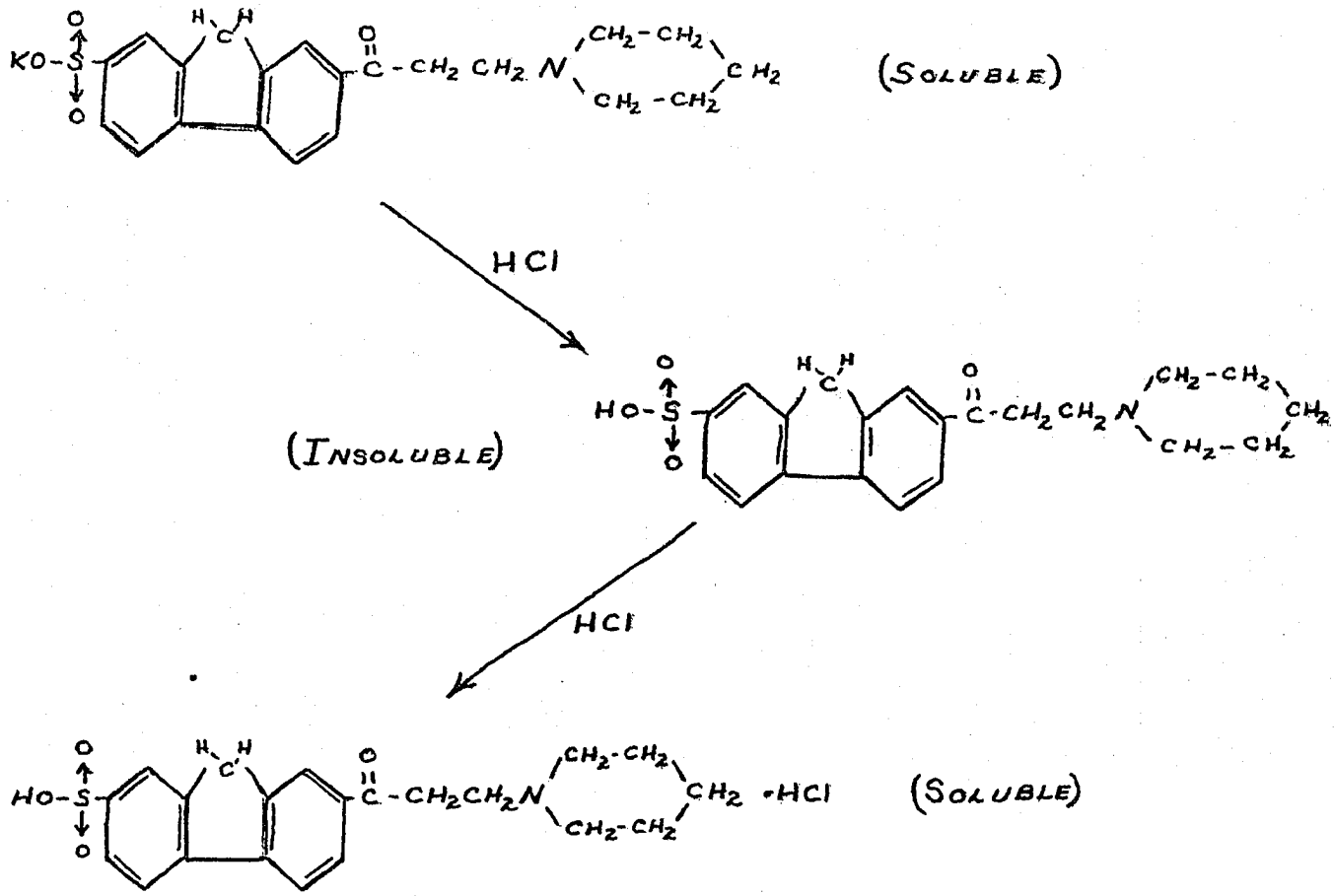
Another method commonly used to increase the water solubility of an organic compound is to prepare a sulfonic acid derivative. It has been found (58) that fluorene carrying one substituent in the 2 position will usually substitute the sulfonic acid group in the 7 position. Since we were starting with a fluorene ring substituted in the 2 position, we therefore expected that an entering SO_3H group would go to the 7 position.



Courtot (58) has reported that 2-nitrofluorene is easily sulfonated by concentrated sulfuric acid at room temperature.

The 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride was added to sulfuric acid and stirred mechanically for 2 hours at room temperature. When the solution was poured over cracked ice, the sulfonic acid derivative separated as a fine white colloid which we were unable to separate by filtration. In order to isolate the compound it was converted into the potassium salt and salted out with KCl. The final product was fairly soluble in water but showed no local anaesthetic action on the tongue. It may be found, however, that it possesses analgesic or perhaps antispasmodic activity.

With hydrochloric acid, the compound underwent a series of reactions which seemed to prove that the compound we had prepared really was a sulfonic acid. When hydrochloric acid was added dropwise to a hot aqueous solution of the potassium sulfonate, a fine white precipitate appeared, which soon redissolved when more hydrochloric acid was added. It seems to us that these observations might be accounted for in the following equations:



The soluble potassium salt is converted to the insoluble free sulfonic acid by the action of the hydrochloric acid. The sulfonic acid is in turn converted to the soluble amine hydrochloride when still more hydrochloric acid is added.

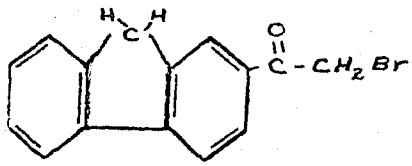
We also prepared sodium-2'-(3-morpholino-1-oxopropyl) fluorene-7'-sulfonate from 2'-(3-morpholino-1-oxopropyl) fluorene hydrochloride in a manner similar to that described above, except that sodium carbonate, in place of potassium

hydroxide, was used to neutralize the sulfuric acid solution. The product was fairly soluble in water but had no noticeable local anaesthetic properties. It will, however, be tested for analgesic and antispasmodic properties.

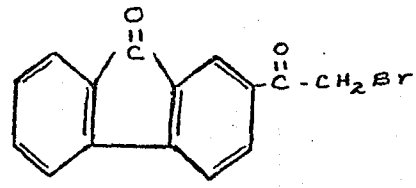
E. AMINES DERIVED FROM OMEGA-HALOGENATED KETONES.

1. Omega-bromo-2-acetylfluorene and fluorenone.

In order to synthesize the second group of non-nuclear amino derivatives of fluorene we prepared the omega-bromo ketones by a method described by Mosettig and van de Kamp (39) for 2-, 3-, and 9-omega-bromoacetyl-phenanthrene. The ketones, 2-acetylfluorene or 2-acetylfluorenone, were suspended in dry ether at 0° and treated with bromine (mol. for mol.). The bromine color faded rapidly as the reaction proceeded and the omega-bromo ketone separated. The halogenated ketones were purified by recrystallization from alcohol. The omega-bromo-2-acetylfluorene was a white crystalline solid which darkened after standing in bright light for a few hours. It was insoluble in water, slightly soluble in ether and in cold alcohol. Omega-bromo-2-acetylfluorenone had the characteristic bright yellow color of 2-acetylfluorenone. Its solubility was about the same as that of the fluorene compound.

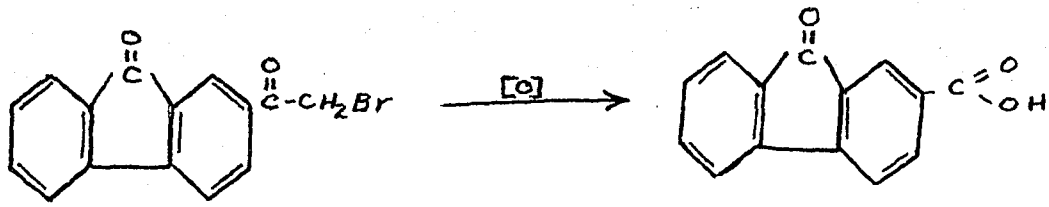


ω-Bromo-2-Acetyl Fluorene



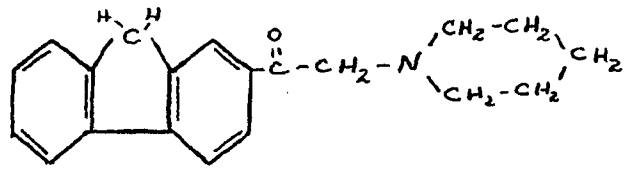
ω-Bromo-2-Acetyl Fluorenone

In order to prove the structure of the latter compound, a small portion of it was oxidized with sodium dichromate to the known fluorenone-2-carboxylic acid (59) which gave no qualitative test for halogen.

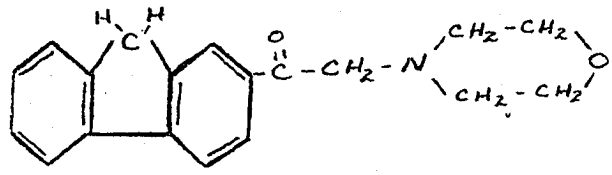


2. Omega-Piperidino and Morpholino-2-acetylfluorene.

Using omega-bromo-2-acetylfluorene we prepared omega-piperidino-2-acetylfluorene hydrochloride and omega-morpholino-2-acetylfluorene hydrochloride.



ω-Piperidino-2-Acetyl Fluorene



ω-Morpholino-2-Acetyl Fluorene

The amines were condensed with the omega-bromo-2-acetylfluorene in absolute ether, 2 mols of the amine being used for each mol. of the bromo compound. It was found that unless anhydrous solvents were used, the hydrochlorides separated as oils which were difficult to crystallize. If, however, the free base was prepared in absolute ether, the ether evaporated, and the compound redissolved in anhydrous alcohol, a crystalline hydrochloride could be obtained by adding an absolute ether solution of hydrogen chloride.

Both hydrochlorides were white crystalline solids, slightly soluble in water and having a mild local anaesthetic action on the tongue. No attempts have yet been made to reduce these ketones to the secondary alcohols.

III EXPERIMENTAL

A. PREPARATION OF THE METHYL KETONES.

1. Preparation of 2-Acetylfluorene (19) (60).

Fluorene (80 g., 0.48 mol.) was dissolved in dry carbon disulfide (350 ml.) at room temperature in a one liter, three necked, round-bottomed flask, equipped with a mercury sealed mechanical stirrer with a strong motor, a dropping funnel and a reflux condenser connected to a hydrogen chloride trap. The contents of a one-quarter pound bottle of anhydrous aluminum chloride (approximately 113 grams, 0.85 mol) was added and the mixture stirred thoroughly until it became homogeneous and a dark red color had developed. By means of the dropping funnel, 37.8 ml. (0.41 mol) of pure, re-distilled acetic anhydride was added dropwise. A pan of warm water was used to warm the flask and initiate the reaction if it did not start at room temperature. Once the reaction had started, the addition of acetic anhydride was adjusted to such a rate that the heat of reaction kept the carbon disulfide in gentle reflux. The addition required about 45 to 55 minutes. When the addition was complete, stirring and refluxing on a 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. After the product had been washed with two 50 ml. portions of carbon disulfide it was air dried and then hydrolyzed by adding it in portions to a stirred mixture of 800 ml. of water and 30 ml. of concentrated hydrochloric acid. The crude 2-acetylfluorene was filtered and washed several times with water. In order to purify it, the crude product (110 grams) was boiled with 800 ml. of 95% ethanol and 20 grams of animal charcoal for two hours. The mixture was filtered through a hot water funnel. The filtrate, slightly orange in color, was allowed to cool and the 2-acetylfluorene crystallized out. The yield was 62.5 grams (73% theoretical) and melted at 127-128°. A second re-crystallization yielded a pure product melting at 132°C. (60).

2. Preparation of 2-Acetylfluorenone (19).

Ninety grams of crude 2-acetylfluorene was dissolved in 650 ml. of glacial acetic acid by heating in a five liter flask equipped with a rubber stopper carrying a reflux condenser and a one inch glass tube, the latter to facilitate the addition of sodium dichromate. Commercial

sodium dichromate (90 grams) was ground to a coarse powder and added in small portions to the hot acetic acid solution of 2-acetylfluorene. The reaction proceeded vigorously at first but soon moderated, permitting the dichromate to be added at a faster rate. About thirty minutes were required for complete addition. The mixture was refluxed for two hours and the hot contents were poured into a four gallon crock containing about two gallons of hot water. This mixture was allowed to cool over night, then filtered through a large Buchner funnel. The insoluble material on the Buchner funnel was washed with water containing a little hydrochloric acid (1 to 100) to remove the chromium salts. The well washed material was placed in a beaker containing 200 ml. of 5% potassium hydroxide and heated to 80° in order to remove any carboxylic acid resulting from the oxidation. The suspension was filtered and the product washed well with water. The yield of the crude 2-acetylfluorenone was 75.3 grams and melted at 147-148°. The crude product was purified by dissolving it in 500 ml. of boiling 95% ethanol with 10 grams of animal charcoal and refluxing for one hour. The yield was 30 grams; m.p. 153°.

B. PREPARATION OF THE AMINE HYDROCHLORIDES.

1. <u>By precipitation from ether solution</u>.

Those amines which were available as liquids at room temperature, and which were soluble in ether as the free base while insoluble as the hydrochloride, were easily converted to the hydrochloride by precipitation from ether solution with anhydrous hydrogen chloride. The free base was dissolved in absolute ether and the solution cooled to 0° in an ice bath. Pure, dry hydrogen chloride, prepared by dropping concentrated hydrochloric acid into concentrated sulfuric acid (61), was passed into the solution until the solution gave an acid reaction. The hydrochloride precipitated out, was isolated, washed with dry ether and dried in a vacuum desiccator over concentrated sulfuric acid. The amine hydrochlorides listed in the following table were prepared in this manner.

AMINE HYDROCHLORIDES

AMINE HYDROCHLORIDE	MELTING POINT		LIT. REF.
	Found	Lit.	
(a) Diethyl	221-222°	223.5°	(62)
(b) Allyl	105-108°	105-110°	(63)
(c) Benzyl	252-254°	255-256°	(64)
(d) Piperidine	240-241°	243.5°	(65)
(e) Morpholine	174-175°	175-176°	(66)

2. By neutralization with hydrochloric acid.

(a) Ethylamine hydrochloride was prepared from a 30% solution of ethylamine. To fifty ml. of the solution was added just enough concentrated hydrochloric acid to make the solution slightly acid. This solution was evaporated to a volume of 20 ml. and cooled to 0° in an ice bath. The ethylamine hydrochloride which crystallized from the solution was collected and was dried in a vacuum desiccator over sulfuric acid; m.p. 106-107°. Curtius and Hille (67) give 109°.

(b) Diethanolamine hydrochloride was prepared by adding concentrated hydrochloric acid (16 ml.) dropwise to 21 grams (0.2 mol) of redistilled commercial diethanolamine. During the addition of the acid the diethanolamine was stirred mechanically and cooled in an ice bath. When all of the hydrochloric acid had been added, the solution, which had become red-brown in color and slightly acid, was heated on a hot plate until most of the water had evaporated. The hot solution was heated in an oven at 120° for 24 hours, removed, and cooled in a vacuum desiccator. The product was a brown viscous liquid. No melting point for diethanolamine hydrochloride is reported in the literature, but it is described as a dark thick sirup (68).

(c) Di-n-propylamine hydrochloride was prepared by neutralizing pure di-n-propylamine with concentrated hydrochloric acid and evaporating the excess water at 120° in an oven. Although the hydrochloride was insoluble in ether, it could not be prepared as a crystalline product by saturating an ether solution with dry hydrogen chloride since it came out of solution as an oil.

The white crystalline hydrochloride melted at 274-275°. No melting point could be found in the literature.

Analysis: Subst., 0.1006; 0.0535 N HCl, 15.66 ml.

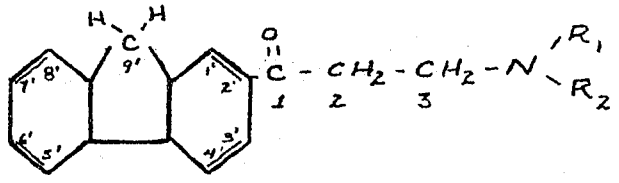
Calc. for $C_6H_{16}Cl$ N : N, 11.71

Found: N, 11.66

3. Preparation of di-n-octylamine hydrochloride.

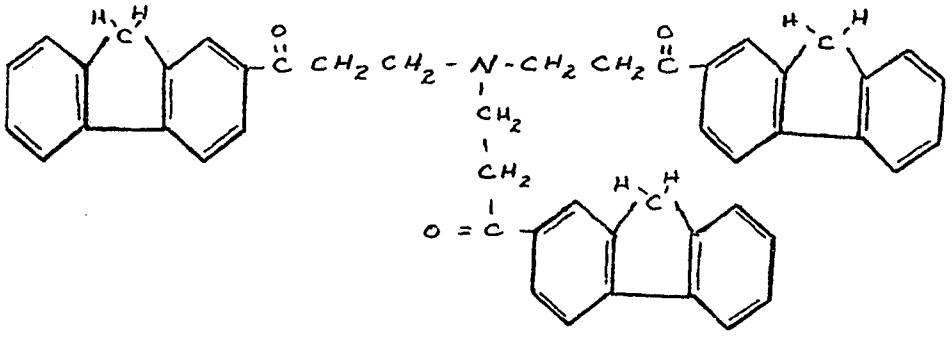
Di-n-octylamine (commercial) is a straw colored oily liquid, miscible with ether. Its hydrochloride was prepared by passing dry hydrogen chloride into an absolute ether solution of the free base at the temperature of an ice bath. The color of the solution gradually darkened until it became dark brown at the neutral point. The hydrochloride was soluble in ether and did not crystallize out. The ether was evaporated, by warming on a water bath, leaving a dark oily liquid as the final product.

C. PREPARATION OF AMINES OF 2'-(1-OXOPROPYL) FLUORENE.



The apparatus used in the preparation of the 2'-(1-oxopropyl) fluorene amines was the same in each case. A three-necked, round-bottomed, flask (500 ml.) was equipped with a mercury sealed Hershberg stirrer (61), and a reflux condenser. The flask, set on an asbestos covered wire gauze, was heated either by means of an electric hot plate or by a Bunsen burner, low type.

1. Preparation of tri-3-(1,2'-fluoryl-1-oxopropyl) amine hydrochloride and its free base.



Into the three-necked flask was placed 5.2 grams (0.025 mol) 2-acetylfluorene, 1.13 grams (0.0375 mol) paraformaldehyde and 2.02 grams (0.0375 mol) ammonium chloride. Twenty five ml. of isoamyl alcohol was added and the mixture stirred and refluxed for three hours. During the first few minutes of refluxing most of the solid material went into solution but part of it, probably the ammonium chloride, remained undissolved. At the end of the refluxing period more solid material had precipitated. The flask and its contents were allowed to cool and then filtered. The crude product was washed with a little alcohol followed by some water to dissolve the excess ammonium chloride. The washed product, insoluble in alcohol, was recrystallized from glacial acetic acid. The white crystalline compound melted at 248-249° and was insoluble in water and in alcohol.

In order to determine whether one, two, or three acetylfluorene units had reacted with each ammonium chloride unit we analyzed the hydrochloride for nitrogen and determined the molecular weight of the free base. The free base was prepared from 0.5 gram of the hydrochloride by suspending it in boiling alcohol and adding concentrated ammonium hydroxide drop by drop until a clear solution was obtained. The solution was cooled and the free base separated as a white crystalline solid melting at 213°. Only slightly soluble in water, it had no local anaesthetic action on the tongue.

Analysis: Subst., 0.1693; 0.05033 N HCl, 4.91 ml.

Calc. for $C_{48}H_{40}O_3$ N Cl : N, 1.96

Found: N, 2.04

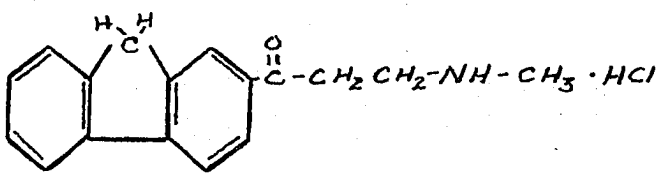
Molecular weight by camphor method:

Subst., 0.0174; camphor, 0.1283; $\Delta T = 8°$

Calc. for $C_{48}H_{39}O_2$ N : M.W., 678

Found: M.W., 675

2. Preparation of 2'-(3-methylamino-1-oxopropyl) fluorene hydrochloride.



Ten grams (0.15 mol) monomethylamine hydrochloride, 20.8 grams (0.10 mol) 2-acetylfluorene, 4.5 grams (0.15 mol) paraformaldehyde, and 60 ml. isoamyl alcohol were mixed in a three-necked flask. The mixture was heated gently until the 2-acetylfluorene had dissolved and the monomethylamine hydrochloride had melted. The mixture was stirred and refluxed for 3 hours, during which time most of the monomethylamine hydrochloride dissolved. Upon cooling, a crystalline product separated, which was filtered off and

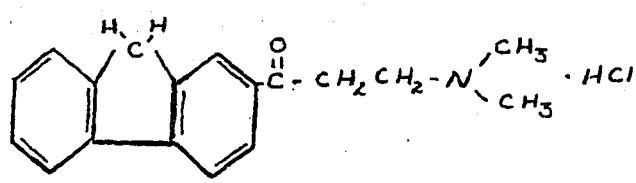
washed with acetone. The crude product, weighing 28 grams, was purified by refluxing it with 1200 ml. of alcohol, filtering off the undissolved residue (2 grams), and allowing the filtrate to cool. The 2'-(3-methylamino-1-oxopropyl) fluorene hydrochloride which crystallized from the solution weighed 12 grams (27.9% theoretical) and melted at 217-218°.

Analysis: Subst., 0.2146; 0.1085 g. AgCl

Calc. for $C_{17}H_{18}O\ N\ Cl$: Cl, 12.36

Found: Cl, 12.50

3. Preparation of 2'-(3-dimethylamino-1-oxopropyl) fluorene hydrochloride.



A mixture of 20.8 grams 2-acetylfluorene (0.10 mol), 12.3 grams (0.15 mol) dimethylamine hydrochloride, 4.5 grams (0.15 mol) paraformaldehyde and 60 ml. of isoamyl alcohol was refluxed with stirring in a three-necked flask for a period of three hours. If the product did not crystallize out on cooling, the solution was heated for 3-5 minutes without the condenser in order to remove some of the water formed in the reaction. The crude product that separated on cooling (26 grams)

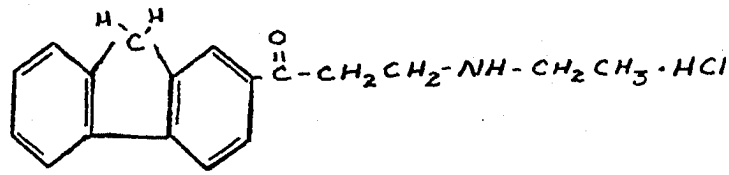
was washed with a little acetone and recrystallized from 275 ml of alcohol. The pure 2'-(3-dimethylamino-1-oxopropyl) fluorene hydrochloride recovered weighed 12.8 grams (32.2% theoretical) and melted at 187-188°.

Analysis: Subst., 0.2011; AgCl, .0950

Calc. for $C_{18}H_{20}OCl\ N$: Cl, 11.74

Found: Cl, 11.69

4. Preparation of 2'-(3-ethylamino-1-oxopropyl) fluorene hydrochloride.



Using the apparatus previously described 10.4 grams (0.05 mol) 2-acetylfluorene, 2.25 grams paraformaldehyde (0.075 mol), 6.11 grams ethylamine hydrochloride and 40 ml. of isoamyl alcohol were refluxed for six hours. Two layers were formed during refluxing requiring rapid stirring to insure a reaction. Upon cooling the solution, the crude 2'-(3-ethylamino-1-oxopropyl) fluorene hydrochloride separated and was washed with a little acetone. Recrystallization of the product from ethyl alcohol gave 6.62 grams (40% theoretical)

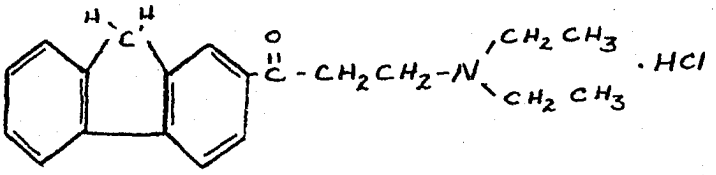
of a white crystalline (plates) product melting at 225-226°.

Analysis: Subst., 0.1433; 0.05130 N HCl, 9.00 ml.

Calc. for $C_{18}H_{20}OCl$ N : N, 4.64

Found: N, 4.51

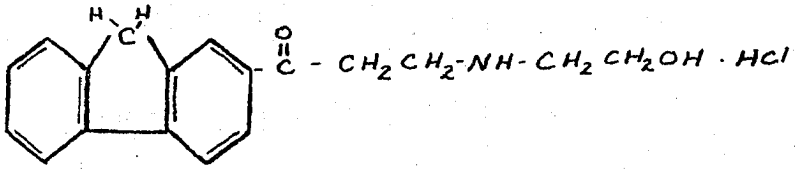
5. Attempted preparation of 2'-(3-diethylamino-1-oxopropyl) fluorene hydrochloride.



A mixture of 10.4 grams (0.05 mol) 2-acetylfluorene, 2.25 grams (0.075 mol.) paraformaldehyde, 8.17 grams (0.075 mol.) diethylamine hydrochloride, and 40 ml. isoamyl alcohol was refluxed with stirring for 6 hours. When refluxing was stopped, no material crystallized out until the solution had been boiled without a condenser for 3-5 minutes. The white product that crystallized after cooling was very soluble in alcohol and in water; after washing with acetone and drying it melted at 220-221°. Its solubility and its melting point led us to believe that the crystalline product was unchanged diethylamine hydrochloride. The crystals, however, were

large leaflets which did not take up water on standing in air as does the diethylamine hydrochloride precipitated from ether by dry hydrogen chloride.

6. Preparation of 2'-(3-ethanolamino-1-oxopropyl) fluorene hydrochloride.



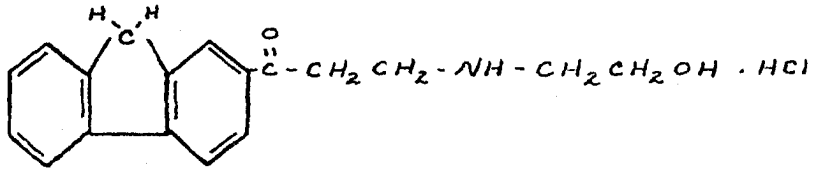
To ten and four tenths grams (0.05 mol.) 2-acetylfluorene, 2.25 grams (0.075 mol.) paraformaldehyde and 60 ml. isoamylalcohol was added 10.61 grams (0.075 mol.) diethanolamine hydrochloride. The mixture was refluxed with stirring for four hours, becoming very dark in color. No solid material separated even though the water was removed by distillation and the solution allowed to stand overnight. The solution was poured into a 400 ml. beaker and warmed on a hot plate to about 50°. Pure dry acetone was added to the warm solution until it became slightly cloudy. Upon cooling, approximately 4 grams of a brown solid material separated. The crude product was dissolved in 25 ml. of ethyl alcohol and refluxed with 2 grams of animal charcoal. The solution

was filtered while hot; the light brown filtrate yielded about 1.5 grams (8.3% theoretical) of a slightly brown crystalline solid melting at 201-202°.

The product was very soluble in alcohol and slightly soluble in water and had little or no anaesthetic effect on the tongue. The material was prone to come out of solution as an oil which resisted attempts to crystallize it.

In one trial 50 ml. of methyl cellosolve was used as a solvent in place of the isoamyl alcohol. The product was isolated by adding pure dry acetone, care being taken to avoid an excess which would cause the product to separate as an oil. The yield in this trial was no better than in the previously described method.

When the compound was analyzed for nitrogen and chlorine it became evident that either the compound was not pure or that some compound other than that expected had been formed. Recrystallization again from ethyl alcohol failed to change the melting point, indicating that the compound was pure. The other possibility, formation of a different compound, seemed to be confirmed since the analysis agreed very well with the calculated analysis for 2'-(3-ethanolamino-1-oxopropyl) fluorene hydrochloride



This would indicate the loss of one ethanol radical ($-CH_2CH_2OH$) during the reaction.

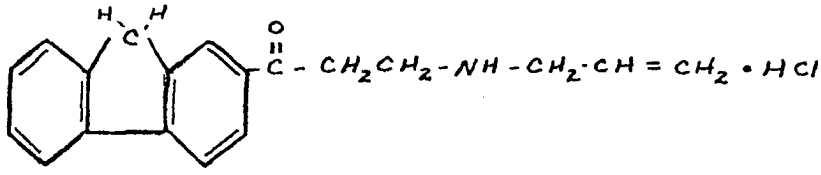
Analysis : For N; Subst., 0.0812; 0.05130 N HCl, 5.30 ml.
For Cl, Subst., 0.1361; 0.0614 AgCl

(Diethanolamine) Calc. for $C_{20}H_{24}O_3$ N Cl : N, 3.87; Cl, 9.80

(Monethanolamine) Calc. for $C_{18}H_{20}O_2$ N Cl : N, 4.42; Cl, 11.15

Found: N, 4.69; Cl, 11.16

7. Preparation of 2'-(3-allylamino-1-oxopropyl) fluorene hydrochloride.



Into a three-necked, round-bottomed flask were introduced 6.24 grams 2-acetylfluorene (0.03 mol), 1.35 grams (0.045 mol.) paraformaldehyde, 3.55 grams (0.045 mol.) allylamine hydrochloride and 30 ml. isoamyl alcohol. The mixture was refluxed for two and one-half hours and cooled

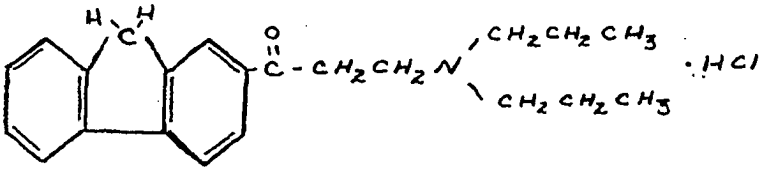
to room temperature. The product, which crystallized out on cooling, was separated from the mother liquor, washed with a little dry acetone and recrystallized from alcohol. The purified product was a white crystalline solid, soluble in alcohol, very slightly soluble in water, and had a melting point of 214-215°. The yield was 5.0 grams (53.2% theoretical). Topical application of a few mgm to the tip of the tongue produced noticeable local anaesthesia accompanied by a strong acid taste.

Analysis: Subst., 0.1977; 0.0533 N HCl, 13.18

Calc. for: $C_{18}H_{20}O$ N Cl; N, 4.49

Found: N, 4.79

8. Preparation of 2'-(3-di-n-propylamino-1-oxopropyl) fluorene hydrochloride.



A mixture of 10.4 grams (0.05 mol.) 2-acetylfluorene, 2.24 grams paraformaldehyde (0.075 mol.) and 10.3 grams (0.075 mol.) di-n-propylamine hydrochloride was refluxed for

four hours, using 40 ml. isoamyl alcohol as a solvent. The solution was cooled to 50° and dry acetone was added until a crystalline product had separated. The solid product was isolated and washed with a little absolute ether. In order to purify it, the crude product was dissolved in 200 ml. of boiling absolute alcohol. Absolute ether was added slowly to the alcohol solution until cloudiness persisted. The pure 2'-(3-di-n-propylamino-1-oxopropyl) fluorene hydrochloride separated in the form of fine white crystals from the alcohol-ether solution after 2 hours. The yield was about 20% theoretical.

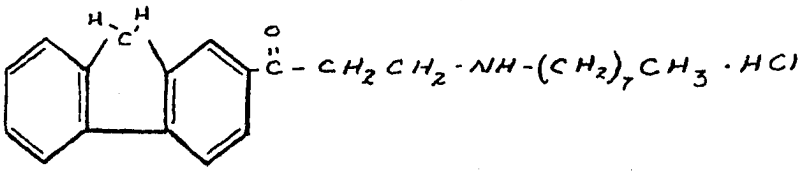
The product was a white crystalline solid melting at 150-151°. It was very soluble in alcohol and fairly soluble in water. A few crystals rubbed on the tip of the tongue produced marked local anaesthesia, having an onset time of 1.5 min. and a duration of 30-45 minutes.

Analysis: Subst., 0.2419; AgCl, 0.0953

Calc. for: $C_{22}H_{28}OCl\ N$; Cl, 9.91

Found: Cl, 9.75

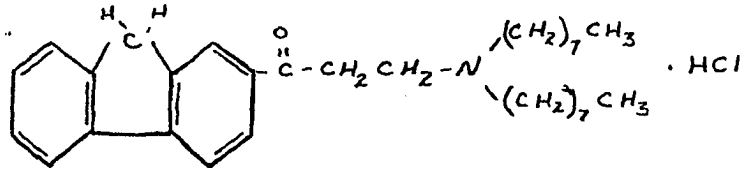
9. <u>Preparation of 2'-(3-n-octylamino-1-oxopropyl) fluorene hydrochloride</u>.



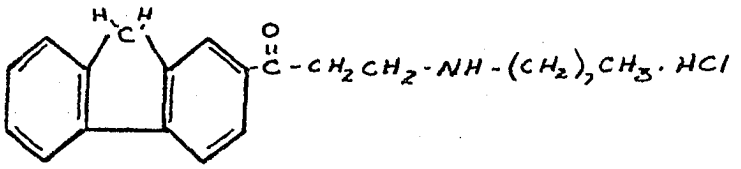
To a mixture of 10.4 grams (0.05 mol) 2-acetylfluorene, 2.25 grams (0.075 mol) paraformaldehyde, and 50 ml. isoamyl alcohol in a three-necked flask was added 20.81 grams (0.075 mol.) of oily di-n-octylamine hydrochloride. The mixture was refluxed with stirring for three hours, forming a dark brown solution which yielded a slightly brown crystalline product upon cooling. The crystals were filtered and washed with two 50 ml. portions of absolute ether. When dried in air the crystals weighed 15 grams (60% theoretical) and melted at 180-185.

Recrystallization of the impure product from 50 ml. of alcohol gave 8.9 grams of plate-like crystals which melted at 184-185°. The product was insoluble in water and very soluble in ethyl alcohol. No local anaesthetic action was noticed when applied topically to the tip of the tongue.

We found upon analyzing the compound that neither the percent of nitrogen nor the percent of chlorine agreed with those calculated for the expected structure.



The analysis did, however, agree with that calculated for 2'-(3-n-octylamino-1-oxopropyl) fluorene hydrochloride.



This indicated that one octyl group was replaced by a hydrogen in the reaction. It would seem that at 130° (the boiling point of the solvent) the di-n-octylamine hydrochloride is unstable and loses one octyl group forming n-octylamine hydrochloride.

Analysis: For N: Subst., 0.1988; 0.05130 N HCl, 10.12 ml

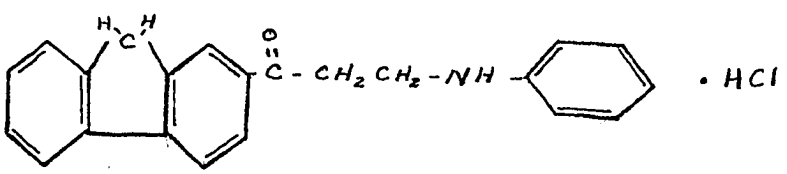
For Cl: Subst., 0.2665; AgCl, 0.0986

Calc. for $C_{32}H_{48}O$ N Cl : N, 2.73 ; Cl, 6.91

Calc. for $C_{24}H_{32}O$ N Cl : N, 3.63; Cl, 9.20

Found: N, 3.66; Cl, 9.15

10. Preparation of 2'-(3-benzylamino-1-oxopropyl) fluorene hydrochloride.



A mixture of 6.24 grams (0.03 mol.) of 2-acetylfluorene, 6.43 grams (0.045 mol.) benzylamine hydrochloride, 1.3 grams (0.045 mol.) paraformaldehyde, and 60 ml. isoamyl alcohol were refluxed with stirring for a period of one hour. The solid material went into solution rapidly and the product began to separate out almost immediately. The resulting suspension was cooled and filtered, the product sucked as dry as possible and washed with a little acetone. Recrystallization from acetic acid gave a white crystalline product which melted at 239-240°.

In order to prepare the free base the hydrochloride was suspended in hot alcohol, in which it was insoluble, and concentrated ammonium hydroxide was added drop by drop until the material went into solution. Upon cooling a white crystalline solid (2.5 grams) separated. Its melting point was 229-230°.

The final compound as the free base had no noticeable effect as a local anaesthetic on the tongue. As the hydrochloride, however, it exhibited slight anaesthetic action.

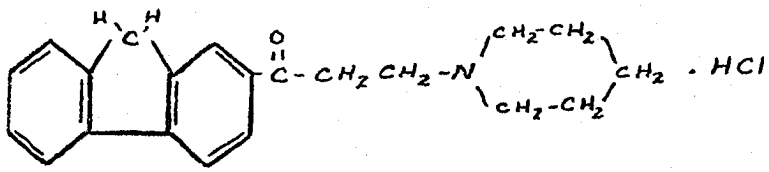
Analysis: Subst., 0.1989; 0.05130 N HCl, 11.05 ml.

Calc. for $C_{33}H_{34}O_2$ N Cl : N, 2.40

Calc. for $C_{23}H_{22}O$ N Cl : N, 3.85

Found: N, 3.98

11. Preparation of 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride.



Into a three-necked flask was placed 42.6 grams (0.20 mol.) 2-acetylfluorene, 36.4 grams (0.30 mol.) piperidine hydrochloride, 9.0 grams (0.30 mol.) paraformaldehyde, and 120 ml. isoamyl alcohol and the mixture refluxed for one hour. The product began to separate out a few minutes after boiling began. At the end of one hour the flask and its contents were cooled to room temperature and filtered. The crude product was washed with a little dry acetone and air dried. Recrystallization from 1000 ml. of alcohol yielded 53.2 grams (78% theoretical) of a white crystalline solid only slightly soluble in water and melting at 212-213°.

A few mgm. of the white crystals, ground to a white powder, when applied to the tip of the tongue produced a marked local anaesthesia. The onset time was about one

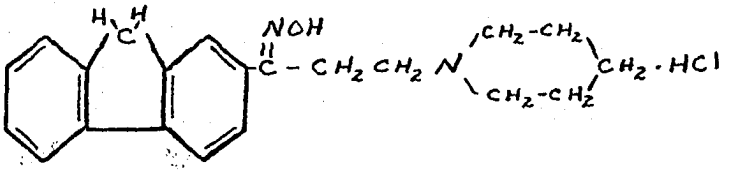
minute; the duration of anaesthesia about 45 minutes.

Analysis: Subst., 0.1978 g.; AgCl 0.0827 g.

Calc. for $C_{21}H_{24}O\ N\ Cl$: Cl, 10.31

Found: Cl, 10.34

(a) 2'-(3-Piperidino-1-oximidopropyl) fluorene hydrochloride was prepared in the hope of increasing the water solubility of 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride without substantially changing the structure, and therefore the local anaesthetic power.



The 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride (8.6 grams, 0.025 mol.) was refluxed for five hours on a water bath with four grams (0.057 mol.) hydroxylamine hydrochloride and 7 grams of barium carbonate in 200 ml. ethyl alcohol. The solution was filtered while hot to remove barium carbonate. Upon cooling, the pure 2'-(3-piperidino-1-oximido-propyl) fluorene hydrochloride separated as white crystals, moderately soluble in hot alcohol and slightly soluble in cold water. Evaporation of the mothor

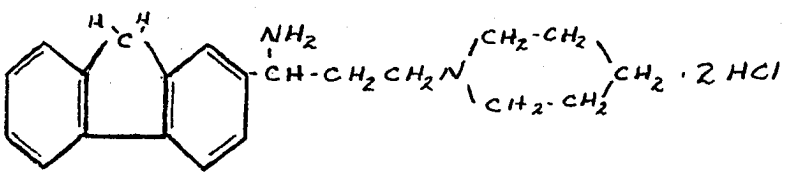
liquor to about one-half its original volume gave another crop of crystals. The total yield was 6 grams (67.3% theoretical), the pure compound melting at 217-218°. Although the water solubility of the oxime was somewhat greater than that of the ketone, the local anaesthetic action on the tongue was decreased.

Analysis: Subst., 0.2201; AgCl, 0.0888

Calc. for $C_{21}H_{25}O\,N_2Cl$: Cl, 9.80

Found: Cl, 9.98

(b) 2' (3-Piperidino-1-aminopropyl) fluorene dihydrochloride



was prepared by catalytic reduction of the oxime. Five grams (0.0156 mol.) 2'-(3-piperidino-1-oximidopropyl) fluorene hydrochloride was suspended in 250 ml. ethyl alcohol in the pressure bottle of a Parr hydrogenation apparatus. The platinum oxide catalyst (0.1 gram) was added, followed by 3 ml. concentrated hydrochloric acid, the latter to help prevent the formation of secondary amines during the reduction. The pressure bottle was connected to

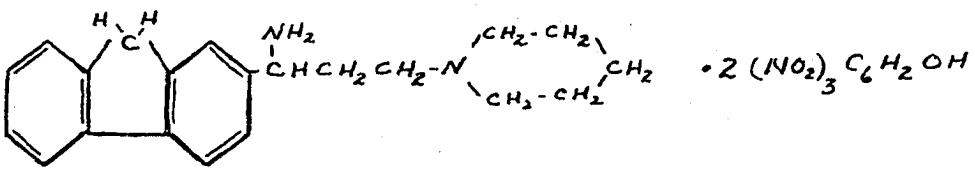
the hydrogen tank under a starting pressure of 58 lb. per sq. in. gauge and shaken for 6 hours, at which time the pressure had dropped to 56.75 lb. The solution was allowed to stand overnight under pressure. After 24 hours (total) the pressure had dropped a total of 2.5 lb. per sq. in. gauge (theoretical drop for 0.0156 mol, 2.5 lb.). The solution was filtered twice through a fine paper in order to recover the platinum catalyst. The filtrate was evaporated to one-half its original volume and dry ether was added until the solution became cloudy. The cloudy solution was allowed to stand overnight and the crystalline compound collected. The compound was purified by dissolving it in 50 ml. absolute alcohol, adding anhydrous ether until the solution was cloudy, and collecting the solid product (2.2 grams, 37.3% theoretical) which melted at 262-263°. The compound was moderately soluble in water and very soluble in ethyl alcohol. It had a strong tendency to come down as an oil if too much ether were added to an alcohol solution of the compound, probably due to the presence of water.

Analysis: Subst., 0.1978 ; 0.05130 N HCl, 19.70 ml.

Calc. for $C_{21}H_{28}ClN_2$: N, 7.07

Found: N, 7.15

We were able to prevent the formation of an oily product and obtain better yields by converting the reduced compound to the dipicrate. The reduction of the oxime was carried out in the same manner as previously described. The solution was evaporated on a steam bath until only a heavy oil remained and no odor of hydrogen chloride was present. The oil was redissolved in 100 ml. hot alcohol and 25 ml. of a saturated alcoholic solution of picric acid was added. Upon cooling, 5.2 grams (59.1% theoretical) of a yellow crystalline solid separated. Recrystallization of 0.5 gram of the dipicrate from alcohol gave pure 2'-(3-piperidino-1-aminopropyl) fluorene dipicrate,



which melted at 237°. The compound had no local anaesthetic action on the tongue.

(c) Potassium 2'-(3-piperidino-1-oxopropyl) fluorene-7'-sulfonate was prepared from 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride using concentrated sulfuric acid as a sulfonating agent. In a 250 ml. beaker was placed 100 grams

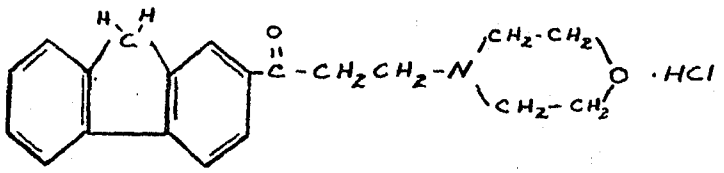
concentrated sulfuric acid. Using a mechanical stirrer the sulfuric acid was stirred rapidly while 10 grams of 2'(3-piperidino-1-oxopropyl) fluorene hydrochloride were added in small portions. Hydrogen chloride gas was evolved and the solution took on a green-brown color. Stirring was continued for 2 hours at room temperature. It was then poured over about 1 Kg. of crushed ice in a 2000 ml. beaker. Attempts to filter off the white solid which precipitated failed, the product passing through the filter paper for a few minutes and then clogging the pores of the paper. The suspension was diluted to 1.5 L., warmed to 80°, and 25% potassium hydroxide solution added until the solution became clear. The product was salted out by adding potassium chloride until no more precipitate resulted. The solid material was collected by filtering. It was soluble in hot water and had little or no local anaesthetic action on the tongue. When dilute hydrochloric acid was added to a hot aqueous solution, a white precipitate (probably the free sulfonic acid) appeared but redissolved upon the addition of more hydrochloric acid.

Analysis: Subst., 0.2084; $BaSO_4$, 0.1148

Calc. for $C_{21}H_{23}O_4NSK$: S, 7.56

Found: S, 7.55

12. Preparation of 2'-(3-morpholino-1-oxopropyl) fluorene hydrochloride.



A mixture of 42.6 grams (0.20 mol.) 2-acetylfluorene, 9.0 grams (0.30 mol.) paraformaldehyde, 36.6 grams (0.30 mol.) morpholine hydrochloride, and 120 ml. isoamyl alcohol was placed in a three-necked flask and refluxed with stirring for 2.5 hours. As in the case of 2'-(3-piperidino-1-oxopropyl) fluorene hydrochloride, the product began to separate after a few minutes of boiling. At the end of two hours the flask was cooled to room temperature and the product was isolated by filtering. The crude 2'-(3-morpholino-1-oxopropyl) fluorene hydrochloride was washed with a little acetone and recrystallized from 1700 ml. of alcohol. The pure compound (46 grams, 68% theoretical) had a melting point of 226-227°. The white crystalline product was moderately soluble in alcohol and only slightly soluble in water. Marked local anaesthesia was noted when a little of the crystalline material was rubbed on the tip of the tongue: onset, 45 sec.,

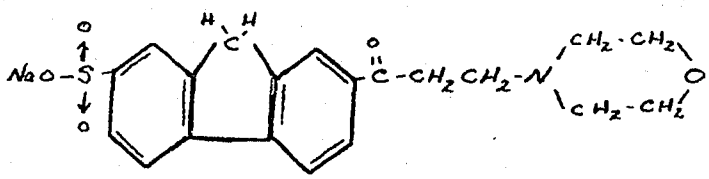
duration, 45 minutes.

Analysis: Subst. 0.2000; 0.05033 N HCl, 11.12 ml.

Calc. for $C_{20}H_{22}O_2$ N Cl : N, 4.08

Found: N, 4.13

(a) Sodium 2'-(3-morpholino-1-oxopropyl) fluorene-7'-sulfonate



was prepared by adding 3.2 grams of 2'-(3-morpholino-1-oxopropyl) fluorene hydrochloride, in small portions, to 100 ml. concentrated sulfuric acid with stirring. The solution darkened in color during the addition, turning from yellow to brown. After stirring for one hour, the solution was poured over 500 grams of crushed ice, producing a colloidal precipitate. The suspension was neutralized with sodium carbonate and the sodium salt brought down by adding alcohol to the solution. The product was a white solid, soluble in hot water and having no melting point below 300°. When dissolved in water and dilute hydrochloric acid added dropwise, a precipitate of the free acid was formed, which redissolved upon addition of more hydrochloric acid,

indicating the formation of the amine hydrochloride.

Analysis: Subst. 0.2010; $BaSO_4$, .1149

Calc. for $C_{20}H_{21}O_5NSNa$: S, 7.81

Found: S, 7.84

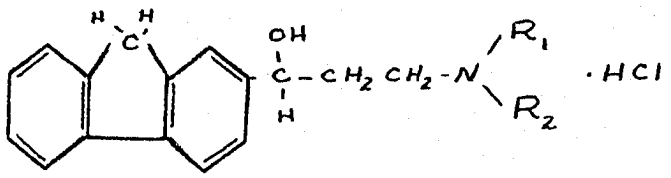
D. PREPARATION OF AMINES OF 2'-(1-HYDROXY PROPYL) FLUORENE.

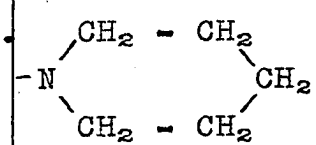
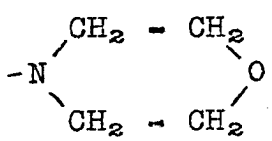
The reduction of the ketones to secondary alcohols was carried out in a Parr hydrogenation apparatus. The pure ketones were suspended in 250 ml. alcohol contained in a pressure bottle and the platinum oxide catalyst (0.05-0.10 grams) was added. Hydrogen under initial pressures of 45 to 55 lb. per sq. inch gauge was shaken with the suspension at room temperature until the gauge pressure had dropped the theoretical number of pounds (82 lb. per sq. in. gauge per mol. of hydrogen, H_2). The reduction in most cases was very slow, usually requiring 24 hours for a pressure drop of 4-5 pounds. During the reduction the suspended ketone dissolved slowly until, at the end of the reduction, the solution was complete, only the platinum catalyst being undissolved.

The platinum catalyst was removed by filtering, the secondary alcohol being recovered from the filtrate by either of two methods:

1) The solution was evaporated to one-half its original volume, the crystalline product separating on cooling.

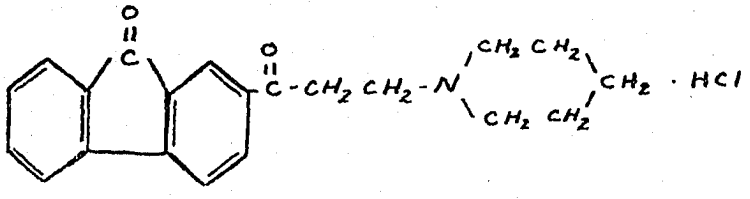
2) Dry ether was added slowly to the warm alcohol solution until the solution became cloudy, the crystalline product separating after standing overnight.



	NITROGEN SUBSTITUENTS		MELTING POINT	
	R_1	R_2	Rx FROM ALCOHOL	Rx FROM ALCOHOL AND ETHER
1.	CH_3	H	261-262	———
2.	CH_3	CH_3	179-180	159-160
3.	CH_3CH_2	H	———	265
4.			217	212-213
5.			———	222-225

E. PREPARATION OF AMINES OF 2'-(1-OXOPROPYL) FLUORENONE.

1. Preparation of 2'-(3-piperidino-1-oxopropyl) fluorenone hydrochloride.



A mixture of 4.4 grams (0.02 mol.) 2-acetylfluorenone, 3.64 grams (0.03 mol.) piperidine hydrochloride, 0.9 grams (0.03 mol.) paraformaldehyde and 30 ml isoamyl alcohol was placed in a three-necked, round-bottomed flask and refluxed for one hour, the product beginning to separate as soon as boiling started. The solution was cooled and filtered; the product was washed with a little dry acetone and recrystallized from 300 ml. ethyl alcohol. The yellow crystalline compound (5.1 grams, 71.8% theoretical) was insoluble in water and moderately soluble in alcohol; it melted at 231-232°. The compound had no noticeable local anaesthetic action on the tongue.

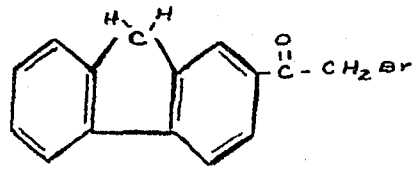
Analysis: Subst., 0.1148; AgCl, 0.0453

Calc. for $C_{21}H_{22}O_2$ N Cl : Cl, 9.96

Found: Cl, 9.76

F. PREPARATION OF OMEGA-BROMO AND AMINO KETONES.

1. Preparation of Omega-bromo-2-acetylfluorene.



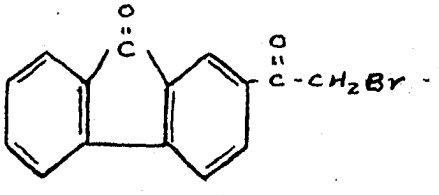
A suspension of 20.8 grams (0.10 mol.) of 2-acetylfluorene in 1000 ml. of anhydrous ether contained in a 2 liter flask was cooled to 0° in an ice bath. To the suspension was added all at once 5 cc (16.0 grams, 0.10 mol.) bromine dissolved in 200 cc of absolute ether at 0°. The mixture was stirred mechanically for two hours at 0°, then allowed to stand for 45 minutes at room temperature. The dark red bromine color had disappeared at the end of two hours and the gray crystalline product which had precipitated was filtered off. The filtrate was treated with solid sodium carbonate, to remove the hydrobromic acid, and evaporated to dryness giving another crop of crystals of crude ω-bromo-2-acetylfluorene. The crude products from these operations were combined and recrystallized from 1100 ml. of ethyl alcohol. The pure white crystalline product which separated weighed 17.8 grams (62% theoretical) and melted at 144-145°. The compound was slightly soluble in ether, moderately soluble in alcohol, and insoluble in water. A qualitative test for

bromine was positive. No attempt was made to prove the structure of the compound.

Analysis: Calc. for $C_{15}H_{11}OBr$: Br, 27.86

Found: Br, 27.67

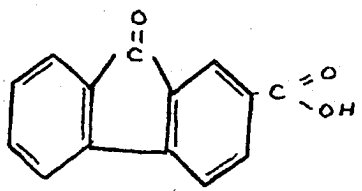
2. Preparation of Omega-bromo-2-acetylfluorenone.



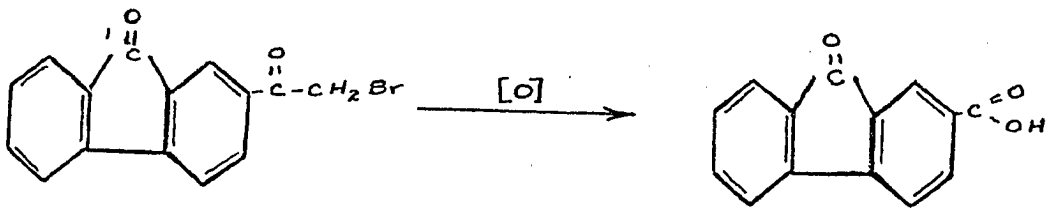
To a suspension of 11.1 grams (0.05 mol.) 2-acetylfluorenone in 500 ml. absolute ether cooled to 0° in an ice bath was added a solution of 8.0 grams (0.05 mol.) bromine in 100 ml. absolute ether. The mixture was stirred for 4 hours at 0° and the resulting product filtered off. Neutralization of the filtrate with sodium carbonate and subsequent evaporation to dryness gave only about 1 gram more of the product. The crude product was recrystallized from 600 ml. of ethyl acetate, yielding 9.5 grams (63.1% theoretical) of a bright yellow crystalline compound melting at 211-212°. The product was insoluble in water, moderately soluble in alcohol, and very slightly soluble in ether. A qualitative test for bromine was positive.

In order to prove the structure, 0.5 grams of the pure omega-bromo-2-acetylfluorenone was refluxed in 50 ml.

of glacial acetic acid with 5 grams of potassium dichromate for 6 hours. The acetic acid solution was poured into 500 ml. of hot water and the resulting precipitate collected and washed with water. The precipitate was suspended in water, heated to 80°, and a solution of potassium hydroxide (25%) added until all of the solid went into solution. A little animal charcoal was added and stirred with the solution to remove adsorbable impurities. The suspension was filtered and the filtrate treated with concentrated hydrochloric acid added dropwise until the free acid separated. The product, fluorenone-2-carboxylic acid,



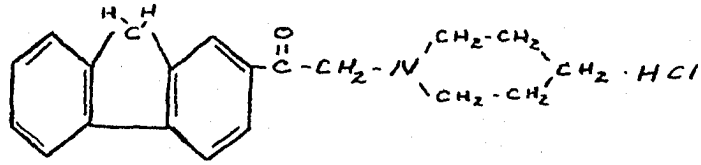
melted at 335-340° (copper block) (59) and gave no qualitative test for halogen. By this oxidation we proved that the bromine was present in the side chain.



Analysis: Calc. for $C_{15}H_9O_2Br$: Br, 26.55

Found: Br, 26.25

3. Preparation of Omega-piperidino-2-acetylfluorene hydrochloride.



A suspension of 5.74 grams (0.02 mol.) omega-bromo-2-acetylfluorene in 600 ml. of absolute ether was stirred rapidly while 3.40 grams (0.04 mol.) piperidine was added. A white precipitate of piperidine hydrobromide began to separate at once. Stirring was continued for 2 hours at room temperature and the resulting suspension filtered to remove the piperidine hydrobromide (3.2 grams, 96.9% theoretical). The filtrate was evaporated on a steam bath until all the ether was removed, leaving a reddish colored oil which crystallized on cooling. The crude crystalline free base was refluxed for 30 minutes with 5 grams of bone-black in 100 ml. absolute alcohol and filtered. To the colorless filtrate was added, dropwise, enough of an absolute ether solution of hydrogen chloride to make it slightly acid. Upon standing, a white crystalline product separated. The pure omega-piperidino-2-acetylfluorene hydrochloride weighed 3.1 grams (47.4% theoretical), and melted at 273-274°. It was

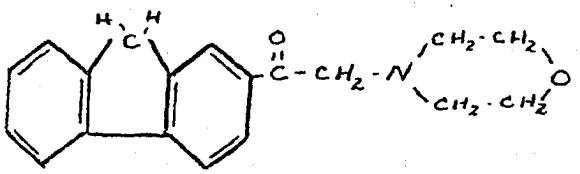
slightly soluble in water, fairly soluble in alcohol, and had a mild local anaesthetic action on the tip of the tongue.

Analysis: Subst., 0.1078; AgCl, 0.1315

Calc. for $C_{20}H_{22}O\ N\ Cl$: Cl, 10.81

Found: Cl, 10.94

4. Preparation of Omega-morpholino-2-acetylfluorene.



To a suspension of 5.74 grams (0.02 mol.) omega-bromo-2-acetylfluorene in 600 ml. of absolute ether was added 3.5 grams (0.04 mol.) morpholine. The mixture was stirred mechanically at room temperature for 2 hours and the resulting precipitate of morpholine hydrobromide was filtered off. The filtrate was evaporated to dryness leaving a solid residue which was recrystallized from alcohol. The pure product, weighing 2.0 grams (33% theoretical), melted at 145-146° and was a white crystalline solid, very soluble in alcohol and slightly soluble in water.

One gram of the pure product was dissolved in 25 ml. absolute alcohol. To this solution was added just

enough of an absolute ether solution of hydrogen chloride to make it slightly acid. The pure omega-morpholino-2-acetyl-fluorene was a white crystalline solid melting at 263-264°. It was slightly soluble in water, more soluble in alcohol, and produced slight local anaesthesia on the tip of the tongue.

Analysis: Subst., 0.2194; AgCl, 0.0938

Calc. for $C_{19}H_{20}O_2$ N Cl : Cl, 10.75

Found: Cl, 10.56

IV SUMMARY

In view of the fact that compounds of the type $R'COO(CH_2)_nNR_2$, $R'CO(CH_2)_nNR_2$, and the corresponding alcohols have been found to be physiologically active as local anaesthetics, analgesics and antispasmodics, we decided to prepare a new series of compounds analogous to the latter two types, in which R' is fluorene or fluorenone. Many of the compounds prepared showed marked local anaesthetic action when applied to the tip of the tongue. The compounds are to be tested to determine whether or not they possess analgesic or antispasmodic activity.

Unfortunately, our imminent entry into the Armed Forces has curtailed further work in this series.

In the following table are listed the new compounds prepared during the course of the investigation. The melting point for each compound that melted below 300° is included. Analysis are given for all but the secondary alcohols that were prepared by catalytic reduction of the amino-ketones.

NEW COMPOUNDS PREPARED

During the Course of This Investigation

COMPOUND	MELTING POINT	FORMULA	CALC.	ANALYSIS FOUND
1. Tri-3-(1,2'-fluoryl-1-oxopropyl amine hydrochloride	248-249	$C_{48}H_{40}O_3NCl$	N, 1.96	N, 2.04
1. (a) free base	213	$C_{48}H_{39}O_3N$	M.W. 678	M.W. 675
2. 2'-(3-Methylamino-1-oxopropyl) fluorene hydrochloride	217-218	$C_{17}H_{18}ONCl$	Cl, 12.36	Cl, 12.50
3. 2'-(3-Dimethylamino-1-oxopropyl) fluorene hydrochloride	187-188	$C_{18}H_{20}ONCl$	Cl, 11.74	Cl, 11.69
4. 2'-(3-Ethylamino-1-oxopropyl) fluorene hydrochloride	225-226	$C_{18}H_{20}ONCl$	N, 4.64	N, 4.51
5. 2'-(3-Monethanolamino-1-oxopropyl) fluorene hydrochloride	201-202	$C_{18}H_{20}O_2NCl$	N, 4.42 Cl, 11.15	N, 4.69 Cl, 11.16

COMPOUND	MELTING POINT	FORMULA	CALC.	ANALYSIS FOUND
6. 2'-(3-Allylamino-1-oxopropyl) fluorene hydrochloride	214-215	$C_{19}H_{20}ONCl$	N, 4.49	N, 4.79
7. 2'-(3-Di-n-propylamino-1-oxopropyl) fluorene hydrochloride	150-151	$C_{22}H_{28}ONCl$	Cl, 9.91	Cl, 9.75
8. 2'-(3-n-Octylamino-1-oxopropyl) fluorene hydrochloride	184-185	$C_{25}H_{32}ONCl$	N, 3.63 Cl, 9.20	N, 3.66 Cl, 9.15
9. 2'(3-Benzylamino-1-oxopropyl) fluorene hydrochloride	239-240	$C_{23}H_{22}ONCl$	N, 3.85	N, 3.98
10. 2'-(3-Piperidino-1-oxopropyl) fluorene hydrochloride	212-213	$C_{21}H_{24}ONCl$	Cl, 10.31	Cl, 10.34
11. 2'-(3-Piperidino-1-oximidopropyl) fluorene hydrochloride	217-218	$C_{21}H_{25}ON_2Cl$	Cl, 9.80	Cl, 9.98

	COMPOUND	MELTING POINT	FORMULA	CALC.	ANALYSIS FOUND
12.	2'-(3-Piperidino-1-aminopropyl) fluorene dihydrochloride	262-263	$C_{21}H_{28}N_2Cl$	N, 7.07	N, 7.15
13.	2'-(3-Piperidino-1-aminopropyl) fluorene dipicrate	237	$C_{33}H_{32}O_{14}N_8$	———	———
14.	Potassium 2'-(3-piperidino-1-oxopropyl) fluorene-7'-sulfonate	300	$C_{21}H_{23}O_4NSK$	S, 7.56	S, 7.55
15.	2'-(3-Morpholino-1-oxopropyl) fluorene hydrochloride	226-227	$C_{20}H_{22}O_2NCl$	N, 4.08	N, 4.13
16.	Sodium 2'-(3-Morpholino-1-oxopropyl) fluorene-7'-sulfonate	300	$C_{20}H_{20}O_5NSNa$	S, 7.81	S, 7.84
17.	2'-(3-Methylamino-1-hydroxypropyl) fluorene hydrochloride	261-262	$C_{17}H_{20}ONCl$		

	COMPOUND	MELTING POINT	FORMULA	CALC.	ANALYSIS FOUND
18.	2'-(Dimethylamino-1-hydroxypropyl) fluorene hydrochloride	179-180	$C_{18}H_{22}ONCl$		
19.	2'-(3-Ethylamino-1-hydroxypropyl) fluorene hydrochloride	265	$C_{18}H_{22}ONCl$		
20.	2'-(3-Piperidino-1-hydroxypropyl) fluorene hydrochloride	217	$C_{21}H_{26}ONCl$		
21.	2'-(3-Morpholino-1-hydroxypropyl) fluorene hydrochloride	222-225	$C_{20}H_{24}O_2NCl$		
22.	2'-(3-Piperidino-1-oxopropyl) fluorenone hydrochloride	231-232	$C_{21}H_{22}O_2NCl$	Cl, 9.96	Cl, 9.76
23.	Omega-bromo-2-acetylfluorene	144-145	$C_{15}H_{11}OBr$	Br, 27.86	Br, 27.67

COMPOUND	MELTING POINT	FORMULA	CALC.	ANALYSIS FOUND
24. Omega-bromo-2-acetylfluorenone	211-212	$C_{15}H_9O_2Br$	Br, 26.55	Br, 26.25
25. Omega-piperidino-2-acetyl-fluorene hydrochloride	273-274	$C_{20}H_{22}ONCl$	Cl, 10.81	Cl, 10.94
26. Omega-morpholino-2-acetyl-fluorene hydrochloride	263-264	$C_{19}H_{20}O_2NCl$	Cl, 10.75	Cl, 10.56

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