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I hereby recommend that the thesis prepared under my supervision by Harry Willard Davis

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

Approved by:

R. F. Reed

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Hobart S. Greene

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SOME THIOPHENE DERIVATIVES AND THEIR ACTION AS LOCAL ANESTHETICS

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

1941

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by

Harry Willard Davis

B.S. in Ch.E. University of South Carolina 1937
M.S. University of Cincinnati 1939

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INTRODUCTION

A. General

The production of local anesthesia presents one of the most interesting problems to be found among the physiological actions of chemical substances. Since the advent into medicine of cocaine, much effort has been expended by chemists and pharmacologists in attempts to correlate chemical structure and local anesthetic activity. While no hard and fast rules can be made, experiment has indicated certain tendencies which are of great help in such a study.

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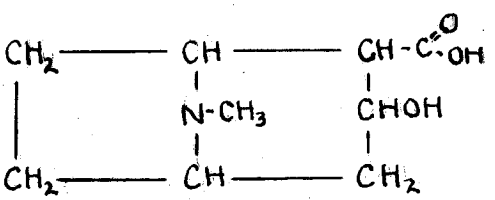
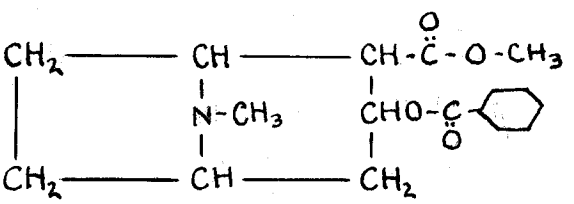
B. Cocaine and Related Compounds

The production of local anesthesia by chemical means started in 1868 when Moreno y Maiz (1) used cocaine for such a purpose. Sixteen years later Koller initiated cocaine into medical practice. Its wide use in medicine attracted the attention of the chemists, who set to work to determine the chemical structure of this interesting substance. Cocaine, when subjected to hydrolysis, was found to produce ecgonine, methyl alcohol, and benzoic acid. Willstätter (2) established the structure of cocaine in 1898 when he showed ecgonine to be



Cocaine is then the di-ester of ecgonine having the following structure:



This was proved to be true by a subsequent synthesis of the molecule (3).

Even before the exact structure of cocaine was determined some interesting facts about it became known. Neither the ecgonine, the benzoyl ecgonine, nor the ecgonine methyl ester showed activity. It didn't seem to make much difference in

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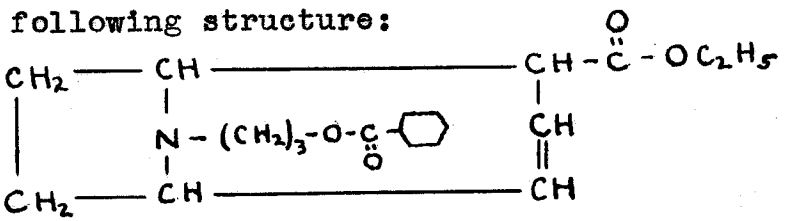
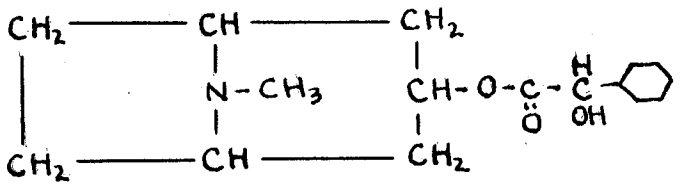
the activity as to which alkyl replaced the hydrogen of the carboxy group in benzoyl ecgonine (4). The benzoyl radical was found to be very important, the use of other acids causing a decrease or complete loss of activity (5). Replacement of the methyl group attached to the nitrogen atom by hydrogen or other alkyls had very little effect on the physiological action (6).

Eucaine (7), which is more active and less toxic than cocaine has the following structure:

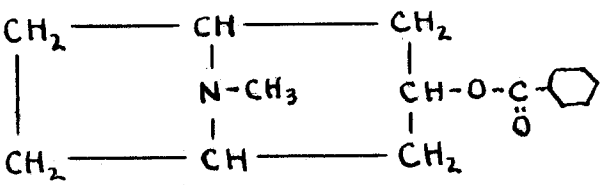


It is interesting to note that the benzoyloxy group is three carbon atoms removed from the nitrogen atom as is the case in the cocaine molecule.

Atropine, used to produce dilation of the eyes, is a weak local anesthetic of the following structure (8):



Replacing the tropic acid portion of atropine with the benzoyl group gives tropacocaine (9)



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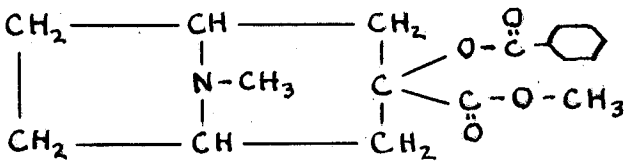
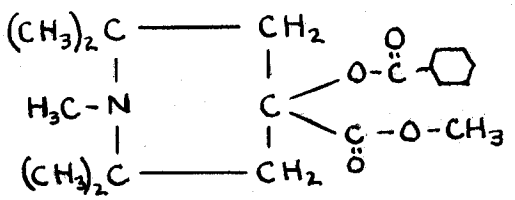
which is more active than cocaine and tess toxic.

α-cocaine, which has the structure,



possesses no local anesthetic power (10).

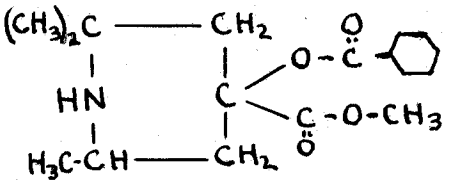
Merling's (11) doubt of the necessity for the double ring of cocaine led him to prepare α-eucaine. This showed considerable



α-eucaine

activity in contrast to the very similar and inactive α-cocaine. Merling concluded that the carbon ring of cocaine was without very much significance, the activity coming from the piperidine ring and its substituents.

α-eucaine possessed some undesirable properties as a cocaine substitue so the structure was modified somewhat to give β-eucaine, a more practical compound.



Einhorn (12) did not agree completely with Merling's conclusions. He observed that the property of causing local anesthesia was very common among soluble aromatic esters, the

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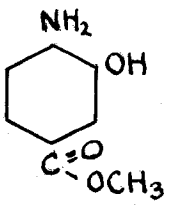
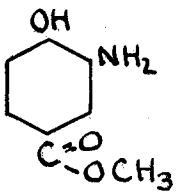
degree of activity and accompanying reactions being determined by the particular relationship of the atoms and groups. Results of early experiments led him to believe that the presence of the amino group in the acyl ring would be beneficial. So, Einhorn investigated certain aromatic amino esters in search of a good cocaine substitute. The best of those considered were "Orthoform" and "Orthoform New." The use of these was



Orthoform



Orthoform New

restricted because of low solubility.

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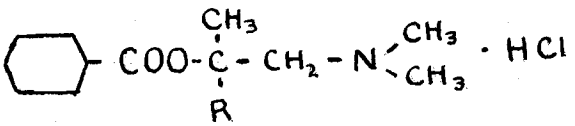
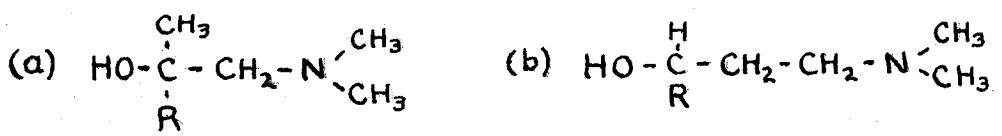
C. Alkamine Esters of Benzoic Acid

Fourneau didn't consider the carbomethoxy group of cocaine essential inasmuch as tropacocaine and ∝-eucaine were quite active without it. He thought that the combination most favorable for the production of local anesthesia resulted from esterifying a tertiary alcohol containing a secondary or tertiary amino group with an aromatic acid. By means of the Grignard reaction, (13) he was able to obtain a series of halohydrins which on subsequent treatment with secondary amines gave the desired alcohols. The benzoic acid esters of these amino alcohols gave soluble salts of strong anesthetic power. The esters included in this study were of the type



where R was methyl, ethyl, propyl, isoamyl, phenyl, and benzyl. The report included no physiological data but the ethyl derivative found some practical use under the name of Stovaine.

Launoy and Fujimori (14) studied the benzoyl esters of two series of alcohols:



In series (a), to which stovaine belongs, nitrogen and oxygen

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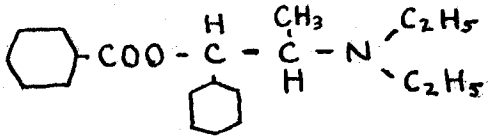
are separated by 2 carbon atoms while in (b) they are separated by 3 carbon atoms. Benzoates of series (a) were found to be more powerful as anesthetics and also to be more toxic than those of series (b). Alcohols with a total of five carbon atoms showed the highest activity and highest toxicity. Also phenyl derivatives were less toxic than benzyl derivatives.

Nagai (15) prepared a benzoyl ester called Allocaine S which has the following structure:



Kubato (16) made a pharmacological study of the hydrochloride of Allocaine S, and found it to be less toxic than novocaine and to stand between novocaine and cocaine in topical activity.

The benzoate of β-piperidinoethanol (17) is irritating and does not produce anesthesia of appreciable duration.

Lynn and Lofgren (18) made a pharmicological study of the hydrochlorides of the benzoates of dimethylaminoethyl, diethylaminomethyl, and diethylaminoethyl alcohols. They found them to have some action, the diethylaminoethyl compound being the strongest.

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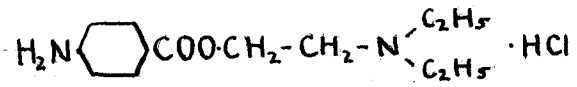
D. Esters of p-Aminobenzoic Acid

Ritsert (19) noted the production of local anesthesia by ethyl p-aminobenzoate as early as 1890, more than ten years before the actual structure of cocaine was established. Einhorn's work among the alkyl esters of the aminohydroxybenzoic acids has already been mentioned. In further attempts to find a simple and synthetic cocaine substitute, Einhorn combined aminobenzoic acid with alkylamino alcohols of the type prepared by Fourneau. The purpose of attaching the amino group on the ring was to produce a slightly more basic compound, thereby rendering the hydrochlorides of the ester bases less irritating. This work was a momentuous one in the field of local anesthetics as it led to the discovery of procaine (novocaine) which has the following structure:



This compound, patented about 1905, rapidly displaced cocaine for injection anesthesia, being much cheaper, less toxic, and non-habit forming. The salts are soluble in water and are stable to sterilizing.

Einhorn and his co-workers (20) extended this work to include p-aminobenzoic acid esters of quite a long list of alcohols but the report gives no physiological data.

Adams and his co-workers took up the study of p-amino-

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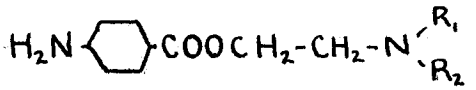
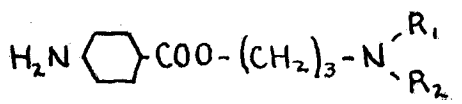
benzoic acid esters of the dialkylaminoalcohols about 1919, patents being obtained on several of their compounds (21). A resume of the work was published in 1937 (22) and included esters of the following types:

(a) 

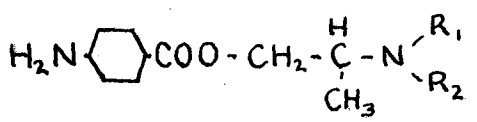
R_1=R_2 = Methyl, n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, sec-Butyl, iso-Amyl

R_1 = n-Butyl, R_2 = Allyl

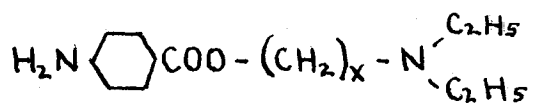
(b) 

R_1 = R_2 = Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, sec-Butyl, n-Amyl, iso-Amyl

R_1 = n-Butyl, R_2 = Allyl

(c) 

R_1 = R_2 = Ethyl, n-Butyl, Allyl

(d) 

x = 3, 4, 5

(e) δ-diethylaminobutyl-p-aminobenzoate
ε- " " amyl "
β- " " isobutyl "
β- " " heptyl "

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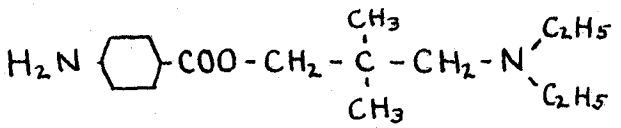
Pharmacological studies showed some definite effects of structure on local anesthetic activity. Increasing the size of the N-alkyls increased the toxicity and activity (especially topical), with the activity increasing more rapidly than the toxicity. Increasing the number of carbon atoms between the oxygen and nitrogen atoms increased the toxicity and more gradually increased the activity. Esters having branched chains on the nitrogen atom were less active and less toxic.

Kamm (23) compared procaine with its trimethylene analogue and found the latter somewhat more toxic but much more active in the production of surface anesthesia.

Loevenhart and Schmitz (24) investigated a series of procaine type compounds but his work was not as extensive as that of Adams. The results were, in general, similar but differed in some details. They found diisopropylamine compounds more active than the n-propyl derivatives and also found toxicity increasing more rapidly than activity with increase in size of the molecules.

Trefuel, Trefuel, and Barbelet (25) investigated the properties of a series of alkamine esters of o-, m-, and p-aminobenzoic acids. The report includes toxicities, pH values, solubilities and some comment on activities.

Larocaine, patented by Mannich (26),



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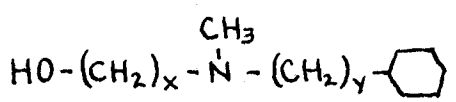
has been found to be twice as active on the rabbit cornea as cocaine and twice as active on the sensory nerve as novocaine (27). It is somewhat less toxic than cocaine.

McElvain and Cope (28) investigated the benzoates and p-aminobenzoates of the following series of alcohols:



In both groups, x was one and two, while y was varied from one to four. The benzoates were extremely irritating while the p-aminobenzoates were not. This is another good example of the beneficial effect of an amino group on the ring of the aromatic acid. The intermediate values of y seemed to give the best anesthetics. The benzoates were surprisingly low in toxicities, even less than procaine, both intravenously and subcutaneously. The aminobenzoates gave unusual toxicity values, having low toxicities tested intravenously and high toxicities tested subcutaneously.

Dialkylaminomethyl alcohol esters of m- and p-aminobenzoic acids were studied by Lynn and Lofgren (29). The particular alkyl groups used were propyl, butyl, and isoamyl. They report some of them as active and all of them as quite irritating.

Adams and collaborators (30) determined the activity of alkyl p-aminobenzoates using goldfish as subjects. Data were obtained from which it was possible to plot time for complete anesthesia against molar concentration of the anesthetic. The

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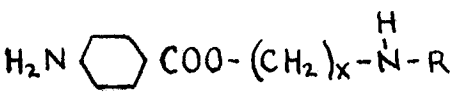
concentration required to produce anesthesia in a specified time was used as a basis for comparing the activity of the various esters. The particular esters considered in order of increasing activity were methyl, ethyl, allyl, isopropyl, tert.-butyl, sec-butyl, n-propyl, isobutyl, n-butyl, n-amyl. Activity definitely increases with length of carbon chain up to four atoms and then levels off, probably due to decreasing solubility. These results also show that, in general, straight chains confer greater anesthetic power on a compound than do branched chains.

Brill (31), a few years prior to the above work, published less detailed information on a few of the alkyl esters. Kluger (32) found the propyl ester of p-aminobenzoic acid too insoluble for use in injection anesthesia. The butyl ester has received some attention as an insoluble local anesthetic (33). Patents have been issued for the benzyl (34) and allyl (35) esters.

Goldberg and Whitmore studied compounds of the type(36)



x = 2, R = Methyl, Ethyl, n-Propyl, isoButyl, n-Butyl, Amyl

x = 3, R = Methyl, Ethyl, n-Propyl, n-Butyl, Amyl

The ethyl esters, x = 2, proved to be good anesthetics, the isobutyl derivative being three times as active as cocaine

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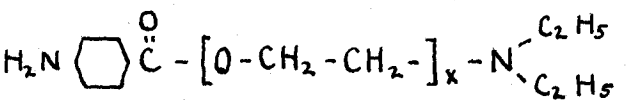
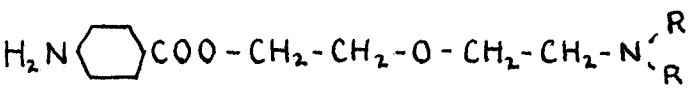
and only slightly more toxic. The same authors prepared a similar series of α,α-dimethyl-β-alkylaminoethanol esters (37). These were too toxic for injection but the amyl derivative showed promise as a surface anesthetic.

Two groups of β-alkyloxy ethanol esters have been reported without pharmacological data. In the first group,(38) R included various alkyl groups while in the second group (39) the alkyl portion consisted of the six possible variations of the amyl radical.

Horne and Shriner (40) investigated some compounds of the type



where x varied from two to five. Activity as measured on the rabbit cornea was a maximum at x = 2, the x = 5 derivative being inactive. The activity as measured by intracutaneous injection on the guinea pig increased sharply as x was raised from two to three and then decreased somewhat as x increased. In a continuation of this investigation (41) the type



was considered where R was methyl, propyl and butyl. Both toxicity and local anesthetic power increased with an increase in the size of R. The compounds were readily oxidized on exposure.

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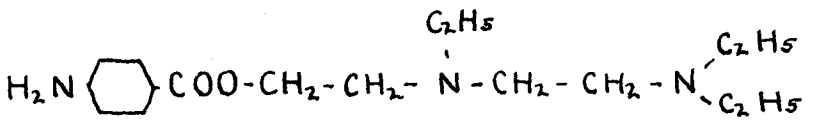
Gryszkiewiez-Trochinowski and Otolski (42) reported the preparation of



and described it as having powerful anesthetic action.

There are many references to esters in the patent literature in which the aminobenzoic acid ring contains substituents such as halogens, alkyl, and alkyoxy groups. More systematic investigation will reveal the value of such substituents.

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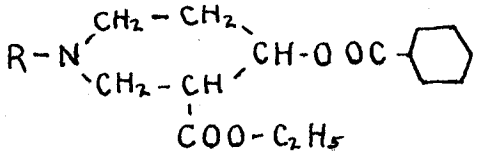
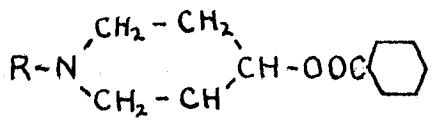
E. Piperidine Derivatives

The piperidine ring is of interest in a study of local anesthetics from a chemical standpoint as cocaine contains such a ring. Most of the information concerning the activity of compounds containing this grouping has come from the work of McElvain. Some of the types studied were:

(I)  (43)

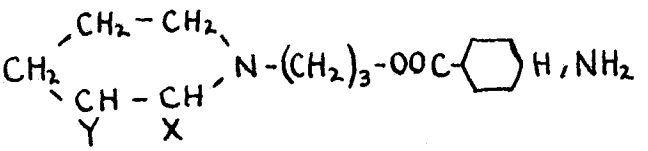
R = Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, sec-Butyl, n-Amyl, isoAmyl

Anesthetic activity increases as the size of R is increased, the amyl derivative being more active than cocaine and only 1/30 as toxic. A very unusual observation in this case is that the toxicity decreases as the size of R increases.

(II)  (43)

R same as in (I)

The same general results were found here as in series (I). The compounds caused a longer lasting anesthesia than the above but were also more toxic.

(III)  (44)

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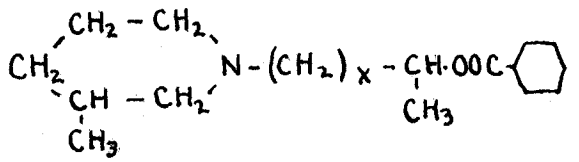
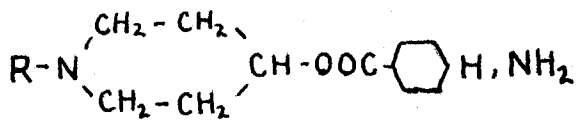
Y = H, X = H, Methyl, Propyl
X = H, Y = H, Methyl, carboethoxy

Only those compounds containing an alkyl group in the piperidine ring were active on mucous membrane. The substituted piperidine ring compounds were also less toxic. Benzoates were less toxic than p-aminobenzoates.

(IV)  (45)

x = 1,2

Introducing the methyl group in the side chain raised both activity and toxicity but the branched chain is less effective than a straight one containing the same number of carbon atoms.

(V)  (46)

R = Methyl, Ethyl, n-Propyl, n-Butyl, iso-Amyl phenylethyl

Pharmacological studies of this series revealed the interesting fact that the benzoates are more active than the p-aminobenzoates and are much less toxic. Substitution of a carbethoxy group on the piperidine ring, as was shown by series (I) and (II), makes the amino derivatives more active. This is another case of an increase in the size of the alkyl causing a decrease in toxicity. The phenylethyl benzoate is seven times as

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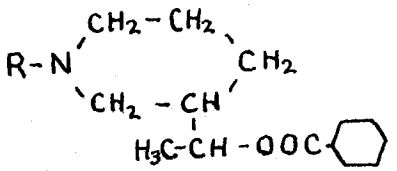
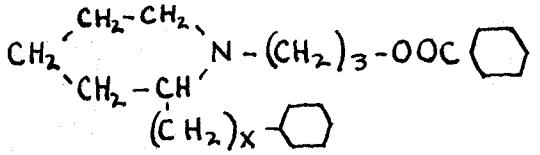
active as cocaine.

(VI)  (47)

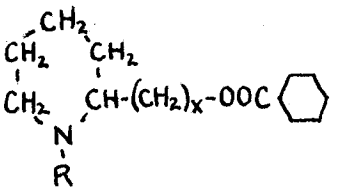
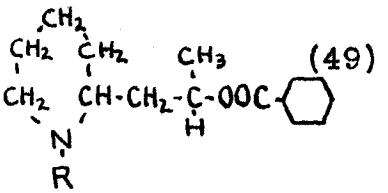
R = benzyl, β-phenylethyl, γ-phenylpropyl, ε-phenylamyl, n-hexyl

These compounds are powerful anesthetics, the phenylamyl derivative being the strongest.

(VII)  (48)

x = 0,1,2,3,4

x = 1 and 2 gave compounds of great activity, the anesthesia lasting for several days. Decreasing x to zero or increasing it to 3 or 4 reduced the duration of anesthesia to a few minutes. These substituents in the 2-position are much more active than corresponding substituents in either the 3 or 4-position.

(VIII)   (49)

x = 2,3

R = Methyl, Ethyl, n-Propyl, n-Butyl

N-ethyl derivatives were the best in both cases.

This work of McElvain's resulted in one compound which has found some practical use. It is the benzoate of γ-(2-

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methyl-piperidino) propanol and is sold under the name of metycaine.

Marvel and Sandborn (50) investigated a group of p-amino-benzoate esters of β-(N-alkylpiperidyl)carbinol. The alkyl groups used were methyl, ethyl, isopropyl, and n-butyl. Activity tests on the cornea of a rabbit's eye showed the ethyl derivative to be the most active, the others being less and about equal to each other. The p-aminobenzoic ester of 1-n-propyl -2-(β-hydroxethyl) piperidine has been found quite active. (51).

Benzoic and p-aminobenzoic acid esters of piperidino-propanediol failed to produce complete anesthesia of the cornea of a rabbit's eye(52).

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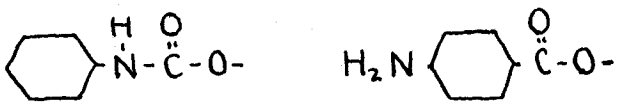
F. Urethanes

Phenylurethanes or phenyl carbamic acid esters are isomeric with the p-aminobenzoic esters. The two structures involved are:



Fromberg (53) compared several urethanes with novocaine and found them to have no particular advantages. Rider considered this type of compound with more promising results. Compounds of the following types were made:

(I) $C_6H_5NHCOOCH_2CHOHCH_2\text{-}NR_2$ (54)

(II) $C_6H_5NHCOOCH_2CH(OOCNHC_6H_5)CH_2NR_2$ (54)

(III) $C_6H_5NHCOOCH_2CH_2CH_2NR_2$ (55)

The R groups were varied from methyl to amyl, including the piperidine ring. As the size of R increased, the duration of anesthesia increased and the time of onset became less. However, changing the alkyl group seemed to have little effect on the toxicity. The diphenylurethane of piperidinopropanediol is 3 to 4 times as active as procaine on injection (56). It is sold commercially under the name of diothane.

A logical extension in the study of urethanes are those which contain an amino group para to the urethane linkage. This has been done for both aliphatic alcohols and dialkylaminoalcohols by Shriner and co-workers (57). All of the

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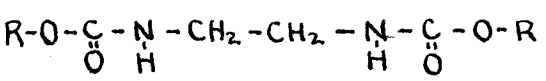
derivatives were found to be topically active, the intensity of the action depending on the particular alkyl. This is of interest, inasmuch as novocaine causes no topical anesthesia. Again, anesthetic power increases with the size of the alkyl group. Another very interesting item in the pharmacological data is that branch chain alkyls give compounds of greater activity. A serious objection to practical use of these compounds is their irritating effects.

Shriner (58) considered the p-phenylenediamine portion of the above urethanes as being responsible for the sever irritation caused by them. An attempt to retain the activity and remove the irritation led to the production of



where R was ethyl and isoamyl. These were non-irritating and had some anesthetic effect on the rabbit cornea. With the same idea in mind, a series of alkyl N-(8-quinolyl) carbamates were prepared (59). These were not irritating but neither did they show anesthetic activity. Separating the urethane linkage from the p-aminophenyl group with a methylene group gave compounds that were active on injection, practically inactive topically and still irritating (60). A series of alkyl-γ-diethylaminopropyl carbamates failed to show topical activity until R reached n-hexyl (61). Duration of injection anesthesia didn't follow any general change as R varied. These were also irritating.

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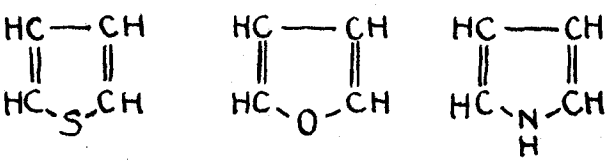
G. Compounds Containing Thiophene, Furan, and Pyrrole Nuclei

The ability to produce local anesthesia is a property possessed by the majority of esters wherein the acid portion of the molecule is aromatic. Then the anesthetic activity of esters prepared from various acids may be considered as a qualitative indication of the aromaticity of the particular acids considered. It is of interest to note the effect of introducing the groups



into molecules where the arrangement has been shown by experience to be favorable for the production of local anesthesia.

Gilman and Pickens (62) included α-carboxy acids of the above nuclei in a series which gives an indication of their relative physiological activities. The alcohol used to form the esters was β-diethylaminoethanol. Tests to determine the activity of the compounds were made by intracutaneous injection on human beings. Cocaine was arbitrarily given a weight of 10 and the others compared as follows:

Cocaine	10
Procaine	6
Diethylaminoethanol Benzoate	4
" Furanacrylate	3
" 2-Pyrrole carboxylate	2
" 2-Thiophene "	1
" 2-Furan "	preceptible
" Acetate	0
" PhenylPropiolate	0

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The ethyl ester of 2-furan carboxylate had already been reported as somewhat active so the inactivity of the diethylaminoethanol ester is surprising. The inactivity of the propiolate was also not to be expected as cinnamic acid gives active compounds. The difference between the activities of the furan and furanacrylate esters is also evidence for the beneficial effect of a double bond between the ring and the carboxy group.

Phatak has made some very interesting observations on the esters of 2-furoic acid. First he considered a series of alkyl esters (63). These he found to be quite active, the activity rising as the alkyl group increased from methyl to amyl. The toxicity rose from methyl to propyl and dropped off for butyl and amyl. This was probably due to decreasing solubility. In a second series (64), 5-alkyl-2-carbethoxy furans were studied. These compounds were found to be inactive when tested on the rabbit cornea. However, 5-alkyl substitution mades the diethylaminoethyl ester quite active whereas Gilman found the unsubstituted ester inactive. The 5-methyl and 5-isopropyl-2-carboxy furan diethylaminoethyl esters are as strong as cocaine. The ethyl-2-furoate was the only one which produced anesthesia on intracutaneous injection on a guinea pig.

The activity of some alkylaminoalkyl 2-furoates has been compared with similar benzoic acid derivatives by Cook and Kreke (65). The compounds were of the type:

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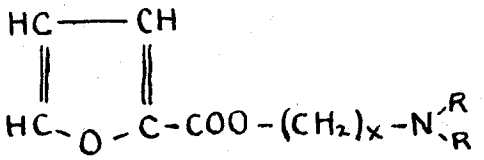

x = 2,3 R = Ethyl, Butyl

Tested on the rabbit cornea, none of them produced anesthesia of long duration. However, the propanol esters of furoic acid appear to be stronger than those of benzoic acid.

The difuroate of piperidinopropanediol was found to have an activity only about half that of the dibenzoate (66). The difuranacrylate, though, was somewhat stronger than the dicinnamate.

Blicke and Blake (67) noted anesthetic action of ethyl pyrrole-2-carboxylate when tested on the tongue. The series was extended to include several alkyl groups, of which the propyl derivative seemed to be the most active. The ethyl esters of several alkyl substituted pyrrole carboxy acids were inactive. The same authors also showed that the pyrrole and pyrrolidine groups could be substituted for the dialkyl-amino portion of procaine analogues without serious loss of activity (68). The heterocyclic nuclei were attached to the alkyl chain at the nitrogen atom.

Steidle (69) has substituted 2-thenoyl for the benzoyl radical in cocaine. The new compound was less toxic than cocaine and produced an anesthesia lasting slightly longer. The same substitution in α-eucaine gave similar results.

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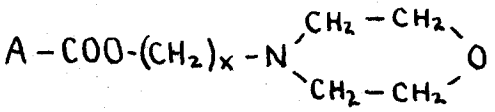
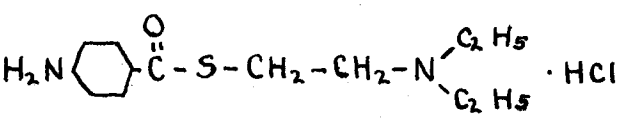
H. Miscellaneous

Gardner and his co-workers have prepared esters of the dialkylaminoalkyl type in which a morpholine ring replaces the N-dialkyl group.



The various groups used included: benzoate and p-aminobenzoate (70), cinnamate (71), and cinchoninate (72). Most of them showed activity, both on injection and on the rabbit cornea if the pH were adjusted to an optimum value. Phenyl urethanes (71) prepared from similar alcohols showed considerable activity and low toxicity. Corresponding derivatives of thiomorpholine were found to be less toxic and to possess a comparable activity (73).

Thiocaine, which has the formula,



when tested by the goldfish method of Adams, was found to act more quickly than novocaine and is of low toxicity (74). Alkyl esters of p-aminobenzoic acid reported in the same paper produced intense anesthesia of mucous membrane. Lischer and Jordon (75) extended the dialkylaminopropyl esters to the higher homologues. The di-n-butyl derivative exhibited very strong action on the tongue.

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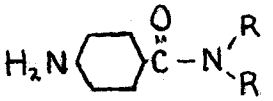
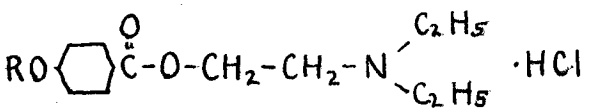
The disubstituted amides are structurally closely related to the alkamine esters but are one oxygen atom short of being isomeric with them. Wenker (76) has prepared the series



where R ranged from methyl to n-amyl. The higher homologues showed strong action on the tongue.

Until recently no thorough investigation of the effect of substituting an alkoxy group in the aromatic nucleus had been made although quite a few such compounds were to be found listed in patents. Rohmann and Scheurle (77) cleared up this point somewhat by a study of the series:



R ranged from H to isoamyl and included allyl and β-diethylamino groups. Replacing the H of the phenolic group by methyl caused a drop in activity but the use of higher molecular weight alkyls caused it to increase again. Compounds containing normal alkyl groups had a more intense action than did those containing branched chains. Lengthening the carbon chain in the alcohol portion of the molecule produced an increase in activity. The presence of an amino group in the alkoxy portion caused a decrease in activity. As a general class, the compounds have high activities and low toxicities.

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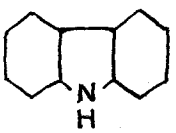
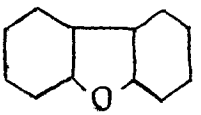
Dialkylaminoalkyl esters of ∝- and β- naphthoic acids were reported as active but irritating (78)(79). It is of interest to note the effect of introducing an amino group into the ring. Such a substitution lowered greatly the irritating effect of benzoic esters. Sergievskaya and Nesvad'ba(80) prepared a series of alkamine esters of 4-amino-1-naphthoic acid. They report them as being more active than cocaine and with "insignificant secondary actions." The toxicities lay between those of procaine and cocaine. Blicke and Parke (81) extended this work to include the 3-, 4-, 5-, and 6-amino-1-naphthoic acids. All of the esters showed activity but complete pharmacological data isn't yet available.

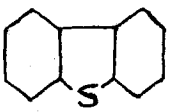
An excellent piece of research on local anesthetics has been reported by Burtner and Lehmann (82). Various esters of 2-, 3-, and 4-carboxy acids of the following nuclei were made:



Carbazole



Dibenzofuran



Dibenzothiophene

Anesthetic activity was measured by the effect on the rabbit cornea and some very interesting facts were revealed. The carbazole derivatives were most active followed by dibenzofuran, the dibenzothiophene compounds being rather weak. The position of the carboxy group in the ring affects the activity of the compound, the results being as follows:

Carbazole	2 = 3 > 4
Dibenzofuran	3 > 2 > 4
Dibenzothiophene	2 = 4

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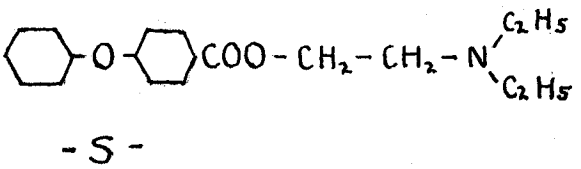
Placing the carboxy group para to the carbon-carbon bridge seems to have a beneficial effect on the activity. The effect of alkylating the nitrogen of carbazole depends on the location of the carbethoxy group. For the 3-isomer, ethylating the nitrogen doubles the activity while such substitution in the 2-isomer reduces both activity and toxicity. Opening the carbon-carbon bridge to give esters of the type



-S-

raised the toxicity more than the activity for the oxygen compound while the activity was increased more than the toxicity for the analogous sulfur derivative.

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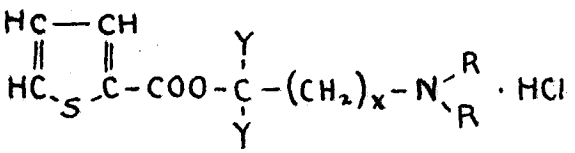
INTRODUCTION TO EXPERIMENTAL WORK

As was shown in the historical section, esters derived from carboxy groups attached to the five membered heterocyclic rings containing one hetero atom have received quite a bit of attention as local anesthetics. However, the one member of this group which has received the least attention, namely thiophene, is more closely related to benzene in properties than the others. The 2-thenoyl group was inferior in anesthetic properties to the benzoyl group in a comparison of the diethylaminoethyl esters (62). The 2-furoic acid ester of the same alcohol was even less active but furoic esters of higher alcohols caused anesthesia of somewhat longer duration than did the benzoates (65). Therefore it seemed to be worthwhile, from an academic standpoint at least, to extend the study of anesthetic type compounds containing the thiophene nucleus.

Consequently, a series of compounds of the type

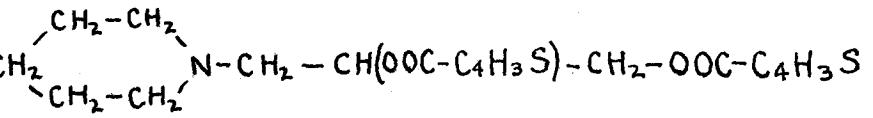


was prepared where

a) Y = H, x = 1, R = Ethyl, Propyl, Butyl, IsoButyl, Piperidino, Morpholino

b) Y = H, x = 2, R = Ethyl, Butyl

c) Y = CH_3, x = 1, R = Ethyl

d) 

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The above esters are all derived from the α-carboxy acid. It would be interesting indeed to compare the activity of esters derived from the β-derivative. Unfortunately, β-thiophene carboxylic acid isn't as readily available as the α-acid. The maximum yield by oxidation of β-methyl thiophene with aqueous potassium permanganate was 8% (83). Voerman (84) tried potassium permanganate of different concentrations, dilute nitric acid, hydrogen peroxide in solutions of different acidities and chromic acid in benzene as oxidizing agents. None of these afforded a good method, as either the methyl group was not oxidized or the thiophene ring was destroyed. The same author tried chlorination of the side chain followed by hydrolysis and oxidation. This procedure failed to give appreciable improvement in yield due to chlorination of the ring in the reactive α-positions. Inasmuch as long alkyl side chains in aromatic rings oxidize more easily than do short ones, Damsky (85) prepared β-ethyl thiophene and tried to oxidize it to the acid. This procedure was found to have no advantage over the oxidation of β-methyl thiophene. Application of the Grignard reaction presents two difficulties. In the first place, β-halogen derivatives cannot be obtained directly. Secondly, substituents in the β-position are more or less inert. Rinckes (86) prepared some β-iodothiophene but was unable to obtain a Grignard reagent from it. Chromic acid in glacial acetic acid and acetic anhydride has been found in certain cases to give improved yields in the pro-

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duction of acids by oxidation. The conditions are completely anhydrous as the acetic anhydride reacts with the water formed during the reaction. It was thought that perhaps this method might give better results in the production of β-thiophene carboxylic acid. So a small quantity of β-methylthiophene was prepared and the oxidation attempted but the results were disappointing.

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EXPERIMENTAL

A. Dialkylaminoalkyl Alcohols

Of the ten alcohols used, the diethylamino and dibutylaminoethanols were purchased from the Eastman Kodak Company and the piperidinopropanediol was a gift. The others were prepared by reacting dialkyl amines with the appropriate chlorohydrin. The best procedure, that of Adams(22), is as follows: 1 mole of chlorohydrin is added to 2.1 moles of amine. The mixture is refluxed on an oil bath, during which time a precipitate of amine hydrochloride forms. After no more precipitate forms, usually about three hours, the mass is cooled and added to an excess of strong (40%) sodium hydroxide solution. The amine layer contains the amino alcohol and is separated, dried over solid sodium hydroxide, filtered, and fractionated. For the higher derivatives, the fractionation must be done at low pressure. Products were collected at the following temperatures and pressures:

Alcohol	Temp., °C	Pressure, mm
β-dipropylaminoethanol	97-100	30
β-diisobutyl " "	110-115	30
β-piperidino "	198-200	atmos.
β-morpholino "	115-120	30
α,α dimethyl-β-diethylaminoethanol	56-59	15
γ-diethylaminopropanol	73-77	14
γ-dibutyl " "	112-114	20

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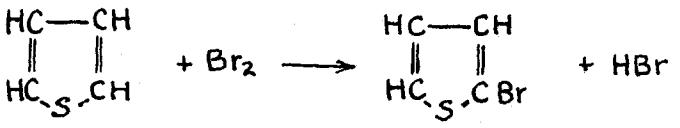
B. α-Bromo Thiophene

Reaction:



Procedure: The method used was essentially that of Krause and Renwanz (87). 50 grams (0.6 mole) of thiophene were dissolved in 250 cc.of glacial acetic acid in a 1 l. three necked flask fitted with a mechanical stirrer. The solution was cooled to 10° and 32 cc.of bromine (100 grams, 0.63 mole) in 500 cc. glacial acetic acid added dropwise. The rate of addition was such that the temperature did not rise above 10°. After all the bromine was added, the mixture was poured into 2 liters of water and the oil separated. The water layer was extracted with 750 cc. of ether. The combined ether extract and oil was washed with sodium carbonate solution to remove acetic acid. Failure to remove all the acetic acid at this point is very undesirable as it will contaminate the final product. The neutral ether solution was dried over calcium chloride. Most of the ether was distilled off at atmospheric pressure and the residue fractionated at low pressure. 55 grams (0.34 mole, 57% of theory) of product boiling at 52-54°C and 17 mms. were obtained.

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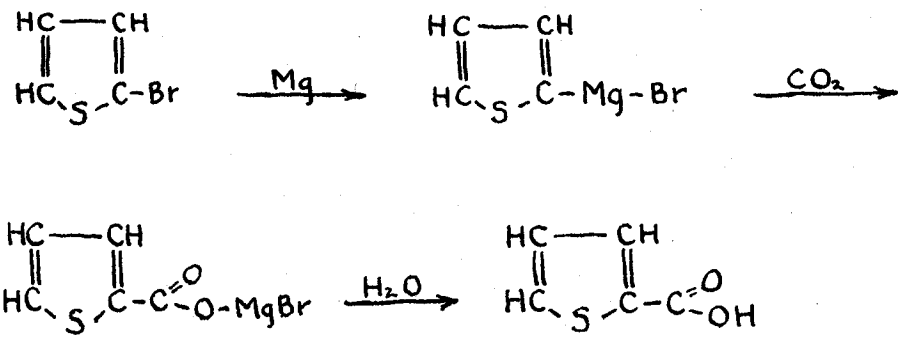
C. ∝-Thiophene Carboxylic Acid

Reaction:



Procedure: With only slight variation, the method of Steinkoff and Ohse was used (88). 14 grams (0.6 atom) of magnesium turnings, which had been washed with ether and dried, a small crystal of iodine, and 50 cc. of anhydrous ether were placed in a 500 cc. three necked flask. The flask was fitted with a dropping funnel, mechanical stirrer, and condenser protected with a calcium chloride tube. 4 grams of ∝-bromo thiophene in 20 cc. of ether were added. With slight warning, the reaction started. 52 grams (a total of 56 grams or 0.35 mole) of ∝-bromo thiophene in 140 cc. of ether were added dropwise to control the rate of reaction. After all the halogen compound was added, the mixture was refluxed 1/2 hour on the water bath to complete the reaction. The ether solution was drawn off into another 500 cc. 3 necked flask without exposing it to the air. A plug of glass wool was inserted into the suction tube to separate unreacted magnesium. An ice-salt mixture was placed

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around the flask and dry CO_2 passed in at such a rate that the temperature rise was small. The mixture, stirred during the addition of CO_2, became very viscous at the end of the reaction. CO_2 was passed in for an additional 15 minutes after further additions caused no rise in temperature. The reaction mixture was poured into ice water and the ether which separated was distilled off from a water bath. The remaining water layer was filtered and the filtrate acidified with dilute sulphuric acid in order to precipitate the thiophene carboxylic acid. A further small amount of acid was obtained by treating the solid separated from the above water layer with sodium hydroxide solution, filtering and acidifying. All of the acid was dissolved in alkaline solution and boiled for a few minutes with charcoal. This solution was filtered, cooled and acidified to re-precipitate the acid. A yield of 34.5 grams (0.27 moles, 77% of theory) of α-thiophene carboxylic acid, melting at 126°, was obtained.

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D. ∝-Thenoyl Chloride

Reaction:

$$SC_4H_3COOH + SOCl_2 \longrightarrow SC_4H_3COCl + SO_2 + HCl$$

Procedure: This was prepared by the general method of reacting with thionyl chloride as used by Jones and Hurd (89). 25 grams (0.2 mole) of thiophene ∝-carboxylic acid and 70 cc. (111 grams, 0.95 mole) of purified thionyl chloride were refluxed over a water bath until no more gas was evolved, about 2 hours being required. The excess thionyl chloride was distilled off and the ∝-thenoyl chloride collected at 195-200°C. The yield was 22 grams (0.15 mole, 75% of theory).

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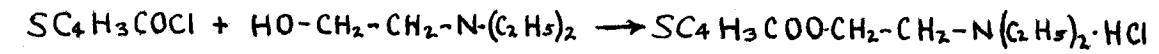
E. β-Diethylaminoethanol Ester of Thiophene-α-Carboxylic Acid

Reaction:



Procedure: Gilman and Pickens (62) prepared this compound by adding the acid chloride in benzene to a benzene solution of the amino alcohol. The mixture was refluxed for an hour to complete the reaction and cooled. The ester-hydrochloride which separated out was filtered off and recrystallized from alcohol. A melting point of 106° was obtained.

This procedure was followed in two attempts with unsatisfactory results. Each time, the solid would dissolve in the alcohol and come out again only when ether was added. Precipitated thus, it came out as an oil which crystallized slowly to give an impure product. The melting points were very low and were not sharp. Redistillation of both aminoalcohol and acid chloride failed to give better results.

A procedure similar to that of Pyman (90), and also used by Cook (65), was found to be much more satisfactory. 1.52 grams (0.013 mole) of diethylaminoethanol were dissolved in 15 cc. of 10% sodium hydroxide solution and the mixture cooled in ice. 2.0 grams (.0137 mole) of the acid chloride were added dropwise with constant shaking and cooling. After all the acid chloride was added, the mixture was allowed to sit in ice for 15 minutes, then extracted with ether, 50 cc. being used. The ether extract

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was dried over anhydrous sodium sulfate and filtered. On the addition of hydrogen chloride gas the ester-hydrochloride precipitated as an oil which quickly crystallized. The solid was dried at 80°C, after which it melted at 106°C. The yield was 2.0 grams (.0076 mole, 55% of theory).

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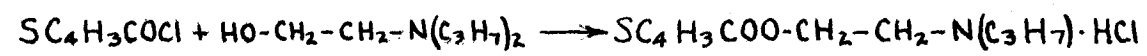
F. β-Di-n-propylaminoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:



Procedure: 2.5 grams (0.017 mole) of α-thenoyl chloride in 15 cc. of dry benzene were added slowly and with stirring to 2.75 grams of β-di-n-propylaminoethanol contained in 35 cc. of benzene. The mixture was refluxed on a water bath for 1 1/2 hours. On cooling, a crystalline precipitate of the ester-hydrochloride came down. This was filtered off and dissolved in hot absolute ethyl alcohol. After filtering and cooling the alcohol solution, the hydrochloride separated as white crystals. 2.5 grams (0.0085 mole, 50% of theory) of product melting at 148-150° were obtained.

Analysis: Percent chlorine calculated - 12.15
Percent chlorine found - 12.34

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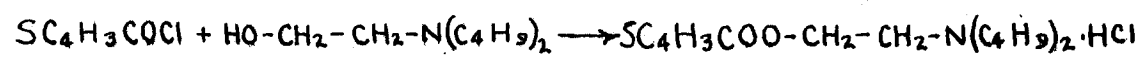
G. β-Di-n-butylaminoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:



Procedure: 2.0 grams (0.0137 mole) of α-thenoyl chloride in 10 cc. of dry benzene were added slowly with stirring to 2.42 grams (.014 mole) of β-di-n-butylaminoethanol in 15 cc. dry benzene. The mixture was warmed on a water bath for 2 hours. On cooling, an oil separated which did not crystallize readily. After several days it partially solidified, still being soft and waxy. This was dissolved in absolute ethyl alcohol and ether added in very small portions over several days. The successive additions of ether were added carefully, forming layers which diffused into the alcohol solution very slowly. The ester-hydrochloride slowly came out as yellowish, impure crystals. These were broken up and washed with ethyl acetate, most of the colored impurity being removed. 0.8 gram (.0026 mole, 20% of theory) melting at 72-75° was obtained. The low yield was brought about by losses during attempts at crystallization and purification.

Analysis: Percent chlorine calculated - 11.02
Percent chlorine found - 11.20

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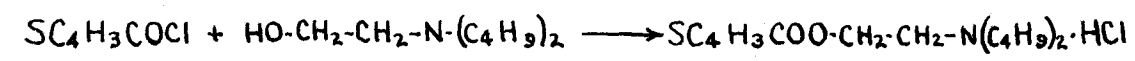
H. β-Diisobutylaminoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:



Procedure: 2.0 grams (0.0137 mole) of α-thenoyl chloride dissolved in 10 cc. dry benzene were added slowly with stirring to 2.42 grams (0.014 mole) of β-diisobutylaminoethanol contained in 15cc. of benzene. The mixture was refluxed on a water bath for 2 hours. On cooling, an oil separated which did not crystallize. No amount of stirring or cooling started crystallization. Only after 6 weeks standing on the desk did it crystallize. The precipitate was filtered from the benzene and dissolved in absolute ethyl alcohol. Ethyl ether was added in small portions over a period of several days. The ester-hydrochloride gradually came out as white crystals, melting at 118-121°. A yield of 1.5 grams (0.004 mole, 30% of theory) was obtained.

Analysis: Percent chlorine calculated - 11.08
Percent chlorine found - 11.02

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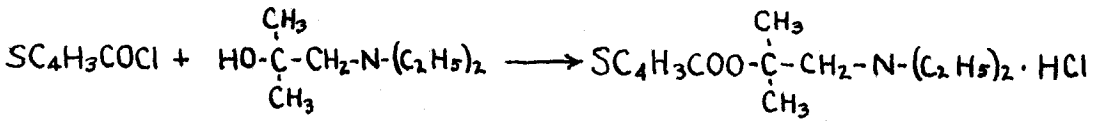
I. α,α-Dimethyl-β-diethylaminoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:



Procedure: 2.0 grams (0.0137 mole) of α-thenoyl chloride in 5 cc. benzene were added gradually with stirring and cooling to 2.05 grams (0.0142 mole) of α,α dimethyl-β-diethylamino-ethanol contained in 20 cc. of benzene. The mixture was refluxed on a water bath for 2 hours. On standing over night, no ester-hydrochloride separated. Addition of ether precipitated a small amount of an oil which crystallized in standing. The ether and part of the benzene was distilled off and more ether added to re-precipitate the material. The crystals so obtained were dissolved in a hot mixture of benzene and absolute ethyl alcohol. Addition of ether to the cooled solution precipitated the ester-hydrochloride which was filtered off and dried at 100°C. The yield was 1.5 grams (0.0052 mole, 38% of theory) of material melting at 181-183°.

Analysis: Percent chlorine calculated - 12.15
Percent chlorine found - 12.24

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J. β-Piperidinoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:

Procedure: 1.7 grams (0.0148 mole) of β-piperidinoethanol were dissolved in 20 cc. of cold 10% sodium hydroxide solution. The solution was well cooled and shaken while 2.0 grams (0.0137) of α-thenoyl chloride were added dropwise. After all the thenoyl chloride had been added fifteen minutes were allowed for completion of the reaction. The mixture was extracted with ether and the extract dried over anhydrous sodium sulfate. Hydrogen chloride gas was passed in until no more precipitate formed. The product was recrystallized twice from anhydrous ethyl alcohol, ether being added to complete the precipitation. 2.0 grams (0.0073 mole, 53% of theory) of material melting at 185-186.5° were obtained.

Analysis: Percent chlorine calculated - 12.86
Percent chlorine found - 12.98

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K. β-Morpholinoethanol Ester of Thiophene-α-carboxylic Acid

Reaction:

$$C_4H_3S\text{-}COCl + HO\text{-}CH_2\text{-}CH_2\text{-}N(CH_2)_4O \longrightarrow C_4H_3S\text{-}COO\text{-}CH_2\text{-}CH_2\text{-}N(CH_2)_4O \cdot HCl$$

Procedure: 2.0 grams (0.0137 mole) of α-thenoyl chloride dissolved in 5 cc. of benzene were added slowly with stirring to a cold solution of 2.0 grams (0.0148 mole) of β-morpholinoethanol contained in 20 cc. of benzene. The mixture was refluxed for 2 hours on a water bath. On cooling, a precipitate of the ester-hydrochloride formed which was filtered off and recrystallized from absolute ethyl alcohol. 1.0 gram (0.0036 mole, 26% of theory) of material melting at 211° was obtained. The low yield was occasioned by losses during the purification.

Analysis: Percent chlorine calculated - 12.77
Percent chlorine found - 12.93

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L. γ-Diethylaminopropanol Ester of Thiophene-α-carboxylic Acid

Reaction:

$$C_4H_3S\text{-}COCl + HO\text{-}(CH_2)_3\text{-}N\cdot(C_2H_5)_2 \longrightarrow C_4H_3S\text{-}COO\text{-}(CH_2)_3\text{-}N\cdot(C_2H_5)_2\cdot HCl$$

Procedure: 2.0 grams (0.0137 mole) of α-thenoyl chloride dissolved in 10 cc. benzene were added slowly with cooling and stirring to 1.84 gram (0.014 mole) of γ-diethylamino-propanol contained in 20 cc. of benzene. Addition of ether caused the precipitation of a small quantity of crystals. The ether and about half the benzene were distilled off and more ether added. The crystals so obtained were dissolved in a hot mixture of benzene and absolute ethyl alcohol and the solution cooled. Ether was added to precipitate the ester-hydrochloride as a crystalline solid. It was necessary to repeat the recrystallization as the product was somewhat colored. 1.0 gram (0.0036 mole, 26.5% of theory) of material melting at 112-115° was obtained.

Analysis: Percent chlorine calculated - 12.76
Percent chlorine found - 12.73

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M. γ-Dibutylaminopropanol Ester of Thiophene-α-carboxylic Acid

Reaction:

$$C_4H_3SCOCl + HO\text{-}(CH_2)_3\text{-}N\text{-}(C_4H_9)_2 \longrightarrow C_4H_3SCOO\text{-}(CH_2)_3\text{-}N\text{-}(C_4H_9)_2 \cdot HCl$$

Procedure: 2.5 grams (0.0182 mole) of α-thenoyl chloride dissolved in 10 cc. benzene were added slowly to a cold solution of 3.2 grams (0.0184 mole) of γ-di-n-butylamino-propanol in 40 cc. of benzene. The mixture was refluxed on a water bath for 2 hours. On cooling neither oil nor solid separated. Addition of ether caused the ester-hydrochloride to separate as a crystalline solid. The crystals were filtered off, dissolved in absolute ethyl alcohol, and reprecipitated with ether. 3.5 grams (0.0114 mole, 76% of theory) of material melting at 96-97° were obtained.

Analysis: Percent chlorine calculated - 10.62
Percent chlorine found - 10.85

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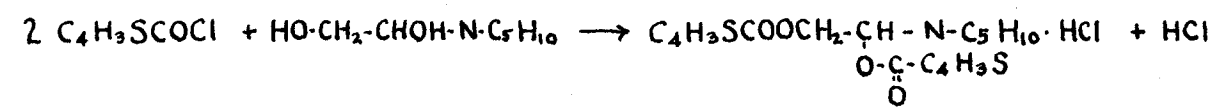
N. Piperidinopropanediol Ester of Thiophene-α-carboxylic Acid

Reaction:



Procedure: This preparation was carried out in a manner similar to that used by Walters (66) for such esters. 1.0 gram (0.0069 mole) of piperidinopropanedial was added to 20 cc. of 10% sodium hydroxide solution and the mixture cooled with water. 3.0 grams (0.0205 mole) of α-thenoyl chloride were added gradually with constant cooling and shaking. Fifteen minutes were allowed for completion of the reaction after all the acid chloride was added. The mixture was extracted with ether and the ether in turn extracted with dilute hydrochloric acid. The acid solution was covered with ether and solid sodium carbonate added to liberate the free base which dissolved in the ether layer. After the ether had been dried over anhydrous sodium sulfate, hydrogen chloride gas was passed in. The ester-hydrochloride came out as an oil which crystallized after an hour or so. The solid was dissolved in anhydrous ethyl alcohol and re-precipitated slowly by gradual addition of ether. 1.7 grams (0.0041 mole, 60% of theory) of material melting at 144° were obtained.

Analysis: Percent chlorine calculated - 8.52
Percent chlorine found - 8.43

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O. Methylsuccinic Acid

The preparation of methyl succinic acid was attempted by the following reactions:

$$CH_3\text{-}\underset{Br}{CH}\text{-}CH_2Br + NaCN \longrightarrow CH_3\text{-}\underset{CN}{CH}\text{-}CH_2\text{-}CN \xrightarrow{H_2O} HOOC\text{-}\overset{CH_3}{\underset{|}{C}}H\text{-}CH_2\text{-}COOH$$

Simpson(91) prepared the dinitrile in this manner but did not state the yield obtained. A similar reaction between trimethylene bromide and sodium cyanide gives 85% of the theoretical yield.

A 1-l. flask fitted with a condenser and dropping funnel, containing 60 cc. of water and 58.8 grams(1.2 mole) of sodium cyanide was heated on a steam bath until most of the cyanide dissolved. 100 grams (.5 mole) of propylene bromide dissolved in 200 cc. of 95 percent alcohol were added through the dropping funnel. About 1/2 hour was required for the addition. The mixture was refluxed on the steam bath for 40 hours, after which the alcohol was distilled off at reduced pressure. The residue was extracted with 100 cc. of ethyl acetate and the filter cake washed with another 100 cc. of ethyl acetate. The solvent was distilled off and the residue fractionated. The yield was very bad, only 8 grams (.085 moles, 1.7% of theory) of material boiling at 277-290°. It was thought that perhaps the period of refluxing had been too long. However, shorter reaction times gave no better results and the method was abandoned.

The method of Bone and Sprankling (92) was found to give much better results. Necessary materials are ethylcyanoacetate (93) and ethyl-α-bromopropionate, the latter being made by

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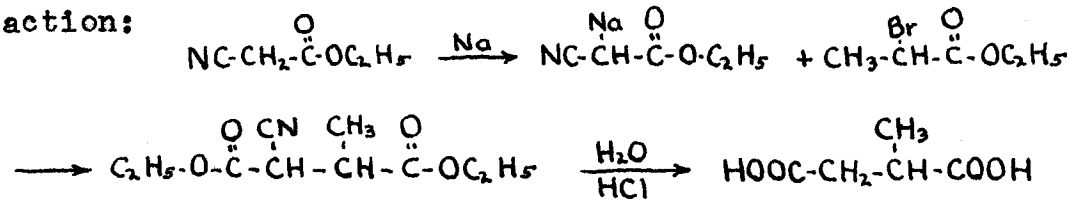
the method of Zelinsky (94).

Reaction:



Procedure: 5.75 grams (0.25 atom) of sodium were dissolved in 90 cc. of absolute ethyl alcohol and 28.5 grams (0.252 mole) of ethyl cyanoacetate added from a dropping funnel with stirring. A white precipitate of the sodium compound formed. 42 grams (0.26 mole) of ethyl-∝-bromopropionate were added from a dropping funnel with stirring and cooling. Heat was evolved and sodium bromide precipitated as the reaction proceeded. The mixture was heated on a water bath for one hour, cooled, and poured into water. The oil which separated was extracted with ether and the extract dried over calcium chloride. The ether was evaporated off and the residue distilled at low pressure. 3.5 grams (0.164 mole, 66% of theory) of material boiling at 140-165° at 20 mm. were obtained. This was added to about six times its volume of concentrated hydrochloric acid and the mixture refluxed for six hours on a sand bath. After cooling, the acid was neutralized with concentrated ammonia solution and heated to boiling. 23 grams (25% excess) of calcium chloride in a minimum of water were added, whereupon the calcium salt of methylsuccinic acid precipitated. The boiling was continued for half an hour to coarsen the precipitate, after which

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the salt was filtered off, washed with hot water and dried at 140°C. A yield of 19.5 grams (0.115 mole, 70% of theory) was obtained. The calcium salt was dissolved in a minimum of boiling dilute hydrochloric acid, from which the methylsuccinic acid deposited on cooling. The quantity obtained was 13.0 grams (0.0985 mole, 86% of theory). A portion of it was recrystallized from benzene, in which it is only moderately soluble, giving a product melting at 111°. The overall yield was 40%.

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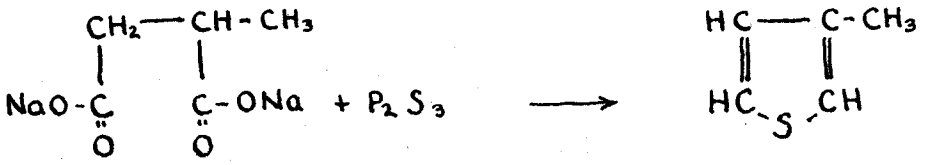
P. β -Methyl Thiophene

Reaction:



Procedure: 27.0 grams (0.205 mole) of methyl succinic acid were converted to the di-sodium salt and dried at 140° for 24 hours. An intimate mixture of this and 45 grams (0.285 mole) of finely ground P_2S_3 (95) was placed in a 300 cc. round bottom flask fitted with a condenser for distillation. The receiver was a filter flask set in an ice-salt mixture and the exit gases were passed into a 500 cc. round bottom flask. The latter contained 40 grams of cracked ice and 20 cc. of 40% sodium hydroxide solution. A stream of dry CO_2 was passed through for 15 minutes to sweep out all the air. Moderate heat from a low Bunsen flame was applied for 30 minutes. The mass darkened and some distillate came over. Towards the end of the reaction, the full force of the burner was used. Quite a bit of sublimate formed in the neck of the flask and in the condenser. The distillate was taken up with ether, dried over calcium chloride and the ether distilled off. The residue was distilled, small equipment being used. 5.5 grams (.056 mole, 27.5% of theory) of material boiling at 114° were obtained. The yield was low but all that could be expected of the reaction.

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Q. Attempted Oxidation of β-Methyl Thiophene

Oxidation of β-methyl thiophene to the corresponding acid was attempted by the use of chromic acid anhydride and acetic anhydride in glacial acetic acid. In the first attempt, a small amount of the β-methyl thiophene was dissolved in 15 cc. of glacial acetic acid containing enough acetic anhydride to react with the theoretical quantity of water formed and a 100 percent excess of chromic acid anhydride added. On gentle warming, a very vigorous reaction occurred. Indications were that the thiophene compound had been destroyed and none of the desired acid was obtained from the residue. A second trial under less stringent conditions was made. 1.0 gram (.01 mole) of β-methylthiophene was dissolved in 15 cc. of glacial acetic acid containing 1 gram (.01 mole) of acetic anhydride. The solution was held at 50° on a water bath and 2.5 grams (.025 mole, 20% excess) of chromic acid anhydride added in very small portions over a period of 10 hours. Each portion was allowed to react before more was added. After all the CrO_3 reacted, the mixture was poured into 100 cc. of water and this extracted with ether. Evaporation of the ether left a small quantity of tarry material. This was treated with dilute sodium hydrochloride solution and undissolved matter removed with ether. The aqueous solution was acidified and extracted once more with ether. Evaporation of the ether left a minute quantity of a

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tarry substance. As this procedure had been demonstrated to give a fair yield of benzoic acid from toluene, the action of the chromic acid must have destroyed the thiophene ring.

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SUMMARY

A series of ten dialkylaminoalkyl esters of thiophene-α-carboxylic acid has been prepared, nine of the preparations being new ones. The esters were characterized as hydrochlorides, the form in which such compounds are most generally applied.

The activities of the compounds are being determined in the laboratory of the William S. Merrell Company, by the rabbit cornea method. At present, the results are not available and will be presented in an appendix. The diethylaminoethyl, the piperidinoethyl, the morpholinoethyl, the piperidinopropanediol, and the diisobutylamino esters showed no definite action when tested on the tongue. The other esters of thiophene-α-carboxylic acid ranked as follows in order of increasing duration of action on the tongue: the γ-diethylaminopropyl, the dipropylaminoethyl and the α,α dimethyl-β-diethylaminoethyl, the dibutylaminoethyl, and the dibutylaminopropyl. The tongue test is purely qualitative but several observations may be made. Increasing the molecular weight of the N-alkyls (straight chains only), increases the activity, an expected result. Alkylating the carbon chain connecting oxygen and nitrogen atoms, thus producing a branched chain as well as an increase in molecular weight, resulted in increased activity. It is interesting to note that within the limits of the tongue test, changing the N-alkyls from ethyl to propyl (an addition of two methyl groups) produced about the same increase in activity as adding two

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methyl groups to the carbon atom adjacent to the carboxy group. Branching the N-alkyls produced a definite decrease in activity, even more so than was expected. Perhaps the more exact pharmacological data will permit a comparison with existing data for benzoic and furoic acid analogues of several of the above compounds.

The preparation of thiophene-β-carboxylic acid by oxidation of β-methylthiophene with chromic acid anhydride and acetic anhydride in glacial acetic acid has been attempted. This method did not yield the desired compound. Indications were that the oxidizing agent destroyed the thiophene nucleus.

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