THE SYNTHESES OF SOME OMEGA-TERTIARY AMINE SALTS OF SUBSTITUTED ACYL-3-AMINOTHIOPHENES

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By

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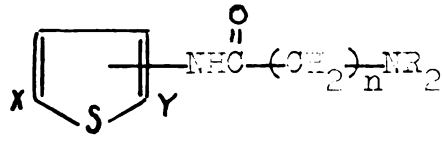
ABSTRACT

THE SYNTHESES OF SOME OMEGA-TERTIARY AMINE SALTS OF SUBSTITUTED ACYL-3-AMINOTHIOPHENES

by Arthur S. Teot

The purpose of this investigation was to develope synthetic methods for the preparation of a series of thiophene derivatives having the following general structure:



It was anticipated that such compounds would show high physiological activity with such an amide group based on studies reported in the literature with similar phenyl compounds.

The starting material for the synthesis of these compounds was 3-theramide. This was prepared from 3-methylthiophene by a simplification of Campaigne's procedure[1]. 3-Thenamide was allowed to undergo a Hofmann rearrangement and the resulting amine was acylated in the alkaline NaOBr reaction media with either chloroacetyl chloride or β-chloropropionyl chloride. The β-chloro-3-propionamidothiophene was isolated and analysed. The 2,5-dibromo and 2-nitro ring substituted derivatives of 3-thenamide were prepared following the procedures of Campaigne and

Monroe[2].

The ω-(N,N-dialkylamino)-3-amidothiophenes were synthesized, in dry dioxane solution at room temperature, by displacement of the ω-chlorine with excess piperidine, diethylamine or morpholine respectively. The products were separated from the dioxane solvent and the excess secondary amine was removed by steam distillation or by precipitation with water and water washing of the precipitate. After several additional purification steps, the final products were characterized either as their hydrochloride or quaternary methyl-iodide salts. Results of pharmacological testing of these compounds will be reported elsewhere.

2-Thenamide was subjected to a Hofmann rearrangement but failed to react thus confirming Campaigne's previous results[2]. Additional studies on the 2-thienyl series included an attempted preparation of N-bromo-2-thenamide, the synthesis of 2-thenoyl azide and an attempted Curtius rearrangement of the latter which failed to give a definative result.

References

(1) Campaigne, E. et al, Org. Syntheses, 33, 93, 94 and 96 (1953).

(2) Campaigne, E. and Monroe, P.A., J. Am. Chem. Soc., 76. 2447 (1954).

DEDICATION

To My Wife

ACKNOWLEDGMENT

The author wishes to express his appreciation
for the aid and guidance given by
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which made possible the completion
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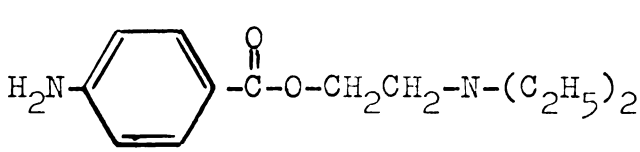
INTRODUCTION

The relationships between chemical structure and physiological effect in organic materials have interested man since the beginnings of the science of chemical theropeutics. In 1937, Lofgren[1] generalized the structural requirements for an organic chemical which would have local anesthetic properties, as

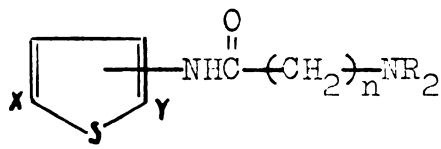
$$A\text{-}M\text{-}(CH_2)_nNR_2$$

where A represents an aryl group and M is a heteroatom or a group having one or more such atoms. The length of the polymethylene chain (ie., the value of "n") between the aromatic and tertiary amine groups is important but the optimum value of n varies with the remainder of the chemical structure. Usually, however it is 2 or 3. In the majority of the commercially important local anesthetics, A is a phenyl or substituted phenyl group and M is an ester linkage. For example, "Procaine" or "Novocaine" which was first synthesized and shown to be superior to the naturally occurring "Cocaine" by Einhorn[2] has the structure:



The thiophene analog of "Procaine"[3] and a number of other esters of 2- and 3- thenoic acids[4] have been prepared and tested pharmacologically.

It was the primary purpose of this investigation to synthesize thiophene derivatives which might possess outstanding local anesthetic properties by replacing the ester linkage with an amide group. The compounds prepared in this study can be represented by the general formula:

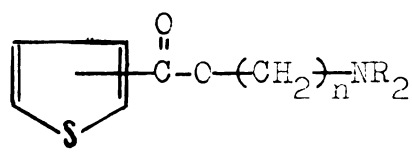


Anticipation for high physiological activity with the amide group can be found in the recent literature. "Lidocaine", ω-diethylamino-2,6-dimethyl-acetanilide has been found to have twice the potency of "Procaine", with less toxic and fewer side effects[5]. Further it was the purpose of the present investigation to determine the effect of various substituents on the thiophene ring, length of hydrocarbon residue (value of "n") and the importance of the tertiary amine grouping on the anesthetic properties. This thesis, however, will concern itself with the preparation of the heterocyclic amides as the pharmacological results will be reported elsewhere.

HISTORICAL

A comparison of the physiological effects of certain benzene and thiophene compounds has aroused considerable interest for several years and the status of the field has been reviewed by Blinke[6] and more recently by Campaigne[7]. Some work has been reported substituting the thiophene for the benzene nucleus in local anesthetics, mostly analogs of effective phenyl compounds. Dann[3] made and tested the 2-thienyl analog of "Procaine" and reported an average duration of anesthesia of 120 minutes for the 5-amino-2-thienyl ester as compared to 100 minutes for "Procaine" in the rabbit cornea test.

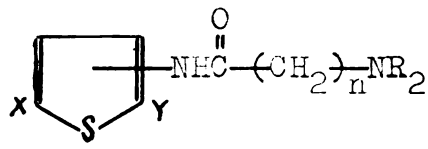
The most complete study was that of Campaigne and LeSuer[8] who prepared a series of compounds having the formula



substituted in both the 2 and 3 positions of the thienyl ring. The only two compounds having local anesthetic activity were the 2- and 3-thienyl derivatives where n=3 and R=n-butyl. In the corneal irrigation test, both compounds gave 20 - 22 minutes of anesthesia which is in the range for "Butyn".

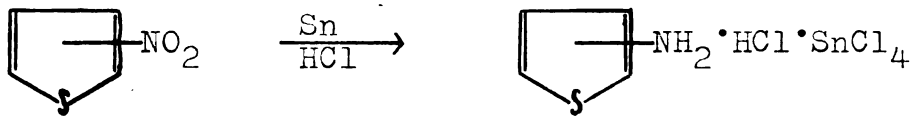
The general type of compounds investigated in the present study can be represented by the general

formula:



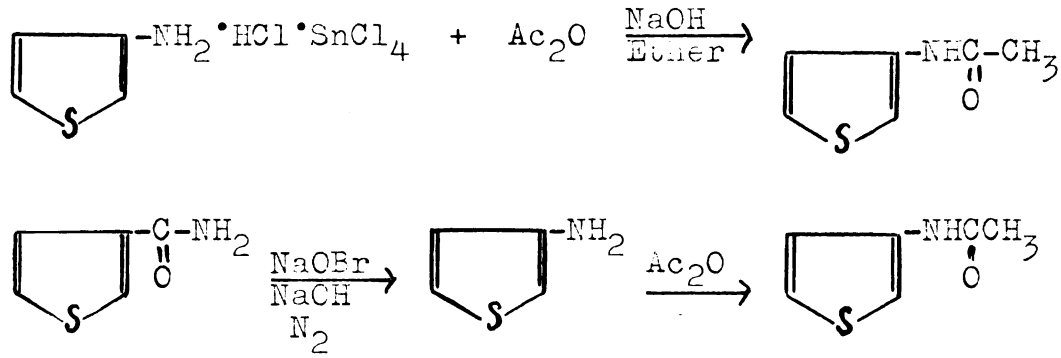
It is to be noted that they are acylated amines, rather than amides of 2- and 3-thenoic acid, and hence might be expected to show a greater difference in their physiological properties than just the substitution of an amide linkage for an ester group. The work reported in this thesis deals with the synthesis of these ω-alkylamino substituted acyl aminothiophenes and does not include the physiological studies, which will be reported elsewhere.

The first step in the preparation of the desired compounds was to obtain the aminothiophenes. Both 2- and 3-aminothiophenes have been prepared in fair yield by the reduction of the corresponding nitrothiophenes and their isolation as a double salt of stannic chloride[9] [10] [11] according to the following equation:

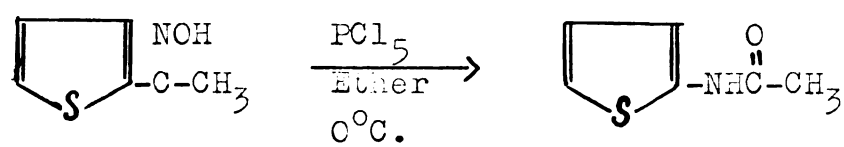


The free 2-aminothiophene has been distilled in an inert atmosphere[10] but rapidly becomes a gummy tar in an ordinary atmosphere. The hydrochloride salt of 2-aminothiophene has supposedly been made by Tohl[12]

but it was "too hygroscopic" to obtain a melting point. The 3-aminothiophene has not been isolated either as the free amine or as its hydrochloride[11][13] but the N-acetyl derivative of this amine has been prepared by the action of acetic anhydride on 3-aminothiophene obtained from the $SnCl_4$ double salt[11] or by Hofmann rearrangement of 3-thenamide[13].

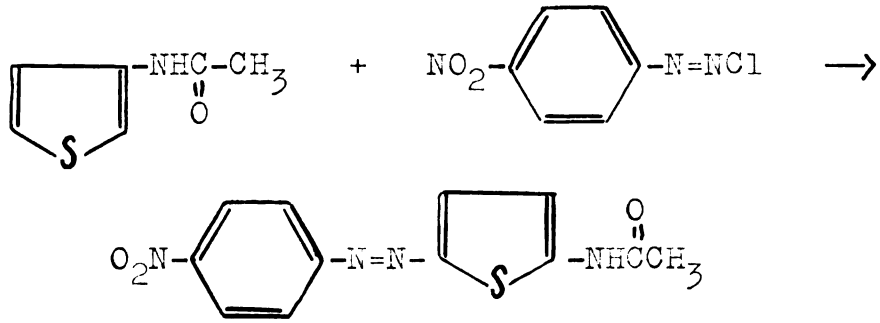


The isomeric 2-acetamidothiophene has been synthesized both from the double salt[10] and by a Beckmann rearrangement of the oxime of 2-acetylthiophene[10].



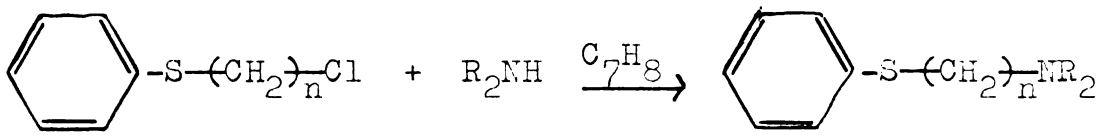
Nuclear substitution reactions of 2-acetamidothiophene were first described by Steinkopf[11] and more recently in the studies by Hurd et al[14] [15] [16]. Nitration, bromination, sulfonation and mercuration occur first in the 5-position of the thiophene ring with a second substituent entering the 3-position.

A nitro group can be displaced by a chloro, the 5-position being the most susceptible[15]. An azo dye readily formed when 2-acetamidothiophene was coupled with *p*-nitrobenzenediazonium chloride[16].



Campaigne et al[13] have carried out bromination, chlorination, iodination, nitration and coupling reactions with 3-acetamidothiophene. Substitution occurs initially in the 2-position while a second group attacks the 5-position.

Reaction of the *ω*-chloro group in a *ω*-chloroalkylphenyl sulfide with a secondary amine has been carried out previously by Kim and Schuetz[17] to obtain tertiary amine derivatives of mixed phenyl alkyl sulfides.



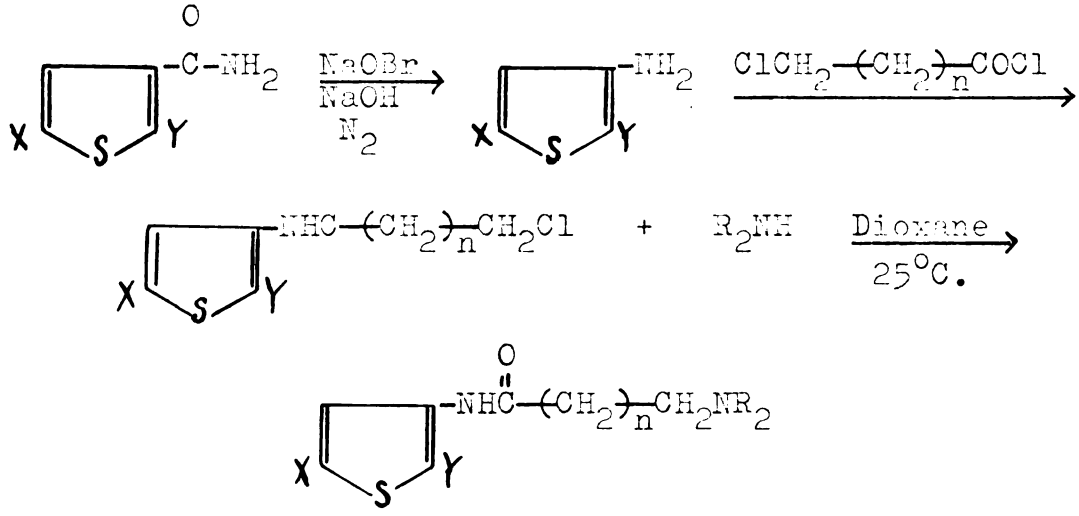
A two mole excess of the secondary amine was employed which, together with removal of the hydrogen chloride formed in the reaction as the secondary amine hydro-

chloride salt, served to drive the reaction to completion.

DISCUSSION

3-AMINOTHIOPHENE DERIVATIVES

The aminoalkyl substituted acyl-3-aminothiophenes studied in this investigation were prepared by the following sequence of reactions:



where X = H, Br n = 0, 1

Y = H, Br, NO_2 R_2 = piperydyl, morpholyl, diethylamino.

A. β-Chloro Acyl-3-Aminothiophenes

The β-chloro substituted acyl-3-aminothiophenes were synthesized by carrying out a Hofmann rearrangement on 3-thenamide and acylating directly the resulting amine with an ω-chloro-acid chloride without isolation of the intermediate amine following the procedure of Campaigne and Monroe[13]. A sodium hypobromite solution was prepared by adding bromine to an ice cold (0-10° C.) aqueous NaOH solution containing

excess NaOH. The solution of the 3-thenamide or substituted 3-thenamide was stirred under a nitrogen atmosphere for about an hour after the amide had dissolved. Usually the reaction solution darkened and warmed spontaneously to 30-40° C. The rearrangement was completed by heating the alkaline reaction mixture for 30-60 minutes at 70-85° C. During this time, the 3-thenamide reaction mixture remained clear and took on a deep red coloration although the 2,5-dibromo-3-thenamide turned black and an insoluble product formed. After immediately cooling the reaction mixture in an ice bath, the amine was acylated directly with an ω-chloro acid chloride without attempting isolation of the free amine. The product was recovered by filtration, washed with water and recrystallized from a hot water-ethanol mixture, decolorizing with activated carbon. The Hofmann rearrangement was carried out many times (Table I A) and the yield is usually 25-30%. The principal side reaction is presumably polymerization of the amine[13] but some decomposition also occurs during the recrystallization as evidenced by darkening in color of the product and formation of a small amount of a tarry material. Darkening of the aqueous solution of the product has even been observed while it was set aside at room temperature in the dark.

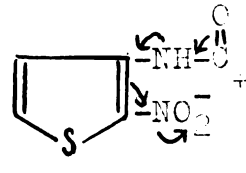
The thiophene nucleus was substituted in the 2-position with a nitro group and in the 2,5-positions

with bromine. Usually the substitution was carried out after the Hofmann rearrangement but 2,5-dibromo-β-chloro-3-propionamidothiophene has also been prepared by rearrangement of the substituted 3-thenamide. The 2,5-dibromo-3-thenoic acid was first prepared[18] by brominating 3-thenoic acid in glacial acetic acid at room temperature. This was converted to the amide via its acid chloride and the Hofmann rearrangement was carried out with the 2,5-dibromo-3-thenamide in a manner similar to that employed for the 3-thenamide. The overall yield of the amide from 3-thenoic acid was rather low, 4.9%. Conducting the Hofmann rearrangement on the unsubstituted amide and brominating the β-chloro-3-propionamidothiophene in glacial acetic acid gave a 7.8% overall yield from 3-thenoic acid. (Tables I A and I B). This difference in the yields of the amide obtainable from the two procedures is not significant since it is based on only a single set of experiments.

Nitration in the 2-position of the thiophene ring was accomplished by very slowly adding concentrated HNO_3 to β-chloro-3-propionamidothiophene dissolved in acetic anhydride at -15 to -5°.[13] The product was isolated by immediately pouring the reaction mixture into ice water and neutralizing the anhydride with Na_2CO_3. The product was recovered by filtration, washing it with water and recrystallizing it from a

water-ethanol mixture following treatment of the latter with activated carbon (Table I B).

The physical, chemical properties and analyses of the β-chloro-acyl-3-aminothiophenes are summarized in Table II. Both the 2-nitro and the 2,5-dibromo-β-chloro-3-propionamidothiophenes have been prepared a sufficient number of times during the course of this work to establish that the yield of the nitro is higher than the 2,5-dibromo compound (Table I B). It is not known whether this is due primarily to an increased yield in the reaction or less decomposition in the isolation of the products. If it were the latter, the still lower average yield of the unsubstituted compound could legitimately be considered and the general conclusion might be drawn that the more electronegative the substituent on the thiophene ring the higher the yield. This is the observed fact but the most likely decomposition mechanism (hydrolysis of the amide and polymerization of the amine thus formed) would be expected to show the opposite order of stability. Attack by a nucleophilic reagent (H_2O or OH^-) on the carbonyl group should be facilitated by electron withdrawing groups in the thiophene ring, viz.



Therefore hydrolysis would be easier with the 2-NO_2 compound and the expected yield should be poorer.

B. ω-N,N-(Dialkylamino)-Acyl-3-Aminothiophenes

Initially the tertiary amine salts were synthesized according to the method of Kim and Schuetz[17] in which the ω-chloro compound was refluxed in dry toluene with excess secondary amine and the excess amine was separated by steam distillation from the reaction mixture. Extensive decomposition occurred with this procedure as evidenced by the acid insolubility and black, tarry appearance of the product which remained in the distillation flask thus necessitating development of an alternative method for the preparation of these compounds.

The following successful preparation was eventually developed. The amination was performed in dry dioxane at room temperature during at least a 16 hour period in the presence of a two molar excess of the secondary amine. Water was then added to the reaction mixture to dissolve the amine hydrochloride and precipitate the higher molecular weight product, β-morpholyl-3-propionamidothiophene was an exception in that it had to be steam distilled. The precipitate was then thoroughly washed with water to remove any remaining secondary amine. It was then dissolved in aqueous hydrogen chloride and any unreacted starting material was re-

moved by extraction with ether. The aqueous phase was made alkaline, ether extracted, the ether layer dried with anhydrous sodium sulfate, filtered and the tertiary amine precipitated with gaseous hydrogen chloride. A variety of solvents (usually dry isopropyl alcohol or ethanol) were used for recrystallization of the hydrochloride salts. One product (β-diethylamino-3-propionamidothiophene) failed to yield a solid hydrochloride so a quarternary salt was prepared[19] by agitating an ether solution of the β-chloro-3-propionamidothiophene with excess methyl iodide for 39 hours at room temperature. The crude product was a sticky solid adhering to the bottom of the flask and was isolated by decanting the solvent, dissolving the residue in absolute alcohol, treating with activated carbon, filtering and allowing the salt to recrystallize. The preparations of the ω-(N,N-dialkylamino)-acyl-3-aminothiophenes are summarized in Table III and the properties and analysis of the hydrochloride and methyl iodide quarternary salts are tabulated in Table IV.

The preparation of α-piperidyl-3-acetamidothiophene differed from the propanamido derivative in that the intermediate chloro compound from the chloroacetyl chloride acylation of the 3-aminothiophene formed by the Hofmann rearrangement was not purified and isolated to prevent the hydrolysis of the α-chloro atom in α-chloroacetamidothiophene. The amination reaction

with piperidine was accomplished as usual in a dry dioxane solution but some difficulty was experienced with recrystallization of the product and the yield was only 6.6%, possibly because of the impure starting material.

There is no pattern discernible regarding the yields of the various salts but the melting points are in the order morpholyl > piperidyl > diethylamino. Regarding the influence of ring substituents on the melting point; the unsubstituted ring compounds have the highest melting points, the 2-nitro derivatives are intermediate and the 2,5-dibromo compounds have the lowest melting points.

C. 3-Thenal

Campaigne et al[20] [21] describe a method of preparing 3-thenal from 3-methylthiophene in satisfactory yields according to the equations given on page 49. The first step in this synthesis was the preparation of 3-thenyl bromide by the free radical bromination of the methyl group with N-bromosuccinimide in benzene as a solvent. Isolation of the 3-thenyl bromide is hazardous because it is a powerful lachrymator and has been known to explode during distillation. The Sommelet reaction was utilized to convert the 3-thenyl bromide to 3-thenal, i.e., a quaternary bromide was formed with hexamethylenetetraamine which was decomposed to the

aldehyde and amines by steam distillation. The aldehyde was extracted into ether from an acid solution and distilled.

When the aldehyde is desired, a simplified procedure giving comparable yields has been developed. Following preparation of the 3-thenyl bromide and removal of the succinimide by filtration, the quaternary bromide was formed by adding hexamethylenetetramine to the benzene solution employed in synthesis of the 3-thenyl bromide. The mixture was usually allowed to react overnight at room temperature and completed by warming it to 50° C. for a couple of hours. The remainder of the preparation was the same as that described by Campaigne.

D. 3-Thenamides

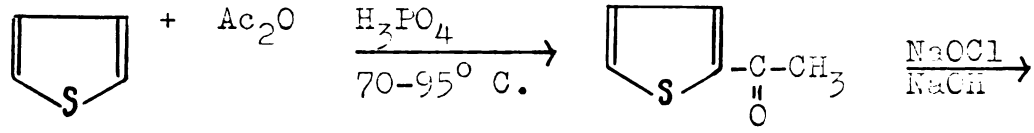
The 3-thenal was oxidized to 3-thenoic acid by silver oxide following the procedure of Campaigne et al[21]. This is a very clean reaction and the yield was always greater than 90%. The acid was converted to the acid chloride by refluxing it with excess $SOCl_2$; the unreacted $SOCl_2$ was removed by distillation and the 3-thenamide was formed by slowly pouring the acid chloride into concentrated ammonium hydroxide at room temperature. The 3-thenamide was recrystallized from hot water.

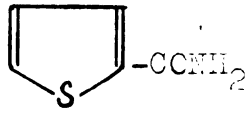
2,5-Dibromo-3-thenamide was synthesized employing

the procedure just described starting with 2,5-dibromo-3-thenoic acid. The acid was made by adding bromine to 3-thenoic acid dissolved in glacial acetic acid at room temperature[18].

2-Substituted Thiophenes

It seemed worthwhile to repeat the Hofmann rearrangement of 2-thenamide attempted by Campaigne and Monroe[13]. The preparation of 2-thenamide was accomplished by the following series of reactions[22][23][24].





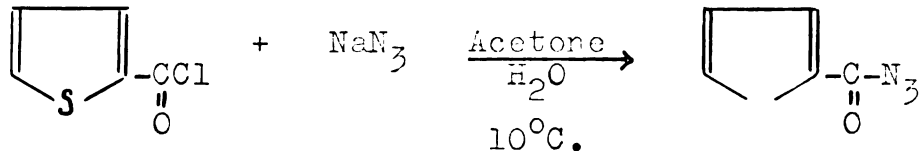
The process is straightforward and will not be described here in detail (experimental section). The overall yield for the four steps, based on a single trial, was 49.7%. This compares with a 30.7% yield for the six step synthesis (only three products were isolated) of 3-thenamide from 3-methylthiophene.

The Hofmann rearrangement of 2-thenamide was

attempted employing the identical procedure as that used successfully for 3-thenamide except that the acylating agent was acetic anhydride and the temperature was not allowed to rise above 37° C. Only a small amount of an unidentified, very water soluble solid and about 6% of unreacted amide were recovered. Campaigne and Monroe[13] also failed to isolate any 2-acetamidothiophene. When heated to 60-70° C., they observed ammonia evolution and 2-thenoic acid was recovered in about 80% yield.

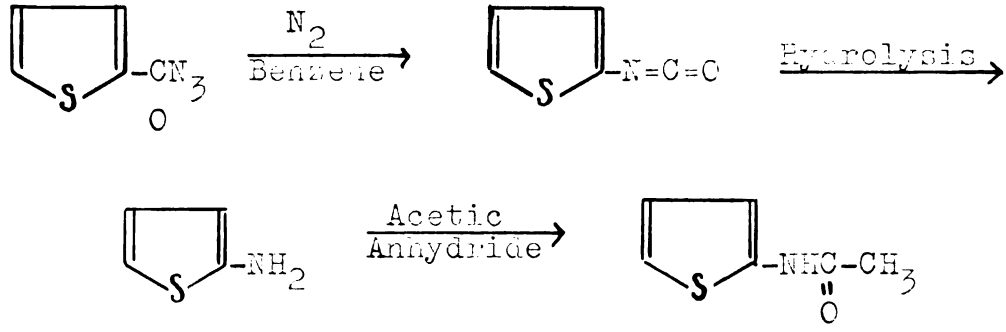
Since it is known that the first step in the Hofmann rearrangement is the formation of a N-bromo compound, preparation of N-bromo-2-thenamide was attempted in chloroform to eliminate hydrolysis which could occur in the alkaline hypobromite solution. The 2-thenamide and bromine were heated to reflux in a chloroform solution, cooled, potassium hydroxide was added and the precipitate which formed was recrystallized from water. From the melting point of this material (163° C.), it was concluded that bromination of the thiophene ring had occurred.

After failure of the Hofmann rearrangement with 2-thenamide, a Curtius rearrangement of 2-thenoyl azide was attempted. The azide was prepared in accordance with the equation [25]:



The sodium azide was dissolved in ice water and the 2— thenoyl chloride dissolved in acetone was added portionwise, during a period of 1 - 1.5 hours. The azide product was recovered by filtration and dried in a vacuum dessicator (73.3% yield).

The Curtius rearrangement was accomplished in refluxing benzene as a reaction mixture under a nitrogen atmosphere[26] to give 2-thienyl isocyanate which supposedly could be hydrolysed to 2-aminothiophene.



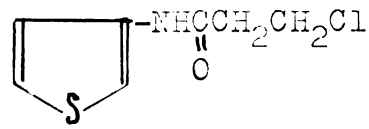
It is thought that the isocyanate was formed but alkaline hydrolyse and warming with acetic anhydride failed to yield any 2-acetamidothiophene. An acid hydrolysis of the isocyanate was also tried and reaction of the supposed amine with chloroacetyl chloride gave a tarry material. No pure compounds could be obtained from the tarry material.

It is worth describing an experimental observation

which should be investigated further and could lead to some interesting dye chemistry. Following the Hofmann rearrangement, crude β-chloro-3-propionamido-amidothiophene was customarily treated with activated carbon in a hot water-alcohol mixture and vacuum filtered through a fritted glass funnel. Part of the time, a solid which was only slowly soluble in acetone (β-chloro-3-propionamidothiophene is very soluble) collected on the underside of the filter. If this is treated with a warm concentrated nitric acid, a brilliant blue color is formed. The color is soon discharged, presumably being oxidized by the nitric acid.

EXPERIMENTAL

β-CHLORO-3-PROPIONAMIDOTHIOPHENE



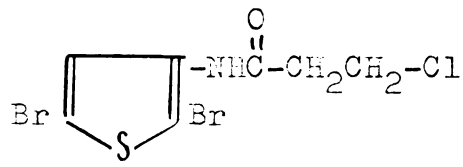
A 500 ml., three-necked, round bottom flask equipped with standard taper joints and fitted with a N_2 gas inlet tube, stirrer, dropping funnel and supported in an ice bath was charged with 22g. (0.55 moles) of NaOH dissolved in 180 ml. distilled water. A 23.3 g. (0.145 moles) quantity of bromine was added slowly to the ice cold alkaline solution. The flow of nitrogen was started, the ice bath was removed and 12.79 g. (0.1 moles) of 3-thenamide were added to the reaction mixture. The amide dissolved while the reaction temperature was allowed to rise during a period of about 1 hour to 30 - 40° C. The reaction solution then was heated at 70 - 80° C. until its color became dark red (about 45 minutes). The flask was immediately cooled with an ice bath to below 10° C. and 12.7 g. (0.1 moles) of β-chloropropionyl chloride were added dropwise during about 3 minutes while a slow flow of nitrogen was maintained. After stirring the mixture for 10 - 15 minutes, the brown precipitate was recovered by filtration, washed, heated to boiling in 600 ml. of water and enough alcohol was added to dissolve all the solid. The solution was then decolorized with activated carbon and filtered

hot through a fritted glass filter precoated with filter-aid. Upon cooling in ice water, a flocculant white precipitate formed, which after filtering and drying overnight in a convection oven at 50° C., gave a light tan colored powder. Additional product was obtained by washing the filter cake with acetone and alcohol until the effluent was substantially colorless, adding the amber solution to 500 - 600 ml. of water and evaporating it on a hot plate until the first sign of a precipitate began to appear. The activated carbon from the previous crystallization was employed to decolorize the product and the previously described recovery procedure was used. The combined product weighed 4.1 g., 21.8% of the theoretical, and melted at 159 - 61° C.

Anal.*: Calc'd. for C_7H_8ClNOS: C, 42.3; Cl, 18.72; S, 16.9.

Found: C, 44.24; H, 4.31; Cl, 18.55; S, 16.79.

2,5 DIBROMO-β-CHLORO-3-PROPIONAMIDOTHIOPHENE



To a 300 ml., three necked flask equipped as described were added 8 g. (0.0422 moles) of β-chloro-

(*) All micro analyses performed by Micro-Tech Laboratories, Skokie, Ill.

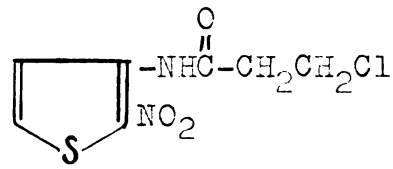
3-propionamidothiophene and 95 ml. of glacial acetic acid. A solution containing 13.5 g. (0.084 moles) of bromine dissolved in 70 ml. glacial acetic acid was placed in the dropping funnel and added to the thiophene derivative during a period of 20 minutes. During the addition of the halogen, the solution cleared and darkened and, after stirring an additional 20 minutes, it was poured into a liter of ice water. A pink colored emulsion resulted which became a sticky material as it was warmed but eventually formed a flocculant, easily filtered precipitate. This was heated with an equal volume of water and alcohol, but part of the solid fused to the bottom of the beaker so the clear, yellow liquid was decanted and cooled. After filtering and drying in an oven at 50° C., 2.5 g. of a tan colored crystalline material in the form of needles was obtained which melted at 120 - 121° with darkening. The fused solid was dissolved in hot alcohol, water added until the initial turbidity appeared and, after decolorizing with activated carbon, filtration was attempted. Difficulty was experienced with solidification of the product in the filter which necessitated cleaning the filter with acetone and repeating the crystallization procedure. Eventually, 3.5 g. of tan colored powder was obtained which melted at 120 - 121° with darkening. The combined product weighed 6 g., which is 41.4% of the theoretical.

Anal.: Calc'd for $C_7H_6Br_2ClNOS$: C, 24.2; H, 1.73;
Halogen, 56.31; N, 4.03; S, 9.22.
Found: C, 24.31; H, 1.95; Halogen, 56.15;
N, 4.07; S, 9.23.

The 2,5-dibromo-β-chloro-3-propionamidothiophene can also be prepared by the Hofmann rearrangement of 2,5-dibromo-3-thenamide. Following the same general procedure as employed in rearranging the unsubstituted 3-thenamide, a solution of NaOBr was prepared by dissolving 8.6 g. (0.215 moles) of NaOH in 70 ml. of ice water and slowly adding 9.1 g. (0.058 moles) of bromine. The ice bath was removed, the flow of nitrogen gas was started and 11.1 g. (0.039 moles) of 2,5-dibromo-3-thenamide was added to the reaction mixture. As the solution warmed, it took on a bright yellow coloration, which turned green and a precipitate settled to the bottom of the flask. After an additional hour of stirring, the solution had become quite dark in appearance and apparently was homogeneous. It was then heated for approximately a half hour during which time a black precipitate was observed to form. Then, after cooling it in an ice bath, 4.8 g. (0.038 moles) of β-chloropropionyl chloride was added to the reaction mixture. The black colored solution was filtered, the precipitate was washed with water, dissolved in hot water containing some alcohol, treated with activated carbon, filtered and the filtrate on cooling precipi-

tated a crystalline solid. Recrystallization of the crude product was repeated twice and gave, after drying 2.1 g. of yellow colored powder. Another 0.3 g. of product was recovered by concentrating the mother liquor to about one third its original volume and cooling. The total weight of product was 2.4 g., which is 17.8% of the theoretical. The compound melted sharply at 120 - 121° C., which is the same as that obtained above by an alternative synthesis.

2-NITRO-β-CHLORO-3-PROPIONAMIDOTHIOPHENE



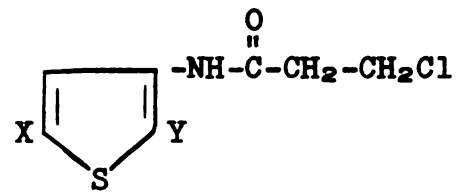
In a 300 ml., three necked flask equipped with a stirrer, thermometer and dropping funnel, were placed 8.4 g. (0.043 moles) β-chloro-3-propamidothiophene and 140 ml. of acetic anhydride and this mixture was cooled to -15° C. with a dry ice-isopropyl alcohol bath. The dropping funnel was charged with 12.6 g. of concentrated HNO_3 (0.14 moles HNO_3). This was added to the reaction mixture very slowly a drop at a time while applying and withdrawing the cooling bath to control the reaction temperature between -15° C. and -5° C. The nitric acid addition required 40 minutes, the reaction mixture was stirred an additional 20

minutes while holding the temperature within the prescribed limits and then the mixture was poured into 600 ml. of ice water. The quenched mixture was neutralized with solid sodium carbonate. This was very slow because of excessive foaming, but the latter served to indicate when all the acid had been neutralized. The neutralized solution was filtered and the black precipitate was washed with water and dissolved in hot alcohol. Sufficient water was added to the hot solution to give a slight turbidity and it was then treated with activated carbon, filtered and the filtrate on cooling precipitated a crystalline solid which was recovered by filtration. The filtrate was concentrated and crystallization again occurred. This procedure was repeated twice, which gave, after drying, the following four fractions of material: 1.5 g. of a yellow colored powder, m. p. 103 - 109°; 2.8 g. of a crystalline solid in the form of long yellow needles, m. p. 118 - 120°; 0.8 g. of a dark colored yellow crystalline solid in the form of needles, m. p. 108 - 109° and 0.9 g. of an amber colored powder, m. p. 107 - 108°. The total weight of product was 6.0 g., which is 57.7% of the theoretical.

Anal.: Calc'd. for $C_7H_7ClN_2O_3S$: Cl, 15.1; N, 11.92; S, 13.65.

Found: Cl, 15.1; N, 11.35; S, 13.8.

Table IA: Preparation of Substituted β-Chloro-3-Propionamidothiophenes



X	Y	Moles NaOH	Mls H_2O	Moles Br_2	Moles 3-Thenamide	Moles CPC[a]	Stirring Mins.	Stirring Temp. ° C	Heating Mins.	Heating Temp. ° C	% Yield[b][c]
H	H	0.55	180	0.15	0.1	0.1	45-60	8-30	45	30-90	21.8
H	H	0.55	180	0.15	0.1	0.1	45-60	8-30	60	30-80	50.9
H	H	1.48	486	0.39	0.27	0.27	90	10-35	50	35-83	29.2
H	H	0.74	243	0.19	0.14	0.14	50-70	8-30	60	30-80	26.2
H	H	0.73	240	0.19	0.13	0.13	50-70	8-30	60	30-80	25.2
Br	Br	0.21	70	0.06	0.04[d]	0.04	60	8-30	30	30-70	17.8
Br	Br	0.14	46	0.04	0.03[d]	0.03	60	8-30	15	30-70	48.6

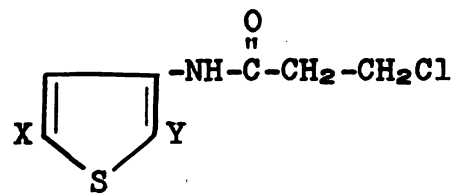
(a) β-Chloro-Propionyl Chloride

(b) Recrystallized from a water-ethanol mixture

(c) Based on weight of 3-thenamide or 2,5-dibromo-3-thenamide.

(d) 2,5-Dibromo-3-Thenamide.

Table IB: Preparation of Substituted β-Chloro-3-Propionamidothiphenes



					Solvent			Reaction		
X	Y	Moles CPT(a)	Other Reagent Name	Other Reagent Moles	Name	Mls. with CPT(a)	Mls. with Br_2	Temp. °C	Mins.	% Yield (b)(c)
Br	Br	0.04	Br_2	0.08	HOAc	95	70	25	40	41.4
Br	Br	0.04	Br_2	0.08	HOAc	95	70	25	50	43.6
Br	Br	0.08	Br_2	0.16	HOAc	184	135	25	75	47.6
H	NO_2	0.04	HNO_3(d)	0.2(e)	Ac_2O	140	-	-5 to -15	60	57.7
H	NO_2	0.03	HNO_3(d)	0.11(e)	Ac_2O	78	-	"	65	55.0
H	NO_2	0.04	HNO_3(d)	0.16(e)	Ac_2O	115	-	"	60	22.3
H	NO_2	0.03	HNO_3(d)	0.15(e)	Ac_2O	107	-	"	85	59.4

(a) β-Chloro-3-Propionamidothiophene

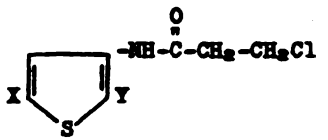
(b) Based on weight of β-chloro-3-propionamidothiophene

(c) Recrystallized from a water-ethanol mixture

(d) 70% HNO_3

(e) Calculated as 100% HNO_3

Table II: Properties and Analyses of Substituted β-Chloro-3-Propionamidothiophenes

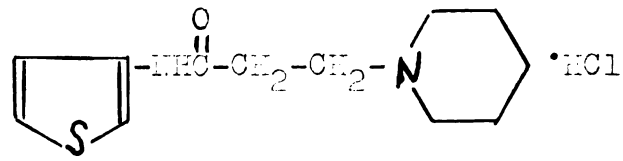


				Analyses[a]									
				% C		% H		% Halogen			% N		% S
X	Y	Formula	m.p. °C	Calc'd.	Found	Calc'd.	Found	Name	Calc'd.	Found	Calc'd.	Found	Calc'd.	Found
H	H	C_7H_6ClNOS	159-61[b]	44.24	42.3	4.31	6.2	Cl	18.5	18.72	-	-	16.79	16.9
Br	Br	$C_7H_6Br_2ClNOS$	120-21[b]	24.31	24.2	1.95	1.73	Total	56.31	56.31	4.07	4.03	9.23	9.22
H	NO_2	$C_7H_7ClN_2O_3S$	118-20[b]	-	-	-	-	Cl	15.1	15.1	11.35	11.92	13.8	13.65

(a) Microanalyses by Microtech Labs., Skokie, Illinois.

(b) Recrystallized from a water-ethanol mixture.

β-PIPERIDYL-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



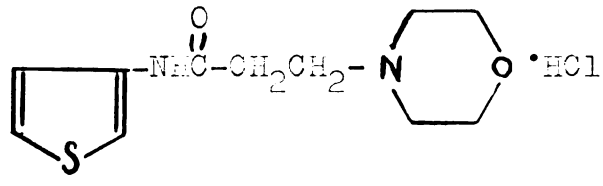
Into a dry, 300 ml. three necked flask fitted with a stirrer, reflux condenser, dropping funnel and electric heating mantle, were placed 9.4 g. (0.111 moles) of piperidine and 30 ml. dry n-butyl ether. The latter mixture was heated to its reflux temperature and from the dropping funnel was added to it a solution of 7.0 g. (0.037 moles) of β-chloro-3-propionamidothiophene dissolved in a mixture of 75 ml. dry dioxane and 60 ml. dry n-butyl ether. This required 50 minutes and the reaction mixture was heated an additional 4 hours. The reflux condenser was replaced with a goose-neck adaptor and straight condenser and the stirrer with a course, fritted glass sparger for injection of steam. The reaction mixture was made alkaline with dilute, aqueous NaOH solution and steam distillation begun to remove the excess piperidine and the organic solvents. From time to time, the Simon's color test for secondary amines[27] was applied to the distillate and approximately 3 l. of distillate had to be collected before a negative Simon's test was obtained. Sufficient conc. HCl was added to the distillation residue to make the aqueous phase acidic but the major part of the black colored oil failed to dis-

solve. The aqueous phase was extracted three times with chloroform, made alkaline with a NaOH solution, extracted again with chloroform, dried with anhydrous Na_2SO_4 and filtered. The chloroform was removed on a steam bath, and ether was added but the amine precipitated so sufficient $CHCl_3$ was added to the ether solution to make homogenous. Gaseous HCl was passed into the solution and a sticky precipitate formed which became filterable after being set aside overnight. The solid was separated by filtration, dissolved in hot, dry isopropyl alcohol, treated with activated carbon, filtered and allowed to crystallize. The product was recrystallized again, dried 4 hours in a 45° oven and 1.4 g. of a light tan colored powder, m.p. 209 - 210° was obtained. This was 13.3% of the theoretical yield.

Anal.: Calc'd for $C_{12}H_{19}ClN_2O_3$: C, 52.7; H, 6.56; Cl, 12.96; S, 11.7.

Found: C, 52.01; H, 6.94; Cl, 12.76; S, 11.45.

β-MORPHOLYL-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



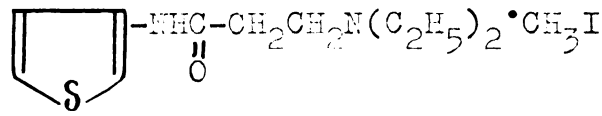
A 250 ml., round bottom, single necked flask was charged with 4.7 g. (0.0248 moles) of β-chloro-3-propionamidothiophene and 20 ml. of dry dioxane. This

was stirred by a magnetic stirrer but only part of the solid dissolved, however a clear solution was obtained upon the addition of 6.5 g. (0.075 moles) of morpholine. A large dropping funnel served as an air condenser. In about an hour a precipitate began to form, stirring was continued at room temperature for 24 hours and then 200 ml. of water was added to the reaction mixture but no precipitation occurred. The turbid yellow colored solution was steam distilled (about 3.5 l. of distillate collected) and the residue in the distillation flask was made alkaline with NaOH. The amine was extracted with ether and the latter was shaken three times with approximately 10% aqueous HCl which caused the yellow color to shift to the acid layer. The latter was then extracted once with ether, neutralized with NaOH and again ether extracted. The ether layer was dried with anhydrous Na_2SO_4, filtered and gaseous HCl was passed into it to obtain a white dispersion. The ether was allowed to evaporate at room temperature and the tan colored solid which formed was dried in a 50° oven. This was recrystallized from absolute ethanol, dried and 0.6 g. of a very light tan colored crystalline solid was obtained (8.8% of the theoretical yield). The salt melted at 230.5 - 231° and was analyzed to give the following results. Anal.: Calc'd. for $C_{11}H_{17}ClN_2O_2S$: C, 47.6; H,6.14;

Cl, 11.65; N, 10.12; S, 12.84.

Found: C, 47.55; H, 6.18; Cl, 11.67; N, 10.21; S, 13.01.

β-DIETHYLAMINO-3-PROPIONAMIDOTHIOPHENE METHYL IODIDE

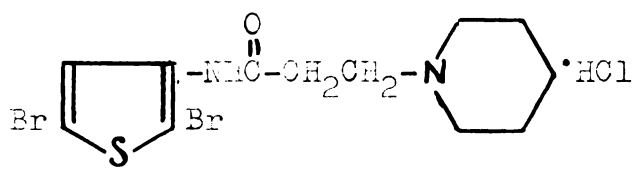


Using the apparatus described in the previous example, 6.7 g. (0.035 moles) of β-chloro-3-propionamidothiophene was dispersed in 20 ml. dry dioxane and 9.1 g. (0.13 moles) of diethylamine was added. After a few minutes of stirring, the mixture became clear and within 15 minutes there was evidence of a precipitate being formed. The reaction was carried out during 21 hours at room temperature. At this point, about 100 ml. of water was added to the reaction mixture and a brown oil separated. This was water-washed three times in a separatory funnel and shaken with dilute HCl in which most of the oil was soluble. The acid solution was extracted three times with ether, made alkaline with NaOH and the amine product was extracted into the ether layer. This was dried with anhydrous Na_2SO_4, filtered and treated with gaseous HCl which gave an emulsion. Evaporation of the ether left an oil residue which was taken up in dry isopropyl alcohol, treated with activated carbon and

cooled. Crystallization could not be induced so the alcohol was evaporated at 50°. The residual amber colored oil was dissolved in water and made alkaline with dilute NaOH. The precipitate was extracted into ether, dried with anhydrous Na_2SO_4, filtered and placed in a magnetically stirred, 250 ml., round bottom flask. To this was added 10 g. (0.071 moles) of CH_3I and the solution was stirred at room temperature for 39 hours at which time there was a sticky solid adhering to the bottom of the flask. The essentially clear liquid was decanted; the solid was dissolved in absolute alcohol, and, following the usual activated carbon treatment, filtration and drying, a pale yellow colored powder was obtained. The product was recrystallized again and gave 0.45 g. pale, yellow colored solid in the form of needles, m.p. 165 - 166°, (3.6% of the theoretical).

Anal.: Calc'd for $C_{12}H_2IN_2OS$: C, 38.9; H, 6.22; I, 34.3.
Found: C, 39.2; H, 6.06; I, 34.12.

2,5-DIBROMO-β-PIPERIDYL-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



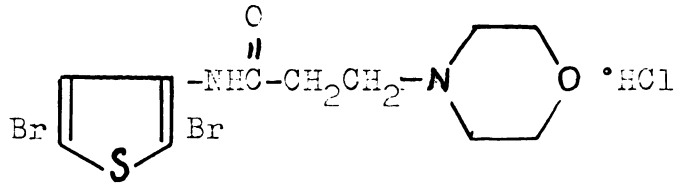
Employing the magnetically stirred equipment discussed previously, 6 g. (0.017 moles) of 2,5-dibromo-

β-chloro-3-propionaridothiophene was dissolved in 27 ml. of dry dioxane and 5.2 g. (0.061 moles) of piperidine was added to the solution. The solution was stirred for 44 hours at room temperature during which time piperidine hydrochloride precipitated. About 100 ml. of water was added to the reaction mixture to complete the precipitation of the product. This was recovered by filtration and throughly washed with water. The solid practically all dissolved in a moderately strong HCl solution (ca. 15%) but, after standing a few minutes, a flocculant precipitate formed transforming the solution into a thixotropic paste. This was made alkaline with NaOH and the resultant slurry was ether extracted. The ether solution was dried with anhydrous Na_2SO_4, filtered and treated with anhydrous HCl gas which formed a copious white precipitate. This was filtered, crystallized twice from dry isopropyl alcohol, decolorizing with activated carbon each time. The solid was given a third crystallization from absolute alcohol. Additional product was recovered from the filtrate by concentration of the latter. A total of 0.9 g. of colorless powder was obtained (12% of the theoretical), m.p. 170 - 172° C.

Anal.: Calc'd for $C_{12}H_{17}Br_2ClN_2CS$: C, 33.40; H, 3.93; Halogen, 45.10; S, 7.40.

Found: C, 33.34; H, 3.90; Halogen, 44.85; S, 7.26.

2,5-DIBROMO-β-MORPHOLYL-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



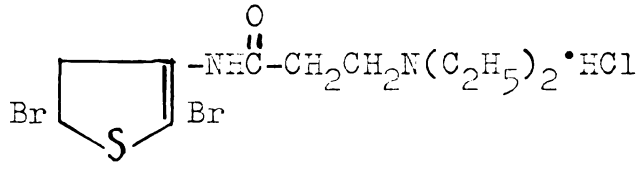
The general procedure and apparatus were the same as used in the previous preparation. A 3.7 g. (0.011 moles) quantity of 2,5-dibromo-β-chloro-3-propionamidothiophene was readily dissolved in 20 ml. of dry dioxane, and 2.8 (0.032 moles) of morpholine was added to it. The reaction mixture was stirred at room temperature for about 38 hours. There was no evidence of heat evolution when the morpholine was added. The previously described product isolation procedure was followed. Water was added to the reaction mixture and the precipitated product was filtered. It was water-washed, dissolved in HCl solution and ether extracted to remove any unreacted material. The aqueous layer was made alkaline with NaOH and ether extracted again; the latter was dried, filtered and treated with gaseous HCl to obtain a white emulsion. The ether was evaporated at 50° and the resultant brown colored solid was recrystallized twice from dry 2-propanol, treating the solution with activated carbon each time. The light, tan colored powder weighed 0.7 g.

which was 15.1% of the theoretical and melted at 177 - 178° with discoloration.

Anal. : Calc'd for $C_{11}H_{15}Br_2ClN_2O_2S$: C, 30.4; H, 3.44; Halogen, 45.01; S, 7.35.

Found: C, 30.91; H, 3.66; Halogen, 44.78; S, 7.24.

2,5-DIBROMO-β-DIETHYLAMINO-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



A 3.7 g. (0.011 moles) quantity of 2,5-dibromo-β-chloro-3-propionamidothiophene was dissolved in 20 ml. of dry dioxane followed by the addition of 2.3 g. (0.032 moles) of diethylamine. The reaction mixture was set aside for 72 hours at room temperature, being stirred during approximately a third of this time. After precipitation of the product by adding water, the waxy solid was recovered by filteration. The physical characteristics of the precipitate made washing it with water rather difficult. The product isolation procedure was the same as that outlined in the previous preparation except that a single crystallization from dry isopropyl alcohol was employed. After being set aside overnight, the product separated

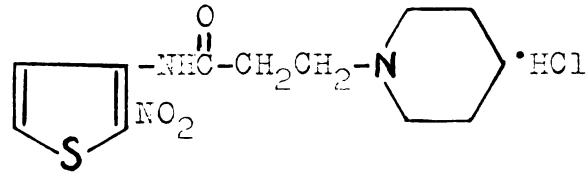
as a thick yellow colored solid in the form of needles which, when dried, weighed 1.8 g. and melted at 133 - 134°.

Anal.: Calc'd for $C_{11}H_{17}Br_2ClN_2OS$: C, 31.36; H, 4.04; Halogen, 46.62; S, 7.61.

Found: C, 31.45; H, 4.07; Halogen, 46.43; S, 7.36.

2-NITRO-β-PIPERIDYL-

-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



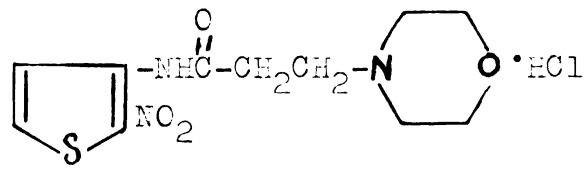
Using the equipment described above, 5.6 g. (0.024 moles) of 2-nitro-β-chloro-3-propionamido-thiophene was dissolved in 25 ml. dry dioxane. To this solution was added 6 g. (0.071 moles) of piperidine, at room temperature. The reaction mixture became warm spontaneously, a precipitate formed and stirring was continued overnight. The product was precipitated with water, filtered, washed, dissolved in dilute HCl and extracted with ether. The aqueous solution was made alkaline using NaOH and ether extracted again. Some difficulty was encountered in obtaining a good separation of the phases because of the increased viscosity. After isolating the amine,

the hydrochloride salt was formed in the ether solution by treatment of the latter with gaseous HCl. The dark colored precipitate was recrystallized three times from absolute alcohol, treating the solution each time with activated carbon. A total of 2.5 g. (32.7% yield) of a greenish amber colored solid, m.p. 204 - 205° (darkened) was obtained.

Anal.: Calc'd for $C_{12}H_{15}ClN_3O_3S$: Cl, 11.12; N, 13.14; S, 10.01.

Found: Cl, 11.4; N, 12.98; S, 9.9.

2-NITRO-β-MORPHOLYL-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



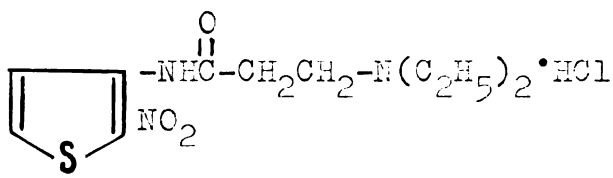
Interaction of 5.2 g. (0.06 moles) of morpholine and 4.7 g. (0.02 moles) of 2-nitro-β-chloro-3-propionamidothiophene which had previously been dissolved in 20 ml. of dry dioxane was carried out during a period of 14 hours at room temperature. An additional 25 ml. of dioxane had to be added soon after beginning the reaction because the slurry became too heavy to stir. The product was isolated by the usual procedure except that the precipitate which formed when the aqueous solution was made alkaline proved to be insoluble in

ether. The amine was extracted with $CHCl_3$, dried with anhydrous Na_2SO_4, filtered, and the latter was treated with gaseous HCl. The sticky precipitate was set aside for several days at room temperature and a bright yellow colored dry powder resulted. This was dissolved in a mixture of hot isopropyl alcohol and sufficient water to just bring about solubility, decolorized with activated carbon and allowed to slowly crystallize overnight. The yellow colored solid was recrystallized from the same solvent mixture to yield 2.8 g., after drying, of a yellow colored solid in the form of plates (43.4% of the theoretical). The product melted at 215 - 217° with darkening.

Anal.: Calc'd for $C_{11}H_{16}ClN_3O_4S$: C, 41.21; H, 4.98; Cl, 10.89.

Found: C, 40.98; H, 4.91; Cl, 11.03.

2-NITRO-β-DIETHYLAMINO-3-PROPIONAMIDOTHIOPHENE HYDROCHLORIDE



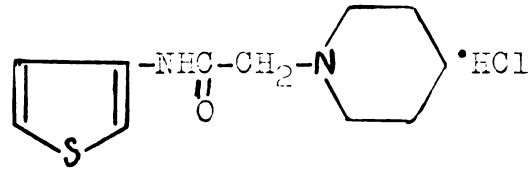
To a solution of 3.2 g. (0.014 moles) of 2-nitro-β-chloro-3-propionamidothiophene dissolved in 20 ml. of dry dioxane was added 3 g. (0.041 moles) of diethyl-

amine. Heat was evolved spontaneously. After stirring the mixture for 24 hours at room temperature, water was added to it to precipitate the crude product. This was purified by the procedure previously described. The only difficulty encountered was the separation of the ether and aqueous phases during the extraction. The hydrochloride salt was recrystallized twice from absolute alcohol, treating the solution each time with activated carbon. The light tan colored powder weighed 0.5 g. (11.9% of theory), and melted at 175 - 176° with darkening.

Anal.: Calc'd for $C_{11}H_{18}ClN_3O_3S$: C, 42.8; H, 5.85; Cl, 11.54; N, 13.67; S, 10.41.

Found: C, 42.98; H, 5.88; Cl, 11.33; N, 13.45; S, 10.38.

α-PIPERIDYL-3-ACETAMIDOTHIOPHENE HYDROCHLORIDE



Preparation of this compound differed from the propionamidothiophene derivatives in that the intermediate chloro compound was not isolated since it would be expected to undergo easy hydrolysis of the chlorine. In a 300 ml. three-necked round bottom flask fitted with a stirrer, nitrogen sparger and

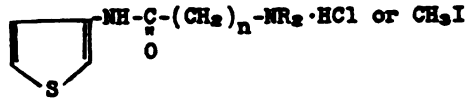
dropping funnel was placed 19.1 g. (0.49 moles) of NaOH dissolving in 156 ml. distilled water. After cooling the alkaline solution below 10°, 20.1 g. (0.126 moles) of bromine was added followed by 11.1 g. (0.087 moles) of 3-thenamide. The Hofmann rearrangement was conducted following the same general procedure discussed previously except acylation of the 3-aminothiophene present in the solution after rearrangement was accomplished with 9.9 g. (0.087 moles) chloroacetyl chloride. The crude α-chloro-3-acetamidothiophene was filtered while the solution was still cold, washed with ice water, dissolved in dioxane, treated with activated carbon, filtered, dried with anhydrous Na_2SO_4, and filtered again. This solution was placed in the magnetically stirred apparatus described previously. A 10 g. (0.12 moles) quantity of piperidine was added and the reaction mixture was set aside at room temperature for a week (a shorter time could have been used). Water was added to precipitate the product and this was isolated and converted to the hydrochloride salt as previously described. A little difficulty was experienced with recrystallization but it was accomplished eventually from isopropyl alcohol, decolorizing the solution twice with activated carbon. A final crystallization was carried out from a pentane-absolute alcohol mixture

yielding 1.5 g. (6.6% of theory) of the desired product which melted at 198 - 199°.

Anal.: Calc'd for $C_{11}H_{17}ClN_2OS$: C, 50.6; H, 6.1; Cl, 13.5; N, 10.7; S, 12.1.

Found: C, 50.61; H, 6.32; Cl, 13.66; N, 10.53; S, 12.08.

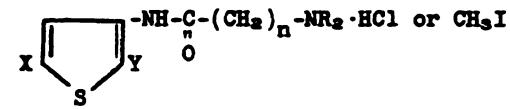
Table III: Preparation of ω-Tertiary Amine Salts of Substituted Acyl-3-Aminothiophenes



X	Y	NR_2	n	Moles CPT[a]	Moles Secondary Amine	Mls Dioxane	Reaction Temp. °C	Reaction Hrs.	Isolation Method	% Yield[b]
H	H	Piperidyl (d)	2	0.04	0.11	75 + 60 (c)	Reflux	4.9	Steam Distillation	13.8 (e)
H	H	Morpholyl (d)	2	0.03	0.08	20	Room	24	" "	8.8 (f)
H	H	Diethylamino (g)	2	0.04	0.13	20	"	21	Water Precipitation	3.6 (f)
Br	Br	Piperidyl (d)	2	0.02	0.06	27	"	44	" "	12.0 (f)
Br	Br	Morpholyl (d)	2	0.01	0.03	20	"	38	" "	15.1 (e)
Br	Br	Diethylamino (d)	2	0.01	0.03	20	"	72	" "	39.4 (e)
H	NO_2	Piperidyl (d)	2	0.02	0.07	25	"	18	" "	32.7 (f)
H	NO_2	Morpholyl (d)	2	0.02	0.06	45	"	14	" "	43.4 (h)
H	NO_2	Diethylamino (d)	2	0.01	0.04	20	"	24	" "	11.9 (f)
H	H	Piperidyl (d)	1	(i)	0.12	ca. 50	"	160	" "	6.6 (e)

(a) β-Chloro-3-Propionamidothiophene
(b) Based on weight of β-Chloro-3-Propionamidothiophene
(c) Mls of n-butyl ether
(d) Hydrochloride salt
(e) Recrystallized from isopropyl alcohol
(f) Recrystallized from absolute ethanol
(g) Quaternary methyl iodide salt
(h) Recrystallized from isopropyl alcohol - water mixture
(i) Not isolated

Table IV: Properties of ω-Tertiary Amine Salts of Substituted Acyl-3-Aminothiophenes



X	Y	n	NR_2	Formula	m. p. °C	Analyses(a) % C		% H		% Halogen			% N		% S	
						Calc'd	Found	Calc'd	Found	Name	Calc'd	Found	Calc'd	Found	Calc'd	Found
H	H	2	Piperidyl (b)	$C_{12}H_{19}ClN_2OS$	209-10 (d)	52.7	52.01	6.56	6.94	Cl	12.96	12.76	-	-	11.70	11.45
H	H	2	Morpholyl (b)	$C_{11}H_{17}ClN_2O_2S$	230.5-31 (e)	47.6	47.55	6.14	6.18	Cl	12.84	13.01	10.12	10.21	11.65	11.67
H	H	2	Diethylamino (c)	$C_{12}H_{21}IN_2OS$	165-67 (e)	38.9	39.2	6.22	6.06	I	34.3	34.12	-	-	-	-
Br	Br	2	Piperidyl (b)	$C_{12}H_{17}Br_2ClN_2OS$	170-71.5(d)(e)	33.4	33.34	3.93	3.90	Total	45.1	44.85	-	-	7.61	7.36
Br	Br	2	Morpholyl (b)	$C_{11}H_{15}Br_2ClN_2O_2S$	179-81 (d)	30.4	30.91	3.44	3.66	Total	45.01	44.78	-	-	7.35	7.24
Br	Br	2	Diethylamino (b)	$C_{11}H_{17}Br_2ClN_2OS$	133-34 (d)	31.36	31.45	4.04	4.07	Total	46.62	46.32	-	-	7.61	7.36
H	NO_2	2	Piperidyl (b)	$C_{12}H_{18}ClN_3O_3S$	204-5 (e)	-	-	-	-	Cl	11.12	11.4	13.14	12.98	10.01	9.9
H	NO_2	2	Morpholyl (b)	$C_{11}H_{16}ClN_3O_4S$	215-17.5 (f)	41.21	40.98	4.98	4.91	Cl	10.89	11.03	-	-	-	-
H	NO_2	2	Diethylamino (b)	$C_{11}H_{18}ClN_3O_3S$	175 (e)	42.8	42.98	5.85	5.88	Cl	11.54	11.33	13.67	13.45	10.41	10.38
H	H	1	Piperidyl (b)	$C_{11}H_{17}ClN_2OS$	198-99 (d)	50.6	50.61	6.10	6.32	Cl	13.5	13.66	10.70	10.53	12.10	12.08

(a) Microanalyses by Microtech Labs., Skokie, Ill.

(b) Hydrochloride salt

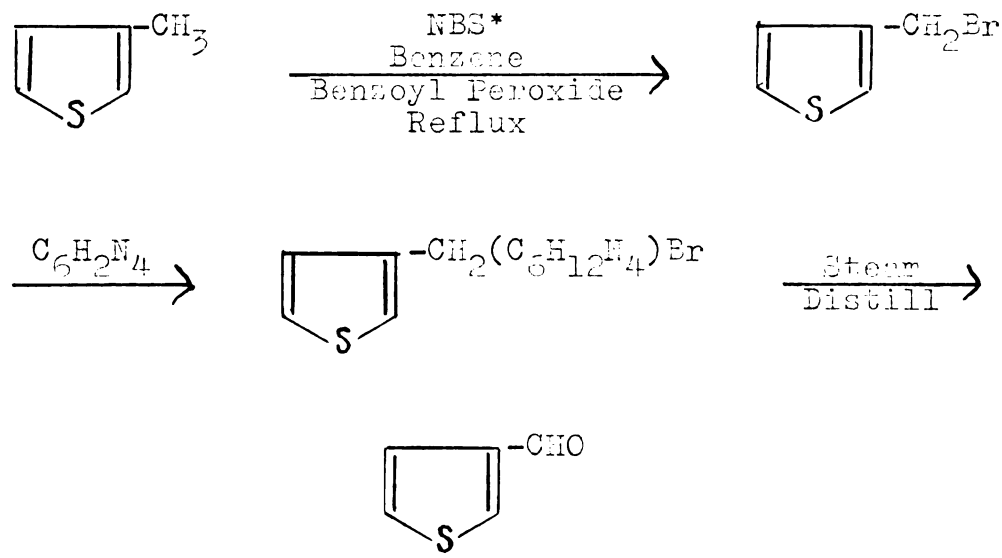
(c) Quaternary CH_3I salt

(d) Recrystallized from isopropyl alcohol

(e) Recrystallized from absolute ethanol

(f) Recrystallized from isopropyl alcohol-water mixture.

3-THENALDEHYDE



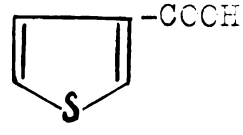
The initial synthesis of 3-thenaldehyde from 3-methylthiophene is that described by E. Campaigne et al[20][21] and has been carried out stepwise with with an average yield of 54% (literature reports 38 - 57%). A modified procedure has been developed which saves considerable time and will be described in detail. In a well ventilated hood, a 5 l. three necked flask (standard taper joints) was fitted with a good reflux condenser, stirrer, heating mantle and a special 10" long condenser for solids addition having a cylindrical 0.5" diameter opening. A solution containing 275 g. (2.81 moles) of 3-methylthiophene, 5 g. (0.0206 moles) of benzoyl peroxide and 875 ml. of dry benzene was heated to vigorous reflux. In a large crystallizing dish were dry blended 445 g. (2.48 moles) of N-bromo-

* N-Bromosuccinimide

succinimide and 5 g. (0.0206 moles) of benzoyl peroxide. This was added to the reaction mixture portionwise through the large bore condenser as rapidly as foaming would permit and pushed down the condenser with a glass rod. The addition of the brominating agent required about 40 minutes. The mantle was replaced first by a water and then by an ice bath to reduce the solubility of the succinimide. The succinimide was removed by filtration and washed with dry benzene. The yellow colored filtrate was returned to the reaction flask and 306 g. (2.18 moles) of hexamethylene tetramine was added. The slurry was stirred for about a half hour, set aside overnight, and then heated for an additional 2 hours at 50 - 60° C. About 600 ml. of water was added and the water layer was separated in a large funnel. The benzene layer was extracted twice with water and the combined water extracts were placed in a 2 l. three necked flask equipped for steam distillation. When the distillate showed no turbidity (about 4 l. had been collected), it was acidified with HCl and extracted three times with ether. The ether extracts were combined, dried with anhydrous Na_2SO_4, filtered and distilled through a 10" column packed with glass helices. The ether was removed at atmospheric pressure and the 3-thenaldehyde distilled at 70 - 73° /12 mm. The product was a colorless liquid, n_D^{25} 1.5833 (Campaigne reports n_D^{20} 1.5860) which took

on a yellow coloration even when stored in an amber bottle. The yield was 156.2 g. (49.7% of theory).

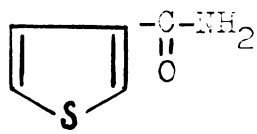
3-THENOIC ACID



Silver oxide was prepared by slowly adding a solution containing 300 g. (1.77 moles) of $AgNO_3$ in 600 ml. of water to a solution containing 140 g. (3.5 moles) of NaOH in 600 ml. of water; the latter being contained in a 2 l. three necked flask equipped with an agitator. The brown, semi-solid suspension was cooled with an ice bath and 95 g. (0.79 moles) of 3-thenal was added in small portions from a dropping funnel. The slurry was stirred for 5 - 10 minutes after addition of the aldehyde and the black, silver suspension was removed by vacuum filtration through a fine, fritted glass funnel. The filtercake was washed with "wet" steam from an untrapped line, the combined filtrates were heated to coagulate the colloidal silver which came through the filter and the solution refiltered employing a filter-aid coated funnel. The cold filtrate on acidification with concentrated HCl gave a voluminous white precipitate which was recovered by filtration and dried at 50° for 12 hours. The white powdered product weighed 92.7 g.,

and had a m.p. of 137 - 139°. An additional 7.4 g. of product was recovered from the filtrate by making it alkaline, concentrating to two thirds of its volume and reacidifing. Total weight of product was 100 g., which is 92.4% of the theoretical. Campaigne and LeSuer[27][28], whose procedure was used in the above preparation, reported a melting point of 137 - 138°. They report a yield of 95 - 97%.

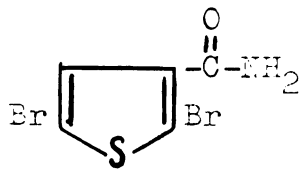
3-THENAMIDE



Into a 500 ml., single necked flask fitted with a reflux condenser and heating mantle were placed 110.3 g. (0.852 moles) of 3-thenoic acid and 275 ml. (3.76 moles) of $SOCl_2$. These were heated gently for 3.5 hours while the major part of the gas evolution was occurring and then the mixture was heated at its reflux temperature for another 4.5 hours. After cooling, the reflux condenser was replaced with a distillation head and the excess $SOCl_2$ was removed at atmospheric pressure. While still warm, the dark colored residual liquid was poured, in small portions, into approximately 1 l. of a well stirred concentrated NH_4OH solution contained in a 1500 ml. beaker. A vigorous reaction occurred with each addition of acid

chloride. The precipitated amide was recovered by filtration, water washed and recrystallized from about 800 ml. of hot water. After cooling, filtering and drying, 66.8 g. (67.2% yield) of a tan colored product in the form of needles m.p. 178 - 179° was obtained. Campaigne and Monroe[13] report a melting point of 178 - 179° and 87.5% yield.

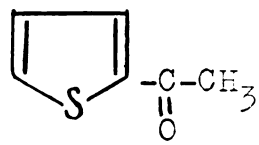
2,5-DIBROMO-3-THENAMIDE



The 2,5-dibromo-3-thenoic acid was prepared by the procedure of Campaigne and Bourgeois[18] from either 3-thenoic acid or 5-bromo-3-thenoic acid. A well stirred solution containing 8 g. (0.038 moles) of 5-bromo-3-thenoic acid dissolved in 100 ml. of glacial acetic acid was placed in a 300 ml. three necked flask and 24 g. (0.156 moles) of bromine was added from a dropping funnel during a 15 minute period. After stirring the reaction mixture an additional 3 hours at room temperature, the contents of the flask were poured into 800 ml. of ice water. Excess bromine was destroyed by adding $NaHSO_3$ until the bromine color was discharged. The product was recovered by filtration and dried at 50°. The 9.9 g.

of 2,5-dibromo-3-thenoic acid was converted to its amide by the procedure described in the preparation of 3-thenamide. The amide was recrystallized from a 3:2 water-ethanol mixture to give 7.6 g. of a colorless product (69.1% yield), m.p. 146 - 147°.

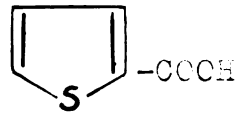
2-ACETYLTHIOPHENE



The 2-acetylthiophene was prepared by the method of Kosak and Hartough[22]. A 252 g. (3 moles) quantity of redistilled thiophene and 117 g. (1.1 moles) of acetic anhydride were placed in a 1 l., three necked flask fitted with a reflux condenser, stirrer, thermometer, heating mantle and 125 ml. dropping funnel containing 10 g. (0.087 moles) of 85% H_3PO_4. The flask was heated to 70° and the catalyst was added which caused the reaction temperature to rise to 90°. After the initial reaction had subsided, the solution was heated at its reflux temperature (95°) for 2 hours. It was then cooled, transferred to a separatory funnel and extracted first with 200 ml. of distilled water and then with 200 ml. of a 10% aqueous Na_2CO_3 solution The organic layer was placed in a distillation apparatus and the thiophene-water azeotrope and excess

thiophene were removed at atmospheric pressure. The 2-acetylthiophene was distilled under 3 mm. of pressure and 108.2 g. (86% of theory) distilled between 68 - 70°, n_D^{26} 1.5640 (literature reports n_D^{20} 1.5667).

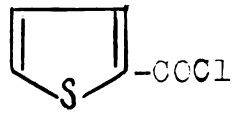
2-THENOIC ACID



Into a 4 l. beaker placed on a large balance was placed 440 g. (11 moles) of NaOH, 600 ml. of water and 2500 g. of ice. Chlorine gas was bubbled into the solution until 322 g. (4.5 moles) had been absorbed. This solution was then transferred to a 5 l., three necked flask equipped with a stirrer, thermometer, dropping funnel and heating mantle. The contents of the flask were heated to 60°, the mantle removed and 126 g. (1 mole) of 2-acetylthiophene added at such a rate that the reaction temperature was held between 60 - 70° with the aid of a water bath. The solution was allowed to cool, 100 g. of $NaHSO_3$ dissolved in 200 ml. of water was added and the reaction mixture was acidified with concentrated HCl. The white, fluffy precipitate was removed by filtration, recrystallized from about 1200 ml. of hot water, and dried to yield 98 g. of a white crystalline solid (needles). An additional 5.7 g. of acid was obtained

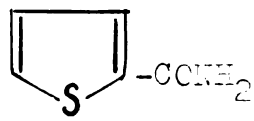
from the crystallisation filtrate by concentration, ether extracting, removing the ether and crystallizing the acid from hot water. The total yield was 80.3% of the theoretical, m.p. 127 - 128° (Ford and Mackay[29] reported a m.p. 127 - 128°, and Hartough[23] reported a m.p. 128 - 129°).

2-[illegible]OYL CHLORIDE



In a 250 ml., single necked flask, a mixture of 102.4 g. (0.8 moles) of 2-thenoic acid and 400 g. (3.36 moles) of $SOCl_2$ was heated at its reflux temperature for 6.5 hours. Distillation of the reaction mixture removed excess $SOCl_2$ followed by 99.1 g. of clear liquid boiling between 76° @ 10 mm. and 97° at 2 mm. This was a yield of 82% of theory, (Ford and Mackay[29] report an "almost quantitative" yield by this procedure and a b.p. 77° /10 mm.

2-[illegible]IDE



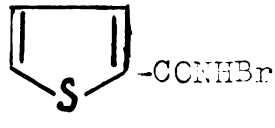
To a well stirred solution of 750 ml. of concentrated NH_4OH, contained in a 2 l. beaker was slowly added 99 g. (0.68 moles) of 2-thenoyl chloride. The

amide was recovered by filtration and crystallized from 1750 ml. of hot water and dried in an oven. It weighed 74.7 g. (87.4% yield), m.p. 179°. Hartough[30] reports a m.p. 180°.

ATTEMPTED HOFMANN REARRANGEMENT OF 2-THENAMIDE

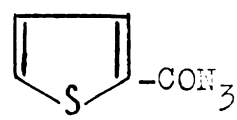
A NaOBr solution was prepared from 22 g. of NaOH dissolved in 130 ml. of water and 21.1 g. of bromine as described previously in the synthesis of -chloro-3-propionamidothiophene[13]. While passing a stream of nitrogen through the NaOBr solution, 12.7 g. (0.1 moles) of 2-thenamide was added. The reaction mixture allowed to warm up spontaneously and 45 minutes later the temperature had reached 37° during which time a precipitate had formed. The dark mixture was cooled to 20°, 20 ml. (0.21 moles) acetic anhydride was added, and it was stirred for about 2 hours and then filtered. The solid was crystallized from hot water after activated carbon treatment and gave 0.8 g. of unreacted amide, m.p. 179°. Ether extraction of the aqueous layer gave only a small amount of an unidentified, very water soluble solid.

ATTEMPTED PREPARATION OF N-BROMO-2-THENAMIDE



Employing the procedure given in Hickinbottom[31] for the synthesis of N-bromobenzamide, a mixture of 12.7 g. (0.1 mole) of 2-thenamide, 16 g. (0.1 mole) of bromine and 160 g. of $CHCl_3$ was heated at its reflux temperature before a homogenous solution was obtained. After cooling the mixture a solution containing 5.6 g. (0.1 mole) of KOH dissolved in 30 ml. of water was added gradually in small portions with occasional shaking of the reaction mixture. The addition of the alkali caused a precipitate to form. This was crystallised from water giving a white solid (needles), m.p. 165 - 166°. The addition of $AgNO_3$ to a small quantity of the product dissolved in water gave no precipitate. The recovered product was probably 5-bromo-2-thenamide, m.p. 163° [9] or 4,5-dibromo-2-thenamide, m.p. 167° [32].

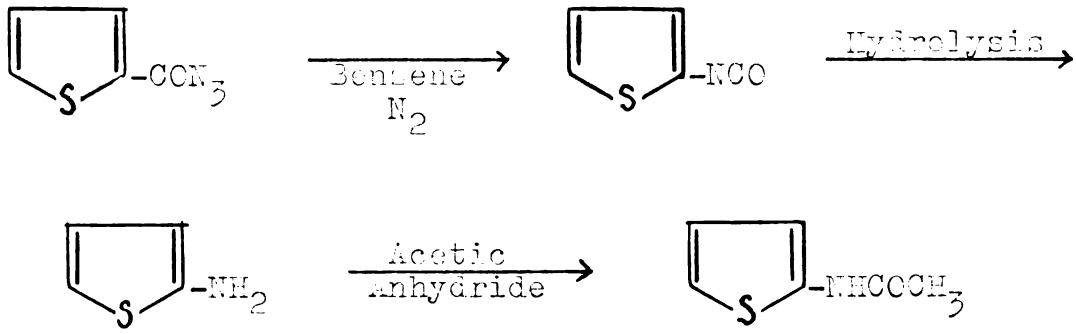
2-THENOYL AZIDE



The procedure employed was an adaptation taken from Organic Reactions. [25] An Erlenmeyer flask containing 7 g. (0.108 moles) of NaN_3 dissolved in 25 ml. of water was cooled in an ice bath and 14.7 g. (0.1 moles) of 2-thenoyl chloride dissolved in 30 ml. of acetone were added. A precipitate formed almost

immediately; however, the flask was kept in the ice bath for an hour with periodic swirling. An additional 50 ml. of water was added to the reaction solution and the precipitate was removed by filtration and pressed as dry as possible with filter paper. After drying in a vacuum dessicator at room temperature, 11.2 g. of the azide was obtained (73.3% of theory). The melting point was not taken for fear of explosion[33].

ARNDT-EISTERT REARRANGEMENT OF 2-THENOYL AZIDE



The rearrangement of the azide to the isocyanate and its hydrolysis to the amine were carried out by following the description given in "Organic Reactions"[21] A 300 ml. three necked flask was charged with 5.1 g. (0.033 moles) of the 2-thenoyl azide and 50 ml. of dry benzene. While sparging N_2, the solution was heated at its reflux temperature for 2 hours, during which time it took on a maroon coloration. The solution was kept at its reflux temperature about 2 hours after adding 50 ml. of 15% aqueous NaOH to it. It was then transferred to a separatory funnel. The benzene layer

was separated, dried, warmed with 10 ml. (0.11 moles) of acetic anhydride and poured into water. No precipitate formed. A solid was precipitated from the water layer by the addition of HCl but this was not investigated further.

Following this failure, an acid hydrolysis was attempted. Employing the same general procedure as just described except that a reaction period of 4 hours was used, 6.1 g. (0.039 moles) of 2-thenoyl azide were rearranged in 50 ml. of benzene. Concentrated HCl (50 g.) was then added, the reaction mixture was heated for 1.5 hours at 50 - 60° and the water layer was cooled and made alkaline. The greenish colored benzene layer was separated, dried and warmed with 10 g. (0.11 moles) of acetic anhydride. There was no visible change in the benzene solution so a little chloroacetyl chloride was added. A vigorous reaction occurred and tarry material formed in the bottom of the flask. Acidification of the aqueous layer caused it to take on a turbidity but no precipitation occurred.

REFERENCES

1. Erdtmann, E. and Lofren, N., Svensk Kem. Tid., 42, 173 (1937); Chem. Abstracts, 31, 7854[8] (1937).

2. Einhorn, A. and Uhlfelder, E., Ann., 371, 131 (1909).

3. Dunn, O., Ber., 76, 419 (1943).

4. Hartough, H.D., "Thiophene and its Derivatives", Interscience Publishers, Inc., New York, N.Y., 37 (1952).

5. Wilson, C.O. and Gisvold, O., "Textbook of Organic Medicinal and Pharmaceutical Chemistry", 3rd Ed., J.B. Lippincott Co., Philadelphia, Pa., 434 (1956).

6. Hartough, H.D., "Thiophene and Its Derivatives", Chap. 2, Interscience Publishers, Inc., New York, N.Y., 29 (1952).

7. Campaigne, E., J. Am. Pharm. Assoc., 46, 129 (1957).

8. Campaigne, E. and Lesuer, W.M., J. Am. Chem. Soc., 70, 3498 (1948).

9. Stadler, O., Ber., 18, 1490 (1885).

10. Steinkopf, W., Ann., 403, 17 (1914).

11. Steinkopf, W. and Hopner, T., Ann., 501, 178 (1933).

12. Tohl, A., Ber., 28, 2217 (1895).

13. Campaigne, E. and Monroe, P.A., J. Am. Chem. Soc., 76, 2447 (1954).

14. Hurd, C. D. and Moffat, J., J. Am. Chem. Soc., 73, 613 (1951).

15. Priestly, H.M. and Hurd, C.D., J. Am. Chem. Soc., 69, 1173 (1947).

16. Hurd, C.D. and Hurd, C.D., J. Am. Chem. Soc., 69, 659 (1951).

17. Kim, L.H. and Schuetz, R.D., J. Am. Chem. Soc., 74, 5102 (1952).

18. Campaigne, E. and Bourgeois, M. C., J. Am. Chem. Soc., 76, 2445 (1954).

19. Schuetz, R.D. and Baldwin, R.A., J. Am. Chem. Soc., 80, 182 (1958).

20. Campaigne, E. and Tullar, B.F., Org. Syn., 33, 96 (1953).

21. Campaigne, E., Bourgeois, R.D. and McCarthy, J.C., Org. Syn., 33, 93 (1953).

22. Kosak, A.J. and Hartough, H.D. Org. Syn., 28, 1 (1948).

23. Hartough, H.D., "Thiophene and Its Derivatives", Interscience Publishers, Inc., New York, N.Y., 505 (1952).

24. Jones, M.C. and Kurd, C.D., J. Am. Chem. Soc., 43, 2444 (1921).

25. Adams, Roger et al, "Organic Reactions" Vol. III, John Wiley and Sons, Inc., New York. N.Y., 374 (1946).

26. Adams, Roger et al, "Organic Reactions" Vol. III, John Wiley and Sons, Inc., New York, N.Y., 378 (1946).

27. Mulliken, S.P., "A Method for Identification of Pure Organic Compounds" Vol. II, John Wiley and Sons, Inc., New York, N.Y., 43 (1916).

28. Campaigne, E. and Lesuer, W.M., J. Am. Chem. Soc., 1555 (1945).

29. Ford, M.C. and Mackay, D., J. Chem. Soc., 4620 (1957).

30. Hartough, H.D., "Thiophene and Its Derivatives", Interscience Publishers, Inc., New York, N.Y., 376 (1952).

31. Hickinbottom, W.J., "Reactions of Organic Compounds", Longmans Green and Co., London, England, 252 (1948).

32. Hartough, H.D., "Thiophene and Its Derivatives", Interscience Publishers, Inc., New York, N.Y., 379 (1952).

33. Curtius, T. and Thyssen, H., J. Prackt. Chem., 65, 14 (1902).