DERIVATIVES OF 2- AND 3-AMINOTHIOPHENES. SYNTHESIS OF UREAS, CARBAMATES, THIOLCARBAMATES, ISOTHIOCYANATES, THIOUREAS, THIONECARBAMATES, AND DITHIOCARBAMATES

by

LANNY EDWIN FOSS

A dissertation submitted in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF WASHINGTON

1974

Approved by Walter C. McCarthy
(Chairman of Supervisory Committee)

Department Pharmaceutical Sciences
(Departmental Faculty sponsoring candidate)

Date Sept. 24, 1974

UNIVERSITY OF WASHINGTON

Date: August 30, 1974

We have carefully read the dissertation entitled Derivatives of 2- and 3-aminothiophenes. Synthesis of ureas, carbamates, thiolcarbamates, isothiocyanates, thioureas, thionecarbamates, and dithiocarbamates submitted by Lanny E. Foss in partial fulfillment of the requirements of the degree of Doctor of Philosophy and recommend its acceptance. In support of this recommendation we present the following joint statement of evaluation to be filed with the dissertation.

This thesis presents the synthesis of 2- and 3-thienyl isothiocyanates and represents the first reported preparation of this functional group attached to the thiophene ring.

Preparative methods for the conversion of thienyl isocyanates to urea and urethan derivatives have been improved, and the isocyanates have been converted to thiolcarbamate derivatives. The isothiocyanates have been converted to thiourea, thionecarbamate, and dithiocarbamate derivatives.

Mr. Foss has completed and reported work that represents a significant contribution to chemical knowledge. He has demonstrated much skill in the difficult handling of unstable compounds.

DISSERTATION READING COMMITTEE: Walter C. McCarthy

Glenn C. Hunstiger

Arnold L. Nelson

In presenting this dissertation in partial fulfillment of the requirements for the doctoral degree at the University of Washington, I agree that the Library shall make its copies freely available for inspection. I further agree that extensive copying of this dissertation is allowable only for scholarly purposes. Requests for copying or reproduction of this dissertation may be referred to University Microfilms, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom the author has granted "the right to reproduce and sell (a) copies of the manuscript in microform and/or (b) printed copies of the manuscript made from microform."

Signature Fanny E. Foss

Date September 24, 1974

TABLE OF CONTENTS

Chapter Page

LIST OF CHARTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation to the following:

To Dr. Walter C. McCarthy for his suggestion of the problem and for his advice and understanding;

To my wife Linda, for her constant encouragement, understanding, and patience;

To Beth, Lisa, and Leah whose joie de vivre brightened my world;

To my family and my wife's family for their encouragement and help;

To Paulina F. Ervin for her understanding and encouragement;

To the faculty and staff of the department for their advice and assistance;

To my fellow graduate students for their interest and encouragement;

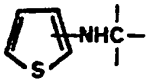
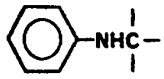
To the National Science Foundation and to the American Foundation for Pharmaceutical Education for their financial support of part of my studies and research.

CHAPTER I

INTRODUCTION

The concept of isosterism as expounded by Erlenmeyer and Leo[1] includes the proposal that the thiophene ring is an isostere of benzene. Thus the synthesis and testing of thiophene analogs of biologically active compounds containing benzene rings is of great interest. Much work has been done along these lines as can be seen from the reviews of Blicke,[2] Campaigne,[3] Martin-Smith and Reid[4] and Bellenghi and Wittgens.[5] The classes of compounds studied include pressor amines, amino acid antagonists, antibiotics, antihistamines, anticholinergics, estrogens, analgesics, CNS depressants, and insecticides.

It is difficult to generalize on the results of these studies, because the thienyl compounds have varied from no pharmacological activity to greater activity than the phenyl prototypes. Further, while Martin-Smith and Reid[4] generalize that the thienyl compounds are usually of greater toxicity than the phenyl compounds, there are several cases, notably in compounds prepared by Steinkopf and Ohse,[6] and Warren and co-workers[7] where toxicity is lower. Thus we are still unable to predict the overall effects of substituting isosteres for each other in biologically active compounds.

In spite of the fact that many classes of drugs include compounds containing the aniline moiety, the aminothiophene moiety occurs in only one analog studied, a weakly active sulfonamide.[8] Not one compound contained the  moiety isosteric to the  moiety found in so many biologically active compounds.

This lack undoubtedly arises from the fact 2- and 3-aminothiophenes are unstable compounds and are difficult to incorporate using methods involving reaction of the free amine. Furthermore, the synthesis and purification of 2- or 3-aminothiophene are tedious and give low yields.

The problems of preparation and purification of the aminothiophenes are well documented. The instability of 2-aminotiophene when exposed to air was reported by Steinkopf.[9] The decomposition of 2-aminothiophene under an inert atmosphere was reported by Hoffman and Gronowitz.[10]

Steinkopf and Hopner[11] reported the successful isolation of 3-aminothiophene as the hydrochloride stannic chloride double salt in 1933, but they were unable to isolate the free base. Hoffman and Gronowitz[10] prepared a cyclohexane solution of 3-aminothiophene and found that it also quickly decomposed even under an inert atmosphere. They, too, were unable to isolate the free base. Campaigne and Monroe[12] also prepared a solution of 3-aminothiophene and used this for preparation of a number of derivatives. Like previous workers, they were unsuccessful in isolating the free base. The purification of 3-aminothiophene was accomplished by 1966, at which time Brunett[13] reported it from these laboratories. This isolation was accomplished using preparatory gas-liquid

chromatography but a very low yield was obtained, possibly due to problems with the collector system of the chromatograph used.

Over twenty years ago Hartough[14] wrote,

> Despite the potential importance of the aminothiophenes in pharmaceuticals and dyestuffs, only a few investigators have been active in this field. Perhaps potential investigators have been discouraged by earlier literature. The tendency of these compounds to decompose in air is well recognized.

This still rings true today. In addition, we now know that the aminothiophenes are unstable under inert atmosphere. Nonetheless, some derivatives of these compounds have been prepared in the intervening years. This thesis reports the preparation of more related compounds.

In addition to extending the use of the Curtius rearrangement for such preparations, the synthesis and purification of the thienyl isothiocyanates has been accomplished, and a number of derivatives prepared. Attempted synthesis of the thienyl isothiocyanates by the classical method, reaction of the free amine with thiophosgene, has undoubtedly been discouraged by two facts: first, the instability of the aminothiophenes, as documented above; second, the lability of aminothiophene derivatives in acidic solution (one product of this reaction is HCl).

The first problem has now been circumvented by use of a recently developed method which effects conversion of the isocyanate to the isothiocyanate. The second problem remains, as discussed later.

Synthesis of the thienyl isothiocyanates opens up new areas for isosteric replacements by thiophene in biologically active compounds by

permitting synthesis of thienylthioureas, thienylthionecarbamates, and thienyldithiocarbamates.

CHAPTER II

PURPOSE OF THIS INVESTIGATION

The purpose of this investigation was to exploit further the Curtius rearrangement for preparation of 2- and 3-thienyl isocyanate in order to expand our knowledge of the amine and alcohol derivatives, and to expand the known reactions of these isocyanates by finding appropriate conditions for reactions with mercaptans to form thiolcarbamates.

In addition to this, the heretofore unknown 2- and 3-thienyl isothiocyanates were to be synthesized and characterized. Although two possible routes for these syntheses were considered, as outlined in the discussion, the method reported by Ottmann and Hooks[15] in 1966 was used. This method involved pyrolysis of S-[N-(thienyl)carbamoyl]-O, O'-diethyl dithiophosphate, an intermediate readily prepared by addition of O, O'-diethyl hydrogen dithiophosphate to the appropriate thienyl isocyanate.

The study was to be completed by development of methods for the preparation of thioureas, thionecarbamates and dithiocarbamates by reaction of the isothiocyanates with amines, alcohols, and mercaptans. These reactions were to be done with reagents having both primary and tertiary alkyl groups in order to insure that appropriate methods could be developed in each case. It is our hope that these methods will enable future workers to synthesize desired biologically active compounds without the necessity

of developing alternative synthetic methods. All compounds were to be characterized by mp or bp, ir and nmr spectra, and elemental analyses to insure that the named compounds were obtained.

CHAPTER III

DISCUSSION

The preparations of the thienylureas and thienylcarbamates from the thienyl isocyanates are extensions of the work of Brunett[13] and Sullivan[16] to obtain and characterize previously unknown compounds.

The necessary 3-thenoic acid was prepared by the method of Gronowitz[17] rather than the longer method employed previously. The method used involved metalation of 3-bromothiophene with n-butyl lithium at -70°, followed by reaction with dry ice and then acidification to 3-thenoic acid.

Reaction of 3-thenoic acid with thionyl chloride at reflux gave 3-thenoyl chloride, which was reacted with sodium azide to give 3-thenoyl azide. Curtius rearrangement of the 3-thenoyl azide yielded 3-thienyl isocyanate which was used for synthesis of the desired derivatives. This reaction sequence is shown in Chart I.

The preparation of 2-thienyl isocyanate was done in the same manner except that commercially available 2-thenoic acid was the starting point.

It was found to be convenient to prepare the desired isocyanate in multigram quantities in inert solvent, purify it by distillation, and then allow this to react with the appropriate amine, alcohol, or mercaptan in

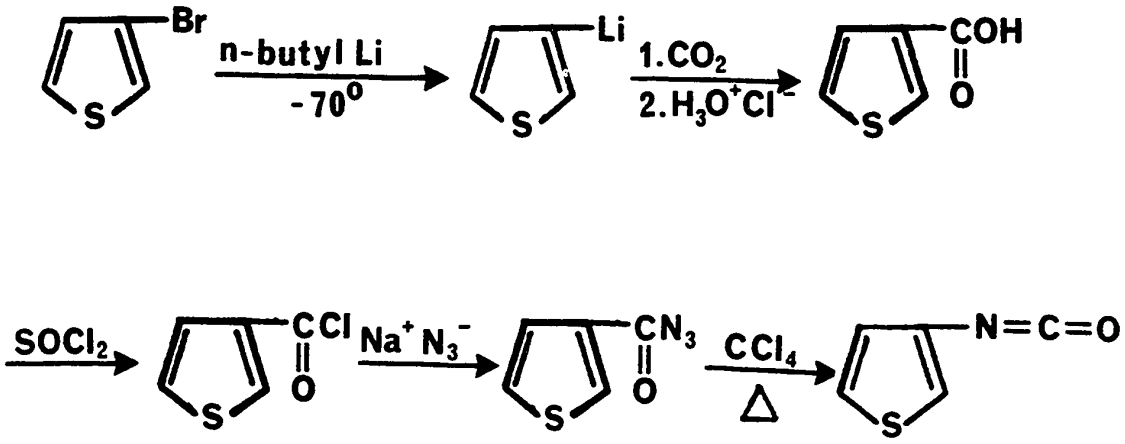


CHART I

dry inert solvent to obtain the desired compounds. In addition to the obvious advantage of requiring less equipment for the Curtius rearrangement (i.e., one setup instead of several) this yielded purer crude products than the methods previously employed which involved reaction of the isocyanate with the desired reagent in the flask in which the Curtius rearrangement was carried out. Distillation effected removal of the deeply colored impurities which always appeared shortly after the Curtius rearrangement was begun. Thus one distillation obviated the necessity for several recrystallizations on each of several compounds to be prepared.

The N-(2-thienyl)ureas were prepared by adding excess amine to 2-thienyl isocyanate slowly and then agitating the reaction mixture for 15-60 minutes. The reaction was done in inert solvents under anhydrous conditions.

The alkyl N-(2-thienyl)carbamates were similarly prepared except that triethylamine catalyst was used and the reaction was refluxed for

10-60 minutes after the addition was complete. The use of the triethylamine catalyst was based on the study of the kinetics of phenyl isocyanate reaction with mercaptans reported by Dyer and Glenn.[18] It was adopted for use with the carbamates when it was found that this produced a much lighter colored crude product.

The preparation of the alkyl N-(2-thienyl)thiolcarbamates was similar to the alkyl N-(2-thienyl) carbamates except that stirring at room temperature replaced the refluxing.

The derivatives of 2-thienyl isocyanate prepared are shown in Chart II.

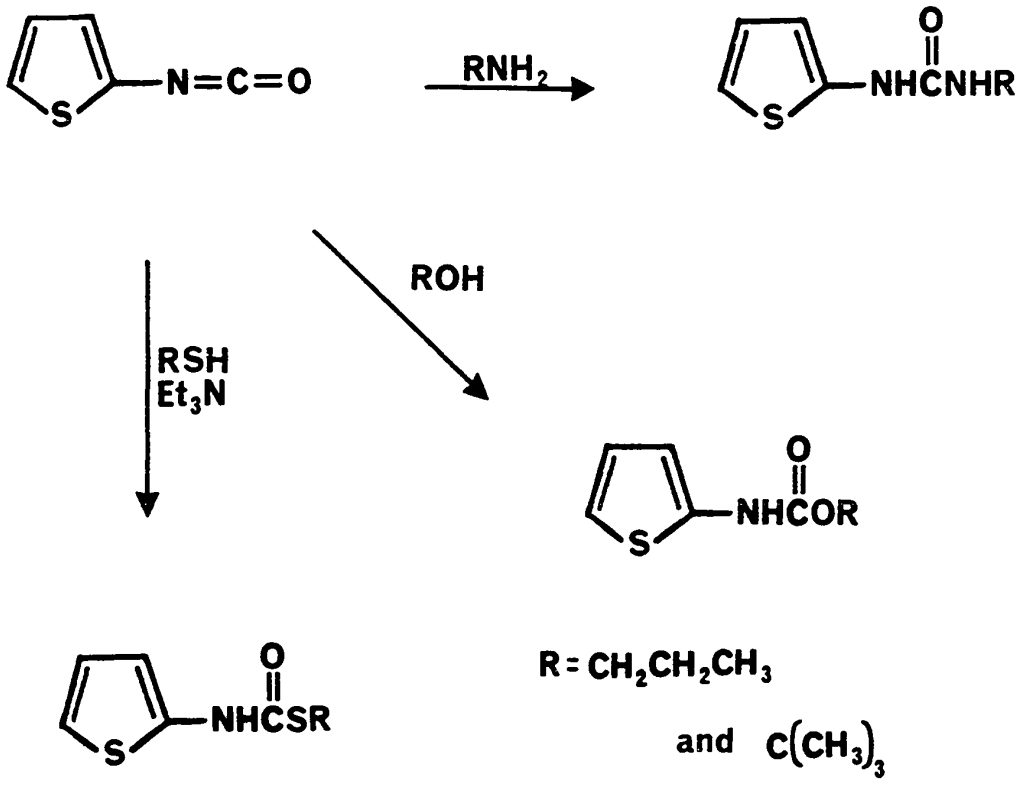


CHART II

The nmr spectra of these compounds were taken and are reported here with the peaks assigned insofar as that is possible. Assignment of the aromatic protons was accomplished by comparison of the observed coupling constants with the published values[19,20] for these constants, ($J_{2,4} = J_{3,5} = 1.6 \pm 0.3$ Hz, $J_{2,5} = 2.7 \pm 0.4$ Hz, $J_{3,4} = 3.8 \pm 0.3$ Hz, and $J_{4,5} = 5.4 \pm 0.6$ Hz) in those cases where identifiable doublets of doublets were obtained. In several cases very narrow complex multiplets were obtained for the aromatic protons and precise assignments for each proton could not be made.

For N-(2-thienyl)urea and its substituted homologs a doublet integrating for two protons and a triplet integrating for one proton was observed in the aromatic region. As stated by Brunett,[13] such a pattern does not allow assignment of the protons on the basis of the coupling constant(s) observed. These protons were tentatively assigned by analogy to N-(2-thienyl)thiourea for which each doublet of doublets is assignable, and the 3-H is farther upfield than the 4-H and 5-H. This same pattern holds true for the substituted N-(2-thienyl)thioureas, although they were observed in acetone-d_6 and $CDCl_3$, as opposed to DMSO-d_6 for the others.

The spectrum obtained for N-(2-thienyl)urea shows broad singlets at δ 6.09 for the NH_2 and at δ 9.63 for the N-H. The aromatic region shows a triplet of one proton at δ 6.56 and a doublet of two protons at 6.87, with the coupling constant 2.6 ± 0.2 Hz. As indicated above the upfield proton is tentatively assigned as 3-H while the lower field protons are assigned as 4-H and 5-H.

The same pattern is observed in the spectrum of N-n-propyl-N'-(2-thienyl)urea except that the 3-H triplet is now observed at δ 6.43 and the 4-H, 5-H doublet at δ 6.77. As for N-(2-thienyl)urea the coupling constant is 2.6 ± 0.2 Hz. The aliphatic NH is observed as a poorly resolved triplet at δ 6.18 and the aromatic NH as a broad singlet at δ 9.33. The aliphatic protons are observed as follows: δ 0.85, the methyl protons as a triplet; δ 1.43, the interior methylene as a sextet; and δ 3.16, the N-methylene as a quartet.

In the aromatic region of the nmr spectrum of N-t-butyl-N'-(2-thienyl)urea (Figure 9) this pattern is again observed. In this case the 3-H is a triplet at δ 6.38 and the 4-H, 5-H doublet is at δ 6.74. Again the coupling constant is 2.6 ± 0.2 Hz. For this compound the aliphatic NH is a broad singlet at δ 5.99 and the aromatic NH a broad singlet at δ 9.12. The methyl groups are observed as a singlet at δ 1.31.

The nmr spectrum of n-propyl N-(2-thienyl)carbamate in acetone-d_6 is an example of a case where one aromatic proton gives the expected doublet of doublets but the other two are so close in chemical shift that the other peaks may not be exactly assigned. The 3-H is observed as a doublet of doublets at δ 6.70 with the apparent $J_{3,4}$ = 3.1 Hz, and $J_{3,5}$ = 1.9 Hz. However, the 4-H and 5-H appear as a multiplet from δ 6.77-6.97. The NH is observed as a broad band at δ 9.35. The aliphatic protons are observed as follows: δ 0.93, a triplet for the methyl group; δ 1.66, a sextet for the interior methylene; and δ 4.13, a triplet for the O-methylene.

Not surprisingly a similar spectrum was obtained for t-butyl N-(2-thienyl)carbamate in acetone-d_6. Now the 3-H is observed as a doublet of doublets at δ 6.74 with apparent $J_{3,4}$ = 3.1 Hz and $J_{3,5}$ = 2.0 Hz and the 4-H, 5-H multiplet is from δ 6.80-6.97. The NH is a broad band at δ 9.33. The aliphatic protons are observed at δ 1.50.

Unlike the alkyl N-(2-thienyl)carbamates, the alkyl N-(2-thienyl)-thiolcarbamates yielded well resolved spectra in which each aromatic proton is assignable. For n-propyl N-(2-thienyl)thiolcarbamate in acetone-d_6, the 3-H is observed at δ 6.78, the 4-H at δ 6.89, and the 5-H at δ 7.01. In each case a doublet of doublets is obtained. The coupling constants are $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.8 Hz, $J_{4,5}$ = 5.2 Hz. The NH is observed as a broad band centered on δ 10.30. The aliphatic protons are observed as follows: δ 0.98, the methyl protons as the expected triplet; δ 1.68, the interior methylene as a sextet; δ 2.99, the S-methylene as a triplet.

Similarly for t-butyl N-(2-thienyl)thiolcarbamate in acetone-d_6, the 3-H is observed as a doublet of doublets at δ 6.78; the 4-H is a doublet of doublets at δ 6.90; and the 5-H is a doublet of doublets at δ 7.08. The observed coupling constants are: $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.2 Hz. The NH is a broad band at δ 10.00. The aliphatic protons are observed as a singlet at δ 1.54.

The next step in preparation of derivatives of 2-aminothiophene involved the synthesis of 2-thienyl isothiocyanate. Up to this time, no thienyl isothiocyanates have been reported in the literature. Classically,

isothiocyanates are prepared by reaction of the appropriate amine with thiophosgene. As documented above 2-aminothiophene is not stable in either the purified form or in solution. Therefore, to avoid the problems inherent in handling such an unstable compound, we considered two alternative approaches to the synthesis of 2- (and 3-) thienyl isothiocyanate.

One approach considered was the possibility of a Curtius rearrangement of thio-2-thenoyl azide which theoretically could be prepared by the route outlined in Chart III.

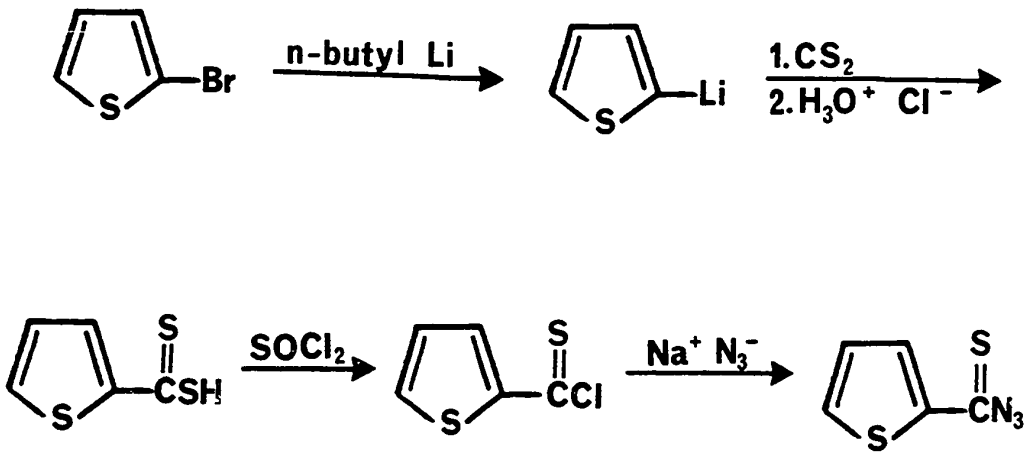


CHART III

This possibility was abandoned when a review of the literature showed that analogous work with thiobenzoyl azide had been unsuccessful. Bacchetti and Alemagna[21] reported that reaction of thiobenzoyl chloride with sodium azide gave 5-phenyl-1, 2, 3, 4-thiatriazole and that heating this decomposed it to benzonitrile, nitrogen, and sulfur. Jensen and

Pedersen[22] confirmed this and obtained similar results for substituted phenyl compounds.

Smith and Kenney[23] showed that the concentration of open-chain azide in these compounds must be very low for they failed to undergo several reactions characteristic of azides, including reaction with Grignard reagents. They also showed that reaction of aromatic 1,2,3,4-thiatriazoles with concentrated sulfuric acid gave nitriles, nitrogen, and sulfur.

That aromatic isothiocyanates could be prepared from the triazole intermediate was shown by Kirmse[24] who used a photochemical reaction. However, he obtained only 5-10% isothiocyanate and much of the rest of the starting material went to nitrile, nitrogen and sulfur. Therefore this was not considered to be practical for our purposes.

The other procedure considered was the one reported by Ottman and Hooks[15] in 1966. Their method involves reaction of the isocyanate with O,O'-diethyl hydrogen dithiophosphate at room temperature to form an adduct which can be pyrolyzed to give the desired isothiocyanate plus various partially esterified thiophosphoric acids. Their work with transforming various alkyl and aryl isocyanates to the corresponding isothiocyanates via this route indicated that good yields might be expected. This, however, was not to be the case with the preparation of 2- or 3-thienyl isothiocyanate, apparently because the acidic byproducts cause decomposition of the iminothiophene moiety. Yields of approximately 11% of 2-thienyl isothiocyanate were obtained.

It was necessary to modify the procedure of Ottmann and Hooks[15] to obtain even this low yield. First, it was necessary to dissolve the 2-thienyl isocyanate in carbon tetrachloride before adding the O, O'-diethyl hydrogen dithiophosphate in order to keep the reaction mixture from solidifying before addition was complete. They report mixing the neat reactants. Second, it was necessary to distill the isothiocyanate as it was formed in order to remove it from the acidic medium of the pyrolysis. They pyrolyzed for two hours, decanted the upper layer, extracted with ice water, dried and then distilled.

In the case of the thienyl isothiocyanates the crude distillate decomposed badly when redistillation was attempted. This was caused by substituted thiophosphoric acids which distilled at about the same temperature as the desired product. This problem was overcome by chromatography of the crude distillate on silica gel 60 (EM Laboratories 70-230 mesh) with elution by carbon tetrachloride. The desired isothiocyanate came through close behind the solvent front while most of the byproducts stayed at the origin. The chromatographed product was stable to vacuum distillation.

The preparation of S-[N-(2-thienyl) carbamoyl] -O, O'-diethyl dithiophosphate was accomplished by reacting 2-thienyl isocyanate in carbon tetrachloride with O, O'-diethyl hydrogen dithiophosphate. The product obtained gave the following nmr in $CDCl_3$ (Figure 10): δ 1.38, a triplet of six protons representing the methyl group; δ 4.27 two

overlapping quartets of four protons; δ 6.73-7.00, a complex multiplet for the three aromatic protons; and δ 9.50, a broad band for the NH proton.

The pyrolysis of the S-[N-(2-thienyl)carbamoyl]-O, O'-diethyl dithiophosphate was accomplished by heating the neat crystalline material to 145-155° with an oil bath while the pressure in the system was maintained at approximately 20 mm Hg. This allowed distillation of the 2-thienyl isothiocyanate soon after it was formed, the necessity for which was pointed out above. Further purification by chromatography followed by distillation gave a sample whose elemental analysis was unsatisfactory. It was necessary to purify this material by preparative gas chromatography in order to obtain pure 2-thienyl isothiocyanate. The material employed for synthesis was not further purified, however.

Several modifications of this procedure were tried with varying degrees of success. All attempts to achieve the pyrolysis in solvents were unsuccessful, as determined by absence of the -NCS peak in the ir spectrum of the reaction mixture.

A lower yield of 2-thienyl isothiocyanate was obtained when a heating mantel was substituted for the oil bath with other conditions as above. Heating the S-[N-(2-thienyl)carbamoyl]-O, O'-diethyl dithiophosphate to 140° for 5 minutes at one atmosphere pressure, followed by cooling and low pressure distillation of the thienyl isothiocyanate also gave a decreased yield.

The nmr spectrum of 2-thienyl isothiocyanate in CCl_4 (Figure 11) shows a complex multiplet δ 6.63-7.01 for the three aromatic protons.

The N-(2-thienyl)thioureas were prepared by reactions analogous to those used for the N-(2-thienyl)ureas. The need for anhydrous conditions was rendered unnecessary by the fact that isothiocyanates are much less reactive than isocyanates. Whereas the latter will react with traces of moisture to produce sym-disubstituted ureas the former may be steam distilled without significant decomposition.

This comparative unreactivity of the isothiocyanates is also apparent in the problems encountered in preparation of the thionecarbamates. It was possible to prepare n-propyl N-(2-thienyl)thionecarbamate by refluxing a solution of 2-thienyl isothiocyanate and n-propyl alcohol in n-heptane as was done for the preparation of n-propyl N-(2-thienyl)carbamate but it was necessary to increase the reflux time to 18 hours.

Attempts to prepare t-butyl N-phenylthionecarbamate in this manner failed, even when the dibutyltin diacetate catalyst of Saunders and Frisch[25] or triethylamine catalyst was used. The use of 10 mole % sodium t-butoxide in t-butyl alcohol was also unsuccessful. Use of equimolar quantities of phenyl isothiocyanate and sodium t-butoxide in t-butyl alcohol gave a 34% yield of t-butyl N-phenylthionecarbamate. This was eventually modified to equimolar quantities of potassium t-butoxide and phenyl isothiocyanate in dried tetrahydrofuran, which gave an 88% yield. The latter method was eventually used for t-butyl N-(2-thienyl)thionecarbamate but the yield was 49%.

This method was also used to prepare n-propyl N-phenyldithiocarbamate from phenyl isothiocyanate and lithium n-propyl mercaptide, yielding a mixture of the desired dithiocarbamate and a compound believed to be sym-diphenylthiourea. This method was not employed for the preparation of n-propyl N-(2-thienyl)dithiocarbamate as two more successful alternative methods were developed.

Reaction of 5 mole % lithium n-propylmercaptide with phenyl isothiocyanate and excess n-propyl mercaptan in n-heptane by stirring for one week at room temperature in the dark gave a high yield of n-propyl N-phenyldithiocarbamate without a noticeable amount of sym-diphenylthiourea. This method was used for preparation of n-propyl N-(2-thienyl)dithiocarbamate.

The other successful preparation of n-propyl N-phenyldithiocarbamate was accomplished by reacting sodium metal with n-propyl mercaptan and adding phenyl isothiocyanate to the refluxing slurry. The reaction was then refluxed for 5 more minutes and stirred at room temperature for 18 hours, giving an 88% yield. Since the reaction conditions of the previous method were milder it was chosen for the preparation of n-propyl N-(2-thienyl)dithiocarbamate.

An attempt to prepare t-butyl N-phenyldithiocarbamate by the method used for t-butyl N-(2-thienyl)thionecarbamate yielded a mixture of the desired product and sym-diphenylthiourea. Use of the method employed for preparation of n-propyl N-(2-thienyl)dithiocarbamate yielded practically no reaction.

Attempts to modify this latter system by using equimolar quantities of lithium t-butylmercaptide and phenyl isothiocyanate in benzene and in 9:1 n-heptane:THF yielded no reaction in the latter case and < 5% of the desired product in the former case.

The successful preparation of t-butyl N-phenyldithiocarbamate was accomplished by reacting equimolar quantities of lithium t-butylmercaptide and phenyl isothiocyanate in t-butyl mercaptan. These were refluxed for 5 minutes and stirred at room temperature for 2 hours. This method was used for preparation of t-butyl N-(2-thienyl)dithiocarbamate.

The reactions used for preparation of the derivatives of 2-thienyl isothiocyanate are shown in Chart IV.

The nmr spectra of these compounds were recorded and are reported here with peak assignments.

The nmr spectrum of N-(2-thienyl)thiourea in DMSO-d_6 has three doublets of doublets for the aromatic protons, the 3-H at δ 6.72, the 4-H at δ 6.98, and the 5-H proton at δ 7.04. The observed coupling constants are $J_{3,4}$ = 3.5 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.4 Hz. The NH_2 peak is a broad singlet at δ 7.45, and the NH proton a broad singlet at δ 10.45.

The spectrum of N-n-propyl-N'-(2-thienyl)thiourea in acetone-d_6 (Figure 12) is similar except for the addition of the aliphatic protons. In this case the aromatic doublets of doublets are observed at δ 6.73 for 3-H, δ 6.82 for 4-H, and δ 7.03 for the 5-H. The observed coupling

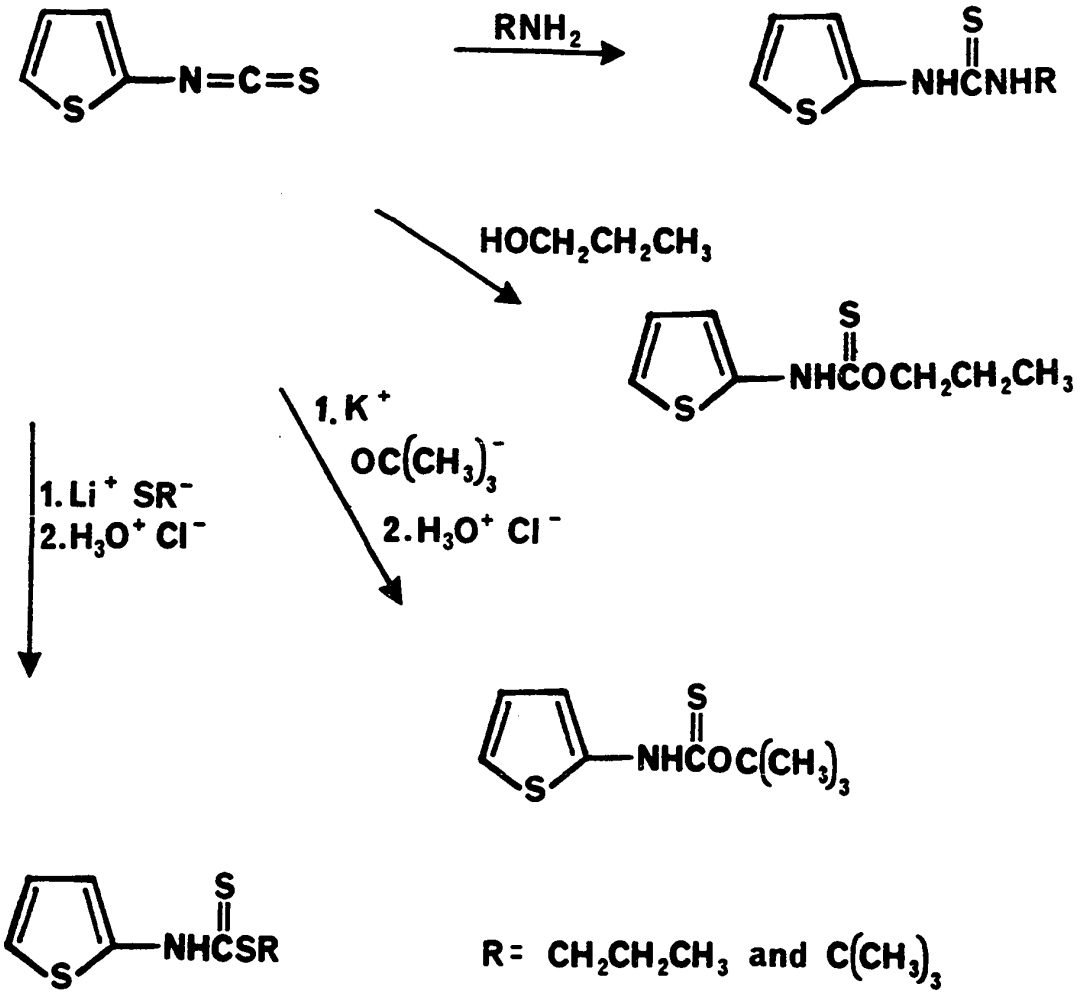


CHART IV

constants are: $J_{3,4}$ = 3.7 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.3 Hz. The aliphatic NH peak is at approximately δ 7.22 (obscured by 5-H) and the aromatic NH at δ 9.27. The aliphatic protons are observed at: δ 0.88, a triplet for the methyl group; δ 1.59, a sextet for the interior methylene, and δ 3.52, a quartet for the N-methylene.

In order to avoid the downfield shift of the NH's caused by hydrogen bonding with deuterioacetone, this spectrum was rerun in $CDCl_3$ (Figure

13). This allowed a definite determination of the position of the aliphatic NH peak. In this solvent the 3-H proton appears as a multiplet centered on δ 6.78, the 4-H proton as a multiplet (apparently a doublet of doublets) at δ 6.90, and the 5-H proton as two doublets at δ 7.15. The coupling constants could not be obtained from this spectrum. The aliphatic NH is a broad band centered on δ 6.23 and the aromatic NH a broad singlet at δ 8.27. The methyl and interior methylene peaks are in the same positions as in the acetone-d_6 spectrum but the N-methylene is now a poorly resolved triplet at δ 3.58.

It was also necessary to run the spectrum of N-t-butyl-N'-(2-thienyl)thiourea in both acetone-d_6 and $CDCl_3$ to definitely determine the position of each peak and the coupling constants. In acetone-d_6 the 3-H proton is seen at δ 6.72, the 4-H at δ 6.87, and the 5-H at δ 7.03. For each proton a doublet of doublets is observed. The coupling constants are: $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.6 Hz, $J_{4,5}$ = 5.3 Hz. The aliphatic NH is obscured by the 3-H and 4-H protons to the point that its center cannot be approximated. The aromatic NH is a broad band at δ 9.17. The methyl protons are observed as a singlet at δ 1.53.

In $CDCl_3$ the 3-H and 4-H protons are observed as a complex multiplet, δ 6.78-7.03, the 5-H proton a doublet of doublets at δ 7.19. The coupling constants could not be measured. The aliphatic NH is a broad band at δ 6.22, while the aromatic NH is now a broad band at δ 8.05. The methyl protons are seen as a singlet at δ 1.51.

The spectrum of n-propyl N-(2-thienyl)thionecarbamate in $CDCl_3$ showed the three aromatic protons as a complex multiplet δ 6.70-7.03. The NH is seen as a broad band at δ 9.99. The aliphatic protons are observed as a triplet for the methyl protons at δ 1.02, a sextet for the interior methylene at δ 1.83, and a triplet for the O-methylene at δ 4.19.

The spectrum of t-butyl N-(2-thienyl)thionecarbamate in acetone-d_6 is similar except for the obvious difference in the aliphatic region. For this compound the aromatic protons appear as a complex multiplet δ 6.80-7.08. The NH is observed as a broad band at δ 10.57, and the methyl protons as a singlet at δ 1.77.

The spectrum for n-propyl N-(2-thienyl)dithiocarbamate in CCl_4 (Figure 14) also shows the aromatic protons as a complex multiplet, in this case δ 6.78-7.04. The NH is observed as a broad band δ 9.23. The aliphatic proton peaks are: δ 0.98, a triplet for the methyl group; δ 1.69 a sextet for the interior methylene; and δ 3.20 a triplet for the S-methylene.

As has been the case for the last three compounds the aromatic protons of t-butyl N-(2-thienyl)dithiocarbamate give a complex multiplet, in this instance δ 6.80-7.01. The NH is observed as a broad band at δ 9.17. The methyl protons appear as a singlet at δ 1.63. This spectrum was run in CCl_4.

The preparation of 3-thienyl isocyanate has been described above (p. 8).

The preparations of the N-alkyl-N'-(3-thienyl)ureas and alkyl N-(3-thienyl)thiolcarbamates were done by the same methods as the corresponding 2-thienyl compounds. The alkyl N-(3-thienyl)carbamates were prepared by a similar method, the difference being that no triethylamine catalyst was used.

The nmr spectra of these compounds were recorded and are reported here with the peak assignments.

The spectrum of N-n-propyl-N'-(3-thienyl)thiourea was observed in DMSO-d_6. The aromatic protons are seen as doublets of doublets with the 4-H at δ 7.00, the 2-H at δ 7.22, and the 5-H at δ 7.35. The observed coupling constants are $J_{2,4}$ = 1.6 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.0 Hz. The aliphatic NH gives a triplet at δ 6.10 and the aromatic NH a broad singlet at δ 8.66. The aliphatic protons are observed as follows: δ 0.87, a triplet for the methyl protons; δ 1.45, a sextet for the interior methylene; and δ 3.21, a quartet for the N-methylene.

The nmr spectrum of N-t-butyl-N'-(3-thienyl)thiourea has a similar aromatic region. The 4-H peaks are centered about δ 6.88; the 2-H peaks, δ 7.13; and the 5-H, δ 7.30. The observed coupling constants in this instance are $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.0 Hz. The aliphatic NH is a broad singlet at δ 5.51 and the aromatic NH a broad singlet at δ 8.43. The methyl proton peak is a singlet at δ 1.30.

The assignment of the aromatic proton peaks in the nmr spectrum (acetone-d_6) of n-propyl N-(3-thienyl)carbamate (Figure 15) is done by analogy with the assignments of Brunett[13] who determined his assignments by deuterating neopentyl N-methyl-N-(3-thienyl)carbamate in the 2 position to show that the upfield triplet represents the 2-H proton.

The aromatic protons of n-propyl N-(3-thienyl)carbamate are thus assigned as follows: the triplet of one proton at δ 7.12 is the 2-H, while the doublet at δ 7.31 which integrates for two protons is the 4-H and 5-H. The apparent coupling constant is 3.5 ± 0.2 Hz. The NH appears as a broad band at δ 8.87. The aliphatic protons are assigned as follows: δ 0.92, a triplet for the methyl protons; δ 1.63, a sextet for the interior methylene; and δ 4.08, a triplet for the O-methylene.

Although t-butyl N-(3-thienyl)carbamate was reported by Brunett,[13] the nmr spectrum in acetone-d_6 is reported here with the corresponding values for Brunett's spectrum in $CDCl_3$ in parentheses. The 2-H is a triplet at δ 7.13 (6.91) and the 4-H and 5-H a doublet at δ 7.31 (7.13). The NH is observed as a broad band δ 8.63 (6.91) and the methyl protons a singlet at δ 1.48 (1.52). Thus, while the major change is seen in the position of the NH due to the increased hydrogen bonding in acetone, there are some slight changes in the positions of the other peaks.

The nmr spectrum of n-propyl N-(3-thienyl)thiolcarbamate in acetone-d_6 (Figure 16) shows the aromatic protons as doublets of doublets. The 4-H is seen at δ 7.13, the 5-H at δ 7.33, and the 2-H at δ 7.49. The coupling constants are $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.1 Hz, and

$J_{4,5}$ = 5.0 Hz. The NH peak is a broad band at δ 9.56. The aliphatic protons are observed as follows: δ 0.97, a triplet for the methyl group; δ 1.65, a sextet for the interior methylene; and δ 2.94, a triplet for the S-methylene.

The nmr spectrum of t-butyl N-(3-thienyl)thiolcarbamate in acetone-d_6 shows similar values for the aromatic protons, which again appear as doublets of doublets. In this case the 4-H is at δ 7.12, the 5-H at δ 7.31, and the 2-H at δ 7.50. The observed coupling constants are $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.3 Hz, and $J_{4,5}$ = 5.1 Hz. The NH is observed as a broad band at δ 9.38, and the methyl protons as a singlet at δ 1.52.

The S-[N-(3-thienyl)carbamoyl]-O, O'-diethyl dithiophosphate was prepared in a manner similar to that used for preparation of the corresponding 2-thienyl compound. In this case 3-thenoyl azide was rearranged to 3-thienyl isocyanate by refluxing in carbon tetrachloride, part of the solvent was removed by distillation, and O, O'-diethyl hydrogen dithiophosphate was added to the cooled solution of 3-thienyl isocyanate.

The nmr spectrum of this compound in $CDCl_3$ showed the aromatic protons as doublets of doublets, with the 4-H at δ 7.03, the 5-H at δ 7.25, and the 2-H at δ 7.44. The observed coupling constants are $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.2 Hz. The NH is a broad band at δ 9.07. The methyl protons appear as a singlet integrating for six protons at δ 1.39, and the methylenes as a doublet of quartets at δ 5.97.

The preparation of 3-thienyl isothiocyanate was the same as the preparation of 2-thienyl isothiocyanate except that the pyrolysis was performed at a lower temperature. The nmr spectrum in CCl_4 (Figure 17) showed the aromatic protons as three doublets of doublets, with the 4-H at δ 6.87, the 2-H at δ 7.02, and the 5-H at δ 7.20. The observed coupling constants are $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.1 Hz, $J_{4,5}$ = 4.8 Hz.

The preparations of the 3-thienylthioureas were done differently than the preparations of the 2-thienylthioureas. In an early attempt to prove that 3-thienyl isothiocyanate was really being formed in the pyrolysis reaction, the reaction was heated to 120-130° for two hours, cooled to room temperature and 10 ml of concentrated aqueous ammonia added. After the reaction mixture had stood overnight, ether was added, causing precipitation of a low yield of N-(3-thienyl)thiourea. Later preparation of this compound in a manner similar to N-(2-thienyl)thiourea gave a somewhat better yield. In no case has a high yield of an unsubstituted thienylthiourea been obtained. The yields could probably be improved by using the method used for preparationof 2-thienylthiourea and increasing reaction times to several hours.

The preparations of the N-alkyl-N'-(3-thienyl)thioureas differ from the preparations of the corresponding 2-thienyl compounds in that no solvent was used. Neat alkylamine was added to neat 3-thienyl isothiocyanate, followed by refluxing for a few minutes. This is definitely a less satisfactory method than the one employing solvent, both from the standpoint of yield and the standpoint of purity of the crude product

obtained. Indeed, preparation of N-n-propyl-N'-(2-thienyl)thiourea by this method yielded a tarry mass which resisted purification to the point that it was discarded and fresh material prepared using the solvent method.

The preparation of n-propyl N-(3-thienyl)thionecarbamate was similar to the preparation of the 2-thienyl compound. The difference was that no solvent was used in this case. The use of solvent seems desirable in view of the greater yield obtained.

The preparationof t-butyl N-(3-thienyl)thionecarbamate was the same as the preparationof t-butyl N-(2-thienyl)thionecarbamate.

The synthesis of n-propyl N-(3-thienyl)dithiocarbamate was done by a method very similar to that used for preparation of t-butyl N-(2-thienyl)thionecarbamate. The reflux time was reduced to 5 minutes but the reaction was then stirred for 18 hours at room temperature. This gave only a 13% yield and should be avoided in the future as the room temperature synthesis in heptane used for n-propyl N-(2-thienyl)-dithiocarbamate employs much milder conditions and will give an improved yield if the detrimental and unnecessary purification steps are avoided.

The synthesis of t-butyl N-(3-thienyl)dithiocarbamate was done by the same method as the corresponding 2-thienyl compound.

The nmr spectra of these compounds were observed and are reported here with the peak assignments.

The spectrum of N-(3-thienyl)thiourea in DMSO-d_6 showed three sets of doublets of doublets for the aromatic region, with the 4-H at δ 7.20, the 5-H at δ 7.65, and the 2-H at δ 7.71. The observed coupling

constants are $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.0 Hz. The NH_2 peak is a broad singlet at δ 7.47 and the NH peak is a broad singlet at δ 10.03.

The spectrum of N-n-propyl-N'-(3-thienyl)thiourea in acetone-d_6 shows the aromatic region very similar to that of the last spectrum. In this case the pairs of doublets appear as follows: the 4-H at δ 7.08, the 5-H at δ 7.38, and the 2-H at δ 7.52. The observed coupling constants are $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.2 Hz. The aliphatic NH is a broad band under the aromatic peaks at approximately δ 7.2. The aromatic NH is a broad band at δ 8.93. The aliphatic protons are observed at δ 0.88, a triplet for the methyl group; at δ 1.61, a sextet for the interior methylene; and at δ 3.55, a quartet for the N-methylene group.

The spectrum of N-t-butyl-N'-(3-thienyl)thiourea in DMSO-d_6 is also similar to the above except for the obvious difference in the aliphatic region. As for the previous two compounds the aromatic protons appear as doublets of doublets. In this case the 4-H is at δ 7.07, the 5-H is at δ 7.38, and the 2-H is at δ 7.67. The observed coupling constants are $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.2 Hz. In this case the aliphatic NH is a broad singlet at δ 7.23, and the aromatic NH is a broad singlet at δ 9.48. The methyl protons are seen at δ 1.47 as a singlet.

In the 37° spectra of the alkyl N-(3-thienyl)thionecarbamates and dithiocarbamates the 2-H proton is not well resolved, appearing as a

broad band. It was thought that this may be caused by partially hindered rotation of the C=S allowing us to observe a series of peaks for this proton, with this series of peaks showing up as a poorly resolved broad band. It was desired to obtain low temperature spectra for these compounds but this has not been possible because of equipment breakdown. These will be obtained at a later date. In some cases some of the other peaks are also poorly resolved and these are noted with the assignments below.

The spectrum of n-propyl N-(3-thienyl)thionecarbamate in acetone-d_6 (Figure 18) shows the 4-H and 5-H protons as a poorly resolved multiplet from δ 7.17-7.47, and the 2-H as a broad band centered on δ 8.12. The NH gives a broad band at δ 10.27. The aliphatic protons appear as a triplet at δ 0.98 for the methyl group, a sextet at δ 1.80 for the interior methylene, and a partially resolved triplet at δ 4.52 for the O-methylene.

The spectrum of t-butyl N-(3-thienyl)thionecarbamate in acetone-d_6 (Figure 19) is similar except for the aliphatic region. In this case the 4-H and 5-H protons appear as a poorly resolved multiplet δ 6.93-7.43, and the 2-H as an extremely broad band centered at approximately δ 8.0. The NH is seen as a broad band at δ 10.00. The methyl protons give a singlet at δ 1.73.

In each of these spectra the peak assigned to the 2-H proton does not integrate to the equivalent of one full proton, yet the total area of the peaks assigned to the aromatic protons is equivalent to three protons

when compared to the area of the aliphatic proton peaks. This indicates that some part of the 2-H peak appears with the 4-H and 5-H multiplet, even though the centers of these are separated by over $\frac{1}{2}\delta$ unit in each case. This is not the case in the spectra of the alkyl N-(3-thienyl)dithiocarbamates reported below, where the integration of the band assigned to the 2-H equals one proton.

The spectrum of n-propyl N-(3-thienyl)dithiocarbamate in acetone-d_6 shows the 4-H and 5-H protons as a multiplet at δ 7.26-7.47 and the 2-H as a broad band at δ 8.23. The NH is seen as a broad band at δ 10.78. The aliphatic protons appear as follows: δ 0.98, a triplet for the methyl protons; δ 1.70, a sextet for the interior methylene; and δ 3.28, a triplet for the S-methylene.

The spectrum of t-butyl N-(3-thienyl)dithiocarbamate in CCl_4 (Figure 20) shows the aromatic protons as two doublets of doublets and a broad band, allowing the coupling constants to be measured. In this case the 4-H appears at δ 7.02; the 5-H at δ 7.21 and the 2-H as an unresolved band at δ 7.83. The apparent coupling constants are $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.2 Hz, and $J_{4,5}$ = 5.2 Hz. The NH appears as a broad band at δ 8.95 and the methyl protons as a singlet at δ 1.63.

In each case the integration of the assigned peaks has been as expected for the named compound except in the cases of the alkyl N-(3-thienyl)thionecarbamates already cited above. As previously mentioned for these cases the total area for the three aromatic protons is consistent when compared with the other peaks in the spectra.

The observed coupling constants are generally in agreement with the published values cited above (p. 10), in those cases where coupling constants are obtainable. The values of $J_{4,5}$ obtained (4.8-5.4 Hz) are all within the published value of 5.4 ± 0.6 Hz. The observed values of $J_{3,5}$ and $J_{2,4}$ (1.4-1.8 Hz) likewise fall within the published value, 1.6 ± 0.3 Hz.

The observed values of $J_{2,5}$ (3.1-3.3 ± 0.2 Hz) are close to the published value (2.7 ± 0.4 Hz), but most are just beyond the high end of this range. In view of the fact that the literature value was determined from 3-substituted thiophenes other than 3-aminothiophenes and that all ten compounds for which $J_{2,5}$ has been determined in this study have values of 3.2 ± 0.2 Hz, this range should be accepted for derivatives of 3-aminothiophene.

A similar situation is observed for $J_{3,4}$ except that in this case the observed values (3.4-3.7 Hz) fall at the low end of the scale of published values (3.8 ± 0.3 Hz). In light of this it seems reasonable to amend this value to 3.8 ± 0.4 Hz.

The possibility of O to S and S to O alkyl migrations in the thione- and thiolcarbamates has been considered. That these are not occurring can be seen from the following data. The chemical shifts of the X-methylene group protons in compounds containing the moiety, $-NHC(O)SCH_2-$, have values of δ 2.94 and δ 2.99. For the X-methylene group in compounds containing the moiety, $-NHC(S)OCH_2-$ the chemical shift values observed are δ 4.52 and δ 4.39. This is consistent with

the well known fact that oxygen exerts a greater deshielding effect on the protons attached to adjacent carbon atoms than does sulfur.

That this effect is partly due to the adjacent oxygen or sulfur and not just the change from carbonyl to thiocarbonyl may be seen from the data of Tables I and II. Thus for similar compounds where the only change is from a carbonyl to a thiocarbonyl changes in chemical shift of 0.26 - 0.46 δ are observed. The thiocarbonyl compounds appear further downfield. This is much smaller than the differences noted above for the change from thiol to thione carbamates.

The analogous effects for like compounds containing a t-butyl group are smaller, making a similar analysis difficult. However, the combination of effects causes the methyl protons of the thiolcarbamates to be observed upfield from those of the thionecarbamates. The observed values are δ 1.52 and δ 1.54 for the thiolcarbamates and δ 1.73 and δ 1.77 for the thionecarbamates.

The conclusion that alkyl migrations are not occurring is confirmed by the ir spectral data. Compounds assigned structures containing the moiety -NHC(O)SR show a characteristic carbonyl absorption in the range 1632-1645 cm^{-1} while those with the moiety -NHC(S)OR show no absorption in this area below 1573 cm^{-1}, which peak is present in both types of compounds.

The elemental analyses of all new compounds were determined by A. Bernhardt Laboratories, Elsbach über Engelskirchen, West Germany. The values determined for each element agree with the theoretical values

within ± 0.3% with three exceptions. Because it was not possible to recrystallize N-t-butyl-N'-(2-thienyl)thiourea without effecting decomposition, this compound was prepared from freshly distilled 2-thienyl isothiocyanate and t-butylamine in carbon tetrachloride as reported in the experimental section and the elemental analysis determined on the first crop of crude product obtained. The C, N, and S analyses fall within ± 0.3% of the theoretical value but the H analysis is 0.37% below the expected value. If the mode of decomposition is loss of isobutylene, yielding N-(2-thienyl)thiourea, as we believe it to be, then this low value for hydrogen is not surprising. The decomposition is not noted by coloration of the product as is so often the case with these compounds, rather it was first noted by the fact that gas appeared to be evolved when the compound melted, and was confirmed by the observation that the ratio of the integration of the methyl peak to the integration of the aromatic peaks decreases with the successive recrystallizations of the product. The ratio of the integration of the aromatic peaks: methyl peak in the sample sent for analysis was 24.5; 72.5 (i.e., 0.338 instead of the theoretical 0.333), which is within the limits we normally accepted before sending a compound for analysis. It was therefore concluded that the named compound was prepared but not brought to a state of high purity.

Another compound for which elemental analyses deviated from theoretical values by more than 0.3% was S-[N-(3-thienyl)carbamoyl]-O,O'-diethyl dithiophosphate. In this case the hydrogen analysis found was 0.35% higher than the theoretical value, and the sulfur analysis

was low by 0.32%. In view of the small deviations, the lack of extraneous peaks in the nmr, and the fact that this compound was successfully used for the preparationof 3-thienyl isothiocyanate by the method of Ottman and Hooks[13] we felt that no further proof was necessary.

The third compound for which a satisfactory elemental analysis was not obtained was t-butyl N-(3-thienyl)dithiocarbamate. In this case the analysis obtained on material chromatographed and recrystallized from petroleum ether (bp 30-60°) (see experimental chapter) gave these results: % C, 48.26; H, 5.62; N, 5.94; and S, 40.34. The calculated values are: % C, 46.71; H, 5.60; N, 6.05; S, 41.57. The experimental values are close to those that may be calculated for a sample impure with approximately 3% pet ether. The sample had been dried under low vacuum for 24 hours prior to submission for analysis.

A second sample for elemental analysis was prepared by rechromatography of the recrystallized material. This sample gave the following analysis: % C, 45.11; H, 5.35; N, 6.30; and S, 42.23, with a 1.10% residue. The residue is probably silica gel, in spite of the fact that the chromatography fractions were reduced to small volume and filtered through sintered glass. These analyses are close enough to the desired values to let us conclude that t-butyl N-(3-thienyl)dithiocarbamate has been synthesized but not purified to the extent necessary to obtain a conclusive elemental analysis.

On the basis of the data discussed in this chapter it is concluded that the named compounds have been prepared.

CHAPTER IV

EXPERIMENTAL

The reported melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 spectrometer except in those cases where it was necessary to use the Varian A-60 to obtain the aromatic coupling constants. Such cases are noted in the text. Chemical shifts are reported as delta values from internal TMS standard. The aromatic coupling constants were determined from expanded spectra and are accurate to ± 0.2 Hz, but the aliphatic and NH coupling constants were measured from 500 Hz sweep width spectra and are only accurate to ± 0.5 Hz. The ir spectra were recorded on a Beckman IR-5A spectrophotometer, with calibration by a known peak of polystyrene. The elemental analyses were performed by A. Bernhardt, Elsbach über Engelskirchen, West Germany.

Dry-packed columns were used for column chromatography. The reactions which were run under anhydrous conditions were protected from water by a drying tube containing anhydrous calcium sulfate.

Model Preparations With Phenyl Isothiocyanate

Great difficulty was encountered in four of the series of compounds reported here. The preparation of the thienyl isothiocyanates was complicated by the fact that the synthesis used gives acidic byproducts which cause decomposition of the aminothiophene moiety to tar. Because the aminobenzene moiety does not exhibit this acid lability it was not useful to attempt developmental work using the preparation of phenyl isothiocyanate from S-(N-phenylcarbamoyl)-O, O'-diethyl dithiophosphate as a model. This work was therefore done on the appropriate thienyl compounds as reported below.

However, it was expedient to study the preparation of t-butyl N-phenylthionecarbamate, n-propyl N-phenyldithiocarbamate, and t-butyl N-phenyldithiocarbamate as models for the corresponding thienyl compounds. These model syntheses are reported here in the hope that this may save others fruitless repetition of this work.

Model preparations of t-butyl N-phenylthionecarbamate

a. The use of dibutyltin diacetate as a catalyst for this reaction was adapted from the report by Saunders and Frisch.[25]

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), dried t-butyl alcohol (3.8 g, 50 mmol) and 0.6 ml dibutyltin diacetate was refluxed for 3 hours, followed by removal of part of the t-butyl alcohol by distillation. Ir spectra observed at 1, 2, and 3 hours showed no evidence of

disappearance of the isothiocyanate peak and no product could be isolated from the reaction mixture.

b. The use of triethylamine catalyst was adapted from the work of Dyer and Glenn[18] who developed the use of this catalyst for the reaction of thiols with phenyl isocyanate.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), dried t-butyl alcohol (3.8 g, 50 mmol), and 0.2 g triethylamine was refluxed in p-xylene. An additional 0.2 g triethylamine was added at 36, 62, 90 and 140 hours. Evaporation of aliquots withdrawn from the reaction at 36 and 160 hours yielded only viscous brown oil. Because it was feared that the thienyl compounds would not survive such reaction conditions as well as the phenyl compound, no extensive attempt was made to isolate product from this reaction and another method was sought.

c. The method of Orndorff and Richmond[26] was modified by the use of dibutyltin diacetate as adapted from the report of Saunders and Frisch.[25]

A solution of phenyl isothiocyanate (3.4 g, 25 mmol) dried t-butyl alcohol (3.8 g, 50 mmol) and 0.6 ml dibutyltin diacetate in 50 ml p-xylene was refluxed under anhydrous conditions. Evaporation of a 5 ml aliquot withdrawn after 36 hours yielded a small amount of crystalline material. Evaporation of a 50 ml aliquot withdrawn after 160 hours yielded 60 mg of crystalline material.

The refluxing was terminated after 162 hours and the reaction liquor evaporated to 1/5 its original volume. When the residue was

cooled in ice a crystalline precipitate formed. This precipitate (657 mg) was collected, mp 98.0-100.0°. After 1 recrystallization from toluene the mp was 99.0-101.0° (lit mp 86.5°[28]). The nmr spectrum indicates that the desired t-butyl N-phenylthionecarbamate is present but impure with some substance having aromatic protons. This may very well be sym-diphenylthiourea, a side product mentioned by Orndorff and Richmond.[26] No attempt was made to purify further the desired product because of the low yield obtained.

d. The method of Roshdestwenski[27] was modified.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol) and sodium t-butoxide (24 mg, 2.5 mmol) in 26 ml of dried t-butyl alcohol was refluxed for 30 minutes followed by stirring at room temperature overnight. The reaction mixture was then acidified with 0.1 N HCl, the precipitated NaCl removed by filtration, and the volume of the excess alcohol reduced by vacuum distillation. Cooling the residue in ice gave a low yield of sym-diphenylthiourea, mp 147.0-148.0 (lit mp 154°[28]).

e. The method of Bost and Andrews[29] was used.

A solution of sodium t-butoxide (240 mg, 25 mmol) in dried t-butyl alcohol (51.0 g, 0.69 mol) was brought to reflux under anhydrous conditions and phenyl isothiocyanate (3.4 g, 25 mmol) added dropwise. When the addition was complete heating was discontinued and the reaction mixture stirred for 45 minutes. The reaction mixture was then poured into 50 mls of ice water and acidified to pH3 with 6N HCl. After cooling in ice the precipitate was collected and recrystallized from ligroine

(bp 63-75°), yielding 1.77 g (34%) of t-butyl N-phenylthionecarbamate as white needles, mp 96.0-98.0°. The nmr spectrum is appropriate for the compound.

f. The method of Bost and Andrews[29] was modified.

The reaction was carried out as in e, except that the refluxing was omitted and acidification was stopped at pH5. This yielded 1.02 g (19%) of crude t-butyl N-phenylthionecarbamate, mp 97.0-98.0° (dec), and 0.9 g sym-diphenylthiourea, mp 154.0-157.0°.

g. Further modification of the method of Bost and Andrews[29] was attempted.

In this reaction the sodium t-butoxide was added to the stirred phenyl isothiocyanate, followed by addition of cold water and acidification to pH1, but this gave only 0.75 g of crude product, mp 87.0-90.0°. Extraction of the aqueous reaction liquor with $CHCl_3$ yielded sym-diphenylthiourea.

h. Method g was repeated except that acidification was stopped at pH7. The yield of crude product was 1.34 g, mp 87.0-92.0°. Again sym-diphenylthiourea was isolated by extraction of the reaction liquor with $CHCl_3$.

i. Another modification of the method of Bost and Andrews[29] was used.

Sodium t-butoxide was prepared by refluxing 25 mg atom of sodium metal in 11 g dried t-butyl alcohol. Heating was discontinued and phenyl isothiocyanate (3.4 g, 25 mmol) was added dropwise to the

hot alcohol solution. The reaction mixture was stirred for 5 minutes after the addition was complete and then was poured into 50 ml of ice water. This yielded 3.81 g of crude t-butyl N-phenylthionecarbamate, mp 88.0-90.0°. Acidification of the aqueous filtrate to pH7 yielded an additional 0.44 g of product, mp 86.0-88.0°. The total crude yield was therefore 81%.

Two attempts to prepare t-butyl N-(2-thienyl)thionecarbamate by this method were unsuccessful, as the solid material isolated resisted numerous attempts at purification.

j. An attempt was made to replace the t-butyl alcohol with tetrahydrofuran in which potassium t-butoxide is more soluble than in t-butyl alcohol.[30]

A solution of phenyl isothiocyanate (1.0 g, 7.1 mmol) and potassium t-butoxide (90 mg, 7.1 mmol) in 50 ml of sodium-dried tetrahydrofuran was refluxed for 1.5 hours, 14 mmol water was added and refluxing continued for 30 minutes. Cooling yielded a precipitate of KOH which removed by filtration. The filtrate was added to 50 ml water and extracted with ether. Evaporation of the dried ether solution yielded 1.3 g (88%) of crude t-butyl N-phenylthionecarbamate, mp 90.0-93.0°.

Acidification of the aqueous layer with 6N HCl until no further cloudiness occurred, followed by extraction with ether, and drying and evaporation of the ether solution, yielded 0.1 g of yellow oil with a few crystals. This was mostly phenyl isothiocyanate.

This reaction, slightly modified, was eventually used for the preparation of the t-butyl N-thienylthionecarbamtes.

k. In an attempt to find even milder conditions for the preparation of these compounds, the following reaction, analogous to the successful preparation of n-propyl N-(2-thienyl)dithiocarbamate, was tried.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol) potassium t-butoxide (90 mg, 8 mmol) and 4 g dried t-butanol in 250 ml dried n-heptane was stirred under anhydrous conditions at room temperature for one week.

The reaction mixture was then acidified by adding 0.13 ml of 6N HCl in 50 ml of water. This was stirred for 15 minutes, by which time the cloudy organic layer had cleared. Ether was added to insure that the product remained in solution and the layers separated. The organic layer was washed with water, dried, and evaporated, yielding an oil which was shown to be unreacted phenyl isothiocyanate.

Model preparations of n-propyl N-phenyldithiocarbamate

a. The dibutyltin diacetate catalyst of Saunders and Frisch[25] was tried.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), n-propylmercaptan (4.5 g, 50 mmol) and 0.6 ml dibutyltin diacetate was refluxed under anhydrous conditions for 7.5 hours and then allowed to stand overnight. Cooling in ice caused solidification of the entire

reaction mixture. Collection and washing with n-heptane yielded 4.09 g (78%) of crude n-propyl N-phenyldithiocarbamate, mp 70.0-71.0° (lit mp 66-67°[27]).

b. The method of Roshdestwenski[27] was employed.

Sodium n-propylmercaptide was prepared by refluxing 25 mg atom sodium metal in 16.7 g n-propyl mercaptan under anhydrous conditions. To this slurry was added phenyl isothiocyanate (3.4 g, 25 mmol) and refluxing was continued for 5 minutes. The reaction mixture was then stirred at room temperature for 18 hours. The resultant gelatinous mixture was treated with 75 ml 0.1 N HCl and then neutralized with 6N HCl. The aqueous reaction mixture was then extracted with $CHCl_3$. The dried $CHCl_3$ extracts were evaporated to approximately 4 ml volume, cooled in ice and the precipitate collected, yielding 4.61 g (88%) n-propyl N-phenyldithiocarbamate, mp 71.5-73.0° (lit mp 66-67°).[27]

c. An attempt was made to use the method which had been successful in the preparation of t-butyl N-phenylthionecarbamate.

A slurry of lithium n-propylmercaptide (2.1 g, 25 mmol) and phenyl isothiocyanate (3.4 g, 25 mmol) in 15 ml sodium-dried tetrahydrofuran was refluxed for 1 hour and then stirred at room temperature for 1 hour. The reaction mixture was then treated with 50 ml ice water and was neutralized with 6N HCl. Extraction with $CHCl_3$, followed by drying and evaporation of the organic extract yielded 3.43 g of crystalline material. Part of this melted 68.5-70.5° and is believed to be n-propyl

N-phenyldithiocarbamate; the rest melted ca 140° and is believed to be sym-diphenylthiourea. No attempt was made to separate and quantitate the two compounds as the earlier reactions appeared to be more useful.

d. An attempt was made to find milder reaction conditions.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), lithium n-propylmercaptide (102 mg, 1.2 mmol) and n-propyl mercaptan (8.4 g, 110 mmol) in 250 ml n-heptane was stirred at room temperature for 1 week under anhydrous conditions. Aliquots were withdrawn and worked up in the manner that the entire reaction mixture was worked up at the end of the week. The nmr spectra of the material from these aliquots was used to determine the extent to which the reaction had gone to completion as measured by the relative integration of the methyl and aromatic proton peaks. Thus it was determined that the reaction was 47% complete at 16 hr, 57% at 40 hr, and 77% at 112 hr.

When the week of stirring was completed, 3 ml 6N HCl in 50 ml water was added and stirring continued for 15 minutes. The layers were separated and the organic layer washed twice with water. The organic solution was dried over calcium sulfate and then evaporated to dryness, yielding a crystalline product, mp 62-67°, with no unmelted residue. This was recrystallized once from petroleum ether (bp 30-60°), yielding 980 mg n-propyl N-phenyldithiocarbamate, mp 75-77° (rapid heating). Evaporation of the pet ether mother liquor yielded 280 mg of oil, which was shown to be mainly phenyl isothiocyanate.

The remainder of the product was shown to have stayed with calcium sulfate used in drying the heptane solution. However, it was not possible to quantitate the yield as most of the drying agent had been discarded by the time this was discovered.

Model preparations of t-butyl N-phenyldithiocarbamate

a. Use of the dibutylthin diacetate catalyst of Saunders and Frisch[25] was attempted.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), t-butylmercaptan (5.6 g, 50 mmol) and 0.6 ml dibutyltin diacetate was refluxed for 14.5 hours. The ir spectrum of the crude reaction mixture was observed at 1.75, 5, 8 and 11.5 hours, but showed no evidence of disappearance of the -N=C=S peak at 4.5-5.5μ. No solid product was isolated from the reaction mixture.

b. This procedure is adapted from the method of Dyer and Glenn[18] for the reaction of phenyl isocyanate with mercaptans.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol), t-butyl mercaptan (5.6 g, 50 mmol) and 0.2 g triethylamine in 50 ml dried p-xylene was refluxed under anhydrous conditions for 160 hours. Triethylamine (0.2 g) was added to the reaction mixture at 36, 62, 90 and 140 hours. Aliquots withdrawn at 36 and 160 hours yielded only tarry oil and no further attempt at workup was made pending an attempt to find milder conditions more suitable for the thienyl compounds.

c. The method of Roshdestwenski[27] was modified in this procedure.

A slurry of sodium t-butylmercaptide was prepared by reacting 25 mg atom sodium metal with 27.0 g t-butyl mercaptan. After 29 hours of refluxing, reaction of the sodium was not complete but gas evolution had stopped so approximately $\frac{1}{3}$ of phenyl isothiocyanate (3.4 g, 25 mmol) was added, yielding renewed gas evolution. The rest of the phenyl isothiocyanate was added at irregular intervals over the next 32 hours. The sodium apparently had all reacted after 77 hours (total) reflux time and heating was terminated.

The cooled reaction mixture was treated with 50 ml cold water and the resultant mixture neutralized with 6N HCl. The neutralized mixture was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract yielded 3.02 g (54%) of crude t-butyl N-phenylidithiocarbamate, mp 98.0-101.0° (lit mp 103-104.5°[30]).

d. The method used for the successful preparation of t-butyl N-phenylthionecarbamate was tried.

To a stirred solution of lithium t-butylmercaptide (2.4 g, 25 mmol) and t-butyl mercaptan (5.0 g, 45 mmol) in 15 ml sodium-dried tetrahydrofuran was added dropwise 25 mmol phenyl isothiocyanate under anhydrous conditions. The reaction mixture was refluxed for 5 minutes and then stirred at room temperature for 17 hours. The reaction mixture was then treated with 50 ml cold water, neutralized with 6N HCl, and extracted with $CHCl_3$.

The dried $CHCl_3$ extracts were evaporated to dryness, yielding an oil which crystallized when cooled in the refrigerator. This gave 4.28 g (74%) of crude product, mp 85-105° with some unmelted residue which was assumed to be sym-diphenylthiourea.

e. An attempt to employ the method which was used for the successful preparation of n-propyl N-phenyldithiocarbamate was made.

A solution of phenyl isothiocyanate (3.4 g, 25 mmol) lithium t-butylmercaptide (115 mg, 1.2 mmol) and 8.0 g t-butyl mercaptan in 250 ml dried n-heptane was stirred at room temperature for 1 week. The reaction mixture was then acidified with 0.2 ml 6N HCl in 25 ml water and stirring was continued for 15 minutes. The phases were separated, ether was added to the heptane layer to insure that the product stayed in solution, and the organic solution washed with water. Evaporation of the dried organic solution yielded an oil which nmr showed to be substantially all phenyl isothiocyanate.

f. An attempt was made to combine methods d and e in order to obtain reaction but avoid synthesis of sym-diphenylthiourea.

A solution of phenyl isothiocyanate (1.0 g, 7.4 mmol) lithium t-butylmercaptide (709 mg, 7.4 mmol) and 25 ml dried tetrahydrofuran in 225 ml n-heptane was refluxed for 24 hours. The reaction mixture was then cooled to room temperature, 1.2 ml 6N HCl in 50 ml water added, and stirring continued for 20 minutes.

The organic and aqueous layers were separated, ether was added to the organic layer to insure that the product stayed in solution and the

organic layer washed with water. Evaporation of the dried organic solution yielded an oil which ir and nmr spectra showed to be phenyl isothiocyanate.

g. The method of Carpino, Terry and Crowley[31] was modified for this procedure.

To a stirred solution of phenyl isothiocyanate (1.0 g, 7.4 mmol) in 8 ml sodium-dried benzene was added lithium t-butylmercaptide (7.09 mg, 7.4 mmol). The slurry was refluxed for 5 minutes and then stirred at room temperature for 5.5 hours under anhydrous conditions.

The benzene was evaporated to dryness and the resultant solid washed with 0.1 N HCl. This yielded an oil which was dissolved in ether and separated from the aqueous layer. The ether solution was dried and evaporated yielding oil and crystals which were separated. The nmr spectrum shows the oil to be phenyl isothiocyanate and the crystals to be sym-diphenylthiourea, mp 157-159°. As measured by the integration of the nmr peak for the methyl group, less than 5% of the desired product was obtained.

h. Another modification of Roshdestwenski[27] was tried.

A slurry of phenyl isothiocyanate (1.0 g, 7.4 mmol) and lithium t-butylmercaptide (709 mg, 7.4 mmol) in 10 ml t-butyl mercaptan was refluxed for 5 minutes and then stirred at room temperature for 2 hours under anhydrous conditions. The excess mercaptan was then evaporated under a stream of nitrogen.

The resultant pasty residue was treated with 0.1 N HCl yielding an oil which was dissolved in ether. The aqueous layer was extracted with ether. The combined extracts were evaporated and dried under vacuum. This gave crystals which spectral data indicates are mostly t-butyl N-phenyldithiocarbamate with some unreacted phenyl isothiocyanate. The crystals after washing with cold petroleum ether (bp 30-60°) melted 100-103° (rapid heating).

2-Thenoyl Chloride

The procedure of Jones and Hurd[32] was used for this preparation.

A solution of 2-thenoic acid (100 g, 0.78 mol) in thionyl chloride (278 g, 2.3 mol) was refluxed under anhydrous conditions for 2 hours. The reflux condenser was replaced by distillation apparatus and the excess thionyl chloride removed by distillation, still under anhydrous conditions. The 2-thenoyl chloride was then distilled at 190-205°, yielding 109 g (95%).

2-Thenoyl Azide

This synthesis was done according to the general method described by Smith.[33]

Solutions of 2-thenoyl chloride (109 g, 0.74 mol) in 800 ml acetone and sodium azide (192.5 g, 2.96 mol) in 800 ml distilled water were cooled to approximately 0°. The acid chloride was then added slowly to the stirred azide solution while the temperature was maintained

near 0°. After the addition had been completed, stirring and cooling were continued for 45 minutes. The reaction mixture was then allowed to warm to room temperature.

The aqueous and acetone layers were then separated and the aqueous layer extracted with ether. The combined organic solution was evaporated until only a small pool of water remained. The water was decanted and the crystalline product dissolved in anhydrous ether and dried over calcium sulfate. Evaporation of the ether yielded 100 g (88%) of 2-thenoyl azide, mp 34-36° (lit mp 37°[34]).

The thenoyl azides may explode if they are heated while dry, caution must be exercised in their storage and use.

2-Thienyl Isocyanate

The method of Curtius and Thysson[34] was modified to allow purification of the product.

A solution of 2-thenoyl azide (100 g, 0.65 mol) in 500 ml CCl_4 was refluxed under anhydrous conditions for 27 hours. The reflux condenser was then replaced with a distillation apparatus and the CCl_4 distilled under anhydrous conditions. The pressure in the system was then reduced to 7 mm Hg and the 2-thienyl isocyanate distilled at 55-65°, yielding 64.7 g (80%) as a colorless liquid.

This reaction was run several times and 16 hours is actually sufficient reflux time in CCl_4. Longer reflux times were used, as in the

case reported here, when this was more convenient. The reflux time may be reduced to 1 hour if toluene is used as the reaction solvent.

N-(2-thienyl)urea

The method of Jones and Mason[35] was used.

Anhydrous ammonia was bubbled through a solution of 2-thienyl isocyanate (0.5 g, 4 mmol) in 10 ml of dried n-heptane for 1 hour. The resultant precipitate was collected and recrystallized once from acetone-toluene with decolorization by acid-washed Norit A charcoal, yielding 540 mg (94%) of N-(2-thienyl)urea as white plates, mp 148.0-149.0° (lit mp 144-146°[36]).

Nmr (DMSO-d_6) (A-60): δ 6.09 (br s, 2, NH_2), 6.56 (t, 1, 3-H), 6.87 (d, 2, 4-H 5-H), 9.63 (br s, 1, NH); apparent $J_{3,4} = J_{3,5} = 2.6$ Hz.

Anal. calcd for $C_5H_6N_2OS$: C, 42.24; H, 4.25. Found: C, 42.38; H, 4.34.

N-n-propyl-N'-(2-thienyl)urea

The method of Sah and Ma[37] was modified for this synthesis.

To a vigorously stirred solution of n-propylamine (1.5 g, 25 mmol) in 4 ml n-heptane was added dropwise a solution of 2-thienyl isocyanate (1.0 g, 8 mmol) in 3 ml n-heptane under anhydrous conditions. Stirring was continued for 15 minutes after the addition was complete.

This gave a precipitate which was collected and recrystallized 4 times from acetone-water with one decolorization by Norit A charcoal, yielding 1.39 g (94%) of N-n-propyl-N'-(2-thienyl)urea as white needles, mp 144.0-145.0°.

Nmr (DMSO-d_6): δ 0.85 (t, 3, CH_3), 1.43 (sextet, 2, CCH_2C), 3.06 (q, 2, NCH_2), 6.18 (t, 1, RNH), 6.43 (t, 1, 3-H), 6.77 (d, 2, 4-H 5-H), 9.33 (br s, 1, ArNH); apparent $J_{3,4} = J_{3,5} = 2.6$ Hz, $J_{CH_2,CH_3} = 7.5$ Hz, $J_{CH_2,CH_2} = 6.7$ Hz, $J_{NH,CH_2} = 6.0$ Hz.

Anal. calcd for $C_8H_{12}NO_2S$: C, 52.14; H, 6.57; N, 15.21; O, 8.68; S, 17.40. Found: C, 52.12; H, 6.37; N, 15.13; O, 8.83; S, 17.39.

N-t-Butyl-N'-(2-thienyl)urea

The method of Sah and Ma[37] was modified for this synthesis.

A solution of 2-thienyl isocyanate (1.0 g, 8 mmol) in 3 ml n-heptane was added dropwise to stirred t-butylamine (1.8 g, 25 mmol) under anhydrous conditions. Stirring was continued for 15 minutes after the addition was complete.

The precipitate was collected and recrystallized 3 times from acetone-water with one decolorization by Norit A charcoal, yielding 1.39 g (88%) of N-t-butyl-N'-(2-thienyl)urea as white needles, mp 199.5-200.0°.

Nmr (DMSO-d_6): δ 1.31 (s, 9, CH_3), 5.99 (br s, 1, RNH), 6.38 (t, 1, 3-H), 6.74 (d, 2, 4-H 5-H), 9.12 (br s, 1, ArNH); apparent $J_{3,4} = J_{3,5} = 2.6$ Hz (Figure 9).

Anal. calcd for $C_9H_{14}N_2OS$: C, 54.51; H, 7.12; N, 14.13; O, 8.07; S, 16.17. Found: C, 54.41; H, 6.99; N, 14.02; O, 8.08; S, 16.34.

n-Propyl N-(2-thienyl)carbamate

The procedure of Baker and Gaunt[38] was used.

To a stirred solution of dried n-propyl alcohol (1.5 g, 25 mmol) in 4 ml n-heptane containing 1% (v/v) triethylamine was added slowly a solution of 2-thienyl isocyanate (1.0 g, 8 mmol) in 3 ml n-heptane. After the addition was complete the reaction mixture was heated at reflux for 1 hour under anhydrous conditions.

When cooling failed to produce a crystalline precipitate, approximately half of the solvent and excess alcohol was evaporated, yielding an oil which crystallized when cooled in ice. The precipitate was collected and recrystallized once from acetone-water with decolorization by acid-washed Norit A charcoal, and once from ligroine (63-75°), yielding 1.4 g (94%) of n-propyl N-(2-thienyl)carbamate as white needles, mp 53.0-53.5°.

Nmr (acetone-d_6) (A-60): δ 0.93 (t, 3, CH_3), 1.66 (sextet, 2, CCH_2C), 4.13 (t, 2, OCH_2), 6.70 (q, 1, 3-H), 6.77-6.97 (m, 2, 4-H 5-H), 9.35 (br band, 1, NH); $J_{3,4}$ = 3.1 Hz, $J_{3,5}$ = 1.9 Hz, $J_{CH_2CH_3}$ = 7.5 Hz, $J_{CH_2CH_2}$ = 6.5 Hz.

Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; O, 17.27; S, 17.31. Found: C, 51.95; H, 5.98; N, 7.62; O, 17.12; S, 17.31.

This reaction was also carried out as described above except that no triethylamine catalyst was used. This gave an 86% yield of crude n-propyl N-(2-thienyl)carbamate, but this was much darker than the crude product obtained with the use of catalyst.

t-Butyl N-(2-thienyl)carbamate

The method of Baker and Gaunt[38] was used.

To a stirred solution of dried t-butyl alcohol (1.9 g, 25 mmol) in 4 ml n-heptane containing 1% (v/v) triethylamine was added dropwise a solution of 2-thienyl isocyanate (1.0 g, 8 mmol) in 3 ml n-heptane. After the addition was complete the reaction mixture was refluxed for 10 minutes. The addition and refluxing were carried out under anhydrous conditions. This gave a crystalline precipitate which was collected and recrystallized once from acetone-water with decolorization by acid-washed Norit A charcoal, yielding 1.29 g (81%) of t-butyl N-(2-thienyl)carbamate as white needles, mp 153.0-153.5°.

Nmr (acetone-d_6) (A-60): δ 1.50 (s, 9, CH_3), 6.74 (q, 1, 3-H), 6.80-6.97 (m, 2, 4-H 5-H), 9.33 (br band, 1, NH); $J_{3,4}$ = 3.1 Hz, $J_{3,5}$ = 2.0 Hz.

Anal. calcd for $C_9H_{13}NO_2S$: C, 54.24; H, 6.57; N, 7.03; O, 16.06; S, 16.09. Found: C, 54.33; H, 6.53; N, 7.10; O, 16.14; S, 16.15.

n-Propyl N-(2-thienyl)thiolcarbamate

The method of Dyer and Glenn[18] for preparation of alkyl N-phenylthiolcarbamates was used.

To a stirred solution of n-propyl mercaptan (1.9 g, 25 mmol) in 4 ml n-heptane containing 1% (v/v) triethylamine was added dropwise a solution of 2-thienyl isocyanate (1.0 g, 8 mmol) in 3 ml n-heptane. The addition was done under anhydrous conditions. When the addition was complete the reaction mixture was stirred for one hour.

The crystalline precipitate was collected and recrystallized once from acetone-water, yielding 1.43 g (89%) of n-propyl N-(2-thienyl)-thiolcarbamate as white needles, mp 107.0-107.5°.

Nmr (acetone-d_6) (A-60): δ 0.98 (t, 3, CH_3), 1.68 (sextet, 2, CCH_2C), 2.99 (t, 2, SCH_2), 6.78 (q, 1, 3-H), 6.89 (q, 1, 4-H), 7.01 (q, 1, 5-H), 10.30 (br band, 1, NH); $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.8 Hz, $J_{4,5}$ = 5.2 Hz, J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} = 7.0 Hz.

Anal. calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; O, 7.95; S, 31.86. Found: C, 47.66; H, 5.41; N, 7.10; O, 7.93; S, 31.73.

The ir spectrum is reproduced as Figure 1.

t-Butyl N-(2-thienyl)thiolcarbamate

The method of Dyer and Glenn[18] for preparation of alkyl N-phenylthiolcarbamates was used.

To a stirred solution of t-butyl mercaptan (3.1 g, 33 mmol) in 4 ml n-heptane containing 1% (v/v) triethyl isocyanate (1.3 g, 10.4 mmol) in 3 ml n-heptane. When the addition was complete the reaction mixture was stirred for 1 hour. The addition and stirring were done under anhydrous conditions.

The precipitate was collected and recrystallized once from acetone-water and once from ligroine (bp 63-75°), yielding 1.98 g (89%) of t-butyl N-(2-thienyl)thiolcarbamate as white needles, mp 159.0-160.0° (dec).

Nmr (acetone-d_6): δ 1.54 (s, 9, CH_3), 6.78 (q, 1, 3-H), 6.90 (q, 1, 4-H), 7.08 (q, 1, 5-H), 10.00 (br band, 1, NH); $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.2 Hz.

Anal. calcd for $C_9H_{13}NOS_2$: C, 50.20; H, 6.08; N, 6.51, O, 7.43; S, 29.78. Found: C, 50.05; H, 5.96; N, 6.62; O, 7.45; S, 29.91.

S-[N-(2-thienyl)carbamoyl]-O,O'-diethyl Dithiophosphate

This compound was prepared by the procedure of Ottman and Hooks.[15]

A solution of 2-thenoyl azide (8.0 g, 52 mmol) in 50 ml CCl_4 was refluxed under anhydrous conditions for 17 hours. The reflux condenser was then replaced by a fractional distillation apparatus and approximately half of the CCl_4 was removed by distillation. The residual solution was cooled to room temperature, and while the temperature of the stirred reaction mixture was maintained below 40°, 9.20 g of

O, O'-diethyl hydrogen dithiophosphate was added dropwise. A few minutes after the addition was complete stirring was discontinued and the reaction mixture was cooled in the refrigerator. The crystalline product was collected yielding 15.5 g (90%) of crude S-[N-(2-thienyl)-carbamoyl] -O, O'-diethyl dithiophosphate. A portion of this material was recrystallized from n-heptane, in which the product is nearly insoluble (approx. 0.5 g/200 ml) at the recrystallization temperature of 60°. The colored impurities did not dissolve and were removed by filtration. After 2 recrystallizations the product melted 103.5-104.5° (dec). The crystals are white needles.

Nmr ($CDCl_3$): δ 1.38 (t, 6, CH_3), 4.27 (octet, 4, CH_2) 6.73-7.00 (m, 3, ArH), 9.50 (br band, 1, NH); J_{CH_2, CH_3} = 7.5 Hz, J_{POCH_2} = 9.5 Hz (lit value range 6.5-10.0 Hz[39]) (Figure 10).

Anal. calcd for $C_9H_{14}NO_3PS_3$: C, 34.71; H, 4.53; N, 4.50; P, 9.95; S, 30.89. Found: C, 34.83; H, 4.58; N, 4.54; P, 10.16; S, 30.64.

This reaction was initially attempted by adding neat 2-thienyl isocyanate dropwise to neat O, O'-diethyl hydrogen dithiophosphate. This proved to be unsatisfactory as the reaction mixture became warm and solidified when approximately one third of the isocyanate had been added. This problem was overcome by using solvent as in the procedure above.

The recrystallization could be accomplished from either toluene or n-heptane. The colored impurities were insoluble in n-heptane and

could conveniently be removed by filtration. Recrystallization from toluene yielded white crystals only if the solution was decolorized with acid-washed charcoal. Use of commercial charcoal yielded a dark green solution on removal of the charcoal and much of this color remained with the crystals. It is thought that the green color is the result of formation of chelates of the product with metal ions in the charcoal.

It was not possible to recrystallize this product at the boiling point of the solvents used. No decomposition was detected when the recrystallization was carried out at 60°, but at 70° noticeable decomposition occurred.

The mp of this compound was also observed at 105.0-106.0° and 107.0-108.5° with decomposition in each case. A note was made at the time that the decomposition point depended on the rate of heating, but the nature of the dependence was not noted.

This reaction was repeated several times for the sole purpose of pyrolysis of the product to 2-thienyl isothiocyanate. It was found to be convenient to prepare S-[N-(2-thienyl)carbamoyl]-O,O'-diethyl dithiophosphate for this purpose by reaction of distilled 2-thienyl isocyanate with purified O,O'-diethyl hydrogen dithiophosphate, followed by evaporation of the CCl_4 and pyrolysis in the same flask. The O,O'-diethyl hydrogen dithiophosphate was purified by the method of Bacon and LeSuer.[40]

2-Thienyl Isothiocyanate

A modification of the method of Ottman and Hooks[15] was used for this preparation.

Crude S-[N-(2-thienyl)carbamoyl]-O, O'-diethyl dithiophosphate (319 g, 1.03 mol) was pyrolyzed in a 2-liter. flask equipped for vacuum distillation. The pressure in the system was reduced and stabilized at approximately 20 mm Hg. The flask was then heated to and maintained at 150 ± 5° by a preheated oil bath. When the pressure increased to more than 100 mm Hg the heating bath was removed and the reaction was cooled in a tap water bath until the pressure returned to the desired level. Crude product distilled at 108-114°, 7 mm Hg. The nmr spectrum indicated that it is less than 50% of the desired product, much of the remainder being various phosphates and thiophosphates.

The crude product was then chromatographed, in six approximately equal batches, on dry-packed 1.5 kg silica gel 60 (EM Laboratories, 70-230 mesh) columns. Elution with CCl_4 brings the isothiocyanate through close behind the solvent front. The various phosphates seem to stay at the origin under these conditions and it has been possible to reuse these columns for as many as three runs, and they could possibly be used for more.

The partially purified product from the columns (21 g) was rechromatographed on a fresh column (1.5 kg) and was then distilled at 44°, 0.4 mm Hg, yielding 15.8 g (11%) of 2-thienyl isothiocyanate as as a pale yellow oil.

An elemental analysis sample prepared in this way failed to give a proper elemental analysis, so another sample was prepared by preparative gas chromatography on a Hewlett Packard 5750 Prep GC, using a 12 ft x $\frac{1}{2}$ in. 10% QF-1 column, carrier flowrate 80 cc/min., and an oven temperature of 150°. This gave a retention time of 10 min.

Nmr (CCl_4): 6.63-7.01 (m, 3H, ArH) (Figure 11).

Anal. calcd for $C_5H_3NS_2$: C, 42.53; H, 2.14 ; N, 9.92; S, 45.41. Found: C, 42.50; H, 2.11; N, 9.75; S, 45.49.

The ir spectrum is reproduced as Figure 2.

This pyrolysis was attempted in $CHCl_3$, toluene, trichloroethylene, and 2,6-lutidine, but in each case the ir spectrum of the reaction mixture showed no indication of formation of the isothiocyanate. In the case of $CHCl_3$, the slightly darkened crystalline starting material was recoverable, in the other cases only tar resulted.

The above procedure was modified by use of a heating mantle in place of the oil bath, but this resulted in reduction of the crude yield by approximately one third. A similar reduction in yield resulted when the reaction was heated in a 140° oil bath at one atmosphere pressure for 5 minutes, followed by cooling and low pressure distillation of the 2-thienyl isothiocyanate.

When the pyrolysis was attempted on material that had been stored in the refrigerator under nitrogen for a period of months and was dark brown colored but still apparently crystalline, it was not possible to isolate any 2-thienyl isothiocyanate.

N-(2-thienyl)thiourea

The method of Otterbacher and Whitmore [41] was modified for this synthesis.

Anhydrous ammonia was bubbled through a solution of 2-thienyl isothiocyanate (0.5 g, 3.5 mmol) in 10 ml dried n-heptane for 1 hour. This yielded a crystalline precipitate which was collected and recrystallized once from water with decolorization by acid-washed Norit A charcoal, yielding 294 mg (53%) of N-(2-thienyl)thiourea as white plates, mp 186.0-186.5°.

Nmr (DMSO-d_6) (A-60): δ 6.72 (q, 1, 3-H), 6.89 (q, 1, 4-H), 7.04 (q, 1, 5-H), 7.45 (br s, 2, NH_2), 10.45 (br s, 1, NH); $J_{3,4}$ = 3.5 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.4 Hz.

Anal. calcd for $C_5H_6N_2S_2$: C, 37.95; H, 3.82; N, 17.71; S, 40.52. Found: C, 38.13; H, 3.87; N, 17.85; S, 40.37.

N-n-Propyl-N'-(2-thienyl)thiourea

The method of Otterbacher and Whitmore [41] was modified for this synthesis.

To a stirred solution of 2-thienyl isothiocyanate (0.4 g, 2.8 mmol) in 10 ml CCl_4 was added n-propylamine (0.7 g, 12 mmol) and stirring was continued for 20 minutes. The solvent and excess amine were partially evaporated yielding a crystalline precipitate, which was

recrystallized once from CCl_4-pet ether (bp 30-60°). This gave 480 mg (85%) of N-n-propyl-N'-(2-thienyl)thiourea as white plates, mp 100.0-100.5°.

Nmr ($CDCl_3$): δ 0.88 (t, 3, CH_3), 1.59 (sextet, 2, CCH_2C), 3.58 (t, 2, NCH_2), 6.23 (br band, 1, RNH), 6.78 (m, 1, 3-H), 6.90 (m, 1, 4-H), 7.15 (q, 1, 5-H), 8.27 (br s, 1, ArNH), (Figure 13).

Nmr (acetone-d_6) (A-60): δ 0.88 (t, 3, CH_3), 1.59 (sextet, 2, CCH_2C), 3.52 (q, 2, NCH_2), 6.73 (q, 1, 3-H), 6.82 (q, 1, 4-H), 7.03 (q, 1, 5-H), ca. 7.22 (partially obscured by the 5-H) (br band, 1, RNH), 9.27 (br s, 1, ArNH); $J_{3,4}$ = 3.7 Hz, $J_{3,5}$ = 1.7 Hz, $J_{4,5}$ = 5.3 Hz, $J_{CH_2CH_3}$ = 7.5 Hz, $J_{CH_2CH_2}$ = 6.4 Hz (Figure 12).

Anal. calcd for $C_8H_{12}N_2S_2$: C, 47.96; H, 6.04; N, 13.99; S, 32.01. Found: C, 48.16; H, 5.95; N, 13.91; S, 31.87.

The ir spectrum is reproduced as Figure 3.

An attempt to prepare N-n-propyl-N'-(2-thienyl)thiourea by refluxing 2-thienyl isothiocyanate (500 mg, 35 mmol) in n-propylamine (7.2 g, 120 mmol) for 30 minutes, followed by evaporation of the excess amine, yielded a tarry mass which resisted attempts at recrystallization from acetone, toluene, and toluene-ligroine. Chromatography on silica gel 60 (EM Laboratories, 70-230 mesh) with elution by $CHCl_3$ did purify the product to the extent that yellow crystals were obtained, but the method reported above is definitely to be preferred.

N-t-Butyl-N'-(2-thienyl)thiourea

The method of Otterbacher and Whitmore[41] was modified in this procedure.

To a stirred solution of 2-thienyl isothiocyanate (0.4 g, 2.8 mmol) in 20 ml CCl_4 was added dropwise t-butylamine (0.7 g, 9.5 mmol). The reaction mixture was stirred for 30 minutes after the addition was complete. The precipitate was collected and dried yielding 280 mgs (47%) of N-t-butyl-N'-(2-thienyl)thiourea, mp 162.0-162.5° (dec). Partial evaporation of the reaction liquor yielded an additional 200 mg, mp 157.5-158.5°. Evaporating the reaction liquor to dryness yielded another 115 mg, mp 156.0-157.0°. Since this compound had previously been shown to decompose during recrystallization no purification was attempted.

Nmr ($CDCl_3$): δ 1.51 (s, 9, CH_3), 6.22 (br band, 1, RNH), 6.78-7.03 (m, 2, 3-H 4-H), 7.19 (q, 1, 5-H) 8.05 (br band, 1, ArNH).

Nmr (acetone-d_6) (A-60): δ 1.53 (s, 9, CH_3), 6.72 (q, 1, 3-H), 6.87 (q, 1, 4-H), 7.03 (q, 1, 5-H), 9.17 (br band, 1, ArNH), the RNH is obscured by the 3-H and 4-H; $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.6 Hz, $J_{4,5}$ = 5.3 Hz.

Anal. calcd for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07; S, 29.92. Found: C, 50.67; H, 6.21; N, 13.08; S, 29.91.

n-Propyl N-(2-thienyl)thionecarbamate

The method of Bost and Andrews[29] was modified for this synthesis.

A solution of 2-thienyl isothiocyanate (420 mg, 3.0 mmol) and dried n-propyl alcohol (1.6 g, 27 mmol) in 15 ml n-heptane was refluxed for 18 hours. The reaction liquor was partially evaporated, yielding 485 mg (80%) of n-propyl N-(2-thienyl)thionecarbamate, mp 46.0-48.5°. Part of this material was vacuum sublimed (37-43°, 0.3-0.6 mm Hg) yielding white needle crystals, mp 48.0-48.5°.

Nmr ($CDCl_3$): δ 1.02 (t, 3, CH_3), 1.83 (sextet, 2, CCH_2C), 4.39 (t, 2, OCH_2), 6.70-7.03 (m, 3, ArH), 9.99 (br band, 1, NH); $J_{CH_2,CH_3} = 7.5$ Hz, $J_{CH_2,CH_2} = 6.5$ Hz.

Anal. calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; O, 7.95; S, 31.86. Found: C, 47.66; H, 5.56; N, 7.03; O, 8.03; S, 32.00.

t-Butyl N-(2-thienyl)thionecarbamate

The method used for the successful preparation of t-butyl N-phenylthionecarbamate was employed.

To a stirred slurry of potassium t-butoxide (895 mg, 7.1 mmol) in sodium-dried tetrahydrofuran was added 2-thienyl isothiocyanate (1.0 g, 7.1 mmol). The reaction was refluxed for 1 hour under anhydrous conditions, 0.25 ml water was added and refluxing was continued for 15 minutes. The reaction mixture was then cooled to room temperature and 1 ml of 6N HCl was added followed by stirring for 5 minutes.

The precipitate of KCl was filtered out. The THF solution was evaporated to a few ml volume and 35 ml of distilled water was added, yielding an oil which crystallized on standing.

This crude product was collected and recrystallized once from petroleum ether (bp 30-60°) yielding 760 mg (49%) of t-butyl N-(2-thienyl)thionecarbamate as light brown crystals, mp 95-96° (dec). A portion of this was sublimed (60 ± 5°, 0.2 mm Hg) yielding very small white crystals, mp 92.5-93.5° (dec).

Nmr (acetone-d_6): δ 1.77 (s, 9, CH_3), 6.80-7.08 (m, 3, ArH), 10.57 (br band, 1, NH).

Anal. calcd for $C_9H_{13}NOS_2$: C, 50.20; H, 6.08; N, 6.51; O, 7.43; S 29.78. Found: C, 50.12; H, 6.13; N, 6.41; O, 7.58; S, 29.69.

n-Propyl N-(2-thienyl)dithiocarbamate

The method used for the successful preparation of n-propyl N-phenyldithiocarbamate was modified for this synthesis.

A solution of lithium n-propylmercaptide (29 mg, 0.35 mmol), n-propyl mercaptan (4.2 g, 55 mmol) and 2-thienyl isothiocyanate (1.0 g, 7.1 mmol) in 65 ml of sodium-dried n-heptane was stirred at room temperature under anhydrous conditions for one week in a foil-covered flask. HCl (0.05 ml, 6N) in 15 ml distilled water was then added and stirring was continued for 15 minutes.

The heptane layer was separated from the aqueous layer and was washed twice with distilled water. Ether was added to the heptane solution to insure that the product did not precipitate during the drying process and this solution was dried over calcium sulfate.

Evaporation of the ether and heptane to dryness yielded an oil which would crystallize in a dry ice-acetone bath but remelted below room temperature. The oil was then distilled in a microdistillation apparatus (cold finger type) yielding a yellow oil which was shown by nmr and ir spectra to consist of the desired product and 2-thienyl isothiocyanate.

The distillate was chromatographed on silica gel 60 (EM Laboratories, 70-230 mesh) with elution by CCl_4. The nmr spectra of the chromatographed fractions showed that stopcock grease had been mixed with the product in this procedure. The fractions obtained were therefore recombined and again chromatographed as before except that Teflon stopcocks were used in order to avoid use of stopcock grease.

This procedure yielded n-propyl N-(2-thienyl)dithiocarbamate which was shown by nmr and ir spectra to contain neither 2-thienyl isothiocyanate nor stopcock grease. Part of this was again distilled with the same unfortunate results as with the previous distillation, indicating that the 2-thienyl isothiocyanate obtained from the previous distillation was not entirely from unreacted starting material.

All of the n-propyl N-(2-thienyl)dithiocarbamate was again chromatographed on 50 gm of silica gel 60 (EM Laboratories, 70-230

mesh) with elution by carbon tetrachloride. The product in carbon tetrachloride solution was filtered through sintered glass and the solvent removed by evaporation. This yielded 673 mgs (44%) of n-propyl N-(2-thienyl)dithiocarbamate as a viscous yellow oil. This was dried under low vacuum for 36 hours. Attempts to get the product to crystallize failed and the material submitted for analysis was the oil.

The yield of the named product can undoubtedly be increased by omitting the distillations and the chromatography they necessitate.

Nmr (CCl_4): δ 0.98 (t, 3, CH_3), 1.69 (sextet, 2, CCH_2C), 3.20 (t, 2, SCH_2), 6.78-7.04 (m, 3, ArH), 9.23 (br band, 1, NH); J_{CH_2,CH_3} = 7.5 Hz, $J_{CH_2CH_2}$ = 7.0 Hz (Figure 14).

Anal. calcd for $C_8H_{11}NS_3$: C, 44.20; H, 5.10; N, 6.44; S, 44.25. Found: C, 44.12; H, 5.20; N, 6.61; S, 44.23.

t-Butyl-N-(2-thienyl)dithiocarbamate

A modification of the method of Roshdestwenski[27] is employed for this synthesis.

To a stirred slurry of lithium t-butylmercaptide (682 mg, 7.1 mmol) in 10 ml t-butyl mercaptan was added 2-thienyl isothiocyanate (1.0 g, 7.1 mmol). The reaction mixture was refluxed for 5 minutes and then stirred at room temperature in a foil covered flask for 20 hours under anhydrous conditions. The mercaptan was evaporated under a stream of nitrogen and the pasty residue neutralized with 0.1 N HCl.

The resultant oil was extracted with ether and the extract dried over anhydrous sodium sulfate. Evaporation of the ether gave a crystalline product.

The crude product was chromatographed on a drypacked 40 g silica gel 60 (EM Laboratories, 70-230 mesh) column with elution by CCl_4. This effectively separates unreacted 2-thienyl isothiocyanate, which comes with the solvent front, from the product which comes a little later. The chromatographed product was recrystallized from petroleum ether (bp 30-60°) with decolorization by acid-washed Norit A charcoal, yielding 1.42 g (86%) of t-butyl N-(2-thienyl)dithiocarbamate as yellow needles, mp 87.5-88.5° (dec).

Nmr (CCl_4): δ 1.63 (s, 9, CH_3), 6.80-7.01 (m, 3, ArH), 9.17 (br band, 1, NH).

Anal. calcd for $C_9H_{13}NS_3$: C, 46.71; H, 5.66; N, 6.05; S, 41.57. Found: C, 46.82; H, 5.56; N, 6.06; S, 41.72.

3-Thenoic Acid

The method of Gronowitz[17] was used.

A solution of 3-bromothiophene (16.1 g, 99 mmol) in 50 ml anhydrous ether was cooled to -70° in a dry ice-acetone bath. A solution of n-butyl lithium in n-hexane and under an atmosphere of nitrogen was similarly cooled. The 3-bromothiophene was then added to the stirred n-butyl lithium solution in a slow stream while the

temperature was maintained at -70°. Stirring was continued for 10 minutes after the addition was complete.

The reaction mixture was then poured on a slurry of dry ice in ether in a 3-l. beaker and this was allowed to stand at room temperature overnight. Water was then added and the reaction mixture was heated for approximately 5 minutes on a steam bath.

The layers were separated and the ether layer was extracted with 5% sodium hydroxide solution. The combined aqueous layers were then acidified with 6N HCl, precipitating crude 3-thenoic acid which was recrystallized once from water, yielding 7.0 g (56%).

When this reaction was run using 1 mole of 3-bromothiophene, 2,3-thiophenedicarboxylic acid, mp 284.0-286.5° (lit. mp 270°[42]), was also isolated in approximately 2% yield.

3-Thenoyl Chloride

As for 2-thenoyl chloride, the method of Jones and Hurd[32] was used.

A solution of 3-thenoic acid (6.2 g, 48 mmol) in thionyl chloride (41.0 g 340 mmol) was refluxed under anhydrous conditions for 2 hours. The reaction mixture was cooled and the excess thionyl chloride removed on a rotary evaporator using benzene as co-distillant. The crystalline residue was recrystallized twice from CCl_4, yielding 4.0 g (57%) of 3-thenoyl chloride, mp 51-53° (lit mp 51-52°,[43] 53-54°,[44] 52-52°[10]).

It was found that the crude 3-thenoyl chloride could be used for 3-thenoyl azide preparation if great care was taken to insure that the last traces of thionyl chloride were removed. When this was done much higher yields of 3-thenoyl chloride were obtained (> 90%).

3-Thenoyl Azide

As for 2-thenoyl azide the method of Smith[33] was employed.

Solutions of 3-thenoyl chloride (4.0 g, 27 mmol) in 32 ml acetone and sodium azide (8.0 g, 120 mmol) in 32 ml distilled water were cooled to approximately 0°. The acid chloride solution was then added slowly to the azide solution while the temperature was maintained near 0°. The reaction mixture was then allowed to warm slowly to room temperature.

The acetone and aqueous layers were separated and the aqueous layer was extracted with ether. The acetone-ether solution was evaporated until only a small amount of water remained. This was decanted off, the oily azide dissolved in anhydrous ether, and dried over calcium sulfate. Evaporation of the ether yielded 4.0 g (96%) of 3-thenoyl azide as a pale yellow oil.

It was noted that the crude oil was crystalline at low temperature. The observed mp was 13-16° on one observation, and 14.5-16.5° on another. These observations were done on the entire 4 g of crude product; a narrower range could undoubtedly be observed if a smaller amount of purified 3-thenoyl azide were used.

It was found that the acetone-ether solution could be dried directly with a very large amount of calcium sulfate, but that the yield was reduced to 88%.

The thenoyl azides may explode if they are heated while dry and caution must be exercised regarding their storage and use.

3-Thienyl Isocyanate

The method of Curtius and Thysson[34] is used for this preparation except that it has been modified to allow purification of the product.

A solution of 3-thenoyl azide (10.1 g, 67 mmol) in 60 ml CCl_4 was refluxed under anhydrous conditions for 17 hours. The reflux condenser was then replaced by distillation apparatus and the CCl_4 removed by distillation at atmospheric pressure under anhydrous conditions. The 3-thienyl isocyanate was then distilled, yielding 6.0 g (72%) as a colorless liquid, bp 74-79° at 20 mm Hg.

N-n-Propyl-N'-(3-thienyl)urea

The procedure of Sah and Ma[37] was modified for this synthesis.

To a stirred solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 10 ml CCl_4 was added dropwise n-propylamine (1.5 g, 25 mmol). Stirring was continued for 1 hour after the addition was complete. No precipitate had formed, so the reaction was refluxed for 1 hour. Cooling yielded no precipitate, so the reaction mixture was evaporated to dryness. This yielded a solid residue.

The residue was recrystallized 3 times from acetone-water, with one decolorization by acid-washed Norit A charcoal, yielding 426 mg (29%) of N-n-propyl-N'-(3-thienyl)urea as white needles, mp 132.5-133.0°.

Nmr (DMSO-d_6): δ 0.87 (t, 3, CH_3), 1.45 (sextet, 2, CCH_2C), 3.21 (q, 2, NCH_2), 6.10 (t, 1, RNH), 7.00 (q, 1, 4-H), 7.22 (q, 1, 2-H), 7.35 (q, 1, 5-H), 8.66 (br s, 1, ArNH); $J_{2,4}$ = 1.6 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.0 Hz, J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} = 6.6 Hz, J_{NH,CH_2} = 5.5 Hz.

Anal. calcd for $C_8H_{12}N_2OS$: C, 52.14; H, 6.57; N, 15.21; O, 8.68; S, 17.40. Found: C, 52.29; H, 6.43; N, 15.17; O, 8.76; S, 17.41.

The ir spectrum is reproduced as Figure 4.

N-t-Butyl-N'-(3-thienyl)urea

The procedure of Sah and Ma[37] was modified in this procedure.

To a stirred solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 10 ml CCl_4 was added slowly t-butylamine (1.8 g, 25 mmol). The precipitate which formed immediately was collected and recrystallized 3 times from acetone-water with one decolorization by acid-washed Norit A charcoal. This yielded 702 mg (43%) of N-t-butyl-N'-(3-thienyl)-urea as white needles, mp 205.0-205.5°.

Nmr (DMSO-d_6): δ 1.30 (s, 9, CH_3), 5.51 (br s, 1, RNH), 6.88 (q, 1, 4-H), 7.13 (q, 1, 2-H), 7.30 (q, 1, 5-H), 8.43 (br s, 1, ArNH); $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.0 Hz.

Anal. calcd for $C_9H_{14}N_2OS$: C, 54.51; H, 7.12; N, 14.13; O, 8.07; S, 16.17. Found: C, 54.73; H, 6.95; N, 14.02; O, 8.12; S, 16.22.

n-Propyl N-(3-thienyl)carbamate

The procedure of Baker and Gaunt[38] was modified for this synthesis.

To a stirred solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 10 ml of CCl_4 was slowly added dried n-propyl alcohol (1.5 g, 25 mmol). After the addition was complete the reaction was refluxed for 1 hour and the CCl_4 and excess alcohol evaporated, yielding a solid residue. The residue was recrystallized 3 times from acetone-water, with one decolorization by acid-washed Norit A charcoal, yielding 674 mg (46%) of n-propyl N-(3-thienyl)carbamate as white needles, mp 80.0-82.0°.

Nmr (acetone-d_6): δ 0.92 (t, 3, CH_3), 1.63 (sextet, 2, CCH_2C), 4.08 (t, 2, OCH_2), 7.12 (t, 1, 2-H), 7.31 (d, 2, 4-H 5-H), 8.87 (br band, 1, NH); apparent $J_{2,4} = J_{2,5}$ = 3.5 Hz, J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} = 6.5 Hz (Figure 15).

Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; O, 17.27; S, 17.31. Found: C, 51.87; H, 6.03; N, 7.52; O, 17.27; S, 17.38.

The ir spectrum is reproduced as Figure 5.

t-Butyl N-(3-thienyl)carbamate

The procedure of Baker and Gaunt[38] was modified in this procedure.

To a stirred solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 10 ml CCl_4 was added slowly t-butyl alcohol (1.9 g, 25 mmol). The reaction was refluxed for 1 hour and the CCl_4 and excess alcohol then evaporated yielding a crystalline residue. This residue was recrystallized 5 times from acetone-water with one decolorization by acid-washed Norit A charcoal, yielding 812 mg (51%) of t-butyl N-(3-thienyl)-carbamate as white needles, mp 144.5-145.0° (lit 139.5-140.5°).[13]

Nmr (acetone-d_6): δ 1.48 (s, 9, CH_3), 7.13 (t, 1, 2-H), 7.31 (d, 2, 4-H 5-H), 8.63 (br band, 1, NH); apparent $J_{2,4} = J_{2,5} = 3.5$ Hz.

Anal. calcd for $C_9H_{13}NO_2S$: C, 54.24; H, 6.57; N, 7.03; O, 16.06; S, 16.09. Found: C, 54.31; H, 6.50; N, 7.17; O, 16.22; S, 15.96.

n-Propyl N-(3-thienyl)thiolcarbamate

The method of Dyer and Glenn[18] was used.

To a stirred solution of n-propyl mercaptan (1.9 g, 25 mmol) in 15 ml n-heptane containing 1% (v/v) triethylamine was added dropwise a solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 15 ml n-heptane under anhydrous conditions. Stirring was continued for 1 hour after the addition was completed. The precipitate was collected and recrystallized

once from petroleum ether, yielding 1.61 g (88%) of n-propyl N-(3-thienyl)thiolcarbamate as white needles, mp 99.5-100.0°.

Nmr (acetone-d_6): δ 0.97 (t, 3, CH_3), 1.65 (sextet, 2, CCH_2C), 2.94 (t, 2, SCH_2), 7.13 (q, 1, 4-H), 7.33 (q, 1, 5-H), 7.49 (q, 1, 2-H), 9.56 (br band, 1, NH); $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.1 Hz, $J_{4,5}$ = 5.0 Hz, J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} = 7.5 Hz (Figure 16).

Anal. calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; O, 7.95; S, 31.86. Found: C, 47.65; H, 5.42; N, 6.97; O, 7.90; S, 32.00.

t-Butyl N-(3-thienyl)thiolcarbamate

The method of Dyer and Glenn[18] was used.

To a stirred solution of t-butyl mercaptan (2.3 g, 25 mmol) in 15 ml n-heptane containing 1% (v/v) triethylamine was added dropwise a solution of 3-thienyl isocyanate (1.0 g, 8 mmol) in 15 ml n-heptane under anhydrous conditions. Stirring was continued for 1 hour after the addition was complete. The crystalline precipitate was collected and recrystallized once from petroleum ether (bp 30-60°), yielding 1.45 g (84%) of t-butyl N-(3-thienyl)thiolcarbamate as white needles, mp 136.5-137.0°.

Nmr (acetone-d_6): δ 1.52 (s, 9, CH_3), 7.12 (q, 1, 4-H), 7.31 (q, 1, 5-H), 7.50 (q, 1, 2-H), 9.38 (br band, 1, NH); $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.3 Hz, $J_{4,5}$ = 5.1 Hz.

Anal. Calcd for $C_9H_{13}NOS_2$: C, 50.20; H, 6.08; N, 6.51; O, 7.43; S, 29.78. Found: C, 50.14; H, 6.00, N, 6.63; O, 7.38; S, 29.79.

S-[N-(3-Thienyl)carbamoyl]-O,O'-diethyl Dithiophosphate

The isocyanate was prepared by the method of Curtius and Thysson;[34] the named product by the method of Ottman and Hooks.[15]

A solution of 3-thenoyl azide (24.1 g, 0.16 mmol) in 150 ml of CCl_4 was refluxed under anhydrous conditions for 18 hours. The reflux condenser was then replaced by a distillation apparatus and approximately half of the CCl_4 was removed by distillation under anhydrous conditions.

The residual solution was cooled to room temperature and O,O'-diethyl hydrogen dithiophosphate (27.6 g, 0.15 mmol) was added dropwise while the reaction was stirred and maintained below 35° by cooling in a tap water bath. The product crystallized out on standing overnight in the refrigerator.

The crystalline product was collected and recrystallized 3 times from n-heptane with 1 decolorization by acid-washed Norit A charcoal, yielding 35.0 g (76%) of S-[N-(3-thienyl)carbamoyl]-O,O'-diethyl dithiophosphate, mp 83.5-85.0°.

Nmr ($CDCl_3$): δ 1.39 (t, 6, CH_3), 5.97 (octet, 4, CH_2), 7.03 (q, 1, 4-H), 7.25 (q, 1, 5-H), 7.44 (q, 1, 2-H), 9.07 (br band, 1, NH); $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.2 Hz, J_{CH_2,CH_3} = 7.2 Hz, J_{POCH_2} = 10 Hz (lit value range 6.5-10.0 Hz[39]).

Anal. calcd for $C_9H_{14}NO_3S_3P$: C, 34.71; H, 4.53, N, 4.50; S, 30.89; P, 9.95. Found: C, 34.80; H, 4.88; N, 4.65; S, 30.57; P, 9.93.

3-Thienyl Isothiocyanate

The method of Ottman and Hooks[15] was used, modified to allow distillation of the product as it is produced in the pyrolysis rather than extracting after the reaction has run its course. This is necessary because of the lability of the aminothiophene moeity in the acid medium of the by-products of this reaction.

In a low pressure distillation apparatus was placed S-[N-(3-thienyl)carbamoyl]-O,O'-diethyl dithiophosphate (15 g, 48 mmol) and 2.5 ml of diethyl phthalate. The pressure in the system was reduced to 18 mm Hg and the pyrolysis flask immersed in an oil bath preheated to 135°. The oil bath was maintained at 135-140° until distillation stopped and was then raised slowly to 220° while the pressure was maintained at 18-20 mm Hg. The crude distillate was then fractionally redistilled, 104-110° at 15 mm Hg. It is dangerous and unnecessary to heat the pyrolysis to 220°, maintaining the initial temperature is adequate for distillation.

Since this did not give a pure product, the material was chromatographed on 50 g of silica gel 60 (EM Laboratories, 70-230 mesh) with elution by cyclohexane/chloroform, 10:1. The partially purified chromatographed material was then distilled on a Nester-Faust Teflon spinning band column yielding a yellow oil, bp 98-99° (uncorrected still head reading) at 15 mm Hg. There were still some very small extraneous peaks in the nmr spectrum but the product was submitted for elemental analysis, giving the results below.

The 98-99° fraction used for elemental analysis plus two smaller fractions of nearly equal purity from the spinning band distillation totaled 2.28 g (34%) of nearly pure 3-thienyl isothiocyanate.

Nmr (CCl_4): δ 6.87 (q, 1, 4-H), 7.02 (q, 1, 2-H), 7.20 (q, 1, 5-H); $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.1 Hz, $J_{4,5}$ = 4.8 Hz (Figure 17).

Anal. calcd for $C_5H_3NS_2$: C, 42.53; H, 2.14; N, 9.92; S, 45.41. Found: C, 42.67; H, 2.00; N, 10.05; S, 45.27.

The ir spectrum is reproduced as Figure 6.

The refractive index was observed as 1.6771 at 25°.

Later repetition of this synthesis showed that the diethyl phthalate, which was added in an attempt to distill all of the product from the reaction pot, is unnecessary as the higher boiling byproducts serve this function. The crude distillate from the pyrolysis is readily purified by chromatography on silica gel 60 with elution by CCl_4, as was reported above for the preparation of 2-thienyl isothiocyanate. This avoids the necessity for redistilling the product in the presence of the acidic byproducts, thus avoiding decomposition and allowing higher yields to be obtained.

As was the case for the preparation of 2-thienyl isothiocyanate, it was not possible to obtain 3-thienyl isothiocyanate from S-[N-(3-thienyl)carbamoyl]-O, O'-diethyl dithiophosphate which had been stored for several months and had become highly colored.

N-(3-Thienyl)thiourea

The method of Otterbacher and Whitmore[41] was modified for this synthesis.

Crystalline S-[N-(3-thienyl)carbamoyl]-O,O'-diethyl dithiophosphate (1.3 g, 4.2 mmol) was heated in a 120-130° oil bath for 2 hours in a flask equipped with an air-cooled reflux condensor. The crude pyrolysis mixture was allowed to cool to room temperature and then 10 ml concentrated aqueous ammonia was added. This mixture was stirred for 5 hours and then was allowed to stand overnight. The reaction mixture was still very alkaline (pH 10) at that time.

Addition of 30 mls ether caused formation of a precipitate which was collected and recrystallized twice from water with 1 decolorization by acid-washed Norit A charcoal, yielding 74 mg (11%) of N-(3-thienyl)thiourea as white plates, mp 192.0-193.0°. Further extraction of the reaction liquor with ether followed by evaporation of the ether yielded less than 5 mg of additional material.

Nmr (DMSO-d_6) (A-60): δ 7.20 (q, 1, 4-H), 7.47 (br s, 2, NH_2), 7.65 (q, 1, 5-H), 7.71 (q, 1, 2-H), 10.03 (br s, 1, NH); $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.0 Hz.

Anal. calcd for $C_5H_6N_2S_2$: C, 37.95; H, 3.82; N, 17.71; S, 40.52. Found: C, 37.94; H, 3.93; N, 17.62; S, 40.67.

This preparation was also carried out by bubbling anhydrous ammonia through a solution of 3-thienyl isothiocyanate (397 mg, 2.8

mmol) in CCl_4. This yielded an immediate precipitate which was collected. Evaporation of the reaction liquor yielded an oil, which was shown by ir to be unreacted 3-thienyl isothiocyanate. The oil was then reacted with concentrated aqueous ammonia by heating for 10 minutes. This yielded more precipitate, which was collected. The combined precipitates were recrystallized 3 times from water with one decolorization by acid-washed Norit A charcoal, yielding 153 mg (35%) of N-(3-thienyl)thiourea as white plates, mp 191.0-192.5°.

N-n-Propyl-N'-(3-thienyl)thiourea

The method of Otterbacher and Whitmore[41] was modified for this synthesis.

To stirred 3-thienyl isothiocyanate (510 mg, 3.6 mmol) was added n-propylamine (1.67 g, 28 mmol). The reaction mixture was refluxed for 5 minutes and then stirred while it cooled to room temperature. Addition of 10 ml cold water, followed by cooling in ice yielded an oil which was extracted from the aqueous layer with $CHCl_3$. The combined extracts were dried over calcium sulfate.

Evaporation of the $CHCl_3$ yielded a crystalline product which was recrystallized 4 times from toluene-ligroine (63-75°), yielding 150 mg (21%) of N-n-propyl-N'-(3-thienyl)thiourea as white needles, mp 54.0-55.0°.

Nmr (acetone-d_6): δ 0.88 (t, 3, CH_3), 1.61 (sextet, 2, CCH_2C), 3.55 (q, 2, NCH_2), 7.08 (q, 1, 4-H), ca. 7.2 (br band, 1, RNH), 7.38

(q, 1, 5-H), 7.52 (q, 1, 2-H), 8.93 (br band, 1, ArNH); $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.2 Hz, J_{CH_2,CH_3} = 7.2 Hz, J_{CH_2,CH_2} = 6.7 Hz.

Anal. calcd for $C_8H_{12}N_2S_2$: C, 47.96; H, 6.04; N, 13.99; S, 32.01. Found: C, 47.82; H, 5.95; N, 13.84; S, 32.02.

N-t-Butyl-N'-(3-thienyl)thiourea

The method of Otterbacher and Whitmore[41] was modified in this procedure.

To stirred 3-thienyl isothiocyanate (500 mg, 35 mmol) was added quickly t-butylamine (7.0 g, 95 mmol). The reaction mixture was refluxed for 30 minutes, followed by evaporation of the excess amine. Attempts to recrystallize the residue from water, and from acetone-water did not effect color removal and after one recrystallization from each of these solvents the product was recrystallized twice from toluene with one decolorization by acid-washed Norit A charcoal. This yielded 351 mg (47%) of N-t-butyl-N'-(3-thienyl)thiourea as white needles, mp 161.0-161.5°.

Nmr (DMSO-d_6): δ 1.47 (s, 9, CH_3), 7.07 (q, 1, 4-H), 7.23 (br s, 1, RNH), 7.38 (q, 1, 5-H), 7.67 (q, 1, 2-H), 9.48 (br s, 1, ArNH); $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.2 Hz.

Anal. calcd for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07; S, 29.92. Found: C, 50.55; H, 6.52; N, 13.05; S, 29.70.

It is very possible that this synthesis could be improved by running it in CCl_4 at room temperature, as was done in the preparation of N-t-butyl-N'-(2-thienyl)thiourea. Another solvent which could work as well or better might be n-heptane.

In contrast to N-t-butyl-N'-(2-thienyl)thiourea this compound is stable to recrystallization.

n-Propyl N-(3-thienyl)thionecarbamate

The procedure of Bost and Andrews[29] is used.

A solution of 3-thienyl isothiocyanate (505 mg, 3.6 mmol) in 4 g dried n-propyl alcohol was refluxed for 17 hrs under anhydrous conditions. Addition of 25 ml ice water to the cooled reaction mixture precipitated the crude product. This crude precipitate was recrystallized 4 times from ligroine (bp 63-75°) yielding 400 mg (57%) of n-propyl N'-(3-thienyl)thionecarbamate as white needles, mp 67.5-68.0°.

Nmr (acetone-d_6): δ 0.98 (t, 3, CH_3), 1.80 (sextet, 2, CCH_2C), 4.52 (t, 2, OCH_2) (poorly resolved), 7.17-7.47 (m, 2, 4-H 5-H) (poorly resolved), 8.12 (br band, 1, 2-H), 10.27 (br band, 1, NH); J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} was not determinable due to poor resolution of the OCH_2 peak (Figure 18).

Anal. calcd for $C_8H_{11}NOS_2$: C, 47.73 ; H, 5.51; N, 6.96; O, 7.95; S, 31.86. Found: C, 47.74; H, 5.29; N, 7.15; O, 7.80; S, 31.92.

The ir spectrum is reproduced as Figure 7.

t-Butyl N-(3-thienyl)thionecarbamate

The method used in the successful preparation to t-butyl N-phenyl thionecarbamate was employed.

To a stirred slurry of potassium t-butoxide (895 mg, 7.1 mmol) in 50 ml sodium-dried tetrahydrofuran was added 3-thienyl isothiocyanate (1.0 g, 7.1 mmol). The reaction was refluxed under anhydrous conditions for 1 hour, 0.25 ml distilled water was added and refluxing was continued for 15 minutes. The reaction mixture was cooled to room temperature and 1.1 ml 6N HCl added with vigorous stirring.

The precipitated KCl was removed by filtration and the filtrate evaporated to small volume under a stream of nitrogen. To the residual filtrate was added 35 ml distilled water yielding an oil which crystallized on standing.

The precipitate was collected and then was dissolved in 200 ml ether insofar as this was possible at room temperature. The insoluble material was removed by filtration and the ether solution was dried over sodium sulfate. Evaporation of the ether to dryness gave a straw colored residue which was extracted in a Soxhlet apparatus for 48 hours with petroleum ether (bp 30-60°). The residue from evaporation of the Soxhlet solvent was recrystallized 3 times from petroleum ether (bp 30-60°), yielding 320 mg (21%) of t-butyl N-(3-thienylthionecarbamate as white needles, mp 109.0-110.0° (dec with gas evolution).

Nmr (acetone-d_6): δ 1.73 (s, 9, CH_3), 6.93-7.43 (m, 2, 4-H 5-H), ca 8.0 (extremely broad band, 1, 2-H), 10.00 (br band, 1, NH) (Figure 19).

Anal. calcd for $C_9H_{13}NOS_2$: C, 50.20; H, 6.08; N, 6.51; O, 7.43; S, 29.78. Found: C, 50.28; H, 5.93; N, 6.66; O, 7.40.

n-Propyl N-(3-thienyl)dithiocarbamate

The method used in the successful preparations of t-butyl N-phenylthione carbamate and n-propyl N-phenyldithiocarbamate was employed.

To a stirred slurry of lithium n-propylmercaptide (344 mg, 4.2 mmol) and n-propyl mercaptan (640 mg, 8.4 mmol) in 2 mls sodium-dried tetrahydrofuran was added 3-thienyl isothiocyanate (606 mg, 4.2 mmol). The reaction mixture was refluxed for 5 minutes and then stirred at room temperature for 18 hours under anhydrous conditions. To the reaction mixture was then added 10 ml cold distilled water and the resultant two-phase system was neutralized with 6N HCl. This was then extracted with $CHCl_3$ and the extract dried over calcium sulfate.

Evaporation of the $CHCl_3$ yielded a solid residue which was recrystallized 6 times from ligroine (63-75°) with one decolorization by acid-washed Norit A charcoal, yielding 115 mg (13%) of n-propyl N-(3-thienyl)dithiocarbamate as white needles, mp 46.5-47.0°.

Nmr (acetone-d_6): δ 0.98 (t, 3, CH_3), 1.70 (sextet, 2, CCH_2C), 3.28 (t, 2, SCH_2), 7.26-7.47 (m, 2, 4-H 5-H), 8.23 (br band,

1, 2-H), 10.78 (br band, 1, NH); J_{CH_2,CH_3} = 7.5 Hz, J_{CH_2,CH_2} = 7.5 Hz.

Anal. calcd for $C_8H_{11}NS_3$: C, 44.20; H, 5.10; N, 6.44; S, 44.25. Found: C, 44.14; H, 4.98; N, 6.57; S, 44.29.

The ir spectrum is reproduced as Figure 8.

This synthesis could undoubtedly be improved by using a room temperature synthesis in n-heptane as was done for n-propyl N-(2-thienyl)dithiocarbamate.

t-Butyl N-(3-thienyl)dithiocarbamate

A modification of the method of Roshdestwenski[27] was used in this procedure.

To a stirred slurry of lithium t-butylmercaptide (341 mg, 3.5 mmol) in 10 ml t-butyl mercaptan was added 3-thienyl isothiocyanate (500 mg, 3.5 mmol). The reaction mixture was refluxed for 5 minutes and then stirred at room temperature for 24 hours under anhydrous conditions. The mercaptan was then evaporated under a stream of nitrogen and the resultant solid neutralized with 0.1 N HCl. This yielded a solid which was dissolved in ether and dried over sodium sulfate. Evaporation of the ether solution to dryness yielded a solid which was chromatographed on a dry-packed column of silica gel 60 (EM Laboratories, 70-230 mesh) with elution by CCl_4. The product recovered from the chromatography column was recrystallized 3 times from petroleum ether (bp 30-60°) with one decolorization by acid-washed

Norit A charcoal, yielding 688 mg (84%) of t-butyl N-(3-thienyl)-dithiocarbamate as pale yellow needles, mp 88.5-89.5° (dec).

Nmr (CCl_4): δ 1.63 (s, 9, CH_3), 7.02 (q, 1, 4-H), 7.21 (q, 1, 5-H), 7.83 (br band, 1, 2-H), 8.95 (br band, 1, NH); apparent $J_{2,4}$ = 1.4 Hz, $J_{2,5}$ = 3.2 Hz, $J_{4,5}$ = 5.2 Hz (Figure 20).

Anal. calcd for $C_9H_{13}NS_3$: C, 46.71; H, 5.66; N, 6.05; S, 41.57. Found: C, 48.26; H, 5.62; N, 5.94; S, 40.34.

Two more recrystallizations from petroleum ether (bp 30-60°) yielded product whose nmr spectrum in CCl_4 indicated the presence of a small amount of hydrocarbon, even after drying under low vacuum for one week.

All of the product on hand was then rechromatographed on silica gel 60 (EM Laboratories, 70-230 mesh) with elution by CCl_4, the fractions containing the product evaporated to small volume, and the residual solution filtered through sintered glass. Evaporation of the remainder of the solvent and drying under low vacuum for several days yielded a crystalline product for which the nmr spectrum showed no extraneous peaks. The elemental analysis of this sample gave the following results: %C, 45.11; H, 5.35; N, 6.30; S, 42.23, with a 1.10% residue, probably silica gel.

From these results we conclude that t-butyl N-(3-thienyl)-dithiocarbamate has been synthesized but not brought to a high state of purity.

Liden and Sandstrom[45] have recently reported that the ortho protons in N-arylthionecarbamates and N-aryldithiocarbamates are observed as a broad band in 24°C nmr spectra. This is analogous to the effect that has been observed for the 2-H in the 37° nmr spectra of N-(3-thienyl)thionecarbamates and N-(3-thienyl)dithiocarbamates. They attribute this effect to hindered internal rotation about the N-C(X) band.

BIBLIOGRAPHY

1. H. Erlenmeyer and M. Leo, Helv. Chim. Acta, 16, 1381 (1933).

2. F. F. Blicke, in H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York (1952), pp. 29-45.

3. E. Campaigne, J. Pharm. Sci., 46, 129 (1957).

4. M. Martin-Smith and S. Reid, J. Med. and Pharm. Chem., 1, 507 (1959).

5. M. Bellenghi and A. Wittgens, Arzneimittel Forschung, 8, 263 (1958).

6. W. Steinkopf and W. Ohse, Ann., 448, 205 (1926).

7. M. Warren, D. Marsh, C. Thompson, R. Shelton and T. Becker, J. Pharmacol., 79, 187 (1943).

8. A. Rune Frisk, Acta Med. Scand., 110, 337 (1942).

9. W. Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopf, Dresden (1941).

10. R. Hoffmann and S. Gronowitz, Arkiv Kemi, 16, 515 (1960).

11. W. Steinkopf and T. Hopner, Ann., 501, 174 (1933).

12. E. Campaigne and P. Monroe, J. Amer. Chem. Soc., 76, 2447 (1954).

13. E. W. Brunett, Ph. D. Thesis, University of Washington, 1966.

14. H. D. Hartough, "Thiophene and its Derivatives," Inrerscience Publishers, Inc., New York (1952), p. 228.

15. G. Ottman and H. Hooks, Jr., Angew. Chem., Int'l. Ed., 5, 725 (1966).

16. J. B. Sullivan, Jr., Ph. D. Thesis, University of Washington, 1963.

17. S. Gronowitz, Arkiv Kemi, 7, 361 (1954).

18. E. Dyer and J. Glenn, J. Amer. Chem. Soc., 79, 366 (1957).

19. R. F. M. White, "Physical Methods in Heterocyclic Chemistry," Vol. II, A. Katritzky, Ed., Academic Press, New York (1963), p. 116.

20. S. Gronowitz, "Advances in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York (1963), p. 8.

21. T. Bacchetti and A. Alemagna, Rend. Inst. Lombardo Sci., Pt. I, Classe Sci., Mat., e Nat., 91, 617 (1957) as abstracted in CA 53:6217g (1959).

22. K. Jensen and C. Pedersen, Acta Chem. Scand., 15, 1104 (1961).

23. P. Smith and D. Kenney, J. Org. Chem., 41, 926 (1963).

24. W. Kirmse, Chem. Ber., 93, 2353 (1960).

25. J. Saunders and K. Frisch, "High Polymers, Vol. XVI, Polyurethanes: Chemistry and Technology, Part I, Chem.," Interscience Publishers, Inc., New York (1962), p. 209.

26. W. Orndorff and F. Richmond, Amer. Chem. J., 22, 464 (1899).

27. M. Roshdestwenski, Chem. Zentralblatt, 81, 910 (1910).

28. "The Merck Index," P. Stecher, Ed., 8th Ed., Merck and Co., Rahway, N. J. (1968), p. 390.

29. R. Bost and E. Andrews, J. Amer. Chem. Soc., 65, 900 (1943).

30. L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, J. Wiley and Sons, New York (1967), p. 911.

31. L. Carpino, P. Terry and P. Crowley, J. Org. Chem., 26, 4336 (1961).

32. L. Jones and D. Hurd, J. Amer. Chem. Soc., 43, 2444 (1921).

33. P. A. S. Smith, "Organic Reactions," Vol. III, R. Adams, Ed., J. Wiley and Sons, New York (1946), pp. 373, 376.

34. T. Curtius and H. Thysson, J. prakt. chem., 65, 5 (1902).

35. L. Jones and J. Mason, J. Amer. Chem. Soc., 49, 2528 (1927).

36. B. Baker, J. Joseph, R. Schaub, F. McEvoy and J. Williams, J. Org. Chem., 18, 138 (1953).

37. P. Sah and T. Ma, J. Chin. Chem. Soc., 2, 159 (1934).

38. J. Baker and J. Gaunt, J. Chem. Soc., London, 1949, 27.

39. L. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Vol. 5 of International Series of Monographs in Organic Chemistry, Pergamon Press, New York (1969), p. 352.

40. W. Bacon and W. LeSuer, J. Amer. Chem. Soc., 76, 670 (1954).

41. T. Otterbacher and F. Whitmore, J. Amer. Chem. Soc., 51, 1909 (1929).

42. M. Gerlach, Ann., 267, 145 (1892).

43. E. Campaigne and W. LeSuer, J. Amer. Chem. Soc., 70, 1556 (1948).

44. W. Steinkopf and H. Schmitt, Ann., 533, 264 (1938).

45. A. Liden and J. Sandstrom, Acta Chem. Scand., 27, 2567 (1973).

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF DERIVATIVES OF 2-AMINOTHIOPHENE[a]

Sidechain (Solvent)	Proton Chemical Shifts (δ)[b] CH_3	CCH_2C	CH_2X	RNH	3-H	4-H	5-H	ArNH	Observed Coupling Constants (Hz ± 0.2)
$NHC(O)NH_2$ (DMSO-d_6)				6.09 (NH_2)	6.56	6.87	6.87	9.63	$J_{3,4}=J_{3,5}$ =2.6[c]
$NHC(O)NHCH_2CH_2CH_3$ (DMSO-d_6)	0.85	1.43	3.06	6.18	6.43	6.77	6.77	9.33	$J_{3,4}=J_{3,5}$ =2.6[c]
$NHC(O)NHC(CH_3)_3$ (DMSO-d_6)	1.31			5.99	6.38	6.74	6.74	9.12	$J_{3,4}=J_{3,5}$ = 2.6[c]
$NHC(O)OCH_2CH_2CH_3$ (acetone-d_6)	0.93	1.66	4.13		6.70	6.77-6.97[d]		9.35	$J_{3,4}$=3.1 $J_{3,5}$=1.9
$NHC(O)OC(CH_3)_3$ (acetone-d_6)	1.50				6.74	6.80-6.97[d]		9.33	$J_{3,4}$=3.1 $J_{3,5}$=2.0

[a] Aliphatic coupling constants are presented in the experimental section.

[b] Reported as δ (ppm) values from internal TMS standard.

[c] Apparent coupling constants representing an averaging of coupling constants.

[d] A complex multiplet from which exact assignments cannot be made.

TABLE I (cont'd)

Sidechain (Solvent)	CH_3	CCH_2C	CH_2X	RNH	3-H	4-H	5-H	ArNH	J's
$NHC(O)SCH_2CH_2CH_3$ (acetone-d_6)	0.98	1.68	2.99		6.78	6.89	7.01	10.30	$J_{3,4}$=3.4 $J_{3,5}$=1.8 $J_{4,5}$=5.2
$NHC(O)SC(CH_3)_3$ (acetone-d_6)	1.54				6.78	6.90	7.08	10.00	$J_{3,4}$=3.4 $J_{3,5}$=1.7 $J_{4,5}$=5.2
$NHC(O)SP(S)(OCH_2CH_3)_2$ ($CDCl_3$)	1.38		4.27		--6.73-7.00[d]-------			9.50	e
$N=C=S$ (CCl_4)					--6.63-7.01[d]-------				e
$NHC(S)NH_2$ (DMSO-d_6)				7.45 (NH_2)	6.72	6.89	7.04	10.45	$J_{3,4}$=3.5 $J_{3,5}$=1.7 $J_{4,5}$=5.4
$NHC(S)NHCH_2CH_2CH_3$ (acetone-d_6)	0.88	1.59	3.52	~7.22	6.73	6.82	7.03	9.27	$J_{3,4}$=3.7 $J_{3,5}$=1.7 $J_{4.5}$=5.3
($CDCl_3$)	0.88	1.59	3.58	6.23	6.78	6.90	7.15	8.27	e

[e]This data cannot be derived from the spectra obtained.

TABLE I (cont'd)

Sidechain (Solvent)	CH_3	CCH_2C	CH_2X	RNH	3-H	4-H	5-H	ArNH	J's
$NHC(S)NHC(CH_3)_3$ (acetone-d_6)	1.53			e	6.72	6.87	7.03	9.17	$J_{3,4}$=3.4 $J_{3,5}$=1.6 $J_{4,5}$=5.3
($CDCl_3$)	1.51			6.22	6.78-7.03[d]		7.19	8.05	e
$NHC(S)OCH_2CH_2CH_3$ ($CDCl_3$)	1.02	1.83	4.39		----6.70-7.03[d]----			9.99	e
$NHC(S)OC(CH_3)_3$ (acetone-d_6)	1.77				----6.80-7.08[d]----			10.57	e
$NHC(S)SCH_2CH_2CH_3$ (CCl_4)	0.98	1.69	3.20		----6.78-7.04[d]----			9.23	e
$NHC(S)SC(CH_3)_3$ (CCl_4)	1.63				----6.80-7.01[d]----			9.17	e

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF DERIVATIVES OF 3-AMINOTHIOPHENE[a]

Sidechain (Solvent)	Proton Chemical Shifts (δ)[b]								Observed Coupling Constants Hz ± 0.2)
	CH_3	CCH_2C	CH_2X	RNH	2-H	4-H	5-H	ArNH	
$NHC(O)NHCH_2CH_2CH_3$ ($DMSO-d_6$)	0.87	1.45	3.21	6.10	7.22	7.00	7.35	8.66	$J_{2,4}=1.6$ $J_{2,5}=3.2$ $J_{4,5}=5.0$
$NHC(O)NHC(CH_3)_3$ ($DMSO-d_6$)	1.30			5.51	7.13	6.88	7.30	8.43	$J_{2,4}=1.5$ $J_{2,5}=3.2$ $J_{4,5}=5.0$
$NHC(O)OCH_2CH_2CH_3$ ($acetone-d_6$)	0.92	1.63	4.08		7.12	7.31	7.31	8.87	$J_{2,4}=J_{2,5}=3.5$[c]
$NHC(O)OC(CH_3)_3$ ($acetone-d_6$)	1.48				7.13	7.31	7.31	8.63	$J_{2,4}=J_{2,5}=3.5$[c]
$NHC(O)SCH_2CH_2CH_3$ ($acetone-d_6$)	0.97	1.65	2.94		7.49	7.13	7.33	9.56	$J_{2,4}=1.4$ $J_{2,5}=3.1$ $J_{4,5}=5.0$

[a] Aliphatic coupling constants are recorded in the experimental section.

[b] Reported as δ (ppm) values from internal TMS standard.

[c] Apparent coupling constants representing an averaging of coupling constants.

TABLE II (cont'd)

Sidechain (Solvent)	CH_3	CCH_2C	CH_2X	RNH	2-H	4-H	5-H	ArNH	J's
$NHC(O)SC(CH_3)_3$ (acetone-d_6)	1.52				7.50	7.12	7.31	9.38	$J_{2,4}$=1.4 $J_{2,5}$=3.3 $J_{4,5}$=5.1
$NHC(O)SP(S)(OCH_2CH_3)_2$ ($CDCl_3$)	1.39		5.97		7.44	7.03	7.25	9.07	$J_{2,4}$=1.5 $J_{2,5}$=3.2 $J_{4,5}$=5.2
N=C=S (CCl_4)					7.02	6.87	7.20		$J_{2,4}$=1.4 $J_{2,5}$=3.1 $J_{4,5}$=4.8
$NHC(S)NH_2$ (DMSO-d_6)				7.47 (NH_2)	7.71	7.20	7.65	10.03	$J_{2,4}$=1.5 $J_{2,5}$=3.2 $J_{4,5}$=5.0
$NHC(S)NHCH_2CH_2CH_3$ (acetone-d_6)	0.88	1.61	3.55	~7.2	7.52	7.08	7.38	8.93	$J_{2,4}$=1.5 $J_{2,5}$=3.2 $J_{4,5}$=5.2
$NHC(S)NHC(CH_3)_3$ (acetone-d_6)	1.47			7.23	7.67	7.07	7.38	9.48	$J_{2,4}$=1.4 $J_{2,5}$=3.2 $J_{4,5}$=5.2

TABLE II (cont'd)

Sidechain (Solvent)	CH_3	CCH_2C	CH_2X	RNH	2-H	4-H	5-H	ArNH	J's
$NHC(S)OCH_2CH_2CH_3$ ($acetone\text{-}d_6$)	0.98	1.80	4.52		8.12	-7.17-7.47-[d]		10.27	[e]
$NHC(S)OC(CH_3)_3$ ($acetone\text{-}d_6$)	1.73				~8.0	-6.93-7.43-[d]		10.00	[e]
$NHC(S)SCH_2CH_2CH_3$ ($acetone\text{-}d_6$)	0.98	1.70	3.28		8.23	-7.26-7.47-[d]		10.78	[e]
$NHC(S)SC(CH_3)_3$ (CCl_4)	1.63				7.83	7.02	7.21	8.95	$J_{2,4}=1.4$ $J_{2,5}=3.2$ $J_{4,5}=5.2$

[d] A complex multiplet from which exact assignments cannot be made.

[e] This data cannot be derived from the spectra obtained.

Figure 1. Ir Spectrum of n-Propyl N-(2-Thienyl)thiolcarbamate, KBr Pellet.

Figure 2. Ir Spectrum of 2-Thienyl Isothiocyanate, Liquid Film.

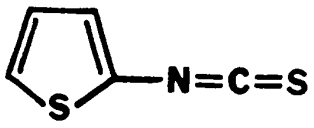
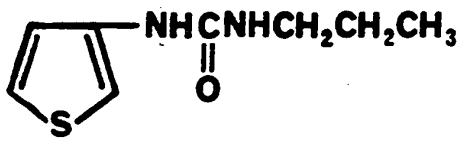
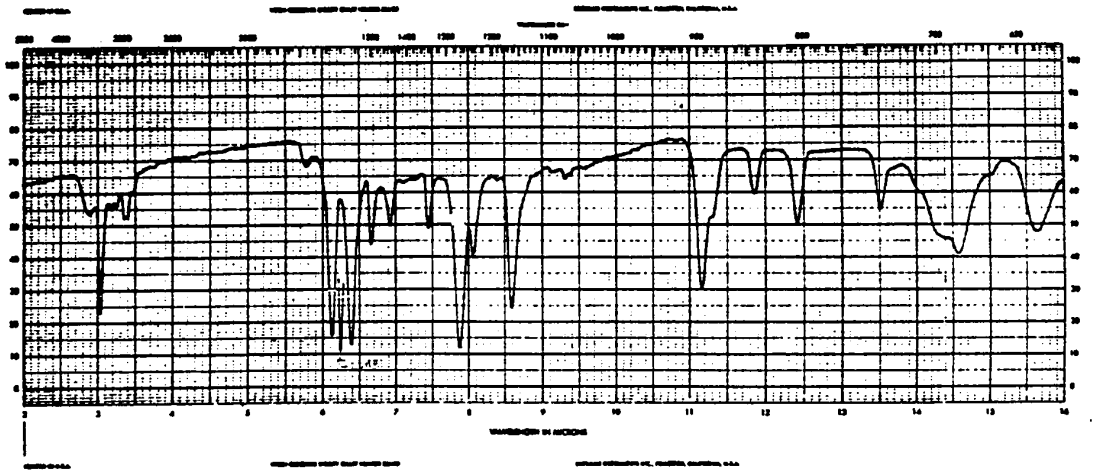
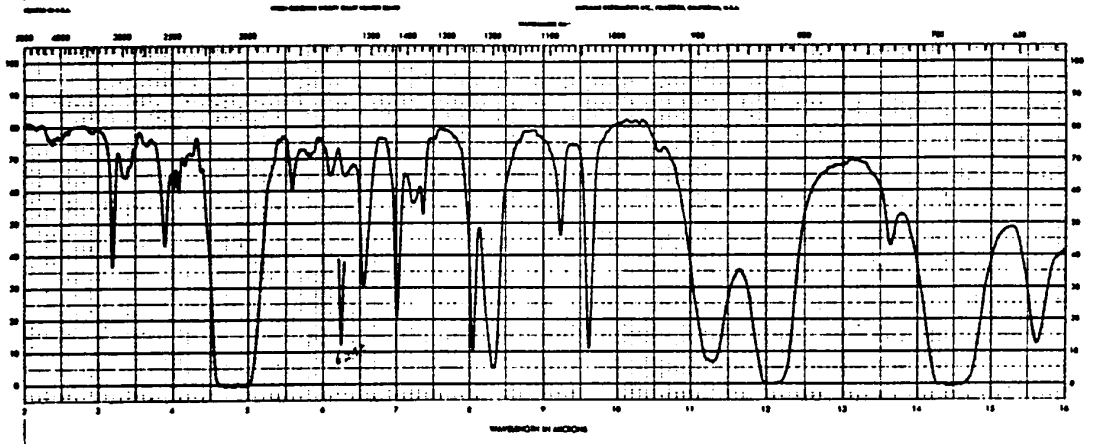


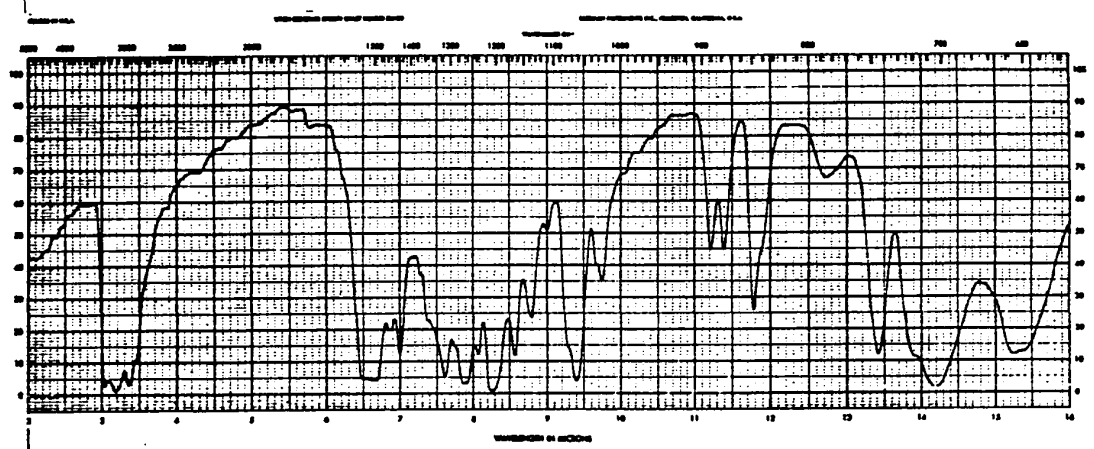
Figure 3. Ir Spectrum of N-n-Propyl-N'-(2-thienyl)thiourea, KBr Pellet.

Figure 4. Ir Spectrum of N-n-Propyl-N'-(3-thienyl)urea, KBr Pellet.









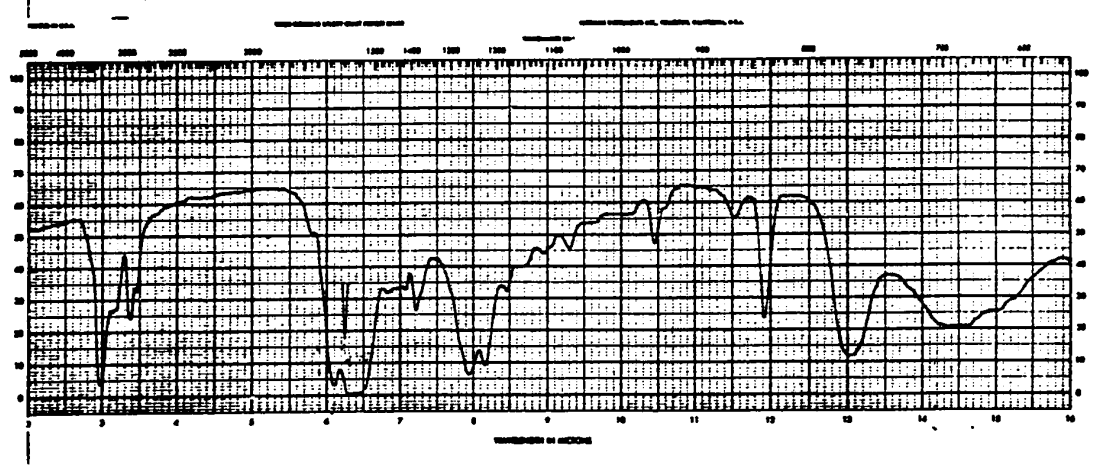


Figure 5. Ir Spectrum of n-Propyl N-(3-Thienyl)carbamate, KBr Pellet.

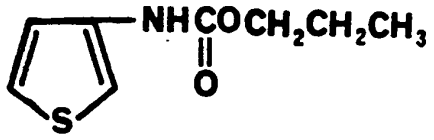


Figure 6. Ir Spectrum of 3-Thienyl Isothiocyanate, Liquid Film.

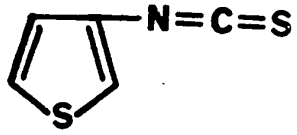
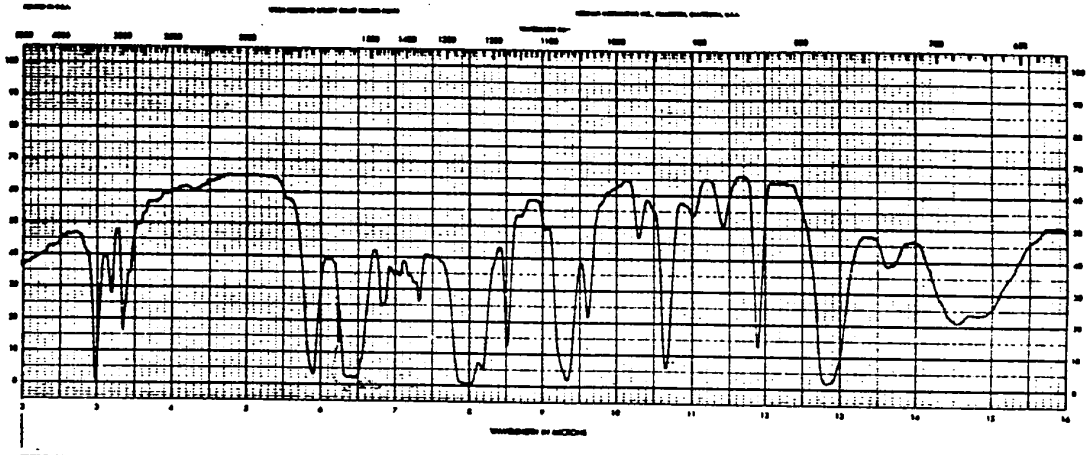
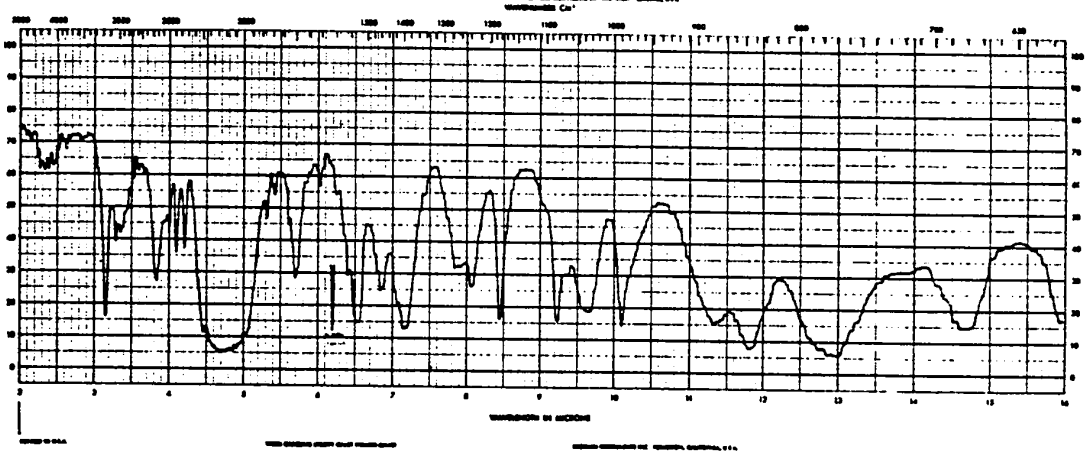
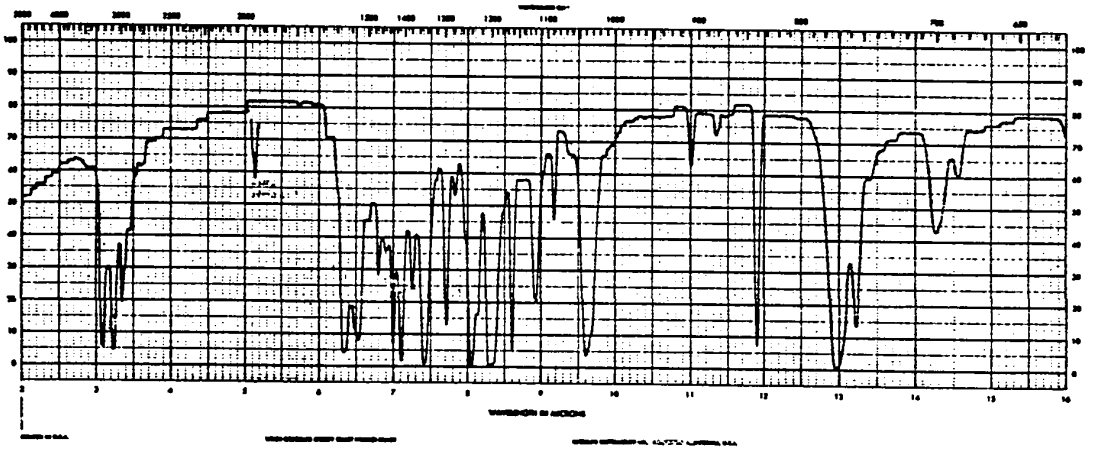


Figure 7. Ir Spectrum of n-Propyl N-(3-Thienyl)thionecarbamate, KBr Pellet.

Figure 8. Ir Spectrum of n-Propyl N-(3-Thienyl)dithiocarbamate, KBr Pellet.







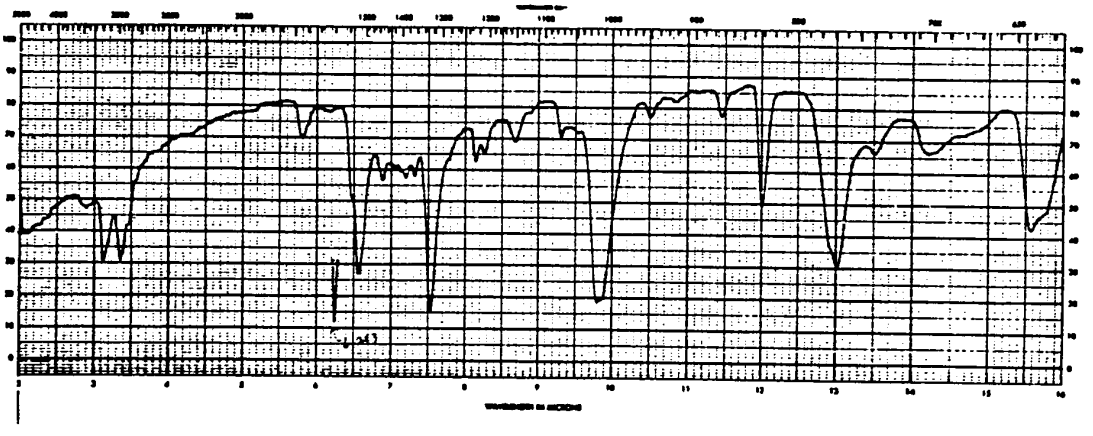


Figure 9. Nmr Spectrum of N-t-Butyl-N'-(2-thienyl)urea in DMSO-d_6 at 37°.

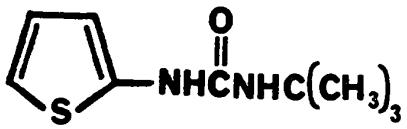
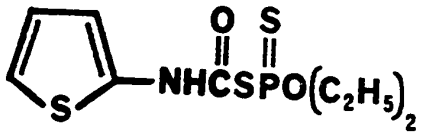
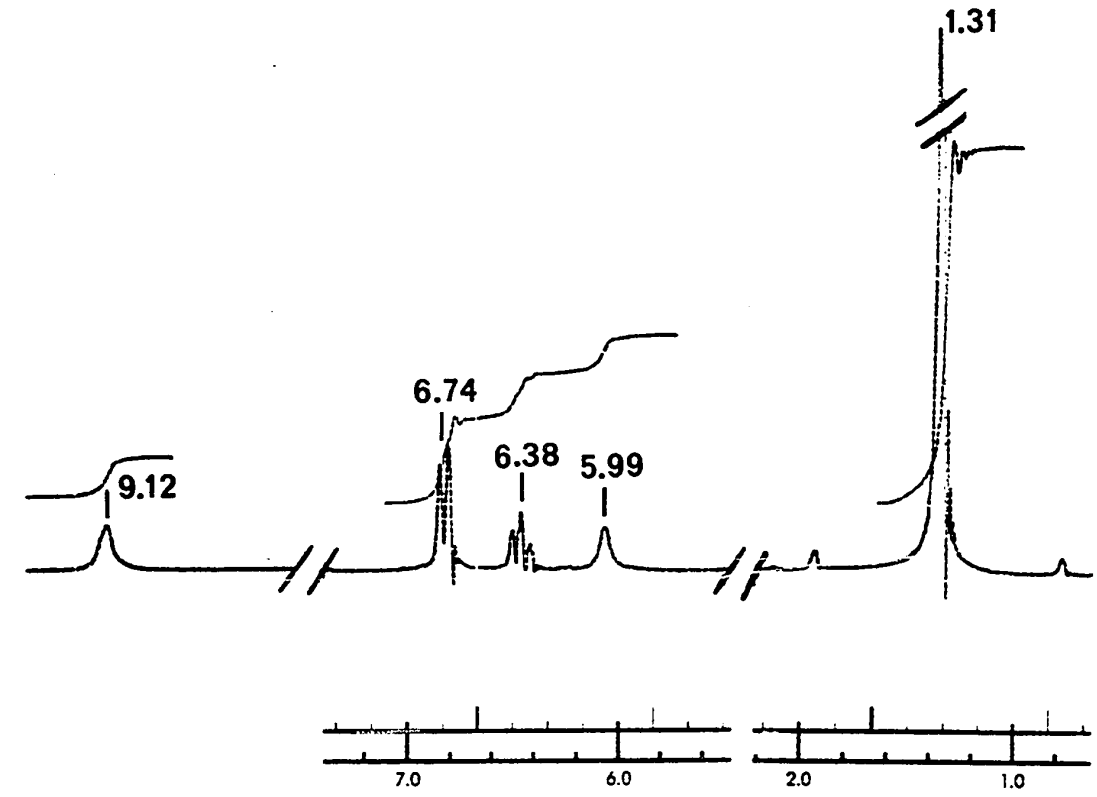


Figure 10. Nmr Spectrum of S-[N-(2-Thienyl)carbamoyl]-O, O'-diethyl Dithiophosphate in $CDCl_3$ at 37°.




1.31
6.74
6.38
5.99
9.12
7.0
6.0
2.0
1.0

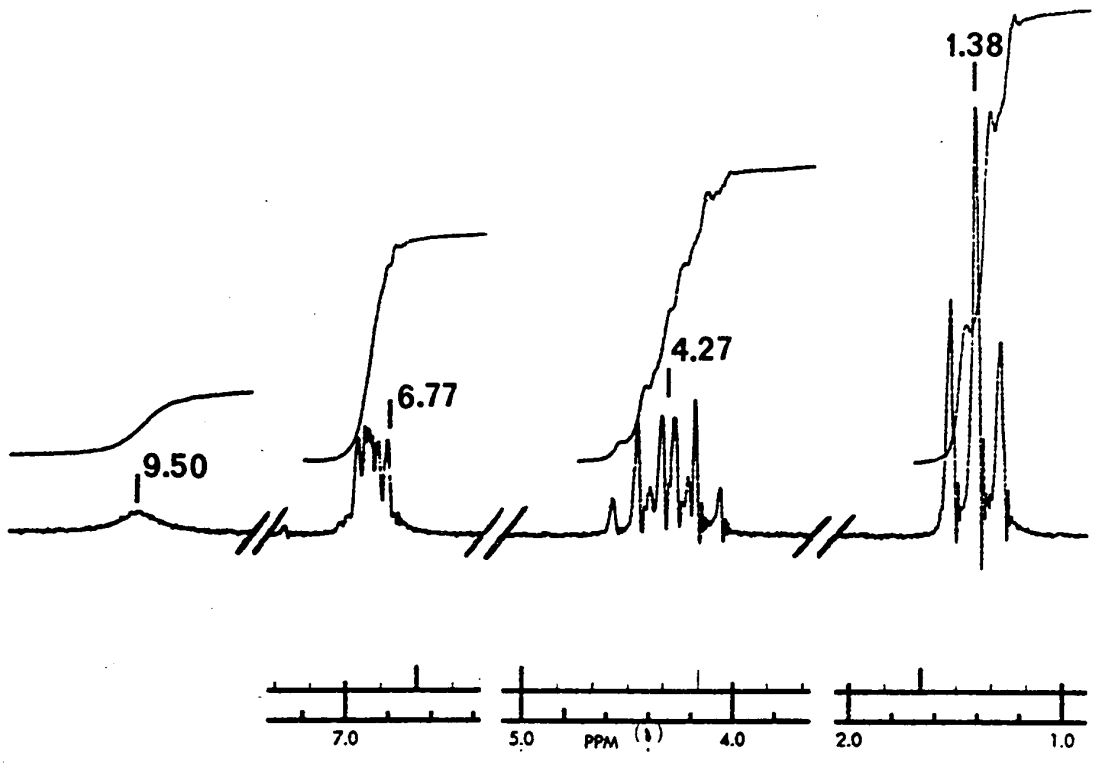

1.38
4.27
6.77
9.50
7.0
5.0
PPM
4.0
2.0
1.0

Figure 11. Nmr Spectrum of 2-Thienyl Isothiocyanate in CCl_4 at 37°.

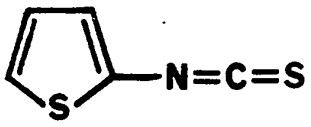


Figure 12. Nmr Spectrum of N-n-Propyl-N'-(2-thienyl)thiourea in Acetone-d_6 at 37°.

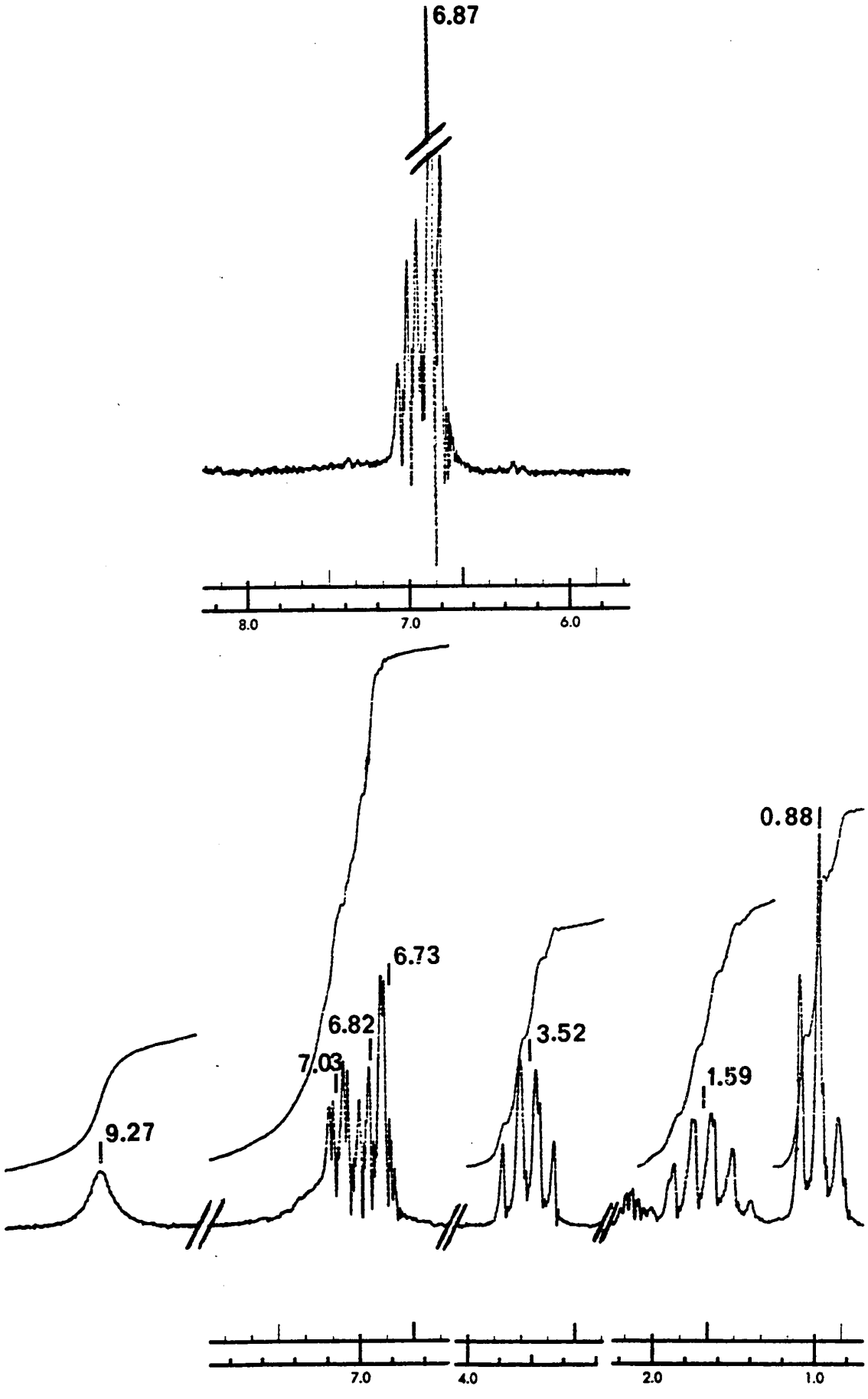
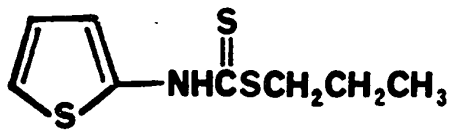
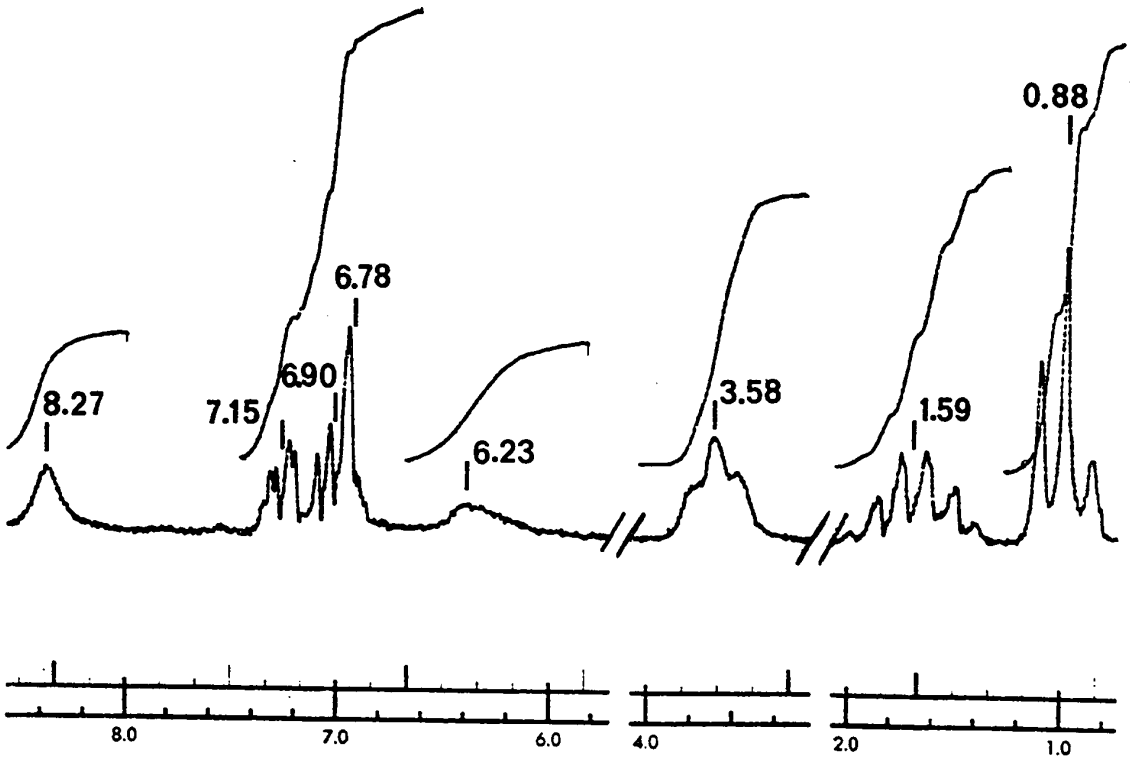

6.87
8.0
7.0
6.0
9.27
7.03
6.82
6.73
3.52
1.59
0.88
7.0
4.0
2.0
1.0

Figure 13. Nmr Spectrum of N-n-Propyl-N'-(2-thienyl)thiourea in $CDCl_3$ at 37°.

Figure 14. Nmr Spectrum of n-Propyl N-(2-Thienyl)dithiocarbamate in CCl_4 at 37°.




8.27
7.15
6.90
6.78
6.23
3.58
1.59
0.88
8.0
7.0
6.0
4.0
2.0
1.0

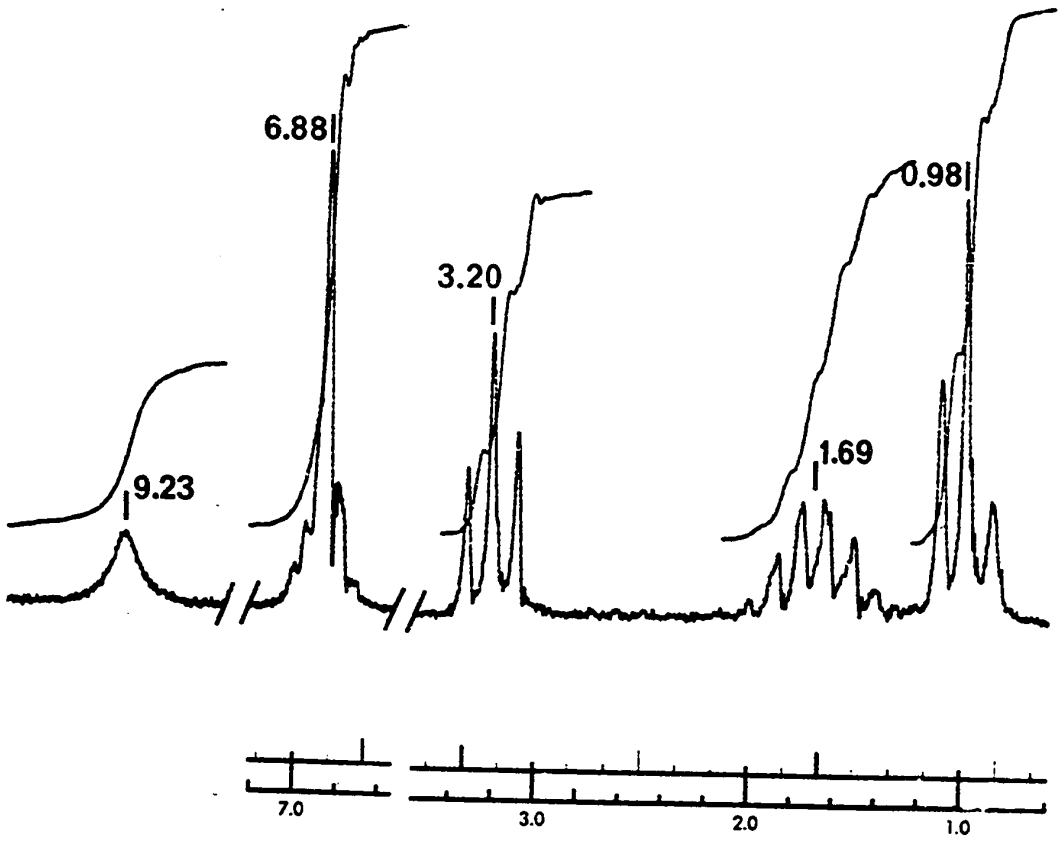

9.23
6.88
3.20
1.69
0.98
7.0
3.0
2.0
1.0

Figure 15. Nmr Spectrum of n-Propyl N-(3-Thienyl)carbamate in Acetone-d_6 at 37°.

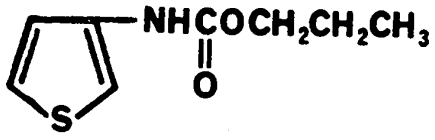
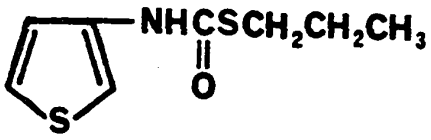
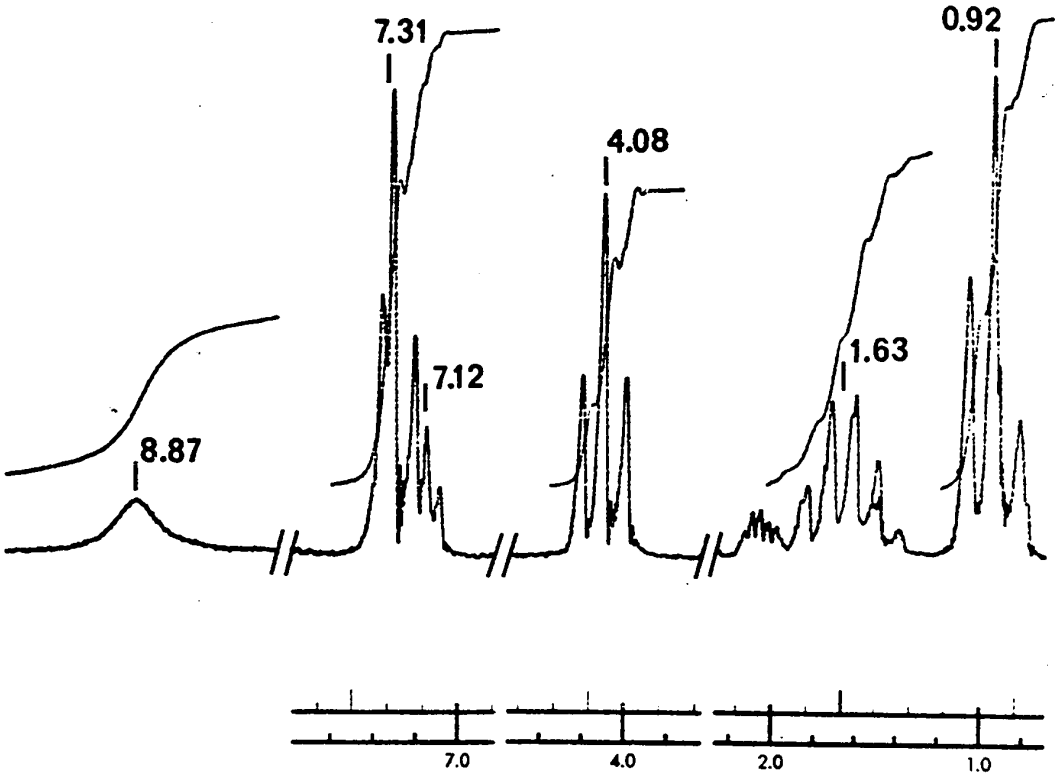


Figure 16. Nmr Spectrum of n-Propyl N-(3-Thienyl)thiolcarbamate in Acetone-d_6 at 37°.




7.31
0.92
4.08
1.63
7.12
8.87
7.0
4.0
2.0
1.0

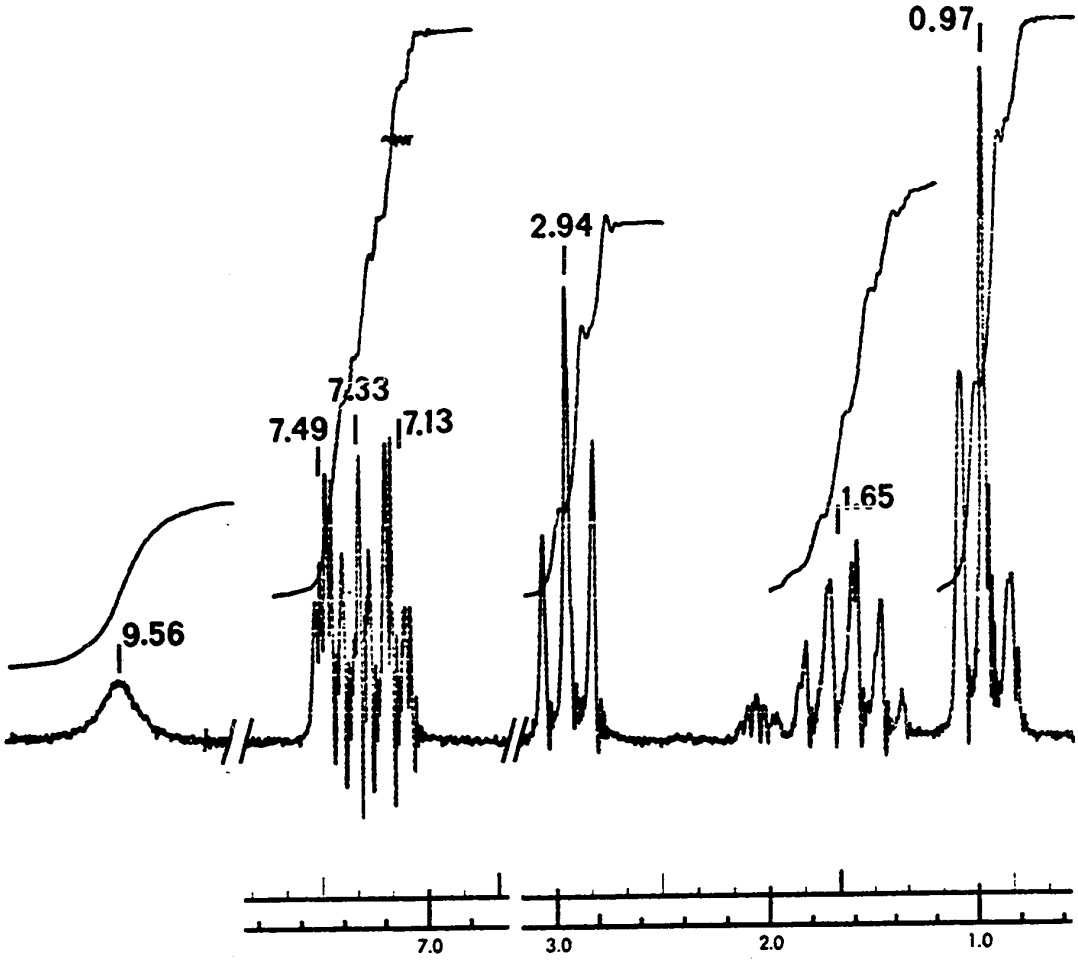

0.97
2.94
7.33
7.49
7.13
1.65
9.56
7.0
3.0
2.0
1.0

Figure 17. Nmr Spectrum of 3-Thienyl Isothiocyanate in CCl_4 at 37°.

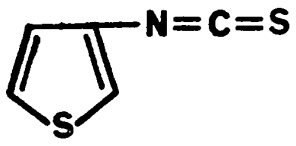
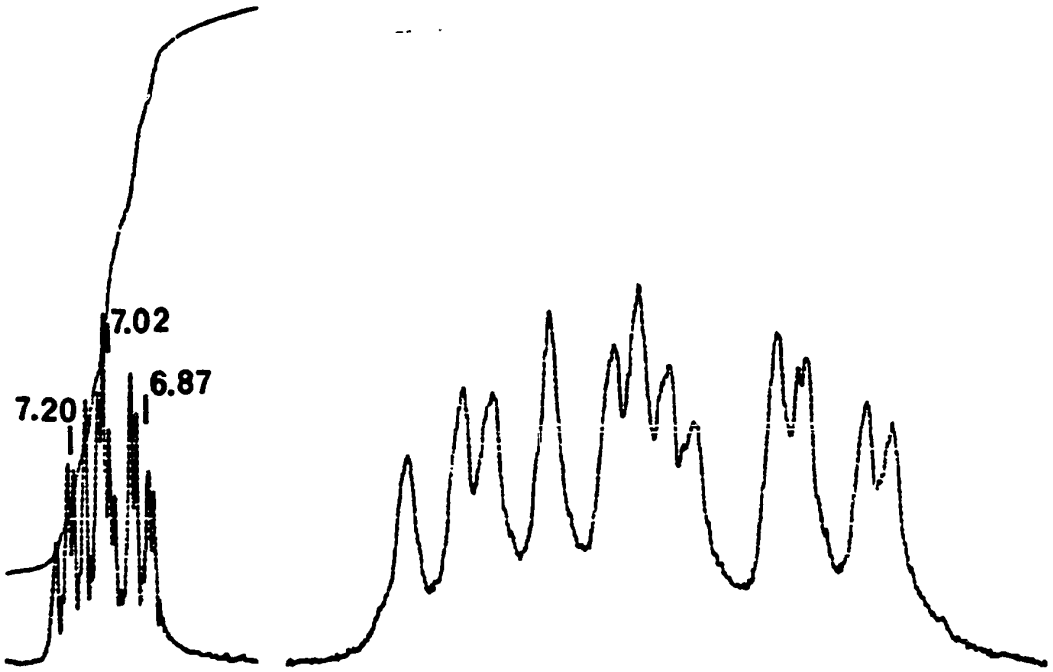


Figure 18. Nmr Spectrum of n-Propyl N-(3-Thienyl)thionecarbamate in Acetone-d_6 at 37°.



sweep width 100 Hz

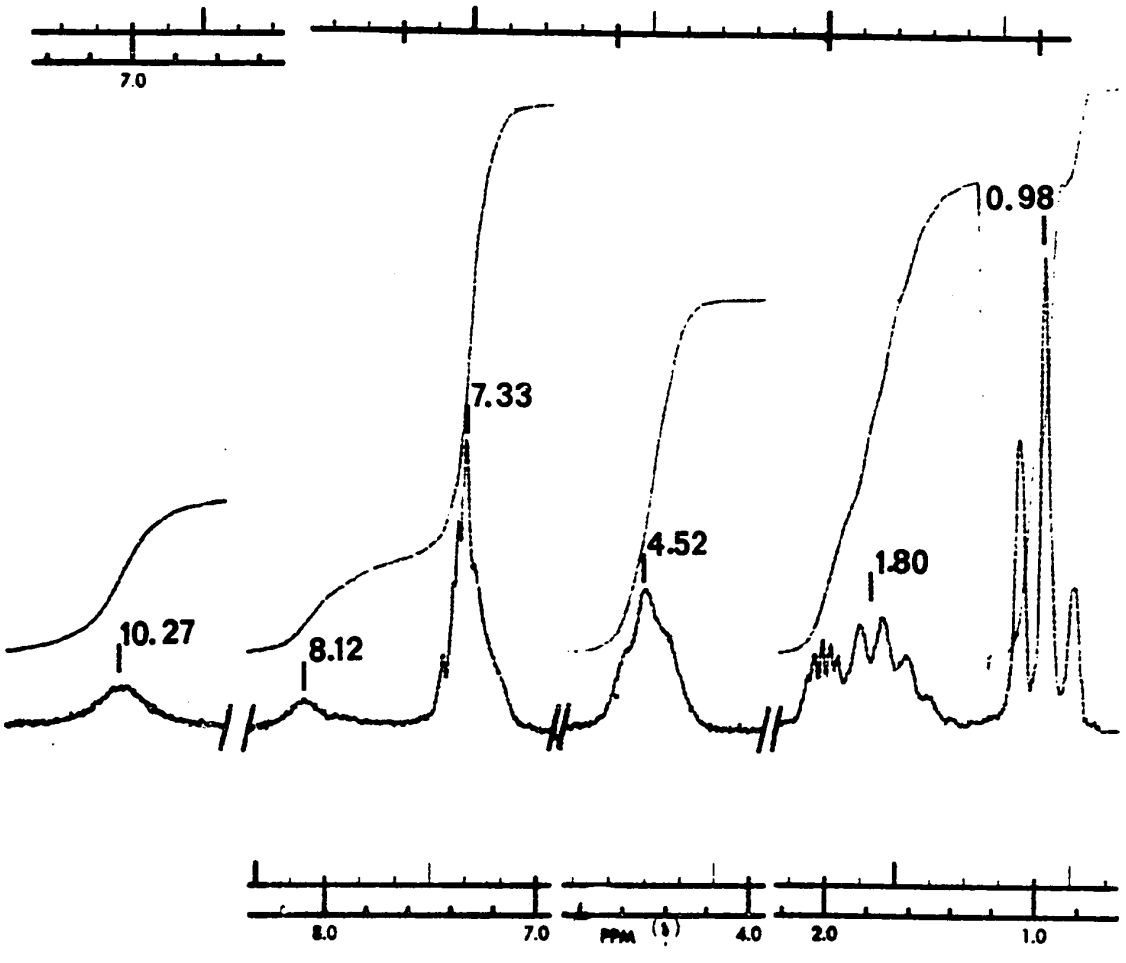


Figure 19. Nmr Spectrum of t-Butyl N-(3-Thienyl)thionecarbamate in Acetone-d_6 at 37°.

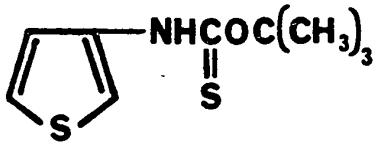
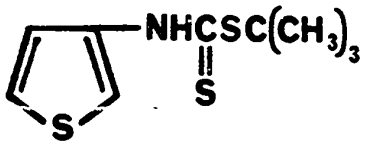
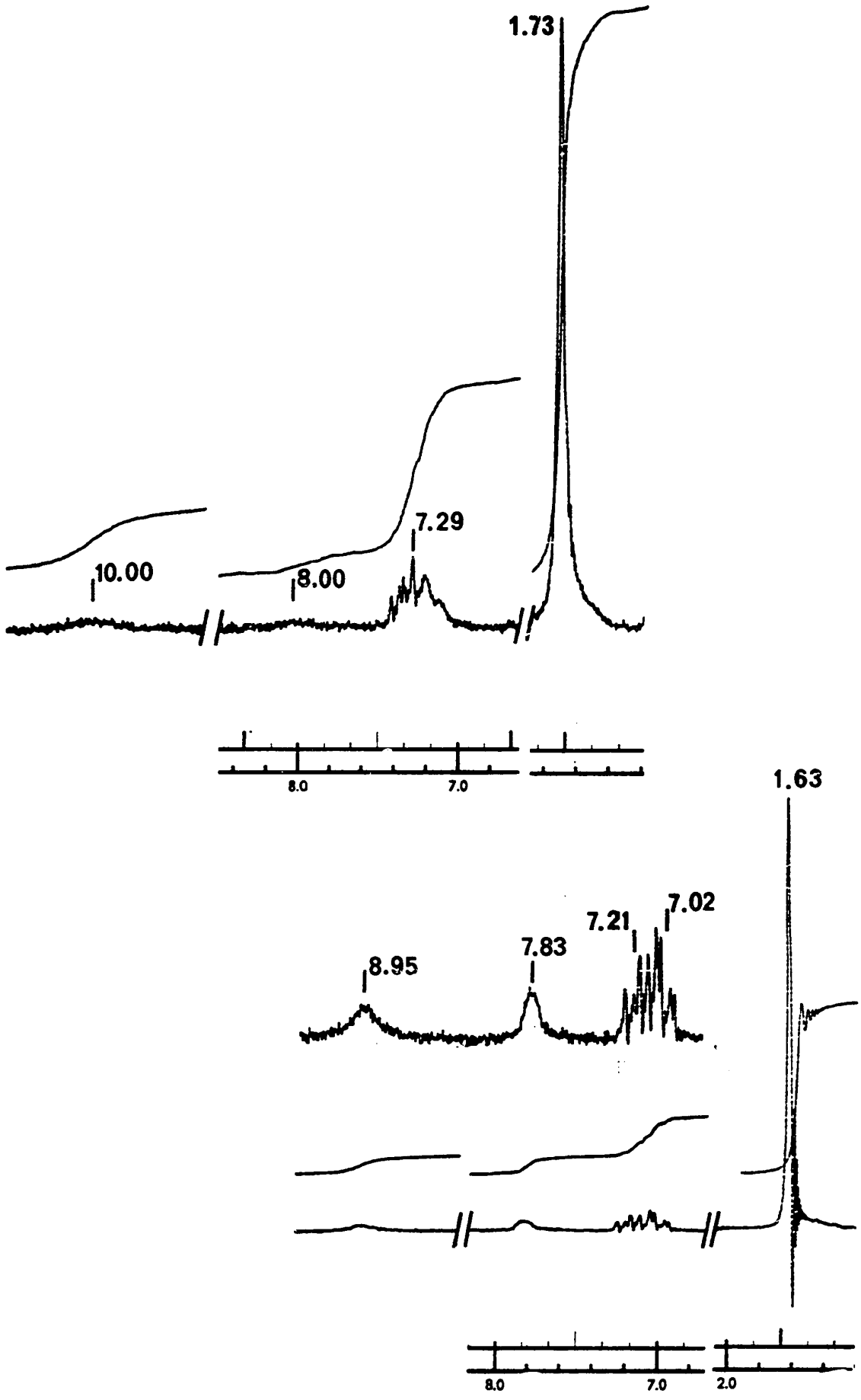


Figure 20. Nmr Spectrum of t-Butyl N-(3-Thienyl)dithiocarbamate in CCl_4 at 37°.




1.73
10.00
8.00
7.29
8.0
7.0
1.63
8.95
7.83
7.21
7.02
8.0
7.0
2.0