"OPEN" SULFUR HETEROCYCLIC ANALOGS OF THE PHENOTHIAZINES AND RELATED PHENYLTHIENYL SYSTEMS

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Charles Okolo Okafor
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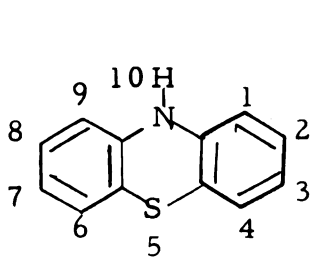
ABSTRACT

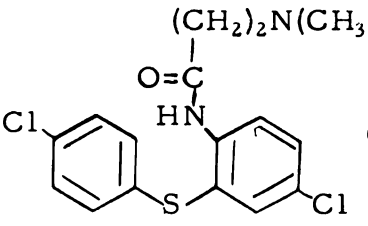
"OPEN" SULFUR HETEROCYCLIC ANALOGS OF THE PHENOTHIAZINES AND RELATED PHENYLTHIENYL SYSTEMS

by Charles Okolo Okafor

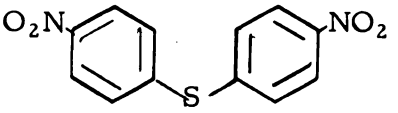
The present investigation was undertaken to develop synthetic procedures for obtaining a series of phenylthienyl sulfides, N-aryl-2-thienylamines and polynitro-2, 5-bis-thiophenoxythiophenes. It was anticipated that such compounds would have enhanced physiological activities as tranquilizers compared to phenothiazine and its derivatives (1, 2, 3).



phenothiazine



I

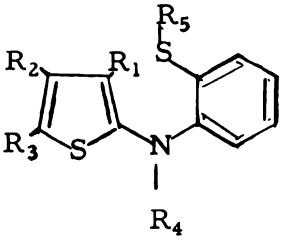


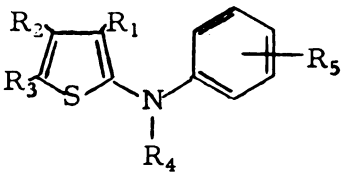
II

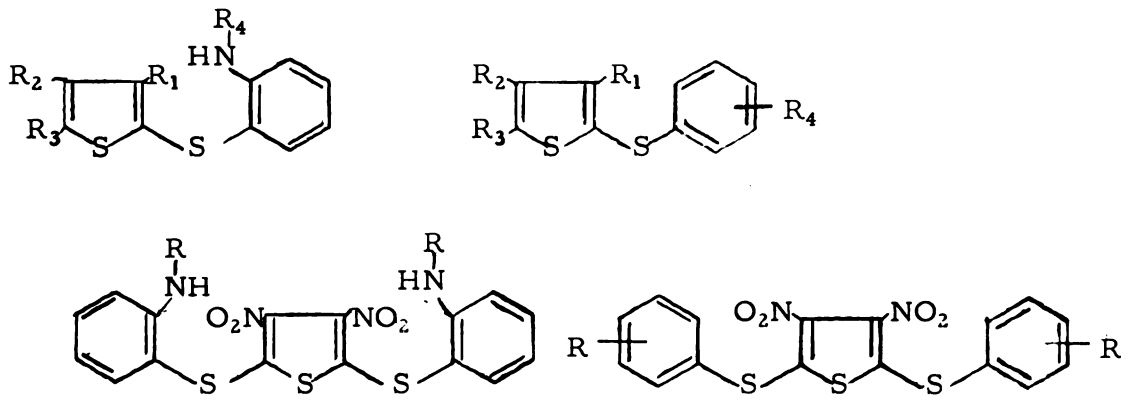
Analogs of phenothiazine in which the hetero-ring has been "opened" have been prepared in recent years. Among them were 2-dialkyl aminoalkylamino and 2-dialkylaminoacyl-diphenyl sulfides (4, 5). It has been reported that 2-(2-dimethylaminopropylamino)diphenyl

sulfide prevents nicotine tremors to the same degree as 10-(2-diethylaminopropylamino)phenothiazine. Several diethylaminoalkylaminodiphenyl sulfides had been prepared (6) and had been reported to possess anesthetic and amebacidal properties. A series of "open" o-aminodiphenyl sulfide analogs of the antiemetic phenothiazines have been described by Burger and his collaborators (7, 8, 9). The compound, 4', 5-dichloro-2-(3- dimethylaminopropionamido)diphenyl sulfide (5),(I), markedly prolonged the survival time of mice which had received a lethal dose of X-rays. The sulfides, 4, 4'- and 4', 5-dichloro-2-(3-dimethylaminopropylamino)diphenyl sulfides (7) were active against a considerable number of pathogenic fungi in vitro. Thus, it is not unreasonable to expect that the o-aminophenyl-2-thienyl sulfides, N- o-thiomethoxyphenyl-2-thienylamines and the 2, 5-bis-o-aminothiophenoxythiophenes could be potential tranquilizers, antiseptics, etc. Some of the dinitrophenylthienyl sulfides, dinitro-N-aryl-2-thienylamines and the 3, 4-dinitro-2, 5-bis-thiophenoxythiophenes could also have high germicidal properties as compared to bis-(4-nitrophenyl)sulfide (10), (II), 5-nitrothiophene-2-carboxylic acid (11) and penicillin. However, only laboratory and clinical tests can establish the real value of their physiological usefulness.

The thienylphenyl sulfides, N-aryl-2-thienylamines and the polynitro-2, 5-bis-monosubstituted thiophenoxythiophenes investigated in the present study are indicated by the general structures:

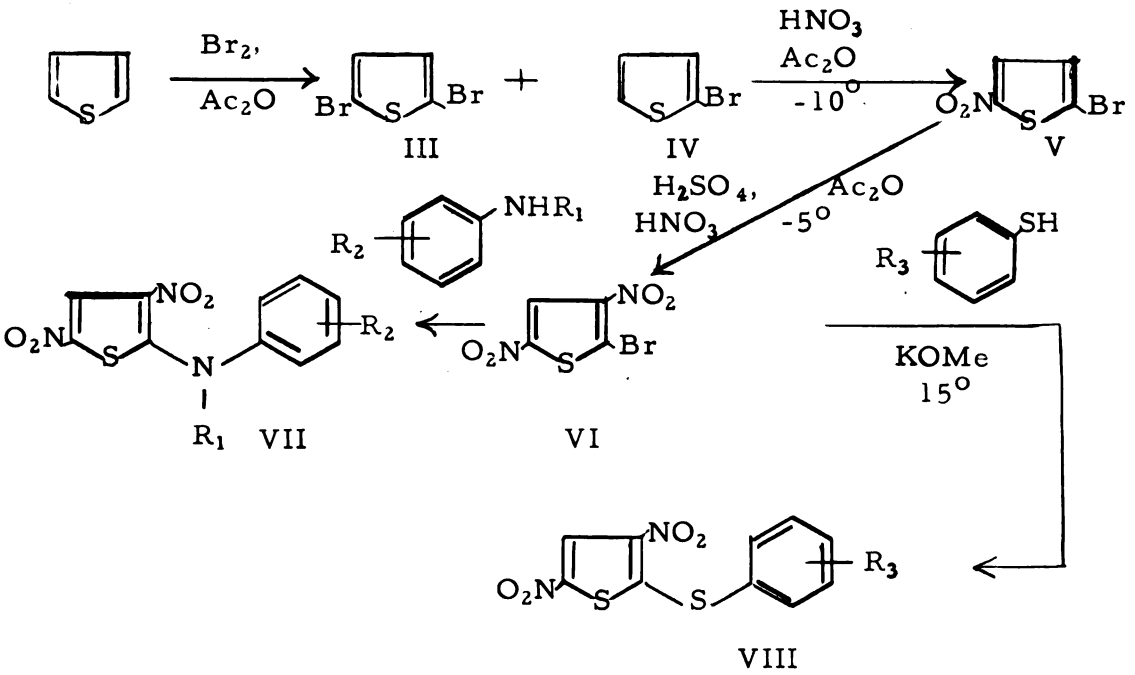


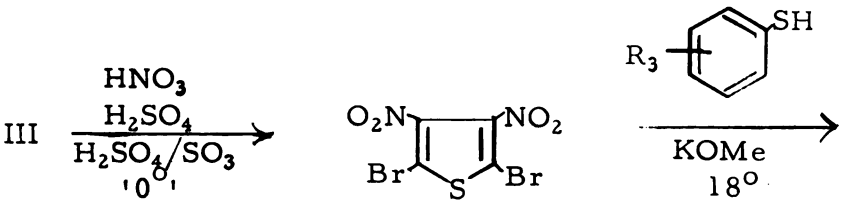


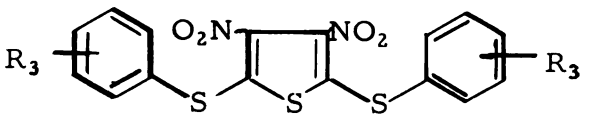


Molecular models of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide, 3, 5 - dinitro - N (-2-thiomethoxyphenyl)-2-thienylamine, 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophene and their amine derivatives show these structures to be rather highly hindered; the ortho-substituent on the benzene is in close proximity to the 3-substituent on the thiophene ring.

The general experimental procedures developed for the synthesis of these compounds involved the following sequence of reactions:





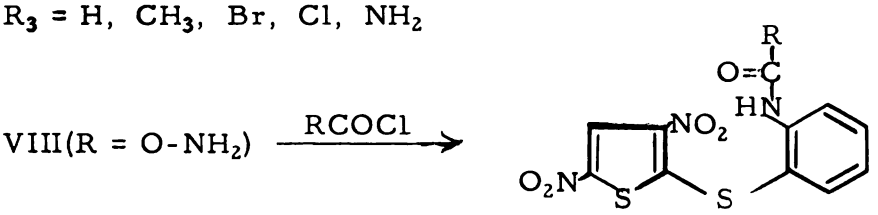


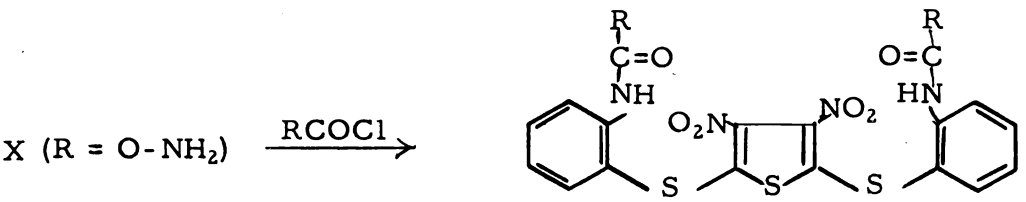
X

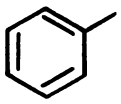
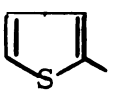
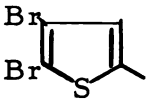
R_1 = H, CH_3

R_2 = NH_2, X, R, OR, SR, CO_2Et, Ar, OH, COOH

R_3 = H, CH_3, Br, Cl, NH_2





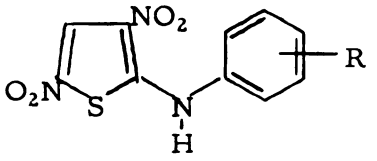
R =  ,  ,  , CH_3, $CH_3(CH_2)_{1-6}$-, $Cl(CH_2)_2$ -

$(CH_3)_2CHCH_2$-

The bromination of thiophene readily gave a mixture of 2-bromo and 2, 5-dibromothiophenes. The mixed halothiophenes were easily separated by fractional distillation under vacuum. Nitration of 2-bromothiophene with nitric acid in acetic anhydride as a reaction medium gave 2-bromo-5-nitrothiophene (12, 13). Further nitration of the latter with mixed acids produced 3, 5-dinitro-2-bromothiophene. Since this compound has not been reported, it was also characterized.

Treatment of the dinitrobromothiophene with potassium thioaryloxide gave the aryl-3, 5-dinitro-2-thienyl sulfides, while its reaction with arylamines gave 3, 5-dinitro-N-aryl-2-thienylamines in excellent yields.

During the course of this investigation it was observed that compounds of the general structure,



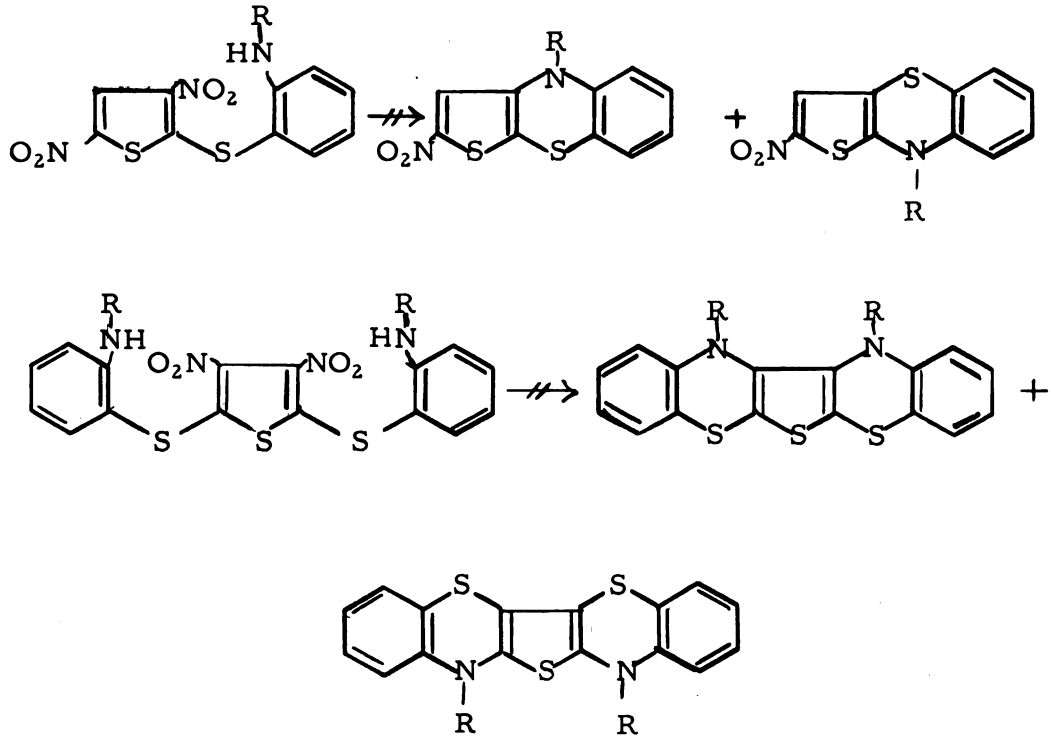
develop a characteristic purple coloration in aqueous organic solvents, the intensity of the coloration being greatest in aqueous acetone. Sharp color changes with pH were also observed.

Treatment of 2-bromo-3, 5-dinitrothiophene with o-aminothiophenol in the absence of acid or base gave 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide through a Smiles rearrangement of the intermediate 3, 5-dinitro-N(2-mercaptophenyl)-2-thienylamine.

The 3, 4-dinitro-2, 5-bis-thiophenoxythiophenes were obtained by the reaction of 2, 5-dibromo-3, 4-dinitrothiophenes (14) with nuclear substituted benzenethiols in the presence of alcoholic potassium hydroxide. The 2'-amidophenylthienyl sulfides and 2, 5-bis-2'-amidothiophenoxy thiophenes were made by the acylation of their respective amines. Altogether, a total of fifty-five previously undescribed phenylthienylamines, sulfides and polynitro-2, 5-bis-thiophenoxy thiophenes were synthesized and characterized.

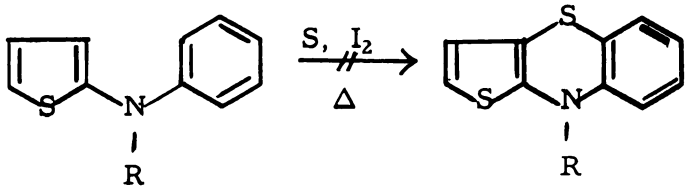
The research described here is concerned with the synthesis and chemistry of phenylthienyl sulfides, N-aryl-2-thienylamines and polynitro-2, 5-bis-thiophenoxythiophenes and does not include the physiological studies of these materials which will be reported elsewhere.

Because of the presence of suitably placed nitro and amino groups in these nitroaminodiaryl sulfides, it was anticipated that, by suitable ring closure procedures (15), these compounds could be converted to the thiophene analogs of the phenothiazines. Unfortunately attempts to obtain the thiophene analogs of the phenothiazines from the sulfides described above in the presence or absence of acid or base were unsuccessful.



R = H, Acyl.

Also, attempts at the ring closure of 2-thienylphenylamine and N-phenyl-2-acetamidothiophene through thionation reaction in the presence (16) or absence (17) of a solvent were equally unsuccessful.



R = H, Acetyl

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By

Charles Okolo Okafor

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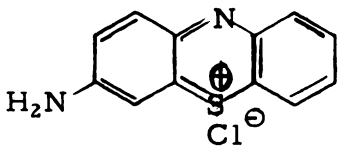
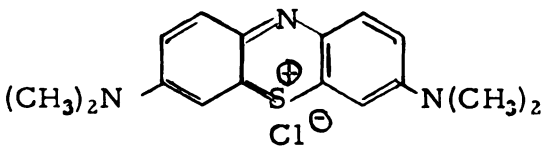
INTRODUCTION

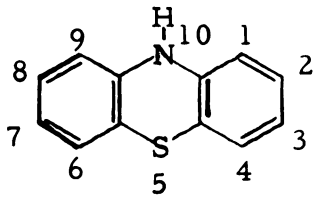
The initial synthesis of phenothiazine dates back to 1883 when Bernthsen (1) prepared it in the course of his structural studies on Lauth's violet and methylene blue.



Lauth's Violet



Methylene Blue



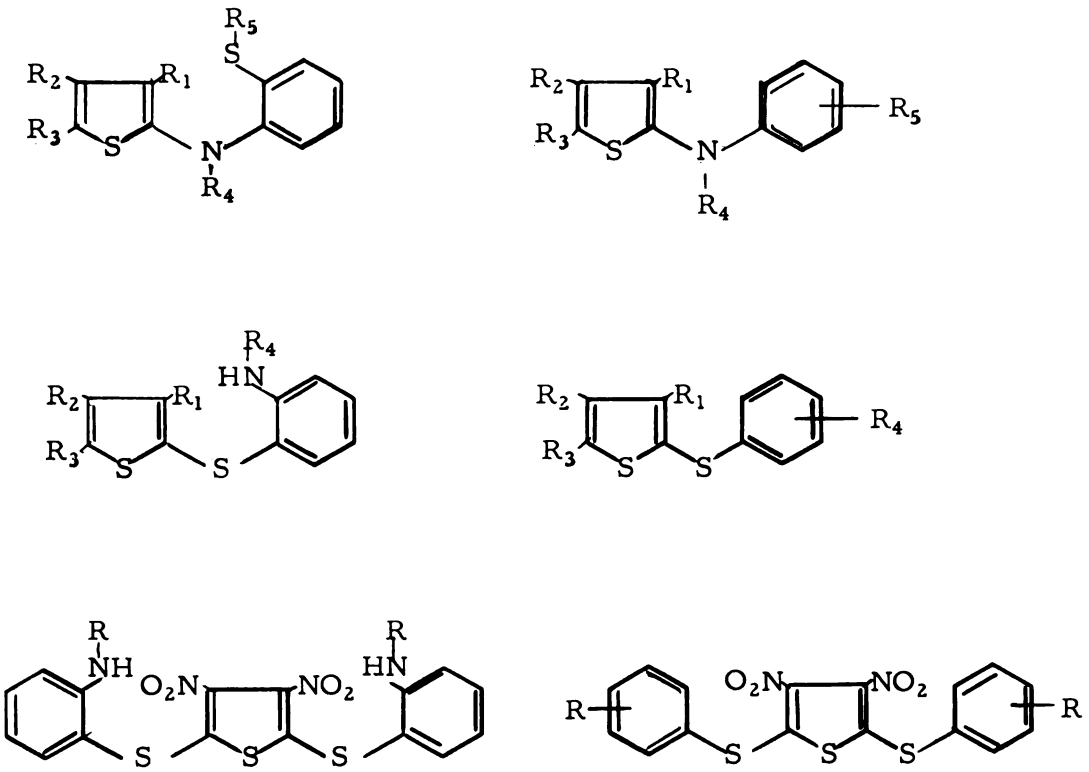
Phenothiazine

Since then phenothiazine and its derivatives have been used in the dye industry as the parent compound of the thiazine dyes and in the field of medicine as a tranquilizer. Campbell and his collaborators (2), discovered that the phenothiazines have insecticidal properties. Further research has demonstrated their usefulness as antiseptics, antituberculostatic compounds (3), anthelmintics (4), urinary antiseptics (5, 6), antihistamines (7, 8, 9), in the treatment of Parkinson's disease (10) and as antiemetics (11) to mention a few. Phenothiazines also supress nausea and vomiting caused by a wide variety of clinical conditions such as carcinomatosis, labyrinthitis, lymphomatosis, uremia and by antabuse administered to patients under the influence of alcohol. Such antabuses are caused by coedine, mepercrine, morphine, nitrogen mustards, auromycins, urethan therapy and protoveratrines.

While phenothiazine and its derivatives have many useful physiological properties, they have several undesirable side effects such as drowsiness, lassitude, light heartedness, aching limbs, dryness of the mouth, flushing of the face, etc. Therefore some modifications in the molecular structure of the phenothiazines are necessary if it is hoped to reduce or eliminate these undesirable side effects.

A comparison of the physiological effects of certain benzene and thiophene compounds has been reviewed by Blinke (12) and more recently by Campaigne (13). Some work has been reported substituting the thiophene for the benzene nucleus in local anaesthetics, mainly in analogs of effective phenyl compounds. Dann (14) prepared and tested the 2-thienyl analog of "Procaine" and reported an average duration of anaesthesia of 120 minutes for the 5-amino-2-thienyl ester as compared to 100 minutes for "Procaine" in the rabbit cornea test. Schuetz and Houff (15) synthesized a number of ω-(N, N-dialkylamino)alkyl-2-thenoate hydrochlorides. The pharmacological studies showed these compounds to be comparable to procaine in the interdermal wheal test in guinea pigs. The toxicities were low, especially in the morpholino compounds.

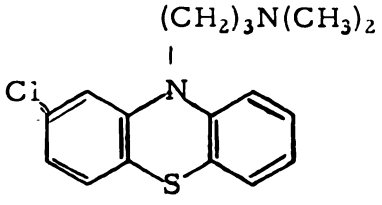
The present investigation was undertaken to prepare a series of new phenylthienyl sulfides, N-aryl-2-thienylamines and polynitro-2, 5-bis-monosubstituted thiophenoxy thiophenes and to examine their potential physiological activities as tranquilizers, antiseptics, etc. Since their diphenyl analogs are readily converted to phenothiazine derivatives, the preparation of thiophene analogs of phenothiazine through these amines and sulfides as intermediates was also investigated. The thienylphenyl sulfides, N-aryl-2-thienylamines and the polynitro-2, 5-bis-thiophenoxy thiophenes investigated in the present study, are indicated by the general structures,



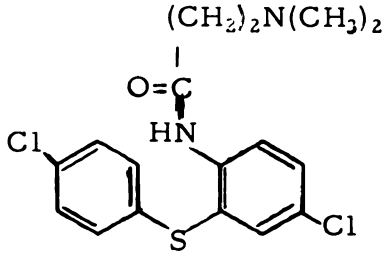
Molecular models of the o-aminophenyl-2-thienyl sulfide, N-o-thiomethoxyphenyl-2-thienylamine and 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophenes indicate these structures to be quite hindered; the o-substituent on the benzene is in close proximity to the 3-substituent on the thiophene ring. It was anticipated that these compounds would have enhanced physiological activities as tranquilizers compared to phenothiazine and its derivatives.

In view of the varied and useful physiological activities of 10-dialkylaminoalkylphenothiazine derivatives, analogs derived from systems in which the hetero-ring has been "opened" have been prepared in recent years. Among them were 2-dialkylaminoalkylamino and 2-dialkylaminoacyl-diphenylsulfides (16, 17). It has been reported (17)

that 2-(2-dimethylaminopropylamino)diphenyl sulfide prevents nicotine tremors to the same degree as 10-(2-diethylaminopropylamino)phenothiazine but lacks the antihistaminic properties of this drug. The dimethylaminopropionamido analog showed similar effects, while 2-(2-dimethylaminoethylamino)diphenyl sulfide was somewhat antihistaminic. Earlier, several diethylaminoalkylaminodiphenyl sulfides had been prepared (18) in a systematic variation of plasmodicidal structures and had been reported to possess anesthetic and amebacidal properties. In a series of "open" o-aminodiphenyl sulfide analogs of the antiemetic phenothiazines of the chlorpromazine type, 4', 5-dichloro-2-(3-dimethylaminopropionamido)diphenyl sulfide markedly prolonged the survival time of mice which had received a



Chlorpromazine



lethal dose of X-rays (19, 20, 21). The sulfides, 4, 4' and 4', 5-dichloro-2-(3-dimethylaminopropylamino)diphenyl sulfides (19) were active against a considerable number of pathogenic fungi in vitro. Thus, it is not unreasonable to anticipate that o-aminophenylthienyl sulfides, N-o-thiomethoxyphenylthienylamines and the 2, 5-bis-2'-aminothiophenoxy thiophenes could be potential tranquilizers, antiemetics (11), urinary antiseptics (5, 6), etc. However, only laboratory and clinical tests can establish the real value of their physiological usefulness.

Following a study of growth suppression in a variety of bacteria and moulds by known nitrothiophene derivatives and the relative effectiveness of these (22) compared to penicillin, sulfathiazole and

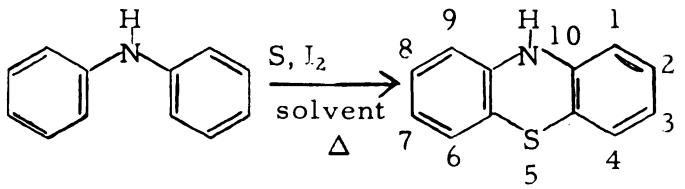
8-hydroxyquinoline, a number of new polynitrothienylphenyl sulfides and dinitro-N-aryl-2-thienylamines were synthesized. It was anticipated that these compounds could be effective against Staphylococcus aureus and albus, Streptococcus plantarum and hemolyticus, Bacillus subtilis, Escherichia coli and Pseudomonas ovalis compared to such materials as penicillin, bis-(4-nitrophenyl) sulfide, ethyl p-aminobenzoate, p-nitrobenzoic acid and bis(3, 5-dichloro-2-hydroxyphenyl) sulfides, (bithionols) (23, 24, 25). Again, only laboratory and clinical tests can establish the real value of the physiological usefulness of the new thiophene derivatives.

HISTORICAL

Thionation Reactions in Diphenylamines

One of the best methods for the preparation of diphenylamine is that described by Goldberg and Nimerovsky (26, 27). It involves a high temperature reaction between bromobenzene and acetanilide in the presence of cuprous iodide, potassium carbonate and nitrobenzene as a reaction solvent. The N, N-diphenylacetamide obtained was hydrolysed to yield the diphenylamine in an overall yield of 50-60%. Its ring closure to obtain phenothiazine was accomplished by reacting diphenylamine with sulfur at 250-260^{o} (1)--the well-known thionation reaction. The yield of product obtained in this reaction was greatly improved by the discovery (28, 29) that the addition of 1% of iodine as catalyst lowered both the reaction temperature and its duration. Conducting the reaction in an inert atmosphere (CO_2 or N_2) also improves the product yield by giving a purer product (30). Sulfuryl chloride (SO_2Cl_2) has also been used as a thionating agent (31) but product yield is reduced to only 15%.

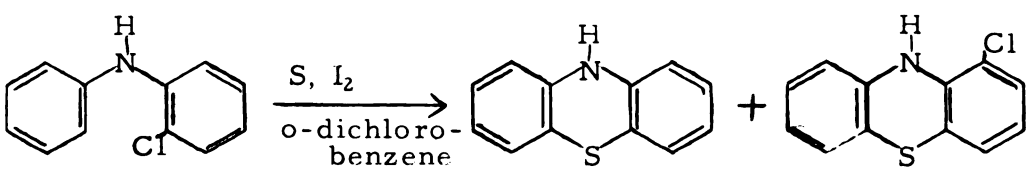
Initially these thionation reactions were carried out in the absence of a solvent and at fairly high temperatures. Under such reaction conditions, a tarry product always resulted and the product yields were never good. Studies were then directed towards the selection of solvents suitable for the thionation reaction. Massie (32) carried out the thionation reaction of diphenylamine in the presence of various solvents. His results showed that o-dichlorobenzene is an excellent solvent since the product yield obtained in this reaction medium is about 80%. Massie's results may be summarized as,



Solvent	B.P. °C	Time, Hrs.	Yield, %	M.P. °C
Benzene	80	7	30	155-165
o-Dichlorobenzene	180-3	2.5	84	181
Pyridine	115	5	0	---
N, N-DMF	153	3	0	---
Naphthalene	218	2.5	33	177
Xylene	144	4	Quant.	180

The results show that the best yields and purer products were obtained if the thionation reactions were run in o-dichlorobenzene or xylene.

However, the use of o-dichlorobenzene does not eliminate all problems in the thionation reaction. The synthesis of 1-chlorophenothiazine presented difficulties because of the simultaneous formation of phenothiazine.

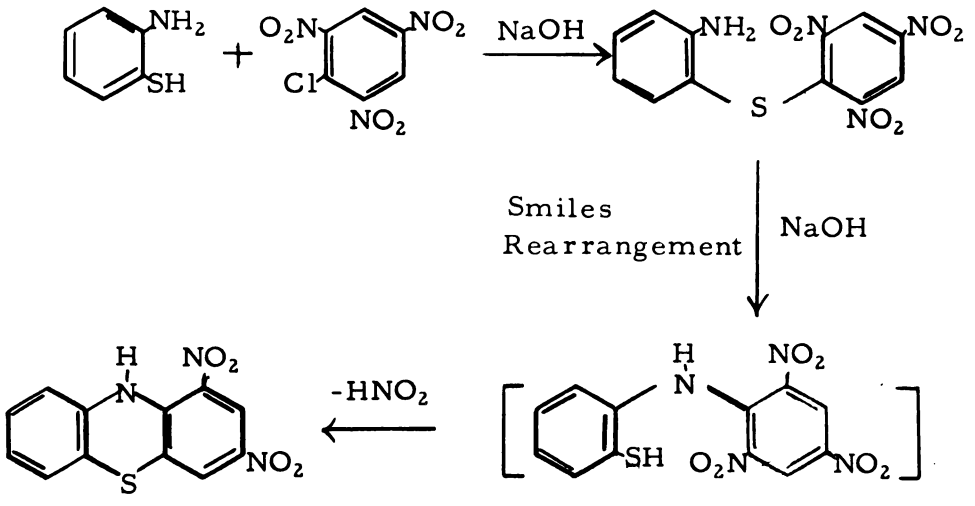


A similar observation was made by Roe and Little (33) in their preparation of 1-fluorophenothiazine from 2-fluorodiphenylamine. Also, 1-carboxyphenothiazine was obtained in low yield by the thionation of N-phenylanthranilic acid in o-dichlorobenzene. A large part of the

acid was decarboxylated so that a 75% yield of the phenothiazine was obtained. Previous attempts by Gilman and his collaborators (34) to obtain this compound by thionation gave neither 1-carboxyphenothiazine nor phenothiazine.

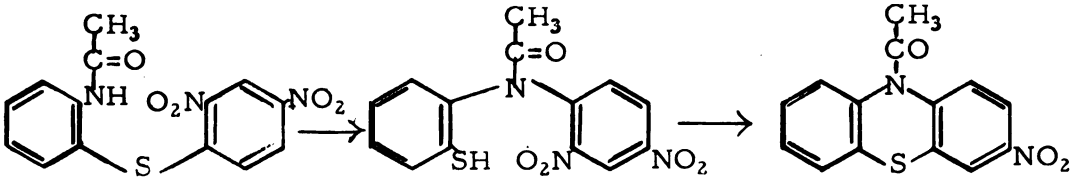
Smiles Rearrangement of Diphenyl Sulfides

The Smiles rearrangement has also been utilized for the synthesis of phenothiazine and its derivatives. This rearrangement is generally considered to be an intramolecular nucleophilic aromatic substitution reaction resulting in the migration of an aromatic ring from one heteroatom to another. Such rearrangements have been reported to take place in saturated systems (35). Thus, a mixture of o-aminothiophenol and picryl chloride followed by treatment with alkali gave 1, 3-dinitrophenothiazine (36).

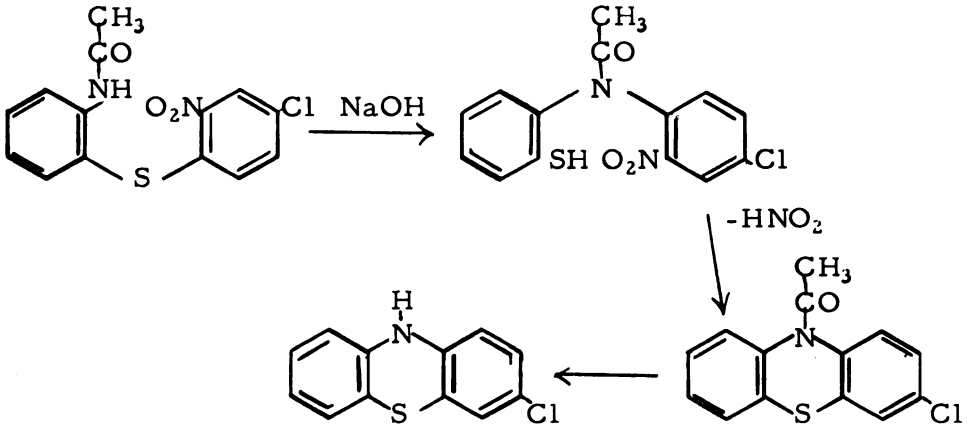


The Smiles rearrangement has been found useful in the preparation of some phenothiazine derivatives although it fails in others. The sulfide, 2'-acetamido-2, 4-dinitrodiphenyl sulfide readily underwent rearrangement in an acetone-alcohol solution containing sodium

hydroxide to give N-acetyl-2'-mercapto-2, 4-dinitrodiphenylamine which on boiling gave 10-acetyl-3-nitrophenothiazine.



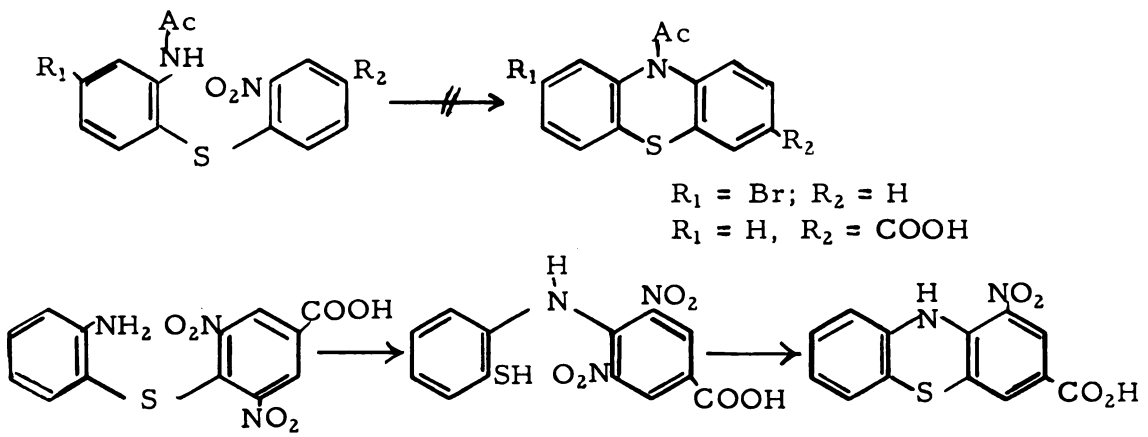
Likewise 2'-acetamido-4-chloro- 2-nitrodiphenyl sulfide underwent rearrangement to give, subsequent to hydrolysis, 3-chlorophenothiazine (37).



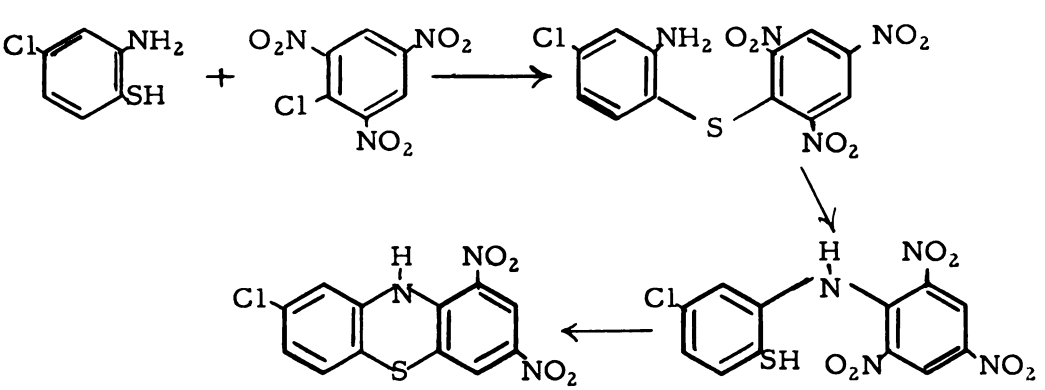
Florey and Restivo (38) were able to synthesize 2-trifluoromethylphenothiazine in 35% overall yield without the formation of isomers by the Smiles rearrangement. This compound had been prepared by Smith (39) by thionation of 3-(trifluoromethyl)diphenylamine which led to a mixture of 2-(trifluoromethyl)phenothiazine in 45% yield and its undesired isomer 4-trifluoromethylphenothiazine in 35% yield.

2-Bromo-7-nitrophenothiazine was prepared in 64% yield by the rearrangement and cyclization of 2-acetamido-4-bromo-2', 4'-dinitrodiphenylsulfide (40). The same investigators (40) found, however, that

neither 2-acetamido-4-bromo-2'-nitrodiphenyl sulfide nor 2'-acetamido-4-carboxy-2-nitrodiphenyl sulfide would undergo cyclization. This last failure is in contrast to the successful rearrangement and cyclization of 2'-amino-4-carboxy-2, 6-dinitrodiphenyl sulfide to form 3-carboxy-1-nitrophenothiazine (41).



It will also be noted that the last mentioned rearrangement involved not the acylated amine, as Evans and Smiles (42) stated was necessary, but the free amine. Other examples involving the use of the free amine include the preparation of 8-chloro-1, 3-dinitrophenothiazine from 2-amino-4-chlorothiophenol and picryl chloride (43).



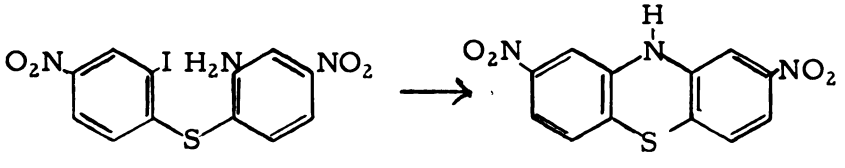
The reaction of o-aminothiophenol, 2,6-dinitrochlorobenzene and sodium acetate in refluxing alcohol for 24 hours gave a poor yield of 1-nitrophenothiazine (44).

These varied results demonstrate that the Smiles rearrangement is affected by many factors. For example, when the halogen (chlorine) was in the same ring as the nitro group in a halomononitroacetamido-diphenyl sulfide, rearrangement and cyclization took place. When the halogen (bromine) was situated in a different ring from the nitro group, however, no cyclization occurred (40). However, even though the halogen (bromine) was in a different ring, the presence of two nitro groups in the same ring caused rearrangement and ring closure (40) occurred. Finally, although a carboxy in the same ring as the nitro group failed to cause cyclization (40), the presence of two nitro groups in the carboxy derivative caused it to undergo cyclization (41). It thus appears that rearrangement and ring closure depend on many factors; further study of these factors should improve the utility of this rearrangement as a synthetic route to phenothiazine derivatives.

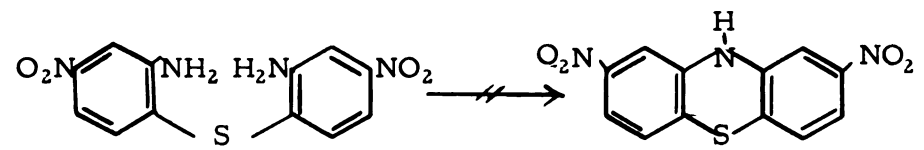
Diphenyl Sulfides

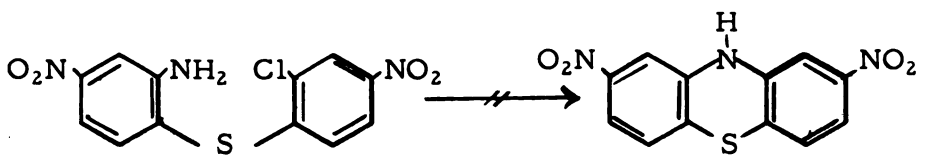
In contrast to the ready formation of phenothiazine derivatives by the ring closure of diphenylamine derivatives, only a few cases of ring closure involving diphenyl sulfide derivatives have been reported.

The first definite formation of a phenothiazine derivative by the ring closure of a diphenyl sulfide was reported by Michels and Amstutz (45) who prepared 2,8-dinitrophenothiazine in a 50% yield by heating at 220-230° for 30 hours, a mixture of 2-amino-2'-iodo-4,4'-dinitro-diphenyl sulfide, cuprous iodide and sodium carbonate.



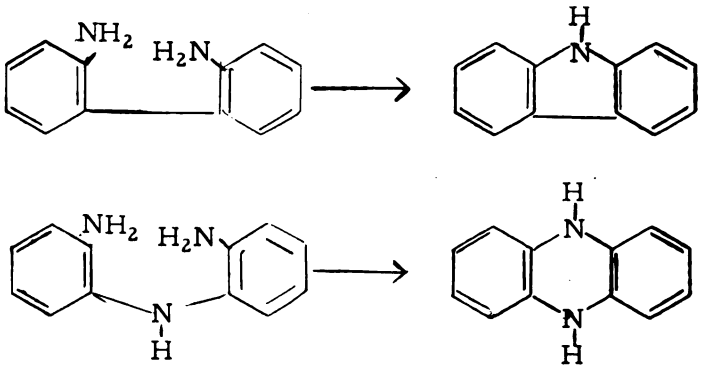
Hodgson, Dodgson and Smith (46) were unable to prepare a single phenothiazine derivative by the ring closure of diphenyl sulfides. The reduction of 2, 2', 4, 4'-tetranitrodiphenyl sulfide was attempted in anticipation that the tetraamine might undergo cyclization to form 2, 8-diaminophenothiazine during the reduction process, but only m-phenylene diamine was obtained. These investigators also were unable to cyclize either 2'-amino-2-chloro-4, 4'-dinitrodiphenyl sulfide or 2, 2'-diamino-4, 4'-dinitrodiphenyl sulfide by heating them in nitrobenzene with potassium carbonate and cuprous chloride at 180° for seven hours.





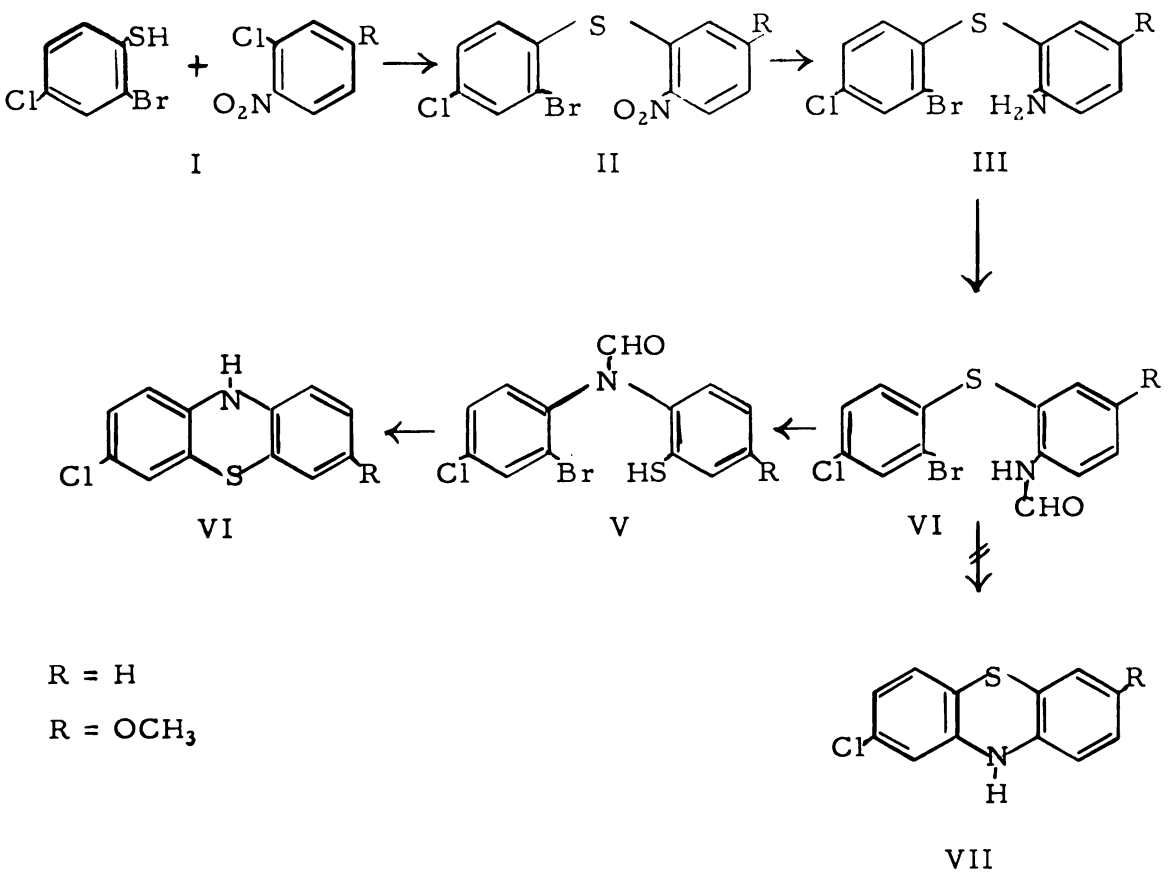
These are only a few of the unsuccessful attempts at the cyclization of diphenyl sulfides. A similar difficulty in attempts to cyclize diphenyl ether derivatives had been noted (47). The diaryl ether, 2, 2'-4, 4'-tetraaminodiphenyl ether could not be cyclized by heating its hydrochloride salt alone or with zinc chloride in an atmosphere of carbon dioxide for 20 hours at 200°. In the preparation of the tetraamine, by the reduction of the tetranitrocompound with stannous chloride, an appreciable amount of oxygen was liberated, corresponding to the analogous elimination of sulfur for the sulfur analog. The failure of these diphenyl ethers and diphenyl sulfides to undergo cyclization is

in sharp contrast to the ease with which diaminobiphenyl (48) and 2, 2'-diaminodiphenylamine (49) undergo cyclization to carbazole and phenazine, respectively.



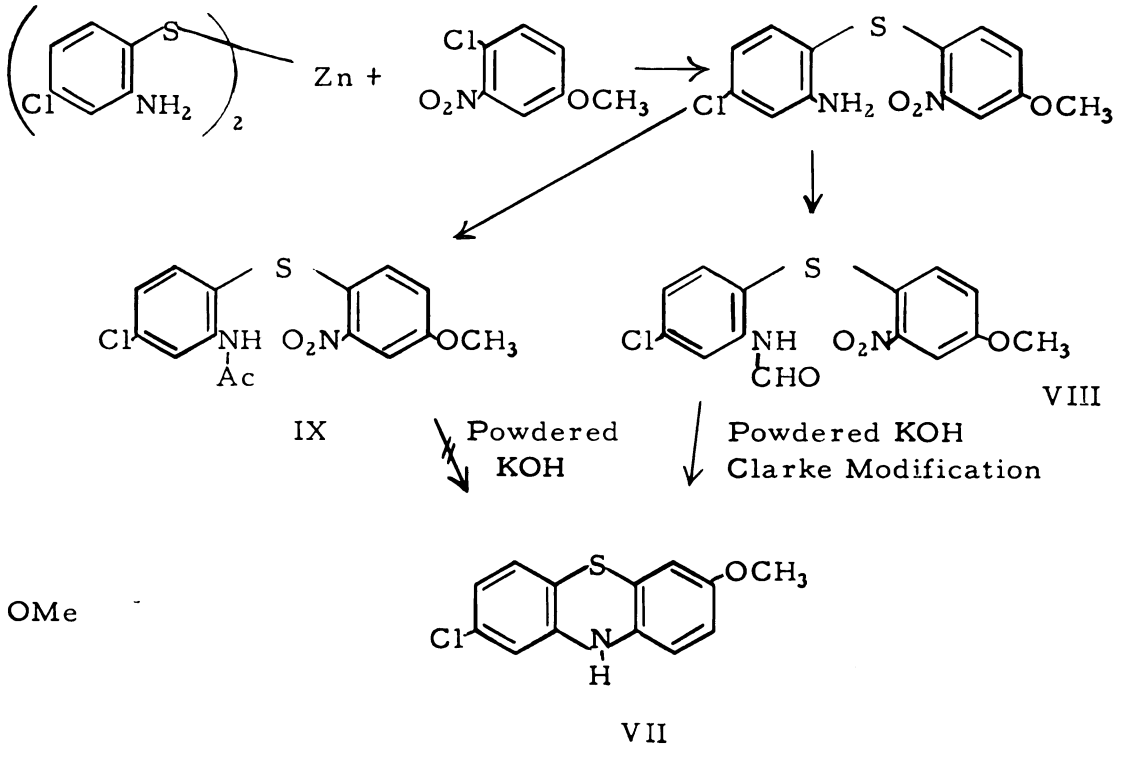
Hodgson (46) explained this difficulty on the basis of the non-coplanarity of the benzene rings in the sulfide and ether, and supported this view with an example of the difference in the affinity of cotton for dyes made from 4, 4'-diaminodiphenylamine and from 4, 4'-diaminodiphenyl sulfide (50). He also pointed out that in a diphenylamine the whole molecule can resonate and is therefore coplanar, whereas in an o, o'-diaminodiphenyl sulfide, resonance is prevented, so that a diphenylamine cyclization with sulfur will be facilitated, whereas elimination of ammonia from o, o'-diaminodiphenyl sulfide would be hindered.

Recently (51) phenothiazine has been synthesized by an induced Smiles rearrangement. Earlier Bonvicino (52) and his collaborators had reported a new Smiles-type rearrangement in which a bromo substituent replaced the nitro substituent as the activating group. They (52) encountered this rearrangement in the synthesis of phenoxazines by the dehydrohalogenation of o-bromo-o'-alkylaminodiphenyl ethers in benzene in the presence of sodamide. Nodiff and Hausman (51) have shown that this halogen-induced Smiles rearrangement can indeed take place in a dimethylformamide-potassium carbonate reaction medium.



Cyclization of IV via a Smiles rearrangement was effected by heating it under reflux in N, N-dimethylformamide in the presence of anhydrous potassium carbonate and copper-bronze as a catalyst. Instead of the anticipated 2-chlorophenothiazine (VII, R = H, m.p. 198.5-199.5°) and 2-chloro-7-methoxyphenothiazine (VII, R = OMe, m.p. 174.5-175°), 3-chlorophenothiazine (VI, R = H, m.p. 201-201.5°) and 3-chloro-7-methoxyphenothiazine (VI, R = OMe, m.p. 202-203°) were obtained.

To permit melting point and infra red comparison, an authentic sample of 2-chloro-7-methoxyphenothiazine (VII, R = OMe) was prepared.



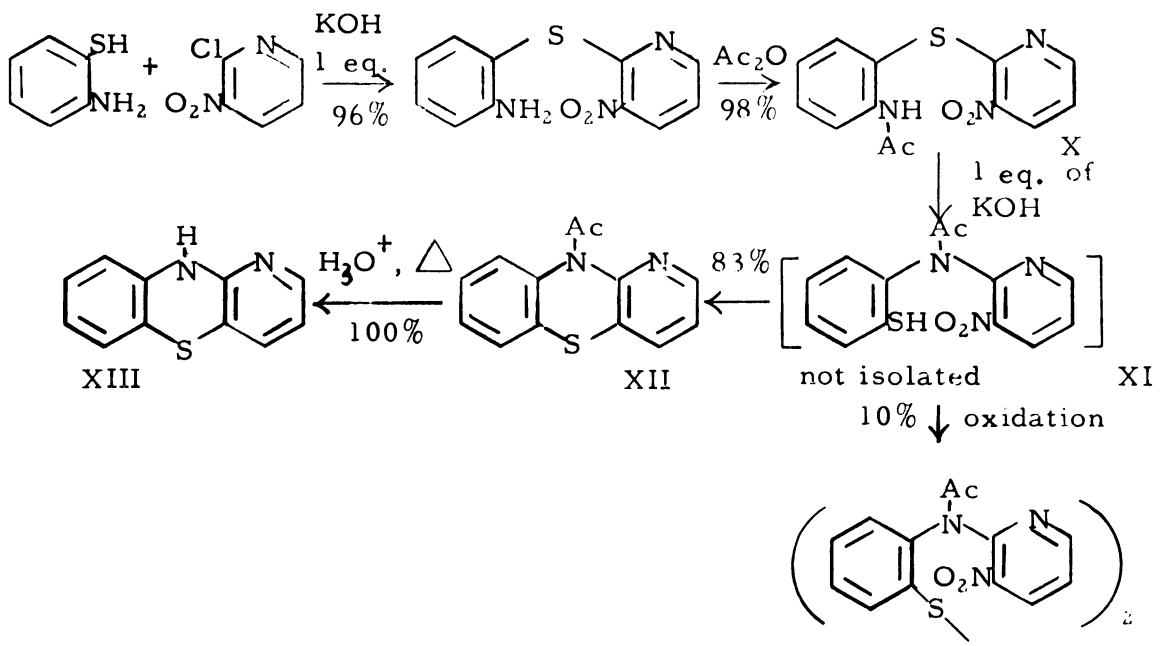
Application of Clarke modification (53) which employs the use of powdered KOH to the formamido compound VIII gave VII (R = OCH_3) in a 44% yield but failed when applied to the acetamido derivative, IX. Also, attempts to use standard conditions (54), for the conversion of VIII and IX to VII were unsuccessful. The starting materials, deacylated diphenyl sulfides and intractable oils were obtained.

Heterocyclic Sulfides, Amines and Their Ring Closures

A survey of the preparation of diphenylamines, diphenyl sulfides and their ring closures by thionation and the Smiles rearrangements as synthetic procedures for the preparation of phenothiazine has been made for benzenoid compounds. This survey can readily be extended to cover the heterocyclic compounds studied to date. Only a little work has in fact been done in this direction and only on the pyridine and pyrimidine systems.

1-Azaphenothiazine

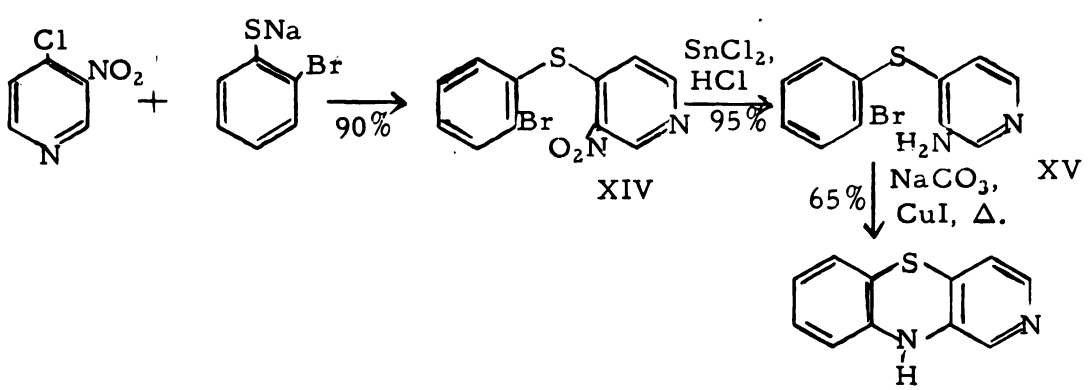
1-Azaphenothiazine has been prepared by Yale and Sowinski (55) via the Smiles rearrangement of 2'-(3-nitro-2-pyridylthio)-acetanilide. The authors preferred the rearrangement procedure involving the use of one equivalent of alkali in a mixture of acetone and ethanol. This made possible the isolation of the intermediate 10-acetyl-1-azaphenothiazine, XII.



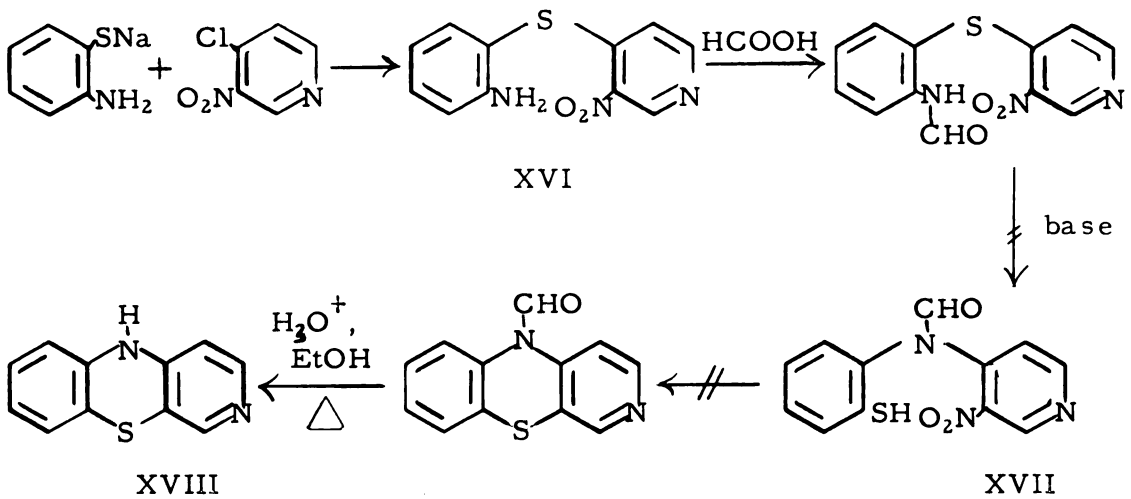
Subsequent to its isolation, XII was subjected to acid hydrolysis to yield 1-azaphenothiazine XIII in an 83% overall yield. When two equivalents of alkali were used in the rearrangement step, it leads directly to XIII (one equivalent of alkali for the Smiles rearrangement to XIII and a second equivalent for the hydrolysis of XII to XIII) and only a 25% yield of XIII was obtained.

2-Azaphenothiazine

Saggiomo and his collaborators (56) were able to synthesize 2-azaphenothiazine, not by thionation of phenylpyridylamine or a Smiles rearrangement of the diaryl sulfide, but by the reduction of a nitrophenylpyridyl sulfide followed in situ by dehydrohalogenation. The reaction of 4-chloro-3-nitropyridine (57, 58) and the sodium salt of o-bromothiophenol (59) gave 2'-bromophenyl-3-nitro-4-pyridyl sulfide, XIV, in a 90% yield. The nitrogroup in XIV was reduced by stannous chloride and concentrated hydrochloric acid in a 95% yield. The heterocyclic amine XV was dehydrobrominated in the presence of sodium carbonate, cuprous iodide at 180-190° in a nitrogen atmosphere for 2.5 hours to give 2-azaphenothiazine in a 65% yield.



Attempts to prepare 3-azaphenothiazine by the Smiles rearrangement were also made by the same investigators (56). In the presence of base the formamido derivative of XVI failed to yield the expected product, XVIII.

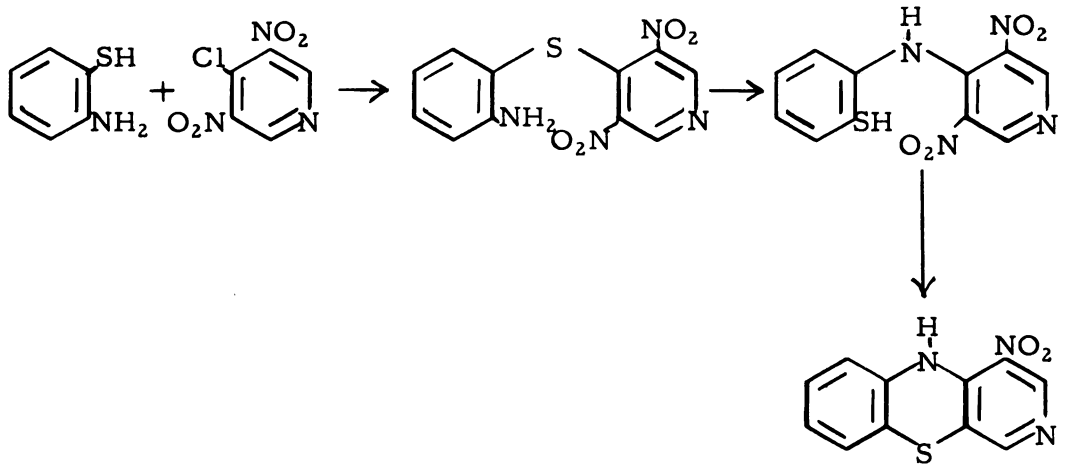


In addition, efforts to prepare XVIII from the hydrochloride salt of o-aminothiophenol and 4-chloro-3-nitropyridine in the presence of sodium acetate followed by treatment with base also failed. The product isolated was demonstrated by mixed melting point to be the sulfide XVI.

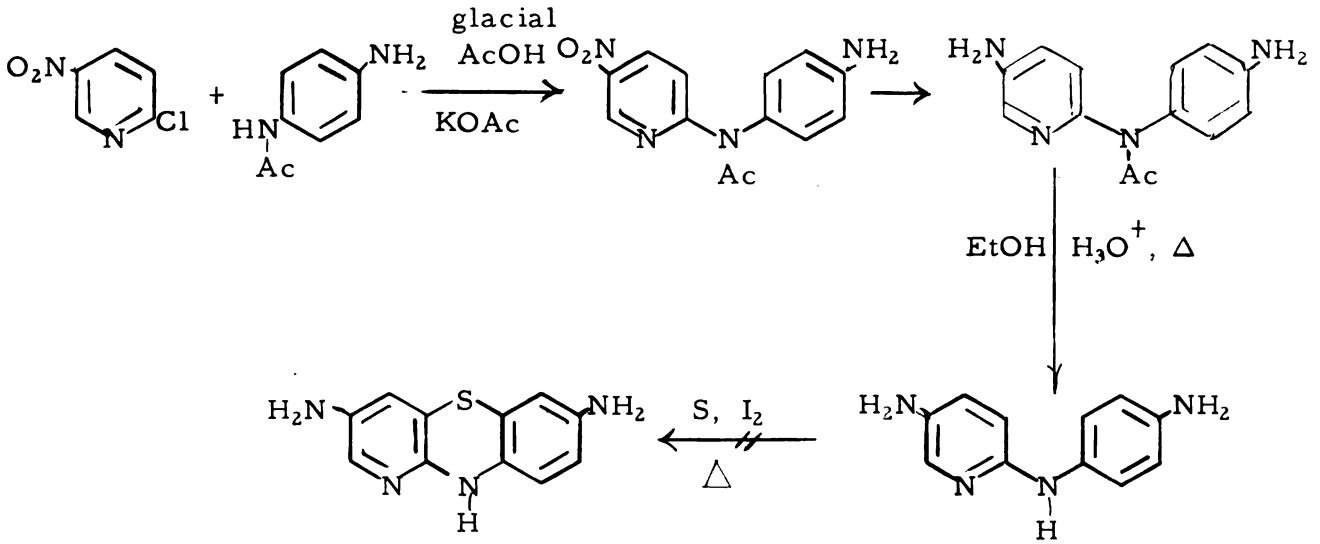
3-Azaphenothiazine

Following an earlier successful synthesis of azaphenoxazines by Petrow and Rewald (60), the same authors (60) extended their synthetic studies to azaphenothiazines. Condensation of 4-chloro-3, 5-dinitropyridine with o-aminothiophenol or its readily accessible zinc double salt (61) in the presence of a base led to the formation of 1-nitro-3-azaphenothiazine with the evolution of oxides of nitrogen (62). However, they were unable to isolate the intermediate dinitropyridyl-o-aminothiophenol, which appeared to undergo a spontaneous ring closure

on formation. A Smiles rearrangement probably occurred to give the product.



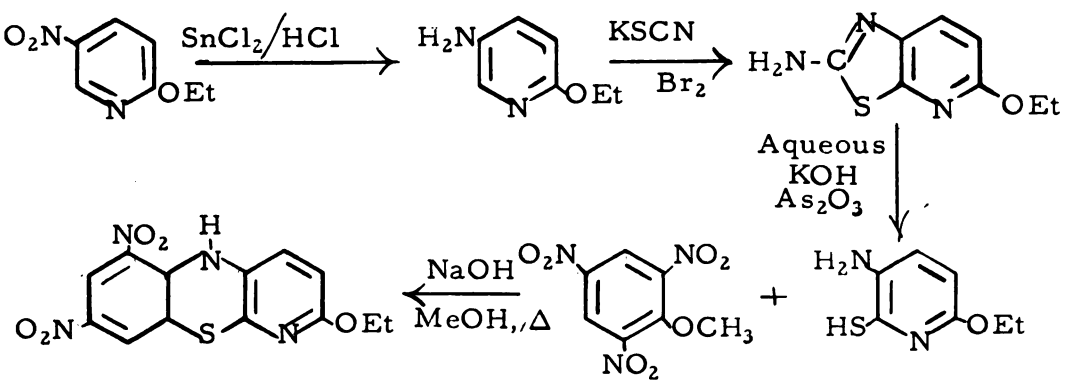
Petrow and Rewald also examined the possibility of extending Bernthsen's synthesis (1, 63) of phenothiazine (thionation reaction) from diphenylamine and sulfur fusion to the following suitably constituted pyridine analogs, 4-anilinopyridine (64), 4-anilinoquinaldine (65), 4-p-acetamidophenylamino-2-methylquinoline (66) and 5-amino-2-(4'-aminophenylamino)pyridine. The latter compound was prepared by the condensation of 5-nitro-2-chloropyridine with p-aminoacetanilide in glacial acetic acid solution in the presence of potassium acetate to give 5-nitro-2(4'-acetamidophenylamino)pyridine.



The authors were unable to convert any of these diphenylamine pyridine analogs into the azaphenothiazine by the known standard procedures. For example, attempted thionation of these aza analogs of diphenylamine in o-dichlorobenzene (32) as a cyclization solvent gave in all instances black, micro crystalline substances containing C, H, N and S resembling in general properties the so-called "sulfur dyes" to which they are probably analogous structurally.

4-Azaphenothiazine

4-Azaphenothiazine was prepared by Takahashi and Yoshii (67) in the following manner.

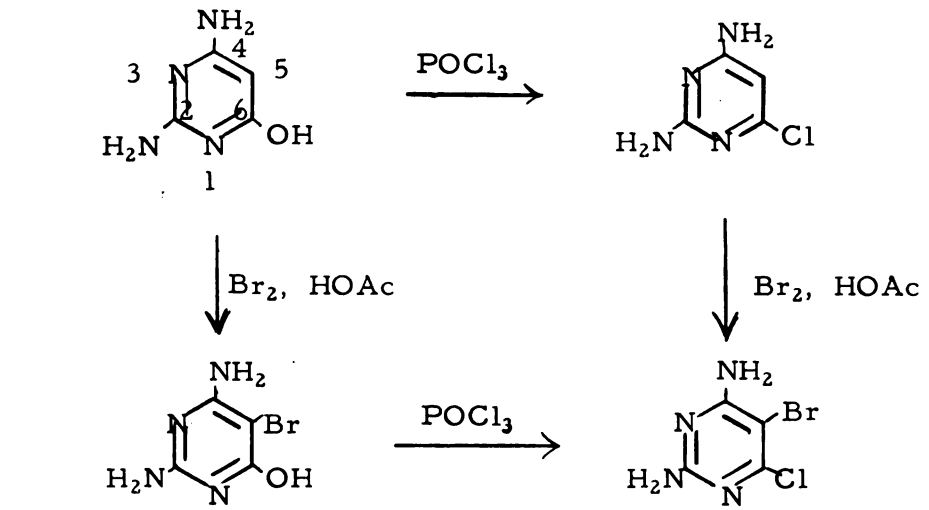


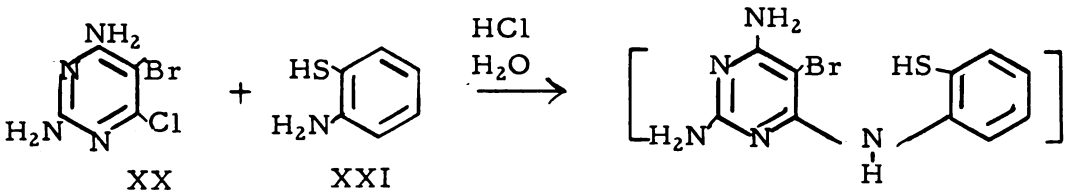
XIX

The 2-mercapto-3-amino-6-ethoxypyridine, XIX, served as a starting material to prepare 4-azaphenothiazine and its derivatives. 2-Mercapto-3-amino-6-ethoxy pyridine was also prepared in good yields by reducing 2-ethoxy-5-nitropyridine with stannous chloride to the corresponding amino derivative, and converting this by potassium thiocyanate (KSCN) and bromine to 2-aminopyrido[2, 3:5', 4']-thiazole, which on treatment with boiling aqueous alkali containing As_2O_3 gave 2-mercapto-3-amino-6-ethoxypyridine. A mixture of this compound and trinitroanisole refluxed in methanol and treated with sodium hydroxide gave 7, 9-dinitro-3-ethoxy-4-azaphenothiazine in the form of black needles.

1, 3-Diazaphenothiazines

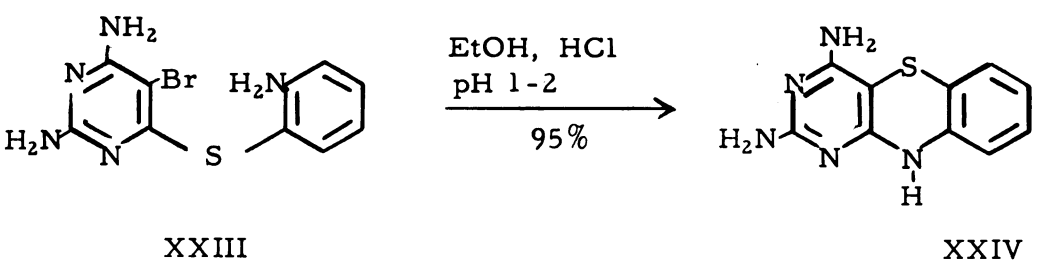
Excellent yields of 2, 4-diamino-1, 3-diazaphenothiazine (68) have been made by the reaction of o-mercaptoaniline and 2, 4-disubstituted-5-bromo-6-chloropyrimidines under either acidic or basic conditions. The chlorobromopyrimidine reacted with o-mercaptoaniline under two different sets of experimental conditions to give the desired 1, 3-diazaphenothiazine. The success of these syntheses depended on several features of reactivity peculiar to pyrimidine derivatives. The reactivity for nucleophilic displacement reactions of halogens in the 2, 4 or 6 positions of pyrimidines is well-known, while halogen in the 5-position is relatively inert. Although 5-halogenopyrimidines have usually been found to be inert in displacement reactions, when activated by the presence of one or more carbonyl compounds in the 2 and 4 positions as in 5-bromouracil (69) and 5-bromoisocytosine (70), displacement of the bromo substituent by an amino group has been accomplished. Furthermore, Banks (71) showed that the reaction of aromatic amines with such chloropyrimidines was greatly accelerated by the use of acid catalysts.



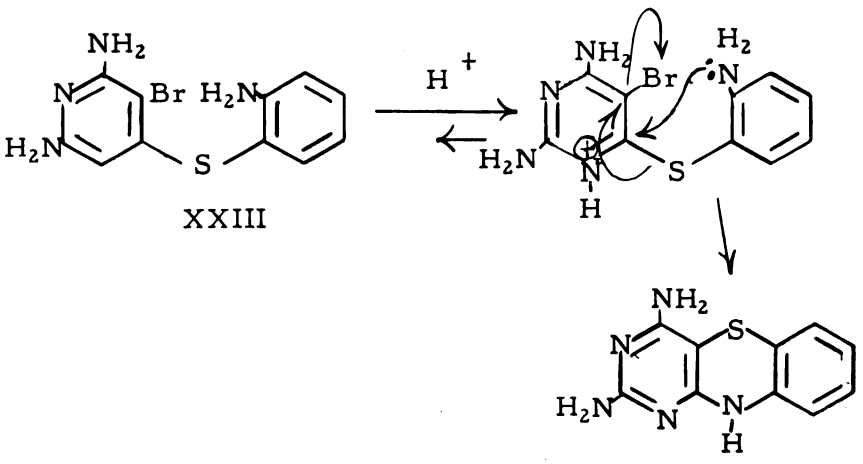


95% NEt3, EtOH

90% NH3, pH 8-10



A suggested mechanism for the acid catalyzed conversion of XXIII to XXIV involves the protonation of the pyrimidine ring at the 1-nitrogen. This activates the 6-position for an initial intramolecular attack of the sulfide bond by the anilino nitrogen. Subsequently, a nearly synchronous rupture of sulfide bond at the 6-position of the pyrimidine should place the newly formed and highly nucleophilic sulfide anion in a favorable steric position such that rotation around the newly formed C-N bond, would allow the mercaptide ion to attack the C-Br bond at the adjacent 5-position.



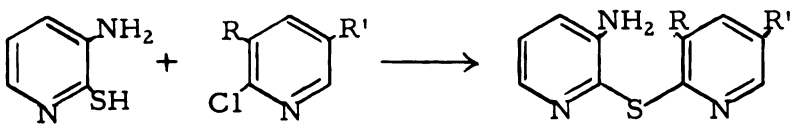
XXIII

XXIV

In the cyclic 5-membered transition state hypothesized, the two rings would appear in a spiro-type arrangement of 2-planes at right angles. While the Smiles rearrangement of benzenoid compounds is usually accomplished in basic media, it is quite reasonable that this sort of migration in the pyrimidine series should be facilitated by acid catalysis just as in the bimolecular displacement of the 6-chlorine by aniline.

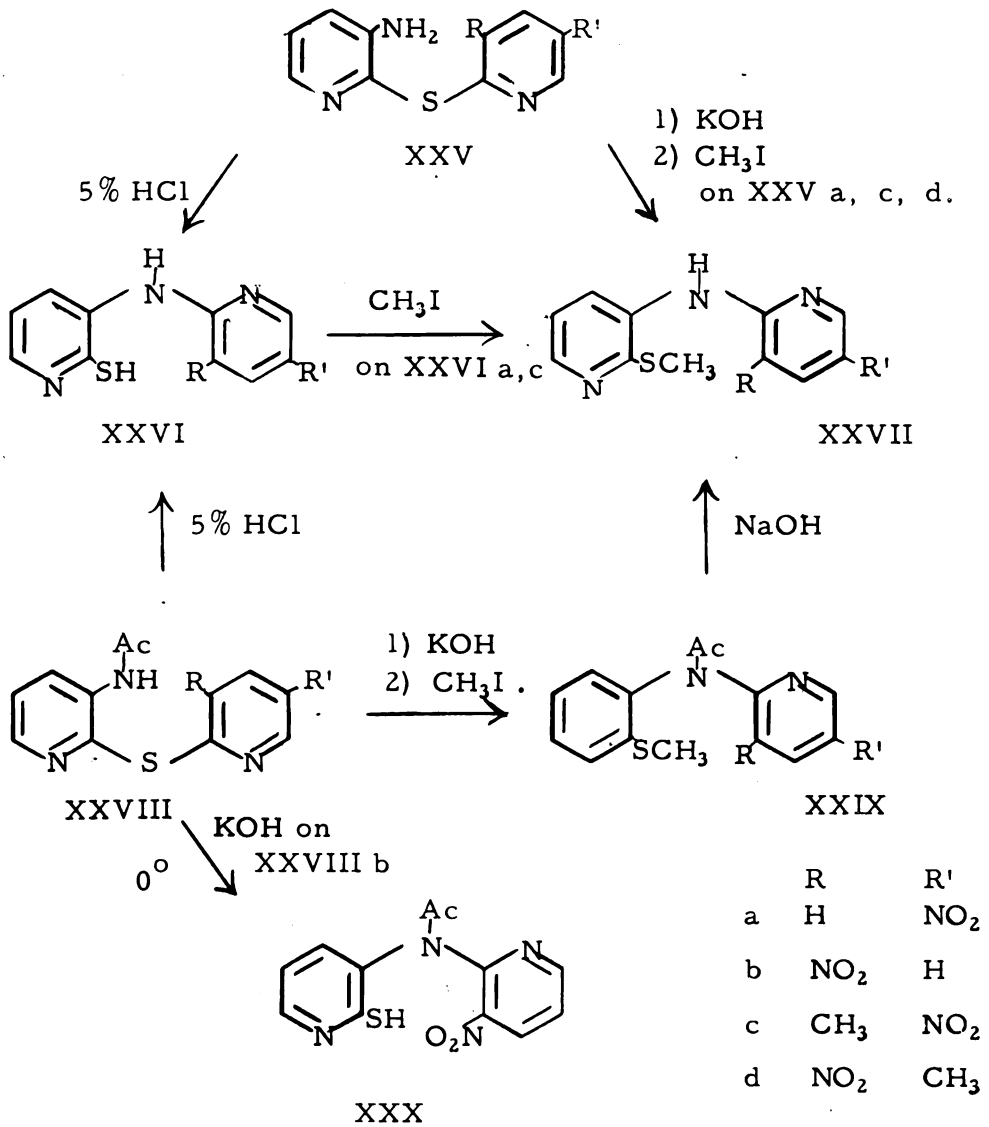
The Smiles Rearrangement of the Dipyridyl Sulfide System

The Smiles rearrangement of 3-amino-2, 2'-dipyridyl sulfides and their N-acetyl derivatives has been recently studied (72). It was shown that these rearrangements could be acid, base or heat catalyzed. The 3-amino-2, 2'-dipyridyl sulfide was obtained by the condensation of 2-mercapto-3-aminopyridine with the appropriate 2-chloropyridines in the presence of methanolic potassium hydroxide.



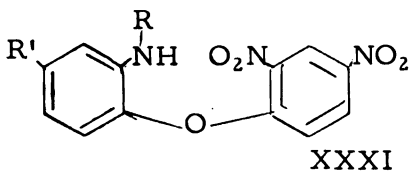
Under basic conditions. The aminodipyridyl sulfides as well as their N-acetyl derivatives readily rearranged in alcoholic potassium hydroxide, the products being isolated as their thiomethyl ether derivatives.

Under acid conditions. Since it is known that protonation of the ring nitrogen in pyridine derivatives increases the ease of nucleophilic substitution (73, 74, 75), the acid catalyzed Smiles rearrangement of 3-amino-2, 2'-dipyridyl sulfides was attempted. Rodig and his collaborators (72) found that dipyridyl sulfides rearranged smoothly in 5% HCl. The rearrangement occurred even more smoothly in concentrated hydrochloric acid.



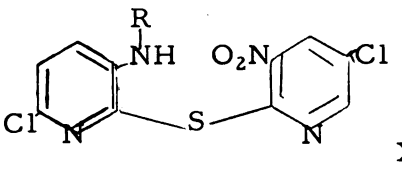
Under thermal conditions. There are a few cases reported in the literature where the Smiles rearrangement has been thermally initiated. Roberts and de Worms (76) found that heat would rearrange aminodiphenyl ethers of the type XXXI while Takahashi and Maki (77)

found that heating the dipyridyl sulfide XXXII in a sealed tube with methyl iodide also gave a rearranged product.



XXXI

R = H, Ac
R' = H, CH_3, Halogen.



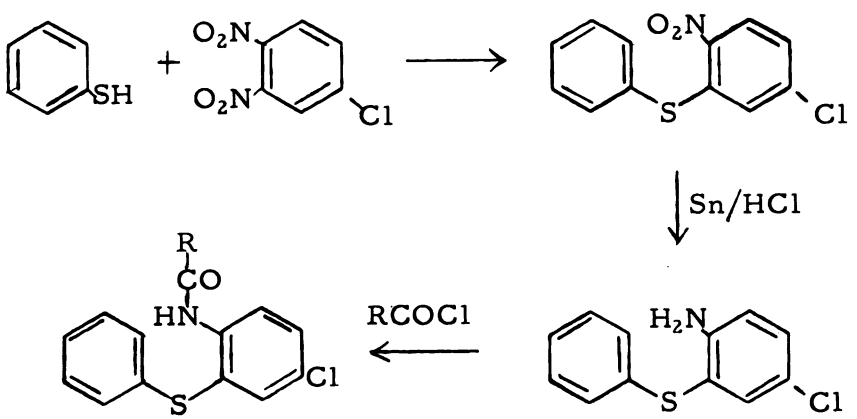
XXXII

R = H, Ac.

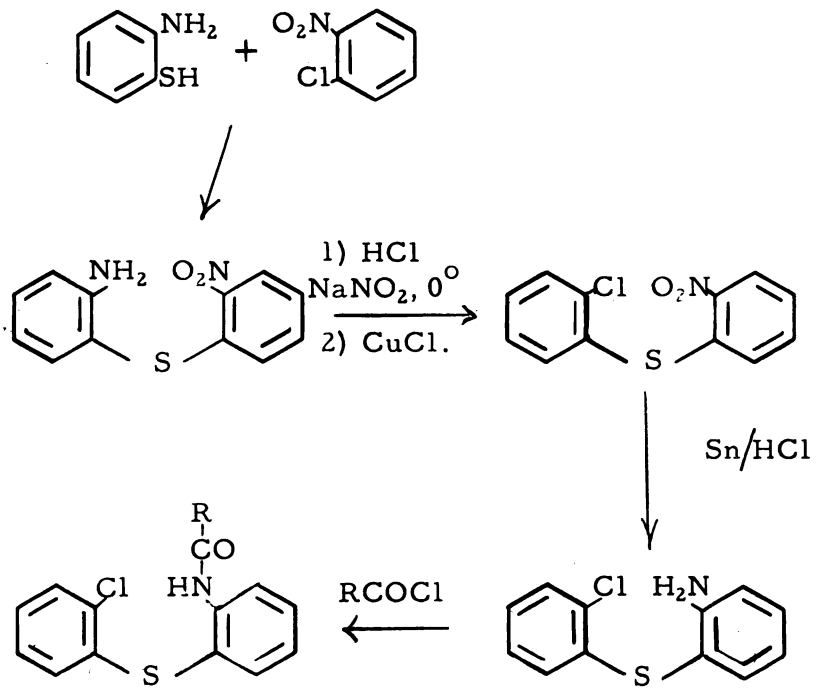
Rodig (72) also observed a heat-induced rearrangement during an attempted recrystallization of the N-acetyl-dipyridyl sulfide from ethanol to obtain the 3, 2'-dipyridylamine.

"Open" o-Aminodiphenyl Sulfides

These sulfides have been made (19) by the condensation of dinitrochlorobenzene with thiophenols followed by the reduction of the nitro-diaryl sulfides.



Where 2-aminothiophenol was used in the condensation, the resulting 2'-amino-2-nitrodiphenyl sulfide derivatives were subjected to Sandmeyer reaction to replace the amino group by chlorine.



RESULTS AND DISCUSSION

The reaction between thiophene halides and aromatic amines, followed by thionation reaction was investigated as a possible synthetic route to the thiophene analog of phenothiazine.

N-Phenyl-2-acetamidothiophene was synthesized by a modification of the procedures described by Goldberg (26, 27), Hickinbottom (78) and Hager (79). A mixture of acetanilide (0.2962 mole), 2-bromothiophene (0.515 mole), anhydrous potassium carbonate (0.2173 mole), in nitrobenzene (500 ml) as a reaction solvent and cuprous iodide (6.5 g.) as a catalyst was refluxed for forty hours at 200°. Copper-bronze could be used in place of cuprous iodide as the catalyst. The solvent, excess 2-bromothiophene and the other more volatile materials were removed by steam distillation. Extraction followed by crystallization from ethanol gave a 29% yield of N-phenyl-2-acetamidothiophene. The presence of a few crystals of iodine increased the yield to 44.3%. The structure of this tertiary amide was confirmed by its infrared and nuclear magnetic resonance spectra.

Cuprous Iodide

The cuprous iodide used as a catalyst for this reaction was prepared by the reduction of cupric sulfate with sodium thiosulfate in the presence of potassium iodide.

$$2\ CuSO_4 + 4KI + 2\ Na_2S_2O_3 \longrightarrow \underline{2\ Cu\ I} + 2\ K_2SO_4 + Na_2S_4O_6 + 2\ Na\ I$$

Actually $Cu\ I_2$ and I_2 are formed as intermediates, but they are consumed during the course of the reaction.

$$2\ CuSO_4 + 4\ KI \longrightarrow 2\ CuI_2 + 2\ K_2SO_4$$

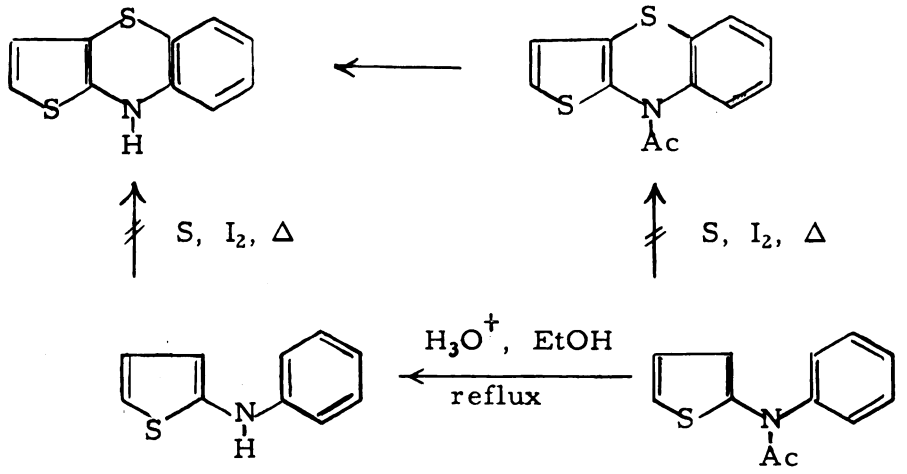
$$2\ CuI_2 \longrightarrow 2\ CuI + I_2$$

$$2\ Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2\ NaI$$

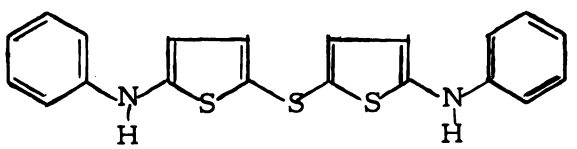
The only stable cuprous salts are those which are either insoluble in water or largely covalent. In agreement with Fajan's rules, the stability of $Cu^{(I)}$ halides increases from F $\longrightarrow$ I, the $I^{\ominus}$ ion being the largest and most polarizable of the halide ions. Thus, it is easy to understand why cuprous iodide was chosen for the catalysis of this arylation reaction requiring forty hours of refluxing. The cupric iodide initially formed by the combination of Cu^{II} ion and iodide ion in aqueous solution decomposes almost immediately by a redox reaction to yield Copper (I) iodide and free iodine; a reaction which is the basis of the well-known iodometric determination of copper. It is extremely difficult, however, to remove the iodine completely from the product, and therefore sodium thiosulfate was used to react with the iodine. Since excess thiosulfate may result in the formation of copper-thiosulfate complexes, while excess iodide may dissolve the product to give copper-iodide complexes, a solution of KI and $Na_2S_2O_3$ mixed in stoichiometric amounts was used to titrate the copper (II) sulfate solution in this synthesis.

Miscellaneous methods such as heating copper with iodine, dissolution of copper in hot concentrated HI and treatment of CuCN with HI are of little preparative significance.

Ring closure by thionation of N-phenyl-2-thienylamine obtained by the hydrolysis of the N-acetyl derivative was unsuccessful either in the presence (32) or absence of a solvent (80).



It appeared that the thiophene ring is unstable under the vigorous reaction condition demanded by the thionation reaction. Further, since the 3-position of the thiophene ring is less reactive than the 2-position, it may be that a coupling reaction at the 2-position could have intervened to yield,

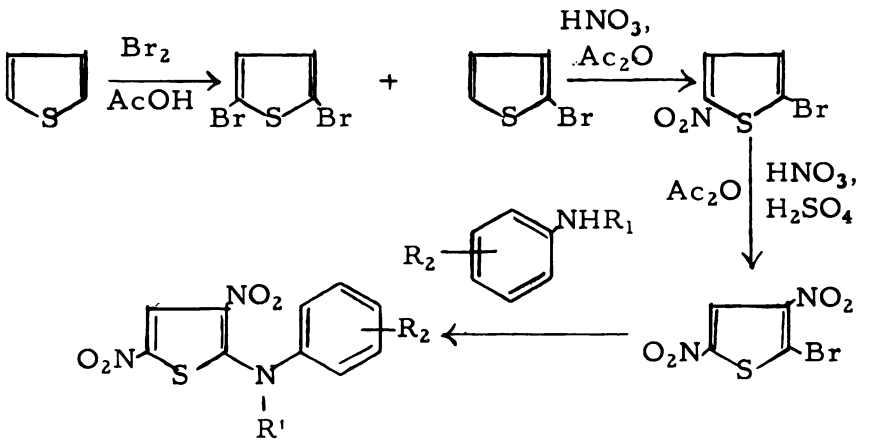


However, since no crystalline products were isolated, the possible formation of compounds of this type was rejected. Only a dark intractable material was obtained from the thionation reaction. It will be recalled from the historical section of this thesis that the same reaction was unsuccessful in the attempted thionation of pyridylphenylamine by Petrow and Rewald (62). It appears that heterocyclic rings are unstable under the reaction conditions of the thionation of diarylamines. It was assumed that the greater reactivity of a properly substituted thiophene ring would be an advantage in ring closure

reactions and attention was directed towards the preparation of dinitrophenyl-2-thienyl sulfides, dinitro-N-aryl-2-thienylamines and polynitro-2, 5-bis-thiophenoxythiophenes and their derivatives.

3, 5-Dinitro-N(Substituted phenyl)-2-thienylamines

The substituted N-phenyl-2-thienylamines studied in this investigation were prepared by the following sequence of reactions:



R_1 = H, CH_3

R_2 = H, o, m, p-Cl, o, p-Br, o, m, p-CH_3, o, m, p-OH, o, m, p-COOH, p-COOEt, o-NH_2, p-OCH_3, p-C_6H_5, o-SCH_3, etc.

This general reaction sequence had the advantage of excellent yields especially in the last step, with few side reactions and simple methods for purification of the products. Further, an important consideration was that the difficult to prepare substituted thiophenes are used in the final reaction step thus reducing the quantities of those intermediates needed compared to alternate procedures employing them in earlier steps in the reaction sequence. Direct bromination of thiophene with 1.5 times the stoichiometric amount of the halogen gave

a 73.4% combined yield of the 2, 5 dibromo and 2-bromothiophene. Separation of these gave 39% of the 2-bromothiophene and 34.4% of the 2, 5-dibromothiophene.

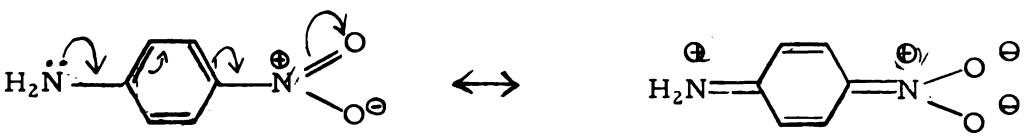
The 2-bromo-5-nitrothiophene was obtained by the nitration of 2-bromothiophene with concentrated nitric acid in acetic anhydride at -5°. The nitration reaction was highly exothermic and a freezing mixture of ice and acetone was used to hold the reaction temperature below -5° for the reaction period of fifteen hours. The 2-bromo-5-nitrothiophene was crystallized from the reaction mixture by storage overnight, in a refrigerator at -10°.

Further nitration of 2-bromo-5-nitrothiophene gave 2-bromo-3, 5-dinitrothiophene. The nitrating agent used was a mixture of concentrated nitric acid (specific gravity 1.42) and concentrated sulfuric acid (specific gravity 1.84). The reaction temperature had to be held below 0° to prevent the excessive formation of dark colored oily decomposition products caused by attack of nitric acid on the thiophene ring.

Since the production of nitronium ions by the addition of sulfuric acid to nitric acid is highly exothermic, special precautions were taken to avoid an explosion which could result from improper preparation of this nitrating mixture. Nitric acid was first cooled by immersion in an acetone-ice bath. Sulfuric acid was then added to the stirred nitric acid at a rate such that the temperature of the nitrating mixture remained below 0°. The 2-bromo-5-nitrothiophene was then added during an hour to the mixed acids at a rate which permitted holding the reaction temperature below 0°. The heavy yellow slurry which developed was stirred for an additional 90 minutes to complete the reaction. The nitration product was isolated by pouring the reaction mixture onto crushed ice recovering the yellowish brown colored solid by filtration. The crude product was thoroughly washed with ice-water

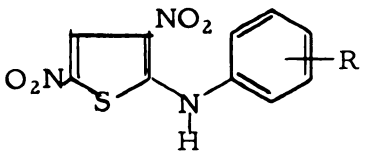
and immediately recrystallized from methanol; the yield was 69.1%. Since this bromodinitrothiophene has not been reported, it was also characterized. An alkaline solution of the bromodinitrothiophene has a blood red coloration. The presence of two nitro groups on the thiophene ring labilizes the bromine atom making it very reactive towards nucleophilic reagents. A comparison of the reactivities of a number of nitrochlorothiophenes with 2, 4-dinitrochlorobenzene was made by Hurd (81). He found that 5-nitro-2-chlorothiophene was nearly twice as reactive as 3-nitro-2-chlorothiophene and that the former is less reactive than 2, 4-dinitrochlorobenzene. The same author also reported that 3, 5-dinitro-2-chlorothiophene is at least four times as reactive as 2, 4-dinitrochlorobenzene.

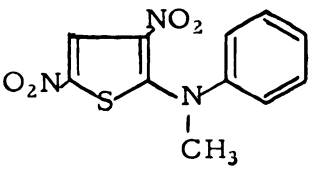
The enhanced reactivity of 3, 5-dinitro-2-bromothiophene was used to advantage in the synthesis of the substituted N-phenylthienylamines. Mild reaction conditions were necessary in the preparation of these compounds to reduce the formation of decomposition products. The yields varied from 70 to 98%. Steric factors seem to affect the yields considerably. Only 20% and 23% yields were obtained when R_2 = ortho chloro or bromo respectively. No reaction occurred between p-nitroaniline and 3, 5-dinitro-2-bromothiophene under the normal reaction conditions used in the preparation of these substituted phenyl-2-thienylamines. Rather, the starting materials were recovered in 90% yield. The failure of this reaction cannot be attributed to steric effects since the more sterically hindered o-bromo aniline, o-aminothioanisole, anthranilic acid., etc. react with 2-bromo-3, 5-dinitroaniline, at least, to some extent (Table II).

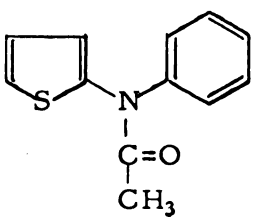


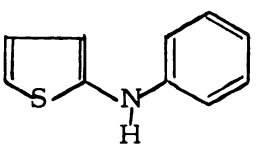
Probably, the nucleophilicity of p-nitroaniline was greatly reduced by the strongly electron withdrawing nitro group situated para to the amino group to the extent that a nucleophilic displacement of bromine in 2-bromo-3, 5-dinitrothiophene is no longer possible. Since a reaction between p-nitroaniline and 2-chloro-3, 5-dinitrothiophene did actually occur (81), a difference in reactivity between chloro and bromothiophenes is apparent.

During the course of these syntheses, it was observed that all the N-monosubstituted phenyl-3, 5-dinitro-2-thienylamines develop a purple-red coloration when they were dissolved in aqueous organic solvents such as dimethylsulfoxide, dimethylformamide, tetrahydro furan and acetone. The intensity of the coloration was greatest in aqueous acetone. N, N-Methylphenyl-3, 5-dinitro-2-thienylamine, N-Phenyl-2-acetamidothiophene and N-phenyl-2-thienylamine failed to show such coloration.







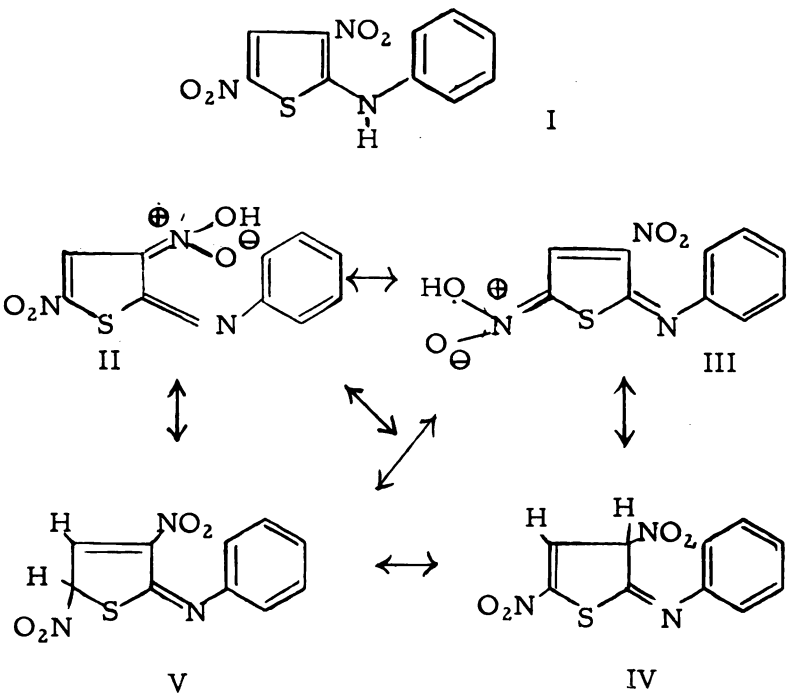


This suggests that probably the single proton on the secondary amine and the dinitro substituents on the thiophene ring have important roles

in the characteristic coloration observed. The formation of a purple red coloration in aqueous organic mixtures by the products of the reaction of nuclear substituted anilines with 3, 5-dinitro-2-bromothiophene was utilized as a spot test for the formation of such products. When 3, 5-dinitro-2-bromothiophene was treated with o-aminobenzenethiol in the absence of acid or base, a product was obtained which did not give a purple coloration in aqueous acetone. This suggested that the product was not N-(2-mercaptophenyl)-3, 5-dinitro-2-thienylamine. The structure of this product will be discussed at some length later.

A further cursory investigation into the nature of this purple coloration showed that the color was retained on high dilution with water. Addition of acid caused a sharp color change from violet to yellow at pH 7, while addition of base gave a color change from purple to colorless at pH 11. These color changes were reversible. The sharp color changes, noticed on changing the pH of these solutions, shows a possible utility of these compounds as indicators and in the dye industry. The origin of the coloration was not further investigated.

The physical and chemical properties determined agree with the structures assigned to the phenyl-2-thienylamines. As an example, the nuclear magnetic resonance spectrum of 3, 5-dinitro-N-phenyl-2-thienylamine shows a broad peak centered at -1.4 τ. This peak was assigned to the amino proton.



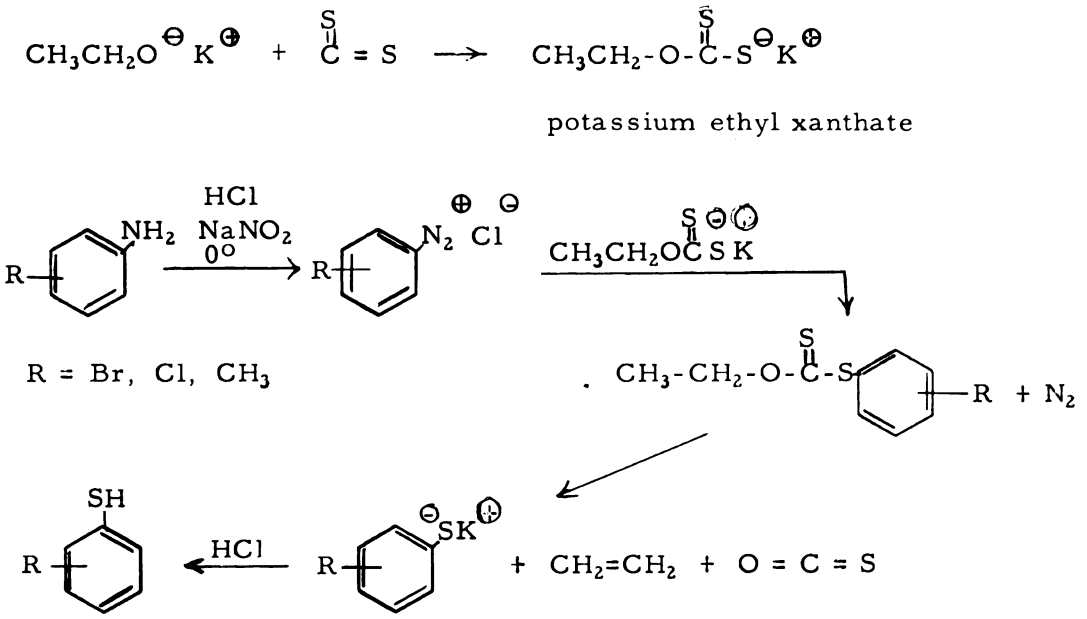
A broad peak at 1.72τ (S) was assigned to the lone proton on the thiophene ring. The four benzene protons showed up as a multiplet centered at 2.34τ. Tautomerism in these amines was also considered. It was thought that perhaps the assigned structure could enolize to the aci-nitro forms, II and III. Since the hydrogen should be acidic, it would be expected to be picked up downfield in the n.m.r. Further, the proton at the 4-position on the thiophene should be split because of possible resonance contributions by structures such as IV and V. In the absence of any additional peaks and in as much as the lone thiophene proton is unsplit, these resonance structures do not

contribute to the structure of I in any great extent. The insolubility of these compounds in sodium hydroxide solution supports this conclusion.

3, 5-Dinitro-phenyl-2- thienyl Sulfides

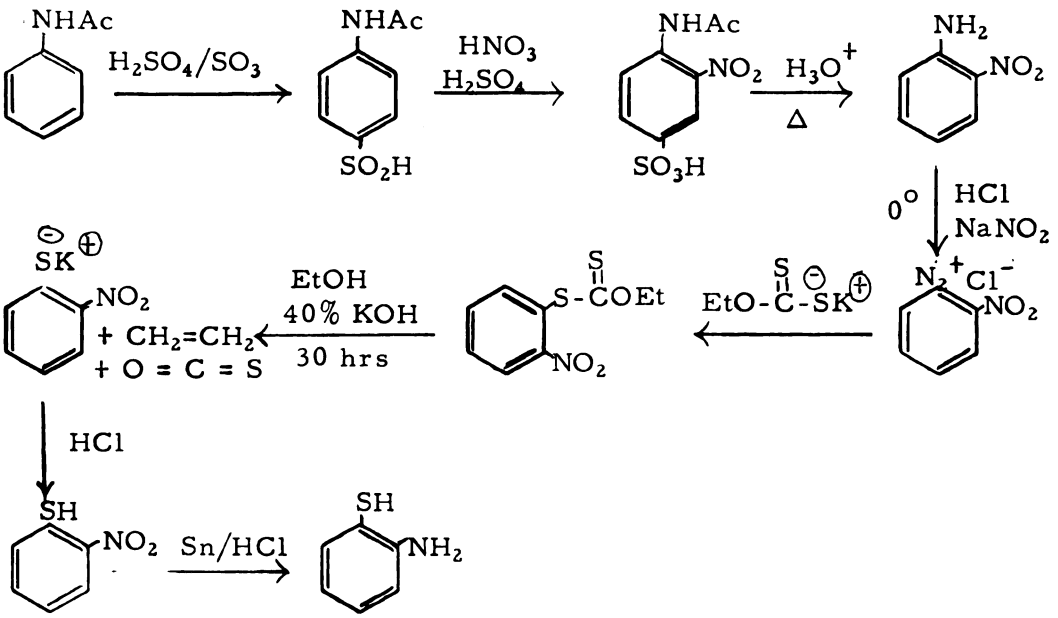
These sulfides were obtained by the low temperature reaction of equimolar quantities of 3, 5-dinitro-2-bromothiophene and a solution of the potassium thioaryloxide. The solution of potassium thioaryloxide was prepared by adding potassium methoxide (obtained by dissolving potassium hydroxide pellets in methanol) to the methanolic solution of the thiophenol. The mixture was stirred and the reaction temperature was maintained below 20°. The product, which separated from the reaction mixture was recrystallized from an acetone water mixture in yields varying from 65 to 97%. This class of compounds does not give a purple-red coloration in aqueous acetone. The structures of these compounds were confirmed by their n.m.r. spectra. In the case of 2'-bromophenyl-3, 5-dinitro-2-thienyl sulfide, a single peak at 1.60τ was assigned to the lone proton on the thiophene ring whilst a multiplet between 2.00 and 2.50τ was assigned to the four benzene protons. The area ratio of the peaks is 1:4 as expected based on the assigned structure.

The arylmercaptans used in the preparation of these phenylthienyl sulfides were obtained by first preparing their xanthates followed by the base catalyzed decomposition of these xanthates.



The yields vary from good to excellent. Even o-bromo thiophenol was prepared in an 81% yield.

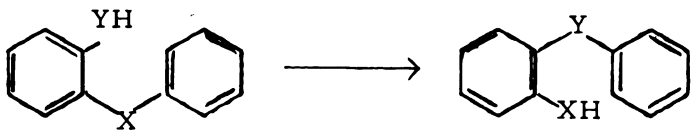
Several methods were considered for the preparation of o-amino-thiophenol. Direct nitration of aniline gives a complex mixture of mono, di and tri-nitro compounds as well as oxidation products, since the amino group activates the ortho and para positions of aniline to a very high degree. This renders the method of rather limited utility. Direct nitration of acetanilide gives a mixture of p-nitroacetanilide in 90% yield and o-nitroaniline in only 1-2%. Thus there is little doubt that the eight step synthesis shown is probably the best synthetic method for the preparation of this compound.



Although the number of the synthesis steps are too many, the overall yield is good.

Preparation of o-Aminophenyl-3, 5-dinitro-2- thienyl Sulfide through a Smiles Rearrangement of the Intermediate 3, 5-Dinitro-N(o-mercaptophenyl)-2- thienylamine

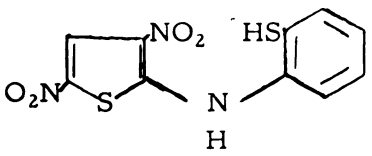
The Smiles rearrangement (35, 82) is generally considered to be an intramolecular nucleophilic aromatic substitution reaction resulting in the migration of an aromatic ring from one heteroatom to another. The change which occurs can be generally represented by,



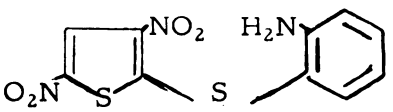
where -YH may be -OH, -SH, -NHR, -CONHR or $-SO_2NHR$ while X may be O, S, SO or SO_2. Such rearrangements have been reported to take place in saturated systems (35). The rearrangement is influenced by a number of factors; the activation present in the aromatic ring, the nucleophilicity of χ, the strength of $-Y^{\ominus}$ as a nucleophilic reagent, and the acidity of the -YH function since in many cases -YH must be converted to the anionic $-Y^{\ominus}$ form before reaction can occur.

The rearrangement of 3, 5-dinitro-N(2-mercaptophenyl)-2-thienylamine does not require the presence of a base since the mercapto group is sufficiently nucleophilic for the rearrangement to take place without its conversion to an anion by a base; though the reaction proceeds faster in the presence of a base.

A methanolic solution of 2-bromo-3, 5-dinitrothiophene was treated with an equimolar quantity of o-aminothiophenol. A blood red solution was obtained. This was stirred for thirty minutes, cooled and the red precipitate was collected by filtration. Upon recrystallization from acetone, a red crystalline product melting at 164° separated. The pure product was obtained in yields between 90 and 98%. This was insoluble in water, dilute acid or base, sparingly soluble in ether, slightly soluble in ethanol, methanol, benzene; soluble in acetone and very soluble in dimethylsulfoxide, dimethyl formamide and tetrahydrofuran. Molecular weight determination and elemental analyses favored both structures, VI and VII.



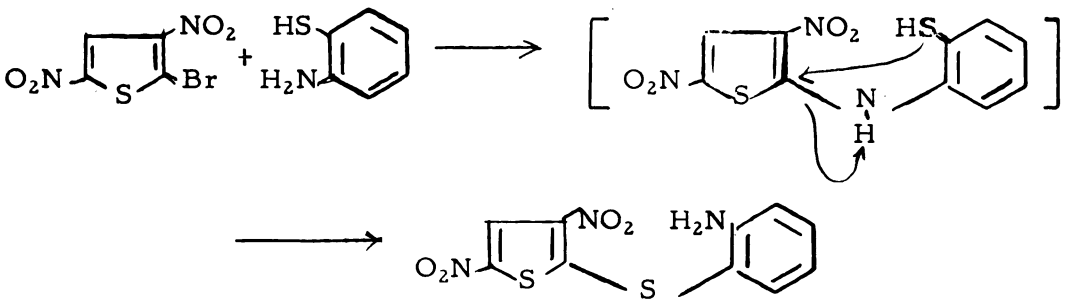
VI



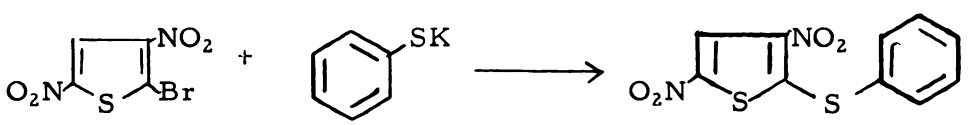
VII

The ultraviolet spectrum of the product shows two peaks at 358 mμ (log ϵ_{max} 4.21) and 252 mμ (log ϵ_{max} 4.31). The compound does not absorb in the visible region of the spectrum. Its infrared spectrum was also examined. A doublet in the region 3μ (actually 2.96 and 3.05 μ) may be assigned to the NH_2 group since aniline shows bands at 2.90 and 2.97 μ. Supporting evidence in favor of structure VII was obtained by the n.m.r. spectrum of the compound. A sharp peak at 1.60τ was assigned to the single proton on the thiophene ring; a multiplet peak between 2.6 and 3.5τ was assigned to the four benzene protons. The single peak with a broad base centered at 4.53τ was assigned to the NH_2 group. The latter peak shifted when the concentration was changed. There were no additional peaks. The ratio of the peak areas of the thiophene, benzene and amino protons was approximately 1:4:2. These evidences prove unequivocally that the product of the reaction between 2-bromo-3, 5-dinitrothiophene and o-aminothiophenol is 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide (VII).

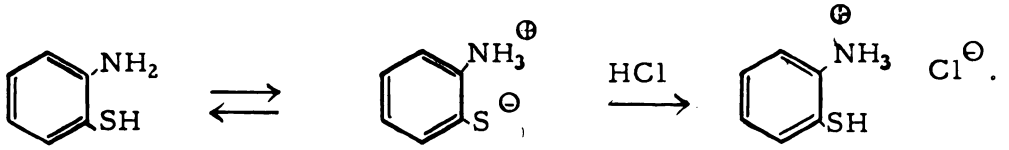
A two step mechanism can be suggested for its formation. The initial step is the formation of the intermediate 3, 5-dinitro-N(2-mercaptophenyl)-2-thienylamine followed by a Smiles rearrangement to the aminodiaryl sulfide.



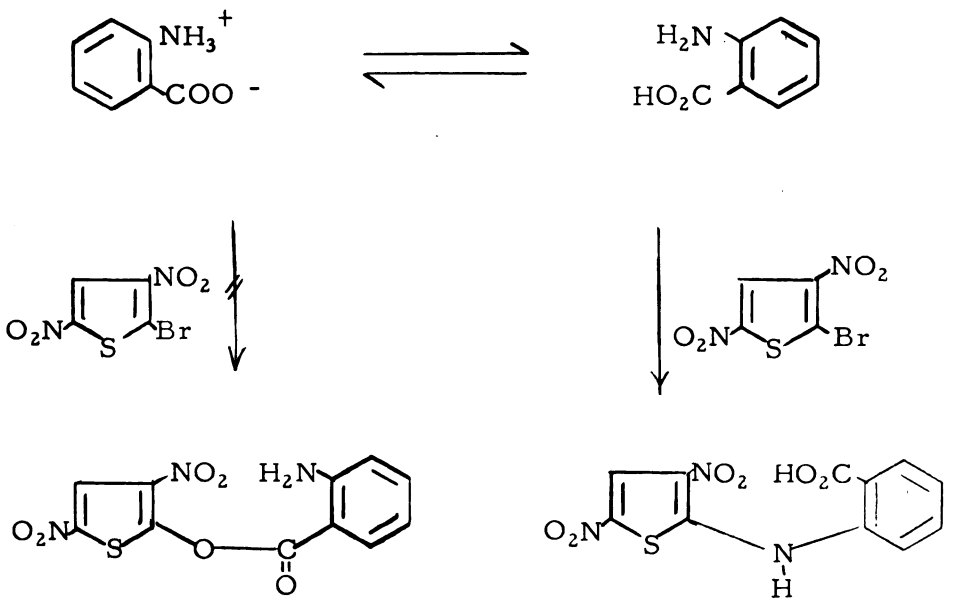
Several pieces of evidence support the intermediate formation of 3, 5-dinitro-N(2-mercaptophenyl)-2-thienylamine followed by an intramolecular nucleophilic substitution (Smiles rearrangement) to 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide. 2-Bromo-3, 5-dinitrothiophene reacts with aniline under the same reaction conditions to yield 3, 5-dinitro-N-phenyl-2-thienylamine in 98% yield. The same bromothiophene failed to react with thiophenol under the same reaction conditions. However, only a 6% yield of the phenyl-3, 5-dinitro-2-thienyl sulfide was obtained after 24 hours of reaction. Since a mercapto group is more nucleophilic than the amino group, the failure of thiophenol to react under the same conditions suggests that probably a mercapto diaryl amine intermediate is initially formed followed by a Smiles rearrangement to the aminodiaryl sulfide. The 3, 5-dinitro-2-bromothiophene, however, reacts with potassium thiophenoxide in yields greater than 87%.



Since o-aminothiophenol has both basic and acidic groups, it is possible for it to exist as a zwitterion.



On this basis, it was anticipated that use of the acid-catalyzed procedures of Banks (71) and Phillips (68) could favour the replacement of the 2-bromine of the thiophene by the anilino nitrogen and additionally it could possibly minimize attack by the sulfur. Thus, 2-bromo-3, 5-dinitrothiophene was treated with o-aminothiophenol in the presence of hydrochloric acid (dilute or concentrated). Again, 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide was obtained in nearly 98% yield. The failure to obtain 3, 5-dinitro-N(2-mercaptophenyl)-2-thienylamine is further evidence favouring a Smiles rearrangement in the second step of the synthesis. As expected, the same product was obtained in the presence of alcoholic potassium hydroxide. Additional support for the mechanism was based on the fact that a mercapto group is more nucleophilic and more acidic than a hydroxy group. Therefore, it is not surprising to find that o-aminophenol reacts with 2-bromo-3, 5-dinitrothiophene to yield 3, 5-dinitro-N(2-hydroxyphenyl)-2-thienylamine in a 68% yield. This material is soluble in 10% NaOH and gave the purple coloration characteristic of 3, 5-dinitro-N-phenyl-2-thienylamines. However, a mercapto group is more nucleophilic but less acidic than a carboxyl group. Thus, anthranilic acid was expected to be more dipolar in character than o-aminothiophenol and could thus be expected to react with the 2-bromine of the thiophene to form an ester. But, again 3, 5-dinitro-N(2-carboxyphenyl)-2-thienylamine was obtained.



The same amine was obtained with potassium o-aminobenzoate. There was no reaction between 2-bromo-3, 5-dinitrothiophene and benzoic acid or potassium benzoate.

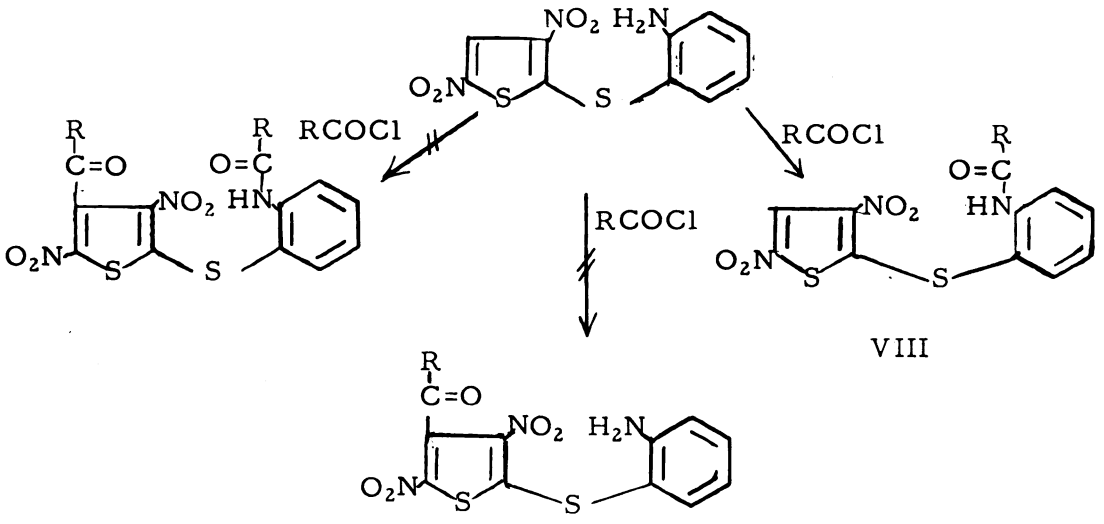
For these reasons, it is probable that o-aminothiophenol reacts first with 3, 5-dinitro-2-bromothiophene to yield the intermediate mercapto diarylamine which then undergoes a Smiles rearrangement to yield 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide.

2'-Amidophenyl-3, 5-dinitro-2-thienyl Sulfides

These compounds were prepared by refluxing a mixture of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfides and the acid chloride for periods varying from twenty minutes to several hours. With the highly reactive β-chloropropionyl chloride, the reaction was conducted at room temperature for two days, since heating the reaction mixture always led to the formation of decomposition products. 2-Thenoyl chloride as well as 4, 5-dibromo-2-thenoyl chloride required fairly low temperature reaction conditions in their reactions with 2-amino-phenyl-3, 5-dinitro-2-thienyl sulfide. The reaction time was twelve hours for 2-thenoyl chloride and four days in the case of

4, 5-dibromo-2-thenoyl chloride. The amides were prepared in the absence of a base because the amine sulfides are unstable in a basic solution. The yields varied from good to excellent.

The structural assignments were made by molecular weight determination, elemental analyses, chemical properties, infrared and nuclear magnetic resonance spectra. It was easy to recognize the lability of the single proton on the thiophene ring because of the two suitably placed nitro groups. Therefore, it was possible to acylate the 4-position on the thiophene ring in addition to the amino group on the benzene ring.



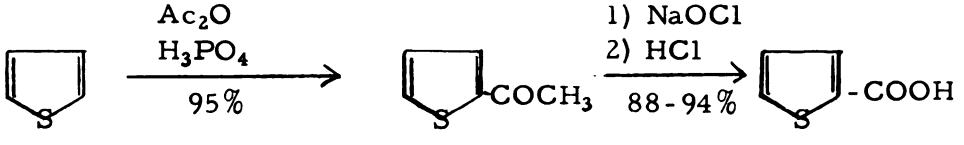
However, only a single product was isolated and in high yield. Both physical and chemical evidence agree with the assigned structure, VIII. This shows that the nucleophilicity of the amino group is much greater than that expected at C-4 of the thiophene ring because of the proximity and positions of the strongly electron withdrawing nitro groups. The infrared absorption of these compounds show the characteristic amide I and amide II bands in the region 6.00-6.08 μ and 6.30-6.35 μ respectively. Furthermore, these compounds show a single peak

between 3.00 and 3.12 μ characteristic of secondary amides. The n.m.r. of these amides confirm the assigned structures. In the case of 2'-acetamidophenyl-3, 5-dinitro-2-thienyl sulfide, the ratio of the amino, thiophene, benzene and methyl protons is approximately 1:1:4:3 which was expected from the assigned structure.

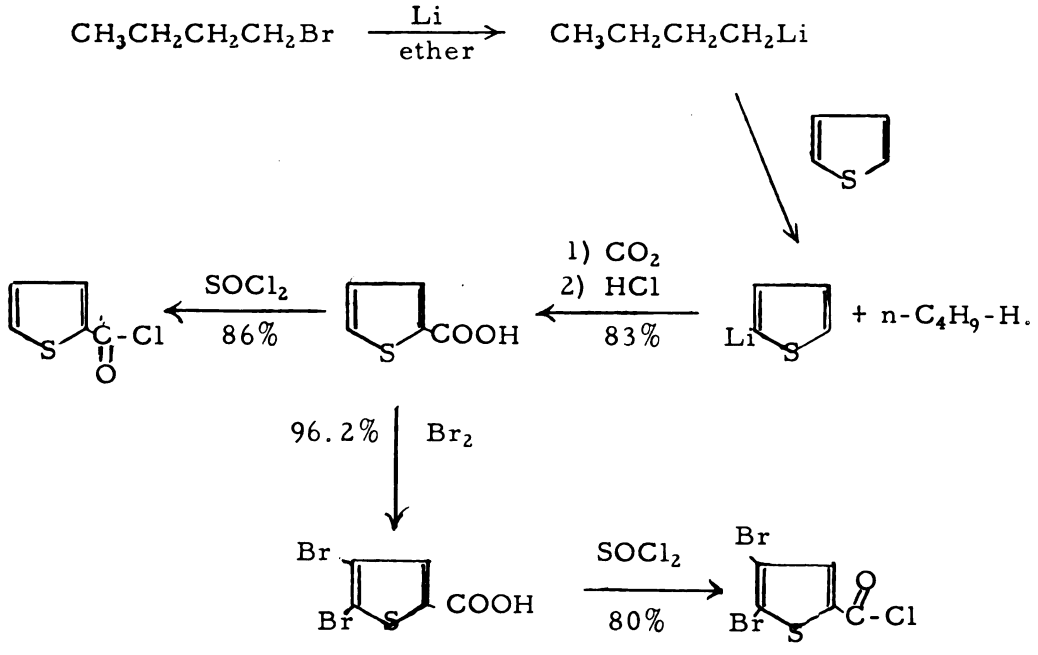
In the n.m.r. spectrum of 2'-β-chloropropionamidophenyl-3, 5-dinitro-2-thienyl sulfide, a singlet with a broad base at -0.28τ was assigned to the amino proton. Another single peak at 1.21τ was assigned to the single proton on the thiophene ring. A multiplet between 1.70 and 2.50τ was assigned to the four benzene protons. A triplet centered at 5.98τ was assigned to the methylene protons alpha to the carbonyl while the other triplet centered at 6.96τ was assigned to the other methylene beta to the carbonyl group. Again, the ratio of the area of these peaks agrees with the expected values.

The 2-thenoyl chloride used to prepare these amides was obtained by two methods. The first consisted in the acetylation of thiophene followed by oxidation to 2-thenoic acid with sodium hypochlorite prepared in situ. The 2-thenoic acid thus prepared was converted to the acid halide with thionyl chloride. The alternative method consists in the preparation of 2-thienyl lithium from thiophene and n-butyllithium . Carbonation of the heterocyclic organometallic followed by acidification with hydrochloric acid gave 2-thenoic acid in good yield. The latter method was preferred because it is less time consuming to conduct. Bromination of 2-thenoic acid with liquid bromine gave a 96.2% yield of 4, 5-dibromo-2-thenoic acid. The acid chloride was obtained by treating the acid with thionyl chloride

Method A



Method B



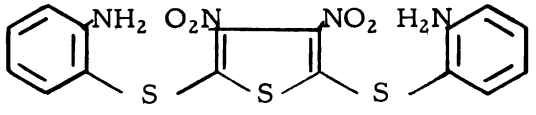
3, 4-Dinitro-2, 5-bis-thiophenoxythiophenes

The 2, 5-dibromo-3, 4-dinitrothiophene used in this preparation was prepared by the method described by Mozingo (83). A flask containing 1.45 moles of 2, 5-dibromothiophene was charged with a mixture of 400 ml. of concentrated sulfuric acid, 500 ml. of fuming sulfuric acid and 350 ml. of concentrated nitric acid. The temperature of the reaction mixture was held below 20° during the one hour reaction period. The product was recovered by filtration, taken up in ether, decolorized with Norite and recrystallized from methanol to obtain a 31.3% yield of pure 3, 4-dinitro-2, 5-dibromothiophene.

The dinitrodibromothiophene was used to prepare the dinitro-bis-thiophenoxy thiophenes. Potassium thioaryloxide was prepared from an equimolar quantity of the thiophenol and methanolic potassium hydroxide. A two to one molar ratio of potassium thioaryloxide and

3, 4-dinitro-2, 5-dibromothiophene, respectively, were stirred for several minutes immersed in an ice bath to keep the reaction temperature below 15°. The crude product was recrystallized from an acetone, methanol mixture in yields ranging from 87 to 97% for the unsubstituted, meta or para substituted thiophenols. Steric effects tend to reduce the yields in the case of ortho substituted thiophenols.

Structural assignments to the products were based on molecular weight determination, elemental analysis, chemical properties, ultra violet, infrared and nuclear magnetic resonance spectra. As an example, the structure of 3, 4'-dinitro-2, 5-bis-2'-aminothiophenoxy thiophene was confirmed from such data.

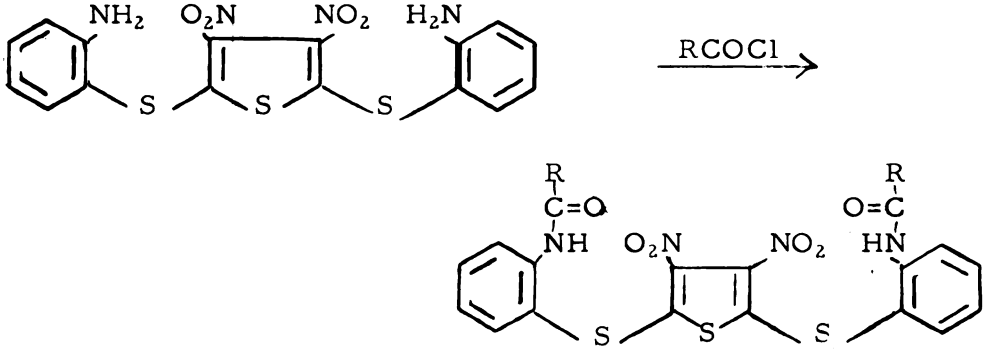


Elemental analysis and a molecular weight determination agreed with the molecular formula, $C_{16}H_{12}N_4S_3O_4$. Diazotization followed by treatment with an alkaline solution of β- naphthol gave the red dye characteristic of an aromatic primary amine. The ultraviolet spectrum of this compound shows two peaks at 385 mμ (log ϵ_{max} 3.87) and 310 mμ (log ϵ_{max} 4.06). The infrared spectrum shows a doublet at 2.98 μ and 3.05 μ. These bands correspond to the asymmetrical and symmetrical vibrational modes of the protons associated with the nitrogen atoms. The absence of a peak in the region 3.85-3.92 μ indicated the absence of a mercapto group, though this is not conclusive because a mercapto group shows a weak absorption in that region. This peak may not appear in very dilute solutions. The structural assignment was confirmed by the n.m.r. spectrum. A multiplet between 2.73 and 3.7τ

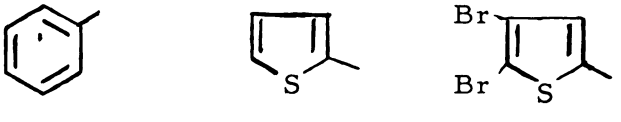
was assigned to the eight aromatic protons. A single peak with a broad base centered at 4.47τ was assigned to the four amino protons. This peak was shifted when the concentration of the solution was varied. The ratio of the areas of the peaks associated with the aromatic and amino protons was approximately 2 to 1. These data clearly support the assigned structure.

3,4-Dinitro-2,5-bis-2'-amidothiophenoxythiophenes

These amides were prepared in a manner analogous to the procedures described for the synthesis of 2'-amidophenyl-3,5-dinitro-2-thienyl sulfides. Since the starting amine has two symmetrically placed amino groups, a diamide was obtained.



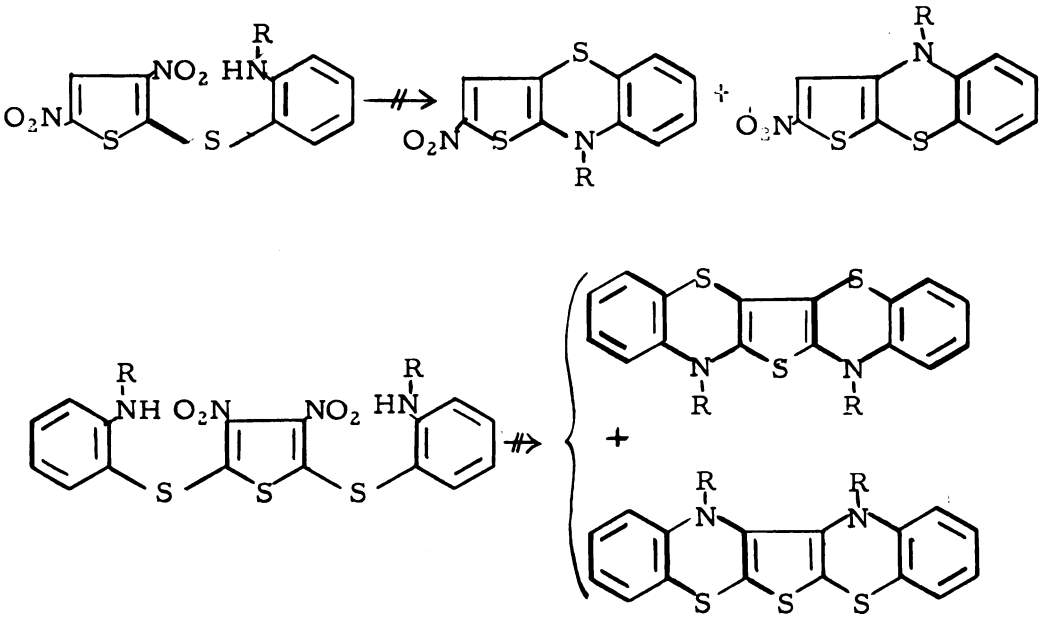
R = CH_3-, $CH_3(CH_2)_{1-6}$-, $ClCH_2CH_2$-, $(CH_3)_2CHCH_2$-,



These secondary amides show a carbonyl absorption (Amide I band) in the region 6.00-6.11 μ. The amide II band resulting from a mixed vibration of N-H bending and C-N stretching appears in the region 6.30-6.35 μ. These amides display an additional characteristic band (NH) in the 3.00-3.15 μ region of the spectrum. This band is due to the free N-H stretching of secondary amides.

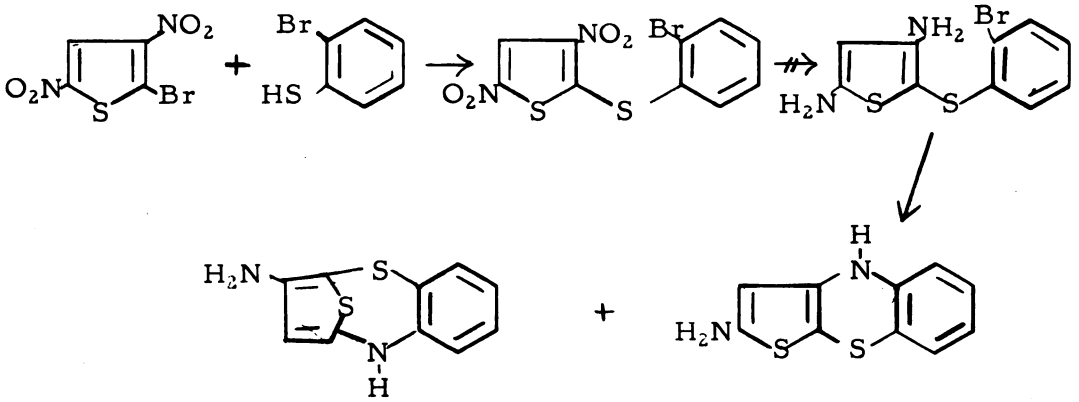
The structures of these compounds were confirmed by n.m.r. spectra. An n.m.r. spectrum of 3,4-dinitro-2,5-bis-2'-β-chloroproprionamidothiophenoxythiophene showed a multiplet between 2.1 and 2.9τ . This band was assigned to the aromatic ring protons. The two protons on the two NH groups appeared as a singlet peak with a broad base centered at 0.0τ . A triplet centered at 6.1τ was assigned to the methylene group alpha to each carbonyl group. An additional triplet peak at 7.1τ was assigned to the methylene group beta to each carbonyl group. The ratio of the area of the amino, benzene, alpha methylene and beta methylene protons was 1:4:1:1 respectively. This evidence confirms the assigned structure.

Attempts were made to bring about a ring closure in 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide and 3,4-dinitro-2,5-bis-2'-aminothiophenoxythiophene and their amine derivatives by reaction with methanolic potassium hydroxide. It was anticipated that the ring would close either with or without a Smiles rearrangement.



In each case an intractable red solution was obtained. The experimental technique of high dilution was also tried in an effort to bring about the ring closure but without success.

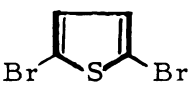
The 2'-bromophenyl-3, 5-dinitro-2-thienyl sulfide was prepared with the expectation that the nitro groups could be reduced followed by a ring closure reaction in the presence of potassium carbonate and cuprous iodide.



The attempt at ring closure was thwarted by the unsuccessful reduction of 2'-bromophenyl-3, 5-dinitro-2-thienyl sulfide either with stannous chloride or tin (16-80 mesh) in concentrated hydrochloric acid.

EXPERIMENTAL

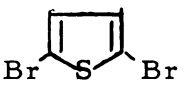
2-Bromothiophene and 2,5-dibromothiophene



Hartough's experimental procedure (84) was used to obtain these compounds. A solution containing 1008 g. (6.3 moles) of bromine dissolved in 1600 ml. of glacial acetic acid, precooled to 10°, was added to a stirred solution of 336 g. (4.0 moles) of thiophene dissolved in 1600 ml. of glacial acetic acid, precooled to 10°, and contained in a five-liter three-necked flask fitted with a reflux condenser, a stirrer, and a liter separatory funnel. The reaction mixture was allowed to warm to room temperature and stirred for an additional seven hours during which it became dark brown in color. Excess bromine and solvent were removed by adding five liters of water to the mixture. The organic layer was separated, extracted with ether, washed with 10% sodium hydroxide until the washings showed a pH of 7. It was then dried with anhydrous sodium sulfate, filtered, and the ether was removed by distillation at atmospheric pressure. To the residue, heated to 80°, in a three-liter three-necked flask fitted with a reflux condenser and stirrer was added, with stirring, 200 g. (3.03 moles) of potassium hydroxide pellets during an hour. The reaction mixture was kept at its reflux temperature for nine hours,

filtered under vacuum and the filtrate was dried over anhydrous sodium sulfate. The products were distilled through a 12" helices packed column to obtain 254 g (1.56 moles, 39%) of colorless 2-bromothiophene boiling at 149.5-152° (1 atmosphere pressure) or 4.1° (12 mm) and 333 g (1.376 moles, 34.4%) of 2,5-dibromothiophene boiling at 209-212° (1 atm) or 88° (12 mm). This was a combined yield of 73.4% of the halothiophenes. Literature values (84), b.p. 149-152° for 2-bromothiophene and 210-212° for 2,5-dibromothiophene.

2,5-Dibromothiophene



2,5-Dibromothiophene, free from other halothiophenes was prepared in a high yield by modification of Victor Meyer's procedure (85,86). A 252 g (3.0 moles) quantity of thiophene was placed in a two liter three-necked flask fitted with a dropping funnel, a mechanical stirrer, and an Allihn condenser. The flask was cooled to 0° by immersion in an ice bath, and bromine (960 g, 6 moles) was added to the stirred solution at such a rate that hydrogen bromide evolution was moderate. After the halogen had been added, the solution was stirred at room temperature, until hydrogen bromide evolution ceased (24 hours). The viscous oil was washed first with 500 ml. of water, then with two 500 ml. portions of a 20% sodium hydroxide solution, and dried over calcium chloride. The yellow oil was distilled in vacuo to obtain 523 g (2.16 moles, 72%) of a colorless oil, b.p. 89-90° at 13 mm, $n_D^{25} = 1.6265$. Literature value (86) b.p. 210.3° at 1 atm., $n_D^{25} = 1.6288$.

Cuprous Iodide

CuI

The procedure of Kauffman and Pinnell (87) was used for the preparation of this material. A 25 g. (0.1 mole) quantity of $CuSO_4 \cdot 5H_2O$ was placed in a 400 ml. beaker and dissolved in 150 ml. of water without acidification to repress hydrolysis, since in the later addition of sodium thiosulfate, colloidal sulfur could form, contaminating the product.

A second solution was prepared by placing 36.5 g. (0.22 mole) of potassium iodide and 28 g. (0.11 mole) of $Na_2S_2O_3 \cdot 5H_2O$ in a 100 ml. volumetric flask, and adding water to the volumetric mark.

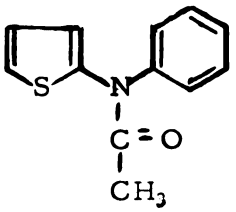
This solution was added to the first from a burette with continuous, rapid, stirring until no further precipitation occurred (90.9 ml. required theoretically). During the titration, the color of the suspension changes from dark brown, through khaki to light tan, becoming pale at the equivalence point. The exceedingly fine precipitate settled slowly, and the color provided a convenient indication of the equivalence point. The dense white precipitate after settling (15 minutes) was recovered on a sintered glass-funnel, washed with several 20 ml. portions of water, ethyl alcohol and finally with ether.

The essentially quantitative yield of powdered product was dried in vacuo over sulfuric acid for several days as cuprous iodide retains moisture tenaciously. The air-dried product contains about 4% water, while the drying procedure recommended reduces this to about 0.2% water. The product may also be dried for 12 hours in a P_2O_5 drying pistol at 100°. When heated in air below 200°, oxygen displaces the iodine of cuprous salt, yielding cupric oxide ($Cu^{II}O$) and free iodine.

$$2CuI + O_2 \longrightarrow 2CuO + I_2.$$

Thus cuprous iodide changes color on heating in air above 200° from white to brown.

N-Phenyl-2-acetamidothiophene



The procedures of Goldberg and Nimerovsky (26), Hickinbottom (78) and Hager (79) for the preparation of diphenylamine and triphenyl amine were used with modifications to prepare this compound. In a two-liter three-necked round bottomed flask, fitted with a stirrer, a 100 ml. separatory funnel and a large air cooled reflux condenser, the upper part of which was bent downwards and attached to a vertical water condenser, were placed 40 g. (0.2963 mole)of acetanilide, 84 g. (0.515 mole) of 2-bromothiophene, 30 g. (0.2177 mole) of finely powdered anhydrous potassium carbonate, 6.5 g. of cuprous iodide, 500 ml. of nitrobenzene and several crystals (0.3 g.) of iodine. The flask and air condenser were covered with asbestos tape to reduce heat loss.

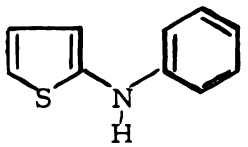
The vigorously stirred reaction mixture was heated at such a rate that the nitrobenzene vaporized up into the upper third of the air-cooled reflux condenser, condensed and flowed back into the reaction flask in a steady stream. The water formed in the reaction passed over together with a little nitrobenzene and 2-bromothiophene, and these materials were condensed in the water-cooled condenser. The distillate was dried by shaking with anhydrous sodium sulfate and the organic material was returned to the reaction flask at intervals through the separatory funnel. Heating of the reaction mixture was continued for about 40 hours (temperature $>190^{\circ}$) until reaction was complete,

indicated by no further formation of water. The time required for the complete removal of the water from the reaction flask at a reaction temperature of 190-211°, varied with the rate of stirring. When stirring was vigorous, the water could be removed in thirty hours.

The reaction mixture was allowed to cool, then transferred to a five liter flask and the nitrobenzene together with some excess 2-bromothiophene was removed by steam distillation, heating the flask to minimize condensation of steam. Steam distillation was continued until a liter of the distillate contained less than 5 ml. of water insoluble material. The removal of nitrobenzene by steam distillation must be fairly complete to avoid the formation of a gummy residue, and leave it as a dark oil. The initial distillate was itself then steam distilled to recover the N-phenyl-2-acetamidothiophene along with some nitrobenzene and unreacted 2-bromothiophene. The organic distillate, from the second distillation was nearly yellow indicating that only nitrobenzene (yellow) and 2-bromothiophene (colorless) had distilled.

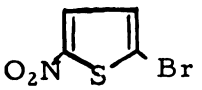
The combined residues from both steam distillations containing the crude N-phenyl-2-acetamidothiophene were taken up in petroleum ether (30-60°), dried over anhydrous sodium sulfate and the solvent was removed by evaporation at room temperature, following decolorization with Norite. The product was recrystallized from ethyl alcohol to obtain 28.4 g. (0.131 mole, 44.3%) of brown colored flakes of N-phenyl-2-acetamidothiophene, m.p. 97-8°. Anal. calc'd for $C_{12}H_{11}NSO$:C, 66.33; H, 5.10; N, 6.45; S, 14.77; O, 7.36. Found: C, 66.15, H, 5.16; N, 6.52; S, 15.02; O, 7.55. This compound shows an intense infrared carbonyl absorption peak at 6.00 μ.

N-Phenyl-2-thienylamine



A 300 ml. two-necked flask was charged with 21.7 g. (0.1 mole) of N-phenyl-2-acetamidothiophene, 60 ml. of 20% HCl and 60 ml. of ethanol. The flask was fitted with a stirrer, and a reflux condenser. The stirred reaction mixture was heated at its reflux temperature on a steam bath for 4.5 hours, during which it turned from a brown color to a deep green solution. The solvent was removed from the green colored solution by distillation at atmospheric pressure. The amine salt was neutralized with a 20% solution of sodium hydroxide and the free amine was extracted with petroleum ether (30-60°), dried with anhydrous sodium sulfate and decolorized with Norite. The ether was removed by evaporation under vacuum and the dark brown oily residue remaining was distilled to obtain 14 g. (0.08 mole, 80%) of crude N-phenyl-2-thienylamine distilling in the temperature range 240-260° as a yellow colored oil.

2-Bromo-5-nitrothiophene



The procedure of Barbasinian (88) with some modification was employed to synthesize this compound. A 125 g. (0.767 mole) quantity

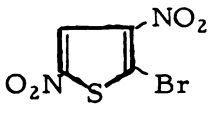
of 2-bromothiophene, dissolved in 250 ml. of glacial acetic anhydride was introduced into a two liter three-necked flask provided with a mechanical stirrer, a dropping funnel and a cooling device. A second solution was prepared by dissolving 134 g. (specific gravity 1.42) of nitric acid in 50 ml. acetic anhydride at 0°. The acetic anhydride was added to the nitric acid dropwise at a temperature below -5° since the mixture is explosive if its temperature exceeds 10°.

The nitric acid-acetic anhydride nitrating mixture was added, with stirring, to the reaction mixture dropwise during an hour and three-quarters while the reaction temperature was held below -4°. After the nitrating mixture had been added, the reaction mixture was stirred for an additional 15 hours, at -5°, to complete the nitration.

The heavy yellow colored oily product was transferred to a two liter Erlenmeyer flask containing crushed ice and set aside in a refrigerator at -10° for 48 hours.

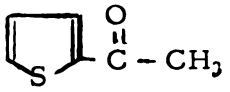
The crude 2-bromo-5-nitrothiophene (163 g.), obtained on filtration, was dissolved in a large volume of petroleum ether ($30-60^{\circ}$), decolorized with Norite, filtered and the filtrate was dried with anhydrous sodium sulfate. The petroleum ether was removed by evaporation by setting the solution aside, in a hood, for 48 hours to obtain 95 g. (0.457 mole, 59.6%) of yellow colored needles of 2-bromo-5-nitrothiophene with a melting point of 45° and distilling at $234-6^{\circ}$ (750 mm.). Literature values (88); m. p. $45-6^{\circ}$, b.p. $235-7^{\circ}$ (750 mm.).

2-Bromo-3,5-dinitrothiophene



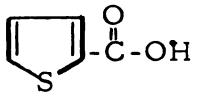
The procedure of Hurd (81) was modified and used to prepare this compound. A 114 g. (0.549 mole) quantity of 5-nitro-2-bromothiophene (m.p. 45°) was added with stirring during an hour to a nitrating mixture prepared from 482 g. of nitric acid (specific gravity 1.42) and 450 g. (specific gravity 1.84) of sulfuric acid, at 0° C, and contained in a liter three-necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. The reaction mixture formed a heavy yellow slurry during the addition of the nitrating mixture. After stirring the mixture for an additional hour and a half the product was isolated by pouring the mixture onto crushed ice in a three-liter beaker, separating the yellowish brown colored solid and washing it with ice-cold water. The product was recovered by filtration to obtain 138 g. of crude 3,5-dinitro-2-bromothiophene. Crystallization of the product from methyl alcohol was carried out immediately since the nitrating acid mixture still retained by the product attacked it to form a dark oily material. Since there was considerable tenaciously retained nitrating mixture with the crude product even after washing it several times, the first fraction of material crystallized from 150 ml. of methanol was dark in color. This was redissolved in methanol and decolorized with Norite. The remainder of the crude product was dissolved in a large volume of methanol, treated with Norite, filtered and the filtrate was cooled to precipitate pure yellow colored crystals of 2-bromo-3,5-dinitrothiophene; these were recovered by filtration. Additional quantities of product were recovered from the filtrate by concentration, treatment with Norite, filtration and cooling. The combined quantities of 2-bromo-3,5-dinitrothiophene obtained from several crystallization was 96 g. (0.3794 mole, 69.1%) m.p. 135-6°. Anal. calc'd for $C_4HN_2SO_4Br$: C, 18.99; H, 0.40; N, 11.07; S, 12.67; Br, 31.58. Found: C, 19.20; H, 0.34; N, 10.76; S, 12.59; Br, 31.66.

2-Acetylthiophene



The method of Hartough and Kosak (89) was used to prepare this material. A solution containing 1008 g. (12 moles) of thiophene dissolved in 468 g. (4.4 moles) of 95% acetic anhydride was heated to 70° in a three-liter three-necked flask fitted with a reflux condenser, a dropping funnel and a stirrer. To this vigorously stirred solution, 85% orthophosphoric acid (40 g.) was added during a quarter hour. A modest temperature rise occurred at the start of the addition of the orthophosphoric acid and external cooling of the reaction mixture was necessary towards the end of the addition of the catalyst to keep the reaction temperature below 90°. The reaction solution was held at its reflux temperature, 96-7°, for two hours and then cooled to 50°. A volume of 800 ml. of water was added and the solution was stirred for another quarter of an hour to complete the reaction. The organic layer was separated and washed with a 10% sodium carbonate solution until the wash water showed a pH of 10 to Hydrion paper. It was then given a final washing with 800 ml. of water. The thiophene water azeotrope was removed by distillation at 68°, followed by excess thiophene distilling at 84°. Vacuum distillation of the residue using a 12" helices packed column gave 480 g. (3.81 moles, 86.6%) of colorless 2-acetylthiophene boiling at 78° (2 mm) $n_D^{20} = 1.5659$. Literature value (89) b.p. 77° (4 mm.) $n_D^{20} = 1.5666$.

2-Thenoic Acid



Method A

The general procedure described by Hartough (90) and Conley (91) was used to prepare this acid. A 440 g. (11.0 moles) quantity of sodium hydroxide pellets was dissolved in 600 ml. of water, cooled, transferred to a five liter flask containing 2500 g. of crushed ice. A chlorine gas inlet tube was extended to the bottom of the flask. The flask was placed upon a balance, tared and chlorine (332 g., 4.5 moles) was introduced as rapidly as possible (about 15 minutes). The sodium hypochlorite solution formed, was transferred to a steam bath and warmed to 55-60°. The flask was then transferred to a cooling bath and the addition of 126 g. (1 mole) of 2-acetylthiophene was cautiously initiated from a dropping funnel. Addition of the 2-acetylthiophene was conducted at a rate which held the reaction temperature at 60-70° with the reaction flask immersed in a cooling bath. After adding the ketone, stirring was continued until the reaction temperature fell to 25-30°, without external cooling. Sodium bisulfite, 100 g., dissolved in 200 ml. of water, was added to remove excess sodium hypochlorite. The chlorine free solution was then poured into two four-liter beakers and cautiously acidified with concentrated hydrochloric acid. The product was collected by filtration and recrystallized from 1200 ml. of hot water to obtain a material melting at 128-9°. The yield of acid obtained in several preparations varied between 88% and 94%. The higher yields were obtained by concentrating the mother liquors at a pH of 8 or above, followed by subsequent acidification and extraction with ether.

2-Thenoic acid is highly volatile with steam and prolonged boiling during the recrystallization was avoided to prevent excessive losses of the acid.

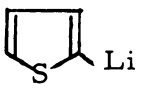
n-Butyllithium

$$CH_3CH_2CH_2CH_2Li$$

The method of Gilman and Morton (92) was modified in this preparation. A suspension of 1.76 g. (0.253 g. atom) of lithium metal, cut into fine slivers, and 50 ml. of anhydrous ethyl ether (previously stored over sodium wire) was placed in a 500 ml. three-necked flask which had been flushed with a rapid flow of dry nitrogen for 20 minutes. The flask was fitted with a mechanical stirrer, a dropping funnel and an Allihn condenser through which was suspended a -35° to $+50^{\circ}$ thermometer. The apparatus was protected from moisture by a six inch calcium chloride or Drierite tube. In other preparations, the reflux condenser, thermometer and drying tube were replaced by a two-hole rubber stopper fitted with the thermometer and a 6 mm. tubing connected with Tygon tubing to a cold trap immersed in a dry-ice methyl cellosolve bath. The cold trap was protected against moisture with a calcium chloride drying tube. The cold trap system was flushed with nitrogen prior to immersing it in the low temperature bath and proved superior to the first previously described system in excluding moisture when the humidity exceeded 50%. To the slowly stirred suspension, cooled to -10° to -5° suspended in a dry-ice methyl cellosolve bath, was added dropwise a solution containing 17.5 g. (0.12 mole) of n-butyl bromide (Matheson Coleman and Bell) dissolved in 25 ml. of anhydrous ether. In five to ten minutes, the reaction mixture became cloudy and bright spots appeared on the lithium. After initiation of the

reaction, the reaction temperature was held below -10° by immersion of the reaction flask in the dry ice-methyl cellosolve bath during the addition of the remaining alkyl halide solution (20 minutes). The mixture was stirred for an additional hour, maintaining its temperature below -10° or until only traces of unreacted lithium remained. The purple butyl lithium-ether complex was cooled to -30° and filtered through a Tygon tube, fitted with a wool plug on one end, directly into a nitrogen flushed flask and used immediately in the next reaction. The experimental procedure for separating the butyllithium from unreacted lithium could also be accomplished by suspending a gauze net on a wire loop into the solution under rapid stirring. This latter method was preferred when the humidity exceeded 50%.

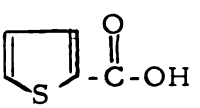
2-Thienyllithium



A solution of n-butyllithium, prepared as described from 9 g. (1.3 g.-atoms) of lithium, 82.2 g. (0.6 mole) of n-butyl bromide, and 400 ml. of anhydrous ethyl ether, was transferred to a liter three-necked flask, fitted with a stirrer, a -50° to +35° thermometer (below liquid level) suspended through an Allihn condenser, with the latter protected from moisture by a drying tube. The reaction flask and its contents were precooled to -10° by immersion in a dry-ice methyl cellosolve bath, and a solution containing 42 g. (0.50 mole) of thiophene dissolved in 130 ml. of anhydrous ethyl ether was added during a half hour to the stirred alkyl lithium solution. Two methods of forcing the equilibrium metallation reaction to completion were utilized. One involves evacuating the flask at 0° with a water aspirator to remove

the butane formed in the reaction. Upon equalizing the pressure with dry nitrogen, traces of moisture entered the system so that the alternate experimental method was preferred. In the other procedure to remove butane, the reaction mixture was heated to 20° by immersion in a water bath to accelerate vigorously the evolution of butane. The bath temperature was allowed to rise to 30° until butane evolution had ceased. The green 2-thienyl lithium solution was cooled to -10°, stirred for an hour and used immediately in subsequent reactions.

2-Thenoic Acid

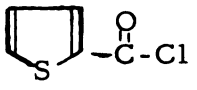


Method B

A 2-thienyl lithium ether solution, containing one mole of 2-thienyl lithium, dissolved in one liter of anhydrous ethyl ether was prepared as described previously. The 2-thienyl lithium was cautiously added to a rapidly stirred slurry of dry ice, suspended in anhydrous ether. A vigorous reaction ensued, after which the mixture was allowed to warm to room temperature. The yellow slurry was poured into a beaker containing 40 ml. of concentrated hydrochloric acid, 200 g. of ice and 300 ml. of water. The ether layer was separated; the aqueous layer was extracted several times with ether, and the combined ethereal extracts were washed with a 20% sodium hydroxide solution. The alkaline extract was decolorized at its boiling point with Norite, set aside overnight and filtered. The filtrate was acidified with concentrated hydrochloric acid to a pH of one (Hydrion). The precipitated white solid was recovered by filtration on a Buchner funnel, washed with 50 ml. of cold water and dried to obtain 121 g. (0.94 mole,

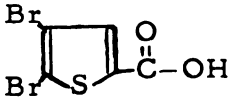
94%) of crude 2-thenoic acid. The crude acid was recrystallized from hot water, being decolorized with Norite at the same time, to obtain 106 g. (0.83 mole, 83%) of a white crystalline material (needles) melting at 129-130°. Literature value (91), m.p. 130°.

2-Thenoyl Chloride



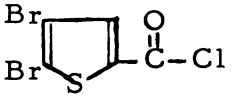
In a 250 ml. single necked flask, a mixture of 128 g. (1.0 mole) of 2-thenoic acid and 400 g. (3.36 moles) of thionyl chloride was heated at its reflux temperature for 6.5 hours. Distillation of the reaction mixture at atmospheric pressure removed excess thionyl chloride. The resulting straw colored liquid was fractionated under a vacuum using a column 30 cm. in height and 12 mm. in diameter, packed with 1/8" glass helices to yield 126 g. (0.86 mole, 86%) of 2-thenoyl chloride as a colorless lachrimatory liquid with the physical properties, m.p. 0°, b.p. 78° (10 mm.), 58° (2 mm.), and 190° (170 mm.). Ford and Mackay (93) reported a b.p. 77° (10 mm.) for this material.

4,5-Dibromo-2-thenoic acid



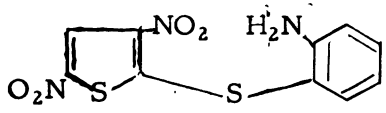
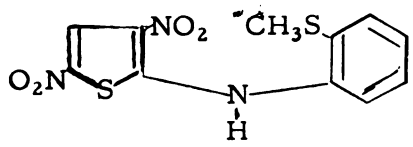
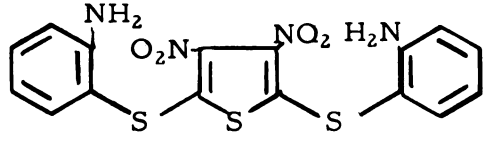
The procedure described by Hartough (94) was used to prepare this compound. A three-liter beaker, fitted with a mechanical stirrer was charged with 64 g. (0.5 mole) of 2-thiophene carboxylic acid. Liquid bromine, 480 g. (3.0 moles) was added to the acid with stirring at low speed in a well ventilated hood. The resulting slurry was set aside until most of the excess bromine had evaporated. The reaction mixture was then dissolved in excess ammonium carbonate solution which removed the last traces of bromine from the mixture. The aqueous carbonate solution was acidulated with hydrochloric acid and the product was recovered by filtration, dried and recrystallized once from ethyl alcohol to obtain 138 g. (0.482 mole, 96.4%) of white crystalline 4, 5-dibromo-2-thenoic acid melting at 225-226°. Literature value (94), m.p. 225-7°.

4, 5-Dibromo-2-thenoyl Chloride



In a 300 ml. single necked flask was added a mixture of 28.6 g. (0.1 mole) of 4, 5-dibromo-2-thenoic acid and 140 ml. of thionyl chloride. The reaction flask was then fitted with a reflux condenser and the mixture was heated at its reflux temperature for five hours on a steam bath. Excess thionyl chloride was removed by distillation at atmospheric pressure. Further distillation in vacuo afforded 24.3 g. (0.8 mole, 80%) of crystalline 4, 5-dibromo-2-thenoyl chloride melting at 36-8°. Anal. calc'd for $C_5HSOClBr_2$: C, 19.73; H, 0.33; combined halogens (Cl + Br) 64.15. Found: C, 19.53; H, 0.51; halogens, 64.35.

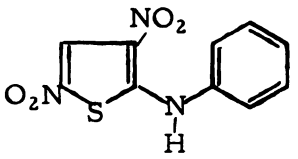
Table I. Ultraviolet Spectral Analyses

Compound [a]	Solvent	λ_{max} in mμ	Log ϵ_{max}	M.p. °C	Color
	1,4-dioxane	358	4.21	164	red
	1,4-dioxane	252	4.31		
	1,4-dioxane	396	4.27	167.5-168.5	yellow
	1,4-dioxane	358	4.12		
	1,4-dioxane	252	4.36		
	1,4-dioxane	385	3.87	163	orange-yellow
	1,4-dioxane	310	4.06		

[a] These compounds do not absorb in the visible region of the spectrum.

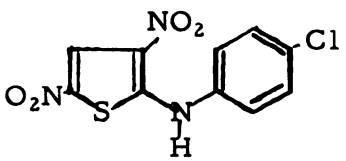
3, 5-Dinitro-N-aryl-2-thienylamines

N-Phenyl-3, 5-dinitro-2-thienylamine



To 1.265 g. (0.005 mole) of 2-bromo-3, 5-dinitrothiophene dissolved in 30 ml. of redistilled methanol was added a 0.5 g. (0.00538 mole) quantity of aniline. The reaction mixture was stirred at room temperature until glistening brown colored plates of N-phenyl-3, 5-dinitro-2-thienylamine separated from solution. Stirring was continued for another quarter hour to ensure completion of the reaction. The crude product was recovered by filtration and recrystallized from dry methanol to obtain 1.3 g. (0.0049 mole, 98%) of an orange crystalline product melting at 162.5-163.° Anal. calc'd for $C_{10}H_7N_3SO_4$: C, 45.28; H, 2.66; N, 15.84; S, 12.09. Found: C, 45.23; H, 2.83; N, 15.61; S, 12.33.

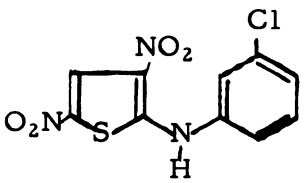
N(4-Chlorophenyl)-3, 5-dinitro-2-thienylamine



The general procedure previously described for the preparation of N-phenyl-3, 5-dinitro-2-thienylamine was employed to obtain this

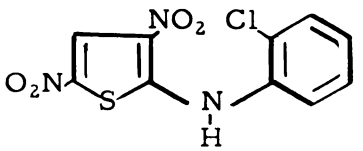
compound. A solution containing 2.53 g. (0.01 mole) of 2-bromo-3,5-dinitrothiophene dissolved in 20 ml. of freshly dried methanol was placed in a 250 ml. two-necked flask fitted with a mechanical stirrer and a dropping funnel. A 1.40 g. (0.011 mole) quantity of p-chloroaniline, dissolved in 10 ml. of dry methanol was added to the vigorously stirred solution from the dropping funnel. The reaction solution was initially blood red in color. The color change was followed by the precipitation of the crude amine product. The mixture was stirred for an additional quarter hour to complete the reaction, and then it was cooled by immersion in an ice bath. The crude product was recovered by filtration and recrystallized from a dry acetone methanol mixture (1:1) to obtain 2.8 g. (0.00935 mole, 93.5%) of a yellow colored crystalline product in the form of needles and melting at 180-180.5° (dec). Anal. calc'd for $C_{10}H_6N_3SO_4Cl$: C, 40.08; H, 2.02; N, 14.02; S, 10.70; Cl, 11.83. Found: C, 40.09; H, 2.10; N, 13.77; S, 10.61; Cl, 11.72.

N-(3-Chlorophenyl)-3,5-dinitro-2-thienylamine



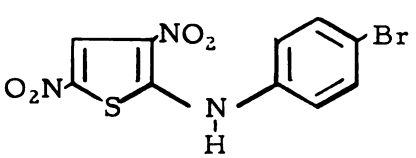
The general procedure previously described for the preparation of the 4-chloro isomer was employed to obtain this compound. The quantities of reactants used were: 1.5 g. (0.00593 mole) of 2-bromo-3,5-dinitrothiophene, 0.8 g. (0.00625 mole) of m-chloroaniline. Recrystallization of the crude product from dry acetone-methanol mixture yielded 1.34 g. (0.004474 mole, 75.4%) of a dull yellow colored crystalline product, melting at 185-6° (dec). Anal. calc'd for $C_{10}H_6N_3SO_4Cl$: C, 40.08; H, 2.02; N, 14.02; S, 10.70; Cl, 11.83. Found: C, 40.29; H, 2.03; N, 13.91; S, 10.78; Cl, 11.92.

N-(2-Chlorophenyl)-3, 5-dinitro-2-thienylamine



A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene, dissolved in 20 ml. of dry methanol was placed in a 300 ml. three-necked flask fitted with a mechanical stirrer and a dropping funnel. A solution containing 1.40 g. (0.011 mole) of o-chloroaniline, dissolved in 10 ml. of dry methanol was added from the dropping funnel to the stirred halonitrothiophene solution. The reaction mixture was stirred, at room temperature, for another hour to complete the reaction. The crude product was recovered by filtration and crystallized from a dry methanol acetone mixture after decolorizing it with Norite to obtain 0.6 g. (0.002 mole, 20%) of a dull red colored crystalline product melting at 178-9°. Anal. calc'd for $C_{10}H_6N_3SO_4Cl$: C, 40.08; H, 2.02; N, 14.02; S, 10.70; Cl, 11.83. Found: C, 40.22; H, 1.85; N, 13.76; S, 10.62 and Cl, 11.88.

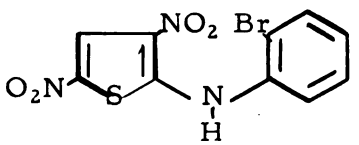
N-(4-Bromophenyl)-3, 5-dinitro-2-thienylamine



A 1.5 g. (0.00593 mole) quantity of 2-bromo-3, 5-dinitrothiophene dissolved in 15 ml. of dry methanol, was placed in a 250 ml. two-necked flask fitted with a mechanical stirrer and a dropping funnel. A solution containing 1.032 g. (0.006 mole) of p-bromoaniline dissolved

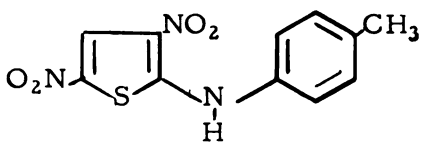
in 15 ml. of methanol was added from the dropping funnel to the halonitrothiophene solution. The resulting red colored solution was stirred until a quantitative precipitation of the crude product had occurred. The product was collected by filtration and crystallized from a dry acetone-methanol mixture to obtain 1.98 g. (0.00576 mole, 95.4%) of a bright yellowish colored crystalline product melting at 172.5-3°. Anal. calc'd for $C_{10}H_6N_3SO_4Br$: C, 34.90; H, 1.76; N, 12.21; S, 9.32; Br, 23.22. Found: C, 34.64; H, 1.78; N, 12.08; S, 9.24 and Br, 23.29.

N-(2-Bromophenyl)-3,5-dinitro-2-thienylamine



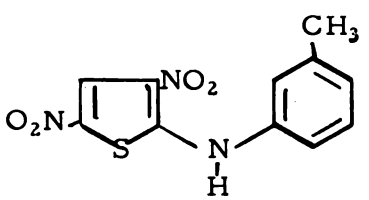
The general procedure previously described for the preparation of the 4-bromo isomer was employed to obtain this compound except that a considerably longer reaction time was required. To 2.53 g. (0.01 mole) of 2-bromo-3,5-dinitrothiophene dissolved in 15 ml. of freshly dried methanol was added a solution containing 2.064 g. (0.012 mole) of 2-bromoaniline dissolved in 15 ml. of methyl alcohol. The reaction mixture was stirred, at room temperature for a day. The precipitate was collected by filtration and recrystallized from a dry acetone, methanol mixture to obtain 0.805 g. (0.00234 mole, 23.4%) of a brownish yellow colored crystalline product melting at 162-3°. Anal. calc'd for $C_{10}H_6N_3SO_4Br$: C, 34.90; H, 1.76; N, 12.21; S, 9.32; Br, 23.22. Found: C, 35.12; H, 1.89; N, 12.00; S, 9.55 and Br, 23.43.

N-(4-Methylphenyl)-3, 5-dinitro-2-thienylamine



A 1.0 g. (0.00395 mole) quantity of 2-bromo-3, 5-dinitrothiophene, was placed in a 250 ml. two-necked flask fitted with a stirrer and a dropping funnel and dissolved in 15 ml. of dry methanol. A second solution containing 0.4708 g. (0.0044 mole) of p-methylaniline dissolved in 10 ml. of methanol was added to the halonitrothiophene solution from the dropping funnel. The reaction mixture was stirred until a reaction had occurred, and then for an additional 10 minutes. The precipitated product was collected by filtration and recrystallized from a dry acetone, methanol mixture after decolorizing it with Norite to obtain 1.09 g. (0.00391 mole, 98.9%) of a pure yellow colored crystalline product melting at 146-7°. Anal. calc'd for $C_{11}H_9N_3SO_4$: C, 47.31; H, 3.25; N, 15.05; S, 11.48. Found: C, 47.41; H, 3.37; N, 15.10 and S, 11.49.

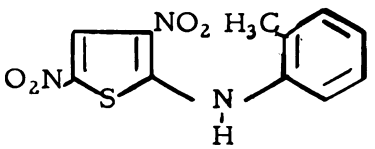
N-(3-Methylphenyl)-3, 5-dinitro-2-thienylamine



The experimental procedure used to synthesize the 4-methyl isomer was employed in the preparation of this compound. The quantities of the reactants used were: 2.0 g. (0.0079 mole) of 2-bromo-3, 5-dinitrothiophene and 0.9416 g. (0.0088 mole) of m-methylaniline.

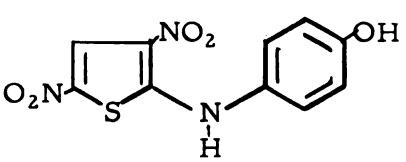
The crude product was crystallized from a dry acetone, methanol mixture after decolorization with Norite to obtain 2.1 g. (0.00753 mole, 95.3%) of a pure red colored crystalline product melting at 148-9°. Anal. calc'd for $C_{11}H_9N_3SO_4$: C, 47.31; H, 3.25; N, 15.05; S, 11.48. Found: C, 47.52; H, 3.40; N, 15.06; S, 11.43.

N-(2-Methylphenyl)-3,5-dinitro-2-thienylamine



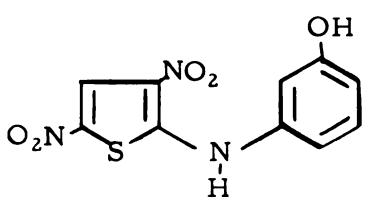
The general procedure used to prepare the 4-methyl isomer was employed in this synthesis, with the exception that a long reaction time was necessary in this case. The quantities of the reactants used were 2.53 g. (0.01 mole) of 2-bromo-3,5-dinitrothiophene and 1.8 g. (0.011 mole) of o-methylaniline. The crude product was crystallized from a freshly dried acetone-methanol mixture to obtain 2.3 g. (0.00828 mole, 82.8%) of a pure red colored crystalline product after decolorizing it with Norite. The product melted at 161-2°. Anal. calc'd for $C_{11}H_9N_3SO_4$: C, 47.31; H, 3.25; N, 15.05; S, 11.48. Found: C, 47.58; H, 3.54; N, 15.15 and S, 11.51 (Singlet infrared absorption peak of a secondary amine at 2.97 μ).

N-(4-Hydroxyphenyl)-3,5-dinitro-2-thienylamine



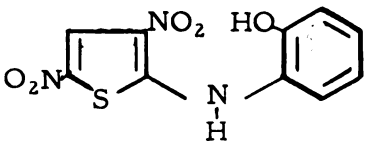
To a solution containing 1.265 g. (0.005 mole) of 2-bromo-3,5-dinitrothiophene dissolved in 15 ml. of freshly dried methanol was added 0.5995 g. (0.0055 mole) of p-aminophenol. The reaction mixture was stirred vigorously at room temperature for an hour. The red product initially precipitated, was collected by filtration. Additional quantities of the crude product were recovered by concentrating the mother liquor under vacuum and removing the product by filtration. The combined crude product was recrystallized from an acetone, methanol mixture after decolorizing it with activated charcoal. The yield of the dark red colored crystalline product was 0.96 g. (0.00342 mole, 68.4%). It had a melting point of 235.5-236.5°. Anal. calc'd for $C_{10}H_7N_3SO_5$: C, 42.70; H, 2.51; N, 14.94; S, 11.40. Found: C, 42.97; H, 2.74; N, 15.04; S, 11.39.

N-(3-Hydroxyphenyl)-3,5-dinitro-2-thienylamine



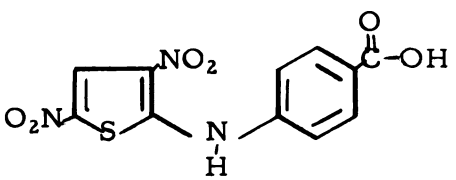
The experimental procedure used to prepare the 4-hydroxy isomer was used to obtain this material. The quantities of reagents used were: 0.6325 g. (0.0025 mole) of 2-bromo-3,5-dinitrothiophene and 0.436 g. (0.004 mole) of m-aminophenol. Crystallization of the crude product from acetone after decolorization with activated charcoal gave 0.61 g. (0.00217 mole, 86.8%) of a yellowish red colored crystalline product melting at 219-220°. Anal. calc'd for $C_{10}H_7N_3SO_5$: C, 42.70; H, 2.51; N, 14.94; S, 11.40. Found: C, 42.76; H, 2.57; N, 14.70; S, 11.31.

N-(2-Hydroxyphenyl)-3, 5-dinitro-2-thienylamine



The same general experimental procedure used to prepare the 4-hydroxy isomer was again employed in this preparation. The quantities of reagents used were: 0.6325 g. (0.0025 mole) of 2-bromo-3, 5-dinitrothiophene and 0.327 g. (0.003 mole) of o-aminophenol. Crystallization of the crude product from acetone, after decolorization with Norite, gave 0.57 g. (0.00203 mole, 81.2%) of a red colored crystalline product melting at 216-7°. This compound, as expected, was soluble in 10% sodium hydroxide solution but insoluble in dilute hydrochloric acid. Anal. calc'd for $C_{10}H_7N_3SO_5$: C, 42.70; H, 2.51; N, 14.94; S, 11.40. Found: C, 42.83; H, 2.52; N, 14.74 and S, 11.16.

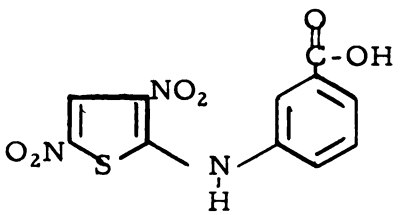
N-(4-Carboxyphenyl)-3, 5-dinitro-2-thienylamine



A solution prepared from 2.53 g. (0.01 mole) of 2-bromo-3, 5-dinitrothiophene and 20 ml. of methanol was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a reflux condenser. A 1.507 g. (0.011 mole) quantity of p-aminobenzoic acid, dissolved in 15 ml. of methyl alcohol, was added dropwise from the dropping funnel to the stirred halonitrothiophene solution. When the acid had been added the reaction mixture was heated at its reflux

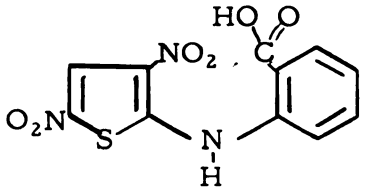
temperature on a steam bath for a half hour, cooled and the precipitate was collected by filtration. Recrystallization of the crude product from an acetone, methanol mixture, after decolorizing it with Norite B, gave 2.69 g. (0.0087 mole, 87%) of a yellow colored crystalline product melting at 254-5°. Anal. calc'd for $C_{11}H_7N_3SO_6$: C, 42.72; H, 2.28; N, 13.59; S, 10.37. Found: C, 42.93; H, 2.31; N, 13.60; S, 10.32.

N-(3-Carboxyphenyl)-3, 5-dinitro-2-thienylamine



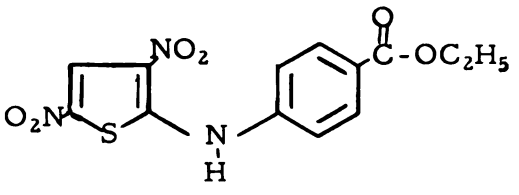
A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene, dissolved in 15 ml. of freshly dried methanol was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a reflux condenser. A solution containing 1.507 g. (0.011 mole) of m-amino-benzoic acid dissolved in 15 ml. of methanol was added dropwise to the stirred halonitrothiophene solution. Following the addition of the acid, the reaction mixture was heated at its reflux temperature on a steam bath for a half hour, cooled by immersion in an ice bath. The precipitated crude product was collected by filtration and crystallized from a dry acetone, methanol mixture after decolorizing it with Norite to obtain 2.4 g. (0.00777 mole, 77.7%) of a reddish brown colored pure material melting at 240-1° after drying it at 60° for seven days. Anal. calc'd for $C_{11}H_7N_3SO_6$: C, 42.72; H, 2.28; N, 13.59; S, 10.37. Found: C, 42.71; H, 2.57; N, 13.65; S, 10.48.

N-(2-Carboxyphenyl)-3, 5-dinitro-2-thienylamine



The experimental procedure used to prepare the 3-carboxy isomer was employed in this preparation. The quantities of reagents used were: 0.6325 g. (0.0025 mole) of 2-bromo-3, 5-dinitrothiophene and 0.4521 g. (0.0033 mole) of anthranilic acid. The reaction time was 40 minutes. Recrystallization of the crude product from a freshly dried acetone, methanol mixture gave 0.7 g. (0.002265 mole, 90.6%) of a yellow colored product melting at 262-3°. This compound was readily soluble in 10% NaOH, as expected, and is insoluble in dilute acid. Anal. calc'd for $C_{11}H_7N_3SO_6$: C, 42.72; H, 2.28; N, 13.59; S, 10.37. Found: C, 42.75; H, 2.36; N, 13.50; S, 10.32. This material showed infrared absorptions at 3.4-3.7 μ (broad), 5.97 (strong), characteristic of carboxylic acids.

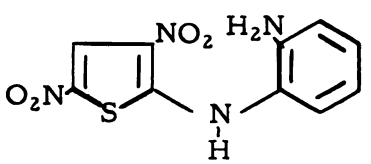
N-(4-Carbethoxyphenyl)-3, 5-dinitro-2-thienylamine



The general experimental procedure described above was used to prepare this compound. A solution prepared from 2.0 g. (0.0079 mole)

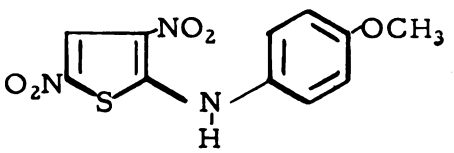
of 2-bromo-3, 5-dinitrothiophene and 15 ml. of methanol was placed in a 300 ml. three-necked flask fitted with a reflux condenser, a stirrer and a dropping funnel. A 1.485 g. (0.009 mole) quantity of ethyl p-aminobenzoate dissolved in 10 ml. of methanol was added dropwise to the halonitrothiophene solution. The reaction mixture was then heated at its reflux temperature on a steam bath for thirty minutes, cooled, and the precipitate was collected by filtration. The crude material was recrystallized as previously described in similar synthesis to obtain 1.701 g. (0.00505 mole, 64%) of a yellow colored product after decolorizing it with activated carbon. The product melted at 148-9° after drying it for seven days at 60°. Anal. calc'd for $C_{13}H_{11}N_3SO_6$: C, 46.29; H, 3.29; N, 12.46; S, 9.51. Found: C, 46.53; H, 3.51; N, 12.16; S, 9.57.

N-(2-Aminophenyl)-3, 5-dinitro-2-thienylamine



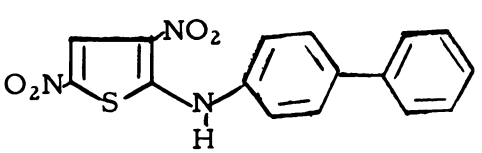
To a solution containing 1.5 g. (0.00593 mole) of 2-bromo-3, 5-dinitrothiophene dissolved in 20 ml. of anhydrous methanol was added 0.756 g. (0.007 mole) of o-phenylenediamine dissolved in 20 ml. of methanol. The mixture was stirred until a brown colored precipitate had formed. The crude product was collected by filtration and crystallized from anhydrous acetone after decolorizing it with Norite to obtain 1.6 g. (0.00572 mole, 96.4%) of yellowish brown colored product in the form of plates melting at 186.5°. Anal. calc'd for $C_{10}H_8N_4SO_4$: C, 42.86; H, 2.88; N, 19.99; S, 11.44. Found: C, 43.32; H, 2.98; N, 19.48 and S, 11.38.

N-(4-Methoxyphenyl)-3, 5-dinitro-2-thienylamine



The experimental procedure described above was employed again in the preparation of this compound. The quantities of reagents used were: 1.265 g. (0.005 mole) of 2-bromo-3, 5-dinitrothiophene and 0.6765 g. (0.0055 mole) of p-methoxyaniline. The red colored precipitated crude product was recrystallized from acetone to give 1.37 g. (0.004644 mole, 92.9%) of a red colored crystalline pure solid melting at 158-9°. Anal. calc'd for $C_{11}H_9N_3SO_5$: C, 44.74; H, 3.07; N, 14.23; S, 10.86. Found: C, 45.04; H, 3.13; N, 14.19; S, 10.82.

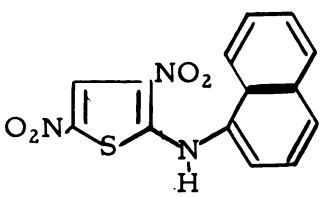
N-(p-Biphenyl)-3, 5-dinitro-2-thienylamine



To a solution containing 2.53 g. (0.01 mole) of 2-bromo-3, 5-dinitrothiophene dissolved in 15 ml. of freshly dried methanol was added 1.859 g. (0.011 mole) of Xenylamine dissolved in 10 ml. of methanol. The reaction mixture was stirred vigorously, at room temperature, until product precipitation had ceased. The reaction mixture was cooled; the crude product was collected by filtration and recrystallized from acetone, methanol mixture after decolorizing

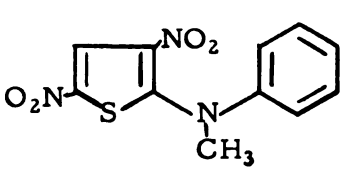
it with carbon to obtain 2.2 g. (0.00645 mole, 64.5%) of a reddish brown colored powdery product melting at 207-8°. Anal. calc'd for $C_{16}H_{11}N_3SO_4$: C, 56.30; H, 3.25; N, 12.31; S, 9.40. Found: C, 56.55; H, 3.54; N, 12.32; S, 9.39.

N-(α-Naphthyl)-3, 5-dinitro-2-thienylamine



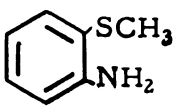
The general experimental procedure described above was employed in the preparation of this compound. A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene and 1.573 g. (0.011 mole) of 1-naphthylamine were the amounts of reactants used. The crude product was crystallized from a dry acetone, methanol mixture after decolorizing it with Norite to afford 2.4 g. (0.00762 mole, 76.2%) of a yellow colored pure product melting at 215-6°. Anal. calc'd for $C_{14}H_9N_3SO_4$: C, 53.33; H, 2.88; N, 13.33; S, 10.17. Found: C, 53.54; H, 2.97; N, 13.29; S, 10.14.

N, N-Methylphenyl-3, 5-dinitro-2-thienylamine



A 1.265 g. (0.005 mole) quantity of 2-bromo-3, 5-dinitrothiophene dissolved in 20 ml. of methanol was placed in a 250 ml. two-necked flask fitted with a dropping funnel and a stirrer. N-Methylaniline, 0.5885 g. (0.0055 mole) was added dropwise to the stirred halonitrothiophene solution. When the N-methylaniline had been added, stirring was continued for another twenty minutes to complete the reaction. The crude product was recovered by filtration and crystallized from acetone to obtain 1.06 g. (0.0038 mole, 76%) of a yellow colored crystalline product melting at 121-2°. An aqueous acetone solution of this compound failed to give a purple coloration found to be generally characteristic of phenyl-3, 5-dinitro-2-thienylamines. Anal. calc'd for $C_{11}H_9N_3SO_4$: C, 47.30; H, 3.25; N, 15.05; S, 11.48. Found: C, 47.23; H, 3.32; N, 14.96; S, 11.30.

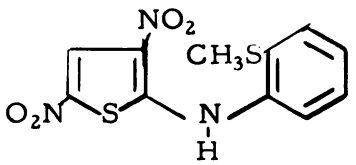
o-Aminothioanisole



A modification of the procedure described by Vogel (95) was used in the preparation of this compound. A 125 g. (1 mole) quantity of o-aminothiophenol was placed in a liter three-necked flask fitted with a dropping funnel, a stirrer and a reflux condenser. The potassium methoxide solution made by dissolving 66 g. (1.0 mole) of potassium hydroxide pellets in 200 ml. of methanol was added to the stirred o-aminothiophenol contained in the reaction flask. The dropping funnel was then replaced by a gas inlet tube and methyl bromide was bubbled continuously through the stirred reaction solution while the reaction mixture was heated at its reflux temperature for an hour on

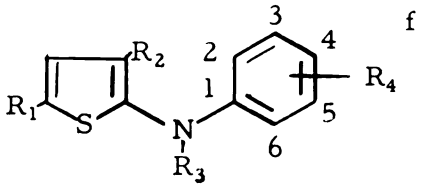
a steam bath. It was then cooled, and the potassium bromide which had formed (120 g.) was removed by filtration. The methyl alcohol solvent was removed by distillation at atmospheric pressure. Distillation was continued until the o-aminothioanisole boiling between 255 and 260° had been removed. Fractional distillation of this crude product in vacuo gave 111.2 g. (0.8 mole, 80%) of pure o-aminothioanisole as a yellow colored oil. Anal. calc'd for C_7H_9NS: C, 60.39; H, 6.51; N, 10.06; S, 23.03. Found: C, 60.57; H, 6.72; N, 9.92; S, 23.16.

N-(2-Thiomethoxyphenyl)-3, 5-dinitro-2-thienylamine



A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene dissolved in 20 ml. of freshly dried methanol was placed in a 300 ml. two-necked flask fitted with a stirrer and a dropping funnel. A solution prepared from 1.53 g. (0.011 mole) of o-aminothioanisole and 10 ml. of methanol was added from the dropping funnel to the halonitrothiophene solution. The reaction mixture was stirred at room temperature and almost immediately a massive precipitation of crude N-(2-thiomethoxyphenyl)-3, 5-dinitro-2-thienylamine occurred. The crude product collected by filtration melted at 170-2°. It was recrystallized from a dry acetone, methanol mixture to afford 3.0 g. (0.00965 mole, 96.5%) of a brilliant yellow colored product with a melting point of 167.5-168.5° (dec). Anal. calc'd for $C_{11}H_9N_3S_2O_4$: C, 42.44; H, 2.91; N, 13.50; S, 20.60. Found: C, 42.43; H, 3.19; N, 13.61 and S, 20.41.

Table II. Properties and Analyses of N-phenyl-2-thienylamines



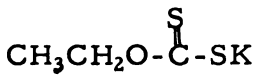
#	R_1	R_2	R_3	R_4	Yield %	M.p.[g], °C	Formula
1	H	H	CH_3CO	H	44.3	97-8[h]	$C_{12}H_{11}NSO$
2	NO_2	NO_2	H	H	98	162.5-163[d]	$C_{10}H_7N_3SO_4$[c]
3	NO_2	NO_2	H	4-Cl	93.5	180-180.5[b]	$C_{10}H_6N_3SO_4Cl$[c]
4	NO_2	NO_2	H	3-Cl	75.4	185-186[b]	$C_{10}H_6N_3SO_4Cl$[c]
5	NO_2	NO_2	H	2-Cl	20	178-179[b]	$C_{10}H_6N_3SO_4Cl$[c]
6	NO_2	NO_2	H	4-Br	95.4	172.5-173[b]	$C_{10}H_6N_3SO_4Br$[c]
7	NO_2	NO_2	H	2-Br	23.4	162-163[b]	$C_{10}H_6N_3SO_4Br$[c]
8	NO_2	NO_2	H	4-CH_3	98.9	146-147[b]	$C_{11}H_9N_3SO_4$[c]
9	NO_2	NO_2	H	3-CH_3	95.3	148-149[b]	$C_{11}H_9N_3SO_4$[c]
10	NO_2	NO_2	H	2-CH_3	82.8	161-162[b]	$C_{11}H_9N_3SO_4$[c]
11	NO_2	NO_2	H	4-OH	68.4	235.5-236.5[b]	$C_{10}H_7N_3SO_5$[c]
12	NO_2	NO_2	H	3-OH	86.8	219-220[e]	$C_{10}H_7N_3SO_5$[c]
13	NO_2	NO_2	H	2-OH	81.2	216-217[e]	$C_{10}H_7N_3SO_5$[c]
14	NO_2	NO_2	H	4-COOH	87	254-255[b]	$C_{11}H_7N_3SO_6$[c]
15	NO_2	NO_2	H	3-COOH	77.7	240-241[b]	$C_{11}H_7N_3SO_6$[c]
16	NO_2	NO_2	H	2-COOH	90.6	262-263[b]	$C_{11}H_7N_3SO_6$[c]
17	NO_2	NO_2	H	4-CO_2Et	64	148-149[b]	$C_{13}H_{11}N_2SO_6$[c]
18	NO_2	NO_2	H	2-NH_2	96.4	186.5[e]	$C_{10}H_8N_4SO_4$[c]
19	NO_2	NO_2	H	4-OCH_3	92.9	158-159[e]	$C_{11}H_9N_3SO_5$[c]
20	NO_2	NO_2	H	4-C_6H_5	64.5	207-208[b]	$C_{16}H_{11}N_3SO_4$[c]
21	NO_2	NO_2	H	4,5-$(CH)_4$	76.2	215-216[b]	$C_{14}H_9N_3SO_4$[c]
22	NO_2	NO_2	CH_3	H	76	121-122[e]	$C_{11}H_9N_3SO_4$
23	NO_2	NO_2	H	2-SCH_3	96.5	167.5-168.5[b]	$C_{11}H_9N_3S_2O_4$[c]

a) Microanalyses were done by Microtech. Laboratories, Skokie, Illinois.
b) Recrystallized from a dry methanol, acetone mixture.
c) A solution of this compound in aqueous acetone is purple in color.
d) Recrystallized from methanol.
e) Recrystallized from acetone.
f) These preparations were carried out in anhydrous conditions.
g) Dried at 60° for several days.
h) Recrystallized from ethyl alcohol.

Analyses, %[a]										
Carbon		Hydrogen		Nitrogen		Sulfur		Haolgen		
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Name	Calcd	Found
66.33	66.15	5.10	5.16	6.45	6.52	14.77	15.02			
45.28	45.23	2.66	2.83	15.84	15.61	12.09	12.33			
40.08	40.09	2.02	2.10	14.02	13.77	10.70	10.61	Cl	11.83	11.72
40.08	40.29	2.02	2.03	14.02	13.91	10.70	10.78	Cl	11.83	11.92
40.08	40.22	2.02	1.85	14.02	13.76	10.70	10.62	Cl	11.83	11.88
34.90	34.64	1.76	1.78	12.21	12.08	9.32	9.24	Br	23.22	23.29
34.90	35.12	1.76	1.89	12.21	12.00	9.32	9.55	Br	23.22	23.43
47.31	47.41	3.25	3.37	15.05	15.10	11.48	11.49			
47.31	47.52	3.25	3.40	15.05	15.06	11.48	11.43			
47.31	47.58	3.25	3.54	15.05	15.15	11.48	11.51			
42.70	42.97	2.51	2.74	14.94	15.04	11.40	11.39			
42.70	42.76	2.51	2.57	14.94	14.70	11.40	11.31			
42.70	42.83	2.51	2.52	14.94	14.74	11.40	11.16			
42.72	42.93	2.28	2.31	13.59	13.60	10.37	10.32			
42.72	42.71	2.28	2.57	13.59	13.65	10.37	10.48			
42.72	42.75	2.28	2.36	13.59	13.50	10.37	10.32			
46.29	46.53	3.29	3.51	12.46	12.16	9.51	9.57			
42.86	43.32	2.88	2.98	19.99	19.48	11.44	11.38			
44.74	45.04	3.07	3.13	14.23	14.19	10.86	10.82			
56.30	56.55	3.25	3.54	12.31	12.32	9.40	9.39			
53.33	53.54	2.88	2.97	13.33	13.29	10.17	10.14			
47.30	47.23	3.25	3.32	15.05	14.96	11.48	11.30			
42.44	42.43	2.91	3.19	13.50	13.61	20.60	20.41			

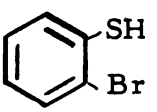
Phenyl-3, 5-dinitro-2-thienyl Sulfides

Potassium Ethyl Xanthate



The procedure described by Villars (96) was employed in this synthesis. A solution of potassium ethoxide was prepared by adding 607 g (9.2 moles) of potassium hydroxide pellets to 2500 ml. of absolute ethanol and heating the mixture at its reflux temperature for an hour. It was then cooled to room temperature, filtered to remove insoluble materials, and the filtrate was transferred to a five-liter, three-necked round bottomed flask, equippped with a stirrer, a thermometer and a dropping funnel. Carbon disulfide (700 g., 9.2 moles) was added dropwise to the vigorously stirred potassium ethoxide solution. The reaction mixture was stirred for an hour following the addition of the disulfide, cooled to room temperature by immersion, in an ice water bath, and filtered on a Buchner funnel to recover the potassium ethyl xanthate. The solid xanthate was slurried in ether to remove the orange coloration, vacuum filtered as dry as possible, and finally dried thoroughly in a vacuum dessicator. The yield of product obtained as a creamy yellow solid, was 1,056 g. (6.6 moles, 71.7%). This material was used for the preparation of arylthiophenols by interaction with a substituted benzene diazonium chloride and subsequent reduction of the intermediate to the thiol.

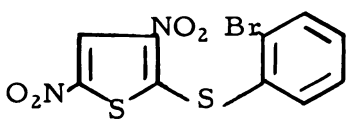
o-Bromothiophenol



A modification of the procedure described by Saggiomo (56) was employed in the preparation of this thiophenol. A 258 g. (1.5 moles) quantity of o-bromoaniline was stirred with a solution of hydrochloric acid prepared by diluting 264 ml. of concentrated hydrochloric acid with 942 ml. of water. The solid white amine hydrochloride formed was insoluble in the excess acid. The mixture was stirred and allowed to cool to -10° in a refrigerator maintained at -14°. A sodium nitrite solution containing 1.5 moles of sodium nitrite was prepared by dissolving 103.5 g. of the salt in 300 ml. of water. When the temperature of the amine hydrochloride suspension had reached -10°, a 187.5 g. quantity of crushed ice was added to it, and the temperature was maintained below -5° by adding ice when necessary. The sodium nitrite solution was poured into the chilled amine salt solution and the mixture was vigorously stirred for five to ten minutes. The amine hydrochloride dissolved on conversion to its soluble diazonium salt. A flattened stirring rod was used to break up the lumps of solid as completely as possible. This orange colored diazonium solution was then added, in portions, with a pipette beneath the surface of the stirred solution of potassium ethyl xanthate containing 415 g. of the xanthate salt dissolved in 755 ml. of water, heated to $70\text{-}80^{\circ}$ on a steam bath. Severe sputtering occurred if the diazonium solution was not added beneath the warm solution. It was found to be more expedient to use a long-necked funnel in place of a pipette to introduce the diazonium solution beneath the surface of the potassium ethyl zanthate solution. The reaction mixture was heated for another hour after the addition of the diazonium salt solution was completed. The red oil which separated from solution during the reaction was washed with 10% potassium hydroxide solution and then with water. It was added, in portions, to a hot alcoholic alkaline solution containing 456 g. (6.91 moles) of potassium hydroxide pellets dissolved in 346 ml. of water and 1040 ml. of ethyl alcohol.

After heating the alkaline reaction mixture at its reflux temperature for thirty hours, it was diluted with ice water and acidified with 20% HCl. The dark oily product which formed on acidification was separated, washed with water and dried over Drierite. On vacuum distillation, it gave 230 g. (1.22 moles, 81.2%) of pure o-bromothiophenol as a pale yellow colored oil. This had the physical properties: b.p. 92-4° (6 mm.), n_D^{28} 1.6295. Literature values (56); b.p. 96-8° (11 mm.), n_D^{24} 1.6321. Other thiophenols used in these preparations were made in a similar way.

2'-Bromophenyl-3, 5-dinitro-2-thienyl Sulfide

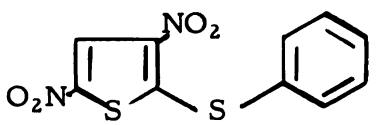


A solution containing 2.53 g. (0.01 mole) of 2-bromo-3, 5-dinitrothiophene dissolved in 70 ml. of methanol was placed in a 300 ml. two-necked flask fitted with a dropping funnel and a mechanical stirrer. The solution was maintained below 15° by immersion of the reaction flask in an ice bath. A 0.01 mole solution of potassium methoxide was prepared by dissolving 0.726 g. (0.011 mole) of potassium hydroxide pellets in 30 ml. of methanol. To the latter basic solution was added a 2.08 g. (0.011 mole) quantity of o-aminothiophenol and the mixture was stirred vigorously while cooling it by immersion in an ice bath. When the temperature of the alkaline mixture reached 4°, it was added dropwise to the stirred alcoholic solution of 2-bromo-3, 5-dinitrothiophene while holding its temperature below 15°. The purple red colored reaction solution was stirred for a half hour to complete the reaction after adding the thiol salt solution. The crude product which separated was collected by filtration, washed with ice cold water to remove the

inorganic materials and recrystallized from an acetone, water mixture (2:1) to obtain 3.21 g. (0.0089 mole, 89%) of a bright yellow colored crystalline product melting at 130-2°. Anal. calc'd for $C_{10}H_5N_2S_2O_4Br$: C, 33.25; H, 1.40; N, 7.76; S, 17.75; Br, 22.13. Found: C, 33.32; H, 1.45; N, 7.82; S, 17.71; Br, 22.08.

The intense purple coloration characteristic of aqueous acetone solution of N-phenyl-3, 5-dinitro-2-thienylamines failed to develop with these sulfides. The infrared spectrum of this material agreed with its assigned structure, and the n.m.r. spectrum gave the correct ratio of the single proton on the thiophene ring to the four protons on benzene ring (1:4).

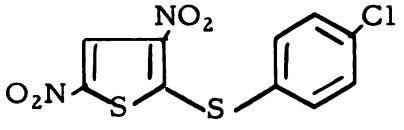
Phenyl-3, 5-dinitro-2-thienyl Sulfide



A modification of the procedure described by Yale (55) was employed in the preparation of this compound. A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene, dissolved in 30 ml. of methanol was placed in a 300 ml., two-necked flask fitted with a mechanical stirrer and a dropping funnel. The reaction flask was cooled by immersion in an ice bath. A potassium thiophenoxide solution, prepared by adding 0.726 g. (0.011 mole) of potassium hydroxide pellets dissolved in 10 ml. of methyl alcohol to 1.21 g. (0.011 mole) of thiophenol in 10 ml. of methanol, was added to the stirred halonitrothiophene solution, while holding the reaction temperature below 20°. The reaction mixture was stirred for twenty minutes at 20° after

adding the thiophenoxide solution to complete the reaction. The product was recovered by filtration, washed with water and recrystallized from an acetone, water mixture to obtain 2.4 g. (0.00851 mole, 85.1%) of a greenish yellow colored crystalline product melting at 155-6°. The purple coloration characteristic of aqueous acetone solution of the N-phenyl-3, 5-dinitro-2-thienylamines failed to develop with these sulfides. Anal. calc'd for $C_{10}H_6N_2S_2O_4$: C, 42.55; H, 2.14; N, 9.92; S, 22.72. Found: C, 42.77; H, 2.24; N, 9.66; S, 22.63. The same product was obtained in a 6% yield when the above synthesis was repeated with 24 hours stirring in the absence of a base.

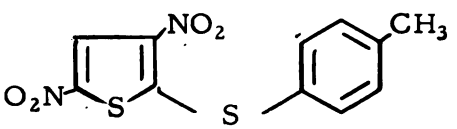
4'-Chlorophenyl-3, 5-dinitro-2-thienyl sulfide



The general experimental procedure described above was employed in the preparation of this compound. A 2.53 g. (0.01 mole) quantity of 2-bromo-3, 5-dinitrothiophene dissolved in 30 ml. of methanol was placed in a 250 ml. two-necked flask fitted with a stirrer, and a dropping funnel. The flask was cooled to 5° by immersion in an ice bath. A solution containing a 0.011 molar quantity of potassium p-chlorothiophenoxide was prepared by adding a solution containing 0.726 g. (0.011 mole) of potassium hydroxide pellets dissolved in 20 ml. of methanol to 1.59 g. (0.011 mole) of p-chlorothiophenol, cooled by immersion in an ice bath. The latter solution was stirred vigorously for several minutes and then added to the halonitrothiophene solution from the dropping funnel, in small quantities, while holding the reaction temperature below 15° throughout the reaction period which extended twenty minutes after adding the thiophenoxide solution to the reaction

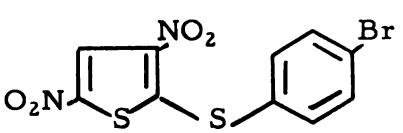
flask. The crude product was recovered by filtration and washed with water to remove inorganic materials. This was recrystallized from an acetone, water mixture to obtain 2.88 g. (0.0091 mole, 91%) of a yellow colored crystalline product melting at 132-4°. Anal. calc'd for $C_{10}H_5N_2S_2O_4Cl$: C, 37.92; H, 1.59; N, 8.85; S, 20.25; Cl, 11.19. Found: C, 37.96; H, 1.61; N, 9.09; S, 20.09 and Cl, 11.09.

4'-Methylphenyl-3,5-dinitro-2-thienyl Sulfide



The experimental procedure used in the preceding preparation was employed to obtain this material. The quantities of reagents used were: 1.265 g. (0.005 mole) of 2-bromo-3,5-dinitrothiophene, 0.682 g. (0.0055 mole) of p-methylthiophenol, 0.363 g. (0.0055 mole) of potassium hydroxide pellets. Recrystallization of the crude product from an acetone, alcohol mixture gave 0.97 g. (0.00321 mole, 64.2%) of a yellow colored crystalline product melting at 128-130°. Anal. calc'd for $C_{11}H_8N_2S_2O_4$: C, 44.59; H, 2.72; N, 9.46; S, 21.64. Found: C, 44.73; H, 2.49; N, 9.56; S, 21.71.

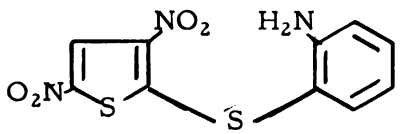
4'-Bromophenyl-3,5-dinitro-2-thienyl Sulfide



The general experimental procedure used in the two previous preparations was employed in making this compound. The quantities of reagents used were: 1.265 g. (0.005 mole) of 2-bromo-3,5-dinitrothiophene, 1.034 g. (0.0055 mole) of p-bromothiophenol and 0.363 g.

(0.0055 mole) of potassium hydroxide pellets. Recrystallization of the crude product from an acetone, water mixture gave 1.6 g. (0.00444 mole, 88.8%) of a yellow colored crystalline product melting at 133-4°. Anal. calc'd for $C_{10}H_5N_2S_2O_4Br$: C, 33.25; H, 1.40; N, 7.76; S, 17.75 and Br, 22.13. Found: C, 33.49; H, 1.67; N, 7.76; S, 17.67 and Br, 22.04.

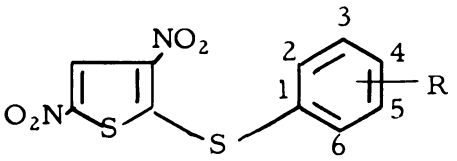
2'-Aminophenyl-3, 5-dinitro-2-thienyl Sulfide



A 6.325 g. (0.025 mole) quantity of 2-bromo-3, 5-dinitrothiophene was dissolved in 100 ml. of methanol and cooled to 20°. The solution was transferred to a 300 ml. three-necked flask fitted with a stirrer and a dropping funnel. While maintaining the temperature of the stirred halonitrothiophene solution, by means of a special cooling device, a 3.75 g. (0.03 mole) quantity of o-aminothiophenol was added to it from the dropping funnel. A red colored precipitate of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide separated from solution. When the aminothiophenol had been added, the reaction mixture was stirred for another half hour to ensure completion of the reaction. The crude product was recovered by filtration and recrystallized from an acetone, water mixture to obtain 7.2 g. (0.0242 mole, 96.8%) of a bright red colored crystalline product. It had a melting point of 164° (dec.). An analytical sample was dried for two days at 70°. The same product in the same yield was obtained in the presence of alcoholic KOH or dilute hydrochloric acid. The intense purple coloration characteristic of aqueous acetone solution of N-phenyl-3, 5-dinitro-2-thienylamines failed to develop with this sulfide. Anal. calc'd for $C_{10}H_7N_3S_2O_4$:

C, 40.40; H, 2.37; N, 14.13; S, 21.57. Found: C, 40.11; H, 2.73; N, 13.89; S, 21.56. The results of a Rast's molecular weight determination gave: Calc'd: 297; Found: 292. The material also showed infrared absorption peaks at 2.97 μ and 3.05 μ, characteristic of a primary amine. The structure was confirmed by its n.m.r. spectrum.

Table III. Properties and Analyses of Phenyl-3, 5-dinitro-2-thienyl Sulfides



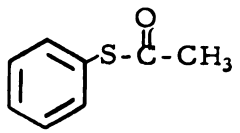
No.	R	Yield %	M.p.[c] °C	Formula
1	H	85.1	155-156[b]	$C_{10}H_6N_2S_2O_4$
2	4-Cl	91	132-134[b]	$C_{10}H_5N_2S_2O_4Cl$
3	4-CH_3	64.2	128-130[d]	$C_{11}H_8N_2S_2O_4$
4	4-Br	88.8	133-134[b]	$C_{10}H_5N_2S_2O_4Br$
5	2-Br	89	130-132[b]	$C_{10}H_5N_2S_2O_4Br$
6	2-NH_2	96.8	164[b]	$C_{10}H_7N_3S_2O_4$

a) Microanalyses were carried out by the Microtech. Laboratories, Skokie, Ill.
b) Recrystallized from an acetone, water mixture.
c) Dried at 60° for several days.
d) Crystallized from an acetone, ethyl alcohol mixture.

Analyses, %[a]										
Carbon		Hydrogen		Nitrogen		Sulfur		Halogen		
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Name	Calcd	Found
42.55	42.77	2.14	2.24	9.92	9.66	22.72	22.63			
37.92	37.96	1.59	1.61	8.85	9.09	20.25	20.09	Cl	11.19	11.09
44.59	44.73	2.72	2.49	9.46	9.56	21.64	21.71			
33.25	33.49	1.40	1.67	7.76	7.76	17.75	17.67	Br	22.13	22.04
33.25	33.32	1.40	1.45	7.76	7.82	17.75	17.71	Br	22.13	22.08
40.40	40.11	2.37	2.73	14.13	13.89	21.57	21.56			

2'-Amidophenyl-3, 5-dinitro-2-thienyl Sulfides

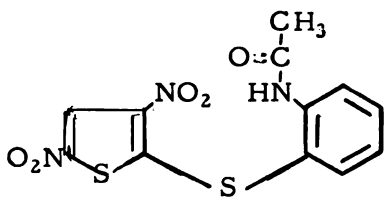
Phenyl Thiolacetate



The purpose in preparing this thiolester (97) was to determine whether thiophenol could be acylated under the experimental conditions used to acylate the amines, prepared during the course of the present investigation.

A mixture containing 11.0 g. (0.1 mole) of thiophenol and 78.5 g. (1.0 mole) of acetyl chloride was heated at its reflux temperature on a steam bath for an hour. The excess acetyl chloride was then removed by distillation (b.p. 52°). Distillation was continued, collecting the product (13.68 g., 0.09 mole, 90%) boiling in the range 240-243°. Anal. calc'd for C_8H_8SO: C, 63.13; H, 5.30; S, 21.07. Found: C, 62.93; H, 5.36 and S, 20.83.

2'-Acetamidophenyl-3, 5-dinitro-2-thienyl Sulfide

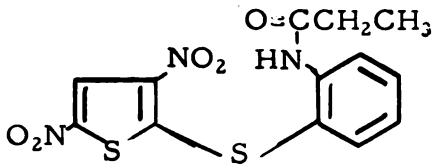


To 1.5 g. (0.00505 mole) of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide contained in a 300 ml. three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel was added 78.5 g. (1.0 mole) of acetyl chloride. The mixture was heated at its reflux temperature on a steam bath until the solid dissolved (45 minutes). Additional

quantities of acetyl chloride could be added if complete solution of the sulfide was not obtained. Excess acetyl chloride was then removed by distillation at atmospheric pressure, leaving a yellowish green colored residue of 2'-acetamidophenyl-3, 5-dinitro-2-thienyl sulfide. This was recrystallized from an acetone, water mixture (4:1) to obtain 1.7 g. (0.005015 mole, 99.3%) of yellowish green colored plates of 2'-acetamidophenyl-3, 5-dinitro-2-thienyl sulfide. The pure sulfide melted at 218-221°. Anal. calc'd for $C_{12}H_9N_3S_2O_5$: C, 42.43; H, 2.67; N, 12.38; S, 18.90. Found: C, 42.62; H, 2.88; N, 12.34; S, 18.66.

The same product was also obtained but in a lower yield (82%) by using acetic anhydride as the acylating agent in place of acetyl chloride. Infra red absorption of this material showed singlet peaks at 3.11 μ (m) and 6.05 μ (s) characteristic of secondary amides. The n.m.r. spectra of these amides confirm the assigned structures.

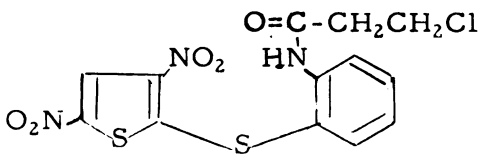
2' - Propionamidophenyl - 3, 5-dinitro-2-thienyl Sulfide



To 1.485 g. (0.005 mole) of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide contained in a 300 ml. three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel, was added 46.25 g. (0.5 mole) of propionyl chloride (b.p. 80°) from the dropping funnel. The vigorously stirred mixture was heated at its reflux temperature on a steam bath until the sulfide dissolved. The clear solution was concentrated on a steam bath, cooled and the bright greenish yellow colored platelets of product were separated by filtration. This crude product was recrystallized from ethanol to obtain 1.6 g. (0.004816 mole, 96.3%)

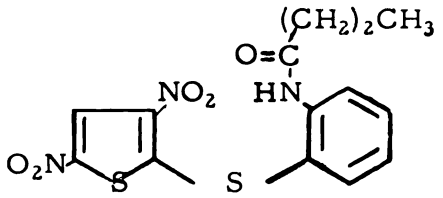
of 2'-propionamidophenyl-3,5-dinitro-2-thienyl sulfide in the form of bright greenish yellow colored plates. The pure product melted at 177.5-178.5°. Anal. calc'd for $C_{13}H_{11}N_3S_2O_5$: C, 44.19; H, 3.14; N, 11.89; S, 18.15. Found: C, 44.11; H, 3.04; N, 11.98; S. 18.10.

2'-β-Chloropropionamidophenyl-3,5-dinitro-2-thienyl Sulfide



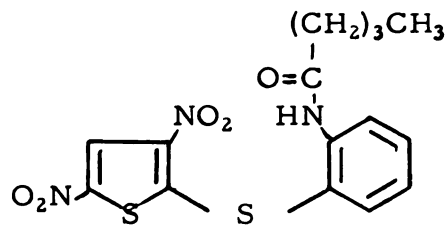
To a solution of 2 g. (0.006734 mole) of 2'-aminophenyl-3,5-dinitro-2-thienylsulfide dissolved in 30 ml. of acetone, contained in a 200 ml. three-necked flask equipped with a dropping funnel and a stirrer was added 31.75 g. (0.25 mole) of β-chloropropionyl chloride. A spontaneous exothermic reaction occurred with the liberation of a considerable amount of heat and hydrogen chloride evolution. The reaction was completed by stirring the reaction mixture moderately for 3 days at room temperature. The product was isolated by adding ice-cold water, to the stirred reaction mixture and recovering the light greenish yellow colored product by filtration. Recrystallization of the crude product from methanol, after decolorizing it with carbon afforded 2.4 g. (0.00619 mole, 92%) of pure 2'-β-chloropropionamidophenyl-3,5-dinitro-2-thienyl sulfide. This material was dried at 60° for four days. Its melting point was 144-5°. Anal. calc'd for $C_{13}H_{10}N_3S_2O_5Cl$: C, 40.26; H, 2.60; N, 10.84; S, 16.54; Cl, 9.14. Found: C, 40.29; H, 2.65; N, 10.66; S, 16.38 and Cl, 9.18.

2'-Butyramidophenyl-3,5-dinitro-2-thienyl Sulfide



A 2.97 g. (0.01 mole) quantity of 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide was placed in a 300 ml. three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel. A 53.25 g. (0.5 mole) quantity of n-butyryl chloride (b.p. 102°) was added to the sulfide from the dropping funnel and the reaction mixture was heated at its reflux temperature by immersion in an oil bath until the sulfide dissolved (20 minutes). The reaction solution was concentrated and cooled to precipitate a greenish yellow colored solid. This was separated by filtration and recrystallized from ethanol to obtain 3.6 g. (0.0098 mole, 98%) of 2'-n-butyramidophenyl-3,5-dinitro-2-thienyl sulfide in the form of greenish yellow colored glistening crystals. The pure product melted at 165.5-166.5°. Anal. calc'd for $C_{14}H_{13}N_3S_2O_5$: C, 45.77; H, 3.57; N, 11.44; S, 17.46. Found: C, 45.89; H, 3.56; N, 11.59 and S, 17.32.

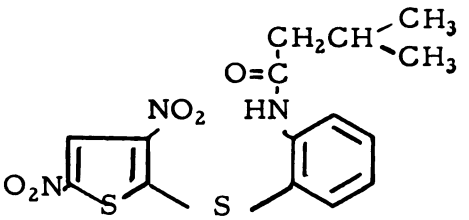
2'-Valeramidophenyl-3,5-dinitro-2-thienyl Sulfide



The experimental procedure used to obtain this amide was the same as that described in the previous preparation. A 1.0 g. (0.003367 mole) quantity of 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide was placed in a 250 ml. three-necked flask fitted with a reflux

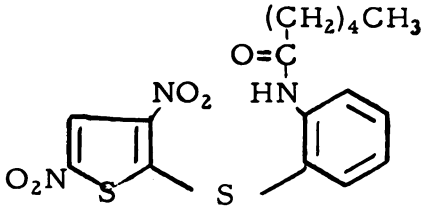
condenser, a stirrer and a dropping funnel. A 24.1 g. (0.2 mole) quantity of valeryl chloride was added and the mixture heated at its reflux temperature on a steam bath for twenty minutes. On cooling, the crude product precipitated as a yellowish green solid. This was separated by filtration and the crude 2'-valeramidophenyl-3, 5-dinitro-2-thienyl sulfide was recrystallized from an acetone, water mixture to yield 1.22 g. (0.0032 mole, 95%) of a pure material melting at 154-5°. Anal. calc'd for $C_{15}H_{15}N_3S_2O_5$: C, 47.23; H, 3.96; N, 11.02; S, 16.81. Found: C, 47.39; H, 3.94; N, 11.16; S, 16.60.

2'-Isovaleramidophenyl-3, 5-dinitro-2-thienyl Sulfide



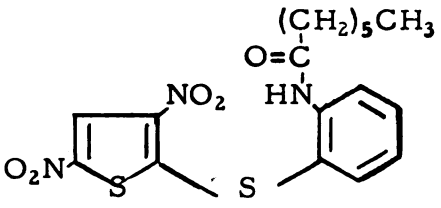
Following the procedure described above, a 24.1 g. (0.2 mole) of isovaleryl chloride was added to 1.485 g. (0.005 mole) of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide. The reaction mixture was heated at its reflux temperature by immersion in an oil bath for twenty minutes, cooled and the precipitate separated by filtration. Recrystallization of the crude product from ethanol afforded 1.85 g. (0.004855 mole, 97.1%) of 2'-isovaleramidophenyl-3, 5-dinitro-2-thienyl sulfide in the form of greenish yellow colored needles, melting at 176-7°. The analytical sample was recrystallized two times from ethanol and dried at 60° for three days. Anal. calc'd for $C_{15}H_{15}N_3S_2O_5$: C, 47.23; H, 3.96; N, 11.02; S, 16.81. Found: C, 47.50; H, 4.08; N, 11.14 and S, 16.76.

2'-Hexanamidophenyl-3, 5-dinitro-2-thienyl Sulfide



This amide was prepared using the procedure previously described. To a 1.0 g. (0.003367 mole) quantity of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide dissolved in a 15 ml. volume of acetone was added a 13.45 g. (0.1 mole) quantity of hexanoyl chloride. The reaction mixture was heated at its reflux temperature on a steam bath for twenty minutes. On cooling the reaction mixture, the precipitate which formed was recovered by filtration and recrystallized from an acetone, water mixture to obtain 1.29 g. (0.003266 mole, 97%) of a yellowish green colored crystalline product melting at 152-3°. Anal. calc'd for $C_{16}H_{17}N_3S_2O_5$: C, 48.60; H, 4.33; N, 10.63; S, 16.22. Found: C, 48.40; H, 4.23; N, 10.79 and S, 16.28.

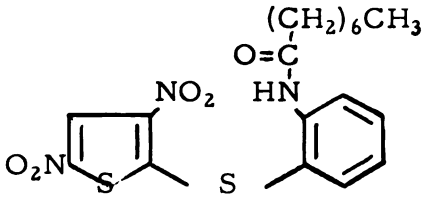
2'-Heptamidophenyl-3, 5-dinitro-2-thienyl Sulfide



The identical experimental procedure and apparatus used to obtain the preceding compound was employed in the synthesis of this material. The quantities of the reagents used were: 1.0 g. (0.003367 mole) of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide dissolved in 20 ml. of acetone and 14.85 g. (0.1 mole) of heptanoyl chloride. Isolation of the product was accomplished as previously described and

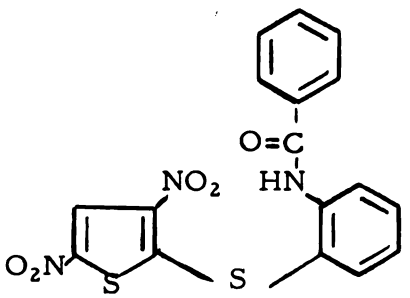
recrystallization of the crude product from methanol gave 1.3 g. (0.00318 mole, 94.4%) of a dull yellow colored material after treatment with decolorizing carbon. This compound melted at 142-3°. Anal. calc'd for $C_{17}H_{19}N_3S_2O_5$: C, 49.86; H, 4.68; N, 10.26; S, 15.66. Found: C, 50.14; H, 4.70; N, 10.19; S, 15.48.

2'-Octanamidophenyl-3, 5-dinitro-2-thienyl Sulfide



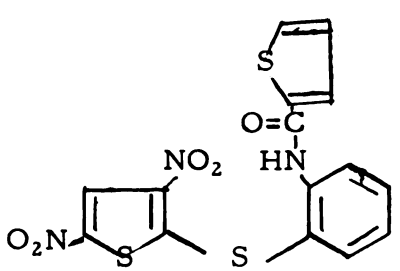
The same general experimental procedure and apparatus used to obtain the previous compound was employed to obtain this mixed heterocyclic aromatic sulfide. To 1.0 g. (0.003367 mole) of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide, dissolved in 20 ml. of acetone and contained in a 250 ml. three-necked flask fitted with a reflux condenser, was added a solution containing 11.375 g. (0.07 mole) of octanoyl chloride dissolved in 10 ml. of acetone. The reaction mixture was heated at its reflux temperature on a steam bath for twenty minutes and later cooled. Crushed ice (50 g.) was added to the dark oily mass and the mixture was scratched with a glass rod to induce crystallization of a massive dark yellow colored precipitate. The crude product was collected on a filter paper, washed with ice-cold water and recrystallized from methanol, using Norite A to decolorize the material. The still dull yellow colored platelets of 2'-octanamidophenyl-3, 5-dinitro-2-thienyl sulfide, after drying at 56° for two days, weighed 1.3 g. (0.00307 mole, 91.3%) and melted at 136-7°. Anal. calc'd for $C_{18}H_{21}N_3S_2O_5$: C, 51.05; H, 5.00; N, 9.92; S, 15.14. Found: C, 50.98; H, 4.96; N, 10.08 and S, 15.35.

2'-Benzamidophenyl-3,5-dinitro-2-thienyl Sulfide



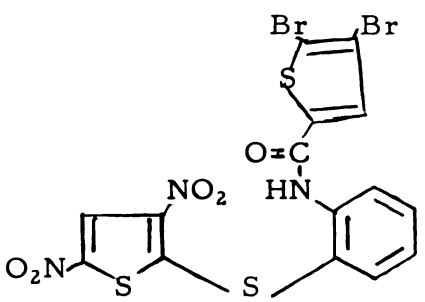
A 1.2 g. (0.00404 mole) quantity of o-aminophenyl-3,5-dinitro-2-thienyl sulfide, dissolved in 40 ml. of acetone was transferred to a 250 ml. three-necked flask fitted with a reflux condenser, a stirrer and a dropping funnel. A 28.1 g. (0.2 mole) quantity of benzoyl chloride was added to the nitrothienyl sulfide solution from the dropping funnel. After heating the reaction mixture at its reflux temperature for seven minutes, the color changed from brown to green and finally to a yellowish green color. The reaction mixture was cooled and the greenish yellow solid collected by filtration (34.5 g.). The weight of the product suggested that a lot of the benzoyl chloride was retained in the caked product. The pure product was obtained by recrystallization from an acetone, ethanol mixture (2:1). A second recrystallization from the same solvent yielded 1.601 g. (0.004 mole, 99%) of yellowish green platelets of 2'-benzamidophenyl-3,5-dinitro-2-thienyl sulfide melting at 213.5-214.5°. Anal. calc'd for $C_{17}H_{11}N_3S_2O_5$: C, 50.87; H, 2.76; N, 10.47 and S, 15.98. Found: C, 50.99; H, 2.75; N, 10.72 and S, 15.72.

2'-(2-Thenamido)phenyl-3,5-dinitro-2-thienyl Sulfide



A solution containing 2.97 g. (0.01 mole) of 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide dissolved in 20 ml. of acetone was placed in a 300 ml. three-necked flask fitted with a stirrer and a dropping funnel. Another solution prepared from 7.325 g. (0.05 mole) of 2-thenoyl chloride dissolved in 10 ml. of acetone was added in small portions from the dropping funnel to the stirred nitrothienyl sulfide solution. After adding the acid chloride, the reaction mixture was stirred slowly at room temperature for two days. The reaction solution was concentrated in vacuo and the yellow precipitate was collected by filtration. Recrystallization from an acetone, water mixture (4:1) after treatment with Norite A afforded 3.52 g. (0.00865 mole, 86.5%) of the pure product in the form of yellow colored glistening needles. The pure material melted at 184.5-185.5°.
Anal. calc'd for $C_{15}H_9N_3S_3O_5$: C, 44.22; H, 2.23; N, 10.31; S, 23.61.
Found: C, 44.41; H, 2.36; N, 10.31; and S, 23.51.

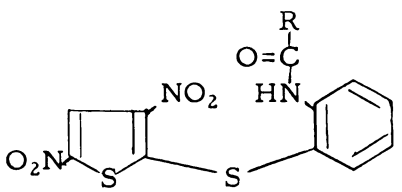
2'-(4,5-Dibromo-2-thenamido)phenyl-3,5-dinitro-2-thienyl Sulfide

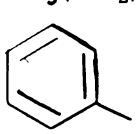
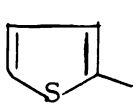
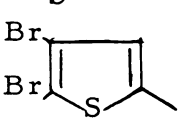


A solution containing 2.97 g.(0.01 mole) of 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide, dissolved in 30 ml. of acetone, was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a thermometer. The reaction flask was immersed in an ice bath and a solution prepared from 6.09 g. (0.02 mole) of 4,5-dibromo-2-thenoyl chloride and 10 ml. of acetone was slowly

added from the dropping funnel to the stirred nitrothienyl sulfide solution. After a half-hour of constant stirring of the reaction mixture, the ice bath was removed and the mixture was stirred at room temperature for four days. The greenish colored precipitate which separated was filtered and recrystallized from acetone, after decolorization with Norite A, to yield 3.95 g. (0.007 mole, 70%) of a yellowish green product. This melted at 220-221° after drying at 60° for two days. Anal. calc'd for $C_{15}H_7N_3S_3O_5Br_2$: C, 31.87; H, 1.25; N, 7.43; S, 17.02; Br, 28.27. Found: C, 32.38; H, 1.36; N, 7.45; S, 16.66 and Br, 27.72.

Table IV. Properties and Analyses of 2'-Amidophenyl-3, 5-dinitro-2-thienyl Sulfides



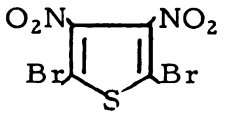
No.	R	Yield %	M.p.[c] °C	Formula
1	CH_3-	99.3	218-221 [b]	$C_{12}H_9N_3S_2O_5$
2	CH_3CH_2-	96.3	177.5-178.5 [d]	$C_{13}H_{11}N_3S_2O_5$
3	$ClCH_2CH_2$-	92	144-145 [e]	$C_{13}H_{10}N_3S_2O_5Cl$
4	$CH_3CH_2CH_2$-	98	165.5-166.5 [d]	$C_{14}H_{13}N_3S_2O_5$
5	$CH_3CH_2CH_2CH_2$-	95	154-155 [b]	$C_{15}H_{15}N_3S_2O_5$
6	$(CH_3)_2CHCH_2$-	97.1	176-177 [d]	$C_{15}H_{15}N_3S_2O_5$
7	$CH_3(CH_2)_4$-	97	152-153 [b]	$C_{16}H_{17}N_3S_2O_5$
8	$CH_3(CH_2)_5$-	94.4	142-143 [e]	$C_{17}H_{19}N_3S_2O_5$
9	$CH_3(CH_2)_6$	91.3	136-137 [e]	$C_{18}H_{21}N_3S_2O_5$
10		99	213.5-214.5 [f]	$C_{17}H_{11}N_3S_2O_5$
11		86.5	184.5-185.5 [b]	$C_{15}H_9N_3S_3O_5$
12		70	220-221 [g]	$C_{15}H_7N_3S_3O_5Br_2$

a) Microanalyses were carried out by Microtech Laboratories, Skokie, Illinois.
b) Recrystallized from an acetone, water mixture.
c) Dried at 60° for several days.
d) Recrystallized from ethanol.
e) Recrystallized from methanol.
f) Recrystallized from an acetone-ethanol mixture.
g) Recrystallized from acetone.

Analyses, % [a]										
Carbon		Hydrogen		Nitrogen		Sulfur		Halogen		
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Name	Calcd	Found
42.43	42.62	2.67	2.88	12.38	12.34	18.90	18.66			
44.19	44.11	3.14	3.04	11.89	11.98	18.15	18.10			
40.26	40.29	2.60	2.65	10.84	10.66	16.54	16.38	Cl	9.14	9.18
45.77	45.89	3.57	3.56	11.44	11.59	17.46	17.32			
47.23	47.39	3.96	3.94	11.02	11.16	16.81	16.60			
47.23	47.50	3.96	4.08	11.02	11.14	16.81	16.76			
48.60	48.40	4.33	4.23	10.63	10.79	16.22	16.28			
49.86	50.14	4.68	4.70	10.26	10.19	15.66	15.48			
51.05	50.98	5.00	4.96	9.92	10.08	15.14	15.35			
50.87	50.99	2.76	2.75	10.47	10.72	15.98	15.72			
44.22	44.41	2.23	2.36	10.31	10.31	23.61	23.51			
32.87	32.38	1.25	1.36	7.43	7.45	17.02	16.66	Br	28.27	27.72

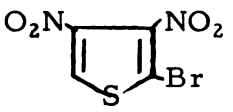
3, 4-Dinitro-2, 5-bis-thiophenoxythiophenes

2, 5-Dibromo-3, 4-dinitrothiophene



The general experimental procedure described by Mozingo (83) was employed in the preparation of this thiophene derivative. Into a three-liter three-necked flask, fitted with a dropping funnel and a stirrer, was placed 400 ml. of concentrated sulfuric acid. The third neck of the flask was left open as a vent for nitrous oxide fumes. The stirred acid was cooled to -5° by immersion of the reaction flask in an acetone-ice bath and a 500 ml. volume of fuming sulfuric acid was added slowly from the dropping funnel. This was followed by the addition of 350 ml. of concentrated nitric acid. A 351.0 g. (1.45 moles) quantity of 2, 5-dibromothiophene was then added dropwise to the mixed acids at such a rate that the reaction temperature remained between 15 and 20°. Nitration was completed by stirring the reaction mixture for one hour after adding the 2, 5-dibromothiophene. The reaction mixture was then poured into a four liter beaker containing crushed ice. A brown slurry developed. The aqueous layer was removed by decantation and the dark product was washed several times with ice water to remove as much acid as possible. The crude product (220.0 g.) was then filtered, washed again with ice water and crystallized from methanol (13 ml./g.) to obtain 15.5 g. (0.467 mole, 32.2%) of a light yellow colored crystalline product melting at 135°. Anal. calc'd for $C_4N_2SO_4Br_2$: C, 14.47; N, 8.44; S, 9.66 and Br, 48.15. Found: C, 14.74; N, 8.53; S, 9.55 and Br, 48.04.

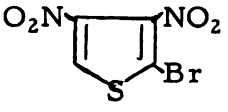
2-Bromo-3, 4-dinitrothiophene



Method A

This compound was prepared by a modification of the procedure described by Blatt (98). To a solution containing 20 g. (0.06024 mole) of 2, 5-dibromo-3, 4-dinitrothiophene dissolved in 200 ml. of precooled acetone (10-15°) were added 36 ml. (0.03 mole) of hypophosphorous acid. The reaction temperature was not allowed to rise above 10°. The reaction mixture initially developed an orange red color and a mildly exothermic reaction occurred during the following five minutes, after which the mixture was set aside at room temperature for three hours. It was poured into water and formed a whitish yellow colored precipitate. It was recovered by filtration (24 g.) and recrystallized from methyl alcohol (2 cc./g.) to obtain 14.5 g. (0.0573 mole, 95%) of a dull white crystalline product melting at 89°. Literature value (98) 88-9°.

2-Bromo-3, 4-dinitrothiophene

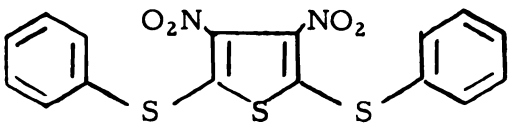


Method B

This compound was prepared by an alternate method described by Blatt (98). A solution containing 45 g. (0.3 mole) of sodium iodide

dissolved in 125 ml. of acetone was cooled to 10-15° and added to a precooled solution (10-15°) prepared from 20 g. (0.06024 mole) of the dibromodinitrothiophene, 100 ml. of acetone and 20 ml. of glacial acetic acid. The reaction mixture developed an orange, yellow color and a precipitate (NaBr) was formed. After it had been set aside for eight days at -10°, the reaction mixture was poured into 800 ml. of water containing 10 g. of sodium bisulfite. Treatment with the bisulfite removed the majority of the color leaving a grey colored precipitate of the crude bromodinitrothiophene that weighed 15 g. and melted at 87°. Recrystallization of the crude product from methanol gave 14.3 g. (0.566 mole, 94%) of a colorless crystalline product melting at 89-90°. Literature value (98) m.p. 88-9°.

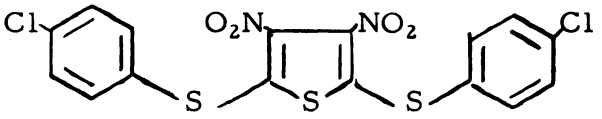
3,4-Dinitro-2,5-bis-thiophenoxythiophene



A solution containing 1.0 g. (0.003 mole) of 2,5-dibromo-3,4-dinitrothiophene dissolved in 45 ml. of methyl alcohol was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a thermometer extending below the level of the alcohol solution. The solution was cooled to 5° by immersion of the reaction flask in an ice bath. A second solution prepared from 0.4356 g. (0.0066 mole) of KOH pellets, 15 ml. of methyl alcohol and 0.726 g. (0.0066 mole) of thiophenol was added to an Erlenmeyer flask immersed in a freezing mixture. It was stirred for five minutes and then added to the stirred solution of the dibromodinitrothiophene through the dropping funnel. During the addition of the potassium thiophenoxide the reaction

temperature was held below 10°. The blood red colored alkaline reaction solution was stirred for an additional half-hour during which the 3, 4-dinitro-2, 5-bis-thiophenoxythiophene precipitated. The crude product was collected by filtration, washed with water to remove soluble inorganic materials and recrystallized from an acetone, water mixture (2:1) to obtain 1.1 g. (0.00282 mole, 94%) of an orange yellow colored crystalline product melting at 172-173°. Anal. calc'd for $C_{16}H_{10}N_2S_3O_4$: C, 49.22; H, 2.58; N, 7.18 and S, 24.64. Found: C, 49.25; H, 2.64; N, 7.24 and S, 24.40.

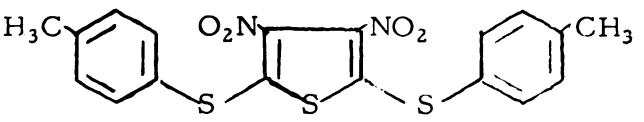
3, 4-Dinitro-2, 5-bis-4'-chlorothiophenoxythiophene



Utilizing the experimental procedure described above for the preparation of 3, 4-dinitro-2, 5-bis-thiophenoxythiophene, a 3.32 g. (0.01 mole) quantity of 2, 5-dibromo-3, 4-dinitrothiophene dissolved in 30 ml. of methyl alcohol was placed in a 300 ml. three-necked flask fitted with a thermometer, a stirrer and a dropping funnel and cooled to -5° by immersion in freezing mixture. A second solution containing 0.022 mole of potassium p-chlorothiophenoxide was prepared by mixing for five minutes, a solution of 1.452 g. (0.022 mole) of KOH pellets dissolved in 30 ml. of methanol with 3.179 g. (0.022 mole) of p-chlorothiophenol dissolved in 30 ml. of methanol. The p-chlorothiophenolate solution was cooled to 5° and added to the stirred dibromodinitrothiophene. The reaction temperature was held below 20°, during the thirty minutes reaction period. The crude product was recovered by filtration, and washed with water to remove inorganic materials.

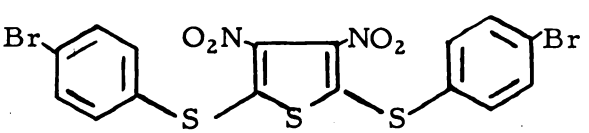
Recrystallization of the crude product from an acetone, water mixture yielded 4.14 g. (0.00902 mole, 90.2%) of a yellow colored crystalline solid melting at 215-217°. Anal. calc'd for $C_{16}H_8N_2S_3O_4Cl_2$: C, 41.84; H, 1.75; N, 6.10; S, 20.94; Cl, 15.44. Found: C, 41.52; H, 1.94; N, 6.19; S, 21.07 and Cl, 15.61.

3,4-Dinitro-2,5-bis-4'-methylthiophenoxythiophene



The general experimental procedure described previously for the preparation of 3,4-dinitro-2,5-bis-thiophenoxythiophene was employed in the preparation of this compound. The quantities of reagents used were: 3.32 g. (0.01 mole) of 2,5-dibromo-3,4-dinitrothiophene, 2.728 g. (0.022 mole) of p-methylthiophenol and 1.452 g. (0.022 mole) of KOH pellets. Recrystallization of the crude product from an acetone, methanol mixture yielded 3.14 g. (0.00751 mole, 75.1%) of a yellow colored crystalline pure material melting at 215-6°. Anal. calc'd for $C_{18}H_{14}N_2S_3O_4$: C, 51.66; H, 3.37; N, 6.70 and S, 22.99. Found: C, 51.87; H, 3.61; N, 6.84 and S, 22.71.

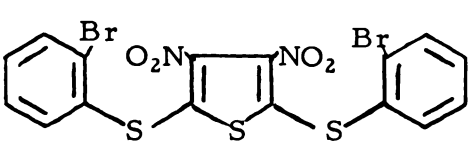
3,4-Dinitro-2,5-bis-4'-bromothiophenoxythiophene



Utilizing the procedure described previously for the synthesis of 3,4-dinitro-2,5-bis-thiophenoxythiophene, a solution containing 1.66 g.

(0.005 mole) of 2, 5-dibromo-3, 4-dinitrothiophene dissolved in 40 ml. of methyl alcohol was placed in a 300 ml. three-necked flask fitted with a thermometer, a stirrer and a dropping funnel. The reaction flask was immersed in an ice bath and its contents were maintained at 15°. To a second flask immersed in an ice bath and containing 2.08 g. (0.011 mole) of p-bromothiophenol, dissolved in 25 ml. of methyl alcohol was added 0.726 g. (0.011 mole) of KOH pellets dissolved in 25 ml. of methanol. The p-bromothiophenolate solution was stirred for ten minutes and then added to the reaction flask containing the well stirred dibromodinitrothiophene solution. The reaction temperature was held below 18° throughout the reaction period of forty minutes. The crude product was collected by filtration and washed with water to remove inorganic materials. Recrystallization of the crude product from an acetone, water mixture gave 2.6 g. (0.00474 mole, 94.8%) of a yellow colored crystalline material melting at 246-247°. Anal. calc'd for $C_{16}H_8N_2S_3O_4Br_2$: C, 35.05; H, 1.47; N, 5.11; S, 17.55 and Br, 29.15. Found: C, 35.15; H, 1.54; N, 5.13; S, 17.45 and Br, 29.30.

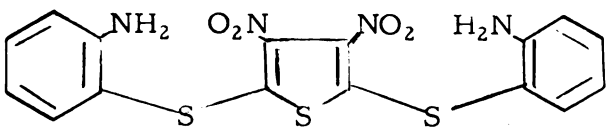
3, 4-Dinitro-2, 5-bis-2'-bromothiophenoxythiophene



The general experimental procedure described above was used to obtain this compound. The quantities of reagents used were: 3.32 g. (0.01 mole) of 2, 5-dibromo-3, 4-dinitrothiophene, 1.452 g. (0.022 mole) of KOH pellets and 4.158 g. (0.022 mole) of o-bromothiophenol. Recrystallization of the crude product from an acetone, water mixture

gave 4.1 g. (0.00748 mole, 74.8%) of a bright yellow colored pure crystalline product melting at 149-150°. Anal. calc'd for $C_{16}H_8N_2S_3O_4Br_2$: C, 35.05; H, 1.47; N, 5.11; S, 17.55 and Br, 29.15. Found: C, 35.24; H, 1.43; N, 5.37; S, 17.62 and Br, 29.28.

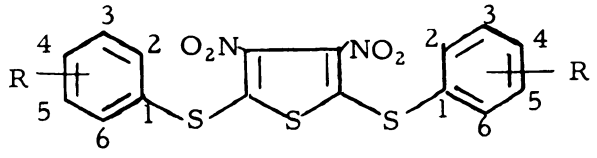
3,4-Dinitro-2,5-bis-2'-aminothiophenoxythiophene



To a solution containing 1.452 g. (0.022 mole) of potassium hydroxide pellets, dissolved in 20 ml. of methyl alcohol was added a 2.75 g. (0.022 mole) quantity of o-aminothiophenol. The alkaline aminobenzenethiolate solution was stirred, cooled to 5° and added to a reaction flask fitted with a thermometer, a stirrer, a dropping funnel and containing a solution prepared from 3.32 g. (0.01 mole) of 2,5-dibromo-3,4-dinitrothiophene and 40 ml. of methanol and pre-cooled to 10°. Addition of the aminobenzene thiolate was done at such a rate that the reaction temperature was held below 15°. The reaction mixture was stirred for twenty minutes after adding the amino-benzenethiolate to complete the reaction. The precipitate produced was collected by filtration, washed with water to remove soluble inorganic salts. Recrystallization of the crude product from an acetone, water mixture yielded 3.5 g. (0.00833 mole, 83.3%) of an orange yellow colored pure crystalline product melting at 163°. Anal. calc'd for $C_{16}H_{12}N_4S_3O_4$: C, 45.70; H, 2.88; N, 13.32; S, 22.88. Found: C, 45.58; H, 2.85; N, 13.31 and S, 22.94. Molecular weight determination on this material gave: calc'd 420 g.; Found 435 g. The infrared absorption determinations on the pure material showed peaks at 3.0 μ

and 3.05 μ characteristic of a primary amine. The assigned structure was confirmed by its n.m.r. spectrum.

Table V. Properties and Analyses of 3, 4-dinitro-2, 5-bis-thiophenoxythiophenes



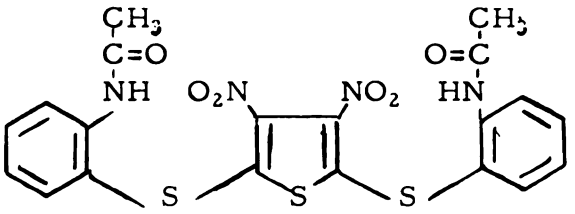
No.	R	Yield %	M.p.[b] °C.	Formula
1	H	94	172-173[c]	$C_{16}H_{10}N_2S_3O_4$
2	4-Cl	90.2	215-217[c]	$C_{16}H_8N_2S_3O_4Cl_2$
3	4-CH_3	75.1	215-216[d]	$C_{18}H_{14}N_2S_3O_4$
4	4-Br	94.8	246-247[c]	$C_{16}H_8N_2S_3O_4Br_2$
5	2-Br	74.8	149-150[c]	$C_{16}H_8N_2S_3O_4Br_2$
6	2-NH_2	83.3	163[c]	$C_{16}H_{12}N_4S_3O_4$

a) Microanalyses were done by Microtech Laboratories, Skokie, Illinois.
b) Dried at 60° for several days.
c) Recrystallized from an acetone, water mixture.
d) Recrystallized from an acetone, methanol mixture.

Analyses, %[a]										
Carbon		Hydrogen		Nitrogen		Sulfur		Halogen		
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Name	Calcd	Found
49.22	49.25	2.58	2.64	7.18	7.24	24.64	24.40			
41.84	41.52	1.75	1.94	6.10	6.19	20.94	21.07	Cl	15.44	15.61
51.66	51.87	3.37	3.61	6.70	6.84	22.99	22.71			
35.05	35.15	1.47	1.54	5.11	5.13	17.55	17.45	Br	29.15	29.30
35.05	35.24	1.47	1.43	5.11	5.37	17.55	17.62	Br	29.15	29.28
45.70	45.58	2.88	2.85	13.32	13.31	22.88	22.94			

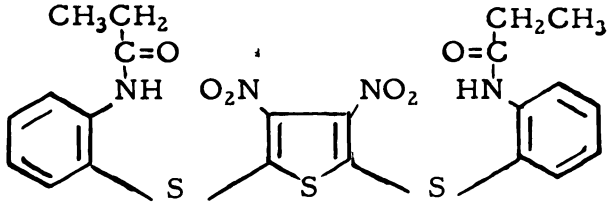
3, 4-Dinitro-2, 5-bis-2'-amidothiophenoxythiophenes

3, 4-Dinitro-2, 5-bis-2'-acetamidothiophenoxythiophene



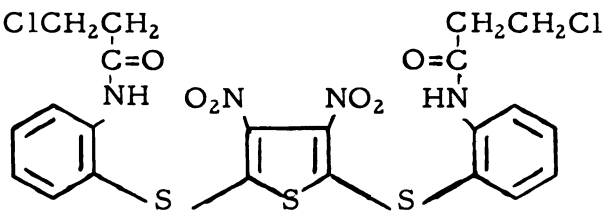
A 1.25 g. (0.00298 mole) quantity of 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophene was placed in a 300 ml. three-necked flask fitted with a reflux condenser, a stirrer and a dropping funnel. A 39.25 g. (0.5 mole) quantity of acetyl chloride was added to the aminonitrothiophene solution and the mixture was heated at its reflux temperature on a steam bath for one hour. About 80% of the excess acetyl chloride was removed by distillation. The reaction mixture was cooled and the crude product separated by filtration and recrystallization from an acetone, water mixture to obtain 1.43 g. (0.002837 mole, 95.2%) of a greenish yellow colored material in the form of plates, melting at 260.5-261°. Anal. calc'd for $C_{20}H_{16}N_4S_3O_6$: C, 47.61; H, 3.20; N, 11.10; S, 19.07. Found: C, 47.79; H, 3.20; N, 71.08 and S, 19.10. An infrared absorption spectrum of this material showed peaks at 3.16 μ (singlet) and 6.07 μ (singlet) characteristic of secondary amides.

3, 4-Dinitro-2, 5-bis-2'-propionamidothiophenoxythiophene



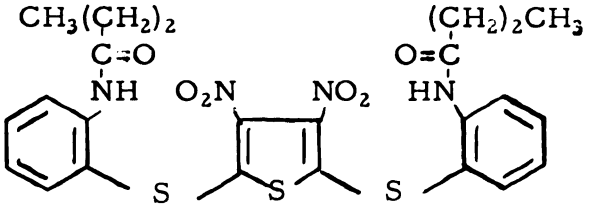
To 1.5 g. (0.00357 mole) of 3,4-dinitro-2,5-bis-2'-aminothiophenoxythiophene was added 46.25 g. (0.5 mole) of propionyl chloride. The reaction mixture was heated at its reflux temperature for a half-hour on a steam bath. On cooling the reaction mixture, a yellow product, melting at 189-199.5°, separated from solution. This was recrystallized from an acetone, water mixture to yield 1.35 g. (0.002538 mole, 71.1%) of a pure yellow colored product melting at 202-203°. Anal. calc'd for $C_{22}H_{20}N_4S_3O_6$: C, 49.61; H, 3.79; N, 10.52 and S, 18.06. Found: C, 49.69; H, 3.77; N, 10.65 and S, 17.36.

3,4-Dinitro-2,5-bis-2'-β-chloropropionamidothiophenoxythiophene



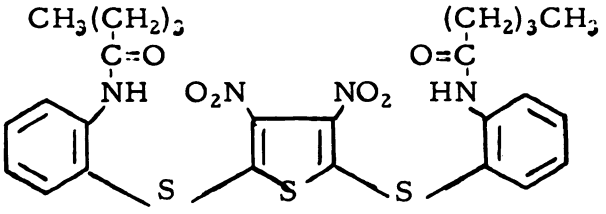
A 1.0 g. (0.00238 mole) quantity of 3,4-dinitro-2,5-bis-2'-aminothiophenoxythiophene was added to 25.4 g. (0.2 mole) of β-chloropropionyl chloride. A spontaneous exothermic reaction occurred liberating a considerable amount of heat. When the initial reaction had subsided the reaction mixture was stirred at room temperature for three days. Crushed ice (20 g.) was then added to the mixture and the green colored precipitate was collected by filtration and recrystallized from an acetone, methanol mixture, dried at 60° for seven days to obtain 1.4 g. (0.00233 mole, 98%) of an orange yellow colored pure crystalline product melting at 178-179°. Anal. calc'd for $C_{22}H_{18}N_4S_3O_6Cl_2$: C, 43.93; H, 3.02; N, 9.31; S, 15.99 and Cl, 11.79. Found: C, 44.01; H, 3.08; N, 9.29; S, 16.14 and Cl, 11.94.

3, 4-Dinitro-2, 5-bis-2'-butyramidothiophenoxythiophene



A 1.88 g. (0.00448 mole) quantity of 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophene was placed in a 300 ml. three-necked flask fitted with a reflux condenser, a stirrer and a dropping funnel. A 42.6 g. (0.4 mole) quantity of n-butyroyl chloride was added to the stirred aminonitrothiophene solution from the dropping funnel. When the acid chloride had been added, the reaction mixture was heated at its reflux temperature on an oil bath for forty minutes and then cooled. The crude product was collected by filtration and recrystallized from an ethyl alcohol, acetone mixture to obtain 2.3 g. (0.00411 mole, 91.7%) of a yellow colored pure crystalline product melting at 198-199.5°. Anal. calc'd for $C_{24}H_{24}N_4S_3O_6$: C, 51.41; H, 4.31; N, 9.99 and S, 17.16. Found: C, 51.48; H, 4.42; N, 9.94 and S, 17.25.

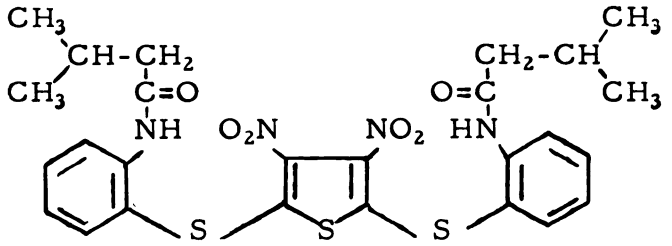
3, 4-Dinitro-2, 5-bis-2'-valeramidothiophenoxythiophene



The experimental procedure described above for the synthesis of similar sulfides was followed in the preparation of this compound. The quantities of reagents used were: 1.0 g. (0.00238 mole) of 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophene, 30.125 g. (0.25 mole) of valeryl chloride. Recrystallization of the crude amide in

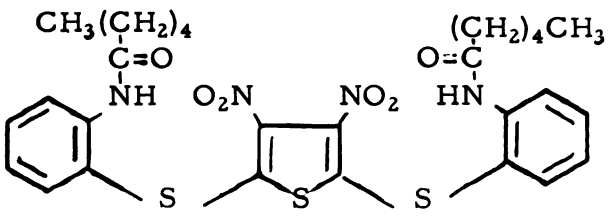
the manner previously discussed for the purification of such compounds gave 1.3 g. (0.002211 mole, 93%) of greenish yellow colored pure material in the form of plates melting at 178-179°. Anal. calc'd for $C_{26}H_{28}N_4S_3O_6$: C, 53.04; H, 4.79; N, 9.52 and S, 16.34. Found: C, 52.98; H, 4.84; N, 9.51; S, 16.23.

3,4-Dinitro-2,5-bis-2'-isovaleramidothiophenoxythiophene



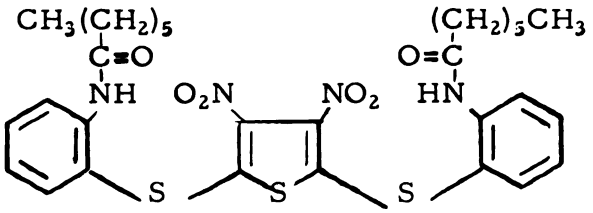
The general experimental procedure described for the synthesis of 2,5-bis-(2-butyramidothiophenoxy)-3,4-dinitrothiophene was used to prepare this compound. The quantities of the reagents used were: 2.0 g. (0.00476 mole) of 3,4-dinitro-2,5-bis-2'-aminothiophenoxythiophene and 24.1 g. (0.2 mole) of isovaleroyl chloride. Recrystallization of the crude product from an ethyl alcohol, acetone solvent mixture gave 2.6 g. (0.00442 mole, 92.8%) of a yellow colored pure crystalline product melting at 206-207°. Anal. calc'd for $C_{26}H_{28}N_4S_3O_6$: C, 53.04; H, 4.79; N, 9.52 and S, 16.34. Found: C, 52.80; H, 4.67; N, 9.68 and S, 16.31.

3,4-Dinitro-2,5-bis-2'- hexanamidothiophenoxythiophene



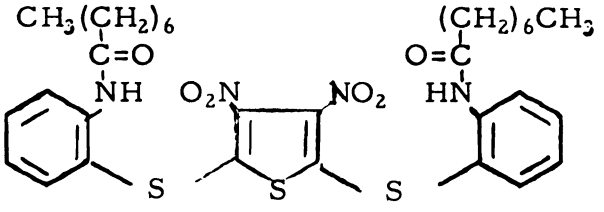
To 1.0 g. (0.00238 mole) of 3,4-dinitro-2,5-bis-2'-amino-thiophenoxythiophene dissolved in 15 ml. of acetone was added a 26.9 g. (0.2 mole) quantity of hexanoyl chloride. The reaction mixture was heated at its reflux temperature on a steam bath for twenty minutes, cooled and the precipitate recovered by filtration. Recrystallization of the crude product from an acetone, water mixture gave 1.4 g. (0.002273 mole, 95.5%) of an off white colored pure product melting at 169-170°. Anal. calc'd for $C_{28}H_{32}N_4S_3O_6$: C, 54.53; H, 5.23; N, 9.08 and S, 15.60. Found: C, 54.90; H, 5.51; N, 9.27; S, 15.88.

3,4-Dinitro-2,5-bis-2'-heptamidothiophenoxythiophene



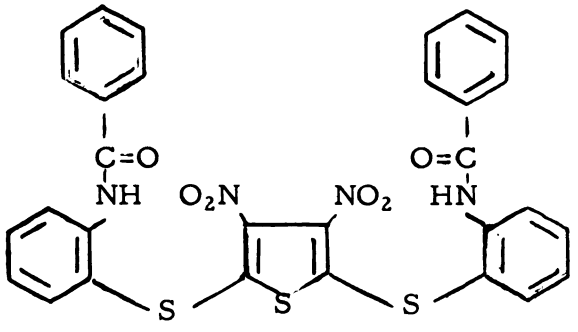
A 1.0 g. (0.00238 mole) quantity of 2,5-bis-(2-aminothiophenoxy)-3,4-dinitrothiophene was dissolved in 20 ml. of acetone. To this solution was added 14.85 g. (0.1 mole) of heptanoyl chloride and the mixture was heated at its reflux temperature for twenty-five minutes on a steam bath. The reaction flask was cooled and the crude product was collected by filtration. Recrystallization of the crude product from an acetone, water solvent mixture gave 1.4 g. (0.002174 mole, 91.4%) of a yellowish white pure product melting at 167.5-168.5°. Anal. calc'd for $C_{30}H_{36}N_4S_3O_6$: C, 55.88; H, 5.63; N, 8.69 and S, 14.92. Found: C, 56.00; H, 5.74; N, 8.92 and S, 14.86.

2, 5-Bis-(2-octanamidothiophenoxy)-3, 4-dinitrothiophene



To 1.0 g. (0.00238 mole) of 3, 4-dinitro-2, 5-bis-2'-amino-thiophenoxythiophene dissolved in 20 ml. of acetone was added 16.25 g. (0.1 mole) quantity of octanoyl chloride. The mixture was heated at its reflux temperature for twenty-five minutes, cooled and the light yellow colored product collected by filtration. Recrystallization of this crude product from an acetone, water mixture gave 1.5 g. (0.002306 mole, 97%) of a light yellow product melting at 164.5-165.5°.
Anal. calc'd for $C_{32}H_{40}N_4S_3O_6$: C, 57.12; H, 5.99; N, 8.33 and S, 14.30.
Found: C, 57.01; H, 6.07; N, 8.30 and S, 14.39.

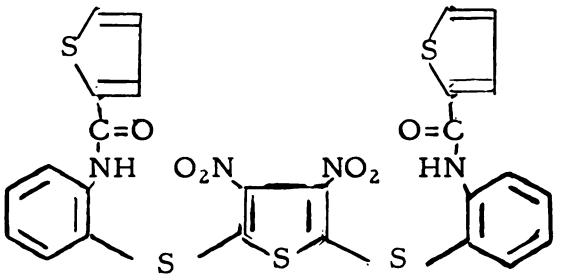
3, 4-Dinitro-2, 5-bis-2'-benzamidothiophenoxythiophene



The general experimental procedure used to prepare 3, 4-dinitro-2, 5-bis-2'-octanamidothiophenoxythiophene was used to obtain this material. A reaction mixture containing 1.26 g. (0.003 mole) of 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxythiophene dissolved in 35 ml. of acetone and 14.05 g. (0.1 mole) of benzoyl chloride was heated at its reflux temperature on a steam bath for a half-hour. The mixture was

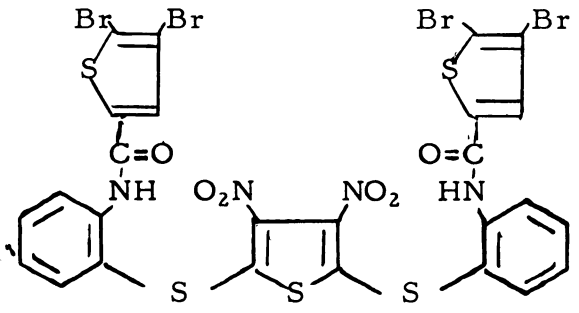
then concentrated by removing 60% of the solvent by distillation. Upon cooling the reaction flask, the crude product separated from solution and was collected by filtration. Recrystallization of the crude product from an acetone, water mixture gave 1.696 g. (0.0027 mole, 90%) of a greenish yellow colored pure product melting at 240-241.5°. Anal. calc'd for $C_{30}H_{20}N_4S_3O_6$: C, 57.31; H, 3.21; N, 8.91; S, 15.30. Found: C, 56.94; H, 3.34; N, 9.35 and S, 15.17.

3,4-Dinitro-2,5-bis-2'(2-thenamido)thiophenoxythiophene



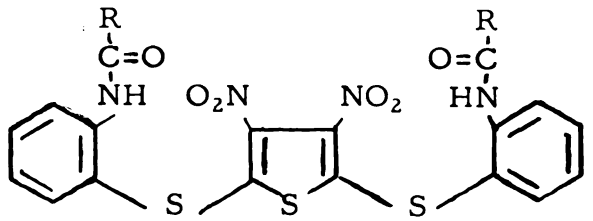
A 2.1 g. (0.005 mole) quantity of 3,4-dinitro-2,5-bis-2'-amino-thiophenoxythiophene dissolved in 20 ml. of acetone was placed in a 300 ml. three-necked flask fitted with a stirrer and a dropping funnel. A 14.65 g. (0.1 mole) quantity of 2-thenoyl chloride was added to the nitroaminothiophene solution. To the well-stirred resulting yellow colored suspension was added 20 ml. of anhydrous acetone. After adding the anhydrous acetone, the reaction mixture was stirred for a day to complete the reaction. The small dark solid which had separated was removed by filtration and discarded. Crushed ice (15 g.) was added to the filtrate to precipitate a yellow solid. The crude product was collected by filtration and washed with warm acetone to remove the unreacted reagents. This product was dried for seven days at 60° to obtain 3.1 g. (0.00484 mole, 96.8%) of a yellow colored pure product melting at 257.5-258.5°. Anal. calc'd for $C_{26}H_{16}N_4S_5O_6$: C, 48.74; H, 2.52; N, 8.74 and S, 25.02. Found: C, 48.70; H, 2.78; N, 8.97 and S, 25.30.

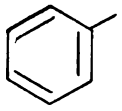
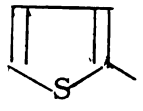
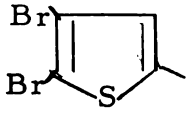
3, 4-Dinitro-2, 5-bis-2'-(4, 5-dibromo-2-thenamido)thiophenoxy-thiophene



A 2.1 g. (0.005 mole) quantity of 3, 4-dinitro-2, 5-bis-2'-amino-thiophenoxy thiophene dissolved in 30 ml. of acetone was placed in a 300 ml. three-necked flask fitted with a thermometer, a stirrer and a dropping funnel. The reaction flask was immersed in an ice bath; and to the stirred cooled solution was added a 6.09 g. (0.02 mole) quantity of 4, 5-dibromo-2-thenoyl chloride, dissolved in 15 ml. of acetone. Following the addition of the acid halide, the reaction mixture was stirred for five minutes. The ice bath was then removed and the mixture was stirred at room temperature for four days to complete the reaction. The yellow precipitate was recovered by filtration and washed with warm acetone to obtain 3.5 g. (0.00366 mole, 73.2%) of a yellow colored pure product melting at 248-249°. Anal. calc'd for $C_{26}H_{12}N_4S_5O_6Br_4$: C, 32.65; H, 1.27; N, 5.86; S, 16.76 and Br, 33.42. Found: C, 33.20; H, 1.56; N, 6.12; S, 16.65 and Br, 33.00.

Table VI. Properties and Analyses of 3,4-Dinitro-2,5-bis-2'-amidothiophenoxythiophene

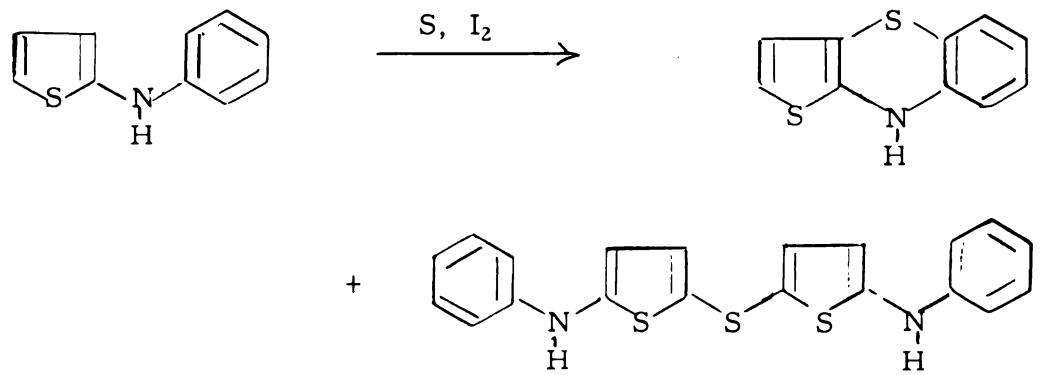


No.	R	Yield %	M.p.[b] °C.	Formula
1	CH_3-	95.2	260.5-261[c]	$C_{20}H_{16}N_4S_3O_6$
2	CH_3CH_2-	71.1	202-203[c]	$C_{22}H_{20}N_4S_3O_6$
3	$ClCH_2CH_2$-	98	178-179[d]	$C_{22}H_{18}N_4S_3O_6Cl_2$
4	$CH_3GH_2CH_2$-	91.7	198-199.5[e]	$C_{24}H_{24}N_4S_3O_6$
5	$CH_3(CH_2)_3$-	93	178-179[e]	$C_{26}H_{28}N_4S_3O_6$
6	$(CH_3)_2CHCH_2$-	92.8	206-207[e]	$C_{26}H_{28}N_4S_3O_6$
7	$CH_3(CH_2)_4$	95.5	169-170[c]	$C_{28}H_{32}N_4S_3O_6$
8	$CH_3(CH_2)_5$-	91.4	167.5-168.5[c]	$C_{30}H_{36}N_4S_3O_6$
9	$CH_3(CH_2)_6$-	97	164.5-165.5[c]	$C_{32}H_{40}N_4S_3O_6$
10		90	240-241.5[c]	$C_{30}H_{20}N_4S_3O_6$
11		96.8	257.5-258.5	$C_{26}H_{16}N_4S_5O_6$
12		73.2	248-249	$C_{26}H_{12}N_4S_5O_6Br_4$

a) Microanalyses were carried out by Microtech Laboratories, Skokie, Illinois.
b) Dried at 60°.
c) Recrystallized from an acetone, water mixture.
d) Recrystallized from an acetone, methanol mixture.
e) Recrystallized from an acetone, ethyl alcohol mixture.

Analyses, % [a]									
Carbon		Hydrogen		Nitrogen		Sulfur		Halogen		
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Name	Calcd	Found
47.61	47.79	3.20	3.20	11.10	11.08	19.07	19.10			
49.61	49.69	3.79	3.77	10.52	10.65	18.06	17.36			
43.93	44.01	3.02	3.08	9.31	9.29	15.99	16.44	Cl	11.79	11.94
51.41	51.48	4.31	4.42	9.99	9.94	17.16	17.25			
53.04	52.98	4.79	4.84	9.52	9.51	16.34	16.23			
53.04	52.80	4.79	4.67	9.52	9.68	16.34	16.31			
54.53	54.90	5.23	5.51	9.08	9.27	15.60	15.88			
55.88	56.00	5.63	5.74	8.69	8.92	14.92	14.86			
57.12	57.01	5.99	6.07	8.33	8.30	14.30	14.39			
57.31	56.94	3.21	3.34	8.91	9.35	15.30	15.17			
48.74	48.70	2.52	2.78	8.74	8.97	25.02	25.30			
32.65	33.20	1.27	1.56	5.86	6.12	16.76	16.65	Br	33.42	33.00

Attempted Thionation of N-Phenyl-2-thienylamine

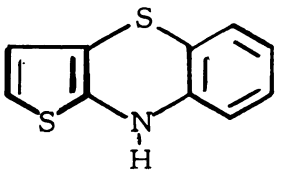


The procedure described by Roe (80) was employed in an attempted preparation of the above compound. A 50 ml. flask was charged with 0.875 g. (0.005 mole) of N-phenyl-2-thienylamine, 0.352 g. (0.011 mole) of sulfur and 0.035 g. of iodine. The mixture was heated in the absence of a solvent under a nitrogen atmosphere at 170-180° for periods varying from 15 minutes to three hours. The evolution of hydrogen sulfide indicates that either the expected thionation reaction had occurred yielding the thiophene analog of phenothiazine and bis-(5-anilino-2-thienyl)sulfide or that the thermally unstable thiophene ring decomposed leading to polymers with hydrogen sulfide evolution. In an attempted extraction of the product from the dark tarry pyrolysis material with a number of different solvents--petroleum ether, ethanol, benzene, ethyl ether--no crystalline product was isolated.

The above general experimental procedure was also used in an attempt to prepare the N-acetyl thiophene analog of phenothiazine. The quantities: 1.085 g. (0.005 mole) of N-phenyl-2-acetamidothiophene, 0.325 g. (0.011 mole) of sulfur and 0.035 g. of iodine were the amounts of the reagents used. The thionation reaction was again conducted in

the absence of a solvent. No crystalline product could be isolated from the dark tarry pyrolysis material.

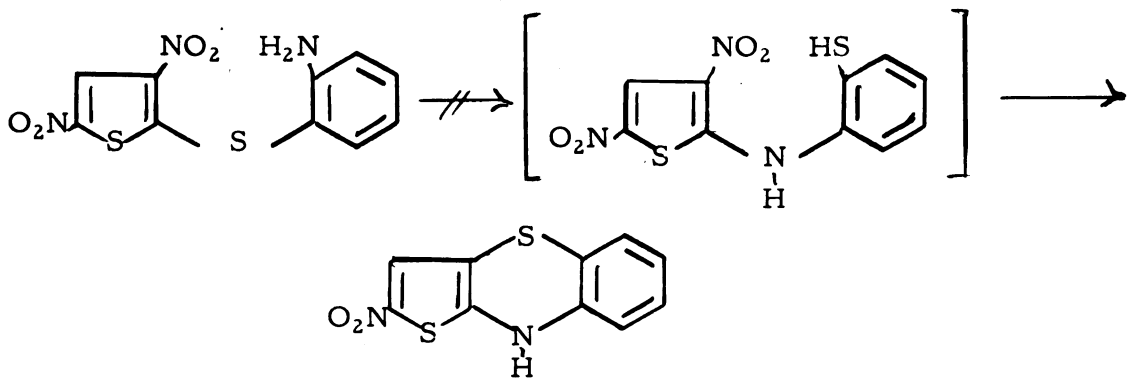
Attempted Thionation of N-Phenyl-2-thienylamine in the Presence of a Solvent



The general experimental procedure described by Massie and Kadaba (32) was employed in an attempted synthesis of the thiophene analog of phenothiazine in the presence of a solvent. A mixture of 5.25 g. (0.03 mole) of N-phenyl-2-thienylamine, 2.08 g. (0.065 mole) of sulfur, 25 mls. of o-dichlorobenzene and 0.21 g. of iodine was placed in a 300 ml. three-necked flask fitted with a thermometer, a stirrer and a reflux condenser. The reaction mixture was heated at its reflux temperature for periods varying from a half-hour to three hours, during which there was a color change in the mixture from a brown to a purple color. At 170°, hydrogen sulfide evolution again occurred. The solvent and the more volatile materials were removed by steam distillation of the reaction mixture. The hard dark residue was dissolved in ether or benzene and treated with decolorizing carbon. The still dark solution was concentrated in vacuo. On cooling the solution, no crystalline product was isolated.

The above general experimental procedure was followed in an attempt to synthesize the N-acetyl thiophene analog of phenothiazine. The quantities of reagents used were: 6.51 g. (0.03 mole) of N-phenyl-2-acetamidothiophene, 2.08 g. (0.03 mole) of sulfur, 0.21 g. of iodine and 25 ml. of o-dichlorobenzene. Again no crystalline product was isolated.

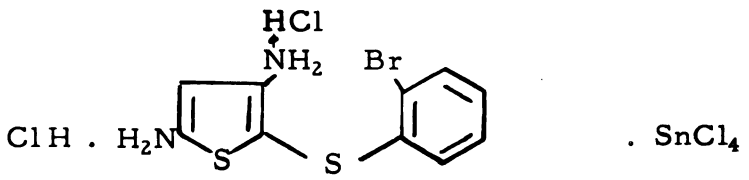
Attempted Ring Closure of 2'-Aminophenyl-3, 5-dinitro-2-thienyl Sulfide



The general procedure described by Florey (38) was employed in the attempted Smiles Rearrangement and ring closure of 3, 5-dinitro-N-2'-aminophenyl-2-thienyl sulfide. A 2.97 g. (0.01 mole) quantity of 3, 5-dinitro-N-2'-aminophenyl-2-thienyl sulfide dissolved in 30 ml. of acetone was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a reflux condenser. An alkaline solution containing 0.726 g. (0.011 mole) of potassium hydroxide pellets dissolved in 15 ml. of methyl alcohol was added to the reaction flask, and the dropping funnel was replaced by a nitrogen inlet tube. The reaction mixture was heated at its reflux temperature on a steam bath under an atmosphere of nitrogen. After heating the reaction mixture at its reflux temperature for fifteen to thirty minutes period, the blood red colored solution was cooled and the solvent was removed by distillation under vacuum. Extraction of the residue with petroleum ether or benzene in a Soxhlet extractor for several days, yielded no crystalline material.

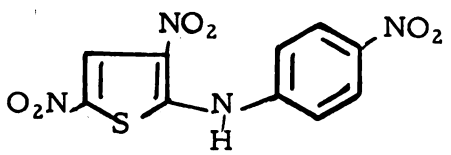
In a second attempt to prepare the N-acetyl derivative of the above compound, the same experimental procedure was used. A 3.39 g. (0.01 mole) of 2'-acetamidophenyl-3, 5-dinitro-2-thienyl sulfide dissolved in 30 ml. of acetone and 0.66 g. (0.01 mole) of potassium hydroxide pellets dissolved in 10 ml. of methanol were the reagents. Again no crystalline products were isolated.

Attempted Preparation of the Stannic Chloride Double Salt of 2'-Bromophenyl-3, 5-diamino-2-thienyl Sulfide Hydrochloride



The procedure described by Hartough (99) was followed in an attempt to synthesize this compound. A 1.8 g. (0.005 mole) quantity of 2'-bromophenyl-3, 5-dinitro-2-thienyl sulfide and 33 ml. of concentrated hydrochloric acid were warmed and stirred together at 40-45°. A 4.4 g. quantity of tin (16-80 mesh) was added in small amounts to the acid solution during fifteen minutes. The reaction temperature was maintained at 40-45° by immersion of the reaction flask from time to time in an ice bath during the addition of the tin. The ice bath was removed and the unreacted tin in the flask was allowed to react without external cooling. The resulting yellow acidic reaction solution was cooled, and neutralized with 40% KOH. A dark grey colored precipitate formed. This was collected by filtration. It was insoluble in water, acetone, dimethylsulfoxide or tetrahydrofuran but soluble in 10% NaOH. Elemental analysis of the material showed that it was not the expected 2'-bromophenyl-3, 5-diamino-2-thienyl sulfide.

Attempted Preparation of N-(4-Nitrophenyl)-3, 5-dinitro-2-thienylamine

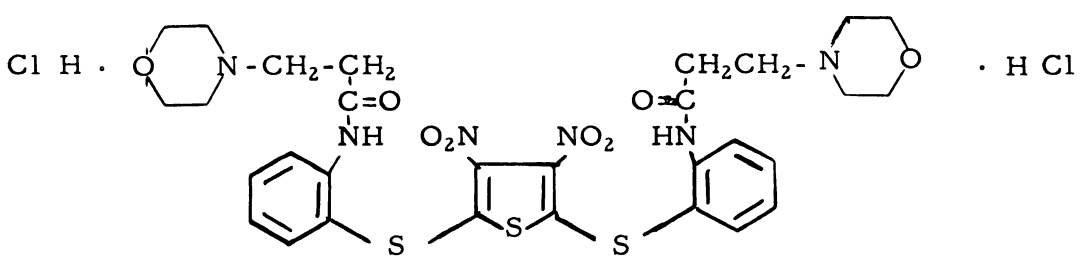


A solution prepared from 2.53 g. (0.01 mole) of 2-bromo-3, 5-dinitrothiophene and 20 ml. of methanol was placed in a 300 ml. three-necked flask fitted with a dropping funnel, a stirrer and a reflux

condenser. A 5.52 g. (0.04 mole) quantity of p-nitroaniline dissolved in 15 ml. of methyl alcohol was added dropwise from the dropping funnel to the stirred halonitrothiophene solution. When the p-nitroaniline had been added the reaction mixture was heated at its reflux temperature on a steam bath for two hours, cooled and the precipitate collected by filtration. On recrystallization of the crude product from methanol, 2.28 g. of a product melting at 135-6° was obtained. Infrared and nuclear magnetic resonance spectra showed that it was the starting 3,5-dinitro-2-bromothiophene. This material was therefore recovered in 90% yield. The p-nitroaniline could be recovered by concentrating the filtrate.

More vigorous reaction conditions were again employed in the hope that a reaction would take place. The reaction mixture was refluxed in ethanol for a day. Again the starting materials were recovered in a high yield.

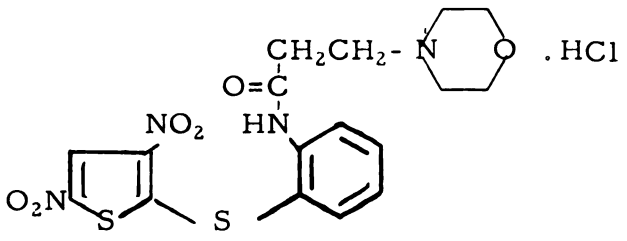
Attempted Preparation of the Hydrochloride Salt of 3,4-Dinitro-2,5-bis-2'-β-morpholinopropionamidothiophenoxythiophene



The general experimental procedure described by Teot (100) was used in an attempt to synthesize the above compound. A 6.01 g. (0.01 mole) quantity of 3,4-dinitro-2,5-bis-2'-β-chloropropionamidothiophenoxythiophene was dissolved in 50 ml. of p-dioxane. A 6.96 g. (0.08 mole) quantity of morpholine was added to the solution of the thiophene derivative. The resulting yellowish red colored solution was heated at its reflux temperature for three days, yielding a

permanent red colored solution after two hours of reaction. The solvent was removed from the reaction solution by distillation under vacuum. The residue was taken up in ether, dried with anhydrous sodium sulfate and decolorized with Norite. Dry hydrogen chloride gas was bubbled through the ether solution. This procedure resulted only in the formation of a tarry product from which a pure hydrochloride salt could not be isolated.

Attempted Preparation of the Hydrochloride Salt of 2'-β-Morpholinopropionamidophenyl-3, 5-dinitro-2-thienyl Sulfide



The procedure previously described for the synthesis of the preceding mixed heterocyclic aryl sulfides was used in an attempt to prepare this compound. The quantities of reagents used were: 3.875 g. (0.01 mole) of 2'-β-chloropropionamidophenyl-3, 5-dinitro-2-thienyl sulfide dissolved in 20 ml. of p-dioxane and 6.96 g. (0.08 mole) of morpholine. Again, no crystalline product could be isolated from the reaction mixture.

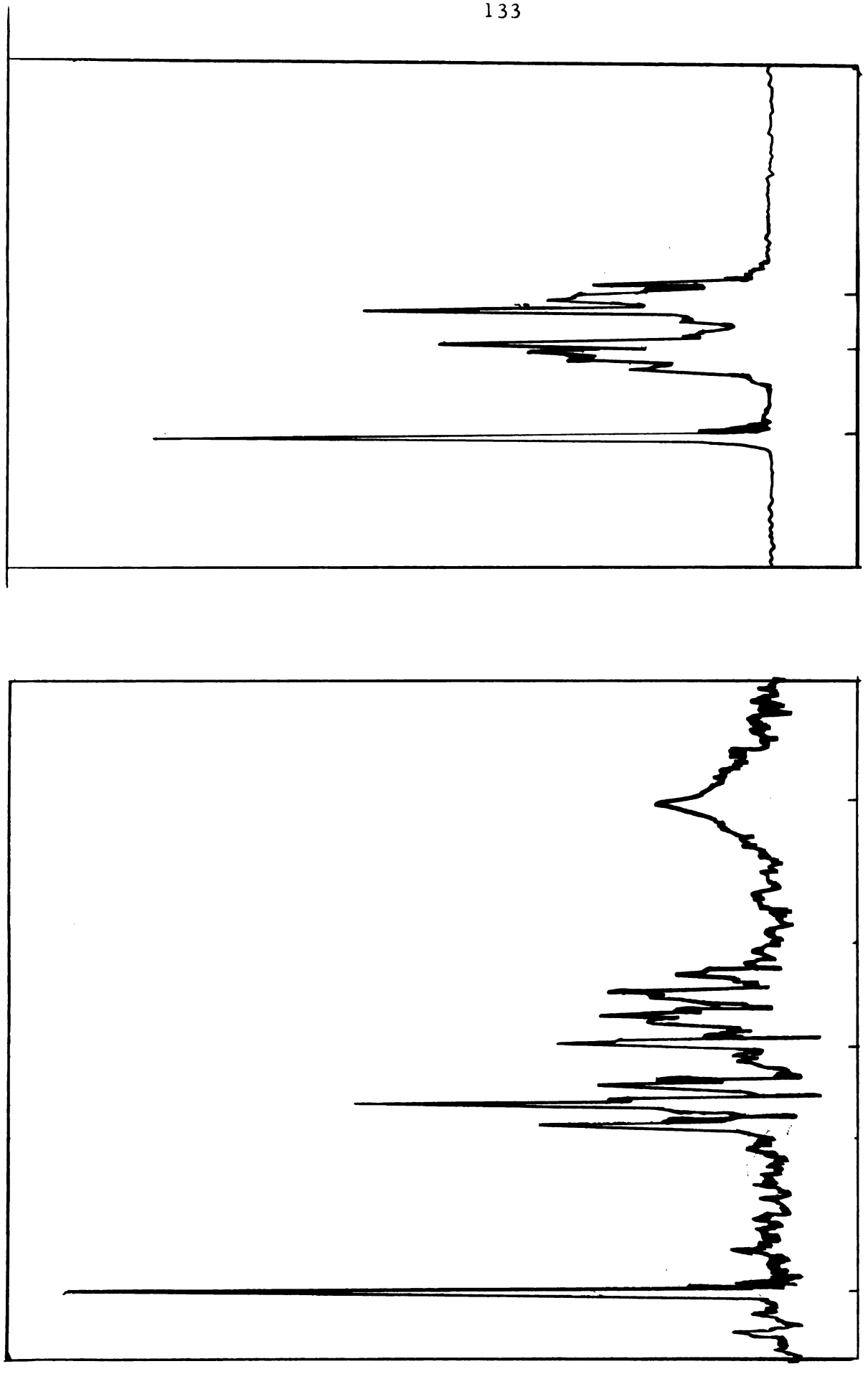


Figure I. N.m.r. spectra of the aromatic regions of 2'-aminophenyl-3, 5-dinitro-2-thienyl sulfide and 2'-bromophenyl-3, 5-dinitro-2-thienyl sulfide in DMSO-d_6 and THF respectively taken at a sweep width of 1000 cps.

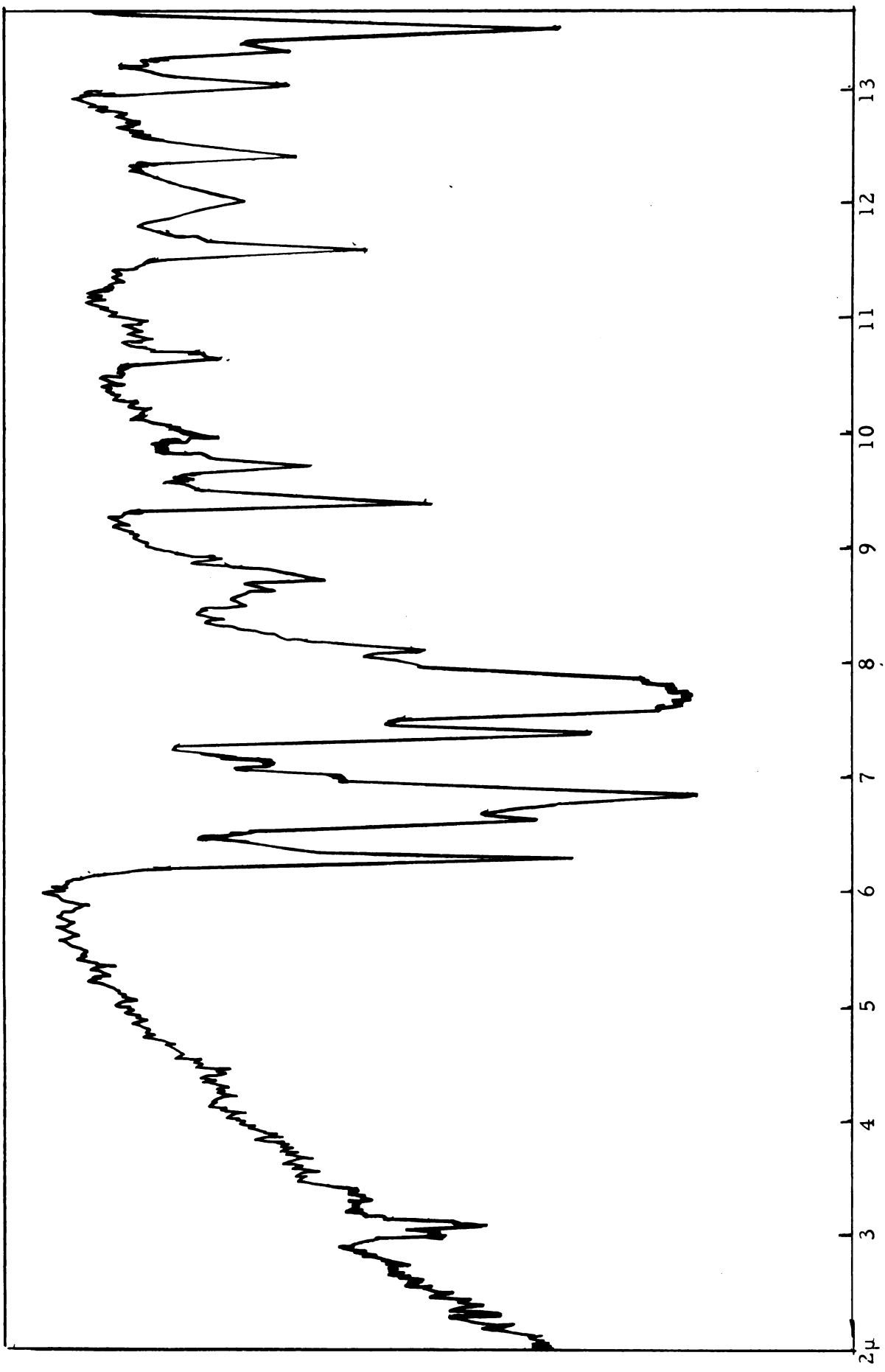


Figure II. Infrared spectrum of KBr pellet of 2'-aminophenyl-3,5-dinitro-2-thienyl sulfide.

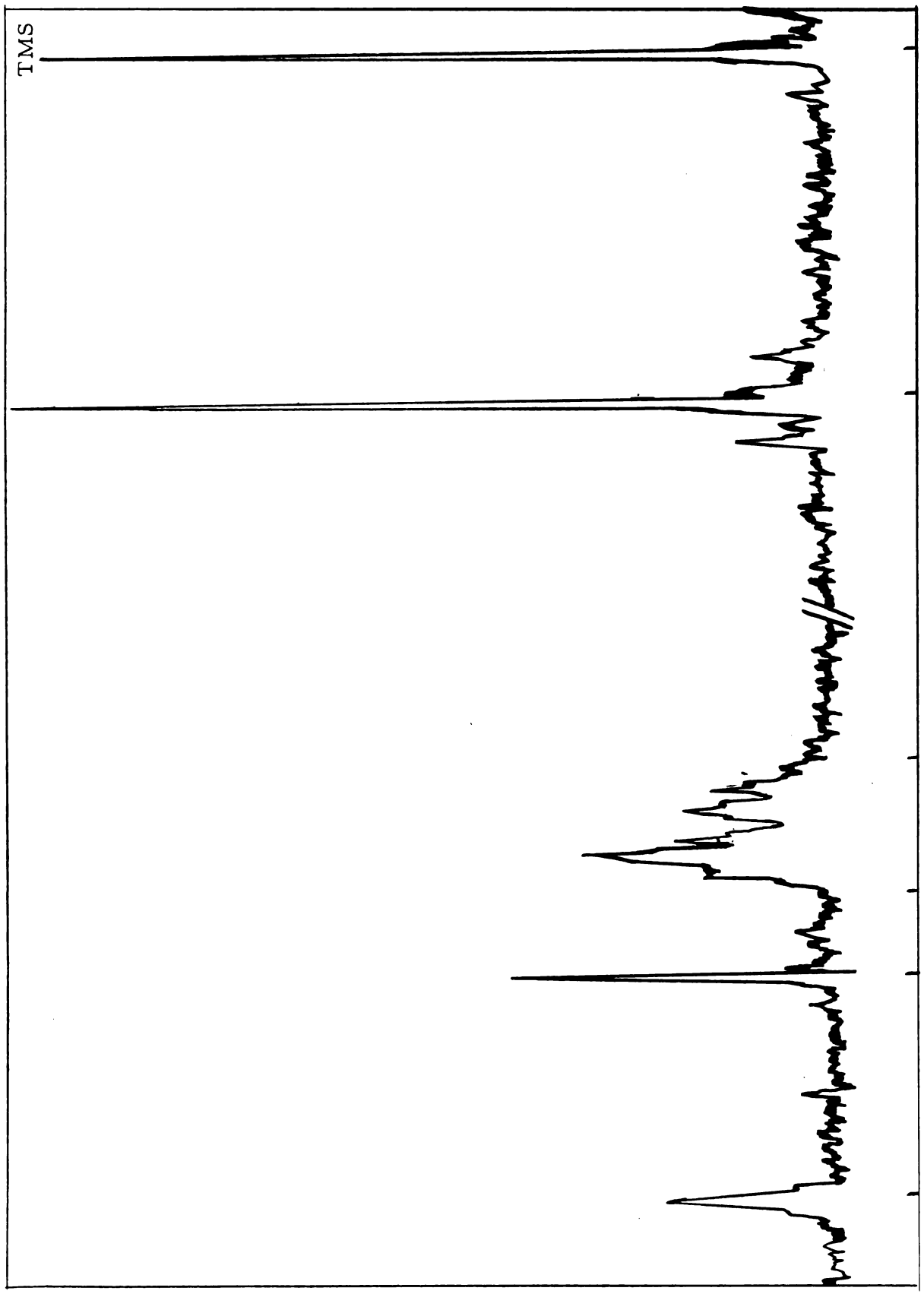


Figure III. N.m.r. spectrum of 2'-acetamidophenyl-3,5-dinitro-2-thienyl sulfide in hexadeutero dimethyl sulfoxide (DMSO-d_6) taken at a sweep width of 1000 cps.

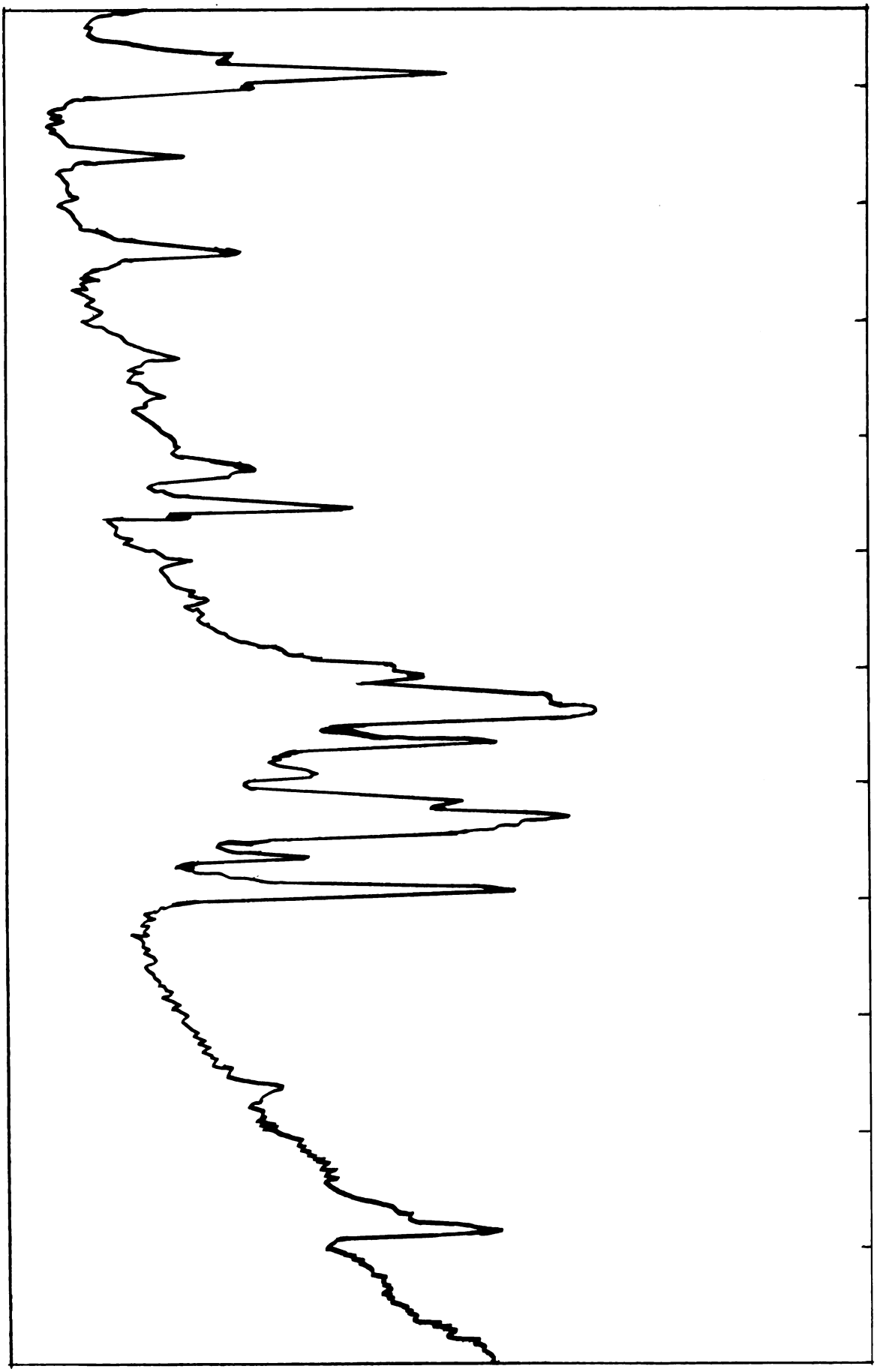


Figure IV. Infrared spectrum of KBr pellet of 2'-acetamidophenyl-3,5-dinitro-2-thienyl sulfide.

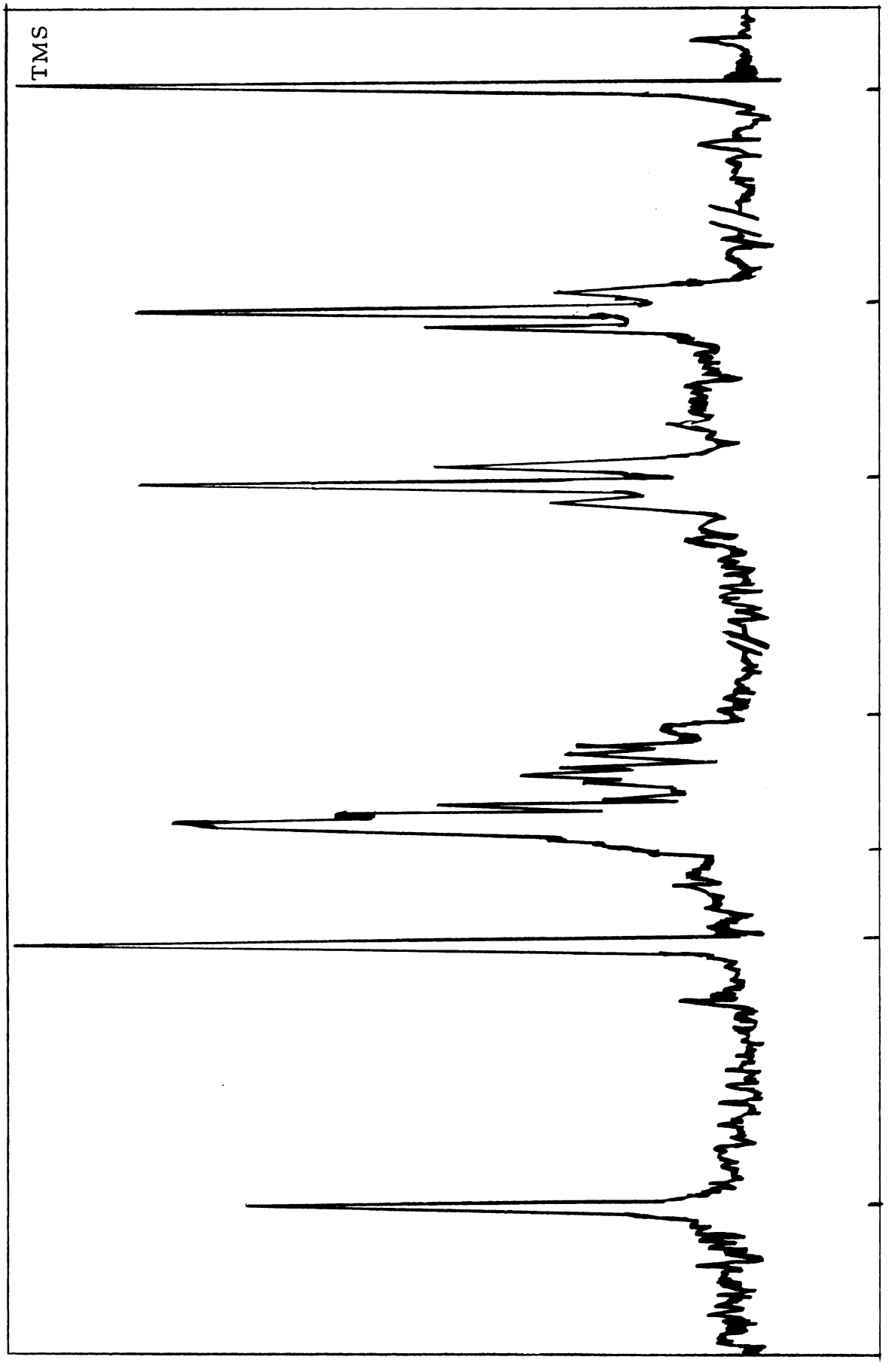


Figure V. N.m.r. spectrum of 2'-β-chloropropionamidophenyl-3, 5-dinitro-2-thienyl sulfide in DMSO-d_6 taken at a sweep width of 1000 cps.

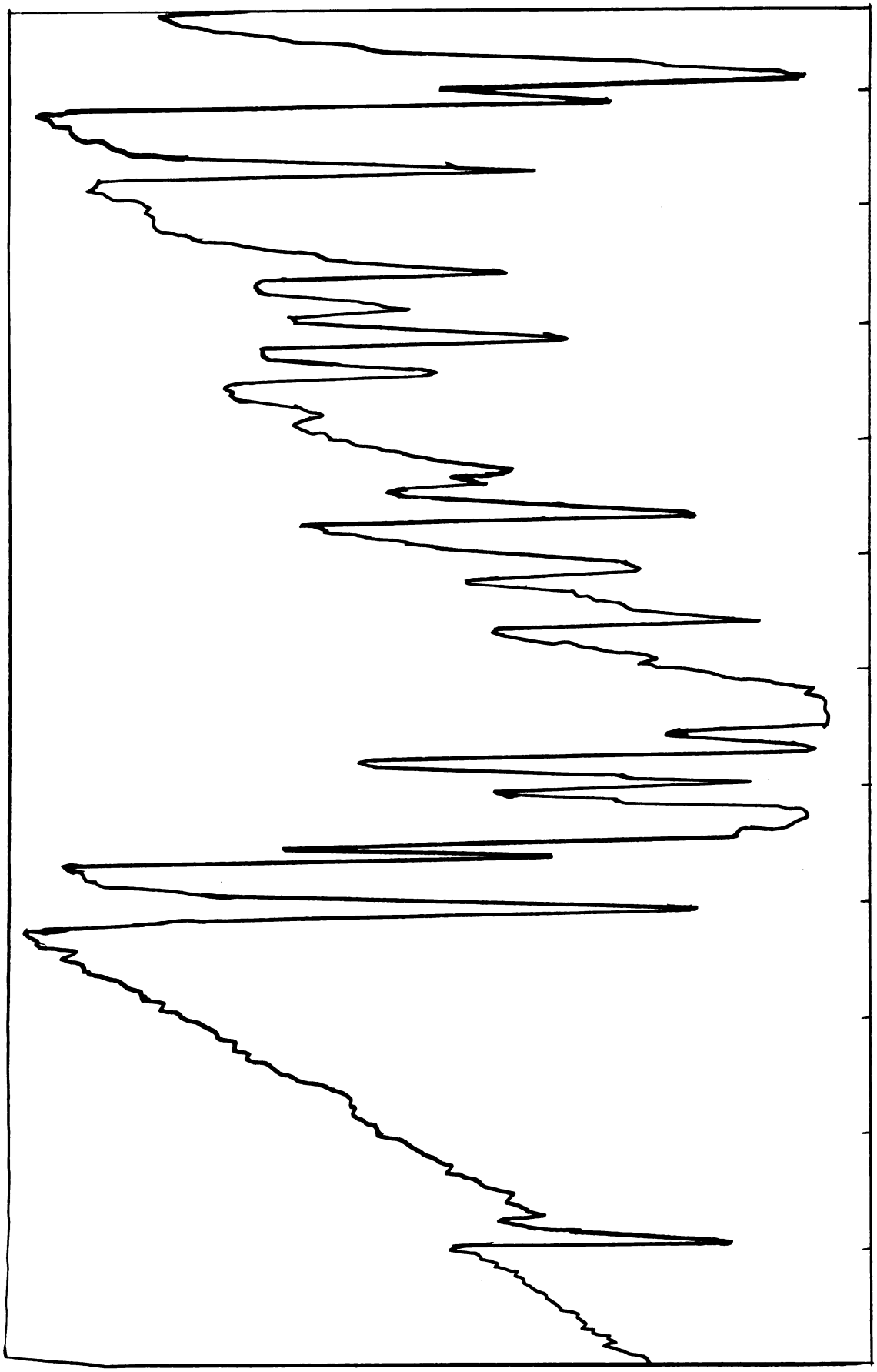


Figure VI. Infrared spectrum of KBr pellet of 2'-β-chloropropionamidophenyl-3, 5-dinitro-2-thienyl sulfide.

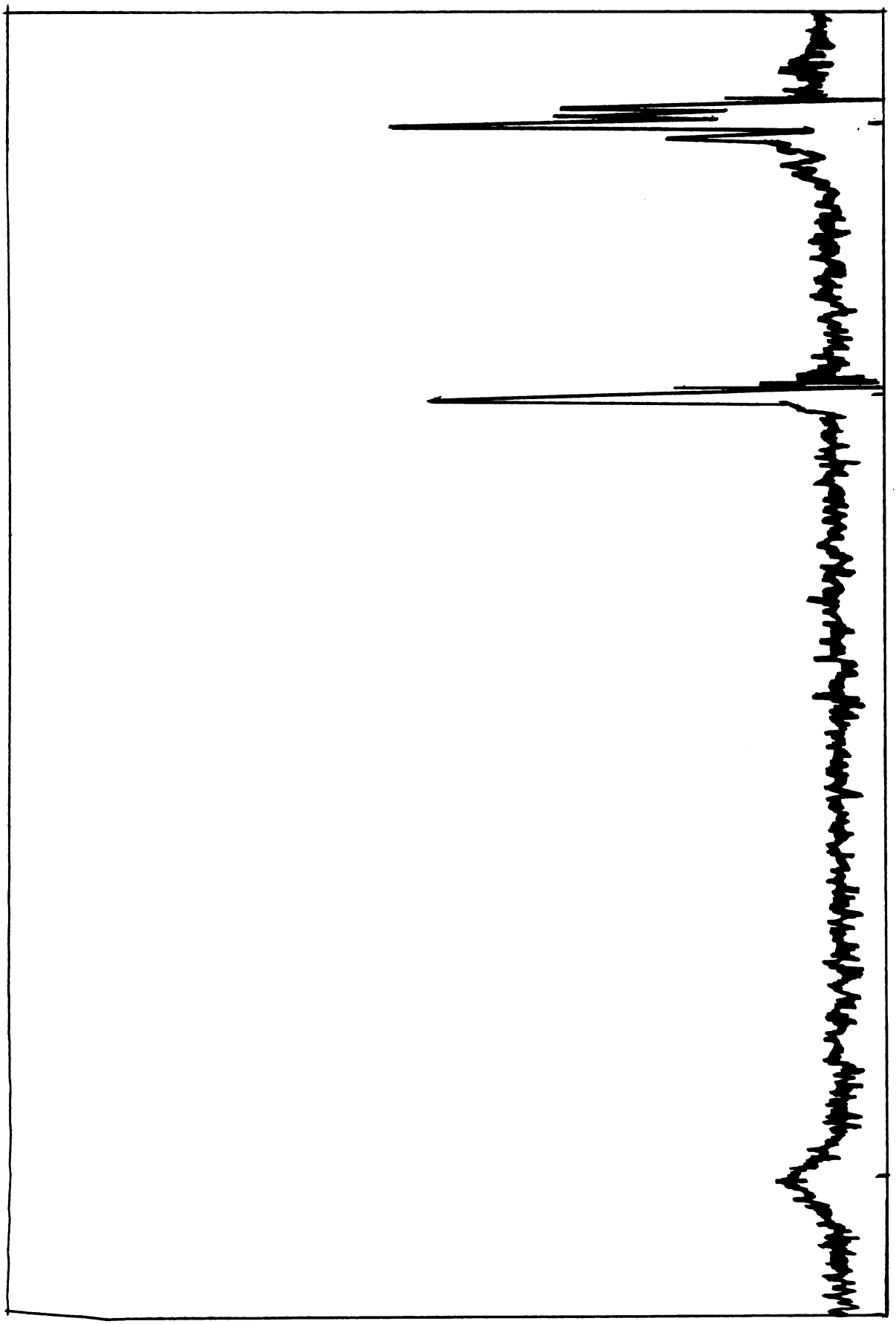


Figure VII. N.m.r. spectrum of the aromatic region of 3,5-dinitro-N(2-thiomethoxyphenyl)-2-thienylamine in tetrahydrofuran taken at a sweep width of 500 cps.

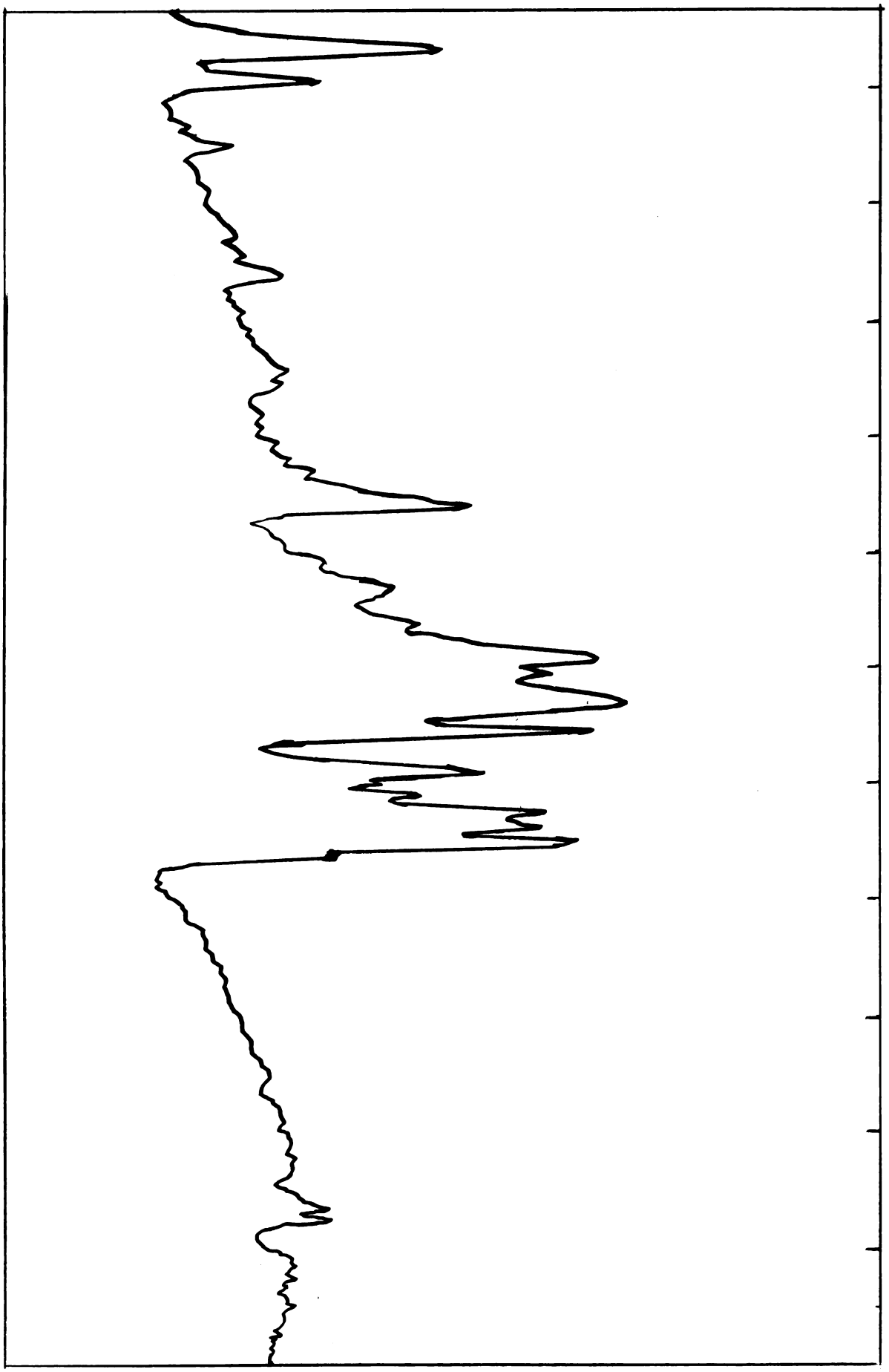


Figure VIII. Infrared spectrum of KBr pellet of 3, 5-dinitro-N-(2-thiomethoxyphenyl)-2-thienylamine.

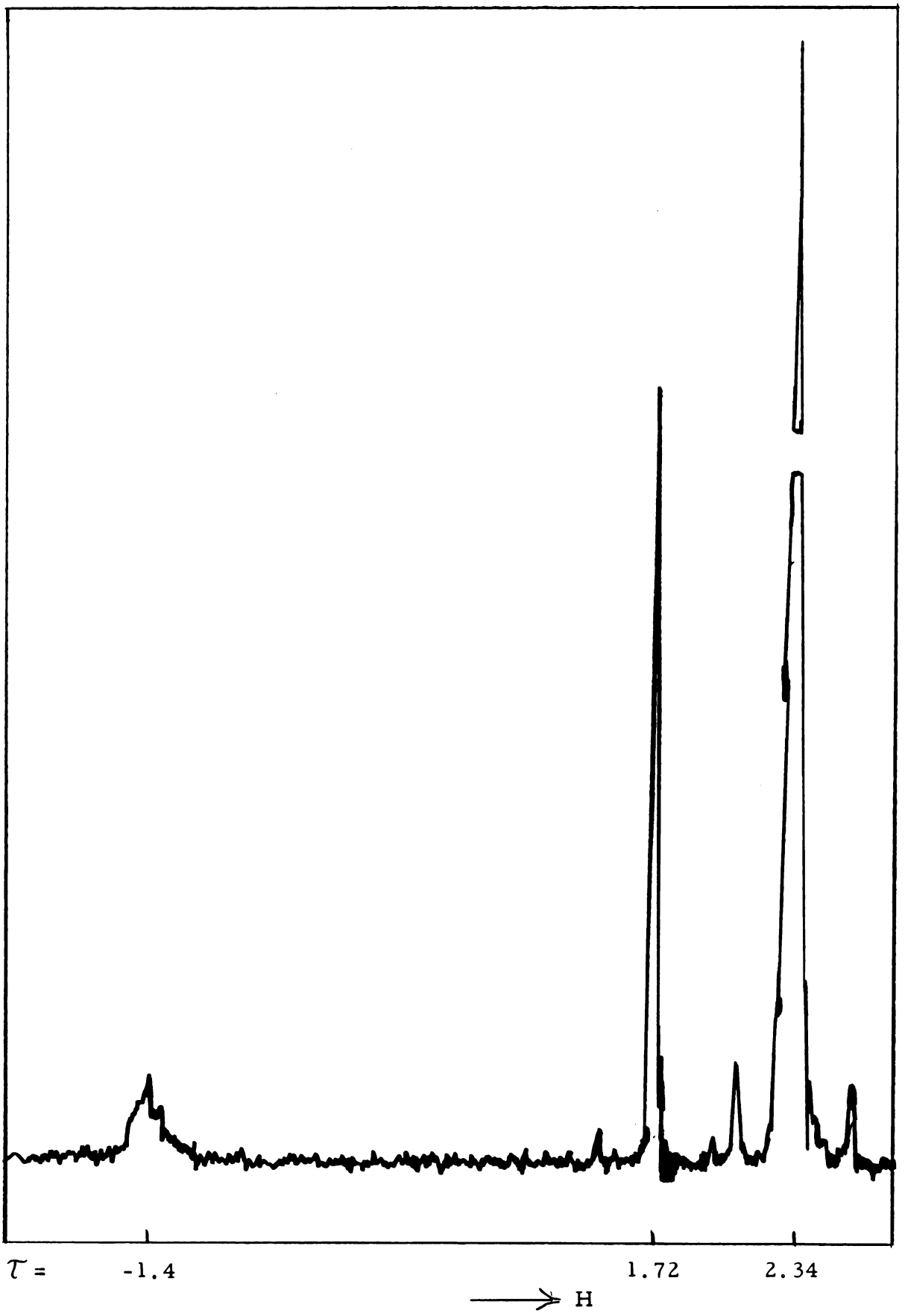


Figure IX. N.m.r. spectrum of the aromatic region of 3, 5-dinitro-N-phenyl-2-thienylamine in DMSO-d_6 taken at a sweep width of 1000 cps.

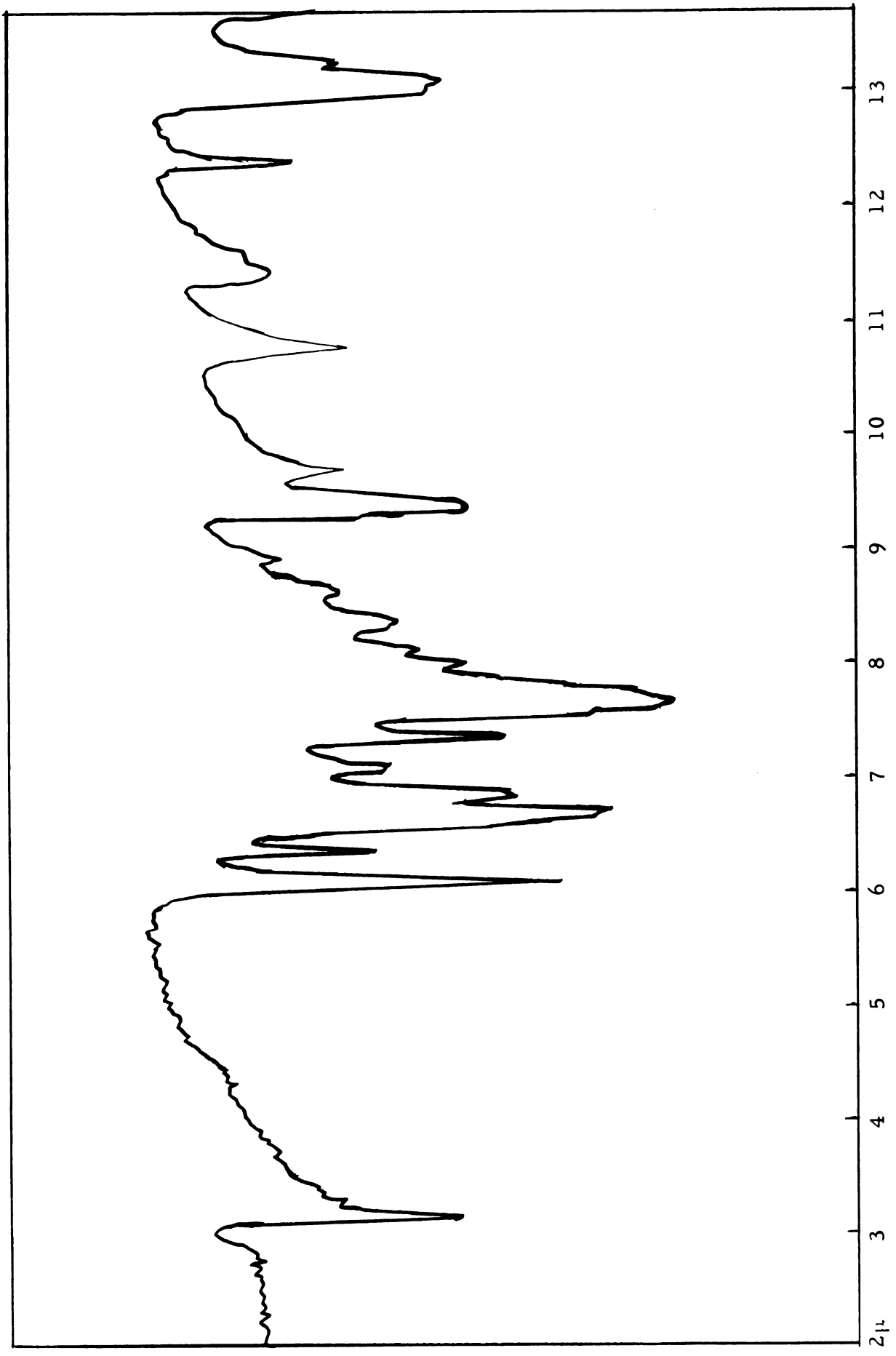


Figure X. Infrared spectrum of KBr pellet of 2'-propionamidophenyl-3, 5-dinitro-2-thienyl sulfide.

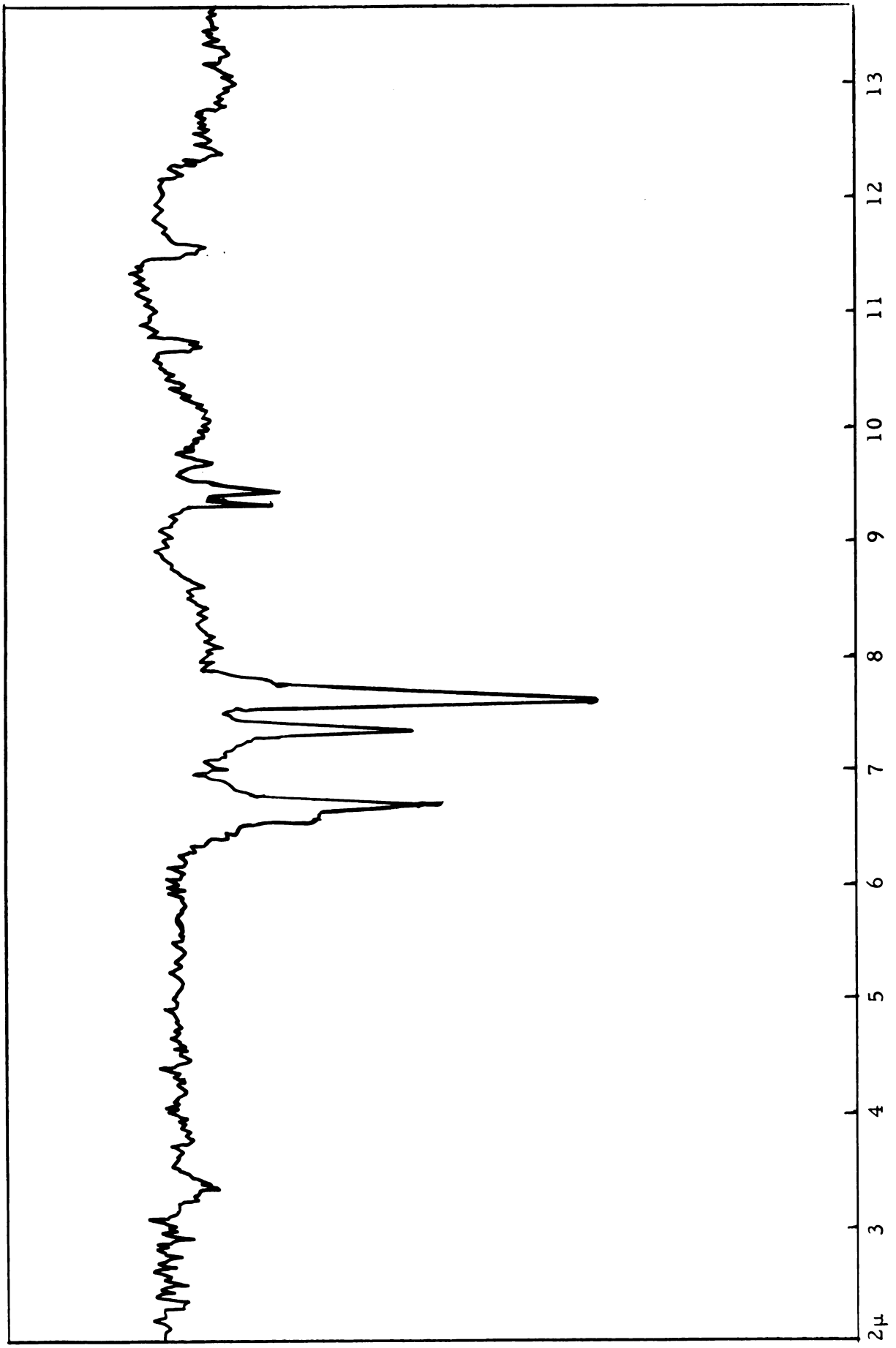


Figure XI. Infrared spectrum of KBr pellet of phenyl-3,5-dinitro-2-thienyl sulfide.

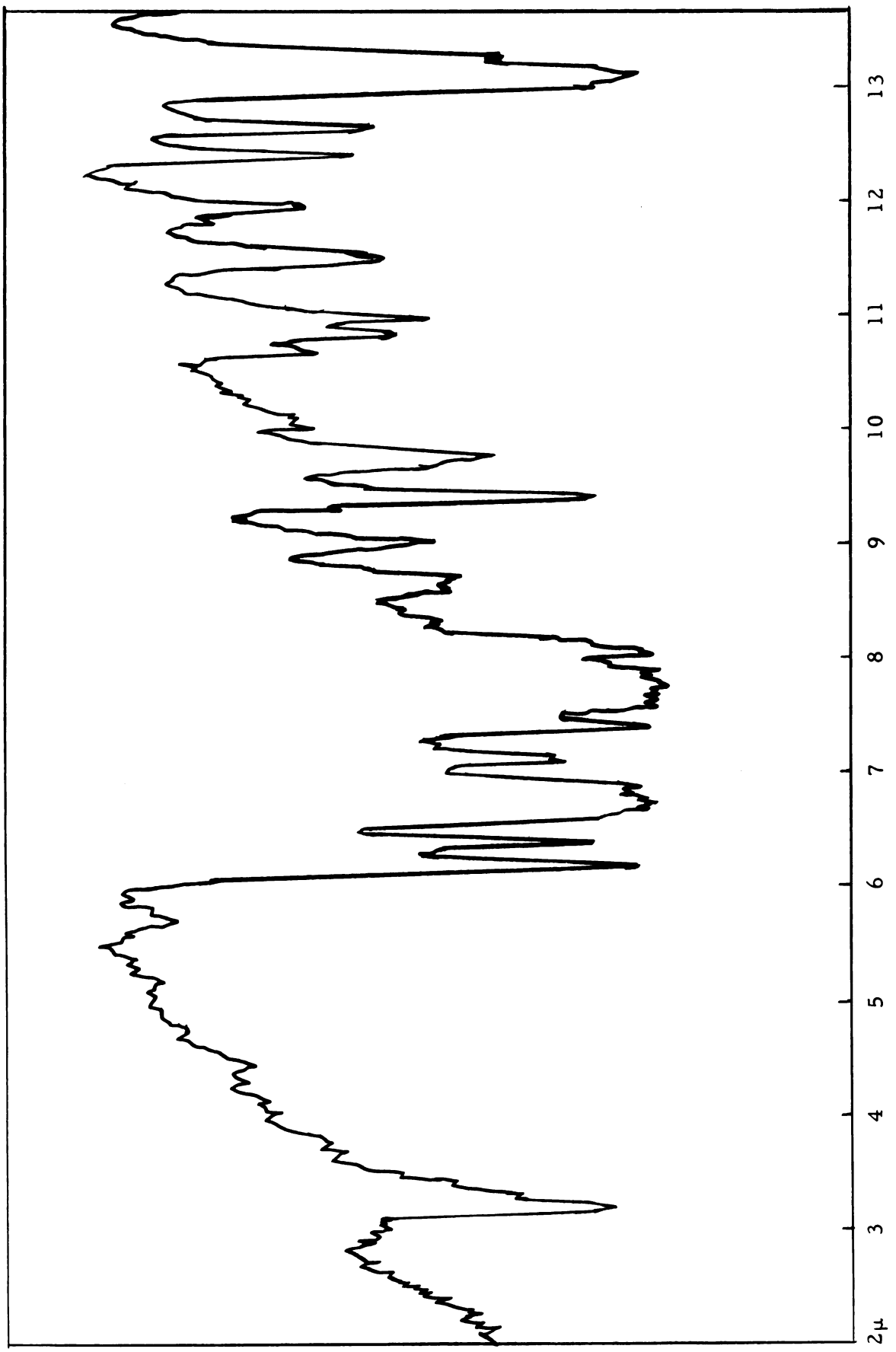


Figure XII. Infrared spectrum of KBr pellet of 2'-benzamidophenyl-3,5-dinitro-2-thienyl sulfide.

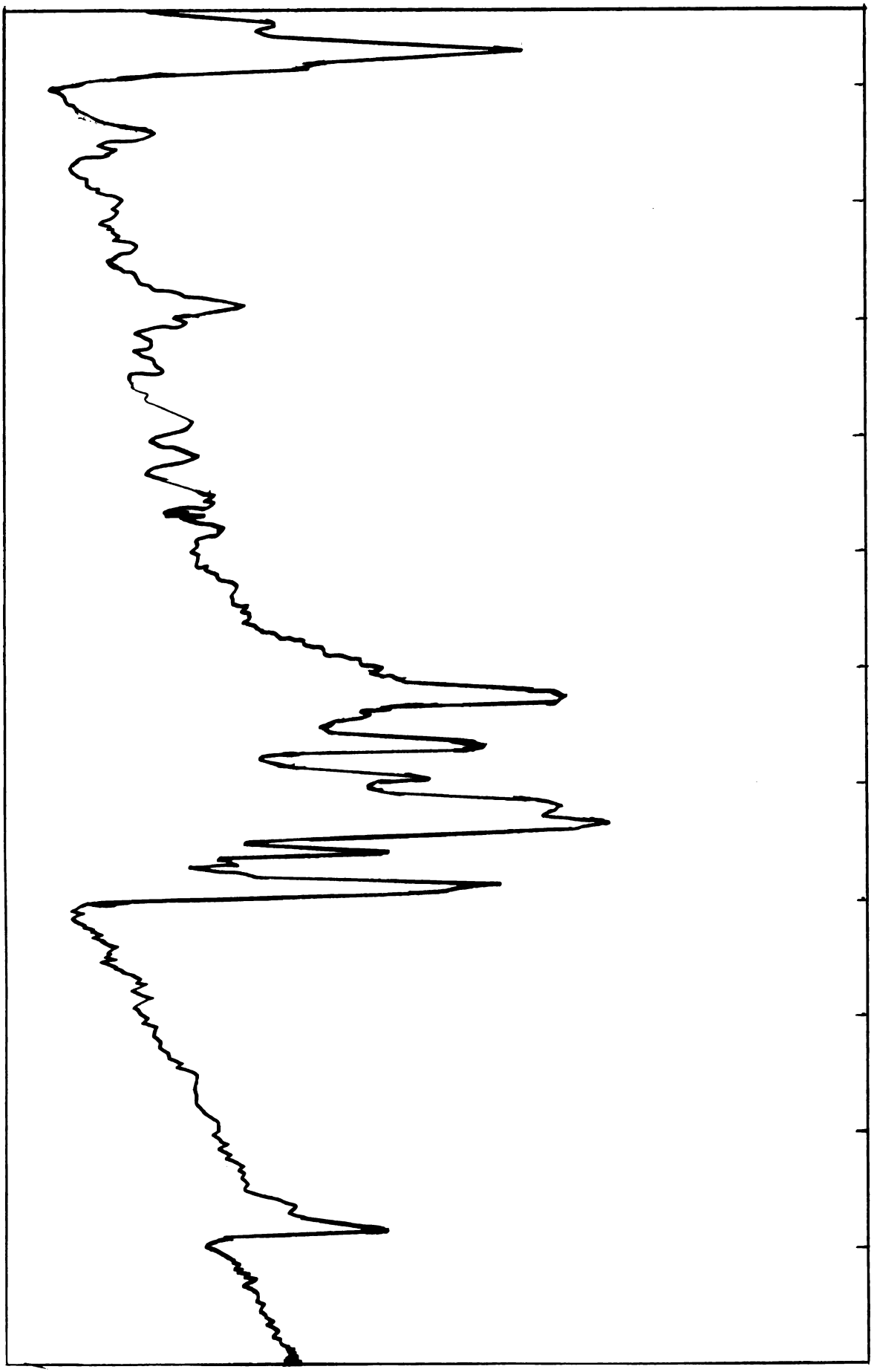


Figure XIII. Infrared spectrum of KBr pellet of 3,4-dinitro-2,5-bis-2'-benzamidothiophenoxythiophene.

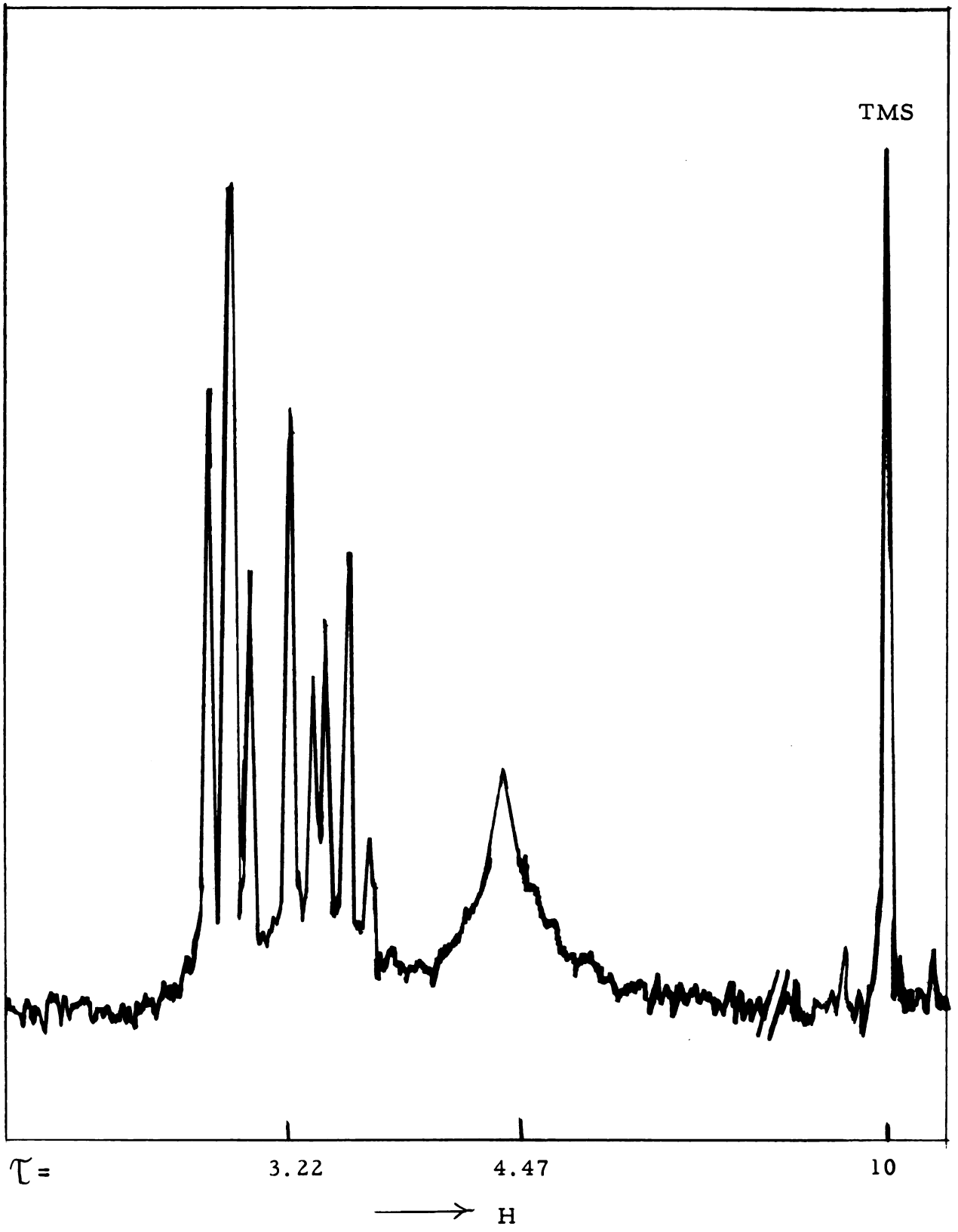


Figure XIV. N.m.r. spectrum of 3, 4-dinitro-2, 5-bis-2'-aminothiophenoxy-thiophene in DMSO-d_6 taken at a sweep width of 1000 cps.

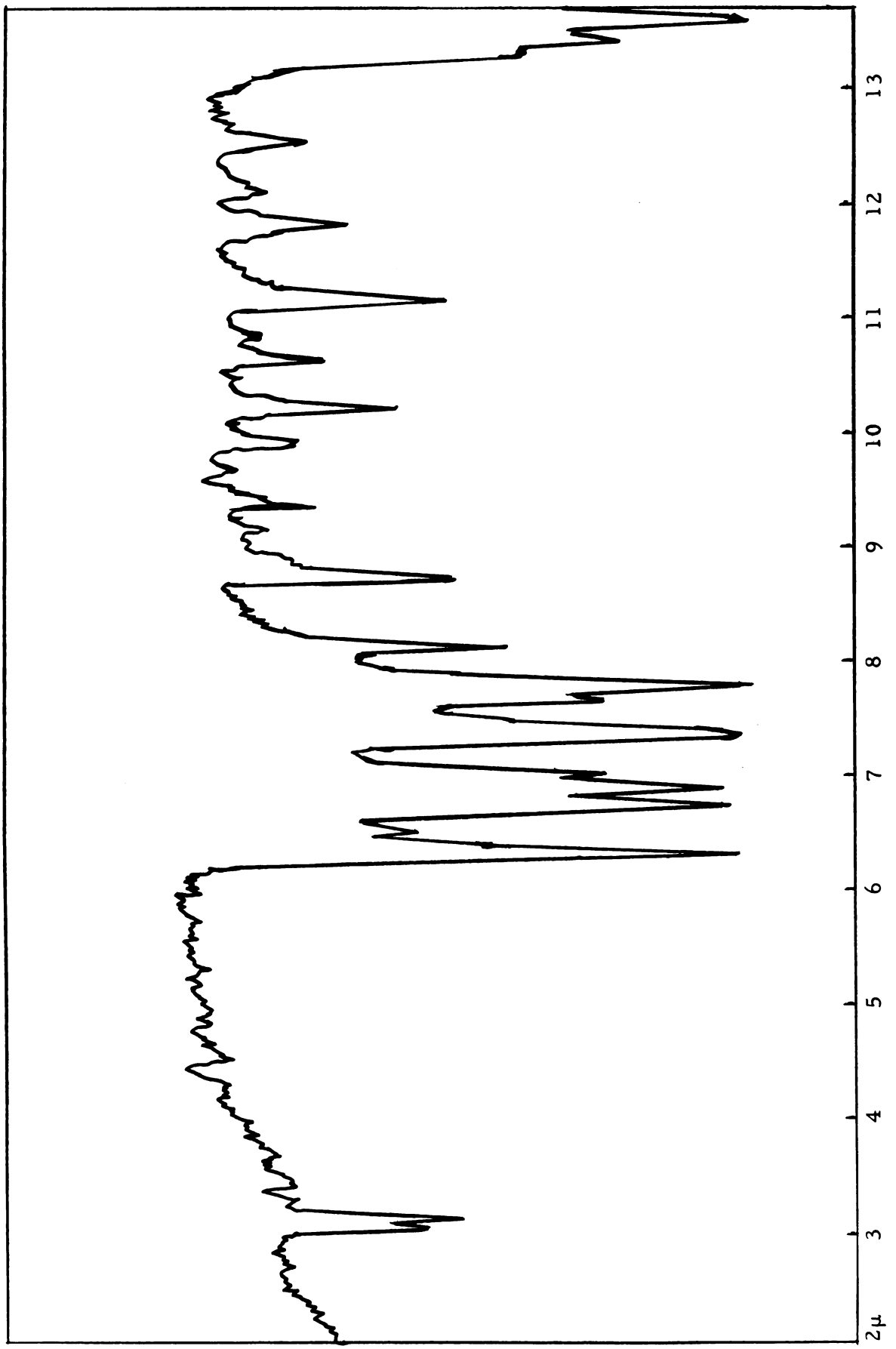


Figure XV. Infrared spectrum of KBr pellet of 3,4-dinitro-2,5-bis-2'-aminothiophenoxythiophene.

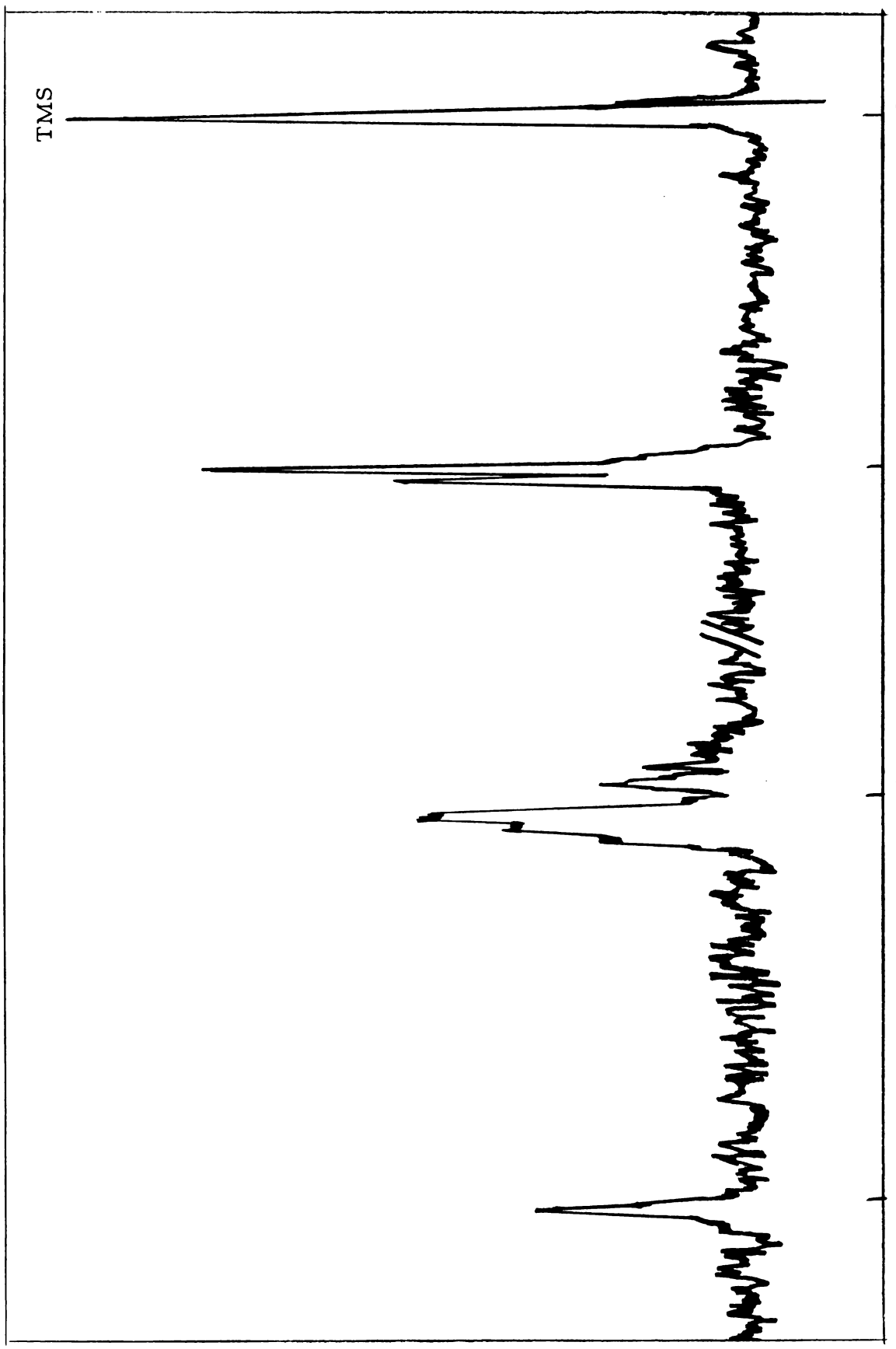


Figure XVI. N.m.r. spectrum of 3,4-dinitro-2,5-bis-2'-acetamidothiophenoxythiophene in DMSO-d_6 taken at a sweep width of 1000 cps.

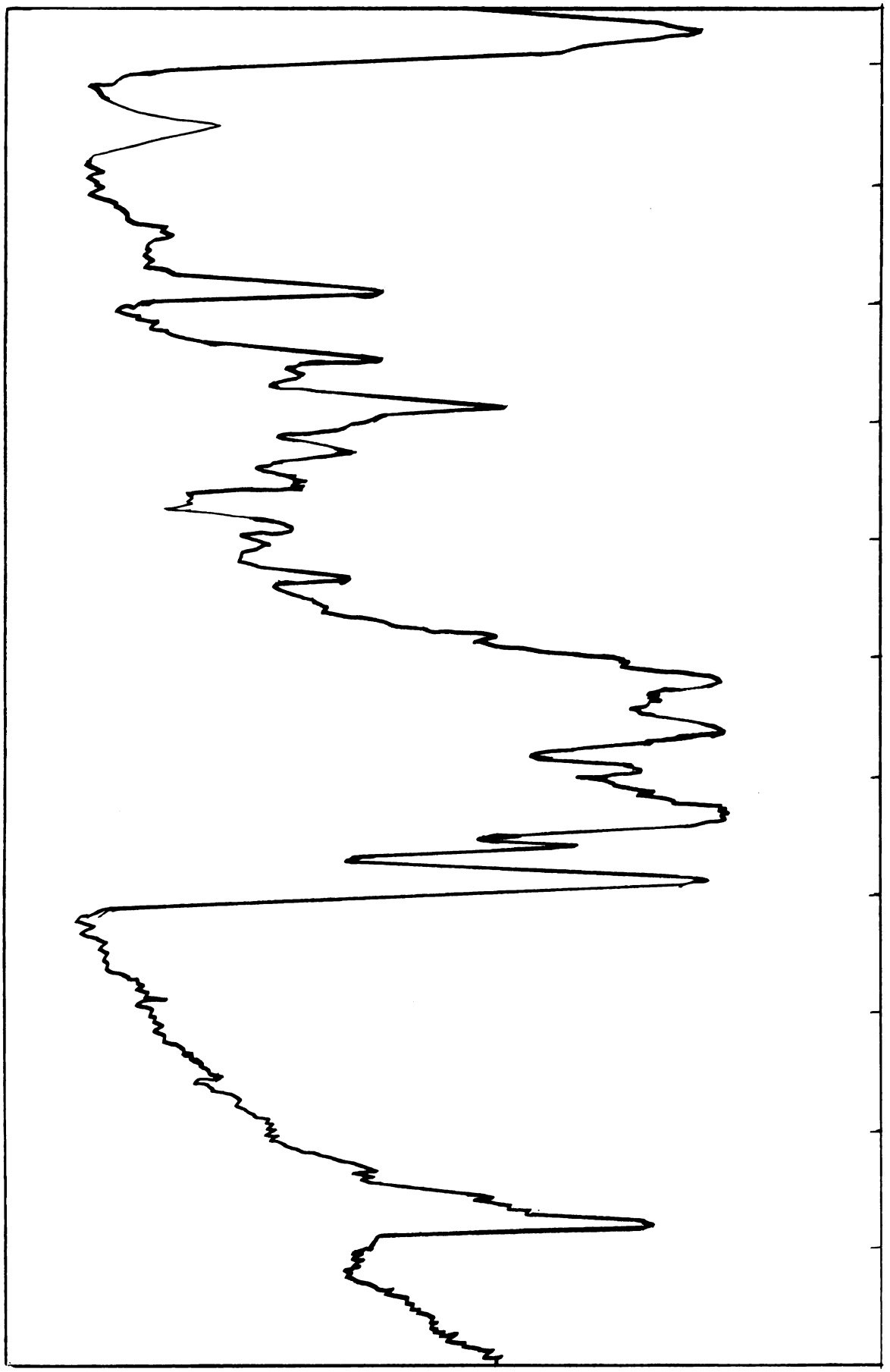


Figure XVII. Infrared spectrum of KBr pellet of 3, 4-dinitro-2, 5-bis-2'-acetamidothiophenoxythiophene.

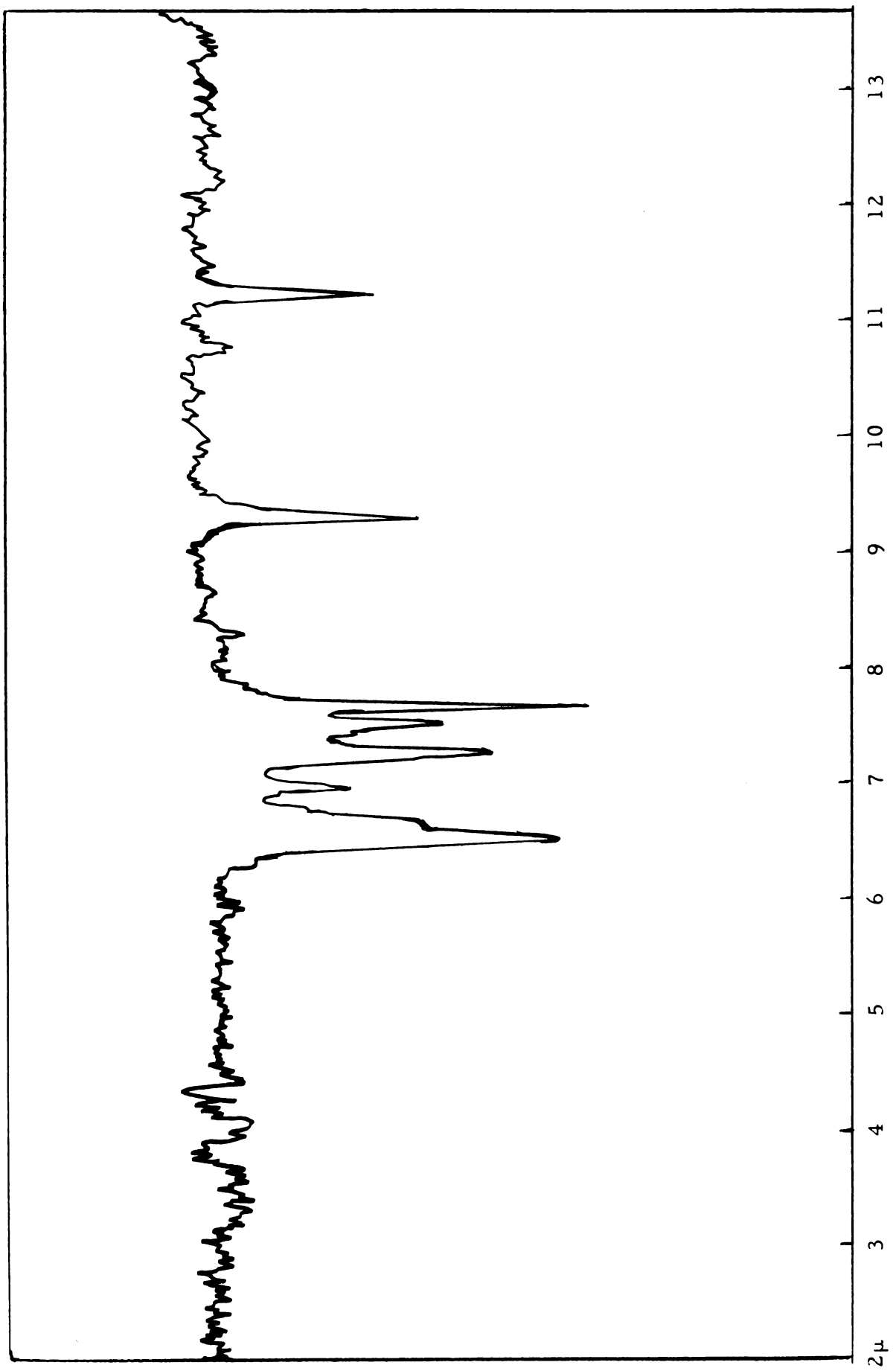


Figure XVIII. Infrared spectrum of 2,5-dibromo-3,4-dinitrothiophene in carbon tetrachloride.

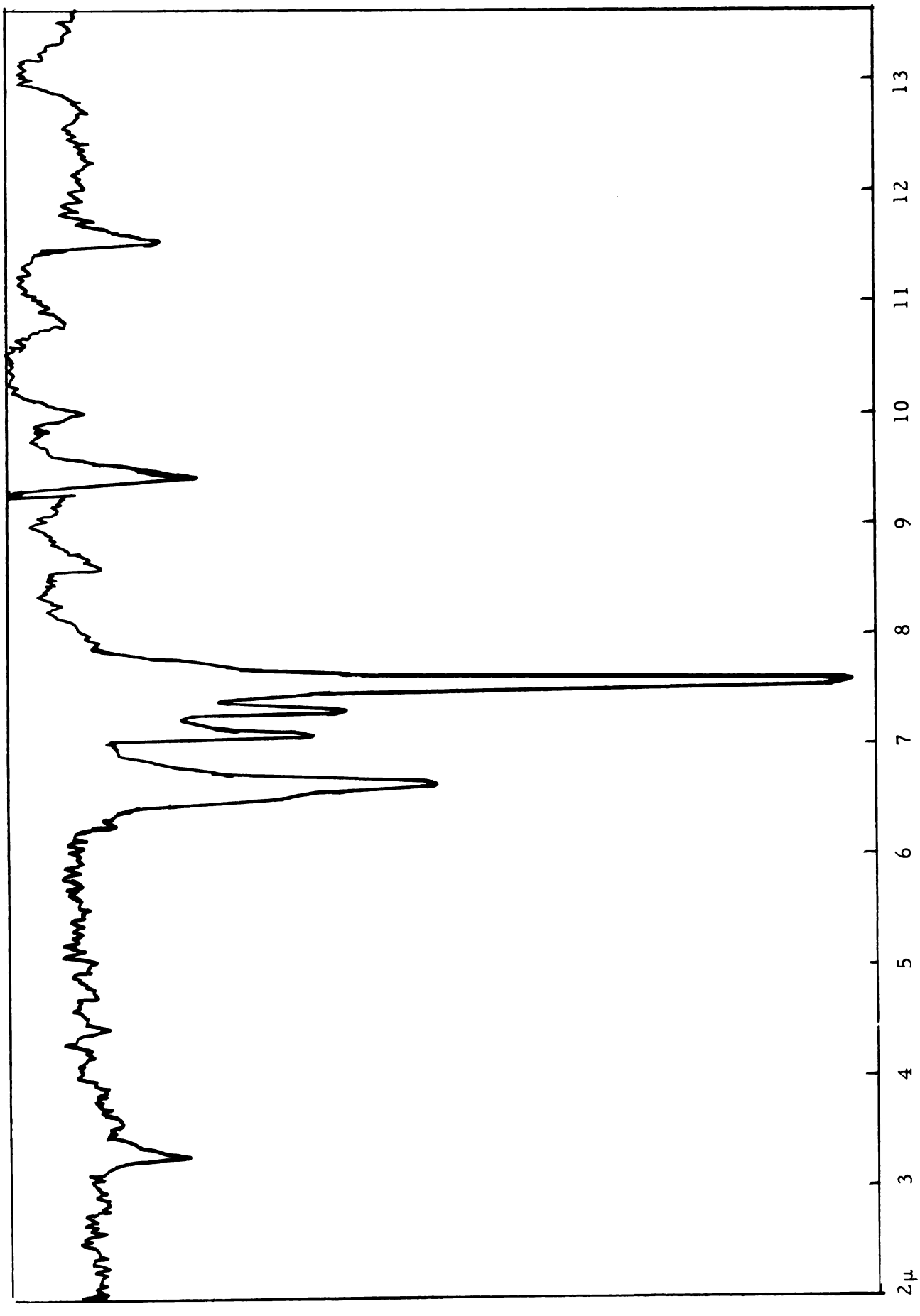


Figure XIX. Infrared spectrum of 2-bromo-3, 5-dinitrothiophene in carbon tetrachloride.

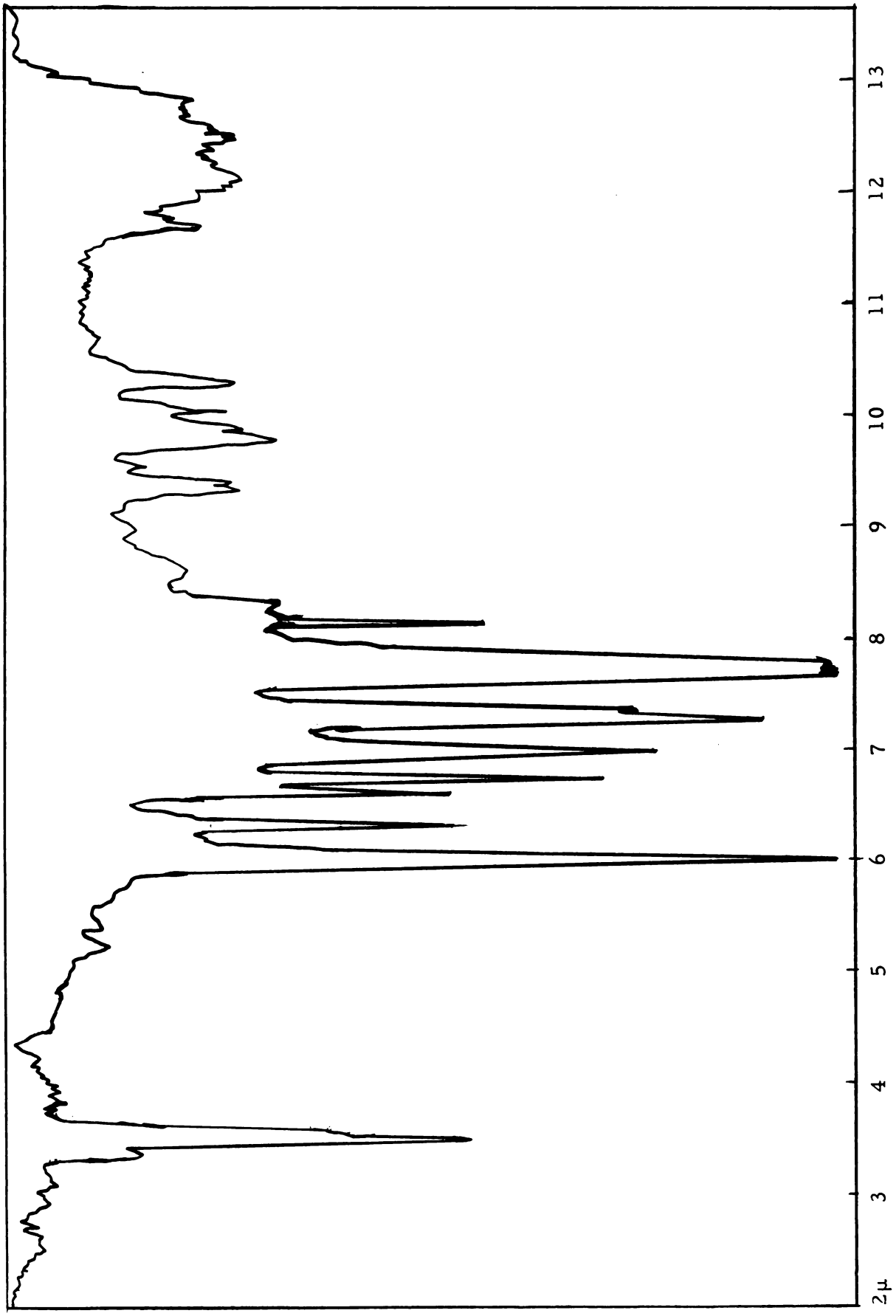


Figure XX. Infrared spectrum of N-phenyl-2-acetamidothiophene in carbon tetrachloride.

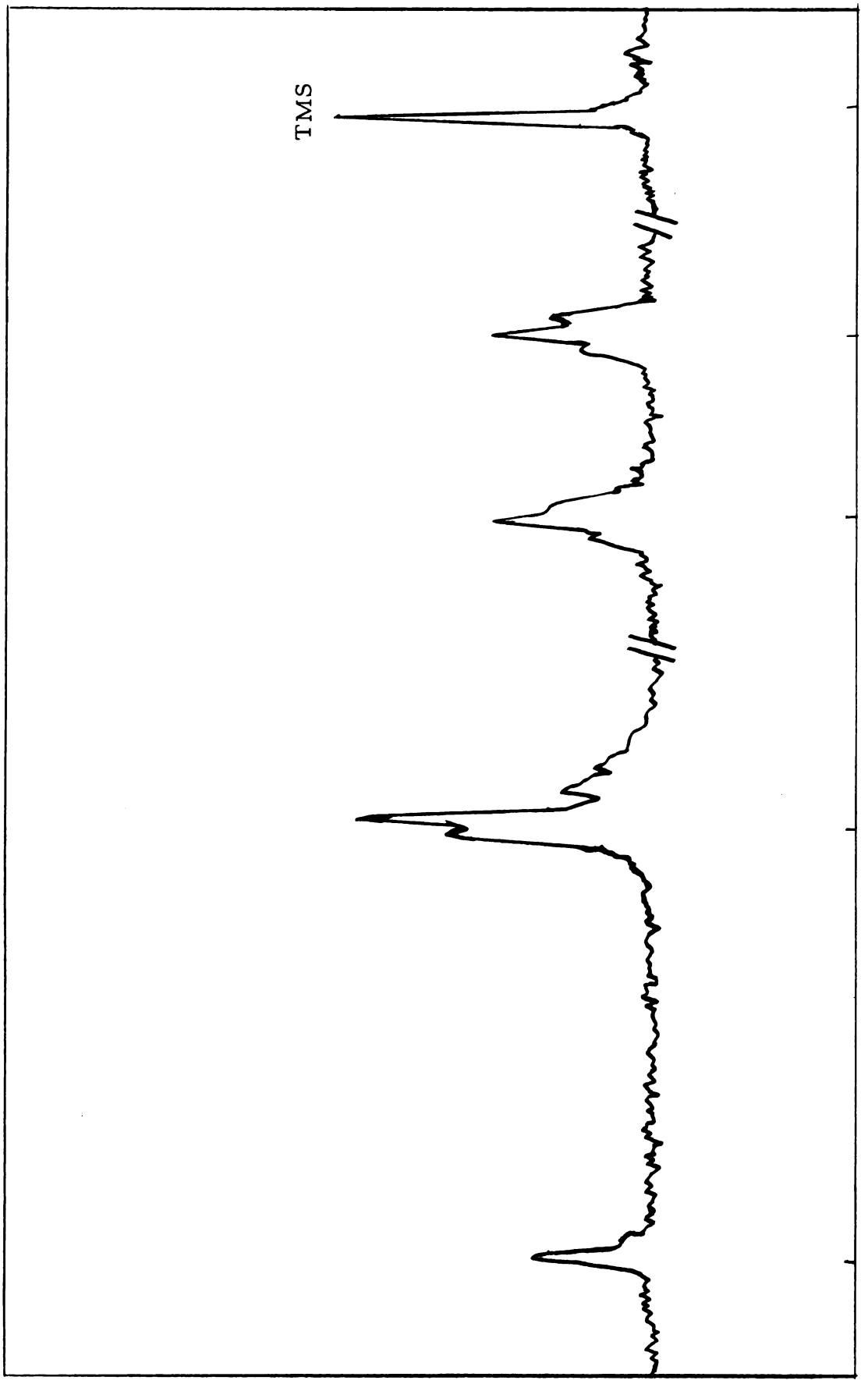


Figure XXI. N.m.r. spectrum of 3,4-dinitro-2,5-bis-2'-β-chloropropionamidothiophenoxythiophene in DMSO-d_6 taken at a sweep width of 1000 cps.

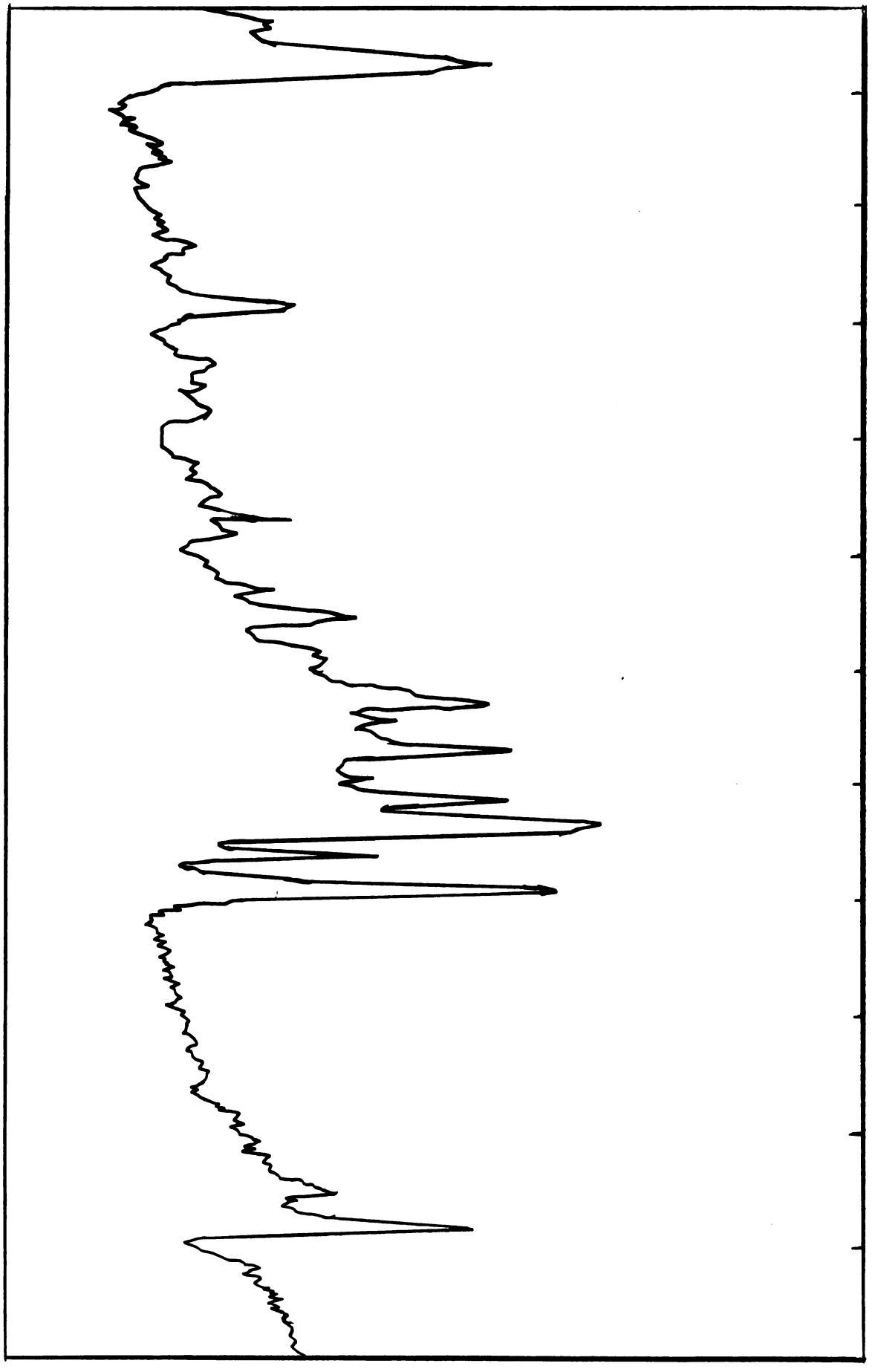


Figure XXII. Infrared spectrum of KBr pellet of 3,4-dinitro-2,5-bis-2'-butyramidothiophenoxythiophene.

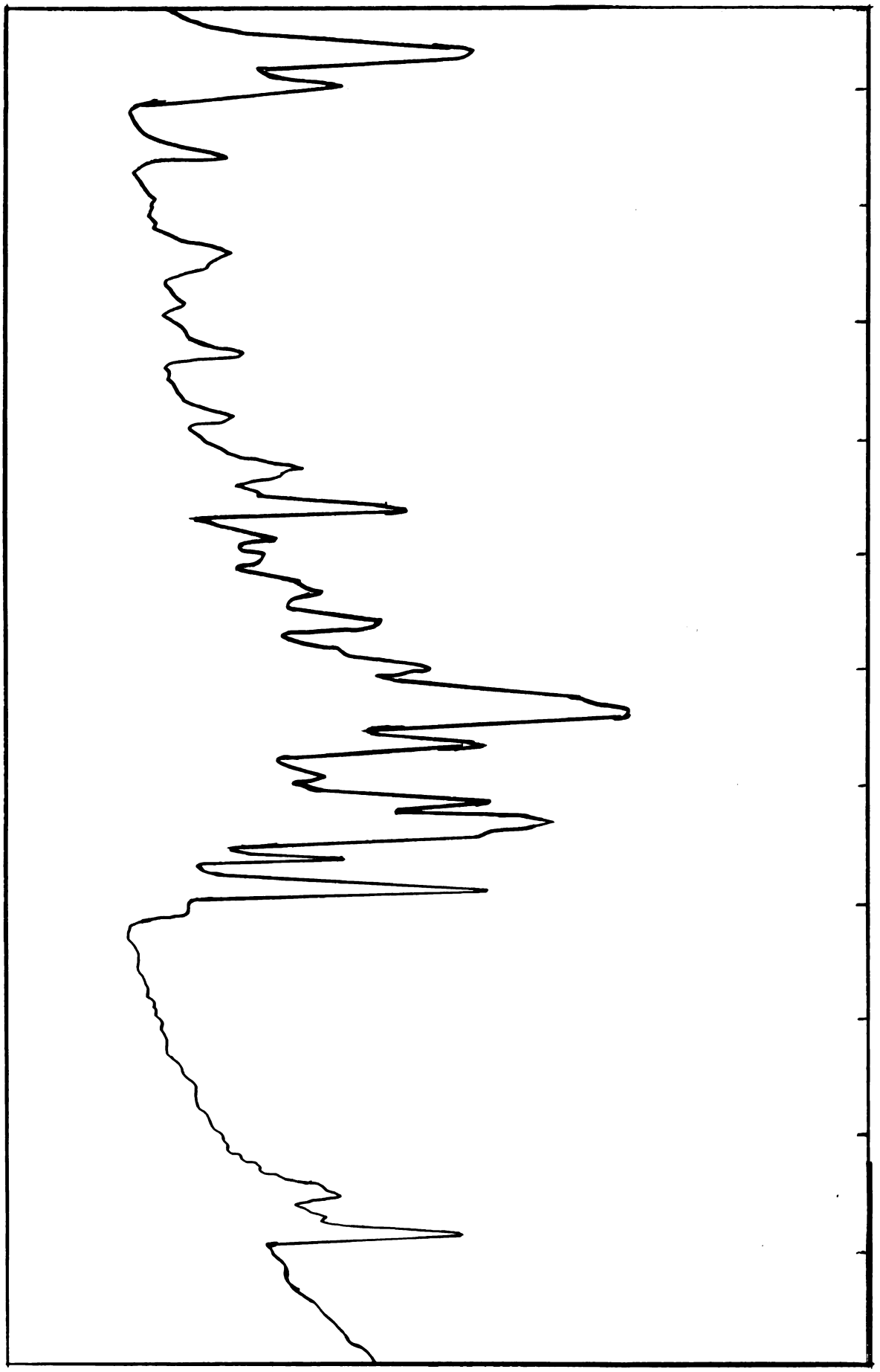


Figure XXIII. Infrared spectrum of KBr pellet of 2'-isovaleramidophenyl-3,5-dinitro-2-thienyl sulfide.

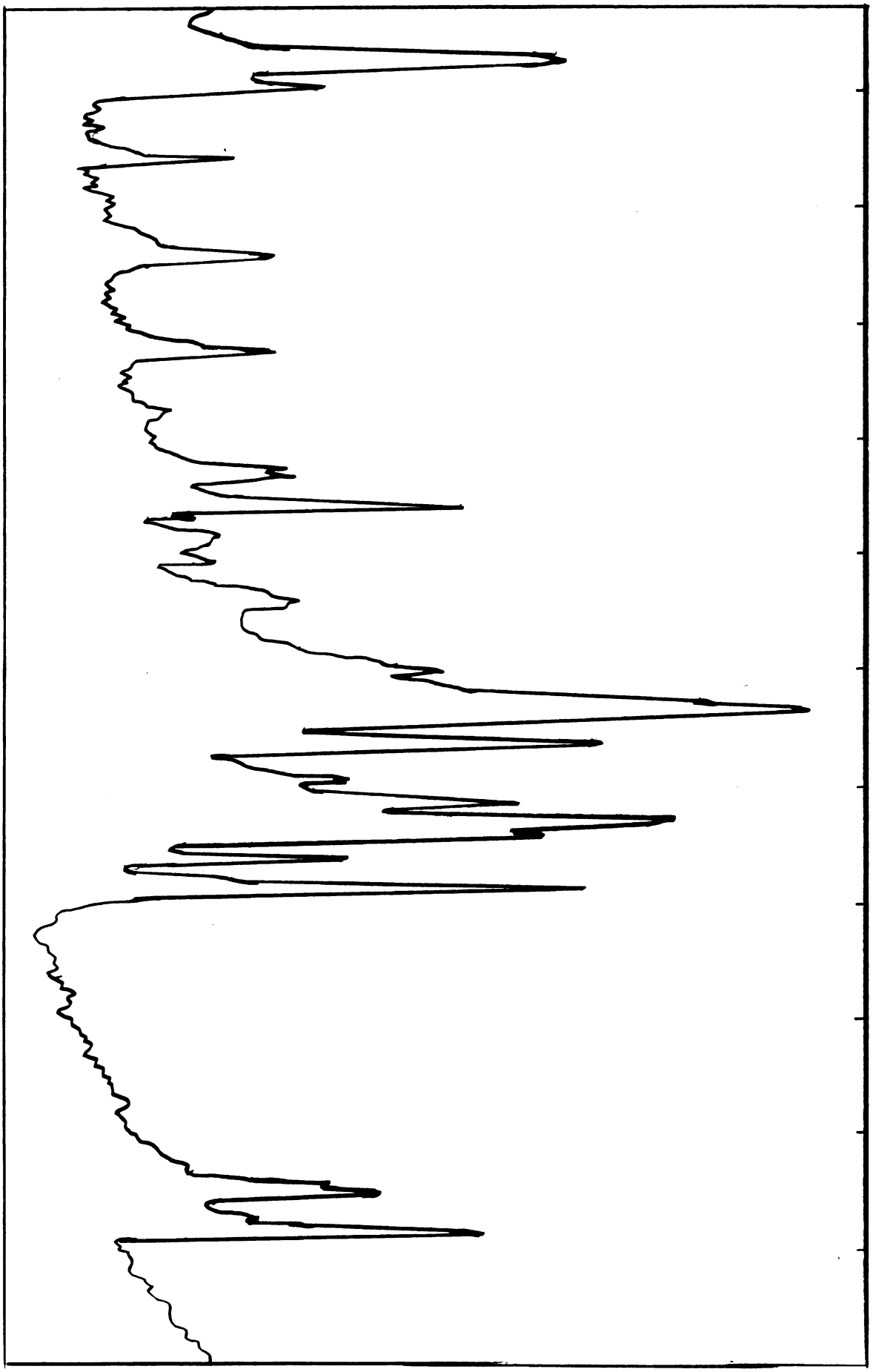


Figure XXIV. Infrared spectrum of KBr pellet of 2'-heptamidophenyl-3,5-dinitro-2-thienyl sulfide.

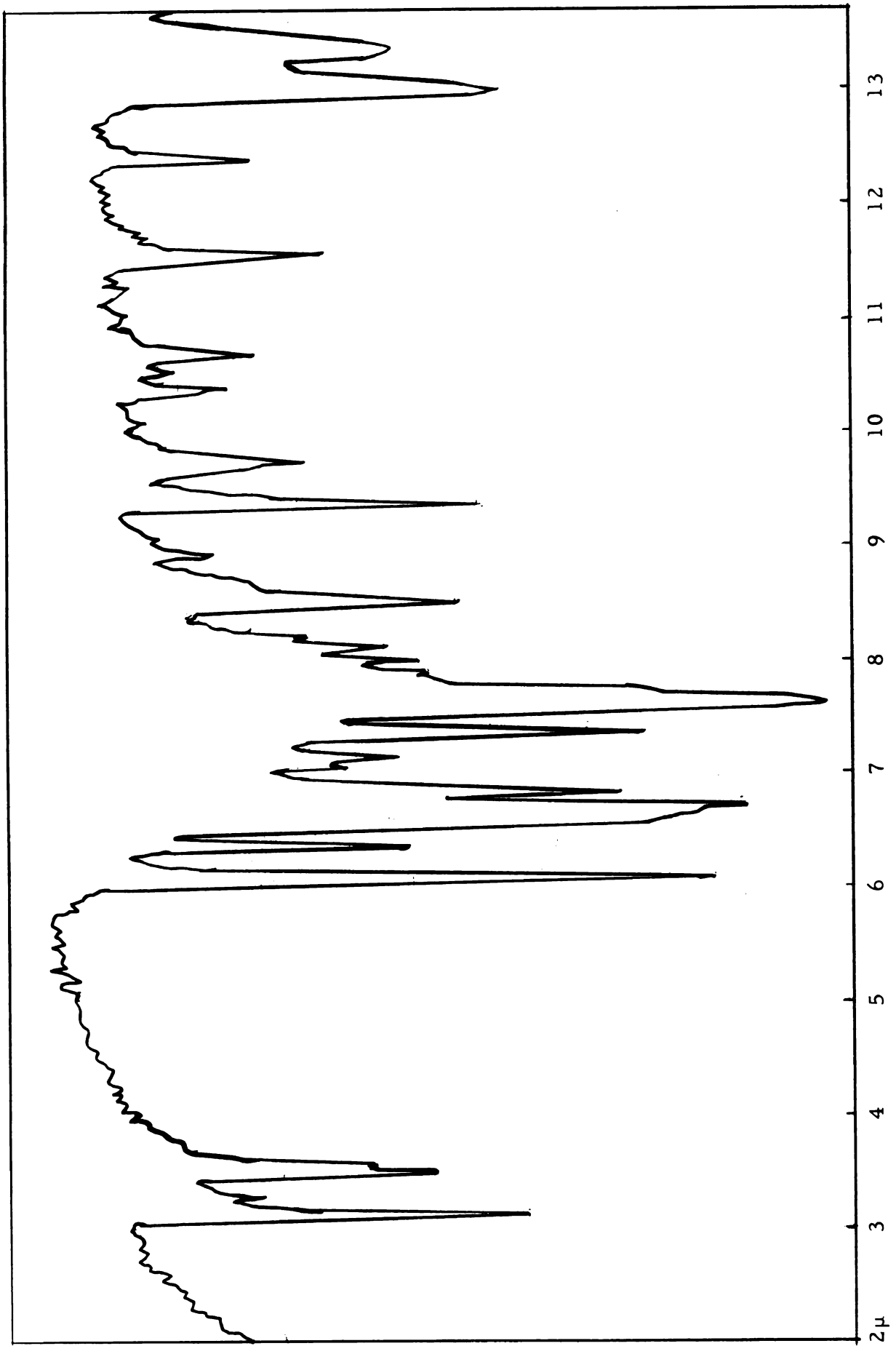


Figure XXV. Infrared spectrum of KBr pellet of 2'-octanamidophenyl-3,5-dinitro-2-thienyl sulfide.

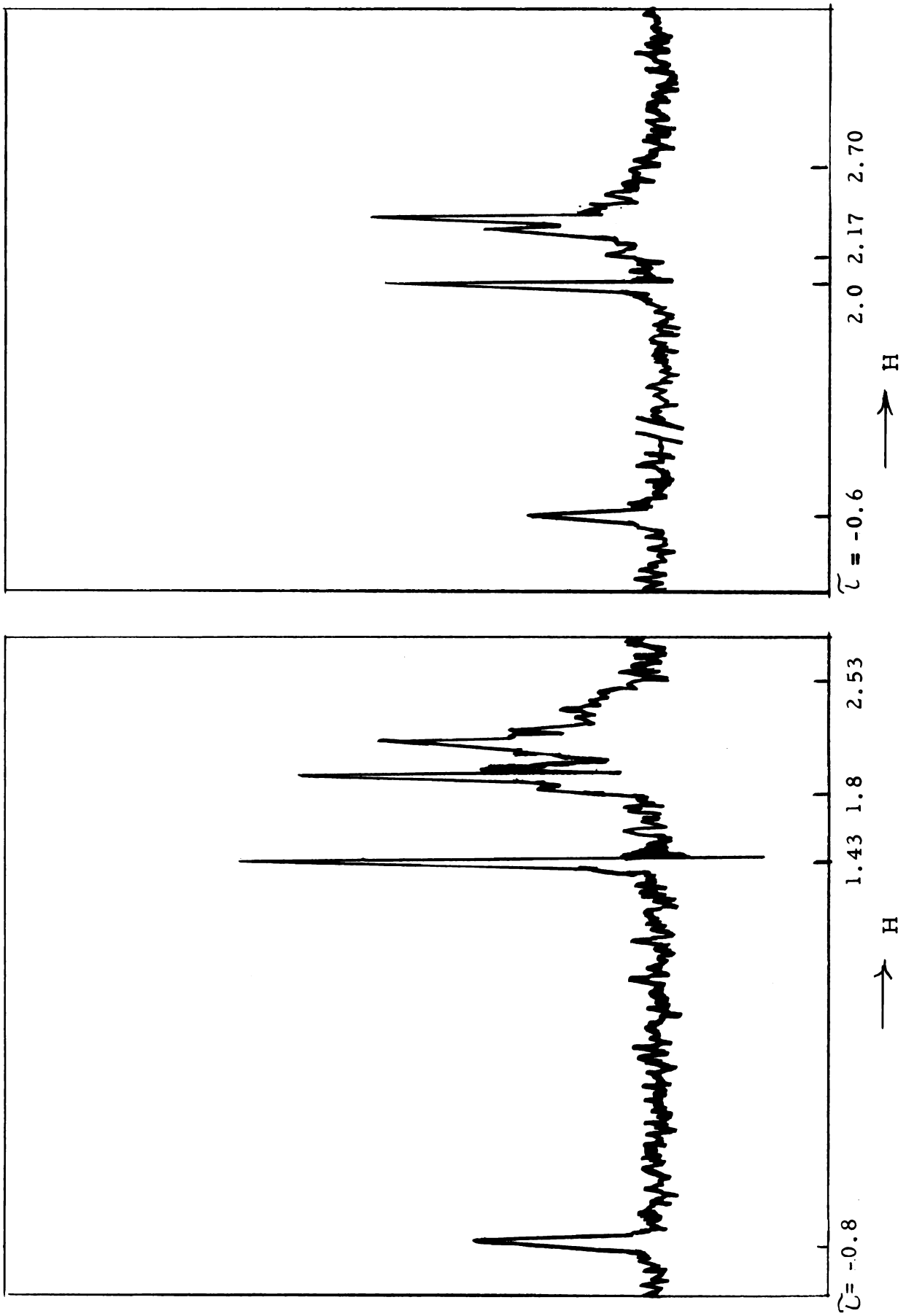


Figure XXVI. N.m.r. spectra of the aromatic regions of 2'-(4, 5-dibromo-2-thenamido)phenyl-3, 5-dinitro-2-thienyl sulfide and 3, 4-dinitro-2, 5-bis-2'-(4, 5-dibromo-2-thenamido)thiophenoxythiophene in DMSO-d_6 at a sweep width of 1000 cps.

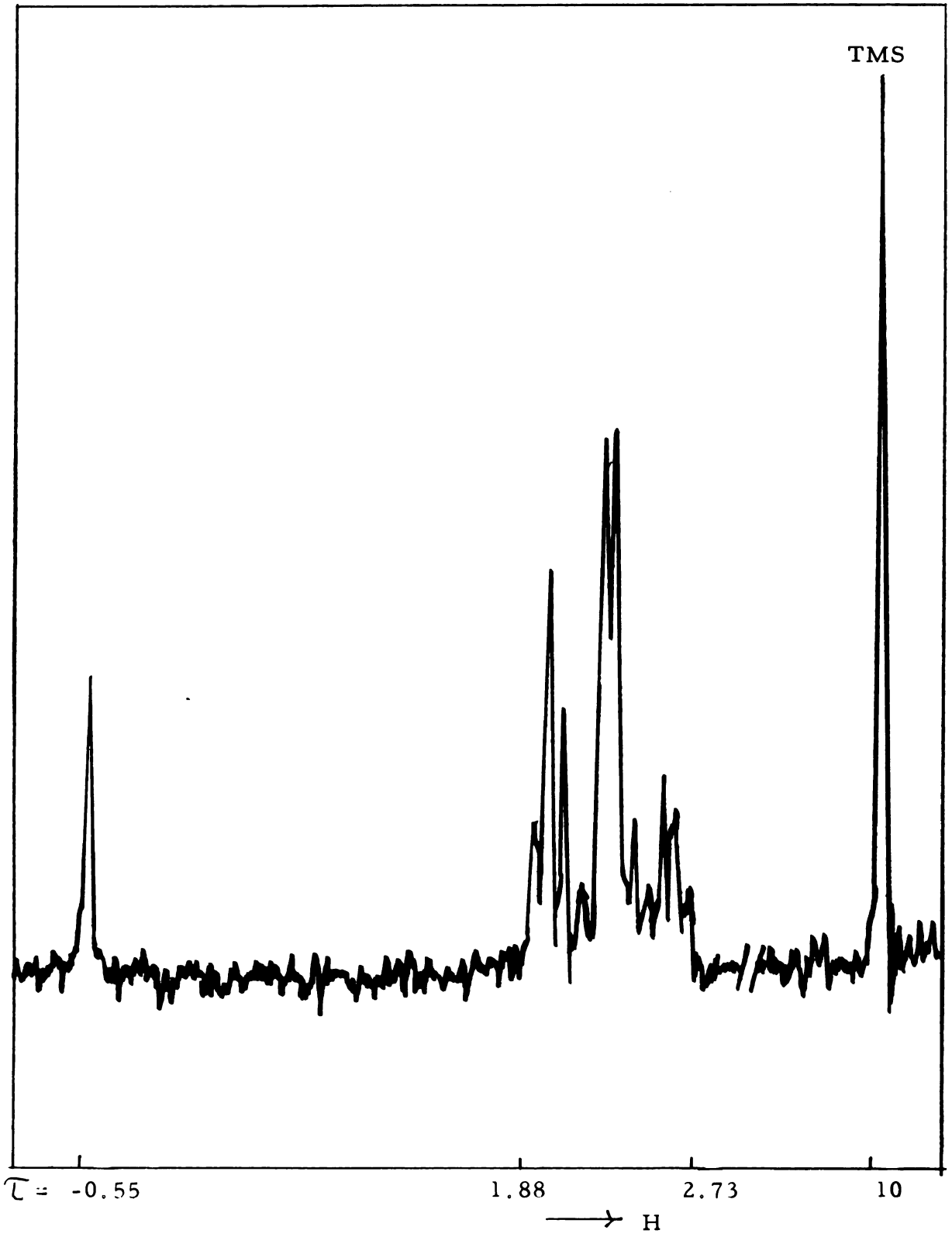


Figure XXVII. N.m.r. spectrum of 3, 4-dinitro-2, 5-bis-2'-(2-thenamido)-thiophenoxythiophene in DMSO-d_6 at a sweep width of 1000 cps.

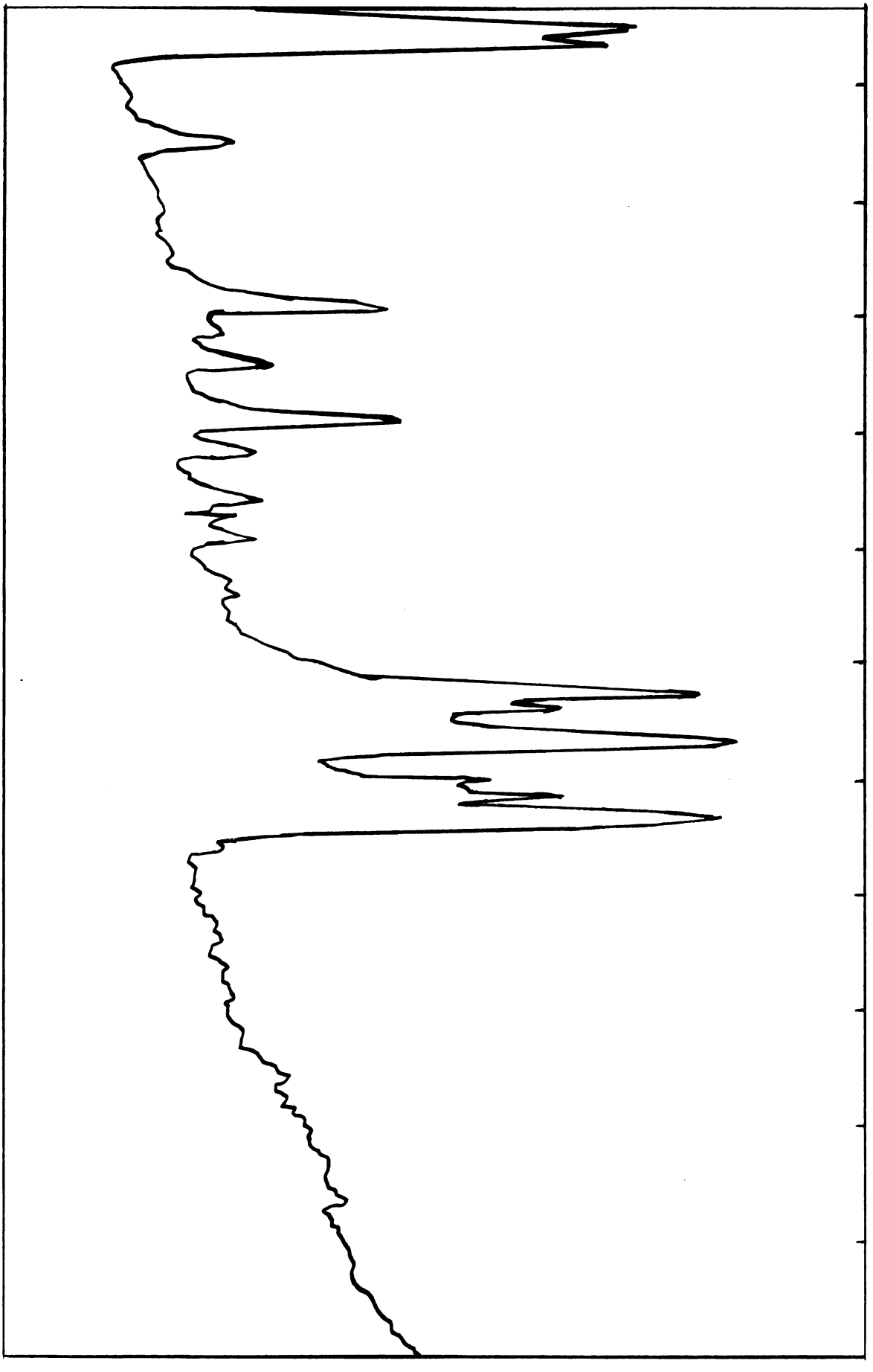


Figure XXXVIII. Infrared spectrum of KBr pellet of 3,4-dinitro-2,5-bis-thiophenoxythiophene.

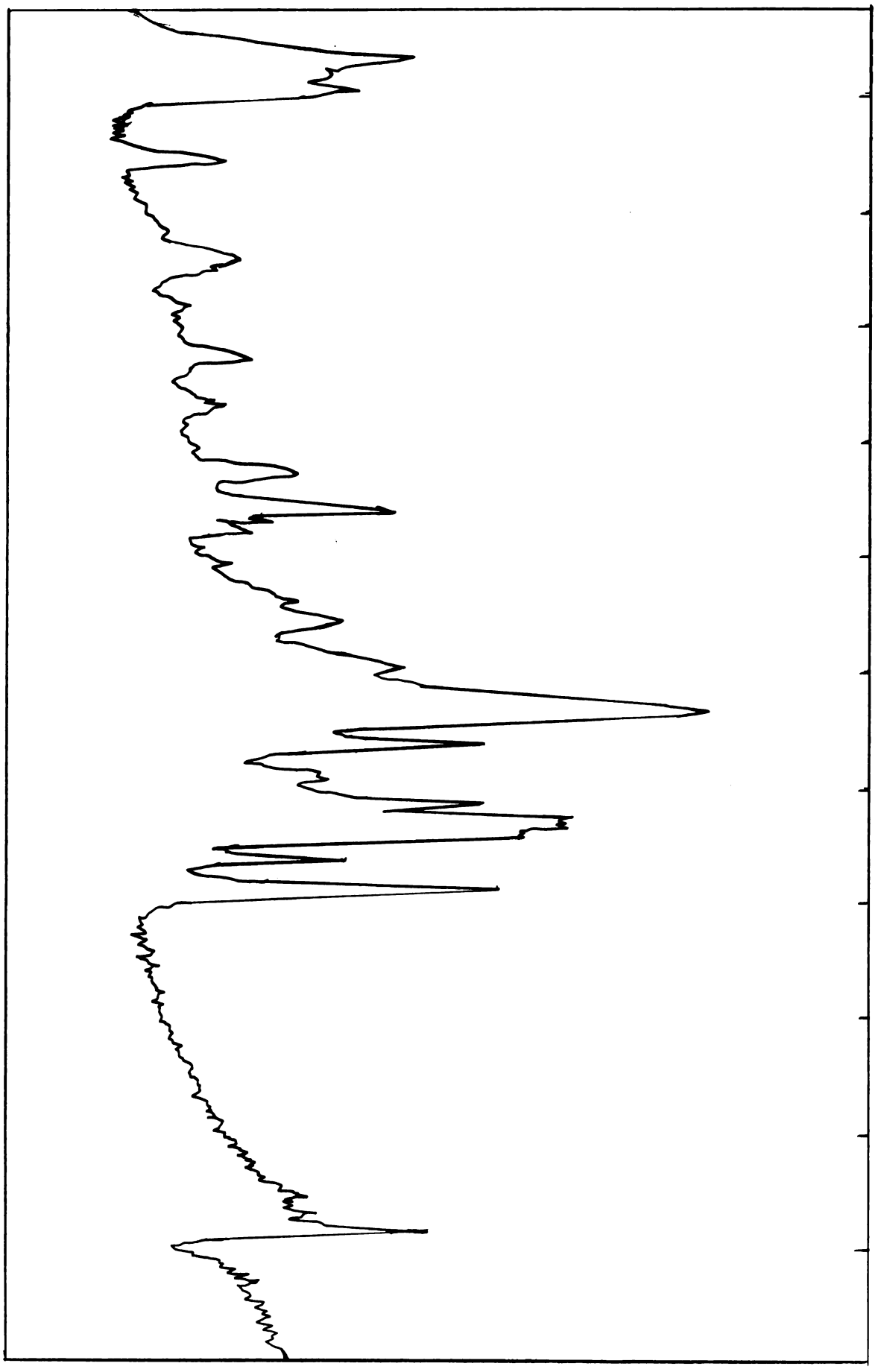


Figure XXIX. Infrared spectrum of KBr pellet of 2'-butyramidophenyl-3,5-dinitro-2-thienyl sulfide.

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