SYNTHESIS OF THIAZOLYL- AND PYRIDYLTHIOUREAS

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SYNTHESIS, REACTIONS AND SPECTRA OF THIAZOLYL- AND PYRIDYLTHIOUREAS AND DERIVATIVES

A thesis

by

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SYNTHESIS, REACTIONS AND SPECTRA OF THIAZOLYL- AND PYRIDYLTHIOUREAS AND DERIVATIVES

ABSTRACT

Various new thiazolyl- and pyridylthioureas were synthesized and their reactions studied.

Attempts to prepare several N-phenyl-N'-2-thiazolylcarbodiimides by the treatment of the thiazolylthioureas mentioned above with lead oxide lead to the formation of new unexpected products, N-phenyl-N,N'-di-(2-thiazolyl)guanidines. Similarly, treatment of N-phenyl-N'-2-thiazolylthioureas with ethyl chloroformate produced N-carbethoxy-N'-phenyl-N-2-thiazolylthioureas or O-ethyl-N-phenyl-N'-2-thiazolylisoureas, instead of the corresponding carbodiimides.

The action of oxidizing agents on mono N-pyridylthioureas resulted in the formation of N-pyridylureas,[1,2,4] thiadiazolo[2,3-a]pyridinium salts or pyridylguanidine sulfides, but not thiazolopyridines.

Contrary to the claims in the literature, 2-aminopyridine 1-oxides do not form substituted thioureas with ammonium thiocyanate, but only thiocyanate salts of 2-aminopyridine 1-oxides. These salts do not isomerize into thioureas.

Reaction of 2-aminopyridine 1-oxides or their 2-acetamido derivatives or their ethyl carbamate derivatives produced unusual cyclic compounds with thiophosgene, but not the expected N-2-pyridylthiourea 1-oxides. The experimental evidence indicates that these compounds have the structure of [1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones.

Département de Chimie

Ph.D.

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SYNTHESE, REACTIONS ET SPECTRES DES THIAZOLYL- ET PYRIDYLTHIOUREES ET DE LEURS DERIVES

RESUME

On a synthétisé plusieurs nouvelles thiazolyl- et pyridylthiourées et on a étudié leurs réactions.

Des essais pour préparer plusieurs N-phényl-N'-thiazolyl-2-carbodiimides en traitant les thiazolylthiourées pré-citées avec l'oxyde de plomb ont conduit à la formation de nouveaux produits inattendus: les N-phényl-N,N'-thiazolyl-2-guanidines. De la même façon, le traitement des N-phényl-N'-thiazolyl-2-thiourées avec le chloroformate d'éthyle a donné les N-carbéthoxy-N'-phényl-N-(thiazolyl-2)thiourées ou des O-éthyl-N-phényl-N'-(thiazolyl-2)isourées, au lieu des carbodiimides correspondants.

L'action des agents oxydants sur les mono N-pyridylthiourées a abouti à la formation de N-pyridylurées, de sels de [1,2,4]thiadiazolo[2,3-a]pyridinium ou de sulfures de pyridylguanidine mais jamais aux thiazolopyridines.

Contrairement aux résultats publiés dans la littérature, les amino-2 pyridine oxydes-1 ne forment pas de

thiourées substituées avec le thiocyanate d'ammonium, mais donnent seulement des thiocyanates d'amino-2 pyridine oxydes-1 Ces sels ne s'isomérisent pas en thiourées.

La réaction avec le thiophosgène des amino-2 pyridine oxydes-1, de leurs dérivés acétamido-2 ou de leurs dérivés de carbamate d'éthyle a donné des composés cycliques inhabituels et non pas les N-pyridyl-2-thiourées attendues. Les données expérimentales indiquent que ces composés ont la structure des [1,2,4]oxadiazolo[2,3-a]pyridinethiones-2.

To my parents,

Rebecca and J.B.

and to

Minou and Baby

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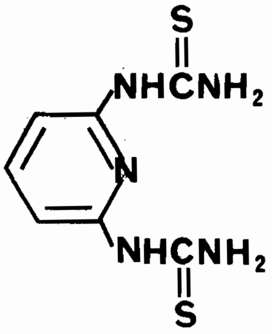

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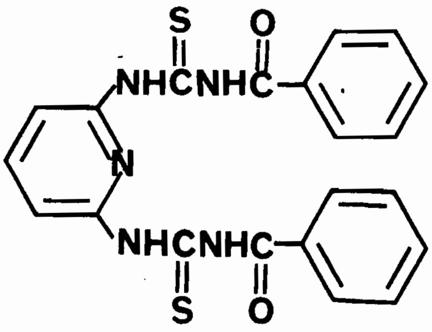

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GENERAL INTRODUCTION

N-Substituted thioureas, $RNHCSNH_2$ and RNHCSNHR, have proven to be valuable intermediates in organic syntheses. For example, they are precursors in the preparation of cyanamides, RNHCN, carbodiimides, RN=C=NR, guanidines, $RNHC(NH_2)=NR$ (or RNHC(NHR)=NH), thiazoles and benzothiazoles. Unsubstituted thiourea, in particular, is used in the synthesis of 2-aminothiazoles.

Before the advent of i.r. and n.m.r. spectroscopy, aliphatic and aromatic amines were often characterized by transforming them into substituted thioureas.

The objective of this work was to study different reactions which could eventually transform various N-phenyl-N'-thiazolylthioureas into the corresponding N-phenyl-N'-thiazolylcarbodiimides which have remained largely unknown. Since only a limited number of N-pyridylthioureas were known, they were synthesized during the course of this work and were then subjected to reactions which could lead to the formation of thiazolopyridines.

During the course of this work, several unexpected reactions were observed and since they produced new compounds, they were studied in detail.

The mass spectra of thiazole and pyridine derivatives available in this work were studied.

HISTORICAL INTRODUCTION

A. GENERAL

Several N-aryl-N'-2-thiazolyl- (1,2), mono-2-thiazolyl- (3), and N-aryl-N'-2-pyridylthiourea derivatives (4,5) have already been investigated. On the other hand, few studies have been reported on monopyridylthioureas of which only N-2-pyridyl- (6,7), N-3-pyridyl- (6) and N-(4-methyl-2-pyridyl)thiourea (8) have been prepared and characterized.

Carbodiimides, R-N=C=N-R, which may be obtained from disubstituted thioureas, are becoming an increasingly important class of compounds. They have been reviewed by Khorana in 1953 (9) and more recently by Kurzer and Douraghi-Zadeh (10). Heterocyclic carbodiimides, however, still remain largely unknown although the N,N'-di-(2-pyridyl)carbodiimide was prepared by Meyer et al.at a relatively early date (11). Benzothiazolylcarbodiimides (12a,b) and 2-thiazolylcarbodiimides containing a 4-aryl substituent (1) have also been synthesized.

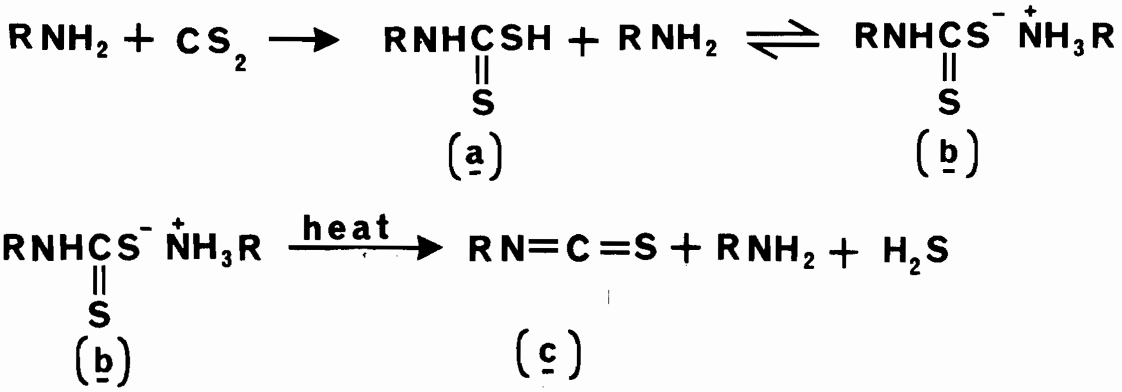
Thiazolopyridines have been prepared by several methods (13,14,15,16) but always in poor yields. None of the procedures employed the Hugerschoff method involving the cyclization of a thiourea derivative with bromine. It was considered of interest to investigate this method as a possible method of synthesis.

B. PREPARATION OF N-SUBSTITUTED THIOUREAS

Thiourea derivatives may be synthesized by a variety of common methods, the choice being dictated by the desired degree of substitution.

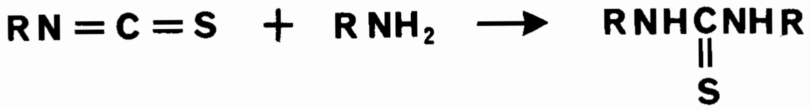
1. Symmetrical thioureas

(a) Heating a primary amine with carbon disulfide in alcohol, benzene or acetone leads to the formation of a 1,3-disubstituted thiourea (17). The reaction may be accelerated by the use of catalysts such as sulfur (18), hydrogen peroxide (18), sodium or potassium hydroxide (19,20) and a variety of others. Since secondary amines do not yield the corresponding tetrasubstituted thioureas (21) and thiourethanes are sometimes formed as side-products if an alcohol is used as solvent (19), isothiocyanates are believed to be intermediate products. According to Schroeder (21), the most reasonable mechanism for this reaction appears to be the following:



$$RNH_2 + CS_2 \longrightarrow \underset{(\underline{a})}{RNH\underset{\underset{S}{\|}}{C}SH} + RNH_2 \rightleftharpoons \underset{(\underline{b})}{RNH\underset{\underset{S}{\|}}{C}S^- \overset{+}{N}H_3R}$$

$$\underset{(\underline{b})}{RNH\underset{\underset{S}{\|}}{C}S^- \overset{+}{N}H_3R} \xrightarrow{heat} \underset{(\underline{c})}{RN{=}C{=}S} + RNH_2 + H_2S$$



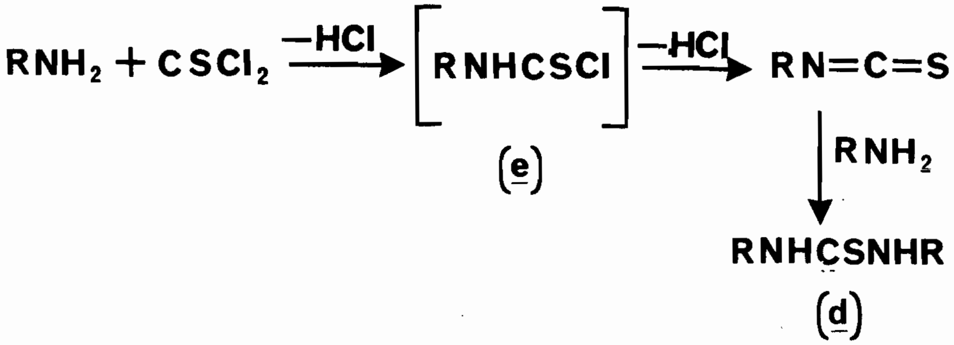
$$RN{=}C{=}S \; + \; RNH_2 \longrightarrow RNH\underset{\overset{\|}{S}}{C}NHR$$

(c) (d)

When the primary amine is treated with carbon disulfide, it first forms a dithiocarbamic acid (a) which is usually unstable and reacts with a second mole of amine to give a substituted ammonium dithiocarbamate (b). When these salts are formed from ammonia or aliphatic amines, they are usually stable enough for identification. Those formed from aromatic amines are less stable, probably due to the decreased basicity of the amine, and may revert back to the acid form or decompose into the isothiocyanate (c) which then adds the amine to form the thiourea (d).

(b) In a second method, thiophosgene reacts with two moles of primary or secondary amine in an aqueous (22), chloroform- (23) or acetone-aqueous (24) medium at reflux temperatures. The use of an equimolar mixture of thiophosgene and a primary amine leads to the formation of an isothiocyanate instead. This reaction has been shown to proceed via a thiocarbamoyl chloride intermediate (e) which eliminates

HCl on heating (25).



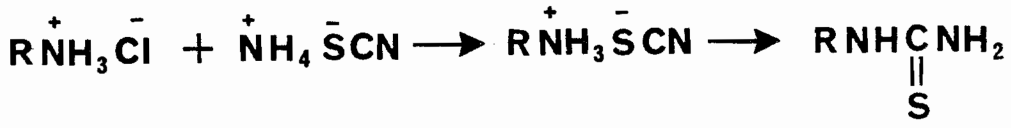
If only one mole of amine is used, the reaction stops at the isothiocyanate stage. When a second mole of amine is added, the reaction goes to completion and forms the desired thiourea (d).

2. Unsymmetrical thioureas

The most common method used in preparing unsymmetrical thioureas consists of reacting an isothiocyanate with an amine, whether primary or secondary, usually in alcohol or benzene. This reaction is so versatile that aromatic, aliphatic, alicyclic and heterocyclic amines have been used to prepare the thioureas. The isothiocyanates themselves may be prepared by several methods: reaction of an equimolar mixture of an amine and thiophosgene; by decomposition of 1,3-disubstituted thioureas with acid (26); by decomposition of ammonium dithiocarbamate salts by heavy metal salts or other reagents (26), or by isomerization of organic thiocyanates (26).

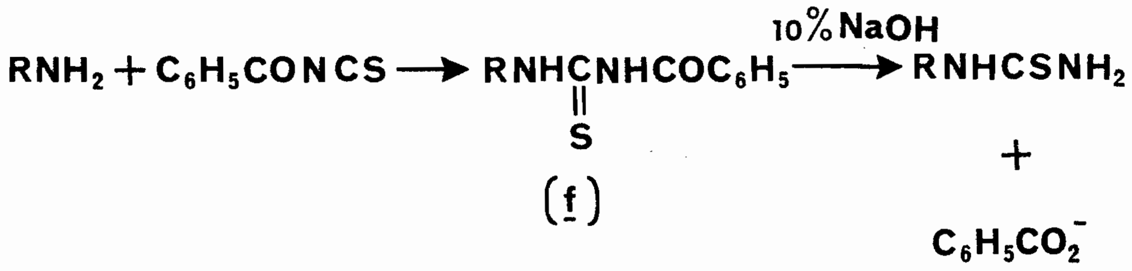
3. Monosubstituted thioureas

(a) The classic rearrangement of ammonium thiocyanate into thiourea on heating at 160° for several hours (27) serves as the basis for this method. An aromatic or aliphatic amine, as a free base or its salt, is heated with ammonium thiocyanate at 110-120° for several hours in an aqueous or inert solvent such as chlorobenzene (28). Evaporation of the solvent yields the isomerized product.



$$R\overset{+}{N}H_3\overset{-}{Cl} + \overset{+}{N}H_4\overset{-}{S}CN \longrightarrow R\overset{+}{N}H_3\overset{-}{S}CN \longrightarrow RNH\underset{\underset{S}{\|}}{C}NH_2$$

(b) By reacting an amine with benzoyl isothiocyanate a benzoylthiourea (f) is obtained which, upon being heated shortly with dilute base, yields the monothiourea directly.

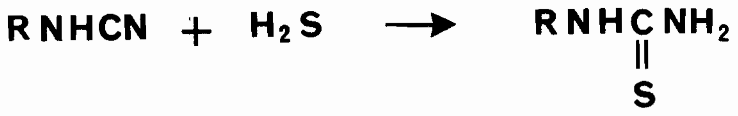


$$RNH_2 + C_6H_5CONCS \longrightarrow RNH\underset{\underset{S}{\|}}{C}NHCOC_6H_5 \xrightarrow{10\%\,NaOH} RNHCSNH_2 + C_6H_5CO_2^-$$

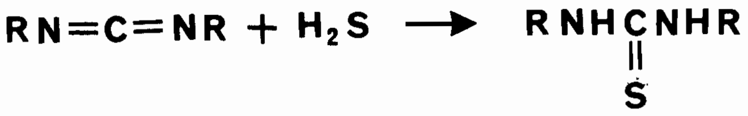
(f)

This facile method may be used with primary or secondary amines and has been applied in the preparation of 2- and 3-pyridylthioureas (7,6), as well as 2-thiazolythioureas (3).

(c) Treatment of a cyanamide with hydrogen sulfide yields a monothiourea. However, in practice the cyanamide is usually obtained first from the thiourea by desulfurization with lead or mercuric oxide. Similarly carbodiimides yield with hydrogen sulfide disubstituted thioureas (29).

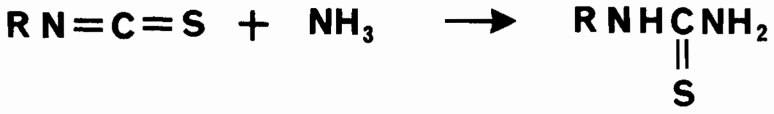


$$RNHCN + H_2S \longrightarrow RNH\underset{\underset{S}{\|}}{C}NH_2$$



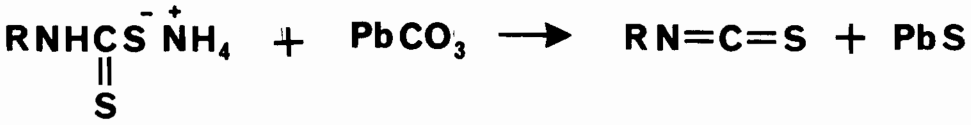
$$RN{=}C{=}NR + H_2S \longrightarrow RNH\underset{\underset{S}{\|}}{C}NHR$$

(d) Other methods include the treatment of an isothiocyanate with ammonia to produce a monothiourea.



$$RN{=}C{=}S + NH_3 \longrightarrow RNH\underset{\underset{S}{\|}}{C}NH_2$$

The former may be obtained from the decomposition of a dithiocarbamate, formed from the reaction of an amine with carbon disulfide and ammonia, followed by treatment with a heavy metal salt such as lead carbonate (30).



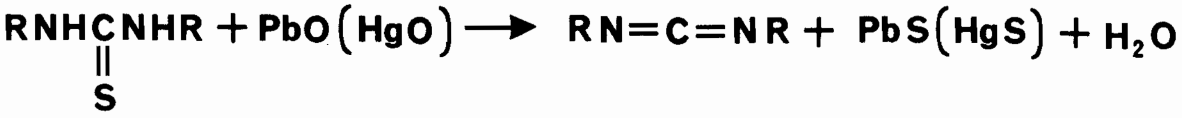
$$\mathrm{RNH}\underset{\overset{\|}{\mathrm{S}}}{\mathrm{C}}\overset{-}{\mathrm{S}}\,\overset{+}{\mathrm{N}}\mathrm{H_4} + \mathrm{PbCO_3} \longrightarrow \mathrm{RN{=}C{=}S} + \mathrm{PbS}$$

C. PREPARATION OF CARBODIIMIDES

Although carbodiimides may be prepared by a variety of methods (10), only those starting from thioureas will be considered. Undesirable side-reactions unfortunately often accompany these preparations: formation of ureas, or isothiocyanates and guanidines, and polymerization of the aromatic carbodiimides (31).

1. Metal oxide desulfurization

Desulfurization of disubstituted thioureas with metal oxides such as lead or mercuric oxide is the most widely used method for the preparation of carbodiimides (10).

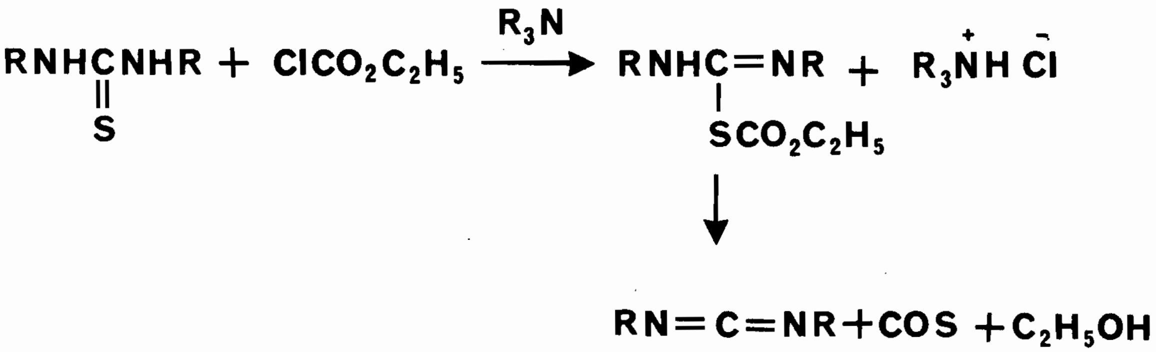


$$\mathrm{RNH}\underset{\overset{\|}{\mathrm{S}}}{\mathrm{C}}\mathrm{NHR} + \mathrm{PbO(HgO)} \longrightarrow \mathrm{RN{=}C{=}NR} + \mathrm{PbS(HgS)} + \mathrm{H_2O}$$

It was reported as early as 1873 by Weith (32) and has remained greatly in use ever since. N,N'-Di-(2-pyridyl)carbodiimide was prepared by the desulfurization of the corresponding thiourea with lead oxide (11). Ether, acetone or benzene are the preferred solvents although toluene, xylene and carbon disulfide have been used, but these usually facilitate polymerization and the formation of side-products (31). N-Phenyl-N'-(4-phenyl-2-thiazolyl)carbodiimide was obtained by treatment of the thiourea with lead oxide(1).

2. Desulfurization with ethyl chloroformate

Treatment of disubstituted thioureas in chloroform at -5° to -10° with lower alkyl chloroformates in the presence of a tertiary amine affords low yields of carbodiimides (33). This method was only applied to alkyl thioureas such as dicyclohexyl- or di-tert-butylthiourea.



$$\mathrm{RNH\underset{\underset{S}{\|}}{C}NHR + ClCO_2C_2H_5 \xrightarrow{R_3N} RNH\underset{\underset{SCO_2C_2H_5}{|}}{C}{=}NR + R_3\overset{+}{N}H\,\overset{-}{Cl}}$$

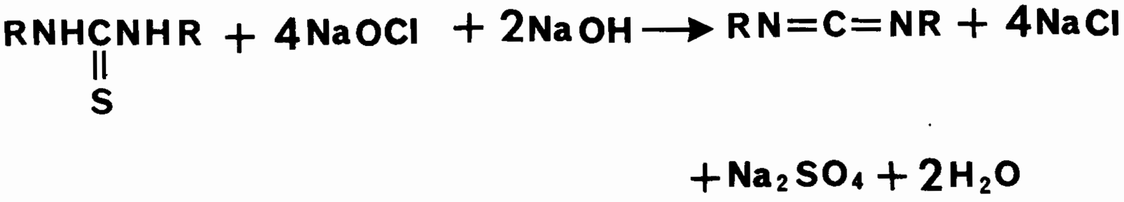
$$\downarrow$$

$$\mathrm{RN{=}C{=}NR + COS + C_2H_5OH}$$

This reaction is initiated by the nucleophilic attack of the sulfur on the carbethoxy carbon displacing a chloride ion. The intermediate product then forms the carbodiimide, eliminating the sulfur as carbon oxysulfide. Ethanol is also produced.

3. Oxidation with sodium hypochlorite

N,N'-Dialkylthioureas are readily oxidized to the corresponding carbodiimides by alkaline hypochlorite below 0° in excellent yields (34).



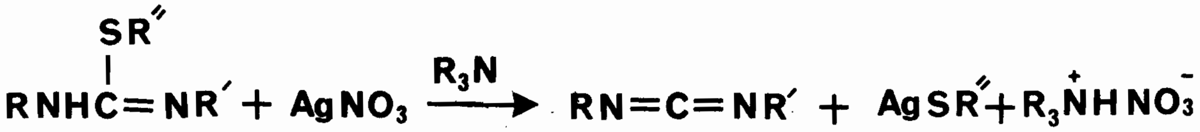
$$\underset{\underset{S}{\|}}{RNHCNHR} + 4NaOCl + 2NaOH \longrightarrow RN{=}C{=}NR + 4NaCl + Na_2SO_4 + 2H_2O$$

The sulfur is removed by the oxidizing agent as sulfate. This oxidation when applied to monosubstituted thioureas or dithiocarbamic acids affords cyanamides or isothiocyanates, respectively.

This method is of fairly general applicability, the main side reaction being the formation of urea.

4. From S-alkylisothioureas

Thioureas and alkyl halides react to form S-alkyl isothioureas which have long been known to undergo fission into an alkylmercaptan and a disubstituted carbodiimide (35). Thus diphenylthiourea affords N,N-diphenylcarbodiimide (36). Ferris and Schutz (37) pointed out that the mercaptide group may be removed from aliphatic and aromatic isothioureas by silver nitrate or mercuric chloride in the presence of base in organic solvents such as dimethylformamide.



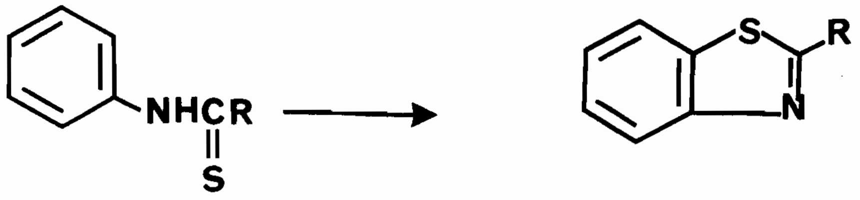
$$\mathrm{RNH}\overset{\mathrm{SR''}}{\overset{|}{\mathrm{C}}}\mathrm{=NR'} + \mathrm{AgNO_3} \xrightarrow{\mathrm{R_3N}} \mathrm{RN=C=NR'} + \mathrm{AgSR''} + \mathrm{R_3}\overset{+}{\mathrm{N}}\mathrm{HNO_3^-}$$

The silver-alkyl mercaptides precipitate from the solution and are filtered off, leaving the carbodiimides to be used directly for any desired subsequent reaction.

D. PREPARATION OF THIAZOLOPYRIDINES

Thiazolopyridines have been prepared by many methods which bring about the annelation of the thiazole ring to the pyridine ring. Precursors used in these synthesis include o-aminomercaptopyridines (38,39,40,41,42), o-aminothiocyanopyridines (15,14) and thioacylamidopyridines (16,43). This last group is of particular interest since it includes pyridylthioureas as possible precursors.

Thioacylamidoaromatic compounds may undergo ring closure by the use of various reagents.

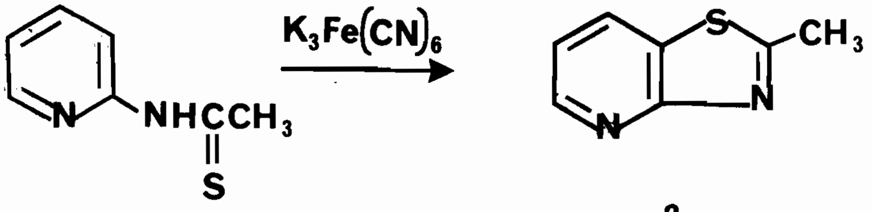


R = alkyl
alkoxyl
carbonyl
amino

Depending on the nature of the particular thioacylamido-compound used, either the Jacobsen synthesis or the Hugerschoff synthesis may be used.

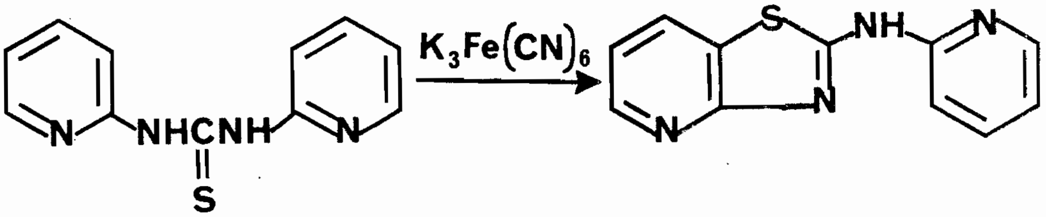
1. <u>The Jacobsen synthesis</u>

Jacobsen observed that treatment of thioanilides and thiourethanes with potassium ferricyanide yielded benzothiazoles and their alkoxy derivatives (44).



1 2

Thioacetanilide was cyclized in this way to 2-methylbenzothiazole. Similarly 2-methylthiazolo[4,5-b]pyridine (2) was prepared from 2-thioacetamidopyridine (1) (16). Baker and Hill cyclized N,N'-di-(2-pyridyl)thiourea (3) to 2-(2-pyridylamino)thiazolo[4,5-b]pyridine (4) also with potassium-ferricyanide (43).



3

4

2. The Hugerschoff synthesis

In 1903, Hugerschoff cyclized diphenylthiourea to 2-phenylaminobenzothiazole by using bromine in an inert solvent (45). Since then, this method has been extensively used for the cyclization of arylthioureas to benzothiazoles (46). No thiazolopyridines have been synthesized by this method, however.

E. SULFUR BONDING

Sulfur belongs to the subgroup VIB and in normal conditions is bivalent since its electronic valence configuration is $3s^2 3p_x^2 3p_y 3p_z$. Since it lies directly below oxygen in the Periodic Table, it has often been compared with oxygen in terms of behaviour. However, unlike oxygen, sulfur possesses 3d orbitals of sufficiently low energy to be used for bond formation, a feature reflected also by phosphorus and other elements of the third row. Thus sulfur can achieve higher valence states in inorganic compounds such as SF_4 or SF_6, or in organic compounds such as sulfonium salts, sulfoxides, sulfones, S-ylides or S-oxides.

In order to use its 3d orbitals, sulfur must promote one or two electrons to the 3d orbitals where sp^3d or sp^3d^2 hybridization then occurs. However, since the 3d orbitals are diffuse and weakly bound, the energy gained by the increased covalency does not compensate for the energy required for the electronic promotion. On the other hand, if the ligands attached to sulfur are electronegative atoms, such as oxygen or the lighter halogens, the 3d orbitals become polarized, that is, they undergo a contraction in size allowing them the possibility of substantial overlap with the orbitals of these atoms at normal bond distance, with the formation of σ or π bonds. The electronegativity of the ligand is the decisive factor and is well reflected by the fact that sulfur can form a hexahalide only with fluorine (47). In the unmodified or unpolarized sulfur atom, only the s and p orbitals are of suitable size for binding and polarization affects them only slightly.

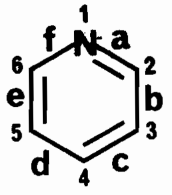
A comparison between C=O and C=S bond energies points to a higher stability of the C=O bond. Thus, the bond energy for C=O is 152 kcal and for C=S, 103 kcal. On the other hand, the bond energy of a C-O single bond is 70 kcal (2x70 = 140 kcal, less than 152 kcal, increased stability of C=O) and of a C-S single bond, 54.5 kcal (2x54.5 = 109 kcal, greater than 103 kcal, decreased stability of C=S) (48a). From these data, it is easily seen why the thione group is relatively unstable in the monomeric form, as in thioaldehydes and alkyl thioketones, and has a marked tendency to revert to stable C-S single bonds. Overlapping of 3p-2p orbitals to produce a π bond in C=S is much less favorable than the 2p-2p overlapping in C=O. Because of this, thione-thiol tautomerism is often present in compounds containing a thiocarbonyl group (49). If the thiocarbonyl group is bound to heteroatoms such as S,O or N its stability is increased because of resonance.

The bond length for C=O is 1.26 Å, for C=S, 1.61 Å, for C-O, 1.43 Å and for C-S, 1.82 Å. The longer bond lengths for the bonds to sulfur are reasonable in view of the increased size of the sulfur atom.

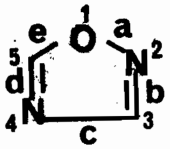
F. NOMENCLATURE

The oxadiazolopyridines are named and numbered according to the rules on nomenclature given in the Ring Index (50). Pyridine is chosen as the parent compound since it is the largest nitrogen-containing component present. The prefix "oxadiazolo-" is then used to denote the other component, the oxadiazole.

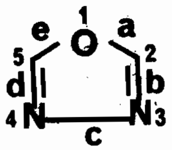
Similarly in thiadiazolopyridines, pyridine is the parent compound and the thiadiazole is denoted by the prefix "thiadiazolo".



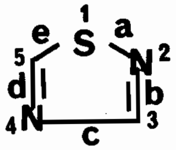
pyridine



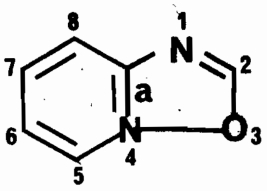
1,2,4-
oxadiazole



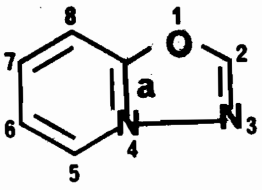
1,3,4-
oxadiazole



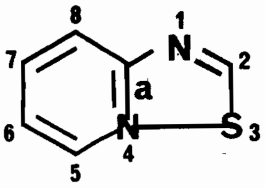
1,2,4-
thiadiazole



[2,3-a]



[3,2-a]



[2,3-a]

DISCUSSION OF RESULTS

A. REACTIONS OF N-PHENYL-N'-2-THIAZOLYLTHIOUREAS

In order to study the possibilities of synthesizing thiazolylcarbodiimides, it was necessary to investigate the reactions of N-phenyl-N'-2-thiazolylthioureas which should lead to carbodiimides. To accomplish this, a number of N-2-thiazolylthioureas had to first be prepared from the appropriate 2-aminothiazoles.

It was found, however, that the N-2-thiazolylthioureas reacted differently from what was expected in attempts to convert them into the corresponding carbodiimides and gave some unexpected products.

1. Synthesis of N-phenyl-N'-2-thiazolylthioureas

(a) N-Phenyl-N'-2-thiazolylthiourea (5) and N-phenyl-N'-(4-methyl-2-thiazolyl)thiourea (6)

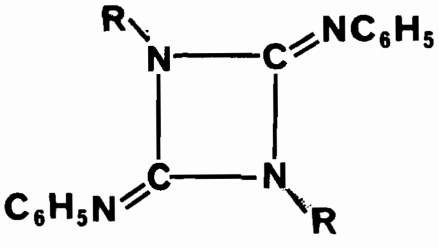
Both 5 and 6 were obtained in good yields following the method of Buu-Hoi et al. (2) by treatment of the 2-aminothiazoles with phenyl isothiocyanate in a small amount of absolute ethanol.

(b) N-Phenyl-N'-(4-phenyl-2-thiazolyl)- (7) and N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thioureas (8)

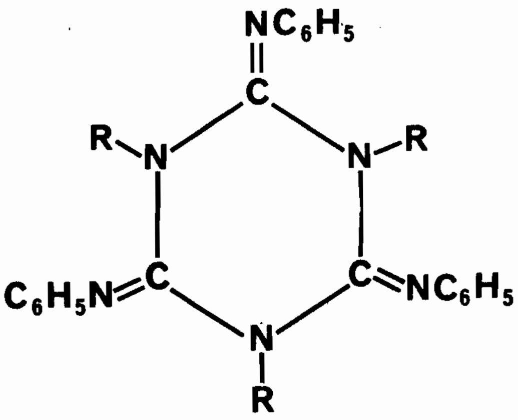
The starting 2-aminothiazoles were prepared by the method of Dodson and King (51) in good yields by treatment of acetophenone or propiophenone with thiourea and iodine. The resulting 2-aminothiazoles were then condensed with phenyl isothiocyanate to yield 7 and 8 in good yield.

2. Treatment of N-phenyl-N'-2-thiazolylthioureas with lead oxide: Preparation of N-phenyl-N',N''-di-(2-thiazolyl) guanidines

Bhargava and Sharma (1) claimed to have prepared a series of N-aryl-N'-(4-phenyl-2-thiazolyl)carbodiimides by desulfurizing the corresponding thioureas with lead oxide in refluxing benzene. Beautiful colorless crystals were deposited whose elemental N and S values agreed with values calculated for a carbodiimide structure. No mention was made, however, of the i.r. spectra of these compounds which should give a characteristic carbodiimide band in the 2160-2120 cm^{-1} region. Therefore, the possibility that these carbodiimides were actually present in the dimeric (a) or trimeric (b) form cannot be dismissed.



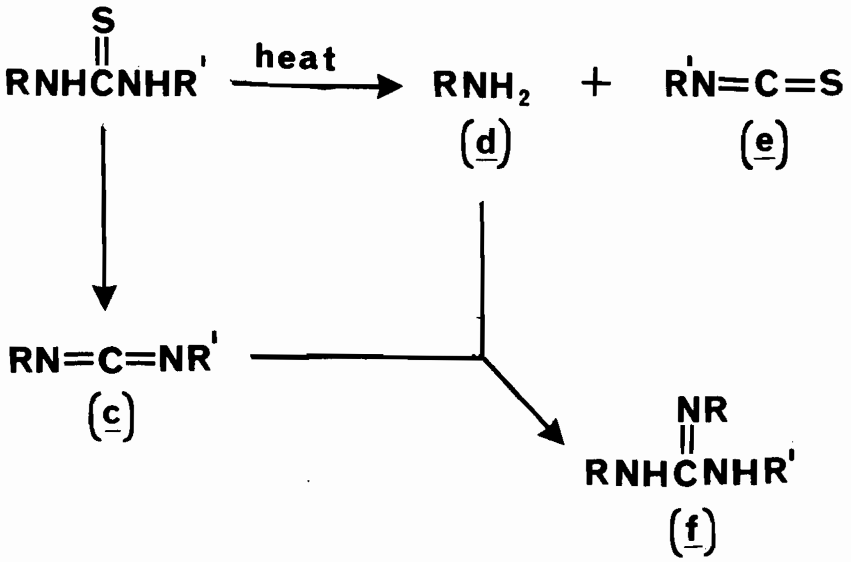
(a)



(b)

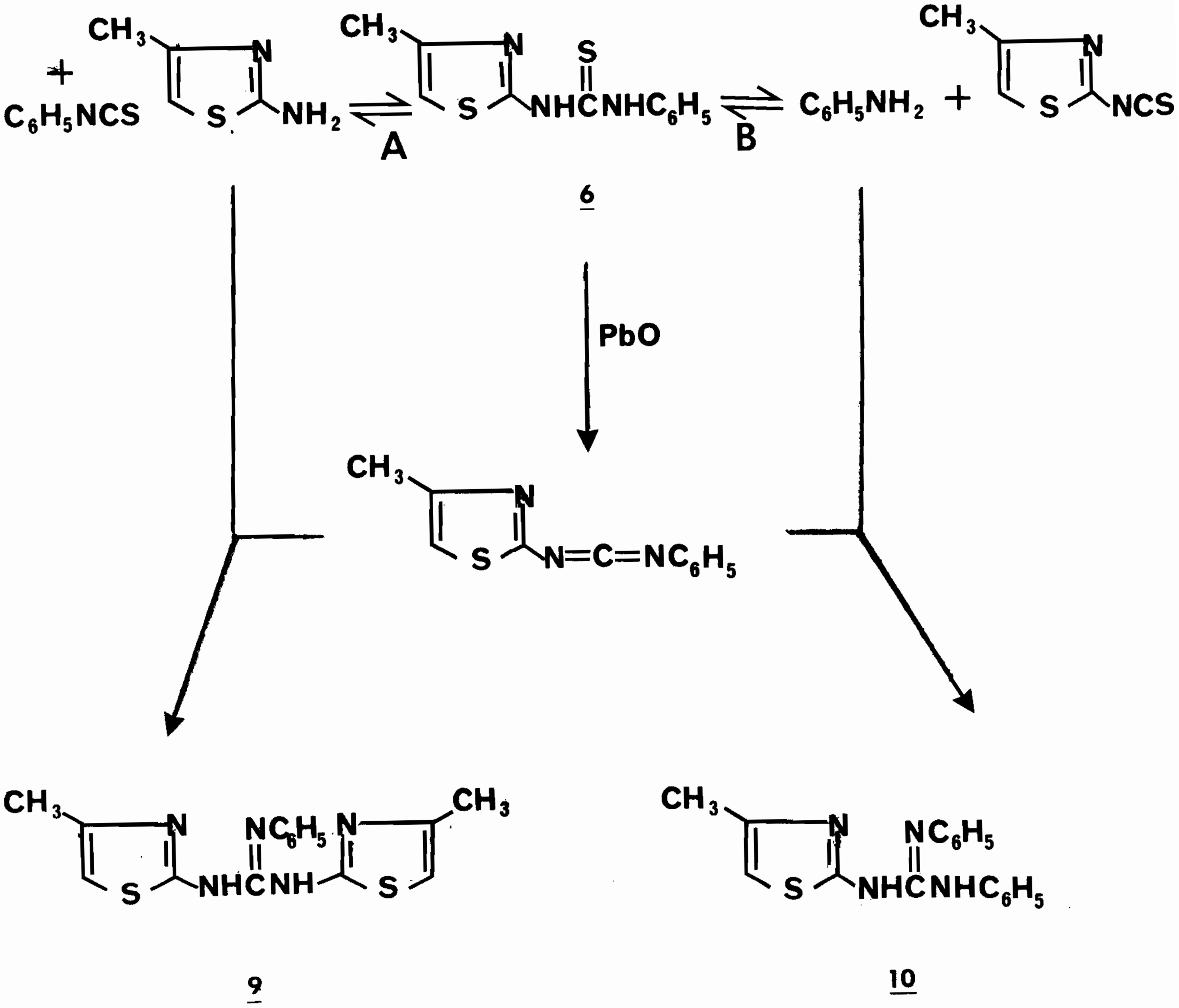
In the present investigation, none of the N-2-thiazolylthioureas gave the desired carbodiimides on being treated with lead oxide for several hours in refluxing dry benzene. Desulfurization was confirmed by the appearance of black lead sulfide about an hour after the start of the reaction. In each case, the work-up yielded a solid whose i.r. spectrum was different from that of the starting material but which did not show any of the characteristic carbodiimide bands. However, a rather strong absorption was present in the 1611-1658 cm^{-1} region indicating the presence of the imino link -C=N-. The formation of this group may be understood by considering the conditions in which the desulfurization of the N-2-thiazolylthioureas took place. It is known that if high-boiling solvents such as toluene are used, side products, like guanidines, are often formed (10) from substituted thioureas.

The following explanation may be proposed. The thiourea on being heated in a solvent in the presence of lead oxide may be desulfurized to the corresponding carbodiimide (c) or may undergo thermal dissociation into an amine (d) and an isothiocyanate (e). If these two routes are followed simultaneously, the amine (d) may react with the carbodiimide (c) to form a guanidine derivative (f).



In this work, the desulfurization of N-phenyl-N'-2-thiazolylthioureas led to the formation of N-phenyl-N',N"-di-(2-thiazolyl)guanidines. The corresponding N,N'-diphenyl-N"-2-thiazolylguanidines were not observed although theoretically they could have been formed. For example, depending on the thermal dissociation route (A or B) followed, N-phenyl-N'-(4-methyl-2-thiazolyl)thiourea (6) may give either N-phenyl-N',N"-di-(4-methyl-2-thiazolyl)guanidine (9) or N,N'-diphenyl-N"-(4-methyl-2-thiazolyl)guanidine (10) as illustrated in Scheme 1.

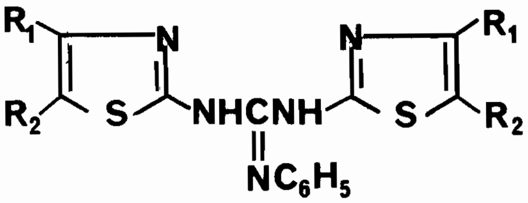
The choice of route A or B appears to depend on the relative stability of the intermediate isothiocyanates. Phenyl isothiocyanate is a stable liquid whereas the 4-methyl-2-thiazolyl isothiocyanate is an unstable red oil which polymerizes readily (52). Obviously route A leading to the formation of phenyl


C6H5NCS
CH3
N
S
NH2
A
S
NHCNHC6H5
B
C6H5NH2
NCS
6
PbO
N=C=NC6H5
NHCNH
NC6H5
NHCNHC6H5
9
10

Scheme 1

isothiocyanate will be favored and product (9) will predominate.

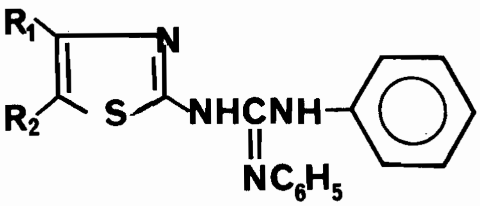
The same reasoning applies to all the thioureas examined: thus 5 gave N-phenyl-N',N''-di-(2-thiazolyl)guanidine (11); 7 afforded N-phenyl-N',N''-di-(4-phenyl-2-thiazolyl)guanidine (12) and 8 produced N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13).



11: $R_1=R_2=H$

12: $R_1=C_6H_5$ $R_2=H$

13: $R_1=C_6H_5$ $R_2=CH_3$



14: $R_1=R_2=H$

16: $R_1=C_6H_5$ $R_2=H$

17: $R_1=C_6H_5$ $R_2=CH_3$

The identity of guanidines 9, 11, 12, 13 was established by comparison with authentic samples prepared by desulfurizing the starting thioureas in the presence of the appropriate 2-aminothiazoles. The melting points, the mass and i.r. spectra were compared and found to be identical.

Furthermore, by desulfurizing the thioureas in the presence of aniline, the corresponding N,N'-diphenyl-N''-2-thiazolylguanidines 14, 10, 16, 17 were synthesized. Compound 14 was also obtained by treatment of S-methyl-N-phenyl-N'-2-thiazolylisothiourea (5a) with mercuric chloride in the presence of aniline.

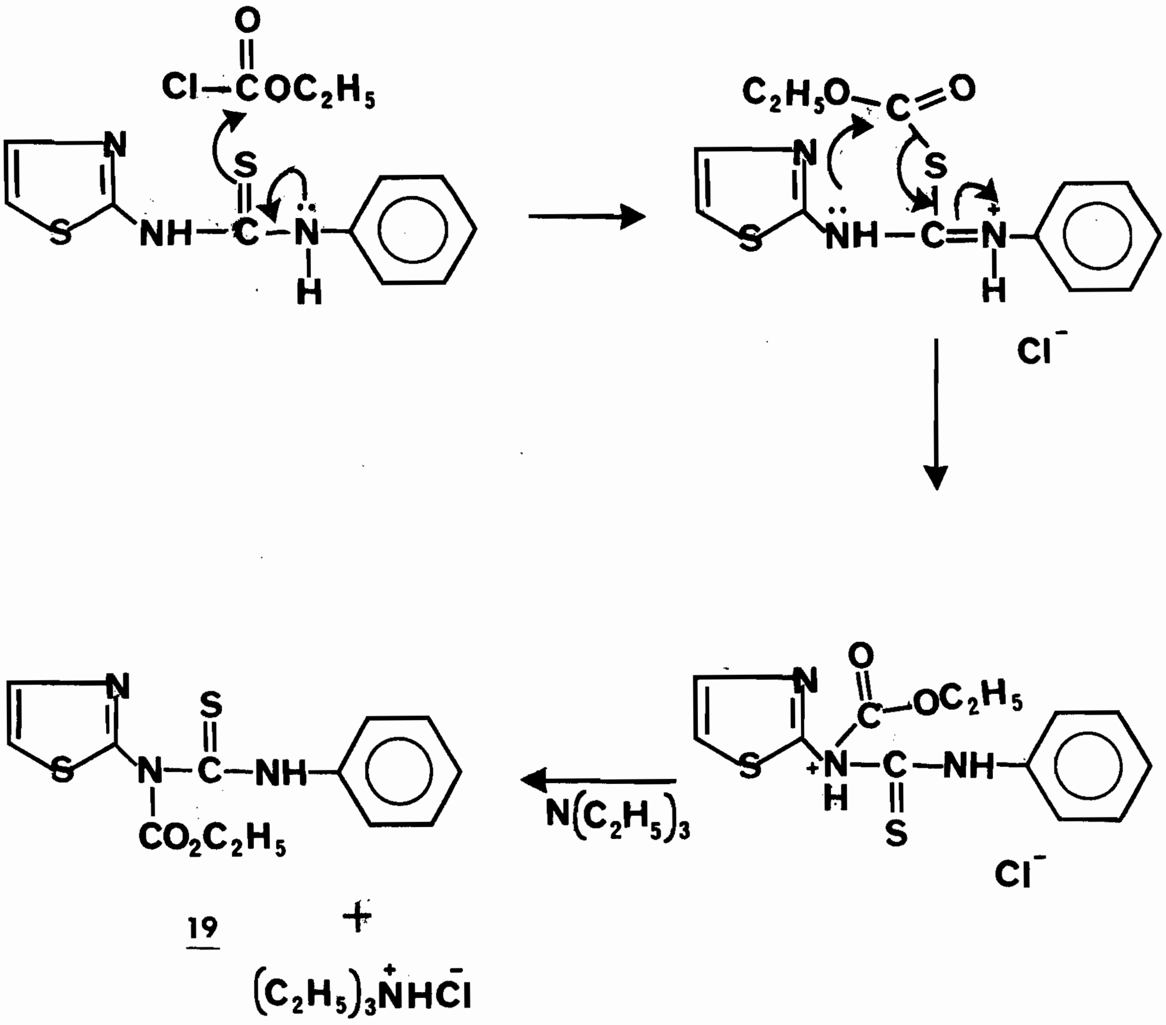
3. Treatment of N-phenyl-N'-2-thiazolylthioureas with ethyl chloroformate: Preparation of N-carbethoxy-N'-phenyl-N-2-thiazolylthioureas and O-ethyl-N-phenyl-N'-2-thiazolylisoureas

The treatment of aliphatic N-substituted thioureas with ethyl chloroformate in chloroform has been investigated by Coles and Levine (33). In the present study, the thioureas examined were all aromatic and heteroaromatic.

Thus, N-phenyl-N'-2-thiazolylthiourea (5) on treatment with ethyl chloroformate at room temperature gave a 38% yield of N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19), m.p. 94-5° (ethanol). Its i.r. spectrum showed a very strong band at 1704 cm^{-1} (C=O) characteristic of disubstituted urethanes. The n.m.r. spectrum revealed a triplet at δ 1.14 and a quartet at δ 4.26 attributed to the $-CH_3$ and $-CH_2$ protons of the carbethoxy group. The mass spectrum showed the expected molecular ion of m/e 307. The major decomposition products of 19 were phenyl isothiocyanate of m/e 135 and ethyl N-2-thiazolylcarbamate (18) of m/e 172. Exact mass measurement confirmed the empirical formula of 19 to be $C_{13}H_{13}N_3O_2S_2$.

Treatment with excess ethyl chloroformate afforded, however, ethyl N-2-thiazolylcarbamate (18) in 52% yield, identified with an authentic sample obtained from 2-aminothiazole and ethyl chloroformate.

That the carbethoxy group is on the nitrogen next to the thiazole ring and not on the nitrogen next to the phenyl group may be rationalized by the following proposed reaction mechanism:

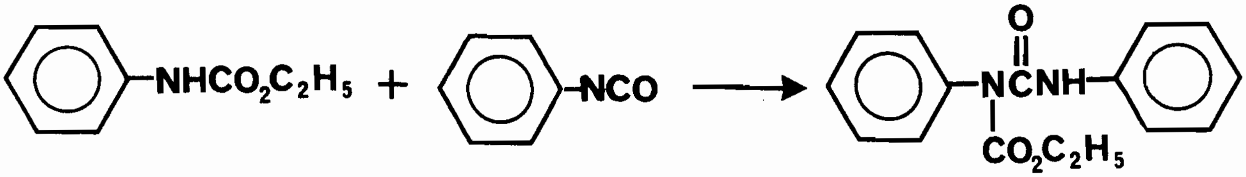


It is very likely that the nucleophilic attack on the ethyl chloroformate is initiated by the sulfur atom since it is known to react rapidly with acylating agents to form S-substituted derivatives. If ethanol and carbon oxysulfide are then expelled, a carbodiimide will be formed. On the other hand, the aniline nitrogen may attack through its lone pair followed by a migration of the carbethoxy group from the sulfur to the more basic aminothiazole nitrogen. Rearrangement to nitrogen is quite common in the products of thioureas and thioamides. For example, acylation of thiourea under mild conditions yields the S-acylisothiouronium salts whereas, upon heating or in the presence of pyridine, the N-acylthiourea is formed (53).

The fact that the carbethoxy group is placed on the nitrogen adjacent to the thiazole ring is in agreement with the decomposition path observed in the mass spectrum of 19, as mentioned earlier. To produce ethyl N-2-thiazolylcarbamate as a major fragment, 19 must possess its carbethoxy group near the thiazole ring, otherwise the formation of ethyl phenylcarbamate should predominate.

Likewise, N-phenyl-N'-(4-methyl-2-thiazolyl)thiourea (6) gave upon treatment with ethyl chloroformate N-carbethoxy N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20) in 37% yield. The presence of a disubstituted N-carbethoxy group was supported by a very strong C=O absorption at 1702 cm^{-1} in its i.r. spectrum. The n.m.r. spectrum indicated the presence of an ethyl group by displaying a triplet at δ 1.07 and a quartet at δ 4.14. The mass spectrum showed the parent ion of m/e 321 in agreement with the empirical formula $C_{14}H_{15}N_3O_2S_2$ established by elemental analysis. The fragmentation pattern of 20 again pointed to the presence of the carbethoxy group on the nitrogen next to the thiazole ring.

Attempts to prepare N-carbethoxy N'-phenyl-N-2-thiazolylthiourea (19) and N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)-thiourea (20) by an alternate route proved unsuccessful. Although it is known that ethyl phenylcarbamate (g) and phenyl isocyanate (h) react to give N-carbethoxy-N,N'-diphenylurea (i) (54),

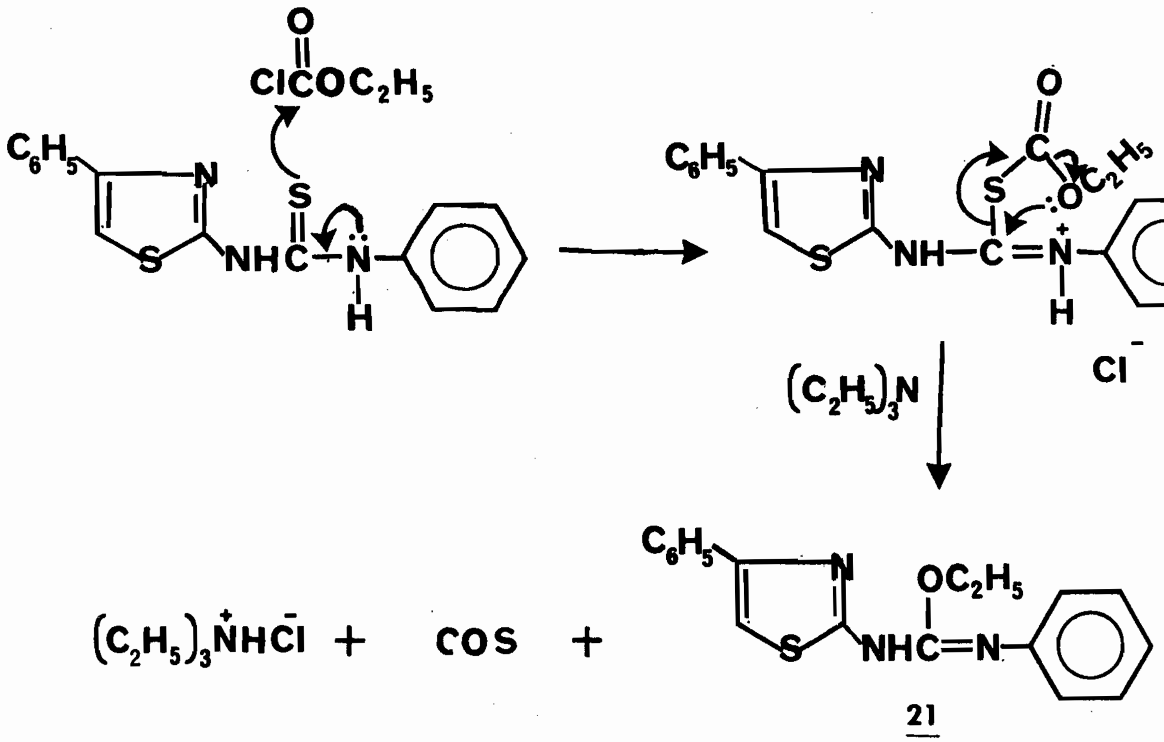


(g) (h) (i)

it was observed that treatment of ethyl N-2-thiazolylcarbamate (18) or its 4-methyl analogue with phenyl isothiocyanate at reflux for several days failed to induce any reaction at all. This may be attributed to the lower reactivity of phenyl isothiocyanate towards nucleophilic attack by the ethyl N-2-thiazolylcarbamate (18).

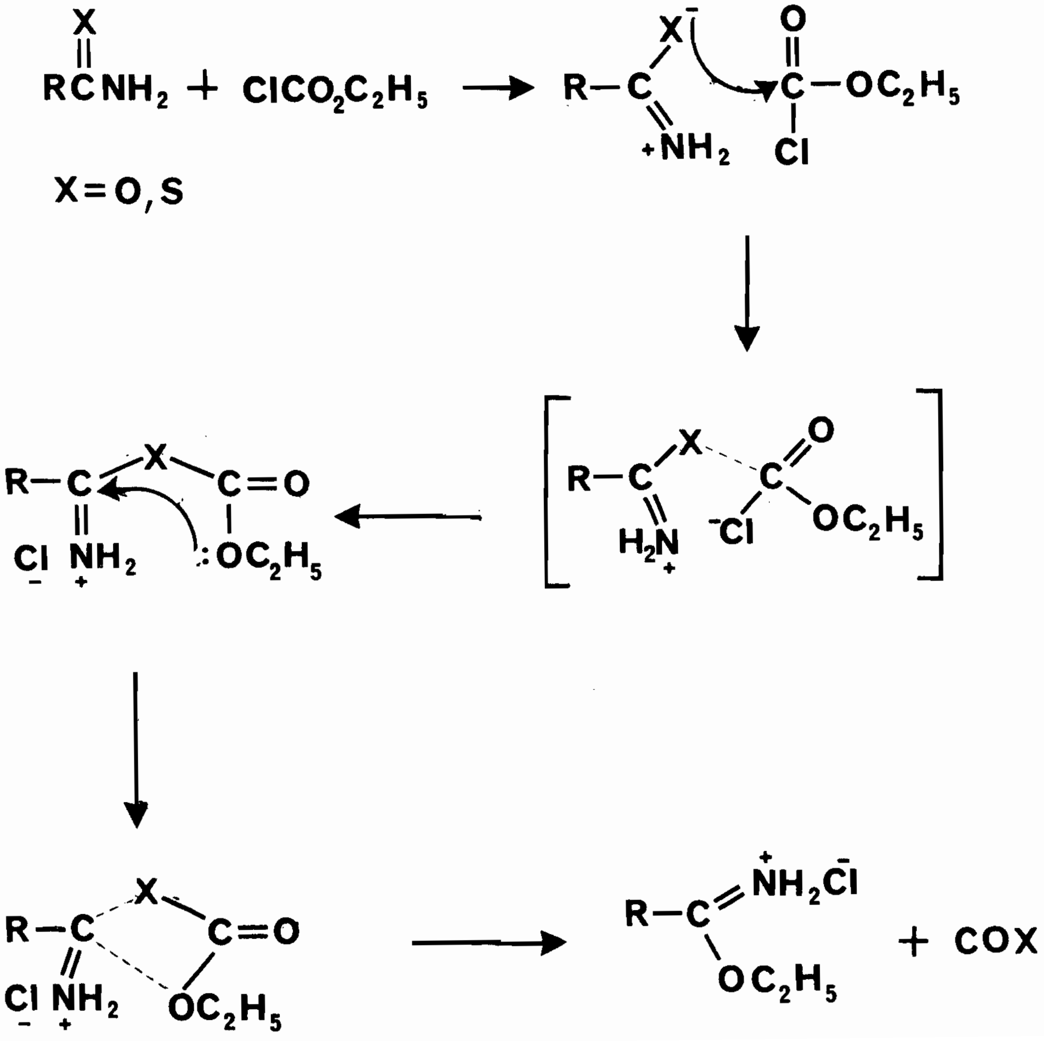
Reaction of N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) with ethyl chloroformate afforded a different type of product. The i.r. spectrum revealed a very strong band at 1638 cm^{-1}, too low to be assigned to a carbethoxy group. The presence of an ethyl group (triplet at δ 1.39; quartet at δ 4.47) was again evident in the n.m.r. spectrum but the u.v. spectrum held no similarity to the spectra of 19 or 20. A molecular ion of m/e 323 was present in the mass spectrum whose formula proved to be $C_{18}H_{17}N_3OS$ by exact mass measurement. From these data, the compound was assigned the structure of O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21).

Two possible mechanisms may be considered to account for the formation of 21. Firstly, a nucleophilic attack by sulfur on the ethyl chloroformate, with elimination of the chloride ion, is then followed by an intramolecular nucleophilic attack of the ethoxy oxygen on the central carbon, with the expulsion of sulfur as carbon oxysulfide.



21

This type of internal rearrangement has been observed by Suydam et al. (55) in the case of amides and thioamides. When treated with ethyl chloroformate, these products afforded imidate hydrochlorides. Thioamides were considerably more reactive than the amides. Thioacetamide reacted within 5 minutes at room temperature whereas the reaction with acetamide was complete only after 1.5 hours at 45°. The following mechanism was postulated by the authors (55):



In the present work, it was observed that whereas thiazolylthioureas reacted with ethyl chloroformate, the thiazolylureas were completely unreactive and were recovered unchanged from the reaction mixture.

A second mechanism that could be considered to explain the presence of an isourea involves the formation of a thiazolylcarbodiimide which then reacts with ethanol to give the O-isourea. This implies that the carbodiimide must be formed first, then allowed to react. It is doubtful, however, that under these mild conditions the carbodiimide is formed. Furthermore, it is known that in the absence of catalysts (10), alcohols are fairly inert toward carbodiimides at room temperature. For instance, N,N'-diphenylcarbodiimide reacts with ethanol only under drastic conditions to form O-ethyl-N,N'-diphenylisourea. In addition, tertiary bases have not been found suitable as catalysts, thus eliminating the possibility of triethylamine acting as the catalyst in this particular reaction. It may be pointed out that desulfurization of N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) with lead oxide in refluxing ethanol produced O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21) but in this case, a much higher temperature was used. In view of these facts, the mechanism mentioned earlier is preferred.

In the reaction of N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8) with ethyl chloroformate, three products were obtained. The first, obtained in 30% yield, was identified as ethyl N-(5-methyl-4-phenyl-2-thiazolyl)carbamate (22), m.p. 132-3°. It was characterized by a strong carbonyl absorption at 1719 cm^{-1} (C=O) and a molecular ion of m/e 262 with a typical carbamate fragmentation in its mass spectrum. The second product was O-ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23), analogous to 21. It was obtained in 13% yield and crystallised as long colorless needles melting at 99-100°. Its i.r. spectrum exhibited a very strong absorption at 1641 cm^{-1} (C=N) and its n.m.r. spectrum showed the presence of an ethyl group (triplet at δ 1.42; quartet at δ 4.50) as well as a methyl group (singlet at δ 2.52). The molecular ion of m/e 337 corresponded to the formula $C_{19}H_{19}N_3OS$, determined by exact mass measurement.

The third product, however, was unexpected. It melted at 198-9° and was insoluble in ethanol. Although it was obtained in very poor yield, its i.r. spectrum established its identity with N-phenyl-N'-N''-di-(5-methyl-4-phenyl-2-thiazolyl) guanidine (13).

The formation of 13 may be rationalized in the following manner: under the action of ethyl chloroformate, 8 may undergo desulfurization to the carbodiimide. At the same time 8 may dissociate into phenyl isothiocyanate and the amino thiazole which then reacts with the carbodiimide to give the guanidine 13.

Another possible mechanism may be the attack of the newly-formed amine on the isourea 23, displacing the ethoxy group. This appears reasonable since isoureas are known to yield guanidines readily on treatment with amines at 20° for 24 hours (56).

As a note of interest, N,N'-diphenylthiourea (24) was also treated with ethyl chloroformate under the same conditions as for the thiazolylthioureas. Long colorless needles, m.p. 99-100°, were obtained and identified as N-carbethoxy-N,N'-diphenylthiourea (25), with the formula $C_{10}H_{16}N_3O_2S$. The C=O function absorbed strongly at 1701 cm^{-1} in the i.r. spectrum while the n.m.r. displayed a well-resolved quartet at δ 4.06 (CH_2) and triplet at δ 1.02 (CH_3).

In one of the trial runs on N,N'-diphenylthiourea (24), the product obtained was diphenylcarbodiimide, as a colorless liquid, identified by its i.r. spectrum which exhibited an intense band at 2145 cm^{-1} and a smaller band at 2120 cm^{-1}, typical of aromatic carbodiimides (2152-2128 cm^{-1}). All the other runs gave 25 only. Thus, the reaction of aromatic thioureas and ethyl chloroformate is more suited to the preparation of carbethoxythioureas than of aromatic carbodiimides.

B. SYNTHESIS AND OXIDATION OF N-PYRIDYLTHIOUREAS

1. Synthesis of N-pyridylthioureas

The previously known N-2- (26) and N-3-pyridylthiourea (27) were prepared according to the method outlined by Taurins and Blaga (6). The appropriate 2- and 3-aminopyridines were treated with benzoyl isothiocyanate to yield the benzoylpyridylthioureas (35) and (36) which were then hydrolyzed with dilute base to give 26 and 27 in good yield.

The new N-(3-methyl- (28), 5-methyl- (30), 6-methyl- (31), 4,6-dimethyl- (32) and N-(5-bromo-2-pyridyl)thiourea (33) as well as 2,6-dithioureidopyridine (34) were similarly prepared from the corresponding benzoylpyridylthioureas (37, 39-43). The N-(4-methyl-2-pyridyl)thiourea (29) was also prepared although it has been previously synthesized by Barkonikow and Abraham (8) from the benzoylpyridylthiourea (38) which, however, they did not characterize. Neville and McGee (57) claim to have prepared 28 from 2-amino-3-methylpyridine and silicon isothiocyanate. They give the melting point for 28 as 115° whereas in the present work, it was found to be 153-4°. Since N,N'-di-(2-pyridyl)thiourea is known to exist in two different modifications, a high-melting form, m.p. 163° and a low-melting form, m.p. 147°, depending by which method it was obtained (58), perhaps a similar situation exists in the case of 28 thus explaining the two different melting point values.

2. Attempted oxidation of N-pyridylthioureas to thiazolopyridines

(a) Reagents in alkaline media

Reagents requiring basic conditions such as alkaline potassium ferricyanide, sodium hypobromite and hydrogen peroxide were used in an effort to oxidize N-2- (26), N-3- (27) and N-(5-methyl-2-pyridyl)thiourea (30) to thiazolopyridines. The only products isolated were the starting thioureas or the corresponding pyridylureas, identified by their i.r. or mass spectra.

(b) Treatment with bromine

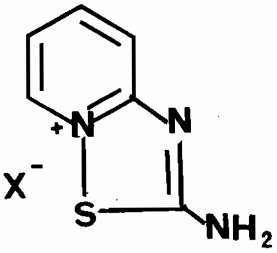
Treatment of N-2-pyridylthiourea with bromine in chloroform led to the rapid formation of an insoluble cream-colored product with discoloration of the bromine. After filtration and further treatment of the filtrate with bromine, a new portion of the product was obtained, m.p. 232-3° (dec.). The same product was obtained whether glacial acetic acid, ethanol, acetonitrile or chloroform were used.

The n.m.r. spectrum of this compound in DMSO showed signals at δ 8.0 (triplet, 6-H), 8.65 (doublet, 8-H), 9.40 (triplet, 7-H), 11.51 (doublet, 5-H) and 12.2 (broad singlet, NH_2). There was no substitution on the pyridine ring as would require a thiazolopyridine.

Hydrolysis of this product with dilute ammonium hydroxide produced a deep yellow colour throughout the solution which, on standing, deposited N-2-pyridylurea, m.p. 171°, identified by its i.r. spectrum and mass spectrum.

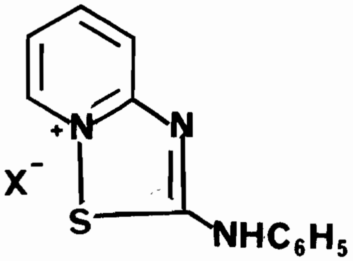
These results point to a 2-amino[1,2,4]thiadiazolo-[2,3-a]pyridinium bromide (44a) structure for this compound.

Elemental analysis for the formula $C_6H_6BrN_3S$ requires N, 18.1 and Br, 34.4. Compound 44a gave N, 17.8 and Br, 34.2. Structure 44a is further supported by the fact that recently Harris (59) has obtained 2-amino[1,2,4]thiadiazolo[2,3-a]-pyridinium chloride (44b), m.p. 220-5° (dec.) by oxidation of N-2-pyridylthiourea (26) with sulfuryl chloride in dry chloroform. He further observed that oxidation of N-phenyl-N'-2-pyridylthiourea with either bromine or sulfuryl chloride gave the corresponding 2-phenylamino[1,2,4]thiadiazolo[,2,3-a]-pyridinium bromide (44c) or chloride (44d).



44a: X=Br

44b: X=Cl



44c: X=Br

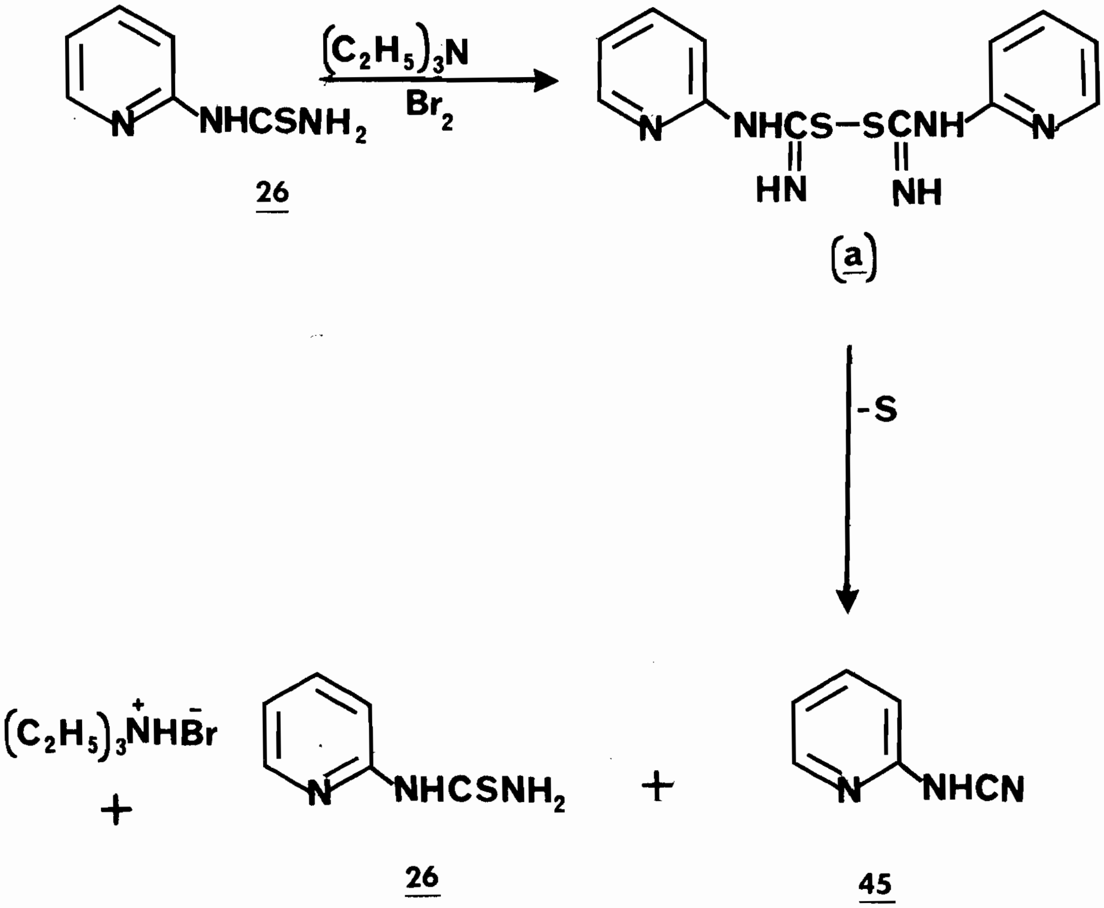
44d: X=Cl

Hydrolysis of 44c with 10% NaOH solution also gave the corresponding N-phenyl-N'-2-pyridylurea.

In the present work, it was observed that N-(5-methyl-2-pyridyl)thiourea (30) and N-(3-methyl-2-pyridyl)-thiourea (28) gave, on treatment with bromine, compounds melting at 235-6° (dec.) and 220° (dec.), respectively. The i.r. spectra of these compounds were very similar to that of 44a and hydrolysis with dilute NH_4OH also produced a yellow colour and afforded the corresponding ureas. In view of these observations, the structures were assumed to be[1,2,4]thiadiazolo[2,3-a]pyridinium bromides in analogy to 44a although they were not further investigated.

When N-2-pyridylthiourea (26) was treated with bromine in acetonitrile or chloroform in the presence of triethylamine, a different type of compound was produced. It was identified as 2-pyridylcyanamide (45), m.p. 153-4°, by comparison of its i.r. spectrum with an authentic sample.

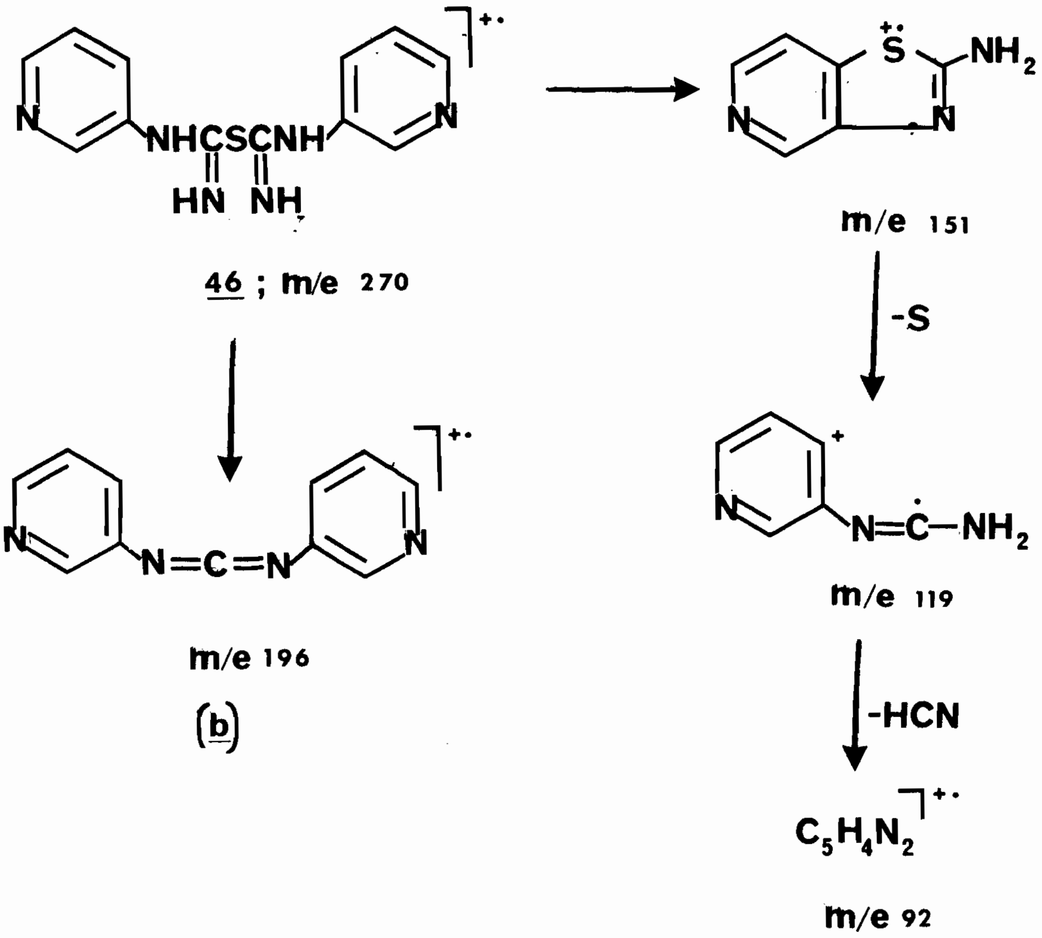
The following mechanism similar to the one proposed by Barkonikow and Bodeker (60) for the oxidation of phenylthiourea may be postulated for this reaction: 26 is oxidized to the disulfide (a) which in turn decomposes into 45 and 26 and triethylamine hydrobromide. Since a 55% yield of 45 was obtained, the process must be repeated again with the newly-formed 26 to yield more 2-pyridylcyanamide (45).



N-3-Pyridylthiourea (27), on the other hand, gave two different products when treated with bromine in ethanol. The first product melted at 177-8° and the second product, obtained from further addition of bromine, melted at 235-6°.

Again the n.m.r. spectra of these products clearly indicated that no substitution had occurred on the pyridine ring to form a thiazolopyridine. In this case, a thiadiazolopyridinium bromide structure cannot be postulated. It appears more likely that these products are addition compounds of the pyridine ring nitrogen and bromine.

The mass spectrum of the product, m.p. 235-6°, obtained from N-3-pyridylthiourea (27) gave a very small peak at m/e 303, corresponding to a disulfide, less one hydrogen, the main peak being at m/e 270 assigned to the monosulfide (46). The peak at m/e 196 could arise from a N,N'-di-(3-pyridyl)-carbodiimide structure (b) while the ions of m/e 151, 119 and 92 agree with a thiazolopyridine fragmentation in analogy to 2-aminobenzothiazole (61), suggesting that cyclization may be taking place under electron impact as follows:



The calculated values for 46 if it contains three bromine atoms with the formula $C_{12}H_{15}Br_3N_6S$ are: C, 28.0;

H, 2.9; N, 16.3. The elemental analysis gave C, 27.3; H, 3.2; N, 16.1. Thus the product 46 appears to be a 3-pyridylguanidine sulfide.

These compounds were not studied any further since they were not producing the desired cyclized thiazolopyridines.

C. ATTEMPTED PREPARATION OF PYRIDYLTHIOUREA 1-OXIDES: FORMATION OF AMINOPYRIDINE 1-OXIDE THIOCYANATES

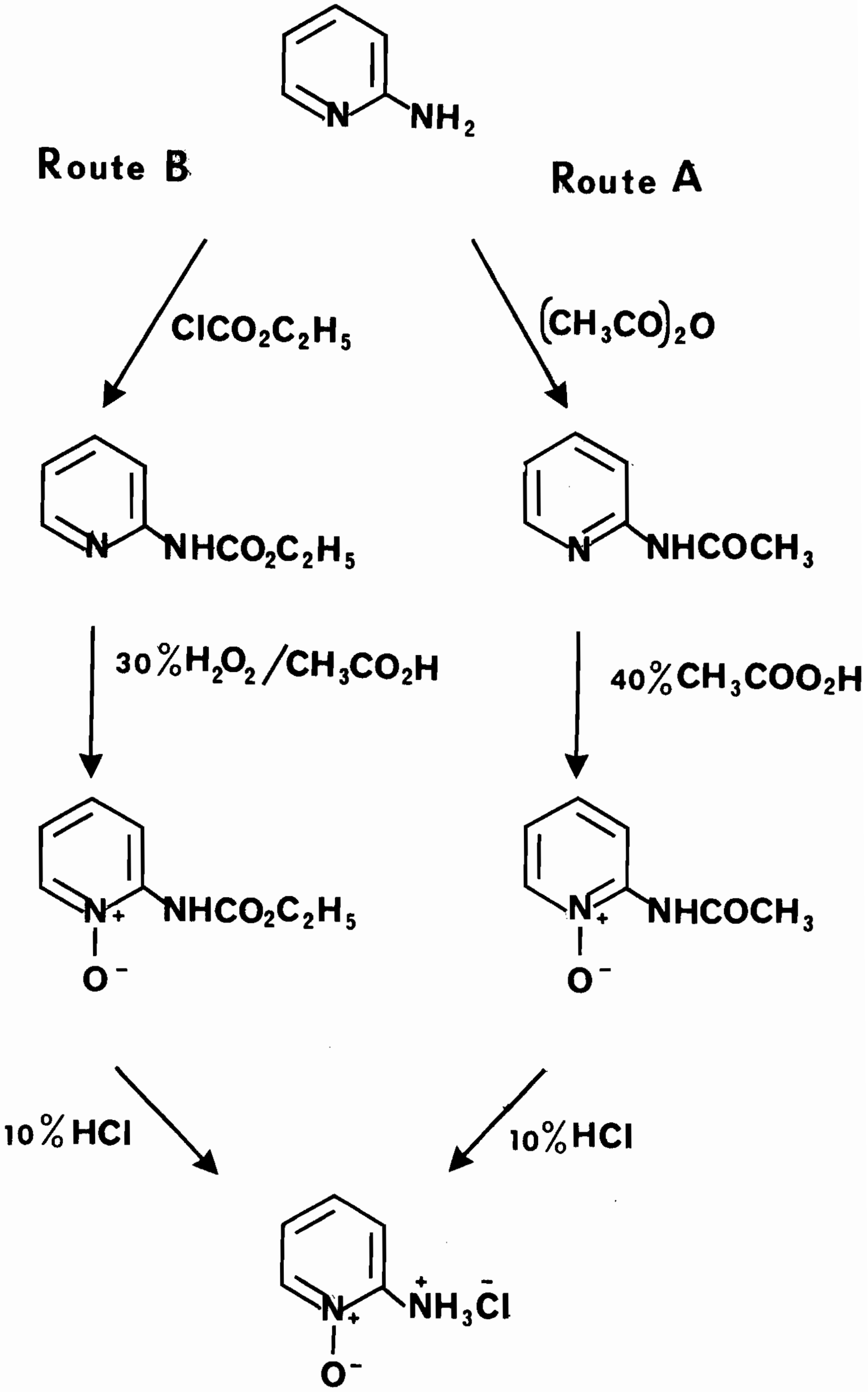
1. Synthesis of aminopyridine 1-oxide hydrochlorides

Aminopyridine 1-oxides or their salts were considered to be useful precursors for the formation of thiourea derivatives. Since aminopyridines cannot be oxidized directly due to the formation of undesirable side-products, the amino group must first be protected (62). Accordingly, the 2-aminopyridine 1-oxide hydrochlorides were obtained by following the method of Brown (63) and Adams and Miyano (64), as illustrated by Route A in Scheme 2.

The 2-aminopyridine is acetylated with acetic anhydride and the resulting crude 2-acetamidopyridine is then oxidized with 40% peracetic acid to the corresponding N-oxide. Hydrolysis with dilute hydrochloric acid yields 2-aminopyridine 1-oxide hydrochloride.

For the 2-amino-4-methyl-, 2-amino-5-methyl- and 2-amino-6-methylpyridines, an alternate method described by Katritzky (65) making use of the ethoxycarbonyl group as protective group was utilized (Route B). The aminopyridine was treated with ethyl chloroformate to give the ethyl carbamate which was then oxidized with 30% hydrogen peroxide to give the N-oxide. In turn, the N-oxide was hydrolyzed with 10% hydrochloric acid to give the desired 2-aminopyridine 1-oxide hydrochloride.

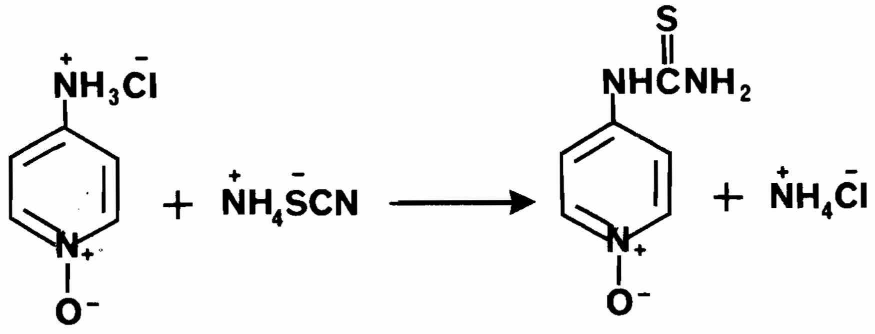
Scheme 2


NH$_2$
Route B
Route A
ClCO$_2$C$_2$H$_5$
(CH$_3$CO)$_2$O
NHCO$_2$C$_2$H$_5$
NHCOCH$_3$
30%H$_2$O$_2$/CH$_3$CO$_2$H
40%CH$_3$COO$_2$H
N+
O$^-$
10%HCl
10%HCl
$\overset{+}{N}$H$_3\overset{-}{Cl}$

2. Reactions of 2-aminopyridine 1-oxide hydrochlorides

(a) Reaction with ammonium thiocyanate

Gardner et al. (66) claimed to have prepared N-4-pyridylthiourea 1-oxide (47), m.p. 126-127°, by refluxing a mixture of 4-aminopyridine 1-oxide hydrochloride (47a) with ammonium thiocyanate in ethanol. They obtained an experimental N value of 24.5% as compared to a calculated value of 24.9% for $C_6H_7N_3OS$.



47a

47

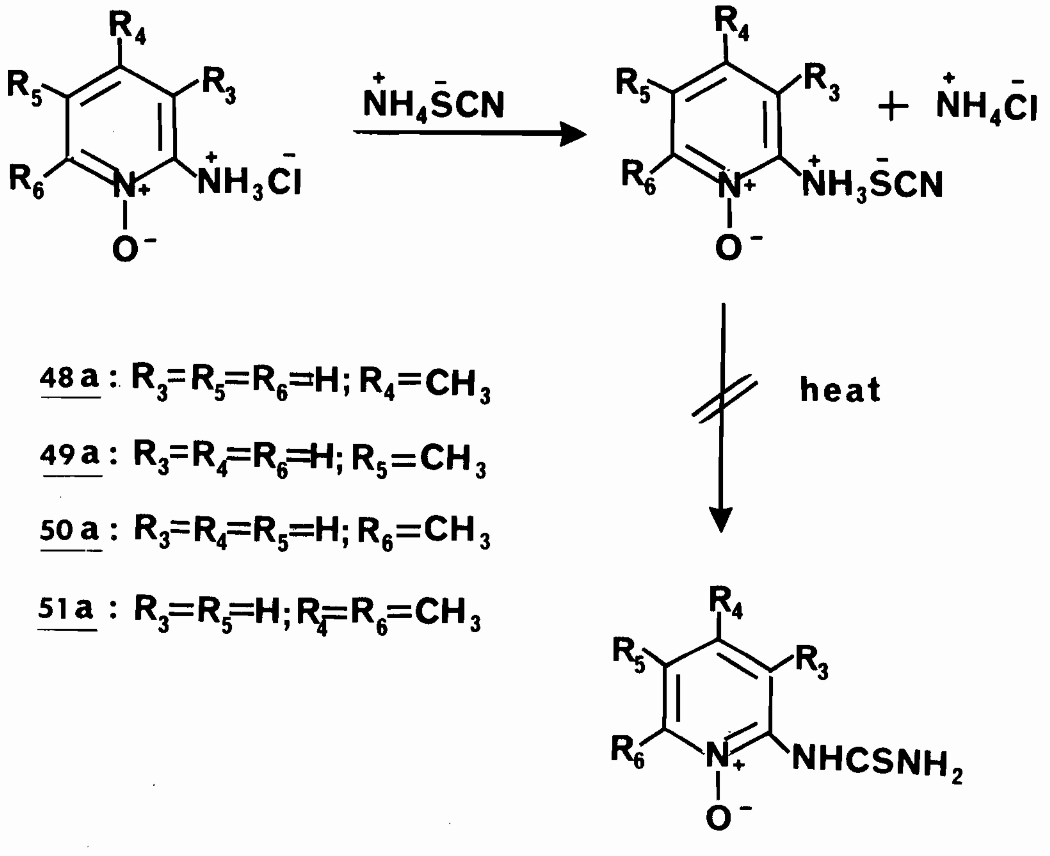
The same method had been previously used by Lieberman et al. (67) in the preparation of N-4-pyridylthiourea, m.p. 116°. The calculated N value for this product is 27.45% whereas Lieberman obtained an experimental value of only 26.87%. He was interested in this compound for its possible anti-tubercular activity but apparently made no attempt to fully elucidate its structure. Neither Gardner nor Lieberman offered spectral evidence to support their proposed structures nor were the chemical reactivity of these two compounds investigated.

On repeating both reactions, we obtained compounds whose melting points were identical to those quoted by the authors. However, a strong band appeared around 2060 cm^{-1} in the i.r. spectra of both compounds, and the band could only be assigned to the $-S-C{\equiv}N$ group of the isomeric amine thiocyanates.

When amines are treated with thiocyanate salts, they first yield amine thiocyanates which can usually be isomerized to the corresponding thioureas, either by prolonged heating or even simply by slow evaporation of the reaction mixture (21). In this case, however, the i.r. evidence points to the fact that no isomerization has taken place. Refluxing the products in high-boiling solvents such as water or toluene for extended periods of time brought no change in the i.r. spectra. Heating the amine thiocyanates above the melting points likewise produced no isomerization. Similarly, it has been pointed out by Le Perdriel and Charonnat (7) that 2-aminopyridine thiocyanate could not be converted into its thiourea by prolonged heating.

Treatment of the two products with bromine gave the corresponding amine hydrobromides, displacing the thiocyanate group. In view of these observations, it is necessary to reject the claims by Gardner and Lieberman that they have obtained the thioureas.

In this work, several C-methyl homologues of 2-aminopyridine 1-oxide (<u>48a</u>-<u>51a</u>) were treated with ammonium thiocyanate, giving the corresponding thiocyanate salts identified by the i.r. spectra. Elemental analysis of these products was not considered reliable enough as these salts were very hygroscopic and readily acquired a yellowish color after standing a day. None of these salts could be isomerized to the corresponding thioureas.



48a : $R_3=R_5=R_6=H$; $R_4=CH_3$

49a : $R_3=R_4=R_6=H$; $R_5=CH_3$

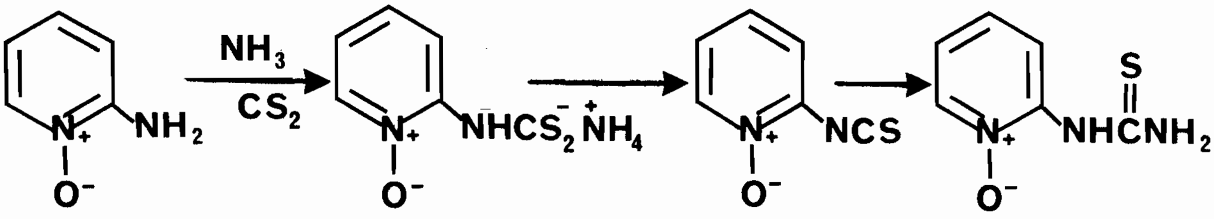
50a : $R_3=R_4=R_5=H$; $R_6=CH_3$

51a : $R_3=R_5=H$; $R_4=R_6=CH_3$

(b) Reaction with carbon disulfide and ammonium hydroxide

Salts of dithiocarbamic acid, readily obtained by reaction of primary amines with carbon disulfide and alkali hydroxides or ammonia, are cleaved by heavy metal salts to H_2S and isothiocyanates (68), which in turn can be converted into thioureas by treatment with ammonia.

Thus, when treated with carbon disulfide in aqueous ammonia, 2-aminopyridine yields a dithiocarbamate salt (69) which is transformed into 2-pyridyl isothiocyanate with phosgene, and then into N-2-pyridylthiourea. It was hoped that a similar reaction would convert 2-aminopyridine 1-oxide (52) into the N-2-pyridylthiourea 1-oxide (52c) as follows:

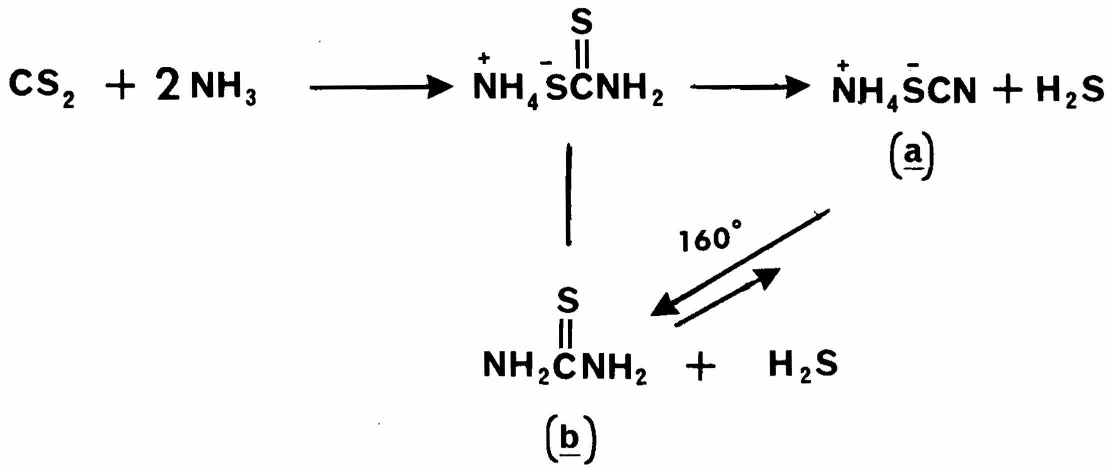


52

52c

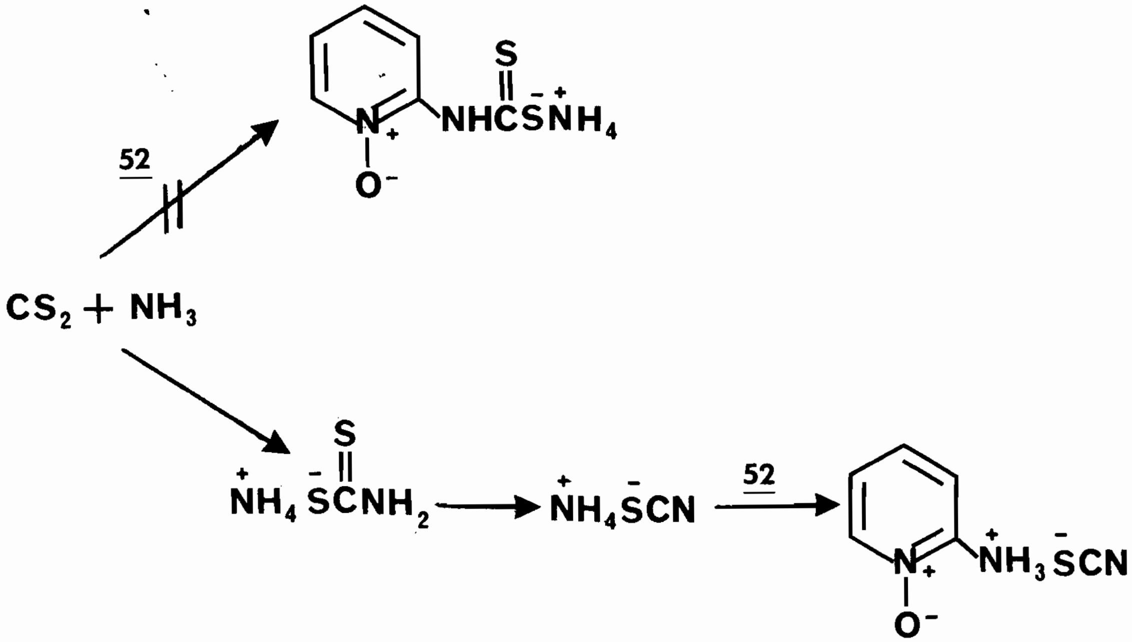
However, on refluxing 52 or one of its C-methyl analogues with carbon disulfide in aqueous ammonia for several hours, the product isolated was identical to the corresponding 2-aminopyridine 1-oxide thiocyanate salt, by comparison of the melting points, i.r. spectra and thin layer chromatography.

The formation of these salts may be explained by considering the reaction conditions used. Carbon disulfide and ammonium hydroxide react to form ammonium dithiocarbamate which then loses H_2S to give either ammonium thiocyanate (a) or thiourea (b)(48b).



If the temperature is below 120°, ammonium thiocyanate (a) is the chief product whereas at higher temperatures, especially near 160°, the yield of thiourea (b) becomes high, although this may be partly due to the isomerization of (a) into (b) at high temperatures.

Once ammonium thiocyanate (a) is produced, it reacts with the available 2-aminopyridine 1-oxide (52) to give the amine thiocyanate salt. This appears to be the preferred reaction path for 52 since the presence of a pyridyl dithiocarbamate salt was not detected at all.



The presence of 2-aminopyridine thiocyanate is also encountered in the reaction of 2-aminopyridine with CS_2 and ammonia but only as a minor product from the concentration of the mother liquor (69), the main product being 2-aminopyridine dithiocarbamate salt.

Failure of 2-aminopyridine 1-oxide (52) to give a dithiocarbamate salt is best explained by the fact that 52 is a much weaker base than 2-aminopyridine. Thus, the pK_a of 2-aminopyridine 1-oxide is 2.67 while the pK_a of 2-aminopyridine is 6.86 (70).

Furthermore, it has been observed that 52 does not react smoothly with ethyl chloroformate or phenyl isocyanate. In the latter case, the reaction requires two days at room temperature whereas 2-aminopyridine reacts within a few minutes (71).

(c) Reaction with benzoyl isothiocyanate

As mentioned previously, the monopyridylthioureas (28-34) have been successfully prepared by the hydrolysis of the benzoylpyridylthioureas (37-43). Therefore, it was thought possible to apply the same method for the preparation of monopyridylthiourea 1-oxides.

Thus, 2-aminopyridine 1-oxide (52) was treated with benzoyl isothiocyanate to give a very small yield of yellow product, m.p. 173-4°, identified as the N-benzoyl-N'-(2-pyridyl)thiourea 1-oxide by the i.r. spectrum which exhibited a strong carbonyl band at 1680 cm^{-1}. Hydrolysis of this compound resulted in decomposition with the formation of hydrogen sulfide and benzoic acid.

This decomposition is not unusual. For example, substituted thiazolylthioureas may be prepared by the hydrolysis of their corresponding benzoylthiazolylthioureas (3) similar to the synthesis of the pyridylthioureas. However, no mention has been made in the literature about the preparation of either N-benzoyl-N'-2-thiazolylthiourea or 2-thiazolylthiourea by this method. This reaction was investigated in the present work. It was found that although a poor yield of N-benzoyl-N'-2-thiazolylthiourea, m.p. 262-3°, could be obtained, attempted basic hydrolysis to yield the thiazolylthiourea resulted only in decomposition with the production of hydrogen sulfide.

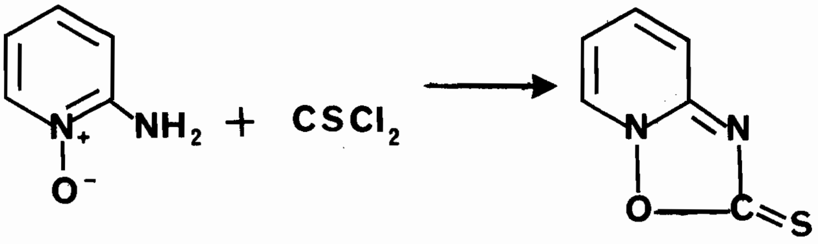
Therefore, this method was not considered to be appropriate for the synthesis of pyridylthiourea 1-oxides and was not pursued further.

D. SYNTHESIS OF [1,2,4]OXADIAZOLO[2,3-a]PYRIDINE-2-THIONES

The reaction of thiophosgene with primary amines leading to the formation of isothiocyanates has long been known (72). Although the reaction resembles the treatment of amines with phosgene to produce isocyanates (73), thiophosgene and isothiocyanates have the advantage of being relatively insensitive to water at room temperature and the reaction may be carried out in aqueous medium.

Thus the thiophosgenation of 2-aminopyridine leads to 2-pyridyl isothiocyanate (69) which may then be converted into N-2-pyridylthiourea by treatment with ammonia.

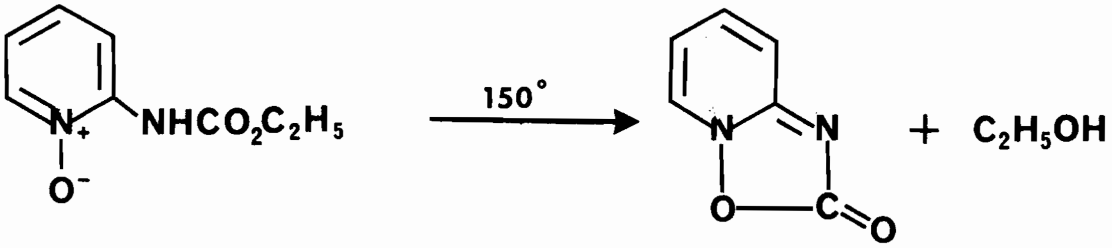
In this study, the reaction of thiophosgene with 2-aminopyridine 1-oxide (52) was carried out. An ether solution of thiophosgene was added to 52 dissolved in dilute ethanol, in the presence of sodium bicarbonate. An insoluble cream-colored solid was immediately deposited. On being heated to 125° in a melting-point tube, this product unexpectedly exploded. Its i.r. spectrum did not exhibit any N=C=S bands and thus it could not be an isothiocyanate. The product was insoluble in most organic solvents but could be successfully recrystallized from DMSO. When heated in ethanol, or left to stand in ethanol for several days at room temperature, it afforded only ethyl N-2-pyridylcarbamate, identified with an authentic sample as well as by its mass spectrum. The n.m.r. spectrum and elemental analysis agreed with the structure[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53) for this product.



52

53

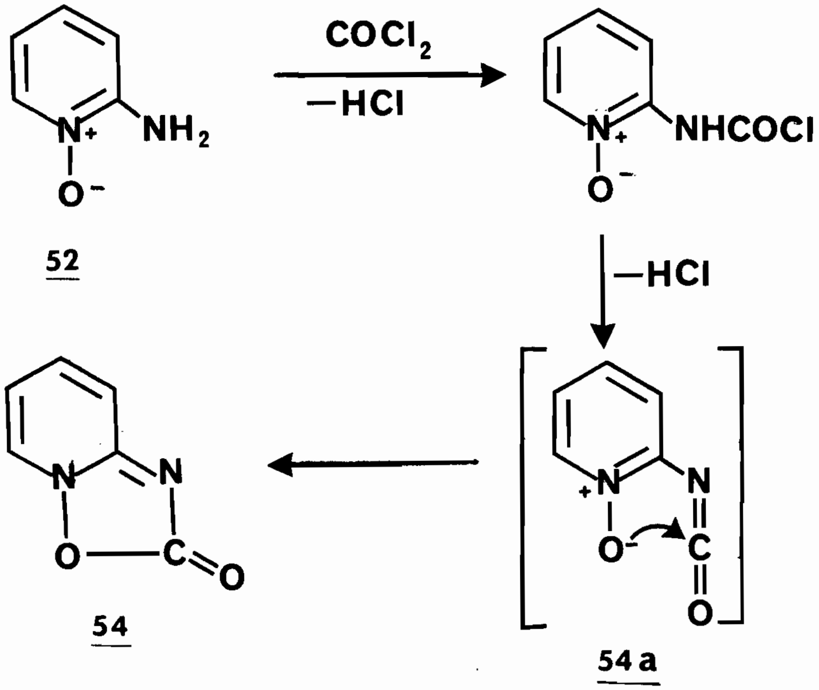
Although 53 is a new compound, its oxygen analogue, [1,2,4]oxadiazolo[2,3-a]pyridine-2-one (54) has already been prepared by Katritzky (65) who heated ethyl N-2-pyridylcarbamate 1-oxide (55) at 150° causing a cyclization to occur to produce 54 and ethanol.



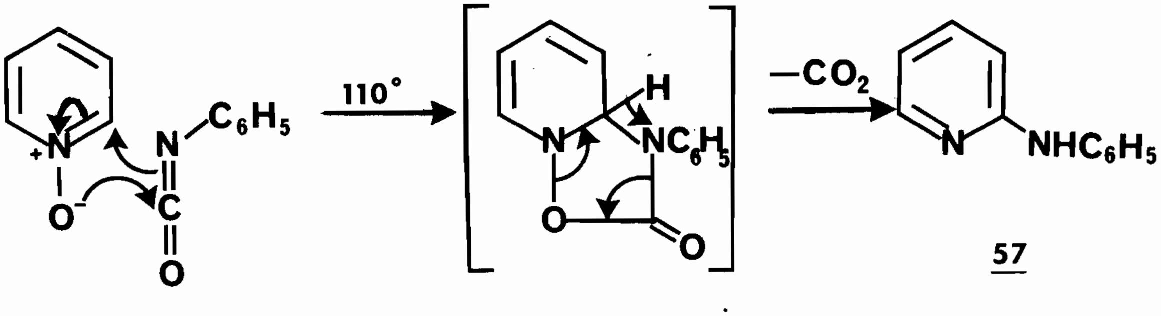
55

54

Boyer et al. (74) and later Hoegerle (75) arrived at 54 by simply treating 2-aminopyridine 1-oxide (52) with phosgene. Hoegerle postulated that the reaction first proceeded through an isocyanate intermediate (54a) which then reacted at the N-oxide function to give 54.

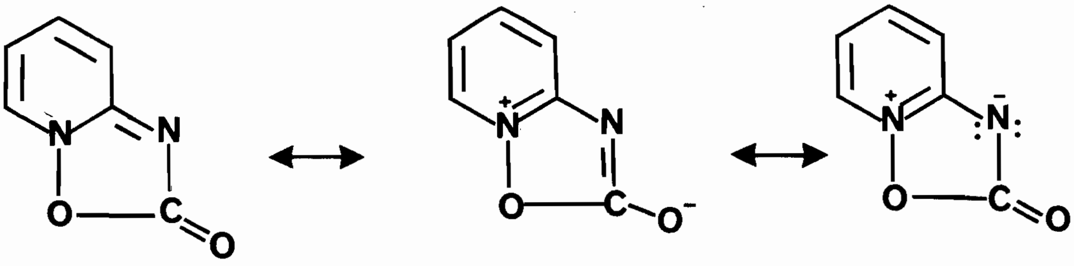


This mechanism appears plausible since aromatic N-oxides may be regarded as nitrones $(C{=}\underset{+}{N}{-}O^{-})$ or their conjugated systems and consequently are known to undergo 1,3-dipolar cycloaddition with compounds containing active double or triple bonds or isocyanates (76). For example, Huisgen (77), in his comprehensive review on 1,3-dipolar cycloaddition, mentions the reaction of pyridine 1-oxide (56) with phenyl isocyanate to give 2-phenylaminopyridine (57) in 81% yield. The intermediate oxadiazolopyridine-2-one (57a) was not isolated but readily expelled carbon dioxide to give the observed 57.



56 57a 57

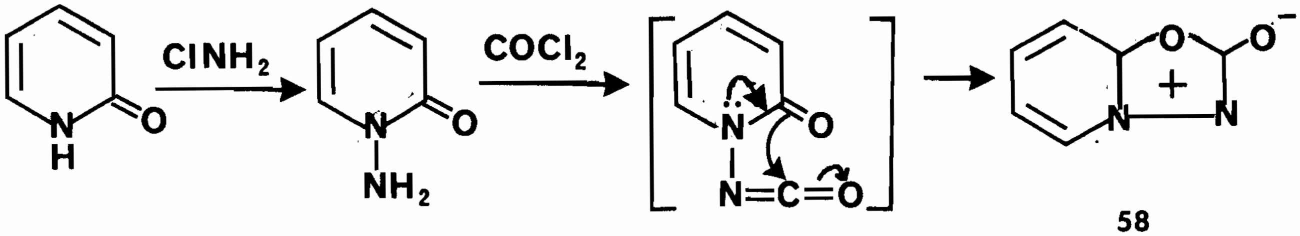
Contrary to 57a, which is too unstable an intermediate to be isolated, [1,2,4]oxadiazolo[2,3-a]pyridine-2-one (54) showed considerable stability to heat and oxidizing agents such as bromine and acid permanganate. In view of this, Katritzky considered structure 54 to represent only one of several possible resonance structures, others being given by 54b and 54c.



54 54b 54c

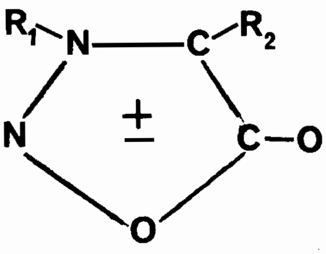
Since the i.r. spectrum of 54 exhibited a carbonyl absorption at 1773 cm^{-1}, close to the value for γ-lactones (∿ 1770 cm^{-}), Katritzky considered compound 54 to possess a normal C=O group within a five-membered ring.

In order to study the structure of 54 in more detail, Hoegerle (78) prepared the isomeric[1,3,4]oxadiazolo[3,2-a] pyridine-2-one (58) by treating 1-amino-2-pyridone, obtained from 2-pyridone and chloramine, with phosgene as depicted in the following scheme:

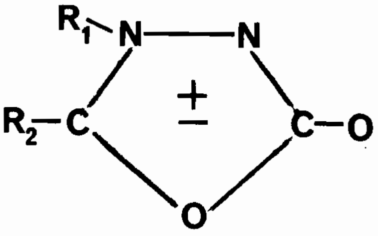


58

In this case, however, 58 could not be described appropriately by a classical formula but by a meso-ionic structure. Meso-ionic compounds constitute a separate class of organic compounds of which the sydnones (59a) were the first to be investigated (79).



59a



59b

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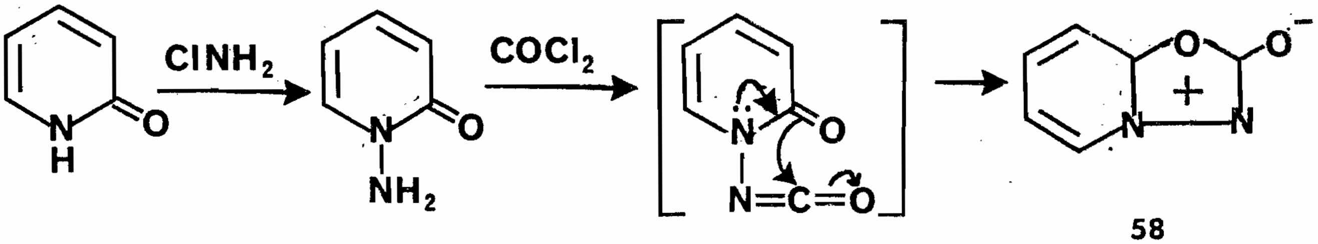

58

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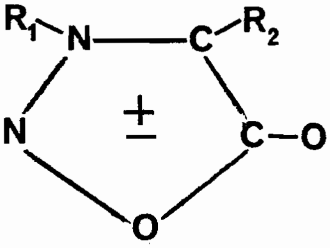
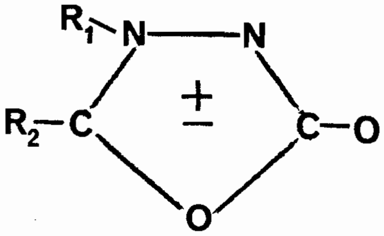


59a



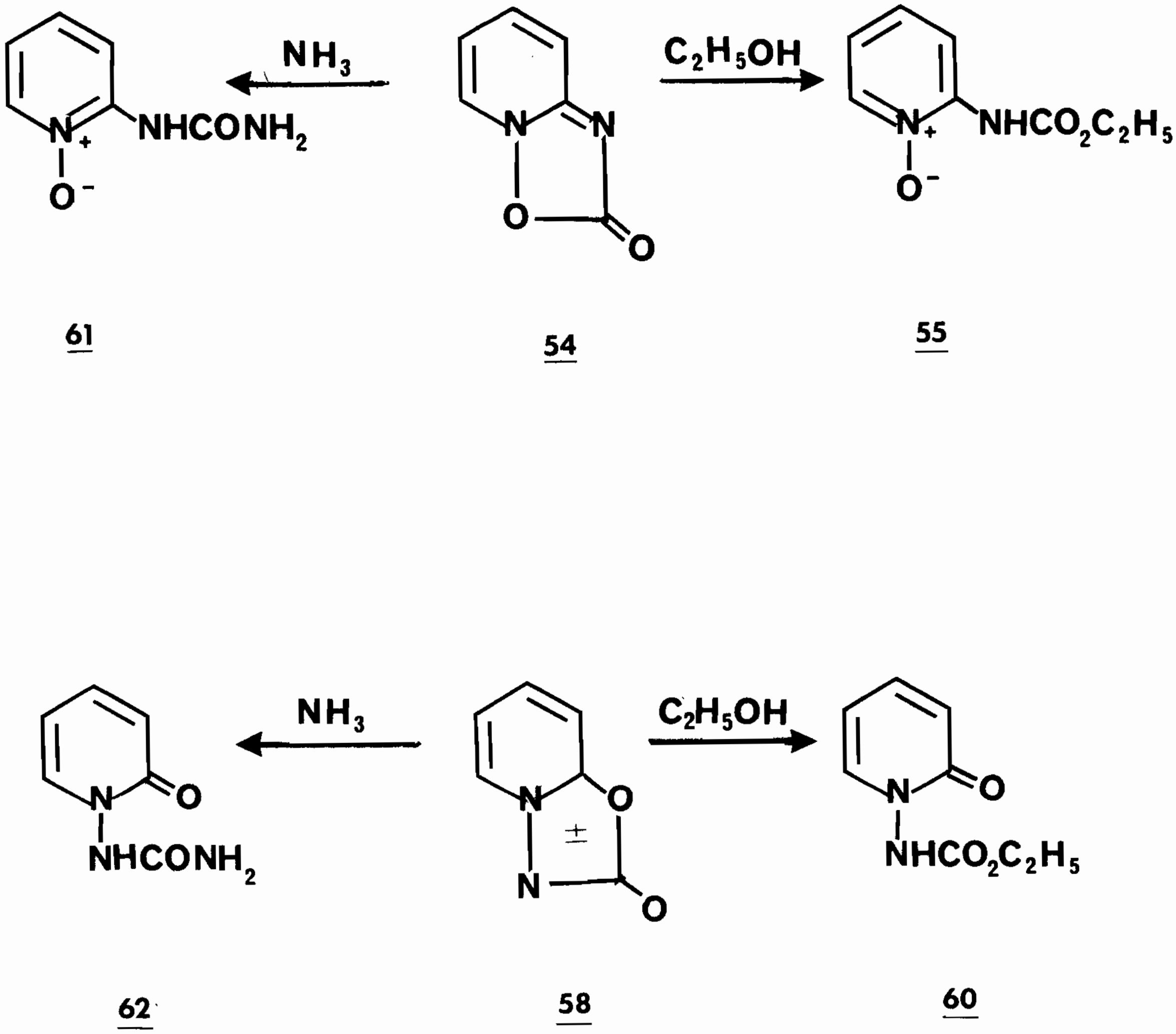
59b

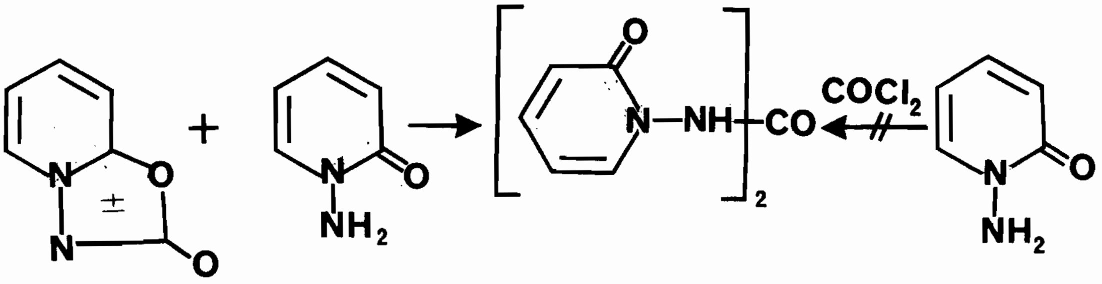
Structurally, [1,3,4]oxadiazolo[3,2-a]pyridine-2-one (58) resembles more an "isosydnone" (59b). Hoegerle's representation of 58 as a meso-ionic compound was based on i.r. and u.v. evidence. The i.r. of 58 showed strong and medium bands at 1745 cm^{-1} and 1785 cm^{-1} and its C-methyl homologues absorbed in the 1782-1766 cm^{-1} range (75) all within the 1820-1730 cm^{-1} region assigned to sydnones. The u.v. spectra of sydnones show maximum absorption at 300 nm raised to 333 nm in the presence of conjugated substituents and lowered to about 290 nm by non-conjugated substituents. The [1,3,4]oxadiazolo[3,2-a]pyridine-2-ones absorbed in the 290-305 nm region although this may depend partly on the second aromatic ring in these compounds.

Both [1,2,4]oxadiazolo[2,3-a]pyridine-2-one (54) and [1,3,4]oxadiazolo[3,2-a]pyridine-2-one (58) showed similar chemical behaviour. Treatment of 54 or 58 with ethanol gave, after five days, ethyl N-2-pyridylcarbamate 1-oxide (55) or ethyl N-(1-pyridone-2-yl)carbamate (60) whereas reaction with ammonia led to the formation of N-2-pyridylurea 1-oxide (61) or N-(1-pyridone-2-yl)urea (62) as shown in Scheme 3.

Hoegerle observed that heating 58 with 1-amino-2-pyridone (63) for 5 minutes at 260° yielded the symmetrical urea (64), precisely the product that had been anticipated from the reaction of 63 with phosgene.

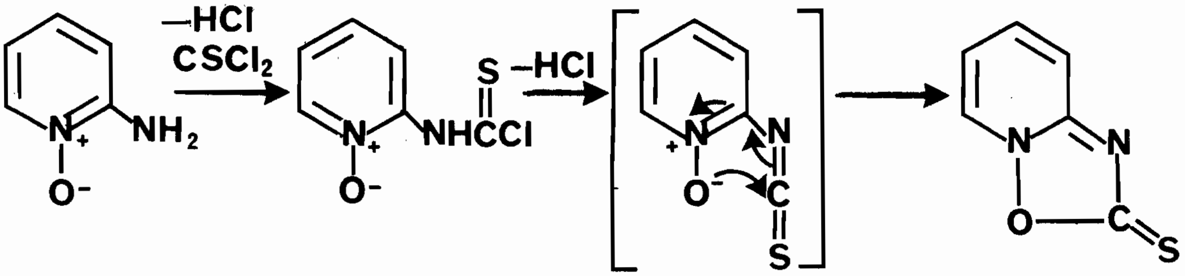
Scheme 3


NH$_3$
C$_2$H$_5$OH
NHCONH$_2$
NHCO$_2$C$_2$H$_5$
61
54
55
NH$_3$
C$_2$H$_5$OH
NHCONH$_2$
NHCO$_2$C$_2$H$_5$
62
58
60



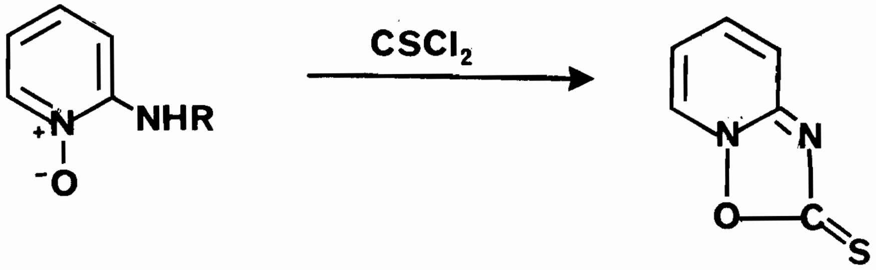
58 63 64 63

In the present work, thiophosgene exhibited a behaviour similar to phosgene towards 2-aminopyridine 1-oxide (52) to give the[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53). Here again, an isothiocyanate intermediate (53a) may be postulated for the formation of 53.



52 53a 53

However, it was observed that 53 could be obtained not only by treatment of 52 with thiophosgene but also by treatment of 2-acetamidopyridine 1-oxide (52d) or ethyl N-2-pyridylcarbamate 1-oxide (55) with thiophosgene.



52: R=H

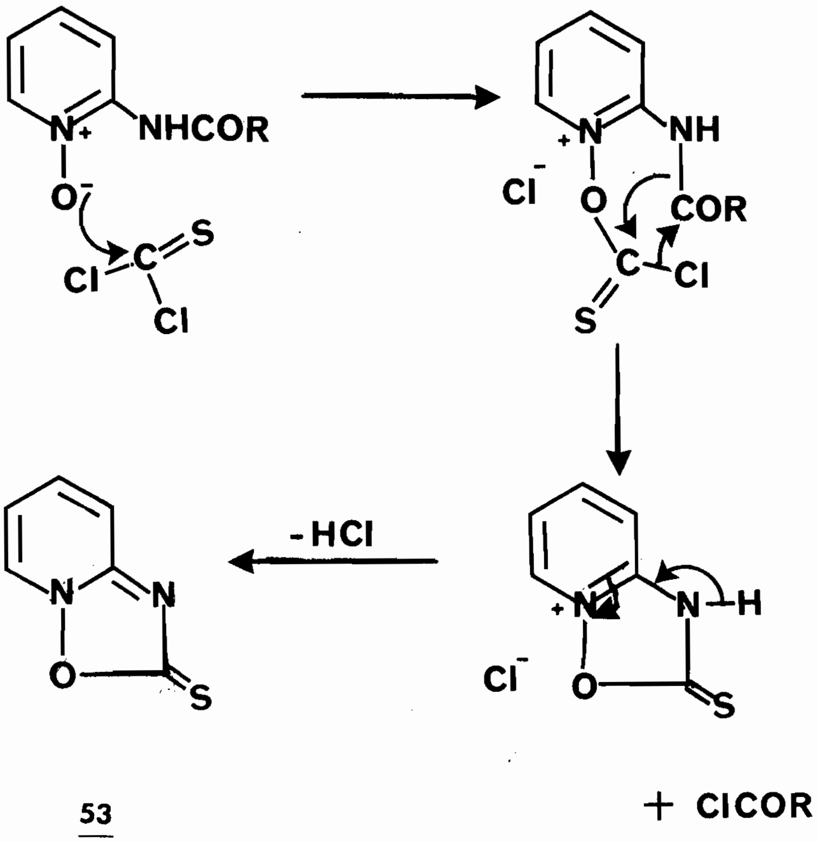
52d: R=$COCH_3$

55: R=$CO_2C_2H_5$

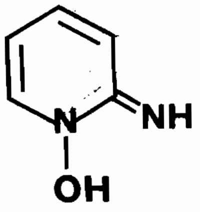
Obviously, an isothiocyanate intermediate cannot be postulated in the case of 52d and 55 and another mechanism illustrated in Scheme 4 may be considered under these circumstances. Considering the rapidity of the reaction in all three cases, it is more reasonable to assume that the oxygen of the N-oxide group initiates the reaction by attacking the carbon atom of the thiophosgene, displacing a chloride ion. A cyclization then occurs between the side-chain nitrogen and the thiophosgene carbon. An attack on the carbonyl group by the second chlorine atom results in the displacement of the acyl or carbethoxy groups and then the elimination of hydrogen finally leads to[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53).

This mechanism is supported by the fact that acylations of 2-aminopyridine 1-oxide (52) are believed to go via labile O-acyl intermediates which isomerize to N-acyl derivatives before isolation since 52 in its tautomeric form (52e) resembles a cyclic amidoxime which should give O-acylated derivatives (71).

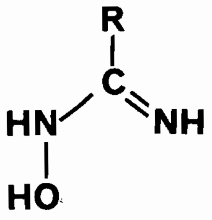
Scheme 4



53

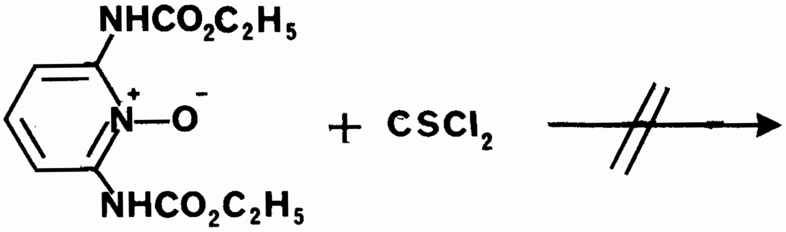


52e



Thus the benzoylation of 2-aminopyridine 1-oxide (52) in pyridine affords only 2-benzamidopyridine 1-oxide but the isomeric O-benzoylated compound may be isolated if the reaction is carried in acetonitrile (71).

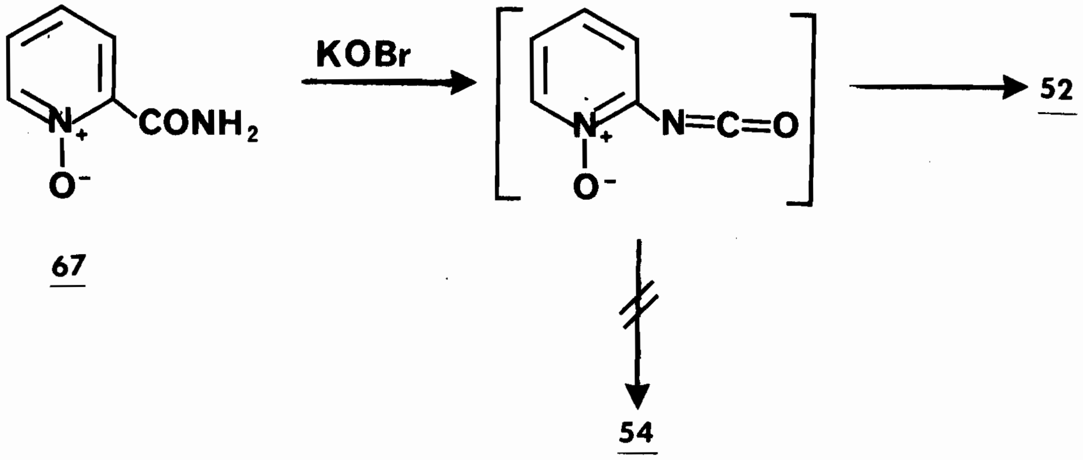
Furthermore it was observed in this work that 2,6-diethoxycarbonylaminopyridine 1-oxide (65) did not react with thiophosgene presumably due to steric hindrance resulting from the presence of two bulky carbethoxy groups at positions ortho to the N-oxide group. The 2,6-diaminopyridine 1-oxide (66) on the other hand immediately underwent reaction.



65

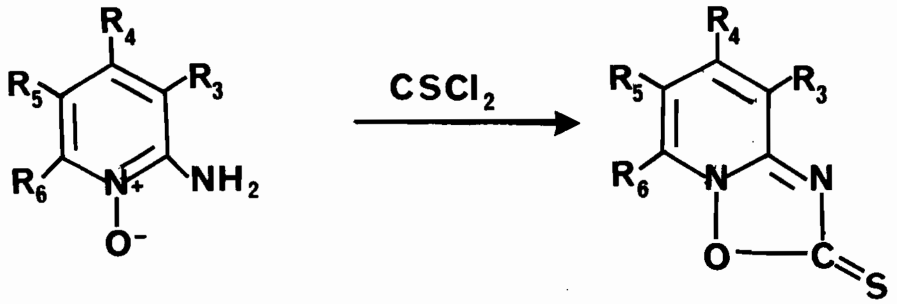
These observations lend support to the mechanism proposed above which requires free access to the N-oxide in order to initiate the reaction.

Moreover, it is known that 2-aminopyridine 1-oxide (52) may be obtained from picolinamide 1-oxide (67) and potassium hypobromite by the Hoffman degradation reaction (80).



Since it is well established that Hoffman degradation reactions involve the formation of intermediate isocyanates, one should expect the formation of[1,2,4]oxadiazolo[2,3-a]-pyridine-2-one (54) as final product. The fact that 54 has never been isolated under these conditions raises some serious doubts about Hoegerle's proposal of an isocyanate intermediate necessary for its formation. Since basic conditions are used in the preceeding reaction, it may be argued that 54 is indeed formed but then quickly hydrolyzed to 2-aminopyridine 1-oxide (52). This possibility must be discarded, however, since 54 can only be hydrolyzed under much more drastic conditions. Thus Katritzky (65) succeeded in hydrolyzing 54 to 52, in 22% yield, only after an 8-h reflux with ethanolic sodium ethoxide.

In this work, the reaction of various 2-aminopicoline 1-oxides with thiophosgene led in each case, to the formation of methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones (68-72) which all exploded on being heated in a melting-point tube.



68: $R_3=CH_3$; $R_4=R_5=R_6=H$

69: $R_4=CH_3$; $R_3=R_5=R_6=H$

70: $R_5=CH_3$; $R_3=R_4=R_6=H$

71: $R_6=CH_3$; $R_3=R_4=R_5=H$

72: $R_4=R_6=CH_3$; $R_3=R_5=H$

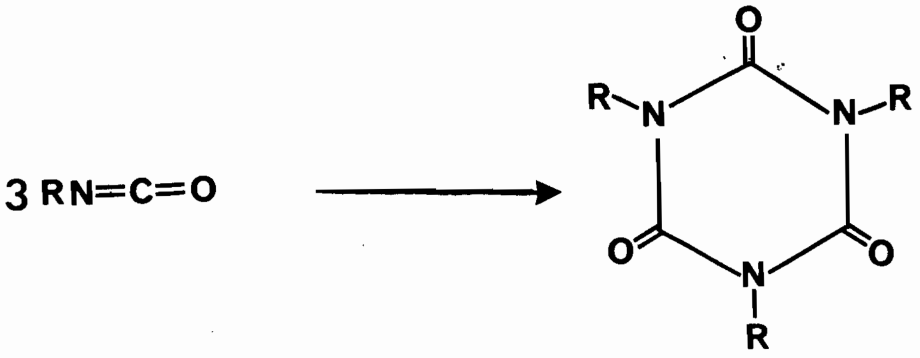
Unlike their oxygen counterparts, the products (68-72) were completely insensitive to refluxing aqueous ammonia failing to give the desired pyridylthiourea 1-oxides. On the other hand, they underwent smooth reaction with alcohols to give deoxygenated pyridylcarbamates and not the expected pyridylcarbamate 1-oxides.

This apparently anomalous behaviour was made clearly evident by examination of the u.v. spectra in absolute ethanol at different time intervals. For example, the u.v. spectrum of[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53) in absolute ethanol showed absorption maxima at 228, 292 and 340 nm if taken immediately on dissolution. One day later, the absorption maxima underwent a shift to 231 and 289 nm with the disappearance of the last band, and a week later, the maxima had shifted to 231 and 278 nm, coinciding exactly with the spectrum of ethyl N-2-pyridylcarbamate taken separately in absolute ethanol. Similarly, the u.v. spectrum of 5,7-dimethyl[1,2,4]-oxadiazolo[2,3-a]pyridine-2-thione (72) showed at first absorption maxima at 220, 291 and 334 nm with a gradual shift to 283 and 234 nm after one week, again coinciding with the u.v. spectrum of ethyl N-(4,6-dimethyl-2-pyridyl)carbamate taken separately. In the case of 7-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (69) and 6-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (70), only the u.v. absorption maxima characteristic of the corresponding deoxygenated carbamate derivatives could be observed since reaction with ethanol appeared to be instantaneous. Because of the insolubility of these products in other solvents, no other u.v. spectra could be recorded.

The mass spectra of 6-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (70) and 5,7-dimethyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (72) were also investigated. However, in line with their thermal instability, 70 and 72 proved unstable to electron impact and did not show any molecular ions but only fragmentation products identified as pyridyl isocyanates.

A study of the thermal explosion products of 7-methyl [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (69) revealed the presence of starting material (69) and a second product whose i.r. spectrum exhibited three bands in the carbonyl region at

1662, 1689 and 1749 cm^{-1}. This may be assigned to an isocyanurate structure (73) resulting from the trimerization of 4-methyl-2-pyridyl isocyanate which is probably formed during the thermal explosion since it is also produced under electron impact. Isocyanurates are frequently encountered in reactions giving rise to isocyanates and usually absorb in the i.r. around 1680, 1710 and 1760 cm^{-1} (81).



74

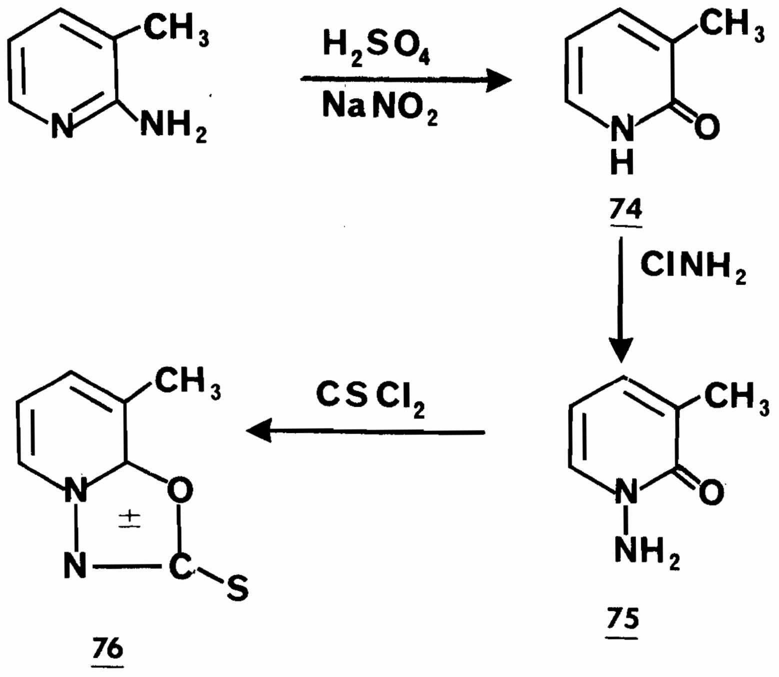
Isocyanates appear to be important decomposition products of the [1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones (53,68-72). The oxygen necessary for the formation of the isocyanate function appears to arise from the N-oxide although the fate of the sulfur atom is less evident. Since sulfur no longer appears in the final product, it must have been removed prior to the completion of the reaction. The explosive nature of these compounds may cause the sulfur to be forcefully expelled, perhaps as carbon oxysulfide, although this would require the participation of C=O which, as already seen, must remain present to form the isocyanate function. Another possibility is that the sulfur is extruded in its elemental form, or again as SO_2.

Compound [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53) was treated with methyl iodide in methanol, only to give methyl 2-pyridylcarbamate, the methyl iodine having not reacted. This is another instance of the ease of reaction of these products with alcohols leading to deoxygenated pyridylcarbamates. In the absence of solvent, 53 did react with methyl iodide to give a product which also exploded on being melted at 116° and produced a purple liquid. The mass spectrum afforded an ion of m/e 127, identified as iodine, as the principal fragment. No molecular ion could be observed and all other fragments were thought to arise through the decomposition of this product under electron impact.

The elemental analyses carried out on the [1,2,4]-oxadiazolo[2,3-a]pyridine-2-thiones (53,68-72) were generally in agreement with an oxadiazolopyridine thione structure although in some cases, the carbon or sulfur value was inferior to the calculated value. Once again, the instability of these compounds to heat constituted a handicap in the determination of the elemental composition and resulted in lowered values.

In order to investigate the applicability of the reaction with thiophosgene to 1-amino-2-pyridones, 3-methyl-2-pyridone (74) was synthesized from 2-amino-3-methyl-pyridine (82) and then reacted with chloramine, following the method of Hoegerle (78) as illustrated below. The preparation of chloramine proved to be quite difficult and only a small yield of 1-amino-3-methyl-2-pyridone (75) could be obtained. It was treated with thiophosgene affording a cream-colored product melting at 249-50° without exploding. Its mass spectrum revealed the presence of a molecular ion of m/e 166 and a peak at m/e 109 corresponding to 74.

The molecular ion of m/e 166 corresponds to 8-methyl-[1,3,4]-oxadiazolo[3,2-a]pyridine-2-thione (76). In this case, a conventional structure cannot be assigned to 76 but in analogy to Hoegerle's products from phosgene and 1-amino-2-pyridones, it is necessary to formulate it in terms of a meso-ionic structure. Exact mass measurement confirmed the formula



of 76 to be $C_7H_6N_2OS$.

INFRARED SPECTRA OF THIAZOLYL- AND PYRIDYL-THIOUREAS AND OTHER DERIVATIVES

In the present work, the infrared spectra of N-carbethoxy-N'-phenyl-N-thiazolylthioureas (19, 20), N-carbethoxy-N,N'-diphenylthiourea (25), O-ethyl-N-phenyl-N'-thiazolylisoureas (23, 21), N-phenyl-N'-thiazolylguanidines (10, 11, 14, 16) as well as N-benzoyl-N'-pyridylthioureas (37-43), N-pyridylthioureas (28, 30-33) and[1,2,4]oxadiazolo-[2,3-a]pyridine-2-thiones (53, 68-72) have been recorded in the region 4000-400 cm^{-1}.

A. GENERAL CONSIDERATIONS

In general, five- and six-membered nitrogen-containing heteroaromatic compounds present similar infrared spectra. The molecular vibrations of thiazoles and pyridines may be classified into the following categories: C-H stretching vibrations near 3100-3000 cm^{-1}; skeletal ring vibrations near 1650-1350 cm^{-1}; in-plane C-H deformations ca. 1250-1000 cm^{-1}; the ring-breathing mode ca. 1030-850 cm^{-1}; out-of-plane C-H deformations near 1000-700 cm^{-1}; in-plane ring deformations near 700-650 cm^{-1} and out-of-plane ring deformations ca. 750-370 cm^{-1}.

The infrared spectrum of thiazole was elucidated by Sbrana et al. (83) while Wilmhurst and Bernstein (84) carried out studies on pyridine and deuterated pyridines. The derivatives of thiazole were investigated by Taurins, Fenyes and Jones (85), Chouteau et al. (86,87,88) and by Mijovic and Walker (89). Katritzky (90,91,92) and Shindo (93,94,95) examined many pyridines and pyridine 1-oxides.

1. The 3500-2500 cm^{-1} region

Thiazole shows three fundamental ν C-H modes at 3123, 3083 and 3067 cm^{-1} in the solid form (83), with only two bands appearing at 3115 and 3083 cm^{-1} in the liquid form. The corresponding modes in pyridine appear at 3083, 3054 and 3036 cm^{-1} (84). Substituted pyridines often show bands in the 3095-3060 and 3055-3010 cm^{-1} ranges (96). 2-Substituted thiazoles exhibit two bands near 3110 and 3080 cm^{-1} while 2,4-disubstituted thiazoles possess only one band near 3110 cm^{-1} (86). 2-Aminopyridine reveals its ν C-H bands at 3073, 3026 and 2950 cm^{-1} while the 3- and 4-aminopyridine possess two bands each at 3065, 3038 cm^{-1} and 3038, 2995 cm^{-1}, respectively (97).

Nonbonded N-H stretching vibrations occur in the region 3450-3300 cm^{-1} with a slight lowering of the frequency upon hydrogen-bonding. Thus both 2-amino- and 2-amino-4-methylthiazole absorb at 3490 cm^{-1} (ν_{as} NH_2) and 3393 cm^{-1} (ν_s NH_2) (88). Similarly, 2-aminopyridine absorbs at 3445 and 3164 cm^{-1} while the 3-amino derivative shows its bands at 3376 and 3159 cm^{-1} (97).

2. The overtone region

In analogy to benzene derivatives, alkylpyridines show typical absorption in the 2000-1650 cm^{-1} region due to weak overtone and combination bands, characteristic of the type of substitution. Thus 2-alkylpyridines show bands at 1960 and 1755 cm^{-1}, the 3-alkyl analogues at 1930-1905 cm^{-1} (98) and the 4-analogues at 1950-1920 cm^{-1} (93).

3. The 1650-1350 cm^{-1} region

This region characterizes the aromatic C=C skeletal ring vibrations as well as C=N stretching vibrations. Because of this, it is difficult to assign these vibrations individually whether in pyridines or thiazoles. In the solid form, thiazole reveals skeletal modes at 1482, 1473, 1383, 1378, 1369 and 1315 cm^{-1} (86). In the liquid state, these appear at 1477, 1378 and 1317 cm^{-1}. Pyridine absorbs similarly at 1583, 1572, 1482, 1439 and 1375 cm^{-1} (84). Its monosubstituted derivatives usually show only four bands in this region (96). Pyridine 1-oxides usually possess four bands also, although in the parent compound and the 4-substituted derivatives, the second band is present but too weak to be discerned (90,91,92).

The symmetric NH_2 bending vibrations appear near 1600 cm^{-1}. Thus 2-aminothiazole absorbs at 1626 cm^{-1} and 2-amino-4-methylthiazole at 1628 cm^{-1} (88). Similarly aminopyridines absorb in the 1645-1614 cm^{-1} region (97).

This region is also host to CH_3- and CH_2- deformation vibrations which give rise to absorptions near 1460 (asymmetric) and 1375 cm^{-1} (symmetric) (86). Taurins et al. (85) concluded that bands at 1445 and 1435 cm^{-1} in methylthiazoles were due to the methyl group, as well as the bands at ca. 1385-1375 cm^{-1} although these are also partly due to thiazole skeletal vibrations.

Disubstituted and trisubstituted methylpyridines possess two bands near 1600 cm^{-1} due to skeletal modes (99). The 2,6-disubstituted pyridines have an additional band near 1529 cm^{-1}. Bands appear also in the 1450-1440 cm^{-1} region as well as near 1410 cm^{-1}. The methyl vibrations are found ca. 1380-1355 cm^{-1}.

4. The 1350-1000 cm^{-1} region

According to Sbrana et al. (83), thiazole displays three C-H in-plane deformation modes at 1237, 1119 and 1039 cm^{-1} while Chouteau et al. (86) prefer to assign these vibrations to the bands at 1318, 1238 and 1038 cm^{-1} and the band at 1119 cm^{-1} to an in-plane ring deformation. In pyridine, the corresponding bands are observed at 1218, 1148, 1085 and 1068 cm^{-1} (84).

Two bands are observed in mono-2-substituted thiazoles, one in the 1330-1305 cm^{-1} range and the other in the 1061-1030 cm^{-1} range (87). Disubstituted thiazoles possess only one band, in the 1330-1305 cm^{-1} range. For example, 2-aminothiazole absorbs at 1325 and 1035 cm^{-1} while the 4-methyl analogue absorbs only at 1331 cm^{-1} (87). According to Chouteau et al. (87), the strong bands appearing in the 1160-1080 cm^{-1} region in substituted thiazoles arise from in-plane ring deformations. Moreover, the asymmetric NH_2 absorption of 2-aminothiazole appears at 1020 cm^{-1} and for the 4-methyl analogue at 1090 cm^{-1} in dilute solution.

Disubstituted methylpyridines show typical absorption bands in the 1136-1099 cm^{-1} region (99). The ring vibrations appear near 1001-988 cm^{-1} except for 2,5-disubstituted compounds which display bands near 1034-1021 cm^{-1}. Bands near 1330-1280 cm^{-1} and 1253-1222 cm^{-1} appear to be characteristic of alkylpyridines.

Pyridine N-oxides also show intense bands in the 1200-1030 cm^{-1} region. The parent compound and 3-substituted pyridine N-oxides show a strong ring-breathing mode near 1015 cm^{-1} (90) although it cannot be located precisely in the 2- and 4-analogues. The $\overset{+}{N}\text{-}O^{-}$ stretching vibration usually produces a strong band near 1250 cm^{-1} although it is very sensitive to its environment and its range may extend from 1310-1200 cm^{-1} (96). For example, pyridine 1-oxide absorbs at 1301 cm^{-1} as a gas, at 1270 cm^{-1} in a nonpolar solvent, at 1242 cm^{-1} as a solid and at 1235 cm^{-1} in methanol-carbon tetrachloride solution (94).

5. The 1000-650 cm^{-1} region

Ring-breathing modes for thiazole have been assigned to the bands at 878 and 862 cm^{-1} by Sbrana et al. (86). Furthermore, they assigned the bands at 799 and 722 cm^{-1} to out-of-plane C-H deformations and the shoulder at 750 cm^{-1} to ring vibrations. The 2-monosubstituted thiazoles show two very strong bands in the 760-740 cm^{-1} and 722-715 cm^{-1} ranges assigned to C-H vibrations by Chouteau et al. (86), whereas disubstituted thiazoles reveal only one band. 2-Aminothiazole absorbs at 756 and 689 cm^{-1} while the 4-methyl compound absorbs only at 693 cm^{-1} (87). Mijovic and Walker observed that only thiazoles containing a phenyl group, an amino group or certain methyl derivatives showed bands in the 700-650 cm^{-1} region (89).

Pyridine exhibits out-of-plane C-H deformation modes at 981, 942, 886 and 700 cm^{-1} (84), but they are too weak to be observed in pyridine derivatives. Two bands are generally found, however, one of which is near 700 cm^{-1} (96). Thus aminopyridines and aminopicolines absorb in the 855-840 cm^{-1} region and in the 705-790 cm^{-1} region (97).

Disubstituted alkylpyridines show their out-of-plane vibrations near 833-816 cm^{-1} and 743-725 cm^{-1} except for trisubstituted compounds which only exhibit one strong peak near 732-725 cm^{-1} (99).

In pyridine 1-oxides, besides the usual C-H deformation modes, two further bands are observed near 850 and 780 cm^{-1} which Shindo considers to arise partly from N-O bending vibrations (95).

6. The 650-400 cm^{-1} region

The bands occurring in the far infrared region arise from the thiazole and the pyridine ring vibrations. Thiazole exhibits bands at 605 and 470 cm^{-1} (83) while pyridine absorbs at 652 and 605 cm^{-1} (in-plane ring deformations) and at 749, 405 and 374 cm^{-1} (out-of-plane ring deformations) (84). The 2- and 3-monosubstituted pyridines display a medium to strong band in the region 635-606 cm^{-1} and a strong band between 417-385 cm^{-1}. On the other hand, 4-substituted pyridines show no characteristic absorption in this region (100).

B. THE INFRARED SPECTRA OF THIAZOLE AND PYRIDINE DERIVATIVES

1. Thiazolyl- and pyridylthioureas and derivatives

The thiocarbonyl group being less polar than the carbonyl group and possessing a much weaker bond absorbs at low frequencies, estimated at 1225-1025 cm^{-1} in simple derivatives. Thus thiophosgene absorbs at 1180 cm^{-1}, its C=S bond behaving more as a C=C bond since halogen substitution does not raise its absorption frequency (101), unlike its oxygen-analogue, phosgene, which absorbs strongly at 1828 cm^{-1}.

On the other hand, the assignment of C=S stretching frequency in nitrogen-containing compounds is a much more difficult task. The strong "thioureide band" resulting from the coupling of C-N and C=S stretching vibrations and N-H deformation vibration appears in the wide range 1570-850 cm^{-1} (102). For example, thiourea absorbs at 1472, 1415 and 1086 cm^{-1}

presumably due to $-NH_2$ bending, C-N and C=S stretching vibrations. Substituted thioureas absorb in the 1400-1130 cm^{-1} range (101). Diphenylthiourea, for example, absorbs at 1344 cm^{-1} (102).

Generally, thioureas, thioamides and thiohydantoins all exhibit three main bands in the region 1570-1395 cm^{-1}, 1420-1260 cm^{-1} and 1140-940 cm^{-1} due to mixed vibrations and designated by Rao as the "-N-C=S I, II and III" bands (102).

(a) N-Pyridylthioureas

The N-pyridylthioureas (28,30-33) all exhibited several medium to very strong bands in the 1650-1350 cm^{-1} region arising from skeletal vibrations of the pyridine ring. The pyridylthioureas also possessed at least one medium to very strong band in each of the regions 1336-1292 cm^{-1}, 1245-1205 cm^{-1} and 1132-1071 cm^{-1}. It is probable that most of these bands arise from the thiourea group $R-NH-CS-NH_2$ although there should be overlapping with the C-H in-plane deformations of the pyridine ring in this region. The position and number of methyl groups on the pyridine ring has no significant influence on the band positions in the i.r. spectra of 28,31-32 and 30 (Fig. 1) since the same bands are also present in 34. A substituent such as bromine in the 5-position appears to have a certain influence on the band positions in this region.

The infrared absorption bands of N-pyridylthioureas are listed in Table I.

(b) N-Benzoyl-N'-pyridylthioureas

The N-benzoyl-N'-pyridylthioureas (37-43) differ from the previous compounds in having replaced $RNHCSNH_2$ by $RNHCSNHCOC_6H_5$. Accordingly, they display a strong C=O absorption in the 1710-1665 cm^{-1} region. Thus N-benzoyl-N'-(5-methyl-2-pyridyl)thiourea (39; Fig.2) absorbs at 1677 cm^{-1}. The usual amide I (C=O stretching in amides) range is considered to be 1680-1630 cm^{-1} in the solid state for secondary amides, the frequency being raised to about 1700 cm^{-1} by N-aryl substitution (102). The presence of a very strong band in the region 1560-1524 cm^{-1} may be due to an amide II band arising from a mixed N-H bending and C-N stretching vibration since the normal range for this band is usually 1570-1510 cm^{-1}.

The N-benzoyl-N'-pyridylthioureas also possess at least three medium to very strong bands in the 1343-1145 cm^{-1} region assigned to thiourea absorption as well as C-H in-plane deformation. Moreover, the characteristic amide III band of secondary amides consisting of a mixed C-N stretching and N-H bending vibration appears in the 1310-1200 cm^{-1} region.

The position and number of methyl groups on the pyridine ring again have no effect on the bands although, the 5-bromo substituent lowers the frequencies of the strong bands.

Phenyl absorption was responsible for the appearance of strong bands in the 713-660 cm^{-1} region since these were absent in the spectra of the corresponding N-pyridylthioureas.

A band present at 713-701 cm^{-1} may also arise from amide V absorption which usually appears near 720 cm^{-1} (102).

The infrared spectral data of N-benzoyl-N'-pyridylthioureas are summarized in Table II.

(c) N-Carbethoxythioureas

In the i.r. spectra of the N-carbethoxythioureas (25,19,20) very strong bands are observed near 1700 cm^{-1} due to the stretching vibrations of the C=O group in the carbethoxy group. Thus N-carbethoxy-N,N'-diphenylthiourea (25). N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19) and N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20; Fig. 3) absorb at 1701, 1704 and 1702 cm^{-1} respectively, all within the 1701-1690 cm^{-1} range attributed by Rao to the carbamate "amide I" band (C=O stretching) (102).

The compounds 25,19,20 possessed a very strong band in the region 1279-1263 cm^{-1} which may possibly arise from a C-O-C asymmetric stretching vibration of the carbethoxy group.

The medium band present at 1317-1311 cm^{-1} in the spectra of 19 and 20 but absent in 25 is assigned to C-H in-plane deformations of the thiazole ring. The other medium to strong bands for all three compounds in the range 1375-1034 cm^{-1} probably arise from $R_2N\text{-}\overset{S}{\overset{\|}{C}}NHC_6H_5$ absorption as well as methyl and skeletal ring vibrations.

The monosubstituted benzene rings in 25, 19 and 20 all absorbed in the region 773-694 cm^{-1}. The C-H out-of-plane vibrations of the thiazoles also appear in this region.

Table III lists the infrared absorption bands of the N-carbethoxythioureas.

(d) N-Phenyl-N'-thiazolylguanidines

The substituted guanidines (14,11,9,10,16) absorbed very strongly in the 1656-1611 cm^{-1} region, presumably due to the C=N stretching vibrations. Generally, the N,N'-diphenyl-N''-thiazolylguanidines (14,10,16) absorbed at lower frequencies than the corresponding N-phenyl-N',N''-dithiazolylguanidines (11,9). According to Suresh et al. (103), monophenyl-, diphenyl- and triphenylguanidine absorb at 1692, 1647 and 1659 cm^{-1}, respectively.

Strong bands at ca. 1596-1586 cm^{-1}, as well as a second medium to strong band in the region 1579-1568 cm^{-1} may arise from a combination of the stretching vibrations of the C=C bonds in the benzene ring and of the C=C and C=N bonds in the thiazole ring.

The strong band in the region 748-743 cm^{-1} as well as a second medium to strong band in the range 720-701 cm^{-1} are due to the monosubstituted benzene absorption. The very strong band in the region 698-683 cm^{-1} may be assigned to the C-H out-of-plane deformation mode of the phenyl ring.

Table IV summarizes the infrared spectral data of N-phenyl-N'-thiazolylguanidines.

(e) O-Ethyl-N-thiazolylisoureas

The C=N stretching vibrations of O-ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23) and O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21; Fig. 4) appear as a very strong band at 1641 and 1638 cm^{-1}, respectively. The general range quoted by Forman et al. for isoureas is 1680-1590 cm^{-1} (104).

The strong band at 1574 cm^{-1} for 23 and at 1579 cm^{-1} for 21 probably arises from a combination of the C=C and C=N stretching vibrations of the thiazole ring as well as the C=C stretching of the phenyl group.

The medium bands present at 1383-1373 cm^{-1} may be due to CH_3- and CH_2- deformation vibrations as well as thiazole skeletal vibrations. The band at 1239 cm^{-1} present in 21 but missing in 23 may be assigned to a C-H in-plane deformation of the thiazole ring.

The strong band present at 749-746 cm^{-1} and a second strong band at 718-701 cm^{-1} are typical of monosubstituted benzene rings.

The infrared spectral data of O-ethyl-N-thiazolylisoureas are found in Table V.

2. [1,2,4]Oxadiazolo[2,3-a]pyridine-2-thiones

The bands present at 1628-1607 cm^{-1} and 1582-1557 cm^{-1} in the spectra of 53,68,70,72 arise from the aromatic C=C skeletal ring vibrations and C=N stretching vibrations of both the pyridine and oxadiazole ring. The bands in the region 1449-1442 cm^{-1} are again due to both rings (105). The bands in the 1388-1370 cm^{-1} range may be assigned to the methyl vibrations since they are absent in[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (53; Fig. 5) although the oxadiazole ring also generally absorbs in this region.

These compounds also possessed three bands in the 1335-1310 cm^{-1}, 1290-1255 cm^{-1} and 1159-1123 cm^{-1} regions. These may arise from the thioamide (C=N-$\overset{\overset{S}{\|}}{C}$-) mixed vibrations. The bands present at 1064-1020 cm^{-1} are due possibly to pyridine and oxadiazole ring vibrations. The pyridine C-H out-of-plane vibrations may be responsible for the absorption in the 851-835 cm^{-1} region.

Table VI summarizes the infrared spectral data of[1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones.

TABLE I

INFRARED SPECTRA OF MONOPYRIDYLTHIOUREAS

28	30	31	32	34	33
1622shw	1619shm		1620vs		
	1612s	1608vs	1614shm	1604vs	1610vs
1598s	1593vs				
1586vs		1584shvw			1584vs
		1550w	1566shm		
	1534m	1535m	1536s	1547shm	
1519vsbr				1525s	1520sbr
					1504shm
1460shm	1490mbr		1449w	1457shm	1473m
1453m	1435w	1451s	1436w	1435vs	1436sbr
1426w		1426w			
1411w		1400m	1406m		
1381vw			1391shw		
		1373vw	1372m		
	1332m		1336m		1336m
1317m	1314w	1306m	1325shw	1327m	1320m
		1296shw	1292m		
1268w	1271w		1261vw	1267w	
1245m	1259w	1244w	1238shvw		1249w
	1240shm				
1225shw	1229s	1220vs			1216s

28	30	31	32	34	33
	1218shm		1207vs	1205s	
1179m			1162m		
	1142vw	1156m		1156m	1133vs
1122s					
			1103s	1101w	
1057s	1072vs	1095s		1074m	1092m
1033vw	1049shw	1071s	1035w	1065shm	1050vs
1001w	1033w			1010m	1004w
970vw	962vw	996vs	996w		
941vw			936vw	948vw	914w
	867vw				865vw
841m		836w	834vs		
	827vs			826m	
787s				790m	
777m	776m	780s			
759vw	741m	741vw	729m	734m	725w
			710m	710m	
739vw	699vw	700mbr	683m		686w
637m	637sbr			657wbr	666w
629s		630m	613s	632m	635w
614sbr		625shw	604shm		625vw
579m	568m		568w		572wbr
549w		551vw			

28	30	31	32	34	33
536vw			532 m	531m	
	514m				504w
490w			488w	482m	486m
	463m	469w	446m	446vw	
425w			421vw		
				408vw	

vs = very strong

s = strong

m = medium

w = weak

vw = very weak

sh = shoulder

br = broad

TABLE II

INFRARED SPECTRA OF N-BENZOYL-N'-PYRIDYLTHIOUREAS

37	38	39	40
			1709vs
1675s	1678s	1677s	1682vw
1602w	1608m		1610s
	1599shw	1599vw	
1579w	1582shm	1578vw	1584vw
	1560vsbr	1548shw	1561shm
		1536vsbr	1547vsbr
1525vsbr	1524vsbr		1529shm
1513vs		1519sbr	
1491shm	1493m	1492w	1492w
1455m	1439mbr	1470w	1448s
1448shm	1424mbr		1442s
	1413mbr		1423shm
1379vw	1383vw	1384w	1379w
1333w	1336s	1335s	1332s
1321vw	1323shm	1319m	1318shm
		1308m	
	1296shw	1292m	
1273shm	1282m		1287vw
1253m	1249m	1244s	1251shm
1227vw		1234shm	1238vs

37	38	39	40
		1215w	1214s
1187w	1190w	1189w	1195s
	1165shm	1162shw	1160s
1159s	1156s	1154s	
1120w	1106w	1129m	
		1102vw	
1090w	1083w	1082vw	1085m
1075vw	1069w	1069vw	1070w
1024w	1024w	1024m	1024w
		1001w	1002w
985vw	999w		992vw
		976vw	982w
952w	938w	956vw	945vw
		928vw	929vw
	896w		902m
			895m
868w	883w	859shw	882w
847vw	832m	832m	845m
810shm		804w	803m
799m	795m	794w	792s
775m			
	735m	732vw	748w
712mbr	713s	711s	725w

37	38	39	40
705shm			705vs
	693s	688m	688m
670m	653m	653s	682shm
	624vw	622vw	634m
615w	615vw	612w	
	583vw		
545vw	553w		556w
		518w	519m
454vw	453w		477w
	447w	447vw	
	419vw	422vw	

TABLE II (CONTINUED)

INFRARED SPECTRA OF N-BENZOYL-N'-PYRIDYLTHIOUREAS

41	43	42
1670s	1666s	1676s
1603m		
1601vw	1599w	1599w
		1585vw
1579shs	1578s	1575w
1553vs	1560-1510sbr	1559shm
1531vs		1531-1515svbr
1490w	1489s	1491m
1445m	1449vs	1453m
1399w	1399w	1384shvw
1375w		1374m
1343vs		1343shm
1320w	1328vsbr	1329m
	1318vsbr	1316s
		1297m
1251shm	1250shm	1287m
1221s	1237s	1241m
		1193w
1168vs	1175vw	1168vw
1153shw	1150vs	1153shm
		1145s

41	43	42
		1125shw
	1099vw	1099vw
1084w	1082w	1089w
	1069m	1077w
1026w	1019m	1025w
993vw	998m	999m
969vw	973vw	952w
931w	936vw	919w
891w	835m	851w
851m	823shw	832s
799w	793m	793m
781w	770m	769w
	732w	739vw
	710m	701vs
694vs	685m	
	670m	672m
661w	660m	663m
	646w	627m
616w	608m	
		596m
		566vw
	546m	572m
	477vw	
	465vw	
	411vw	415vw

TABLE III

INFRARED SPECTRA OF N-CARBETHOXYTHIOUREAS

25	19	20
1701vs	1704vs	1702vs
1590m	1593w	1591vw
	1549vsbr	1569shm
1520sbr		1538vsbr
1505shm		
1496m	1484m	1487w
1487m	1472w	1475w
1464m	1452vw	1454vw
1448w	1437w	1445vw
		1428vw
1388m	1395m	1396m
1367m	1375s	1375s
	1363shm	1363shm
1308shw	1317m	1311m
1293shm	1293shs	1295shm
1272vsbr	1279vsbr	1263vsbr
	1245shm	1249shm
1215w		
	1189w	
1172vw		1176w
1157w	1153w	1154vw
1148shvw		1135m

25	19	20
1088m		
1069vw	1061w	1071w
1034s	1041m	1040s
1022s	1025w	1024m
1003w	1009vw	1008m
989w		984w
950vw	946w	931m
	916vw	914vw
	889vw	
864m	871w	861m
	858vw	840m
	835vw	832shw
	799w	794w
769m	773m	761s
737s	713m	730m
694m	691w	694vs
679shvw	674vw	661m
656vw	651w	639vw
627vw	628vw	629vw
	618ww	614m
574m	594vw	
505w	519vw	503vw
455vw	418w	419w

TABLE IV

INFRARED SPECTRA OF N-PHENYL-N'-THIAZOLYLGUANIDINES

14	11	10	9	16
	1658vssh		1656vs	
	1650shvs		1649br	
1637shs	1637vsbr	1618shs	1635vsbr	1636shs
1618mbr	1622shs	1611s		1629vs
1596s	1597m	1586vs	1598w	1593s
1579m	1568m		1583w	1577s
1562s	1557shm		1571w	1542vs
1516m	1516w	1525vs	1532vw	
1487s	1477sbr	1491m	1512w	1491m
			1495m	
1452vs	1451s	1455vs	1456mbr	1472shs
				1465vs
1441shm				1445vw
	1430m	1434shm	1435mbr	1437m
				1403w
		1389m	1396vw	
		1374shvw	1370w	1362m
1338vs	1343s	1356m	1349s	
1315shw		1309vw	1313m	1319w
1308shvw				
		1296w		

14	11	10	9	16
1270s	1283m	1280vw	1279w	1288m
	1252vw	1256w	1251vw	1251w
1219m	1211vw	1204m	1205vw	1205w
1182ww			1190m	1189w
1173vw			1171vw	1170w
1141vs	1135mbr	1159vw	1128w	1148vw
1100vw	1101vw			
			1095vw	
1077w	1077w	1071w	1073w	1069w
1064s	1063w			1059w
1025vw	1027vw	1023w		1023w
1017w		1011w	1017w	
995vw	976m	978vw	991vw	979w
		966w	960w	
		922vw	931vw	
			915vw	913vw
895vw	892w	901vw	887w	895w
885vw	875w	855m	856m	864w
873w	853m		843shvw	830vw
866w	841shw		823vw	
835w				
788w		760m		
754m	747s	748s	743s	745s

14	11	10	9	16
745s	727vw		720sbr	719s
701m	703s			
689s	698s	695s	683mbr	697shvw
	683vw	670w	667vw	672vw
651w	667vw	654w		658w
634m	628vw	646vw	648vw	
627m	621vw	616vw	621vw	614vw
618vw	604m	586w	587w	
551w	567vw	576shvw	550vw	573w
524w	522vw			526w
509w		512w	503vw	
499w	499vw	493vw		485w
		430w		447w

TABLE V

INFRARED SPECTRA OF O-ETHYL-N-THIAZOLYLISOUREAS

23	21
	1717wbr
1646shm	1638vs
1641vs	1600m
1595m	
1574s	1579s
1500m	1504m
1485m	1488m
1467m	1467m
1445vw	
1435vw	1439m
1415mbr	1411w
1379m	1383m
1373m	
1341w	1344m
1335w	1331w
1328m	1307vw
1318m	
1285vw	1290vw
	1275vw
1228w	1239m
1221m	1218s

23	21
	1197vw
1179w	1178vw
1152w	1152vw
1104w	1114vw
1080w	1082shw
	1072w
1054vs	1057s
1029vw	1036vw
1002w	1026vw
982m	998vw
	985w
891shw	907vw
885m	885vw
855vw	862s
829vw	834m
806vw	
793vw	771m
765mbr	758shw
749s	746s
	727s
701s	718s
685m	685w

23	21
671w	670vw
657m	661vw
625vw	
518vw	553vw
502w	504vw

TABLE VI

INFRARED SPECTRA OF [1,2,4]OXADIAZOLO[2,3-a]PYRIDINE-2-THIONES

53	68	70	71	72
1619vs	1607s	1622m	1623m	1628s
	1572shw			
1557m			1569m	1569s
			1502m	
1485s	1497s	1503s		1489w
1449s	1465vw		1454vw	
	1440m			
1400vsbr	1428m	1418vs	1413s	1418vs
	1388vs	1387vs	1381w	1381s
1328vs	1377shs	1332vs	1370s	1335s
1290vs	1310s		1322vs	
1264vw	1278s	1266s	1274vw	1271s
			1255m	1245s
1177vw			1172w	1175vw
1146s	1158w	1144w	1159m	1149m
1123m	1096vw	1105vw	1086m	1104w
	1064m		1070vw	
1030m		1041vw	1039vw	1027m
1005s	1002m	1024m	1020m	
		972vw	975vw	
903m	950w			956vw

53	68	70	71	72
851m	891w	862w	856w	848s
834w	809s	835msh	812wsh	
780shm	780s	819s	799s	798m
763vs	741m	733w		728
755shs	713w			678w
		659w	662vw	659w
623m	626w			
543w	547wsh	559w	544vw	599w
	510vw			534w
434m	452vw	415w	427w	403w
420w	433w			

FIGURE 1

Infrared Spectrum of N-(5-Methyl-2-pyridyl)thiourea (30) in a KBr disc.

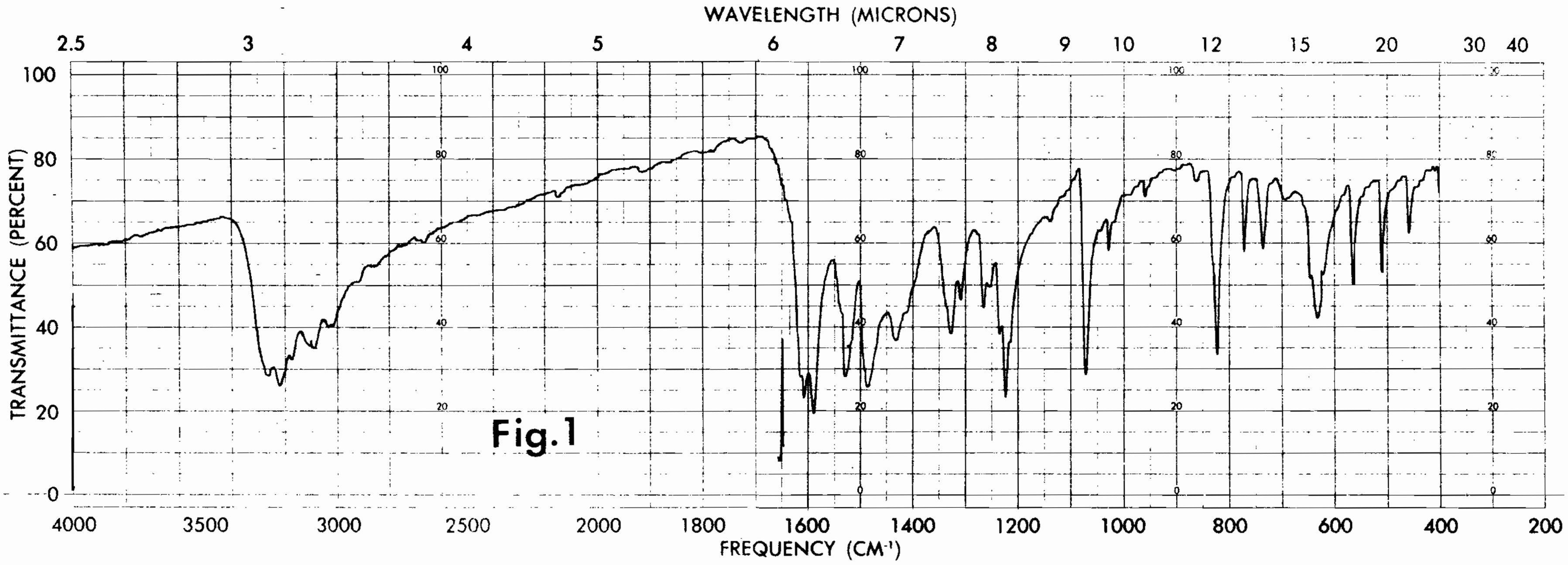

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Fig.1

FIGURE 2

Infrared Spectrum of N-Benzoyl-N$'$-(5-methyl-2-pyridyl)-thiourea (39) in a KBr disc.

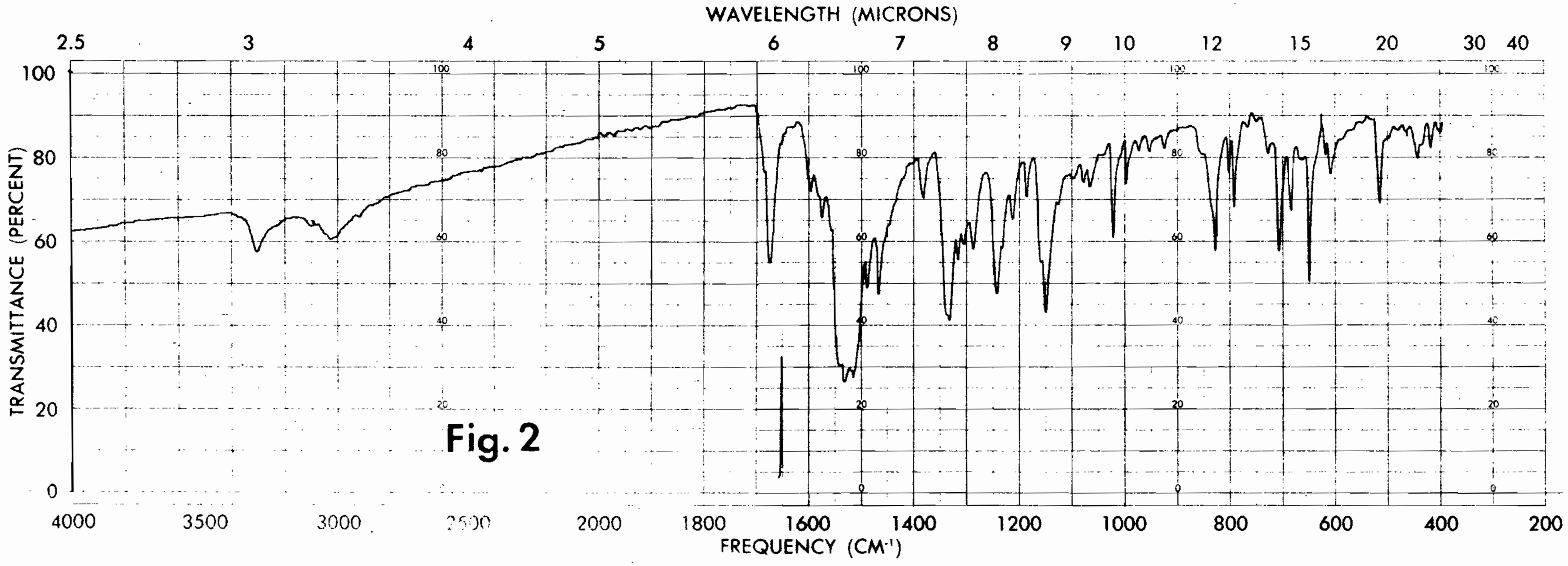

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Fig. 2

FIGURE 3

Infrared Spectrum of N-Carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20) in a KBr disc.

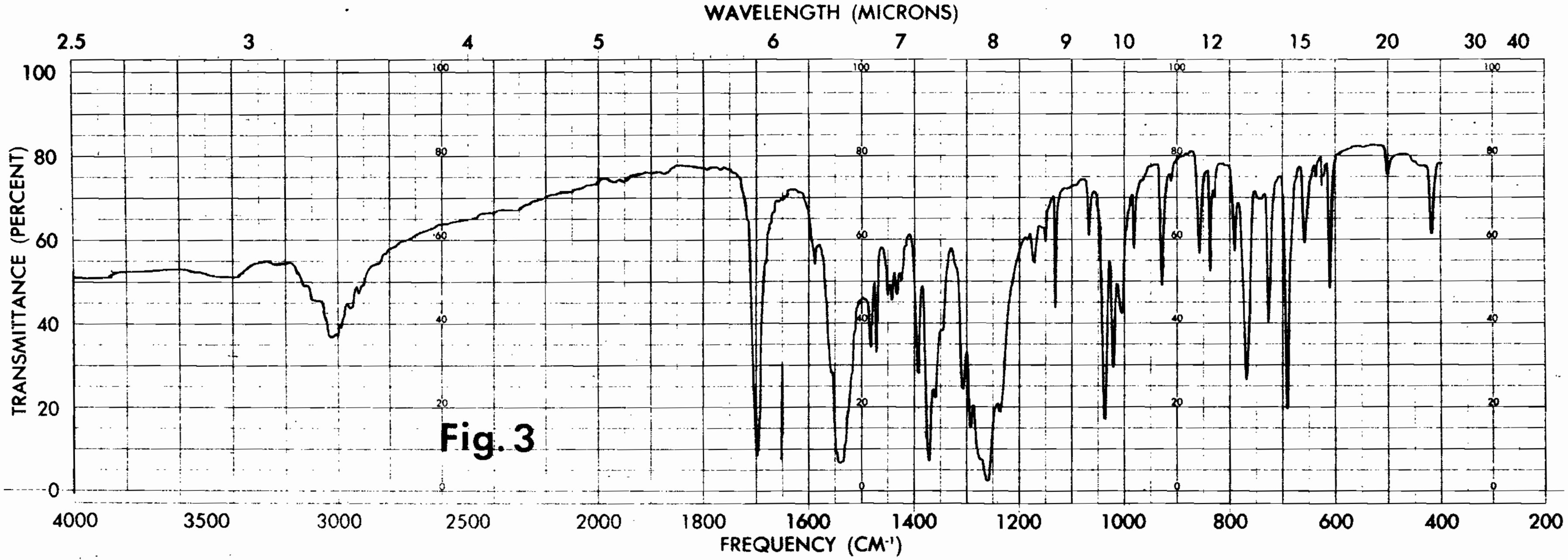

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Fig. 3

FIGURE 4

Infrared Spectrum of O-Ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21) in a KBr disc.

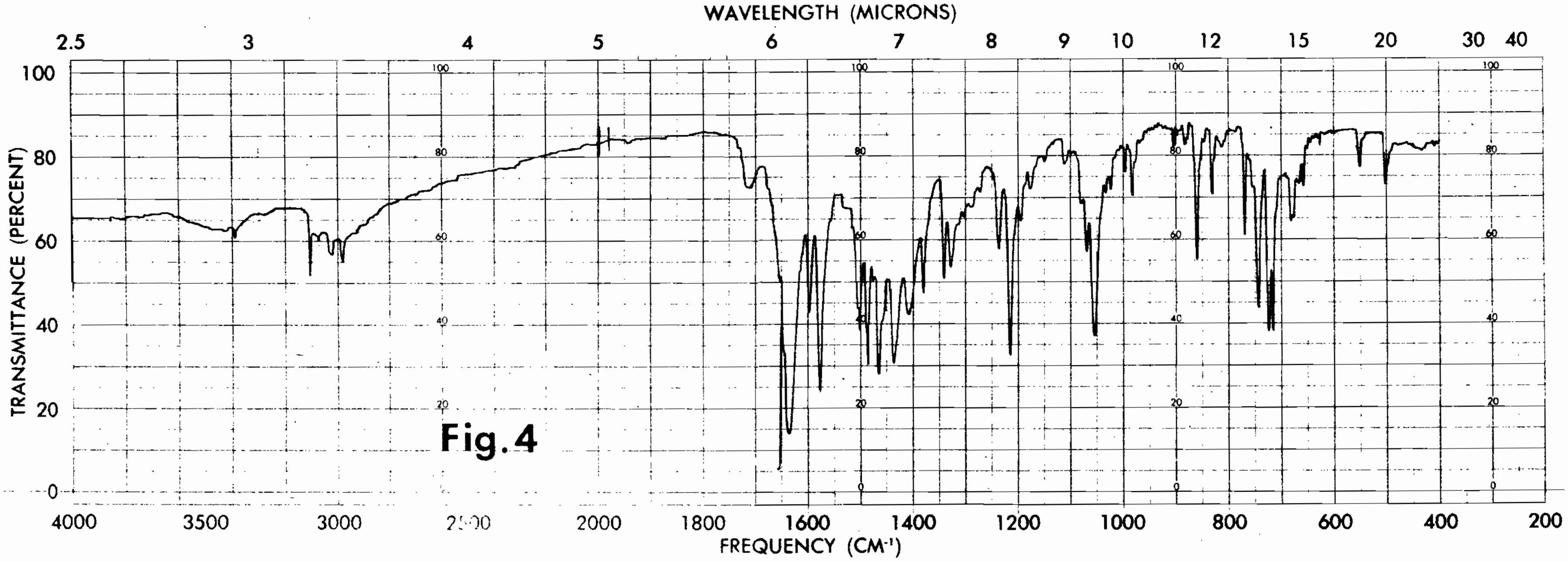

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Fig. 4

FIGURE 5

Infrared Spectrum of [1,2,3]Oxadiazolo[2,3-a]pyridine-2-thione (53) in a KBr disc.

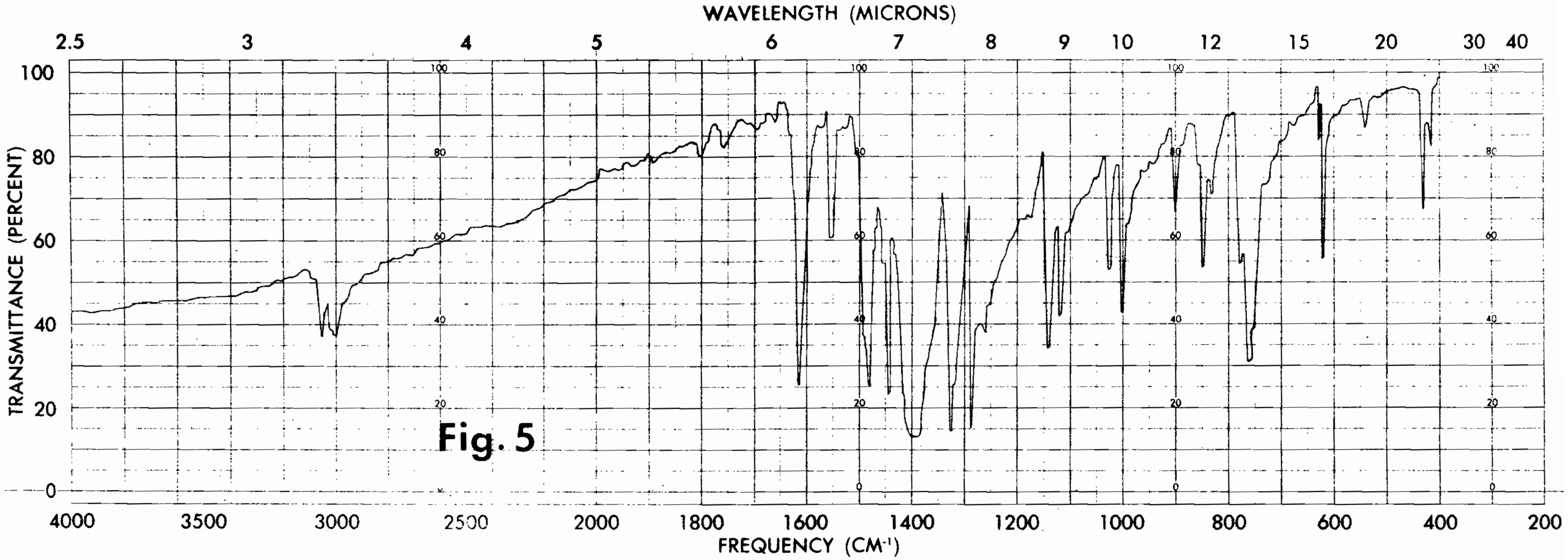

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)

Fig. 5

THE ULTRA-VIOLET SPECTRA OF THIAZOLE AND PYRIDINE DERIVATIVES

A. GENERAL

Aromatic hydrocarbons reveal three main types of ultra-violet absorption bands, classified by Clar (106) as the α, p and β bands, according to their positions and intensities. The wavelengths associated with these bands are in the order of $\alpha > p > \beta$, while the intensity is $\beta > p > \alpha$. In many aromatics, a weak triplet absorption band t may be found at still longer wavelengths. The α- and β-bands appear to be related, and also the p- and t-bands, for the members of each pair undergo similar wavelength shifts on annellation.

In benzene, all three bands result from the electronic transitions of the π-electron system. The intense β- and p-bands are found around 180 ($\varepsilon_{max} \sim 47,000$) and 200 nm ($\varepsilon_{max} \sim 7,000$) respectively, while the weak α-band, arising from a forbidden transition consists in fact of a series of fine-structure bands in the 230-270 nm region of the spectrum. These bands are observed principally in non-polar solvents and are referred to as the "benzenoid band", since they appear in benzene derivatives and other aromatic species, such as pyridine. For the sake of convenience, the band at 230 nm ($\varepsilon \sim 220$) is taken as representative of the α-band. The well-resolved vibrational structure arises from the distortion of the benzene ring caused by a bending vibration allowing the α-band to borrow intensity from the β-band.

B. PYRIDINE AND DERIVATIVES

The spectra of monoaza heteroaromatic six-membered ring compounds also show an absorption pattern of three bands, related to the α-, p- and β-bands of the corresponding aromatic hydrocarbon. In pyridine, the α-band is more intense and undergoes partial loss of vibrational structure. The loss of symmetry of pyridine with respect to benzene is responsible for rendering the α-band less "forbidden", and thus increases its intensity. Thus benzene absorbs at 255 nm (ε_{max} 250) and pyridine at 256 nm (ε_{max} 1,860) (107).

Pyridine contains an additional feature. The presence of non-bonding electrons gives rise to an $n-\pi^*$ transition, in addition to the benzenoid type of absorption. In the solution spectrum of pyridine, this transition is observed as a series of shoulders on the long-wavelength side of the α-band. If more nitrogens are introduced in the molecule, this $n-\pi^*$ band shifts to longer wavelengths, in contrast to $\pi-\pi^*$ bands which are rather insensitive to aza substitution (108).

Substituents usually cause a bathochromic shift of the $\pi-\pi^*$ bands in aromatic hydrocarbons and the azines. However, the azine $n-\pi^*$ bands undergo hypsochromic shifts by electron-donating substituents and bathochromic shifts by electron-accepting substituents. Since in the excited state of an n-π^* transition, the azine π- electron system carries an excess electronic charge, it will be stabilized by electron-accepting groups and destabilized by electron-donating groups. The magnitude of this n-π^* band shift depends upon the position of the substituents since the promoted electronic charge is not equally distributed over the carbon atoms of the azine in the excited state.

The conjugative effect of substituents generally shifts the π-π^* absorption of both benzene and pyridine to longer wavelengths by reducing the energy level between the highest occupied and the lowest unoccupied π-orbitals. However, the electron-donating alkyl groups produce a blue shift of the α-band in pyridine if placed in the 4- position but give rise to red shifts if present in the 2- or 3- positions (109). On the other hand,electron-donating groups such as amino-, hydroxy- and mercapto-, capable of strong conjugation with the nucleus, cause a marked red shift of the α-band, especially in the 2- and 3- positions. Cumper et al.(110) illustrate this well in their work on aminopyridines. Thus the α-band of pyridine was found to absorb at 251 nm in n-hexane. Introduction of an amino group in the 2- position shifted the absorption to 289.5 nm, in the 3- position to 293 nm, whereas in the 4- position, the band was present rather as a shoulder in the 260-265 nm region. As expected, 2,6-diaminopyridine underwent the greatest shift, absorbing at 299.5 nm. Comparison of the 2-aminopicolines gave the following results: 5- and 6-methyl compounds underwent red shifts to 297.5 and 290.5 nm, respectively; on the other hand, the 3-methyl compound underwent a small blue shift to 288 nm relative to the 2-aminopyridine (289.5 nm) and the 4-methyl derivative gave the greatest blue shift, to 287.5 nm.

In order to be complete, it should be mentioned that strong electronegative cyano- and nitro-groups cause larger red shifts of the α-band if placed in the 4-position of pyridine than in the 2- or 3-positon (109).

In the present work, all the pyridine derivatives were obtained from the parent 2-aminopyridine or the appropriate 2-aminopicoline. It is of interest to note the variation in the absorption as one goes from the parent aminopyridine to the benzoylpyridylthiourea and then to the pyridylthiourea. For instance, 2-amino-6-methylpyridine (λ_{max} 290.5 nm) undergoes a red shift in its benzoylthiourea (<u>40</u>; Fig. 6) (314 nm) due to the increased conjugation. Removal of the benzoyl portion to give the N-(6-methyl-2-pyridyl)thiourea (<u>31</u>; Fig. 7) (297 nm) reduces the conjugation provoking a blue shift in the absorption of this compound. The same trends were observed in all the pyridylthioureas examined and have been recorded in Tables VII and VIII.

Janssen has assigned two characteristic bands to alkylthioureas (111). The first, due to an n-π* transition of an electron in a lone-pair on the sulfur atom to an antibonding π-orbital, appears in the 280-360 nm range and is usually of low intensity or exists as a shoulder. The second band arises around 240 nm. Aromatic thioureas, such as phenylthiourea, and diphenylthiourea possess only one absorption maximum, in this case at 266 and 273 nm, respectively (112).

The pyridylthioureas (28,30,31,32) all showed three relatively well-resolved bands, in the 295-298 nm, 269-272 nm and 238-240 nm regions. Contrary to the usual absorption pattern of pyridines, the α-band, at the longest wavelength, was the most intense, with the p- and β-bands in decreasing intensity. It is possible that in these cases, the π-π^* transition band of the pyridines appears in the same region as the n-π^* transition of the thiourea portion, and thus the intensity of the band is augmented.

The benzoylpyridylthioureas (37-42) likewise absorbed in distinct regions, in 274-324 nm and 245-268 nm ranges. In this case, however, the absorptions arise due to the presence of both the pyridyl- and the phenyl- rings. The α-band is shifted to longer wavelengths as expected for a longer conjugated system.

Conversion of pyridine to its N-oxide brings about a bathochromic shift in the spectrum. Thus 2-aminopyridine 1-oxide absorbs at 310, 239 and 221 nm in 0.1N NaOH (113) and 301 and 231 nm in 0.1N HCl (114). The spectra of the 2-

aminopyridine 1-oxide thiocyanates displayed close similarity with the spectrum of 2-aminopyridine 1-oxide in acidic conditions. The range for the first band was 307-325 nm and for the second band, 227-231 nm. Shoulders were present on the second band from 250-256 nm.

Table IX summarizes the ultra-violet spectral data of the pyridine 1-oxide thiocyanates.

C. THIAZOLE AND DERIVATIVES

The ultra-violet spectra of five-membered heterocycles such as thiazole, thiophene and pyrrole resemble that of cyclopentadiene (115). In general, they give a band of moderate intensity in the 200-204 nm region followed by a stronger band in the 230-240 nm. Contrary to pyridine, there is absence of bands due to $n-\pi^*$ transitions. Thus thiazole absorbs at 209 (ε_{max} 2,750) and 232 nm (ε_{max} 3,550) in heptane (116). According to Metzger, the $\pi-\pi^*$ transition in thiazole appears at 233.5 nm in ethanol and 232.5 nm in water (117). Substituents cause a bathochromic shift of the long-wave band. The magnitude of the effect depends upon the nature and the position of the substituent. For example, the presence of both a nitro- and a dimethylamino-group gives rise to a greater conjugation than, say, a bromo- or ethoxy-group and thus produces a greater red shift (117). Whereas 2-aminothiazole absorbs at 252 nm, 2-amino-4-phenylthiazole absorbs at 283 nm (118), the shift obviously resulting from the greater conjugation due to the phenyl ring.

In this work, N-phenyl-N′-2-thiazolylthiourea (5; Fig. 8) was found to absorb at 269 nm, whereas its N-carbethoxy derivative (19; Fig. 9) absorbs at 268 nm with a shoulder at 278 nm, and also at 221 nm. The α- and p-bands appear to have coalesced in this compound. The same holds true for the 4-methylthiazole analogue (20) which absorbs maximally at exactly the same wavelengths. In line with this behaviour, diphenylthiourea (24) (λ_{max} 276, 212 nm) undergoes a bathochromic shift in its N-carbethoxy derivative (25) (λ_{max} 300, 222 nm), but an hypsochromic shift in its S-methyl derivative (24a) (λ_{max} 262, 213 nm) because of the restriction imposed on extended conjugation throughout the molecule.

On the other hand, the 4-phenylthiazole isourea (21) suffers a much larger bathochromic shift (λ_{max} 310 nm, 288 nm shoulder) in view of its greater conjugated system. Again the α- and p-bands have coalesced, leaving the β-band to absorb at 232 nm. The N-phenyl-N′-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8; Fig. 10) absorbs at 309 nm with a shoulder at 286 and 226 nm, whereas its isourea derivative (23; Fig. 11) absorbs at 312 and 230 nm. Again it is observed that the isourea (23) undergoes a slight bathochromic shift relative to the thiourea (8).

A further example of how extended conjugation may shift absorption bands considerably is apparent in N,N′-diphenyl-N″-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17) which absorbs at 335, 289 and 228 nm.

The ultra-violet spectral data of the thiazolyl derivatives have been summarized in Table X.

TABLE VII

ULTRA-VIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF N-BENZOYL-N'-PYRIDYLTHIOUREAS IN ABSOLUTE ETHANOL

Compound	α-Band		p-Band		β-Band	
	nm	log ε	nm	log ε	nm	log ε
N-Benzoyl-N'-(3-methyl-2-pyridyl)thiourea	274	4.29			245	4.37
(37)						
(4-methyl-	312	4.18			286sh	4.06
(38)					266	4.44
(5-methyl-	314	4.14			268	4.40
(39)					245sh	4.22
(6-methyl-	314	4.12	282	4.24	266	4.33
(40)					240sh	4.15
(4,6-dimethyl-	317	4.19			286sh	4.31
(41)					265	4.43
					240sh	4.24
(5-bromo-	316	4.23	270	4.47		
(42)						

TABLE VIII

ULTRA-VIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF N-PYRIDYLTHIOUREAS IN ABSOLUTE ETHANOL

Compound	α-Band		p-Band		β-Band	
	nm	log ε	nm	log ε	nm	log ε
N-(3-methyl-2-pyridyl)thiourea (28)	295	4.36	270	4.17	238	4.10
(5-methyl- (30)	298	4.28	272	4.36	240	4.05
(6-methyl- (31)	297	4.45	269	4.30	240	4.14
(4,6-dimethyl- (32)	296	4.35	270	4.20	240	3.98

TABLE IX

ULTRA-VIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF 2-AMINOPYRIDINE 1-OXIDE THIOCYANATES IN ABSOLUTE ETHANOL

Compound	nm	log ε	nm	log ε
2-Aminopyridine 1-oxide thiocyanate (52b)	320	3.75	252sh 229	3.82 4.48
2-Amino-4-methylpyridine 1-oxide thiocyanate (48b)	307	3.79	256sh 228	3.68 4.39
5-methyl- (49b)	325	3.88	252sh 231	3.99 4.63
6-methyl- (50b)	317	3.89	252sh 227	3.89 4.64
4,6-dimethyl- (51b)	308	3.85	256sh 228	3.56 4.39

TABLE X

ULTRA-VIOLET ABSORPTION MAXIMA AND THEIR CORRESPONDING LOG ε VALUES OF PHENYL AND THIAZOLYL DERIVATIVES IN ABSOLUTE EHTANOL

Compound	α-Band		p-Band		β-Band	
	nm	log ε	nm	log ε	nm	log ε
N-Carbethoxy-N,N'-diphenylthiourea (25)	300sh	3.97			240sh	4.31
	280	4.11			222	4.48
N-Carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19)	278sh	4.17			221	4.54
	268	4.29				
N-Carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20)	278sh	4.18			221	4.48
	268	4.26				
O-Ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21)	310	4.29			232	4.49
	288sh	4.30				
O-Ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23)	312	4.33			230	4.35

Compound	α-Band		p-Band		β-Band	
	nm	log ε	nm	log ε	nm	log ε
N-Phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8)	309 286sh	4.35 4.32			226	4.38
N,N'-Diphenyl-N''-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17)	335	4.21	289	4.25	228	4.05
N,N'-Diphenyl-N''-2-thiazolylguanidine (14)	312	4.34	280sh	4.18		
N-Phenyl-N'-2-thiazolylthiourea (5)	269	4.21				
N,N'-Diphenylthiourea (24)	276	4.42			212	4.41
S-Methyl-N,N'-diphenylthiourea (24a)	262	4.22			213	4.29

FIGURE 6

Ultra-Violet Spectrum of N-Benzoyl-N'-(6-methyl-2-pyridyl)-thiourea (40) in Absolute Ethanol.

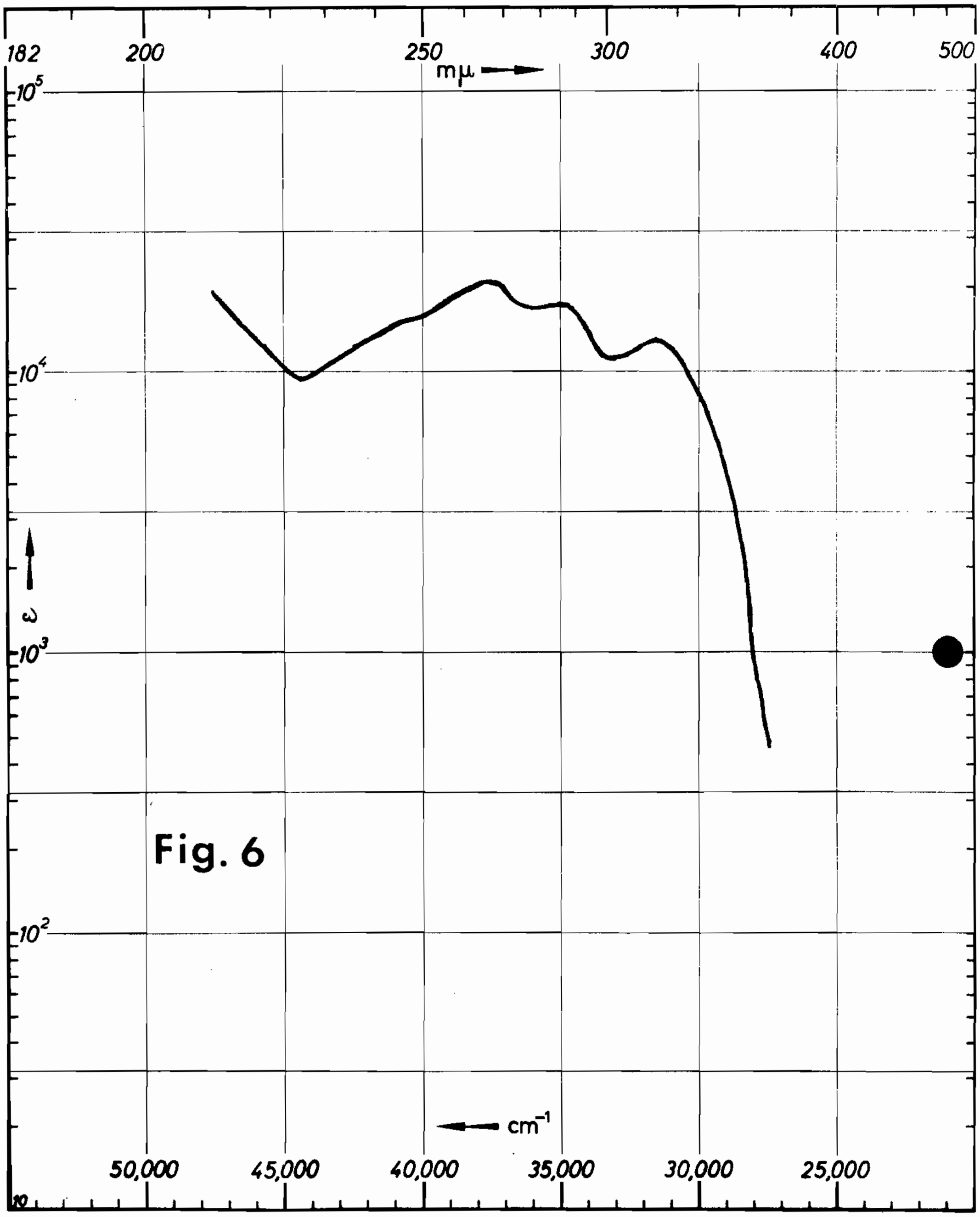

182
200
250
300
400
500
mμ
10^5
10^4
10^3
10^2
10
ε
cm⁻¹
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 6

FIGURE 7

Ultra-Violet Spectrum of N-(6-Methyl-2-pyridyl)thiourea (31) in Absolute Ethanol.

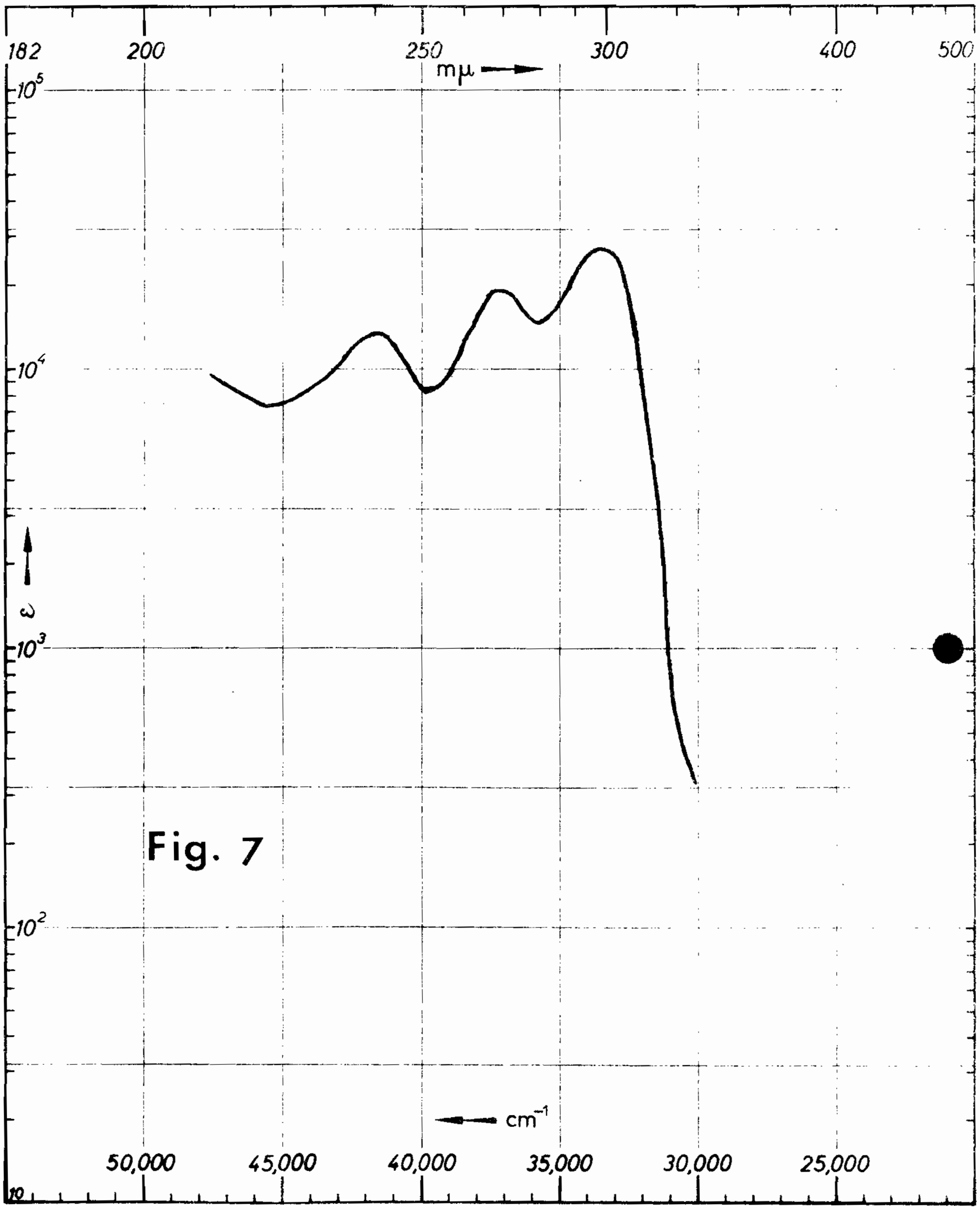

182
200
250
300
400
500
mμ →
10^5
10^4
ε ↑
10^3
10^2
10
← cm^{-1}
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 7

FIGURE 8

Ultra-Violet Spectrum of N-Phenyl-N'-2-thiazolylthiourea (5) in Absolute Ethanol.

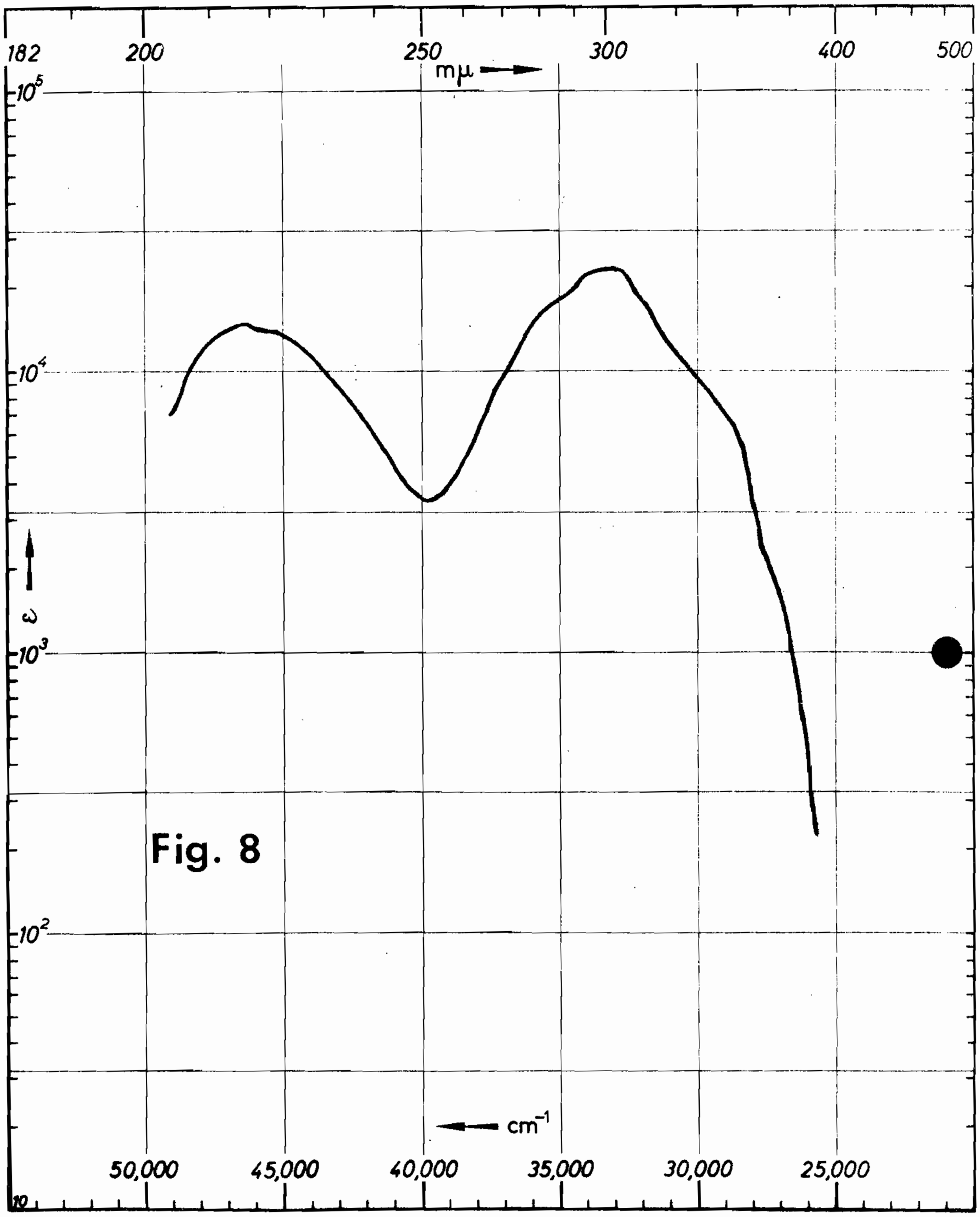
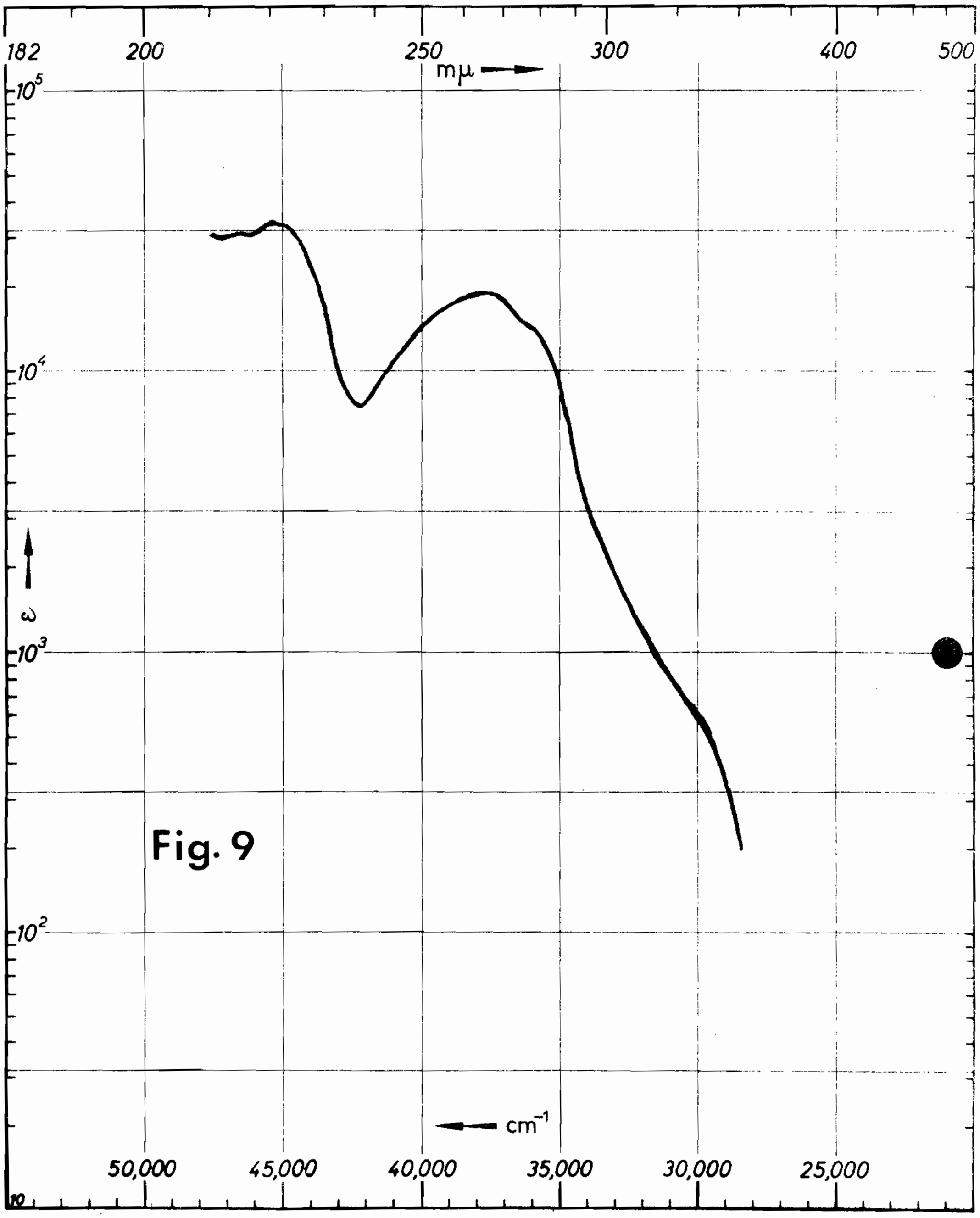

182
200
250
300
400
500
mμ
10^5
10^4
10^3
10^2
10
ε
cm⁻¹
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 8

FIGURE 9

Ultra-Violet Spectrum of N-Carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19) in Absolute Ethanol.


182
200
250
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500
mμ
10^5
10^4
ε
10^3
10^2
10
cm^{-1}
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 9

FIGURE 10

Ultra-Violet Spectrum of N-Phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8) in Absolute Ethanol.

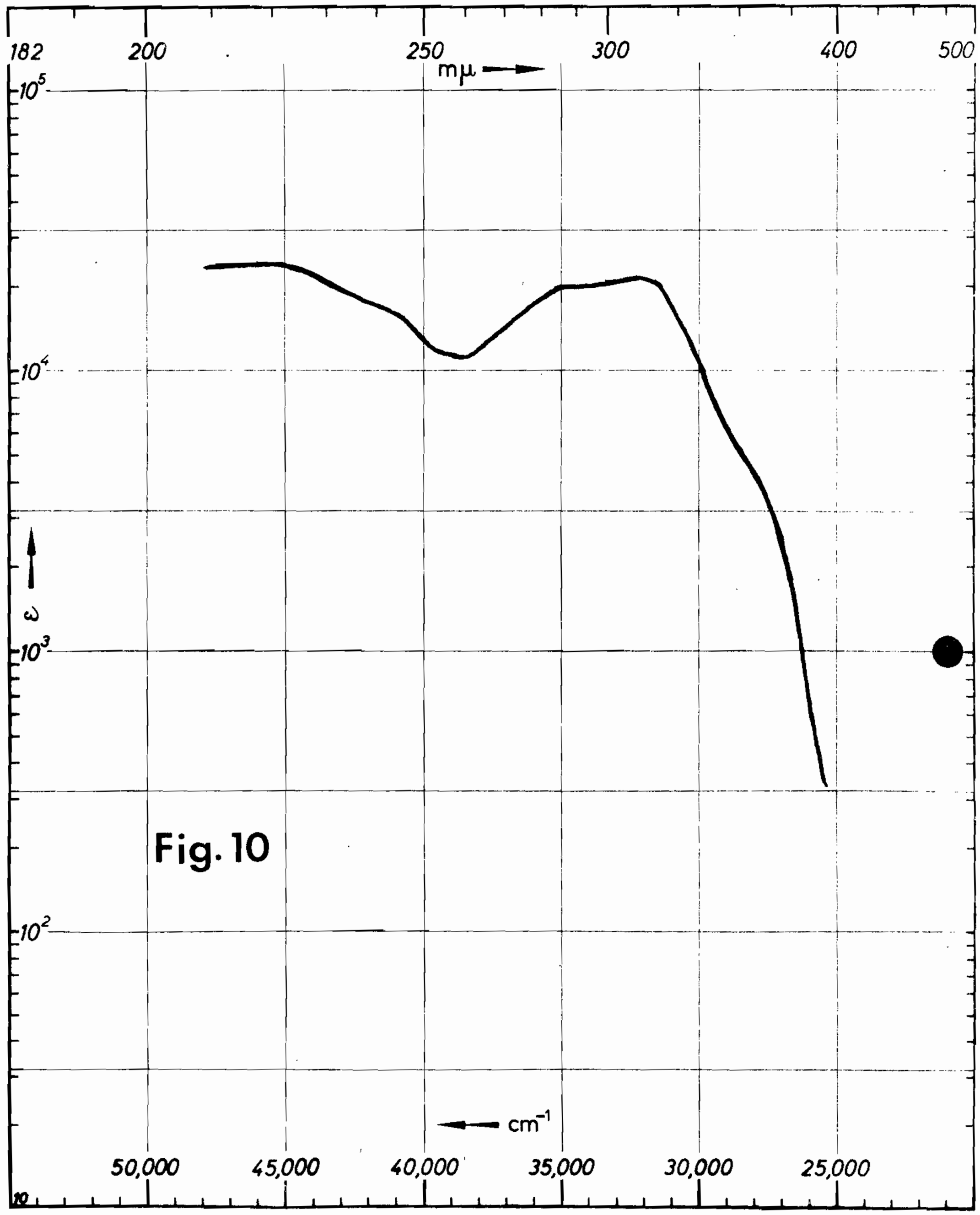
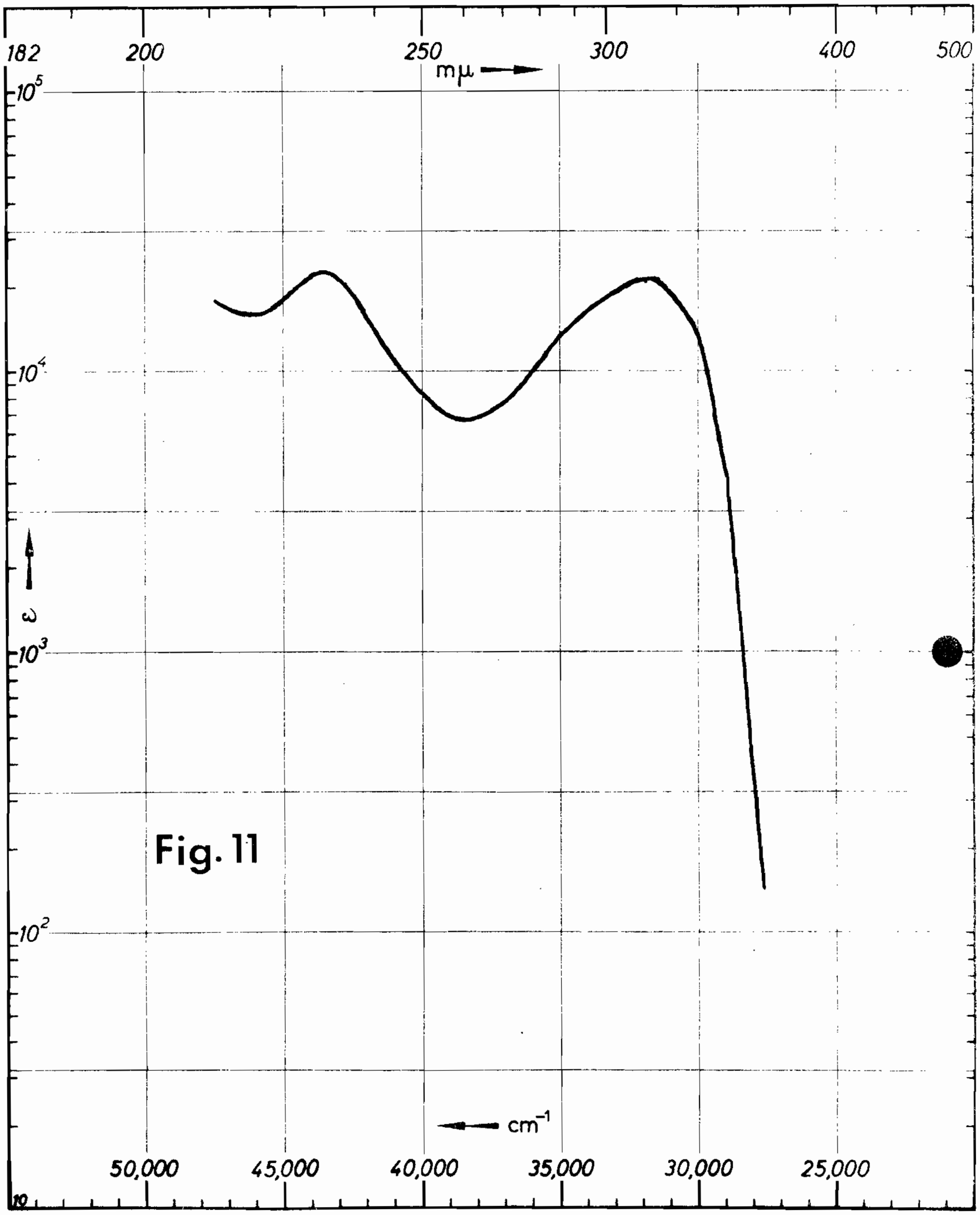

182
200
250
300
400
500
mμ →
10^5
10^4
ε ↑
10^3
10^2
10
← cm⁻¹
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 10

FIGURE 11

Ultra-Violet Spectrum of O-Ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23) in Absolute Ethanol.



182
200
250
300
400
500
mμ
10^5
10^4
ε
10^3
10^2
10
cm^{-1}
50,000
45,000
40,000
35,000
30,000
25,000

Fig. 11

NMR SPECTRA OF SOME SUBSTITUTED THIAZOLES AND PYRIDINES

A. THIAZOLES

The substituted thiazoles (19, 20, 21, 23, 11) investigated in this work show simple and easily analyzed first-order n.m.r. spectra. In the spectra of N-phenyl-N',N''-di-(2-thiazolyl)guanidine (11) and N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19) two doublets appear at low field due to H-4 and H-5 with $J_{4,5}$ = 3.5 Hz in each case. The doublet at lower field is assigned to H-4 since it is more deshielded than H-5 because of its proximity to nitrogen which is more electronegative than sulfur or carbon.

The spectra of N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20; Fig. 12) and O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21; Fig. 13) show a singlet in the aromatic region due to the lone H-5. Moreover 20 shows a long-range coupling between H-5 and the 4-methyl side-chain hydrogens (J_{5,CH_3} : 1.0 Hz). In addition, the phenyl groups present in all the thiazoles examined show a multiplet at low field near the thiazole ring proton peaks. In all compounds containing an ethyl group, 19, 20, 21, 23 and 25, a well-resolved quartet (CH_2-) and triplet (CH_3-) are observed with J_{CH_3,CH_2} : 6.5 to 7.0 Hz.

These results are summarized in Tables XI and XII.

B. PYRIDINES

1. 2,3- Disubstituted pyridines

The n.m.r. spectra of the 2,3- disubstituted pyridines (28, 37, 68, 76) were examined in order to study the variation in the spectra caused by the change in the 2-substituent. These compounds show an AMX pattern due to the three adjacent H-4, H-5 and H-6 protons of the pyridine ring. An AMX system is obtained when the chemical shift differences involved are all large compared with the spin-spin coupling constants. Three sets of well-separated quartets are then observed and the coupling constants J_{AM}, J_{AX} and J_{MX} may be obtained by direct measurement from the spectrum. The H-6 proton adjacent to the electronegative pyridine ring nitrogen is the most deshielded and thus appears at lowest field, followed by H-4 and then H-5 towards higher field.

The n.m.r. spectra of N-(3-methyl-2-pyridyl)thiourea (28; Fig. 14) is of the AMX type and can be interpreted by first-order analysis. The doublet furthest downfield at δ 8.49 is assigned to H-6. It is coupled to both H-5 (J = 6 Hz) and H-4 (J = 2 Hz) as seen by the splitting in the peaks. The complex doublet appearing further upfield at δ 7.99 is ascribed to H-4 which couples with H-6 and H-5 (J = 8 Hz) as well as to the methyl group at the 3 position (J = 1 Hz). This long-range coupling has also been observed in 2-amino-3-picoline and other 2-substituted picolines by Bell et al. (119). The very sharp quartet at δ 7.36 due to H-5 shows no coupling to the methyl protons. The singlet at δ 2.66 arises from the methyl group.

The situation for N-benzoyl-N'-(3-methyl-2-pyridyl)-thiourea (37; Fig. 15) was quite similar except for a shift further downfield observed for all the pyridine ring protons. The H-6 appeared at δ 8.72 as a broad doublet again coupled to H-4 (J = 1.5 Hz) and H-5 (J = 5 Hz). A poorly-split doublet at δ 8.38 was assigned to H-4, coupled to H-6 and H-5 (J = 8 Hz) although there was no indication of coupling to the methyl protons. Again H-5 absorbed as a sharp quartet at δ 7.67 while the 3-methyl protons appeared as a sharp singlet at δ 2.69.

The situation changes drastically in the spectrum of 8-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (68; Fig. 16). In this case, the absorption of H-5 has been shifted further downfield to δ 9.44 due to combined deshielding effect of the nitrogen and oxygen atoms. It appears as a sharp doublet coupled only to H-6 (J = 7 Hz). Similarly H-7 absorbs as a doublet at δ 8.28 coupled to H-6 (J = 7 Hz). A slight splitting of the doublet may be assigned to long-range coupling to the methyl protons (J = 1 Hz). The sharp triplet at δ 7.64 assigned to H-6 is in reality a quartet since it couples to both H-5 and H-7 but because of identical coupling constants, it is reduced in complexity. The methyl group again absorbs at δ 2.80 as a singlet.

The spectrum of 8-methyl[1,3,4]oxadiazolo[3,2-a]-

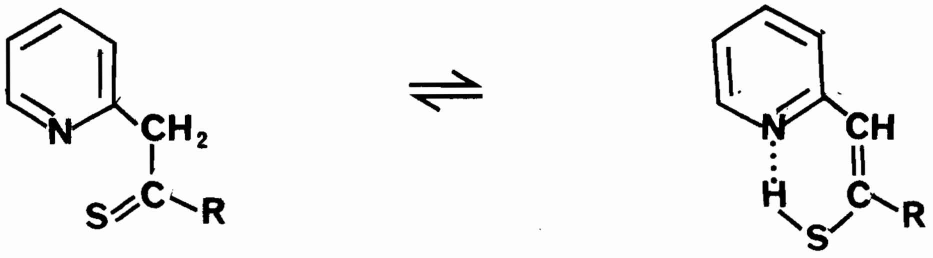
pyridine-2-thione (76) is very similar. Again the coupling constants between H-6 and H-5, and H-6 and H-7 are identical (J = 7 Hz) and thus two doublets and one triplet are present. H-5 is less deshielded than previously since it is under the influence of two nitrogen atoms and appears as a doublet at δ 9.16. On the other hand, H-7 (doublet at δ 8.42) and H-6 (triplet at δ 7.94) are further downfield than previously since they are deshielded by the oxygen atom instead of a nitrogen atom. The methyl group is also deshielded by the oxygen atom and appears as a singlet at δ 2.87. A slight splitting of the H-7 doublet may be ascribed to long-range coupling to the methyl group.

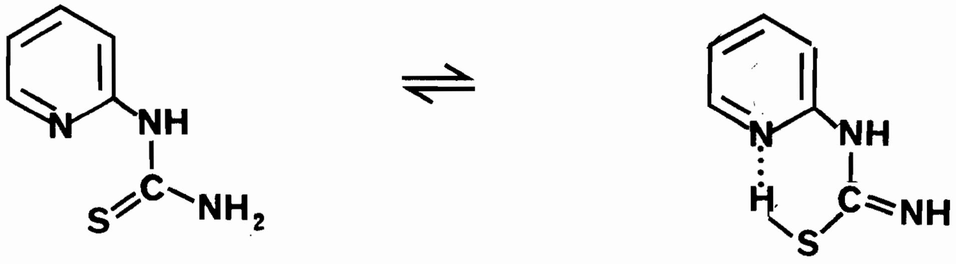
2. N-Pyridylthioureas

The n.m.r. spectra of the N-2-pyridylthioureas (26, 28, 30-32) in DMSO-d_6 all showed three absorption peaks in the δ 9-12 region due to the $-NHCSNH_2$ group, one proton being present per peak as indicated by the integration curve (see Fig. 14). This was contrary to the expected broad amide (N-H) absorption band containing one proton and a sharper peak for the $-NH_2$ group containing the other two protons.

Several explanations may be offered to account for this apparent anomaly. Firstly, amide and thioamide group protons often show two broad bands in the n.m.r. spectra due to the fact that the C-N bond possesses a partial double-bond character and can hold one proton in a cis configuration and the other in a trans configuration (120). Thus, the two protons behave as if they were in different environments and give rise to different signals.

Another possibility may be the following. Since thioureas are known to undergo tautomerism to the corresponding isothiourea forms, it is possible that the N-2-pyridylthiourea exists partly or totally in the isothiourea form in DMSO solution. The -SH group so formed may then hydrogen-bond to the pyridine ring nitrogen, in analogy to the picolyl thioketones which exist as totally chelated enethiols (121).





This tendency to chelation is quite pronounced in the thioketones and may also be operative in the thioureas which are capable of chelation. This is supported by the fact that the n.m.r. spectrum of N-3-pyridylthiourea (27), in which chelation is impossible, showed a signal at δ 7.59 (sharp singlet, 2 protons) for a normal $-NH_2$ group and a signal at δ 9.78 (sharp singlet, 1 proton) for the -NH group but no signal for an -SH group. Thus it appears that the driving force in the N-2-pyridylthioureas for tautomerism is the possibility of chelation to the ring nitrogen, a situation not encountered in N-3-pyridylthiourea.

TABLE XI

NMR SPECTRA OF SOME THIAZOLYL- AND PHENYL- DERIVATIVES

			CHEMICAL SHIFTS (δ)					
COMPOUND	R_4	R_5	H-4	H-5	CH_3	CH_2	Ph	OTHER
19	H	H	7.67	7.01	1.14	4.26	7.14-7.59	....
20	CH_3	H	....	6.40	1.07	4.14	7.11-7.49	2.30 (CH_3)
21	Ph	H	....	6.94	1.39	4.47	7.30-7.90	....
23	Ph	CH_3	....	....	1.42	4.50	7.22-7.70	2.52 (CH_3)
11	H	H	7.24	6.66	....	....	....	7.24-7.44 (Ph)
25	....	....	....	....	1.02	4.06	7.08-7.40	....

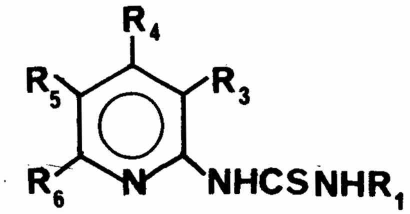
TABLE XII

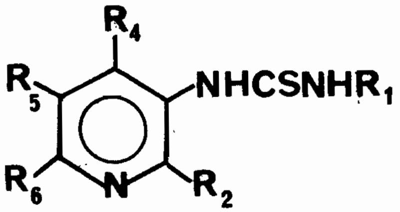
SPIN-SPIN COUPLING CONSTANTS OF SOME THIAZOLYL- AND PHENYL- DERIVATIVES

COMPOUND	R_4	R_5	SPIN-SPIN COUPLING CONSTANTS (Hz)		
			$J_{4,5}$	J_{CH_3,CH_2}	J_{5,CH_3}
19	H	H	3.5	7.0	....
20	CH_3	H	....	7.0	1.0
21	Ph	H	....	7.0	....
23	Ph	CH_3	....	7.0	....
11	H	H	3.5	....	....
25	....	....	....	6.5	....

TABLE XIII

NMR SPECTRA OF N-PYRIDYLTHIOUREAS





						CHEMICAL SHIFTS (δ)				
COMPOUND	R_1	R_3	R_4	R_5	R_6	H-3	H-4	H-5	H-6	OTHER
26	H	H	H	H	H	7.22	7.75	7.05	8.26	8.80 (NH) 10.50 (SH) 10.70 (NH)
28	H	CH_3	H	H	H	....	7.99	7.36	8.49	2.66 (CH_3) 9.10 (SH) 9.33 (NH) 10.80 (NH)

						CHEMICAL SHIFTS (δ)				
COMPOUND	R_1	R_3	R_4	R_5	R_6	H-3	H-4	H-5	H-6	OTHER
30	H	H	H	CH_3	H	7.44	7.91	....	8.36	2.55 (CH_3) 9.09 (NH) 10.79 (SH) 10.89 (NH)
31	H	H	H	H	CH_3	7.24	7.99	7.33	....	2.76 (CH_3) 9.16 (NH) 10.78 (SH) 11.03 (NH)
32	H	H	CH_3	H	CH_3	7.16	....	7.11	....	2.60 (R_6=CH_3) 2.83 (R_4=CH_3) 9.14 (NH) 10.71 (SH) 11.12 (NH)

						CHEMICAL SHIFTS (δ)				
COMPOUND	R_1	R_3	R_4	R_5	R_6	H-3	H-4	H-5	H-6	OTHER
37	CONHPh	CH_3	H	H	H	....	8.38	7.67	8.72	2.69 (CH_3) 7.80-8.19 (Ph) 12.14 (NH) 12.62 (NH)
27	H	H(R_2)	H	H	H	8.58(H-2)	7.98	7.31	8.30	7.59 (NH_2) 9.78 (NH)

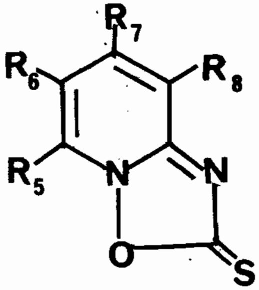
TABLE XIV

SPIN-SPIN COUPLING CONSTANTS OF N-PYRIDYLTHIOUREAS

COMPOUND	SPIN-SPIN COUPLING CONSTANTS (Hz)					
	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	OTHER
28	....	....	8	2	6	$J_{4',CH_3}=1$
30	8.5	....	....	2	....	
31	8	....	8	....	....	
37	....	....	8	1.5	5	

TABLE XV

NMR SPECTRA OF[1,2,4]OXADIAZOLO[2,3-a]PYRIDINE-2-THIONES



COMPOUND	R_8	R_7	R_6	R_5	CHEMICAL SHIFTS (δ) H-8	H-7	H-6	H-5	OTHER
53	H	H	H	H	8.08	8.47	7.75	9.59	
68	CH_3	H	H	H	....	8.28	7.64	9.44	2.80 (CH_3)
69	H	CH_3	H	H	7.91	....	7.60	9.47	2.88 (CH_3)
70	H	H	CH_3	H	8.00	8.33	....	9.50	2.77 (CH_3)
72	H	CH_3	H	CH_3	7.71	....	7.10	....	2.74 ($R_5=CH_3$) 2.61 ($R_7=CH_3$)
76	CH_3	H	H	H	....	8.42	7.94	9.16	2.87 (CH_3)

TABLE XVI

SPIN-SPIN COUPLING CONSTANTS OF[1,2,4]OXADIAZOLO-[2,3-a]PYRIDINE-2-THIONES

COMPOUND	SPIN-SPIN COUPLING CONSTANTS (Hz)						
	$J_{8,7}$	$J_{8,6}$	$J_{8,5}$	$J_{7,6}$	$J_{7,5}$	$J_{6,5}$	OTHER
68	....	....	....	7	....	7	$J_{7,CH_3}=1$
76	....	....	....	7	....	7	$J_{7,CH_3}=1$
69	....	....	....	....	....	7	$J_{6,CH_3}=1.5$
70	9	....	....	....	....	....	$J_{7,CH_3}=1$

FIGURE 12

NMR Spectrum of N-Carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)-thiourea (20) in $CDCl_3$.

Fig. 12

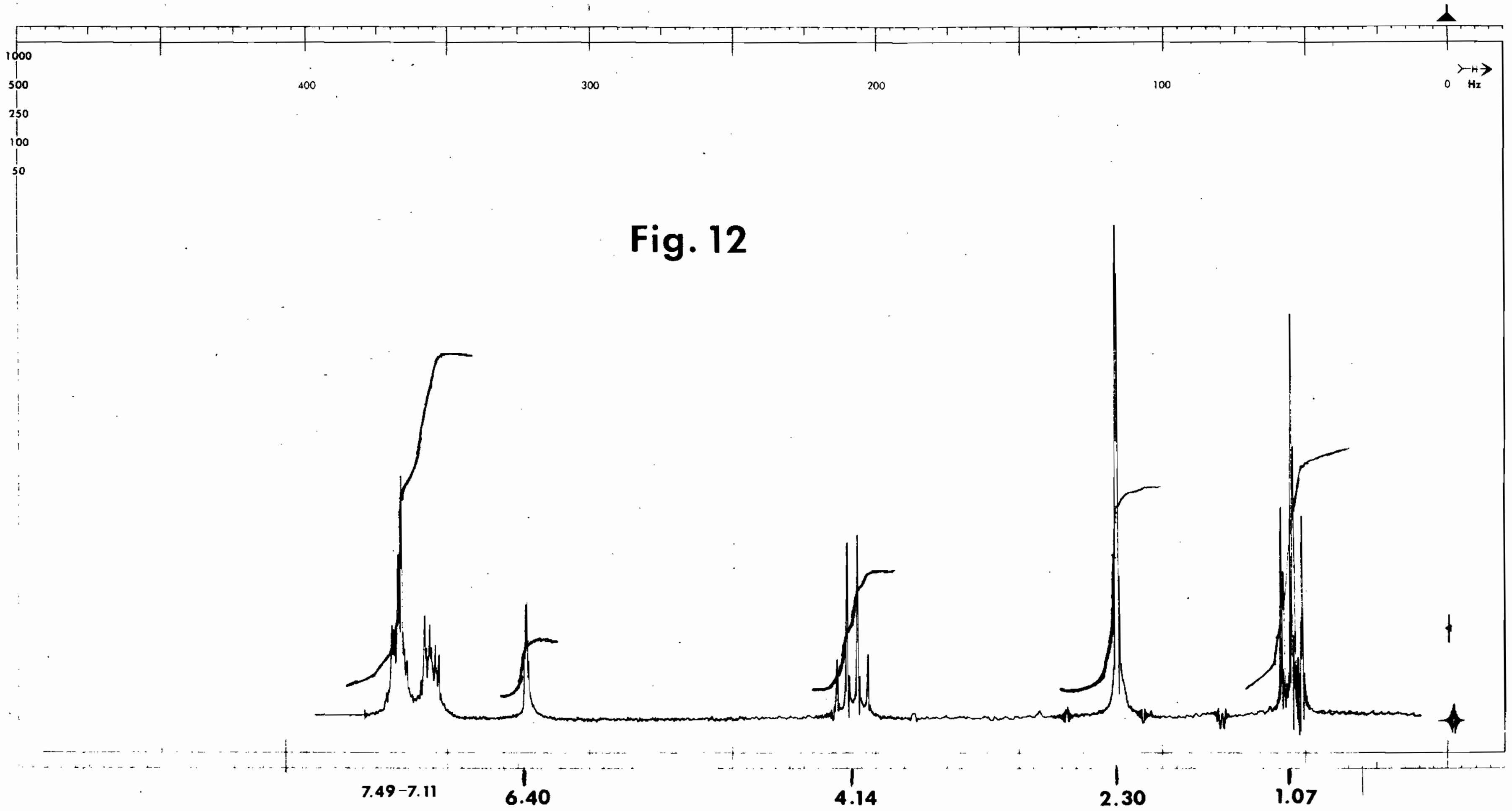


FIGURE 13

NMR Spectrum of O-Ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)-isourea (21) in $CDCl_3$.

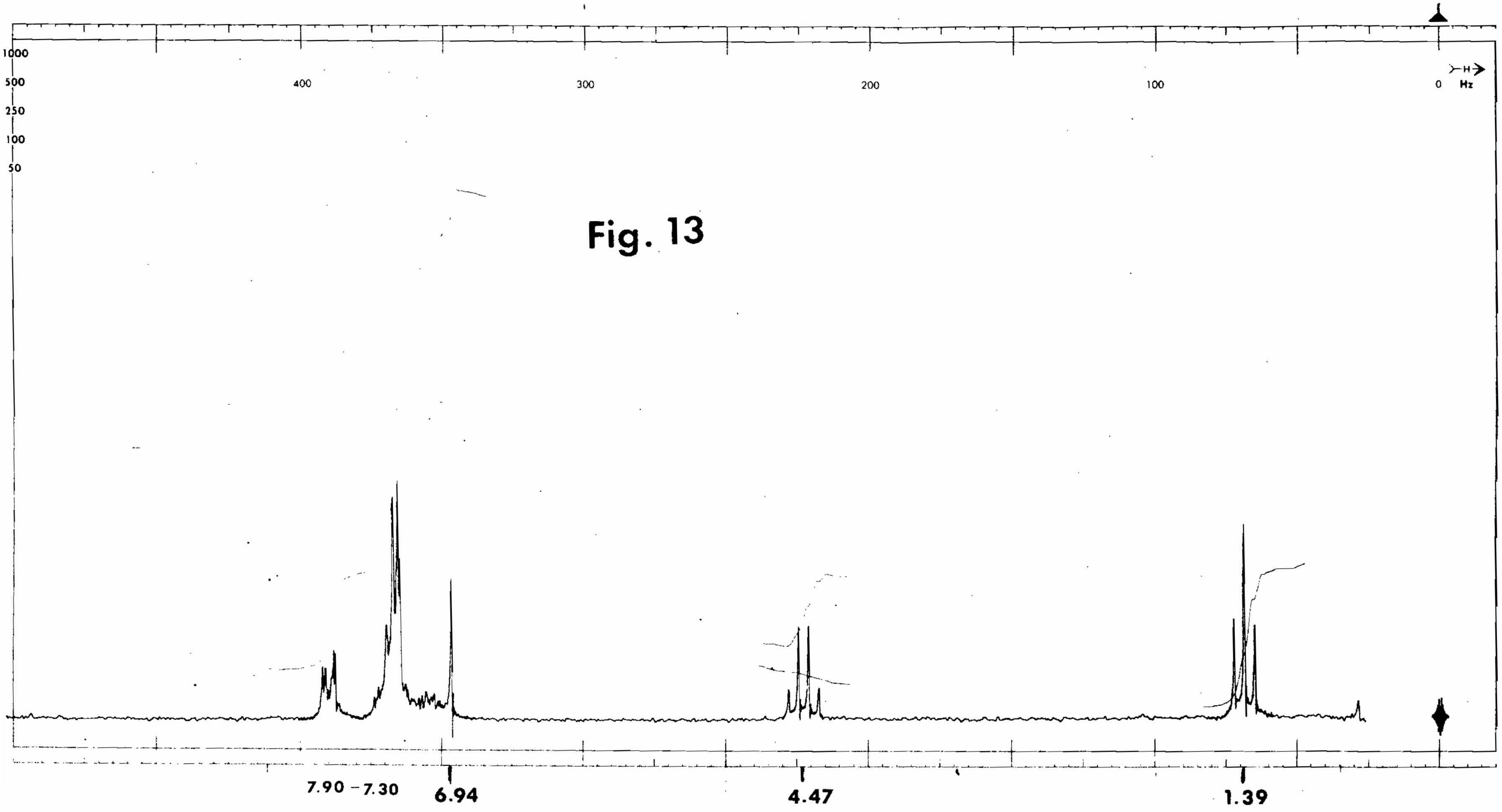


Fig. 13

FIGURE 14

NMR Spectrum of N-(3-Methyl-2-pyridyl)thiourea (28) in DMSO-d_6.

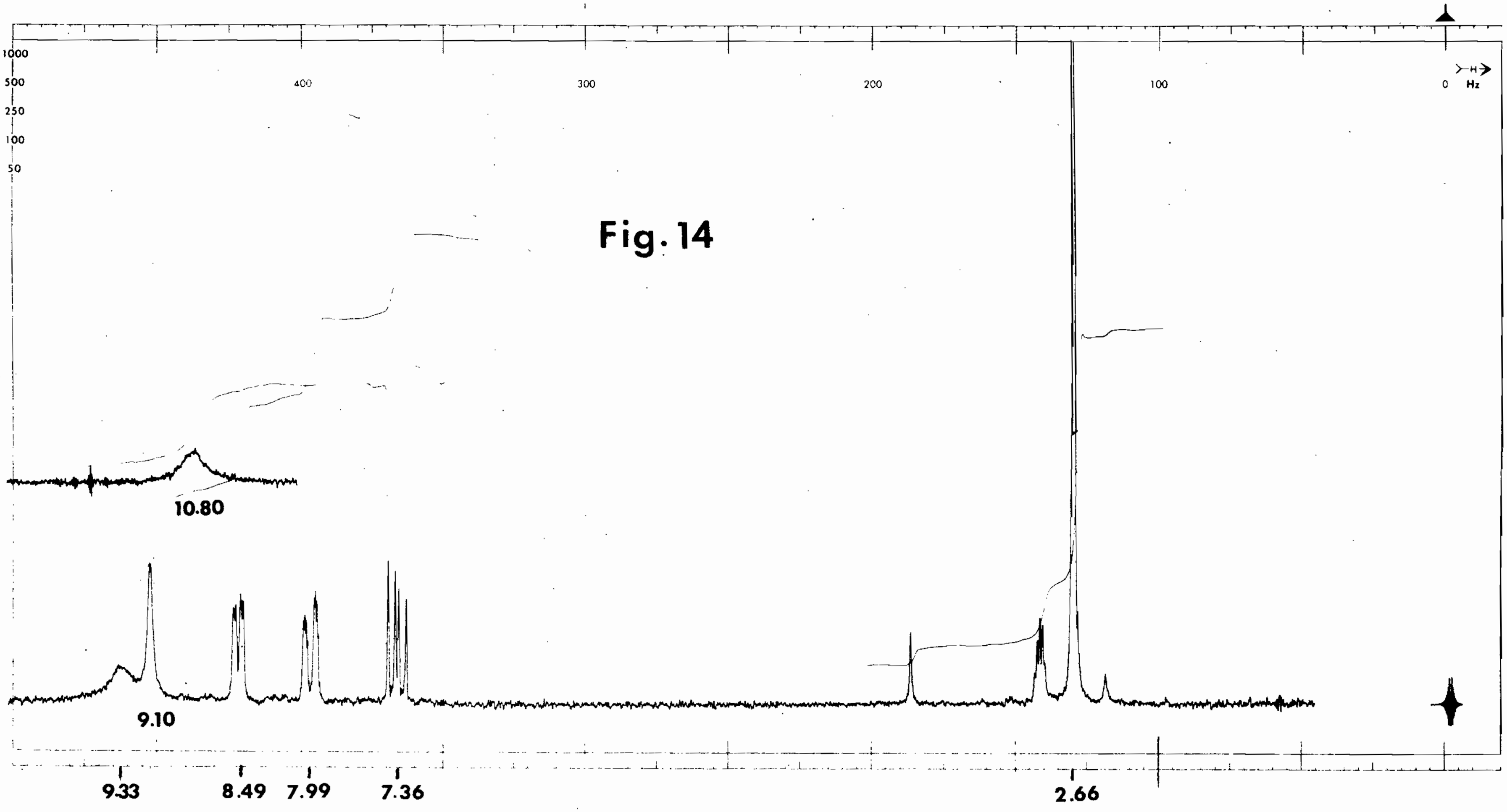

1000
500
250
100
50
400
300
200
100
0
H
Hz
10.80
9.10
9.33
8.49
7.99
7.36
2.66

Fig. 14

FIGURE 15

NMR Spectrum of N-Benzoyl-N'-(3-methyl-2-pyridyl)thiourea (37) in DMSO-d_6.

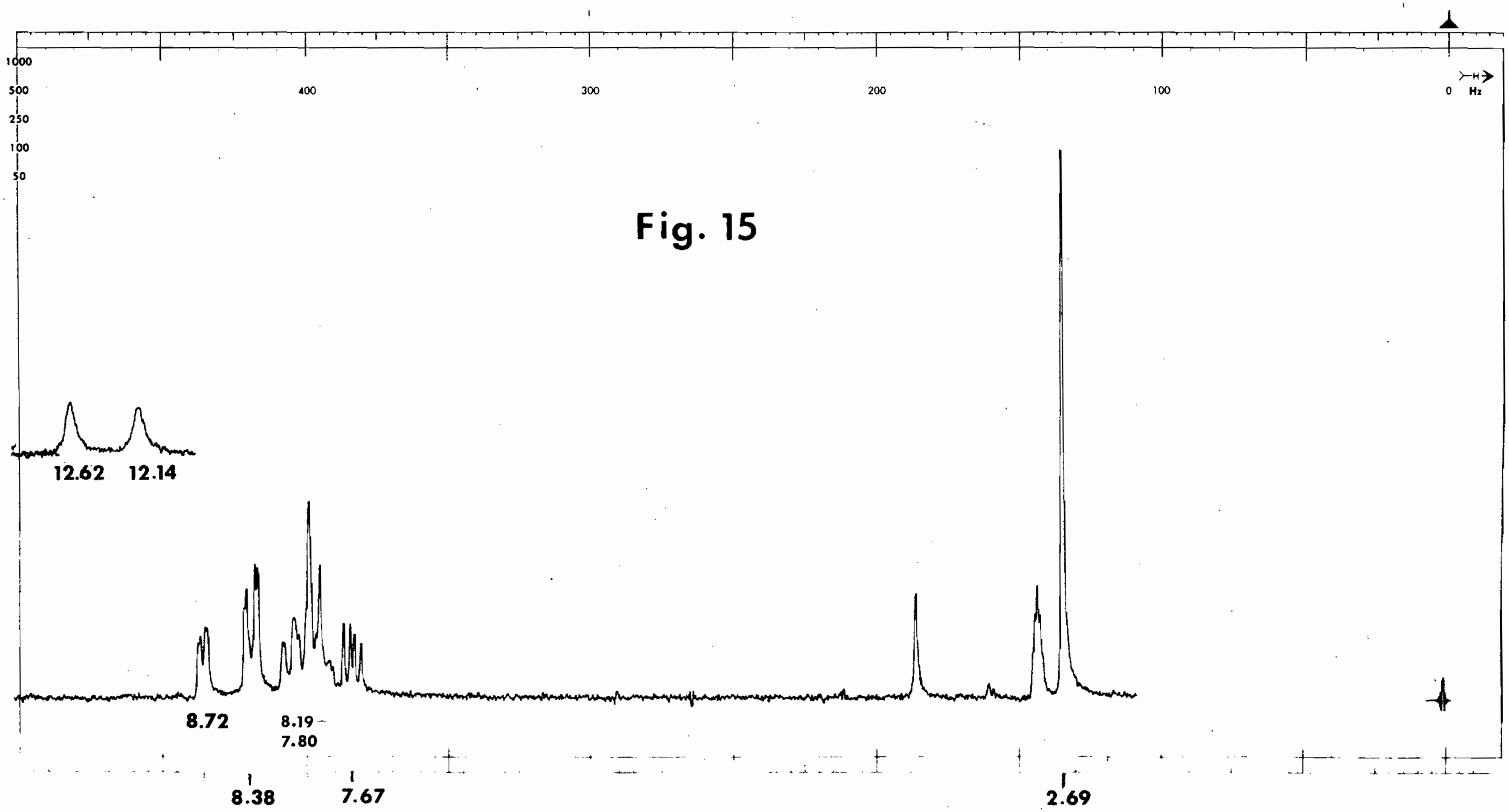
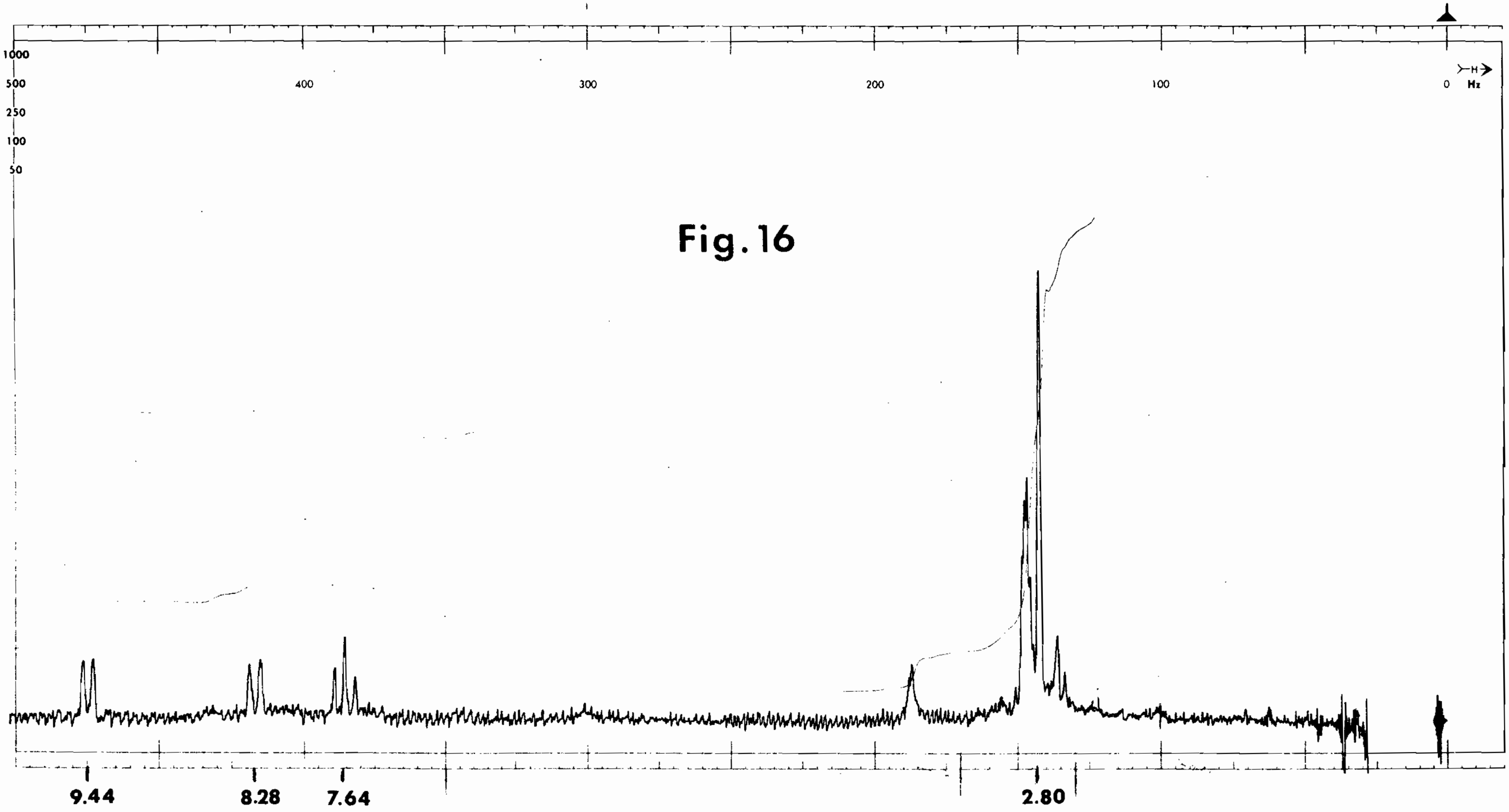


Fig. 15
1000
500
250
100
50
400
300
200
100
0 Hz
12.62
12.14
8.72
8.19
7.80
8.38
7.67
2.69

FIGURE 16

NMR Spectrum of 8-Methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (68) in DMSO-d_6.

Fig. 16

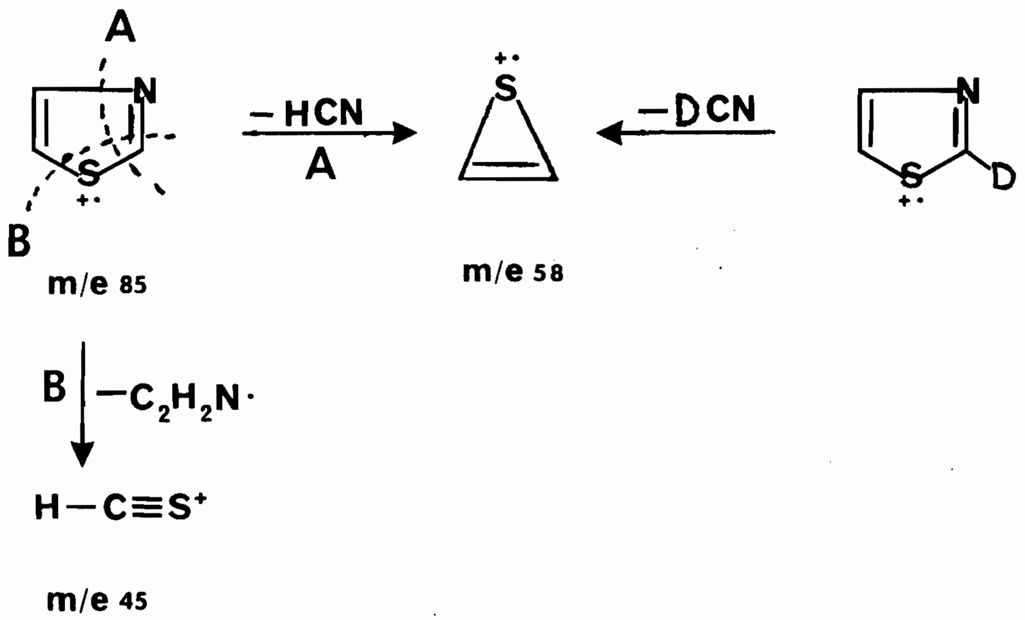


MASS SPECTRA OF THIAZOLE AND PYRIDINE THIOUREAS AND DERIVATIVES

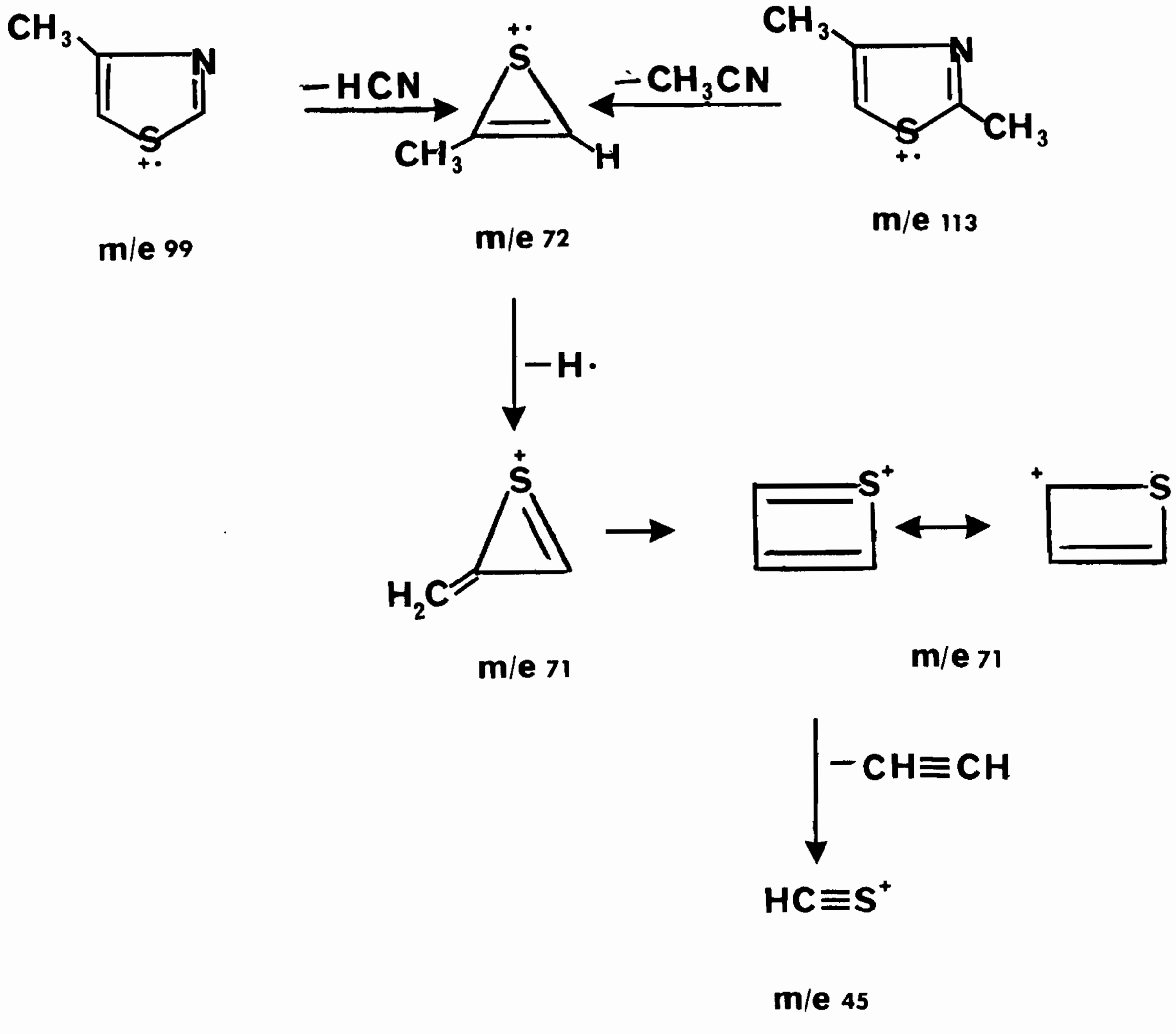
A. GENERAL CONSIDERATIONS

1. Thiazoles

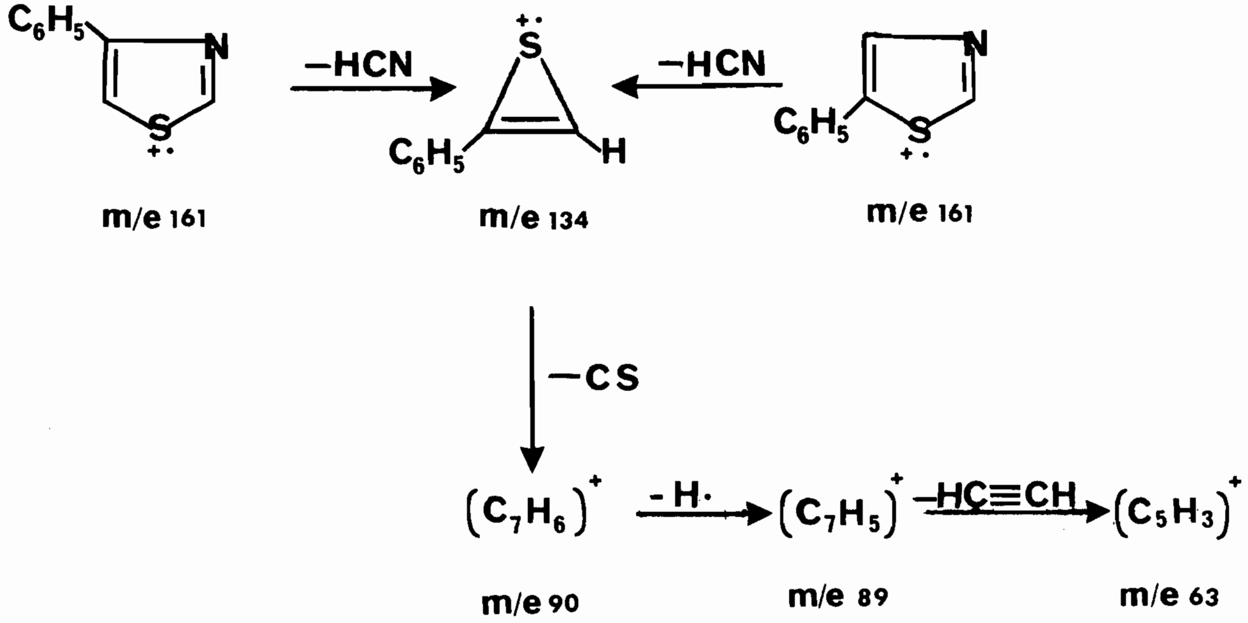
Clarke et al. (122), who examined the mass spectra of amino-, methyl-, bromo- and other substituted thiazoles, observed that the molecular ion of thiazole is the base peak of the spectrum. The main fragmentation of thiazole is loss of HCN to give the thiiren ion-radical of m/e 58. A less important process gives the thioformyl cation of m/e 45. Fragmentation of deuterated thiazole-2-d established that C(2) and not C(4) is involved in the elimination of HCN (123).



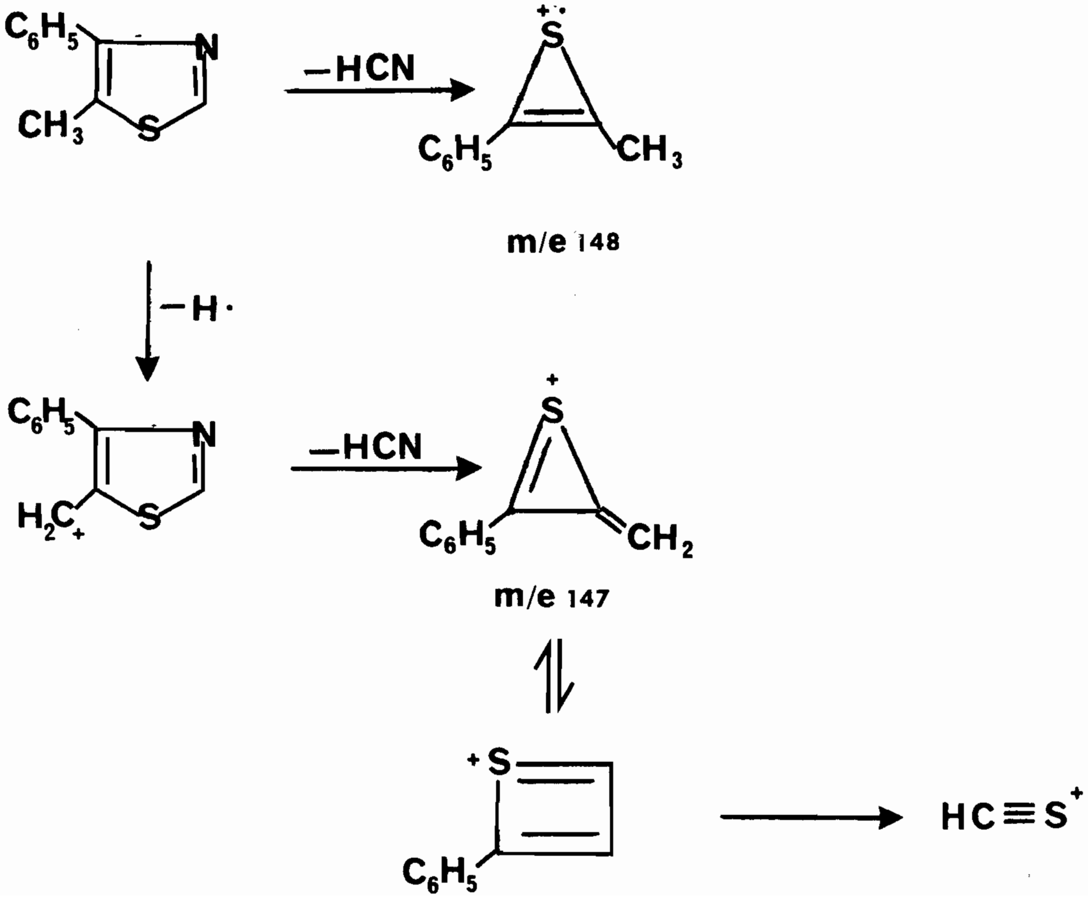
Fragments formed by the cleavage of 1,2 and 3,4-bonds (route A) are also prevalent in methylthiazoles, as well as phenylthiazoles (124), the charge remaining on the sulfur atom.



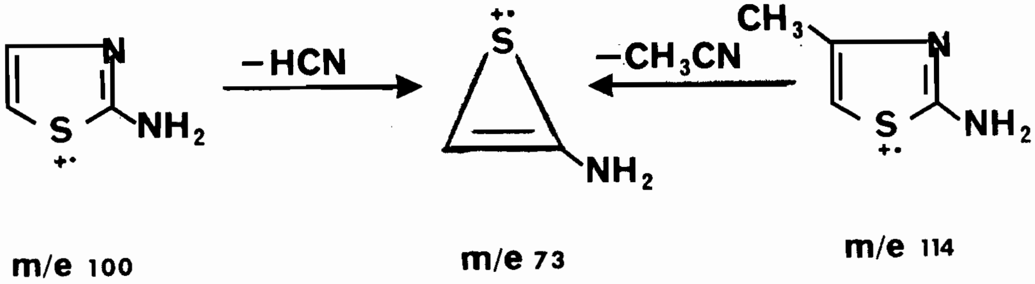
In the case of 4- and 5-phenylthiazoles, the fragment obtained after elimination of HCN further loses CS to give an ion of m/e 90, $C_7H_6^+$ (124).



In the mass spectrum of 5-methyl-4-phenylthiazole, there is an important (M - 1) fragment which also eliminates HCN.

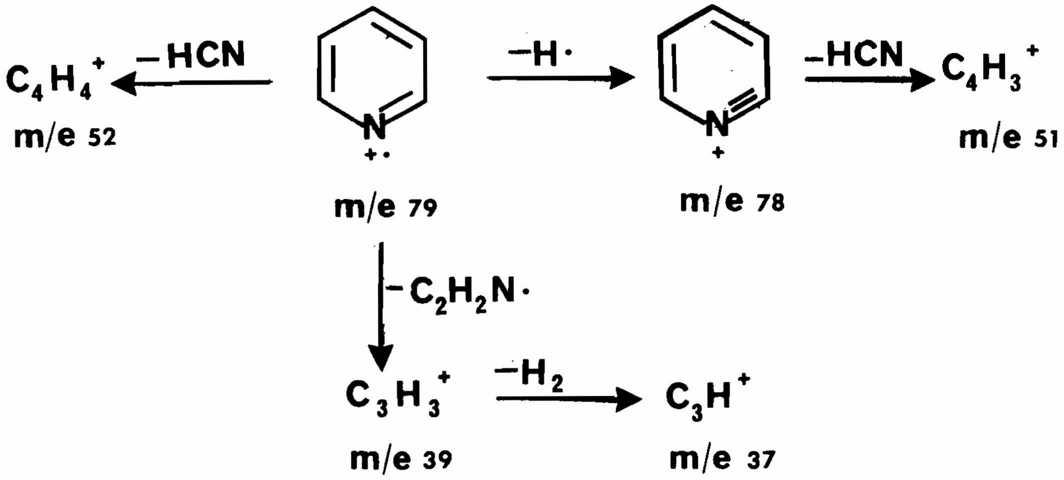


The 2-aminothiazoles whose molecular ions are also the base peaks are especially noteworthy for their appreciable (M + 1) ions (122). In contrast to the alkyl- and phenylthiazoles, rupture of the 2,3- and 4,5- bonds represents an important process in aminothiazoles. This is made clear in 2-amino-4-methylthiazole where only a small (M-HCN) ion appears of m/e 87 (4% of the base peak) but a more important (M-CH_3CN) ion of m/e 73 is present (122).



2. Pyridines

Pyridine ring is remarkably stable under electron impact as reflected by the high abundance of its molecular ion peak which serves also as the base peak. The main fragmentation of pyridine is the loss of neutral HCN to produce a peak at m/e 52 (125). A minor process is loss of HCN from the (M - 1) ion giving rise to the peak at m/e 51, as illustrated in the following scheme:

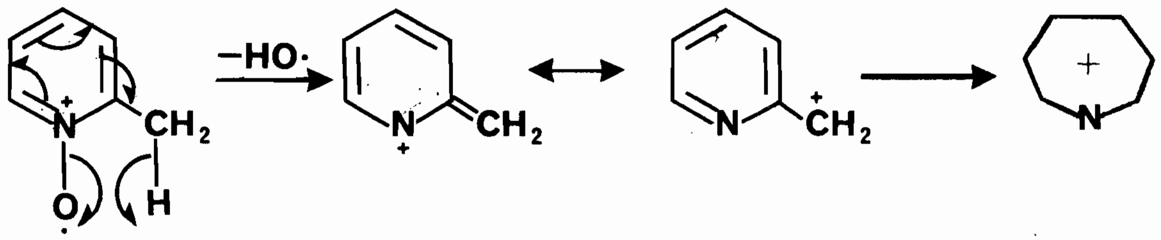


Substituted pyridines exhibit additional fragmentations according to the nature of the substituents. The spectra of methylpyridines reveal that loss of HCN from the molecular ion is important but that a significant (M - 1) ion is also present, especially for 3-picoline (125). In 2-chloro- and 2-nitropyridines, loss of the substituents preceedes the loss of HCN from the ring (126). The 2-, 3- and 4-aminopyridines show loss of HCN directly from the molecular ion, which is the base peak, to produce an ion of m/e 67 (126). In 2-aminopyridine, this ion is considered to be a pyrrole ion which in turn loses 26, 27 and 28 mass units assigned to CN, HCN and H_2CN (126). It has not been established definitely which nitrogen atom is involved in the loss of HCN from the molecular ion of the aminopyridines. Indeed both pyridine and aniline lose HCN as a major fragmentation of their molecular ion.

The spectra of these three aminopyridines were taken and re-examined more closely in the present work. The 3- and 4-aminopyridines were found to give their molecular ions of m/e 94 as base peaks, which then lost HCN to furnish the ion of m/e 67. The 2-aminopyridine, on the other hand, revealed its base peak at m/e 67 and the molecular ion of m/e 94 only in 63% abundance. This is surprising since previous reports (125, 126) have always given the molecular ion as the base peak for all the aminopyridines. The same pattern was observed in 2-aminopyridine whether the spectrum was run at 30°, 50° or 60°.

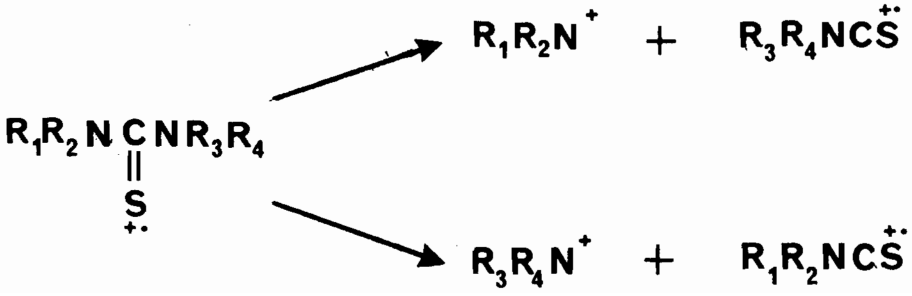
Important fragments of m/e 39, 40 and 41 resulting from the expulsion of H_2CN, HCN and CN from the ion of m/e 67 were found in the spectra of all three amines, in 20-50% abundance (Table XVII).

The mass spectra of pyridine N-oxides show an abundant (M - 16) fragment due to the loss of an oxygen atom (125). This phenomenon serves to identify N-oxides since it is seldom encountered in oxygenated compounds (127). Competition with an "ortho-effect" in 2-alkylpyridine N-oxides reduces the abundance of the (M - 16) fragment, due to the elimination of an hydroxyl radical (128) as depicted in the following scheme for 2-methylpyridine N-oxide:



3. Thioureas and guanidines

Few studies have been made on the mass spectra of thioureas and guanidines. Apart from the mass spectra of 1-substituted-3-phenylthioureas (129), arylsulfonylthioureas (130) and alkylthioureas (131), no systematic data have been published on the mass spectra of aromatic or heterocyclic thioureas. Similarly, only alkylguanidines have been investigated (132). Shapiro et al. (130) observed a great sensitivity of N,N-dialkyl-N'-phenylthioureas to heat and their facile pyrolysis in the mass spectrometer to form their corresponding amines and isothiocyanates as well as the simultaneous loss of hydrogen sulfide. Baldwin et al. (131) later concluded that loss of H_2S in alkylthioureas arose from pyrolysis and then ionization, whereas (M - HS) ions, resulting from the loss of a sulphydryl radical, appeared to be genuine electron-impact fragmentations. However, the most important fragmentation in alkylthioureas consists of cleavage of the bond between a nitrogen and the central carbon atom.



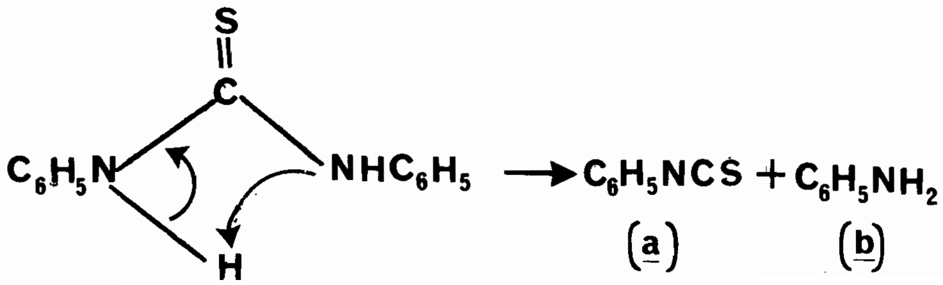
Similar fragments are formed in guanidines (132) although their mode of formation may be more complex.

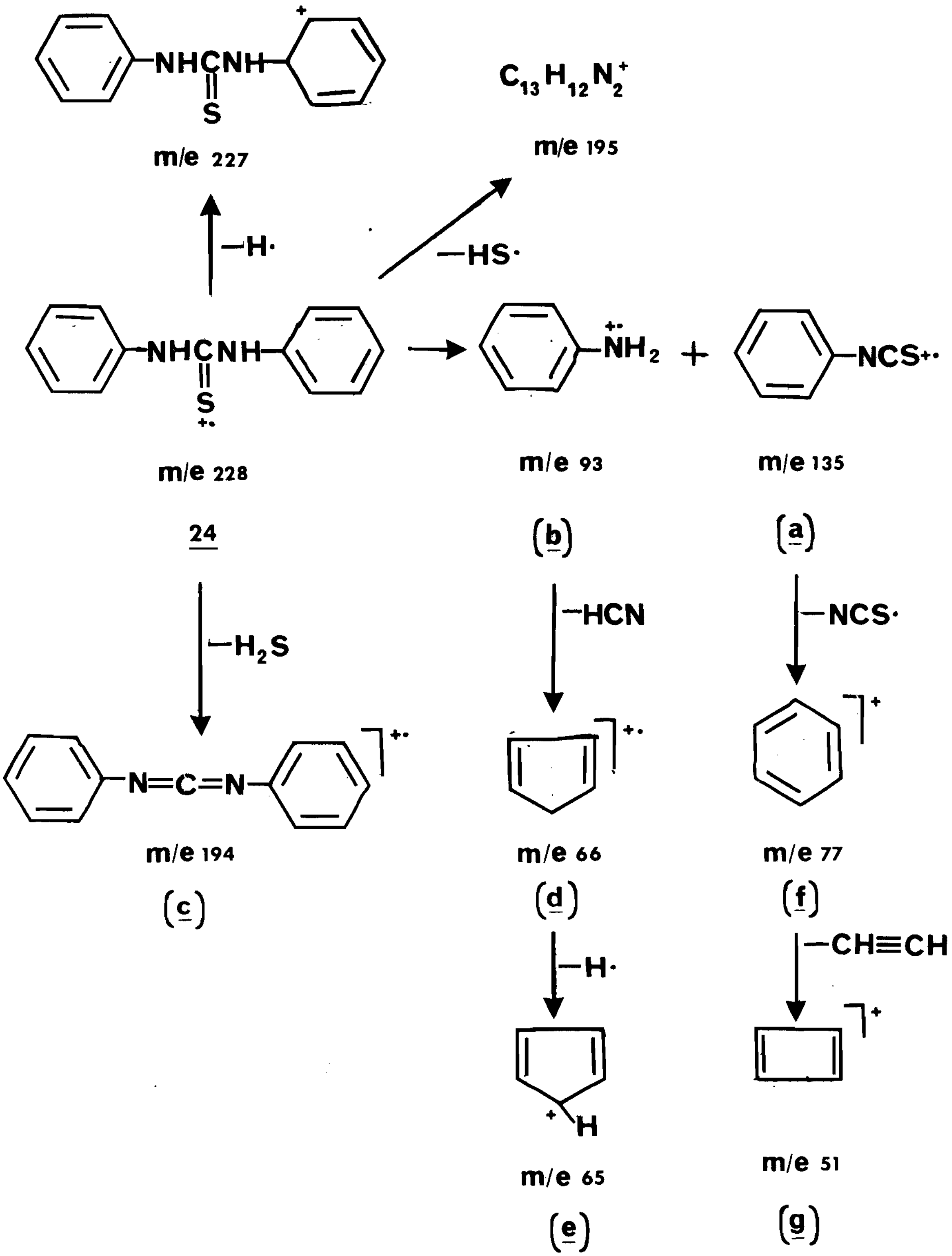
B. INTERPRETATION OF THE MASS SPECTRA OF PHENYL- AND THIAZOLYLTHIOUREAS AND DERIVATIVES

The limited information on the mass spectra of aromatic thioureas provided an incentive to examine in detail the behaviour of phenyl- and thiazolylthioureas and some S-alkyl derivatives under electron impact.

1. N,N'-Diphenylthiourea (24)

The fragmentation pattern of N,N'-diphenylthiourea (24) starts with the thermal fission of the parent compound into neutral molecules which are subsequently ionized. Thus 24 (Fig.17) gives phenyl isothiocyanate (a) of m/e 135 and aniline (b) of m/e 93, which is also the base peak. This process may be visualized as going through a four-membered cyclic transition state:




NHCNH
S
m/e 227
C13H12N2+
m/e 195
–H·
–HS·
NHCNH
S
m/e 228
24
NH2
m/e 93
(b)
NCS+·
m/e 135
(a)
–H2S
–HCN
–NCS·
N=C=N
m/e 194
(c)
m/e 66
(d)
m/e 77
(f)
–H·
–CH≡CH
H
m/e 65
(e)
m/e 51
(g)

Scheme 5

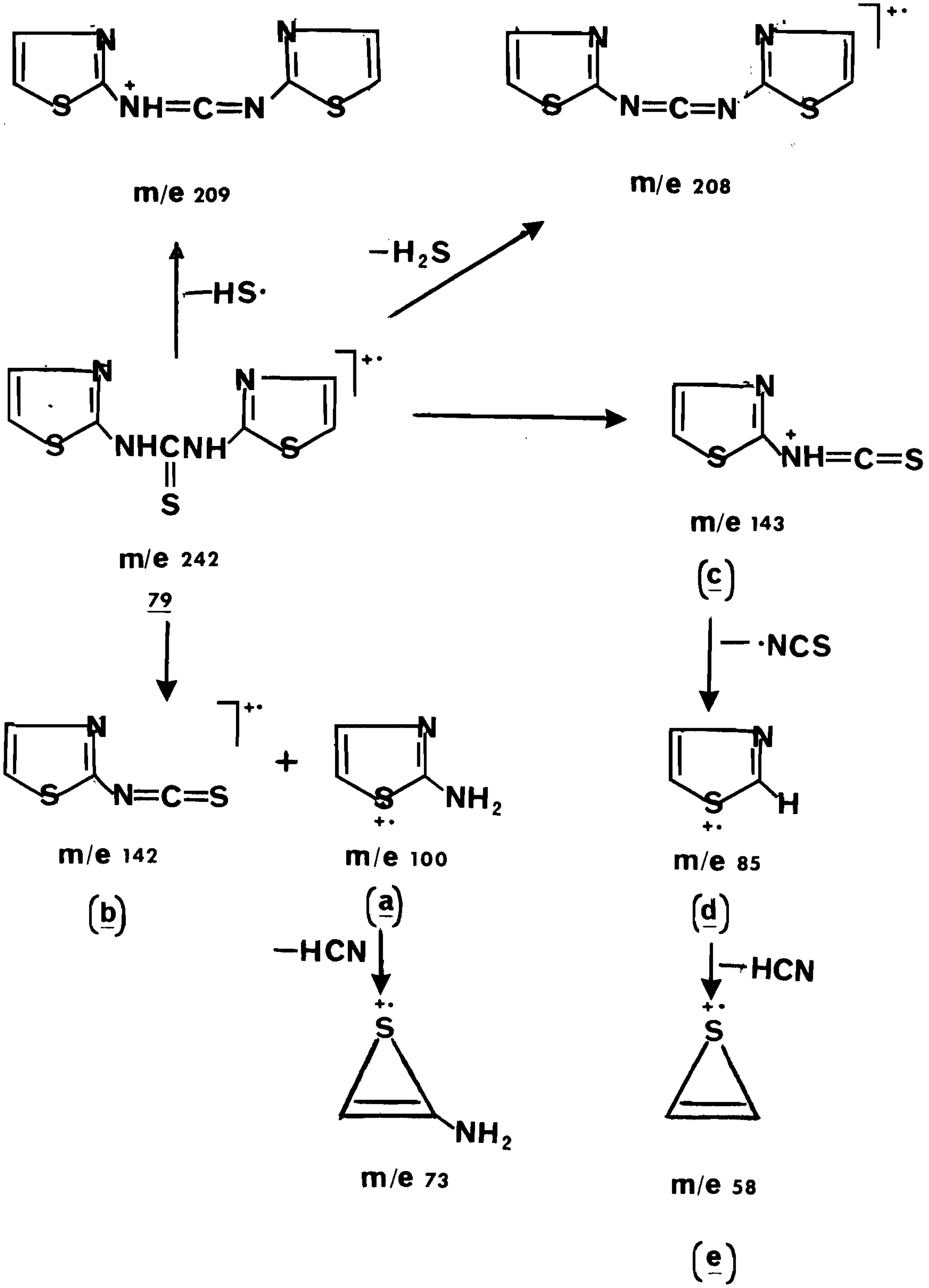
Expulsion of H_2S from 24 yields an ion of m/e 194 which may be represented by a diphenylcarbodiimide structure (c) in Scheme 5. The rest of the spectrum shows all the fragments associated with aniline (b) and phenyl isothiocyanate (a). Thus the ion (d) at m/e 66 results from the loss of HCN from (b), this process being accompanied by a metastable of m* = 46.8 ($66^2/_{93}$ = 46.8). This ion $C_5H_6^+$ (d) may be formulated as cyclopentadiene and decomposes further by loss of a hydrogen radical to give the cyclopentadienyl cation (e) of m/e 65 (127).

The phenyl isothiocyanate radical-ion (a) loses NCS to give the phenyl cation (f), $C_6H_5^+$, of m/e 77 which in turn eliminates acetylene to give the butadiene cation (g), $C_4H_3^+$, of m/e 51, supported by a metastable m* = 33.4 ($51^2/_{77}$ = 33.4).

Several other minor fragments are observed in the spectrum. Ejection of a sulphydryl radical from 24 leads to the formation of an ion of m/e 195 while removal of a hydrogen provides an ion of m/e 227.

2. N,N'-Di-(2-thiazolyl)thiourea (79)

The mass spectrum of N,N'-di-(2-thiazolyl)thiourea (79; Fig. 18) exhibits fragments which could arise by thermal fission. As seen in Scheme 6, the molecular ion of m/e 242 is split into 2-aminothiazole (a), the base peak at m/e 100, and 2-thiazolyl isothiocyanate (b) of m/e 142. The presence of a metastable


m/e 209
m/e 208
−HS·
−H_2S
m/e 242
79
m/e 143
(c)
—·NCS
+
m/e 142
(b)
m/e 100
(a)
m/e 85
(d)
−HCN
−HCN
m/e 73
m/e 58
(e)

Scheme 6

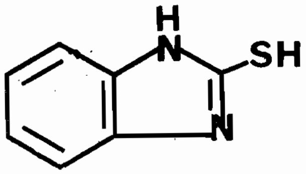
ion at m* = 41.3 ($100^2/_{242}$ = 41.3) indicates that (a) arises at least in part from electron-impact. Expulsion of a HS· and H_2S from (79) accounts for the presence of small peaks at m/e 209 and 208. An abundant ion of m/e 143, which may be represented by a protonated 2-thiazolyl isothiocyanate (c) originates from the molecular ion (79) as indicated by a metastable ion at m* = 84.5 ($143^2/_{242}$ = 84.5).

The low mass end of the spectrum reflects the expected decomposition pattern of the amine (a) and the isothiocyanate (c). Thus loss of HCN from (a) leads to the ion of m/e 73, via the rupture of the 2,3- and 4,5- bonds. Removal of NCS from the protonated isothiocyanate (c) leads to the thiazole (d) of m/e 85 which then splits off HCN to give (e) of m/e 58. Cleavage of the 1,2- and 3,4-bonds of (a) also leads to ion (e) which may explain its high 95% abundance. It has been observed by Clarke et al. (122) that 2-aminothiazole alone gives fragment (e) in 75% abundance. The isothiocyanate radical similarly of 58 mass units certainly contributes also to the presence of a peak at m/e 58.

3. S-Alkyl-N,N'-diphenylisothioureas

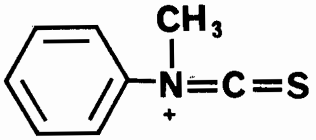
The mass spectra of the S-methyl- (24a) and S-ethyl (24b; Fig. 19) derivatives of N,N'-diphenylthiourea (24) have not been previously recorded. An investigation of their spectra revealed the following fragmentation paths: the expulsion of methyl mercaptan, CH_3SH, from the molecular ion of m/e 242 of

24a gives the base peak at m/e 194 with the formula $C_{13}H_{10}N_2$ determined from exact mass measurement and probably best represented by the diphenylcarbodiimide (a). An ion of m/e 195, which may be assigned to a protonated diphenylcarbodiimide (b), can be explained by the ejection of a $CH_3S\cdot$ radical from the molecular ion (24a). A weakly abundant ion of m/e 150 could be assigned either structure (c) or (d).



(c)

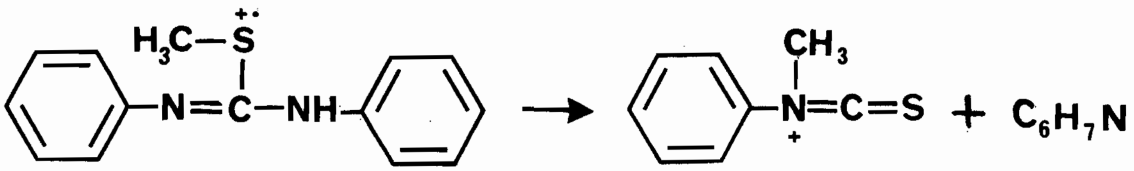
$C_7H_6N_2S$



(d)

C_8H_8NS

Exact mass measurement gave C_8H_8NS (d) as the correct formula. The following mechanism may be postulated for the formation of (d).

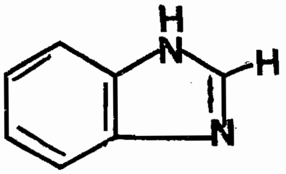


24a

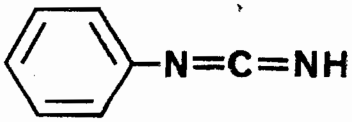
(d)

A similar fragment (e) of m/e 164 containing an ethyl instead of a methyl group is observed in the spectrum of 24b, as illustrated in Scheme 7 although the ethyl group may be situated on the nitrogen or the sulfur atom. The ion (e) in turn expels ethylene to give a protonated isothiocyanate (f) of m/e 136, this process being supported by a metastable ion at m* = 112.7 ($\frac{136^2}{164}$ = 112.7). This cation (f) gives rise to an ion (g) of m/e 109 and formula $C_6H_5S^+$ after expulsion of HCN and to the phenyl cation (h) of m/e 77 by removal of HCNS. These processes are accompanied by appropriate metastable ions m* = 87.4 ($109^2/_{136}$ = 87.4) and m* = 43.6 ($77^2/_{136}$ = 43.6).

Both the spectra of 24a and 24b contain a peak of low abundance at m/e 118 which possesses the formula $C_7H_6N_2$ according to exact mass measurement and may be represented by either structure (i) or (j).

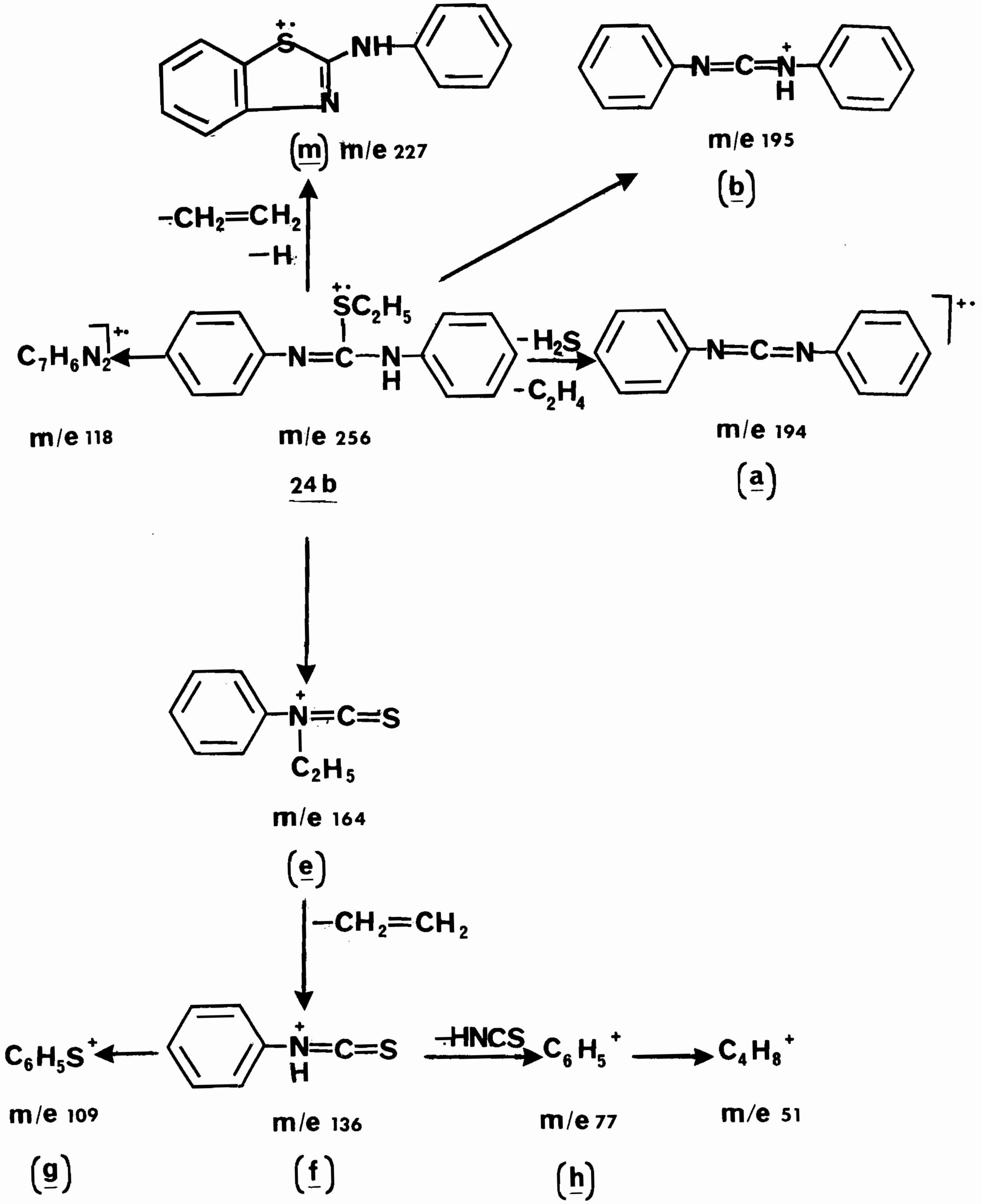


(i)



(j)

In the spectrum of 24b as shown in Scheme 7 ion (a) of m/e 194 is obtained from the molecular ion after loss of hydrogen sulfide and ethylene whereas the fragment (b)



(m) m/e 227
m/e 195
(b)
−CH₂=CH₂
−H
C₇H₆N₂
m/e 118
m/e 256
24 b
-H₂S
-C₂H₄
m/e 194
(a)
m/e 164
(e)
−CH₂=CH₂
C₆H₅S⁺
m/e 109
(g)
m/e 136
(f)
-HNCS
C₆H₅⁺
m/e 77
(h)
C₄H₈⁺
m/e 51

Scheme 7

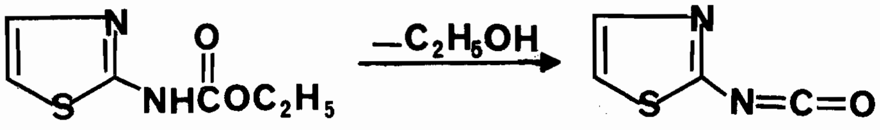
arises from loss of HS· and ethylene. A less abundant ion (m) of m/e 227 can be explained in terms of the loss of an ethylene molecule and a hydrogen molecule.

4. N-Carbethoxythioureas

The mass spectra of the following three thioureas containing a carbethoxy group on a nitrogen were examined: N-carbethoxy-N,N'-diphenyl-thiourea (25), N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19) and N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20).

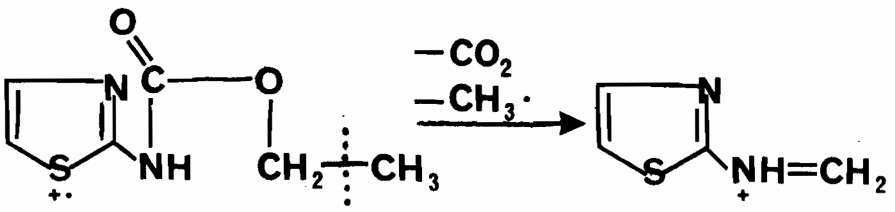
All three spectra exhibited fragments due to the splitting of the molecular ion into its corresponding carbamate and phenyl isothiocyanate (a) which served as base peak in every case. In the spectra of 20 and 19, some cross-over of the carbethoxy function appears to have taken place since fragments assigned to the corresponding thiazolyl isothiocyanate (h) and (i) and ethyl phenylcarbamate (b) were present in lower abundance. The ion (b) of m/e 165 was identified by exact mass measurement. For example, in the spectrum of 19 (Fig.20) as shown in Scheme 8, the ion of m/e 143 can be assigned to the protonated 2-thiazolyl isothiocyanate (h) while in the spectrum of 20 (Fig. 21) an analogous ion (i) of m/e 156 may be related to the 4-methyl-2-thiazolyl isothiocyanate. Nevertheless, in both spectra, the more abundant ions are due to phenyl isothiocyanate (a) and the thiazolylcarbamates (c) and (d), reflecting the greater stability of these products. These same fragments would also be expected to arise from thermal fission.

Fragments reflecting the expected degradation products of carbamates and isothiocyanates were also observed in these spectra. Thus ethyl N-2-thiazolylcarbamate (c) produced ions of m/e 113 and m/e 126 of low abundance assigned to a 2-thiazolyl Schiff base (e) and 2-thiazolyl isocyanate (f), respectively.



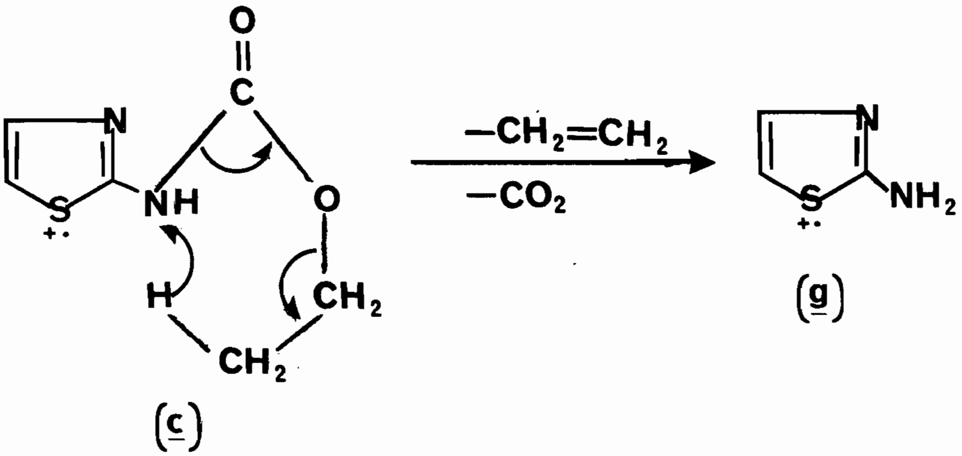
(c) (f)

The formation of (f) is due to the splitting off ethanol from (c), the isocyanate being also the expected thermolysis product of the carbamate. As for (e), it is brought about by a skeletal rearrangement of (c) involving the expulsion of carbon dioxide and the splitting of a methyl radical.



(c) (e)

A third more abundant ion of m/e 100 is also observed and is ascribed to 2-aminothiazole (g). It is furnished by the splitting of ethylene and CO_2 from (c) through a McLafferty rearrangement. The analogous 2-amino-4-methylthiazole (l) is also the most abundant ion in the spectrum of 20.



A similar fragmentation was again observed in the spectra of 20 and 19 for ethyl phenylcarbamate (b). Thus fragments of m/e 93 for aniline, of m/e 106 for phenylimine and of m/e 119 for phenyl isocyanate were observed, although all in low abundance.

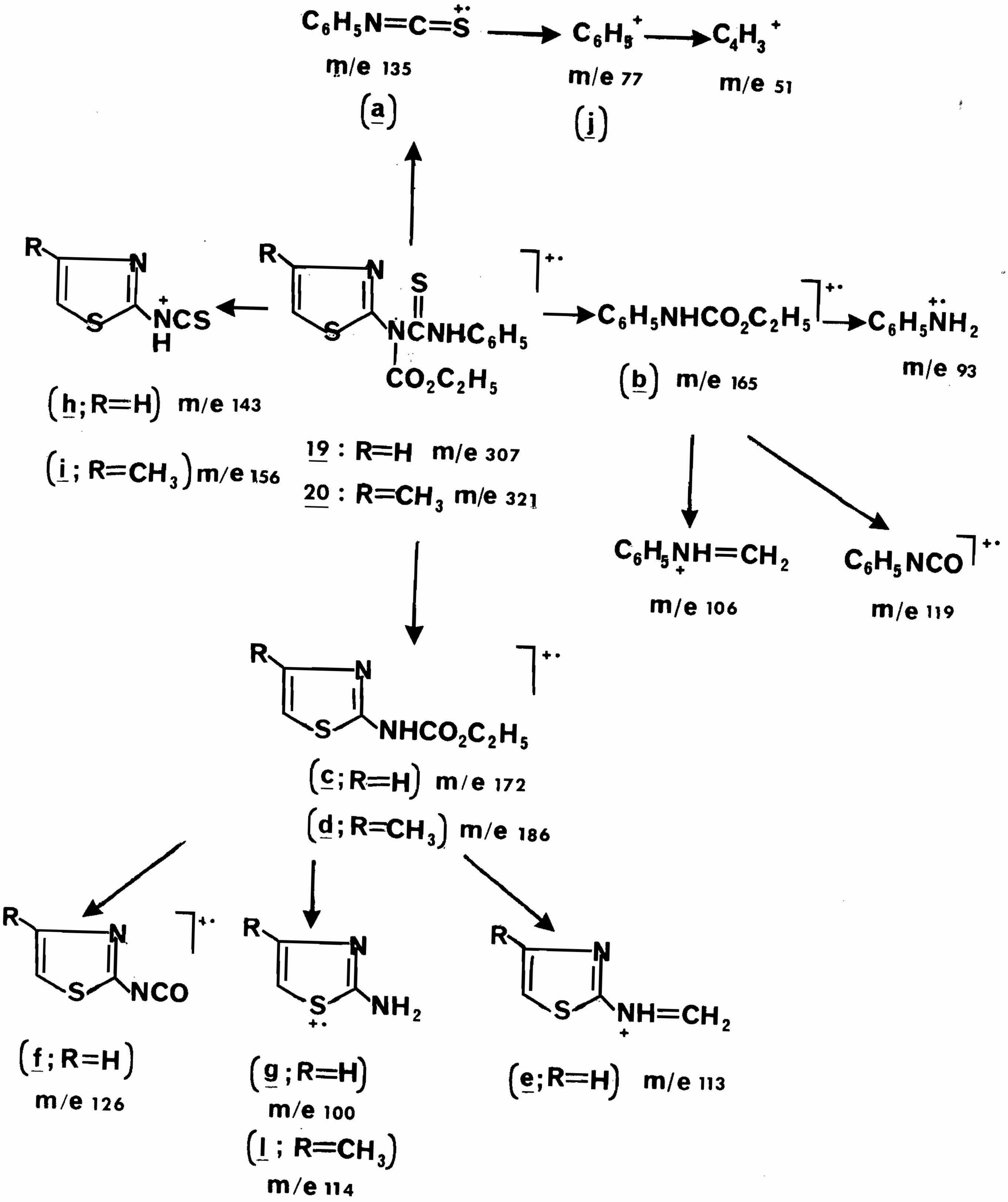
The phenyl isothiocyanate (a) present in all three spectra undergoes expulsion of N=C=S to give the phenyl cation (j) of m/e 77 in fairly high abundance. This cation in turn affords $C_4H_3^+$ of m/e 51 supported by a metastable ion of $m^* = 33.8$ ($51^2/_{77} = 33.8$).

The ion of m/e 156 in the spectrum of 20 was identified by exact mass measurement as having the formula $C_5H_4N_2S_2$ and is thus assigned to 4-methyl-2-thiazolyl isothiocyanate (i). In the spectrum of 19, the ion of m/e 143 may be considered as the protonated 2-thiazolyl isothiocyanate (h). A metastable ion of mass 65.5 establishes the origin of (h) as a one-step fragmentation of the molecular ion (19). Neither (h) nor (i) showed further fragments due to the expulsion of HNCS or NCS.

The spectrum of 19 reveals the presence of an unexpected ion of m/e 188 in low abundance with the composition $C_6H_8N_2OS_2$ from the exact mass measurement and which may be represented by a thioncarbamate structure (k):

(k)

It presumably splits into the isothiocyanate of m/e 142, although there is no metastable ion present to substantiate this assumption.

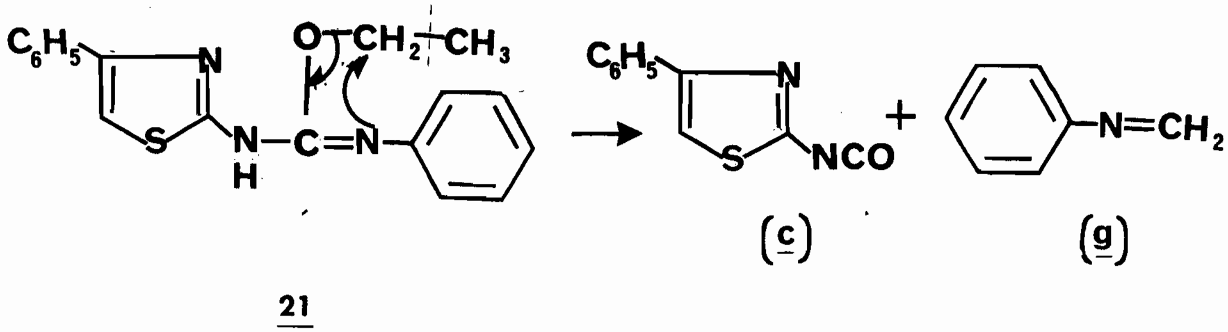

$C_6H_5N{=}C{=}\overset{+\cdot}{S}$
m/e 135
(a)
$C_6H_5^+$
m/e 77
(j)
$C_4H_3^+$
m/e 51
R
N
S
$\overset{+}{N}CS$
H
(h; R=H) m/e 143
(i; R=CH$_3$) m/e 156
$NCNHC_6H_5$
$CO_2C_2H_5$
19 : R=H m/e 307
20 : R=CH$_3$ m/e 321
$C_6H_5NHCO_2C_2H_5$
(b) m/e 165
$C_6H_5\overset{+\cdot}{N}H_2$
m/e 93
$C_6H_5\underset{+}{N}H{=}CH_2$
m/e 106
C_6H_5NCO
m/e 119
$NHCO_2C_2H_5$
(c; R=H) m/e 172
(d; R=CH$_3$) m/e 186
NCO
(f; R=H)
m/e 126
NH_2
(g; R=H)
m/e 100
(l; R=CH$_3$)
m/e 114
$\underset{+}{N}H{=}CH_2$
(e; R=H) m/e 113

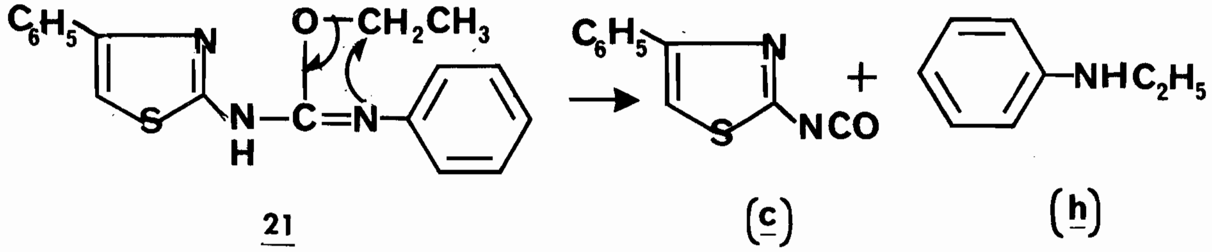
Scheme 8

5. Thiazolylisoureas

The O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21) and O-ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23) underwent very similar fragmentation under electron impact. Three major products were encountered: a carbodiimide, an isocyanate and an imine or Schiff base. Thus in the spectrum of 21 (Fig.22) an ion of m/e 277, with the composition $C_{16}H_{11}N_3S$ from the exact mass measurement, corresponds to a carbodiimide structure (a) formed after ejection of ethanol from the molecular ion. An analogous ion of m/e 291 (b) is present in the spectrum of 23. The ion of m/e 202 in the spectrum of 21 has composition $C_{10}H_6N_2OS$ and corresponds to the isocyanate (c) arising from the molecular ion, supported by a metastable ion of mass 126.3 ($202^2/_{323} = 126.3$). A more abundant ion of m/e 203 assigned to a protonated isocyanate (d) also originates from 21 (Fig. 22) as evidenced by the metastable ion of mass 127.6 ($203^2/_{323} = 127.6$). Corresponding ions of high abundance (e) and (f) of m/e 216 and 217 are found in the spectrum of 23 (Fig. 23).

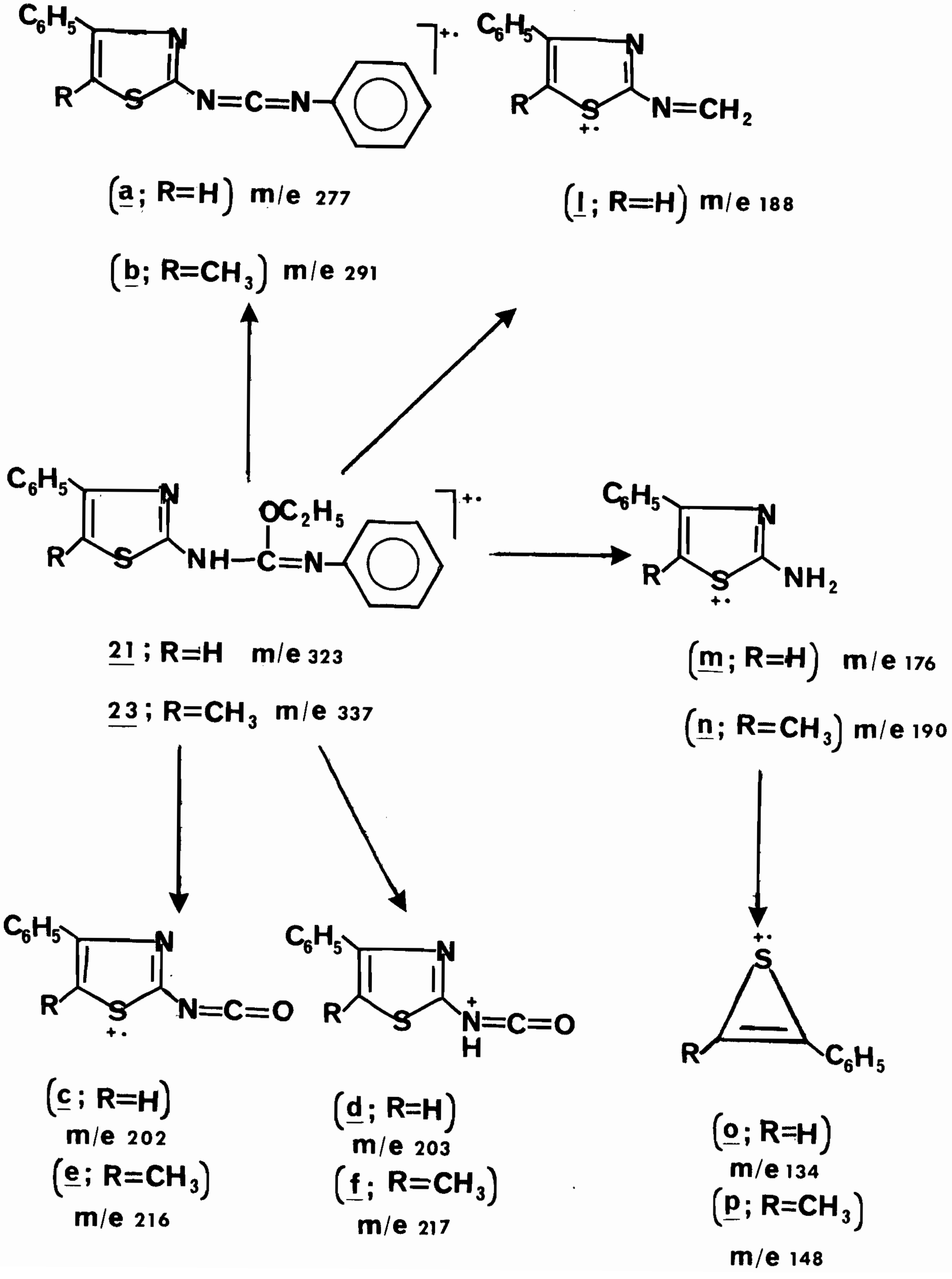
If the previously mentioned ions result from the splitting of the molecular ions, corresponding ions containing the residual phenyl group should be observed. Indeed in both spectra, ions of m/e 105 and m/e 121 may be assigned to a phenyl Schiff base (g) and N-ethylaniline (h). The identity of these ions has not been established definitely. Nevertheless, their formation may be illustrated by the following mechanisms:





The formation of the third major product, the thiazolyl Schiff base (l) should give rise to a corresponding ion containing the phenyl group. Phenyl isocyanate (i) of m/e 119 or its protonated form of (j) m/e 120 appears to be a likely candidate. Both spectra contained (i) in low abundance and (j) in higher abundance. The same mechanism as above may be postulated but the products are reversed. The thiazole becomes the Schiff base and the phenyl ring carries the isocyanate function. Furthermore fragments containing the thiazole group in analogy to (h) are found of m/e 204 and m/e 218 and may be assigned to N-ethyl-2-aminothiazoles. These ions, however, are very close to the ions

Scheme 9


C6H5
R
S
N
N=C=N
]+·
(a; R=H) m/e 277
(b; R=CH3) m/e 291
C6H5
R
S
+·
N
N=CH2
(l; R=H) m/e 188
C6H5
R
S
N
NH—C=N
OC2H5
]+·
21 ; R=H m/e 323
23 ; R=CH3 m/e 337
C6H5
R
S
+·
N
NH2
(m; R=H) m/e 176
(n; R=CH3) m/e 190
C6H5
R
S
+·
N
N=C=O
(c; R=H) m/e 202
(e; R=CH3) m/e 216
C6H5
R
S
N
+
N=C=O
H
(d; R=H) m/e 203
(f; R=CH3) m/e 217
+·
S
R
C6H5
(o; R=H) m/e 134
(p; R=CH3) m/e 148

arising from the isocyanates and since no exact mass measurements were taken on them, their structures cannot be proven.

Several other important fragments are present in the spectra of 21 and 23. The ions of m/e 176 (m) and 190 (n) correspond to the 2-amino-4-phenylthiazole and 2-amino-5-methyl-4-phenylthiazole, respectively. Their origin is not well established since they could arise from the carbodiimide or the molecular ion itself. No metastable ion is present to elucidate this point. These aminothiazoles in turn give the expected degradation fragments of m/e 134 (o) and m/e 148 (p), respectively. Aniline appears in both spectra of m/e 93 and gives the anticipated ions of m/e 66 and m/e 65. Scheme 9 shows the major fragmentation products of 21 and 23.

6. Thiazolylguanidines

The mass spectra of N-phenyl-N',N''-di(2-thiazolyl)-guanidine (11), N-phenyl-N',N''-di(4-methyl-2-thiazolyl)guanidine (9), N,N'-diphenyl-N''-(4-methyl-2-thiazolyl)guanidine (10), N-phenyl-N,N'-di-(4-phenyl-2-thiazolyl)guanidine (12), N,N'-diphenyl-N''-(4-phenyl-2-thiazolyl)guanidine (16), N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13) and N,N'-diphenyl-N''-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17) were examined.

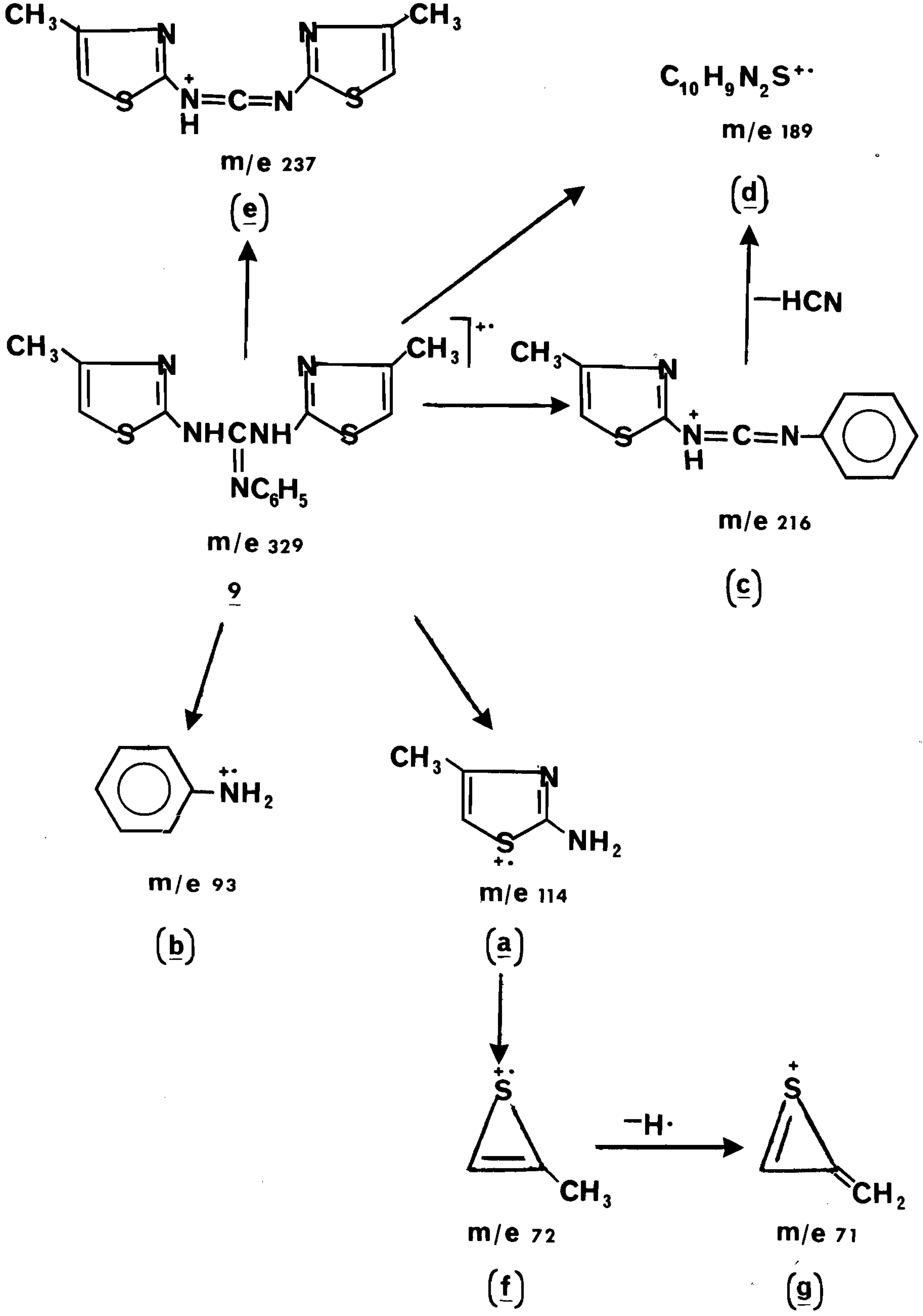
A characteristic aspect of these spectra is the very low abundance or even absence of the molecular ion. Loss of aniline or a substituted aminothiazole from the molecular ion gives the base peak which may be regarded as a carbodiimide. This is not surprising since guanidines undergo thermal dissociation into a carbodiimide and a substituted amine. If the groups in the guanidine are different, several carbodiimides are possible, depending which substituted amine is lost. Thus in 9, as shown in Scheme 10, the loss of 2-amino-4-methylthiazole (a) which is preferred over the loss of aniline (b) yields the base peak, the protonated N-phenyl-N'-(4-methyl-2-thiazolyl)carbodiimide (c) of m/e 216. This process is supported by a metastable ion of m = 141.8 ($216^2/_{329}$). In turn, the carbodiimide (c) undergoes loss of HCN to give the ion (d) of m/e 189. A metastable ion of m = 108.5 ($189^2/_{329}$) provides some evidence that (d) may also result from a one-step decomposition from 9 (Fig. 24).

Another protonated carbodiimide arising from the loss of aniline from 9 may be postulated for the ion (e) of m/e 237. of low abundance.

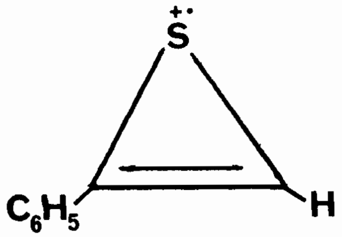
The remainder of the spectrum of 9 simply displays the fragments associated with the decomposition of (a) and (b). For example, ion (f) of m/e 72 arises from (a) and in turn loses a hydrogen radical yielding the ion (g) of m/e 71. An ion of m/e 77 probably represents the phenyl cation, $C_6H_5^+$, which expels acetylene to give the butadiene cation, $C_4H_3^+$, of m/e 51.

The spectra of the remaining guanidines (11, 10, 12, 16, 13, 17) (Table XX) closely resemble the spectrum of 9 in

Scheme 10


m/e 237
(e)
$C_{10}H_9N_2S^{+\cdot}$
m/e 189
(d)
−HCN
m/e 329
9
m/e 216
(c)
m/e 93
(b)
m/e 114
(a)
−H·
m/e 72
(f)
m/e 71
(g)

their fragmentation pathways. In the case of 12 and 16 the base peak is not a carbodiimide but an ion of m/e 134 which probably corresponds to the structure (h):



(h)

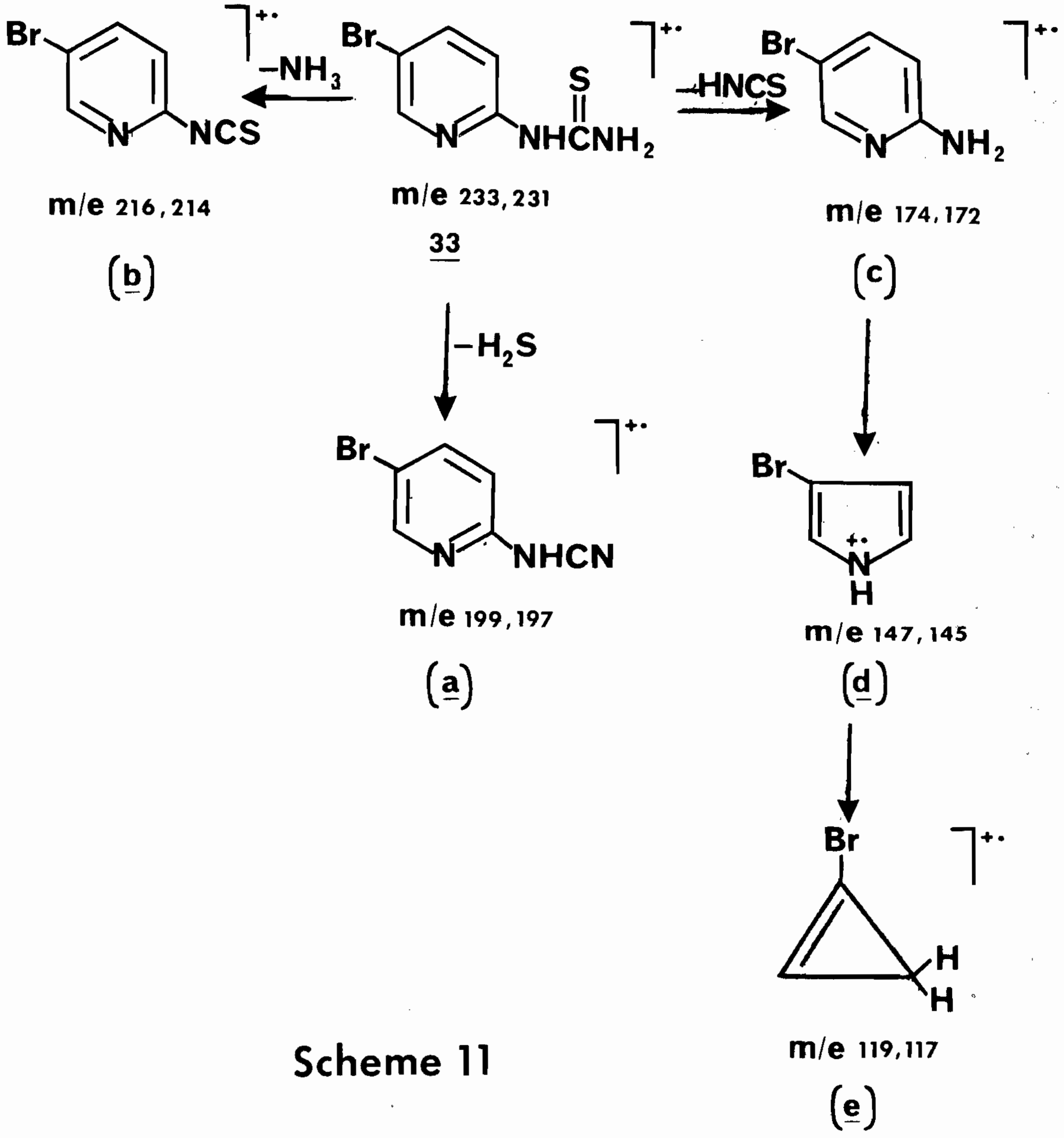
Compound 17 exhibits its base peak at m/e 78 which may be assigned to a benzene structure.

C. PYRIDYLTHIOUREAS

The mass spectra of 2,6-dithioureidopyridine (34) and N-(5-bromo-2-pyridyl)thiourea (33) reveal that there are three main degradation paths of pyridylthioureas. These involve expulsion of H_2S from the parent ion to give a pyridylcyanamide ion, expulsion of ammonia to give a pyridyl isothiocyanate and expulsion of HNCS to yield an aminopyridine which in turn expells HCN to give a pyrrole fragment.

Thus, as illustrated in Scheme 11, loss of H_2S from 33 (Fig. 25) of m/e 233, 231 (bromine isotopes) yields the cyanamide (a) of m/e 199, 197. Expulsion of ammonia from the molecular ion affords the isothiocyanate (b) of m/e 216, 214 while removal of HNCS from 33 gives 2-amino-5-bromopyridine (c) of m/e 174, 172 which in turn expels HCN to give the pyrrole fragment (d) of m/e 147, 145. Expulsion of HCN from (d) leads to the fragment (e) of m/e 119, 117.

There are no metastable ions present to confirm any of these postulated steps.



Scheme 11

Similarly 34 (Table XXI) of m/e 227 loses a molecule of H_2S to give the ion of m/e 193. It may also lose ammonia to produce the ion of m/e 210. The ion of m/e 168 probably arises by expulsion of HNCS from 34. Again no metastable ion was observed to confirm these steps and it could not be distinguished whether both thioureido groups were fragmented simultaneously or successively.

TABLE XVII

MAJOR PEAKS IN THE MASS SPECTRA OF AMINOPYRIDINES

Compound											
2-Aminopyridine	m/e	27	36	37	38	39	40	41	42	43	49
	I(%)	4.7	1.5	10.6	20	36.6	20	36.6	4.4	4.5	2.2
	m/e	50	51	52	53	54	62	63	64	65	66
	I(%)	9	10	8	2.2	3.5	1.2	2.2	4.4	6	19.5
	m/e	67	68	74	75	76	77	78	79	92	93
	I(%)	100	6	.3	1	1	.6	1.3	.3	.6	5
	m/e	94M	95	96							
	I(%)	63	4.4	.3							
3-Aminopyridine	m/e	27	37	38	39	40	41	42	49	50	51
	I(%)	4	11.2	25.2	53.2	25.2	56	3.5	1.7	5.1	5.6
	m/e	52	53	54	55	62	63	64	65	66	67
	I(%)	7.9	2.5	5	.6	.8	2.4	4	7.3	11.2	77.1
	m/e	68	75	76	77	78	79	92	93	94M	95
	I(%)	7.2	1.1	.8	.8	1.1	.6	1.7	14	100	11.2
	m/e	96									
	I(%)	.6									

Compound											
4-Amino- pyridine	m/e	27	37	38	39	40	41	42	43	44	49
	I(%)	52	52.5	23.9	25.2	18.9	35.6	8.5	3.8	1	2
	m/e	50	51	52	53	54	63	64	65	66	67
	I(%)	6.3	7.6	13.7	3.8	7.6	1.9	2.9	6.3	15.2	47.9
	m/e	68	74	75	76	77	78	79	93	94M	95
	I(%)	7.6	.8	1.6	.8	1.6	1.4	1.4	11.4	100	8.9

The base peak is taken as 100% abundance.

M = Molecular ion   I = Abundance

TABLE XVIII

MAJOR PEAKS IN THE MASS SPECTRA OF PHENYL AND THIAZOLYLTHIOUREAS

Compound											
N,N'-Di-(2-thiazolyl)-thiourea (<u>79</u>)	m/e	26	27	33	34	39	40	41	43	44	45
	I(%)	3.5	5.5	2.1	3.5	2.0	3.8	3.2	8.8	5.4	21.6
	m/e	46	55	57	58	59	60	72	73	84	85
	I(%)	8.8	13.2	16.7	95.2	30.8	7.6	6.5	16.7	3.2	8.8
	m/e	100	101	102	142	143	144	145	208	209	210
	I(%)	100	6	8.1	36	90.5	9.7	9.2	4.4	6.5	2.2
	m/e	242M	243	244							
	I(%)	33.3	3.8	4.6							
S-Ethyl-N,N'-diphenyliso-thiourea (<u>24b</u>)	m/e	26	27	28	34	51	59	65	77	78	91
	I(%)	4.4	23	100	5.8	40	2.9	30.7	86.7	11.6	12.4
	m/e	92	93	109	118	135	136	137	138	164	165
	I(%)	39.4	22.6	8	4.4	5.8	73.3	7.3	4.4	100	11.6
	m/e	166	167	194	195	196	227	228	255	256M	257
	I(%)	6.6	3.7	34.3	93.3	16.1	7.3	7.3	5.8	73.3	14.6
	m/e	258									
	I(%)	5.1									

Compound											
S-Methyl-N,N'-diphenylisothiourea (24a)	m/e	26	27	28	45	47	48	51	77	91	102
	I(%)	2.5	5	3.7	18.2	50.7	44.2	26	45.5	23.4	5.1
	m/e	103	118	135	150	192	193	194	195	196	242M
	I(%)	3.9	3.8	3.6	8.8	2.5	5.6	100	26	3.1	5.2
	m/e	243									
	I(%)	1.8									
N-Carbethoxy-N'-phenyl-N-2-thiazolyl-thiourea (19)	m/e	26	27	28	29	44	46	51	58	59	74
	I(%)	3	16.5	12	60	5.5	4	22.3	31.5	6	4.2
	m/e	75	76	77	78	91	93	99	100	101	102
	I(%)	3.6	3.6	65.9	6.3	5.2	11.2	5.7	70	4.8	3.2
	m/e	103	106	113	119	126	127	134	135	136	137
	I(%)	2.6	5.7	13.5	3.6	8.3	7.3	1.6	100	16.8	7.9
	m/e	142	143	144	145	163	164	165	166	172	173
	I(%)	5.7	12.6	6.8	1	2.6	2.6	26.3	3.2	26.3	26
	m/e	174	175	188	189	190	307M	308	309		
	I(%)	2.1	1	13.5	1.6	1.6	11.4	2.1	1.6		

Compound											
N-Carbethoxy-N,N'-diphenylthiourea (25)	m/e	26	27	28	29	37	38	39	44	45	46
	I(%)	6	28	13	76.8	4.4	8.1	24.3	5.1	5.4	2
	m/e	50	51	52	63	64	65	66	74	75	76
	I(%)	25.6	59.5	8.1	13.2	18.9	32.4	21.6	5.5	5.5	11
	m/e	77	78	79	90	91	92	93	94	103	104
	I(%)	100	13.5	5.5	4.4	37.8	23	97.2	9.5	13.5	8.1
	m/e	105	106	107	108	109	110	117	118	119	120
	I(%)	2.7	63.1	5.4	2.7	2.7	4.4	2.7	6.8	27.2	14.9
	m/e	121	135	136	137	164	165	166	167	191	192
	I(%)	5.4	94.5	20.3	13.2	13.5	89	10.8	2.7	13.2	4.4
	m/e	193	194	195	299	300M	301	302			
	I(%)	6.8	99.5	23	1.3	13.5	3.2	1.3			
N,N'-Diphenylthiourea (24)	m/e	26	27	28	34	39	50	51	65	66	77
	I(%)	2.5	5.3	6.7	1.4	13.0	10.2	26.7	15.3	23	57.4
	m/e	78	91	92	93	94	135	136	137	194	195
	I(%)	6.4	3.9	10.8	100	8.8	60	10.8	2.5	5.5	3.2
	m/e	227	228M	229	230						
	I(%)	3.7	18.2	3.7	1.6						

Compound											
N-Carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)-thiourea (20)	m/e	26	27	28	29	42	43	44	45	46	51
	I(%)	3	16	4.5	40	14.3	7	5.3	21	4.2	32.5
	m/e	71	72	77	91	93	106	113	114	119	127
	I(%)	26.8	27.7	75	9	20	6.2	14.9	67.5	2.3	20
	m/e	135	136	137	140	141	156	157	158	159	165
	I(%)	100	12.8	8.5	43	4.6	14.9	6.4	2.3	1.5	12.8
	m/e	166	186	187	188	321M	322	323			
	I(%)	2.1	40	5.3	3	2.7	.9	.9			

TABLE XIX

MAJOR PEAKS IN THE MASS SPECTRA OF THIAZOLE DERIVATIVES

Compound											
O-Ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21)	m/e	26	27	28	29	44	45	46	50	51	65
	I(%)	2.5	13.5	10.3	26.5	2.2	9.9	4.1	4.5	14.3	9.5
	m/e	75	76	77	78	79	89	90	91	92	93
	I(%)	2.1	4.9	37.5	4.9	2.5	4	12.3	6.5	8	80.3
	m/e	94	105	119	120	121	132	133	134	135	136
	I(%)	8	17	5.1	15.2	13.9	1.5	6	89.3	19.8	6.4
	m/e	174	175	176	177	178	187	188	189	190	201
	I(%)	2.5	9.2	48.2	6.1	3	6.4	41.1	18.7	3.7	1.9
	m/e	202	203	204	205	206	207	277	278	279	280
	I(%)	35.7	64.3	17.7	18.3	2.7	9	25	11.3	5.2	1.5
	m/e	322	323M	324	325	326					
	I(%)	4	100	23.2	8.3	1.8					

Compound											
Ethyl N-(5-methyl-4-phenyl-2-thiazolyl)-carbamate (<u>22</u>)	m/e	27	28	29	44	45	50	51	58	59	76
	I(%)	14.	3.1	36.1	5.1	3.3	2.4	5.4	2.8	14.5	3.7
	m/e	77	78	103	104	105	146	147	148	149	150
	I(%)	11.3	1.7	11.8	14.6	2	2.8	36.8	42.1	10.5	3.5
	m/e	188	189	190	191	192	203	204	215	216	217
	I(%)	2.8	27.2	57.9	9.3	3.7	13.8	2.4	1	5.7	12.6
	m/e	218	219	262M	263	264	265				
	I(%)	2.8	1.2	100	17	6.5	1.2				
O-Ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (<u>23</u>)	m/e	26	27	28	29	46	50	51	65	66	77
	I(%)	3.8	9.4	20	12.3	10.5	3.5	7.5	5.3	3	30
	m/e	93	94	105	119	120	121	147	148	149	189
	I(%)	80	75	17.4	7	12.1	13.8	36.3	33.8	10	7.5
	m/e	190	191	192	201	202	203	204	215	216	217
	I(%)	30	6.3	2.5	6.3	56.3	20	6.3	3.8	40	62.5
	m/e	218	219	220	221	290	291	292	293	294	336
	I(%)	17.5	26.3	3.8	2.5	2.5	28.8	12.5	6.3	25	5
	m/e	337M	338	339	340						
	I(%)	100	37.5	12.5	3.8						

TABLE XX

MAJOR PEAKS IN THE MASS SPECTRA OF THIAZOLYLGUANIDINES

Compound											
N-Phenyl, N',N''-di-(2-thiazolyl)-guanidine (11)	m/e	26	27	28	29	32	39	45	50	51	55
	I(%)	2.8	6.3	30.5	2	4	12.7	22.3	5.8	31.4	19.5
	m/e	57	58	59	64	65	66	73	76	77	78
	I(%)	8.2	60	22.3	4.1	11.6	7.3	6.8	4.5	42.3	5.4
	m/e	85	91	92	93	100	175	182	201	202	203
	I(%)	7.7	5.8	5.4	2.5	1.8	18.6	2.7	15	100	12.7
	m/e	204	208	209	301M	302	303				
	I(%)	5	2.7	10.8	20.9	5	2.7				
N,N'-Diphenyl-N''-(4-methyl-2-thiazolyl)guanidine (10)	m/e	26	27	28	29	31	32	39	45	50	51
	I(%)	2.9	8.5	28.5	2	37.7	3	23.2	18.3	7.9	30.5
	m/e	63	64	65	66	67	71	72	73	76	77
	I(%)	4.8	6.1	24	14.4	7.4	21.5	28.8	7.9	5.2	56.6
	m/e	78	91	92	93	94	104	114	139	144	189
	I(%)	6.1	8.3	15.3	35	3.9	6.1	9.6	18.9	10	14.9
	m/e	194	215	216	217	218	307	308M	309	310	
	I(%)	11.4	28.8	100	14	5.2	2.2	21.5	4.8	2.2	

Compound											
N-Phenyl-N',N"-di-(4-methyl-2-thiazolyl)guanidine (9)	m/e	27	28	39	40	41	42	43	44	45	51
	I(%)	3.1	8.6	10.3	2.1	3.4	10.7	4.1	1.1	17.5	9.5
	m/e	65	66	67	68	69	70	71	72	73	76
	I(%)	4.4	2.2	3.5	2.8	7.4	1.3	19.2	21.4	7.8	1.5
	m/e	77	78	91	92	93	94	113	114	115	138
	I(%)	19.6	1.8	2.2	2.4	5.9	1.4	3.9	14.8	2	1
	m/e	139	140	144	189	190	215	216	217	218	236
	I(%)	2.8	3.6	6.3	11.2	2.6	12	100	16.1	6.3	3.6
	m/e	237	238	329M	330	331					
	I(%)	10.7	1.8	16.1	5.2	2.6					
N-Phenyl-N',N"-di-(4-phenyl-2-thiazolyl)guanidine (12)	m/e	27	28	32	39	41	42	43	44	50	51
	I(%)	2.3	12	4.0	7.9	5.9	4	2.9	4	4.9	7.4
	m/e	57	65	66	77	90	91	93	133	134	135
	I(%)	3.9	5.7	7.2	9.8	12.2	13.2	24.4	8.9	100	16.3
	m/e	136	176	178	200	201	202	277	278	279	280
	I(%)	5.7	47.9	16.3	2.4	7.2	24.4	3.3	31.7	32.6	8.1
	m/e	281	358	360	361	362	453M	454	455		
	I(%)	3.3	1.6	4.6	5.7	3.3	3.3	1.6	1.1		

Compound											
N,N'-Diphenyl-N''-(4-phenyl-2-thiazolyl)guanidine (16)	m/e	26	27	28	29	31	32	39	50	51	52
	I(%)	6.8	13.7	41.6	4.1	8.7	8.7	34.7	21.2	44.9	19.4
	m/e	64	65	66	76	77	78	79	89	90	91
	I(%)	6.8	20.4	26.3	11.9	58.2	78.8	8.5	28.8	34.7	20.4
	m/e	92	93	94	133	134	135	136	176	194	195
	I(%)	21.2	93.2	7.5	9.3	100	12.5	5.9	10.2	10.2	3.4
	m/e	251	276	277	278	279	280	370M	371		
	I(%)	5.1	5.9	71.9	45.8	11	2.5	13.6	2.5		
N,N'-Diphenyl-N''-(5-methyl-4-phenyl-2-thiazolyl)-guanidine (17)	m/e	26	27	28	29	32	39	45	50	51	52
	I(%)	6	14.4	26.8	6.4	32.1	24.3	16.7	18.1	36.2	19.1
	m/e	75	76	77	78	79	89	90	91	92	93
	I(%)	3.8	10.5	62.9	100	6.6	10	2.9	13.8	11.9	59.5
	m/e	94	103	104	105	115	116	147	148	149	190
	I(%)	5.3	19.1	25.8	5.7	34.8	9	25.8	27.6	10.5	8.1
	m/e	194	291	292	293	294	295	383	384M	385	386
	I(%)	8.1	11.4	78.6	48.6	11.9	3.3	1.5	14.3	3.3	1.5

Compound											
N-Phenyl-N',N"-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13)	m/e	26	27	28	38	39	40	41	45	50	51
	I(%)	2.5	6.3	17.5	6.7	22.6	5.1	5.5	8.7	11.4	28.4
	m/e	52	59	60	63	64	65	66	69	70	71
	I(%)	12.5	23.6	6	10	4.7	18.7	22.5	5.8	8	5
	m/e	75	76	77	78	79	89	90	91	92	93
	I(%)	3.4	6.4	51.8	39.8	3.6	14.4	2.9	12.7	9.3	28.8
	m/e	94	102	103	104	105	114	115	116	117	145
	I(%)	4.1	4.5	27.7	37.8	6.8	2	66.7	25.2	4.9	2
	m/e	146	147	148	149	150	187	188	189	190	191
	I(%)	3.4	75.3	62.7	14.2	4.1	2.9	3.2	9	42.5	6.4
	m/e	192	264	265	290	291	292	293	294	387	388
	I(%)	2.9	1.8	1.3	4.7	40.9	100	21.6	6.7	1.8	38.7
	m/e	389	390	391	481M	482	483	484			
	I(%)	12.9	5.8	1.8	35.5	10.7	5.4	1.3			

TABLE XXI

MAJOR PEAKS IN THE MASS SPECTRA OF SOME PYRIDYLTHIOUREAS

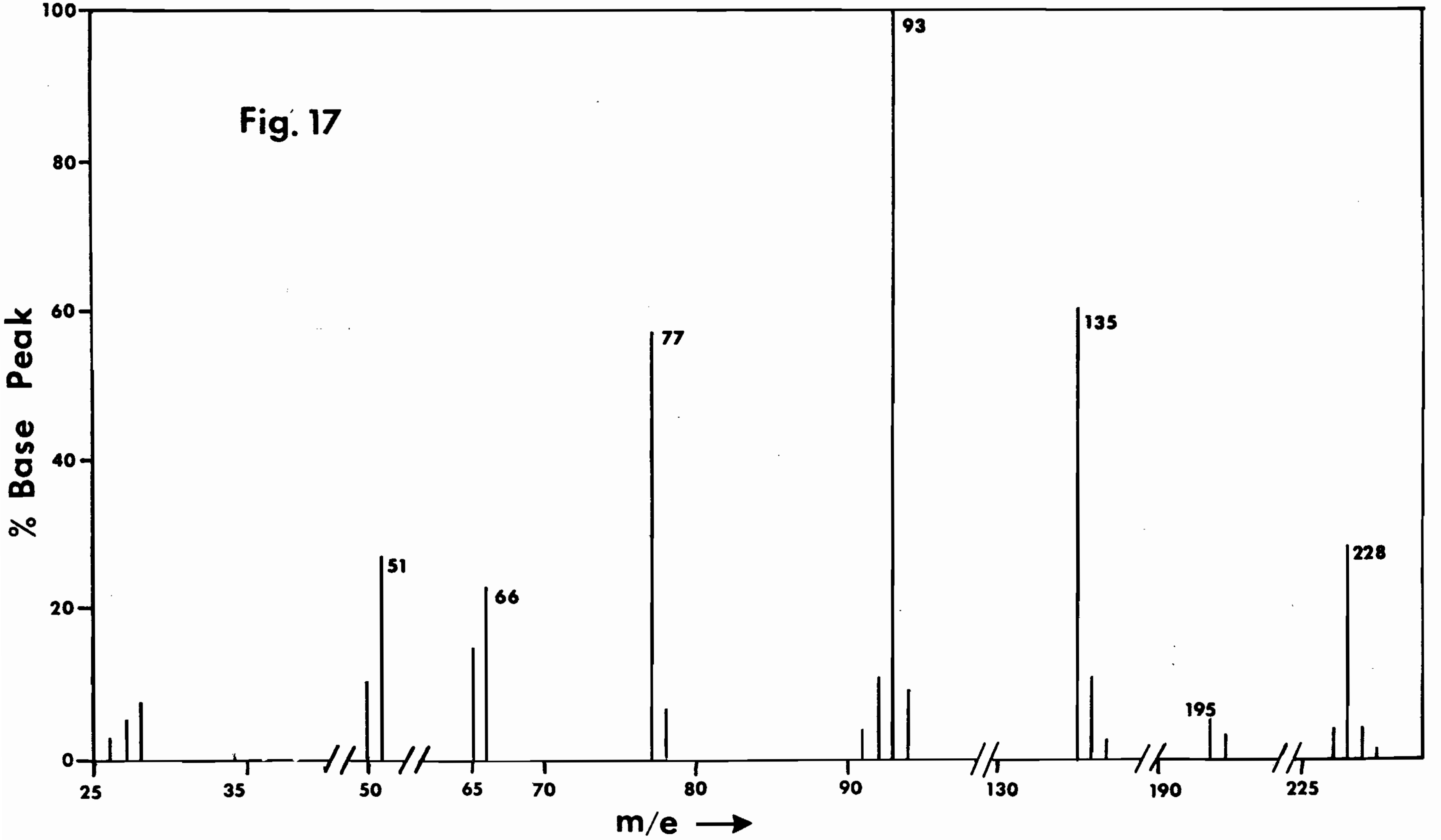
Compound											
N-(5-bromo-2-pyridyl)thiourea (33)	m/e	26	27	28	29	32	33	34	37	38	39
	I(%)	6.6	6.8	44.2	2.6	11.5	6.6	11.1	15.1	31.6	41.5
	m/e	40	41	42	43	50	51	59	60	64	65
	I(%)	9.2	11.2	5.2	19.8	33.5	32.2	11.2	32.2	30.5	20.4
	m/e	66	74	75	76	77	78	91	92	93	103
	I(%)	32.2	10.2	18.5	100	27.2	16.8	49.1	18.5	13.6	20.4
	m/e	104	117	118	119	144	145	146	147	148	156
	I(%)	32.2	12.0	5.1	13.6	3.4	40.8	5.1	66.3	5.1	59
	m/e	157	158	159	172	173	174	175	197	198	199
	I(%)	6.8	57.6	6.8	72.9	3.4	66.3	5.1	52.1	18.5	55.5
	m/e	200	214	215	216	217	230	231M	232	233M	234
	I(%)	18.5	33.5	3.4	35.7	4.2	3.4	46.6	6.8	47.6	5.1

Compound											
2,6-Dithioureidopyridine (34)	m/e	26	27	34	39	58	59	60	66	76	91
	I(%)	6.8	17	13.6	34.0	11.9	91.5	30.6	54.4	86.4	11.9
	m/e	92	93	94	107	108	109	110	117	118	119
	I(%)	23.8	91.5	8.4	5.1	11.9	39.0	3.4	3.4	11.9	5.1
	m/e	123	124	125	126	134	135	136	137	150	151
	I(%)	5.1	18.7	3.4	5.1	5.1	42.3	5.1	3.4	3.4	100
	m/e	152	153	166	176	177	178	193	194	195	209
	I(%)	13.6	6.8	20.4	8.4	23.8	3.4	50.8	8.4	5.1	6.8
	m/e	210	211	212	227M						
	I(%)	94.9	11.9	10.2	8.4						

FIGURE 17

Mass Spectrum of N,N'-Diphenylthiourea (24).

Fig. 17



100
80
60
40
20
0
% Base Peak
93
135
77
228
51
66
195
25
35
50
65
70
80
90
130
190
225
m/e →

FIGURE 18

Mass Spectrum of N,N'-Di-(2-thiazolyl)thiourea (79).

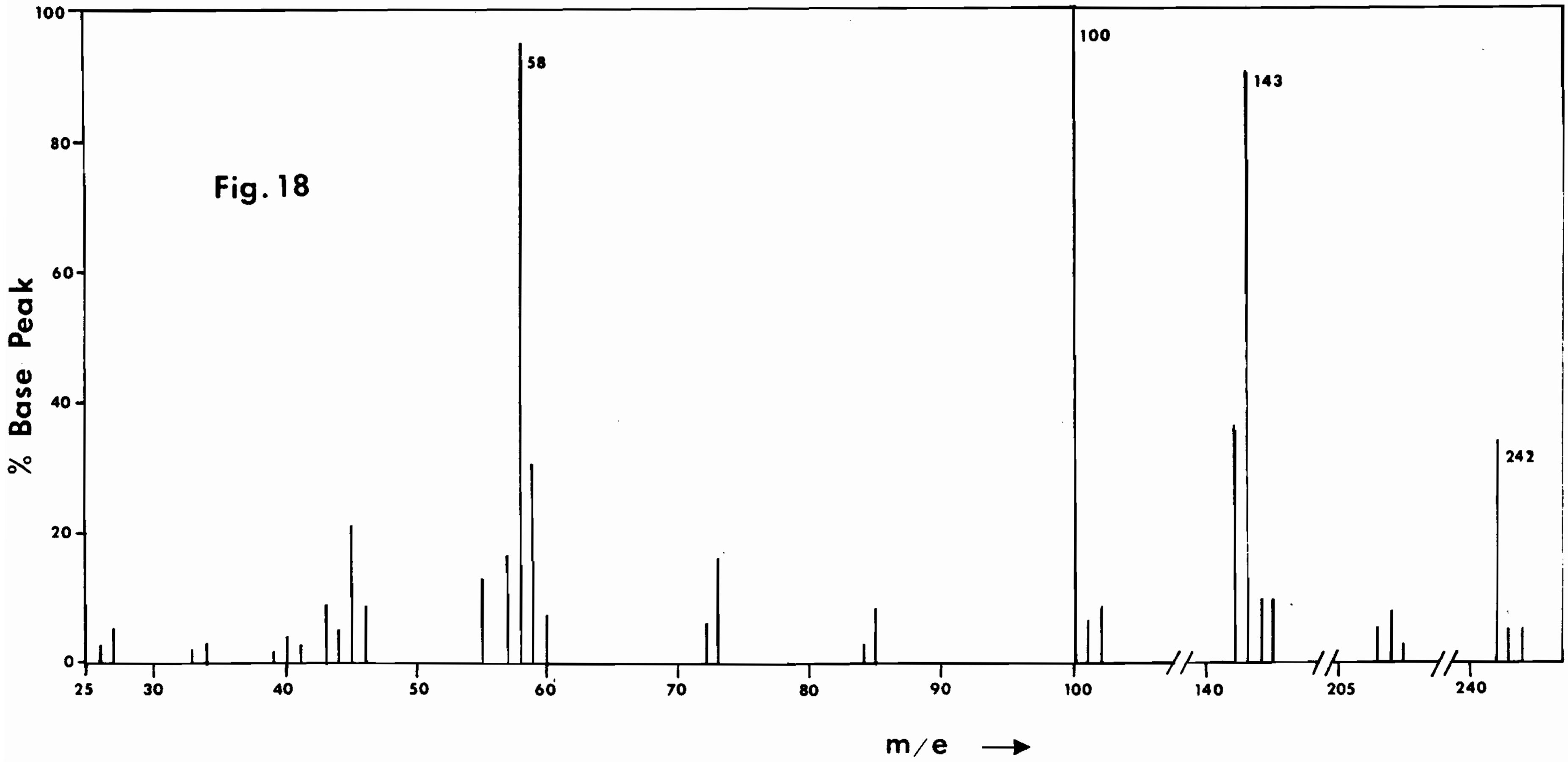

% Base Peak
100
80
60
40
20
0
25
30
40
50
60
70
80
90
100
140
205
240
m/e →
58
100
143
242

Fig. 18

FIGURE 19.

Mass Spectrum of S-Ethyl-N,N'-diphenylthiourea (24b).

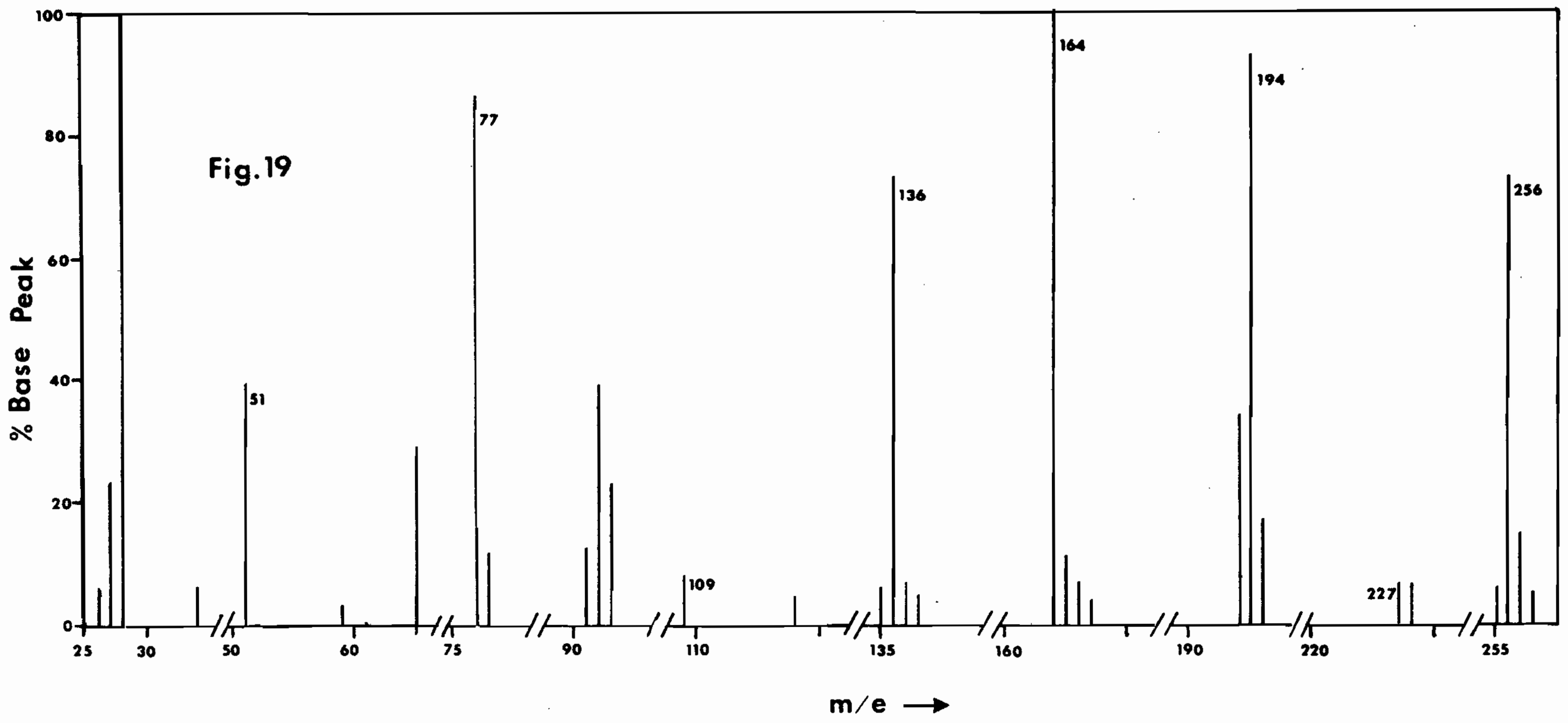


Fig.19
% Base Peak
100
80
60
40
20
0
25
30
50
60
75
90
110
135
160
190
220
255
m/e →
51
77
109
136
164
194
227
256

FIGURE 20

Mass Spectrum of N-Carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19).

Fig. 20

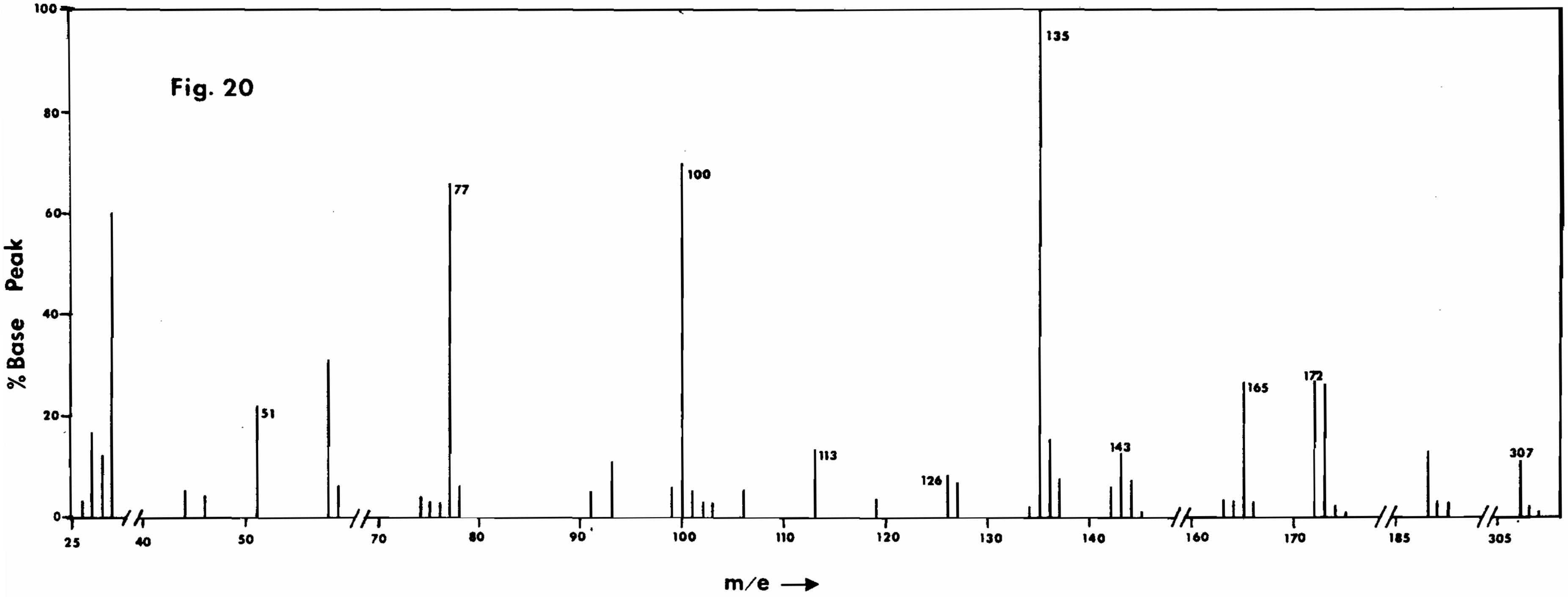

100
80
60
40
20
0
% Base Peak
25
40
50
70
80
90
100
110
120
130
140
160
170
185
305
m/e →
51
77
100
113
126
135
143
165
172
307

FIGURE 21

Mass Spectrum of N-Carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20).

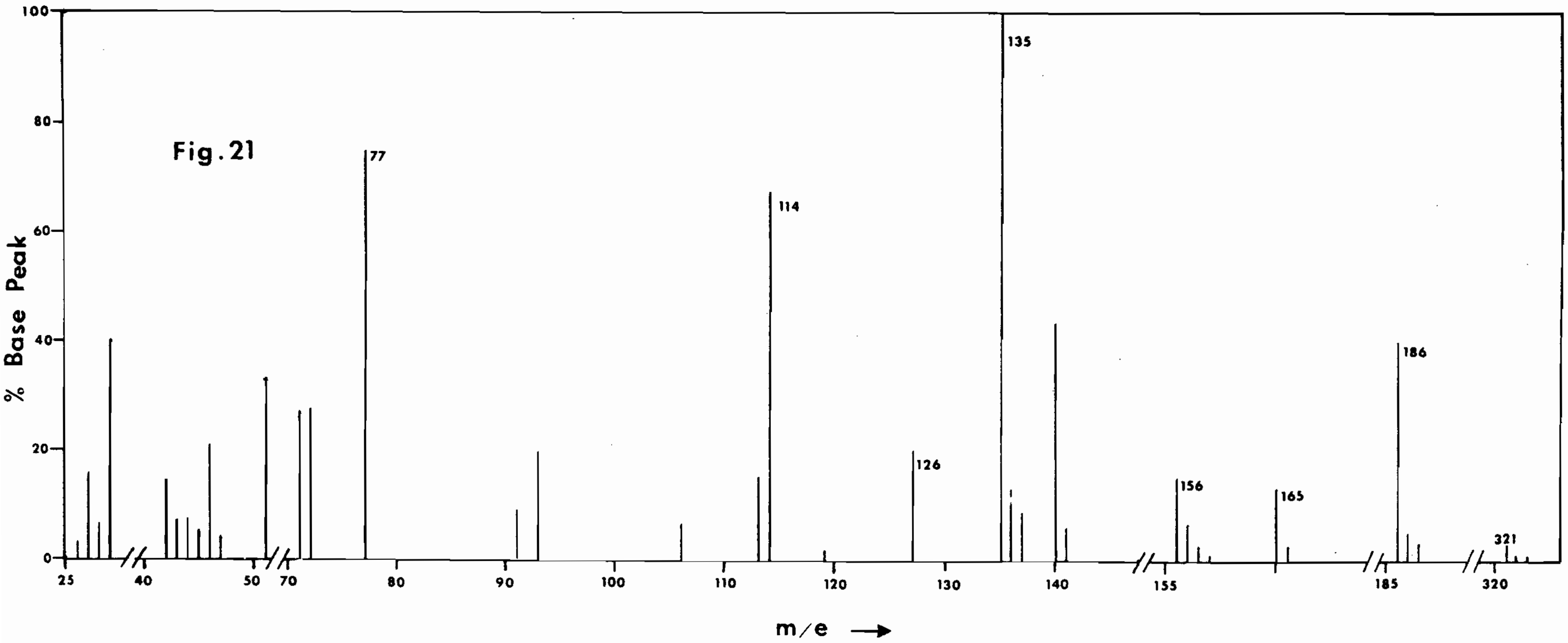


Fig. 21

% Base Peak
100
80
60
40
20
0
25
40
50
70
80
90
100
110
120
130
140
155
185
320
m/e →
77
114
126
135
156
165
186
321

FIGURE 22

Mass Spectrum of O-Ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)-isourea (21).

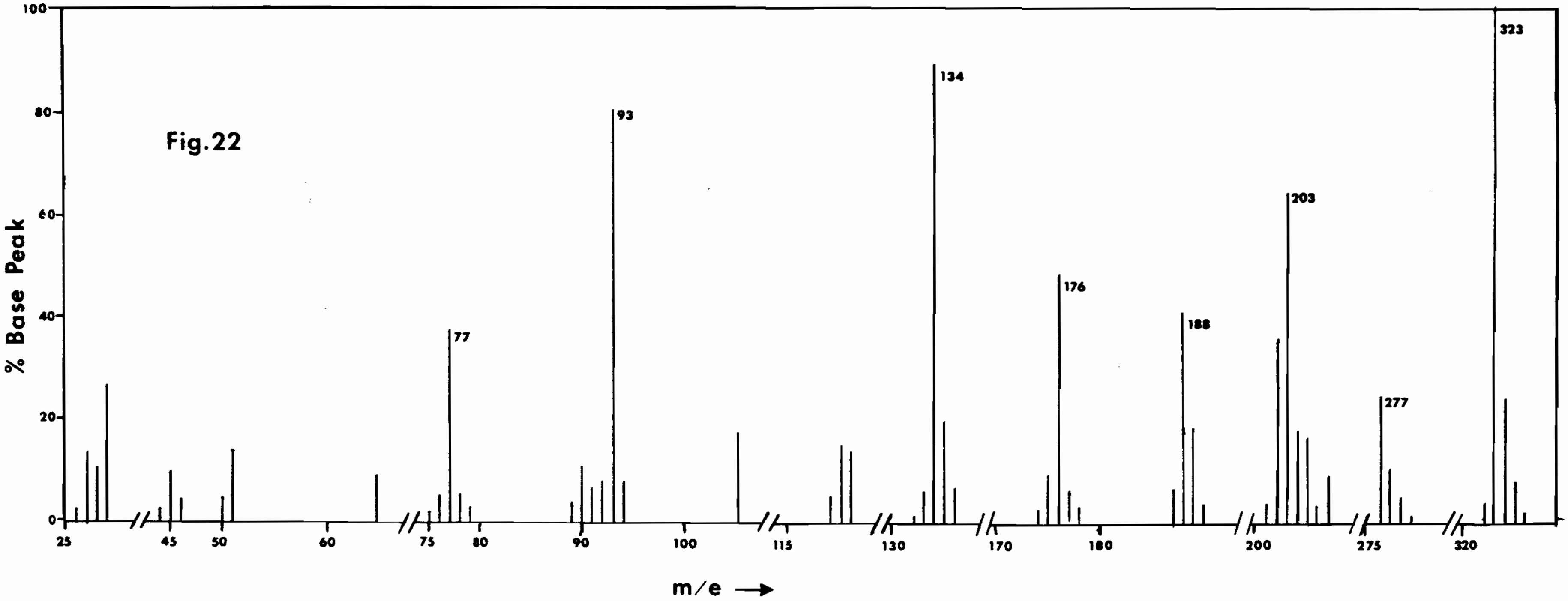
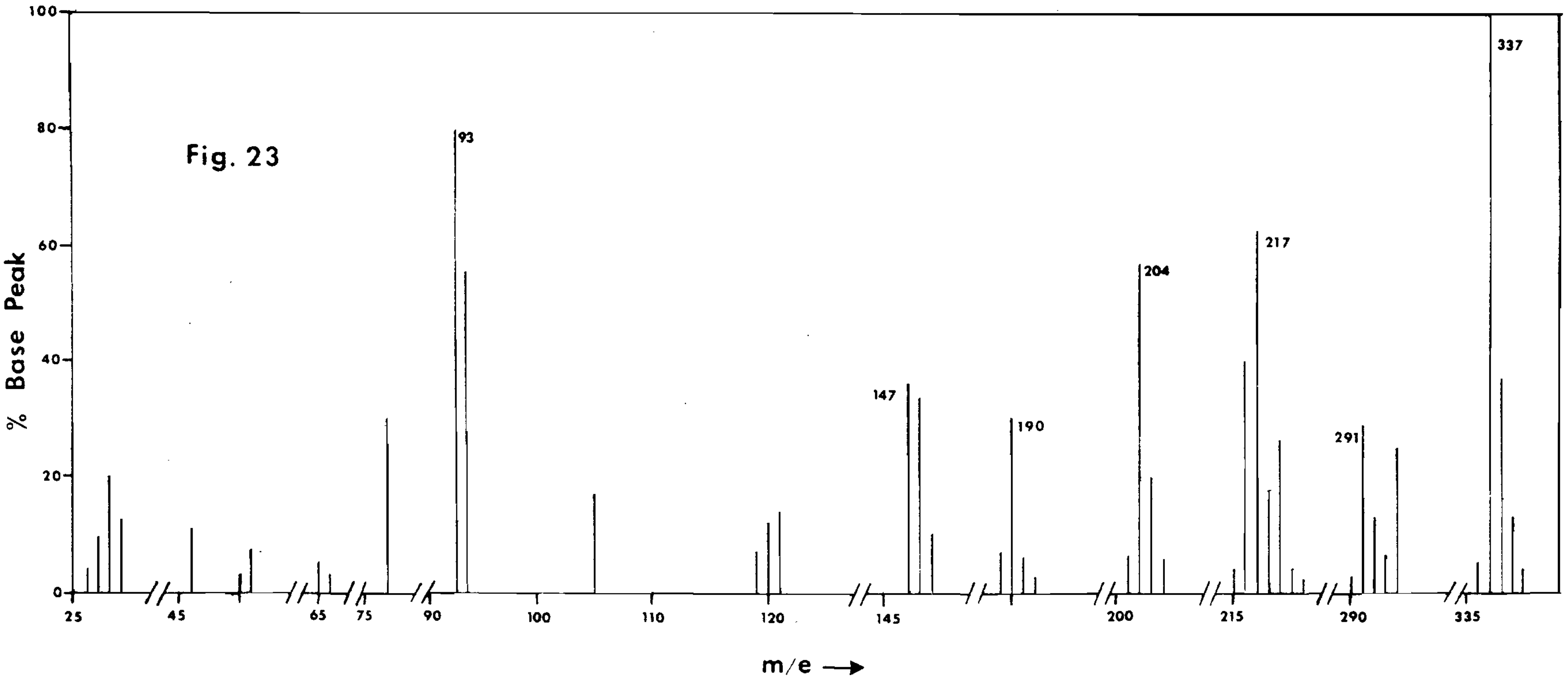

100
80
60
40
20
0
% Base Peak
25
45
50
60
75
80
90
100
115
130
170
180
200
275
320
m/e →
77
93
134
176
188
203
277
323

Fig.22

FIGURE 23

Mass Spectrum of O-Ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23).

Fig. 23



100
80
60
40
20
0
% Base Peak
93
147
190
204
217
291
337
25
45
65
75
90
100
110
120
145
200
215
290
335
m/e →

FIGURE 24

Mass Spectrum of N-Phenyl-N',N''-di-(4-methyl-2-thiazolyl)-guanidine (9).

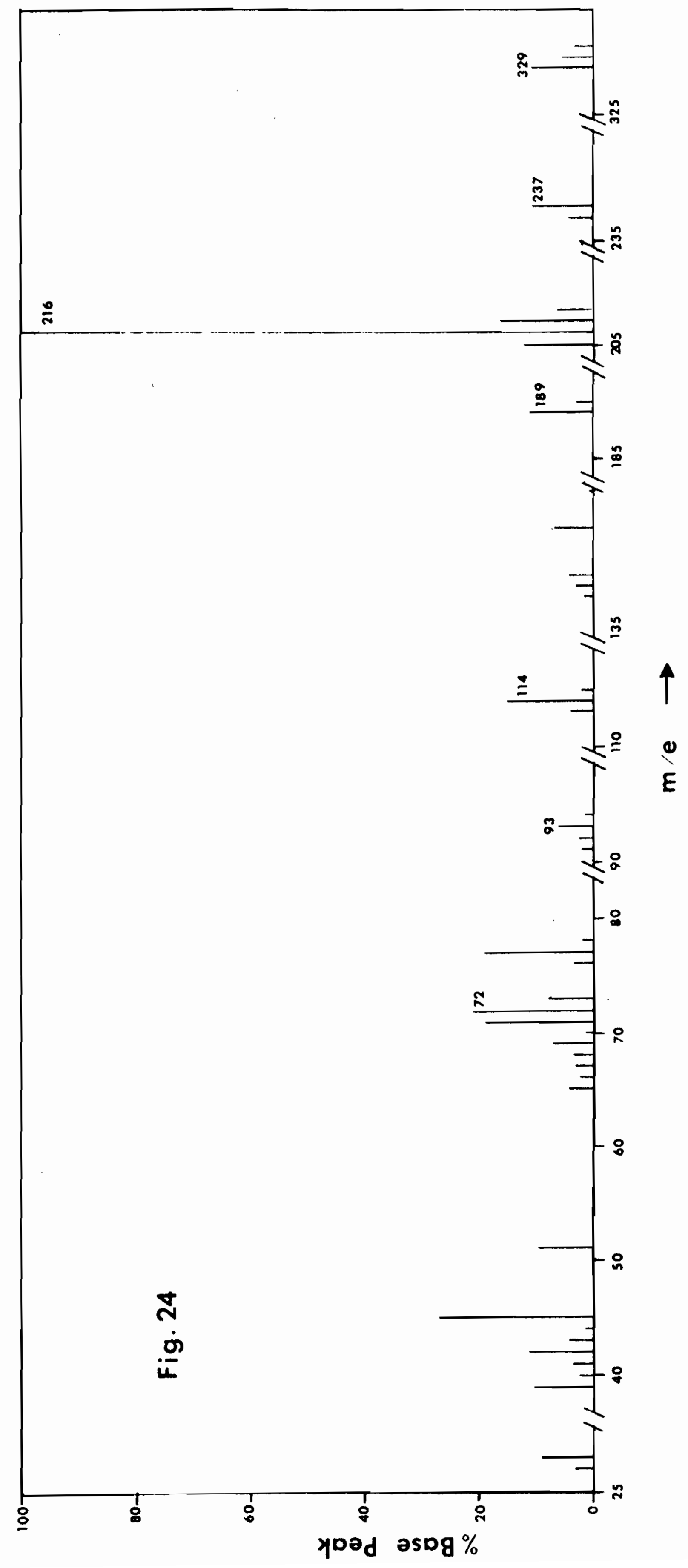


Fig. 24

% Base Peak
100
80
60
40
20
0
m/e →
25
40
50
60
70
80
90
110
135
185
205
235
325
72
93
114
189
216
237
329

FIGURE 25

Mass Spectrum of N-(5-Bromo-2-pyridyl)thiourea (33).

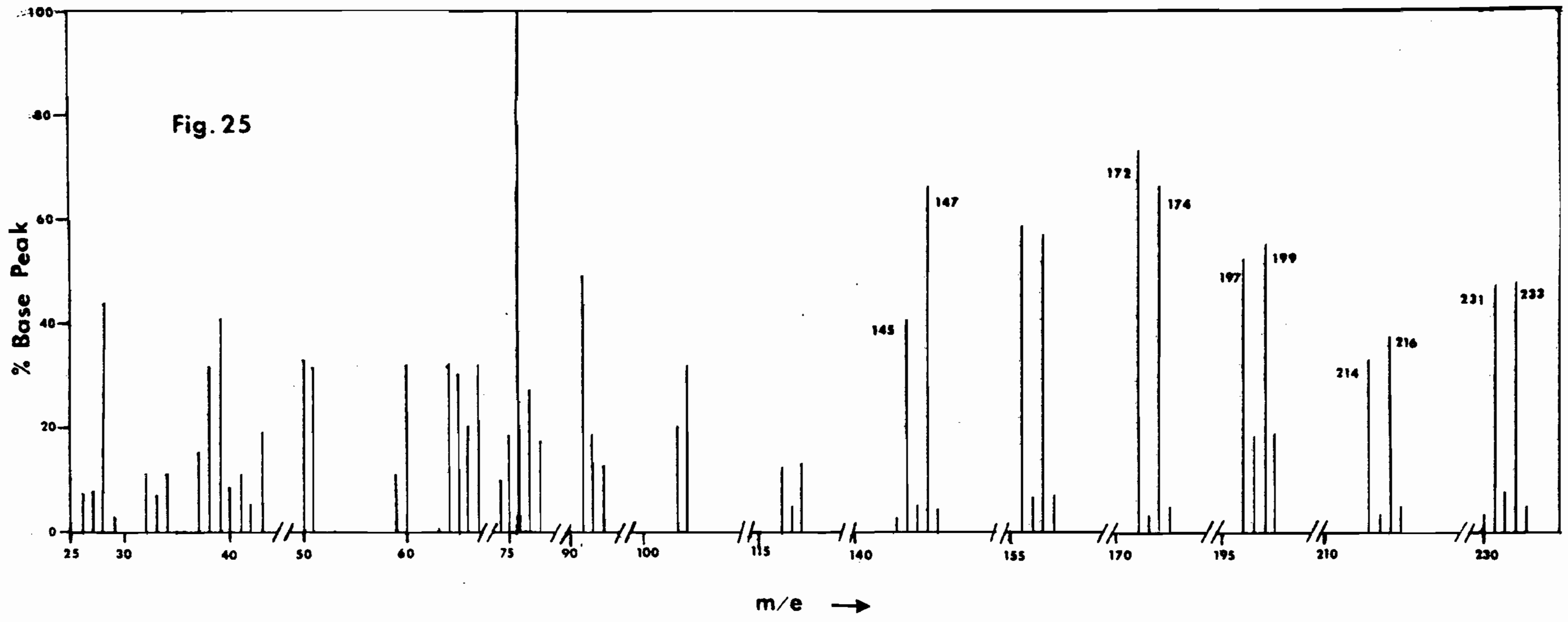


Fig. 25

% Base Peak
100
80
60
40
20
0
25
30
40
50
60
75
90
100
115
140
155
170
195
210
230
m/e →
145
147
172
174
197
199
214
216
231
233

EXPERIMENTAL

1. The melting points were determined on a Gollenkamp melting point apparatus and are corrected.

2. The i.r. spectra were recorded in potassium bromide pellets using a Perkin-Elmer Model 521 grating spectrophotometer.

3. The u.v. spectra were obtained on an Unicam SP-800 spectrophotometer using absolute ethanol as solvent.

4. The n.m.r. spectra were determined on a Varian High Resolution Nuclear Magnetic Resonance Model HA-100 Spectrometer. Solvents used were deuteriochloroform ($CDCl_3$) and dimethyl sulfoxide-d_6 (DMSO-d_6). Tetramethylsilane (TMS) was used as an internal reference (TMS = δ 0.000).

5. The low resolution mass spectra were taken on an Hitachi RMU-6 mass spectrometer and others on an AEI-MS-902 mass spectrometer. High resolution exact mass measurements were also taken on some of the compounds using the AEI-MS-902 double focusing mass spectrometer.

6. The elemental analyses were carried out by Dr. C. Dassle, Montreal and Dr. A. Bernhardt, Germany. The high resolution exact mass measurements were recorded in place of some elemental analyses.

EXPERIMENTAL

A. SYNTHESIS OF N-PHENYL-N'-2-THIAZOLYLTHIOUREAS

1. Preparation of N-phenyl-N'-2-thiazolylthiourea (5)

The general procedure given by Buu-Hoi et al. (3) for the synthesis of arylthioureas was followed to prepare N-phenyl-N'-2-thiazolylthiourea (5) in quantitative yield from 2-aminothiazole and phenyl isothiocyanate; pale yellow crystals from ethanol, m.p. 176-8°; lit. value: 178.5° (3).

2. Preparation of N-phenyl-N'-(4-methyl-2-thiazolyl)-thiourea (6)

Heating 2-amino-4-methylthiazole and phenyl isothiocyanate for 0.75 h afforded an 89% yield of N-phenyl-N'-(4-methyl-2-thiazolyl)thiourea (6). Recrystallization from ethanol gave short beige needles of 6, m.p. 171-2°; lit. value: 174-5° (3).

3. Preparation of N-phenyl-N'-(4-phenyl-2-thiazolyl)-thiourea (7)

(a) The procedure given by Dobson and King (51) was used to prepare 2-amino-4-phenylthiazole (15a) in 75% yield from acetophenone, thiourea and iodine. Long beige needles of

15a were obtained from benzene, m.p. 146-8°; lit. value: 151-2° (51).

(b) Heating 2-amino-4-phenylthiazole (15a) with a slight excess of phenyl isothiocyanate for 1.5 h gave N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) in 56.6% yield. Recrystallization from ethanol produced small beige needles, m.p. 205-6°; lit. value: 209.5° (3).

4. Preparation of N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8)

(a) The method of Dobson and King (46) was followed to prepare 2-amino-5-methyl-4-phenylthiazole (15b) in quantitative yield from a slurry of propiophenone, thiourea and iodine. Beautiful white needles of 15b were obtained from benzene, m.p. 122-4°; lit. value: 116-8° (51).

(b) A mixture of 2-amino-5-methyl-4-phenylthiazole (15b) (9.5 g; 0.05 mol) and phenyl isothiocyanate (6.75 g; 0.05 mol) was refluxed in 5 ml absolute ethanol for 0.75 h. A product solidified in the reaction flask. It was scraped out, washed with ether and then a small amount of dilute hydrochloric acid was added to remove unreacted amine and isothiocyanate. The product was then recrystallized from a mixture of ethanol/acetone to give 6 g of small, white needles of N-phenyl-N'-

(5-methyl-4-phenyl-2-thiazolyl)thiourea (8), m.p. 209-10°. Concentration of the mother liquor furnished 2.2 g more of fluffy white needles. The total yield amounted to 65.1%.

Anal. calcd. for $C_{17}H_{15}N_3S_2$: C, 62.7; H, 4.7; N, 12.9.

Found: C, 63.0; H, 4.6; N, 12.8.

B. SYNTHESIS OF N-PHENYL-N'-2-THIAZOLYLGUANIDINES BY DESULFURIZATION OF N-PHENYL-N'-2-THIAZOLYLTHIOUREAS WITH LEAD OXIDE

1. Preparation of N-phenyl-N',N''-di-(2-thiazolyl)-guanidine (11)

A mixture of finely powdered N-phenyl-N'-2-thiazolylthiourea (5) (2.35 g; 0.01 mol) and yellow lead oxyde (4.5 g) was suspended in dry benzene (50 ml) and refluxed for 20 minutes. The black lead sulfide was filtered off from the hot solution and extracted with fresh boiling benzene. The combined filtrate and benzene extract was partially evaporated and then left to stand. A pale yellow solid was deposited which gave, after recrystallization from benzene, 0.684 g (45%) of small beige crystals of N-phenyl-N',N''-di-(2-thiazolyl)guanidine (11), m.p. 152-3° (decomp.).

Anal. calcd. for $C_{13}H_{14}N_5S_2$: C, 51.8; H, 3.7; N, 23.2.

Found: C, 51.6; H, 3.4; N, 23.2.

When 5 was desulfurized in the presence of 2-aminothiazole, a 16.8% yield of 11 was obtained as well as a 48% recovery of 2-aminothiazole.

2. Preparation of N,N′-diphenyl-N″-2-thiazolylguanidine (14)

(a) By desulfurization of N-phenyl-N′-2-thiazolylthiourea (5) in the presence of aniline

To a mixture of finely powdered 5 (2.0 g; 8.5 mmol), yellow lead oxide (4.7 g) and a little of anhydrous sodium sulfate suspended in dry benzene (75 ml) was added aniline (0.83 g; 8.9 mmol). After a ten-minute reflux, the mixture was filtered to remove the black lead sulfide and then refluxed for two h more. After work-up, 0.333 g (13.4%) of N,N′-diphenyl-N″-2-thiazolylguanidine (14) was collected; shiny beige crystals from benzene, m.p. 151-2°.

Anal. calcd. for $C_{16}H_{14}N_4S$: C, 65.3; H, 4.8; N, 19.0.

Found: C, 65.6; H, 4.9; N, 18.9.

(b) By treatment of S-methyl-N-phenyl-N′-2-thiazolylisothiourea (5a) with mercuric chloride in the presence of aniline

S-Methyl-N-phenyl-N′-2-thiazolylisothiourea (5a) was obtained in quantitative yield from N-phenyl-N′-2-thiazolylthiourea (5) and methyl iodide in absolute ethanol according to the procedure of Klayman and Shrine (133)

To a solution of 5a (4.4 g; 17.8 mmol) in dimethylformamide (10 ml) and aniline (0.36 g; 0.04 mol) was added a solution of mercuric chloride (1.04 g) in dimethylformamide (15 ml). A white solid immediately precipitated. The reaction mixture was kept at 50-70° for 31 h, then filtered and the precipitate washed with dimethylformamide. The filtrate was poured into a dilute sodium hydroxide solution (0.143 g in 100 ml water). A creamy white solid precipitated. Recrystallization from ethanol gave N,N'-diphenyl-N''-2-thiazolylguanidine (14) as a beige solid, m.p. 151-2°.

3. Preparation of N-phenyl-N',N''-di-(4-methyl-2-thiazolyl)-guanidine (9)

Refluxing and work-up of a suspension of N-phenyl-N'-(4-methyl-2-thiazolyl)thiourea (6) (2.5 g; 0.01 mol) and yellow lead oxide (0.241 g) in dry benzene (50 ml) gave 0.241 g (14.5%) of a yellow solid which gave beautiful yellow needles of N-phenyl-N',N''-di-(4-methyl-2-thiazolyl)guanidine (9) from ethanol, m.p. 118-9°.

Anal. calcd. for $C_{15}H_{15}N_5S_2$: C, 54.7; H, 4.6; 21.3.

Found: C, 54.6; H, 4.6; N, 21.2.

Desulfurization of 6 in the presence of excess 2-

amino-4-methylthiazole gave a 34.8% yield of 9.

4. Preparation of N,N'-diphenyl-N"-(4-methyl-2-thiazolyl)-guanidine (10)

Yellow lead oxide (4.8 g) was added in portions to a benzene suspension (75 ml) of N-phenyl-N'-(4-methyl-2-thiazolyl)-thiourea (6) (2.7 g; 10.7 mmol) and excess aniline (1.1 g; 11.8 mmol). After work-up, 1.996 g (48.1%) of N,N'-diphenyl-N"-(4-methyl-2-thiazolyl)guanidine (10). Recrystallization from ethanol furnished beige needles of 10, m.p. 122-3°.

Anal. calcd. for $C_{17}H_{16}N_4S$: C, 66.2; H, 5.2; N, 18.2.

Found: C, 65.9; H, 5.2; N, 18.4.

5. Preparation of N-phenyl-N',N"-di-(4-phenyl-2-thiazolyl)-guanidine (12)

By following the procedure given for 9, N-phenyl-N',N"-di-(4-phenyl-2-thiazolyl)guanidine (12) was obtained in 53% yield from N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) and yellow lead oxide as a flocculent white solid. Recrystallization from ethanol afforded short white needles of 12, m.p. 210-2°.

Anal. calcd. for $C_{25}H_{19}N_5S_2$: C, 66.2; H, 4.2; N, 15.4.

Found: C, 65.8; H, 3.9; N, 15.7.

Desulfurization of 7 in the presence of 2-amino-4-phenylthiazole gave a 66.4% yield of 12.

6. Preparation of N,N'-diphenyl-N''-(4-phenyl-2-thiazolyl)-guanidine (16)

By desulfurization of N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) with yellow lead oxide in the presence of excess aniline, a 44% yield of N,N'-diphenyl-N''-(4-phenyl-2-thiazolyl)guanidine (16) as a grey solid was obtained. Recrystallization from an ethanol/benzene mixture afforded short beige needles of 16, m.p. 151°.

Anal. calcd. for $C_{22}H_{18}N_4S$: C, 71.3; H, 4.9; N, 15.1.

Found: C, 70.9; H, 5.2; N, 15.0.

7. Preparation of N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13)

Desulfurization of N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8) with yellow lead oxide in the usual fashion gave N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)-guanidine (13) in 40.4% yield. Recrystallization from ethanol gave pale yellow crystals of 13, m.p. 206-7°.

Anal. calcd. for $C_{27}H_{23}N_5S_2$: C, 67.3; H, 4.8; N, 14.6.

Found: C, 67.4; H, 4.7; N, 14.8.

Desulfurization of 8 in the presence of 2-amino-5-methyl-4-phenylthiazole (15b) gave 13 in 56% yield.

8. Preparation of N,N'-diphenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17)

A mixture of N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)-thiourea (8), yellow lead oxide and aniline gave, after work-up, an orange residue which crystallized within a few minutes to a white solid (72.3%). Recrystallization from an ethanol/benzene mixture gave beige crystals of N,N'-di-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17), m.p. 164-5°.

Anal. calcd. for $C_{23}H_{20}N_4S$: C, 71.8; H, 5.2; N, 14.6.

Found: C, 71.8; H, 5.1; N, 14.5.

C. SYNTHESIS OF N-CARBETHOXY-N'-PHENYL-N-2-THIAZOLYLTHIOUREAS AND O-ETHYL-N-PHENYL-N'-2-THIAZOLYLISOUREAS BY TREATMENT OF N-PHENYL-N'-2-THIAZOLYLTHIOUREAS WITH ETHYL CHLOROFORMATE

1. Preparation of N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19)

To a suspension of N-phenyl-N'-2-thiazolylthiourea (5) (2.8 g; 11.8 mmol) and triethylamine (2.4 g; 24 mmol) in chloroform (50 ml), cooled to -10° by an acetone-Dry Ice bath, was added dropwise ethyl chloroformate (1.3 g; 12 mmol). During the addition, the mixture became intense yellow. It was stirred with cooling for 0.5 h, then gradually warmed to room temperature and stirred for an additional 4 h.

Ether was added and the precipitated triethylamine hydrochloride filtered off. The filtrate was evaporated and the oily orange residue solidified upon standing into cream-colored crystals (1.37 g; 37.8% yield) of N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (<u>19</u>) m.p. 94-5° (ethanol).

If an excess of ethyl chloroformate was used, beautiful colorless needles of ethyl N-2-thiazolylcarbamate (<u>18</u>) were obtained, identified by the comparison of m.m.p., thin layer chromatography and i.r. spectrum with an authentic sample. The yield of <u>18</u> was 52%.

Anal. calcd. for $C_{13}H_{13}N_3O_2S_2$: C, 50.8; H, 4.3;
N, 13.7; S, 20.9.

Found: C, 50.5; H, 4.3; N, 13.9; S, 21.0.

Calculated mass from exact mass measurement: 307.043218

Calculated mass for $C_{13}H_{13}N_3O_2S_2$: 307.044916

Delta mass: 0.001698

2. Preparation of N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20)

To a mixture of N-phenyl-N'-(4-methyl-2-thiazolyl)-

thiourea (6) (2.0 g; 8.1 mmol), triethylamine (2.6 g; 16.2 mmol) in cooled chloroform (50 ml) was added gradually ethyl chloroformate (0.88 g; 8.1 mmol). The mixture was stirred for 4 h and worked-up as described for 19 to give 0.960 g (37%) of a pale yellow solid. Recrystallization from ethanol gave beige plates of N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20), m.p. 141-3°.

Anal. calcd. for $C_{14}H_{15}N_3O_2S_2$: C, 52.3; H, 4.7; N, 13.1; S, 20.0.

Found: C, 52.5; H, 4.7; N, 13.2; S, 19.9.

Calculated mass from exact mass measurement: 321.059599

Calculated mass for $C_{14}H_{15}N_3O_2S_2$: 321.060565

Delta mass: 0.000966

3. Preparation of O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21)

Ethyl chloroformate (0.65 g; 6 mmol) was added to an ice-cooled chloroform solution (50 ml) of N-phenyl-N'-(4-phenyl-2-thiazolyl)thiourea (7) (1.88 g; 6 mmol) and triethylamine (1.2 g; 12 mmol). The yellow mixture was stirred for 2 h, then left to stand overnight. After the usual work-up, a white solid was obtained, insoluble in water and cold ethanol, but soluble in benzene. A total yield of 0.825 g (42.4%) was obtained of O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21), affording cream-colored needles from ethanol, m.p. 101-2°.

Anal. calcd. for $C_{18}H_{17}N_3OS$: C, 66.9; H, 5.2; N, 13.0; S, 9.1.

Found: C, 67.2; H, 5.1; N, 12.8; S, 9.6.

Calculated mass from exact mass measurement:	323.109729
Calculated mass for $C_{18}H_{17}N_3OS$:	323.109227
Delta mass :	-0.000502

4. Preparation of O-ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23)

A mixture of N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8) (2.30 g; 7.1 mmol), triethylamine (1.47 g; 14.5 mmol) and ethyl chloroformate (0.78 g; 7.2 mmol) in ice-cooled chloroform (50 ml) was stirred for 2 h and worked-up as usual. The solid residue was dissolved in ethanol. A small amount (0.131 g) of insoluble material was filtered off as a beige crystalline solid, m.p. 201-2°, identified as N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13).

From the ethanol filtrate crystallized small pale yellow needles (13% yield), m.p. 96-8°, of O-ethyl-N-phenyl-

N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23).

Anal. calcd. for $C_{18}H_{19}N_3OS$: C, 67.6; H, 5.6;
N, 12.5; S, 9.5.

Found: C, 67.1; H, 5.3; N, 12.5; S, 9.5.

Calculated mass from exact mass measurement:	337.123569
Calculated mass for $C_{18}H_{19}N_3OS$:	337.124877
Delta mass:	0.001307

Concentration of the ethanol filtrate yielded a third product as a pale yellow crystalline solid. Recrystallization from ethanol furnished colorless crystals of ethyl N-(5-methyl-4-phenyl-2-thiazolyl)carbamate (22), m.p. 132-3°, in 30.9% yield.

Anal. calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.4; N, 10.7.

Found: C, 58.9; H, 5.5; N, 10.9.

The mass spectrum of 22 gave a molecular ion of m/e 262 as expected for $C_{13}H_{14}N_2O_2S$ with the expected fragments associated with a thiazolylcarbamate.

5. Preparation of N-carbethoxy-N,N'-diphenylthiourea (25)

A mixture of N,N'-diphenylthiourea (24) (3.7 g; 24 mmol) and triethylamine (4.8 g; 48 mmol) in cooled chloroform (75 ml) was treated in the usual manner with ethyl chloroformate (2.6 g; 24 mmol). Work-up gave a first crop of beige crystals, m.p. 137-40°, identified with starting material 24 by thin-layer chromatography. The residual pale orange liquid solidified on standing 1 h in the ice-box to give 1.623 g (33%) of white, crystalline N-carbethoxy-N,N'-diphenylthiourea (25) which gave colorless crystals from ethanol, m.p. 99-100°.

Anal. calcd. for $C_{16}H_{16}N_2O_2S$: C, 64.0; H, 5.4; N, 9.3; S, 10.7.

Found: C, 63.6; H, 5.3; N, 9.4; S, 10.8.

A trial run on a 10 g quantity yielded diphenylcarbodiimide as the major product, although all other trials on smaller quantities gave only 25.

D. SYNTHESIS OF MONOPYRIDYLTHIOUREAS

1. Preparation of N-2-pyridylthiourea (26)

(a) N-Benzoyl-N'-2-pyridylthiourea (35)

This compound was prepared according to the method described by Taurins and Blaga (6) from ammonium thiocyanate, benzoyl chloride and 2-aminopyridine. A bright yellow precipitate of N-benzoyl-N'-2-pyridylthiourea (35) was isolated in quantitative yield. Recrystallization from dilute ethanol furnished long pale yellow needles of 35, m.p. 140-1°; lit. value: 144° (7).

(b) N-2-Pyridylthiourea (26)

As described by Charonnat and Le Perdriel (7), a mixture of N-benzoyl-N'-2-pyridylthiourea (35) and 10% sodium hydroxide solution was refluxed for 5 minutes to give, on cooling, colorless crystals of N-2-pyridylthiourea (26) in 87% yield. Thin colorless plates were obtained from dilute ethanol, m.p. 146.5-147.5°; lit. value: 147° (7).

2. Preparation of N-3-pyridylthiourea (27)

(a) N-Benzoyl-N'-3-pyridylthiourea (36)

An 85% yield of N-benzoyl-N'-3-pyridylthiourea (36) was obtained from ammonium thiocyanate, benzoyl chloride and 3-aminopyridine. Recrystallization of 36 from 75% ethanol afforded small, colorless crystals, m.p. 168-9°; lit value: 165-165.5° (6).

(b) N-3-Pyridylthiourea (27)

The procedure outlined by Taurins and Blaga (6) was followed to prepare N-3-pyridylthiourea (27). A mixture of N-benzoyl-N'-3-pyridylthiourea (36) and 2.5 N sodium hydroxide solution was refluxed for 15 minutes, cooled and filtered. The filtrate was acidified with dilute hydrochloric acid, made alkaline with ammonium hydroxide and allowed to stand overnight. An 85% yield of colorless crystals of 27 was obtained, m.p. 154-5° (ethanol); lit. value: 153.5-154° (6).

3. Preparation of N-(3-methyl-2-pyridyl)thiourea (28)

(a) N-Benzoyl-N'-(3-methyl-2-pyridyl)thiourea (37)

The method used for 35 was followed to prepare N-benzoyl-N'-(3-methyl-2-pyridyl)thiourea (37) in 62% yield from ammonium thiocyanate, benzoyl chloride and 2-amino-3-methylpyridine. Small, yellow crystals of 37 were obtained from aqueous ethanol, m.p. 125-6°.

Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 62.0; H, 4.8; N, 15.5; S, 11.8.

Found: C, 62.1; H, 4.9; N, 15.4; S, 12.0.

(b) N-(3-Methyl-2-pyridyl)thiourea (28)

Hydrolysis of N-benzoyl-N'-(3-methyl-2-pyridyl)thiourea (37) with 10% sodium hydroxide solution, as described for 26, gave N-(3-methyl-2-pyridyl)thiourea (28) in 89% yield. Small, colorless crystals of 28 melted at 153-4° (ethanol); lit. value: 115° (57).

Anal. calcd. for $C_7H_9N_3S$: C, 50.3; H, 5.4; N, 25.1.

Found: C, 50.3; H, 5.5; N, 25.2.

4. Preparation of N-(4-methyl-2-pyridyl)thiourea (29)

(a) N-Benzoyl-N'-(4-methyl-2-pyridyl)thiourea (38)

A 44% yield of N-benzoyl-N'-(4-methyl-2-pyridyl)thiourea (38) was obtained from 2-amino-4-methylpyridine, ammonium thiocyanate and benzoyl chloride. Recrystallization of 38 furnished pale yellow needles melting at 161-2°.

Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 62.0; H, 4.8;
N, 15.5; S, 11.8.

Found: C, 62.2; H, 5.1; N, 15.6; S, 11.8.

(b) N-(4-Methyl-2-pyridyl)thiourea (29)

Hydrolysis of N-benzoyl-N'-(4-methyl-2-pyridyl)thiourea (38) with 10% NaOH afforded a quantitative yield of N-(4-methyl-2-pyridyl)thiourea (29), m.p. 216-7° (ethanol); lit. value: 214° (8).

5. Preparation of N-(5-methyl-2-pyridyl)thiourea (30)

(a) N-Benzoyl-N'-(5-methyl-2-pyridyl)thiourea (39)

By treatment of 2-amino-5-methylpyridine with ammonium thiocyanate and benzoyl chloride, an 82.3% yield of N-benzoyl-N'-(5-methyl-2-pyridyl)thiourea (39) was obtained, as colorless needles, m.p. 162-3° (ethanol).

Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 62.0; H, 4.8;
N, 15.5; S, 11.8.

Found: C, 62.2; H, 4.7; N, 15.4; S, 11.7.

(b) N-(5-Methyl-2-pyridyl)thiourea (30)

A quantitative yeild of N-(5-methyl-2-pyridyl)thiourea (30) was obtained by the hydrolysis of 39 with 10% sodium hydroxide solution. Large colorless crystals of 30 melted at 198-9° (dilute ethanol).

Anal. calcd. for $C_7H_9N_3S$: C, 50.3; H, 5.4; N, 25.1.

Found: C, 50.5; H, 5.5; N, 25.1.

6. Preparation of N-(6-methyl-2-pyridyl)thiourea (31)

(a) N-Benzoyl-N'-(6-methyl-2-pyridyl)thiourea (40)

A 75.4% yield of N-benzoyl-N'-(6-methyl-2-pyridyl)-thiourea (40) was obtained from the treatment of 2-amino-6-methylpyridine with ammonium thiocyanate and benzoyl chloride. Yellow crystals of 40 melted at 135-6° (ethanol).

Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 62.0; H, 4.8;
N, 15.5; S, 11.8.

Found: C, 62.1; H, 4.7; N, 15.3; S, 11.7.

(b) N-(6-Methyl-2-pyridyl)thiourea (31)

From the hydrolysis of 40 by a 10% sodium hydroxide solution, a quantitative yield of N-(6-methyl-2-pyridyl)-thiourea (31) was obtained. White crystalline 31 melted at 194-5° (ethanol); lit. value: 170° (5).

Anal. calcd. for $C_7H_9N_3S$: C, 50.3; H, 5.4; N, 25.1.

Found: C, 50.4; H, 5.0; N, 25.3.

7. Preparation of N-(4,6-dimethyl-2-pyridyl)thiourea (32)

(a) N-Benzoyl-N'-(4,6-dimethyl-2-pyridyl)thiourea (41)

Treatment of 2-amino-4,6-dimethylpyridine with ammonium thiocyanate and benzoyl chloride afforded N-benzoyl-N'-(4,6-dimethyl-2-pyridyl)thiourea (41) in 72.3% yield. Pale yellow needles of 41 melted at 145-6° (aqueous ethanol).

Anal. calcd. for $C_{15}H_{15}N_3OS$: C, 63.1; H, 5.3;
N, 14.7; S, 11.2.

Found: C, 62.8; H, 5.5; N, 14.8; S, 11.5.

(b) N-(4,6-Dimethyl-2-pyridyl)thiourea (32)

Hydrolysis of 41 with 10% sodium hydroxide solution produced a quantitative yield of N-(4,6-dimethyl-2-pyridyl)-

thiourea (32), as cream-colored needles, m.p. 245-7° (ethanol/glacial acetic acid).

Anal. calcd. for $C_8H_{11}N_3S$: C, 53.0; H, 6.1; N, 23.2.

Found: C, 52.9; H, 6.5; N, 23.2.

8. Preparation of 2,6-dithioureidopyridine (34)

(a) 2,6-Dibenzoylthioureidopyridine (43)

By treatment of 2,6-diaminopyridine with two molar equivalents of ammonium thiocyanate and benzoyl chloride, a 79.3% yield of 2,6-dibenzoylthioureidopyridine (43) was obtained. Recrystallization of 43 from boiling glacial acetic acid gave colorless crystals melting 221-2°.

Anal. calcd. for $C_{21}H_{17}N_5O_2S_2$: C, 57.9; H, 3.9;
N, 16.1; S, 14.7.

Found: C, 58.3; H, 3.9; N, 16.4; S, 14.9.

(b) 2,6-Dithioureidopyridine (34)

Hydrolysis of 43 with 10% sodium hydroxide solution afforded 2,6-dithioureidopyridine (34) in 49% yield, m.p. 260-2°

Calculated mass from exact mass measurement:	227.0301
Calculated mass for $C_7H_9N_5S_2$:	227.0299
Delta mass:	-0.0002

9. Preparation of N-(5-bromo-2-pyridyl)thiourea (33)

(a) N-Benzoyl-N'-(5-bromo-2-pyridyl)thiourea (42)

Treatment of 2-amino-5-bromopyridine with ammonium thiocyanate and benzoyl chloride gave an 83% yield of N-benzoyl-N'-(5-bromo-2-pyridyl)thiourea (42) as small white needles, m.p. 154° (ethanol).

Anal. calcd. for $C_{13}H_{10}BrN_3OS$: C, 46.4; H, 3.0; Br, 23.8; N, 12.5; S, 9.5.

Found: C, 46.5; H, 3.2; Br, 23.7; N, 12.4; S, 9.5.

(b) N-(5-Bromo-2-pyridyl)thiourea (33)

Heating 42 with 10% sodium hydroxide solution for 1.5 h gave N-(5-bromo-2-pyridyl)thiourea (33) as yellow prisms from ethanol, m.p. 238°.

Calculated mass from exact mass measurement:	230.94660
Calculated mass for $C_6H_6BrN_3S$:	230.94663
Delta mass:	0.00003

E. REACTION OF MONOPYRIDYLTHIOUREAS WITH BROMINE

1. Treatment of N-2-pyridylthiourea (26) with bromine

To N-2 pydirylthiourea (26) (1,576 g; 10.2 mmol) dissolved in ethanol (45 ml) was added slowly a solution of bromine (1.65 g; 10.3 mmol) in ethanol (7 ml). A cream-colored solid precipitated immediately. The mixture was stirred for 15 minutes and then filtered to remove 1.072 g of product (44a), m.p. 224-5°. The filtrate was treated further with bromine (1.65 g) to yield another 1.027 g of white crystals, m.p. 232-3° (dec.) (ethanol).

A total yield of 83.6% of 2-amino [1,2,4]thiadiazolo[2,3-a]pyridinium bromide (44a) was obtained. If left to stand, the mother liquor deposited long yellow needles of sulfur, m.p. 116-7°.

Anal. calcd. for $C_6H_6BrN_3S$: N, 18.1; Br, 34.4.

Found: N, 17.8; Br, 34.2.

Treatment of 26 with bromine in the presence of triethylamine

A solution of bromine (1.1 g; 6.9 mmol) in acetonitrile (12 ml) was added slowly to N-2-pyridylthiourea (26)

(1.067 g; 6.9 mmol) dissolved in acetonitrile (100 ml) in the presence of triethylamine (1.4 g; 13.8 mmol). The colorless solution soon became yellow, precipitating a beige solid which was filtered (0.066 g) m.p. 261-3°.

Ether was added to precipitate triethylamine hydrobromide which was filtered. Concentration of the filtrate gave 0.464 g (55%) of 2-pyridylcyanamide (45), m.p. 153-4° (chloroform/ethanol), identified by comparison of the i.r. spectra with an authentic sample. A yield of 39% of 45 was obtained if chloroform was used as solvent.

2. Treatment of N-3-pyridylthiourea (27) with bromine

N-3-Pyridylthiourea (27) (1.89 g; 12.2 mmol) dissolved in ethanol (65 ml) was treated with bromine (1.97 g; 12.2 mmol). The reaction mixture was partially evaporated and left to stand in the ice-box overnight. A white crystalline solid (1.564 g) was collected, m.p. 177-8° (ethanol).

Treatment of the filtrate with additional bromine (1.97 g; 12.2 mmol) afforded a second product (0.285 g), m.p. 235-6° (ethanol).

This product appears to be a 3-pyridylguanidine sulfide (46) since its mass spectrum showed an important ion of m/e 270.

The calculated values for 46 if it contains three bromine atoms are for $C_{12}H_{15}Br_3N_6S$: C, 28.0; H, 2.9; N, 16.3. The elemental analysis gave: C, 27.3; H, 3.2; N, 16.1.

F. SYNTHESIS OF AMINOPYRIDINE 1-OXIDES THIOCYANATES

1. Attempted preparation of N-4-pyridylthiourea 1-oxide (47)

The method outlined by Gardner et al. (66) was followed in an attempt to prepare N-4-pyridylthiourea 1-oxide (47).

(a) Preparation of 4-aminopyridine 1-oxide hydrochloride (47a)

4-Aminopyridine (9.4 g; 0.1 mol) was treated with excess acetic anhydride (25 ml) on the water bath for 1 h. Water was then added to destroy the excess acetic anhydride and the volatile material evaporated under reduced pressure. The residual oil crystallized immediately upon standing to give a 90.4% yield of 4-acetamidopyridine.

The crude 4-acetamidopyridine was dissolved in glacial acetic acid (33 ml) and carefully treated with 40% peracetic acid (18 ml) under cooling. The resulting mixture was heated at 50-60° for 3 h, then at 65-70° for 4 h. The solvents were evaporated to give 4-acetamidopyridine 1-oxide as long pale yellow needles in quantitative yield. This product was hydrolyzed with 3N HCl at 100° for 4 h. The reaction mixture was evaporated till dry, and the residue recrystallized from ethanol to give 4-aminopyridine 1-oxide hydrochloride (47a) in 40% yield, m.p. 156-60°.

(b) Preparation of 4-aminopyridine 1-oxide thiocyanate (47b)

4-Aminopyridine 1-oxide hydrochloride (47a) was treated with an equimolar amount of ammonium thiocyanate for 6 h in refluxing ethanol. The mixture was filtered while hot, the filtrate evaporated to dryness and extracted with hot acetone. The insoluble ammonium chloride was removed by filtration and the acetone evaporated to give a 74% yield of a pale yellow solid, m.p. 125-7° (acetone); lit. value: 126-7° (66). Although Gardner et al. (66) claim that this compound is N-4-pyridylthiourea 1-oxide, its i.r. spectrum displayed a strong band at 2060 cm^{-1}, typical of -S-C≡N absorption which must belong to 4-aminopyridine 1-oxide thiocyanate (47b).

2. Preparation of 2-aminopyridine 1-oxide thiocyanates

(a) From 2-aminopyridine 1-oxide hydrochloride: First method

The following general method described by Brown (63) was followed to prepare the 2-aminopyridine 1-oxides. 2-Aminopyridine (0.1 mol) was refluxed for 1 h with acetic anhydride (10 ml). The resulting 2-acetamidopyridine was isolated by evaporation of the solution under reduced pressure and then crystallization of the residue from ethanol. It was then oxydized by a mixture of 40% peracetic acid (12.5 ml) and glacial acetic acid (15 ml). The temperature was moderated in the beginning by a salt-ice bath, then held at 70° for 4 h. Evaporation of the solution in vacuo gave 2-acetamidopyridine 1-oxide which was then refluxed with 3N hydrochloric acid for 4 h to give, after evaporation of the reaction mixture till dryness and recrystallization of the residue from a mixture of ethanol and ether, the 2-aminopyridine 1-oxide hydrochloride.

The following amine hydrochlorides were prepared, the yield being based on the starting amine:

2-aminopyridine 1-oxide hydrochloride, 79.0%, m.p. 149-50°;
lit. value: 153-6° (80);
2-amino-3-methyl-, 63.7%, m.p. 163-5°;
2-amino-4-methyl-, 76.0%, m.p. 207-9°;
2-amino-5-methyl-, 54.7%, m.p. 195-7°; lit. value: 195-8° (134);
2-amino-6-methyl-, 40.8%, m.p. 212-3°; lit. value: 212-4° (134);
2-amino-4,6-dimethyl-, 65.4%, m.p. 227-30° (dec.); lit.
value: 230-1° (dec.) (134).

(b) Second method

The method employed by Katritzky (65) was also followed to prepare several 2-aminopyridine 1-oxide hydrochlorides. In this case, the starting amines were first transformed into ethyl carbamate derivatives by treatment with ethyl chloroformate in pyridine, then oxidized by 30% hydrogen peroxide in glacial acetic acid to give the ethyl N-2-pyridylcarbamate 1-oxides. These were then hydrolyzed with 3N HCl to give the

2-aminopyridine 1-oxide hydrochlorides. This method, however, favoured the formation of N,N'-dipyridylureas $1:1'$-dioxides as side products thus reducing the yield of final product.

(c) Preparation of 2-aminopyridine 1-oxide thiocyanates

The general procedure described for the 4-aminopyridine 1-oxide thiocyanate (47b) was followed to prepare the 2-aminopyridine 1-oxide thiocyanates. The products were identified as amine thiocyanates from the i.r. spectra which showed a strong band at 2060 cm^{-1}. They were too hygroscopic to give precise elemental analysis values.

The following compounds were prepared and are listed here with the melting point and yield:

2-aminopyridine 1-oxide thiocyanate (52b), white crystals, m.p. 130-1° (benzene/acetone); 98.5%;

2-amino-4-methyl- (48b), white crystals, m.p. 112-112.5° (acetone); 71.1%;

2-amino-5-methyl- (49b), white crystals, m.p. 164-5° (acetone/benzene); 80.2%;

2-amino-6-methyl- (50b), colorless needles, m.p. 166-8° (ethanol/acetone); 72.3%;

2-amino-4,6-dimethyl- (51b), colorless needles, m.p. 142-3° (benzene); 77.4%.

3. Attempted preparation of ammonium N-2-pyridyldithiocarbamate 1-oxides by treatment of aminopyridine 1-oxides with carbon disulfide and ammonium hydroxide

(a) Powdered 2-aminopyridine 1-oxide (52) (0.956 g; 8.7 mmol) was added slowly to an ice-cooled mixture of concentrated ammonium hydroxide (3 ml) and carbon disulfide (1 ml). The mixture was stirred overnight. More ammonium hydroxide (6 ml) was added and the mixture warmed to 75-80° for 0.5 h, cooled, and neutralized with hydrochloric acid. Extraction with chloroform removed the unchanged amine. The aqueous layer was evaporated till dry, extracted with hot absolute ethanol and concentrated to give a 38.2% yield of long colorless needles of 2-aminopyridine 1-oxide thiocyanate (52b), m.p. 128-30°. It was identified by comparison of its i.r. spectrum with that of an authentic sample.

(b) Similarly treatment of 2-amino-6-methylpyridine 1-oxide hydrochloride (50a) with concentrated ammonium hydroxide and carbon disulfide gave colorless crystals, m.p. 154-5° (ethanol/benzene), of 2-amino-6-methylpyridine 1-oxide thiocyanate (50b) (39.3%), identified by comparison of its i.r. spectrum.

G. SYNTHESIS OF [1,2,4]OXADIAZOLO[2,3-a]PYRIDINE-2-THIONES

1. Preparation of [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53)

(a) 2-Aminopyridine 1-oxide (52) and thiophosgene

To 2-aminopyridine 1-oxide (52) (0.546 g; 5 mmol) dissolved in water (10 ml) in presence of sodium bicarbonate (0.85 g; 10 mmol) was added gradually a solution of thiophosgene (0.6 g; 5 mmol) in ether (15 ml). A white cakey solid was immediately formed. The mixture was stirred for 2 h at room temperature, then filtered to give 0.660 g (87.5%) of [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53), exploding at 132-3° in the melting point tube. Recrystallization of 53 from an ethanol/benzene mixture afforded pure 53 as well as a second product, m.p. 102-3°, arising from the reaction of 52 with ethanol, identified as ethyl N-2-pyridylcarbamate from its mass spectrum which showed a molecular ion of m/e 166, and its i.r. spectrum exhibiting a sharp band at 1722 cm^{-1} typical of carbamate carbonyl bands.

Anal. calcd. for $C_6H_4N_2OS$: C, 47.4; H, 2.6; N, 18.4.

Found: C, 47.1; H, 2.9; N, 18.2.

Treatment of 53 with methyl iodide in refluxing absolute methanol for 2.5 h gave, upon cooling, long beautiful colorless needles of methyl N-2-pyridylcarbamate, m.p. 122-3°; lit. value: 128-9° (135). By carrying the reaction in the absence of methanol, 0.624 g of a product exploding at 116° into a purple liquid was obtained. The mass spectrum of this last compound indicated the presence of a peak at m/e 127 assigned to iodine. No molecular ion was present.

(b) 2-Acetamidopyridine 1-oxide (52c) and thiophosgene

A mixture of 2-acetamidopyridine 1-oxide (52c) (1.037 g; 6.8 mmol) and sodium bicarbonate (1.28 g; 15.2 mmol) in aqueous ethanol (25 ml) was treated with thiophosgene (0.88 g; 7.7 mmol) in ether (15 ml). A solid precipitated during the addition. The mixture was stirred for 1 h and filtered to give 0.606 g (58.4%) of[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (53), exploding at 134°.

2. Preparation of 8-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (68)

(a) 2-Acetamido-3-methylpyridine 1-oxide (77) and thiophosgene

In a similar fashion, a mixture of 2-acetamido-3-methylpyridine 1-oxide (77) (3.57 g; 21.5 mmol) gave, upon treatment with thiophosgene (2.63 g; (22.8 mmol), 2.687 g (75.4%) of 8-methyl [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (68) as a cream-colored crystalline solid, exploding at 134°. Recrystallization from DMSO/benzene gave colorless needles of 68.

The n.m.r. spectrum of 68 showed two doublets at δ 9.44 (H-5) and δ 8.28 (H-7) and a triplet at δ 7.64 (H-6). A singlet also appeared at δ 2.87 (8-CH_3).

Anal. calcd. for $C_{17}H_6NOS$: C, 50.5; H, 3.6;
N, 16.9; S, 19.3.

Found: C, 49.6; H, 3.8; N, 16.6; S, 19.2.

3. Preparation of 7-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (69)

(a) 2-Amino-4-methylpyridine 1-oxide hydrochloride (48a) and thiophosgene

By treatment of 2-amino-4-methylpyridine 1-oxide hydrochloride (48a) (1.062 g; 6.6 mmol) with thiophosgene (0.76 g; 6.6 mmol), 0.836 g (76.3%) of 7-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (69), exploding at 131.5° was obtained. Recrystallization from a mixture of DMSO/benzene gave colorless needles of 69.

The n.m.r. spectrum of 69 revealed a doublet at δ 9.47 (H-5), a singlet at δ 7.91 (H-8) and δ 2.88 (7-CH_3) and a split doublet at δ 7.60 (H-6).

Anal. calcd. for C_7H_6NOS: C, 50.5; H, 3.6; N, 16.9.

Found: C, 49.9; H, 3.7; N, 16.7.

(b) 2-Acetamido-4-methylpyridine 1-oxide (48c) and thiophosgene

Similarly, reaction of 2-acetamido-4-methylpyridine 1-oxide (48c) (8.09 g; 48.7 mmol) with thiophosgene (5.94 g; 51.6 mmol) gave 69 in 70.0% yield.

(c) Ethyl N-(4-methyl-2-pyridyl)carbamate 1-oxide (48d) and thiophosgene

The treatment of ethyl N-(4-methyl-2-pyridyl)carbamate 1-oxide (48d) (0.634 g; 3.2 mmol) with thiophosgene (0.355 g; 3.2 mmol) afforded 0.477 g (90%) of 69.

4. Preparation of 6-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (70)

(a) 2-Amino-5-methylpyridine 1-oxide hydrochloride (49a) and thiophosgene

Treatment of 2-amino-5-methylpyridine 1-oxide hydrochloride (49a) (1.006 g; 6.2 mmol) with thiophosgene (0.81 g; 7 mmol) gave 0.585 g (56.4%) of 6-methyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (70) as small beige needles, exploding at 121°.

Recrystallization from an ethanol/carbon tetrachloride mixture gave 70 and long colorless needles of ethyl N-(5-methyl-2-pyridyl)carbamate, m.p. 141-3° arising from the reaction of 70 with ethanol; lit. value 144.5-145° (134).

The n.m.r. spectrum of 70 contained a singlet at δ 9.50 (H-5) and δ 2.77 (6-CH_3) as well as a doublet at δ 8.33 (H-7) and δ 8.00 (H-8).

Anal. calcd. for C_7H_6NOS: C, 50.5; H, 3.6; N, 16.9.

Found: C, 50.7; H, 3.9; N, 16.6.

(b) 2-Acetamido-5-methylpyridine 1-oxide (49c) and thiophosgene

Similarly, 2-acetamido-5-methylpyridine 1-oxide (49c) (7.043 g; 42.4 mmol) and thiophosgene (5.1 g; 44.3 mmol) gave 5.098 g (72.3% yield) of 70, exploding at 121.5°.

5. Preparation of 5-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (71)

(a) 2-Amino-6-methylpyridine 1-oxide hydrochloride (50a) and thiophosgene

Compound (50a) (1.501 g; 9.3 mmol) and thiophosgene (1.15 g; 10 mmol) afforded 1.286 g (81.1%) of 5-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (71) as cream-colored crystals from a DMSO/benzene mixture, exploding at 134°.

Anal. calcd. for $C_7H_6N_2OS$: C, 50.5; H, 3.6;
N, 16.9; S, 19.3.

Found: C, 50.2; H, 3.7; N, 16.8; S, 18.9.

(b) 2-Acetamido-6-methylpyridine 1-oxide (50c) and thiophosgene

By reacting 2-acetamido-6-methylpyridine 1-oxide (51c) (9.117 g; 54.9 mmol) and thiophosgene (6.6g; 57.4 mmol), 7.773 g (85.2%) of 71 was obtained.

6. Preparation of 5,7-dimethyl[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione (72)

(a) 2-Amino-4,6-dimethylpyridine 1-oxide hydrochloride (51a) and thiophosgene

In the same manner, the amine hydrochloride (51a) (2.44 g; 14 mmol) and thiophosgene (1.73 g; 15 mmol) gave 1.874 g (74.4%) of 5,7-dimethyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (72) as shiny cream-colored crystals, exploding at 137°. Its mass spectrum showed no molecular ion but only a peak at m/e 148 assigned to 4,6-dimethyl-2-pyridyl isocyanate

The n.m.r. spectrum of 72 displays a singlet at δ 7.71 (H-8), δ 7.10 (H-6), δ 2.74 ($5\text{-}CH_3$) and δ 2.61 ($7\text{-}CH_3$).

Anal. calcd. for $C_8H_8N_2OS$: C, 53.3; H, 4.4;

N, 15.5; S, 17.8.

Found: C, 52.9, H, 4.4; N, 15.8; S, 17.8.

(b) <u>2-Acetamido-4,6-dimethylpyridine 1-oxide</u> (<u>51c</u>) <u>and thiophosgene</u>

Similarly, 6.811 g (80.8% yield) of <u>72</u> was obtained by the treatment of <u>51c</u> (8.425 g; 46.7 mmol) with thiophosgene (5.4 g; 47.0 mmol). Small colorless crystals from DMSO/benzene melting sharply at 139-40°.

7. <u>Preparation of 5-amino[1,2,4]oxadiazolo[2,3-a]-pyridine-2-thione</u> (<u>78</u>)

(a) <u>2,6-Diaminopyridine 1-oxide hydrochloride</u> (<u>66a</u>) <u>and thiophosgene</u>

Compound (<u>66a</u>) (0.94 g; 5.2 mmol) was treated in the usual manner with thiophosgene (0.60 g; 5.2 mmol) to give 5-amino [1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (<u>78</u>), exploding at 110°. Since this compound could not be recrystallized in sufficiently pure state, its structure was not confirmed by elemental analysis.

(b) 2,6-Diethoxycarbonylaminopyridine 1-oxide (65) and thiophosgene

Compound (65) (0.769 g; 2.9 mmol) was treated with thiophosgene (0.33 g; 2.9 mmol) in the usual manner. The light orange solution was stirred overnight and then evaporated to give 0.611 g of starting material (65) (79.5% recovery), identified by its i.r. spectrum. No other product was isolated.

H. SYNTHESIS OF 8-METHYL[1,3,4]OXADIAZOLO[3,2-a]PYRIDINE-2-THIONE (76)

1. Preparation of 3-methyl-2-pyridone (74)

This compound was prepared in 92% yield according to the procedure described by Adams and Schrecker for the preparation of the 6-methyl analogue (82). Thus a cold solution of 2-amino-3-methyl-pyridine (10.8 g; 0.1 mol) in concentrated sulfuric acid (11.1 ml) and water (83 ml) was slowly treated with a solution of 97% sodium nitrite (7.3 g) in water (14 ml) at 5°. It was stirred for an additional hour below 10° and then heated until the temperature reached 90°. The solution was made alkaline by the addition of anhydrous potassium carbonate (20.5 g) and evaporated to dryness. The residue was extracted with boiling ethanol, the inorganic salts removed and the ethanol evaporated to yield 10.043 g of pale yellow 3-methyl-2-pyridone (74) identified by its i.r.

spectrum.

2. Preparation of 1-amino-3-methyl-2-pyridone (75)

Chloroamine was prepared as reported by Reid and Meyer (136). To an ice-cooled 2N sodium hydroxide solution (100 ml) was added chlorine gas till the weight had increased by 6 g. To 59 ml (0.05 mol) of this alkaline solution was added, under ice-cooling, a mixture of concentrated ammonium hydroxide (9.7 ml), water (60 ml) and gelatine (0.2 g). It was left to stand for 1 hour at 0°. Then a mixture of 3-methyl-2-pyridone (74) (4.44 g; 40.7 mmol) and sodium hydroxide (1.6 g in 2 ml water) was added and the resulting yellow mixture was stirred for 1 h under ice-cooling, after which it was left to stand overnight at 0°. It was then extracted with ether, the solution was dried, and the ether removed to give light brown 1-amino-3-methyl-2-pyridone (75), m.p. 95-8°; lit. value: 95-6° (79).

3. Preparation of 8-methyl[1,3,4]oxadiazolo[3,2-a]-pyridine-2-thione (76)

1-Amino-3-methyl-2-pyridone (75) was dissolved in aqueous ethanol (25 ml) in presence of sodium bicarbonate (1.6 g) and then treated with a solution of thiophosgene (1 g) in ether (20 ml). A beige solid was deposited, filtered off, extracted with boiling ethanol, the insoluble products being filtered off, the ethanol evaporated to give a beige product (0.245 g); short colorless needles, m. 249°-50° (DMSO).

The mass spectrum revealed a molecular ion of m/e 166 in agreement with the 8-methyl[1,3,4]oxadiazolo[3,2-a]pyridine-2-thione (76) structure. A second fragment ion of m/e 109 may be assigned to 3-methyl-2-pyridone (74) whose presence may be rationalized by the expulsion of -SCN from the molecular ion. The n.m.r. spectrum of 76 indicated the presence of a methyl group at δ 2.87 and three pyridine protons at δ 8.42 (H-7), δ 7.94 (H-6) and δ 9.16 (H-5). No other proton was present in the spectrum.

Calculated mass from exact mass measurement:	166.0200
Calculated mass for $C_7H_6N_2OS$:	166.0201
Delta mass:	0.0001

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. The preparation of N-phenyl-N′,N″-di-(2-thiazolyl)guanidines was accomplished by treatment of the N-phenyl-N′-2-thiazolylthioureas with lead oxide in anhydrous benzene. A mechanism was proposed to account for the formation of the guanidines in this reaction.

2. The preparation of N,N′-diphenyl-N″-2-thiazolylguanidines was realized by desulfurization of the N-phenyl-N′-2-thiazolylthioureas with lead oxide in the presence of aniline. The preparation of N,N′-diphenyl-N″-2-thiazolylguanidine was also carried out by treatment of the S-methyl-N-phenyl-N′-2-thiazolylisothiourea with mercuric chloride in the presence of aniline.

3. The preparation of N-carbethoxy-N′-phenyl-N-2-thiazolylthioureas was achieved by treatment of the N-phenyl-N′-2-thiazolylthioureas with ethyl chloroformate in chloroform in the presence of triethylamine. A mechanism was suggested to account for the formation of the N-carbethoxy-N′-phenyl-N-2-thiazolylthioureas.

4. The preparation of O-ethyl-N-phenyl-N′-(4-phenyl-2-thiazolyl)-isoureas was accomplished by treatment of the N-phenyl-N′-(4-phenyl-2-thiazolyl)thioureas with ethyl chloroformate in chloroform and in the presence of triethylamine. A mechanism

was also proposed to account for the formation of the isoureas.

5. The synthesis of the N-pyridylthioureas was accomplished in two steps:

   a) Treatment of the 2-aminopyridine with benzoyl isothiocyanate to give the N-benzoyl-N'-pyridylthioureas;

   b) Hydrolysis of the N-benzoyl-N'-pyridylthioureas with dilute sodium hydroxide to give the N-pyridylthioureas.

6. Oxidation of N-2-pyridylthiourea with bromine in acetonitrile or chloroform in the presence of triethylamine produced 2-pyridylcyanamide. A mechanism was proposed to account for the formation of 2-pyridylcyanamide.

7. Contrary to published results, reaction of 4-aminopyridine 1-oxide hydrochloride with ammonium thiocyanate in ethanol did not yield N-4-pyridylthiourea 1-oxide but the isomeric 4-aminopyridine 1-oxide thiocyanate salt. Similarly, treatment of 4-aminopyridine with ammonium thiocyanate did not produce N-4-pyridylthiourea but 4-aminopyridine thiocyanate.

8. Treatment of the 2-aminopyridine 1-oxide hydrochlorides with ammonium thiocyanate gave the amine thiocyanate salts which did not isomerize into the corresponding thioureas under prolonged heating.

9. Refluxing 2-aminopyridine 1-oxide hydrochloride with carbon

disulfide in aqueous ammonia afforded 2-aminopyridine 1-oxide thiocyanate. A mechanism was proposed to account for the formation of this product.

10. The synthesis of [1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones was accomplished by treatment of the 2-aminopyridine 1-oxides, 2-acetamidopyridine 1-oxides or ethyl N-2-pyridylcarbamate 1-oxides with thiophosgene in dilute ethanol in presence of sodium bicarbonate. A mechanism was proposed to account for the formation of the [1,2,4]oxadiazolo[2,3-a]-pyridine-2-thiones.

11. Reaction of the [1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones with alcohol gave the corresponding deoxygenated alkyl N-pyridylcarbamates.

12. Evidence was presented to refute the mechanism involving an isocyanate intermediate postulated to account for the formation of [1,2,4]oxadiazolo[2,3-a]pyridone-2. An alternate mechanism was proposed for the formation of this compound.

13. The synthesis of 8-methyl[1,3,4]oxadiazolo[3,2-a]pyridine-2-thione was accomplished in three steps:

    a) Diazotization of 2-amino-3-methylpyridine with sodium nitrite in acid solution followed by hydrolysis to give 3-methyl-2-pyridone.

    b) Treatment of 3-methyl-2-pyridone with chloramine to give 1-amino-3-methyl-2-pyridone.

c) Reaction of 1-amino-3-methyl-2-pyridone with thiophosgene in dilute ethanol in the presence of sodium bicarbonate to give 8-methyl[1,3,4]oxadiazolo[3,2-a]-pyridine-2-thione.

14. The following new compounds were prepared and characterized:

N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)thiourea (8)
N-phenyl-N',N''-di-(2-thiazolyl)guanidine (11)
N,N'-diphenyl-N''-2-thiazolylguanidine (14)
N-phenyl-N',N''-di-(4-methyl-2-thiazolyl)guanidine (9)
N,N'-diphenyl-N''-(4-methyl-2-thiazolyl)guanidine (10)
N-phenyl-N',N''-di-(4-phenyl-2-thiazolyl)guanidine (12)
N,N'-diphenyl-N''-(4-phenyl-2-thiazolyl)guanidine (16)
N-phenyl-N',N''-di-(5-methyl-4-phenyl-2-thiazolyl)guanidine (13)
N,N'-diphenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)guanidine (17)
N-carbethoxy-N'-phenyl-N-2-thiazolylthiourea (19)
N-carbethoxy-N'-phenyl-N-(4-methyl-2-thiazolyl)thiourea (20)
O-ethyl-N-phenyl-N'-(4-phenyl-2-thiazolyl)isourea (21)
O-ethyl-N-phenyl-N'-(5-methyl-4-phenyl-2-thiazolyl)isourea (23)
Ethyl N-(5-methyl-4-phenyl-2-thiazolyl)carbamate (22)
N-carbethoxy-N,N'-diphenylthiourea (25)
N-benzoyl-N'-(3-methyl-2-pyridyl)thiourea (37)
N-(3-methyl-2-pyridyl)thiourea (28)
N-benzoyl-N'-(4-methyl-2-pyridyl)thiourea (38)
N-benzoyl-N'-(5-methyl-2-pyridyl)thiourea (39)

N-(5-methyl-2-pyridyl)thiourea (30)

N-benzoyl-N'-(6-methyl-2-pyridyl)thiourea (40)

N-(6-methyl-2-pyridyl)thiourea (31)

N-benzoyl-N'-(4,6-dimethyl-2-pyridyl)thiourea (41)

N-(4,6-dimethyl-2-pyridyl)thiourea (32)

2,6-dibenzoylthioureidopyridine (43)

2,6-dithioureidopyridine (34)

N-benzoyl-N'-(5-bromo-2-pyridylthiourea (42)

N-(5-bromo-2-pyridyl)thiourea (33)

[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (53)

8-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (68)

7-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (69)

6-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (70)

5-methyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (71)

5,7-dimethyl[1,2,4]oxadiazolo[2,3-a]pyridine-2-thione (72)

8-methyl[1,3,4]oxadiazolo[3,2-a]pyridine-2-thione (76)

15. The infrared spectra of the new N-pyridylthioureas, N-benzoyl-N'-pyridylthioureas, N-carbethoxythioureas, N-phenyl-N'-thiazolylguanidines, O-ethyl-N-phenyl-N'-thiazolylisoureas and [1,2,4]oxadiazolo[2,3-a]pyridine-2-thiones were recorded and correlated with their structure.

16. The ultra-violet spectra of the new N-pyridyl- and N-benzoyl-N'-pyridylthioureas, the 2-aminopyridine 1-oxide thiocyanates and the phenyl- and thiazolylthioureas and isoureas were recorded and interpreted.

17. The n.m.r. spectra of several new thiazole derivatives of the N-pyridylthioureas and the [1,2,4] oxadiazolo[2,3-a]-pyridine-2-thiones were recorded and interpreted.

18. The mass spectra of N,N-diphenylthiourea, N,N'-di-(2-thiazolyl)-thiourea, S-methyl- and S-ethyl-N,N'-diphenylisothiourea, N-carbethoxythioureas, O-ethyl-N-2-thiazolylisoureas, N-phenyl-N'-2-thiazolylguanidines and several N-pyridylthioureas were investigated and interpreted.

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