CHAPTER III
SYNTHESIS OF AMINOISOTHIAZOLES AND ISOTHIAZOLO(3,4-d)PYRIMIDINES

Introduction

The simple and relatively new ring system such as isothiazole is of considerable interest to the medicinal chemists engaged in the search for novel biologically active molecules. Among isothiazoles, the synthesis and biological activity of a few 3-aminoisothiazole derivatives (328) and 5-aminoisothiazole derivatives (329) have been reported.

However, 3,5-diaminoisothiazoles (330), as a class, have hitherto remained unexplored. The only report on the synthesis of some 3,5-diaminoisothiazoles is that of Goerdeler and Keuser,¹⁴¹ who have described the preparation of 3,5-diaminoisothiazole derivatives (331b) by the oxidative cyclization of the corresponding
thiocarbamoyl acetamidines (331a). The oxidative cyclization of the thiocarbamoyl amidine (331c) to the 3,5-diaminoisothiazole (331d) has been described in a patent. 

\[
\begin{align*}
\text{(331a)} & \quad R = \text{CN}, R_1 = \text{PhCO} \quad \text{;} \\
\text{(331b)} & \quad R = \text{CO}_2\text{Et}, R_1 = \text{PhCO}, \text{p-NO}_2\text{C}_6\text{H}_4 \\
\text{(331c)} & \quad \text{NG} \quad \text{NMe}_2 \\
\text{(331d)} & \quad \text{H}_2\text{N} \quad \text{NMe}_2 
\end{align*}
\]

Present Work

In view of the fact that 3,5-diaminoisothiazoles have received scant attention, it was thought of interest to undertake an investigation on the synthesis and study of the chemistry and biological activity of 3,5-diaminoisothiazole derivatives.

Though the synthesis of some 3-halogeno- and 3-méthylsulfonyl-5-aminoisothiazoles (333) has been
described in the literature, their reaction with ammonia or amines does not appear to be a synthetically useful method for the preparation of 3,5-diaminoisothiazoles, since these isothiazoles (332) are prone to undergo ring cleavage reactions with nucleophiles.  

![Chemical structure](image)

\[ X = \text{Cl, Br, SO}_2\text{CH}_3 \]

Therefore, the synthesis of 3,5-diaminoisothiazoles by the cyclization of appropriate open-chain substrates appeared to be the method of choice.

The oxidative cyclization method employed by Gördeler and Keuser is of limited applicability because of the inaccessible nature of the \( \alpha \)-thiocarbamoyl acetamidine intermediates. The S-alkylation and cyclization of 3-amino-3-mercaptoacrylonitriles (333) has served as a versatile method of synthesis of diaminothiophenes (334). Therefore, the aminative
cyclization of 3-amino-3-mercaptoacrylonitriles (333) was thought of as a possible approach to the synthesis of 3,5-diaminoisothiazoles (335) (Scheme I).

\[ R_1R_2N \overset{X-CH_2-R_3}{\longrightarrow} R_1R_2N \]  
\[ (333) \quad \overset{X-NH_2}{\longrightarrow} \quad (334) \]

\[ R_1R_2N \overset{X-NH_2}{\longrightarrow} \]

\[ (335) \]

\( X = \text{halogeno or other leaving group} \)

**SCHEME I**

This approach to the synthesis of 3,5-diaminoisothiazoles is particularly attractive because of the ready accessibility of a variety of 3-amino-3-mercaptoacrylonitrile derivatives through different synthetic routes. 3-Amino-3-mercaptoacrylonitrile derivatives have been synthesized by the following methods:
a) The reaction of active methylene nitriles with isothiocyanates or other thiocarbamoylating agents.

\[
\text{R-CH}_2\text{CN} \quad \text{base} \quad \text{R}_1\text{NH} \\
\text{R}_1\text{N}=\text{C}=\text{S}
\]

\[
\text{R-CH}_2\text{-CN} \quad \text{base} \quad \text{R}_1\text{R}_2\text{NH} \\
\text{R}_1\text{N} \quad \text{N-C-X} \quad \text{S}
\]

\[\text{M}^+ = \text{H}^+, \text{alkalimetal or ammonium ion} \]
\[\text{X} = \text{leaving group} \]

b) The reaction of amines with \(\alpha\)-cyanomethylene-1,3-dithetanes (333a) or \(\alpha\)-cyanomethylene-1,2,4-trithiacyclopentanes (333b).

\[
\text{R-CH}_2\text{CN} \quad \text{base} \quad \text{R}_1\text{R}_2\text{NH} \\
\text{R}_1\text{N} \quad \text{N-C-X} \quad \text{S}
\]

\[\text{M}^+ = \text{H}^+ \text{ or ammonium ion} \]
c) The reaction of 3-amino-3-halogenoacrylonitriles (333c) or 3-amino-3-alkylthioacrylonitriles (333d) with hydrosulfides.\textsuperscript{228, 229}

\[
\begin{align*}
R & \quad \text{CN} \\
\text{R}_1\text{R}_2\text{N} & \quad \text{X}
\end{align*}
\]

(333c) $X = \text{halogen}$

(333d) $X = \text{SR}$

$M^+ = H^+$, alkalimetal or ammonium ion

Chloramine or hydroxylamine-O-sulfonic acid has been employed for the cyclization of 3-mercaptoacrylonitrile derivatives to 3-aminoisothiazoles by Hartke and co-workers.\textsuperscript{348, 489, 490} Gewald and co-workers\textsuperscript{647} have employed these reagents for the cyclization of 2-mercapto-3-cyano-pyridines to 3-aminoisothiazolo(5,4-b)pyridines.

In the present study, it was found that N-substituted 3-amino-3-mercaptoacrylonitrile derivatives, when reacted with chloramine, cyclized in a facile manner to afford 3,5-diaminoisothiazole derivatives in satisfactory yields, despite the fact that chloramine is an oxidizing
agent, and the thiol substrates employed were multifunctional and therefore, prone to undergo a variety of transformations under oxidizing conditions.

In view of the encouraging results obtained in the preparation of 3,5-diaminoisothiazole derivatives, the chloramine cyclization method was extended to the synthesis of 3-amino- and 5-aminoisothiazole derivatives \((336)\) and \((337)\).

\[
\begin{align*}
(336) & \quad R_1 \quad \text{NH}_2 \\
(337) & \quad R_2 \quad R_1 \\
(338) & \quad Y = \text{R}_1 \quad \text{R}_2 \\
\end{align*}
\]

\(X = 0, S\)

An attempt was also made to study the chemistry of 3-aminoisothiazole derivatives and to synthesize some isothiazolo(3,4-d)pyrimidines \((338)\) from 3-aminoisothiazole-4-carboxylic acid derivatives.

**Result and Discussion**

The reaction of active methylene nitriles such as malononitrile, alkyl cyanoacetates and benzoylacetonitrile with isothiocyanates has usually been performed in the
presence of alkali metal alkoxides as the base. The base promoted condensation of active methylene nitriles with isothiocyanates leads to the corresponding alkali metal salts of 3-amino-3-mercaptoacrylonitrile intermediates (339). Though, the free thioamides (339a) or the enethiol tautomers (339b) are isolable in some of the reactions, the solutions of alkali metal salts of the 3-amino-3-mercaptoacrylonitriles have generally been employed in situ in the alkylation reactions to obtain $\alpha$-cyanoketene $S,N$-acetals or cyclic products derived from them.

In the present work similar procedures were employed for the condensation of active methylene nitriles with isothiocyanates to obtain solutions of alkali metal salts
of enethiolates (339) which were subsequently employed without isolation, in the reaction with chloramine. Thus, the generation of 3-mercapto-3-aminoacrylonitrile salts in situ and their cyclization with aqueous chloramine constitutes a one-pot synthesis of 3,5-diaminoisothiazole derivatives.

Alkyl isothiocyanates were reacted with active methylene nitriles such as malononitrile and ethyl cyanoacetate, employing sodium ethoxide in ethanol as the base. The intermediates thus obtained, when reacted with aqueous chloramine solution, yielded products characterized as the 3-amino-5-alkylaminoisothiazole-4-carbonitriles and 4-carboxylic acid esters (351-357) by their elemental analysis, UV, IR, NMR and mass spectral data (Scheme II) (Table VI).

Similarly, the condensation product of phenyl
isothiocyanate with active methylene nitriles, such as malononitrile, methyl cyanoacetate, ethyl cyanoacetate, t-butyl cyanoacetate and phenylsulfonylacetonitrile, when reacted with chloramine, yielded the corresponding 3-amino-5-phenylaminoisothiazoles (358-362). Sodium ethoxide in ethanol was employed as the base in the reaction of phenyl isothiocyanate with malononitrile, ethyl cyanoacetate and phenylsulfonylacetonitrile. Sodium methoxide in methanol and potassium t-butoxide in t-butanol were employed in the reaction of phenyl isothiocyanate with methyl cyanoacetate and t-butyl cyanoacetate, respectively.

\[
\text{(358) } R = \text{CH}_3 \\
\text{(359) } R = \text{C}_2\text{H}_5 \\
\text{(360) } R = \text{C(CH}_3\text{)}_3 \\
\text{(361) } R = \text{C(CH}_3\text{)}_3 \]

\[
\text{(359) } R = \text{CH}_3 \\
\text{(360) } R = \text{C}_2\text{H}_5 \\
\text{(361) } R = \text{C(CH}_3\text{)}_3 \\n\text{(362)}
\]
3-Amino-5-arylaminoisothiazole-4-carbonitriles and 4-carboxylic acid esters (363-376) were similarly obtained by the cyclization of the intermediates resulting from the reaction of substituted phenyl isothiocyanates with malononitrile or ethyl cyanoacetate (Scheme III) (Table VI).

![Scheme III]

The 3-amino-4-cyano-5-p-toluenesulfonylaminoisothiazole (377) could, similarly, be prepared by the cyclization of the intermediate resulting from the condensation of p-toluenesulfonyl isothiocyanate with malononitrile.

![Image of compound 377]

In general, the overall yields of the 4-cyanoiso-
thiazoles obtained by the cyclization of malononitrile-derived intermediates (339; R=CN) were better than those of the 4-carbethoxyisothiazoles obtained by the cyclization of ethyl cyanoacetate-derived intermediates (339; R = CO₂Et). The observed difference in the yields cannot be attributed to the difference in the yields in which the enethiolate intermediates are formed from the nitriles in the first step of the reaction because of the fact that under the reaction conditions employed, ethyl cyanoacetate is known to give excellent yields of isolable α-cyanothioacetamides (339a; R = CO₂Et) or their enethiol tautomers (339b; R = CO₂Et).¹³⁵-¹³⁷

Therefore, an attempt was made to isolate any alkali soluble byproducts formed in the cyclization of the intermediates derived from ethyl cyanoacetate. The acidification of the alkaline aqueous mother liquor obtained in the reaction leading to the aminooester (360), yielded a small quantity (<10%) of the product identified as the 3-hydroxy-4-cyano-5-phenylaminoisothiazole (393). The hydroxycyanoisothiazoles (394) and (395)
were, similarly, identified as minor by-products of the reactions leading to the aminoesters (364) and (366).

It is of interest to note that the 3-mercapto-3-arylamino-2-cyanoacrylamide salts (393a, 394a and 395a) resulting from the condensation of aryl isothiocyanates with cyanoacetamide, when reacted with chloramine, yielded only 3-hydroxy-4-cyanoisothiazoles (393, 394 and 395) as the major products of the reaction and not the 3-amino-5-arylaminoisothiazole-4-carboxamides (Scheme IV) (Table X).
The condensation of phenyl isothiocyanate with ethyl cyanoacetate under different conditions, and the cyclization of the resulting intermediates (360a) with aqueous chloramine was studied. The reaction of ethyl cyanoacetate with phenyl isothiocyanate in the presence of potassium t-butoxide in t-butanol or potassium hydroxide in dimethylformamide or dimethyl sulfoxide and the cyclization of the resulting intermediates (360a; M=K) with chloramine, gave the isothiazole (360) in nearly the same yield as that obtained from the cyclization of the intermediate (360a; M=Na) obtained by the condensation of phenyl isothiocyanate with ethyl cyanoacetate in the presence of sodium ethoxide in ethanol. Similarly, no significant difference in the yield of 360 was observed in the cyclization of the intermediate (360a; M=Na),
prepared by the reaction of sodium salt of ethyl cyanoacetate with phenyl isothiocyanate in dimethylformamide.

The cyclization of the intermediates obtained by the condensation of phenyl isothiocyanate with ethyl cyanoacetate in the presence of anhydrous potassium carbonate or triethylamine in dimethylformamide or by the reaction of methyl N-phenyldithiocarbamate with ethyl cyanoacetate in the presence of sodium ethoxide, gave poor yields of isothiazole (360), possibly due to the formation of intermediate (360a) in low yields in these reactions.

An alternative approach to the 3-mercapto-3-aminoacrylonitrile derivatives (333) involves the reaction of the readily obtainable $\alpha'$-cyanoketene S,N-acetals (340) with hydrosulfide anion.

\[
\begin{align*}
\begin{array}{c}
\text{R}_1\text{R}_2\text{N} & \text{CN} & \text{SCH}_3 & \text{CN} & \text{R}_1\text{R}_2\text{N} & \text{S}^+ \\
\text{R}_1\text{R}_2\text{N} & \text{CH}_3 & \text{S}^+ & \text{R}_1\text{R}_2\text{N} & \text{S}^+ \\
\end{array}
\end{align*}
\]

(340)

In the present study, it was found that the
α'-cyanoketene S,N-acetal (341b) could be made to react with sodium sulfide in aqueous dimethylformamide and the sodium enethiolate (360a; $M = Na$) thus generated could be cyclized with chloramine to afford the aminoisothiazole (360). Similarly, the 3-amino-4-cyano-5-phenylaminoisothiazole (358) and 3-amino-4-cyano-5-p-toluenesulfonaminoisothiazole (377) were obtained from the corresponding ketene S,N-acetals (341a) and (341c) by the sequential reaction with sodium sulfide and chloramine (Scheme V).

This method was successfully extended to the preparation of 3-amino-5-dialkylamino-4-cyanoisothiazoles (378-381) from the corresponding dicyanoketene S,N-acetals (340) by reaction with sodium sulfide and
The 5-morpholinoisothiazole (378) was also obtained by the cyclization of the intermediate (378a) obtained by the reaction of malononitrile with 4-morpholinethiocarbonyl chloride, O-ethyl 4-morpholinethionoformate or methyl 4-morpholinedithioformate (Scheme VI).
This method was extended to the synthesis of other 3-aminoisothiazoles by the cyclization of thiono- and dithioester intermediates derived from active methylene nitriles. Thus, the 5-ethoxy-, 5-aryloxy- and 5-arylthio-4-cyano-3-aminoisothiazoles (382-387) were obtained by the cyclization of the intermediates formed from the reaction of malononitrile with O-ethyl chlorothionoformate, O-aryl chlorothionoformates or phenyl chlorodithioformate (Scheme VII) (Table VIII).

The 3-amino-4-cyano-5-methylthioisothiazole (388) was obtained by the cyclization of the methylthiomercaptomethylenemalononitrile salts (388a). These intermediates (388a, M=Na, K or Et₃NH) were generated in situ by the
monomethylation of the dithiolate anions (388b) or by the reaction of dimethylthiomethylene-malononitrile with sodium sulfide. The isothiazole (388) has earlier been prepared by Hartke and Peshkar\textsuperscript{348} by the cyclization of the intermediate resulting from the base catalyzed condensation of malononitrile with dimethyl thiotrichocarbonate (Scheme VIII).

![Chemical structure](attachment:image.png)

The salt of ethyl 2-cyano-3-mercapto-3-methylthioacrylate (389a) obtained by similar sequence of reactions, when cyclized with chloramine, yielded the 3-amino-4-carbethoxy-5-methylthiocisothiazole (389) (Scheme IX). Acidification and work-up of the alkaline
aqueous mother liquor afforded a small quantity of product identified as the 3-hydroxy-4-cyano-5-methylthioisothiazole (396).

Interestingly, the 3-mercapto-3-methylthio-2-cyanoacrylamide salts (390a), when subjected to the cyclization with chloramine, yielded the aminoamide (390) as the major product of the reaction, in sharp contrast to the cyclization of the intermediate (393a) to the hydroxy-cyano-isothiazoles (Scheme X),
Treatment of the bis(triethylammoniothiomethylene) malononitrile (388b; \(M = \text{Et}_3\text{NH}\)), obtained by the reaction of malononitrile with carbon disulfide in the presence of triethylamine, \(^{18}\) with chloramine yielded a compound of molecular weight 172 devoid of any cyano group absorption in IR. The compound obtained was characterised as the 3,4-diaminoisothiazolo(4,5-d)isothiazole (391).

\[
\text{Et}_3\text{N} \quad \begin{array}{c}
\text{S=\text{C=S}} \\
\text{NC-CH}_2\text{CN}
\end{array} \quad \begin{array}{c}
\text{S} \\
\text{NC-CN}
\end{array} \quad \begin{array}{c}
\text{S} \\
\text{C=S}
\end{array} \quad \begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{NH}_2
\end{array} \\
\text{(388b)} \\
\text{M} = \text{Et}_3\text{NH}
\]

Similar sequence of reactions with ethyl cyanoacetate yielded the stable isothiazole-5-sulfenamide (392).

\[
\begin{array}{c}
\text{EtO}_2\text{C-CH}_2\text{CN} \\
\text{S=\text{C=S}} \\
\text{S=\text{C=S}}
\end{array} \quad \begin{array}{c}
\text{EtO}_2\text{C-CH}_2\text{CN} \\
\text{S} \\
\text{S}
\end{array} \quad \begin{array}{c}
\text{EtO}_2\text{C} \\
\text{NH}_2
\end{array} \\
\text{M}^+ = \text{Et}_3\text{NH}
\]
The isothiazole formation in the reaction of 3-mercaptoacrylonitriles with chloramine presumably proceeds via the initial formation of nonisolable sulfenamide intermediates (342) followed by their intramolecular cyclization.

(342)

Primary sulfenamides have been isolated in the reactions of chloramine or hydroxylamine-O-sulfonic acid with thiol derivatives such as thiol acids,\textsuperscript{548} dithioacids,\textsuperscript{548} thioamides,\textsuperscript{548,549} thiourethanes,\textsuperscript{551} thioureas,\textsuperscript{552} 2-mercaptobenzothiazole,\textsuperscript{553-554} 2-mercaptopyridines\textsuperscript{547,555} and 2-mercaptopyrimidines.\textsuperscript{556} N-Substituted sulfenamide derivatives have been prepared by the reaction of thiols with N-haloamines, by the reaction of thiols with amines in the presence of an oxidizing agent or by the reaction of amines with sulfenyl halides or disulfides.\textsuperscript{557,558}

In the cyclization of mercaptoacrylonitrile intermediates (360a), it was found that the addition of aqueous
chloramine solution to the salt or the reverse order of addition did not affect the yield of isothiazole (360). However, the addition of hypohalite solution to a mixture of the salt (360a) and ammonia gave only a very small amount of isothiazole (360). The addition of oxidizing agents such as aqueous sodium hypobromite or hydrogen peroxide to 360a and ammonia did not yield isothiazole 360. Similarly, addition of 360a to sodium hypobromite-ammonia or potassium hypobromite-ammonia did not yield the aminoisothiazole (360). However, the cyclization of aminomercaptoacrylonitrile salts (343) and (388a) to isothiazoles (352) and (388) could be effected with aqueous N-chloro-p-toluenesulfonamide-ammonia combination.
Attempted cyclization of (360b) with aqueous \( \text{N-chloromethylamine} \), obtained by reacting methylamine with sodium hypochlorite, did not yield any \( \text{N-methylisothiazole derivatives} \). However, the product obtained from this reaction was characterized as the thiazolylidene derivative (397) that has earlier been prepared by the reaction of \( (360a; M=H) \) with iodine in the presence of \( \text{triethylamine} \).

Some \( \text{N-cyanodithiocarbamates (344a)} \) have been cyclized to \( 3\text{-imino-1,2,4-thiadiazolines (344)} \) with
However, in an attempted reaction of N-chloro- or N-bromoure-rea with the adduct 360a (M=Na), prepared by the condensation of ethyl cyanoacetate with phenyl isothiocyanate in the presence of sodium ethoxide in ethanol, the product obtained was identified as the thiazoline aminoester (398).

The intermediates (360a; M=H or Na) were found to cyclize to benzothiazole (399) with N-bromosuccinimide or hypohalite solutions. The benzothiazole (399) has
earlier been prepared by the reaction of (360a; M\(\equiv\)H) with bromine. 263

![Sulfenamide structure](image)

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Sulfenamides have been prepared by the reaction of disulfides with primary or secondary amines in the presence of silver salts. 558 Sulfenimines have been obtained by this method by the reaction of disulfides with ammonia and aldehyde. The sulfenamide synthesis has also been applied for the preparation of 3,5-dimethyl-1,2-benzisothiazole (345) from the disulfide (345a) by its reaction with ammonia in the presence of silver nitrate. 561

![Chemical reaction](image)
The preparation of disulfide (360b), and its reaction with amines has earlier been investigated. The disulfide (360b) when reacted with amines, in the absence of any added catalysts, yields the ammonium salt (360c) as the only isolable product. Therefore, the reaction of ammonia with the disulfide (360b) in the presence of silver nitrate was attempted to study the possible formation of isothiazole (360) via the sulfenamide intermediate (342a).

However, the reaction of disulfide (360b) with ammonia in the presence of silver nitrate or cuprous chloride yielded only the aminal (400) as the isolable product of the reaction.
Thus, chloramine seems to be a specific and generally applicable reagent for effecting the cyclization of mercaptoacrylonitrile intermediates to isothiazoles. Though the reaction has been successful for the synthesis of a variety of 3-amino-5-(N-substituted)aminoisothiazoles, the attempted cyclization of cyanothioacetamide (346a) and the salt of 3-mercapto-3-aminoacrylonitrile (347a) to the 3,5-diaminoisothiazoles (346) and (347) with chloramine was not successful.

The failure to obtain diaminoisothiazoles may be due to a variety of side reactions taking precedence over the sulfenamide formation, or due to the decomposition of the sulfenamide (342b) by deprotonation of the NH, under the alkaline conditions employed in the reaction, before
the sulfenamide intermediate could stabilize by intramolecular cyclization to aminoisothiazole.

\[
\begin{align*}
\text{NO. ON} & - Y - Y - (342b) \\
\end{align*}
\]

The amino groups of primary sulfenamides are known to undergo normal condensations with carbonyl compounds. Some of the methods of synthesis of 1,2-benzisothiazoles and analogues can be considered as proceeding by the intramolecular cyclization of an arylsulfenamide with an ortho carbonyl function. Therefore, it appeared likely that chloramine could also be employed for the cyclization of other enethiolizable monothio \(\beta\)-dicarbonyl derivatives such as the thioamide derivatives obtainable from the reaction of isothiocyanates with ketones and enamines. Indeed, such an approach was found successful for the preparation of \(N\)-substituted, 5-aminoisothiazole derivatives. Thus, the cyclization of the phenyl isothiocyanate adducts of \(\alpha\)-methylene ketones such as ethyl
acetoacetate, acetylacetone, benzoylacetonitrile, benzoylacetone, dimedone, cyclohexanone and benzoylacetonitrile yielded the 5-phenylaminoisothiazoles (401-406) (Scheme XI) (Table XI).

The isothiazoles 401, 402, 405 and 406 were also obtained by the reaction of the enamine-isothiocyanate adducts 401a, 402a, 405a and 406a with chloramine.
The isothiazoles (401) and (402), thus obtained, have earlier been synthesized by Goerdeler and co-workers\textsuperscript{190,199} by the oxidative cyclization of phenyl isothiocyanate adducts derived from primary enamines. The present method of cyclization with chloramine is attractive in that the thioamides derived by the reaction of isothiocyanates with \(\alpha\)-methylene ketones, as well as primary, secondary or tertiary enamines can be employed as the starting material in place of the C-adducts of primary enamines necessary in the oxidative cyclization method.

During the course of this work, a few reports have appeared on the synthesis of mononuclear and condensed isothiazoles by the cyclization of mercaptocarbonyl intermediates and analogues. The isothiazolo(5,4-b)-quinoline (347)\textsuperscript{562} and thieno(2,3-d)isothiazole (348)\textsuperscript{45} have been prepared by the cyclization of 2-mercapto-3-formylquinoline (347a) and 2-mercapto-3-acetyltiophene (348a) employing chloramine. 5-Arylisothiazoles have been prepared by the cyclization of aryl 2-dimethylaminovinyl thiokerones with hydroxylamine-O-sulfonic acid.\textsuperscript{491}
Cyanamide is known to undergo reactions analogous to malononitrile. Similar to the cyclization of cyanothioamide derivatives of active methylene nitriles to 3-aminoisothiazoles, the N-cyanothiourea derivative (407a) resulting from the condensation of phenyl isothiocyanate with cyanamide could be cyclized to the 3-aminothiadiazole (407) with chloramine.
Reactions of Aminoisothiazoles and Synthesis of Isothiazolo(3,4-d)pyrimidines.

The aminoisothiazoles obtained in the present study are all functionally substituted isothiazoles. Therefore, it was thought of interest to investigate some of the reactions of the isothiazoles synthesized.

The amino group at the 3-position undergoes normal acylation reactions with acid chlorides or anhydrides yielding the corresponding acylamino compounds (408-411). The aminoisothiazole (360) reacts with isothiocyanates to yield the thioureas (412) and (413).

The reaction of aminoamide (390) with dimethylformamide and phosphorous oxychloride proceeds with dehydration of the amide function to give the o-cyanofor-
mamidine derivative (414) which was also obtained by the reaction of 3-amo-4-cyanoisothiazole (388) with dimethylformamide-phosphorous oxychloride.

The cyano, ester and amide groups present at the 4-position of the isothiazoles undergo the normal reactions expected of them. The esters (360) and (366) could be hydrolyzed to the isothiazole-4-carboxylic acids (418) and (419) with aqueous alkali. The 3-aminoisothiazole-4-carboxylic acid (420) was obtained by the alkaline hydrolysis of the corresponding nitrile, ester or the amide (388-390).
Treatment of the nitrile (388) with sulfuric acid followed by aqueous work up yielded the amide (390). While the hydrolysis of 3-amino-4-cyano-5-phenylaminoisothiazole (358) was unsuccessful under acidic conditions, the isothiazoles (358, 363 and 365) could, smoothly, be converted to the amides (422, 423 and 424) by alkaline hydrolysis.

The isothiazole-N-methyl carboxamide (421) was obtained by the reaction of 3-amino-4-carbethoxyisothiazole (360) with methylamine. The aminoamide (421) when reacted with triethyl orthoformate yielded 3-ethoxy-
methyleneaminoisothiazole (415) as the product of the reaction.

The 3-amino-4-cyano-5-methylthioisothiazole (388) when reacted with 30% hydrogen peroxide in acetic acid yielded the sulfone (425). This 5-methylsulfonyl-3-amino-4-cyanoisothiazole (425) reacted smoothly with aqueous methylamine to yield the 3-amino-4-cyano-5-methylaminoisothiazole (351) which was found to be identical with the compound obtained by the alternative route involving the reaction of methyl isothiocyanate with malononitrile and cyclization of the intermediate with chloramine.

However, attempts to react (425) with aqueous ammonia at room temperature or gaseous ammonia in refluxing
dioxane led to the recovery of the unreacted starting material instead of 3,5-diamino-4-cyanoisothiazole.

It is of interest to note that 4-cyano-3,5-bis(methylsulfonyl)isothiazole (349) has been found to undergo facile displacement reaction not only with alkylamines but also with ammonia under mild conditions to
yield the corresponding 3-methylsulfonyl-4-cyano-5-amino-isothiazole (349a). Thus the failure of (425) to react with ammonia reflects the diminished reactivity of 425 towards nucleophiles due to the presence of an electron donating NH₂ group at the 3-position as against the electron withdrawing methylsulfonyl group present at the 3-position in 349.

An interesting ring transformation reaction was observed in an attempted diazotization of the aminoester (360). The treatment of the aminoester in phosphoric acid with aqueous sodium nitrite yielded a product exhibiting a cyanogroup absorption in the IR spectrum. The product was characterized as the cyanomethylene
benzothiazoline (399) by its identity with an authentic sample prepared by the known method. The formation of (399) can be rationalized as occurring via the intramolecular nucleophilic attack by the arylamine moiety on the ring sulfur atom, with the concomitant S-N bond cleavage and elimination of nitrogen as depicted in the Scheme XII.

\[
\begin{align*}
&\text{R} = \text{CO}_2\text{C}_2\text{H}_5 \\
\end{align*}
\]

SCHEME XII

3-Aminoisothiazole derivatives, as well as, 5-arylamino-3-amino-1,2,4-thiadiazoles have been reported to undergo normal diazotization reactions.\(^{331, 563, 564}\) The reaction of 3-amino-1,2-benzisothiazole (350a) with HNO\(_2\)
has been found to yield the disulfide (350) by ring cleavage reaction.\(^\text{565}\)

![Chemical structure](image)

The ring transformation of isothiazole (360) to benzothiazole (399) has a formal resemblance to the reported base catalyzed transformation of some isothiazolines (445a) and 1,2,4-thiadiazolines (446a) to benzothiazoles (445) and (446).\(^\text{156, 566}\)

![Chemical structure](image)
Isothiazolo(3,4-d)pyrimidines

Among a variety of condensed ring systems incorporating isothiazoles, the synthesis of isothiazolopyrimidines has attracted considerable attention. The synthesis of compounds belonging to isothiazolo(3,4-d)-,\textsuperscript{96,219,220,348,567} -(4,3-d)-,\textsuperscript{488,568} -(5,4-d)-,\textsuperscript{200,541,569-571} -(4,5-d)-,\textsuperscript{488,568} and -(2,3-a)pyrimidines\textsuperscript{212} have been reported.

\[ \begin{array}{cc}
\text{(3,4-d)} & \text{(4,3-d)} \\
\text{(5,4-d)} & \text{(4,5-d)} \\
\text{(2,3-a)} & 
\end{array} \]

Biological activities such as cyclic nucleotide phosphodiesterase inhibitory activity,\textsuperscript{567} sedative\textsuperscript{571} and antitumor activities\textsuperscript{541} have been reported in isothiazolo(3,4-d)pyrimidines (447)\textsuperscript{567} and isothiazolo(5,4-d)pyrimidines (448)\textsuperscript{571} and (449).\textsuperscript{541}
The synthesis of isothiazolo(3,4-d)pyrimidines by the cyclization of appropriate isothiazole intermediates, or by the construction of isothiazole ring on a suitably substituted pyrimidine has been reported. Hartke and Peshkar have synthesized a few isothiazolopyrimidines of the type (450) by the reaction of corresponding 3-amino-4-cyanoisothiazoles (450a) with triethyl orthoformate followed by the cyclization of the ethoxymethylene derivative with amines.

Isothiazolopyrimidines (451) have been synthesized by the oxidative cyclization of 5-thiocarbamoyl-6-amino-
pyrimidines (451a) obtained by the reaction of the corresponding 6-aminopyrimidines with isothiocyanates.\textsuperscript{219,220}

The reaction of 6-aminopyrimidines with dimethylformamide and thionylchloride has been found to yield, directly, 3-dimethylaminoisothiazolo(3,4-d)pyrimidines.\textsuperscript{567}

As a part of the investigations on the reaction of 3-aminoisothiazoles obtained in the present study, an attempt was made to cyclize some of the 4-functionalized 3-aminoisothiazoles to isothiazolo(3,4-d)pyrimidines.

The reaction of the o-cyanoamidine (414) with ammonium acetate yielded the 4-aminoisothiazolo(3,4-d)-pyrimidine (426). This was also obtained by the reaction of the aminonitrile (388) with triethyl orthoformate and
ammonium acetate. Similarly, the aminonitrile (358) yielded the pyrimidine (428) on reaction with triethyl orthoformate and ammonium acetate.

\[ \text{(414)} \quad \text{(426)} \quad \text{(388)} \]

The α-aminonitrile (358) when reacted with triethyl orthoformate and aniline yielded a compound, analysing for \( \text{C}_{17}\text{H}_{13}\text{N}_{5}\text{S} \), which did not exhibit cyano absorption in the IR spectrum. It exhibited UV maxima at 203, 237, 270, 287, 324, and 425 nm and therefore assigned the bisphenylamino isothiazolopyrimidine structure (429). The formation of (429) can occur by several pathways. But it appears likely that the formation of the pyrimidine (429) takes place by
The reaction of the o-aminonitrile (388) with acetonitrile under the influence of dry hydrogen chloride yielded the 4-aminoisothiazolopyrimidine (427). Similarly, the acid-catalyzed condensation of 3-amino-4-carbethoxyisothiazole (389) or isothiazole-4-carboxamide (390) with acetonitrile gave the 4-oxoisothiazolo(3,4-d)pyrimidine (433).
The reaction of o-aminonitriles (388) and (358) with carbon disulfide, according to the method of Taylor, yielded the 4,6-dimercaptoisothiazolo(3,4-d)-pyrimidines (430) and (431).
The 3-methylthio-4-oxoisothiazolopyrimidine (432) was obtained by the reaction of the o-aminoamide (390) with triethyl orthoformate. The reaction of the o-aminoamide (390) with triethyl orthoacetate yielded an intermediate, probably the acetiminoether (433a) which cyclized to 4-oxo-6-methylisothiazolopyrimidine (433) in refluxing.
acetic acid.

The cyclization of the aminoamides (422) and (424) with triethyl orthoformate yielded the isothiazolopyrimidines (434) and (435). The pyrimidines (432) and (434) were also obtained by a one-pot reaction involving the condensation of the 3-amino-4-carbethoxy-isothiazoles (389) and (360) with triethyl orthoformate and ammonium acetate. Similar reactions of the aminoesters (389) and (360) with triethyl orthoformate and benzylamine gave the corresponding 5-benzylisothiazolo(3,4-d)pyrimidines (436) and (437).

\[
\begin{align*}
\text{(422) } &\text{ } R = \text{H} \\
\text{(424) } &\text{ } R = \text{CH}_3 \\
\text{(389) } &\text{ } RX = \text{MeS} \\
\text{(360) } &\text{ } RX = \text{PhNH} \\
\text{(434) } &\text{ } R = \text{H} \\
\text{(435) } &\text{ } R = \text{CH}_3 \\
\text{(436) } &\text{ } RX = \text{MeS} \\
\text{(437) } &\text{ } RX = \text{PhNH}
\end{align*}
\]
The reaction of the aminoester (360) with triethyl orthoformate and aniline, when conducted in the presence of a trace of sulfuric acid or hydrochloric acid, yielded a compound identified as the formylaminoisothiazole (408). However, when this reaction was conducted in the absence of any acidic catalyst, the product obtained was the amidine (416) which could be cyclized to the pyrimidine (438) by refluxing in a high boiling solvent.

The 3-aminoisothiazole (360) when reacted with diethyl ethoxymethyleneimalonate yielded the enaminoester (417). Attempts to cyclize 417 to the isothiazolo(2,3-a)-
pyrimidine (439) under acidic, basic or thermal conditions failed to yield the expected pyrimidine (439). While the attempted cyclization under mild conditions gave back the uncyclized starting material, even a brief period of reflux in diphenyl ether lead to extensive decomposition of the starting material.

Physical and Spectroscopic Properties

All the isothiazoles and isothiazole(3,4-d)pyrimidines synthesized are crystalline solids. 3-Amino-5-alkylamino- and 5-dialkylaminoisothiazole-4-carbonitriles,
as well as the 5-alkylamino- and 5-arylamino-3-amino-isothiazole-4-carboxylic acid esters are colorless compounds and the 3-amino-5-arylamino-4-cyanoisothiazoles are pale brown to buff colored compounds. While most of the 3-amino-4-carbethoxyisothiazoles are moderately soluble in ethanol, the corresponding 4-cyanoisothiazoles are only sparingly soluble in ethanol. In general, the melting points of 4-cyanoisothiazoles are much higher than those of the corresponding esters. While the 3-amino-5-arylamino-isothiazoles are weakly basic compounds and nearly insoluble in dilute hydrochloric acid, the 5-alkylamino and 5-dialkylamino substituted 3-aminoisothiazole derivatives are freely or moderately soluble in dilute hydrochloric acid. Nearly all the diaminoisothiazoles are insoluble in dilute sodium hydroxide solution.

In the IR spectrum all the 3-aminoisothiazoles exhibit three or four characteristic N-H stretching absorptions in the region 3500-3180 cm$^{-1}$. The N-H stretching absorptions of 3-amino-4-cyanoisothiazoles with dialkylamino, aryloxy, arylthio or alkylthio substituents at the 5-position appear in the region 3420-3180 cm$^{-1}$. 
4-Cyanoisothiazoles exhibit strong C≡N stretching absorption around 2240 cm⁻¹ to 2200 cm⁻¹ due to the conjugated nitrile group. In most of the 4-cyanoisothiazoles, this absorption appears in the region 2220 cm⁻¹ to 2210 cm⁻¹. The aminoisothiazoles derived from cyanoacetic esters and phenylsulfonylacetonitrile are devoid of any cyano group absorptions in this region. Most of the aminoisothiazoles exhibit intense absorption in the region 1650 cm⁻¹ to 1610 cm⁻¹.

The UV spectral data of the 3,5-diaminoisothiazoles, 5-methylthio- and 5-phenylthio-3-aminoisothiazoles are presented in Table XVI and that of isothiazolo(3,4-d)pyrimidines are given in Table XVII.

![Chemical Structure](image)

(330)

An examination of the UV spectra of 3,5-diaminoisothiazoles (330; $R_1R_2N =$ alkylamino or dialkylamino)
reveals the presence of two characteristic absorptions around 215nm and 260nm. The spectra of the corresponding 5-arylaminoisothiazoles (330; $R_1R_2N = \text{aryl amino}$) are characterized by the presence of three absorptions around 220, 285 and 315nm. The longer wavelength absorption around 315nm is of lower intensity and is often seen as a shoulder to the main absorption at 285nm. 4-Cyanoisothiazoles and the corresponding 4-carbethoxyisothiazoles exhibit similar absorption pattern.

The 3-amino-4-cyanoisothiazoles with an alkylamino substituent at 5-position (351, 353, 355 and 356) exhibit absorption around 218nm ($\log \varepsilon 4.07-4.11$) and 262nm ($\log \varepsilon 4.26-4.3$). The 5-benzylaminoisothiazole (357) absorbs at 212 and 262nm. The 3-amino-4-carbethoxy-5-methylaminoisothiazole (352) and the ethylaminoisothiazole (354) exhibit absorption peaks at 225, 262nm and at 218, 262nm, respectively. The 5-morpholino- and 5-pyrrolidino-3-amino-4-cyanoisothiazoles (378) and (381) also show the characteristic absorption peaks at 214, 267nm and at 220, 267nm, respectively.

The UV spectra of the 5-arylaminoisothiazoles
(358, 360, 362 and 366) are characterized by the presence of a longer wavelength absorption at 310-320nm (log ε 4.02-4.06), in addition to the absorptions at 282-285nm (log ε 4.18-4.19) and at around 215nm. The presence of an aryl substituent on the 5-amino nitrogen possibly contributes to the bathochromic shift of the characteristic absorption occurring at 262nm in the spectra of 5-alkylaminoisothiazoles.

While the spectra of the 5-alkylaminoisothiazoles (352-356, 378 and 381) show no significant change in the absorption pattern in 0.1N HCl, the 5-arylaminoisothiazoles (358, 360 and 366) exhibit marked changes. The addition of acid leads to the complete disappearance of the absorption at 315nm and the absorption at 285nm also undergoes a hypsochromic shift to 275nm. The spectra of 3-amino-5-methylthioisothiazoles (387-390) are similar to that of the corresponding 5-arylaminoisothiazoles and exhibit three absorption maxima around 210, 280 and 310nm. The longer wavelength absorption of 5-methylthioisothiazole-4-carboxamide (390) occurs as a barely observable shoulder around 310nm.
The 4-amino-3-methylthioisothiazolo(3,4-d)pyrimidines (426) and (427) exhibit absorption maxima at 230, 302 and 346nm. The 3-methylthioisothiazoloypyrimidin-4-ones (433) and (436) exhibit common absorption maxima in the region of 255, 285 and 320nm. The isothiazolopyrimidines (434) and (437) show common absorptions at 203, 237 and 341nm.

The NMR spectrum of 3-amino-4-carbethoxy-5-methylaminoisothiazole (352) in DMSO-d$_6$ shows a broad two proton singlet at $\delta$ 6.22, exchangeable with D$_2$O, due to the primary NH$_2$ group. Of interest is the appearance of N-CH$_3$ signal at $\delta$ 2.85 as a three proton doublet ($J$=4.9 Hz) due to the coupling with the N-H proton which appears as a broad, poorly resolved, one proton quartet at $\delta$ 7.70 ($J$=4.9 Hz). Addition of D$_2$O results in the disappearance of the NH signal and the collapse of the methyl doublet to a singlet.
The presence of primary NH₂ group in the 3,5-diaminoisothiazole (352) receives confirmation from both IR and NMR spectra. This observation along with the fact that the CH₃ group protons couple with the proton residing on the adjacent nitrogen, leads to the conclusion that the 3,5-diaminoisothiazole (352) exists, predominantly, in the diamine form 352 and not in the iminotautomeric forms 352a-c.

Protons attached to weakly basic nitrogen atoms (pKa 1-3.5) are known to couple with those on the adjacent carbon atoms. The observation of characteristic splitting of a methyl, methylene or methine protons by the adjacent N-H proton has been adduced to as the evidence for the existence of N-alkyl secondary enamines and potentially tautomerizable secondary alkylamino compounds in the amine form. 87,157,178,196,302,574,575
The NMR spectrum of 3-amino-4-carbethoxy-5-ethylaminoisothiazole (354) in CDCl$_3$ also exhibits the characteristic broad two proton singlet due to the primary NH$_2$ group at $\delta$ 5.7. The methylene protons of the CH$_3$CH$_2$NH group occurs as a quintet at $\delta$ 3.2 due to its coupling with the adjacent CH$_3$ as well as the NH protons. The signal due to the NH$_2$ group at the 3-position in the 3,5-diaminoisothiazoles (360, 364, 366, 372, 374 and 379) occurs as a broad two proton singlet at $\delta$ 4.9-5.7.
The NMR spectral data together with the UV and IR spectral characteristics suggest that the potentially tautomerizable 3,5-diaminoisothiazoles 453 exist predominantly in the diamine form. The establishment of the tautomeric nature of a wide variety of heterocyclic compounds by physical and spectroscopic methods has attracted considerable attention during recent years and has been the subject of a recent review by Elguero et al. 575

The mass spectra of all the aminoisothiazoles exhibit intense molecular ion peaks which is often the base peak. The fragmentation pattern exhibited by the 3-amino-4-cyano-5-alkylaminoisothiazoles (351, 353, 355, 356 and 357) is shown in Scheme XIII. The loss of H from the molecular ion of 351 or an alkyl radical from the molecular ions of 353, 356 and 357 by the radical initiated α-cleavage, possibly, leads to the iminium ion of m/e 153, observed in the spectra of these compounds. Loss of NH2CN from this fragment yields the ion of m/e 111. Loss of ethylene or butylene from (353) or (356), by McLafferty rearrangement, yields the ion of m/e 140 which may be formulated as 454. The peak observed at m/e 125 corresponds to the loss of the 5-alkylamino substituent as aldimine. The radical
\( R = H \) m/e 153
\( R = CH_3 \) m/e 167
\( R = CH_2=CH \) m/e 179
\( R = C_3H_7 \) m/e 195
\( R = C_2H_5 \) m/e 229

\( (455a) \) m/e 125
\( (455b) \)

\( (456) \) \( R = H \), m/e 123
\( (456a) \) \( R = CH_3 \), m/e 137

\( (457) \) m/e 97
\( (458) \) m/e 92
\( (459) \) m/e 106

SCHEME XIII
cation thus formed may be formulated as 455a or 455b.

Some of the other common ions of m/e 123, 97 and 92 found in the spectra of 353, 355, 356 and 357 may be formulated as the ions 456-458. The ions of m/e 137 and 106 found in the spectrum of 351 are possibly due to the ions 456a and 459, respectively.

The 3-amino-4-carbethoxy-5-alkylaminoisothiazoles (352) and (354) exhibit the fragmentation pattern depicted in Scheme XIV. Loss of ethylene or ethyl radical from the parent ions give peaks of low intensity. Loss of EtO* from the molecular ions lead to the acylium ions which fragment further by loss of CO or NH₂CN. Direct loss of EtOH molecule from the molecular ions of 352 and 354, due to the ortho effect, gives ions of m/e 155 and 169, respectively. The direct loss of EtOH is confirmed by the observation of metastable ion peaks at m/e 119.5 (201 → 155), and at m/e 132.8 (215 → 165) in the spectrum of 352 and 354, respectively. Loss of R* from the ions of m/e 155 and 169 yields the ion of m/e 154 which loses CO to give the fragment of m/e 126. The peaks observed at m/e 128 and 107 in the spectra of
SCHEME XIV
(354) and (352) may be formulated as the ions 460 and 461.

The mass spectrum of 3-amino-4-cyano-5-morpholino-isothiazole (378) exhibits peaks at m/e 195, 181 and 179 which may be due to the ions formed by the loss of CH$_3$, CHO$^-$ and CH$_3$O$^-$ from the molecular ion of m/e 210. The peak at m/e 152 corresponds to the loss of CH$_2$O and CH$_2$ = CH$_2$ from the parent ion. The 3-amino-4-cyano-5-(4-methylpiperazino)isothiazole (379) gives an intense molecular ion peak at m/e 223 and additional peaks at m/e 181, 152 and 138 which are in common with those observed in the spectrum of 378.
Some of the intense peaks observed in the spectrum of 3-amino-4-cyano-5-arylaminoisothiazoles (358, 365 and 369) are due to the loss of NH$_3$, S, SNH$_2$ and SNH$_2$CN from the molecular ions. The ions of m/e 168, 182 and 236 can be formulated as 462 and the fragments of m/e 142 and 156 may be due to the radical cation 463.

The above mode of fragmentation is also observed in the spectrum of 3-amino-4-cyano-5-(4-methoxyphenylamino)-
SCHEME XV
isothiazole (367). Some of the other peaks observed in the spectrum are due to the fragmentation of the molecular ion, as depicted in Scheme XV.

As in the case of 3-amino-4-carbethoxy-5-alkylaminoisothiazoles, the 5-phenylamino-4-carbethoxyisothiazole (360) shows a direct loss of $C_2H_5OH$ which could be confirmed by the observation of the corresponding metastable ion peak. The loss of $S$, $SH$, $SNH^-$, and $SNH_2CN$ from this ion accounts for most of the intense peaks observed in the spectrum as shown in Scheme XVI. Similar fragmentation patterns were observed in the spectra of the 5-arylamino-4-carbethoxyisothiazoles (364) and (370).

3-Amino-4-t-butoxycarbonyl-5-(phenylamino)isothiazole (361) gives a peak at m/e 235 which can be formulated as the odd electron ion 469. The metastable peak at m/e 189.8 corresponds to this transformation (291→235). The loss of $CO_2H$ from the ion 469 yields the ion of m/e 190. Of interest is the observation of a metastable ion
SCHEME XVI
peak at m/e 200.4 corresponding to the loss of H$_2$O from the ion 469 to yield the ion of m/e 217. The peaks at m/e 218, 185, 169 and 144 are in common with the peaks observed in the mass spectrum of the corresponding ethyl ester (360).

3-Amino-5-(phenylamino)isothiazole-4-carboxylic acid (418) also exhibits peaks at m/e 217 and 144, in common with those observed in 360 and 361. The peak of m/e 191 may be due to the formation of ion 470 by the decarboxylation of the acid (418). The ion 470 further
loses NH$_3$ and SNH$_2$ to yield the observed ions 471 and 472 at m/e 174 and 143, respectively. The spectrum of the 3-amino-5-(4-methylphenylamino)isothiazole-4-carboxylic acid (419) shows degradation pattern similar to that of 418.

3-Amino-5-(phenylamino)isothiazole-4-carboxamide (422) exhibits similar degradation pattern. Some of the intense peaks in the mass spectrum of the amide (422) can be rationalized as shown in Scheme XVII. The 5-(4-methylphenylamino)isothiazole-4-carboxamide (424) exhibits analogous degradation pattern.

The spectra of 3-amino-4-cyano-5-(phenylthio)isothiazole (387) exhibits peaks at m/e 216, 201 and 169 due to the loss of NH$_3$ and one or two sulfur atoms. Some of the intense peaks observed are explained on the basis of
SCHEME XVII
formation of thiirenium ion of m/e 191 due to the loss of NH₂CN from the parent ion and its subsequent degradation as shown in Scheme XVIII. The spectrum also exhibits an intense peak at m/e 109 due to C₆H₅S⁺.

Some of the fragments observed in the spectra of 3-amino-4-cyano-5-aryloxyisothiazoles (383-386) are due to the loss of S, SNH₂ and SNH₂CN from the corresponding molecular ions to yield the ions 473, 474 and 474a.

3-Amino-4-cyano-5-(p-toluenesulfonamido)isothiazole (377) exhibits an intense peak at m/e 155 due to the ion 475 and at m/e 139 due to the loss of p-CH₃C₆H₄SO₂ from the molecular ion. The intense peak observed at m/e 91 is due to the tropylium ion.
SCHEME XVIII

\[
\begin{align*}
\text{NC} & \quad \text{NH}_2 \\
\text{S} & \quad \text{S} \\
-\text{SNH}_2\text{CN} & \quad \rightarrow & -\text{NH}_2\text{CN} \\
\text{m/e 159} & \quad \rightarrow & \text{m/e 191} \\
-\text{CN} & \quad \rightarrow & -\text{S} \\
\text{m/e 133} & \quad \rightarrow & \text{m/e 127} \\
-\text{Ph}^+ & \quad \rightarrow & \text{m/e 114}
\end{align*}
\]

SCHEME XVIII
3-Amino-4-cyano-5-(methylsulfonyl)isothiazole (425) exhibits an even electron ion peak at m/e 124 due to the loss of CH$_3$SO$_2$ from the molecular ion and at m/e 79 due to CH$_3$SO$_2^+$. 

3-Amino-4-phenylsulfonyl-5-phenylaminoisothiazole (362) loses C$_6$H$_5$SO$_2$ from the molecular ion to yield an ion of m/e 190. Other intense ion peaks observed in the mass spectrum are at m/e 266, 250, 173, 163, 148 and 143. The fragments of m/e 190, 173 and 148 may be formulated as the ions 476a, 476b and 476c, respectively.
The mass spectrum of 3-amino-5-(methylthio)isothiazole-4-carboxamide (390) exhibits an intense peak at m/e 172 due to the loss of ammonia. Loss of CO, CH$_2$S from the ion of m/e 172 and the loss of NH$_2$CN and CO from the acylium ion of m/e 173 may account for the fragments of m/e 144, 126, 131 and 103 found in the spectrum of this compound (Scheme XIX).

The mass spectrum of the ester (388) also exhibits peaks at m/e 173 and 172 due to the loss of EtO$^+$ or EtOH from the molecular ion of m/e 218. Of interest is the observation of intense peaks at m/e 130 and 102 in the spectrum of this compound in contrast to the intense peaks at m/e 131 and 103 in the amide (390).
It appears unlikely that the fragment of m/e 130 arises from the molecular ion by the successive loss of (NH₂CN and CH₂S) or (CH₂S and NH₂CN). If it is assumed that this ion of m/e 130 arises from the radical cation of m/e 172, its formulation as 478a-c instead of 477 can explain the formation of fragments of m/e 130, 126 and 102 observed in the spectrum of this compound.

(388) m/e 218

(477) m/e 172

(478a)

(478b)

(478c)

m/e 130

m/e 130

m/e 126

m/e 102
SCHEME XX

(392) m/e 219

- NH₂

m/e 203

H₂N-S

H₂N-S

m/e 173

m/e 173

M⁺ →

m/e 158

- S

m/e 126

m/e 110

- NH₂
3-Amino-4-carbethoxyisothiazole-5-sulfenamide (392) exhibits intense molecular ion peak. The fragmentation pattern exhibited by this compound can be represented as shown in Scheme XX.

3,4-Diaminoisothiazolo[3,4-d]isothiazole (391) exhibits fragments of m/e 156, 145, 140 and 141 which may be due to the loss of NH\textsubscript{2}, HCN, S and (NH\textsubscript{2} and NH\textsubscript{2}CN) from the molecular ion.

Under electron impact, isothiazoles are known to yield fragments arising from the cleavage of N-S or S-C...
bonds, as shown in Scheme XXI.\textsuperscript{331,333,426}

\begin{center}
\begin{tikzpicture}

\node (s) at (0,0) {\textbf{SCHEME XXI}};

\node (r1) at (-1.5,0) {R_1};
\node (r2) at (0,0) {R_2};
\node (r3) at (1.5,0) {R_3};
\node (s1) at (0,-1) {\text{S}};
\node (n1) at (0,-2) {\text{N}};
\node (c1) at (0,-3) {\text{C}};
\node (n2) at (0,-4) {\text{N}};
\node (c2) at (0,-5) {\text{C}};
\node (n3) at (0,-6) {\text{N}};

\draw[-stealth] (r1) -- (r2);
\draw[-stealth] (r2) -- (r3);
\draw[-stealth] (r3) -- (s1);
\draw[-stealth] (s1) -- (n1);
\draw[-stealth] (n1) -- (c1);
\draw[-stealth] (c1) -- (n2);
\draw[-stealth] (n2) -- (c2);
\draw[-stealth] (c2) -- (n3);

\node (r4) at (3,0) {R_4};
\node (r5) at (4,0) {R_5};
\node (s2) at (3,-1) {\text{S}};
\node (n4) at (3,-2) {\text{N}};
\node (c3) at (3,-3) {\text{C}};
\node (n5) at (3,-4) {\text{N}};
\node (c4) at (3,-5) {\text{C}};
\node (n6) at (3,-6) {\text{N}};

\draw[-stealth] (r4) -- (r5);
\draw[-stealth] (r5) -- (s2);
\draw[-stealth] (s2) -- (n4);
\draw[-stealth] (n4) -- (c3);
\draw[-stealth] (c3) -- (n5);
\draw[-stealth] (n5) -- (c4);
\draw[-stealth] (c4) -- (n6);

\node (r6) at (5,0) {R_6};
\node (r7) at (6,0) {R_7};
\node (s3) at (5,-1) {\text{S}};
\node (n7) at (5,-2) {\text{N}};
\node (c5) at (5,-3) {\text{C}};
\node (n8) at (5,-4) {\text{N}};
\node (c6) at (5,-5) {\text{C}};
\node (n9) at (5,-6) {\text{N}};

\draw[-stealth] (r6) -- (r7);
\draw[-stealth] (r7) -- (s3);
\draw[-stealth] (s3) -- (n7);
\draw[-stealth] (n7) -- (c5);
\draw[-stealth] (c5) -- (n8);
\draw[-stealth] (n8) -- (c6);
\draw[-stealth] (c6) -- (n9);

\node (r8) at (7,0) {R_8};
\node (r9) at (8,0) {R_9};
\node (s4) at (7,-1) {\text{S}};
\node (n10) at (7,-2) {\text{N}};
\node (c7) at (7,-3) {\text{C}};
\node (n11) at (7,-4) {\text{N}};
\node (c8) at (7,-5) {\text{C}};
\node (n12) at (7,-6) {\text{N}};

\draw[-stealth] (r8) -- (r9);
\draw[-stealth] (r9) -- (s4);
\draw[-stealth] (s4) -- (n10);
\draw[-stealth] (n10) -- (c7);
\draw[-stealth] (c7) -- (n11);
\draw[-stealth] (n11) -- (c8);
\draw[-stealth] (c8) -- (n12);

\end{tikzpicture}
\end{center}

The mass spectra of 3-aminoisothiazoles synthesized in the present study, in general, do not exhibit the loss of NH\textsubscript{2}• or HCN from the molecular ion. Similarly, the formation of thioacylium ion (479) or the azirinium ion (480) does not seem to be a significant mode of fragmentation of the molecular ions.

Some of the significant peaks observed are due to the acetylenic fragment (482) or the thiirenium ion (481) formed by the loss of NH\textsubscript{2}CNS or NH\textsubscript{2}CN from the molecular ions.
ions or stable fragment ions derived from the molecular ions.

The fragments arising by the loss of NH₃, S, SH⁻ and SNH₂⁺ from the molecular ions or other stable ions derived from the molecular ions, can be given many isomeric formulations and many mechanistic pathways can be envisaged for such transformations. The loss of NH₃ from 3-amino-5-(N-monosubstituted)aminoisothiazoles can occur by the pathways (a), (b) or (c) involving S-N, N-C or S-C bond cleavage as shown in Scheme XXII. Loss of S can be explained as depicted in Scheme XXIII.
SCHEME XXII
SCHEME XXII (continued)
SCHEME XXIII

(a)  \[
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{CN} \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\end{align*}

(b)  \[
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}

(c)  \[
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
\rightarrow
\begin{align*}
\text{Y} & \text{H} \text{N} \text{R} \\
\text{S} & \text{NH}_2 \\
\text{R} & \text{HN} \\
\end{align*}
The formation of an ion of m/e 125 observed in the mass spectra of 3-amino-4-cyano-5-alkylaminosothiazoles can be thought of as occurring by the loss of alkylamine as an aldimine with a hydrogen transfer as shown below:

\[
\begin{align*}
\text{R} & \quad \text{NC} \quad \text{NH}_2 \\
 & \quad \text{HN} \quad \text{C} \quad \text{H} \\
\end{align*}
\]

The spectra of 3-methyl- and 3-phenyl-4-acetyl-5-phenylaminoisothiazoles (402) and (403) exhibit intense peak at m/e 43 due to CH$_3$C=O. The intense M-15 peak at m/e 217 in the spectrum of the isothiazole (402) corresponds to the acylium ion (483) or the nitrilium ion (485). The peaks of high intensity at m/e 279 and 103 and of moderate intensity at m/e 217 and 251 observed in the spectrum of 403 may be due to the ions 484, PhC=N$, 485 and 486, respectively.
The intense peak at m/e 141 in the spectrum of 402 and at m/e 203 in the spectrum of 403 corresponds to the loss of C₆H₅N from the molecular ion. The ion thus formed may be formulated as 487a or 487b.

\[
\begin{align*}
\text{487a} & : \text{CH}_3 \\ 
\text{487b} & : \text{CH}_3 \\
R & = \text{CH}_3, \text{m/e 141} \\
R & = \text{C}_6\text{H}_5, \text{m/e 203}
\end{align*}
\]

The mass spectrum of the benzisothiazole (404) shows ion peaks at m/e 176, 148, 136 and 128; in common with the peaks deserved in the spectrum of 403. The intense peak at m/e 190 corresponds to the loss of \((\text{CH}_3)_2\text{S}-\text{CH}_2\text{CN}\) from the molecular ion. This ion of m/e 190 could be formulated as 490 or 491. Some of the peaks observed at the higher mass region arise by the loss of \(\text{CH}_3\cdot\), \(\text{HCO}\cdot\), \(\text{HS}^-\) and by the loss of \((\text{CH}_3, \text{CO and butylene})\). The ions of m/e 216 and 188 could be formulated as the ions 488 and 489.

\[
\begin{align*}
\text{404) m/e 272} & : \text{CH}_3 \\
\text{488) m/e 216} & : \text{CH}_3 \\
\text{489) m/e 188} & : \text{CH}_3
\end{align*}
\]
The spectrum of the tetrahydrobenzisothiazole (405) shows peaks of moderate intensity at m/e 202, 197 and 190 which may be due to the loss of CH₂=CH₂, SH⁺ and CH₂CN⁺ from the molecular ion. Loss of CH₂CN⁺ from the fragment of m/e 202 possibly yields the observed ion of m/e 162. A peak of moderate intensity at m/e 138 may be due to fragment ion arising by the loss of C₆H₅NH⁺ from the molecular ion.
The mass spectrum of the 4-cyano-3-phenyl-5-phenylaminoisothiazole (406) shows a peak of low intensity at m/e 251 due to the loss of CN\textsuperscript{-} from the molecular ion. Loss of C\textsubscript{6}H\textsubscript{5} from the molecular ion yields the nitrilium ion of m/e 200. The intense peak at m/e 174 may be due to the thiirenium ion (492) and the peak at m/e 142 may be due to the ion 493. Intense peaks observed at m/e 103 and 104 may be attributed to C\textsubscript{6}H\textsubscript{5}-C≡N\textsuperscript{+} and C\textsubscript{6}H\textsubscript{5}-C≡N\textsuperscript{-}-H, respectively.

Isothiazolo(3,4-d)pyrimidines exhibit intense molecular ion peaks which are often the base peaks. The
4-amino-3-(methylthio)isothiazolopyrimidines (426) and (427) exhibit similar degradation pattern. They show the loss of S and SH from the molecular ion. The other major peaks observed in the spectra of these compounds can be attributed to the formation of fragment ions shown in Scheme XXIV. The peak observed at m/e 114 may be due to the nitrilium ion (494).

Some of the peaks observed in the spectrum of 4-amino-3-(phenylamino)isothiazolo(3,4-d)pyrimidine (428) may be due to the fragmentation of the molecular ion as depicted in Scheme XXV.

The mass spectra of 3-(methylthio)isothiazolo(3,4-d)-pyrimidin-4(3H)-ones (432) and (433) exhibit M-15, M-33 and M-43 peaks due to the loss of CH$_3^-$, SH$^-$ and HNCO from the molecular ion. Loss of SH$^-$ and HCN from the molecular ion of 432 and of SH$^-$ and CH$_3$CN from the molecular ion of 433 possibly leads to the ion of m/e 139. Some of the other peaks observed in the spectra of 432 and 433 are attributable to the fragments formed by the degradation of the
\[ R = \text{H}, \text{m/e 156} \]
\[ R = \text{CH}_3, \text{m/e 170} \]

\[ R = \text{H}, \text{m/e 152} \]
\[ R = \text{CH}_3, \text{m/e 166} \]

\[ R = \text{H}, \text{m/e 183} \]
\[ R = \text{CH}_3, \text{m/e 197} \]

\[ (494) \text{ m/e 114} \]
\[ \text{m/e 125} \]

\[ \text{R = H, m/e 125} \]
\[ \text{R = CH}_3, \text{m/e 139} \]

\text{SCHEME XXIV}
SCHEME XXVI
ions of m/e 154 and 168. These ions of m/e 154 and 168 may be formulated as the even electron ions 495 and 496 arising from the molecular ion by the loss of CH3 by hydrogen transfer rearrangement reactions. Some of the fragments observed in these spectra can be represented as shown in Scheme XXVI.

In the absence of confirmatory evidence from labelling studies or high resolution data, the mass spectral interpretations made, the structural formulations assigned to the fragment ions and the mechanistic ion decomposition pathways proposed in the present study are only tentative.

Biological Activity

The 3-aminoisothiazoles 358, 360, 364, 366, 367, 383 and 388-390 were screened for analgesic and antiinflammatory activities. The compounds 358, 360, 364, 366, 388-390 did not show any significant analgesic activity in mice when tested by writhing test. The isothiazole 383 exhibits 32.8% inhibition and 366 shows 30% inhibition of writhing response as against 70% by aspirin at the same dosage level of 300mg/kg p.o.
Compounds 358, 360, 364, 366, 383, and 389 did not exhibit any significant antiinflammatory activity when tested by carrageenin induced rat paw oedema method. While the compound 390 showed 13% inhibition of inflammation, 388 exhibited 36.45% inhibition as against 73.4% inhibition by phenylbutazone. The most active compound of the series was 425 which showed 60.24%, 52.28%, 21.66% and 11.66% inhibition of inflammation at 300, 200, 100 and 50mg/kg, respectively as compared to 70.34% inhibition exhibited by phenylbutazone at 300mg/kg p.o.

The isothiazolopyrimidine 437 did not exhibit any significant analgesic and antiinflammatory activities.

The isothiazoles 358, 360, 364, 367, 375, 376, 378, 383, 386, 388-392, 406 and 425 and isothiazolopyrimidines 433 and 437 were screened for antimicrobial activity. The preliminary reports indicate the absence of any significant antimicrobial activity in 390, 392, 416, 420, 433 and 437 against B. subtilis, E. coli, S. aureus, S. marcescens, S. typhi, P. aeruginosa, S. shigae and P. mirabilis
at 200 μg/ml concentration. However, the 3-amino-4-cyano-
5-(methylsulfonyl)isothiazole (425) was found to be highly
active against all the bacterial strains tested. The
minimum inhibitory concentration against *S. typhi* was found
to be 1.56 μg/ml. At 25 μg/ml the compound exhibited total
inhibition of growth of *S. typhi*, *E. coli*, *P. mirabilis*,
*S. shigae*, *B. subtilis*, *S. aureus* and *B. cereus*.

The aminoisothiazoles 358 and 360 did not show any
significant blood schizonticidal activity against *P. berghei*
in mice at 40-640 mg/kg, s.c. In the presumptive
causal prophylactic screen against *P. berghei* yoelii in
mice, the compounds 360 and 376 were inactive at 10-160
mg/kg, s.c., and the compounds 378 and 383 effected 1/5
cures at 10 mg/kg and 160 mg/kg, s.c., respectively. The
compound 358 did not show any significant antitrypanosomal acti-
vity against *T. rhodsiense* in mice at 106-424 mg/kg s.c. The
compounds 378 and 425 are under screening for anticancer activity.
**TABLE VI**

3-Aminoisothiazoles synthesized by the cyclization of isothiocyanate adducts of active methylene nitriles.

![Chemical Reaction Diagram](attachment:image.png)

<table>
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<tr>
<th>Compound No.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recryst. Solvent*</th>
<th>Molecular Formula</th>
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<td>60</td>
<td>E</td>
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<td>375</td>
<td>CN</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>236-238</td>
<td>48</td>
<td>D-E</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;SCl</td>
</tr>
<tr>
<td>376</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>144-146</td>
<td>40</td>
<td>E</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;SCl</td>
</tr>
<tr>
<td>377</td>
<td>CN</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-</td>
<td>287-289</td>
<td>27</td>
<td>D-E</td>
<td>C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

B = t-Butanol  
D = Dimethylformamide  
E = Ethanol
TABLE VII

3-Aminoisothiazoles synthesized by the cyclization of 3-mercapto-acrylonitrile salts resulting from the reaction of 3-methylthioacrylonitriles with sodium sulfide

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recryst. Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>358</td>
<td>CN</td>
<td>C₆H₅NH</td>
<td>230-232</td>
<td>69</td>
<td>D-E</td>
<td>C₁₀H₈N₄S</td>
</tr>
<tr>
<td>360</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>148-150</td>
<td>38</td>
<td>E</td>
<td>C₁₂H₁₃N₃O₂S</td>
</tr>
<tr>
<td>377</td>
<td>CN</td>
<td>p-CH₃C₆H₄SO₂NH</td>
<td>287-289</td>
<td>54</td>
<td>D-E</td>
<td>C₁₁H₁₀N₄O₂S₂</td>
</tr>
<tr>
<td>378</td>
<td>CN</td>
<td>Morpholino</td>
<td>194-196</td>
<td>71</td>
<td>D-E</td>
<td>C₈H₁₀N₄OS</td>
</tr>
<tr>
<td>379</td>
<td>CN</td>
<td>N-Methylpiperazino</td>
<td>158-160</td>
<td>51</td>
<td>M</td>
<td>C₉H₁₃N₅S</td>
</tr>
<tr>
<td>380</td>
<td>CN</td>
<td>Piperdine</td>
<td>186-188</td>
<td>56</td>
<td>M</td>
<td>C₉H₁₂N₄S</td>
</tr>
<tr>
<td>381</td>
<td>CN</td>
<td>Pyrrolidino</td>
<td>212-214</td>
<td>53</td>
<td>M</td>
<td>C₈H₁₀N₄S</td>
</tr>
<tr>
<td>388</td>
<td>CN</td>
<td>CH₃S</td>
<td>180-182</td>
<td>78</td>
<td>D-E</td>
<td>C₅H₅N₃S₂</td>
</tr>
<tr>
<td>389</td>
<td>CO₂C₂H₅</td>
<td>CH₃S</td>
<td>133-135</td>
<td>32</td>
<td>E</td>
<td>C₇H₁₀N₂O₂S₂</td>
</tr>
<tr>
<td>390</td>
<td>CONH₂</td>
<td>CH₃S</td>
<td>184-186</td>
<td>53</td>
<td>D-E</td>
<td>C₅H₇N₃O₂S₂</td>
</tr>
</tbody>
</table>

* D = Dimethylformamide; E = Ethanol; M = Methanol
### TABLE VIII

3-Aminoisothiazoles synthesized by the cyclization of 3-mercaptoacrylonitrile salts resulting from the reaction of active methylene nitriles with thionocarbonic acid derivatives.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁</th>
<th>X</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrst. Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>360</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>SCH₃</td>
<td>148-150</td>
<td>8</td>
<td>E</td>
<td>C₁₂H₁₃N₃O₂S</td>
</tr>
<tr>
<td>378</td>
<td>CN</td>
<td>Morpholine</td>
<td>Cl</td>
<td>194-196</td>
<td>38@</td>
<td>D-E</td>
<td>C₈H₁₀N₄OS</td>
</tr>
<tr>
<td>382</td>
<td>CN</td>
<td>C₂H₅O</td>
<td>Cl</td>
<td>200-202</td>
<td>40</td>
<td>E</td>
<td>C₆H₇N₃OS</td>
</tr>
<tr>
<td>383</td>
<td>CN</td>
<td>C₆H₅O</td>
<td>Cl</td>
<td>152-154</td>
<td>55</td>
<td>E</td>
<td>C₁₀H₇N₃OS</td>
</tr>
<tr>
<td>384</td>
<td>CN</td>
<td>o-CH₃C₆H₄O</td>
<td>Cl</td>
<td>111-112</td>
<td>26</td>
<td>M</td>
<td>C₁₁H₉N₃OS</td>
</tr>
<tr>
<td>385</td>
<td>CN</td>
<td>m-CH₃C₆H₄O</td>
<td>Cl</td>
<td>152-154</td>
<td>30</td>
<td>M</td>
<td>C₁₁H₉N₃OS</td>
</tr>
<tr>
<td>386</td>
<td>CN</td>
<td>p-CH₃C₆H₄O</td>
<td>Cl</td>
<td>151-153</td>
<td>43</td>
<td>M</td>
<td>C₁₁H₉N₃OS</td>
</tr>
<tr>
<td>387</td>
<td>CN</td>
<td>C₆H₅S</td>
<td>Cl</td>
<td>144-146</td>
<td>39</td>
<td>M</td>
<td>C₁₀H₇N₃S₂</td>
</tr>
<tr>
<td>389</td>
<td>CO₂C₂H₅</td>
<td>CH₃S</td>
<td>SCH₃</td>
<td>133-135</td>
<td>32</td>
<td>E</td>
<td>C₇H₁₀N₂O₂S₂</td>
</tr>
<tr>
<td>390</td>
<td>CONH₂</td>
<td>CH₃S</td>
<td>SCH₃</td>
<td>184-186</td>
<td>32</td>
<td>D-E</td>
<td>C₅H₇N₃OS₂</td>
</tr>
</tbody>
</table>

* D = Dimethylformamide;  E = Ethanol;  M = Methanol

@ The compound 378 was also obtained in 25% and 19% yield by employing ethyl 4-morpholinethionoformate and methyl 4-morpholinedithioformate, respectively, as the thiocarbonoylating agents.
**TABLE IX**

3-Aminoisothiazoles synthesized by the cyclization of the dithiolate salts derived from the reaction of active methylene nitriles with carbon disulfide.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁S</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystn. solvent</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>388</td>
<td>CN</td>
<td>CH₃S</td>
<td>180-182</td>
<td>55</td>
<td>D-E</td>
<td>C₅H₅N₃S₂</td>
</tr>
<tr>
<td>389</td>
<td>CO₂C₂H₅</td>
<td>CH₃S</td>
<td>133-135</td>
<td>28</td>
<td>E</td>
<td>C₇H₁₀N₂O₂S₂</td>
</tr>
<tr>
<td>390</td>
<td>CONH₂</td>
<td>CH₃S</td>
<td>184-186</td>
<td>51</td>
<td>D-E</td>
<td>C₅H₇N₃O₂S₂</td>
</tr>
<tr>
<td>391</td>
<td>NH₂-C=N-S</td>
<td></td>
<td>273-275</td>
<td>70</td>
<td>D-E</td>
<td>C₄H₄N₄S₂</td>
</tr>
<tr>
<td>392</td>
<td>CO₂C₂H₅</td>
<td>NH₂S</td>
<td>151-153</td>
<td>27</td>
<td>E</td>
<td>C₆H₉N₃O₂S₂</td>
</tr>
</tbody>
</table>

* D = Dimethylformamide
  E = Ethanol
TABLE X

3-Hydroxy-4-cyanoisothiazoles obtained by the cyclization of ethyl 2-cyano-3-mercaptoacrylate and 2-cyano-3-mercaptoacrylamide salts

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>RX</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystn. Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>393</td>
<td>C₆H₅NH</td>
<td>224-226</td>
<td>28</td>
<td>D-E</td>
<td>C₁₀H₇N₃OS</td>
</tr>
<tr>
<td>394</td>
<td>o-CH₃C₆H₄NH</td>
<td>199-201</td>
<td>26</td>
<td>M</td>
<td>C₁₁H₉N₃OS</td>
</tr>
<tr>
<td>395</td>
<td>p-CH₃C₆H₄NH</td>
<td>222-224</td>
<td>29</td>
<td>M</td>
<td>C₁₁H₉N₃OS</td>
</tr>
<tr>
<td>396</td>
<td>CH₃S</td>
<td>228-231(d)</td>
<td>9</td>
<td>E</td>
<td>C₅H₄N₂O₂S²</td>
</tr>
</tbody>
</table>

* D = Dimethylformamide  
  E = Ethanol  
  M = Methanol
TABLE XI

5-Aminoisothiazoles synthesized by the cyclization of ketone-isothiocyanate adducts and enamine-isothiocyanate adducts.

![Chemical structures](image)

| Compound No. | R₁ | R₂ | NR₃R₄ | Method | M.P. °C | Yield % | Recry- | Molecular  |
|--------------|----|----|-------|--------|--------|--------| solvent* | Formula    |
| 401          | CO₂C₂H₅ | CH₃ | -     | A      | 70-72  | 61     | H      | C₁₃H₁₄N₂O₂S |
| 401          | CO₂C₂H₅ | CH₃ | NH₂   | B      | 70-72  | 82     | H      | C₁₃H₁₄N₂O₂S |
| 402          | COCH₃  | CH₃ | -     | A      | 132-134| 69     | E      | C₁₂H₁₂N₂O₅S |
| 402          | COCH₃  | CH₃ | N     | B      | 132-134| 35     | E      | C₁₂H₁₂N₂O₅S |
| 403          | COCH₃C₆H₅| -   | A     | 99-101 | 48     | E      | C₁₇H₁₄N₂O₅S |
| 404          | COCH₃C(CH₃)₂CH₂ | - | A | 129-131 | 25     | E | C₁₅H₁₆N₂O₅S |
| 405          | -H₂C-CH₂-CH₂-CH₂ - | A | 190-192 | 26     | E | C₁₃H₁₄N₂O₅S |
| 405          | -H₂C-CH₂-CH₂-CH₂ - | B | 190-192 | 79     | E | C₁₃H₁₄N₂O₅S |
| 406          | CN    | C₆H₅ | -     | A     | 268-270| 72     | D      | C₁₆H₁₄N₃S  |
| 406          | CN    | C₆H₅ | NH₂   | B     | 268-270| 72     | D      | C₁₆H₁₄N₃S  |

* D = Dimethylformamide; E = Ethanol; H = n-Hexane
### TABLE XII

**Derivatives of 3-Aminoisothiazoles**

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R1</th>
<th>R2R3N</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystn.</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>408</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>HCONH</td>
<td>140-142</td>
<td>69</td>
<td>E</td>
<td>C_{13}H_{13}N₃O₃S</td>
</tr>
<tr>
<td>409</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>CH₃CONH</td>
<td>148-150</td>
<td>66</td>
<td>E</td>
<td>C_{14}H_{15}N₃O₃S</td>
</tr>
<tr>
<td>410</td>
<td>CN</td>
<td>C₆H₅NH</td>
<td>C₆H₅CONH</td>
<td>289-291</td>
<td>47</td>
<td>D</td>
<td>C_{17}H_{12}N₄OS</td>
</tr>
<tr>
<td>411</td>
<td>CN</td>
<td>CH₃S</td>
<td>CH₃CONH</td>
<td>195-197</td>
<td>70</td>
<td>E</td>
<td>C₇H₇N₃OS₂</td>
</tr>
<tr>
<td>412</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>C₆H₅NHCSNH</td>
<td>128-130</td>
<td>75</td>
<td>E</td>
<td>C_{19}H_{18}N₄O₂S₂</td>
</tr>
<tr>
<td>413</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>p-CH₃C₆H₄NHCSNH</td>
<td>145-147</td>
<td>58</td>
<td>E</td>
<td>C_{20}H_{20}N₄O₂S₂</td>
</tr>
<tr>
<td>414</td>
<td>CN</td>
<td>CH₃S</td>
<td>(CH₃)₂N=CH=N</td>
<td>100-102</td>
<td>53</td>
<td>EA-CH</td>
<td>C₈H₁₀N₄S₂</td>
</tr>
<tr>
<td>415</td>
<td>CONHC₃</td>
<td>C₆H₅NH</td>
<td>C₂H₅OCH=N</td>
<td>126-128</td>
<td>66</td>
<td>E</td>
<td>C_{14}H_{16}N₄O₂S</td>
</tr>
<tr>
<td>416</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>C₆H₅N=CHNH</td>
<td>152-154</td>
<td>55</td>
<td>E</td>
<td>C_{19}H_{18}N₄O₂S</td>
</tr>
<tr>
<td>417</td>
<td>CO₂C₂H₅</td>
<td>C₆H₅NH</td>
<td>(C₂H₅O₂C)₂=CHNH</td>
<td>92-94</td>
<td>69</td>
<td>E</td>
<td>C_{20}H_{23}N₃O₆S</td>
</tr>
</tbody>
</table>

* GH = Cyclohexane
D = Dimethylformamide
E = Ethanol
EA = Ethyl acetate
### TABLE XIII

3-Aminoisothiazole-4-carboxylic acid derivatives synthesized from 3-amino-4-substituted isothiazoles

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recryst. solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>418</td>
<td>CO₂H</td>
<td>C₆H₅NH₈</td>
<td>165-167(d)</td>
<td>64</td>
<td>D-E</td>
<td>C₁₀H₉N₃O₂S</td>
</tr>
<tr>
<td>419</td>
<td>CO₂H</td>
<td>p-CH₃C₆H₄NH</td>
<td>165-167(d)</td>
<td>60</td>
<td>D-E</td>
<td>C₁₁H₁₁N₃O₂S</td>
</tr>
<tr>
<td>420</td>
<td>CO₂H</td>
<td>CH₃S</td>
<td>217-219(d)</td>
<td>79</td>
<td>E</td>
<td>C₅H₆N₂O₂S²</td>
</tr>
<tr>
<td>421</td>
<td>CONHCH₃</td>
<td>C₆H₅NH₈</td>
<td>185-187</td>
<td>65</td>
<td>E</td>
<td>C₁₁H₁₂N₄O₅S</td>
</tr>
<tr>
<td>422</td>
<td>CONH₂</td>
<td>C₆H₅NH₈</td>
<td>232-234</td>
<td>77</td>
<td>D-E</td>
<td>C₁₀H₁⁰N₄O₅S</td>
</tr>
<tr>
<td>423</td>
<td>CONH₂</td>
<td>o-CH₃C₆H₄NH</td>
<td>208-210</td>
<td>56</td>
<td>D-E</td>
<td>C₁₁H₁₂N₄O₅S</td>
</tr>
<tr>
<td>424</td>
<td>CONH₂</td>
<td>p-CH₃C₆H₄NH</td>
<td>220-224</td>
<td>73</td>
<td>D-E</td>
<td>C₁₁H₁₂N₄O₅S</td>
</tr>
<tr>
<td>425</td>
<td>CN</td>
<td>CH₃SO₂</td>
<td>207-209</td>
<td>59</td>
<td>EA</td>
<td>C₅H₅N₃O₂S²</td>
</tr>
</tbody>
</table>

* D = Dimethylformamide; E = Ethanol; EA = Ethyl acetate
### TABLE XIV

4-Amino- and 4-mercaptoisothiazolo(3,4-d)pyrimidines

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystn.</th>
<th>Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>426</td>
<td>CH₃S</td>
<td>NH₂</td>
<td>H</td>
<td>248-250</td>
<td>57</td>
<td>D-E</td>
<td>C₆H₆N₄S₂</td>
<td></td>
</tr>
<tr>
<td>427</td>
<td>CH₃S</td>
<td>NH₂</td>
<td>CH₃</td>
<td>240-242</td>
<td>47</td>
<td>D-E</td>
<td>C₇H₈N₄S₂</td>
<td></td>
</tr>
<tr>
<td>428</td>
<td>C₆H₅NH</td>
<td>NH₂</td>
<td>H</td>
<td>252-254</td>
<td>70</td>
<td>D-E</td>
<td>C₁₁H₉N₅S</td>
<td></td>
</tr>
<tr>
<td>429</td>
<td>C₆H₅NH</td>
<td>C₆H₅NH</td>
<td>H</td>
<td>246-248</td>
<td>47</td>
<td>D-E</td>
<td>C₁₇H₁₃N₅S</td>
<td></td>
</tr>
<tr>
<td>430</td>
<td>CH₃S</td>
<td>SH</td>
<td>SH</td>
<td>&gt;360</td>
<td>41</td>
<td>D-E</td>
<td>C₆H₅N₃S₄</td>
<td></td>
</tr>
<tr>
<td>431</td>
<td>C₆H₅NH</td>
<td>SH</td>
<td>SH</td>
<td>&gt;360</td>
<td>51</td>
<td>D-E</td>
<td>C₁₁H₈N₄S₃</td>
<td></td>
</tr>
</tbody>
</table>

* D = Dimethylformamide  
E = Ethanol
### TABLE XV

**Isothiazolo(3,4-d)pyrimidin-4(5H)-ones**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystn. Solvent</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>432</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>H</td>
<td>H</td>
<td>300-302(d)</td>
<td>80</td>
<td>D-E</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>433</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>331-333</td>
<td>75</td>
<td>D-E</td>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>434</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>H</td>
<td>H</td>
<td>270-272</td>
<td>66</td>
<td>D-E</td>
<td>C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>435</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NH</td>
<td>H</td>
<td>H</td>
<td>258-260</td>
<td>58</td>
<td>E</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>436</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>H</td>
<td>160-162</td>
<td>69</td>
<td>D-E</td>
<td>C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>437</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>H</td>
<td>200-202</td>
<td>75</td>
<td>D-E</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>438</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>H</td>
<td>202-204</td>
<td>63</td>
<td>E</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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* D = Dimethylformamide  
E = Ethanol
**TABLE XVI**

UV Spectral data of 3-aminoisothiazole derivatives

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>X</th>
<th>R</th>
<th>( \lambda_{max}(\text{C}_2\text{H}_5\text{OH or CH}_3\text{OH}) ) nm (log( \varepsilon ))</th>
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</thead>
<tbody>
<tr>
<td>351</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>218(4.30), 260(4.11).</td>
</tr>
<tr>
<td>352</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NH</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>225(4.42), 262(4.25).</td>
</tr>
<tr>
<td>353</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>218(4.27), 262(4.07).</td>
</tr>
<tr>
<td>354</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>218(4.29), 266(4.08).</td>
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<tr>
<td>355</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>217(4.28), 262(4.10).</td>
</tr>
<tr>
<td>356</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>217(4.26), 262(4.09).</td>
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<tr>
<td>357</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>212(4.35), 262(4.14).</td>
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<tr>
<td>358</td>
<td>Morpholino</td>
<td>CN</td>
<td></td>
<td>214(4.12), 267(4.06).</td>
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<tr>
<td>359</td>
<td>Pyrralidino</td>
<td>CN</td>
<td></td>
<td>220(4.29), 267(4.66).</td>
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<tr>
<td>360</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>CN</td>
<td></td>
<td>212(4.33), 282(4.19), 310(4.03).</td>
</tr>
<tr>
<td>361</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>222(4.32), 286(4.18), 316(4.02).</td>
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<tr>
<td>362</td>
<td>p-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NH</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>222(4.34), 285(4.18), 320(4.06).</td>
</tr>
<tr>
<td>363</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;NH</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>207(4.48), 223(4.41), 230(4.25), 312(4.03).</td>
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<tr>
<td>364</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;S</td>
<td>CN</td>
<td></td>
<td>209, 278, 314.</td>
</tr>
<tr>
<td>365</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>CN</td>
<td></td>
<td>207(4.14), 279(4.08), 310Sh.(3.66)</td>
</tr>
<tr>
<td>366</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
<td>212(4.27), 281(4.23), 312Sh.(3.74)</td>
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<tr>
<td>367</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td>212(4.18), 279(4.02), 310Sh.(3.63)</td>
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</table>
## TABLE XVII
UV Spectral data of isothiazolo(3,4-d)pyrimidines

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Type</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>( R_3 )</th>
<th>( \lambda_{max}(C_{2}H_{5}OH \text{ or } CH_{3}OH) \text{ nm (log } \epsilon \text{) }</th>
</tr>
</thead>
<tbody>
<tr>
<td>426</td>
<td>A</td>
<td>( CH_{3}S )</td>
<td>( NH_{2} )</td>
<td>( H )</td>
<td>230, 304, 349</td>
</tr>
<tr>
<td>427</td>
<td>A</td>
<td>( CH_{3}S )</td>
<td>( NH_{2} )</td>
<td>( CH_{3} )</td>
<td>230(4.40), 302(4.08), 346(4.02)</td>
</tr>
<tr>
<td>429</td>
<td>A</td>
<td>( C_{6}H_{5}NH )</td>
<td>( C_{6}H_{5}NH )</td>
<td>( H )</td>
<td>203(4.57), 237(4.28), 270(4.26), 287(4.26), 324(4.22), 425(3.67)</td>
</tr>
<tr>
<td>433</td>
<td>B</td>
<td>( CH_{3}S )</td>
<td>( H )</td>
<td>( CH_{3} )</td>
<td>221(4.26), 252(4.09), 269(4.08), 284sh(3.98), 295(4.07), 317(4.01)</td>
</tr>
<tr>
<td>434</td>
<td>B</td>
<td>( C_{6}H_{5}NH )</td>
<td>( H )</td>
<td>( H )</td>
<td>204(4.22), 237(4.11), 251(4.22), 341(4.07)</td>
</tr>
<tr>
<td>436</td>
<td>B</td>
<td>( CH_{3}S )</td>
<td>( C_{6}H_{5}CH_{2} )</td>
<td>( H )</td>
<td>204(4.26), 227(4.19), 259(4.10), 267(4.04), 285(3.85), 296(3.86), 322(3.91)</td>
</tr>
<tr>
<td>437</td>
<td>B</td>
<td>( C_{6}H_{5}NH )</td>
<td>( C_{6}H_{5}CH_{2} )</td>
<td>( H )</td>
<td>203(4.30), 237(4.07), 266(4.2), 342(3.98)</td>
</tr>
<tr>
<td>438</td>
<td>B</td>
<td>( C_{6}H_{5}NH )</td>
<td>( C_{6}H_{5} )</td>
<td>( H )</td>
<td>221(4.38), 234(4.22), 261(4.21), 284(4.13), 295(4.20), 320(4.20)</td>
</tr>
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</table>
EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded in Nujol mulls on Perkin-Elmer Model 337 spectrophotometer and in potassium bromide pellets on Perkin-Elmer Model 377 spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer. Nuclear Magnetic Resonance spectra were taken on a Varian A-60 spectrometer, and the chemical shifts are given in $\delta$ units as parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a Varian Atlas CH-7 electron-impact mass spectrometer at 70ev using direct insertion probe. Thin layer chromatography was performed on microscope slides (2 x 7.5cm) coated with silice gel G using chloroform, chloroform-methanol (9:1), and cyclohexane-ethyl acetate (4:1) as solvent systems and the spots were visualized by exposure to iodine vapors.
Preparation of aqueous chloramine solution.

An alkaline solution of sodium hypochlorite was prepared by passing 14g of chlorine into a mixture of 150g of ice and 100ml of 25% aqueous sodium hydroxide solution, maintained at 0°C by external cooling. To the hypochlorite solution was added 100g of ice and the mixture was treated with 100ml of an ice-cold 10% aqueous ammonium hydroxide solution with vigorous stirring and cooling. The volume of the resulting aqueous chloramine solution was made upto 500ml with ice-cold water.

The ice-cold aqueous chloramine solution (500ml) thus prepared normally contains 0.15-0.17 moles of chloramine as determined by iodometric method and was usually employed immediately after preparation, for the cyclization reaction with 0.1 mole of the thiol substrate.

In the above procedure, an aqueous solution of potassium hypochlorite of appropriate strength prepared by the treatment of calcium hypochlorite with aqueous potassium carbonate-potassium hydroxide can also be employed in place of aqueous sodium hypochlorite solution.
3-Amino-4-cyano-5-(methylamino)isothiazole (351).

To a solution of sodium ethoxide (0.025 mole), prepared by dissolving 0.6g of sodium in 25ml of absolute ethanol, was added, with cooling, 1.65g (0.025 mole) of malononitrile, followed by 1.85g (0.025 mole) of methyl isothiocyanate. The mixture was stirred at room temperature for 12 hours and added to 125ml of ice-cold aqueous chloramine solution prepared as described above. The reaction mixture was allowed to stand at room temperature for 12 hours, and the solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 2.5g (65%) of colorless crystalline product, m.p. 257-259°C.

Analysis: C₅H₆N₄S(154.2) Requires C, 38.96; H, 3.90%
  Found C, 39.05; H, 4.14%

IR (Nujol): 3450, 3350, 3220(NH); 2200(CN); 1615, 1585, 1155, 1085, 1020, 900, 795 cm⁻¹
IR (KBr): 3450, 3350, 3210(NH); 2200(CN); 1625, 1590, 1520, 1460, 1405, 1170, 1100, 1020, 910, 800, 710, 640 cm⁻¹

UV (EtOH): 218nm(log ε 4.30), 260(4.11)
UV (0.1NHCl): 223nm(log ε 4.32), 262(4.24)

NMR (CF₃CO₂H): δ 3.2(3H, s, CH₃NH); 7.8(broad s, NH)

MS, m/e: 154(M⁺), 137, 106, 81
3-Amino-4-carbethoxy-5-(methylamino)isothiazole (352).

To a solution of sodium ethoxide (0.025 mole), prepared by dissolving 0.6g of sodium in 25ml of absolute ethanol, was added, with cooling, 2.83g (0.025 mole) of ethyl cyanoacetate, followed by 1.85g (0.025 mole) of methyl isothiocyanate. The mixture was refluxed for 10 minutes, allowed to stand at room temperature for 12 hours and added to 125ml of ice-cold aqueous chloramine solution prepared as described earlier. The reaction mixture was allowed to stand at room temperature for 12 hours, and the solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 3.0g (60%) of colorless crystalline product, m.p. 145-147°C.

Analysis: \( C_7H_{11}N_3O_2S(201.25) \) Requires C, 41.77%; H, 5.51%; Found C, 41.92%; H, 5.81%

IR (Nujol): 3500, 3360, 3300, 3180(NH); 1630, 1590, 1550, 1225, 1075, 1000, 910, 760, 745 cm\(^{-1}\)

UV (EtOH): 225nm(log \( \epsilon \) 4.42), 262(4.25)

UV (0.1N HCl): 228nm(log \( \epsilon \) 4.42), 262(4.22)

NMR (\( \text{Me}_2\text{SO-d}_6 \)): 8 1.28(3H, t, J=7.1 Hz, \( \text{CH}_3\text{CH}_20 \)); 2.85(3H, d, J=4.9 Hz, \( \text{CH}_3\text{NH} \), collapses to a singlet on \( \text{D}_2\text{O} \) exchange); 4.26(2H, q, J=7.1 Hz, \( \text{CH}_2\text{CH}_20 \)); 6.22(2H, broad s, \( \text{NH}_2 \), exchangeable with \( \text{D}_2\text{O} \)); 7.70(1H, q, J=4.8 Hz, \( \text{CH}_3\text{NH} \), exchangeable with \( \text{D}_2\text{O} \)).

MS, m/e: 201(\( \text{M}^+ \)), 155, 127, 107, 82
3-Amino-4-cyano-5-(ethylamino)isothiazole (353).

Malononitrile 1.65g (0.025 mole) was reacted with 2.18g (0.025 mole) of ethyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of freshly prepared aqueous chloramine solution according to the procedure described for 351. Recrystallization from dimethylformamide-ethanol yielded 2.5g (60%) of colorless crystalline product, m.p. 203-205°C.

Analysis: C₆H₈N₄S (168.22) Requires C, 42.83; H, 4.79% Found C, 43.01; H, 5.03%

IR (Nujol): 3470, 3380, 3260(NH); 2200(C≡N); 1640, 1600, 1520, 1180, 1130, 960, 890, 830 cm⁻¹

UV (EtOH): 218nm (log ε 4.27), 262 (4.07)

UV (0.1N HCl): 224nm (log ε 4.30), 264 (4.25)

NMR (CF₃COOH): 1.5 (3H, t, CH₃CH₂NH); 3.4 (2H, m, CH₂CH₂NH); 7.7 (broad m, NH)

MS, m/e: 168(M⁺), 153, 140, 123, 97, 92
3-Amino-4-carbethoxy-5-(ethylamino)isothiazole (354).

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 2.18g (0.025 mole) of ethyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of freshly prepared, ice-cold aqueous chloramine solution according to the procedure described for 352. Recrystallization from ethanol afforded 2.7g (50%) of colorless crystalline product, m.p. 103-105°C.

Analysis: C₈H₁₃N₃O₂S (215.27) Requires C, 44.63%; H, 6.09%
Found C, 44.86%; H, 6.39%

IR (Nujol): 3440, 3410, 3300, 3180 (NH); 1675, 1590, 1530, 1245, 1190, 1125, 1035, 905, 835, 795 cm⁻¹

UV (EtOH): 218nm (log ε 4.29), 266 (4.08)
UV (0.1N HCl): 229nm (log ε 4.40), 266 (4.23)

NMR (CDCl₃): δ 1.32(3H, t, CH₃CH₂NH); 1.34(3H, t, CH₃CH₂O); 3.2(2H, quintet, CH₃CH₂NH); 4.4(2H, q, CH₃CH₂O); 5.7(2H, broad s, NH₂); 7.45(1H, m, CH₃CH₂NH)

MS, m/e: 215(M⁺), 169, 141, 128, 124
5-(Allylamino)-3-Amino-4-cyanoisothiazole (355).

Malononitrile 1.55g (0.025 mole) was reacted with 2.48g (0.025 mole) of allyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of aqueous chloramine solution according to the procedure described for 351. The crude product thus obtained was recrystallized from ethanol to obtain 2.5g (56%) of colorless crystalline product, m.p. 153-155°C.

Analysis: C₇H₈N₄S(180.23) Requires C, 46.65%; H, 4.47%
Found C, 46.96%; H, 4.84%

IR (Nujol): 3440, 3350, 3220(NH); 2210(C≡N); 1620, 1575, 1505, 1340, 1240, 1170, 1100, 1015, 980, 950, 910, 800 cm⁻¹

UV (EtOH): 217nm(log 4.28), 262(4.10)

UV (0.1N HCl): 224nm(log 4.29), 264(4.26)

NMR (CF₃COOH): δ 4.1(2H, broad m, CH₂ = CH-CH₂NH); 5.7(3H, m, CH₂=CH-CH₂NH); 7.9(broad m, NH)

MS, m/e: 180(M⁺), 163, 153, 111, 100
3-Amino-5-(n-butylamino)-4-cyanoisothiazole (356).

Malononitrile 1.65g (0.025 mole) was reacted with 2.88g (0.025 mole) of n-butyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of freshly prepared aqueous chloramine solution according to the procedure described for 351. Recrystallization from ethanol afforded 2.0g (41%) of colorless crystalline product, m.p. 165-167°C.

Analysis: C₈H₁₂N₄S (196.27) Requires C, 48.95; H, 6.16%
            Found    C, 49.10; H, 6.17%

IR (Nujol) : 3470, 3380, 3260(NH); 2220(C≡N); 1640,
            1590, 1130, 920, 810 cm⁻¹

UV (EtOH) : 217nm (logε 4.26), 262(4.09)
UV (0.1N HCl) : 224nm (logε 4.29), 264(4.26)
MS, m/e : 196(M⁺), 179, 167, 153, 140, 125
3-Amino-5-(benzylamino)-4-cyanoisothiazole (357).

Malononitrile 1.55g (0.025 mole) was reacted with 3.73g (0.025 mole) of benzyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the resulting adduct was treated with 125ml of aqueous chloramine solution according to the procedure described for 351. The crude product obtained was recrystallized from dimethylformamide-ethanol to yield 3.0g (52%) of colorless crystalline product, m.p. 192-194°C.

Analysis

IR (Nujol) : C, 3480, 3400, 3260(NH); 2240(C≡N); 1650, 1600, 1260, 1185, 1115, 925, 910, 820, 750 cm⁻¹

UV (EtOH) : 212nm(log ε 4.35), 262(4.14)

NMR (CDCl₃ + CF₃COOH) : δ 4.6(2H, broad s, C₆H₅OH₂NH); 7.45(5H, s, C₆H₅); 8.2(broad m, NH)

MS, m/e : 230(M⁺), 153, 139, 104, 97, 91
3-Amino-4-cyano-5-(phenylamino)isothiazole (358).

Method I: To a solution of sodium ethoxide (0.025 mole), prepared by dissolving 0.6g of sodium in 25ml of absolute ethanol was added, with cooling, 1.65g (0.025 mole) of malononitrile, followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and added to 125ml of ice-cold aqueous chloramine solution prepared as described earlier. The reaction mixture was allowed to stand at room temperature for 24 hours, cooled and the pH was adjusted to 7-8 with dilute hydrochloric acid. The solid obtained was filtered, washed with water, and dried. Recrystallization from dimethylformamide-ethanol yielded 3.8g (65%) of crystalline product, m.p. 230-232°C.

Analysis: C10H8N4S(216.26) Requires C, 55.54; H, 3.73% Found C, 55.87; H, 3.94%

IR (KBr): 3460, 3360, 3240(NH); 2210(C=N);
1630, 1595, 1570, 1495, 1450, 1235,
1105, 1025, 765, 700 cm⁻¹

UV (EtOH): 212nm(log ε 4.33), 282(4.19), 310(4.03)

UV (0.1N HCl): 222nm(log ε 4.28), 278(4.19)
Method II: To a solution of 4.30 g (0.02 mole) of 2-cyano-3-(methylthio)-3-(phenylamino)acrylonitrile in 20 ml of dimethylformamide, was added, with cooling, a solution of 2.23 g (0.02 mole) of fused sodium sulfide (70%) in 10 ml of water. The reaction mixture was stirred at room temperature for 24 hours and treated with 100 ml of ice-cold aqueous chloramine solution prepared as described earlier. The reaction mixture was allowed to stand at room temperature for 12 hours, cooled and the pH adjusted to 7-8 with dilute hydrochloric acid. The crude product thus obtained was filtered, washed, and dried. Recrystallization from dimethylformamide-ethanol yielded 3.0 g (69%) of the product, m.p. 230-232°C identical (mmp, TLC, IR) with the product obtained by Method I.
3-Amino-4-methoxycarbonyl-5-(phenylamino)isothiazole (359).

To a solution of sodium methoxide, prepared by dissolving 0.6g of sodium in 30ml of methanol, was added, with cooling and stirring, 2.48g (0.025 mole) of methyl cyanoacetate followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and added to 125ml of freshly prepared ice-cold aqueous chloramine solution. The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from methanol afforded 1.5g (24%) of colorless crystalline product, m.p. 166-168°C.

Analysis : C_{11}H_{11}N_{3}O_{2}S (249.29) Requires C, 53.00; H, 4.45%
Found C, 53.01; H, 4.66%

IR (Nujol) : 3500, 3270, 3180(NH); 1650, 1620, 1600, 1550, 1270, 1220, 1190, 1120, 1005, 920, 845, 815, 800, 780 cm^{-1}
3-Amino-4-carbethoxy-5-(phenylamino)isothiazole (360).

To a solution of sodium ethoxide (0.025 mole), prepared by dissolving 0.6g of sodium in 25ml of absolute ethanol was added, with cooling, 2.83g (0.025 mole) of ethyl cyanoacetate, followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and added to 125ml of ice-cold aqueous chloramine solution prepared as described earlier. The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 3.0g (46%) of colorless crystalline product, m.p. 148-150°C.

Analysis: C_{12}H_{13}N_{3}O_{2}S (263.31) Requires C, 54.73; H, 4.98; N, 15.96% Found C, 54.38; H, 5.14; N, 16.11%

IR (Nujol): 3490, 3290, 3180(NH); 1650, 1600, 1530, 1540, 1240, 1185, 1090, 1010, 800, 780, 760, 680 cm⁻¹

IR (KBr): 3500, 3290, 3180(NH); 1660, 1610, 1550, 1445, 1375, 1250, 1200, 1100, 1020, 790, 695 cm⁻¹

UV (EtOH): 222mn (log ε 4.32), 236(4.18), 316(4.02)

UV (0.1N HCl): 224mn (log ε 4.32), 272(4.18)
The following procedures were also employed for the preparation of salts of ethyl 2-cyano-3-mercapto-3-(phenyl-amino)acrylate in situ for reaction with aqueous chloramine solution to obtain $360$.

1. To a solution of potassium t-butoxide (0.025 mole), prepared by dissolving 0.98g of potassium in 30ml of t-butanol, was added, with cooling, 2.83g (0.025 mole) of ethyl cyanoacetate, followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and then reacted with 125ml of aqueous chloramine solution. The usual work-up yielded 3.0g (46%) of $360$.

2. To a suspension of 1.65g (0.025 mole) of finely divided potassium hydroxide (85%) in 20ml of dimethylformamide or dimethylsulfoxide was added, with cooling,
a mixture of 2.83g (0.025 mole) of ethyl cyanoacetate and 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and then reacted with 125ml of aqueous chloramine solution. The usual work-up yielded 2.4g (37%) of 360.

3. A solution of ethyl 2-cyano-3-mercapto-3-(phenyl-amino)acrylate 137 1.5g (6 mmole) in minimum quantity of ice-cold 10% sodium hydroxide was treated with 50ml of aqueous chloramine solution. Work-up of the reaction mixture yielded 0.7g (44%) of 360.

4. To a suspension of 3.38g (0.025 mole) of sodium salt of ethyl cyanoacetate in 15ml of dimethylformamide was added, with cooling, 2.33g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and reacted with 125ml of aqueous chloramine solution. Work-up of the reaction mixture yielded 2.0g (30%) of 360.

5. To a suspension of 7.0g (0.05 mole) of anhydrous potassium carbonate in 20ml of dimethylformamide was added, with cooling, a mixture of 5.65g (0.05 mole) of ethyl cyanoacetate and 6.75g (0.05 mole) of phenyl isothiocyanate.
After stirring at room temperature for 24 hours the mixture was reacted with 250ml of aqueous chloramine solution. The usual work-up yielded 3.5g (27%) of 360.

6. To a mixture of 2.83g (0.025 mole) of ethyl cyanoacetate and 3.38g (0.025 mole) of phenyl isothiocyanate in 20ml of dimethylformamide was added 2.53g (0.025 mole) of triethylamine. The mixture was stirred at room temperature for 6 hours, heated under reflux for 6 hours, cooled and reacted with 125ml of aqueous chloramine solution. The usual work-up yielded 0.8g (12%) of 360.

7. To a solution of sodium ethoxide (0.05 mole) in absolute ethanol was added, with cooling, 5.65g (0.05 mole) of ethyl cyanoacetate followed by 9.15g (0.05 mole) of methyl N-phenyldithiocarbamate. The reaction mixture was stirred at room temperature for 3 days and then reacted with 250ml of aqueous chloramine solution. Work-up of the reaction mixture yielded 1.0g (8%) of 360.

8. A solution of 3.34g (0.03 mole) of fused sodium sulfide (70%) in 10ml of water was added, with cooling, to a solution of 7.86g (0.03 mole) of ethyl 2-cyano-3-(methylthio)-3-(phenylamino)acrylate in 30ml of dimethylformamide. The mixture was heated on a steam bath for 8 hours, cooled and
reacted with aqueous chloramine solution. Work-up of the reaction mixture yielded 3.0g (38%) of 360.

3-Amino-4-t-butoxycarbonyl-5-(phenylamino)isothiazole (361).

$t$-Butyl cyanoacetate 3.53g (0.025 mole) was reacted with 3.38g (0.025 mole) of phenyl isothiocyanate in the presence of potassium t-butoxide (0.025 mole), prepared by dissolving 0.98g of potassium in 30ml of t-butanol. The mixture was treated with 125ml of freshly prepared aqueous chloramine solution according to the procedure described for 360. Recrystallization from t-butanol yielded 3.7g (51%) of colorless crystalline product, m.p. 145-147°C.

Analysis : $C_{14}H_{17}N_3O_2S(291.37)$ Requires C,57.71; H,5.88%
Found C,57.96; H,6.06%

IR (Nujol) : 3500, 3280, 3180(NH); 1670, 1620, 1600, 1560, 1285, 1270, 1175, 1120, 960, 855, 830, 790, 760 cm$^{-1}$

MS, m/e : 291(M$^+$), 235, 217, 185, 174, 144, 116, 104

3-Amino-5-(phenylamino)-4-(phenylsulfonyl)isothiazole (362).

Phenylsulfonylacetonitrile 4.88g (0.025 mole) was reacted with phenyl isothiocyanate 3.38g (0.025 mole) in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of ice-cold aqueous chloramine solution according to the procedure described for 358. Recrystallization from ethanol yielded 4.0g (48%) of crystalline product, m.p. 162-164°C.
Analysis: $C_{15}H_{13}N_{3}O_{2}S_{2}(331.41)$ Requires C, 54.36; H, 3.95%  
Found C, 54.73; H, 4.26%

IR (Nujol): 3450, 3310(NH); 1600, 1540, 1155, 1095, 915, 850, 810, 765 cm$^{-1}$

UV (MeOH): 207nm($\log \epsilon$ 4.48), 223(4.41), 280(4.25), 312(4.03)

NMR (CDCl$_3$): $\delta$ 5.50(2H, broad s, replaceable with D$_2$O, NH$_2$); 7.2-8.2(10H, m, Ar-H); 9.2(1H, broad s, replaceable with D$_2$O, C$_6$H$_5$NH)

MS, m/e: 331(M$^+$), 314, 266, 250, 224, 190, 173, 163, 148, 143, 104, 77

3-Amino-4-cyano-5-(2-methylphenyl)aminoisothiazole (363).

Malononitrile 1.65g (0.025 mole) was reacted with o-tolyl isothiocyanate 3.73g (0.025 mole) in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of freshly prepared ice-cold aqueous chloramine solution according to the procedure described for 358. Recrystallization from ethanol yielded 3.5g (61%) of the product, m.p. 176-178°C.

Analysis: $C_{11}H_{10}N_{4}S(230.29)$ Requires C, 57.37; H, 4.38%  
Found C, 57.04; H, 4.54%

IR (Nujol): 3470, 3370(NH); 2220(C$\equiv$N); 1610, 1580, 1270 1210, 1125, 1055, 970, 810, 775, 760 cm$^{-1}$

MS, m/e: 230(M$^+$), 213, 188, 180, 155, 128, 91
3-Amino-4-carbethoxy-5-[(2-methylphenyl)amino]isothiazole (364).

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.73g (0.025 mole) of o-tolyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of ice-cold aqueous chloramine solution according to the procedure described for 360.

Recrystallization from ethanol yielded 4.3g (62%) of colorless crystalline product, m.p. 138-140°C.

Analysis : \( \text{C}_{13}\text{H}_{15}\text{N}_{3}\text{O}_{2}\text{S} (277.34) \) Requires C, 56.30; H, 5.45%

Found C, 56.50; H, 5.79%

IR (Nujol) : 3500, 3290, 3180(NH); 1680, 1630, 1600, 1570, 1290, 1240, 1120, 1050, 855, 840, 785, 755 cm\(^{-1}\)

NMR (CDCl\(_3\)) : \( \delta \) 1.40(3H, t, \( \text{CH}_3\text{CH}_2\text{O} \)); 2.36(3H, s, o-\( \text{CH}_3\text{C}_6\text{H}_4 \)); 4.42(2H, q, \( \text{CH}_3\text{CH}_2\text{O} \)); 5.70(2H, broad s, replaceable with D\(_2\)O, \text{D}_2\text{O} ); 7.20(4H, m, Ar-4); 9.87(1H, broad s, o-\( \text{CH}_3\text{C}_6\text{H}_4\text{NH} \))

MS, m/e : 277(N\(^+\)), 231, 214, 198, 186, 160, 91, 77

3-Amino-4-cyano-5-[(4-methylphenyl)amino]isothiazole (365).

Malononitrile 1.65g (0.025 mole) was reacted with 3.73g (0.025 mole) of p-tolyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the
mixture was treated with 125ml of freshly prepared aqueous chloramine according to the procedure described for 358. Recrystallization from dimethylformamide-ethanol yielded 2.5g (44\%) of crystalline product, m.p. 233-235\degree C.

Analysis : C_{11}H_{10}N_{4}S(230.28) Requires C, 57.37; H, 4.38\%; Found C, 57.45; H, 4.44\%

IR (Nujol) : 3460, 3280, 3170(NH); 2220(C\equiv N); 1630, 1600, 1570, 1255, 955, 850, 830, 815, 780 \text{ cm}^{-1}

NMR (CF_{3}COOH) : 2.43(3H, s, o-CH_{3}C_{6}H_{4}); 7.33(4H, s, Ar-H); 9.25(broad s, NH)

MS, m/e : 230(M^{+}), 213, 198, 182, 155, 149, 116, 91, 77

3-Amino-4-carbethoxy-5-\((4\text{-methylphenyl})\text{amino}\)isothiazole (366).

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.73g (0.025 mole) of p-tolyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of freshly prepared aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol yielded 3.6g (52\%) of colorless crystalline product, m.p. 133-140\degree C.

Analysis : C_{13}H_{15}N_{3}O_{2}S(277.34) Requires C, 56.30; H, 5.45\%; Found C, 56.42; H, 5.80\%
239

IR (Nujol) : 3490, 3270 (NH); 1660, 1600, 1580, 1550,
1270, 1215, 1120, 1045, 820, 790 cm⁻¹

UV (EtOH) : 222nm (log ε 4.34); 285 (4.18), 320 (4.06)

UV (0.1N HCl) : 222nm (log ε 4.40); 270 (4.22)

NMR (CDCl₃) : 2.40 (3H, t, CH₃CH₂O); 230 (3H, p-CH₃C₆H₄NH);
4.40 (2H, q, CH₃CH₂O); 5.50 (2H, broad s, NH₂);
7.13 (4H, m, Ar-H); 9.83 (1H, broad s,
p-CH₃C₆H₄NH)

3-Amino-4-cyano-5-[(4-methoxyphenyl)amino]isothiazole (367).

Malononitrile 3.3g (0.05 mole) was reacted with 8.25g
(0.05 mole) of p-methoxyphenyl isothiocyanate in the presence
of sodium ethoxide (0.05 mole) in absolute ethanol and the
mixture was treated with 250ml of aqueous chloramine solution
according to the procedure described for 358. Recrystallization
from ethanol yielded 5.4g (44%) of crystalline product,
m.p. 213-215°C.

Analysis : C₁₁H₁₀N₄OS(246.29) Requires C, 53.64; H, 4.09%
Found C, 53.86; H, 4.48%

IR (Nujol) : 3440, 3340, 3220 (NH); 2210 (C≡N); 1620, 1580,
1550, 1245, 1190, 1120, 1045, 965, 840, 810,
755 cm⁻¹

MS, m/e : 246 (M⁺), 231, 203, 189, 157, 129, 108
3-Amino-4-carbethoxy-5-(4-methoxyphenyl)aminoisothiazole (353)

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 4.13g (0.025 mole) of p-methoxyphenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was reacted with 125ml of aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol yielded 3.5g (48%) of crystalline product, m.p. 114-116°C.

Analysis: $C_{13}H_{15}N_3O_3S$ (293.34) Requires C, 53.23%; H, 5.15%
Found C, 53.34%; H, 5.35%

IR (Nujol): 3480, 3300, 3180(NH); 1670, 1620, 1560, 1270, 1215, 1120, 1040, 835, 790 cm$^{-1}$

MS, m/e: 293($M^+$), 264, 247, 232, 204, 163, 134

3-Amino-4-cyano-5-(3-(trifluoromethyl)phenyl)aminoisothiazole (369).

Malononitrile 1.65g (0.025 mole) was reacted with 5.08g (0.025 mole) of m-(trifluoromethyl)phenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of aqueous chloramine solution according to the procedure described...
Recrystallization from ethanol yielded 4.0 g (56%) of crystalline product, m.p. 204-206°C.

Analysis: C_{11}H_{17}N_{4}SF_{3} (284.26) Requires C, 46.47%; H, 2.48%
Found: C, 46.57%; H, 2.72%

IR (Nujol): 3460, 3350, 3280, 3240 (NH); 2210 (C=O); 1610, 1560, 1245, 1185, 1130, 885, 835, 805 cm^{-1}

MS, m/e: 284 (M^+), 267, 244, 236, 224, 216, 211, 191, 145

3-Amino-4-carbethoxy-5-3-(trifluoromethyl)phenyl/amine/isothiazole (370).

Ethyl cyanoacetate 2.83 g (0.025 mole) was reacted with 5.08 g (0.025 mole) of m-(trifluoromethyl)phenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was reacted with 125 ml of aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol yielded 3.5 g (42%) of colorless crystalline product, m.p. 112-114°C.

Analysis: C_{13}H_{12}N_{3}O_{2}SF_{3} (331.22) Requires C, 47.12%; H, 3.65%
Found: C, 47.08%; H, 3.94%

IR (Nujol): 3460, 3360, 3180 (NH); 1600, 1550, 1270, 1200, 1170, 1125, 1080, 1035, 900, 890, 870, 830, 790, 780, 750 cm^{-1}

MS, m/e: 331 (M^+), 312, 285, 265, 253, 237, 212, 172, 145, 125
3-Amino-5-(2-chlorophenyl)amino-4-cyanoisothiazole (371).

Malononitrile 1.65g (0.025 mole) was reacted with 4.24g (0.025 mole) of o-chlorophenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was reacted with 125ml of ice-cold aqueous chloramine solution according to the procedure described for 358. Recrystallization from ethanol yielded 3.0g (48%) of crystalline product, m.p. 158-160°C.

Analysis: C₁₀H₇N₄SCl (250.71) Requires C, 47.90; H, 2.81%
Found C, 47.79; H, 3.04%

IR (Nujol): 3450, 3350, 3220(NH); 2220(C=N); 1630, 1570, 1250, 1120, 1070, 970, 845, 810, 765 cm⁻¹

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 4.24g (0.025 mole) of o-chlorophenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was treated with 125ml of aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol afforded 3.0g (40%) of colorless crystalline product, m.p. 147-149°C.
Analysis : \( C_{12}H_{23}N_{3}O_2SCl \) (297.76) Requires C, 48.40; H, 4.06%  
Found C, 48.33; H, 4.24%

IR (Nujol) : 3480, 2380, 3180 (NH); 1660, 1610, 1580, 1520,  
1270, 1210, 1110, 1055, 945, 850, 830, 795,  
755 cm\(^{-1}\)

NMR (CDCl\(_3\)) : 1.48 (3H, t, CH\(_3\)CH\(_2\)O); 4.50 (2H, q, CH\(_3\)CH\(_2\)O);  
5.62 (2H, broad s, NH\(_2\)); 7.40 (4H, m, Ar-H)

3-Amino-5-(3-chlorophenyl)amino-4-cyanoisothiazole (373).

Malononitrile 1.65g (0.025 mole) was reacted with  
4.24g (0.025 mole) of m-chlorophenyl isothiocyanate in the  
presence of sodium ethoxide in absolute ethanol and the  
mixture was treated with aqueous chloramine solution  
according to the procedure described for 358. Recrystallization from dimethylformamide-ethanol afforded 2.5g (40%)  
of crystalline product, m.p. 236-238°C.

Analysis : \( C_{10}H_{7}N_{4}SCl \) (250.71) Requires C, 47.90; H, 2.81%  
Found C, 47.82; H, 2.82%

IR (Nujol) : 3470, 3320, 3180 (NH); 2220 (C\(_\equiv\)N); 1640, 1610  
1560, 1265, 1010, 970, 885, 865, 835, 785,  
720 cm\(^{-1}\)
3-Amino-4-carbethoxy-5-\(\cdot\)(3-chlorophenyl)amino/isothiazole (374).

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with m-chlorophenyl isothiocyanate 4.24g (0.025 mole) in the presence of sodium ethoxide in absolute ethanol and the mixture was treated with aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol yielded 2.5g (34%) of colorless crystalline product, m.p. 120-122°C.

Analysis: \(\text{C}_{12}\text{H}_{12}\text{N}_{2}\text{O}_{2}\text{SCl} (297.76)\) Requires C, 48.40; H, 4.06%  
Found C, 48.64; H, 4.36%

IR (Nujol): 3490, 3270, 3160(NH); 1660, 1610, 1580, 1550, 1275, 1215, 1115, 1035, 970, 840, 820, 790, 770 \text{cm}^{-1}

NMR (CDCl3): 1.48(3H, t, CH\text{CH}_2\text{O}); 4.50(2H, q, CH\text{CH}_2\text{O})  
5.60(2H, broad s, NH\text{H}); 7.18(4H, m, Ar-H)

3-Amino-5-\(\cdot\)(4-chlorophenyl)amino/4-cyanoisothiazole (375).

Malononitrile 1.65g (0.025 mole) was reacted with p-chlorophenyl isothiocyanate 4.24g (0.025 mole) in the presence of sodium ethoxide in absolute ethanol and the mixture was treated with aqueous chloramine solution
according to the procedure described for 358. Recrystallization from dimethylformamide-ethanol yielded 3.0g (48%) of crystalline product, m.p. 236-238°C.

Analysis : C_{10}H_{7}N_{4}Cl (250.71) Requires C, 47.90; H, 2.81%
            Found C, 48.16; H, 2.98%

IR (Nujol) : 3460, 3300, 3180(NH); 2220(C=O); 1630, 1610, 1570, 845, 820, 775 cm\(^{-1}\)

3-Amino-4-carbethoxy-5-\((4\text{-chlorophenyl})\text{amino}\) isothiazole (376).

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 4.24g (0.025 mole) of p-chlorophenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture treated with 125ml of aqueous chloramine solution according to the procedure described for 360. Recrystallization from ethanol afforded 3.0g (40%) of colorless crystalline product, m.p. 144-146°C.

Analysis : C_{12}H_{12}N_{3}O_{2}SCl (297.76) Requires C, 48.40; H, 4.06%
            Found C, 48.50; H, 4.35%

IR (Nujol) : 3500, 3320, 3180(NH); 1670, 1620, 1600, 1560, 1270, 1210, 1120, 1040, 820, 795 cm\(^{-1}\)
3-Amino-4-cyano-5-[4-(4-methylphenyl)sulfonyl]amino]isothiazole (377).

Method I: To a solution of sodium ethoxide (0.025 mole) prepared by dissolving 0.6g of sodium in 30ml of absolute ethanol was added with cooling, 1.65g (0.025 mole) of malononitrile followed by 5.33g (0.025 mole) of p-toluenesulponyl isothiocyanate and stirred at room temperature for 24 hours. The mixture was added to 125ml of freshly prepared, ice-cold, aqueous chloramine solution. The reaction mixture was stirred at room temperature for 12 hours and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid. The solid that separated was filtered and washed with water. The crude product was dissolved in dilute sodium hydroxide solution, filtered, acidified with dilute hydrochloric acid and the colorless product thus obtained was filtered, washed with water, dried in air and recrystallized from dimethylformamide-ethanol to obtain 2.0g (27%) of colorless crystalline product, m.p. 287-289°C.

Analysis :  C_{11}H_{10}N_{4}O_{2}S_{2} (294.35) Requires C, 44.88; H, 3.42%
            Found    C, 45.14; H, 3.72%
IR (KBr) s 3440, 3340, 3220(NH); 2230(C=O); 1660, 1635, 1575, 1520, 1450, 1315(SO$_2$); 1285, 1135(SO$_2$); 1080, 935, 855, 840, 810, 665 cm$^{-1}$

MS, m/e : 294(M$^+$), 155, 139, 122, 107, 91, 77

Method II: To a solution of 2.0g (6.83 mmole) of 2-cyano-3- (methylthio)-3-[(4-methylphenyl)sulfonyl]-aminoacrylonitrile$^{279}$ in 15ml of dimethylformamide was added a solution of 0.76g (6.83 mmole) of fused sodium sulfide (70%) in 5ml of water. The mixture was heated on a steam bath for 24 hours, cooled and reacted with 50ml of ice-cold aqueous chloramine solution. The reaction mixture was worked-up according to the procedure described under Method I to yield 1.1g (54%) of the product, m.p. 287-289°C, identical (mmp, TLC and IR) with the product obtained by Method I.

3-Amino-4-cyano-5-(4-morpholinyl)isothiazole (378).

Method I: A 50% dispersion of sodium hydride in mineral oil, 4.8g (0.1 mole) was washed free of mineral oil with anhydrous benzene and suspended in 30ml of anhydrous dimethylformamide. To this was added with cooling a solution of 3.3g (0.05 mole) of malononitrile in 20ml of
dimethylformamide and stirred at room temperature for 3 hours. The mixture was cooled to 0°C and treated dropwise with a solution of 8.28g (0.05 mole) of 4-morpholinethiocarbonyl chloride in 10ml of dimethylformamide. The mixture was allowed to attain room temperature, stirred for 12 hours and added to 250ml of freshly prepared, ice-cold, aqueous chloramine solution. The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 4.0g (38%) of colorless crystalline product, m.p. 194-196°C.

Analysis: C₈H₁₆N₄O₅S (210.26) Requires C, 45.70; H, 4.79%
Found C, 45.39; H, 4.97%

IR (Nujol): 3390, 3300, 3180(NH); 2210(C=NS); 1640
1550, 1275, 1130, 1045, 985, 890, 850, 830 cm⁻¹

IR (KBr): 3390, 3300, 3180(NH); 2220(C=NS); 1635
1550, 1435, 1380, 1275, 1255, 1110,
1025, 875, 835, 720 cm⁻¹

UV (MeOH): 214nm( log ε 4.12), 267(4.06)

UV (10% HCl): 224nm( log ε 4.28), 274(4.30)

MS, m/e: 210(M⁺), 195, 179, 164, 152, 138, 125
Method II: To a solution of sodium ethoxide (0.05 mole), prepared by dissolving 1.15g of sodium in 50ml of absolute ethanol, was added 3.3g (0.05 mole) of malononitrile, followed by 8.75g (0.05 mole) of o-ethyl 4-morpholinethionomethane. The mixture was stirred at room temperature for 12 hours and added to 250ml of ice-cold, aqueous chloramine solution. Work-up of the reaction mixture yielded a 2.6g (25%) of the product, m.p. 194-196°C, identical (m.m.p., TLC, IR) with the product obtained by Method I.

Method III: A mixture of 1g (0.015 mole) of malononitrile, 1.0g (0.015 mole) of finely divided potassium hydroxide and 2.66g (0.015 mole) of methyl 4-morpholine-dithioformate in 20ml of dimethylformamide was stirred at 60°C for 72 hours. The reaction mixture was treated with 75ml of aqueous chloramine solution. The usual work-up for the reaction mixture yielded 0.60g (19%) of 378, m.p. 194-196°C, identical (m.m.p., TLC) with the product obtained by Method I.

Method IV: To a solution of 4.18g (0.02 mole) of 2-cyano-3-(methylthio)-3-(4-morpholinyl)acrylonitrile in 30ml of dimethylformamide was added a solution of 2.23g
(0.02 mole) of fused sodium sulfide (70%) in 10ml of water. The reaction mixture was heated on a steam bath for 14 hours and reacted with 100ml of aqueous chloramine solution. Work-up yielded 3.0g (71%) of 378, m.p. 194-196°C, identical (m.m.p., TLC, I.R) with the compound obtained by Method I.

3-Amino-4-cyano-5-(4-methyl-1-piperazinyl)isothiazole (379).

To a solution of 3.3g (0.015 mole) of 2-cyano-3-(4-methyl-1-piperazinyl)-3-methylthioacrylonitrile in 30ml of dimethylformamide was added a solution of 1.67g (0.015 mole) of fused sodium sulfide (70%) in 10ml of water. The reaction mixture was heated on a steam bath for 24 hours and treated with 75ml of aqueous chloramine solution according to the procedure described for 378. Recrystallization from methanol yielded 1.7g (51%) of colorless crystalline product, m.p. 158-160°C.

Analysis: C_{9}H_{13}N_{5}S(223.3) Requires C, 48.41; H, 5.87%  
Found C, 48.67; H, 5.99%

IR (Nujol): 3420, 3310, 3190(NH); 2210(C=N); 1650, 1550, 1280, 1175, 1155, 1075, 870, 825, 795 cm^{-1}

NMR (CDCl_{3}): 6 2.36(3H, s, CH_{3}-N)  
2.56(4H, t, piperazinyl methylene)  
3.60(4H, t, piperazinyl methylene)  
4.90(2H, broad s, NH_{2})

MS, m/e: 223(M^+) , 181, 152, 138, 71
3-Amino-4-cyano-5-(l-piperidinyl)isothiazole (380).

To a solution of 2.48g (0.012 mole) of 2-cyano-3-(methylthio)-3-(l-piperidinyl)acrylonitrile in 20ml dimethylformamide was added a solution of 1.34g (0.012 mole) of fused sodium sulfide (70%) in 10ml of water. The reaction mixture was heated on a steam bath for 24 hours, cooled and treated with 75ml of aqueous chloramine solution according to the procedure described for 378. Recrystallization from methanol yielded 1.4g (56%) of colorless crystalline product, m.p. 186-188°C.

Analysis: C_{9}H_{12}N_{4}S (208.28) Requires C, 51.90; H, 5.81%

IR (Nujol): 3440, 3280, 3180(NH); 2200(C≡N); 1620, 1570, 1285, 1130, 1030, 880, 865, 835 cm\(^{-1}\)

3-Amino-4-cyano-5-(l-pyrrolidinyl)isothiazole (381).

To a solution of 1.5g (7.77 mmole) of 2-cyano-3-(methylthio)-3-(l-pyrrolidinyl)acrylonitrile in 20ml of dimethylformamide was added 0.87g (7.77 mmole) of fused sodium sulfide (70%) in 5ml of water. The mixture was heated on a steam bath for 16 hours, cooled and treated with 50ml of aqueous chloramine solution according to the procedure described for 378. Recrystallization from methanol yielded 0.8g (53%) of colorless crystalline product, m.p. 212-214°C.
Analysis

Analysis: C_{8}H_{10}N_{4}S (194.26) Requires C, 49.46%; H, 5.19%
Found C, 49.27%; H, 5.29%

IR (Nujol): 3420, 3320, 3220 (NH); 2220 (C=CN); 1650, 1570, 1240, 1175, 1115, 885, 810 cm^{-1}

UV (MeOH): 220nm (log ε 4.29), 267 (4.66)
UV (10% HCl): 227nm (log ε 4.36), 273 (4.32)

3-Amino-4-cyano-5-ethoxyisothiazole (382).

To a solution of potassium ethoxide (0.05 mole) prepared by dissolving 1.96 g of potassium in 80 ml of absolute ethanol or sodium ethoxide (0.05 mole) prepared by dissolving 1.2 g of sodium in 60 ml of absolute ethanol, was added, with cooling, 3.3 g (0.05 mole) of malononitrile followed by 6.23 g (0.05 mole) of 0-ethyl thionochloroformate.

The mixture was stirred at room temperature for 12 hours and reacted with 250 ml of ice-cold aqueous chloramine solution. The mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to yield 2.5 g (40%) of colorless crystalline product, m.p. 200-202°C. The product was found to be identical (mmp, TLC, IR) with an authentic sample prepared by the reported method m.p. 348°C. Reported m.p. 198°C.
3-Amino-4-cyano-5-phenoxyisothiazole (383).

To a solution of sodium ethoxide (0.05 mole) prepared by dissolving 1.2g of sodium in absolute ethanol (50ml) was added, with cooling, 3.3g (0.05 mole) of malononitrile followed by 8.63g (0.05 mole) of O-phenyl thionocloroformate, stirred at room temperature for 12 hours, and treated with 250ml of chloramino solution. The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 6g (55%) of crystalline product, m.p. 152-154°C.

Analysis: \( \text{C}_{10}\text{H}_7\text{N}_3\text{O}_3(217.25) \) Requires C, 55.28; H, 3.25%; Found C, 55.38; H, 3.50%

IR (Nujol): 3400, 3320, 3200(NH); 2220(O\(\equiv\)N); 1630, 1540, 1205, 1135, 1035, 850, 810, 780 cm\(^{-1}\)

UV (MeOH): 218nm(log \(\epsilon\) 4.36), 246sh.(4.05), 289sh(3.67)

MS, m/e: 217(M\(^+\)), 189, 185, 173, 169, 150, 146, 120, 116, 109, 103

3-Amino-4-cyano-5-(2-methylphenoxy)isothiazole (384).

To a solution of sodium ethoxide (0.05 mole) in 50ml ethanol was added, with cooling, 3.3g (0.05 mole) of
malononitrile, followed by 9.33g (0.05 mole) of O-o-tolyl thionochloroformate prepared according to the general method described for the preparation of O-aryl thionochloroformates. The reaction mixture was stirred at room temperature for 12 hours and reacted with 250ml of freshly prepared ice-cold aqueous chloromine solution. The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from methanol yielded 3.0g (26%) of crystalline product, m.p. 111-112°C.

Analysis: \( C_{11}H_{9}N_3O_3(231.27) \) Requires: C, 57.12%; H, 3.92%    
Found: C, 57.06%; H, 4.13%

IR (Nujol): 3420, 3340, 3230(NH); 2240(C≡N); 1660, 1640, 1570, 1215, 1135, 1030, 970, 835, 775 cm\(^{-1}\)

MS, m/e: 231(M\(^+\)), 214, 202, 198, 186, 170, 161, 157, 144, 130, 117, 107

3-Amino-4-cyano-5-(3-methylphenoxy)isothiazole (385).

Malononitrile 3.3g (0.05 mole) was reacted with 9.33g (0.05 mole) of O-m-tolyl thionochloroformate in the presence of sodium ethoxide (0.05 mole) in absolute ethanol and the mixture was treated with 250ml of ice-cold
aqueous chloramine solution according to the method described for 383. Recrystallization from methanol afforded 3.5g (30%) of crystalline product, m.p. 152-154°C.

Analysis : $C_{11}H_9N_3OS(231.27)$ Requires C,57.12; H,3.92%
Found C,57.32; H,4.20%

IR (Nujol) : 3430, 3300, 3220(NH); 2230(C=O); 1630, 1560, 1500, 1215, 1190, 1135, 1035, 970, 840, 755 cm$^{-1}$

MS, m/e : 231(M$^+$), 214, 202, 199, 186, 183, 176, 170, 151, 157, 144, 130, 117, 107

3-Amino-4-cyano-5-(4-methylphenoxy) isothiazole (386).

Malononitrile 3.3g (0.05 mole) was reacted with 9.33g (0.05 mole) of O-p-tolyl thionochloroformate in the presence of sodium ethoxide (0.05 mole) in absolute ethanol and the mixture was treated with an aqueous solution of chloramine according to the procedure described for 383. Recrystallization from methanol yielded 5g (43%) of crystalline product, m.p. 151-153°C.

Analysis : $C_{11}H_9N_3OS(231.27)$ Requires C,57.12; H,3.92%
Found C,57.11; H,4.04%

IR (Nujol) : 3430, 3330, 3230(NH); 2230(C=O); 1640, 1570, 1520, 1215, 1185, 1135, 1035, 970, 840, 755 cm$^{-1}$
UV (MeOH) : 209nm(\text{log } ε 4.30), 278(4.09)

MS, m/e : 231(M⁺), 214, 202, 199, 198, 186, 183, 176, 170, 161, 157, 144, 130, 123, 117, 107

3-Amino-4-cyano-5-(phenylthio)isothiazole (387).

Malononitrile, 3.3g (0.05 mole) was reacted with 9.43g (0.05 mole) of phenyl dithiocarbonic anhydride in the presence of sodium ethoxide (0.05 mole) in absolute ethanol and the mixture was treated with 250ml of ice-cold aqueous chloramine solution according to the method described for 383. Recrystallization from methanol yielded 4.5g (39\%) of crystalline product, m.p. 144-146°C.

Analysis : C_{10}H_{7}F_{3}S_{2}(233.31) Requires C,51.48\%; H,3.02\%

Found C,51.81\%; H,3.34\%

IR (Nujol) : 3380, 3320, 3200(NH); 2220(C≡N); 1660, 1540, 1190, 1130, 1040, 1010, 835, 755 cm⁻¹

UV (MeOH) : 209nm(\text{log } ε 4.30), 278(4.09), 314sh(3.60)

MS, m/e : 233(M⁺), 216, 201, 191, 169, 159, 146, 133, 127, 121, 114, 109, 104

3-Amino-4-cyano-5-(methylthio)isothiazole (388).

Method I: A solution of sodium methoxide in methanol was prepared by dissolving 2.29g of sodium in 25ml of
methanol and the volume was made up to 30 ml. To 17 ml of the sodium methoxide solution was added, with cooling, 3.77 g (0.057 mole) of malononitrile. The mixture was cooled to 5°C and with vigorous stirring successively treated with 1.7 ml of carbon disulfide, 9 ml of sodium methoxide, 0.85 ml of carbon disulfide, 4 ml of sodium methoxide and 0.43 ml of carbon disulfide. The reaction mixture was stirred below 20°C for an additional 30 minutes, cooled to 5°C and treated dropwise with 6.3 g (0.05 mole) of dimethyl sulfate with vigorous stirring. The reaction mixture was stirred at room temperature for one hour and treated with 250 ml of ice-cold aqueous chloramine solution. The mixture was stirred at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 3.0 g (35%) of colorless crystalline product, m.p. 180-182°C. Reported m.p. 176°C.

Analysis : C₅H₅N₂S₂ (171.25) Requires C, 35.07; H, 2.94%
Found C, 35.43; H, 3.21%

IR (KBr) : 3400, 3330, 3210(NH); 2210(C≡N); 1650, 1535, 1460, 1385, 1325, 1215, 1110, 1015, 970, 880, 830, 715 cm⁻¹

UV (MeOH) : 207 nm (log ε 4.14), 279(4.08), 310 sh(3.66)
Method II: To a suspension of 6.6g (0.1 mole) of finely powdered potassium hydroxide (85%) in 30ml of dimethylformamide was added, with cooling, 3.3g (0.05 mole) of malononitrile followed by 3.8g (0.05 mole) of carbon disulfide and the mixture was stirred until a clear solution was obtained. The mixture was then cooled to 0°C and treated dropwise with 6.3g (0.05 mole) of dimethyl sulfate. The reaction mixture was stirred at room temperature for 12 hours and treated with 250ml of ice-cold aqueous chloramine solution. The usual work-up yielded 4.7g (55%) of \text{388}, m.p. 180-182°C.

Method III: A mixture of 3.3g (0.05 mole) of malononitrile and 3.8g (0.05 mole) of carbon disulfide in 10ml acetonitrile was cooled in ice bath and treated dropwise with 10.1g (0.1 mole) of triethylamine. The reaction mixture was stirred at room temperature for 12 hours, cooled to 0°C and treated with 5.3g (0.05 mole) of dimethyl sulfate. The mixture was stirred at room temperature for 24 hours and reacted with 250ml of aqueous chloramine solution according to the procedure described in Method I. Recrystallization from dimethylformamide–ethanol yielded 3.5g (45%) of \text{388}, m.p. 180-182°C.
Alternatively, bis(triethylammoniothio)methylene-malononitrile, isolated from the reaction of malononitrile, carbon disulfide and triethylamine, was dissolved in water, methylated with one equivalent of dimethyl sulfate and reacted with aqueous chloramine solution as described above to obtain 388 in 45% yield.

**Method IV:** A solution of 3.34g (0.03 mole) of fused sodium sulfide (70%) in 10ml of water was added to a solution of 5.1g (0.03 mole) of di(methylthio)methylene-malononitrile in 20ml of dimethylformamide. The reaction mixture was stirred at room temperature for 24 hours and treated with 150ml of aqueous chloramine solution according to the procedure described under Method I. Recrystallization from dimethylformamide-ethanol yielded 4.0g (78%) of 388.

**Method V:** 6.9g (0.05 mole) of dimethyl trithiocarbonate obtained by the methylation of sodium, potassium, or ammonium trithiocarbonate, was reacted with 3.3g (0.05 mole) of malononitrile in the presence of 0.05 mole of sodium ethoxide in 30ml of absolute ethanol. The solution of sodium salt of 2-cyano-3-mercapto-
3-(methylthio)acrylonitrile thus obtained was reacted with 250ml of aqueous chloramine solution and the product obtained on recrystallization from dimethylformamide-ethanol yielded 5.0g (58%) of \textbf{388}, m.p. 180-182°C.

3-Amino-4-carbethoxy-5-(methylthio)isothiazole (389).

**Method I:** Ethyl cyanoacetate 6.46g (0.057 mole) was reacted with 2.98ml of carbon disulfide according to the procedure described under Method I for \textbf{388}, employing a solution of sodium ethoxide prepared from 2.2g of sodium in 60ml of absolute ethanol in place of sodium methoxide solution. The reaction mixture was cooled to 5°C and treated dropwise with 5.3g (0.05 mole) of dimethyl sulfate with vigorous stirring. The mixture was stirred at room temperature for 4 hours and then added to 250ml of ice-cold aqueous chloramine solution. The reaction mixture was allowed to stand at room temperature for 12 hours and the solid obtained was filtered, washed with water and dried. The crude product on recrystallization from ethanol yielded 2.0g (18%) of colorless crystalline product, m.p. 133-135°C.
Analysis: $C_7H_{10}N_2O_2S_2 (218.24)$ Requires C, 38.52%; H, 4.62%
Found C, 38.28%; H, 4.80%

IR (Nujol): 3450, 3290, 3180 (NH); 1700, 1610, 1510, 1135, 1030, 840, 790 cm$^{-1}$

IR (KBr): 3450, 3290, 3170 (NH); 1680, 1615, 1515, 1455, 1390, 1370, 1305, 1130, 1110, 1030, 840, 790 cm$^{-1}$

UV (MeOH): 212 nm ($\log \epsilon$ 4.27), 281 (4.23), 312 sh. (3.74)

MS, m/e: 218 ($M^+$), 173, 172, 159, 144, 130, 126, 102, 98, 83

Method II: A suspension of 6.6g (0.1 mole) of finely divided potassium hydroxide (85%) in 30ml dimethylformamide was cooled to 0°C and treated with 5.65g (0.05 mole) of ethyl cyanoacetate, followed by 3.8g (0.05 mole) of carbon disulfide. The reaction mixture was stirred at room temperature for 12 hours, cooled and reacted with 6.3g (0.05 mole) of dimethyl sulfate. The mixture was stirred for 8 hours and added to 250ml of ice-cold aqueous chloramine solution. The usual work-up yielded 3.0g (28%) of 389, m.p. 133-135°C.

Method III: Ethyl cyanoacetate 5.65g (0.05 mole) was reacted with 3.8g (0.05 mole) of carbon disulfide in the presence of 10.1g (0.1 mole) of triethylamine in
in acetonitrile, treated with 6.3g (0.05 mole) of dimethyl sulfate and the mixture was reacted with 250ml of aqueous chloramine solution according to the procedure described for 388 under Method II. Recrystallization from ethanol afforded 3.0g (28%) of 389, m.p. 133-135°C.

Method IV: A solution of 5.57g (0.05 mole) of fused sodium sulfide (70%) in 15ml water was added to a solution of 10.85g (0.05 mole) of ethyl di(methylthio)-methylenecyanoacetate in 30ml of dimethylformamide. The mixture was stirred at room temperature for 24 hours and treated with 250ml of aqueous chloramine solution according to the procedure described for 388 under Method IV. Recrystallization from ethanol yielded 3.5g (32%) of 389, m.p. 133-135°C.

Method V: To a suspension of 6.6g (0.1 mole) of finely divided potassium hydroxide in 30ml of dimethylformamide was added 11.3g (0.1 mole) of ethyl cyanoacetate followed by 13.8g (0.1 mole) of dimethyl trithiocarbonate. The mixture was stirred at room temperature for 48 hours and treated with 500ml of chloramine solution. The usual work-up yielded 7g (32%) of 389, m.p. 133-135°C.
3-Amino-5-(methylthio)isothiazole-4-carboxamide (390).

**Method I:** To a suspension of 13.2 g (0.2 mole) of powdered potassium hydroxide (85%) in 25 ml of dimethylformamide was added, with cooling, 8.4 g (0.1 mole) of cyanoacetamide followed by 7.6 g (0.1 mole) of carbon disulfide. The mixture was vigorously stirred until a homogeneous deep red colored solution was obtained. The mixture was allowed to stand at room temperature for 12 hours, cooled and treated dropwise with 12.6 g (0.1 mole) of dimethyl sulfate. The reaction mixture was allowed to stand at room temperature for 12 hours, and reacted with 500 ml of ice-cold aqueous chloramine solution. The solid separated was filtered, washed with water, dried and recrystallized from dimethylformamide-ethanol to yield 9.6 g (51%) of the product, m.p. 184-186°C.

**Analysis:**

\[ C_5H_7N_3OS_2 (189.26) \]

Requires C, 31.73; H, 3.73%  
Found C, 32.00; H, 3.95%

**IR (Nujol):**

3400, 3240, 3130 (NH); 1640, 1580, 965, 845, 795 cm\(^{-1}\)

**IR (KBr):**

3410, 3330, 3260, 3150 (NH); 1655, 1600, 1440, 1385, 1100, 960, 840, 795 cm\(^{-1}\)
UV (MeOH) : 212nm (log ε 4.18), 279(4.02), 310sh.(3.63)

MS, m/e : 189(M+), 172, 171, 158, 156, 144, 131,
117, 103, 99, 88, 84

Method II: 2-Cyano-3-mercapto-3-(methylthio)-
acrylamide, 5g (0.029 mole) was dissolved in minimum
quantity of cold 10% sodium hydroxide solution and added
to 150ml of aqueous chloramine solution. The mixture
was stirred for 24 hours and the solid obtained was filter-
ed, washed with water and dried. Recrystallization from
dimethylformamide-ethanol yielded 4.5g (83%) of 390
m.p. 184-186°C.

Method III: A solution of 2.8g (0.025 mole) of
fused sodium sulfide (70%) in 15ml of water was added to a
solution of 4.7g (0.025 mole) of di(methylthio)methylene-
cyanoacetamide 9 in 30ml of dimethylformamide. The
mixture was heated on steam bath for 24 hours, cooled and
treated with 125ml of chloramine solution according to the
procedure described for 388. Recrystallization from
dimethylformamide-ethanol yielded 2.5g (53%) of 390
m.p. 184-186°C.
Method IV: To a suspension of 3.3g (0.05 mole) of finely divided potassium hydroxide (85%) in 30ml of dimethylformamide, was added 4.2g (0.05 mole) of cyanoacetamide followed by 6.9g (0.05 mole) of dimethyl trithiocarbonate. The reaction mixture was stirred at room temperature for 24 hours and treated with 250ml of aqueous chloramine solution. The usual work-up yielded 3g (32%) of 390, m.p. 184-186°C.

Method V: 3-Amino-4-cyano-5-(methylthio)isothiazole (388) 1.2g (7 mmole) was added to 20ml of ice-cold, concentrated sulfuric acid. The mixture was stirred at room temperature for 12 hours, poured onto crushed ice and neutralized with dilute sodium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.6g (45%) of 390, m.p. 184-186°C, identical (mmp, TLC, IR) with the product obtained by above methods.

3,4-Diaminoisothiazolo(4,5-d)isothiazole (391).

To a mixture of 1.65g (0.025 mole) of malononitrile
and 1.9g (0.025 mole) of carbon disulfide in 5ml of acetonitrile was added, with cooling, 5.05g (0.05 mole) of triethylamine. The mixture was stirred at room temperature for 12 hours and added to 250ml of ice-cold aqueous chloramine solution. The reaction mixture was stirred for 24 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 3g (70%) of crystalline product, m.p. 273-275°C. The product 391 was also obtained in 74% yield by the reaction of aqueous solution of bis(triethylammoniothiomethylene)malononitrile with aqueous chloramine solution.

Analysis: \( \text{C}_4\text{H}_4\text{N}_4\text{S}_2 (172.24) \) Requires C, 27.89%; H, 2.34%

\[ \text{Found C, 28.06%; H, 1.96%} \]

IR (KBr): 3370, 3295, 3200 (NH); 1630, 1530, 1485, 1415, 1360, 1110, 1080, 860, 800, 750 cm\(^{-1}\)

UV (MeOH): 205nm (log \( \varepsilon \) 4.05), 216(4.08), 243(4.28), 300(3.82)

MS, m/e: 172(M\(^+\)), 156, 145, 140, 126, 114, 109, 108, 97
3-Amino-4-carbethoxy-5-isothiazolesulfenamide (392).

To a mixture of 5.65g (0.05 mole) of ethyl cyanoacetate and 3.8g (0.05 mole) of carbon disulfide in 10ml of acetonitrile was added, with cooling, 10.1g (0.1 mole) of triethylamine. The mixture was stirred at room temperature for 24 hours and added to 500ml of ice-cold, aqueous chloramine solution. The reaction mixture was stirred for 2 hours, the solid obtained was filtered, washed with water, dried and recrystallized from ethanol to yield 3g (27%) of colorless crystalline product, m.p. 151-153°C.

Analysis: $C_6H_9N_3O_2S_2$ (219.29) Requires C, 32.86; H, 4.14%
Found C, 33.12; H, 4.44%

IR (Nujol): 3460, 3400, 3300, 3180(NH); 1700, 1620, 1510, 1175, 1135, 1030, 920, 835, 795 cm$^{-1}$

MS, m/e: 219(M$^+$), 203, 190, 173, 158, 149, 130, 126, 105, 89

4-cyano-3-hydroxy-5-(phenylamino)isothiazole (393).

Method I: To a suspension of 3.3g (0.05 mole) of finely divided potassium hydroxide (85%) in 30ml of dimethylformamide was added, with cooling, 4.2g (0.05 mole) of cyanoacetamide, followed by 6.75g (0.05 mole) of phenyl
isothiocyanate. The mixture was stirred at room temperature for 24 hours, added to 250ml of ice-cold aqueous chloramine solution and allowed to stand at room temperature for 24 hours. The solution was filtered, and the clear filtrate was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 3.0g (28%) of crystalline compound, m.p. 224–226°C (d).

Analysis : \( C_{10}H_7N_3OS(217.25) \) Requires C, 55.28; H,3.25%
Found C, 55.06; H,3.53%

IR (Nujol) : 3260(OH,NH); 2230(C=EN); 1610, 1580, 1250, 1165, 885, 755 cm\(^{-1}\)

IR (KBr) : 3260(OH,NH); 2220(C=EN); 1645, 1620, 1530, 1495, 1470, 1435, 1370, 1230, 870, 750 cm\(^{-1}\)

UV (EtOH) : 206nm(log \( \varepsilon \) 4.36), 285(4.14)

UV (0.1N NaOH): 224nm(log \( \varepsilon \) 4.27), 280(3.99), 328(4.05)

NMR (CF\(_3\)COOH): \( \delta \) 7.55(5H, broad s, Ar-H)

MS, m/e : 217(M\(^+\)), 162, 143, 142, 132, 131, 114

Method II: A solution of 1.49g (0.013 mole) of fused sodium sulfide (70%) in 10ml of water was added to a solution of 3.4g (0.013 mole) of 2-cyano-3-(methylthio)-3-(phenylamino)acrylamide in 20ml of dimethylformamide
and the mixture was heated on a steam bath for 16 hours, cooled and reacted with 75ml of ice-cold aqueous chloramine solution. The work-up of the reaction mixture as described in Method I yielded 0.60g (18%) of 393, m.p. 224-226°C (d).

Method III: Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.38g (0.025 mole) of phenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol and the mixture was reacted with 125ml of ice-cold aqueous chloramine solution. The 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360) obtained was filtered and the aqueous alkaline filtrate was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.5g (9%) of the product 393, m.p. 224-226°C (d), identical (mm, TLC, IR) with the product obtained by Method I.

Method IV: A solution of 2.19g (0.01 mole) of 2-cyano-3-mercapto-3-(phenylamino)acrylamide in ethyl acetate was reacted with 1.6g (0.01 mole) of bromine according to the reported method to obtain 1.2g (55%) of 393, m.p. 224-226°C (d). Reported m.p. 236-237°C.
The product obtained was identical (mp, TLC, IR) with the product obtained by the above methods.

4-Cyano-3-hydroxy-5-\(\text{N}(2\text{-methylphenyl})\text{amino}\)isothiazole (394).

**Method I:** Cyanoacetamide 2.1g (0.025 mole) was reacted with 3.73g (0.025 mole) of o-tolyl isothiocyanate in the presence of 1.65g (0.025 mole) of potassium hydroxide (85%) in dimethylformamide (20ml) and the mixture was reacted with a 125ml of ice-cold aqueous chloramine solution. The work-up of the reaction mixture according to the procedure described for 393 under Method I, yielded the crude product which on recrystallization from methanol yielded 1.5g (26%) of crystalline product, m.p. 199-201°C (d).

**Analysis:** \(\text{C}_{11}\text{H}_9\text{N}_5\text{O}_3\) (231.27) Requires C, 57.12; H, 3.92% Found C, 56.85; H, 4.20%

**IR (Nujol):** 3240(OH, NH); 2220(C=N); 1650, 1590, 1205, 875, 770 cm\(^{-1}\)

**MS, m/e:** 231(M\(^+\)), 161, 160, 155, 129, 117, 116, 97, 91

**Method II:** Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.73g (0.025 mole) of o-tolyl isothiocyanate in the presence of 0.025 mole of sodium
ethoxide in absolute ethanol and the mixture was treated with 125ml of ice-cold aqueous chloramine solution. The alkaline aqueous mother liquor obtained after the filtration of 3-amino-4-carbethoxy-5-$\text{-}(2$-methylphenyl)amino-$\text{-}$isothiazole (364) was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from methanol yielded 0.6g (10%) of $\text{394}$ m.p. 199-201°C (d).

4-Cyano-3-hydroxy-5-$\text{-}(4$-methylphenyl)amino-$\text{-}$isothiazole (395).

**Method I:** Cyanoacetamide 2.1g (0.025 mole) was reacted with 3.73g (0.025 mole) of p-tolyl isothiocyanate in the presence of 1.65g (0.025 mole) of potassium hydroxide (85%) in dimethylformamide (20ml) and the mixture was reacted with 125ml of ice-cold aqueous chloramine solution. The work-up of the reaction mixture according to the procedure described for 393 under Method I yielded the crude product which on recrystallization from methanol yielded 1.7g (29%) of crystalline product, m.p. 222-224°C (d).

Analysis : $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_8$(231.27) Requires C,57.12; H,3.92% Found C,57.16; H,4.17%

IR (Nujol) : 3240(OH,NH), 2240(C=S); 1620, 1580, 1250, 1160, 870, 805 cm\(^{-1}\)
MS, m/e : 231(M⁺), 195, 183, 167, 162, 156, 133, 124, 106, 91.

Method II: Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.73g (0.025 mole) of p-tolyl isothiocyanate in the presence of 0.025 mole of sodium ethoxide in absolute ethanol and the mixture was reacted with 125ml of aqueous chloramine solution as described for 366. The aqueous mother liquor obtained after the filtration of 3-amino-4-carbethoxy-5-(4-methylphenyl)aminoisothiazole (366) was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from methanol yielded 0.40g (7%) of 395 m.p. 222-224°C (d).

4-Cyano-3-hydroxy-5-(methylthio)isothiazole (396).

Method I: Ethyl cyanoacetate, 6.46g was reacted with carbon disulfide, methylated with dimethyl sulfate and reacted with aqueous chloramine solution as described for 389 under Method I. The alkaline aqueous mother liquor obtained after filtration of 389 was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization
from ethanol yielded 0.75g (9%) of crystalline product, m.p. 228-231°C (d), Reported m.p. 237-242°C.\textsuperscript{12}

Analysis : \( \text{C}_5\text{H}_4\text{N}_2\text{S}_2(172.23) \) Requires C, 34.87; H, 2.34% Found C, 35.23; H, 2.57%

\text{IR (KBr)} : 3460, 3250(\text{OH, NH}); 2220(\text{C=\text{N}}); 1680, 1610, 1550, 1500, 1420, 1370, 1330, 1310, 1270, 1200, 1020, 980, 890, 860, 720 cm\(^{-1}\)

\text{MS, } m/e : 172(\text{M}^+), 157, 139, 130, 127, 125, 114, 110, 108, 98, 93

\textbf{Method II:} Ethyl di(methylthio)methyleneacyanoacetate\textsuperscript{11,14} was reacted with sodium sulfide and then treated with aqueous chloramine solution as described for \textit{389} under Method IV. The alkaline aqueous mother liquor obtained after filtration of \textit{389} was cooled and acidified with dilute hydrochloric acid. The usual work-up yielded 2g (23%) of the product, m.p. 228-231°C (d).

\textbf{Method III:} Ethyl cyanoacetate, 11.3g (0.1 mole) was reacted with 13.8g (0.1 mole) of dimethyl trithiocarbonate\textsuperscript{48,587} and then with 500ml of aqueous chloramine solution as described for \textit{389}. The aqueous mother liquor obtained after filtration of \textit{389} was cooled and acidified
with dilute hydrochloric acid. Work-up yielded 2g (12%) of the product, m.p. 228-232°C (d).

**Method IV:** To a solution of 1.74g (0.01 mole) of 2-cyano-3-mercapto-3-(methylthio)acrylamide in 30ml of dilute ammonium hydroxide was added, with stirring, a solution of 2.54g (0.01 mole) of iodine in 30ml of 10% potassium iodide. The mixture was allowed to stand for 12 hours, poured onto ice-water and acidified with dilute hydrochloric acid. Work-up of the reaction mixture yielded 1.3g (76%) of 396 m.p. 228-232°C (d).

**Reaction of sodium salt of ethyl 2-cyano-3-mercapto-3-(methylamino)acrylate with aqueous sodium N-chloro-p-toluenesulfonamide-ammonia mixture.**

To 100ml of ice-cold aqueous ammonium hydroxide (25%) maintained at 0°C by external cooling, was added portion-wise, with stirring, 7.0g (0.025 mole) of sodium N-chloro-p-toluenesulfonamide trihydrate. To the resulting mixture was added a solution of sodium salt of ethyl 2-cyano-3-mercapto-3-(methylamino)acrylate prepared by reacting 2.83g (0.025 mole) of ethyl cyanoacetate with 1.83g (0.025 mole) of methyl isothiocyanate in the presence of
sodium ethoxide (0.025 mole) in absolute ethanol, as described for 352. The reaction mixture was stirred at room temperature for 24 hours, cooled and stirred with 20ml of 10% sodium hydroxide solution. The solid was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 0.20g of the colorless crystalline product m.p. 145-147°C, identical with 3-amino-4-carbethoxy-5-(methylamino)isothiazole (352).

Reaction of triethylammonium salt of 2-cyano-3-mercapto-3-(methylthio)acrylonitrile with aqueous sodium N-chloro-p-toluenesulfonamide-ammonia mixture.

To 50ml of ice-cold ammonium hydroxide solution (25%), maintained at 0°C by external cooling, was added portionwise, with stirring, 7.0g (0.025 mole) of sodium N-chloro-p-toluenesulfonamide. To the resulting mixture, was added a solution of triethylammonium salt of 2-cyano-3-mercapto-3-(methylthio)acrylonitrile (0.025 mole) prepared by reacting 1.65g (0.025 mole) of malononitrile with 1.9g (0.025 mole) of carbon disulfide in the presence of 5.05g (0.05 mole) of triethylamine in 10ml of acetonitrile, followed by methylation with 3.15g (0.025 mole) of dimethyl sulfate as described under Method III for the
The reaction mixture was stirred at room temperature for 12 hours, cooled and treated with 20ml of 10% sodium hydroxide solution. The solid was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.6g of colorless crystalline product, m.p. 180-182°C. The product obtained was identical (mmp, TLC, IR) with 3-amino-4-cyano-5-(methylthio)isothiazole (388).

**Reaction of sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate with N-chloromethylamine:**

Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.38g (0.025 mole) of phenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) in absolute ethanol according to the procedure described earlier. The solution of sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate thus obtained was reacted with an ice-cold aqueous solution of N-chloromethylamine prepared by the addition of 12.5ml of 40% aqueous methyamine to an aqueous sodium hypochlorite solution obtained by passing 3.5g of chlorocrine into a mixture of 100g of ice and 50ml of a 15% solution of sodium hydroxide taking
care to conduct all the operations at 0°C. After the addition of the sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate to the N-chloromethylamine solution, the mixture was stirred at room temperature for 24 hours, cooled and the pH adjusted to 7 by the addition of dilute hydrochloric acid. The compound obtained was filtered and dried in air. Recrystallization from ethanol yielded 1.0g of crystalline compound, m.p. 212-214°C. The product obtained was characterized as ethyl 5-cyano-4-(phenylamino)-3-phenyl-2(3H)-thiazolylidene/cyanoacetate. Reported m.p. 213°C. 139

Analysis : C_{21}H_{16}N_{4}O_{2}S (388.44) Requires C, 64.93; H, 4.15%
            Found   C, 64.89; H, 4.48%

UV (EtOH) : 206nm (log ε 4.52), 273(4.00), 354(4.23)

UV (0.1N NaOH) : 211nm (log ε 4.25), 230(3.89), 263(3.93), 357(4.08)

NMR (CDCl₃) : 5 1.28 (3H, t, CH₃CH₂O); 4.28 (2H, q, CH₃CH₂O); 5.32 (1H, broad s, replaceable with D₂O, C₆H₅NH); 7.2-7.8 (10H, m, Ar-H)

MS, m/e : 388(M⁺), 360, 343, 316, 315, 291, 265, 240, 195, 187, 174, 173, 142, 115, 103
Reaction of sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate with N-chloro- or N-bromourea

To a solution of sodium ethoxide (0.02 mole), prepared by dissolving 0.6g of sodium in 30ml of absolute ethanol, was added, with cooling, 2.83g (0.025 mole) of ethyl cyanoacetate, followed by 3.38g (0.025 mole) of phenyl isothiocyanate and the mixture was stirred at room temperature for 12 hours. The solution of sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate thus obtained was added, with cooling, to an aqueous solution of N-chloroureia (0.025 mole), or N-bromoureia (0.025 mole). The mixture was stirred at room temperature for 24 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 0.9g of crystalline product, m.p. 287-289°C. The product obtained was characterized as ethyl (4-amino-5-carbethoxy-3-phenyl-2(3H)-thiazolylidene)-cyanoacetate (398).

Analysis: \[ \text{C}_{17} \text{H}_{17} \text{N}_{3} \text{O}_{4} \text{S} (359.4) \] Requires C, 56.31; H, 4.77% Found C, 56.79; H, 4.94%

IR (Nujol): 3460, 3350(NH); 2190(C=N); 1660, 1610, 1280, 1215, 1125, 1015, 770, 755 cm\(^{-1}\)

MS, m/e: 359(M\(^{+}\))
Reaction of ethyl 2-cyano-3-mercapto-3-(phenylamino)-
acrylate with N-bromosuccinimide.

To a solution of 0.79g (3 mmole) of ethyl 2-cyano-
3-mercapto-3-(phenylamino)acrylate in 10ml of carbon
tetrachloride was added 0.53g (3 mmole) of N-bromosuccini-
mide. The mixture was refluxed on a waterbath for 4
hours. The solvent was removed under reduced pressure.
The residue was triturated with water, filtered and dried.
Recrystallization from ethyl acetate yielded 0.50g of
crystalline product, m.p. 233-235°C. The product obtained
was characterized as ethyl α-cyano-Δ²,α-benzothia-
zoline acetate (399). Reported m.p. 233-234°C.

Analysis:

IR (Nujol):

3160(NH); 2200(C=O); 1660, 1590, 1570,
1530, 1285, 1185, 1125, 1090, 885, 855,
805, 755 cm⁻¹

NMR (CDCl₃):

δ 1.42(3H, t, CH₂CH₂O); 4.38(2H, q,
CH₂CH₂O); 7.68(4H, m, Ar-H)

MS, m/e:

246(M⁺), 200, 174, 172, 146, 128, 120
Ethyl cyanoacetate 2.83g (0.025 mole) was reacted with 3.38g (0.025 mole) of phenyl isothiocyanate in the presence of sodium ethoxide (0.025 mole) as described earlier. The mixture was diluted with ice-water and treated with ice-cold aqueous sodium hypochlorite or sodium hypobromite solution (0.025 mole). The reaction mixture was stirred at room temperature for 12 hours. The solid separated was filtered, washed with water and dried. Recrystallization from ethanol yielded 2.5g of the crystalline product, m.p. 212-214°C. The product was found to be identical with 397 (mmp, TLC, IR, NMR).

Reaction of diethyl 3,3-dithiobis(2-cyano-3-(phenylamino)acrylate or sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate with ammonia in the presence of silver nitrate or cuprous chloride.

To a suspension of 0.5g (1 mmole) of diethyl 3,3-dithiobis(2-cyano-3-(phenylamino)acrylate in 40ml of methanol was added 0.17g (1 mmole) of silver nitrate. The mixture was warmed, stirred for 10 mins, cooled and treated
with 25ml of ice-cold ethanolic ammonia solution. The reaction mixture was allowed to stand at room temperature for 24 hours and filtered. The filtrate was concentrated under reduced pressure. The residue obtained was triturated with water, filtered and dried. Recrystallization from ethanol afforded 0.20g of sulfur free compound, m.p. 170-172°C. The product obtained was characterized as ethyl 3-amino-2-cyano-3-(phenylamino)acrylate (400).

Analysis : C_{12}H_{13}N_{3}O_{2}(231.25) Requires C, 62.32; H, 5.67% Found C, 62.47; H, 6.01%

IR (Nujol) : 3460, 3300, 3200(NH); 2200(C≡N); 1600, 1560, 1200, 1170, 1135, 1070, 780 cm⁻¹

IR (KBr) : 3460, 3310, 3220(NH); 2200(C≡N); 1650, 1570, 1500, 1450, 1400, 1370, 1300, 1190, 1120, 1060, 770, 720 cm⁻¹

UV (MeOH) : 268nm

NMR (CDCl₃) : 5.1.32(3H, t, CH₃CH₂O); 4.25(2H, q, CH₃CH₂O); 5.65(2H, broad s, NH₂); 7.46(5H, m, Ar-H)

MS, m/e : 231(M⁺), 214, 186, 185, 169, 157, 142, 131, 119, 117, 104, 103, 93

Reaction of sodium salt of ethyl 2-cyano-3-mercapto-3-(phenylamino)acrylate with ammonia in the presence of an
equimolar quantity of an aqueous solution of silver nitrate or cuprous chloride resulted in the formation of 400 in 50-60% yield.

**Attempted synthesis of 3,5-diaminoisothiazole.**

Cyanothioacetamide\(^{247}\) 2.5g (0.025 mole) was dissolved in minimum quantity of ice-cold 10% aqueous sodium hydroxide solution and was added to 125ml of ice-cold aqueous chloramine solution. The reaction mixture after stirring for 24 hours at room temperature did not yield any solid product. Attempted isolation of the product by neutralization and extraction with organic solvents did not yield the desired 3,5-diaminoisothiazole.

**Attempted Synthesis of 3,5-diamino-4-cyanoisothiazole.**

A solution of 3.34g (0.03 mole) of fused sodium sulfide (70%) in 15ml of water was added to a solution of 4.17g (0.03 mole) of 3-amino-2-cyano-3-(methylthio)acrylonitrile\(^{282}\) in 30ml of dimethylformamide, with cooling and stirring. The mixture was heated on a steam bath for 24 hours, cooled and added to 150ml of ice-cold aqueous chloramine solution. The reaction mixture after stirring
for 24 hours at room temperature did not yield any solid material. Neutralization with dilute hydrochloric acid and extraction with organic solvents did not yield the desired product.

4-Carbethoxy-3-methyl-5-(phenylamino)isothiazole (401).

Method I: To a solution of potassium t-butoxide (0.025 mole) prepared by dissolving 0.98g of potassium in 30ml of t-butanol, was added, with cooling, a mixture of 3.25g (0.025 mole) of ethyl acetoacetate and 3.38g (0.025 mole) of phenyl isothiocyanate. The reaction mixture was stirred at room temperature for 12 hours and was added to 125ml of freshly prepared, ice-cold aqueous chloramine solution. The mixture was allowed to stand for 24 hours at room temperature. The solid obtained was filtered, washed with water and dried in air. Recrystallization from n-hexane yielded 4g (61%) of colorless crystalline product, m.p. 70-72°C.

Analysis : C_{13}H_{14}N_{2}O_{2}S(262.32) Requires C, 59.52; H, 5.38%  
Found C, 59.46; H, 5.59%

IR (Nujol) : 3260(NH); 1650, 1580, 1530, 1265, 1210, 1095, 1035, 910, 800, 830, 795 cm^{-1}

IR (KBr) : 3260(NH); 1660, 1590, 1530, 1380, 1250, 1200, 1080, 1025, 900, 860, 830, 790, 780, 760, 690 cm^{-1}

UV (MeOH) : 204nm(log ε 4.33), 227(4.32), 309(4.31)
Method II: To a suspension of 7.60g (0.05 mole) of sodium salt of ethyl acetoacetate in 25ml of dimethylformamide was added, with cooling, 6.75g (0.05 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and treated with 250ml of ice-cold, aqueous chloramine solution. The work-up of the reaction mixture yielded 6g (46%) of 401.

Method III: 3.7g (14 mmole) of ethyl 3-amino-2-(N-phenylthiocarbamoyl)crotonate was dissolved in minimum quantity of dimethylformamide and added to 70ml of freshly prepared, ice-cold aqueous chloramine solution. The mixture was stirred at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried. Recrystallization from n-hexane yielded 3.0g (82%) of 401.

Method IV: A solution of 2.64g (0.01 mole) of ethyl 3-amino-2(N-phenylthiocarbamoyl)crotonate in 30ml ethanol was reacted with a solution of 2.54g (0.01 mole) of iodine in 30ml ethanol in the presence of 1.6g (0.02 mole) of pyridine according to the method reported in the literature. Recrystallization from n-hexane afforded 2.1g (80%) of 401, m.p. 70-72°C. Reported m.p. 71°C.
4-Acetyl-3-methyl-5-(phenylamino)isothiazole (402).

**Method I:** Acetylacetone 2.5g (0.025 mole) was reacted with 3.38g (0.025 mole) of phenyl isothiocyanate in the presence of potassium tert-butoxide (0.025 mole) in 30ml of t-butanol and the mixture was reacted with 125ml of ice-cold aqueous chloramine solution according to the procedure described for 401. Recrystallization from ethanol yielded 4g (69%) of crystalline product, m.p. 132-134°C.

Analysis : \( C_{12}H_{12}N_2O_3(232.3) \) Requires C, 62.04; H, 5.21%

Found C, 62.31; H, 5.21%

**IR (Nujol):** 1610, 1590, 1540, 1255, 990, 810, 790, 750 cm\(^{-1}\)

**IR (KBr):** 1610, 1590, 1550, 1500, 1485, 1455, 1440, 1410, 1380, 1360, 1240, 1165, 1065, 1020, 980, 800, 750, 675 cm\(^{-1}\)

**UV (MeOH):** 203nm(log \( \varepsilon \) 4.33), 225 sh(4.16), 244(4.28), 275 sh(3.81), 328(4.22)

**NMR (CDCl\(_3\)):** 6 2.58(3H, s, CH\(_3\)); 2.65(3H, s, COCH\(_3\)); 7.18-7.5(5H, m, Ar-H)

**MS, m/e:** 232(M\(^+\)), 217, 199, 190, 173, 148, 141, 104, 77, 51, 43

**Method II:** To a suspension of 3.0g (0.025 mole) of sodium salt of acetylacetone\(^{590}\) in 15ml of dimethyl-
Formamide was added, with cooling, 3.38 g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred for 16 hours at room temperature and treated with 125 ml of ice-cold aqueous chloramine solution. The work-up of the reaction mixture yielded 3 g (52%) of 402.

**Method III:** A solution of 7.2 g (0.025 mole) of 3-(N-phenylthiocarbamoyl)-4-(1-pyrrolidinyl)-3-penten-2-one in minimum quantity of dimethylformamide was reacted with 125 ml of ice-cold aqueous chloramine solution according to the procedure described under Method III for 401. Work-up yielded 2.0 g (35%) of 402, m.p. 132-134°C.

**Method IV:** A solution of 2.34 g (0.01 mole) of 4-amino-3-(N-phenylthiocarbamoyl)-3-penten-2-one in 30 ml ethanol was reacted with a solution of 2.54 g (0.01 mole) of iodine in 30 ml of ethanol in the presence of 1.6 g (0.02 mole) of pyridine according to the method reported in the literature. Recrystallization from ethanol yielded 1.5 g (65%) of 402, m.p. 132-134°C. Reported m.p. 140°C.
4-Acetyl-3-phenyl-5-(phenylamino)isothiazole (403).

To a solution of potassium t-butoxide (0.025 mole) prepared by dissolving 0.95g of potassium in 30ml of t-butanol was added, with cooling, 4.1g (0.025 mole) of benzoylacetone followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and was added to 125ml of freshly prepared ice-cold aqueous chloramine solution. The reaction mixture was stirred for 24 hours, the solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol afforded 3.5g (48%) of crystalline product m.p. 99-101°C.

Analysis : C_{17}H_{14}N_{2}O_{5}(294.36) Requires C, 69.36; H, 4.79%
Found C, 69.61; H, 5.17%

IR (Nujol) : 1610, 1580, 1255, 1160, 960, 815, 760 cm^{-1}

UV (MeOH) : \( \lambda_{max} \) 230nm, 298 sh, 330

MS, m/e : 294(M^{+}), 279, 251, 217, 203, 190, 185, 175, 174, 162, 161, 148, 144, 136, 128, 121, 109, 104, 103, 89, 51, 43

6,7-Dihydro-6,6-dimethyl-3-(phenylamino)-2,1-benzisothiazol-4(5H)-one (404).

A mixture of 3.5g (0.025 mole) of dimedone, 3.38g
(0.025 mole) of phenyl isothiocyanate and 5 drops of triethylamine in 25ml of acetonitrile was refluxed for 20 hours, cooled and added to 125ml of ice-cold, aqueous, chloramine solution. The mixture was stirred at room temperature for 24 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 1.7g (25%) of crystalline product, m.p. 129-131°C.

Analysis : $C_{15}H_{16}N_2O_3$ (272.36) Requires $C, 66.14; H, 5.92$
            Found $C, 66.10; H, 6.18$

IR (Nujol) : 1620, 1590, 1550, 1260, 1175, 1080, 995,
             890, 815, 765, 755 cm$^{-1}$

NMR (CDCl$_3$) : 6 1.1(6H, s, C(CH$_3$)$_2$); 2.45(2H, s, CH$_2$ at 7);
                 2.75(2H, s, CH$_2$ at 5); 7.15-7.65(5H, m, Ar-H).

MS, m/e : 272(M$^+$), 257, 243, 229, 216, 190, 188, 183,
          170, 148, 142, 136, 128, 115, 109, 104, 103

3-(Phenylamino)-4,5,6,7-tetrahydro-2,1-benzisothiazole (405).

Method I: To a suspension of sodium t-butoxide (0.025 mole) in 50ml of t-butanol was added, with cooling, a mixture of 2.45g (0.025 mole) of cyclohexanone and 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 12 hours. To the
reaction mixture was added 5ml of methanol followed by 50ml of ice-cold water. The mixture was transferred to a separating funnel and extracted with 2x50ml solvent ether and the aqueous layer was added to 125ml of ice-cold aqueous chloramine solution. The mixture was stirred at room temperature for 12 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 1.5g (26%) of crystalline product, m.p. 190-192°C.

**Analysis**

- **IR (Nujol)**: 3230(NH); 1610, 1580, 1510, 1240, 1175, 1040, 955, 900, 860, 825, 805, 760 cm⁻¹
- **IR (KBr)**: 3220, 3180(NH); 1600, 1560, 1495, 1450, 1435, 1410, 1290, 1160, 950, 890, 850, 800, 750, 700 cm⁻¹
- **UV (MeOH)**: 203nm(log ε 4.41), 234(4.04), 305(4.38)
- **NMR (CDCl₃)**: 6 1.86(4H, broad s, CH₂ at 4 & 7); 2.15(4H, m, CH₂ at 5 & 6); 6.85(1H, broad s, C₆H₅NH); 724(5H, m, Ar-H)
- **MS, m/e**: 230(M⁺), 229, 202, 201, 197, 190, 162, 155, 143, 138, 136, 130, 128, 121, 115, 109, 104, 103
Method II: A solution of 2.5g (8.3 mmole) of 2-(4-morpholiny1)-l-(N-phenylthiocarbamoy1)-l-cyclo-
hexene in minimum quantity of dimethylformamide was added to 50ml of freshly prepared ice-cold aqueous chloramine solution. The mixture was stirred for 12 hours at room temperature. The usual work-up of the reaction mixture yielded 1.5g (79%) of 405 m.p. 190-192°C.

4-Cyano-3-phenyl-5-(phenylamino)isothiazole (406).

Method I: To a solution of sodium ethoxide (0.025 mole) in absolute ethanol was added, with cooling, 3.63g (0.025 mole) of benzoylacetonitrile, followed by 3.38g (0.025 mole) of phenyl isothiocyanate. The mixture was stirred at room temperature for 24 hours and added to 125ml of ice-cold aqueous chloramine solution. The reaction mixture was stirred at room temperature for 24 hours. The solid obtained was filtered, washed with water and dried in air. Recrystallization from dimethylformamide yielded 5.0g (72%) of colorless crystalline product, m.p. 268-270°C.

Analysis : C_{16}H_{11}N_{3}(277.34) Requires C, 69.29; H, 4.00%
            Found   C, 69.50; H, 4.32%

IR (Nujol) : 3250(NH); 2220(C=N); 1610, 1570,1015,
            810, 795, 775, 760 cm\(^{-1}\)
IR (KBr) : 3250, 3200 (NH); 2220 (C=NO); 1605, 1565, 1500,
1480, 1455, 1430, 1400, 1310, 1240, 1180,
1075, 1030, 1010, 805, 790, 760, 750,
705, 695 cm⁻¹
UV (MeOH) : ƛmax 250, 305 nm
MS, m/e : 277(M⁺), 276, 251, 244, 231, 219, 200, 181,
174, 173, 149, 146, 142, 135, 115, 109,
104, 103

Method II: A solution of 1.4 g (5 mmole) of 2-amino-
3-(N-phenylthiocarbamoyl)cinnamionitrile in minimum
quantity of dimethylformamide was added to 30 ml of ice-
cold aqueous chloramine solution. The mixture was
stirred at room temperature for 24 hours. The solid
obtained was filtered, washed with water and dried in air.
Recrystallization from dimethylformamide yielded 1.0 g
(72%) of 406 , m.p. 268-270° C.

3-Amino-5-(phenlamino)-1,2,4-thiadiazole (407).

To a solution of 4.2 g (0.1 mole) of cyanamide in
10 ml of water was added with cooling a solution of 4.0 g
(0.1 mole) of sodium hydroxide in 20 ml of water, followed
by 6.75 g (0.05 mole) of phenyl isothiocyanate. Sufficient
alcohol was added to make the mixture homogenous. The
mixture was stirred at room temperature for 3 hours,
heated on a steam bath for 20 min., allowed to stand at room temperature for 12 hours and added to 250ml of ice-cold aqueous chloramine solution. The reaction mixture was stirred at room temperature for 24 hours. The solid obtained was filtered, washed with water, and dried. Recrystallization from methanol-water yielded 5.5g (57%) of colorless crystalline product, m.p. 210-212°C. Reported m.p. 210-212°C.\(^{591}\)

Analysis: \(\text{C}_8\text{H}_8\text{N}_4\text{S}(192.24)\) Requires C, 49.98; H, 4.19%  
Found  
C, 50.01; H, 4.47%

IR (Nujol): 3470, 3310, 3190(NH\(_2\)); 1640, 1600, 1560, 1520, 1230, 1045, 1035, 905, 865, 835, 760 cm\(^{-1}\)

4-Carbethoxy-3-(formylamino)-5-(phenylamino)isothiazole (408).

Formic acid (98%) 4.3ml was treated dropwise, at room temperature, with 10.2ml of acetic anhydride. The mixture was stirred at room temperature for 12 hours. To this was added 1.32g (5 mmole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360) and stirred at room temperature for 48 hours. The reaction mixture was
concentrated under reduced pressure. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to obtain 1.0g (69%) of colorless crystalline product, m.p. 140-142°C.

Analysis : C_{13}H_{13}N_{3}O_{3}S (291.32) Requires C, 53.59; H, 4.50%

Found : C, 53.53; H, 4.77%

IR (KBr) : 3320, 3200 (NH); 1710, 1660, 1600, 1510, 1475, 1400, 1370, 1260, 1230, 1200, 1100, 1030, 900, 785, 750 cm^{-1}

A mixture of 2.63g (0.01 mole) of 360, 0.9ml of aniline, 15ml of triethyl orthoformate and 2-drops of concentrated sulfuric acid or hydrochloric acid was refluxed for 2 hours. Excess of triethyl orthoformate was removed under vacumm. Recrystallization of the residue from ethanol yielded 2g of the product identified (mp, TLC, IR) as the 3-(formylamino)isothiazole (408).

3-(Acetlamino)-4-carbethoxy-5-(phenylamino)isothiazole (409).

To a solution of 1.32g (5 mmole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360) in 10ml of pyridine was added with cooling 0.4g (5 mmole) of acetyl chloride. The reaction mixture was stirred at room
temperature for 24 hours and poured onto crushed ice. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 1g (66%) of colorless crystalline product, m.p. 148-150°C.

Analysis : C_{14}H_{15}N_{3}C_{3}S(305.35) Requires C, 55.07%; H, 4.95% Found C, 54.99%; H, 5.30%

IR (Nujol) : 3340, 3240(NH); 1700, 1670, 1580, 1520, 1245, 1215, 1120, 1030, 1015, 970, 945, 885, 860, 785, 765 cm⁻¹

3-(Benzoylamino)-4-cyan-5-(phenylamino)isothiazole (410).

To a mixture of 2.16g (0.01 mole) of 3-amino-4-cyan-5-(phenylamino)isothiazole (358) and 2ml of triethylamine in 50ml of dioxane was added, with cooling, 1.4g (0.01 mole) of benzoyl chloride. The reaction mixture was refluxed for 4 hours, cooled and the solid that separated was filtered, washed with water and dried. Recrystallization from dimethylformamide afforded 1.5g (47%) of crystalline product, m.p. 289-291°C.

Analysis : C_{17}H_{12}N_{4}O_{5}(320.36) Requires C, 63.73%; H, 3.78% Found C, 63.95%; H, 4.07%

IR (Nujol) : 3380, 3240, 3180(NH); 2720(CEN); 1680, 1640, 1590, 1500, 1285, 1200, 1120, 1080, 1025, 975, 825, 790, 760 cm⁻¹
3-(Acetylamino)-4-cyano-5-(methylthio)isothiazole (411).

3-Amino-4-cyano-5-(methylthio)isothiazole (388)

1.71g (0.01 mole) was refluxed for 10 minutes with 5ml of acetic anhydride. The reaction mixture was concentrated under reduced pressure, solid obtained was triturated with ethanol, filtered and dried. Recrystallization from ethanol yielded 1.5g (70%) of colorless crystalline product, m.p. 195-197°C.

Analysis : C₇H₇N₃S₂ (213.28) Requires C, 39.42; H, 3.31%
            Found C, 39.85; H, 3.43%

IR (Nujol) : 3240, 3180(NH); 2220(C≡N); 1675, 1555
            1265, 985, 965, 820 cm⁻¹

N'-4-carbethoxy-5-(phenylamino)-3-isothiazolyl-N-phenyl thiourea (412).

A mixture of 1.32g (5 mmole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360) and 0.68g (5 mmole) of phenyl isothiocyanate in 40ml of dioxane was refluxed for 3 hours, cooled and poured into ice-water. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.5g (75%) of colorless crystalline product, m.p. 128-130°C.
N'-4-carbethoxy-5-(phenylamino)-3-isothiazolyl-N-(4-methylphenyl)thiourea (413).

3-Amino-4-carbethoxy-5-(phenylamino)isothiazole (360) 1.32g (5 mmole) was reacted with 0.75g (5 mmole) of p-tolyl isothiocyanate in 40ml dioxane according to the procedure described for 412. Recrystallization from ethanol yielded 1.2g (58%) of colorless crystalline product, m.p. 145-147°C.

\[ \text{Analysis: } C_{19}H_{18}N_4O_2S_2 (398.5) \text{ Requires } C, 57.26\%; H, 4.55\% \]
\[ \text{Found } C, 57.00\%; H, 4.86\% \]

\[ \text{IR (Nujol): } \nu_{\text{max}} \text{ cm}^{-1}; 3380(\text{NH}); 1680, 1630, 1600, 1570, 1530, 1280, 1220, 1175, 1110, 1035, 885, 825, 790, 765 \]

\[ \text{UV (EtOH): } 238\text{nm} (\log \epsilon 4.31), 284(4.49) \]

\[ \text{MS, m/e: } 398(M^+), 365, 352, 318, 304, 292, 263, 259, 244, 217, 202, 201, 185, 174, 159, 144, 135 \]
4-Cyano-3-(dimethylaminomethyleneamino)-5-(methylthio)isothiazole (414).

**Method I:** To a solution of 1.7g (0.01 mole) of 3-amino-4-cyano-5-(methylthio)isothiazole (388) in 10ml of dimethylformamide was added, with cooling, 1.53g (0.01 mole) of phosphorous oxychloride. The mixture was stirred at room temperature for 24 hours, poured into ice-water and the mixture was made neutral by the careful addition of 10% NaOH. The solid that separated was filtered, washed with water and dried. Recrystallization from ethyl acetate-cyclohexane afforded 1.2g (53%) of colorless crystalline product, m.p. 100-102°C.

**Analysis:** 
\[ \text{C}_8\text{H}_{10}\text{N}_4\text{S}_2 (226.32) \] 
Requires C, 42.45; H, 4.45% 
Found C, 42.29; H, 4.22%

**IR (KBr):** 
2210 (C=N); 1620, 1475, 1425, 1380, 1350, 1315, 1255, 1110, 990, 975, 920, 860, 835, 760 cm\(^{-1}\)

**IR (Nujol):** 
2210 (C=N); 1620, 1250, 1105, 985, 970, 915, 860, 830 cm\(^{-1}\)

**UV (MeOH):** 
220nm (log \( \varepsilon \) 4.04), 281(4.54), 314 sh(3.97)

**Method II:** To a solution of 1.89g (0.01 mole) of 3-amino-5-(methylthio)isothiazole-4-carboxamide (390) in 10ml of dimethylformamide was added, with cooling, 3.06g
(0.02 mole) of phosphorous oxychloride. The mixture was stirred at room temperature for 24 hours. Work-up of the reaction mixture as described under Method I yielded 1.09g (44%) of colorless crystalline product, m.p. 100-102°C, identical (mmp, TLC, IR) with the product obtained by Method I.

3-(Ethoxymethyleneamino)-5-(phenylamino)-4-isothiazole-N-methylcarboxamide (415).

3-Amino-5-(phenylamino)-4-isothiazole-N-methylcarboxamide (421), 0.75g (3 mmole) in 5ml of triethyl orthoformate was refluxed for 24 hours. Excess of triethyl orthoformate was removed by distillation under reduced pressure. The residue was triturated with cold dilute ethanol, filtered and dried. Recrystallization from ethanol afforded 0.6g (66%) of colorless crystalline solid, m.p. 126-128°C.

Analysis : $C_{14}H_{16}N_4O_2S$ (304.37) Requires C, 55.24; H, 5.30% Found C, 55.27; H, 5.64%

IR (Nujol) : 3230(NH); 1620, 1580, 1550, 1265, 1175, 1125, 1030, 925 cm$^{-1}$

UV (MeOH) : 204nm($\log_{e} 4.31$), 248(4.31), 311(4.32)

MS, m/e : 304($M^+$)
4-Carbethoxy-5-(phenylamino)-3-(phenylamino)methyleneamino/isothiazole (416).

A mixture of 2.63g (0.01 mole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360), 0.9ml of aniline and 5ml of triethyl orthoformate was refluxed for 24 hours. The mixture was cooled and the solid that separated was filtered, washed with dilute ethanol and dried. Recrystallization from ethanol yielded 2g (55%) of colorless crystalline product, m.p. 152-154°C.

Analysis : C_{19}H_{18}N_{4}O_{2}S (366.75) Requires C, 62.22; H, 4.95%
            Found C, 61.90; H, 5.29%

IR (Nujol) : 3360, 3310 (NH); 1670, 1640, 1590, 1560,
              1510, 1275, 1255, 1215, 1125, 1035, 1000,
              780, 765, 755 cm^{-1}

IR (KBr)   : 3350, 3310 (NH); 1675, 1635, 1590, 1565,
              1520, 1475, 1450, 1370, 1350, 1320, 1245,
              1190, 1000, 1015, 980, 950, 775, 765,
              750 cm^{-1}

MS, m/e     : 366(M^+), 337, 320, 287, 263, 243, 228,
              217, 206, 185, 174, 159, 144, 124,
              119, 104.
Diethyl \( \left[ \text{4-carbethoxy-5-(phenylamino)-3-isothiazolyl} \right] \text{amino/methylenemalonate (417)} \).

A mixture of 2.63g (0.01 mole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360) and 3.24g (0.015 mole) of diethyl ethoxymethylenemalonate was heated for 12 hours on a steam bath allowing the ethanol formed during the reaction to distill out. The reaction mixture was cooled, triturated with ether and the solid obtained was filtered and dried. Recrystallization from ethanol yielded 3g (69%) of product, m.p. 92-94°C.

**Analysis**  
\( \text{C}_{20}\text{H}_{23}\text{N}_{3}\text{O}_{6}\text{S} (433.47) \) Requires C,55.41; H,5.35%  
Found C,55.40; H,5.73%

**IR (Nujol)**  
3280-3200(NH); 1690, 1670, 1640, 1600, 1570, 1550, 1285-1245, 1110, 1080, 1030, 905, 865, 805, 790, 755 cm\(^{-1}\)

**NMR (CDCl\(_3\))**  
\( \delta \, 1.12-1.6(9\text{H, m, CH}_3\text{CH}_2\text{-O}); \)  
4.05-4.65(6H, m, CH\(_3\)CH\(_2\)-O);  
6.9-7.5(5H, m, Ar-H);  
8.85(1H, d, NH-CH=);  
10.0(1H, broad s, CH\(_6\)\(_2\)NH);  
11.83(1H, broad d, NH-CH=)

**MS, m/e**  
433(M\(^+\)), 388, 360, 342, 314, 296, 286, 269, 241.
3-Amino-5-(phenylamino)isothiazole-4-carboxylic acid (418).

3-Amino-4-carbethoxy-5-(phenylamino)isothiazole (360)

2.63g (0.01 mole) was added to a solution of 5g of potassium hydroxide in 75ml of water. The mixture was refluxed for 4 hours, poured onto ice-water and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.5g (64%) of colorless crystalline product, m.p. 165-167°C (d).

Analysis : $C_{10}H_{9}N_{3}O_{2}S$ (235.25) Requires C, 51.05; H, 3.86%; Found C, 51.28; H, 4.10%

IR (Nujol) : 3480, 3350(NH); 1640, 1590, 1560, 1270, 855, 830, 805, 760 cm$^{-1}$

IR (KBr) : 3480, 3340(NH); 1640, 1615, 1600, 1500, 1470, 1450, 1330, 1250, 1200, 1120, 845, 820, 795, 750, 725 cm$^{-1}$

MS, m/e : 235(M$^+$), 217, 191, 148, 143, 135, 121, 117, 116, 109
3-Amino-5-\((4\text{-methylphenyl})\)aminoisothiazole-4-carboxylic acid (419).

3-Amino-4-carbethoxy-5-\((4\text{-methylphenyl})\)aminoisothiazole (366) 2.77g (0.01 mole) was added to a solution of 5g of potassium hydroxide in 75ml of water. The mixture was refluxed for 4 hours, poured onto ice-water and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid. The solid separated was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.5g (60%) of colorless crystalline product, m.p. 165-167°C (d).

Analysis: C\textsubscript{11}H\textsubscript{11}N\textsubscript{3}O\textsubscript{2}S (249.29) Requires C, 53.00; H, 4.45%
Found C, 53.23; H, 4.65%

IR (Nujol): 3480, 3280(NH), 1600, 1550, 1280, 1120, 860, 800, 770 cm\textsuperscript{-1}

MS, m/e: 249(M\textsuperscript{+}), 231, 205, 188, 163, 162, 157, 118, 107, 91

3-Amino-5-(methylthio)isothiazole-4-carboxylic acid (420).

3-Amino-4-cyano-5-(methylthio)isothiazole (388) 1.71g (0.01 mole) was added to 40ml of 10% sodium hydroxide solution. The mixture was refluxed for 3 hours, cooled,
poured onto ice-water and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.5g (79%) of colorless crystalline product, m.p. 217-219°C (d).

3-Amino-5-(methylthio)isothiazole-4-carboxylic acid (420) was also obtained in 84 or 74% yields by the hydrolysis of 3-amino-4-carbethoxy-5-(methylthio)isothiazole (389) or 3-amino-5-(methylthio)isothiazole-4-carboxamide (390) employing the above procedure.

Analysis : C₅H₆N₂O₂S₂ (190.25) Requires C, 31.56; H, 3.18%
Found   C, 31.81; H, 3.58%
IR (Nujol) : 3480, 3300(NH); 1630, 1280, 865, 795 cm⁻¹
IR (KBr)  : 3480, 3300(NH); 1665, 1610, 1520, 1460, 1420, 1390, 1280, 1170, 1120, 1010, 960, 855, 785, 720 cm⁻¹
MS, m/e   : 190(M⁺)

3-Amino-5-(phenylamino)-4-isothiazole-N-methylcarboxamide (421).

To a solution of 1.32g (5 mmole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360), in 20ml of dimethylformamide was added 20ml of 40% aqueous methylamine solution. The reaction mixture was stirred for 3 days at room
temperature and poured onto ice-water. The solid separated was filtered, washed with water and dried. Recrystallization from ethanol yielded 0.8g (65%) of colorless crystalline product, m.p. 185-187°C.

**Analysis**  
\[ C_{11}H_{12}N_4O_2S \] (248.3) Requires C, 53.21; H, 4.87\%  
Found C, 53.22; H, 5.14\%

**IR (Nujol)**  
3400, 3340, 3280, 3200(NH); 1620, 1590, 1550, 1500, 1260, 1160, 1120, 1030, 910, 810, 780, 765, 750 cm\(^{-1}\)

**UV (MeOH)**  
204 nm (log \(ε\) 4.3), 224 (4.24), 292 (4.18), 310 (4.22)

3-Amino-5-(phenylamino)isothiazole-4-carboxamide (422).

3-Amino-4-cyano-5-(phenylamino)isothiazole (358)  
2.16g (0.01 mole) was suspended in 60ml of 10% sodium hydroxide solution and the mixture refluxed for 8 hours, cooled to room temperature and filtered. The clear filtrate was cooled and neutralized with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.8g (77%) of crystalline product, m.p. 232-234°C.
Analysis: $C_{10}H_{10}N_4O_2S$ (234.28) Requires C, 51.26%; H, 4.30%
Found C, 51.40%; H, 4.47%

IR (Nujol): 3400, 3350, 3200, 3180 (NH); 1650, 1580, 1540, 1160 cm$^{-1}$

UV (EtOH): 205 nm (log $\varepsilon$ 4.26), 223 (4.17), 310 (4.18)
UV (0.1 N HCl): 213 nm (log $\varepsilon$ 4.13), 225 (4.22), 284 (4.19)

MS, m/e: 234 (M$^+$), 217, 201, 185, 169, 147, 144, 116, 104

3-Amino-5-[(2-methylphenyl)amino]isothiazole-4-carboxamide (423).

3-Amino-4-cyano-5-[(2-methylphenyl)amino]isothiazole (363), 1.15 g (5 mmole) was suspended in 30 ml of 10% sodium hydroxide solution. The mixture was refluxed for 8 hours, cooled to room temperature and clarified by filtration. The clear solution was cooled and acidified with dilute hydrochloric acid. The solid that separated was filtered, washed with water and dried. Recrystallization from dimethylformamide–ethanol yielded 0.7 g (56%) of crystalline product, m.p. 208–210°C.
3-Amino-5-(4-methylphenyl)aminoisothiazole-4-carboxamide (424).

3-Amino-4-cyano-5-(4-methylphenyl)aminoisothiazole (365), 1.15g (5 mmole) was suspended in 30ml of 10% sodium hydroxide solution. The mixture was refluxed for 8 hours, cooled to room temperature and filtered. The filtrate was neutralized with dilute hydrochloric acid and the solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.9g (73%) of crystalline product, m.p. 220-224°C.

Analysis : \( \text{C}_{11}\text{H}_{12}\text{N}_{4}\text{O}_{3} (248.3) \) Requires C, 53.21; H, 4.87% 
Found C, 53.22; H, 4.97%

IR (Nujol) : 3400, 3300(NH); 1660, 1590, 1550, 1265, 1150, 865, 840, 815 cm\(^{-1}\)

MS, m/e : 248(M\(^+\)), 231, 214, 199, 183, 170, 161, 158, 130, 118, 117, 106, 91
3-Amino-4-cyano-5-(methylsulfonyl)isothiazole (425).

To a suspension of 8.55g (0.05 mole) of 3-amino-4-cyano-5-(methylthio)isothiazole (388) in 60ml of glacial acetic acid was added, with cooling, 12.5ml of 30% hydrogen peroxide. The mixture was stirred at room temperature for 3 days. The solid obtained was filtered, washed with water and dried. Recrystallization from ethyl acetate yielded 6g (59%) of colorless crystalline product, m.p. 207-209°C (d).

Analysis: $C_5H_5N_3O_2S_2$ (203.25) Requires C, 29.55; H, 2.48% 
Found C, 29.85; H, 2.71%

IR (Nujol): 3410, 3340, 3230(NH); 2220(C=N); 1630, 1530, 1215 cm⁻¹

IR (KBr): 3420, 3330, 3230(NH); 2220(C=N); 1635, 1545, 1470, 1425, 1370, 1315(SO₂); 1200, 1140(SO₂); 1100, 1060, 1030, 975, 965, 900, 850, 765, 720 cm⁻¹

UV (MeOH): 220nm (log ε 4.26), 238sh (4.05), 345 (3.98)

MS, m/e: 203(M⁺), 187, 172, 156, 141, 124, 109, 108, 98

Reaction of 3-Amino-4-cyano-5-(methylsulfonyl)isothiazole with aqueous methylamine.

A suspension of 1g (5 mmole) of 3-amino-4-cyano-5-(methylsulfonyl)isothiazole (425) in 10ml of 40% aqueous methylamine solution was stirred at room temperature for 32 hours. The solid was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded
0.55g (71%) of colorless crystalline solid, m.p. 257-259°C. The product obtained was found to be identical (mmp, TLC and IR) with 3-amino-4-cyano-5-(methylamino)isothiazole (351).

Reaction of 3-amino-4-cyano-5-(methylsulfonyl)isothiazole with ammonia.

3-Amino-4-cyano-5-(methylsulfonyl)isothiazole (425) 1g (5 mmole) was stirred with 30% aqueous ammonia solution according to the procedure described for 351. The usual work-up yielded 0.75g (75%) of the unreacted starting material. Alternatively, dry ammonia gas was bubbled through a boiling solution of 1g (5 mmole) of 425 in 25ml of dioxane for 4 hours. The usual work-up of the reaction mixture yielded 0.8g of solid, identified as the unreacted starting material.

Reaction of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole with HNO₂.

3-Amino-4-carbethoxy-5-(phenylamino)isothiazole (360) 3.95g (0.015 mole) was dissolved in 50ml of phosphoric acid (89%) by gentle warming. The solution was cooled to 0°C in an ice-salt bath and treated dropwise with a solution of 1.05g (0.015 mole) of sodium nitrite in 15ml of water.
under vigorous stirring. The reaction mixture was allowed to stand at room temperature for 4 hours. The mixture was poured onto ice-water and neutralized with ice-cold 10% sodium hydroxide solution. The solid obtained was filtered, washed with water and dried in air. Recrystallization from ethanol yielded 1.5g of crystalline product, m.p. 233-235°C. The product obtained was found to be identical (mmp, TLC, UV, IR and NMR) with an authentic sample of ethyl α-cyano-Δ²α-benzothiazoline-acetate (399).

4-Amino-3-(methylthio)isothiazole(3,4-d)pyrimidine (426).

**Method I:** A mixture of 1g (4.43 mmole) of 4-cyano-3-(dimethylaminomethyleneamino)-5-(methylthio)-isothiazole (414) and 5g of ammonium acetate in 15ml of ethanol containing 1ml of water was refluxed for 6 hours, cooled and poured onto ice-water. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.5g (57%) of crystalline product, m.p. 248-250°C (d).

Analysis : C₆H₆N₄S₂(198.27) Requires C, 36.34; H, 3.05%
         Found   C, 36.61; H, 3.34%
IR (Nujol) : 3310(NH); 1640, 1560, 1520, 1250, 1020, 985, 940, 860, 830, 805 cm^{-1}

IR (KBr) : 3310(NH); 1650, 1555, 1530, 1490, 1430, 1360, 1240, 1110, 980, 930, 800 cm^{-1}

UV (MeOH) : \( \lambda_{\text{max}} 230\text{nm}, 304, 349 \)

MS, m/e : 198(M^+), 183, 165, 156, 152, 138, 125, 114, 109, 108, 98

Method II: A mixture of 1.71g (0.01 mole) of 3-amino-4-cyano-5-(methylthio)isothiazole (388), 3g of ammonium acetate, 10ml of triethyl orthoformate and 1ml of glacial acetic acid was refluxed for 4 hours. Excess of triethyl orthoformate was removed under reduced pressure and the residue was triturated with cold water and filtered. Recrystallization of the crude product from dimethylformamide-ethanol yielded 1g (51%) of the crystalline product, m.p. 248-250°C (d), identical (mmp, TLC, IR) with the product obtained by Method I.

4-Amino-6-methyl-3-(methylthio)isothiazolo(3,4-d)pyrimidine (427).

A stream of dry hydrogen chloride gas was passed through a mixture of 1.71g (0.01 mole) of 3-amino-4-cyano-5-(methylthio)isothiazole (388) and 50ml of acetonitrile
for 10 hours. The mixture was allowed to stand at room temperature for 24 hours, poured onto ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1g (47%) of crystalline product, m.p. 240-242°C (d).

Analysis : C_7H_8N_4S_2 (212.3) Requires C, 39.60%; H, 3.80%
            Found   C, 39.72%; H, 3.91%

IR (KBr) : 3480, 3300(NH); 1645, 1565, 1520, 1420,
          1380, 1285, 1010, 980, 830, 795 cm⁻¹

UV (MeOH) : 230nm (log ε 4.40), 302(4.08), 346(4.02)

4-Amino-3-(phenylamino)isothiazolo(3,4-d)pyrimidine (428).

3-Amino-4-cyano-5-(phenylamino)isothiazole (358)

2.16g (0.01 mole) was reacted with 3g of ammonium acetate and 10ml of triethyl orthoformate in the presence of 1ml of glacial acetic acid according to the procedure described for 426. Recrystallization from dimethylformamide-ethanol yielded 1.7g (70%) of crystalline product, m.p. 252-254°C.

Analysis : C_{11}H_{9}N_{5}S (243.29) Requires C, 54.30%; H, 3.73%
            Found   C, 54.47%; H, 4.05%

IR (Nujol) : 3280(NH); 1670, 1600, 1105, 1025, 940 cm⁻¹

MS, m/e : 243(M⁺), 226, 216, 199, 168, 143, 109
3.4-Bis(phenylamino)isothiazolo(3,4-d)pyrimidine (429).

A mixture of 2.16g (0.01 mole) of 3-amino-4-cyano-5-(phenylamino)isothiazole (358), 1ml of aniline, 1ml of glacial acetic acid and 10ml of triethyl orthoformate was refluxed for 4 hours and cooled. The solid obtained was triturated with hexane and filtered. Recrystallization from dimethylformamide-ethanol yielded 1.5g (47%) of crystalline product, m.p. 246-248°C.

Analysis : C_{17}H_{13}N_{5}S(319.38) Requires C, 63.93; H, 4.10% Found C, 64.28; H, 4.15%
IR (KBr) : 1640, 1580, 1525, 1495, 1480, 1445, 1420, 1380, 1345, 1270, 1080, 930, 830, 750 cm⁻¹
UV (MeOH) : 203nm (log ε 4.57), 237(4.28), 270(4.26), 287(4.26), 324(4.22), 425(3.67)

4,6-Dimercapto-3-(methylthio)isothiazolo(3,4-d)pyrimidine (430).

A mixture of 1.71g (0.01 mole) of 3-amino-4-cyano-5-(methylthio)isothiazole (388), 20ml of pyridine and 20ml of carbon disulfide was heated under reflux for 4 hours. Excess of carbon disulfide was removed under reduced pressure. The residue was treated with 50ml of 10% sodium hydroxide solution and the mixture was stirred at room temperature for 24 hours and filtered to remove
insoluble material. The clear filtrate was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.0g (41%) of crystalline product, m.p. >360°C.

Analysis:
\[ \text{C}_9\text{H}_5\text{N}_3\text{S}_4 \text{(247.39)} \]
Requires: C, 29.13; H, 2.04%  
Found: C, 29.53; H, 2.40%  

IR (KBr): 3450 (NH); 1660, 1590, 1530, 1470, 1420, 1350, 1320, 1295, 1160, 1070, 1010, 870, 830, 740 cm\(^{-1}\)

4,6-Dimercapto-3-(phenylamino)isothiazolo(3,4-d)pyrimidine (431)

A mixture of 2.16g (0.01 mole) of 3-amino-4-cyano-5-(phenylamino)isothiazole (358), 20ml of pyridine and 20ml of carbon disulfide was heated under reflux for 4 hours. Excess of carbon disulfide was removed under reduced pressure. The residue was treated with 50ml of 10% sodium hydroxide solution and the mixture was stirred at room temperature for 24 hours, filtered and the clear filtrate was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-
ethanol afforded 1.5g (51%) of crystalline product, m.p. >360°C.

Analysis : C_{11}H_{8}N_{4}S_{3}(292.4) Requires C, 45.18; H, 2.76%  
            Found   C, 45.08; H, 3.00%
IR (Nujol) : 1600-1500, 1270, 1210, 1150, 1060, 760 cm^{-1}
IR (KBr)  : 1610-1520, 1480, 1430, 1260, 1200, 1140, 1060, 890, 830, 750 cm^{-1}

3-(methylthio)isothiazolo(3,4-d)pyrimidin-4(5H)-one (432).

**Method I:** A mixture containing 1.89g (0.01 mole) of 3-amino-5-(methylthio)isothiazole-4-carboxamide, 10ml of triethyl orthoformate and 4ml of glacial acetic acid was refluxed for 8 hours. The solid that separates on cooling was filtered, washed with n-hexane and dried. Recrystallization from dimethylformamide-ethanol yielded 1.6g (80%) of colorless crystalline product, m.p. 300-302°C (d).

Analysis : C_{6}H_{5}N_{3}OS_{2}(199.26) Requires C, 36.16; H, 2.53%  
            Found   C, 36.45; H, 2.68%
IR (Nujol) : 1670, 1580, 1285, 1185, 1105, 1010, 985, 935, 890, 850, 815, 800 cm^{-1}
IR (KBr) : 1685, 1590, 1490, 1415, 1385, 1345, 1320, 1270, 1170, 1105, 1005, 980, 950, 930, 880, 845, 810, 800, 715 cm⁻¹

MS, m/e : 199(M⁺), 184, 166, 154, 137, 126, 125, 116

**Method II:** A mixture of 1.1g (5 mmole) of 3-amino-4-carbethoxy-5-(methylthio)isothiazole (389), 1g of ammonium acetate and 5ml of triethyl orthoformate in 5ml of N-methyl-2-pyrrolidone was refluxed for 24 hours, cooled and poured onto ice-water. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 0.2g (20%) of the product, m.p. 300-302°C, identical (mmp, TLC, IR) with the product obtained by Method I.

6-Methyl-3-(methylthio)isothiazolo(3,4-d)pyrimidin-4(5H)-one (433).

**Method I:** A mixture of 1.89g (0.01 mole) of 3-amino-5-(methylthio)isothiazole-4-carboxamide (390), 5ml of triethyl orthoacetate and 1ml of glacial acetic acid was refluxed for 4 hours. The reaction mixture was cooled, the solid obtained was filtered, suspended in 10ml of glacial acetic acid and refluxed for 8 hours. The solid that separates on cooling was filtered, washed with water.
and dried. Recrystallization from dimethylformamide-ethanol yielded 1.0g (47%) of colorless crystalline product, m.p. 331-333°C (d).

Analysis : C₇H₇N₃OS₂(213.28) Requires C, 39.42; H, 3.31%
           Found     C, 39.80; H, 3.57%

IR (Nujol) : 1690, 1590, 1160, 1010, 990, 900, 880, 800 cm⁻¹

IR (KBr) : 3170(NH); 1675, 1625, 1515, 1475, 1430, 1400, 1320, 1290, 1260, 1150, 980, 860, 825, 795 cm⁻¹

UV (MeOH) : 221nm(log ε 4.25), 252(4.09), 269(4.08), 284sh(3.98), 295(4.07), 317(4.01)

MS, m/e : 213(M⁺), 198, 196, 180, 169, 140, 127, 114, 108, 99, 97

Method II: A stream of dry hydrogen chloride gas was passed through a mixture of 2.18g (0.01 mole) of 3-amino-4-carbethoxy-5-(methylthio)isothiazole and 50ml of acetonitrile for 10 hours. The reaction mixture was allowed to stand at room temperature for 24 hours, poured into ice-water and basified with cold 10% ammonium hydroxide solution. The solid obtained was filtered and dried. Recrystallization from dimethylformamide-ethanol
yielded 1.5g (70%) of colorless crystalline product, m.p. 331-333°C. The product obtained was identical (TLC, IR) with the product obtained by the Method I.

**Method III**: 3-Amino-5-(methylthio)isothiazole-4-carboxamide 1.89g (0.01 mole) when reacted with acetonitrile in the presence of dry hydrogen chloride gas according to the procedure described under Method II, yielded 1.6g (75%) of 433.

3-(Phenylamino)isothiazolo(3,4-d)pyrimidin-4(5H)-one (434).

**Method I**: To 2.34g (0.01 mole) of 3-amino-5-(phenylamino)isothiazole-4-carboxamide (422) in 15ml of triethyl orthoformate was added 0.1g of p-toluene-sulfonic acid and the mixture was refluxed for 24 hours. The solid that separates on cooling was filtered, washed with dilute ethanol and dried. Recrystallization of the crude product from dimethylformamide-ethanol yielded 1.6g (66%) of crystalline product, m.p. 270-272°C.

**Analysis** : \( C_{11}H_{8}N_{4}O_{8}S (244.27) \) Requires C, 54.08; H, 3.30%

Found C, 54.21; H, 3.68%

**IR (Nujol)** : 3300(NH); 1690, 1630, 1610, 1580, 1275, 1220, 1160, 1155, 965, 890, 835, 805, 765, 755 cm\(^{-1}\)
IR (KBr) :  3280(NH), 1670, 1620, 1590, 1550, 1460, 1360, 1260, 1200, 1135, 950, 875, 820, 790, 745 cm\(^{-1}\)

UV (MeOH) :  204nm(\(\varepsilon \text{ 4.22}\)), 237(4.11), 251(4.22), 341(4.07)

MS, m/e :  244(M\(^+\)), 227, 217, 200, 174, 172, 169, 167, 147, 144, 142, 135, 122, 115, 109, 103

Method II:  A mixture of 2.63g (0.01 mole) of
3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360), 3.25g of ammonium acetate, 1ml of glacial acetic acid and 10ml of triethyl orthoformate was refluxed for 8 hours. The reaction mixture was cooled, the solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.2g (49%) of crystalline product, m.p. 270-272\(^\circ\)C, identical (mmp, TLC) with the product obtained by Method I.

\(3-\text{L-(4-Methylphenyl)amino} \text{isothiazolo(3,4-d)pyrimidin-4(5H)-one} \ (435)\).

A mixture of 1.24g (5 mmole) of 3-amino-5-\(\text{L-(4-methylphenyl)amino} \text{isothiazole-4-carboxamide} \ (423)\), 10ml of triethyl orthoformate and 0.1g of p-toluene-sulfonic acid was refluxed for 24 hours, cooled and the solid
obtained was filtered, washed with dilute ethanol and dried. Recrystallization from ethanol gave 0.75g (58%) of crystalline product, m.p. 258-260°C.

Analysis : C_{12}H_{10}N_{4}O_{3}(253.3) Requires C, 55.80; H, 3.90%  
           Found C, 55.72; H, 4.21%

IR (Nujol) : 3270(NH); 1680, 1620, 1600, 1570, 1275, 1215, 885, 840, 820, 800 cm\(^{-1}\)

5-Benzyl-3-(methylthio)isothiazolo(3,4-d)pyrimidin-4-(5H)-one (436).

A mixture of 2.18g (0.01 mole) of 3-amino-4-carbethoxy-5-(methylthio)isothiazole (389), 2ml of benzylamine, a drop of acetic acid and 5ml of triethyl orthoformate was refluxed for 24 hours. The reaction mixture was cooled and the solid obtained was filtered, washed with dilute ethanol and dried. Recrystallization from dimethylformamide-ethanol yielded 2g(69%) of colorless crystalline product, m.p. 160-162°C.

Analysis : C_{13}H_{11}N_{3}O_{2}(289.37) Requires C, 53.95; H, 3.83%  
           Found C, 53.91; H, 4.04%

IR (Nujol) : 1670, 1590, 1285, 1225, 1200, 1160, 1090, 1060, 1015, 975, 955, 870, 810, 795, 745 cm\(^{-1}\)
UV (MeOH) : 204nm (log ε 4.26), 227(4.19), 259(4.10),
267(4.04), 285(3.85), 296(3.86), 322(3.91)

NMR (CDCl₃) : 8 2.71(3H, s, CH₃S);
5.18(2H, s, CH₂C₆H₅);
7.42(5H, s, Ar-H);
8.17(1H, s, H at C-6)

MS, m/e : 289(M⁺), 274, 255, 198, 185, 183, 168,
125, 123, 114, 110, 107, 104, 91

5-Benzyl-3-(phenylamino)isothiazolo(3,4-d)pyrimidin-4-(5H)-one (437).

A mixture of 2.63g (0.01 mole) of 3-amino-4-carbethoxy-5-(phenylamino)isothiazole (360), 2ml of benzylamine, 1ml of glacial acetic acid and 10ml of triethyl orthoformate was refluxed for 4 hours. The mixture was cooled and the solid obtained was filtered, washed with dilute ethanol and dried. Recrystallization from dimethylformamide-ethanol yielded 2.5g (75%) of colorless crystalline product, m.p. 200-202°C.

Analysis : C₁₈H₁₄N₄O₅S(334.39) Requires C, 64.65; H, 4.22%
Found C, 64.72; H, 4.41%

IR (KBr) : 3240(NH); 1640, 1590, 1540, 1470, 1450,
1380, 1310, 1255, 1180, 1120, 1080, 940,
850, 795, 740, 700 cm⁻¹
UV (MeOH) : 203 nm (log ε 4.30), 237 (4.07), 266 (4.2), 342 (3.98)
MS, m/e : 334 (M⁺)

5-Phenyl-3-(phenylamino)isothiazolo(3,4-d)pyrimidin-4-(5H)-one (438).

4-Carbethoxy-5-(phenylemino)-3-(phenylamino)-methyleaminothiazole (416) 1.8 g (5 mmole) was refluxed in 10 ml of N-methyl-2-pyrrolidone for 4 hours. The reaction mixture was cooled and poured onto ice-water. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.0 g (63%) of crystalline product, m.p. 202-204°C.

Analysis : C₁₇H₁₂N₄O₅S (320.35) Requires C, 63.73; H, 3.78%
            Found   C, 63.34; H, 4.12%

IR (Nujol) : 1660, 1600, 1560, 1295, 1260, 1220, 1090, 880, 830, 800, 770, 750 cm⁻¹

UV (MeOH) : 221nm (log ε 4.35), 254 (4.22), 261 (4.21), 284 (4.13), 295 (4.20), 320 (4.20)
MS, m/e : 320 (M⁺)