SYNTHESIS OF CONDENSED PYRIMIDINES BY REACTION OF NITRILES WITH o-AMINOCARBONYL COMPOUNDS UNDER ACIDIC CONDITIONS

Nitriles have played a major role in the synthesis of a variety of open-chain and heterocyclic compounds. The polar C\textequiv N group of the nitriles is prone towards electrophilic attack at the nitrogen and nucleophilic attack at the carbon. The interaction of a nitrile (678) with an acid or the complexation of a nitrile with a Lewis acid leads to the formation of a species (679) possessing greater electrophilicity and, therefore, many of the reactions of nitriles with nucleophilic reagents are acid catalysed.

\[
\begin{align*}
R-\text{C}\equiv N + A^+ & \rightarrow R-\text{C}\equiv N^-A \\
\text{(678)} & \quad \text{(679)}
\end{align*}
\]

Halogen acids are particularly effective in promoting the reaction of nitriles with a variety of nucleophiles. Nitriles react with halogen acids, in the absence of other nucleophilic species, to yield unstable adducts of different composition. The nature of these adducts, as
well as the possible involvement of such nitrile-halogen acid adducts in the hydrogen halide catalysed reactions of nitriles with nucleophiles, has been the subject of considerable discussion. 646-655

The reaction of nitriles with halogen acids yields products of varying composition such as $\text{RCN} \cdot \text{HX}$, $2\text{RCN} \cdot \text{HX}$, $2\text{RCN} \cdot n\text{HX}$, etc., depending upon the nature of the nitriles and the reaction conditions employed. The unstable, hygroscopic adducts resulting from the reaction of a variety of aliphatic and aromatic nitriles with halogen acids, at low temperatures, have been found to be of the general composition $\text{RCN} \cdot 2\text{HX}$. Physical and spectroscopic studies have led to the assignment of imidoyl halide hydrohalide structure (680) for many of these adducts which were formerly believed to have the amide halide or nitrilium halide hydrohalide structures (681) and (682). 646-648, 653

$$
\begin{align*}
\text{R-C=NH \cdot HX} & \quad \text{R-C-NH}_2 \quad \text{R-C=N-H \cdot HX}_2 \\
\uparrow & \quad \uparrow & \quad \uparrow \\
\text{X} & \quad \text{X} & \quad \text{X} \\
\text{(680)} & \quad \text{(681)} & \quad \text{(682)}
\end{align*}
$$

The sequence of reactions leading to the formation of imidoyl halide hydrohalide from a nitrile and hydrogen
halide can be depicted as shown in Scheme XLVI. The protonation of the nitrile yields the nitrilium ion (683) which combines with a halide ion to form the imidoyl halide (684). The imidoyl halide thus formed is sufficiently basic to react with another molecule of hydrogen halide to yield the imidoyl halide hydrohalide salt. In this reversible reaction, the formation of the imidoyl halide salt (680) is frequently slow and is favoured by the presence of a high hydrogen halide concentration.

\[
\text{R-} \text{C} = \text{N} \xrightarrow{+ \text{HX}} \left[ \begin{array}{c} \text{R-C}=\text{N}+\text{H}^- \\ \text{R-C}=\text{N}^- \text{H} \end{array} \right] \xrightarrow{X^-} \text{R-C}=\text{NH} \xrightarrow{X} \text{R-C}=\text{NH}_2 \xrightarrow{-\text{HX}} \left[ \begin{array}{c} \text{R-C}=\text{NH}+\text{H}^- \end{array} \right] \\
\text{(683)} \quad \text{(684)} \quad \text{(680)}
\]

SCHEME XLVI

The isolation of nitrilium halide (683) or imidoyl halide (684) of composition R\text{CN} \cdot \text{LHX} has been claimed in a few cases.\textsuperscript{656-658} In general, the imidoyl halides (684) of the composition R\text{CN} \cdot \text{LHX} are not isolable from the reaction of nitriles with hydrogen halides because of their...
unstable nature. However, N-unsubstituted nitrilium salts (685) have been obtained from the reactions of certain aromatic nitrile-tin tetrachloride adducts with hydrogen chloride under appropriate conditions.659

\[
\left[ \text{R-C-} \text{N-H} \right]_2 \text{SnCl}_6^{2-}
\]

(685)

Dimeric salts of composition 2RCN.HCl obtained in the reactions of some \( \alpha \)-chloroacetonitriles with hydrogen chloride in ether have been assigned the structures (686) or (687).660

\[
\begin{array}{c}
\text{NH} \\
\text{R-C} \text{-N=C-R}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \\
\text{R-C-N=C-R}
\end{array}
\]

(686)

\[
\begin{array}{c}
\text{NH} \\
\text{R-O-N=O-R}
\end{array}
\]

\[
\begin{array}{c}
\text{NH} \\
\text{R-C-N=C-R}
\end{array}
\]

(687)

The unstable acetimidoyl chloride has been found to undergo slow transformation to a dimeric salt of composition 2CH₃CN·2HCl.661 Such 2:2 adduct formation has also been observed in the reaction of chloroacetonitrile with hydrogen chloride.662 These 2:2 adducts have been assigned the structure (688).
In a detailed investigation of several stable adducts obtained from the reaction of hydrogen chloride with nitriles possessing an \( \alpha \)-hydrogen atom, Yanagida and co-workers have found that most of the adducts have the composition \( 2 \text{RCN} \cdot 2\text{HCl} \). The NMR and mass spectral analysis of these adducts have lead to the conclusion that the adducts have the \( \text{N-(}\alpha'\text{-chloroalkenyl)}\text{alkylamidine structure (689). Similar studies have established the structure (690) for the 2:3 adduct obtained from chloroacetonitrile and hydrogen chloride.} \)

\[
\begin{align*}
\text{NH}_2 \quad \text{R-C-N=C-R Cl}^- \\
\text{Cl} \\
\text{(688)}
\end{align*}
\]

Only a few reactions of the isolated nitrile-halogen acid adducts have been investigated. Their reaction with alcohols, amines and water leads to the formation of the corresponding imidates, amidines and amide derivatives.
The dimeric imidoyl halide salts (691) and (693) have been utilized in the reaction with phosgene to obtain dichloropyrimidines (692) and (694).\textsuperscript{654}

\[ R-CH_2-CN + HCl \rightarrow R-N=CH_2 + Cl^- \]
\[ R_1R_2CH-CN + HCl \rightarrow R_1R_2-N=CHR_3 + Cl^- \]

\[ R_1R_2-N=CHR_3 + COCl_2 \rightarrow R_1R_2-N=CHR_3Cl \]

Though only a few reactions of the isolated nitrile-halogen acid adducts with nucleophiles have been studied, the nitrile-halogen acid adducts, such as nitrilium halides, imidoyl halides, imidoyl halide hydrohalides and the dimeric salts have been proposed as the transient intermediates in a variety of reactions of nitriles with nucleophiles, performed in the presence of halogen acids.\textsuperscript{646,652-655,662,663}

The role of the protonated nitrile or imidoyl chloride derivatives in the Pinner synthesis of imidate hydrochlorides (695) from nitriles and alcohols in the presence of
hydrogen chloride has been discussed.\(^{646}\)

\[
R-\text{C}N + R'-\text{OH} \xrightarrow{\text{HCl}} R'-\text{OR} \cdot \text{HCl} \quad \text{(695)}
\]

The Gattermann\(^{664,665}\) and Houben-Hoesch\(^{646,652}\) synthesis, involving the reactions of hydrogen cyanide or other nitriles with an arene or a phenol to obtain aldehydes or ketones (697), are usually conducted in the presence of dry hydrogen chloride and an electrophilic metal halide. Imidoyl chloride derivatives that are in equilibrium with nitrilium chloride salts are, presumably, the active intermediates involved in these reactions.\(^{646,649}\) Improved yields of ketimine derivatives (696) have been obtained in the Hoesch reaction by the prior preparation of imidoyl chloride salts followed by their reaction with phenols.\(^{666,667}\)

The influence of electrophilic metal halides on the yield of the products formed in some of these reactions has been attributed to the effect of the metal on the nitrilium ion-imidoyl halide equilibrium.\(^{649,659}\)
Imidoyl halide hydrohalides (680a) or the nitrilium salts (680b) have been proposed as the intermediates in the Stephen reduction of nitriles to aldehydes.  

The reaction of certain nitriles with thioamides in the presence of hydrogen chloride yields thioacylamidine hydrochlorides (700) via the isomerization of the intermediate
formed by the nucleophilic attack of the sulfur atom of the thioamide upon the protonated nitrile or imidoyl halide intermediate. The conversion of nitriles to the corresponding thioamides \( 702 \) by the reaction with thioacetamide in dimethylformamide in the presence of dry hydrogen chloride has been suggested to proceed via the initial formation of the intermediate \( 701 \) which undergoes dissociation to the thioamide \( 702 \) and acetonitrile.254

\[
\begin{align*}
S & \quad R-C-N\ddot{H} + R'\text{-C}&&\text{HCl} \rightarrow [R-G-S-G-R'] \\
\downarrow & \quad S \quad NH \quad \text{NH} \\
S & \quad R-C-NH-C-R'. \quad \text{HCl} \\
\downarrow & \quad (699) \\
\downarrow & \quad (700) \\
S & \quad \text{CH}\ddot{3}-\text{C}-\text{NH}_2 + \text{R-\text{C}&&\text{N}} \\
\downarrow & \quad \text{NH} \quad \text{NH} \\
\downarrow & \quad \text{(701)} \\
\downarrow & \quad \text{CH}\ddot{3}-\text{C-\text{N}&&\text{N}} + \text{S} \quad \text{NH}_2 \\
& \quad \text{(702)}
\end{align*}
\]

Though the synthesis of amidines from nitriles andamines have been performed by employing a variety of
amine salts or an amine and an electrophilic metal catalyst, only a few reports are available on the synthesis of amidines by the reaction of nitriles with amines in the presence of halogen acids.\textsuperscript{670,671} Cooper and Partridge\textsuperscript{672} have found that acetonitrile reacts with aniline, in the presence of dry hydrogen chloride in dry ether, at room temperature, over a long period of time, to afford N-phenylacetamidine (703, \( R = \text{CH}_3 \)) in 90\% yield. Similarly, N-phenylbenzamidine (703; \( R = \text{C}_6\text{H}_5 \)) has been obtained in 23\% yield from the reaction of benzonitrile with aniline under the influence of hydrogen chloride.

\[
\begin{align*}
\text{R-C\(\equiv\)N} + \text{H}_2\text{N-}\text{C} & \rightarrow \text{R-C-NH} - \\
(703) & \\
\text{R} = \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}
\]

Sugiyama and co-workers\textsuperscript{673} have prepared some N-aryl amidinoformic acid derivatives (704) by the reaction of arylamines with ethyl cyanoformate in the presence of catalytic excess of hydrogen chloride.

\[
\begin{align*}
\text{EtO}_2\text{C-\(\equiv\)N} + \text{H}_2\text{N-R} & \rightarrow \text{EtO}_2\text{C-NH-R} \\
(704)
\end{align*}
\]
Malononitrile is known to dimerize in the presence of halogen acids to yield the enaminonitrile (705) or the pyridine derivative (706) by C–C bond formation reaction.674

\[
\begin{align*}
\text{(705)} & \quad \text{(706)} \\
\end{align*}
\]

The reaction of trichloroacetonitrile with oxathiazidine dioxides (707) in the presence of dry hydrogen chloride leads to the formation of trichloromethyltriazines (708). The reaction has been suggested to proceed via the initial formation of imidoyl chloride intermediate from trichloroacetonitrile and hydrogen chloride, followed by its reaction with 707.675

\[
\begin{align*}
\text{(707)} & \quad \text{(708)} \\
\end{align*}
\]

The intramolecular cyclization of an appropriately functionalized nitrile derivative has been widely employed
for the synthesis of a variety of heterocycles. These intramolecular cyclizations, in general, are acid or base catalyzed. The synthesis of aza-heterocycles by the intramolecular cyclization of functionalized nitriles under acidic conditions has been reviewed by Johnson and Madronero. In such acid catalyzed heterocyclization reactions involving a nitrile function, halogen acids have been found to be particularly effective cyclizing agents.

Pyridone derivatives (710) have been obtained in good yield by the cyclization of the \( \delta \)-ketonitriles (709) with hydrogen halides. The reaction of (711) with hydrogen chloride has been reported to yield a mixture of pyridine derivatives (712) and (713) by intramolecular cyclization and disproportionation.

\[
\begin{align*}
\text{(709)} & \quad \text{(710)} \\
\text{(711)} & \quad \text{(712)} & \quad \text{(713)}
\end{align*}
\]
5-Aryl-6-chloro-1,2,3,4-tetrahydropyridin-2-ones have been obtained by the reaction of 4-aryl-4-cyanobutyroyl chloride with hydrogen chloride in dioxane. Similarly, 6-chloro-2-pyridones (715) have been prepared by the reaction of the carboxylic acid chloride (714) with hydrogen chloride.\(^{679,680}\)

\[ \text{(714)} \]

\[ \begin{array}{c}
\text{Ar} \\
\text{Cl} \\
\text{CN} \\
\end{array} \]

2-Halopyridines (717) have been obtained by the cyclization of enaminonitriles (716) with halogen acids.\(^ {399}\)

\[ \text{(716)} \]

\[ \begin{array}{c}
\text{SCH}_3 \\
\text{CN} \\
\text{CN} \\
\text{NEt}_2 \\
\text{R}_1 \\
\text{R}_2 \\
\end{array} \]

\[ \begin{array}{c}
\text{SCH}_3 \\
\text{CN} \\
\text{CN} \\
\text{X} \\
\text{R}_1 \\
\text{R}_2 \\
\end{array} \]

The reaction of primary amines with 4-chlorobutyronitrile yields directly the corresponding 2-iminopyrroolidine hydrochlorides (719) \textit{via} 4-aminobutyronitrile hydrochloride intermediates (718). The intermediates 718
which are isolable under certain conditions, also cyclize on treatment with hydrogen chloride to afford the pyrrolidine derivatives (719) in excellent yield.

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{R} & \quad \text{N} \quad \text{HCl} \\
\text{(718)} & \quad \text{N} \\
\text{R} \quad \text{N} \quad \text{HCl} \\
\text{(719)} &
\end{align*}
\]

\[
\begin{align*}
\text{N,N-Dialkylaminobutyronitrile (720; } n = 1) & \text{ when heated at elevated temperature in the presence of a stream of dry hydrogen chloride gas leads to the formation of 1-alkyl-2-iminopyrrolidine hydrochloride (721; } n = 1) \text{ by intramolecular cyclization with the concomittant loss of an alkyl group as alkyl chloride. 1-Alkyl-2-iminopiperidine derivatives have similarly been obtained by the cyclization of appropriate } \omega \text{-dialkylaminonitrile intermediates.}
\end{align*}
\]

\[
\begin{align*}
\text{(720)} & \quad \text{(721)}
\end{align*}
\]
2-Thiocyanato- and 2-selenocyanobenzoylchlorides (722) have been cyclized to 2-chloro-1,3-benzothiazines and benzoselenazines (723) by treatment with dry hydrogen chloride gas.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{X} = \text{S}, \text{Se} \\
(722) & \\
(723)
\end{align*}
\]

The reaction of 2-cyanomethylbenzoylchlorides (724) with halogen acids in solvents such as ether, dioxane, and dibutyl ether leads to the formation of 3-halogenoisoquinolin-1-ones (727). The reaction has been suggested to proceed via the initial formation of the imidoyl halide hydrohalide (725), its tautomerization to the enamine (726) followed by intramolecular cyclization to 727.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
(724) & \\
(726) & \\
(725) & \\
(727)
\end{align*}
\]
Hydrogen chloride, in different solvent systems, has been found to be effective in the intramolecular cyclizations of o-acylaminonitriles (728) to condensed 4-oxopyrimidines (729). Hydrogen chloride or hydrogen bromide has been used to bring about the direct cyclization of certain o-aminonitriles (730) to condensed pyrimidine derivatives (731-733) by reaction with reagents such as dimethylformamide, dimethylacetamide and thioamides.

\[
\begin{align*}
\text{HCl} & \rightarrow \text{Product} \\
(728) & \rightarrow (729) \\
(730) & \rightarrow (731) \quad R = H \\
 & \quad (732) \quad R = CH_3 \\
 & \quad (733)
\end{align*}
\]

The direct formation of 4-chloroquinazoline (736) has been observed in the reaction of 2-cyanophenyl isocyanates and 2-cyanophenyl isothiocyanates (734) with excess of dry hydrogen chloride at about 70°C. The reaction when
conducted in di-n-butyl ether at room temperature, initially, affords the carbamoyl halides (735) which cyclize to quinazolines in the presence of excess of dry hydrogen chloride. 4-Flomoquinazolin-2-one has, similarly, been prepared by the reaction of o-cyanophenyl isocyanate with hydrogen bromide.

\[
\text{R-CN} \xrightarrow{\text{HCl}} \text{R-CN} \xrightarrow{\text{HCl}} \text{R-Cl}
\]

\( X = 0 \text{ or } S \)  

The reaction of \( \beta \)-cyano-\( \alpha \),\( \beta \)-unsaturated isocyanates (737) with hydrogen chloride in dioxane at 100°C in a sealed tube leads to the formation of 5,6-disubstituted uracils (740). The reaction proceeds via the initial formation of 6-chloropyrimidines (738) which react with chloroethoxyethanol, formed from dioxane, to yield the alkoxyprimidinone (739). The alkoxyprimidinones (739) undergo dealkylation under the reaction conditions to yield the uracils (740). The suggested pathway for the
formation of 740 is supported by the fact that 4-chloro-
pyrimidinone (738) could be obtained as the product under
milder reaction conditions.691

\[
\begin{array}{ccc}
\text{R}_1 & \text{CN} & \text{HCl} \\
\text{R}_2 & \text{N=O=O} & \text{Cl} \text{NHCOCl} \\
\end{array}
\]

(737) \quad (738)

(739)

Similar to the halogen acid catalyzed cyclization of
functionalized mononitriles, the intramolecular cyclization
of \(\alpha,\omega\)-dinitriles with halogen acids has yielded a variety
of halogen substituted aza-heterocycles. The variety of
ring systems that have been prepared by this versatile
approach has been reviewed by Johnson and Madronero,651
and by Meyers and Sircar.692

The formation of 2-halogeno aza-heterocycles (742)
in the reaction of \(\alpha,\omega\)-dinitriles (741) with halogen
acids can be depicted as shown in the Scheme XLVII.

\[
\begin{align*}
\text{C} & \equiv \text{N} \quad \text{HX} \\
\rightarrow & \\
\text{C} & \equiv \text{N} \\
\end{align*}
\]

\(\text{SCHEME XLVII}\)

A number of heterocyclic systems, such as pyrroles (747), pyridines (748), isoquinolines (749) and benzazepines (750) have been obtained by the cyclization of the appropriate dinitrile intermediates (743-746). The mechanistic pathway of the cyclization, the role of the halogen acid and the mode of cyclization, where isomeric possibilities exist, has been the subject of considerable discussion.\(^{651}\)
The cyclization of appropriate thiocyanato- and cyanamidonitrile intermediates (751) and (752) with halogen acids has led to the formation of a variety of heterocyclic ring systems such as thiazoles, 1,2,4-thiadiazoles, 1,3,5-dithiazines, imidazoles, pyrimidines and triazines (753,754).651
2-Chloro-4,6-diaminopyrimidines (756) have been prepared by the cyclization of 3-amino-3-cyaniminopropionitriles (755) with hydrogen chloride. The reaction of cyanoacetylcyanamide (757) with halogen acids has been the subject of a detailed study. The nature of the product formed in the reaction has been found to be dependent upon the reaction time and the molar concentration of hydrogen halide employed. The imidoyl halides (758; \( X = \text{Cl, Br} \)) were obtained in the reactions with excess of hydrogen chloride or hydrogen bromide over a short period of time or in the reactions with only two equivalents of acid. The imidoyl halide intermediate
(758; X = Cl, Br) cyclizes to the 2-halogeno-6-amino-pyrimidine (759; X = Cl, Br) on prolonged stirring under the influence of acid catalyst. The reaction of 757 with hydrogen iodide has been found to yield only the imidoyl halide (758; X = I) as the product of reaction.

Present Work:

The intermolecular condensation of a nitrile with a substrate containing electrophilic (E) and nucleophilic (Nu) centers often leads to the direct formation of an aza-heterocycle incorporating the C=N moiety of the nitrile. Such condensations could, conceivably, proceed by a concerted cycloaddition process (type A) or by discreet steps involving either the initial electrophilic attack on the nitrile nitrogen (type E) or by the initial nucleophilic attack at the nitrile carbon (type C) followed by ring closure (Scheme XLVIII). Meyers and Sircar have briefly reviewed such heterocycle syntheses from nitriles.
Many of the reactions of nitriles with substrates containing an oxygen, sulfur, nitrogen or carbon nucleophilic centers possessing an additional appropriately placed electrophilic group, capable of undergoing cyclization, lead to the heterocycle formation by the type C pathway involving the initial nucleophilic addition followed by ring closure. Thus, the condensation of o-aminocarbonyl compounds(760) such as o-aminoketones, o-aminoesters, o-aminoamides, and o-aminonitriles with a nitrile should, in principle, lead to the formation of condensed pyrimidines (761).
The synthesis of quinazolines and condensed pyrimidines by the cyclization of an appropriate o-aminocarbonyl compound with a variety of reagents has been widely studied. 

Reagents such as, lower aliphatic amides, thioamides, N-substituted imidoyl halides, imidates and amidines have been extensively used for the cyclization of o-aminocarbonyl compounds to condensed pyrimidines. While the nitrile-derived reagents such as imidates and amidines have generally been utilized in this approach, the direct use of nitriles for cyclizing o-aminocarbonyl compounds to condensed pyrimidines has, so far, received only scant attention. The available literature on the synthesis of quinazolines (763) from 2-aminoacetophenones, 2-aminobenzophenones, anthranilic acid derivatives such as the acid,
amide or nitrile (762), and the isosteric thieno(2,3-d)pyrimidines (765) from 2-amino-3-acyl, 2-amino-3-carbalkoxy, 2-amino-3-carbamoyl or 2-amino-3-cyanothiophenes (764), reveal only a few scattered reports on the use of nitriles as reagents for effecting the cyclization.

\[
\begin{align*}
&\begin{array}{c}
(762) \\
\end{array} \\
&\begin{array}{c}
(763) \\
\end{array} \\
&\begin{array}{c}
(764) \\
\end{array} \\
&\begin{array}{c}
(765) \\
\end{array} \\
\end{align*}
\]

\[
\text{X} - \text{Y} = \text{COR}, \text{CO}_{2}\text{R}, \text{CONHR}, \text{CN}; \quad \text{Z} = \text{R}, \text{OH}, \text{NH}_{2}
\]

A few quinazolin-4-one derivatives have been obtained, in poor yields, from the reaction of nitriles with anthranilic acids or esters in the presence of bases.\(^{698-700}\) 2-Methylquinazolin-4-one (767) has been obtained in low yield by heating a mixture of anthranilic acid (766) and acetonitrile in a sealed tube.\(^{701}\)

\[
\begin{align*}
&\begin{array}{c}
(766) \\
\end{array} \\
&\begin{array}{c}
(767) \\
\end{array} \\
\end{align*}
\]
The reaction of anthranilic acid with nitriles in the presence of the corresponding acids or anhydrides at high temperatures has been found to give the corresponding 4-oxoquinazolines in poor yields. \[702, 703\] o-Amino-benzamide, in the form of its hydrochloride (768), has been reacted with acetonitrile, propionitrile, and benzonitrile in a sealed tube at 200°C for 2 hours to obtain the corresponding quinazolines (769; \(R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5\)) in about 20% yield. When o-aminobenzamide was used in place of its hydrochloride salt, the reaction with acetonitrile gave less than 6% of quinazoline (767), thus indicating the catalytic effect of the acid in this condensation. \[704\]

\[
\begin{align*}
(768) & \quad \begin{array}{c}
\text{O} \\
\text{NH}_2 \\
\text{NH}_3 \text{Cl}
\end{array} \\
(769) & \quad \begin{array}{c}
\text{O} \\
\text{NH} \\
\text{R}
\end{array}
\end{align*}
\]

Hardmann and Partridge \[705\] have found that the reaction of benzenesulfonate salt of ethyl anthranilate with ethyl cyanoacetate at 140°C yields the quinazoline (770) along with the by-product (771). When the reaction temperature was raised to 210°C, the product obtained was
found to be the benzenesulfonate salt of 2-methylquinazolin-4-one (767).

\[
\begin{array}{c}
\text{C}_{6}\text{H}_{5} \text{N} + \text{C}_2\text{H}_5\text{CO}_2\text{Et} \rightarrow \text{C}_{6}\text{H}_{5}\text{N} + \text{C}_2\text{H}_5\text{CO}_2\text{Et} \\
\end{array}
\]

(770)

2-Methyl- and 2-phenyl-7-chloro-4-oxo-1,4-dihydroquinazolines (772) have been prepared by the reaction of methyl 4-chloroanthranilate with a large excess of acetonitrile or benzonitrile in the presence of dry hydrogen chloride.

\[
\begin{array}{c}
\text{Cl} \text{N} \text{R} \\
\end{array}
\]

(772) \( R = \text{CH}_3, \text{C}_6\text{H}_5 \)

Catalytic excess of dry hydrogen chloride in acetic acid has been employed for the condensation of methyl anthranilate (773) with ethyl cyanoformate to obtain the
quinazoline (774).  

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \quad \rightarrow \\
\text{NH}_2 & \quad \text{CO}_2\text{H}_5
\end{align*}
\]

(773) \quad (774)  

The p-toluenesulfonate salt of o-aminobenzonitrile (775), on heating, dimerizes to the 4-aminoquinazoline (776) which is also obtained as the product of reaction of o-aminobenzonitrile with sodium amide. 685,699 Similar dimerizations have been observed in the preparation of 2-amino-5-nitrobenzonitrile by the reaction of 2-chloro-5-nitrobenzonitrile with ammonia. 707  

\[
\begin{align*}
\text{ON} & \quad \text{NH}_2 \\
\text{NH}_2 & \\
(775) & \\
(776)
\end{align*}
\]

The base catalyzed condensation of aliphatic or aromatic nitriles with an o-aminonitrile has been found to
be a general and useful method of synthesis of fused 4-aminopyrimidines. Recently, anthranilonitrile has been found to condense with aliphatic and aromatic nitriles in the presence of hydroxide ion catalyst to yield the corresponding 2-substituted 4-aminoquinazolines (777; R = alkyl, aryl). 4-Aminoquinazolines (777, R = CH₂COR) have also been obtained by the cyanide ion catalyzed condensation of o-ethoxalylaminobenzonitriles with the corresponding nitriles.

\[
\begin{align*}
&\text{CN} \\
&\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
&\text{N} \quad \text{C} \quad \text{R} \\
&\rightarrow \\
&\text{NH}_2 \\
&\text{N} \quad \text{R}
\end{align*}
\]

The reaction of 2-amino-5-chlorobenzophenone (778) with aliphatic nitriles in the presence of phosphorous tribromide has been found to yield 2-alkyl-4-phenyl-6-chloroquinazolines (779).

\[
\begin{align*}
&\text{Cl} \quad \text{Ph} \\
&\text{Cl} \quad \text{R} \\
&(778) \\
&(779)
\end{align*}
\]

\[
\begin{align*}
&\text{R} = \text{Me}, \text{Et}, \text{CH}_2\text{Cl}, \text{CH}_2\text{Ph}, \text{CH}_2-\text{CH}=\text{CH}_2
\end{align*}
\]
Reid and Giesse\textsuperscript{712} have reported the synthesis of the 4-hydroxythieno(2,3-d)pyrimidine (781) by the condensation of \textit{o}-aminoester (780) with trichloroacetonitrile. The condensation of the \textit{o}-aminoester (782) with phenylacetanitrile at elevated temperature in the presence of anhydrous aluminium chloride has yielded the thienopyrimidine (783).

\begin{align*}
\text{(780)} & \quad \text{(781)} \\
\text{(782)} & \quad \text{(783)}
\end{align*}

2-Methyl- and 2-phenyltetrahydro(1)benzothieno(2,3-d)pyrimidin-4-ones have been obtained by the condensation of ethyl \textit{2}-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate or its amide with acetonitrile and benzonitrile in the presence of dry hydrogen chloride.\textsuperscript{713, 714}
The enhancement of reactivity of nitriles towards nucleophiles by acids, particularly halogen acids, though known since a long time, the utilization of the enhanced reactivity of nitriles under acidic conditions, for the synthesis of condensed pyrimidines by reaction with o-aminocarbonyl compounds has, hitherto, remained largely unexplored. Therefore, it was thought of interest to study the reaction between nitriles and o-aminocarbonyl compounds (784) under the influence of halogen acids as a possible method of synthesis of quinazolines and condensed pyrimidines (785).

\[
\begin{align*}
\text{X} & \quad \text{Y} \\
\text{NH}_2 & \quad \text{N} \\
\text{C} & \quad \text{R}
\end{align*}
\]

Result and Discussion

A variety of o-aminocarbonyl compounds were found to react with nitriles in the presence of dry hydrogen chloride to afford the condensed pyrimidines in good yields under mild reaction conditions. The reaction was
studied especially with o-aminocarbonyl compounds of benzene and thiophene to obtain quinazolines and thienopyrimidines. An attempt was also made to apply the method to synthesize other fused pyrimidines from o-aminocarbonyl derivatives of heterocyclic systems such as isothiazole, pyridine and pyrrole.

**Quinazolines**

The reaction between methyl anthranilate and acetonitrile was conducted by passing a stream of dry hydrogen chloride gas through a solution of methyl anthranilate (773) in excess of acetonitrile at room temperature for 8 hours. The reaction mixture, when diluted with water and basified, afforded 2-methylquinazolin-4-one (801) in 75% yield. Methyl anthranilate (773) when refluxed with excess of acetonitrile

\[
\begin{align*}
\text{CO}_2\text{CH}_3 &+ \text{HN} & \xrightarrow{\text{HCl}} & \text{N} \\
(773) & & \rightarrow & (801)
\end{align*}
\]
in the presence of a slight molar excess of p-toluenesulfonic acid monohydrate gave the quinazoline (801) in about 10% yield along with unreacted starting material 773. Surprisingly, in a similar experiment employing a molar equivalent of aqueous concentrated hydrochloric acid in place of p-toluenesulfonic acid, the quinazoline (801) was obtained in about 40% yield, thus indicating the superiority of hydrogen chloride as the acid catalyst for the condensation of 773 with acetonitrile. The presence of a large excess of dry hydrogen chloride gas in the condensation, possibly, assists in the shifting of an otherwise unfavorable equilibrium between the reactants and the products towards the products.

Other nitriles such as phenylacetonitrile, ethyl cyanoacetate, chloroacetonitrile, p-chlorophenoxyacetonitrile, p-chlorophenylthioacetonitrile, phenylsulfonylacetonitrile, benzonitrile, p-chlorobenzonitrile and nicotinonitrile were also found to undergo smooth reaction with methyl anthranilate to yield the corresponding 2-substituted
quinazolin-4-ones (Scheme XLIX) (Table XXVII).

\[
\begin{align*}
\text{R} &= \text{CH}_2 \text{C}_6 \text{H}_5, \text{CH}_2 \text{COC}_2 \text{H}_5, \text{CH}_2 \text{Cl}, \text{CH}_2 \text{CO}_6 \text{H}_4 \text{Cl}-p \\
&\quad \text{CH}_2 \text{SO}_6 \text{H}_4 \text{Cl}-p, \text{CH}_2 \text{SO}_2 \text{Ph}, \text{C}_6 \text{H}_5, \text{C}_6 \text{H}_5 \text{Cl}-p, 3-\text{C}_5 \text{H}_4 \text{N}
\end{align*}
\]

The reaction of the above nitriles with methyl anthranilate was performed employing approximately a molar equivalent of the nitrile in a solvent such as dioxane. Dioxane has earlier been used as the solvent in some of the intramolecular cyclizations of functionalized nitriles employing hydrogen chloride as the cyclizing agent. Dioxane was found to be an ideal solvent for conducting the reaction. It possesses the capacity to absorb large quantity of hydrogen chloride gas and its miscibility with water allows for easy work-up of the reaction mixture.
The yield of the quinazolines (802-810) was found to be in the range of 60-75% and even the crude products obtained were found to be practically pure. No other major by-product formation could be observed in these reactions. Many of these quinazolin-4-ones are known and have been synthesized by different methods. In contrast to the earlier methods described in the literature, the present method possesses the advantages of employing readily available starting materials and mild reaction conditions to obtain the products in excellent yields.

The 4-amino-2-substituted quinazolines (811) and (812) were obtained by the reaction of anthranilonitrile with excess of acetonitrile, or phenylacetonitrile in dioxane, in the presence of dry hydrogen chloride.

Similarly, the reaction of 2-amino-5-chlorobenzophenone (778) with acetonitrile and chloroacetonitrile yielded the corresponding 2-substituted-4-phenyl-6-chloroquinazolines (813) and (814) (Table XXVIII).
The formation of quinazolines (786) in the reaction of a nitrile with an ortho functionalized arylamine (784a), such as 2-aminobenzoic acid esters, 2-aminobenzonitrile or 2-aminobenzophenone, possibly, proceeds via the initial formation of the amidine intermediate (785) followed by the intramolecular cyclization through the nucleophilic attack of the amidine nitrogen on the ester, nitrile or ketone function. The sequence of reactions leading to the formation of the amidine intermediate (785) may involve the nucleophilic attack of the ortho functionalized arylamine (784a) on the nitrile present as the N-protonated nitrilium species (683) or the imidoyl halide derivative (680a) formed from the nitrile and hydrogen chloride (Scheme L).
A variety of fused pyrimidine syntheses involving the condensation of an o-aminocarbonyl compound with an imidoyl derivative have been assumed to proceed via the amidine intermediates of the type 785.

An o-aminoketoxime, such as 787, can function as a 1,5-binucleophilic compound and its reaction with acylating agents leads to the formation of quinazolin-3-oxides. The reaction of 787 with a nitrile should in principle, lead to the formation of an amidine intermediate (787a) which
can cyclize to the quinazoline \( 787b \) (path a) or the quinazolin-3-oxide \( 787c \) (path b).

When the 2-aminobenzophenone oxime \( 787 \) was reacted with acetonitrile in the presence of hydrogen chloride, the sole product of the reaction was found to be the quinazoline \( 813 \) (\( 787b; R = \text{CH}_3 \)) and no quinazolin-3-oxide (\( 787c; R = \text{CH}_3 \)) formation could be detected. The reaction of the oxime (\( 787 \)) with chloroacetonitrile also yielded the quinazoline \( 814 \) (\( 787b; R = \text{CH}_2\text{Cl} \)) and not the quinazolin-3-oxide (\( 787c; R = \text{CH}_2\text{Cl} \)).

The proposed amidine intermediate \( 787a \), under the acidic conditions employed, possibly undergoes N-protonation
of the oxime nitrogen with the consequent decrease in the nucleophilic reactivity of the nitrogen and enhancement of the electrophilic reactivity of the ketoxime carbon atom thereby leading to the preferential formation of the quinazoline (787b) by the pathway a over that of the quinazolin-3-oxide (787c) by pathway b.

Thus, in addition to the enhancement of the reactivity of nitrile by hydrogen chloride, the acid, probably, also facilitates the intramolecular cyclization of the amidine intermediates (785) by the protonation of the carbonyl oxygen of the ester or ketone or of the nitrile nitrogen.

**Thieno(2,3-d)pyrimidines**

A variety of 2-aminothiophenes possessing a nitrile, ester or ketone function at the 3-position have become readily accessible \(^{718}\) and have been used as starting materials for the synthesis of thieno(2,3-d)pyrimidines. The method involving the reaction of a nitrile with an o-aminocarbonyl compound in the presence of dry hydrogen chloride was found applicable to the reaction of
2-amino-3-functionally substituted thiophene derivatives to obtain thieno(2,3-d)pyrimidine derivatives.

Thus, a variety of aliphatic, aromatic and heterocyclic nitriles were found to react with 2-amino-3-carbethoxythiophenes in a facile manner, under mild reaction conditions, to yield the corresponding 2-substituted thieno(2,3-d)-pyrimidin-4-ones (Scheme LI) (Table XXIX). Some of the thieno(2,3-d)pyrimidin-4-ones thus obtained have earlier been synthesized by the condensation of the o-aminooesters (788) with iminoethers at elevated temperature.719

\[
\begin{align*}
R_3 &= \text{CH}_3, \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5, \text{CH}_2\text{CH}_2\text{Cl}, \\
     &\quad \text{CH(Cl)}\text{CH}_2\text{Cl}, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{Cl}-p, 3-\text{C}_5\text{H}_4\text{N}, \\
     &\quad \text{CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

SCHEME LI

The reaction of 2-amino-3-carbethoxythiophenes with acrylonitrile in the presence of dry hydrogen chloride
yielded directly the corresponding 2-(2-chloroethyl)thieno(2,3-d)pyrimidin-4-ones (818) and (826), possibly, by the initial formation of 2-chloropropionitrile from acrylonitrile and hydrogen chloride followed by its reaction with the o-aminoesters. The 2-(2-chloroethyl)thieno(2,3-d)pyrimidin-4-one (818) undergoes normal displacement reaction with diethylamine and morpholine to yield the corresponding 2-(2-dialkylamino)thieno(2,3-d)pyrimidin-4-ones (840) and (841).

\[
\begin{align*}
\text{(818)} & \quad \text{NR}_2 = \text{NET}_2 \\
\text{(826)} & \quad \text{NR}_2 = \text{NEt}_2 \\
\text{(840)} & \quad \text{NR}_2 = \text{NO} \\
\text{(841)} & \quad \text{NR}_2 = \text{N} \\
\end{align*}
\]

The reaction of 2-amino-3-carbethoxythiophene (782) with malononitrile in the presence of hydrogen chloride,
followed by the usual aqueous work-up, yielded the thienopyrimidinyl acetamide (817) as the product of reaction instead of the nitrile (817a).

\[
\begin{align*}
\text{Et}_{2} \text{CO} (817a) & \quad \text{R} = \text{CN} \\
\text{(817)} & \quad \text{R} = \text{CONH}_{2}
\end{align*}
\]

(782)

Ethyl cyanoformate also reacted smoothly with 2-amino-3-carbethoxythiophene (782) in the presence of hydrogen chloride to afford the 2-carbethoxythieno(2,3-d)pyrimidin-4-one (823) which has earlier been prepared by the condensation of the aminoamide (789) with diethyl oxalate at elevated temperature,\textsuperscript{720} by the pyrolysis of the oxamate (823a) or by the ammonolysis of the thieno(2,3-d)oxazine (823b).\textsuperscript{721}

\[
\begin{align*}
\text{(823)} & \\
\text{(823a)} & \\
\text{(823b)}
\end{align*}
\]
The acid catalysed reaction of 2-amino-3-carbethoxy-thiophenes with nitriles to obtain thieno(2,3-d)pyrimidin-4-ones has been found successful with a variety of other substituted aliphatic nitriles. The method has also been found applicable for the condensation of 2-amino-3-carbethoxy-thiophenes (788) and other o-aminocarbonyl compounds with cyanates, thiocyanates, and cyanamides to obtain the corresponding 2-substituted thieno(2,3-d)pyrimidin-4-ones (790) and related fused pyrimidines.

\[ \text{R}_1 \text{R}_2 - 3 \quad - s' \quad \text{TfH} \quad kA \thinspace X = O, S, NR' \]  

(790)

The thieno(2,3-d)pyrimidin-4-one derivatives, which have become readily accessible by this facile one-pot method, have been utilized in this laboratory for the synthesis of condensed systems such as triazoloc(4,3-c)thieno(3,2-e)pyrimidines (790a), triazoloc(2,3-c)thieno(3,2-e)pyrimidines (790b), and tetrazoloc(1,5-c)thieno(3,2-e)pyrimidines (790c).
The 2-amino-3-benzoyl-4,5,6,7-tetrahydrobenzo(b)thiophene (791) when reacted with acetonitrile, ethyl cyanoacetate and chloroacetonitrile in the presence of hydrogen chloride yielded the corresponding 2-substituted-4-phenylthieno(2,3-d)pyrimidines (844, 845 and 846) (Table XXX). The thienopyrimidine 844 has earlier been obtained by the cyclization of the 2-acylaminothiophene (791a) by reaction with ethanolic ammonia in sealed tube at 175°C or by fusion with ammonium acetate at 160°C in a current of ammonia. 726
Reaction of the 2-aminothiophene-3-carboxamide (789) with acetonitrile and benzonitrile yielded the thieno-(2,3-d)pyrimidin-4-ones (815) and (820), respectively. The pyrimidines 815 and 820 could, conceivably, arise by the loss of ammonia from the amidine intermediate (785a) by either of the pathways involving the nucleophilic attack by the amidine nitrogen on the amide carbonyl group (a), or through the nucleophilic attack of the amide nitrogen on the amidine carbon (b) as indicated in Scheme LII.

The fact that the reaction of the o-amino-N-methyl-carboxamide (792) with acetonitrile leads to the exclusive formation of the 3-N-unsubstituted thienopyrimidine (815) and not the 3-N-methylthienopyrimidine (793) indicates that
the reaction with the amide (789) also, possibly, proceeds by the pathway $a$ involving the loss of $\text{NH}_3$ from the amide function.

In the reaction of 2-aminothiophene-3-carboxamides (794) with nitriles, it has been found$^7$ that under carefully controlled conditions the amidine intermediates of the type (794a) are isolable and that these amidines show a propensity to cyclize to the 3-unsubstituted thienopyrimidin-4-ones (794b) under acid catalysis. Some of the intermediates (794a) have been found to cyclize to 3-arylthienopyrimidin-4-ones (794c) in refluxing ethanol in the absence of added catalysts.
2-Amino-3-cyanothiophenes (795) have been found to undergo facile reaction with aliphatic and aromatic nitriles in the presence of hydrogen chloride, to yield the corresponding 2-substituted 4-aminothieno(2,3-d)pyrimidines (796).\textsuperscript{715,724} Similarly, the reaction of nicotinonitrile with 2-amino-3-cyano-7-benzyltetrahydropyridothiophene (843a) yielded the 4-amino-2-(3-pyridyl)tetrahydropyrido-thienopyrimidine (843).

Recently, it has been found that the intermolecular condensation of thiophene o-aminonitriles with acetonitriles possessing an electron withdrawing group, yield 4-aminothienopyrimidines (799) or the 4-chlorothienopyrimidines.
(798) depending upon the nature of the reactants and the reaction conditions employed. The formation of 798 and 799, possibly, proceeds via the initial formation of the amidine intermediate 797 which cyclizes by either of the two pathways (a) or (b) to afford the thienopyrimidines as depicted in Scheme LIII. Similar chloropyrimidine formation
has been observed in the reaction of certain nitriles with other o-aminonitriles. The detailed mechanism of this reaction is under investigation.\textsuperscript{389}

The reaction between nitriles and 2-aminothiophene-3-carboxylic esters and 3-carbonitriles was studied under different experimental conditions. The reaction of the o-aminonitrile (800) with excess of acetonitrile in the presence of a large excess of hydrogen chloride normally leads to the formation of the 4-aminothienopyrimidine (842) in about 50\% yield. The reaction of the o-aminonitrile 800 with excess of acetonitrile in the presence of a molar equivalent of hydrogen chloride as a 10\% solution in dioxane, at the refluxing point of acetonitrile, led to the formation of pyrimidine 842 in diminished yield of about 25\%. The only other product isolable from the reaction was the unreacted starting material 800.

\begin{center}
\begin{tabular}{ll}
(800) & (842) \\
\end{tabular}
\end{center}
Similarly, the reaction between the aminoester (782) and excess of acetonitrile in the presence of only an equivalent of hydrogen chloride yielded the thienopyrimidine (815) in 32% yield as against 82% yield in which it was obtained in the typical experiment employing a large excess of hydrogen chloride.

![Chemical Structures](image)

The use of a large excess of hydrogen bromide gas was found to give results comparable to that obtained in the experiments with hydrogen chloride. Refluxing a solution of the aminoester (782) in excess of acetonitrile in the presence of a molar equivalent of a protic acid such as 35% aqueous hydrochloric acid, 48% aqueous hydrobromic acid, 70% aqueous perchloric acid and p-toluenesulfonic acid monohydrate gave the thienopyrimidine (815) in 46, 23, 14 and 27% yield, respectively.
Concentrated sulfuric acid, 85% phosphoric acid and 57% aqueous hydroiodic acid were found unsuitable for effecting the reaction between 782 and acetonitrile. Lewis acid catalysts such as boron trifluoride ethereate, anhydrous aluminium chloride, phosphorous trichloride and phosphorous tribromide effectively catalyzed the condensation between 782 and acetonitrile to afford the thienopyrimidine (815) in 10, 27, 32 and 50% yield, respectively.

The reaction of the o-aminoester (782) with nitriles such as acetonitrile, benzonitrile and ethyl cyanoacetate in the presence of sodium ethoxide was attempted so as to study the effectiveness of bases in promoting such condensation. The reaction of aminoester (782) with excess of acetonitrile at reflux in the presence of a 10% solution of sodium ethoxide in ethanol gave the thienopyrimidine (815) in <15% yield. The condensation of 782 with benzonitrile in the presence of sodium ethoxide in ethanol afforded the thienopyrimidine (820) in about 20% yield.

\[ \text{(815)} \quad R = \text{CH}_3 \]

\[ \text{(820)} \quad R = \text{C}_6\text{H}_5 \]
The reaction of the aminoester (782) with ethyl cyanoacetate in the presence of sodium ethoxide in ethanol yielded 2,4-dihydroxy-3-cyanothieno(2,3-c)pyridine (847) as the product of the reaction instead of the thieno(2,3-d)-pyrimidine (816) which was obtained in the acid catalyzed condensation. Similarly, thienopyridines (848) and (849) were obtained as the products of the base catalyzed reaction of the corresponding o-aminoesters (848a) and (849a) with ethyl cyanoacetate.

\[
\begin{align*}
\text{(847)} & \quad \begin{array}{c}
\text{OH} \\
\text{CN}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
\text{(816)} & \quad \begin{array}{c}
\text{O} \\
\text{NH}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{(848a)} & \quad R_1 = R_2 = \text{CH}_3 \\
\text{(849a)} & \quad R_1 = \text{Ph}; R_2 = \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{(848)} & \quad R_1 = R_2 = \text{CH}_3 \\
\text{(849)} & \quad R_1 = \text{Ph}; R_2 = \text{H}
\end{align*}
\]
Other Condensed Pyrimidines

The condensation of nitriles with an o-aminocarbonyl compound under the influence of hydrogen chloride to obtain condensed pyrimidines has successfully been applied to the synthesis of condensed pyrimidines such as benzothieno-(3,2-d)pyrimidines, pyrido(3',2':4,5)thieno(3,2-d)pyrimidines and furo(2,3-d)pyrimidines.\(^7\)

The successful application of the method to the synthesis of isothiazolo(3,4-d)pyrimidines (427) and (433) by the reaction of acetonitrile with the o-aminonitrile (388) or the o-aminoester (389) or the amide (390) is described in Chapter III. The synthesis of 4-aminothieno(3,4-d)pyrimidines (647) and (648) by the reaction of the aminonitrile (615) with acetonitrile and benzonitrile, the 4-oxothieno(3,4-d)pyrimidines (650) and (651) by the reaction of the aminoamide (618) and (625) with acetonitrile and that of the thieno(3,2-d)pyrimidine (649) by the reaction of the thiophene (619) with acetonitrile are described in Chapter IV. The reaction of 2-amino-3-cyanopyrrole (850a) with acetonitrile yielded the 4-aminopyrrolo(2,3-d)pyrimidine (850).
However, the attempted condensation of acetonitrile with the 5-amino-4-carbethoxy-3-methylisothiazole (851), prepared by the dealkylative decarboxylation of the urethane (851a) with anhydrous aluminium chloride in benzene, to obtain the isothiazolo (5,4-d)pyrimidine (851b), as well as the attempted condensation of the 2-amino-3-carbethoxypyridine (853) with acetonitrile to obtain the pyrido(2,3-d)pyrimidine (854) met with failure. The failure of these aminoesters (851) and (853) to condense with acetonitrile under the influence of hydrogen chloride may in part be attributed to the poor nucleophilicity of the amino group present in these substrates as compared to the nucleophilicity of the NH₂ group present in anthranilic acid derivatives, 2-aminothiophene-3-carboxylic acid derivatives and 3-aminothiophene-2- or 4-carboxylic acid derivatives which have been found to undergo cyclization essentially under similar reaction conditions.
The enhancement of the reactivity of the nitrile in the presence of halogen acids has been utilized for effecting the condensation of nitriles with o-aminocarbonyl compounds to obtain condensed pyrimidines. It appears that the enhanced reactivity of nitriles under the influence of halogen acids can be utilized for effecting the condensation between nitriles and substrates analogous to o-aminocarbonyl compounds, to obtain heterocyclic systems incorporating the C=O moiety of the nitrile. As expected, the reaction of o-aminobenzenesulfonylamide (852a) with acetonitrile in the presence of dry hydrogen chloride.
afforded the 3-methyl-1,2,4-benzothiadiazin-1,1-dioxide (852) in good yields.

Thus, the reaction of a nitrile with an appropriate substrate, such as an o-aminocarbonyl compound, under the influence of dry hydrogen chloride, is facile and versatile and, therefore, the method offers an attractive alternative to the existing methods of synthesis of quinazolines, condensed pyrimidines and related heterocyclic ring systems.

Physical and Spectroscopic Properties

Quinazolines, thieno(2,3-d)pyrimidines, and other condensed pyrimidine derivatives synthesized, are crystalline solids. The 4-oxopyrimidines of the type 855, possessing a hydrogen on the pyrimidine nitrogen are, in general, high melting solids in contrast to the pyrimidines of the type 856. Among thieno(2,3-d)pyrimidines of the general
structure 857, the thienopyrimidines possessing a carboxethoxy- methyl substituent at the 2-position (857; R = CO$_2$Et) are lower melting compounds than the corresponding thienopyrimidines possessing a methyl (857; R = H) or a benzyl substituent at the 2-position (857; R = C$_6$H$_5$).

The IR spectra of the quinazolin-4-ones (801-810) exhibit the carbonyl stretching absorption due to the 4-oxo group in the region 1650-1660 cm$^{-1}$. In the thieno (2,3-d)-pyrimidin-4-ones (815-841) this absorption occurs at 1675-1640 cm$^{-1}$. The C=O stretching absorption due to the ester function in the 2-carboxethoxythienopyrimidines (825, 829, 836 and 845) and 2-carboxethoxymethylquinazolin-4-one (803) appears around 1740 cm$^{-1}$. The thienopyrimidines (823) and (833), possessing a carboxethoxy group at the pyrimidine and thiophene moiety, exhibit the ester group
carbonyl stretching absorption at 1740 and 1710 cm⁻¹; respectively. The spectra of 2-methyl- and 2-chloromethyl-4-phenylthienopyrimidines (844) and (846) are devoid of any absorption in the region 1740-1570 cm⁻¹.

The NMR spectra of the 2-carbethoxymethylthienopyrimidines (825) and (829) reveal the presence of two proton singlet due to the methylene group of the carbethoxymethyl substituent at δ3.73 and 3.80, respectively, thus indicating the existence of these compounds as the 2-carbethoxymethyl-3,4-dihydro-4-oxo-thienopyrimidines (825) and (829) and not as the 2-carbethoxymethylene-1,2,3,4-tetrahydro-4-oxothienopyrimidine tautomers (825a) and (829a).
The mass spectrum of 2-carbethoxymethylquinazoline-4-one (803) exhibits an intense molecular ion peak at m/e 232. Other intense peaks in the spectrum are at m/e 160, 132 and 119. The peak at m/e 119 corresponds to the ion 860 formed by the loss of EtO₂CCH₂CN from the molecular ion. The ion of m/e 160 may be formulated as the radical cation (858), arising from the molecular ion by a hydrogen transfer from the ester group to the pyrimidine nitrogen, followed by the loss of CO₂C₂H₄, or as the radical cation (858a), formed by the successive loss of C₂H₄ and CO₂ from the molecular ion. Loss of CO from these ions, possibly, leads to the odd electron ion of m/e 132 (859) or (859a).
Some of the low intensity peaks observed at m/e 187, 145 and 117 may be attributed to the even electron ions (861, 862 and 863). The low intensity peak at m/e 186 corresponds to the fragment formed by the loss of ethanol from the molecular ion. The ion thus formed may be formulated as the radical cation (861a) or (861b).

\[
\text{(861) m/e 187} \quad \text{(861a) m/e 186} \quad \text{(861b) m/e 186}
\]

The mass spectrum of 2-benzyl-4-aminooquinazoline (812) exhibits an intense molecular ion peak at m/e 235. Peaks of high intensity are observed at m/e 117 and 118, and a peak of medium intensity occurs at m/e 119. These may be attributed to the odd electron ions of the nitriles (864).
and (865) and the nitrilium ions (866) and (867). An ion peak observed at m/e 144 corresponds to the nitrilium ion (868) derived by the elimination of PhCH₂⁺ from the molecular ion.

\[
\begin{align*}
&\text{(812) m/e 235} & \quad & \text{(864) m/e 117} & \quad & \text{(865) m/e 118} \\
&\text{(866) m/e 119} & \quad & \text{(867) m/e 118} & \quad & \text{(868) m/e 144}
\end{align*}
\]

The degradation pattern of 2-methyl-4-phenyl-6-chloro quinazoline (813) can be depicted as shown in Scheme LIV.

The molecular ion peaks of most of the thieno(2,3-d)-pyrimidines are very intense and are often observed as the
base peaks. The 4-oxo-tetrahydrobenzo(b)thienopyrimidines of the general structure \(869\) and the 4-phenyl-tetrahydrobenzo­thienopyrimidines \((844-846)\) exhibit intense \(M-28\) peak due to the ions of the general structure \(870\) and \(870a\) which are formed by the loss of \(\text{CH}_2 = \text{CH}_2\) through the retro Diels-Alder cleavage of the cyclohexenyl moiety.

\[
\begin{align*}
\text{(869)} & \\
\text{(815) } R = \text{CH}_3 & \text{(817) } R = \text{CH}_2\text{CONH}_2 & \text{(817) } R = \text{CH}_3 \\
\text{(820) } R = \text{C}_6\text{H}_5 & \text{(845) } R = \text{CH}_2\text{CO}_2\text{Et} & \text{(846) } R = \text{CH}_2\text{Cl} \\
\text{(821) } R = \text{C}_6\text{H}_5\text{Cl}-p & \\
\text{(870) } & \\
\text{(870a) } &
\end{align*}
\]

This mode of fragmentation receives further confirmation by the presence of intense peaks at \(m/e\) 255 and 254 due to the ions \(871\) and \(872\) in the spectra of the tetrahydro­pyridothienopyrimidines \((838\text{ and }843)\), respectively.
Intense peak due to RC=NH is observed in the spectra of most of the thieno(2,3-d)pyrimidines. Loss of RC≡N from the molecular ions of the 4-oxothienopyrimidines by the retro Diels-Alder cleavage of the pyrimidine moiety leads to the formation of the ion 873 which is observed as a peak of moderate intensity in the spectra of 4-oxothienopyrimidines (815, 817, 820 and 821). Similar loss of RC≡N from the M-28 fragment gives the ion 874, which is more abundant than the ion 873. The ion of m/e 151 as well as the ions of m/e 123 and 91, formed by the successive loss of CO and S from 874, are common to the spectra of the tetrahydrobenzothienopyrimidines (815, 817, 820, 821 and 838).
A peak of moderate intensity at M-15 observed in the spectrum of 2-methylthienopyrimidine (815) corresponds to the nitrilium ion (877). But the absence of intense ion peak at m/e 205 in the spectra of other 2-substituted thieno(2,3-d)-pyrimidin-4-ones (817, 818, 820 and 821) indicates that the loss of 2-substituents as a radical, to
yield the nitrilium ion (877), is not a significant mode of decomposition of the parent ions.

\[
\begin{array}{c}
\text{(877) } m/e 205
\end{array}
\]

A peak corresponding to M-15 is also observed in the spectra of the tetrahydrobenzo(b)thienopyrimidino-4-ones (818, 820 and 821) possessing substituents other than a methyl group at the 2-position. Therefore, it appears that the M-15 peak may be due to the ions formed by the expulsion of a CH$_3$ radical from the cyclohexenyl moiety through ring cleavage and rearrangement reactions. The M-15 ions thus formed may be formulated as the cations (878-881).
Elimination of R-C=N from the M-15 ion, or the loss of CH$_3^*$ from the radical cation leads to the formation of an ion of m/e 164, observed as a common peak in the spectra of the tetrahydrobenzothienopyrimidines (815, 817, 818, 820 and 821). The structure represents one of the possible isomeric formulations for this ion of m/e 164.

The degradation pattern of 2-methyl- and 2-aryltetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4-ones (815, 820 and 821) and of the tetrahydrobenzo(b)thieno(2,3-d)pyrimidine-2-acetamide (817) can be depicted as shown in Scheme LV and LVI, respectively.

The parent ion of 2-(2-chloroethyl)thienopyrimidin-4-one (818) occurs as a peak of low intensity at m/e 286. Other peaks found in the spectrum of this compound are due
(815) R=CH$_3$ m/e 220
(820) R=C$_6$H$_5$ m/e 282
(821) R=C$_6$H$_5$Cl-p m/e 316

SCHEME IV
SCHEME IVI

\[
\begin{align*}
\text{(817) m/e 263} & \quad \rightarrow \quad \text{m/e 218} \\
& \quad \rightarrow \quad \text{m/e 203} \\
& \quad \rightarrow \quad \text{m/e 246} \\
& \quad \rightarrow \quad \text{m/e 235} \\
& \quad \rightarrow \quad \text{m/e 218} \\
& \quad \rightarrow \quad \text{m/e 192} \\
& \quad \rightarrow \quad \text{m/e 179} \\
& \quad \rightarrow \quad \text{m/e 151} \\
& \quad \rightarrow \quad \text{m/e 164} \\
& \quad \rightarrow \quad \text{m/e 123}
\end{align*}
\]
to the ions formed by the decomposition of the odd electron ion (883), observed as a peak of high intensity at m/e 232.

\[ \text{CH}_2\text{CH}_2\text{Cl} \]

(818) m/e 286

\[ \text{CH}=\text{CH}_2 \]

(883) m/e 232

The mass spectrum of 2-(3-pyridyl)-6-ethylthienopyrimidin-4-one (832) shows an intense M-15 peak due to the cation (884) or (885) formed by the elimination of CH\(_3\) radical from the molecular ion.

\[ \text{CH}_3\text{CH}_2\]

(832) m/e 257

\[ \text{CH}_2 \]

(884) m/e 242

\[ \text{CH} \]

(885) m/e 242

Loss of nicotinonitrile from the ion 884 or 885 possibly yields the ions 886 or 887 observed as an intense peak at m/e 138. The direct loss of nicotinonitrile from
the molecular ion leads to the ion of m/e 153 (888) observed as a peak of only moderate intensity. The intense peaks at m/e 105 and 78 are possibly due to the nitrilium ions (889) and (890).

\[ \text{(886) } m/e \ 138 \]

\[ \text{(887) } m/e \ 138 \]

\[ \text{(888) } m/e \ 153 \]

\[ \text{(889) } m/e \ 105 \]

\[ \text{(890) } m/e \ 78 \]

The peaks of moderate intensity at m/e 201 and 173 in the spectrum of 2-methyl-5-phenylthieno(2,3-d)pyrimidin-4-one (834) can be attributed to the ions 891 and 892 arising by the successive loss of CH$_3$CN and CO from the molecular ion. The ion of m/e 172, which is more abundant than the ion of m/e 173, may be formulated as the cations 893 or 894. The peak of moderate intensity at m/e 128 may be due to the ion 895.
The 2-methyl-4-phenyltetrahydrobenzothiophene (844) exhibits an intense M-1 peak at m/e 279 which may be attributed to the formation of the thienodiazepine cation (896). Some of the other peaks found in the spectrum of this compound can be explained on the basis of the fragmentation pattern depicted in Scheme LVII.

The 2-carbethoxymethyl-4-phenylthienopyrimidine (845) exhibits peaks of low intensity at m/e 324, 323, 307 and 306 due to the loss of C₂H₄, C₂H₅, C₂H₅O⁻ and C₂H₅OH from the molecular ion. The intense peak at m/e 280 and 279 may be due to the ions (897) and (896), respectively. The degradation pattern of these ions are similar to that of the ions formed from 844.
SCHEME LVII
The 2-chloromethylthienopyrimidine (846) exhibits intense M-1 and M-35 peaks which may be attributed to the ions (898) and (896) arising by the loss of H\(^+\) and Cl\(^-\), respectively, from the molecular ion. Loss of ethylene from 898 possibly yields the ion 899, observed as a peak of medium intensity at m/e 285. A peak of low intensity at m/e 299 corresponds to the loss of CH\(_3\) from the molecular ion.

The 2,4-dihydroxy-3-cyano-5,6,7,8-tetrahydrobenzothienopyridine (847) exhibits an intense molecular ion peak at m/e 246. A peak of low abundance at m/e 231 corresponds to the loss of CH\(_3\) from the molecular ion. The intense
peak at \( M-28 \) may be due to the ions (900-902) formed by the loss of ethylene or CO from the molecular ion. Elimination of \( \text{CN-CH} = \text{C}=\text{O} \) from the molecular ion and from the ion 900 leads to the ion of \( m/e \) 179 and 151, respectively. These ions of \( m/e \) 179 and 151 have also been observed in the spectra of 4-oxo-tetrahydrobenzothienopyrimidin-4-ones.

\[
\begin{align*}
(847) &~ m/e~246 \\
(900) &~ m/e~218 \\
(902) &~ m/e~218 \\
(901) &~ m/e~218 \\
\end{align*}
\]

The spectrum of 2,3-dimethyl-4,6-dihydroxy-5-cyanothienopyridine (848) shows intense \( M-15, M-23 \) and \( M-56 \) peaks at \( m/e 205, 192 \) and 164 due to the loss of \( \text{CH}_3^+ \), one or two molecules of CO from the molecular ion, respectively. Loss of cyanoketene from the parent ion yields the ion (903), observed as a high intensity peak at \( m/e 153 \). Other
prominent peaks found in the spectrum of this compound are due to the fragmentation of these ions of m/e 205, 192, 164 and 153.

The 3-methylbenzothiadiazine 1,1-dioxide (852) exhibits an intense molecular ion peak at m/e 309. Loss of CH$_3$CN from the parent ion gives the ion (904) of high abundance at m/e 268. The intense peaks at m/e 188 may be due to the ion 905 or 906. The peaks of moderate intensity at m/e 293 and 204 are possibly due to the ions 907 and 908, respectively.
532

(905) m/e 188

(906) m/e 188

(907) m/e 293

(908) m/e 204
### TABLE XXVI

**Quinazolin-4(3H)-ones**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>M.P.</th>
<th>Yield</th>
<th>Recryst. Solvent</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>801</td>
<td>CH₃</td>
<td>240-242</td>
<td>75</td>
<td>E</td>
<td>C₉H₈N₂O</td>
</tr>
<tr>
<td>802</td>
<td>CH₂C₆H₅</td>
<td>256-258</td>
<td>64</td>
<td>D-E</td>
<td>C₁₅H₁₂N₂O</td>
</tr>
<tr>
<td>803</td>
<td>CH₂CO₂C₂H₅</td>
<td>162-164</td>
<td>69</td>
<td>E</td>
<td>C₁₂H₁₂N₂O₃</td>
</tr>
<tr>
<td>804</td>
<td>CH₂Cl</td>
<td>246-248</td>
<td>72</td>
<td>DI</td>
<td>C₉H₇N₂OCl</td>
</tr>
<tr>
<td>805</td>
<td>CH₂OC₆H₄Cl-p</td>
<td>241-243</td>
<td>65</td>
<td>D-E</td>
<td>C₁₅H₁₁N₂O₂Cl</td>
</tr>
<tr>
<td>806</td>
<td>CH₂SC₆H₄Cl-p</td>
<td>229-231</td>
<td>76</td>
<td>D-E</td>
<td>C₁₅H₁₁N₂OSCl</td>
</tr>
<tr>
<td>807</td>
<td>CH₂SO₂C₆H₅</td>
<td>239-241</td>
<td>67</td>
<td>D-E</td>
<td>C₁₅H₁₂N₂O₃S</td>
</tr>
<tr>
<td>808</td>
<td>C₆H₅</td>
<td>239-241</td>
<td>77</td>
<td>D-E</td>
<td>C₁₄H₁₀N₂O</td>
</tr>
<tr>
<td>809</td>
<td>C₆H₅Cl-p</td>
<td>310-312</td>
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<td>D-E</td>
<td>C₁₄H₉N₂OCl</td>
</tr>
<tr>
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<td>3-C₅H₄N</td>
<td>278-280</td>
<td>58</td>
<td>D-E</td>
<td>C₁₃H₉N₃O</td>
</tr>
</tbody>
</table>

* B = Bimethylformamide  
E = Ethanol  
DI = Dioxane  

* D = Dimethylformamide  
E = Ethanol  
DI = Dioxane
### TABLE XXVII

**4-Amino- and 4-Phenylquinazolines**

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recryst. Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>811</td>
<td>CH₃</td>
<td>NH₂ H</td>
<td>227-229</td>
<td>63</td>
<td>EA-CH</td>
<td>C₉H₉N₃</td>
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<tr>
<td>812</td>
<td>CH₂C₆H₅</td>
<td>NH₂ H</td>
<td>252-254(d)</td>
<td>40</td>
<td>EA-CH</td>
<td>C₁₅H₁₃N₃</td>
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<tr>
<td>813</td>
<td>CH₃</td>
<td>C₆H₅ Cl</td>
<td>106-108</td>
<td>70</td>
<td>B-H</td>
<td>C₁₅H₁₁N₂Cl</td>
</tr>
<tr>
<td>814</td>
<td>CH₂Cl</td>
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<td>126-128</td>
<td>70</td>
<td>B-H</td>
<td>C₁₅H₁₀N₂Cl₂</td>
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</tbody>
</table>

* B = Benzene  
CH = Cyclohexane  
EA = Ethyl acetate  
H = n-Hexane
### TABLE XXVIII

**Thieno(2,3-d)pyrimidin-4(3H)-ones**

![Chemical Structure](image_url)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystl. Solvent*</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>815</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃</td>
<td></td>
<td>300-302(d)</td>
<td>85</td>
<td>D-E</td>
<td>C₁₁H₁₂N₂O₅S</td>
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<tr>
<td>816</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂CO₂C₂H₅</td>
<td></td>
<td>186-188</td>
<td>72</td>
<td>E</td>
<td>C₁₄H₁₆N₂O₃S</td>
</tr>
<tr>
<td>817</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂CO NH₂</td>
<td></td>
<td>296-298</td>
<td>46</td>
<td>D-E</td>
<td>C₁₂H₁₃N₃O₂S</td>
</tr>
<tr>
<td>818</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂CH₂Cl</td>
<td></td>
<td>&gt;360</td>
<td>50</td>
<td>E-C</td>
<td>C₁₂H₁₃N₂O₅Cl</td>
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<tr>
<td>819</td>
<td>-(CH₂)₄⁻</td>
<td>CHClCH₂Cl</td>
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<td>&gt;360</td>
<td>40</td>
<td>E</td>
<td>C₁₂H₁₂N₂O₅Cl</td>
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<tr>
<td>820</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅</td>
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<td>300-302</td>
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<td>D</td>
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Table XXVIII (Contd.)

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<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Re-crystn. Solvent*</th>
<th>Molecular Formula</th>
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<td>68</td>
<td>E</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>58</td>
<td>D, E</td>
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<td>70</td>
<td>E</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>57</td>
<td>D, E</td>
<td>C&lt;sub&gt;15&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>
<td></td>
</tr>
<tr>
<td>839</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;CH—NH—CH—</td>
<td>CH&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>310-313</td>
<td>45</td>
<td>D, E</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>840</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;—</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;N(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>168-170</td>
<td>59</td>
<td>E</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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</tr>
<tr>
<td>841</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;—</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;NO</td>
<td>199-200</td>
<td>75</td>
<td>E</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;21&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;S</td>
<td></td>
</tr>
</tbody>
</table>

* C = Chloroform
D. = Dimethylformamide
DI = Dioxane
E = Ethanol
TABLE XXIX

4-Amino- and 4-Phenylthieno(2,3-d)pyrimidines

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>M.P. °C</th>
<th>Yield%</th>
<th>Recryst.</th>
<th>Molec. Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>842</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃</td>
<td>NH₂</td>
<td></td>
<td>224-226</td>
<td>46</td>
<td>B</td>
<td>C₁₁H₁₃N₃S</td>
</tr>
<tr>
<td>843</td>
<td>-CH₂-CH₂-N-CH₂⁻</td>
<td>3-C₅H₄N</td>
<td>NH₂</td>
<td>233-235</td>
<td>43</td>
<td>D-E</td>
<td>C₂₁H₁₉N₅S</td>
<td></td>
</tr>
<tr>
<td>844</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td></td>
<td>118-120</td>
<td>54</td>
<td>E</td>
<td>C₁₇H₁₆N₂S</td>
</tr>
<tr>
<td>845</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂CO₂C₂H₅</td>
<td>C₆H₅</td>
<td>82-84</td>
<td>57</td>
<td>E</td>
<td>C₂₀H₂₀N₂O₂S</td>
<td></td>
</tr>
<tr>
<td>846</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂Cl</td>
<td>C₆H₅</td>
<td>144-146</td>
<td>51</td>
<td>E</td>
<td>C₁₇H₁₅N₂SCl</td>
<td></td>
</tr>
</tbody>
</table>

* B = Benzene
D = Dimethylformamide
E = Ethanol
2-Methylquinazolin-4(3H)-one (801).

A stream of dry hydrogen chloride gas was passed through a solution of 1.51g (0.01 mole) of methyl anthranilate and 30ml of acetonitrile for about 5 hours. The mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.2g (75%) of colorless crystalline product, m.p. 240-242°C. Reported m.p. 240-241°C. 705

Analysis : C_{9}H_{8}N_{2}O (160.17) Requires C, 67.48; H, 5.03%
       Found   C, 67.32; H, 5.31%

IR (Nujol) : 1680, 1610, 1290, 1250, 1145, 995, 900, 775 cm^{-1}

2-Benzylquinazolin-4(3H)-one (802).

A stream of dry hydrogen chloride gas was passed through a solution of 1.51g (0.01 mole) of methyl anthranilate and 1.3g (0.011 mole) of phenylacetonitrile in 30ml of dioxane for 5 hours. The mixture was allowed to stand
at room temperature for 12 hours, poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol yielded 1.5g (64%) of crystalline product, m.p. 256-258°C. Reported m.p. 256°C.

Analysis: \( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O} \) (236.26) Requires C, 76.25; H, 5.12% Found C, 76.12; H, 5.00%

IR (Nujol): 1680, 1620, 1255, 1180, 1160, 1030, 1000, 980, 860, 770, 750 cm\(^{-1}\)

UV (MeOH): 203nm (log \( \varepsilon \) 4.47), 226(4.50), 266(3.99), 302(3.75), 315sh(3.68)

2-Carbethoxymethylquinazolin-4(3H)-one (803).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 1.25g (0.011 mole) of ethyl cyanoacetate in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from ethanol yielded 1.6g (69%) of colorless crystalline product, m.p. 162-164°C. Reported m.p. 163-164°C.
2-Chloromethylquinazolin-4(3H)-one (804).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 0.85g (0.011 mole) of chloroacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dioxane yielded 1.4g (72%) of colorless crystalline product, m.p. 246-248°C. Reported m.p. 247-248°C. 

Analysis  :  C_{12}H_{12}N_{2}O_{3}(232.23) Requires C, 62.06; H, 5.21%
Found    :  C, 62.09; H, 5.34%

IR (Nujol) :  1740, 1690, 1630, 1520, 1280, 1250, 1210,
           :  1160, 1130, 1055, 1045, 1020, 955, 905, 870,
           :  800, 780, 770 cm^{-1}

MS, m/e    :  232(M^+), 187, 186, 160, 146, 145, 132, 119

Analysis  :  C_{9}H_{7}N_{2}OCl(194.62) Requires C, 55.54; H, 3.63%
Found    :  C, 55.24; H, 3.90%

IR (KBr)   :  3180(NH); 1690, 1620, 1520, 1470, 1330, 1270,
           :  1260, 1160, 1140, 1035, 1010, 945, 900,
           :  780, 760 cm^{-1}
2-(4-Chlorophenoxyethyl)quinazolin-4(3H)-one (805).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 1.85g (0.011 mole) of 4-chlorophenoxyacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 1.86g (65%) of crystalline product, m.p. 241-243°C.

Analysis: C_{15}H_{11}N_{2}OCl (286.71) Requires C, 62.83; H, 3.87%
Found C, 63.01; H, 4.05%

IR (Nujol): 1680, 1610, 1290, 1250, 1150, 995, 900, 770 cm⁻¹

2-(4-Chlorophenylthiomethyl)quinazolin-4(3H)-one (806).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 2.2g (0.011 mole) of 4-chlorophenylthioacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 2.3g (76%) of crystalline product, m.p. 229-231°C.

Analysis: C_{15}H_{11}N_{2}OSCl (302.78) Requires C, 59.50; H, 3.66%
Found C, 59.50; H, 3.95%

IR (Nujol): 1680, 1620, 1260, 1160, 1090, 1010, 910, 825, 780, 770 cm⁻¹
2-(Phenylsulfonylmethyl)quinazolin-4(3H)-one (807).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 2.0g (0.011 mole) of phenylsulfonylacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 2.0g (67%) of crystalline product, m.p. 239-241°C.

Analysis: C_{15}H_{12}N_{2}O_{3}S (300.33) Requires C, 59.98%; H, 4.02%
Found C, 60.00%; H, 4.22%

IR (Nujol): 1660, 1620, 1250, 1150, 1080, 1005, 900, 785, 775 cm^{-1}

2-Phenylquinazolin-4(3H)-one (808).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 1.15g (0.011 mole) of benzonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 1.7g (77%) of colorless crystalline product, m.p. 239-241°C. Reported m.p. 236°C. 729
Analysis : C_{14}H_{10}N_{2}O(222.24) Requires C,75.66; H,4.54%
Found C,75.78; H,4.57%

IR (Nujol) : 1670, 1605, 1560, 1145, 1100, 940, 820, 765 cm\(^{-1}\)

UV (MeOH) : 205nm(log \(\varepsilon\) 4.49), 217sh(4.37), 236(4.44), 290(4.17)

2-(4-Chlorophenyl)quinazolin-4(3H)-one (809).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 1.5g (0.011 mole) of 4-chlorobenzenonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 1.8g (70%) of crystalline product, m.p. 310-312\(^\circ\)C. Reported m.p. 306\(^\circ\)C.

Analysis : C_{14}H_{9}N_{2}OCl(256.69) Requires C,65.60; H,3.53%
Found C,65.70; H,3.74%

IR (Nujol) : 1680, 1600, 1560, 1280, 1150, 1120, 1097, 1010, 940, 840, 825, 760 cm\(^{-1}\)

UV (MeOH) : 206, 220sh, 240, 290nm

2-(3-Pyridyl)quinazolin-4(3H)-one (810).

Methyl anthranilate 1.51g (0.01 mole) was reacted with 1.15g (0.011 mole) of nicotinonitrile in 30ml of
dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from dimethylformamide-ethanol yielded 1.3g (58%) of crystalline product, m.p. 278-280°C. Reported m.p. 278°C. 733

Analysis : C_{13}H_{10}N_{3}O(223.23) Requires C, 69.94%; H, 4.06%
            Found   C, 70.14%; H, 4.27%

IR (Nujol) : 1680, 1610, 1570, 1560, 1500, 1260, 1150, 1110, 1025, 945, 870, 810, 775 cm⁻¹

UV (MeOH) : 206nm(logε 4.46), 230(4.50), 294(4.19)

4-Amino-2-methylquinazoline (811).

2-Aminobenzonitrile 1.18g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 801. Recrystallization from ethyl acetate-cyclohexane yielded 1.0g (63%) of crystalline product, m.p. 227-229°C. Reported m.p. 228-229°C. 708

Analysis : C_{9}H_{8}N_{3}(159.19) Requires C, 67.90%; H, 5.70%
            Found   C, 68.28%; H, 5.93%

IR (KBr) : 3510, 3380(NH); 1685, 1660, 1620, 1580, 1510, 1480, 1400, 1380, 1130, 990, 880, 770, 755 cm⁻¹
4-Amino-2-benzylquinazoline (812).

2-Aminobenzonitrile 1.18g (0.01 mole) was reacted with 1.3g (0.011 mole) of phenylacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from ethyl acetate-cyclohexane yielded 0.95g (40%) of crystalline product, m.p. 252-254°C (d).

Analysis : C_{15}H_{13}N_{3}(235.29) Requires C,76.57; H,5.57%; Found C,76.51; H,5.76%
IR (Nujol) : 1670, 1600, 1255, 1160, 1030, 1000, 890, 860, 775, 750 cm^{-1}
MS, m/e : 235(M^{+})

6-Chloro-2-methyl-4-phenylquinazoline (813).

2-Amino-5-chlorobenzophenone 2.32g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 801. Recrystallization from benzene-hexane yielded 1.8g (70%) of crystalline product, m.p. 106-108°C. Reported m.p. 105-106°C. 717
Analysis

IR (Nujol)

MS, m/e

C_{15}H_{11}N_2Cl (254.71) Requires C, 70.73; H, 4.35%

Found C, 70.57; H, 4.57%

1540, 1170, 1150, 1095, 1010, 930, 890, 850, 820, 765 cm$^{-1}$

256, 254 (M$^+$), 253, 219, 177, 151, 112, 110, 100

Reaction of 2-amino-5-chlorobenzophenone-α-oxime with acetonitrile

2-Amino-5-chlorobenzophenone-α-oxime$^{717}$ 2.46g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 801. Recrystallization from benzene-hexane yielded 1.9g (75%) of crystalline product, m.p. 106-108°C. The product obtained was found to be identical (mmp, TLC, IR) with the compound 813 obtained by the reaction of 2-amino-5-chlorobenzophenone with acetonitrile.

6-Chloro-2-chloromethyl-4-phenylquinazoline (814).

2-Amino-5-chlorobenzophenone 2.32g (0.01 mole) was reacted with 0.85g (0.011 mole) of chloroacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802.
Recrystallization from benzene-hexane yielded 2.0g (70\%) of crystalline product, m.p. 126-128°C, Reported m.p. 126-127°C. \textsuperscript{717}

Analysis : \( \text{C}_{15}\text{H}_{10}\text{N}_{2}\text{Cl}_{2} \) (289.16) Requires C, 62.30; H, 3.49\%

\text{Found C, 62.31; H, 3.65\%}

\text{IR (Nujol)} : 1590, 1520, 1150, 1095, 1010, 960, 895, 850, 825, 810, 770 cm\textsuperscript{-1}

\text{Reaction of 2-amino-5-chlorobenzophenone-\( \alpha \)-oxime with chloroacetonitrile.}

2-Amino-5-chlorobenzophenone-\( \alpha \)-oxime \textsuperscript{717} 2.46g (0.01 mole) was reacted with 0.85g (0.011 mole) of chloroacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 802. Recrystallization from benzene-hexane yielded 2.2g (76\%) of crystalline product, m.p. 126-128°C. The product was found to be identical (mmp, TLC, IR) with the compound 814 obtained by the reaction of 2-amino-5-chlorobenzophenone with chloroacetonitrile.

2-Methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (815).

A stream of dry hydrogen chloride gas was passed through a solution of 1.96g (0.01 mole) of 2-amino-4,5,6,7-
tetrahydrobenzo(b)thiophene-3-carboxamide in 30ml of acetonitrile for 5 hours. The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol afforded 1.9g (85%) of colorless crystalline product, m.p. 300-302°C. Reported m.p. 302°C.

Analysis: C_{11}H_{12}N_{2}O_{3}(220.29) Requires C,59.97%; H,5.49%  
Found  C,59.71%; H,5.85%

IR (Nujol): 1660, 1610, 1270, 1220, 1185, 1165, 1070, 975, 965, 930, 920, 855, 830, 785 cm\(^{-1}\)

MS, m/e: 220(M\(^+\)), 205, 192, 164, 162, 151, 123

Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene with acetonitrile in the presence of hydrogen bromide.

A thin stream of dry hydrogen bromide gas was bubbled through a solution of 2.25g (0.01 mole) of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene in 30ml of acetonitrile for 5 hours. The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and basified with 10% ammonium hydroxide solution.
The solid obtained was filtered, washed with water and dried. Recrystallization from dimethylformamide-ethanol afforded 1.8g (84%) of 2-methyl-5,6,7,8-tetrahydrobenzo(b)thieno-(2,3-d)pyrimidin-4(3H)-one (815) which was obtained in 80% yield by the reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene\(^{718}\) with acetonitrile in the presence of dry hydrogen chloride in place of hydrogen bromide in the above procedure.

**Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene with acetonitrile in the presence of equimolar amounts of acid catalysts**

To a solution of 2.25g (0.01 mole) of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene\(^{718}\) in 50ml of acetonitrile was added 0.01 mole of an appropriate acidic catalyst. The reaction mixture was refluxed for 8 hours on a steam bath, cooled to room temperature, poured into 300ml of ice-water and basified with saturated aqueous sodium bicarbonate solution. The solid obtained was filtered, washed with water and dried. The crude product obtained was extracted with 15ml of hot ethanol and the ethanol insoluble residue on recrystallization from dimethylfor-
amido-ethanol afforded 2-methyl-5,6,7,8-tetrahydrobenzo(b)-thieno(2,3-d)pyrimidin-4(3H)-one (815). The acid catalyst employed and the yield of 815 obtained are given below:

<table>
<thead>
<tr>
<th>Acid catalyst employed</th>
<th>% yield of 815</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen chloride in dioxane (10%)</td>
<td>32</td>
</tr>
<tr>
<td>Aqueous hydrochloric acid (35%)</td>
<td>46</td>
</tr>
<tr>
<td>Aqueous hydrobromic acid (48%)</td>
<td>23</td>
</tr>
<tr>
<td>Aqueous perchloric acid (70%)</td>
<td>14</td>
</tr>
<tr>
<td>p-Toluenesulfonic acid monohydrate</td>
<td>27</td>
</tr>
<tr>
<td>Boron trifluoride ethereate</td>
<td>10</td>
</tr>
<tr>
<td>Anhydrous aluminium chloride</td>
<td>27</td>
</tr>
<tr>
<td>Phosphorous trichloride</td>
<td>32</td>
</tr>
<tr>
<td>Phosphorous tribromide</td>
<td>50</td>
</tr>
</tbody>
</table>

Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene with acetonitrile in the presence of sodium ethoxide

To a solution of 2.25g (0.01 mole) of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene in 50ml of acetonitrile was added a solution of 0.23g of sodium in 4.6ml of absolute ethanol. The reaction mixture was refluxed for 8 hours, cooled, poured into 300ml of ice-water. The
solution was filtered and the filtrate was adjusted to pH 7 with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. The crude product on recrystallization with dimethylformamide-ethanol yielded 0.3g (14%) of 2-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidin-4(3H)-one (815).

Reaction of 2-amino-3-(N-methylcarboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophene with acetonitrile.

2-Amino-3-(N-methylcarboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophene\textsuperscript{734} 2.1g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 815. Recrystallization from dimethylformamide-ethanol afforded 1.7g (70%) of colorless crystalline product, m.p. 300-302°C (d). The product obtained was found to be identical (mmp, TLC, IR) with 815 obtained by the reaction of 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxamide with acetonitrile.

2-Carbethoxymethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidin-4(3H)-one (816).

A stream of dry hydrogen chloride gas was passed through a solution of 2.25g (0.01 mole) of 2-amino-3-
carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene$^7_{18}$ and 1.25g (0.011 mole) of ethyl cyanoacetate in 30ml of dioxane for 5 hours. The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 2.1g (72%) of crystalline product, m.p. 186-188°C. The product was found to be identical (mmp, TLC, IR) with the compound prepared by the reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene with excess of ethyl cyanoacetate in the presence of dry hydrogen chloride in the absence of a solvent.$^7_{13}$

Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene with malononitrile.

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene$^7_{18}$ 2.25g (0.01 mole) was reacted with 0.75g (0.011 mole) of malononitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for $^8_{16}$. Recrystallization from dimethylformamide-ethanol yielded 1.2g of crystalline
product, m.p. 296-298°C. The product obtained was charac-
terized as 3,4,5,6,7,8-hexahydro-4-oxobenzo(b)thieno(2,3-d)-pyrimidine-2-acetamide (817).

Analysis : C_{12}H_{13}N_{2}O_{2}S(263.31) Requires C, 54.73; H, 4.98%
Found C, 54.42; H, 5.24%

IR (KBr) : 3400, 3320, 3200(NH), 1675, 1595, 1510,
1385, 1290, 1260, 1210, 1060, 970, 930 cm^{-1}

MS, m/e : 263(M^+), 246, 218, 192, 179, 164, 151

2-(2-Chloroethyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidin-4(3H)-one (818).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene 2.25g (0.01 mole) was reacted with 2.12g
(0.04 mole) of acrylonitrile in 30ml of dioxane in the
presence of dry hydrogen chloride gas according to the
procedure described for 816. Recrystallization from
ethanol-chloroform afforded 1.35g (50%) of crystalline
product, m.p. >360°C.

Analysis : C_{12}H_{13}N_{2}O_{2}S(268.76) Requires C, 53.62; H, 4.84%
Found C, 53.13; H, 5.00%

IR (KBr) : 3400(NH), 1670, 1590, 1300, 1200, 970, 920 cm^{-1}

MS, m/e : 270, 268(M^+), 266, 233, 178, 162, 135, 116
2-(1,2-Dichloroethyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (819).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene\textsuperscript{718} 2.25g (0.01 mole) was reacted with 1.35g (0.011 mole) of 2,3-dichloropropionitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dioxane yielded 1.2g (40\%) of crystalline product, m.p. >360\textdegree C.

Analysis :  \( C_{12}H_{12}N_2OSCl_2 \) (303.21) Requires C, 47.53\%; H, 3.99\%; Found C, 47.72\%; H, 4.09\%

IR (Nujol) : 1650, 1585, 1290, 1210, 1150, 1040, 1020, 965 cm\textsuperscript{-1}

UV (MeOH) : 236nm(\( \log \varepsilon \) 4.24), 322(3.95)

2-Phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (820).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene\textsuperscript{718} 2.25g (0.01 mole) was reacted with 1.15g (0.011 mole) of benzonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure
described for 816. Recrystallization from dimethylformamide-ethanol yielded 2.25g (80%) of colorless crystalline product, m.p. 300-302°C(d). Reported m.p. 306-307°C. 719

Analysis : C₁₆H₁₄N₂O₅S(282.35) Requires C, 68.06; H, 5.00%  
Found C, 68.03; H, 5.30%

IR (Nujol) : 1640, 1225, 1180, 1020, 980, 945, 830, 780 cm⁻¹

MS, m/e : 282(M⁺), 267, 254, 178, 164, 151, 150, 141

2-Phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidin-4(3H)-one (820) was also obtained in 71% yield by the reaction of 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxamide 718 with benzonitrile under similar conditions.

Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene with benzonitrile in the presence of sodium ethoxide.

To a solution of 0.23g of sodium in 25ml of absolute ethanol was added 2.25g (0.01 mole) of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene 718 followed by 1.55g (0.015 mole) of benzonitrile. The mixture was refluxed on a steam bath for 18 hours, cooled, poured into ice-water and acidified with dilute hydrochloric acid. The solid
obtained was filtered, washed with water and dried. The crude product was extracted with 15ml of hot ethanol and the ethanol insoluble residue was recrystallized from dimethylformamide-ethanol to obtain 0.3g (10%) of the product which was identified as 2-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (820).

2-(4-Chlorophenyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (821).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene 718 2.25g (0.01 mole) was reacted with 1.5g (0.011 mole) of p-chlorobenzonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide yielded 2.1g (66%) of crystalline product, m.p. 315-316°C.

Analysis: C_{16}H_{13}N_{2}OSCl (316.80) Requires C, 60.66; H, 4.14%

Found C, 60.98; H, 4.50%

IR (Nujol): 1650, 1590, 1570, 1540, 1500, 1210, 1130, 1105, 1030, 1020, 980, 900, 865, 845, 820, 780 cm^{-1}

MS, m/e: 316(M^{+}), 301, 288, 275, 253, 178, 158, 151, 138
2-(3-Pyridyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (822).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene 2.25g (0.01 mole) was reacted with 1.15g (0.011 mole) of nicotinonitrile in dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.7g (60%) of crystalline product, m.p. 281-283°C.

Analysis : C_{15}H_{13}N_{3}OS (283.34) Requires C, 63.58%; H, 4.63%
Found C, 63.82%; H, 4.94%

IR (Nujol) : 1650, 1580, 1220, 1010, 970, 865, 820, 780 cm^{-1}

2-Carbethoxy-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (823).

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)-thiophene 2.25g (0.01 mole) was reacted with 1.1g (0.011 mole) of ethyl cyanoformate in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.9g (68%) of crystalline product, m.p. 218-220°C. Reported m.p. 219-220°C. 720
Analysis : C_{13}H_{14}N_{2}O_{3}(278.32) Requires C, 56.10; H, 5.07%  
Found      C, 56.10; H, 5.14%  
IR (Nujol)  : 1740, 1670, 1570, 1290, 1205, 1190, 1165,  
1140, 1100, 1035, 1000, 965, 910, 900, 870,  
820, 775, 750 cm^{-1}  
UV (MeOH)  : 218nm(log ε 4.38), 260(3.75), 340(4.17)  

2-Methyl-4H-3,5,6,7-tetrahydrocyclopenta(4,5)thieno(2,3-d)- 
pyrimidin-4-one (824).  

2-Amino-3-carbethoxy-5,6-dihydro-4H-cyclopenta(b)- 
thiophene 2.11g (0.01 mole) was reacted with excess of  
acetonitrile (30ml) in the presence of dry hydrogen chloride  
gas according to the procedure described for 815. Re- 
crystallization from dimethylformamide-ethanol yielded 1.5g  
(73%) of crystalline product, m.p. 284-286°C. Reported  
m.p. 292°C.  

Analysis : C_{10}H_{10}N_{2}O_{3}(206.26) Requires C, 58.23; H, 4.89%  
Found      C, 57.82; H, 5.00%  
IR (Nujol)  : 1670, 1590, 1200, 1160, 1020, 920, 860, 780 cm^{-1}  
UV (MeOH)  : 210nm(log ε 4.29), 240(4.12), 270sh(3.86),  
310(4.05)
2-Carbethoxymethyl-4H-3,5,6,7-tetrahydrocyclopenta(4,5)-thieno(2,3-d)pyrimidin-4-one (825).

2-Amino-3-carbethoxy-5,6-dihydro-4H-cyclopenta(b)-thiophene\(^{718}\) 2.11g (0.01 mole) was reacted with 1.25g (0.011 mole) of ethyl cyanoacetate in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol yielded 1.9g (68%) of crystalline product, m.p. 170-172°C.

Analysis : C\(_{13}\)H\(_{14}\)N\(_2\)O\(_3\)S (273.32) Requires C, 56.10; H, 5.07%  
Found C, 55.93; H, 5.13%

IR (Nujol) : 1730, 1670, 1585, 1290, 1260, 1210, 1160, 1060, 1020, 920, 775 cm\(^{-1}\)

NMR (CDCl\(_3\)) : 6 1.02(3H, t, COOCH\(_2\)CH\(_3\)); 2.4(2H, m, CH\(_2\)CH\(_2\)CH\(_2\)); 2.9(4H, m, CH\(_2\)CH\(_2\)CH\(_2\)); 3.73(2H, s, CH\(_2\)COOCH\(_2\)CH\(_3\)); 4.1(2H, q, COOCH\(_2\)CH\(_3\))

2-(2-Chloroethyl)-4H-3,5,6,7-tetrahydrocyclopenta(4,5)-thieno(2,3-d)pyrimidin-4-one (326).

2-Amino-3-carbethoxy-5,6-dihydro-4H-cyclopenta(b)-thiophene\(^{718}\) 2.11g (0.01 mole) was reacted with 2.15g (0.04 mole) of acrylonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure
described for 816. Recrystallization from ethanol-chloroform yielded 1.2g (47%) of crystalline product, m.p. >360°C.

Analysis: \text{C}_{11}\text{H}_{11}\text{N}_{2}\text{O}_{3}\text{Cl}(254.74) \text{ Requires } \text{C}, 51.86\%; \text{H}, 4.35\%
\text{Found } \text{C}, 51.62\%; \text{H}, 4.53\%

IR (KBr): 1675, 1590, 1460, 1410, 1380, 1340, 1300, 1270, 1210, 1010 cm\(^{-1}\)

2,5,6-Trimethylthieno(2,3-d)pyrimidin-4(3H)-one (827).

2-Amino-3-carbethoxy-4,5-dimethylthiophene\textsuperscript{718} 2.0g
(0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 815. Recrystallization from ethanol-chloroform afforded 1.65g (85%) of colorless crystalline product, m.p. 286-288°C. Reported m.p. 291°C.\textsuperscript{719}

Analysis: \text{C}_{9}\text{H}_{10}\text{N}_{2}\text{O}_{3}(194.52) \text{ Requires } \text{C}, 55.57\%; \text{H}, 5.18\%
\text{Found } \text{C}, 55.88\%; \text{H}, 5.45\%

IR (Nujol): 1650, 1600, 1380, 1310, 1200, 1040, 905, 780, 765 cm\(^{-1}\)

2-Benzyl-5,6-dimethylthieno(2,3-d)pyrimidin-4(3H)-one (828).

2-Amino-3-carbethoxy-4,5-dimethylthiophene\textsuperscript{718} 2.0g
(0.01 mole) was reacted with 1.30g (0.011 mole) of phenylacetonitrile in 30ml of dioxane in the presence of
dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.9g (70%) of crystalline product, m.p. 268-270°C. Reported m.p. 271°C.\(^{719}\)

Analysis: \(C_{15}H_{14}N_2O_3(270.34)\) Requires C, 66.64; H, 5.22%  
Found C, 66.79; H, 5.37%

IR (KBr): 1660, 1590, 1500, 1460, 1440, 1385, 1330, 1210, 1045, 930, 910, 790, 780 cm\(^{-1}\)

2-Carbethoxymethyl-5,6-dimethylthieno(2,3-d)pyrimidin-4(3H)-one (829).

2-Amino-3-carbethoxy-4,5-dimethylthiophene\(^{718}\) 2.0g (0.01 mole) was reacted with 1.25g (0.011 mole) of ethyl cyanoacetate in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol yielded 1.8g (68%) of crystalline product, m.p. 196-198°C.

Analysis: \(C_{12}H_{14}N_2O_3(266.31)\) Requires C, 54.12; H, 5.30%  
Found C, 54.05; H, 5.31%

IR (Nujol): 1740, 1660, 1590, 1270, 1210, 1170, 1035 cm\(^{-1}\)

NMR (CDCl\(_3\)): \(\delta\) 1.2(3H, t, \(\text{COOHCH}_2\text{CH}_3\)); 2.37(3H, s, \text{CH}_3\) at C-5); 2.45(3H, s, \text{CH}_3\) at C-6); 3.8(2H, s, \text{CH}_2\text{COOHCH}_2\text{CH}_3\); 4.2(2H, q, \text{COOHCH}_2\text{CH}_3\)}
2-Phenyl-5,6-dimethylthieno(2,3-d)pyrimidin-4(3H)-one (830).

2-Amino-3-carbethoxy-4,5-dimethylthiophene 2.0g
(0.01 mole) was reacted with 1.15g (0.011 mole) of benzonitrile
in 30ml of dioxane in the presence of dry hydrogen chloride
gas according to the procedure described for 816. Recrystallization
from dimethylformamide-ethanol yielded 1.7g
(66%) of crystalline product, m.p. 299-301°C. Reported m.p.
296-297°C. 719

Analysis : C_{14}H_{12}N_{2}O_{3}(256.32) Requires C, 65.60; H, 4.72%
Found C, 65.84; H, 4.91%
IR (Nujol) : 1640, 1220, 1010, 825, 770 cm\(^{-1}\)

2-(3-pyridyl)-5,6-dimethylthieno(2,3-d)pyrimidin-4(3H)-one (831).

2-Amino-3-carbethoxy-4,5-dimethylthiophene 2.0g
(0.01 mole) was reacted with 1.15g (0.011 mole) of nicotinonitrile
in 30ml of dioxane in the presence of dry hydrogen chloride
gas according to the procedure described for 816. Recrystallization
from dioxane afforded 1.7g (66%) of crystalline product, m.p. 311-313°C.

Analysis : C_{13}H_{11}N_{3}O_{3}(257.31) Requires C, 60.68; H, 4.31%
Found C, 60.49; H, 4.56%
IR (Nujol) : 1640, 1580, 1230, 1040, 1010, 930, 885, 865,
810, 785 765 cm\(^{-1}\)
2-(3-Pyridyl)-7-ethylthieno(2,3-d)pyrimidin-4(3H)-one (832).

2-Amino-3-carbethoxy-5-ethylthiophene\(^7�8\) 2.0g
(0.01 mole) was reacted with 1.15g (0.011 mole) of nicotinonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.8g (70\%) of crystalline product, m.p. 228-230\(^\circ\)C.

Analysis: \(C_{13}H_{11}N_3OS\) (257.31) Requires C, 60.68; H, 4.31\%  
Found C, 60.40; H, 4.57\%  
IR (Nujol): 1680, 1580, 1540, 1200, 1150, 1105, 1040, 910, 880, 840, 815, 785 cm\(^{-1}\)  
MS, m/e: 257(M\(^+\)), 242, 213, 163, 153, 138, 124, 111, 107, 105

2-Benzyl-6-carbethoxy-5-methylthieno(2,3-d)pyrimidin-4(3H)-one (833).

2-Amino-3,5-dicarbethoxy-4-methylthiophene\(^7�8\) 2.5g  
(0.01 mole) was reacted with 1.3g (0.011 mole) of phenylacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.9g (58\%) of crystalline product, m.p. 256-258\(^\circ\)C.
2-Methyl-5-phenylthieno(2,3-d)pyrimidin-4(3H)-one (834).

2-Amino-3-carbethoxy-4-phenylthiophene 2.47g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 315. Recrystallization from ethanol-chloroform afforded 1.8g (74%) of colorless crystalline product, m.p. 274-276°C. Reported m.p. 274-275°C. 719

Analysis : C_{17}H_{16}N_{2}O_{3}S (328.28) Requires C, 62.19; H, 4.91%  
Found C, 62.31; H, 4.97%  
IR (Nujol) : 1710, 1660, 1580, 1530, 1250, 1200, 1120, 1100, 1075, 1040, 910, 835, 765 cm^{-1}

UV (MeOH) : 204nm (log ε 4.43), 240(4.25), 300(3.91)

MS, m/e : 242(M^+), 201, 172, 146, 145, 140, 128, 121
2-Benzyl-5-phenylthieno(2,3-d)pyrimidin-4(3H)-one (835).

2-Amino-3-carbethoxy-4-phenylthiophene \( \text{718} \) 2.47 g (0.01 mole) was reacted with 1.3 g (0.011 mole) of phenylacetonitrile in 30 ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol-chloroform yielded 1.6 g (50%) of crystalline product, m.p. 220-222°C. Reported m.p. 221-222°C. \( \text{719} \)

Analysis: \( \text{C}_{19}\text{H}_{14}\text{N}_{2}\text{O}_{5} \) (318.38) Requires C, 71.67; H, 4.43%  
Found C, 71.43; H, 4.75%

IR (KBr): 1660, 1590, 1450, 1300, 1220, 1050, 930, 750 cm\(^{-1}\)

2-Carbethoxymethyl-5-phenylthieno(2,3-d)pyrimidin-4(3H)-one (836)

2-Amino-3-carbethoxy-4-phenylthiophene \( \text{718} \) 2.47 g (0.01 mole) was reacted with 1.25 g (0.011 mole) of ethyl cyanoacetate in 30 ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol afforded 2.2 g (70%) of crystalline product, m.p. 165-167°C.
Analysis :  C$_{16}$H$_{14}$N$_2$S (314.35) Requires C, 61.13; H, 4.49%
           Found   C, 61.17; H, 4.43%
IR (Nujol) :  1740, 1660, 1600, 1240, 1210, 1105, 1090, 1050,
            1025, 900, 850, 790, 750 cm$^{-1}$
NMR (CDCl$_3$) :  8 1.25(3H, t, COOCH$_2$CH$_3$); 3.7(2H, s, CH$_2$-
                COOCH$_2$CH$_3$); 4.13(2H, q, COOCH$_2$CH$_3$);
                7.15(1H, s, H at C-6); 7.43(5H, m, Ar-H);
                12.77(1H, broad s, exchangeable with D$_2$O, NH)

2,5-Diphenylthieno(2,3-d)pyrimidin-4(3H)-one (837).

2-Amino-3-carbethoxy-4-phenylthiophene$^7$ 2.47g (0.01 mole) was reacted with 1.15g (0.011 mole) of benzonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dioxane yielded 1.7g (56%) of colorless crystalline product, m.p. 290-292°C. Reported m.p. 287°C.$^7$19

Analysis :  C$_{18}$H$_{12}$N$_2$O$_3$ (304.36) Requires C, 71.03; H, 3.97%
           Found   C, 71.03; H, 4.08%
IR (Nujol) :  1660, 1210, 1070, 970 cm$^{-1}$

7-Methyl-2-(3-pyridyl)-5,6,7,8-tetrahydropyrido(4',3':4,5)-
thieno(2,3-d)pyrimidin-4(3H)-one (838).

2-Amino-3-carbethoxy-6-methyl-4,5,6,7-tetrahydro-
thieno(2,3-c)pyridine$^7$ 2.4g (0.01 mole) was reacted with
1.15g (0.011 mole) of nicotinonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.7g (57%) of crystalline product, m.p. 295-297°C.

Analysis : C\textsubscript{15}H\textsubscript{14}N\textsubscript{4}O\textsubscript{8}(298.36) Requires C, 60.38; H, 4.73% Found C, 60.26; H, 5.00%

IR (Nujol) : 1640, 1210, 1170, 1140, 1025, 1010, 980, 950, 875, 850, 810, 775 cm\textsuperscript{-1}

MS, m/e : 298(M\textsuperscript{+}), 297, 255, 226, 213, 151

2-Benzyl-6,8-diphenyl-5,6,7,8-tetrahydropyrido(4',3':4,5)-thieno(2,3-d)pyrimidin-4(3H)-one (839).

2-Amino-3-carbethoxy-6,8-diphenyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine was prepared by the following procedure:

To a mixture of 5.02g (0.02 mole) of 2,6-diphenylpiperidin-4-one, 736 2.26g (0.02 mole) of ethyl cyanoacetate and 0.72g (0.02 gatom) of sulfur in 100ml absolute ethanol was added dropwise with stirring 4ml of diethylamine. The mixture was stirred at room temperature for 8 hours and allowed to stand at 0°C for 48 hours. The solid obtained
was filtered, washed with cold ethanol and dried. Recrystallization from ethanol yielded 4g (53%) of crystalline product, m.p. 142-144°C.

Analysis : $C_{22}H_{22}N_2O_2S$ (378.48) Requires C, 69.81; H, 5.86%

Found C, 70.00; H, 6.08%

IR (Nujol) : 3480, 3340, 3200(NH); 1650, 1600, 1240, 1150, 1050, 945, 795, 760 cm$^{-1}$

MS, m/e : 378(M$^+$)

2-Amino-3-carbethoxy-6,8-diphyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine 3.78 (0.01 mole) was reacted with 1.30g (0.011 mole) of phenylacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 2.0g (45%) of crystalline product, m.p. 310-313°C(d).

Analysis : $C_{28}H_{23}N_3OS$ (449.55) Requires C, 74.80; H, 5.16%

Found C, 74.66; H, 5.34%

IR (KBr) : 3320(NH); 1670, 1595, 1500, 1460, 1425, 1410, 1285, 1210, 1200, 1080, 1070, 1040, 1030, 1000, 980, 835, 785, 770 cm$^{-1}$
Reaction of 2-(2-chloroethyl)-5,6,7,8-tetrahydrobenzo(b)-
thiено(2,3-d)pyrimidin-4(3H)-one with diethylamine

A mixture of 1.35g (5 mmole) of 2-(2-chloroethyl)-
5,6,7,8-tetrahydrobenzo(b)thiено(2,3-d)pyrimidin-4(3H)-one
(818) and 10ml of diethylamine was refluxed for 4 hours.
The reaction mixture was cooled to room temperature and
poured into crushed ice-water. The solid obtained was
filtered, washed with water and dried. Recrystallization
from ethanol yielded 0.9g (59%) of colorless crystalline
product, m.p. 168-170°C. The product obtained was
characterized as 2-(2-diethylaminoethyl)-5,6,7,8-tetra-
hydronbenzo(b)thiено(2,3-d)pyrimidin-4(3H)-one (840).

Analysis : C_{16}H_{23}N_{3}OS (305.43) Requires C, 62.91; H, 7.59%
Found C, 62.60; H, 7.42%
IR (Nujol) : 1660, 1590, 1290, 1230, 1200, 1150, 1135,
1110, 1070, 1030, 960, 900 cm^{-1}
NMR (CDCl_{3}) : δ 1.1(6H, t, CH_{3}); 1.83(4H, m, CH_{2} at 6 & 7);
2.48-3.0(12H, m, methylene protons)

Reaction of 2-(2-chloroethyl)-5,6,7,8-tetrahydrobenzo(b)-
thiено(2,3-d)pyrimidin-4(3H)-one with morpholine.

A mixture of 1.35g (5 mmole) of 2-(2-chloroethyl)-
5,6,7,8-tetrahydrobenzo(b)thiено(2,3-d)pyrimidin-4(3H)-
one (818) and 0.87g (0.01 mole) of morpholine in 30ml of dioxane was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured into crushed ice-water. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.2g (75%) of colorless crystalline product, m.p. 199–200°C. The product obtained was characterized as 2-(2-morpholinoethyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (841).

Analysis: \( C_{16}H_{21}N_3O_2S \) (319.42) Requires C, 60.16; H, 6.63%
Found C, 59.72; H, 6.47%

IR (Nujol): 1660, 1590, 1500, 1290, 1200, 1110, 1070, 1030, 1000, 960, 920, 865, 780 cm\(^{-1}\)

NMR (CDCl\(_3\)): \( \delta 1.93(4H, \text{ broad s, CH}_2\text{-at 6 & 7}); 2.6-2.98(12H, \text{ m, methylene protons}); 3.8(4H, \text{ m, CH}_2O-\text{CH}_2); 1277(1H, \text{ broad s, NH}) \)

4-Amino-2-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidine (842).

To a solution of 1.8g (0.01 mole) of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene in 30ml of acetonitrile was added 3.7ml of 10% solution of hydrogen chloride
in dioxane. The mixture was refluxed on a steam bath for 8 hours, cooled to room temperature and poured into 300ml of ice-water. The unreacted starting material that separated was filtered off and the aqueous mother liquor was cooled and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from benzene yielded 0.55g (25%) of the product, m.p. 224-226°C. The product obtained was found to be identical (mmp, TLC) with the compound obtained by the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)-thiophene with acetonitrile in the presence of excess of dry hydrogen chloride gas in 50% yield. 715,724

4-Amino-2-methyl-5,6,7,8-tetrahydrobenzo(b)thieno-(2,3-d)pyrimidine (842) was obtained in 46% yield by the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene with acetonitrile in the presence of excess of hydrogen bromide gas.

4-Amino-2-(3-pyridyl)-7-benzyl-5,6,7,8-tetrahydropyrido-(4',3';4,5)thieno(2,3-d)pyridine (843).

2-Amino-6-benzyl-3-cyano-4,5,6,7-tetrahydrothieno-(2,3-c)pyridine 737 2.69g (0.01 mole) was reacted with 1.15g
(0.011 mole) of nicotinonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from dimethylformamide-ethanol yielded 1.6g (43%) of crystalline product, m.p. 233-235°C.

Analysis: $C_{21}H_{19}N_5S$ (373.47) Requires C, 67.53%; H, 5.13%; Found C, 67.65%; H, 5.36%

IR (Nujol): 3370 (NH); 1620, 1570, 1530, 1500, 1140, 1110, 1050, 1025, 950, 855, 820, 780 cm$^{-1}$

MS, m/e: 373 (M$^+$), 282, 254

2-Methyl-4-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidine (844).

2-Amino-3-benzoyl-4,5,6,7-tetrahydrobenzo(b)thiophene 718 2.57g (0.01 mole) was reacted with excess of acetonitrile (30ml) in the presence of dry hydrogen chloride gas according to the procedure described for 815. Recrystallization from ethanol yielded 1.5g (54%) of crystalline product m.p. 118-120°C. Reported m.p. 115-116°C. 726
Analysis : \( C_{17}H_{16}N_2S \) (280.38) Requires C, 72.82; H, 5.75%
Found C, 73.02; H, 5.07%

IR (Nujol) : 1560, 1520, 1260, 1170, 1035, 925, 855, 830, 800, 765 cm\(^{-1}\)

MS, m/e : 280(M\(^+\)), 279, 251, 238, 219, 211, 177

2-Carbethoxymethyl-4-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno-(2,3-d)pyrimidine (845).

2-Amino-3-benzoyl-4,5,6,7-tetrahydrobenzo(b)thiophene 718 2.57g (0.01 mole) was reacted with 1.25g (0.011 mole) of ethyl cyanoacetate in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol yielded 2.0g (57%) of crystalline product, m.p. 82-84°C.

Analysis : \( C_{20}H_{20}N_2O_2S \) (352.44) Requires C, 68.15; H, 5.72%
Found C, 68.08; H, 5.81%

IR (Nujol) : 1730, 1550, 1510, 1210, 1160, 1040, 960, 870, 850, 775 cm\(^{-1}\)

MS, m/e : 352(M\(^+\)), 324, 307, 280, 251, 250, 211, 176
2-Chloromethyl-4-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine (846).

2-Amino-3-benzoyl-4,5,6,7-tetrahydrobenzo(b)thiophene 718 2.57g (0.01 mole) was reacted with 0.35g (0.011 mole) of chloroacetonitrile in 30ml of dioxane in the presence of dry hydrogen chloride gas according to the procedure described for 816. Recrystallization from ethanol yielded 1.6g (51%) of crystalline product, m.p. 144-146°C.

Analysis : C₁₇H₁₅N₂SCl (314.83) Requires C, 64.85%; H, 4.30%
Found C, 64.75%; H, 5.09%

IR (Nujol) : 1540, 1510, 1285, 1260, 1170, 1035, 970, 865, 855, 830, 775 cm⁻¹

MS, m/e : 316, 314(M⁺), 313, 299, 285, 279, 251, 250

Reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene with ethyl cyanoacetate in the presence of sodium ethoxide

To a solution of sodium ethoxide (0.02 mole), prepared by dissolving 0.46g of sodium in 30 ml of absolute ethanol was added 2.25g (0.01 mole) of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene, 718 followed by 1.13g (0.01 mole)
of ethyl cyanoacetate. The mixture was refluxed for 12 hours, cooled to room temperature, diluted with 50ml of ice-water and filtered. The filtrate was cooled and acidified with 10% hydrochloric acid. The solid obtained was filtered, dried in air and extracted twice with 20ml of boiling dioxane. The dioxane insoluble material on recrystallization from dimethylformamide-ethanol yielded 1.2g of colorless crystalline product, m.p. 321-323°C(d). The product was characterized as 3-cyano-2,4-dihydroxy-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-b)-pyridine (847).

Analysis

\[ C_{12}H_{10}N_{2}O_{2}S(246.28) \]

Requires C, 58.52; H, 4.09%

Found C, 58.65; H, 4.09%

IR (KBr)

3480 broad(OH); 3130, 2230(\text{C=}N), 1620, 1575, 1540, 1450, 1385, 1285, 1240, 1050, 970, 840, 810, 765, 740 cm\textsuperscript{-1}.

UV (MeOH)

214nm(\text{log }€ 4.29), 232(4.31), 244(4.36), 254(4.38), 286sh(3.84)

MS, m/e

246(M\textsuperscript{+}), 231, 218, 205, 190, 178, 162, 151

Reaction of 2-amino-3-carbethoxy-4,5-dimethylthiophene with ethyl cyanoacetate in the presence of sodium ethoxide.

2-Amino-3-carbethoxy-4,5-dimethylthiophene 1.99g (0.01 mole) was reacted with 1.13g (0.01 mole) of ethyl...
cyanoacetate in the presence of 0.02 mole of sodium ethoxide according to the procedure described for 847. Recrystallization from dimethylformamide-ethanol yielded 1.0g of colorless crystalline product, m.p. 325-327°C(d). The product was characterized as 5-cyano-2,3-dimethyl-4,6-dihydroxythieno(2,3-b)-pyridine (848).

**Analysis**

$\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}(220.25)$ Requires C, 54.53; H, 3.66%  

Pound C, 54.39; H, 3.67%

**IR (Nujol)**

3140, 2220(\text{C=\text{N}}); 1650, 1580, 1535, 1500, 1280, 1225, 1140, 1095, 1000, 940, 890, 840, 770 cm$^{-1}$

**UV (MeOH)**

$213\text{nm}(\log \varepsilon 4.35), 245(4.40), 252(4.42)$,

$285(3.84)$

**MS, m/e**

$220(\text{M}^+)$, 205, 192, 187, 180, 164, 153, 138, 125, 110

**Reaction of 2-amino-3-carbethoxy-4-phenylthiophene with ethyl cyanoacetate in the presence of sodium ethoxide.**

2-Amino-3-carbethoxy-4-phenylthiophene $\text{CH}_3$ 

(0.01 mole) was reacted with 1.13g (0.01 mole) of ethyl cyanoacetate in the presence of 0.02 mole of sodium ethoxide in absolute ethanol according to the procedure described for 847.
Recrystallization from dimethylformamide-ethanol yielded 1.0g of crystalline product, m.p. 245°-247°C (d). The product was characterized as 5-cyano-4,6-dihydroxy-3-phenylthieno(2,3-b)pyridine (849).

**Analysis**

\[ C_{14}H_{8}N_{2}O_{2}S (268.29) \] Requires C, 62.67%; H, 3.01%

Found C, 62.47%; H, 3.25%

**IR (Nujol)**

2240 (C=O); 1710, 1640, 1580, 1520, 1275, 1225, 1200, 1170, 1070, 1005, 945, 855, 838, 765 cm⁻¹

4-Amino-2-methyl-5,6,7-triphenylpyrrolo(2,3-d)pyrimidine (850).

2-Amino-3-cyano-1,4,5-triphenylpyrrole\(^7\) 3.35g (0.01 mole) was reacted with excess of acetonitrile (30mL) in the presence of dry hydrogen chloride gas according to the procedure described for 815. Recrystallization from dimethylformamide yielded 2.25g (60%) of crystalline product, m.p. 287°-289°C.

**Analysis**

\[ C_{25}H_{20}N_{4} (376.44) \] Requires C, 79.76%; H, 5.36%

Found C, 79.56%; H, 5.53%

**IR (KBr)**

3480, 3300 (NH); 1645, 1585, 1560, 1500, 1350, 1310, 745 cm⁻¹
Reaction of 5-amino-4-carbethoxy-3-methylisothiazole with acetonitrile

5-Amino-4-carbethoxy-3-methylisothiazole (851) was prepared by the following procedure:

A mixture of 5.16g (0.02 mole) of 4-carbethoxy-5-(ethoxycarbonylamino)-3-methylisothiazole,200 6.65g (0.05 mole) of aluminium chloride and 60ml of benzene was refluxed on a steam bath for 8 hours. The mixture was cooled and decomposed with ice-water containing dilute hydrochloric acid. The organic layer was separated, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue on recrystallization from cyclohexane yielded 1.0g (27%) of colorless crystalline product, m.p. 113-115°C. Reported m.p. 113.5°C.200

Analysis: C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S (186.23) Requires C, 45.14% H, 5.41% Found C, 45.45% H, 5.55%

IR (Nujol): 3420, 3310(NH); 1655, 1590, 1500, 1420, 1470, 1330, 1265, 1130, 1080, 1020, 1000, 780 cm<sup>-1</sup>

UV (MeOH): 222nm(log ε 4.52), 266(4.01)

NMR (CHCl<sub>3</sub>): 6 1.36(3H, t, COOCH<sub>2</sub>CH<sub>3</sub>); 2.48(3H, s, CH<sub>3</sub> at C-3); 4.3(2H, q, COOCH<sub>2</sub>CH<sub>3</sub>); 6.43(2H, broad s, NH<sub>2</sub>)
A stream of dry hydrogen chloride gas was passed through a solution of 0.75g (4 mmole) of 5-amino-4-carbethoxy-3-methylisothiazole in 25ml of acetonitrile for 8 hours. The mixture was allowed to stand at room temperature for 12 hours and refluxed on a steambath for 8 hours. Excess of acetonitrile was removed under reduced pressure, and the residue was triturated with ice-cold aqueous sodium bicarbonate solution. The solid obtained was filtered, washed with water and dried. Recrystallization from cyclohexane yielded 0.6g of crystalline product, m.p. 113-115°C, identified as the unreacted starting material.

**Reaction of 2-amino-3-carbethoxy-4,6-dimethylpyridine with acetonitrile.**

A stream of dry hydrogen chloride gas was passed through a solution of 2.08g (0.01 mole) of 2-amino-3-carbethoxy-4,6-dimethylpyridine739 in 30ml of acetonitrile for 10 hours. The reaction mixture was allowed to stand at room temperature for 12 hours, refluxed gently on a steambath for 6 hours, cooled and poured onto 300ml of ice-water and
basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 1.5g of the product m.p. 110-112°C, identified as the unreacted starting material.

6-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (852).

A stream of dry hydrogen chloride gas was passed through a mixture of 2.86g (0.01 mole) of 4-amino-6-chloro-1,3-benzenedisulfonamide in 50ml of acetonitrile for 8 hours. The reaction mixture was allowed to stand at room temperature for 12 hours and refluxed for 8 hours on a steambath. Excess of acetonitrile was removed under reduced pressure. The residue was triturated with water and the solid obtained was filtered, washed with water and dried. Recrystallization from ethanol-water yielded 2.3g (74%) of colorless crystalline product, m.p. 337-339°C(d), Reported m.p. 332°C(d).740

Analysis: C₈H₆N₃O₄S₂Cl(309.76) Requires C, 31.02; H, 2.60%; Found C, 31.40; H, 2.88%

IR (KBr): 3450, 3350(NH); 1650, 1550, 1325, 1175, 1100, 1150, 950, 900, 860, 810 cm⁻¹

MS, m/e: 311, 309(M⁺), 293, 270, 268, 251, 204, 190, 188, 187, 150, 104