Sulfur and its inorganic salts have been used in medicine since ancient times. Role of sulfur containing organic compounds including thiophene derivatives as drugs has been extensively reviewed.\(^1\)

Thiophene was discovered in 1882 through accident when Victor Meyer was demonstrating indophenine test for benzene, who confirmed its structure by synthesis.\(^2\) Thiophenes can be synthesized from succinic anhydride,\(^3\) succinaldehyde\(^4\) or sodium succinate\(^3\) and phosphorous pentasulfide. On the other hand, 1,4-diketones when reacted with phosphorous trisulfide or pentasulfide give substituted thiophenes\(^5\) (Eq. I).

\[
\begin{align*}
R_2 & \quad R_3 \\
R_1-\text{CO-CH-CH-} & \quad \text{CO-R}_4 \\
P_2S_3/P_2S_5 \rightarrow \quad \text{Thiophene ring} \\
\end{align*}
\]

\(\text{... (Eq. I)}\)

In 1910, Wilhelm Steinkoff undertook a study of thiophene chemistry which lasted several decades culminating in the publication of the first monograph\(^6\) on thiophene chemistry. A commercial synthesis\(^7\) of thiophene from butane and sulfur was perfected in 1946. As a result, an extensive industrial research and development of thiophene compounds followed.\(^8\) This process is essentially a dehydrogenation of \(n\)-butane in presence of sulfur, followed by cyclization to form thiophene ring. The reaction is believed to proceed stepwise with conversion of butane to butene, butadiene and finally to thiophene. Thiophenes are also synthesized from acetylene,\(^9\) olefins\(^10\) or other hydrocarbons\(^11\) with sulfur or \(H_2S\).
THIOPHENE COMPOUNDS IN NATURE

Thiophene and its homologs exist in products derived from natural sources like petroleum, lignite, coal and shale oil. However, there is no definite proof that thiophene compounds actually exist as such in these natural products. Apparently, they are the end products of thermal or catalytic treatment of carbonaceous deposits.

Occurrence of thiophene derivatives in plants was first reported by Zechmeister and Sease in 1947. A blue fluorescent compound, isolated from African marigold, *Tagetes erecta*, was proved to be terthiienyl (1). This was followed by the isolation of Junipal thiophene aldehyde (2), from *Daedalea juniperina* (basidiomycete). Its structure has been confirmed by Schulte et al. using the biogenetically significant method of H₂S addition to a polyacetylene compound. Two more thiophene derivatives viz., 2-lactoyl-5-(prop-1-ynyl) thiophene and 2-(prop-1-ynyl)-5-pyruvoylthiophene have been isolated from the same fungus.
Sorensen isolated 2-phenyl-5-(α-propynyl)thiophene from *Coreopsis grandiflora*. Thiope derivative (3), the main acetylene constituent of *Calocephalus citreus*, has yielded bithienyl compound (4a) by the addition of $H_2S$ under the experimental conditions of Schulte. 5-Buten-(3)-yn(1)-yl-2,2'-bithienyl (4b) is the nematocidal principle of *Tagetes* species, isolated by Uhlenbrock and Bijloo.

\[
\begin{align*}
\text{(5)} & \quad \text{R} = \text{CH}_3\text{CSC, -CSC-CHO, CH}_2\text{COOH}_3 \quad \text{R} = \text{H or CH}_3 \\
\text{R} = \text{-CSC.CH}_2\text{OH, -CHO, -CH}_2\text{OH, etc.} & \quad \text{R}_1 = \text{OH, R}_2 = \text{H} \\
\text{R}_1\text{R}_2 = 0 & \\
\end{align*}
\]

Bohlmann et al. have carried out an extensive study of naturally occurring acetylenic compounds. They have isolated sixteen new biogenetically closely related thiophene derivatives from *Eclipta erecta*. Thiophene derivatives previously found in nature are also present in *Coreopsis verticillata*. 2-Formyl-α-terthienyl has been isolated from *Eclipta alba*. Recently, a number of thiophene derivatives (5) and dihydro derivatives (6) have been

\[
\begin{align*}
\text{(7)} & \quad \text{H}_3\text{C-CSC-CSC-CH=C} & \quad \text{H}_3\text{C-CSC-CSC-S} \\
\text{(8)} & \\
\end{align*}
\]
isolated from plants belonging to the genus *Berkheya*. Structure of a novel thiophene compound 7 isolated from *Berkheya barbata* has been confirmed by synthesis. Earlier, it was assigned structure 8. Recently, the structure of thiophenes 9 isolated from *Berkheya* species has been established by synthesis.

Literature survey reveals that more than 200 thiophenes have been isolated from plants mostly from compositae family. In general, thiophenes isolated are 2,5-disubstituted, of which at least one is an acetylene moiety. Since they are always present in these plants along with polyacetylene compounds, it is believed that thiophenes are synthesized in plants from polyacetylene compounds by the addition of $H_2S$. However, the exact mechanism is not clear.

ISOSTERISM

The close similarity in physical properties of thiophene and benzene and their corresponding derivatives has been the subject of much speculation (Table 1).
<table>
<thead>
<tr>
<th>Property</th>
<th>Thiophene</th>
<th>Benzene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. wt.</td>
<td>84.14</td>
<td>78.11</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Colorless</td>
</tr>
<tr>
<td>M.P. ($^\circ$C)</td>
<td>-38.30</td>
<td>5.5</td>
</tr>
<tr>
<td>B.P. ($^\circ$C; 760 mm)</td>
<td>84</td>
<td>80.1</td>
</tr>
<tr>
<td>Refr. index ($n_D^{20}$)</td>
<td>1.5287</td>
<td>1.5011</td>
</tr>
<tr>
<td>Parachor</td>
<td>187.4</td>
<td>192.1</td>
</tr>
<tr>
<td>Dipole moment (D)</td>
<td>0.54</td>
<td>0</td>
</tr>
<tr>
<td>Density ($20^\circ$C)</td>
<td>1.06494</td>
<td>0.87865</td>
</tr>
<tr>
<td>Flash point ($^\circ$C)</td>
<td>-38.3</td>
<td>-11.1°</td>
</tr>
<tr>
<td>Solubility</td>
<td>Insoluble in water, miscible with most org. solvents.</td>
<td>Insoluble in water, miscible with most org. solvents.</td>
</tr>
<tr>
<td>Resonance energy (Kcal/M)</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Molar refraction</td>
<td>24.3</td>
<td>26.1</td>
</tr>
</tbody>
</table>
A closer look at the electronic structure of thiophene provides a possible explanation for the similar physical properties to those of benzene. There is good evidence that the sulfur atom is able, in certain cases, to expand its outer electron shell to ten electrons by participation of its 3d orbitals. Shoemaker and Pauling suggested that the structure of thiophene can be represented as the hybrid of the following resonance forms (A - E).

Forms F-H are possible owing to the capacity of the sulfur atom to use its d orbitals. Molecular orbital treatment of thiophene seems to provide good qualitative justification of this picture of d orbitals participation. Hybridization of 3pz, 3dz, 3dyz orbitals of the sulfur atom produces three new pd orbitals. One of these orbitals is an unoccupied high energy form. The other 2pd orbitals are localized along the S-C bond and each has surprising resemblance to a orbital of carbon. Thus, there arises a physical picture of a possible structure for thiophene in which the sulfur atom shows a rare electronic similarity to a combination of two aromatic carbon atoms.

Erlenmeyer and his co-workers extended the concept of isosterism as developed for inorganic compound by Langmuir and Grimm to organic
substances, particularly to those of thiophene series. In Erlenmeyer's concept of isosterism, the vinylene group (-CH=CH-) of an aromatic ring and S atom of the thiophene ring are considered isosteric by virtue of each group having the same number of binding electrons. Today, isosters are interpreted to mean every nuance from similarity of outer electron shells to similarity in location of high or low electron density regions in molecules of analogous size and shape. In other words, molecules having similar electron density distribution and similar steric configuration may be called isosters.

BIOISOSTERISM

The first indication that isosters can have similar physiological properties was provided through immunological studies by Erlenmeyer. It was demonstrated that the isosters, p-aminodiphenylamine (10a), p-aminodiphenylmethane (10b) and p-aminodiphenylether (10c) show similar antigen activity.

\[ \text{a; } X = -\text{NH}_2 \]
\[ \text{b; } X = -\text{CH}_3 \]
\[ \text{c; } X = -\text{O} \]

\[ \text{(10)} \]
The following isoster pairs (11 and 11a, 12 and 12a) were also oerologically indistinguishable.

(12)  
\[ \text{H}_2\text{N}-\text{NHCO}-\text{phenyl} \]

(12a)  
\[ \text{H}_2\text{N}-\text{NHCO}-\text{pyrrole} \]

This remarkable piece of work helped to bring out the potentialities of isosterism in the field of medicinal chemistry and led to the development of the concept of 'bioisosterism'. Thus, today, the most frequent use of isosters occurs in the field of medicinal chemistry where their biological similarity is expressed in the term 'bioisosterism'.

Friedman\textsuperscript{46} defined the word 'bioisosterism' for application to compounds which "fit the broadest definition for isosters and have the same type of biological activity". Isosters with antagonistic activity may also be considered as bioisosters, since they may be regarded as acting by similar mechanism at least up to a certain point. According to Ariens,\textsuperscript{47} bioisosteric groups have equal influence on lipid solubility and/or charge distribution (equal molar values) and with equal steric properties. Moreover, such information yields clues to the mechanism of action of a drug molecule.\textsuperscript{49,50} With the information thus obtained, a medicinal chemist is in a position to prepare more effective, specific and safer drugs.
THIOPHENE BIOISOSTERS

The concept of bioisosterism has been fully exploited and justified in the synthesis of thiophene analogs of established drug molecules.\(^8,48\)

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
\text{(13)} & \quad \text{(13a)} \\
\end{align*}
\]

The earliest example\(^51\) is the thiophene analog (13) of cinchonic acid (13a).

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{(14)} & \quad \text{(15)} \\
\end{align*}
\]

The 2-thienyl analog (13) possesses greater antiphlogistic and analgesic properties than cinchonic acid (13a). However, it was found to be toxic. Thiophene isosters of cocaine,\(^52\) atropine,\(^54\) \&-eucaine\(^53\) and phenacetin\(^53\) have been prepared by Steinkof and his co-workers. These analogs were found, in general, to have activity comparable to that of parent drug molecule. Thiophene analogs of methadone and isomethadone are found to be active as analgesics.\(^55\) Earlier work on thiophene derivatives and bioisosterism has been extensively reviewed.\(^8,48\)
β-2-Thienyl alanine (14) and its 3-isomer (15) have long been recognised as antagonists of phenylalanine in both microbial and mammalian systems. It has been observed that L-isomer of 14 and 15 inhibits the growth of S. cerevisiae and L. delbrueckii. 56

Peptides containing 2- and 3-thienyl-dl-alanine units have been synthesized. 57 These peptides are more potent inhibitors of bacterial growth than thienylalanine itself. 57, 58 Thi enylalanine has been used to replace histidine in angiotensin II 59 and tyrosine 60 in hexapeptide fragment of angiotensin II. The most potent bradykinin analog, 5,8-bis(thienylalanine) bradykinin is ten times as active as bradykinin in rat uterus and rat blood pressure assays. 61

Recently, 2-thienylalanine has been used orally to reduce serum levels of phenylalanine in phenylketonuria condition. 62

![Chemical structures](image)

In a series of N, N-substituted 1-arylcyclohexylamines synthesized as analogs of phenylcyclidine (16a), thienyl derivative (16a) was found to be the most active compound having sedative properties. 63
N-Thienylmethyl-6,7-benzomorphan (17) and morphinan (17a) and their salts are found to be narcotic antagonists.\textsuperscript{64,65}

\[
\begin{align*}
\text{(17)} & \quad R_1 = 2\text{-} or 3\text{-thienylmethyl} \\
\text{(17a)} & 
\end{align*}
\]

Thiophene analogs (19a, 19b) of mefenamic acid (18a) and meclofenamic acid (18b) have exhibited antiinflammatory activity.\textsuperscript{66}

\[
\begin{align*}
\text{(18)} & \quad X = 2,3\text{-}(\text{CH}_3)_2 \\
\text{(19)} & \quad X = 3\text{-Cl, 2\text{-CH}_3} \\
\text{a; } & X = 2,3\text{-}(\text{CH}_3)_2 \\
\text{b; } & X = 2,6\text{-Cl}_2
\end{align*}
\]

With a view to improve upon the hypnotic sedative activity of methaqualone (20), several thiophene analogs (20a, 20b, 20c) have been prepared.\textsuperscript{67,68} Compound 20c showed antispasmodic activity equal to methaqualone HCl at the same dosage level with LD\textsubscript{50}, 23 to 45mg/kg i.p. vs 23mg/kg for methaqualone hydrochloride.\textsuperscript{69}

\[
\begin{align*}
\text{(20)} & \\
\text{(20a)} & 
\end{align*}
\]
Recently, synthesis of a series of thiophene analogs of tricyclic antidepressants have been described. Thiophene analog (21) of amitriptyline (21a) as a mild tranquilizer gave good results in about 80% patients. The analogs (22a and 22b) have been tested as inhibitors of neuronal reuptake of noradrenaline and 5-hydroxytryptamine. These compounds inhibit reserpine induced hypothermia. Thiophene analogs have activities similar to the parent compounds but are less potent. Preliminary reports on the potent serotonin inhibitor and
antihistaminic agent (23), an analog of cyproheptadine (23a), are encouraging. Heteroanalog (24) exhibits a significant antirepacrine effect.

Erythro and threo analogs (25a and 25b) of ephedrine have been synthesized and evaluated pharmacologically. Erythro 2-thienyl analog (25a) showed one third activity of (-)ephedrine; whereas, threo diastereoisomer (25b) was found to be totally inactive. Thiophene analog (26) of diethylpropion (26a) has anorexigenic activity comparable to amphetamine with much less CNS stimulation.
Extensive literature\textsuperscript{77} has accumulated on thiophene analogs of known antihistaminic drugs in view of the fact that for a long time three thiophene derivatives have been in use as antihistaminic drugs.

Replacement of phenyl group by 2-thienyl moiety produces the drug methaphenilene\textsuperscript{78} (27a) which is usually less sedative than antergan\textsuperscript{78,79} (28a). Methapyrilene (27b) is closely related in activity and toxicity to tripelenamine\textsuperscript{78,80} (28b).

\begin{align*}
\text{Antihistaminic activity increases and toxicity decreases by} \quad & \text{chlorination of thiophene nucleus.}\textsuperscript{81} \quad \text{The chloro derivative}\textsuperscript{82} \text{is} \\
& \text{used in therapy as chlorotheylpyramine (27c).}
\end{align*}
Replacement of benzene by thiophene ring system in diazepam molecule (29) has resulted in thienodiazepinone (30a) which is 2-3 times more active as tranquilizer. At least one thienyl isoster of diazepam (30b) is undergoing clinical trials.

There seems to be no slackening in the interest of medicinal chemist with regard to isosteric relationship of thiophene to known biologically active agents, in spite of the earlier reservations. Thus, bioisosterism has proved to be one of the important approaches to drug design.
THIOPHENE SYNTHESSES

Earlier work on the synthesis of thiophene has been reviewed exhaustively up to 1962. Recently, a brief review has appeared summarizing literature up to 1970.

Smutny has described a novel synthesis of 2,5-disubstituted thiophenes (32) from amino dithioacrylates (31) and α-halocarboxyl compounds in acetone in the presence of a basic catalyst. The proposed mechanism involves initial nucleophilic displacement of bromine from ethyl bromoacetate to form salt 31a. Triethylamine base converts the salt to sulfur ylide (31b) which undergoes intramolecular cyclization to form dihydrothiophene (31c). Loss of morpholine results in the formation of thiophene derivative (32).

Simultaneously, Rajappa and his co-workers described a two step synthesis of multi-substituted thiophene, mechanistically bearing a close resemblance to the synthesis described by Smutny.
A suitable enamine like $\beta$-amino-$\alpha$, $\beta$-unsaturated carbonyl derivative reacts with an isothiocyanate to form 1:1 adduct (Eq. II).

$$\text{CH}_3-\text{C}=\text{CH}-\text{C}_2\text{H}_5 + R_2\text{N=C=S} \rightarrow \text{CH}_3-\text{C}=\text{C}_2\text{H}_5$$

(Eq. II)

This is followed by reaction with an $\alpha$-haloketone to yield thiophene derivative (Eq. III). The reaction is carried out by refluxing

$$\text{CH}_3-\text{C}=\text{C}_2\text{H}_5 + \text{C}_6\text{H}_5-\text{C}=\text{CH}_2-X \rightarrow \text{C}_6\text{H}_5-\text{S}=\text{C}=\text{CH}_2$$

(Eq. III)

$R_2$ = alkyl, aryl or acyl.

$R_1$ = $-\text{OC}_2\text{H}_5$; $\text{CH}_3$

equimolecular quantities, without addition of any base and is completed within 30 minutes. The yield ranges from 30 to 90%. Thus, benzoyli- isothiocyanate reacts with ethyl-$\beta$-aminocrotonate (33) to give an adduct (33a). Nucleophilic attack of the sulfur on phenacyl bromide yields salt 33b. Active methylene group in the intermediate 33b
adds to the imine system, followed by elimination of ammonia

\[ \text{CH}_3\text{C} = \text{C} - \text{C} - \text{CO}_2\text{R} \quad \text{(33c)} \]

\[ \text{ArC} = \text{C} - \text{C} - \text{CO}_2\text{R} \quad \text{(34)} \]

(as ammonium bromide) from 33c to yield 34. In a similar manner, enamine adducts like 35a and 36a react with phenacyl bromide to

\[ \text{CO}_2\text{C}_6\text{H}_5 \quad \text{(35)} \]

\[ \text{C} - \text{NH}_2 \quad \text{(35a)} \]

\[ \text{CO}_2\text{C}_6\text{H}_5 \quad \text{(36)} \]

\[ \text{C} - \text{NH}_2 \quad \text{(36a)} \]
produce cyclopentanothiophene (35) and cyclohexanothiophene (36) derivatives. The scope of this general reaction has been extended by using ethyl α-chloroacetoacetate instead of α-haloketones. Further, the reaction has been employed to synthesize thiophene analogs of fenamic acids. Thiophene-3-carboxylic acid (37a) is obtained from the corresponding t-butyl ester (37) in the presence of trifluoroacetic acid at 0°C. At higher temperatures, the carboxylic acid gets decarboxylated to yield 2-substituted aminothiophenes (37b).

Another closely related thiophene synthesis starts from monothio-β-diketones (38). Triethylamine catalyzes reaction between 38 and α-halogenocarbonyl compound, such as phenacyl bromide, to yield 38a which cyclizes to dihydrothiophene derivative (38c) through a carbanion intermediate (38b). On boiling 38c with methanolic HCl, thiophene ring system (39a) is obtained in quantitative yield. The
scope of this reaction has been extended by the use of ethyl-\(\alpha\)-bromoacetate to yield \(39b\).

\[
\begin{align*}
R_1\text{-C-CH}_2\text{-C-} & \text{- C}_6\text{H}_5 \\
\text{S} & \text{ O}
\end{align*}
\]

\(38\)

A number of thiophene derivatives have been synthesized using ethylene-1, 1-dithiolates \((40)\). Stable dianions of the dithio acids bearing one or two strongly electron attracting substituents on C-2 have been called dithiolates.\(^{92}\) In presence of a base, compounds containing active methylene groups (ethyl cyanoacetate, \(\omega\)-cyanoacetophenone, nitromethane, etc.) react with \(\text{CS}_2\) probably through a carbanion intermediate (Eq. IV). Thus treatment of 2-nitroethylene-1,
1-dithiolate (41) with α-halogenoaldehydes or ketones leads to the formation of 3-nitrothiophene-2-thiols (42). The initial formation of the 1-(acylmethylthio)-2-nitroethylene (41a) presumably proceeds very rapidly. The cyclization is visualized as an electrophilic attack of the carbonyl carbon atom on the C-2 of 41a, the latter atom serving as the nucleophilic center. Since the addition of acids accelerates the rate of cyclization, the acid must be required for the protonation of the carbonyl group. However, the thiol (42) is isolated as S-alkylated compound (42b) or as an oxidation product (42a).

In presence of sodium methoxide in methanol, alkylated dithiolate (43) cyclizes to give a mixture of 4-aminothiophene (44) and...
4-hydroxythiophene\textsuperscript{93} (44a), the later being soluble in a base, can be separated from 44. Transesterification, due to solvent methanol, appears to be responsible for the formation of methyl ester (44) instead of ethyl ester. On the other hand, when dithiolate (45), obtained from

\[
\begin{align*}
&\text{HO} &\text{CN} \\
&\text{CH}_3-O- &\text{SCH}_3
\end{align*}
\]

(44a)

\[
\begin{align*}
&C_6H_5-O- &\text{C} &\text{CN} \\
&C_6H_5 &\text{S} &\text{S} \\
&\text{H}_2 &\text{S} &\text{CH}_2-C-OCH_3
\end{align*}
\]

(45a)

\[
\begin{align*}
&\text{CH}_3-O- &\text{C} &\text{S} &\text{CH}_2-C-OCH_3 \\
&\text{H}_2 &\text{S} &\text{CH}_2-C-OCH_3
\end{align*}
\]

(46)

o-cyanoacetophenone, is reacted with 2 molecules of methyl chloroacetate, \(46\) is obtained directly, probably through Diels-Alder type cyclization of the intermediate \(45a\). \textsuperscript{93a}

Gompper et al\textsuperscript{94} were one of the first to synthesize thiophenes (48) by reacting dithiolates (47) with \(\alpha\)-halogeo derivative (47a) in presence of a basic catalyst via intermediate (47b). Recently, thiophenecarboxamides

\[
\begin{align*}
&Y &\text{CN} &\text{Na} &\text{S} &\text{C-S} &\text{Na} \\
&\text{H}_2 &\text{N} &\text{Y} &\text{S} &\text{CH}_3 &\text{Z} \\
&\text{H}_2 &\text{N} &\text{Y} &\text{S} &\text{CH}_3 &\text{Z}
\end{align*}
\]

(47)

(47a)

(47b)

(48)

(49)

(50)
(49 and 50) have been synthesized from 2-cyanoethylene-1,1-dithiolates under similar conditions.\textsuperscript{95}

Laliberte and Medawar\textsuperscript{96} have synthesized selectively 2-amino-3-thiophene esters and amides (52) from 3-amino-2-cyano-3-thioacrylic esters and amides (51\(b\)). The base catalyzed reaction between

![Chemical structure image]

isothiocyanate (RN=C=S) and derivatives of cyanoacetic acid (51) yields 51\(a\) which when condensed with \(\alpha\)-halomethyl ketones affords 51\(b\). This cyclizes to give iminothiophene (51\(c\)); presumably via carbanion intermediate.

4-Iminothiophene (51\(c\)) stabilizes immediately to aromatic structure 4-aminothiophene (52). However, stable 4-imino thiophenes\textsuperscript{97} (53) can be synthesized by reacting 3-amino-2-cyano-3-mercapto acrylhydrazides (53\(a\)) with \(\alpha\)-haloketones like 2-bromo-butanone.
A new synthesis of thiophene has been proposed involving 1,3-dipolar cyclo addition of mesionic compounds with acetylenic dipolarophiles. Thus, 2,4-diphenyl-anhydro-5-hydroxy-1,3-dithiolium hydroxide (54) adds to dimethyl acetylene dicarboxylate to give tetra substituted thiophene (55) with loss of carbonyl sulfide via 1,3-dipolar cycloaddition intermediate 54a. Isothiazolium salt (56) when reacted

\[ \text{54a} \]

\[ \text{55} \]
with sodium benzoyl acetate gives 2-benzoyl thiophene \textsuperscript{100} (57).

Nucleophilic attack of phenacyl ion on ring sulphur of (56) opens

\[
\text{(56)} \quad \text{R}_3 = H
\]

\[
\text{(56a)}
\]

\[
\text{(56b)}
\]

\[
\text{(56c)}
\]

the ring to give (56a). Attack of the activated methylene group on the imine function (56b), results in recyclization to the dihydrothiophene (56c) which stabilizes to give aromatic structure \textsuperscript{57} with loss of amine.

Six decades ago, Hinsberg\textsuperscript{101,102} described the reaction between benzil and diethyl thiodiacetate to produce thiophene ring system (Eq. V). The reaction proved to be quite general with all \(\alpha,\alpha\)-diketo compounds,\textsuperscript{103} However, there has been some confusion about the final

\[
\text{(58)}
\]

\[
\text{(59)} \quad \text{R}^\prime = \text{Et, Me.}
\]

\[
\text{(60)}
\]
product obtained. Wynberg\textsuperscript{104} has very elegantly cleared the confusion by proving that the product obtained is half acid, half ester thiophene derivative (60) and not the 2,5-diester as reported earlier.\textsuperscript{105} It has been shown that the reaction between $\alpha,\alpha$-diketones (58) and thio-diacetates (59) yielding thiophenes (60) proceeds via $\delta$-lactone intermediate. Using $^{18}$O benzil, it was shown that the half ester acid is formed by non-hydrolytic route.

\begin{align*}
C_6H_5-C-C-C_6H_5 & \\
\text{(61)}
\end{align*}

\begin{align*}
\text{EtO} - C - CH_2 & \quad S \\
\text{(-)} & \quad HC
\text{COOEt}
\end{align*}

\begin{align*}
\text{(62)}
\end{align*}

\begin{align*}
\text{EtO} - C - C_6H_5 & \\
\text{(63)}
\end{align*}

\begin{align*}
\text{(63a)}
\end{align*}

\begin{align*}
\text{(63b)}
\end{align*}

\begin{align*}
\text{(63c)}
\end{align*}

\begin{align*}
\text{(64)}
\end{align*}
Initial condensation of thiodiacetate (62) with benzil (61) in presence of a base gives 63 followed by δ-lactone (63b) formation through the intermediate 63a. Opening of the lactone ring furnishes the unsaturated half acid ester (63c) which then cyclizes through Stobbe-type condensation to yield thiophene ring (64). Hinüberg reaction has been used to prepare a series of 3,4-disubstituted thiophene-2-carboxylates (65) and 2,5-dicarboxylates (66).^106

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_1 \\
\text{R}_2 & \quad \text{R}_2 \\
\text{C-O} & \quad \text{C-O} \\
\end{align*}
\]

(65)

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_1 \\
\text{R}_2 & \quad \text{R}_2 \\
\text{C-O} & \quad \text{C-O} \\
\end{align*}
\]

(66)

\[
\begin{align*}
\text{R}_1 = \text{Me}, \text{Ph}, \text{p-MeOC}_6\text{H}_4 \\
\text{R}_2 = \text{H}, \text{Me}, \text{Et}, \text{Bu}
\end{align*}
\]

Thiophene derivatives were obtained in higher yields by Chakrabarti et al.,^107 when one mole of chlorine (instead of I₂) in anhydrous carbon tetrachloride was employed to cyclize buta-1,3-diene-1-thiols (67). The mechanism of this oxidative ring closure has been studied in detail.^108 It is postulated that in aprotic solvents, chlorine transforms thiols into a sulfonyl chloride (67a) which then cyclizes to thiophene derivative (68) through intermediate (67b).

\[
\begin{align*}
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\text{C} & \quad \text{C} \\
\text{HC} & \quad \text{HC} \\
\text{HS} & \quad \text{HS} \\
\text{C-O} & \quad \text{C-O} \\
\text{COOH} & \quad \text{COOH} \\
\text{Cl} & \quad \text{Cl} \\
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\end{align*}
\]

(67)

\[
\begin{align*}
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{COOH} & \quad \text{COOH} \\
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\end{align*}
\]

(67a)

\[
\begin{align*}
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{COOH} & \quad \text{COOH} \\
\text{H}_5\text{C}_6 & \quad \text{H}_5\text{C}_6 \\
\end{align*}
\]

(67b)

(68)
Three aliphatic acids 69a, 70a and 71a have been reacted with thionyl chloride in presence of pyridine to form thiophene derivatives 69, 70 and 71.

\[
\begin{align*}
\text{(69)} \\
\text{(70)} \\
\text{(71)}
\end{align*}
\]

Thiophenophane (72) has been obtained by means of the classical Paal-Knorr synthesis when 1,4-cyclododecanedione (72a) is reacted with phosphorous pentasulfide.

\[
\begin{align*}
\text{(72)} \\
\text{(72a)}
\end{align*}
\]

Interaction of ethyl mercaptoacetate (73) and vinyl ketone (74)
in presence of piperidine results in formation of 2-carbethoxy-3-hydroxy-3-
alkyl thiophanes (75) in one step.\textsuperscript{111} The reaction is general for the
synthesis of thiophenes. Instead of vinyl ketones, ethyl 2-benzoyl acrylates,
chalcones or Mannich bases can also be employed.\textsuperscript{112} Dehydration of
thiophane (75) with polyphosphoric acid followed by dehydrogenation of
dihydrothiophene (76) using chloranil or diphenyl disulfide affords
thiophene 77. The disproportionation products, encountered during dehydration
of certain dihydro-thiophenes, arise as a result of intermolecular hydride
shift.

\begin{align*}
\text{HSCH}_2\text{COOC}_2\text{H}_5 & \quad \text{O} \\
& \quad \text{CH} - \text{C} - \text{R}_2 \\
& \quad \text{R}_1 - \text{CH} \\
(73) & \\
& \\
\text{R}_1 & \quad \text{S} \quad \text{COOC}_2\text{H}_5 \\
(76) & \quad \text{R}_2
\end{align*}

Recently, substituted thiophenes and pyrroles\textsuperscript{113} have been prepared
from 2-chlorovinylaldehydes (78a) which are easily obtained from a reaction
between ketone and DMF-POCl\textsubscript{3}.\textsuperscript{114} The chloraldehyde(78a) is condensed with
ethyl mercaptoacetate in presence of triethylamine to give thiophenes (78).
The reaction bears a close resemblance to thiophene synthesis reported earlier
by Fieselmann.\textsuperscript{115,116}
When diethyl acetylenedicarboxylate is refluxed with mercaptoacetone in ethanol, compound 72 is formed. On the other hand, ethyl mercaptoacetate with dimethyl acetylene dicarboxylate yields diester which during extraction with alkali gets hydrolyzed to thiophene carboxylic acid (80). The reaction proceeds through Michael addition to acetylenecarbonyl compound followed by intramolecular cyclization. The same principle has been applied to prepare salicylic acid analogs (81) by condensation of ethyl mercaptoacetate with substituted acetylenes.

\[
\begin{align*}
\text{(79)} & \quad \text{(80)} & \quad \text{(81)} \\
\end{align*}
\]

A convenient synthesis of thiophene (82) consists of the addition of mercaptoaldehyde diethylacetal to 2-cyclohexen-1-one in presence of a base to form 82a, followed by an intramolecular aldol condensation to 82b. Oxidation of 82b with chloranil gives 4-oxo-4,5,6,7-
The synthesis appears to be an extension of Tilak's work. By merely refluxing two molecules of \(\ell\)-chlorothiacetanilides (83a) in methanol, the corresponding hydrochloride salts of diamines have been obtained which are converted to their stable bases (83). The proposed mechanism involves initial alkylation of sulfur to give 83b, followed by reaction of a carbanion 83c with the positive centre of the remaining thiocarbonyl group to yield 83d. Elemental sulfur is split out rather than the more commonly found hydrogen sulfide or water through either epi-sulfide or anion group to give 83. Thiophene diamines (83) are susceptible to electrophilic attack at 5-position. Isocyanates,
isothiocyanates and acid chlorides react with $83^\circ$ to yield $84$ and $85$.

$$W - R^N-C-H \xrightarrow{X} R^C \xrightarrow{X} (84)$$

$$X = O, S$$

$$(85)$$

**Willgerodt-Kindler Reaction**

1-Phenyl butanones ($86a$-$86c$) when reacted with 2-molecules of morpholines and 2g. atom of sulfur at $130^\circ$C, yield an identical product, 2-morpholino-5-phenylthiophene ($88$) in addition to the normal expected product, 4-phenyl butyrothiomorpholide ($87$). $^{121}$ Thiomorpholide ($87$) when subjected to similar treatment affords the same thiophene derivative ($88$). $^{122}$

$$C_6H_5 \xrightarrow{O} CH_2.C.H_2.CH_3$$

$$(86a)$$

$$C_6H_5 \xrightarrow{O} CH_2.COH.C.CH_3$$

$$(86b)$$

$$C_6H_5 \xrightarrow{O} CH_2.C.H_2.C.CH_3$$

$$(86c)$$

$$C_6H_5 \xrightarrow{O} CEC - C.H_3$$

$$(89)$$

$$C_6H_5 \xrightarrow{O} (CH_2)\xrightarrow{3} C - S - \bigcirc$$

$$(87)$$

$$(88b)$$

$$C_6H_5 \xrightarrow{O} N - \bigcirc$$

$$(88a)$$
The reaction has been applied to bi-functional compounds like acetylene ketones (89). Acetyl phenyl acetylene (89) yields 5-phenyl-3-morpholino thiophene (88a) and small quantities of its isomer 88 instead of the expected thiomorpholide (89a).

**Gewald Reaction:**

Ketones and aldehydes with free methylene group at \( \alpha \)-position (90), condense with nitrile (91) and elemental sulfur in presence of a secondary amine (diethylamine, piperidine, morpholine) to yield 2-amino-3-substituted thiophene (92). The same product 92 is obtained if 2-mercapto ketone (93) is condensed with nitriles (91) in presence of a secondary amine. The intermediate alkylidene malononitrile (92a) is not isolated but is subjected in situ to thiolation on the methylene group beta to nitrile in presence of a basic catalyst. Probably, in order to stabilize, the mercapto intermediate (92b) cyclizes immediately to 2-aminothiophene (92).

\[
\begin{align*}
R-\text{C}=\text{O} & \quad \text{CH}_2 - X \\
R'-\text{CH}_2 & \quad \text{C}=\text{N} \\
\text{(90)} & \quad \text{(91)} & \quad \text{(92)} \\
X = \text{CN, COOEt, CONH}_2, \text{COPh, CSNH}_2
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{CH} \\
\text{C}=\text{C} & \quad \text{C}=\text{N} \\
\text{R'}-\text{CH}_2 & \quad \text{C}=\text{N} \\
\text{(92a)} & \quad \text{(92b)}
\end{align*}
\]

The condensation of carbonyl compound, sulfur and malononitrile derivatives in presence of secondary amine catalyst which involves the
formation of alkylidene nitrile, thiolation and finally the intramolecular cyclization to substituted thiophene system proceeds smoothly and uniformly around 45°C. This one-pot modified Willgerodt-Kindler reaction, 135 has become known as Gewald reaction. 126

Carbonyl compounds with less reactive carbonyl groups such as α-alkyl ketones are first converted to alkylidene derivatives (92a) separately in a Dean Stark apparatus. 123,127,131 After isolation, 92a is subjected to thiolation with sulphur, followed by simultaneous intramolecular cyclization to yield 92. In a variation of this method, 127 α-chloro-ketone (94) is condensed with malononitrile derivative (91). 2-Chloro alkylidene intermediate (95a) on treatment with sodium bisulfide, gives 2-aminothiophene (95). Similarly, enamines have been condensed with nitriles to obtain 2-amino thiophenes. 123,128,129 However, it offers few preparative advantages. 124

Gewald reaction has been exploited to synthesize thiophenes (96) from appropriately substituted crotononitriles (96a) in the presence of

\[
\begin{align*}
R=CH_3 & \quad (R) \quad (93) \\
& \quad (94) \\
& \quad (95) \\
& \quad (95a)
\end{align*}
\]

considering the chemical structures provided.
diethylamine.\textsuperscript{126} Under the same reaction conditions,\textsuperscript{131,131a} cycloalkanones (97) have been used to prepare fused 2-amino thiophenes (98 and 99) through cycloalkylidene intermediates (97a and 99a).

\begin{align*}
\text{(97)} \quad n = 1,2,3,7,10 \\
\text{(97a)} \quad X = \text{CN, CONH}_2, \text{COOEt}
\end{align*}

A series of novel 2-amino-3-cyano thiophenes has been prepared through Gewald reaction starting with 2,6-diaryl piperidine-4 and 2,6-diaryl thiacyclohexanone-4.\textsuperscript{134} A variety of cyclic ketones viz., 1-or 2-indanone, 2-or 4-phenylcyclohexanone, 1-or 2-tetralone and thiapyrone-4 have been employed to synthesize 2-amino-3-cyano thiophenes under similar reaction conditions.\textsuperscript{135}
First synthesis of a thieno(2,3-d)pyrimidine was carried out by Baker and co-workers\textsuperscript{136} as part of their study of thiophene isosters of antimalarial hydrangea alkaloids. Action of methanolic ammonia on 2-formamido-3-carbethoxythiophene gave thieno(2,3-d)pyrimidine-4-one in very low yields (4\%).

An access to the thieno(2,3-d)pyrimidine system was made available with the synthesis of 2-aminothiophenes having a suitable substituent at 3-position through Gewald reaction.\textsuperscript{123} Chacko\textsuperscript{132} has performed ring closure by reacting 2-amino-3-substituted thiophenes (100) with formamide, urea, cyanamide, acetamidine HC\textsubscript{1}, benzamidine hydrochloride and alkali to obtain thieno(2,3-d)pyrimidines. Through a variation of Niementowsky reaction, 4-amino(2,3-d)pyrimidine (101a) was prepared by boiling 2-aminonitrile (100a) with excess of freshly distilled formamide. Reacting 101a with HNO\textsubscript{2} yielded 4-hydroxy derivative (101b).
2-Substituted-4-hydroxythieno(2,3-d)pyrimidine (102a) was obtained in high yields by refluxing 2-acetylamino-3-carbamoylthiophene with alkali. Fusion of 2-amino-3-cyanothiophene (100a) with cyanamide in the presence of pyridine hydrochloride gave 2,4-diaminothienopyrimidine (102b). On the other hand, 100b when fused with cyanamide gave 2-amino-4-hydroxythienopyrimidine (102c). Fusion of carboxamide derivative (100b) and nitrile derivative (100a) with urea yielded thienopyrimidine derivatives (102d, 102e). German workers have prepared similar thieno(2,3-d)pyrimidine derivatives using essentially the same synthetic approach as above.\footnote{130}

An alternate synthesis of 4-oxo-thienopyrimidine under milder conditions consists of reacting 100c with dimethylformamide chloride.\footnote{137} Intermediate 103a cyclizes to 103 at room temperature in presence of ammonia or amines in ethanolic medium.

\[
\begin{align*}
\text{R} & \quad \text{CO}_{2}\text{Et} \\
\text{R} & \quad \text{NH-CH=N(CH}_3)_2 \text{Cl} \\
& \quad \text{(103a)} \\
\end{align*}
\]

Manhas and his co-workers\footnote{138} have synthesized thieno(2,3-d)pyrimidin-4-thiones (104) in 30\% to 70\% yield by condensing 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene with substituted thioamides in glacial acetic acid saturated with hydrogen bromide. Trifluoroacetic acid, in place of acetic acid and HBr, gives better yields. Similarly, thiophene derivative (105) prepared from cholestan-3-one when
treated with thioamide affords thieno(2,3-d)pyrimidine derivative (106).

\[ \text{(104)} \]

4-Oxo-2-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine (107) has been prepared in 70% yield by refluxing benzoyl derivative (107a) in ethanol saturated with dry hydrogen chloride.\(^{138}\) In POCl\(_3\)/DMF, 4-hydroxy pyrimidine derivative (107) was converted to 4-chlorothieno (2,3-d)pyrimidine (108a). Nucleophilic substitution of 108a with a variety of reagents has been studied.\(^{139}\) When treated with phenyl lithium and \((\text{CH}_3)_2\text{CuLi}\), chloroderivative (108a) gives 4-phenyl analog (108b) and 4-methyl analog (108c) respectively, in

\[ \text{(107)} \] \[ \text{(107a)} \]

\[ \text{(108)} \]

\(a; R = \text{Cl} \quad b; R = \text{Ph} \)

\(c; R = \text{CH}_3 \quad d; R = -\text{CH}_2\text{SOCH}_3 \)

\(e; R = \text{OCH}_3 \)
high yields. 4-(Methyl sulfinyl)methyl analog (108d) is obtained by reacting 108a with strong nucleophile methyl sulfinyl carbanion (-CH₂SOCH₃). On reacting 108a with sodium methoxide, 108a is obtained in quantitative yields.

Taylor and Burger¹³³ prepared several 4-amino-5,6-substituted thieno(2,3-d) pyrimidines (109) by treating 2-amino-3-cyano-thiophenes with excess of ethyl orthoformate followed by alcohol and ammonia. The intermediate formamidine (109a) cyclizes by brief heating in DMF at 80° to 100° in presence of a trace of sodium to afford 109.

\[ \text{(109)} \]

\[ \text{NH}_2 \]

\[ \text{R}_1 \]

\[ \text{R}_2 \]

\[ \text{N} = \text{CH-NH}_2 \]

\[ \text{(109a)} \]

Synthesis of a number of thieno(2,3-d)pyrimidines has been described by Arya and his co-workers.¹⁴⁰ 4-Chloro-thieno(2,3-d)pyrimidines (110a) when reacted with hydrazine hydrate gave hydrazino derivative (110b) which in turn cyclized to form condensed triazole (111) in presence of formic acid. Sodium azide with 110a yields tetrazole derivative (112). In a variation of Gewald reaction, methyl ethyl

\[ \text{(110)} \]

\[ a; \text{X} = \text{Cl} \]

\[ b; \text{X} = -\text{NHNH}_2 \]

\[ \text{(112)} \]
ketone was reacted with N-cyanoacetylurethane and sulfur in presence of diethylamine to obtain 2,4-dioxo thieno(2,3-d)pyrimidine (113). A novel boron heterocycle (114) has been synthesized by reacting 3-acetamido-2-amino-5-phenylthiophene with phenyl boronate.

\[
\begin{align*}
\text{(113)} \\
\text{(114)}
\end{align*}
\]

2,4-Dioxo-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidines (116) have been synthesized by Sauter in three different ways: (i) by a reaction of thiophene-carboxamide (115a) with phosgene, (ii) by thermal cyclization of phenylureid derivative (115c), and (iii) by cyclization of 115b in alkaline medium. Thieno-pyrimidine derivative (117) is obtained by refluxing 115a with ethyl chloroformate.

\[
\begin{align*}
\text{(115)} \\
\text{(116)} \\
\text{(117)}
\end{align*}
\]

A novel approach to the synthesis of thieno(2,3-d)pyrimidine system involves the condensation of readily available 2,4-diamino-6-
mercaptopyrimidine (118a) with α-haloketones (118b) to give intermediate pyrimidyl sulfide derivative (118) followed by dehydration in presence of acid to yield cyclic product 119.

\[ \text{CH—X} \]

Santilli et al have prepared esters and amides of thieno(2,3-d)pyrimidines (121) from 4-chloro-5-pyrimidine carbonitrile (121a) and substituted mercapto acetic acid esters and amides (HS—CH₂—C—R₂) in refluxing ethanol containing sodium carbonate. The postulated intermediate 121b is not isolated under the reaction conditions but cyclizes to 121, presumably by a Dieckmann type process.

\[
\begin{align*}
\text{(121)} & \quad \text{(121a)} & \quad \text{(121b)} \\
\end{align*}
\]

\[
R₂ = \text{OR}' \\
R₂ = \text{NHR}''
\]

Suitably substituted pyrimidines (122) have been converted to thieno(2,3-d)pyrimidines by Rajappa and his co-workers. The adduct of β-aminocrotononitrile (33a) and acyl isothiocyanate undergoes base cyclization to pyrimidine (122). Alkylation of 122 with phenacyl bromide yields 123 which cyclizes readily in presence of alkali to
thieno pyrimidine (124). Same workers have prepared thiophene isosters of methaqualone by synthesizing oxazinone (125a) from 2-amino-thiophene-3-carboxylic acid with acetic anhydride. Reacting oxazinone (125a) with ortho toluidine resulted in thieno(2,3-d)pyrimidine (125). Condensation of 2-arylamino-3-carbethoxy thiophene (126a) with methyl isocyanate in the presence of sodium hydride affords thienopyrimidine derivative (126).
Gewald reaction has been extended to cyanoacetic acid hydrazides to form 2,3-substituted thieno(2,3-d)pyrimidines (127). Cycloalkanones when treated with sulfur cyanoacetic acid hydrazide in presence of a basic catalyst yields 127 in a single step. Spiro compound (127) on hydrolysis affords 2-amino-3-thienohydrazides (128). Direct hydrazinolysis of 2-amino-3-carbethoxythiophene fails to yield 3-thienylhydrazide (128).

**Thieno(2,3-e)diazepin-2-ones** - A series of 1,3-dihydro-2H-thieno (2,3-e) (1,4)-diazepin-2-ones has been synthesized and evaluated for CNS activity. Thienodiazepin-2-ones have been synthesized from readily obtainable 2-amino-3-benzylthiophenes (129), using a variety of procedures. Haloacetamide intermediates (130a) are ammonolyzed by passing NH₃ in methanol which readily cyclize in situ to give 130 directly. Chloro- or bromoacetamides are obtained by the corresponding halogenoacetylation of 129 in boiling

![Chemical Structures](image-url)

(a) \( n=1 \) \( R = \text{cyclopentylidene} \)

(b) \( n=2 \) \( R = \text{cyclohexylidene} \)

(c) \( n=3 \) \( R = \text{cycoheptylidene} \)
chloroform. Similarly, 2-phthalimido intermediate (129a) is hydrazinolyzed with anhydrous hydrazine to give the cyclic product (130). Condensing 2-amino-3-benzoylthiophenes (129) with N-chlorosacetyl phthalimide gives 2-phthalimide intermediate (129a). Finally, 130 has been alkylated to give the corresponding 1-substituted derivative (131).

(129)

(129a)

(130)

(130a)

(131)
BIOLOGICAL ACTIVITY IN THIOPHENES

A broad spectrum anthelmintic activity has been discovered in a novel series of imidazolines (132) and tetrahydropyrimidines (132a) substituted at 2-arylethyl or arylvinyl groups. One member of this series, trans-1,4,5,6-tetrahydro-1-methyl-2\(\frac{2}{2}\)-(2-thienyl)vinylpyrimidine tartrate (pyrantel tartrate) (132a) has gained acceptance as a veterinary anthelmintic agent in many areas of the world. Non-cyclic amidines have also been synthesized. Structure activity relationship in amidines has been discussed.

\[
\begin{align*}
\text{R} (132) & \quad R = H, \text{Pyrantel} \\
\text{R} (132a) & \quad R = CH_3, \text{Morantel}
\end{align*}
\]

The synthesis and pharmacological properties of N-substituted 2-amino-1-(2-thienyl)ethanols (133) have been described. A strong \(\beta\)-adrenergic blocking activity has been observed in N-isopropyl substituted ring-chlorinated compounds (133a, 133b).
Amides of thiophene-2-carboxylic acids with various aromatic and heteroaromatic amines are reported to have antiviral activity. Muscle relaxant, bisquartenary esters of 3,4-diphenyl thiophene 2,5-dicarboxylic acid (134) have been synthesized. Highest neuromuscular blocking activity of the competitive type was found in compounds

\[
\begin{align*}
&\text{R} = \text{alkyl, aryl, acyl or aroyl.} \\
&\text{135a: } R = -\text{CH}_2\text{C}_6\text{H}_5
\end{align*}
\]

having distance between two nitrogen equal to 14.8, 17.0 and 19.0 Å.

For short periods, 134b is more active than tubocurarine.

A series of 4,5,6,7-tetrahydrothieno(2,3-c)pyridines has been synthesized. Hydrochloride salt of 6-benzylation derivative (135a) (y-3642) possesses interesting pharmacological properties. While analgesic and antipyretic activity is comparable to aminopyrine, antiinflammatory activity is superior. Mode of antiinflammatory action is similar to aspirin. Besides, the compound shows marked inhibition of the aggregation of rabbit platelets induced by ADP. In Japan, the compound 135a has been introduced in therapy as
antiinflammatory and analgesic agent under the trade name of Tinoridine hydrochloride.

Japanese workers \textsuperscript{159-162} have prepared a series of pyridine carbonyl thiophene derivatives for antiinflammatory and antipyretic activity (136a-136c). Compound 136a is a potent analgesic and antiinflammatory agent. In general, activity is maximum when \( R_1 = H, R_2 = \text{Et group} \).

Acrylonitrile and ethyl mercaptoacetate are condensed to give 137a which when reacted with aniline yields 137b. \textsuperscript{163} Chloranil oxidizes 137b to thiophene derivative (137c). Thiophene 3-carboxylic acid (137d) is obtained on hydrolysis of 137c. Reacting 137d with methyl chloroacetate yields 3-carboxylic acid-acetoxy methyl ester (138). Thiophene derivative (133) (Hoe 473) has proved to be highly active antiinflammatory agent as compared to phenylbutazone and indomethacin. \textsuperscript{163} It is also compatible with gastric mucosa. 4-Amino-3-carboxylic acids (137d) are reported to have significant
antiinflammatory activity as compared to phenylbutazone. 2-Chloro-
6-methyl anilino derivatives (137d) is a potent inhibitor of collagen
induced aggregation of human platelets in vitro. 164

\[
\begin{align*}
(137a) & \quad (137b) \\
(137c) & \quad (137d) \\
(138) & \quad (139)
\end{align*}
\]

R_1 = 3-CF_3; R_2 = H \quad (137d) \\
R_1 = 3-Cl; R_2 = 2-CH_3 \quad (138) \\
R_1 = 2-Cl; R_2 = 6-CH_3

Methyl 4-methyl-3-\(\text{I-oxo-2-(propylamino)propyl-} \)amino -2-thiophene
carboxylate HCl (Hoe 40045) (139) when injected with adrenaline showed
frequency, duration and extent of analgesia superior to Lidocaine. 165
With adrenaline (5mcg/ml), 139 has a greater duration of analgesia than
mepivacaine. When administered with adrenaline it has a frequency of
analgesia which lasts for 43 minutes and has a latency period of 3
minutes at a dosage level of 2%. Compound 139 has good potentialities
as dental anaesthetic.

\[
(139)
\]
Biological activity in thienopyrimidines.

2,4-Disubstituted thienopyrimidines are reported to be useful as coronary and peripheral blood vessel dilators. Some of the derivatives (140a) inhibit ADP induced platelets aggregation and reduce platelets adhesiveness. Thieno(2,3-d)pyrimidine (140b) has significant diuretic activity.

\[
\begin{align*}
\text{(140a)} & \\
R_1, R_2 &= H \text{ or } CH_3 \\
X, Y &= 1\text{-pyrrolidino} \\
X, Y &= 1\text{-piperazino} \\
X, Y &= 1\text{-piperidino}
\end{align*}
\]

5-Hydroxy-2-aryl substituted thieno(2,3-d)pyrimidine-6-carboxylic acid derivatives (141) are useful as CNS depressants. Anti-histaminic properties have been reported in 4-piperazino thieno(2,3-d)pyrimidines (142). 2-Mercapto-3,4-dihydrothieno(2,3-d)pyrimidin
4-ones (143) possessing antitussive, sedative and hypocholesterolemic properties have been synthesized. At 100 mg/kg i.v., 143a lowered cholesterol level in blood by 30%.

\[ R_1 = H, \quad R_2 = CH_3 \]
\[ R = H, \quad R_1 = CH_3, R_2 = CH_3 \]
\[ R_1 R_2 = -(CH_2)_4^- \]

Ethyl 5-nitrofuran-2-carboxamidate when condensed with methyl 2-amino thiophene-3-carboxylate gives pyrimidin-4-one derivative which on reacting with POCl_3 affords 4-chloropyrimidine. 4-Chloro derivative when reacted with various amines yields 144.

\[ R = \text{substituted amino groups} \]

(144)

(145a)

(145b)
4-Amino thienopyrimidines (144) have bactericidal and trichomonacidal activity. Thienopyrimidines (145a and 145b) were prepared by NaBH₄ reduction of the corresponding 3,4-dihydrothieno(2,3-d)pyrimidines. Both these compounds exhibit sedative action.

Analgesia and antiviral activity have been reported in pyrrolidinonaphtho(2,3-b)thiophenes (146).

\[ \text{(146)} \]

2-Amino-3-substituted thiophenes (147) have been cyclized to give 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno(2,3-d)pyrimidines (148). 2-Amino thiophenes (147) are prepared through Gewald reaction from 3-quinuclidinone. Both the derivatives (147 and 148) have shown antiviral activity. Analgesic and antiinflammatory activity have been disclosed for 147.

Thieno(2,3-d)pyrimidines (149) are reported to possess antibacterial, antiparasitic, especially antimalarial properties. Thieno(2,3-d)pyrimidines (150) have been synthesized with antimalarial
activity against chloroquine-resistant plasmodia.

Manhas and his co-workers were one of the first to report antiinflammatory activity associated with thienopyrimidines. In presence of acetic anhydride, 2-amino-3-thiophene carboxylic acids gave lactones (151) which on heating with arylamines gave 3-aryl substituted pyrimidones (152). Significant antiinflammatory activity is exhibited by 152a and 152b.
2,4-Diamino thieno(2,3-d)pyrimidines - 2,4-Diaminopyrimidine derivatives are potent inhibitors of the enzyme dihydrofolate reductase which plays a major role in folic metabolism by catalyzing the reduction of dihydrofolate to its active co-factor form, tetrahydrofolate. This co-factor participates in at least fifteen biosynthetic transfer reactions of 1-C fragments involved in amino acid and nucleic acid synthesis. Impetus to the search for new compounds which block the action of this enzyme has been given by the fact that dihydroreductases from microbial and mammalian sources differ greatly in their binding capacity for different diaminopyrimidines and related compounds. Antibacterial agent, trimethoprim, binds itself 50,000 times more strongly to bacterial than to mammalian enzyme. This provides a sound explanation for its therapeutic effectiveness.

Based on the above principle, a series of thiophene isosters of known diaminopyrimidines has been prepared for their antibacterial, antimalarial and antimetabolic effects. Roth was the first to synthesize 2,4-diamino-6-mercaptopyrimidine from alphahaloketones. 2,4-Diamino-6-benzyl-5-methylthieno(2,3-d)pyrimidine (153a) was found to have strong inhibitory effect against Lactobacillus casei. It

\[
\begin{align*}
R = \text{C}_6\text{H}_5 & \quad (n = 1) \\
R = \text{C}_6\text{H}_5 & \quad (n = 2)
\end{align*}
\]
also displayed a favorable inhibition ratio against isolated dihydrofolate reductases from bacterial and mammalian sources. This important lead was followed by many workers interested in antibacterial and antimalarial agents. Rosowsky and his co-workers synthesized $153a$ through a different route. Significant activity has been exhibited by $153a$ and $153b$ against *Streptococcus faecium*. Compound $153b$ is active against *Plasmodium berghei* at a dose level of 640 mg/kg.

As a part of their continued interest in antimalarial program, Elslager and co-workers have synthesized a series of fused 2,4-diaminothieno(2,3-d)pyrimidines (154) by fusing 2-amino-3-cyano thiophenes with chloroformamidine HCl. Several compounds in this series exhibited inhibitory effects *in vitro* against *Streptococcus faecalis*, *Staphylococcus aureus*, *Streptococcus faecium*, *Lactobacillus casei* and *Pediococcus cerevisiae*. Three of the compounds (154a-154c) showed *in vitro* antimalarial activity against *Plasmodium berghei* and *Plasmodium falciparum*. 
2,4-Diaminothieno(2,3-d)pyrimidines with a carbocyclic or heterocyclic ring at 5,6 position have been synthesized for evaluation as small molecule folate antagonist. Hydrophobic groups at 5,6 position have marked effect on the growth inhibition of *Streptococcus faecium*. The introduction of alkyl substituents on the cyclohexane ring of 154 results in a marked enhancement of activity. ID$_{50}$ value in the 0.001 mcg/ml. range could be obtained comparable to the most active tricyclic pyrimethamine derivatives, in compounds 154a-154f. From the same laboratory has come the synthesis of 2,4-diamino-6,8-diaryl-5,6-dihydro-8H-thiopyrano(4', 3':4', 5) thiophenopyrimidines (155) including its oxidation products sulfoxide and sulfone derivatives as potential antifolates and antimalarials. Antibacterial activity against *Streptococcus faecium* was observed only with 155a though not of high order. Increasing the polar character of the compound by oxidation to sulfoxide or sulfone resulted in a markedly unfavorable effect.
Thiényl Penicillins

A number of new derivatives of 6-aminopenicillanic acid have been made in order to resist penicillinase hydrolysis. The resistance appears to be associated with steric hindrance around the side chain carbon adjacent to the amide carbonyl group. Of particular interest is 6-(R-amino-3-thienylacetamide)penicillanic acid (156), whose *in vitro* antibacterial activity is comparable with the clinically useful ampicillin but is significantly more active in animal protection tests when administered orally. Besides, thiényl derivative is better absorbed orally.

\[ \text{(156)} \]

The only cephalosporin present in nature, cephalosporin C, leaves much to be desired. It is difficult to isolate and purify. Besides, it has low potency.

Two side chains, 7-acylamines and 3-acetoxyethyl, present in cephalosporin lend themselves to chemical manipulation. Both side chains have been subjected to extensive alterations with a reasonable degree of success from the standpoint of enhancing the biological activity. These manipulations have led to clinically successful products involving both 3 and 7 positions. Cephalothin, 7-(thiophene-2-acetamido) cephalosporanic acid (157a) was the first cephalosporin to find clinical use. It is effective *in vitro* against Gram +ve
and Gram -ve organisms. It has good penicillinase resistance and is less toxic than that of benzylpenicillin.

![Chemical structure of Cephaloridin](image)

Cephaloridin, 7-(2-thienyl)-acetamido-3-(1-pyridylmethyl)-3-cephem-4-carboxylic acid betain (157b) appears to have number of advantages over cephalothin.\(^{193,194}\) It is 2-8 times more active than cephalothin against Gram *+ve* and approximately as active as later against Gram -ve bacteria. There have been many other attempts made to manipulate 7-ACA, using 2-thiophene acetic acid and other thiophene acids.\(^{195-203}\)

**Condensed thiophenes with CNS activity**

During the past decade, members of 1,4-benzodiazepin' class of compounds have generated considerable interest in the CNS field as psychotherapeutic agents.\(^{147,204,205}\) A number of thiophen\(2,3-e\) diazepin-2-ones have been synthesized and their structure activity relationship studied.\(^{83,84,145,146}\) The extensive work carried out in this field has resulted in the clinical trials of at least two compounds 30a and 30b. These two compounds are superior to known drugs.\(^{84,206}\)

![Chemical structures of 30a and 30b](image)
4-(Aminopropionyl)thieno(3,2-b)(f)benzazepines (158a and 158b) have been synthesized. Some of these derivatives have antidepressant activity.\textsuperscript{71,208}

\[
\text{R} = \text{CH}_2\text{CH}_2\text{CH}_2\text{N} \quad \text{N} \quad \text{CH}_3
\]

\[
\text{R} = \text{CH}_2\text{CH(CH}_3\text{)}\text{CH}_2\text{N} \quad \text{O}
\]

\[
\text{R} = \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2
\]

Analgesic, sedative and antiinflammatory activity has been reported in thienobenzothiazepinones (159, 160a, 160b).\textsuperscript{209,210}

\[
\text{(159)}
\]

\[
\text{(160a)}
\]

\[
\text{(160b)}
\]

\[
R = \text{4-Piperazino, morpholine, piperidino}
\]
CHAPTER II

2-AMINO-3-SUBSTITUTED THIOPHENES

INTRODUCTION

Substituted anthranilic acids inhibit the growth of E. typhi and E. Coli. This inhibition is reversed by anthranilic acid, indole, tryptophan, amino acids, purines and vitamins. These acids probably interfere with the biosynthesis of tryptophan at the anthranilic acid stage. Fluoroanthranilic acids are more potent inhibitors of anthranilic acid biosynthesis in bacteria. Methyl esters of anthranilic acid have bactericidal and fungicidal activity. N-Aryl anthranilic acids have been described as active antiinflammatory compounds. 2-Amino-3-carbethoxy thiophene may be considered to be an isoster of ethyl anthranilate.

2-Amino-4,5,6,7-tetrahydro-4,7-ethanothieno(2,3-b)pyridines (147) have been synthesized with antiviral, antiinflammatory and analgesic activity. A series of 2-amino-3-nicotinoyl thiophene derivatives (136a-136c) has been prepared and is reported to have significant analgesic and antiinflammatory activity. Analgesic activity has been reported in 2-amino-3-nicotinoyl-5-ethyl thiophene with ED$_{50}$ of 50 mg/kg in rats and mice.

Antiinflammatory and sedative activity have been exhibited by 2-amino-4,5,6,7-tetrahydrothieno(2,3-c)pyridines. 6-Benzyl derivative of thieno(2,3-c)pyridine (135a) is used clinically as antiinflammatory and analgesic agent. Dithiocarbamates of 2-amino-3-carbethoxy thiophene have been tested for radiation protection.
It was, therefore, thought of interest to synthesize 2-amino-3-substituted thiophenes and to screen them for antimicrobial and other biological activities. Besides, 2-amino-3-substituted thiophenes undergo facile cyclization to give thieno(2,3-d)pyrimidines. \(^{132}\)

**RESULTS AND DISCUSSION**

2-Amino-3-substituted thiophenes (162-179) were synthesized by the application of Gewald reaction. \(^{123}\) Ketones with free \(\alpha\)-methylene group (I) were reacted with nitriles of the type \(X-\text{CN} \) (II) in the presence of sulfur and a secondary amine (diethylamine or morpholine) to give 3-substituted-2-aminothiophenes (III). This one pot reaction goes to completion at about 45°C in 1-4 hours. At the end of the reaction, sulfur dissolves completely and a clear dark brown solution results. On cooling for 24-48 hours, crystalline precipitate obtained

\[
\begin{align*}
\text{(I)} & & \text{(II)} \\
R_1 & \text{C} & + & H_2 & \text{C} & + & \text{S} \text{diethylamine or morpholine}
\end{align*}
\]

\[
\begin{align*}
\text{(III)} & \\
\text{X} & = & \text{CN, COOC}_2\text{H}_5, \text{CONHR,} & \\
& & \text{CONHNHC}_6\text{H}_5
\end{align*}
\]

(Eq. I)
61

162. \( R = -\text{CNH}_2C_6H_5 \)
163. \( R = -\text{CH}_2\text{CO}_2H \)

164. \( R_1 = -\text{CH}_3; R_2 = \text{H}; X = -\text{COOC}_2H_5 \)
165. \( R_1 = R_2 = \text{H}; X = -\text{CN} \)
166. \( R_1 = R_2 = \text{CH}_3; X = -\text{CN} \)

167. \( R = \text{H}; X = -\text{CONHCH}_3 \)
168. \( R = \text{H}; X = -\text{CONHC}_2H_5 \)
169. \( R = \text{H}; X = -\text{CONHC}_6H_5 \)
170. \( R = -\text{CH}_3; X = -\text{COOC}_2H_5 \)
171. \( R = -\text{CH}_3; X = -\text{CN} \)
172. \( R = -C_6H_5; X = -\text{COOEt} \)
173. \( R = -\text{CH}_2-N; X = \text{COOEt} \)
174. \( R = -\text{CH}_2-N; X = -\text{CN} \)
175. \( R = \text{H}; X = -\text{CO}_2\text{CH}_2\text{CH}(\text{CH}_3)_2 \)
was filtered. However, when no solid precipitate was obtained on cooling, the reaction mixture was poured over ice-water mixture and the precipitated solid was filtered and dried. In these cases yields were lower. In general, 2-aminothiophenes could be crystallized from ethanol. However, compounds \textbf{163}, \textbf{175}, \textbf{177} soluble in ethanol, chloroform and benzene were crystallized from less polar solvents.

In instances where the single step reaction proved to be unsatisfactory (167,169-172), a stepwise process was employed. Ketones and nitriles in benzene were reacted, in the presence of a basic catalyst, in a Dean Stark apparatus with an arrangement for water separation to afford corresponding acrylonitrile intermediates (IV)\textsuperscript{216}. The intermediates were isolated and utilized without further purification. Treatment with sulfur and basic catalyst afforded 2-aminothiophene (V) (167,169-172).

\[
\begin{align*}
\text{(IV)} & \quad \text{(V)}
\end{align*}
\]

2-Amino-3-thiophene esters (163, 172, 173, 175, 177) exhibit two strong absorption peaks in UV around 228 nm (log \(\varepsilon\), 4.40) and 308 nm (log \(\varepsilon\), 3.76) with a shoulder at 260-265 nm. In the case of 3-cyano derivatives (171, 174, 176, 178) both the peaks are slightly at lower wave lengths, 215-221 nm (4.3), 293 (3.78) with a shoulder at 260.
Absorption in IR region due to carbonyl group in amides is found around 1630 cm\(^{-1}\) (167, 169). On the other hand, carbonyl function in esters (163, 172, 173, 175, 177) absorbs around 1670 cm\(^{-1}\). Ordinarily, aromatic esters exhibit a carbonyl peak at 1720 cm\(^{-1}\). The shift towards lower wave numbers in 2-amino-3-carbethoxy thiophenes may be attributed to hydrogen bonding between carbonyl and amino groups in vicinal positions. This is also the case with ethyl anthranilate where carbonyl function is found to absorb at 1680 cm\(^{-1}\) (chloroform).\(^{217}\)

3-Cyano thiophenes (165, 166, 171, 178) exhibit a strong absorption peak around 1630 cm\(^{-1}\), over and above an absorption peak at 2210 cm\(^{-1}\) due to \(\text{C}=\text{N}\) function. The peak at 1630 cm\(^{-1}\) may be assigned to \(-\text{C}=\text{N}-\) group in the tautomeric form (VII). This would also account for the weakly basic character of the amino group at 2 position in thiophenes (VI) which fails to form salts with mineral acids and also resists alkylation.\(^{218}\)

\[ \text{(VI)} \quad \leftrightarrow \quad \text{(VII)} \]

However, \(-\text{C}=\text{N}-\) peak is seen only as a shoulder at 1610 cm\(^{-1}\) in carbethoxy thiophenes.

2-Amino-3-substituted 9-aza thieno(2,3-b)bicyclo(3,2,1) octanes (177, 178) were synthesized from tropinone under Gewald conditions.

3-Carbethoxy derivative (177) is soluble in ethanol and chloroform. It was recrystallized from benzene-\(n\)-hexane mixture. The elemental analysis
revealed that the compound contained one molecule of benzene. This was confirmed from NMR spectra where a singlet for aromatic protons at δ 7.4 was present. Mass spectrum of 177 showed a prominent M⁺ = 266. Loss of -NCH₃ and -OC₂H₅ fragments produced m/e peaks at 237 and 192, respectively. The base peak was present at m/e 237. On the other hand, cyano derivative (178) is sparingly soluble in ethanol and chloroform. It showed M⁺ = 219 with a base mass peak at 190 due to the loss of N-CH₃ fragment. Literature survey reveals that 9-aza-thieno(2,3-b)bicyclo(3,2,1)octane is a new ring system.

Hydrochlorides of cyclohexanone Mannich bases (180a - 180c) were synthesized by a known method. 2-Morpholinomethyl cyclohexanone HCl (180a) was condensed with ethyl cyanoacetate under Gewald conditions to afford 173 in 50% yield. Mass spectrum of compound 173 exhibited a prominent M⁺ at 324. Loss of -OCH₂CH₃ (m/e, 45) and CH⁺₂-N-CH₂-O (m/e, 100) afforded two prominent mass peaks at 279, 224, respectively. When Mannich bases 180b and 180c were reacted under similar conditions using morpholine as a catalyst, product obtained in each case showed M⁺ = 324. Mass spectrum of both 173a and 173b showed identical fragmentation patterns to that of 173 with m/e at 279, 224, 100 and 45.
IR and UV spectra of 173a and 173b were identical to that of 173. The spectral data confirmed the structure of 173a and 173b to be

\[
\text{2-amino-3-carbethoxy-4-(morpholinomethyl)-4,5,6,7-tetrahydrobenzo(b) thiophene (173).}
\]

Further, mixed melting point of 173a or 173b with 173 remained undepressed. The formation of identical products under Gewald reaction conditions with hydrochloride of Mannich bases (180a), (180b) and (180c) may probably be due to amine exchange reaction between morpholine (catalyst) and the amine moiety of 173b and 173c. Exchange reactions between Mannich bases and amines are well established. 220-222

Synthesis of 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylic acid phenylhydrazide (179a) by reacting the corresponding ethyl ester with \( \text{H}_2\text{NNNH}_2 \) resulted in the recovery of original ester. Therefore, an attempt was made to prepare 179a from N-cyanoacetyl-phenylhydrazine as starting material under Gewald reaction conditions.
However, the product isolated showed absence of primary amine in IR and exhibited mass peak at 367. The two absorption peaks in UV spectrum were present at 234 and 328 nm.

The spectral data support the structure of 179, which must be formed from the intermediate Schiff's base (179b) by an attack of lone pair of electrons of nitrogen on the carbon of the azine bond.

Analogous compounds (181) have been reported earlier. Compound 181 exhibits $\lambda_{\text{max}}$ at 230 nm (0.27) and 333 (3.51). Carbonyl function absorbs at 1630 cm$^{-1}$ in IR.
Phenyl analog 182 of 179 has been synthesized through a different route and exhibits two absorption bands in IR at 3300 and 1620 cm\(^{-1}\). When cyclohexanone and N-cyanoacetylphenylhydrazine were reacted in 1:1 molar proportion under similar reaction conditions, only product obtained was 179, though in lower yields.

Compounds (164-166) were prepared by employing the corresponding 2,6-diphenyl-4-piperidones (183a-183c). \(^{225}\) Cis orientation of the phenyl groups has been shown by the failure to resolve 1-methyl-2,6-diphenyl-4-piperidone (183a). \(^{226}\) Further, reduction of 183a and 183b resulted in the formation of corresponding two epimeric 4-piperidinols. \(^{225}\) This indicates that 2,6-diphenyl-4-piperidones (183a and 183b) have cis orientation of phenyl groups since trans configuration of these compounds should afford only one corresponding piperidinol on reduction. Besides, studies on cyclohexane have shown that the phenyl group has large preference for equitorial position. \(^{227}\) In case of 183c, the methyl group to carbonyl function should also be present in the stable equitorial position.
refluxing with sodium ethoxide in ethanol, 183c was recovered unchanged. The cis configuration is likewise assigned to the 2-amino thiophenes (164-166) on the basis that there is no particular reason to expect racemisation during the reaction leading to these compounds. Physical constants of compounds 162-179 are recorded in Table 2.

Biological activity - Compounds 164, 167, 169, 172, 173, 178, and 179 were tested for analgesic, anticonvulsant, antihypertensive and antiinflammatory activity. Compound 178, (50 mg/kg, orally) when tested for analgesic activity exhibited 39.6% inhibition against 68% by aspirin (200 mg/kg). It also showed 50% protection against electroshock seizures at the same dosage level. The calculated LD50 value of compounds 178 in mice was between 100-250 mg/kg by oral route and between 50-100 mg/kg by intraperitoneal route.

Compound 167 (5 mg/kg) by intravenous route produced 35% fall in blood pressure for 1 hour in dogs. During this period, the compound exhibited 100% blockade of carotid occlusion. When screened for antiinflammatory activity, compound 173 (200 mg/kg, orally) showed 24.3% inhibition as compared to 53.7% by phenylbutazone (100 mg/kg) orally.

Antimicrobial Screening

Compounds 164, 167, 169, 172, 173, 176, 178, and 179 were tested for antimicrobial activity. Compound 172 showed activity against S. aureus, S. aureus A/R and Phialophora jeanselmei at 6.25 mcg/ml concentration. All the compounds tested were devoid of any antifungal activity.
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Cryst. solvent</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>162.</td>
<td>180-81</td>
<td>30</td>
<td>E</td>
<td>C_{15}H_{16}N_{2}O_{3}S</td>
</tr>
<tr>
<td>163.</td>
<td>145-48</td>
<td>30</td>
<td>EA-H</td>
<td>C_{10}H_{13}NO_{4}S</td>
</tr>
<tr>
<td>164.</td>
<td>195-96</td>
<td>40</td>
<td>E</td>
<td>C_{23}H_{24}N_{2}O_{3}S</td>
</tr>
<tr>
<td>165.</td>
<td>171-73</td>
<td>35</td>
<td>E</td>
<td>C_{20}H_{17}N_{3}S</td>
</tr>
<tr>
<td>166.</td>
<td>225-27</td>
<td>53</td>
<td>E</td>
<td>C_{22}H_{21}N_{3}S</td>
</tr>
<tr>
<td>167.</td>
<td>193-95</td>
<td>70</td>
<td>AA</td>
<td>C_{10}H_{14}N_{2}OS</td>
</tr>
<tr>
<td>168.</td>
<td>118-20</td>
<td>35</td>
<td>M</td>
<td>C_{11}H_{16}N_{2}O_{3}S</td>
</tr>
<tr>
<td>169.</td>
<td>143-45</td>
<td>41</td>
<td>AA</td>
<td>C_{15}H_{16}N_{2}S</td>
</tr>
<tr>
<td>170.</td>
<td>80-81</td>
<td>50</td>
<td>E-W</td>
<td>C_{12}H_{17}NO_{3}S</td>
</tr>
<tr>
<td>171.</td>
<td>129-31</td>
<td>45</td>
<td>E</td>
<td>C_{10}H_{12}N_{2}O_{5}S</td>
</tr>
<tr>
<td>172.</td>
<td>106-10</td>
<td>50</td>
<td>E</td>
<td>C_{17}H_{19}NO_{2}S</td>
</tr>
<tr>
<td>173.</td>
<td>212-14</td>
<td>50</td>
<td>E</td>
<td>C_{16}H_{24}N_{2}O_{3}S</td>
</tr>
<tr>
<td>174.</td>
<td>182-84</td>
<td>50</td>
<td>AA</td>
<td>C_{14}H_{19}N_{2}O_{5}S</td>
</tr>
<tr>
<td>175.</td>
<td>68-70</td>
<td>40</td>
<td>H</td>
<td>C_{13}H_{19}N_{2}O_{5}S</td>
</tr>
<tr>
<td>176.</td>
<td>226-30</td>
<td>80</td>
<td>M</td>
<td>C_{10}H_{11}N_{2}O_{3}S</td>
</tr>
<tr>
<td>177.</td>
<td>154-56</td>
<td>43</td>
<td>B-H</td>
<td>C_{13}H_{18}N_{2}O_{2}S.C_{6}H_{6}</td>
</tr>
<tr>
<td>178.</td>
<td>276(d)</td>
<td>50</td>
<td>E</td>
<td>C_{11}H_{13}N_{3}S</td>
</tr>
<tr>
<td>179.</td>
<td>242-44</td>
<td>41</td>
<td>M</td>
<td>C_{21}H_{25}N_{3}O_{5}S</td>
</tr>
</tbody>
</table>

Contd...
### Table 2 (Contd.)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$\lambda_{\text{max}}$ nm in U.V.</th>
<th>$\nu_{\text{max}}$ cm$^{-1}$ in IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>163.</td>
<td>227(4.42), 265(3.68) (s), 305(3.76)</td>
<td>3460, 3340(-NH$_2$), 1740(COH), 1630(COEt)</td>
</tr>
<tr>
<td>164.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>165.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>166.</td>
<td>215(4.0), 290(3.78)</td>
<td>3480, 3330, 3220(-NH$_2$), 2220(CN)</td>
</tr>
<tr>
<td>167.</td>
<td>228(4.29), 263(s), 300(3.66)</td>
<td>3510, 3420(-NH$_2$), 1620(CONH)</td>
</tr>
<tr>
<td>168.</td>
<td>215(3.89), 225(4.14), 263(3.81) (s), 317(3.86)</td>
<td></td>
</tr>
<tr>
<td>169.</td>
<td>257(4.25), 319(3.87)</td>
<td>3430, 3320(-NH$_2$), 1640 (-CONH)</td>
</tr>
<tr>
<td>170.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>171.</td>
<td>221(4.39), 260(s), 293(3.77)</td>
<td>3460, 3340, 3220(-NH$_2$), 2210(-CN)</td>
</tr>
<tr>
<td>172.</td>
<td>228(4.37), 260(s), 309(3.77)</td>
<td>3430, 3330, 3180(-NH$_2$), 1650(-COEt)</td>
</tr>
<tr>
<td>173.</td>
<td>229(4.42), 262(s), 310(3.77)</td>
<td>3400, 3300, 3160(-NH$_2$), 1670(-COEt)</td>
</tr>
<tr>
<td>174.</td>
<td>215(4.32), 293(3.78)</td>
<td>3380, 3320, 3220(-NH$_2$), 2210(CN)</td>
</tr>
<tr>
<td>175.</td>
<td>229(4.38), 263(s), 310(3.73)</td>
<td>3440, 3330, 3180(-NH$_2$), 1670(-C-)</td>
</tr>
<tr>
<td>176.</td>
<td>215(4.1), 258(s), 295(3.85)</td>
<td>3440, 3320, 3200(-NH$_2$), 2210(CN), 1640(-C=S-)</td>
</tr>
<tr>
<td>177.</td>
<td>227(4.42), 261(3.63), 308(3.75)</td>
<td>3400, 3280, 3230(-NH$_2$), 1670(COEt)</td>
</tr>
<tr>
<td>178.</td>
<td>221(4.36), 289(3.84)</td>
<td>3390, 3310(-NH$_2$), 2210(CEN)</td>
</tr>
<tr>
<td>179.</td>
<td>234(4.30), 328(3.29)</td>
<td>3360, 3200(-NH), 1620(-CNH)</td>
</tr>
</tbody>
</table>

AA = Absolute ethanol; B = Benzene; E = Ethanol; EA = Ethyl acetate; H = Hexane; M = Methanol; W = Water
EXPERIMENTAL

All melting points are uncorrected. Ultra-violet absorption spectra were determined in absolute ethanol using DK 2A spectrophotometer; log ε values are given in parenthesis. Infra-red spectra were taken in Nujol mulls unless mentioned otherwise. NMR spectra were run on a Varian A 60 spectrophotometer and the chemical shifts are reported as (δ) ppm using TMS as internal standard. Mass spectra were recorded on a Varian-Atlas CH-7 mass spectrophotometer at 70eV ionizing beam and using direct insertion probe.
N-Cyanoacetylphenylhydrazine (161)

Solution of ethyl cyanoacetate (23.73g; 0.21 mole), phenylhydrazine (21.6g; 0.2 mole) in absolute ethanol (100 ml) was refluxed for 12 hours. The solvent was removed under vacuum. To the oily residue was added ether (250 ml) and cooled for 2-3 days. Brownish solid obtained was filtered and recrystallized from isopropanol to afford 161, 17.5g(50%), m.p. 109-111°C.

Analysis: C_{15}H_{16}N_{2}O_{3}S requires: C, 59.16%; H, 5.25%; N, 9.21%

Found: C, 59.06%; H, 5.45%; N, 9.28%

2-Amino-3-carbethoxy-4-methyl-5-carboxamidothiophene (162)

To a mixture of acetoacetanilide (17.7g; 0.10 mole), ethyl cyanoacetate (11.3g; 0.1 mole), finely powdered sulfur (3.2g; 0.1 atom) and ethanol (30 ml) was added dropwise diethylamine (10 ml). The mixture was stirred for one hour at 45-50°C. On chilling the mixture for 3 days, the solid obtained was filtered and washed with cold isopropanol. Recrystallization from ethanol yielded 162, 9.0g(30%), m.p. 180-181°C.

Analysis: C_{15}H_{16}N_{2}O_{3}S requires: C, 59.20%; H, 5.26%; N, 9.21%

Found: C, 59.06%; H, 5.45%; N, 9.28%

2-Amino-3-carbethoxy-4-methylthienyl-5-acetic acid (163)

To a mixture of levulinic acid (11.6g; 0.1 mole), ethyl cyanoacetate (11.3g; 0.1 mole) and sulfur (3.2g; 0.1 atom) in ethanol (30 ml) was added diethylamine (10 ml) and was treated according to procedure described for 162. The solid obtained was filtered and dissolved in water. On acidifying the solution to pH 4-5, the precipitate obtained
was filtered. Recrystallization from ethyl acetate and petroleum ether (60-80°) mixture yielded 163, 7.3g (30%), m.p. 145-148°C.

Analysis: C_{10}H_{13}NO\textsubscript{4}S requires: C, 49.39; H, 5.35; N, 5.76%

Found: C, 49.64; H, 5.12; N, 5.43%

λ\textsubscript{max} nm (log ε): 227(4.42), 265(3.68), 305(3.76)

ν\textsubscript{max} cm\textsuperscript{-1}: 3460, 3340 (–NH\textsubscript{2}), 1740 (+C=O), 1636 (+C–OEt)

2-Amino-3-carbethoxy-5,7-diphenyl-6-methyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine (164)

To a mixture of 2,6-diphenyl-N-methyl-4-piperidone \textsuperscript{225} (13.4g; 0.05 mole), ethyl cyanoacetate (5.6g; 0.05 mole), finely powdered sulfur (1.6g; 0.05 atom) and ethanol (40 ml) was added morpholine (0.5 ml) dropwise. The reaction was carried out according to the procedure described for 162. Recrystallization from ethanol yielded 164, 7.8g (40%), m.p. 195-196°C.

Analysis: C_{23}H_{24}N_2S requires: C, 70.41; H, 6.12; N, 7.14%

Found: C, 70.10; H, 6.40; N, 7.34%

2-Amino-3-cyano-5,7-diphenyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine (165)

To a well stirred mixture of 2,6-diphenyl-N-methyl-4-piperidone \textsuperscript{225} (12.0g; 0.05 mole), malononitrile (3.3g; 0.05 mole), sulfur (1.6g; 0.05 atom) and ethanol (30 ml) was added diethylamine (6.0 ml) dropwise and treated according to the procedure described for 162. Recrystallization from ethanol yielded 165, 7.0g (35%), m.p. 171-173°C.

Analysis: C_{20}H_{17}N_3S requires: C, 72.50; H, 5.13%

Found: C, 72.59; H, 5.35%

ν\textsubscript{max} cm\textsuperscript{-1}: 3500, 3350, 3250 (–NH\textsubscript{2}), 2210 (–C=NH).
2-Amino-3-cyano-4,6-dimethyl-5,7-diphenyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine (166)

To a mixture of 1,3-dimethyl-2,6-diphenyl-4-piperidone (14.8 g; 0.05 mole), malononitrile (3.3 g; 0.05 mole), sulfur (1.6 g; 0.05 atom) and ethanol (30 ml) was added morpholine (5.0 ml) and treated according to the procedure described for 162. Recrystallization from ethanol yielded 166, 17.0 g (53%), m.p. 225-227°C.

Analysis: C_{22}H_{21}N_{3}S

<table>
<thead>
<tr>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, 73.53</td>
<td>C, 73.59</td>
</tr>
<tr>
<td>H, 5.84%</td>
<td>H, 5.85%</td>
</tr>
</tbody>
</table>

λ_{max} nm (log ε): 215 (4.0), 290 (3.78)

ν_{max} cm⁻¹: 3480, 3330, 3220 (-NH₂), 2220 (-C≡N)

2-Amino-3-(N-methylcarboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophene (167)

To a solution of cyclohexanone (9.8 g; 0.1 mole) in benzene (50 ml) was added N-methylcyanoacetamide (9.8 g; 0.1 mole), ammonium acetate (2.5 g) and glacial acetic acid (5 ml) and was refluxed for 24 hours with an arrangement for water separation. The reaction mixture was cooled and washed successively with water, sodium carbonate solution (5%) and water. The solvent was removed under vacuum. The crude product was employed directly for further reaction.

To a mixture of α-methylcarboxamido-α-cyclohexylidene acetonitrile (15.0 g), sulfur (3.2 g) and ethanol (30 ml) was added diethylamine (8 ml) and was treated according to the procedure described for 162. On chilling the reaction mixture overnight, solid obtained was filtered and recrystallized from absolute ethanol to yield 167, 14.7 g (70%), m.p. 193-195°C.
Analysis: \( \text{C}_{10} \text{H}_{14} \text{N}_{2} \text{OS} \) requires: C, 57.14%; H, 6.66%; N, 13.33%

Found: C, 57.13%; H, 6.95%; N, 13.22%

\( \lambda_{\text{max}} \) nm (logε): 228(4.29), 263(S), 300(3.66)

\( V_{\text{max}} \) cm\(^{-1}\) (CH\(_2\)-): 3510, 3420(-NH\(_2\)), 1620(-OH-)

2-Amino-3-\((\text{N-ethylcarboxamido})\)-4,5,6,7-tetrahydrobenzo(b)thiophene (168)

To a mixture of cyclohexanone (9.9g; 0.10 mole), sulfur (3.2g; 0.1 atom), \( \text{N-ethyl cyanoacetamide} \) (9.7g; 0.1 mole) and ethanol (30 ml) was added dropwise morpholine (9.0 ml) and treated according to the procedure described for 162. Recrystallization from methanol yielded 168, 7.8g (35%), m.p. 118-120°C.

Analysis: \( \text{C}_{11} \text{H}_{16} \text{N}_{2} \text{OS} \) requires: C, 58.93%; H, 7.14%

Found: C, 59.00%; H, 7.07%

\( \lambda_{\text{max}} \) nm (logε): 215(3.89), 225(4.14), 263(3.81), 317(3.86)

2-Amino-3-carboxanilido-4,5,6,7-tetrahydrobenzo(b)thiophene (169)

\( \alpha \)-Carboxanilido-\( \alpha \)-cyclohexylidene acetonitrile was prepared from cyclohexanone (3.92g; 0.04 mole), \( \text{N-phenyl cyanoacetamide} \) (6.4g; 0.04 mole) ammonium acetate (1.0g) and glacial acetic acid (2 ml) according to the procedure described for 167. To the mixture of the crude solid product (6.0g) thus obtained, sulfur (0.96g) and ethanol (20 ml) was added diethylamine (4.0 ml) and treated according to the procedure described for 162. Recrystallization from absolute ethanol yielded 169, 4.5g (41%), m.p. 143-145°C.
2-Amino-3-carbethoxy-4-methyl-4,5,6,7-tetrahydrobenzo(b)thiophene (170)

α-Carbethoxy-α-(2-methylcyclohexylidene) acetonitrile was prepared from 2-methylcyclohexanone (5.6g; 0.05 mole) and ethyl cyanoacetate (5.65g; 0.05 mole) according to the procedure described for 167. To the mixture of crude product (9.5g) thus obtained, sulfur (1.0g) and ethanol (20 ml) was added diethylamine (4 ml) and treated according to the procedure described for 162. Recrystallization from a mixture of ethanol and H₂O yielded 170, 6.0g (50%), m.p. 80-81°C.

Analysis : C₁₂H₁₇N₂O₂S requires : C, 60.25; H, 7.11%; Found : C, 60.12; H, 7.40%

2-Amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo(b)thiophene (171)

α-Cyano-α-(2-methylcyclohexylidene) acetonitrile was prepared from 2-methylcyclohexanone (11.2g; 0.1 mole) and malononitrile (6.6g; 0.1 mole) and treated according to the procedure described for 167. To the mixture of crude product (10g) thus obtained, sulfur (2.0g) and ethanol (20 ml) was added diethylamine (3.0 ml) and treated according to the procedure described for 162. Recrystallization from ethanol yielded 171, 5.0g (45%), m.p. 129-131°C.
Analysis: $C_{10}H_{12}N_2S$ requires: C, 62.48; H, 6.24; N, 14.58%  
Found: C, 62.76; H, 6.41; N, 14.79%  

$\lambda_{\text{max}} \text{nm (log } \epsilon) = 221(4.39), 260(5), 293(3.77)$  
$\nu_{\text{max}} \text{cm}^{-1} = 3460, 3340, 3220(-\text{NH}_2), 2210 \text{ (-C\equiv N)}$

2-Amino-3-carbethoxy-4-phenyl-4,5,6,7-tetrahydrobenzo(b)thiophene (172)

\(\alpha\)-Carbethoxy-\(\alpha\)-(2-phenylcyclohexylidene)acetonitrile was prepared from 2-phenylcyclohexanone (8.75 g, 0.05 mole) and ethyl cyanoacetate (5.65 g) according to the procedure described for 167. Diethylamine (3.0 ml) was added dropwise to the mixture of crude product (10 g), sulfur (1.0 g) and ethanol (20 ml) and was treated according to the procedure described for 162. Recrystallization from ethanol yielded 172, 5.7 g (50%), m.p. 108–110°.

Analysis: $C_{17}H_{19}NO_2S$ requires: C, 67.78; H, 6.31; N, 4.65%  
Found: C, 67.70; H, 6.60; N, 5.00%  

$\lambda_{\text{max}} \text{nm (log } \epsilon) = 228(4.37), 260(5), 309(3.77)$  
$\nu_{\text{max}} \text{cm}^{-1} = 3430, 3330, 3180(-\text{NH}_2), 1650(-\text{OEt})$

2-Amino-3-carbethoxy-4-(morpholinomethyl)-4,5,6,7-tetrahydrobenzo(b) thiophene (173)

A mixture containing 2-(morpholinomethyl)cyclohexanone HCl (23.1 g; 0.1 mole), ethyl cyanoacetate (11.3 g; 0.1 mole), sulfur (3.2 g; 0.1 atom) and ethanol (30 ml) was warmed to 45° in a water bath. Morpholine (12 ml) was added dropwise to the mixture and treated according to the procedure described for 162. Recrystallization
from ethanol yielded 173, 16.0g(50%), m.p. 212-214°C.

Analysis : \( \text{C}_{16}\text{H}_{24}\text{N}_{2}\text{O}_{3}\text{S} \) requires : C, 59.26; H, 7.40; N, 8.64; S, 9.89%

Found : C, 59.34, H, 7.59; N, 8.76; S, 9.77%

\( \lambda_\text{max} \text{nm(log } \varepsilon) = 229(4.42), 262\text{(s), }310(3.77) \)

\( \nu_\text{max} \text{cm}^{-1} = 3400, 3300, 3160\text{(-NH}_2\text{)}, 1670\text{(-C-OEt)} \)

MS, m/e = 324(M\(^+\)), 279, 224, 100 and 45

**Attempted synthesis of 2-amino-3-carbethoxy-4-(piperidinomethyl)-4,5,6,7-tetrahydrobenzo(b)thiophene (173a)**

The mixture of 2-(piperidinomethyl)cyclohexanone HCl \( 219 \) (11.5g; 0.05 mole), ethyl cyanoacetate (5.65g; 0.05 mole), sulfur (1.6g; 0.05 atom) and ethanol (20 ml) was warmed to 45°C in a water bath. Morpholine (8 ml) was added to the mixture dropwise and then treated according to the procedure described for 162. Recrystallization from ethanol yielded 6.0g of a compound melting at 210-212°C.

Analysis : \( \text{C}_{17}\text{H}_{26}\text{N}_{2}\text{O}_{3}\text{S} \) requires : C, 63.33; H, 8.07%

Found : C, 59.47; H, 7.59%

\( \lambda_\text{max} \text{nm(log } \varepsilon) = 229(4.33), 269\text{(s), }310(3.70) \)

\( \nu_\text{max} \text{cm}^{-1} = 3430, 3330, 3190\text{(-NH}_2\text{)}, 1670\text{(-C-OEt)} \)

MS, m/e = 324(M\(^+\)), 279, 224, 100, 45

Mixed melting point with 173 remained undepressed
Attempted synthesis of 2-amino-3-carbethoxy-4-(diethylaminomethyl)-4,5,6,7-tetrahydrobenzo(b)thiophene (173b)

A mixture of 2-(diethylaminomethyl)cyclohexanone HCl (21.9 g; 0.1 mole), ethyl cyanoacetate (11.3 g; 0.1 mole), sulfur (3.2 g; 0.1 atom) in ethanol (30 ml) was warmed to 45°C. Morpholine (16 ml) was added dropwise to it with continuous stirring. The mixture was treated according to the procedure described for 162. Recrystallization from ethanol yielded 11 g of a compound melting at 210-211°C.

Analysis: C_{16}H_{26}N_{2}S requires: C, 61.94%; H, 8.38%
Found: C, 59.32%; H, 7.46%

λ_{max} nm (log ε) : 229 (4.37), 265 (S), 310 (3.73)
ν_{max} cm^{-1} : 3420, 3315, 3180 (NH₂), 1680 (C-CH₂)

Mixed melting point with 173 remained undepressed.

2-Amino-3-cyano-4-(morpholinomethyl)-4,5,6,7-tetrahydrobenzo(b)thiophene (174)

Mixture of 2-(morpholinomethyl)cyclohexanone HCl (11.6 g; 0.05 atom) malononitrile (3.3 g; 0.05 mole), sulfur (1.6 g; 0.05 atom) and ethanol (20 ml) was cooled in an ice bath and morpholine (6.0 ml) was added dropwise and then treated according to the procedure described for 162. Recrystallization from absolute ethanol yielded 174, 14.0 g (50%), m.p. 182-184°C.

Analysis: C_{14}H_{19}N_{3}O requires: C, 60.69%; H, 6.85%; N, 15.19%
Found: C, 60.84%; H, 7.07%; N, 15.20%

λ_{max} nm (log ε) : 215(4.32), 293(3.78)
ν_{max} cm^{-1} : 3380, 3320, 3220 (NH₂), 2210 (C≡N)
Isobutyl 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate (175)

To a mixture of cyclohexanone (9.8 g, 0.1 mole), isobutyl cyanoacetate (14.1 g, 0.1 mole), sulfur (3.2 g, 0.1 atom) and ethanol (25.0 ml) was added diethylamine (8.0 ml) dropwise and treated according to the procedure described for 162. After cooling overnight, the dark brown solution was poured over a mixture of ice and water. The solid precipitated was filtered and dried. Recrystallization from n-hexane yielded 175, 10.1 g (40%), m.p. 68-70°C.

Analysis: requires: C, 61.66%; H, 7.50%; N, 5.53%

Found: C, 61.90%; H, 7.76%; N, 5.79%

$\lambda_{\text{max}}$ nm (log ε): 229 (4.38), 263 (5), 310 (3.73)

$\nu_{\text{max}}$ cm$^{-1}$: 3440, 3330, 3180 (-NH$_2$), 1670 (-CO$_2$H$_2$)

6-Acetyl-2-amino-3-cyano-4,5,6,7-tetrahydrothieno(2,3-c)pyridine (176)

Mixture of N-acetyl-4-piperidone (5.6 g, 0.04 mole), malononitrile (2.64 g, 0.04 mole), powdered sulfur (1.28 g, 0.04 atom) and ethanol (20 ml) was cooled in an ice bath and morpholine (4 ml) was added to it dropwise. The mixture was treated according to the procedure described for 162. Recrystallization from methanol yielded 176, 7.0 g (80%), m.p. 228-230°C.

Analysis: requires: C, 54.30%; H, 4.97%; N, 19.00%

Found: C, 54.38%; H, 5.01%; N, 19.12%

$\lambda_{\text{max}}$ nm (log ε): 215 (4.1), 258 (S), 295 (3.85)

$\nu_{\text{max}}$ cm$^{-1}$: 3400, 3320, 3200 (-NH$_2$), 2210 (CEN), 1640 (-C=N-)
2-Amino-9-aza-3-carbethoxy-9-methylthieno(2,3-b)bicyclo(3,2,1)octane (177)

To a mixture of a tropinone (6.95 g; 0.05 mole), ethyl cyanoacetate (5.65 g; 0.05 mole), sulfur (1.6 g; 0.05 atom) and ethanol (30 ml) was added morpholine (5.0 ml) dropwise and treated according to the procedure described for 162. Recrystallization from a mixture of benzene and n-hexane yielded 177, 3.0 g (43%), m.p. 154-156°C.

Analysis: C_{13}H_{18}N_{2}O_{2}S requires: C, 66.28; H, 6.97; N, 8.14%

Found: C, 66.02; H, 7.32; N, 8.31%

$\lambda_{\text{max}} \text{nm (log} \epsilon) = 227(4.42), 261(3.63), 308(3.75)$$^Q$

$\nu_{\text{max}} \text{cm}^{-1} = 3400, 3280, 3230(-\text{NH}_2)$, 1670 (-COEt)

NMR (δ: CDCl₃): 1.3 (t, 3H, -COCH₂CH₃), 2.4 (s, 3H, -NO₂), 4.2 (q, 2H, $^O$-COCH₂CH₃), 7.4 (s, 6H, C₆H₆)

MS, m/e: 266(M⁺), 237, 192, 45 and 29

2-Amino-9-aza-3-cyano-9-methylthieno(2,3-b)bicyclo(3,2,1)octane (178)

A mixture of tropinone (6.50 g; 0.05 mole), malononitrile (33 g; 0.05 mole), sulfur (1.6 g; 0.05 atom) and ethanol (30 ml) was cooled in an ice bath and morpholine (5.0 ml) was added dropwise. The reaction was treated according to the procedure described for 162. Recrystallization from ethanol yielded 178, 5.5 g (50%), m.p. 276°C (dec).

Analysis: C_{11}H_{13}N₃S requires: C, 60.27; H, 5.94; N, 19.17%

Found: C, 60.26; H, 6.14; N, 18.90%

$\lambda_{\text{max}} \text{nm (log} \epsilon) = 221(4.36), 289(3.84)$$^Q$

$\nu_{\text{max}} \text{cm}^{-1} = 3390, 3310(-\text{NH}_2)$, 2210 (-CSN)
NMR(δ:CDCl₃): 2.3(s, 3H, N-CH₃), 3.7(d, IH, C-8), 6.8(s, 2H, NH₂),
three hours after the addition of D₂O, the singlet at 6.8 disappeared.

MS, m/z: 219(M⁺), 190

3-Anilino-1,2,5,6,7,8-hexahydro-2,2-pentamethylene benzob(thieno)
(2,3-d)pyrimidin-4(3H)-one (179)

To a mixture of N-cyanoacetylphenylhydrazine (3.5g; 0.02 mole) cyclo-
hexanone (3.92g; 0.04 mole), sulfur (0.64g; 0.02 atom) and ethanol
(30 ml) was added morpholine (3 ml) dropwise. The mixture was stirred
at 45°C. After 30 minutes stirring, another portion of morpholine
(1 ml) was added to it and stirred for further one hour. On cooling
overnight, the solid obtained was filtered and washed successively
with isopropanol (20 ml) and methanol (10 ml). Recrystallization
from methanol yielded 179, 3g(41%), m.p. 242-244°C.

Analysis : C₂₁H₂₅N₃OS requires : C, 68.66; H, 6.81; N, 11.44%
Found : C, 68.69; H, 7.08; N, 11.60%

λmax nm(log ε): 234(4.34), 328(3.29)

νmax cm⁻¹: 3360, 3200(-NH), 1620 ω (-CNH₃)
CHAPTER III
N^2-SUBSTITUTED-N^1-23-CARBETHOXY THIENYLTHIOUREAS

INTRODUCTION

Thioureas are known to have antimicrobial and various other pharmacological properties. In 1952, a number of thiourea derivatives of p-amino-salicylic acid (184) showed in vitro antimicrobial activity equal to or more than that of the acid itself. In the following year, 4,4'-disethoxy-thiocarbanilide (185a) was found to possess high order of antitubercular activity in mice infected with Bacillus H37RV. This was followed by the synthesis of more than 300 carbanilides. In vitro and in vivo tests revealed that 1/3 of the compounds were active against M. tuberculosis. Two of these compounds, 4-ethoxy-4'-isobutoxythiocarbanilide (185b) and 4-n-butoxy-4'-dimethylaminothiocarbanilide (185c) when tested in mice and guinea-pigs exceeded the antitubercular
activity of PAS and streptomycin and approached to that of INH. Thiambutosine (185c) is used clinically as antileprosy drug. 234

Structure activity relationship studies of alkyl and aryl substituted p-acylphenylthioureas (186) has been reported. 235 Maximum activity against M. tuberculosis is exhibited by derivatives with the terminal N-substituted by a single straight chain alkyl groups not exceeding 4 carbons. There is a continued interest in thiourea compounds as antitubercular agents. 236

Antihypertensive activity has been reported in thioureas. 237 A series of 2- and 2,6-substituted phenylthioureas (187) have potent antihypertensive activity in metacortical hypertensive rats.

\[
\begin{array}{c}
\text{X} \\
\text{NH-C-NH}_2 \\
\text{X}
\end{array}
\]

\[
X = \text{Cl, OCH}_3
\]

(187)

Burimamide (188) antagonizes completely the effects of histamine H2 receptors. 238 Piperazinothioureas are found to have anticonvulsant activity. 239 Phenylalkyl thioureas (189) have shown antiinflammatory activity at 1-100 mg/kg dosage level. 240

\[
\begin{array}{c}
\text{(CH}_2\text{)}_4\text{NH-C-NH}_3 \\
\text{S}
\end{array}
\]

\[
\begin{array}{c}
\text{R} \\
\text{N-C-NH}_2 \\
\text{R}_1
\end{array}
\]

\[
R = \text{H, Cl, F} \\
R_1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{Propyl, Isopropyl}
\]

(188) (189)
Cystostatic effect has been exhibited by N-allyl- and N-phenyl thiourea derivatives. Significant antifungal activity has been reported in N-alkyl-N-aryl thioureas. A series of N-phenyl thioureas has been tested for antiviral activity. Compound 184a has high order of activity against Polio virus.

Psychotropic activity has been found in benzothiophene derivatives (190). Recently, Sauter et al have synthesized thioureas (191) from 2-amino-3-carboxamide thiophenes.

It was, therefore, thought of interest to synthesize thiophene isosters (II-Scheme I) of N-phenyl-N-alkyl-thiourea with a view to obtain biologically active compounds and to study structure activity relationship in the series.

Results and Discussion
2-Amino-3-carbethoxy-4,5-substituted thiophene (I) was reacted with appropriate alkyl or aryl isothiocyanates in ethanol to obtain the corresponding thiourea derivatives (II).
Physical constants of thienyl thioureas (192-222) prepared are recorded in Table 3. Thienyl thioureas are yellowish crystalline compounds, sparingly soluble in ethanol and chloroform.

**Pharmacological activity** - Compounds 193, 195, 196, 198, 199, 207, 209, 217 and 219 were screened for analgesic and antiinflammatory activities (Table 4). Compound 219 showed analgesic activity at 200 mg/kg, which was more than 5th as potent as aspirin. On the other hand, compounds 196 and 199 were 1/2 as active as aspirin. Antiinflammatory activity exhibited by 209 and 217 was not significant.

**Microbiological activity** - Compounds 193-218 and 222 were screened for antibacterial and antifungal activity by the serial dilution technique using dimethylformamide as solvent. The dilutions were made such that in no instance there was more than 1% DMF in the medium under study. DMF at such concentration has no inhibitory effect on the organisms under test.

None of these compounds at 50mcg/ml concentration showed any appreciable inhibition on the growth of E. Coli, S. Shigae, S. typhi, Pr. Ox. 19, Pr. aeruginosa, M. tuberculosae, G. albicans, P. Fleasemiel, N. asteroids, and A. Fumigatus. It is evident from the data recorded in Table 5 that compounds 193, 195, 196, 199, 210, 211, 213, 214 and 218 exhibit significant antibacterial activity against gram +ve organisms. Among the series, compound 195 is the most active antibacterial agent. Besides the antibacterial property, methyl and allyl-thiourea derivatives 193, 198, 210 and 218 showed antifungal activity (Table 5).

In general, derivatives having the terminal nitrogen substituted
by a single short chain alkyl or aralkyl groups show maximum antibacterial activity. With the increase in the chain length beyond butyl group, the activity falls off drastically. Replacement of the terminal alkyl moiety by phenyl or wide variety of substituted phenyl groups gave substantially inactive compounds. Similar structure activity relationship has been observed earlier with phenylalkylthioureas. 235
### Table 3

Physical constants of $N^2$-substituted-$N^1$-thienyl thioureas

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>M.P. $^\circ$C</th>
<th>Yield</th>
<th>Crystallization solvent</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>192. H</td>
<td>C$_2$H$_5$-</td>
<td>CH$_2=$CH-CH$_2$-</td>
<td>211-214</td>
<td>60</td>
<td>A</td>
<td>C$<em>{13}$H$</em>{16}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>193. CH$_3$-</td>
<td>CH$_3$-</td>
<td>CH$_3$-</td>
<td>182-184</td>
<td>80</td>
<td>A-B</td>
<td>C$<em>{11}$H$</em>{16}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>194. CH$_3$-</td>
<td>CH$_3$-</td>
<td>C$_2$H$_5$-</td>
<td>164-166</td>
<td>82</td>
<td>A-B</td>
<td>C$<em>{12}$H$</em>{18}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>195. CH$_3$-</td>
<td>CH$_3$-</td>
<td>n-C$_4$H$_9$-</td>
<td>128-130</td>
<td>70</td>
<td>A</td>
<td>C$<em>{14}$H$</em>{22}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>196. CH$_3$-</td>
<td>CH$_3$-</td>
<td>n-C$<em>6$H$</em>{13}$-</td>
<td>92-94</td>
<td>78</td>
<td>A</td>
<td>C$<em>{16}$H$</em>{26}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>197. CH$_3$-</td>
<td>CH$_3$-</td>
<td>c-C$<em>6$H$</em>{11}$-</td>
<td>179-181</td>
<td>75</td>
<td>A</td>
<td>C$<em>{16}$H$</em>{24}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>198. CH$_3$-</td>
<td>CH$_3$-</td>
<td>CH$_2=$CH-CH$_2$-</td>
<td>133-135</td>
<td>70</td>
<td>A-B</td>
<td>C$<em>{13}$H$</em>{18}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>199. CH$_3$-</td>
<td>CH$_3$-</td>
<td>C$_6$H$_5$-CH$_2$-</td>
<td>146-148</td>
<td>65</td>
<td>A-B</td>
<td>C$<em>{17}$H$</em>{20}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>200. CH$_3$-</td>
<td>CH$_3$-</td>
<td>C$_6$H$_5$-</td>
<td>169-172</td>
<td>74</td>
<td>A</td>
<td>C$<em>{16}$H$</em>{18}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>201. CH$_3$-</td>
<td>CH$_3$-</td>
<td>2-CH$_3$-C$_6$H$_4$-</td>
<td>164-165</td>
<td>70</td>
<td>A</td>
<td>C$<em>{17}$H$</em>{20}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>202. CH$_3$-</td>
<td>CH$_3$-</td>
<td>4-CH$_3$-C$_6$H$_4$-</td>
<td>169-171</td>
<td>80</td>
<td>A</td>
<td>C$<em>{17}$H$</em>{20}$N$_2$O$_2$S$_2$</td>
<td></td>
</tr>
<tr>
<td>203. -(CH$_2$)$_3$-</td>
<td>CH$_3$-</td>
<td>186-188</td>
<td>60</td>
<td>A-B</td>
<td>C$<em>{12}$H$</em>{16}$N$_2$O$_2$S$_2$.</td>
<td>C$_2$H$_5$OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>204.</td>
<td>-(CH₂)₃⁻</td>
<td>C₂H₅⁻</td>
<td></td>
<td></td>
<td>200-202</td>
<td>72 A</td>
<td></td>
</tr>
<tr>
<td>205.</td>
<td>-(CH₂)₃⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td></td>
<td></td>
<td>161-163</td>
<td>84 A-B</td>
<td></td>
</tr>
<tr>
<td>206.</td>
<td>-(CH₂)₃⁻</td>
<td>C₆H₅-C₂H₄⁻</td>
<td></td>
<td></td>
<td>154-156</td>
<td>70 A-B</td>
<td></td>
</tr>
<tr>
<td>207.</td>
<td>-(CH₂)₃⁻</td>
<td>C₆H₅⁻</td>
<td></td>
<td></td>
<td>183-185</td>
<td>65 A-B</td>
<td></td>
</tr>
<tr>
<td>208.</td>
<td>-(CH₂)₃⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>162-164</td>
<td>62 A-B</td>
<td></td>
</tr>
<tr>
<td>209.</td>
<td>-(CH₂)₃⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>198-200</td>
<td>60 A-B</td>
<td></td>
</tr>
<tr>
<td>210.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃⁻</td>
<td></td>
<td></td>
<td>193-195</td>
<td>80 A-B</td>
<td></td>
</tr>
<tr>
<td>211.</td>
<td>-(CH₂)₄⁻</td>
<td>C₂H₅⁻</td>
<td></td>
<td></td>
<td>161-164</td>
<td>82 A-B</td>
<td></td>
</tr>
<tr>
<td>212.</td>
<td>-(CH₂)₄⁻</td>
<td>n-C₆H₁₃⁻</td>
<td></td>
<td></td>
<td>87-89</td>
<td>73 A</td>
<td></td>
</tr>
<tr>
<td>213.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td></td>
<td></td>
<td>154-156</td>
<td>85 A-B</td>
<td></td>
</tr>
<tr>
<td>214.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅CH₂⁻</td>
<td></td>
<td></td>
<td>136-138</td>
<td>87 A-B</td>
<td></td>
</tr>
<tr>
<td>215.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅⁻</td>
<td></td>
<td></td>
<td>184-187</td>
<td>82 A-B</td>
<td></td>
</tr>
<tr>
<td>216.</td>
<td>-(CH₂)₄⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>176-178</td>
<td>84 A-B</td>
<td></td>
</tr>
<tr>
<td>217.</td>
<td>-(CH₂)₄⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>165-167</td>
<td>80 A-B</td>
<td></td>
</tr>
<tr>
<td>218.</td>
<td>-(CH₂)₅⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td></td>
<td></td>
<td>114-116</td>
<td>76 A-B</td>
<td></td>
</tr>
<tr>
<td>219.</td>
<td>-(CH₂)₅⁻</td>
<td>C₆H₅-C₂H₄⁻</td>
<td></td>
<td></td>
<td>129-131</td>
<td>70 A</td>
<td></td>
</tr>
<tr>
<td>220.</td>
<td>-(CH₂)₅⁻</td>
<td>C₆H₅⁻</td>
<td></td>
<td></td>
<td>156-157</td>
<td>75 A</td>
<td></td>
</tr>
<tr>
<td>221.</td>
<td>-(CH₂)₅⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>153-155</td>
<td>73 A-B</td>
<td></td>
</tr>
<tr>
<td>222.</td>
<td>-(CH₂)₅⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td></td>
<td></td>
<td>149-151</td>
<td>70 A-B</td>
<td></td>
</tr>
</tbody>
</table>

A = Ethanol;  B = Chloroform
**TABLE 4**
Pharmacological screening of thienyl thioureas*

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Analgesia (writhing test) % inhibition 200mg/kg p.o</th>
<th>Antiinflammatory activity % inhibition 200mg/kg p.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>8.0</td>
<td>$\phi$</td>
</tr>
<tr>
<td>196</td>
<td>27.0</td>
<td>$\phi$</td>
</tr>
<tr>
<td>199</td>
<td>30.0</td>
<td>$\phi$</td>
</tr>
<tr>
<td>207</td>
<td>$\phi$</td>
<td>$\phi$</td>
</tr>
<tr>
<td>209</td>
<td>$\phi$</td>
<td>14.0</td>
</tr>
<tr>
<td>217</td>
<td>$\phi$</td>
<td>19.0</td>
</tr>
<tr>
<td>219</td>
<td>45.4</td>
<td>13.6</td>
</tr>
<tr>
<td>Aspirin</td>
<td>55.0</td>
<td>-</td>
</tr>
<tr>
<td>Phenylbutazone, 100mg/kg</td>
<td>-</td>
<td>60.0</td>
</tr>
</tbody>
</table>

* All the compounds tested showed LD$_{50}$ more than 1000mg/kg, p.o., while by i.p. route more than 100mg/kg.

$\phi$ = no significant activity
### TABLE 5

Antimicrobial activity of thienyl thioureas
(minimum inhibitory conc. values in mcg/ml)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>S. aureus</th>
<th>S. aureus (A/R)</th>
<th>S. lutea</th>
<th>B. subtilis</th>
<th>T. mentagrophytes</th>
<th>M. gypseum</th>
</tr>
</thead>
<tbody>
<tr>
<td>193.</td>
<td>50.000</td>
<td>25.000</td>
<td>25.500</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
</tr>
<tr>
<td>198.</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
</tr>
<tr>
<td>199.</td>
<td>25.000</td>
<td>50.000</td>
<td>25.000</td>
<td>50.000</td>
<td>50.000</td>
<td>50.000</td>
</tr>
<tr>
<td>211.</td>
<td>12.500</td>
<td>12.500</td>
<td>12.500</td>
<td>25.000</td>
<td>25.000</td>
<td>25.000</td>
</tr>
<tr>
<td>213.</td>
<td>12.500</td>
<td>12.500</td>
<td>12.500</td>
<td>25.000</td>
<td>25.000</td>
<td>25.000</td>
</tr>
<tr>
<td>214.</td>
<td>50.000</td>
<td>50.000</td>
<td>12.500</td>
<td>12.500</td>
<td>12.500</td>
<td>12.500</td>
</tr>
</tbody>
</table>

$\emptyset$ = MIC more than 50 mcg/ml.
from ethanol yielded 200, 12.40g (74%), m.p. 169-172°C.

Analysis: \( \text{C}_{16\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2} \) requires: C, 57.48; H, 5.38; N, 8.38%

Found: C, 57.22; H, 5.73; N, 8.66%

\( \text{N}^2\text{-o-Tolyl-} \text{N}^{1}\underline{\text{S}^2}\text{-} \left( 3\text{-carbethoxy-4,5\text{-dimethylthienyl}} \right) \text{/thiourea} \) (201)

A mixture of 2-amino-3-carbethoxy-4,5-dimethylthiophene \(^{123} \) (9.90g; 0.05 mole) in ethanol (50 ml) and o-tolylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 201, 12.20g (70%), m.p. 164-165°C.

Analysis: \( \text{C}_{17\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2} \) requires: C, 58.61; H, 5.74; N, 8.04%

Found: C, 58.75; H, 6.00; N, 8.44%

\( \text{N}^2\text{-p-Tolyl-} \text{N}^{1}\underline{\text{S}^2}\text{-} \left( 3\text{-carbethoxy-4,5\text{-dimethylthienyl}} \right) \text{/thiourea} \) (202)

A mixture of 2-amino-3-carbethoxy-4,5-dimethylthiophene \(^{123} \) (9.9g; 0.05 mole) in ethanol (50 ml) and p-tolylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 202, 13.9g (80%), m.p. 169-171°C.

Analysis: \( \text{C}_{17\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2} \) requires: C, 58.62; H, 5.74; N, 8.04; S, 18.41%

Found: C, 58.95; H, 6.05; N, 7.88; S, 18.39%

\( \text{N}^2\text{-Methyl-} \text{N}^{1}\underline{\text{S}^2}\text{-} \left( 3\text{-carbethoxy cyclopenta(b)thienyl} \right) \text{/thiourea} \) (203)

A mixture of 2-amino-3-carbethoxy cyclopenta(b)thiophene \(^{124} \) (10.5g; 0.05 mole) in ethanol (50 ml) and methylisothiocyanate (3.65g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from a mixture of ethanol and chloroform yielded 203, 8.52g (60%), m.p. 186-188°C.
Analysis: \( C_{12}H_{16}N_2O_2S_2 \). \( C_2H_5OH \) requires: C, 50.93%; H, 6.66%

Found: C, 51.23%; H, 6.35%

\( \nu_{\text{max}} \text{ cm}^{-1}: 3230 (-\text{NH}), 1670 (-\text{C-}), 1240 (-\text{CNH}) \)

**N\(^2\)-Ethyl-N\(^1\)-2-(3-carbethoxy cyclopenta(b) thienyl) thiourea (204)**

A mixture of 2-amino-3-carbethoxy cyclopenta(b) thiophene\(^{124} \) (10.5g; 0.05 mole) in ethanol (50 ml) and ethylisothiocyanate (4.35g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 204, 10.6g (72%), m.p. 200-202°C.

Analysis: \( C_{13}H_{18}N_2O_2S_2 \) requires: C, 52.34%; H, 6.03%; N, 9.39%

Found: C, 52.52%; H, 6.00%; N, 9.55%

\( \lambda_{\text{max}} \text{ nm(log E)} : 258(4.07), 348(4.08), \)

\( \nu_{\text{max}} \text{ cm}^{-1}: 3230 (-\text{NH}), 1670 (-\text{COEt}), 1225 (-\text{C-}) \)

**N\(^2\)-Allyl-N\(^1\)-2-(3-carbethoxy cyclopenta(b) thienyl) thiourea (205)**

A mixture of 2-amino-3-carbethoxy cyclopenta(b) thiophene\(^{124} \) (10.5g; 0.05 mole) in ethanol (50 ml) and allylisothiocyanate (4.95g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 205, 13.0g (84%), m.p. 161-163°C.

Analysis: \( C_{14}H_{18}N_2O_2S_2 \) requires: C, 54.19%; H, 5.80%

Found: C, 54.06%; H, 5.95%

\( \nu_{\text{max}} \text{ cm}^{-1}: 3220 (-\text{NH}), 1660 (-\text{C-}), 1240 (-\text{C-}) \)
N\textsuperscript{2}-Benzyl-N\textsuperscript{1}-\text{\textit{\textcrayon\textsuperscript{-2-\text{(3-carbethoxy cyclopenta(b)thienyl)}\thiourea (206)}}

A mixture of 2-amino-3-carbethoxy cyclopenta(b)thiophene\textsuperscript{124} (10.5 g; 0.05 mole) in ethanol (50 ml) and benzylisothiocyanate (7.45 g; 0.05 mole) was treated according to the procedure described for 192. The product recrystallized from a mixture of ethanol and chloroform yielded 206, 12.6 g (70%), m.p. 154-156°C.

Analysis: \(C_{18}H_{20}N_2O_2S_2\) requires: C, 60.00; H, 5.55%  
Found: C, 60.00; H, 5.82%

N\textsuperscript{2}-Phenyl-N\textsuperscript{1}-\text{\textit{\textcrayon\textsuperscript{-2-\text{(3-carbethoxy cyclopenta(b)thienyl)}\thiourea (207)}}

A mixture of 2-amino-3-carbethoxy cyclopenta(b)thiophene\textsuperscript{124} (10.5 g; 0.05 mole) in ethanol (50 ml) and phenylisothiocyanate (6.75 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 207, 11.7 g (65%), m.p. 183-185°C.

Analysis: \(C_{17}H_{18}N_2O_2S_2\) requires: C, 58.96; H, 5.20%  
Found: C, 59.2; H, 5.44%

N\textsuperscript{2}-m-Tolyl-N\textsuperscript{1}-\text{\textit{\textcrayon\textsuperscript{-2-\text{(3-carbethoxy cyclopenta(b)thienyl)}\thiourea (208)}}

A mixture of 2-amino-3-carbethoxy cyclopenta(b)thiophene\textsuperscript{124} (10.5 g; 0.05 mole) in ethanol (50 ml) and m-tolylisothiocyanate (7.45 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 208, 11.1 g (62%), m.p. 162-164°C.

Analysis: \(C_{18}H_{20}N_2O_2S_2\) requires: C, 60.00; H, 5.55%  
Found: C, 60.15; H, 5.80%
A mixture of 2-amino-3-carbethoxy cyclopenta(b)thiophene (10.5 g; 0.05 mole) in ethanol (50 ml) and p-tolylisothiocyanate (7.4 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 209, 10.8 g (60%), m.p. 198-200°C.

Analysis: C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> requires: C, 60.01; H, 5.55%
Found: C, 60.20; H, 5.90%

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.25 g; 0.05 mole) in ethanol (50 ml) and methylisothiocyanate (3.65 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 210, 12.0 g (80%), m.p. 193-195°C.

Analysis: C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> requires: C, 52.34; H, 6.03; N, 9.39; S, 21.50%
Found: C, 52.69; H, 6.25; N, 9.40; S, 21.22%

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.25 g; 0.05 mole) in ethanol (50 ml) and ethylisothiocyanate (4.35 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 211, 12.79 g (82%), m.p. 161-164°C.
Analysis: $C_{14}H_{20}N_{2}O_{2}S_{2}$ requires: C, 53.84; H, 6.40; N, 8.97; S, 20.53%

Found: C, 53.91; H, 6.49; N, 8.94; S, 19.86%

$N^2$-n-Hexyl-$N^1$-Z-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)thiourea (212)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.25g; 0.05 mole) in ethanol (50 ml) and n-hexylisothiocyanate (7.15g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 212, 13.46g (73%), m.p. 87-89°C.

Analysis: $C_{15}H_{20}N_{2}O_{2}S_{2}$ requires: C, 58.69; H, 7.60; N, 7.61; S, 17.41%

Found: C, 58.79; H, 7.88; N, 7.68; S, 17.27%

$N^2$-Allyl-$N^1$-Z-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)thiourea (213)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.25g; 0.05 mole) in ethanol (50 ml) and allylisothiocyanate (4.95g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from a mixture of ethanol — chloroform yielded 213, 13.8g (85%), m.p. 154-156°C.

Analysis: $C_{15}H_{20}N_{2}O_{2}S_{2}$ requires: C, 55.55; H, 6.17; N, 8.64%

Found: C, 55.32; H, 6.26; N, 8.56%

$N^2$-Benzyl-$N^1$-Z-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)thiourea (214)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.25g; 0.05 mole) in ethanol (50 ml) and benzylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192.
Recrystallization from ethanol-chloroform mixture yielded 214. 16.26g (87%), m.p. 136-138°C.

Analysis: C_{19}H_{22}N_{2}O_{2}S requires: C, 60.96; H, 5.88; N, 7.40; S, 17.12%

Found: C, 61.15; H, 6.18; N, 7.58; S, 16.91%

N²-Phenyl-N¹-[2-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thieryl)] thiourea (215)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene\(^{123}\) (11.25g; 0.05 mole) in ethanol (50 ml) and phenylisothiocyanate (6.75g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from a mixture of ethanol-chloroform yielded 215, 14.76g (82%), m.p. 184-187°C.

Analysis: C_{18}H_{20}N_{2}O_{2}S requires: C, 59.99; H, 5.55; N, 7.78%

Found: C, 60.02; H, 5.87; N, 7.93%

N²-m-Tolyl-N¹-[2-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thieryl)] thiourea (216)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene\(^{123}\) (11.25g; 0.05 mole) in ethanol (50 ml) and m-tolylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform yielded 216, 15.5g (84%), m.p. 176-178°C.

Analysis: C_{19}H_{22}N_{2}O_{2}S requires: C, 60.96; H, 5.88%

Found: C, 60.95; H, 5.92%

N²-p-Tolyl-N¹-[2-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thieryl)] thiourea (217)

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene\(^{123}\)
(11.25 g; 0.05 mole) in ethanol (50 ml) and p-tolylisothiocyanate (7.45 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from a mixture of ethanol-chloroform yielded 217, 15.0 g (80%), m.p. 165-167°C.

Analysis: C_{19}H_{22}N_2S_2 requires C, 60.96; H, 5.88; N, 7.48; S, 17.12%
Found: C, 60.91; H, 6.02; N, 7.30; S, 17.36%

N^2-allyl-N^1{(3-carbethoxy cyclohepta(b)thienyl)}thiourea (218)

A mixture of 2-amino-3-carbethoxy cyclohepta(b)thiophene (11.95 g; 0.05 mole) in ethanol (50 ml) and allylisothiocyanate (4.95 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 218, 12.85 g (76%), m.p. 114-116°C.

Analysis: C_{16}H_{22}N_2O_2S requires C, 56.80; H, 6.50; N, 8.28%
Found: C, 56.65; H, 6.64; N, 8.40%

N^2-benzyl-N^1{(3-carbethoxy cyclohepta(b)thienyl)}thiourea (219)

A mixture of 2-amino-3-carbethoxy cyclohepta(b)thiophene (11.95 g; 0.05 mole) in ethanol (50 ml) and benzylisothiocyanate (7.45 g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 219, 13.60 g (70%), m.p. 129-131°C.

Analysis: C_{20}H_{24}N_2O_2S_2 requires C, 61.85; H, 6.18; N, 7.21%
Found: C, 61.59; H, 6.47; N, 7.29%
N^2-Phenyl-N^1-\{2-(3-carbethoxy cyclohepta(b)thienyl)\}thiourea (220)

A mixture of 2-amino-3-carbethoxy cyclohepta(b)thiophene\(^{140}\) (11.95g; 0.05 mole) in ethanol (50 ml) and phenylisothiocyanate (6.75g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol yielded 220, 14.02g(75%), m.p. 155-157°C.

Analysis: \(C_{19}H_{22}N_2O_2S_2\) requires: C, 60.96; H, 5.88; N, 7.48%

Found: C, 61.01; H, 6.02; N, 7.33%

N^2-m-Tolyl-N^1-\{2-(3-carbethoxy cyclohepta(b)thienyl)\}thiourea (221)

A mixture of 2-amino-3-carbethoxy cyclohepta(b)thiophene\(^{140}\) (11.95g; 0.05 mole) in ethanol (50 ml) and m-tolylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 221, 14.16g(73%), m.p. 153-155°C.

Analysis: \(C_{20}H_{24}N_2O_2S_2\) requires: C, 61.85; H, 6.18; N, 7.21%

Found: C, 61.49; H, 6.36; N, 7.04%

N^2-p-Tolyl-N^1-\{2-(3-carbethoxy cyclohepta(b)thienyl)\}thiourea (222)

A mixture of 2-amino-3-carbethoxy cyclohepta(b)thiophene\(^{140}\) (11.95g; 0.05 mole) in ethanol (50 ml) and p-tolylisothiocyanate (7.45g; 0.05 mole) was treated according to the procedure described for 192. Recrystallization from ethanol-chloroform mixture yielded 222, 13.6g (70%), m.p. 149-151°C.

Analysis: \(C_{20}H_{24}N_2O_2S_2\) requires: C, 61.85; H, 6.18; N, 7.21%

Found: C, 61.60; H, 6.49; N, 7.29%
CHAPTER IV

2-MERCAPTO THIENO(2,3-d)PYRIMIDIN-4(3H)-ONES

INTRODUCTION

A variety of pharmacological properties are reported in 4-quinazolones. This has been comprehensively reviewed.\textsuperscript{247} Antihistaminic and antispasmodic activity has been reported in 2-alkylthio-4-quinazolones.\textsuperscript{248} 3-(3-Amino-2-benzoyloxypropyl)-1(\textit{H}), 3(\textit{H})-quinazolin-4-one-2-thiones having coronary dilatory properties\textsuperscript{249} have been synthesized. 2-(Alkylthio)pyrido(2,3-d)pyrimidin-4(3H)-ones have long lasting diuretic and selective natriuretic activity.\textsuperscript{250} 2-Alkylthio-3-phenyl-4(3H)-quinazolones have been synthesized as potential ataractic agents.\textsuperscript{251} Murav'eva et al synthesized a series of 3-(p-alkoxyphenyl)-2-alkylthio-4(3H)-quinazolinones with tuberculostatic activity.\textsuperscript{252} Recently, similar derivatives have been synthesized with antitubercular and antifungal activity.\textsuperscript{253,254} Significant antiinflammatory effect has been reported in 1-alkyl-4-aryl-2-\textit{(1H)}-quinazoline-thiones.\textsuperscript{255} Hypocholesterolemic, sedative and antitussive properties of 2-mercapto-3,4-dihydrothieno(2,3-d)pyrimidin-4-ones have been disclosed.\textsuperscript{173}

It was, therefore, thought of interest to prepare thiophene analogs (II, Scheme I) of 2-mercaptoquinazolin-4-one for pharmacological screening.
RESULTS AND DISCUSSION

2-Mercapto-4-quinazolones have been obtained directly by refluxing anthranilic acids with isothiocyanates without isolating the intermediate thioureas. Fusing esters or amides of 2-amin thiophene-3-carboxylic acid with thiourea at 170-173°C, Sauter et al. have obtained 2-mercapto thieno(2,3-d)pyrimidin-4(3H)-ones in one step. However, substituted thioureas were cyclized in presence of NaOH. Similar derivatives have been synthesized by Russian workers. In the present work, N₂-alkyl or aryl-N¹-(2-thienyl) thiourea (I) was refluxed for 8-12 hours in ethanol saturated with dry HCl to obtain 2-mercaptop-3-substituted thieno(2,3-d)pyrimidin-4(3H)-
one (II) in 60-80\% yield (Scheme I). Thieno(2,3-d)pyrimidin-4(3H)-
one obtained were colorless, sparingly soluble in ethanol and chloro-
form (Table 6).

UV spectra showed strong absorption bands at 220 nm (4.4),
242-255 nm (3.93) and 310 nm (4.25). These compounds exhibited -NH
(3200 cm\(^{-1}\)), carbonyl (1690 cm\(^{-1}\)) and thiocarbonyl (1215 cm\(^{-1}\))
functions in IR spectra.

When allyl thiourea (III) was refluxed in ethanol saturated with
dry HCl, instead of the expected product IV, thiazolo(3,2-a) thieno
(2,3-d)pyrimidin-5-one (V) was obtained. The structure of these
compounds (244-247) was supported by their spectral data. In UV,
thiazolo compounds (V) exhibit absorption bands at 210 nm (4.3),
275 nm (3.9) and 320 nm (4.0) with a shoulder at 245 nm. The absorption
band at 275 nm distinguishes thiazolo compounds (V) from 2-mercapto
thieno pyrimidones (IV). IR spectra of these compounds (244-247)
showed absence of -NH- and -C- functions. A doublet at (1.48)
corresponding to 2-methyl group and absence of vinyl proton in NMR
support the structure (V) and rules out structure (VI).

Thiazolo pyrimidones (244-247) are soluble in alcohol and
completely soluble in chloroform in contrast to 2-mercapto thieno
(2,3-d) pyrimidones (Table 6). Earlier, pyrido thiazolopyrimidones
have been synthesized by Narang et al.\(^{260}\) using HCl/EtOH to cyclize allyl
thioureas.
3-Allyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one \(^\text{V}a\) when refluxed with ethanol saturated with \(\text{HCl}\) afforded thiazolo derivative (V). Spectral data were identical with the product obtained starting with III. This confirms the structure of thiazolo(3,2-a)thieno(2,3-d)pyrimidin-5-one (V).

**Pharmacological Screening**

Compounds 224, 228, 230, 234, 236-239, 241-244 were tested for analgesic, antiinflammatory, anticonvulsant and antihypertensive activity. However, test compounds were devoid of any significant anticonvulsant or antihypertensive activity.

Antiinflammatory and analgesic activities exhibited by the test compounds are recorded in Table 8. Significant antiinflammatory and analgesic activity was found in thiazolo compound 244. Analgesic activity of 241 was \(\frac{3}{8}\)th of aspirin at same dosage level.

**Antimicrobial Screening**

Compounds 224, 228, 230, 234, 236-239, 241-244 were screened for antibacterial and antifungal activity. None of the test compounds showed any antifungal activity at 50 mcg/ml concentration. Compounds 237 and 241 were active against \(S.\) aureus and \(S.\) aureus (A/R) at 3.125 mcg/ml and 6.25 mcg/ml concentration, respectively. Significant activity against these two organisms was also found in 234 (MIC, 12.15 mcg/ml).
TABLE 6
2-Mercapto thieno(2,3-d)pyrimidin-4(3H)-ones

<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>Crystallization solvent</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>223.</td>
<td>H</td>
<td>C₂H₅⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td>203-207</td>
<td>80</td>
<td>AA</td>
<td>C₁₁H₁₂N₂O₂S₂</td>
</tr>
<tr>
<td>224.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>270-274</td>
<td>84</td>
<td>B</td>
<td>C₉H₁₀N₂O₂S₂</td>
</tr>
<tr>
<td>225.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>C₃H₂⁻</td>
<td>255-257</td>
<td>82</td>
<td>EA</td>
<td>C₁₀H₁₂N₂O₂S₂</td>
</tr>
<tr>
<td>226.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td>207-210</td>
<td>85</td>
<td>A</td>
<td>C₁₁H₁₂N₂O₂S₂</td>
</tr>
<tr>
<td>227.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>n-C₄H₉⁻</td>
<td>201-202</td>
<td>80</td>
<td>A</td>
<td>C₁₂H₁₆N₂O₂S₂</td>
</tr>
<tr>
<td>228.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>n-C₆H₁₃⁻</td>
<td>172-175</td>
<td>77</td>
<td>A-C</td>
<td>C₁₄H₂₀N₂O₂S₂</td>
</tr>
<tr>
<td>229.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>C₆H₅CH₂⁻</td>
<td>235-240</td>
<td>74</td>
<td>B</td>
<td>C₁₅H₁₄N₂O₂S₂</td>
</tr>
<tr>
<td>230.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>C₆H₅⁻</td>
<td>306-310</td>
<td>72</td>
<td>B</td>
<td>C₁₄H₁₂N₂O₂S₂</td>
</tr>
<tr>
<td>231.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>C₆H₅⁻ 4-Ch₃-C₆H₄⁻</td>
<td>218-220(d)</td>
<td>72</td>
<td>B</td>
<td>C₁₅H₁₄N₂O₂S₂</td>
</tr>
<tr>
<td>232.</td>
<td>-(CH₂)₃⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td>215-220</td>
<td>80</td>
<td>A</td>
<td>C₁₂H₁₂N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>233.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃⁻</td>
<td>298-301</td>
<td>83</td>
<td>B</td>
<td>C₁₁H₁₂N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>234.</td>
<td>-(CH₂)₄⁻</td>
<td>C₂H₅⁻</td>
<td>259-261</td>
<td>77</td>
<td>B</td>
<td>C₁₂H₁₄N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>235.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₂=CH-CH₂⁻</td>
<td>204-209</td>
<td>90</td>
<td>AA</td>
<td>C₁₃H₁₄N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
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</tr>
<tr>
<td>236</td>
<td>-(CH₂)₄⁻</td>
<td>n-C₆H₁₃⁻</td>
<td>194-196</td>
<td>69</td>
<td>B</td>
<td>C₁₆H₂₂N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>237</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅CH₂⁻</td>
<td>244-246</td>
<td>67</td>
<td>E-C</td>
<td>C₁₇H₁₅N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>238</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅⁻</td>
<td>315(d)</td>
<td>72</td>
<td>B</td>
<td>C₁₆H₁₄N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>239</td>
<td>-(CH₂)₄⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>260-283(d)</td>
<td>70</td>
<td>B</td>
<td>C₁₇H₁₅N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>-(CH₂)₅⁻</td>
<td>n-C₆H₁₃⁻</td>
<td>189-190</td>
<td>71</td>
<td>B</td>
<td>C₁₇H₂₄N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>241</td>
<td>-(CH₂)₅⁻</td>
<td>C₆H₅⁻</td>
<td>255-257</td>
<td>71</td>
<td>B</td>
<td>C₁₈H₁₈N₂O₂S₂</td>
<td></td>
</tr>
<tr>
<td>242</td>
<td>-(CH₂)₅⁻</td>
<td>C₆H₅⁻</td>
<td>250-253</td>
<td>72</td>
<td>F-A</td>
<td>C₁₇H₁₅N₂O₂S₂·3H₂O</td>
<td></td>
</tr>
<tr>
<td>243</td>
<td>-(CH₂)₅⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td>305(d)</td>
<td>69</td>
<td>B</td>
<td>C₁₈H₁₈N₂O₂S₂</td>
<td></td>
</tr>
</tbody>
</table>

A = Ethanol; AA = Absolute ethanol; B = Acetic acid; C = Chloroform
EA = Ethyl acetate; E = Isopropanol; F = DMF
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystallization solvent</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>244.</td>
<td>$\text{CH}_3^-$</td>
<td>$\text{CH}_3^-$</td>
<td>150-151</td>
<td>70</td>
<td>A</td>
<td>$\text{C}<em>{11}\text{H}</em>{12}\text{N}_2\text{OS}_2$</td>
</tr>
<tr>
<td>245.</td>
<td>$-(\text{CH}_2)_3^-$</td>
<td></td>
<td>149-151</td>
<td>65</td>
<td>A</td>
<td>$\text{C}<em>{12}\text{H}</em>{12}\text{N}_2\text{OS}_2$</td>
</tr>
<tr>
<td>246.</td>
<td>$-(\text{CH}_2)_4^-$</td>
<td></td>
<td>149-150</td>
<td>77</td>
<td>A</td>
<td>$\text{C}<em>{13}\text{H}</em>{14}\text{N}_2\text{OS}_2$</td>
</tr>
<tr>
<td>247.</td>
<td>$-(\text{CH}_2)_5^-$</td>
<td></td>
<td>144-146</td>
<td>60</td>
<td>A</td>
<td>$\text{C}<em>{14}\text{H}</em>{16}\text{N}_2\text{OS}_2$</td>
</tr>
</tbody>
</table>
### TABLE 8
Pharmacological screening of 2-mercapto thieno(2,3-d)pyrimidin-4(3H)-ones*

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Analgesia (writhing test)</th>
<th>Antiinflammatory activity (Rat Paw oedema)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% inhibition</td>
<td>% inhibition, 200mg/kg p.o.</td>
</tr>
<tr>
<td>224.</td>
<td>φ</td>
<td>23.5</td>
</tr>
<tr>
<td>230.</td>
<td>16.6</td>
<td>φ</td>
</tr>
<tr>
<td>239.</td>
<td>φ</td>
<td>15.8</td>
</tr>
<tr>
<td>241.</td>
<td>45</td>
<td>18.3</td>
</tr>
<tr>
<td>244.</td>
<td>25</td>
<td>68.0</td>
</tr>
<tr>
<td>246.</td>
<td>φ</td>
<td>30.5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>57.3</td>
<td>-</td>
</tr>
<tr>
<td>Phenyl butazone 100mg/kg, p.o.</td>
<td>-</td>
<td>56.2</td>
</tr>
</tbody>
</table>

*All the compounds tested showed LD$_{50}$ more than 1000mg/kg, p.o. and more than 100mg/kg i.p.

φ = no activity.
EXPERIMENTAL

3-Allyl-6-ethyl-2-mercapto-thieno(2,3-d)pyrimidin-4(3H)-one (223)

A mixture of N\textsuperscript{2}-allyl-N\textsuperscript{3}-[(3-carbethoxy-5-ethyl thienyl)thiourea (192) (2.98 g; 0.01 mole) and NaOH (20 ml; 1N) was heated on a steam bath for one hour. The solution was allowed to cool and filtered. The filtrate was acidified with concentrated HCl. The solid obtained was filtered, washed repeatedly with water and dried. Recrystallization from absolute ethanol yielded 223, 2.01 g (80%), m.p. 203-207°C.

Analysis: C\textsubscript{11}H\textsubscript{12}N\textsubscript{2}O\textsubscript{3}S\textsubscript{2}
requires: C, 52.37; H, 4.76; N, 11.11%

Found: C, 52.31; H, 5.02; N, 11.45%

λ\textsubscript{max} nm (log ε): 221 (4.38), 242 (3.99), 310 (4.21)

υ\textsubscript{max} cm\textsuperscript{-1}:
3120 (-NH), 1670 (-C-)

2-Mercapto-3,5,6-trimethyl-thieno(2,3-d)pyrimidin-4(3H)-one (224)

A suspension of N\textsuperscript{2}-methyl-N\textsuperscript{3}-[(3-carbethoxy-4,5-dimethyl thienyl)thiourea (193) (13.6 g; 0.05 mole) in ethanol saturated with dry HCl (250 ml) was refluxed on a steam bath for 12 hours. The reaction mixture was chilled overnight. The precipitated solid was filtered, washed with ethanol and dried. Recrystallization from acetic acid yielded 224, 9.5 g (84%), m.p. 270-274°C (d).

Analysis: C\textsubscript{9}H\textsubscript{10}N\textsubscript{2}O\textsubscript{3}S\textsubscript{2}
requires: C, 47.79; H, 4.42; N, 12.38%

Found: C, 47.87; H, 4.59; N, 12.21%

υ\textsubscript{max} cm\textsuperscript{-1}:
3120 (-NH), 1690 (-C-), 1215 (-C-)
5,6-Dimethyl-3-ethyl-2-mercapto-thieno(2,3-d)pyrimidin-4(3H)-one (225)

A mixture of N-ethyl-N^2-(3-carbethoxy-4,5-dimethylthienyl)thiourea (194) (14.30 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from ethyl acetate yielded 225, 9.9 g (82%), m.p. 255-257°C.

Analysis: C_{10}H_{12}N_{2}OS_{2} requires: C, 49.99; H, 5.00%. Found: C, 50.14; H, 5.35%.

3-Allyl-5,6-dimethyl-2-mercapto-thieno(2,3-d)pyrimidin-4(3H)-one (226)

A mixture of N-allyl-N^2-(3-carbethoxy-4,5-dimethylthienyl)thiourea (198) (2.98 g; 0.01 mole) and NaOH solution (20 ml; 1 N) was treated according to the procedure described for 223. Recrystallization from ethanol yielded 226, 3.19 g (85%), m.p. 207-210°C. (reported m.p. 209-212°C).

Analysis: C_{11}H_{12}N_{2}OS requires: C, 52.37; H, 4.73%. Found: C, 52.01; H, 4.56%.

λ_{max} nm (log ε): 221 (4.38), 242 (3.99), 310 (4.21)

υ_{max} cm^{-1}: 3130(-NH), 1700(-C), 1230(-O)

3-n-Butyl-5,6-dimethyl-2-mercapto-thieno(2,3-d)pyrimidin-4(3H)-one (227)

A mixture of N-n-butyl-N^2-(3-carbethoxy-4,5-dimethylthienyl)thiourea (195) (15.70 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from ethanol yielded 227, 10.70 g (80%), m.p. 201-202°C.
Recrystallization from acetic acid yielded 230, 10.20g (72%), m.p. 308-310°C.

**Analysis**: \( C_{14}H_{12}N_2O_2 \) requires: C, 58.33; H, 4.20%; Found: C, 58.01; H, 4.36%

5,6-Dimethyl-2-mercapto-3-p-tolyl-thieno(2,3-d)pyrimidin-4(3H)-one (231)

A mixture of \( R^2-p\)-tolyl-\( N_1 \)-(3-carbethoxy-4,5-dimethylthienyl)\( \) thiourea (202) (17.40g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 231, 10.90g (72%), m.p. 218-220°C (d).

**Analysis**: \( C_{15}H_{14}N_2S_2 \) requires: C, 59.60; H, 4.63; N, 5.27; S, 21.12%; Found: C, 59.91; H, 4.93; N, 5.18; S, 20.90%

\( \lambda_{\text{max}} \text{ nm} \) (log e): 222(4.24), 235(S), 295(4.07)

\( \nu_{\text{max}} \text{ cm}^{-1} \) : 3140(-NH-), 1700(-C=), 1230(-C=).

3-Allyl-2-mercapto-cyclopenta(b)thieno(2,3-d)pyrimidin-4(3H)-one (232)

A mixture of \( R^2\)-allyl-\( N_1 \)-(3-carbethoxy-cyclopenta(b)thienyl)\( \) thiourea (205) (3.1g; 0.01 mole) and NaOH solution (20 ml; 1N) was treated according to the procedure described for 223. Recrystallization from ethanol yielded 232, 2g (80%), m.p. 215-220°C.

**Analysis**: \( C_{12}H_{12}N_2O_2 \) requires: C, 54.54; H, 4.54; N, 10.6%; Found: C, 54.79; H, 4.82; N, 10.6%

\( \lambda_{\text{max}} \text{, nm} \) (log e): 222(4.24), 235(S), 295(4.07)

\( \nu_{\text{max}} \text{ cm}^{-1} \) : 3250(-NH-), 1645(-C=).
2-Mercapto-3-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (233)
A mixture of \(N^2\)-methyl-\(N^1\)-\(2\)-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)\(\overline{7}\)thiourea (210) (14.90 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 233, 10.30 g (83%), m.p. 298-301°C.
Analysis: C11H12N2O2S2 requires C 52.37%; H, 4.76%; N, 11.11%
                 Found  C, 52.32; H, 5.04; N, 10.86%

3-Ethyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (234)
A mixture of \(N^2\)-ethyl-\(N^1\)-\(2\)-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)\(\overline{7}\)thiourea (211) (15.6 g; 0.05 mole) and ethanol saturated with HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 234, 10.5 g (77%), m.p. 259-261°C.
Analysis: C12H14N2O2S2 requires C, 54.13%; H, 5.26%; N, 10.52%
                 Found  C, 53.95; H, 5.43; N, 10.35%

3-Allyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (235)
A mixture of \(N^2\)-allyl-\(N^1\)-\(2\)-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)\(\overline{7}\)thiourea (213) (3.2 g; 0.01 mole) and NaOH solution (20 ml; 1N) was treated according to the procedure described for 223. Recrystallization from absolute ethanol yielded 235, 2.5 g (90%), m.p. 204-209°C (reported245 m.p. 205-208°C).


Analysis: $C_{13}H_{14}N_{2}S_{2}$ requires: C, 56.04; H, 5.11; N, 10.17%  
Found: C, 56.21; H, 5.06; N, 10.35%

$max \text{ nm}(\log \varepsilon) = 221 (4.36), 315 (4.23)$
$max \text{ cm}^{-1} = 3260 (-\text{NH}), 1640 (-\text{C=}), 1200 (-\text{C-})$

3-n-Hexyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidin-4(3H)-one (236)

A mixture of $N^2$-n-hexyl-$N^1$-$\text{C}(2\text{-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thi}enyl)_2$thiourea (212) (18.40g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 236, 11.0g (69%), m.p. 194-196°C.

Analysis: $C_{16}H_{22}N_{2}S_{2}$ requires: C, 59.62; H, 6.83; N, 8.69%  
Found: C, 59.75; H, 7.18; N, 9.00%

3-Benzyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (237)

A mixture of $N^2$-benzyl-$N^1$-$\text{C}(2\text{-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thi}enyl)_2$thiourea (214) (18.7g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from a mixture of iso-propanol and chloroform yielded 237, 11.40g (67%), m.p. 244-246°C.

Analysis: $C_{17}H_{16}N_{2}S_{2}$ requires: C, 62.19; H, 4.87%  
Found: C, 62.49; H, 5.13%

$max \text{ cm}^{-1} = 3140 (-\text{NH}), 1715 (-\text{C=}), 1210 (-\text{C-})$
2-Mercapt-3-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (238)

A mixture of N^-N^-2-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)thiourea (215) (18.0 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 238, 11.25 g (72%), m.p. 315°C (d).

Analysis: C_{16}H_{14}N_{2}O_{2} requires C, 61.14; H, 4.45; N, 8.91; S, 20.40%.

Found: C, 61.04; H, 4.72; N, 8.82; S, 20.33%.

2-Mercapt-3-4-tolyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (239)

A mixture of N^-p-tolyl-N^-N^-2-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)thiourea (217) (18.70 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 239, 11.5 g (70%), m.p. 280-283°C (d).

Analysis: C_{17}H_{16}N_{2}O_{2} requires C, 62.19; H, 4.87; N, 8.53; S, 19.53%.

Found: C, 61.98; H, 5.10; N, 8.34; S, 19.49%.

3-n-Hexyl-2-mercapt-cyclohepta(b)thieno(2,3-d)pyrimidin-4(3H)-one (240)

A mixture of N^-n-hexyl-N^-N^-2-(3-carbethoxy-cyclohepta(b)thienyl)thiourea (18.7 g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 240, 10.9 g (71%), m.p. 189-190°C.
Analysis: \( C_{17}H_{24}N_2O_2 \) requires: C, 60.71; H, 7.14%

Found: C, 60.71; H, 7.35%

\[ \lambda_{\text{max}} \text{nm} \log \varepsilon \]: 223 (4.37), 245 (4.04), 310 (4.23)

\[ \text{max \ cm}^{-1} \]: 3170 (-NH), 1715 (-C=O), 1215 (-C-)

3-Benzyl-2-mercapto-cyclohepta(b)thieno(2,3-d)pyrimidin-4(3H)-one (241)

A mixture of \( N^2 \)-benzyl-\( N^1 \)-\( S \)-\( S \)-\( S \)-\( S \)-\( C \)-carbethoxy cyclohepta(b)thienyl \( ) \)
thiourea (219) (19.4g; 0.05 mole) and absolute ethanol saturated with
dry HCl (250 ml) was treated according to the procedure described for
224. Recrystallization from acetic acid yielded 241, 12.2g(71%), m.p.
255-257°C.

Analysis: \( C_{18}H_{18}N_2O_2 \) requires: C, 63.15; H, 5.26%

Found: C, 63.25; H, 5.51%

\[ \lambda_{\text{max}} \text{nm} \log \varepsilon \]: 220 (4.46), 250 (4.95); 312 (4.14)

2-Mercapto-3-phenyl-cyclohepta(b)thieno(2,3-d)pyrimidin-4(3H)-one (242)

A mixture of \( N^2 \)-phenyl-\( N^1 \)-\( S \)-\( S \)-\( C \)-carbethoxy cyclohepta(b)thienyl \( ) \)
thiourea (220) (18.7g; 0.05 mole) and absolute ethanol saturated with
dry HCl (250ml) was treated according to the procedure described for
224. Recrystallization from a mixture of dimethylformamide and ethanol
yielded 242, 11.8g(72%), m.p. 250-253°C.

Analysis: \( C_{17}H_{16}N_2O_2 \cdot 2H_2O \) requires: C, 60.53; H, 5.04; N, 8.31%

Found: C, 60.44; H, 4.99; N, 8.32%
A mixture of N\(^{-}\)-m-tolyl-N\(^{1}\)-2\(^{-}\)carbethoxy-cyclohepta(b)thienyl thiourea (221) (19.4g; 0.05 mole) and absolute ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 224. Recrystallization from acetic acid yielded 243, 11.75g(69%), m.p. 305°C (d).

Analysis: C\(_{18}\)H\(_{18}\)N\(_{2}\)S\(_{2}\) requires C, 63.15%; H, 5.26%

Found: C, 63.20%; H, 5.49%

\(\lambda_{\text{max}} \text{ nm (log}\ e)\) : 225(4.52); 250(4.65)(S); 312(4.21)

2,3-Dihydro-2,6,7-trimethylthieno(2,3-d)thiazolo(3,2-a)pyrimidin-5-one (244)

A suspension of N\(^{2}\)-allyl-N\(^{1}\)-2\(^{-}\)carbethoxy-4,5-dimethylthienyl thiourea (198) (14.9g; 0.05 mole) in ethanol saturated with dry HCl (250 ml) was refluxed on a water bath for 12 hours. The reaction mixture was cooled overnight. The precipitated solid was filtered and washed with isopropyl alcohol. Recrystallation from ethanol yielded 244, 7.8g(70%), m.p. 150-151°C.

Analysis: C\(_{11}\)H\(_{12}\)N\(_{2}\)S\(_{2}\) requires C, 52.38%; H, 4.76%

Found: C, 52.60%; H, 5.09%

\(\lambda_{\text{max}} \text{ nm (log}\ e)\) : 210 (4.32), 274 (3.90), 319 (4.10)

\(\nu_{\text{max}} \text{ cm}^{-1}\) : 1660 (\(\nu\) (C\(=\)N))

NMR (\(\delta\), CDCl\(_{3}\)) : 1.6 (d, 3H, C\(_{2}\)-CH\(_{3}\)), 2.4 (q, 3H, C\(_{7}\)-CH\(_{3}\)), 2.3 (s, 3H, C\(_{6}\)-CH\(_{3}\)), 3.9-4.6 (m, 3H, C\(_{2}\)-CH and C\(_{3}\)-CH\(_{2}\)).
2-Methyl-2,3-dihydrocyclopenta(b)thieno(2,3-d)thiazolo(3,2-a)pyrimidin-5-one (245)

A mixture of N\textsuperscript{2}-allyl-N\textsubscript{1}-\(\sqrt{2}\)-(3-carbethoxy-cyclopenta(b)thienyl)\textsubscript{7} thiourea (205) (15.5g; 0.05 mole) in ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 244. Recrystallization from ethanol yielded 245, 8.6g(65%), m.p. 149-151°C.

Analysis: C\textsubscript{12}H\textsubscript{12}N\textsubscript{2}O\textsubscript{2} requires: C, 54.54; H, 4.54; N, 10.60%

Found: C, 54.80; H, 4.80; N, 10.91%

\(\lambda_{\text{max}}\) nm(log \(\varepsilon\)) = 220(4.2), 245(s), 277(3.88), 325(4.12)

\(\nu_{\text{max}}\) cm\(^{-1}\) = 1665(-C-)

NMR (\(\varepsilon\), CDCl\textsubscript{3}) = 1.6(d, 3H, C\textsuperscript{2}-CH\textsubscript{3})

2-Methyl-2,3,6,7,8,9-hexahydrobenzo(b)thieno(2,3-d)thiazolo(3,2-a)pyrimidin-5-one (246)

A mixture of N\textsuperscript{2}-allyl-N\textsubscript{1}-\(\sqrt{2}\)-(3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)\textsubscript{7} thiourea/(16.2g; 0.05 mole) in ethanol saturated with dry HCl (250 ml) was treated according to the procedure described for 244. Recrystallization from ethanol yielded 246, 11.15g(77%), m.p. 149-150°C.

Analysis: C\textsubscript{13}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} requires: C, 56.11; H, 5.03%

Found: C, 56.22; H, 5.36%

\(\lambda_{\text{max}}\) nm(log \(\varepsilon\)) = 211(4.32), 275 (3.88), 320 (4.14)

\(\nu_{\text{max}}\) cm\(^{-1}\) = 1675 (-CNH)

NMR (\(\varepsilon\), CDCl\textsubscript{3}) = 1.5 (d, 3H, C\textsuperscript{2}-CH\textsubscript{3}), 1.9 (t, 4H, C\textsuperscript{7}-CH\textsubscript{2}) and

(C\textsubscript{6}-CH\textsubscript{2}), 2.7 (m, 4H, C\textsubscript{6}-CH\textsubscript{2} and C\textsubscript{9}-CH\textsubscript{2}),

4-4.7 (m, 3H, C\textsubscript{2}-CH and C\textsubscript{3}-CH\textsubscript{2})
2-Methyl-2,3,6,7,8,9-hexahydrobenzo(b)thieno(2,3-d)thiazolo(3,2-a)
thiazolo(3,2-a)pyrimidin-5-one (246a) from 3-allyl-2-mercaptothiene
(2,3-d)pyrimidin-4(3H)-one (235)

A mixture of 3-allyl-2-mercaptot-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)
pyrimidin-4(3H)-one (2.78g; 0.01 mole) and ethanol saturated with dry
HCl was treated according to the procedure described for 244, 1.95 (70%),
m.p. 149-150°C.

Analysis: \( \text{C}_{13}\text{H}_{14}\text{N}_{2}\text{OS}_{2} \) requires: C, 56.11; H, 5.03%

\[ \text{Found} : \text{C}, 55.95; \text{H}, 5.16\%

\( \lambda_{\text{max}} \text{nm}(\log \varepsilon) : 211 (4.32), 242(5), 275 (3.88); 320 (4.14)\]

\( \nu_{\text{max}} \text{cm}^{-1} : 1670 (-\text{CNH}) \)

Mixed melting points of 246 and 246a remained unpressed.

2-Methyl-2,3-dihydrocyclohepta(b)thieno(2,3-d)thiazolo(3,2-d)pyrimidin-
5-one (247)

A mixture of \( N^2-\text{allyl}-N^1-\text{L}(3-\text{carbethoxy cyclohepta(b)thienyl})_7\text{thiourea}(218) \)
(16.9g; 0.05 mole) in ethanol saturated with dry HCl (250 ml) was treated
according to the procedure described for 244. Recrystallization from
ethanol yielded 247, 8.7g(60%), m.p. 144-146°C.

Analysis: \( \text{C}_{14}\text{H}_{16}\text{N}_{2}\text{OS}_{2} \) requires: C, 57.53; H, 5.47; N, 9.59%

\[ \text{Found} : \text{C}, 57.85; \text{H}, 5.80; \text{N}, 9.87\%

\( \lambda_{\text{max}} \text{nm}(\log \varepsilon) : 210 (4.3), 245(5), 280 (3.92), 320 (4.13)\]

\( \nu_{\text{max}} \text{cm}^{-1}\text{CH}_{2}\text{Cl}_{2} : 1660 \text{c}^{-1} (-\text{C-}) \)

NMR (\( \delta , \text{CDCl}_{3} ) : 1.5(\text{d}, 3\text{H},-\text{CH}_{3}) \)
2,4-(1H, 3H)-Quinazolinediones and their 1,3-dimethyl derivatives have shown protective action against electroshock and pentylenetetrazole induced seizures in mice.261 A series of 2-thioquinazolin-4-ones with varying substituents at position 2, 3 or 6 (248) was synthesized and studied for their ability to prevent maximal electroshock and chemoshock.262 At 600 mg/kg, i.p., 248b showed 100% protection against electroshock seizures. However, these compounds were devoid of any protective action against chemoshock. Dwivedi et al.263 synthesized 2-mercapto acetic acid derivatives for anticonvulsant activity. 249a exhibited 70% protection against pentylenetetrazole induced seizures in mice at 100 mg/kg.

It was, therefore, thought of interest to synthesize thiophene analogs (II & III, Scheme - I) of 249 for possible anticonvulsion activity.
Results and Discussion

3-Substituted thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acids and their esters were synthesized from 2-mercapto-3-substituted thieno(2,3-d)pyrimidin-4(3H)-one (I). Refluxing 2-mercapto compounds (I) with chloroacetic acid, in presence of KOH yielded (II). On the other hand, when I was refluxed with ethyl chloroacetate, mercaptoacetic acid ester (III) was obtained.

SCHEME - I

Physical constants of compounds 250-262 are recorded in Table 9. In IR, mercaptoacids and their esters showed absence of amino function and presence of a carbonyl function due to ester or acid group. Recently, Russian workers have synthesized analogous compounds essentially in a similar manner.

Compounds 256, 258, and 262 were tested for analgesic and
antiinflammatory activity (Table 10). Compounds 256, 258, and 262 are half as active as aspirin. Antiinflammatory activity of 256, 259, 262 is not significant in comparison to phenylbutazone.

Anticonvulsant activity of compounds 254, 260-262 against maximal electric shock seizure was studied in mice (Table 11). The test compounds were less potent than diphenylhydantoin. The compounds under study were devoid of any activity against chemoshock seizures. Compounds 254 and 260 raised the maximum electric shock seizures threshold above the control level but not equal to that of diphenylhydantoin in hyponatremic mice (Table 12), thereby indicating probable different mechanism of anticonvulsant activity from diphenylhydantoin. Test compounds 254 and 260 afforded 100% protection against maximum electroshock seizure in mice at 300 mg/kg p.o. Apparently these two compounds are more potent than their benzene analogs 248b and 249a. Compound 248b gave 100% protection at 600 mg/kg i.p. against maximal electroshock, while 248a was inactive. Compound 249a afforded 70% protection in mice against pentylenetetrazol induced seizures at 100 mg/kg i.p.

All the compounds tested (254, 260-262) show varying degree of reduction in spontaneous and methylamphetamine induced motor activity (Tables 13 & 14). The intensity of reduction in motor activity was slightly less than that of methaqualone but even then it may be considered significant since the test compounds were administered by oral route. These observations indicate CNS depressant action like
methaqualone. They are also capable of antagonizing the methylamphetamine induced hyper motor activity. Further support to the sedative action of the test compounds is coming from the significant potentiation of the hexabarbitones induced sleeping time in mice (Table 15).

The compounds seem to be devoid of tranquilizing action since the condition avoidance response (CAR) in trained rats was not blocked by the test compounds, whereas, chlorpromazine used as a reference drug, could do it well.

These observations suggest that the test compounds 254, 260-262 are devoid of any tranquilizing action but have a sedative action. \( \text{ID}_{50} \) of compounds 254, 260 - 262 are recorded in Table 15a.
### TABLE 9

Thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acids and ethyl esters.

![Chemical Structure](image)

<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>Crystallization solvent*</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>250.</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
<td>H</td>
<td>192-195</td>
<td>87</td>
<td>A</td>
<td>C₁₁H₁₂N₂O₃S₂</td>
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<tr>
<td>251.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃⁻</td>
<td>H</td>
<td>187-190</td>
<td>81</td>
<td>A</td>
<td>C₁₃H₁₄N₂O₃S₂</td>
<td></td>
</tr>
<tr>
<td>252.</td>
<td>-(CH₂)₄⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
<td>188-190</td>
<td>77</td>
<td>A</td>
<td>C₁₄H₁₆N₂O₃S₂</td>
<td></td>
</tr>
<tr>
<td>253.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅CH₂⁻</td>
<td>H</td>
<td>190-193</td>
<td>50</td>
<td>A-B</td>
<td>C₁₉H₁₈N₂O₃S₂&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>254.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅⁻</td>
<td>H</td>
<td>239-241</td>
<td>50</td>
<td>A-B</td>
<td>C₁₈H₁₆N₂O₃S₂</td>
<td></td>
</tr>
<tr>
<td>255.</td>
<td>-(CH₂)₄⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td>H</td>
<td>220-222</td>
<td>78</td>
<td>A</td>
<td>C₁₉H₁₆N₂O₃S₂</td>
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<tr>
<td>256.</td>
<td>-(CH₂)₄⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>H</td>
<td>245-247</td>
<td>71</td>
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<td></td>
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<tr>
<td>257.</td>
<td>CH₃⁻</td>
<td>GH₃⁻</td>
<td>CH₃⁻</td>
<td>C₂H₅⁻</td>
<td>124-127</td>
<td>65</td>
<td>A</td>
<td>C₁₃H₁₆N₂O₃S₂</td>
</tr>
<tr>
<td>258.</td>
<td>-(CH₂)₄⁻</td>
<td>CH₃⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
<td>137-138</td>
<td>68</td>
<td>A</td>
<td>C₁₅H₁₈N₂O₃S₂</td>
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<tr>
<td>259.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅CH₂⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
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<td>90</td>
<td>A</td>
<td>C₂₁H₂₂N₂O₃S₂</td>
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<tr>
<td>260.</td>
<td>-(CH₂)₄⁻</td>
<td>C₆H₅⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
<td>202-204</td>
<td>55</td>
<td>A</td>
<td>C₂₀H₂₀N₂O₃S₂</td>
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<tr>
<td>261.</td>
<td>-(CH₂)₄⁻</td>
<td>3-CH₃-C₆H₄⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
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<td>85</td>
<td>A</td>
<td>C₂₁H₂₂N₂O₃S₂</td>
</tr>
<tr>
<td>262.</td>
<td>-(CH₂)₄⁻</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>C₂H₅⁻</td>
<td>H</td>
<td>189-191</td>
<td>78</td>
<td>A-B</td>
<td>C₂₁H₂₂N₂O₃S₂</td>
</tr>
</tbody>
</table>

A, Ethanol; B, Chloroform
### TABLE 10

**Analgesic and antiinflammatory activity**

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Analgesia (writhing test) % inhibition, 200mg/kg, p.o.</th>
<th>Antiinflammatory activity (Rat Paw oedema) % inhibition, 200mg/kg, p.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td>255.</td>
<td>23.2</td>
<td>19.4</td>
</tr>
<tr>
<td>258.</td>
<td>26.3</td>
<td>¤</td>
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<td>16.1</td>
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<td>Aspirin</td>
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<td>-</td>
</tr>
<tr>
<td>Phenylbutazone, 100mg/kg, p.o.</td>
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<td>55.2</td>
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</tbody>
</table>

All the compounds tested showed LD\textsubscript{50} more that 1000 mg/kg p.o.

¤ = no activity
<table>
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<tr>
<th>Compound No.</th>
<th>Dose in mg/kg (orally)</th>
<th>No. of mice used</th>
<th>No. of mice protected</th>
<th>Corrected % protection</th>
<th>Probit</th>
<th>PD$_{50}$ value in mg/kg</th>
</tr>
</thead>
<tbody>
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<td>5.25 35.48 ± 23</td>
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<tr>
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<td>5.84</td>
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<td>100</td>
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<td>6.64</td>
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<td>0</td>
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<td>3</td>
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<td>5</td>
<td>100</td>
<td>95</td>
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<tr>
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<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>3.36</td>
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<td>3</td>
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<td>60</td>
<td>5.25 125.9 ± 20.55</td>
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<tr>
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<td>5</td>
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<td>80</td>
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<td>100</td>
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<td>5</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>4.75 6.31 ± 2.991</td>
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<td>5</td>
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<td>5</td>
<td>5</td>
<td>100</td>
<td>95</td>
<td>6.64</td>
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</table>
## TABLE 12
Anticonvulsant activity in hyponatremic mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose mg/kg Orally</th>
<th>MES threshold seizures* mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Glucose (6%)</td>
<td>2ml/kg</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>37</td>
</tr>
<tr>
<td>254</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>37</td>
</tr>
<tr>
<td>Diphenylhydantoin</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>360</td>
</tr>
</tbody>
</table>

* No. of observations = 5 in each case
### TABLE 13

**Spontaneous motor activity***

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Drug oral route</th>
<th>Before count</th>
<th>% reduction 1 hr.</th>
<th>% reduction 2 hr.</th>
<th>% reduction 4 hr.</th>
<th>Mean reduction in 4 hrs period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle**</td>
<td>0.1ml/10 g</td>
<td>399</td>
<td>9.70</td>
<td>18.25</td>
<td>29.50</td>
<td>19.15</td>
</tr>
<tr>
<td>Methaqualone**</td>
<td>40mg/kg</td>
<td>494</td>
<td>75.50</td>
<td>78.25</td>
<td>78.25</td>
<td>77.33</td>
</tr>
<tr>
<td></td>
<td>100mg/kg</td>
<td>936</td>
<td>78.06</td>
<td>81.47</td>
<td>83.76</td>
<td>81.09</td>
</tr>
<tr>
<td></td>
<td>150mg/kg</td>
<td>711</td>
<td>85.70</td>
<td>78.90</td>
<td>78.89</td>
<td>81.16</td>
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<tr>
<td>260.</td>
<td>50mg/kg</td>
<td>228</td>
<td>2.00</td>
<td>45.00</td>
<td>48.00</td>
<td>31.60</td>
</tr>
<tr>
<td></td>
<td>100mg/kg</td>
<td>306</td>
<td>13.00</td>
<td>65.00</td>
<td>67.00</td>
<td>48.30</td>
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<tr>
<td></td>
<td>200mg/kg</td>
<td>186</td>
<td>60.00</td>
<td>86.00</td>
<td>89.00</td>
<td>71.70</td>
</tr>
<tr>
<td>254.</td>
<td>50mg/kg</td>
<td>328</td>
<td>43.90</td>
<td>65.70</td>
<td>57.50</td>
<td>55.70</td>
</tr>
<tr>
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<td>100mg/kg</td>
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<td>43.80</td>
<td>63.80</td>
<td>64.40</td>
<td>57.30</td>
</tr>
<tr>
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<td>200mg/kg</td>
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<td>47.90</td>
<td>63.70</td>
<td>65.50</td>
<td>59.00</td>
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<tr>
<td>261.</td>
<td>50mg/kg</td>
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<td>41.00</td>
<td>0</td>
<td>14.30</td>
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<td>100mg/kg</td>
<td>256</td>
<td>56.00</td>
<td>64.00</td>
<td>64.00</td>
<td>61.30</td>
</tr>
<tr>
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<td>200mg/kg</td>
<td>265</td>
<td>65.00</td>
<td>77.00</td>
<td>58.00</td>
<td>66.60</td>
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<tr>
<td>262.</td>
<td>50mg/kg</td>
<td>400</td>
<td>21.00</td>
<td>26.00</td>
<td>37.00</td>
<td>28.00</td>
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<tr>
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<td>100mg/kg</td>
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<td>29.00</td>
<td>49.00</td>
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<tr>
<td></td>
<td>200mg/kg</td>
<td>404</td>
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<td>69.00</td>
<td>91.00</td>
<td>75.30</td>
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* Activity was recorded for 10 minutes and number of observations (n) = 10.

** Vehicle & Methaqualone were given intraperitoneally
TABLE 14
Methyl amphetamine induced hyperactivity in mice (five mice per group)

<table>
<thead>
<tr>
<th>No. of groups</th>
<th>Compound No.</th>
<th>Dose mg/kg (orally)</th>
<th>Methylamphetamine dose Sub. cut</th>
<th>Cumulative activity</th>
<th>% inhibition</th>
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<td></td>
<td></td>
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<tr>
<td>2</td>
<td>Vehicle</td>
<td>(0.1ml/10g)</td>
<td>Nil</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Vehicle</td>
<td>(0.1ml/10g)</td>
<td>4mg/kg</td>
<td>335</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Methaqualone*</td>
<td>40</td>
<td>do-</td>
<td>55</td>
<td>278</td>
</tr>
<tr>
<td>2</td>
<td>254</td>
<td>50</td>
<td>do-</td>
<td>203</td>
<td>133</td>
</tr>
<tr>
<td>2</td>
<td>254</td>
<td>100</td>
<td>do-</td>
<td>183</td>
<td>150</td>
</tr>
<tr>
<td>b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vehicle</td>
<td>(0.1ml/10g)</td>
<td>Nil</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
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<td>Vehicle</td>
<td>(0.1ml/10g)</td>
<td>4mg/kg</td>
<td>320</td>
<td>-</td>
</tr>
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<td>Methaqualone*</td>
<td>40</td>
<td>do-</td>
<td>63</td>
<td>257</td>
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<td>2</td>
<td>250</td>
<td>50</td>
<td>do-</td>
<td>203</td>
<td>117</td>
</tr>
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<td>2</td>
<td>250</td>
<td>100</td>
<td>do-</td>
<td>192</td>
<td>128</td>
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<td>2</td>
<td>250</td>
<td>200</td>
<td>do-</td>
<td>184</td>
<td>136</td>
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<td>c)</td>
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<td></td>
<td></td>
<td></td>
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<td>Nil</td>
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<td>-</td>
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<td>4mg/kg</td>
<td>597</td>
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<td>261</td>
<td>50</td>
<td>do-</td>
<td>575</td>
<td>22</td>
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<td>261</td>
<td>100</td>
<td>do-</td>
<td>393</td>
<td>204</td>
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<td>2</td>
<td>261</td>
<td>200</td>
<td>do-</td>
<td>332</td>
<td>265</td>
</tr>
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<td>d)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vehicle</td>
<td>(0.1ml/10g)</td>
<td>Nil</td>
<td>100</td>
<td>-</td>
</tr>
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<td>4mg/kg</td>
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<td>-</td>
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<td>Methaqualone*</td>
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<td>do-</td>
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<td>do-</td>
<td>318</td>
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<td>do-</td>
<td>260</td>
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<td>252</td>
<td>200</td>
<td>do-</td>
<td>236</td>
<td>105</td>
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</table>

* as Hydrochloride salt by i.p. route
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Dose mg/kg (orally)</th>
<th>Hexabarbitone mg/kg i.p. (90 min. after administration of drug)</th>
<th>No. of mice</th>
<th>Sleeping time (min; mean + SE)</th>
<th>'P' value</th>
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<td>Control</td>
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<tr>
<td>Methaqualone*</td>
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<td>125</td>
<td>5</td>
<td>174 ± 29</td>
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<td>125</td>
<td>5</td>
<td>410 ± 18</td>
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<tr>
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<td>100</td>
<td>125</td>
<td>5</td>
<td>334 ± 31</td>
<td>&gt; 0.05&lt;0.01</td>
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<td>(B)</td>
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<td>Control</td>
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<td>5</td>
<td>54.24 ± 0.13</td>
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<td>100</td>
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<td>86.00 ± 3.00</td>
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</tr>
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<td>262.</td>
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<td>100</td>
<td>5</td>
<td>63.00 ± 2.32</td>
<td>&gt; 0.05</td>
</tr>
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<td></td>
<td></td>
<td>72.00 ± 4.8</td>
<td>&gt; 0.01</td>
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</tbody>
</table>

* As hydrochloride salt by intraperitoneal route
### TABLE 15a

Acute toxicity for LD\(_{50}\) estimation

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<tr>
<th>Compound No.</th>
<th>Dose in mg/kg i.p.</th>
<th>No. of mice used</th>
<th>No. of mice dead</th>
<th>% mortality</th>
<th>Corrected % mortality</th>
<th>Probit</th>
<th>LD(_{50}) value in mg/kg i.p.</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>150</td>
<td>250</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
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<td>40</td>
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<td></td>
</tr>
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<td>500</td>
<td>5</td>
<td>3</td>
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<td>60</td>
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<td>269 ± 43.38</td>
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<td>40</td>
<td>40</td>
<td>4.75</td>
<td>1585 ± 185.40</td>
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<td>4.16</td>
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<td>5</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>4.75</td>
<td>389 ± 47.3</td>
</tr>
<tr>
<td></td>
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<td>4</td>
<td>80</td>
<td>80</td>
<td>5.84</td>
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<td></td>
<td>600</td>
<td>5</td>
<td>5</td>
<td>100</td>
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<td>150</td>
<td>200</td>
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<td>20</td>
<td>20</td>
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<td>300</td>
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<td>2</td>
<td>40</td>
<td>40</td>
<td>4.75</td>
<td>316.2 ± 70.08</td>
</tr>
<tr>
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<td>600</td>
<td>5</td>
<td>4</td>
<td>80</td>
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<tr>
<td></td>
<td>700</td>
<td>5</td>
<td>5</td>
<td>100</td>
<td>95</td>
<td>6.64</td>
<td></td>
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</tbody>
</table>
3,5,6-Trimethyl thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (250)

A mixture of 2-mercapto-3,5,6-trimethyl thieno(2,3-d)pyrimidin-4(3H)-one (224) (4.52g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and ethanol (180 ml) was heated gently to obtain a clear solution. To the hot solution was added chloroacetic acid (1.88g; 0.02 mole) dissolved in ethanol (10 ml). The reaction mixture was refluxed for 8 hours on a steam bath and concentrated under vacuum to remove ethanol and added dilute hydrochloric acid (10%) to obtain pH 3-4. The solid precipitated was filtered, washed with water and dried. Recrystallization from ethanol yielded 250, 4.9 (87%), m.p. 192-195°C.

Analysis: C11H12N2O3S requires C, 46.48; H, 4.22%

\[ \text{Found: C, } 46.20; \text{ H, } 4.60\%

\[ \lambda_{\text{max}} \text{ nm (Log } \epsilon) \] 217(4.30), 272(3.74), 319(4.11)

\[ \nu_{\text{max}} \text{ cm}^{-1} \] 3150(OH), 1730(-COH), 1630(-C-N)

3-Methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (251)

A mixture of 2-mercapto-3-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (233) (5.04g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole) was treated according to the procedure described for 250. Recrystallization from ethanol yielded 251, 5.0g (81%), m.p. 187-190°C.

Analysis: C13H14N2O3S2 requires C, 50.31; H, 4.51%

\[ \text{Found: C, } 50.70; \text{ H, } 4.50\% \]
3-Ethyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (252)

A mixture of 3-ethyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (234) (5.32g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole) was treated according to the procedure described for 250. Recrystallization from ethanol yielded 252, 5.0g (77%), m.p. 188-190°C.

Analysis: \( \text{C}_{14} \text{H}_{16} \text{N}_2 \text{O}_3 \text{S} \), requires: C, 51.85; H, 4.93%
Found: C, 51.80; H, 5.30%

3-Benzyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (253)

A mixture of 3-benzyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (237) (6.56g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole) was treated according to the procedure described for 250. Recrystallization from a mixture of ethanol and chloroform yielded 253, 3.7g (50%), m.p. 190-193°C.

Analysis: \( \text{C}_{19} \text{H}_{18} \text{N}_2 \text{O}_3 \text{S}_2 \text{C}_2 \text{H}_5 \text{OH} \), requires: C, 58.33%; H, 5.55%
Found: C, 58.22; H, 5.54%

3-Phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (254)

A mixture of 2-mercapto-3-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (238) (6.28g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole)
was treated according to the procedure described for 250. Recrystallization from a mixture of ethanol and chloroform yielded 254, 3.7g(50%), m.p. 239-241°C.

Analysis: \( \text{C}_{18} \text{H}_{16} \text{N}_2 \text{O}_3 \text{S}_2 \) requires: C, 58.06; H, 4.30%

Found: C, 58.05; H, 4.62%

\( \lambda_{\text{max}} \) nm (log \( \varepsilon \)) = 214(4.4), 245(S), 319(4.14)

\( \nu_{\text{max}} \) cm\(^{-1}\) = 3200(OH), 1730(-COH), 1660(-CNH)

3-m-Tolyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (255)

A mixture of 2-mercapto-3-m-tolyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (6.56g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole) was treated according to the procedure described for 250. Recrystallization from ethanol yielded 255, 6.0g(78%), m.p. 220-222°C.

Analysis: \( \text{C}_{19} \text{H}_{18} \text{N}_2 \text{O}_3 \text{S}_2 \) requires: C, 59.06; H, 4.66%

Found: C, 59.06; H, 5.05%

3-p-Tolyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetic acid (256)

A mixture of 2-mercapto-3-p-tolyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (239) (6.5g; 0.02 mole), potassium hydroxide (2.24g; 0.04 mole) and chloroacetic acid (1.88g; 0.02 mole) was treated according to the procedure described for 250. Recrystallization from ethanol yielded 256, 5.5g(71%), m.p. 245-247°C.
Analysis: \( C_{19}H_{18}N_2O_3S_2 \) requires: C, 58.98; H, 4.93%.
Found: C, 59.06; H, 4.67%

**Ethyl 3,5,6-trimethyl-thieno(2,3-d)pyrimidin-4(3H)-one mercaptoacetate (257)**

To a mixture of 2-mercapto-3,5,6-trimethyl-thieno(2,3-d)pyrimidin-4(3H)-one (224) (4.52g; 0.02 mole), potassium hydroxide (1.2g; 0.02 mole) and ethanol (180 ml) was added ethyl chloroacetate (2.6g; 0.02 mole) dissolved in ethanol (10 ml) and refluxed for 8 hours. On cooling the reaction mixture overnight, solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 257, 4.0g(65%), m.p. 124-127°C.

Analysis: \( C_{13}H_{16}N_2S_2 \) requires: C, 53.25; H, 5.32%
Found: C, 53.45; H, 5.40%

**Ethyl 3-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetate (258)**

Mixture of 2-mercapto-3-methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (233) (5.04g; 0.02 mole), potassium hydroxide (1.2g; 0.02 mole) and ethyl chloroacetate (2.6g; 0.02 mole) was treated according to the procedure described for 257. Recrystallization from ethanol yielded 258, 4.6g(68%), m.p. 137-138°C.

Analysis: \( C_{15}H_{18}N_2O_3S_2 \) requires: C, 53.25; H, 5.32%
Found: C, 53.45; H, 5.40%

\( \lambda_{\text{max}} \text{ nm}(\log \varepsilon) = 212(4.38), 238(5)(4.07), 310(4.01) \)

\( \nu_{\text{max}} \text{ cm}^{-1} = 1730(-\text{COEt}), 1650(-\text{CN}) \)
Ethyl 3-benzyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetate (259)

Mixture of 3-benzyl-2-mercapto-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (237) (6.56g; 0.02 mole), potassium hydroxide (1.2g; 0.02 mole) and ethyl chloroacetate (2.6g; 0.02 mole) was treated according to the procedure described for 257. Recrystallization from ethanol yielded 259, 7.5g(90%), m.p. 160-162°C.

Analysis: C_{21}H_{22}N_{2}O_{3}S_{2} requires: C, 60.87; H, 5.31%

Found: C, 61.02; H, 5.60%

$\lambda_{max}$ nm(log ε): 205(4.45), 275(3.75), 322(4.12)

$\nu_{max}$ cm$^{-1}$: 1730(-C-OEt), 1680(-C-N)

Ethyl 3-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one-2-mercaptoacetate (260)

Mixture of 2-mercapto-3-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (238) (6.28g; 0.02 mole), potassium hydroxide (1.2g; 0.02 mole) and ethyl chloroacetate (2.6g; 0.02 mole) was treated according to procedure described for 257. Recrystallization from ethanol yielded 260, 4.4g(55%), m.p. 202-204°C.

Analysis: C_{20}H_{20}N_{2}O_{3}S_{2} requires: C, 60.00; H, 5.00%

Found: C, 60.01; H, 5.19%

$\lambda_{max}$ nm(log ε): 213(4.44), 324(4.14)

$\nu_{max}$ cm$^{-1}$: 1730(-C-OEt), 1680(-C-N)
At the turn of the century and prior to his discovery of procaine, Einhorn and his coworkers synthesized a group of alkylaminoacetylamino benzoates. The clinical use of one of these, Nirvanine, was discontinued because of its irritating properties. Discovery of \( \omega \)-diethylamino-2,6-dimethylacetanilide (Lidocaine) in 1946 has revived the interest in substituted aminoacylaminobenzoates. Carney has listed the local anaesthetic activity of 1060 esters of benzoic acid and substituted benzoic acids. A number of compounds derived from the esters of anthranilic acid and p-aminobenzoic acid have been studied. In one of these studies it was noted that ortho alkoxy carbonyl substituted compounds exhibit better activity than the para substituted compounds.

![Chemical structures](image)

The 2-thienyl analogs of cocaine, \( \alpha \)-eucaine and stovocaine have shown local anaesthetic activity. 2-Thienyl-\( \beta \)-piperidinoethyl, (263), like its benzene analog falicain (263a) has local anaesthetic activity. 272-274

Alkyl and basic alkyl esters of thiophene have been tested for local anaesthetic activity. 275-277 Thiophene analog (264) of benzocaine
produces anaesthesia on the rabbit's cornea when applied as a powder. Thiophene bioisoster (265) of procaine has been found to be as potent as the parent compound, while thiazole analog of it is completely inactive.

Aminoacyl derivatives of 3-aminothiophenes (266) are reported to have potent local anaesthetic activity. Methyl 4-methyl-3-oxo-2-(propylamino)propyl-amino-2-thiophene carboxylate HCl (139) has good potentialities as dental anaesthetic. 2-Aminoacetamido-3-(2-pyridyl carbonyl)-5-ethyl thiophene (136c) is reported to have tranquilizing activity.

Therefore, the present work to synthesize and study the pharmacological activity of some 2-aminoacetamido-3-carbethoxy-4,5-disubstituted thiophene derivatives was undertaken.
Results and Discussion

2-Amino-3-carbethoxythiophene (I, Scheme I) was reacted with chloroacetyl chloride to obtain the 2-chloroacetamido-3-carbethoxy-4,5-disubstituted thiophene (II). The 2-Chloroacetamido derivative (II) was then condensed with various secondary amines in benzene to obtain the 2-amino acetamido-3-carbethoxy-4,5-substituted thiophenes (III). Physical constants of compounds 268-286 are recorded in Table 16.
Compound 269, 271, 273, 274, 276, 278, 281, 283-286 were screened for analgesic, anticonvulsive, antiinflammatory and antihypertensive activity (Table 17). All the compounds were devoid of any antihypertensive activity. Hydrochloride salts of 273 and 281 at 200 mg/kg when administered orally, exhibited analgesic activity superior to aspirin at the same dosage level. Compound 280 orally was almost 4 times as active as aspirin. Significant analgesic activity was observed in hydrochloride salts of 269, 271, 283, 285, 286. In general, compounds in this series were more active as hydrochloride salts. This may be due to better oral absorption of salts. Significant antiinflammatory activity was observed in hydrochloride salts of 269, 283, 286. Compound 286 (200 mg/kg) orally showed the maximum antiinflammatory activity among the series when compared to phenylbutazone (100mg/kg). Compounds 278, 281, 283 at 200 mg/kg offered negligible protection against metrazole induced seizures.

Local Anaesthetic Activity - Compound 268, 270, 273, 285 were screened for local anaesthetic activity. All the compounds showed significant activity when compared to lignocaine. However, compound 273 and 285, being more active, were studied in detail. Intradermal local anaesthetic activity of compound 285 is better than lignocaine (Table 18). The analysis of the data of foot-withdrawal response (Table 19) shows that compound 285 has better local anaesthetic activity than compound 273 and is twice as active as procaine at 0.5% concentration (Table 19). The test compounds were devoid of surface anaesthetic activity and produced irritant action at the conjunctiva of the eye. However, they do not exhibit any local irritation when administered subcutaneously.
TABLE 16

2-Aminocetamido-3-carbethoxy thiophenes

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>X</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystallization solvent</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>268.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(C₂H₅)₂</td>
<td>58-60</td>
<td>50</td>
<td>H</td>
<td>C₁₅H₂₄N₂O₃S</td>
</tr>
<tr>
<td>269.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(C₃H₇)₂</td>
<td>62-64</td>
<td>60</td>
<td>H</td>
<td>C₁₇H₂₈N₂O₃S</td>
</tr>
<tr>
<td>270.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(CH₃)₂</td>
<td>118-120</td>
<td>65</td>
<td>H</td>
<td>C₁₅H₂₄N₂O₃S</td>
</tr>
<tr>
<td>271.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(CH₃)₂</td>
<td>86-88</td>
<td>66</td>
<td>H</td>
<td>C₁₇H₂₆N₂O₃S</td>
</tr>
<tr>
<td>272.</td>
<td>CH₂</td>
<td>CH₃</td>
<td>N(CH₃)₂</td>
<td>94-95</td>
<td>67</td>
<td>H</td>
<td>C₁₇H₂₆N₂O₃S</td>
</tr>
<tr>
<td>273.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(CH₃)₂</td>
<td>93-95</td>
<td>80</td>
<td>H</td>
<td>C₁₆H₂₅N₃O₃S</td>
</tr>
<tr>
<td>274.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>N(CH₃)₂</td>
<td>112-114</td>
<td>60</td>
<td>H</td>
<td>C₁₅H₂₂N₂O₄S</td>
</tr>
<tr>
<td>275.</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>N(CH₃)₂</td>
<td>94-95</td>
<td>87</td>
<td>E-W</td>
<td>C₁₇H₂₆N₂O₃S</td>
</tr>
<tr>
<td>276.</td>
<td>H</td>
<td>C₂H₅</td>
<td>N(CH₃)₂</td>
<td>65-67</td>
<td>70</td>
<td>H</td>
<td>C₁₆H₂₄N₂O₃S</td>
</tr>
<tr>
<td>277.</td>
<td>H</td>
<td>C₂H₅</td>
<td>N(CH₃)₂</td>
<td>90-91</td>
<td>76</td>
<td>H</td>
<td>C₁₇H₂₆N₂O₃S</td>
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<tr>
<td>278.</td>
<td>H</td>
<td>C₂H₅</td>
<td>N(CH₃)₂</td>
<td>95-98</td>
<td>75</td>
<td>H</td>
<td>C₁₃H₂₅N₃O₃S</td>
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</table>

(Contd.)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>H</th>
<th>C$_2$H$_5$-</th>
<th>-N</th>
<th>64-65</th>
<th>70</th>
<th>H</th>
<th>C$<em>{15}$H$</em>{22}$N$_2$O$_4$S</th>
</tr>
</thead>
<tbody>
<tr>
<td>281.</td>
<td>H</td>
<td>C$_2$H$_5$-</td>
<td>-N</td>
<td>102-103</td>
<td>92</td>
<td>H</td>
<td>C$<em>{18}$H$</em>{26}$N$_2$O$_3$S</td>
<td></td>
</tr>
<tr>
<td>283.</td>
<td>(CH$_2$)$_4$-</td>
<td>-N</td>
<td>76-78</td>
<td>78</td>
<td>H</td>
<td>C$<em>{19}$H$</em>{28}$N$_2$O$_3$S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>284.</td>
<td>(CH$_2$)$_4$-</td>
<td>-N-CH$_3$</td>
<td>93-95</td>
<td>80</td>
<td>H</td>
<td>C$<em>{18}$H$</em>{27}$N$_3$O$_3$S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>285.</td>
<td>(CH$_2$)$_4$-</td>
<td>-N-CH$_3$</td>
<td>108-109</td>
<td>90</td>
<td>H</td>
<td>C$<em>{17}$H$</em>{24}$N$_2$O$_4$S</td>
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<td></td>
</tr>
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</table>

H = n-Hexane; E = Ethanol; W = Water.
Intradermal Local Anaesthetic Activity in Guinea Pig

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Volume and % of concentration</th>
<th>% of response failure ± S.E.</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>0.2 ml; 0.5</td>
<td>68 ± 5</td>
<td>0.05</td>
</tr>
<tr>
<td>285</td>
<td>0.2 ml; 0.2</td>
<td>57 ± 2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Local Anaesthetic Activity by Foot Withdrawal Reflex of Frog

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Concentration g/100 ml</th>
<th>No. of withdrawals reflex during 25 minutes ± S.E.</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate buffer</td>
<td></td>
<td>17±1 (n=4)</td>
<td>-</td>
</tr>
<tr>
<td>285</td>
<td>0.1</td>
<td>11±2. (n=5)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>9±4 (n=6)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>3±1 (n=6)</td>
<td>0.02</td>
</tr>
<tr>
<td>273</td>
<td>0.1</td>
<td>13±1 (n=5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Procaine</td>
<td>0.1</td>
<td>17.06 ± 4.1(n=3)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>6.0 ± 1 (n=4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>0.1</td>
<td>16±1 (n=3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
3-Carbethoxy-2-(ω-chloroacetamido)-4,5-dimethyl thiophene (267)

To a mixture of 2-amino-3-carbethoxy-4,5-dimethyl-thiophene\(^{123}\) (9.95g; 0.05 mole) in glacial acetic acid (20.0 ml) cooled in an ice bath, was added chloroacetylchloride (6.78g; 0.06 mole) dropwise. The solution was maintained at 10\(^{\circ}\)C for two hours and then poured over crushed ice. The crude product was filtered, washed successively with water, saturated sodium bicarbonate solution and finally with water. It was then dried in a desiccator. Recrystallization from ethanol yielded 267, 10.5g(76\%), m.p. 150-152\(^{\circ}\)C. The compound was employed for further reaction without analysis.

3-Carbethoxy-4,5-dimethyl-2-(diethylaminoacetamido)thiophene (268)

A mixture of 3-carbethoxy-4,5-dimethyl-2-(ω-chloroacetamido)thiophene (267) (5.51g; 0.02 mole) and diethylamine (2.99g; 0.041 mole) in dry benzene (100 ml) was refluxed for 8 hours on a water bath. The reaction mixture was cooled, diluted with 100 ml dry benzene and filtered. The filtrate was washed with water and dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under vacuum. The residue obtained was recrystallized from n-hexane to yield 268, 3.1g(50\%), m.p. 58.60\(^{\circ}\)C.

Analysis: \(C_{15}H_{24}N_2O_8\) requires: C, 57.69; H, 7.69%

Found: C, 57.74; H, 7.52%

\(\nu_{max} \text{ cm}^{-1}\): 3200 (-NH); 1700(-COEt), 1680(-C-)

MS, m/e: \(= 312 (M^{+})\), 267, 180, 86, 45, 28
3-Carbethoxy-4,5-dimethyl-2-(\(\text{n-dipropylamino acetamido}\)) thiophene (269)

A mixture of 3-carbethoxy-4,5-dimethyl-2(\(\omega\)-chloroacetamido) thiophene (267) (5.51g; 0.02 mole) and \(\text{n-dipropylamine}\) (4.41g; 0.041 mole) in dry benzene (100 ml) was treated according to the procedure described for 268. Recrystallization from \(\text{n-hexane}\) yielded 269, 4.16g(65%), m.p. 62-64°C.

Analysis: \(\text{C}_{17}\text{H}_{28}\text{N}_{2}\text{S}\) requires: C, 60.00; H, 8.23; N, 8.23%

Found: C, 60.38; H, 8.39; N, 8.05%

\(\nu_{\text{max}}\) cm\(^{-1}\): 3200 (-NH), 1700 (\(\text{-COEt}\)), 1680 (-CNH)

3-Carbethoxy-4,5-dimethyl-2(\(\text{piperidino acetamido}\))thiophene (270)

A mixture of 3-carbethoxy-4,5-dimethyl-2(\(\omega\)-chloroacetamido) thiophene (267) (5.5g; 0.02 mole) and piperidine (3.5g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from \(\text{n-hexane}\) yielded 270, 4.16g(65%), m.p. 118-120°C.

Analysis: \(\text{C}_{16}\text{H}_{24}\text{N}_{2}\text{S}\) requires: C, 59.26; H, 7.40; N, 8.64%

Found: C, 59.11; H, 7.66; N, 8.89%

\(\nu_{\text{max}}\) cm\(^{-1}\): 3200 (-NH), 1700 (\(\text{-COEt}\)), 1680 (-CNH)

3-Carbethoxy-4,5-dimethyl-2(\(\text{3-methylpiperidino acetamido}\)) thiophene (271)

A mixture of 3-carbethoxy-4,5-dimethyl-2(\(\omega\)-chloroacetamido) thiophene (267) (5.50g; 0.02 mole) and 3-methylpiperidine (4.1g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from \(\text{n-hexane}\) yielded 271, 4.50g(66%), m.p. 86-88°C.

Analysis: \(\text{C}_{17}\text{H}_{26}\text{N}_{2}\text{S}\) requires: C, 60.36; H, 7.68; N, 8.29%

Found: C, 60.34; H, 7.98; N, 8.00%

\(\nu_{\text{max}}\) cm\(^{-1}\): 3220 (-NH), 1690 (\(\text{-COEt}\)), 1670 (-CNH)
3-Carbethoxy-4,5-dimethyl-2-(4-methylpiperidino)acetamidothiophene (272)

A mixture of 3-carbethoxy-4,5-dimethyl-2-(2-chloroacetamido)thiophene (267) (5.50 g; 0.02 mole) and 4-methylpiperidine (4.1 g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 272, 4.53 g (67%), m.p. 94-95°C.

Analysis: C17H26N2O3S requires: C, 60.36; H, 7.68%
Found: C, 59.43; H, 7.79%

$\nu_{\text{max}} \text{ cm}^{-1}$: 3240 (-NH), 1690 (-COEt); 1670 (-C-NH)

3-Carbethoxy-4,5-dimethyl-2-(4-methylpiperazino) acetamidothiophene (273)

A mixture of 3-carbethoxy-4,5-dimethyl-2-(2-chloroacetamido)thiophene (267) (5.50 g; 0.02 mole) and 4-methylpiperazine (4.2 g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 273, 5.24 g (80%), m.p. 93-95°C.

Analysis: C15H25N3O3S requires: C, 56.66; H, 7.37; N, 12.39; S, 9.43%
Found: C, 56.86; H, 7.70; N, 12.72; S, 10.22%

3-Carbethoxy-4,5-dimethyl-2-(morpholino acetamido)thiophene (274)

A mixture of 3-carbethoxy-4,5-dimethyl-2-(2-chloroacetamido)thiophene (267) (5.5 g; 0.02 mole) and morpholine (3.6 g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 274, 3.9 g (60%), m.p. 112-114°C.

Analysis: C15H22N2O4S requires: C, 55.22; H, 6.74; N, 8.59%
Found: C, 55.35; H, 6.58; N, 8.38%
3-Carbethoxy-2-((\(\_\_\_\) -chloroacetamido)-5-ethyl-4-methyl thiophene (275)

To a mixture of 2-amino-3-carbethoxy-5-ethyl-4-methyl thiophene\(^{124}\) in (10.65g; 0.05 mole) in glacial acetic acid (20.0 ml)/cooled ice bath was added chloroacetylchloride (6.78g; 0.06 mole) dropwise with stirring and treated according to the procedure described for 267. Recrystallization from ethanol yielded 275. The compound was employed for further reaction without analysis.

3-Carbethoxy-5-ethyl-4-methyl-2-((piperidino)acetamido)thiophene (276)

A mixture of 3-carbethoxy-4-ethyl-5-methyl-2-(\(\_\_\_\) -chloroacetamido) thiophene (275) (5.78g; 0.02 mole) and piperidine (3.5g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from a mixture of ethanol and water yielded 276, 5.88g (87%), m.p. 94-95°C.

Analysis requires \(\text{C}_7\text{H}_6\text{N}_2\text{O}_3\) requires: C, 60.36; H, 7.68; N, 8.29%

Found: C, 60.46; H, 7.49; N, 8.05%

3-Carbethoxy-2-((\(\_\_\_\) -chloroacetamido)-5-ethylthiophene (277)

To a mixture of 2-amino-3-carbethoxy-5-ethylthiophene\(^{124}\) (9.95g; 0.05 mole) in glacial acetic acid (20.00 ml) cooled in an ice bath was added chloroacetyl chloride (7.78g; 0.06 mole) dropwise with stirring and treated according to the procedure described for 267. Recrystallization from ethanol yielded 277, 11.60g (85%), m.p. 84-87°C. The compound was employed for further reaction without analysis.
3-Carbethoxy-5-ethyl-2-[(piperidino)acetamido]thiophene (278)

A mixture of 3-carbethoxy-5-ethyl-2-([p-chloroacetamido]thiophene (277) (5.50 g; 0.02 mole) and piperidine (3.5 g; 0.04 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane afforded 278, 4.53 g (74%), m.p. 65-67°C.

Analysis: \(\text{C}_{16}\text{H}_{24}\text{N}_{2}\text{S}\) requires: C, 59.27%; H, 7.40%

Found: C, 59.25%; H, 7.70%

3-Carbethoxy-5-ethyl-2-[(4-methyl piperidino)acetamido]thiophene (279)

A mixture of 3-carbethoxy-5-ethyl-2-([p-chloroacetamido]thiophene (277) (5.50 g; 0.02 mole) and 4-methylpiperidine (4.1 g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 279, 5.13 g (76%), m.p. 90-91°C.

Analysis: \(\text{C}_{17}\text{H}_{26}\text{N}_{2}\text{S}\) requires: C, 60.35%; H, 7.68%; N, 8.29%

Found: C, 60.59%; H, 7.98%; N, 8.21%

3-Carbethoxy-5-ethyl-2-[(4-methylpiperazino)acetamido]thiophene (280)

A mixture of 3-carbethoxy-5-ethyl-2-([p-chloroacetamido]thiophene (277) (5.50 g; 0.02 mole) and 4-methylpiperazine (4.1 g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 280, 5.1 g (75%), m.p. 95-96°C.

Analysis: \(\text{C}_{16}\text{H}_{25}\text{N}_{3}\text{S}\) requires: C, 56.64%; H, 7.37%

Found: C, 56.83%; H, 7.63%

\(\lambda_{\text{max}}\) nm (log \(\epsilon\)): 225 nm (4.31), 247 (3.81), 310 (4.0)

\(\nu_{\text{max}}\) cm\(^{-1}\): 3335 (\(-\text{NH}\)), 1695 (\(-\text{COEt}\)), 1650 (\(-\text{CNH}\))
3-Carbethoxy-5-ethyl-2-(morpholino acetamido) thiophene (281)

A mixture of 3-carbethoxy-5-ethyl-2-(γ-chloroacetamido) thiophene (277) (5.50g; 0.02 mole) and morpholine (3.6g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 281, 4.56g(70%), m.p. 64-65°C.

Analysis: C_{15}H_{22}N_{2}O_{4}S requires: C, 55.22; H, 6.74%

Found: C, 55.53; H, 6.99%

$\lambda_{\text{max}}$ nm (log ε): 225(4.34), 247(3.8), 259(s), 310(4.00)

$\nu_{\text{max}}$ cm$^{-1}$: 3270(-NH), 1690(-C), 1670(-CNH)

3-Carbethoxy-2-(γ-chloroacetamido)-4,5,6,7-tetrahydrobenzo(b)thiophene (282)

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (11.5g; 0.05 mole) was dissolved in water glacial acetic acid (20 ml) and allowed to cool in an ice bath. To the cold solution was added chloroacetyl chloride (6.78g; 0.06 mole) dropwise and then treated according to the procedure described for 267. Recrystallization from ethanol yielded 282, 12.0g(80%), m.p. 116-118°C. The compound was employed for further reaction without analysis.

3-Carbethoxy-2-(piperidinoacetamido)-4,5,6,7-tetrahydrobenzo(b)thiophene (283)

A mixture of 3-carbethoxy-2-(γ-chloroacetamido)-4,5,6,7-tetrahydrobenzo(b)thiophene (282) (6.02g; 0.02 mole) and piperidine (3.5g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 283, 6.5g(92%), m.p. 102-103°C.

Analysis: C_{18}H_{26}N_{2}O_{3}S requires: C, 61.72; H, 7.42; N, 8.00%

Found: C, 61.71; H, 7.72; N, 8.22%
A mixture of 3-carbethoxy-2-(ω-chloroacetamido)-4,5,6,7-tetrahydrobenzothiophene (282) (6.02g; 0.02 mole) and 3-methylpiperidine (4.10g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 284, 5.6g(78%), m.p. 76-78°C.

Analysis: \( C_{19}H_{22}N_2O_3S \) requires: C, 62.64; H, 7.68; N, 7.68%

Found: C, 62.34; H, 7.61; N, 7.28%

A mixture of 3-carbethoxy-2-(ω-chloroacetamido)-4,5,6,7-tetrahydrobenzothiophene (282) (6.02g; 0.02 mole) and 4-methylpiperazine (4.1g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 285, 5.84g(80%), m.p. 93-95°C.

Analysis: \( C_{18}H_{27}N_3O_3S \) requires: C, 59.19; H, 7.40; N, 11.50; S, 8.76%

Found: C, 59.54; H, 7.48; N, 11.61; S, 8.73%

A mixture of 3-carbethoxy-2(ω-chloroacetamido)-4,5,6,7-tetrahydrobenzothiophene (282) (0.02g; 0.02 mole) and morpholine (3.6g; 0.041 mole) was treated according to the procedure described for 268. Recrystallization from n-hexane yielded 286, 6.3g(90%), m.p. 108-109°C.

Analysis: \( C_{17}H_{24}N_2O_4S \) requires: C, 57.96; H, 6.81%

Found: C, 58.18; H, 7.26%

\( \nu_{\text{max}} \text{ cm}^{-1} \): 3200(-NH), 1700(-COEt), 1680(-CNH)
During a routine screening for anthelmintic activity, 2-(2-thienylthio)-2-imidazoline (287) was reported to have nematocidal activity in mice. However, the compound was found to be inactive in sheep, probably because the compound 287 decomposed in sheep to the inactive substance 2-thiaryl thiol (288) and 2-imidazolidone (289).

\[
\begin{align*}
\text{(287)} & \\
\text{(288)} & \\
\text{(289)} & 
\end{align*}
\]

This chance discovery was followed by synthesis of a large number of analogs in order to obtain a chemically stable linkage between 2-thiaryl and imidazoline ring system. Among a large number of compounds screened for anthelmintic activity, 2-(2-thiaryl)ethyl-2-imidazoline (290), was found active both in mice and sheep.

\[
\begin{align*}
\text{(290)} & \\
\text{(291)} & 
\end{align*}
\]
Pyrantel and Morental (132a) were discovered as a consequence of a systematic structure activity study following the synthesis of stable thienyl derivative 290. In early sixties, structure 291 was generalized as essential for anthelmintic activity. Decreasing order of potency for the various aryl systems (Ar) is 2-thiencyl > 3-thiencyl oxyphenyl analogs (292) of Pyrantel have been synthesized and are very effective against whipworms (Trichuris species).

It was, therefore, thought of interest to synthesize compounds of the type (293), with carboxamide group, closely related to 2-2-(thienyl)ethyl 2-imidazoline.
Results and Discussion

2-(ω-chloroacetamido)thiophenes (I) in toluene when condensed with ethylenediamine in presence of sulfur yielded 2-thienyl aminocarbonyl-2-imidazoline (II, Scheme I).

SCHEME I

The reaction appears to have completed when H₂S evolution ceases.

Ethylenediamine reacts with chloroacetamido thiophene(I) to give Ia and HCl.
In presence of basic catalyst ethylenediamine, sulfur probably attacks methylene group to give α-mercapto compound Ib, which immediately cyclizes to afford (Ic). One more atom of sulfur is consumed to dehydrogenate Ic to yield imidazoline derivative II, which stabilizes itself through conjugation with thiophene ring system (IIa). Tautomeric structure IIa may also explain yellow color of these derivatives and strong absorption of these compounds in UV at 340nm (3.97).

Mass spectra of compound 297 shows prominent m/e fragments at 321(M⁺), 279, 251, 206, 179.

Similar fragmentation pattern (m/e, 295(M⁺), 255, 253, 180, 153) is observed for compound 294. NMR is consistent with the structure assigned to compound 294 and 297. The physical constants of compound 294-298 are recorded in Table 20. Imidazolines synthesized form soluble hydrochloride salts.
Pharmacological activity - Compounds 294-298 were screened for analgesic, antiinflammatory, anticonvulsive and antihypertensive activities. Only compound 296, (200 mg/kg) orally, showed significant analgesic activity (37.7% inhibition) when compared with aspirin (43.7% inhibition) at the same dosage level. Compound 296 (200 mg/kg) orally exhibited 1/3 antiinflammatory activity of phenylbutazone (100 mg/kg).

Antimicrobial activity - Compound 294-298 were screened for antifungal and antibacterial activity. Compound 294, 295, and 297 showed significant antibacterial activity (Table 21). However, none of the compounds showed any activity against, E. coli, S. shigae, S. typhi, P. vulgaris and P. aeruginosa at 50 mcg/ml concentration. All the test compounds were inactive against T. mentagrophytes, M. gypseum, C. albicans, Ph. jeanselmei, N. asteroids, and A. fumigatus at 50 mcg/ml concentration.

Anthelmintic screening - Compound 294-298 were devoid of any appreciable activity against N. dubius, H. nana, S. obvelata in mice when administered 400 mg/kg orally for 3 days.
TABLE 20

2-(2-Aminocarbonyl-3-carbethoxythienyl)-2-imidazolines

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>M.P. °C</th>
<th>Yield</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>294.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>182-184*</td>
<td>54</td>
<td>C₁₃H₁₇N₃O₃S</td>
</tr>
<tr>
<td>295.</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>129-130</td>
<td>60</td>
<td>C₁₄H₁₉N₃O₃S</td>
</tr>
<tr>
<td>296.</td>
<td>H</td>
<td>C₂H₅</td>
<td>163-165</td>
<td>50</td>
<td>C₁₃H₁₇N₃O₃S</td>
</tr>
<tr>
<td>297.</td>
<td>-(CH₂)₄-</td>
<td></td>
<td>195-196</td>
<td>62</td>
<td>C₁₅H₁₉N₃O₃S</td>
</tr>
<tr>
<td>298.</td>
<td>CH₃</td>
<td></td>
<td>159-161</td>
<td>55</td>
<td>C₁₆H₂₁N₃O₃S</td>
</tr>
</tbody>
</table>

* All compounds were recrystallized from ethanol
TABLE 21
Antibacterial activity of
2-(2-aminocarbonyl-3-carbethoxythienyl)-2-imidazoline
(MIC mcg/ml)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>S. aureus</th>
<th>S. aureus (A/R)</th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>294</td>
<td>3.125</td>
<td>3.125</td>
<td>3.125</td>
</tr>
<tr>
<td>295</td>
<td>6.250</td>
<td>6.250</td>
<td>-</td>
</tr>
<tr>
<td>297</td>
<td>50.000</td>
<td>50.000</td>
<td>-</td>
</tr>
</tbody>
</table>
EXP E R I M E N T A L

2-(2-Aminocarbonyl-3-carbethoxy-4,5-dimethyl thienyl)-2-imidazoline (294)

In a two necked round bottom flask, fitted with a reflux condenser and dropping funnel, 2-(ω-chloroacetamido)-3-carbethoxy-4,5-dimethylthiophene (267, 6.9g; 0.025 mole) and finely powdered sulfur (1.6g) in toluene (60 ml) was brought to reflux. To the refluxing mixture was added excess of ethylenediamine (7.0g) drop by drop from a dropping funnel. The mixture was allowed to be refluxed for 2 hours and filtered hot.

After chilling it overnight, the solid obtained was filtered, washed repeatedly with water and dried. Recrystallization from ethanol yielded 294, 7.0g (54%) yellow crystalline material, m.p. 182-184°C.

Analysis : \( C_{13}H_{17}N_{3}O_{3}S \) requires : C, 52.90; H, 5.76; N, 14.24%

Found : C, 53.08; H, 6.07; N, 14.54%

\( \lambda_{\text{max}} \) nm (log \( \varepsilon \)) : 210(4.25), 226(4.13), 260(3.95), 340(3.95)

\( \nu_{\text{max}} \) cm\(^{-1} \) : 3390, 3210(-NH); 1685(-COEt); 1670(-CNH); 1605(-C=O)

MS, m/e : 295(M\(^+\)), 253, 225, 180

2- (2-Aminocarbonyl-3-carbethoxy-5-ethyl-4-methyl thienyl)-2-imidazoline (295)

To a mixture of 2-(ω-chloroacetamido)-3-carbethoxy-5-ethyl-4-methyl thiophene (6.3g; 0.025 mole) and finely powdered sulfur (1.6g) in toluene (60 ml) was added excess of ethylenediamine (7.0g) and treated according to the procedure described for 294. Recrystallization from ethanol yielded 295, 4.63g (60%), m.p. 129-130°C.

Analysis : \( C_{14}H_{19}N_{3}O_{3}S \) requires : C, 54.38; H, 6.14; N, 13.59%

Found : C, 54.65; H, 6.39; N, 13.66%

\( \lambda_{\text{max}} \) nm (log \( \varepsilon \)) : 210(4.25), 225(4.15), 260(3.9), 340(4.00)

\( \nu_{\text{max}} \) cm\(^{-1} \) : 3360, 3225(-NH); 1685(-COEt); 1665(-CNH)

MS, m/e : 309(M\(^+\)), 267, 239, 236, 194.
2-(2-Aminocarbonyl-3-carbethoxy-5-ethyl thienvl)-2-imidazoline (296)

To a mixture of 2-(ω-chloroacetamido)-3-carbethoxy-5-ethylthiophene (277) (6.9g; 0.025 mole) and finely powdered sulfur (1.6g) in toluene (60 ml) was added excess of ethylenediamine (7.0g) and treated according to the procedure described for 294. Recrystallization from ethanol yielded 296, 3.7g(50%), m.p. 163-165°C.

Analysis: \( \text{C}_{13}\text{H}_{17}\text{N}_{3}\text{O}_{3}\text{S} \) requires: C, 52.90%; H, 5.76%; N, 14.24%

Found: C, 52.72%; H, 6.00%; N, 14.44%

2-(2-Aminocarbonyl-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thienyl)-2-imidazoline (297)

To a mixture of 2-(ω-chloroacetamido)-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene (7.5g; 0.023 mole) and powdered sulfur (1.6g) in toluene (60 ml) was added excess of ethylenediamine (7.0g) and treated according to the procedure described for 294. The product recrystallized from ethanol yielded 297, 5.0g(62%), m.p. 195-196°C.

Analysis: \( \text{C}_{15}\text{H}_{19}\text{N}_{3}\text{O}_{3}\text{S} \) requires: C, 56.09%; H, 5.92%; N, 13.09%

Found: C, 56.30%; H, 6.28%; N, 13.26%

\( \nu_{\max} \text{cm}^{-1} \) : 3380, 3247(-NH), 1690(ODet), 1670(-OONH)

\( \text{MS, } m/e \) : 321(M+), 279, 251, 206

2-(2-Aminocarbonyl-3-carbethoxy-4-methyl-4,5,6,7-tetrahydrobenzo(b)thienyl)-2-imidazoline (298)

To a mixture of 2-(ω-chloroacetamido)-3-carbethoxy-4-methyl-4,5,6,7-tetrahydrobenzo(b)thiophene (7.9g; 0.025 mole) and powdered sulfur (1.6g) in toluene (60 ml) was added excess of ethylenediamine (7.0g) and treated according to the procedure described for 294. Recrystallization from ethanol yielded 298, 4.6g(55%), m.p. 159-161°C.

Analysis: \( \text{C}_{16}\text{H}_{21}\text{N}_{3}\text{O}_{3}\text{S} \) requires: C, 57.33%; H, 6.26%; N, 12.54%

Found: C, 57.48%; N, 6.54%; N, 12.62%
Diverse pharmacological activities have been encountered in compounds containing quinazolinone ring system. Antimalarial activity of febrifugine alkaloid (299) is superior to quinine. Some febrifugine analogs synthesized are as active as febrifugine.

Another alkaloid, vascinone (300) is known to possess bronchodilator activity. It appears that bronchodilator activity is inherent in the 4-quinazolone molecule itself. A number of quinazolin-4(3H)-ones have better activity than vascinone. Quinazolinones with CNS activity are known. 2-Methyl-3-o-tolyl-4(3H)-quinazolinone (methaqualone) is used in therapy as hypnotic. 7-Chloro-2-ethyl-6-sulphonamido-1,2-dihydro-4(3H)-quinazolinone (quinethazone) is a diuretic. Other quinazolinones have muscle relaxant, antiinflammatory, antimitotic, antihistaminic, and hypertensive activity.

Aminopyrine level analgesia associated with antiinflammatory activity has been reported in 1-acyl derivatives of 2-methyl-3-aryl tetrahydroquinazolin-4-ones. At least four compounds in this series have antiinflammatory activity better than that of phenylbutazone.
1-Alkyl-4-(1H)-quinazolinones have been synthesized for their analgesic and antiinflammatory activity. Analgesic activity of four quinazolinones were equal to or better than that of codeine when tested by hot plate analgesic assay method. The most promising compound, 1-allyl-4(1H)-quinazolinone was twice as active as codeine phosphate. Of the 54 2-amino-4(3H)-quinazolinones tested in hypertensive dogs, 2-diethylamino-6,7-dimethoxy quinazolinone is the most active compound. A series of 1-tert-aminoacetyl-2-alkyl-3-phenyl-4-oxo-tetrahydroquinazolinones has been synthesized for choleretic activity. 1-Morpholinoacetyl-2-methyl-3-phenyl-4-quinazolinone is the most effective choleretic agent. 2-Hydroxymethyl-4(3H)-quinazolinone carbamates with antithrombotic activity have been reported. Significant analgesic and antiinflammatory activity of 1-alkyl-4-aryl-2(1H)-quinazolinones have been described. On the other hand, 4-aryl-2(1H)-quinazolines exhibit analgesic, antiinflammatory and CNS activity. 2,3-Dipyridylquinazolinones have analgesic, antiinflammatory and sedative properties.

4-Aryl-thieno(2,3-d)pyrimidin-2-ones are reported to have diuretic activity. 2-Methyl-3-aryl-5,6,7,8-tetrahydrobenzo(b)thieno (2,3-d) pyrimidin-4(3H)-ones have been synthesized with significant antiinflammatory activity.

4-Aminopyrimidines

4-(Substituted amino)-2-(5-nitrofuryl) quinazolines are found to possess broad spectrum in vitro activity against a variety of organisms. On the other hand, 2-(5-nitro-2-thienyl) quinazoline analogs have anthelmentic activity against Ascaris suum, Syphacia obvelata and Hymenolepis nan.
Antiviral activity has been encountered in 4-amino and 1-alkyl substituted amino derivatives of 5,6,7,8-tetrahydro-5,8-ethano-pyridino(2,3-b)thieno(2,3-d)pyrimidines (148). 4-Piperazinylthieno(2,3-d)pyrimidines with antihistaminic activity have been synthesized (142).

Thrombocyte aggregation inhibition activity has been reported in 2,3-diamino substituted thieno(2,3-d)pyrimidines (140, 141).

2-(5-Nitro-2-furyl)thieno(2,3-d)pyrimidines have bactericidal and trichomonacidal activity (144).

Results and Discussion

2-Amino-3-carbethoxy thiophene on heating with formamide at 180°C afforded thieno(2,3-d)pyrimidin-4(3H)-one (301, 303). Carbonyl and -NH-functions absorbed in IR at 1760 and 3160 cm\(^{-1}\), respectively.

However, when 2-amino-3-carbethoxy-4-morpholinomethyl-4,5,6,7-tetrahydrobenzo(b)thiophene (173) was refluxed with formamide, the product obtained analyzed for C\(_{10}\)H\(_{10}\)N\(_2\)S. It did not depress the mixed melting point of compound 306b. The IR and UV spectra were identical with 5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (306b).

It appears that during heating with formamide morpholinomethyl group is lost by retro-Mannich type reaction. The thermal instability of Mannich bases under alkaline conditions is known. Physical constants of thieno(2,3-d)pyrimidin-4-ones are recorded in Table 22.
301. \( R, X = -\text{OC}_2\text{H}_5 \)
302. \( X = -\text{NH}-\text{NH}_2 \)

303. \( R_1 = \text{CH}_3; R_2 = \text{H} \)
304. \( R_1 = \text{H}; R_2 = \text{C}_6\text{H}_5 \)

305. \( R_1 = \text{CH}_3, R_2 = -\text{COC}_2\text{H}_5 \)

306. \( R_1 R_2 = \)

307. \( R_1 R_2 = \)

(312 - 327, Table 23)

\( X = \text{Basic groups} \)
2-Amino-5-carbethoxy-3-cyanothiophene was condensed with formamide to afford 4-amino-thieno(2,3-d)pyrimidine (305) (Eq. I). The IR spectrum showed two absorption bands at 3400, 3330 cm\(^{-1}\) corresponding to \(-\text{NH}_2\) function. However, there was also a prominent absorption band at 1670 cm\(^{-1}\). This may be assigned to \(-\text{C}=\text{NH}\) due to the following tautomeric structures. This may also explain the weakly basic nature.
of 4-amino pyrimidines. Similarly, 2-amino-4-cyano-4-morpholinomethyl 4,5,6,7-tetrahydrobenzo(b)thiophene (174) when heated with formamide at 180°C, yielded 5-morpholinomethyl-4-amino thieno(2,3-d) pyrimidine (306). It is of interest to note that during this reaction, morpholinomethyl group was retained and not lost by retro Mannich reaction as in 306a. It is possible, in the absence of a base like ethoxide ion (C₂H₅O⁻), retro Mannich reaction does not get catalyzed. 2-Acetamido-3-cyanothiophene (308a) when refluxed with ethanolic HCl, cyclized to give 2-methyl-thieno(2,3-d)pyrimidin-4(3H)-one (308). IR spectra of the product showed absence of cyanide band and presence of a carbonyl function. 2-Amino-3-phenylcarboxamido thiophene (169) was cyclized in presence of triethyl orthoformate and acetic anhydride to give 3-phenyl thieno(2,3-d)pyrimidin-4(3H)-one (304).

A mixture of 2-amino-3-carboxamido thiophene and furfural in ethanol when refluxed in presence of HCl yielded tetrahydro pyrimidin-4-ones (309, 310). IR showed absence of primary amino grouping and presence of amide grouping at 3140 and 1670 cm⁻¹.
4-Hydrazinothieno(2,3-d)pyrimidine was treated with divinyl sulfone in DMSO-alcohol mixture to give 311. The compound was highly insoluble in organic solvents. In IR, primary amino group was absent and secondary arylamine function was observed at 3396 cm\(^{-1}\). Vinyl protons were absent in NMR. Elemental analysis precludes dimeric structure of 311 when 311a reacts with divinylsulfone to afford a 2:1 adduct. The other possible structures for 311 are as follows:

![Structures (311b), (311c), (311d), and (311e)](image)

Structures 311b, 311c, and 311d have been ruled out on the basis of NMR data, since the product shows no vinyl protons. Structure 311e cannot be ruled out exclusively, though entropy considerations would not favour it over a six-membered ring system (311).

4-Substituted amino thieno(2,3-d)pyrimidines

Thieno(2,3-d)pyrimidin-4-one (I, Eq. II) when treated with POCl\(_3\) gave 4-chloro thieno(2,3-d)pyrimidine (II). 4-Chloro thieno pyrimidines
are low-melting compounds and are highly soluble in non-polar solvents. These properties are in contrast with those of 4-hydroxypyrimidines (I) which are high melting and insoluble in non-polar solvents due to intermolecular hydrogen bonding. 4-Chloro thieno(2,3-d)pyrimidines (II) undergo facile nucleophilic displacement with amines to give 4-substituted amino thieno(2,3-d)pyrimidines (III).\(^{286,287}\) Manhas and his coworkers have studied nucleophilic reactions of 4-chloro thieno(2,3-d)pyrimidines (II).\(^{139}\) 4-Chloro thieno(2,3-d)pyrimidine (II) was refluxed with 2 moles of amine in benzene or with excess of amine without any solvent to obtain 4-amino thieno(2,3-d)pyrimidines (III). Since in the presence of excess of amine, 6-carbethoxy function also gets converted to the corresponding amide, it is preferable to use benzene for selective amination reaction of 4-chloro pyrimidine. 4-Substituted amino derivatives (III) are soluble in non-polar solvents. These amino derivatives (III) could be crystallized from a mixture of benzene and n-hexane. Table 23.

![Diagram](image-url)
### TABLE 22

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Recrystallization solvent*</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>301.</td>
<td>246-248</td>
<td>84</td>
<td><strong>E</strong></td>
<td>C_{10}H_{10}N_{0.5}O_{0.5}S</td>
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<tr>
<td>302.</td>
<td>&gt; 320</td>
<td>80</td>
<td><strong>D-E</strong></td>
<td>C_{8}H_{11}N_{0.5}O_{0.5}S</td>
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<tr>
<td>303.</td>
<td>179-181</td>
<td>70</td>
<td><strong>E</strong></td>
<td>C_{11}H_{12}N_{0.5}O_{0.5}S</td>
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<tr>
<td>304.</td>
<td>189-190</td>
<td>53</td>
<td><strong>E</strong></td>
<td>C_{16}H_{14}N_{0.5}O_{0.5}S</td>
</tr>
<tr>
<td>305.</td>
<td>250-253(d)</td>
<td>40</td>
<td><strong>D-E</strong></td>
<td>C_{10}H_{11}N_{0.5}O_{0.5}S</td>
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<tr>
<td>306.</td>
<td>227-230</td>
<td>50</td>
<td><strong>E-C</strong></td>
<td>C_{15}H_{20}N_{0.5}O_{0.5}S</td>
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<tr>
<td>307.</td>
<td>202-204</td>
<td>60</td>
<td><strong>E</strong></td>
<td>C_{14}H_{11}N_{0.5}O_{0.5}S</td>
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<tr>
<td>308.</td>
<td>301-302</td>
<td>60</td>
<td><strong>E-C</strong></td>
<td>C_{23}H_{21}N_{0.5}O_{0.5}S</td>
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<tr>
<td>309.</td>
<td>310-312</td>
<td>50</td>
<td><strong>E-C</strong></td>
<td>C_{14}H_{14}N_{0.5}O_{0.5}S</td>
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<tr>
<td>310.</td>
<td>190-192</td>
<td>80</td>
<td><strong>E-C</strong></td>
<td>C_{20}H_{18}N_{0.5}O_{0.5}S</td>
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<tr>
<td>311.</td>
<td>240-244(d)</td>
<td>80</td>
<td><strong>E</strong></td>
<td>C_{14}H_{18}N_{0.5}O_{0.5}S</td>
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</table>

*C = Chloroform; D = Dimethylformamide; E = Ethanol.*
<table>
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<th>Compound No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>X</th>
<th>M.P.</th>
<th>Yield %</th>
<th>Recrystallization solvent</th>
<th>Molecular formula</th>
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<tr>
<td>312.</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-</td>
<td>H</td>
<td>Cl</td>
<td>135-138</td>
<td>55</td>
<td>B-C</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;SCl</td>
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<td>H</td>
<td>Piperidino</td>
<td>125-127</td>
<td>85</td>
<td>C</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>H</td>
<td>Morpholino</td>
<td>160-162</td>
<td>50</td>
<td>B-C</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;15&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>
<td>315.</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sup&gt;4&lt;/sup&gt;-</td>
<td>HN(CH&lt;sub&gt;3&lt;/sub&gt;)-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>140-141</td>
<td>65</td>
<td>B-C</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sup&gt;4&lt;/sup&gt;-</td>
<td>HN(CH&lt;sub&gt;2&lt;/sub&gt;)&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>110-111</td>
<td>66</td>
<td>B-C</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
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<td>Piperidino</td>
<td>87-89</td>
<td>55</td>
<td>B-C</td>
<td>C&lt;sub&gt;15&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>Cl</td>
<td>116-120</td>
<td>40</td>
<td>B-C</td>
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<td>-HN-(CH&lt;sub&gt;2&lt;/sub&gt;)&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>133-135</td>
<td>80</td>
<td>B</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Morpholino</td>
<td>116-118</td>
<td>66</td>
<td>B-C</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>Piperidino</td>
<td>123-126</td>
<td>70</td>
<td>C</td>
<td>C&lt;sub&gt;15&lt;/sub&gt;H&lt;sub&gt;19&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>
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<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3-methyl-piperidino</td>
<td>93-95</td>
<td>75</td>
<td>C</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;3&lt;/sub&gt;</td>
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<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4-Piperazino</td>
<td>125-127</td>
<td>70</td>
<td>B-C</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
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<td>4-Me Piperazino</td>
<td>99-102</td>
<td>78</td>
<td>C</td>
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<tr>
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<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NH-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>174-176</td>
<td>88</td>
<td>B</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;24&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;OS</td>
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<tr>
<td>327.</td>
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<td>H&lt;sub&gt;2&lt;/sub&gt;N,NH-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-NH-NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>246-248</td>
<td>80</td>
<td>B</td>
<td>C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;6&lt;/sub&gt;OS</td>
<td></td>
</tr>
</tbody>
</table>

B = Benzene; C = n-Hexane
EXPERIMENTAL

6-Carbethoxy-5-methylthieno(2,3-d)pyrimidin-4(3H)-one (301)
A mixture of 2-amino-3,5-dicarbethoxy-4-methylthiophene \(124\) \((25.9\, \text{g}; 0.1 \text{ mole})\) and formamide \((240\, \text{g})\) was heated in an oil bath at 200\(^\circ\)C for 18 hours. On chilling overnight, crystalline precipitate obtained was filtered and washed with cold isopropanol. Recrystallization from ethanol yielded \(301\), 20g(84%), m.p. 246-248\(^\circ\)C. (reported m.p. 233-234\(^\circ\)C). \(^{305}\)

Analysis: \(\text{C}_9\text{H}_9\text{N}_2\text{O}_5\) requires: C, 50.43; H, 4.20; N, 11.76%

Found: C, 50.66; H, 4.39; N, 11.69%

\(\lambda_{\text{max}}\) (log \(\varepsilon\)) : 225(4.26), 245(4.01), 252(3.96), 307(4.13)

\(\nu_{\text{max}}\) cm\(^{-1}\) : 3180(-NH), 1700(C0Et), 1680(-C=N)

5-Methyl thieno(2,3-d)pyrimidin-4(3H)-one-6-hydrazide (302)
A mixture of 6-carbethoxy-5-methylthieno(2,3-d)pyrimidin-4(3H)-one \(301\) \((2.4\, \text{g}; 0.01 \text{ mole})\) and hydrazine hydrate \((2.0\, \text{g}; 80\%)\) in ethanol was refluxed for 12 hours. After chilling overnight, the precipitate obtained was filtered, washed with water and dried. Recrystallization from a mixture of DMF and ethanol yielded \(302\), 1.89(80%), m.p. > 320\(^\circ\)C.

Analysis: \(\text{C}_9\text{H}_8\text{N}_4\text{O}_5\) requires: C, 42.86; H, 3.57; N, 24.96%

Found: C, 42.68; H, 3.80; N, 25.10%

\(\nu_{\text{max}}\) cm\(^{-1}\) : 3200(NH), 1690(-C-NH)

5-Methyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (303)
A mixture of 2-amino-3-carbethoxy-4-methyl-4,5,6,7-tetrahydrobenzo(b)thiophene \(124\) \((12.0\, \text{g}; 0.1 \text{ mole})\) and formamide \((60 \,\text{ml})\) was heated in an
oil bath at 200°C for 6 hours. On cooling, solid obtained was filtered, washed with water, and dried over P₂O₅ in a vacuum desiccator.

Recrystallization from ethanol yielded 303, 14.7g(70%), m.p. 179-181°C.

Analysis: C₁₁H₁₂N₂OS requires C, 60.0; H, 5.50; N, 12.73%
Found: C, 60.09; H, 5.69; N, 12.72%

λ(max) (log ε): 230(4.27), 300(4.03)

3-Phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (304)

A mixture of 2-amino-3-carboxanilido-4,5,6,7-tetrahydrobenzo(b)thiophene and (169) (6.8g; 0.025 mole) /triethyl orthoformate (50 ml) was refluxed for 12 hours. The mixture was concentrated under vacuum. On chilling, crystalline product obtained was filtered and washed with cold isopropyl alcohol. Recrystallization from ethanol yielded 304, 4g(53%), m.p. 189-190°C.

Analysis: C₁₆H₁₄N₂O₂S requires C, 68.08; H, 4.96; N, 9.92%
Found: C, 68.23; H, 5.12; N, 9.84%

λ(max) (log ε): 213(4.42), 315(3.96)

4-Amino-6-carbethoxy-5-methylthieno(2,3-d)pyrimidine (305)

A mixture of 2-amino-5-carbethoxy-3-cyano-4-methyl thiophene (3.0g; 0.0142 mole) and formamide (25g) was refluxed in an oil bath for 8 hours at 180°C. The mixture was cooled overnight. The precipitate obtained was filtered and washed with ethanol. Recrystallization from DMF and ethanol mixture yielded 305, 1.32g(40%), m.p. 250-253°C (dec.)

Analysis: C₁₀H₁₁N₂O₂S requires C, 50.63; H, 4.64; N, 17.73%
Found: C, 50.53; H, 4.73; N, 17.90%

λ(max) (log ε): 225(4.45), 250(s), 288(3.90), 312(4.73)

ν(max) cm⁻¹ : 3450, 3340, 3120, 1700, 1650(=NH)
4-Amino-5-(morpholinomethyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)-pyrimidine (306)

A mixture of 2-amino-3-cyano-4-morpholinomethyl-4,5,6,7-tetrahydrobenzo(b)thiophene (174) (2.7g; 0.01 mole) and formamide (15 ml) was treated according to the procedure described for 305. Recrystallization from a mixture of ethanol and chloroform yielded 306, 1.5g(50%), m.p. 227-230°C.

Analysis: \( \text{C}_{15}\text{H}_{20}\text{N}_4\text{OS} \) requires: C, 59.21; H, 6.57; N, 18.42%

Found: C, 58.98; H, 6.63; N, 18.33%

Attempted synthesis of 5-(morpholinomethyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (306a)

A mixture of 2-amino-3-carbethoxy-4-(morpholinomethyl)-4,5,6,7-tetrahydrobenzo(b)thiophene (173) (8.1g; 0.03 mole) and formamide (60 ml) was treated according to the procedure described for 301. Recrystallization from ethanol yielded 3g of a product which melted at 254-257°C. Mixed melting point with compound 306b remained undepressed.

Analysis: \( \text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2\text{S} \) requires: C, 59.02; H, 6.22; N, 13.77%

Found: C, 58.00; H, 5.14; N, 13.73%

\( \lambda_{\max} \text{nm (log } \epsilon) \) 197 (4.26), 238(4.03), 270(3.68), 307(3.88)

\( \nu_{\max} \text{cm}^{-1} \) 3180(-NH), 1670(-N-H)

5,6,7,8-Tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(3H)-one (306b)

A mixture of 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzo(b)thiophene (9.8g; 0.05 mole), triethylorthoformate (40 ml) and acetic anhydride was treated according to the procedure described for 304. Recrystallization from ethanol yielded 306b, 12.4g(60%), m.p. 256-258°C. (reported m.p. 258-259°C.)
Analysis: \( \text{C}_{10} \text{H}_{10} \text{N}_2 \text{O}_2 \) requires: C, 58.25; H, 4.85; N, 13.59%

Found: C, 58.40; H, 5.01; N, 13.71%

\( \lambda_{\text{max}} \text{ nm (log e)} \): 242 (3.96), 272 (3.70), 307 (3.89)

\( \nu_{\text{max}} \text{ cm}^{-1} \): 3160 (N-H), 1660 (-C-)

4-Aminoo-9,10-dihyodronaphtho(2,1-b)thiophen(2,3-d)pyrimidine (307)

A mixture of 2-amino-3-cyano-4,5-dihyodronaphtho(2,1-b)thiophene (4.6g) and formamide (35 ml) was treated according to the procedure described for 305. Recrystallization from ethanol yielded 307, 3.0g (60%), m.p. 202-204°C.

Analysis: \( \text{C}_{14} \text{H}_{11} \text{N}_3 \) requires: C, 66.40; H, 4.34%

Found: C, 66.31; H, 4.53%

2-Acetvlamido-3-cyano-5,7-diphenyl-6-methyl-4,5,6,7-tetrahydrothieno
(2,3-c)pyridine (308a)

A mixture of 2-amino-3-cyano-5,7-diphenyl-6-methyl-4,5,6,7-tetrahydrothieno (2,3-c) pyridine (3.17g; 0.01 mole) and acetic anhydride (20 ml) was refluxed for 2 hours. On cooling, white crystalline precipitate obtained was filtered. Recrystallization from ethanol yielded 308a, 2.5g (70%), m.p. 245-247°C. The product was used for further reaction without analysis.

2,7-Dimethyl-6,8-diphenyl-5,6,7,8-tetrahydropyrido(4';3' : 4,5)thieno
(2,3-d)pyrimdin-4-one (308)

A mixture of 2-acetlylamino-3-cyano-5,7-diphenyl-6-methyl-4,5,6,7-tetrahydrothieno(2,3-c)pyridine (308a) (1.8g; 0.005 mole) and ethanol saturated with dry HCl (20 ml) was refluxed for 6 hours. On chilling,
solid obtained was filtered, washed with water, sodium carbonate solution (5%), and dried. Recrystallization from a mixture of ethanol and chloroform yielded 1.2g (50%), m.p. 301-302°C.

Analysis: \( C_{23}H_{21}N_3O \) requires: C, 71.32; H, 5.43%

Found: C, 71.60; H, 5.46%

**2,3-Dihydro-2-(2-furyl)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(1H)-one (309)**

To a mixture of 2-amino-3-carboxanido-4,5,6,7-tetrahydrobenzo(b)thiophene \(^{124}\) (3.92g; 0.02 mole) in hot ethanol was added concentrated HCl (2 ml). To this well stirred mixture was added dropwise a solution of furfuraldehyde (1.92g; 0.02 mole) in ethanol (10 ml). The mixture was stirred for 3 hours at room temperature and chilled overnight. The solid obtained was filtered and washed with water and ethanol, and dried in a desiccator. Recrystallization from a mixture of ethanol and chloroform yielded, 309, 2.7g (50%), m.p. 310-312°C.

Analysis: \( C_{14}H_{14}N_2O_2S \) requires: C, 61.32; H, 5.11; N, 10.22%

Found: C, 61.13; H, 4.85; N, 10.52%

\( \lambda_{\text{max}} \text{ nm (log } \varepsilon) = 209(4.29); 263(4.07) \)

\( \nu_{\text{max}} \text{ cm}^{-1} = 3135(\text{-NH})_1, 1650(\text{-CN})_1 \)

**2,3-Dihydro-2-(2-furyl)-3-phenyl-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidin-4(1H)-one (310)**

To a mixture of 2-amino-3-carboxanido-4,5,6,7-tetrahydrobenzo(b)thiophene (169) (5.44g; 0.02 mole) in hot ethanol (40 ml) was added concentrated HCl (2 ml). To this well stirred mixture was added dropwise a solution of furfuraldehyde (1.92g; 0.02 mole) dissolved in ethanol (10 ml). The
mixture was stirred at 30°C for 3 hours. On chilling overnight, solid obtained was filtered washed with water and ethanol. Recrystallization from a mixture of ethanol and chloroform yielded a yellow product 310, 5.6g(80%), m.p. 190-192°C.

Analysis : C_{29}H_{18}N_{2}O_{2}S \text{ requires: } C, 68.57; H, 5.14; N, 8.00%

Found : C, 68.56; H, 5.12; N, 8.19%

\[ \nu_{\text{max}} \text{ cm}^{-1} : 3130(-\text{NH}), 1670(-\text{C-N-}) \]

4-(4-thiomorpholino-1,1-dioxide) amino-5,6,7,8-tetrahydrobenzo(b)thieno
(2,3-d)pyrimidine (311)

To a mixture of 4-hydrazino-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine \(^{140}\) (2.2g; 0.01 mole) in a 1:1 solution of dimethylsulfoxide and ethanol (20 ml) was added divinylsulfone (2.36g; 0.02 mole) with stirring. The mixture was refluxed for 6 hours. After cooling overnight, it was filtered and washed with ethanol.

The compound being highly insoluble could not be recrystallized. On washing successively with hot alcohol, chloroform, DMF, and alcohol, the product (311) obtained was 3.4g(80%), m.p. 240-244°C (d).

Analysis : C_{14}H_{18}N_{2}O_{2}S \text{ requires: } C, 49.70; H, 5.32; N, 16.57%

Found : C, 49.52; H, 5.54; N, 16.26%

\[ \nu_{\text{max}} \text{ cm}^{-1} : 3395(-\text{NH}), 1390, 1150(-\text{S=S}) \]

NMR (\(\delta,\text{CF}_{3}\text{COOH}\)) : Vinyl protons absent.
5-Phenyl thieno(2,3-d)pyrimidin-4(3H)-one (312a)

A mixture of 2-amino-3-carbethoxy-4-phenylthiophene (24.7g; 0.1 mole) and formamide (250 ml) was treated according to the procedure described for 301. Recrystallization from alcohol yielded 312a, 15.96g (70%), m.p. 220-222°C. (reported m.p. 210-211°C)

Analysis: \( C_{12}H_{8}N_{2}O_{2} \) requires: C, 63.16%; H, 3.50%

Found: C, 63.28%; H, 3.87%

\( \lambda_{\text{max}} \) nm (log ε): 243(4.21), 299(3.82)

\( \nu_{\text{max}} \) cm\(^{-1}\): 3100(-NH), 1695(-CNH)

4-Chloro-5-phenyl thieno(2,3-d)pyrimidine (312)

A mixture of 5-phenyl thieno(2,3-d)pyrimidin-4(3H)-one (45.6g; 0.2 mole) and POCl\(_3\) (400 ml) was refluxed for 12 hours in a fuming chamber. Excess of POCl\(_3\) was removed under vacuum. To the residue was added dry benzene (30 ml) and then solvent was distilled under vacuum to remove the traces of POCl\(_3\). Gummy mass obtained was triturated with ice and NaHCO\(_3\). The solid was collected, washed with water and dried in a vacuum desiccator over P\(_2\)O\(_5\).

The solid was then extracted with benzene and filtered. Filterate was washed with saturated solution of sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed under vacuum. Recrystallization from benzene and n-hexane yielded 312, 26.5g (55%), m.p. 135-138°C.

Analysis: \( C_{12}H_{8}N_{2}S\Cl \) requires: C, 58.43%; H, 2.84%

Found: C, 58.64%; H, 2.94%

\( \lambda_{\text{max}} \) nm (log ε): 230(4.51), 290(4.25)
4-Piperidino-5-phenyl thieno(2,3-d)pyrimidine (313)

A mixture of 4-chloro-5-phenyl thieno(2,3-d)pyrimidine (312) (4.92 g; 0.02 mole) and excess of piperidine (5.0 g) was heated under reflux in an oil bath at 100°C for 12 hours. On cooling, the mixture was poured over ice and triturated to obtain solid which was filtered and washed with water. Recrystallization from n-hexane yielded 313, 5.1 g (85%), m.p. 125-127°C.

Analysis: C_{17}H_{17}N_{3}S requires: C, 69.13; H, 5.80; N, 14.23%

Found: C, 68.93; H, 6.08; N, 14.03%

\[ \lambda_{\text{max}} \text{nm(log } \varepsilon) : 224(4.35), 300(4.13), \]

4-Morpholino-5-phenyl thieno(2,3-d)pyrimidine (314)

A mixture of 4-chloro-5-phenyl thieno(2,3-d)pyrimidine (4.92 g; 0.02 mole) and excess of morpholine (5.0 g) was treated according to the procedure described for 313. Recrystallization from benzene and n-hexane yielded 314, 3.0 g (50%), m.p. 160-162°C.

Analysis: C_{16}H_{15}N_{3}OS requires: C, 64.63; H, 5.09; N, 14.14%

Found: C, 64.37; H, 5.25; N, 14.34%

\[ \lambda_{\text{max}} \text{nm(log } \varepsilon) : 224(4.53), 229(4.11) \]

4-(1-Phenylethylamino)-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine (315)

A mixture of 4-chloro-5,6,7,8-tetrahydrobenzo(b)thieno(2,3-d)pyrimidine (4.50 g; 0.02 mole) and excess of 1-phenyl ethylamine (6 g) was treated according to the procedure described for 313. Recrystallization from benzene and n-hexane mixture yielded 315, 6.2 g (65%), m.p. 140-141°C.

Analysis: C_{18}H_{19}N_{3}S requires: C, 69.90; H, 6.14%

Found: C, 69.65; H, 6.15%
6-Carbethoxy-5-methyl-4-(2-phenylethylamino)thieno(2,3-d)pyrimidine (319)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added 2-phenylethylamine (2.4g; 0.02 mole) dropwise and refluxed over steam bath for 12 hours. The mixture on cooling was filtered and washed twice with benzene (10 ml). Filtrate and the washings were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue on recrystallization from benzene yielded 319, 2.7g(80%), m.p. 133-135°C.

Analysis: C_{18}H_{19}N_{3}O_{2}S requires: C, 63.35; H, 5.57; N, 12.31%

Found: C, 63.50; H, 5.77; N, 12.47%

\[ \lambda_{\text{max}} \text{nm (log E)} = 227(4.42), 280(S), 290(3.89), 323(4.16) \]

\[ \nu_{\text{max}} \text{cm}^{-1} = 3470(\text{NH}), 1720(-C-) \]

6-Carbethoxy-5-methyl-4-morpholino thieno(2,3-d)pyrimidine (320)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added morpholine (1.75g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from a mixture of benzene and n-hexane yielded 320, 2.0g(66%), m.p. 116-118°C.

Analysis: C_{14}H_{17}N_{3}O_{6}S requires: C, 54.73; H, 5.53; N, 13.68%

Found: C, 54.82; H, 5.69; N, 13.94%

\[ \nu_{\text{max}} \text{cm}^{-1} = 1715(-\text{OOC}_{2}\text{H}_5) \]
6-Carbethoxy-5-methyl-4-piperidino thieno(2,3-d)pyrimidine (321)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added piperidine (1.75g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from n-hexane yielded 321, 2.1g(70%), m.p. 123-126°C.

Analysis: C_{15}H_{19}N_{2}O_{2}S requires: C, 59.02; H, 6.27; N, 13.77%

Found: C, 59.12; H, 6.41; N, 13.92%

\( \lambda_{\text{max}} \text{ nm (log } \varepsilon) = 232 (4.35), 334(4.13) \)

\( \nu_{\text{max}} \text{ cm}^{-1} = 1710 (\text{COEt}) \)

6-Carbethoxy-5-methyl-4-(3-methyl piperidino)thieno(2,3-d)pyrimidine (322)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added 3-methylpiperidine (1.98g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from n-hexane yielded 322, 2.4g(75%), m.p. 93-95°C.

Analysis: C_{16}H_{21}N_{2}O_{2}S requires: C, 60.21; H, 6.58; N, 13.17%

Found: C, 60.43; H, 6.76; N, 13.38%

\( \lambda_{\text{max}} \text{ nm (log } \varepsilon) = 233(4.36), 255(5), 335(4.14) \)

\( \nu_{\text{max}} \text{ cm}^{-1} = 1720 (\text{COEt}) \)

6-Carbethoxy-5-methyl-4-(4-methyl piperidino)thieno(2,3-d)pyrimidine (323)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added 4-methylpiperidine (1.96g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from n-hexane yielded 323, 2.2g(70%), m.p. 86-88°C.
Analysis: $C_{16}H_{21}N_4O_2S$ requires: $C$, 60.19; $H$, 6.58; $N$, 13.16%

Found: $C$, 60.28; $H$, 6.73; $N$, 13.32%

6-Carbethoxy-5-methyl-4-piperazino)thieno(2,3-d)pyrimidine (324)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added piperazine (2.36g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from a mixture of benzene and n-hexane yielded 324, 2.1g (70%), m.p. 125-127°C.

Analysis: $C_{14}H_{18}N_4O_2S$ requires: $C$, 54.90; $H$, 5.88%

Found: $C$, 55.13; $H$, 6.15%

$\lambda_{\text{max}} \text{nm (log E)}$: 234(4.38), 325(4.12)

$\nu_{\text{max}} \text{cm}^{-1}$: 3320(-NH), 1695(-COEt)

6-Carbethoxy-5-methyl-4-(4-methyl piperazino)thieno(2,3-d)pyrimidine (325)

To a hot solution of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) in benzene (50 ml) was added 4-methyl piperazine (2.0g; 0.02 mole) dropwise and treated according to the procedure described for 319. Recrystallization from n-hexane yielded 324, 2.5g (78%), m.p. 99-102°C.

Analysis: $C_{15}H_{20}N_4O_2S$ requires: $C$, 56.25; $H$, 6.25; $N$, 17.50%

Found: $C$, 56.06; $H$, 6.42; $N$, 17.61%

5-Methyl-4-(2-phenylethylamino)-6-$\sqrt{N}$-(2-phenylethylamino)carboxamido, thieno(2,3-d)pyrimidine (326)

A mixture of 6-carbethoxy-4-chloro-5-methyl thieno(2,3-d)pyrimidine (318) (2.56g; 0.01 mole) and excess of β-phenylethylamine (4g) was heated in
an oil bath at 100°C under reflux for 12 hours. The reaction mixture was cooled and poured over crushed ice and triturated. The solid obtained was filtered and washed with water. Recrystallization from benzene yielded \(325\), 3.0g (88%), m.p. 174-176°C.

Analysis: \(\text{C}_{24}\text{H}_{24}\text{N}_{4}\text{O}_{5}\) requires: C, 69.24; H, 5.76; N, 13.46%

Found: C, 69.25; H, 6.02; N, 13.41%

\(\lambda_{\text{max}} \text{nm(} \log \varepsilon \text{)} = 226(4.65); 284(4.05), 314(4.12)\)

\(\nu_{\text{max}} \text{ cm}^{-1} = 3450 (-\text{NH}), 3330 (-\text{CNH}), 1635 (-\text{C=})\).

4-Hydrazino-5-methyl thieno(2,3-d)pyrimidine-6-hydrazide (327)

A mixture of 4-chloro-6-carbethoxy-5-methyl thieno(2,3-d)pyrimidine (2.5g; 0.01 mole) and excess of 80% hydrazine hydrate (6.0 ml) was treated according to the procedure described for 326. The solid product obtained was washed successively with DMF, chloroform and alcohol which yielded \(326\), 1.9g (80%), m.p. 246-248°C.

Analysis: \(\text{C}_{10}\text{H}_{10}\text{N}_{6}\text{O}_{5}\) requires: C, 40.33; H, 4.20; N, 35.29%

Found: C, 40.69; H, 4.27; N, 34.99%