PART 2
INTRODUCTION - PART - 2
Six-membered heterocyclic compounds containing one nitrogen and sulphur atom are known as thiazines. They are named 1:2, 1:3 or 1:4 thiazines depending upon the respective positions of nitrogen and sulphur atoms. For example:

1:2 thiazines  1:3 thiazines  1:4 thiazine

Nomenclature throughout the literature is varied. The system employed in "The Ring Index" is unambiguous, but because the majority of the known members of the thiazine group do not contain the unsaturation of the parent compounds, this usage frequently becomes awkward. The terms metathiazine and parathiazine, in place of 1:3 thiazine and 1:4 thiazine respectively, are frequently encountered.

Of the many thiazines and monobenzothiazines possible, only those derived from the parent structures
listed below have been reported.

1,3,2-thiazine  1,3,4-thiazine  1,3,6-thiazine

\[
\begin{align*}
\text{1,4-thiazine} & \\
\text{1,4,2-benzothiazine} & \\
\text{phenpenthiazole} & \\
\text{tautomeric with} & \\
\text{1,4,2-benzothiazine} & \\
\text{Benzoparathiazine} & \\
\text{Phenpazthine} & \\
\text{automeric with} & \\
\text{1,4,2-benzothiazine.} & 
\end{align*}
\]
The nomenclature, 5,6-dihydro-4-H-1,3-thiazine is given to the following structure
and its Revised Ring Index number is 224.

\[ \text{5, 6-Dihydro-4-H-1, 3-thiazine} \]

**Synthesis of 1,3 thiazines.**

Different substituted thiazines are prepared from proper reactants rather than by substitution reactions. They are generally prepared from thioamides, thioureas or mercaptans or by cyclization reactions. These are summarized in the Theoretical Part-2.

Recently Giordano have reported a new method of synthesis of 2-aryl-5,6-dihydro-4-H-1,3-thiazines from N-(hydroxymethyl)-thio-carboxamides and olefins. The reaction was described as analogue to that of N-(hydroxymethyl)-carboxamide with olefins. The reaction was regarded as a regio specific cis cycloaddition of the thioamidomethyl ion(\(a\)) to the olefin (2).
The evidence was given by the N.M.R. spectra of compounds.

More recently Giordano and Abis \textsuperscript{11} prepared some 5,6-dihydro-4-H-1,3-thiazines from thioamides, aldehydes and olefins.

The reaction is 1,4-cycloaddition reaction and two different structures are possible.
The authors reported that only one isomer (structure I and not II) was obtained when styrene was used as an olefin. For example, thiobenzamide, benzaldehyde, and styrene reacted to give 2,4,6-triphenyl-5,6-dihydro-4H-1,3-thiazine with structure (I).

\[
\text{Ph-C-NH}_2 + \text{Ph-CHO} + \text{PhCH}_2 = \text{CH}_2 \xrightarrow{(i) H^+} \xrightarrow{(ii) \text{BH}^-} \text{Ph-C-NH}_2 + \text{Ph-CHO} + \text{PhCH}_2 = \text{CH}_2
\]

The reaction was regarded as stereospecific and regiospecific.10

**Regiospecificity:**

Hassner10 proposed a new terminology, "Regiospecificity", in addition and elimination reactions.12 He proposed the prefix "Regio" to complement that of "stereo" to describe orientational or directional preference in reaction specificity and selectivity involving bond making or breaking. These terms are useful in describing stereochemical
preference in organic reactions, namely, the propensity to a certain relative spatial arrangement of reacting groups, e.g., cis or trans additions.

The addition of an unsymmetrical reagent $X-Y$ to an unsymmetrical olefin $RCH=CH_2$, often occurs in a highly specific manner, with one segment of the reagent (i.e., $X$) being directed to assume one of the two possible positions in the final product (e.g., 1 or 2)

\[ R-CH=CH_2 + X-Y \rightarrow R-CHCH_2 \]

\[ Y \quad X \]

or

\[ R-CHCH_2 \]

\[ X \quad Y \]

(1)

Here the problem is of describing the preferential making or breaking of bonds in one of two possible orientations.

The term "regiospecific"\(^\text{13}\), derived from the Latin word, "regio" denoting direction, was proposed for the course of such reactions. Regiospecificity then refers to the directional preference of bond formation. If a reaction proceeds without skeletal rearrangement to give exclusively one of two or more possible isomers, it is called "regiospecific." If there is a significant preponderance of one isomer formed, it is said to be "regioselective." A nearly equimolar isomer distribution is the result of a
"nonregiospecific" reaction.

These terms are useful not only in addition reactions but equally in a variety of chemical processes including eliminations, ring opening and cycloaddition reactions.

As modifying terms in regiospecific addition reactions the indication of two vicinal groups in the product (one derived from the reagent and one from the unsaturated substrate) is proposed. Thus eq. 3 (below) shows Br-phenyl regiospecificity and eq. 4 shows H-carbonyl regiospecificity. (Br-H regiospecificity is equally valid).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH} = \text{CH}_2 + \text{HBr} & \rightarrow \text{C}_6\text{H}_5\text{-CH-CH}_3 \\
\text{C}_2\text{H}_5\text{-C-CH} = \text{CH}_2 + \text{HBr} & \rightarrow \text{C}_2\text{H}_5\text{-C-CH}_2\text{-CH}_2\text{Br}
\end{align*}
\]

Other examples are (1) the S-H- regiospecific nucleophilic addition of thioalkoxide to acetylenes\(^{14}\) (eq. 5) (2) the Br-phenyl regiospecific free radical addition of bromine azide\(^{13}\) (eq. 6) and (3) the H-CH\(_3\) regiospecific hydroboration of methylcyclohexene.\(^{15}\) (eq. 7).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C} = \text{CH} + \text{CH}_3\text{SN} & \rightarrow \text{C}_6\text{H}_5\text{CH} = \text{CH}_2\text{CH}_3 \\
\text{C}_6\text{H}_5\text{CH} = \text{CH}_2 + \text{BrN}_3 & \rightarrow \text{C}_6\text{H}_5\text{-CH-CH}_2\text{-N}_3
\end{align*}
\]

\[
\text{CH}_3 + \text{B}_2\text{H}_6 \rightarrow \text{[Structure]} \rightarrow \text{[Structure]} \rightarrow \text{[Structure]} \rightarrow \text{[Structure]}
\]

\[
\text{H}_2\text{O}_2 \text{ OH}^{-} \rightarrow \text{[Structure]}
\]
Cycloadditions, dimerizations, 1,3-dipolar additions, and Diels-Alder reactions can be regiospecific or regioselective. Equation 8 is an example of a nonvicinally regiospecific dimerization.

\[
\text{EtO}_2\text{C-C=C=O} \rightarrow \text{EtO}_2\text{C-C-C=O}
\]  

Diels-Alder reactions usually are vicinally regioselective (eq. 9).

\[
\text{CH}_3 \quad + \quad \text{CO}_2\text{CH}_3 \quad \rightarrow \quad \text{CH}_3\text{CO}_2\text{CH}_3
\]

The term vicinal is employed when the two identical groups or the two largest groups originally on separate molecules are found in the closest of the two possible positions in the product. Additional classification may be required on occasion as for the phenyl phenyl nonvicinally regiospecific dipolar addition shown in equation - 10 below:

\[
\text{H}_7\text{C}_3\text{CH} = \text{N} + \text{C}_6\text{H}_5\text{CH}=\text{CH}_2 \rightarrow \text{H}_7\text{C}_3\text{N} = \text{O} \quad \text{C}_6\text{H}_5
\]
Properties of 1,3 thiazines:

The simple and monobenzometathiazines and their 2-alkyl derivatives are strong bases, generally insoluble in water but soluble in aqueous acids. They readily form methiodides.  

A methyl group in 2-position is active and condenses with benzaldehyde and with suitable second components to give cyanine dyes.

The ring system is quite stable. However, when 2-phenyl-5,6-dihyrdro-1,3-thiazine is heated with concentrated hydrochloric acid at 210°C., it is slowly cleaved to benzoic acid and γ-aminopropyl mercaptan.

\[
\text{HCl} 
\xrightarrow{210^\circ C.} 
\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{SH} + \text{C}_6\text{H}_5\text{COOH}
\]

In contrast, 2-methyl-3,1 benzothiazine is cleaved in 2 hours to 2,2′-diamino-dibenzyl sulphide and acetic-acid.
SPECTRAL STUDIES:

Infrared absorption, nuclear magnetic resonance and mass spectra of the following three compounds are studied.

(A) Infrared Absorption spectra of Dihydro-1,3-thiazines.

Meyers studied Infrared absorption of the C=N link in different substituted dihydro-1,3-oxazines and thiazines. The stretching frequency of C=N link varied from 6.11 to 6.32 μ in various 2-substituted dihydro-1,3-thiazines.

He obtained the absorption band at 6.22 μ for the following compound.
For all the three compounds, we studied a strong absorption band at 1600 cm\(^{-1}\) (\(\sim 6.3\mu\)) was obtained which is in the range of results obtained by Meyers.\(^{19}\)

Different absorption bands obtained are summarized in the following table.
(B) **Nuclear Magnetic Resonance Spectra:**

The Spectra for all the three compounds have been measured for solutions in CDCl\textsubscript{3}. Three signals are obtained. The values obtained are summarized in the following table:

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \delta ) (CDCl\textsubscript{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.00; 4.2; 7.3 &amp; 7.8</td>
</tr>
<tr>
<td>2</td>
<td>2.00; 4.15; 7.3 &amp; 7.8</td>
</tr>
<tr>
<td>3</td>
<td>2.05; 4.10; 6.8; 7.3 &amp; 7.8</td>
</tr>
</tbody>
</table>

**Proton Counting.**

**Compound - 1.**

The signals at 7.3 and 7.8\( \delta \) correspond to total 10 aromatic protons.

The signal at 4.2 \( \delta \) value corresponds to 3 protons, these may be axial or equitorial.

The signal at 2.0\( \delta \) value corresponds to 2 protons making total of 15 protons which is exactly the same number present in the compound.

**Compound - 2.**

The signals at 7.3 \( \delta \) and 7.8 \( \delta \) correspond to total 9 aromatic protons.

The signal at 4.15 \( \delta \) value corresponds to 3 protons, which may be axial or equitorial.

The signal at 2.0 \( \delta \) value corresponds to 5 protons in which 2 alicyclic protons must have been overlaped.
**Compound - 3.**

The signal at 6.8, 7.3 and 7.8 δ corresponds to total 9 aromatic protons.

The signal at 4.10 δ corresponds to 6 protons out of which, 3 protons must be of -OCH3 group and the remaining may be axial or equitorial.

The signal at 2.05 δ corresponds to 2 protons which may be axial or equitorial.

The position of phenyl ring at C-6 will depend upon alicyclic protons.

Giordano and Abis11 found that only one isomer (I) was isolated in case of the following compound, and the isomer (II) was not isolated. The evidence was given from the N.M.R. Spectral Study.

![Diagram of compounds I and II](image)

( I ) ( II )

In our case also only one isomer is possible and we presume that the structure of the compounds may be similar to the above structure (I). Thus the general structure
Klayman and Milne\textsuperscript{20} studied the mass spectra of 2-amino-$\Delta^2$-thiazolines and 2-amino-5,6-dihydro-4$H$-1,3-thiazine: (I).

They pointed out that the most important primary process in the fragmentation of this compound is, probably, the collapse of the ring in the reverse Diels-Alder Sense.\textsuperscript{21}
Molecular weight of the compounds studied are 253, 267, and 283 for compound numbered 1, 2 and 3 respectively. The base peaks are obtained exactly at 253, 267 and 283 for compound no. 1, 2 and 3 respectively.

Compound no.1 may have been split into the following fragments.

\[ \text{Ph} \quad \text{S} \quad \text{Ph} \rightarrow \text{C}_6\text{H}_5\text{NCS} + \text{C}_6\text{H}_5\text{CH} = \text{CH} - \text{CH} \]

M.W. 253 M.W. 135 116-118

The peaks at 117 & 115 show \( \text{C}_6\text{H}_5\text{CH} = \text{CH} - \text{CH} \) fragment with isotopes. This fragment may have been split into another two fragments giving the peaks at 91 for benzylic group and at 28 for \( \text{CH}_2 = \text{CH}_2 \).

Similarly the peaks at 28 for \( \text{CH}_2 = \text{CH}_2 \) fragment at 91 for benzylic group, 117 and 115 for \( \text{C}_6\text{H}_5\text{CH} = \text{CH} - \text{CH} \) fragment are obtained for compounds numbered 2 and 3.
N. M. R. Spectra of compounds No. 1
Mass Spectra of compound No. 1
Mass Spectra of compound No. 1
THEORETICAL - PART - 2
Preparation of substituted cinnamic acids.

Substituted cinnamic acids can be prepared from the substituted benzaldehyde by the condensation reaction i.e. by Parkin reaction, Knoevenagel modification, Doebner modification or Claisen condensation reaction.

The Perkin reaction is the base-catalyzed reaction of an active methylene group. Basic catalysts such as the sodium salt of the acid corresponding to the anhydride, $\text{K}_2\text{CO}_3$, or tertiary amines may be used satisfactorily.\(^{22}\)

Knoevenagel modification is the condensation of aldehydes with the active methylene group of malonic acid to give α,β-unsaturated acids. The carboxylation occurs at room temperature or heating to 100°C. to give the unsaturated acids.\(^{23,24}\) Pyridine, ammonia, diethylamine are used as catalysts.\(^{25}\)

In Doebner modification, malonic acid and pyridine with traces of piperidine are used as condensing agents.\(^{22}\)

Claisen condensation is the condensation of an ester and aromatic aldehyde catalyzed by sodium sand. The product is an ester,\(^{26}\) which can be saponified readily to obtain the acid.

During present work, p-methoxy, p-methyl and p-chloro cinnamic acids are prepared from the corresponding benzaldehydes; adopting any one suitable method from the
above discussed methods.

The detailed procedures of their preparation are described in the experimental part-2, pages 163-164.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Methoxy Cinnamic acid</td>
<td>Johnson, J. R.</td>
</tr>
<tr>
<td>p-Methyl Cinnamic acid</td>
<td>do</td>
</tr>
<tr>
<td>p-Chloro Cinnamic acid</td>
<td>Pandya, K. C. &amp; Pandya, R.</td>
</tr>
</tbody>
</table>

Section - II

Preparation of Substituted Styrenes.

Olefins are commonly prepared by elimination reactions and condensation reactions.

The elimination reactions are summarized by the following equation:

\[
\text{Acids, Bases} \\
\text{R-CH=CH}_3 \xrightarrow{\text{or heat}} \text{R-CH=CH}_2 + ZH
\]

where Z may be a hydroxyl, halogen ester, ether, methylxanthate, carbamate, carbonate, sulphite, amine, quaternary ammonium hydroxide (Hofmann degradation), amine oxide or one of many other labile groups.
Another elimination reaction involves disubstituted derivatives as in the following equation:

\[ R-CH \quad CH_2 \quad \rightarrow \quad R-CH = CH_2 \]

where Z may be hydroxyl or halogen.

Condensation reactions, such as the Boord synthesis, are good methods for converting aliphatic aldehydes to substituted olefins via the preparation of bromoethyl ethers, Grignard coupling and elimination of bromo ethoxy zinc.

\[ R-CH_2 - CH = O \quad \rightarrow \quad R-CH = CR'R'' \]

Elimination Reactions.

(A) Dehydration of alcohols:

Tertiary arylcarbinols have been reported to be converted within 30 seconds to the corresponding alkenes (70 % yield) with warm 20 % sulphuric-acetic acid (by volume). The yields are much lower with aliphatic tertiary or secondary arylcarbinols. Some tertiary alcohols such as those obtained from tetralone and the Grignard reagent dehydrate on simple distillation and in the presence of anhydrous cupric sulphate as a catalyst.
Aluminium oxide induced vapour phase dehydrations at 300-400°C. have the advantage that isomerization is reduced as a result of the short contact time of the alcohol and olefins with the catalyst. The main by-products are ethers.\textsuperscript{29,30} The dehydration of alcohol on an alumina catalyst may involve the preliminary formation of a surface alkoxide which then thermally decomposes to an olefin.\textsuperscript{31} Styrenes are obtained from arylcarbinols by this procedure\textsuperscript{32} and by dehydration using not over 1% of fused potassium disulphate in conjunction with suitable pressures.\textsuperscript{33} The carbinols were prepared by reduction of the corresponding ketone or by addition of a Grignard reagent to an aldehyde.

Dehydration of alcohols can also occur under basic conditions as in the case of /3-Phenylethyl-alcohols. Molten sodium or potassium hydroxide and the alcohols are heated to give the styrenes in good yields.\textsuperscript{34} However, the phenylmethylcarbinols require acidic catalysts for successful dehydration to the styrene.

(B) \textit{Pyrolysis Reactions}.

(i) The pyrolysis of acetate esters\textsuperscript{35-37} is usually carried out at 300-600°C. but that of the xanthates employed in the Chugaev\textsuperscript{38} method requires only 100-250°C. Esters of boric acid appear to be hydrolyzed easily at 260-270°C.\textsuperscript{39,40}
The pyrolysis of quaternary ammonium salts (Hofmann exhaustive methylation) is an useful method mainly for proof of structure since carbon skelton rearrangement does not occur.

(ii) Decarbonylation of Olefinic acids:

Thermal decomposition of cinnamic acids (without catalysts) gives styrenes in 41 % yield. Galimberti has reported that almost quantitative yields are obtained by slow distillation of the acid with quinoline in the presence of anhydrous copper sulphate.
The decarboxylation of olefinic acids at 220°C. in the presence of quinoline and copper powder gives olefins in yields up to 86%.\textsuperscript{44}

\[
\text{Quinoline} \quad \text{Ar-CH = CH-COOH} \xrightarrow{\text{Cu powder}} \text{Ar-CH = CH}_2 \\
220^\circ\text{C.}
\]

Nuclear substituents affect the ease of decarboxylation but halo, methoxy, cyano and nitro styrenes have been prepared in yields ranging from 30% to 76%.\textsuperscript{44,45,46} Unsaturated aliphatic acids also decarboxylate thermally.\textsuperscript{47}

(C) Dehydrohalogenation Reactions.

The elimination of hydrogen halide is a very general method for the formation of 1-olefins. Basic reagents such as alkali hydroxides, alkoxides, and amines are usually employed. Primary halides react less readily than secondary halides and tertiary halides are the most reactive.\textsuperscript{48} The dehydrochlorination of \(\beta\)-chloroalkyl-benzene by methanolic potassium hydroxide yield substituted \(\alpha\)-methyl styrenes.

\[
\text{KOH} \quad \text{Ar-CH-CH}_2\text{-Cl} \xrightarrow{\text{CH}_3\text{OH}} \text{Ar=C=CH}_2 \\
R \quad \text{R}
\]
Dehydrohalogenation can also occur during decarboxylation reactions to give olefins.\(^\text{49}\)

\[
\begin{align*}
R-\text{CH}=\text{C}-\text{COOH} + \text{HX} & \rightarrow R-\text{CH}-\text{CH}-\text{COOH} \\
& \downarrow \quad \downarrow \\
& R' \quad X \\
& \quad \downarrow \\
& \quad \text{Na}_2\text{CO}_3 \\
& \quad \downarrow \\
& R-\text{CH}=\text{CHR}'
\end{align*}
\]

(D) **Dehalogenation of Dihalides.**

\[
\begin{align*}
R-\text{CH}-\text{CH}_2 + \text{Zn dust} & \rightarrow R-\text{CH} = \text{CH}_2 \\
& \downarrow \quad \downarrow \\
& \quad \text{Br} \quad \text{Br} \\
& \quad \downarrow \\
& \quad \text{Ethanol}
\end{align*}
\]

This reaction has very little preparative value since one usually prepares the dibromide from the olefins by the addition of bromine. Usually no isomerization of the carbon-chain takes place in the regeneration of the olefin. Zinc dust and 95% ethanol are the most common dehalogenation reagents.\(^\text{50}\)

The following styrenes have been prepared from corresponding cinnamic acids using decarboxylation described by Walling.\(^\text{44}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference</th>
</tr>
</thead>
</table>
Section - III

Preparation of 2,6-diaryl-4-H-5,6-dihydro-1,3 thiazines.

A large number of 1,3-thiazines and their derivatives are found in the literature. However, the methods employed for their preparations are very versatile. In fact, they are prepared by the proper choice of reactants rather than by the general reactions:

(A) Jansen et al\textsuperscript{51} reported that the condensation of diacetoneamind with carbon disulphide gave the product which on treatment with a dehydrating agent formed 2-mercapto- 4,6-trimethyl-1,3,4-thiazine. The same product was obtained by the reaction of 2-methyl-2-isothiocyanato pentanone-4 with dithiocarbamic acid.
(B) Substituted 5,6-dihydro-1,3,4-thiazines are prepared from substituted thioamides.

(i) Condensation of trimethylene chlorobromide with a thioamide yields 2-substituted-5,6-dihydro-1,3,4-thiazines. 2, 52, 53

\[ \text{CH}_2\text{Br} + \text{HSC}-\text{R} \xrightarrow{\text{Reflux}} \text{S} + \text{HBr} + \text{HCl} \]

Benzometathiazines cannot be prepared by this method.

(ii) When a γ-haloamine is condensed with a thioamide a 5,6-dihydro-1,3,4-thiazine is formed. This method is very satisfactory for the synthesis of metathiazines and monobenzometathiazines carrying an aryl substitution in the 2-position. 4, 54-58
(iii) Giordano prepared 5,6-dihydro-4H-1,3-thiazines from N-hydroxy methyl thiobenzamides and olefins.

(iv) Recently Giordano et al synthesized some 5,6-dihydro-4H-1,3-thiazines from thioamides, aldehydes and olefins.

(C) 1,3-Thiazines may be prepared by cyclization reactions:

(i) 2-Substituted-5,6-dihydro-1,3,4-thiazines are prepared by ring closure of N-acyl derivatives of \( \gamma \)-amino mercaptans.\(^3,54,58\)
(ii) 2-Mercapto-4-keto-4,5-dihydro-1,3-thiazine is prepared by cyclization of \( \beta \)-dithiocarbamylpropionate which in turn is prepared from methyl acrylate and dithiocarbamic acid.\(^{59}\)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S} & \quad \text{C} & \quad \text{S} \\
\text{CH}_2 & \quad \text{NH} & \quad \text{COCCH}_3
\end{align*}
\]

\[
\begin{array}{c}
\xrightarrow{+} \\
\xrightarrow{H}
\end{array}
\]

\[
\begin{align*}
\text{S} & \quad \text{SH} \\
\text{O}
\end{align*}
\]

(iii) Smith and Sullivan\(^{60}\) prepared some thiazolines and dihydrothiazines by the cyclization of N-alkylthmonamides.

\[
\begin{align*}
\text{H}_3\text{CCH} & \quad \text{CH} & \quad \text{CH}_2 \\
\text{S} & \quad \text{C} & \quad \text{S} \\
\text{C}_6\text{H}_5 & \quad \text{NH} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

\[
\begin{array}{c}
\xrightarrow{\text{AlCl}_3}
\end{array}
\]

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

The structure of the thiazines obtained was identified by its synthesis from N-(3-hydroxy-butyl) benzamide and phosphorous pentasulphide.

\[
\begin{align*}
\text{CH}_3\text{-CHOH-CH}_2\text{-CH}_2\text{-NH-} & \quad \text{CO-C}_6\text{H}_5 \\
& \quad \text{P}_2\text{S}_5
\end{align*}
\]
(D) Bayer\textsuperscript{61-65} reported some 2-amino derivatives from mustard oils.

(i) Amino alcohol is treated with substituted phenylmustard oil and the resultant thiourea is cyclized to give 2-phenylamino-4-H,5,6-dihydro-1,3-thiazine.\textsuperscript{61}

\[
\text{Ph-CH(OH)-CH}_2\text{-CH}_2\text{-NH}_2 + 2,6\text{ Me}_2\text{C}_6\text{H}_3\text{NCS}
\]

(ii) Phenylamino substituted 6-methyl-4-H,5,6-dihydro-1,3-thiazines (I) may be prepared by (a) reaction of PhNCS or a nuclear substituted analog with Me-CH(OH)-CH\(_2\)-CH\(_2\)-NH\(_2\) (II) and the treatment of the resultant thiourea with acid; (b) reaction of PhNCS with Me-CH\(_X\)-CH\(_2\)-CH\(_2\)-NH\(_2\) (III) (X=halo); (c) reaction of nuclear substituted N-phenylthioureas with 1:3 dihalobutenes or salts of III; (d) reaction of nuclear substituted aromatic amines with MeCHXCH\(_2\)-CH\(_2\)-NCS.\textsuperscript{62}
Substituted 2-amino-4H-5,6-dihydro-1,3-thiazines are prepared from NCS-CH-Ph-CH$_2$-CH$_2$-NH$_2$.HBr and KCN.\(^63\)

\[
\text{NCS-CHPh-CH$_2$-CH$_2$NH$_2$.HBr + KCN} \quad \xrightarrow{\text{acidified}} \quad \text{PhS}\quad \text{NH}_2
\]
(iv) Substituted \(\gamma\)-halopropyl mustard oils are treated with tert. butylamine, followed by acid to give compounds (I).\(^6\)

![Chemical Structure](image)

(V) Similar compounds are prepared by reaction of \(\gamma\)-halopropylamines with acylated mustard oils followed by acid hydrolysis of the resulting product.\(^6\)

(E) Some 2-substituted-1,3-thiazines are prepared from mercaptans.

(i) Meyers\(^6\) reported the formation of dihydro-1,3-thiazines and 2-thiazolines from mercaptoalcohols and nitriles in cold cond. \(\text{H}_2\text{SO}_4\). Thus 2-substituted-4-4-dimethyl-5,6-dihydro-1,3-thiazines were prepared when 3-methyl-3-hydroxy-n-butane thiol was added to a previously cooled solution of a nitrile in con. \(\text{H}_2\text{SO}_4\).
(ii) Koch prepared substituted thiazines and thiazolines from mercaptans. In an example, \( \beta \)-oxo-\( \gamma \)-thiophenepropionitrile, 3-mercaptopropylamine, triethylamine, and ethanol were refluxed to give 5,6-dihydro-2\(^{-}\)-2-hydroxy-2-(2-thienyl) vinyl-4H-1,3-thiazine.

(iii) Meyers & Greene prepared some 2-carboxyalkyl-4,4-dimethyl-5,6-dihydro-4H-1,3-thiazines by the reaction of 3-hydroxy-3-methyl butanethiol with \( \beta \)-cyanoacetic & cyanoacrylic ester in \( BF_3 \cdot Et_2 O \).
All the thiazines reported in this thesis (page-168) are prepared by the method of Giordano. Substituted N-hydroxymethylthiobenzamide and substituted styrene are dissolved in acetic acid in equimolar amounts. The mixture was cooled and conc. H$_2$SO$_4$ was added as a dehydrating agent. The compound is obtained by neutralizing with 40% NaOH solution. The crude base obtained, is purified by dissolving it in dilute hydrochloric acid and reprecipitating the base with NaOH solution.

In case of liquid thiazines, the hydrochloride salt is prepared by passing dry HCl gas into the solution of thiazine in ether.
Materials:

p-Tolualdehyde was prepared by the Sommelet reaction described in Organic Reactions Vol. 8, page 197 (1954).

Cu-powder was prepared according to the method described in Practical Organic Chemistry by A. I. Vogel (1966), page 192.

The substituted N-hydroxymethylthiobenzamides were prepared according to the method described in Experimental Part-1, page 89.

The following starting materials were purchased from:

(1) E. Merk, 61, Darmstadt, Germany.
Anisaldehyde (purified by distillation; b.p. 246-4°C.).
Styrene (stabilized with 20 ppm. p-tert-butyl-pyrocatechol and distilled, just before use; b.p. 146°C.).

(2) Riedel, Dehaenag, Seelze-Hannover; Germany.
Melic acid (M.P. 132-4°C.); Quinoline (dried over caustic and distilled under reduced pressure; B.P. 238°C.).

(3) Eastman Kodak Co., New York, U. S. A.
p-Chlorobenzaldehyde (M.P. 46-49°C.).

Analysis and Instrumentation:

The melting points and boiling points recorded are uncorrected. Melting points were determined on a Gallenkamp melting-point apparatus. Routine nitrogen analyses were
carried-out by Dumas's method. Sulphur analyses were carried-out by Carus's method using Gallenkamp-Carius bomb. I. R., N. M. R. and Mass spectea were obtained from Ciba-Giegy Research Centre, Bombay.

Section - I

Preparation of Cinnamic acids from substituted benzaldehydes

Method - A.

Preparation of p-Methoxy-cinnamic acid.

In a round-bottom flask, fitted with a reflux condenser, solution of 14.6 g. (0.1 mole) of anisaldehyde and 12.6 g. (0.16 mole) of malonic acid in a small quantity of 95% ethyl alcohol, was treated with 21 g. of an 8% solution of ammonia (0.1 mole) in 95% ethyl alcohol, and the mixture was heated on a steam-bath. Then, the alcohol was distilled off and the oily residue was heated on a vigorously boiling water-bath until evolution of carbon dioxide and ceased had the mixture became solid (about two hours).

The product was treated with warm water and dissolved by the addition of a minimum amount of sodium carbonate. The solution was boiled for a few minutes with 1-2 g. of decolourizing charcoal and filtered through a fluted paper. The warm filtrate was poured with stirring
into an excess of cold 20 % sulphuric acid containing some chopped ice. The acid precipitated was collected with suction, washed with several small portions of cold water, and dried. The yield was 14-15 g. (80-90 % of the theoretical).


Method - B.

Preparation of p-Chloro-and p-Methyl Cinnamic acids.

In a round-bottomed flask, 0.01 mole substituted benzaldehyde, 1.04 g. malonic acid and 0.14 ml. of pyridine were mixed and heated on water-bath, without condenser for about four hours. Then the reaction mixture was allowed to cool and treated with 10 % sodium carbonate solution and the small amount of residue was removed by filtration. The filtrate was poured with stirring into cold 20 % sulphuric acid containing some chopped ice. The acid precipitated, was filtered on a Buchner funnel, washed with several small portions of cold water and dried.

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Method</th>
<th>M.P.</th>
<th>Reference</th>
</tr>
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<tr>
<td>1.</td>
<td>p-Methoxy Cinnamic acid</td>
<td>A</td>
<td>168°C</td>
<td>Johnson, J. R.</td>
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<td>2.</td>
<td>p-Methyl Cinnamic Acid</td>
<td>B</td>
<td>198-99°C</td>
<td>- do -</td>
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<tr>
<td>3.</td>
<td>p-Chloro Cinnamic acid</td>
<td>B</td>
<td>240-42°C</td>
<td>Pandya, K. C. &amp; Pandya, R.</td>
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<td>14A, 112(1941).</td>
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</table>
Section - II

Preparation of substituted styrenes from Cinnamic acids.

In a Claissen flask, 1 part of the substituted cinnamic acid, 2 parts of quinoline and one-tenth part of freshly prepared Cu-powder were mixed. The flask was heated so that the vapours remain below 220°C. One-third to two-thirds of the reaction mixture was distilled. The end of the reaction was evidenced in the rise of temperature of the vapours to the boiling point of quinoline. The styrenes thus obtained were redistilled under reduced pressure.


Table - II

<table>
<thead>
<tr>
<th>No.</th>
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<td>1.</td>
<td>p-Methyl styrene</td>
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<td>Titley, A. F.</td>
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<td></td>
<td></td>
<td>170-175°C</td>
<td>J. Chem. Soc. 519(1926).</td>
</tr>
<tr>
<td>2.</td>
<td>p-Methoxy styrene</td>
<td>95-96°C/16 mm</td>
<td>Quelet, R.</td>
</tr>
<tr>
<td>3.</td>
<td>p-Chloro styrene</td>
<td>53-4°C/3 mm</td>
<td>Brooks, L. A.</td>
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</tbody>
</table>
Section - III

Preparation of 2,6-diaryl-5,6-dihydro-4H-1,3-thiazines.

100 % sulphuric acid (4.4 g., 0.045 mole) was added dropwise to a solution of substituted-N-\((\text{hydroxymethyl})\)-thiobenzamide (0.045 mole) and substituted styrene (0.045 mole) in glacial acetic acid (70 g.) at \(\sim 15^\circ\text{C.}\). After the addition was complete, the solution was kept at this temperature for 6 hours and was allowed to stand at room temperature overnight. The reaction mixture was then poured onto ice, made alkaline with 40 % aqueous sodium hydroxide (keeping the temperature at \(\sim 10^\circ\text{C.}\)), and extracted with ether. The ether extract was washed with 2N hydrochloric acid (2 x 50 ml.) at \(\sim 10^\circ\text{C.}\). The acid aqueous extracts were made alkaline by the addition of 40 % aqueous sodium hydroxide at 10\(^{\circ}\text{C.}\) and extracted with ether. The ether extracts were evaporated and the residue, if solid, was recrystallized from dry ether. If liquid, was dissolved in dry ether and dry hydrochloric gas was passed into the solution. The hydrochloride salts of the thiazines were obtained.
Table - III

2,6-Diaryl-5,6-dihydro-4H-1,3-thiazines

<table>
<thead>
<tr>
<th>R</th>
<th>R₁</th>
<th>Mol. formula</th>
<th>B.P./M.P.</th>
<th>HCl M.P.</th>
<th>% N Found</th>
<th>% N Calcd</th>
<th>% S Found</th>
<th>% S Calcd</th>
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<td>-H</td>
<td>-H</td>
<td>C₁₆H₁₅NS</td>
<td>86-87°C.</td>
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<td>C₁₇H₁₇NS</td>
<td>65°C.</td>
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<td>p-Cl</td>
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<tr>
<td>p-Br</td>
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<td>3,4-methylene dioxy</td>
<td>-CH₃</td>
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<td>103-105°C</td>
<td>-</td>
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<td>4.62</td>
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<td>-CH₃</td>
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<td>70°C</td>
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<td>C₁₈H₁₉NO₂S.HCl</td>
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<td>p-Cl</td>
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<td></td>
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<td>760 mm.</td>
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<td>p-OCH₃</td>
<td>-Cl</td>
<td>C₁₇H₁₆ClNS.HCl</td>
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<td>80-81°C</td>
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