Chemistry of
Thiazoles, Imidazothiazoles
and Oxadiazolothiazines
CHEMISTRY OF THIAZOLES

An enormous amount of research in the field of pharmacologically active thiazoles has been reported and among the many products which have emerged, are antibiotics such as sulfathiazole and a host of related compounds. Here a brief and comprehensive theoretical background of thiazole ring system is presented.

(A) Structure and reactivity of thiazole:

Although the history of thiazole dates from 1879 with the work of Hoffman\textsuperscript{1} on benzothiazoles, the systematic study of parent heterocycle and its derivatives was reported\textsuperscript{2} from Hantzsch laboratory in 1887. Since then a vast amount of work in the field of thiazole chemistry has been reported in the literature covering different aspects such as methods of synthesis, physical properties, structure and reactivity, reaction mechanism, industrial and biological applications. Excellent books\textsuperscript{3-5} on thiazole containing up to date information on the subject have appeared. It is felt necessary to give here a gist of modern concepts of structure and reactivity of thiazoles as a background.

It is well known that the thiazole molecule exhibits marked aromatic character\textsuperscript{6,7} and resembles pyridine in most of its physical and chemical properties\textsuperscript{6}. Its aromatic character was explained as early as 1920 by the classical structure (I) with fixed double bonds at 2,3- and 4,5- positions.

\[
\begin{array}{c}
\text{I} \\
\begin{array}{c}
1 \\
S \\
2 \\
N^3 \\
3 \\
4 \\
5
\end{array}
\end{array}
\]
However, the validity of thiazole structure (I) was questioned since it could not account for the mobility of the double bonds in the alternative positions as required for an aromatic system. Erlenmeyer and co-workers\textsuperscript{8,12} attempted to explain the aromatic behavior of thiazole on the basis of concept of isosterism, i.e. bicovalent sulfur atom with lone pair of electrons being equivalent to the vinylene part of pyridine structure. If so, then such structure should call for the symmetric nature of reactivity of groups at 2- and 4- position similar to the 2- and 6- position of pyridine nucleus.

Actually 2- and 4- positions of thiazole ring are not similar in chemical reactivity for example; 2-methylthiazole undergoes aldol type reactions with benzaldehyde in acid medium while 4-methylthiazole\textsuperscript{13,14} is inactive. Quaternisation of ring nitrogen to a thiazolium salt enhances the reactivity of 2-methyl group but fails to activate the 4-methyl group in 4-methylthiazolium salt\textsuperscript{15}. Thiazole- 2-carboxylic acid is readily decarboxylated on heating while thiazole- 4-carboxylic acid is stable\textsuperscript{16}. Amination of 4-methylthiazole using sodamide leads to the formation of 2-amino-4-methylthiazole\textsuperscript{17}, whereas 2-methyl thiazole remains unaffected. Thus the inadequacy of explanation for thiazole behavior by isosterism led to the application of resonance concept to thiazole structure\textsuperscript{8,18} as shown below:

\[ \text{I} \quad \leftrightarrow \quad \text{II} \]
Erlenmeyer tried to explain the validity and contribution of the resonance structure (II) by means of deuterium exchange experiments in 2-methyl and 4-methylthiazoles. But the structure could not explain the observed chemical reactivity satisfactorily. Also this structure (II) containing sulfur atom in its expanded valence state called for its typical reactions which were not noticed in many cases, so it was concluded that the structure (II) contributed very little to the thiazole structure.

Roberts in 1947 suggested the behavior of thiazole and its derivatives towards the electrophilic and nucleophilic reagents, which may be adequately explained by considering the following resonance structures (II) and (III) of the conventional structure (I) without recourse to the resonance involving the sulfur atom.

All electrophilic and nucleophilic reactions of thiazole and its derivatives can be explained on the basis of these resonance structures.

**Nucleophilic reactions:**

Conventional structure (I) having a lone pair of electrons on nitrogen explains the electrophilic attack of proton acids and alkyl halides to form thiazolium salts.
Canonical form (I) accounts for the reactivity of a proton or an appropriate group towards nucleophilic attack at position 2, ex. Amination of 4-methylthiazole to 2-amino-4-methylthiazole\textsuperscript{17}, nucleophilic displacement\textsuperscript{22-24} of chlorine in 2-chlorothiazoles, low basicity of the amino group in 2-aminothiazoles\textsuperscript{25} and the reactivity of the methyl group in 2-methyl thiazole\textsuperscript{7} and 2,4-dimethylthiazole towards aldehydes. Particularly, the reactivity of 2-halogenothiazoles by nucleophilic reagents according to $S_{N}Ar$ mechanism is noteworthy.

\[
\begin{array}{c}
\text{S} \quad \text{N} \\
\text{X} \\
+ \text{Nu}^- \rightarrow \text{S} \quad \text{N} \\
\text{X} \\
\text{Nu}^- \rightarrow \text{S} \quad \text{N} \\
\text{X} \\
+ \text{Nu}^-
\end{array}
\]

A more unusual fact observed in thiazole chemistry is the response of halogen at position-4 and -5 towards the nucleophilic substitution reactions. For example, reactivity of methoxide ion with chlorothiazole is in the order 5-chloro > 2-chloro > 4-chloro. However, the reaction with phenoxide ion is reported in the order 2-chloro > 4-chloro > 5-chloro.

In nucleophilic displacement reactions, it is preferred to take a 2-substituted- 5-bromothiazole derivative as synthon instead of 5-chloro derivatives. It is interesting to note from the reports in the literature\textsuperscript{26,27} that the bromine of 2-amino- 5-bromothiazole undergoes much faster nucleophilic displacement than 2-bromo thiazole. This means that the presence of 2-amino group or its N-substituted derivative activates bromine at the 5-position. In fact, bromine in 2-amino-4-methyl-5-bromothiazole\textsuperscript{26} and 2-acetamido-5-bromothiazole\textsuperscript{28,29} is replaced by a thiophenoxide anion very easily.
Where \( R = H, Me; R_1 = H, COCH_3 \)

**Electrophilic substitution:**

Canonical structure (III) of 2-substituted thiazole through the transient form (II) is facilitated when delocalisation of \( \pi \)-electrons of (I) from electron donating group at 2-position to 5-position via ring nitrogen takes place according to the principle of vinylogy. The presence of a strong electron donating group like \( \text{NH}_2, \text{OH}, \text{SH} \) or their alkyl or acyl derivative promotes delocalisation to a great extent as illustrated by the following structures.

Accordingly, electrophilic substitution reactions of 2-substituted thiazoles at 5-position can be explained. For example 2-aminothiazole\(^{25,30}\), 2-hydroxythiazole\(^2\) and their alkyl derivatives\(^{31}\) readily undergo halogenation, nitration and sulphonation to form the corresponding 5-substituted thiazole derivatives. Chloromercuration and thiocyanation\(^{32}\) of 2-aminothiazole derivatives takes place at 5-position. However, if the 2-position of the thiazole is unsubstituted or has an electron accepting group like \( \text{NO}_2, \text{SO}_3H, \text{C}=\text{N}, \text{C}=\text{O} \) etc the delocalisation of
π-electrons is difficult. Ring nitrogen of these compounds behaves as an electron sink and does not promote delocalisation of π-electrons to 5-position. In other words, such compounds resist electrophilic attack at 5-position, e.g. simple thiazole can be brominated to 5-bromothiazole\textsuperscript{33} with great difficulty in vapour phase, while 2-nitrothiazole\textsuperscript{34} cannot be brominated at all.

The double bond between 4- and 5- positions:

The double bond doesn't behave as an aliphatic double bond because halogen does not add to it. Amino group of 5-aminothiazole exhibits aromatic character and undergoes diazotisation\textsuperscript{35}. A halogen atom in 2-unsubstituted 5-halothiazoles is inert. Hence, the 4,5 double bond is aromatic and undergoes electrophilic substitution at 4- or 5- position depending on the activation mechanism governed by a substituent occupied by the 2-position. Of the two heteroatoms, the nitrogen behaves as an electron sink or electron source depending on the nature of the substituent at the 2-position. The sulfur atom always behaves as an electron donor in a limited capacity to its adjacent carbons in the thiazole molecule. These aspects must be taken into consideration during the electrophilic and nucleophilic substitution reactions.

The electrophilic attack should take place at the 5-position first and then at 4-position of the unsubstituted thiazole if the reverse polarization of the π-electrons of the sulfur atom takes place via 4,5-double bond as shown below.
On the other hand, if the 2-position has an electron accepting group like NO₂, the reverse delocalisation may extend up to the 2-position making an electrophilic substitution very difficult. 2-Nitrothiazole does not undergo electrophilic substitution, which is indicated by the following structure.

![Structure of 2-Nitrothiazole](image)

**Nitration and Sulphonation:**

Protonation of thiazole molecule with nitric acid and sulphuric acid results in the formation of stable thiazolium ion. The positive charge on the protonated nitrogen of the thiazolium ion deactivates the ring considerably towards electrophilic attack. It is the thiazolium ion that undergoes substitution and the strength of the positive charge should govern the case of electrophilic substitution. Ganapathi and Kulkarni suggested that the farthest position from the positive pole is the first choice for the electrophilic attack so 5-position is first attacked and then 4-position. For example, bromination of 2-aminothiazole gives 2-amino-5-bromothiazole under the acidic condition.

Modern investigations by M.O. Calculations and spectral studies of a number of thiazole derivatives have been reported in the literature. UV and IR spectroscopic study of several thiazoles contributed to the knowledge of their bond strength, bond distances and bond orders. Also investigations have been made to shed more light on the structure by means of \(^1\)H, \(^{13}\)C and \(^{14}\)N nuclear magnetic resonance spectrometry, M.O. calculations on thiazoles and its
derivatives by HMO, iterative and ab initio methods contributed to the understanding of the correct electronic structure. These calculations have clearly shown the predominance of dienic nature of the thiazole molecule. The molecular geometry and charge distribution figures are shown below.

![Bond length in Å
Bond angle in degree](image)

It is interesting to note from these diagrams that sulfur makes bond angle of 90° with C-2 and C-5 atoms of the thiazole ring suggesting its $3S^2P_xP_yP_z^2$ electronic configuration.

Since 2-aminothiazole moiety forms skeletal component of all the compounds described in the present investigation, the charge diagram for
2-aminothiazole and 2-iminothiazole protomers calculated using HMO and PPP approximations is illustrated in the following figure. It gives charge values at different atoms of the molecule.

![Graph showing charge values of different atoms](image)

Thiazole carboxylic acids:

The thiazole carboxylic acids are generally stronger acids than their counter part in pyridine series. As expected, thiazole-2-carboxylic acid is stronger than 4- or 5- thiazole carboxylic acids. The order of decarboxylation of thiazole carboxylic acids is $2 > 5 > 4$. It shows the greater stability of thiazole-4-carboxylic acids. Such stability may be accounted due to the zwitter ion formation as shown below.

![Zwitter ion formation](image)
Thiazole-4-carboxylic acids are also a typical case of unsubstituted cyclic α-amino acid. Various structures of 2-aminothiazole-4-carboxylic acid indicating greater stability are given below.

Such internal salt formation is also possible in the case of thiazole-2-carboxylic acids. Thiazole-4-carboxylic acids in general show all the tests of usual carboxylic acids such as esterification, amide formation, acid halide formation and reduction etc.

Some important conclusions of structure of thiazole and 2-amino thiazole and their typical properties are given below.

a) Thiazole is a planar five membered hetero aromatic compound contributing largely to the dienic behavior.

b) Its structure is best shown by conventional formula (I).

c) Proton and a substituent like CH₃, X, NH₂, COOH occupying 2-position are reactive.
d) Thiazole is protonated with protic acids on the ring nitrogen and the reactivity of 2-position in the thiazolium cations is more than that in the corresponding thiazoles.

e) Thiazole ring is cleaved by heating in aqueous NaOH solution (>4N).

f) Thiazole is a weaker base (pKₐ = 2.52) than pyridine (pKₐ = 5.20). However, 2-aminothiazole is more basic (pKₐ = 5.28) than thiazole. First protonation of 2-aminothiazole occurs on the ring nitrogen. In strongly acidic medium, the exocyclic nitrogen is also protonated.

g) Thiazole resists electrophilic substitution reactions when 2-position is free or occupied by an electron accepting group. However, presence of an electron donating group like amino at 2-position activates the 5-position towards electrophilic substitution.

h) Presence of 2-amino group decreases the positive charge at C-2 position. But it increases the negative charge at ring nitrogen and C-5 position. Contrastingly in 2-imino-4-methylthiazoline, there is a greater negative charge on exocyclic nitrogen suggesting preferential protonation there.

i) 2-Hydroxythiazole, 2-mercaptothiazole and 2-aminothiazole exist in tautomeric forms. 2-aminothiazole and its derivatives exist predominantly in the amino form than the tautomeric imino form53-54. Greater the electronegativity of the substituent on 2-aminogroup, greater is the contribution of imino-tautomer, E.g.: 2-sulfonamidothiazole, 2-benzyledenthiadiazole etc.

j) According to MO calculations, C-5 position is more negatively charged than o- and p- positions of benzene ring in 2-anilinothiazoles. Accordingly, halogenation takes place at 5-position even when there is anilino substituent at C-2 position.
According to charge density calculations of 2-amino-5-halothiazoles, 5-halogen is less sensitive to nucleophilic displacement. But several workers have shown that it is not so. On the contrary, the reaction is nearly 10,000 times faster in this case than in 2-unsubstituted-5-halothiazoles. The reason for this is contribution of protomeric structures shown below:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{III} &
\end{align*}
\]

Contribution of structure (III) explains greater reactivity of bromine as in the case of allylic bromides. Further, the presence of methyl group in 2-amino-4-methyl-5-bromothiazole renders 5-bromine group more labile due to hyperconjugative effect.

Thiazole ring system is generally stable to oxidation by permanganate, chromic acid, selenium dioxide and concentrated nitric acid. It resists catalytic hydrogenation by platinum and reduction by metal in hydrochloric acid. However, active raney nickel reduction induces desulphurisation of thiazole ring followed by decomposition of the intermediates.

If there is electron donating group like NH₂, NHCOCH₃, NHAr, OH, SH at 2-position of thiazole-4-carboxylic acid or its ester, it is easy to introduce halogen at 5-position. For chlorination, N-chlorosuccinimide or chlorine generated by KClO₃ and HCl is used. For bromination, bromine is a proper solvent and is directly used to give 2-substituted 5-bromothiazole derivatives. Sometimes
N-bromosuccinimide is also used. For iodination, generally iodine monochloride in dilute HCl is used.

**Spectral data of 2-aminothiazole**

<table>
<thead>
<tr>
<th>Spectral Data</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV (CH₃OH)</td>
<td>$\lambda_{\text{max}}$ 270 nm (log $\varepsilon$ 4.17) due to $\pi-\pi^*$ transitions</td>
</tr>
<tr>
<td>IR</td>
<td>3542 and 3495 (2-amino) and skeletal absorption at 1485 and 1540 cm⁻¹</td>
</tr>
<tr>
<td>NMR (DMSO-d₆)</td>
<td>$\delta$ 7.86(2-NH₂), 6.97(4-H) and 6.53 (5-H) respectively.</td>
</tr>
<tr>
<td>$^{13}$C NMR (DMSO-d₆)</td>
<td>$\delta$ values from TMS as internal reference and $^1$H decoupled.</td>
</tr>
<tr>
<td>Thiazole</td>
<td>$\delta$ C-2 (153.6), C-4 (143.3) and C-5 (119.6) respectively.</td>
</tr>
<tr>
<td>2-aminothiazole</td>
<td>$\delta$ C-2 (170.3), C-4 (139.0) and C-5 (107.7) respectively.</td>
</tr>
<tr>
<td>Mass: (Thiazole)</td>
<td>m/z (relative intensity) 102(8), 101(25), 100(100), 74(3), 73(18), 60(7), 59(4), 58(75), 57(10), 55, 46, 45, 44, 42, 41, 40, 29, 27.</td>
</tr>
<tr>
<td>Mass (2-amino-4-methylthiazole)</td>
<td>117(2), 116(10), 115(36), 114(100), 113(3), 87(4), 82(2), 74(73), 72(58), 71(61), 70, 69, 60(4), 57(3), 47(2), 46(9), 45(14), 40, 39(11).</td>
</tr>
</tbody>
</table>
Mass fragmentation pattern of 2-amino-4-(2-fluorophenyl)thiazole:
Synthetic pathways:

Synthesis of thiazole nucleus could be done using the following methods.

1. By Hantzsch’s thiazole synthesis:

This is the most common method involving the usual condensation of \( \alpha \)-haloketone with a thioamide in an appropriate solvent. Example,

\[
\begin{align*}
\text{R} - \text{CO} & \quad + \quad \text{NH}_2 \\
\text{R}_1 \text{C} \quad \text{S} \quad \text{C} \quad \text{R}_2 & \quad \rightarrow \quad \text{R} - \text{CO} - \text{CO} \\
\text{R}_1 \text{C} \quad \text{S} & \quad \text{C} \quad \text{R}_2
\end{align*}
\]

Where, \( R=\text{OH, OEt, OMe} \); \( R_1=\text{H, alkyl, aryl} \); \( R_2=\text{H, CH}_3, \text{aryl, NHAc, NHAr} \) etc.

Ethyl thiazole-4-carboxylate\(^6^0\), 2-aminothiazole-4-carboxylic acid\(^6^1\), methyl 2-amino-5-ethylthiothiazole-4-carboxylate\(^6^2\) and 2-anilino-5-phenyl-4-carbethoxy-thiazole\(^6^3\) were prepared by this method choosing appropriate synthons. 2-amino compounds were converted into acetamido derivatives by heating with acetic anhydride.

Takaya\(^6^5\) prepared 2-anilino-4-carbethoxy-5-phenylthiazole by the condensation of phenylthiourea with \( \alpha \)-haloketoester.

\[
\begin{align*}
\text{Ph} - \text{COCOC}_2 \text{H}_3 & \quad + \quad \text{PhNHCSNH}_2 & \rightarrow & \quad \text{H}_2 \text{C}_2 \text{O} \\
\text{Br} & \quad \rightarrow & \quad \text{PhNPHNPh}
\end{align*}
\]

Bogina et al.,\(^6^6\) synthesised the following esters by the condensation of ethylbromopyruvate and vinylthioformamide.
They were also prepared by the condensation of ethyl-2-methylthiazole-4-carboxylate with different aldehydes in acetic acid. By this route, 2-aryl-4-carboxy-thiazole$^{67}$ and 2-aryl-4-carbethoxy thiazole$^{68}$ were prepared using appropriate synthons.

Mamedov et al.,$^{69}$ synthesised the following compounds by the same reaction scheme as shown below.

$$\text{P} \quad \text{COCOR} + \text{R},\text{CSNH}_2 \xrightarrow{\Delta} \text{EtO} \quad \text{R}_1$$

Where $R = \text{OMe}, \text{OEt}, \text{N(CH}_3)_2, \text{N(Et)}_2, \text{N(CH}_2\text{CHMe}_2)_2$ and $R_1 = \text{NH}_2, \text{NHAc, Me, Ph.}$

2. By the condensation of isothiocyanate with $\alpha$-isocynoacetate:

Suzuki et al.,$^{70}$ have reported the synthesis of 5-substituted aminothiazole-4-carboxylic acid by the treatment of methyl $\alpha$-isocynoacetate with a proper isothiocyanate in the presence of potassium tertiary butoxide in THF at room temperature.
3. By the condensation with α-acylamino-cyanoacetate and a phosphate disulfide

Golankiewitz et al.,71 devised an ingenious method for the synthesis of 2-substituted-5-amino-4-carbethoxythiazoles by the following reactions.

\[
\text{MeO-} \text{P=S=S-P=OMe} + 2 R' \text{NH}_2 \text{COCH}_2 \text{CN} \rightarrow \text{H}_2\text{C}_2\text{OOC} \text{N} \rightarrow \text{N}_R^
\]

This is a good method of preparing 5-aminothiazole-4-carboxy derivatives.

4. By one pot cyclocondensation of EMIC with carbon disulfide

Alvarez Ibarra72 reported one pot synthesis of 2-methylthio-5-mercaptothiazole-4-carboxylate by the reaction of EMIC and CS\(_2\) in t-butoxide at 78-80°C for 30 minutes followed by alkylation with an alkyl halide.

\[
\text{S} = \text{C} = \text{S} + \text{H}_2\text{C}_2\text{OOC} \rightarrow \text{H}_2\text{C}_2\text{OOC} \rightarrow \text{H}_2\text{C}_2\text{OOC} \rightarrow \text{H}_2\text{C}_2\text{OOC}
\]

Where R= CH\(_3\), CH\(_3\)COCH\(_2\), C\(_6\)H\(_5\)COCH\(_2\), CH\(_3\)OCOCH\(_2\), isopropyl and n-butyl.
5. **By the cyclocondensation of isothiocyanates with EMIC:**

Alvarez Ibarra et al., 74 have further reported the synthesis of 2-methylthio-4-carbethoxy-5-alkyl/arylaminothiazoles (I) by treatment of EMIC in the presence of potassium t-butoxide with isothiocyanate in THF

\[
\begin{align*}
R-\text{NCS} + H_2C\text{OOC-CH}_2-N=\overset{\text{Me}}{\text{SMe}} & \xrightarrow{\text{k-CO(Me)}_3} H_2C\text{OOC} \\
\text{THF} & \xrightarrow{\text{R-HN}^-} N=\overset{\text{SMe}}{\text{SMe}} \\
\end{align*}
\]

Where \( R = \text{Ph, p-tolyl, p-anisyl, p-FPh, Et, n-Bu} \)

6. **By the reaction of substituted ethyl dithiocarbamate with carbon disulfide:**

Patra et al., 75 prepared 1,3-thiazole-2-thiones (I) \( (R=\text{Me, Et, Propyl, CH}_2\text{Ph, } \text{R}_1=\text{Me, CH}_2\text{COCH}_3, \text{CH}_2\text{COPh, CH}_2\text{OCOCH}_3) \) by the interaction of ethyl dithiocarbamate derivative with carbon disulfide in the presence of t-butoxide in DMF followed by alkylation with alkyl halide

\[
\begin{align*}
\text{S}=\text{C}=\text{S} + H_2C\text{OOC} & \xrightarrow{\text{EMIC}} H_2C\text{OOC} \\
\text{DMF} & \xrightarrow{\text{ii } RX} H_2C\text{OOC} \\
\end{align*}
\]

7. **By the condensation of aldehydes with dichloroacetate:**

Takeda et al., 76 have devised an ingenious method of synthesizing 2-amino-5-aryltiazole-4-carboxylates by the following route.

\[
\begin{align*}
\text{R-CHO} + \overset{\text{Cl}}{\text{COOC}}_2H_3 & \xrightarrow{\text{CH}_3\text{ONa, Ether}} \overset{\text{Cl}}{\text{O}} \xrightarrow{\text{NH}_2\text{CSNH}_2} \overset{\text{H}_2\text{C}}{\text{OOC}} \overset{\text{N}}{\text{NH}_2} \\
\end{align*}
\]

Where \( R = \text{Me, Et, isopropyl etc.} \)
If \( R = C_6-C_8n\text{-}alkyl \), \( R\text{-}CHClCOOEt \) is directly obtained in the above reaction which can be used in Hantzsch synthesis with different thioformamides.

Generally, the esters of thiazole-4-carboxylic acids are prepared and then they are converted to acids when required. The ester group responds to the reactions such as reduction, conversion to amides, conversion to hydrazides, acid chlorides etc.

In the light of the above reports, we adopted the Hantzch’s method for the synthesis of ethyl 2-arylaminothiazole-4-carboxylates.
CHEMISTRY OF IMIDAZO[2,1-b]THIAZOLEs:

The above fused ring system (I) containing a bridge headed nitrogen atom at 4-position can be constructed by

i) Starting with a 2-aminothiazole derivative and building imidazole ring by condensation with a α-(2-imino-3-thiazolyl)ketone (I), which on cyclodehydration results in substituted imidazo[2,1-b]thiazole (II).

Kickenhoffen and Krohnke\textsuperscript{77} have demonstrated formation of the intermediates of type II in case of reaction with 2-aminothiazole and phenacyl bromides. Endo nitrogen of the thiazole attacks preferentially on the α-carbon of the ketone in such cases. Meakins et al.,\textsuperscript{78} have discussed this reaction with
respect to structure, properties and yield. The intermediate (I) can be isolated by controlled reaction and under milder conditions.

ii) Starting with 2-thioimidazole and building a thiazole ring by condensation with α-haloketone. Here also, intermediate α-(2-imidazolyl) thioketone (I) is subjected to cyclodehydration to afford the desired imidazo[2,1-b]-thiazole (II).

\[
\begin{array}{c}
R_1-\text{CO} \\
\text{CH} \\
\text{Br}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{S} \\
\text{HS} \\
\text{R}_2 \\
\text{R}_3
\end{array}
\]

\[
\Delta \quad \text{EtOH} \rightarrow \left[ \begin{array}{c}
\text{R}_1-\text{CO} \\
\text{CH} \\
\text{S} \\
\text{S} \\
\text{R}_2 \\
\text{R}_3
\end{array} \right] \cdot \text{HBr}
\]

The bicyclic ring system does not behave as either thiazole or imidazole. Merchetti et al., (1973) have reported its properties by physico-chemical studies and gave possible theoretical account.

**Structure and Reactivity of Imidazo[2,1-b]thiazoles**

Imidazo[2,1-b]thiazole is represented by three major canonical structures I, II, III, of which (I) is the maximum contributing structure. The structure IV does not exist because imidazole part is more electronegative than thiazole part of this bicyclic ring system.
Imidazo[2,1-b]thiazole is pseudoaromatic and quite stable. Pentimali et al.,\textsuperscript{79-80} have reported the reactivity and chemical properties while Merchetti et al.,\textsuperscript{81} have attempted to correlate chemical and NMR spectral properties of imidazo[2,1-b]-thiazole system. Some important conclusions of their study are summarised below.

1. The condensed bicyclic ring containing bridge headed nitrogen is planar and pseudoaromatic.

2. $\pi$ charge is almost localized at 2,3 positions while it is delocalised in imidazole ring as shown by canonical structures II and III. Electrophilic substitution occurs exclusively at C-5 position in imidazole part suggesting that $\pi$ charge delocalisation is not prominent in thiazole ring.

3. Halogen does not add to the double bond at 2,3 positions indicating that it is not isolated alkene type double bond.

4. Magnetic susceptibility normal to the molecular plane of the molecule is $3.12 \times 10^{-5}$ cgs, emu indicating tendency of the molecule towards aromatic behavior. Imidazo[1,2-a]pyrimidine, which is definitely more aromatic showed magnetic susceptibility value of $5.36 \times 10^{-5}$ cgs, emu.
5. Calculation of net π-electron density by more reliable PPP method showed highest negative charge on C-5 compared to that on the remaining carbon atoms. It also showed that imidazo part of the condensed system is richer in electron density compared to the thiazole part.

6. Negative charge calculated on N-7 is higher than that on N-4. Infact N-7 is more basic and protonation of imidazo[2,1-b]thiazole occurs at N-7 position.

7. π-electron delocalisation charge calculated by NMR and X-ray analysis also corroborated the PPP calculations regarding higher net negative charge on imidazole part of the bicyclic ring. In other words, it means delocalisation of electrons is more associated with the imidazole ring i.e., ring current effect is more pronounced in the imidazole part.

Substitution reactions:

Imidazo[2,1-b]thiazoles readily undergo electrophilic substitution at 5-position.

Bromination:

Bromination of I has been reported by several workers\textsuperscript{82-86} to give corresponding 5-bromo derivatives. Bromine in acetic acid or chloroform/CH\textsubscript{2}Cl\textsubscript{2} is used. Use of excess of bromine in the reaction gave a labile perbromide, which on treating with aqueous methanol gave back, the original 5-bromo compounds. In case of I (R=furyl/thienyl), the reaction with equimolar quantity of bromine yielded exclusively 5-bromo derivatives and excess of bromine gave dibromo derivative having additional bromine in furyl/thienyl ring
Paolini and Lendvay\textsuperscript{86} have reported bromination of I (R= R\textsubscript{i}= H and Me; R\textsubscript{2}= Cl) with NBS to give corresponding 5-bromo-6-chloro derivatives. They also prepared 5,6-dichloro derivatives by the reaction with N-chlorosuccinimide.

**Nitration:**

Addition of fuming nitric acid (d, 1.4) to a solution of I in conc. H\textsubscript{2}SO\textsubscript{4} drop wise at 20 °C for 2h gave 5-nitro derivative\textsuperscript{79,80,86,87,88}.

Where R= R\textsubscript{i}= R\textsubscript{2}= H, Me; R=R\textsubscript{i}=H, Me and R\textsubscript{2}= Cl

When R=R\textsubscript{i}=H and R\textsubscript{2}= Ph, nitration leads to give the 5-nitro-6-p-nitrophenyl derivative.

**Nitrosation:**

Treatment of I with a solution of NaNO\textsubscript{2} in acetic acid or isoamyl nitrite in CH\textsubscript{2}Cl\textsubscript{2} gave 5-nitroso derivative\textsuperscript{79,83,85,88,89}. 

---


\textsuperscript{79,80,83,84,85,88,89} Additional references are given for these reactions.
 Thiocyanation:

Addition of bromine to a solution of I followed by treatment with potassium thiocyanate in acetic acid resulted in 5-thiocyanato derivative.\textsuperscript{85,86,90}

\[ \text{R=H, Me, Ph; R}_2=\text{H, Me, Ph or substituted Ph or Cl or heteroaryl} \]

Vilsmeier-Haack Formylation:

Imidazo[2,1-\text{b}]thiazoles react with \(\text{POCl}_3\) in DMF resulting into formylation at 5-position\textsuperscript{85,86,91,92,93}. Even when the 2-position of imidazothiazole is free the formylation only takes place at 5-position.

\[ \text{R=H, Me, Ph; R}_2=\text{H, Ph, Cl, heteroaryl etc.} \]

Selenium dioxide oxidation of I also yielded 5-formyl derivative\textsuperscript{88}.

\[ \text{R=R}_1=\text{H, Me, Ph; R}_2=\text{H, Me, Ph or substituted Ph or Cl or heteroaryl} \]

\[ \text{R=R}_1=\text{H, Me, Ph; R}_2=\text{H, Me, Ph or substituted Ph or Cl or heteroaryl} \]
Trifluoroacetylation:

Anne O’Daly et al.,\textsuperscript{85} have reported introduction of COCF\textsubscript{3} group directly at 5-position by heating I with trifluoroacetic acid in chloroform.

\[
\begin{array}{c}
R_1 \quad N \quad N \quad N \quad R_2 \\
\text{I} \\
\end{array}
\]

R=R\textsubscript{1}= H, Me, Ph; R\textsubscript{2}= H, Ph, Me

Introduction of benzene diazo group (-N=N-Ph):

Pentimalli et al.,\textsuperscript{79} observed that when diazotised solution of aniline was added to a solution of 6-phenylimidazo[2,1-b]thiazole in pyridine at 0-5°C and mixture left for overnight. 5-benzenediazo derivative was obtained in good yield.

Deuteration:

Treatment of 6-\(p\)-methoxyphenylimidazo[2,1-b]thiazole on treatment with 20% DCl-D\textsubscript{2}O at 70°C for 4h and basification of the reaction mixture at 0°C gave 5-deutero derivative\textsuperscript{85}.
Mannich reaction:

Paolini and Lendvay\(^{86}\) have prepared a series of following Mannich bases (II) by heating 6-chloroimidazo[2,1-\(b\)]thiazole (I) with formaldehyde and a secondary amine in presence of acetic acid. The acidic nature of medium is critical. A bismethylene compound (III) is reported if HCl is used in the reaction instead of acetic acid.

\[
\text{IR : 1540 (v_C-N), 735 and 697 (\delta_{\text{Ar-H}})}
\]

\[
\text{NMR : 8 7.51 (s, 1H, 5-H), 6.35 (s, 1H, 2-H), 7.38-7.18 (m, 5H, ArH), 2.35 (s, 3H, 3-CH}_3\text{)}
\]

\[
\text{13C NMR : 8 105.9 (C-2), 134.1 (C-3), 106.5 (C-5), 147.4 (C-6), 149.6 (C-7a), 13.22 (3-CH}_3\text{), 125.0-128.5 (6C of Ph).}
\]

\[
\text{Mass (m/z) : 214 (M}^+\text{, 100%).}
\]
During the mass spectral fragmentation it is always thiazole ring, which is fragmented first, followed by imidazole ring as shown below.

```
Ph
m/z 103
```

| Ph-----^ |
| m/z 117 |

| m/z 116 |
| m/z 174 |

Synthetic pathways:

A brief account of the synthetic pathways of imidazothiazole ring is described below.

1. **By the condensation of 2-mercaptoimidazole with phenacyl bromide:**

   This is the most common approach for synthesising imidazo [2,1-b]thiazoles. The method involves the preparation of intermediate 2-(β-oxomethylthio)imidazole (II) from 2-mercaptoimidazole (I) and its cyclisation to the corresponding imidazo[2,1-b]thiazole (III) by means of an acidic cyclising agent such as PPA/POCl₃.
For example

a. Kochergin et al.,94-95 prepared 2-phenyl-5,6,7,8-tetrahydroimidazo[2,1-b]-thiazole in excellent yield by the condensation of 5-phenylimidazole-2-thione and 2-chlorocyclohexanone by heating in hydrochloric acid (11%) for 30 minutes.

b. De Stevens et al.,96 employed this method to synthesise 1,2,3,4,5,6,7,8,9-octa-hydrobenzimidazo[2,1-b]benzothiazole and the related polycyclic analogues for studying their biological properties. A reaction of the 2-mercapto 4,5,6,7-tetrahydro benzimidazole and 2-chlorocyclohexanone in ethanol directly gave the required compound.

2. By the condensation of 2-aminothiazole derivatives with 2-halo ketones:

In this approach, the reactivity of endo nitrogen of thiazole is taken advantage to introduce a substituent at 3-position which can further react with the
2-amino group to form an imidazole ring fused to thiazole ring. As in the earlier method, a reactive 2-haloketone is commonly employed to produce the thiazolium halide intermediate, which is then made to cyclise intramolecularly under suitable conditions. For example,

a. Ochigi and Nisisawa\textsuperscript{97} synthesised 2-phenylimidazo[2,1-\textit{b}]benzothiazole from a reaction of phenacyl bromide and 2-aminobenzothiazole in boiling ethanol.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_2\text{Br} \\
\text{NH}_2 & \quad \text{CO-Ph} \\
\text{HCl} & \quad \text{EtOH}
\end{align*}
\]

Similarly 2-\textit{p}-nitrophenylimidazo[2,1-\textit{b}]thiazole was later synthesized by Matsukawa and Ban\textsuperscript{98} from \textit{p}-nitrophenacylbromide.

b. Kickhofen and Krohnke\textsuperscript{99} studied this reaction in detail. They isolated the intermediate 2-imino-3-acylthiazolines and cyclised them under acidic or neutral conditions to yield imidazo[2,1-\textit{b}]thiazoles. Their findings are summarized below.

\[
\begin{align*}
\text{I} & \quad \text{NH}_2 \\
\text{II} & \quad \text{NHCOCH}_3 \\
\text{III} & \quad \text{Ac}_3\text{O+NaOAc} \\
\text{IV} & \quad \text{2N HBr}
\end{align*}
\]
c. Kochergin and coworkers\textsuperscript{95,100} have prepared 3-methyl-6-phenylimidazo-[2,1-\(b\)]thiazole from condensation of 2-amino-4-methylthiazole and phenacylbromide. They reported that 2-amino-4-phenylthiazole did not react to give the required product. Probably steric hindrance by neighbouring 4-phenyl group may reduce nucleophilicity of the \textit{endo} nitrogen for attack on the carbon carrying halogen atom.

d. Rudner\textsuperscript{101} has reported the synthesis of 7-hydroxybenzimidazo[2,1-\(b\)]thiazoles by heating a mixture of appropriately substituted 2-aminothiazole and \(p\)-benzoquinone in glacial acetic acid, for example

\[ \text{2-aminothiazole} + \text{haloketone} \rightarrow \text{cyclised product} \]

\[ \text{R} = \text{R}_1 = \text{H, CH}_3, \text{Ph}; \text{R}_2 = \text{H and R}_3 = \text{H, CH}_3, \text{Ph} \]

e. Pyl \textit{et al.},\textsuperscript{102,103} have reported that the reaction of 2-aminothiazole with a haloketone depended on the nature of the ketone. It may give either a hydrohalide salt of the intermediate or directly give the cyclised product in presence of a suitable solvent like desylchloride. Their observations are summarized in the form of reactions shown below.

\[ \text{2-aminothiazole} + \text{haloketone} \rightarrow \text{cyclised product} \]

\[ \text{Where R} = \text{R}_1 = \text{H, CH}_3, \text{Ph}; \text{R}_2 = \text{H and R}_3 = \text{H, CH}_3, \text{Ph} \]

f. Werbel \textit{et al.},\textsuperscript{104} studied the reaction of phenacylbromide and 2-aminothiazoles. They obtained imidazo[2,1-\(b\)]thiazoles in good yield and proposed
the mechanism. Formation of 2-imino-3-phenylthiazole intermediate (I) first took place by preferable nucleophilic attack of *endo* nitrogen on carbon bearing bromine. Then imino-nitrogen of I attacked the carbonyl carbon to yield II, which on dehydration gave imidazo[2,1-b]thiazole derivatives (III).

![Chemical reaction diagram]

**g. Buu-Hoi et al.**\(^{105}\) synthesised a number of imidazo[2,1-b]thiazoles of the following type by refluxing a mixture of the starting 2-aminothiazole derivative and a phenacyl bromide in ethanol for 15-18h. They did not isolate the intermediate products and directly got the final products in good yield.

![Chemical structures]

Where \(R = H, \text{Cl}, \text{Br}, \text{F}; R_1 = H \text{ or Et}\)

**h. Sawney et al.**\(^{106}\) synthesised intermediate (I) by treating ethyl 2-amino-4-thiazoleacetate with a phenacylbromide at room temperature. It was
converted to the corresponding imidazo[2,1-b]thiazoles (II) by refluxing with ethyl alcohol.

Heating the mixture of the starting 2-aminothiazole and a phenacyl bromide in ethanol for 8-10h also gave directly II.

i. Andreani et al., \textsuperscript{107} prepared imidazo[2,1-b]thiazoles (II) (R=Cl, Me; R1=H, Me; R2=Cl, 4-MeC\textsubscript{6}H\textsubscript{4}, 4-PhC\textsubscript{6}H\textsubscript{4}, 3,4-(NO\textsubscript{2})Cl C\textsubscript{6}H\textsubscript{3}) by the cyclocondensation of 2-aminothiazoles (I) with phenacyl bromide in the presence of hydrobromic acid.

j. Meakins et al., \textsuperscript{108} reported a number of 3-arylimidazo[2,1-b]thiazoles by the reaction of 2-aminothiazoles with phenacyl bromide. They proposed the following mechanism.
3. By the reaction of propargyl bromide with 2-amino thiazole:

Iwai and Hiraoka\(^{109}\) obtained 6-methylimidazo[2,1-\(b\)]thiazole by the reaction of propargyl bromide and 2-aminothiazole in ethanol containing sodium ethoxide.

They confirmed the structure of the product by an independent synthesis of the authentic sample by the reaction of 2-aminothiazole and bromoacetone.

35
4. One pot synthesis of 6-chloroimidazo[2,1-b]thiazoles:

Paolini and Lendvay\textsuperscript{110} reported a new method for the synthesis of 6-chloro-imidazo[2,1-b]thiazole starting with a 2-aminothiazole and chloroacetic acid to yield the intermediate 3-carboxymethyl-2-iminothiazoline (I). Its cyclisation with POCl\textsubscript{3} gave directly the 6-chloroimidazo[2,1-b]thiazole (II) in excellent yields.

\[ \text{I} \xrightarrow{\text{POCl}_3} \text{II} \]

5. By intramolecular cyclisation:

Barluenga \textit{et al.},\textsuperscript{111} reported a thermal intramolecular cyclisation of 1-vinyl-2,3-dihydro-3H-imidazole-2-thiones (I) (R\textsubscript{1}= Ph, 4-Me-C\textsubscript{6}H\textsubscript{4}, R\textsubscript{2}= Me, Et, Pr) to imidazo[2,1-b]thiazoles (II). A heteronuclear correlation study of these systems was made in order to establish the configuration of the products.

\[ \text{I} \xrightarrow{\Delta} \text{II} \]

6. By the condensation of 2-aminothiazole in presence of NaCN:

Lantos and Mc Guire\textsuperscript{112} have reported a novel synthesis of imidazo[2,1-b]-thiazoline (II). Condensation of 2-amino-4,5-dihydrothiazole (I) with \textit{p}-substituted benzaldehyde in the presence of sodium cyanide at room temperature gave II in 60 to 80% yield. Acid hydrolysis of II gave III.
7. Condensation of thioarylamide with substituted phenacylbromide:

Shinji Aki et al.,\textsuperscript{113} have reported 6-[2-(3,4-diethoxyphenyl)thiazol-4-yl]-pyridine-2-carboxylic acid, which has an inhibitory activity of superoxide production by human neurophils.

We have adopted the second method for the synthesis of compounds described in the present investigations. A mixture of equimolar quantities of 2-aminothiazole derivative and a phenacyl bromide is heated in anhydrous ethanol for 12h. When the corresponding 6-arylimidazo[2,1-b]thiazole was directly obtained, the intermediate compounds were not isolated.
Domenico Spinelli et al.,\textsuperscript{114} first reported this novel fused ring system in 1992, during the ring-ring interconversion studies and rearrangement of nitrosoimidazothiazoles into [1,2,4]oxadiazolo[3,4-c][1,4]thiazines by the action of mineral acids. In continuation of their studies on nitrogen compounds with mutagenic activity they further reported the physicochemical and crystallographic studies on the above ring interconversion. A brief sketch of their work is presented below in order to gain insight into the newly reported fused ring system. Only a few reports regarding its chemistry and physicochemical studies are available in the literature.

It is well known that some 4(5)-nitroso-5(4)phenylimidazoles (1) by the action of acids undergo a ring opening and ring closing reaction furnishing 3-benzoyl-1,2,4-oxadiazole (4) by elimination of ammonia (Scheme I).
The reaction can be regarded as an acid-catalysed nucleophilic attack of a water molecule to the conjugated system C₄=C₅-N=O of 1, which causes the opening of the imidazole ring, followed by the hydrolytic elimination of ammonia. The cation intermediate 3 by rotation along the nitrogen-carbon bond collapses by a ring-closing reaction to the 1,2,4-oxadiazole 4, losing a hydronium ion.

A similar reaction of nitrosoimidazothiazole having 3-methyl substituent was the first report of extension of the above rearrangement of nitrosoimidazothiazoles by Andreani et al., wherein 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-b]-[1,3]thiazole was rearranged to 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8H-[1,4]-thiazino[3,4-c][1,2,4]oxadiazol-3-one in presence of hydrochloric acid.
They have proposed the following mechanism just similar to that of conversion of nitrosoimidazole to oxadiazole.

Scheme II

The complete mechanism of the rearrangement is as shown in the scheme.

As noticed in the rearrangement of imidazole to oxadiazole (1-4), a relevant role is probably played by the fact that the final product contains the aromatic
1,2,4-oxadiazole as the newly formed heterocyclic ring. In contrast, the ring-ring interconversion involving 5, if the course of the reaction were the same, would furnish 8 where the newly formed ring i.e. the 1,2,4-oxadiazole ring would not be aromatic and this certainly would be an important factor. Moreover, it is probable that the intermediate thiazolone 7 does not give 8 by a nucleophilic addition (AN) but 9 by an acyclic nucleophilic substitution (SNAc) at the same carbon atom with the cleavage of the feeble carbonyl-sulfur bond. By rotation about the nitrogen-carbon bond the thiol group of 9 can in turn add to the ketonic carbonyl carbon (formation of a six membered cyclic hemithioacetal) giving 6.

This study also shows that the 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazole 5 as 4(5)-nitroso-5(4)-phenylimidazoles 1, can be converted into an 1,2,4-oxadiazole derivative, in this instance giving an unexpected derivative of a new fused ring system: the 1,2,4-oxadiazolo[3,4-c][1,4]thiazine. It has been possible to establish the structure of the reaction product 6 on the basis of 1H and 13C NMR spectroscopy as well as of X-ray analysis, while mass spectrometry has been able to give non-definitive information on its structure.

Robert Billi et al., extended the scope of the reaction to several meta- and para-substituted (H, F, Cl, Br, Me, OMe, CN, CF3, NO2, Ph) 6-arylnitrosoimidazothiazoles enlightening the effect of the substituent on the yield of the interconversion. Moreover an interesting insight can be made into the reaction mechanism carrying out the reaction at room temperature in dioxane;
thus they were able to isolate a reaction intermediate (A) which can evolve to 2a via several possible intermediates (e.g. B, formed by an acyclic nucleophilic substitution with the cleavage of the feeble carbonyl-sulphur bond) (Scheme III).

Scheme III

In order to evaluate any effect of substituents in the thiazole ring, they have carried out the reaction on nitroso derivatives containing different substitution patterns.

Thus, they tested the reactivity of 6-(4-chlorophenyl)-5-nitrosoimidazo[2,1-b]-[1,3]thiazole (1b: R1=R2=H), 6-(4-chlorophenyl)-2-methyl-5-nitrosoimidazo[2,1-b]-[1,3]thiazole (1c: R1=Me, R2=H), 6-(4-chlorophenyl)-2,3-dimethyl-5-nitrosoimidazo[2,1-b][1,3]thiazole (1d:R1=R2=Me) and 2-(4-chlorophenyl)-3-nitrosobenzo[d]imidazo[2,1-b][1,3]thiazole (1e:R1,R2=C6H5) with hydrochloric acid (Scheme IV).
Scheme IV:

![Scheme IV](image)

The results of the reactions, carried out under the same conditions adopted for the ring-ring interconversion of 1a (as well as of its derivatives of meta- and para-substitution in the 6-phenyl moiety), are reported in following table, together with those for 1a itself for homogeneity sake. The crude products 2b-e were purified by column chromatography and their structures were easily identified by comparison with the spectra ('H and 13C NMR as well as MS) of 2a.

Results for the Ring-ring interconversion of compounds 1a-e in EtOH/2M HCl

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction time[a]</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a [c]</td>
<td>1 hour</td>
<td>2a: 65%</td>
</tr>
<tr>
<td>1b</td>
<td>1 hour</td>
<td>2b: 26%</td>
</tr>
<tr>
<td>1c</td>
<td>1 hour</td>
<td>2c: 37%</td>
</tr>
<tr>
<td>1d</td>
<td>11 hours</td>
<td>2d: 26%[d]</td>
</tr>
<tr>
<td>1e</td>
<td>1 hour</td>
<td>2e: 38%</td>
</tr>
</tbody>
</table>

The data of above table clearly show that, against the good yield of 2a (65% after chromatography) [2], the ring-ring interconversion of 1b-e lead to modest yields of the desired thiazino[1,2,4]oxadiazolones 2b-e, which were found to be accompanied by several unidentified by-products. Thus, the presence of a methyl group at C-3 (as in 1a) seems essential to guarantee a significant yield increase (65%) with respect to the unsubstituted 1b (26%), while a methyl at C-2 (as in 1c) proves less effective (37%). As far as 1d is concerned, the contemporaneous presence of a methyl at both C-2 and C-3 plays a negative effect (most likely of steric origin), mirrored by a very slow reaction. Thus, after 11 hours of reflux some substrate (20%) could be recovered unreacted while the prolonged reaction time itself could well be responsible for the low yield of 2d (26%): as a matter of fact a further increase of the reaction time was observed to cause a significant increase of decomposition products.

Same authors have reported the determination of structure of compounds by comparison with the NMR spectra. In particular, it is relevant that the substituents on the phenyl ring weakly affect the $^1$H and $^{13}$C chemical shifts of hydrogens and carbons of the 8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c]-[1,2,4]oxadiazol-3-one moiety (ΔSCS 0.3-0.9 ppm). In spite of the low ΔSCS measured, the $^{13}$C SCS gave significant correlations with the Hammett substituent constants and the $\rho$ and $r$ values calculated for SCS of some carbon atoms of the condensed rings are reported in formulas 1 and 2. Small susceptibility constants
have been observed $0.2 < |p| < 1.3$, which were useful for signal attributions. Only $^1H$ and $^{13}C$ chemical shifts of the 8-aryl ring being much affected by the nature of the substituent, excellent ($r = 0.994$) cross-corrections for ipso-, ortho- and para- carbon atoms versus SCS of monosubstituted benzenes have been observed with slopes near to unity ($s = 0.98-1.09$).

$^1H$ and $^{13}C$ NMR Chemical shifts of 8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-one

Susceptibility constants $p$ and $r$ for SCS of 8-hydroxy-5-methyl-8H-[1,4]-thiazino[3,4-c][1,2,4]oxadiazol-3-one
The use of data concerning substituent effects on yields of reaction to gain information on reaction mechanism can be misleading (particularly in multistep reactions), but in the reactions studied the variations of the yields seem largely substituent-dependent. Nitroso derivatives 1 containing electron-repelling or withdrawing substituents rearrange into 6 with low or high yields, respectively. This effect operates notwithstanding the distance of the substituent in the 6-aryl group from the reaction center, at least until the stage of formation of 5.
A stage for which a relevant effect of the above substituent can be expected is the final step (the 5→6 ring closure), the rate of which must depend on the electron density of the carbonyl carbon atom: the lower (or higher) is its electrophilic character, then the lower (or higher) the cyclisation rate would be expected to be and therefore the decomposition of the intermediate products could be higher (or lower). Kinetic and spectroscopic data have shown how the electron density on a carbonyl carbon atom directly bound to an aryl group depends on the electronic effect of the meta- and para-substituents. Accordingly, they have observed lower or higher yields when an electron -repelling or -withdrawing substituent is present in the 6-aryl group respectively.

Spectral data of 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-one

IR (KBr) cm\(^{-1}\) : 3284(OH), 1750(C=O; typical for C=O conjugated with oxygen or nitrogen), 1590(aromatic C=C), 1345, 1230, 1180, 910, 895.

\(^{1}\)H NMR \(\delta\) (DMSO) : 8.30(1H, br s, exch. OH), 7.66(2H, AA' part of AA'BB' system, H-Ar), 7.53(2H, BB' Part of AA'BB' system H-Ar), 6.24(1H, q, H-6), 2.42(3H, d, Me).
$^{13}$C NMR:
- 155.55 (s, C-3), 154.85 (s, C-8a), 135.87 (t, C-1'), 133.94 (tt, C-4'), 128.99 (dd, C-2'), 128.73 (qd, C-5), 128.17 (dd, C-3'), 103.03 (dq, C-6), 76.25 (dt, C-8), 16.67 (qd, Me).

Mass El (m/z)(%):
- 296 (M$^+$, 26), 263 (M$^+$-32, 8), 252 (M$^+$-CO$_2$, 2), 219 (M$^+$-32-CO$_2$, 2), 165 (4-ClC$_6$H$_4$COCN, 2), 157 (M$^+$-4-ClC$_6$H$_4$COCN, 36), 139 (4-ClC$_6$H$_4$CO, 100), 111 (4-ClC$_6$H$_4$, 40), 75 (C$_6$H$_3$, 16).

X-ray diffraction studies:

C$_{12}$H$_9$ClN$_2$O$_3$S, M= 296.7. Triclinic, a=7.501(2), b=7.770(2), c=11.293(2) Å, α=85.43(2), β=72.84(2), γ=82.26(3)° \( \sqrt{A} = 622.6(3) \) Å$^3$ (by least-squares refinement on diffractometer angles for 25 automatically centered reflections, \( \lambda = 0.7107 \) Å, space group p(No.2), Z=2, \( D_c = 1.583 \) g cm$^{-3}$, F(000)=304. Crystal dimensions 0.38 x 0.42 x 0.29 mm, \( \mu(Mo-K\alpha) = 4.79 \) cm$^{-1}$.

This is the first crystal structure determination of a 1,4-thiazine ring condensed with a 1,2,4 oxadiazole system. Selected bond distances and bond angles are reported in Table 2. In the crystal a hydrogen bond O(2)-H(2)...O(3) connects the molecules in chains parallel to the y axis: O(2)-H(2) 0.79(2), O(2)...O(3) 2.797(2), H(2)...O(3) 2.01(2) Å, O(2)-H(2)...O(3) 171(2)°, O(3) in x, -1+y, z. With the exception of a rather short Cl...Cl intermolecular distance (3.321Å) there are no further contacts shorter by more than 0.10 Å with respect to the sum of the van der waals radii involved. The oxadiazole moiety is planar.
within 0.004 Å, whereas the thiazine ring is in a distorted half-chair conformation, with a displacement asymmetry parameter $\Delta C_2(S-C3)=0.031$.

ORTEP view of the structure of 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-one in the crystal
Selected bond distances (Å) and angles (°) with their c.s.d. values. Atoms are numbered according to figure.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance Å</th>
<th>Angle</th>
<th>(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-N(2)</td>
<td>1.432(2)</td>
<td>O(1)-N(2)-C(2)</td>
<td>104.4(1)</td>
</tr>
<tr>
<td>N(2)-C(2)</td>
<td>1.284(2)</td>
<td>N(2)-C(2)-C(3)</td>
<td>124.9(1)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.500(2)</td>
<td>O(1)-N(2)-C(2)</td>
<td>104.4(1)</td>
</tr>
<tr>
<td>C(3)-S</td>
<td>1.841(2)</td>
<td>C(3)-S-C(5)</td>
<td>99.1(1)</td>
</tr>
<tr>
<td>S-C(5)</td>
<td>1.748(2)</td>
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Recently, Roberta Budriesi et al.,\textsuperscript{118} already synthesized [1,4]thiazino [3,4-c][1,2,4]oxadiazolones were evaluated as calcium entry blockers by functional studies namely, in isolated guinea pig left and right atria and K$^+$ depolarised aortic strips. Results shows that, with previous SAR’s and information from computational data, enlighten some structural features which improve negative inotropic activity and reduce the chronotropic and vasorelaxant effects of [1,4]thiazino[3,4-c][1,2,4]-oxadiazolones, namely a methyl group at position 5 of the thiazinoxadiazolo ring, a free -OH at C-8 and an unsubstituted or $p$-bromosubstituted 8-phenyl ring.

With this literature background, we adopted the same method to build oxadiazolothiazine ring with carbethoxy functional group at position 3 of imidazo[2,1-b]thiazole.
References:


874.


2177.


2177.

871; *Chem. Abstr.*, 112 (1990) 235211r.


