GENERAL INTRODUCTION - III
PART - III

GENERAL INTRODUCTION

Thiazolidine is the most important saturated derivative of thiazole ring system. Thiazolidinone and thiazolidinedione are compounds having respectively one and two keto groups in the thiazolidine ring. While oxazole is the least stable of the azole ring system, thiazole ring is extremely stable. The various ring systems related to thiazole are shown below:

![Thiazole, Thiazolidine, 2-Thiazolidinone, 4-Thiazolidinone, 2,4-Thiazolidinedione](image-url)
Rhodanine or 2-Mercapto-4-Thiazolidinone

The above hetero nuclei have attained great importance, as they are present in naturally occurring substances and also in synthetic substances of immense value. 2-Aminothiazole is an intermediate used in the preparation of sulphathiazole, an important member of sulpha drugs.

Sulphathiazole OR 2-Sulphanilamidothiazole

Sulphasuxidine is N-succinyl derivative of sulphathiazole. It is useful in bacillary dysentery and cholera.
Promizole contains 2-aminothiazole ring. It has been tested in animals and men and up to forty percent of lepers lost their positive skin reaction for lepra bacilli.

![Chemical Structure of Promizole]

In 1935, Williams and co-workers demonstrated the existence of the simple thiazole ring in Vitamin B₁.

![Chemical Structure of Vitamin B₁]

Thiazolidine ring is present in all penicillins, one of the most important antibiotics.
Penicillin

Actithiazio acid is an antibiotic isolated from a species of streptomyces. It has high specific in vitro activity against M. Tuberculosis, but it is inactive in vivo, probably due to antagonisation by biotin.

Study of similar synthetic compounds shows that a change in the number of carbon atoms between the acid group and the 4-thiazolidinone moiety, putting substituents on the methylene group, substitution of the -NH group, removal of the oxo or sulphur groups, or conversion of the acid into ester or amide function, produced compounds with little or no activity. Some activity was
retained when the carboxyl group was reduced to the corresponding alcohol, but further reduction to methyl group caused complete loss of activity\textsuperscript{1,2,3,4}.

2-Ethyl thiobenzothiazole possesses antitubercular activity\textsuperscript{5}.

\[ X = \text{SC}_2\text{H}_5, \text{Cl} \]

\[ X = \text{NH}_2 \text{ OR } \text{Cl} \text{ group.} \]

Semi-synthetic oxacillin and its 3-(2-chlorophenyl) derivative (cloxacillin) has moderate antitubercular activity in vitro\textsuperscript{6}. This activity can be increased by the addition of a small amount of benzylpenicillin.

\textbf{Oxacillin}
1-(5-Nitro-2-thiazolyl)-2-imidazolidinone (nitridazole) exhibits antibacterial and antiparasitic activity.7

![Chemical Structure](image)

Nitridazole

Hydrazone derivatives of 2,4-thiazolidinedione obtained from thiosemicarbazones by reaction with chloroacetic acid show antitubercular activity, though lower than the original thiosemicarbazones. Maximum activity was observed when, $R^1 = H$; $R = \sigma$-hydroxyphenyl group in the following compound8,9,10.

![Chemical Reaction](image)
In this type of similar compounds, 2-hydrazino group is more effective than the 2-imino, the 2-thioxo (2-mercapto) or the 2-oxo group. Nevertheless 2-phenyl-hydrazino-4-thiazolidinone is less active than isonicotinyld hydrazide$^{11, 12}$.

3-Aryl-2-arylimino-4-thiazolidinones containing an alkoxy substituent possessing three to six carbon atoms in ether part, showed good in vivo activity, while the corresponding 3-aryl-2,4-thiazolidinediones were found to be inactive$^{13, 14, 15, 16}$.

2-Aryl-(or 2-Furanyl)-substituted-4-thiazolidinones exhibit moderate bacteriostatic activity$^{17, 18}$. 2-Aryl-3-arylimino-5-methyl-4-thiazolidinones show fungicidal activity$^{19}$. Efforts have been made to improve the fungicidal activity of some 2-arylimino-4-thiazolidinones by bromination and mercuration of the aryl - nucleus.

Das and Rout$^{21, 22}$, Pujari and Rout$^{23, 24}$ and Rout and Mahapatra$^{25, 26}$ prepared 2-arylimino or 2-naphthylimino-4-thiazolidinones. Bhargava$^{27}$, Bhargava and Kaul$^{28}$ synthesized 2-arylimino-3-aryl-4-thiazolidinones. Recently Bhargava and Verma$^{29}$ prepared 1,5'-,5''-acetylamino-2',2''-arylimino-3',3''-aryl, 4''-thiazolidinonyl-1', 4-piperazines(I) and their hydrochlorides. The hydrochlorides were tested for
local-anesthetic activity. It was of interest that all compounds required less time for the onset of anesthesia than the standard drug procaine hydrochloride.

Shah, Kshatriya and Trivedi\textsuperscript{30} prepared 2-benzylimino-4-thiazolidinones, while Rawal and Trivedi\textsuperscript{31} prepared 2-arylimino-5-aryl-4-thiazolidinones and also 5-alkyl/benzyl-2-arylimino-4-thiazolidinones. Kashatriya, Rawal and Trivedi\textsuperscript{32} prepared 2-arylimino-3-benzyl and 5-alkyl/aryl-2-benzylimino-4-thiazolidinones and also 5-alkyl/aryl-2-aryl/benzylimino-4-thiazolidinones.

Kharidia and Trivedi\textsuperscript{33} prepared 5-alkyl-2-aryl/alkylimino-4-thiazolidinones. Shah and Trivedi\textsuperscript{34} prepared 2-aryloxethylimino-3-aryloxethyl-4-thiazolidinones and Shroff and Trivedi\textsuperscript{35} prepared 2-(alkoxy-benzyl)-imino-4-thiazolidinones and also alkylene bis-4-thiazolidinones.
Modi and Trivedi prepared \( \text{S-aryloxy-alkyl-2-(p-alkoxy-phenyl)} \)-imino-4-thiazolidinones, 3-benzyl-2-(ureido/2-methylpyridyl/3-methylpyridyl/2-thiasolyl)-imino-4-thiazolidinones from appropriate thioureas and haloalkanoic acid. Motiwala and Trivedi prepared 5-aryl-3-aryl/benzyl-2-aryl-benzylimino-4-thiazolidinones.

Some of the above compounds have been tested and 2-(2,5-dichlorophenoxy-ethylimino)-4-thiazolidinones showed some antifungal activity. 2-Aryl-4-thiazolidinone 1,1-dioxides, exhibit amebicidal activity. 2-(Arsenosobenzyl)-3-arylimino-4-thiazolidinones also showed amebicidal activity.

Thiazolidinone derivatives containing biguinidine substituent in the 5-position have also been prepared.

Anticonvulsant activity has been observed in the case of 2-phenyl-3-methyl/ethyl-4-thiazolidinones. 2-(p-chlorophenyl)-3-methyl and 2-(2-furanyl)-3-methyl-4-thiazolidinones are also active against metrazol induced convulsions as in the case of 2-phenyl-3-ethyl-4-thiazolidinones.
2-Aryl-3-alkylaminoalkyl-4-thiazolidinone possesses a high degree of activity in producing sciatic nerve block in guinea pigs and spinal anesthesia in rabbits.

Leduena and Hoppe reported that 3-(alkyl, dialkyl and cycloalkyl-aminoalkyl)-2-phenyl-4-thiazolidinone derivatives possesses local anesthetic activity.

Satzinger prepared amides of 4-thiazolidinones and found them to possess analgesic and sedative activity. The same author also prepared substituted bis-(4-thiazolidinones) (II) having analgesic, sedative and choleric properties.

Where \( A = -\text{CH}_2\text{CH}_2- \)

\( -\text{CH}_2\text{CH(OH)}\text{CH}_2- \) OR \( \text{Me-N-}(\text{CH}_2\text{CH}_2)_2^- \) groups

Warner-Lambert pharmaceutical company prepared 2-cyano-4-thiazolidinones and found them to possess analgesic and sedative activities. Shaikh and Thaker prepared...
synthesized 3-aryl-5-(2-methyl-butyl)-2-mercapto-4-thiazolidinones as potential anticonvulsants. Surrey\textsuperscript{47} prepared 3-(2-oxazolidinon-3-yl)-4-thiazolidinones, which showed psychomotor stimulant, psychomotor depressant and barbiturate potentiating activity.

Same author\textsuperscript{48} also prepared 4-thiazolidinone and their oxides which were found to possess psychomotor stimulant, anticonvulsant and barbiturate potentiating activity. 3-Phenyl and 3-(p-chlorophenyl)-2, 4-thiazolidinediones show antifungal activity towards Alternaria solani and Sclerofinia americana\textsuperscript{49}. 3-Trichloromethyl-2,4-thiazolidinediones have been patented as being effective in preventing the growth of bacteria, fungi and insects\textsuperscript{50}, while its alkyl or 5-alkylidene derivatives have been claimed as pesticides. It is probable that the halogenated moiety is responsible for the toxic action. 2-Aryl-3-phenylimino and 2-aryl-3-Ureido-4-thiazolidinones\textsuperscript{18} have been found to possess bacteriostatic activity against \textit{Eberthella typhi}, \textit{Escherichia coli}, \textit{Staphylococcus pyogenes aureus} and \textit{Streptococcus equi}.

2-Aryl-4-thiazolidinones with an aminoalkyl group attached to nitrogen atom show strong local anesthetic activity but are more toxic and somewhat irritating as compared to procaine\textsuperscript{42, 51}. 
Sedative activity has been observed for 3-methyl-5, 5-diphenyl-2,4-thiazolidinediones\textsuperscript{52}, for 5,5-disubstituted 2-imino-4-thiazolidinediones\textsuperscript{53,54} and also for 2-dialkyl-amino-4-thiazolidinones\textsuperscript{55}.

3-Methyl/ethyl-2-phenyl-4-thiazolidinones show anticonvulsant properties against electric shock\textsuperscript{40,56} and are also active against metrazole induced convulsions.

Increasing the length of alkyl chain or oxidation of sulphur to sulphone, decreases the activity\textsuperscript{40,57}. 2-Imino-4-thiazolidinone also shows weak antithyroid activity\textsuperscript{2, 58, 59, 60}.

Surrey and Cutler prepared 2-aryl-3-(2-methoxyethyl)-4-thiazolidinones and their dioxides and he found them to be active as psychomotor stimulants and anticonvulsants\textsuperscript{61}. Fenech synthesized 2-aryl-3-(2/3/4-pyridyl)-4-thiazolidinones which showed central nervous system (CNS) stimulating activity and also antimicrobial activity\textsuperscript{62}. 5,5-Dialkyl-2,4-thiazolidinediones which are similar in structure to barbituric acid have been found to show narcotic properties, however undesirable properties limit their practical importance as drugs\textsuperscript{53}. 5-Spiro cyclohexyl-2,4-thiazolidinediones is less active as narcotic and analgesic agent\textsuperscript{63}. 
As certain 2,4-oxazolidinones show activity against metrazole induced convulsions, the corresponding thiazolidinones were examined but were found to be less active.\textsuperscript{64-66} 5-Phenyl-2, 4-thiazolidinediones have been found to give protection against metrazole induced convulsions and also potentiate the hypnotic activity of pento-barbital.\textsuperscript{67} 2,4-thiazolidinediones also showed weak antithyroid activity.\textsuperscript{58-60, 67}

5-(Nitrofuranyl)-4-thiazolidinones and 5-(5-nitro-2-furfurylidine)-4-thiazolidinones\textsuperscript{68} have been found to show antibacterial activity. Antiviral activity has been observed in some arylidinepyridines and pyridylethyl-thiazolidinones\textsuperscript{69} and also in 2-(9-ethyl-carbazol-3-y1) -3-(phenyl/-2-naphthyl)-4-thiazolidinones, 3-Anilino-2-(9-ethyl-carbazol-3-y1)-4-thiazolidinones, 3-(3-naphthyl-amino)-2-(9-ethyl-carbazol-3-y1)-4-thiazolidinones\textsuperscript{70} and 1,2-bis(2-phenyl-thiazolidin-4-on-3-y1)-ethane\textsuperscript{71} have been found to exhibit radiation protective properties. 2-Aryl-3-(2-alkoxyethyl)-4-thiazolidinones have been found to possess psychomotor stimulator properties in addition to anticonvulsant and barbiturate potentiating activities.\textsuperscript{48}

Dhal, Acharya et al\textsuperscript{72} synthesized 5-benzal derivatives of 2-(substituted benzothiazol-2-ylimino)
-4-thiazolidinones and they were found to be active against Trichophyto mentagrophytes and Mycoplasma canis. Kondratenko et al found that 2-phenyl-3-morpholinomethyl-4-thiazolidinone-hydrochloride showed antibacterial activity in vitro. 2, 2'-[(1'-Biphenyl)-4, 4'-diyl-dinitrilo]-bis-[-5-(aryl-methylene)]J-4-thiazolidinones possess both antibacterial and antifungal activities.

Bhargava and Tiwari have prepared 3-ethyl-5-methyl-2-[(4-, or 6-chloro)-benzothiazol-2-ylimino]-4-thiazolidinones (III) and found them effective fungicides against Alternaria tenuis. 3-(2,3-Disubstituted-4,6-dinitrophenyl)-2-mercapto-4-thiazolidinones also showed fungicidal activity and were used for inhibition of Alternaria tenuis. Shyam, Radhey and Tiwari also synthesized compounds similar in structure to (III). 5-methyl-2-[(4,5,6-trisubstituted-2-benzothiazolyl)-imino]-3-aryl/benzyl-4-thiazolidinones which showed fungicidal activity.
-5-methyl-4-thiazolidinones were prepared by Singh\textsuperscript{19} which possessed fungicidal activity.

5-2-Bromo-3-(substituted-nitrophenyl)-2-propenylidene-7-2-mercapto-4-thiazolidinones showed antimicrobial activity\textsuperscript{78}.

Zsolnai found that 5-alkyl-3-aralkyl-2-mercapto-4-thiazolidinones possessed insecticidal activity\textsuperscript{79}.

5,5-Dialkyl-3-alkyl-2-(substituted carbamoyloximino)-4-thiazolidinones (IV) act as insecticidal, miticidal or nematocidal agents\textsuperscript{80} with low phytotoxicity.

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{R}^2 \\
\text{R}^4 \\
\text{S} \\
\text{C}=\text{NO}-\text{C}-\text{NRR}^1 \\
\text{N=O-C-NRR}^1 \\
\end{array}
\end{align*}
\]

Where $R = R^1 = R^3 = R^4 = H$ or methyl group.

$R^2$ = alkyl group.

Recently Croix and Eric\textsuperscript{81} have found that 3-aryl-2-mercapto-4-thiazolidinones are useful as herbicides\textsuperscript{81}.
2-Arylimino-3-(3-morpholino-propyl)-4-Thiazolidinones showed CNS depressant activity in mice\textsuperscript{82} in addition to some degree of anticonvulsant activity. In 1976, Astik, Acharya et al synthesized 2-alkyl, 2-\(\text{2-hydroxy-5-methyl-phenyl}\)aryl/naphthyl/alkyl-4-thiazolidinones (V) and found them as mild central depressants\textsuperscript{83}.

\[
\begin{align*}
\text{O}=\text{C} & \quad \text{N}-\text{R} \\
\text{H}_2\text{C} & \quad \text{S} \quad \text{CH}_3 \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2
\end{align*}
\]

(V)

Where \(\text{R}^1 = \text{OH group}\)
\(\text{R}^2 = \text{CH}_3\) group

Chaudhary et al\textsuperscript{84} tested 2-arylimino-3-(2-pyrimidyl)-4-thiazolidinones and found them CNS depressants as well as anticonvulsants.
Dwivedi et al. synthesized 2-arylimino-3-\(\text{C}_2\)2-(3,4-dimethoxyphenyl)-ethyl-7-4-thiazolidinones and tested their anticonvulsant activity in mice. Nagar et al. synthesized 2-substituted cyclohexylimino-3-substituted-phenyl-4-thiazolidinones-5-acetic acid (VI) and found them to possess anticonvulsant and cardiovascular activity, while 2-(substituted imino-3-(3-diethyl aminopropyl)-4-thiazolidinone-5-acetic acid showed anti-inflammatory and antiproteolytic activity.

\[
\begin{align*}
&\text{HOOCH}_2\text{C-CH} \\
&\text{C} = \text{NR}
\end{align*}
\]

(VI)

Dynachim observed that 3-methyl-5-(p-nitrophenyl) azo 7-2-mercapto-4-thiazolidinones showed anthelmintic activity in domestic animals like horse, pig, and cat. Aries et al. observed same activity in 3-methyl-5-(2,4-dintrophenyl)-azo 7-2-mercapto-4-thiazolidinones. Husain et al. synthesized 3-aryl-5-(4-methyl-4-piperazinyl phenyl)-azo 7-2-mercapto-4-thiazolidinones and tested them as potent anthelmintics in mice.
2,4-Thiazolidinediones show a variety of physiological properties. According to Broke et al., 3-[(3,4,4-trihalogen-substituted-3-butyl)-2,4-thiazolidinediones possessed nematocidal activity\textsuperscript{91, 92}. Recently 5-[(4-hydroxy-3-methoxy-phenyl) methylene]-2,4-thiazolidinediones showed significant tuberculostatic activity\textsuperscript{93} against Mycobacterium tuberculosis H 37. Skinner et al.\textsuperscript{94} observed 3-alkyl-2-mercapto-4-thiazolidinones and 3-alkyl-2,4-thiazolidinediones as insect repellent and mosquito repellent.

Recently in 1976, Diamond et al.\textsuperscript{95} synthesized 5-[(3-chloro-4-cyclohexyl) phenyl]-2-imino-4-thiazolidinones (VII) and 5-[(3-chloro-4-cyclohexyl) phenyl]-2,4-thiazolidinediones (VIII) by the condensation reaction between appropriate thiourea and ethylester of \(\text{OH}-\text{chloro}, \text{CH}-\text{Cl}\) (3-chloro-4-cyclohexyl)-phenyl \(-\text{acetic acid}. These compounds possessed anti-inflammatory, analgesic and antipyretic activity.

![Chemical Structure Diagram]

When, \(Z = \text{NH}\) it is VII and
\(Z = 0\), it is VIII.
The compounds similar to the above structure, 2-mercaptop-3-alkyl/aralkyl/5-alkyl/aralkyl/aryl/-4-thiazolidinones (A) and 3-alkyl/aralkyl-5-alkyl/aralkyl/aryl-2,4-thiazolidinones (B) were prepared by Tong et al. and evaluated on human skin for repellency against female Aedes aegypti mosquitoes. Moreover (A) series compounds with b.p. 95/0.5 mm and (B) series compounds with b.p. in ranges of 90° to 115°/0.5 mm exhibited the longest duration of repellency.

Patel and Trivedi also synthesized 2,3-disubstituted-4-thiazolidinones containing ether group in side chain and these compounds showed anti-inflammatory activity. Moreover Dhruwa and Trivedi also prepared this type of compounds having anti-inflammatory activity. Mehta, Chawda and Parikh have synthesized 2-methyl, 2-(2-methyl-4-hydroxy-5-isopropyl) phenyl 7-3-aryl-5-H/methyl-4-thiazolidinones which possessed antimicrobial activity against S. aureus, E. Coli and A. niger and it was observed that they were moderately active against Gram positive and Gram negative bacteria.

Recently in 1979 Omar et al. have prepared 2-substituted-imino-3-substituted alkyl/aralkyl-4-thiazolidinones of the following type by condensing substituted-theophylline-thiosemicarbazide and C-bromo ethyl acetate.
When, \( R^2 = \text{butyl/phenyl/substituted-methyl-phenyl/benzyl group.} \) It is IX series; and

\[ R^2 = 2\text{-substituted phenyl group.} \]

It is X series.

The compounds of IX series have shown anticonvulsant activity, while compounds of X series have shown anticancer activity in mice, however they do not possess anticonvulsant activity.
PRESENT WORK

Thiazolidinones show a wide variety of biological activities such as anticonvulsant, anesthetic, sedative, amebicidal, hypnotic, antibacterial, antifungal, and anti-tubercular activity.

It was of interest to prepare substituted 4-thiazolidinones containing some novel features in the molecule.

(A) Isoniazid is perhaps the most important and cheap tuberculostatic compound among the common drugs used for the treatment of TB. It was thought interesting to incorporate acylhydrazide group in the thiazolidinones. This was achieved by using the acylhydrazide in place of amine for the preparation of Schiff bases which can be converted subsequently to 4-thiazolidinones by reaction with thioglycolic acid.

Compounds described in Part III (A) have been prepared by using the reaction sequence shown below.

\[
RCONHNH_2 + R^1CHO \rightarrow RCONHN = CHR^1
\]

\[
RCONHN = CHR^1 + SHOH_2COOH \rightarrow RCONH-N-\overset{\text{C}}{\text{H}}-\overset{\text{O}}{\text{C}}-\overset{\text{S}}{\overset{\text{H}}{\text{H}}}_2
\]

4-Thiazolidinone
In light of the importance of 1,3,4-thiadiazole ring in endowing a compound with physiological activity it was thought interesting to incorporate this in the thiazolidinone molecule. Compounds of Part II(B) were prepared from the schiff bases obtained from 2-amino-1,3,4-thiadiazole and aldehyde and condensation of the resulting schiff base with thioglycolic acid. The reactions are shown below:

\[ R-\text{NH}_2 + R'_1-\text{CHO} \longrightarrow R.N = \text{CHR}_1 \]

Amine Aldehyde Schiff base

\[ R-N = \text{CHR}_1 + \text{SHCH}_2\text{COOH} \longrightarrow R-N\text{--CH-}R_1 \]

4-Thiazolidinone

Where \( R_1 = \text{C}_6\text{H}_5, \text{p-CH}_2\text{-C}_6\text{H}_4, \text{p-OCH}_2\text{-C}_6\text{H}_4, \text{p-Cl-C}_6\text{H}_4, \text{p-OH-C}_6\text{H}_4 \text{OOHH}, \text{p-Cl-C}_6\text{H}_4 \text{COHH}. \)

\[ R = \text{C}_6\text{H}_5\text{-CONH}, \text{p-CH}_2\text{-C}_6\text{H}_4\text{CONH}, \text{p-OCH}_2\text{-C}_6\text{H}_4\text{CONH}, \text{p-Cl-C}_6\text{H}_4\text{CONH}, \text{p-OH-C}_6\text{H}_4\text{CONH}. \]

and

5-alkyl-1,3,4-thiadiazoles.
PART - III

THEORETICAL.

4-Thiazolidinones are the derivatives of thiazolidine ring with a carbonyl group in the 4-position. Substituents in the 2,3 and 5-position may be varied. But the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position.

Such groups include alkyl or aryl, oxygen (2,4-thiazolidinediones), sulphur (rhodanine), imino (pseudo-thiohydantoin, 2-imino-4-thiazolidinone), and hydrazino (4-oxo-2-thiazolin-2-yl-hydrazones of aldehydes or ketones).

![Chemical structures](attachment:chemical Structures.png)

4-Thiazolidinone          Alkyl or aryl 4-Thiazolidinones

2,4-Thiazolidinediones          Rhodanine
Considerable confusion concerning the structure of 4-thiazolidinone exists in the early literature and non-cyclic formula were at first proposed for pseudothiohydantoin and for rhodanine\textsuperscript{103, 104, 105}. An alternative cyclic formula, that of thiohydantoin was proposed for 2-imino thiazolidinone\textsuperscript{106} but recognition of mercaptoacetic acid as a primary product of the hydrolysis of 3-phenyl-2-phenyl imino-4-thiazolidinone led to the choice of the correct formula for 2-imino derivatives.

Some important methods for the synthesis of 4-thiazolidinone derivatives are described below:

\textbf{2, or 2,3-disubstituted-4-thiazolidinones}:

Majority of the methods used for the synthesis of 2, or 2,3-disubstituted-4-thiazolidinones can be considered as variation of a general method using the reaction of
QC-mercaptoalkanoic acids with compounds of structure RN = CHX. The reaction takes place in an inert solvent such as dry ether\textsuperscript{107} or dry benzene\textsuperscript{108, 109}. With the above solvents, yields are of the order of 60-70%; while in ethanolic solution the yield drops to below 10\%\textsuperscript{107}.

The use of water separator has been found advantageous and the course of the reaction can be followed by the volume of water collected.

(I) Surrey and Cutler\textsuperscript{37} obtained 2-substituted-4-thiazolidinone by heating a mixture of an appropriate aldehyde or ketone with thioglycolic acid and ammonia or an ammonium salt such as ammonium acetate or carbonate. The use of ammonium carbonate as the source of ammonia and benzene as a solvent were found to be very convenient.

\[
\text{R-CHO + HS-CH}_2\text{-COOH} + \text{NH}_3 \rightarrow \text{R-CH}_2\text{-S-CH}_2\text{-CO-NH}_2
\]

They postulated the following mechanism for the above reaction. An aldimine is supposed to be formed in the beginning of the reaction (Step - a).
The reaction proceeds by the nucleophilic attack of mercapto acetic acid upon the $\text{C}=\text{N}$ group with the addition of $\text{SCH}_2\text{COOH}$ group to the carbon and it follows the capture of a proton by nitrogen atom and then subsequent cyclisation takes place (Step - c).

In several cases the uncyclized addition product has been isolated\textsuperscript{13}. Subsequent cyclisation of certain compounds was effected by heating the open chain compounds with phosphorus pentoxide in dioxane solution for thirty minutes\textsuperscript{15}. Effect of substituents on the yield of thiazolidinones has also been studied\textsuperscript{18, 110}.
Formation of thioglycolamide as the principle intermediate in sequence is ruled out, since these authors found that the amide reacts with aromatic aldehydes under conditions employed to give only a small yield of 4-thiazolidinone.

II.

(a) 2,3-Diphenyl-4-thiazolidinones were prepared by Surrey from Schiff bases and thioglycolic acid with benzene as a solvent.

\[
\text{C}_6\text{H}_5\text{CH} = \text{NO}_2\text{H}_5 + \text{HS}.\text{CH}_2 \quad \xrightarrow{\text{COOH}} \quad \text{HS}.\text{CH}_2 \quad \xrightarrow{\text{C}=\text{S}} \quad \text{H}_5\text{C}_6\text{CH} \quad \text{N} \quad \text{C}=\text{O} \quad \text{C}_6\text{H}_5
\]

The use of ethyl thioglycolate was found to give lower yield of 4-thiazolidinones.

Erlenmeyer and Oberlin reacted Schiff bases from tuberculostatic amines with thioglycolic acid and obtained 4-thiazolidinone derivatives.
Martini also obtained 2,3-disubstituted-4-thiazolidinones from Schiff bases and thioglycolic acid in a similar way.

(b) Recently Astik, Acharya et al synthesized 2,3-disubstituted-4-thiazolidinones by directly condensing the arylmethylketone with thioglycolic acid and respective amine in benzene for 10 hrs. The yield of 4-thiazolidinones markedly decreased when the Schiff base was not isolated. They tried anhydrous zinc chloride and p-toluene sulfonic acid as catalyst.

\[ R\text{COCH}_3 + H_2NR^1 \rightarrow R\text{C}_ = NR^1 \rightarrow \text{SHCH}_2\text{COOH} \]

Here \( R = \text{aryl group} \quad 2\text{-substituted, 2,3-disubstituted} \quad 4\text{-thiazolidinone} \)

\( R^1 = \text{alkyl / cyclohexyl / naphthyl / aryl / benzyl.} \)
It has been concluded that the addition of anhydrous zinc chloride enhances the yield (62%), but p-toluene sulfonic acid has no effect.

Mehta, Chawda and Parikh also synthesized 2,3-disubstituted-4-thiazolidinones by condensing Schiff bases, obtained from substituted acetothymols and appropriate aromatic amines, with thioglycolic acid in presence of anhydrous zinc chloride. They have also isolated Schiff bases which were prepared by the method of Reddelien.

III. Surrey obtained a series of 2-aryl-3-dialkylaminoalkyl derivatives of 4-thiazolidinones by reaction between benzylidene dialkylaminoalkylamine and methylthioglycolate. The reactants are refluxed in skellysolve and methyl alcohol collected, is a measure of the progress of the reaction.

\[
(x) \quad \ce{C6H4-CH} + \ce{CH2-SH} \quad \rightarrow \\
\ce{R1-N} \quad \ce{COOCH3}
\]

\[
(x) \quad \ce{C6H4-CH} + \ce{CH2OH} \quad \rightarrow \\
\ce{R1-N} \quad \ce{O=O} \quad \ce{CH2-SH}
\]
Surrey prepared 2-aryl-3-alkylaminoalkyl derivatives of 4-thiazolidinones by reaction between the aldimine and methylthioglycolate.

\[
\text{Ar.CHO} + \text{H}_2\text{N-(CH}_2)_n\text{-NHR} \rightarrow \text{ArCH-N (CH}_2)_n\text{-NHR}
\]

\[
\text{Ar.CH} = \text{N (CH}_2)_n\text{-NHR} + \text{HS} = \text{CH}_2 \quad \rightarrow \quad \text{COOCH}_3
\]

T Troutmann and Long also prepared 2-aryl-3-alkyl and 2-hetero-3-alkyl derivatives of 4-thiazolidinones by the use of thioglycolate and benzylidenealkylamines.

\[
\text{R-CHO} + \text{H}_2\text{NR} \rightarrow \text{R.CH} = \text{N-R}^1
\]

\[
\text{R-CH} = \text{NR}^1 + \text{CH}_2\text{SH} \quad \rightarrow \quad \text{COOR}^2
\]

\[
\text{R-CH} \quad \text{N} \quad \text{O}=0 \quad \rightarrow \quad \text{R-CH} \quad \text{NH} \quad \text{OOR}^2
\]

+ \text{R}^2\text{.OH}
They also found that the use of thioglycolic ester was more suitable with benzylidene alkylamine, while with schiff bases, ester gave poor yield. Surrey also oxidized 4-thiazolidinones to the corresponding 1:1 dioxides.

![Chemical structure](image1)

(VI) Surrey prepared 3-Ureido-4-thiazolidinone by reaction of thioglycolic acid with semicarbazones.

![Chemical structure](image2)
p-Toluenesulfonic acid was found to have a catalytic effect on the reaction.

(V) In this method, O^-mercaptoacetamide instead of the acid, is reacted with the carbonyl compound. The reaction takes place in an inert solvent in the presence of p-toluenesulfonic acid, with water being removed by a water-separator. This method has been mainly used for aliphatic aldehydes and ketones, aldehydes giving better yields than ketones. McLamore et al^2, 4 synthesized 4-thiazolidinones by this method.

\[
\begin{align*}
R\text{CHO} + \text{SH-CH}_2 & \rightarrow R\text{-CH} \\
& \quad \text{R}^1 \text{NHCO}
\end{align*}
\]

Actithiazic acid is the best known example of a substance synthesized by this method. It is synthesized from ethyl O^-aldehydropimelate and mercapto acetamide, followed by saponification of the ester and resolution of the racemic acid as under^1, 2, 4, 114.
Davies, Ramsay and Stove\textsuperscript{115} claimed to have prepared 2-phenyl-4-thiazolidinone by heating a mixture of thioglycolamide and benzaldehyde, but Fennigton\textsuperscript{4} and Surrey and Culter\textsuperscript{37} have shown that this compound supposed to be 2-phenyl-4-thiazolidinone is a hemimercaptal (A) of benzaldehyde and mercaptoacetamide.

\[
\begin{align*}
\text{C}_6\text{H}_5- & | \quad \text{C} - \text{OH} \\
S\text{CH}_2\text{CONH}_2 & \\
\end{align*}
\]

This (A) is mainly formed when benzaldehyde and mercaptoacetamide are heated without removal of water.
(VI) In stead of the carbonyl compound, di-iodo-methane can be used to prepare 4-thiazolidinones.

\[ \text{Condensation} \]

\[
\begin{align*}
\text{C}_6\text{H}_5\text{NHOOC}_2\text{SH} & + \text{CH}_2\text{I}_2 \\
\text{KOH} & \quad \text{CH}_3\text{COOH} \\
\text{K}_2\text{CO}_3 & \quad \text{CH}_3\text{COCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} \quad \text{N} \quad \text{C} = 0 \\
\text{H}_2\text{C} \quad \text{S} \quad \text{CH}_2
\end{align*}
\]

3-phenyl-4-thiazolidinone (Methylene-bis(2-mercaptoacetanilide))

Satisfactory experimental conditions for S- and N- alkylation are found by using potassium hydroxide in dry acetone. The concentration of base is important. With higher concentrations of base, the chief product is the result of S- alkylation, methylene bis-(2-mercaptoacetanilide).

Under similar conditions 1,1-dibromoacetone gives 2-acetyl-3-phenyl-4-thiazolidinone.
2-acetyl-3-phenyl-4-thiazolidinone

Now, the inter-relationship between derivatives of 4-thiazolidinones with reference to their preparations from thioglycolic acid can be given as under.
GENERAL METHOD FOR THE PREPARATION OF ETHYL ESTERS OF
SUBSTITUTED BENZOIC ACIDS

Aromatic acid ester were prepared by refluxing an aromatic acid (1 mole) with an excess of (up to about 10 moles) of ethyl alcohol in the presence of a small proportion of concentrated sulphuric acid or hydrogen chloride (catalyst). The excess of ethyl alcohol was largely removed by distillation from a water bath and residue was poured into a large excess of water. Lower layer of ester was separated carefully and was washed with a strong solution of sodium bicarbonate until all free acid is removed and was washed again with water and dried over anhydrous magnesium sulphate. Ester was filtered and purified by distillation.

Following esters were prepared by the above method.

\[
R \quad \text{--COOC}_2\text{H}_5
\]

Ethyl-Substituted Benzoates
<table>
<thead>
<tr>
<th>R</th>
<th>B.P. °C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-OH</td>
<td>231-234</td>
<td>- do -</td>
</tr>
<tr>
<td>4-OH₃</td>
<td>228</td>
<td>Noad, Ann. 63, 295</td>
</tr>
<tr>
<td>4-OOH₃</td>
<td>269</td>
<td>Cahours, Ann. 56, 310</td>
</tr>
<tr>
<td>4-Cl</td>
<td>238</td>
<td>Van Raalte, Rec trav Chim. 18, 398 (1899).</td>
</tr>
<tr>
<td>2-Cl</td>
<td>243</td>
<td>Glutz, Ann. 143, 196 (1867).</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF SUBSTITUTED BENZYDRAZIDES:

Appropriate ethyl esters were heated with hydrazine hydrate in alcohol on water-bath for 3 to 5 hours. After the removal of the alcohol, on cooling, the solid product obtained was filtered and crystallised from alcohol.

In few cases esters were heated with hydrazine hydrate without alcohol.

Following hydrazides were prepared by the above method.

\[
\begin{align*}
R & \quad \text{CONHNH}_2 \\
\end{align*}
\]

Substituted Benzhydrazides
<table>
<thead>
<tr>
<th>R</th>
<th>M.P. °C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>112</td>
<td>Gatterman and Wieland, &quot;Laboratory Methods of Organic Chemistry&quot;</td>
</tr>
<tr>
<td>4-OC₃H₅</td>
<td>136</td>
<td>San and Chang, Ber. 69. 2762 (1936).</td>
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<tr>
<td>4-Cl</td>
<td>162-63</td>
<td>Kahl, Cent. 4(II) Page 1493 (1904).</td>
</tr>
<tr>
<td>2-Cl</td>
<td>109-10</td>
<td>Kalb, Gross, Ber. 52. 732 (1926).</td>
</tr>
</tbody>
</table>
2-Amino-5-alkyl-thiadiazoles required in this Part is prepared according to the method described in the Experimental Part-II. On Page No.

Following were prepared.

![Chemical Structure](image)

2-Amino-5-alkyl-thiadiazole.

<table>
<thead>
<tr>
<th>R</th>
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<th>References</th>
</tr>
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<tbody>
<tr>
<td>CH₃</td>
<td>223</td>
<td>As described in Experimental Part-II.</td>
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<tr>
<td>C₂H₅</td>
<td>196</td>
<td>- do -</td>
</tr>
<tr>
<td>n-C₃H₇</td>
<td>203-06</td>
<td>- do -</td>
</tr>
<tr>
<td>iso-C₃H₇</td>
<td>182-85</td>
<td>- do -</td>
</tr>
</tbody>
</table>
A mixture of substituted aldehyde (0.02 mole) and appropriate amine/hydrazide (0.02 mole) in dry benzene (100 ml.) was refluxed with a Dean and Stark apparatus. After the theoretical quantity of water was separated (7 to 8 hours), thioglycolic acid (2.0 gms) was added and heating was continued till no more water separated.


The solid residue after the removal of benzene, was treated by sodium bicarbonate solution to remove unused thioglycolic acid. Residue was washed with water and dried.

They were crystallized from absolute alcohol.
The following 2,3-disubstituted-4-thiazolidinones were prepared by the above method.

### Table I

**2-Aryl-3-bensamido-4-thiazolidinones.**

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
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<th>Molecular Formula</th>
<th>% of Nitrogen Found</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Sulphur Found</th>
<th>% of Sulphur Calcd.</th>
<th>% of Chlorine Found</th>
<th>% of Chlorine Calcd.</th>
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</thead>
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<td>H</td>
<td>181</td>
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<td>8.97</td>
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<td>10.25</td>
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<td>-</td>
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<td>H</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
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**TABLE II.**

2-Aryl-3-(5-alkyl-1,3,4-thiadiazolyl)-4-thiazolidinones.

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<th>% of Sulphur</th>
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| (4) | CH₃ | 4-Cl  | 116    | C₁₃H₁₀ClN₂O₂S₂   | 13.22         | 13.48        | 20.41        | 20.54       | 11.20         | 11.39

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PHARMACOLOGICAL STUDY
Out of the forty-two compounds prepared, shown in Table-I, twenty-four were screened for the invitro tuberculostatic activity which was determined on culture of M. tuberculosis var. Hominis (Strain H$_3$Rv) cultivated in Youmans' medium containing 10% horse serum using a modified (1) method of Doub and Youmans (2). Due to the sparing solubility of the present compounds in most of the solvents, they were used in the suspension form in gum accacia for antituberculosis screening.


The result of the tuberculostatic activity of compounds mentioned above are shown below.
The following 2,3-disubstituted-4-thiazolidinones were tested for the anti TB activity:

![Chemical structure](image)

2-Aryl-3-benzamido-4-thiazolidinones.

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<th>Sr. No.</th>
<th>R</th>
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<th>M.P.°C</th>
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<td>(4)</td>
<td>(5)</td>
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<td>4-OOH₃</td>
<td>144</td>
<td>C₁₇H₁₅ClN₂O₃S</td>
</tr>
<tr>
<td>16.</td>
<td>4-Cl</td>
<td>4-Cl</td>
<td>116</td>
<td>C₁₆H₁₂Cl₂N₂O₂S</td>
</tr>
<tr>
<td>17.</td>
<td>2-Cl</td>
<td>H</td>
<td>210</td>
<td>C₁₆H₁₃ClN₂O₂S</td>
</tr>
<tr>
<td>18.</td>
<td>2-Cl</td>
<td>4-CH₃</td>
<td>196</td>
<td>C₁₇H₁₅ClN₂O₂S</td>
</tr>
<tr>
<td>19.</td>
<td>2-Cl</td>
<td>4-OOH₃</td>
<td>157</td>
<td>C₁₇H₁₅ClN₂O₃S</td>
</tr>
<tr>
<td>20.</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>200</td>
<td>C₁₆H₁₂Cl₂N₂O₂S</td>
</tr>
<tr>
<td>21.</td>
<td>2-OH</td>
<td>H</td>
<td>181</td>
<td>C₁₆H₁₄N₂O₃S</td>
</tr>
<tr>
<td>22.</td>
<td>2-OH</td>
<td>4-CH₃</td>
<td>235</td>
<td>C₁₇H₁₆N₂O₃S</td>
</tr>
<tr>
<td>23.</td>
<td>2-OH</td>
<td>4-OOH₃</td>
<td>205</td>
<td>C₁₇H₁₆N₂O₄S</td>
</tr>
<tr>
<td>24.</td>
<td>2-OH</td>
<td>4-Cl</td>
<td>215</td>
<td>C₁₆H₁₃ClN₂O₃S</td>
</tr>
<tr>
<td>25.</td>
<td>. . . I S O N I A Z I D . . .</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Infra-Red Spectra.
N.M.R. Spectra.
INTERPRETATION OF SPECTRAS.

(A) I. R. SPECTRA: Infra-Red spectra of the compound is taken in CHCl₃.

Following important frequencies were observed.

1. C = O stretching vibration 1675 cm⁻¹ (Amide I Band)
2. C = O stretching vibration 1720 cm⁻¹ (Ketone)
3. Symmetrical N-H stretching 3410 cm⁻¹
4. C - H Stretching 3005 cm⁻¹

(B) N. M. R. - SPECTRA: Spectra was taken in CDCl₃.

Proton counting:

1. Peaks at 3.62 to 4.07 ppm corresponds to proton 2H₁
2. Peak at 6.15 ppm corresponds to proton H₂
3. Peak 7.42 to 7.78 ppm corresponds to 10H phenyllic protons.
4. Peak at 8.62 ppm corresponds to H₃ proton.
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