PART II
GENERAL INTRODUCTION - II
PART - II.

GENERAL INTRODUCTION.

Heterocyclic compounds occur in nature widely as alkaloids, vitamins, pigments, hormones and a variety of plant and animal cell constituents. Their vital role in biological processes, their availability from agricultural wastes and coal-tar and their economic value as solvents, dyes and pharmaceuticals are the main factors which have directed the attention of organic chemists to this field. A third of the compounds listed in the Beilstein have heterocyclic nuclei. Over half of the types of compounds produced by nature have heterocyclic systems. Today heterocyclic chemistry constitutes a major branch of organic chemistry ranking in importance with the aliphatic and isocyclic branches.

The study of sulphur compounds and their importance has been increasingly recognised in recent years. The importance of these sulphur compounds is becoming more strong in the field of industry and biochemical research. Many crude products such as petroleum, shale-oil, tars etc., contain a wide variety of sulphur compounds.

Synthetic organic sulphur compounds are of great economic importance. Application of these compounds on
commercial basis has been found to be useful in dyestuff, plastic, photography and preservative, in textile industries as accelerators, in the rubber vulcanization process, in the formation of polymers and to improve the qualities of lubricating oils. Their applications also have been observed with successful results in medicine and pharmaceuticals. From the biological point of view, it has been observed that some of the organic sulphur compounds possess numerous biological properties such as bacteriostatic, tuberculostatic, insecticidal, anti-thyroid, anthelmintic, rodenticidal etc.,

The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazine and hydrazine. The first 1,3,4-thiadiazole was described by Fischer in 1882, but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh. From 1894 to the first decades of the twentieth century Busch and his school developed and expanded this field. After a period of relatively low activity between the wars, interest was renewed due to the discovery of sulpha drugs and of potent representatives in the thiadiazole series. The pharmaceutical line of interest has continued and new interesting drugs have been discovered. This development has considerably enriched the preparative
side of 1,3,4-thiazole chemistry. Members of this ring system found their way into such diverse applications as pharmaceuticals, oxidation inhibitors, cyanine dyes, azodyes and metal complexing agents.

NOMENCLATURE AND NUMBERING :-

Five membered heterocyclic compounds containing one sulphur and two nitrogen atoms are known as thiadiazoles. They are named as 1:2:3, 1:2:5, 1:2:4 and 1:3:4-thiadiazoles depending upon their respective position of nitrogen and sulphur atoms.

For example :-

\[ \text{N} \quad \text{CH} \quad \text{HC} \quad \text{CH} \quad \text{HC} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \]

1:2:3 1:2:5 1:2:4 1:3:4 thiadiazole thiadiazole thiadiazole thiadiazole

The nomenclature, 1:3:4-thiadiazole, or thio (bb\textsubscript{1}) diazole is given to the following structure its revised Ring Index\textsuperscript{1} number is 90.
The numbering of 1,3,4-thiadiazole ring follows from (I).

Clockwise or anticlockwise numbering is used according to convenience. In 2- or 5-imino-, or or thiono-, 1,3,4-thiadiazoles, the position of the "extra" hydrogen atom is shown by corresponding number in parentheses, e.g. 1,3,4-thiadiazoline-2(3)-one (II).
PROPERTIES OF 1,3,4-THIADIAZOLES:

Unsubstituted 1,3,4-thiadiazole is colourless stable compound melting at 42° and having no ultraviolet absorption higher than 220 μ. The 1,3,4-thiadiazole ring is susceptible to attack by strong nucleophiles. Thus the parent compound is stable to acids, but it is readily cleaved by bases. Zinc and hydrochloric acid or 30% hydrogen peroxide destroys the ring structure, although 1,3,4-thiadiazole isomer is more stable than 1,2,4-thiadiazole isomer towards peroxide.

It is interesting to note the similarity between the boiling points at atmospheric pressure of 1,3,4-thiadiazole (204°) and pyridazine (208°).

According to albert² 1,3,4-thiadiazole ring is π-excessive, the presence of two nitrogen atoms of pyridine type in the ring leaves the carbon atoms with rather low electron density and consequently no electrophilic substitutions in the unsubstituted 1,3,4-thiadiazole ring have been recorded. However, a 2-amino group does activate the ring towards electrophilic agents, since Bak et al.⁴ could prepare 2-amino-5-bromo-1,3,4-thiadiazole by bromination of 2-amino-1,3,4-thiadiazole in 40% hydrobromic acid. The product was not
isolated but was diazotized in situ to give 2,5-dibromo-1,3,4-thiadiazole.

Amino thiadiazoles are rather weak bases, they are nucleophilic enough to be readily acylated by acid chlorides, and they are easily sulphonated by aromatic sulphonyl chloride. Deacylation is generally performed in hot acid solution without destroying the ring.

2-Acylamino-1,3,4-thiadiazole has been reduced with lithium aluminiumhydride to the corresponding 2-alkylamino derivatives.

2-Amino-5-aryl-1,3,4-thiadiazoles have been found to undergo the Mannich reaction with a variety of methylene compounds.

Schiff bases are formed by reaction between 2-amino-1,3,4-thiadiazoles and aromatic aldehyde, when \( R = \text{NH}_2 \), only a monocondensation product is formed.
In most cases 2-amino-1,3,4-thiadiazoles are alkylated on the ring nitrogen atom in position-3.

\[
\begin{align*}
\text{H}_2\text{N} - \text{C} - \text{Ph} & \rightarrow \text{Ph} - \text{C} - \text{NH}_2\text{I}^- \\
& + \text{Et.I} \rightarrow 
\end{align*}
\]

2-Acylamino and 2-tosylamino-1,3,4-thiadiazoles are alkylated in the same position by alkyl halides in alkaline medium.

One case is known, however, where the base directs the alkylating agents. 2-Acetylamino-5-benzylthio-1,3,4-thiadiazole was methylated in the ring by methyl bromide, and sodium methoxide (a) but in the acetylamino group by methyl iodide and potassium tert-butoxide in tert-butyl alcohol (b).
Bacchetti has found new ways to ring-alkylated iminothiadiazolines, starting from 0-chlorobenzaldehyde hydrazones.

\[ \text{Ph-C-Cl} = \text{N.NHR} + \text{CS(NH}_2\text{)}_2 \rightarrow \text{Ph-C} = \text{N.NHR} \quad \text{Cl}^- \]

\[ \text{Ph-C-Cl} = \text{N.NHR} + \text{SCN} \rightarrow \left[ \text{Ph-C} = \text{N.NHR} \quad \text{SCN} \right] \]
Amino-1,3,4-thiadiazoles are diazotized in strong acidic medium and diazotized amines may also be coupled to form azo-dyes. When 2,5-diamino-1,3,4-thiadiazole is diazotized in strong hydrochloric acid, only the mono-diazonium salt is formed, coupling with phenol produces 2-(\(\gamma\)-hydroxyphenyl azo)-5- amino-1,3,4-thiadiazole.

Chemistry of 1,3,4-thiadiazoles has been summarized in reviews.\(^{14-16}\)
PRESENT WORK.

A large number of 1,3,4-thiadiazole derivatives exhibit a wide variety of activities such as anticonvulsant, antihistaminic, carbonic anhydrase inhibitor, diuretic, tuberculostatic, bacteriostatic, acaricidal, light and ray protective and also they are useful in the protection against infection in the gastrointestinal tract.

In this laboratory Parikh and Trivedi have synthesized several 1,3,4-thiazolyl alcloic-acid basic amides and esters. Some of these compounds possess surface anesthetic and intradermal anesthetic properties.

It was therefore of considerable interest to prepare basic amides from substituted amino-thiadiazoles. The compounds described in Part-II have been prepared as per scheme shown below:

\[ \text{R-C-NH}_{2} + \text{ClCH}_{2}\text{COCl} \rightarrow \text{R-C-NHOCH}_{2}\text{Cl} \]
Where \( R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7(\text{iso}), \text{G}_4\text{H}_9(\text{n}), \text{G}_4\text{H}_9(\text{iso}), \text{C}_5\text{H}_{11}, \text{C}_6\text{H}_5, \text{C}_6\text{H}_5\text{CH}_2, \text{o-NO}_2\text{-C}_6\text{H}_4, \text{p-NO}_2\text{-C}_6\text{H}_4, \text{o-OHC}_6\text{H}_4, \text{p-OCH}_3\text{-C}_6\text{H}_4, \text{p-Cl-C}_6\text{H}_4. \)

\( \text{HNR}_1\text{R}_2 = \text{Diethylamine, Morpholine, Piperidine.} \)
Some important methods for the preparation of 1,3,4-thiadiazoles required in the present work are discussed below. These methods fall into four main groups.

(A) Cyclization reactions.

(B) Cyclo condensation reactions.

(C) Oxidative cyclization reactions.

(D) Replacement reactions.

(A) CYCLIZATION REACTIONS:

(1) FROM THIOSEMICARBAZIDE:

1,3,4-Thiadiazoles have been prepared by the cyclization of thiosemicarbazides with hot concentrated hydrochloric acid\(^\text{26}\) by boiling with inert solvents\(^\text{27, 28}\), N-dichloromethylene aniline\(^\text{29}\), concentrated sulphuric acid\(^\text{30}\), acetylchloride\(^\text{31}\), benzoyl chloride\(^\text{32}\), phosphoric acid\(^\text{30, 33}\) and formic acid\(^\text{34}\).
1,3,4-Thiadiazoles also have been prepared by the cyclization of 3-acyldithiocarbazic esters with acids.\textsuperscript{35, 36}

\[
\begin{align*}
0 & \quad S \\
R-\text{O-NH-NH-C-S-}R^1 & \quad H^+ \\
\end{align*}
\]

Mechanism of above reaction is shown below:
Many 1,3,4-thiadiazoles have been prepared by cyclization of bithiourea or its derivatives in the presence of hydrochloric acid, phosgene and other reagents. \(^{37-39}\)

\[
\begin{align*}
S & \quad S \\
R-NH-C-NH-NH-C-NHR & \quad \rightarrow \\
\text{HS} & \quad C-NHR + \quad \text{HS} & \quad C-SH
\end{align*}
\]

(3) \underline{FROM BITHIOUREA} \:-

(3) \underline{CYCLOCONDENSATION REACTIONS} \:-

(1) \underline{FROM THIOSEMICARBAZIDES} \:-

Many 1,3,4-thiadiazoles have been prepared by condensing thiosemicarbazides with a variety of reagents.
(a) ACYL HALIDE

\[ \text{HgN-CS-ME-Hg} + R^+ \text{COO}^{-} \rightarrow \text{R-CO-NH}_{2} \]

(b) CARBONICACIDE IN THE PRESENCE OF SODIUM CARBONATE AND ALCOHOLIC ALKALI

(i) \[ \text{R-NH-C-NH-NH}_{2} + \text{CS}_{2} + \text{Na}_2\text{CO}_3 \rightarrow \text{R-CO-NH}_{2} \]

(ii) \[ \text{H}_2\text{N-C-NH-NH}_{2} + \text{CS}_{2} \xrightarrow{\text{KOH}} \text{KS-C-NH-NH-C-NH}_{2} \]

Heat \[ \xrightarrow{130-40^\circ C} \]

\[ \text{KS-C} - \text{C-NH}_{2} \]
(iii) \[ S \overset{H_2N-C-NH-NH_2 + CS_2}{\longrightarrow} \overset{(i) \text{CH}_3I}{\longrightarrow} \overset{(ii) \text{Alcoholic alkali}}{\longrightarrow} \]

\[ \text{SCH}_3 \quad S \]

\[ \text{NH} = \overset{1}{\text{C}} - \text{NH-NH} - \overset{\text{C}}{\text{S}} - \text{CH}_3 \]

\[ \overset{H^+}{\longrightarrow} \]

\[ \text{H}_2\text{N}- \]

\[ \overset{\text{N}}{\text{C}} - \overset{\text{S}}{\text{CH}_3} \]

(C) CARBOXYLIC ACID IN THE PRESENCE OF CONCENTRATED SULFURIC ACID. \[31, 44, \]

\[ \overset{S}{\text{R-NH-C-NH-NH}_2 + R^1\text{-COOH}} {\overset{\text{Con.}}{\longrightarrow}} \overset{\text{H}_2\text{SO}_4}{\longrightarrow} \]

\[ \text{R}^1 \overset{\text{O}}{\text{C}} - \overset{\text{NHR}}{\text{C-NHR}} \]

(d) \[ N-N^1\text{-DIPHENYL CARBODIAMIDE} \[45, \]

\[ \overset{S}{\text{R-NH-C-NH-NH}_2 + \text{Ph-N} = \overset{\text{C}}{\text{= N-Ph}} \]

\[ \overset{S}{\text{C-(NHPH)}} \]

\[ \overset{\text{R-NH-C-NH-N}}{\longrightarrow} \overset{\text{Ph-NH-}}{\longrightarrow} \]

\[ \text{C-NHPh} \]
(e) **ETHYL ORTHO FORMATE OR ETHYL CHLOROPROPIONATE**

\[
\text{H}_2\text{N} \overset{\text{S}}{\text{O}} \text{NH-NH}_2 + \text{HCO(OCH}_3\text{H}_2)_{3} \xrightarrow{\text{Steam-bath \ overnight}} \]

\[
\text{H}_2\text{N} \overset{\text{S}}{\text{O}} \text{NH-NH}_2 + \text{HOCOCH}_3\text{H}^+ \xrightarrow{\text{Hydrolysis.}} \]

(f) **POTASSIUM XANTHATE.**

\[
\text{R-NH-O-NH-NH}_2 + \text{C}_2\text{H}_5\text{OC-SK} \rightarrow \text{HS-C-O-NHR} \]

(g) **N-DICHLOROMETHYLENE ANILINE.**

\[
\text{R-NH-O-NH-NH}_2 + \text{Ph-N = C-Cl}_2 \rightarrow \text{Ph-NH-C-R} \]
(h) **CARBOXYLIC ACID CHLORIDE IN THE PRESENCE OF PHOSPHORUS TRICHLORIDE**\(^{49}\) AND CONCENTRATED SULFURIC ACID\(^{50-54}\).  

\[
S \quad R-NH-C-NH-NH_2 + R^1-COCl \rightarrow R^1-CO-NHR
\]

(1) **CARBOXYLIC ACID ESTER IN THE PRESENCE OF PHOSPHORUS TRICHLORIDE**\(^{54}\).  

\[
S \quad R-NH-C-NH-NH_2 + R^1-COOR \xrightarrow{\text{POCl}_3} R^1-CO-NHR
\]

(2) **FROM AMINOGUANIDINES**  

Many 1,3,4-thiadiazoles have been prepared by cyclization of aminoguanidines in the presence of thioacetylation agents. Thus thioacylation of aminoguanidines with carboxymethyl dithiobenzoate
gives N-(Thiobenzamido) guanidines, which are cyclized by hot hydrochloric acid to 2-amino-5-phenyl-1,3,4-thiadiazole and acetic anhydride to the corresponding derivatives.

\[
\begin{align*}
\text{N-NH}_2 & \quad \text{Thioacylation} \quad \text{N-NH-C-Ph} \\
\text{H}_2\text{N} - \text{C} - \text{NH}_2 & \quad \rightarrow \quad \text{H}_2\text{N} - \text{C} - \text{NH}_2 \\
\text{N-NH-C-Ph} & \quad \text{S} \\
(\text{i}) \quad \text{H}_2\text{N} - \text{C} - \text{NH}_2 + \text{HCl} & \quad \rightarrow \quad \text{Ph-C-S-C-NH}_2 \\
\text{S} & \quad \text{N-NH-C-Ph} \\
(\text{ii}) \quad \text{H}_2\text{N} - \text{C} - \text{NH}_2 + \text{AC}_2\text{O} & \quad \rightarrow \quad \text{Ph-C-S-C-NHAC} \\
\end{align*}
\]

Aminoguanidines in the presence of isothiocyanates gives 1-amidino thiosemicarbazides. Thiadiazoles were obtained by cyclization of 1-amidinothiosemicarbazides in acidic media. 56, 57
Many 1,3,4-thiadiazoles have been prepared by cyclizing thionocarbazates with cyanogen chloride and cyanogen bromide. 58

Arylcyanates serve the same purpose in reaction with thiobenzhydrazide. 59

\[
\begin{align*}
\text{Ph-C-NH-NH}_2 + \text{Ar-O-C} & \equiv \text{N} \rightarrow \text{Ph-C-NH-N} = \text{C} \left(\begin{array}{c}
\text{NH}_2 \\
\text{OAr}
\end{array}\right) \\
\text{Cyclization} & \rightarrow \text{Ph-C} \equiv \text{C-NH}_2
\end{align*}
\]
(4) **FROM Dihydrazides**

Many 1,3,4-thiadiazoles have been prepared from dihydrazides e.g. preparation of diamine, bis \( \left( \text{-5-} \right) \) (2-amino-1,3,4-thiadiazolyl) \( \text{7 from oxalic acid dihydrazide} \). 

\[
\begin{align*}
\text{R-G-HH-NH-C-R} & \quad \text{P}_{2}\text{S}_{5} \\
\text{O-NH-NH}_{2} & \quad \text{O-NH-NH-C-NH}_{2}
\end{align*}
\]

(5) **FROM Hydrazines**

Many 1,3,4-thiadiazoles have been prepared by condensing 5-diarylhydrazines with phosphorus pentasulphide. \( 61,62 \)

\[
\begin{align*}
\text{R-C-NH-NH-C-R} & \quad + \quad \text{P}_{2}\text{S}_{5} \\
\text{O-NH-NH-C-NH}_{2} & \quad \text{R-C-S-C-R}
\end{align*}
\]
For example, preparation of 2-benzhydryl-5-phenyl-1,3,4-thiadiazoles from \( N,N' \)-diphenyl acetyl \( N', N' \)-benzoylhydrazines.\(^6\)

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} \\
\text{OH-C-NH-C-Ph} & + \quad \text{P}_2\text{S}_5 & \longrightarrow \\
\text{Ph} & \quad & \\
\end{align*}
\]

Many 1,3,4-thiadiazoles have been prepared by condensing 1,5-diphenyl thiocarbohydrazone with phosgene.\(^6\)

\[
\begin{align*}
\text{S} \quad & \quad \text{Ph-N = N-C-NH-NH-Ph} + \quad \text{CSCl}_2 & \longrightarrow \\
\quad & \quad \text{Ph-N} & \quad \text{N} \quad \text{N} \\
\quad & \quad \text{S-C} & \quad \text{C-N=N-Ph} \\
\quad & \quad \text{S} & \quad \text{S} \\
\end{align*}
\]

2-phenylazo-4-phenyl-1,3,4-thiadiazole-5-(4)thione.

\[
\begin{align*}
\text{(NH}_4\text{)}_2\text{Sx} & \quad \text{Reduction} \quad \rightarrow \\
\text{Ph-N} & \quad \text{N} \quad \text{N} \\
\text{S-C} & \quad \text{C-NHNHP} \phantom{Ph} \\
\text{S} & \quad \text{S} \\
\end{align*}
\]
Many 1,3,4-thiazoles have been prepared from dithiocarbazates. Dithiocarbazic esters may be converted to thiosemicarbazidodithiocarbazic esters by the action of thiocyanic acid, alkylisothiocyanates, or aryl isothiocyanates. The thiosemicarbazide derivatives may be cyclized to 1,3,4-thiadiazoles by the action of mild acid or heat.43,65

For example, preparation of 2-methylmercapto-5-mercapto-1,3,4-thiadiazole from methyl dithiocarbazate and potassium thiocyanate.43

\[
\begin{align*}
S & \\
H_2N-NH-C-S-CH_3 + KSCN \xrightarrow{HCl} \\
\xrightarrow{\text{(H}_2N-C-NH-NH-C-SOH}_3) \\
\text{HS-C-SCH}_3
\end{align*}
\]
Many 1,3,4-thiadiazoles have been prepared by condensing thiobenzohydrazine or dithiocarbazic acids with aliphatic aldehydes. 66, 67

\[
S
\]

\[
R-\text{NH-NH-C-R} + R''-\text{CHO} \rightarrow \text{Structure}
\]

Many 1,3,4-thiadiazoles have been prepared by condensing thioacylhydrazines with ethylorthoformate. 68

\[
S
\]

\[
R-\text{C-NH-NH}_2 + \text{HCl}(\text{CH}_3\text{C}_2\text{H}_5)_3 \rightarrow \text{Structure}
\]
Thiobenzhydrazines are converted to the 1,3,4-thiadiazoles by the action of ethyl orthoacetate, formic acid and xanthogenic acid. For example, preparation of 2-ethoxy-5-phenyl-1,3,4-thiadiazole.

\[
\begin{align*}
(1) & \quad \text{Et-O-C-S-CH}_2\text{-C-OH} + \text{H}_2\text{N-NH-C-Ph} \rightarrow \\
& \quad \text{Et-O-C-NH-NH-C-Ph} \\
\text{(A)}
\end{align*}
\]

\[
\begin{align*}
(\text{ii}) & \quad \text{Et-O-C-NH-NH}_2 + \text{Ph-C-CH}_2\text{-C-OH} \rightarrow \\
& \quad \text{Et-O-C-NH-NH-C-Ph} \\
\text{(A)}
\end{align*}
\]

\[
\begin{align*}
(\text{iii}) & \quad \text{Et-O-C-NH-NH-C-Ph} \rightarrow \\
& \quad \text{Et-O-C-NH-NH-C-Ph} \\
\text{2-ethoxy-5-phenyl-1,3,4-thiadiazole}
\end{align*}
\]
Many 1,3,4-thiadiazoles have been prepared by condensing bithioureas with acetic anhydride. The acetyl groups are easily removed by hydrolysis to give parent thiadiazole.

\[
\text{H}_2\text{N-C-NH-NH-C-NH}_2 + (\text{CH}_2\text{CO}_2 \text{O})_2 \rightarrow \text{AC-NH-C-NHAC}
\]

(1) **FROM BITHIOUREAS**

(0) **OXIDATIVE CYCLIZATION REACTIONS**

(1) **FROM THIOSEMICARBAZONES**

Many 1,3,4-thiadiazoles have been prepared from thiosemicarbazones by their oxidative cyclization with sulfonyl chloride, cadmium ferricyanide, and hydrogen peroxide.

\[
\text{R-OH} = \text{N-NH-C-NH}_2 \rightarrow \text{R-O-C-NH}_2
\]
(2) \textbf{FROM DITHIOCARBAZATES}\textemdash

Many 1,3,4-thiadiazoles have been prepared by oxidative cyclization of dithiocarbazates with ferric chloride\textsuperscript{79} and formic acid\textsuperscript{36}.

\[
\begin{align*}
\text{S} \\
R-\text{CH} = \text{N}-\text{NH-C-SR'} \quad \rightarrow \\
\text{N} \\
& \quad \text{R-C} \\
& \quad \text{C-S-R'}
\end{align*}
\]

(3) \textbf{FORM BITHIOUREAS}\textemdash

Many 1,3,4-thiadiazoles have been prepared by treating bithiourea with 3\% hydrogen peroxide\textsuperscript{30}.

\[
\begin{align*}
\text{S} & \quad \text{S} \\
\text{NH}_2-C-\text{NH-NH-C-NH}_2 \quad \rightarrow \\
\text{N} & \quad \text{N} \\
& \quad \text{H}_2\text{N-C} \\
& \quad \text{C-NH}_2
\end{align*}
\]
Many 1,3,4-thiadiazoles have been prepared by replacement reactions. In this method 1,3,4-thiadiazoles have been prepared by replacing the oxygen atom of the corresponding 1,3,4-oxadiazoles by sulphur atom. The oxygen atom of 1,3,4-oxadiazole is replaced by refluxing it with phosphorus pentasulphide in an inert solvent like benzene, toluene, xylene and ligroin.

\[
\text{R-C} \quad \text{O-R} \quad + \quad \text{P}_2\text{S}_5 \quad \text{Benzene} \quad \rightarrow \quad \text{R-C} \quad \text{S-R}
\]

The 1,3,4-thiadiazole derivatives required for the present work were prepared by the following methods.

1. By the condensation of thiosemicarbazide with carboxylic acid in presence of concentrated \( \text{H}_2\text{SO}_4 \).
(ii) By oxidative cyclization of thiosemicarbazones with ferric chloride

\[
\begin{align*}
R^1\text{-COOH} + R\text{-NH\text{-C-NH-NH}_2} & \xrightarrow{\text{CO}_n\cdot\text{H}_2\text{SO}_4} \\
& \xrightarrow{\text{FeCl}_3\cdot6\text{H}_2\text{O}} \\
R\text{-CH = N-NH\text{-C-NH}_2} & \xrightarrow{} \\
\end{align*}
\]
EXPERIMENTAL - II
METHODS FOR THE PREPARATION OF 2-AMINO-5-ALKYL-1,3,4-
THIADIAZOLES

(A) A mixture of 120 g. acetic acid, 100 g. concentrated sulphuric acid and 60 g. thiosemicarbazide is boiled for 2 hours, cooled, poured into 400 g. ice-water, and neutralised with 200 cc. of 28% ammonium hydroxide to give 70 g. of product.

Ref: G. Fanatsukuri and M. Ueda
(Sumito Chemical Co., Ltd.)
Japan 20, 944, Dec. 7, 1966;

(B) A well-stirred mixture of 0.3 mole of fatty acid, 31.5 ml. of concentrated sulphuric acid, and 0.25 mole of thiosemicarbazide was slowly heated to 80-90 and maintained at that temperature for 7-hours. After the reaction mixture was cooled, it was poured into ice-water and made basic with concentrated ammonia. The crude product, which precipitated upon addition of ammonia, was filtered and washed with water. It was recrystallised from alcohol-water.

Ref: Francis L. Chubb and Jaqueline Nissenbaum,
Compounds prepared by the above methods is shown below:

![Chemical structure](image)

2-Amino-5-alkyl-1,3,4-thiadiazoles.

<table>
<thead>
<tr>
<th>R</th>
<th>M.P. °C.</th>
<th>Method used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>223</td>
<td>A</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>196</td>
<td>A</td>
</tr>
<tr>
<td>C₃H₇(n)</td>
<td>203-206</td>
<td>B</td>
</tr>
<tr>
<td>C₃H₇(iso)</td>
<td>182-185</td>
<td>B</td>
</tr>
<tr>
<td>C₄H₉(n)</td>
<td>194-196</td>
<td>B</td>
</tr>
<tr>
<td>C₄H₉(iso)</td>
<td>228-230</td>
<td>B</td>
</tr>
<tr>
<td>C₅H₁₁</td>
<td>194-196</td>
<td>B</td>
</tr>
</tbody>
</table>
METHOD FOR THE PREPARATION OF SUBSTITUTED-BENZHYDRAZIDES.

All the benzhydrazides were prepared according to the method described in Experimental Part-III.

Following were prepared in addition to those described in Experimental Part - III.

R.CO(NH)NH₂

<table>
<thead>
<tr>
<th>R</th>
<th>M.P.°C</th>
<th>Reference</th>
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<tbody>
<tr>
<td>C₆H₅-CH₂</td>
<td>116</td>
<td>Curtius and Boetzelien</td>
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<td></td>
<td></td>
<td>J. Prakt. Chem. 54, 314</td>
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<td></td>
<td>(1901).</td>
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<td>o-NO₂-C₆H₄</td>
<td>123</td>
<td>Curtius, Traochmann</td>
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<td>J. Prakt. Chem. 51</td>
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<tr>
<td></td>
<td></td>
<td>168 (1895).</td>
</tr>
<tr>
<td>p-NO₂-C₆H₄</td>
<td>210</td>
<td>-do -</td>
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</table>
METHODS FOR THE PREPARATION OF 2-AMINO-5-SUBSTITUTED PHENYL/BENZYL-1,3,4-THIADIAZOLES.

(A) A mixture of the finely powdered thiosemicarbazones of appropriate aldehyde (0.05 mole) and ferric chloride hexahydrate (0.2 mole) in ethanol (450 ml.) was heated slowly on a water-bath with stirring to gentle reflux and the refluxing was continued for 45-minutes. Most of the alcohol was distilled off under reduced pressure. The residue and treated with concentrated hydrochloric acid (40 ml.) and cooled in ice-salt bath for 2-hours. The precipitated hydrochloride, collected and washed with concentrated hydrochloric acid (2 X 20 ml.). The free-base was liberated with aqueous ammonia and mixture was heated on water-bath for 15-minutes. The aminothiadiazole was extracted from iron residue with boiling ethanol. Concentration of ethanolic extract give crude amino compound.

Following were prepared by the above method.

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

2-amino-5-substituted phenyl-1,3,4-thiadiazoles.

<table>
<thead>
<tr>
<th>R</th>
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</thead>
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<tr>
<td>4-0CH$_3$-O$_6$H$_4$</td>
<td>187-9</td>
</tr>
<tr>
<td>4-01-0$_6$H$_4$</td>
<td>229-30</td>
</tr>
</tbody>
</table>

(B) \( p-\text{NO}_2C_6H_4\text{CONNH}_2 \) (3.6 g.) in 2 g. concentrated HCl and 30 ml. water, heated 2-hours on a water bath with 2.5 g. KSCN, cooled, and the product filtered and recrystallized from hot water gives 2 g of \( R-\text{CONHNHCNH}_2 \) were \( R = \text{NO}_2C_6H_4 \). Similarly following, were prepared.

\[
\begin{array}{ccc}
\text{R} & \text{M}_{p,0}^\circ & \\
\text{p-NO}_2C_6H_4 & 214 & \\
\text{o-NO}_2C_6H_4 & 210 & \\
\text{C}_6H_5 & 198 & \\
\text{C}_6H_5\text{CH}_2 & 183-84 & \\
o-\text{OH} & 202 & \\
\end{array}
\]

The above compounds, portionwise to 10 times its wt. or concentrated sulphuric acid with cooling, let stand 15 minutes, the solution was poured on to ice, neutralized with ammonium hydroxide and the precipitates were recrystallized from the dilute alcohol to give desired aminothiadiazoles.
Following were prepared by the above method.

![Diagram](image)

2-amino-5-substituted phenyl/benzyl-1,3,4-thiadiazoles.

<table>
<thead>
<tr>
<th>R</th>
<th>M.P.°C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-NO$_2$-C$_6$H$_4$</td>
<td>232-34</td>
</tr>
<tr>
<td>p-NO$_2$-C$_6$H$_4$</td>
<td>260</td>
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<tr>
<td>C$_6$H$_5$</td>
<td>225</td>
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<tr>
<td>C$_6$H$_5$OH$_2$</td>
<td>203</td>
</tr>
<tr>
<td>o-OH-C$_6$H$_4$</td>
<td>233</td>
</tr>
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</table>

METHODS FOR THE PREPARATION OF 2-(6-CHLOROACETANIDO)-5-
ALKYL-1,3,4-THIADIAZOLEs 

(A) A mixture of the respective, amino-thiadiazole
(0.1 mole) and 10% excess chloroacetylchloride
(0.11 mole) was refluxed for 3-5 hours with mechanical
stirring. The reaction mixture was cooled, filtered
and the precipitates separated, was washed with
benzene and dried in air to give the desired compounds.

Ref.: Gagiu, F.; Dajcoviciu C.; Binder, Ursula
25th 1965, 1, 151-54 (Fr.) Chem. Abstr.

(B) To 7.87 g. 2-amino-5-propyl-1,3,4-thiadiazole
in 100 cc. benzene, 6.98 g. of monochloroacetylchloride
in 10 cc. benzene was added, the mixture was refluxed
for 5-6 hours. The benzene was distilled off, 20 cc.
of H_2O added and PH was brought to 7 with 4% NaHCO_3
solution.

1010-12 (Fr. Chem. Abstr. 67 82164b (1967).
Compounds prepared by the above methods are shown below:

\[
\begin{align*}
\text{R} & \quad \text{C} & \quad \text{O} & \quad \text{S} & \quad \text{O-NHCOCH₂Cl} \\
\text{CH₃} & \quad 232-3 & \quad \text{A} \\
\text{C₂H₅} & \quad 208-9 & \quad \text{A} \\
\text{C₃H₇(n)} & \quad 202-3 & \quad \text{B} \\
\text{C₃H₇(iso)} & \quad 187 & \quad \text{B} \\
\text{C₄H₉(n)} & \quad 198 & \quad \text{B} \\
\text{C₄H₉(iso)} & \quad 174 & \quad \text{B} \\
\text{C₅H₁₁} & \quad 189 & \quad \text{B}
\end{align*}
\]
METHODS FOR THE PREPARATION OF 2-(<CHLOROACETAMIDO)-5-
SUBSTITUTEDPHENYL/BENZYL-1,3,4-THIADIAZOLES:

(A) A mixture of the respective, amino-thiadiazole
(0.1 mole) and 10% excess chloroacetylchloride (0.11 mole)
was refluxed for 3-5 hours with mechanical stirring. The
reaction mixture was cooled, filtered and the precipitates
separated, was washed with benzene and dried in air to
give the desired compounds.

Ref.:- Gagiu, F.; Dajcoviciu C.; Binder, Ursula
25th 1965, 1, 151-54 (Fr.) Chem.

(B) The 5-substituted-2-amino-1,3,4-thiadiazoles
(0.01 mole) were dissolved in 30-40 ml. benzene and
treated with (0.011 mole) monochloroacetylchloride with
stirring. After refluxing 6-12 hours, the benzene was
separated by distillation, the residue was neutralised
with 5% NaHCO₃ solution, filtered off, dried and
recrystallised.

Ref.:- F. Gagiu and A. Mavrodin ( Oncological Inst.,
Cluj, Romania ) Pharmazie, 22 (8), 434-36
### 2-(\(\alpha\)-Chloroacetamido)-5-substituted phenyl/benzyl-1,3,4-thiadiazoles.

<table>
<thead>
<tr>
<th>R</th>
<th>M. P. °C.</th>
<th>Method used.</th>
<th>% of Nitrogen</th>
<th>% of Sulphur</th>
<th>% of Halogen</th>
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<td>(\text{C}_6\text{H}_5)</td>
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<td>A</td>
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<td>-</td>
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<tr>
<td>(\text{C}_6\text{H}_5-\text{CH}_2)</td>
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<td>A</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(\text{p-NO}_2\text{C}_6\text{H}_4)</td>
<td>261-62</td>
<td>B</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>(\text{p-Cl-C}_6\text{H}_4)</td>
<td>226-27</td>
<td>B</td>
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<td>-</td>
<td>-</td>
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<td>(\text{p-OCH}_3\text{C}_6\text{H}_4)</td>
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<td>B</td>
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<tr>
<td>(\text{o-NO}_2\text{C}_6\text{H}_4)</td>
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<td>18.08</td>
<td>10.60</td>
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<tr>
<td>(\text{o-OH-C}_6\text{H}_4)</td>
<td>238-40</td>
<td>B</td>
<td>15.42</td>
<td>15.53</td>
<td>11.70</td>
</tr>
</tbody>
</table>

\(\text{R} = \text{phenyl/benzyl-1,3,4-thiadiazoles}\)
GENERAL METHOD FOR THE PREPARATION OF 2-O-DIALKYLAMINO-ACETAMIDO-5-ALKYL/ARYL/BENZYL-1,3,4-THIADIAZOLES.:

2-(2-Chloroacetamido)-5-alkyl/aryl/benzyl-1,3,4-thiadiazole (0.01 mole), absolute alcohol (40.0 ml.), anhydrous sodium carbonate (1.09 g.) and secondaryamine (0.01 mole) were placed in a round bottomed flask fitted with reflux condensor. The reaction mixture was refluxed on a water-bath for twelve hours with occasional shaking. The reaction mixture was cooled and the alcohol was distilled off under reduced pressure. The residue was treated with water (50.0 ml), and filtered, washed with water and dried. The crude amino compound from aqueous alcohol.

Compounds prepared by the above method is shown in Table I & II.
TABLE I.

\[
\begin{array}{c}
R - C \quad \text{G -NHCOCH}_2\text{NR}_1\text{R}_2 \\
\end{array}
\]

2-OC-Secondaryamino-acetamido-5-alkyl-1,3,4-thiadiazole.

<table>
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<tr>
<th>R</th>
<th>NR$_1$R$_2$</th>
<th>Molecular Formula</th>
<th>M.P. $^\circ$C</th>
<th>% of Nitrogen Found</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Sulphur Found</th>
<th>% of Sulphur Calcd.</th>
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</thead>
<tbody>
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<td>24.56</td>
<td>14.10</td>
<td>14.03</td>
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<td>$C_9H_{14}N_4O_2S$</td>
<td>136</td>
<td>23.00</td>
<td>23.14</td>
<td>13.30</td>
<td>13.22</td>
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<tr>
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<td>13.33</td>
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<tr>
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<td>23.14</td>
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<td>13.22</td>
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<td>21.87</td>
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<td>12.50</td>
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<td>(4)</td>
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<td>(8)</td>
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<td>20.74</td>
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<td>20.89</td>
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<td>11.94</td>
</tr>
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<td>$C_4H_9(n)$</td>
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<td>20.74</td>
<td>11.80</td>
<td>11.85</td>
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<tr>
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<td>$C_{12}H_{20}N_4O_2S$</td>
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<td>19.63</td>
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<td>(1)</td>
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<tr>
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<td>19.71</td>
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</table>
### TABLE II.

![Chemical structure](image)

2-**O**-Secondaryamino-acetamido-5-substituted phenyl/benzyl-1,3,4-thiadiazole.

<table>
<thead>
<tr>
<th>R</th>
<th>NR&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Molecular Formula</th>
<th>M.P.°C.</th>
<th>% of Nitrogen</th>
<th>% of Sulphur</th>
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<td>Calcd.</td>
</tr>
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<td>% of Nitrogen</td>
<td>Found</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;^-</td>
<td>Diethylamino</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;S</td>
<td>109</td>
<td>19.25</td>
<td>19.31</td>
</tr>
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<td>18.42</td>
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<td>18.51</td>
<td>18.54</td>
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<td>18.31</td>
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<td>17.61</td>
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<tr>
<td>p-Cl-C_6H_4</td>
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<td>16.54</td>
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<td>17.50</td>
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<td>17.59</td>
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</tr>
<tr>
<td>o-NO₂-C₆H₄</td>
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<td>20.71</td>
<td>20.80</td>
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<td>20.05</td>
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REFERENCE - II
REFERENCES.


(14) Bambas L. L., "Five membered Heterocyclic Compounds" P. 81, Wiley (Inter Science), New York, (1952).


(38) Busch M., Schmidt W., Chem. Ber., 46, 2240 (1913).


(64) Freund H., Chem. Ber. 23, 283 (1890), ibid., 24, 4178 (1891).


