THEORETICAL - PART - II
Compounds having a five-membered ring containing one sulphur and two nitrogen atoms are called thiadiazoles or in the older literature thiobiazoles. There are four classes of oxadiazoles and thiadiazoles.

(a) 1:2:3-THIADIAZoles

(Diazosulphides)

(1) Compounds containing this ring system are obtained by the action of hydrogen sulphide on (aliphatic) diazo oxides (L. Wolff, Ann. 1904, 233, 1; H. Wieland and S. Bloch, Ber., 1906, 39, 1491)

(2) Pechmann and Nold allowed diazomethane to react with phenylisothiocyanate and obtained 5-anilino-1,2,3-thiadiazole.
C\text{H}_2\text{NCS} + \text{H}_2\text{C} = \text{N} \rightarrow \text{C}_6\text{H}_5\text{N} = \text{C} \quad \text{or} \quad \text{C}_6\text{H}_5\text{NH}-\text{N}

(3) Mazak and suszko (Roczniki Chem., 1929, 2, 431; Chem. Abstracts, 1929, 22, 4187) prepared \text{A}^3-1,2,3-Thiadiazoline-5-dioxides, according to the following reactions.

\begin{align*}
\text{CH}_3\text{COCH}_2\text{C}1 + \text{K}_2\text{SO}_3\cdot2\text{H}_2\text{O} & \rightarrow \text{CH}_3\text{COCH}_2\text{SO}_3\text{K} \\
\text{CH}_3\text{COCH}_2\text{SO}_3\text{K} + \text{C}_6\text{H}_5\text{NNNH}_2 & \rightarrow \text{CH}_3\text{C} \cdot \text{CH}_2\text{SO}_3\text{K} \\
\text{CH}_3 \text{C} \cdot \text{CH}_2\text{SO}_3\text{K} + \text{PCl}_3 & \rightarrow \text{H}_2\text{C} \cdot \text{N} - \text{C}_6\text{H}_5 \\
\text{CH}_3 \text{C} \cdot \text{C}_6\text{H}_5 & \text{N-NH} \quad \text{PCl}_3
\end{align*}

(b) Benzo-1:2:3-thiadiazoles

These compounds, called "diazosulphides" in the older literature, are formed by the action of nitrous acid.
on o-aminothiophenols (P. Jacobson et al, Ann., 1893, 277. 209) or o-aminobenzethiosulphonic acids (Glayton aniline Co., G.P. 120,504, Friedl., 5, 88):

They are stable, weakly basic compounds which add alkyl halides to give quaternary salts and show resemblance to naphthalene rather than to benzene in their substitution reactions (Hodgson and D. P. Dodgson, J. Soc. Dy. Col., 1948, 64 65.)

(C) 1:2:5-THIADIAZOLE.

The 1:2:5-thiadiazole ring is known in the piazthioles, which are benzo (1:2:3:4)-1:2:5-thiadiazoles. These compounds are obtained by reaction of o-phenylenediamines with sulphur dioxide, solutions of sulphurous acid or thionyl chloride (O. Hinsberg, Ber., 1889, 22, 2895; Bayer and Co., Gif., 49191, Friedl. 2,534):
Benzo-1:2:5-selenadiazoles, piazselenols, closely resemble the piazoles and are readily obtained from o-phenylenediamines and selenium dioxide or selenious acid. They are weakly basic and form quaternary salts which can be obtained directly from N-substituted o-phenylenediamine salts and selenious acid (M. Battegay and J. Vechot, Bull. Soc. Chim. Fr., 1925, 27, (iv), 1271):

(d) 1:2:4-Thiadiazoles

(azosulphimes)

(1) Amidoximes with carbon disulphide give 1:2:4-thiadiazoles (G. Crayen. Ber., 1891, 24, 388)

(3) The action of oxidising agents on N-arylthioureas gives di-iminothiazolidines (the products of this reaction were originally formulated as 1:3:4-thiadiazoles) (D.S. Hector, *Ber.*, 1890, 23, 357, 1892, 25, 799): 

\[ \text{PhC} \quad \text{N} \quad \text{C} \quad \text{Ph} \]

(4) Koch (*Ber.*, 1891, 24, 394), working in Tiemann's laboratory (*Ber.*, 1891, 24, 369), found that by condensing phenyl isothiocyanate and benzhydroxamidine in refluxing chloroform 3-phenyl-5-anilino-1,2,4-thiadiazole was formed.

\[ \text{C}_6\text{H}_5\text{NCS} + \text{C}_6\text{H}_5\text{C}=\text{NOH} \rightarrow \text{C}_6\text{H}_5\text{NH} - \text{C} - \text{C}_6\text{H}_5 \]

(e) **1,3,4-THIADIAZOLES**

A few of the important methods used for the preparation of 1,3,4-thiadiazoles and related compounds are described below:

(1) By reaction of 5-diacylhydrazines with phosphorus pentasulphide (R. Stolle, *Ber.*, 1899, 32, 797; Brit. patent


(4 b) Aliphatic aldehydes condense with dithiocarbazinic acids or thiobenzoylhydrazine derivatives to give dihydro-1:3:4-thiadiazoles (thiadiazolines) (M. Bush, Ber, 1895, 28, 2635; H. Wuyts and A. Lacourt, Chem. Abstract, 1934, 28, 3407):
(5) Cyclisation of derivatives of hydrazine NH$_2$N'-thiadi-
carboxylic acid may give a 1:3:4-triazole derivative depending
upon conditions (F. Arndt and F. Bielich, Ber., 1923, 56,
2276). Thus the diamide NH$_2$.CS.NH.NH.CS.NH$_2$ under acid
condition gives a mixture of the thiadiazoles (I) and (II)
(M. Busch et al, J. Pr. Chem., 1914, (ii) 20, 257) and with
acetic anhydride the diacetyl derivative of (II) shown as (III)
exclusively (P. C. Guha, J. Amer. Chem. Soc., 1923, 45, 1036)

\[
\begin{align*}
\text{(I)} & : \quad \text{NH}_2.C & \quad \text{C-SH} \\
\text{(II)} & : \quad \text{NH}_2.C & \quad \text{C.NH}_2 \quad \text{AC.NHC} & \quad \text{C-NH.AC} \\
\text{(III)} & : \quad \text{R} \quad \text{NH.C} & \quad \text{NH.NH} & \quad \text{SH} \quad \text{N} & \quad \text{R} \quad \text{NH.C} & \quad \text{NH.NH} & \quad \text{SH} \\
\end{align*}
\]

(6) Reaction of a thiosemicarbazide with carbon disulphide
in presence of Na$_2$CO$_3$ (V. Petrov et al, Brit. patent 801, 394,
sept. 10, (1958) - Chem. Abstract 1959, 52, 6255)

\[
\text{R-NH.C} \quad \text{NH.NH} & \quad \text{SH} \quad \text{N} & \quad \text{R-NH.C} \quad \text{NH.NH} & \quad \text{SH} \\
\text{CS}_2 & \quad \text{Na}_2\text{CO}_3 & \quad \text{R-NH.C} \quad \text{NH.NH} & \quad \text{SH} \\
\]

(7) Reacting a thiosemicarbazide with a carboxylic acid in
presence of con. H$_2$SO$_4$. (Francis et al, Can. J. Chem., 1959,
(8) Fusco, et al., (Gozz. Chem. Ital., 1937, 67, 3; ibid., 1938, 68, 147; ibid., 1938, 68, 665; Rend. ist. lombardo sci., 1938, 71, 425) prepared 2,4-diphenyl-5-imino-1,3,4-thiadiazoline from \( \alpha \)-chlorobenzalphenylhydrazone and thiourea.

The 1,3,4-thiadiazole-5-(4)-thiones were prepared in a similar manner from potassium xanthate and \( \alpha \)-halobenzalphenylhydrozones.
Freund and co-workers (Ber., 1890, 22, 2831; ibid 1891, 24, 4178) investigated the reaction between thiophosgene and 1,5-diphenylthiocarbohydrazone and found that 2-phenylazo-4-phenyl-1,3,4-thiadiazole-5(4)-thione was produced. Reduction of this compound with ammonium sulfide yield the 2-p-phenylhydrazino-4-phenyl-1,3,4-thiadiazole-5(4)-thione.

(I) \[ C_6H_5N=NCSNH NH C_6H_5 \]

\[ \text{CSCl}_2 \]

\[ S =C \]

\[ CN=NC_6H_5 \]

\[ C_6H_5.N \]

\[ N \]

(II) \[ S=CN=NC_6H_5 \]

\[ C_6H_5.N \]

\[ N \]

\[ (NH_4)_2Sx \]

\[ S=C \]

\[ CNH.NHC_6H_5 \]

\[ C_6H_5.N \]

\[ N \]
(10) 2-Mercapto - $\Delta^2$ - 1,3,4-thiadiazolines

Busch (Ber., 1895, 28, 2635) found that aldehydes reacted with 2-substituted dithiocarbazic acids to give 2-mercapto-4- and 5-substituted $\Delta^2$ - 1,3,4-thiadiazolines. Formaldehyde, acetaldehyde, and benzaldehyde were used in this reaction. Busch and Best (J.pract.Chem., 1899, (z) 60, 225) also made 5,5-dialkyl - $\Delta^2$ - 1,3,4-thiadiazolines by allowing ketones such as acetone and methylethyl ketone to react with 2-phenyl-dithiocarbazic acid. Acetophenone did not react with either the acid or the ester.

\[
\begin{align*}
R' \text{NH NH CSSK} + \text{RCHO} \rightarrow \\
\text{CH}_3\text{COCH}_3 + \text{KSSCNH NH C}_6\text{H}_5 \rightarrow (\text{CH}_3)_2\text{C}^{\text{CSK}} \text{C}_6\text{H}_5, N \rightarrow N
\end{align*}
\]

The 2-thioethers were prepared by alkylating the 2-mercapto group or by forming the ring with an ester of a dithiocarbazic acid and an aldehyde.

\[
\begin{align*}
\text{C}_6\text{H}_5, \text{NH NH CSS CH}_3 + \text{C}_6\text{H}_5\text{CHO} \rightarrow \text{C}_6\text{H}_5, C \rightarrow \text{C}_6\text{H}_5, N \rightarrow N
\end{align*}
\]

Methods (2), (3), (6), and (7) were used to prepare 2,5-(disubstituted)-1,3,4-thiadiazoles described in this part.
The following table shows the different 2,5-(disubstituted)-1,3,4-thiadiazoles prepared:

**Method (2):**

\[
\begin{align*}
\text{RCH} & \quad \text{CS} \quad \text{NH}_2 \\
\overset{\text{oxidative}}{\longrightarrow} & \\
\text{R} & \quad \text{C} \quad \text{C} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

**Method (3):**

\[
\begin{align*}
R \quad \text{NH} & \quad \overset{\text{S}}{\text{C}} \quad \text{NH} \quad \text{NH}_2 + \quad R' \text{COCl} \\
\downarrow & \\
R \quad \text{NH} & \quad \text{C} \quad \text{NH} \quad \text{NH} \quad \text{CO} \quad \text{R}' \\
\downarrow & \\
\text{acid} & \\
R \quad \text{NH} & \quad \text{C} \quad \text{C} \quad \text{R}'
\end{align*}
\]

**Method (6):**

\[
\begin{align*}
R \quad \text{NH} & \quad \overset{\text{S}}{\text{C}} \quad \text{NH} \quad \text{NH}_2 + \quad \text{CS}_2 \quad \overset{\text{Na}_2\text{CO}_3}{\longrightarrow} \quad R \quad \text{NH} \quad \text{C} \quad \text{C} \quad \text{SH}
\end{align*}
\]

**Method (7):**

\[
\begin{align*}
R \quad \text{NH} & \quad \overset{\text{S}}{\text{C}} \quad \text{NH} \quad \text{NH}_2 + \quad R' \quad \text{COOH} \quad \overset{\text{H}_2\text{SO}_4}{\longrightarrow} \quad R \quad \text{NH} \quad \text{C} \quad \text{R}'
\end{align*}
\]
<table>
<thead>
<tr>
<th>No.</th>
<th>Name of Thiadiazole</th>
<th>M. P.</th>
<th>Method used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2-m-chlorophenylamino-5-phenyl-1:3:4-thiadiazole</td>
<td>197</td>
<td>(2)</td>
</tr>
<tr>
<td>2.</td>
<td>2-m-chlorophenylamino-5-p-methoxyphenyl-1:3:4-thiadiazole</td>
<td>264</td>
<td>(2)</td>
</tr>
<tr>
<td>3.</td>
<td>2-m-chlorophenylamino-5-o-chlorophenyl-1:3:4-thiadiazole</td>
<td>231</td>
<td>(2)</td>
</tr>
<tr>
<td>4.</td>
<td>2-m-chlorophenylamino-5-p-chlorophenyl-1:3:4-thiadiazole</td>
<td>280</td>
<td>(2)</td>
</tr>
<tr>
<td>5.</td>
<td>2-m-chlorophenylamino-5-p-hydroxyphenyl-1:3:4-thiadiazole</td>
<td>250</td>
<td>(2)</td>
</tr>
<tr>
<td>6.</td>
<td>2-p-chlorophenylamino-5-phenyl-1:3:4-thiadiazole</td>
<td>220</td>
<td>(2)</td>
</tr>
<tr>
<td>7.</td>
<td>2-p-chlorophenylamino-5-o-hydroxyphenyl-1:3:4-thiadiazole</td>
<td>158</td>
<td>(2)</td>
</tr>
<tr>
<td>8.</td>
<td>2-p-chlorophenylamino-5-p-hydroxyphenyl-1:3:4-thiadiazole</td>
<td>238</td>
<td>(2)</td>
</tr>
<tr>
<td>9.</td>
<td>2-p-chlorophenylamino-5-p-methoxyphenyl-1:3:4-thiadiazole</td>
<td>222</td>
<td>(2)</td>
</tr>
<tr>
<td>10.</td>
<td>2-p-chlorophenylamino-5-o-chlorophenyl-1:3:4-thiadiazole</td>
<td>250</td>
<td>(2)</td>
</tr>
<tr>
<td>11.</td>
<td>2-p-chlorophenylamino-5-(2:4-dichlorophenyl)-1:3:4-thiadiazole</td>
<td>272</td>
<td>(2)</td>
</tr>
<tr>
<td>12.</td>
<td>2-p-bromophenylamino-5-phenyl-1:3:4-thiadiazole</td>
<td>228</td>
<td>(2)</td>
</tr>
<tr>
<td>13.</td>
<td>2-p-bromophenylamino-5-p-chlorophenyl-1:3:4-thiadiazole</td>
<td>274</td>
<td>(2)</td>
</tr>
<tr>
<td>14.</td>
<td>2-p-bromophenylamino-5-o-chlorophenyl-1:3:4-thiadiazole</td>
<td>253</td>
<td>(2)</td>
</tr>
<tr>
<td>15.</td>
<td>2-p-bromophenylamino-5-(2:4-dichlorophenyl)-1:3:4-thiadiazole</td>
<td>264</td>
<td>(2)</td>
</tr>
<tr>
<td>16.</td>
<td>2-p-bromophenylamino-5-p-hydroxyphenyl-1:3:4-thiadiazole</td>
<td>304</td>
<td>(2)</td>
</tr>
</tbody>
</table>
17. 2-p-bromophenylamino-5-m-hydroxyphenyl-1,3:4-thiadiazole 192 (2)
18. 2-p-bromophenylamino-5-p-dimethylaminophenyl-1,3:4-thiadiazole 178 (2)
19. 2-p-bromophenylamino-5-p-methoxyphenyl-1,3:4-thiadiazole 174 (2)
20. 2-p-methoxyphenylamino-5-phenyl-1,3:4-thiadiazole 156 (2)
21. 2-p-methoxyphenylamino-5-p-chlorophenyl-1,3:4-thiadiazole 197 (2)
22. 2-p-methoxyphenylamino-5-o-chlorophenyl-1,3:4-thiadiazole 214 (2)
23. 2-p-methoxyphenylamino-5(2:4-dichlorophenyl)-1,3:4-thiadiazole 212 (2)
24. 2-p-methoxyphenylamino-5-p-methoxyphenyl-1,3:4-thiadiazole 160 (2)
25. 2-p-methoxyphenylamino-5-o-methoxyphenyl-1,3:4-thiadiazole 200 (2)
26. 2-p-methoxyphenylamino-5-p-methoxyphenyl-1,3:4-thiadiazole 183 (2)
27. 2-p-methylphenylamino-5-phenyl-1,3:4-thiadiazole 194 (2)
28. 2-p-methylphenylamino-5-p-chlorophenyl-1,3:4-thiadiazole 213 (2)
35. 2-p-methylphenylamino-5-p-chlorophenyl-1:3:4-thiadiazole 226 (2)
36. 2-p-methylphenylamino-5-(2:4-dichlorophenyl)-1:3:4-thiadiazole 217 (2)
37. 2-p-methylphenylamino-5-o-hydroxyphenyl-1:3:4-thiadiazole 226 (2)
38. 2-p-methylphenylamino-5-p-methoxyphenyl-1:3:4-thiadiazole 177 (2)
39. 2-m-methylphenylamino-5-phenyl-1:3:4-thiadiazole 171 (2)
40. 2-m-methylphenylamino-5-(2:4-dichlorophenyl)-1:3:4-thiadiazole 244 (2)
41. 2-m-methylphenylamino-5-o-chlorophenyl-1:3:4-thiadiazole 200 (2)
42. 2-m-methylphenylamino-5-p-chlorophenyl-1:3:4-thiadiazole 218 (2)
43. 2-m-methylphenylamino-5-p-methoxyphenyl-1:3:4-thiadiazole 158 (2)
44. 2-p-chlorobenzylamino-5-o-chlorophenyl-1:3:4-thiadiazole 167 (2)
45. 2-p-chlorobenzylamino-5-p-chlorophenyl-1:3:4-thiadiazole 175 (2)
46. 2-p-chlorobenzylamino-5-p-o-hydroxyphenyl-1:3:4-thiadiazole 195 (2)
47. 2-p-chlorobenzylamino-5-phenyl-1:3:4-thiadiazole 162 (2)
48. 2-p-chlorobenzylamino-5-m-hydroxyphenyl-1:3:4-thiadiazole 160 (2)
49. 2-p-chlorobenzylamino-5-p-dimethylaminophenyl-1:3:4-thiadiazole 178 (2)
50. 2-o-methylphenylamino-5-benzyl-1:3:4-thiadiazole 149 (3)
51. 2-p-methylphenylamino-5-benzyl-1:3:4-thiadiazole 165.6 (3)
52. 2-m-methylphenylamino-5-benzyl-1:3:4-thiadiazole 142.3 (3)
53. 2-o-methoxyphenylamino-5-benzyl-1:3:4-thiadiazole 111.2 (3)
<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.</td>
<td>2-p-methoxyphenylamino-5-benzyl-1:3:4-thiadiazole</td>
<td>160 (3)</td>
</tr>
<tr>
<td>55.</td>
<td>2-p-chlorophenylamino-5-benzyl-1:3:4-thiadiazole</td>
<td>181-8 (3)</td>
</tr>
<tr>
<td>56.</td>
<td>2-m-chlorophenylamino-5-benzyl-1:3:4-thiadiazole</td>
<td>145-6 (3)</td>
</tr>
<tr>
<td>57.</td>
<td>2-p-bromophenylamino-5-benzyl-1:3:4-thiadiazole</td>
<td>199-200 (3)</td>
</tr>
<tr>
<td>58.</td>
<td>2-p-chlorobenzylamino-5-benzyl-1:3:4-thiadiazole</td>
<td>135-6 (3)</td>
</tr>
<tr>
<td>59.</td>
<td>2-p-chlorophenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>224 (6)</td>
</tr>
<tr>
<td>60.</td>
<td>2-m-chlorophenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>231 (6)</td>
</tr>
<tr>
<td>61.</td>
<td>2-p-methylphenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>216-7 (6)</td>
</tr>
<tr>
<td>62.</td>
<td>2-o-methylphenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>215 (6)</td>
</tr>
<tr>
<td>63.</td>
<td>2-m-methylphenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>225 (6)</td>
</tr>
<tr>
<td>64.</td>
<td>2-o-methoxyphenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>195 (6)</td>
</tr>
<tr>
<td>65.</td>
<td>2-p-methoxyphenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>181-2 (6)</td>
</tr>
<tr>
<td>66.</td>
<td>2-p-bromophenylamino-5-mercapto-1:3:4-thiadiazole</td>
<td>232 (6)</td>
</tr>
<tr>
<td>67.</td>
<td>2-o-methylphenylamino-5-n-propyl-1:3:4-thiadiazole</td>
<td>124-5 (7)</td>
</tr>
<tr>
<td>68.</td>
<td>2-o-methylphenylamino-5-ethyl-1:3:4-thiadiazole</td>
<td>152-4 (7)</td>
</tr>
<tr>
<td>69.</td>
<td>2-o-methylphenylamino-5-aminomethyl-1:3:4-thiadiazole</td>
<td>212-3 (7)</td>
</tr>
<tr>
<td>70.</td>
<td>2-o-methylphenylamino-5-chloromethyl-1:3:4-thiadiazole</td>
<td>142-3 (7)</td>
</tr>
</tbody>
</table>