CHAPTER IV

Bis[1-aryl-3-methyl-5-oxo-$\Delta^2$-1,2,4-triazol-4-yl]
PURPOSE OF WORK

In the previous chapter we studied the ring transformation reaction of 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazoles with nucleophilic reagents like hydrazine hydrate. The resulting compounds 4-amino-1-aryl-3-methyl-\(\Delta^2\)-5-oxo-1,2,4-triazoles contained a potential amino group which undergoes reactions typical of a primary amino group. Now, we thought of carrying out the ring conversion of 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazoles with the above N-aminotriazoles, which would also serve as nucleophilic reagents. With this simple reaction we have prepared the so far unknown N-N\'-bis-1,2,4-triazoles. Though many fused bis heterocyclic compounds are known, there are very few examples of bisheterocyclic systems wherein the two heterocyclic rings are joined through the ring heteroatoms.

PRESENT WORK

The 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazoles were condensed with 4-amino-aryl-3-methyl-\(\Delta^2\)-5-oxo-1,2,4-triazoles at high temperature to get the 4-N-N\'-bis-[(1-aryl-3-methyl-\(\Delta^2\)-5-oxo)-1,2,4-triazoles]. The N-amino group of the 1,2,4-triazoles being less basic, the reaction takes place at a very slow rate. These bisis triazoles were also prepared by reaction of the 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazoles with 2:1 mole of hydrazine hydrate in pyridine. During the present work we have synthesised some symmetrical bis-1,2,4-triazoles.
SCHEME

\[ \text{[Reactions and structures]} \]
The formation of the bistriazoles is confirmed by the IR, $^1$H & $^{13}$C -NMR & Mass spectral data. The IR spectra show the absence of bands for $\nu_{\text{NH}_{2}}$ and two C=O bonds are observed at 1809 and 1795 cm$^{-1}$ due to symmetric and asymmetric $\nu_{C=O}$ (similar to anhydride C=O).

$^1$H-NMR spectra of all these compounds show the presence of a singlet at $\delta$ 2.4 (6 H) for the two methyl groups. 4,4'-Dichloro-N,N-bis triazole (Spectrum No-16) shows two doublets (4H each) in the aromatic region for the phenyl ring protons. Magnetic equivalency is observed for the CH$_3$ protons and the two sets of aromatic protons.

However, the 13C-NMR spectrum (spectrum No 17 & 18) shows two signals for the two methyl groups at $\delta$ 10.7 and 11.7 ppm. Similarly, eight weak singlets are observed for the eight quartenary carbon atoms indicating the magnetic non-equivalence of the carbon atoms in both the halves of the molecule. This could be explained by assuming that one triazole ring acts as an electron withdrawing group on the other triazole ring. Hence the carbon atoms of one half of the molecule appear deshielded, and accordingly the assignment of the signals has been made. The carbons carrying chlorine (C-10 & C-10') appear at $\delta$ 116.7 and 129.7 respectively. Signals at $\delta$ 134.9 and 137.1 are due to C-7 and C-7'. The C-3 and C-3' carbons appear at $\delta$ 147.1 and 150.5. These are the highly shielded carbons due to the adjacent heteroatoms. The C=O carbons of C-5 and C-5' are observed as the most deshielded carbons at $\delta$ 151.3 and 154.6.

The formation of the bis compound is also confirmed by its mass spectrum (No.19 ) which shows molecular ions at m/z 417(CI 35.5), 419 and 421.
This agrees with the molecular weight of the compound and also the presence of two chlorine atoms. The base peak at m/e 125 and its isotopic peak at m/e 127 (3:1) obtained by the major fragmentation are assigned to the following fragment. This fragment loses Nitrogen to give the fragment at m/e 111 & 108 (3:1).
SPECTRAL DATA

N,N'-bis-[1-p-(chloro)phenyl]-3-methyl-5-oxo-Δ²-1,2,4-triazole.

IR SPECTRUM:
SPECTRUM No.15

1795 cm⁻¹, 1809 cm⁻¹ : for two νC=O

1597 cm⁻¹, 1645 cm⁻¹ : νC=N for two bis triazole

¹H-NMR SPECTRUM:
SPECTRUM No.16

δ 2.4 (s, 6H) : C₃ and C₃'-methyl protons

δ 7.5 (d, 2H J 7.8 Hz) : 4 protons of aromatic ring A in AA' Pattern

δ 7.8 (d, 2H J 7.7 Hz) : 4 protons of aromatic ring B in BB' pattern
BIOLOGICAL PROPERTIES OF 1,2,4-BIS TRIAZOLES

Though some bis-1,2,4-triazoles are reported in the literature, none of them have the two heterocyclic rings joined through the ring N-N bond.

Katritzky, Alan R; Pastor et al (1) synthesized 1,1-bis(1,2,4-triazol-1-yl)-bases (A) as potential aromatase inhibitors.

Reactions of 1,1'-sulfonylbis[1H-1,2,4-triazol] with carbonyl compounds lead to the formation of twelve corresponding alkylidene bis[triazole] derivatives having structures resembling closely some previously prepared aromatase inhibitors.

\[
\text{(A)}
\]

Chu, Chang-Hu; Hui, Xin-ping (2) and co-workers prepared w-[4-aryl-5-(1-phenyl-5-methyl-1,2,3-triazol-4-yl)-1,2,4-triazol-3-thio]-w-(1H-1,2,4-triazol-1-yl)acetophenones and studied their antifungal activities.

Wang, Zhongyi (3) prepared prepared (s) 1,2-bis(3-aryl-[1,2,4] triazolo-[3,4-b][1,3,4]thiadiazol-6-yl)-ethylamine by condensation of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles (aryl = ph, 3-NO2, 4-EtO, 2-MeOC6H4, C6H5OCH2) with different L-amino acids (L-proline, L-alanine, l-aspartic acid) in the presence of phosphorous oxychloride and evaluated their antibacterial activity.

Panasenko,O.I; Shevchenko et al(4). synthesized 1,2-bis(1,2,4-triazoly1-5-thio) ethanes and studied their biological activity.

1,2,4-Triazoline-5-thiones were N-alkylated with dibromomethane. Antimicrobial, antifungal, diuretic, anti-inflammatory and sedative activity and acute toxicity of obtained compounds were studied.
Wang, Zhongyi; Shi, et. al. (5) synthesized 1,3-bis(2-phenyl-1,3,4-triazol-5-yl-thio)propane, 1,2-bis[2-9m-nitrophenyl]-1,3,4-triazol-5-yl-thio] ethane, showed bacterial activity at 0.002%.

Shah, V; Pant, C.K; Joshi, P. C. Jr (6) synthesized and studied antifungal activity of bis-1,4-(5-mercapto-4-aryl-1,2,4-triazol-3-yl) benzenes (B) and still more related compounds (B) were screened for their antifungal activity against Aspegillus florus, Helminthosporium tetramere and penicillrin decommbens.

![Bis-Mannich reaction product](image)

(B)

Shi, Haijian and other (7) synthesized chiral 5-aryltriazolo[3,4-b]-3-a-phenylethyl-2,4-2H-1,3,5-thiadiazines by bis-Mannich reactions. Seven novel title compounds were synthesized by bis Mannich reaction of 3-aryl-5-mercapto-1,2,4-triazole, formalin and 5-(-)-α-phenylethylamine in the presence of acid. These heterocyclic compounds were screened for anti-bacterial activities and some possess strong biological activities.
EXPERIMENTAL:

1. Preparation of symmetrical bis[1-3-methyl-5-oxo-Δ²-1,2,4-triazoles. General Procedure.

   a. A mixture of 4-amino-3-methyl-1-[p-chlorophenyl]-5-oxo-Δ²-1,2,4-triazole (2.24 g, 0.01 mole) and 3-[p-chlorophenyl]-5-methyl-2-oxo-Δ⁴-1,3,4-oxadiazole (2.10 g, 0.01 mole) in 10 ml dry DMF was refluxed on a oil bath at 240°C for 8 hrs. The reaction mixture was then cooled and poured into water. The solid separated was filtered, washed with water and dried. The compound was further purified by crystallization from absolute ethanol.

   b. A mixture of 3-[p-chlorophenyl]-5-methyl-2-oxo-Δ⁴-1,3,4-oxadiazole (2.10 g, 0.01 mole) and hydrazine hydrate (3 ml, 0.02 mole) in dry pyridine was refluxed on a oil bath for 15 hrs. The reaction mixture was then cooled, and poured in ice water; the excess of pyridine in the mixture was neutralized slowly by adding cold and diluted HCl with constant stirring. The resulting solid was filtered, washed with water and dried. The compound was purified by absolute alcohol.

Similarly were prepared the other bis-triazoles are listed in Table No.23.
CHARACTERISATION DATA OF COMPOUNDS

\[
\text{N,N'-bis-[1-aryl]-3-methyl-5-oxo-A} \text{2-1,2,4-triazoles}
\]

Table No.23

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<tr>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>M.P. °C</th>
<th>Molecular Formula</th>
<th>Elemental Analysis Found &amp; (Calc)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C% (Calc)</td>
</tr>
<tr>
<td>4-Cl</td>
<td>H</td>
<td>60</td>
<td>172-75</td>
<td>C\text{\textsubscript{18}}H\text{\textsubscript{14}}N\text{\textsubscript{6}}O\text{\textsubscript{2}}Cl\text{\textsubscript{2}}</td>
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<tr>
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<td>58</td>
<td>198-99</td>
<td>C\text{\textsubscript{18}}H\text{\textsubscript{14}}N\text{\textsubscript{6}}O\text{\textsubscript{2}}Br\text{\textsubscript{2}}</td>
<td>45.60 (45.56)</td>
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<tr>
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<td>63.75 (63.77)</td>
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<tr>
<td>4-OCH\text{\textsubscript{3}}</td>
<td>H</td>
<td>59</td>
<td>150-51</td>
<td>C\text{\textsubscript{20}}H\text{\textsubscript{20}}N\text{\textsubscript{6}}O\text{\textsubscript{4}}</td>
<td>58.80 (58.78)</td>
</tr>
<tr>
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<td>54</td>
<td>152-54</td>
<td>C\text{\textsubscript{20}}H\text{\textsubscript{20}}N\text{\textsubscript{6}}O\text{\textsubscript{4}}</td>
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</tr>
<tr>
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<td>C\text{\textsubscript{18}}H\text{\textsubscript{12}}N\text{\textsubscript{6}}O\text{\textsubscript{2}}Cl\text{\textsubscript{4}}</td>
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<td>3-Cl</td>
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<td>60</td>
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<td>C\text{\textsubscript{20}}H\text{\textsubscript{20}}N\text{\textsubscript{6}}O\text{\textsubscript{2}}Cl\text{\textsubscript{2}}</td>
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<tr>
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RESULTS OF ANTIMICROBIAL SCREENING

The antimicrobial testing of bis-1,2,4-triazoles showed very weak antibacterial activity against *E.coli* and *C.bacillus* when compared to the standard drug Norfloxacin. Only the 4-methyl (No.3), 4-methoxy (No.4) and 2-methoxy(No.5) substituted bis-triazoles showed slightly higher antifungal activity against *pencillum* and *A. candida*, while the others were found to exhibit activity equal to that of the reference compound. (Table No. 24)
ANTIMICROBIAL ACTIVITY OF COMPOUNDS

\[
N,N'-\text{bis-}[1\text{-aryl}] - 3\text{-methyl-5-oxo-}\Delta^2\text{-1,2,4-triazoles}
\]

Table No.24

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<td>15</td>
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<td>15</td>
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</tr>
<tr>
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<td>H</td>
<td>14</td>
<td>_</td>
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Reference

<table>
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<tr>
<th>Reference</th>
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<th>C-bacillus mm</th>
<th>Pencillium mm</th>
<th>A-candida mm</th>
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<td>34</td>
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<tr>
<td>Griseofulvin</td>
<td>_</td>
<td>_</td>
<td>17</td>
<td>18</td>
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</table>

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Reference:

1. Katritzky, Alan. R; Pastor, Alfredo; Voronkov, Michael. V.

2. Chu, Chang-Hu; hui, Xin-Ping; Zhang, Yan; Zhang, Zi-Yi; Li, Zhi-Chun; Liao, Ren-An

3. Wang, Zhongyi; Shi, Haoxin; Shi, Haijian,

4. Panasonko. O. I; Sherchenko, I. M; et. al

5. Wang, Zhongyi; Shi, Haijian; Shi, Haoxin

6. Shah, R; Pant. C. K; Joshi, P. C. Jr

7. Shi, Haijiani Wong, Zhongyi; Shi, Haoxin