CHAPTER-V

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Synthesis and \textsuperscript{13}C NMR spectral analysis of 10-substituted-5, 10-dihydrophenarsazines.

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Compounds of arsenic have been used as therapeutic agents for over 2500 years\textsuperscript{268,269} and it was believed that arsenic compounds were of value in the treatment of infectious diseases, skin disorders, asthma etc. Arsenicals were used for a long time and with considerable success for the treatment of a variety of spirochetal and protozoal diseases. Butarsen\textsuperscript{270} has been tried extensively for treating human trypanosomiasis in Africa. The drug is highly effective in early infections.

Aromatic arsenicals have been of considerable importance in the control of intestinal amoebiasis. Some derivatives were earlier used for the oral therapy of syphilis\textsuperscript{271} and were later found to be useful for the treatment of amoebic dysentery\textsuperscript{272}. Various studies have been directed toward the 'isosteric' replacement of the heteroatoms of the phenothiazine ring system\textsuperscript{273}. In particular, the sulfur atom has been replaced by other heteroatoms which have included oxygen, selenium and arsenic. Phenothiazine has been utilized as an anthelmintic for the past 30 years\textsuperscript{274}. Its action against a wide variety of nematode species in numerous hosts has been reviewed\textsuperscript{275,276}. Craig and Tate\textsuperscript{277} have reviewed the chemotherapeutic activity of derivatives
and analogues of phenothiazine. Isenbrandt et al.\textsuperscript{278} have reported $^{13}$C NMR spectra of phenothiazine, phenoxazine and several other isosterically related systems. Jay and his co-workers\textsuperscript{152} have reported the $^{13}$C NMR spectra of 10-chloro-5,10-dihydrophenarsazine (XXIX). In view of these reports, author's attention was directed towards the synthesis of 10-chloro-5,10-dihydrophenarsazine (XXIX) and replace chlorine by morpholino and diethylamino groups with the hope that these derivatives may be biologically active\textsuperscript{279}.

10-Chloro-5,10-dihydrophenarsazine (XXIX) was prepared from diphenylamine and arsenic trichloride in xylene according to the known procedure\textsuperscript{280}. The compound XXIX was reacted with morpholine and diethylamine to procure 10-morpholino- (XXX) and 10-diethylamino-5,10-dihydrophenarsazine (XXXI) to undertake $^{13}$C NMR spectral analysis of XXIX, XXX and XXXI. For the compound XXIX, $^{13}$C NMR spectral data reported by Jay and Martin\textsuperscript{152} was taken as authentic. The chemical shifts of various carbons of compounds XXIX-XXXI are appended in table-5.1.

In $^{13}$C NMR spectrum of the compound XXIX under completely decoupled mode of irradiation, it has been observed that the carbons C-1 and C-9 flanking the arsenic have been
XXX : $X = \begin{array}{c}\text{} \\
\text{} \end{array}$

XXXI : $X = N(CH_2CH_3)_2$

1. AsCl$_3$  2.  3. HN(CH$_2$CH$_3$)$_2$
\[ ^{13}C \text{ Chemical shifts of 10-substituted phenarsazines in } \delta_{\text{ppm.}} \]

(substituent chemical shifts in parenthesis)*

<table>
<thead>
<tr>
<th>Carbon atom</th>
<th>XXIX</th>
<th>XXX</th>
<th>XXXI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1/C-9</td>
<td>135.10</td>
<td>135.50</td>
<td>137.38</td>
</tr>
<tr>
<td></td>
<td>(0.40)</td>
<td>(2.28)</td>
<td></td>
</tr>
<tr>
<td>C-2/C-8</td>
<td>119.86</td>
<td>119.23</td>
<td>120.90</td>
</tr>
<tr>
<td></td>
<td>(-0.63)</td>
<td>(1.04)</td>
<td></td>
</tr>
<tr>
<td>C-3/C-7</td>
<td>132.13</td>
<td>131.32</td>
<td>128.38</td>
</tr>
<tr>
<td></td>
<td>(-0.81)</td>
<td>(-3.75)</td>
<td></td>
</tr>
<tr>
<td>C-4/C-6</td>
<td>116.50</td>
<td>115.90</td>
<td>116.82</td>
</tr>
<tr>
<td></td>
<td>(-0.60)</td>
<td>(0.32)</td>
<td></td>
</tr>
<tr>
<td>C-9a/C-10a</td>
<td>120.78</td>
<td>135.94</td>
<td>145.75</td>
</tr>
<tr>
<td></td>
<td>(15.16)</td>
<td>(24.97)</td>
<td></td>
</tr>
<tr>
<td>C-4a/C-5a</td>
<td>140.14</td>
<td>150.42</td>
<td>151.13</td>
</tr>
<tr>
<td></td>
<td>(10.28)</td>
<td>(10.99)</td>
<td></td>
</tr>
<tr>
<td>C-2'/C-2&quot;</td>
<td>-</td>
<td>60.56</td>
<td>19.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-3'/C-3&quot;</td>
<td>-</td>
<td>87.50</td>
<td>57.45</td>
</tr>
</tbody>
</table>

* Positive substituent shifts indicate deshielding and negative substituent shifts shielding.
found to be downfield as compared to the carbons C-4 and C-6 which are found to be most upfield protonated carbons. Out of the carbons C-2/C-8 and C-3/C-7, the carbons C-2/C-8 resonated upfield as compared to carbons C-3/C-7. Out of the bridge carbons, the carbons C-4a and C-5a, which are flanking the nitrogen are downfield as compared to the carbons flanking the arsenic i.e. the carbons C-9a and C-10a. In the $^{13}$C NMR spectrum of 10-morpholino-5,10-dihydrophenarsazine (XXX), the most downfield resonance at 150.42$\delta$ has been assigned to the carbons C-4a/C-5a, as it remains unsplit in the OFR mode of irradiation. Its downfield shift has been attributed to steric crowding and anisotropy of the C-N bond. The carbons C-9a and C-10a are deshielded even further by ca.15$\delta$ and these effects are as one would expect. The rationale for this shift lies in the electron withdrawal by the nitrogen atom. Amongst the protonated carbons, which are confirmed by their OFR spectra, the signal at 135.50$\delta$ has been assigned to carbons C-1 and C-9 followed by the signal at 131.32$\delta$ which has been ascribed to the carbons C-3 and C-7. Slight upfield shift perhaps may be due to anisotropy of the morpholine ring. Signal at 119.23$\delta$ has been assigned to the carbons C-2 and C-8, whereas the signal at 115.90$\delta$ has been attributed to carbons C-4 and C-6, which have been shifted.
upfield, as expected, because of the electron-releasing mesomeric effect of the nitrogen at the position-5. The morpholine carbons C-3' and C-3" are located at 87.50 $\delta$, whereas the carbons C-2' and C-2" resonate at 60.56 $\delta$. Both these signals get split into a triplet each in its OFR mode of irradiation.

The $^{13}$C NMR spectrum of 10-diethylamino-5,10-dihydro-phenarsazine(XXXI) shows that there is a downfield shift of the carbons C-9a/C-10a as well as C-1 and C-9 with respect to the compound XXIX as well as XXX. This downfield shift is due to the crowding by the two ethyl groups, which is more than that of the morpholino ethylene carbons. Since in the morpholine ring, the ethylene carbons are tied back, whereas in compound (XXXI) these carbons are not tied back and, therefore, the crowding has increased. This trend is in view of the observations that the rate of adduct formation between quinuclidine and trimethylborane is far greater as compared to the triethylamine and trimethylborane. This has been attributed to the removal of the back strain in quinuclidine in comparison of triethylamine. The rationale for deshielding due to steric crowding is not unwarranted. Therefore, the most downfield signal at 151.13 $\delta$ has been assigned to the carbons C-4a and C-5a and the signal at
145.75 $\delta$ has been assigned to the carbons C-9a and C-10a. These assignments are ascribed to the bridge carbons in view of their nonsplitting in the OFR spectrum. The resonance at 137.38 $\delta$ has been assigned to the carbons C-1 and C-9 as it gave doublet in the $^{13}$C NMR spectrum recorded under OFR mode of irradiation. The signal at 128.38 $\delta$ which also gets split in the OFR mode of irradiation has been assigned to carbons C-3 and C-7 and its upfield shift by approximately 3.0 $\delta$ with respect to XXX and approximately 4.0 $\delta$ with respect to XXIX are probably due to change in bond length in the ring system due to steric crowding. The signals at 120.90 $\delta$ and 116.82 $\delta$ have been assigned to the carbons C-2/C-8 and C-4/C-6, respectively. The carbons C-3'/C-3" have been located at 19.05 $\delta$ whereas the carbons C-2'/C-2" resonate at 57.45 $\delta$. 