13C NMR SPECTRA OF SOME SUBSTITUTED 1,2,4-OXADIAZOLES AND 4,5-DIHYDRO-1,2,4-OXADIAZOLES

Rajendra M. Srivastava(a), Leda M. Mendes e Silva(b) and J. Bhattacharyya(b)

(a) Departamento de Química Aplicada, Universidade Federal de Pernambuco; 50739 – Recife (PE), Brazil
(b) Laboratório de Tecnologia Farmacêutica, Universidade Federal de Paraíba; 58000 – João Pessoa (PB), Brazil

Recebido em 06/10/88

ABSTRACT

The 13C NMR spectral characteristics of some 3-aryl-5-methyl-1,2,4-oxadiazoles, 2-5, as well as of the parent compound, 3-phenyl-1,2,4-oxadiazole, I, and of the partially saturated oxadiazoles, 3-aryl-5-methyl-4,5-dihydro-1,2,4-oxadiazoles, 6-9, have been studied and the chemical shifts of all the carbons assigned.

INTRODUCTION

Two reviews1,2 describe the important pharmacological properties which have been found in several substituted 1,2,4-oxadiazoles. Because of this, we have been interested in these substances and in 1984 reported3,4 the synthesis of various 3,5-disubstituted, 1,2,4-oxadiazoles. Although 13C spectra of 1,2,4-oxadiazoles5,6 have been recorded, no substituent effects have been studied. In this communication, we wish to describe the 13C spectral characteristics of compounds I-9 with complete study of the methyl substituent effects on the phenyl ring of 3-phenyl-1,2,4-oxadiazole as well as 3-phenyl-4,5-dihydro-1,2,4-oxadiazole.

EXPERIMENTAL

The 13C NMR spectra were recorded on a Bruker WM 250 spectrometer operating at 62.896 MHz for 0.3 M solution in CDCl3, using 5 mm sample tubes at 297K with TMS as internal standard. The broad band decoupling and DEFT (Driven Equilibrium Fourier Transform) techniques were applied. The typical experimental parameters were: pulse width 5μs (flip angle ca. 90°), acquisition time 0.983s, spectral width 16666 Hz, repetition time 1.017s, about 1000 transients for each spectrum, number of data points 32K, digital resolution 12 and exponential multiplication for sensitivity enhancement with a line broadening factor of 0.5 Hz. The accuracies of the 13C chemical shift are better than ± 0.02 ppm.

RESULTS AND DISCUSSION

The chemical shifts of compounds I-5 are listed in Table 1. The results show that CH3 substituent at C-5 of the heterocyclic ring has very little effect on the chemical shifts of C-3 (ΔδC-3 = +0.6 ppm) which is usual for the other 5-membered ring heterocyclics.5 At the substituted carbon atom, however, the CH3 group induces a rather large downfield shift (+11.8 ppm) which is intermediate between the CH3 substituent effect in C-2 of thiophene and furan.9

There seems to be no effect at C-3 of the 1,2,4-oxadiazole ring when the substituent changes from a phenyl to m- or p-tolyl group. However, a small downfield shift (+0.7 ppm) is observed when the substituent at C-3 is a α-tolyl group. This can be explained on the basis of steric hindrance between the CH3 group and the heterocyclic ring disturbing the planarity between the latter and the phenyl ring. Similar shift of carbonyl carbon is observed when benzophenone is substituted in position 2. Thus carbonyl carbon in 2-methylbenzophenone moves downfield (+1.7 ppm) when compared with benzophenone.10 The authors concluded10 that as the degree of steric interference increases at the ortho position, the carbonyl carbon becomes deshielded.

We determined the substituent effect of the oxadiazole ring on the benzene ring. This was obtained by taking the difference in the chemical shift of compound I or 2 and the benzene ring carbon. These values are shown in table 2.

+ Taken in part from the M.S. thesis (1979) of the author.
Table 1. Carbon-13 Chemical Shift Assignments of some 3-Aryl-1,2,4-oxadiazoles

<table>
<thead>
<tr>
<th>Compound</th>
<th>3</th>
<th>5</th>
<th>1'</th>
<th>2'</th>
<th>3'</th>
<th>4'</th>
<th>5'</th>
<th>6'</th>
<th>C-5-CH₃</th>
<th>Ar-CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>167.8</td>
<td>164.7</td>
<td>126.3</td>
<td>127.6</td>
<td>129.0</td>
<td>131.4</td>
<td>129.0</td>
<td>127.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>168.4</td>
<td>176.5</td>
<td>126.9</td>
<td>127.4</td>
<td>129.8</td>
<td>131.1</td>
<td>128.9</td>
<td>129.0</td>
<td>127.4</td>
<td>12.4</td>
</tr>
<tr>
<td>3</td>
<td>168.4</td>
<td>176.4</td>
<td>124.1</td>
<td>127.3</td>
<td>129.6</td>
<td>141.4</td>
<td>129.6</td>
<td>127.3</td>
<td>12.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Calcd.</td>
<td>164.0</td>
<td>127.3</td>
<td>129.6</td>
<td>140.0</td>
<td>129.6</td>
<td>127.3</td>
<td>129.6</td>
<td>127.3</td>
<td>12.4</td>
<td>21.3</td>
</tr>
<tr>
<td>4</td>
<td>168.5</td>
<td>176.4</td>
<td>126.9</td>
<td>128.0</td>
<td>138.7</td>
<td>131.9</td>
<td>128.8</td>
<td>124.5</td>
<td>12.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Calcd.</td>
<td>162.8</td>
<td>128.1</td>
<td>137.8</td>
<td>131.8</td>
<td>128.8</td>
<td>124.5</td>
<td>12.5</td>
<td>22.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>169.1</td>
<td>175.4</td>
<td>126.3</td>
<td>138.2</td>
<td>130.0</td>
<td>131.4</td>
<td>126.0</td>
<td>130.5</td>
<td>12.2</td>
<td>22.0</td>
</tr>
<tr>
<td>Calcd.</td>
<td>172.7</td>
<td>136.3</td>
<td>129.6</td>
<td>131.0</td>
<td>126.0</td>
<td>127.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \delta_{\text{cal}} = \delta_{\text{exp}} + \delta_{\text{subs}} \]

\( \delta_{\text{cal}} \) being calculated using the experimental values (\( \delta_{\text{exp}} \)) of compound 2 and adding the substituent chemical shifts (\( \delta_{\text{subs}} \)).

Next we turned our attention to 3-aryl-5-methyl-4,5-dihydro-1,2,4-oxadiazoles, 6-9, in order to compare these with compounds 2-5. The carbons 3 and 5 of the heterocyclic ring have gone upfield. The former and the latter have moved up about 12.0 and 86.5 ppm respectively. Another interesting phenomenon was found when a comparison was made between the carbon resonances (C-1', C-2' and C-6') of 3-aryl-5-methyl-1,2,4-oxadiazoles (compounds 2-5) and 3-aryl-5-methyl-4,5-dihydro-1,2,4-oxadiazoles (compounds 6-9). The cited carbons in the latter resonate upfield indicating the lesser electron-withdrawing power of this heterocyclic ring than the 1,2,4-oxadiazole moiety. Table 3 provides the values of the substituent effect of a 4,5-dihydro-1,2,4-oxadiazole function over the benzene ring. The values were obtained in a manner described earlier for Table 2. The calculated values of Table 4 were based on the equation mentioned above for Table 1.

The chemical shifts of the meta and para substituted ring carbon atoms showed remarkable proximity between the calculated and observed values. In other words the additivity rule applies well. When the substituent is in ortho position as in 5, 9, and 10, the shifts of C-1', C-2' and C-6' show the deviation from the additivity law. The C-1' resonates ~1.3 ppm upfield whereas C-2' and C-6' move downfield by ca. 2 to 3 ppm (Tables 1 and 4). The shielding effect of 2-substituent on C-1 in anisole, phenol and biphenyl is known. The steric hindrance due to ortho-substitution upsets the planarity between the heterocyclic and phenyl rings. The attenuation of conjugation leads to the diminution of electron density principally at C-2' and C-6' and also to a lesser extent at C-4'. This causes the downfield shifts of these carbons. Biphenyl on substitution at 2-position with –OH behaved similarly. Substitution of a methyl group at 2-position in diphenyl ether produced the same effect.

It is interesting to compare the chemical shifts (CDCl₃) of benzamidoxime, 11 (the starting material for the synthesis of oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles), with 2 and 6. When the amidoxime function is transformed to 1,2,4-oxadiazole, 2, or 4,5-dihydro-1,2,4-oxadiazole, 6, the C-1' in 2 and 6 move 6.2 and 6.8 ppm upfield. The chemical shift difference of aromatic carbons of completable.
Table 4. Carbon-13 Chemical Shift Assignments of some 3-Aryl-4,5-Dihydro-1,2,4-Oxadiazoles.

$$\text{H}$$

$$\text{N}$$

$$\text{N}$$

$$\text{CH}_3$$

$$\text{R}_2$$

$$\text{R}_1$$

$$\text{R}_3$$

$$\text{R}_4$$

$$\text{R}_5$$

$$\text{1'}$$

$$\text{2'}$$

$$\text{3'}$$

$$\text{4'}$$

$$\text{5'}$$

$$\text{6'}$$

$$\text{C}-\text{5-CH}_3$$

$$\text{Ar-CH}_3$$

<table>
<thead>
<tr>
<th>Compound</th>
<th>3</th>
<th>5'</th>
<th>1'</th>
<th>2'</th>
<th>3'</th>
<th>4'</th>
<th>5'</th>
<th>6'</th>
<th>C-5-CH$_3$</th>
<th>Ar-CH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>156.1</td>
<td>89.8</td>
<td>125.7</td>
<td>126.5</td>
<td>128.7</td>
<td>130.8</td>
<td>128.7</td>
<td>126.5</td>
<td>22.1</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>156.0</td>
<td>89.5</td>
<td>122.9</td>
<td>126.4</td>
<td>129.4</td>
<td>141.2</td>
<td>129.4</td>
<td>126.4</td>
<td>22.1</td>
<td>21.5</td>
</tr>
<tr>
<td>Calcd.</td>
<td>122.8</td>
<td>126.4</td>
<td>129.4</td>
<td>139.7</td>
<td>129.4</td>
<td>126.4</td>
<td>126.4</td>
<td>22.1</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>156.4</td>
<td>89.8</td>
<td>125.5</td>
<td>127.0</td>
<td>138.5</td>
<td>131.6</td>
<td>128.6</td>
<td>123.6</td>
<td>22.0</td>
<td>21.2</td>
</tr>
<tr>
<td>Calcd.</td>
<td>125.6</td>
<td>127.2</td>
<td>137.6</td>
<td>131.5</td>
<td>128.6</td>
<td>123.6</td>
<td>123.6</td>
<td>22.1</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>156.1</td>
<td>88.9</td>
<td>125.1</td>
<td>138.0</td>
<td>130.2</td>
<td>131.3</td>
<td>125.9</td>
<td>128.5</td>
<td>22.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Calcd.</td>
<td>126.4</td>
<td>135.4</td>
<td>129.4</td>
<td>130.7</td>
<td>125.8</td>
<td>126.4</td>
<td>126.4</td>
<td>22.1</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>10$^b$</td>
<td>157.6</td>
<td>90.5</td>
<td>111.9</td>
<td>157.7</td>
<td>118.1</td>
<td>133.6</td>
<td>121.0</td>
<td>129.2</td>
<td>23.2</td>
<td>23.2</td>
</tr>
<tr>
<td>Calcd.</td>
<td>113.0</td>
<td>153.4</td>
<td>116.0</td>
<td>132.2</td>
<td>121.4</td>
<td>127.9</td>
<td>127.9</td>
<td>23.2</td>
<td>23.2</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Calculated relative to benzene (128.5 ppm in CDCl$_3$) with CH$_3$ (for compounds 6-9) or OH (for compound 10) and 5-methyl-4,5-dihydro-1,2,4-oxadiazol-3-yl as substituents.

$^b$ See ref. 12 for the observed chemical shifts. DMSO-d$_6$ was the solvent.

Table 5. Chemical Shift Difference of Aromatic Carbons of Compounds 2 and 6 with respect to Benzamidoxime.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>ortho</th>
<th>meta</th>
<th>para</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-6.2</td>
<td>+1.7</td>
<td>+0.4</td>
<td>+1.5</td>
</tr>
<tr>
<td>6</td>
<td>-6.8</td>
<td>+0.6</td>
<td>+0.1</td>
<td>+0.9</td>
</tr>
</tbody>
</table>

Compounds 2 and 6 were obtained by subtracting the values of benzamidoxime carbons (Table 5).

ACKNOWLEDGMENT

The authors express their gratitude to the Brazilian National Research Council (CNPq) for financial help. Ms. Jane E. Hawkes of Imperial College, London, recorded the $^{13}$C NMR spectra of all compounds for which we are thankful. We are grateful to Dr. R. Kandiyoti for his interest. Thanks are also due to Drs. Fred Fujisawa and Anita J. Marsolli, both from the Universidade Estadual de Campinas, Campinas, São Paulo, for their help and to Marilu L. de Oliveira for technical assistance in the laboratory.

REFERENCES


QUÍMICA NOVA 12(3) (1989) 223