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

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ABSTRACT

The ^{13}C 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, *1*, 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 reviews[1,2] 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 reported[3,4] the synthesis of various 3,5-disubstituted, 1,2,4-oxadiazoles. Although ^{13}C spectra of 1,2,4-oxadiazoles[5,6] have been recorded, no substituent effects have been studied. In this communication, we wish to describe the ^{13}C spectral characteristics of compounds *1-9* 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 ^{13}C NMR spectra were recorded on a Bruker WM 250 spectrometer operating at 62.896 MHz for 0.3 M solution in $CDCl_3$ 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 0.983 s, spectral width 16,666 Hz, repetition time 1.017 s, 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 ^{13}C chemical shift are better than ± 0.02 ppm.

3-Phenyl-1,2,4-oxadiazole, *1*, was prepared by the method of Arbasino & Gruenanger.[7] Its 90 MHz NMR spectrum (CCl_4) showed the following signals: δ 8.70, H-5 (1H); 7.90-8.37, ortho protons (2H); and 7.23-7.70, meta and para protons (3H). Other oxidiazoles, *2-5*, were synthesized by the procedure cited earlier.[3] 3-Aryl-5-methyl-4,5-dihydro-1,2,4-oxadiazoles, *6-9*, were prepared by the method of Srivastava et al.[8]

RESULTS AND DISCUSSION

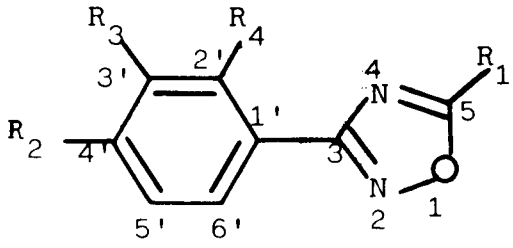
The chemical shifts of compounds *1-5* are listed in Table 1. The results show that CH_3 substituent at C-5 of the heterocyclic ring has very little effect on the chemical shifts of C-3 ($\Delta\delta_{C-3}$ = +0.6 ppm) which is usual for the other 5-membered ring heterocyclics.[9] At the substituted carbon atom, however, the CH_3 group induces a rather large downfield shift (+11.8 ppm) which is intermediate between the CH_3 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 *o*-tolyl group. This can be explained on the basis of steric hindrance between the CH_3 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 concluded[10] 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 *1* 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



1. $R_1 = R_2 = R_3 = R_4 = H$

2. $R_1 = CH_3; R_2 = R_3 = R_4 = H$

3. $R_1 = R_2 = CH_3; R_3 = R_4 = H$

4. $R_1 = R_3 = CH_3; R_2 = R_4 = H$

5. $R_1 = R_4 = CH_3; R_2 = R_3 = H$

Compound	Carbons									
	3	5	1'	2'	3'	4'	5'	6'	C-5-CH_3	Ar-CH_3
1	167.8	164.7	126.3	127.6	129.0	131.4	129.0	127.6	–	–
2	168.4	176.5	126.9	127.4	128.9	131.1	128.9	127.4	12.4	–
3	168.4	176.4	124.1	127.3	129.6	141.4	129.6	127.3	12.4	21.5
Calcd.[a]			124.0	127.3	129.6	140.0	129.6	127.3		
4	168.5	176.4	126.9	128.0	138.7	131.9	128.8	124.5	12.4	21.3
Calcd.[a]			126.8	128.1	137.8	131.8	128.8	124.5		
5	169.1	175.4	126.3	138.2	130.0	131.4	126.0	130.5	12.2	22.0
Calcd.[a]			127.6	136.3	129.6	131.0	126.0	127.3		

[a] Calculated relative to benzene = 128.5 ppm in $CDCl_3$ with CH_3 and 5-methyl-1,2,4-oxadiazol-3-yl as substituents.

Table 2. Substituent Effect of the 1,2,4-Oxadiazole Ring on the Benzene Ring.*

Substituent	C-1	*ortho*	*meta*	*para*
1,2,4-Oxadiazol-3-yl	−2.2	−0.9	+0.5	+2.9
5-Methyl-1,2,4-oxadiazol-3-yl	−1.6	−1.1	+0.4	+2.6

* Benzene taken as 128.5 ppm is used throughout the other tables.

Table 3. Substituent Effect of the 4,5-Dihydro-1,2,4-Oxadiazole Ring on the Benzene Ring.

Substituent	C-1	*ortho*	*meta*	*para*
5-Methyl-4,5-dihydro-1,2,4-oxadiazol-3-yl	−2.8	−2.0	+0.2	+1.5

The chemical shifts of the benzene ring carbons of compounds *3-5* were calculated (Table 1) using the following equation:

$$\delta_{cal} = \delta_{exp} + \delta_{subs}$$

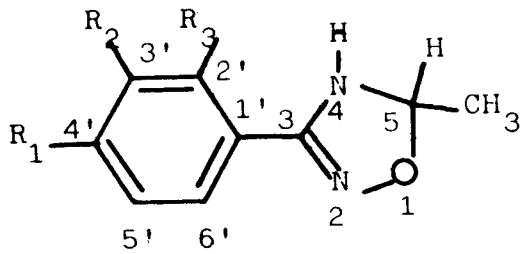
δ_{cal} being calculated using the experimental values (δ_{exp}) of compound *2* and adding the substituent chemical shifts (δ_{subs}).[11]

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*,[12] 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,[13] phenol and biphenyl[14] 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.[14] Substitution of a methyl group at 2-position in diphenyl ether produced the same effect.[13]

It is interesting to compare the chemical shifts ($CDCl_3$) 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 com-

Table 4. Carbon-13 Chemical Shift Assignments of some 3-Aryl-4,5-Dihydro-1,2,4-Oxadiazoles.



6. $R_1 = R_2 = R_3 = H$

7. $R_1 = CH_3; R_2 = R_3 = H$

8. $R_1 = R_3 = H; R_2 = CH_3$

9. $R_1 = R_2 = H; R_3 = CH_3$

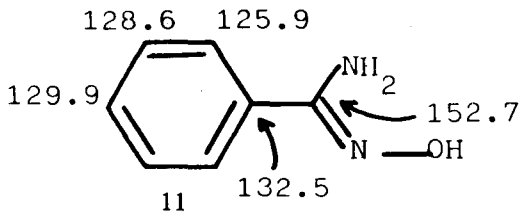
10. $R_1 = R_2 = H; R_3 = OH$

Compound	Carbons									
	3	5'	1'	2'	3'	4'	5'	6'	C-5-CH_3	Ar-CH_3
6	156.1	89.8	125.7	126.5	128.7	130.8	128.7	126.5	22.1	–
7	156.0	89.5	122.9	126.4	129.4	141.2	129.4	126.4	22.1	21.5
Calcd.[a]			122.8	126.4	129.4	139.7	129.4	126.4		
8	156.4	89.8	125.5	127.0	138.5	131.6	128.6	123.6	22.0	21.2
Calcd.[a]			125.6	127.2	137.6	131.5	128.6	123.6		
9	156.1	88.9	125.1	138.0	130.2	131.3	125.9	128.5	22.1	21.4
Calcd.[a]			126.4	135.4	129.4	130.7	125.8	126.4		
10[b]	157.6	90.5	111.9	157.7	118.1	133.6	121.0	129.2	23.2	
Calcd.[a]			113.0	153.4	116.0	132.2	121.4	127.9		

[a] Calculated relative to benzene (128.5 ppm in $CDCl_3$) with CH_3 (for coumpounds *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.

Compound	C-1	*ortho*	*meta*	*para*
2	−6.2	+1.7	+0.4	+1.5
6	−6.8	+0.6	+0.1	+0.9



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

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