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USE OF ^{13}C NMR SPECTROSCOPY TO ESTABLISH THE STRUCTURE OF 6(7)-R-QUINOXALINE N,N'-DIOXIDES

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The effect of substituents in position 6 on the positions of the signals of the carbon atoms in the ^{13}C NMR spectra of substituted 1,2,3,4-tetrahydro-5,10-phenazine N,N'-dioxides has been analyzed, increments of substituents have been found, and a scheme has been proposed for the calculation of the chemical shifts of carbon atoms in the ^{13}C NMR spectra of 6(7)-R-quinoxaline N,N'-dioxides.

Keywords: 1,2,3,4-tetrahydro-5,10-phenazine N,N'-dioxides, 6(7)-R-quinoxaline N,N'-dioxides.

Derivatives of quinoxaline N,N'-dioxides have considerable chemotherapeutic activity against acute bacterial infections, including infections which are difficult to control with other antimicrobial preparations [1, 2]. The original examples of this new chemotherapeutic group are quinoxidine and dioxidine – antibacterial preparations with a wide range of activity [3]. The interest in this class of compounds is explained by the observation that compounds containing the 1,4-di-N-oxide unit are cytotoxic and selective relative to cancer cells [4-7].

One of the means for the synthesis of quinoxaline N,N'-dioxides is the reaction of benzofuroxanes with nucleophilic reagents (bipolar reactions). However a mixture of isomers is not uncommonly formed as a result of this reaction and their separation and the determination of their ratio is not possible.

The use of ^{13}C NMR spectra is proposed for the determination of the structure of the isomeric products of the bipolar reaction. Information on the ^{13}C NMR spectra of this class of compounds is very scarce. However knowledge of their characteristics can facilitate considerably the assignment of the signals of the carbon atoms in new examples of this class.

To determine the influence of substituents in position 6 of the benzene ring of quinoxaline N,N'-dioxides on the chemical shifts of the carbon atoms (increments of the substituents) we used the spectra of substituted 1,2,3,4-tetrahydro-5,10-phenazine N,N'-dioxides **1a-h**, obtained by interaction of substituted benzofuroxanes with morpholinocyclohexene [8]. Their structures were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectra, and mass spectra.

Assignment of the signals of the carbon atoms in the ^{13}C NMR spectra was made by analysis of spectra registred without suppression of spin-spin coupling (SSC) with protons and by experiments with selective suppression of heteronuclear SSC. In addition the assignment of signals for compounds **1e** and **1f** is facilitated by the spin-spin coupling between the fluorine atoms and the carbon nuclei 5,6,7,8,10 (**1e**) and 5,6,7 (**1f**).

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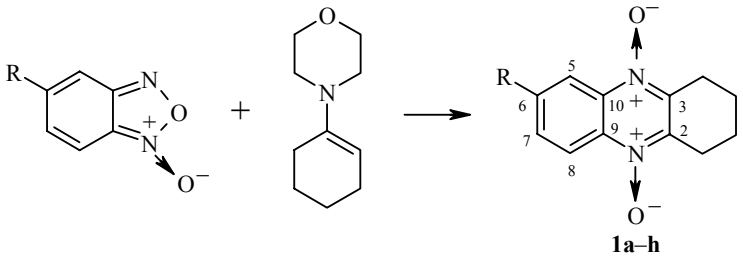
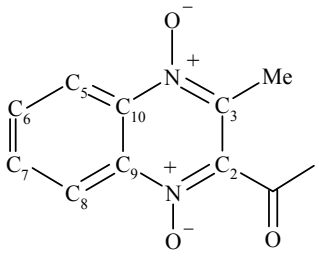


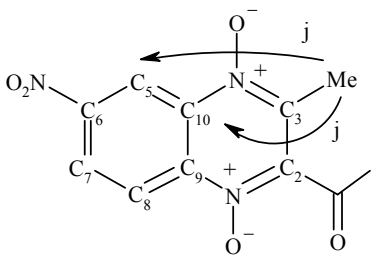
1a–h

a R = OMe, **b** R = Me, **c** R = Br, **d** R = Cl, **e** R = F, **f** R = CF_3, **g** R = COOMe, **h** R = H

To illustrate the proposed method we shall examine the spectrum of 6-bromoquinoxaline N,N'-dioxide (**1c**). The signals of atoms $C_{(5)}$, $C_{(7)}$, and $C_{(8)}$ (Table 1) are easily assigned because of their relatively high intensities (Overhauser effect) and these assignments are evident from spectra taken with selective suppression of the proton at position 5 (δ 8.635 ppm, $^2J_{H(5)-H(7)}$ = 2.07 Hz). The signals of atoms $C_{(2)}$ and $C_{(3)}$ are also easily assigned – they have the same form in the spectrum recorded without suppression of coupling with ^1H, and they do not change on suppressing the proton at position 5. Their mutual position depends on the electronic effect of the substituent at position 6. In the presence of an electron-donating substituent the signal of atom $C_{(2)}$ is found at stronger field and in the presence of an electron-accepting substituent at weaker field [9]. The assignment of the remaining signals is based on analysis of spectra recorded with suppression of the hydrogen at position 5 (Fig. 1), in which the signal of the carbon in the *ipso* position appears as a doublet of doublets (interaction with protons at positions 7 and 8 with coupling constants of 7 and 4 Hz respectively), and the signals of atoms $C_{(9)}$ and $C_{(10)}$ appear as doublets (interaction with protons at positions 5 and 7 respectively). The signal of carbon $C_{(9)}$ is broadened because of coupling with the proton at position 8 ($J \approx 2$ Hz). The chemical shifts of the carbon atoms of the 6-substituted 1,2,3,4-tetrahydro-5,10-phenazine N,N'-dioxides are cited in Table 1.



2a



2b

The effect of the nitro group in the benzene ring of quinoxaline N,N'-dioxides on the chemical shifts of the carbon nuclei was determined on the basis of the spectra of 2-acetyl-3-methylquinoxaline N,N'-dioxide (**2a**) and 2-acetyl-3-methyl-6-nitroquinoxaline N,N'-dioxide (**2b**) which we described previously [11].

The correctness of the determination of the position of the substituent in compound **2b** was confirmed by the presence of SSC between the protons of the methyl group in position 3 and atoms $C_{(5)}$ and $C_{(10)}$ which was demonstrated using the COLOC impulse sequence and the spectrum recorded with selective suppression of the protons of the methyl group in position 3. The values of the substituent increments (Table 2) were calculated from the equation

$$\Delta\delta_{nR} = \delta_{nR} - \delta_{nH}$$

where $\Delta\delta_{nR}$ is the increment for substituent R at position n, δ_{nR} is the chemical shift for atom $C_{(n)}$ in the 6-R-quinoxaline N,N'-dioxide, and δ_{nH} is the chemical shift of atom $C_{(n)}$ in 6-H-quinoxaline N,N'-dioxide.

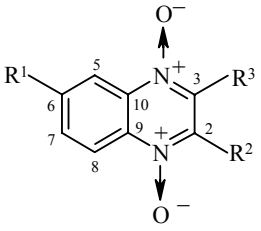
TABLE 1. ^{13}C NMR Spectra of Compounds **1a-h**

Compound	Chemical shifts, δ, ppm							
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$
1a	140.10	142.66	98.16	161.80	122.96	121.15	131.85	137.74
1b	141.46	142.28	118.66	142.14	132.76	119.48	134.96	136.41
1c	142.49	143.15	122.24	125.48	134.13	121.22	135.27	136.74
1d	142.43	143.23	119.04	137.54	131.51	121.27	134.96	136.64
1e	141.66	143.13	104.40	162.62	120.18	122.56	133.15	136.75
1f	143.58	144.13	118.27	132.76	126.67	121.38	137.73	136.14
1g	144.00	143.11	118.34	132.30	125.89	120.33	138.28	136.32
1h	142.33	142.33	119.76	130.85	130.85	119.76	136.60	136.60

TABLE 2. Substituent Increments ($\Delta\delta_{nR}$) for Calculation of the ^{13}C NMR Spectra of 6-R-Quinoxaline N,N'-Dioxides

R	$\Delta\delta_{nR}$							
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$
OMe	-2.23	0.33	-21.60	30.95	-7.89	1.39	-4.75	1.14
Me	-0.87	-0.05	-1.10	11.29	1.91	-0.28	-1.64	-0.19
Br	0.16	0.82	2.48	-5.37	3.28	1.46	-1.33	0.14
Cl	0.10	0.90	-0.72	6.69	0.66	1.51	-1.64	0.04
F	-0.67	0.80	-15.36	31.77	-10.67	2.80	-3.45	0.15
CF_3	1.25	1.80	-1.49	1.91	-4.18	1.62	1.13	-0.46
COOMe	1.67	0.78	119.76	1.45	-130.85	0.57	1.68	-0.28

The utility of the proposed scheme was confirmed by calculation of the spectra of the quinoxaline N,N'-dioxides **3a-f**. Table 3 shows that a satisfactorily good agreement between the experimental and calculated data was observed on the whole.



3a–f

a R^1 = OMe, R^2 = Me, R^3 = COMe; **b** R^1 = OMe, R^2 = NH_2, R^3 = CN; **c** R^1 = F, R^2 = Me, R^3 = COMe; **d** R^1 = F, R^2 = NH_2, R^3 = CN; **e** R^1 = Me, R^2 = NH_2, R^3 = CN; **f** R^1 = Me, R^2 = CN, R^3 = NH_2

TABLE 3. ^{13}C NMR Spectra of Compounds **3a-f**

Compound	Chemical shifts, δ, ppm (calculated / experimental)							
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$
3a	136.5 / 137.0	139.9 / 140.6	98.2 / 99.2	162.3 / 162.4	124.5 / 124.7	121.4 / 122.1	132.9 / 133.5	137.7 / 138.3
3b	143.5 / 145.0	108.8 / 108.3	97.9 / 98.3	158.3 / 158.5	126.1 / 125.8	119.2 / 119.6	131.9 / 132.5	132.7 / 132.4
3c	138.0 / 137.8	140.3 / 140.1	104.4 / 104.7	163.1 / 162.9	121.7 / 121.8	122.8 / 122.9	134.2 / 134.7	136.7 / 137.3
3d	145.0 / 145.7	109.3 / 109.3	104.1 / 104.6	159.1 / 160.3	123.3 / 123.3	120.6 / 120.6	133.2 / 134.1	131.7 / 131.9
3e	144.8 / 145.4	108.5 / 108.5	118.4 / 118.3	138.6 / 138.1	135.9 / 136.4	117.5 / 117.8	135.0 / 135.2	131.3 / 131.5
3f	107.6 / 107.8	145.7 / 145.7	116.7 / 116.8	145.3 / 145.6	129.3 / 129.4	119.2 / 119.5	129.9 / 130.1	136.5 / 136.6

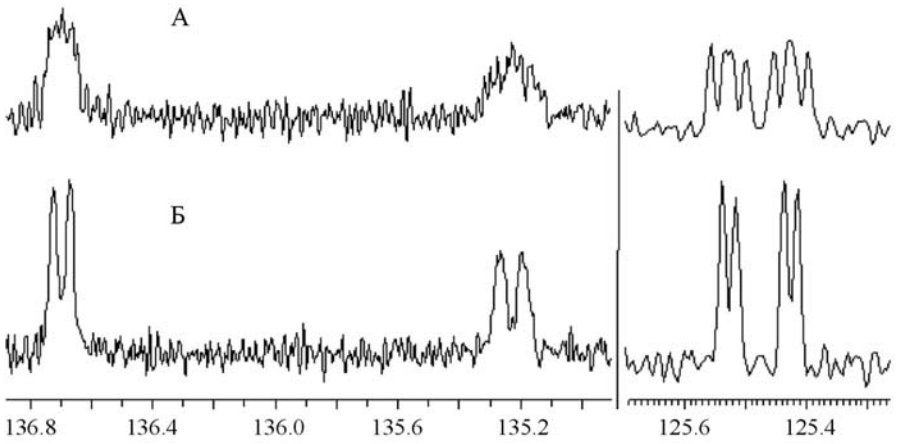


Fig. 1. Sections of the ^{13}C NMR spectra of compound **1c** recorded without suppression of the spin-spin coupling with ^{1}H nuclei (A) and with selective suppression of the proton at position 5 (B).

EXPERIMENTAL

^{13}C NMR spectra were recorded with a Bruker AM 500 (500 and 125 MHz) machine. Chemical shifts were measured relative to the signals of the solvent (77 ppm for $CDCl_3$ and 39.43 ppm for DMSO-d_6) and converted to the δ-scale.

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