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Assignment of the ^1H and ^{13}C Spectra of 5-Methylthio-4H-1-(p- R_1 -phenyl)-3a-(p- R_2 -Phenyl)-3a, 4-dihydro (1,2,4) oxadiazolo(4,5-a), 1, 5-benzodiazepines Using 2D NMR Spectroscopy

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Assignment of the ^1H and ^{13}C Spectra of 5-methylthio-4H-1-(p-R₁-phenyl)-3a-(p-R₂-Phenyl)-3a,4-dihydro (1,2,4)-oxadiazolo(4,5-a), 1,5-benzodiazepines using 2D NMR Spectroscopy.

Key words. ^1H and ^{13}C NMR assignment of benzodiazepine derivatives.

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Abstract

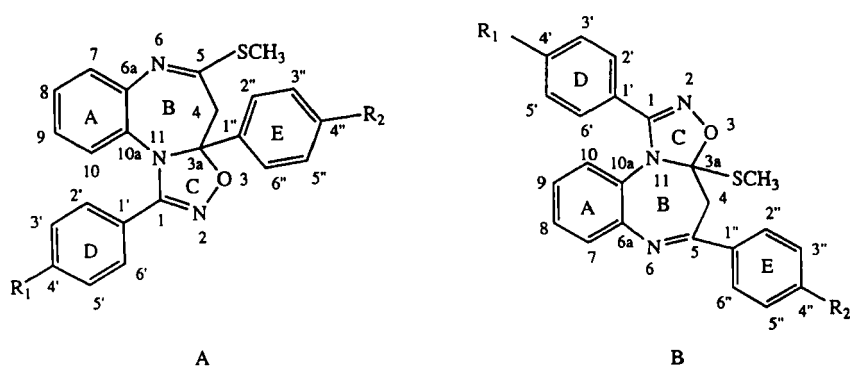
The ^1H NMR spectra of the title benzodiazepines derivatives is highly congested because all the protons are in aromatic environment so many proton signals remain overlap even 300 MHz or higher fields. With this in mind, the assignment of the ^1H and ^{13}C spectra of these compounds obtained using COSY, NOESY, HMQC and HMBC experiments is reported.

INTRODUCTION

The synthesis and purification of title compounds are discussed elsewhere.¹ Because under synthetic scheme it is possible to obtain either of the two structures (A or B, scheme 1), 2D ^1H - ^{13}C heteronuclear correlation and NOE experiments were carried out using the standard VARIAN UNITY microprograms in order to prove the correct structure (A), of the compounds 1-10 (scheme 2)

RESULTS AND DISCUSSION

The structures of the title compounds have been confirmed by detailed analysis of their NMR spectra and their resonances were assigned by standard methods as ^1H - ^{13}C correlations and NOESY experiments including the NOESY² cross peaks between methylene protons on C₄ and the protons H2"/ H6" on aromatic ring E.



SCHEME 1

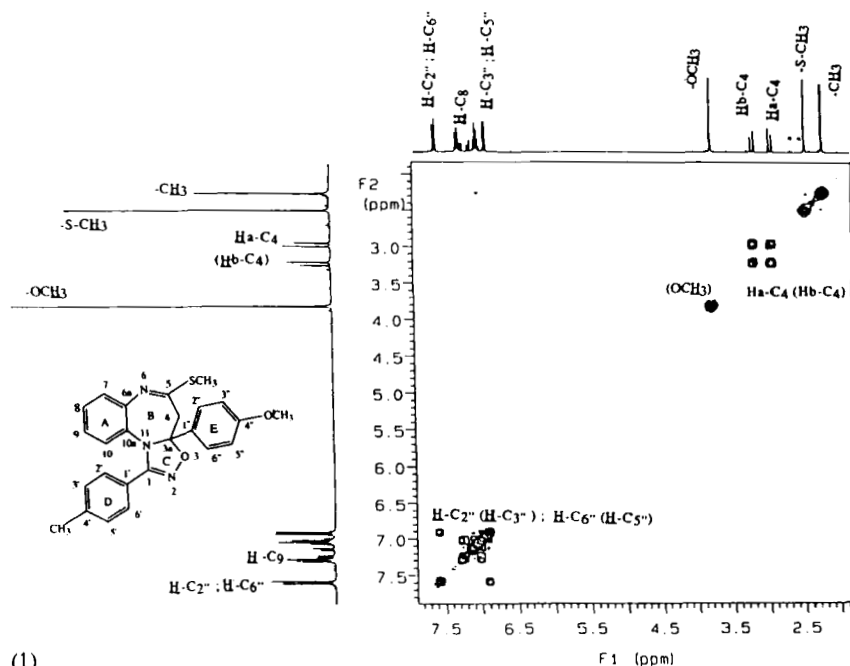
On the other hand, the structures having the B model have been excluded because the HMBC³ experiments ($^2J_{C-H}$, $^3J_{C-H}$) where long range correlations between the protons of the methylthio group with the imidine C₅ carbon was observed.

The approach chosen to the assignment of the proton spectra was first using COSY⁴ (figs 1-2) and NOESY experiments. With the combination of these two experiments we have made a complete assignment of the resolvable protons. With the information obtained from the proton assignment we were able to assign the ^{13}C spectrum using HMQC⁵ and HMBC for short and long range proton-carbon correlated spectroscopy. At first, we can readily assign the H₇, H₈, H₉ and H₁₀ protons because their characteristic ABCD patterns easily recognized due their multiplicity and coupling constants. The first feature of the COSY spectrum enabled correlate the protons of A-ring by their cross peaks. In order to assign the proton spectrum using exclusively proton methods, it is essential to differentiate one four spin system for the other on ring D and ring E. Patterns for both p-substituted aromatic rings in each one of the compounds were assigned due the cross peaks on NOESY experiment between methylene protons on C₄ and the *ortho* protons of the positions 2"/6".

The proton spectrum shows a number of multiplets of overlapping resonances. However, there are several resonances characteristic of the *para* substituted systems that are completely resolved (The part

	R ₁	R ₂
1	CH ₃	CH ₃
2	CH ₃	OCH ₃
3	CH ₃	Cl
4	CH ₃	Br
5	Cl	CH ₃
6	Cl	OCH ₃
7	Cl	Br
8	Br	CH ₃
9	Br	Cl
10	Br	Br

SCHEME 2

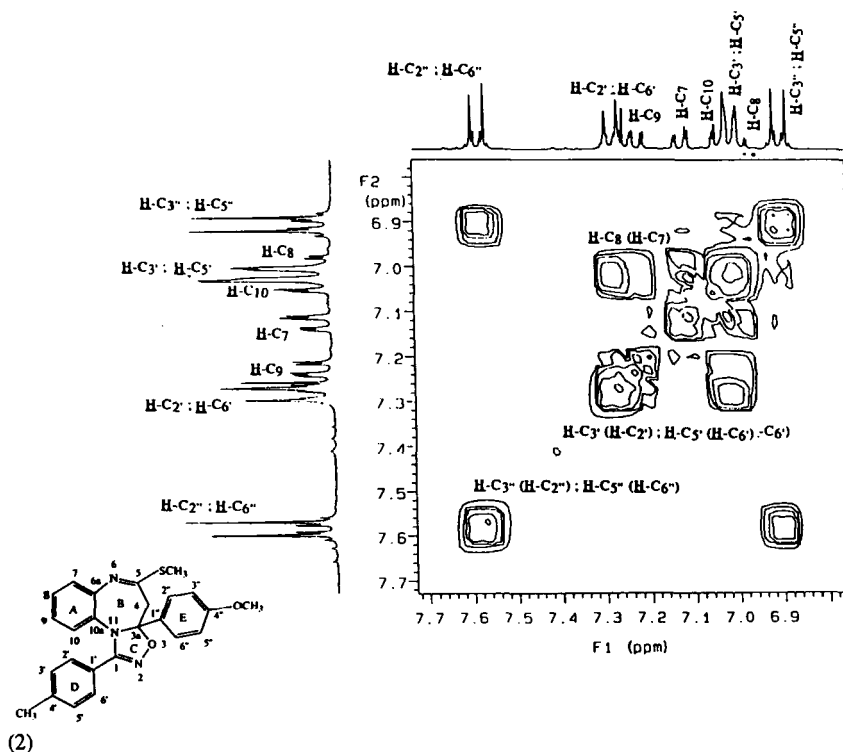


Figures 1 and 2. COSY spectrum of compound 2. 300 Mhz

AA' for each one of the system AA'XX' on the rings D and E). For instance, in compound 2 there are a doublet multiplet at $\delta=7.28$ and 7.02 assigned to the protons (2',6' and 3'/5' respectively. Also we detected a doublet multiplet at $\delta=7.58$ and doublet multiplet at $\delta=6.91$ assigned for the protons 2''/6'' and 3''/5'' respectively from the ring E. The COSY spectrum shows how these two systems are coupled with the part XX' of both aromatic rings. This clearly showed the two different systems for each one of the four-spin patterns.

Examinations of the ^{13}C chemical shifts of C_4 , C_5 , C_{3a} and C_1 are good indication that substitution on C_4 and C_4'' has negligible effect on the ^{13}C chemical shifts of these carbons.

$\text{C}_{1''}$ and C_1 shows a constant behaviour in their chemical shifts, except when the substituent on C_4 is an OMe group where such ipso carbon is shifted to lower field and being $\text{C}_{1''}$ shifted to higher field.



Figures 1 and 2. Continued

Substitution on C_4 has only a very small effect on the ^{13}C chemical shifts of C_1 and C_1' , and this assumption has been confirmed through our study.

The short range proton-carbon spectra (HMQC) shows those carbons which are directly attached to protons. With the proton spectrum already assigned we can assign some of the protonated carbons directly. For example, in compound 2, H_7 absorbing at $\delta=7.13$ is one bond coupled to the carbon peak at 130.2ppm giving us C_7 directly (figs 3-4). Similarly, we can assign the peak at 125.8 ppm to C_{10} and that at 124.9 ppm to C_8 . Also, we were able to assign C_9 , C_3 -, C_5 -, and C_2 -, C_6 - unambiguously from the short range spectrum.

Table 1
 ^{13}C NMR Spectral Data for Compounds 1, 2, 5, 8 and 10

Compounds	1	2	5	8	10
R ₁	CH ₃	CH ₃	Cl	Br	Br
R ₂	CH ₃	OCH ₃	CH ₃	CH ₃	Br
C-1	157.1	157.1	156.2	156.3	156.3
C-3a	112.2	112.3	112.8	112.8	111.8
C-4	44.5	44.5	44.6	44.6	44.2
C-5	171.2	171.1	171.4	171.4	170.8
C-6a	131.0	131.0	130.5	131.6	130.5
C-7	130.4	130.2	130.5	130.4	131.7
C-8	124.9	124.9	125.1	124.8	124.1
C-9	128.9	128.8	128.6	129.1	127.5
C-10	125.8	125.8	125.9	125.7	125.2
C-10a	147.9	147.9	148.2	148.3	147.7
C-1'	122.5	122.5	123.9	124.3	123.5
C-2', C-6'	127.7	127.7	128.2	126.0	126.2
C-3', C-5'	129.0	129.0	129.3	129.3	129.9
C-4'	140.5	140.5	136.4	141.2	139.4
C-1''	137.5	132.5	137.1	137.2	134.1
C-2'', C-6''	128.9	127.3	129.1	129.2	129.3
C-3'', C-5''	125.7	113.7	125.7	125.1	125.2
C-4''	138.9	160.1	139.3	139.1	138.3
C=R ₁	21.1	21.4	-	-	-
C=R ₂	21.4	55.3	21.1	21.2	-
S-CH ₃	14.1	14.1	14.2	14.2	14.2

Note: The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbons in ^{13}C NMR Spectra.

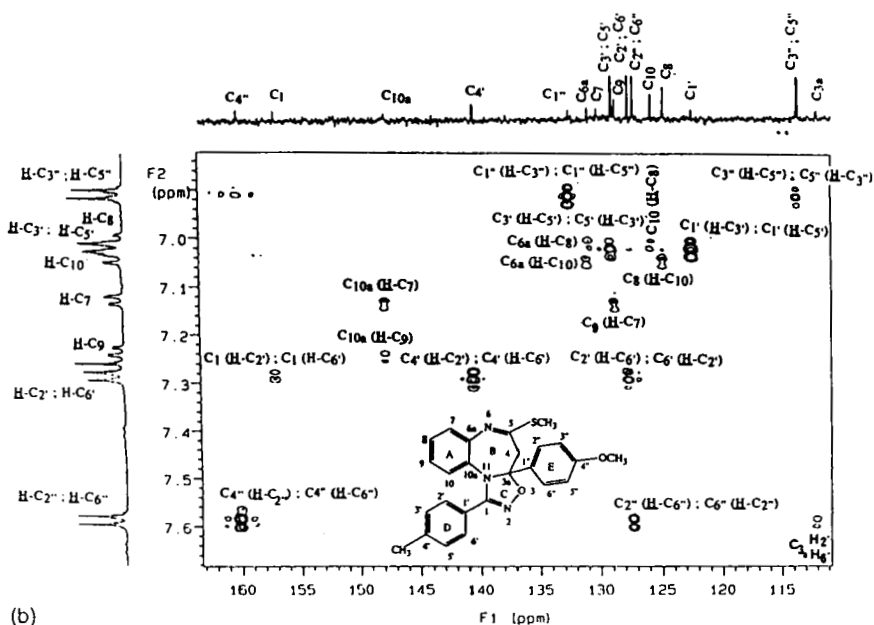
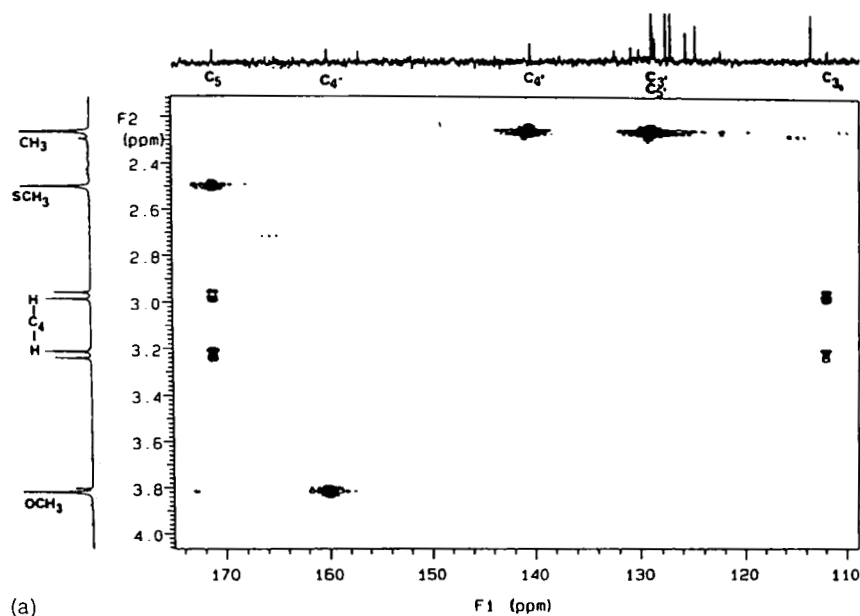
Table 2.- ^1H NMR chemical shifts for compounds 1-10

H, δ comp	4	7	8	9	10	2'/6'	3'/5'	2"/6"	3"/5"	R ₁	R ₂	SCH ₃
1	2.97 3.22	7.15	7.00	7.24	7.04	7.28	7.03	7.54	7.20	2.25	2.35	2.50
2	2.90 3.22	7.13	7.01	7.24	7.04	7.28	7.02	7.58	6.91	2.26	3.81	2.49
3	2.95 3.20	7.04	7.08	7.26	7.01	7.29	7.04	7.60	7.37	2.27		2.50
4	2.94 3.20	7.09	7.01	7.25	7.06	7.29	7.03	7.54	7.51	2.26		2.49
5	2.97 3.25	7.15	7.03	7.28	7.05	7.33	7.20	7.53	7.21		2.35	2.50
6	2.97 3.23	7.13	7.03	7.28	7.05	7.33	7.19	7.57	6.92		3.82	2.50
7	2.93 3.23	7.10	7.04	7.30	7.09	7.32	7.20	7.55	7.51			2.50
8	2.96 3.22	7.14	7.03	7.27	7.05	7.26	7.35	7.53	7.26		2.36	2.50
9	2.95 3.20	7.10	7.05	7.30	7.07	7.38	7.27	7.59	7.37			2.50
10	2.92 3.20	7.09	7.04	7.29	7.07	7.37	7.25	7.54	7.51			2.49

With regard to those carbon peaks that cannot be assigned unambiguously using the short range spectrum, the long range proton-carbon correlation (HMBC) was performed.

The HMBC proton-carbon spectrum (optimized for three bond couplings) shows correlations between protons and carbons that are, optimally, separated three bonds. Again, a good entry point is the methylthio group (S-CH_3) which the protons whose signal is shifted furthest higher field (2.49 ppm). We see that SCH_3 is coupled to the carbon whose signal is furthest down field (C_5 , 171.14 ppm). This carbon is also coupled to the AB pattern absorbing between 2.90-3.22 ppm which corresponds to C_4 methylene protons. We see that H_7 ($\delta=7.13$) is coupled with the carbon whose signal has the chemical shift 147.9 ppm (C_{10a}). This carbon is also coupled to the proton absorbing at $\delta=7.24$ (H_9) that is proton-proton coupled to the triplet at $\delta=7.01$ which corresponds to H_8 .

Examination of the structure reveals that C_{6a} is separated from H_{10} and H_8 by three bonds; therefore C_{6a} corresponds to the carbon signal at $\delta=131.0$. Similarly, we can assign $\text{C}_{1'}$, $\text{C}_{4'}$, $\text{C}_{1'}$, and $\text{C}_{4'}$ using the



Figures 3 and 4 HMBC spectrum of compound 2. 500 / 125 Mhz

following correlations. The carbon signal at $\delta=132.5$ is coupled with both protons on C_4 as well as the protons $\text{H}_{3-/5}$ at $\delta=6.91$. The only other carbon signal that is coupled to these protons is at $\delta=160.1$. This then must be C_{4a} and the coupling is through two bonds.

Using the same strategy, we can assign the quaternary carbons C_1 and C_{4a} . Therefore, C_1 can be identified as one of carbon signals at $\delta=122.5$ by their couplings to proton signal at 7.02 ppm corresponding to $\text{H}_{3-/5}$ and 7.28 ppm corresponding to $\text{H}_{2-/6}$. The carbon signal at $\delta=147.9$ is correlated with the triplet at 7.24 ppm and with the doublet at $\delta=7.13$ corresponding to H_9 and H_7 respectively. These two correlations allow us to assign this carbon signal to C_{10a} .

Conclusions

Although the carbon signals of the title compound appears on a narrow range, we were able to differentiate between all of these assignments using 2D NMR techniques. It is significant that the proton spectrum was assigned on the basis of the COSY and NOESY experiments without aid of any carbon techniques.

The carbon spectrum was assigned using the information gained from the proton spectrum and applying that information to the carbon spectrum through the short and long range proton-carbon correlated spectra. Unlike the proton assignments, the carbon assignments could not have been made without that aid of the proton assignments and both the HMQC and HMBC proton-carbon correlated spectra.

Experimental

For initial ^1H and ^{13}C spectra, the sample was dissolved in 0.6 ml of CDCl_3 and the probe temperature was set at 298K. The ^1H chemical shifts are referenced to TMS. For ^{13}C reference, the centre peak of the 1:1:1 multiplet of CDCl_3 was assigned the value of 77.00 ppm. The experiments were performed on a Varian Unity 300 operating at observation frequency of 300.0 MHz for ^1H and 75.0 MHz for ^{13}C .

High resolution spectra were recorded on Varian Unity 500 operating at 500.3 MHz for ^1H and 125.0 MHz for ^{13}C . The experiments were performed using an inverse detection 5 mm probe. The proton spectrum was recorded with 8192 data points. The ^{13}C spectrum was recorded with 65356 data points and was zero filled to 128K data points. For the most experiments the observation windows were 2.0-8.0 ppm for ^1H and 110-170 ppm for ^{13}C . For the COSY experiment we used the standard VARIAN UNITY program. The HMQC experiment used the standard VARIAN UNITY 500 pulse program using the BIRD

sequence optimized for short range couplings (140 Hz $^1J_{C-H}$). The long range proton-carbon experiment (HMBC) uses the VARIAN UNITY 500 pulse program optimized for long range couplings (9.0 Hz $^3J_{C-H}$). Both HMQC and HMBC proton carbon correlated spectra were acquired with 1024 x 256 points and the processing the F_2 dimension was zero filled to achieve 1024 x 512 data matrix.

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