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Structure and Stereochemistry of Pyrazolines, Precursors to *gem*-Dimethylcyclopropane

Marie-Thérèse Martin,[1]* Rafik Gharbi,[2] Abdelkader Khemiss[2] and Zine Mighri[2]
[1] Institut de Chimie des Substances Naturelles CNRS, 91190 Gif-sur-Yvette, France
[2] Laboratoire de Chimie des Substances Naturelles et de Synthèse Organique, Faculté des Sciences de Monastir, Monastir, Tunisia

A complete and unambiguous assignment of the ^{1}H and ^{13}C NMR spectra of 5,5-dimethyl-4-(*p*-methoxyphenyl)-3-(naphthalen-2-yl-carbonyl)-Δ^{2}-pyrazoline, 2-[4-(*p*-methoxyphenyl)-5,5-dimethyl-4,5-dihydro-3*H*-pyrazol-3-yl]-5,5-dimethyl-2-(naphthalen-2-yl)-2,5-dihydro[1,3,4]oxadiazole, 2,5,5,9-tetramethyl-3,4-diazatricyclo[6.3.1.$0^{2,6}$]-dodeca-3,9-diene-7,11-dione and 2,5,5,12,12,9-hexamethyl-3,4,10,11-tetraazatetracyclo[1.3.6.6.$0^{2,6}$.$0^{9,13}$]undeca-3,11-diene-7,14-dione was accomplished by inverse two-dimensional chemical shift correlation methods and their conformations were determined by NOESY experiments.

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INTRODUCTION

A *gem*-dimethylcyclopropane unit fused, or not, to a six-membered carbocycle is a commonly displayed architectural feature of natural products such as phorbol, aristolone and chrysanthemic acid. A suitable precursor is a pyrazoline obtained by 1–3 dipolar cycloaddition of a 2-diazopropane and an α,β-ethylenic ketone which provides this unit after photochemical nitrogen extrusion. It had been shown earlier that light-induced decomposition is stereospecific.[1] Hence it is important to know the relative configuration of the pyrazolines obtained. In this paper, the elucidation of the isomeric structures obtained in the cycloaddition of 2-diazopropane, their relative configuration and the complete ^{1}H and ^{13}C NMR assignments of the pyrazolines are discussed.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.6 MHz, respectively, on a Bruker AM-400 spectrometer at 300 K using a triple-resonance probe head with self-shielded gradient coils and a Bruker Z-gradient accessory delivering squared gradients. The ^{1}H and ^{13}C chemical shifts are expressed in ppm relative to TMS, but were measured against the solvent peak ($CDCl_3$) set at 7.24 and 77.00 ppm, respectively. The Fourier transform NMR spectrometer was equipped with an Aspect 3000 computer working under DISNMR version 92. The ^{1}H spectra were collected at 16 K data sets over a spectral width of 4.40 kHz using a 40° pulse. The ^{13}C BB spectrum was collected as a 16 K data set over a spectral width of 23.8 kHz using a 30° pulse and processed using exponential multiplication with a 2 Hz line broadening.

The homonuclear dipolar correlated 2D NMR NOESY spectra, in the phase-sensitive mode using TPPI, were obtained using the NOESYPH program from the Bruker software library. The spectral widths were $F_2 = 5000$ and $F_1 = 2500$ Hz. The spectra were collected as 2048 × 512 blocks of data. A squared sine-bell window multiplication shifted by $\pi/3$ was used in the F_2 dimension and a sine-bell window multiplication shifted by $\pi/2$ in the F_1 dimension. Other parameters were as follows: number of increments in t_1, 512; scans, 96; phase cycling, 16 steps; relaxation delay, 1 s and mixing time, 0.6 s. The 2D heteronuclear shift correlation spectra were recorded in the inverse mode. One-bond 2D XH correlation experiments via heteronuclear zero- and double-quantum coherence (HMQC) used the following sequence: D_1–90°(^{1}H)–D_2–90°(^{13}C)–D_0–t_g × 2–t_m–180°(^{1}H)–t_g × 2–t_m–D_0–90°(^{13}C)–t_g–D_2–t_2 and GARP decoupling during acquisition.[2,3] The parameters were relaxation delay $D_1 = 1$ s, evolution delay $D_2 = 3.70$ ms, gradient-on time $t_g = 400$ μs, after-gradient recovery time $t_m = 300$ μs, F_2 spectral width = 3.6 kHz over 2 K real data using 16 transients per t_1 increment and F_1 spectral width = 7.0 kHz over 256 t_1 increments (zero-filled to 1 K). A squared sine-bell window multiplication shifted by $\pi/3$ was applied in each dimension.

Long-range 2D heteronuclear shift correlations via heteronuclear zero- and double-quantum coherences with a low-pass *J*-filter to suppress one-bond correlations were obtained using the following sequence: D_1–90°(^{1}H)–D_2–90°(^{13}C)–D_4–90°(^{13}C)–D_0–t_g × 2–t_m–180°(^{1}H)–t_g × 2–t_m–D_0–90°(^{13}C)–t_g–t_m–t_2.[2,4] Delays D_1 and D_2 and times t_g and t_m were the same as

* *Correspondence to*: M.-T. Martin.

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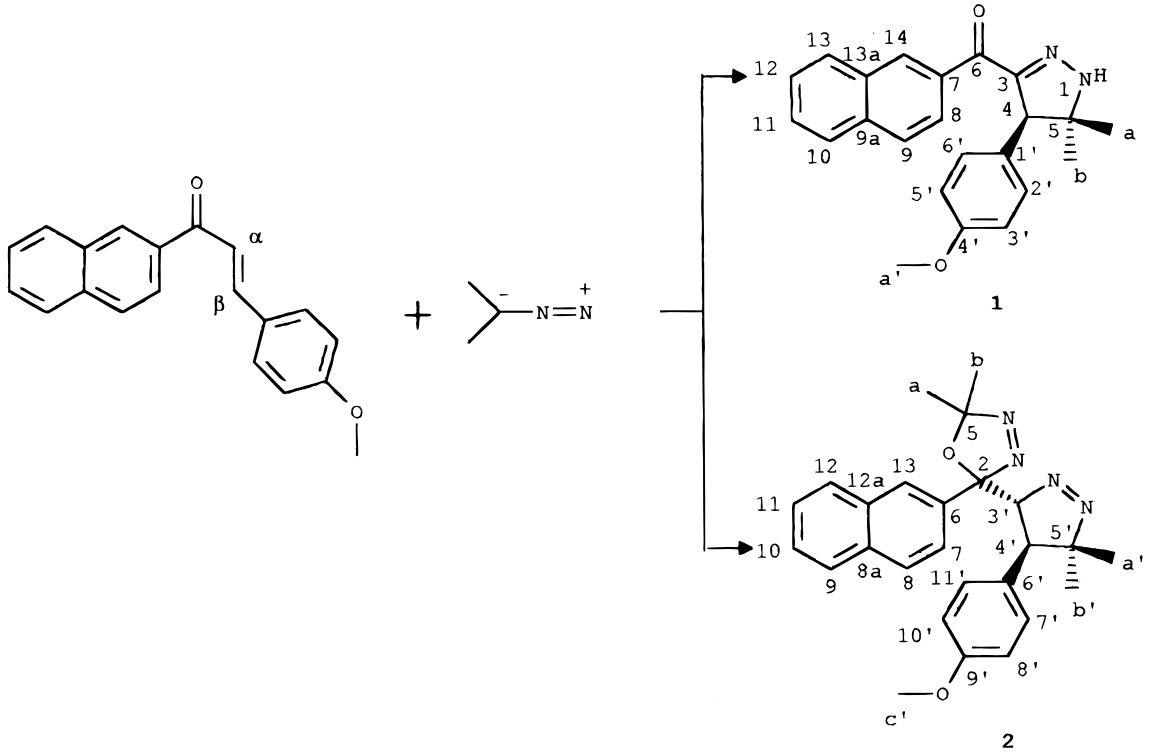
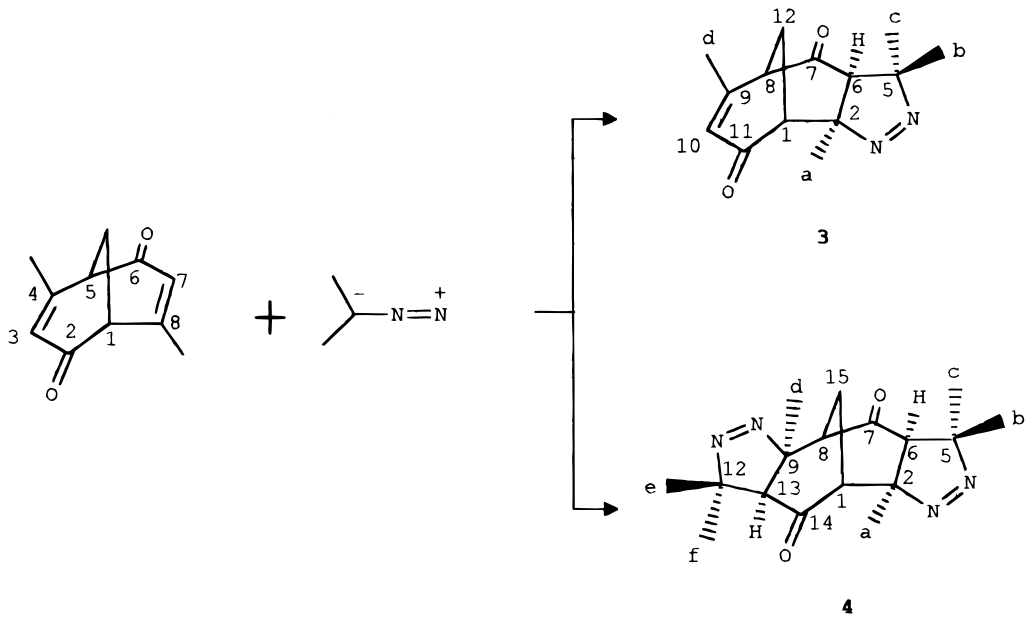


Scheme 1. Synthetic pathway, structural formulae and numbering schemes for **1** and **2**.

in the previous HMQC experiment while the evolution delay D_4 for CH long-range coupling was adjusting to 70 ms. Typically, 2048 data points were acquired using a 2.5 kHz spectral width for the proton dimension and 256 times increments for a 6.7 kHz spectral width for carbons. The data were then zero-filled to give a final 2 K × 1 K data matrix. A squared sine-bell window multiplication shifted by $\pi/3$ was applied in each dimension.

Synthesis

We choose to illustrate the cycloaddition of 2-diazopropane and an α,β-ethylenic ketone by two examples including aromatic and aliphatic products. The first is the cycloaddition of 2-diazopropane, in excess, to a 3-aryl-1-(naphthalen-2-yl)-propenone carried out in CH_2Cl_2 at $-50\,^{\circ}C$. Two products were obtained: one is the normally expected product (**1**) whereas the other results from the cycloaddition of two equivalents of 2-diazopropane (**2**) (Scheme 1). The second example is the cycloaddition of 2-diazopropane, in excess, to bicyclo[3,3,1]nona-3,7-diene-2,6-dione carried out in CH_2Cl_2 at $5\,^{\circ}C$. Two products were obtained: a monocycloaddact (**3**) and a bicycloaddact (**4**) of 2-diazopropane (Scheme 2). Steric hindrance could explain the attack mechanism. The synthesis of these compounds will be described elsewhere.



Scheme 2. Synthetic pathway, structural formulae and numbering schemes for **3** and **4**.

The characteristics of the various products were as follows.

1: 5,5-Dimethyl-4-(*p*-methoxyphenyl)-3-(naphthalen-2-yl-carbonyl)-Δ^2-pyrazoline, yellow crystals, m.p. 137 °C. Analysis: calculated for $C_{23}H_{22}N_2O_2$, C 77.09, H 6.15, N 7.82; found, C 76.86, H 6.41, N 7.77%. MS [fast atom bombardment (FAB)], *m/z* 359, $[M + H]^+$.

2: 2-[4-(*p*-Methoxyphenyl)-5,5-dimethyl-4,5-dihydro-3*H*-pyrazol-3-yl]-5,5-dimethyl-2-(naphthalen-2-yl)-2,5-dihydro[1,3,4]oxadiazole, colorless crystals, m.p. 113 °C. Analysis: calculated for $C_{26}H_{28}N_4O_2$, C 72.90, H 6.54, N 13.08; found, C 72.38, H 6.67, N 13.01%. MS (FAB), *m/z* 429, $[M + H]^+$.

3: 2,5,5,9-Tetramethyl-3,4-diazatricyclo[6.3.1.$0^{2,6}$]dodeca-3,9-diene-7,11-dione, colorless needles, m.p. 108 °C. Analysis: calculated for $C_{14}H_{18}N_2O_2$, C 68.29, H 7.32, N 11.38; found, C 67.73, H 6.98, N 11.79%. MS (FAB), *m/z* 247, $[M + H]^+$.

4: 2,5,5,12,12,9-Hexamethyl-3,4,10,11-tetraaza-tetracyclo-[1.3.6.6.$0^{2,6}$.$0^{9,13}$]undeca-3,11-diene-7,14-dione, colorless crystals, m.p. 212 °C. Analysis: calculated for $C_{17}H_{24}N_4O_2$, C 64.56, H 7.59, N 17.72; found, C 64.64, H 7.57, N 17.75%. MS (electron impact ionization), *m/z* 316, $[M^+.1]$.

RESULTS AND DISCUSSION

Structure and stereochemical analysis

Compound **1** is a derivative resulting from attack of the nucleophilic carbon, C-2, of 2-diazopropane on the β-position of an α,β-ethylenic ketone. As expected, the ^{1}H spectrum shows the presence of two aromatic systems (corresponding to the *para*-disubstituted benzene ring and naphthyl group) and five singlets: three methyls which can be readily assigned to two methyls of pyrazole (0.92 and 1.33 ppm) and a methoxy (3.73 ppm), and two singlets (1H) at 4.17 and 6.31 ppm.

In the HMQC spectrum, the singlet at 4.17 ppm correlates with C-4 whereas the singlet at 6.31 ppm does not correlate with any carbon, demonstrating that this proton is linked to a heteroatom (nitrogen); its HMBC correlations with C-4, C-5 and Me-a show that it is H-1. Further assignments and the location of the two methyls were deduced from the HMBC spectrum. Two singlet methyls, Me-a and Me-b, correlate only with two carbons atoms at 67.2 ppm (Cq) and 58.1 ppm (CH) and each other, suggesting that they are directly linked to the quaternary carbon at 67.2 ppm. In a similar manner, H-2′ and H-6′ correlate with the carbon at 58.1 ppm, which is C-4 and is directly bonded to the aromatic ring. Consequently, this latter correlation reveals a ϕ—C-4—C-5—(Me-a, Me-b) linkage. In the same way, a whole set of linkages confirming this structure was established and is reported in Table 1.

Having established the 2D structure of **1**, it is now possible to investigate the relative position of the a and b methyls with respect to H-4 from a NOESY map. As shown in Table 1, no stereochemical information arose from H-1 and H-4, both having NOE cross peaks with

Table 1. ^{1}H and ^{13}C NMR chemical shifts (ppm), multiplicity, coupling constants, HMBC and NOESY correlations for 1 and 2

Atom *n*	δ^{13}C	δ^1H *J* (Hz)	HMBC $H_n \rightarrow C_j$	NOE
		1		
1		6.31 s	3,4,5,a	a,b
3	152.7			
4	58.1	4.17 s	5,1′ 2′6′,a	a,b
5	67.2			
6	187.3			
7	134.7			
8	125.7	8.13 d (8.4)	9a,14	9
9	127.6	7.84 d (8.4)	7,10,13a	8
9a	135.1			
10	127.6	7.82 m	9,12,13a	11
11	127.9	7.55 m	9a,13	10
12	126.3	7.49 m	10,13a	13
13	129.6	7.96 d (8.0)	9a,11,14	12,14
13a	132.4			
14	131.7	8.81 s	8,9a,13	13
a	28.9	1.33 s	4,5,b	1,4,2′ 6′,b
b	22.4	0.92 s	4,5,a	1,4,a
1′	128.8			
2′6′	129.1	7.05 m	4,3′,4′ 5′	4,a
3′5′	114.0	6.81 m	1′,4′	
4′	158.7			
a′	55.1	3.73 s	4′	3′,5′
		2		
2	123.7			
5	122.9			
6	134.4			
7	123.1	7.60 d (8.4)	8a,13	8,3′
8	128.0	7.54 d (8.4)	6,12a	7,9
8a	132.8			
9	127.3	7.64 m	8,11,12a	8,10
10	126.1[a]	7.39 m	8a,12	9,11
11	126.0[a]	7.39 m	9,12a	10,12
12	128.0	7.69 m	8a,10,13	11,13
12a	132.6			
13	124.9	7.85 s	7,8a,12	3′,b
a	24.2	1.63 s	b,5	
b	25.0	1.40 s	a,5	13
3′	94.8	5.68 d (10.1)	2,4′,6′	7,13,7′ 11′,a′
4′	49.9	2.73 d (10.1)	2,a′,b′ 3′,5′,6′	7′11′,b′
5′	90.4			
6′	128.5			
7′11′	128.7	6.55 m	4′,6′,8′ 9′,10′	3′,4′,8′ 10′,a′
8′10′	113.1	6.31 m	1′,6′,9′	7′11′,c′
9′	157.8			
a′	21.5	0.81 s	4′,5′,b′	3′,7′ 11′,b′
b′	26.4	1.52 s	4′,5′,a′	4′,a′
c′	55.0	3.48 s	9′	8′10′

[a] Chemical shifts may be interchanged.

Me-a and Me-b. The observed NOE cross peaks between both H-2′, H-6′ and Me-a placed these three units on the same side of average pyrazole ring plane, so H-4 and Me-b are both on the other side of this plane.

Compound **2** was an unexpected derivative. The mass spectrum and microanalyses indicate the addition of a second equivalent of 2-diazopropane compared with **1**. Indeed, the ^{1}H spectrum shows two more methyls than in the spectrum of the preceding compound, and there is no carbonyl signal in the ^{13}C spectrum. The second diazopropane unit must have added to the carbonyl function.

The assignment procedure for the pyrazole ring is analogous to that for **1**, but here we have two vicinal protons, H-3′ and H-4′. The HMBC spectrum established the C-3′—C-4′ (ϕ)—C-5′ (Me-a′, Me-b′) linkage (Table 1). Moreover, the existence of a NOESY cross peak between H-3′ and Me-a′ indicates that they are on the same side of the average plane of the pyrazole ring.

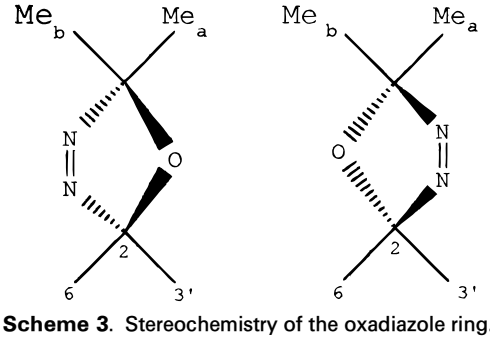
The more interesting feature of the molecule was the presence of an oxadiazole ring due to the second addition. No carbonyl carbon is present, but two new quaternary carbons appear at 123.7 and 122.9 ppm. The first, showing cross peaks with H-3′, H-4′ and H-13 in the HMBC spectrum in a similar way to the carbonyl carbon in **1**, is C-2. On the other hand, methyls at 1.40 and 1.63 ppm correlate with each other and with only one carbon at 122.9 ppm, C-5. This structure was supported by the very similar chemical shifts of C-2 and C-5, which should experience the same electronic environment and be very deshielded. Here, steric hindrance of C-2 leads to its attack by the terminal nitrogen atom of 2-diazopropane instead of C-2 bearing two methyls. Finally, we turned our attention to the phase-sensitive NOESY spectrum for more information about this ring. It was very interesting that if there were, of course, rotation around the C-6—C-2 and C-2—C-3′ bonds (NOE cross peaks between H-3′ and both protons H-7 and H-13), there are NOE effects between H-7, H-13 and Me-b. Nevertheless, we could not determine the C-2 and C-5 relative configurations because the ether function might be on either side of the plane defined by C-6, C-3′, Me-a, Me-b (Scheme 3); the pseudo-symmetry of this ring makes any NMR experiment unsuccessful.

The mass spectrum and microanalysis of **3** agree with a monocycloaddition of 2-diazopropane and an aliphatic α,β-ethylenic ketone (Scheme 2). A preliminary examination of the NMR spectrum allows part of the signals to be readily assigned by comparison with the spectrum of the reagent; these attributions are given in Table 2. The resonance signal at 5.94 ppm is assigned to H-10 and the methyl at 2.05 ppm is linked to a double bond. An AB pattern (1.67, 2.42 ppm) is assigned to the protons of the methylene group (12-CH_2). The non-equivalence of these protons is attributed to molecular chirality, and they have small coupling constants with H-1 and H-8 (broad singlets at 3.30 and 2.88 ppm, respectively). To obtain all the assignments, an HMBC experiment was carried out. Correlation of Me-d with C-8 establishes the chemical shift of this carbon at 49.2 ppm. As we now know where the H-8 signal is located, we could observe its correlation with the carbonyl carbon C-7 at 202.4 ppm. In a similar manner, H-10 correlates with C-1 (44.9 ppm) and H-1 with the second carbonyl carbon C-11 at 196.4 ppm. The chemical shift of C-2 (93.2 ppm) was determined by the cross peaks with H-1, H-12a, H-12b and Me-a.

We now have to determine the addition mode of 2-diazopropane. Two methyls, b and c, correlate with each other and with the quaternary C-5 (97.7 ppm) and methine C-6 (57.9 ppm). They do not correlate with either C-7 or C-2. Therefore, they are directly bound to C-5 and α to methine-6. Moreover, the assignment of C-5 is consistent with that of C-2; the carbon resonances (97.7 and 93.2 ppm, respectively) are obviously deshielded by the presence of a nitrogen atom. In a similar manner to **2**, steric hindrance led to an attack by the terminal nitrogen atom of the 2-diazopropane.

Table 2. ^{1}H and ^{13}C NMR chemical shifts (ppm), multiplicity, coupling constants, HMBC and NOESY correlations for 3 and 4

Atom *n*	$\delta^{13}C$	$\delta^{1}H$ *J* (Hz)	HMBC $H_n \rightarrow C_j$	NOE
		3		
1	44.9	3.30 bs	2,6,8,11,12	12a,a
2	93.2			
5	97.7			
6	57.9	2.28 s	1,2,5,7,8,a,c	a,c
7	202.4			
8	49.2	2.88 bs	1,7,9,10,d	d
9	159.0			
10	127.3	5.94 s	1,8,d	d
11	196.4			
12a	26.7	1.67 bd (14.0)	1,2,7,8,9,11	1
12b		2.42 bd (14.0)		b
a	25.5	1.29 s	1,2,6	1,6
b	23.6	1.36 s	5,6,c	12b
c	30.4	1.55 s	5,6,b	6
d	23.2	2.05 s	7,8,9,10,11	10,8
		4		
1 (8)	45.6	3.10 s	2,6,7,8,15 (1,9,14,15)	15,a (15,d)
2 (9)	94.0			
5 (12)	99.0			
6 (13)	60.3	2.16 s	1,5,7,8,a,c (1,8,12,14,d,f)	a,c (d,f)
7 (14)	207.0			
15	20.7	1.36 s	1,2,7,8,9,14	1,8
a (d)	25.3	1.40 s	1,2,6 (8,9,13)	1,6,c (8,13,f)
b (e)	23.1	1.36 s	5,6,c (12,13,f)	c (f)
c (f)	30.1	1.53 s	5,6,b (12,13,e)	6,a,b (e,d,13)



Scheme 3. Stereochemistry of the oxadiazole ring.

The stereochemistry of this cycloaddition product was determined from a phase-sensitive NOESY spectrum. First, cross peaks between H-6 and both Me-a and Me-c and, on the other hand, a cross peak between H-12b and Me-b show that 2-diazopropane attacks on the same side of the molecule as C-12. Hence the relative configuration of this molecule is defined.

The mass spectrum and microanalysis of **4** provide evidence for a cycloaddition of two equivalents of 2-diazopropane.

The extremely simple ^{1}H and ^{13}C spectra contain only five and nine singlets, respectively, indicative of a symmetric structure for **4**. The reagent being a symmetric molecule, we can think that cycloaddition of the second molecule of 2-diazopropane takes place in the same way as the first (Scheme 2), giving a new symmetric molecule. Indeed, in the same way as **3**, methyls Me-c and Me-b (Me-e and Me-f) correlate with each other and with quaternary C-5 (C-12) and with methine C-6 (C-13). The chemical shifts of these carbons are very similar to those of **3**. Me-a (Me-d) correlates with C-1 (C-8) at 45.6 ppm, C-6 (C-13) at 60.3 ppm and C-2 (C-9) at 94.0 ppm. The relative integration value of the singlet at 1.36 ppm is of four protons: a methyl Me-b (Me-e) and half a methylene CH_2-15, the carbon of which has the C_2 symmetry axis passing through. This methylene correlates with C-7 (C-14) at 207.0 ppm, C-2 (C-9) at 94.0 ppm and C-1 (C-8) at 45.6 ppm. As expected, H-6 (H-13) correlates with Me-a (Me-d), Me-c (Me-f), C-1 (C-8) and C-7 (C-14). However, the most interesting point is correlations of H-1 (H-8) because here is the unique position where we can observe the symmetry of the molecule. Indeed, there is a long-range cross peak between the frequencies of a proton and the carbon which seems to carry it. In fact, this peak indicates long-range correlation between H-1 and C-8 and between H-8 and C-1 (Fig. 1).

The NOESY spectrum shows only a few peaks but among them the correlations between H-6 (H-13), Me-a (Me-d) and Me-c (Me-f) suggest that the cycloaddition takes place in the same way as for **3**. Although the overlapping of Me-b (Me-e) and CH_2-15 does not allow NOE effects to be distinguished, the previous results are sufficient to establish the relative configuration of this compound as presented in Scheme 2.

CONCLUSION

Through 1D and 2D NMR techniques, this study has assigned unambiguously the ^{1}H and ^{13}C spectral data of these four compounds and established their structures and relative configurations, except for **2**, where the pseudo-symmetry of the oxazole ring does not allow it.

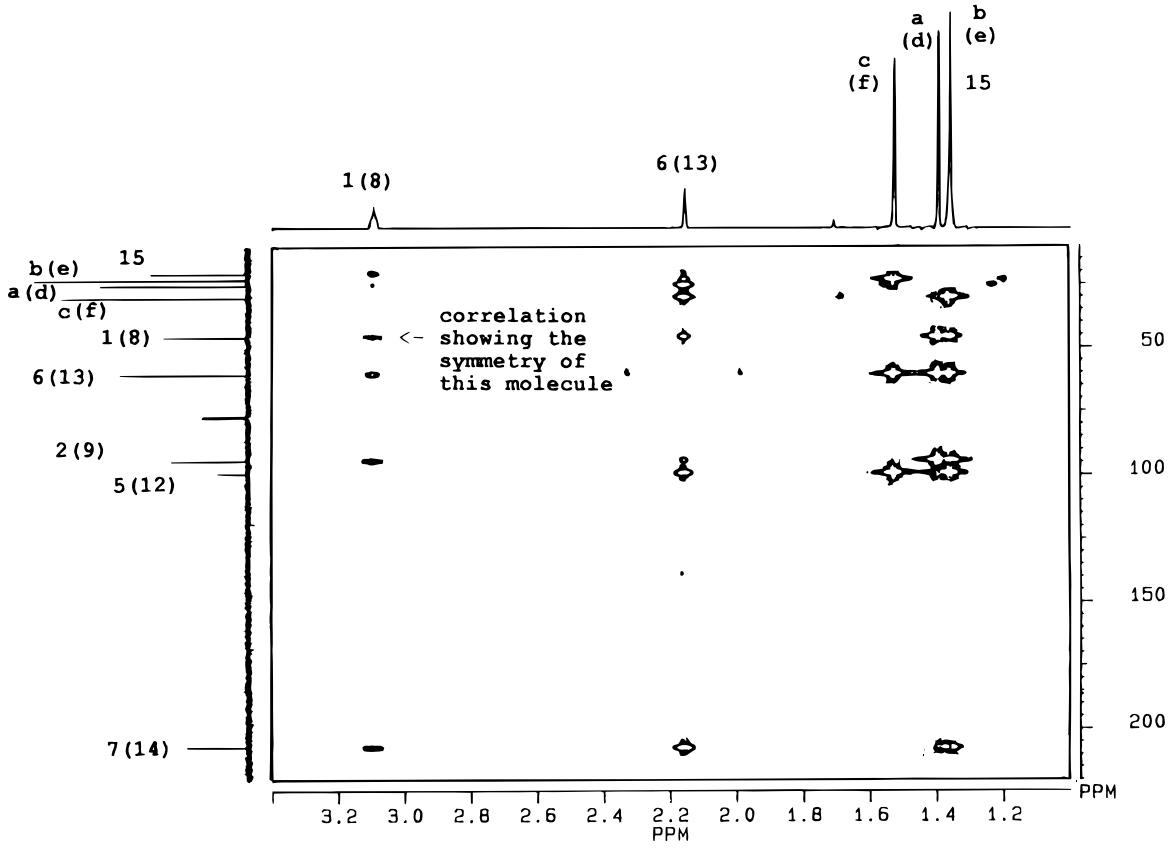


Figure 1. HMBC spectrum of **4**. Instead of F_2 and F_1 projections, the one-dimensional ^{1}H and ^{13}C spectra are depicted.

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