Total ^1H and ^{13}C Chemical Shift Assignment of Indolizino[3,4,5-*a*,*b*]-isoindole and 2-Methylthiobenz[*f*]imidazo[5,1,2-*c*,*d*]indolizine

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The ^1H and ^{13}C nmr spectral assignment of indolizino[3,4,5-*a*,*b*]isoindole and 2-methylthiobenz[*f*]-imidazo[5,1,2-*c*,*d*]indolizine are described. A concerted interpretation of the HMQC, HMQC-TOCSY, HMBC and nOe-difference experiments were used to assign the ^1H and ^{13}C resonances of indolizino-[3,4,5-*a*,*b*]isoindole, whereas for 2-methylthiobenz[*f*]imidazo[5,1,2-*c*,*d*]indolizine a concerted interpretation of the COSY, HMQC and HMBC experiments were used to generate spectral assignments.

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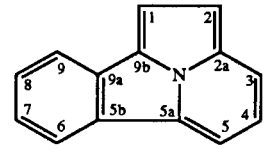
Compound **1**.

The approach used to assign **1** was to identify the spin systems using the HMQC and HMQC-TOCSY spectra (Figures 1 and 2), then to determine the identity of the individual members of each spin system *via* spectral connections arising from nOe and long-range heteronuclear responses.



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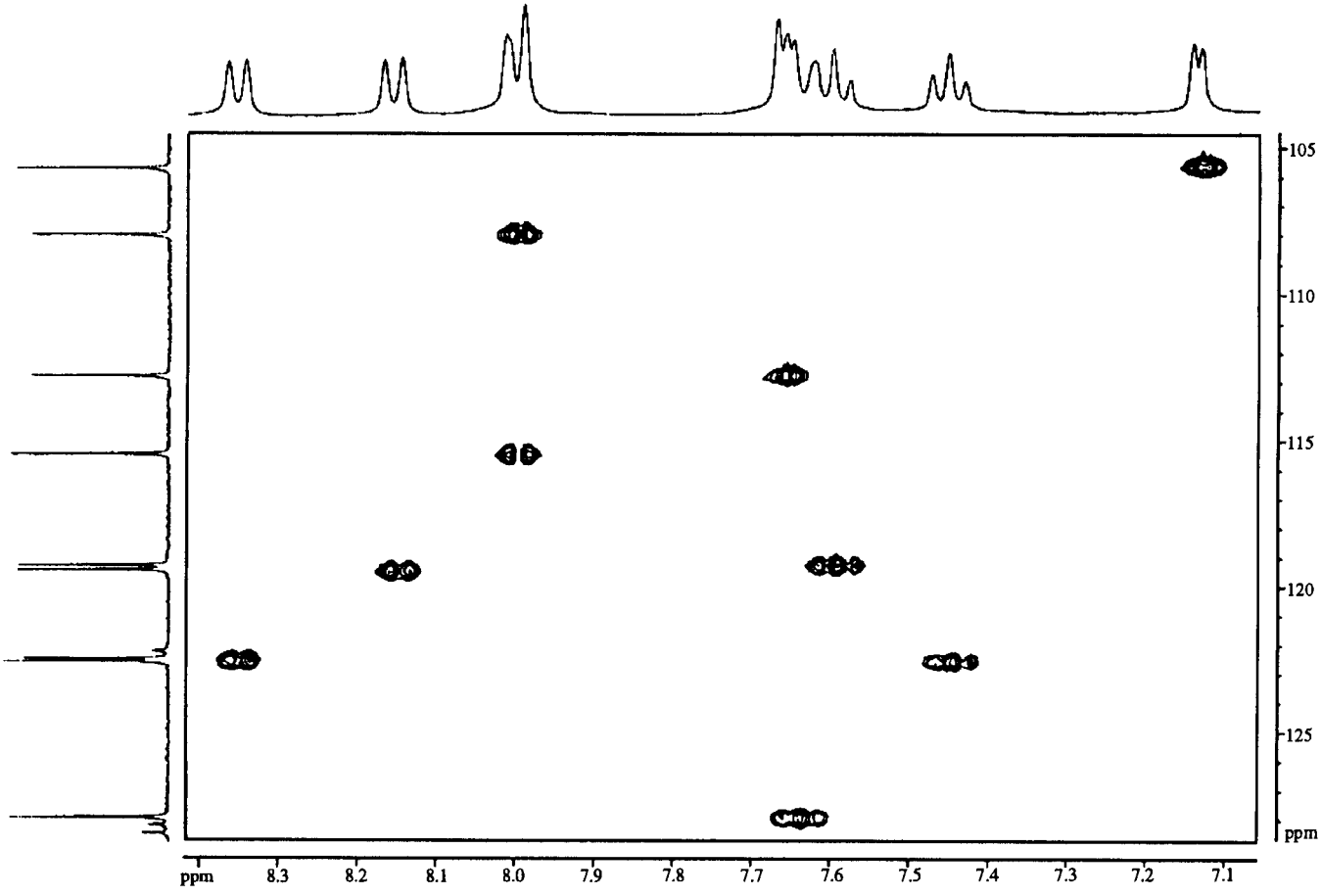


Figure 1. HMQC spectrum of **1**.

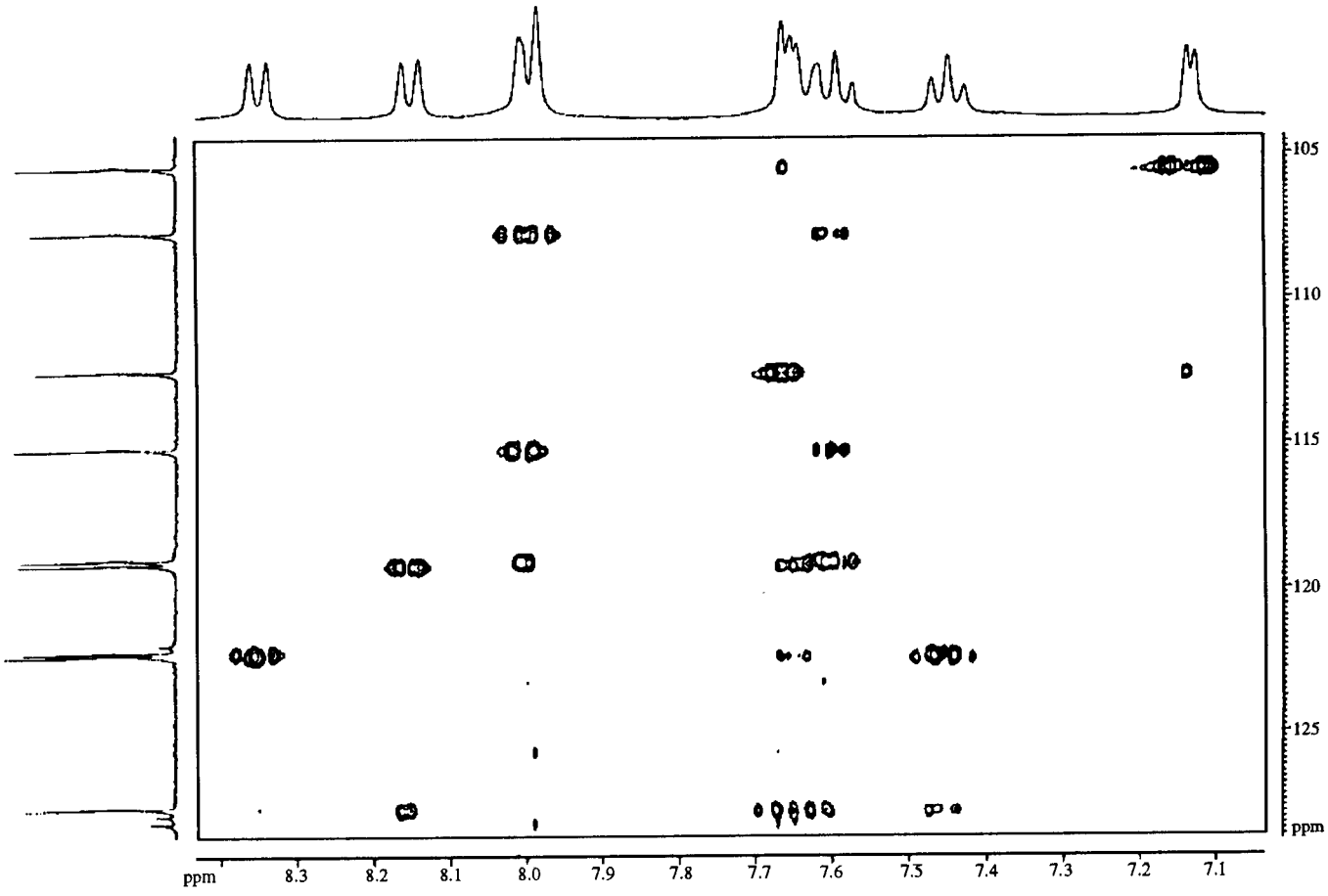


Figure 2. HMQC-TOCSY spectrum of **1** acquired with a 12 msec mixing time.

The two-spin system is the easiest to identify, from relayed responses observed in the HMQC-TOCSY spectrum. The proton resonance farthest upfield, at 7.14, is completely resolved, and is linked to the proton resonance at 7.66 through a relayed response. With the two-spin system identified, an nOe-difference experiment was performed to determine the identity of each member, and to gain an entry point into the four-spin system. A pair of nOe-difference experiments showed that the protons corresponding to the resonances at 7.14 ppm and 8.35 ppm are close to one another in space. Inspection of the HMQC-TOCSY spectrum shows that the proton resonance at 8.35 is a member of the four-spin system and as described above the resonance at 7.14 is a member of the two-spin system. The results of the nOe-difference experiments coupled with those of the HMQC-TOCSY show that the resonance at 7.14 corresponds to H1 and the resonance at 8.35 corresponds to H9. Furthermore, the resonance at 7.66, the other member of the two-spin system, corresponds to H2.

With the resonance corresponding to H9 identified, it is now possible to identify the other members of the four-spin system from relayed responses observed in the HMQC-TOCSY spectrum. Because H9 does not show any visible relayed response along the F_1 axis (carbon) at the proton chemical shift of H9, we must assume that the relayed response is overlapped with the direct response corresponding to H9/C9. Inspection of the carbon spectrum shows that the carbon resonance at 122.5 corresponding to C9 is close to another resonance at 122.3. Therefore, the direct responses for the proton/carbon pairs corresponding to H9/C9 and H8/C8 are overlapped with the relayed responses between H9 and H8. From this observation H8 is assigned to the triplet resonance at 7.45; also the resonance corresponding to H7 is identified as the resonance at 7.64 from a relayed response with H8. Finally, then the doublet at 8.15 is assigned to H6 from the relayed response between H7 and H6. Because the HMQC-TOCSY spectrum resolves proton spin systems as a function of chemical shift of the carbons to which they are attached, one obtains all of the protonated carbon assignments concurrently with those of the protons (Table 1).

In the proton spectrum, the "doublet" at 8.00 ppm integrates to two protons and therefore corresponds to two

overlapping doublets. Also, in the HMQC spectrum two direct responses are observed, one at 107.8 ppm and the other at 115.3 ppm; both correlate with the doublet at 8.00 ppm. The HMQC-TOCSY spectrum shows that both protons at 8.00 ppm relayed coherence to the triplet at 7.60 ppm. These results show that the overlapping doublets at 8.00 corresponds to H3 and H5 and the triplet at 7.60 ppm corresponds to H4. From the direct responses in both the HMQC and HMQC-TOCSY spectra C4 is assigned to the resonance at 119.1 ppm. However, the carbon resonances corresponding to C3 and C5 (*i.e.*, those at 107.8 and 115.3) cannot be differentiated from one another, for the following reasons: first, H3 and H5 have the same chemical shift, second, for both H3 and H5 relayed responses are observed with H4, and third, the HMBC spectrum (Figure 3) doesn't provide any long-range correlations that can differentiate between C3 and C5. In fact, the only long-range correlations that these carbon resonances are involved in are those of H3 with C5 and H5 with C3.

With the proton and protonated carbon assignments complete, the quaternary carbon assignments are made from long-range correlations observed in the HMBC spectrum. Correlations are observed between the carbon resonating at 122.1 and the proton resonances corresponding to H1 and H2, revealing that this carbon resonance corresponds to C9b. Likewise, C2a is identified as the resonance at 128.3 from correlations with H1, H2, H3 and H4. C5a is identified as the resonance at 128.0 from correlations with H4 and H5; the resonance at 129.8 is assigned to C5b, from correlations with H7 and H9. Finally, C9a is assigned to the resonance at 128.9 based on correlations observed with H6 and H8. The proton and carbon chemical shift assignments of **1** are listed in Table 1.

Compound **2**.

The ^{1}H spectrum of **2** is completely resolved, and its appearance is first-order. Therefore, it is easy to identify the two- and four-spin systems in the COSY spectrum. To initiate chemical shift assignments, H5 is assigned to the singlet resonating at 8.00 ppm. In the HMBC spectrum (Figure 4), correlations are observed between the resonance corresponding to H5 and the protonated ^{13}C resonances at 115.5 and 129.0 ppm. The resonance at 115.5 is

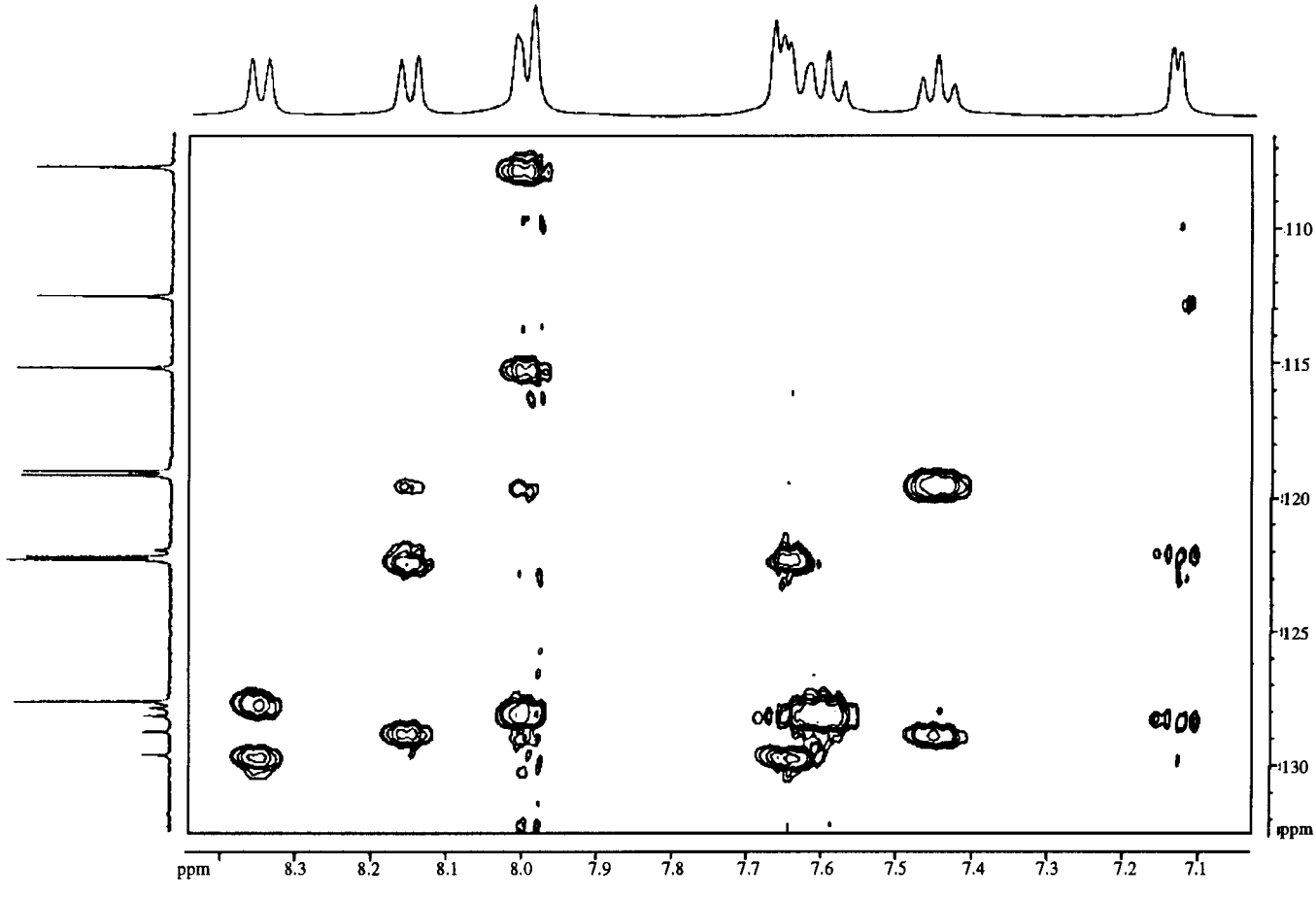


Figure 3. HMBC spectrum of **1**.

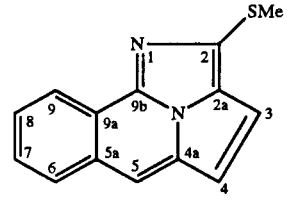
Table 1

The ^1H and ^{13}C NMR Chemical Shifts of **1**

Position	δ ^1H	Carbons to which long-range correlations are observed	δ ^{13}C
1	7.14	C2, C9b, C2a	105.6
2	7.66 [a]	C9b, C2a, C1	112.7
2a			128.3
3	8.00	C5, C2a	107.8 [b]
4	7.60	C2a, C5a	119.1
5	8.00	C3, C5a	115.3 [b]
5a			128.0
5b			129.8
6	8.15	C8, C9a	119.3
7	7.64 [a]	C9, C5b	127.8
8	7.45	C6, C9a	122.3
9	8.35	C7, C5b	122.5
9a			128.9
9b			122.1

[a] Taken from 1D-slices of the HMQC spectrum. [b] These two assignments are interchangeable.

assigned to C4 based on the long-range correlation with H5 and the direct correlation, observed in the HMQC spectrum (Figure 5), with the doublet at 7.22 ppm. The doublet at 7.22 ppm is a member of the two-spin system and therefore, must correspond to H4. The resonance at 129.0 ppm is assigned to C6 based on the long-range correlation with H5, and the direct correlation observed with the doublet at 8.14. The doublet at 8.14 is a member of the four-spin system and therefore, must correspond to H6.



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With H4 and H6 assigned, the other members of their respective spin systems are easily assigned from correlations observed in the COSY spectrum. H3 is assigned to the doublet resonating at 7.55 ppm from correlation with H4. The triplet at 7.68, the triplet at 7.76 and the doublet at 8.86 are assigned to H7, H8 and H9, respectively, based on correla-

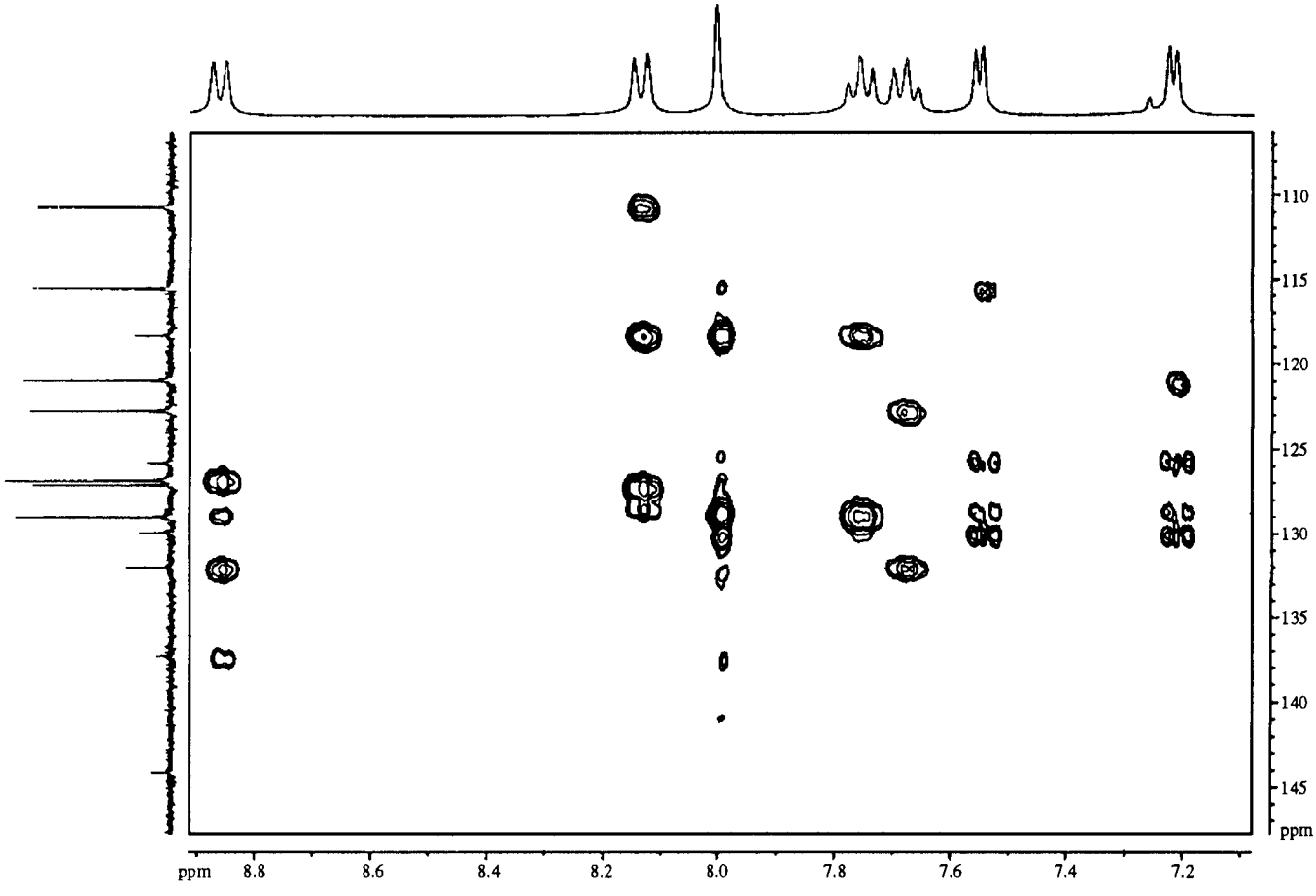

Figure 4. HMBC spectrum of **2**.

Table 2

The ^1H and ^{13}C NMR Chemical Shifts of **2**

Position	δ^1H	Carbons to which long-range correlations are observed	$\delta^{13}C$
2			144.1
2a			125.8
3	7.55, d	C4, C2a, C4a	120.9
4	7.22, d	C3, C2a, C4a	115.5
4a			130.0
5	8.00, s	C4, C6, C4a, C5a, C9a	110.7
5a			132.0
6	8.14, d	C5, C8, C9a	129.0
7	7.68, t	C9, C5a	126.8
8	7.76, t	C7, C5a, C9b	127.1
9	8.86, d		122.7
9a			118.3
9b			137.3
SCH_3	2.91, s		15.7

tions observed in the COSY spectrum and long-range correlations observed in the HMBC spectrum. With all of the protons assigned, the protonated carbon assignments are made directly from correlations observed in the HMQC spectrum.

Finally, all that remains is to assign the quaternary carbons using long-range correlations observed in the HMBC spectrum. The resonance at 118.3 is identified as C9a from long-range correlations with H5, H6 and H8. Likewise C5a is identified as the resonance at 132.0 from correlations with H7, H9 and H5; C9b is identified as the resonance at 137.3 from a correlation with H9. Long-range correlations are observed between the carbon resonating at 130.0 and the ^1H resonances corresponding to H3, H4 and H5, identifying this resonance as C4a; C2a is identified as the resonance at 125.8 from correlations with H3 and H4. Finally, C2 is assigned to the resonance at 144.1 based on chemical shift and because, as expected, long-range correlations with this resonance are not observed. The chemical shift assignments of **2** are listed in Table 2.

EXPERIMENTAL

All nmr spectra were acquired on a Bruker AMX 360 MHz NMR spectrometer operating at an observation frequency of 360.13 MHz for ^1H and 90.56 for ^{13}C. All 2D-nmr experiments were performed using a reverse geometry 5-mm broad-band probe. The ^1H and ^{13}C 90° pulses were calibrated, and values of 7.2 and 14.4 μsec, respectively, were obtained. The ^1H spectra

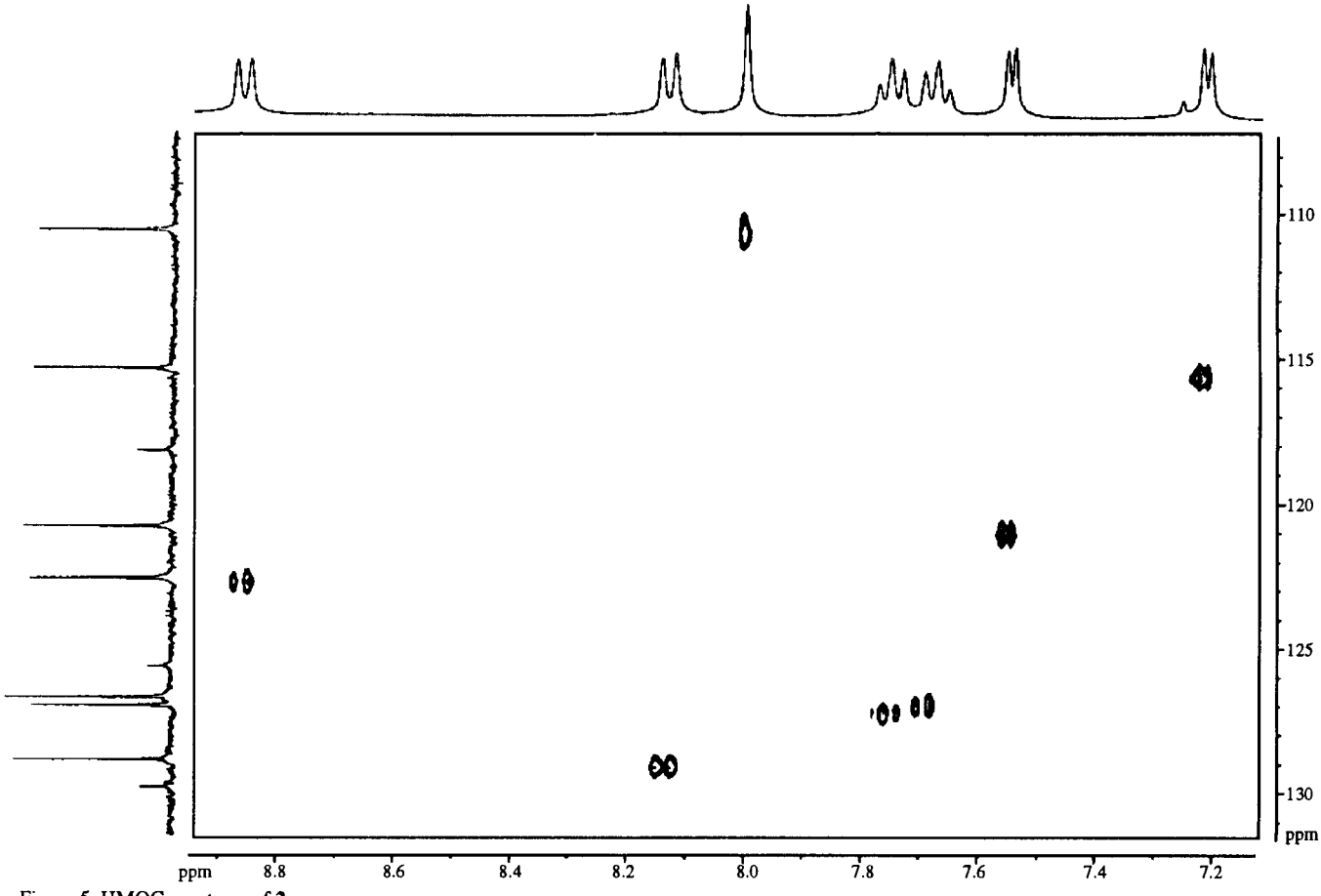

Figure 5. HMQC spectrum of **2**.

were recorded using 16384 data points and were not zero filled; the carbon spectra were recorded using 65536 data points and were then zero-filled to 128K points.

The COSY experiment was performed using the standard Bruker pulse program (*cosy90*) [2]. The COSY spectra were acquired with 1024 by 256 points and upon processing F_1 were zero-filled to achieve a final real data matrix of 512 by 512 points. All COSY spectra were symmetrized. An interpulse delay of 2 seconds was used for all COSY experiments. The HMQC experiment used the Bruker pulse program (*invbdgtp*) optimized for 165 Hz $^1J_{CH}$ (3 msec delay) [3]. The HMQC-TOCSY experiment used the standard Bruker pulse program (*invbmltp*) with a 12 msec mixing time [4]. For the HMBC experiment the Bruker pulse program (*inv4lplrnd*) [5] was used. The HMBC experiment was optimized for 10.6 Hz $^3J_{CH}$ giving a delay of 47msec; a delay for the suppression of short-range responses of 3 msec was used. The HMQC and HMQC-TOCSY spectra were acquired at 1024 by 256 points and the HMBC spectra were acquired with 1024 by 128 points and upon processing were zero-filled to achieve a real data matrix of 512 by 512 points. An interpulse delay of 1 second was used for the HMQC and HMQC-TOCSY experiments and 2.5 seconds was used for the HMBC experiment.

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REFERENCES AND NOTES

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[2] K. Nagayama, A. Kumar, K. Wüthrich and R. R. Ernst, *J. Magn. Reson.*, **40**, 321 (1980).

[3] A. Bax and S. Subramanian, *J. Magn. Reson.*, **67**, 565 (1986).

[4] L. Lerner and A. Bax, *J. Magn. Reson.*, **69**, 375 (1986).

[5] A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, **108**, 2093 (1986).