Total Assignment of the ^{1}H and ^{13}C NMR Spectra of Pyrrolizino-[3,4,5-*a,b*]isoquinoline, Benzo[1,2]pyrrolizino[3,4,5-*a,b*]isoquinoline and 2-Methylthiopyrrolizino[3,4,5-*a,b*]isoquinoline

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The total ^{1}H and ^{13}C nmr spectral assignments of pyrrolizino[3,4,5-*a,b*]isoquinoline, benzo-[1,2]pyrrolizino[3,4,5-*a,b*]isoquinoline and 2-methylthiopyrrolizino[3,4,5-*a,b*]isoquinoline are reported. The concerted use of the COSY, HMQC, HMBC and nOe-difference experiments is used to generate total assignments of the ^{1}H and ^{13}C nmr spectra.

Introduction.

The ^{1}H and ^{13}C nmr spectral assignments of pyrrolizino-[3,4,5-*a,b*]isoquinoline (1), benzo[1,2]pyrrolizino[3,4,5-*a,b*]isoquinoline (2) and 2-methylthiopyrrolizino[3,4,5-*a,b*]isoquinoline (3) are described. The ^{1}H and ^{13}C nmr resonances are identified through interactive interpretation of nOe-differance, COSY, HMQC and HMBC spectra.

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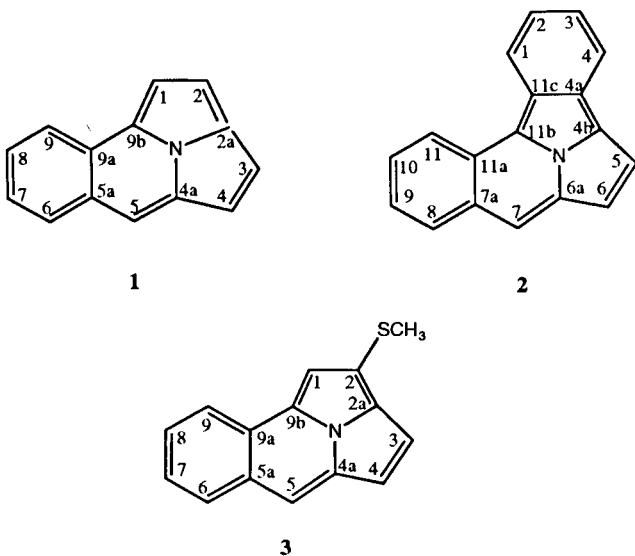
Compound 1.

To initiate chemical shift assignments for **1** the singlet resonating at 8.14 ppm was irradiated and transferred nOe to the doublets resonating at 7.33 and 8.18 ppm. From the COSY spectrum (Figure 1) it is observed that the doublet resonating at 7.33 is a member of a two-spin system and the doublet resonating at 8.18 is a member of a four-spin system. These results then show that the doublet resonating at 7.33 ppm corresponds to H4 and the doublet at 8.18 to H6. With H4 and H6 identified, the other members of their respective spin systems are easily assigned from correlations observed in the COSY spec-

trum. All that remains is to differentiate between the proton resonances corresponding to H1 and H2.

In the COSY spectrum, the resonance corresponding to H5 shows a long-range correlation with the doublet resonating at 7.43 ppm. Inspection of the structure of **1** reveals that H5 and H2 are separated by six bonds in an epi-zig-zag pattern. Therefore we assign H2 to the doublet resonating at 7.43 ppm. Likewise the doublet at 7.33 corresponding to H4 shows a long-range correlation with the resonance at 7.60 ppm. H4 and H1 are also separated by six bonds, which are oriented in an epi-zig-zag pattern. Therefore, the resonance at 7.60 corresponds to H1. The six-bond response is very interesting because $^6J_{HH}$ couplings are very rare. Also, H5 is long-range coupled through five bonds with H9 as well. These long-range correlation pathways are highlighted using bold and dashed lines in structure **4**.

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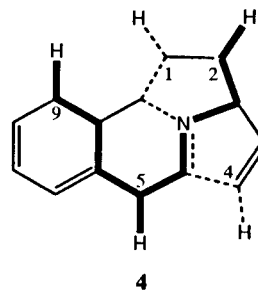
With all of the protons assigned, most of the protonated carbon assignments were determined from one-bond correlations observed in the HMQC spectrum (Figure 2). In the proton spectrum the resonances corresponding to H3 and H8 are overlapped as are those corresponding to H1 and H7. Therefore the ^{13}C resonances corresponding to these positions cannot be assigned directly from the HMQC correlations. However, these resonances are easily identified from long-range correlations observed in the
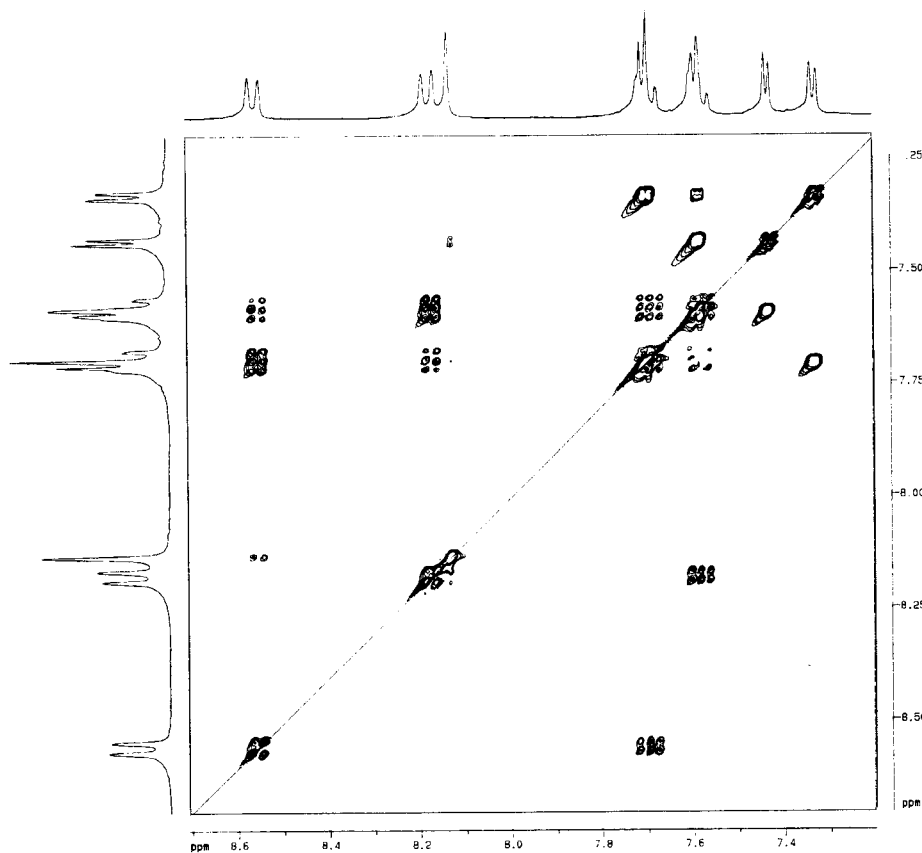
Figure 1. COSY Spectrum of **1**. The data above the diagonal were subjected to sine multiplication prior to fourier transformation of both F_2 and F_1. The data below the diagonal were subjected to gaussian multiplication prior to fourier transformation of F_2 and then with sine multiplication prior to fourier transformation of F_1. The spectrum above the diagonal shows correlation responses for both long- and short-range couplings whereas the spectrum below the diagonal shows correlations between vicinal protons exclusively.
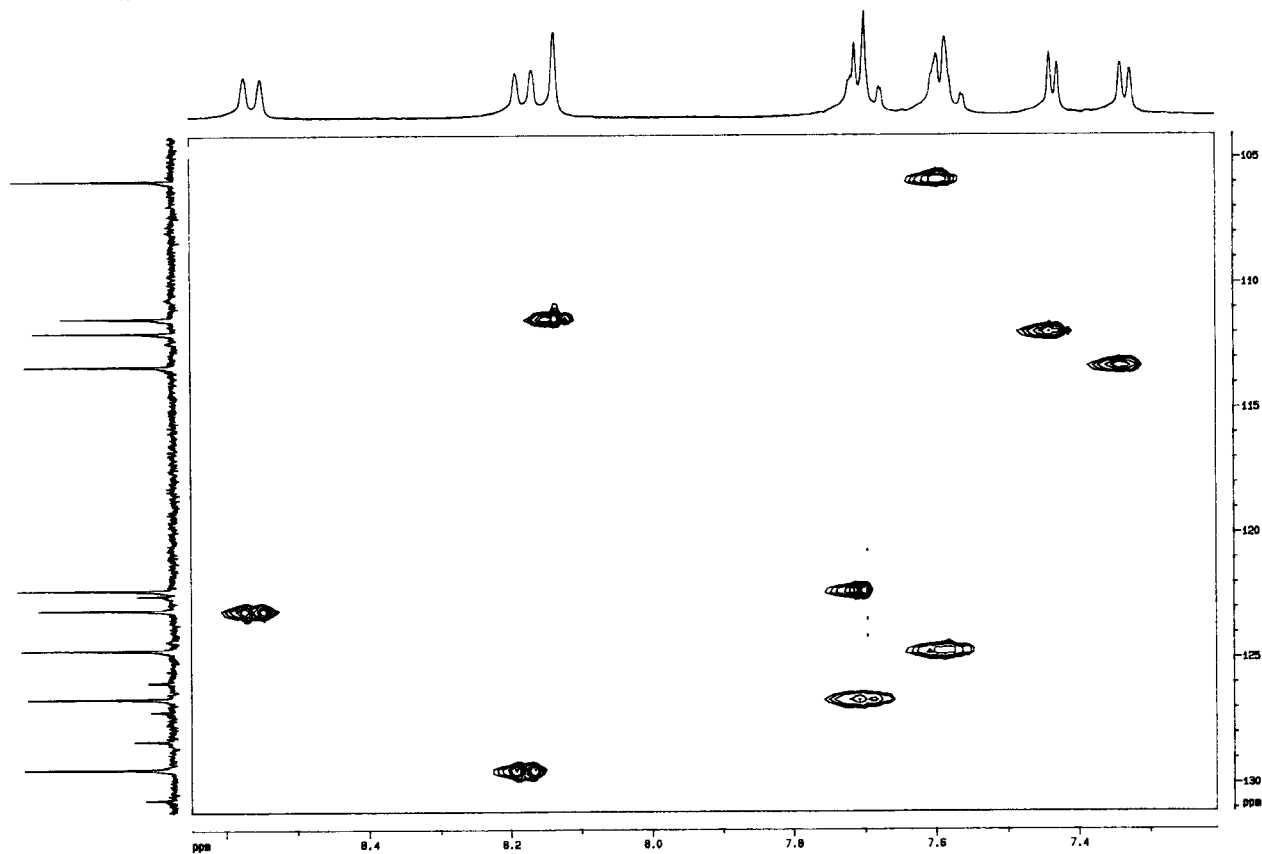
Figure 2. HMQC spectrum of **1**.

HMBC spectrum (Figure 3). In the HMBC spectrum, the carbon resonating at 122.5 ppm correlates with the proton resonance corresponding to H4, and therefore corresponds to C3. The carbon resonating at 126.6 ppm correlates with the proton resonance corresponding to H6 identifying this resonance as C8. Likewise, the resonance at 111.9 ppm correlates with the proton resonance corresponding to H2 identifying the resonance at 111.9 as C1; the resonance at 124.9 correlates with the proton resonance corresponding to H9 identifying the resonance at 124.9 as C7.

Finally then all that remains is to identify the quaternary carbon resonances from correlations observed in the HMBC spectrum. The quaternary carbon resonating at 122.5 ppm correlates with the proton resonances corresponding to H5, H6 and H8. These correlations identify the resonance at 122.5 ppm as that corresponding to C9a. Likewise the resonance at 128.3 ppm correlates with the proton resonances corresponding to H7, H9 and weakly with that of H5 thus identifying this resonance as C5a. The resonance at 125.9 ppm correlates with the proton resonances corresponding to H9, H1 and H2 identifying this resonance as C9b, and the resonance at 127.1 ppm correlates with the proton resonances corresponding to H1, H2, H3 and H4 identifying this resonance as C2a. Finally the resonance at 130.6 ppm correlates with the proton resonances corresponding to H3, H4 and H5 thus

identifying this resonance as C4a. These correlation pathways are shown in structure 5. For the benzo-moiety, mostly three-bond responses are observed in the HMBC spectrum. However, for the portion of the molecule that surrounds the nitrogen atom all possible two- and three-bond responses are observed. The ^{1}H and ^{13}C chemical shift assignments of 1 and the long-range correlations observed in the HMBC spectrum are listed in Table 1.

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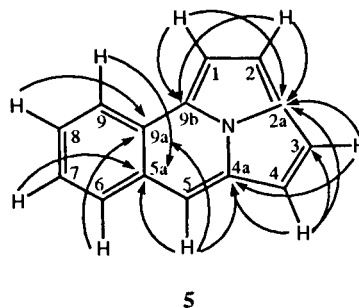
Compound 2.

As for 1 the singlet corresponding to H7 serves as the entry point for the assignment of the [1]H- and ^{13}C-nmr spectra of 2. Irradiation of the singlet resonaating at 8.58 ppm transferred nOe to the doublets resonating at 8.34 and 7.43 ppm. The COSY spectrum (Figure 4) shows that the doublet at 8.34 is a member of a four-spin system
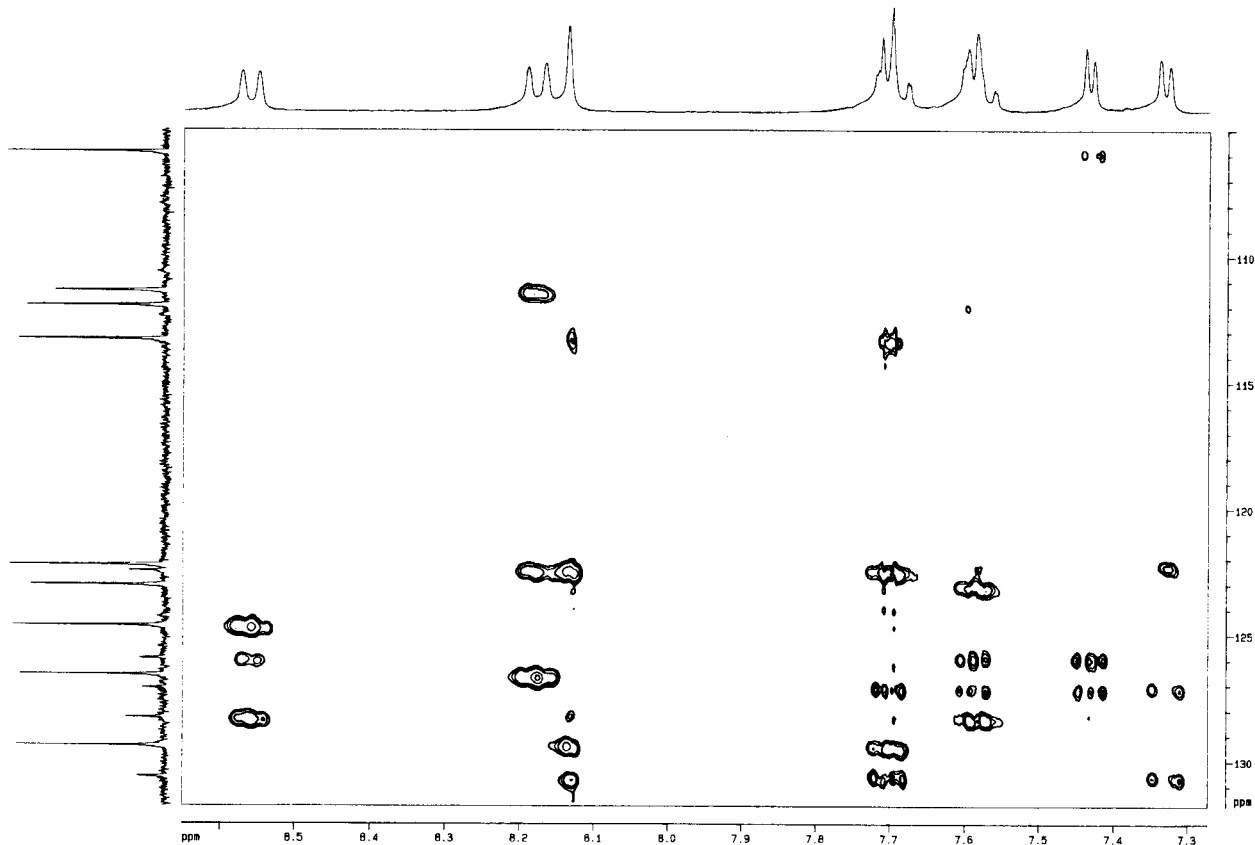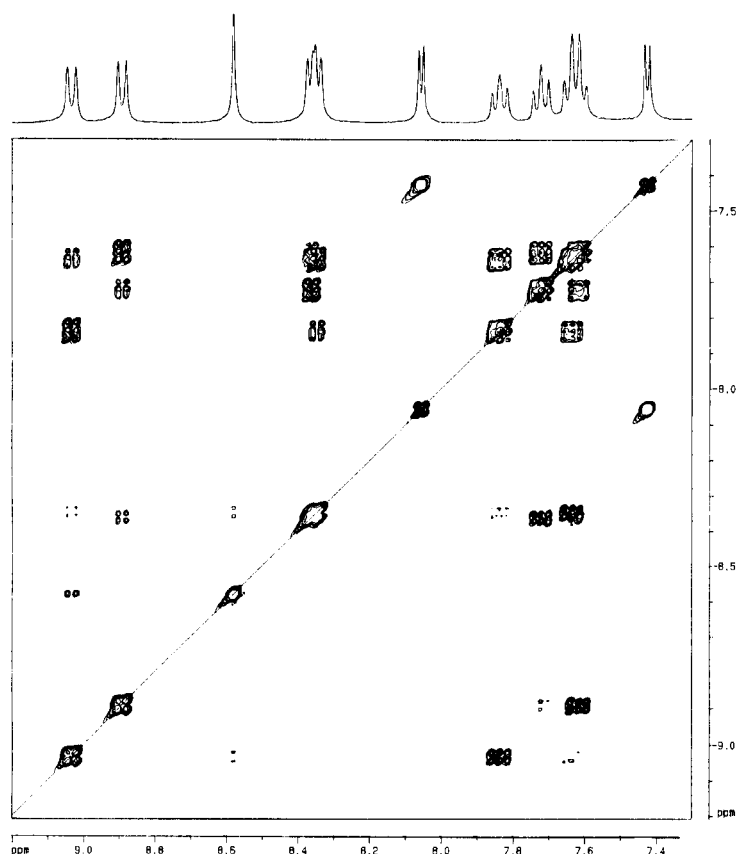

Figure 3. HMBC spectrum of 1.

Figure 4. COSY Spectrum of **2**. The data above the diagonal weres subjected to sine multiplication prior to fourier transformation of both F_2 and F_1. The data below the diagonal were subjected to gaussian multiplication prior to fourier transformation of F_2 and then with sine multiplication prior to fourier transformation of F_1. The spectrum above the diagonal shows correlation responses for both long- and short-range couplings whereas the spectrum below the diagonal shows intense correlations between vicinal protons exclusively.

identifying this resonance as H8, and the doublet at 7.43 ppm is a member of a two-spin system identifying this resonance as H6. With H8 assigned, H9, H10 and H11, the other members of this four-spin system, are assigned from correlations observed in the COSY spectrum, as is H5, the other member of the two-spin system. By assigning H1 to the doublet resonating at 8.90 ppm, based on
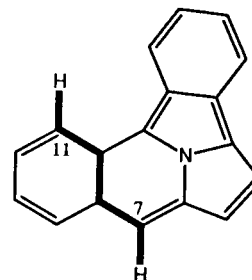
chemical shift, H2, H3 and H4 are all assigned from correlations observed in the COSY spectrum. Also observed in the COSY spectrum is the five-bond coupling response between H7 and H11. This correlation pathway is highlighted in structure **6**. With the ^{1}H spectrum assignment completed the protonated carbons are all assigned directly from one-bond correlations observed on the HMQC spectrum (Figure 5).

The quaternary carbon resonances are assigned from long-range correlations observed in the HMBC spectrum (Figure 6). The quaternary carbon resonating at 120.3 ppm correlates with the proton resonances corresponding to H5 and H6 identifying this resonance as C4b, and the resonance at 120.5 correlates with the proton resonances corresponding to H1 and H11 identifying this resonance
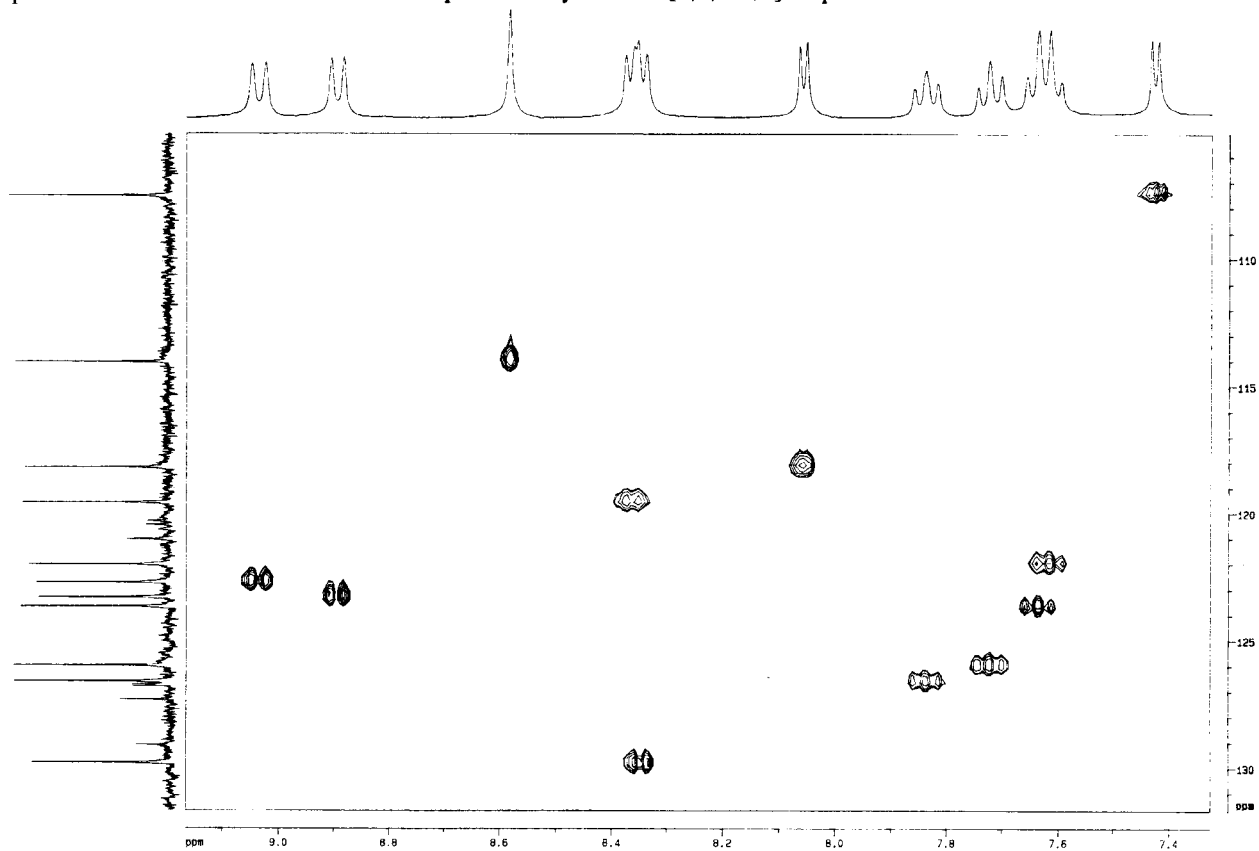
Table 1

[1]H and [13]C Assignments for Compound **1** and the
Long-range Correlations Observed in the HMBC Spectrum

Position	δ^1H (ppm)	Carbons to which long-range correlations are observed	δ^{13}C (ppm)
1	7.60 [a]	C2, C2a, C9b	105.9
2	7.43	C1, C2a, C9b	111.9
2a			127.1
3	7.71 [a]	C4, C2a, C4a	122.5
4	7.33	C3, C2a, C4a	113.3
4a			130.6
5	8.14	C4, C6, C4a, C5a, C9a	111.4
5a			128.3
6	8.18	C5, C8, C9a	129.4
7	7.59 [a]	C9, C5a	124.7
8	7.71 [a]	C6, C9a	126.6
9	8.56	C7, C5a, C9b	123.0
9a			122.5
9b			126.0

[a] Chemical shifts taken from 1D-slices of the HMQC spectrum.

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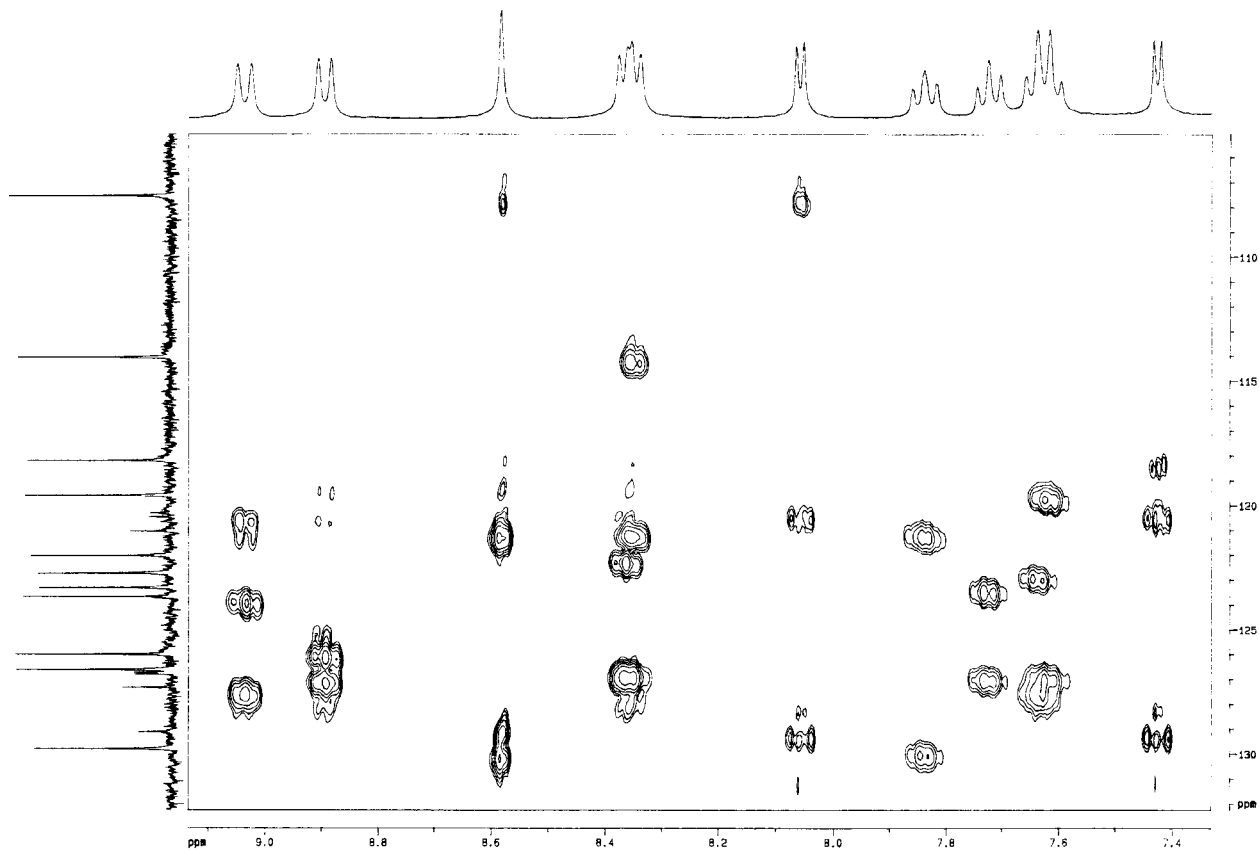Figure 5. HMQC spectrum of **2**.

Figure 6. HMBC spectrum of **2**.

as C11b. The carbon resonance at 121.0 ppm correlates with the proton resonances corresponding to H7, H8 and H10 identifying the resonance at 121.0 as C11a. The resonance at 126.7 ppm correlates with the proton resonances corresponding to H4 and H2 thus identifying this resonance as C11c. The resonance at 126.8 is identified as C4a from correlations with H1 and H3 and C7a is identified as the resonance at 127.3 from correlations with H9, H11 and weakly with H8 and finally the resonance at 129.1 ppm is identified as C6a from correlations with H5, H6 and H7. These correlation pathways are shown in structure 7. The ^{1}H and ^{13}C chemical shift assignments and long-range correlations are listed in Table 2.

Table 2

^{1}H and ^{13}C Assignments for Compound 2 and the Long-range Correlations Observed in the HMBC Spectrum
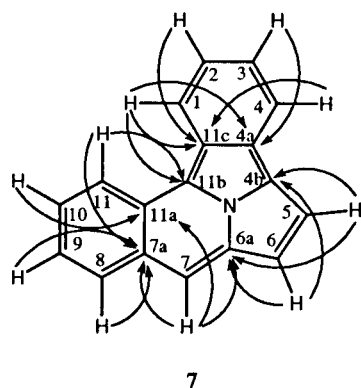
Position	δ^{1}H	Carbons to which long-range correlations are observed	δ^{13}C
1	8.90	C3, C4a, C11b	123.3
2	7.62	C4, C11c	122.0
3	7.73	C1, C4a	126.0
4	8.37	C2, C11c	119.6
4a			126.8
4b			120.3
5	8.06	C6, C4b, C6a	118.2
6	7.43	C5, C4b, C6a	107.5
6a			129.1
7	8.58	C6, C8, C6a, C11a	114.1
7a			127.3
8	8.35	C7, C10, C7a, C11a	129.8
9	7.64	C11, C7a	123.7
10	7.84	C8, C11a	126.6
11	9.04	C9, C7a, C11b	122.7
11a			121.0
11b			120.5
11c			126.7

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Compound 3.

For compound 3 the two singlets in the ^{1}H spectrum were differentiated using nOe-difference experiments. Irradiation of the singlet resonating at 7.41 ppm transferred nOe to the doublet resonating at 8.43 ppm, identi-
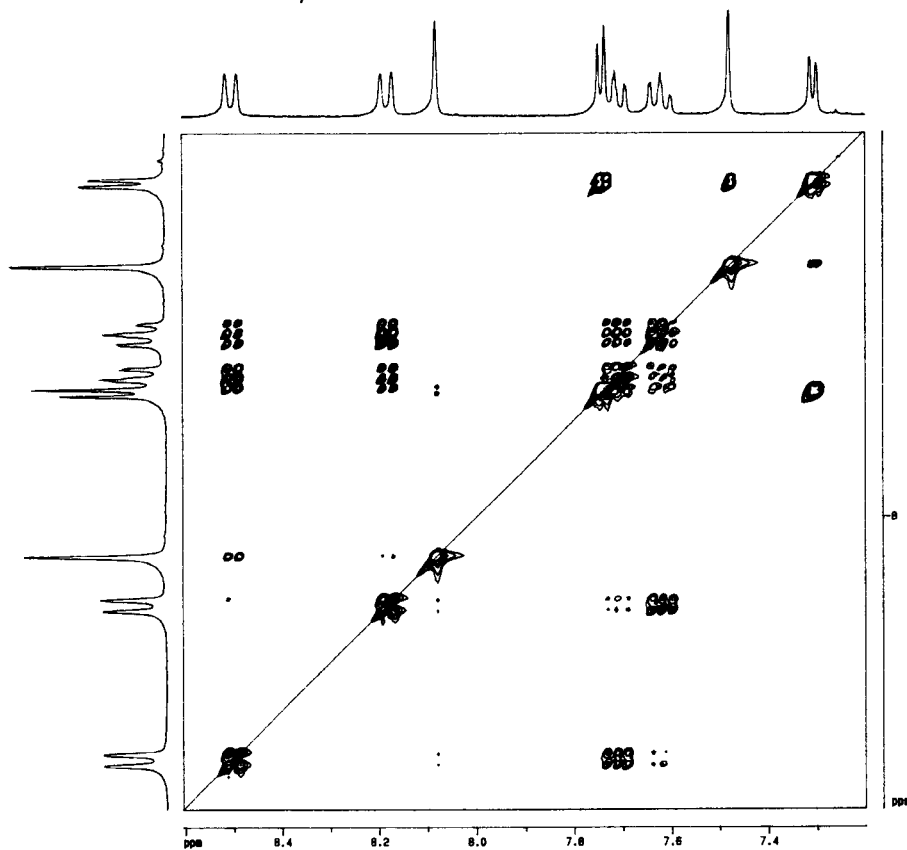

Figure 7. COSY Spectrum of 3. The data above the diagonal were subjected to sine multiplication prior to fourier transformation of both F_2 and F_1. The data below the diagonal were subjected to gaussian multiplication prior to fourier transformation of F_2 and then with sine multiplication prior to fourier transformation of F_1. The spectrum above the diagonal shows correlation responses for both long- and short-range couplings whereas the spectrum below the diagonal shows intense correlations between vicinal protons exclusively.
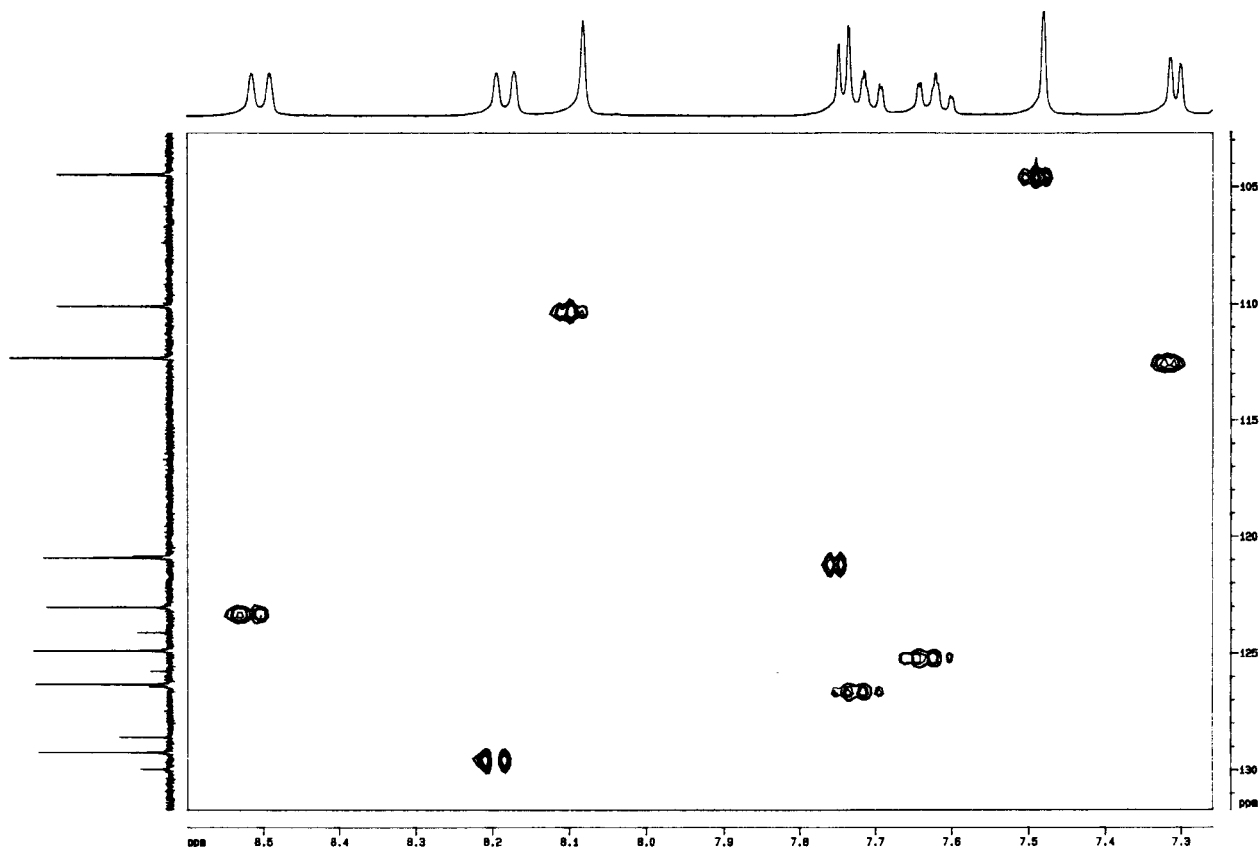
Figure 8. HMQC spectrum of 3.

fying the singlet as H1 and the doublet as H9. Irradiation of the singlet resonating at 8.01 ppm transferred nOe to two proton doublets resonating at 7.24 and 8.11 ppm. The doublet at 7.24 is identified as H4 because it is a member of the two-spin system and the doublet at 8.11 is identified as H6 because it is a member of the four-spin system. With these protons assigned from the nOe experiments the remaining protons are all assigned from correlations observed in the COSY spectrum (Figure 7). Also observed in the COSY spectrum is the five-bond coupling response between H5 and H9 as well as the six-bond coupling response between H1 and H4. These correlation pathways are shown in structure 8. Because the proton spectrum is well resolved the protonated carbon assignment is obtained directly from one-bond correlations observed on the HMQC spectrum (Figure 8).
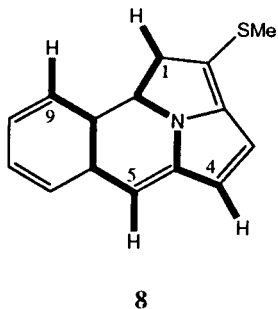
The quaternary carbons are all assigned from long-rang correlations observed in the HMBC spectrum (Figure 9). Long-range correlations are observed between the quaternary carbon resonating at 120.8 ppm and the and the triplet corresponding to H8, the singlet corresponding to H5 and the doublet corresponding to H6, identifying this carbon resonance as C9a. The quaternary carbon resonating at 124.1 ppm correlates with the singlet corresponding

Table 3

^{1}H and ^{13}C Assignments for Compound 3 and the Long-range Correlations Observed in the HMBC Spectrum

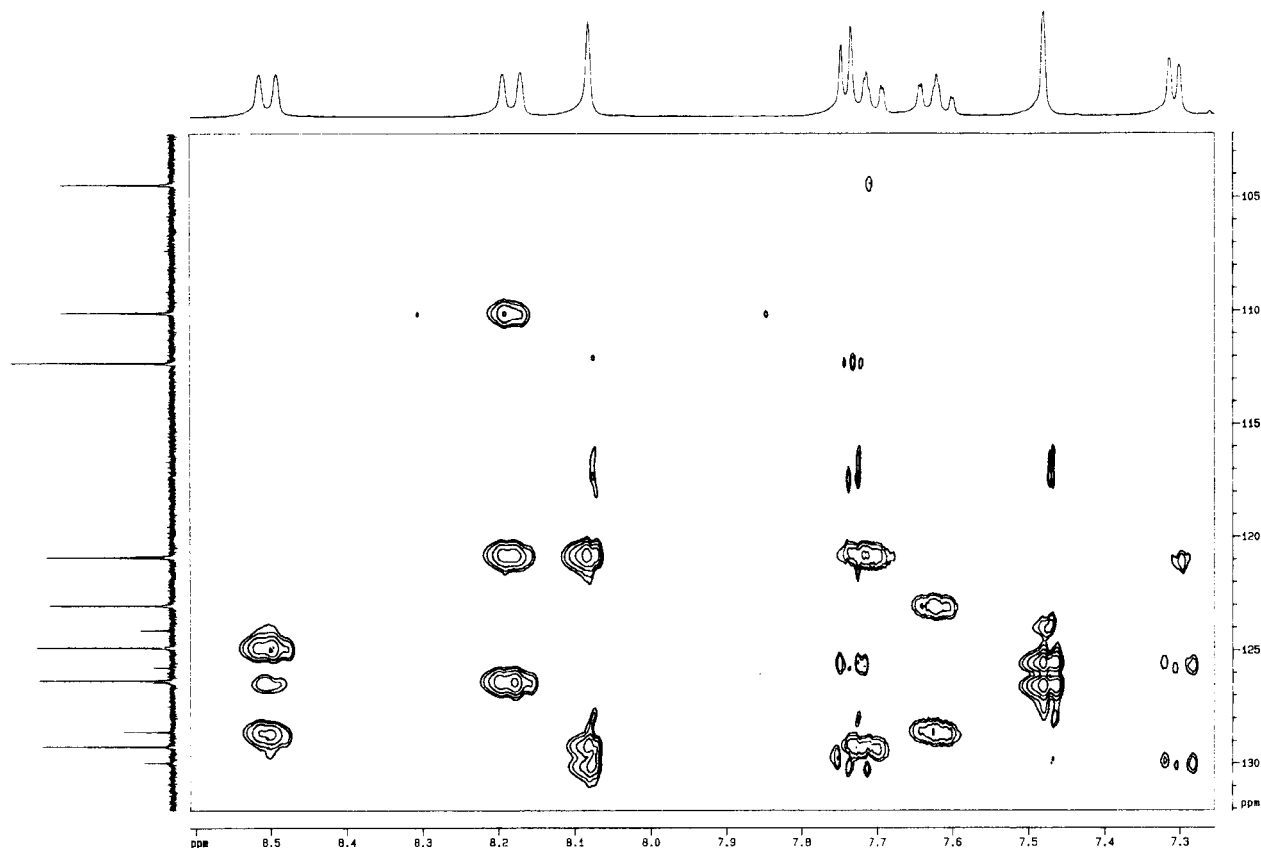| Position	δ^1H	Carbons to which long-range correlations are observed	$\delta^{13}C$
1	7.41	C2, C2a, C9b	104.5
2			124.1
2a			125.8
3	7.67	C4, C2a, C4a	120.9
4	7.24	C3, C2a, C4a	112.3
4a			130.0
5	8.01	C6, C4a, C9a	110.1
5a			128.6
6	8.11	C5, C8, C9a	129.2
7	7.55	C9, C5a	124.9
8	7.65	C6, C9a	126.3
9	8.43	C7, C5a, C9b	123.0
9a			120.8
9b			126.4
Me	2.76		18.0

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Figure 9. HMBC spectrum of 3.

to H1 identifying this resonance as C2. The carbon resonating at 125.8 ppm correlates with the proton resonances corresponding to H1, H3 and H4 identifying this resonance as C2a. The carbon resonating at 126.4 ppm correlates with the proton resonances corresponding to H1 and H9 identifying this resonance as C9b, also, the carbon resonance at 128.6 ppm correlates with the proton resonances corresponding to H7 and H9 identifying this resonance as C5a. Finally the carbon resonating at 130.0 ppm correlates with the proton resonances corresponding to H3, H4 and H5 identifying this resonance as C4a. These correlation pathways are shown in structure 9, and the ^{1}H and ^{13}C chemical shift assignments of 3 and the long-range correlations observed in the HMBC spectrum are listed in Table 3.

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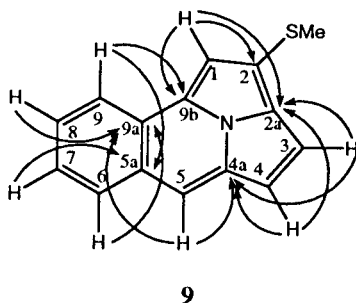
EXPERIMENTAL

All nmr spectra were acquired on a Bruker AMX 360 MHz NMR spectrometer operating at an observation frequency of 360.13 MHz for ^{1}H and 90.56 for ^{13}C. All 2D-nmr experiments were performed using a reverse geometry 5-mm broad-band probe. The ^{1}H and ^{13}C 90° pulses were calibrated, and values of 7.2 and 14.4 μsec, respectively, were obtained. The ^{1}H spectra were recorded at 16384 data points and was not zero filled and the carbon spectra at 65536 data points which was then zero-filled to 128K data 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 was 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]. For the HMBC experiment the Bruker pulse program (inv4lplrnd) [4] was used. The HMBC experiment was optimized for 10.6 Hz $^3J_{CH}$ giving a delay of 47 msec; a delay for the suppression of short-range responses of 3 msec was used. The HMQC 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 experiment and 2.5 seconds was used for the HMBC experiment.

REFERENCES AND NOTES

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[3]   A. Bax and S. Subramanian, *J. Magn. Reson.*, **67**, 5655 (1986).

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