

Complete ^{13}C NMR Assignment of Annelated Phenanthridines
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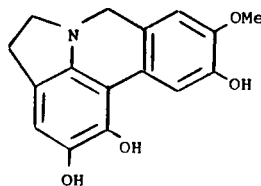
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Two-dimensional nmr techniques were used for the complete assignment of ^{13}C nmr spectra of pyrrolo[1,2-f], pyrazolo[1,5-f], and 1,2,4-triazolo[1,5-f]phenanthridines.

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We recently reported a new synthesis and the preliminary anticancer tests results of the pyrrolo[1,2-f]-phenanthridines **1** [1], structurally related to



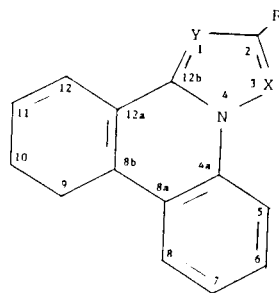
PSEUDOLICORINE

pseudolicorine, a natural product which attracted considerable interest through its anticancer activity [2-5]. Considering that ethidium derivatives, antitumor drugs, bind to DNA by intercalation [6], we thought to undertake nmr studies on the interaction between DNA and annelated phenanthridine derivatives.

In anticipation of such an approach we have found it necessary to make complete ^{13}C nmr assignments for compounds **1-3**. Although this would have been difficult to

achieve using one-dimensional nmr techniques, the use of two-dimensional nmr spectroscopy (homo- and heteronuclear shift correlation), which has attracted growing attention over the past few years [7-15] allowed us to provide complete and unambiguous ^{13}C assignments for compounds **1-3**.

We wish to discuss in detail the approach used for the assignment of the ^{13}C resonances for 2-acetyl-1-bromo-3-methylpyrrolo[1,2-f]phenanthridine (**1a**).



- | | | |
|---|---|-------------------------------|
| 1 | a | X = C-Me; Y = C-Br; R = COMe |
| | b | X = C-Me; Y = C-Br; R = COOEt |
| 2 | | X = N; Y = C-Br; R = Me |
| 3 | a | X = Y = N; R = COMe |
| | b | X = Y = N; R = COOEt |

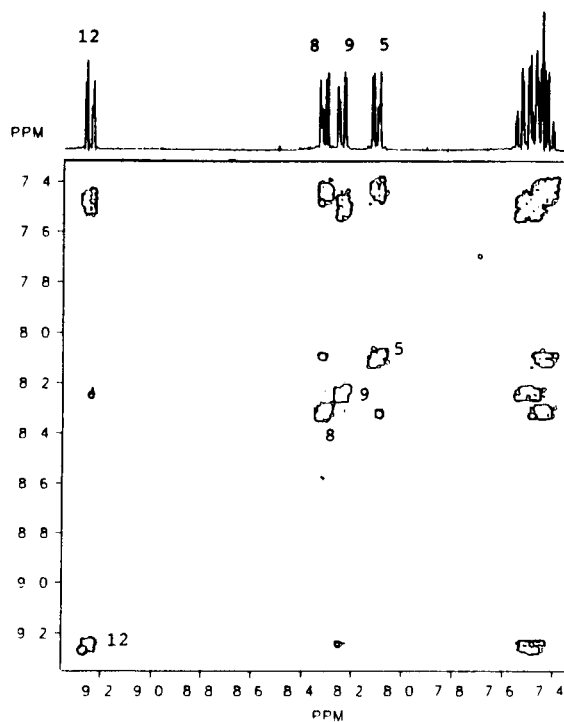


Figure 1. Contour plot of the ^1H - ^1H homocorrelated two-dimensional nmr spectrum of **1a**.

The homocorrelated two-dimensional nmr spectrum obtained for **1a** is shown in Figure 1. Protons H-5, H-8, H-9 and H-12 appear as four distinct resonances in the spectrum, downfield from the remaining H-6, H-7, H-10 and H-11 multiplets. The HOMOCOR spectrum further identifies the two pairs of resonances H-5, H-8 and H-9, H-12 *via* their long-range coupling interactions. The bromo substituent at C-1 causes H-12 to occupy the most downfield position, and H-5 can be expected to be found upfield from H-8 due to its proximity to the nitrogen atom at position 4. The remaining multiplets, corresponding to H-6, H-7, H-10 and H-11 cannot be resolved at 300 MHz.

The ^1H - ^{13}C heterocorrelated two-dimensional nmr spectrum detecting only direct coupling interactions (Figure 2, coupling constant optimized for $^1J_{\text{CH}} = 160$ Hz [16]) demonstrates that the assignments for C-5, C-8, C-9 and C-12 become known once H-5, H-8, H-9 and H-12 are identified.

Figure 3 shows the ^1H - ^{13}C heterocorrelated two-dimensional nmr spectrum detecting long-range ^1H - ^{13}C coupling interactions. In aromatic systems $^3J_{\text{CH}}$ is most prominent with a value of *ca.* 7 Hz [16], and we can thus use Figure 3 to identify carbon resonances which are in

the *meta* positions to the known proton resonances H-5, H-8, H-9 and H-12.

The four pyrrole carbon atoms are readily assigned. Due to its bromo substituent, the C-1 resonance experiences a marked upfield shift with δ C-1 being 90.58 ppm. C-2 and C-3 correspond to the only two resonances in the ^{13}C nmr spectrum showing long-range coupling to non-aromatic protons, and C-12b displays *meta* coupling to H-12, yet to no other protons (Figure 3).

Two further carbon resonances can be assigned *via* their being in the *meta* position to H-12: C-8b and C-10, both also showing coupling interaction with H-10. It was interesting to note that no resonance was observed for the coupling interaction between H-8 and C-8b (Figure 3b). No ready explanation for this observation appears available. Although a proton coupled carbon spectrum has been recorded, it was not possible to determine the magnitude of the $^3J_{\text{C8b-H8}}$ coupling due to extensive overlap of the carbon multiplets.

Finally, in an analogous, straightforward fashion, using Figure 3, the remaining carbon resonances are assigned: C-12a (H-9, H-11), C-11 (H-9, H-11), C-8a (H-9, H-5, H-7), C-7 (H-5, H-7), C-6 (H-8, H-6), C-4a (H-8, H-6). Following

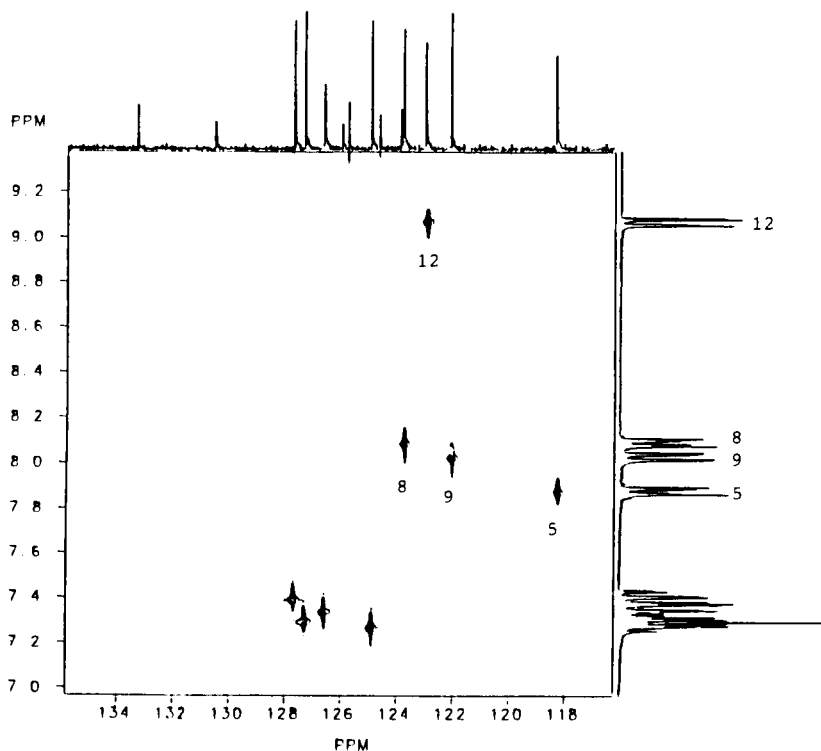


Figure 2. Contour plot of the ^1H - ^{13}C heterocorrelated two-dimensional nmr spectrum of **1a** detecting direct coupling.

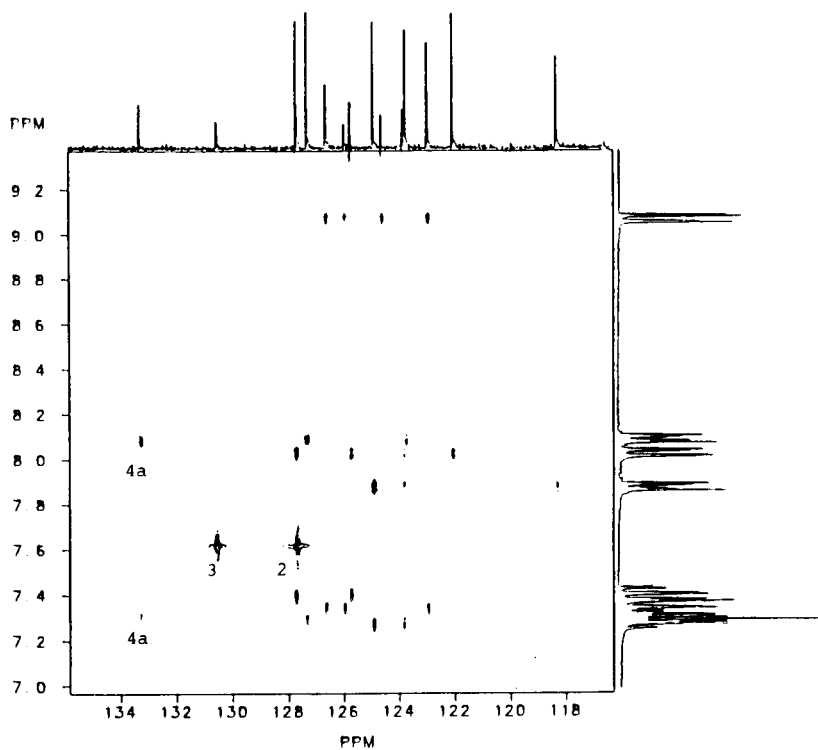


Figure 3a. Contour plot of the ^1H - ^{13}C heterocorrelated two-dimensional nmr spectrum of **1a** detecting long-range coupling. The responses observed for C-2 and C-3 are due to methyl resonances which fold in from outside the spectral window range.

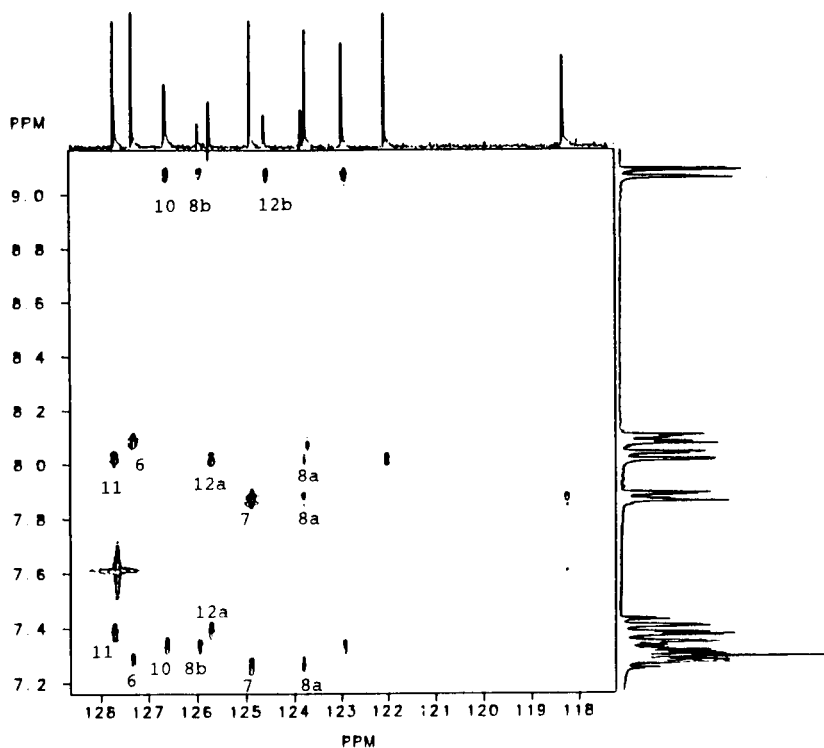


Figure 3b. Contour plot of the ^1H - ^{13}C heterocorrelated two-dimensional nmr spectrum of **1a** detecting long-range coupling. Expansion of the region between 121.7 ppm and 127.8 ppm.

procedures analogous to the one outlined above, complete assignments were also made for compounds **1b**, **2** and **3**. The ^1H and ^{13}C nmr chemical shift values for the various compounds are given in Tables 1 and 2.

Table 1

 ^1H NMR Resonance Assignments for Compounds 1-3

Position	1a	1b	2	3a	3b
5	8.11	8.10	8.52	8.61	8.65
6 [a]	7.58	7.59	7.66	7.76	7.76
7 [a]	7.55	7.55	7.46	7.67	7.66
8	8.32	8.32	8.36	8.48	8.48
9	8.24	8.23	8.40	8.51	8.50
10 [a]	7.63	7.63	7.64	7.82	7.82
11 [a]	7.69	7.68	7.63	7.74	7.75
12	9.25	9.33	9.06	8.77	8.78
2-Sub	2.76 (CH ₃)	4.41 (CH ₂)	2.52 (CH ₃)	2.87 (CH ₃)	4.60 (CH ₂)
		1.43 (CH ₃)			1.44 (CH ₃)
3-Sub	2.95 (CH ₃)	3.04 (CH ₃)			

[a] The resonances of H-6, H-7, H-10, and H-11 were assigned using Figure 1 once the resonances of the corresponding carbons were known.

Table 2

 ^{13}C NMR Resonance Assignments for Compounds 1-3

Position	1a	1b	2	3a	3b
1	90.58	92.21	89.22	--	--
2	127.57	117.91	149.69	159.39	154.70
3	130.48	131.78	--	--	--
4a	133.18	133.22	133.34	131.25	131.45
5	118.20	118.13	115.57	116.48	116.96
6	127.23	127.14	129.04	128.42	128.56
7	124.83	124.73	124.69	126.64	126.83
8	123.66	123.62	123.02	122.19	122.36
8a	123.72	123.68	120.50	121.59	121.77
8b	125.86	125.73	126.98	128.76	129.02
9	121.98	121.81	122.27	123.12	123.27
10	126.55	126.47	128.13	130.61	130.79
11	127.62	127.58	127.52	129.19	129.38
12	122.89	123.12	123.44	125.14	125.39
12a	125.62	125.73	123.32	120.70	120.77
12b	124.52	124.80	132.25	148.87	149.01
2-Sub	197.87 (CO) 32.40 (CH ₃)	164.72 (CO) 60.56 (CH ₂)	12.79 (CH ₃)	191.99 (CO) 27.39 (CH ₃)	160.34 (CO) 62.31 (CH ₃)
3-Sub	17.42 (CH ₃)	17.40 (CH ₃)			14.38 (CH ₃)

EXPERIMENTAL

The samples of compounds **1a,b** [1], **2** [17] and **3a,b** [18] utilized in these studies were prepared by dissolving either 0.1 mmole (for HOMOCOR experiments) or 0.3 mmole (for HETCOR experiments) of pure material in 0.5 ml of deuteriochloroform. All spectra were recorded using a Varian XL 300 FT nmr spectrometer operating at 75.429 and 299.943 MHz, respectively.

The acquisition and processing parameters for HOMOCOR (COSY-45) experiment [19] were as follows: 90° pulse width 17.4 μs , spectral window 710.3 Hz, acquisition time 0.360 s, number of points 512, number of transients 4, number of increments 256, final size of data matrix (512 x 512), not zero filled.

The acquisition and processing parameters for HETCOR experiments [20,21] were as follows: 90° pulse width 17 μs , calibrated by the procedure described by Martin and co-workers [22], duration of the 90°

pulse from the decoupler coils 50.1 μs , calibrated by the procedure described by Ernst [23], spectral window in the evolution domain 1474.7 Hz, spectral window in the detection domain 719.7 Hz, acquisition time 0.347 s, number of points 1024, number of transients 8, with a 4 step phase cycling procedure being used [24]. The receiver was phase-cycled to record the echo, number of increments 128, exponential line broadening factor in the first domain 1b = 1.000, in the second domain 1b2 = 0.318; final size of the data matrix (1024 x 512), zero filled in F1.

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