

The Use of NMR Measurements in the Orientation  
of Pyrrolic Substitution in 5,6-Dihydro-7-methyl-6-oxopyrrolo[1,2a]-  
[3,1,6]benzothiadiazocine

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Received January 21, 1988

The title compound **1**, has been shown to give a 1-bromo derivative **2** when subjected to free-radical bromination and a 1-dimethylaminomethyl derivative **3** by reaction under standard Mannich conditions. Vilsmeier formylation, however, furnishes the 3-substituted derivative **4**.

*J. Heterocyclic Chem.*, **26**, 81 (1989).

In a previous paper [1] we reported that free-radical bromination of the title compound **1** gave a monobromo derivative in 82% yield and that reaction under standard Mannich and Vilsmeier conditions gave a monodimethylaminomethyl and monoformyl derivative in yields of 50 and 32%, respectively. The integrity of the thiadiazocine ring in each of the substitution products was indicated by a characteristic AB quartet in the region of  $\delta$  3.1-3.6 observed in the  $^1\text{H}$ -nmr spectrum of both starting material and products (Table I). Preliminary examination of the spectra revealed the presence of two coupled pyrrolic protons, the magnitude of the coupling being 3.8, 3.5 and 3.2 Hz for the bromo, dimethylaminomethyl and formyl derivatives, respectively (Table II). This suggested that substitution had occurred in either the 1- or 3-position since in the case of 1-substitution, the three-bond coupling between protons 2 and 3 would be expected to be in the range of 3.4-4.0 Hz and if 3-substitution had occurred the

vicinal 1- and 2-proton coupling would have been predicted to be in the range of 2.4-3.1 Hz [2]. The corresponding magnitude of the four-bond coupling of protons in the 1- and 3-positions would have been expected to be in the range of 1.35-1.8 Hz [2], thus making it unlikely that 2-substituted products had been formed. Previous studies [3] on the halogenation of pyrrolo[1,2-a]quinoxaline **5** had showed that the preferential site of substitution was the 1-position and with these data in mind we began a more detailed examination of the nmr spectra of our compounds.

Table I

Proton Chemical Shifts in ppm of Compounds 1-4

Compound	H-1	H-2	H-3	H-5a	H-5b
<b>1</b>	6.87	6.24	6.51	3.54	3.20
<b>2</b>	-	6.23	6.47	3.38	3.14
<b>3</b>	-	6.135	6.48	3.46	3.22 [a]
<b>4</b>	6.87	6.80	-	3.63	3.30 [b]

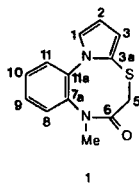
[a] The non-equivalent protons of the side-chain methylene group appeared as an AB quartet centred at 3.16 and 2.99 ppm. The methyl singlet was at 2.06 ppm. This pattern of absorption was unchanged over a temperature range of  $-50$  to  $50^\circ$  in deuteriochloroform and  $30^\circ$  to  $150^\circ$  in  $\text{DMSO-d}_6$  solution. [b] The formyl proton appeared at 9.99 ppm.

Table II

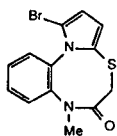
Proton-Proton Coupling Constants in Hz of Compounds 1-4

Compound	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{5a,5b}$
<b>1</b>	3.0	1.7	3.4	10.0
<b>2</b>	-	-	3.8	10.0
<b>3</b>	-	-	3.5	10.0 [a]
<b>4</b>	3.2	-	-	10.4

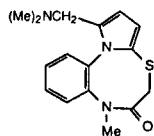
[a] The geminal coupling of the side-chain methylene group was 13.6 Hz.



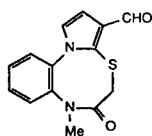
1



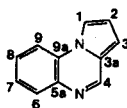
2



3



4



5

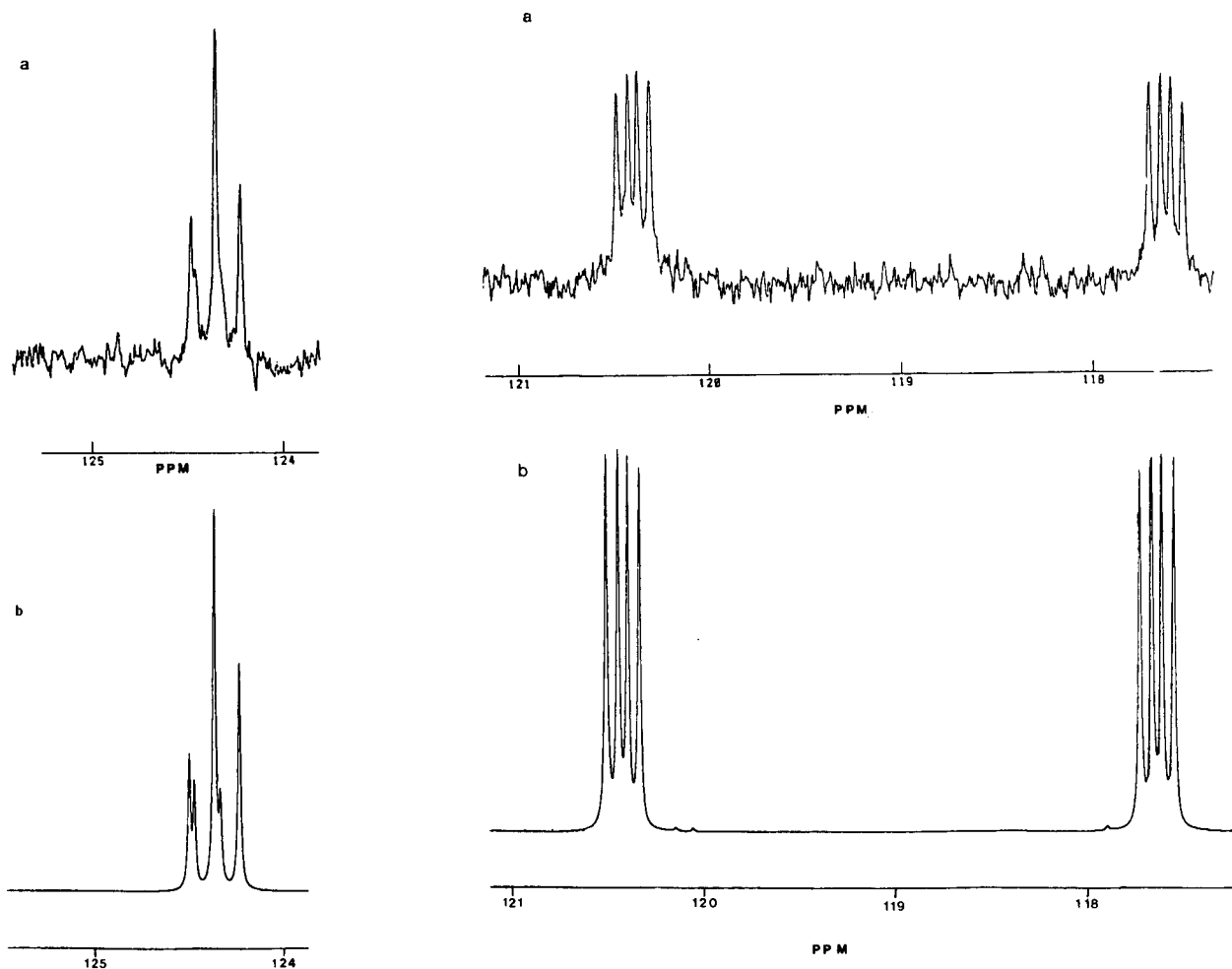


Figure 1a shows the upfield half of the signal arising from carbon 1 in compound **1**, the downfield part of the signal being obscured by signals arising from the benzene carbons. The recorded spectrum shows non-first-order transitions [8] which have been simulated in the calculated spectrum in figure 1b.

Although the magnitude of the pyrrolic coupling suggested that a 1-bromo and 1-dimethylaminomethyl derivative had been isolated, we did not regard a pyrrolic coupling of 3.2 Hz in the formyl compound as definitive evidence of either 1- or 3-substitution. Since SCS values for the formyl group in both the  $\alpha$ - and  $\beta$ -position of pyrrole were available [2], we were able to calculate the expected chemical shift values of the pyrrolic protons in the two alternative structures. The predicted values for H-2 and H-3 in the 1-formyl derivative were 7.04 and 6.64 ppm and those for H-1 and H-2 in the 3-formyl derivative were both 6.88 ppm. These compare with the experimentally determined values of 6.87 and 6.80 ppm and thus the proton data point to the formation of a 3-formyl compound.

Our conclusions were confirmed by examination of the  $^{13}\text{C}$ -nmr spectra (Tables III, IV). It will be noted that the one-bond coupling constants in the parent compound **1** to

Figure 2a shows the recorded spectrum of carbon 3 in compound **1** and is compared with the calculated spectrum 2b. The spectrum of carbon 2 showed no evidence of non-first-order behaviour.

the three protonated pyrrolic carbons C-1, C-2 and C-3 are 187, 173 and 175 Hz, respectively. Thus in this compound, and analogous compounds such as pyrrolo[1,2-*a*]quinoxaline **5** [4] a significant difference is observed in the magnitude of the one-bond coupling to  $\alpha$ - and  $\beta$ -pyrrolic carbons, the coupling to  $\alpha$ -carbons being consistently 10-20 Hz greater in magnitude. When the  $^{13}\text{C}$ -nmr spectra

Table III  
Carbon Chemical Shifts in ppm of Compounds **1-4**

Compound	C-1	C-2	C-3	C-3a	C-5
<b>1</b>	125.67	110.30	118.90	120.23	35.65
<b>2</b>	104.76	112.95	119.97	121.48	36.02
<b>3</b>	135.29	110.61	118.00	120.07	36.10
<b>4</b>	126.48	109.41	130.34 [a]	130.57 [a]	35.05

[a] These assignments may be reversed.

Table IV  
Pyrrolic Carbon to Proton Coupling Constants in Hz for Compounds 1-4

Compound	C-1, H-1	C-1, H-2	C-1, H-3	C-2, H-1	C-2, H-2	C-2, H-3	C-3, H-1	C-3, H-2	C-3, H-3
1	187.0	8.2	7.5	7.2	173.3	4.1	6.9	4.1	175.1
2	-	4.0	11.5	-	179.2	4.2	-	3.3	178.0
3	-	~8	~8	-	171.6	4.3	-	4.3	174.8
4	190.3	8.3	-	7.3	178.0	-	[a]	[a]	-

[a] At 250 MHz these coupling constants were not resolved.

for the three substituted products are compared, it will be seen (Table IV) that in the case of the bromo- and dimethylaminomethyl compounds the one-bond carbon-to-proton constants are very similar suggesting that two  $\beta$ -protonated carbons are present and therefore that 1-substituted products have been formed. One-bond carbon to proton coupling constants of 190 and 178 Hz in the spectrum of the formyl compound point to the presence of one protonated  $\alpha$ -pyrrolic carbon and one protonated  $\beta$ -pyrrolic carbon and thus confirm the  $^1\text{H}$ -nmr evidence that a 3-formyl derivative has been isolated. Moreover it can be seen that in the parent compound 1 the carbon to proton coupling constants observed between  $\alpha$ -carbons and  $\beta$ -protons (or  $\beta$ -carbons and  $\alpha$ -protons) are in the range of 7-8 Hz whereas the  $\beta$ -carbon to  $\beta$ -proton coupling is of the order of 3-4 Hz (Table IV). The coupling constants tabulated in Table IV, fit into the ranges expected for a 1-dimethylaminomethyl derivative and a 3-formyl derivative. The C-1, H-2 and C-1, H-3 couplings in the bromo compound of 4 and 11.5 Hz, respectively appear to be anomalous, however bromine substitution has been reported to lower the two-bond coupling between an alkenic carbon and a proton in the *cis*-position [6].

Finally the availability of SCS values for the formyl group in the  $\alpha$ - and  $\beta$ -position of a pyrrole [5] enabled us to calculate the chemical shift values for carbons 1,2,3 and 3a in the 3-formyl derivative. The calculated values of 129, 109, 130.5 and 131 ppm compare well with the experimentally determined values of 126, 109, 130 and 131 ppm (Table III). The predicted values for a 1-formyl derivative are significantly different and are 141, 123.5, 123 and 131 ppm, respectively.

## EXPERIMENTAL

Spectra were obtained on a Bruker WM 250 spectrometer operating at 28°. All measurements were carried out in deuteriochloroform solution. For the proton spectra, solutions of 2-3% w/w concentration were used. Proton-decoupled carbon spectra were measured with solutions of approximately 10% w/w concentration and for proton-coupled carbon spectra the solution concentration was approximately 20% w/w. DEPT editing was used for coupled and decoupled spectra and a published sequence was used for displaying only quaternary carbons [7]. In this way the necessary signal to noise enhancement was obtained. The digital resolution for the proton spectra was 0.2 Hz/point with a measured line width of less than 0.2 Hz. For carbon spectra, the digital resolution was 0.25 Hz/point and the measured line width was 0.5 Hz. The relatively high digital resolution was achieved by reducing the spectral width. The spectral width and spectral offset were adjusted to avoid aliased signals in the region of interest. A Laocoon III programme was used to calculate coupling constants and the rms errors were less than the digital resolution. Assignments of carbon chemical shift were made by selective proton decoupling and by literature analogy [4].

### Acknowledgements.

We thank the British Council for financial assistance to G. Varvounis, and J. Hawkes and F. Gallwey for some of the nmr measurements which were obtained on a spectrometer funded by the University of London Intercollegiate Research Services Scheme.

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