Amidomethylation of Phenanthridines: Synthesis and Structure Determination by ^{1}H NMR

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Phenanthridine reacts with *N*-(hydroxymethyl)phthalimide to give, in two steps, three monosubstituted aminomethylphenanthridines. The three isomers were separated by chromatography on silica gel. The position of substitution was determined using one- and two-dimensional ^{1}H nmr methods.

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Introduction.

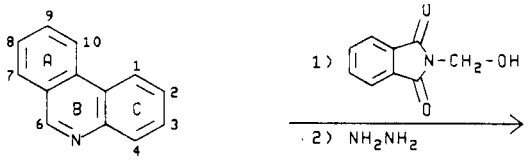
We have investigated methods to introduce the aminomethyl group into the phenanthridine nucleus, pursuing the Tscherniac-Einhorn reaction [1,2] which has been used in the amidomethylation of heterocyclic compounds such as acridine and indoles [3,4]:

$$ArH + RCONHCH_2X \dashrightarrow ArCH_2NHCOR + HX$$

where: X = OH, Cl, OR, *etc.*

Reported here are our findings involving electrophilic aromatic addition of *N*-(hydroxymethyl)phthalimide to phenanthridine in acid medium, followed by treatment with hydrazine to yield the aminomethylphenanthridines (Scheme I, below). The ^{1}H nmr analysis of the reaction product structures is described below.

Scheme I



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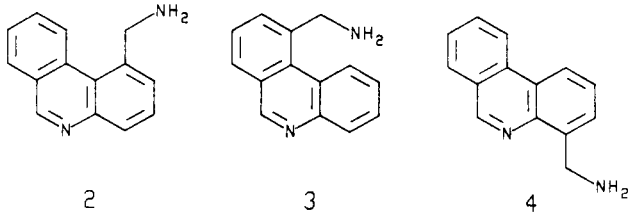

2 3 4

A limited volume of work appears in the literature regarding electrophilic substitution of phenanthridine. Early molecular-orbital calculations of electron densities in polyaromatic heterocycles [5] predicted for phenanthridine that the 4 and 10 positions [6] would be most reactive towards electrophilic attack, followed in reactivity by positions 1, 2, 3, and 8; the remaining positions possess significant positive character and are predicted to be unreactive towards electrophiles. Subsequent nitration studies [7] have agreed, in part, with these predictions, with the 1 (26% yield) and 10 isomers (21%) predominating; however, the 8 isomer (11%) was the next most abundant. The 2, 3, and 4 nitro isomers were recovered in very low yields (<5%). These experimental results indicate that factors other than just electron density may be directing substitution on the phenanthridine ring. We kept these theoretical and experimental results in mind when analyzing the products of the amidomethylation reaction.

Results and Discussion.

Amidomethylation was carried out at room temperature and was monitored by tlc. After three weeks the crude reaction mixture of amidomethylated products was treated with hydrazine and the reaction products separated by repeated chromatography to yield the 4- (29% yield), 1- (13%), and 10-aminomethylphenanthridines (13%).

The identification of the three positional isomers was accomplished using one- and two-dimensional ^{1}H nmr techniques. First, we assigned all resonances of phenanthridine in dilute deuteriochloroform solution. Two-dimensional correlation spectroscopy (2D COSY) and single frequency decoupling experiments were used to identify the two four-spin systems for hydrogens 1, 2, 3, and 4, and 7, 8, 9, and 10, as traced in the 2D COSY spectrum shown in Figure 1. Hydrogen 6 exhibits no large couplings and appears as a broadened singlet (9.31 ppm) in the 1D ^{1}H nmr spectrum shown in Figure 1; however, two low intensity cross peaks (9.31 ppm, F_2 axis; 8.64 ppm, F_1 axis and vice versa) do appear in the 2D COSY spectrum indicating long-range coupling between H-6 and H-10. This type of five-bond coupling, which allows the assignment of the H-7, -8, -9, and -10 spin system, has been observed previously in other polyaromatic molecules [8].

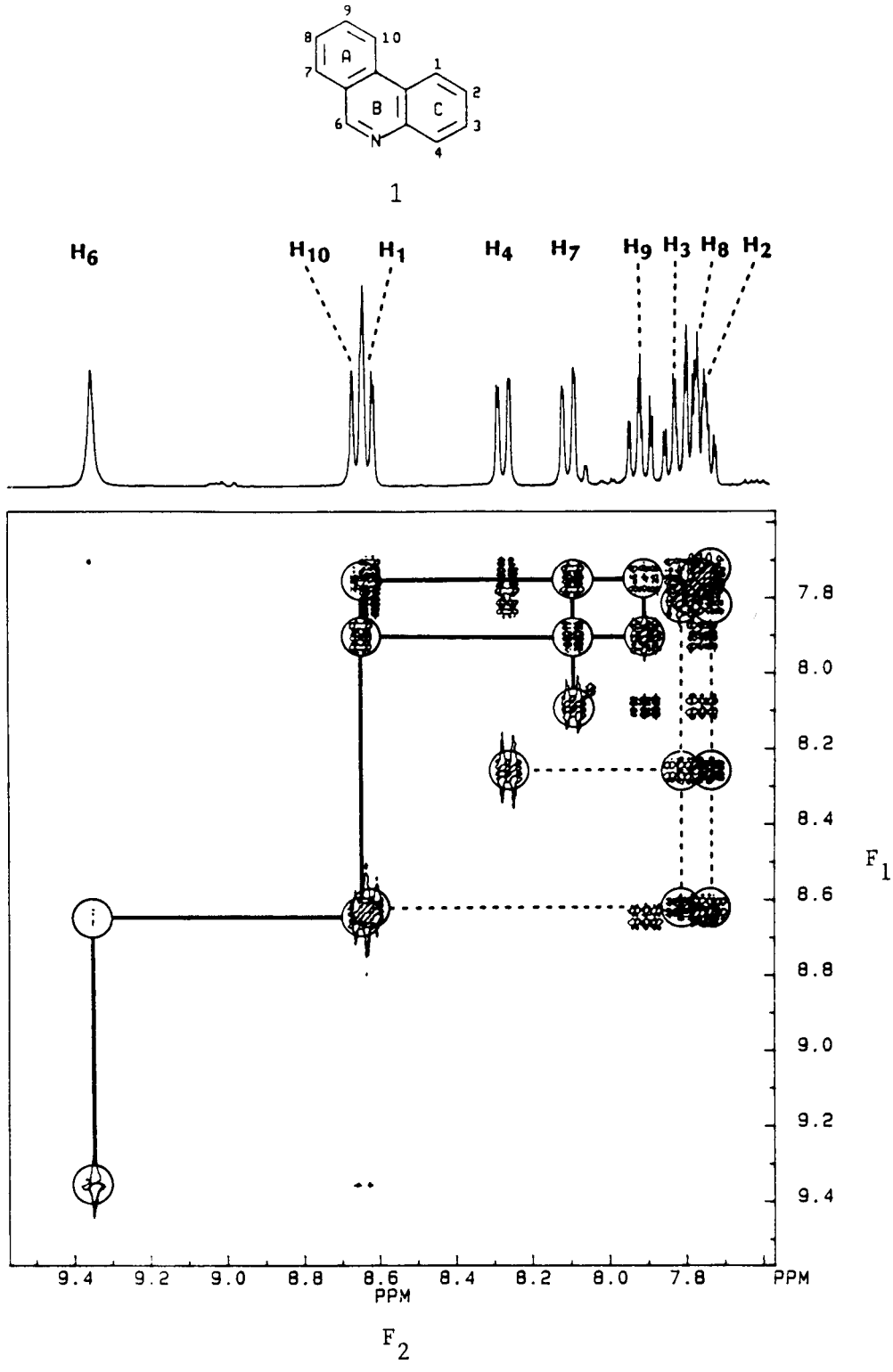

Figure 1. Contour plot of positive and negative levels of phase-sensitive ^{1}H 2D COSY spectrum of phenanthridine (**1**). Dashed lines indicate connectivity in H-1 through H-4 spin system, solid lines indicate connectivity in H-6 through H-10 spin system.

One-dimensional ^1H difference nuclear Overhauser effect (NOE) experiments were performed to confirm these assignments with NOE's observed between the following hydrogens: H-1 (and H-10, due to resonance overlap) and H-2 (and H-9, due to irradiation of H-10); H-6 and H-7; and H-7 and H-8. An NOE between two hydrogens results usually, for small molecules, in an increase in the intensity of the resonance of one hydrogen upon selective irradiation of a second hydrogen resonance, and the observation of this effect indicates that the two hydrogens are close in space (within about 4 angstroms) [9]. The NOE between H-6 and H-7 confirms the assignments for the A ring hydrogens, and by default, the C ring hydrogens. Complete assignments for phenanthridine appear in Table I.

Table I

^1H NMR Chemical Shift Assignments for Phenanthridine (**1**) and Compounds **2**, **3** and **4** Dissolved in Deuteriochloroform

Hydrogen Position	^1H Chemical Shift [a] **1**	**2**	**3**	**4**
1	8.60	—	8.89	8.52
2	7.70	7.68	7.72	7.63
3	7.77	8.15	7.78	7.69
4	8.21	7.68	8.24	—
6	9.31	9.28	9.26	9.31
7	8.07	8.08	8.01	8.07
8	7.73	7.72	7.71	7.72
9	7.88	7.90	7.94	7.87
10	8.64	8.95	—	8.63
$-CH_2NH_2$	—	4.64	4.47	4.47
$-CH_2NH_2$	—	1.80	1.72	1.97

[a] Referenced to internal tetramethylsilane at 0.00 ppm.

The ^1H nmr spectra of the three aminomethylphenanthridine isomers were assigned using an analogous procedure, with coupling information from 2D COSY and 1D decoupling experiments used to identify spin systems and NOE's between the $-CH_2NH_2$ substituent and neighboring hydrogens used to determine the site of substitution. In all cases, these data provide definitive proof of the structure. Figure 2 shows the 1D difference NOE spectra for compound **3**. Trace (a) shows enhancement of H-7 upon irradiation of H-6, allowing the assignment of the H-7, H-8, and H-9 spin system when these data are considered along with the 2D COSY data. Trace (b) shows enhancement of the $-CH_2NH_2$ and H-2 upon irradiation of H-1, fixing the site of substitution as position 10, while trace (c) shows enhancement of H-1 and H-9 upon irradiation of the $-CH_2NH_2$, further confirming the spatial relationship between these hydrogens. Also, trace (c) shows the $-CH_2NH_2$ resonance to be negative, indicating a negative NOE. This effect can be explained by understanding that the amine hydrogens undergo chemical exchange with the solvent H_2O hydrogens as evidenced by the broadness of the $-NH_2$ resonance. This exchange can

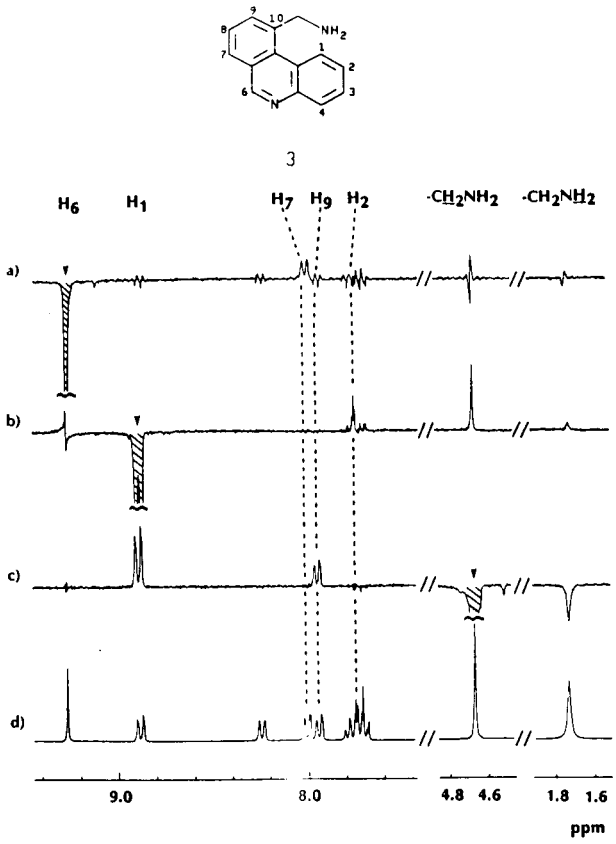

Figure 2. ^1H Difference NOE spectra for compound **3**, with irradiation (indicated by arrow and hashing) at, (a) H-6, (b) H-1, and (c) $-CH_2NH_2$. Spectrum (d) is unperturbed and is for reference.

Table II

^1H NOE Enhancements Observed for Phenanthridine (**1**) and Compounds **2**, **3** and **4**

Compound under study	Resonance Irradiated	Resonance(s) showing NOE
1	H-6	H-7
	H-7	H-6, H-8
	H-1 + H-10 [a]	H-2, H-9
2	H-6	H-7
	H-10	H-9, $-CH_2NH_2$
	$-CH_2NH_2$	H-2, H-10
3	H-1	H-2
	H-6	H-7
	$-CH_2NH_2$	H-1, H-9
4	H-1	H-2, H-10
	H-6	H-7
	H-7	H-6
	H-10	H-1, H-9
	$-CH_2NH_2$	H-3

[a] Overlapping resonances.

modulate the scalar coupling between the methylene and amine hydrogens causing the NOE to become negative through the scalar relaxation mechanism [9]. Similar NOE data, as discussed above, were compiled for compounds **2** and **4**, as reported in Table II, with Table I giving all chemical shift assignments.

Conclusion.

We have determined the preferred positions of substitution in the amidomethylation of phenanthridine and believe the selectivity is governed by the distribution of partial negative character within the phenanthridine ring system as previously predicted by molecular-orbital theory and that this reaction can be characterized as classical electrophilic aromatic substitution.

EXPERIMENTAL

Chemistry.

Thin layer chromatography was performed on Analtech silica gel prescored plates using methylene chloride/2-propanol/ammonium hydroxide (89:10:1) as the development solvent, spots were visualized by exposure to iodine vapor. Melting points are uncorrected.

1-, 4-, and 10-Aminomethylphenanthridines **2**, **4**, and **3**.

Into 300 ml of concentrated sulfuric acid, previously cooled to 10°, were added successively *N*-hydroxymethylphthalimide (63 g, 0.36 mole) and phenanthridine (63 g, 0.35 mole). The resulting mixture was stirred for three weeks at room temperature. The reaction mixture was poured on ice and basified with a 28% ammonium hydroxide solution. The crude product was extracted into chloroform and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate concentrated to give 100 g of a mixture of phthalimidomethylphenanthridines. The residue was dissolved in ethanol (3 *l*) with stirring, 85% hydrazine hydrate (68 g, 1.15 mole) was added and the solution heated to reflux for 5 hours. The reaction mixture was cooled, the precipitate filtered off, and washed with ethanol. The filtrate was concentrated, diluted with water, and basified with a 5*N* sodium hydroxide solution (100 ml). The crude product was extracted into chloroform, dried over sodium sulfate, concentrated and chromatographed on a silica gel column. The column was initially eluted with benzene/methanol (95:5). The first fraction contained unreacted phenanthridine (**1**). The polarity of the solvent was gradually increased until the second fraction eluted as a mixture of two products (Rf = 0.74 and 0.70) 25.8 g (35%). The last fraction (R_f = 0.21) eluted with benzene/methanol (7:3), and gave, after evaporation of the solvent, 21.3 g (29%) of 4-aminomethylphenanthridine (**4**); nmr (deuteriochloroform): see Table I.

A sample of **4** was acidified with dry hydrogen chloride and recrystallized as a mono hydrochloride from methanol mp 259-260°; ir (potassium bromide): 770, 920, 1140, 1255, 1590, 1620 cm^{-1}; uv (water): max 249.4 nm, E 1%/cm = 1851.2.

Anal. Calcd. for $C_{14}H_{12}N_2 \cdot HCl$: C, 68.71; H, 5.35; Cl, 14.49; N, 11.45. Found: C, 68.78; H, 5.17; Cl, 14.49; N, 11.31.

An aliquot of 2.1 g of the second fraction was rechromatographed on a 40 cm silica gel column (230-400 mesh) using methylene chloride/2-propanol (9:1). The first compound isolated (Rf = 0.74) was concentrated to dryness, and the product was crystallized from methylene chloride/petroleum ether to give 1.0 g (13%) of 10-aminomethylphenanthridine, **3**, mp 92-93°; nmr (deuteriochloroform): see Table I; ir (potassium bromide): 725, 735, 770, 1135, 1350, 1460, 1600, 1610 cm^{-1}; uv (dissolved in 2 eq. hydrochloric acid): max 247.0 nm, E 1%/cm = 1604.5.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.49; H, 6.08; N, 13.35.

The second compound eluted from the column (Rf = 0.70) was crystallized from methylene chloride/petroleum ether to give 1.0 g (13%) of 1-aminomethylphenanthridine, **2**, mp 94-96°; nmr (deuteriochloroform): see Table I; ir (potassium bromide): 725, 760, 810, 1250, 1390, 1450, 1530, 1600, 1610, 1620 cm^{-1}; uv (dissolved in 2 eq. hydrochloric acid): max 246.8 nm, E 1%/cm = 1753.1.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.60; H, 5.86; N, 13.32.

NMR Spectroscopy.

The ^1H nmr spectra of compounds **1**, **2**, **3**, and **4** dissolved in deuteriochloroform (approximately 10 mg/ml) were obtained in the pulsed Fourier transform mode using either a Bruker Instruments WM-250 (250 MHz for ^1H) or an IBM Instruments AF-270 (270 MHz for ^1H) nmr spectrometer operating at ambient room temperature (292 K). Both spectrometers were equipped with an Aspect 3000 computer operating under the current version of DISNMR software. Difference NOE experiments were performed according to the procedure of Hall *et al.* [10] in a sequential manner to minimize the effects of instrumental instabilities. The 2D COSY experiments [11] were performed in the phase-sensitive mode using time-proportional-phase-incrementation (TPPI) according to Weuthrich *et al.* [12] including phase cycling for the elimination of axial peaks [13] and CYCLOPS for the elimination of quadrature artifacts [14].

The 90° pulse width at 250 MHz was 4.8 μsec and 270 MHz was 4.6 μsec. The shifted-sinebell (20-45 degrees) window function was applied in both domains. The time domain data, 1k x 512w, was zero-filled to 1k x 1k. Spectra are referenced to internal tetramethylsilane at 0.00 ppm.

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