Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 8410–8418
Tetrahedron

An unusual substitution reaction directed by an intramolecular re-arrangement

Alexis D.C. Parenty, Louise V. Smith and Leroy Cronin*

Department of Chemistry, University of Glasgow, Joseph Black Building, Glasgow G12 8QQ, UK

Received 27 April 2005; revised 9 June 2005; accepted 23 June 2005

Available online 18 July 2005

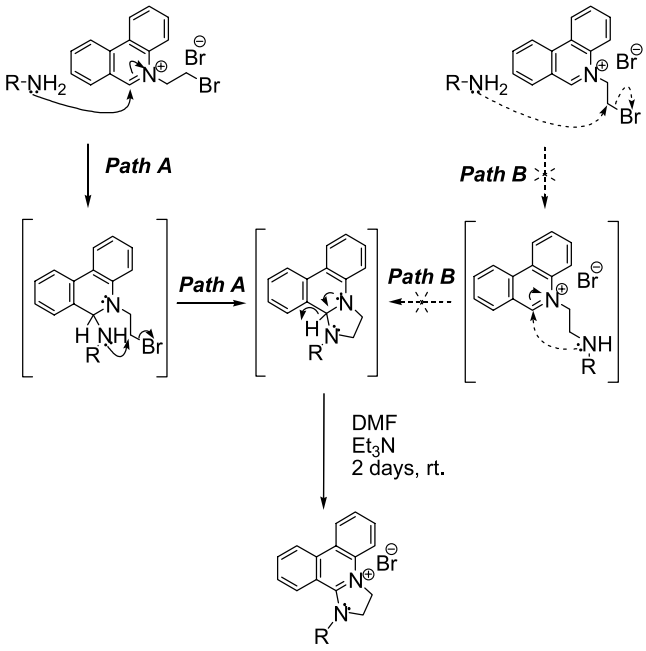
Abstract—Secondary amines and thiols undertake a substitution reaction on the side chain of 2-bromoethyl-pyridinium derivatives 'directed' by an intramolecular re-arrangement. Experimental investigations strongly indicate that the reaction is initiated by an alpha addition of the nucleophile onto the iminium moiety of the N-heteroaromatic cation, followed by a cyclisation and an oxidative ring opening. This novel substitution process is able to occur with less reactive nucleophiles that would not undergo conventional substitution with 'isolated' bromoethyl moieties.

1. Introduction

It is almost impossible to imagine a biological process that does not involve a heterocyclic compound.[1] Heterocycles also form the building blocks of many important pharmaceuticals.[2] One of the reasons for the widespread use of heterocyclic compounds in nature as well as in the pharmaceutical industry is their implication in a wide range of reaction types allowing subtle structural modification.[3–5] Therefore, investigations working towards the understanding of the reactivity of heterocyclic compounds is of great practical significance. Efficient syntheses leading to N-heteroaromatic cations are especially interesting as they often form the framework of DNA intercalating agents and have anticancer properties.[6,7] In this respect, molecules containing a phenanthridinium core are one important subset of heteroaromatic cations.[8–11]

Recently, we have discovered a flexible methodology allowing the ring extension of *N*-heterocyclic cations.[12] Specifically, we found that a primary amine reacted with 2-bromoethyl-phenanthridinium leading to the corresponding dihydro-imidazo-phenanthridinium derivative (DIP) via a nucleophilic addition followed by a cyclisation and an in-situ oxidation step (Path A, Scheme 1).

Evidence strongly suggesting Path A as a mechanism was confirmed by isolation of intermediates demonstrating the alpha addition step. The alternative pathway, (Path B, Scheme 1), was ruled out when experiments highlighted the poor reactivity of the 2-bromoethyl side chain, as well the necessity for a disfavoured 5-*endo*-trig-cyclisation.[12,13]

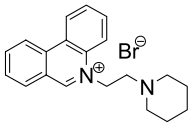
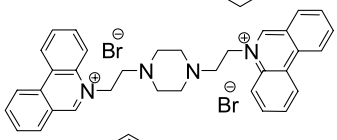
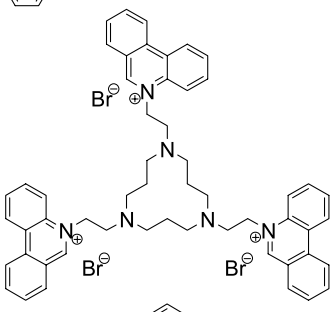
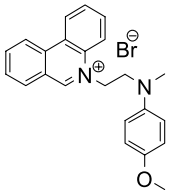


Scheme 1. The cascade reaction leading to the Dihydro-Imidazo-Phenanthridinium DIP derivative.[12] Note that the hydride loss could also be viewed as two consecutive electron transfers and a proton loss.

Keywords: *N*-Heterocyclic; Substitution; Intramolecular re-arrangement; Mechanism; Phenanthridinium.
* Corresponding author. Tel.: +44 141 330 6650; fax: +44 141 330 4888; e-mail: l.cronin@chem.gla.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.06.074

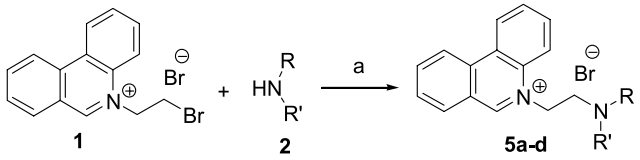
Table 1. Products and yields

Entry	Structure **5**	Secondary amine **2**	Yield %
5a		Piperidine	71
5b		Piperazine	73
5c		1,5,9-Triaza-cyclododecane	93
5d		*p*-Methoxy methyl aniline	77

Following the discovery of this useful one-pot-methodology, we were interested in utilising nucleophiles other than primary amines: for example, what would be the result if a nucleophile with only one available valence is used with the same reaction conditions? Herein, we report a surprising reaction that allows substitution of the bromo-ethyl side chain via a 'directed' cyclisation process with secondary amines and thiol-derivatives.

2. Results and discussion

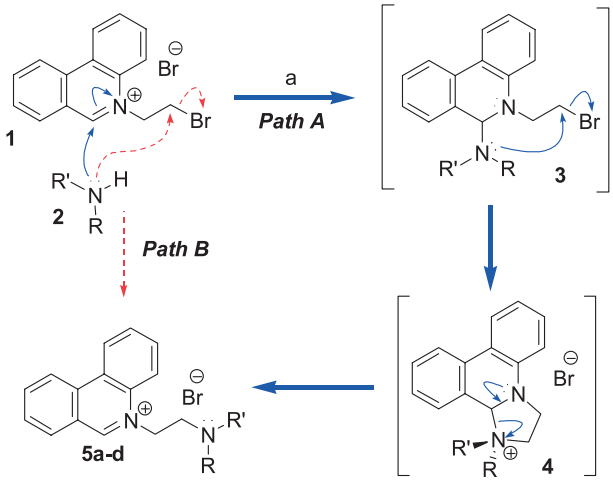
Under mild reaction conditions, the starting material 2-bromoethyl-phenanthridinium bromide **1** reacts with a series of secondary amines **2** to give the corresponding 2-aminoethyl-phenanthridinium bromide derivatives **5a–d** (Scheme 2 and Table 1).



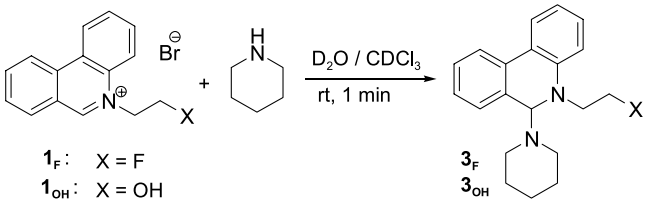
Scheme 2. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.

Upon initial inspection, this result seems to be in direct contradiction with the previously published Path A mechanism shown in Scheme 1, which states that direct bromine substitution on the side chain of molecule **1**, that is, Path B, does not take place.[12] Nevertheless, another pathway, avoiding direct substitution could also explain the formation of substituted products **5a–d** (Path A, Scheme 3). This intricate mechanism would involve an alpha addition on the iminium moiety of molecule **1**, followed by a ring cyclisation and a retro-5-*endo*-trig ring opening leading to re-oxidation of the heterocyclic middle ring.

Strong arguments in favour of Path A mechanism of Scheme 3 were obtained in the course of our experiments. Firstly, the reactivity of the iminium moiety of starting material **1** was assessed by reacting piperidine with the fluoro- and hydroxyl analogues of molecule **1** (respectively, $\mathbf{1}_F$ and $\mathbf{1}_{OH}$, Scheme 4). These two analogues, with their iminium moiety assumed to be as reactive as the one of molecule **1** (this assumption was made on the basis of DFT



Scheme 3. The two possible mechanistic pathways leading to **5a–d**. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.



Scheme 4. NMR phase transfer experiment with fluoro and hydroxyl analogue of molecule **1**.

calculations),[14] have the advantage of being unable to undertake the cyclisation of the hypothetic second step of Path A (Scheme 3). For reason of simplicity, and in order to evaluate how quickly the alpha addition step takes place, the reaction was undertaken in a biphasic system with D_2O/$CDCl_3$; this was done in practice in a NMR tube, where $\mathbf{1}_F$ or $\mathbf{1}_{OH}$ were partitioned between the organic and aqueous layers. Upon addition of piperidine, a white precipitate appears instantaneously in the D_2O layer and shifts towards the bottom $CDCl_3$ layer where ^1H and ^{13}C NMR measurements were used to characterize the corresponding alpha adduct $\mathbf{3}_F$ or $\mathbf{3}_{OH}$ (Scheme 4), analogues of intermediate **3** (Scheme 3).

The efficiency of the alpha addition step was also realised by isolating and analysing the D_2O layer during an identical NMR phase transfer reaction: following the addition of piperidine to the biphasic system, no starting material could be detected after only 1 min of reaction time.

This NMR phase transfer experiment highlights the high reactivity of the iminium moiety of starting material **1**. Moreover, other examples of alpha addition of secondary amines onto N-heteroaromatic cations like phenanthridinium,[15,16] isoquinolinium[17] and pyridinium[18,19] systems are also reported to lead to stable products.

Secondly, further support for the involvement of the central aromatic ring in the substitution reaction of Scheme 3 was obtained by UV absorption spectroscopy measurements. The absorption was measured between 200 and 500 nm and the λ_{max} determined to be at ca. 320 nm. If the reaction proceeds via Path A, the UV absorption of the de-aromatized intermediates (**3** and **4**), at this wavelength, should be different from both the starting material **1** and the final product **5**. Subsequently, the UV absorption was continuously monitored at 320 nm over a period of 12 h. On addition of the piperidine to a solution of starting material **1**, the absorbance drops instantly from 0.75 to 0.50 (formation of intermediates **3** and **4**) and rises back slowly to 0.75 due to the formation of final product **5** (Fig. 1).

This data allow us to conclude that the intermediate is present for at least 2 h. Therefore, in a subsequent reaction, a UV spectrum of the starting material was taken between 200 and 500 nm, and compared with both the UV spectrum of the intermediate after 30 min and the final product after 12 h reaction time (Fig. 2). The difference in absorbance between the intermediate and the starting material confirms the de-aromatisation process involved in the proposed mechanism of Path A.

Lastly, the hypothetical Path B depicted in Scheme 3, is not consistent with the observation that compound **5d** can be

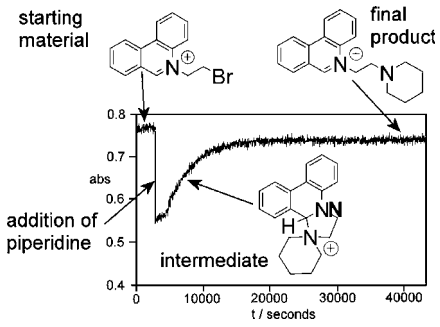


Figure 1. Absorbance at 320 nm versus time showing the formation of **5** from the reaction of **1** with piperidine highlighting the de-aromatisation/re-aromatisation process expected for Path A.

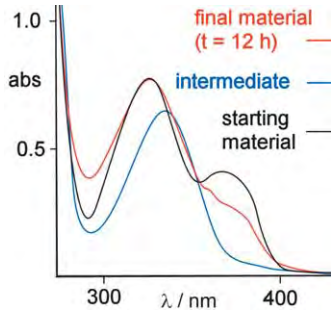
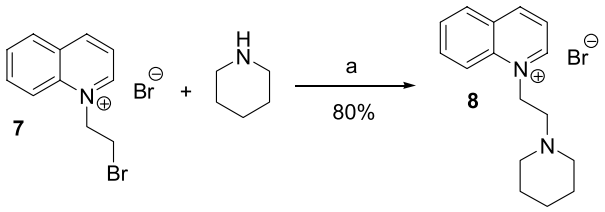


Figure 2. The alpha adduct intermediate(s) **3** and/or **4** can be observed by UV spectroscopy. λ_{max} for the starting and final material is ca. 320 nm.

synthesized. This is because, under the mild reaction conditions implemented (Scheme 3), it seems unlikely that the weakly nucleophilic aromatic amine *p*-methoxy-methylaniline is capable of performing a direct substitution on the ethyl-bromine side chain of starting material **1** (Path B). On the contrary, in the synthesis of **5d** via Path A, the ethyl-bromine side chain substitution of the corresponding aromatic amine intermediate **3** (Scheme 3) would be favoured entropically by the formation of a five-membered ring. Therefore, to test the reactivity of the ethyl-bromine side chain of **1** on its own, *p*-methoxy-methylaniline was added to a DMF solution of 1,2-dibromoethane, using the same reaction conditions as for the synthesis of **5a–d**. Under these mild conditions, no substitution on this bromoethyl-analogue of **1** could be detected by TLC. The same test was repeated with 2-bromoethyl-trimethyl-ammonium bromide, with identical outcome. Therefore, assuming that those two bromoethyl derivatives have reactivity similar to the bromoethyl side chain of staring material **1**, the isolation of final molecule **5d** is not likely to occur via Path B. This result also highlights the more effective substitution reaction of Path A allowing somewhat weaker nucleophiles to ultimately undergo this substitution reaction. Consequently, the alpha addition step of Path A can be seen as a 'directing step' helping the side chain substitution leading to **5**.

In order to examine the generality of the reaction to other N-heteroaromatic cations with an available alpha position, the reaction was also attempted using 2-bromoethyl-quinoline **7** to obtain with good yield the corresponding 2-aminoethyl-quinolinium derivative **8** (Scheme 5).

In this context, it is interesting to note that the



Scheme 5. Reaction on quinolinium system. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.

functionalization of N-heteroaromatic systems with a 2-aminoethyl side chain is often encountered in DNA intercalators where the resulting tertiary amine is either used as a spacer in bis-intercalating agents,[20–24] or used for structural/solubility/charge reasons.[25–29]

In addition, the substitution reaction of 2-bromoethyl-phenanthridinium **1** was also successful with thiol-derivatives. The nucleophile *p*-methoxybenzyl mercaptan leads to the corresponding substituted 2-mercaptoethyl-phenanthridinium derivative **9** in good yield (Scheme 6).

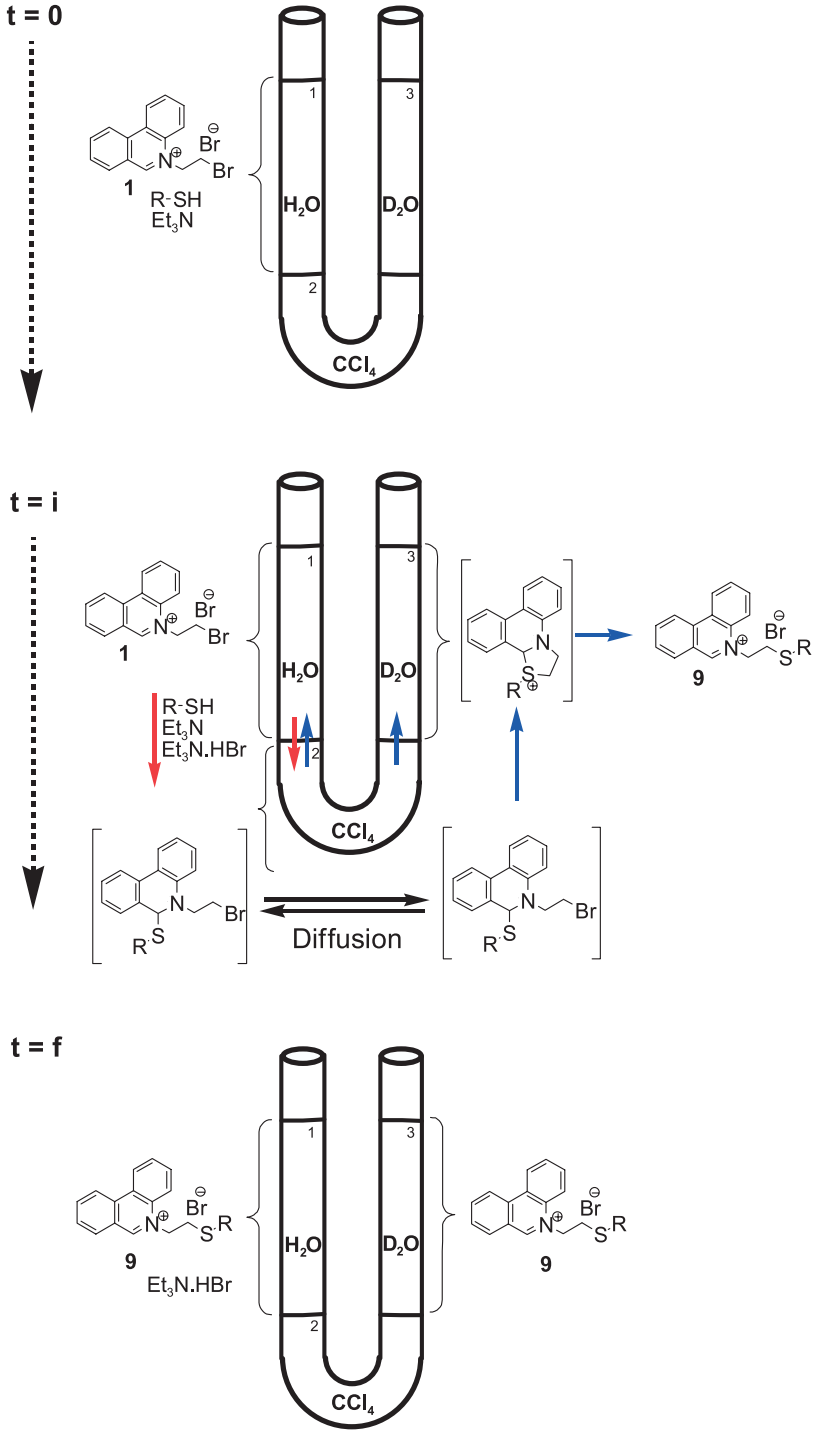
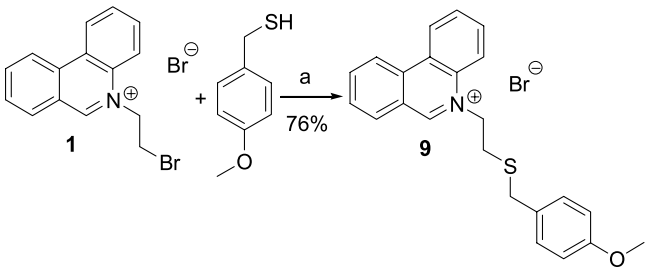


Figure 3. Phase transfer reaction in a 'U-Tube' highlighting the existence of an organic soluble intermediate. R = *p*-methoxybenzyl.



Scheme 6. Substitution reaction with a thiol derivative. Reagents and conditions: DMF, Et_3N, N_2, rt, 48 h.

Moreover, indirect proof of the alpha adduct intermediates could be obtained, using a phase transfer reaction in a 'U-tube' (Fig. 3). In this experiment, a 'U-tube' containing CCl_4 in the bottom (compartment 2, Fig. 3), was filled with water in one side (compartment 1, Fig. 3) and D_2O in the other (compartment 3, Fig. 3). Molecule **1** was added to compartment 1, followed by *p*-methoxybenzyl mercaptan and triethylamine. The organic layer of compartment 2 was gently stirred with a small magnet, taking care not to exchange any water from compartment 1 with D_2O from compartment 3. After 48 h, the deuterated solution of compartment 3 was analyzed by ^1H and ^{13}C NMR spectroscopy, and final molecule **9** was characterized. It is unlikely that the cationic starting material **1** nor the cationic final product **9** could diffuse from one aqueous medium to the other through the organic medium. Therefore, the occurrence of molecule **9** in compartment 3 can be best explained by the formation of an intermediate soluble in the organic phase, being able to diffuse between the two aqueous layers. Furthermore, the exchange of water between the two opposite layers (i.e., D_2O with H_2O and vice versa) was not observed during the NMR experiments and acts as a further control.

Consequently, the substitution of **1** by thiol-derivatives is also believed to be 'directed' by a similar re-arrangement as Path A of Scheme 3, that is: an alpha addition forming an intermediate soluble in organic solvent, followed by a five-membered ring cyclisation and an oxidative ring opening leading to the final material **9**, which is soluble in aqueous solution.

3. Conclusions

We have described the mechanism of a new type of nucleophilic substitution on 2-bromoethyl-pyridinium-like-cations. The substitution appears to be 'directed' by an initial alpha addition step on the iminium moiety, followed by a five-membered ring cyclisation and a re-aromatisation process via an oxidative C–N bond breakage. This intricate substitution was shown to be more effective than conventional types of nucleophilic substitution. In further work, we intend to examine the reaction of secondary amines with the 3-bromopropyl-pyridinium framework whereby any substitution taking place is also likely to occur via a similar re-arrangement requiring the formation of a six-membered ring intermediate. We will also examine the reaction pathways outlined here using theoretical methods.

4. Experimental

4.1. General

All reactions were carried out using oven-dried glassware under a nitrogen atmosphere using standard Schlenk line techniques. Commercial starting materials and solvents were used as supplied, without further purification. ^1H and ^{13}C NMR were recorded using a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are given in ppm relative to residual solvent peak. Coupling constants (J) are given in Hz. Infrared spectral analysis were performed on a JASCO 410 spectrophotometer, using a KBr disc unless otherwise stated; peaks are quoted in wave numbers (cm^{-1}) and their relative intensity are reported as follows: s = strong, m = medium, w = weak. Mass spectra were obtained using a JEOL JMS 700 spectrometer operating, in FAB, EI, CI or ES mode. Microanalyses were performed on a CE-440 elemental analyzer. Melting points were determined on a digital IA9000 series melting point apparatus, using capillary tubes. UV spectrums were recorded on a Shimadzu UV-310PC UV–VIS–NIR Scanning Spectrophotometer.

Definitions of abbreviations: DMF, dimethylformamide; DIP, dihydro-imidazo-phenanthridinium bromide; TEA, triethylamine; rt, room temperature.

4.2. Synthesis and analytical data

4.2.1. General procedure for the synthesis of 2-bromoethyl-pyridinium derivative (1 and 7). Phenanthridine or quinoline (30.3 mmol) was dissolved in 1,2-dibromoethane (114.2 g; 52 mL; 608 mmol) and stirred at 90 °C for a week. During that time, any precipitate formed was recovered by filtration. After each filtration, the precipitate was rinsed with an additional 5 mL of 1,2-dibromoethane and the mother liquor stirred at 90 °C until the next filtration. The reaction was deemed to be complete when no more precipitate formed. The precipitates were combined and washed thoroughly with ethyl acetate to give **1** or **7**.

4.2.1.1. 2-Bromoethyl-phenanthridinium bromide (1). Product **1** (10.55 g; 28.8 mmol) was recovered as a beige powder in a 95% yield; mp: 234–235 °C (dec); ^1H NMR (D_2O, 400 MHz): δ 9.81 (s, 1H), 8.72 (d, 1H, J=7.2 Hz), 8.63 (d, 1H, J=7.2 Hz), 8.37 (d, 1H, J=7.2 Hz), 8.26 (d, 1H, J=7.2 Hz), 8.18 (t, 1H, J=7.2 Hz), 7.98 (t, 1H, J=7.2 Hz), 7.90 (m, 2H), 5.37 (t, 2H, J=5.8 Hz), 4.05 (t, 2H, J=5.8 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 155.27 (CH), 139.03 (CH), 135.59 (C), 133.18 (CH), 132.78 (C), 132.58 (CH), 130.85 (CH), 130.72 (CH), 126.57 (C), 125.13 (CH), 123.32 (C), 123.00 (CH), 118.91 (CH), 58.87 (CH_2), 29.41 (CH_2); IR (KBr, cm^{-1}): 2947 (w), 1620 (m), 763 (s), 717 (m); MS (ES): 288.1 (M–Br) (100), 206.2 (8). Anal. Calcd for $C_{15}H_{13}NBr_2$: C, 49.32; H, 3.59; N, 3.84. Found: C, 49.15; H, 3.48; N, 3.76.

4.2.1.2. 2-Bromoethylquinolinium bromide (7). Product **4** (9.10 g; 28.7 mmol) was recovered as a beige powder in a 95% yield; mp: 289–290 °C (dec); ^1H NMR (D_2O, 400 MHz): δ 9.24 (d, 1H, J=8.4 Hz), 9.12 (d, 1H,

J=8.4 Hz), 8.87 (d, 1H, J=8.4 Hz), 8.33 (d, 1H, J=8.4 Hz), 8.20 (t, 1H, J=8.4 Hz), 7.98 (m, 2H), 5.41 (t, 2H, J=5.8 Hz), 4.05 (t, 2H, J=5.8 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 149.80 (C), 149.20 (CH), 138.08 (C), 136.66 (CH), 131.43 (CH), 130.68 (CH), 130.55 (CH), 121.59 (CH), 118.08 (CH), 58.59 (CH_2), 29.28 (CH_2); IR (KBr, cm^{-1}): 3437 (s), 3045 (w), 2981 (m), 2947 (m), 1624 (s), 1599 (m), 1585 (m), 1525 (s), 1489 (w), 1450 (m), 1400 (m), 1363 (s), 1242 (s), 1126 (m), 1161 (m), 1144 (m), 1049 (w), 874 (w), 816 (m), 800 (m), 775 (s); MS (FAB): 237 (M–Br) (98), 236 (100), 209.9 (2), 172 (2), 156 (12), 129.1 (6), 107.2 (2), 89.5 (2), 72.7 (1), 59.9 (1). Anal. Calcd for $C_{11}H_{11}NBr_2$: C, 41.67; H, 3.49; N, 4.42. Found: C, 41.75; H, 3.50; N, 4.51.

4.2.2. General procedure for the synthesis of 2-aminoethyl-pyridinium derivative (5a–d; 8) and 2-thioethyl-pyridinium derivative (9). 2-Bromoethyl-pyridinium **1** or **7** (1.9 mmol) was dissolved in 20 mL DMF. Secondary amine or thiol derivative (2.1 mmol) and TEA (0.576 mg; 795 μL; 5.7 mmol) were added successively to the stirred solution. After stirring for 48 h at rt under nitrogen, the final product and TEA hydrobromide salt were precipitated from the solution by adding diethyl ether (40 mL) and were recovered by filtration. The precipitate was washed thoroughly with ethyl acetate and then triturated twice with 0.5 mL of water to get rid of the TEA salt. The residue was dried by successive diethyl ether addition/suction cycles to obtain **5a–d**; **8** or **9**.

4.2.2.1. 5-(2-Piperidin-1-yl-ethyl)-phenanthridinium bromide (5a). Product **5a** was obtained as a pale yellow powder in a 71% yield; mp: 167–168 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 1H), 8.90 (d, 1H, J=7.2 Hz), 8.83 (d, 1H, J=8.4 Hz), 8.41 (d, 1H, J=8 Hz), 8.28 (m, 2H), 7.99 (m, 3H), 5.15 (t, 2H, J=7.2 Hz), 3.04 (t, 2H, J=7.2 Hz), 2.56 (m, 4H), 1.50 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 154.63 (CH), 147.71 (C), 138.61 (CH), 136.45 (C), 135.35 (C), 132.72 (CH), 132.47 (CH), 130.67 (CH), 126.56 (CH), 125.11 (CH), 123.83 (C), 123.04 (CH), 119.06 (CH), 56.40 (CH_2), 54.87 (CH_2), 54.18 (CH_2), 25.11 (CH_2), 23.42 (CH_2); IR (KBr, cm^{-1}): 3448 (s), 2923 (m), 2852 (w), 2794 (w), 2360 (w), 1628 (s), 1535 (w), 1506 (w), 1454 (m), 1352 (w), 1257 (w), 1161 (w), 1122 (w), 1036 (w), 769 (s); MS (FAB): 291.2 (M–Br) (100); 273.1 (4), 206.1 (7), 193 (7), 154 (92), 137 (60), 136 (60), 112.3 (45), 98.4 (16), 89.5 (11), 77.6 (5), 56.9 (2), 52 (2). Anal. Calcd for $C_{20}H_{23}N_2Br$: C, 64.69; H, 6.24; N, 7.54. Found: C, 64.17; H, 6.10; N, 7.58.

4.2.2.2. Piperazine diethyl-phenanthridinium bromide (5b). Product **5b** was obtained as a yellow powder in a 73% yield; mp: 260–261 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 2H), δ 8.95 (d, 2H, J=8.0 Hz), δ 8.88 (d, 2H, J=8.0 Hz), δ 8.42 (d, 2H, J=8.0 Hz), δ 8.33 (d, 2H, J=8.0 Hz), δ 8.29 (t, 2H, J=8.0 Hz), δ 8.01 (m, 6H), δ 5.14 (t, 4H, J=6.8 Hz), δ 3.05 (t, 4H, J=6.8 Hz), δ 2.57 (s, 8H); ^{13}C NMR (D_2O, 100 MHz): δ 155.94 (CH), δ 138.46 (CH), δ 134.63 (C), δ 133.28 (CH), δ 133.07 (C), δ 132.41 (CH), δ 130.89 (CH), δ 130.54 (CH), δ 126.03 (C), δ 125.48 (CH), δ 123.66 (CH), δ 120.19 (CH), δ 55.43 (CH_2), δ 55.08 (CH_2), δ 52.95 (CH_2); IR (KBr, cm^{-1}): 3430.74 (s), 2923 (w), 2360 (w), 1626 (s), 1456 (m), 1261 (w), 1026 (w), 758 (w); MS (FAB): 498.4 (M–2Br) (60), 318.2 (30), 292.1 (50), 249.1 (80), 206.1 (70), 154.0 (100), 136.0 (80), 112.3 (35), 56.9 (30). Anal. Calcd for $C_{34}H_{34}N_4Br_2$: C, 62.01; H, 5.20; N, 8.51. Found: C, 62.30; H, 5.45; N, 8.51.

4.2.2.3. Triazacyclododecane triethyl phenanthridinium bromide (5c). Product **5c** was obtained as a yellow-orange powder in a 93% yield; ^{1}H NMR (CD_3OD, 400 MHz): δ 9.93 (s, 3H), 8.99 (t, 6H, J=8.8 Hz), 8.45 (d, 3H, J=8.0 Hz), 8.42 (d, 3H, J=6.8 Hz), 8.30 (t, 3H, J=7.6 Hz), 8.00 (m, 6H), 7.85 (t, 3H, J=7.6 Hz), 5.02 (m, 6H), 2.57 (m, 6H), 1.41 (m, 12H), 0.05 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz): δ 156.53 (CH), 140.11 (CH), 136.93 (C), 135.00 (C), 134.23 (CH), 133.95 (CH), 132.28 (CH), 132.19 (CH), 128.13 (C), 126.71 (CH), 125.14 (C), 124.85 (CH), 121.43 (CH), 57.57 (CH_2), 53.34 (CH_2), 49.39 (CH_2), 23.25 (CH_2); IR (KBr, cm^{-1}): 3430.74 (s), 2923 (w), 2360 (w), 1626 (s), 1456 (m), 1261 (w), 1026 (w), 758 (w); MS (FAB): 498.4 (M–2Br) (60), 318.2 (30), 292.1 (50), 249.1 (80), 206.1 (70), 154.0 (100), 136.0 (80), 112.3 (35), 56.9 (30). Anal. Calcd for $C_{54}H_{57}N_6Br_3$: C, 62.98; H, 5.58; Br, 23.28; N, 8.16. Found: C, 63.08; H, 4.51; N, 8.10.

4.2.2.4. 5-{2-[(4-Methoxy-phenyl)-methyl-amino]-ethyl}phenanthridinium bromide (5d). Product **5d** was obtained as brown powder in a 77% yield; mp: 66–67 °C; ^{1}H NMR (D_2O, 400 MHz): δ 9.42 (s, 1H), δ 8.71 (d, 1H, J=7.6 Hz), δ 8.58 (d, 1H, J=7.6 Hz), δ 8.34 (d, 1H, J=7.6 Hz), δ 8.13 (t, 1H, J=7.6 Hz), δ 8.03 (m, 2H), δ 7.95 (t, 1H, J=7.6 Hz), δ 7.82 (t, 1H, J=7.6 Hz), δ 6.10 (d, 2H, J=8.8 Hz), δ 5.89 (d, 2H, J=8.8 Hz), δ 5.17 (m, 2H), δ 3.97 (m, 2H), δ 3.20 (s, 3H), δ 2.87 (s, 3H); ^{13}C NMR (D_2O, 100 MHz): δ 155.16 (CH), δ 151.02 (C), δ 142.00 (C), δ 138.21 (CH), δ 134.85 (C), δ 132.31 (CH), δ 132.11 (C), δ 130.45 (CH), δ 129.94 (CH), δ 126.11 (C), δ 124.61 (CH), δ 122.92 (C), δ 122.29 (CH), δ 119.07 (CH), δ 115.46 (CH), δ 113.90 (CH), δ 55.59 (CH_2), δ 55.09 (CH_3), δ 50.00 (CH_2), δ 37.59 (CH_3); MS (FAB): 342.2 (M–Br) (100), 327.2 (10), 218.1 (5), 206.1 (13), 164.1 (75), 133.1 (30), 120.2 (4). Anal. Calcd for $C_{23}H_{23}BrN_2O$: C, 65.25; H, 5.48; N, 6.62. Found: C, 65.28; H, 5.60; N, 6.58.

4.2.2.5. 1-(2-Piperidin-1-yl-ethyl)-quinolinium bromide (8). Product **8** was obtained as a brown powder in an 80% yield; mp: 220–221 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.20 (d, 1H, J=7.6 Hz), 9.06 (d, 1H, J=8.4 Hz), 8.32 (t, 2H, J=7.6 Hz), 8.20 (t, 1H, J=8.2 Hz), 7.97 (d, 1H, J=8.2 Hz), 7.94 (d, 1H, J=8.4 Hz), 5.14 (t, 2H, J=7.4 Hz), 3.03 (t, 2H, J=7.4 Hz), 2.58 (m, 4H), 1.53 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 149.40 (CH), 148.57 (CH), 138.42 (C), 136.55 (CH), 131.37 (CH), 130.69 (C), 130.45 (CH), 122.03 (CH), 118.17 (CH), 56.57 (CH_2), 54.57 (CH_2), 54.14 (CH_2), 25.04 (CH_2), 23.39 (CH_2); IR (KBr, cm^{-1}): 3448 (s), 2923 (m), 2852 (w), 2794 (w), 2360 (w), 1628 (s), 1535 (w), 1506 (w), 1454 (m), 1352 (w), 1257 (w), 1161 (w), 1122 (w), 1036 (w), 769 (s); MS (FAB): 241.1 (M–Br) (100), 156 (73), 140 (15), 112.3 (33). Anal. Calcd for $C_{16}H_{21}N_2Br$: C, 59.82; H, 6.59; N, 8.72. Found: C, 59.70; H, 6.62; N, 8.70.

4.2.2.6. 5-[2-(4-Methoxy-benzylsulfanyl)-ethyl]phenanthridinium bromide (9). Product **9** was obtained as a pale yellow powder in a 76% yield; mp: 182–183 °C (dec);

^{1}H NMR (CD_3OD, 400 MHz): δ 9.91 (s, 1H), δ 9.08 (t, 2H, J=8.0 Hz), δ 8.85 (d, 1H, J=8.0 Hz), δ 8.47 (t, 1H, J=8.0 Hz), δ 8.37 (m, 1H), δ 8.15 (t, 1H, J=8.0 Hz), δ 8.11 (m, 2H), δ 6.80 (d, 2H, J=8.8 Hz), δ 6.33 (d, 2H, J=8.8 Hz), δ 5.17 (t, 2H, J=6.0 Hz), δ 4.90 (t, 2H, J=6.0 Hz), δ 3.69 (s, 3H), δ 3.56 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 161.8 (C), δ 156.84 (C), δ 140.00 (CH), δ 137.21 (C), δ 134.41 (CH), δ 133.77 (CH), δ 132.07 (CH), δ 131.96 (CH), δ 131.31 (C), δ 130.96 (CH), δ 128.00 (C), δ 126.72 (CH), δ 125.21 (CH), δ 124.74 (CH), δ 120.76 (CH), δ 114.96 (CH), δ 58.90 (CH_2), δ 55.92 (CH_3), δ 36.97 (CH_2), δ 31.70 (CH_2); IR (KBr, cm^{-1}): 3435 (s), 1626 (s), 1533 (w), 1510 (s), 1450 (m), 1304 (w), 1248 (s), 1174 (w), 1030 (s), 829 (s), 764 (s); MS (FAB): 360.0 (M–Br) (70), 309.0 (20), 290.0 (15), 238.0 (5), 206.0 (10), 179 (7), 155.0 (100), 136.0 (50), 121.1 (50), 108.2 (20), 89.5 (12). Anal. Calcd for $C_{23}H_{22}$-NOSBr: C, 62.72; H, 5.03; N, 3.18. Found: C, 62.72; H, 5.01; N, 3.78.

4.2.3. 2-Fluoroethyl-phenanthridinium bromide ($\mathbf{1_F}$). 2-Fluoroethyltosylate was prepared: 2-Fluoroethanol (1 g; 15.6 mmol) dissolved in dry pyridine (15 mL) under nitrogen. The solution was stirred at 0 °C and *p*-toluene sulfonyl chloride (6.5 g; 34.1 mmol) was added slowly to the solution over a period of 30 min, keeping the temperature below 5 °C. The solution was then stirred at 0 °C for another 4 h before quenching by slow addition of ice (15 g) then water (20 mL). Ethyl acetate (50 mL) was added, the organic layer separated and washed with water. Excess pyridine was removed by washing the organic layer with a 1 M HCl solution until the aqueous layer became acidic. The excess tosyl chloride was removed by washing the organic layer with an aqueous solution of Na_2CO_3 (pH$\approx$10). The organic layer was then washed with brine, dried over $MgSO_4$ and concentrated under vacuum to obtain 2-fluoroethyltosylate (3.29 g; 15 mmol) as an oil in a 96% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J=8.0 Hz), 7.38 (d, 2H, J=8.0 Hz), 4.65 (t, 1H, J=4.2 Hz), 4.53 (t, 1H, J=4.2 Hz), 4.32 (t, 1H, J=4.2 Hz), 4.25 (t, 1H, J=4.2 Hz), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.53 (C), 133.05 (C), 130.32 (CH), 128.37 (CH), 81.78 (CH_2), 80.06 (CH_2), 68.91 (CH_2), 68.70 (CH_2), 22.05 (CH_3); MS (EI): 218.2 (M+1) (50), 185.2 (8), 155.1 (100), 139.1 (5), 107.1 (8), 91.1 (100), 65.1 (30), 63.1 (10). Phenanthridine (690 mg; 3.84 mmol) was added to a solution of 2-fluoroethyltosylate (1.68 g; 7.68 mmol) in DMF (10 mL) and stirred at 100 °C for 48 h. The solution was then concentrated to a brown oil and precipitated by addition of acetone (10 mL) followed by diethyl ether (60 mL). The precipitate was recovered by filtration, washed with diethyl ether and dried under vacuum to obtain the tosylate salt of $\mathbf{1_F}$ (1.52 g; 3.84 mmol) as an off white powder in a quantitative yield. Finally, the tosylate salt was passed through an anionic exchange column (Dowex 1X-850) preloaded with a saturated NaBr solution and flushed with distilled water. The compound was eluted with distilled water. The resulting aqueous solution was washed twice with ethyl acetate before being concentrated under vacuum to obtain $\mathbf{1_F}$ (1.12 g; 3.68 mmol) as a pale yellow powder in a 96% yield; mp: 239–240 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 1H), 8.79 (d, 1H, J=8.0 Hz), 8.71 (d, 1H, J=8.0 Hz), 8.36 (d, 1H, J=8.0 Hz), 8.29 (d, 1H, J=8.4 Hz), 8.21 (t, 1H, J=7.2 Hz), 8.01 (t, 1H, J=7.2 Hz), 7.94 (m, 2H), 5.40 (t, 1H, J=4.4 Hz), 5.33 (t, 1H, J=4.4 Hz), 5.12 (t, 1H, J=4.4 Hz), 5.00 (t, 1H, J=4.4 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 155.22 (CH), 138.89 (CH), 135.09 (C), 133.08 (C), 132.96 (CH), 132.60 (CH), 130.85 (CH), 130.70 (CH), 126.20 (C), 124.88 (CH), 123.37 (C), 122.79 (CH), 119.18 (CH), 82.08 (CH_2), 80.39 (CH_2), 58.17 (CH_2), 57.98 (CH_2); IR (KBr, cm^{-1}): 3404 (m), 1534 (m), 1460 (m), 1447 (m), 1371 (m), 1265 (s), 1165 (s), 1048 (s), 1031 (s), 764 (s), 718 (m); MS (FAB): 226.2 (M–Br) (100), 199.2 (10), 180.1 (25), 101.4 (20); MS (FAB): 226.2 (M–Br) (100), 199.2 (10), 180.1 (25), 101.4 (20). Anal. Calcd for $C_{15}H_{13}BrFN$: C, 58.84; H, 4.28; N, 4.57. Found: C, 59.00; H, 4.23; N, 4.45.

4.2.4. 2-Hydroxyethyl-phenanthridinium bromide ($\mathbf{1_{OH}}$). Phenanthridine (2 g; 11.17 mmol) was added to a solution of 2-bromoethanol (3.2 mL; 44.8 mmol). The reaction mixture was refluxed for 4 h under N_2. After cooling, crystallisation was aided by the addition of ether. After 2 h, the crystals were recovered by filtration and washed with ether to produce $\mathbf{1_{OH}}$ (3.10 g; 10.13 mmol) as a beige powder in a 90% yield; mp: 239–240 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.71 (s, 1H), 8.81 (d, 1H, J=8.0 Hz), 8.74 (d, 1H, J=8.0 Hz), 8.37 (d, 1H, J=8.0 Hz), 3.32 (d, 1H, J=8.0 Hz), 8.22 (t, 1H, J=8.0 Hz), 7.97 (m, 3H), 5.11 (t, 2H, J=5.0 Hz), 4.14 (t, 2H, J=5.0 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 156.71 (CH), 140.70 (CH), 136.62 (C), 134.88 (CH), 134.68 (CH), 132.81 (CH), 127.93 (C), 126.75 (C), 125.09 (C), 124.65 (CH), 121.33 (CH), 62.31 (CH_2), 61.19 (CH_2); IR (KBr, cm^{-1}): 3232 (s), 1624 (s), 1581 (w), 1535 (m), 1446 (s), 1423 (m), 1346 (m), 1261 (s), 1157 (s), 1084 (s), 1033 (s), 899 (s), 867 (m), 756 (s), 717 (s), 609 (s); MS (ES): 224.1 (M–Br) (100), 222.1 (25), 210.1 (10), 206.1 (40), 194.1 (8), 193.1 (18), 182.1 (10), 181.1 (80), 180.1 (100). Anal. Calcd for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60. Found: C, 59.10; H, 4.73; N, 4.52.

4.2.5. 5-(2-Fluoroethyl)-6-piperidin-1-yl-5,6-dihydrophenanthridine ($\mathbf{3_F}$). In an NMR tube, $\mathbf{1_F}$ (10 mg; 0.032 mmol) was dissolved in D_2O (0.6 mL). $CDCl_3$ (0.6 mL) was added followed by 2 equiv of piperidine (6.30 μL; 5.4 mg; 0.064 mmol) used both as a reactant and as a base. The NMR tube was energetically shaken for 1 min to allow the phase transfer process to occur. A ^{1}H and ^{13}C NMR spectrum as well as an MS of the bottom organic layer was taken, characterising $\mathbf{3_F}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, 1H, J=8.0 Hz), 7.76 (d, 1H, J=8.0 Hz), 7.31 (t, 1H, J=7.2 Hz), 7.22 (t, 1H, J=7.2 Hz), 7.15 (t, 1H, J=8.0 Hz), 7.05 (d, 1H, J=8.0 Hz), 6.75 (t, 2H, J=7.2 Hz), 4.97 (s, 1H), 4.75 (m, 1H), 4.60 (m, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 2.20 (m, 4H), 1.30 (m, 4H), 1.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.35 (C), 139.72 (C), 131.65 (C), 129.14 (CH), 127.21 (CH), 126.35 (CH), 123.76 (CH), 123.26 (CH), 122.44 (CH), 121.70 (CH), 120.51 (C), 111.16 (CH), 83.47 (CH), 82.70 (CH_2), 82.19 (CH_2), 81.03 (CH_2), 80.51 (CH_2), 50.06 (CH_2), 48.63 (CH_2), 26.29 (CH_2); MS (EI+): 311.37 (M+1) (3), 292.38 (M–F) (4), 241.2 (15), 226.3 (100), 195.2 (20), 179.2 (40), 152.2 (15), 84 (100).

4.2.6. 2-(6-Piperidin-1-yl-6*H*-phenanthridin-5-yl)-ethanol ($\mathbf{3_{OH}}$). In an NMR tube, $\mathbf{1_{OH}}$ (10 mg; 0.033 mmol) was dissolved in D_2O (0.6 mL). $CDCl_3$ (0.6 mL) was added

followed by 2 equiv of piperidine (6.50 μL; 0.066 mmol) used both as a reactant and as a base. The NMR tube was energetically shaken for 1 min to allow the phase transfer process to occur. A ^{1}H and ^{13}C NMR spectrum as well as an MS of the bottom organic layer was taken, characterising $\mathbf{3}_{OH}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, 1H, J=7.6 Hz), 7.81 (dd, 1H, J=7.6, 1.2 Hz), 7.37 (dt, 1H, J=7.6, 1.2 Hz), 7.26 (dt, 1H, J=7.6, 1.6 Hz), 7.16 (dt, 1H, J=7.6, 1.6 Hz), 7.02 (d, 1H, J=7.6 Hz), 6.77 (dt, 1H, J=7.6, 1.2 Hz), 6.68 (d, 1H, J=7.6 Hz), 4.84 (s, 1H), 4.17 (dd, 1H, J=15.6, 2.0 Hz), 4.01 (t, 1H, J=11.2 Hz), 3.60 (d, 1H, J=11.2 Hz), 3.31 (ddd, 1H, J=15.6, 11.2, 2 Hz), 2.25 (m, 4H), 1.45 (m, 4H), 1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.14 (C), 131.73 (C), 129.20 (CH), 128.23 (CH), 127.69 (CH), 126.21 (CH), 125.30 (C), 123.14 (CH), 122.13 (CH), 119.63 (C), 117.16 (CH), 111.27 (CH), 80.35 (CH), 59.28 (CH_2), 57.54 (CH_2), 48.10 (CH_2), 25.01 (CH_2), 23.87 (CH_2); MS (CI+): 307.41 (M–1) (2), 281.39 (4), 240.29 (1), 226.30 (2), 224.29 (2), 196.25 (1), 180.22 (3), 103.2 (10), 86.2 (100), 52.1 (35).

4.2.7. UV spectroscopy determination of the substitution reaction intermediate(s) 6-(2-bromoethyl)-5-(2-piperidin-1-yl-ethyl)-5,6-dihydro-phenanthridine (3) and/or piperidinium-1,2,3,12*b*-tetrahydro-imidazo[1,2-*f*]phenanthridine bromide (4). Starting material **1** (37 mg; 0.1 mmol) was dissolved in 100 mL water. Ten millilitre aliquot was diluted by 10 to obtain a 0.1 mM stock solution. One millilitre of the stock solution was transferred to a UV cell and the UV spectrum of the starting material **1** measured between 200 and 500 nm. Two λ_{max} can be observed at 320 and 361 nm. At 320 nm, the absorption of the starting material **1** was recorded every 40 s, and after 1 h, piperidine (10 μL; 0.01 μmol) added. UV absorption measurements were carried on for 12 h, characterizing the slow transformation of the intermediate(s) into the final material **3a**. After this reaction time, a UV scan was also undertaken between 200 and 500 nm, characterizing the final product **3a** without intermediate. Subsequently, using the same reaction conditions, a UV spectrum of the intermediate was measured after 30 min reaction time between 200 and 500 nm and compared with the UV spectrum of both the starting material **1** and the final material **3a**.

4.2.8. U-tube experiment: formation of 5-[2-(4-methoxybenzylsulfanyl)-ethyl] phenanthridinium bromide (9) via a necessary organic soluble intermediate. In a U-tube, containing a layer of CCl_4 (1 mL) with 10 mg of $MgSO_4$, was added a layer of H_2O (1 mL) in one harm and a layer of D_2O (1 mL) in the other harm. In the H_2O compartment, was added starting material **1** (12.6 mg; 0.034 mmol) followed by *p*-methoxybenzyl mercaptan (4.7 μL; 0.03 mmol) and triethylamine (4.7 μL; 0.04 mmol). A white precipitate appears instantaneously in the H_2O compartment. The phase transfer was assisted by gently stirring the inter-phase with the tip of a Pasteur pipette before sealing the two extremity of the U-tube with parafilm. The underneath organic layer was gently stirred with a small magnet for 48 h, taking care not to contaminate the D_2O compartment with H_2O. The D_2O layer was analyzed by ^{1}H NMR spectroscopy and final molecule **9** was cleanly characterized, along with some triethylamine.

Acknowledgements

This work was supported by EPSRC. We thank Dr. Jesus M. de la Fuente and Dr. Richard Hartley for fruitful discussions.

References and notes

1. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*, Wiley: Chichester, UK, 1997.
2. Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112–113.
3. Fagnoni, M. *Heterocycles* **2003**, *60*, 1921–1958.
4. Hajos, G.; Riedl, Z.; Kollenz, G. *Eur. J. Org. Chem.* **2001**, 3405–3414.
5. Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239–6278.
6. Brana, M. F.; Cacho, M.; Gradillas, A.; Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745–1780.
7. Martinez, R.; Chacon-Garcia, L. *Curr. Med. Chem.* **2005**, *12*, 127–151.
8. Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, *62*, 864–867.
9. Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2321–2323.
10. Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235–4239.
11. Geen, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *Tetrahedron* **1998**, *54*, 9875–9894.
12. Parenty, A. D. C.; Smith, L. V.; Pickering, A. L.; Long, D. L.; Cronin, L. *J. Org. Chem.* **2004**, *69*, 5934–5946.
13. Baldwin, J. E.; Tomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846–3852.
14. DFT calculations were carried out using HyperChem with the 6-31G** basis set and the B2-LPY combination potential.
15. Dostal, J.; Potacek, M.; Nechvatal, M. *Collect. Czech. Chem. Commun.* **1993**, *58*, 395–403.
16. Anne, A.; Moiroux, J. *J. Org. Chem.* **1990**, *55*, 4608–4614.
17. Krohnke, F.; Vogt, I. *Justus Liebigs Ann. Chim.* **1956**, *600*, 211–224.
18. Lavilla, R.; Gotsens, T.; Guerrero, M.; Masdeu, C.; Santano, M. C.; Minguillon, C.; Bosch, J. *Tetrahedron* **1997**, *53*, 13959–13968.
19. Moracci, F. M.; Rienzo, B. D.; Tortorella, S.; Liberatore, F. *Tetrahedron* **1980**, *36*, 785–789.
20. Berge, T.; Jenkins, N. S.; Hopkirk, R. B.; Waring, M. J.; Edwardson, J. M.; Henderson, R. M. *Nucl. Acids Res.* **2002**, *30*, 2980–2986.
21. Leon, P.; Garbayjaureguiberry, C.; Lepecq, J. B.; Roques, B. P. *Tetrahedron Lett.* **1985**, *26*, 4929–4932.
22. Pelaprat, D.; Delbarre, A.; Le Guen, I.; Roques, B. P. *J. Med. Chem.* **1980**, *23*, 1336–1343.
23. Leon, P.; Garbayjaureguiberry, C.; Lambert, B.; Lepecq, J. B.; Roques, B. P. *J. Med. Chem.* **1988**, *31*, 1021–1026.
24. Molina, A.; Vaquero, J. J.; GarciaNavio, J. L.; AlvarezBuilla,

J.; dePascualTeresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587–5599.
25. Pelaprat, D.; Oberlin, R.; Le Guen, I.; Roques, B. P.; Le Pecq, J. B. *J. Med. Chem.* **1980**, *23*, 1330–1335.
26. Werbel, L. M.; Angelo, M.; Fry, D. W.; Worth, D. F. *J. Med. Chem.* **1986**, *29*, 1321–1322.
27. Leon, P.; Garbayjaureguiberry, C.; Barsi, M. C.; Lepecq, J. B.; Roques, B. P. *J. Med. Chem.* **1987**, *30*, 2074–2080.
28. Acton, E. M.; Narayanan, V. L.; Risbood, P. A.; Shoemaker, R. H.; Vistica, D. T.; Boyd, M. R. *J. Med. Chem.* **1994**, *37*, 2185–2189.
29. Scala, S.; Akhmed, N.; Rao, U. S.; Paull, K.; Lan, L. B.; Dickstein, B.; Lee, J. S.; Elgemeie, G. H.; Stein, W. D.; Bates, S. E. *Mol. Pharmacol.* **1997**, *51*, 1024–1033.