Preparation of 3-substituted 10-methylphenothiazines

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Lithiation at the C-3 position of 10-methylphenothiazine can be achieved by a Bu^{s}Li–Br exchange reaction starting from 3-bromo-10-methylphenothiazine. Reaction of the lithiated species with different electrophiles gives rise to different new and well known compounds which due to their radical properties are important enzyme enhancers. The described procedure gives moderate to high yield and easy access to C-3 substituted derivatives.

Introduction

Various 10-alkylated phenothiazine derivatives can be used to enhance the reaction of different oxidative enzymes as *e.g.* peroxidases[1,2] and laccases.[3] The systems can be used for a number of different industrial processes as *e.g.* waste water purification, prevention of dye transfer during wash, denim bleaching and as a glucose sensor system.[4] To investigate the importance of different substituents at the C-3 position of 10-methylphenothiazine different derivatives were needed.

Phenothiazines substituted in the C-1 position[5] can be synthesised by *in situ* protection of the *N*-10 position followed by deprotonation and reaction with various electrophiles. Reaction of phenothiazine with 2 equiv. of *n*-butyllithium is also reported to give access to different C-1 substituted compounds.[6–11] 10-Alkylphenothiazine can be lithiated at the C-4 position with *n*-butyllithium[7,12,13] or *sec*-butyllithium–TMEDA[14] and subsequently reacted with electrophiles to give various products in respectively low and good yields. It can be concluded that methods for the introduction of electrophiles into the C-1 position of phenothiazine and the C-4 position of 10-alkylphenothiazine are well known.

Metallation procedures giving access to the C-3 position of 10-alkylphenothiazine have only sparingly been described. Gilman *et al.*[12] have reported that 10-ethylphenothiazine-3-carboxylic acid can be synthesised from 10-ethylphenothiazine by a five step procedure with low overall yield. Gilman and Eisch[15] have described the synthesis of the same compound in a crude yield of 39% starting from 3-bromo-10-ethylphenothiazine by preparation of the Grignard reagent and subsequent carboxylation.

Different C-1, C-2 and C-3 substituted phenothiazine derivatives can be formed from substituted diphenylamines by cyclisation with sulfur.[16–19] The synthesis of the substituted diphenylamines, the cyclisation procedure and the *N*-10 alkylation is however a quite elaborate procedure for the preparation of the derivatives. Some C-3 substituted *N*-10 alkylphenothiazines can also be synthesised by an electrophilic aromatic substitution reaction and subsequent derivatisation.[20–22]

Herein we describe the introduction of different substituents into the C-3 position of 10-alkylphenothiazine (10-methylphenothiazine **1** used as an example) by a bromine–lithium exchange reaction.

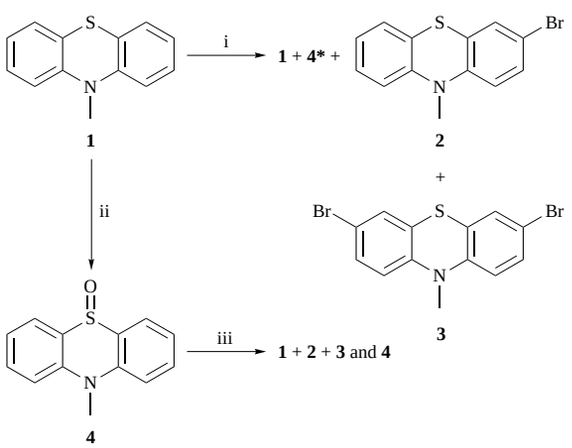
Results and discussion

Synthesis of 3-bromo-10-methylphenothiazine 2

Reductive monobromination of 10-ethylphenothiazine 5-oxide by reaction with 24% hydrobromic acid gives a 44% yield of crude product but no yield of pure **2** is reported.[15] Bodea and Terdic have described the bromination of 10-methylphenothiazine **1** with bromine in acetic acid.[23] Flash chromatography followed by recrystallisation did however not give pure product. The bromination of **1** with pyridinium hydrobromide perbromide (PHP) has been reported by Biehl *et al.*[24] A crude yield of 90% is reported but an attempted purification of **2** by recrystallisation did not give pure product. The bromination of **1** with *N*-bromosuccinimide (NBS) is described by Biehl *et al.*[24] to give only disubstituted product. The bromination with NBS has also been described by Smith *et al.*[25] for different tricyclic compounds such as carbazoles and iminodibenzyles. For iminodibenzyle a content of 76% of monobrominated product could be found in the crude product mixture.

None of the four procedures document in a reliable way that pure 10-alkyl-3-bromophenothiazine has been obtained. As a substantial amount of pure **2** was needed, it was decided to investigate the different procedures by evaluating the product distribution of the crude product by a GC assay.

It can be seen from Table 1 entries 1–4 that none of the four methods are selective. For all described procedures, **1**, **2** and 3,7-dibromo-10-methylphenothiazine **3** can be found (Scheme 1).



Scheme 1 *Reagents and conditions:* i, Br_2, PHP or NBS; ii, H_2O_2; iii, HBr. *Compound **4** only formed when NBS was used as brominating reagent.

The best procedure is the bromination with Br_2 (entry 1) and PHP (entry 2), as both methods give about 70% of **2**. The NBS bromination procedure (entry 3) gives a considerable amount of 10-methylphenothiazine 5-oxide **4** and the HBr procedure (entry 4) gives a considerable amount of **1** formed by *S*-oxide reduction without bromination. As the amount of HBr exceeds 1 equiv. it was investigated if the use of only 1 equiv. of HBr would give a more optimal product distribution. This was unfortunately not the case as the content of **2** was only 13% under these conditions (entry 5).

It was decided to prepare **2** by a modified procedure of the one originally described by Bodea and Terdic[23] using 1 equiv. of

Table 1

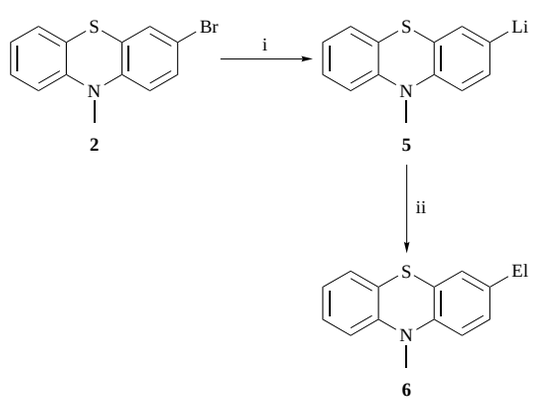
Entry	Reagent	Product (%) 1	2	3	4	Other
1 [a]	Br_2	20	71	8	0	1
2 [23]	PHP	27	67	6	—	0
3 [24]	NBS	20	53	5	23	—
4 [14]	HBr	25	60	7	4	4
5 [14, b]	HBr	10	13	2	75	0

Reagents and conditions: [a] The conditions for the bromination with Br_2 are slightly modified (see Experimental section) compared to the procedure described by Bodea.[22] [b] Bromination with 1 equiv. HBr.

Br_2 in acetic acid–sodium acetate at 5–10 °C under an atmosphere of nitrogen protected from light. The content of **2** in the crude mixture was increased by recrystallisation and additional flash chromatography gave pure **2.**

Synthesis of 3-substituted phenothiazines 6a–g

3-Bromo-10-methylphenothiazine **2** was treated with *sec*-butyllithium in tetrahydrofuran to give 3-lithio-10-methylphenothiazine **5** which subsequently was reacted with various electrophiles to produce C-3 substituted derivatives (**6a**–**g**) (Scheme 2). The electrophiles chosen for this study and the products obtained are listed in Scheme 2.



Comp.	Electrophile	E1	Yield (%)
6a	MeI	Me	87
6b	DMF	CHO	90
6c	CO_2	CO_2H	85
6d	Bu^tCHO	$CHOHBu^t$	92
6e	Oxirane	CH_2CH_2OH	54
6f	$(CH_2O)_n$	CH_2OH	38
6g	Me_2S_2	SMe	86

Scheme 2 *Reagents and conditions:* i, Bu^sLi, −78 °C, 0.5 h; ii, electrophile added, −78 °C, 0.5–1 h

3,10-Dimethylphenothiazine **6a** (obtained in 87% yield) has previously been prepared by a Wolf–Kishner reduction of 3-formyl-10-methylphenothiazine **6b** in an overall yield of 64–72% by two steps from 10-methylphenothiazine **1**[20,26] and also by a ring closure reaction of 4-methyldiphenylamine and subsequent *N*-methylation in a yield below 20%.[27,28] 3-Formyl-10-methylphenothiazine **6b** (90%) has also been synthesised by a Vilsmeier–Haack [19–21] reaction in yields of 37–80% from **1**. 10-Methylphenothiazine-3-carboxylic acid **6c** (85%) has been prepared [22,29] by a silver oxide oxidation of **6b** in an overall yield of 18% starting from **1**. 3-(2-Hydroxyethyl)-10-methylphenothiazine **6e** (54%) is referenced in a patent by Rhone-Poulenc [30] but the compound described is 2-(2-hydroxyethyl)phenothiazine. 3-Hydroxymethyl-10-methylphenothiazine **6f** (38%) has previously been prepared [21,22] by reduction of **6c** in overall yields between 28–53% from **1**.

^{13}C NMR data (Table 2) are consistent with the site of substitution being C-3. The assignments of the ^{13}C NMR signals are based on values given in the literature.[5,14,31]

In conclusion, different new and well known C-3 substituted 10-methylphenothiazines can be prepared in moderate to high yields by a convenient one step procedure starting from 3-bromo-10-methylphenothiazine **2**. The process is superior to known procedures for **6a**–**c** and **6f** with respect to number of steps and for **6a**–**c** also in yields.

Experimental

General methods

All air-sensitive reactions were performed under nitrogen or argon using syringe–septum cap techniques and all glassware was flame dried prior to use. At work up, magnesium sulfate was used for drying the organic solvents and the solvents were evaporated to dryness under reduced pressure.

The melting points are uncorrected. All compounds were colourless, unless otherwise stated. Microanalyses were determined at Novo Nordisk A/S. The NMR spectrometers were a Bruker DRX 400 and a Bruker 300 ie. ^1H NMR spectra were determined at 400 and 300 MHz and tetramethylsilane was used as internal standard. The ^{13}C NMR spectra were recorded at 100 and 75.5 MHz and the centre peak was respectively set at δ 76.90 for $CDCl_3$ and at 39.60 for $[^2H_6]$DMSO. Coupling constants (J) are given in Hz. The gas chromatograph used to measure the product distribution for the bromination experiments was a Varian Star 3400DX.

Thin layer chromatography was performed on Merck DC-Alufolien, silica gel 60 F_{254} and components were visualised by UV_{254}. Flash chromatography [32] was performed using silica gel Merck 60 size 40–63 μm.

Materials

All solvents and reagents were obtained from Merck and Aldrich and used without further purification. Tetrahydrofuran was dried by distillation from sodium and sodium benzophenone ketyl. Trimethylacetaldehyde was distilled and paraformaldehyde was dried over P_2O_5 prior to use. *sec*-Butyllithium was obtained from Fluka. Phenothiazine was obtained from Hoechst/Casella. 10-Methylphenothiazine **1** was prepared by slightly modifying a literature procedure.[33,34] A mixture of phenothiazine (18 g, 90 mmol), absolute methanol (8 cm^3) and methyl iodide (7 cm^3, 110 mmol) was heated in a glass screw cap vessel [35] for 18 h at 105 °C. Standard work-up followed by recrystallisation from ethyl acetate–ethanol (1:3) gave pure product (32.6 g, 79%), mp 99–100 °C (lit.,[33] 102–104 °C; lit.,[36] 99 °C). Pyridinium hydrobromide perbromide was prepared by the method of Fieser and Fieser.[37] 10-Methylphenothiazine 5-oxide **4** was prepared as described by Nelson,[13] mp 187–189 °C (lit.,[38] 187–189 °C; lit.,[39] 192–194 °C). Crude **2** was prepared from **1** by bromination using NBS,[25] Br_2 (procedure described below) pyridinium hydrobromide perbromide [24] and by reductive bromination [15] from **4** using the equivalents of HBr described by Gilman and Eisch [15] and also by using only 1 equiv. *sec*-Butyllithium, was titrated as previously described.[40]

3-Bromo-10-methylphenothiazine 2

Sodium hydroxide (8.63 g, 216 mmol) was dissolved in glacial acetic acid, (525 cm^3) under an atmosphere of nitrogen. **1** (15 g, 70.3 mmol) was added followed by chloroform (100 cm^3). Bromine (3.62 cm^3, 70.3 mmol) was dissolved in glacial acetic acid (75 cm^3) and added dropwise during 1.5 h at 5–10 °C. The suspension was stirred at room temperature for 1 h, evaporated to dryness and redissolved in aqueous sodium hydrogen carbonate (5% w/v, 100 cm^3) and dichloromethane (100 cm^3). The aqueous phase was separated from the organic phase and

Table 2 ^{13}C NMR data of compounds **1**, **2** and **6a**–**f**

Compound	Carbon atom, δ_C												
	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a	C-11
1	115.0	127.1	122.2	127.3	124.4	124.4	127.3	122.2	127.1	115.0	144.9	144.9	35.1
2	115.0	129.2	114.6	129.9	125.5	122.5	127.5	122.6	127.1	114.1	144.9	145.3	35.2
6a[b]	113.7	127.5*	131.8	127.7	123.2	123.1	127.3*	122.0	127.0	113.7	143.3	145.9	35.1
6b[c]	113.6	127.9	131.1	130.3	123.9	122.5	127.7	123.5	127.2	114.7	144.0	151.0	35.8
6c[d]	115.2	128.1	121.9	129.7	124.7	123.3	127.6	121.5	127.0	114.3	144.3	149.2	35.5
6d[e]	113.0	126.1	136.4	127.3	122.5	123.2	127.1	122.3	126.6	113.9	144.8	145.7	35.2
6e[f]	113.8*	127.4†	132.5	127.9	123.5	123.0	127.3†	122.2	127.0	113.9*	144.2	145.7	35.1
6f[g]	113.8*	125.9	135.0	127.3	123.5	123.0	127.0	122.3	126.3	113.9*	145.2	145.5	35.2
6g[h]	114.2	126.7	131.1	127.5*	124.2	122.8	127.4*	122.3	127.0	113.9*	143.9	145.5	35.2

[a] Recorded at 100 MHz in $CDCl_3$ except for **6d** which was recorded in [$^2H_6$]DMSO. Assignment based on refs. 5, 14 and 31. Chemical shift values marked * or † may be interchangeable. [b] δ 20.2 ($ArCH_3$). [c] δ 190.0 (ArCHO). [d] δ 166.6 ($ArCO_2H$). [e] δ 26.3 [$C(CH_3)_3$], 36.1 (ArCHOH), 82.1 [$C(CH_3)_3$]. [f] δ 38.5 ($ArCH_2$), 64.0 (CH_2OH). [g] δ 64.5 (CH_2OH). [h] δ 17.4 (SCH_3).

extracted with dichloromethane. The combined organic phases were dried, filtered through silica gel (100 g) and evaporated to dryness (20.3 g). The crude product was recrystallised twice (ethyl acetate–ethanol) (1:3) and (toluene–ethanol) (1:10). Flash chromatography on silica gel with ethyl acetate–heptane (1:13) as the eluent yielded **2** (8.2 g, 40%), mp 113–113.5 °C (lit.,[23] 108–112 °C; lit.,[24] 112–112.5 °C); R_f(ethyl acetate–heptane) (1:6) 0.47 (Found C, 53.6; H, 3.5; N, 4.7; S, 10.8; Br, 27.4. Calc. for $C_{13}H_{11}NSBr$: C, 53.4; H, 3.45; N, 4.8; S, 11.0; Br, 27.35%); δ_H(400 MHz; $CDCl_3$) 3.33 (3 H, s, NCH_3), 6.62 (1 H, d, *J* 9, 1-H), 6.79 (1 H, dd, *J* 1 and 8, 9-H), 6.93 (1 H, dt, *J* 1 and 7.5, 7-H), 7.11 (1 H, dd, *J* 1 and 8, 6-H), 7.17 (1 H, dt, *J* 1.5 and 7.5, 8-H), 7.23 (1 H, d, *J* 2.5, 4-H), 7.23 (1 H, dd, *J* 2.5 and 9.5, 2-H).

General procedure for the bromine–lithium exchange reaction of 2

3-Bromo-10-methylphenothiazine **2** (0.5 g, 1.74 mmol) was dissolved in dry tetrahydrofuran (20 cm^3) under an atmosphere of nitrogen. Slow addition of *sec*-butyllithium (2.6 cm^3 of a 1.3 M solution in cyclohexane, 3.5 mmol) was carried out at −78 °C and the mixture stirred for 0.5 h. The electrophile was slowly added and the mixture stirred for an additional 1 h (for some experiments 0.5 h) at −78 °C.

3,10-Dimethylphenothiazine 6a. The general procedure was used with iodomethane (0.31 cm^3, 5.2 mmol) as the electrophile. After warming to room temperature the reaction mixture was stirred for an additional 2 h. The reaction mixture was poured into saturated aqueous ammonium chloride (20 cm^3) and water (5 cm^3) and the organic phase separated. The aqueous phase was extracted with dichloromethane and the combined organic phases dried and evaporated to dryness to give the crude product (0.41 g). Flash chromatography on silica gel with ethyl acetate–heptane (1:10) as the eluent yielded **6a** as crystals (0.34 g, 87%), mp 142–143 °C (from ethanol) (lit.,[20] 148 °C; lit.,[26] 143 °C); R_f(ethyl acetate–heptane) (1:8) 0.58 (Found C, 73.7; H, 5.9; N, 6.1; S, 14.0. Calc. for $C_{14}H_{13}NS$: C, 74.0; H, 5.8; N, 6.2; S, 14.1%); δ_H(400 MHz; $CDCl_3$) 2.24 (3 H, s, $ArCH_3$), 3.34 (3 H, s, NCH_3), 6.70 (1 H, d, *J* 8.5, H-1), 6.79 (1 H, dd, *J* 1.0 and 8.0, H-9), 6.90 (1 H, dt, *J* 1.0 and 7.5, H-7), 6.95 (1 H, dd, *J* 1.5 and 7.5, H-2), 7.00 (m, 1H, H-4), 7.13 (1 H, dd, *J* 1.5 and 7.5, H-6), 7.15 (1 H, dt, *J* 1.5 and 7.5, H-8).

3-Formyl-10-methylphenothiazine 6b. The general procedure was used with *N*,*N*-dimethylformamide (0.29 cm^3, 3.7 mmol) as the electrophile, stirring for 0.5 h. The reaction mixture was added to hydrochloric acid (4.3% w/v, 15 cm^3) and stirred for 0.5 h and the organic phase evaporated. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and evaporated to dryness (0.43 g). Flash chromatography on silica gel with ethyl acetate–heptane (1:8→1:4) as the eluent yielded **6b** as yellow crystals (0.38 g, 90%), mp 86–87 °C (from ethyl acetate–heptane) (1:2) (lit.,[20] mp 89 °C; lit.,[21] 85 °C); R_f(ethyl acetate–heptane) (1:8) 0.17 (Found C, 69.6; H, 4.7; N, 5.6; S, 13.4. Calc. for $C_{14}H_{11}NSO$: C, 69.7; H, 4.6; N, 5.8; S, 13.3%); δ_H(400 MHz; $CDCl_3$) 3.43 (3 H, s, CH_3), 6.84 (1 H, dd, *J* 1.0 and 7.0, 9-H), 6.86 (1 H, dd, *J* 8.5, 1-H), 6.99 (1 H, dt, *J* 1.5 and 7.5, 7-H), 7.13 (1 H, dd, *J* 1.5 and 7.5, 6-H), 7.19 (1 H, dt, *J* 1.5 and 7.0, 8-H), 7.60 (1 H, d, *J* 2.0, 4-H), 7.66 (1 H, dd, *J* 2.0 and 8.5, 2-H) 9.81 (1 H, s, COH).

10-Methylphenothiazine-3-carboxylic acid 6c. The general procedure was used with carbon dioxide as the electrophile. The reaction mixture was poured into solid carbon dioxide (25 g) in dry diethyl ether (20 cm^3). When the carbon dioxide had evaporated, aqueous sodium hydroxide (8% w/v, 20 cm^3) was added and the two phases separated. The aqueous phase was acidified with sulfuric acid (25% w/v) and the suspension extracted with dichloromethane. The organic phase was dried and evaporated to dryness to provide **6c** as yellow crystals (0.38 g, 85%), mp 240–244 °C (decomp.) (from toluene–acetone) (5:3) (lit.,[22] 244–245 °C; lit.,[29] 260 °C); R_f(glacial acetic acid–ethyl acetate–heptane (1:30:69) 0.30 (Found C, 65.4; H, 4.3; N, 5.4; S, 12.35. Calc. for $C_{14}H_{11}NSO_2$: C, 65.35; H, 4.3; N, 5.4; S, 12.5%); δ_H(400 MHz; [$^2H_6$]DMSO) 3.36 (3 H, s, NCH_3), 6.99 (1 H, dd, *J* 1.5 and 8.5, 9-H), 7.00 (1 H, t, *J* 6.5, 7-H), 7.01 (1 H, d, *J* 8.5, 1-H), 7.17 (1 H, dd, *J* 1.5 and 8.0, 6-H), 7.24 (1 H, dt, *J* 1.5 and 8.0, 8-H), 7.63 (1 H, d, *J* 2.0, 4-H), 7.78 (1 H, dd, *J* 1.5 and 8.0, 2-H).

3-(2,2-Dimethyl-1-hydroxypropyl)-10-methylphenothiazine 6d. The general procedure was used with trimethylacetaldehyde (0.41 cm^3, 6.3 mmol) as the electrophile, stirring for 1 h before quenching with hydrochloric acid (5% w/v, 30 cm^3). After stirring for 0.5 h the organic phase was evaporated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried and evaporated to dryness to give the crude product as a light yellow oil (0.6 g). Flash chromatography on silica gel with ethyl acetate–heptane (1:8) as the eluent yielded **6d** as light yellow crystals (0.48 g, 92%), mp 73.5–74.5 °C (from ethanol); R_f(ethyl acetate–heptane) (1:2) 0.47 (Found: C, 72.5; H, 7.3; N, 4.5; S, 10.8. Calc. for $C_{18}H_{21}NSO$: C, 72.2; H, 7.1; N, 4.7; S, 10.7%); δ_H(400 MHz; $CDCl_3$) 0.82 [9 H, s, $C(CH_3)_3$], 1.69 (1 H, br s, COH), 3.29 (3 H, s, NCH_3), 4.22 (1 H, s, ArCH), 6.67 (1 H, d, *J* 9, H-1), 6.73 (1 H, dd, *J* 1 and 8, H-9), 6.85 (1 H, dt, *J* 1 and 7.5, H-7), 7.01 (1 H, dd, *J* 2 and 9, H-2), 7.02 (1 H, d, *J* 2, H-4), 7.07 (1 H, dd, *J* 1.5 and 7.5, H-6), 7.09 (1 H, dt, *J* 2 and 7.5, H-8).

3-(2-Hydroxyethyl)-10-methylphenothiazine 6e. The general procedure was used, with ethylene oxide (0.75 cm^3, 15 mmol), added in two portions, as the electrophile. Work-up as described for **6a** gave the crude product (0.46 g). Flash chromatography on silica gel with ethyl acetate–heptane (1:8→1:1) as the eluent yielded **6e** as light yellow crystals (0.24 g, 54%), mp 86–87 °C. Recrystallisation gave mp 87–87.5 °C (from ethanol); R_f(ethyl acetate–heptane) (1:4) 0.17 (Found C, 70.3; H, 6.0; N, 5.3; S, 12.4. Calc. for $C_{15}H_{15}NSO$: C, 70.0; H, 5.9; N, 5.4; S, 12.5%);

δ_H(400 MHz; $CDCl_3$) 1.47 (1 H, br s, COH), 2.75 (2 H, t, *J* 6.5, CH_2O), 3.34 (3 H, s, CH_3), 3.78 (2 H, t, *J* 6.5, $ArCH_2$), 6.74 (1 H, d, *J* 8.5, H-1), 6.79 (1 H, dd, *J* 1.0 and 8.0, H-9), 6.91 (1 H, dt, *J* 1.0 and 7.5, H-7), 7.00 (1 H, d, *J* 2, H-4), 7.00 (1 H, dd, *J* 2.0 and 8.5, H-2), 7.13 (1 H, dd, *J* 1.5 and 8.0, H-6), 7.15 (1 H, dt, *J* 1.5 and 7.5, H-8).

3-(Hydroxymethyl)-10-methylphenothiazine 6f. The general procedure was used with paraformaldehyde (0.65 g, 21.7 mmol), added in four portions over 20 min, as the electrophile. The reaction mixture was poured into hydrochloric acid (5% w/v, 25 cm^3) and the phases separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried and evaporated to dryness to give the crude product (0.49 g). Flash chromatography on silica gel with ethyl acetate–heptane (1 : 6→1 : 3) as the eluent yielded **6f** as light yellow crystals (0.16 g, 38%), mp 133–133.5 °C (from ethanol) (lit.,[21] 137–138 °C; lit.,[22] 130.5–131.5 °C); R_f(ethyl acetate–heptane) (1 : 4) 0.13 (Found C, 69.4; H, 5.5; N, 5.5; S, 13.2. Calc. for $C_{14}H_{13}NSO$: C, 69.1; H, 5.4; N, 5.8; S, 13.2%); δ_H(400 MHz; $CDCl_3$) 1.69 (1 H, br s, COH), 3.35 (3 H, s, CH_3), 4.55 (2 H, s, CH_2), 6.76 (1 H, d, *J* 8.5, H-1), 6.79 (1 H, dd, *J* 1.0 and 8.0, H-9), 6.91 (1 H, dt, *J* 1.0 and 7.5, H-7), 7.13 (1 H, d, *J* 2, H-4), 7.13 (2 H, m, H-2 and H-6), 7.16 (1 H, dt, *J* 1.5 and 7.5, H-8).

10-Methyl-3-(methylthio)phenothiazine 6g. The general procedure was used with methyl sulfide (0.37 cm^3, 5 mmol) as the electrophile. Work-up as described for **6a** gave the crude product as a light yellow oil (0.75 g). Flash chromatography on silica gel with ethyl acetate–heptane (1 : 12→1 : 6) as the eluent yielded **6g** as light yellow crystals (0.39 g, 86%), mp 79–79.5 °C; R_f(ethyl acetate–heptane) (1 : 8) 0.46 (Found C, 64.9; H, 5.1; N, 5.25; S, 24.4. Calc. for $C_{14}H_{13}NS_2$: C, 64.8; H, 5.05; N, 5.4; S, 24.7%); δ_H(400 MHz; $CDCl_3$) 2.42 (3 H, s, SCH_3) , 3.33 (3 H, s, NCH_3), 6.70 (1 H, d, *J* 7.5, H-1), 6.78 (1 H, dd, *J* 1.0 and 8.0, H-9), 6.91 (1 H, dt, *J* 1.0 and 7.5, H-7), 7.09 (1 H, d, *J* 2, H-4), 7.10 (1 H, dd, *J* 2.0 and 8.0, H-2), 7.12 (1 H, dd, *J* 1.5 and 7.0, H-6), 7.15 (1 H, dt, *J* 1.5 and 7.5, H-8).

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