# Preparation of 4-substituted 10-ethylphenothiazines

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**Under appropriate reaction conditions 10-ethylphenothiazine 1 undergoes lithiation at C-4 using an excess of *sec*-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine in diethyl ether. Reaction of the lithiated intermediate with a variety of carbon, halogen, sulfur and silicon electrophiles affords several new 4-substituted 10-ethylphenothiazines 3a–i in good yields.**

## Introduction

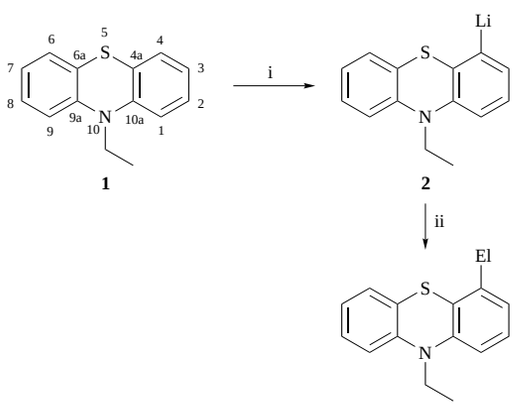
*N*-Alkylated phenothiazine derivatives can be used to enhance various reactions of different oxidative enzymes such as peroxidases and laccases,[1–4] *e.g.* for prevention of dye transfer[1–3] during washing or for glucose detection.[4] In order to investigate the influence of various ring substituents in *N*-alkylated phenothiazines, procedures for selective introduction of ring substituents were required. Phenothiazines substituted at C-1 can be made by C-1 lithiation of *N*-lithiocarbamate protected phenothiazine[5] or by 1,10-dilithiation of phenothiazine followed by reaction with an electrophile.[6–10] In addition, phenothiazines substituted at C-1 or C-3 can be made from the respective *ortho*- or *para*-substituted diphenylamines by cyclization using sulfur in the presence of iodine.[11] The appropriate diphenylamines are synthesized from 2-chlorobenzoic acid and the appropriately substituted aminobenzene in two steps.[12] When *meta*-substituted diphenylamines are subjected to cyclization using sulfur and iodine a mixture of C-2 and C-4 substituted phenothiazines is formed with the former as the predominant isomer.[11,13]

A few 4-substituted phenothiazines have been prepared by lithiation of *N*-alkyl phenothiazines[7,14,15] followed by reaction with an electrophile, but yields are low. Cauquil *et al*. have reported that a mixture of the 1-carboxylic acid and 4-carboxylic acid is obtained in yields of 13 and 14% respectively by the *n*-butyllithium metalation over 30 h of 10-ethylphenothiazine and subsequent reaction with carbon dioxide.[7]

Obviously there is no good and high yielding synthesis available for the preparation of 4-substituted phenothiazines. We now report a new approach to 4-substituted 10-ethylphenothiazines **3a**–**i** from 10-ethylphenothiazine **1**† based on lithiation at C-4 and subsequent reaction with electrophiles.

## Results and discussion

The lithiation of 10-ethylphenothiazine **1** followed by reaction with methyl iodide was investigated under various reaction conditions. As shown in Table 1, lithiation of 10-ethylphenothiazine **1** using Bu$^s$Li in the presence of *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) or Bu$^t$Li–TMEDA (entries 3 and 4) was superior to Bu$^n$Li–TMEDA (entry 2). The lithiation was greatly improved when it was effected in the presence of TMEDA (compare entries 1 and 3). Performing the lithiation using Bu$^s$Li–TMEDA or Bu$^t$Li in the presence of Bu$^t$OK followed by methylation gave 4-methyl-10-ethylphenothiazine **3a** in 0–45% (entries 5–7). The best result was obtained using Bu$^s$Li–TMEDA–Bu$^t$OK in THF as solvent (entry 7). By comparing entries 3 and 8–10 it is evident that 2.5 equiv. of Bu$^s$Li–TMEDA is the optimum for maximum formation of **3a** and for almost complete conversion of starting material. Applying THF as solvent (entry 12) in order to increase solubility and to perform the reaction at lower temperature resulted in only 25% formation of **3a**. Furthermore, decreasing the lithiation time from 2.5 to 0.5 h did not affect the yield of **3a** (entries 3 and 11).




| Compd. | Electrophile | El | Yield (%) |
|---|---|---|---|
| **3a** | MeI | Me | 72[a] |
| **3b** | DMF | CHO | 69 |
| **3c** | $CO_2$ | $CO_2H$ | 63 |
| **3d** | Bu$^t$CHO | CHOHBu$^t$ | 72 |
| **3e** | $C_2Cl_6$ | Cl | 62 |
| **3f** | $I_2$ | I | 69 |
| **3g** | $Me_3SiCl$ | $SiMe_3$ | 59 |
| **3h** | $Me_2S_2$ | SMe | 69 |
| **3i** | DMF/$NaBH_4$ | $CH_2OH$ | 50 |

**Scheme 1** *Reagents*: i, *sec*-BuLi–TMEDA; ii, addition of different electrophiles El. [a] Yield in reaction mixture.

In all cases the formation of by-products was observed. GC–MS of the crude reaction mixtures indicated the presence of other regioisomers and some dimethylated 10-ethylphenothiazines. The following standard procedure for the selective preparation of 4-substituted 10-ethylphenothiazines **3a**–**i** was adopted based on the data presented in Table 1. Lithiation experiments were conducted at room temperature in diethyl ether for 0.5 h using 2.5 equiv. of Bu$^s$Li–TMEDA, followed by reaction with the electrophilic reagent at 0 °C. In this way a wide variety of carbon, halogen, sulfur and silicon substituents were introduced at the 4-position of 10-ethylphenothiazine **1** in good yields (Scheme 1). Using DMF as the electrophile gave 10-

† An ethyl group was used to block the ring nitrogen since more bulky substituents would result in low water solubility, making the substrates unsuitable as enzyme mediators. Use of an *N*-methyl group was expected to give more C-1 substituted products.

**Table 1** Optimization of the conditions for the deprotonation of 10-ethylphenothiazine **1** and subsequent reaction with iodomethane

| | | | | | Products (%) | | |
|---|---|---|---|---|---|---|---|
| Entry | Base/TMEDA | Equiv. | Solvent | T/°C | **3a** | By-products | **1** |
| 1 | Bu$^s$Li[a] | 2.5 | $Et_2O$ | 20 | 17 | 5 | 78 |
| 2 | Bu$^n$Li | 2.5 | $Et_2O$ | 20 | 47 | 51 | 2 |
| 3 | Bu$^s$Li | 2.5 | $Et_2O$ | 20 | 72 | 21 | 7 |
| 4 | Bu$^t$Li | 2.5 | $Et_2O$ | 20 | 67 | 31 | 2 |
| 5 | Bu$^s$Li[b] | 2.5 | $Et_2O$ | 20 | 0 | 6 | 94 |
| 6 | Bu$^t$Li[a,b] | 2.5 | THF | −50 | 20 | 7 | 73 |
| 7 | Bu$^s$Li[b] | 2.5 | THF | −50 | 45 | 14 | 32 |
| 8 | Bu$^s$Li | 1.1 | $Et_2O$ | 20 | 49 | 13 | 38 |
| 9 | Bu$^s$Li | 1.6 | $Et_2O$ | 20 | 67 | 20 | 13 |
| 10 | Bu$^s$Li | 2.0 | $Et_2O$ | 20 | 69 | 22 | 9 |
| 11[c] | Bu$^s$Li | 2.5 | $Et_2O$ | 20 | 72 | 24 | 4 |
| 12 | Bu$^s$Li | 2.5 | THF | −20 | 25 | 11 | 64 |

[a] TMEDA not added. [b] 2.5 equiv. Bu$^t$OK added. [c] Deprotonation for 0.5 h, all other experiments 2.5 h.

**Table 2** $^{13}C$ NMR Spectral data of 10-ethylphenothiazine **1** and various synthesized 4-substituted 10-ethylphenothiazines **3a–i** ($CDCl_3$)

| | Carbon atom, $\delta_C$ | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compd | 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 | C-12 |
| **1**[a] | 115.0 | 127.1 | 122.2 | 127.3 | 124.4 | 124.4 | 127.3 | 122.2 | 127.1 | 115.0 | 114.9 | 144.9 | 13.0 | 41.7 |
| **3a**[a,d] | 113.0 | 126.3 | 123.6 | 135.5 | 124.4[k] | 124.6[k] | 127.4 | 122.0 | 127.1 | 114.9 | 144.8 | 145.3 | 13.1 | 41.8 |
| **3b**[a,e] | 119.6 | 126.6 | 123.5 | 132.9 | 130.3 | 124.3 | 127.7 | 122.6 | 127.5 | 115.2 | 145.8 | 145.1 | 12.8 | 42.2 |
| **3c**[a,f] | 119.7 | 126.0 | 124.7 | 131.5 | 126.9 | 124.9 | 127.4 | 122.5 | 127.4 | 115.1 | 145.5 | 145.3 | 13.0 | 42.2 |
| **3d**[a,g] | 114.2 | 125.9 | 122.0 | 140.8 | 125.0 | 125.4 | 127.3 | 122.0 | 127.1 | 114.9 | 146.0[k] | 145.9[k] | 13.0 | 41.7 |
| **3e**[b] | 113.3 | 127.5 | 122.5[k] | 131.2 | 123.4 | 124.4 | 127.5 | 122.4[k] | 127.1 | 115.1 | 146.0 | 144.4 | 12.9 | 42.2 |
| **3f**[b] | 115.1 | 128.0 | 132.2 | 97.0 | 130.5 | 124.7 | 127.5[k] | 122.6 | 127.4[k] | 115.0 | 144.6 | 145.3 | 13.0 | 42.2 |
| **3g**[b,c,h] | 116.3 | 126.2 | 128.4 | 138.7 | 131.5 | 125.4 | 127.3 | 122.2 | 127.1 | 115.0 | 145.7 | 145.1 | 13.2 | 41.6 |
| **3h**[b,i] | 112.5 | 126.9 | 120.0 | 136.1 | 123.9[l] | 124.0[l] | 127.6 | 122.3 | 127.3 | 114.9 | 144.9[k] | 145.1[k] | 13.0 | 41.9 |
| **3i**[a,i] | 114.9[k] | 126.7 | 121.8 | 138.1 | 124.1[l] | 124.2[l] | 127.4[m] | 122.2 | 127.3[m] | 115.1[k] | 145.5 | 145.3 | 13.0 | 41.8 |

[a] Recorded at 75 MHz. Assignments based on those of ref. 5 and 16 and by comparison with the assignment of **3g**. [b] Recorded at 100 MHz. Assignment based on those of ref. 5 and 16 and by comparison with the assignment of **3g**. [c] Assignment based on HSQC and HMBC ($J$ 6 Hz) experiments. [d] $\delta$ 19.9 ($ArCH_3$). [e] $\delta$ 189.9 (CHO). [f] $\delta$ 170.7 ($CO_2H$). [g] $\delta$ 25.9 [$C(CH_3)_3$], 36.6 [$C(CH_3)_3$], 77.0 (CHOH). [h] $\delta$ −0.4 ($SiCH_3)_3$. [i] $\delta$ 16.3 ($SCH_3$). [j] $\delta$ 63.4 ($CH_2OH$). [k] These $\delta_C$ assignments may be interchangeable. [l] These $\delta_C$ assignments may be interchangeable. [m] These $\delta_C$ assignments may be interchangeable.

ethyl-4-formylphenothiazine **3b** in 69% yield together with 7% of 10-ethyl-1,6-diformylphenothiazine. In all other cases minor amounts of by-products were present but not identified. The site of lithiation was confirmed as being C-4, by comparison of the melting point of 10-ethylphenothiazine-4-carboxylic acid **3c** (mp 178.5 °C, uncorrected) with that reported by Cauquil *et al.* (mp 182 °C). They unambiguously proved the structure by desulfurisation of **3c** to give *N*-phenyl-*N*-(3-carboxyphenyl)-ethylamine.[7]

Furthermore $^{13}C$ NMR data (Table 2) are in agreement with the site of substitution being at C-4. The assignment of $^{13}C$ NMR signals are based on values given in the literature[5,16] and by comparison with the assignment of **3g** (see below). Unambiguous assignment of the protonated carbons in **3g** was obtained *via* a 2D heterocorrelation experiment (HSQC). Long-range correlations were determined by a long-range HMBC experiment optimized for 6 Hz. The following long-range correlations were observed (long-range correlations to protonated carbons are omitted): C-10a with N-$CH_2$ and H-2; C-9a with N-$CH_2$ and H-8; C-4 with H-2 and H-3; C-4a with H-1 and H-3; C-5a with H-7 and H-9.

In conclusion the experiments above demonstrate that 4-substituted 10-ethylphenothiazines **3a–i** are now accessible through lithiation of 10-ethylphenothiazine **1** and subsequent reaction with an electrophile.

## Experimental

### General methods

All reactions involving air-sensitive reagents were performed under nitrogen or argon using syringe–septum cap techniques. All glassware was flame dried prior to use. $MgSO_4$ was used to dry solutions. Solvents were removed *in vacuo* by rotary evaporation. Melting points are uncorrected. Microanalyses were conducted at Novo Nordisk A/S. Bruker DRX 400 and Bruker 300 ie instruments were used to record $^1H$ NMR spectra at 400 and 300 MHz with tetramethylsilane (TMS) as internal standard, and $^{13}C$ NMR spectra at 100 and 75.5 MHz respectively with the solvent peak at 76.9 ppm for $CDCl_3$ and 39.6 ppm for [$^2H_6$]DMSO as internal reference. Coupling constants ($J$) are given in Hz. Mass spectra were recorded at Novo Nordisk A/S using electron impact ionisation on a Carlo-Erba 8000 GC coupled to a VG autospec Ultima sector MS instrument. The GC used for the optimization of the deprotonation reaction was a Varian Star 3400 CX. Thin layer chromatography was performed on Merck DC-Alufolien, silica gel 60 $F_{254}$, and components were visualised by $UV_{254}$. Flash chromatography[17] 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. The solvents used were: tetrahydrofuran (THF) dried (LabScan 4103/3), *N*,*N*-dimethylformamide (DMF) (Aldrich 22,705–6), 1,4-dioxane dried (Merck 3110) and diethyl ether (ether) dried (Aldrich 29,608–2). Phenothiazine was from Hoechst (99%). 10-Ethylphenothiazine **1** was prepared with slight modification of the procedure described by Gilman *et al.*[14] A mixture of phenothiazine (18 g, 90 mmol), absolute ethanol (8 $cm^3$) and ethyl iodide (8 $cm^3$, 99 mmol) was heated in a glass screw cap vessel[18] for 18 h at 105 °C to give **1** (32.6 g, 79%), mp 101.5–102.5 °C (from ethyl acetate–ethanol) (lit.,[14] 101–103 °C).

*n*-Butyllithium, *sec*-butylithium and *tert*-butyllithium were titrated prior to use.[19]

**Procedure for the optimization of the deprotonation reaction of 10-ethylphenothiazine 1**

10-Ethylphenothiazine **1** (1.03 g, 4.5 mmol) was dissolved in a dry solvent (ether 30 $cm^3$, THF 18 $cm^3$ or dioxane 10 $cm^3$) followed by addition of TMEDA and a base (*n*-, *sec*- or *tert*-butyllithium for some experiments together with sodium *tert*-butoxide). After stirring for 0.5 or 2.5 h, respectively, at room temperature, iodomethane (0.84 $cm^3$, 14 mmol) was added at 0 °C and stirring was continued at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (15 $cm^3$) and water (5 $cm^3$) and the aqueous phase extracted with dichloromethane (3 × 15 $cm^3$). The combined organic phases were dried and evaporated to give the crude product. The composition of the crude products was analysed by GC (results are shown in Table 1).

**General procedure for preparation of 4-substituted 10-ethylphenothiazines 3**

10-Ethylphenothiazine **1** (2 g, 8.8 mmol) was dissolved in dry ether (50 $cm^3$) under an atmosphere of argon. After 10 min, TMEDA (3.32 $cm^3$, 22 mmol) was added followed by *sec*-butyllithium (15.9 $cm^3$ of a 1.38 M solution in hexane, 22 mmol). The mixture was kept at room temperature for 0.5 h before the electrophile was added at 0 °C.

**10-Ethyl-4-methylphenothiazine 3a.** The general procedure was used with MeI (1.7 $cm^3$, 27.2 mmol) as the electrophile, stirring for 1 h before quenching with saturated aqueous $NH_4Cl$ (30 $cm^3$). The ether phase was separated and washed with water (30 $cm^3$) and the combined water phases were extracted with dichloromethane (3 × 25 $cm^3$). The combined organic phases were dried and evaporated to give the crude product as a light yellow oil (2.71 g); GC yields: 72%, **3a**; 5%, **1** and 21% of six different mono- and di-substituted by-products in concentrations above 1%. The crude product was recrystallized twice from ethanol–water (7:1) to give white crystals (1.12 g); GC yields: 85%, **3a** and 14% of five by-products, mp 52–54 °C. A third recrystallization did not increase the purity; $\delta_H$(400 MHz; $CDCl_3$) 1.39 (t, 3H, *J* 7, $CH_2CH_3$), 2.34 (s, 3H, $ArCH_3$), 3.90 (q, 2 H, *J* 7.0, $CH_2$), 6.72 (br d, 1H, *J* 8, 1-H), 6.81 (br d, 1H, *J* 7.5, 9-H), 6.84 (br d, 1H, *J* 8.0, 3-H), 6.88 (dt, 1H, *J* 1.5 and 7.5, 7-H), 7.04 (t, 1H, *J* 7.5, 2-H), 7.13 (dt, 1H, *J* 1.5 and 7.5, 8-H), 7.15 (dd, 1H, *J* 8.0 and 1.5, 6-H) (Found: $M^+$, 241.092 743. $C_{15}H_{15}NS$ requires $M^+$, 241.092 521).

**10-Ethyl-4-formylphenothiazine 3b.** The general procedure was used with dry DMF (2.11 $cm^3$, 27.3 mmol) as the electrophile, stirring for 20 min. The reaction mixture was poured into aqueous HCl (4.5% w/v; 180 $cm^3$) at 0 °C, stirring for 30 min. The ether phase was separated and the water phase was extracted with chloroform (4 × 100 $cm^3$). The combined organic phases were dried and evaporated to give an orange oil (2.8 g). The crude product was subjected to flash chromatography (ethyl acetate–heptane, 1:8) to provide **3b** as yellow crystals (1.56 g, 69%) and 10-ethyl-1,6-diformylphenothiazine as yellow crystals (0.167 g, 7%). Data for **3b**, mp 46–48 °C (from ethyl acetate–heptane, 1:10); $R_f$ (ethyl acetate–heptane, 1:2) 0.52 (Found: C, 70.9; H, 5.3; N, 5.3; S, 12.5. Calc. for $C_{15}H_{13}NOS$: C, 70.6; H, 5.1; N, 5.5; S, 12.6%); $\delta_H$(400 MHz; $CDCl_3$) 1.41 (t, 3H, *J* 7, $CH_3$), 3.92 (q, 2H, *J* 7, $CH_2$), 6.86 (dd, 1H, *J* 8 and 1, 9-H), 6.93 (dt, 1H, *J* 1.0 and 7.5, 7-H), 7.01 (dd, 1H, *J* 8.0 and 1.5, 1-H), 7.15 (dd, 1H, *J* 7.5 and 1.5, 6-H), 7.18 (dt, 1H, *J* 1.5 and 8.0, 8-H), 7.24 (t, 1H, *J* 7.5, 2-H), 7.43 (dd, *J* 8.0 and 1.5, 3-H), 10.26 (s, CHO). Data for 10-ethyl-1,6-diformylphenothiazine, mp 132 °C (from ethyl acetate–heptane, 1:10); $R_f$ (ethyl acetate–heptane, 1:2) 0.45 (Found: C, 68.0; H, 4.65; N, 4.8. Calc. for $C_{16}H_{13}NO_2S$: C, 67.8; H, 4.6; N, 4.9%); $\delta_H$(400 MHz; $CDCl_3$) 1.21 (t, 3H, *J* 7, $CH_3$), 3.87 (q, 2H, *J* 7, $CH_2$), 7.12 (t, 1H, *J* 8, 3-H), 7.30 (dd, 1H, *J* 8.0 and 1.5, 9-H), 7.36 (t, 1H, *J* 8.0, 8-H), 7.36 (dd, 1H, *J* 7.5 and 1.5, 7-H), 7.55 (dd, 1H, *J* 7.5 and 1.5, 2-H), 7.65 (dd, 1H, *J* 7.5 and 1.5, 4-H), 10.19 (s, CHO), 10.23 (s, CHO); $\delta_C$(100 MHz; $CDCl_3$) 14.7 ($CH_3$), 53.8 ($CH_2$), 123.9 (C-9), 126.9 (C-7), 126.9 (C-3), 128.2 (C-4), 128.3 (C-1), 129.6 (C-8), 132.0 (C-2), 132.3 (C-4a), 133.0 (C-5a), 134.2 (C-6), 145.1 (C-9a), 147.3 (C-10a), 189.6 (CHO), 190.2 (CHO).

**10-Ethylphenothiazine-4-carboxylic acid 3c.** The general procedure was used with carbon dioxide as the electrophile. The reaction mixture was poured into dry ice (30 g) in ether (40 $cm^3$). When the carbon dioxide had evaporated, aqueous NaOH (8% w/v; 100 $cm^3$) was added and the two phases separated. The aqueous phase was washed with ether (4 × 150 $cm^3$), acidified with aqueous HCl (37% w/v; 45 $cm^3$) and the precipitated crude product dissolved in dichloromethane (200 $cm^3$). The organic phase was washed with water (200 $cm^3$), dried and evaporated to give a yellow oil (2.4 g). The crude product was subjected to flash chromatography (glacial acetic acid–ethyl acetate–heptane, 1:35:64) to provide **3c** as yellow crystals (1.5 g, 63%), mp 178.5 °C (from toluene) (lit.,[7] 182 °C), $R_f$ (glacial acetic acid–ethyl acetate–heptane, 1:35:64) 0.24 (Found: C, 66.3; H, 4.9; N, 5.0; S, 11.8. Calc. for $C_{15}H_{13}NO_2S$: C, 66.4; H, 4.8; N, 5.2; S, 11.8%); $\delta_H$(400 MHz; [$^2H_6$]DMSO) 1.27 (t, 3H, *J* 7, $CH_3$), 3.88 (q, 2H, *J* 7, $CH_2$), 6.91 (dt, 1H, *J* 1.0 and 7.5, H-7), 6.97 (dd, 1H, *J* 8 and 1, H-9), 7.13 (dd, 1H, *J* 8.0 and 1.5, 6-H), 7.15 (dd, 1H, *J* 8.0 and 1.0, 1-H), 7.20 (dt, 1H, *J* 1.5 and 7.5, 8-H), 7.24 (t, 1H, *J* 7.5, 2-H), 7.43 (dd, 1H, *J* 7.5 and 1.0, 3-H).

**10-Ethyl-4-(2,2-dimethyl-1-hydroxypropyl)phenothiazine 3d.** The general procedure was used with trimethylacetaldehyde (3.00 $cm^3$, 27.3 mmol) as the electrophile. The mixture was stirred for 40 min at room temp. before HCl (5% w/v; 50 $cm^3$) was added followed by stirring for 1 h. The ether phase was separated and washed with water (40 $cm^3$). The aqueous phases were combined and extracted with dichloromethane (3 × 80 $cm^3$). The combined organic phases were dried and evaporated to give a light yellow oil (4.28 g) which was subjected to flash chromatography (ethyl acetate–heptane, 1:10 ⟶ 1:8) to provide **3d** as a light yellow oil (1.98 g, 72%) which crystallized upon standing, mp 94–95 °C (from ethanol–water, 4:1); $R_f$ (ethyl acetate–heptane, 1:2) 0.54 (Found: C, 72.8; H, 7.6; N, 4.3; S, 10.2. Calc. for $C_{19}H_{23}NOS$: C, 72.8; H, 7.4; N, 4.5; S, 10.2%); $\delta_H$(400 MHz; $CDCl_3$) 1.01 [s, 9H, $C(CH_3)_3$], 1.40 (t, 3H, *J* 7.0, $CH_2CH_3$), 1.84 (br s, 1H, COH), 3.94 (q, 2H, *J* 7.0, $CH_2$), 5.04 (s, 1H, ArCH), 6.84 (dd, 1H, *J* 10 and 4, 1-H), 6.88 (dd, 1H, *J* 7.5 and 1.5, 9-H), 6.91 (dt, 1H, *J* 1.0 and 7.5, 7-H), 7.15–7.20 (m, 4H, 2-H, 3-H, 6-H and 8-H).

**4-Chloro-10-ethylphenothiazine 3e.** The general procedure was used with hexachloroethane (6.46 g, 27 mmol) as the electrophile, stirring for 1 h. Work-up as described for **3a** afforded an oil (4.14 g). The crude product was subjected to flash chromatography (ethyl acetate–heptane, 0:1 ⟶ 1:8) to provide **3e** as light yellow crystals (1.43 g, 62%), mp 44–44.5 °C (from ethanol); $R_f$ (ethyl acetate–heptane, 1:6) 0.49 (Found: C, 63.9; H, 4.5; N, 5.2; S, 12.0. Calc. for $C_{14}H_{12}ClNS$: C, 64.2; H, 4.6; N, 5.35; S, 12.25%); $\delta_H$(400 MHz; $CDCl_3$) 1.28 (t, 3H, *J* 7, $CH_3$), 3.77 (q, 2H, *J* 7, $CH_2$), 6.60 (dd, 1H, *J* 8.0 and 1.0, 1-H), 6.72 (dd, 1H, *J* 8.5 and 1.5, 9-H), 6.80 (dt, 1H, *J* 1.5 and 7.5, 7-H), 6.85 (dd, 1H, *J* 8.0 and 1.0, 3-H), 6.93 (t, 1H, *J* 8.0, 2-H), 7.03 (dt, 1H, *J* 1.5 and 8.5, 8-H), 7.04 (dd, 1H, *J* 7.5 and 1.5, 6-H).

**10-Ethyl-4-iodophenothiazine 3f.** The general procedure was used with iodine (6.92 g, 27.3 mmol) as the electrophile, stirring for 1 h. Quenching with aqueous $Na_2S_2O_3$ (25% w/v; 60 $cm^3$) was followed by stirring for 0.5 h. The ether phase was separated and washed with water (30 $cm^3$). The combined water phases were extracted with dichloromethane (3 × 30 $cm^3$) and the combined organic phases were dried and evaporated to give an oil (3.0 g). The crude product was subjected to flash chromatography (ethyl acetate–heptane, 0:1 ⟶ 1:10) to provide **3f** (2.07 g, 69%), mp 116–117 °C (from ethyl acetate); $R_f$ (ethyl

acetate–heptane, 1:6) 0.56 (Found: C, 47.9; H, 3.4; N, 3.9; S, 9.1. Calc. for: $C_{14}H_{12}INS$: C, 47.6; H, 3.4; N, 4.0; S, 9.1%); $\delta_H$(400 MHz; $CDCl_3$) 1.42 (t, 3H, *J* 7, $CH_3$), 3.89 (q, 2H, *J* 7, $CH_2$), 6.82–6.86 (m, 2H, 2-H and 1-H or 9-H), 6.86 (dd, 1H, *J* 8.0 and 1.5, 9-H or 1-H), 6.95 (dt, 1H, *J* 1.5 and 7.5, 7-H), 7.17 (dt, 1H, *J* 1.5 and 7.5, 8-H), 7.19 (dd, 1H, *J* 7.5 and 1.5, 6-H), 7.43 (dd, 1H, *J* 6.0 and 3, 3-H).

**10-Ethyl-4-trimethylsilylphenothiazine 3g.** The general procedure was used with chlorotrimethylsilane (4.04 $cm^3$, 32 mmol) as the electrophile, stirring for 1 h. Work-up as described for **3a** afforded a yellow oil (2.89 g). The crude product was subjected to flash chromatography (ethyl acetate–heptane, 0:1 ⟶ 1:8) to provide **3g** as a yellow oil (1.55 g, 59%), mp 50–50.5 °C (from ethanol–water, 8:1); $R_f$ (ethyl acetate–heptane, 1:3) 0.75 (Found: C, 68.2; H, 7.15; N, 4.7; S, 10.45. Calc. for $C_{17}H_{21}NSSi$: C, 68.2; H, 7.1; N, 4.7; S, 10.7%); $\delta_H$(400 MHz; $CDCl_3$) 0.40 [s, 9H, $Si(CH_3)_3$], 1.40 (t, 3H, *J* 7, $CH_3$) 3.92 (q, 2H, *J* 7, $CH_2$), 6.87 (dd, 1H, *J* 8 and 1, 9-H), 6.91 (dd, 1H, *J* 8.0 and 1.5, 1-H), 6.91 (dt, 1H, *J* 1.5 and 7.5, 7-H), 7.09 (dd, 1H, *J* 7.5 and 1.5, 3-H), 7.14 (t, 1H, *J* 7.6, 2-H), 7.15 (dt, 1H, *J* 1.5 and 7.5, 8-H), 7.19 (dd, 1H, *J* 7.6 and 1.5, 6-H).

**10-Ethyl-4-(methylthio)phenothiazine 3h.** The general procedure was used with dimethyl disulfide (2.42 $cm^3$, 27 mmol) as the electrophile, stirring for 1 h. Work-up as described for **3a** afforded a yellow oil (2.69 g). The crude product was subjected to flash chromatography (ethyl acetate–heptane, 1:10) to provide **3h** as a light yellow oil (1.66 g, 69%); $R_f$ (ethyl acetate–heptane, 1:6) 0.48 (Found: C, 65.7; H, 5.7; N, 4.8; S, 24.0. Calc. for $C_{15}H_{15}NS_2$: C, 65.9; H, 5.5; N, 5.1; S, 23.5%); $\delta_H$(400 MHz; $CDCl_3$) 1.39 (t, 3H, *J* 7, $CH_3$), 2.47 (s, 3H, $SCH_3$), 3.88 (q, 2H, *J* 7, $CH_2$), 6.68 (dd, 1H, *J* 8.0 and 1.0, 1-H), 6.83 (dd, 1H, *J* 8.0 and 1.0, 9-H or 3-H), 6.84 (dd, 1H, *J* 8.0 and 1.0, 3-H or 9-H), 6.89 (dt, 1H, *J* 1.5 and 7.5, 7-H), 7.10 (t, 1H, *J* 8.0, 2-H), 7.12 (dd, 1H, *J* 8.0 and 1.5, 6-H), 7.18 (dt, *J* 1.5 and 7.5, 8-H) (Found: $M^+$, 273.065 407. $C_{15}H_{15}NS_2$ requires $M^+$, 273.063 593).

**10-Ethyl-4-(hydroxymethyl)phenothiazine 3i.** 10-Ethyl-4-formylphenothiazine **3b** (1.46 g, 5.7 mmol) was dissolved in methanol (75 $cm^3$), and $NaBH_4$ (1.41 g, 37 mmol) predissolved in cold methanol (50 $cm^3$) was added. The reaction mixture was stirred for 18 h at 0 °C, quenched with HCl (3.5% w/v; 30 $cm^3$) and stirred for an additional 0.5 h before evaporation. Water (75 $cm^3$) and dichloromethane (75 $cm^3$) were added and the aqueous phase extracted with dichloromethane (3 × 80 $cm^3$). The combined organic phases were dried and evaporated to give a light brown oil (1.42 g). The crude product was recrystallized from ethyl acetate to give crystalline **3i** (1.16 g, 80%), mp 98–99 °C (from ethyl acetate); $R_f$ (ethyl acetate–heptane, 1:2) 0.39 (Found: C, 69.7; H, 6.0; N, 5.25; S, 12.3. Calc. for $C_{15}H_{15}NOS$: C, 70.0; H, 5.8; N, 5.4; S, 12.5%) $\delta_H$(400 MHz; $CDCl_3$) 1.41 (t, 3H, *J* 7, $CH_3$), 1.91 (br s, 1H, OH), 3.64 (q, 2H, *J* 7, $CH_2CH_3$), 4.74 (s, 2H, $ArCH_2$), 6.85 (dd, 1H, *J* 8 and 1.5, 1-H), 6.87 (dd, 1H, *J* 8.0 and 1.0, 9-H), 6.91 (dt, 1H, *J* 1.0 and 7.5, 7-H), 7.03 (dd, 1H, *J* 7.5 and 1, 3-H), 7.16 (dt, 1H, *J* 1.0 and 7.5, 8-H), 7.16 (t, 1H, *J* 7.5 and 7.5, 2-H), 7.17 (dd, *J* 7.5 and 1.0, 6-H).

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