1,2-Didehydrophenothiazines: Preparation of 1-Alkyl and 1-Aryl-substituted Phenothiazines by Lithium-directed Alkylation

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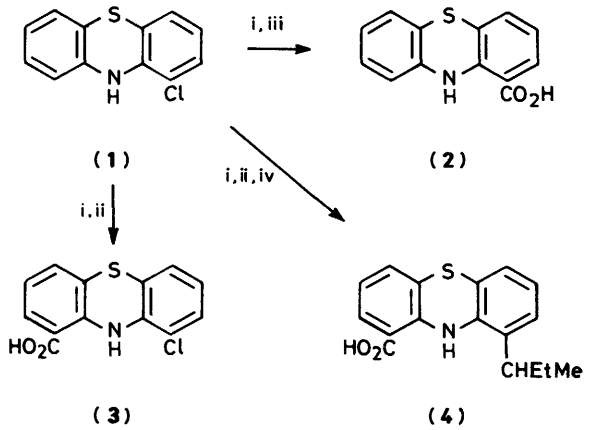
A general route to 1-alkyl substituted phenothiazines is described. Reactions of 2-chlorophenothiazine with an excess of methyl-, n-butyl-, s-butyl, t-butyl-or phenyl-lithiums give the corresponding 1-substituted phenothiazines *via* 10-lithio-1,2-dehydrophenothiazine. Attempts to trap the presumed 1,10-dilithio intermediate failed. The reaction of 1-chlorophenothiazine with s-butyl-lithium results in preferential metallation of the 9-position. 2-Chlorophenothiazine reacts with nitrogen nucleophiles (lithium dialkylamides) to give 2-substituted products.

As a part of our study of the structure–activity relationships of phenothiazine derivatives related to promazine with restricted rotation in the side chain,[1] we were interested in investigating the activity of compounds possessing a large alkyl substituent in the 1-position of the phenothiazine ring system. We expected that a bulky 1-substituent would affect the flexibility of the side chain, thus changing the pharmacological profile away from neuroleptic–antipsychotic activity. Further impetus to this idea is provided by the observation that '1-chloropromazine' is reported to exhibit antidepressant-like activity in experimental animals, but not the neuroleptic–antipsychotic activity characteristic of the 2-chloro derivative, chlorpromazine.[2]

We planned to synthesize 1-alkyl substituted phenothiazines *via* 1,2-didehydrophenothiazine intermediates starting from 1- and 2-chlorophenothiazines (**1**) and (**5**), based on the report that 2,3-didehydroanilides give *ortho*-substituted anilides on reaction with potassium amide in liquid ammonia.[3] On the other hand, addition to *N,N*-dialkyl substituted-2,3-dehydroanilines give exclusive attack at the *meta* position. Jones[4] has applied the last-named reaction in the phenothiazine series to prepare a variety of 2-amino-substituted 10-methylphenothiazines. The failure to detect the 1-amino isomer in these reactions was attributed to steric hindrance by the methyl group. However, 2-(4-methylpiperazin-1-yl)phenothiazine (**6**) was similarly formed when 2-chlorophenothiazine was treated with 4-lithio-1-methylpiperazine.[4] We were somewhat surprised by this result, as we expected the 1-isomer to be formed. We report here the synthesis of some 1-substituted phenothiazine derivatives *via* 10-lithio-1,2-didehydrophenothiazine as a plausible intermediate.

Metallation of 1-chlorophenothiazine (**1**) using an excess of s-butyl-lithium in ether at −70 °C and subsequent trapping with solid carbon dioxide gave exclusively 1-carboxyphenothiazine (**2**), as a result of halogen metal exchange (see Scheme 1). When the same reaction was performed in tetrahydrofuran, 1-chloro-9-carboxyphenothiazine (**3**) was obtained. Changing the solvent apparently had a dramatic effect on the course of the reaction and now metallation at the free position *ortho* to the nitrogen was preferred to halogen metal exchange. By using stronger conditions (s-butyl-lithium–tetramethylethylenediamine) we were also able to metallate *ortho* to the chlorine atom as indicated by the isolation of 9-carboxy-1-(1-methylpropyl)-phenothiazine (**4**) formed *via* a didehydrophenothiazine intermediate. Surprisingly, no 2,9-dicarboxy-1-(1-methylpropyl)phenothiazine could be detected. Trapping the reaction mixture with water gave 1-(1-methylpropyl)phenothiazine (**7a**), but in low yield.

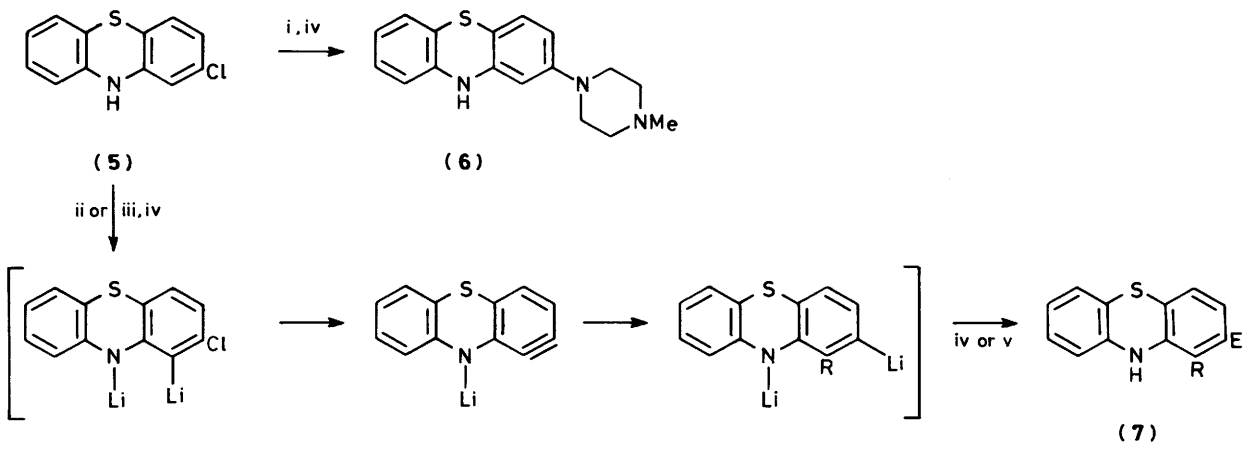
A considerably better yield of compound (**7a**) was obtained using 2-chlorophenothiazine (**5**) where the lithiation apparently



Scheme 1. *Reagents:* i, 4-Lithio-1-methylpiperazine; ii, Bu^sLi or Bu^tLi, THF, −70 °C, 2 h; iii, MeLi or PhLi, ether, 25 °C, 6 h; iv, H_2O

took place at the 1-position activated by both the nitrogen and chloro substituents (see Scheme 2). Attempts to trap the intermediate 1-lithio derivative with solid carbon dioxide at −100 °C failed. A low yield (5%) of 2-carboxy-1-(1-methylpropyl)phenothiazine (**7b**) was obtained and most of the starting material was recovered after a reaction time of 2 h. Reaction for 2 h at −70 °C gave a 35% yield of compound (**7b**) as the only isolated carboxylic acid. Similarly, 2-formyl-1-(1-methylpropyl)-phenothiazine (**7c**) was obtained after trapping the reaction mixture with dimethylformamide, indicating that the lithiated 2-position may be used for the introduction of different and potentially interesting (from a pharmacological point of view) functionalities. The structures of compounds (**7b**) and (**7c**) were established by ^1H n.m.r. spectroscopy. It appears that lithiation of the 1-position and the elimination of lithium chloride occur almost simultaneously at low temperature, conceivably because of strong interaction between the 1- and 10-positions. The addition of the alkyl-lithium reagent afforded the 1-isomer, and the 2-isomer could not be detected. The use of methyl, n-butyl-, t-butyl-, or phenyl-lithium similarly gave exclusively the 1-isomers (**7d—g**).

We have reconfirmed the result Jones obtained after treating compound (**5**) with 1-lithio-4-methylpiperazine.[4] ^1H N.m.r. analyses (250 MHz), including decoupling experiments, on the product of this reaction (**6**) revealed the presence of a four spin and a three spin system in the aromatic region. The three spin system consisted of a shielded doublet at δ 6.40 (1 H, $J_{1,3}$ 2.3



a; R = CHEtMe, E = H
b; R = CHEtMe, E = CO_2H
c; R = CHEtMe, E = CHO
d; R = Me, E = H
e; R = Bu^n, E = H
f; R = Bu^t, E = H
g; R = Ph, E = H

Scheme 2. *Reagents:* i, 4-Lithio-1-methylpiperazine; ii, Bu^sLi or Bu^tLi, THF, −70 °C, 2 h; iii, MeLi or PhLi, ether, 25 °C, 6 h; iv, H_2O; v, CO_2 or DMF

Hz), a double doublet at δ 6.45 (3 H, $J_{3,4}$ 8.0, $J_{1,3}$ 2.3 Hz), and a doublet at δ 6.80 (4 H, $J_{3,4}$ 8.0 Hz). The ^{13}C n.m.r. chemical shifts, applying the principle of substituent additivity relative to the phenothiazine nucleus,[5] further strongly support the proposed structure (**6**). Thus, C-1, C-2, and C-4a appear at δ 101.85, 150.77, and 105.05, respectively, in $(CD_3)_2SO$. For purposes of comparison, we have performed the reaction in both tetrahydrofuran and ether, with similar results.

Contrasting Jones' result[4] with our reactions using alkyl- or aryl-lithiums, we find it remarkable that such a dramatic change in regiochemistry is achieved by changing from a nitrogen to a carbon nucleophile. Alkyl- and aryl-lithiums are electron deficient and exhibit properties of Lewis acids capable of co-ordinating with Lewis bases such as amines. Lithium dialkylamides, on the other hand, exhibit negligible Lewis acid character. Phenothiazine is known to undergo directed *ortho* metallation when treated with excess of alkyl-lithium reagent.[6–9] The formal negative charge of the monoanion of phenothiazine formed by *N*-deprotonation is considered to be delocalized over the entire π-system and the non-bonding pair of electrons of the nitrogen atom, non-coplanar with the tricyclic system, becomes available for chelation with the organolithium reagent, leading to deprotonation at the atom nearest the ligand.[10] Similarly, co-ordination of the alkyl- or aryl-lithium reagent with the nitrogen lone pair is believed to direct attack at the 1-position of 10-lithio-1,2-didehydrophenothiazine, thus explaining the regioselectivity of the reaction. On the other hand, the lithiodialkylamide reagents may experience electrostatic repulsion from the nitrogen lone pair, causing nucleophilic attack of these reagents to occur at the 2-position.*

Our result is similar to that recently reported by Meyers and Pansegrau,[12] who demonstrated *ortho*-directed attack of organolithium reagents on the benzyne derived from 2-(*m*-chlorophenyl)-2-oxazoline. Co-ordination of the organolithium reagent with the N atom of the oxazoline ring was suggested as the explanation for the regiochemistry observed in this reaction.

* Alternatively, we favour a radical nucleophilic substitution ($S_{RN}1$)[11] mechanism to explain the apparently regiospecific formation of *compound* (**6**). Thus, neither 10-lithio-1,2-didehydrophenothiazine nor the presumed 1,10-dilithio precursor are indeed formed in this reaction. Similarly, the exclusive formation of 3-substituted phenothiazines from reactions of 3-chlorophenothiazines with lithium dialkylamides[5] is readily explained by invoking a $S_{RN}1$ mechanism. Both 2- and 3-substituted products would be expected from a 2,3-didehydrophenothiazine intermediate.

Experimental

All metallations were performed in dry solvents under nitrogen, using the septum technique. I.r. spectra were obtained on a Beckman IR-33 spectrophotometer. The n.m.r. spectra were recorded on a Jeol FX 90Q spectrometer (90 MHz) and on a Bruker WM-250 spectrometer (250 MHz) using tetramethylsilane as an internal standard. The mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer. Elemental analyses were performed by the University of Arizona Analytical Center or by MicAnal, Inc. (Tucson, Arizona). Ether refers to diethyl ether.

1-*Carboxyphenothiazine* (**2**).—To a solution of 1-chlorophenothiazine (**1**)[7] (115 mg, 0.5 mmol) in anhydrous ether (20 ml), s-butyl-lithium (4 ml, 5 mmol) was added at −70 °C and the reaction mixture was stirred for 4 h. Solid carbon dioxide was added and the temperature was allowed to reach 0 °C. After addition of water the organic phase was separated. Acidification of the alkaline aqueous solution followed by extraction with ether gave, after drying (Mg_2SO_4) and evaporation of the combined ether solutions, *compound* (**2**) (90 mg, 37%), m.p. 265—267 °C (lit.,[8] m.p. 264—264.5 °C) from 1:1 methanol–water.

9-*Carboxy*-1-*chlorophenothiazine* (**3**).—To a solution of compound (**1**) (230 mg, 1 mmol) in anhydrous THF (20 ml), s-butyl-lithium (3.5 ml, 4.3 mmol) was added at −70 °C, and the reaction mixture was stirred for 4 h. After the addition of solid carbon dioxide and work-up as above, *compound* (**3**) (180 mg, 65%) was obtained as a yellow powder, m.p. 227—229 °C (4:1 methanol–water); δ [$(CD_3)_2SO$] 10.66 (s, 1 H, NH), 7.69 (dd, 1 H, 8-H), 7.24 (dd, 1 H, 8-H), 7.24 (dd, 1 H, 6-H), 7.22 (dd, 1 H, 2-H, or 4-H), 6.98 (dd, 1 H, 2-H or 4-H), 6.90 (t, 1 H, 7-H), and 6.87 (t, 1 H, 3-H) (the assignments were based on decoupling experiments) (Found: C, 55.9; H, 3.1; N, 4.8. $C_{13}H_8ClHO_2S$ requires C, 56.22; H, 2.90; N, 5.04%).

9-*Carboxy*-1-(1-*methylpropyl*)*phenothiazine* (**4**).—A mixture of s-butyl-lithium (6.4 ml, 8 mmol) and TMEDA (1.21 ml, 8

mmol) in anhydrous THF (40 ml) was prepared at −70 °C. After the mixture had been stirred for 20 min, *compound* (**1**) (230 mg, 1 mmol) was added and the solution was stirred for a further 4 h. Solid carbon dioxide was then added and the reaction mixture was allowed to warm to 0 °C. After work-up as above, *compound* (**4**) (80 mg, 27%) was isolated as yellow crystals, m.p. 267—270 °C (1:1 ethanol–water); δ [$(CD_3)_2SO$] 10.12 (s, 1 H, NH), 7.69 (dd, 1 H, 8-H), 6.7—7.3 (m, 5 H, arom.) (decoupling at δ 7.69 revealed two 3-spin systems and verifies the position of the 1-methylpropyl group), 2.85 (m, 1 H, CH), 1.78 (p, 2 H, CH_2), 1.30 (d, 3 H, CH_3), 0.85 (t, 3 H, CH_3), and 0.85 (t, 3 H, CH_3) (Found: C, 67.9; H, 5.7; N, 4.6. $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.72; N, 4.68%).

General Procedure for the Preparation of Compounds (**7a**) *and* (**7d—g**).—To a solution of 2-chlorophenothiazine (**5**) (4.6 g, 20 mmol) in anhydrous THF, [for (**7a**) and (**7f**)] or ether [for (**7d**), (**7e**), or (**7g**)] methyl-, n-butyl-, s-butyl-, t-butyl-,or phenyllithium (80 ml) was added at −70 °C [(**7a**), (**7f**)] or at room temperature [(**7d**), (**7e**), (**7g**)]. After the mixture had been stirred for 2 h [(**7a**), (**7f**)] or 6 h [(**7d**), (**7e**), (**7g**)], ice-water was added and the stirring was continued for 30 min. The organic layer was separated and combined with ether extracts of the aqueous phase. The combined organic phases were washed with water, dried ($MgSO_4$) and evaporated to give the crude products.

1-(1-*Methylpropyl*)*phenothiazine* (**7a**) (2.19 g, 43%), m.p. 72—73 °C, chromatography (silica, 95:5 hexane–ethyl acetate), δ ($CDCl_3$) 7.1—6.5 (m, 7 H, arom.), 6.50 (br s, 1 H, NH), 2.65 (m, 1 H, CH), 1.6 (p, 2 H, CH_2), 1.23 (d, 3 H, CH_3), and 0.9 (t, 3 H, CH_3) (Found: C, 75.4; H, 6.7; N, 5.3. $C_{16}H_{17}NS$ requires C, 75.25; H, 6.70; N, 5.48%). When the reaction was carried out using *compound* (**1**), 0.71 g (14%) of (**7a**) was obtained.

1-Methylphenothiazine (**7d**) (1.79 g, 42%), m.p. 137—138 °C (lit,[13] m.p. 137—138 °C). Chromatography (silica, 95:5 hexane–ethyl acetate), δ ($CDCl_3$) 7.1—6.5 (m, 7 H, arom.), 6.50 (br s, 1 H, NH), and 2.19 (s, 3 H, CH_3).

1-*Butylphenothiazine* (**7e**), obtained as a pale yellow oil (28%) after preparative t.l.c. (silica, 95:5 hexane–ethyl acetate); δ ($CDCl_3$) 7.3—6.5 (m, 7 H, arom.), 2.62 (t, 2 H), 1.45 (m, 4 H, CH_2), and 0.92 (t, 3 H, CH_3) (Found: C, 75.2; H, 6.75; N, 5.3. $C_{16}H_{17}NS$ requires C, 75.25; H, 6.70; N, 5.48%).

1-(1,1-*Dimethylethyl*)*phenothiazine* (**7f**) (2.24 g, 44%), m.p. 63—65 °C, chromatography (silica, 95:5 hexane–ethyl acetate); δ ($CDCl_3$) 7.4—6.6 (m, 7 H, arom.), 6.50 (br s, 1 H, NH), 1.48 (s, 9 H, CH_3) (Found: C, 74.9; H, 6.5; N, 5.4. $C_{16}H_{17}NS$ requires C, 75.25; H, 6.72; N, 5.48%).

1-*Phenylphenothiazine* (**7g**) (2.75 g, 40%), m.p. 85—86 °C, chromatography (silica 95:5 hexane–ethyl acetate); δ ($CDCl_3$) 7.6—6.7 (m, 12 H, arom.), 6.40 (br s, 1 H, NH) (Found: C, 78.2; H, 4.7; N, 4.9. $C_{18}H_{13}NS$ requires C, 78.50; H, 4.76; N, 5.09%).

2-*Carboxy*-1-(1-*methylpropyl*)*phenothiazine* (**7b**).—To a solution of *compound* (**5**) (460 mg, 2 mmol) in THF, s-butyllithium (4.8 ml, 6 mmol) was added at −70 °C. After the mixture had been stirred for 2 h at −70 °C, the temperature was raised to −30 °C and solid carbon dioxide was added. Work-up in the usual manner gave *compound* (**7b**) (210 mg, 35%) as yellow crystals, m.p. 132—135 °C (ethanol–water); δ ($CDCl_3$) 10.55 (br s, 1 H, CO_2H), 7.00 (m, 3 H, 3-H, 4-H, 6-H), 6.83 (m, 2 H, 7-H, 8-H), 6.58 (d, 1 H, 9-H), 6.20 (s, 1 H, NH), 3.38 (m, 1 H, CH), 1.68 (p, 2 H, CH_2), 1.29 (d, 3 H, CH_3), and 0.76 (t, 3 H, CH_3) (decoupling experiments confirmed the presence of one 2-spin system and one 4-spin system in the aromatic region) (Found: C, 67.9; H, 5.9; N, 4.5. $C_{17}H_{17}NO_2S$ requires C, 68.19; H, 5.72; N, 4.68%).

2-*Formyl*-1-(1-*methylpropyl*)*phenothiazine* (**7c**).—To a solution of compound (**5**) (460 mg, 2 mmol) in THF (50 ml), s-butyllithium (4.8 ml, 6 mmol) was added at −70 °C. The reaction mixture was stirred for 2 h and DMF (0.32 ml, 4 mmol) in ether (5 ml) then added dropwise. When the red solution had warmed to 25 °C, 5M-hydrochloric acid solution was added. The organic phase was separated and the water phase was extracted several times with ether. The combined ether extracts were washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. Chromatography (silica, 1:1 toluene–hexane) gave *compound* (**7c**) (120 mg, 21%) as a red oil, δ ($CDCl_3$) 10.13 (s, 1 H, CHO), 7.26 (d, 1 H, 3-H), 7.03 (d, 1 H, 4-H), 7.02 (dt, 1 H, 8-H), 7.01 (br d, 1 H, 6-H), 6.87 (dt, 1 H, 7-H), 6.64 (dd, 1 H, 9-H), 6.29 (br s, 1 H, NH), 4.04 (br m, 1 H, CH), 1.82 (p, 2 H, CH_2), 1.43 (d, 3 H, CH_3), and 0.91 (t, 3 H, CH_3) (decoupling experiments confirmed the presence of one 2-spin system and one 4-spin system in the aromatic region) (Found: C, 72.1; H, 6.0; N, 4.8. $C_{17}H_{17}NOS$ requires C, 72.05; H, 6.05; N, 4.94%).

2-(4-*Methylpiperazin*-1-*yl*)*phenothiazine* (**6**).—To a solution of 1-methylpiperazine (1.0 g, 10 mmol) in dry THF (50 ml) at 0 °C was added n-butyl-lithium (6.25 ml, 10 mmol) in hexane. 2-Chlorophenothiazine (**1**), (466 mg, 2 mmol) was added at room temperature and the solution refluxed for 8 h. Water was added and the organic phase was separated, washed twice with water, and extracted twice with 5% hydrochloric acid solution. The combined acid extracts were adjusted to pH 11 with 10% NaOH solution and then extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to give compound (**6**) (262 mg, 44%) as a brown solid, m.p. 202—204 °C (lit.,[5] 200—202 °C); δ [$(CD_3)_2SO$] 8.56 (s, 1 H, NH), 7.28 (dd, 1 H, 9-H), 7.05 (dt, 1 H), 6.98 (dd, 1 H, 6-H), 6.82 (d, 1 H, 4-H), 6.78 (dt, 1 H, 7-H), 6.45 (dd, 1 H, 3-H), 6.40 (d, 1 H, 1-H), 3.11 (t, *J* 44.9 Hz, 4 H, 2′, 6′-CH_2), 2.49 (t, *J* 4.9 HZ, 4 H, 3′, 5′-CH_2), and 2.27 (s, 3 H, CH_3); δ_C [$(CD_3)_2SO$] 150.77 (C-2), 142.70 (C-1a), 142.05 (C-9a) 127.97 (C-4), 126.88, 126.29 (C-6, C-8), 121.20 (C-7), 117.24 (C-5a), 114.21 (C-9), 109.27 (C-3), 105.05 (C-4a), 101.85 (C-1), 54.34 (C-3′), 47.95 (C-2′), and 45.51 (C-4′).

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