Synthesis of 4*H*-1,4-Benzothiazines *via* Lithiation Alpha to Sulphur of 2-Acylaminophenyl Alkyl Sulphides, Sulphoxides, and Sulphones

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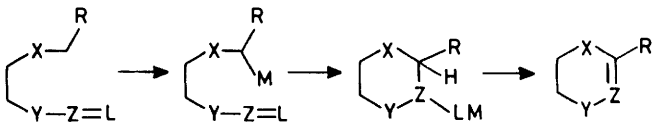
4*H*-1,4-Benzothiazines, their monoxides, and their dioxides are readily prepared *via* lithiation and intramolecular cyclisation of 2-acylaminophenyl alkyl sulphides, sulphoxides, and sulphones with lithium di-isopropylamide in tetrahydrofuran at −50 °C.

Metallation alpha to a heteroatom to give an organometallic species that can be trapped by electrophiles has become a synthetically useful and mechanistically interesting process in recent years.[1]

The ease of the α-metallation depends largely on the nature of the heteroatom. Electronegative atoms directly attached to the carbanionic site stabilise the carbanion by inductively dispersing part of the charge. The more polarizable third-row elements show a greater effect than second-row elements: d orbitals may participate in (p–d)π bonding to disperse further the negative charge.[2] Thus metallation alpha to sulphur is much easier than that alpha to oxygen or nitrogen: indeed thioanisole and dimethyl sulphide can be converted into anions, whereas anisole and dimethyl ether cannot.[3] The capacity of the heteroatom to accommodate a positive charge *via* a 'dipolar structure,' that would make an α-hydrogen atom removable, greatly favours α-carbanion formation: the so-called 'dipole-stabilised carbanions' have been applied extensively in synthesis in recent years.[4]

The methodology of α-metallation might in principle be applied to the synthesis of heterocycles if the metallated intermediate is allowed to react with an electrophilic centre in the same molecule (Scheme 1). In the course of studies directed to the synthesis and reactivity of heterocyclic compounds[5] we reasoned that this sequence might be applied to 4*H*-1,4-benzothiazines, of interest because of their pharmacological activity and incidence in natural products,[6] if X and Y were sulphur and nitrogen, respectively, and Z=L were C=O. A number of synthetic routes to 4*H*-1,4-benzothiazines have been developed, including: (i) reaction of α-halogeno-ketones or α-cyano-α-methylthioacetophenones with 2-aminobenzenethiol;[7] (ii) reaction of enolizable ketones with 2,2′-dithiodianilines[8] or 2-aminobenzenethiol;[9] (iii) ring enlargement of benzothiazolines;[10] (iv) reaction of 2,2′-dithiodianiline with activated alkynes.[11] All such routes are limited to 1,4-benzothiazines bearing at least one electron-withdrawing group in the 2-, 3- or 4-position.

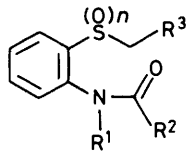


Scheme 1.

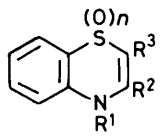
We now report here the results of a new synthetic procedure for 4*H*-1,4-benzothiazines involving the metallation of 2-acylaminophenyl alkyl sulphides and related sulphoxides and sulphones.

Treatment of 2-(*N*-methylbenzamido)phenyl ethyl sulphide (**1a**) with lithium di-isopropylamide (LDA) in tetrahydrofuran at −50 °C readily gave a mixture of 2-(*N*-phenacylbenzamido)-phenyl ethyl sulphide (**11**) and 2-methylaminophenyl ethyl sulphide (**12**). Lithiation alpha to nitrogen of (**1a**) followed by condensation of the 'dipole-stabilised'[4] lithiated intermediate (**10**) with a second molecule of the starting amide sulphide (**1a**) might account for this reaction (Scheme 2).

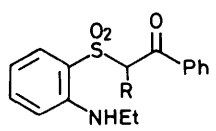
In contrast, the reaction of the amide sulphide (**1b**) with LDA under the same conditions rapidly afforded good yields of the benzothiazine (**5a**). Analogously, the benzamide (**1c**) smoothly reacted with LDA, providing very good yields of the benzothiazine (**5b**) (see Table 1). These results may be accounted for if in the case of (**1b** and **c**) lithiation alpha to sulphur occurs rather than alpha to nitrogen as in the case of (**1a**); then ring



(**1**) **a**; $n = 0$, $R^1 = R^3 = Me$, $R^2 = Ph$
b; $n = 0$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
c; $n = 0$, $R^1 = Et$, $R^2 = R^3 = Ph$
d; $n = 0$, $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
(**2**) **a**; $n = 1$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
b; $n = 1$, $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
(**3**) **a**; $n = 2$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
b; $n = 2$, $R^1 = Et$, $R^2 = R^3 = Ph$
c; $n = 2$, $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
(**4**) **a**; $n = 2$, $R^1 = R^2 = R^3 = H$
b; $n = 2$, $R^1 = R^2 = H$, $R^3 = Me$
c; $n = 2$, $R^1 = R^3 = H$, $R^2 = Ph$



(**5**) **a**; $n = 0$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
b; $n = 0$, $R^1 = Et$, $R^2 = R^3 = Ph$
(**6**) **a**; $n = 1$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
b; $n = 1$, $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
(**7**) **a**; $n = 2$, $R^1 = Et$, $R^2 = Ph$, $R^3 = H$
b; $n = 2$, $R^1 = Et$, $R^2 = R^3 = Ph$
c; $n = 2$, $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
(**8**) **a**; $n = 2$, $R^1 = R^2 = R^3 = H$
b; $n = 2$, $R^1 = R^2 = H$, $R^3 = Me$
c; $n = 2$, $R^1 = R^3 = H$, $R^2 = Ph$

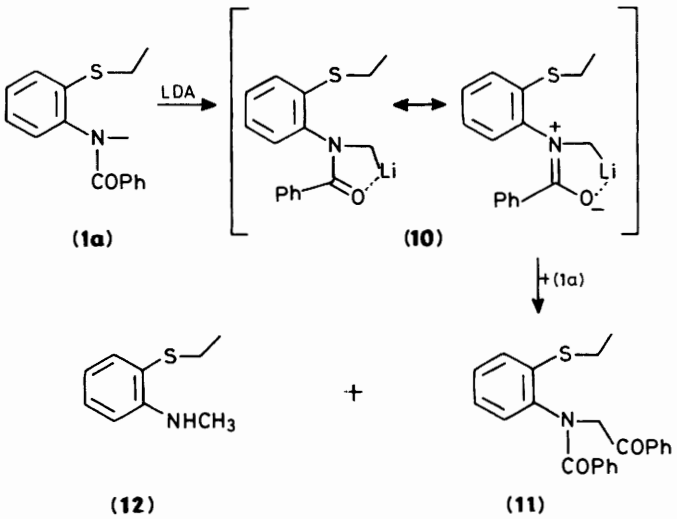


(**9**) **a**; R = H
b; R = Ph
c; R = Me

Table 1. Benzothiazines (**5**)—(**8**) from benzamides (**1b** and **c**) and (**2**)—(**4**)

Benzamide	Benzothiazine[a]	Yield (%)[b]	M.p. (°C) (solvent)	δ($CDCl_3$)
(**1b**)	(**5a**)	50	Oil	1.2 (t, 3 H), 3.6 (q, 2 H), 5.3 (s, 1 H), 6.8—7.6 (m, 9 H)
(**1c**)	(**5b**)	87	91—92 (petroleum)	1.1 (t, 3 H, *J* 7 Hz), 3.4 (q, 2 H, *J* 7 Hz), 6.5—7.5 (m, 14 H)
(**2a**)	(**6a**)	78	147—148 (CH_2Cl_2–Et_2O)	1.2 (t, 3 H, *J* 7 Hz), 4.05 (q, 2 H, *J* 7 Hz), 6.05 (s, 1 H), 7.2—8.1 (m, 9 H)
(**2b**)	(**6b**)	80	Oil	0.65 (t, 3 H), 2.2 (s, 3 H), 3.1 (m, 3 H), 6.1—7.7 (m, 9 H)
(**3a**)	(**7a**)	90	140—142 (EtOH)	1.1 (t, 3 H, *J* 7 Hz), 3.8 (q, 2 H, *J* 7 Hz), 5.8 (s, 1 H), 6.9—8.1 (m, 9 H)
(**3b**)	(**7b**)	80	160—162 (EtOH)	1.1 (t, 3 H, *J* J Hz), 3.8 (q, 2 H, *J* 7 Hz), 6.6—8.2 (m, 14 H)
(**3c**)	(**7c**)	80	134—135 (EtOH)	1.1 (t, 3 H, *J* 7 Hz), 1.9 (s, 3 H), 3.7 (q, 2 H, *J* 7 Hz), 7.1—8.2 (m, 9 H)
(**4a**)	(**8a**)	66	208—210 (CH_2Cl_2)[c]	6.0 (d, 1 H, *J* 9 Hz), 7.2—7.9 (m, 5 H, aromatic + H-3), 10.8 (brs, 1 H, exchanged with D_2O)[d]
(**4b**)	(**8b**)	84	178—179 (EtOH)	2.0 (s, 3 H), 6.9—7.9 (m, 5 H, aromatic + H-3), 10.4 (brs, 1 H, exchanged with D_2O)[d]
(**4c**)	(**8c**)	79	265—267 (EtOH)	6.3 (s, 1 H), 7.2—8.1 (m, 10 H, aromatic + NH, exchanged with D_2O)[d]

[a] Satisfactory microanalyses obtained: see Supplementary Publication SUP no. 23931 (2 pp.). For details of Supplementary Publications see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1. [b] Yield of pure, isolated product. [c] Lit.,[16] m.p. 195—196 °C. [d] Spectra run in $(CD_3)_2SO$.

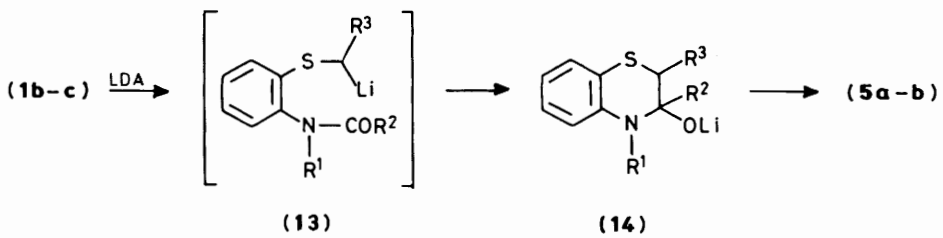


Scheme 2.

makes lithiation α to sulphur preferred; evidently, the 'back-bonding' stabilising effect[2] provided by the sulphur atom for the adjacent lithiated species and the 'dipole-stabilisation' exerted by the carbamoyl function[4] on the species metallated alpha to nitrogen are roughly equal in magnitude; small structural changes can make one effect prevail over the other.

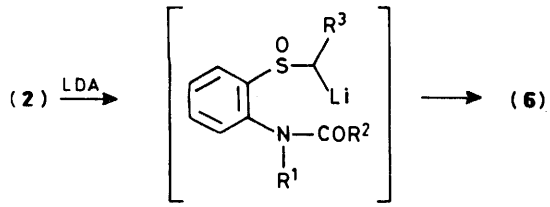
The sulphoxides (**2a** and **b**), readily available from the corresponding sulphides (**1b** and **c**) by oxidation with peracetic acid, smoothly reacted with LDA to give very good yields of the benzothiazine 1-oxides (**6a** and **b**), respectively. It is not unexpected that in the case of the sulphoxides (**2**) lithiation occurs alpha to the sulphinyl group; subsequent annelation and elimination would then produce (**6**) (Scheme 4). The conversion of sulphides (**1b** and **c**) and sulphoxides (**2**) into the corresponding benzothiazines (**5**) and (**6**) has no precedent; it has recently been reported that some alkylthiobenzamides undergo N ⟶ C intramolecular acyl transfer upon treatment with base,[12] but in no case was benzothiazine formation observed.

The synthesis of the benzothiazine 1,1-dioxides *via* the



Scheme 3.

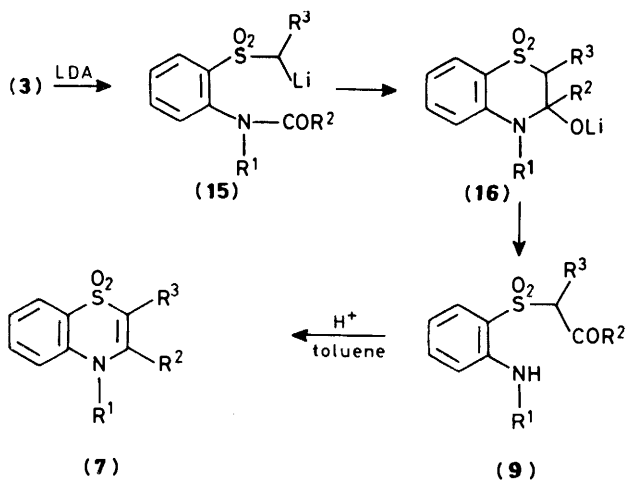
closure of the lithiated intermediate (**13**) on the carbamoyl function and subsequent dehydration of the cyclic intermediate (**14**) would produce the benzothiazines (**5a** and **b**) (Scheme 3). However, attempted trapping of the metallated species (**13**) with methyl iodide failed; apparently cyclisation of (**13**) on the carbamoyl group proceeds much faster than alkylation. Interestingly, the mere replacement of alkyl alpha to nitrogen foregoing procedure was not straightforward. Indeed, the reaction of the amide sulphones (**3**) with LDA under the usual conditions gave the sulphones (**9**). The formation of these sulphones (**9**) is probably the result of lithiation alpha to the sulphonyl group to give the lithiated species (**15**), followed by intramolecular benzoyl transfer, perhaps *via* a cyclic intermediate such as (**16**) (Scheme 5). Nevertheless, benzothiazine



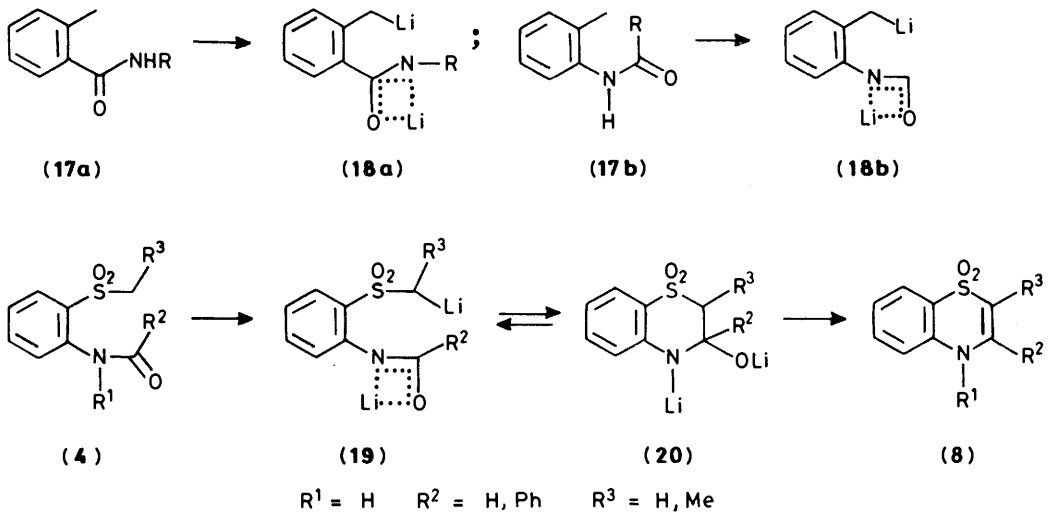
Scheme 4.

1,1-dioxides (**7**) can be obtained readily on heating the sulphones (**9**) in toluene in the presence of toluene-*p*-sulphonic acid in a Dean–Stark apparatus. An intramolecular nucleophilic attack of the amino group of (**9**) on the benzoyl function, cyclisation, and dehydration to give the corresponding benzothiazine is the likely course of the reaction.

Hauser's[13] and Houlihan's[14] reports that the organolithium reagents (**18a** and **b**) could be formed by treating the



Scheme 5.



Scheme 6.

benzamides (**17a** and **b**), respectively with 2 equiv. of n-butyllithium prompted us to extend these conditions to the formation of the dilithiated intermediate (**19**) from the amide sulphone (**4**) and thereby effect a synthesis of 4-unsubstituted benzothiazines (**8**) (Scheme 6). In a model reaction we found that the formation of the benzothiazine (**8**) can be effected by treating 2-formylaminophenyl methyl sulphone (**4a**) with 2 mol equiv. of LDA in tetrahydrofuran at −50 °C and then leaving the reaction mixture at room temperature for 1 h.

Extension of this procedure to 2-formylaminophenyl ethyl sulphone (**4b**) and 2-benzamidophenyl methyl sulphone (**4c**) gave benzothiazines (**8b** and **c**), respectively. Unlike the sulphones (**3**), the amide sulphones (**4**) do not undergo intramolecular acyl transfer. Therefore cyclisation to the related benzothiazines is straightforward.

In conclusion, 4*H*-1,4-benzothiazines, their monoxides, and their dioxides can conveniently be prepared from 2-acylaminophenyl alkyl sulphides, sulphoxides, and sulphones, readily available from 2-aminobenzenethiol, by the new procedure here described, involving lithiation alpha to sulphur, cyclisation on the amido function, and dehydration.

Work is in progress to extend the procedure to the synthesis of other heterocyclic compounds such as oxazines, diazines, oxathiines.

Experimental

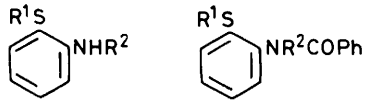
I.r. spectra were taken with a Perkin-Elmer 681 spectrometer. ^{1}H N.m.r. spectra were recorded with a Varian EM 360A spectrometer; chemical shifts are reported in p.p.m. (δ) from internal Me_4Si. Microanalyses were performed with a Hewlett-Packard C,H,N analyser. M.p.s were determined with an Electrothermal apparatus. T.l.c. was performed on silica gel sheets with fluorescent indicator (Stratocrom SIF 254 Carlo Erba); for preparative t.l.c. we employed Merck 20 × 20 cm (2 mm) plates. Column chromatography was conducted with 70—230 mesh silica gel (Merck).

Reactions requiring anhydrous conditions were performed in oven-dried glassware under nitrogen. Tetrahydrofuran (Carlo Erba) was purified by distillation (twice) from sodium (wire) and stored under nitrogen. Commercial n-butyl-lithium (Fluka) was standardised by titration. Di-isopropylamine (Fluka) was purified by distillation prior to use. 'Petroleum' refers to the b.p. 40—70 °C fraction.

Amide sulphides (**1**) were prepared by benzoylation of 2-alkylthioanilines (**21**) (Table 2) and subsequent alkylation of the resulting benzamides (**22**) (Table 3). 2-Alkylthioanilines (**21**) were prepared following the procedure reported for (**21b**).[15]

General Procedure for Benzoylation of Amines (**21**).—A solution of benzoyl chloride (4.3 ml, 36.9 mmol) in ether (20 ml)

Table 2. Benzoylation of amines (**21**) to amides (**22**)



(**21**) (**22**)

a; R^1 = Et, R^2 = Me
b; R^1 = Me, R^2 = Et
c; R^1 = $PhCH_2$, R^2 = Et

Amine	Amide	M.p. (°C) (solvent)	Yield (%)	δ($CDCl_3$)
(**21a**)	(**22a**)	37—38 (ether)	85	1.2 (t, 3 H), 2.8 (q, 2 H), 6.8—8.7 (m, 9 H), 10.4 (brs, 1 H)
(**21b**)	(**22b**)	90—92 (ethanol)	64	2.35 (s, 3 H), 6.8—8.6 (m, 9 H), 9.2 (brs, 1 H)
(**21c**)	(**22c**)	64—65 ether–petroleum	89	3.85 (s, 2 H), 6.5—8.7 (m, 14 H), 9.2 (brs, 1 H)

Table 3. Alkylation of amides (**22**) to give compounds (**1**)

Amide	RX	Product	M.p. (°C) (solvent)	Yield (%)	δ($CDCl_3$)
(**22a**)	CH_3I	(**1a**)	100—102 (petroluem)	91	1.35 (t, 3 H), 2.0 (q, 2 H), 3.4 (s, 3 H), 6.3—7.6 (m, 9 H)
(**22b**)	C_2H_5Br	(**1b**)	64—66 (ethanol)	77	1.2 (t, 3 H), 2.35 (s, 3 H), 3.4 (q, 1 H), 4.1 (q, 1 H), 6.7—7.5 (m, 9 H)
(**22c**)	C_2H_5Br	(**1c**)	99—101 (ether)	75	1.2 (t, 3 H), 3.5 (q, 2 H), 4.0 (s, 2 H), 6.6—7.6 (m, 14 H)
(**22d**)	C_2H_5Br	(**1d**)	72—73 (ether)	>95	1.2 (t, 3 H), 1.3 (t, 3 H), 2.85 (q, 2 H), 3.55 (m, 1 H), 4.2 (m, 1 H), 6.8—7.5 (m, 9 H)

was added dropwise to a stirred solution of the amine (**21**) (36.9 mmol) and pyridine (2.92 ml, 36.9 mmol) in ether (90 ml) at 0 °C. After 4 h, water was added and the organic layer was washed several times with 10% HCl and then with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure left the benzamide (Table 2).

General Procedure for Alkylation of Amides (**22**).—A solution of (**22**) (31.4 mmol) and KOH (6.64 g, 118.6 mmol) in acetone (15 ml) was heated at reflux, and then CH_3I (2.91 ml, 46.8 mmol) in acetone (20 ml) was added. Refluxing was continued with stirring for 2 h. The reaction mixture was then cooled and concentrated to small volume. Dilution with water, extraction with CH_2Cl_2 (3 × 30 ml), drying (Na_2SO_4), and removal of the solvent under reduced pressure left the amide sulphide (**1**) (Table 3).

2-(N-*Ethylbenzamido*)*phenyl Methyl Sulphoxide* (**2a**).—The amide sulphide (**1b**) (2 g, 7.4 mmol), conc. AcOH (4.7 ml, 7.4 mmol), H_2SO_4 (0.45 ml), and 36% H_2O_2 (0.69 ml, 7.4 mmol) were heated at 60 °C for 2 h. The mixture was then poured into cold water and extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation under reduced pressure left a residue that was substantially one product. Purification by column chromatography (ether first and then ethyl acetate) gave the sulphoxide (**2a**) (52%), m.p. 115—117 °C; $\nu_{max.}$(CH_2Cl_2) 1 640 and 1 040 cm^{-1}; δ($CDCl_3$) 1.2 (t, 3 H), 2.7 (br, s, 3 H), 3.8 (m, 2 H), and 7.2—8.2 (m, 9 H).

2-(N-*Ethylbenzamido*)*phenyl Ethyl Sulphoxide* (**2b**).—This compound was prepared from the benzamide (**1d**) according to the procedure described for (**2a**) (60%); m.p. 79—80 °C; $\nu_{max.}$(CH_2Cl_2) 1 650 and 1 050 cm^{-1}; δ($CDCl_3$) 1.2 (t, 3 H), 1.3 (t, 3 H), 2.75 (m, 2 H), 3.8 (m, 2 H), and 7.2—8.1 (m, 9 H).

2-(N-*Ethylbenzamido*)*phenyl Methyl Sulphone* (**3a**).—*m*-Chloroperbenzoic acid (8.70 g, 44 mmol) in CH_2Cl_2 (100 ml) was added dropwise to a solution of (**1b**) (6 g, 22 mmol) in CH_2Cl_2 (50 ml) at 0 °C with stirring. After 3 h the mixture was washed with $Na_2S_2O_3$ (sat. soln.; 2 × 25 ml), then with 10% $NaHCO_3$ (3 × 30 ml), and finally with water. Drying of the organic phase (Na_2SO_4) and removal of the solvent under reduced pressure gave (**3a**), which was purified by crystallisation (5.4 g, 80% yield); m.p. 72—73 °C (petroleum); $\nu_{max.}$(CH_2Cl_2) 1 640, 1 310, and 1 150 cm^{-1}; δ($CDCl_3$) 1.1 (t, 3 H), 3.2 (s, 3 H), 3.65 (q, 2 H), and 7.3—8.3 (m, 9 H).

2-(N-*Ethylbenzamido*)*phenyl Benzyl Sulphone* (**3b**).—This compound was prepared from (**1c**) as described for (**3a**) (92% yield); m.p. 144—145 °C (ethanol); δ($CDCl_3$) 1.1 (t, 3 H, *J* 7 Hz), 3.7 (q, 2 H, *J* 7 Hz), 4.45 (dd, 2 H, *J* 9 Hz), and 7.1—8.0 (m, 14 H).

2-(N-*Ethylbenzamido*)*phenyl Ethyl Sulphone* (**3c**).—This compound was prepared from (**1d**) as described for (**3a**) (83% yield); m.p. 72—73 °C (ether); $\nu_{max.}$(CH_2Cl_2) 1 640, 1 310, and 1 150 cm^{-1}; δ($CDCl_3$) 0.9 (t, 3 H, *J* 9 Hz), 1.1 (t, 3 H, *J* 7 Hz), 3.1 (q, 2 H, *J* 9 Hz), 3.5 (q, 2 H, *J* 7 Hz), and 7.1—8.1 (m, 9 H).

Preparation of the Amide Sulphones (**4**).—The amide sulphones (**4a** and **b**) were prepared from the amine sulphides (**1a** and **b**) by formylation with formic acid and subsequent oxidation with *m*-chloroperbenzoic acid in CH_2Cl_2. The sulphone (**4c**) was prepared from the sulphide (**1b**) by benzoylation with benzoyl chloride in ether and oxidation with *m*-chloroperbenzoic acid. 2-*Formylaminophenyl methyl sulphone* (**4a**) had m.p. 118—120 °C (ethanol); $\nu_{max.}$(CH_2Cl_2) 3 340, 1 710, 1 320, and 1 140 cm^{-1}; δ($CDCl_3$) 3.1 (s, 3 H), 7.1—8.7 (m, 5 H, aromatic and formyl protons), and 9.5 (br, s, 1 H) exchanged with D_2O). 2-*Formylaminophenyl ethyl sulphone* (**4b**) had m.p. 73—74 °C (ethanol); $\nu_{max.}$(CH_2Cl_2) 3 320, 1 710, 1 320, and 1 140 cm^{-1}; δ($CDCl_3$) 1.2 (t, 3 H), 3.15 (q, 2 H), 7.2—7.7 (m, 5 H, aromatic and formyl protons), and 9.5 (br, s, 1 H, exchanged with D_2O). 2-*Benzoylaminophenyl methyl sulphone* (**4c**) had m.p. 115—116 °C (ethanol); $\nu_{max.}$(CH_2Cl_2) 3 350, 1 690, 1 290, and 1 150 cm^{-1}; δ($CDCl_3$) 3.05 (s, 3 H), 7.1—8.8 (m, 9 H), and 10.5 (br, s, 1 H, exchanged with D_2O).

Reaction of the Amide Sulphide (**1a**) *with Lithium Di-isopropylamide* (*LDA*).—To a nitrogen-flushed, three-necked flask (100 ml), equipped with magnetic stirrer and nitrogen inlet and containing anhydrous tetrahydrofuran (20 ml), was added di-isopropylamine (0.55 g, 5.49 mmol). The solution was cooled at −50 °C and 1.22N-Bu^nLi (4.5 ml, 5.40 mmol) was added *via* a dropping funnel. The mixture was stirred for 30 min and then a solution of (**1a**) (1 g, 3.7 mmol) in tetrahydrofuran (20 ml) was

added. After 3 h at −50 °C, the red solution was allowed to warm to room temperature, quenched with sat. aqueous NH_4Cl, and extracted with ether. T.l.c. (ether–petroleum, 1:1) showed the presence of two main products, which were separated by column chromatography. The first eluted was characterised as 2-(N-*phenacylbenzamido*)*phenyl ethyl sulphide* (**11**) (57% yield), m.p. 96—98 °C (ether–petroleum); $\nu_{max.}(CH_2Cl_2)$ 1 700 and 1 640 cm^{-1}; $\delta(CDCl_3)$ 1.4 (t, 3 H, *J* 7 Hz), 3.0 (q, 2 H, *J* 7 Hz), 4.55 (d, 1 H, *J* 18 Hz), 5.85 (d, 1 H, *J* 18 Hz), and 6.7—8.1 (m, 14 H). The second eluted was 2-*methylaminophenyl ethyl sulphide* (**12**) (40% yield; oil); $\nu_{max.}$(neat) 3 380 cm^{-1}; $\delta(CDCl_3)$ 1.1 (t, 3 H), 2.6 (q, 2 H), 2.7 (s, 3 H), 4.9 (br, s, 1 H), and 6.4—7.5 (m, 4 H).

General Procedure for the Preparation of Benzothiazines (**5**) *and* (**6**).—The preparation of the benzothiazine (**5b**) is described as an example. A solution of the benzamide (**1c**) (0.45 g, 1.3 mmol) was added dropwise at −50 °C under nitrogen to 1.9 mmol of LDA, prepared *in situ* from Bu^nLi (1.9 mmol) and diisopropylamine (1.9 mmol). The mixture was kept at −50 °C for 1 h and then allowed to warm to room temperature. Quenching with aqueous ammonium chloride (sat. soln.), extraction with water, washing of the extract with water, drying (Na_2SO_4), and evaporation gave the benzothiazine (**5b**), which was purified by column chromatography (ether–petroleum as eluant) and crystallisation (see Table 1).

Reaction of Benzamides (**3**) *with LDA*.—For example, the sulphone (**3a**) (2 g, 6.6 mmol) in tetrahydrofuran (30 ml) was added to 9.9 mmol of LDA prepared *in situ* at −50 °C. The mixture was kept at −50 °C for 1 h and then allowed to warm to room temperature and quenched with aqueous NH_4Cl (sat. soln.). Usual work-up gave 2-*ethylaminophenyl phenacyl sulphone* (**9a**) as an oil (1.6 g, 80% yield); $\nu_{max.}$(neat) 3 400, 1 680, 1 320—1 280, 1 145—1 110 cm^{-1}; $\delta(CCl_4)$ 1.2 (t, 3 H), 3.1 (q, 2 H), 4.55 (s, 2 H), 6.0 (br, s, 1 H), and 6.4—8.0 (m, 9 H).

2-*Ethylaminophenyl α-Phenylphenacyl Sulphone* (**9b**).—This was prepared from (**3b**) as described for (**3a**) (95% yield); m.p. 110—112 °C (ether); $\nu_{max.}(CH_2Cl_2)$ 3 405, 1 690, 1 330, and 1 100 cm^{-1}; $\delta(CDCl_3)$ 1.1 (t, 3 H), 2.9 (q, 2 H), 6.0 (br, s, 1 H), 6.2 (s, 1 H), and 6.4—7.9 (m, 14 H).

2-*Ethylaminophenyl α-Methylphenacyl Sulphone* (**9c**).—This was prepared from (**3c**) as described for (**3a**) (oil; 98% yield); $\nu_{max.}$(neat) 3 400, 1 690, 1 330, and 1 130 cm^{-1}; $\delta(CDCl_3)$ 1.2 (t, 3 H), 1.6 (d, 3 H), 3.0 (q, 2 H), 5.1 (q, 1 H), 6.1 (br, s, 1 H), and 6.3—7.9 (m, 9 H).

General Procedure for Cyclisation of Amino Sulphones (**9**) *to Benzothiazines* (**7**).—For example the sulphone (**9a**) (0.74 g, 2.4 mmol) in dry toluene (20 ml) was heated at reflux in the presence of a catalytic amount of toluene-*p*-sulphonic acid for 7 h in a Dean–Stark apparatus. Toluene was then removed under reduced pressure and the residue was extracted with CH_2Cl_2 (2 × 25 ml) and dried (Na_2SO_4). Evaporation left the benzothiazine (**7a**) (see Table 1).

General Procedure for Cyclisation of Amide Sulphones (**4**) *to Benzothiazines* (**8**).—A solution of (**4**) (1 equiv.) in tetrahydrofuran (20 ml) was added to the *in-situ*-prepared LDA (2.2 equiv.) at −50 °C. The mixture was kept at −50 °C for 20 min and then allowed to warm to room temperature. Quenching with 10% HCl after 1 h, extraction with CH_2Cl_2 (3 × 15 ml), drying (Na_2SO_4), and evaporation left (**8**) almost pure. Further purification was achieved by crystallisation (see Table 1).

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