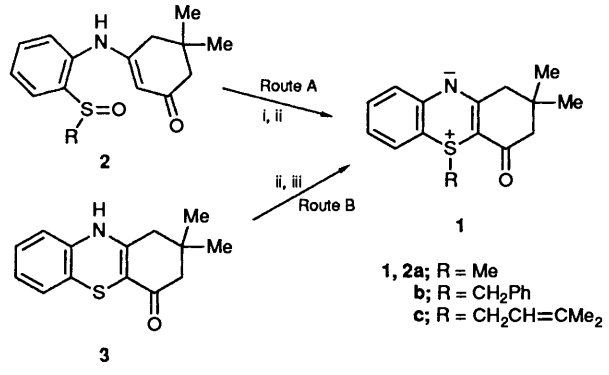
Rearrangement of Sulphonium Ylides of the 1*H*-1,4-Thiazine Type

Robert Foster and Thomas L. Gilchrist*
Department of Chemistry, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK

1*H*-Phenothiazinones **1** bearing benzyl and 3-methylbut-2-enyl substituents on sulphur have been generated. These ylides are not isolable but undergo rearrangement to 2*H*-phenothiazinones. Migration of the methylbutenyl substituent takes place with allylic inversion at low temperature, consistent with a [3,2] sigmatropic shift mechanism. Benzyl group migration to nitrogen competes with the 1,2-migration. Migration of a 1-(3-methylbut-2-enyl) substituent also takes place in the ylide derived from methyl 3-methyl-1,4-thiazine-2-carboxylate **16**: this leads to the isomeric 2*H*-benzothiazines **17** and **18**, the [3,2] sigmatropic shift product **17** predominating at low temperature. Attempts have been made to generate the first monocyclic 1*H*-1,4-thiazines and evidence is presented for the formation of two such ylides, the 1-ethyl-1*H*-thiazines **24a** and **24b**, as isolable but labile solids. An analogous preparation of 1-(3-methylbut-2-enyl)-3,5-diphenyl-1*H*-1,4-thiazine **25** leads to the isolation of the product of [3,2] rearrangement, the 2*H*-thiazine **26**.

We have previously described two methods of preparing cyclic *S*-methylsulphonium ylides containing a benzo fused 1,4-thiazine ring system.[1] These methods are illustrated in Scheme 1 for the preparation of the ylide **1a**: the cyclodehydration of an appropriate sulphoxide **2a** (route A) and the methylation of a

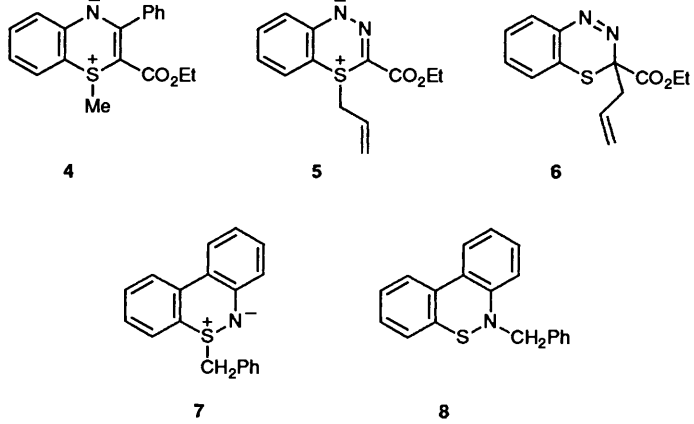


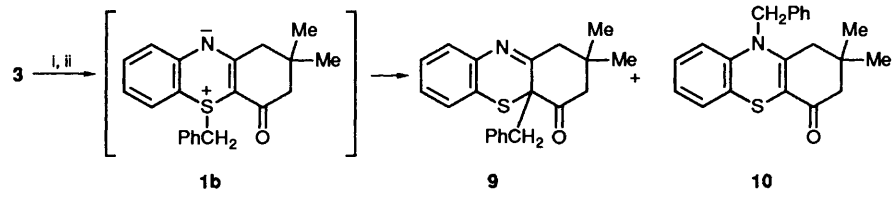
Scheme 1 *Reagents:* i, $(CF_3CO)_2O$; ii, base; iii, RX

salt derived from the parent heterocycle **3** (route B). Compound **1a** has also been prepared from **3** by methylation of the anion under phase transfer conditions with aqueous sodium hydroxide as the base.[2] A procedure which has been used for a related ylide **4** is the *S*-methylation of the parent heterocycle followed by deprotonation of the resulting sulphonium salt.[3]

In common with other sulphonium ylides,[4] cyclic ylides of these types can be expected to undergo thermal rearrangement. Olofson and his co-workers have shown that the *S*-methyl substituent of the 1*H*-1,4-benzothiazine **4** undergoes a 1,2-shift (a Stevens rearrangement) when the ylide is heated above 120 °C.[3] We set out to investigate the course of the rearrangement of ylides **1** bearing allylic and benzylic substituents on sulphur. By analogy with the chemistry of acyclic ylides[4] these ylides should rearrange easily. There are also several examples of cyclic ylides bearing such substituents on sulphur which rearrange spontaneously. The 1-allyl-1,3,4-benzothiadiazine **5** has been shown to rearrange to its 2-allyl isomer **6**[5] and the cyclic sulphimide **7** rearranges when generated at 0 °C to its *N*-benzyl isomer **8**.[6] We have attempted to synthesise the ylides **1b** and **1c** by both of the routes outlined in Scheme 1. The substituent on sulphur in **1c** was chosen to distinguish between a simple 1,2-shift and a [3,2] sigmatropic shift in any subsequent rearrangement. We have also briefly investigated the synthesis of related ylides containing the monocyclic 1,4-thiazine ring system.

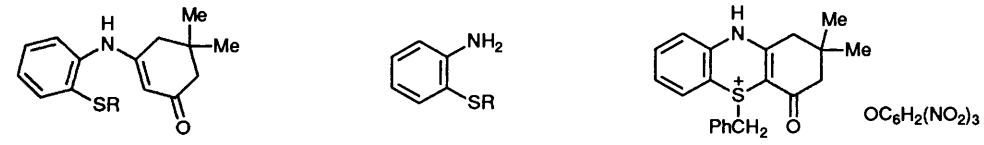
Generation and Rearrangement of the S-*Benzyl Ylide* **1b**.—The preparation of compound **1b** was attempted first by the alkylation method (route B) used earlier for **1a**. The phenothiazinone **3** was converted into its potassium salt by reaction with potassium hydride in *N*,*N*-dimethylformamide (DMF). Benzyl chloride was added to the salt, after which two products were isolated by chromatography. The major component was identified as the 4a-benzyl derivative **9** on the basis of its ^1H





1b **9** **10**

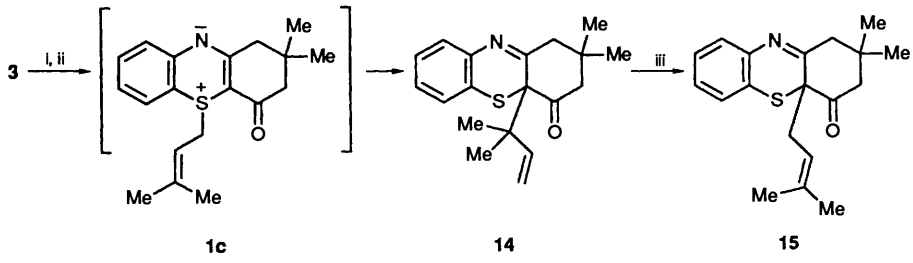
Scheme 2 *Reagents:* i, KH, Me_2NCHO; ii, $PhCH_2Cl$



11 a; R = CH_2Ph
b; R = $CH_2CH{=}CMe_2$

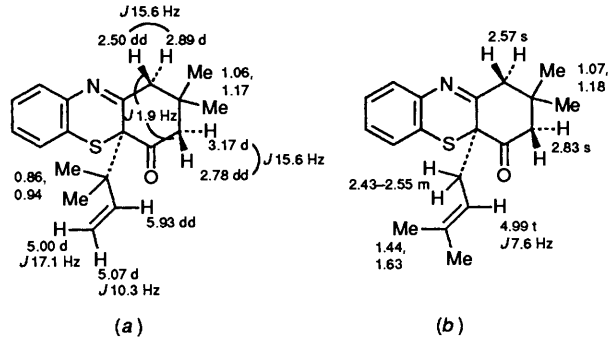
12 a; R = CH_2Ph
b; R = $CH_2CH{=}CMe_2$

13



1c **14** **15**

Scheme 3 *Reagents:* i, KH, $MeOCH_2CH_2OMe$; ii, $Me_2C{=}CHCH_2Br$, −61 °C; iii, silica



(*a*) (*b*)

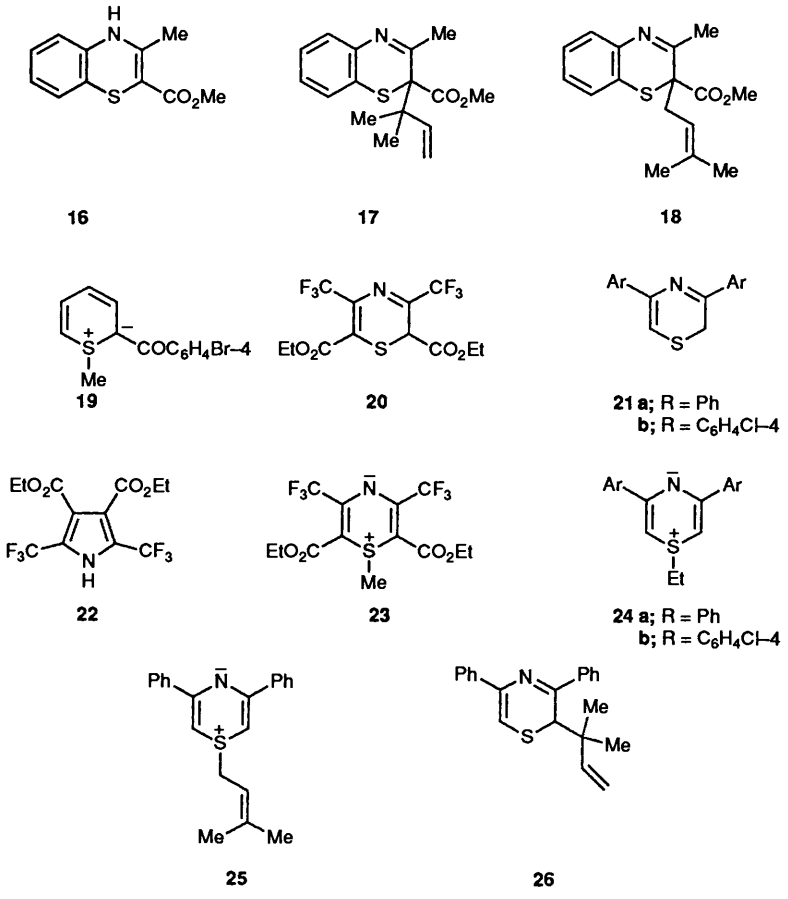
Fig. 1 ^1H NMR spectra (*a*) of **14** and (*b*) of **15**

NMR spectrum. This showed signals for diastereotopic benzylic hydrogen atoms and for non-equivalent methyl groups at C-2. The minor component was identified as the *N*-benzyl derivative **10**. Since neither of the corresponding methyl derivatives had been detected when compound **3** was methylated it seems likely that both **9** and **10** are being produced by the rearrangement of a transient *S*-benzyl ylide **1b** (Scheme 2). There is no evidence that the *N*-benzyl derivative **10** is formed by way of compound **9** because **9** was recovered quantitatively after being stirred with potassium hydride in DMF for 24 h. Compound **9** is formed from **1b** by a 1,2-shift of the benzyl group. Compound **10**, is formally the product of an allowed [1,4] sigmatropic benzyl shift but we have no evidence that the reaction leading to its formation is unimolecular.

Support for the proposal that the ylide **1b** is an intermediate in the formation of **9** and **10** was obtained by generating it independently. The sulphide **11a**, prepared from the aniline **12a** and dimedone, was oxidised to the sulphoxide **2b**. This was cyclised by reaction with trifluoroacetic anhydride and picric acid was then added to produce the picrate **13**. Reaction of this salt with potassium hydride led to the formation of the same two products **9** and **10** as had been obtained previously, and in similar yield.

Generation and Rearrangement of the S-(3-*Methylbut*-2-*enyl*) *Ylide* **1c**.—The preparation of this ylide was again attempted first by the method analogous to route B in Scheme 1. The potassium salt of the phenothiazinone **3** was alkylated by reaction with 1-bromo-3-methylbut-2-ene at −61 °C (Scheme 3). The crude product was essentially a single component, the ^1H NMR spectrum of which is consistent with the structure **14**. Assignments of signals to hydrogen atoms in structure **14** are shown in Fig. 1(*a*). This compound, an oil, was subjected to column chromatography on silica in order to obtain an analytically pure specimen. This resulted in the isolation of a major component as a crystalline solid in 70% yield. When this was examined by NMR spectroscopy, however, its spectrum was different from that obtained for compound **14**; in particular, it was evident from the spectrum that the isobutenyl substituent was attached through the methylene group. All four methyl groups have different chemical shifts, which rules out a planar structure, and the signals for the exocyclic methylene hydrogens are at δ 2.43–2.55, which indicates that the substituent is attached to a carbon atom of the ring system rather than to nitrogen or sulphur. The spectrum, shown in Fig. 1(*b*), is consistent with the structure **15** for this solid.

Attempts to synthesise the ylide **1c** independently by route A were not successful: the sulphoxide **2c** gave a mixture on



16 17 18

19 20 21 a; R = Ph b; R = C_6H_4Cl-4

22 23 24 a; R = Ph b; R = C_6H_4Cl-4

25 26

reaction with trifluoroacetic anhydride. The major component, and the only one which was identified, was the phenothiazinone **3**.

A related series of experiments was carried out with the benzothiazine **16**. The compound was deprotonated and alkylated with 1-bromo-3-methylbut-2-ene under two sets of conditions and the products were identified from their NMR spectra. Alkylation at 0 °C led to the formation of the 2-substituted benzothiazine **17** together with its isomer **18** in a ratio of 1:5. When the alkylation was performed at −78 °C, however, the ratio of the two products was 4.6:1. This is consistent with a concerted [3,2] sigmatropic shift (to give **17**) having a lower activation energy than the Stevens rearrangement to **18**, as has been observed with acyclic sulphonium ylides.[7] In the case of ylide **1c** it is possible that the rearrangement to **14** is reversible (as has been suggested for the ylide **5** and its rearrangement product **6**)[5] and that this reversible process is accompanied by an irreversible rearrangement of **1c** to **15**. An alternative for the conversion of **14** into **15** is an ionic dissociation–recombination process which takes place on the silica support.

Attempts to Generate Monocyclic 1H-1,4-*Thiazines*.—Having successfully used the deprotonation and alkylation method to generate 1*H*-1,4-benzothiazines we attempted to apply the same method to the generation of monocyclic ylides of this type. Sulphonium ylides based on monocyclic 1,4-thiazines are unknown[8] but a series of oxosulphonium ylides has been described.[9] The first monocyclic 'thiabenzenes' such as **19** have also been prepared recently.[10] We have used two types of 2*H*-1,4-thiazines as starting materials, the diester **20** and the 3,5-diarylthiazines **21**.

Lee and Howe described the preparation of the thiazine **20** from ethyl trifluoroacetoacetate, ammonia and sulphur dichloride.[11] They also described its conversion into the pyrrole **22** by warming it with triethylamine. Reaction of triethylamine with the thiazine at low temperature (−40 °C) was shown to lead to the development of a deep blue solution. This colour was discharged when the solution was warmed and the pyrrole could then be isolated. The reaction is one of a group of related extrusion reactions and rearrangements which have been ascribed to the electrocyclic ring closure of 8π electron heterocyclic anions.[12] We repeated the preparation of the thiazine **20** and generated the anion from it with several different bases (lithium diisopropylamide, *sec*-butyllithium, potassium hydride and sodium ethoxide) at −78 °C. In each case a deep blue solution of the anion was produced. A methylating agent (either iodomethane or methyl trifluoromethanesulphonate) was then added and the reaction mixture was allowed to warm to room temperature. The deep blue colour was discharged above *ca.* −20 °C but in every case the only product detected was the pyrrole **22**; there was no evidence for methylation of the anion. Although the ylide **23** is well stabilised, the sulphur atom of the anion derived from **20** is apparently insufficiently nucleophilic to allow alkylation to occur.

The 3,5-diarylthiazines **21a**[13] and **21b**[14] were prepared in good yield by literature procedures. Compound **21a** was treated with lithium diisopropylamide at −78 °C and a deep crimson solution of the anion was produced. This was quenched with iodomethane but the only detectable component was the starting thiazine **21a**: there was no evidence either for alkylation or for ring contraction of the anion to a pyrrole analogous to **22**. An alkylation was then attempted with iodoethane. In this case a product was formed, and was isolated by column chromatography as an unstable amorphous solid. The NMR spectrum of the solid showed that the compound had a symmetrical structure, the spectrum being consistent with the ylide structure **24a**. The signals for the hydrogens at C-2 and C-6

appear as a singlet at δ 4.73, which is well upfield of the signal for 6-H in the thiazine **21a** (δ 6.45) but at a similar position to that in an acyclic sulphonium ylide (for example, the CH signal in $Me_2S^+CH{=}CO^-Ph$ is at δ 4.31 [15]). The instability of the solid precluded further characterisation. An analogous ylide **24b** was prepared from **21b**; for this compound additional evidence for the ylide structure was obtained from the NMR spectrum in trifluoroacetic acid, which showed an NH signal, and by converting the compound into an unstable oxalate salt. Compound **24b** was found to revert to the thiazine **21b** when heated in toluene.

The anion derived from the thiazine **21a** was also alkylated with 1-bromo-3-methylbut-2-ene. The reaction resulted in the formation of a single product, which was isolated in good yield as a crystalline solid. The ylide structure **25** could be discounted for this product but analytical and NMR data are consistent with its formulation as the 2*H*-thiazine **26**, the product of [3,2] rearrangement of the ylide.

On the basis of these limited experiments we conclude that the anions derived from 3,5-diaryl-2*H*-thiazines are alkylated on sulphur rather than on nitrogen or carbon. This preference also appears to hold for the benzothiazines studied, since all the products detected can be rationalised on the basis of initial alkylation on sulphur.

Experimental

^1H NMR spectra were recorded at 250 MHz on a Bruker WM250 instrument, and at 220 MHz using a Perkin-Elmer R34 instrument, in deuteriochloroform (except where indicated otherwise) and with tetramethylsilane as an internal reference. *J* values are given in Hz and signals are singlets unless indicated otherwise. Mass spectra were recorded under electron impact on a VG Micromass 7070E instrument. Microanalyses were performed in the microanalytical laboratory at Liverpool University. M.p.s were obtained on a Reichert hot stage apparatus and are uncorrected. THF (tetrahydrofuran) and 1,2-dimethoxyethane were distilled from sodium–benzophenone ketyl immediately before use. LDA (lithium diisopropylamide) was prepared from diisopropylamine and butyllithium immediately before use.

4a-*Benzyl*-2,3-*dihydro*-2,2-*dimethyl*-4a*H*-*phenothiazin*-4(1*H*)-*one* **9** *and* 10-*Benzyl*-2,3-*dihydro*-2,2-*dimethyl*-10*H*-*phenothiazin*-4(1*H*)-*one* **10**.—(*a*) *By benzylation of* 2,3-*dihydro*-2,2-*dimethyl*-10*H*-*phenothiazin*-4(1*H*)-*one* **3**. The phenothiazinone **3** [16] (3.0 g, 9.3 mmol) in 1,2-dimethoxyethane (DME) (10 cm^3) was added to a stirred suspension of potassium hydride (0.4 g, 10.0 mmol) in DMF (30 cm^3) at 0 °C. After 0.5 h benzyl chloride (1.1 cm^3, 10.0 mmol) was added dropwise. The solvents were distilled off and the residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3). The organic layer was separated off, washed with water (20 cm^3), dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography (silica) which gave [with hexane–ethyl acetate (1:1)] the *title compound* **9** (1.39 g, 45%), m.p. 144–146 °C (from ethyl acetate–hexane) (Found: C, 75.3; H, 6.4; N, 4.0. $C_{21}H_{21}NOS$ requires C, 75.2; H, 6.3; N, 4.2%); ν_{max}/cm^{-1} 1702 (C=O) and 1601; δ 0.96 (3 H, 2-Me), 1.06 (3 H, 2-Me), 2.07 (1 H, d, *J* 15.5, 1-H), 2.09 (1 H, d, *J* 15.5, 3-H), 2.51 (1 H, dd, *J* 15.5 and 3.2, 1-H), 2.65 (1 H, dd, *J* 15.5 and 3.2, 3-H), 3.00 (1 H, d, *J* 13.8, benzyl CH), 3.14 (1 H, d, *J* 13.8, benzyl CH) and 6.87–7.40 (9 H, m); *m/z* 335 (M^+) and 244 ($M^+ - PhCH_2$) (base). Further elution gave the *title compound* **10** (0.22 g, 7%), m.p. 187–189 °C (from ethyl acetate–hexane) (Found: C, 75.4; H, 6.4; N, 4.0%); ν_{max}/cm^{-1} 1624 and 1589; δ 0.95 (6 H, 2-Me), 2.27 (2 H, 1-H), 2.29 (2 H, 3-H), 4.95 (2 H, benzyl CH), 6.57–6.62 (1 H, m), 6.68–7.04 (3 H, m) and 7.26–7.41 (5 H, m); *m/z* 335 (M^+) and 244 ($M^+ - PhCH_2$) (base).

(*b*) *By cyclisation of* 3-(2-*benzylsulphinylanilino*)-5,5-*dimethylcyclohex*-2-*enone* **2b**. 2-(Benzylthio)aniline **12a** [17] (10.0 g, 0.046 mol), 5,5-dimethylcyclohexane-1,3-dione (6.25 g, 0.046 mol) and toluene-4-sulphonic acid (100 mg) were heated together in toluene (50 cm^3) under reflux for 18 h with azeotropic removal of water. The reaction mixture was evaporated to dryness and the residue was recrystallised to give the 3-(2-*benzylthioanilino*)-5,5-*dimethylcyclohex*-2-*enone* **11a** (11.43 g, 74%), m.p. 127 °C (from ethyl acetate) (Found: C, 74.9; H, 6.9; N, 4.0. $C_{21}H_{23}NOS$ requires C, 74.8; H, 6.9; N, 4.15%); ν_{max}/cm^{-1} 3180, 3125, 1635 and 1597; δ 1.08 (6 H), 2.21 (4 H), 3.91 (2 H), 5.60 (1 H), 6.44 (1 H, br, NH) and 7.00–7.42 (9 H, m); *m/z* 337 (M^+) and 249 (base).

The sulphide **11a** (5.00 g, 0.015 mol), acetic acid (5 cm^3) and aqueous hydrogen peroxide (30% w/v) (5.0 cm^3) were stirred in dichloromethane (100 cm^3) for 18 h at room temperature. The mixture was poured into aqueous sodium carbonate (10% w/v) (20 cm^3) and the organic layer was separated off, dried (Na_2SO_4) and evaporated. Crystallisation of the residue gave the 3-(2-*benzylsulphinylanilino*)-5,5-*dimethylcyclohex*-2-*enone* **2b** (3.10 g, 59%), m.p. 208 °C (from ethanol) (Found: C, 71.3; H, 6.65; N, 3.85. $C_{21}H_{23}NO_2S$ requires C, 71.35; H, 6.6; N, 4.0%); ν_{max}/cm^{-1} 3200 (NH), 1625, 1596 and 1000 (S=O); δ 1.12 (3 H), 1.15 (3 H), 2.23 (1 H, d, *J* 17.1), 2.28 (1 H, d, *J* 17.1), 2.35 (1 H, d, *J* 17.1), 2.45 (1 H, d, *J* 17.1), 4.21 (1 H, d, *J* 13.4), 4.35 (1 H, d, *J* 13.4), 5.89 (1 H), 6.93–7.10 (3 H, m), 7.23–7.27 (4 H, m), 7.37–7.54 (2 H, m) and 8.52 (1 H, br, NH); *m/z* 353 (M^+), 262, 245 and 91 (base).

Trifluoroacetic anhydride (2.0 cm^3) was added to a solution of the sulphoxide **2b** (2.0 g, 5.6 mmol) in dry dichloromethane (50 cm^3) at −61 °C. The reaction mixture was stirred for 2.5 h at this temperature. Picric acid (1.3 g, 5.6 mmol) was then added and the mixture was stirred at room temperature overnight. The solvent was then distilled off and the residue was triturated with ether to leave a solid. This was filtered off and crystallised to give the 5-*benzyl* 1,2,3,4-*tetrahydro*-2,2-*dimethyl*-4-*oxo*-10*H*-*phenothiazin*-5-*ium picrate* **13** (1.1 g, 35%), m.p. 140 °C (decomp.) (from dichloromethane–hexane) (Found: C, 57.1; H, 4.25; N, 10.0. $C_{27}H_{24}N_4O_8S$ requires C, 57.4; H, 4.3; N, 9.9%); ν_{max}/cm^{-1} 3210, 3160, 1620 and 1605; δ 0.94 (3 H), 0.98 (3 H), 2.23 (1 H, d, *J* 17.6), 2.35 (1 H, d, *J* 17.6), 2.45 (1 H, d, *J* 19.1), 2.60 (1 H, d, *J* 19.1), 3.98 (1 H, d, *J* 13.2), 4.16 (1 H, d, *J* 13.2), 6.60–6.75 (9 H, m) and 8.72 (2 H); *m/z* 335 [$M^+ - C_6H_2(NO_2)_3OH$] and 244.

The picrate **13** (0.49 g, 0.87 mmol) in DMF (10 cm^3) was added to a stirred suspension of potassium hydride (0.35 g, 0.87 mmol) in DMF (20 cm^3) at 0 °C. The mixture was then stirred at room temperature for 18 h. The solvent was distilled off and the residue was partitioned between water (20 cm^3) and dichloromethane (20 cm^3). The organic layer was dried ($MgSO_4$) and evaporated to yield an oil. Column chromatography (silica) gave [with hexane–ethyl acetate (1:1)] the phenothiazinones **9** (0.12 g, 41%) and **10** (0.03 g, 10%), which were identified by comparison with specimens obtained by the benzylation route.

Cyclisation of Sulphoxide **2c**.—(*a*) 2-(3-*Methylbut*-2-*enylthio*)*aniline* **12b**. This was prepared from 2-aminothiophenol (5.0 g, 0.040 mol), 1-bromo-3-methylbut-2-ene (6.55 g, 0.043 mol) and sodium ethoxide (0.043 mol) in ethanol. Distillation (Kugelrohr) gave the sulphide **12b** (6.6 g, 85%), b.p. 150 °C (bath) at 0.4 mmHg [Found: M^+ 193.0913. $C_{12}H_{15}NS$ requires *M*, 193.0925]; ν_{max}/cm^{-1} 3435, 3340 and 1600; δ 1.37 (3 H, d, *J* 1.4), 1.64 (3 H, d, *J* 1.4), 3.32 (2 H, d, *J* 8.0), 4.31 (2 H, br, NH), 5.24 (1 H, t, *J* 8.0, showing further splitting), 6.61 (1 H, t, *J* 7.8), 6.64 (1 H, d, *J* 7.8), 7.05 (1 H, t, *J* 7.8) and 7.29 (1 H, d, *J* 7.8).

(*b*) 5,5-*Dimethyl*-3-[2-(3-*methylbut*-2-*enylthio*)*anilino*]*cyclohex*-2-*enone* **11b**. A solution of the sulphide **12b** (5.0 g, 0.023 mmol), 5,5-dimethylcyclohexane-1,3-dione (3.6 g, 0.023 mol) and toluene-*p*-sulphonic acid (100 mg) in toluene (50 cm^3) was heated under reflux for 18 h with a Dean and Stark trap. The reaction mixture was evaporated to dryness and the residue (7.2 g) was recrystallised to give the *sulphide* **11b** (6.0 g, 83%), m.p. 87–88 °C (from ethyl acetate) (Found: C, 72.6; H, 8.0; N, 4.05. $C_{19}H_{25}NOS$ requires C, 72.3; H, 8.0; N, 4.4%); ν_{max}/cm^{-1} 3190 and 1660; δ 1.13 (6 H), 1.39 (3 H), 1.66 (3 H), 2.26 (2 H), 2.40 (2 H), 3.37 (2 H, d, *J* 7.6), 5.21 (1 H, t, *J* 7.6), 5.70 (1 H), 6.70 (1 H, br, NH), 7.05 (1 H, t, *J* 7.8), 7.25 (1 H, t, *J* 7.8), 7.33 (1 H, d, *J* 7.8) and 7.44 (1 H, d, *J* 7.8); *m*/*z* 315 (M^+) and 246 (base).

(*c*) 5,5-*Dimethyl*-3-[2-(3-*methylbut*-2-*enylsulphinyl*)*anilino*]-*cyclohex*-2-*enone* **2c**. The sulphide **11b** (1.0 g, 3.2 mmol), acetic acid (2.0 cm^3) and aqueous hydrogen peroxide (30% w/v; 2.0 cm^3) were stirred in dichloromethane (25 cm^3) for 18 h. The mixture was poured into aqueous sodium carbonate (10% w/v; 20 cm^3) and the organic layer separated off, dried ($MgSO_4$) and evaporated. The residue was crystallised to give the *sulphoxide* **2c** (1.0 g, 89%), m.p. 163 °C (decomp.) (from dichloromethane–hexane) (Found: C, 68.8; H, 7.7; N, 3.95. $C_{19}H_{25}NO_2S$ requires C, 68.8; H, 7.6; N, 4.2%); ν_{max}/cm^{-1} 3180, 1625 and 1610; δ 1.10 (3 H), 1.15 (3 H), 1.41 (3 H), 1.69 (3 H), 2.21 (1 H, d, *J* 14.7), 2.32 (1 H, d, *J* 17.1), 2.33 (1 H, d, *J* 14.7), 2.49 (1 H, d, *J* 17.1), 3.76 (1 H, d, *J* 7.7), 3.79 (1 H, d, *J* 7.7), 5.06 (1 H, t, *J* 7.7), 5.87 (1 H), 7.12 (1 H, t, *J* 7.3), 7.22 (1 H, d, *J* 7.3), 7.44 (1 H, d, *J* 7.3), 7.52 (1 H, d, *J* 7.3) and 8.92 (1 H, br, NH); *m*/*z* 263 ($M^+ - CH_2C{=}CMe_2$).

(*d*) *Cyclisation of* **2c**. Trifluoroacetic anhydride (1.0 cm^3) was added to a solution of the sulphoxide **2c** (150 mg, 0.45 mmol) in dry dichloromethane (25 cm^3) at −61 °C. The mixture was stirred at this temperature for 2.5 h and then allowed to attain room temperature. Several components were present (TLC) and after quenching with water the mixture gave the phenothiazinone **3** (120 mg, 72%).

2,3-*Dihydro*-2,2-*dimethyl*-4a-(1,1-*dimethylprop*-2-*enyl*)-4aH-*phenothiazin*-4(1H)-*one* **14** *and* 2,3-*Dihydro*-2,2-*dimethyl*-4a-(3-*methylbut*-2-*enyl*)-4aH-*phenothiazin*-4(1H)-*one* **15**.—The phenothiazinone **3** (1.0 g, 4.1 mmol) was suspended in DME (10 cm^3). Potassium hydride (0.18 g, 4.5 mmol) was added in one portion as a slurry in DME (5 cm^3) at room temperature. The mixture was placed in a sonic bath and heated at 60 °C for 0.5 h. The reaction mixture was cooled to −61 °C and 1-bromo-3-methylbut-2-ene (0.67 g, 4.5 mmol) was added. After 4 h the reaction mixture was allowed to warm to room temperature and the solvent was distilled off. The residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3). The organic layer was dried ($MgSO_4$) and evaporated to leave an oil (1.2 g). TLC showed the presence of a single component. The NMR spectrum of the oil is depicted in Fig. 1(*a*). On this basis it was assigned the structure **14**. Column chromatography of the oil (silica) gave [with hexane–ethyl acetate (7:3)] the *title compound* **15** (0.90 g, 70%), m.p. 104.5–107 °C (from hexane–ethyl acetate) (Found: C, 72.7; H, 7.6; N, 4.2. $C_{19}H_{23}NOS$ requires C, 72.8; H, 7.4; N, 4.5%); ν_{max}/cm^{-1} 1698 (C=O) and 1605; *m*/*z* 313 (M^+) and 244 (base). The NMR spectrum is depicted in Fig. 1(*b*).

Methyl 3-*Methyl*-4H-1,4-*benzothiazine*-2-*carboxylate* **16**.—2-Aminothiophenol (25.0 g, 0.2 mol), methyl acetoacetate (23.2 g, 0.2 mmol) and dimethyl sulphoxide (DMSO) (30 cm^3) were heated together for 1 h at 120 °C. The reaction mixture was then evaporated to an oil which partially crystallised. Recrystallisation gave the *benzothiazine* **16** (13.0 g, 29%), m.p. 137–143 °C (from methanol) (Found: C, 59.7; H, 5.1; N, 6.1. $C_{11}H_{11}NO_2S$ requires C, 59.7; H, 5.0; N, 6.3%); ν_{max}/cm^{-1} 3280, 1602 and 1560; δ 2.28 (3 H), 3.70 (3 H), 6.05 (1 H, br, NH), 6.33–6.44 (1 H, m) and 6.72–6.92 (3 H, m).

Methyl 3-*Methyl*-2-(1,1-*dimethylprop*-2-*enyl*)-2H-*benzothiazine*-2-*carboxylate* **17** *and Methyl* 3-*Methyl*-2-(3-*methylbut*-2-*enyl*)-2H-*benzothiazine*-2-*carboxylate* **18**.—(*a*) *Alkylation of benzothiazine* **16** *at* 0 °C. The benzothiazine **16** (0.30 g, 1.35 mmol) in DME (10 cm^3) was added to a suspension of potassium hydride (0.06 g, 1.5 mmol) in DME (30 cm^3) at 0 °C. After 0.5 h 1-bromo-3-methylbut-2-ene (0.22 g, 1.5 mmol) was added. The mixture was allowed to warm to room temperature after which the solvent was distilled off. The residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3). Column chromatography (silica) gave [with ethyl acetate–hexane (2:1)] the *benzothiazine* **18** (0.20 g, 51%) as an oil (Found: M^+ 289.1143. $C_{16}H_{19}NO_2S$ requires *M*, 289.1137); δ 1.48 (3 H, Me of 2-substituent), 1.72 (3 H, Me of 2-substituent), 2.41 (3 H, 3-Me), 2.49 and 2.80 (each 1 H, dd, *J* 14.6 and 5.9, CH_2 of 2-substituent), 3.77 (3 H, OMe), 5.19 (1 H, t, *J* 5.9, CH of 2-substituent) and 7.14–7.47 (4 H, m). Further elution gave the benzothiazine **17** (0.04 g, 10%) as an oil which was identified from its NMR spectrum; δ 1.13 (3 H, Me of 2-substituent), 1.19 (3 H, Me of 2-substituent), 2.40 (3 H, Me-3), 3.74 (3 H, OMe), 4.92 (1 H, d, *J* 12.2), 4.99 (1 H, d, *J* 17.6), 6.13 (1 H, dd, *J* 17.6 and 12.2) and 7.02–7.29 (4 H, m); *m*/*z* 289 (M^+) and 220 ($M^+ - Me_2CCH{=}CH_2$, base). This compound was not characterised further.

(*b*) *Alkylation of benzothiazine* **16** at −78 °C. The alkylation was carried out as above except that 1-bromo-3-methylbut-2-ene was added to the reaction mixture at −78 °C and this temperature was maintained for 4 h before the mixture was quenched. The products, isolated by column chromatography and identified from their NMR spectra, were the benzothiazines **18** (14%) and **17** (64%).

3,5-*Diphenyl*-2H-1,4-*thiazine* **21a**.—1,1′-Diphenyl-2,2′-thiobis(ethanone) was prepared by a literature procedure[13] from sodium sulphide and phenacyl chloride. A solution of this sulphide 15.0 g, 0.06 mol) and ammonium acetate (8.4 g, 0.11 mol) in ethanol (150 cm^3) was heated under reflux for 1.5 h. When the solution was cooled a solid crystallised out. This was filtered off, washed and dried to give the thiazine **21a** (9.87 g, 71%), m.p. 77.5–78.5 °C (from ethanol) (lit.,[13] 81–82 °C) (Found: C, 76.2; H, 5.4; N, 5.55. Calc. for $C_{16}H_{13}NS$: C, 76.5; H, 5.2; N, 5.6%); ν_{max}/cm^{-1} 1591 and 1561; δ 3.41 (2 H, 2-H), 6.45 (1 H, 6-H), 7.31–7.50 (6 H, m), 7.85 (2 H, d, *J* 6.8) and 8.03–8.10 (2 H, m).

3,5-*Bis*-4-*chlorophenyl*-2H-1,4-*thiazine* **21b**.—This was prepared (85%) in the same way as **21a** from 1,1′-bis(4-chlorophenyl)2,2′-thiobis(ethanone)[14] and ammonium acetate. It had m.p. 121–123 °C (from ethanol) (lit.,[14] 121–122 °C); ν_{max}/cm^{-1} 1585 and 1556; δ 3.37 (2 H), 6.44 (1 H), 7.37 (2 H, d, *J* 8.8), 7.46 (2 H, d, *J* 8.3), 7.74 (2 H, d, *J* 8.3) and 8.00 (2 H, d, *J* 8.8).

Attempted Methylation of Diethyl 3,5-*Bis*(*trifluoromethyl*)-2H-1,4-*thiazine*-2,6-*dicarboxylate* **20**.—The thiazine **20**[11] (1.0 g, 2.6 mmol) in THF (10 cm^3) was added during 10 min at −78 °C to a solution of LDA (2.9 mmol) in THF (10 cm^3). An intense deep-blue colour developed. After 0.5 h iodomethane (2.0 cm^3, 3.2 mmol) was added and the reaction mixture was allowed to warm to room temperature. The blue colour persisted at −78 °C but gradually faded, to leave a yellow solution, as the temperature was raised. The solvent was distilled off and the residue was dissolved in dichloromethane. The solution was washed with water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to leave diethyl 2,5-bis(trifluoromethyl)-

pyrrole-3,4-dicarboxylate **22** (0.64 g, 100%), m.p. 49–54 °C (from hexane) (lit.,[11] m.p. 44–53 °C).

Similar experiments were carried out with the bases sodium ethoxide in ethanol, *sec*-butyllithium in THF, and potassium hydride with 18-crown-6 in dimethoxyethane. Methyl trifluoromethanesulphonate was also used in place of iodomethane. The pyrrole **22** was the only product detected in every case.

1-*Ethyl*-3,5-*diphenyl*-1H-1,4-*thiazin*-1-*ium*-4-*ide* **24a**.—The thiazine **21a** (3.0 g, 11.8 mmol) in THF (10 cm^3) was added during 10 min at −78 °C to LDA (13.0 mmol) in THF (10 cm^3). A deep crimson colour developed. The mixture was stirred for 0.5 h at −78 °C and iodoethane (2.2 g, 14.0 mmol) was added. The reaction mixture was allowed to attain room temperature. The solvent was distilled off and the residue was partitioned between water (20 cm^3) and dichloromethane (20 cm^3). The organic layer was separated off, dried ($MgSO_4$) and evaporated. Column chromatography (silica) gave [with methanol–dichloromethane (1:1)] a violet resin, which when triturated with ether yielded an amorphous orange solid (3.3 g), m.p. 85–91 °C (decomp.). This solid was assigned the structure **24a** on the basis of its NMR spectrum; δ 1.01 (3 H, t, *J* 7.8, CH_3 of Et), 2.21 (2 H, q, *J* 7.8, CH_2 of Et), 4.73 (2 H, 2-H and 6-H), 7.38–7.46 (6 H, m) and 7.93–7.99 (4 H, m).

3,5-*Bis*(4-*chlorophenyl*)-1-*ethyl*-1H-1,4-*thiazin*-1-*ium*-4-*ide* **24b**.—A solution of the thiazine **21b** (6.0 g, 0.018 mol) in THF (10 cm^3) was added during 10 min to LDA (0.020 mol) in THF (10 cm^3) at −78 °C. A deep red colour developed. The mixture was stirred for 0.5 h at −78 °C then iodoethane (3.4 g, 0.022 mol) was added. The reaction mixture was allowed to warm to room temperature and was maintained at this temperature until reaction appeared complete by TLC. The solvent was distilled off and the residue was partitioned between water (30 cm^3) and dichloromethane (30 cm^3). The organic layer was separated off, dried ($MgSO_4$) and evaporated to give an orange resin (7.2 g). This was homogeneous by TLC and was assigned the structure **24b** on the basis of its NMR spectra; δ($CDCl_3$) 1.01 (3 H, t, *J* 8.3), 2.21 (2 H, q, *J* 8.3), 4.67 (2 H, 2-H and 6-H), 7.32 (4 H, d, *J* 7.8) and 7.84 (4 H, d, *J* 7.8); δ(CF_3CO_2H) 1.49 (3 H, t, *J* 6.4), 3.06 (2 H, q, *J* 6.4), 5.31 (2 H, 2-H and 6-H), 7.59–7.70 (8 H, m) and 8.81 (1 H, br, NH). The compound and oxalic acid in acetone gave a solid oxalate, m.p. 145–146.5 °C (decomp.) (from nitromethane) but this decomposed rapidly on exposure to air. The thiazine **24b** (0.3 g, 1.1 mmol) when heated in toluene under reflux under nitrogen for 3.5 h gave the 2*H*-thiazine **21b** (0.28 g, 100%), m.p. 121–123.5 °C (from ethanol).

3,5-*Diphenyl*-2-(3-*methylbut*-2-*enyl*)-2H-1,4-*thiazine* **26**.—The thiazine **21a** (0.50 g, 2.0 mmol) in dimethoxyethane (10 cm^3) was added at −78 °C to LDA (4.4 mmol) in dimethoxyethane (10 cm^3). The solution immediately developed a deep crimson colouration. The mixture was stirred at −78 °C for 0.5 h then 1-bromo-3-methylbut-2-ene (0.70 g, 5.0 mmol) was added. The mixture was stirred at −78 °C for 2.5 h then warmed to room temperature. The solvent was distilled off and the residue was partitioned between dichloromethane (20 cm^3) and water (20 cm^3). The organic layer was separated off, dried ($MgSO_4$) and evaporated to leave an oil. Column chromatography (silica) gave [with ethyl acetate–hexane (1:40)] the *thiazine* **26** (0.49 g, 77%), m.p. 93–95 °C (from hexane) (Found: C, 78.9; H, 6.6; N, 4.1. $C_{21}H_{21}NS$ requires C, 78.95; H, 6.6; N, 4.4%); ν_{max}/cm^{-1} 1594, 1564 and 1001; δ 0.98 (3 H), 1.04 (3 H), 4.06 (1 H, d, *J* 2.1, 2-H), 4.75 (1 H, dd, *J* 10.5 and 1.0), 4.89 (1 H, dd, *J* 17.7 and 1.0), 5.72 (1 H, dd, *J* 17.7 and 10.5), 6.19 (1 H, d, *J* 2.1, 6-H), 7.32–7.43 (6 H, m), 7.76 (2 H, d, *J* 6.8) and 8.04–8.08 (2 H, m).

Acknowledgements

We thank Lipha Pharmaceuticals for financial support and for a Studentship (to R. F.).

References

1 T. L. Gilchrist and G. M. Iskander, *J. Chem. Soc., Perkin Trans. 1*, 1982, 831.
2 Ž. Saničanin, A. Jurić, I. Tabaković and N. Trinajstić, *J. Org. Chem.*, 1987, **52**, 4053.
3 V. M. Sakoda, R. R. Whittle and R. A. Olofson, *Tetrahedron Lett.*, 1984, **25**, 2635.
4 B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York, 1975, p. 108.
5 L. Bruché, L. Garanti and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2535.
6 H. Shimizu, K. Ikedo, K. Hamada, H. Matsumoto, M. Ozawa, T. Kataoka and M. Hori, *Tetrahedron Lett.*, 1990, **31**, 7021.
7 J. E. Baldwin and W. F. Erickson, *J. Chem. Soc., Chem. Commun.*, 1971, 859.
8 R. J. Stoodley, *Adv. Heterocycl. Chem.*, 1979, **24**, 293.
9 W. Ried and D. Kuhnt, *Liebigs Ann. Chem.*, 1986, 1648; 1987, 551.
10 H. Shimizu, N. Kudo, T. Kataoka and M. Hori, *Tetrahedron Lett.*, 1990, **31**, 115.
11 L. F. Lee and R. K. Howe, *J. Org. Chem.*, 1984, **49**, 4780.
12 R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 581.
13 K. Fujii, *Yakugaku Zasshi*, 1957, **77**, 359 (*Chem. Abstr.*, 1957, **51**, 12103).
14 D. Sica, C. Santacroce and R. A. Nicolaus, *Gazz. Chim. Ital.*, 1968, **98**, 17.
15 A. W. Johnson and R. T. Amel, *J. Org. Chem.*, 1969, **34**, 1240.
16 S. Miyano, N. Abe, K. Sumoto and K. Teramoto, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1146.
17 C. S. Davis, G. L. Jenkin, A. M. Knevel and C. Paget, *J. Pharm. Sci.*, 1962, **51**, 840.

Paper 1/01026C
Received 5th *March* 1991
Accepted 15th *March* 1991