A New Synthesis of 4*H*-1,4-Thiazines and Benzothiazines

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We have previously reported[1] the facile reaction of 2,3-dihydro-1,3-benzothiazoles, e.g. **1**, with sulphuryl chloride to give 1,4-benzothiazines by way of a ring-opened sulphenyl chloride. In the present paper we wish to describe an alternative route to this heterocyclic system involving an acid-catalysed rearrangement of dihydrobenzothiazole 1-oxides **2** which is reminiscent of the now-classical conversion of penicillin sulphoxides into cephalosporins[2].

The sulphoxides **2** were conveniently prepared by oxidation of the corresponding 3-acetyl-2,3-dihydro-1,3-benzothiazoles[1] **1** with *m*-chloroperbenzoic acid in chloroform at 0°. Under these conditions, unsymmetrical 2-substituted dihydrobenzothiazoles gave a mixture of two diastereoisomeric sulphoxides, one of which was preponderant (*trans* to the larger group, Table 2).

Attempts to achieve the ring-expansion of **2** by thermal rearrangement in aprotic solvents as described[3] for the analogous transformation of 1,3-dithiolane 1-oxides into dihydro-1,4-dithiins were unsuccessfull. Eventually, the sulphoxides **2** could be converted into the corresponding 1,4-benzothiazines **4** (Table 1) in 40–60% yields by heating in anhydrous toluene in the presence of *p*-toluenesulphonic acid.

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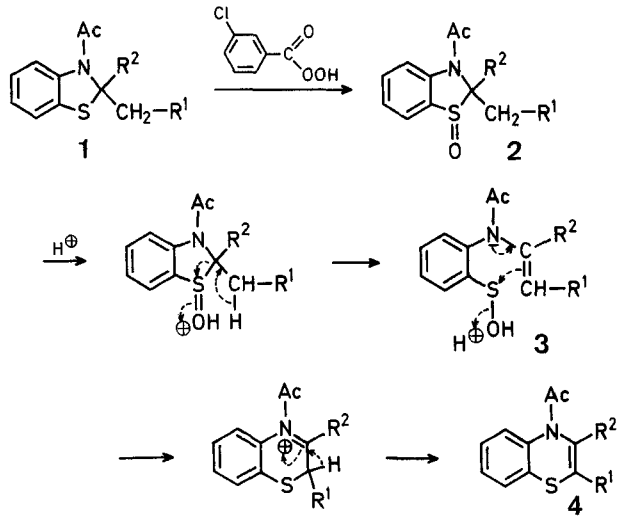
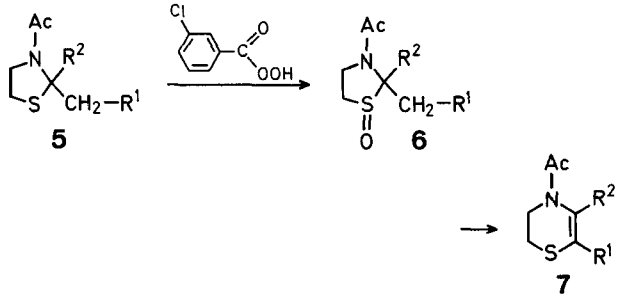


A possible pathway accounting for the formation of **4** is shown in the preceding scheme and involves an acid-catalysed ring-opening of the sulphoxide **2** to generate the sulphenic acid intermediate **3**, followed by ring-closure. Such a mechanism differs from that proposed for the ring-expansion of 1,3-dithiolane oxides requiring an initial six-electron [2,3] sigmatropic rearrangement to give the analogous sulphenic acid intermediate. Indeed, the ring-expansion of the dihydrobenzothiazole 1-oxides **2** proceeds equally well with either the *cis* or the *trans* isomers, while a sigmatropic process would be possible only for the *cis* configuration. Consequently the reaction is likewise applicable to both *cis* and *trans* sulphoxides and does not require the time-consuming fractionation of the stereoisomers arising by oxidation of parent dihydrobenzothiazoles.

Thus, for example, treatment of 2-ethyl-2-phenyl-2,3-dihydrobenzothiazole(**1c**) with *m*-chloroperbenzoic acid afforded *cis* and *trans* sulphoxides **2d** in similar amounts, and their mixture was directly converted into the corresponding benzothiazines **4c** under the usual conditions (37% yield).

It is notheworthy that the ring-expansion of the same 2,3-dihydrobenzothiazole **1c** with sulphuryl chloride afforded the corresponding benzothiazine **4c** in poor yield because of the concomitant formation of a dimeric product[4].

Apart from this case, no substantial difference was observed in the ring enlargement reactions of the dihydrobenzothiazoles[1] via sulphoxides or via chlorosulphonium salts, including that of the spirane compound **1d** which gave the expected tetrahydrophenothiazines **4d** and **4d'** in the same molar ratio (1 : 2). The general character of the described reaction is further substantiated by its applicability to the synthesis of simple 1,4-thiazines **7** (Table 1), which can be similarly obtained by acid-catalysed ring-expansion of the corresponding tetrahydrothiazole 1-oxides **6**.



2,2-Disubstituted 3-Acetyl-2,3-dihydro-1,3-benzothiazole 1-Oxides (2a–d); General Procedure:

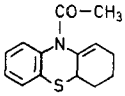
To a solution of the 3-acetyl-2,3-dihydro-1,3-benzothiazole **1** (10 mmol) in anhydrous chloroform (50 ml) at 0°, *m*-chloroperbenzoic acid (10 mmol) in anhydrous chloroform (150 ml) is added drop-wise over a period of ~ 60 min. After the addition, the reaction mixture is washed with aqueous sodium hydrogen carbonate and water, dried over anhydrous sodium sulphate, and evaporated under reduced pressure. The oily residue is crystallised from the appropriate solvent directly (**2a, d**) or after fractionation on a column of silica gel, using benzene/ethyl acetate (3:7) (**2b**) or dichloromethane/ethyl acetate (7:3) (**2c**) as eluent.

The tetrahydrothiazole 1-oxides (**6a–b**) are obtained by essentially the same procedure as described above.

Synthesis of 4-Acetyl-4*H*-1,4-benzothiazines (4a–d) and Thiazines (7a–b); General Procedure:

A solution of 3-acetyl-2,3-dihydro-1,3-benzothiazole 1-oxides (**2a–d**; 1 mmol) and *p*-toluenesulphonic acid (5 mg) in toluene (10 ml) is heated under reflux with stirring for 30 min. After cooling, the reaction mixture is diluted with ethyl acetate (20 ml) and washed with aqueous sodium hydrogen carbonate and water. The organic layer is dried over anhydrous sodium sulphate and evaporated under reduced pressure. The oil is purified by preparative T.L.C. on silica gel to give, after crystallisation, the 4*H*-1,4-benzothiazines **4a–d**; yield: ~ 50%.

Table 1. Ring-Expansion Reactions of 2,3-Dihydro-1,3-benzothiazole 1-Oxides (**2a–d**) and 2,3,4,5-Tetrahydro-1,3-thiazole 1-Oxides (**6a–b**)

Product No.	R^1	R^2	Yield [%]	m.p.[a] (solvent)	Molecular formula[b] or Lit. m.p.
4a	H	CH_3	46	oil	oil[1]
4b	H	C_6H_5	53[c], 59[d]	oil	oil[1]
4c	CH_3	C_6H_5	37	161–162° (C_2H_5OH)	$C_{17}H_{15}NOS$[e] (281.4)
4d	$-(CH_2)_4-$		23	141–142° (C_2H_5OH)	139–140°[1]
4d'			40	94–95° (C_2H_5OH)	91–92°[1]
7a	H	CH_3	44	71–72° (hexane)	$C_7H_{11}NOS$[f] (153.3)
7b	$-(CH_2)_4-$		42	oil	$C_{10}H_{15}NOS$[g] (197.3)

[a] Melting points were determined with a Kofler Apparatus and are uncorrected.

[b] Products **4c** and **7b** gave satisfactory microanalyses (C ±0.23, H ±0.07, N ±0.11).

[c] From the *cis*-isomer **2b**.

[d] From the *trans*-isomer **2b'**.

[e] M.S.: *m/e* for $M^+ = 281.0842$ (calc. 281.0874).
I.R. ($CHCl_3$): $\nu = 1670\,cm^{-1}$ (C=O).
^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.4$ (m, 9 H_{arom}); 2.20 (s, 3H, $-COCH_3$); 1.88 ppm (s, 3H, $=C-CH_3$).

[f] M.S.: *m/e* for $M^+ = 157.0561$ (calc. 157.0553).
I.R. ($CHCl_3$): $\nu = 1650\,cm^{-1}$ (C=O).
^{1}H-N.M.R. (CCl_4): $\delta = 5.50$ (m, 1H, $=CH-$); 3.7 (m, 2H, $S-CH_2$); 2.9 (m, 2H, $N-CH_2$); 2.08 (d, 3H, $J = 1$ Hz, $=CH-CH_3$); 2.02 ppm (s, 3H, $-COCH_3$).

[g] M.S.: *m/e* for $M^+ = 197.0874$ (calc. 197.0858).
I.R. ($CHCl_3$): $\nu = 1640\,cm^{-1}$ (C=O).
^{1}H-N.M.R. (CCl_4): $\delta = 3.62$ (m, 2H, $-S-CH_2$); 3.02 (m, 2H, $N-CH_2$); 1.99 (s, 3H, $-COCH_3$); 2.7–1.5 ppm [cm, $-(CH_2)_4-$]

Table 2. 3-Acetyl-2,3-dihydro-1,3-benzothiazole 1-Oxides (**2a–d**) and 3-Acetyl-2,3,4,5-tetrahydrothiazole 1-Oxides (**6a–b**)

Product	Yield [%]	m.p.[a] (solvent)	I.R.[b] ν [cm^{-1}] C=O and S=O	^{1}H-N.M.R.[c] δ [ppm]	M.S.[d] *m/e* for M^+ (calc.)
2a	72	115–116° (CCl_4)	1680, 1030	8.0–7.0 (m, $4H_{arom}$); 2.45 (s, 3H, $-COCH_3$); 2.0 (s, 3H, CH_3 *cis*); 1.45 (s, 3H, CH_3 *trans*)	223.0666 (223.0667)
2b'[e]	70	oil	1680, 1050	8.1–7.0 (m, $9H_{arom}$); 2.24 (s, 3H, $-COCH_3$); 2.18 (s, 3H, CH_3)	285.0789 (285.0823)
2b''[f]	13	134–135° (hexane)	1680, 1060	8.4–7.0 (m, $9H_{arom}$); 1.98 (s, 3H, $-COCH_3$); 1.85 (s, 3H, CH_3)	285.0794 (285.0823)
2c'[e]	41	oil	1680, 1050	8.3–7.1 (m, $9H_{arom}$); 3.15 (q, 1H, J = 7 Hz, CH_2); 2.57 (q, 1H, J = 7 Hz, CH_2); 2.11 (s, 3H, $-COCH_3$); 1.10 (t, 3H, J = 7 Hz, CH_3)	299.0955 (299.0980)
2c''[f]	30	125–126° (CCl_4)	1680, 1080	8.5–7.0 (m, $9H_{arom}$); 2.65 (q, 2H, J = 7 Hz, CH_2); 1.73 (s, 3H, $-CO-CH_3$); 0.83 (t, 3H, J = 7 Hz, CH_3)	299.0961 (299.0980)
2d	81	153–154° (cyclohexane)	1670, 1040	8.0–7.0 (m, $4H_{arom}$); 2.43 (s, 3H, $-CO-CH_3$); 3.2–1.1 [m, $-(CH_2)_5-$]	263.0978 (263.0980)
6a	53	oil	1660, 1060	4.1 (m, 2H, $-N-CH_2$); 2.9 (m, 2H, $-S-CH_2$); 2.05 (s, 3H, $-CO-CH_3$); 1.68 (s, 3H, CH_3 *cis*); 1.52 (s, 3H, CH_3 *trans*)	175.0665 (175.0667)
6b	85	120–121° (CCl_4)	1650, 1050	4.2 (m, 2H, $-N-CH_2$); 2.9 (m, 2H, $-S-CH_2$); 2.10 (s, 3H, $-CO-CH_3$); 3.2–1.0 [m, $-(CH_2)_5-$]	215.0953 (215.0980)

[a] Melting points were determined with a Kofler apparatus and are uncorrected.
[b] The I.R. spectra were recorded on a Perkin-Elmer 137 spectrophotometer in $CHCl_3$ (**2a, 2b', 2b'', 2c', 2c'', 2d, 6b**) or in CCl_4 (**6a**) solution.
[c] The ^{1}H-N.M.R. spectra were recorded on a Perkin-Elmer R-12A and R-32 spectrometers in $CDCl_3$ (**2a, 2b'', 2d, 6b**) or in CCl_4 (**2b', 2c', 2c'', 6a**) solution.
[d] Determined on a high resolution mass spectrometer (AEI-MS 902).
[e] C_6H_5 *trans* to sulphoxide.
[f] C_6H_5 *cis* to sulphoxide.

The 5,6-dihydro-4*H*-1,4-thiazines **7a–b** are obtained from the parent tetrahydro-1,3-thiazole 1-oxides **6a–b** by essentially the same procedure as described above.

3-Acetyl-2,2-dimethyl-2,3,4,5-tetrahydro-1,3-thiazole (5a):
A suspension of 2,2-dimethyl-2,3,4,5-tetrahydrothiazole hydrochloride[5] (5 mmol) in acetic anhydride (10 ml) and pyridine (2 ml) is heated on a water bath (50°) for 5–10 min till the solid dissolves and the resultant solution is stirred at room temperature for 4 h. The reaction mixture is concentrated in vacuo to a small volume, diluted with diethyl ether, and washed with 1 normal aqueous hydrochloric acid and water. The organic layer is evaporated to dryness under reduced pressure to afford **5a** as a colourless oil which is used without further purification; yield: 89%.

$C_7H_{13}NOS$	calc.	C 52.80	H 8.23	N 8.80
(159.3)	found	52.91	8.13	8.64

M.S.: *m/e* for M^+ = 159.0725 (calc. 159.0718).

I.R. ($CHCl_3$): ν = 1645 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.88 (t, 2H, J = 6 Hz, $N-CH_2$); 2.98 (t, 2H, J = 6 Hz, $-S-CH_2$); 2.07 (s, 3H, $-COCH_3$); 1.80 ppm (s, 6H, CH_3).

Compound **5b** is prepared similarly; yield: 70%; m.p. 92–94° (cyclohexane).

$C_{10}H_{17}NOS$	calc.	C 60.26	H 8.60	N 7.03
(199.3)	found	60.13	8.67	6.56

M.S.: *m/e* for M^+ = 199.1043 (calc. 199.1031).

I.R. ($CHCl_3$): ν = 1645 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.90 (t, 2H, J = 6 Hz, $N-CH_2$); 2.86 (t, 2H, J = 6 Hz, $-S-CH_2$); 2.08 (s, 3H, $-COCH_3$); 3.2–1.0 ppm [cm, $-(CH_2)_5-$].

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