A Novel Route to 4*H*-1,4-Benzothiazines by Ring-Expansion of 2,3-Dihydro-1,3-benzothiazoles

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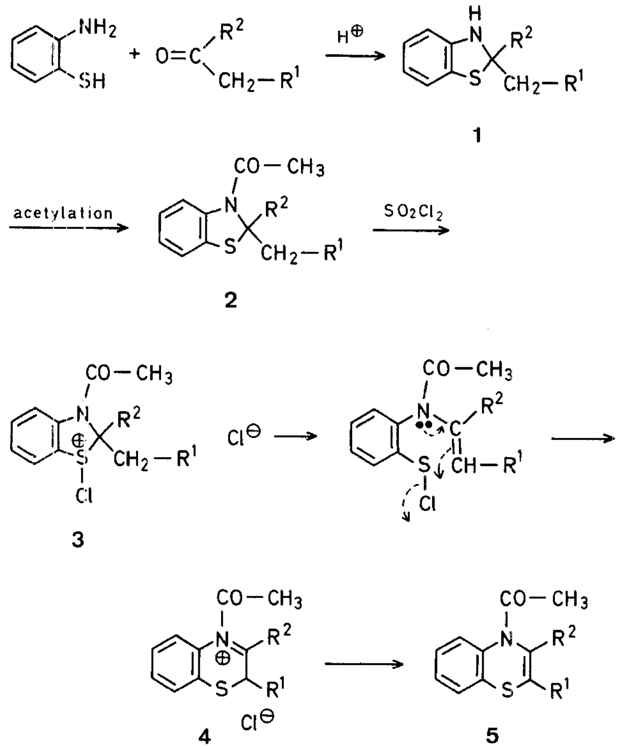
Appropriately substituted cyclic sulphides have been reported to undergo ring-expansion reactions via the *S*-chlorosulphonium salts, formed *in situ* by chlorination in non-aqueous media. Thus, for example, 1,3-oxathiolanes and 1,3-dithiolanes are converted into dihydro-1,4-oxathiins and dihydro-1,4-dithiins by treatment with molecular chlorine and ethyl *N*-chlorocarbamate, respectively[1,2].

The present paper describes an extension of this type of reaction to 2,3-dihydro-1,3-benzothiazoles **2**[3] which, on treatment with sulphuryl chloride, are readily converted into the novel 4*H*-1,4-benzothiazines **5**, presumably by way of **3** (Scheme **A**).

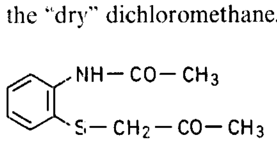
The 3-acetyl-2,3-dihydro-1,3-benzothiazoles **2a–g**, required in the present investigation, were conveniently prepared by acid-catalysed condensation of *o*-aminothiophenol with the appropriate ketones, and subsequent acetylation of the resulting 2,3-dihydro-1,3-benzothiazoles **1a–g**. Physical properties and analytical data of these compounds are reported in Table 2.



Scheme **A**

In a typical experiment 3-acetyl-2,2-dimethyl-2,3-dihydrobenzothiazole (**2a**) was treated with sulphuryl chloride (1.1 equiv) in anhydrous dichloromethane at room temperature and the hydrogen chloride formed was swept from the mixture with a flow of nitrogen. After 30 minutes, fractionation of the reaction mixture by chromatography on silica gel led to the isolation of two new products, the major of which was identified as 4-acetyl-3-methyl-4*H*-1,4-benzothiazine (**5a**) by spectral analysis (Table 1). Chemical evidence for this assignment was provided by reaction of **5a** with boiling 6 normal hydrochloric acid which gave 3-methyl-2*H*-1,4-benzothiazine hydrochloride, identified by comparison with an authentic sample[4].

The minor product, $C_{11}H_{13}NO_2S$ (m.p. 79–80°; from carbon tetrachloride), showed diagnostic I.R. absorptions (in carbon disulphide) at 3290 (NH, amide), 1724 sh (CO, alicyclic ketone), and 1708 cm^{-1} (CO, amide) and was identified as the acetamidoketone **6** on the basis of its ^{1}H-N.M.R. spectrum (in deuteriochloroform), characterised by two methyl singlets at $\delta = 2.12$ and 2.25, and a methylene singlet at $\delta = 3.62$. Accordingly, the product was assigned structure **6** arising most probably by ring-opening of the benzothiazinyl cation **3** ($R^1 = H$; $R^2 = CH_3$) by traces of water in the "dry" dichloromethane.



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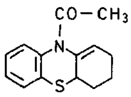
It is noteworthy that, on heating in benzene with *p*-toluenesulphonic acid as catalyst, **6** underwent ring-closure to give the benzothiazine **5a** in good yield (66%).

As illustrated in Table 1, the ring-expansion of the 2,3-dihydro-1,3-benzothiazoles **2b, c, d, f** with sulphuryl chloride proceeded similarly to give the expected 4*H*-1,4-benzothiazines **5b, c, d, f**, while, in the case of compound **2e**, the

Table 1. Ring Expansion Reactions of 2,3-Dihydro-1,3-benzothiazoles **2a–g** with Sulphuryl Chloride

Prod-uct	R^1	R^2	Yield [%]	m.p.[a] (solvent)	Molecular formula[b]	I.R.[c] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R.[d] δ [ppm]	U.V. (CH_3OH)[e] λ [nm] (log ε)	M.S.[f] m/e (M^+) (calc.)
5a	H	CH_3	52	oil	$C_{11}H_{11}NOS$ (205.3)	1660	7.3 (m, 4 H_{arom}); 6.30 (q, 1 H, $J=1$ Hz, =CH—); 2.24 (d, 3 H, $J=1$ Hz, =CH—CH_3); 2.08 (s, 3 H, —CO—CH_3)	206 (4.16); 230 (4.06); 260 (4.02)	205.0564 (205.0561)
5b	H	C_6H_5	58	oil	$C_{16}H_{13}NOS$ (267.4)	1690	7.9–6.9 (cm, 9 H_{arom}); 6.70 (s, 1 H, =CH—); 1.83 (s, 3 H, —CO—CH_3)	208 (4.35); 230 sh (4.17), 280 (3.49)	267.0729 (267.0717)
5c	H	4-H_3CO—C_6H_4	60	111–112° (C_2H_5OH)	$C_{17}H_{15}NO_2S$ (297.4)	1695	7.8–6.6 (cm, 8 H_{arom}); 6.56 (s, 1 H, =CH—); 3.70 (s, 3 H, OCH_3); 1.82 (s, 3 H, —CO—CH_3)	216 (4.39); 253 (4.07); 310 (4.17)	297.0798 (297.0823)
5d	H	4-O_2N—C_6H_4	70	176–177° (C_2H_5OH)	$C_{16}H_{12}N_2O_3S$ (312.4)	1680	8.19 and 7.60 (AB-q, 4 H_{arom}, $J=9$ Hz); 7.4 (cm, 4 H_{arom}); 7.10 (s, 1 H, =CH—), 2.02 (s, 3 H, —CO—CH_3)	207 (4.32); 231 (4.14); 260 (4.06); 356 (4.11)	312.0578 (312.0568)
5e	H	C_6H_5—CH_2	16	113–114° (C_2H_5OH)	$C_{17}H_{15}NOS$ (281.4)	1660	7.7–7.0 (cm, 9 H_{arom}); 6.75 (t, 1 H, $J=1$ Hz, =CH—); 4.09 (d, 2 H, $J=1$ Hz, CH_2); 2.22 (s, 3 H, —CO—CH_3)	210 (4.34); 233 (4.37); 255 (4.40)	281.0863 (281.0874)
5e′	C_6H_5	CH_3	47	133–134° (C_2H_5OH)	$C_{17}H_{15}NOS$ (281.4)	1665	7.4 (cm, 9 H_{arom}); 2.18 (s, 3 H, =CH—CH_3); 2.15 (s, 3 H, —CO—CH_3)	211 (4.30); 220 (4.25); 269 (3.94); 288 sh (3.84)	281.0863 (281.0874)
5f	—(CH_2)$_3$—		35	105–106° (C_2H_5OH)	$C_{13}H_{13}NOS$ (231.3)	1670	7.1 (m, 4 H_{arom}); 2.08 (s, 3 H, —CO—CH_3); 3.2–1.8 [cm, —(CH_2)$_3$—]	209 (4.10); 236 (3.87); 263 (3.87); 285 (3.57)	231.0738 (231.0718)
5g	—(CH_2)$_4$—		25	139–140° (C_2H_5OH)	$C_{14}H_{15}NOS$ (245.3)	1660	7.2 (m, 4 H_{arom}); 2.06 (s, 3 H, —CO—CH_3); 3.1–1.1 [cm, —(CH_2)$_4$—]	218 (4.22); 256 (3.94)	245.0889 (245.0875)
5g′			41	91–92° (hexane)	$C_{14}H_{15}NOS$ (245.3)	1655	7.6–6.9 (cm, 4 H_{arom}); 5.89 (dt, 1 H, $J=1$, 4 Hz, =CH—); 4.18 (m, 1 H, >CH); 2.14 (s, 3 H, —CO—CH_3); 2.4–1.4 [cm, —(CH_2)$_3$—]	209 (4.13); 233 (4.25); 254 sh (3.98); 292 (3.11)	245.0885 (245.0875

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

[b] All products gave satisfactory microanalyses (C ±0.31%, H ±0.18%, N ±0.21%); analyses were performed by the Laboratorio per la Chimica di Molecole di Interesse Biologico del C.N.R., Arco Felice (Napoli).

[c] The I.R. spectra were recorded on a Perkin-Elmer 137 spectrophotometer in $CHCl_3$ (**5a, d, e, f, g**) or in CCl_4 (**5b, c**) solution.

[d] The ^{1}H-N.M.R. were recorded on a Perkin-Elmer R-12A and R-32 spectrometers in $CDCl_3$ (**5a, d, e, g**) or in CCl_4 (**5b, c, f**) solution.

[e] The U.V. spectra were recorded on a Perkin-Elmer 402 spectrophotometer.

[f] Determined on a high resolution mass spectrometer (AEI-MS 902).

Table 2. 2,3-Dihydro-1,3-benzothiazoles **1a–g** and *N*-Acetyl-2,3-dihydro-1,3-benzothiazoles **2a–g**

Prod-uct[a]	Yield [%]	m.p.[b] (solvent)	Molecular formula[c] or Lit. m.p.	I.R.[d] ν [cm^{-1}] NH or C=O	^{1}H-N.M.R.[e] δ [ppm]	M.S.[f] m/e (M^+) (calc.)
1a	84	45–46° (hexane)	46–48°[5]	3315	7.3–6.4 (cm, 4 H_{arom}); 3.85 (bs, 1 H, NH, removed by D-exchange); 1.62 (s, 6 H, CH_3)	—
1b	75	59–60° (C_2H_5OH)	b.p.: 252–255°/20[6]	3350	7.7–6.4 (cm, 9 H_{arom}); 3.95 (bs, 1 H, NH, removed by D-exchange); 1.90 (s, 3 H, CH_3)	—
1c	80	57–58° (C_2H_5OH)	$C_{15}H_{15}NOS$ (257.4)	3360	7.6–6.3 (cm, 8 H_{arom}); 3.95 (bs, 1 H, NH, removed by D-exchange); 3.56 (s, 3 H, OCH_3); 1.85 (s, 3 H, CH_3)	257.0860 (257.0874)
1d	82	103–104° (CH_3OH)	$C_{14}H_{12}N_2O_2S$ (272.3)	3320	8.13 and 7.76 (AB-q, 4 H_{arom}, $J=9$ Hz); 6.9 (cm, 4 H_{arom}); 4.20 (bs, 1 H, NH, removed by D-exchange); 2.06 (s, 3 H, CH_3)	272.0638 (272.0620)

Table 2. (Continued)

Product[a]	Yield [%]	m.p.[b] (solvent)	Molecular formula[c] or Lit. m.p.	I.R.[d] ν [cm⁻¹] NH or C=O	¹H-N.M.R.[e] δ [ppm]	M.S.[f] m/e (M⁺) (calc.)
1e	80	56–57° (C_2H_5OH)	59–61°[7]	3370	7.3–6.3 (cm, 9 H_{arom}); 3.72 (bs, 1 H, NH, removed by D-exchange); 3.06 (dd, 2 H, J = 18 Hz, CH_2); 1.54 (s, 3 H, CH_3)	—
1f	74	53–54° (C_2H_5OH)	57–58°[5]	3340	7.0–6.4 (cm, 4 H_{arom}); 3.75 (bs, 1 H, NH, removed by D-exchange); 2.4–1.5 [cm, —$(CH_2)_4$—]	—
1g	90	110–111° (CCl_4)	114–115°[5]	3340	7.2–6.5 (cm, 4 H_{arom}); 3.95 (bs, 1 H, NH, removed by D-exchange); 2.5–1.1 [cm, —$(CH_2)_5$—]	—
2a	90	49–50° (C_2H_5OH)	$C_{11}H_{13}NOS$ (207.3)	1670	7.0 (m, 4 H_{arom}); 2.27 (s, 3 H, —CO—CH_3); 1.88 (s, 6 H, CH_3)	207.0711 (207.0718)
2b	65	86–87° (C_2H_5OH)	81–82°[8]	1660	7.8–6.9 (cm, 9 H_{arom}); 2.83 (s, 3 H, —CO—CH_3); 2.07 (s, 3 H, CH_3)	—
2c	82	76–77° (CH_3OH)	$C_{17}H_{17}NO_2S$ (299.4)	1670	7.8–6.7 (cm, 8 H_{arom}); 3.75 (s, 3 H, OCH_3); 2.27 (s, 3 H, —CO—CH_3); 2.00 (s, 3 H, CH_3)	299.0932 (299.0980)
2d	63	111–112° (C_2H_5OH)	$C_{16}H_{14}N_2O_3S$ (314.4)	1670	8.19 and 7.72 (AB-q, 4 H_{arom}, J = 9 Hz); 7.2 (cm, remaining 4 H_{arom}); 2.34 (s, 3 H, —CO—CH_3); 2.32 (s, 3 H, CH_3)	314.0725 (314.0743)
2e	76	58–59° (C_2H_5OH)	$C_{17}H_{17}NOS$ (283.4)	1670	7.3–6.7 (cm, 9 H_{arom}); 3.34 (s, 2 H, CH_2); 2.25 (s, 3 H, —CO—CH_3); 1.94 (s, 3 H, CH_3)	283.0995 (283.1030)
2f	85	32–33° (C_2H_5OH)	$C_{13}H_{15}NOS$ (233.3)	1670	6.9 (m, 4 H_{arom}); 2.24 (s, 3 H, —CO—CH_3); 3.1–1.0 [cm, —$(CH_2)_4$—]	233.0864 (233.0874)
2g	80	46–47° (hexane)	$C_{14}H_{17}NOS$ (247.4)	1660	7.4–6.9 (cm, 4 H_{arom}); 2.34 (s, 3 H, —CO—CH_3); 3.1–1.1 [cm, —$(CH_2)_5$—]	247.1026 (247.1031)

[a] Reaction time: 14 h for **1a**; 20 h for **1d, e, g**; 24 h for **1b, c, f**; 4 h for **2c, f, g**; 6 h for **2a, b, d, e**.

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

[c] All new compounds gave satisfactory microanalyses (C ±0.33%, H ±0.18%, N ±0.21%).

[d] The I.R. spectra were recorded on a Perkin-Elmer 137 spectrophotometer in $CHCl_3$ (**1c, f** and **2a, b, c, d, e, g**) or in CCl_4 (**1a, b, d, e, g** and **2f**) solution.

[e] The ¹H-N.M.R. spectra were recorded on a Perkin-Elmer R-12A and R-32 spectrometers in $CDCl_3$ (**1a, d, g** and **2a, b, c, d, g**) or in CCl_4 (**1b, c, f, e** and **2e, f**) solution.

[f] Determined on a high resolution mass spectrometer (AEI-MS 902).

reaction afforded two isomeric 1,4-benzothiazines **5e** and **5e′** in a ratio 3:1. Chlorination of the spirane analogue **2g** also gave a mixture of two isomeric products (~1:2 ratio) which were identified as the novel tetrahydrophenothiazines (**5g** and **5g′**) on the basis of their spectral properties.

2,2-Disubstituted-2,3-dihydro-1,3-benzothiazoles 1a–g; General Procedure:

A solution of 2-aminothiophenol (0.1 mol), the appropriate ketone (0.1 mol) and *p*-toluenesulphonic acid (0.5 g) in benzene (200 ml) is refluxed with stirring for 14–24 h while the water formed is continuously separated. After cooling, the reaction mixture is filtered and the solvent removed under reduced pressure. The resulting residue is crystallised from the appropriate solvent directly or after purification on a column of silica gel (eluent: benzene or chloroform). All compounds gave I.R., M.S., and ¹H-N.M.R. spectra fully consistent with the assigned structures.

3-Acetyl-2,2-disubstituted-2,3-dihydro-1,3-benzothiazoles 2a–g; General Procedure:

A solution of the 2,3-dihydro-1,3-benzothiazole **1** (0.05 mol) in acetic anhydride (20 ml) is stirred at 100° for 4–6 h. Removal of the solvent under reduced pressure leaves an oil which is crystallised from the appropriate solvent after purification on a column of silica gel (eluent: benzene or chloroform); except for **2b** and **2c** which can be directly crystallised from ethanol and methanol, respectively. Analytical and spectral data are reported in Table 2.

Synthesis of 4-Acetyl-4*H*-1,4-benzothiazines 5a–g; General Procedure:

To a solution of the 3-acetyl-2,3-dihydro-1,3-benzothiazole **2** (1 mmol) in anhydrous dichloromethane (15 ml) at room temperature, sulphuryl chloride (0.1 ml) in anhydrous dichloromethane (5 ml) is added dropwise over a period of ~40 minutes, under nitrogen. After the addition, the reaction mixture is diluted with chloroform (20 ml) and washed with water and aqueous sodium hydrogen carbonate. The oily residue obtained after evaporation of the organic layer is purified by preparative T. L. C. on silica gel to give, after crystallisation, the 4*H*-1,4-benzothiazines **5a–g** in ~60% yield. All compounds gave spectral data fully consistent with the assigned structures.

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