2*H*-Benzimidazoles (Isobenzimidazoles). Part 6.[1] Sulfur Derivatives

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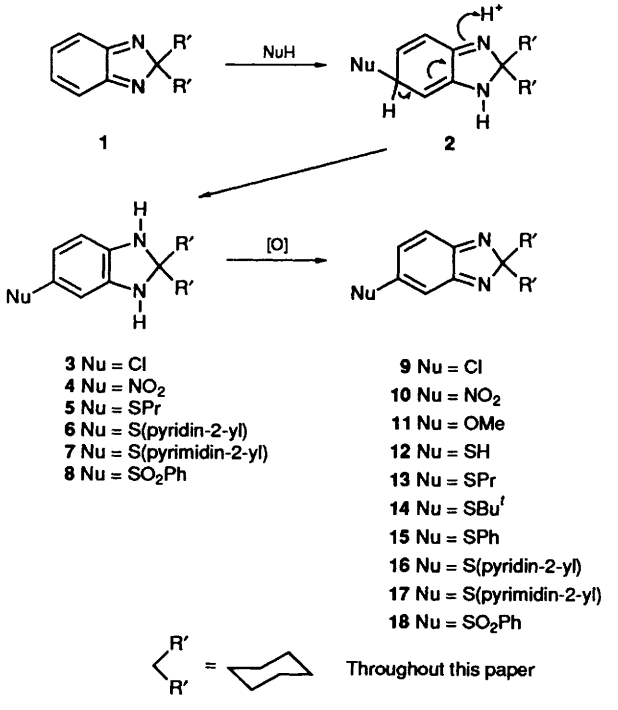
The products obtained by treating 2*H*-benzimidazole-2-spirocyclohexane **1** or its 5-chloro derivative **9** with various thiols (PrSNa, Bu^{t}SNa, PhSNa, pyridine-2-thiol, or pyrimidine-2-thiol) depend on the reaction conditions. Monosubstitution is possible and any number of alkylthio groups can be introduced up to four.

5-Phenylsulfonyl- **18** and 5-nitro-2*H*-benzimidazole-2-spirocyclohexane **10** react with pyridine-2-thiol or pyrimidine-2-thiol in position-4 whilst the 5-(pyridin-2-ylthio) derivative **16** reacts with sodium benzenesulfinate in position-6. In all cases the products isolated were the 1,3-dihydro compounds **26**, **38**, **39** or **21**, respectively.

Previously we have studied the reactions of 2*H*-benzimidazole-2-spirocyclohexane **1**[2–4] and a number of its derivatives[1–7] with various sulfur nucleophiles. These reactions proceed (Scheme 1) *via* an initial Michael-type 1,4-conjugate addition



Scheme 1

and a prototropic shift in the adduct **2**. Where Nu is an electron-withdrawing group (*e.g.* $PhSO_2$), 1,3-dihydro compounds are isolable but, where Nu is an electron-donating group (*e.g.* RS), these are oxidised *in situ*. In view of the fact that the parent system **1** is extremely reactive towards thiols, which hitherto has prevented the isolation of monosubstituted products,[2–4] and with an alternative synthesis of anthelminthics such as albendazole **19** in mind, we decided to study these reactions in greater detail.

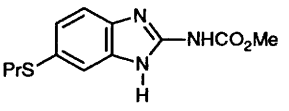
For reactions of 1 equiv. of sodium propane thiolate with the parent compound **1** we have used propanol, acetone, dimethyl sulfoxide (DMSO), and diethyl ether as solvents. Only in propanol at −10 to 0 °C could a good yield (60%) of the 5-monosubstituted product **13** be obtained (see Experimental section for details). Conditions have been found also for the synthesis of 5-*tert*-butylthio- **14** (70% yield) and 5-phenylthio-2*H*-benzimidazole-2-spirocyclohexane **15** (50%). Compound **15** (54%) was prepared similarly from 5-chloro-2*H*-benzimidazole-2-spirocyclohexane **9** (PhSNa–PrOH—2.5 h at ambient temperature).

Pyridine-2-thiol, a less reactive thiol, when treated with compound **1** (MeOH at ambient temperature) gave mainly 1,3-dihydro-5-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **6** (69% yield) together with a trace (3%) of a disubstituted compound **20** whose structure was proved by converting it into the selenadiazole derivative **25**.[2] 4-H and 7-H of this product appeared as a singlet in its ^{1}H NMR spectrum at δ 8.05. Compound **6** was converted similarly into benzoselenadiazole **24**.

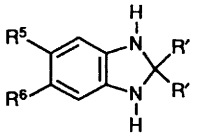
2*H*-Benzimidazole-2-spirocyclohexane **1** reacted similarly with pyrimidine-2-thiol, to give mainly compound **7** (62% yield). The small amount (5.5%) of disubstituted product isolated in this case, however, is assigned structure **27** on the basis of an examination of its ^{1}H NMR spectrum.

Presumably a small amount of compound **6** is oxidised to the 2*H*-benzimidazole **16** whose 5-(pyridin-2-ylthio) group directs a second Michael type 1,4-conjugate addition into position-6, yielding compound **20**. Likewise, compound **7** is oxidised presumably to give a small amount of the 2*H*-benzimidazole **17** but, in this case, the 5-(pyrimidin-2-ylthio) group directs the incoming nucleophile to undergo a Michael-type 1,6-conjugate addition at position-4, involving an intermediate of type **28** and leading to the formation of compound **27**. Both compounds, **6** and **7**, were oxidised with manganese dioxide in dichloromethane to give compound **16** or **17**, respectively.

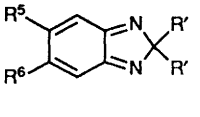
2*H*-Benzimidazole-2-spirocyclohexane **1** reacted with 1 or 2 equiv. of sodium propanethiolate in propanol at ambient temperature to give a mixture of 5-propylthio- **13** (29% yield), 5,6-dipropylthio- **22** (20%), 4,6-dipropylthio- **29** (17%) and 4,5,7-tripropylthio-2*H*-benzimidazole-2-spirocyclohexane **31** (18%). 5-Chloro-2*H*-benzimidazole-2-spirocyclohexane **9** gave a similar mixture—**13** (40%), **22** (20%), **29** (12%) and **31** (8%)—when it was treated with 1 equiv. of sodium propanethiolate in refluxing propanol for 2 h. Six equiv. of sodium propanethiolate reacted with compound **1** in DMSO, heated under reflux for 3 h, to give a mixture of compounds **22** (40%), **29** (27%) and **31** (12%). Separation of the components of these mixtures proved extremely tedious. However, this was achieved by flash chromatography on silica[8] (see Experimental section for details). These compounds, which are unstable to light, heat and air and decompose during chromatography on alumina or silica, are all brightly coloured, ranging from bright yellow,



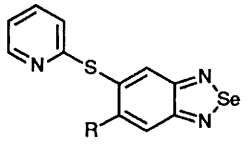
19



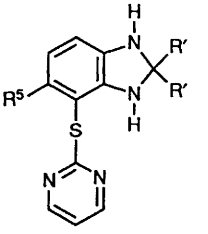
20 $R^5 = R^6 = S(pyridin\text{-}2\text{-}yl)$
21 $R^5 = S(pyridin\text{-}2\text{-}yl)$, $R^6 = SO_2Ph$



22 $R^5 = R^6 = SPr$
23 $R^5 = R^6 = SBu^t$

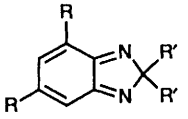


24 R = H
25 R = S(pyridin-2-yl)

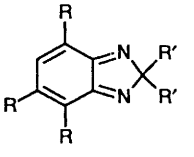


26 $R^5 = SO_2Ph$
27 $R^5 = S(pyrimidin\text{-}2\text{-}yl)$

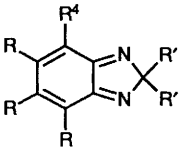
28



29 R = SPr
30 R = SBu^t



31 R = SPr
32 R = SBu^t



33 R = SPr, R^4 = H
34 R = R^4 = SPr
35 R = SBu^t, R^4 = H

through orange, to deep red. Most of them are fluorescent under UV irradiation.

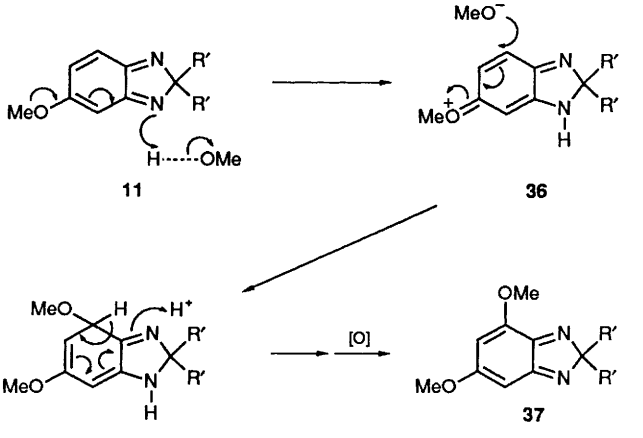
The 5-propylthio compound **13** was identical in all respects with a sample prepared by condensing commercial 4-propylthio-*o*-phenylenediamine with cyclohexanone at 50–60 °C followed by oxidation of the intermediate 1,3-dihydro compound **5** with aqueous potassium permanganate under phase-transfer conditions. When the 5-propylthio compound **13** was treated with 2 equiv. of sodium propanethiolate in anhydrous propanol, it gave a mixture of 5,6-dipropylthio- **22** (22%), 4,6-dipropylthio- **29** (11%), 4,5,6-tripropylthio- **33** (54%) and 4,5,7-tripropylthio-2*H*-benzimidazole-2-spirocyclohexane **31** (8%). With 4 equiv. of the reagent under identical reaction conditions, the same products were obtained together with 4,5,6,7-tetrapropylthio-2*H*-benzimidazole-2-spirocyclohexane **34** (23% yield).

The parent compound reacted with 2 equiv. of sodium 1,1-dimethylethanethiolate in anhydrous methanol to give a mixture of 5-*tert*-butylthio- **14** (43% yield), 5,6-di-*tert*-butylthio- **23** (19%), 4,6-di-*tert*-butylthio-**30** (4%) and 4,5,7-tri-*tert*-butylthio-2*H*-benzimidazole-2-spirocyclohexane **32** (7%).

The structures of the polythio-substituted 2*H*-benzimidazoles **22**, **23**, **29**–**33** and **35** (see below) were established as follows. The 4,6- **29** and **30** and 5,6-disubstituted compounds **22** and **23** could be identified from their mass and ^{1}H NMR spectroscopic data. The 4,5,6- **33** and **35** and 4,5,7-trisubstituted compounds **31** and **32** each display a singlet in the aromatic region of their ^{1}H NMR spectrum. They were distinguishable following further reaction of the 4,6- **29** and **30** and 5,6-disubstituted compounds **22** and **23** with sodium propanethiolate or 1,1-dimethylethanethiolate, respectively. 5,6-Dipropylthio-2*H*-benzimidazole-2-spirocyclohexane **22** was treated with 4 equiv. of sodium propanethiolate to give a mixture of starting material, 4,5,6-tripropylthio- **33** (16% yield), and 4,5,6,7-tetrapropylthio-2*H*-benzimidazole-2-spirocyclohexane **34** (42%). With 1 equiv. of sodium 1,1-dimethylethanethiolate the 5,6-disubstituted compound **23** gave only a small amount (3% yield) of the 4,5,6-trisubstituted compound **35**; the starting material was recovered in 75% yield. Presumably the third *tert*-butylthio group is introduced only with difficulty due to steric hindrance between the starting material and reagent.

Reaction of the 4,6-disubstituted compound **29** with 4 equiv. of sodium propanethiolate gave a mixture of the trisubstituted compounds **31** (7% yield) and **33** (12%) together with the tetrasubstituted product **34** (25%). Similarly, the 4,6-disubstituted compound **30** was treated with 1 equiv. of sodium 1,1-dimethylethanethiolate to give exclusively the 4,5,7-trisubstituted compound **32** (75% yield) together with starting material (17%).

Compounds **13** and **14** and **22** and **23** are formed presumably *via* successive Michael-type 1,4-conjugate additions followed by oxidation of the intermediate 1,3-dihydro compounds, as shown in Scheme 1. Formation of the 4,6-disubstituted compounds **29** and **30** can be rationalised by invoking a similar mechanism (see Scheme 2) to the one proposed to explain the



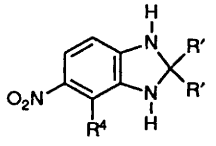
Scheme 2

formation of 4,6-dimethoxy-2*H*-benzimidazole-2-spirocyclohexane **37** from the 5-methoxy compound **11**.[2,3] The key intermediate is an oxonium ion **36**. The conversions **22** or **23** ⟶ **33** or **35** are the result of Michael-type 1,6-conjugate additions proceeding through intermediates akin to **28**. Similar intermediates are probably involved in conversions of the 5,6-disubstituted compound **22** into the 4,5,6-tri- **33** and 4,5,6,7-tetra-substituted **34** compounds by Michael-type 1,6-conjugate additions. The 4,6-disubstituted compounds **29** and **30** may react further either by a 1,4-conjugate or 1,6-conjugate addition process, leading to compounds **33** and **35** or **31** and **32**, respectively. Either 1,4-conjugate addition to compound **31** or 1,6-conjugate addition to compound **33** would account for formation of the tetrasubstituted product **35**. We have attempted but unsuccessfully to apply the HSAB concept[9] to explain our results.

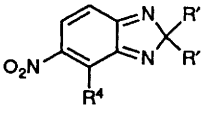
We had hoped to dealkylate the 5-*tert*-butylthio compound **14** as a route to 2*H*-benzimidazole-2-spirocyclohexane-5-thiol **12** and other 5-alkyl(and aryl)thio-substituted derivatives. However, its attempted dealkylation with sodium in pyridine, a technique used recently to completely dealkylate 1,2,4,5-tetra-isopropylthiobenzene,[10] produced only an intractable tar following addition of methyl iodide. Use of a mixture of hydrochloric acid and acetic acid [11] was similarly unsuccessful.

5-Phenylsulfonyl-2*H*-benzimidazole-2-spirocyclohexane **18** was treated with pyrimidine-2-thiol in dichloromethane in the presence of manganese dioxide, to give 5-phenylsulfonyl-4-(pyrimidin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **26** (23% yield) together with recovered starting material, whilst 5-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **16** was treated with sodium benzenesulfinate in the presence of acetic acid, to give 1,3-dihydro-6-phenylsulfonyl-5-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **21** (63% yield).

5-Nitro-2*H*-benzimidazole-2-spirocyclohexane **10** [12] was treated with either pyridine-2-thiol or pyrimidine-2-thiol to give good yields of the corresponding red 4-substituted 1,3-dihydro compound, **38** or **39**, respectively (*cf.* ref. 1). Oxidation of these compounds with manganese dioxide gives compound **40** (87% yield) or **41** (89%), respectively.



38 R^4 = S(pyridin-2-yl)
39 R^4 = S(pyrimidin-2-yl)



40 R^4 = S(pyridin-2-yl)
41 R^4 = S(pyrimidin-2-yl)

Experimental

IR spectra were recorded for liquid films or Nujol mulls between sodium chloride plates with a Perkin-Elmer 257 or 297 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, unless stated otherwise, using either a Varian EM360 (60 MHz), a Perkin-Elmer R32 (90 MHz), or a Bruker AC300 (300.13 MHz) instrument with tetramethylsilane as internal standard (*J* values are given in Hz), whilst EI mass spectra were recorded with a Kratos MS30 spectrometer. Reported molecular weights are given for the isotopes ^{35}Cl, ^{79}Br and ^{80}Se. Isotopic abundance ratios were as expected for the molecular formulae given for compounds containing these elements.

Chromatographic separations were carried out on columns packed with 100–250 mesh Camag basic alumina (pH 9.3–9.7) supplied by Fisons Ltd, silica M.F.C. of 60–120 mesh supplied by BDH Ltd, or Merck silica, Kieselgel 60 ASTM (of 230–400 mesh) (for flash chromatography) also supplied by BDH Ltd.

Light petroleum had b.p. 60–80 °C unless stated otherwise. Ether refers to diethyl ether. Solvents were dried by standard procedures. In all cases organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure using a rotary evaporator.

M.p.s were recorded with a Buchi m.p. apparatus and are uncorrected.

Microanalytical (C, H and N) results were supplied by Butterworth Laboratories Ltd of Teddington.

Details of reaction conditions, products, yields, physical properties and analytical data are given in Tables 1 and 2.

The following compounds were prepared by literature procedures: 1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane (80%), m.p. 138–140 °C (lit.,[13] m.p. 138 °C); 2*H*-benzimidazole-2-spirocyclohexane **1** (95%), m.p. 63–65 °C (lit.,[13] 64 °C); 5-chloro-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane **3** (80%), m.p. 83–85 °C (lit.,[3] 85 °C); 5-chloro-2*H*-benzimidazole-2-spirocyclohexane **9**, m.p. 57 °C (lit.,[3] m.p. 58 °C); 1,3-dihydro-5-phenylsulfonyl-2*H*-benzimidazole-2-spirocyclohexane **8** (72.5%), m.p. 165–167 °C (from ethanol) (lit.,[5] m.p. 167–168 °C); 5-phenylsulfonyl-2*H*-benzimidazole-2-spirocyclohexane **18** (95%), m.p. 132–134 °C (lit.,[5] m.p. 133–134 °C); 1,3-dihydro-5-nitro-2*H*-benzimidazole-2-spirocyclohexane **4** (73%), m.p. 163–164 °C (lit.,[12] 75% and m.p. 164 °C); and 5-nitro-2*H*-benzimidazole-2-spirocyclohexane **10** (95%), m.p. 97–98 °C (lit.,[12] 85% and m.p. 100 °C).

1,3-*Dihydro*-5-*propylthio*-2H-*benzimidazole*-2-*spirocyclohexane* **5**.—Commercial 4-propylthio-*o*-phenylenediamine (12.0 g, 65.8 mmol) was distilled, b.p. 145–160 °C at 0.5 mmHg, to yield a bright yellow solid (11.4 g, 62.5 mmol) which was heated with cyclohexanone (6.17 g, 63.0 mmol) at 50–60 °C for 30 min. The excess of cyclohexanone and the water produced were distilled off under reduced pressure and the dark yellow oil (14.7 g, 90%) was chromatographed. Light petroleum–ethyl

Table 1 Summary of reaction conditions and products

Starting material	Reagent	Solvent	Temp.	Time	Products [yield (%)]
1	PrSNa (1 equiv.)	PrOH	−10 °C	7 days	**13**(60), **1**(35)[a]
1	PrSNa (1 or 2 equiv.)	PrOH	ambient	2.5 l	**31**(18), **29**(17), **22**(20), **13**(29)[b]
1	PrSNa (1 or 2 equiv.)	PrOH	at reflux	2.5 h	**31**(18), **29**(17), **22**(20), **13**(29)[b]
9	PrSNa (1 or 2 equiv.)	PrOH	at reflux	2.0 h	**31**(8), **29**(12), **22**(20), **13**(40)[b]
1	PrSNa (6 equiv.)	DMSO	at reflux	3.0 h	**31**(12), **29**(27), **22**(40)[c,d]
13	PrSNa (2 equiv.)	PrOH	ambient	24 h or 7 d	**33**(54), **31**(8), **29**(11), **22**(22)[b]
13	PrSNa (4 equiv.)	PrOH	ambient	12 h	**34**(23), **33**(40), **31**(10), **29**(4), **22**(7)[b]
22	PrSNa (4 equiv.)	PrOH	ambient	4 d	**34**(42), **33**(16), **22**(5)[c]
29	PrSNa (4 equiv.)	PrOH	at reflux	12 h	**34**(25), **33**(12), **31**(7)[b]
1	Bu^{t}SNa (1 equiv.)	MeOH	ambient	12 h	**14**(70)[a]
1	Bu^{t}SNa (2 equiv.)	MeOH	ambient	24 h	**32**(7), **30**(4), **23**(19), **14**(43)[e]
23	Bu^{t}SNa (1 equiv.)	MeOH	at reflux	5.0h	**35**(3), **23**(75)[e]
30	Bu^{t}SNa (1 equiv.)	MeOH	ambient	2 d	**32**(75), **30**(17)[e]
1	PhSNa (1 equiv.)	PrOH	ambient	2.5 h	**15**(50)[a]
9	PhSNa (1 equiv.)	PrOH	ambient	2.5 h	**15**(54)[a]

[a] Crude product chromatographed on alumina. Light petroleum (b.p. 40–60 °C)–ethyl acetate (19:1) eluted the product. [b] Crude product flash chromatographed on silica. Light petroleum (b.p. 40–60 °C)–ethyl acetate (24:1) eluted the products in the order given. [c] The PrSNa was prepared and added to the solvent. The crude product was flash chromatographed on silica: light petroleum (b.p. 40–60 °C)–ethyl acetate (19:1) eluted the products in the order given. [d] Use of 3 equiv. of PrSNa in DMSO (at reflux for 4 h) or 1 equiv. of PrSNa in Me_2CO (at reflux for 3 h), Et_2O (ambient temperature for 12 h), or Et_2O (at reflux for 5 h) gave the same three compounds (TLC) in varying amounts together with some of the 5-propylthio compound **13** in each case. [e] Light petroleum (b.p. 40–60 °C)–ethyl acetate (9:1) eluted the products.

Table 2 Yields (%), physical properties, and analytical data for compounds prepared

Compound	Yield (%)	M.p. or b.p.,[a] (T/°C)	Found (%) C	H	N	Found M^+	Formula	Required (%) C	H	N	Required M	ν_{max}/cm^{-1} (Assignment)	δ_H(Assignment)[b]
5	82	Bright yellow oil[c]				262.1494	$C_{15}H_{22}N_2S$				262.1504		0.95 (3 H, t, J 6.0, Me), 1.00–2.20 (12 H, m, aliphatic protons), 2.70 (2 H, t, J 6.0, CH_2S), 3.80 br (2 H, s, exchangeable, NH), 6.30 (1 H, s, 4-H) and 6.35–6.85 (2 H, m, 6-H and 7-H)
6	69	142–144 (A)	68.4	6.6	13.6	297	$C_{17}H_{19}N_3S$	68.6	6.4	14.1	297	3400 (NH)	1.30–2.00 (10 H, m, cyclohexyl), 3.90–4.30 br (2 H, s, exchangeable, NH), 6.54 (1 H, d, J 9.0, 7-H), 6.70 (1 H, d, J 1.0, 4-H), 6.80–7.00 (3 H, m, 6-H and Ar_H), 7.30–7.60 (1 H, m, Ar_H) and 8.30–8.50 (1 H, m, Ar_H) (at 90 MHz)
7	62[d]	152–154 (A)	64.6	6.4	18.55	298	$C_{16}H_{18}N_4S$	64.4	6.1	18.8	298	3400 (NH)	1.20–1.90 (10 H, m, cyclohexyl), 3.80–4.30 br (2 H, s, exchangeable, NH), 6.50 (1 H, d, J 9.0, 7-H), 6.70 (1 H, d, J 1.0, 4-H), 6.8–7.00 (2 H, m, 6-H, Ar_H) and 8.40–8.60 (2 H, d, J 7.0, Ar_H) (at 90 MHz)
13	82,[e] 60[f]	Bright yellow oil[c]				260.1358	$C_{15}H_{20}N_2S$				260.1347		1.05 (3 H, t, J 6.0, Me), 1.20–2.40 (12 H, m, aliphatic protons), 2.90 (2 H, t, J 6.0, CH_2-S), 6.65 (1 H, d, J 8.0, 6-H or 7-H), 6.75 (1 H, s, 4-H) and 7.20 (1 H, d, J 8.0, 6-H or 7-H)
14	70	80.5–81 (B)	70.2	8.2	10.2	274	$C_{16}H_{22}N_2S$	70.0	8.1	10.2	274		1.00–2.50 (19 H, m, aliphatic protons), 6.80 (1 H, dd, J 8.0 and 2.0, 6-H), 7.10 (1 H, d, J 8.0, 7-H) and 7.25 (1 H, s, 4-H)
15	50,[g] 54[h]	83.5–84.5 (C)	73.5	6.25	9.7	294	$C_{18}H_{18}N_2S$	73.4	6.2	9.5	294		1.00–2.00 (10 H, m, cyclohexyl), 6.35 (1 H, s, 4-H), 6.50–7.20 (2 H, m, 6-H and 7-H) and 7.50 *br* (5 H, s, Ar_H)
16	93	91–93 (D)[c]				295.1141	$C_{17}H_{17}N_3S$				295.1143		1.50–2.10 (10 H, m, cyclohexyl), 6.90 (1 H, dd, J 9.0, 2.0, 6-H), 7.10–7.40 (3 H, m, 7-H and Ar_H), 7.45 (1 H, d, J 2.0, 4-H), 7.60–7.80 (1 H, m, Ar_H) and 8.50–8.70 (1 H, m, Ar_H) (at 90 MHz).
17	95	87–89 (D)[c]				296.1065	$C_{16}H_{16}N_4S$				296.1096		1.40–2.20 (10 H, m, cyclohexyl), 7.00–7.40 (3 H, m, 6-H, 7-H and Ar_H), 7.65 (1 H, d, J 2.0, 4-H), 8.60 (2 H, d, J 8.0, Ar_H) (at 90 MHz)
20	3[i]	194–196 (E)	65.0	5.7	13.9	406	$C_{22}H_{22}N_4S_2$	65.0	5.45	13.8	406	3300 (NH)	1.40–1.90 (10 H, m, cyclohexyl), 4.10–4.30 br (2 H, s, exchangeable, NH), 6.80–7.00 (6 H, m, 4-H, 7-H and Ar_H), 7.30–7.50 (2 H, m, Ar_H) and 8.30–8.50 (2 H, m, Ar_H) (at 90 MHz)
21	63	198–200 (F)	63.1	5.3	9.6	437	$C_{23}H_{23}N_3O_2S_2$	62.85	5.2	9.8	437	3300 (NH)	1.10–1.42 (10 H, m, cyclohexyl), 5.50–5.60 br (2 H, s, exchangeable, NH), 5.79–5.85 (1 H, m, Ar_H), 6.06 (1 H, s, 4-H), 6.48–6.52 (1 H, m, Ar_H), 6.78–6.96 (4 H, m, Ar_H), 7.00 (1 H, s, 7-H), 7.48 (2 H, d, J 6.0, Ar_H) and 7.90 (1 H, d, J 6.0, Ar_H) (at 300 MHz in [$^2H_6$]-DMSO)
22	See Table 1	Bright yellow oil[c]				334.1545	$C_{18}H_{26}N_2S_2$				334.1537		1.05 (6 H, t, J 6.0, Me), 1.20–2.50 (14 H, m, aliphatic protons), 2.95 (4 H, t, J 6.0, CH_2S) and 6.65 (2 H, s, 4-H and 7-H)
23	See Table 1	125.5 (B)	66.3	8.4	7.5	362	$C_{20}H_{30}N_2S_2$	66.25	8.3	7.7	362		1.00–2.50 (28 H, m, aliphatic protons) and 7.45 (2 H, s, 4-H and 7-H)
24	68	90–91 (E)	45.3	2.5	14.45	293	$C_{11}H_7N_3SeS$	45.25	2.4	14.4	293		6.40–6.60 (1 H, d, J 9.0, 7-H), 6.70–6.80 (1 H, s, 4-H), 6.80–7.00 (3 H, m, 6-H, Ar_H), 7.30–7.60 (1 H, m, Ar_H) and 8.30–8.50 (1 H, d, J 6.0, Ar_H) (at 90 MHz)

Table 2 (*continued*)

25	64	166–67 (A)	47.9	2.6	13.8	402	$C_{16}H_{10}N_4SeS_2$	47.9	2.5	14.0	402		7.00–7.40 (4 H, m, Ar_H), 7.40–7.70 (2 H, m, Ar_H), 8.05 (2 H, s, 4-H and 7-H) and 8.48 (2 H, d, *J* 6.0, Ar_H) (at 90 MHz)[a]
26	23[j]	139–140 (E)	60.3	4.6	12.9	437	$C_{22}H_{20}N_4O_2$	60.5	4.6	12.8	437		1.30–2.00 (10 H, m, cyclohexyl), 6.88 (1 H, t, *J* 6.0, Ar_H), 7.20–7.60 (4 H, m, Ar_H) and 7.80–8.50 (5 H, m, Ar_H) (at 90 MHz)
27	5.5[k]	168–170 (E)	58.3	4.9	20.5	408	$C_{20}H_{20}N_6S_2$	58.8	4.9	20.6	408	3300 (NH)	1.10–2.00 (10 H, m, cyclohexyl), 4.20–4.40 br (1 H, s, exchangeable, NH), 4.40–4.60 br (1 H, s, exchangeable, NH), 6.50 (1 H, d, *J* 9.0, 7-H), 6.70–7.10 (2 H, m, Ar_H), 7.06 (1 H, d, *J* 9.0, 6-H) and 8.30–8.50 (4 H, t, *J* 7.0, Ar_H) (at 90 MHz)
29	See Table 1	59–60 (D)[c]				334.1501	$C_{18}H_{26}N_2S_2$				334.1537		1.15 (6 H, t, *J* 6.0, Me), 1.50–2.50 (14 H, m, aliphatic protons), 3.00 (4 H, t, *J* 6.0, CH_2S), 6.35 (1 H, d, *J* 2.0, 7-H) and 6.70 (1 H, d, *J* 2.0, 5-H) (at 90 MHz).
30	See Table 1	Bright orange oil[c]				362.1893	$C_{20}H_{30}N_2S_2$				362.1850		0.80–2.50 (28 H, m, aliphatic protons), 7.20 (1 H, d, *J* 2.0, 7-H) and 7.40 (1 H, d, *J* 2.0, 5-H)
31	See Table 1	55–57 (D)[c]				408.1607	$C_{21}H_{32}N_2S_3$				405.1727		0.75–1.40 (9 H, m, Me), 1.30–2.50 (16 H, m, aliphatic protons), 2.60–3.10 (4 H, m, CH_2-S), 3.50 (2 H, t, *J* 6.0, CH_2S) and 6.70 (1 H, s, 6-H)
32	See Table 1	171–172 (B)	63.5	8.7	5.9	450	$C_{24}H_{38}N_2S_3$	63.95	8.5	6.2	450		0.90–2.30 (37 H, m, aliphatic protons) and 7.75 (1 H, s, 6-H)
33	See Table 1	70–70.5 (B)	61.6	7.9	6.8		$C_{21}H_{32}N_2S_3$	61.7	7.9	6.85			1.10 (9 H, t, *J* 6.0, Me), 1.40–2.40 (16 H, m, aliphatic protons), 2.50–3.50 (6 H, m, CH_2S) and 6.75 (1 H, s, 7-H)
34	See Table 1	Burgundy red oil[c]				482.1911	$C_{24}H_{38}N_2S_4$				482.1917		0.95 (12 H, t, *J* 6.0, Me), 0.90–2.10 (18 H, m, aliphatic protons), 2.55 (4 H, t, *J* 6.0, CH_2-S), 2.90 (2 H, t, *J* 6.0, CH_2S) and 3.30 (2 H, t, *J* 6.0, CH_2S)
35	See Table 1	Burgundy red oil[c]				450.2328	$C_{24}H_{38}N_2S_3$				450.2353		0.70–2.50 (37 H, m, aliphatic protons) and 7.40 (1 H, s, 7-H)
38	88	86–88 (E)[l]				342	$C_{17}H_{18}N_4O_2S$				342	3450 (NH)	1.00–1.80 (10 H, m, cyclohexyl), 4.75 br (1 H, s, exchangeable, NH), 4.90 br (1 H, s, exchangeable, NH), 6.18 (1 H, d, *J* 9.0, 7-H), 6.80–7.00 (2 H, m, Ar_H), 7.20–7.50 (1 H, m, Ar_H), 7.39 (1 H, d, *J* 9.0, 6-H) and 8.20–8.40 (1 H, m, Ar_H) (at 90 MHz)
39	86	172–173 (E)	55.9	5.0	20.1	343	$C_{16}H_{17}N_5O_2S$	56.0	5.0	20.4	343	3300 (NH) and 3400 (NH)	1.00–1.80 (10 H, m, cyclohexyl), 4.65 br (1 H, s, exchangeable, NH), 4.75 br (1 H, s, exchangeable, NH), 6.25 (1 H, d, *J* 9.0, 7-H), 6.80–7.00 (1 H, t, *J* 6.0, Ar_H), 7.52 (1 H, d, *J* 9.0, 6-H) and 8.40 (2 H, d, *J* 6.0, Ar_H) (at 90 MHz)
40	87	133–134 (G)	60.4	4.8	16.3	340	$C_{17}H_{16}N_4O_2S$	60.0	4.7	16.5	340		1.00–1.80 (10 H, m, cyclohexyl), 7.10–7.18 (1 H, m, Ar_H), 7.20 (1 H, d, *J* 9.0, 7-H), 7.50–7.65 (3 H, m, 6-H and Ar_H) and 8.28 (1 H, m, Ar_H) (at 300 MHz)
41	89	138–140 (G)	56.9	4.5	20.6	341	$C_{16}H_{15}N_5O_2S$	56.3	4.4	20.5	341		1.20–1.90 (10 H, m, cyclohexyl), 7.05 (1 H, t, *J* 5.0, Ar_H), 7.32 (1 H, d, *J* 9.0, 7-H), 7.55 (1 H, d, *J* 9.0, 6-H) and 8.42 (2 H, d, *J* 5.0, Ar_H) (at 300 MHz).

[a] Recrystallisation solvents given in parentheses: *A*, Light petroleum (b.p. 80–100 °C)–ethyl acetate; *B*, Light petroleum (b.p. 40–60 °C)–dichloromethane; *C*, Light petroleum (b.p. 40–60 °C)–ethyl acetate; *D*, Light petroleum (b.p. 40–60 °C); *E*, Light petroleum–ethyl acetate; *F*, Ethyl acetate; *G*, Light petroleum. [b] At 60 MHz and in $CDCl_3$ unless stated otherwise, *J* values are given in Hz. [c] Unstable. [d] Yield after crystallisation, 45%. [e] By oxidation of the 1,3-dihydro-compound **5**. [f] By reaction of PrSNa with compound **1**; Starting material (35%) recovered. [g] From compound **1**. [h] From compound **9**. [i] By-product obtained during the synthesis of compound **6**. [j] Starting material (65%) recovered: Use of ethanol as the solvent gave a similar result. [k] By-product obtained during the synthesis of compound **7**. [l] Characterised by oxidation to compound **40**.

acetate (9:1) eluted 1,3-*dihydro*-5-*propylthio*-2H-*benzimidazole*-2-*spirocyclohexane* **5** (13.4 g) (details in Table 2).

Oxidation of 1,3-*Dihydro*-2H-*benzimidazole*-2-*spirocyclohexane and its* 5-*Chloro Derivative* **3** *with Potassium Permanganate*.—A solution of potassium permanganate (2.70 g, 17.0 mmol) in water (120 cm^3) was added to a vigorously stirred solution of 1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane (3.20 g, 17.0 mmol) in dichloromethane (70 cm^3) followed by a catalytic amount of tetrabutylammonium bromide. After 10 min the purple colour had disappeared and TLC examination of the organic phase showed absence of starting material. The mixture was filtered through Celite, then diluted with water (100 cm^3) and dichloromethane (100 cm^3). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 50 cm^3). The organic layer and extracts were combined, dried ($MgSO_4$), and distillation of the solvent gave 2*H*-benzimidazole-2-spirocyclohexane **1** (2.1 g, 66%), m.p. 63–65 °C [from light petroleum (b.p. 40–60 °C)] (lit.,[13] 64 °C).

Oxidation of 5-chloro-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane **3** in the same way gave 5-chloro-2*H*-benzimidazole-2-spirocyclohexane **9** (75%), m.p. 57 °C (lit.,[3] m.p. 58 °C).

5-*Propylthio*-2H-*benzimidazole*-2-*spirocyclohexane* **13**.—(*a*) The 1,3-dihydro compound **5**, prepared as described before, was oxidised with potassium permanganate as described in the preceding paragraph for oxidation of 1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane. The crude *product*, a dark yellow oil (90% yield), was chromatographed on alumina. Light petroleum–ethyl acetate (19:1) eluted pure material (details in Table 2).

(*b*) Sodium (0.32 g, 13.91 mmol) was allowed to react with anhydrous propanol (100 cm^3) and propanethiol (1.04 g, 13.68 mmol) was added to the resulting mixture, cooled to −10 to 0 °C, followed by 2*H*-benzimidazole-2-spirocyclohexane **1** (2.54 g, 13.66 mmol). Stirring was continued for 7 days at −10 °C. Alumina was added and the solvent removed by distillation under reduced pressure. The preadsorbed crude product was loaded onto an alumina column and chromatographed. Light petroleum–ethyl acetate (19:1) eluted the product which was repurified by flash chromatography on silica. Light petroleum (b.p. 40–60 °C)–ethyl acetate (19:1) eluted starting material (0.89 g, 35% recovery) and product **13** (2.13 g, 60%), identical with the sample prepared as described in (*a*).

5-tert-*Butyl*- **14**, a beige-yellow solid, and 5-*phenylthio*-2H-*benzimidazole*-2-*spirocyclohexane* **15**, a bright yellow solid, were prepared similarly (details in Tables 1 and 2). The latter compound **15** was prepared similarly starting with 5-chloro-2*H*-benzimidazole-2-spirocyclohexane **9**.

2*H*-Benzimidazole-2-spirocyclohexane **1** (or its 5-chloro derivative **9**) was treated also with varying amounts of sodium propanethiolate in propanol or other solvents, as described in the Discussion section. The reaction conditions and the products obtained are summarised in Table 1 and Table 2 gives the % yields, physical properties, and analytical data for these products.

Attempted Dealkylation of 5-tert-*Butylthio*-2H-*benzimidazole*-2-*spirocyclohexane* **14**.—(*a*) *With sodium in pyridine*. A solution of the 2*H*-benzimidazole **14** (0.5 g, 1.8 mmol) in anhydrous pyridine (10 cm^3) under nitrogen was heated quickly to 105–110 °C when sodium (0.224 g, 9.74 g atom) was added quickly. The mixture turned brown as the sodium reacted. The mixture was kept between 100 °C and reflux temperature over 1 h, when all the sodium had reacted, then it was cooled to 10 °C and methyl iodide (1.48 g, 10.44 mmol) was added dropwise. The resulting dark yellow solution was stirred at 10 °C for 40 min, then quenched by slow and cautious addition of saturated aqueous sodium chloride (15 cm^3). Water (70 cm^3) was added and extraction with dichloromethane (3 × 50 cm^3) gave an intractable tar.

(*b*) *With acetic acid–hydrochloric acid*.—To a stirred solution of compound **14** (0.5 g, 1.8 mmol) in acetic acid (4 cm^3) was added hydrochloric acid (1 mol dm^{-3}; 1 cm^3) and the resulting mixture was heated on a steam bath for 1.5 h, then cooled and poured into water (35 cm^3). The solution obtained was neutralised by addition of sodium hydrogen carbonate, and extraction with dichloromethane (3 × 35 cm^3) gave an intractable tar.

Reactions of 2H-*Benzimidazole*-2-*spirocyclohexane* **1**.—(*a*) *With pyrimidine*-2-*thiol*. Pyrimidine-2-thiol (3.0 g, 27.0 mmol) was added to a stirred solution of 2*H*-benzimidazole-2-spirocyclohexane **1** (5.0 g, 27.0 mmol) in anhydrous methanol (50 cm^3) at ambient temperature and the resulting solution was stirred at this temperature overnight, then poured into cold water (150 cm^3). Extraction with ethyl acetate (3 × 75 cm^3) gave the crude product which was chromatographed on alumina. Light petroleum–ethyl acetate (4:1) eluted 1,3-*dihydro*-5-(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **7** (4.9 g) and 1,3-*dihydro*-4,5-*di*(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **27** (0.6 g) (details in Table 2).

(*b*) *With pyridine*-2-*thiol*. A similar reaction to that described in (*a*) carried out between compound **1** (5.0 g, 27.0 mmol) and pyridine-2-thiol (3.0 g, 27.0 mmol) gave, after chromatography, 1,3-*dihydro*-5-(*pyridin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **6** (5.5 g) and 1,3-*dihydro*-5,6-*di*(*pyridin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **20** (0.3 g) (details in Table 2).

Reaction of 5-*Nitro*-2H-*benzimidazole*-2-*spirocyclohexane* **10** *with Pyrimidine*-2-*thiol*.—The reaction was carried out and worked-up using exactly the same procedures as those described in the preceding two experiments and gave, after chromatography, 1,3-dihydro-5-nitro-2*H*-benzimidazole-2-spirocyclohexane **4** (2%), identical (m.p. and TLC) with an authentic sample, and 1,3-*dihydro*-5-*nitro*-4-(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **39** (details in Table 2).

1,3-*Dihydro*-5-*nitro*-4-(*pyridin*-2-*ylthio*-)2H-*benzimidazole* **38** was prepared similarly from compound **10** as was 5-*phenylsulfonyl*-4-(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **26** from compound **18** (dichloromethane as the solvent in this case). Use of ethanol as the solvent for the synthesis of compound **26** gave a similar yield (details in Table 2).

1,3-*Dihydro*-6-*phenylsulfonyl*-5-(*pyridin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **21**.—A solution of sodium benzenesulfinate (3.34 g, 20.34 mmol) in water (25 cm^3) was added to a stirred solution of freshly prepared 5-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **16** (5.0 g, 16.9 mmol) in ethanol (40 cm^3) followed by addition of acetic acid (1.2 cm^3) and the resulting solution was stirred rapidly at ambient temperature for 2 h, then poured into cold water (250 cm^3). Extraction with ethyl acetate (3 × 75 cm^3) gave a sticky solid which was chromatographed on silica. Light petroleum–ethyl acetate eluted, as the major product, 1,3-*dihydro*-6-*phenylsulfonyl*-5-(*pyridin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **21** (4.67 g) (details in Table 2).

5-*Nitro*-4-(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **41**.—Manganese dioxide (15.0 g, 0.17 mol) was added to a stirred solution of 1,3-dihydro-5-nitro-4-(pyrimidin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **39** (5.0 g, 14.54 mmol) in dichloromethane (150 cm^3) at ambient temperature

and the resulting mixture was stirred at this temperature for a further 30 min, then filtered through Celite. Distillation of the solvent afforded a red solid which was flash chromatographed on silica. Light petroleum–ethyl acetate eluted the *product* **41** (4.42 g) as orange crystals.

The following compounds were prepared similarly: 5-*nitro*-4-(*pyridin*-2-*ylthio*)-**40**, 5-(*pyridin*-2-*ylthio*)- **16**, and 5-(*pyrimidin*-2-*ylthio*)-2H-*benzimidazole*-2-*spirocyclohexane* **17** (from compounds **38**, **6** and **7**, respectively) (details in Table 2).

5-(*Pyridin*-2-*ylthio*)-2,1,3-*benzoselenadiazole* **24**.—A solution of selenium dioxide (0.40 g, 3.60 mmol) in water (5 cm^3) was added to a stirred solution of 1,3-dihydro-5-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **6** (1.0 g, 3.37 mmol) in a mixture of ethanol (20 cm^3) and water (20 cm^3) and the resulting solution was heated under reflux for 15 min, then cooled and poured into water (50 cm^3). The yellow precipitate was filtered off, washed with water and dried in air, to give the *product* **24** (0.67 g).

5,6-*Di*(*pyridin*-2-*ylthio*)-2,1,3-*benzoselenadiazole* **25** was prepared similarly (details in Table 2).

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