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## 2H-Benzimidazoles (Isobenzimidazoles). Part 9.<sup>1</sup> Synthesis and Reactions of 4,6-Dibromo-2H-benzimidazole-2-spirocyclohexane

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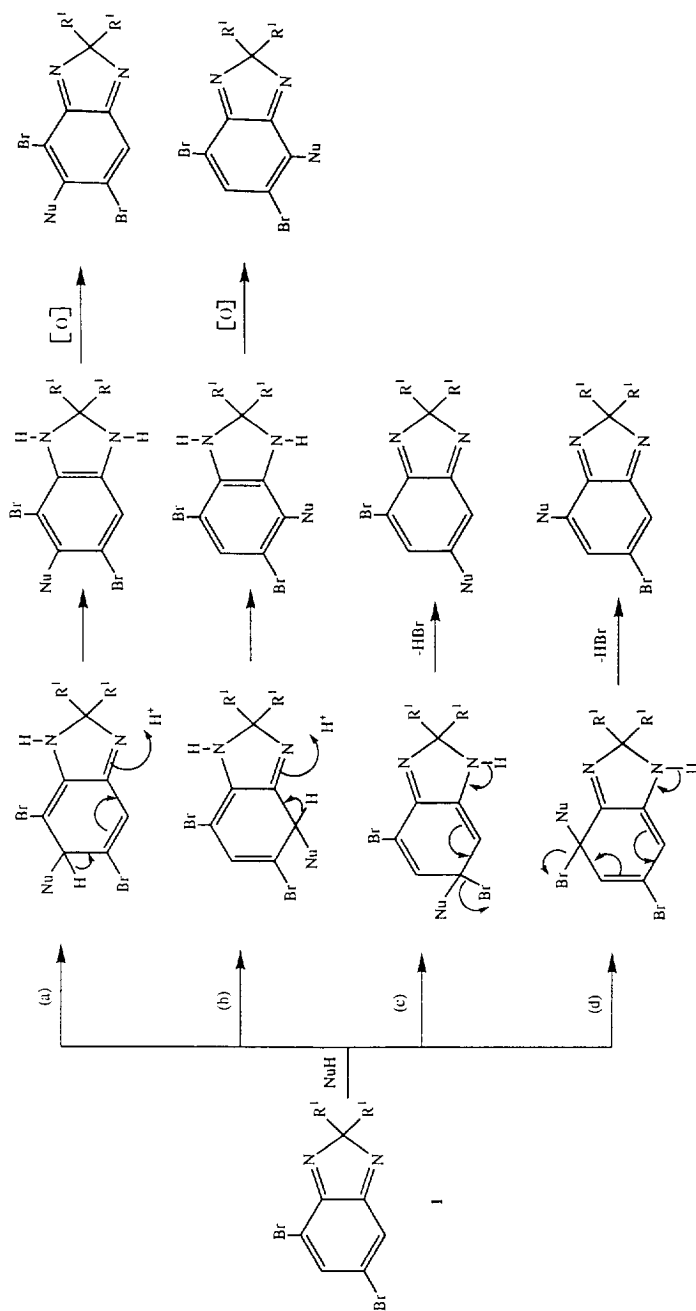
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Dedicated to Professor Dr. Fritz Sauter, Institut für Organische Chemie der Technischen Universität Wien, Getreidemarkt 9, A-1060  
WIEN, on the occasion of his 65th birthday (May 23rd, 1995)

**Abstract:** The title compound **1** was prepared by condensation of 3,5-dibromo-*o*-phenylenediamine **10** with cyclohexanone and oxidation of the resulting 4,6-dibromo-1,3-dihydro-2H-benzimidazole-2-spirocyclohexane **5** with manganese dioxide. With sodium 2,3-dichlorophenoxide, sodium benzenesulfinate, or piperidine it reacts by loss of bromine, to give the 6-substituted derivatives **2**, **3**, and **4**, respectively. Morpholine, however, gives 5,7-dibromo-4-morpholino-2H-benzimidazole-2-spirocyclohexane **15** whilst pyrid-2(1H)-thione and pyrimidin-2(1H)-thione give 4-bromo-1,3-dihydro-6-(pyridin-2-ylthio)-2H-benzimidazole-2-spirocyclohexane **6** and 5,7-dibromo-1,3-dihydro-4-(pyrimidin-2-ylthio)-2H-benzimidazole-2-spirocyclohexane **14**, respectively. In the presence of 1 or 2 mol equiv. of sodium methoxide an aryne mechanism appears to operate, leading to the formation of either a mixture of 5-bromo-6-methoxy- **11** and 6-bromo-4-methoxy-2H-benzimidazole-2-spirocyclohexane **12** or 5,6-dimethoxy-2H-benzimidazole-2-spirocyclohexane **13**, respectively. Oxidation of the title compound **1** with *m*-chloroperoxybenzoic acid yields the 1-oxide **7** exclusively, which reacts with piperidine and morpholine by loss of the 4-bromine atom, to give compounds **16** and **17**, respectively, in the latter case with concomitant loss of oxygen.

Previously we<sup>1-5</sup> have studied the reactions of 2H-benzimidazole-2-spirocyclohexane and several of its derivatives, including 5,6-dichloro-2H-benzimidazole-2-spirocyclohexane,<sup>4</sup> with various nucleophiles. We now describe the synthesis and reactions of the title compound **1** which, on the basis of our previous work,<sup>1-5</sup> might be expected to react with nucleophiles by 1,4- or 1,6-conjugate addition, as shown in Scheme 1. The 1,4-conjugate addition pathway (a) is unfavourable by comparison with pathway (b) in view of the size of bromine-atoms whilst displacement of bromine is expected to occur *via* route (c) rather than route (d). We describe too the synthesis and reactions of the 1-oxide **7** and attempts to prepare 4,5,6,7-tetrabromo-2H-benzimidazole-2-spirocyclohexane **8**.

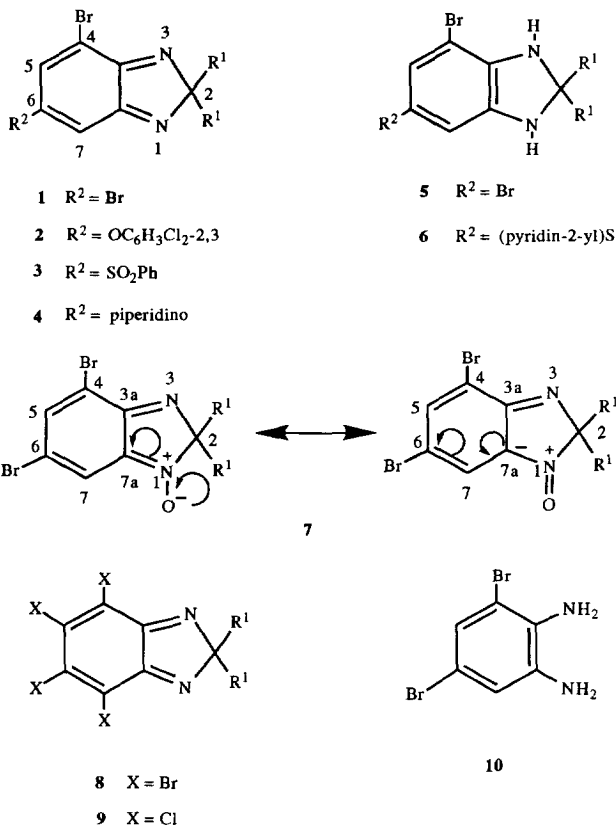
3,5-Dibromo-*o*-phenylenediamine **10**<sup>6</sup> was condensed with cyclohexanone in refluxing acetonitrile and the resulting 4,6-dibromo-1,3-dihydro-2H-benzimidazole-2-spirocyclohexane **5** (obtained as a yellow oil in 46% yield) was oxidised with manganese dioxide in dichloromethane, to give the title compound **1** in 95% crude yield. <sup>1</sup>H NMR signals for the 5-H ( $\delta$  7.35) and 7-H ( $\delta$  7.43) protons in this compound **1** are readily distinguishable by addition of successive amounts of a europium shift reagent, tris[3-(trifluoromethyl)hydroxymethylene]-(+)-camphorato] europium(III) [Eu(tfc)<sub>3</sub>], to a sample placed in the <sup>1</sup>H NMR probe, which results in successive



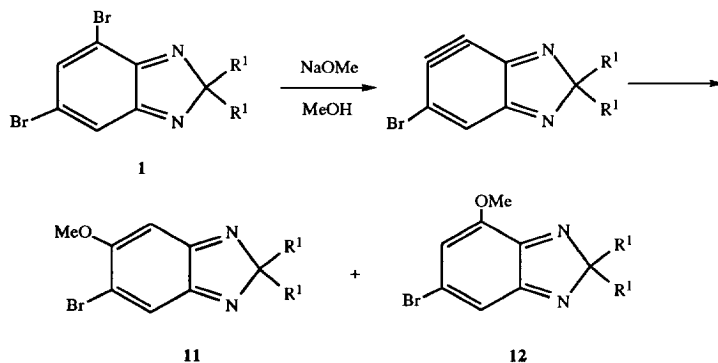
SCHEME 1

broadening and ultimate collapse of the signal for 7-H at  $\delta$ 7.43 (d with  $J$  2.0 Hz), due to complexation of the shift reagent with N-1.

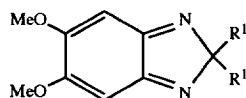
2*H*-Benzimidazole-2-spirocyclohexane reacts very slowly with oxygen nucleophiles whilst its 5-chloro- and 5,6-dichloro-derivatives react more readily by displacement of a chlorine atom.<sup>4,5</sup> 4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1**, however, reacts with 1 mol equiv. of sodium methoxide in refluxing



methanol to give an inseparable mixture (43% yield) of 5-bromo-6-methoxy- **11** and 6-bromo-4-methoxy-2*H*-benzimidazole-2-spirocyclohexane **12** whose formation can be rationalised by invoking an aryne (elimination-addition) mechanism, as shown in Scheme 2. In the  $^1\text{H}$  NMR spectrum of this mixture signals for two methoxy groups are clearly visible at  $\delta$  3.75 and 3.85 (ratio 9:7). For compound **11** two doublets are seen at  $\delta$  6.34 and 7.60,  $J$  1.0 Hz, for 4-H and 7-H, respectively, whilst isomer **12** displays two doublets at  $\delta$  6.25 and 7.05,  $J$  3.0 Hz, for 5-H and 7-H, respectively. 4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** reacts with 2 mol equiv. of sodium methoxide in refluxing methanol to give 5,6-dimethoxy-2*H*-benzimidazole-2-spirocyclohexane **13** as the major isolable compound (30% yield) (TLC of the crude mixture indicated the presence of lesser amounts of other compounds but these were not isolated). The major product **13**, identical with an authentic sample,<sup>4</sup> could arise through reaction of compound **11** with methoxide ion (or methanol) either by its 1,4-conjugate addition followed by elimination of hydrogen bromide or *via* a second elimination-addition process.



SCHEME 2



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Elimination-addition reactions involving compounds **11** and **12** would be expected to yield up to five products.

4,6-Dibromo-2H-benzimidazole-2-spirocyclohexane **1** reacts also with sodium 2,3-dichlorophenoxide in hot, dry methanol, to give compound **2** (38%), presumably formed by nucleophilic displacement of the 6-bromine atom.<sup>4</sup> Conclusive proof of the structure of this compound came from an X-ray crystallographic study (Fig. 1) (see Experimental Section for details).

With sodium benzenesulfinate in aqueous ethanol in the presence of acetic acid 4,6-dibromo-2H-benzimidazole-2-spirocyclohexane **1** gave a good yield (85%) of the 6-phenylsulfonyl derivative **3**. Reaction was only possible after addition of the acetic acid. Reactions of the title compound **1** with sodium benzenethiolate, sodium 2-aminobenzenethiolate, or sodium 4-chlorobenzenethiolate, either with or without addition of manganese dioxide, gave complex intractable mixtures. Pyridin-2(1H)-thione, however, gave 4-bromo-1,3-dihydro-6-(pyridin-2-ylthio)-2H-benzimidazole-2-spirocyclohexane **6** (51%). The structures of compounds **3** and **6** are assigned by analogy with the proven structure of compound **2**. The presence of only one bromine atom is evident from the mass spectroscopic data and from the microanalytical results for compound **3**. In the <sup>1</sup>H NMR spectrum of each compound the signals for 5-H and 7-H overlap other signals. By contrast with pyridin-2(1H)-thione, pyrimidin-2(1H)-thione reacts with the title compound **1** through initial 1,6-conjugate addition of the thiol,<sup>5</sup> to give isolable 5,7-dibromo-1,3-dihydro-4-(pyrimidin-2-ylthio)-2H-benzimidazole-2-spirocyclohexane **14** (38%). The structure of this compound follows from its mass spectroscopic analysis and microanalytical data, indicating the presence of two bromine atoms, and from an examination of its <sup>1</sup>H NMR spectrum (6-H as a singlet at  $\delta$  6.65). Compounds **6** and **14** were obtained following chromatography as cream solids which rapidly turned orange on standing or attempted recrystallisation, presumably through loss of bromine. Consequently, it was impossible to confirm their structures through X-ray crystallography.

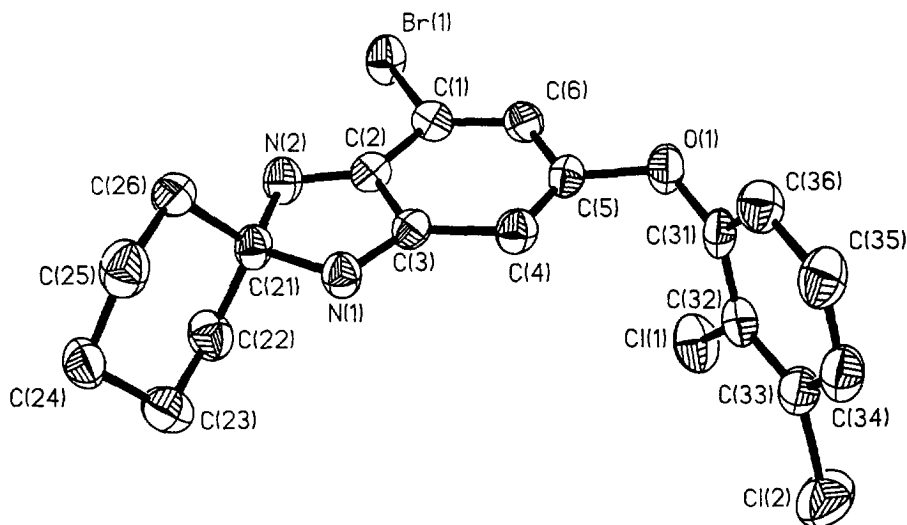
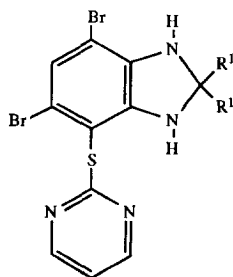
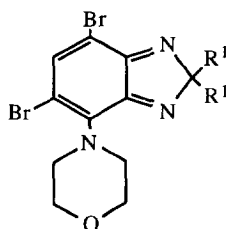


Fig. 1: Molecular structure of 4-bromo-6-(2,3-dichlorophenoxy)-2*H*-benzimidazole-2-spirocyclohexane **2**



14



15

4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** reacts with morpholine in ethanol (but not in benzene) also *via* initial 1,6-conjugate addition, to give compound **15** (32%).<sup>5</sup> The mass spectrum of this product and its microanalytical data indicated the presence of two bromine atoms, whilst 6-H was clearly visible as a singlet at  $\delta$  7.61 in its <sup>1</sup>H NMR spectrum. Unfortunately it was not possible to grow suitable crystals of this compound for X-ray analysis. By contrast, piperidine reacts with the title compound by displacement of a bromine atom, to give 4-bromo-6-piperidino-2*H*-benzimidazole-2-spirocyclohexane **4** (43%),  $\delta$  6.13 (1H, d, *J* 2.0 Hz, 5-H) and 7.33 (1H, d, *J* 2.0 Hz, 7-H) (mass spectroscopy confirmed the presence of a single bromine atom). Reaction of the title compound **1** with aniline afforded a multicomponent mixture (TLC) from which we were unable to isolate pure compounds by chromatography.

Attempted bromine-lithium exchange reactions of compound **1** with *n*-butyllithium or deprotonation reactions with lithium di-isopropylamide (LDA) were similarly unsuccessful. Thus, e.g., its reaction with one or two mol equiv. of *n*-butyllithium at -90 °C in anhydrous tetrahydrofuran (THF) followed by quenching of the

resulting mixture with acetophenone gave an intractable tar. Similar results were obtained in anhydrous ether and using carbon dioxide or dimethyl disulfide as quenching reagents in either solvent.

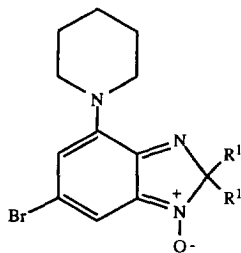
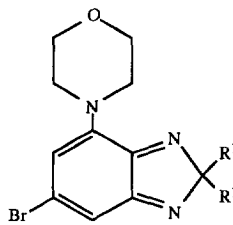
Oxidation of 4,6-dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** with an excess of *m*-chloroperoxybenzoic acid in dichloromethane yielded only one *N*-oxide (48% yield) and no 1,3-dioxide. Presumably steric hindrance by the bulky 4-bromine atom prevents formation of the 3-oxide or 1,3-dioxide. A direct comparison between the <sup>1</sup>H NMR spectra of starting material **1** and product was not helpful in determining the structure of the latter. The differences observed for the <sup>13</sup>C chemical shifts of compounds **1** and **7** are shown in Table 1. The data show clearly that mesomeric interaction of the *N*-oxide oxygen atom in compound **7** affects carbon atoms C-7a, C-7, and C-6 to a greater extent than those at C-3a, C-4, or C-5, thus confirming the structure **7** assigned. This mesomeric interaction also allows us to predict that, in bromine displacement reactions, the bromine atom on C-4 should be more reactive to nucleophiles than that on C-6. This prediction is borne out by experiment.

TABLE 1

<sup>13</sup>C CHEMICAL SHIFTS FOR COMPOUNDS **1** AND **7**

CARBON ATOM	COMPOUND		DIFFERENCE
	<b>1</b>	<b>7</b>	
2	108.4	107.3	1.1
3a	158.0	158.7	-0.7
4	139.4	140.8	-1.4
5	120.0	118.4	1.6
6	129.1	122.6	6.5
7	126.7	135.8	-9.1
7a	155.85	133.6	22.25

Thus, by contrast with the parent compound, the 1-oxide **7** reacts with piperidine by displacement of the 4-bromine atom, to give 6-bromo-4-piperidino-2*H*-benzimidazole-2-spirocyclohexane 1-oxide **16** (53%). Morpholine reacts similarly, with concomitant deoxygenation in this case (possibly thermally during recrystallisation of the product), to give a product assigned structure **17** (46%). Entry of the morpholino-group must occur prior to deoxygenation, otherwise the expected product would be **15**, as described before.

**16****17**

In our attempts to synthesise other brominated derivatives of 2*H*-benzimidazole-2-spirocyclohexane we have studied bromination reactions of the parent compound. Elemental bromination in acetic acid or tetrachloromethane, even at 0 °C, produced intractable tars whilst attempted bromination with either *N*-bromosuccinimide or *N*-bromoacetamide in refluxing tetrachloromethane in the presence of a radical initiator (AIBN or dibenzoyl peroxide) afforded mainly starting material. Irradiation of a mixture of 2*H*-benzimidazole-2-spirocyclohexane and bromine in refluxing tetrachloromethane produced a black, intractable precipitate. Attempted bromination with one, two, or more equivalents of *N*-bromosuccinimide in anhydrous dichloromethane in the presence of silica<sup>7</sup> afforded only starting material, even when a large excess of the reagent was employed and the solvent refluxed.

4,5,6,7-Tetrachloro-2*H*-benzimidazole-2-spirocyclohexane **9** has been synthesised *via* chlorination of benzotriazole,<sup>8</sup> reduction of the 4,5,6,7-tetrachlorobenzotriazole produced with zinc and hydrochloric acid in ethanol, condensation of the resulting tetrachloro-*o*-phenylenediamine (obtained in 65% yield<sup>9</sup>) with cyclohexanone, and oxidation of the 4,5,6,7-tetrachloro-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane obtained with manganese dioxide.<sup>10</sup> We prepared 4,5,6,7-tetrabromobenzotriazole in 46% yield by elemental bromination of benzotriazole in nitric acid<sup>11</sup> but all attempts to reduce it to tetrabromo-*o*-phenylenediamine, e.g. with zinc and hydrochloric acid in ethanol at 0 °C, gave complex and intractable mixtures. Reduction with tin and hydrochloric acid similarly failed; in this case starting material was recovered. Presumably the ease with which bromine is lost during reduction procedures will make the availability of the hitherto unknown tetrabromo-*o*-phenylenediamine *via* this route more difficult than the corresponding availability of tetrachloro-*o*-phenylenediamine.

## EXPERIMENTAL

IR spectra were recorded for liquid films or Nujol mulls between sodium chloride plates using either a Perkin-Elmer 257 or 297 spectrometer. <sup>1</sup>H NMR spectra were recorded in deuteriochloroform (CDCl<sub>3</sub>) at 300.13 MHz with a Bruker AC300 FT instrument using TMS as internal standard (coupling constants *J* in Hz). <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> at 75.47 MHz using the same instrument with reference to the solvent signal, whilst mass spectra (EI) were recorded with a Kratos MS30 spectrometer. Mass spectral data refers to ions containing <sup>79</sup>Br and <sup>35</sup>Cl only; the isotope pattern was observed for the molecular composition given.

Chromatographic separations were carried out on columns packed either with silica M.F.C. of 60-120 mesh, supplied by BDH Ltd., or on CAMAG basic alumina of 100-250 mesh and pH 9.3-9.7, supplied by Fisons Ltd.

Light petroleum refers to the b.p. range 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<sub>4</sub>), and evaporated under reduced pressure using a rotary evaporator.

M.p.'s were recorded with a Buchi m.p. apparatus.

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

The following compounds were prepared by literature procedures: 1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane (81.5% yield), m.p. 138-140 °C (from ethanol) (lit.,<sup>12</sup> 96% and m.p. 138 °C); 2*H*-benzimidazole-2-spirocyclohexane (95%), m.p. 63-65 °C (from light petroleum) (lit.,<sup>10</sup> 70% and m.p. 64-65 °C); 4,6-dibromo-2-nitroaniline (29%), m.p. 126-127 °C (from ethanol) (lit.,<sup>6</sup> 29% and m.p. 126-127 °C); 3,5-

dibromo-*o*-phenylenediamine **10** (55%), m.p. 81-82 °C (from cyclohexane) (lit.,<sup>6</sup> 55% and m.p. 81-82 °C); and 4,5,6,7-tetrabromobenzotriazole (46%), m.p. 262-266 °C (from acetic acid) (lit.,<sup>11</sup> 54% and m.p. 262-266 °C).

4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1**. - (a) Cyclohexanone (4.3 cm<sup>3</sup>, 4.07 g, 41.5 mmol) was added to 3,5-dibromo-*o*-phenylenediamine (10.0 g, 38.0 mmol) in acetonitrile (100 cm<sup>3</sup>) and the resulting solution was heated under reflux for 1 h and cooled, then ice-cold water (150 cm<sup>3</sup>) was added. The product was extracted with ethyl acetate (3 x 75 cm<sup>3</sup>) and, after removal of the solvents, chromatographed on alumina. Light petroleum eluted 4,6-dibromo-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane **5** (6.0 g, 46%) as a yellow oil which was used without further purification. Trituration and prolonged cooling failed to produce a solid.

(b) Manganese dioxide (18.0 g, 0.20 mmol) was added to a vigorously stirred solution of 4,6-dibromo-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane **5** (6.0 g, 17.3 mmol) in dichloromethane (150 cm<sup>3</sup>) at ambient temperature and the resulting mixture was stirred for a further 30 min, then filtered through Celite. Removal of the solvent gave the crude **product 1** (5.6 g, 95%) which was recrystallised from light petroleum (b.p. 40-60 °C), to give yellow needles, m.p. 91-93 °C;  $\delta_{\text{H}}$  1.0-2.4 (10H, br, m, cyclohexyl), 7.35 (1 H, d, *J* 2.0, 5-H), and 7.43 (1 H, d, *J* 2.0, 7-H) (Found: C, 41.6; H, 3.6; N, 8.3%; *M*<sup>+</sup>, 342. C<sub>12</sub>H<sub>12</sub>Br<sub>2</sub>N<sub>2</sub> requires C, 41.9; H, 3.5; N, 8.1%; *M*, 342). 7-H and 5-H were assigned as follows. Compound **1** (8.9 mg) was dissolved in deuteriochloroform (500  $\mu$ l) and tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato] europium(III) [Eu(tfc)<sub>3</sub>] (98.4 mg) was dissolved in deuteriochloroform (100  $\mu$ l). The <sup>1</sup>H NMR spectrum of **1** was run with 16K data points along a 2,700 Hz sweep. Then 1,3,5,7,9,11,13, and 17  $\mu$ l aliquots of the europium shift reagent solution were added successively and, after shaking the tube to achieve homogeneity, the spectra were recorded. The spectra were stack-plotted with absolute intensities scaled to the initial spectrum with the result described in the Discussion.

Reactions of 4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1**. - (a) With one mol equiv. of sodium methoxide. - Sodium methoxide was prepared by addition of sodium (0.3 g, 13.0 mmol) to cool, anhydrous methanol (50 cm<sup>3</sup>) under nitrogen. 4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** (2.2 g, 6.40 mmol), was added and the resulting solution was stirred and heated under reflux for 3 h, then cooled and poured into cold water (150 cm<sup>3</sup>). Ethyl acetate (3 x 75 cm<sup>3</sup>) extracted a solid which was chromatographed on silica. Light petroleum-ethyl acetate eluted a mixture (0.8 g, 43%) of 5-bromo-6-methoxy-**11** and 6-bromo-4-methoxy-2*H*-benzimidazole-2-spirocyclohexane **12**, m.p. 111-163 °C (from light petroleum);  $\delta_{\text{H}}$  1.20-2.20 (10 H, m, cyclohexyl), 3.75 (3 H, s, OMe), 3.85 (3 H, s, OMe), 6.25 (1 H, d, *J* 3.0, 5-H), 6.34 (1 H, d, *J* 1.0, 4-H), 7.05 (1 H, d, *J* 3.0, 7-H), and 7.60 (1 H, d, *J* 1.0, 7-H) (Found: C, 52.6; H, 5.2; N, 9.45%; *M*<sup>+</sup>, 294. C<sub>13</sub>H<sub>15</sub>BrN<sub>2</sub>O requires C, 52.9; H, 5.1; N, 9.5%; *M*, 294). The ratio of the OMe signals at  $\delta$  3.75 and 3.85 was 9:7.

(b) With two mol equiv. of sodium methoxide. - The reaction described in (a) was repeated using two mol equiv. of the reagent and a 6 h reaction period. A solid was extracted which was chromatographed as before. The major product was 5,6-dimethoxy-2*H*-benzimidazole-2-spirocyclohexane **13** (0.42 g, 30%), m.p. 166-168 °C (lit.,<sup>3</sup> 167 °C);  $\delta_{\text{H}}$  1.40-2.00 (10 H, m, cyclohexyl), 3.79 (6 H, s, 2 x OMe) and 6.46 (2 H, s, 4-H and 7-H).



(c) With sodium 2,3-dichlorophenoxide. - 4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** (2.0 g, 5.81 mmol) was added to a stirred solution of sodium 2,3-dichlorophenoxide (1.08 g, 5.85 mmol) in dry methanol (30 cm<sup>3</sup>) under nitrogen and the resulting solution was heated under reflux for 3 h, then poured into ice-cold water (150 cm<sup>3</sup>). Extraction with ethyl acetate (3 x 75 cm<sup>3</sup>) gave a solid which was chromatographed on silica. Light petroleum-ethyl acetate eluted 4-bromo-6-(2,3-dichlorophenoxy)-2*H*-benzimidazole-2-spirocyclohexane **2** (0.94 g, 38%), as the major product, m.p. 176-177 °C (from light petroleum);  $\delta_{\text{H}}$  1.15-2.20 (10 H, m, cyclohexyl), 6.00 (1 H, d, *J* 1.0, 5-H), 7.05-7.30 (2 H, m, ArH), and 7.32-7.45 (2 H, m, ArH + 7-H) (Found: C, 51.0; H, 3.7; N, 6.7%; *M*<sup>+</sup>, 424. C<sub>18</sub>H<sub>15</sub>BrCl<sub>2</sub>N<sub>2</sub>O requires C, 50.75; H, 3.55; N, 6.6%; *M*, 424). Another fraction (0.32 g, 19%) was isolated which was shown to be a mixture of compounds **11** and **12**.

(d) With sodium benzenesulfinate. - A solution of sodium benzenesulfinate (1.05 g, 6.4 mmol) in water (25 cm<sup>3</sup>) was added to a stirred solution of 4,6-dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** (2.0 g, 5.81 mmol) in ethanol (40 cm<sup>3</sup>) followed by acetic acid (0.38 cm<sup>3</sup>), and the resulting solution was stirred at ambient temperature for a further 30 min, then poured into ice-cold water (250 cm<sup>3</sup>). Dichloromethane (3 x 75 cm<sup>3</sup>) extracted a solid which was chromatographed on silica. Light petroleum-ethyl acetate (4:1) eluted 4-bromo-6-phenylsulfonyl-2*H*-benzimidazole-2-spirocyclohexane **3** (2.0 g, 85%), m.p. 133-135 °C (from light petroleum-ethyl acetate),  $\nu_{\text{max}}/\text{cm}^{-1}$  1140 and 1320 (SO<sub>2</sub>);  $\delta_{\text{H}}$  0.65-2.30 (10 H, m, cyclohexyl), 7.43-7.75 (4 H, m, ArH and 4-H), and 7.78-8.09 (3 H, m, ArH and 7-H) (Found: C, 53.4; H, 4.4; N, 6.7%; *M*<sup>+</sup>, 404. C<sub>18</sub>H<sub>17</sub>BrN<sub>2</sub>O<sub>2</sub>S requires C, 53.4; H, 4.2; N, 6.9%; *M*, 404).

(e) With pyridin-2(1*H*)-thione. - Pyridin-2(1*H*)-thione (0.72 g, 6.5 mmol) was added to a stirred a solution of 4,6-dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** (2.0 g, 5.81 mmol) in dry methanol (25 cm<sup>3</sup>) at ambient temperature (a fluorescent orange colour developed) and the resulting solution was stirred at ambient temperature for a further 3 h, then poured into cold water (150 cm<sup>3</sup>). Ethyl acetate (3 x 75 cm<sup>3</sup>) extracted a product which was chromatographed on silica. Light petroleum-ethyl acetate eluted 4-bromo-1,3-dihydro-6-(pyridin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **6** (1.1 g, 51%) as the major product, a cream solid which turned rapidly orange in air, m.p. 182-184 °C (from light petroleum-ethyl acetate),  $\nu_{\text{max}}/\text{cm}^{-1}$  3200 (NH) and 3350 (NH);  $\delta_{\text{H}}$  0.65-1.90 (10 H, m, cyclohexyl), 4.12 (1 H, br s, exchangeable, NH), 4.47 (1 H, br s, exchangeable, NH), 6.68-6.72 (3 H, m, ArH and 5-H and 7-H), 6.92-6.96 (1 H, m, ArH), 7.38-7.44 (1 H, m, ArH), and 8.37-8.39 (1 H, d, ArH) (*M*<sup>+</sup>-1, 374.0303. C<sub>17</sub>H<sub>18</sub>BrN<sub>3</sub>S requires *M*-1, 374.0326). Due to the instability of this compound it was not possible to obtain microanalytical results.

(f) With pyrimidin-2(1*H*)-thione. - A similar reaction to that described in (e) with pyrimidin-2(1*H*)-thione gave 5,7-dibromo-1,3-dihydro-4-(pyrimidin-2-ylthio)-2*H*-benzimidazole-2-spirocyclohexane **14** (38%), cream solid, m.p. 186-188 °C (from light petroleum - ethyl acetate),  $\nu_{\text{max}}/\text{cm}^{-1}$  3250 (NH) and 3360 (NH);  $\delta_{\text{H}}$  1.32-2.00 (10 H, br m, cyclohexyl), 4.10 (1 H, br s, exchangeable, NH), 4.44 (1 H, br s, exchangeable, NH), 6.65 (1 H, s, 6-H), 6.92 (1 H, t, ArH), and 8.45 (2 H, d, ArH) (Found: C, 42.3; H, 3.8; N, 12.0%; *M*<sup>+</sup>, 454. C<sub>16</sub>H<sub>16</sub>Br<sub>2</sub>N<sub>4</sub>S requires C, 42.2; H, 3.5; N, 12.3%; *M*, 454).

(g) With morpholine. - Morpholine (0.51 ml, 0.51 g, 5.85 mmol) was added to a stirred solution of 4,6-dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** (2.0 g, 5.81 mmol) in ethanol (15 cm<sup>3</sup>) at ambient

temperature and the resulting solution was stirred overnight, then poured into ice-cold water (150 cm<sup>3</sup>). Ethyl acetate (3 x 75 cm<sup>3</sup>) extracted the crude product which was chromatographed on silica. Light petroleum-ethyl acetate eluted 5,7-dibromo-4-morpholino-2H-benzimidazole-2-spirocyclohexane 15 (0.8 g, 32%), an orange solid with m.p. 125-127 °C (from light petroleum);  $\delta_{\text{H}}$  1.00-2.15 (10 H, br m, cyclohexyl), 3.10 (2 H, br m, morpholino), 3.56 (2H, br m, morpholino), 3.78 (4 H, t, morpholino), and 7.61 (1 H, s, 6-H) (Found: C, 44.0; H, 4.5; N, 9.6%;  $M^+$ , 427.  $\text{C}_{16}\text{H}_{19}\text{Br}_2\text{N}_3\text{O}$  requires C, 44.4; H, 4.4; N, 9.8%;  $M$ , 427).

(h) With piperidine. - A similar reaction with piperidine gave 4-bromo-6-piperidino-2H-benzimidazole-2-spirocyclohexane 4 (43%) as a purple, amorphous solid;  $\delta_{\text{H}}$  1.16-2.24 (16 H, br m, cyclohexyl + piperidino), 3.20-3.28 (4H, br m, piperidino), 6.13 (1 H, d,  $J$  2.0, 5-H), and 7.33 (1 H, d,  $J$  2.0, 7-H) (Found:  $M^+$ , 347.1010.  $\text{C}_{17}\text{H}_{22}\text{BrN}_3$  requires  $M$ , 347.0998).

(i) Oxidation. - *m*-Chloroperoxybenzoic acid (technical grade, 85%) (1.01 g, 5.85 mmol) was added to a stirred solution of 4,6-dibromo-2H-benzimidazole-2-spirocyclohexane **1** (1.0 g, 2.90 mmol) in dichloromethane (25 cm<sup>3</sup>) at ambient temperature and the resulting solution was stirred in the dark overnight. Then the reaction mixture was filtered and the solid residue was washed with dichloromethane until it was colourless. The solvent was evaporated under reduced pressure and the crude product chromatographed on silica. Light petroleum-ethyl acetate (20:1) eluted 4,6-dibromo-2H-benzimidazole-2-spirocyclohexane 1-oxide 7 (0.5 g, 48%), an orange solid with m.p. 95-97 °C [from light petroleum (b.p. 40-60 °C)];  $\delta_{\text{H}}$  0.70-2.10 (10 H, br m, cyclohexyl), 7.40 (1 H, d,  $J$  2.0, 5-H), and 7.46 (1 H, d,  $J$  2.0, 7-H) (Found: C, 39.3; H, 3.5; N, 7.6%;  $M^+$ , 358.  $\text{C}_{12}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}$  requires C, 40.0; H, 3.4; N, 7.8%;  $M$ , 358).

Reactions of 4,6-Dibromo-2H-benzimidazole-2-spirocyclohexane 1-Oxide 7. - (a) With piperidine. Piperidine (0.5 ml, 0.43 g, 5.0 mmol) was added to a stirred solution of 4,6-dibromo-2H-benzimidazole-2-spirocyclohexane 1-oxide **7** (0.6 g, 1.67 mmol) in ethanol (10 cm<sup>3</sup>) at ambient temperature, whereupon the colour of the solution changed from yellow to purple. The resulting solution was stirred overnight, then poured into ice-cold water (150 cm<sup>3</sup>). Ethyl acetate (3 x 25 cm<sup>3</sup>) extracted the crude product which was chromatographed on silica. Light petroleum-ethyl acetate (2:1) eluted 6-bromo-4-piperidino-2H-benzimidazole-2-spirocyclohexane 1-oxide 16 (0.32 g, 53%), dark-red solid, m.p. 142-143 °C (from light petroleum);  $\delta_{\text{H}}$  1.19-2.32 (16 H, br m, cyclohexyl + piperidino), 3.14-3.28 (4 H, br m, piperidino), 6.07 (1 H, d,  $J$  2.0, 5-H), and 7.43 (1 H, d,  $J$  2.0, 7-H) (Found: C, 56.3; H, 6.1; N, 11.2%;  $M^+$ , 363.  $\text{C}_{17}\text{H}_{22}\text{BrN}_3\text{O}$  requires C, 56.05; H, 6.1; N, 11.5%;  $M$ , 363).

(b) With morpholine. - A similar reaction to that described in (a) with morpholine gave 6-bromo-4-morpholino-2H-benzimidazole-2-spirocyclohexane 17 (46%), m.p. 198-200 °C (from light petroleum);  $\delta_{\text{H}}$  0.80-2.15 (10 H, br m, cyclohexyl), 3.17-3.20 (4 H, m, morpholino), 3.78-3.82 (4 H, m, morpholino), 6.15 (1 H, d,  $J$  2.0, 5-H), and 7.41 (1 H, d,  $J$  2.0, 7-H) (Found: C, 54.3; H, 5.45; N, 11.6%;  $M^+$ , 349.  $\text{C}_{16}\text{H}_{20}\text{BrN}_3\text{O}$  requires C, 54.8; H, 5.8; N, 12.0%;  $M$ , 349).

X-Ray Crystallographic Analysis Data for 4-Bromo-6-(2,3-dichlorophenoxy)-2H-benzimidazole-2-spirocyclohexane 2. - Crystal data. Compound **2**:  $\text{C}_{18}\text{H}_{15}\text{BrCl}_2\text{N}_2\text{O}$ ,  $M = 426.1$ , monoclinic,  $a = 10.860(3)$ ,  $b =$

7.081(2),  $c = 11.939(3)$  Å,  $\beta = 107.57(2)^\circ$ ,  $U = 875.3(4)$  Å<sup>3</sup>, space group P2<sub>1</sub>,  $Z = 2$ ,  $D_c = 1.617$  Mg m<sup>-3</sup>,  $\mu(\text{Mo-K}\alpha) = 2.639$  mm<sup>-1</sup>,  $\lambda = 0.71073$  Å,  $F(000) = 428$ , crystal size 0.3 x 0.3 x 0.2 mm.

**Data Collection.** All data were collected on a Siemens R3m/V diffractometer with Mo-K $\alpha$  radiation, graphite monochromated, and using the  $\omega$ -2 $\theta$  scan mode. Data were corrected for a 2.2% deterioration in the intensities of three standard reflections collected every 50 reflections. The 2 $\theta$  range was 2-50°, and the index range was  $0 \leq h \leq 12$ ,  $-8 \leq k \leq 8$ ,  $-14 \leq l \leq 13$ . 4643 reflections were collected, of which 3,095 were independent ( $R_{\text{int}} = 0.025$ ) and 2823 satisfied the restriction  $F > 4.0\sigma(F)$  and were used in the refinement. The data were corrected of absorption using an empirical azimuthal scan technique.

**Structure Determination and Refinement.** The structure was solved by direct methods and refined by full-matrix least squares routines [quantity minimized  $\sum w(F_o - F_c)^2$ ]. The hydrogen atoms were found from difference maps and allowed to ride on their parent carbon atoms with fixed isotropic thermal parameters  $U = 0.08$  Å<sup>2</sup> during refinement.

At convergence  $R = 0.043$ , and  $wR = 0.053$  where  $w^{-1} = \sigma^2(F) + 0.0004F^2$ . The corresponding residuals for all data were  $R = 0.049$  and  $wR = 0.054$ . The goodness-of-fit was 1.77, the largest  $\Delta/\sigma$  0.001 with a data-to-parameter ratio of 13.0:1. The final difference map showed no feature greater than  $+0.63$  eÅ<sup>-3</sup> or less than  $-1.10$  eÅ<sup>3</sup>.

Fig. 1 (see Discussion) shows the numbering scheme used together with the thermal ellipsoids for each atom. All calculations were performed using the SHELXTL PLUS program write.<sup>13</sup> Thermal parameters and hydrogen atom coordinates have been deposited at the Cambridge Crystallographic Data Centre.

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