2*H*-Benzimidazoles (Isobenzimidazoles). Part 7.[1] A New Route to Triclabendazole [5-Chloro-6-(2,3-dichlorophenoxy)-2-methylthio-1*H*-benzimidazole] and Congeneric Benzimidazoles

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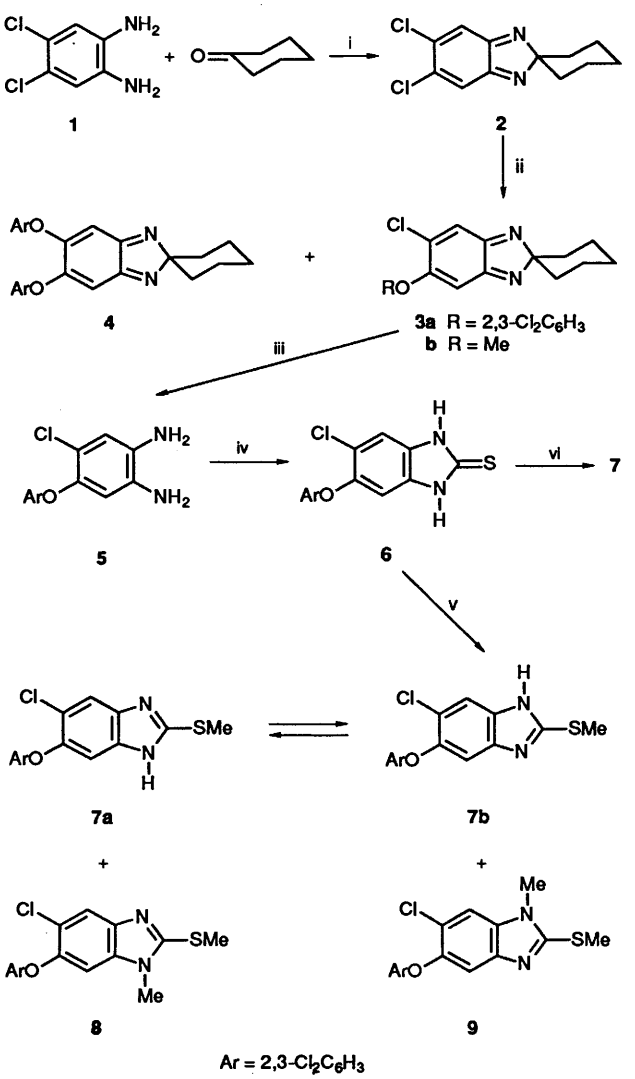
A new synthesis of the selective anthelmintic agent triclabendazole **7** from the readily available 5,6-dichloro-2*H*-benzimidazole-2-spirocyclohexane **2** by simple steps is described. Analogous benzimidazoles difficult to prepare by conventional methods are similarly obtained. Triclabendazole can exist as a low-melting metastable solid (m.p. 85–90 °C) convertible by heating or recrystallisation from ethanol into its stable form (m.p. 176–178 °C).

The importance of benzimidazole derivatives as anthelmintics is well established.[2] For instance triclabendazole **7** was recently shown[3] to be a safe and effective drug at low doses against all stages of *Fasciola hepatica* in sheep and cattle by a mechanism apparently different from that of other benzimidazole anthelmintics.

The synthetic versatility of 2*H*-benzimidazoles especially for the preparation of 1*H*-benzimidazoles with nucleophilic substituents in the C-5(6)-position[4–6] prompted us to explore an alternative and more convenient route (Scheme 1) for the preparation of triclabendazole **7** than the published one.[3c,7] Dichloro-2*H*-benzimidazole **2** is obtained in excellent yield[4] from the condensation of 4,5-dichloro-*o*-phenylenediamine **1** and cyclohexanone followed by oxidation with manganese dioxide. Both 'vinylic' chlorines in **2**, as we have shown,[4b] are subject to ready replacement by nucleophiles owing to 'umpolung'. Thus, an excess of sodium 2,3-dichlorophenoxide under reflux in methanol gave the diphenoxy-2*H*-benzimidazole **4** in 80% yield.

However, a more selective replacement occurred on treatment of the dichloro compound **2** with a 1.5 mol excess of sodium 2,3-dichlorophenoxide in boiling methanol to yield the mono-substituted 2*H*-benzimidazole **3a** in 62% yield (*cf.* Table 1). It was readily separable by chromatography (Al_2O_3) from the disubstituted product **4** (29%) as well as from other by-products. The reductive ring-opening of **3a** with sodium dithionite in aqueous ethanol occurred rapidly to give the *o*-phenylenediamine **5** (85%). Treatment with carbon disulfide in DMF gave the 2-thione **6** (90%), which on alkylation with methyl iodide in acetone in the presence of potassium carbonate gave three methylated compounds readily separable by chromatography (Al_2O_3). The two minor products were identified as the isomeric *N*-methylbenzimidazoles **8** and **9** (*ca.* 8% each), m.p.s 132–134 °C and 181–182 °C, respectively. Since benzimidazolethiones may react as ambident nucleophiles at both nitrogen and sulfur, dimethylated products were to be expected, but alkyl halides give preferentially 2-thioalkylbenzimidazoles.[8]

The assignment of the two dimethylated products was made on the following basis. Each compound showed two distinct singlets in their ^1H NMR spectra which, by analogy with a previous observation,[4a] are assigned to the 4-H and 7-H protons in **8** and **9** situated next to the pyridine-type and pyrrole-type nitrogen respectively. Irradiation of the singlet at δ 7.57 in the lower melting isomer (m.p. 132–134 °C) caused enhancement of the *N*-methyl peak at δ 3.65 and the NOE also extended to the doublet of 6′-H in the phenoxy ring. This evidence clearly



Scheme 1 *Reagents:* i, MnO_2, heat; ii, 2,3-$Cl_2C_6H_3ONa$; iii, $Na_2S_2O_4$; iv, CS_2; v, MeI–Me_2CO–K_2CO_3; vi, MeI–EtOH–KOH

Table 1 Ratios of products using different ratios of sodium 2,3-dichlorophenolate to **2**[a]

2,3-$Cl_2C_6H_3ONa$:**2**[b]	Products[b] **2**	**3a**	**4**	**3b**
1:1.2	10	54	36	—
1:1.5	4.5	62	29	4.5
1:2.5	1.0	39	60	—

[a] Boiling MeOH, 3 h. [b] Mol ratio.

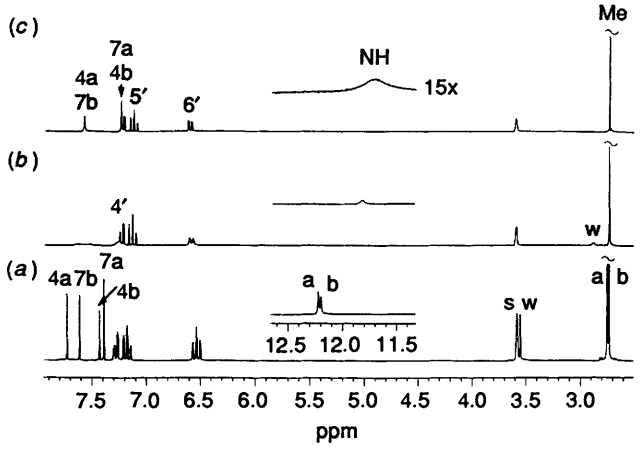
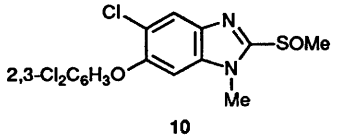


Fig. 1 ^1H NMR 250.13 MHz spectra of triclabendazole **7** (m.p. 176–178 °C) in [$^2H_6$]-THF: (*a*) 223 K; (*b*) 283 K; (*c*) 300 K. The peak numbers correspond to the positions in the tautomers **7a** ⇄ **7b**.

shows that the isomer has structure **8** in which the phenoxy group and the methyl substituent are on the same side of the molecule as 7-H (*cf.* ref. 8). By contrast, irradiation of the proton at δ 7.85 in the higher melting isomer (m.p. 181–182 °C) resulted only in enhancement of the *N*-methyl group. The 7-H proton in **8** appears upfield (δ 7.57) from 4-H (δ 7.79) owing to the influence of the electron-releasing pyrrole-type nitrogen N-1. This situation is unexpectedly reversed in **9** where 7-H (δ 7.85) is found downfield from 4-H (δ 7.45), although it is next to the pyrrole nitrogen. It is in contrast to the shielding effect on C-7 in the ^{13}C NMR spectrum (*cf.* Table 3) in both isomers **8** and **9** exerted by the *N*-methyl group as in an analogous case of *N*-methylpyrrole.[9]

The main product (65%) had the expected analytical and spectral data for triclabendazole **7**. It is noteworthy that methylation with methyl iodide in aqueous ethanol in the presence of potassium hydroxide gave the triclabendazole **7** (92%) without any of the dialkylated products **8** and **9**. Its oxidation (*m*-chloroperoxybenzoic acid) gave the reported[3c] but analytically unconfirmed sulfoxide **10**.



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Unexpectedly, our product **7** had a low melting point ranging over several degrees (85–90 °C) which is significantly different from that quoted in the literature[3c] (m.p. 175–176 °C). However, when kept for a few weeks or recrystallised from aqueous ethanol it was converted into the reported high-melting product. Conversely, addition of water to a solution of the high-melting sample in ethanolic potassium hydroxide precipitated the low-melting compound (90%). On TLC (Al_2O_3) the two compounds

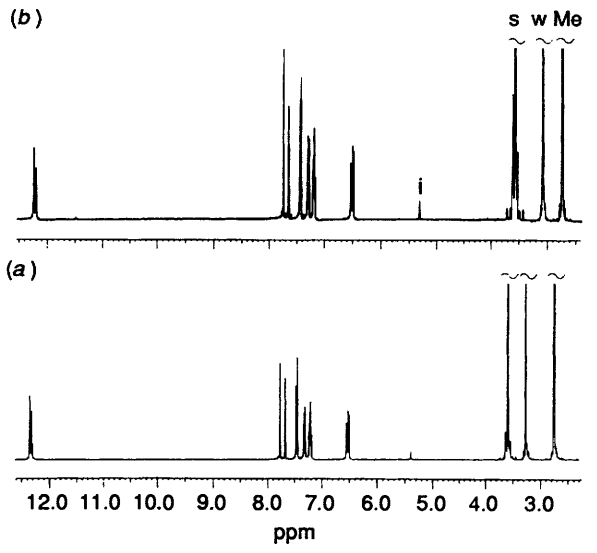


Fig. 2 ^1H NMR (500.15 MHz) spectra in [$^2H_6$]-THF at 233 K: (*a*) **7** (m.p. 85–90 °C); (*b*) **7** (m.p. 176–178 °C). The peaks i, Me, s, and w denote impurity, methyl, solvent and water.

(R_F value) behaved similarly. Also the ^1H and ^{13}C NMR spectra of the two triclabendazoles were closely similar at room temperature (*cf.* Tables 2 and 3). We tentatively considered that the two melting points could be accounted for on the following basis. Benzimidazoles normally undergo an intermolecular proton transfer between N-1 and N-3 in the azole ring (*cf.* **7a** ⇄ **7b**) which at room temperature is very rapid and has been widely studied by ^1H NMR spectroscopy.[10] In view of the spectral similarity of the two compounds we surmised that the low melting compound could be one of the tautomers **7a** or **7b** being metastable at room temperature possibly owing to a substituent effect. Large substituents are known to influence the tautomeric equilibrium.[9,10a] We tested this hypothesis by carrying out a variable temperature ^1H NMR study on the two triclabendazoles, with a view to finding out whether both or only one of the compounds consists of a tautomeric mixture. In the high-melting compound the singlet peaks began to broaden on lowering the temperature and became eventually distinct doublets (*cf.* Fig. 1*a–c*) corresponding to the tautomers **7a** ⇄ **7b**. Their proportion was estimated from the integration as being 55.5:44.5 respectively. The ^1H NMR spectrum of the low-melting form (m.p. 85–90 °C) also showed splitting of the singlets into doublets at low temperature (*cf.* Fig. 2*a*). Moreover, comparison of this spectrum with that of the high-melting compound at this temperature (Fig. 2*b*) proved the two compounds to be practically identical. Also, on warming, gradual coalescence of the doublets in each spectrum occurred and was complete at ambient temperature. These observations confirm that both triclabendazoles are tautomeric mixtures **7a** ⇄ **7b** and chemically identical in solution. Hence the difference in their m.p.s cannot be attributed to a metastable tautomer. Water or solvent of crystallisation was also excluded as a possible reason for the variation in the m.p.s. It appears that the existence of the two interconvertible modifications of triclabendazole are best accounted for by a dimorphism[11] probably arising from different crystalline forms. Visual inspection showed the lower-melting compound to be microcrystalline. We were not able to obtain crystals from the higher-melting amorphous triclabendazole. Also, attempts to grow suitable crystals from either compound for an X-ray analysis failed.

The advantage of our alternative synthesis of triclabendazole (Scheme 1) lies in the availability of the starting material **1** but, more importantly, in its versatility for preparing congeneric compounds of potential anthelmintic activity. For instance, the

Table 2 ^{1}H NMR spectra of triclabendazole 7 and related benzimidazoles[a]

Compound	4-H	7-H	4′-H	5′-H	6′-H	Me	Me	NH
7 (m.p. 85–90 °C)	7.68 (s)	7.34 (s)	7.35 (dd)	7.25 (dd)	6.64 (dd)	2.68 (s)	—	12.80 (s)
7 (m.p. 176–178 °C)	7.66 (s)	7.35 (s)	7.37 (dd)	7.27 (dd)	6.62 (dd)	2.68 (s)	—	12.68 (s)
8	7.79 (s)	7.57 (s)	7.36 (dd)	7.26 (dd)	6.65 (dd)	2.75 (s)	3.65 (s)	—
9	7.45 (s)	7.85 (s)	7.32 (dd)	7.24 (dd)	6.61 (dd)	2.75 (s)	3.69 (s)	—
11d	7.66 (s)	7.66 (s)	—	—	—	2.68 (s)	—	12.82 (s)
11a	7.42 (s)	7.42 (s)	7.28 (dd)	7.19 (dd)	6.73 (dd)	2.69 (s)	—	12.79 (s)

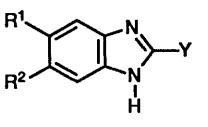
[a] Spectra were recorded in [$^2H_6$]-DMSO (δ values).

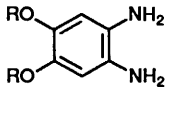
Table 3 ^{13}C NMR chemical shifts of triclabendazole 7 and related benzimidazoles[a,b]

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	SMe	NMe
7 (m.p. 85–90 °C)	154.0	115.3	118.3	144.8	106.5	137.7 (sh)	138.9 (sh)	154.6	121.2	132.8	124.1	128.3	114.9	13.7	—
7 (m.p. 176–178 °C)	154.1	115.2 (br)	118.4	144.6	106.9 (br)	137.0 (br)	137.0 (br)	154.6	121.1	132.8	124.2	128.5	115.1	13.8	—
8	155.3	118.4	119.0	144.7	103.8	136.3	140.7	154.8	120.6	132.8	124.2	128.7	115.0	14.0	30.0
9	155.5	11.2	144.7	118.7	110.6	135.0	142.1	154.8	120.8	132.8	124.2	128.6	114.9	14.0	30.0
11d	154.7	114.7 (br)	123.5	123.5	114.7 (br)	138.95 (br)	138.95 (br)	—	—	—	—	—	—	13.6	—
11a	153.3	110.8	140.7	140.7	103.9	*c*	*c*	154.7	120.8	132.5	123.8	128.5	115.0	12.9	—

[a] Spectra were measured in [$^2H_6$]-DMSO with Me_4Si as internal standard (δ values). [b] br = broad; sh = sharp. [c] Not observed.

diphenoxy derivative **4** obtained in good yield (80%) by using an excess of the dichlorophenol, was converted by an analogous sequence of reactions (*cf.* Scheme 1) into the bis(dichlorophenoxy) compound **11a** without the problem of adventitious production of *S*,*N*-dimethyl compounds. Conversion of the bis(dichlorophenoxy)-*o*-phenylenediamine**12**intothe2-trifluoromethylbenzimidazole **11b** occurred in good yield (70%) with trifluoroacetic acid. This was also true for the preparation of the trifluoromethyl analogue **11c** from the diamine **5**. Treatment of the spiro compound **3a** with sodium benzenesulfinate gave rise to two products. The major compound resulted from nucleophilic displacement of the chlorine atom by the phenylsulfonyl group yielding the 2*H*-benzimidazole **15** together with the ring-opened **16**. Ring fission of 2*H*-benzimidazoles with sulfinic acid has been noted by us previously.[12] The corresponding diamine **13** which is a convenient starter for potential anthelmintic benzimidazoles was readily prepared (66%) in a one pot reaction from **3a** on treatment with sodium benzenesulfinate in a solution of acetic acid and ethanol followed by reaction with sodium dithionite and hydrochloric acid. With carbon disulfide it gave the thione **17** (91%). The 2*H*-benzimidazole **2** also reacted with sodium benzenesulfinate to give **18** which was converted ($Na_2S_2O_4$) into the diamine **19** (36%) a potentially useful intermediate for heterocyclic synthesis. The methoxycarbonylaminobenzimidazoles **11e**, **f** were made from the corresponding diamines **5** or **12** by interaction with methoxycarbonylisothiocyanate and dicyclohexylcarbodiimide in acetonitrile as a convenient way of introducing the carbamate moiety.[13]





11a $R^1 = R^2 = 2,3\text{-}Cl_2C_6H_3O$, Y = MeS
b $R^1 = R^2 = 2,3\text{-}Cl_2C_6H_3O$, Y = F_3C
c R^1 = Cl, $R^2 = 2,3\text{-}Cl_2C_6H_3O$, Y = F_3C
d $R^1 = R^2$ = Cl, Y = MeS
e R^1 = Cl, $R^2 = 2,3\text{-}Cl_2C_6H_3O$, Y = MeO_2CNH
f $R^1 = R^2 = 2,3\text{-}Cl_2C_6H_3O$, Y = MeO_2CNH

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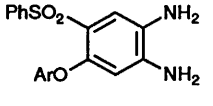

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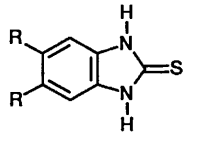
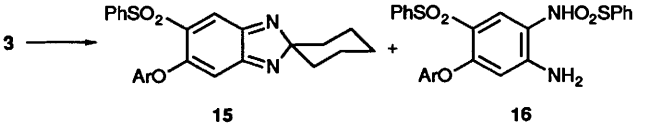
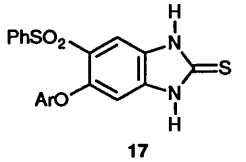


14 a R = $2,3\text{-}Cl_2C_6H_3O$
b R = Cl



15 **16**



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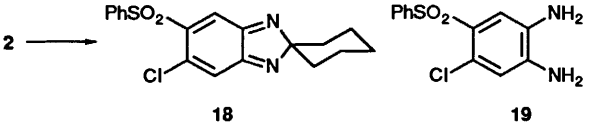

18 **19**

Ar = $2,3\text{-}Cl_2C_6H_3$

Experimental

IR spectra were recorded for Nujol mulls between sodium chloride plates with a Perkin-Elmer 257 or 297 spectrometer, ^{1}H NMR and ^{13}C NMR spectra were run on a Varian EM360 (60 MHz), Perkin-Elmer R32 (90 MHz) or Bruker Spectrospin (360 or 500 MHz) spectrometer using Me_4Si as internal standard. Mass spectra were recorded using a Kratos MS30 spectrometer: values given based on ^{35}Cl. Microanalyses (C, H, N) were carried out by Butterworth Laboratories Ltd. For column chromatography CAMAG basic alumina pH 9.3–9.7, 100–250 mesh (Fisons Ltd) or flash silica (Merck Ltd) were used. Light petroleum refers to the fraction b.p. 60–80 °C unless stated otherwise. The 4,5-dichloro-*o*-phenylenediamine **1** was supplied by Hoechst A.G. and was recrystallised twice from light petroleum (b.p. 80–100 °C)–ethyl acetate and had m.p. 160–162 °C.

Triclabendazole **7**.—A solution of sodium methoxide (1.62 g, 30 mmol) in methanol (60 cm^3) and 2,3-dichlorophenol (4.9 g, 30 mmol) was heated under reflux for 30 min under nitrogen. The mixture was slightly cooled and 5,6-dichloro-2*H*-benzimidazole-2-spirocyclohexane **2**[4a] (5.1 g, 20 mmol) was added. The reaction mixture was boiled for 3 h, cooled and then quenched by pouring into cold water (250 cm^3). The oily solid was extracted with ethyl acetate (4 × 75 cm^3) and the extracts were washed with dilute aqueous sodium hydroxide and water, dried ($MgSO_4$) and evaporated. The brown residue was chromatographed on alumina with light petroleum–ethyl acetate (10:1).

The first band gave 5-*chloro*-6-(2,3-*dichlorophenoxy*)-2H-*benzimidazole*-2-*spirocyclohexane* **3a** (4.7 g, 62%), m.p. 135–136 °C (from hexane); δ_H(90 MHz; $CDCl_3$) 7.5 (1 H, s, 7-H), 7.45–7.1 (3 H, m, ArH), 6.2 (1 H, s, 4-H) and 2.1–1.4 (10 H br, m, C-C_6H_{10}) (Found: C, 56.6; H, 4.0; N, 7.2%; M^+, 380. $C_{18}H_{15}Cl_3N_2O$ requires C, 56.6; H, 3.95; N, 7.3%; *M*, 380).

The second band gave 5,6-bis(2,3-*chlorophenoxy*)-2H-*benzimidazole*-2-*spirocyclohexane* **4** (3.0 g, 29%), m.p. 181–183 °C (from hexane–dichloromethane); δ_H(90 MHz; $CDCl_3$) 7.5–7.1 (6 H, m, ArH), 6.2 (2 H, s, 4- and 7-H) and 2.0–1.4 (10 H, br, m, C-C_6H_{10}) (Found: C, 57.1; H, 3.9; N, 5.6%; M^+, 506. $C_{24}H_{18}Cl_4N_2O_2$ requires C, 56.7; H, 3.6; N, 5.5%; *M*, 506).

The third band proved to be 5-*chloro*-6-*methoxy*-2H-*benzimidazole*-2-*spirocyclohexane* **3b** (0.24 g, 4.5%), a yellow solid, m.p. 151–153 °C (lit.,[4b] m.p. 152–153 °C).

For other reactant ratios see Table 1.

To a boiling solution of the derivative **3a** (6.2 g, 16 mmol) in ethanol (150 cm^3) and water (50 cm^3) was added sodium dithionite (13.3 g, 75 mmol). More hot aqueous ethanol was added to keep the solution clear. Heating was continued for 30 min and the solution was then quenched by pouring into cold water (500 cm^3). The solid was extracted with ethyl acetate (4 × 75 cm^3) and the combined extracts were washed with water, dried ($MgSO_4$) and chromatographed on flash silica with light petroleum–ethyl acetate (1:1) as eluent, to give 4-*chloro*-5-(2,3-*dichlorophenoxy*)-o-*phenylenediamine* **5** (4.2 g, 85%), m.p. 108–110 °C [from ethyl acetate–light petroleum (b.p. 80–100 °C)]; ν_{max}/cm^{-1} 3410 and 3340 (NH_2); δ_H(90 MHz; $CDCl_3$) 7.3–6.9 (2 H, m, ArH), 6.75 (1 H, s, 3-H), 6.6 (1 H, dd, ArH), 6.4 (1 H, s, 6-H) and 3.4 (4 H, br d, 2 × NH_2) (Found: C, 47.7; H, 3.1; N, 9.4%; M^+, 302. $C_{12}H_9Cl_3N_2O$ requires C, 47.5; H, 3.0; N, 9.2%; *M*, 302).

To a dimethylformamide (DMF) solution (50 cm^3) of the *o*-phenylenediamine **5** (4.86 g, 16 mmol) was added carbon disulfide (1.45 cm^3, 24 mmol). The reaction mixture was stirred and heated to 80 °C for 5 h under anhydrous conditions and then poured into water (250 cm^3). The aqueous suspension was extracted with ethyl acetate (4 × 75 cm^3) and the combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on flash silica with light petroleum–ethyl acetate (1:1), to give 5-*chloro*-6-(2,3-*dichlorophenoxy*)-1H-*benzimidazole*-2(3H)-*thione* **6** (4.9 g, 90%), m.p. 303–306 °C [from light petroleum (b.p. 80–100 °C)–ethyl acetate] ν_{max}/cm^{-1} 3200–3000 (NH); δ_H(90 MHz; [$^2H_6$]-DMSO) 12.7 (2 H, br s, NH), 7.5–7.2 (3 H, m, ArH), 6.95 (1 H, s, 4-H) and 6.75 (1 H, s, 7-H) (Found: C, 45.4; H, 2.1; N, 7.8%; M^+, 346. $C_{13}H_7Cl_3N_2OS$ requires C, 45.2; H, 2.0; N, 8.1%; *M*, 346).

To a solution of the above thione **6** (3.46 g, 10 mmol) in dry acetone (100 cm^3) containing potassium carbonate (anhyd.) (1.38 g, 10 mmol) was added methyl iodide (1.42 g, 10 mmol). The mixture was kept under reflux for 4 h, then cooled and the inorganic residue filtered off and washed with acetone. The brown solid obtained from evaporating the filtrate under reduced pressure was purified on flash silica by elution with dichloromethane.

The first band gave 6-*chloro*-5-(2,3-*dichlorophenoxy*)-1-*methyl*-2-*methylthio*-1H-*benzimidazole* **9** (0.29 g, 8%), m.p. 181–182 °C (from hexane–dichloromethane) (for NMR details see Tables 2 and 3) (Found: C, 47.9; H, 2.9; N, 7.3%; M^+, 372. $C_{15}H_{11}Cl_3N_2OS$ requires C, 48.2; H, 3.0; N, 7.5%; *M*, 372).

The second band gave the isomeric 5-*chloro*-6-(2,3-*dichlorophenoxy*)-1-*methyl*-2-*methylthio*-1H-*benzimidazole* **8** (0.3 g, 8%), m.p. 132–134 °C (from hexane) (for NMR details see Tables 2 and 3) (Found: C, 48.3; H, 2.9; N, 7.3%; *M*, 372).

The third band gave 5-*chloro*-6-(2,3-*dichlorophenoxy*)-2-*methylthio*-1H-*benzimidazole* **7** (triclabendazole) (2.35 g, 65%), m.p. 85–90 °C (from hexane) (For NMR details see Tables 2 and 3) (Found: C, 47.1; H, 2.85; N, 7.45%; M^+, 358. $C_{14}H_9Cl_3N_2OS$ requires C, 46.75; H, 2.5; N, 7.8%; *M*, 358).

Alternative methylation of the thione **6** (0.5 g, 1.45 mmol) dissolved in a mixture of ethanol (0.44 cm^3), potassium hydroxide (0.22 g, 3.9 mmol) and water (0.22 cm^3) occurred by addition of methyl iodide (0.21 g, 0.16 cm^3, 1.47 mmol). The mixture was stirred at ambient temperature for 30 min and then at 50 °C on a water bath for 1 h; finally it was poured into water (15 cm^3). The precipitate was filtered off, washed and dried to yield triclabendazole **7** (0.48 g, 92%), m.p. 85–90 °C. On recrystallisation from aqueous ethanol the compound had m.p. 176–178 °C (lit.,[3c] m.p. 175–176 °C). It was convertible into the low-melting form (m.p. 85–90 °C) as follows. A sample (179 mg) dissolved in a solution of potassium hydroxide (72 mg), water (0.1 cm^3), and ethanol (0.2 cm^3) was poured into water (40 cm^3). The precipitate had m.p. 85–90 °C, identical with the above compound.

5-*Chloro*-6-(2,3-*dichlorophenoxy*)-2-*methylsulfinyl*-1H-*benzimidazole* **10**.—To a solution of triclabendazole **7** (1.5 g, 4.2 mmol) in dichloromethane (200 cm^3) was added technical grade *m*-chloroperoxybenzoic acid (0.94 g, 4.6 mmol, 85% pure) and the mixture stirred for 1 h at 10 °C and then at ambient temperature for 12 h. The solution was washed with aqueous sodium bisulfite, saturated aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to yield the *sulfoxide* **10** (1.5 g, 95%) as a white solid, m.p. 176–178 °C; ν_{max}/cm^{-1} 3300–3100 (NH) and 1050 (SO); δ_H(90 MHz; $CDCl_3$) 7.85 (1 H, br s, 4-H), 7.4–7.0 (3 H, m, ArH), 6.65 (1 H, s, 7-H) and 3.2 (3 H, s, Me) (Found: C, 44.3; H, 2.5; N, 7.5%; M^+, 374. $C_{14}H_9Cl_3N_2O_2S$ requires C, 44.7; H, 2.4; N, 7.45%; *M*, 374).

5,6-*Bis*(2,3-*dichlorophenoxy*)-2-*methylthio*-1H-*benzimidazole* **11a**.—To a solution of sodium methoxide (3.24 g, 60 mmol) in methanol (60 cm^3) was added 2,3-dichlorophenol (9.8 g, 60 mmol). After the mixture had been heated under reflux for 30 min under nitrogen it was slightly cooled and the benzimidazole-2-spirocyclohexane **2** (5.1 g, 20 mmol) added to it. The solution was again heated under reflux for 5 h and then cooled and poured into cold water (250 cm^3). The oily solid was extracted with ethyl acetate (4 × 75 cm^3) and the combined extracts were washed with dilute aqueous hydroxide and water, dried ($MgSO_4$), and evaporated. The residue on recrystallisation [from light petroleum (b.p. 80–100 °C)–ethyl acetate with charcoal] gave *compound* **4** (8.1 g, 80%), m.p. 180–182 °C (*cf.* above).

Reduction with sodium dithionite as described for triclabendazole gave 4,5-bis(2,3-*dichlorophenoxy*)-o-*phenylenediamine* **12** (89%), m.p. 217–219 °C (from ethanol); ν_{max}/cm^{-1} 3420 and 3340 (NH_2); δ_H(90 MHz; [$^2H_6$]-DMSO + $CDCl_3$) 7.05 (4 H, d, ArH), 6.85–6.65 (2 H, m, ArH), 6.45 (2 H, s, 3- and 6-H) and 4.35 (4 H, br s, 2 × NH_2) (Found: C, 50.2; H, 2.8; N, 6.6%; M^+, 428. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.3; H, 2.8; N, 6.5%; *M*, 428).

This *o*-phenylenediamine **12** was converted into 5,6-bis(2,3-*dichlorophenoxy*)-1H-*benzimidazole*-2-(3H)-*thione* **14a** (88%), m.p. 248–250 °C [from ethyl acetate–light petroleum (b.p. 80–

100 °C)] by the method described for **6** (above); ν_{max}/cm^{-1} 3300–3000 (NH); δ(90 MHz; [$^2H_6$]-DMSO) (12.7 (2 H, br s, NH) and 7.4–6.88 (8 H, m, ArH) (Found: C, 48.6; H, 2.1; N, 6.0%; M^+, 470. $C_{19}H_{10}Cl_4N_2O_2S$ requires C, 48.3; H, 2.1; N, 5.9%; *M*, 470).

To a solution of this thione (1.6 g, 3.4 mmol) in dry acetone (50 cm^3) was added potassium carbonate (anhyd.) (0.47 g, 3.4 mmol) and methyl iodide (0.48 g, 3.4 mmol). After being heated under reflux (2.5 h), the mixture was poured into water and the product worked up as described for triclabendazole to give the *title compound* **11a** (1.45 g, 88%), m.p. 202–205 °C [from light petroleum (b.p. 80–100 °C)–ethyl acetate] (For NMR details see Tables 2 and 3) (Found: C, 49.5; H, 2.7; N, 5.85%; M^+, 486. $C_{20}H_{12}Cl_4N_2O_2S$ requires C, 49.4; H, 2.5; N, 5.8%; *M*, 486).

5,6-*Bis*(2,3-*dichlorophenoxy*)-2-*trifluoromethyl*-1H-*benzimidazole* **11b**.—A solution of the *o*-phenylenediamine **12** (1.5 g, 3.5 mmol) described above in trifluoroacetic acid (10 cm^3) and concentrated hydrochloric acid (2 cm^3) was heated under reflux for 2.5 h and then cooled and quenched in water (250 cm^3). After addition of an excess of sodium carbonate the product was extracted with ethyl acetate (3 × 50 cm^3). The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from light petroleum–ethyl acetate (1:1) gave the title *trifluoromethylbenzimidazole* **11b** (1.25 g, 70%), m.p. 223–225 °C; δ(90 MHz; [$^2H_6$]-DMSO + $CDCl_3$) 13.6 (1 H br s, NH), 7.6–7.0 (6 H, m, ArH) and 7.75 (2 H, s, 4- and 7-H) (Found: C, 46.9; H, 1.95; N, 5.5%; M^+, 508. $C_{20}H_9Cl_4F_3N_2O_2$ requires C, 47.3; H, 1.8; N, 5.5%; *M*, 508).

5-*Chloro*-6-(2,3-*dichlorophenoxy*)-2-*trifluoromethyl*-1H-*benzimidazole* **11c**.—The *o*-phenylenediamine **5** (1.05 g, 3.5 mmol) was treated with trifluoroacetic acid (10 cm^3) and hydrochloric acid (2 cm^3) for 3.5 h and the crude product worked up as described in the previous preparation. Recrystallisation from dichloromethane–hexane gave the title *trifluoromethylbenzimidazole* **11c** (1.06 g, 80%), m.p. 207–209 °C; δ_H([$^2H_6$]-DMSO) 14.19 (1 H, s, NH), 8.06 (1 H, s, 4-H), 7.58 (1 H, s, 7-H), 7.42 (1 H, dd, 4-H), 7.41 (1 H, dd, 5′-H) and 6.79 (1 H, dd, 6′-H) (Found: C, 44.5; H, 1.3; N, 7.3%; M^+, 380. $C_{14}H_6Cl_3F_3N_2O$ requires C, 44.1; H, 1.6; N, 7.3%; *M*, 380).

5,6-*Dichloro*-2-*methylthio*-1H-*benzimidazole* **11d**.—A reaction mixture consisting of 4,5-dichloro-*o*-phenylenediamine (3.72 g, 25 mmol), dry DMF (75 cm^3) and carbon disulfide (2.86 g, 2.26 cm^3, 37.5 mmol) was stirred for 4 h at 85–90 °C on an oil-bath. After the mixture had been allowed to cool to ambient temperature it was poured into cold water (400 cm^3) and the precipitate was filtered off, dried, and recrystallised from ethyl acetate–hexane to give the 5,6-*dichloro*-1H-*benzimidazole*-2-(3H)-*thione* **14b** (4.7 g, 86%), m.p. 344–346 °C (decomp.) (Found: C, 38.6; H, 1.7; N, 12.6%; M^+, 219. $C_7H_4Cl_2N_2S$ requires C, 38.4; H, 1.8; N, 12.8%; *M*, 219).

Methylation of the thione (1.1 g, 5.0 mmol) with methyl iodide (0.73 g, 0.32 cm^3, 5.1 mmol) in a mixture containing ethanol (2 cm^3), potassium hydroxide (0.78 g, 13.9 mmol) and water (0.8 cm^3) as described in the preparation of triclabendazole (*cf.* above) gave the title *benzimidazole* **11d** (0.98 g, 84%), m.p. 232–234 °C (from ethyl acetate–hexane) (For NMR details see Tables 2 and 3) (Found: C, 41.1; H, 2.3; N, 11.8%; M^+, 233. $C_8H_6Cl_2N_2S$ requires C, 41.2; H, 2.6; N, 12.0%; *M*, 233).

5-*Chloro*-6-(2,3-*dichlorophenoxy*)-2-*methoxycarbonylamino*-1H-*benzimidazole* **11e**.—The *o*-phenylenediamine **5** (0.71 g, 2.33 mmol) was added to a solution of methoxycarbonylisothiocyanate[13] (0.27 g, 2.33 mmol) and dicyclohexylcarbodiimide (0.55 g, 2.66 mmol) in dry acetonitrile (5 cm^3) and the mixture was heated under reflux for 1 h. The precipitate was filtered off, washed with aqueous methanol (20 cm^3, 80% methanol) dried and recrystallised from ethyl acetate, to give the title benzimidazole **11e** (0.36 g, 40%), m.p. 327–330 °C (decomp.); ν_{max}/cm^{-1} 1701 (C=O) and 3343 (NH); δ_H($CDCl_3$, [$^1H_6$]-DMSO) 11.56 (1 H, s, NH), 7.15 (1 H, s, 4-H), 6.77 (1 H, s, 7-H), 6.75 (1 H, dd, 4′-H), 6.75 (1 H, dd, 5′-H), 6.15 (1 H, dd, 6′-H) and 3.4 (3 H, s, Me) (Found: C, 46.7; H, 2.6; N, 10.7%; M^+, 386. $C_{15}H_{10}Cl_3N_3O_3$ requires C, 46.4; H, 2.6; N, 10.9%; *M*, 386). When crude methoxycarbonylisothiocyanate made from dry potassium thiocyanate (0.23 g, 2.33 mmol) and methyl chloroformate (0.22 g, 2.33 mmol) was used the yield of the title benzimidazole was 48%.

5,6-*Bis*(2,3-*dichlorophenoxy*)-2-*methoxycarbonylamino*-1H-*benzimidazole* **11f**.—The procedure was the same as in the preceding experiment except for the use of the double quantity of solvent (10 cm^3 acetonitrile) because of the low solubility of the *o*-phenylenediamine **12**. The title benzimidazole **11f** (35%) had m.p. 325–330 °C (decomp.) (from acetone); ν_{max}/cm^{-1} 1719 (C=O) and 3404 (NH); δ_H($CDCl_3$, [$^2H_6$]-DMSO) 11.07 (1 H, s, NH), 10.72 (1 H, s, NH), 6.45 (2 H, s, 4- and 7-H). 6.34 (2 H, dd, 4′-H), 6.31 (2 H, dd, 5′-H), 5.90 (2 H, dd, 6′-H) and 3.00 (3 H, s, Me) (Found: C, 49.2; H, 2.1; N, 8.1. $C_{21}H_{13}Cl_4N_3O_4$ requires C, 49.15; H, 2.55; N, 8.2%).

5-(2,3-*Dichlorophenoxy*)-6-*phenylsulfonyl*-2H-*benzimidazole*-2-*spirocyclohexane* **15**.—To a solution of 5-chloro-6-(2,3-dichlorophenoxy)-2*H*-benzimidazole-2-spirocyclohexane **3a** (2.5 g, 6.5 mmol) in ethanol (75 cm^3) and water (25 cm^3) was added sodium benzenesulfinate (1.5 g, 9.1 mmol). To the rapidly stirred mixture acetic acid (0.6 cm^3, 10.5 mmol) was added and stirring continued for 1 h at ambient temperature. The mixture was then poured into water (250 cm^3) and the products extracted with ethyl acetate (3 × 75 cm^3). The combined extracts were washed with water and brine, dried ($MgSO_4$) and, after evaporation, chromatographed on flash silica with light petroleum–ethyl acetate as eluent.

The first band gave the title spiro compound **15** (2.0 g, 63%), m.p. 171–173 °C (from ethanol); ν_{max}/cm^{-1} 1320 and 1160 (SO_2); δ_H(90 MHz; [$^2H_6$]-DMSO, $CDCl_3$) 8.4 (1 H, s, 4- or 7-H), 8.0 (2 H, dd, ArH), 7.8–7.2 (5 H, m, ArH), 6.95 (1 H, dd, ArH), 6.0 (1 H, s, 4- or 7-H) and 2.0–1.4 (10 H, br m, C-C_6H_{10}) (Found: C, 58.8; H, 4.1; N, 5.9%; M^+, 486. $C_{24}H_{20}Cl_2N_2O_3S$ requires C, 59.1; H, 4.1; N, 5.7%; M, 486).

The second band gave 4-(2,3-*dichlorophenoxy*)-N′,5-*diphenylsulfonyl*-*o*-*phenylenediamine* **16** (1.0 g, 28%), m.p. 271–273 °C; ν_{max}/cm^{-1} 3460, 3350 and 3200 (NH) and 1320 and 1140 (SO_2); δ_H(90 MHz; [$^2H_6$]-DMSO) 9.45 (1 H, s, NH), 7.9–7.2 (13 H, m, ArH), 6.75 (1 H, dd, ArH), 6.1 (2 H, br s, NH_2) and 5.95 (1 H, s, 3- or 6-H) (Found: C, 52.2; H, 3.4; N, 5.4%; M^+, 548. $C_{24}H_{18}Cl_2N_2O_5S_2$ requires C, 52.45; H, 3.3; N, 5.1%; *M*, 548).

5-*Chloro*-6-*phenylsulfonyl*-2H-*benzimidazole*-2-*spirocyclohexane* **18**.—To a solution of the spiro compound **2** (8.0 g, 31 mmol) in ethanol (100 cm^3) was added a solution of sodium benzenesulfinate (5.7 g, 35 mmol) in water (30 cm^3) followed by acetic acid (2.0 cm^3, 35 mmol). The reaction mixture was stirred at room temperature (0.5 h) and then poured into water (300 cm^3). The precipitated solid was extracted with dichloromethane (4 × 75 cm^3), and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified [Al_2O_3–light petroleum–ethyl acetate (1:1)] to give the title compound, m.p. 153–154 °C; ν_{max}/cm^{-1} 1325 and 1150 (SO_2); δ_H(60 MHz; $CDCl_3$) 8.5 (1 H, s, 4- or 7-H), 8.2–7.9 (2 H, br d, ArH), 7.75–7.3 (4 H, m, ArH) and 2.2–1.4 (10 H, br m, C-C_6H_{10}) (Found: C, 60.0; H, 4.7; N, 7.9. $C_{18}H_{17}ClN_2O_2S$ requires C, 59.9; H, 4.75; N, 7.8%).

4-(2,3-*Dichlorophenoxy*)-5-*phenylsulfonyl*-o-*phenylenediamine* **13**.—To a solution of **3a** (1.9 g, 5 mmol) in ethanol (50 cm^3) was added a solution of sodium benzenesulfinate (1.0 g, 6 mmol) in water (20 cm^3) followed by acetic acid (0.4 cm^3, 7 mmol). After the mixture had been stirred for 15 min concentrated hydrochloric acid (0.31 cm^3, 10 mmol) and sodium dithionite (4.0 g, 20 mmol, 85% pure) were added. The reaction mixture was then heated under reflux for 1 h after which it was poured into water (250 cm^3). The mixture was made alkaline (sodium carbonate) after which the precipitate was filtered off, washed with water and air dried. Recrystallisation (from ethanol with charcoal) gave the *title product* **13** (1.35 g, 66%), m.p. 186–188 °C; ν_{max}/cm^{-1} 3450, 3350 and 3200 (NH) and 1280 and 1120 (SO_2); δ_H(90 MHz; [$^2H_6$]-DMSO) 7.85 (2 H, dd, ArH), 7.3–6.9 (6 H, m, ArH), 6.5 (1 H, dd, ArH), 6.1 (1 H, br s, 3- or 6-H), 5.0 (2 H, br s, NH_2) and 4.2 (2 H, br s, NH_2) (Found: C, 53.1; H, 3.4; N, 6.8%; M^+, 408. $C_{18}H_{14}Cl_2N_2O_3S$ requires C, 52.8; H, 3.4; N, 6.8%; *M*, 408).

5-(2,3-*Dichlorophenoxy*)-6-*phenylsulfonyl*-1H-*benzimidazole*-2(3H)-*thione* **17**.—To a solution of the above diamine **13** (3.0 g, 7.3 mmol) in dry DMF (25 cm^3) was added carbon disulfide (0.7 g, 9.2 mmol). The solution was stirred and heated for 4 h at *ca.* 70 °C and then cooled and poured into water (250 cm^3). The resulting precipitate was filtered off, washed with water and air dried to give the thione **17** (3.0 g, 91%), m.p. >325 °C (from ethanol); ν_{max}/cm^{-1} 3300–3000 (NH) and 1300 and 1140 (SO_2); δ_H(90 MHz; [$^2H_6$]-DMSO) 13.0 (2 H, br s, 2 × NH), 7.95 (2 H, br s, 4- or 7-H), 7.7–7.1 (6 H, m, ArH) and 6.65 (2 H, d, ArH) (Found: C, 50.8; H, 2.7; N, 6.4. $C_{19}H_{12}Cl_2N_2O_3S_2$ requires C, 50.6; H, 2.7; N, 6.2%).

4-*Chloro*-5-*phenylsulfonyl*-o-*phenylenediamine* **19**.—To a solution of **2** (2.55 g, 10 mmol) in ethanol (75 cm^3) was added a solution of sodium benzenesulfinate (2.0 g, 12 mmol) in water (25 cm^3) followed by acetic acid (0.75 cm^3, 13 mmol). The solution was stirred at ambient temperature for 0.5 h and then concentrated hydrochloric acid (0.66 cm^3, 21 mmol) and a solution of sodium dithionite (8.0 g, 46 mmol) in water (30 cm^3) were added. Work-up as described for *o*-phenylenediamine **13** above gave the *title compound* **19** (1.0 g, 36%), m.p. 176–178 °C (from ethanol with charcoal); ν_{max}/cm^{-1} 3440, 3350 and 3200 (NH_2) and 1280 and 1140 (SO_2); δ_H(90 MHz; [$^2H_6$]-DMSO) 8.0–7.4 (6 H, m, ArH), 6.6 (1 H, s, 3- or 6-H), 5.9–5.5 (2 H, br s, NH_2) and 5.2–4.8 (2 H, br s, NH_2) (Found: C, 50.7; H, 3.9; N, 9.4. $C_{12}H_{11}ClN_2O_2S$ requires C, 51.0; H, 3.9; N, 9.9%).

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