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2*H*-Benzimidazoles (Isobenzimidazoles). Part 10.[1,2] Synthesis of Polysubstituted *o*-Phenylenediamines and their Conversion into Heterocycles, Particularly 2-Substituted Benzimidazoles with Known or Potential Anthelminthic Activity

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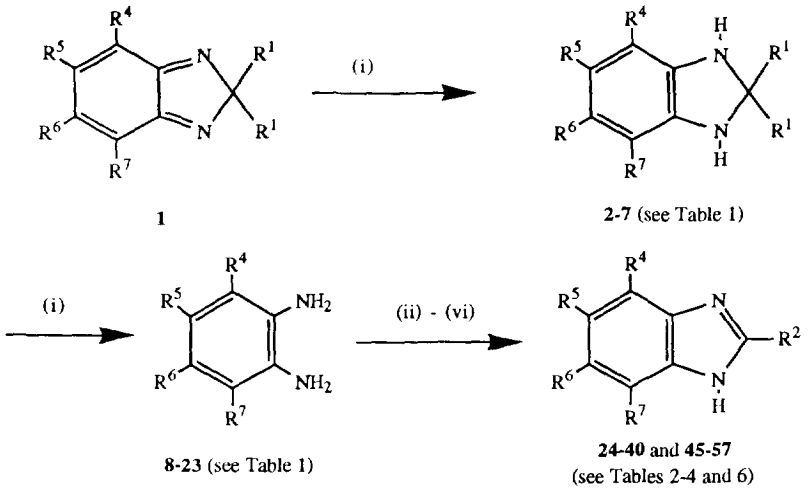
Dedicated to Professor Dr. Richard Neidlein, Pharmazeutisch-Chemisches Institut, Ruprecht-Karls-Universität, Heidelberg on the occasion of his 65th birthday (October 25th, 1995).

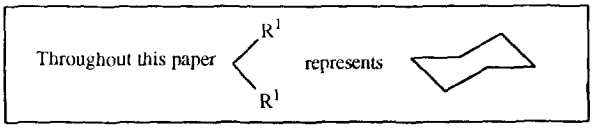
Abstract: Polysubstituted *o*-phenylenediamines were synthesised in moderate to high yield by reductive cleavage of the corresponding 2*H*-benzimidazole-2-spirocyclohexane with sodium dithionite in aqueous ethanol and converted into methyl benzimidazole-2-carbamates and 2-methylthio- and 2-trifluoromethylbenzimidazoles with known or potential anthelminthic activity. 5-(Pyrimidin-2-ylthio)-benzimidazole and 11-(pyridin-2-ylthio)dibenzo[*a,c*]phenazine were synthesised too. Attempts to oxidise 1,3-dihydro-2*H*-4,9-diazanaphth[2,3-*d*]imidazole, prepared by condensation of 2,3-diaminoquinoxaline with cyclohexanone, to an analogue of the title system failed.

2*H*-Benzimidazole-2-spirocyclohexanes **1** are reduced to their 1,3-dihydro-derivatives with hydrogen in the presence of palladium-charcoal; if acetic acid[3,4] or, better, trifluoroacetic acid[5] is used as the solvent, the 1,3-dihydro-compound is hydrolysed to the corresponding *o*-phenylenediamine (OPD) (Scheme 1). 1,3-Dihydro-2*H*-benzimidazole-2-spirocyclohexanes react like the corresponding OPD with certain reagents.[6,7] Sodium dithionite is the preferred reagent for the conversion of 2*H*-benzimidazole-2-spirocyclohexanes **1** into the corresponding OPD's.[3,4,8-13] We have used this methodology (Scheme 1) to synthesise a number of *poly*substituted heterocycles, particularly the benzimidazoles **24-40** and **45-57** (where R^2 = $NHCO_2Me$, SH, SMe or CF_3) with known or potential anthelminthic activity. Since the first report, in 1961,[14] of benzimidazoles with anthelminthic activity a number have been marketed with broad spectrum activity.[15]

Reductions of 2*H*-benzimidazole-2-spirocyclohexanes **1** with an excess of sodium dithionite were carried out mostly in refluxing aqueous ethanol (see Table 1 in Experimental section). Reductions became progressively slower with increasing numbers of substituents and, in some cases, separable mixtures of the corresponding OPD, **8**, **13-15**, or **22** and **23** (Table 1), and the corresponding intermediate 1,3-dihydro-compound **2-7** (Table 1) were obtained, even after prolonged reaction times. In some cases a 2-step process works better. Thus, e.g., when 5-phenylsulfonyl-4-piperidino-2*H*-benzimidazole-2-spirocyclohexane **1** (R^4 = piperidino, R^5 = $PhSO_2$, R^6 = R^7 = H)[4] was treated with an excess of sodium dithionite in aqueous acetone, the corresponding 1,3-dihydro-



Reagents: (i) $Na_2S_2O_4$/aq. EtOH; (ii) $NC.NH_2/ClCO_2Me$/aq. Me_2CO; (iii) $MeS(=N.CO_2Me)NHCO_2Me$/MeOH; (iv) $MeO_2C.NCS$/DCCI/MeCN; (v) CS_2/KOH/EtOH or CS_2/KOH/DMF, then MeI/K_2CO_3/Me_2CO or MeI/DMF-PhMe; (vi) CF_3CO_2H/HCl or $CF_3CO_2H/(CF_3CO)_2O$/HCl.

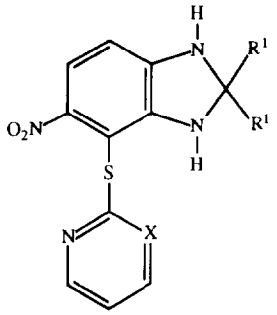


SCHEME 1

compound **6** (see Table 1) (89% yield) precipitated. This was isolated and heated with 20% *w/v* sulfuric acid for 2 h when the OPD **22** (46%) (Table 1) was obtained. The corresponding morpholino-compound **23** (Table 1) was prepared similarly (yields for the 2 steps were 90% and 82%, respectively). Most of the 1,3-dihydro-compounds **2-7** and OPD's **8-23** listed in Table 1 are unstable to air, heat and light and, once prepared, were used immediately in subsequent reactions. Electron-withdrawing groups seem to enhance stability. Thus, e.g., 4-phenylsulfonyl-3-piperidino-OPD **22** and its morpholino-analogue **23** were obtained as salmon-pink solids which, unlike most of the other OPD's listed in Table 1, did not decolourise on being kept in air in daylight.

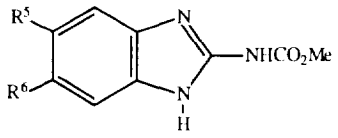
Sodium dithionite reductions of 5-nitro-4-(pyridin-2-ylthio)(or pyrimidin-2-ylthio)-1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane, **58** or **59**,[16] respectively, were unsuccessful as was their attempted hydrolysis with 10% *w/v* hydrochloric acid or glacial acetic acid.

4,6-Dibromo-2*H*-benzimidazole-2-spirocyclohexane **1** ($R^4 = R^6 = Br$, $R^5 = R^7 = H$) was treated with sodium benzenesulfinate in aqueous ethanol containing glacial acetic acid, as described previously,[1] then an excess of sodium dithionite was added and, after reduction was complete (by TLC), hydrochloric acid was added. This produced the OPD **21** in 59% overall yield without the need to isolate the intermediate **1** ($R^4 = Br$, $R^6 = PhSO_2$, $R^5 = R^7 = H$) or its 1,3-dihydro-derivative. Likewise, OPD **20** was synthesised in 54% in a "one pot" procedure through reaction of the 4,6-dibromo-compound **1** ($R^4 = R^6 = Br$, $R^5 = R^7 = H$) with pyridin-2(1*H*)-thione in ethanol[1] followed by addition of aqueous sodium dithionite. However, for higher overall yields it is better to isolate the intermediates **1** and reduce them in a separate procedure.



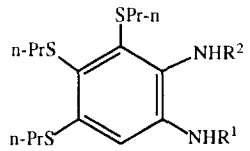
58 X = CH
59 X = N

A number of commercial anthelminthics are derivatives of methyl benzimidazole-2-carbamate, e.g. compounds **24**, **25**, **60** and **61**.[14,15,17-21] We prepared oxibendazole **24** (47% yield) and albendazole **25** (30%) by reacting the corresponding OPD, **8** or **10**, respectively (Table 1), with a mixture of cyanamide and methyl chloroformate in refluxing aqueous acetone, at pH 5-8.5 (reagent system A in Table 2). Albendazole **25** was synthesised also, in 44% yield, by reacting OPD **10** with *N,N'*-bis(methoxycarbonyl)-*S*-methylisothiourea[20-24] in refluxing methanol (reagent system B in Table 2). Carbamates **26** (12%) and **27** (95%) (see



(see Table 2)

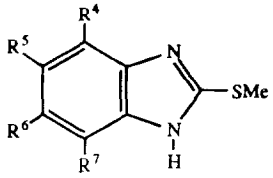
60 R^5 = n-Bu (perbendazole), R^6 = H
24 R^5 = n-PrO (oxibendazole), R^6 = H
25 R^5 = n-PrS (albendazole), R^6 = H
61 R^5 = PhS (fenbendazole), R^6 = H
26 R^5 = R^6 = n-PrS
27 R^5 = *tert*-BuS, R^6 = H
28 R^5 = pyridin-2-ylS, R^6 = H
29 R^5 = pyrimidin-2-ylS, R^6 = H



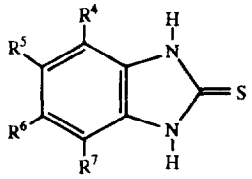
62 R^1 = H, R^2 = CO_2Me
63 R^1 = CO_2Me, R^2 = H

Table 2) were synthesised similarly. *N,N'*-Bis(methoxycarbonyl)-S-methylisothiourea reacted also with 1,3-dihydro-5-*n*-propylthio-2*H*-benzimidazole-2-spirocyclohexane[16] to give albendazole **25** (30% yield), but an attempt to react 3,4,5-tri-*n*-propylthio-OPD **13** (Table 1) with this reagent resulted in formation of compound **62**, or its isomer **63**, in 80% yield. Yields of methyl benzimidazole-2-carbamates, e.g. compounds **28** and **29** in Table 2, were greatly improved by reacting the OPD with methoxycarbonyl isothiocyanate (reagent C in Table 2).[25]

The 2-methylthiobenzimidazoles **30-36** (see Table 3; Experimental section) were prepared by reacting the corresponding OPD (Table 1) with carbon disulfide in the presence of potassium hydroxide (in ethanol) (reagent system A in Table 3) or, better, *N,N*-dimethylformamide (DMF) (reagent system B in Table 3; see Experimental



30-36 (see Table 3)



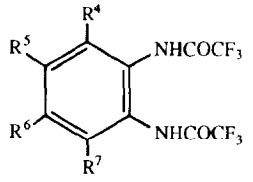
(see Table 4)

37 R^5 = piperidino, $R^4 = R^6 = R^7$ = H
38 R^4 = piperidino, $R^5 = PhSO_2$, $R^6 = R^7$ = H
39 R^4 = Br, $R^6 = 2,3\text{-}Cl_2C_6H_5O$, $R^5 = R^7$ = H
40 R^4 = Br, $R^6 = PhSO_2$, $R^5 = R^7$ = H

section)[26,27] followed by removal of the solvent and alkylation of the potassium benzimidazole-2-thiolate (without purification) or benzimidazol-2(3*H*)-thione **37-39** (listed in Table 4; Experimental section) produced with iodomethane in refluxing acetone in the presence of potassium carbonate or with iodomethane in a DMF-toluene mixture. 2-Alkylthiobenzimidazoles have demonstrated a broad spectrum of significant biological activity including anthelminthic activity.[11,28]

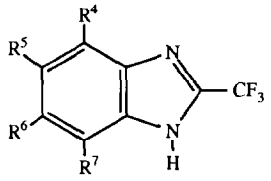
Attempted methylation of 4-bromo-6-phenylsulfonylbenzimidazol-2(3*H*)-thione **40** gave a multiple component mixture, possibly containing *S*- and *N*-alkylated products.

Our OPD's reacted readily with hot trifluoroacetic acid[29] or a hot mixture of the acid and its anhydride, in the presence of a small quantity of hydrochloric acid, to give either the corresponding *N,N'*-bis(trifluoro-acetamido)-OPD **41-44** (42-80% yield) (see Table 5: Experimental section) or 2-trifluoromethylbenzimidazole



(see Table 5)

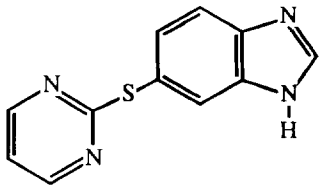
41 $R^4 = R^6$ = n-PrS, $R^5 = R^7$ = H
42 $R^4 = R^5 = R^6$ = n-PrS, R^7 = H
43 $R^4 = R^5 = R^6 = R^7$ = n-PrS
44 R^5 = piperidino, $R^4 = R^6 = R^7$ = H



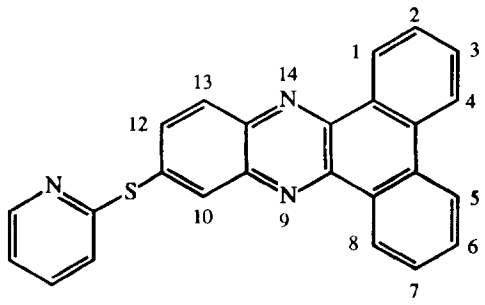
45-57 (see Table 6)

45, **47**, **49**, **51** or **53-57** (55-80% yield) (see Table 6: Experimental section). Under the same reaction conditions prolonged heating of compounds **41** and **42** gave the corresponding 2-trifluoromethyl-compound, **46** (65%) or **48** (85%), respectively (Table 6). 3,4,5,6-Tetra-*n*-propylthio-*N,N'*-bis(trifluoroacetamido)-OPD **43** cyclised to 4,5,6,7-tetra-*n*-propylthio-2-trifluoromethylbenzimidazole **50** (41%) on being kept in moist air. Hydrogenation of 5-piperidino-2*H*-benzimidazole-2-spirocyclohexane **1** (R^5 = piperidino, $R^4 = R^6 = R^7$ = H)[4] in a mixture of trifluoroacetic acid and its anhydride gave the *N,N'*-bis(trifluoroacetamido)-OPD **44** which was treated, without purification, with concentrated hydrochloric acid in hot ethanol, to give the known 5-piperidino-2-trifluoromethylbenzimidazole **52** (55% yield).[4]

Benzimidazole **64** (80% yield) was obtained by heating 4-(pyrimidin-2-ylthio)-OPD **19** (Table 1) with formic acid, whilst condensation of OPD **18** with phenanthraquinone gave the bright yellow fluorescent dibenzo[*a*,*c*]-phenazine **65** (82%).



64



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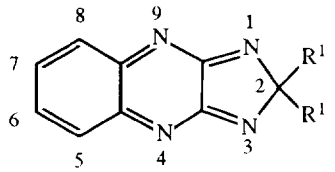
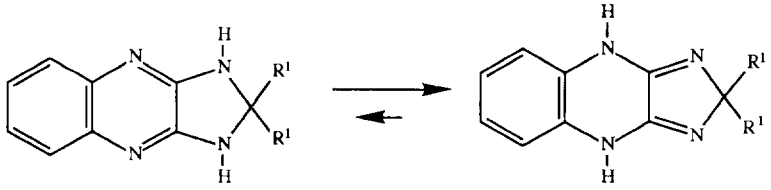


66

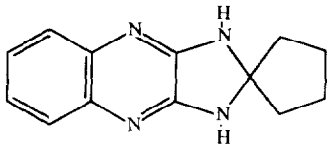
In order to extend our "umpolung" methodology[2] we attempted the synthesis of 2*H*-4,9-diazanaphth[2,3-*d*]imidazole-2-spirocyclohexane **66**. 2,3-Diaminoquinoxaline was synthesised by a literature procedure[30] and condensed with cyclohexanone, which gave a compound **67** (65% yield), capable of tautomerism, as shown. ^{1}H NMR spectroscopy suggests that this compound exists in solution in deuteriochloroform mainly as tautomer **67b**. For 1,3-dihydro-2*H*-benzimidazole-2-spirocyclohexane **1** ($R^4 \rightarrow R^7$ = H) the NH signals appear at δ 3.5-4.5 whilst those for compound **67** appear considerably downfield (Table 8).



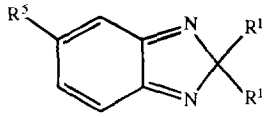
67a **67b**

Attempts to oxidise compound **67** to compound **66** with manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) failed: starting material was recovered (100%). Stronger oxidising agents, such as cerium(IV) ammonium nitrate (CAN) (used in glacial acetic acid with perchloric acid added), gave intractable mixtures (by TLC). Compound **67** failed to react with carbon disulfide, trifluoroacetic acid or selenous acid. In all cases starting material was recovered quantitatively.

Noteworthy is the fact that 2,3-diaminoquinoxaline condensed with cyclopentanone, to give a low yield (9%) of a spiro-compound **68** analogous to **67** (*cf.* ref. 6).



68



69 R^5 = MeO
70 R^5 = EtO
71 R^5 = n-PrO

Previous attempts to react 2*H*-benzimidazole-2-spirocyclohexane **1** ($R^4 \rightarrow R^7$ = H) with oxygen nucleophiles have been unsuccessful.[2] However, 5-chloro-2*H*-benzimidazole-2-spirocyclohexane **1** (R^5 = Cl, $R^4 = R^6 = R^7$ = H) reacts with sodium methoxide in methanol to give a good yield of the corresponding 5-methoxy compound **69**.[2,4] The 5-ethoxy- **70** (48% yield) and 5-*n*-propoxy-compounds **71** (63%) (required for the synthesis of OPD **8**) were prepared similarly as bright yellow fluorescent solids..

EXPERIMENTAL

The instruments used and the general experimental conditions were the same as those described in Parts 6,[16] 7[11] and 9[1] of this Series. Yields, m.p.'s and solvents of crystallisation of most new compounds are given in the relevant Table (Tables 1-6) whilst microanalytical and mass spectral data (M^+ peak for ^{79}Br isotope measured where appropriate) are given in Table 7 and IR and ^1H NMR spectroscopic data are given in Table 8.

The following compounds were prepared by literature methods: 2,3-dihydroxyquinoxaline (96% yield), m.p. > 360 °C (lit.,[30] m.p. > 360 °C); 2,3-dichloroquinoxaline (98%), m.p. 152-153 °C (lit.,[30] m.p. 152-154 °C); and 2,3-diaminoquinoxaline (96%), m.p. 325-327 °C (lit.,[30] m.p. 328-330 °C).

The syntheses of most of the starting materials have been described in Parts 6[16] and 9[1] of this Series. 5-Piperidino-,[4] 5-phenylsulfonyl-4-piperidino-[4] and 4-morpholino-5-phenylsulfonyl-2*H*-benzimidazole-2-spiro-cyclohexane[4] were prepared as described before.

5-Ethoxy-2*H*-benzimidazole-2-spirocyclohexane **70**. - Sodium (0.5 g, 21.7 mmol) was reacted with anhydrous ethanol (50 cm^3), then 5-chloro-2*H*-benzimidazole-2-spirocyclohexane[16] (2.0 g, 9.07 mmol) was added and the resulting mixture was stirred for 2 h at ambient temperature. Removal of the solvent gave the crude product, which was chromatographed on alumina. Light petroleum-ethyl acetate (gradient elution) eluted 5-ethoxy-2*H*-benzimidazole-2-spirocyclohexane **70** (1.0 g, 48%), m.p. 115-116 °C [from light petroleum (b.p. 40-60 °C)-ethyl acetate].

5-*n*-Propoxy-2*H*-benzimidazole-2-spirocyclohexane **71** (63%) was prepared similarly, m.p. 75.5-77 °C [from light petroleum (b.p. 40-60 °C)].

Reductive Cleavage of 2*H*-Benzimidazole-2-spirocyclohexanes **1** with Sodium Dithionite. - General Method. Powdered sodium dithionite (1.87 g, 10.75 mmol) was added to a stirred solution of 2*H*-benzimidazole-2-spirocyclohexane **1** ($R^4 \rightarrow R^7$ = H)[16] (1.0 g, 5.40 mmol) in a mixture of water (50 cm^3) and

TABLE 1

Reductive Cleavage of 2*H*-Benzimidazole-2-spirocyclohexanes 1 with Sodium Dithionite (Scheme 1)[a]

R^4	R^5	R^6	R^7	Compound No.	Yield (%)	M.p.[b] (T/°C)	Compound No.	Yield (%)	M.p.[b] T/°C
H	PrO	H	H	**2**	15		**8**	80	
H	$OC_6H_3Cl_2$-2,3	H	Br				**9**	67	200-202 (A)
H	PrS	H	H				**10**	74	
H	PrS	PrS	H				**11**	76	
H	PrS	H	PrS				**12**	87	
PrS	PrS	PrS	H	**3**	8		**13**	88	
PrS	PrS	H	PrS	**4**	8		**14**	78	
PrS	PrS	PrS	PrS	**5**	40		**15**	55	
H	*tert*-BuS	H	H				**16**	85	
H	*tert*-BuS	*tert*-BuS	H				**17**	70	159.5-160.5 (B)
H	pyridin-2-ylS	H	H				**18**	82	107-109 (A)
H	pyrimidin-2-ylS	H	H				**19**	86	135-137 (A)
Br	H	pyridin-2-ylS	H				**20**	84	184-186 (A)
Br	H	$PhSO_2$	H				**21**	87	187-189 (A)
piperidino	$PhSO_2$	H	H	**6**	89[c]	185-186 (C)	**22**	46[c]	198-199 (A)
morpholino	$PhSO_2$	H	H	**7**	90[c,d]	200-201 (C)	**23**	82[c,e]	211-213 (D)

[a] Compounds **2-5**, **16** and compound **20** were extremely unstable (see Discussion) and full characterisation was not possible; the OPD's were used immediately following their isolation in subsequent steps. [b] Recrystallisation solvents given in parenthesis: A = light petroleum-$MeCO_2Et$; B = light petroleum (b.p. 40-60 °C)-CH_2Cl_2; C = EtOH; D = $MeCO_2Et$. [c] Slow reduction in aqueous acetone (1:1) at 50°C; the major product was the 1,3-dihydro-compound which was hydrolysed to the OPD with hot 20% *w/v* H_2SO_4 (see Discussion and Experimental sections). [d] Lit.,[9] 90% and m.p. 200-201 °C. [e] Lit.,[9] 82% and m.p. 211-213 °C.

ethanol (50 cm^3) at ambient temperature, then the resulting mixture was warmed up to 80 °C and stirred at this temperature for a further 45 min. After cooling the mixture to ambient temperature, it was poured into cold water and the product was extracted with dichloromethane (3 x 75 cm^3). The extracts were combined, washed with water, dried ($MgSO_4$) and the solvent evaporated off under reduced pressure. The brown oil obtained was triturated with light petroleum to give *o*-phenylenediamine (OPD) (0.39 g, 67%), m.p. 100-102 °C (lit.,[31] m.p. 104 °C).

For compounds **8-17** (Table 1) the reaction time was increased to 2 h and 6 mol. equiv. of sodium dithionite was used. For compounds **9** and **18-21** ethyl acetate was used to extract the crude product. All crude products were purified/separated by rapid flash chromatography on silica. Light petroleum (b.p. 40-60 °C)-ethyl acetate (ratio 9:1 for compounds **2-5** and **8** and **10-17** and 1:2 for compounds **9** and **18-21**) eluted the products given in Table 1 (mass spectral and microanalytical data for new compounds are given in Table 7 at the end of this paper whilst spectroscopic data are in Table 8). Most of these products are unstable to heat, light and air (some decomposition arises during chromatographic separations); those that could not be fully characterised were used in subsequent reactions immediately following their isolation.

4-Piperidino-*o*-phenylenediamine.[4] - A mixture of 5-piperidino-2*H*-benzimidazole-2-spirocyclohexane **1** (R^5 = piperidino, $R^4 = R^6 = R^7 = H$)[4] (3.0 g, 11.15 mmol), 10% palladium-charcoal (catalytic amount; enough to cover the end of a spatula), and acetic acid (75 cm^3) was hydrogenated overnight at 1 atmosphere (320 cm^3 of hydrogen taken up), then the mixture was filtered and the solvent distilled off under reduced pressure. The residue was neutralised by addition of solid sodium hydrogen carbonate, and extraction with dichloromethane (3 x 50 cm^3) gave a pale brown, hygroscopic solid which was kept under nitrogen and used as soon as possible without purification to prepare compounds **37** and **44** (see later). TLC on alumina with light petroleum-ethyl acetate as eluent indicated only one spot.

1,3-Dihydro-5-phenylsulfonyl-4-piperidino-2*H*-benzimidazole-2-spirocyclohexane **6**. - Sodium dithionite (2.1 g, 12.01 mmol) was added portionwise to a stirred red solution of 5-phenylsulfonyl-4-piperidino-2*H*-benzimidazole-2-spirocyclohexane **1** (R^4 = piperidino, $R^5 = PhSO_2$, $R^6 = R^7 = H$)[4] (1.0 g, 2.45 mmol) in acetone (50 cm^3) - water (50 cm^3) at 50 °C, then the decolourised mixture was placed in an ice-bath and stirred for a further 30 min. The white precipitate was filtered off, washed with water, air dried, then crystallised from ethanol, to give the product **6** (0.9 g, 89%).

1,3-Dihydro-4-morpholino-5-phenylsulfonyl-2*H*-benzimidazole-2-spirocyclohexane **7** (90%) was prepared similarly, ν_{max}/cm^{-1} 3350 (NH).

4-Phenylsulfonyl-3-piperidino-*o*-phenylenediamine **22**. - 1,3-Dihydro-5-phenylsulfonyl-4-piperidino-2*H*-benzimidazole-2-spirocyclohexane **6** (2.0 g, 4.87 mmol) was added with stirring to 20% *w/w* sulphuric acid (50 cm^3), and the resulting mixture was heated under reflux for 2 h. Activated charcoal (0.2 g) was added and the mixture was boiled for a further 10 min. The hot solution was filtered through Celite and the Celite was washed with hot water. To the cooled filtrate was added 20% *w/w* aqueous sodium hydroxide until the pH was adjusted to 5, then solid sodium hydrogen carbonate was added to complete neutralisation of the solution. After cooling the resulting mixture in an ice-bath for 30 min, the red precipitate was filtered off, washed with cold

(0 °C) water, and air dried. The resulting product (1.32 g, 82%) was chromatographed on alumina. Light petroleum-ethyl acetate (gradient elution) eluted 4-phenylsulfonyl-3-piperidino-*o*-phenylenediamine **22** (0.74 g, 46%) as a pale pink solid.

3-Morpholino-4-phenylsulfonyl-*o*-phenylenediamine **23** (82%) was prepared similarly as a pink solid, $\nu_{max.}/cm^{-1}$ 3350 and 3450 (NH_2).

"One-pot" Synthesis of 3-Bromo-5-phenylsulfonyl-*o*-phenylenediamine **21**. - Sodium benzenesulfinate (1.70 g, 10.37 mmol) in water (25 cm^3) was added to a stirred solution of 4,6-dibromo-2*H*-benzimidazole-2-spirocyclohexane[1] (3.20 g, 9.3 mmol) in ethanol (75 cm^3) followed by acetic acid (0.60 cm^3, 0.62 g, 10.3 mmol) and the resulting solution was stirred rapidly at ambient temperature for 30 min. Concentrated hydrochloric acid (0.57 cm^3, 0.68 g, 18.7 mmol) was added followed by a solution of sodium dithionite (6.52 g, 37.5 mmol) in water (30 cm^3), then the mixture was heated under reflux for 1 h, cooled and diluted with cold (0 °C) water (250 cm^3). The resulting mixture was made alkaline by addition of solid sodium carbonate and the resulting precipitate was filtered off, air dried and chromatographed on silica. Light petroleum-ethyl acetate (gradient elution) eluted the product **21** (1.8 g, 59%).

Methyl 5-*n*-Propoxybenzimidazole-2-carbamate (oxibendazole) **24** (Table 2). - Methyl chloroformate (2.28 g, 24.13 mmol) was added to a stirred mixture of cyanamide (50% aqueous solution containing 1.02 g, 24.29 mmol), acetone (12 cm^3) and water (4 cm^3) followed by sufficient 1.5 mol dm^{-3} sodium hydroxide to bring the pH in the range 5.0-8.5 whilst maintaining the temperature of the mixture throughout below 28 °C. The resulting mixture was added dropwise with stirring to 4-*n*-propoxy-*o*-phenylenediamine **8** (2.0 g, 12.05 mmol) in 4 mol dm^{-3} hydrochloric acid (5 cm^3). Then the mixture was heated to 93 °C for 1.5 h with distillation of the acetone. After a further 1 h at this temperature the resulting suspension was cooled to 75-80 °C and the precipitate was filtered off, washed with hot water (30 cm^3) and crystallised from ethanol-ethyl acetate, to give oxibendazole **24** (1.4 g, 47%) as a pale yellow powder.

Methyl 5-*n*-propylthiobenzimidazole-2-carbamate (albendazole) **25** (Table 2) (35% crude; 30% after purification) was prepared similarly.

N,N'-Bis(methoxycarbonyl)-5-methylisothiourea (see ref. 32). - A mixture of thiourea (2.9 g, 38.16 mmol), dimethyl sulfate (2.4 g, 19.08 mmol) and water (7 cm^3) was heated under reflux for 30 min, then cooled to -3 °C when methyl chloroformate (1.8 g, 19.08 mmol) was added. When the temperature of the reaction mixture had reached 10-15 °C, 25% aqueous sodium hydroxide was added dropwise to bring the pH in the range 7.0-8.0 when it was maintained at this level for 10 min at 25 °C or below. Then the pH was adjusted to 5.0 by dropwise addition of glacial acetic acid during 20 min and the product precipitated as a white solid. It was filtered off and used immediately in the following reactions.

Methyl 5-*n*-Propylthiobenzimidazole-2-carbamate (albendazole) **25** (Table 2). - (a) From 1,3-Dihydro-5-*n*-propylthio-2*H*-benzimidazole-2-spirocyclohexane. To the freshly prepared *N,N'*-bis(methoxycarbonyl)-5-methylisothiourea, prepared as described in the preceding experiment, was added at ambient temperature a solution of 1,3-dihydro-5-*n*-propylthio-2*H*-benzimidazole-2-spirocyclohexane[16] (5.0 g, 19.08 mmol) in

methanol (50 cm^3) and water (30 cm^3), then the resulting mixture was heated under reflux for 3 h. It was cooled to 0 °C and the precipitate was filtered off and washed with hot water, to give albendazole **25** (1.52 g, 30%) as a pale yellow powder.

(b) From 4-*n*-propylthio-*o*-phenylenediamine **10**. The reaction was carried out as described in (a) with replacement of 1,3-dihydro-5-*n*-propylthio-2*H*-benzimidazole-2-spirocyclohexane with 4-*n*-propylthio-*o*-phenylenediamine **10** (5.0 g, 27.47 mmol), which gave albendazole **25** (3.2 g, 44%).

Methyl 5,6-di-*n*-propylthiobenzimidazole-2-carbamate **26** and methyl 5-tert-butylthiobenzimidazole-2-carbamate **27** (Table 2) were prepared similarly.

TABLE 2

Methyl Benzimidazole-2-carbamates[a]

Compound No.	R^4	R^5	R^6	R^7	Yield (%)	M.p.[b] (T/°C)
24	H	PrO	H	H	47 (A)	218-222 (D)[c]
25	H	PrS	H	H	30 (A), 44 (B)	200-203 (E) or 196-198 (F)[d]
26	H	PrS	PrS	H	12 (B)	215-216 (G)
27	H	*tert*-BuS	H	H	95 (B)	305-306 (H)
28	H	pyridin-2-ylS	H	H	88 (C)	218-220 (G)
29	H	pyrimidin-2-ylS	H	H	86 (C)	276-278 (G)

[a] Reagent Systems: A = $ClCO_2Me/NC.NH_2/Me_2CO$-H_2O at pH 5.0-8.5; B = $MeSC(=N.CO_2Me)NHCO_2Me$/MeOH; C = $MeO_2C.NCS$. [b] Recrystallisation solvents given in parenthesis; D = EtOH-$MeCO_2Et$; E = dioxane; F = MeOH-H_2O-Me_2CO; G = MeOH-$MeCO_2Et$; H = MeOH-Me_2CO. [c] Lit.,[33] m.p. 234 °C. [d] Lit.,[34] m.p. 204-204.5 °C.

Reaction of 3,4,5-Tri-*n*-propylthio-*o*-phenylenediamine **13** with 1,3-Bis(methoxycarbonyl)-S-methylisothiourea. - The reaction was carried out as described before in (a) with replacement of 1,3-dihydro-5-*n*-propylthio-2*H*-benzimidazole-2-spirocyclohexane with 3,4,5-tri-*n*-propylthio-*o*-phenylenediamine **13** (2.0 g, 6.06 mmol). This gave either 1-amino-2-methylcarbamato-3,4,5-tri-*n*-propylthiobenzene **62** or 1-methylcarbamato-2-amino-3,4,5-tri-*n*-propylbenzene **63** (1.88 g, 80%), m.p. 99.5-100°C [from light petroleum (b.p. 40-60 °C)-dichloromethane].

Methoxycarbonyl Isothiocyanate.[25] - Methyl chloroformate (18.9 g, 200 mmol) was added to a hot saturated solution of potassium thiocyanate (19.4 g, 200.0 mmol) in anhydrous acetone (100 cm^3). The resulting mixture was cooled to ambient temperature, the precipitated potassium chloride was filtered off, and distillation gave acetone followed by the product (15.2 g, 65%) as a clear, almost colourless oil with a pungent odour, b.p.

30 °C at 12 mmHg. This reagent is unstable and was used fresh in the following reactions. Storage for short periods was possible in a refrigerator.

Methyl 5-(Pyridin-2-ylthio)benzimidazole-2-carbamate **28** (Table 2). - **4**-(Pyridin-2-ylthio)-*o*-phenylenediamine **18** (2.3 g, 10.6 mmol) was added to a stirred solution of *N,N'*-dicyclohexylcarbodi-imide (DCCI) (2.47 g, 12.0 mmol) and methoxycarbonyl isothiocyanate (1.1 cm^3, 1.24 g, 10.6 mmol) in anhydrous acetonitrile (20 cm^3) heated under reflux. After 15 min a white precipitate was observed. Stirring and heating were continued for a further 30 min, then the precipitate was filtered off, washed with hot water containing a little methanol and air dried. Recrystallisation from ethyl acetate-methanol gave the product **28** (2.8 g, 88%).

Methyl 5-(Pyrimidin-2-ylthio)benzimidazole-2-carbamate **29** (86%) was prepared similarly.

2-Methylthiobenzimidazoles **30-36** (Table 3). - General procedure. Potassium hydroxide (0.68 g, 12.14 mmol) was added to a stirred mixture of anhydrous ethanol (20 cm^3) and carbon disulfide (0.73 cm^3, 0.92 g, 12.10 mmol) at ambient temperature and the resulting mixture was stirred until all the potassium hydroxide had dissolved. Then a solution of 3,4,5-tri-*n*-propylthio-*o*-phenylenediamine **13** (1.0 g, 3.05 mmol) in anhydrous ethanol (5 cm^3) was added and the reaction mixture was heated under reflux for 3 h, then cooled to ambient temperature and the excess of reagent and the solvent were distilled off under reduced pressure. The residue was filtered off, washed several times with light petroleum (b.p. 40-60 °C), then dissolved in a stirred mixture of anhydrous *N,N*-dimethylformamide (DMF) (7.5 cm^3) and toluene (7.5 cm^3). Iodomethane (0.44 g, 3.10 mmol) in a mixture of anhydrous DMF (2.5 cm^3) and toluene (2.5 cm^3) was added dropwise during 20 min at ambient temperature, and the mixture was heated under reflux for 2 h. Then it was cooled to ambient temperature and the solvents were distilled off under reduced pressure. The residue was added to water, and extraction with dichloromethane (3 x 35 cm^3) gave the crude product which was flash chromatographed on silica. Dichloromethane-ethyl acetate (97:3) gave 2-methylthio-4,5,6-tri-*n*-propylthiobenzimidazole **31** (0.35 g, 30%).

Compounds **32** and **33** were prepared similarly as was compound **30** but, in this case the iodomethane alkylation step was carried out in acetone (not DMF-toluene).

Benzimidazole-2(3H)-thiones **37-40** (Table 4). - Carbon disulfide (0.22 cm^3, 0.28 g, 3.68 mmol) was added to a stirred solution of 4-phenylsulfonyl-3-piperidino-*o*-phenylenediamine **22** (1.0 g, 3.02 mmol) in anhydrous DMF (15 cm^3) and the resulting mixture was heated at 70-80 °C for 3 h, then poured into cold water (150 cm^3). Extraction with ethyl acetate (3 x 50 cm^3) gave the crude product which was flash chromatographed on silica. Light petroleum-ethyl acetate (2:1) eluted 5-phenylsulfonyl-4-piperidinobenzimidazol-2(3H)-thione **38** (0.84 g, 75%).

Compounds **37**, **39** and **40** were prepared similarly.

2-Methylthio-5-piperidinobenzimidazole **34** (Table 3). - Iodomethane (0.12 cm^3, 0.27 g, 1.93 mmol) was added to a stirred solution of 5-piperidinobenzimidazol-2(3*H*)-thione **37** (0.45 g, 1.93 mmol) in anhydrous acetone (30 cm^3) containing anhydrous potassium carbonate (0.27 g, 1.95 mmol) and the resulting mixture was heated under reflux for 2 h, then cooled and the inorganic residues were filtered off and washed with acetone.

Distillation of the solvent from the filtrate gave a brown solid which was flash chromatographed on silica. Light petroleum-ethyl acetate eluted the product **34** (0.42 g, 88%).

Compounds **35** and **36** (Table 3) were prepared similarly.

TABLE 3

2-Methylthiobenzimidazoles[a]

Compound No.	R^4	R^5	R^6	R^7	Yield (%)	M.p.[b] (T°/C
30	PrS	H	PrS	H	75 (A)	74-75.5 (C)
31	PrS	PrS	PrS	H	30 (A)	112.5 (C)
32	PrS	PrS	H	PrS	55 (A)	93-93.5 (D)
33	H	*tert*-BuS	H	H	70 (A)	155-155.5 (D)
34	H	piperidino	H	H	88 (B)	148-149 (E)
35	piperidino	$PhSO_2$	H	H	87 (B)	198-200 (F)
36	Br	H	$OC_6H_3Cl_2$-2,3	H	64 (B)	238-240 (F)

[a] Reagent Systems: A = CS_2/KOH/EtOH; B = CS_2/KOH/DMF [intermediate benzimidazol-2(3*H*)-thione isolated (see Table 4) then alkylated with either MeI/K_2CO_3/Me_2CO, for compounds **30** and **34-36**, or MeI/DMF/PhMe, for compounds **31-33**]. [b] Recrystallisation solvents given in parenthesis: C = light petroleum (b.p. 40-60 °C)-CH_2Cl_2; D = light petroleum (b.p. 40-60 °C)-$MeCO_2Et$: E = light petroleum (b.p. 80-100 °C)-$MeCO_2Et$; F = light petroleum-$MeCO_2Et$.

TABLE 4

Benzimidazol-2(3*H*)-thiones[a]

Compound No.	R^4	R^5	R^6	R^7	Yield (%)	M.p.[b] (T°/C)
37	H	piperidino	H	H	46	252-255 (A)
38	piperidino	$PhSO_2$	H	H	75	274-276 (B)
39	Br	H	$OC_6H_3Cl_2$-2,3	H	68	245 (B)[c]
40	Br	H	$PhSO_2$	H	72	244-245 (B)

[a] Reagent System: CS_2/KOH/DMF. [b] Recrystallisation solvents given in parenthesis: A = $MeCO_2Et$; B = light petroleum-$MeCO_2Et$;. [c] Sublimed at this temperature.

N,N'-Bis(trifluoroacetamido)-*o*-phenylenediamines **41-43** (Table 5). - 3,5-Di-*n*-propylthio-N,N'-bis(trifluoroacetamido)-*o*-phenylenediamine **41**. A mixture of trifluoroacetic acid (10 cm^3) and concentrated hydrochloric acid (1 cm^3) at 0 °C was added during 20 min with stirring to freshly prepared, crude 3,5-di-*n*-propylthio-*o*-phenylenediamine **12** (0.5 g, 1.95 mmol) also at 0 °C. Then the temperature of the mixture was allowed to rise slowly to reflux, then it was heated under reflux on a water bath for 3 h and, finally, allowed to cool to ambient temperature and poured into water. The excess of acid was neutralised by addition of solid sodium hydrogen carbonate and extraction with dichloromethane (3 x 40 cm^3) gave the crude product which was flash chromatographed on silica. Light petroleum (b.p. 40-60 °C)-ethyl acetate (9:1) gave 3,5-di-*n*-propylthio-N,N'-bis(trifluoroacetamido)-*o*-phenylenediamine **41** (0.37 g, 42%) as white crystals.

Compounds **42** [in this case a mixture of trifluoroacetic acid (5 cm^3), trifluoroacetic anhydride (5 cm^3) and concentrated acid (1 cm^3) was used] and **43** (reaction mixture stirred 12 h at ambient temperature; same procedure as that used for compound **42** otherwise), were prepared similarly.

TABLE 5

***N,N'*-Bis(trifluoroacetamido)-*o*-phenylenediamines**

Compound No.	R^4	R^5	R^6	R^7	Yield (%)	M.p.[a] (T°/C)
41	PrS	H	PrS	H	42	127-128 (A)
42	PrS	PrS	PrS	H	80	161-162 (B)
43	PrS	PrS	PrS	PrS	60	118.5-119 (C)
44	H	piperidino	H	H	–[b]	

[a] Recrystallisation solvent given in parenthesis: A = light petroleum (b.p. 40-60 °C)-$MeCO_2Et$: B = light petroleum-$MeCO_2Et$:: C = light petroleum (b.p. 40-60 °C). [b] Converted directly, without isolation, into compound **52**.

2-Trifluoromethylbenzimidazoles **45-57** (Table 6). - General procedure. A mixture of 4-(pyridin-2-ylthio)-*o*-phenylenediamine **18** (2.1 g, 9.68 mmol), trifluoroacetic acid (10 cm^3) and concentrated hydrochloric acid (2 cm^3) was heated under reflux for 3 h, then cooled to ambient temperature and poured into water (50 cm^3) containing ice (50 g). Solid sodium hydrogen carbonate was added to neutralise the excess of acid and extraction with dichloromethane (3 x 50 cm^3) gave the crude product which was chromatographed on alumina. Light petroleum-ethyl acetate (1:1) eluted 5-(pyridin-2-ylthio)-2-trifluoromethylbenzimidazole **54** (1.9 g, 63%).

Unless described otherwise later, the other 2-trifluoromethylbenzimidazoles were prepared similarly (only the reaction times - see Table 6 - varied).

4,5,6,7-Tetra-*n*-propylthio-2-trifluoromethylbenzimidazole **50** (Table 6). - 3,4,5,6-Tetra-*n*-propylthio-*N,N'*-bis(trifluoroacetamido)-*o*-phenylenediamine **43** (0.42 g, 0.70 mmol) was kept in air for 7 days after which

TLC examination [silica plates:light petroleum-ethyl acetate (9:1)] showed 2 spots. The mixture was flash chromatographed on silica and light petroleum (b.p. 40-60 °C)-ethyl acetate (9:1) eluted the product **50** (0.14 g, 41%) as a white, viscous oil and starting material (0.22 g, 53%).

TABLE 6

2-Trifluoromethylbenzimidazoles

Compound No.	R^4	R^5	R^6	R^7	Reaction time (h)	Yield (%)	M.p.[a] (T°/C)
45	H	PrS	H	H	0.5	60	96 (A)
46	PrS	H	PrS	H	6	65	99.5 (B)
47	H	PrS	PrS	H	6	55	152-153 (B)
48	PrS	PrS	PrS	H	6	85	123-124 (A)
49	PrS	PrS	H	PrS	6	70	120.5-121 (B)
50	PrS	PrS	PrS	PrS	3	41[b]	viscous oil
51	H	*tert*-BuS	H	H	3	85	143.5-145.5 (A)
52	H	piperidino	H	H	5	55[c]	191-193 (C)
53	morpholino	$PhSO_2$	H	H	3	68	231-233 (C)
54	H	pyridin-2-ylS	H	H	3	63	128-130 (C)
55	H	pyrimidin-2-ylS	H	H	3	67	167-168 (C)
56	Br	H	$PhSO_2$	H	3	58	195-196 (C)
57	Br	H	pyridin-2-ylS	H	3	62	213-215 (C)

[a] Recrystallisation solvent given in parenthesis: A = light petroleum (b.p. 40-60 °C)-$MeCO_2Et$; B = light petroleum (b.p. 40-60 °C)-CH_2Cl_2; C = light petroleum-$MeCO_2Et$. [b] From the *N,N'-bis*(trifluoro-acetamido)-OPD **43**. [c] From the *N,N'-bis*(trifluoroacetamido)-OPD **44**; lit.,[4] m.p. 191-193 °C.

5-Piperidino-2-trifluoromethylbenzimidazole **52** (Table 6). - A solution of 5-piperidino-2*H*-benzimidazole-2-spirocyclohexane **1** (R^5 = piperidino, $R^4 = R^5 = R^7 = H$)[4] (3.0 g, 11.15 mmol) in trifluoroacetic acid (75 cm^3) and trifluoroacetic anhydride (3 cm^3) containing 10% palladium-charcoal (0.2 g) was hydrogenated at atmospheric pressure until no more hydrogen was consumed. The catalyst was filtered off and distillation of the excess of reagent and solvent under reduced pressure left a brown solid which was heated in a refluxing mixture of ethanol (25 cm^3) and concentrated hydrochloric acid (3 cm^3) for 5 h under nitrogen. The resulting mixture was poured into cold water (250 cm^3), solid sodium hydrogen carbonate was added to neutralise the acid and extraction with ethyl acetate (3 x 50 cm^3) gave the product **52** (1.65 g, 55%), as a white solid.

TABLE 7

Mass Spectral and Microanalytical Data for New Compounds

Compound No.	Found (%)			Found M+	Molecular Formula	Required (%)			Required M
	C	H	N			C	H	N	
2				246.1873	$C_{15}H_{22}N_2O$				246.1888
3				410.1843	$C_{21}H_{34}N_2S_3$				410.1884
4				410.1844	$C_{21}H_{34}N_2S_3$				410.1884
5				484.2068	$C_{24}H_{40}N_2S_4$				484.2074
6	66.8	7.25	9.9	411	$C_{23}H_{29}N_3O_2S$	67.1	7.1	10.2	411
8				166.1115	$C_9H_{14}N_2O$				166.1106
9				345.9274	$C_{12}H_9BrCl_2N_2O$				345.9276
10				182.2817	$C_9H_{14}N_2S$				182.2830
11				256.1065	$C_{12}H_{20}N_2S_2$				256.1067
12				256.1033	$C_{12}H_{20}N_2S_2$				256.1067
13				330.1240	$C_{15}H_{26}N_2S_3$				330.1258
14				330.1258	$C_{15}H_{26}N_2S_3$				330.1258
15				404.1448	$C_{18}H_{32}N_2S_4$				404.1448
16				196.1019	$C_{10}H_{16}N_2S$				196.1034
17	59.4	8.9	9.9	284	$C_{14}H_{24}N_2S_2$	59.1	8.5	9.85	284

18	60.7	5.2	19.6	217	$C_{11}H_{11}N_3S$	60.8	5.1	19.3	217
19	54.6	4.7	25.5	218	$C_{10}H_{10}N_4S$	55.0	4.6	25.7	218
20				293.9697[a]	$C_{11}H_{10}BrN_3S$				293.9700[a]
21	44.0	3.4	8.4	326	$C_{12}H_{11}BrN_2O_2S$	44.05	3.4	8.6	326
22	61.45	6.4	12.5	331	$C_{17}H_{21}N_3O_2S$	61.6	6.4	12.7	331
26	53.0	6.35	12.3	339	$C_{15}H_{21}N_3O_2S_2$	53.1	6.2	12.4	339
27	56.0	6.2	15.1	279	$C_{13}H_{17}N_3O_2S$	55.9	6.1	15.0	279
28	55.7	4.15	18.0	300	$C_{14}H_{12}N_4O_2S$	56.0	4.0	18.65	300
29	51.55	4.0	22.8	301	$C_{13}H_{11}N_5O_2S$	51.8	3.7	23.2	301
30	53.9	6.5	9.1	312	$C_{14}H_{20}N_2S_3$	53.8	6.45	9.0	312
31	52.7	6.9	7.3	386	$C_{17}H_{26}N_2S_4$	52.8	6.8	7.2	386
32	53.0	6.7	7.4	386	$C_{17}H_{26}N_2S_4$	52.8	6.8	7.2	386
33	57.0	6.2	11.2	252	$C_{12}H_{16}N_2S_2$	57.1	6.4	11.1	252
34	63.2	6.9	16.8	247	$C_{13}H_{17}N_3S$	63.1	6.9	17.0	247
35	59.6	5.7	10.3	387	$C_{19}H_{21}N_3O_2S_2$	58.9	5.5	10.8	387
36	41.5	2.3	6.6	402	$C_{14}H_9BrCl_2N_2OS$	41.6	2.2	6.9	402
37	61.5	6.5	17.5	233	$C_{12}H_{15}N_3S$	61.8	6.5	18.0	233
38	57.8	5.2	11.1	373	$C_{18}H_{19}N_3O_2S_2$	57.9	5.1	11.3	373
39	40.2	2.0	7.5	388	$C_{13}H_7BrCl_2N_2OS$	40.0	1.8	7.2	388
40				367.9284	$C_{13}H_9BrN_2O_2S_2$				367.9290

41	42.9	4.15	6.15	448	$C_{16}H_{18}F_6N_2O_2S_2$	42.85	4.05	6.25	448
42	43.5	4.7	5.3	522	$C_{19}H_{24}F_6N_2O_2S_3$	43.7	4.6	5.4	522
43	44.6	5.1	4.6	596	$C_{22}H_{30}F_6N_2O_2S_4$	44.3	5.1	4.7	596
45	50.9	4.3	10.8	260	$C_{11}H_{11}F_3N_2S$	50.8	4.3	10.8	260
46	50.3	5.1	8.3	334	$C_{14}H_{17}F_3N_2S_2$	50.3	5.1	8.4	334
47	50.0	5.1	8.3	334	$C_{14}H_{17}F_3N_2S_2$	50.3	5.1	8.4	334
48	49.9	5.9	6.8	408	$C_{17}H_{23}F_3N_2S_3$	50.0	5.7	6.9	408
49	50.1	5.6	6.85	408	$C_{17}H_{23}F_3N_2S_3$	50.0	5.7	6.9	408
50				482.1144	$C_{20}H_{29}F_3N_2S_4$				482.1165
51				274.0740	$C_{12}H_{13}F_3N_2S$				274.0751
53	52.6	4.1	10.2	411	$C_{18}H_{16}F_3N_3O_3S$	52.55	3.9	10.2	411
54	52.7	2.7	14.2	295	$C_{13}H_8F_3N_3S$	52.9	2.7	14.2	295
55	48.7	2.5	19.0	296	$C_{12}H_7F_3N_4S$	48.65	2.4	18.9	296
56	41.45	2.1	6.8	404	$C_{14}H_8BrF_3N_2O_2S$	41.5	2.0	6.9	404
57				372.9490	$C_{13}H_7BrF_3N_3S$				372.9497
62 or **63**	52.3	7.1	7.2	388	$C_{17}H_{28}N_2O_2S_3$	52.5	7.3	7.2	388
64	57.8	3.5	24.55	228	$C_{11}H_8N_4S$	57.9	3.5	24.5	228
65	76.7	4.1	10.3	389	$C_{25}H_{15}N_3S$	77.1	3.9	10.8	389
67	70.0	6.8	23.6	240	$C_{14}H_{16}N_4$	70.0	6.7	23.3	240

68	69.15	6.1	24.9	226	$C_{13}H_{14}N_4$	69.0	6.2	24.8	226
70	72.9	7.8	12.3		$C_{14}H_{18}N_2O$	73.0	7.9	12.2	
71	73.9	8.4	11.7		$C_{15}H_{20}N_2O$	73.7	8.25	11.5	

[a] M-1 peak measured.

TABLE 8

^{1}H NMR Data of Compounds Synthesised[a]

Compound No.	$\nu_{max.}$/cm^{-1} (Assignment)	δ ($CDCl_3$ and 60 MHz unless stated otherwise)
2	3350 and 3430 (NH)	0.60-2.30 br (15 H, m, Me and 6 x CH_2), 3.20 br (2 H, s, exchangeable, NH), 3.75 (2 H, t, J 6.0, C$\underline{H}_2$O) and 6.15 (1 H, d, J 7.0, 7-H), 6.30 (1 H, s, 4-H) and 6.60 (1 H, dd, J 7.0, 2.0, 6-H)
3	3350 (NH)	1.10 (9 H, t, J 6.0, 3 x Me), 1.30-2.50 (16 H, m, 8 x CH_2), 2.80 (6 H, t, J 6.0, 3 x C$\underline{H}_2$S), 4.45 br (2 H, s, exchangeable, NH) and 6.65 (1 H, s, 7-H)
4	3350 (NH)	0.50-2.00 br (25 H, m, 3 x Me and 8 x CH_2), 2.70 (6 H, t, J 6.0, 3 x C$\underline{H}_2$S), 3.90 br (2 H, s, exchangeable, NH) and 6.65 (1 H, s, 6-H)
5	3350 (NH)	0.90 (12 H, t, J 6.0, 4 x Me), 1.10-2.00 br (18 H, m, 9 x CH_2), 2.90 br (8 H, t, J 6.0, 4 x C$\underline{H}_2$S) and 4.70 br (2 H, s, exchangeable, NH)
6	3350 (NH)	0.70-1.80 br (16 H, m, cyclohexyl + piperidino), 2.40-2.80 br (4 H, m, piperidino), 3.70 br (1 H, s, exchangeable, NH), 4.50 br (1 H, s, exchangeable, NH), 6.38 (1 H, d, J 9.0, 7-H), 7.20-7.50 (3 H, m, ArH), 7.63 (1 H, d, J 9.0, 6-H) and 7.70-7.90 (2 H, m, ArH) (90 MHz)
8	3370 and 3400 (NH_2)	0.95 (3 H, t, J 6.0, Me), 1.30-2.30 (2 H, m, C$\underline{H}_2$Me), 3.25 br (4 H, s, exchangeable, NH_2), 3.75 (2 H, t, J 6.0, C$\underline{H}_2$O), 6.10-6.40 (2 H, m, 3-H and 6-H) and 6.60 br (1 H, d, J 8.0, 5-H)

9	3400 and 3600 (NH_2)	3.43-4.14 br (4 H, s, exchangeable, NH_2), 6.35 (1 H, d, J 3.0, 4-H), 6.63 (1 H, d, J 3.0, 6-H), 6.80 (1 H, dd, J 8.0, 1.5, ArH), 7.10 (1 H, t, J 8.0, ArH) and 7.20 (1 H, dd, J 8.0, 1.5, ArH) (300 MHz)
10		0.85 (3 H, t, J 6.0, Me), 1.45 (2 H, m, $C\underline{H}_2Me$), 2.65 (2 H, t, J 6.0, $C\underline{H}_2S$), 3.30 br (4 H, s, exchangeable, NH_2) and 6.20-6.90 (3 H, m, 3-H, 5-H and 6-H)
11	3300 and 3400 (NH_2)	1.05 (6 H, t, J 6.0, Me), 1.70 (4 H, m, $C\underline{H}_2Me$), 2.90 (4 H, t, J 6.0, $C\underline{H}_2S$), 3.50 br (4 H, s, exchangeable, NH_2) and 6.90 (2 H, s, 3-H and 6-H)
12	3325 and 3400 (NH_2)	1.00 (6 H, t, J 6.0, Me), 1.10-2.00 (4 H, m, $C\underline{H}_2Me$), 2.50 (2 H, t, J 6.0, $C\underline{H}_2S$), 2.60 (2 H, t, J 6.0, $C\underline{H}_2S$), 3.86 br (4 H, s, exchangeable, NH_2), 6.70 (1 H, d, J 2.0, 6-H) and 7.05 (1 H, d, J 2.0, 4-H)
13		0.70-1.30 (9 H, m, 3 x Me), 1.30-2.00 (6 H, m, $C\underline{H}_2Me$), 2.50-3.00 (6 H, m, $C\underline{H}_2S$), 4.10 br (4 H, s, exchangeable, NH_2) and 6.75 (1 H, s, 6-H)
14	3350 and 3450 (NH_2)	0.70-1.20 (9 H, m, Me), 1.20-2.00 (6 H, m, $C\underline{H}_2Me$), 2.50-3.10 (6 H, m, $C\underline{H}_2S$), 3.90 br (4 H, s, exchangeable, NH_2) and 6.55 (1 H, s, 5-H)
15	3300 and 3400 (NH_2)	1.10 (12 H, t, J 6.0, Me), 1.20-2.00 (8 H, m, $C\underline{H}_2Me$), 2.50-3.00 (8 H, m, $C\underline{H}_2S$) and 4.25 br (4 H, s, exchangeable, NH_2)
16		1.20 (9 H, s, CMe_3), 3.50 br (4 H, s, exchangeable, NH_2), 6.50 (1 H, d, J 7.0, 6-H) and 6.70-7.00 (2 H, m, 3-H and 5-H)
17		1.25 (18 H, s, 2 x CMe_3), 3.45 br (4 H, s, exchangeable, NH_2) and 7.05 (2 H, s, 3-H and 6-H) (90 MHz)
18	3100-3400 br (NH_2)	2.00-3.00 br (4 H, s, exchangeable, NH_2), 6.71 (1 H, d, J 8.0, 6-H), 6.76 (1 H, d, J 8.0, 5-H), 6.88-6.98 (3 H, m, ArH), 7.34-7.40 (1 H, m, ArH) and 8.35-8.37 (1 H, m, ArH) (300 MHz)
19	3100-3400 br (NH_2)	1.30-2.10 br (4 H, s, exchangeable, NH_2), 6.73 (1 H, d, J 8.0, 6-H), 6.88-7.00 (3 H, m, 3-H, 5-H and ArH) and 8.46 (2 H, d, J 5.0, ArH) (300 MHz)
20	3340 and 3450 (NH_2)	3.59-4.40 br (4 H, s, exchangeable, NH_2), 6.67 (1 H, d, J 7.5, ArH), 6.90-7.00 (3 H, m, 4-H, 6-H and ArH), 7.36-7.41 (1 H, m, ArH) and 8.33-8.36 (1 H, m, ArH) (300 MHz)
21	3350 and 3440 (NH_2)	3.30-3.80 br (4 H, s, exchangeable, NH_2), 6.63 (1 H, d, J 8.0, ArH), 6.80-6.95 (4 H, m, ArH) and 8.43 (2 H, d, J 8.0, ArH) ($CDCl_3$ + [$^2H_6$]-DMSO) (300 MHz).

22	3300, 3400, and 3450 (NH_2)	1.50-2.10 br (6 H, s, piperidino), 2.80-3.20 br (4 H, s, piperidino), 4.10-4.60 br (4 H, s, exchangeable, NH_2), 7.18 (1 H, d, J 9.0, 6-H),7.25 (1 H, d, J 9.0, 5-H), 7.45-7.70 (3 H, m, ArH) and 7.80-8.20 (2 H, m, ArH) (90 MHz)
24	1620 (CO) and 3325 (NH)	0.95 (3 H, t, J 6.0, $C\underline{H}_3CH_2$), 1.65 (2 H, q, J 6.0, $CH_3C\underline{H}_2$), 3.70 (3 H, s, CO_2Me), 3.85 (2 H, t, J 6.0, $C\underline{H}_2O$), 6.65 (1 H, dd, J 8.0, 2.0, 7-H), 7.02 (1 H, dd, J 7.0, 2.0, 4-H), 7.35 (1 H, dd, J 7.0, 2.0, 6-H) and 11.65 br (2 H, s, exchangeable, 2 x NH) ([$^2H_6$]-DMSO) (90 MHz)
25	1640 (CO) and 3325 (NH)	
26	1620 (CO) and 3300 (NH)	1.00 (6 H, t, J 6.0, 2 x $C\underline{H}_3CH_2$), 1.20-1.80 (4 H, m, 2 x $CH_3C\underline{H}_2$), 2.85 (4 H, t, J 6.0, $C\underline{H}_2S$), 3.75 (3-H, s, CO_2Me), 7.45 (2 H, s, 4-H and 7-H) and 11.60 br (2 H, s, exchangeable, NH) ([$^2H_6$]-DMSO) (90 MHz)
27	1660 and 1705 (CO) and 3340 (NH)	1.20 (9 H, s, CMe_3), 3.75 (3 H, s, CO_2Me), 7.18 (1 H, dd, J 8.0, 2.0, 6-H), 7.40 (1 H, d, J 8.0, 7-H), 7.55 br (1 H, s, 4-H) and 11.80 (2 H, s, exchangeable, NH) ([$^2H_6$]-DMSO) (90 MHz)
28	1700 (CO) and 3340 br (NH)	3.80 (3 H, s, Me), 6.80 (1 H, d, J 9.0, 7-H), 7.00-7.80 (5 H, several x m, ArH), 8.40 (1 H, d, J 5.0, ArH) and 10.90-11.80 br (2 H, s, exchangeable, 2 x NH) ([$^2H_6$]-DMSO) (90 MHz)
29	1720 (CO) and 3320 br (NH)	3.80 (3 H, s, Me), 7.10-7.70 (4 H, m, ArH), 8.50 (2 H, d, J 5.0, ArH) and 11.74 br (2 H, s, exchangeable, NH) ([$^2H_6$]-DMSO) (90 MHz)
30		1.00 (6 H, t, J 6.0, 2 x $C\underline{H}_3CH_2$), 1.30-2.00 (4 H, m, 2 x $CH_3C\underline{H}_2$), 2.50-3.25 (7 H, m, SMe and 2 x $C\underline{H}_2S$), 7.25 (1 H, d, J 2.0, 5-H or 7-H), 7.50 (1 H, d, J 2.0, 7-H or 5-H) and 8.30 br (1 H, s, exchangeable, NH)
31		1.00 (9 H, t, J 6.0, 3 x $C\underline{H}_3CH_2$), 1.30-2.00 (6 H, m, 3 x $CH_3C\underline{H}_2$), 2.50-3.30 (9 H, m, SMe and 3 x $C\underline{H}_2S$), 7.10 (1 H, s, 7-H) and 9.30 br (1 H, s, exchangeable, NH)
32		0.70-1.20 (9 H, m, 3 x $C\underline{H}_3CH_2$), 1.30-2.00 (6 H, m, 3 x $CH_3C\underline{H}_2$), 2.65-3.20 (9 H, m, SMe and 3 x $C\underline{H}_2S$), 7.40 (1 H, s, 6-H) and 8.00 br (1 H, s, exchangeable, NH)
33		1.25 (9 H, s, CMe_3), 2.75 (3 H, s, SMe), 7.35 (1 H, d, J 8.0, 6-H or 7-H), 7.50 (1 H, d, J 8.0, 7-H or 6-H), 7.75 br (1 H, s, 4-H) and 11.00 br (1 H, s, exchangeable, NH)
34		1.40-1.90 (6 H, J 9.0, m, piperidino), 2.72 (3 H, s, SMe), 2.95-3.20 (4 H, m, piperidino), 6.92 (1 H, d, J 9.0, 6-H), 6.97 (1 H, s, 4-H) and 7.40(1 H, d, J 9.0, 7-H) (90 MHz)
35	3250 br (NH)	1.54-1.94 br (6 H, m, piperidino), 2.74 (3 H, s, SMe), 3.05-3.24 br (4 H, s, piperidino), 7.39-7.50 (4 H, m, 7-H and ArH) and 7.89-7.93 (3 H, m, 6-H and ArH) (300 MHz)

36		2.75 (3 H, s, SMe), 6.84 (1 H, dd, J 8.0, 3.0, ArH), 6.99-7.06 [3 H, m, NH (exchangeable), 5-H and 7-H], 7.17 (1H, t, J 8.0, ArH) and 7.25 (1 H, dd, J 8.0, 3.0, ArH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)
37	3100 br (NH)	1.40-1.90 br (6 H, m, piperidino), 2.90-3.30 br (4 H, m, piperidino), 6.70 br (1 H, s, 4-H), 6.78 (1 H, dd, J 9.0, 3.5, 6-H), 7.05 (1 H, d, J 9.0, 7-H) and 12.50-13.00 br (2 H, s, exchangeable, NH) ([$^2H_6$]-DMSO) (90 MHz)
38	3340 (NH)	2.05-2.25 br (6 H, m, piperidino), 2.92-2.96 br (4 H, m, piperidino), 7.22 (1 H, d, J 9.0, 7-H), 7.39-7.51 (4 H, m, 6-H and ArH), 7.82-7.86 (2 H, m, ArH), 11.05 br (1 H, s, exchangeable, NH) and 12.23 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)
39		6.70 br (1 H, s, 5-H), 6.75 (1 H, d, J 8.0, ArH), 6.87 br (1 H, s, 7-H), 7.06 (1 H, t, J 8.0, ArH), 7.18 (1 H, d, J 8.0, ArH), 10.60-10.80 br (1 H, s, exchangeable, NH) and 11.10-11.30 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)
40		6.73-6.82 (3 H, m, ArH), 6.94 (1 H, s, 5-H), 7.09-7.12 (2 H, m, ArH), 7.23 (1 H, s, 7-H), 12.28 br (1 H, s, exchangeable, NH) and 12.45 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)
41	1710 (CO) and 3325 (NH)	1.00 (6 H, t, J 6.0, 2 x $C\underline{H}_3CH_2$), 1.20-2.00 (4 H, m, 2 x $CH_3C\underline{H}_2$), 2.50-3.10 (4 H, m, 2 x $C\underline{H}_2S$), 7.20 (1 H, d, J 1.5, 4-H or 6-H), 7.50 (1 H, d, J 1.5, 6-H or 4-H), 8.55 (1 H, s, exchangeable, NH) and 9.00 (1 H, s, exchangeable, NH)
42	1700 (CO) and 3325 (NH)	0.70-1.20 (9 H, m, 3 x $C\underline{H}_3CH_2$), 1.20-2.00 (6 H, m, 3 x $CH_3C\underline{H}_2$), 2.50-3.20 (6 H, m, 3 x $C\underline{H}_2S$), 7.25 (1 H, s, 6-H), 8.25 (1 H, s, exchangeable, NH) and 8.95 (1 H, s, exchangeable, NH)
43	1710 (CO) and 3275 and 3425 (NH)	1.00 (12 H, t, J 6.0, 4 x $C\underline{H}_3CH_2$), 1.20-2.00 (8 H, m, 4 x $CH_3C\underline{H}_2$), 2.60-3.20 (8 H, m, 4 x $C\underline{H}_2S$) and 8.85 (2 H, s, exchangeable, NH)
45		0.90 (3 H, t, J 6.0, $C\underline{H}_3CH_2$), 1.20-2.00 (2 H, m, $CH_3C\underline{H}_2$), 2.85 (2 H, t, J 6.0, $C\underline{H}_2S$), 7.10-7.80 (3 H, m, 4-H, 6-H and 7-H) and 12.00 br (1 H, s, exchangeable, NH)
46		0.90 (3 H, t, J 6.0, $C\underline{H}_3CH_2$), 1.00 (3 H, t, J 6.0, $C\underline{H}_3CH_2$), 1.20-2.00 (4 H, m, 2 x $CH_3C\underline{H}_2$), 2.60-3.20 (4 H, m, 2 x $C\underline{H}_2S$), 7.35 br (1 H, s, 5-H or 7-H), 7.55 br (1 H, s, 7-H or 5-H) and 13.00 br (1 H, s, exchangeable, NH)
47		1.05 (6 H, t, J 6.0, 2 x $C\underline{H}_3CH_2$), 1.30-2.00 (4 H, m, 2 x $CH_3C\underline{H}_2$), 2.85 (4 H, t, J 6.0, $C\underline{H}_2S$), 7.70 (2 H, s, 4-H and 7-H) and 9.80 (1 H, s, exchangeable, NH)

48		0.90-1.30 (9 H, m, 3 x $C\underline{H}_3CH_2$), 1.40-2.10 (6 H, m, 3 x $CH_3C\underline{H}_2$), 2.80-3.50 (6 H, m, 3 x $C\underline{H}_2S$), 7.25 (1 H, s, 7-H) and 10.20 (1 H, s, exchangeable, NH)
49		1.00 (9 H, t, J 6.0, 3 x $C\underline{H}_3CH_2$), 1.30-2.00 (6 H, m, 3 x $CH_3C\underline{H}_2$), 2.70-3.30 (6 H, m, 3 x $C\underline{H}_2S$), 7.15 (1 H, s, 6-H) and 10.10 (1 H, s, exchangeable, NH)
50		0.90 (12 H, t, J 6.0, 4 x $C\underline{H}_3CH_2$), 1.10-2.00 (8 H, m, 4 x $CH_3C\underline{H}_2$), 2.80-3.60 (8 H, m, $C\underline{H}_2S$) and 8.70 br (1 H, s, exchangeable, NH)
51		1.35 (9 H, s, CMe_3), 7.70-8.10 (3 H, m, 4-H, 6-H and 7-H) and 10.75 (1 H, NH, s, exchangeable, NH)
53		3.50 br (4 H, m, morpholino), 3.85 br (4 H, m, morpholino), 6.90-8.10 (7 H, m, 6-H, 7-H and ArH) and 13.48 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)
54		6.70-7.20 (2 H, m, ArH), 7.40 (1 H, d, J 9.0, 6-H or 7-H), 7.55 (1 H, s, 4-H), 7.70 (1 H, d, J 9.0, 6-H or 7-H), 7.98 (1H, s, ArH), 8.38 (1 H, d, J 5.0, ArH) and 11.10-13.00 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (90 MHz)
55		7.00 (1 H, t, J 5.0, ArH), 7.58 (1 H, dd, J 9.0, 3.0, 6-H), 7.78 (1 H, d, J 9.0, 7-H), 8.02 (1 H, s, 4-H), 8.46 (2 H, d, J 5.0, ArH) and 11.50-13.00 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (90 MHz)
56		7.46-7.56 (3 H, m, ArH), 7.90-7.94 (2 H, m, ArH), 8.00 (1 H, s, 5-H), 8.08 (1 H, s, 5-H), 8.27 (1 H, s, 7-H), 8.42 (1 H, s, 7-H), 11.46 br (1 H, s, exchangeable, NH) and 12.43 br (1 H, s, exchangeable, NH) (300 MHz)[b]
57		6.48-6.54 m, 6.57-6.60 m, 7.23-7.27 m, 7.78 s, 7.98 s, 8.16-8.20 m (all 1 H, ArH), 13.50 br (1 H, s, exchangeable, NH) and 13.75 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (300 MHz)[b]
62 or **63**	1690 (CO) and 3400 (NH_2)	1.00 (9 H, t, J 6.0, $C\underline{H}_3CH_2$), 1.70 (6 H, m, $CH_3C\underline{H}_2$), 2.80 (6 H, t, J 6.0, $C\underline{H}_2S$), 3.70 (3 H, s, OMe), 4.70 br (2 H, s, exchangeable, NH_2), 6.25 (1 H, s, exchangeable, NH) and 6.55 (1 H, s, H) (90 MHz)
64		7.04 (1 H, t, J 5.0, ArH), 7.46 (1 H, d, J 9.0, 7-H), 7.70 (1 H, d, J 9.0, 6-H), 7.94 (1 H, s, 4-H), 8.18 (1 H, s, 2-H), 8.52 (2 H, d, J 5.0, ArH) and 11.10-12.00 br (1 H, s, exchangeable, NH) ([$^2H_6$]-DMSO-$CDCl_3$) (90 MHz)

67	3220 (NH)	1.20-2.20 (10 H, m, cyclohexyl), 6.90-7.40 (4 H, m, ArH), and ~ 12.00 br (2 H, s, exchangeable, NH) (90 MHz)
68	3100-3200 (NH)	1.55-1.64 (4 H, m, cyclopentyl), 1.70-1.78 (4 H, m, cyclopentyl), 5.78 br (2 H, s, exchangeable, NH) and 6.78-7.32 (4 H, three complex m's, ArH) ($[^2H_6]$-DMSO-$CDCl_3$) (300 MHz)
70		1.35 (3 H, t, J 9.0, Me), 1.20-2.25 (10 H, m, cyclohexyl), 4.00 (2 H, q, J 9.0, CH_2), 6.25 (1 H, d, J 2.0, 4-H), 6.75 (1 H, dd, J 8.0, 2.0, 6-H) and 7.15 (1 H, d, J 8.0, 1.0, 7-H) (90 MHz)
71		0.95 (3 H, t, J 9.0, Me), 1.40-2.20 (12 H, m, CH_2 + cyclohexyl), 3.90 (2 H, t, J 9.0, $C\underline{H}_2O$), 6.20 br (1 H, s, 4-H), 6.70 (1 H, dd, J 9.0, 2.0, 6-H) and 7.15 (1 H, d, J 9.0, 7-H).

[a] For NH protons (e.g. in benzimidazole rings) the IR stretching frequencies and ^1H NMR signals often could not be detected. [b] ^1H NMR spectrum of two tautomers (see Discussion).

5-(Pyrimidin-2-ylthio)benzimidazole **64**. - A mixture of 4-(pyrimidin-2-ylthio)-*o*-phenylenediamine **19** (1.2 g, 5.5 mmol) and formic acid (10 cm^3) was boiled for 30 min, then cooled to ambient temperature and poured into ice-cold water (25 cm^3). The excess of acid was neutralised by addition of solid sodium carbonate, the precipitate (1.0 g, 80%) was filtered off and washed with ice-cold water (100 cm^3), to give the product **64**, white prisms, m.p. 205-208 °C (from water) (mass spectral and microanalytical data in Table 7 and spectroscopic details in Table 8).

11-(Pyridin-2-ylthio)dibenzo[*a*,*c*]phenazine **65**. - A solution of phenanthraquinone (1.15 g, 5.53 mmol) in warm acetic acid (70 cm^3) was added to a stirred solution of 4-(pyridin-2-ylthio)-*o*-phenylenediamine **21** (1.2 g, 5.53 mmol) in ethanol (10 cm^3) and the resulting mixture was heated at 100 °C on a water bath for 30 min, then cooled. The resulting bright yellow fluorescent precipitate was filtered off, washed with ice-cold ethanol (2 x 20 cm^3) and dried at 100 °C, to give the product **65** (1.76 g, 82%), m.p. 178-180 °C (from methanol-glacial acetic acid) (mass spectral and microanalytical data in Table 7 and spectroscopic details in Table 8).

1,3-Dihydro-2*H*-4,9-diazanaphth[2,3-*d*]imidazole-2-spirocyclohexane **67**. - A mixture of 2,3-diaminoquinoxaline (5.0 g, 31.25 mmol) and cyclohexanone (10 cm^3, 9.47 g, 96.5 mmol) was heated under reflux and the reaction was followed by TLC to completion. The excess of cyclohexanone was distilled off under reduced pressure and the yellow residue was chromatographed on alumina. Light petroleum-ethyl acetate (2:1) eluted the product **67** (4.9 g, 65%), cream solid, m.p. 287-289 °C (from light petroleum-ethyl acetate) (mass spectral and microanalytical data in Table 7 and spectroscopic properties in Table 8).

1,3-Dihydro-4,9-diazanaphth[2,3-*d*]imidazole-2-spirocyclopentane **68** (9%) was prepared similarly, pale yellow crystals, m.p. 312-314 °C [from light petroleum-ethyl acetate (2:1)] (mass spectral and microanalytical data in Table 7 and spectroscopic details in Table 8).

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