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# Imidazo[1,2-*b*]pyridazines. II*
# 6-Alkylthio- and 6-Arylthio-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazines

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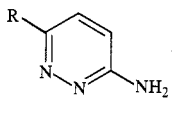
*Abstract*

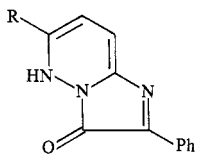
A series of 6-alkylthio- and 6-arylthio-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazines has been prepared from 6-alkylthio- and 6-arylthio-pyridazin-3-amines through the corresponding 6-alkylthio- and 6-arylthio-2-phenylimidazo[1,2-*b*]pyridazin-3(5*H*)-ones.

## Introduction

In Part I[1] of this series we described the preparation of 3-alkoxy-6-halogeno-2-phenyl (and *p*-substituted phenyl)imidazo[1,2-*b*]pyridazines and 3-methoxy-2,6-diphenylimidazo[1,2-*b*]pyridazine for examination for central nervous system activity. We now report the synthesis of 6-alkythio- and 6-arylthio(including *m*- and *p*-substituted arylthio)-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazines (3).



(1)



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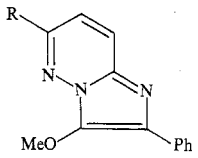

(3)

## Synthesis

Starting material for the synthesis of compounds (3) was 6-chloropyridazin-3-amine which was converted into the 6-alkylthio- or 6-arylthio-pyridazin-3-amine (1) and thence through the 6-alkylthio- or 6-arylthio-2-phenylimidazo[1,2-*b*]pyridazin-3(5*H*)-one (2) into the 6-alkylthio- or 6-arylthio-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine (3).

The reaction of 6-chloropyridazin-3-amine with the sodium salt of an alkanethiol or a benzenethiol was carried out at 130–150° for 16–20 h (conditions somewhat more severe than reported[2] for the methylthio analogue). Condensations of the

* Part I, *Aust. J. Chem.*, 1986, **39**, 1803.

[1] Barlin, G. B., *Aust. J. Chem.*, 1986, **39**, 1803.
[2] Barlin, G. B., *J. Chem. Soc., Perkin Trans. 1*, 1976, 1424.

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pyridazin-3-amines (1) with phenylglyoxal in ethanolic hydrogen chloride to give (2; not characterized in every case) were usually effected by stirring at 20° for 3–17 days but in some instances the mixture was refluxed. For example, the intermediates (2; R = *p*-$ClC_6H_4S$ and *p*-$MeC_6H_4S$) were prepared by refluxing the reaction mixture for 5–6 h; (2; R = *p*-$Me_2NC_6H_4S$) required a reflux time of 24 h. The hydroxy compounds (2) were readily converted with ethereal diazomethane into their *O*-methyl derivatives (3).

3-Methoxy-6-methylthio-2-phenylimidazo[1,2-*b*]pyridazine (3; R = MeS) was also prepared from the chloro compound (3; R = Cl) with sodium methanethiolate at 130–140°, a method similar to that used for the preparation[1] of the 6-methoxy analogue (3; R = MeO). This 6-methylthio compound was converted with *m*-chloroperoxybenzoic acid in chloroform at room temperature into 3-methoxy-6-methylsulfonyl-2-phenylimidazo[1,2-*b*]pyridazine (3; R = $MeSO_2$). The latter compound gave signals in the $^1H$ n.m.r. spectrum for H 7 and H 8 which were considerably downfield of those in the corresponding *S*-methyl compound (as in the pyridine series[3]) and also downfield of those in its 6-phenyl analogue.[1]

Results of our biological testing will be reported in a separate communication.

## Experimental

Solids for analysis were dried in an oven at 100° for 1 h (unless otherwise specified) and melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University Analytical Services Unit. $^1H$ n.m.r. spectra were recorded at 90 MHz and 30° with a JEOL FX90Q Fourier transform spectrometer with tetramethylsilane (in $CDCl_3$) as internal standard.

*6-Methylthio-2-phenylimidazo[1,2-b]pyridazin-3(5H)-one*

Phenylglyoxal (0·34 g) in ethanol (1·0 ml) was added to a mixture of 6-methylthiopyridazin-3-amine[2] (0·35 g) in ethanol (4·0 ml) with concentrated hydrochloric acid (0·2 ml) and the mixture was stirred at 20° for 4 days. The product was filtered off and washed successively with ethanol, water, ethanol and ether to give as a red solid *6-methylthio-2-phenylimidazo[1,2-b]pyridazin-3(5H)-one* (0·404 g) (Found: C, 59·7; H, 4·3; N, 16·0. $C_{13}H_{11}N_3OS$ requires C, 60·7; H, 4·3; N, 16·3%).

*3-Methoxy-6-methylthio-2-phenylimidazo[1,2-b]pyridazine*

(A) 6-Methylthio-2-phenylimidazo[1,2-*b*]pyridazin-3(5*H*)-one (0·388 g) was added to a solution of diazomethane in ether (prepared from 2·6 g nitrosomethylurea) and the mixture was stirred in ice overnight. The solvent was evaporated and the product subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give yellow crystals of *3-methoxy-6-methylthio-2-phenylimidazo[1,2-b]pyridazine* (0·214 g), m.p. 124·5–125·5° (Found: C, 61·6; H, 4·9; N, 15·5. $C_{14}H_{13}N_3OS$ requires C, 62·0; H, 4·8; N, 15·5%). $^1H$ n.m.r. ($CDCl_3$): δ 2·67, s, MeS; 4·17, s, MeO; 6·80, d, $J_{7,8}$ 9·5 Hz, H 7; 7·43, 8·12, complex, Ph; 7·63, d, $J_{7,8}$ 9·5 Hz, H 8.

(B) 6-Chloro-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine (0·1 g) and aqueous sodium methanethiolate (prepared by passing methanethiol into 3 ml 1 M sodium hydroxide) was heated in a Teflon-lined screw-top bomb at 130–140° for 5 h. The product was extracted into chloroform and subjected to t.l.c. (alumina; chloroform, then developed twice on alumina; ether) to give the title compound (0·006 g). The $^1H$ n.m.r. was identical with the product described in (A).

*3-Methoxy-6-methylsulfonyl-2-phenylimidazo[1,2-b]pyridazine*

*m*-Chloroperoxybenzoic acid (1·0 g) in chloroform (15·0 ml) was added to 3-methoxy-6-methylthio-2-phenylimidazo[1,2-*b*]pyridazine (0·3 g) in chloroform (10·0 ml) and the mixture

[3] Barlin, G. B., and Brown, W. V., *J. Chem. Soc. B*, 1967, 648.

stirred at 20° for 2 days. The chloroform solution was chilled, shaken with sodium hydrogen carbonate solution and then water, dried ($Na_2SO_4$) and evaporated at 20°. The product was subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give yellow crystals of *3-methoxy-6-methylsulfonyl-2-phenylimidazo[1,2-b]pyridazine* (0·011 g), m.p. 167–169° (Found, for sample dried at 70°/0·1 mm for 4·5 h: C, 55·6; H, 4·4; N, 13·6. $C_{14}H_{13}N_3O_3S$ requires C, 55·4; H, 4·3; N, 13·8%). $^1$H n.m.r. ($CDCl_3$): δ 3·40, s, $MeSO_2$; 4·20, s, MeO; 7·45, 8·22, complex, Ph; 7·62, d, $J_{7,8}$ 9 Hz, H 7; 8·09, d, $J_{7,8}$ 9 Hz, H 8.

*6-Ethylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (1·942 g) was added to a solution of ethanethiol (1·86 g) in 1 M sodium hydroxide (30 ml) and the mixture heated in a screw-top bomb in an oven at 130° for 16 h. After cooling, the reaction mixture was extracted with chloroform, extract dried ($Na_2SO_4$) and solvent evaporated to give an oil (2·0 g) which slowly crystallized. A portion was subjected to t.l.c. (silica; ethanol/chloroform, 5 : 95) to give *6-ethylthiopyridazin-3-amine*, m.p. 46–48° (Found, for sample dried at 20°/0·1 mm for 6 h: C, 45·9; H, 6·1; N, 26·0. $C_6H_9N_3S$ requires C, 46·4; H, 5·8; N, 27·1%). $^1$H n.m.r. ($CDCl_3$): δ 1·36, t, *J* 7 Hz, $CH_3CH_2$; 3·20, q, *J* 7 Hz, $CH_3CH_2$; 5·0, b, $NH_2$; 6·68, d, $J_{4,5}$ 9 Hz, H 5(4); 7·08, d, $J_{4,5}$ 9 Hz, H 4 (5).

*6-Ethylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

A mixture of phenylglyoxal (0·34 g), 6-ethylthiopyridazin-3-amine (0·38 g), ethanol (9·0 ml) and concentrated hydrochloric acid (0·2 ml) was stirred at 20° for 13 days. No precipitate separated. The solvent was distilled under reduced pressure and the residue broken up with water, filtered and dried to give an orange solid (0·393 g).

This solid was added to diazomethane in ether (prepared from 4·1 g nitrosomethylurea) and the mixture stirred in ice and at 20° overnight. The solvent was evaporated and the product subjected to t.l.c. (silica; chloroform, developed three times), and recrystallized from light petroleum (b.p. 40–60°) to give yellow crystals of *6-ethylthio-3-methoxy-2-phenylimidazo-[1,2-b]pyridazine* (0·095 g), m.p. 86–87° (Found, for sample dried at 20°/0·1 mm for 4 h: C, 63·1; H, 5·3; N, 14·3. $C_{15}H_{15}N_3OS$ requires C, 63·1; H, 5·3; N, 14·7%). $^1$H n.m.r. ($CDCl_3$): δ 1·49, t, *J* 7 Hz, $CH_3CH_2$; 3·27, q, *J* 7 Hz, $CH_3CH_2$; 4·16, s, MeO; 6·78, d, $J_{7,8}$ 9·5 Hz, H 7; 7·40, 8·10, complex, Ph; 7·63, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-Propylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (1·942 g) and aqueous sodium propanethiolate (prepared from 1·2 g sodium hydroxide in 25 ml water with 2·28 g propanethiol) were heated at 140° for 17 h. After cooling, the solid was filtered off, washed with 1 M sodium hydroxide, dried and recrystallized from cyclohexane to give white crystals of *6-propylthiopyridazin-3-amine* (1·7 g), m.p. 77–78° (Found, for sample dried at 50° for 4·5 h: C, 49·3; H, 6·5; N, 24·4. $C_7H_{11}N_3S$ requires C, 49·7; H, 6·5; N, 24·8%). $^1$H n.m.r. ($CDCl_3$): δ 1·03, t, *J* 7 Hz, $CH_3CH_2CH_2S$; 1·71, complex, $CH_3CH_2CH_2S$; 3·22, t, *J* 7 Hz, $CH_3CH_2CH_2S$; 4·65, bs, $NH_2$; 6·64, d, $J_{4,5}$ 9 Hz, H 5; 7·10, d, $J_{4,5}$ 9 Hz, H 4.

*3-Methoxy-2-phenyl-6-propylthioimidazo[1,2-b]pyridazine*

Concentrated hydrochloric acid (0·3 ml) was added to a mixture of phenylglyoxal (0·4 g) in ethanol (1·0 ml) with 6-propylthiopyridazin-3-amine (0·5 g) in ethanol (4·0 ml) and the mixture stirred at 20° for 17 days. The orange solid (0·4 g) was filtered off and washed with ethanol and ether.

This product was then stirred with excess ethereal diazomethane in ice and at 20° overnight and gave, after t.l.c. (alumina; chloroform) and recrystallization from light petroleum (b.p. 40–60°), yellow crystals of *3-methoxy-2-phenyl-6-propylthioimidazo[1,2-b]pyridazine* (0·18 g), m.p. 128–129° (Found, for sample dried at 20°/0·1 mm for 5 h: C, 64·4; H, 5·8; N, 14·0. $C_{16}H_{17}N_3OS$ requires C, 64·2; H, 5·7; N, 14·0%). $^1$H n.m.r. ($CDCl_3$): δ 1·10, t, *J* 7 Hz, $CH_3CH_2CH_2S$; 1·85, complex, $CH_3CH_2CH_2S$; 3·24, t, *J* 7 Hz, $CH_3CH_2CH_2S$; 4·16, s, MeO; 6·78, d, $J_{7,8}$ 9·5 Hz, H 7; 7·40, 8·10, complex, Ph; 7·63, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-Hexylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (0·5 g), hexanethiol (1·48 ml) and 0·55 M sodium hydroxide (18·0 ml) were heated at 140° for 16 h. After cooling, the white solid (0·5 g) was filtered off and recrystallized from cyclohexane to give *6-hexylthiopyridazin-3-amine*, m.p. 68–69° (Found, for sample dried at 20°/0·1 mm for 4 h: C, 56·8; H, 8·4; N, 20·0. $C_{10}H_{17}N_3S$ requires C, 56·8; H, 8·1; N, 19·9%). $^1$H n.m.r. ($CDCl_3$): δ 1·33, complex $CH_3(CH_2)_4CH_2S$; 3·23, t, $J$ 7 Hz, $CH_3(CH_2)_4$ $CH_2S$; 4·60, b, $NH_2$; 6·62, d, $J_{4,5}$ 9 Hz, H 5(4); 7·09, d, $J_{4,5}$ 9 Hz, H 4(5).

*6-Hexylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

A mixture of phenylglyoxal (0·135 g), 6-hexylthiopyridazin-3-amine (0·2 g), ethanol (60 ml) and concentrated hydrochloric acid (0·1 ml) was stirred at 20° for 8 days. The precipitate (0·1 g) was filtered off, washed with a little ethanol and dried at the pump.

This product was added to excess diazomethane in ether and stirred in ice and at 20° for 2 days. The brown oil obtained was subjected to t.l.c. (alumina; chloroform then alumina; ether) to give the *title compound* as a yellow oil (0·037 g) which was dried at 20°/0·1 mm for 6 h (Found: C, 66·9; H, 6·8; N, 12·0. $C_{19}H_{23}N_3OS$ requires C, 66·8; H, 6·8; N, 12·3%). $^1$H n.m.r. ($CDCl_3$): δ 1·38, complex, $CH_3(CH_2)_4CH_2S$; 3·25, t, $J$ 7 Hz, $CH_3(CH_2)_4CH_2S$; 4·15, s, MeO; 6·77, d, $J_{7,8}$ 9·5 Hz, H 7; 7·37, 8·10, complex, Ph; 7·61, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-Cyclohexylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (0·5 g) with cyclohexanethiol (1·32 ml) and 0·55 M sodium hydroxide (18·0 ml) at 140° for 20 h gave white crystals of *6-cyclohexylthiopyridazin-3-amine* (0·6 g), m.p. 124–125° (from cyclohexane) (Found, for sample dried at 70°/0·1 mm for 3 h: C, 57·8; H, 7·5; N, 20·0. $C_{10}H_{15}N_3S$ requires C, 57·4, H, 7·2; N, 20·1%). $^1$H n.m.r. ($CDCl_3$): δ 1·43, 3·87; complex, $C_6H_{11}S$; 4·60, b, $NH_2$; 6·63, d, $J_{4,5}$ 9 Hz, H 5; 7·09, d, $J_{4,5}$ 9 Hz, H 4.

*6-Cyclohexylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

Phenylglyoxal (0·169 g) stirred with 6-cyclohexylthiopyridazin-3-amine (0·25 g), ethanol (5·0 ml) and concentrated hydrochloric acid (0·125 ml) at 20° for 8 days gave a precipitate (0·2 g) which was filtered off, washed with a little ethanol, and dried at the pump.

This product was stirred with excess ethereal diazomethane at 20° for 2 days and gave, after t.l.c. (alumina; chloroform then alumina; ether), *6-cyclohexylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine* (0·064 g) as an oil which slowly crystallized. It was dried at 20°/0·1 mm for 5 h for analysis (Found: C, 67·0, H, 6·4; N, 11·7. $C_{19}H_{21}N_3OS$ requires C, 67·2; H, 6·2; N, 12·4%). $^1$H n.m.r. ($CDCl_3$): δ 1·55, 2·18, complex, $C_6H_{11}S$; 4·16, s, MeO; 6·74, d, $J_{7,8}$ 9·5 Hz, H 7; 7·38, 8·10, complex, Ph; 7·61, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-Phenylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (5·0 g) was added to a solution of thiophenol (10·0 ml) in 1·7 M sodium hydroxide (50 ml) and the mixture heated at 130° for 18 h. After cooling, the white solid was filtered off, washed with 1 M sodium hydroxide and water and dried at the pump. It was divided into two parts and chromatographed separately in chloroform over a column of alumina (12 cm by 4 cm diameter) and recrystallized from benzene to give white crystals of 6-phenylthiopyridazin-3-amine (4·2 g), m.p. 139–140° (lit.[4] 136°).

*2-Phenyl-6-phenylthioimidazo[1,2-b]pyridazin-3(5H)-one*

Phenylglyoxal (0·34 g) in ethanol (6·0 ml) was added to 6-phenylthiopyridazin-3-amine (0·5 g) in ethanol (6·0 ml) containing concentrated hydrochloric acid (0·2 ml) and the mixture stirred at 20° for 3 days. The red solid was filtered off, washed with ethanol, water, ethanol and ether and dried at the pump to give *2-phenyl-6-phenylthioimidazo[1,2-b]pyridazin-3(5H)-one* (0·284 g) (Found, for sample dried at 100° for 3 h: C, 67·1; H, 3·9; N, 13·2. $C_{18}H_{13}N_3OS$ requires C, 67·7; H, 4·1; N, 13·2%).

[4] Morren, H. G., Belg. Pat. 579,291 *(Chem. Abstr.*, 1960, **54**, 9968).

*3-Methoxy-2-phenyl-6-phenylthioimidazo[1,2-b]pyridazine*

2-Phenyl-6-phenylthioimidazo[1,2-*b*]pyridazin-3(5*H*)-one (0·273 g) was added to a solution of excess diazomethane in ether and the mixture stirred in ice and at 20° overnight. The red colour was discharged to give a yellow solution. The product was subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give yellow crystals of *3-methoxy-2-phenyl-6-phenylthioimidazo[1,2-b]pyridazine* (0·110 g), m.p. 150–151° (Found, for sample dried at 80°/0·1 mm for 3 h: C, 68·7; H, 4·6; N, 12·7. $C_{19}H_{15}N_3OS$ requires C, 68·4; H, 4·5; N, 12·6%). $^1$H n.m.r. ($CDCl_3$): δ 3·99, s, MeO; 6·71, d, $J_{7,8}$ 9·5 Hz, H 7; 7·45, 8·10, complex 2×Ph; 7·64, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-p-Chlorophenylthiopyridazin-3-amine*

A mixture of *p*-chlorothiophenol (1·4 g) and 1 M sodium hydroxide (10·0 ml) with 6-chloropyridazin-3-amine (0·5 g) was heated at 130° for 16 h. After cooling, the solid was filtered off, washed with 1 M sodium hydroxide and water and dried. It was dissolved in chloroform and applied to a column of alumina (18 cm by 2·5 cm diameter), eluted with ethanol, and recrystallized from benzene and then acetone to give *6-p-chlorophenylthiopyridazin-3-amine* (0·312 g), m.p. 162–164° (Found: C, 50·6; H, 3·4; N, 17·8. $C_{10}H_8ClN_3S$ requires C, 50·5; H, 3·4; N, 17·7%). $^1$H n.m.r. ($CDCl_3$): δ 5·2, b, $NH_2$; 6·69, d, $J_{4,5}$ 9·5 Hz, H 5; 7·07, d, $J_{4,5}$ 9·5 Hz H 4; 7·35, complex, H 2′,3′,5′,6′.

*6-p-Chlorophenylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

A mixture of 6-*p*-chlorophenylthio)pyridazin-3-amine (0·1 g), phenylglyoxal (0·06 g), ethanol (5·0 ml) and concentrated hydrochloric acid (0·1 ml) was refluxed with stirring for 6 h. It was evaporated to dryness, then evaporated with water (twice) and the red solid (0·111 g) broken up with water, filtered, washed with water and dried at the pump.

This product was added to a solution of excess diazomethane in ether and the mixture stirred in ice and at 20° overnight. The solvent was evaporated and the product subjected to t.l.c. (silica; chloroform) and recrystallized from light petroleum (b.p. 40–60°) to give yellow crystals of *6-p-chlorophenylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine* (0·013 g), m.p. 149–151° (Found, for sample dried in an oven at 70° for 5 h: C, 62·3; H, 3·8; N, 11·1. $C_{19}H_{14}ClN_3OS$ requires C, 62·0; H, 3·8; N, 11·4%). $^1$H n.m.r. ($CDCl_3$): δ 3·99, s, MeO; 6·72, d, $J_{7,8}$ 9·5 Hz, H 7; 7·46, 8·10, complex, ArH; 7·68, d, $J_{7,8}$ 9·5 Hz, H 8.

*6-p-Fluorophenylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine (0·5 g) with *p*-fluorothiophenol (1·327 g) in 0·5 M sodium hydroxide (20·0 ml) was heated at 130° for 16 h. After cooling, the solid was filtered off, dissolved in chloroform and applied to an alumina column (15 cm by 4 cm diameter) and after elution of the first yellow band, the solvent was changed to acetone and the product obtained was recrystallized from benzene to give white crystals of *6-p-fluorophenylthiopyridazin-3-amine* (0·646 g), m.p. 168–169° [after t.l.c. on alumina with acetone/chloroform (1 : 2)] (Found: C, 54·1, H, 3·6; N, 19·0. $C_{10}H_8FN_3S$ requires C, 54·3; H, 3·6; N, 19·0%). $^1$H n.m.r. ($CDCl_3$): δ 4·80, b, $NH_2$; 6·65, d, $J_{4,5}$ 9 Hz, H 5; 7·00, d, $J_{4,5}$ 9 Hz, H 4; 7·05, 7·50, complex, H 2′,3′,5′,6′.

*6-p-Fluorophenylthio-2-phenylimidazo[1,2-b]pyridazin-3(5H)-one*

Phenylglyoxal (0·13 g) in ethanol (2·0 ml) was added to a solution of 6-*p*-fluorophenylthiopyridazin-3-amine (0·16 g) in ethanol (2·0 ml) with concentrated hydrochloric acid (0·1 ml) and the mixture stirred at 20° for 5 days. The reddish orange precipitate was filtered off, washed with ethanol, water, ethanol and ether and dried at the pump to give *6-p-fluorophenylthio-2-phenylimidazo[1,2-b]pyridazin-3(5H)-one* (0·072 g) (Found: C, 64·1; H, 3·5; N, 12·3. $C_{18}H_{12}FN_3OS$ requires C, 64·1; H, 3·6; N, 12·5%).

*6-p-Fluorophenylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

6-*p*-Fluorophenylthio-2-phenylimidazo[1,2-*b*]pyridazin-3(5*H*)-one (0·066 g) was added to excess diazomethane in ether and the mixture stirred in ice and at 20° overnight. The solvent was evaporated and the product subjected to t.l.c. (alumina; chloroform) and recrystallized from light petroleum (b.p. 40–60°) to give *6-p-fluorophenylthio-3-methoxy-2-phenylimidazo[1,2-b]pyridazine*

(0·008 g), m.p. 135–136° (Found, for sample dried in an oven at 80° for 5 h: C, 65·2; H, 4·1; N, 11·9. $C_{19}H_{14}FN_3OS$ requires C, 64·9; H, 4·0; N, 12·0%). $^1$H n.m.r. ($CDCl_3$): δ 3·97, s, MeO; 6·70, d, $J_{7,8}$ 9·5 Hz, H 7; 7·35, d, $J_{7,8}$ 9·5 Hz, H 8; 7·60, 8·10, complex, ArH.

*6*-p-*Tolylthiopyridazin-3-amine*

6-Chloropyridazin-3-amine, *p*-thiocresol (1·3 g) and 0·55 M sodium hydroxide (18·0 ml) were heated at 140° for 17 h. After chilling, the white solid (0·6 g) was filtered off, washed with 1 M sodium hydroxide and water, dried and recrystallized from ethyl acetate to give *6*-p-*tolylthiopyridazin-3-amine*, m.p. 153–154° (Found, for sample dried in an oven at 100° for 4·5 h: C, 60·7; H, 5·3; N, 19·6. $C_{11}H_{11}N_3S$ requires C, 60·8; H, 5·1; N, 19·3%). $^1$H n.m.r. ($CDCl_3$): δ 2·35, s, Me; 4·85, bs, $NH_2$; 6·61; d, $J_{4,5}$ 9 Hz, H 5; 6·96, d, $J_{4,5}$ 9 Hz, H 4; 7·28, complex, ArH.

*3-Methoxy-2-phenyl-6*-p-*tolylthioimidazo[1,2*-b*]pyridazine*

A mixture of phenylglyoxal (0·06 g), 6-*p*-tolylthiopyridazin-3-amine (0·1 g), ethanol (1·5 ml) and concentrated hydrochloric acid (0·2 ml) was refluxed on a steam bath for 5 h. It was then evaporated to dryness under reduced pressure and the residue stirred with excess ethereal diazomethane in an ice bath, and then at 20° overnight. This mixture was then evaporated to dryness on a steam bath and the resulting oil subjected to t.l.c. (alumina; chloroform then alumina; ether) to give, as an oil, *3-methoxy-2-phenyl-6*-p-*tolylthioimidazo[1,2*-b*]pyridazine* (0·055 g) (Found, for sample dried at 20°/0·1 mm for 4·5 h: C, 69·2; H, 5·0; N, 11·3. $C_{20}H_{17}N_3OS$ requires C, 69·1; H, 4·9; N, 12·1%). $^1$H n.m.r. ($CDCl_3$): δ 2·42, s, MeC; 4·02, s, MeO; 6·67, d, $J_{7,8}$ 9·5 Hz, H 7; 7·30, 8·10, complex, ArH; 7·63, d, $J_{7,8}$ 9·5 Hz, H 8.

*6*-m-*Tolylthiopyridazin-3-amine*

A mixture of *m*-thiocresol (1·3 g) in 0·5 M sodium hydroxide (20·0 ml) with 6-chloropyridazin-3-amine (1·0 g) was heated at 150° for 17 h. After chilling the solid was filtered off, washed with 1 M sodium hydroxide and water, dried, and recrystallized from benzene to give *6*-m-*tolylthiopyridazin-3-amine* (1·4 g), m.p. 116–117° (Found, for sample dried at 80°/0·1 mm for 6 h: C, 60·5; H, 5·0; N, 19·4. $C_{11}H_{11}N_3S$ requires C, 60·8; H, 5·1; N, 19·3%). $^1$H n.m.r. ($CDCl_3$): δ 2·33, s, MeC; 4·90, bs, $NH_2$; 6·65, d, $J_{4,5}$ 9 Hz, H 5; 7·02, d, $J_{4,5}$ 9 Hz, H 4; 7·36, complex, ArH.

*3-Methoxy-2-phenyl-6*-m-*tolylthioimidazo[1,2*-b*]pyridazine*

A solution of phenylglyoxal (0·31 g) in ethanol (1·0 ml) was stirred with 6-*m*-tolylthiopyridazin-3-amine (0·5 g) in ethanol (5·0 ml) with concentrated hydrochloric acid (0·3 ml) for 9 days. One half of this clear red solution was evaporated to dryness in a vacuum, then evaporated twice with water and ethanol to give an orange oil.

This oil and excess ethereal diazomethane were stirred in ice and then at room temperature overnight. It was evaporated to dryness and the product subjected to t.l.c. (alumina; chloroform) and recrystallized from light petroleum (b.p. 40–60°) to give yellow crystals of *3-methoxy-2-phenyl-6*-m-*tolylthioimidazo[1,2*-b*]pyridazine* (0·068 g), m.p. 118–119° (Found, for sample dried at 60°/0·1 mm for 4 h: C, 69·4; H, 5·0; N, 12·1. $C_{20}H_{17}N_3OS$ requires C, 69·1; H, 4·9, N, 12·1%). $^1$H n.m.r. ($CDCl_3$): δ 2·39, s, MeC; 4·03, s, MeO; 6·70, d, $J_{7,8}$ 9·5 Hz, H 7; 7·40, 8·10, complex, ArH; 7·65, d, $J_{7,8}$ 9·5 Hz, H 8.

*6*-p-*Dimethylaminophenylthiopyridazin-3-amine*

*p*-Dimethylaminobenzenethiol[5] (1·3 g; prepared from *N,N*-dimethylaniline through bis-*p*-dimethylaminophenyl disulfide[5,6] by reduction with tin and hydrochloric acid[5]) in 0·55 M sodium hydroxide (18 ml) with 6-chloropyridazin-3-amine (0·5 g) were heated at 150° for 16 h. After chilling, the solid (1·0 g) was filtered off, washed with 1 M sodium hydroxide and water, and then recrystallized from chloroform to give *6*-p-*dimethylaminophenylthiopyridazin-3-amine*,

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m.p. 201–202° (Found, for sample dried at 100° for 6 h: C, 58·7; H, 5·8; N, 22·8. $C_{12}H_{14}N_4S$ requires C, 58·5; H, 5·7; N, 22·8%). $^1$H n.m.r. ($CDCl_3$): δ 2·99, s, $Me_2N$; 4·70, bs, $NH_2$; 6·65, d, $J_{4,5}$ 9 Hz, H 5; 6·69, d, $J_{2',3'}$ 9 Hz, H 3′,5′; 6·83, d, $J_{4,5}$ 9 Hz, H 4; 7·42, d, $J_{2',3'}$ 9 Hz, H 2′,6′.

*6-*p*-Dimethylaminophenylthio-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine*

A mixture of phenylglyoxal (0·06 g), and 6-*p*-dimethylaminophenylthio)pyridazin-3-amine (0·1 g), in ethanol (3·0 ml) with concentrated hydrochloric acid (0·1 ml) was refluxed for 24 h. The mixture was then evaporated to dryness under reduced pressure and the yellow residue diluted with water and evaporated twice. The remaining solid was then diluted with water, filtered and dried. This solid (0·106 g) was added to excess ethereal diazomethane and the mixture stirred in ice and at room temperature overnight. The mixture was evaporated to dryness and the solid subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give yellow crystals of *6-*p*-dimethylaminophenylthio-3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine* (0·022 g), m.p. 175–176° (Found, for sample dried at 80°/0·1 mm for 6 h: C, 67·3; H, 5·4; N, 14·9. $C_{21}H_{20}N_4OS$ requires C, 67·0; H, 5·4; N, 14·9%). $^1$H n.m.r. ($CDCl_3$): δ 3·03, s, $Me_2N$; 4·07, s, MeO; 6·60, d, $J_{7,8}$ 9·5 Hz, H 7; 6·74, d, $J_{7,8}$ 9·0 Hz, H 3′,5′; 7·37, 8·10, complex, Ph; 7·48, d, $J_{2',3'}$ 9 Hz, H 2′,6′; 7·71, d, $J_{7,8}$ 9·5 Hz, H 8.

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