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Heterocyclic Amplifiers of Phleomycin. IX* Some Derivatives of Fused and Unfused Mono- and Di-aza Heterocycles

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Abstract

Some mono- and bis-dimethylaminoethylthio, dimethylaminopropylthio and carbamoylmethylthio derivatives of pyridine, pyridazine, 1,3,4-thiadiazole, thiazoline, quinoline, quinoxaline, quinazoline, phthalazine, 6-nitrobenzothiazole and benzimidazo[1,2-*c*]quinazoline have been prepared for testing as amplifiers of phleomycin.

These compounds showed relatively low activity; the highest activity was shown by 4-(2′-dimethylaminoethylthio)quinoline at three star, but a number were antibacterial under the test conditions.

Introduction

In view of the relatively high (four star) amplification shown by 2,3-bis(3′-dimethylaminopropylthio)quinoxaline[1] we have prepared a number of derivatives of readily available mono- and di-mercapto heterocycles for testing as amplifiers of phleomycin. Derivatives with strongly basic side chains and also carbamoylmethylthio groups were prepared from pyridine-2-thiol, pyridazine-3,6-dithiol, 1,3,4-thiadiazole-2,5-dithiol, thiazoline-2-thiol, quinoline-2- and 4-thiol, quinoxaline-2,3-dithiol, quinazoline-2,4-dithiol, phthalazine-1,4-dithiol, 6-nitrobenzothiazole-2-thiol and benzimidazol[1,2-*c*]quinazoline-6-thiol.

Synthesis

Compounds required for this study were, in general, prepared from the corresponding mercapto compound in aqueous sodium hydroxide with 2-chloro-*N*,*N*-dimethylethylamine or chloroacetamide to give the 2-dimethylaminoethylthio or carbamoylmethylthio compounds respectively. The 3-dimethylaminopropylthio analogues were generally prepared from the mercapto compound in ethanolic ammonia with 3-chloro-*N*,*N*-dimethylpropylamine.[1]

Phthalazine-1,4-dithiol was prepared from 1,4-dichlorophthalazine with phosphorus pentasulfide in refluxing pyridine. The literature[2] preparation from 1,4-dichloro-

* Part VIII, *Aust. J. Chem.*, 1985, **38**, 1491.

[1] Barlin, G. B., Ireland, S. J., and Rowland, B. J., *Aust. J. Chem.*, 1984, **37**, 1729.
[2] Yale, H. L., *J. Am. Chem. Soc.*, 1953, **75**, 675.

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phthalazine with sodium hydrogen sulfide in our hands was unsatisfactory as the product contained significant amounts of 4-chlorophthalazine-1-thiol as shown by methylation to 1-chloro-4-methylthiophthalazine; and phthalazine-1,4-diol with phosphorus pentasulfide[3] at 200° gave only partial thiation. 6-Nitrobenzothiazole-2-thiol with 3-chloro-*N*,*N*-dimethylpropylamine in aqueous sodium hydroxide at 20° gave the 2-(3-dimethylaminopropylthio) compound (9b) but a similar preparation (in ethanolic ammonia, and heated on a steam bath with sodium hydroxide also gave 2-ethoxy-6-nitrobenzothiazole, presumably by replacement of the alkylthio group by ethoxide ions. The dihydrobromides of the benzimidazo[1,2-*c*]quinazolines (10a), (10b) lost some hydrogen bromide on drying at 100° under vacuum.

Biological Activities

The compounds tested were examined as described previously[4] (Fig. 1, next page).

The results showed disappointingly low amplification by these compounds. The most active compound was *N*,*N*-dimethylquinoline-4-ylthioethylamine with three-star activity, the carbamoylmethylthio analogue being slightly less active at two-star, and the 2-isomer less active at one-star. Six of the compounds were antibacterial under the test conditions, and the results are recorded as toxic in Fig. 1. Unfortunately, 2,3-biscarbamoylmethylthioquinoxaline (and 2,4-biscarbamoylmethylthioquinazoline) were too insoluble to test under the above conditions.

Experimental

Solids for analysis were dried in an oven at 100° (unless otherwise specified) and melting points were taken in Pyrex capillaries. Analyses were performed by The Australian National University Analytical Services Unit. ^{1}H 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.

N,N-*Dimethyl-2-(pyridin-2′-ylthio)ethylamine (1a)*

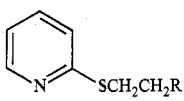
A mixture of pyridine-2-thiol (1·0 g), 1 M sodium hydroxide (30 ml) and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (1·0 g + 0·6 g after 15 min) was stirred at 20° for 1 h. The aqueous solution was extracted with chloroform, the extract dried (Na_2SO_4) and the solvent evaporated to give an oil which was subjected to chromatography in chloroform over alumina (25 cm). The product was treated with ethanolic hydrogen bromide to give N,N-*dimethyl-2-(pyridin-2′-ylthio)ethylamine dihydrobromide* (0·88 g), m.p. 216–218° (from ethanol) (Found: C, 31·6; H, 4·7; N, 8·3. $C_9H_{14}N_2S.2HBr$ requires C, 31·4; H, 4·7; N, 8·1%). ^{1}H n.m.r. (D_2O): δ 3·01, s, Me_2N; 3·69, m, CH_2CH_2; 7·81–8·63, m, H 3–6.

N,N-*Dimethyl-3-(pyridin-2′-ylthio)propylamine (1b)*

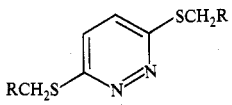
A mixture of pyridine-2-thiol (1·0 g) in ethanolic ammonia (150 ml) with 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride (1·0 g + 0·5 g before reflux) was stirred at 20° for 0·5 h, then refluxed for 1·5 h. After cooling, sodium methoxide was added until a test sample with water had pH > 12·5. The mixture was then diluted with water, the ethanol evaporated and the aqueous solution extracted with chloroform, the extract dried (Na_2SO_4) and the solvent evaporated to give an oil. This oil was subjected to column and thin-layer chromatography in chloroform over alumina and the oil obtained (0·3 g) was treated with ethanolic hydrogen bromide and ether

[3] Radulescu, D., and Georgescu, V., *Bull. Soc. Chim. Fr.*, 1925, [4], **37**, 881 (*Chem. Abstr.*, 1926, **20**, 184).

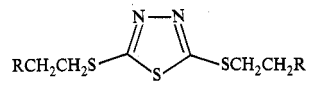
[4] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981 **34**, 2423.



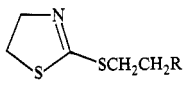
(1a) R = NMe_2 *
(1b) R = CH_2NMe_2 *



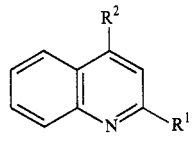
(2a) R = CH_2NMe_2 *
(2b) R = $CONH_2$ *



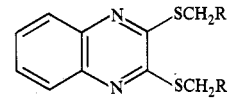
(3a) R = NMe_2 *
(3b) R = CH_2NMe_2 *



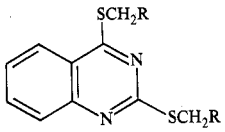
(4a) R = NMe_2 *
(4b) R = CH_2NMe_2 *



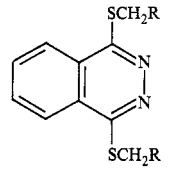
	R^1	R^2	
(5a)	SCH_2CONH_2	H	**
(5b)	H	$SCH_2CH_2NH_2$	***
(5c)	H	SCH_2CONH_2	**



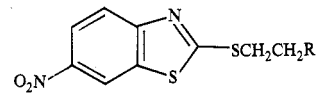
(6a) R = $CONH_2$ A



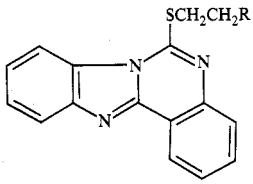
(7a) R = CH_2NMe_2 **
(7b) R = $CH_2CH_2NMe_2$ B
(7c) R = $CONH_2$ A



(8a) R = CH_2NMe_2 B



(9a) R = NMe_2 B
(9b) R = CH_2NMe_2 B



(10a) R = NMe_2 B
(10b) R = CH_2NMe_2 B

Fig. 1. Activities as amplifiers of phleomycin measured at 1 mM, solubility permitting; for details of method and activity see ref. 4. (A, Solubility too low to permit measurment; B, compound toxic at 1 mM.)

to give N,N-*dimethyl-3-(pyridin-2′-ylthio)propylamine hydrobromide*, m.p. 83–84° (Found, for sample dried at 20° and 20 mm Hg: C, 43·0; H, 6·2; N, 10·0. $C_{10}H_{16}N_2S.HBr$ requires C, 43·3; H, 6·2; N, 10·3%). ^1H n.m.r. (D_2O): δ 2·13, m, $CH_2CH_2CH_2$; 2·88, s, Me_2N; 3.22, m, $CH_2CH_2CH_2$; 7·25–8·44, m, H 3–6.

3,6-Bis(2′-dimethylaminoethylthio)pyridazine (2a)

Crude pyridazine-3,6-dithiol[5] (0·5 g) in 1 M sodium hydroxide (10·0 ml) was shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g + 0·5 g after 15 min) for 1 h. The mixture was extracted with chloroform and the product subjected to column and t.l.c. in chloroform over alumina. The component in the band at lower R_F was recrystallized from light petroleum (b.p. 40–60°) to give yellow crystals of *3,6-bis(2′-dimethylaminoethylthio)pyridazine* (0·187 g), m.p. 68·5–70° (Found, for sample dried at 20° and 20 mm Hg for 48 h: C, 50·2; H, 7·6; N, 19·1. $C_{12}H_{22}N_4S_2$ requires C, 50·3; H, 7·7; N, 19·6%). ^1H n.m.r. ($CDCl_3$): δ 2·30, s, Me_2N; 2·69, t, *J* 7 Hz, CH_2N; 3·47, t, *J* 7 Hz, CH_2S; 7·07, s, H 4,5.

[5] Pollak, A., Stanovnik, B., and Tišler, M., *Can. J. Chem.*, 1966, **44**, 829.

The band at higher R_F gave a yellow solid which crystallized from light petroleum (b.p. 40–60°) to give N,N-*dimethyl-2-(6′-chloropyridazin-3′-ylthio)ethylamine* (0·008 g), m.p. 50–52° (Found, for a sample dried at 20° in a vacuum for 24 h: C, 44·2; H, 5·6; N, 18·9. $C_8H_{12}ClN_3S$ requires C, 44·1; H, 5·6; N, 19·3%). (Presumably this was formed from some 6-chloropyridazine-3-thiol in the crude pyridazine-3,6-dithiol.) ^{1}H n.m.r. ($CDCl_3$): δ 2·31, s, Me_2N; 2·70, t, *J* 7 Hz, CH_2N; 3·48, t, *J* 7 Hz, CH_2S; 7·26, s, H 4,5.

3,6-Bis(3′-dimethylaminopropylthio)pyridazine

Pyridazine-3,6-dithiol[5] (0·134 g) in ethanolic ammonia (40 ml) with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·3 g + 0·3 g before reflux) was allowed to react, as described above. The product after t.l.c. (alumina; chloroform, developed three times) was recrystallized from light petroleum (b.p. 40–60°) to give as a low melting solid *3,6-bis(3′-dimethylaminopropylthio)pyridazine* (0·021 g) (Found, for sample dried at 20° and 0·1 mm Hg for 5 h: C, 53·5; H, 8·4; N, 17·6. $C_{14}H_{26}N_4S_2$ requires C, 53·5; H, 8·3; N, 17·8%). ^{1}H n.m.r. ($CDCl_3$): δ 1·92, m, $CH_2CH_2CH_2$; 2·23, s, Me_2N; 2·35, t, *J* 7 Hz, CH_2N; 3·35, t, *J* 7 Hz, CH_2S; 7·06, s, H 4,5.

3,6-Biscarbamoylmethylthiopyridazine (2b)

Crude pyridazine-3,6-dithiol[5] (0·4 g) in 1 M sodium hydroxide (8·0 ml) was shaken with chloroacetamide (0·8 g) for 1 h. The solid (0·35 g) was filtered off, washed with water and recrystallized from water to give *3,6-biscarbamoylmethylthiopyridazine*, m.p. 218–219° (Found: C, 37·1; H, 3·9; N, 21·6. $C_8H_{10}N_4O_2S_2$ requires C, 37·2; H, 3·9; N, 21·7%).

2,5-Bis(2′-dimethylaminoethylthio)-1,3,4,-thiadiazole (3a)

1,3,4-Thiadiazole-2,5-dithiol (1·0 g) was allowed to react in 1 M sodium hydroxide (10·0 ml) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g + 0·5 g after 15 min), as described above, to give *2,5-bis(2′-dimethylaminoethylthio)-1,3,4-thiadiazole dihydrobromide* (1·03 g), m.p. 221–224° (from ethanol) (Found: C, 26·8; H, 4·9; N, 12·3. $C_{10}H_{20}N_4S_3.2HBr$ requires C, 26·4; H, 4·9; N, 12·3%). ^{1}H n.m.r. ($CDCl_3$): δ 2·29, s, Me_2N; 2·70, t, *J* 7 Hz, CH_2N; 3·44, t, *J* 7 Hz, CH_2S.

2,5-Bis(3′-dimethylaminopropylthio)-1,3,4-thiadiazole (3b)

1,3,4-Thiadiazole-2,5-dithiol (0·5 g) was allowed to react in ethanolic ammonia (20 ml) with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (1·0 g + 0·5 g), as described above, to give *2,5-bis(3′-dimethylaminopropylthio)-1,3,4-thiadiazole dihydrobromide* (0·27 g), m.p. 175–178° (Found: C, 30·3; H, 5·5; N, 11·4. $C_{12}H_{24}N_4S_3.2HBr$ requires C, 29·9; H, 5·4; N, 11·6%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·94, m, $CH_2CH_2CH_2$; 2·21, s, Me_2N; 2·39, t, *J* 7 Hz, CH_2N; 3·32, t, *J* 7 Hz, CH_2S.

N,N-*Dimethyl-2-(thiazolin-2′-ylthio)ethylamine (4a)*

Thiazoline-2-thiol (1·0 g) was alkylated with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g + 0·3 g) in 1 M sodium hydroxide to give N,N-*dimethyl-2-(thiazolin-2′-ylthio)ethylamine hydrobromide* (0·630 g), m.p. 227–228° (Found: C, 31·2; H, 5·8; N, 10·3. $C_7H_{14}N_2S_2.HBr$ requires C, 31·0; H, 5·6; N, 10·3%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 2·27, s, Me_2N; 2·60, t, *J* 7 Hz, CH_2N; 3·30, m, H_2 4′,5′; 4·20, t, *J* 7 Hz, CH_2S.

N,N-*Dimethyl-3-(thiazolin-2′-ylthio)propylamine (4b)*

Thiazoline-2-thiol (2·0 g) in ethanolic ammonia (300 ml) with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (2·0 g + 1·0 g) gave N,N-*dimethyl-3-(thiazolin-2′-ylthio)propylamine dihydrobromide* (0·052 g), m.p. 140–141° (from ethanol) (Found: C, 26·5; H, 5·1; N, 7·4. $C_8H_{16}N_2S_2.2HBr$ requires C, 26·2; H, 5·0; N, 7·6%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·86, m, $CH_2CH_2CH_2$; 2·36, t, *J* 8 Hz, CH_2N; 3·26, m, H_2 4′,5′; 4·21, t, *J* 8 Hz, CH_2S.

2-(Quinolin-2′-ylthio)acetamide (5a)

Quinoline-2-thiol[6] (0·4 g) in 1 M sodium hydroxide (4·0 ml) with chloroacetamide (0·35 g) gave *2-(quinolin-2′-ylthio)acetamide* (0·35 g), m.p. 127–128° (from water) (Found: C, 60·8; H, 4·6; N, 13·0. $C_{11}H_{10}N_2OS$ requires C, 60·5; H, 4·6; N, 12·8%).

N,N-*Dimethyl-2-(quinolin-4′-ylthio)ethylamine (5b)*

Quinoline-4-thiol[6] (0·5 g) with 2-chloro-*N,N*-dimethylethylamine (0·25 g + 0·25 g) in 1 M sodium hydroxide (10·0 ml) gave N,N-*dimethyl-2-(quinolin-4′-ylthio)ethylamine* (0·230 g), m.p. 76–78° [from light petroleum (b.p. 40–60°)] (Found, for sample dried at 50° and 0·1 mm Hg for 1 h: C, 67·2; H, 7·1; N, 11·9. $C_{13}H_{16}N_2S$ requires C, 67·2; H, 6·9; N, 12·1%). ^{1}H n.m.r. ($CDCl_3$): δ 2·34, s, Me_2N; 2·72, t, *J* 7 Hz, CH_2N; 3·24, t, *J* 7 Hz, CH_2S; 7·17–8·74, m, ArH.

2-(Quinolin-4′-ylthio)acetamide (5c)

Quinoline-4-thiol[6] (0·5 g) was made to react with chloroacetamide as described above to give the *2-(quinolin-4′-ylthio)acetamide* (0·272 g), m.p. 224–226° (from water) (Found, for sample dried at 100° and 0·1 mm Hg for 3 h: C, 60·1; H, 4·5; N, 12·6. $C_{11}H_{10}N_2OS$ requires C, 60·5; H, 4·6; N, 12·8%). ^{1}H n.m.r. (Me_2SO): δ 3·94, s, CH_2; 7·38–8·75, m, ArH.

2,3-Bis(carbamoylmethylthio)quinoxaline (6a)

Quinoxaline-2,3-dithiol[1] (0·5 g) with chloroacetamide (0·95 g) in 1 M sodium hydroxide (9·0 ml) gave *2,3-bis(carbamoylmethylthio)quinoxaline* (0·55 g), m.p. 253–254° (dec.) (from water) (Found: C, 47·0; H, 3·9; N, 17·9. $C_{12}H_{12}N_4O_2S_2$ requires C, 46·7; H, 3·9; N, 18·2%).

2,4-Bis(2′-dimethylaminoethylthio)quinazoline (7a)

Quinazoline-2,4-dithiol[2] (1·0 g) in 1 M sodium hydroxide (30·0 ml) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g + 1·0 g) gave the base (0·4 g), thence *2,4-bis(2′-dimethylaminoethylthio)quinazoline dihydrobromide*, m.p. 230–231° (from ethanol) (Found: C, 38·8; H, 5·1; N, 11·3. $C_{16}H_{24}N_4S_2.2HBr$ requires C, 38·6; H, 5·3; N, 11·2%). ^{1}H n.m.r. (D_2O): δ 3·06, s, Me_2N; 3·60, bs, CH_2CH_2; 7·80, m, ArH.

2,4-Bis(3′-dimethylaminopropylthio)quinazoline (7b)

Quinazoline-2,4-dithiol[2] in ethanolic ammonia (300 ml) with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (2·0 g + 1·0 g) gave a product which was subjected to t.l.c. [alumina; chloroform/light petroleum (b.p. 60–80°) (1 : 1), then chloroform] and the oil (0·25 g) [^{1}H n.m.r. ($CDCl_3$: δ 1·95, complex, $CH_2CH_2CH_2$; 2·26, s, Me_2N; 2·45, m, CH_2N; 3·32, m, CH_2S; 7·30–8·01, m, ArH] which with ethanolic hydrogen bromide gave *2,4-bis(3′-dimethylaminopropylthio)quinazoline trihydrobromide*, m.p. 244–245° (from ethanol) (Found: C, 36·0; H, 5·2; N, 9·2. $C_{18}H_{28}N_4S_2.3HBr$ requires C, 35·6; H, 5·2; N, 9·2%). ^{1}H n.m.r. (D_2O): δ 2·32, m, $CH_2CH_2CH_2$; 2·95, s, Me_2N; 3·35, complex $SCH_2CH_2CH_2N$; 7·69–8·21, m, ArH.

2,4-Bis(carbamoylmethylthio)quinazoline (7c)

Quinazoline-2,4-dithiol[2] (0·5 g) with chloroacetamide (0·6 g) in 1 M sodium hydroxide (6·0 ml) gave *2,4-bis(carbamoylmethylthio)quinazoline* (0·78 g), m.p. 248–250° (dec.) (from water) (Found: C, 46·3; H, 3·9; N, 18·0. $C_{12}H_{12}N_4O_2S_2$ requires C, 46·7; H, 3·9; N, 18·2%).

1,4-Bis(2′-dimethylaminoethylthio)phthalazine (8a)

1,4-Dichlorophthalazine was prepared from phthalazine-1,4-diol (10·0 g) by refluxing with phosphoryl chloride (40 ml) and phosphorus pentachloride (10·0 g) for 5 h. The product was purified by chromatography in chloroform over alumina and recrystallized from benzene to give the 1,4-dichlorophthalazine (6·3 g), m.p. 163–165° (lit.[7] 164°).

[6] Albert, A., and Barlin, G. B., *J. Chem. Soc.*, 1959, 2384.
[7] Hirsch, A., and Orphanos, D., *Can. J. Chem.*, 1965, **43**, 2708.

1,4-Dichlorophthalazine (4·3 g), phosphorus pentasulfide (25 g) and pyridine (200 ml) were refluxed for 2·5 h, then diluted with water (200 ml) and warmed on the steam bath for 2 h to decompose excess reagent. The mixture was evaporated to dryness under reduced pressure and the solid suspended in water, adjusted to pH 12 and reprecipitated by addition of hydrochloric acid to pH 4–5 to give the crude dimercapto compound (2·2 g)

This dimercapto compound (1·0 g) in 1 M sodium hydroxide (35 ml) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (2·5 g + 1·0 g), as above, gave an oil which was subjected to chromatography in chloroform over alumina (25 cm) and recrystallized from light petroleum (b.p. 40–60°) to afford *1,4-bis(2′-dimethylaminoethylthio)phthalazine* (0·518 g), m.p. 100–102° (Found, for sample dried at 20° and 0·1 mm Hg: C, 57·3; H, 7·2; N, 16·6. $C_{16}H_{24}N_4S_2$ requires C, 57·1; H, 7·2; N, 16·6%). ^{1}H n.m.r. ($CDCl_3$): δ 2·35, s, Me_2N; 2·78, t, *J* 7 Hz, CH_2N; 3·63, t, *J* 7 Hz, CH_2S; 7·75–8·18, m, ArH.

1,4-Bismethylthiophthalazine and 1-Chloro-4-methylthiophthalazine

1,4-Dichlorophthalazine (3·0 g) was allowed to react with sodium hydrogen sulfide in ethanol as described by Yale[2] to give a yellow solid (2·5 g). Part of this solid (0·1 g) was dissolved in 1 M sodium hydroxide (10·0 ml), shaken with methyl iodide (0·1 ml) for 30 min, and the product extracted with chloroform. This product was subjected to t.l.c. (alumina; chloroform) and the compounds in the two bands were recrystallized from light petroleum (b.p. 60–80°) to give 1,4-bismethylthiophthalazine (0·017 g), m.p. 152–153° (lit.[8] 163°) (Found, for sample dried at 80° and 0·1 mm Hg for 3 h: C, 53·8; H, 5·1; N, 12·6. Calc. for $C_{10}H_{10}N_2S_2$: C, 54·0; H, 4·5; N, 12·6%) [^{1}H n.m.r. ($CDCl_3$): δ 2·79, s, MeS; 7·76–8·13, m, ArH] and *1-chloro-4-methylthiophthalazine* (0·039 g), m.p. 123–125° (Found, for sample dried at 80° and 0·1 mm Hg for 3 h: C, 51·1; H, 3·3; N, 13·2. $C_9H_9ClN_2S$ requires C, 51·3; H, 3·3; N, 13·3%) [^{1}H n.m.r. ($CDCl_3$): δ 2·81, s, MeS; 7·86–8·29, m, ArH].

N,N-*Dimethyl-2-(6′-nitrobenzothiazol-2′-ylthio)ethylamine (9a)*

6-Nitrobenzthiazole-2-thiol (0·5 g) in 1 M sodium hydroxide (15 ml) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·5 g + 0·25 g) gave yellow crystals of N,N-*dimethyl-2-(6′-nitrobenzothiazol-2′-ylthio)ethylamine* (0·114 g), m.p. 83–84° [from light petroleum (b.p. 40–60°)] (Found, for sample dried at 50° and 0·1 mm Hg for 4 h: C, 46·6; H, 4·7; N, 15·1. $C_{11}H_{13}N_3O_2S$ requires C, 46·6; H, 4·6; N, 14·8%). ^{1}H n.m.r. ($CDCl_3$): δ 2·33, s, Me_2N; 2·76, t, *J* 7 Hz, CH_2N; 3·58, t, *J* 7 Hz, CH_2S; 7·89, d, $J_{4,5}$ 9 Hz, H 4; 8·29, dd, $J_{4,5}$ 9 Hz; $J_{5,7}$ 2 Hz, H 5; 8·67, d, $J_{5,7}$ 2 Hz, H 7.

N,N-*Dimethyl-3-(6′-nitrobenzothiazol-2′-ylthio)propylamine (9b) and 2-Ethoxy-6-nitrobenzothiazole*

(A) 6-Nitrobenzothiazole-2-thiol (1·0 g) in ethanolic ammonia (150 ml) with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·5 g + 0·5 g before reflux) was stirred at 20° for 0·5 h, then refluxed for 3 h, sodium hydroxide (0·2 g) added and the reflux continued for 2 h. The cooled mixture was treated with sodium methoxide until a test sample with water had pH > 12·5. It was diluted with water, the ethanol evaporated under reduced pressure and the aqueous solution extracted with chloroform. The product was subjected to chromatography over a column of alumina (25 cm) and t.l.c. (alumina; chloroform) and the band at higher R_F was recrystallized from light petroleum (b.p. 60–80°) to give yellow crystals of *2-ethoxy-6-nitrobenzothiazole* (0·379 g), m.p. 147–148° (Found: C, 48·8; H, 3·6; N, 12·7. $C_9H_8N_2O_3S$ requires C, 48·2; H, 3·6; N, 12·5%). ^{1}H n.m.r. ($CDCl_3$): δ 1·52, t, *J* 8 Hz, CH_3; 4, 68, q, *J* 8 Hz, CH_2; 7·70, dd, $J_{4,7}$ 0·5 Hz, $J_{4,5}$ 9 Hz, H 4; 8·24, dd, $J_{5,7}$ 2 Hz, $J_{4,5}$ 9 Hz, H 5; 8·55, dd, $J_{4,7}$ 0·5 Hz, $J_{5,7}$ 2 Hz, H 7.

The band at lower R_F gave a yellow oil which was treated with ethanolic hydrogen bromide and the product precipitated with ether. It was recrystallized from ethanol/ether to give N,N-*dimethyl- 3-(6′-nitrobenzothiazol-2′-ylthio)propylamine hydrobromide* (0·053 g), m.p. 218–219° (Found: C, 38·1; H, 4·4; N, 10·7. $C_{12}H_{15}N_3O_2S_2$.HBr requires C, 38·1; H, 4·3; N, 11·1%). ^{1}H n.m.r. (D_2O): δ 2·32, m, $CH_2CH_2CH_2$; 2·97, s, Me_2N; 3·44, m, $SCH_2CH_2CH_2N$; 7·68, d, $J_{4,5}$ 9 Hz, H 4; 8·15, dd, $J_{5,7}$ 2 Hz, $J_{4,5}$ 9 Hz, H 5; 8·55, d, $J_{5,7}$ 2 Hz, H 7.

[8] Asano, K., and Asai, S., *Yakugaku Zasshi*, 1958, **78**, 450.

(B) 6-Nitrobenzothiazole-2-thiol (0·5 g) in 1 M sodium hydroxide (15 ml) was stirred with 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride (0·5 g + 0·5 g after 15 min) for 1·5 h. The product was extracted into chloroform, and subjected to t.l.c. (alumina; chloroform). It was treated with ethanolic hydrogen bromide and recrystallized from ethanol to give *N*,*N*-dimethyl-3-(6′-nitrobenzothiazol-2′-ylthio)propylamine hydrobromide (0·051 g), m.p. 218–219°, identical with the product obtained in (A).

2-(Benzimidazo[1,2-c]quinazolin-6′-ylthio)-N,N-dimethylethylamine (10a)

Benzimidazo[1,2-*c*]quinazoline-6-thiol (0·5 g) in 1 M sodium hydroxide (10·0 ml) with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0·2 g + 0·2 g) as above gave white crystals of *2-(benzimidazo[1,2-c]quinazolin-6′-ylthio)-N,N-dimethylethylamine* (0·191 g), m.p. 123–124° [from light petroleum (b.p. 40–60°)] (Found, for sample dried at 50° and 0·1 mm Hg for 2 h: C, 67·3; H, 5·6; N, 17·2. $C_{18}H_{18}N_4S$ requires C, 67·1; H, 5·6; N, 17·4%). ^{1}H n.m.r. ($CDCl_3$): δ 2·41, s, Me_2N; 2·83, t, *J* 7 Hz, CH_2N; 3·72, t, *J* 7 Hz, CH_2S; 7·43–8·69, m, ArH.

This product with ethanolic hydrogen bromide gave the *1·85 hydrobromide*, m.p. 257–258° (from ethanol) (Found, for sample dried at 100° and 0·1 mm Hg for 1·5 h: C, 45·8; H, 4·2; N, 11·5. $C_{18}H_{18}N_4S.1·85HBr$ requires C, 45·8; H, 4·2; N, 11·9%).

3-(Benzimidazo[1,2-c]quinazolin-6′-ylthio)-N,N-dimethylpropylamine (10b)

Benzimidazo[1,2-*c*]quinazoline-6-thiol (0·5 g) in ethanolic ammonia (100 ml) with 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride (0·2 g + 0·2 g), as above, gave an oil (0·221 g) which with ethanolic hydrogen bromide afforded *3-(benzimidazo[1,2-c]quinazolin-6′-ylthio)-N,N-dimethylpropylamine 1·9 hydrobromide*, m.p. 238–240° (from ethanol) (Found, for sample dried at 100° and 0·1 mm Hg for 3 h: C, 46·5; H, 4·5; N, 11·2. $C_{19}H_{20}N_4S.1·9HBr$ requires C, 46·5; H, 4·5; N, 11·4%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 2·02, complex, $CH_2CH_2CH_2$; 2·27, s, Me_2N; 2·47, t, *J* 7 Hz, CH_2N; 3·49, t, *J* 7 Hz, CH_2S; 7·35–8·60, multiplet, ArH.

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