Aust. J. Chem., 1986, **39**, 69–75

Heterocyclic Amplifiers of Phleomycin. X† Derivatives of Diazine Mono- and Di-thiols

Gordon B. Barlin, Desmond J. Brown, Barbara J. Cronin and Maria Ngu

Medical Chemistry Group and Department of Pharmacology,
John Curtin School of Medical Research, Australian National University,
G.P.O. Box 334, Canberra, A.C.T. 2601.

Abstract

A series of pyrazinethiols and pyrimidinethiols with phenyl substituents have been prepared and converted into their carbamoylmethylthio, 2-dimethylaminoethylthio and 2-aminoethylthio derivatives. Similar derivatives of pyrazine-2,3- and -2,6-dithiol were also prepared together with *N,N*-dimethyl-2-(1′- and 2′-naphthyloxy)ethylamine.

As amplifiers of phleomycin these compounds showed moderate two-to-three-star activity.

Introduction

In view of the high amplification of the action of phleomycin reported by Brown *et al.*[1,2] for 4,6-bis(2′-dimethylaminoethylthio)-2-phenylpyrimidine and its 6-phenyl isomer and simpler analogues, we have prepared similar series of derivatives (1)–(8) from pyrazinethiols and pyrimidinethiols with phenyl substituents, as well as from pyrazinedithiols. The effect of a non-heterocyclic nucleus was also examined with the preparation and testing of 2-dimethylaminoethyl derivatives (9a,b) from 1- and 2-naphthol.

Syntheses

The 2-dimethylaminoethylthio, 2-aminoethylthio and carbamoylmethylthio compounds reported here were prepared from the corresponding mercapto compounds by reaction with 2-chloro-*N,N*-dimethylethylamine, 2-bromoethylamine or chloroacetamide in aqueous sodium hydroxide; except for 2,3- and 2,6-dichloropyrazine which reacted with 2-dimethylaminoethanethiolate anion in an alcoholic solution.

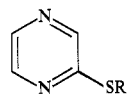
Pyrazine-2-thiol (1a) was prepared from 2-chloropyrazine by reaction with thiourea in 2 M sulfuric acid under conditions similar to those used by Cullen and Harrison[3] for the preparation of *C*-methyl analogues. 3-Phenylpyrazine-2-thiol (2a) was prepared

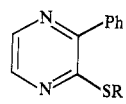
† Part IX, *Aust. J. Chem.*, 1985, **38**, 1685.

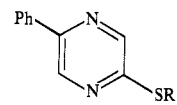
[1] Brown, D. J., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 2093.
[2] Brown, D. J., Cowden, W. B., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 155.
[3] Cullen, J., and Harrison, D., *J. Chem. Soc. C*, 1966, 495.

0004-9425/86/010069$02.00

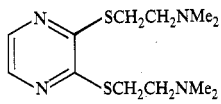
similarly from its chloro analogue with thiourea in 1 M sulfuric acid and also by the reaction of 3-phenylpyrazin-2-ol with phosphorus pentasulfide in refluxing pyridine; it had previously been made by reaction of 2-chloro-3-phenylpyrazine with potassium hydrogen sulfide.[4]

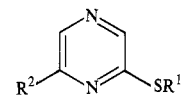

(1)


(2)

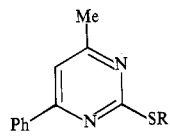

(3)

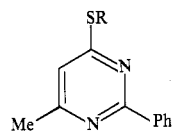
(a) R = H
(b) R = CH_2CONH_2
(c) R = $CH_2CH_2NMe_2$
(d) R = Me

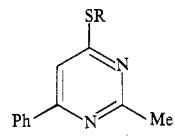

(4)



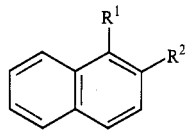
	R^1	R^2
(5a)	$CH_2CH_2NMe_2$	OEt
(5b)	$CH_2CH_2NMe_2$	$SCH_2CH_2NMe_2$


(6)


(7)


(8)

(a) R = H
(b) R = CH_2CONH_2
(c) R = $CH_2CH_2NH_2$



	R^1	R^2
(9a)	$OCH_2CH_2NMe_2$	H
(9b)	H	$OCH_2CH_2NMe_2$

5-Phenylpyrazine-2-thiol (3a), 6-methyl-2-phenylpyrimidine-4-thiol (7a) and 2-methyl-6-phenylpyrimidine-4-thiol (8a) were prepared similarly from their hydroxy analogues and phosphorus pentasulfide in pyridine.

2,3-Dichloropyrazine with 2-dimethylaminoethanethiol and potassium t-butoxide in t-butyl alcohol at reflux gave a reasonable yield of 2,3-bis(2′-dimethylaminoethylthio)pyrazine (4) but the 2,6-dichloro isomer under similar

[4] Wagner, G., and Frenzel, H., *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1967, **300**, 421.

conditions gave a trace only of 2,6-bis(2′-dimethylaminoethylthio)pyrazine (5b). 2,6-Dichloropyrazine with 2-dimethylaminoethanethiol and ethanolic sodium ethoxide at reflux afforded a high yield of 2-(6′-ethoxypyrazin-2′-ylthio)-*N*,*N*-dimethylethylamine (5a) and only a trace of (5b).

N,*N*-Dimethyl-2-(1′- and 2′-naphthyloxy)ethylamine (9a,b) were prepared from the hydroxy compounds with 2-chloro-*N*,*N*-dimethylethylamine and sodium hydroxide in toluene by co-distillation of the water formed.

Table 1. Activities as amplifiers of phleomycin

Measured at 1 mM: for details see Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423

Compound	Activity	Compound	Activity	Compound	Activity
(1b)	**	(3c)	***	(7b)[A]	**
(1c)	**	(4)	**	(7c)	**
(2b)	0	(5a)	**	(8b)	**
(2c)	***	(6b)	***	(9a)[A]	**
(3b)	**	(6c)[A]	***	(9b)	***

[A] In saturated solution <1 mM.

Biological Activities

The compounds tested were examined as outlined previously[5] (Table 1). Whereas the amplification by 2-(pyrazin-2′-ylthio)acetamide (1b) and *N*,*N*-dimethyl-2-(pyrazin-2′-ylthio)ethylamine (1c) was determined as two-star, insertion of a 3- or 5-phenyl group as in (2c) and (3c) increased the amplification to three-star. Similar effects have been observed previously in thiazol-4′-ylpyrazines[6] and pyrimidines.[1,2] Compounds which contained the 2-dimethylaminoethylthio group were, in general, superior to those containing the carbamoylmethylthio group.

The presence of two 2-dimethylaminoethylthio groups in (4) did not increase activity relative to (1c), and the presence of the 6-ethoxy group in (5a) had no observable effect on amplification. Unfortunately (5b) was not available in sufficient quantity to permit testing.

In the pyrimidine series the 2-aminoethylthio and 2-carbamoylmethylthio groups exhibited similar effects on amplification. Compounds (6b,c) with these groups in the 2-position were more active (by one star) than compounds (7b,c) and (8b) where the same groups were in the 4-position. All these compounds were much less active than the phenylpyrimidines reported previously.[1,2]

Amplification was also exhibited by the non-heterocyclic naphthalenes: the 2-substituted naphthalene (9b) at three-star was more active than its 1-isomer (9a) at two-star.

Experimental

Samples for analyses were dried at 100° for 1 h unless otherwise specified, and melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University

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

[6] Barlin, G. B., *Aust. J. Chem.*, 1984, **37**, 1049.

Analytical Services Unit. ^{1}H n.m.r. spectra were recorded at 90 MHz and 30° with a JEOL FX90Q Fourier-transform spectrometer with digital resolution of 0·12 Hz, with tetramethylsilane in $CDCl_3$ as internal standard.

Pyrazine-2-thiol (1a)

A mixture of 2-chloropyrazine (1·14 g), thiourea (1·9 g) and 2 M sulfuric acid (25 ml) was heated on a steam bath for 30 min, cooled and adjusted to pH *c.* 3 with 4 M sodium hydroxide (*c.* 10·5 ml). The reaction mixture was chilled and the orange solid filtered off, washed with water and dried to give crude pyrazine-2-thiol (0·6 g), m.p. 205–207° (lit.[7,8] 215–218°; 229°).

2-(Pyrazin-2′-ylthio)acetamide (1b)

Pyrazine-2-thiol (0·3 g) was dissolved in 1 M sodium hydroxide (5·0 ml), and stirred with chloroacetamide (0·8 g) for 30 min. The precipitate was collected, washed with water, and recrystallized from water to give *2-(pyrazin-2′-ylthio)acetamide* (0·2 g), m.p. 154–156° (Found: C, 42·9; H, 4·2; N, 24·9. $C_6H_7N_3OS$ requires C, 42·6; H, 4·2; N, 24·8%).

N,N-*Dimethyl-2-(pyrazin-2′-ylthio)ethylamine (1c)*

Pyrazine-2-thiol (0·5 g) in 1 M sodium hydroxide (10 ml) was stirred with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·63 g) for 1 h. The product was extracted into chloroform, and the oil (0·5 g) subjected to t.l.c. (alumina; chloroform). The product was treated with 10% ethanolic hydrogen bromide, and the salt precipitated with ether to give the *product* (1c) (0·50 g), m.p. 148–149° (from ethanol/ether) (Found: C, 27·8; H, 4·4; N, 12·1. $C_8H_{15}Br_2N_3S$ requires C, 27·8; H, 4·4; N, 12·2%). ^{1}H n.m.r. ($CDCl_3$): δ 2·31, s, Me_2N; 2·63, t, *J* 8 Hz, CH_2N; 3·33, t, *J* 8 Hz, CH_2S; 8·18, d, $J_{3',5'}$ 3 Hz, H 3′; 8·34, dd, $J_{3',5'}$ 3, $J_{5',6'}$ 1·5 Hz, H 5′; 8·45, d, $J_{5',6'}$ 1·5 Hz, H 6′.

3-Phenylpyrazine-2-thiol (2a)

(A) 2-Chloro-3-phenylpyrazine[9] (0·2 g), thiourea (0·4 g) and 1 M sulfuric acid (5·0 ml) with a little ethanol were heated on a steam bath for 1·25 h with occasional shaking. The deep red mixture was cooled, adjusted with 10 M sodium hydroxide to pH 2·5, and chilled. The solid (0·160 g) was filtered off, washed with ice-water and dried at the pump. It was recrystallized from cyclohexane to give orange crystals of 3-phenylpyrazine-2-thiol, m.p. 150–152° (lit.[4] 148–149°) (Found: C, 64·0; H, 4·3; N, 14·7. Calc. for $C_{10}H_8N_2S$: C, 63·8; H, 4·3; N, 14·9%).

(B) 3-Phenylpyrazin-2-ol[10] (0·5 g) and phosphorus pentasulfide (1·0 g) in pyridine (8·0 ml) were refluxed for 2 h, and the pyridine was evaporated under reduced pressure. The residue was dissolved in 1 M sodium hydroxide, filtered, and the filtrate adjusted with hydrochloric acid to pH 2 to give the thiol (0·35 g), m.p. 143–146°.

2-(3′-Phenylpyrazin-2′-ylthio)acetamide (2b)

3-Phenylpyrazine-2-thiol (0·1 g) in 1 M sodium hydroxide (4·0 ml) was shaken with chloroacetamide (0·15 g + 0·2 g after 15 min) for 45 min. The precipitate (0·080 g) was collected and recrystallized from water to give *2-(3′-phenylpyrazin-2′-ylthio)acetamide*, m.p. 119–121° (Found: C, 59·0; H, 4·4; N, 17·0. $C_{12}H_{11}N_3OS$ requires C, 58·8; H, 4·5; N, 17·1%).

N,N-*Dimethyl-2-(3′-phenylpyrazin-2′-ylthio)ethylamine (2c)*

3-Phenylpyrazine-2-thiol (0·5 g) in 1 M sodium hydroxide (15·0 ml) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·64 g) as described above gave, after t.l.c. (alumina; chloroform), an oil (0·22 g) which with 10% ethanolic hydrogen bromide afforded the *product* (2c) as a *hydrobromide semihydrate*, m.p. 300–305° (with decomposition from 285°) (Found: C, 48·3; H, 5·3; N, 12·0. $C_{14}H_{18}BrN_3S.0{\cdot}5H_2O$ requires C, 48·1; H, 5·5; N, 12·0%). ^{1}H n.m.r.

[7] Roblin, R. O., and Clapp, J. W., *J. Am. Chem. Soc.*, 1950, **72**, 4890.
[8] Albert, A., and Barlin, G. B., *J. Chem. Soc.*, 1962, 3129.
[9] Karmas, G., and Spoerri, P. E., *J. Am. Chem. Soc.*, 1956, **78**, 4071.
[10] Jones, R. G., *J. Am. Chem. Soc.*, 1949, **71**, 78.

(free base in $CDCl_3$): δ 2·29, s, Me_2N; 2·59, t, *J* 8 Hz, CH_2N; 3·29, t, *J* 8 Hz, CH_2S; 7·45, m, 7·70, m, Ph; 8·29, d, *J* 2·5 Hz, 8·34, d, *J* 2·5 Hz, H 5′,6′.

2-Methylthio-3-phenylpyrazine (2d)

3-Phenylpyrazine-2-thiol (0·050 g) in 1 M sodium hydroxide (5·0 ml) was shaken with methyl iodide (0·2 ml) for *c.* 15 min. The mixture was extracted with chloroform, the extract dried (Na_2SO_4), the solvent evaporated, and the product (0·042 g) subjected to t.l.c. (silica; chloroform) to give as a clear oil *2-methylthio-3-phenylpyrazine* (Found, for sample dried at 60° for 1·5 h: C, 65·3; H, 4·7. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0%). ^{1}H n.m.r. ($CDCl_3$): δ 2·51, s, Me; 7·50, m, Ph; 8·29, d, $J_{5,6}$ 3 Hz, 8·36, d, $J_{5,6}$ 3 Hz, H 5,6.

5-Phenylpyrazine-2-thiol (3a)

5-Phenylpyrazin-2-ol[11] (1·0 g) and phosphorus pentasulfide (1·5 g) in pyridine (8·5 ml) were refluxed for 45 min, and the pyridine was evaporated under reduced pressure. The residue was dissolved in 1 M sodium hydroxide (15 ml), and reprecipitated by addition of hydrochloric acid to pH 2 to give the *thiol* (3a) (1·5 g), m.p. *c.* 158–168° (reprecipitation as above) (Found: C, 63·8; H, 4·2; N, 15·0. $C_{10}H_8N_2S$ requires C, 63·8; H, 4·3; N, 14·9%).

2-(5′-Phenylpyrazine-2′-ylthio)acetamide (3b)

5-Phenylpyrazine-2-thiol (0·2 g) in 1 M sodium hydroxide (4·0 ml) was stirred with chloroacetamide (0·3 g) for 30 min. The precipitate was collected and recrystallized from water to give *2-(5′-phenylpyrazin-2′-ylthio)acetamide* (0·097 g), m.p. 204–205° (Found: C, 59·0; H, 4·5; N, 17·1. $C_{12}H_{11}N_3OS$ requires C, 58·8; H, 4·5; N, 17·1%).

N,N-*Dimethyl-2-(5′-phenylpyrazin-2′-ylthio)ethylamine (3c)*

5-Phenylpyrazine-2-thiol (0·5 g) in 1 M sodium hydroxide (15·0 ml) was stirred with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·64 g) for 1 h to give, after t.l.c. (alumina; chloroform), the *product* (3c) (0·45 g), m.p. 62–63° [from light petroleum (b.p. 40–60°)] (Found, for sample dried at 20°/20 mmHg: C, 65·0; H, 6·6; N, 16·3. $C_{14}H_{17}N_3S$ requires C, 64·8; H, 6·6; N, 16·2%). ^{1}H n.m.r. ($CDCl_3$): δ 2·32, s, Me_2N; 2·64, t, *J* 8 Hz, CH_2N; 3·36, t, *J* 8 Hz, CH_2S; 7·42, m, 7·90, m, Ph; 8·46, d, $J_{3',6'}$ 1·5 Hz, H 3′; 8·76, d, $J_{3',6'}$ 1·5 Hz, H 6′.

2-Methylthio-5-phenylpyrazine (3d)

5-Phenylpyrazine-2-thiol (0·050 g) in 1 M sodium hydroxide was shaken with methyl iodide (0·03 ml) for 30 min and the product extracted into chloroform. Removal of the solvent and recrystallization of the residue from light petroleum (b.p. 60–80°) gave *2-methylthio-5-phenylpyrazine* (0·012 g), m.p. 118·5–119° (Found: C, 65·2; H, 5·0; N, 14·1. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0; N, 13·9%). ^{1}H n.m.r. ($CDCl_3$): δ 2·62, s, MeS; 7·45, m, 7·95, m, Ph; 8·51, d, $J_{3,6}$ 1·5 Hz, H 3; 8·81, d, $J_{3,6}$ 1·5 Hz, H 6.

2,3-Dichloropyrazine

Pyrazine-2,3-diol was prepared from aminoacetaldehyde dimethylacetal and diethyl oxalate through ethyl *N*-(2′,2′-dimethoxyethyl)oxamate[12] and *N*-(2′,2′-dimethoxyethyl)oxamide.[12] It was chlorinated with phosphoryl chloride[13,14] to give 2,3-dichloropyrazine.

2,3-Bis(2′-dimethylaminoethylthio)pyrazine (4)

A mixture of 2,3-dichloropyrazine (0·6 g), 2-dimethylaminoethanethiol hydrochloride (2·28 g), potassium t-butoxide and t-butyl alcohol (30 ml) was refluxed for 22 h. The condenser was washed down with methanol, and the combined mixture diluted with water and the alcohols removed at *c.* 40°/50 mmHg. The aqueous solution was extracted with chloroform, the extract dried (Na_2SO_4) and the solvent evaporated to give an oil which was applied to three silica plates

[11] Sato, N., *J. Heterocycl. Chem.*, 1978, **15**, 665.
[12] Palamidessi, G., and Bonanomi, M., *Farmaco, Ed. Sci.*, 1966, **21**, 799.
[13] Bernardi, L., Palamidessi, G., Leone, A., and Larini, G., *Gazz. Chim. Ital.*, 1961, **91**, 1431.
[14] Adachi, J., and Sato, N., *J. Org. Chem.*, 1972, **37**, 221.

(20 by 20 cm). These were developed once with chloroform and then five times with ether. The various bands were removed, extracted with chloroform, examined by ^{1}H n.m.r., and the relevant product was treated with ethanolic hydrogen bromide to give pale yellow crystals of the *amine* (4) as a *dihydrobromide* (0·108 g), m.p. 271–272° (from ethanol) (Found, for sample dried at 80°/0·1 mmHg: C, 32·4; H, 5·5; N, 12·3. $C_{12}H_{22}N_4S_2.2HBr$ requires C, 32·1; H, 5·4; N, 12·5%). ^{1}H n.m.r. (D_2O): δ 2·96, s, Me_2N; 3·55, m, CH_2CH_2; 8·26, s, H 5,6.

^{1}H n.m.r. revealed further quantities of the desired product in other bands, but these were contaminated with excess side chain and monodimethylaminoethylthiopyrazine.

2,6-Bis(2′-dimethylaminoethylthio)pyrazine (5b)

A mixture of 2,6-dichloropyrazine (0·2 g, Aldrich), 2-dimethylaminoethanethiol hydrochloride (0·76 g), potassium t-butoxide (1·2 g) and t-butyl alcohol (10·0 ml) was refluxed for 5·5 h. The condenser was washed down with ethanol, the mixture diluted with water, and the alcohols removed under reduced pressure. The mixture was made strongly alkaline (pH 13–14) and extracted with chloroform to give an oil which was subjected to t.l.c. (silica; methanol). The oily product [^{1}H n.m.r. ($CDCl_3$): δ 2·31, s, Me_2N; 2·63, t, *J* 7 Hz, CH_2N; 3·32, t, *J* 7 Hz, CH_2S; 8·08, s, H 3,5] was treated with freshly prepared ethanolic hydrogen bromide to give the *compound* (5b) as a *dihydrobromide* (0·006 g), m.p. 243–245° (dec.) (from ethanol/ether) (Found: C, 31·8; H, 5·3; N, 12·1. $C_{12}H_{22}N_4S_2.2HBr$ requires C, 32·1; H, 5·4; N, 12·5%).

*2-(6′-Ethoxypyrazin-2′-ylthio)-*N,N*-dimethylethylamine (5a)*

A mixture of 2,6-dichloropyrazine (0·4 g), 2-dimethylaminoethanethiol hydrochloride (1·72 g) and ethanolic sodium ethoxide (from 0·56 g sodium and 24 ml ethanol) was refluxed for 6 h. The ethanol was evaporated under reduced pressure, and the residue diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and solvent evaporated to give an oil (1·1 g) which was chromatographed in methanol over a column of silica (30 cm), and the fractions were examined by ^{1}H n.m.r.

The earlier fractions gave an oil [^{1}H n.m.r. ($CDCl_3$): δ 1·41, t, *J* 8 Hz, CH_3CH_2; 2·30, s, Me_2N; 2·62, t, *J* 7 Hz, CH_2N; 3·27, t, *J* 7 Hz, CH_2S; 4·40, q, *J* 8 Hz CH_2CH_3; 7·83, s, H 3′; 8·00, s, H 5′] which with ethanolic hydrogen bromide gave the *ethoxy compound* (5a) which analysed as a 1·35 *hydrobromide* (0·394 g), m.p. 159–161° (from ethanol/ether) (Found, for sample dried at 60°/0·1 mmHg for 4 h: C, 35·7; H, 5·4; N, 12·5. $C_{10}H_{17}N_3OS.1·35HBr$ requires C, 35·7; H, 5·5; N, 12·5%). Later fractions were subjected to repeated t.l.c. (silica; methanol) to give an oil which with ethanolic hydrogen bromide gave 2,6-bis(2′-dimethylaminoethylthio)pyrazine dihydrobromide (0·004 g), m.p. 243–245° (dec.), with ^{1}H n.m.r. identical with that described above.

2-(4′-Methyl-6′-phenylpyrimidin-2′-ylthio)acetamide (6b)

4-Methyl-6-phenylpyrimidine-2-thiol[2] (6a) (0·20 g), 2-chloroacetamide (0·10 g) and 0·25 M sodium hydroxide (4·0 ml) were heated under reflux for 1 h. The mixture was cooled to give the *product* (6b) (0·11 g), m.p. 171–174° (from ethanol) (Found: C, 60·7; H, 5·1; N, 16·5. $C_{13}H_{13}N_3OS$ requires C, 60·2; H, 5·1; N, 16·2%).

2-(4′-Methyl-6′-phenylpyrimidin-2′-ylthio)ethylamine (6c)

The thiol (6a) (1·10 g), 2-bromoethylamine hydrobromide (1·50 g) and 1 M sodium hydroxide (25 ml) were heated under reflux for 1 h. The cooled solution was adjusted to pH 13 and extracted with ether. Evaporation of the dehydrated extract and treatment of the residue with 10% ethanolic hydrogen bromide gave the *product* (6c) as a *dihydrobromide* (0·85 g), m.p. 250–252° (from ethanol) (Found: C, 38·7; H, 4·3; N, 10·4. $C_{13}H_{17}Br_2N_3S$ requires C, 38·4; H, 4·2; N, 10·3%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 8·03, m, H 2″,6″; 7·45, m, H 3″,4″,5″; 7·21, s, H 5′; 3·30, m, H 2; 3·11, m, H 1; 2·48, s, 4′-Me.

6-Methyl-2-phenylpyrimidine-4-thiol (7a)

6-Methyl-2-phenylpyrimidin-4-ol[2] (4·1 g), phosphorus pentasulfide (5·0 g) and pyridine (40 ml) were heated with stirring under reflux for 1 h. The cooled mixture was diluted with water (50 ml), and the whole was evaporated to dryness at *c.* 60° in a vacuum. After trituration

with a little water, the brown residue was filtered off, dissolved in warm 1 M sodium hydroxide, and treated with charcoal. The filtered alkaline solution was acidified with acetic acid to give the *thiol* (7a) (2·5 g), m.p. 186° (from ethanol) (Found: C, 64·7; H, 5·0; N, 13·8. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0; N, 13·8%).

2-(6′-Methyl-2′-phenylpyrimidin-4′-ylthio)acetamide (7b)

The thiol (7a) underwent *S*-alkylation by 2-chloroacetamide, as for the isomer (6b), to give the *product* (7b) (70%), m.p. 206–208° (from ethanol) (Found: C, 59·7; H, 5·1; N, 16·2. $C_{13}H_{13}N_3OS$ requires C, 60·2; H, 5·1; N, 16·2%). ^{1}H n.m.r. ($CDCl_3$): δ 8·37, m, H 2″,6″; 7·52, m, H 3″,4″,5″; 7·01, s, H 5′; 3·94, s, H 2; 2·52, s, 6′-Me.

2-(6′-Methyl-2′-phenylpyrimidin-4′-ylthio)ethylamine (7c)

The thiol (7a) and 2-bromoethylamine gave, as for the isomer (6c), the *amine* (7c) as a *dihydrobromide* (32%), m.p. 250–252° (from ethanol) (Found: C, 37·7; H, 4·2; N, 10·2. $C_{13}H_{17}Br_2N_3S$ requires C, 38·4; H, 4·2; N, 10·3%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 8·36, m, H 2″,6″; 7·45, m, H 3″,4″,5″; 6·90, s, H 5′; 3·37, m, H 2; 3·06, m, H 1; 2·44, s, 6′-Me.

2-Methyl-6-phenylpyrimidine-4-thiol (8a)

Treatment of 2-methyl-6-phenylpyrimidin-4-ol[2] with phosphorus pentasulfide, as for the isomer (7a), gave the *thiol* (7a) (62%), m.p. 212–214° (from ethanol) (Found: C, 64·9; H, 5·0; N, 13·6. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0; N, 13·8%).

2-(2′-Methyl-6′-phenylpyrimidin-4′-ylthio)acetamide (8b)

The thiol (8a) was converted, by the method used for preparing (6b) above, into the *acetamide* (8b) (71%), m.p. 142–144° (from ethanol) (Found: C, 60·1; H, 5·1; N, 16·2. $C_{13}H_{13}N_3OS$ requires C, 60·2; H, 5·1; N, 16·2%). ^{1}H n.m.r. ($CDCl_3$): δ 8·02, m, H 2″,6″; 7·48, m, H 3″,4″,5″; 7·26, s, H 5′; 3·86, s, H 2; 2·73, s, 2′-Me.

N,N-*Dimethyl-2-(1′- and 2′-naphthyloxy)ethylamine (9a,b)*

2-Chloro-*N*,*N*-dimethylethylamine hydrochloride (8·50 g), 2·5 M sodium hydroxide (25 ml) and toluene (75 ml) were shaken vigorously for 30 min. The organic layer was removed and dried over sodium hydroxide pellets. The filtered solution was added to a mixture of 1-naphthol (8·0 g), finely ground solid sodium hydroxide (2·5 g) and toluene (100 ml) contained in a flask surmounted by a Dean and Stark assembly. The contents were boiled for 24 h and then cooled. The filtered solution was evaporated and the residual oil was treated with 10% ethanolic hydrogen bromide to give the *1′-naphthyloxyethylamine* (9a) as the *hydrobromide* (1·2 g), m.p. 198–200° (from ethanol) (Found: C, 56·7; H, 6·2; N, 4·8. $C_{14}H_{18}BrNO$ requires C, 56·8; H, 6·1; N, 4·7%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 8·25–6·64, m, H 2′–8′; 4·66, t, H 2; 2·83, t, H 1; 2·36, s, NMe_2.

The use of 2-naphthol as substrate similarly gave the *2′-naphthyloxyethylamine* (9b) as the *hydrobromide* (1·1 g), m.p. 178–180° (from ethanol) (Found: C, 57·1; H, 6·5; N, 4·7%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 7·72–7·09, m, H 1′,3′–8′; 4·10, t, H 2; 2·71, t, H 1; 2·30, s, NMe_2.

Acknowledgment

One of us (M.N.) thanks this University for the award of a vacation scholarship.

Manuscript received 1 August 1985