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Heterocyclic Amplifiers of Phleomycin. VII* Phenyl-, Tolyl-, Phenoxy- and Benzyl-pyrimidines; also Some Carbocyclic Analogues

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Abstract

Synthetic routes are described for 5-phenyl-, 5-*p*-chlorophenyl-, 2-*p*-tolyl-, 2- and 4-benzyl- and 4-phenoxy-pyrimidines, each bearing a sulfur-, nitrogen- or oxygen-linked basic side chain; also to analogous biphenyls and a diphenylmethane. These compounds were required for evaluation as amplifiers of phleomycin.

Appropriate 2- and 4-phenylpyrimidines strongly enhance the activity of phleomycin, both as an antibacterial agent against *in vitro* cultures of *Escherichia coli*[1,2] and as an antineoplastic agent against the Ehrlich tumour in mice.[3] We now report synthetic routes to analogous compounds for evaluation as amplifiers.

Syntheses

5-Phenylpyrimidines

2-Chloro-5-phenylpyrimidine[4] (1a) underwent aminolysis by 2-dimethylaminoethylamine to give the potential amplifier (1b) but attempts to make the thio analogue (1c) by alkylthiolysis with ethanolic sodium 2-dimethylaminoethanethiolate gave only 2-ethoxy-5-phenylpyrimidine (1d); the analogous substrate, 2-chloro-5-*p*-chlorophenylpyrimidine[4] (1e) underwent more satisfactory aminolysis, alkylthiolysis and alcoholysis to give the amplifiers (1f–h), respectively. 5-Phenylpyrimidin-4(3*H*)-one[5] was converted into the corresponding thione[6] (2a) by an improved thiation procedure but subsequent *S*-alkylation by 2-chloro-*N*,*N*-dimethylethylamine failed to give a pure

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[1] Brown, D. J., Cowden, W. B., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 155.
[2] Brown, D. J., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 2093.
[3] Aliano, A. N., Allen, T. E., Brown, D. J., Cowden, W. B., Grigg, G. W., Kavulak, D., and Lan, S.-B., *Aust. J. Chem.*, 1984, **37**, 2385.
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[5] Davies, W. H., and Piggott, H. A., *J. Chem. Soc.*, 1945, 347.
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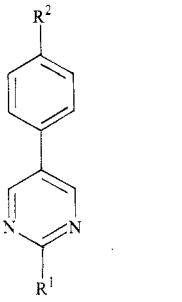
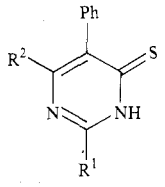
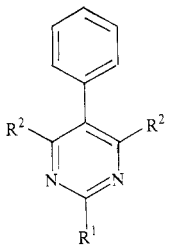
thioether. In contrast, 6-mercapto-5-phenylpyrimidine-4(3*H*)-thione[7] (2b) readily underwent such *S*-alkylations to afford the required bisthioethers (3a) and (3b); the 2-methylated substrate (2c), used as a crude product from the thiation of 6-hydroxy-2-methyl-5-phenylpyrimidin-4(3*H*)-one[8] as for the lower homologue,[7] likewise afforded the thioether (3c). In addition, aminolysis and alcoholysis of 4,6-dichloro-5-phenylpyrimidine[7] (3d) gave the amplifiers (3e) and (3f) respectively, while alcoholysis of the 2-methylated substrate[9] (3g) gave the diether (3h).



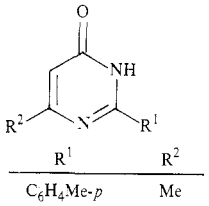
	R^1	R^2
(1a)	Cl	H
(1b)	$NHCH_2CH_2NMe_2$	H
(1c)	$SCH_2CH_2NMe_2$	H
(1d)	OEt	H
(1e)	Cl	Cl
(1f)	$NHCH_2CH_2NMe_2$	Cl
(1g)	$SCH_2CH_2NMe_2$	Cl
(1h)	$OCH_2CH_2NMe_2$	Cl



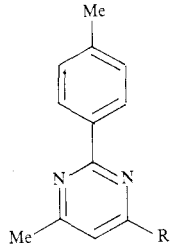
	R^1	R^2
(2a)	H	H
(2b)	H	SH
(2c)	Me	SH



	R^1	R^2
(3a)	H	$SCH_2CH_2NMe_2$
(3b)	H	$SCH_2CH_2CH_2NMe_2$
(3c)	Me	$SCH_2CH_2NMe_2$
(3d)	H	Cl
(3e)	H	$NHCH_2CH_2CH_2NMe_2$
(3f)	H	$OCH_2CH_2NMe_2$
(3g)	Me	Cl
(3h)	Me	$OCH_2CH_2NMe_2$



	R^1	R^2
(4a)	C_6H_4Me-*p*	Me
(4b)	Me	CH_2Ph
(4c)	CH_2Ph	Me



(5a) R = Cl

(5b) R = $SCH_2CH_2NMe_2$

Substituted Phenylpyrimidines

As well as the three 5-*p*-chlorophenylpyrimidines (1f–h) mentioned above, *p*-toluonitrile was converted by the classical route into the corresponding amidine,[10] which reacted with ethyl acetoacetate in ethanolic ethoxide to give 6-methyl-2-*p*-tolylpyrimidin-4(3*H*)-one (4a). Treatment with phosphoryl chloride gave the chloro intermediate (5a) and subsequent thioalcoholysis afforded the required thioether (5b).

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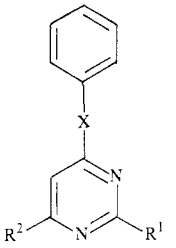
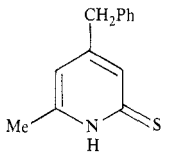
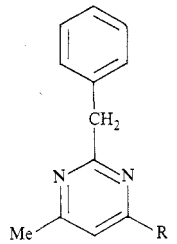
[10] Glock, G., *Ber. Dtsch. Chem. Ges.*, 1888, **21**, 2650.



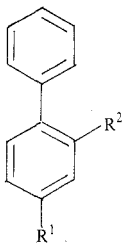
	X	R^1	R^2
(6a)	CH_2	Me	Cl
(6b)	CH_2	Me	$SCH_2CH_2NMe_2$
(6c)	CH_2	$SCH_2CH_2NMe_2$	Me
(6d)	O	Me	Cl
(6e)	O	Me	$SCH_2CH_2NMe_2$
(6f)	O	Cl	Me
(6g)	O	$SCH_2CH_2NMe_2$	Me



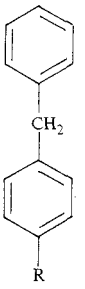
(7)



(8a) R = Cl
(8b) R = $SCH_2CH_2NMe_2$



	R^1	R^2
(9a)	H	H
(9b)	SO_3H	H
(9c)	SO_3K	H
(9d)	SO_2Cl	H
(9e)	SH	H
(9f)	$SCH_2CH_2NMe_2$	H
(9g)	$SCH_2CH_2CH_2NMe_2$	H
(9h)	OH	H
(9i)	$OCH_2CH_2NMe_2$	H
(9j)	NH_2	H
(9k)	$NHCH_2CH_2NMe_2$	H
(9l)	H	OH
(9m)	H	NH_2
(9n)	H	$OCH_2CH_2NMe_2$
(9o)	H	$NHCH_2CH_2NMe_2$



(10a) R = OH
(10b) R = $OCH_2CH_2NMe_2$

Benzyl- and Phenoxy-pyrimidines

Phenylacetylation of diethyl ethoxymagnesiomalonate[11] gave diethyl α-(phenylacetyl)malonate which underwent partial hydrolysis and decarboxylation to ethyl γ-phenylacetoacetate.[12] Subsequent condensation with acetamidine gave the pyrimidinone (4b) which gave the chloropyrimidine (6a) and thence the thioether (6b).

[11] Bowman, R. E., *J. Chem. Soc.*, 1950, 322.
[12] Ames, G. R., and Davey, W., *J. Chem. Soc.*, 1957, 3480; Baker, B. R., Santi, D. V., and Shapiro, H. S., *J. Pharm Sci.*, 1964, **53**, 1317.

Condensation of 1-phenylpentane-2,4-dione[13] with thiourea gave the pyrimidinethione (7) which underwent *S*-alkylation by 2-dimethylaminoethanethiol to give the amplifier (6c). An improved integrated procedure was developed (see Experimental) for the sequence phenylacetonitrile → phenylacetimidate hydrochloride → phenylacetamidine hydrochloride → 2-benzyl-6-methylpyrimidin-4(3*H*)-one (4c) → 2-benzyl-4-chloro-6-methylpyrimidine (8a) → the thioether (8b). The phenoxypyrimidines were approached from the corresponding chloropyrimidines. Thus treatment of 4,6-dichloro-2-methylpyrimidine[14] with sodium phenoxide in acetone at room temperature gave 4-chloro-2-methyl-6-phenoxypyrimidine (6d) which was converted into the thioether (6e) in the usual way; rather similarly, the unsymmetrical 2,4-dichloro-6-methylpyrimidine[14] gave a single monophenoxy derivative (t.l.c., three systems), corresponding in melting point with that of the expected and known[15] isomer (6f): subsequent treatment with sodium 2-dimethylaminoethanethiolate afforded the thioether (6g).

Biphenyls and Related Carbobicycles

The sequence biphenyl (9a) → biphenyl-4-sulfonic acid[16] (9b) → potassium biphenyl-4-sulfonate[17] (9c) → biphenyl-4-sulfonyl chloride[17] (9d), followed by zinc reduction[18] afforded biphenyl-4-thiol (9e) which underwent normal *S*-alkylation to give the thioethers (9f) and (9g). Biphenyl-4-ol (9h) was treated with 2-chloro-*N*,*N*-dimethylethylamine in boiling toluene (cf.[19]) to give the ether (9i); similarly, biphenyl-4-amine (9j) with the same reagent in aqueous sodium hydrogen carbonate (cf.[20]) gave the amplifier (9k). Likewise, the phenol, (9l) and the amine (9m) gave the amplifiers (9n) (cf.[19]) and (9o), respectively, while *p*-benzylphenol (10a) gave the ether (10b).

Experimental

Analyses were done by the Australian National University Analytical Services Unit. The n.m.r. spectra were measured at 90 MHz and 30° (chemical shifts in δ) against tetramethylsilane or sodium trimethylsilylpropane-1-sulfonate, as appropriate.

N-(2′-Dimethylaminoethyl)-5-phenylpyrimidin-2-amine (1b)

2-Chloro-5-phenylpyrimidine[4] (1a) (0·4 g) and 2-dimethylaminoethylamine (9·0 ml) were boiled under reflux for 3 h. The excess of amine was recovered by distillation and the residue was diluted with water (2 ml). This solution was adjusted to pH 11 with 2 M sodium hydroxide and then extracted with ether. The dehydrated extract was evaporated to give the *product* (41%), m.p. 66–67° (from light petroleum) (Found: C, 69·7; H, 7·7; N, 22·9. $C_{14}H_{18}N_4$ requires C, 69·4; H, 7·5; N, 23·1%). N.m.r. ($CDCl_3$) 8·52, s, H4,6; 7·44, m, Ph; 5·75, br, NH; 3·52, q, H1′; 2·55, t, H2′; 2·28, s, NMe_2.

[13] Adams, J. T., and Hauser, C. R., *J. Am. Chem. Soc.*, 1944, **66**, 1220; 1945, **67**, 284.
[14] Boarland, M. P. V., and McOmie, J. F. W., *J. Chem. Soc.*, 1952, 3722.
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[16] Schultz, R. G., *J. Org. Chem.*, 1961, **26**, 5195.
[17] Niwa, H., *Tohoku Yakka Daigaku Kiyo*, 1957, **4**, 19 (*Chem. Abstr.*, 1958, **52**, 7234).
[18] Lester, C. T., Rodgers, G. F., and Reid, E. E., *J. Am. Chem. Soc.*, 1944, **66**, 1674.
[19] Khmelevskii, V. I., Kushkin, V. V., Novikova, A. P., and Getsova, I. N., *Zh. Org. Khim.*, 1965, **1**, 262.
[20] Massarani, E., Nardi, D., Mauri, L., and Bonacina, F., *Boll. Chim. Farm.*, 1966, **105**, 606.

2-Ethoxy-5-phenylpyrimidine (1d)

On attempting to prepare the thioether (1c) from the chloropyrimidine (1a) and 2-dimethylaminoethanethiol in ethanolic sodium hydroxide, the only isolable product was the *ethoxyphenylpyrimidine* (1d) (52%), m.p. 72–73° (Found: C, 71·4; H, 6·1; N, 14·1. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%). N.m.r. ($CDCl_3$) 8·72, s, H4,6; 7·50, m, Ph; 4·48, q, CH_2 of Et; 1·47, t, Me of Et.

5-(p-Chlorophenyl)-N-(2′-dimethylaminoethyl)pyrimidin-2-amine (1f)

2-Chloro-5-*p*-chlorophenylpyrimidine[4] (1e) underwent aminolysis as for the above analogue (1b) to give the *pyrimidinylethylamine* (1f) (75%), m.p. 136–138° (from light petroleum) (Found: C, 61·5; H, 6·2; Cl, 12·8; N, 20·3. $C_{14}H_{17}ClN_4$ requires C, 70·0; H, 5·9; Cl, 12·9; N, 20·3%). N.m.r. ($CDCl_3$) 8·48, s, H4,6; 7·39, s, H2″,3″,5″,6″; 5·80, br, NH; 3·52, q, H1′; 2·54, t, H2′; 2·28, s, NMe_2.

2-[5′-(p-Chlorophenyl)pyrimidin-2′-ylthio]-N,N-dimethylethylamine (1g)

The same substrate (1e) (0·5 g), 2-dimethylaminoethanethiol hydrochloride (0·35 g), ethanol (15 ml) and sodium hydroxide (0·21 g) were heated on the steam bath for 2 h. The residue from evaporation was diluted with 1 M sodium hydroxide (3 ml) and extracted with ether. The dehydrated extract was treated with hydrogen chloride to give a solid which was crystallized from propan-2-ol and allowed to equilibrate in air. The product (1g) as *hydrochloride trihydrate* (54%) had m.p. 200–201° (Found: C, 44·5; H, 6·3; N, 10·8. $C_{14}H_{17}Cl_2N_3S.3H_2O$ requires C, 43·8; H, 6·0; N, 10·9%). N.m.r. (D_2O) 8·75, s, H4′,6′; 7·50, s, H2″,3″,5″,6″; 3·57, br, H2; 3·03, br, H1; 3·00, s, NMe_2.

2-[5′-(p-Chlorophenyl)pyrimidin-2′-yloxy]-N,N-dimethylethylamine (1h)

The substrate (1e) (0·5 g), 2-dimethylaminoethanol (10 ml) and fresh potassium t-butoxide (0·28 g) were heated under reflux for 90 min. The excess of amine was removed by distillation and the residue was diluted with a little water prior to ether extraction. Evaporation of the extract gave the *base* (44%), m.p. 80·82° (from light petroleum) (Found: C, 60·0; H, 5·8; Cl, 12·9; N, 14·8. $C_{14}H_{16}ClN_3O$ requires C, 60·5; H, 5·8; Cl, 12·8; N, 15·1%). N.m.r. ($CDCl_3$) 8·68, s, H4′,6′; 7·45, s, H2″,3″,5″,6″; 4·53, t, H2; 2·79, t, H1; 2·36, s, NMe_2.

5-Phenylpyrimidine-4(3H)-thione (2a)

5-Phenylpyrimidin-4(3*H*)-one[5] (0·5 g), phosphorus pentasulfide (1·5 g) and anhydrous pyridine (6 ml) were heated under reflux with stirring for 2 h. The residue from evaporation was recrystallized (charcoal) from water and then further purified from elemental sulfur by dissolution in 5 M ammonia and reprecipitation with acetic acid. The thione (25%) had m.p. 166–168° (lit.[6] 167–169°) (Found: C, 64·4; H, 4·3; N, 15·0. Calc. for $C_9H_8N_2S$: C, 63·8; H, 4·3; N, 14·9%).

2-[6′-(2″-Dimethylaminoethylthio)-5′-phenylpyrimidin-4′-ylthio]-N,N-dimethylethylamine (3a)

The pyrimidinethione[7] (2b) (2·2 g), 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·45 g) and 1 M sodium hydroxide (40 ml) were heated under reflux with stirring for 2 h. The cooled solution was adjusted to pH 13 with 10 M sodium hydroxide and then extracted with ether. The residue, from evaporation of the dehydrated extract, recrystallized from light petroleum to give the *product* (3a) (*c.* 30%), m.p. 62–64° (Found: C, 59·6; H, 7·5; N, 15·2. $C_{18}H_{26}N_4S$ requires C, 59·6; H, 7·2; N, 15·4%). N.m.r. ($CDCl_3$) 8·69, s, H2′; 7·34, m, Ph; 3·25, t, H1″,2; 2·54, t, H1,2″; 2·26, s, NMe_2.

3-[6′-(3″-Dimethylaminopropylthio)-5′-phenylpyrimidin-4′-ylthio]-N,N-dimethylpropylamine (3b)

Treatment of the same thione (2b) as above with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (1·75 g) at 60° gave an oily product which was treated with 10% ethanolic hydrogen bromide to give the product (3b) as *dihydrobromide* (54%), m.p. 263–264° (from propan-2-ol) (Found: C, 43·9; H, 6·0; N, 10·1. $C_{20}H_{32}Br_2N_4S$ requires C, 43·5; H, 5·8; N, 10·4%). N.m.r. (base in $CDCl_3$) 8·68, s, H2′; 7·37, m, Ph; 3·12, t, H1″,3; 2·34, t, H1,3″; 2·20, s, NMe_2; 1·80, m, H2,2″.

2-[6′-(2″-Dimethylaminoethylthio)-2′-methyl-5′-phenylpyrimidin-4′-ylthio]-N,N-*dimethylethylamine* (*3c*)

6-Hydroxy-2-methyl-5-phenylpyrimidin-4(3*H*)-one[8] was converted into 6-mercapto-2-methyl-5-phenylpyrimidine-4(3*H*)-thione by heating with phosphorus pentasulfide under conditions described[7] for the demethyl homologue. The crude thione (2·0 g), 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (1·5 g) and 1 M sodium hydroxide (40 ml) were heated for 1 h, cooled and then adjusted to pH 13. An ether extract was evaporated to give a base which was treated with 10% ethanolic hydrogen bromide to give the *dihydrobromide* (12%), m.p. 254–256° (from ethanol) (Found: C, 42·3; H, 5·7; N, 10·1. $C_{19}H_{30}Br_2N_4S_2$ requires C, 42·4; H, 5·6; N, 10·4%). N.m.r. (base in $CDCl_3$) 7·34, m, Ph; 3·24, t, H1″,2; 2·62, s, 2′-Me; 2·53, t, H1,2″; 2·28, s, NMe_2.

N,N′-*Bis*(*3′-dimethylaminopropyl*)-*5-phenylpyrimidine-4,6-diamine* (*3e*)

4,6-Dichloro-5-phenylpyrimidine[7] (3d) (5·0 g) and 3-dimethylaminopropylamine (22 ml) were boiled under reflux for 2 h and then cooled. The solid was filtered off and recrystallized from light petroleum to give the *base* (3e) (80%), m.p. 123° (Found: C, 67·1; H, 9·4; N, 23·5. $C_{20}H_{32}N_6$ requires C, 67·4; H, 9·0; N, 23·4%). N.m.r. ($CDCl_3$) 8·28, s, H2; 7·36, m, Ph; 5·63, br, NH; 3·43, q, H1′; 2·22, t, H3′; 1·91, s, NMe_2; 1·62, m, H2′.

2-[6′-(2″-Dimethylaminoethoxy)-5′-phenylpyrimidin-4′-yloxy]-N,N-*dimethylethylamine* (*3f*)

The same substrate[7] (3d) (2·24 g), 2-dimethylaminoethanol (22 ml) and potassium t-butoxide (2·4 g) were boiled under reflux for 1 h. The excess of dimethylaminoethanol was removed by distillation in a vacuum and the residue was diluted with a little water and extracted with ether. The extract furnished an oily base which was converted by ethanolic hydrogen bromide into the *dihydrobromide* (46%), m.p. 214° (from propan-2-ol) (Found: C, 43·8; H, 5·8; N, 11·4. $C_{18}H_{28}Br_2N_4O_2$ requires C, 43·7; H, 5·7; N, 11·4%). N.m.r. (base in $CDCl_3$) 8·39, s, H2′; 7·37, m, Ph; 4·47, t, H1″,2; 2·62, t, H1,2″; 2·23, s, NMe_2.

2-[6′-(2″-Dimethylaminoethoxy)-2′-methyl-5′-phenylpyrimidin-4′-yloxy]-N,N-*dimethylethylamine* (*3h*)

In a similar way, 4,6-dichloro-2-methyl-5-phenylpyrimidine[9] (3 g) gave the product (3h) as *dihydrobromide* (73%), m.p. 219–220° (from propan-2-ol) (Found: C, 44·4; H, 6·1; N, 10·9. $C_{19}H_{30}Br_2N_4O_2$ requires C, 45·0; H, 6·0; N, 11·1%). N.m.r. (base in $CDCl_3$) 7·24, m, Ph; 4·38, t, H1″,2; 2·54, t, H1,2″; 2·45, s, 2′-Me; 2·16, s, NMe_2.

N,N-*Dimethyl-2-(6′-methyl-2′*-p-*tolylpyrimidin-4′-ylthio)ethylamine* (*5b*)

p-Toluonitrile (11·7 g) was converted into *p*-toluamidine hydrochloride (79%), m.p. 208° (from ethanol) (cf.[10] 213°) by the method used for the isomeric phenylacetamidine hydrochloride below. The crude amidine salt (5·0 g), ethyl acetoacetate and ethanolic sodium ethoxide (sodium: 1·4 g; ethanol: 30 ml) were heated under reflux for 5 h. The residue from evaporation was dissolved in water (50 ml) and the solution was acidified to give *6-methyl-2*-p-*tolylpyrimidin-4*(3H)-*one* (4a) (69%), m.p. 216–220° (from ethanol) (Found: C, 72·2; H, 6·1; N, 14·0. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%). This material was treated with phosphoryl chloride (as was its isomer below) to give *4-chloro-6-methyl-2*-p-*tolylpyrimidine* (5a) (82%), m.p. 104–106° (from light petroleum) (Found: C, 66·4; H, 5·1; N, 12·8. $C_{12}H_{11}ClN_2$ requires C, 65·9; H, 5·1; N, 12·8%). The chloropyrimidine (1·5 g), 2-dimethylaminoethanethiol hydrochloride (1·6 g), ethanol (30 ml), and sodium hydroxide (0·28 g) were stirred at 25° for 10 h. The residue from evaporation was diluted with 1 M sodium hydroxide (30 ml) and then ether-extracted. Evaporation of the ether gave the liquid base (5b) (76%) which was characterized as its *dihydrochloride*, m.p. 235–239° (from ethanol) (Found: C, 53·4; H, 6·4; N, 11·4. $C_{16}H_{23}Cl_2N_3S$ requires C, 53·5; H, 6·4; N, 11·7%). N.m.r. (base in $CDCl_3$) 8·34, d, H3″,5″; 7·25, d, H2″,6″; 6·87, s, H5′; 3·43, t, H2; 2·68, t, H1; 2·44, s, 6-Me; 2·40, s, 4″-Me; 2·33, s, NMe_2.

2-(6′-Benzyl-2′-methylpyrimidin-4′-ylthio)-N,N-*dimethylethylamine* (*6b*)

Diethyl ethoxymagnesiomalonate[11] reacted with phenylacetyl chloride to give diethyl α-(phenylacetyl)malonate and thence ethyl γ-phenylacetoacetate.[12] This keto ester (11·0 g), acetamidine hydrochloride (10·0 g) and ethanolic sodium ethoxide (sodium: 3·0 g; ethanol: 60 ml) were heated

under reflux for 24 h with stirring. The residue from evaporation was dissolved in water (50 ml) and the solution was acidified to pH 5. Refrigeration and filtration gave *6-benzyl-2-methylpyrimidin-4(3H)-one* (4b) (76%), m.p. 198–200° (from ethanol) (Found: C, 71·6; H, 5·8; N, 14·2. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%). The pyrimidinone (3·8 g) and phosphoryl chloride (60 ml) were boiled under reflux for 90 min. The excess of phosphoryl chloride was removed by vacuum distillation and the residue was poured into ice-water and stirred for a further 20 min before ether extraction. Distillation of the extract gave a crude product (b.p. 122–128°/10 mm) which was purified further by t.l.c. (silica; ether/light petroleum, 1 : 4) to afford *4-benzyl-6-chloro-2-methylpyrimidine* (6a) (51%) (Found: C, 65·9; H, 4·8; Cl, 16·3. $C_{12}H_{11}ClN_2$ requires C, 65·9; H, 5·1; Cl, 16·2%). This chloropyrimidine (2·50 g), 2-dimethylaminoethanethiol hydrochloride (2·2 g) and ethanol (40 ml) containing sodium hydroxide (1·20 g) were heated under reflux for 4 h. Treatment of the solution, as for the phenoxy analogue (6e) below, gave the *thioether* (6b) as *dihydrobromide* (61%), m.p. 190–195° (from ethanol) (Found: C, 42·3; H, 5·3; N, 9·3. $C_{16}H_{23}Br_2N_3S$ requires C, 42·8; H, 5·2; N, 9·3%). N.m.r. (base in $CDCl_3$) 7·28, s, br, Ph; 6·70, s, H5′; 3·96, s, 6′-CH_2; 3·37, t, H2; 2·72, t, H1; 2·63, s, 2′-Me; 2·43, s, NMe_2.

2-(4′-Benzyl-6′-methylpyrimidin-2′-ylthio)-N,N-dimethylethylamine (*6c*)

1-Phenylpentane-2,4-dione[13] (8·0 g), thiourea (5·2 g), ethanol (40 ml) and 10 M hydrochloric acid (7·0 ml) were boiled under reflux for 24 h. The residue from evaporation was dissolved in water (20 ml) and adjusted to pH 6. The yellow solid was collected and washed with ether prior to recrystallization from ethanol. *4-Benzyl-6-methylpyrimidine-2(1H)-thione* (7) (61%) had m.p. 165–168° (Found: C, 66·9; H, 5·8; N, 13·1; S, 14·8. $C_{12}H_{12}N_2S$ requires C, 66·6; H, 5·6; N, 12·9; S, 14·8%). The thione (2·0 g), 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·6 g) and ethanol (50 ml) containing sodium hydroxide (1·0 g) were boiled under reflux with stirring for 20 h. The residue from evaporation was diluted with water (20 ml) and adjusted to pH 13. Ether extraction, evaporation of the extract, and treatment of the residue with ethanolic hydrogen bromide gave the required *thioether* (6c) as *hydrobromide* (86%), m.p. 160–163° (from ethanol) (Found: C, 52·9; H, 6·0; N, 11·6. $C_{16}H_{22}BrN_3S$ requires C, 52·2; H, 6·0; N, 11·4%). N.m.r. (D_2O) 7·35, s, br, Ph; 7·03, s, H5′; 4·04, s, 4′-CH_2; 3·44, s, br, H1,2; 2·90, s, NMe_2; 2·43; s, 6′-Me.

2-(2′-Benzyl-6′-methylpyrimidine-4′-ylthio)-N,N-dimethylethylamine (*8b*)

Dry hydrogen chloride was bubbled into a mixture of phenylacetonitrile (11·7 g), methanol (4·0 ml) and anhydrous ether (40 ml) at 15–20° (intermittent ice bath) to saturation. After a further 12 h, removal of the ether gave crude methyl phenylacetimidate hydrochloride (16·5 g). This material was added with stirring during 4 h to 15% ethanolic ammonia (160 ml) at 5°. After stirring for a further 20 h at 20–25°, evaporation of the filtered solution gave phenylacetamidine hydrochloride (*c.* 13 g). The crude amidine hydrochloride (6·5 g), ethyl acetoacetate (7·5 g) and ethanolic sodium ethoxide (sodium: 2·2 g; ethanol: 30 ml) were heated under reflux for 40 h. The residue from evaporation was dissolved in water and acidified to give 2-benzyl-6-methylpyrimidin-4(3*H*)-one (4c) (2·8 g), m.p. 172–175° (from ethanol) (cf.[21]) (Found: C, 72·4; H, 6·1; N, 14·2. Calc. for $C_{12}H_{12}N_2O$: C, 72·0; H, 6·0; N, 14·0%). The pyrimidinone (2·1 g) and phosphoryl chloride (45 ml) were boiled under reflux for 90 min. Subsequent treatment as for the 4-benzyl-2-methyl isomer above gave a crude product which crystallized from light petroleum to give 2-benzyl-4-chloro-6-methylpyrimidine (8a) (84%), m.p. 80–82° (lit.[22] 81–83°) (Found after equilibration in air: C, 63·7; H, 5·0; N, 12·1. Calc. for $C_{12}H_{11}ClN_2.0{\cdot}5H_2O$: C, 63·3; H, 5·3; N, 12·3%). This chloro compound was treated with dimethylaminoethanethiol, as for the phenoxy analogue (6e) below, to give the thioether (8b) (78%), characterized as *dihydrobromide*, m.p. 218–220° (from ethanol) (Found: C, 42·9; H, 5·3; N, 9·3. $C_{16}H_{23}Br_2N_3S$ requires C, 42·8; H, 5·2; N, 9·3%). N.m.r. (D_2O) 7·61, s, H5′; 7·44, s, br, Ph; 4·46, s, 2′-CH_2; 3·57, t, H2; 3·18, t, H1; 2·73, s, NMe_2; 2·64, s, 6′-Me.

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N,N-*Dimethyl-2-(2′-methyl-6-phenoxypyrimidin-4′-ylthio)ethylamine* (*6e*)

4,6-Dichloro-2-methylpyrimidine[14] (3·26 g), sodium phenoxide (2·32 g) and acetone (20 ml) were stirred at 25° for 5 h. The residue from evaporation was added to water (20 ml) and then extracted with ether (3 × 30 ml). Removal of the ether and t.l.c. (silica; ether + light petroleum, 1 : 8) gave the *4-chloro-2-methyl-6-phenoxypyrimidine* (6d) (55%), m.p. 53–55° (from cyclohexane) (Found: C, 60·1; H, 4·1; Cl, 15·9; N, 12·7. $C_{11}H_9ClN_2O$ requires C, 59·9; H, 4·1; Cl, 16·1; N, 12·7%). The chloropyrimidine (2·50 g), 2-dimethylaminoethanethiol hydrochloride (2·05 g) and ethanol (50 ml) containing sodium hydroxide (1·20 g) were stirred at 25° for 5 h. The residue from evaporation was mixed with 1 M sodium hydroxide (20 ml) and then ether-extracted. Evaporation of the extract gave crude base (6e) (76%) which was characterized as the *dihydrobromide monohydrate*, m.p. 190–195° (from ethanol) (Found: C, 38·2; H, 5·0; N, 9·4. $C_{15}H_{21}Br_2N_3OS.H_2O$ requires C, 38·4; H, 4·9; N, 9·0%). N.m.r. (base in $CDCl_3$) 7·25, m, Ph; 6·34, s, H5′; 3·29, t, H2; 2·59, t, H1; 2·54, s, 2′-Me; 2·29, s, NMe_2.

N,N-*Dimethyl-2-(4′-methyl-6′-phenoxypyrimidin-2′-ylthio)ethylamine* (*6g*)

2,4-Dichloro-6-methylpyrimidine[14] (2·09 g), sodium phenoxide (1·42 g) and ethanol (12 ml) were stirred at 5° for 20 h. The residue from evaporation was dissolved in water (20 ml) and ether-extracted. Removal of the ether and trituration with light petroleum left 2-chloro-4-methyl-6-phenoxypyrimidine (6f) (76%), m.p. 78–80° (from light petroleum) (cf.[15] 77–79° for material made differently) (Found: C, 59·8; H, 4·1; Cl, 15·8; N, 12·9. Calc. for $C_{11}H_9ClN_2O$: C, 59·9; H, 4·1; Cl, 16·1; N, 12·7%). The chloropyrimidine was converted, as for the above isomer (6e), into the base (6g) (61%), characterized as the *dihydrobromide monohydrate*, m.p. 205–210° (from ethanol) (Found: C, 38·3; H, 4·6; N, 9·1. $C_{15}H_{21}Br_2N_3OS.H_2O$ requires C, 38·4; H, 4·9; N, 9·0%). N.m.r. (D_2O) 7·43, m, Ph; 6·99, s, H5′; 3·55, t, H2; 3·21, t, H1; 2·99, s, 4′-Me; 2·64, s, NMe_2.

2-(Biphenyl-4′-ylthio)-N,N-*dimethylethylamine* (*9f*) *and*
3-(Biphenyl-4′-ylthio)-N,N-*dimethylpropylamine* (*9g*)

Biphenyl-4-thiol[16–18] (9e) (0·58 g) was dissolved in water (10 ml) by the addition of a minimal volume of 2 M sodium hydroxide. To this solution was added 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·40 g) or 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·45 g) and the resulting mixture was adjusted to pH 9–10 with 2 M sodium hydroxide. After stirring at 50–60° for 20 min, the cooled reaction mixture was made alkaline (pH 12–13) and extracted with ether. Evaporation of the dehydrated extract gave the *base* (9f) (35%), m.p. 69–70° (from light petroleum) (Found: C, 74·9; H, 7·4; S, 12·4. $C_{16}H_{19}NS$ requires C, 74·7; H, 7·4; S, 12·4%) [n.m.r. ($CDCl_3$) 7·46, m, aromatics; 3·05, t, H2; 2·63, t, H1; 2·29, s, NMe_2] or the *base* (9g) (15%), m.p. 74–76° (Found: N, 5·1. $C_{16}H_{21}NS$ requires N, 5·2%) [n.m.r. ($CDCl_3$) 7·47, m, aromatics; 3·00, t, H3; 2·40, t, H1; 2·22, s, NMe_2; 1·86, q, H2], respectively.

2-(Biphenyl-4′-yloxy)-N,N-*dimethylethylamine* (*9i*)

2-Chloro-*N,N*-dimethylethylamine hydrochloride (8·0 g), 2·5 M sodium hydroxide (25 ml) and toluene (75 ml) were shaken for 30 min. The toluene layer was separated, dehydrated over anhydrous sodium sulfate and then added to a mixture of biphenyl-4-ol (8·5 g), finely ground sodium hydroxide (2·1 g) and toluene (100 ml). The whole was fitted with a Dean and Stark separator and boiled for 24 h. The cooled solution was filtered and evaporated to give an oil (*c.* 7·7 g) which was mixed with 10% ethanolic hydrogen bromide in slight excess to give product (9i) as *hydrobromide* (75%) (cf. 39% as hydrochloride[19]), m.p. 183–185° (from propan-2-ol) (Found: C, 59·7; H, 6·2; N, 4·5. $C_{16}H_{20}BrNO$ requires C, 59·6; H, 6·3; N, 4·4%). N.m.r. (hydrobromide in $CDCl_3$) 7·49, m, aromatics; 4·54, t, H2; 3·60, t, H1; 2·97, s, NMe_2.

N-(*2′-Dimethylaminoethyl*)*biphenyl-4-amine* (*9k*)

2-Chloro-*N,N*-dimethylethylamine hydrochloride (14·4 g) in water (25 ml) was added to a stirred solution of biphenyl-4-amine (9j) (17·0 g) in ethanol (150 ml) at 70°. Heating and stirring were maintained while sodium hydrogen carbonate (20 g) in water (150 ml) was added dropwise over

3 h and then for a further 3 h. The excess of ethanol was evaporated and the remaining solution was adjusted to pH 13 prior to extraction with ether. Evaporation of the dehydrated extract gave an oil part of which was treated with ethanolic hydrogen bromide to give the product (9k) as *hydrobromide*, m.p. 162–165° (from propan-2-ol) (Found, for material equilibrated in air: C, 58·7; H, 6·6; N, 8·5. $C_{16}H_{21}BrN_2.0{\cdot}25H_2O$ requires C, 59·0; H, 6·6; N, 8·6%) and part of which was converted into the hydrochloride, m.p. 182–184° (lit.[20] 180° for a dihydrochloride) (Found, for material equilibrated in air: C, 66·5; H, 7·8; Cl, 12·8; N, 9·4. Calc. for $C_{16}H_{21}ClN_2.0{\cdot}75$ H_2O: C, 66·2; H, 7·8; Cl, 12·2; N, 9·4%). N.m.r. (base in $CDCl_3$) 7·36, m, aromatics; 3·06, q, H1′; 2·42, t, H2′; 2·15, s, NMe_2.

2-(Biphenyl-2′-yloxy)-N,N-dimethylethylamine (9n)

As for the isomer (9i) above, biphenyl-2-ol (9l) and 2-chloro-*N,N*-dimethylethylamine gave the product (9m), characterized as the hydrochloride (80%), m.p. 139–140° (from ethyl acetate) (cf.[19] 120°) (Found: C, 68·4; H, 7·2; N, 5·2. Calc. for $C_{16}H_{20}ClNO$: C, 69·1; H, 7·2; N, 5·0%). N.m.r. (D_2O+DCl) 7·43, m, aromatics; 4·23, s, br, H2; 3·42, s, br, H1; 2·70, s, NMe_2.

N-(2′-Dimethylaminoethyl)biphenyl-2-amine (9o)

As for the isomer (9k), biphenyl-4-amine (9m) and 2-chloro-*N,N*-dimethylethylamine gave the product (9o), characterized as its *hydrobromide* (36%), m.p. 129–130° (from ethanolic ethyl acetate) (Found: C, 60·1; H, 6·8; N, 8·7. $C_{16}H_{21}BrN_2$ requires C, 59·8; H, 6·6; N, 8·7%). N.m.r. (base in $CDCl_3$) 7·41, m, aromatics; 3·14, q, H1′; 2·44, t, H2′; 2·15, s, NMe_2.

2-(p-Benzylphenoxy)-N,N-dimethylethylamine (10b)

As for the analogue (9i), *p*-benzylphenol (10a) and 2-chloro-*N,N*-dimethylethylamine gave the product (10b) which was dissolved in ether and treated with hydrogen chloride to give the *hydrochloride* (52%), m.p. 178–179° (from propan-2-ol) (Found, for material equilibrated in air: C, 69·1; H, 7·6; N, 4·6. $C_{17}H_{21}ClNO.0{\cdot}25H_2O$ requires C, 69·1; H, 7·4; N, 4·7%). N.m.r. [$(CD_3)_2SO$] 7·10, m, aromatics; 4·31, t, H2; 3·88, s, $PhCH_2$; 3·52, t, H1; 2·50, s, br, NMe_2.

Activities

When tested at 0·5 mM concentration for amplification of phleomycin-G *in vitro*,[23] compound (9i) showed three-star activity; compounds (1b), (3a–c), (5b), (6b), (6c), (6e), (9k) and (10b) showed two-star activities; compounds (3e), (3f), (3h), (6g), (8b), (9n) and (9o) showed one-star activities; compounds (1f–h) and (9f) showed intrinsic antibacterial activities which precluded evaluation; and compound (9g) proved inactive.

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