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Heterocyclic Amplifiers of Phleomycin. IV* Pyrimidinylpurines, Phenylpyrimidines and Related Systems with Basic Side Chains

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Abstract

Syntheses of 4,5,6-triamino-2,4′-bipyrimidines and subsequent conversions into 6-amino-2-pyrimidinylpurine-8-thiones, and their *S*-dimethylaminoethyl derivatives, are described; routes to a series of cyclohexyl- and piperidino-pyrimidines bearing a sulfur-linked side chain, as well as to phenyl- and methyl-pyrimidines bearing two such side chains, are also described. As amplifiers of phleomycin in a bacterial screen, the above purines proved poor, the cyclohexyl- and piperidino-pyrimidines showed medium activities, and the phenylpyrimidines with two side chains (but not the analogous methylpyrimidines) exhibited very high activities.

When fitted with appropriate basic side chains, unfused heterobicyclic systems such as the bipyrimidines have shown consistently good activities as amplifiers of phleomycin in its role as an antibacterial or antitumour agent.[1–4] It was observed recently that the annelation of an imidazole ring to one pyrimidine ring in such a bipyrimidine (to give the corresponding pyrimidinylpurine) had little effect on activity,[5] whereas the replacement of one pyrimidine ring by a thiophen or benzene ring (to give a thienyl- or phenyl-pyrimidine) enhanced activity markedly.[3,5] Lest the disappointing result on annelation might have been due simply to inappropriate positioning of the side chain, we have now prepared several analogues with side chains at the 8-position. We have also made appropriate cyclohexyl- and piperidino-pyrimidines to see whether the flat nature of the thiophene and phenyl rings is essential to the high activities shown by thienyl- and phenyl-pyrimidines. In addition, we have followed an earlier lead in a bipyrimidine system,[1] by synthesizing several analogues, each

* Part III, *Aust. J. Chem.*, 1984, **37**, 1057.

[1] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.
[2] Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1982, **35**, 1203; 1983, **36**, 1469.
[3] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1982, **35**, 1209.
[4] Brown, D. J., and Grigg, G. W., *Med. Res. Rev.*, 1982, **2**, 193.
[5] Brown, D. J., Cowden, W. B., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 155.

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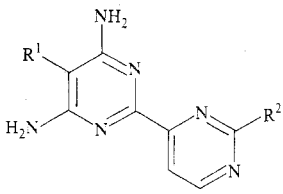
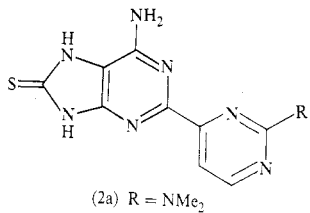
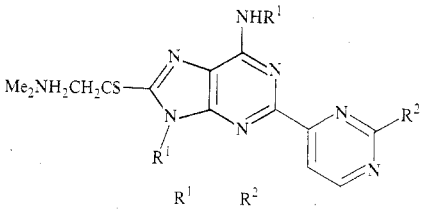


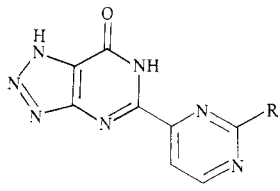
	R^1	R^2
(1a)	NO	NMe_2
(1b)	NO	OMe
(1c)	NH_2	NMe_2
(1d)	NH_2	OMe



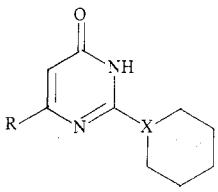
(2a) R = NMe_2
(2b) R = OMe



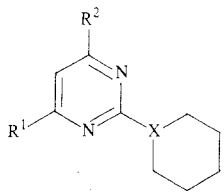
	R^1	R^2
(3a)	H	NMe_2
(3b)	H	OMe
(3c)	Ac	NMe_2



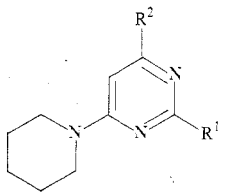
(4a) R = NMe_2
(4b) R = OMe



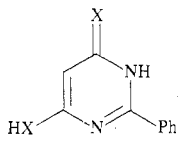
	R	X
(5a)	Me	CH
(5b)	OH	CH
(5c)	Me	N



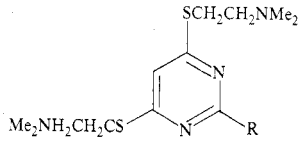
	R^1	R^2	X
(6a)	Me	Cl	CH
(6b)	Me	$SCH_2CH_2NMe_2$	CH
(6c)	Cl	Cl	CH
(6d)	$SCH_2CH_2NMe_2$	$SCH_2CH_2NMe_2$	CH
(6e)	Me	Cl	N
(6f)	Me	$SCH_2CH_2NMe_2$	N



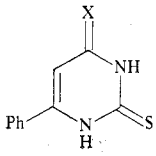
	R^1	R^2
(7a)	Me	Cl
(7b)	Cl	Me
(7c)	Me	$SCH_2CH_2NMe_2$
(7d)	$SCH_2CH_2NMe_2$	Me



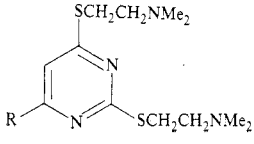
(8a) X = O
(8b) X = S



(9a) R = Ph
(9b) R = Me



(10a) X = O
(10b) X = S



(11a) R = Ph
(11b) R = Me

bearing two sulfur-linked basic side chains, to see what effect this had on activity in the present context.

Syntheses

Condensation of α-hydroxyiminomalononitrile with 2-dimethylamino- and 2-methoxy-pyrimidine-4-carboxamidinium chloride[5] gave 2′-dimethylamino-5-nitroso-2,4′-bipyrimidine-4,6-diamine (1a) and its 2′-methoxy analogue (1b), respectively. The first of these (1a) underwent dithionite reduction in aqueous alkali to afford 2′-dimethylamino-2,4′-bipyrimidine-4,5,6-triamine (1c) but the second (1b) was better so reduced in pyridine to give the 2′-methoxy analogue (1d). Fusion of the dimethylaminotriamine (1c) with thiourea at 220° gave 6-amino-2-(2′-dimethylaminopyrimidin-4′-yl)purine-8(7*H*)-thione (2a) which underwent *S*-alkylation by 2-chloro-*N*,*N*-dimethylethylamine to give 8-(2″-dimethylaminoethyl)thio-2-(2′-dimethylaminopyrimidin-4′-yl)purin-6-amine (3a); the other intermediate triamine (1d) was converted into the thione (2b) by boiling with carbon disulfide in pyridine and subsequent *S*-alkylation gave the methoxy purinamine (3b). Treatment of the product (3a) with acetic anhydride gave a single diacetyl derivative, formulated as the 9-acetyl compound (3c) rather than its 7-acetyl isomer on steric grounds, although either is consistent with the ^{1}H n.m.r. spectrum. In an attempt to prepare analogues in the '8-azapurine' series, 5,6-diamino-2′-dimethylamino- and 5,6-diamino-2′-methoxy-2,4′-bipyrimidin-4(3*H*)-one[5] were treated with nitrous acid to afford 5-(2′-dimethylaminopyrimidin-4′-yl)-(1*H*)-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (4a) and its 2′-methoxy analogue (4b), respectively. However, the attachment of appropriate side chains was precluded because both compounds failed to undergo either chlorination or thiation satisfactorily at the 7-position: the use of a variety of reagents and conditions resulted either in the recovery of substrate or (usually) in the production of black intractable tarry material. Although a few examples of both chlorination and thiation of simple '8-azapurines' are known,[6] additional electron-withdrawal by the conjugated pyrimidinyl substituent in the present substrates probably results in fission of the five-membered ring to exceedingly reactive diaza or triaza species under the acidic conditions pertaining, and hence to the formation of tars.

Ethyl acetoacetate condensed with cyclohexanecarboxamidine in ethanolic sodium ethoxide to give 2-cyclohexyl-6-methylpyrimidin-4(3*H*)-one (5a) which was converted by phosphoryl chloride into the 4-chloro analogue (6a) and thence by 2-dimethylaminoethanethiol into the thioether (6b). A similar condensation of diethyl malonate with cyclohexanecarboxamidine gave the hydroxypyrimidinone (5b) which was converted sequentially into the dichloropyrimidine (6c) and the bisthioether (6d). Likewise, the condensation of ethyl acetoacetate with piperidine-1-carboxamidine furnished a convenient new synthesis of 6-methyl-2-piperidinopyrimidin-4(3*H*)-one (5c) which was converted into its chloro analogue (6e) by phosphoryl chloride and thence into the required thioether (6f). Two isomeric thioethers were made also: monopiperidinolysis of 4,6-dichloro-2-methyl- and 2,4-dichloro-6-methyl-pyrimidine gave 4-chloro-2-methyl-6-piperidinopyrimidine (7a) and its isomer (7b),[7] each of which underwent displacement of its remaining chloro substituent by 2-dimethylaminoethanethiol to afford the potential amplifiers (7c) and (7d).

[6] Albert, A., *J. Chem. Soc. C*, 1968, 2076; 1969, 152; Albert A., and Tratt, K., *J. Chem. Soc. C*, 1968, 344.

[7] Westphal, K., U.S. Pat. 2,219,858 (1941) (*Chem. Abstr.*, 1941, **35**, 1805).

The phenylpyrimidines with two sulfur-linked side chains were made by *S*-alkylation. Thus treatment of 6-hydroxy-2-phenylpyrimidin-4(3*H*)-one[8] (8a) with phosphorus pentasulfide in pyridine gave the dithio analogue (8b) which reacted with 2-chloro-*N*,*N*-dimethylethylamine to afford the bisthioether (9a); a similar thiation of 6-phenyl-2-thiouracil[9] (10a), by use of pyridine instead of tetralin[10] as solvent, gave an improved yield of the phenyldithiouracil (10b) which underwent di-*S*-alkylation to give the bisalkylthio derivative (11a). In contrast, the methylpyrimidines with two side chains were made by displacement of chloro substituents: treatment of 4,6-dichloro-2-methylpyrimidine[11] and 2,4-dichloro-6-methylpyrimidine[12] with 2-dimethylaminoethanethiol gave the bisalkylthio derivatives (9b) and (11b), respectively.

Biological Activities

Relocation of the basic side chain from the 6- to the 8-position in the pyrimidinylpurines had a mildly deleterious effect: thus the 8-thioether (3a) showed (Table 1) a decrease in activity from 3- to 1-star compared with the analogous 6-thioether;[5] the other 8-thioether (3b) showed a marginal improvement from 1- to 2-star activity compared with its 6-analogue, probably on account of the additional change from the nitrogen- to a more desirable sulfur-linkage in the side chain.[1,5]

Table 1. Activities as amplifiers of phleomycin

Measured at 2 mM; for details see ref. 1

Compound	Activity	Compound	Activity	Compound	Activity
(3a)	*	(6d)	***	(9a)	*****[B]
(3b)	**	(6f)	**[B]	(9b)	***
(3c)	[A]	(7c)	***	(11a)	*****[B]
(6b)	***	(7d)	**	(11b)	**

[A] Solubility precluded measurement.
[B] At 1 mM; intrinsic antibacterial activity precluded measurement at 2 mM.

Replacement of the flat aromatic ring in phenyl-[5] and thienyl-pyrimidines[3] by a non-flat carbocyclic or heterocyclic ring, to give the cyclohexylpyrimidine (6b) or the piperidinopyrimidines (6f), (7c) and (7d), resulted in a marked decrease from 4- or 5-star[5] to 2- or 3-star activity.

The insertion of a second basic side chain at the expense of a methyl group in the cyclohexylpyrimidine (6b), to give the bisthioether (6d), resulted in maintenance of 3-star activity; the same was true of the 4,6-bisthioether (9a) in comparison with its 4-methyl analogue,[5] both of which showed 5-star activity. Even better, the 2,4-bisthioether (11a) showed 5-star activity, whereas both its 2-methyl and 4-methyl analogue[5] had but 4-star activity. However, the insertion of a second side chain at

[8] Hendry, J. A., and Homer, R. F., *J. Chem. Soc.*, 1952, 328.
[9] Johnson, T. B., and Hemingway, E. H., *J. Am. Chem. Soc.*, 1915, **37**, 378; Anderson, G. W., Halverstadt, I. F., Miller, W. H., and Roblin, R. O., *J. Am. Chem. Soc.*, 1945, **67**, 2197.
[10] Elion, G. B., and Hitchings, G. H., *J. Am. Chem. Soc.*, 1947, **69**, 2138.
[11] Boarland, M. P. V., and McOmie, J. F. W., *J. Chem. Soc.*, 1952, 3722.
[12] Matsukawa, T., and Ohta, B., *Yakugaku Zasshi*, 1950, **70**, 134.

the expense of a phenyl substituent did not compensate for loss of the latter, as indicated in the respective 3- and 2-star activity of the phenyl-free bisthioethers (9b) and (11b). Thus the attachment of a second sulfur-linked side chain, at the expense of an *inessential* part of an amplifier, certainly has no untoward effect on activity; indeed it may even improve activity and offer certain preparative and solubility advantages in some cases.

Experimental

Analyses were done by the Australian National University Analytical Services Unit. The n.m.r. spectra were measured at 90 MHz and 30°; tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulfonate was used as internal standard in the indicated solvent and chemical shifts are reported in δ.

2′-Dimethylamino-5-nitroso-2,4′-bipyrimidine-4,6-diamine (1a)

The silver salt of α-hydroxyiminomalononitrile[13] (2·2 g) was added little by little to a stirred solution of 2-dimethylaminopyrimidine-4-carboxamidinium chloride[5] (2·0 g) in methanol (100 ml) at room temperature. After the solution had been stirred for a further 60 min, silver chloride was filtered off and the filtrate was evaporated to dryness at 20–25° under reduced pressure. The residual salt was boiled under reflux in α-picoline (15 ml) for 15 min and the cooled reaction mixture was diluted with iced water. Refrigeration gave the *dimethylaminobipyrimidine* (1a) (84%), m.p. 324–326° (from 2-methoxyethanol) (Found: C, 46·3; H, 4·4; N, 43·2. $C_{10}H_{12}N_8O$ requires C, 46·2; H, 4·6; N, 43·1%). N.m.r. [$(CD_3)_2SO$] 8·50, d, H6′; 7·22, d, H5′; 3·18, s, NMe_2.

2′-Methoxy-5-nitroso-2,4′-bipyrimidine-4,6-diamine (1b)

In a similar way, 2-methoxypyrimidine-4-carboxamidinium chloride[5] (1·9 g) gave the hygroscopic *methoxybipyrimidine* (1b) (78%), m.p. 289° (dec.) (Found: C, 39·5; H, 4·0; N, 35·4. $C_9H_9N_7O_2 \cdot 1{\cdot}5H_2O$ requires C, 39·4; H, 4·4; N, 35·7%). N.m.r. [$(CD_3)_2SO$] 8·80, d, H6′; 7·82, d, H5′; 3·98, s, OMe.

2′-Dimethylamino-2,4′-bipyrimidine-4,5,6-triamine (1c)

The nitroso derivative (1a) (1·0 g), sodium dithionite (4·0 g) and 1 M sodium hydroxide (40 ml) were heated under reflux for 1 h. Chilling gave the *dimethylaminotriamine* (1c) (82%), m.p. 269–270° (from ethanol) (Found: C, 48·8; H, 5·9; N, 45·5. $C_{10}H_{14}N_8$ requires C, 48·8; H, 5·7; N, 45·5%) N.m.r. [$(CD_3)_2SO$] 8·32, d, H6′; 7·22, d, H5′; 5·74, s, 4+6-NH_2; 4·23, s, 5-NH_2; 3·36, s, NMe_2.

2′-Methoxy-2,4′-bipyrimidine-4,5,6-triamine (1d)

The nitroso compound (1b) was reduced similarly, but in pyridine (40 ml) with heating for 6 h. The cooled solution was filtered from inorganic matter and subsequent evaporation under reduced pressure gave the *methoxy triamine* (1d) (85%), m.p. 232–233° (from ethanol) (Found: C, 46·4; H, 4·9; N, 42·0. $C_9H_{11}N_7O$ requires C, 46·3; H, 4·8; N, 42·0%). N.m.r. [$(CD_3)_2SO$] 8·56, d, H6′; 7·73, d, H5′; 5·81, s, 4+6-NH_2; 4·36, s, 5-NH_2; 3·94, s, OMe.

6-Amino-2-(2′-dimethylaminopyrimidin-4′-yl)purine-8(7H)-thione (2a)

The triamine (1c) (1·0 g) and thiourea (1·20 g) were ground together and then fused at 220° for 1 h. A solution of the cooled mixture in 2 M sodium hydroxide was decolorized with carbon and acidified with hydrochloric acid to give the *purinethione* (2a) (68%), m.p. 251° (dec.) (from glacial acetic acid) (Found: C, 45·9; H, 4·3; N, 38·7; S, 10·8. $C_{11}H_{12}N_8S$ requires C, 45·8; H, 4·2; N, 38·9; S, 11·1%). N.m.r. [$(CD_3)_2SO$] 8·53, d, H6′; 7·36, d, H5′; 3·28, s, NMe_2.

[13] Longo, G., *Gazz. Chim. Ital.*, 1931, **61**, 575.

6-Amino-2-(2′-methoxypyrimidin-4′-yl)purine-8(7H)-thione (2b)

The triamine (1d) (1·0 g), carbon disulfide (1·5 g), solid sodium hydroxide (0·20 g) and pyridine (20 ml) were heated under reflux for 1 h. The cooled mixture was diluted with 1·25 M hydrochloric acid. The resulting solid was decolorized as above to give the *thione* (2b) (71%), m.p. 230° (dec.) (from glacial acetic acid) (Found: C, 43·9; H, 3·4; N, 35·3. $C_{10}H_9N_7OS$ requires C, 43·6; H, 3·3; N, 35·6%). N.m.r. [$(CD_3)_2SO$] 8·72, d, H6′; 7·83, d, H5′; 7·42, br, NH_2; 3·98, s, OMe.

8-(2″-Dimethylaminoethyl)thio-2-(2′-dimethylaminopyrimidin-4′-yl)purin-6-amine (3a)

2-Chloro-*N*,*N*-dimethylethylamine hydrochloride (0·8 g) was added over 10 min to a stirred solution of the purinethione (2a) (1·0 g) in 2 M sodium hydroxide (20 ml) at room temperature. Stirring was continued for a further 2 h and the alkaline solution was then adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, dehydration of the extract, and evaporation gave the *purinamine* (3a) (61%), m.p. 236° (from ethyl acetate) (Found: C, 49·9; H, 6·0; N, 35·0. $C_{15}H_{21}N_9S$ requires C, 50·1; H, 5·9; N, 35·1%). N.m.r. ($CDCl_3$) 8·46, d, H6′; 7·48, d, H5′; 5·59, br, NH_2; 3·29, s, 2′-NMe_2; 3·11, t, H1″; 2·87, t, H2″; 2·45, s, 2″-NMe_2.

8-(2″-Dimethylaminoethyl)thio-2-(2′-methoxypyrimidin-4′-yl)purin-6-amine (3b)

In a similar way, apart from stirring at 60° for only 30 min, the purinethione (2b) was converted into the *purinamine* (3b) (54%), m.p. 213° (from ethanol) (Found: C, 48·4; H, 5·2; N, 32·2. $C_{14}H_{18}N_8OS$ requires C, 48·5; H, 5·2; N, 32·4%). N.m.r. [$(CD_3)_2SO$] 8·69, d, H6′; 7·88, d, H5′; 7·09, br, NH_2; 3·99, s, OMe; 3·43, t, H2″; 2·68, t, H2″; 2·25, s, NMe_2.

N-[*9-Acetyl-8-(2″-dimethylaminoethyl)thio-2-(2′-dimethylaminopyrimidin-4′-yl)purin-6-yl*]*acetamide (3c)*

The purinamine (3a) (0·3 g) and acetic anhydride (5·0 ml) were heated under reflux for 5 h. The excess of anhydride was distilled off under reduced pressure to leave the *diacetyl* derivative (3c) (62%), m.p. 216° (from ethanol) (Found: C, 51·1; H, 5·8; N, 28·5. $C_{19}H_{35}N_9O_2S$ requires C, 51·4; H, 5·7; N, 28·4%). N.m.r. ($CDCl_3$) 8·50, d, H6′; 8·36, br, NH; 7·45, d, H5′; 3·44, t, H1″; 3·29, s, 2′-NMe_2; 3·15, s, 9-Ac; 2·89, s, Me of NHAc; 2·74, t, H2″; 2·33, s, 2″-NMe_2.

*5-(2′-Dimethylaminopyrimidin-4′-yl)-(1H)-*v*-triazolo[4,5-*d*]pyrimidin-7(6H)-one (4a)*

Sodium nitrite (0·5 g) was added over 10 min to a stirred solution of 5,6-diamino-2′-dimethylamino-2,4′-bipyrimidin-4(3*H*)-one[5] (1·0 g) in 2 M hydrochloric acid (10 ml) at 0°. Stirring was continued at 0° for 30 min and then at 25° for 2 h, after which the *triazolopyrimidinone* (4a) (63%) was filtered off and washed with iced water. It had m.p. 304° (Found: C, 46·8; H, 4·3; N, 43·3. $C_{10}H_{10}N_8O$ requires C, 46·5; H, 3·9; N, 43·4%). N.m.r. (NaOD/D_2O) 8·34, d, H6′; 7·26, d, H5′; 3·14, s, NMe_2.

*5-(2′-Methoxypyrimidin-4′-yl)-(1H)-*v*-triazolo[4,5-*d*]pyrimidin-7(6H)-one (4b)*

In a similar way, 5,6-diamino-2′-methoxy-2,4′-bipyrimidin-4(3*H*)-one[5] gave the *triazolopyrimidinone* (4b) (54%), m.p. 308° (dec.) (Found: C, 44·3; H, 2·9; N, 39·6. $C_9H_7N_7O$ requires C, 44·1; H, 2·9; N, 40·0%). N.m.r. (NaOD/D_2O) 8·52, d, H6′; 7·75, d, H5′; 4·01, s, OMe.

2-Cyclohexyl-6-methylpyrimidin-4(3H)-one (5a)

Hydrogen chloride was bubbled into a mixture of commercial cyclohexanecarbonitrile (20·0 g), methanol (11·0 ml), and anhydrous ether (50 ml) maintained at *c.* 0°. After refrigeration for 12–24 h, methyl cyclohexanecarboximidate hydrochloride (31 g, m.p. *c.* 190°) was filtered off. This crude material (10·0 g) was added to ethanolic ammonia (100 ml of 15% w/v) at 0°. After refrigeration for 24 h, the ethanol was evaporated under reduced pressure and the residue was diluted with ether to assist filtration. Successive extractions of the solid with methanol left ammonium chloride and dilution of the extracts with an equal volume of ether gave *cyclohexanecarboxamidinium chloride* (9·0 g), m.p. 192–194° (from methanol/ether) (Found: C, 51·3; H, 9·3; N, 17·0. $C_7H_{15}ClN_2$ requires C, 51·7; H, 9·3; N, 17·2%).

The above amidinium chloride (1·63 g), ethyl acetoacetate (1·30 g) and ethanolic sodium ethoxide (sodium: 0·23 g; ethanol: 30 ml) were heated under reflux for 5 h. The residue from evaporation of the ethanol was diluted with water (15 ml) and then adjusted to pH 7–8 to precipitate the *cyclohexylpyrimidinone* (5a) (*c.* 90%), m.p. 195–197° (from methanol) (Found: C, 68·6; H, 8·7; N, 14·7. $C_{11}H_{16}N_2O$ requires C, 68·7; H, 8·4; N, 14·6%).

2-Cyclohexyl-6-hydroxypyrimidin-4(3H)-one (*5b*)

A similar condensation with diethyl malonate (1·60 g) gave the *pyrimidinone* (5b) (80%), m.p. 320–322° (from methanol) (Found: C, 62·0; H, 7·4; N, 14·5. $C_{10}H_{14}N_2O_2$ requires C, 61·8; H, 7·3; N, 14·4%).

4-Chloro-2-cyclohexyl-6-methylpyrimidine (*6a*)

The pyrimidinone (5a) (1·0 g) and phosphoryl chloride (25 ml) were heated under reflux for 2 h. The excess of phosphoryl chloride was distilled off under reduced pressure and the cooled residue was stirred into crushed ice. After 15 min, the solution was adjusted to pH 9 at 0° and then extracted with ether. Evaporation of the dehydrated extract gave the *chloro compound* (6a) (82%), b.p. 101–102°/60 mm (Found: C, 62·6; H, 6·9; Cl, 16·8. $C_{11}H_{15}ClN_2$ requires C, 62·7; H, 7·2; Cl, 16·8%).

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

The above chloro compound (6a) (1·0 g), 2-dimethylaminoethanethiol hydrochloride (1·0 g), sodium hydroxide (0·55 g), and ethanol (25 ml) were warmed under reflux for 2 h. The residue from evaporation was diluted with water (10 ml) and extracted with ether. The base, obtained by evaporating the dehydrated extract, was dissolved in ethanol (5 ml) and mixed with fresh 2 M ethanolic hydrogen bromide (5 ml). After being warmed briefly, refrigeration and subsequent filtration gave a solid which was dried in a vacuum and then equilibrated in air to give the *dihydrobromide* as a monohydrate (71%), m.p. 197° (Found: C, 39·0; H, 6·6; N, 9·6. $C_{15}H_{27}Br_2N_3S.H_2O$ requires C, 39·2; H, 6·4; N, 9·2%). N.m.r. (base in $CDCl_3$) 6·81, s, H5′; 3·33, t, H2; 2·62, t, H1; 2·36, s, 6′-Me; 2·31, s, NMe; 2·26, s, NMe; 1·93, m, H1″–6″.

4,6-Dichloro-2-cyclohexylpyrimidine (*6c*)

Treatment of the pyrimidinone (5b) with phosphoryl chloride, as for the chloro compound (6a), gave the *dichloropyrimidine* (6c) (84%), b.p. 100–101°/58 mm (Found: C, 51·6; H, 5·5; Cl, 30·5. $C_{10}H_{12}Cl_2N_2$ requires C, 52·0; H, 5·2; Cl, 30·7%).

2-[2′-Cyclohexyl-6′-(2″-dimethylaminoethylthio)pyrimidin-4′-ylthio]-N,N-*dimethylethylamine* (*6d*)

The dichloro compound (6c) (0·46 g), dimethylaminoethanethiol hydrochloride (0·90 g), sodium hydroxide (0·40 g) and ethanol (20 ml) were warmed under reflux for 20 h. Treatment as for the analogue (6b) gave the *dihydrobromide* as dihydrate (70%), m.p. 183–185° (Found: C, 37·8; H, 6·4; N, 9·8. $C_{18}H_{34}Br_2N_4S_2.2H_2O$ requires C, 38·2; H, 6·7; N, 9·9%). N.m.r. (base in $CDCl_3$) 6·82, s, H5′; 3·29, m, $(SCH_2)_2$; 2·59, m, $(NCH_2)_2$; 2·30, s, NMe_2; 2·25, s, NMe_2.

N,N-*Dimethyl-2-(6′-methyl-2′-piperidinopyrimidin-4′-ylthio)ethylamine* (*6f*)

Piperidine-1-carboxamidinium sulfate[14] (5·0 g), ethyl acetoacetate (2·6 g), and ethanolic sodium ethoxide (ethanol: 70 ml; sodium: 1·0 g) were treated as for the analogue (5a) to afford 6-methyl-2-piperidinopyrimidin-4(3*H*)-one (5c) (46%), m.p. 183° (cf. 185° for material prepared[15] by a less convenient route), which was converted[15] by phosphoryl chloride into 4-chloro-6-methyl-2-piperidinopyrimidine (6e) (70%), b.p. 118°/70 mm (lit.[6] 292°/760 mm) (Found: C, 56·6; H, 6·5. Calc. for

[14] Banyard, R. A. B., Casselman, A. A., Cockburn, W. F., and Brown, G. M., *Can. J. Chem.*, 1958, **36**, 1541.
[15] Hull, R., Lovell, B. J., Openshaw, H. T., Payman, L. C., and Todd, A. R., *J. Chem. Soc.*, 1946, 357.

$C_{10}H_{14}ClN_3$: C, 56·7; H, 6·7%). This chloropyrimidine (1·0 g) was converted, as for the analogue (6b), into the required *thioether* (6f) which was isolated as its hydrated *dihydrobromide* (76%), m.p. 235–238° (Found: C, 34·5; H, 6·2; N, 11·3. $C_{14}H_{26}Br_2N_4S.2·5H_2O$ requires C, 34·5; H, 6·4; N, 11·5%). N.m.r. (D_2O) 6·68, s, H5′; 3·84, m, H2″,6″; 3·58, t, H2; 3·13, t, H1; 2·97, s, NMe_2; 2·41, s, 6′-Me; 1·74, m, H3″–5″.

4-Chloro-2-methyl-6-piperidinopyrimidine (*7a*)

Piperidine (6·0 g) was added dropwise over 30 min to a stirred solution of 4,6-dichloro-2-methylpyrimidine[11] (5·0 g) in ethanol (30 ml) at 20–25°. After the solution was stirred for a further 5 h, the residue from evaporation under reduced pressure was extracted with ether. Removal of the ether left the *piperidinopyrimidine* (7a) (84%), m.p. 60–62° (from light petroleum) (Found: C, 57·1; H, 6·9; Cl, 16·7; N, 19·5. $C_{10}H_{14}ClN_3$ requires C, 56·7; H, 6·7; Cl, 16·7; N, 19·8%).

N,N-*Dimethyl-2-(2′-methyl-6′-piperidinopyrimidin-4′-ylthio)ethylamine* (*7c*)

As for the isomer (6f), the chloro intermediate (7a) was converted into the thioether (7c), purified as its *dihydrobromide* (75%), m.p. 255–257° (from ethanol) (Found: C, 37·8; H, 6·0; S, 7·3. $C_{14}H_{26}Br_2N_4S$ requires C, 38·0; H, 5·9; S, 7·3%). N.m.r. (D_2O) 6·76, s, H5′; 3·83, m, H2″,6″; 3·58, m, H2; 2·99, s, NMe_2; 2·96, m, H1; 2·53, s, 2′-Me; 1·72, m, H3″–5″.

N,N-*Dimethyl-2-(4′-methyl-6′-piperidinopyrimidin-2′-ylthio)ethylamine* (*7d*)

2,4-Dichloro-6-methylpyrimidine[12] was converted into 2-chloro-4-methyl-6-piperidinopyrimidine (7b) by the procedure used to make its isomer (7a): the hygroscopic product (7b) (47%) had m.p. 64–66° (from light petroleum) (lit.[7] gave no m.p.) and showed a single spot on t.l.c. and a single set of peaks in its n.m.r. spectrum (Found: C, 55·8; H, 6·6; Cl, 16·1; N, 19·2. Calc. for $C_{10}H_{14}ClN_2.0·25H_2O$: C, 55·6; H, 6·7; Cl, 16·4; N, 19·4%).

The above chloro compound (7b) was converted, as for the isomer (7c), into the thioether (7d), isolated as the dihydrate of its *dihydrobromide*, m.p. 155–158° (from ethanol) (Found: C, 35·3; H, 5·9; N, 11·7. $C_{14}H_{26}Br_2N_4S.2H_2O$ requires C, 35·2; H, 6·3; N, 11·7%). N.m.r. (D_2O) 6·61, s, H5′; 3·64, m, H1,2,2″,6″; 3·00, s, NMe_2; 2·36, s, 4′-Me; 1·74, m, H3″–5″.

*6-Mercapto-2-phenylpyrimidine-4(3*H*)-thione* (*8b*)

6-Hydroxy-2-phenylpyrimidin-4(3*H*)-one[8] (5·0 g), phosphorus pentasulfide (25·0 g), and pyridine (500 ml) were boiled under reflux for 3 h. The residue from evaporation of the pyridine under reduced pressure was dissolved in 2 M sodium hydroxide (200 ml) at *c.* 25° and, after treatment with carbon, the solution was acidified to give the *mercaptopyrimidinethione* (8b) (82%), m.p. 240–244° (from ethanol) (Found: C, 54·7; H, 3·9; N, 13·0. $C_{10}H_8N_2S_2$ requires C, 54·5; H, 3·7; N, 12·7%).

2-[6′-(2″-Dimethylaminoethylthio)-2′-phenylpyrimidin-4′-ylthio]-N,N-*dimethylethylamine* (*9a*)

The above intermediate (8b) (0·44 g) was dissolved in 1 M sodium hydroxide (*c.* 8 ml) and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0·29 g) was added prior to warming at 80° for 2 h. The cooled mixture was adjusted to pH 13 if necessary and then extracted with ether. Evaporation of the dehydrated extract gave the base (9a) (*c.* 0·38 g) which was dissolved in ethanol (5 ml) and mixed with freshly prepared 1 M ethanolic hydrogen bromide (2·5 ml). After brief warming, the solution was set aside for 12 h to give the *dihydrobromide* (45%), m.p. 235° (from ethanol) (Found: C, 41·2; H, 5·4; N, 10·8; S, 12·1. $C_{18}H_{28}Br_2N_4S_2$ requires C, 41·2; H, 5·4; N, 10·7; S, 12·2%). N.m.r. (D_2O) 8·08, m, H2‴,6‴; 7·68, m, H3‴–5‴; 7·34, s, H5′; 3·64, m, H1,1″,2,2″; 2·99, m, $(NMe_2)_2$.

*6-Phenylpyrimidine-2,4(1*H*,3*H*)-dithione* (*10b*)

2-Mercapto-6-phenylpyrimidin-4(3*H*)-one[9] (10a) (10·0 g), phosphorus pentasulfide (30·0 g), and pyridine (400 ml) were stirred under reflux for 3 h and worked up, as for the isomer (8b), to give the dithione (10b) (84%), m.p. 270° (lit.[10] 73%, m.p. 268°).

2-[4′-(2″-Dimethylaminoethylthio)-6′-phenylpyrimidin-2′-ylthio]-N,N-dimethylethylamine (11a)

The dithione (10b) was converted, as for the isomeric product (9a) but at 25°, into the base (11a) which was characterized as its *dihydrobromide* (61%), m.p. 258–260° (from ethanol) (Found: C, 40·9; H, 5·2; N, 10·4. $C_{18}H_{28}Br_2N_4S_2$ requires C, 41·2; H, 5·4; N, 10·7%). N.m.r. (D_2O) 7·97, m, H2‴,6‴; 7·59, m, H3‴–5‴, 3·26, m, H1,1″,2,2″; 2·99, s, NMe_2; 2·96, s, NMe_2.

2-[6′-(2″-Dimethylaminoethylthio)-2′-methylpyrimidin-4′-ylthio]-N,N-dimethylethylamine (9b)

4,6-Dichloro-2-methylpyrimidine[11] was converted into the base (9b) as for the analogue (6d). Characterization as a salt was best done by treating the crude base (1·05 g) in ethanol (12 ml) with 2 M ethanolic hydrogen bromide (5 ml), warming the solution briefly, and then allowing it to stand at 5° for 12 h. This afforded the *trihydrobromide*, which on drying and subsequent equilibration in air formed the monohydrate, m.p. 210–214° (Found: C, 27·6; H, 5·3; N, 10·0. $C_{13}H_{28}Br_3N_4S_2.H_2O$ requires C, 27·8; H, 5·2; N, 10·0%). N.m.r. (D_2O) 7·39, s, H5′; 3·55, m, H1,1″,2,2″; 2·99, s, $(NMe_2)_2$; 2·61, s, 2′-Me.

2-[4′-(2″-Dimethylaminoethylthio)-6′-methylpyrimidin-2′-ylthio]-N,N-dimethylethylamine (11b)

2,4-Dichloro-6-methylpyrimidine[12] was converted as above into the base (11b) which was again characterized as the hydrate of its *trihydrobromide* (84%), m.p. 230° (from ethanol) (Found: C, 28·0; H, 5·3; N, 9·9. $C_{13}H_{28}Br_3N_4S_2.H_2O$ requires C, 27·8; H, 5·2; N, 10·0%). N.m.r. (D_2O) 7·12, s, H5′; 3·56, m, H1,1″,2,2″; 2·97, s, NMe_2; 2·95, s, NMe_2; 2·41, s, 6-Me.

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