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Heterocyclic Amplifiers of Phleomycin. I Some Pyrimidinylpurines, Pyrimidinylpteridines and Phenylpyrimidines

Desmond J. Brown, William B. Cowden, Shu-Bin Lan and Kenya Mori

John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.

Abstract

Synthetic routes are described to 5,6-diamino-2,4′-bipyrimidin-4-ones and thence to 2-(pyrimidin-4′-yl)purines and 2-(pyrimidin-4′-yl)pteridines, some of which bear a sulfur- or nitrogen-linked basic side chain; also reported are routes to a series of phenyl- and diphenyl-pyrimidines, to each of which is attached a similar sulfur-, nitrogen-, or oxygen-linked side chain. Members of all the above systems show activity as amplifiers of phleomycin in a bacterial screen but the phenylpyrimidines with a sulfur-linked side chain are especially active.

Most of the compounds,[1] which are known to enhance the activity of phleomycin[2] as an antibacterial or antineoplastic agent, fall into two categories: (i) fused heterobicycles, such as purine or its analogues, bearing a sulfur-linked amide side chain;[1,3] (ii) unfused heterobicycles, such as the bipyrimidine or thiazolylpyridine systems, bearing a sulfur- or nitrogen-linked dialkylaminoalkyl side chain.[1,4–6] We now report two developments based on the latter type: in the first, we have replaced one of the single hetero-rings by a fused heterobicyclic system to give, specifically, pyrimidinylpurines and a pyrimidinylpteridine, each equipped with an appropriate nitrogen- or sulfur-linked side chain; in the second, we have replaced one hetero-ring by an homocyclic system, as exemplified in several phenylpyrimidines, each bearing a side chain linked to the pyrimidine ring through sulfur, nitrogen or oxygen.

Syntheses

2-Dimethylaminopyrimidine-4-carbonitrile (1a) was prepared by known steps outlined in the Experimental and then treated, first with methanolic sodium methoxide and then with ammonium chloride, to give the corresponding amidinium chloride (2a). Condensation with ethyl cyanoacetate in ethanolic sodium ethoxide gave a separable mixture of the bipyrimidinone (3a) and the pyrimidinylacrylate (4). Although the first of these did undergo 5-nitrosation normally, it proved more effective to make the nitroso derivative (3b) directly, and without any byproduct, by condensing the amidine

[1] Brown, D. J., and Grigg, G. W., *Med. Res. Rev.*, 1982, **2**, 193.
[2] Takita, T., Muraoka, Y., Naketani, T., Fujii, A., Umezawa, Y., Naganawa, N., and Umezawa, H., *J. Antibiot.*, 1978, **31**, 801.
[3] Barlin, G. B., *Aust. J. Chem.*, 1982, **35**, 2299; 1983, **36**, 983.
[4] Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1982, **35**, 1203.
[5] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1982, **35**, 1209.
[6] Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1983, **36**, 1469.

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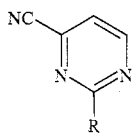
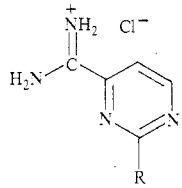
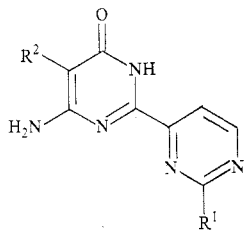


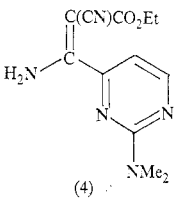
(1a) R = NMe_2
(1b) R = Cl



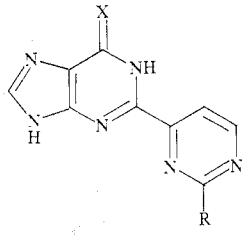
(2a) R = NMe_2
(2b) R = OMe



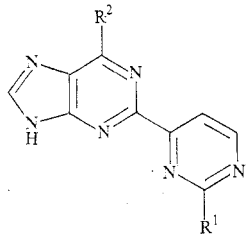
	R^1	R^2
(3a)	NMe_2	H
(3b)	NMe_2	NO
(3c)	NMe_2	NH_2
(3d)	OMe	NO
(3e)	OMe	NH_2



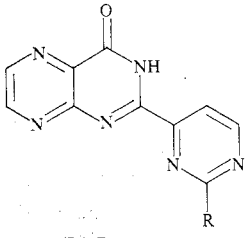
(4)



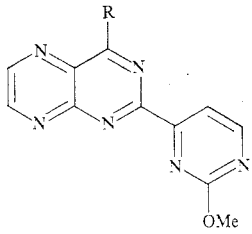
	R	X
(5a)	NMe_2	O
(5b)	NMe_2	S
(5c)	OMe	O



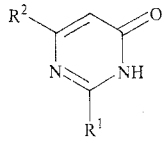
	R^1	R^2
(6a)	NMe_2	Cl
(6b)	NMe_2	SMe
(6c)	NMe_2	$SCH_2CH_2NMe_2$
(6d)	OMe	Cl
(6e)	OMe	$NHCH_2CH_2NMe_2$



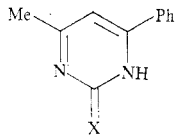
(7a) R = NMe_2
(7b) R = OMe



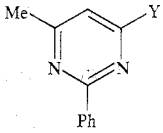
(8a) R = Cl
(8b) R = $NHCH_2CH_2NMe_2$



	R^1	R^2
(9a)	Ph	Me
(9b)	Me	Ph
(9c)	Ph	Ph



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



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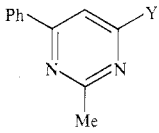

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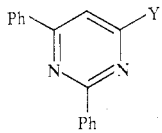

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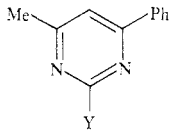

(14)

(a) Y = Cl
(b) Y = $SCH_2CH_2NMe_2$
(c) Y = $NHCH_2CH_2NMe_2$
(d) Y = $OCH_2CH_2NMe_2$

(2a) with ethyl 2-cyano-2-hydroxyiminoacetate. Dithionite reduction of the nitroso compound gave the diaminobipyrimidinone (3c) which reacted with triethyl orthoformate in acetic anhydride to give the purin-6-one (5a). This was converted by phosphoryl chloride into the chloro derivative (6a) and thence by thiourea into the purine-6-thione (5b) which underwent *S*-alkylations to give the thioethers (6b) and (6c), the latter for testing as an amplifier. The diamine (3c) was also condensed with glyoxal to yield the pteridin-4-one (7a) but attempts to convert this into the corresponding chloro derivative or thione were unsuccessful, thereby precluding the addition of an appropriate side chain.

In much the same way, 2-chloropyrimidine-4-carbonitrile (1b) was converted, by successive treatment with methanolic sodium methoxide and ammonium chloride, into the amidinium chloride (2b) which afforded sequentially the nitrosobipyrimidinone (3d), the diamine (3e), the purinone (5c), the chloro derivative (6d), and (by treatment with 2-dimethylaminoethylamine) the dimethylaminoethylaminopurine (6e) for testing; the diamine (3e) also furnished the pteridinone (7b) which proved more amenable than its analogue (7a) to reaction with phosphoryl chloride, thereby giving the chloropteridine (8a) and thence, by aminolysis, the dimethylaminoethylaminopteridine (8b) for testing.

Starting materials for the required phenylpyrimidine amplifiers were already known but, in the main, preparative details were lacking or inadequate. Accordingly, common procedures were developed for primary synthesis of the pyrimidin-4-ones (9a–c) [that for the pyrimidin-2-one (10a) was already adequate[7]] and for their conversion, by means of phosphoryl chloride containing a little phosphorus pentachloride, into the corresponding chloropyrimidines (11a), (12a), (13a), (14a). These methods are described briefly in the Experimental section, along with a logical primary synthesis of the pyrimidine-2-thione (10b): yields were high throughout.

Each of the chloropyrimidines was treated with sodium 2-dimethylaminoethanethiolate to give in turn the thioethers (11b), (12b), (13b), (14b) [the last was better made by *S*-alkylation of the thione (10b) with 2-chloro-*N*,*N*-dimethylethylamine]; with neat 2-dimethylaminoethylamine to give the pyrimidinamines (11c), (12c), (13c), (14c); or with 2-dimethylaminoethanol in the presence of potassium t-butoxide to give the ethers (11d), (12d), (13d), (14d). In most cases, the above dimethylaminoethyl derivatives were characterized and tested as their dihydrochloride, dihydrobromide or hydrobromide, as convenient; several of these salts formed mono- or hemihydrates stable to prolonged drying over phosphorus pentoxide at 20° in a vacuum.

Activities as Amplifiers

The addition of a (fused) imidazole ring onto a 2,4′-bipyrimidine bearing a suitable side chain did not improve activity: thus the 2-(pyrimidin-4′-yl)purine (6c) with 3-star activity (Table 1) and its analogue (6e) with 1-star activity differed but little from comparable 2,4′-bipyrimidines[8] with 3- and 2-star activity, respectively; the effect of similarly adding a pyrazine ring remains unknown because the 2-(pyrimidin-4′-yl)pteridine (8b), so formed, proved to have intrinsic antibacterial activity and hence could not be tested effectively in the only screen[8] available.

[7] Merkatz, A. von, *Ber. Dtsch. Chem. Ges.*, 1919, **52**, 869.

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

The second approach, viz. replacement of one of the pyrimidine rings in bipyrimidine by a benzene ring, was more immediately rewarding. Thus the 2-phenylpyrimidine with a sulfur-linked side chain at the 6-position (11b) showed 5-star activity, comparable with the best known bipyrimidine,[8] thiazolylpyridines,[4,8] or thienylpyrimidine,[5] and superior to other amplifiers in the above or related unfused heterobicyclic systems;[4–6,8,9] its 4-phenylpyrimidine isomers (12b) and (14b), with a similar side chain at the 6- or 2-position respectively, both rated 4-star activity. In each of the systems (11), (12), (14) replacement of a sulfur-linked by a nitrogen- or oxygen-linked side chain reduced activity appreciably, to 3-star or less. Of the three 2,4-diphenylpyrimidines prepared, only one could be tested successfully: that with an oxygen-linked side chain (13d) showed 3-star activity, suggesting that its sulfur-linked analogue (13b) might be a highly effective amplifier in a mammalian system in which its antibacterial activity would not preclude testing.[1]

Table 1. Activities as amplifiers of phleomycin

Measured at 2 mM; for details see ref. 8

Compound	Activity	Compound	Activity	Compound	Activity
(6c)	***	(11d)	**	(13c)	—[A]
(6e)	*	(12b)	****	(13d)	***[C]
(8b)	—[A]	(12c)	***	(14b)	****
(11b)	*****	(12d)	**	(14c)	***
(11c)	*	(13b)	—[B]	(14d)	***

[A] Intrinsic antibacterial activity precluded measurement.
[B] Solubility too low for measurement.
[C] At 0·5 mM; mildly antibacterial at 2 mM.

Experimental

Analyses were done by the Australian National University Analytical Services Unit. The n.m.r. spectra (chemical shifts in δ) were measured at 90 MHz and 30° against tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulfonate as appropriate.

2-Dimethylaminopyrimidine-4-carboxamidinium Chloride (2a)

4,4-Dimethoxybutan-2-one and urea in ethanolic hydrochloric acid gave[10] 4-methylpyrimidin-2(1*H*)-one hydrochloride (73%) which was converted[11] by nitrous acid into 2-oxo-1,2-dihydropyrimidine-4-carboxaldehyde oxime (63%) and thence by treatment[11] with phosphoryl chloride into 2-chloropyrimidine-4-carbonitrile (1b) (58%), which in turn underwent dimethylaminolysis[12] to yield 2-dimethylaminopyrimidine-4-carbonitrile (1a) (66%). This nitrile (14·8 g) and sodium methoxide (from 0·23 g of sodium) in methanol (100 ml) were stirred at 20–25° for 2 h. Then solid ammonium chloride (6·30 g) was added and stirring was continued for 2 h. The solid was filtered off and washed with a little ether prior to recrystallization from ethanol to give the *amidinium chloride* (81%), m.p. 285–286° (Found: C, 42·0; H, 6·1; Cl, 17·9; N, 34·4. $C_7H_{12}ClN_5$ requires C, 41·7; H, 6·0; Cl, 17·6; N, 34·7%).

6-Amino-2′-dimethylamino-2,4′-bipyrimidin-4(3H)-one (3a)

The above amidinium chloride (2·0 g), ethyl cyanoacetate (1·15 g) and sodium ethoxide (from 0·5 g of sodium) in ethanol (20 ml) were heated under reflux for 6 h and then evaporated under

[9] Brown, D. J., Cowden, W. B., Grigg, G. W., and Kavulak, D., *Aust. J. Chem.*, 1980, **33**, 2291.
[10] Burness, D. M., *J. Org. Chem.*, 1956, **21**, 97.
[11] Daves, G. D., O'Brien, D. E., Lewis, L. R., and Cheng, C. C., *J. Heterocycl. Chem.*, 1963, **1**, 130.
[12] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1981, **34**, 1351.

reduced pressure. Water (50 ml) was added to the residue and the resulting solid was filtered off: it proved to be *ethyl 3-amino-2-cyano-3-(2'-dimethylaminopyrimidin-4'-yl)acrylate* (4) (43%), m.p. 143–145° (from ethanol) (Found: C, 55·3; H, 5·8; N, 26·6. $C_{12}H_{15}N_5O_2$ requires C, 55·2; H, 5·8; N, 26·8%). N.m.r. ($CDCl_3$; 25°) 8·50, d, H6′; 7·42, d, H5′; 4·30, q, CH_2 of Et; 3·22, s, NMe_2; 1·36, t, Me of Et. The original aqueous filtrate was adjusted to pH 5 with acetic acid and the resulting solid recrystallized from ethanol to give the *bipyrimidinone* (3a) (42%), m.p. 305–306° (Found: C, 51·7; H, 5·3; N, 36·5. $C_{10}H_{12}N_6O$ requires C, 51·7; H, 5·2; N, 36·2%). N.m.r. ($CDCl_3$; 25°) 8·56, d, H6′; 7·24, d, H5′; 6·64, br, NH_2; 5·13, s, H5; 3·21, s, NMe_2.

6-Amino-2'-dimethylamino-5-nitroso-2,4'-bipyrimidin-4(3H)-one (3b)

(i) The foregoing bipyrimidinone (3a) (2·32 g) in 10 M hydrochloric acid (8·0 ml) was stirred at room temperature while sodium nitrite (2·1 g) was added little by little. The mixture was diluted with water (10 ml) and stirring was continued for 1 h. The solid was filtered off and washed with a little cold water: the *nitrosobipyrimidinone* (73%) had m.p. 273° (dec.) (from ethanol) (Found: C, 46·3; H, 4·3; N, 37·8. $C_{10}H_{11}N_7O_2$ requires C, 45·9; H, 4·2; N, 37·5%). N.m.r. [$(CD_3)_2SO$; 25°] 9·33, br, NH_2; 8·64, d, H6′; 7·29, d, H5′; 3·25, s, NMe_2.

(ii) 2-Dimethylaminopyrimidine-4-carboxamidinium hydrochloride (2a) (2·01 g), ethyl 2-cyano-2-hydroxyiminoacetate[13] (1·44 g) and sodium ethoxide (from 0·90 g of sodium) in ethanol (20 ml) were boiled under reflux for 20 h. After refrigeration, the solid was filtered off and washed with cold ethanol. It was then suspended in water (20 ml) and acidified to pH 5 by the addition of acetic acid to give the same nitrosobipyrimidinone (77%) as in (i) above.

5,6-Diamino-2'-dimethylamino-2,4'-bipyrimidin-4(3H)-one (3c)

The foregoing nitroso compound (13·05 g) was stirred in 1 M sodium hydroxide (200 ml) at 60° while sodium dithionite (*c.* 15–20 g) was added until the suspension become a solution and no further colour change occurred. The solution was boiled gently for 10 min, and then neutralized with acetic acid and cooled to 15° to complete precipitation of the *diaminobipyrimidinone* (82%), m.p. >220° (dec.) (from aqueous methanol) (Found: C, 43·5; H, 5·5; N, 39·4. $C_{10}H_{13}N_7O$ requires C, 43·6; H, 5·3; N, 39·6%). N.m.r. [$(CD_3)_2SO$] 8·52, d, H6′; 7·22, d, H5′; 6·70, s, NH_2; 5·91, s, NH_2; 3·22, s, NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)purin-6(1H)-one (5a)

The above diamine (2·47 g), triethyl orthoformate (18·0 ml) and acetic anhydride (12·5 ml) were boiled under reflux for 15 min and then evaporated to dryness. Recrystallization of the residue from a large volume of chloroform with subsequent concentration gave the *purinone* (93%), m.p. 348° (dec.) (Found: C, 51·5; H, 4·3; N, 38·0. $C_{11}H_{11}N_7O$ requires C, 51·4; H, 4·3; N, 38·1%).

6-Chloro-2-(2'-dimethylaminopyrimidin-4'-yl)purine (6a)

The foregoing purinone (2·57 g) and phosphoryl chloride (25 ml) were heated under reflux for 2 h. The excess of phosphoryl chloride was removed under reduced pressure and the residue was stirred thoroughly with crushed ice and then adjusted to pH 5 at 0–5°. The solid was filtered off and washed with a little water prior to drying in a vacuum; subsequent recrystallization from methoxyethanol gave the *chloropurine* (58%), m.p. 204° (Found: C, 47·7; H, 3·8; Cl, 12·7; N, 35·4. $C_{11}H_{10}ClN_7$ requires C, 47·9; H, 3·7; Cl, 12·9; N, 35·6%). N.m.r. 8·77, s, H8; 8·54, d, H6; 7·47, d, H5; 3·23, s, NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)purine-6(1H)-thione (5b)

The above chloropurine (2·76 g), thiourea (1·0 g) and ethanol (25 ml) were boiled under reflux for 30 min. After refrigeration, the solid was recrystallized from methoxyethanol to give the *purine-thione* (83%), m.p. >325° (dec.) (Found: C, 48·2; H, 4·2; N, 35·8; S, 11·9. $C_{11}H_{11}N_7S$ requires C, 48·3; H, 4·1; N, 35·9; S, 11·7%).

[13] Conrad, M., and Schultz, A., *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 735.

N,N-*Dimethyl-4-(6'-methylthiopurin-2'-yl)pyrimidin-2-amine* (*6b*)

The foregoing pyrimidinethione (2·73 g) was dissolved in 2 M sodium hydroxide (20 ml) and the solution was shaken with methyl iodide (2·0 g) for 2 h at 20–25°. The chilled mixture was adjusted to pH 5 with acetic acid and the product was filtered off. The *methylthiopurine* (74%) had m.p. 307° (from methoxyethanol) (Found: C, 49·9; H, 4·4; N, 33·7; S, 11·0. $C_{12}H_{13}N_7S$ requires C, 50·2; H, 4·6; N, 34·1; S, 11·2%).

2-[2'-(2''-Dimethylaminopyrimidin-4''-yl)purin-6'-ylthio]-N,N-*dimethylethylamine* (*6c*)

A solution of the purinethione (5b) (2·73 g) in 2 M sodium hydroxide (20 ml) was stirred while 2-chloro-*N,N*-dimethylethylammonium chloride (1·70 g) was added over 10 min. After stirring for a further 2 h, the mixture was extracted with chloroform (3 × 40 ml). The dehydrated extract was evaporated to give the *purinylthioethylamine* (57%), m.p. 206–207° (from ethyl acetate) (Found: C, 52·2; H, 5·7; N, 32·1; S, 9·4. $C_{15}H_{20}N_8S$ requires C, 52·3; H, 5·8; N, 32·5; S, 9·3%). N.m.r. ($CDCl_3$; 25°) 8·59, d, H6''; 8·02, s, H8'; 7·72, d, H5''; 3·64, t, H2; 3·28, s, 2''-NMe_2; 2·78, t, H1; 2·38, s, 1-NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)pteridin-4(3H)-one (*7a*)

The diamine (3c) (2·47 g), aqueous glyoxal (40%; 1·5 ml) and ethanol (20 ml) were heated under reflux for 30 min. Refrigeration gave the *pteridinone* (76%), m.p. 266–267° (from dimethylformamide) (Found: C, 53·6; H, 4·1; N, 36·4. $C_{12}H_{11}N_7O$ requires C, 53·5; H, 4·1; N, 36·4%). N.m.r. ($CDCl_3$) 9·02, d, H6; 8·88, d, H7; 8·63, d, H6'; 7·75, d, H5'; 3·30, s, NMe_2.

2-Methoxypyrimidine-4-carboxamidinium Chloride (*2b*)

2-Chloropyrimidine-4-carbonitrile[12] (1b) (13·95 g) was added over 20 min to a stirred solution of sodium methoxide (from 2·5 g of sodium) in methanol (100 ml) at 0° and stirring was continued in the cold room for 12 h. Then ammonium chloride (6·0 g) was added and stirring was maintained at 20–25° for 12 h. Salt was removed from the crude product during recrystallization from propan-2-ol to give the *methoxyamidinium chloride* (86%), m.p. 210° (Found: C, 38·7; H, 4·7; Cl, 18·7; N, 29·6. $C_6H_9ClN_4O$ requires C, 38·2; H, 4·8; Cl, 18·8; N, 29·7%). N.m.r. [$(CD_3)_2SO$] 9·77, s, br, $2NH_2$; 9·04, d, H6; 7·98, d, H5; 4·06, s, Me.

6-Amino-2'-methoxy-5-nitroso-2,4'-bipyrimidin-4(3H)-one (*3d*)

The above amidinium chloride (1·90 g), ethyl 2-cyano-2-hydroxyiminoacetate[13] (1·45 g) and sodium methoxide (from 0·95 g of sodium) in methanol (20 ml) were stirred at 20° for 15 h. The solid was treated as for the analogue (3b) above to give the *methoxynitroso derivative* (82%), m.p. >240° (dec.) (from methoxyethanol) (Found: C, 43·9; H, 3·4; N, 33·7. $C_9H_8N_6O_3$ requires C, 43·6; H, 3·2; N, 33·9%).

5,6-Diamino-2'-methoxy-2,4'-bipyrimidin-4(3H)-one (*3e*)

The preceding nitroso compound (12·4 g) was reduced exactly as for analogue (3c) above. The crude product was purified by dissolution in hot aqueous ammonia and reprecipitation with acetic acid followed by appropriate washing. The *diamine* (80%) had m.p. >264° (dec.) (Found: C, 45·9; H, 4·3; N, 35·7. $C_9H_{10}N_6O_2$ requires C, 46·2; H, 4·3; N, 35·9%).

2-(2'-Methoxypyrimidin-4'-yl)purin-6(1H)-one (*5c*)

The foregoing diamine (2·34 g) was converted, as for the analogue (5a), into the *methoxypyrimidinylpurinone* (85%), m.p. >308° (dec.) (from methoxyethanol) (Found: C, 49·3; H, 3·2; N, 34·5. $C_{10}H_8N_6O_2$ requires C, 49·2; H, 3·3; N, 34·4%). N.m.r. [$(CD_3)_2SO$] 8·85, d, H6'; 8·28, s, H8; 7·93, d, H5'; 4·11, s, Me.

6-Chloro-2-(2'-methoxypyrimidin-4'-yl)purine (*6d*)

The above purinone (5c) (2·44 g) was treated with phosphoryl chloride as for the analogue (6a) to give the *chloropurine* (63%), m.p. >360° (from glacial acetic acid) (Found: C, 45·7; H, 2·9; N, 32·0. $C_{10}H_7ClN_6O$ requires C, 45·7; H, 2·7; N, 32·0%).

N-(2″-Dimethylaminoethyl)-2-(2′-methoxypyrimidin-4′-yl)purin-6-amine (6e)

The preceding chloropurine (1·0 g) and 2-dimethylaminoethylamine (5·0 ml) were boiled under reflux for 1 h. The residue, from removal of the excess of amine under reduced pressure, was added to 2 M sodium hydroxide (5·0 ml) and extracted with chloroform. Evaporation of the dried extract gave the *purinamine* (42%), m.p. 185–186° (from propan-2-ol) (Found: C, 53·8; H, 5·8; N, 35·7. $C_{14}H_{18}N_8O$ requires C, 53·5; H, 5·8; N, 35·6%).

2-(2′-Methoxypyrimidin-4′-yl)pteridin-4(3H)-one (7b)

The diamine (3e) (2·34 g), aqueous glyoxal (40%; 2·0 ml) and water (20 ml) were warmed on the water bath for 15 min. Refrigeration gave the *pteridinone* (92%), m.p. >278° (dec.) (from dimethylformamide) (Found: C, 51·4; H, 3·1; N, 32·7. $C_{11}H_8N_6O_2$ requires C, 51·6; H, 3·1; N, 32·8%). N.m.r. [$(CD_3)_2SO$] 9·08, d, H6; 8·93, d, H7; 8·92, d, H6′; 8·05, d, H5′; 4·14, s, Me.

4-Chloro-2-(2′-methoxypyrimidin-4′-yl)pteridine (8a)

The above pteridinone (1·0 g), phosphoryl chloride (50 ml) and phosphorus pentachloride (1·0 g) were boiled under reflux for 4 h. The phosphoryl chloride was distilled off under reduced pressure and the residue was stirred into crushed ice and allowed to stand at 5° for 15 h. Filtration gave the *chloropteridine* (72%), m.p. 232–233° (from methanol) (Found: C, 47·8; H, 2·6; Cl, 12·5; N, 30·6. $C_{11}H_7ClN_6O$ requires C, 48·1; H, 2·6; Cl, 12·9; N, 30·6%). N.m.r. [$(CD_3)_2SO$] 9·06, d, H6; 8·92, d, H7; 8·90, d, H6′; 8·05, d, H5′; 4·14, s, Me.

N-(2″-Dimethylaminoethyl)-2-(2′-methoxypyrimidin-4′-yl)pteridin-4-amine (8b)

The foregoing chloropteridine (1·0 g) and 2-dimethylaminoethylamine (6·0 ml) were heated under reflux for 1 h. The residue from distilling off the excess of amine under reduced pressure was diluted with 2 M sodium hydroxide and the mixture was extracted with chloroform. Evaporation of the extract gave the *pteridinamine* (34%), m.p. 158–159° (from propan-2-ol) (Found: C, 54·9; H, 5·6; N, 34·0. $C_{15}H_{18}N_8O$ requires C, 55·2; H, 5·6; N, 34·3%). N.m.r. ($CDCl_3$) 9·06, d, H6; 8·72, d, H7; 8·70, d, H6′; 8·18, d, H5′; 7·82, br, NH; 4·16, s, OMe; 3·90, q, H1″; 2·67, t, H2″; 2·17, s, NMe_2.

Preparation of the Pyrimidin-4(3H)-ones (9a–c)

Benzamidinium chloride hydrate (0·1 mol), ethyl acetoacetate (0·11 mol) and sodium ethoxide (0·15 mol) in ethanol (100 ml) were stirred and heated under reflux for 5 h. The residue from evaporation under reduced pressure was dissolved in water (100 ml) and then adjusted to pH 6. After chilling, the solid was filtered off and recrystallization from ethanol gave 6-methyl-2-phenylpyrimidin-4(3*H*)-one (9a) (81%), m.p. 218–219° (lit.[14] 216°) (Found: C, 71·2; H, 5·4; N, 14·9. Calc. for $C_{11}H_{10}N_2O$: C, 71·0; H, 5·4; N, 15·0%); acetamidinium chloride and ethyl benzoylacetate under similar conditions (apart from heating for 24 h) gave the isomeric 2-methyl-6-phenylpyrimidin-4(3*H*)-one (9b) (83%), m.p. 246–248° (lit.[14] 242°) (Found: C, 71·1; H, 5·5; N, 15·3%); and benzamidinium chloride and ethyl benzoylacetate likewise (24 h heating) gave 2,6-diphenylpyrimidin-4(3*H*)-one (9c) (70%), m.p. 286–287° (lit.[14] 289–290°) (Found: C, 77·8; H, 4·8; N, 11·6. Calc. for $C_{16}H_{12}N_2O$: C, 77·4; H, 4·9; N, 11·3%).

4-Methyl-6-phenylpyrimidine-2(1H)-thione (10b)

Benzoylacetone (8·0 g), thiourea (6·0 g), ethanol (50 ml) and concentrated hydrochloric acid (7·0 ml) were boiled gently under reflux for 24 h. The residue from evaporation under reduced pressure was added to 2 M sodium hydroxide (100 ml) and any insoluble material was removed. The filtrate was acidified to pH 6 with 5 M sulfuric acid and chilled. The solid recrystallized from ethanol to give the pyrimidinethione (80%), m.p. 200–201° (lit.[7] 199–200°) (Found: C, 59·4; H, 3·9; N, 13·8. Calc. for $C_{10}H_8N_2OS$: C, 58·8; H, 3·9; N, 13·7%).

[14] Pinner, A., *Ber. Dtsch. Chem. Ges.*, 1889, **22**, 1612.

Preparation of the Chloropyrimidines (11a), (12a), (13a), (14a)

6-Methyl-2-phenylpyrimidin-4(3*H*)-one (9a) (0·02 mol) was added to a solution of phosphorus pentachloride (4·0 g) in phosphoryl chloride (14·0 ml) and the mixture was heated under reflux for 3 h. The excess of phosphoryl chloride was removed (80°/10 mm) and the oily residue was added to crushed ice and stirred for 20 min. Extraction with ether (3 × 100 ml), evaporation of the dehydrated extract, and recrystallization from light petroleum gave 4-chloro-6-methyl-2-phenylpyrimidine (11a) (91%), m.p. 69–70° (lit.[15] 71°) (Found: C, 64·7; H, 4·4; N, 13·6. Calc. for $C_{11}H_9ClN_2$: C, 64·6; H, 4·4; N, 13·7%). Similar treatment of 2-methyl-6-phenylpyrimidin-4(3*H*)-one (9b), 2,6-diphenylpyrimidin-4(3*H*)-one (9c) and 4-methyl-6-phenylpyrimidin-2(1*H*)-one[7] (10a) gave, respectively, 4-chloro-2-methyl-6-phenylpyrimidine (12a) (87%), m.p. 56–57° (lit.[16] 58–59°) (Found: C, 64·1; H, 4·4; N, 13·8. Calc. for $C_{11}H_9ClN_2$: C, 64·6; H, 4·4; N, 13·7%); 4-chloro-2,6-diphenylpyrimidine (13a) (81%), m.p. 109° (lit.[17] 108°) (Found: Cl, 13·1; N, 10·3. Calc. for $C_{16}H_{11}ClN_2$: Cl, 13·3; N, 10·5%); and 2-chloro-4-methyl-6-phenylpyrimidine (14a) (75%), m.p. 50–51° (lit.[7] 50–51°) (Found: C, 64·8; H, 4·6; N, 13·9. Calc. for $C_9H_{11}ClN_2$: C, 64·6; H, 4·4; N, 13·7%).

The Dimethylaminoethylthiopyrimidines (11b), (12b), (13b), (14b)

4-Chloro-6-methyl-2-phenylpyrimidine (11a) (0·01 mol), 2-dimethylaminoethanethiol hydrochloride (1·45 g) and ethanol (60 ml) containing sodium hydroxide (0·85 g) were heated under reflux for 2 h. The residue from evaporation under reduced pressure was diluted with 1 M sodium hydroxide (10 ml) and then extracted with ether. The dried extract was evaporated and the resulting oil was dissolved in ethanol (10 ml) and then treated with freshly prepared 5 M ethanolic hydrogen chloride (5 ml). Brief warming and subsequent refrigeration gave N,N-*dimethyl-2-(6′-methyl-2′-phenylpyrimidin-4′-ylthio)ethylamine* (11b) as *dihydrochloride* (81%), m.p. 82–84° (Found: C, 52·2; H, 6·5; N, 12·3. $C_{15}H_{21}Cl_2N_3S$ requires C, 52·0; H, 6·1; N, 12·1%). N.m.r. (D_2O) 8·19, m, H2″,6″; 7·64, m, H3″–5″; 7·25, s, H5′; 3·58, m, H1,2; 2·93, s, NMe_2; 2·48, s, 6′-Me.

Likewise, 4-chloro-2-methyl-6-phenylpyrimidine (12a) gave N,N-*dimethyl-2-(2′-methyl-6′-phenylpyrimidin-4-ylthio)ethylamine* (12b) as *dihydrochloride* (78%), m.p. 221–223° (Found: C, 51·2; H, 6·2; N, 11·9. $C_{15}H_{21}Cl_2N_3S.0·5H_2O$ requires C, 50·7; H, 6·2; N, 11·8%) (n.m.r. in D_2O 7·96, m, H2″,6″; 7·63, m, H3″–5″,5′; 3·56, m, H1,2; 2·94, s, NMe_2; 2·68, s, 2′-Me); and 4-chloro-2,6-diphenylpyrimidine (13a) gave [with 5 M ethanolic hydrogen bromide (2·2 ml)] 2-(*2′,6′-diphenylpyrimidin-4′-ylthio*)-N,N-*dimethylethylamine* (13b) as *hydrobromide* (76%), m.p. 225–226° (Found: C, 57·3; H, 5·4; N, 10·1. $C_{20}H_{22}BrN_3S$ requires C, 57·7; H, 5·3; N, 10·1%) (n.m.r. in $CDCl_3$ 8·56, m, H2″,6″; 8·19, m, H2‴,6‴; 7·56, m, H3‴–5‴,3″–5″,5′; 3·77, t, H2; 3·36, t, H1; 2·78, s, NMe_2).

4-Methyl-6-phenylpyrimidine-2(1*H*)-thione (10b) (1·0 g) was dissolved in water (10 ml) by the addition of 2 M sodium hydroxide. Then *N*-2-chloroethyl-*N,N*-dimethylammonium chloride was added and the pH was adjusted if necessary to pH 9–10 before shaking for 1 h. Extraction with ether and evaporation of the extract gave N,N-*dimethyl-2-(4′-methyl-6′-phenylpyrimidin-2′-ylthio)-ethylamine* (14b) (61%), m.p. 85–86° (from ethanol) (Found: C, 65·9; H, 7·1; N, 15·2; S, 11·7. $C_{15}H_{19}N_3S$ requires C, 65·9; H, 7·0; N, 15·4; S, 11·7%). N.m.r. ($CDCl_3$) 8·05, m, H2″,6″; 7·47, m, H3″,4″,5″; 7·22, s, H5′; 3·37, t, H2; 2·70, t, H1; 2·49, s, 4′-Me; 2·34, s, NMe_2. The *dihydrobromide* had m.p. *c.* 246° (from ethanol) (Found: C, 41·7; H, 4·9; N, 9·6. $C_{15}H_{21}Br_2N_3S$ requires C, 41·4; H, 4·8; N, 9·7%).

The Dimethylaminoethylaminopyrimidines (11c), (12c), (13c), (14c)

4-Chloro-6-methyl-2-phenylpyrimidine (11a) (0·01 mol) and 2-dimethylaminoethylamine (10 ml) were boiled under reflux for 3 h. The excess of amine was recovered by distillation and the residue was diluted with water (8 ml). The solution was adjusted to pH 11 by 2 M sodium hydroxide and then extracted with ether. The extract was evaporated and the residue was diluted with ethanol (10 ml) to which was then added freshly prepared 5 M ethanolic hydrogen bromide (4·0 ml). After warming for a moment, refrigeration gave N-(*2′-dimethylaminoethyl*)-*6-methyl-2-phenylpyrimidin-4-amine* (11c) as *dihydrobromide* (90%), m.p. 263–265° (from ethanol) (Found: C, 43·4; H, 5·4; N, 13·3.

[15] Pinner, A., *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 2519.
[16] Streef, J. W., and Hertog, H. J. den, *Recl Trav. Chim. Pays-Bas*, 1969, **88**, 1391.
[17] Anker, R. M., and Cook, A. H., *J. Chem. Soc.*, 1941, 323.

$C_{15}H_{22}Br_2N_4$ requires C, 43·1; H, 5·3; N, 13·4%). N.m.r. (D_2O) 8·09, m, H2″,6″; 7·70, m, H3″–5″; 6·69, s, H5; 4·11, t, H1′; 3·52, t, H2′; 2·92, s, NMe_2; 2·54, s, 6-Me.

By similar procedures, 4-chloro-2-methyl-6-phenylpyrimidine (12a) gave N-(*2′-dimethylaminoethyl*)-*2-methyl-6-phenylpyrimidin-4-amine* (12c) as *dihydrobromide* (87%), m.p. 166–167° (Found: C, 42·3; H, 5·4; N, 12·9. $C_{15}H_{22}Br_2N_4.0{\cdot}5H_2O$ requires C, 42·2; H, 5·4; N, 13·1%) (n.m.r. in D_2O 7·74, m, H2″–6″; 6·92, s, H5; 4·06, t, H1′; 3·52, t, H2′; 3·03, s, NMe_2; 2·72, s, 2-Me); 4-chloro-2,6-diphenylpyrimidine (13a) gave N-(*2′-dimethylaminoethyl*)-*2,6-diphenylpyrimidin-4-amine* (13c) as *dihydrobromide* (93%), m.p. 246–247° (Found: C, 49·8; H, 5·2; N, 11·8. $C_{20}H_{24}Br_2N_4$ requires C, 50·1; H, 5·0; N, 11·7%) (n.m.r. in D_2O 8·11, m, H2″,6″,2‴,6‴; 7·75, m, H3″–5″,3‴–5‴; 7·01, s, H5; 4·16, t, H1′; 3·55, t, H2′; 2·99, s, NMe_2); and 2-chloro-4-methyl-6-phenylpyrimidine (14a) gave N-(*2′-dimethylaminoethyl*)-*4-methyl-6-phenylpyrimidin-2-amine* (14c) as *dihydrobromide* (91%), m.p. 274–275° (Found: C, 43·3; H, 5·4; N, 13·1. $C_{15}H_{22}Br_2N_4$ requires C, 43·1; H, 5·3; N, 13·4%) (n.m.r. in D_2O 8·22, m, H2″,6″; 7·69, m, H3″–5″; 7·46, s, H5; 4·09, t, H1′; 3·53, t, H2′; 2·98, s, NMe_2; 2·59, s, 4-Me).

The Dimethylaminoethoxypyrimidines (11d), (12d), (13d), (14d)

4-Chloro-6-methyl-2-phenylpyrimidine (11a) (0·01 mol) and 2-dimethylaminoethanol (20 ml) containing potassium t-butoxide (1·20 g) were heated under reflux for 90 min. The excess of amine was distilled off and the residue was mixed with 2 M sodium hydroxide (10 ml) and extracted with ether. The residue from evaporation of the extract was diluted with ethanol (20 ml) and to the solution was added fresh 5 M ethanolic hydrogen bromide (4·0 ml): after warming, chilling gave N,N-*dimethyl-2-(6′-methyl-2′-phenylpyrimidin-4′-yloxy)ethylamine* (11d) as *dihydrobromide* (94%), m.p. 110–111° (from ethanol) (Found: C, 41·6; H, 5·1; N, 9·7. $C_{15}H_{21}Br_2N_3O.H_2O$ requires C, 41·2; H, 5·3; N, 9·6%). N.m.r. (D_2O) 8·18, m, H2″,6″; 7·75, m, H3″–5″; 7·13, s, H5′; 5·04, t, H2; 3·74, t, H1; 3·03, s, NMe_2; 2·71, s, 6′-Me.

Similarly, 4-chloro-2-methyl-6-phenylpyrimidine (12a) gave N,N-*dimethyl-2-(2′-methyl-6′-phenylpyrimidin-4′-yloxy)ethylamine* (12d) as *dihydrobromide* (91%), m.p. 175–176° (Found: C, 42·8; H, 5·1; N, 9·9. $C_{15}H_{21}Br_2N_2O$ requires C, 43·0; H, 5·1; N, 10·0%) (n.m.r. in D_2O 7·83, m, H2″–6″; 7·45, s, H5′; 4·99, t, H2; 3·74, t, H1; 3·04, s, NMe_2; 2·87, s, 2′-Me); 4-chloro-2,6-diphenylpyrimidine (13a) gave *2-(2′,6′-diphenylpyrimidin-4′-yloxy)*-N,N-*dimethylethylamine* (13d) as *hydrobromide* (83%), m.p. 218–219° (Found: C, 58·7; H, 5·5; N, 10·1. $C_{20}H_{22}BrN_3O.0{\cdot}5H_2O$ requires C, 58·7; H, 5·7; N, 10·2%) (n.m.r. in $CDCl_3$ 8·53, m, H2″,6″; 8·18, m, H2‴,6‴; 7·51, m, H3″–5″,3‴–5‴; 7·15, s, H5′; 5·12, m, H2; 3·60, m, H1; 2·97, s, NMe_2); and 2-chloro-4-methyl-6-phenylpyrimidine (14a) gave N,N-*dimethyl-2-(4′-methyl-6′-phenylpyrimidin-2′-yloxy)ethylamine* (14d) as *dihydrobromide* (95%), m.p. 170–171° (Found: C, 42·2; H, 5·0; N, 9·8. $C_{15}H_{21}Br_2N_2O.0{\cdot}5H_2O$ requires C, 42·1; H, 5·2; N, 9·8%) (n.m.r. in D_2O 8·17, m, H2″,6″; 7·67, m, H3″–5″,5′; 3·72, m, H1,2; 3·04, s, NMe_2; 2·59, s, 4′-Me).

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