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Heterocyclic Amplifiers of Phleomycin. VI* Some Phenylpurines, Phenylpteridines, Phenylquinazolines and Related Compounds

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Abstract

Synthetic routes are described to a series of 2-, 6- and 8-phenylpurines, each with an appropriate S- or NH-linked side chain elsewhere in the molecule; to 2- and 4-phenylpteridines, each with a similar side chain and some with two additional *C*-methyl groups; to 2- and 4-phenylquinazolines, each equipped with an analogous side chain; and to two pyridinyl analogues of the above. Three of the above components are shown to have considerable activity as amplifiers of phleomycin-G in an *in vitro* bacterial system.

The high activities of appropriate unfused heterobicycles, e.g. *N*,*N*-dimethyl-2-[5′-(pyridin-4″-yl)-1′,3′,4′-thiadiazol-2′-ylthio]ethylamine (1), as amplifiers of a phleomycin against *in vitro* cultures of *Escherichia coli*[1] or of other phleomycins against tumours in mice,[2] initially stimulated two fundamental structural variations. The first of these, in which one heterocyclic ring was replaced by a fused heterocyclic system, proved very disappointing[3] in the *in vitro* screen but the second, in which one heterocyclic ring was replaced by an unsubstituted benzene ring, maintained high activities in both the *in vitro*[3] and subsequent *in vivo* screen.[4] In this context and in view of the high activities shown by purines, their analogues and other fused heterocyclic systems,[4,5] it seemed logical to try some such heterocyclic systems bearing a phenyl group as well as an appropriate basic side chain. Accordingly, we now report the synthesis and evaluation results of some 2-, 6- and 8-phenylpurines; 2- and 4-phenylpteridines; 2- and 4-phenylquinazolines; and 2-pyridin-4′-yl analogues in the purine and quinazoline series.

* Part V, *Aust. J. Chem.*, 1984, **37**, 2385.

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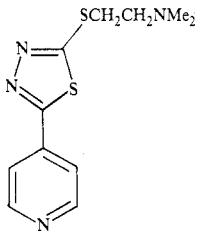

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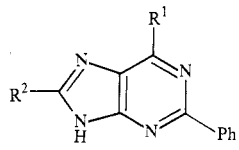
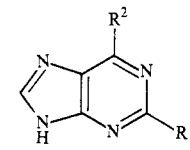
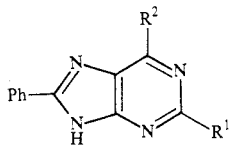


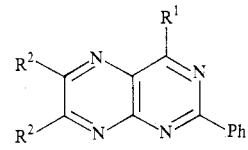
	R^1	R^2
(2a)	$SCH_2CH_2NMe_2$	H
(2b)	Cl	H
(2c)	$NHCH_2CH_2NMe_2$	H
(2d)	NH_2	$SCH_2CH_2NMe_2$



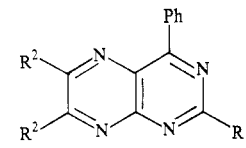
	R^1	R^2
(3a)	SMe	Ph
(3b)	pyridin-4-yl	$SCH_2CH_2NMe_2$



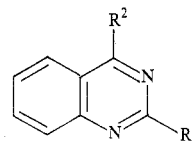
	R^1	R^2
(4a)	H	$SCH_2CH_2NMe_2$
(4b)	$SCH_2CH_2NMe_2$	H
(4c)	SMe	H
(4d)	Cl	H



	R^1	R^2
(5a)	$NHCH_2CH_2NMe_2$	H
(5b)	$NHCH_2CH_2NMe_2$	Me
(5c)	SMe	H
(5d)	SMe	Me



	R^1	R^2
(6a)	SMe	H
(6b)	SMe	Me
(6c)	Cl	Me



	R^1	R^2		R^1	R^2
(7a)	Ph	Cl	(7f)	Ph	$SCH_2CH_2CH_2NMe_2$
(7b)	Cl	Ph	(7g)	$SCH_2CH_2NMe_2$	Ph
(7c)	Ph	$NHCH_2CH_2NMe_2$	(7h)	$SCH_2CH_2CH_2NMe_2$	Ph
(7d)	$NHCH_2CH_2NMe_2$	Ph	(7i)	pyridin-4-yl	$SCH_2CH_2NMe_2$
(7e)	Ph	$SCH_2CH_2NMe_2$			

Syntheses

2-Phenylpurine-6(1*H*)-thione[6] underwent alkylation by 2-chloro-*N*,*N*-dimethylethylamine to give *N*,*N*-dimethyl-2-(2′-phenylpurine-6′-ylthio)ethylamine (2a); aminolysis of 6-chloro-2-phenylpurine[7] (2b) by 2-dimethylaminoethylamine gave the analogous purine (2c) with an NH-linked side chain. Fusion of 2-phenylpyrimidine-4,5,6-triamine[8] with thiourea afforded 6-amino-2-phenylpurine-8(7*H*)-thione which on *S*-alkylation gave the corresponding thioether (2d). 6-Phenylpurines are here represented by 2-methylthio-6-phenylpurine (3a) which was made by methylation of 4,5-diamino-6-phenylpyrimidine-2-(1*H*)-thione[9] to 2-methylthio-

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[7] Traube, W., and Herrmann, L., *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 2267.
[8] Evans, R. M., Jones, P. G., Palmer, P. J., and Stephens, F. F., *J. Chem. Soc.*, 1956, 4106.
[9] Clark, J., and Murdoch, P. N. T., *J. Chem. Soc. C*, 1969, 1883.

6-phenylpyrimidine-4,5-diamine followed by cyclization with boiling diethoxymethyl acetate. The 8-phenylpurine (4a) was prepared by alkylation of 8-phenylpurine-6(1*H*)-thione[10] but an attempt to obtain its isomer (4b) and the simple analogue (4c) by the sequence 2-chloropyrimidine-4,5-diamine[11] → 5-benzylideneamino-2-chloropyrimidin-4-amine → 2-chloro-8-phenylpurine (4d) → 8-phenylpurine-2(1*H*)-thione, followed by *S*-alkylation, failed to produce enough compound for testing (as did also another route described in the Experimental section).

2-Phenylpteridines were first approached from 6-chloro-5-nitro-2-phenylpyrimidin-4-amine[12] by aminolysis to afford 6-(2′-dimethylaminoethyl)amino-5-nitro-2-phenylpyrimidin-4-amine, reduction to the corresponding pyrimidine-4,5-diamine, and condensation with glyoxal and diacetyl to give the pteridinamines (5a) and (5b), respectively; rather similarly, 5,6-diamino-2-phenylpyrimidine-4(3*H*)-thione[12] afforded 2-phenyl-4(3*H*)-thione and its 6,7-dimethyl derivative, both of which underwent *S*-methylation to give the thioethers (5c) and (5d) as candidate amplifiers. Similar 4-phenylpteridines were made by condensing 2-methylthio-6-phenylpyrimidine-4,5-diamine (as above) with glyoxal and diacetyl to give the respective products (6a) and (6b); another approach, beginning by condensation of 2-chloro-6-phenylpyrimidine-4,5-diamine[11] with diacetyl to give the chloropteridine (6c), failed because the latter gave only intractable highly coloured materials on treatment with thiourea, sodium hydrogen sulfide, or sodium methanethiolate.

4-Chloro-2-phenyl-[13] (7a) and 2-chloro-4-phenyl-quinazoline[14] (7b) underwent aminolysis by 2-dimethylaminoethylamine to give quinazolinamines (7c), (7d); 2-phenylquinazoline-4(3*H*)-thione[15] gave the thioethers (7e) and (7f) by appropriate alkylation; and the respective isomers (7g) and (7h) were made from 4-phenylquinazoline-2(1*H*)-thione[16] in a similar way. The 2-(pyridin-4′-yl) analogue (3b) of the phenylpurine (2a) was made by condensing pyridine-4-carboxamidine[17] with ethyl 2-cyano-2-hydroxyiminoacetate[18] to give crude 6-amino-5-nitroso-2-(pyridin-4′-yl)pyrimidin-4(3*H*)-one and thence the 5,6-diamino analogue, which underwent cyclization in triethyl orthoformate: the resulting 2-(pyridin-4′-yl)purin-6(1*H*)-one was converted by phosphorus pentasulfide into the corresponding thione which gave the required thioether (3b) on alkylation.

An analogous pyridinylquinazoline was made by initial fusion of pyridine-4-carboxamidinium chloride[17] with anthranilic acid to give 2-(pyridin-4′-yl)quinazolin-4-(3*H*)-one which underwent thiation to the corresponding thione and subsequent alkylation to the thioether (7i). A similar condensation of 2-dimethylaminopyrimidine-4-carboxamidinium chloride[3] with anthranilic acid gave 2-(2′-dimethylaminopyrimidin-4′-yl)quinazolin-4(3*H*)-one and thence the corresponding thione: yields were so poor as to preclude satisfactory *S*-alkylation.

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[11] Nagal, A., Plas, H. C. van der, and Veldhuizen, A. van, *Recl. Trav. Chim. Pays-Bas*, 1975, **94**, 45.
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[18] Conrad, M., and Schulze, A., *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 735.

Biological Activities

Of the phenylpurines available for evaluation (Table 1), that with a 2-phenyl group and a 6-dimethylaminoethylthio side chain (2a) showed four-star activity although its isomer (4a) as well as the analogues (2c) and (2d) showed only two-star activities; the methylthio derivative (3a) proved virtually inactive and the pyridinyl analogue (3b) of (2a) could not be evaluated because of its intrinsic antibacterial activity. The 2-phenylpteridine bearing an NH-linked side chain at the 4-position (5a) showed only one-star activity but its 6,7-dimethyl homologue (5b) showed a significant improvement to the three-star activity range; although the related methylthiopteridines (5c), (5d), (6a) and (6b) showed minimal acivities, it is clear that the 4-dimethylaminoethylthio analogue of the active amplifier (5b) should be prepared for evaluation. The best quinazoline proved to be that with a 2-phenyl group and a sulfur-linked side chain in the 4-position (7e) (four-star activity); the isomer (7g) and its homologue (7h) showed only two-star activities, while the NH-linked analogues (7c) and (7d) showed one- and two-star activity, respectively, the related compound (7f) and the 2-pyridinyl analogue (7i) of the prime amplifier (7e) exhibited sufficient antibacterial activity to preclude testing.

Table 1. Activities as amplifiers of phleomycin-G *in vitro*

Measured at 0·5 mM; for details see ref. 1

Compound	Activity	Compound	Activity	Compound	Activity
(2a)	****[A]	(5a)	*	(7c)	*
(2c)	**	(5b)	***[A]	(7d)	**
(2d)	**[B]	(5c)	0[B]	(7e)	****
(3a)	0[B]	(5d)	*[A]	(7f)	—[C]
(3b)	—[C]	(6a)	0[B]	(7g)	**
(4a)	**	(6b)	0[B]	(7h)	**
caffeine	*			(7i)	—[C]

[A] At 2 mM.
[B] At $<0·5$ mM (saturated) against caffeine at 0·5 mM.
[C] Intrinsic antibacterial activity precluded measurement.

Experimental

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

N,N-*Dimethyl-2-(2'-phenylpurin-6'-ylthio)ethylamine (2a)*

2-Chloro-*N,N*-dimethylethylamine hydrochloride (0·8 g) was added during 10 min to a stirred solution of 2-phenylpurine-6(1*H*)-thione[6] (1·0 g) in 2 M sodium hydroxide (20 ml) at 25°. Stirring was continued for 2 h and then the solution was adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, dehydration of the extract, and subsequent evaporation gave the *product* (2a) (73%), m.p. 163–165° (from ethyl acetate) (Found: C, 60·1; H, 5·6; N, 23·0. $C_{15}H_{17}N_5S$ requires C, 60·2; H, 5·7; N, 23·4%). N.m.r. ($CDCl_3$) 8·35, m, Ph; 8·05, s, H8′; 7·41, m, Ph; 3·68, t, H2; 2·90, t, H1; 2·43, s, NMe_2.

N-(*2'-Dimethylaminoethyl*)-*2-phenylpurine-6-amine (2c)*

6-Chloro-2-phenylpurine[7] (2b) (1·0 g) and 2-dimethylaminoethylamine (5·0 g) were boiled under reflux for 2 h. The excess of amine was recovered by distillation and the residue was diluted

with water (10 ml), adjusted to pH 11, and then extracted with ether. Evaporation of the extract gave the *purinamine* (2c) (57%), m.p. 214° (from ethanol, dried in air) (Found: C, 60·0; H, 6·3; N, 28·1. $C_{15}H_{18}N_6.H_2O$ requires C, 60·0; H, 6·7; N, 28·0%). N.m.r. ($CDCl_3$) 8·17, m, Ph; 8·00, s, H8; 7·38, m, Ph; 3·97, q, H1′; 3·02, t, H2′; 2·63, s, NMe_2.

8-(2′-Dimethylaminoethylthio)-2-phenylpurin-6-amine (2d)

2-Phenylpyrimidine-4,5,6-triamine[8] (1·0 g) and thiourea (1·0 g) were ground together and then fused at 220° for 1 h. A solution of the residue in 2 M sodium hydroxide was decolorized with carbon and then adjusted to pH 5–6. The precipitated *6-amino-2-phenylpurine-8(7H)-thione* (92%) had m.p. 282° (from ethanol) (Found: C, 54·4; H, 3·7; N, 28·6. $C_{11}H_9N_5S$ requires C, 54·3; H, 3·7; N, 28·8%). N.m.r. (1 M NaOD) 8·00, m, Ph; 7·51, m, Ph. Subsequent *S*-alkylation as for the analogue (2a), gave the *thioether* (2d) (68%), m.p. 215° (from ethanol) (Found: C, 57·7; H, 5·8; N, 26·7. $C_{15}H_{18}N_6S$ requires C, 57·3; H, 5·8; N, 26·7%). N.m.r. [$(CD_3)_2SO$] 8·31, m, Ph; 7·43, m, Ph; 6·98, s, br, NH; 3·41, t, H1′; 2·60, t, H2′; 2·21, s, NMe_2.

2-Methylthio-6-phenylpyrimidine (3a)

4,5-Diamino-6-phenylpyrimidine-2(1*H*)-thione[9] (1·0 g), 1 M sodium hydroxide (20 ml) and methyl iodide (1·0 ml) were stirred at 25° for 2 h. Filtration gave *2-methylthio-6-phenylpyrimidine-4,5-diamine* (69%), m.p. 211° (from ethanol) (Found: C, 56·7; H, 5·2; N, 24·0. $C_{11}H_{12}N_4S$ requires C, 56·9; H, 5·2; N, 24·1%). The diamine (0·50 g) and diethoxymethyl acetate were boiled under reflux for 3 h. Evaporation gave the *methylthiopurine* (3a) (63%), m.p. 258° (from ethanol) (Found: C, 59·6; H, 4·2; N, 23·0. $C_{12}H_{10}N_4S$ requires C, 59·5; H, 4·2; N, 23·1%). N.m.r. [$(CD_3)_2SO$] 8·79, m, Ph; 8·50, s, H8; 2·64, s, Me.

N,N-*Dimethyl-2-(8′-phenylpurin-6′-ylthio)ethylamine (4a)*

Alkylation of 8-phenylpurine-6(1*H*)-thione[10] (0·5 g) with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·5 g) as for the isomer (2a), gave the *product* (4a) (71%), m.p. 232° (from ethanol) (Found: C, 60·5; H, 5·7; N, 22·9. $C_{15}H_{17}N_5S$ requires C, 60·2; H, 5·7; N, 23·4%). N.m.r. (1 M DCl) 8·92, s, H2′; 7·83, m, Ph; 7·47, m, Ph; 3·77, t, H2; 3·10, s, NMe_2; 2·80, t, H1.

2-Chloro-8-phenylpurine (4d)

(A) 2-Chloropyrimidine-4,5-diamine[11] (1·4 g), benzaldehyde (1·2 g) and ethanol (30 ml) were boiled under reflux for 1 h and then cooled. Filtration gave 5-benzylideneamino-2-chloropyrimidin-4-amine (82%), m.p. 229° (from ethanol) (Found: C, 57·1; H, 3·8; Cl, 15·2; N, 23·7. $C_{11}H_9ClN_4$ requires C, 56·8; H, 3·9; Cl, 15·2; N, 24·1%). This Schiff base (1·0 g), *N*-bromosuccinimide (0·9 g), and chloroform (30 ml) were boiled under reflux for 90 min. The residue from evaporation was triturated with water to give the *chlorophenylpurine* (75%), m.p. 285° (from ethanol) (Found: C, 56·7; H, 3·2; N, 23·7. $C_{11}H_7ClN_4$ requires C, 57·3; H, 3·1; N, 24·1%). N.m.r. [$(CD_3)_2SO$] 8·94, s, H6; 8·20, m, Ph; 7·66, m, Ph.

(B) 4,5-Diaminopyrimidin-2(1*H*)-one[19] (1·2 g), benzoyl chloride (1·5 g) and 1 M sodium hydroxide were stirred vigorously for 30 min and then acidified to pH 5. Filtration gave N-*(4-amino-1,2-dihydro-2-oxopyrimidin-5-yl)benzamide* (87%), m.p. 321° (dec.) (from methoxyethanol) (Found: C, 57·0; H, 4·5; N, 24·1. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4; N, 24·3%). N.m.r. [$(CD_3)_2SO$] 9·49, s, H6; 7·94, m, Ph; 7·55, m, Ph; 7·00, s, br, NH.

The amide (0·5 g) and *P,P*-dichloro-*P*-phenylphosphine oxide (10·0 g) were heated under reflux for 6 h. The cooled mixture was added to ice-water and allowed to stand in the refrigerator for 8 h. The solid (76%) proved identical to the product in (A) above.

8-Phenylpurine-2(1H)-thione

The above chloropurine (4d) (0·8 g), thiourea (0·3 g) and ethanol (20 ml) were boiled under reflux for 1 h. After the mixture was cooled the thione (79%) was filtered off. It had m.p. 303°

[19] Johns, C. O., *Am. Chem. J.*, 1911, **45**, 79.

(from ethanol) (cf.[20] >300°; 5%) (Found: C, 57·5; H, 3·2; N, 24·4. Calc. for $C_{11}H_8N_4S$: C, 57·9; H, 3·5; N, 24·5%). N.m.r. [$(CD_3)_2SO$] 9·01, s, H6; 8·21, m, Ph; 7·62, m, Ph.

N-(2'-Dimethylaminoethyl)-2-phenylpteridin-4-amine (5a) and its 6,7-Dimethyl Derivative (5b)

6-Chloro-5-nitro-2-phenylpyrimidin-4-amine[12] (2·0 g) and 2-dimethylaminoethylamine (6·0 g) were boiled under reflux for 20 min. The cooled mixture was diluted with water and filtration gave *6-(2'-dimethylaminoethyl)amino-5-nitro-2-phenylpyrimidine-4-amine* (86%), m.p. 168° (from ethanol) (Found: C, 53·0; H, 5·8; N, 26·7. $C_{14}H_{18}N_6O_2.0{\cdot}75H_2O$ requires C, 53·3; H, 6·2; N, 26·6%). N.m.r. ($CDCl_3$) 8·38, m, Ph; 7·48, m, Ph; 3·84, q, H1'; 2·62, t, H2'; 2·32, s, NMe_2; 1·58, s, NH. The above nitropyrimidine (2·0 g) was stirred in water (40 ml) at 80° while sodium dithionite (10·0 g) was added during 5 min. The mixture was allowed to cool with stirring and then adjusted to pH 10. The suspension was extracted with ether and evaporation of the extract gave the crude base (64%) which was characterized as *6-(2'-dimethylaminoethyl)amino-2-phenylpyrimidine-4,5-diamine dihydrochloride*, m.p. 266° (from ethanol) (Found: C, 48·5; H, 6·6; N, 24·1. $C_{14}H_{20}N_6.2HCl$ requires C, 48·7; H, 6·4; N, 24·3%). N.m.r. (D_2O) 7·97, m, Ph; 7·69, m, Ph; 4·06, q, H1'; 3·50, t, H2'; 2·98, s, NMe_2. The above crude base (0·5 g), 40% aqueous glyoxal (0·5 g) [or diacetyl (0·3 g)], and ethanol (10 ml) were heated under reflux for 1 h. The residue from evaporation in a vacuum was triturated with water and filtration gave, respectively, the *pteridineamine* (5a) (52%), m.p. 173° (from acetone) (Found: C, 65·2; H, 6·2; N, 28·4. $C_{16}H_{18}N_6$ requires C, 65·3; H, 6·2; N, 28·5%) [n.m.r. ($CDCl_3$) 8·97, d, H6; 8·78, d, H7; 8·60, m, Ph; 7·53, m, Ph; 3·86, q, H1'; 2·70, t, H2'; 2·36, s, NMe_2] or the *dimethylpteridinamine* (5b) (61%), m.p. 157° (from acetone) (Found: C, 66·0; H, 6·9; N, 26·0. $C_{18}H_{22}N_6$ requires C, 67·0; H, 6·9; N, 26·1%) [n.m.r. ($CDCl_3$) 8·67, m, Ph; 7·46, m, Ph; 3·86, q, H1'; 2·73, s, 6/7-Me; 2·67, s, 7/6-Me; 2·66, t, H2'; 2·35, s, NMe_2].

4-Methylthio-2-phenylpteridine (5c) and 6,7-Dimethyl-4-methylthio-2-phenylpteridine (5d)

5,6-Diamino-2-phenylpyrimidine-4(3*H*)-thione[12] (1·0 g), 40% aqueous glyoxal (1·0 g) and water (20 ml) were heated under reflux for 1 h. Cooling and filtration gave *2-phenylpteridine-4(3H)-thione* (54%), m.p. >225° (dec.) (from ethanol) (Found: C, 59·9; H, 3·5; N, 23·3. $C_{12}H_8N_4S$ requires C, 60·0; H, 3·4; N, 23·3%). N.m.r. [$(CD_3)_2SO$] 9·07, d, H6; 8·87, d, H7; 8·19, m, Ph; 7·61, m, Ph. The same substrate (1·0 g), diacetyl (0·5 g) and 95% ethanol (20 ml) were heated under reflux for 1 h. The residue from evaporation was diluted with a little water to give *6,7-dimethyl-2-phenylpteridine-4(3H)-thione* (58%), m.p. >210° (dec.) (from ethanol) (Found: C, 62·6; H, 4·4; S, 11·7. $C_{14}H_{12}N_4S$ requires C, 62·7; H, 4·5; S, 11·9%). N.m.r. [$(CD_3)_2SO$] 8·17, m, Ph; 7·59, m, Ph; 2·66, s, 6,7-Me_2.

Each thione (0·5 g), methyl iodide (1·0 ml) and 1 M sodium hydroxide (20 ml) were shaken at 25° for 2 h. Refrigeration gave, respectively: (i) The *thioether* (5c) (92%), m.p. 189° (from ethanol) (Found: C, 61·6; H, 3·9; N, 22·0. $C_{13}H_{10}N_4S$ requires C, 61·4; H, 4·0; N, 22·0%). N.m.r. in $(CD_3)_2SO$: 9·29, d, H6; 8·98, d, H7; 8·64, m, Ph; 7·62, m, Ph; 2·81, s, Me. (ii) Its *6,7-dimethyl derivative* (5d) (97%), m.p. 163° (from ethanol) (Found: C, 61·2; H, 4·8; N, 19·0. $C_{15}H_{14}N_4S.0{\cdot}5H_2O$ requires C, 61·8; H, 5·2; N, 19·2%). N.m.r. in $(CD_3)_2SO$ 8·59, m, Ph; 7·59, m, Ph; 2·76, s, SMe; 2·75, s, 6/7-Me; 2·71, s, 7/6-Me.

2-Methylthio-4-phenylpteridine (6a) and 6,7-Dimethyl-2-methylthio-4-phenylpteridine (6b)

2-Methylthio-6-phenylpyrimidine-4,5-diamine (see below) (0·6 g), ethanol (20 ml) and 40% aqueous glyoxal (0·6 g) or diacetyl (0·2 g) were heated under reflux for 1 h and then refrigerated to give, respectively: (i) The *pteridine* (6a) (68%), m.p. 176° (from ethanol) (Found: C, 61·2; H, 3·9; N, 21·9. $C_{13}H_{10}N_4S$ requires C, 61·4; H, 4·0; N, 22·0%). N.m.r. in $(CD_3)_2SO$ 9·20, d, H6; 9·02, d, H7; 8·24, m, Ph; 7·6, m, Ph; 2·71, s, SMe. (ii) The *dimethylpteridine* (6b) (73%), m.p. 169° (from ethanol) (Found: C, 63·5; H, 5·0; N, 19·8. $C_{15}H_{14}N_4S$ requires C, 63·8; H, 5·0; N, 19·8%). N.m.r. in $(CD_3)_2SO$ 8·28, m, Ph; 7·59, m, Ph; 2·75, s, SMe; 2·69, s, 6/7-Me; 2·67, s, 7/6-Me.

[20] Badger, R. J., Brown, D. J., and Lister, J. H., *J. Chem. Soc., Perkin Trans. 1*, 1973, 1906.

2-Chloro-6,7-dimethyl-4-phenylpteridine (6c)

2-Chloro-6-phenylpyrimidine-4,5-diamine[11] (0·5 g), diacetyl (0·2 g) and 50% aqueous ethanol (20 ml) were heated under reflux for 2 h and then refrigerated to give the *chloropteridine* (6c) (57%), m.p. 185–186° (from ethanol) (Found: C, 60·5; H, 3·9; N, 19·5. $C_{14}H_{11}ClN_4.0·5H_2O$ requires C, 60·1; H, 4·3; N, 20·0%). N.m.r. [$(CD_3)_2SO$] 8·33, m, Ph; 7·66, m, Ph; 2·80, s, 6/7-Me; 2·75, s, 7/6-Me.

N-*(2′-Dimethylaminoethyl)-2-phenylquinazolin-4-amine (7c)*

4-Chloro-2-phenylquinazoline[13] (7a) (1·0 g) and 2-dimethylaminoethylamine (5 g) were boiled under reflux for 2 h. The excess amine was removed by distillation and the residue was diluted with water (8 ml) and adjusted to pH 10. The residue from evaporating an ether extract was dissolved in ethanol (10 ml) and to this was added ethanolic 5 M hydrogen chloride (4·0 ml). After the mixture had been warmed momentarily to attain homogeneity, refrigeration gave the product (7c) as *dihydrochloride* (89%), m.p. 273° (from ethanol) (Found: C, 59·1; H, 6·5; N, 15·3. $C_{18}H_{20}N_4.2HCl$ requires C, 59·2; H, 6·1; N, 15·3%). A dihydrochloride with the same melting point has been described previously[21] as a sesquihydrate.

N-*(2′-Dimethylaminoethyl)-4-phenylquinazolin-2-amine (7d)*

Similar treatment of 2-chloro-4-phenylquinazoline[14] gave the product (7d) as *hydrochloride* (91%), m.p. 234–236° (Found: C, 61·0; H, 6·2; N, 15·8. $C_{18}H_{20}N_4.1·7HCl$ requires C, 61·1; H, 6·3; N, 15·8%; this composition was maintained during several recrystallizations from ethanol).

N,N-*Dimethyl-2-(2′-phenylquinazolin-4′-ylthio)ethylamine (7e) and* N,N-*Dimethyl-3-(2′-phenylquinazolin-4′-ylthio)propylamine (7f)*

2-Phenylquinazoline-4(3*H*)-thione[15] (1·0 g), 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·8 g) and 2 M sodium hydroxide (20 ml) were stirred at 25° for 2 h. The solution was adjusted to pH 8 and extracted with ether. After dehydration of the extract, 5 M ethanolic hydrogen chloride (4·0 ml) was added and refrigeration gave the *ethylamine* (7e) as *hydrochloride* (88%), m.p. 218° (from ethanol) (Found: C, 62·1; H, 5·8; N, 11·7. $C_{18}H_{19}N_3S.HCl$ requires C, 62·5; H, 5·8; N, 12·1%).

The use of 3-chloro-*N,N*-propylamine (1·0 g) in the above preparation afforded the homologous *propylamine* (7f) as *hydrochloride* (67%), m.p. 126–128° (from ethanol) (Found: C, 63·4; H, 6·3; N, 11·8. $C_{19}H_{21}N_3S$ requires C, 63·4; H, 6·2; N, 11·7%).

N,N-*Dimethyl-2-(4′-phenylquinazolin-2′-ylthio)ethylamine (7g) and* N,N-*Dimethyl-3-(4′-phenylquinazolin-2′-ylthio)propylamine (7h)*

S-Alkylation of 4-phenylquinazoline-2(1*H*)-thione,[16] as for the above isomers (7e) and (7f), gave: (i) The *ethylamine* (7g) as hydrated *hydrochloride* (91%), m.p. 208° (from ethanol) (Found: C, 61·5; H, 5·8; N, 12·0. $C_{18}H_{19}N_3S.0·25H_2O.HCl$ requires C, 61·7; H, 5·9; N, 12·0%). (ii) The *propylamine* (7h) as *hydrochloride* (54%), m.p. 173–174° (from ethanol) (Found: C, 63·2; H, 6·1; N, 11·4. $C_{19}H_{21}N_3S.HCl$ requires C, 63·4; H, 6·2; N, 11·7%).

N,N-*Dimethyl-2-[2′-(pyridin-4″-yl)purin-6′-ylthio]ethylamine (3b)*

Pyridine-4-carboxamidinium chloride[17] (3·16 g), ethyl 2-cyano-2-hydroxyiminoacetate[18] (2·88 g) and ethanolic sodium ethoxide (sodium: 1·84 g; ethanol: 40 ml) were boiled under reflux for 20 h. Refrigeration gave crude 4-amino-5-nitroso-2-(pyridin-4′-yl)pyrimidin-4(3*H*)-one as sodium salt, which was filtered off, washed with cold ethanol and then stirred in water (80 ml) at 60° while sodium dithionite was added until the mixture became a clear solution and no further colour change occurred. The solution was boiled for 10 min, then cooled to give *5,6-diamino-2-(pyridin-4′-yl)pyrimidin-4(3*H*)-one* (64)%, m.p. >292° (dec.) (from ethanol) (Found: C, 53·0; H, 4·4; N, 34·3. $C_9H_9N_5O$ requires C, 53·2; H, 4·5; N, 34·5%). This diamine (2·03 g), triethyl orthoformate (18 ml) and acetic anhydride (12·5 g) were boiled under reflux for 15 min. The residue from evaporation in a

[21] Blatter, H. M., U.S. Pat. 3,340,260 (1967) (*Chem. Abstr.*, 1968, **69**, 19205).

vacuum was triturated with water and the solid was removed and washed with ether to give *2-(pyridin-4′-yl)purin-6(1H)-one* (70%), m.p. >360° (from methoxyethanol) (Found: C, 56·5; H, 3·3; N, 33·0. $C_{10}H_7N_5O$ requires C, 56·3; H, 3·3; N, 32·9%). N.m.r. ($NaOD/D_2O$) 8·58, d, H2′,6′; 8·03, d, H3′,5′; 7·94, s, H8.

The above purinone (1·0 g) phosphorus pentasulfide (4·0 g) and pyridine (40 ml) were boiled under reflux for 4 h. The residue from removal of the solvent under reduced pressure was dissolved in 2 M sodium hydroxide (40 ml) and then reprecipitated by acidification with acetic acid. The crude pyridinylpurinethione was redissolved in 1 M sodium hydroxide (40 ml) and 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g) was added. After the mixture had been stirred at 25° for 2 h, chloroform extraction and evaporation gave the *product* (3b) (52%), m.p. 182–183° (from ethyl acetate) (Found: C, 55·8; H, 5·2; N, 27·7. $C_{14}H_{16}N_6S$ requires C, 56·0; H, 5·4; N, 28·0%). N.m.r. ($CDCl_3$) 8·59, d, H2″,6″; 8·18, d, H3″,5″; 8·12, s, H8′; 3·69, t, H2; 2·97, t, H1; 2·47, s, NMe_2.

N,N-*Dimethyl-2-[2′-(pyridin-4″-yl)quinazolin-4′-ylthio]ethylamine (7i)*

Pyridine-4-carboxamidinium chloride[17] (3·0 g) and anthranilic acid (1·0 g) were fused together at 180–190° for 30 min. The cooled residue was triturated with water and filtrated to give 2-(pyridin-4′-yl)quinazolin-4-(3*H*)-one (76%), m.p. 283° (from ethanol) (Found: C, 69·5; H, 4·0; N, 18·8. Calc. for $C_{13}H_9N_3O$: C, 69·8; H, 4·1; N, 18·8%) (cf. 280–284° for the same material made by a less convenient route[21]). The quinazolinone (1·0 g), phosphorus pentasulfide (1·0 g) and pyridine (40 ml) were warmed slowly to boiling and then kept under reflux for 1 h. The cooled mixture was added to ice water (150 ml) and allowed to stand at 5° for 24 h. The crude thione (cf.[21,22]) was dissolved in 1 M sodium hydroxide (40 ml) and stirred with 2-chloro-*N,N*-dimethylethylamine for 2 h. Ether extraction and evaporation of the extract gave the required *ethylamine* (7i) (40%), m.p. 92–93° (from light petroleum) (Found: C, 65·5; H, 5·9; N, 18·0. $C_{17}H_{18}N_4S$ requires C, 65·8; H, 5·8; N, 18·0%). N.m.r. ($CDCl_3$) 8·80, d, H2″,6″; 8·43, d, H3″,5″; 7·84, m, H5′–8′; 3·66, t, H1; 2·80, t, H2; 2·38, s, NMe_2.

2-(2′-Dimethylaminopyrimidin-4′-yl)quinazolin-4(3H)-thione

2-Dimethylaminopyrimidine-4-carboxamidinium chloride[3] (1·5 g) and anthranilic acid (0·5 g) were heated together at 180° for 1 h. The cooled mixture was triturated with a little water and filtration gave *2-(2′-dimethylaminopyrimidin-4′-yl)-quinazolin-4(3H)-one* (0·6 g), m.p. 248° (from ethanol) (Found: C, 62·3; H, 4·8; N, 25·8. $C_{14}H_{13}N_5O$ requires C, 62·9; H, 4·9; N, 26·2%). N.m.r. ($NaOD/D_2O$) 8·29, d, H6′; 7·69, m, H5–8; 7·18, d, H5′; 3·11, s, NMe_2. The quinazoline (0·5 g), phosphorus pentasulfide (0·6 g) and pyridine (30 ml) were heated under reflux for 2 h. The cooled mixture was poured into ice water (150 ml) and refrigeration gave a little of the *quinazolinethione*, m.p. 232° (from ethanol) (Found: C, 59·0; H, 4·6; N, 24·4. $C_{14}H_{13}N_5S$ requires C, 59·3; H, 4·6; N, 24·7%). N.m.r. ($CDCl_3$) 8·78, d, H6′; 8·58, d, H5′; 7·73, m, H5–8; 3·32, s, NMe_2.

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[22] Postovskii, I. Y., Vereschagina, N. N., and Mertsalov, S. L., *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 1966, 130 (*Chem. Abstr.*, 1966, **65**, 710).