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Purine Studies. XVII*
The Synthesis of 2-Substituted 6,9-Di- and 6,8,9-Tri-methylpurines as Amplifiers of Phleomycin

Kul Bhushan,[A] *Desmond J. Brown,*[A,B] *John H. Lister,*[A]
Lawrence G. Stephanson[A,C] *and Fumio Yoneda*[D]

[A] John Curtin School of Medical Research,
P.O. Box 334, Canberra City, A.C.T. 2601.
[B] To whom correspondence should be addressed.
[C] Medical Research Council (Canada) Fellow.
[D] Leverhulme Visiting Fellow (1974) from Kumamoto University, Japan.

Abstract

2-(6′,8′,9′-Trimethylpurin-2′-ylthio)acetamide (1e) and analogous *N*-substituted acetamides are prepared by treatment of 6,8,9-trimethylpurine-2-thione (3a) with an appropriate 2-chloroacetamide. 6,9-Dimethyl-2-(piperidin-1′-yl)purine (1n) and some 2-polymethyleneamino homologues are made by initial amination of 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine (2b) followed by reduction of the nitro group and final cyclization with formic acid. Such purines enhance the lethal effect of phleomycin on *Escherichia coli* cultures.

Previous papers have described how the antibacterial activity of phleomycin towards *Escherichia coli* is potentiated considerably *in vitro* by the addition of certain purines.[1–4] However, if such a combination is to be useful *in vivo*, for example against a urinary tract infection,[1] oxidative metabolism of the purine must be minimized by appropriate substitution; at the same time, this must be consistent with the maintenance of high activity.

Of some seventy purines so far tested, most of those with high *in vitro* activity bore, not only *C*-alkyl groups to prevent hydroxylation, but also an alkylthio or dimethylamino substituent. Although the alkylthiopurine (1a) underwent extensive metabolism in mice to give the corresponding (inactive) sulphoxide (1b),[2] such oxidation was decreased by the addition of an amide grouping to the alkylthio substituent.[5] Thus neither the active amide (1c) nor the dimethylaminopurines underwent appreciable oxidation at their respective functional groupings.

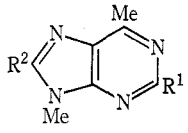
To develop this lead, we now record the preparation and activity of some 6,9-dimethyl- and 6,8,9-trimethyl-purines bearing at the 2-position either a substituted carbamoylmethylthio group or a polymethyleneamino group.

5-Amino-2-chloro-4-methyl-6-methylaminopyrimidine (2a), prepared by an improved route from 6-methyluracil via the nitropyrimidine (2b), was boiled with

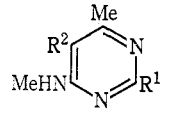
* Part XVI, *J. Chem. Soc., Perkin Trans. 2*, 1975, paper 5/699.

[1] Grigg, G. W., Edwards, M. J., and Brown, D. J., *J. Bacteriol.*, 1971, **107**, 599; Grigg, G. W., *J. Gen. Microbiol.*, 1972, **70**, 221.
[2] Brown, D. J., Jones, R. L., Angyal, A. M., and Grigg, G. W., *J. Chem. Soc., Perkin Trans. 1*, 1972, 1819.
[3] Badger, R. J., Brown, D. J., and Lister, J. H., *J. Chem. Soc., Perkin Trans. 1*, 1974, 152.
[4] Angyal, A. M., Grigg, G. W., Badger, R. J., Brown, D. J., and Lister, J. H., *J. Gen. Microbiol.*, 1974, **85**, 163.
[5] Brown, D. J., and Stephanson, L. G., *Aust. J. Chem.*, 1974, **27**, 1371.

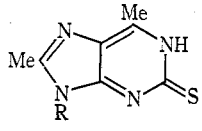
acetic anhydride to give directly the chloropurine (1d). This reacted slowly with sodium hydrogen sulphide to give the thione (3a) previously made[2] by a less convenient route; treatment of the thione with chloroacetamide in aqueous sodium hydrogen carbonate gave the (purinylthio)acetamide (1e). The similar use of appropriate *N*-substituted chloroacetamides gave the analogues (1f–k); another analogue (1l) was made from the same purinethione and 2-chloropropionamide and



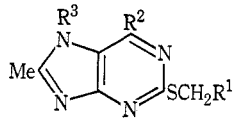
	R^1	R^2
(1a)	SMe	H
(1b)	SOMe	H
(1c)	SCH_2CONH_2	H
(1d)	Cl	Me
(1e)	SCH_2CONH_2	Me
(1f)	SCH_2CONMe_2	Me
(1g)	SCH_2CONEt_2	Me
(1h)	$SCH_2CONHMe$	Me
(1i)	$SCH_2CON[(CH_2CH_2)_2O]$	Me
(1j)	$SCH_2CONHCH_2CH_2OH$	Me
(1k)	$SCH_2CONHPh$	Me
(1l)	$SCHMeCONH_2$	Me
(1m)	SPr^i	Me
(1n)	$N(CH_2)_5$	H
(1o)	$N(CH_2)_4$	H
(1p)	$N(CH_2)_6$	H
(1q)	$N(CH_2)_7$	H
(1r)	$N[(CH_2CH_2)_2O]$	Me
(1s)	$N(CH_2)_5$	Me



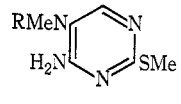
	R^1	R^2
(2a)	Cl	NH_2
(2b)	Cl	NO_2
(2c)	$SCHMeCONH_2$	NHAc
(2d)	$SCHMeCONH_2$	NH_2
(2e)	$N(CH_2)_5$	NO_2
(2f)	$N(CH_2)_5$	NH_2
(2g)	$N(CH_2)_4$	NO_2
(2h)	$N(CH_2)_4$	NH_2
(2i)	$N(CH_2)_6$	NO_2
(2j)	$N(CH_2)_6$	NH_2
(2k)	$N(CH_2)_7$	NO_2
(2l)	$N(CH_2)_7$	NH_2
(2m)	$N[(CH_2CH_2)_2O]$	NO_2
(2n)	$N[(CH_2CH_2)_2O]$	NH_2
(2o)	$N(CH_2)_5$	NHAc



	R
(3a)	Me
(3b)	H



	R^1	R^2	R^3
(4a)	$CONH_2$	Me	H
(4b)	H	H	Me



	R
(5a)	H
(5b)	Ac

also by cyclization of the *N*-(pyrimidin-5′-yl)acetamide (2c), prepared from 5-amino-4-methyl-6-methylaminopyrimidine-2-thione[6] via its derivative (2d). In addition, 2-(6′,8′-dimethylpurin-2′-ylthio)acetamide (4a) was made from the known[2] thione (3b); the purine (1m), from the thione (3a); and 7,8-dimethyl-2-methylthiopurine (4b), from the known[7] diamine (5a) via its acetyl derivative (5b).

[6] Brown, D. J., Ford, P. W., and Tratt, K. H., *J. Chem. Soc., C*, 1967, 1445.
[7] Brown, D. J., *J. Appl. Chem.*, 1955, **5**, 358.

Treatment of the chloronitropyrimidine (2b) with cold ethanolic piperidine gave the piperidinylpyrimidine (2e) which was reduced to the 5-amino analogue (2f). In boiling formic acid, this underwent acylation and subsequent cyclization to the dimethylpiperidinylpurine (1n). The homologous pyrrolidinyl-, hexahydroazepinyl-, and octahydroazocinyl-purines (1o–q) were made similarly by the sequences [(2b) → (2g) → (2h) → (1o)], [(2b) → (2i) → (2j) → (1p)], and [(2b) → (2k) → (2l) and (1q)] respectively; the morpholinylpurine (1r), via the pyrimidines (2m) and (2n); and the trimethylpiperidinylpurine (1s), by two routes: (*a*) directly from the chloropurine (1d) and (*b*) from the 5-aminopyrimidine (2f) via its acetyl derivative (2o).

Values for the biological activity of a selection of the above purines and for several unrelated derivatives[8,9] appear in Table 1. It is evident that some of the amides [(1e), (1f), (1i), (1j), (1l), (4a)] and polymethyleneamino derivatives [(1n), (1r), (1s)] have the expected high to very high *in vitro* activity. Thus they fulfil the first criterion for practical use as amplifiers of phleomycin against infections. Their performance in respect of the second criterion, viz. resistance to metabolic change, will be reported later.

Table 1. Activities of purines as phleomycin amplifiers

For definition of adjusted activity (A_{ad}) see ref. 4, which also explains why some values are printed in *italics*

Purine	Act.	A_{ad}	Purine	Act.	A_{ad}	Purine	Act.	A_{ad}
(1c)	++++	510[A]	(1j)	+++	145	(4a)	+++	265
(1d)	++	65	(1k)	+	*0·2*	7-Et-6-Me-2-SMe[B]	++	22
(1e)	+++	130	(1l)	++++	430	6-Me-2-SMe-8-CF_3[C]	+	0·2
(1f)	+++	290	(1m)	+	*2*	7-Et-6-Me-2-SMe-8-CF_3[C]	+	*0·1*
(1g)	++	20	(1n)	++++	*235*	9-Et-6-Me-2-SMe-8-CF_3[C]	+	*0·1*
(1h)	++	20	(1r)	+++	*40*	caffeine[A]	++	30
(1i)	+++	105	(1s)	+++	*90*	caffeine[A]	++	*11*

[A] From ref. 4. [B] Prep.: ref. 8. [C] Prep.: ref. 9.

Experimental

Analyses were done by the Australian National University Analytical Services Unit. The anhydrous compounds (1k), (1o), (1q), (2c), (2j), (2l) were homogeneous to t.l.c. and paper chromatography but proved to be too hygroscopic for satisfactory analyses as such: accordingly, each was equilibrated in the atmosphere for 12–24 h prior to analysis as the hydrated species described below. Melting points were uncorrected. Ionization constants were measured spectrometrically[10,11] at 20° without thermodynamic corrections. The n.m.r. spectra were measured in $CDCl_3$, except where indicated otherwise, at 35° and 60 MHz on a Varian T60A instrument with Me_4Si as an internal standard (chemical shifts in δ; J values in Hz); u.v. spectra were recorded in aqueous buffer on an SP 1800; and i.r. spectra were measured in Nujol mulls on an SP 200. The method for *in vitro* evaluation of purines as amplifiers of phleomycin against *E. coli B* has been described in detail.[4]

2-Chloro-6,8,9-trimethylpurine (1d)

Nitric acid (*d* 1·5; 125 ml) was added gradually during 2 h to a stirred solution of 6-methyluracil (100 g) in concentrated sulphuric acid (300 ml), maintained at 5–10°. After a further 2 h at 20–25°,

[8] Fenn, M. D., and Lister, J. H., *J. Chem. Soc., Perkin Trans. 1*, 1974, 1300.
[9] Fenn, M. D., and Lister, J. H., *J. Chem. Soc., Perkin Trans. 1*, 1975, 485.
[10] Albert, A., and Serjeant, E. P., 'Determination of Ionization Constants' (Chapman & Hall: London 1971).
[11] Perrin, D. D., *Aust. J. Chem.*, 1963, **16**, 572.

the mixture was poured onto ice (1 kg). The crystalline material was washed with water to give 6-methyl-5-nitrouracil (93%) (cf. lit.[12] 65%). This was converted[13] into 2,4-dichloro-6-methyl-5-nitropyrimidine which underwent methylamination[14] to 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine (2b) [recrystallization of the crude material from light petroleum left an insoluble by-product, identified as 4-methyl-2,6-bis(methylamino)-5-nitropyrimidine, m.p. 252° (from ethanol) (cf. lit.[15] 228 or 235°; different crystalline form?) (Found: C, 42·5; H, 5·5; N, 35·6. Calc. for $C_7H_{11}N_5O_2$: C, 42·6; H, 5·6; N, 35·5%)] and subsequent reduction[14] to 5-amino-2-chloro-4-methyl-6-methylaminopyrimidine (2a). This material (4·3 g) and acetic anhydride (15 ml) were boiled under reflux for 6 h. The residue from concentration under reduced pressure was extracted with boiling ether. Evaporation of the extracts and recrystallization of the residue from light petroleum–methanol gave the *chlorotrimethylpurine* (63%), m.p. 171–172° (Found: C, 48·9; H, 4·8; N, 28·6. $C_8H_9ClN_4$ requires C, 48·9; H, 4·6; N, 28·5%). pK_a 1·83±0·05 (anal. λ 286 nm); u.v. λ_{max} (log ε) at pH 7: 214 (4·37), *245* (3·60), 273 (4·03); at pH 0: 207 (4·39), 234 (3·62), 270 (4·03), *277* (3·97); n.m.r. (Me_2SO) 2·58 (s, 8-Me), 2·63 (s, 6-Me), 3·67 (s, 9-Me).

6,8,9-Trimethylpurine-2(1H)-thione (3a)

The above chloropurine (3 g) was heated under reflux with aqueous 2M sodium hydrogen sulphide (75 ml) for 20 h. The cooled solution was acidified with acetic acic and then evaporated to dryness. Crystallization of the residue from water gave the purinethione (52%), identified with authentic material[2] by i.r. and u.v. spectra.

2-(6′,8′,9′-Trimethylpurin-2′-ylthio)acetamide (1e)

The above purinethione (125 mg), 2-chloroacetamide (85 mg), sodium hydrogen carbonate (72 mg) and water (2·5 ml) were boiled under reflux for 90 min. Refrigeration of the filtered solution gave the *(trimethylpurinylthio)acetamide* (89%), m.p. 212–213° (from methanol) (Found: C, 47·5; H, 5·2; N, 27·8. $C_{10}H_{13}N_5OS$ requires C, 47·8; H, 5·2; N, 27·9%). M^+ 251; ν_{max} 1680 (C=O).

N-*Substituted 2-(6′,8′,9′-Trimethylpurin-2′-ylthio)acetamides*

The purinethione (0·97 g), 2-chloro-*N*,*N*-dimethylacetamide (0·61 g), sodium hydrogen carbonate (0·5 g) and water (20 ml) were heated under reflux for 1 h. The oily residue from evaporation under reduced pressure was extracted with chloroform. The dehydrated extract was evaporated to small bulk and diluted with ether to give N,N-*dimethyl-2-(6′,8′,9′-trimethylpurin-2′-ylthio)acetamide* (1f) (64%), m.p. 194° (from chloroform–ether) (Found: C, 51·8; H, 6·1; N, 25·1. $C_{12}H_{17}N_5OS$ requires C, 51·6; H, 6·1; N, 25·1%). ν_{max} 1644 (C=O); n.m.r. 2·58 (s, 8′-Me), 2·70 (s, 6′-Me), 2·99 (s, Me of NMe_2), 3·18 (s, Me of NMe_2), 3·70 (s, 9′-Me), 4·18 (s, CH_2).

The following were prepared similarly. 2-Chloro-*N*,*N*-diethylacetamide gave N,N-*diethyl-2-(6′,8′,9′-trimethylpurin-2′-ylthio)acetamide* (1g) (57%), m.p. 100° (Found: C, 54·5; H, 6·8; N, 22·9. $C_{14}H_{21}N_5OS$ requires C, 54·7; H, 6·9; N, 22·8%). ν_{max} 1641 (C=O); n.m.r. 1·13 (t, *J* 7, Me of Et), 1·28 (t, *J* 7, Me of Et), 2·57 (s, 8′-Me), 2·68 (s, 6′-Me), 3·43 (q, *J* 7, CH_2 of Et), 3·50 (q, *J* 7, CH_2 of Et), 3·67 (s, 9′-Me), 4·14 (s, SCH_2). 2-Chloro-*N*-methylacetamide gave N-*methyl-2-(6′,8′,9′-trimethylpurin-2′-ylthio)acetamide* (1h) (64%), m.p. 197–198° (Found: C, 49·8; H, 5·7; N, 26·7. $C_{11}H_{15}N_5OS$ requires C, 49·8; H, 5·7; N, 26·4%). ν_{max} 1664 (C=O); n.m.r. 2·60 (s, 8′-Me), 2·71 (s, 6′-Me), 2·76 (d, *J* 5, Me of NHMe), 3·69 (s, 9′-Me), 3·88 (s, CH_2), 7·07 (br s, NH). *N*-(Chloroacetyl)morpholine gave *4-[2′-(6″,7″,8″-trimethylpurin-2″-ylthio)acetyl]morpholine* (1i) (75%), m.p. 169° (Found: C, 52·1; H, 5·9; N, 21·7. $C_{14}H_{19}N_5O_2S$ requires C, 52·3; H, 6·0; N, 21·8%). ν_{max} 1641 (C=O); n.m.r. 2·58 (s, 8″-Me), 2·70 (s, 6″-Me), 3·64 [s, $(CH_2)_4$ of morpholine], 3·68 (s, 9″-Me), 4·17 (s, CH_2).

2-Chloro-*N*-(2-hydroxyethyl)acetamide gave N-*(2′-hydroxyethyl)-2-(6′,8′,9′-trimethylpurin-2′-ylthio)acetamide* (1j) (41%), m.p. 227–229° (Found: C, 48·9; H, 5·8; N, 23·5. $C_{12}H_{17}N_5O_2S$

[12] Gabriel, S., and Colman, J., *Ber. Deut. Chem. Ges.*, 1901, **34**, 1234.
[13] Albert, A., Brown, D. J., and Wood, H. C. S., *J. Chem. Soc.*, 1954, 3832.
[14] Brown, D. J., England, B. T., and Lyall, J. M., *J. Chem. Soc., C*, 1966, 226.
[15] Goldner, H., and Carstens, E., *J. Prakt. Chem.*, 1961, [4] **12**, 242; Cohen, S., and Vincze, A., *Israel J. Chem.*, 1964, **2**, 1.

requires C, 48·8; H, 5·8; N, 23·7%). ν_{max} 1648 (C=O); n.m.r. (Me_2SO) 2·51 (s, 8′-Me), 2·56 (s, 6′-Me), 3·27 (m, CH_2CH_2), 3·65 (s, 9′-Me), 3·87 (s, SCH_2), 8·08 (br s, NH).

The thiopurine (0·5 g), α-chloroacetanilide (0·46 g), sodium hydrogen carbonate (0·25 g) and water (10 ml) were boiled under reflux for 2 h. The cooled solution deposited *2-(6′,8′,9′-trimethylpurin-2′-ylthio)acetanilide* (1k) (46%), m.p. 195° (from methanol) (Found: C, 55·8; H, 5·5; N, 20·0. $C_{16}H_{17}N_5OS,H_2O$ requires C, 55·6; H, 5·5; N, 20·3%). ν_{max} 1668 (C=O); n.m.r. (Me_2SO) 2·51 (s, 8′-Me), 2·57 (s, 6′-Me), 3·62 (s, 9′-Me), 4·08 (s, CH_2), 7·4 (br m, 5H of Ph), 10·23 (br s, NH).

2-(6′,8′,9′-Trimethylpurin-2′-ylthio)propionamide (1l)

(A) 6,8,9-Trimethylpurine-2-thione (195 mg), 2-chloropropionamide (130 mg), sodium hydrogen carbonate (100 mg) and water (2·0 ml) were heated under reflux for 30 min. Refrigeration gave the *(trimethylpurinylthio)propionamide* (31%), m.p. 228–229° (from water) (Found: C, 49·1; H, 5·8; N, 25·8. $C_{11}H_{15}N_5OS$ requires C, 49·0; H, 5·8; N, 26·0%). M^+ 265; ν_{max} 1700 (C=O).

(B) 5-Amino-4-methyl-6-methylaminopyrimidine-2-thione[6] (1·7 g), 2-chloropropionamide (1·08 g), sodium hydrogen carbonate (0·93 g) and water (20 ml) were heated under reflux for 30 min. Then chloropropionamide (0·35 g) in water (30 ml) was added and heating was continued for a further 40 min. The chilled mixture deposited *2-(5′-amino-4′-methyl-6′-methylaminopyrimidin-2′-ylthio)propionamide* (2d) (65%), m.p. 201–203° (from water) (Found: C, 44·6; H, 6·2; N, 28·9. $C_9H_{15}N_5OS$ requires C, 44·8; H, 6·2; N, 29·1%). M^+ 241; ν_{max} 1670 (C=O). This material (120 mg), ethanol (10 ml), and acetic anhydride (60 mg) were boiled under reflux for 10 min. Then more anhydride (30 mg) was added and heating was continued for a further 10 min. The residue from evaporation was washed with a little water to give *2-(5′-acetamido-4′-methyl-6′-methylaminopyrimidin-2′-ylthio)propionamide* (2c) (90%), m.p. 205–206° (from ethanol–light petroleum) (Found: C, 44·5; H, 6·0; N, 23·6. $C_{11}H_{17}N_5O_2S,0·75H_2O$ requires C, 44·5; H, 6·3; N, 23·6%). M^+ 283; ν_{max} 1610, 1680 (C=O). The acetamido derivative (30 mg), potassium carbonate (40 mg) and dimethylformamide (5 ml) were stirred at 120° for 7 h. The residue from evaporation in a vacuum was washed with a little cold water to give the (trimethylpurinylthio)propionamide (37%), identified with that from (A) by mixed m.p.

2-(6′,8′-Dimethylpurin-2′-ylthio)acetamide (4a)

6,8-Dimethylpurine-2-thione (3b)[2] was treated with chloroacetamide as was its trimethyl homologue above. The resulting *(dimethylpurinylthio)acetamide* (25%) had m.p. 264–267° (dec.) (from methanol–ether) (Found: C, 45·4; H, 4·7; N, 29·3. $C_9H_{11}N_5OS$ requires C, 45·6; H, 4·7; N, 29·5%). M^+ 295; ν_{max} 1690 (C=O).

2-Isopropylthio-6,8,9-trimethylpurine (1m)

The trimethylpurinethione (100 mg) and isopropyl iodide (170 mg) were stirred in aqueous 5% sodium hydroxide (10 ml) at 25°. After 25, 50 and 75 h, further portions (170 mg) of isopropyl iodide were added; at 100 h, the product was filtered off and recrystallized from water (charcoal) to give the *isopropylthiotrimethylpurine* (55%), m.p. 112° (Found: C, 56·2; H, 6·6; N, 24·1. $C_{11}H_{16}N_4S$ requires C, 55·9; H, 6·8; N, 23·7%). M^+ 236.

7,8-Dimethyl-2-methylthiopurine (4b)

Acetic anhydride (3 ml) was added to a solution of 4-amino-5-methylamino-2-methylthiopyrimidine (5a)[7] (0·5 g) in ethanol (5 ml). After 2 h at 25°, the mixture was evaporated to give N-*(4′-amino-2′-methylthiopyrimidin-5′-yl)*-N-*methylacetamide* (5b) (60%), m.p. 250–251° (from ethanol) (Found: C, 45·8; H, 5·5; N, 26·5. $C_8H_{12}N_4OS$ requires C, 45·3; H, 5·7; N, 26·4%). This pyrimidine (0·25 g), dimethylformamide (5 ml) and anhydrous potassium carbonate (0·15 g) were heated under reflux for 90 min. The cooled mixture was filtered, diluted threefold with water and evaporated to give the *dimethylmethylthiopurine* (32%), m.p. 197–198° (from ethanol) (Found: C, 49·8; H, 5·4; N, 28·8. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·8%). (It is evident that an isomeric *N*,8-dimethyl-2-methylthiopurine of m.p. 158–159° was incorrectly suspected[16] of having the above structure.)

[16] Brown, D. J., and Ford, P. W., *J. Chem. Soc., C*, 1969, 2620.

6,9-Dimethyl-2-(piperidin-1'-yl)purine (1n)

Piperidine (5·1 g) in ethanol (10 ml) was added slowly to a stirred suspension of the above 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine (2b) (4·07 g) in ethanol (10 ml) maintained at *c.* 5°. After a further 2 h at 20–25°, *4-methyl-6-methylamino-5-nitro-2-(piperidin-1'-yl)pyrimidine* (2e) (92%) was filtered off. Recrystallized from ethanol and then light petroleum, it had m.p. 166–168° (Found: C, 52·1; H, 7·0; N, 27·7. $C_{11}H_{17}N_5O_2$ requires C, 52·6; H, 6·8; N, 27·9%). This nitro compound (4·65 g) was hydrogenated at atmospheric pressure in methanol (600 ml) at 20° over Raney nickel. Evaporation of the filtered solution gave *5-amino-4-methyl-6-methylamino-2-(piperidin-1'-yl)pyrimidine* (2f) (73%), m.p. 121–124° (from light petroleum) (Found: C, 59·7; H, 8·5; N, 32·1. $C_{11}H_{19}N_5$ requires C, 59·7; H, 8·6; N, 31·7%). This 5-aminopyrimidine (1 g) and formic acid (98%; 15 ml) were heated under reflux for 2 h. The residue from evaporation crystallized from light petroleum to give the *dimethylpiperidinylpurine* (53%), m.p. 122–123° (Found: C, 62·2; H, 7·1; N, 30·7. $C_{12}H_{17}N_5$ requires C, 62·3; H, 7·4; N, 30·3%). pK_a 4·66±0·04 (anal. λ 240 nm).

6,9-Dimethyl-2-(pyrrolidin-1'-yl)purine (1o)

2-Chloro-4-methyl-6-methylamino-5-nitropyrimidine (4·4 g) in ethanol (150 ml) was treated with pyrrolidine (5 g) (as for the piperidinyl homologue above) to give *4-methyl-6-methylamino-5-nitro-2-(pyrrolidin-1'-yl)pyrimidine* (2 g) (86%), m.p. 200–202° (from light petroleum) (Found: C, 50·7; H, 6·4; N, 29·6. $C_{10}H_{15}N_5O_2$ requires C, 50·6; H, 6·4; N, 29·5%) which underwent hydrogenation to yield *5-amino-4-methyl-6-methylamino-2-(pyrrolidin-1'-yl)pyrimidine* (2h) (78%), m.p. 127–128° (from light petroleum) (Found: C, 57·8; H, 8·1; N, 33·3. $C_{10}H_{17}N_5$ requires C, 57·9; H, 8·3; N, 33·8%) and subsequent cyclization with formic acid to the *dimethylpyrrolidinylpurine* (45%), m.p. 90–92° (from light petroleum) (Found: C, 59·5; H, 6·8; N, 31·7. $C_{11}H_{15}N_5$,0·25H_2O requires C, 59·4; H, 7·0; N, 31·5%).

2-(Hexahydroazepin-1'-yl)-6,9-dimethylpurine (1p)

Similar procedures with hexahydroazepine in place of pyrrolidine gave successively *2-(hexahydroazepin-1'-yl)-4-methyl-6-methylamino-5-nitropyrimidine* (2i) (67%), m.p. 115–117° (Found: C, 54·6; H, 7·3; N, 26·5. $C_{12}H_{19}N_5O_2$ requires C, 54·4; H, 7·2; N, 26·4%); the hygroscopic *5-amino-2-(hexahydroazepin-1'-yl)-4-methyl-6-methylaminopyrimidine* (2j) (94%), m.p. 82–84° (Found: C, 60·2; H, 9·0; N, 29·1. $C_{12}H_{21}N_5$,0·25H_2O requires C, 60·1; H, 9·0; N, 29·1%); and the *hexahydroazepinyldimethylpurine* (48%), m.p. 62–64° (Found: C, 63·5; H, 7·8; N, 28·9. $C_{13}H_{19}N_5$ requires C, 63·6; H, 7·8; N, 28·6%).

6,9-Dimethyl-2-(octahydroazocin-1'-yl)purine (1q)

Likewise octahydroazocine gave *4-methyl-6-methylamino-5-nitro-2-(octahydroazocin-1'-yl)pyrimidine* (2k) (58%), m.p. 107–109° (Found: C, 55·4; H, 7·8; N, 24·6. $C_{13}H_{21}N_5O_2$ requires C, 55·9; H, 7·6; N, 25·1%) and thence, *5-amino-4-methyl-6-methylamino-2-(octahydroazocin-1'-yl)pyrimidine* (2l) (72%), m.p. 82–84° (Found: N, 26·2. $C_{13}H_{23}N_5$,H_2O requires N, 26·2%). This aminopyrimidine (1 g) and 98% formic acid (15 ml) were boiled under reflux for 4 h. Evaporation gave the crude formyl derivative which cyclized on heating for 40 min in formamide containing a drop of concentrated hydrochloric acid. Refrigeration gave the *octahydroazocinylpurine* (34%), m.p. 79–81° (from light petroleum) (Found: C, 63·8; H, 7·9; N, 26·8. $C_{14}H_{21}N_5$,0·25H_2O requires C, 63·7; H, 8·2; N, 26·6%).

6,9-Dimethyl-2-(morpholin-4'-yl)purine (1r)

Similarly, morpholine gave *4-methyl-6-methylamino-2-(morpholin-4'-yl)-5-nitropyrimidine* (2m) (69%), m.p. 194–195° (Found: C, 47·6; H, 5·8; N, 27·7. $C_{10}H_{15}N_5O_3$ requires C, 47·4; H, 6·0; N, 27·7%); *5-amino-4-methyl-6-methylamino-2-(morpholin-4'-yl)pyrimidine* (2n) (91%), m.p. 115–117° (Found: C, 53·7; H, 7·6; N, 31·6. $C_{10}H_{17}N_5O$ requires C, 53·8; H, 7·7; N, 31·4%); and the *dimethylmorpholinylpurine* (52%), m.p. 151–153° (Found: C, 56·3; H, 6·3; N, 29·9. $C_{11}H_{15}N_5O$ requires C, 56·6; H, 6·5; N, 30·0%). pK_a 3·95±0·05 (anal. λ 240 nm).

6,8,9-Trimethyl-2-(piperidin-1′-yl)purine (*1s*)

(A) 2-Chloro-6,8,9-trimethylpurine (1d) (197 mg), piperidine (0·2 ml) and ethanol (10 ml) were heated for 30 h in a sealed tube at 100–110°. The residue from evaporation was extracted with hot benzene and the clarified extract was evaporated to give the *trimethylpiperidinylpurine* (21%), m.p. 112° (from light petroleum) (Found: C, 63·7; H, 7·7; N, 28·5. $C_{13}H_{19}N_5$ requires C, 63·6; H, 7·8; N, 28·5%). M^+ 245.

(B) 6-Amino-4-methyl-6-methylamino-2-(piperidin-1′-yl)pyrimidine (2f) (220 mg), acetic anhydride (125 mg) and benzene (10 ml) were stirred at 20° for 30 min. The residue from evaporation was dissolved in water and decolorized. Evaporation of the aqueous solution gave N-[*4′-methyl-6′-methylamino-2′-(piperidin-1″-yl)pyrimidin-5′-yl*]*acetamide* (2o) (89%), m.p. 169–170° (from cyclohexane) (Found: C, 59·4; H, 7·3; N, 26·6. $C_{13}H_{21}N_5O$ requires C, 59·3; H, 8·0; N, 26·6%). M^+ 263; ν_{max} 1680 (C=O). The above pyrimidine (26 mg), aqueous 5% sodium hydroxide (1 ml), and ethanol (2 ml) were heated under reflux for 5 h. The solution was adjusted to pH 3 with 2M hydrochloric acid and then evaporated to give the trimethylpiperidinylpurine *hydrochloride* (53%), m.p. 259–260° (sealed tube) (from ethanol–ether) (Found: C, 55·5; H, 7·2; N, 24·6. $C_{13}H_{19}N_5$,HCl requires C, 55·4; H, 7·2; N, 24·9%).

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