Purine Studies. Part X.[1] Further Synthetic Approaches to Purines for the Amplification of Phleomycin Activity against *E. coli*

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In view of the high amplifying activity shown by 6,9-dimethyl-2-methylthiopurine (1; R = SMe), a number of analogues have been synthesised. These include derivatives having the *C*- or *N*-methyl group replaced by an ethyl group, homologues containing an additional 8-methyl or -ethyl group, and derivatives lacking the *C*- or the *N*-methyl group. Some related 2-ethylthio- and 2-dimethylamino-purines are also described, together with the 2-carbamoylmethylthiopurine (1; R = $S{\cdot}CH_2{\cdot}CO{\cdot}NH_2$) and the oxidation product (1; R = SO_2Me) from (1; R = SMe). From the *S*-methylation of 6-ethyl-9-methylpurine-2(3*H*)-thione (3; R^1 = Et, R^2 = Me), bis-(6-ethyl-9-methylpurin-2-yl) sulphide (4) was isolated as the major product.

In a previous paper[2] the activity of the antibiotic phleomycin against *E. coli* was shown to be enhanced by the presence of various purines. That no precise correlation between structure and biological effect could be deduced was due largely to the range of types of purine found to exert significant activity. Some generalisations as to possible structural requirements can, however, be derived from these results. The most active derivatives were 2-alkylthiopurines (usually methylthio) and, to a lesser degree, 2-dimethylamino-purines. It was also apparent that an alkyl group at C-6 or C-8, or an alkyl group on an imidazole nitrogen atom, or a combination of any of these, was beneficial. This is illustrated by 6,9-dimethyl-2-methylthiopurine (1; R = SMe), one of the most active of the compounds so far examined.[2]

In the present programme, modifications to this purine, and also the 2-dimethylamino-analogue (1; R = NMe_2), have been effected, the variants produced having one or other of the methyl groups at C-6 or N-9 replaced by an ethyl group. In order to explore the effect of molecular area on activity the molecule was enlarged by insertion of an additional methyl or ethyl group at the 8-position.

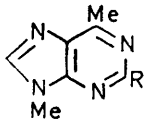
Ionisation and u.v. spectral data are given in the

[1] Part IX, W. Pendergast, *J.C.S. Perkin I*, 1973, 2759.
[2] D. J. Brown, R. L. Jones, A. M. Angyal, and G. W. Grigg, *J.C.S. Perkin I*, 1972, 1819.

Table. While replacing a methyl group by an ethyl group does not, as expected, materially alter the u.v. spectrum it can, surprisingly, have a significant effect on the ionisation. This is noticeably so where the change is made with an alkyl group located on the imidazole ring.

Details of the biological testing and partition coefficients of these purines (in octanol–water) will be published subsequently together with the results of metabolic studies.

Syntheses.—The majority of the 2-methylthio- and 2-dimethylamino-purines were obtained by ring closure of the appropriate 2-methylthio- or 2-dimethylamino-4,5-diaminopyrimidine with phosphoryl chloride and an *NN*-dimethylamide (Vilsmeier reagent).[3] Although this type of reagent tended to give lower yields of purine than the more usual cyclising reagents, such as ortho-esters, it was preferred as the latter often gave rise to mixtures of the purine and uncyclised material. This failure to cyclise (possibly) hindered 5-amino-4-alkylaminopyrimidines to 8,9-dialkylpurines has been noted previously.[4]



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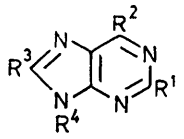


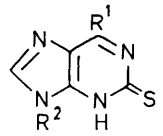
(2)

The 2-methylthiopurines (2a—e), the 2-dimethylamino-analogues (2h—o), and the 2-methylaminopurine (2s) were prepared in this way. Related purines resulting from orthoester–anhydride cyclisations include (2f, j, and q), and ring closures with formic acid have given the 2-methylthio-derivative (2g) and the 2-aminopurines (2p and r) together with the 2-thioxopurines (3; R^1 = Me, R^2 = H or Et). The alternative route to 2-alkylthiopurines, alkylation of the appropriate purine-2-thione, was not satisfactory for preparing the 2-methylthio-derivatives. In the case of 6-ethyl-9-methylpurine-2-thione (3; R^1 = Et, R^2 = Me) only a small amount of the 2-methylthiopurine was obtained, the major product being bis-(6-ethyl-9-methylpurin-2-yl) sulphide (4), arising from oxidation of the thioxopurine. This appears to be the first dipurinyl sulphide reported although many examples of dipurinyl disulphides are known.[5] Satisfactory ethylations, however, were carried out on the respective purine-2-thiones to give (5; R^1 = Me, R^2 = H) and (5; R^1 = H, R^2 = Me).

Other modifications carried out with 2-thiopurines were the reaction of (3; R^1 = R^2 = Me) with chloroacetamide forming the 2-carbamoylmethylthiopurine (1; R = S·CH_2·CO·NH_2) and the oxidation of the *S*-methylated form (1; R = SMe) to the 2-methylsulphonylpurine (1; R = SO_2Me).

[3] J. Clark and J. H. Lister, *J. Chem. Soc.*, 1961, 5048.
[4] J. H. Lister, *J. Chem. Soc.*, 1963, 2228.
[5] J. H. Lister, 'Purines,' Wiley-Interscience, New York, 1971, p. 291.

The 4,5-diaminopyrimidine intermediates were derived from 2,4-dichloro-6-ethyl-[6] or 2,4-dichloro-6-methyl-5-nitropyrimidine by initial amination to give the 4-amino-2-chloro-5-nitropyrimidine followed by replacement of the remaining chlorine atom by a dimethylamino- or a thioxo-group. In the latter reaction



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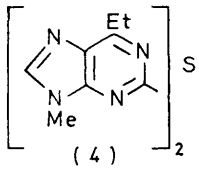
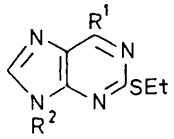
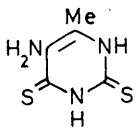


(4)



(5)

	R^1	R^2	R^3	R^4
a;	SMe	Me	H	Et
b;	SMe	Me	Me	Et
c;	SMe	Et	H	H
d;	SMe	Et	Me	H
e;	SMe	Et	Me	Me
f;	SMe	Me	Et	Me
g;	SMe	Et	H	Me
h;	NMe_2	Me	H	H
i;	NMe_2	Me	H	Et
j;	NMe_2	Me	Et	H
k;	NMe_2	Me	Me	Et
l;	NMe_2	Et	H	Me
m;	NMe_2	Et	Me	H
n;	NMe_2	Et	Me	Me
o;	NMe_2	Me	Et	Me
p;	NMe_2	Et	H	H
q;	NMe_2	Me	Me	H
r;	NHMe	Et	H	Me
s;	NHMe	Et	Me	Me



(6)

thiourea was employed, although sodium hydrosulphide solutions can also be used for this purpose, an advantage being that with the latter reagent reduction of the nitro-group also occurs. The application is limited, however, to nitropyrimidines having a primary amino-group at the 4-position, since with secondary amino-groups displacement by a thio-group is found to occur, *e.g.* the conversion of 2-chloro-4-ethylamino-6-methyl-5-nitropyrimidine into 5-amino-6-methylpyrimidine-2,6-(3*H*,1*H*)-dithione (6). The 4-amino-2-dimethylamino-5-nitropyrimidines were reduced by hydrogen catalytically to the 4,5-diamino-analogues; reduction of the 4-amino-5-nitropyrimidine-2-thiones was effected with sodium hydrosulphite in alkaline solution and the products were methylated to give the 4,5-diamino-2-methylthiopyrimidines.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 33° on a Perkin-Elmer R10 60 MHz instrument, with tetramethylsilane or sodium 3-trimethylsilylpropan-1-sulphonate as standard; *J* values

[6] R. Robinson and M. L. Tomlinson, *J. Chem. Soc.*, 1935, 1283.

Ionisation constants and u.v. spectra

Purine	pK_a (analyt. λ) [a]	$\lambda_{max.}$ [b] (log ε) [pH; ionic species]
6-Et-8,9-Me_2-2-SMe	3·14 ± 0·04 (245)	299(3·95), 260(3·94), 233(4·29), [7·0; 0]
		308(3·76), *272*(3·91), *257*(4·04), 243(4·2), 232(4·19) [0; +]
8-Et-6,9-Me_2-2-SMe	3·15 ± 0·05 (320)	298(3·98), 261(3·96), 233(4·26), [7·0; 0]
		306(3·81), *275*(3·84), *257*(4·04), 244(4·21), 232(4·18) [1·0; +]
9-Et-6,8-Me_2-2-SMe	3·51 ± 0·05 (325)	298(3·95), 261(3·94), 233(4·28), [7·0; 0]
		307(3·75), *274*(3·94), *260*(4·05), 243(4·21), 233(4·18) [0; +]
6-Et-8-Me-2-SMe	9·52 ± 0·04 (243)	299(3·95), *266*(3·74), 239(4·31) [12·0; −]
	3·05 ± 0·04 (295)	300(3·90), 254(3·98), 228(4·26), [7·0; 0]
		307(3·77), 256(4·10), 226(4·18) [0; +]
6-Et-9-Me-2-SMe	2·60 ± 0·03 (300)	298(3·88), 258(3·88), 234(4·27) [7·0; 0]
		308(3·66), *273*(3·90), 244(4·29) [0; +]
8-Et-6-Me-2-SMe [c]	9·75 ± 0·03 (260)	299(3·97), *266*(3·73), 239(4·32) [12·0; −]
	3·08 ± 0·02 (275)	300(3·93), 254(3·98), 228(4·25) [7·0; 0]
		308(3·75), 260(4·09), 229(4·18) [0; +]
9-Et-6-Me-2-SMe	2·71 ± 0·04 (275)	297(3·83), 257(3·88), 234(4·23) [7·0; 0]
		306(3·65), *275*(3·90), 244(4·27) [0; +]
6-Et-2-SMe	9·35 ± 0·03 (275)	299(4·90), *265*(3·65), 239(4·28) [12·0; −]
	2·50 ± 0·03 (245)	299(3·81), 253(3·94), 228(4·23), [7·0; 0]
		307(3·66), 257(4·01), 234(4·17) [0; +]
8-Et-2-SMe [c]	9·75 ± 0·04 (245)	303(3·91), 240(4·31) [12·0; −]
	2·80 ± 0·05 (235)	305(3·89), *252*(3·97), 231(4·26) [5·0; 0]
		312(3·80), 254(4·11), 226(4·17) [0·9; +]
8-Et-2-SEt [c]	9·62 ± 0·04 (275)	302(3·91), 241(4·29) [12·0; −]
	2·81 ± 0·04 (330)	304(3·89), *252*(3·98), 232(4·25) [7·0; 0]
		312(3·79), 254(4·11), 227(4·15) [0·8; +]
2-SEt [c]	9·19 ± 0·04 (275)	301(3·83), 241(4·28) [12·0; −]
	d	304(3·80), *250*(3·95), 231(4·22) [7·0; 0]
6-SEt	8·86 ± 0·04 (305)	292(4·18), 220(4·14) [11·0; −]
	1·72 ± 0·02 (310)	291(4·23), *250*(3·46), 219(4·0) [5·0; 0]
		301(4·19), 224(3·96) [0·4; +]
8-SEt	7·72 ± 0·04 (310)	297(4·26), 220(4·19) [10·0; −]
	3·04 ± 0·05 (310)	292(4·28), 246(3·55), 216(4·11) [5·0; 0]
		304(4·29), 232(4·01) [1·0; +]
2-SEt-6-Me	9·43 ± 0·03 (240)	297(3·87), 240(4·27) [12·0; −]
	2·67 ± 0·04 (270)	298(3·83), 254(3·95), 229(4·2) [7·0; 0]
		306(3·65), 260(4·01) [0·8; +]
2-SEt-8-Me [c]	9·5 ± 0·06 (245)	301(3·89), 241(4·29) [12·0; −]
	2·71 ± 0·04 (333)	304(3·86), *252*(3·97), 231(4·24) [7·0; 0]
		312(3·78), 254(4·11) [0·8; +]
2-SEt-9-Me	2·27 ± 0·05 (250)	303(3·85), 258(3·84), 236(4·25) [7·0; 0]
		314(3·59), 276(3·79), 248(4·23), *233*(4·08) [0; +]
9-Me-6-SMe [f]	1·40 ± 0·05 (305)	292(4·23), 285(4·23), 220(4·06), [7·0; 0]
		301(4·22), 224(3·99), 206(4·0) [−0·8; +]
2-NMe_2-6,8-Me_2	10·83 ± 0·03 (285)	319(3·77), *255*(3·84), 233(4·42) [13·0; −]
	4·92 ± 0·03 (320)	324(3·78), 251(4·03), 223(4·39) [8·0; 0]
		332(3·66), 252(4·02), 226(4·50) [2·0; +]
2-NMe_2-6-Et	10·73 ± 0·02 (250)	321(3·74), 232(4·42) [13·0; −]
	4·42 ± 0·05 (310)	325(3·76), 250(4·04), 222(4·42) [8·0; 0]
		334(3·67), 251(3·97), 226(4·49) [2·0; +]
2-NMe_2-6-Et-8,9-Me_2	5·15 ± 0·05 (314)	324(3·83), 255(3·99), 228(4·47) [8·0; 0]
		333(3·67), *254*(3·97), 232(4·56), [2·0; +]
2-NMe_2-8-Et-6,9-Me_2	5·40 ± 0·05 (320)	323(3·84), 254(4·01), 228(4·49) [8·0; 0]
		334(3·59), *255*(4·0), 232(4·61) [1·0; +]
2-NMe_2-9-Et-6,8-Me_2	5·35 ± 0·05 (320)	323(3·86), 256(4·05), 228(4·50) [8·0; 0]
		332(3·67), *254*(3·98), 233(4·58) [2·0; +]
2-NMe_2-6-Et-8-Me	4·90 ± 0·04 (315)	325(3·81), 250(4·07), 222(4·42) [7·0; 0]
		333(3·72), 252(4·05), 226(4·51) [2·0; +]
2-NMe_2-6-Et-9-Me	4·53 ± 0·03 (310)	325(3·79), 253(3·97), 228(4·45) [8·0; 0]
		335(3·61), *255*(3·90), 233(4·54) [2·0; +]
2-NMe_2-8-Et-6-Me	11·11 ± 0·04 (280)	319(3·81), *255*(3·89), 233(4·45) [13·0; −]
	5·05 ± 0·04 (315)	324(3·80), 251(4·06), 223(4·43) [8·0; 0]
		333(3·68), 252(4·07), 226(4·54) [2·0; +]
2-NMe_2-9-Et-6-Me	4·83 ± 0·04 (315)	324(3·80), 254(3·99), 228(4·47) [7·0; 0]
		334(3·59), *255*(3·91), 233(4·56) [1·0; +]
2-NMe_2-6-Me	10·32 ± 0·05 (350)	321(3·66), 232(4·35) [13·0; −]
	4·14 ± 0·05 (320)	324(3·68), 250(3·96), 222(4·34) [8·0; 0]
		333(3·57), 251(3·93), 226(4·46) [2·0; +]
6-Et-8,9-Me_2-2-NHMe	5·25 ± 0·03 (310)	313(3·87), 248(3·88), 224(4·49) [8·0; 0]
		323(3·74), *251*(3·82), 229(4·61) [2·0; +]
6-Et-9-Me-2-NHMe	4·68 ± 0·04 (310)	314(3·82), 249(3·84), 225(4·45) [8·0; 0]
		323(3·66), *251*(3·74), 229(4·58) [2·0; +]
2-S·CH_2·CO·NH_2-6,9-Me_2	2·04 ± 0·04 (315)	292(3·91), 254(3·82), 231(4·31) [7·0; 0]
		300(3·76), 274(3·68), *256*(3·94), 242(4·14), 229(4·17) [−0·2; +]
6,9-Me_2-2-SO_2Me	0·27 ± 0·04 (275)	264(3·95), 211(4·33) [7·0; 0]
		260(3·95) [−1·9; +]

[a] Analytical wavelength (nm). [b] Inflexion wavelength (nm) in italics. [c] Preparation given by R. J. Badger, D. J. Brown, and J. H. Lister (*J.C.S. Perkin I*, 1973, 1906). [d] Unstable in acidic solution. [e] G. B. Elion, I. Goodman, W. Lange, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1959, **81**, 1898. [f] Spectral data for this purine are recorded incorrectly in ref. 12.

are given in Hz. U.v. spectra were recorded on a Unicam SP 800 spectrophotometer; peaks were checked manually with an SP 500 instrument. Ionisation constants were measured spectrometrically at 20° and at concentrations below 10^{-4}M in buffers [7] of 10^{-2}M ionic strength by methods outlined in ref. 8.

2-Chloro-4-ethylamino-6-methyl-5-nitropyrimidine.—To a solution of 4,6-dichloro-6-methyl-5-nitropyrimidine (7 g) in dioxan (25 ml) at 0° was added ethylamine (33% aq. solution; 20 ml), previously adjusted to pH 8 with acetic acid. The brown oil which emerged on addition of water (80 ml) was extracted with ether and the extracts were dried (Na_2SO_4) and evaporated. The resulting low-melting solid (7·1 g, 96%) crystallised from petroleum (b.p. 80—100°) to give the *4-ethylaminopyrimidine* as yellow prisms, m.p. 71—72° (Found: C, 38·9; H, 4·3; N, 25·8. $C_7H_9ClN_4O_2$ requires C, 38·8; H, 4·2; N, 25·8%).

2-Chloro-4-ethyl-6-methylamino-5-nitropyrimidine.— Similarly prepared from 2,4-dichloro-6-ethyl-5-nitropyrimidine [6] and aqueous methylamine (40% w/v), the *product* (75%) had m.p. 75—76° [from petroleum (b.p. 40—60°)] (Found: C, 38·9; H, 4·2; N, 25·8. $C_7H_9ClN_4O_2$ requires C, 38·8; H, 4·2; N, 25·8%).

4-Ethyl-2,6-bismethylamino-5-nitropyrimidine.—To a stirred solution of 2,4-dichloro-6-ethyl-5-nitropyrimidine (10 g) in ethanol (100 ml) was added ethanolic methylamine (30% w/v; 20 ml). The precipitated *bismethylaminopyrimidine* (5·5 g) had m.p. 147° (from methanol) (Found: C, 45·6; H, 6·3; N, 33·5. $C_8H_{13}N_5O_2$ requires C, 45·5; H, 6·2; N, 33·2%).

2-Dimethylamino-4-ethylamino-6-methyl-5-nitropyrimidine.—A mixture of 2-chloro-4-ethylamino-6-methyl-5-nitropyrimidine (3·3 g) in ethanol (30 ml) and ethanolic dimethylamine (33% w/v; 20 ml), left for 1 h, deposited the crystalline *2-dimethylaminopyrimidine* (67%), m.p. 117—118° (from methanol) (Found: C, 47·8; H, 6·5; N, 30·9. $C_9H_{15}N_5O_2$ requires C, 48·0; H, 6·7; N, 31·1%). Similarly prepared from the appropriate 4-amino-2-chloro-5-nitropyrimidines were *2-dimethylamino-4-ethyl-6-methylamino-5-nitropyrimidine* (89%), m.p. 145—146° (from methanol) (Found: C, 47·8; H, 6·4; N, 31·3. $C_9H_{15}N_5O_2$ requires C, 48·0; H, 6·7; N, 31·1%); *4-amino-2-dimethylamino-6-ethyl-5-nitropyrimidine* (81%), m.p. 132—133° (from methanol) (Found: C, 45·8; H, 6·1; N, 33·4. $C_8H_{13}N_5O_2$ requires C, 45·4; H, 6·2; N, 33·2%); and *4-amino-2-dimethylamino-6-methyl-5-nitropyrimidine* (78%), m.p. 148—149° (from ethanol) (Found: C, 42·8; H, 5·5. $C_7H_{11}N_5O_2$ requires C, 42·6; H, 5·6%).

5-Amino-2-dimethylamino-4-ethylamino-6-methylpyrimidine.—A solution of 2-dimethylamino-4-ethylamino-6-methyl-5-nitropyrimidine (4·7 g) in ethanol (150 ml) containing Raney nickel was hydrogenated to completion. The solid, remaining after removal of the catalyst and evaporation, on crystallisation from petroleum (b.p. 80—100°), gave *5-amino-2-dimethylamino-4-ethylamino-6-methylpyrimidine* (95%), m.p. 94—96° (Found: C, 55·3; H, 8·5; N, 36·0. $C_9H_{17}N_5$ requires C, 55·4; H, 8·8; N, 35·9%). Catalytic reductions, under these conditions, of the other 5-nitropyrimidines gave *5-amino-2-dimethylamino-4-ethyl-6-methylaminopyrimidine* (88%), m.p. 69—71° [from petroleum (b.p. 40—60°)] (Found: C, 55·1; H, 9·0; N, 35·8. $C_9H_{17}N_5$ requires C, 55·35; H, 8·8; N, 35·9%); *4,5-diamino-2-dimethylamino-6-ethylpyrimidine* (60%), m.p. 116—117° [from petroleum (b.p. 80—100°)] (Found: C, 53·2; H, 8·2; N, 38·1. $C_8H_{15}N_5$ requires C, 53·0; H, 8·3; N, 38·6%); *4,5-diamino-2-dimethylamino-6-methylpyrimidine* (75%), m.p. 153° (from benzene) (Found: C, 50·7; H, 7·9. $C_7H_{13}N_5$ requires C, 50·3; H, 7·8%); and *5-amino-4-ethyl-2,6-bismethylaminopyrimidine* (91%), m.p. 133—134° [from petroleum (b.p. 60—80°)] (Found: C, 53·1; H, 8·3; N, 38·3. $C_8H_{15}N_5$ requires C, 53·0; H, 8·3; N, 38·6%).

4-Ethyl-6-methylamino-5-nitropyrimidine-2(3H)-thione.—2-Chloro-4-ethyl-6-methylamino-5-nitropyrimidine (4·4 g) and thiourea (2·2 g) in ethanol (80 ml) were heated under reflux (4 h); the mixture was then taken to dryness and the residue triturated with a little cold water. The *pyrimidine-2-thione* (4·1 g) was obtained as yellow microcrystals, m.p. 210—211° (from 4 : 1 water–ethanol) (Found: C, 39·1; H, 4·7; N, 25·9. $C_7H_{10}N_4O_2S$ requires C, 39·25; H, 4·7; N, 26·2%). This procedure with the corresponding 2-chloropyrimidines afforded *4-methyl-6-methylamino-5-nitropyrimidine-2(3H)-thione* (82%), m.p. 217—218° (from water) (Found: C, 36·2; H, 4·1; N, 28·0. $C_6H_8N_4O_2S$ requires C, 36·0; H, 4·0; N, 28·0%); *4-ethylamino-6-methyl-5-nitropyrimidine-2(3H)-thione* (59%), m.p. 198° (from water) (Found: C, 39·7; H, 4·7; N, 26·3. $C_7H_{10}N_4O_2S$ requires C, 39·3; H, 4·7; N, 26·2%); and *4-amino-6-ethyl-5-nitropyrimidine-2(3H)-thione* (94%), m.p. 225° (from water) (Found: C, 36·0; H, 4·0; N, 28·1. $C_6H_8N_4O_2S$ requires C, 36·0; H, 4·0; N, 28·0%).

4-Ethyl-6-methylamino-2-methylthio-5-nitropyrimidine.—4-Ethyl-6-methylamino-5-nitropyrimidine-2-thione (8·4 g) was taken into solution by addition of 0·1N-sodium hydroxide, and methyl iodide (3·2 ml) was added slowly. Recrystallisation of the precipitate from aqueous ethanol gave lemon-yellow crystals of the *2-methylthiopyrimidine*, m.p. 84—85° (Found: C, 42·5; H, 5·2; N, 24·6. $C_8H_{12}N_4O_2S$ requires C, 42·1; H, 5·3; N, 24·6%). Similarly obtained were *4-ethylamino-6-methyl-2-methylthio-5-nitropyrimidine* (63%), m.p. 107—108° (from aqueous ethanol) (Found: C, 42·4; H, 5·5; N, 25·0. $C_8H_{12}N_4O_2S$ requires C, 42·1; H, 5·3; N, 24·6%); and *4-amino-6-ethyl-2-methylthio-5-nitropyrimidine* (95%), m.p. 122° (from methanol) (Found: C, 39·5; H, 5·0; N, 26·2. $C_7H_{10}N_4O_2S$ requires C, 39·3; H, 4·7; N, 26·2%).

5-Amino-4-ethylamino-6-methyl-2-methylthiopyrimidine.—(a) *From 4-ethylamino-6-methyl-2-methylthio-5-nitropyrimidine.* Hydrogenation of the nitropyrimidine (1·7 g) in ethanol (80 ml) over Raney nickel followed by removal of catalyst and evaporation gave the crude *diaminopyrimidine*. Recrystallisation from water–methanol (20 : 1) gave needles, m.p. 143—144° (Found: C, 48·6; H, 7·1; N, 28·7. $C_8H_{14}N_4S$ requires C, 48·5; H, 7·1; N, 28·3%).

(b) *From 5-amino-4-ethylamino-6-methylpyrimidine-2(3H)-thione.* Treatment of the 2-thioxopyrimidine (1·5 g) in 0·1N-sodium hydroxide (20 ml) with methyl iodide (0·5 ml) gave a crystalline precipitate (1·1 g). Recrystallisation from aqueous methanol gave the same product as from (a) (m.p., mixed m.p., and i.r. spectra).

5-Amino-4-ethyl-6-methylamino-2-methylthiopyrimidine.—This derivative, together with the succeeding one, were prepared by catalytic hydrogenation of the 5-nitro-analogue, as in (a). The *5-aminopyrimidine* (80%) had m.p. 154—155° (from 1 : 1 methanol–water) (Found: C, 48·8; H, 7·2; N, 28·8. $C_8H_{14}N_4S$ requires C, 48·5; H, 7·1; N, 28·3%); *4,5-diamino-6-ethyl-2-methylthiopyrimidine*

[7] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.

[8] A. Albert and E. P. Serjeant, 'The Determination of Ionisation Constants,' Chapman and Hall, London, 2nd edn., 1971.

(78%) had m.p. 193—194° (from methanol) (Found: C, 45·5; H, 6·4; N, 30·2. $C_7H_{12}N_4S$ requires C, 45·6; H, 6·6; N, 30·4%).

5-Amino-4-ethyl-6-methylaminopyrimidine-2(3H)-thione.—To a solution of 4-ethyl-6-methylamino-5-nitropyrimidine-2(3*H*)-thione (3·7 g) in 0·5N-sodium hydroxide (40 ml) at 60°, sodium hydrosulphite (10 g) was added slowly. After a further 20 min the solution was cooled and the *5-aminopyrimidine* (1·45 g) filtered off. Recrystallisation from aqueous ethanol (1 : 1) gave a product, m.p. 310° (decomp.) (Found: C, 45·9; H, 6·8; N, 30·3. $C_7H_{12}N_4S$ requires C, 45·6; H, 6·6; N, 30·4%). A similar procedure gave *5-amino-4-ethylamino-6-methylpyrimidine-2-thione* (44%), m.p. >300° (from water) (Found: C, 45·8; H, 6·8; N, 30·3. $C_7H_{12}N_4S$ requires C, 45·6; H, 6·6; N, 30·4%).

Formation of 5-Amino-4-methylpyrimidine-2,6(1H,3H)-dithione.— 2-Chloro-4-ethylamino-6-methyl-5-nitropyrimidine (8·3 g) in a freshly prepared molar solution of sodium hydrosulphide (300 ml) was heated on a water-bath for 1 h. After cooling, acidification (pH 5) with acetic acid produced a yellow precipitate of 5-amino-6-methylpyrimidine-2,6(1*H*,3*H*)-dithione [9] (6·75 g), crystallising from water as yellow needles, m.p. >300° (Found: C, 34·8; H, 4·0; N, 24·4; S, 36·7. Calc. for $C_5H_7N_3S_2$: C, 34·7; H, 4·1; N, 24·3; S, 37·0%).

9-Ethyl-6-methyl-2-methylthiopurine (2a).—To 5-amino-4-ethylamino-6-methyl-2-methylthiopyrimidine (1·1 g) in *NN*-dimethylformamide (4 ml) was added phosphoryl chloride (1 ml), and the mixture was heated on a steam-bath for 45 min. The residue obtained on evaporation was treated with ice–water, ammonia solution was added (to pH 4), and the solution was taken to dryness. Extraction with chloroform followed by removal of the solvent gave *9-ethyl-6-methyl-2-methylthiopurine* (0·2 g), m.p. 67—68° [from petroleum (b.p. 80—100°)] (Found: C, 51·9; H, 5·6; N, 27·4. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%).

6-Ethyl-2-methylthiopurine (2c).—Prepared similarly from 4,5-diamino-6-ethyl-2-methylthiopyrimidine (1·3 g), the product appeared to contain some uncyclised material. It was therefore heated for 1 h at 210°, then extracted with chloroform as before. Crystallisation from ethyl acetate gave the *purine* (0·6 g), m.p. 213—214° (Found: C, 49·4; H, 5·0; N, 29·0. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·9%).

6-Ethyl-8-methyl-2-methylthiopurine (2d).—The action of *NN*-dimethylacetamide and phosphoryl chloride on 4,5-diamino-6-ethyl-2-methylthiopyrimidine (1·4 g) gave directly *6-ethyl-8-methyl-2-methylthiopurine* (0·7 g), m.p. 207—209° [from petroleum (b.p. 100—120°)] (Found: C, 52·2; H, 5·8; N, 26·9. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%). Other purines similarly prepared were *6-ethyl-8,9-dimethyl-2-methylthiopurine* (2e), m.p. 122—123° [from petroleum (b.p. 80—100°)] (Found: C, 54·15; H, 6·3; N, 24·9. $C_{10}H_{14}N_4S$ requires C, 54·0; H, 6·4; N, 25·2%); and *9-ethyl-6,8-dimethyl-2-methylthiopurine* (2b), m.p. 98—99° [petroleum (b.p. 60—80°)] (Found: C, 53·9; H, 6·6; N, 25·1. $C_{10}H_{14}N_4S$ requires C, 54·0; H, 6·4; N, 25·2%). Attempts to form the last two 8,9-dialkylpurines from the appropriate 4,5-diaminopyrimidines with either triethyl orthoacetate–acetic anhydride or acetic anhydride alone gave, in each case, mainly the 4-amino-5-acetamidopyrimidine.

8-Ethyl-6,9-dimethyl-2-methylthiopurine (2f).—After heating under reflux 5-amino-4-methyl-6-methylamino-2-methylthiopyrimidine (2·3 g), triethyl orthopropionate (15 ml), and acetic anhydride (15 ml) for 1·5 h the solution was evaporated to dryness and the residue extracted with hot petroleum (b.p. 60—80°) (3 × 50 ml). The extracts were concentrated (to 60 ml) and on cooling deposited crystals of the *purine* (0·8 g), m.p. 145—146° (Found: C, 54·1; H, 6·3; N, 25·3. $C_{10}H_{14}N_4S$ requires C, 54·0; H, 6·3; N, 25·2%).

6-Ethyl-9-methyl-2-methylthiopurine (2 g).—(*a*) A solution of 5-amino-4-ethyl-6-methylamino-2-methylthiopyrimidine (1·4 g) in formic acid (99%; 20 ml) was heated under reflux for 4 h. The residue obtained on evaporation contained the uncyclised 5-formamidopyrimidine. The product was therefore heated at 210° for 30 min and, after cooling, extracted with hot petroleum (b.p. 60—80°) (3 × 40 ml). Concentration of the extracts (to 15 ml) and cooling gave the *purine* (0·6 g), m.p. 91—92° (Found: C, 51·9; H, 5·7; N, 27·0. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%).

(*b*) 5-Amino-4-ethyl-6-methylaminopyrimidine-2(3*H*)-thione (0·5 g) was heated in formic acid (99%; 8 ml) for 1·5 h. The solution was then evaporated to dryness and the product, which was characterised (i.r.) as a 2-thioxopurine, was taken up in dilute sodium hydroxide (15 ml) and treated with dimethyl sulphate (0·5 ml). After stirring for 1 h the solution was brought to pH 5 with acetic acid, and the resulting precipitate crystallised from benzene–petroleum (b.p. 60—80)°, giving *bis-(6-ethyl-9-methylpurin-2-yl) sulphide* (0·3 g), m.p. 249—250° (Found: C, 54·4; H, 4·8; N, 31·9; S, 9·4. $C_{16}H_{18}N_8S$ requires C, 54·2; H, 5·1; N, 31·6; S, 9·0%). Slow evaporation of the mother liquor gave large crystals (0·1 g) of 6-ethyl-9-methyl-2-methylthiopurine, m.p. 92°, identical (mixed m.p., i.r.) with the product obtained in (*a*).

9-Ethyl-6-methylpurine-2(3H)-thione (3; R^1 = Me, R^2 = Et).—Obtained similarly from 5-amino-4-ethylamino-6-methylpyrimidine-2(3*H*)-thione (1·6 g) and formic acid, *9-ethyl-6-methylpurine-2(3H)-thione* (1·1 g) had m.p. >230° (from benzene) (Found: C, 49·9; H, 5·4; N, 28·9. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·9%).

2-Ethylthio-6-methylpurine (5; R^1 = Me, R^2 = H).—Heating 4,5-diamino-6-methylpyrimidine-2-thione [10] in formic acid gave 6-methylpurine-2(3*H*)-thione [11] (65%), m.p. >300° (from water) as the quarter hydrate (Found: N, 32·8. Calc. for $C_6H_6N_4S,0{\cdot}25H_2O$: N, 32·8%). This 2-thioxopurine (0·4 g) in ethanol (20 ml) in which sodium (0·12 g) had been dissolved was treated with iodoethane (0·55 g) and the mixture was stirred for 1·5 h. The pH was adjusted to 5 (0·1N-hydrochloric acid), the solution was evaporated to dryness, and the residue was extracted with hot chloroform. Removal of the solvent gave *2-ethylthio-6-methylpurine* (0·26 g), m.p. 202—204° (from water) (Found: C, 49·3; H, 5·4; N, 28·6. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·8%), δ [$(CD_3)_2SO$] 1·33 (t, *J* 7, Me or Et), 2·63 (s, 6-Me), 3·1 (q, *J* 7, CH_2 of Et), and 8·4 (s, 8-H).

2-Ethylthio-9-methylpurine (5; R^1 = H, R^2 = Me).—Obtained by ethylation of 9-methylpurine-2(3*H*)-thione [12] under the foregoing conditions, the *ethylthiopurine* (88%) had m.p. 94—96° [from petroleum (b.p. 60—80°)] (Found:

[9] F. L. Rose, *J. Chem. Soc.*, 1954, 4116.
[10] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.
[11] A. Giner-Sorolla, E. Thom, and A. Bendich, *J. Org. Chem.*, 1964, **29**, 3209.
[12] D. J. Brown and P. W. Ford, *J. Chem. Soc.* (*C*), 1969, 2620.

C, 49·1; H, 5·0; N, 28·9. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·8%), δ [$(CD_3)_2SO$] 1·4 (t, Me of Et), 3·3 (q, CH_2 of Et), 3·81 (s, NMe), 8·5 (s, 8-H), and 9·05 (s, 6-H).

2-Carbamoylmethylthio-6,9-dimethylpurine (1; R = $S{\cdot}CH_2{\cdot}CONH_2$).—6,9-Dimethylpurine-2(3*H*)-thione (0·45 g), chloroacetamide (0·3 g), sodium hydrogen carbonate (0·25 g), and water (10 ml) were heated under reflux for 1 h. Refrigeration gave a solid which recrystallised from water to give the *carbamoylmethylthiopurine* (0·40 g), m.p. 163—164° (Found: C, 45·3; H, 4·9; N, 29·2. $C_9H_{11}N_5OS$ requires C, 45·6; H, 4·7; N, 29·5%).

6,9-Dimethyl-2-methylsulphonylpurine (1; R = SO_2Me). —6,9-Dimethyl-2-methylthiopurine (0·49 g),[13] *m*-chloroperoxybenzoic acid (1·125 g), and chloroform (30 ml) were stirred together, first at 0° (2 h) and then at room temperature (16 h). After successive washing with saturated solutions of sodium hydrogen sulphite (2 × 5 ml) and sodium hydrogen carbonate (2 × 5 ml), the chloroform solution was taken to dryness, giving the *methylsulphonylpurine* (0·5 g, 88%), m.p. 204—206° (from methanol) (Found: C, 42·7; H, 4·6; N, 24·4. $C_8H_{10}N_4O_2S$ requires C, 42·5; H, 4·5; N, 24·8%).

2-Dimethylamino-6-ethylpurine (2p).—Heating 4,5-diamino-2-dimethylamino-6-ethylpyrimidine (2 g) with formic acid gave only the 4-amino-5-formamidopyrimidine, which required further heating in a metal bath at 190° for 20 min to effect cyclisation to the *purine* (2·0 g), m.p. 218—219° (from aqueous methanol) (Found: C, 56·6; H, 6·8; N, 36·9. $C_9H_{13}N_5$ requires C, 56·5; H, 6·9; N, 36·6%).

2-Dimethylamino-8-ethyl-6-methylpurine (2j).—(*a*) To 4,5-diamino-2-dimethylamino-6-methylpyrimidine (0·5 g) in NN-dimethylpropionamide (3 ml) was added phosphoryl chloride (1 ml), and the mixture was then heated on a steam-bath for 0·5 h. After cooling, ice–water (8 ml) was added; the solution was left for 30 min, then basified with aqueous ammonia, and evaporated to dryness. The residue was extracted with hot chloroform (3 × 8 ml) and the extracts were taken to dryness, giving the *purine*, m.p. 160—161° (from cyclohexane) (Found: C, 58·2; H, 7·1; N, 34·1. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4; N, 34·1%).

(*b*) The foregoing 4,5-diaminopyrimidine (2·7 g), triethyl orthopropionate (14 ml), and propionic anhydride (10 ml) were heated under reflux for 2 h. Since the product obtained on evaporation contained uncyclised material, it was heated with N-sodium hydroxide on a steam-bath for 15 min. The solution was then neutralised with acetic acid and taken to dryness. Extraction with chloroform and evaporation of the extracts left 2-dimethylamino-8-ethyl-6-methylpurine (1·1 g), i.r. spectrum and m.p. as already cited. Other 2-dimethylaminopurines prepared essentially by ring closure with *NN*-dimethylamide–phosphoryl chloride of the appropriate 2-dimethylamino-diaminopyrimidine were *2-dimethylamino-6-ethyl-8-methylpurine* (2m) (38%), m.p. 199—201° (from benzene) (Found: C, 58·6; H, 7·0; N, 33·9. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4; N, 34·1%); *2-dimethylamino-6-ethyl-9-methylpurine* (2l), isolated as the hydrochloride, m.p. >220° (from methanol) (Found: C, 49·8; H, 6·9; N, 28·8. $C_{10}H_{16}ClN_5$ requires C, 49·7; H, 6·8; N, 29·0%), which on treatment with N-sodium hydroxide, followed by extraction with ether, gave the *base*, m.p. 68—69° [from petroleum (b.p. 40—60°)] (Found: C, 58·3; H, 7·4; N, 34·1. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4; N, 34·1%); *2-dimethylamino-9-ethyl-6-methylpurine* (2i), obtained as the hydrochloride (40%), m.p. >250° (from ethanol–ether) (Found: C, 49·5; H, 6·4; N, 28·9. $C_{10}H_{16}ClN_5$ requires C, 49·7; H, 6·7; N, 29·0%), which on dissolution in N-sodium hydroxide and extraction with ether gave a yellow oil affording the *purine*, m.p. 69—71° on sublimation (80° at 0·5 mmHg) (Found: C, 58·8; H, 7·5. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4%); *2-dimethylamino-6-ethyl-8,9-dimethylpurine* (2n), isolated as the hydrochloride monohydrate (32%), m.p. 222° (decomp.) (from methanol–ether) (Found: C, 48·6; H, 7·4; N, 25·6. $C_{11}H_{18}ClN_5,H_2O$ requires C, 48·3; H, 7·4; N, 25·6%), from which the *purine*, m.p. 94—95° [from petroleum (b.p. 60—80°)], was obtained as before (Found: C, 60·2; H, 7·8; N, 32·25. $C_{11}H_{17}N_5$ requires C, 60·2; H, 7·8; N, 31·9%); *2-dimethylamino-8-ethyl-6,9-dimethylpurine* (2o) (51%), m.p. 104—105° [from petroleum (b.p. 80—100°)] (Found: C, 60·3; H, 7·8; N, 32·3. $C_{11}H_{17}N_5$ requires C, 60·2; H, 7·8; N, 31·9%); *2-dimethylamino-9-ethyl-6,8-dimethylpurine* (2k), obtained as a monohydrate, after drying (27%), m.p. 64—66° [from petroleum (b.p. 60—80°)] (Found: C, 55·3; H, 7·7; N, 29·4. $C_{11}H_{17}N_5,H_2O$ requires C, 55·7; H, 8·1; N, 29·6%); and *2-dimethylamino-6-methylpurine* (2h) (53%), m.p. 285° (from 9 : 1 water–methanol) (Found: C, 54·0; H, 6·4; N, 39·3. $C_8H_{11}N_5$ requires C, 54·2; H, 6·3; N, 39·5%).

2-Dimethylamino-6,8-dimethylpurine (2q).—The diaminopyrimidine (4·0 g), triethyl orthoacetate (20 ml), and acetic anhydride (20 ml) were heated under reflux for 2 h and the solution was then evaporated to dryness. The residue was extracted with hot benzene (50 ml), the extracts were taken to dryness, and the product was heated on a steam-bath with N-sodium hydroxide (30 ml) for 1·5 h. After cooling, the pH was adjusted to 6 with hydrochloric acid, the solution was evaporated to dryness, and the solid remaining was extracted with hot benzene (3 × 15 ml). Removal of the solvent gave the *purine* (0·9 g), m.p. 238—240° (from benzene) (Found: C, 56·9; H, 6·7; N, 36·6. $C_9H_{13}N_5$ requires C, 56·5; H, 6·85; N, 36·6%). Use of either *NN*-dimethylacetamide–phosphoryl chloride or acetamide fusion in the foregoing ring closure gave mixtures of the purine and the 5-acetamido-4-aminopyrimidine.

6-Ethyl-9-methyl-2-methylaminopurine (2r).—5-Amino-4-ethyl-2,6-bismethylaminopyrimidine (0·5 g) in formic acid (99%; 5 ml) was heated under reflux for 1·5 h. The solution was evaporated to dryness; crystallisation of the residue gave the monohydrate of *4-ethyl-5-formamido-2,6-bismethylaminopyridine*, m.p. 151° (Found: C, 47·5; H, 7·2. $C_9H_{15}N_5O,H_2O$ requires C, 47·6; H, 7·5%). Heating in a metal bath (160° for 30 min), in a nitrogen atmosphere, gave the *purine* (0·2 g), m.p. 144—145° [from petroleum (b.p. 60—80°)] (Found: C, 56·9; H, 7·0; N, 36·2. $C_9H_{13}N_5$ requires C, 56·5; H, 6·9; N, 36·6%). In hot formic acid this purine was converted into the 2-(*N-methylformamido*)*purine*, m.p. 140° [from petroleum (b.p. 80—100°)] (Found: C, 54·9; H, 6·1; N, 32·2. $C_{10}H_{13}N_5O$ requires C, 54·8; H, 6·0; N, 32·0%). When ring closure of the diaminopyrimidine was carried out with *NN*-dimethylformamide and phosphoryl chloride a mixture of the 2-methylamino- and 2-(*N*-methylformamido)-purines resulted.

6-Ethyl-8,9-dimethyl-2-methylaminopurine (2s).—Prepared from the diaminopyrimidine (1·5 g) and *NN*-dimethylacetamide–phosphoryl chloride reagent, the *purine* (0·4 g)

[13] D. J. Brown, P. W. Ford, and K. H. Tratt, *J. Chem. Soc.* (*C*), 1967, 1445.

had m.p. 128—129° [from petroleum (b.p. 80—100°)] (Found: C, 58·4; H, 7·2; N, 34·2. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4; N, 34·1%). No indications of the presence of any 2-(*N*-methylacetamido)-analogue were obtained.

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