6-Methylthiopurin-8-ones. A Study of their Tautomerism and their Reactions with Electrophilic Reagents

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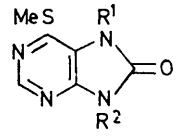
6-Methylthiopurin-8-one (1) is present in aqueous solution as the 7-NH,9-NH-tautomer. Monoanion formation involves predominantly the 9-NH group (*ca.* 80%), and in protonation positions 1 and 3 participate about equally. In compound (1) and its *N*-methyl derivatives, as in other series of purines, formation of ' resonance-stabilised ' ions is preferred over that of ' fixed ' ions. The course of methylation of the neutral molecules or of the anions by electrophilic methylating reagents parallels in general the direction of proton attachment. However, methylation of the neutral molecule of (1) takes place exclusively at N-3, owing to steric interference of the 6-methylthio-substituent with alkylation at N-1.

THE tautomeric structures and the ionisation processes in aqueous solutions of purin-8-one and its *N*-methyl derivatives can be interpreted satisfactorily by the use of u.v. and n.m.r. spectra.[1] We have now applied the same methods to 6-methylthiopurin-8-ones in order to determine the electronic and steric influence of the SMe substituent. We have also examined the methylation of 6-methylthiopurin-8-ones as neutral molecules and as anions by methyl iodide and dimethyl sulphate.

Tautomerism of the Neutral Molecules.—In the series of purin-8-ones, Brown and Mason [2] have shown that only the lactam forms exist. We assume that this is also true for 6-methylthiopurin-8-ones and shall therefore discuss only the three tautomers (I)—(III), bearing an 8-oxo-group.

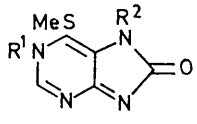
(I) 

a; $R^1 = R^2 = H$ (1)

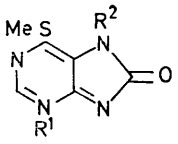
b; $R^1 = Me, R^2 = H$ (4)

c; $R^1 = H, R^2 = Me$ (5)

d; $R^1 = R^2 = Me$ (9)

(II) 

$R^1 = Me, R^2 = H$ (2)

(III) 

a; $R^1 = Me, R^2 = H$ (3)

b, $R^1 = R^2 = Me$ (7)

The u.v. spectra of the parent compound (1) and its 7-methyl derivative (4) are very similar to those of the 9-methyl (5) and the 7,9-dimethyl derivatives (9) (Table 1). Since the latter two compounds can only have structure (I) (c and d), we assign compounds (1) and (4) the corresponding structures (1a and b).

Introduction of a 1-methyl substituent as in (2) forces the molecule to assume the quinonoid structure (II), for which $\lambda_{max.}$ is shifted from *ca.* 298 to 315 nm. Attachment of a methyl group to N-3, as in (3) and (7), creates the quinonoid structure (III) and leads to an even larger bathochromic displacement of $\lambda_{max.}$ to 324—327 nm.

The compounds represented by structures (I)—(III), also differ characteristically in the chemical shift of 2-H. Thus for the four derivatives corresponding to structure (I), $\delta_{2\text{-H}}$ is in the range $8{\cdot}60 \pm 0{\cdot}06$ p.p.m. For compound (2) (II), the corresponding value is 8·80 and for (3) and (7), which are characterised by structure (III), the values are 8·40 and 8·48, respectively (Table 1).

In the case of the 1,9- (6) and 3,9-dimethyl derivatives (8) the ' neutral molecules ' can exist only as zwitterions.

Protonation.—For the cations of the present series, four tautomeric structures have to be considered, *viz.* 1,3,7- (IV), 1,3,9- (V), 1,7,9- (VI), and 3,7,9-trisubstituted (VII) systems. Formulae (IV) and (V) involve ' fixed ' cations with an amidinium-like structure in the pyrimidine ring. Experience with other purines [3-5] has shown that such structures are characterised by values of $\Delta\delta(N - C)_{2\text{-H}}$ † of about 1 p.p.m. However, (Table 1) all 2-H signals show downfield shifts of only 0·2—0·4 p.p.m. This range of values is characteristic of cations capable of spreading the positive charge over both rings of the purine system, as in (VI) and (VII).[6] The latter two structures thus represent all cations of the present series, and (IV) and (V) can be discarded. This result agrees with energy calculations, which demonstrate the lower stability of ' fixed ' purine ions as compared to those in which the charge is spread over both rings.[7]

The values of $\lambda_{max.}$ for the cations of the series are much closer to each other than those for the uncharged molecules (see Table 1). This observation supports the conclusion that the structures of all the cations are similar.

† The difference in the chemical shifts of the neutral form (N) and the cation (C).

[1] D. Lichtenberg, F. Bergmann, M. Rahat, and Z. Neiman, *J.C.S. Perkin I*, 1972, 2950.
[2] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1957, 682.
[3] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc.* (*C*), 1971, 1676.
[4] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J.C.S. Perkin I*, 1972, 1676.
[5] D. Lichtenberg, F. Bergmann, and Z. Neiman, *Israel J. Chem.*, 1972, **10**, 805.
[6] U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J.C.S. Perkin I*, 1973, 793.
[7] Z. Neiman, *Israel J. Chem.*, 1972, **10**, 819.

The cation of (6), represented exclusively by structure (VIf), shows $\delta_{2\text{-H}}$ 9·11. The cationic derivative (10), characterised by structure (VIIh), has $\delta_{2\text{-H}}$ 8·63. These values can be used as standards for comparison with the other cations. The cations of (3), (7), and (8), represented by (VIIe—g), show $\delta_{2\text{-H}}$ values in the range 8·64 ± 0·04, protonation in the 4-methylthiopyrimidine system involves N-1 and N-3 to about the same extent. However when a methyl substituent is attached to position 9, protonation at N-3 introduces marked steric interference, and cation formation procedes predominantly at N-1.

TABLE 1

Physical properties of 6-methylthiopurin-8-one and its *N*-methyl derivatives

No.	Methyl groups at position	$\lambda_{max.}$/nm N	log ε	A	Δ(A − N)	C	Δ(C − N)	p*K* for formation of anion	cation	$\delta_{2\text{-H}}$ N	A	C	R_F in solvent [a] (A)	(B)	(C)	Fluorescence
(1)		299·5	4·09	305	+5·5	325	+25·5	8·2	0·5	8·61	8·35	8·87	0·17	0·40	0·54	Violet
		255sh		274		268		13·8 [b]			8·28 [b]					
(2)	1	315·5	4·17	328	+12·5	320	+4·5	10·3	4·2 [c]	8·80	8·65	8·99 [c]	0·36	0·58	0·56	Sky-blue
(3)	3	324·5	4·34	333	+8·5	324·5	0	9·9	*ca.* 2	8·48	8·36	8·68	0·57	0·60	0·61	Violet
		252		246		247										
(4)	7	299	3·97	303	+4	330	+31	8·35	0·5	8·57	8·20	8·82	0·85	0·75	0·71	Yellow
(5)	9	297·5	4·03	307	+9·5	320·5	+23	9·0	0·5	8·66	8·40	8·96	0·85	0·75	0·75	Light blue
		224		230		237										
(6)	1,9	330	4·01			320	−10		5·2	8·79		9·11	0·50	0·64	0·60	Violet
		225				225										
(7)	3,7	327	4·25			332	+5		1·5	8·40		8·63	0·71	0·75	0·66	Violet
		252				247										
(8)	3,9	337	4·10			327	−10		5·8	8·33		8·62	0·50	0·60	0·60	Dark violet
		247				247										
(9)	7,9	298	3·97			322	+24		0·6	8·54		8·94	0·90	0·85	0·71	Pale blue
		225				237										
(10)	3,7,9					335						8·63	0·70 [d]	*e*	0·61 [d]	Yellow
						249										

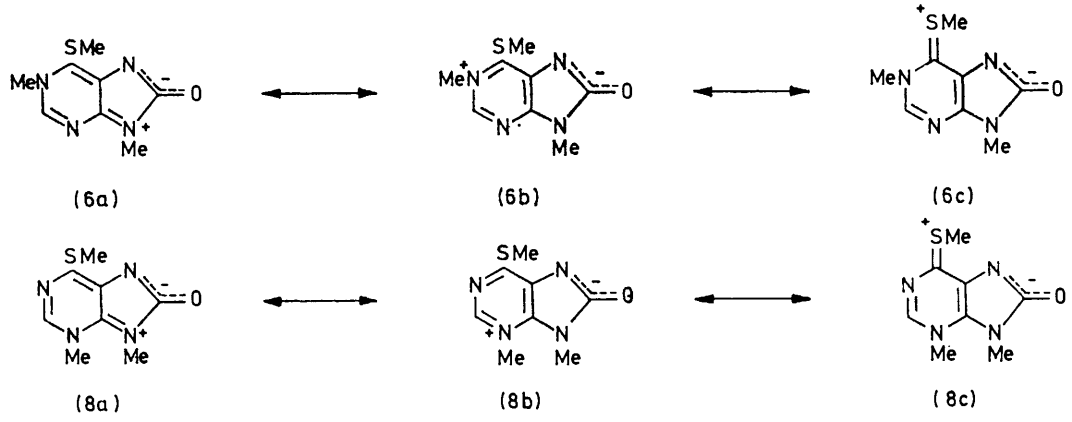
N = Neutral form; A = anion; C = cation.

[a] See Experimental section. [b] The second value of p*K* and $\delta_{2\text{-H}}$ refer to the dianion of (1). [c] Compound (2) also forms a dication, p*K* +0·2, $\delta_{2\text{-H}}$ 9·09. [d] On the paper chromatogram, the picric acid of the picrate separated from the purine (10). [e] In solvent (B) compound (10) decomposed.

i.e. close to that of compound (10). However, for the cations of (1), (4), (5), and (9), both structures (VI) and (VII) (a—d) must be considered. The $\delta_{2\text{-H}}$ values of (5) and (9) are close to that of compound (2); thus structures (VIc and d) are predominant over (VIIc and d). The cation of (1) shows $\delta_{2\text{-H}}$ 8·87, and for (4) the corresponding value is 8·82. These figures are about midway between those of the 'fixed' 1,7,9-structure (VIf) and the 'fixed' 3,7,9-structure (VIIh), suggesting a nearly equal distribution between (VIa and b) and (VIIa and b).

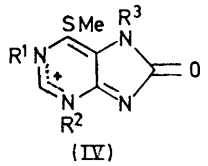
We deduce that in the presence of a 9-NH group, p*K* *Values for Cation Formation.*—According to their p*K* values for cation formation (Table 1), the members of the present series can be divided into several groups. Compounds (1), (4), (5), and (9) exhibit the lowest basicities. Apparently, the 6-methylthio-substituent weakens the basicity of the nitrogen atoms in the aromatic pyrimidine ring of (I).[6,8] A similar effect is lacking in the quinonoid structures (II) and (III).

Compounds (3) and (7) have p*K* values of 1·5 and 2, respectively, characteristic of protonation at N-9. On



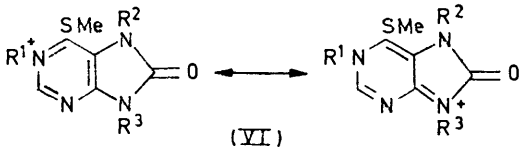
[8] W. C. Coburn, jun., M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, 1965, **30**, 1114.

the other hand, the same process in (2) is characterised by a pK of 4·2. This difference may be ascribed to steric interference by the 3-methyl group in (3) and (7) with proton attachment to N-9.



(IV)

(V)



(VI)

a; $R^1 = R^2 = R^3 = H$ (1)

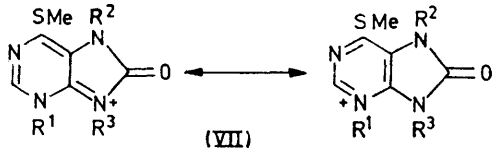
b; $R^1 = R^3 = H$, $R^2 = Me$ (4)

c; $R^1 = R^2 = H$, $R^3 = Me$ (5)

d; $R^1 = H$, $R^2 = R^3 = Me$ (9)

e; $R^1 = Me$, $R^2 = R^3 = H$ (2)

f; $R^1 = R^3 = Me$, $R^2 = H$ (6)



(VII)

a; $R^1 = R^2 = R^3 = H$ (1)

b; $R^1 = R^3 = H$, $R^2 = Me$ (4)

c; $R^1 = R^2 = H$, $R^3 = Me$ (5)

d; $R^1 = H$, $R^2 = R^3 = Me$ (9)

e; $R^1 = Me$, $R^2 = R^3 = H$ (3)

f; $R^1 = R^2 = Me$, $R^3 = H$ (7)

g; $R^1 = R^3 = Me$, $R^2 = H$ (8)

h; $R^1 = R^2 = R^3 = Me$ (10)

Compounds (6) and (8) exhibit the highest pK values in the whole series. In these two cases, however, the 'neutral' form is in fact a zwitterion [see formulae (6a—c) and (8a—c)], so that protonation involves neutralisation of the negative charge.

Methylation of Neutral Molecules with Methyl Iodide in Aprotic Solvents.—Protonation is under thermodynamic control, whereas electrophilic substitution by alkylating agents like methyl iodide is essentially irreversible and therefore kinetically controlled. Nevertheless, one may expect that in the neutral molecules the same positions which attract protons are also preferred for alkylation. However, steric factors are likely to assume greater importance in methylation than in protonation.

Compounds (2), (3), and (7), which undergo protonation at N-9, yield the 1,9- (6) and 3,9-dimethyl (8) and the 3,7,9-trimethyl (10) derivatives, respectively (Table 2).

TABLE 2

Methylation reactions of 6-methylthiopurin-8-ones as neutral molecules and as anions

	Sites of methylation of		
Compound	Neutral molecule	Monoanion	Dianion
(1)	N-3	N-9 (*ca.* 87%) [a]	N-7 (*ca.* 80%)
		N-7 (*ca.* 13%)	N-9 (*ca.* 20%)
(2)	N-9	*b*	
(3)	N-9	N-7	
(4)	N-3	N-9	
(5)	N-1 (*ca.* 77%)	N-7	
	N-3 (*ca.* 23%)		
(7)	N-9		

[a] Figures given in brackets show the approximate composition of the reaction mixture, as determined from n.m.r. measurements. [b] Compound (2) decomposes in alkaline solution. No defined methylation product could be detected.

We have already mentioned that compounds (1) and (4) probably form about equal proportions of the tautomeric cations of structures (VIa and b) and (VIIa and b). However, methylation was found to proceed exclusively at N-3 to yield compounds (3) and (7). We may ascribe this to steric interference with alkylation at N-1 by the 6-SMe group; this effect is more powerful than the influence of the 9-NH on methylation at N-3.

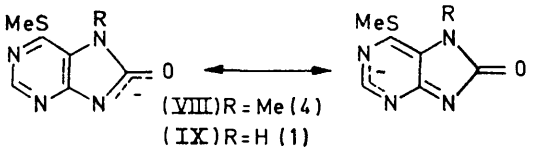
The 9-methyl derivative (5) yields a mixture of 1,9- (6) (*ca.* 75%) and 3,9- (8) (*ca.* 25%) dimethyl derivatives (see Table 2). This corresponds to the fact already discussed that the cation of (5) is preferentially represented as the 1,7,9-form (VIc). In (5), steric hindrance to alkylation at N-3 by the 9-NMe group is more powerful than the interference by the 9-NH group during alkylation of compounds (1) and (4).

The observations summarised in Table 2 establish the following relative scale of steric interference with alkylation by methyl iodide: 9-NH < 6-SMe < 9-NMe.

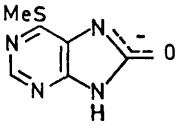
Anion Formation.—In all monomethyl derivatives of the present series, the structure of the anion follows directly from the assignment of one of the formulae (I)—(III) to the neutral molecules. In compounds (2), (3), and (5), the 7-NH group undergoes dissociation and the negative charge is distributed between N-7 and the oxygen at position 8. In the 7-methyl derivative (4), ionisation of the 9-NH group creates the 'resonating' anion (VIII). This may explain the large upfield shift of the 2-H signal [$\Delta\delta(N - A)_{2\text{-H}} = 0{\cdot}37$ p.p.m.] (Table 1).

Compound (1) forms both a mono- and a di-anion. The $\lambda_{max.}$ value of the monoanion is midway between the values for (4) and (5), but the differences are too small to permit definite conclusions. The $\delta_{2\text{-H}}$ value of the monoanion of (1) is much closer to that of (5) than to that of (4), but its first pK_a value is closer to that of

(4). Thus the monoanion (pK 8·2) is probably a mixture of tautomers (IX) and (X).



(VIII) R = Me (4)
(IX) R = H (1)



(X)

Individual values for the two dissociation processes (1) ⟶ (IX) and (1) ⟶ (X) are not known. We may however assume that they are close to the pK values of (4) (8·35) and (5) (9·0), respectively. On this basis, we estimate from the equation c_{IX}/c_X = antilog 0·65 that the monoanion is a mixture of about 80% (IX) and 20% (X). The predominant dissociation of the 9-NH group may again be ascribed to the general tendency to form resonance-stabilised ions. By way of analogy, it has been found previously that monoanion formation in purin-8-one involves preferentially the 9-NH group; dissociation of the 7-NH group contributed only about 5%.[1]

Methylation of Anions with Dimethyl Sulphate in Aqueous Solution.—This process can be compared to the transformation anion ⟶ neutral molecule by proton addition, *i.e.* the same group which undergoes dissociation may also suffer methylation. Table 3 shows that the anion of (4) is indeed alkylated at N-9 [formation of compound (9)], and the same product is obtained from (5) by attack at N-7. The 3-methyl derivative (3) gave the 3,7-dimethyl derivative (7). The most interesting results were obtained with (1). It has already been stated that the monoanion can best be represented as a mixture of the 7-NH (*ca.* 80%) and 9-NH tautomers (*ca.* 20%). In accord with this, the monoanion of (1) yielded a mixture of about 85% of (5) and 15% of (4). When the dianion of (1) was subjected to methylation, the result was reversed: about 80% of (4) and 20% of (5) were formed. This agrees with the fact that in the transformation dianion ⟶ monoanion, the proton becomes attached preferentially to position 7.

Compound (2) was unstable at alkaline pH and a pure methylation product was not isolated.

Chemical Shifts of S-*Methyl Groups.*—Upon introduction of 6-SMe substituents, the u.v. absorption maxima of purines are shifted to longer wavelengths. Thus, a bathochromic displacement of about 20 nm characterises the transition from the neutral molecules of purin-8-ones to their 6-methylthio-derivatives. For the cations, the values of $\Delta\lambda_{max.}$ are about 40 nm, and in fact the maxima approach those of the corresponding 6-mercapto-derivatives. For example, $\lambda_{max.}$ of the cation of (1) is 325 nm and that of the neutral form of 6-mercaptopurin-8-one is 332 nm. This leads to the conclusion that the mesomeric forms (XI) make an important contribution, which increases considerably upon protonation, transforming the zwitterionic form into the positively charged (XIIa) or (XIIIa).

In Table 3, almost all SMe signals of the neutral molecules are in the range 2·71—2·78 p.p.m., as in

TABLE 3

Chemical shifts of N- and S-methyl substituents

Compound	δ_{NMe} [a] N		A		C	δ_{SMe} N	A	C
(1)						2·75	2·71 [b]	2·91
(2)		4·21	4·19		4·33 [c]	2·71	2·70	2·76 [c]
(3)		4·03	4·02		4·23	2·76	2·74	2·85
(4)		3·74	3·60		3·76	2·76	2·63	2·91
(5)		3·52	3·46		3·63	2·76	2·70	2·93
(6)	(1)	4·27			4·36	2·86		2·80
	(9)	3·56			3·62			
(7)	(3)	4·01			4·21	2·78		2·85
	(7)	3·71			3·80			
(8)	(3)	4·38			4·43	2·73		2·83
	(9)	3·80			3·84			
(9)	(7)	3·77 [d]			3·87	2·73		2·95
	(9)	3·47			3·68			
(10)				(3)	4·47 [d]			2·84
				(7)	3·95			
				(9)	3·85			

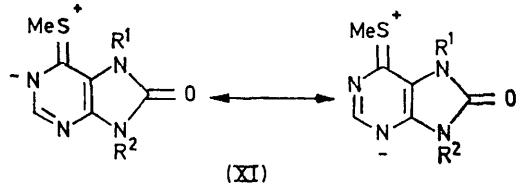
[a] Figures in brackets indicate the assignment of signals in di- and tri-methyl derivatives. [b] For the dianion, δ_{SMe} 2·68. [c] For the dication, $\delta_{1\text{-}Me}$ 4·35, δ_{SMe} 2·84. [d] Assignment of 7- and 9-methyl signals is based on comparison with the respective monomethyl derivatives (4) and (5) and is tentative.

other methylthiopurines.[6] Only the 1,9-dimethyl derivative (6) is different (δ_{SMe} 2·86), suggesting an important contribution of resonance form (6c). The stability of (6c), relative to the mesomeric forms (6a and b), apparently is greater than the stability of (XI) relative to (I). This explanation is supported by the observation that in the cations of compounds (1), (4), (5), and (9), δ_{SMe} is 2·91—2·95, representing a downfield shift of *ca.* 0·2 p.p.m. Therefore in these cations, forms (XIIa) and (XIIIa) make important contributions.

Deshielding of the SMe signal is much less pronounced in the cations of compounds (2), (3), (7), and (8), which all exhibit δ_{SMe} values close to that of (10). It is therefore suggested that (XIIb) and (XIIIb) make a less significant contribution in cations in which the pyrimidine ring bears an N-methyl substituent.

In the cation of (6), the SMe group is shielded relative to the neutral molecule. This may be explained as follows. In the zwitterionic forms (6a—c), the imidiazolone ring assumes a ' pseudo-aromatic ' structure in which the methylthio-group comes under the deshielding influence of the ring current of the ' imidazole-like ' system. Furthermore, the positive charge at the sulphur atom in (6c) is stabilised by the neighbouring negative charge at N-7. Upon protonation at N-7, the imidazolone structure is re-established and the contribution of the resonance form (XII) ($R^1 = R^3 = Me$, $R^2 = H$) to the cation of (6) (VIf) becomes less important.

Chemical Shifts of N-*Methyl Groups*.—The sequence of *N*-methyl signals is (upfield ⟶ downfield) 9, 7, 3, 1, which parallels the order observed for purin-8-ones.[1] The absolute values are similar in the two series, with the exception of the 7-methyl signal, which is shifted downfield by 0·20—0·26 p.p.m. in compounds (4), (7), and (9), relative to its value in 7-methylpurin-8-one.



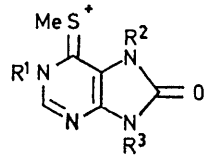
(XI)

a; $R^1 = R^2 = H$ (1)

b; $R^1 = Me$, $R^2 = H$ (4)

c; $R^1 = H$, $R^2 = Me$ (5)

d; $R^1 = R^2 = Me$ (9)

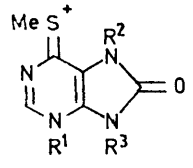


(XII)

a; $R^1 = H$

b; $R^1 = Me$

R^2, $R^3 = H$ or Me



(XIII)

a; $R^1 = H$

b; $R^1 = Me$

R^2, $R^3 = H$ or Me

This suggests steric interference by the 6-methylthio-substituent, which changes the position of the 7-methyl group and thereby alters the influence of the anisotropy of the 8-carbonyl group, leading either to increased deshielding or to decreased shielding. The special behaviour of the 7-methyl signal is also apparent in the anions and cations, including the cationic (10).

Table 3 demonstrates that the position of a given methyl signal is little influenced by introduction of additional methyl substituents [compare the 1-methyl band in (1) and (6); the 7-methyl signal in (4), (7), (9), and (10); and $\delta_{9\text{-Me}}$ in (5), (6), and (9)]. In contrast, strong deshielding is present in compounds (8) and (10) for both the 3- and 9-methyl signals. This is ascribed to steric interference between these two substituents, in accord with previous experience in other series of purines.[3,4,9]

Individual assignment of *N*-methyl signals in dimethyl derivatives is based on comparison with the monomethyl derivatives. For compound (8), the nuclear Overhauser effect was used. The area of the 2-H band is enlarged only upon irradiation at the frequency of the 3-methyl signal.

Synthetic Procedures and Structural Proofs.—The 1-methyl derivative (2) was prepared from the known 6-mercapto-1-methylpurin-8-one.[1] For the synthesis of (5), 9-methylpurine-6,8-dione [10] was thiated selectively at position 6 and subsequently *S*-methylated.

Reaction of (1) with dimethyl sulphate in alkaline solution produced a mixture of (4) and (5), from which (4) was separated by fractional crystallisation. The structure of (4) was established by catalytic dethiation to the known 7-methylpurin-8-one.[2]

The structures of the dimethyl derivatives were established by the fact that the same product was obtained from each of the possible monomethyl precursors (see Table 2). Compound (10) was formed from (7); it cannot be the 1,3,7-trimethyl isomer (IV) because of its $\delta_{2\text{-H}}$ value (see Table 1). As already discussed, the spectral properties of (10) are closely related to those of the cations of (3), (7), (8) (VIIe—g).

EXPERIMENTAL

M.p.s were determined with a Fisher-Johns apparatus. Microanalyses were performed by F. Strauss, Oxford, and by M. Goldstein, Jerusalem. U.v. spectra were measured on a Hitachi–Perkin-Elmer model 124 spectrophotometer, and n.m.r. spectra on a JEOL MH-100 instrument (internal standard sodium 3-trimethylsilyl[2,2,3,3-$^2H_4$]propionate). All n.m.r. measurements were carried out in D_2O at 70°; pH was adjusted by the use of $CF_3{\cdot}CO_2H$, $CD_3{\cdot}CO_2D$, Na_2CO_3, and NaOD.

pK Values were derived from plots of $\lambda_{max.}$ as a function of pH.

For paper chromatography (descending) on Whatman No. 1 paper, the following solvents were used: (A) n-butanol–acetic acid–water (12 : 3 : 5 v/v), (B) propan-2-ol–dimethylformamide–conc. ammonia (13 : 5 : 2 v/v), (C) ethanol–dimethylformamide–water (3 : 1 : 1 v/v). Theophylline (R_F 0·68 in all solvents) served as standard for evaluation of R_F values. Spots were located by their fluorescence under a Mineralight u.v. lamp (λ *ca.* 254 nm).

Purines.—The following compounds were synthesised according to known methods: 6-mercaptopurin-8-one [11,12] and its 1-methyl derivative; [1] 6-methylthiopurin-8-one (1) [11] and its 3-methyl derivative (3); [13] 9-methylpurine-6,8-dione.[10]

1-*Methyl*-6-*methylthiopurin*-8-*one* (2).—A suspension of 6-mercapto-1-methylpurin-8-one (2 g) in dimethylformamide (200 ml) and methyl iodide (8 ml) was stirred at room temperature for 20 min; all the material had then dissolved. The mixture was poured into ether (500 ml) and acetone (50 ml). After 15 min, the precipitate was filtered off and washed with acetone (10 ml). The solid

[9] Z. Neiman, F. Bergmann, D. Lichtenberg, and J. Deutsch, *J. Chem. Soc.* (*C*), 1971, 1822.
[10] E. Fisher and F. Ach, *Ber.*, 1899, **32**, 250.
[11] R. K. Robins, *J. Amer. Chem. Soc.*, 1958, **80**, 6671.
[12] F. Bergmann and A. Kalmus, *J. Org. Chem.*, 1961, **26**, 1660.
[13] D. Diller, Z. Neiman, and F. Bergmann, *J. Chem. Soc.*, 1968, 878.

was then dissolved in water, the pH was brought to 10 by addition of ammonia, and the solution was frozen at once and lyophilised. From the residue, ammonium iodide was removed by repeated extraction with cold acetone. The insoluble residue (0·7 g, 33%) was dissolved in cold glacial acetic acid. Addition of cold propan-2-ol caused crystallisation of (2) as rhombohedral *prisms*, m.p. 255° (Found: C, 43·0; H, 4·25; N, 28·2; S, 16·5. $C_7H_8N_4OS$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%). When kept at pH 10 the product was hydrolysed slowly to 1-methylpurine-6,8-dione.[14]

7-Methyl-6-methylthiopurin-8-one (4).—A mixture of 6-mercaptopurin-8-one (1·5 g), 2N-sodium hydroxide (20 ml), methyl iodide (1 ml), and ethanol (7·5 ml) was stirred at room temperature for 2 h; a clear solution had then formed. Excess of methyl iodide was removed *in vacuo* at room temperature, the solution was then acidified, and the precipitate was recrystallised from 15% acetic acid. The less soluble 7-methyl derivative (4) crystallised first and was collected by rapid filtration (0·7 g, 40%). It formed *needles*, m.p. 276° (from ethanol) (Found: C, 42·6; H, 4·35; N, 28·9; S, 16·2. $C_7H_8N_4OS$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%). The remaining solution contained a mixture of (4) and (5) (n.m.r.).

7-Methylpurin-8-one.—A solution of compound (4) in conc. ammonia was stirred with Raney nickel and refluxed for 90 min. Filtration, evaporation, and crystallisation from ethanol gave needles, m.p. 257°, identical with an authentic sample [2] (u.v. and n.m.r. spectra; m.p. and R_F values).

9-Methyl-6-methylthiopurin-8-one (5).—(*a*) A mixture of 9-methylpurine-6,8-dione (5 g), phosphorous pentasulphide (20 g), and pyridine (250 ml) was stirred and refluxed for 8 h. The solvent was removed *in vacuo* and the residue treated with water at 80° (250 ml). The insoluble portion was dissolved in dilute ammonia (charcoal); subsequently the pH was adjusted to 5 with glacial acetic acid. The precipitate crystallised from water in rectangular plates of *6-mercapto-9-methylpurin-8-one* (2·75 g, 50%), decomp. 300°; $\lambda_{max.}$ (pH 1) 331 nm (log ε 4·1); R_F (A) 0·55, (B) 0·52, (C) 0·60; pale-violet fluorescence (Found: C, 40·0; H, 3·2; N, 30·6. $C_6H_6N_4OS$ requires C, 39·6; H, 3·3; N, 30·8%).

(*b*) The foregoing compound (1 g) was dissolved in N-sodium hydroxide (10 ml) and stirred at room temperature for 2 h with methyl iodide (1·5 ml) in ethanol (2 ml). Excess of methyl iodide was removed *in vacuo* at room temperature and the pH adjusted to 5 with acetic acid. The precipitate of (5) (0·7 g, 66%) crystallised from butanol in rectangular *plates*, m.p. 272° (Found: C, 42·5; H, 4·35; N, 28·3; S, 16·1. $C_7H_8N_4OS$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%).

Methylation of 6-Methylthiopurin-8-one (1) *under Alkaline Conditions*.—(a) *Reaction of monoanion of* (1). A solution of (1) (0·4 g) in sodium carbonate (pH 11) and dimethyl sulphate (0·5 ml) was kept at room temperature for 2 weeks. After adjustment of the pH to 5, the solution was kept in the cold for 2 days. The precipitate (250 mg, 60%) consisted of *ca.* 13% (4) and 87% (5) (n.m.r.).

(b) *Reaction of dianion of* (1). A solution of (1) (0·5 g) in 2N-sodium hydroxide (5 ml) and dimethyl sulphate (0·3 ml) was left at room temperature for 1 week, then brought to pH 5 and kept in the cold for 2 days. The precipitate (0·3 g, 55%) was composed of about 80% of (4) and 20% of (5) (n.m.r.).

Other methylations in alkaline media are described in Table 4.

Methylation of 6-Methylthiopurin-8-ones by Methyl Iodide in Aprotic Solvents.—For description and analysis of the products see Table 5.

Methylation of 1-Methyl-6-methylthiopurin-8-one (2).—A suspension of compound (2) (0·3 g) in dimethylformamide (5 ml) and methyl iodide (2 ml) was stirred at room temperature for 90 min; all the material had then dissolved. The mixture was poured into ether (20 ml); the oil which separated was washed several times with ether until it

TABLE 4

Methylation of 6-methylthiopurin-8-ones in alkaline solution [a]

Derivative used	No.	Derivative formed	No.	Yield (%)	M.p. (°C)	Analysis [b] Found (%) C	H	N	S
3-Me	(3)	3,7-Me_2	(7)	100	284	45·8	4·8	26·3	15·2
4-Me	(4)	7,9-Me_2	(9)	56	185	45·4	5·1	26·6	15·8
9-Me	(5)	7,9-Me_2	(9)	66					

[a] General procedure: A solution of the purine (1 g) in N-sodium hydroxide (10 ml) and dimethyl sulphate (1 ml) was stirred at room temperature for 10 *min*. The precipitate was filtered off and recrystallised from boiling water. Compounds (7) and (9) form needles. [b] $C_8H_{10}N_4OS$ requires C, 45·7; H, 4·8; N, 26·7; S, 15·2%.

TABLE 5

Products of methylation of 6-methylthiopurin-8-ones with methyl iodide in dimethylformamide

Derivative formed	No.	Yield (%)	M.p. or decomp. (°C)	Purification Solvent	Crystal form	Formula	Analysis Found (%) C	H	N	S	Required (%) C	H	N	S
1,9-Me_2	(6)	40	>300	*a*	Elongated plates	$C_8H_{11}IN_4OS$	28·6	3·6	16·4	9·8	28·4	3·3	16·6	9·5
3,9-Me_2	(8)	60	265	H_2O	Needles	$C_8H_{10}N_4OS$	45·5	4·8	26·5	15·0	45·7	4·8	26·7	15·2
3,7,9-Me_3	(10)	60	177 [b]	EtOH	Rectangular plates	$C_{15}H_{17}N_7O_8S$	39·8	3·4			39·7	3·3		

[a] The method used for recrystallisation is described in the experimental section. [b] Picrate.

[14] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1961, 1298.

solidified (6). The solid (0·2 g, 40%) was dissolved in methanol–chloroform (1 : 4) *without warming*, and light petroleum (b.p. 60—80°) was added until a slight turbidity appeared.

Methylation of 3-*Methyl*-6-*methylthiopurin*-8-*one* (3).—A suspension of compound (3) (0·5 g) in dimethylformamide (50 ml) and methyl iodide (6 ml) was stirred at room temperature for 4 days; a clear solution was then obtained. The solvent was evaporated off *in vacuo* and the residue triturated with acetone. The solid was dissolved in dil. ammonia and the pH brought again to 5 with glacial acetic acid. The betaine of (8) crystallised rapidly.

Methylation of 7-*Methyl*-6-*methylthiopurin*-8-*one* (4).—A solution of compound (4) (0·5 g) and methyl iodide (5 ml) in dimethylformamide (40 ml) was kept at room temperature for 4 days and then poured into ether (150 ml). The oil that separated solidified upon trituration with ether and acetone. Paper chromatography revealed the presence of both (7) and (10); the n.m.r. spectrum indicated about 80% of (7) and 20% of (10).

Methylation of 3,7-*Dimethyl*-6-*methylthiopurin*-8-*one* (7).—A suspension of compound (7) (0·5 g) in dimethylformamide (25 ml) and methyl iodide (3 ml) was stirred at room temperature for 4 days; all the material had then dissolved. The mixture was poured into ether (100 ml) and the oil which separated was washed with ether and acetone until it solidified. The crude iodide of (10) could not be recrystallised without decomposition. Therefore the picrate was prepared in ethanol. The physical data given in Table 5 refer to this salt.

Methylation of 9-*Methyl*-6-*methylthiopurin*-8-*one* (5).—A suspension of compound (5) (0·4 g) in dimethylformamide (5 ml) and methyl iodide (1 ml) was kept at 60° for 24 h. The homogeneous solution was poured into ether (20 ml); the oil which separated was washed with ether and acetone until it solidified. Paper chromatography revealed the presence of both (6) and (8). The n.m.r. spectrum indicated about 77% of (6) and 23% of (8).

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