Reactivity of 6-Methylthiopurin-8-ones. Properties of 6-Methylsulphonylpurin-8-ones

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All 6-methylthiopurin-8-ones (except those bearing a 1-methyl substituent, which decompose) are converted by chlorine in methanol at 0° into the corresponding sulphones. In a series of *N*-methyl 6-methylthiopurin-8-ones, only the 1-methyl, the 1,9- and 3,9-dimethyl, and the 3,7,9-trimethyl derivatives undergo thiohydrolysis. In contrast, all the corresponding sulphones are attacked by hydrogen sulphide anion. A 6-methylsulphonyl substituent weakens basicity and increases the acid strength of purines. In 6-methylsulphonylpurin-8-one, anion formation follows the order N-9 ⟶ N-7. A 3-methyl substituent, by virtue of reduction of the ring current in the pyrimidine system, causes a diamagnetic shift of the 2-H signal.

PREVIOUS studies have suggested that introduction of an 8-oxo-group may change the chemical reactivity of 6-methylthiopurines profoundly.[1] This was shown for 3-methyl-6-methylthiopurin-8-one (3), which was resistant to attack by hydrogen sulphide anion, whereas 3-methyl-6-methylthiopurine itself underwent thiohydrolysis readily.[2] Furthermore, compound (3) was oxidised by chlorine in absolute methanol at 0° to the corresponding sulphone (22),[1] whereas the analogue lacking the 8-oxo-group was transformed under the same conditions into 6-chloro-3-methylpurine.[3]

In order to elucidate more thoroughly the factors responsible for this change in reactivity, we have now examined a number of *N*-methyl derivatives of 6-methylthiopurin-8-one (1) (Table 1).[4]

TABLE 1

Substitution patterns of the purines (1)—(28)

Methyl substituents at positions	6-Methylthiopurine-8-ones	6-Thioxopurine-8-ones	6-Methylsulphonylpurin-8-ones
None	(1)	(11)	(21)
1	(2)	(12)	
3	(3)	(13)	(22)
7	(4)	(14)	(23)
9	(5)	(15)	(24)
1,9	(6)	(16)	
3,7	(7)	(17)	(25)
3,9	(8) [a]	(18)	(26) [a]
7,9	(9)	(19)	(27)
3,7,9	(10) [b]	(20)	(28) [b]

[a] Zwitterion. [b] Fixed cation.

Thiohydrolysis.—Six members of the series [compound (1), its 3- (3), 7- (4), and 9-methyl derivatives (5), and the 3,7- (7) and 7,9- (9) dimethyl derivatives] are resistant to thiohydrolysis. On the other hand, four members were converted into the corresponding 6-thioxopurin-8-ones: the 1-methyl derivative (2), the 1,9- (6) and 3,9- (8) dimethyl derivatives, and 3,7,9-trimethyl-6-methylthiopurinium cation (10) [see Table 2(A) and Scheme 1].

Thus, with the exception of compound (2), all derivatives which can form anions, are resistant to attack by SH^-. The negative charge on the anions not only repels the nucleophilic reagent, but also reduces the mesomeric effect of the *N*-methyl group, which plays a fundamental role in nucleophilic attack on methylthiopurines.[5,6] In compounds (7) and (9), which cannot form anions, polarisation of the 3- and 9-alkyl substituents, respectively, places a partial negative charge at N-1 [(7b) and (9b) in Scheme 2]. This effect may be responsible for resistance to attack by SH^-.

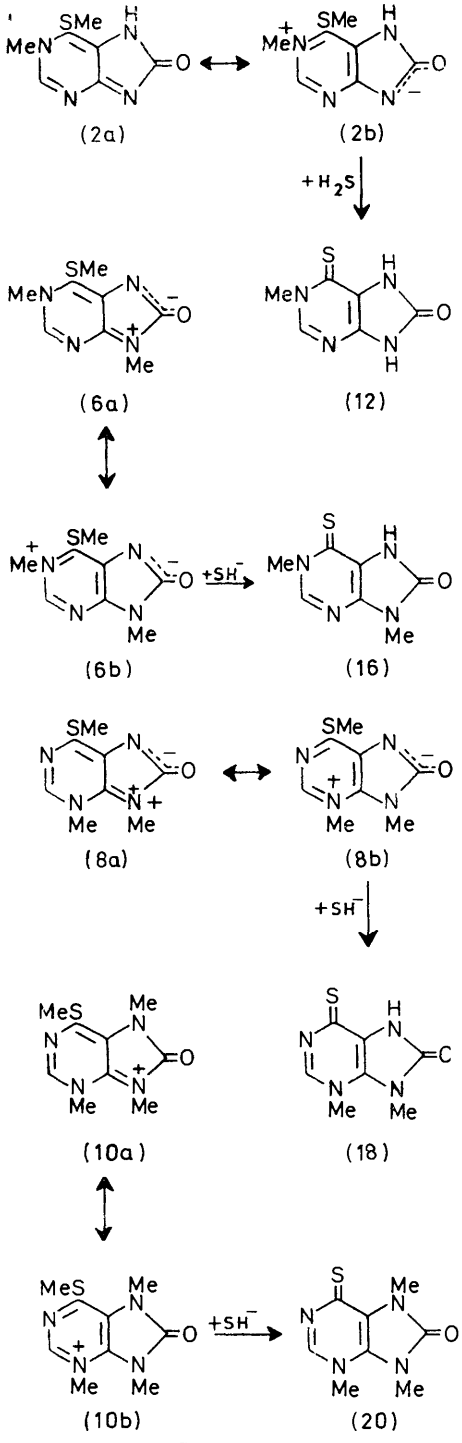
A different situation is encountered with the 1,9- and 3,9-dimethyl derivatives. Above pH 6, compounds (6) and (8) exist as zwitterions,[4] in which the effect of the negative charge at N-7 is neutralised by the positive charge on the *N*-methyl groups (Scheme 1).

3,7,9-Trimethyl-6-methylthio-8-oxopurinium cation can be represented by the resonance forms (10a and b), analogous to (8a and b) (Scheme 1). The susceptibility of (10) to nucleophilic attack is thus easily understood.

The ready reaction of the 1-methyl derivative (2) is surprising. This compound is attacked not only under the usual conditions (pH *ca.* 11), but also by aqueous

[1] D. Diller, Z. Neiman, and F. Bergmann, *J. Chem. Soc.* (*C*), 1968, 878.
[2] Z. Neiman and F. Bergmann, *Israel J. Chem.*, 1965, **3**, 85.
[3] F. Bergmann, Z. Neiman, and M. Kleiner, *J. Chem. Soc.* (*C*), 1966, 10.
[4] F. Bergmann, M. Rahat, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 1225.
[5] U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. Org. Chem.*, 1973, **38**, 2066.
[6] U. Reichman, F. Bergmann, and Z. Neiman, *J. Org. Chem.*, 1973, **38**, 3367.

hydrogen sulphide, *i.e.* by a much weaker nucleophile (see Experimental section). The same applies to the 1,9-dimethyl derivative (6), whereas (8) and (10) are

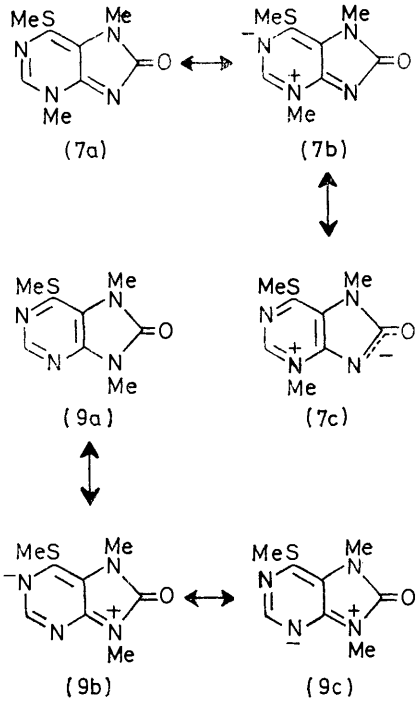


SCHEME 1

resistant to hydrogen sulphide. Likewise the 3-methyl derivative (3), although present as neutral molecule, is not attacked by this reagent.

[7] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J.C.S. Perkin I*, 1973, 2445.

It was thought that the reactions of (2) and (6) might involve ring opening at the 1,6-bond and recyclisation to (12) and (16), respectively. However, monitoring of the u.v. spectrum during the reaction with hydrogen sulphide revealed no other change besides the expected rise of $\lambda_{max.}$ in the conversion of (2) into (12).



SCHEME 2

Strong steric interference is observed between the 1-methyl and 6-methylthio-substituents.[7] The relief of steric strain that is achieved by conversion of (2) and (6) into (12) and (16), respectively, may be the driving force for these reactions. Compounds (8) and (10) are much less reactive and undergo thiohydrolysis only with the stronger nucleophile SH^-.

Reaction of 6-Methylthiopurin-8-ones with Chlorine.— In the reaction with chlorine in absolute methanol at or below 0°, the 1-methyl derivatives (2) and (6) decompose. All other members of the series are converted into the corresponding 6-methylsulphonyl derivatives (21)—(28) (Table 3). In a few cases [*e.g.* in the conversion (7) ⟶ (25)], the crude reaction mixture contained small amounts of a second, unstable product which was not isolated. These by-products may have been the 6-chloro-derivatives.

In general, the reaction of 6-methylthiopurines with chlorine can take two different courses[8] (Scheme 3). Either the dichloro-derivative (B) reacts with solvent to produce the sulphoxide (C) [the latter again adds chlorine (D) and is then converted by solvent into the sulphone (E)], or (B) [or (D)] undergoes electrophilic substitution by Cl^+ to give (F), with elimination of MeSCl (or MeSOCl). Under anhydrous conditions, the

[8] C. W. Noell and R. K. Robins, *J. Amer. Chem. Soc.*, 1959, **81**, 5997.

TABLE 2

Thiohydrolysis of 6-methylthio- and 6-methylsulphonyl-purin-8-ones

No. of purine	*N*-Methyl groups at positions	Reaction time (min)	6-Thioxo-purine formed	Yield (%)	M.p. (°C)	Crystal form and colour	Neutral form $\lambda_{max.}$/nm	Neutral form log ε
(A) 6-Methylthio [a]								
(2)	1	SH^- 5 H_2S 5	(12) [b]	80	>300	Rectangular plates	327 239	4·31 4·16
(6)	1,9	SH^- <1 H_2S 10	(16)	80	>300	Yellowish prisms	330 241	4·31 4·25
(8)	3,9	SH^- 120	(18)	60	>300	Yellow prisms	344 255	4·45 4·08
(10)	3,7,9	SH^- <1	(20)	80	295	Yellow needles	350 258	4·38 4·00
(B) 6-Methylsulphonyl [c]								
(21)		300	(11) [d]	60	>300	Pale yellow needles	332 237	4·32 4·14
(22)	3	10	(13) [e]	60	>300	Yellow needles	337 257	4·45 4·12
(23)	7	30	(14)	90	>300	Yellowish prisms	335 240	4·30 3·93
(24)	9	30	(15) [f]	80	>300	Rectangular plates	333 239	4·20 4·05
(25)	3,7	30	(17)	90	~300	Yellowish prisms	340 259	4·27 3·98
(26)	3,9	120	(18)	60	>300	Yellow prisms	344 255	4·45 4·08
(27)	7,9	30	(19)	50	>300	Yellowish prisms	336 239	4·20 4·08
(28)	3,7,9	15	(20)	80	295	Yellow needles	350 258	4·38 4·00

Analysis of new 6-thioxopurin-8-ones

Compound	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(14)	39·6	3·3	30·8	17·6	$C_6H_6N_4OS$	39·3	3·4	31·1	17·8
(16)	42·9	4·1	28·6	16·3	$C_7H_8N_4OS$	42·65	3·9	28·7	16·5
(17)						42·7	4·3	28·3	16·7
(18)						42·6	4·2	28·3	16·6
(19)						42·8	4·3	28·65	17·0
(20)	45·7	4·8	26·7	15·2	$C_8H_{10}N_4OS$	45·9	5·2	26·4	15·2

[a] At room temp., compounds (2) and (6) reacted with both SH^- and H_2S; (8) and (10) reacted only with SH^- and were resistant to H_2S even at reflux temp. [b] See ref. 12. [c] All reactions with ammonium sulphide were carried out at room temp., with the exception of the thiohydrolysis of (22), which required reflux temp. [d] See ref. 15. [e] See ref. 1. [f] See ref. 16.

TABLE 3

Formation of 6-methylsulphonylpurin-8-ones by chlorination of 6-methylthiopurin-8-ones

6-Methylthio-derivative	Reaction time [a] (min)	Methanol (ml per g)	6-Methylsulphonyl-purine formed	Yield (%)	M.p. or decomp. p. (°C)	Crystal form [b]	R_F in solvent [c] (A)	(B)	(C)	Fluorescence
(1)	30	40	(21)	70	>300	Prismatic columns	0·44	0·55	0·73	Violet
(3)	30	12	(22)	77	>300	Plates	0·20	0·53	0·69	Violet
(4)	60	100	(23)	70	295	Prismatic rods	0·79	0·71	0·75	Violet
(5)	30	40	(24)	80	245	Prisms	0·58	0·65	0·77	Violet
(7)	10	40	(25)	35	*ca.* 300	Hexagonal columns	0·49	0·74	0·69	Brilliant violet
(8)	5	10	(26)	40	167 [d]	Prisms	0·57	*e*	0·63	Brilliant violet
(9)	60	80	(27)	70	194—195	Rhombic plates	0·85	0·85	0·79	Violet
(10)	5	10	(28)	40	186 [d]	Prisms	0·57	*e*	0·61	Violet

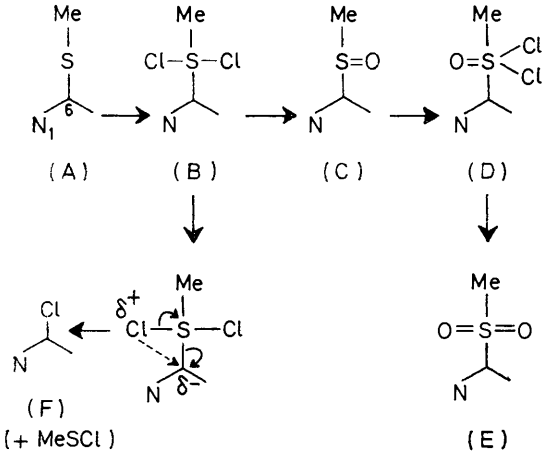
Compound	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(21)	33·6	2·8	26·2	15·0	$C_6H_6N_4O_3S$	33·6	2·75	26·2	15·1
(23)	36·8	3·5	24·6	14·0	$C_7H_8N_4O_3S$	37·1	3·7	24·8	14·5
(24)						36·6	3·5	24·6	14·2
(25)	39·7	4·1	23·1	13·2	$C_8H_{10}N_4O_3S$	39·5	4·1	23·4	
(27)						39·6	4·0	23·2	13·2
(26)	35·7	2·8	20·8	6·8	$C_{14}H_{13}N_7O_{10}S$	35·6	2·7	20·65	
(28)	37·1	3·1	20·2	6·6	$C_{15}H_{15}N_7O_{10}S$	37·1	2·7	20·6	

[a] All chlorinations at 0 to + 5°. [b] All methylsulphonyl derivatives were recrystallised from water. [c] For solvent composition see Experimental section. [d] These purines were isolated as picrates. [e] Decompose in solvent (B).

latter reaction usually takes place at or below 0°, whereas conversion into the sulphone requires warming to 50—60°.[8] The finding that the members of the present series are converted into sulphonyl derivatives at low temperatures suggests that electrophilic substitution, to yield (F), is hampered because the 8-oxo-group reduces the electron density at C-6.

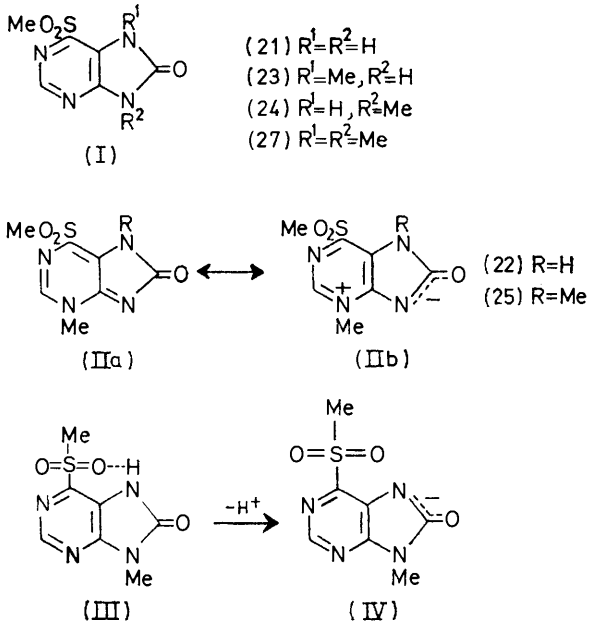
Thiohydrolysis of 6-Methylsulphonylpurin-8-ones.—All members of the 6-methylsulphonyl series (21)—(28) (Table 1) readily undergo thiohydrolysis to the corresponding 6-thiones (11)—(20) (Table 2B) and are thus much more susceptible to nucleophilic attack than the corresponding 6-methylthio-derivatives. The same applies to alkaline hydrolysis, as will be shown in a separate publication. Apparently the strong electronegative character of the methylsulphonyl group facilitates nucleophilic substitution at C-6 and thus overcomes the adverse effect of anion formation in compounds (21)—(24).

Properties of 6-Methylsulphonylpurin-8-ones.—(a) *Tautomerism.* The neutral forms of the mother substance (21), its 7- (23) and 9- (24) methyl derivatives, and the 7,9-dimethyl derivative (27) have very similar absorption spectra (Table 4). Therefore they can be represented by the common structure (I) (Scheme 4). The values of $\lambda_{max.}$ for the 3-methyl derivatives (22) and (25), which have the quinonoid structure (II) (Scheme 4), are higher than those of the purines represented by formula (I). Structure (II) also explains the finding (Table 5) that the protons at C-2 in (22) and (25) are shielded relative to those in the derivatives



SCHEME 3

represented by structure (I). A similar relationship is observed for the 6-methylthio-derivatives (3) and (7), although the difference between their $\delta_{2\text{-H}}$ values and that of (1) is much smaller (see Table 6). Calculations according to the method of McWeeny [9] show that the ring current in the pyrimidine rings of compounds (3) and (22) is less than in compounds (1) and (21). Table 6 demonstrates that the ring current in the aromatic pyrimidine ring of (21) is larger than in (1). It also indicates that the decrease in the J_i value, due to introduction of a 3-methyl substituent, is about twice



SCHEME 4

as large in (22) as in (3), in parallel with the relative shifts of the 2-H signals.

(b) *Anion formation.* All pK values in the 6-methylsulphonyl series are 1·4—2 units lower than those of the corresponding 6-methylthiopurin-8-ones (Table 4), owing to the pronounced electronegative character of the methylsulphonyl substituent.

Anion formation in the sulphones (21)—(24) is accompanied by a bathochromic shift of $\lambda_{max.}$ (Table 4), Dissociation of the 9-NH group in (23) is characterised by $\Delta\lambda_{max.}$ 10 nm and pK 6·4. Ionisation of the 7-NH group in (24) leads to a $\Delta\lambda_{max.}$ of 20 nm and a pK of 7·5. From these values we may derive the sequence of ionisation of the mother substance (21). The latter can form a mono- and a di-anion. The first dissociation step of (21) is characterised by $\Delta\lambda_{max.}$ 12 nm and pK 6·5, almost identical with the values for (23). The difference between the pK values of (23) and (24) is 1·1. We may thus estimate that the monoanion of (21) is a tautomeric mixture of about 93% of the form bearing the charge at N-9, and about 7% of the ion obtained by dissociation of the 7-NH group. Ionisation of the 9-NH group is predominant because spreading of the charge over both rings is now possible by participation of the pyrimidine nitrogen atoms. On the other hand, in the case of dissociation of 7-NH, a similar delocalisation of the negative charge would involve the carbon atoms of the pyrimidine ring. HMO calculations show, however, that the latter carry a positive charge. An additional factor making dissociation of 7-NH more difficult may be loss of the hydrogen bond between

[9] R. McWeeny, *Mol. Phys.*, 1958, **1**, 311.

TABLE 4

U.v. absorption maxima and pK values of 6-methylsulphonylpurin-8-ones

Compound	$\lambda_{max.}$/nm and log ε						pK for formation of	
	N [a]		*A*		Δ(A − N)	C	anion [b]	cation
(21)	296	4·18	308 [c]	4·20	+12	>300	6·5 (8·2)	<−1
(22)	316	4·11	331	4·11	+15	313	8·5 (9·9)	+0·3
	237	3·75	252	3·63	+15			
(23)	300	4·00	310	4·11	+10	>306	6·4 (8·35)	<−1
(24)	297	4·07	317	4·12	+20	>300	7·5 (9·0)	<−1
			233	4·05				
(25)	321	4·16				317		−0·2
	242	3·71						
(26)	355 [d]	(3·88)				338 [e]	*ca.* 8·7 [f]	*ca.* 3·8 [g]
						279		
(27)	300	4·26				>305		<−1
	250sh	3·56						
(28)						322 [h] (3·86)		
						225 (4·33)		

[a] N = neutral form; A = anion; C = cation. [b] Figures in parentheses indicate the pK values of the corresponding 6-methylthio-derivatives [4] (see Table 1). [c] Compound (21) forms a dianion with $\lambda_{max.}$ 325 nm (log ε 4·19); Δ(A_2 − A_1) 17 nm; pK > 11. [d] Approximate $\lambda_{max.}$ of zwitterion; the compound decomposes above pH 9, before conversion into the zwitterion is complete; therefore the value of log ε is only approximate. [e] Compound (26) forms also a dication with $\lambda_{max.}$ 317 nm. [f] pK for the conversion of cation into zwitterion. [g] pK for formation of dication. [h] $\lambda_{max.}$ of fixed cation. At pH values above 4, compound (28) decomposes.

TABLE 5

N.m.r. data of 6-methylsulphonylpurin-8-ones in D_2O at 70° [a]

Compound	Me at positions	$\delta_{2\text{-H}}$				$\delta_{6\text{-SO}_2\text{Me}}$				δ_{NMe}			
		N	A	Δ(N − A)	C	N	A	Δ(N − A)	C	N	A	Δ(N − A)	C
(21)		8·80	8·59 [b]	0·21		3·46	3·41 [b]	0·05					
(22)	3	8·56	8·27	0·29	8·88	3·45	3·40	0·05	3·50	4·08	4·03	0·05	4·24
(23)	7	8·77	8·61	0·16		3·60	3·55	0·05		3·74	3·74	0	
(24)	9	8·91	8·56	0·35		3·47	3·46	0·01		3·57	3·55	0·02	
(25)	3,7	8·57			8·80	3·56			3·53	(3)4·07			4·24
										(7)3·73			3·77
(26)	3,9	8·53 [c]			8·51 [d]	3·48 [c]			3·48 [d]	(3)4·48 [c]			4·50 [d]
										(9)3·93			3·93
(27)	7,9	8·90				3·62				(7)3·79			
										(9)3·62			
(28)	3,7,9				8·92 [e]				3·70	(3)			4·61
										(7)			3·86
										(9)			4·05

[a] For anion formation, NaOD was added; for cation, $CF_3{\cdot}CO_2H$ or D_2SO_4 was used. [b] The δ values for the dianion were measured at room temp., because at pH 14 the compound decomposed upon warming; $\delta_{2\text{-H}}$ 8·27, $\delta_{6\text{-SO}_2\text{Me}}$ 3·36. The corresponding values for the monoanion at room temp. were $\delta_{2\text{-H}}$ 8·52, $\delta_{5\text{-SO}_2\text{Me}}$ 3·37. [c] These values apply to the zwitterion (pH *ca.* 9·0). [d] The dication of compound (26) showed $\delta_{2\text{-H}}$ 9·06, $\delta_{6\text{-SO}_2\text{Me}}$ 3·57, $\delta_{3\text{-Me}}$ 4·67, $\delta_{9\text{-Me}}$ 4·04. [e] The values for fixed cation at pH < 0.

7-NH and the 6-sulphonyl substituent [see structures (III)—(IV) in Scheme 4].

The second ionisation step in (21) involves mainly the 7-NH group and is accompanied by a larger bathochromic displacement (17 nm) of $\lambda_{max.}$. A similar sequence of anion formation (N-9 ⟶ N-7) has been observed previously for purin-8-ones [10] and 6-methylthiopurin-8-ones.[4]

The diamagnetic shifts of the 2-H signals upon anion formation support the foregoing conclusions (Table 5). Thus $\Delta\delta(N - A)_{2\text{-H}} = 0{\cdot}16$ p.p.m. for compound (23) and 0·35 for the 9-methyl isomer (24). For monoanion formation of (21) the difference is 0·21, indicating again preferential dissociation of the 9-NH group, as in (23). For the transformation of the mono- into the di-anion, $\Delta\delta(A_1 - A_2)_{2\text{-H}} = 0{\cdot}25$ p.p.m., *i.e.* the sum of the two shifts in (21) is approximately the same as the sum of the individual shifts in (23) and (24). The greater upfield shift of the 2-H signal upon ionisation of 7-NH may be explained by the same factors which are responsible for the relatively high pK of this group,

TABLE 6

Ring current (J_i) in purines *

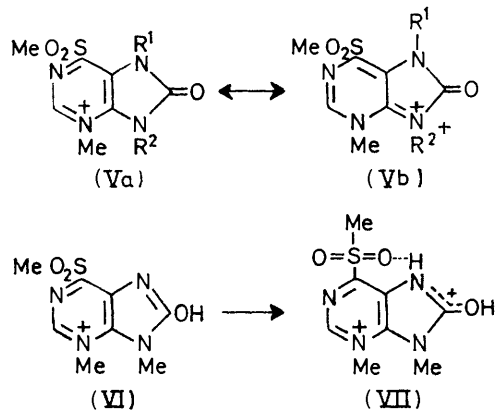
Compound	J_i Value for pyrimidine ring	J_i Value for imidazolone ring	$\delta_{2\text{-H}}$ of neutral molecule
6-Methylthiopurin-8-one (1)	6·55	3·95	8·61
3-Methyl derivative (3)	5·66	3·46	8·48
6-Methylsulphonylpurin-8-one (21)	7·87	4·86	8·80
3-Methyl derivative (22)	5·95	6·72	8·56

* See Experimental section.

i.e. participation of C-2 in charge distribution and loss of hydrogen bonding of the 6-sulphonyl substituent. The latter now exerts a stronger shielding effect on the pyrimidine proton. These considerations also explain the large value of $\Delta\delta(N - A)_{2\text{-H}}$ (0·29 p.p.m.) for (22) upon dissociation of 7-NH.

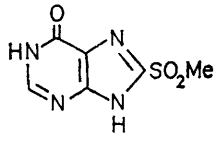
[10] D. Lichtenberg, F. Bergmann, M. Rahat, and Z. Neiman, *J.C.S. Perkin I*, 1972, 2950.

Protonation.—The bathochromic shift indicating cation formation in compounds (21), (23), (24), and (27) (Table 4) takes place only in extremely acidic



SCHEME 5

media (pH < -1). The $\delta_{2\text{-H}}$ values, measured in 50% sulphuric acid, were not significantly different from those of the neutral molecules and are not recorded in Table 5, because cation formation is still incomplete at pH −3.



(29)

Protonation of these four purines may involve either the 8-carbonyl group or the oxygen atoms of the 6-sulphonyl substituent. HMO calculations of electron densities indicate that the charge density on the sulphonyl oxygen atoms (*ca.* −0·78) is substantially higher than on the 8-carbonyl (*ca.* −0·42).

On the other hand in the 3-methyl derivatives (22) and (25), a small *hypsochromic* displacement of $\lambda_{max.}$ appears around pH 0. Protonation of these two compounds at N-1 would create an amidinium-like cation and would therefore cause deshielding of the 2-H signal by about 1 p.p.m.[11,12] However the values of $\Delta\delta$(N — C)$_{2\text{-H}}$ are 0·32 p.p.m. for (22) and 0·23 for (25) (Table 5). Thus protonation probably takes place at position 9 to yield the resonating structure (Va and b; R^2 = H) (Scheme 5), (Va) making the greater contribution. This would explain the slight hypsochromic displacement of $\lambda_{max.}$ and the paramagnetic shift of $\delta_{2\text{-H}}$ in the cations of (22) and (25), so that these chemical shifts come close to the $\delta_{2\text{-H}}$ values of the neutral molecules represented by structure (I) (see Scheme 4 and Table 5).

Compound (26) occupies a special position. Upon conversion of the zwitterion into the cation, $\lambda_{max.}$ is lowered to 338 nm; transformation into the dication leads to $\lambda_{max.}$ 317 nm. This value is similar to those of the cations of (22) and (25) and not much different from that of the fixed cation (28). The positively charged molecules of (22), (25), and (28) are shown in Scheme 5 (Va–b). This however leaves the process of conversion of zwitterion to cation in (26) unexplained. It may involve protonation of the 8-oxo-group (VI). If indeed the monocation of (26) is represented by (VI) and the dication by (VII), then the appearance of a 7-NH group in the latter could explain the relatively large deshielding of the 2-H signal ($\Delta\delta$ 0·55 p.p.m.; Table 5). On the other hand, the transformation zwitterion [structures (8a and b) in Scheme 1] ⟶ cation [(VI) in Scheme 5] leaves the signal of 2-H in (2b) practically unchanged.

^{1}H *N.m.r. signals of* NMe *and* $MeSO_2$ *groups.* The sequence of *N*-methyl signals (upfield ⟶ downfield) for all molecular forms of the 6-methylsulphonyl derivatives is 9 ⟶ 7 ⟶ 3 (Table 5). This order is due to the fact that the methyl groups at N-7 and N-9 are shielded by the 8-oxo-group. The absolute δ values are close to those of the *N*-methyl substituents in the corresponding 6-SMe derivatives,[4] where the same sequence has been found. In both series, the 7-Me group is deshielded relative to the 9-methyl group, because the former is under the influence of the magnetic anisotropy of the substituent at C-6. Indeed, if this substituent is hydrogen, the two signals are practically identical.[10]

The relative position of an *N*-methyl signal is only slightly influenced by the presence of other *N*-methyl substituents (Table 5). Only compounds (26) and (28) show exceptional behaviour. Here the 3-methyl signal is shifted downfield by 0·45—0·50 p.p.m., relative to the position of this signal in (22). Likewise, the 9-methyl group is deshielded by 0·36—0·38 p.p.m., relative to compound (24). These deviations can be ascribed to steric interference between 3- and 9-methyl substituents.[13,14]

The signals of the 6-methylsulphonyl group are 0·7—0·8 p.p.m. downfield of the SMe bands in the corresponding 6-methylthio-derivatives. In the 7-methyl derivatives (23), (25), (27), and (28), the $MeSO_2$ group is deshielded by 0·10—0·20 p.p.m., relative to the other members of the series. We may attribute this paramagnetic shift to steric interference between the 7- and 6-substituents. An even greater steric effect may be expected for 1-methyl-6-methylsulphonylpurines. However, so far we have been unable to synthesise such derivatives.

Evidence for the Structures of New Purines.—All new methylsulphonylpurines were converted into the corresponding 6-thioxopurin-8-ones (11)—(20) (Table 2). The mother substance (11) [15] and its 1- (12),[12] 3- (13),[1] and 9- (15) methyl [4] derivatives are known compounds.

[11] D. Lichtenberg, F. Bergmann, and Z. Neiman, *Israel J. Chem.*, 1972, **10**, 805.
[12] U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J.C.S. Perkin I*, 1973, 793.
[13] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc.* (*C*), 1971, 1676.
[14] Z. Neiman, F. Bergmann, and D. Lichtenberg, *J. Chem. Soc.* (*C*), 1971, 1822.
[15] R. K. Robins, *J. Amer. Chem. Soc.*, 1958, **80**, 6671.

The new members of the 6-thioxo-series [(14) and (16)—(20)] were converted into the corresponding 6-methylthio-derivatives (4) and (6)—(10) (see Table 1), which have been described before.[4]

Noell and Robins[8] have reported a compound derived from 6,8-bismethylthiopurine by reaction with chlorine in aqueous methanol, as '6-methylsulphonyl-8-oxopurine.' However, the physical properties of this product distinguish it clearly from (21) (see Experimental section). We conclude that the authors actually obtained the isomeric 8-methylsulphonylhypoxanthine (29). Indeed the absorption maximum of (29) (265 nm) is closer to that of hypoxanthine (249 nm), whereas the values of (1) and (21) are 299·5 and 296 nm, respectively. Presumably, 6,8-bismethylthiopurine is converted into 6-chloro-8-methylsulphonylpurine, which undergoes hydrolysis to (29).

EXPERIMENTAL

M.p.s were determined on a Fisher–Johns apparatus. Microanalyses were performed by M. Goldstein, Jerusalem, and F. Strauss, Oxford, England. U.v. spectra were measured on a Hitachi–Perkin-Elmer 124 spectrophotometer. pK Values were determined from a plot of $\lambda_{max.}$ as function of pH. For n.m.r. spectra, a JEOL MH-100 instrument was used, with TSP (sodium 3-trimethylsilyl-[2,2,3,3-$^2H_4$]propionate; Merck, Sharp, and Dohme) as standard. For paper chromatography by the descending method, Whatman No. 1 paper was used with the following solvents: (A) (acidic) n-butanol–AcOH–H_2O (12 : 3 : 5 v/v); (B) (basic) propan-2-ol–$Me_2N{\cdot}CHO$–25% ammonia (13 : 5 : 2 v/v); (C) (neutral) ethanol–$Me_2N{\cdot}CHO$–water (3 : 1 : 1 v/v). Spots were located under a Mineralight u.v. lamp (λ *ca.* 254 nm). All R_F values are expressed relative to theophylline (R_F 0·68 in all solvents).

General Procedures.—(1) *Preparation of 6-methylsulphonylpurin-8-ones* (21)—(28). Absolute methanol was saturated at 0° with dry chlorine for 30 min. After addition of a suspension of the 6-methylthiopurin-8-one in cold methanol, the mixture was kept at 0° while chlorine gas was bubbled through. Reaction times are specified in Table 3. The mixture was then concentrated *in vacuo*, first at room temperature and finally on a water-bath at 40°. The residue was neutralised and the precipitate recrystallised from water. With compounds (26) and (28), purification proved difficult; they were therefore characterised as picrates. The properties of compounds (21)—(28) are described in Table 3.

(2) *Thiohydrolysis.* (*a*) Through a solution of ammonia (*d* 0·88) hydrogen sulphide gas was bubbled at room temperature for 30 min. After addition of the purine, more gas was passed through the solution for the period stated in Table 2. The solution was then neutralised; the precipitate was filtered off and recrystallised from water. The properties of the 6-thioxopurin-8-ones (11)—(20) are described in Table 2.

(*b*) Through a solution of the purine in water, hydrogen sulphide was bubbled for the time specified in Table 2. The precipitate formed was recrystallised from water.

(3) S-*Methylation.* A solution of a 6-thioxopurin-8-one in dimethylformamide and methyl iodide (3 equiv.) was gently refluxed for 30 min. The 6-methylthio-derivatives formed were isolated and purified as described previously.[4]

Purines.—The following compounds were prepared by known procedures: 6-thioxopurin-8-one (11)[15] and its 1- (12),[12] 3- (13),[1] and 9- (15) methyl[4] derivatives; 6-methylthiopurin-8-one (1) and its methyl derivatives;[4] 3-methyl-6-methylsulphonylpurin-8-one (22);[1] and 8-methylsulphonylhypoxanthine (29),[8] $\delta_{2\text{-H}}$ 8·14, $\delta_{8\text{-}SO_2Me}$ 3·40 (in Na_2CO_3 at pH 10).

Calculation of Ring Currents.—Ring currents were calculated by the method of McWeeny,[9] as developed by Figeys and Dedieu.[16] These authors used (*a*) self-consistent iterative functions for the variation of the exchange integral β with bond order, and (*b*) the relation of the latter with bond length. They introduced iterative functions for different carbon–carbon bonds and for links of carbon with nitrogen and oxygen, but not for carbon–sulphur and sulphur–oxygen bonds, which are needed for calculations on the compounds included in Table 6.

Häfelinger[17] has derived parameters for the resonance integrals of the carbon–sulphur bond, using HMO bond-bond polarisabilities in combination with bond order–bond length relations. The iterative functions for the C–S bonds which we have used in the present calculations were based on Häfelinger's values, by assuming a linear relation between exchange integral and bond length, and limiting the latter to the range 1·5—1·8 Å.[17] The

$$\beta_{C-S} = 0{\cdot}405 + 0{\cdot}077\ P_{C-S} \quad \text{(i)}$$

$$\beta_{C=S} = 0{\cdot}517 + 0{\cdot}063\ P_{C=S} \quad \text{(ii)}$$

β-value of equation (i) (P indicates bond order) was used for the S–Me bond; the β-value of equation (ii) was assumed to account better for the linkage between sulphur and the 'aromatic' pyrimidine ring.

Since the corresponding parameters for the S=O bond are not available, the exchange integral β was derived from the proportionality between exchange and overlap integrals[18] [equation (iii)]. Here $S_{S=O}$ represents the overlap

$$\beta_{S=O}/\beta_{C-C} = [S_{S=O}/(1 + S_{S=O})]/[S_{C-C}/(1 + S_{C-C})] \quad \text{(iii)}$$

integral for the $3p\pi$-orbital of sulphur and the $2p\pi$-orbital of oxygen; $S_{C=C}$ is the carbon–carbon overlap integral of benzene (0·245).[18] Assuming $r_{S=O}$ = 0·145 Å,[19] and using Mulliken's[20] tables, we find $S_{S=O}$ = 0·168.

The effect of the ring current emanates from the delocalised π-electrons in closed circuits; its magnitude depends on ring size.[9] Since no crystallographic data are available for the compounds included in Table 6, the area of the two component rings was calculated from the data of Ringertz[21] (for the pyrimidine system from X-ray data of purine and for the imidazolone system from the data for uric acid).

Initial parameters for all other bonds were taken from the data of Pullman and Pullman.[22] These parameters were also used to calculate charge densities. All cal-

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culations were carried out with the computer program of Figeys and Dedieu,[16] on a CDC 6400 digital computing machine, using a Fortran IV program.

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