Physical Properties and Chemical Reactivity of 8-(Methylthio)hypoxanthines

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N-Methyl derivatives of 8-(methylthio)hypoxanthine (1) were synthesised by *N*-methylation of various 8-(methylthio)-compounds or by *S*-methylation of appropriate 8-mercaptopurin-6-ones. In 8-(methylthio)hypoxanthines, protonation takes place at the same positions as in the corresponding hypoxanthines. However, the neutral forms of compound (1), its 1- and 7-methyl derivatives and the 1,7-dimethyl homologue are methylated preferentially at N-3, in contrast with the alkylation of the corresponding hypoxanthines which takes place in the imidazole ring. This difference is ascribed to the steric effect of the 8-SMe substituent.

The chemical shift of the *S*-methyl group is influenced little by protonation of the molecule, unless mesomerism can involve the thioether group. Participation of sulphonium-like resonance forms is, however, strongly hindered in the 7,9-dimethyl derivatives of (1). The latter compounds also undergo ready demethylation, hydrolysis, and thiolysis of the 8-methylthio-group.

In continuation of our studies on methylthiopurines,[1-3] we have prepared a series of 8-(methylthio)hypoxanthines in order to test the influence of the 8-substituent on physical properties and reactivity.

Tautomerism.—The 8-(methylthio)hypoxanthines can be divided into four classes, of which class (*a*) comprises

[1] U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J.C.S. Perkin I*, 1973, 793.

[2] F. Bergmann, M. Rahat, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 1225.

[3] U. Reichman, F. Bergmann, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 2647.

TABLE 1

Physical properties of 8-(methylthio)hypoxanthines

Compd.	N-Me positions	$\lambda_{max.}$/nm [a] N	log $\varepsilon_{max.}$	A	C	pK for anion formation	pK for cation formation
(1)		274	4.135	280 [b]	>277.5	7.5 [c]	<−1.5
(2)	1	274	4.080	280	>277	7.5	<−1.5
(3)	3	287	4.324	295	287	7.1	+1.8 [d]
(4)	7	278	3.963	278	277	(>12) [e]	+1.2 [d]
(5)	9	270	4.145	277	275	9.7	+0.8
(6)	1,3	291 [f]	4.204		288		+4.4
(7)	1,7	277.5	4.160		279		+0.8 [d]
(8)	1,9	272	4.135		>276		<−1
(9)	3,7	288	4.383		287		+1.5 [d]
(10)	7,9	289 [f]			278 [g]		+5.2
(11)	1,3,7				288		<−1.5
(12)	1,7.9				279 [h]		

[a] N = neutral; A = anion; C = cation. All compounds in this series show violet fluorescence under a Mineralight u.v. lamp (emission *ca.* 254 nm). [b] Compound (1) also forms a dianion, but without measurable change in the u.v. or n.m.r. spectrum. Only the values of log ε exhibited slight changes upon formation of the dianion. [c] pK of dianion *ca.* 12. [d] Derived from the change of $\delta_{2\text{-H}}$ as function of pH. [e] Anion formation does not find expression in the u.v. spectrum. An approximate pK value was derived from slight changes in the chemical shifts (see Table 2). [f] Zwitterion. [g] The dication of (10) shows $\lambda_{max.} < 270$ nm. [h] The dication of (12) shows $\lambda_{max.}$ 271 nm.

all uncharged derivatives with a free 3-position [compounds (1), (2), (4), (5), (7), and (8)]. Here $\lambda_{max.}$ values are 274 ± 4 nm, with log $\varepsilon_{max.}$ 3.96—4.16 (Table 1).

The 'fixed' structure of the 1,7-dimethyl derivative (7) is characterised by $\lambda_{max.}$ 277.5 nm. This value is close to that of the 7-methyl derivative (4), which should therefore be represented by the 1-NH tautomeric structure (Scheme 1). Similarly the absorption maximum of the 9-methyl derivative (5) is close to that of the 1,9-dimethyl homologue (8), and thus suggests again the 1-NH structure for the former (Scheme 1).

(1)(7-NH tautomer)R^1=R^2=H
(2)(7-NH tautomer)R^1=Me,R^2=H
(4) R^1=H,R^2=Me
(7) R^1=R^2=Me

(1)(9-NH tautomer)R^1=R^2=H
(2)(9-NH tautomer)R^1=Me,R^2=H
(5)R^1=H,R^2=Me
(8)R^1=R^2=Me

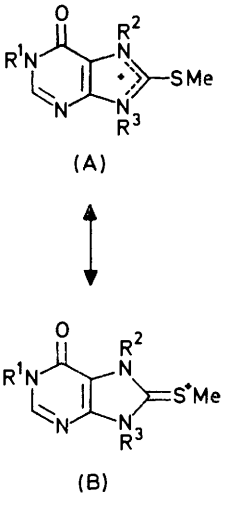
SCHEME 1

As demonstrated previously,[4] hypoxanthine and its 1-methyl derivative exhibit absorption spectra closely related to those of 9-methyl- and 1,9-dimethyl-hypoxanthine. It was therefore suggested that the former two purines are present in aqueous solution predominantly as 9-NH tautomers. In contrast, $\lambda_{max.}$ values of compounds (1) and (2) in the present series are intermediate between the values for the 7- (4) and 9-methyl derivatives (5) (Table 1). On this basis it cannot be decided whether or not the neutral molecules of (1) and (2) are tautomeric mixtures (see Scheme 1). This problem will be discussed again below.

The 3-methyl derivative (3) and the 3,7-dimethyl homologue (9), which can exist as uncharged molecules, with $\lambda_{max.}$ 287.5 ± 0.5 nm and log $\varepsilon_{max.}$ 4.3—4.4, form class (*b*). The bathochromic and hyperchromic shifts characterising this class are due to the *p*-quinonoid structure of the pyrimidine ring. The close similarity of the u.v. spectra of (3) and (9) suggests that the former exists in aqueous solution as the 7-NH tautomer. However, since the 3,9-dimethyl isomer of (9) is still unknown, a final decision is not yet possible.

Class (*c*) comprises the 1,3-dimethyl derivatives (6) and (11), which bear a fixed positive charge in the pyrimidine unit (Scheme 3). In class (*d*) we find the 7,9-dimethyl isomers (10) and (12), with a fixed positive charge in the imidazole ring (Scheme 2). Evidence for these structures will be discussed below.

Cation Formation.—The absorption maxima of the cations of class (*a*) are in the range 277 ± 2 nm. The 2-H signals in the n.m.r. spectra of the protonated forms of compounds (2), (4), (7), and (8) are in the range δ 8.57—8.68 (Table 2), which also includes the $\delta_{2\text{-H}}$ values of (10) and (12) and is characteristic of cation formation in the imidazole unit of hypoxanthines [4] (Scheme 2).



(A)

(B)

Cation of (2)R^2=R^3=H,R^1=Me
Cation of (4)R^1=R^3=H,R^2=Me
Cation of (5)R^1=R^2=H,R^3=Me
Cation of (7)R^3=H,R^1=R^2=Me
Cation of (8)R^2=H,R^1=R^3=Me
Cation of (10)R^1=H,R^2=R^3=Me
(12)R^1=R^2=R^3=Me

SCHEME 2

The cation of (5) shows $\delta_{2\text{-H}}$ 8.42, but shares several properties with the other members of class (a). Thus in the cations of class (a), the 8-SMe band is displaced

[4] D. Lichtenberg, F. Bergmann, and Z. Neiman, *Israel J. Chem.*, 1972, **10**, 805.

TABLE 2

N.m.r. data of 8-(methylthio)purines [a]

Compd.	Me positions	$\delta_{2\text{-H}}$ N	A	Δ (N − A)	C	Δ (N − C)	$\delta_{8\text{-SMe}}$ N	A	Δ (N − A)	C	Δ (N − C)	δ_{NMe} N	A	Δ (N − A)	C	Δ (C − N)
(1)		8.13	8.07	+0.06	8.99	−0.86	2.71	2.71	0	3.01	−0.30					
(2)	1	8.31	8.13	+0.18	8.68	−0.37	2.77	2.70	+0.07	3.01	−0.24	3.71	3.66	+0.05	3.81	−0.10
(3)	3	8.41	8.09	+0.32	9.13 [b]	−0.72	2.82	2.70	+0.12	2.89	−0.07	3.91	3.90	+0.01	4.23	−0.32
(4)	7	8.17	8.15	+0.02	8.61	−0.44	2.80	2.76	+0.04	3.07	−0.27	3.96	3.97	−0.01	4.19	−0.23
(5)	9	8.19	8.15	+0.04	8.42	−0.23	2.77	2.74	+0.03	2.99	−0.22	3.71	3.70	+0.01	3.89	−0.18
(6)	1,3	9.36 [c]			9.51 [d]	−0.15	2.80 [c]			2.86	−0.06	(1) 3.83 [c]			3.91	−0.08
												(3) 4.14			4.22	−0.08
(7)	1,7	8.26			8.61	−0.35	2.77			2.97	−0.20	(1) 3.66			3.76	−0.10
												(7) 3.89			4.13	−0.24
(8)	1,9	8.30			8.57	−0.27	2.76			2.92	−0.16	(1) 3.69			3.78	−0.09
												(9) 3.69			3.92	−0.23
(9)	3,7 [f]	8.35			9.20	−0.85	2.81			2.88	−0.07	(3) 3.96			4.20	−0.24
												(7) 3.96			3.98	−0.02
(10)	7,9	8.42 [c]			8.63	−0.21	2.74 [c]			2.83	−0.09	(7) 4.20 [c]			4.47	−0.27
												(9) 4.11			4.23	−0.12
(11)	1,3,7 [g]				9.44					2.89		(1)			3.88	
												(3)			4.21	
												(7)			4.02	
(12)	1,7,9 [g]				8.65					2.88		(1)			3.88	
												(7)			4.48	
												(9)			4.22	

[a] In D_2O at 70 °C. For making alkaline, solid Na_2CO_3 or NaOD was used; for acidification, D_2SO_4, DCl, $CD_3{\cdot}CO_2D$, or $CF_3{\cdot}CO_2D$. [b] Compound (3) also forms a dication: $\delta_{2\text{-H}}$ 9.21; $\delta_{3\text{-Me}}$ 4.34; $\delta_{8\text{Me}}$ 3.07. [c] This value refers to the zwitterion; it was determined in H_2O, since in D_2O solution immediate H–D exchange took place. [d] The dication of compound (6) shows $\delta_{2\text{-H}}$ 9.30; $\delta_{1\text{-Me}}$ 3.87; $\delta_{3\text{-Me}}$ 4.19; $\delta_{8\text{Me}}$ 2.85. [e] These values refer to the zwitterion. [f] The dication of (9) shows $\delta_{2\text{-H}}$ 9.15; $\delta_{3\text{-Me}}$ 4.26; $\delta_{7\text{-Me}}$ 4.04; $\delta_{8\text{Me}}$ 2.90. [g] The picrates were used, since the iodides were unstable in solution. Compound (12) was studied in $CF_3{\cdot}CO_2D$.

0.16—0.30 p.p.m. to lower field (Table 2). Furthermore, the 7- and 9-Me groups in compounds (4), (5), (7), and (8) are deshielded by 0.18—0.32 p.p.m., whereas the corresponding shift of the 1-Me signal for compounds (2), (7), and (8) is only 0.09—0.10 p.p.m. (Table 2). All these changes are in agreement with preferential protonation of all members of class (*a*), including the 9-methyl derivative (5), in the imidazole ring (Scheme 2).

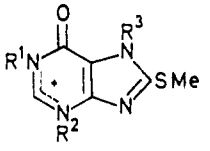
The $\lambda_{max.}$ values of the cations of (3) and (9) are identical with those of the cation of (6) and of compound (11). The $\delta_{2\text{-H}}$ values of the cations of class (*b*) are 9.1 and 9.2, respectively, *i.e.* near the values for the cation of (6) and the fixed cation (11).

The position of the 2-H n.m.r. signals of these four cations is characteristic of purines bearing an amidinium-like structure in the pyrimidine ring (Scheme 3).[3-5] These species also share the ability to form dications in strongly acidic media (see Table 2).

In the cations of compounds (3), (6), and (9) and the fixed cation (11) the SMe signal is in the range δ 2.86—2.89, *i.e.* upfield relative to its position in class (*a*). In addition, protonation of (3) and (9) is accompanied by a downfield shift of the 3-Me signal of 0.28 ± 0.04 p.p.m., whereas the 7-Me group in the cation of (9) is deshielded by only 0.02 p.p.m. (Table 2). Clearly, cation formation in the pyrimidine ring has only a weak influence on the signals of substituents in the imidazole ring.

In summary, the members of the present series are protonated at the same positions as the corresponding hypoxanthines.[4]

Two exceptional cases should be noted. For the protonated form of (1), the $\delta_{2\text{-H}}$ value is 8.99, intermediate between those of classes (*a*) and (*b*), but closer to the latter. This cation probably exists as a mixture of tautomers.



Cation of (3) $R^1 = R^3 = H$, $R^2 = Me$
Cation of (6) $R^3 = H$, $R^1 = R^2 = Me$
Cation of (9) $R^1 = H$, $R^2 = R^3 = Me$
(11) $R^1 = R^2 = R^3 = Me$

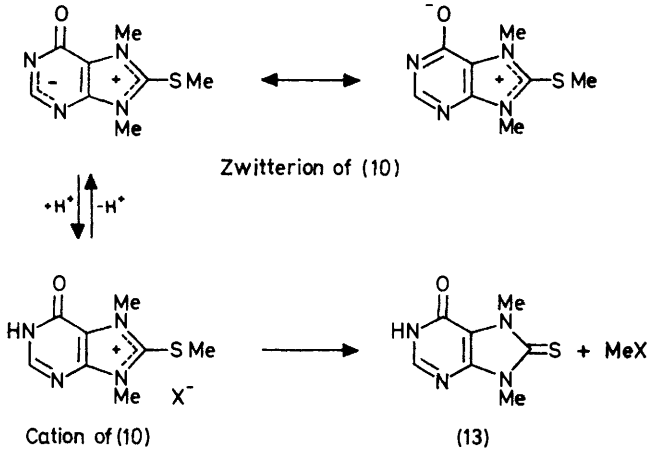
SCHEME 3

In the cation of (10), the 7-Me signal is displaced downfield by 0.28 p.p.m., relative to its position in the cation of (4). The corresponding shift of $\delta_{9\text{-Me}}$ is 0.34 p.p.m. (Table 2). Apparently, the bulky SMe substituent forces the neighbouring NMe substituents into positions differing from those in the cations of (4) and (5). The corresponding signals of (12) closely resemble those of the cation of (10). Surprisingly, in the zwitterion of (10) (Scheme 4), the 9-Me signal is moved downfield by 0.22 p.p.m. relative to the cation of (5), whereas the 7-Me band has practically the same position as in the cation of (4). Presumably the negative charge in the zwitterion of (10), also by delocalisation over the oxygen in position 6 (Scheme 4), neutralizes in part the influence of the positive charge on the 7-Me signal.

In the cation of (10) and in the fixed cation (12) the SMe signal is at relatively high field (δ 2.83 and 2.88, respectively), similar to the corresponding signals in classes (*b*) and (*c*), in spite of the fixed positive charge in the imidazole ring. This may be explained as follows. In the cations of class (*a*), the charge is also delocalised over the sulphur atom, as shown in the resonance form (B) of Scheme 2, involving shortening of the C(8)–S distance. Apparently in (10) and (12) contribution of the

[5] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc.* (*C*), 1971, 1676.

mesomeric form (B) is very small, owing to steric interference amongst the three substituents in the imidazole ring. This may also explain certain differences in the n.m.r. spectra of (10) and the 7,9-dimethylhypoxanthinium ion. For the cationic form of the latter we find (in dil. D_2SO_4) $\delta_{7\text{-Me}}$ 4.28 and $\delta_{9\text{-Me}}$ 4.07 p.p.m. Thus these bands are shifted upfield by 0.19 and 0.16 p.p.m., respectively, relative to the values in the cation of (10). On the other hand, since in the 7,9-dimethylhypoxanthinium ion position 8 is free, the chemical shifts of the NMe groups are not significantly different from those in the cations of 7-($\delta_{7\text{-Me}}$ 4.30) and 9-methylhypoxanthine ($\delta_{9\text{-Me}}$ 4.10).[4]



SCHEME 4

An SMe substituent, by virtue of its electronic properties, should enhance the basicity of the molecule. However, especially for compounds (1), (2), and (8), we find a marked lowering of pK values in comparison with hypoxanthines[4] (see Table 1). This may be another expression of steric hindrance by the bulky SMe group of proton attachment to a neighbouring nitrogen atom.

The highest pK values (4.4 and 5.2, respectively) are found for compounds (6) and (10), characterising the transformation of zwitterions into cations (see *e.g.* Scheme 4).

Methylation of Neutral Molecules in an Aprotic Solvent.—Electrophilic alkylation of neutral molecules can be compared with their protonation and thus may throw light on some of the unsolved problems of cation formation. However, ionisations, being reversible, are thermodynamically controlled whereas *N*-alkylation is irreversible and thus subject to kinetic control. Furthermore methylation is much more sensitive to steric interference than attachment of a proton. Therefore steric factors may become predominant in determining the course of alkylation.[1,2,6]

In the 7-methyl derivative (4), both positions 3 and 9 are available for electrophilic attack. U.v. and n.m.r. spectra indicate protonation at N-9, but methylation yields exclusively the cation of the 3,7-dimethyl derivative (9) (Table 3). It appears that the bulky 8-SMe group opposes alkylation at a neighbouring nitrogen atom. The cation of (9) should be resistant to further electrophilic attack. However after prolonged exposure, the 1,3,7-trimethyl derivative (11) is the end-product. This is explicable if the cation of (9) is in equilibrium with the uncharged molecule. Presumably proton transfer takes place between the cation of (9) and unchanged (4). Indeed (4) and (9) exhibit similar pK values (Table 1).

The 9-methyl derivative (5) is protonated and alkylated at N-7. Presumably reaction at N-3 would be subject to even greater steric interference than is involved in the formation of the 7,9-dimethyl derivative. Thus in accordance with previous observations,[5-8] simultaneous substitution at N-3 and N-9 is avoided. Alkylation of (5) is a slow process. During the long reaction time (about 72 h), part of the cation of (10) undergoes spontaneous *S*-demethylation to yield 8,9-dihydro-7,9-dimethyl-8-thioxopurin-6-one (13) (Scheme 4).[9] Similar observations on related purine derivatives have been reported.[3]

TABLE 3

Methylation of 8-(methylthio)hypoxanthines in dimethylformamide

Compd.	Me positions	Reaction time [a] (h)	Me positions in products	Compds.	Yield (%) [b]	Corresponding product of methylation of hypoxanthine
(1)		48	3; 1,3; 9	(3), (6), (5)	10, 80, 10	7,9-Me_2
(2)	1	5	1,3; 1,7,9	(6), (12)	90, 5	1,7,9-Me_3
(3)	3	48—72	1,3	(6)	>90	1,3-Me_2
(4)	7	8	7; 3,7; 1,3,7	(4), (9), (11)	50, 40, 10	7,9-Me_2
		48	1,3,7	(11)	90	
(5)	9	72	7,9 [c]	(10)	55	7,9-Me_2
(6)	1,3	48	1,3,7	(11)	80 [d]	
(7)	1,7	10	1,3,7 [e]	(11)	>90	1,7,9-Me_3
(8)	1,9	24	1,9; 1,7,9	(8), (12)	10, 90	1,7,9-Me_3
(9)	3,7	2	1,3,7	(11)	>95	

[a] All methylations carried out at room temperature to minimise secondary reactions. [b] Yields estimated gravimetrically or from the areas of the n.m.r. signals. [c] In addition, *ca.* 10% of 8,9-dihydro-7,9-dimethyl-8-thioxopurin-6-one (13) formed. [d] Decomposition products also present. [e] In addition, traces of the 1,7,9-trimethyl derivative (12) detected.

[6] M. Rahat, F. Bergmann, and I. Tamir, *J.C.S. Perkin I*, 1974, 2229.

[7] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J.C.S. Perkin I*, 1972, 1676.

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

[9] Z. Neiman, *Chem. Comm.*, 1968, 200.

In contrast to protonation of the 1-methyl derivative (2) in the imidazole ring, methylation proceeds preferentially in the pyrimidine ring to furnish (6) in 90% yield. A small amount of the 1,7,9-trimethyl derivative (12) was also formed, presumably from the 1,9-dimethyl derivative (8) as intermediate. The latter could not be detected in the n.m.r. spectrum or on paper chromatograms, but pre-formed (8) is converted nearly quantitatively into (12) (Table 3). Compound (7) cannot be an intermediate since it would yield (11) as main end-product (see below). Again for the second step in the series (2) ⟶ (8) ⟶ (12), it is necessary that the cation of (8) be in equilibrium with the uncharged form, *e.g.* by proton transfer to (2).

Table 3 shows that conversion of (3) into (6) is much slower than that of (2). The reverse behaviour was observed with purine-6,8-diones, where the 3-methyl derivative reacted much faster than its 1-methyl isomer.[6] In 1-methylpurine-6,8-dione the 9-NH group opposes alkylation at N-3 whereas approach to position 1 in the 3-methyl isomer is not hindered. The relatively fast methylation of compound (2) in the present series may therefore indicate that the alkylating agent reacts preferentially with the 7-NH tautomer (see left hand side of Scheme 1; R^1 = Me; R^2 = H) or that the activation step involves tautomerisation to the 7-NH form.

Alkylation of (1) proceeds about 90% at N-3 and about 10% at N-9. In the tautomeric structure shown on the left hand side of Scheme 1 (R^1 = R^2 = H), both positions 3 and 9 are available for substitution. Of these two alternatives, N-3 apparently is less hindered. Compound (3), presumably in its uncharged form, undergoes further reaction to give (6), the latter representing the major end-product (about 80%). This is in accord with the practically quantitative conversion of the neutral molecule of (3) into (6) (Table 3).

The 1,7-dimethyl derivative (7) was methylated mainly at position 3 to yield compound (11). The latter is also the ultimate product of alkylation of (9) and of the zwitterion of (6). As with compound (4), methylation and protonation of (7) take different courses. It has already been mentioned that (8) is methylated slowly at N-7 to give (12), a reaction paralleling the protonation of (8).

In hypoxanthines, protonation and methylation always take the same course.[3] In the 8-methylthio-derivatives, methylation avoids as far as possible attack at the imidazole ring with creation of an imidazolinium cation. Thus in compounds (1), (2), and (4), position 3 is alkylated, whereas protonation involves mainly N-9(7). On the other hand, in the 9-methyl derivatives (5) and (8) alkylation at N-3 would create 3,9-dimethylated purines. Therefore in these two compounds protonation as well as methylation is directed to N-7. As shown in Table 3, the results of methylation of compounds (1), (2), (4), and (7) in the present series differ from those of the corresponding hypoxanthines.

Anion Formation.—Dissociation of 9(7)-NH in (2) and of 1-NH in (5) causes about the same bathochromic displacement of $\lambda_{max.}$. However these two processes are characterised by quite different pK values: 7.5 in the former and 9.7 in the latter case (Table 1). Likewise for dissociation of 7-NH in (3), the pK value is 7.1. Since the pK for monoanion formation from (1) is 7.5, we conclude that this step involves essentially the 9(7)-NH and thus derive the main ionisation sequence 9(7) ⟶ 1 for compound (1), similar to the sequence for hypoxanthine.[4] This problem will be discussed again below.

The pK values for anion formation of compounds (1)—(3) and (5) are *ca.* one unit lower than those of the corresponding hypoxanthines,[4] whereas the pK of compound (4) (>12) is much higher than the corresponding value for 7-methylhypoxanthine (9.4). Relief of steric strain upon dissociation of the imidazole NH group may contribute to the higher acidity of compounds (1)—(3), but the increased acidity of the 9-methyl derivative (5), which contrasts with the behaviour of (4), remains unexplained.

Methylation of Anions.—The anions of both (4) and (5) are methylated at N-1, in conformity with the site of their protonation.

Alkylation of the anion of (2) proceeds to *ca.* 90% at N-9 and to *ca.* 10% at N-7 (Table 4). These results may be taken as supporting evidence that in aqueous solutions of (2) both the 7- and 9-NH tautomers are present, but they do not give information about the relative contributions of these two forms.

The anion of (3) yields *ca.* 60% of the 3,7-dimethyl derivative (9), but also considerable amounts of decomposition products. Probably (9), which is present during the reaction as the neutral molecule, is further methylated to give (11) (see Table 3), the latter being highly unstable in alkaline media.

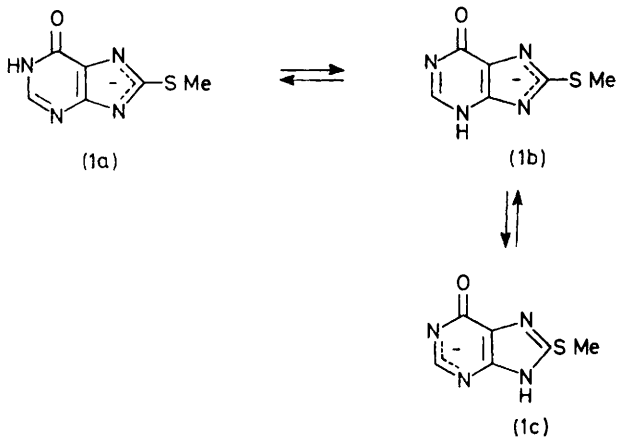
The monoanion of (1) yields equal amounts of (2) and (4), whereas the dianion gives predominantly (2); the latter is rapidly converted into (8) under the conditions used with the dianion (Table 4). No trace of the 9-methyl derivative (5) was detected during alkylation of either the mono- or the di-anion of (1). This represents a marked difference from the behaviour of (2), for which alkylation at N-9 is the preferred process. This discrepancy could be explained if the anion (1a) were in equilibrium with the tautomeric structures (1b) and (1c). In (1b), electrophilic attack would be directed to N-7, and in (1c) to N-1 (Scheme 5).

The predominance of compounds (2) and (8) (together *ca.* 85%) among the products resulting from alkylation of the dianion supports the assumption that the latter attaches the first proton mainly at N-1 and thus its behaviour accords with the ionisation sequence of (1) given before.

Synthesis and Identification of New 8-(Methylthio)hypoxanthines—Apart from compounds (1) [10] and (5),[11] all members of the present series are new. Compounds (2), (3), and (5) were obtained by *S*-methylation of the

[10] R. K. Robins, *J. Amer. Chem. Soc.*, 1958, **80**, 6671.
[11] A. H. Cook and E. Smith, *J. Chem. Soc.*, 1949, 2329.

corresponding 8-mercaptopurin-6-ones. For the synthesis of (5), this method proved preferable to that of Cook and Smith.[11] 1-Methyl-8-mercaptopurin-6-one is known.[12] The corresponding 3- and 9-methyl derivatives are described in the Experimental section.



SCHEME 5 Anion of 8(methylthio)hypoxanthine (1)

dimethyl-8-(methylthio)hypoxanthinium cation (16) and the latter then debenzylated to yield (7). In both (14) and (16), the 8-methylthio-group proved resistant to concentrated hydrobromic acid, in contrast to the rapid removal of 6-methylthio-substituents in analogous purines by this reagent.[14]

The structure of (16) follows from its conversion into (7), the latter being obtained also from compounds (2) and (4) (see Table 4).

The structure of (9) is based on the fact that methylation of the 7-methyl derivative (4) in dimethylformamide and of the 3-methyl isomer (3) in alkaline medium gave the same product. Similarly, compound (6) was obtained both from (2) and (3), and the 1,9-dimethyl derivative (8) from either (2) or (5) under alkaline conditions.

The 1,3,7-trimethyl-8-(methylthio)hypoxanthinium cation (11) was obtained from compounds (6), (7), and (9). Its isomer (12) was formed from (8). Compound (12) cannot be the 1,3,9-trimethyl derivative, since its $\delta_{2\text{-H}}$ value is only 8.65 (Table 2).

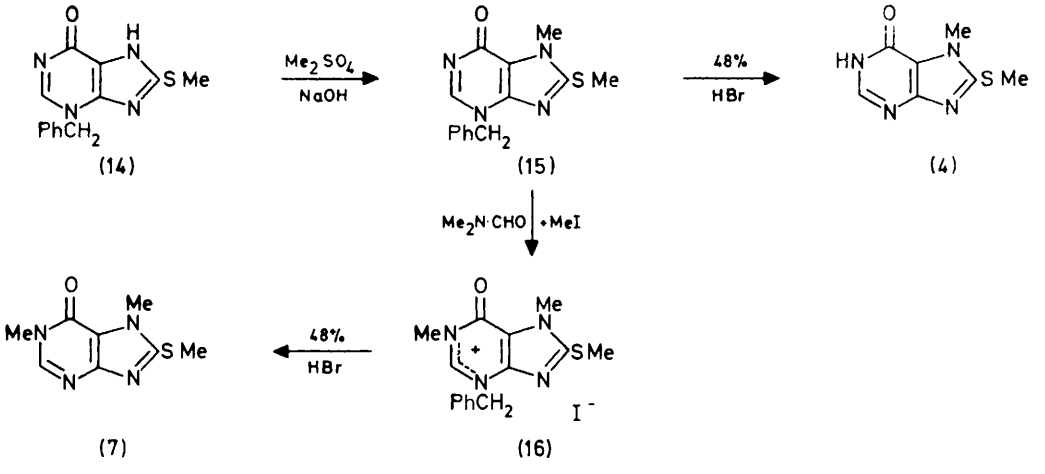
Compound (10), obtained by methylation of (5) in

TABLE 4

Methylation of the anions of 8-(methylthio)hypoxanthines

Compd.	Me positions	Reaction [a] pH	Reaction [a] time	Me positions in products	Compd.	Yield [b] (%)
(1)		9—10	1 h	1; 7; [1,9] [c]	(2), (4), [8]	50, 50
		13—14 [d]	1 h	1,9; 7; 1	(8), (4), (2)	80, 10, 5
(2)	1	14	3—4 h	1,9; 1,7	(8), (7)	90, 10
(3)	3	10	30—60 min	3,7	(9)	60
(4)	7	9—11	20 min	1,7	(7)	*ca.* 80 [e]
(5)	9	14	5 min	1,9	(8)	70

[a] All reactions at room temperature, but the monoanion of compound (1) reacted only at reflux temperature. [b] In all cases, with the exception of compound (2), decomposition products were also present. [c] Formed only in traces. [d] Dianion. [e] Approximate evaluation of the percentage of (7) by paper chromatography.



SCHEME 6

Condensation of 5,6-diamino-1-benzylpyrimidin-4-one with carbon disulphide [13] served as starting point for the synthesis of 3-benzyl-8-(methylthio)hypoxanthine (14). The latter was methylated at N-7 to give the 3-benzyl analogue (15) of compound (9). Debenzylation of (15) with 48% hydrobromic acid [14] yielded (4) (Scheme 6). Furthermore, (15) was converted into 3-benzyl-1,7-dimethylformamide, was identical with the product from cautious *S*-methylation of 8,9-dihydro-7,9-dimethyl-8-thioxopurin-6-one (13).[9] As mentioned earler, the cation of (10) in dimethylformamide solution at

[12] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1961, 1298.
[13] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1965, 1175.
[14] Z. Neiman and F. Bergmann, *Israel J. Chem.*, 1965, **3**, 85.

room temperature undergoes spontaneous *S*-demethylation to (13) (see Scheme 4). Thus these two compounds are interconvertible. Analogous reactions take place in water. Thus when an aqueous solution of (10) was kept at room temperature, the compound was hydrolysed gradually to the known 7,9-dimethylpurine-6,8-dione.[6] Similarly, aqueous hydrogen sulphide converted compound (10) at room temperature quantitatively into (13) within 1 h.

Analogous observations were made with the cations of (4) and (5). However in view of diminished interference between the 8-SMe group and the 7- and 9-substituents in these two compounds, more drastic conditions were required for *S*-demethylation. Solutions of the iodides in dimethylformamide yielded the corresponding 8-mercapto-derivatives, after refluxing for 72 and 24 h, respectively. On the other hand, the neutral forms of (4) and (5) and the zwitterion of (10) proved stable under the same conditions. It is thus evident that *S*-demethylation requires the presence of a mobile anion.

TABLE 5

Synthesis and analysis of 8-(methylthio)hypoxanthines

Compd.	N-Me positions	Procedure for synthesis	Yield (%)	M.p. or decomp. p. (°C)	Crystal form [a,b]	R_F in solvent [c] (A)	(B)	(C)	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(2)	1	*S*-Methylation [d]	70	300	Plates	0.74	0.65	0.73	42.9	4.1	28.6	16.3	$C_7H_8N_4OS$	42.5	4.4	28.9	16.0
(3)	3	*S*-Methylation	85	>300	Needles	0.42	0.62	0.62						42.7	4.2	28.5	16.2
(4)	7	Debenzylation of (15)	95	300	Plates	0.67	0.69	0.69						42.8	4.2	28.9	16.1
(5)	9	*S*-Methylation	73	277 [e]	Needles	0.68	0.63	0.63						42.6	4.1	28.5	16.1
(6)	1, 3	(1C) *f* [from (3)]	>90	202—204	Yellow needles	0.76	0.68	0.68	38.3	3.0	22.3	7.3	$C_{14}H_{13}N_7O_8S$	38.4	2.8	22.4	7.5
(7)	1, 7	Debenzylation of (16)	65	202—203	Needles	0.75	0.68	0.68						45.8	4.9	26.9	15.2
(8)	1, 9	*N*-Methylation of (5)	70	197—198	Needles	0.93	0.72	0.72	45.7	4.8	26.7	15.2	$C_8H_{10}N_4OS$	45.5	4.8	26.8	15.1
(9)	3, 7	(2) [from (3)]	60	209—210	Needles	0.70	0.65	0.65						45.6	4.7	26.9	15.0
(10)	7, 9	(1C) [from (5)]	55	177—179	Yellow prisms	0.86	0.68	0.68	38.3	3.0	22.3	7.3	$C_{14}H_{13}N_7O_8S$	38.4	3.2	22.0	7.4
(11)	1, 3, 7	(2) [from (7) or (9)]	>90	227—229	Yellowish prisms	0.82	0.75	0.75	30.7	3.7	15.9	9.1	$C_9H_{12}N_4IOS$ [i]	30.4	4.0	15.8	9.4
(12)	1, 7, 9 [g]	(1C) [from (8)]	~90 [h]		Yellow prisms												

[a] The free bases of all 8-(methylthio)hypoxanthines gave colourless crystals. Compounds (6) and (10) were analysed as yellow picrates and (11) as the yellowish iodide. [b] All compounds were recrystallised from water except (6), (10), and (11) (from ethanol). [c] See Experimental section. [d] *S*-Methylation of the corresponding 8-mercaptopurin-6-ones (see Experimental section). [e] Lit.[11] 280—282°. [f] These figures refer to the methylation procedures, described in the Experimental section. [g] The picrate of (12) was so unstable that no satisfactory analysis could be obtained. The spectral measurements in Tables 1 and 2 were carried out immediately after isolation of the picrate. [h] Determined from n.m.r. measurements. [i] Found: I, 36.3 Calc. 36.1.

EXPERIMENTAL

M.p.s. were obtained with a Fisher-Johns apparatus. Microanalyses were performed by F. Strauss, Oxford. U.v. spectra were measured with a Hitachi–Perkin-Elmer 124 spectrophotometer. Determination of n.m.r. spectra with a JEOL MH-100 instrument was performed in D_2O at 70 °C, TSP (sodium 3-trimethylsilyl[2,2,3,3-$^2H_4$]propionate) serving as internal standard. The pH was adjusted with Na_2CO_3, NaOD, D_2SO_4, DCl, CF_3CO_2D, or CD_3CO_2D.

p*K* Values of the purines were derived from plots of $\lambda_{max.}$ or of chemical shift against pH. For paper chromatography on Whatman no. 1 paper (descending method), the following solvents were used: (A) (acidic) butan-1-ol–acetic acid–water (12 : 3 : 5 v/v); (B) (basic) propan-2-ol–dimethylformamide–25% ammonia (13 : 5 : 3 v/v); (C) (neutral) ethanol–dimethylformamide–water (3 : 1 : 1 v/v). Spots were located by fluorescence under a Mineralight u.v. lamp (λ *ca.* 254 nm). R_F Values are expressed relative to theophylline (R_F 0.68 in all three solvents).

General Procedures for N-Methylation of Purines.—(1) *Methylation with methyl iodide in dimethylformamide.* A suspension of an 8-(methylthio)hypoxanthine (1g) in dimethylformamide (50 ml) and methyl iodide (10 ml) was stirred at room temperature until the purine had dissolved completely and the u.v. spectrum showed no further change. Then ether (300 ml) was added and the yellow precipitate filtered off. Purification was achieved by one of the following procedures: (A) dissolution of the precipitate in a small volume of 0.1N-NaOH followed by adjustment of the pH to 7 with hydrochloric or acetic acid and final recrystallisation from water; (B) dissolution of the precipitate in concentrated ammonia solution, decolourisation with charcoal, filtration, and acidification as in (A); (C) dissolution of the precipitate in the minimum volume of water and addition of saturated aqueous picric acid, which caused crystallisation of the purine picrate. The products are described in Table 5.

(2) *Methylation of anions with dimethyl sulphate in alkaline media.* A solution of the purine in sodium carbonate or in 1N-NaOH was stirred with dimethyl sulphate at room

TABLE 6

Miscellaneous new purines

	Yield (%)	M.p. or decomp. p. (°C)	Crystal form [a] and colour	$\lambda_{max.}$/nm at pH 1	8
(A) 8-Mercaptopurin-6-ones					
3-Me	93	>300	Yellow plates	306	309
9-Me	90	>300	Yellow needles	289	289
7,9-Me_2 (13)	30	>300	Yellow prisms	289	289
3-$PhCH_2$	94	194	Needles	307	311
(B) 8-(Methylthio)hypoxanthines					
3-$PhCH_2$ (14)	88	290	Prismatic columns	290	293
3-$PhCH_2$-7-Me (15)	30	246—247	Prismatic plates	288	290
3-$PhCH_2$-1,7-Me_2 (16) [b]	60			287	

	pH	δ 2-H	8-SMe	N-Me [c]	3-PhCH_2	3-$PhCH_2$
(A) 8-Mercaptopurin-6-ones						
1-Me	(TFA)*	8.76		3.95		
3-Me	1.0	9.26		4.23		
	7.0	8.20		3.89		
9-Me	(TFA)	8.57		3.89		
7,9-Me_2 (13)	(TFA)	8.58		(7) 4.11 (9) 3.90		
3-$PhCH_2$	1.0	8.95			5.70	7.60
	7.0	8.29			5.50	7.47
(B) 8-(Methylthio)hypoxanthines						
3-$PhCH_2$ (14)	(TFA)	9.10	2.94		5.84	7.57
3-$PhCH_2$-7-Me (15)	(TFA)	8.97	2.93	(7) 4.03	5.79	7.56
3-$PhCH_2$-1,7-Me_2 (16)	(TFA)	9.26	2.93	(1) 3.93 (7) 4.03	5.80	7.52

	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(A) 8-Mercaptopurin-6-ones									
3-Me	37.7	3.7	29.3	16.8	$C_6H_6N_4OS$, $0.5H_2O$	37.8	3.8	29.4	16.5
9-Me	39.6	3.3	30.8	17.6	$C_6H_6N_4OS$	40.0	3.1	30.6	17.3
3-$PhCH_2$	55.8	3.9	21.7	12.4	$C_{12}H_{10}N_4OS$	55.5	4.3	21.5	12.1
(B) 8-(Methylthio)hypoxanthines									
3-$PhCH_2$ (14)	57.4	4.4	20.6	11.8	$C_{13}H_{12}N_4OS$	57.0	4.6	20.5	11.6
3-$PhCH_2$-7-Me (15)	58.7	4.9	19.6	11.2	$C_{14}H_{14}N_4OS$	58.5	5.2	19.5	11.1

* TFA = $CF_3{\cdot}CO_2D$.

[a] All compounds were recrystallised from water. [b] This hypoxanthinium salt was unstable and was therefore converted directly into (7) (see Experimental section). [c] Figures in parentheses indicate positions of *N*-methyl groups.

temperature. The precipitate was recrystallised from water (see Table 5).

Methylation of 8-(*Methylthio*)*hypoxanthine* (1).—(a) *With methyl iodide in dimethylformamide.* A solution of (1) (0.5 g) in dimethylformamide (25 ml) and methyl iodide (5 ml) was kept at room temperature for 48 h. Addition of ether (80 ml) precipitated compound (6) as a yellow mass. The ether layer was lyophilised to yield a mixture of (3) and (5) (see Table 3).

(b) *Methylation of monoanion of compound* (1). Compound (1) (0.5 g) was dissolved in saturated aqueous sodium carbonate and refluxed with dimethyl sulphate (0.25 ml) for 1 h. The solution was neutralized to pH 6—7 and concentrated. The precipitate obtained was a mixture of compounds (2) and (4) (see Table 4).

(c) *Methylation of dianion of compound* (1). A solution of compound (1) (0.5 g) in 1N-NaOH was stirred with dimethyl sulphate (0.25 ml) at room temperature for 1 h. The mixture was then neutralized and lyophilised. The product was a mixture of compounds (8), (4), and (2) (see Table 4).

Known Purines and Pyrimidines.—The following compounds were prepared according to known procedures: 8-(methylthio)hypoxanthine (1),[10] 1-methyl-8-mercaptopurin-6-one,[12] 5-amino-6-methylaminopyrimidin-4-one,[15] 5,6-diamino-1-benzyl-2-mercaptopyrimidin-4-one.[13]

7,9-*Dimethyl*-8-(*methylthio*)*hypoxanthinium Salt* (10).—Since the synthesis of 8,9-dihydro-7,9-dimethyl-8-thioxopurin-6-one (13) [9] presents some difficulties, we describe the method in detail. An intimate mixture of 7,9-dimethylhypoxanthinium tosylate [16] (0.1 g) and sulphur (0.1 g) was heated to 200—210 °C for 2 h. The solid was pulverised and then washed repeatedly with carbon disulphide. The remaining solid portion was dissolved in ammonia, the solution was filtered, and the *product* (13) (yield 30%) was precipitated by acidification to pH 6, m.p. > 300°; $\lambda_{max.}$ (pH 1) 288; (pH 8) 289 nm. Compound (13) was converted into the *picrate* of (10) by procedure (1C).

When the iodide of (10) was kept in dimethylformamide at room temperature for 48 h, about 60% was converted into (13). In aqueous solution, the iodide of (10) was hydrolysed at room temperature to 7,9-dimethylpurine-6,8-dione within 24 h. When the compound was dissolved in aqueous hydrogen sulphide at room temperature, it underwent complete thiolysis within 1 h.

3-*Methyl*-8-*mercaptopurin*-6-*one.*—A mixture of 5,6-diamino-1-methylpyrimidin-4-one (2 g), pyridine (40 ml), sodium hydroxide (0.4 g), and carbon disulphide (2 ml) was refluxed for 5 h. The hot, red-brown mixture was filtered and the insoluble portion washed several times with ether (see Table 6).

9-*Methyl*-8-(*methylthio*)*hypoxanthine* (5).[11]—(a) 9-*Methyl*-8-*mercaptopurin*-6-*one.* An intimate mixture of 5-amino-6-methylaminopyrimidin-4-one (2 g) and thiourea (6 g) was heated to 230—250 °C for 45 min. The temperature was raised to 280 °C for 15 min. The solid was treated with 2N-KOH, the mixture filtered, and the *product* precipitated from the filtrate by acidification to pH 6 (see Table 6).

(b) S-*Methylation.* A solution of the foregoing compound (1 g) in dimethylformamide (50 ml) and methyl iodide (6 ml) was kept at room temperature for 5 h and worked up according to procedure (1B); for properties see Table 5.

The iodide of (5) underwent quantitative *S*-demethylation when its solution in dimethylformamide was refluxed for 24 h. Under the same conditions, the neutral form of (5) was stable.

7-*Methyl*- (4) *and* 1,7-*Dimethyl*-8-(*methylthio*)*hypoxanthine* (7).—(a) 5,6-*Diamino*-1-*benzylpyrimidin*-4-*one.* A suspension of 5,6-diamino-1-benzyl-2-mercaptopyrimidin-4-one [13] (5 g) and Raney nickel (20 g) in water (60 ml) was refluxed for 4 h, then filtered hot, and the filtrate was concentrated *in vacuo.* The precipitate obtained by cooling the concentrate overnight crystallised from water in yellow *needles* (41%), m.p. 242—244°; $\lambda_{max.}$ (pH 1) 263 nm; (pH 8) 284 nm (Found: C, 58.4; H, 5.8; N, 25.0. Calc. for $C_{11}H_{12}N_4O$, 0.5 H_2O: C, 58.7; H, 5.8; N, 24.9%).

(b) 3-*Benzyl*-8-*mercaptopurin*-6-*one.* A mixture of the foregoing pyrimidine (18 g), pyridine (400 ml), sodium hydroxide (4 g), and carbon disulphide (50 ml) was stirred and refluxed for 3.5 h. After cooling, the yellow *precipitate* was filtered off and washed with ether (yield 19.5 g, 94%). After evaporation of the filtrate to dryness, an additional crop (0.5 g) was isolated from the residue (Table 6).

(c) 3-*Benzyl*-8-(*methylthio*)*hypoxanthine* (14). A solution of the foregoing purine (0.4 g) in dimethylformamide (8 ml) and methyl iodide (4 ml) was kept at room temperature for 1.5 h. The *product* (14) was precipitated by addition of ether and dissolved in the minimum volume of ammonia, and the solution was neutralised with acetic acid; yield 88% (see Table 6).

(d) 3-*Benzyl*-7-*methyl*-8-(*methylthio*)*hypoxanthine* (15). A solution of compound (14) (0.3 g) in 1N-NaOH (6 ml) was stirred at room temperature with dimethyl sulphate (0.2 ml) for 10 min. The *precipitate* (0.17 g, 30%) crystallised from water (see Table 6).

(e) 7-*Methyl*-8-(*methylthio*)*hypoxanthine* (4). A mixture of compound (15) (1 g) and 48% hydrobromic acid (20 ml) was refluxed for 40 min. After cooling, benzyl bromide was removed by three extractions with ether. The aqueous layer was brought to pH 7 by addition of solid NaOH (see Table 5).

The iodide of (4) underwent quantitative *S*-demethylation when its solution in dimethylformamide was refluxed for 72 h; under the same conditions the neutral molecule was unchanged. The demethylation product, 7-methyl-8-mercaptopurin-6-one, shows $\lambda_{max.}$ (pH 8.0) 236 and 292 nm.

(f) 3-*Benzyl*-1,7-*dimethyl*-8-*methylthiohypoxanthinium iodide* (16). A suspension of compound (15) (0.25 g) in dimethylformamide (10 ml) was stirred at room temperature with methyl iodide (3 ml) for 50 min. The *product* was precipitated by addition of ether (50 ml); crude yield 60%; $\lambda_{max.}$ (pH 1) 287 nm. The compound decomposes slowly in aqueous solution at pH 8.0. It was used without further purification for the next step.

(g) 1,7-*Dimethyl*-8-(*methylthio*)*hypoxanthine* (7). A suspension of the crude compound (16) (1.5 g) in 48% hydrobromic acid (20 ml) was heated to 70 °C for 3 h. Treatment as described for the debenzylation of (14) gave (7) as long, white *needles* (see Table 5).

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