Tautomerism and Ionization Processes in 6-Thioxanthine and its *N*-Methyl Derivatives

By **D. Lichtenberg, F. Bergmann,*** and **Z. Neiman,** Department of Pharmacology, Hebrew University–Hadassah Medical School, Jerusalem, Israel

U.v. and n.m.r. spectra have been measured for 6-thioxanthine and all its *N*-methyl derivatives. In aqueous solutions of 6-thioxanthines with a free NH-group in the imidazole ring, the 7-NH-tautomer is predominant, while the monoanion of 6-thioxanthine and its 1-methyl derivative are mainly present as the 9-NH-tautomers. Whenever possible, anion formation occurs first by dissociation of the 3-NH-group; the order of acidities is 3 > 7 > 1. The anions of 6-thioxanthine and its 1-methyl derivative tautomerize to the 9-NH form.

Steric interactions between substituents (H and Me) at positions 3 and 9 are evident in the p*K* values of the 9-methyl-6-thioxanthines and in the large displacement to lower field of the n.m.r. signals of the 3- and 9-methyl groups in 3,9-dimethyl derivatives.

RECENTLY, u.v. and n.m.r. spectra of *N*-methylxanthines were used to obtain information on the fine structure of these purines, especially tautomeric and ionization processes.[1] 6-Thioxanthines exhibit a marked bathochromic shift in the u.v. spectra by comparison with the corresponding xanthines. This reflects the greater polarizability of the thiocarbonyl than the carbonyl group. The present study is devoted to the problem of whether the thiocarbonyl group also influences tautomeric and ionization processes.

Tautomerism of 6-Thioxanthines.—Comparison of the data in Tables 1 and 2 makes it probable that the thiolactim form ‒N=C‒SH does not make an important contribution. With the exception of compound (9), a marked hypsochromic shift of the long-wavelength maximum (of 26—28 nm) accompanies conversion of the thiolactam into the *S*-methylthiolactim group (see Table 2).† Therefore if any of the molecules are present in aqueous solution as thiolactims, alkylation at N(1) should raise $\lambda_{max.}$. However, introduction of a 1-methyl substituent causes a hypsochromic shift of 1—4 nm [*cf.* pairs (1)—(2), (3)—(4), (5)—(6), (7)—(8), (9)—(10), and (11)—(12) in part A of Table 1].

Methyl substitution at N(3) raises $\lambda_{max.}$ by 2—5 nm [*cf.* pairs (1)—(3), (2)—(4), (5)—(7), (6)—(8), (9)—(11), and (10)—(12) in Table 1A]. This shift is too small to permit reliable conclusions about participation of the 3-NH-group in enolization; it may in fact be entirely due to the inductive effect of the 3-methyl group.[2]

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† The structure of 9-methyl-6-methylthio-2-oxopurine will be discussed in a separate publication.

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

[2] B. Pullman and A. Pullman, 'Quantum Biochemistry,' Interscience, New York, 1963, p. 217.

It thus appears probable that 6-thioxanthines are present in water predominantly as lactam-thiolactams.

In order to decide the tautomeric structure of the imidazole ring, we have divided the thioxanthines into 3 classes (see Table 1A): class (*a*) comprises all derivatives with a free imidazole ring; in class (*b*), all members bear a 7-methyl group; class (*c*) is characterized by a 9-methyl substituent. The absorption maxima in class (*b*) are 1—2 nm higher than those of class (*a*). Conversely, in class (*c*), all values of $\lambda_{\text{max.}}$ are 2—5 nm lower than in class (*a*). Although these differences suggest that the members of class (*a*) are predominantly present in aqueous solution as 7-NH-tautomers, they are too small to permit a reliable decision.

TABLE 1

U.v. absorption maxima ($\lambda_{\text{max.}}$/nm) of neutral and charged forms of 6-thioxanthines

A Long-wavelength maxima

Compound	Substituents	Neutral form (*a*)	Monanion (*b*)	$\Delta\lambda_{\text{max.}}$ (*b*) − (*a*)	Dianion (*c*)	$\Delta\lambda_{\text{max.}}$ (*c*) − (*b*)	Cation (*d*)	$\Delta\lambda_{\text{max.}}$ (*d*) − (*a*)
Class (*a*)								
(1)		342	342	0	337	−5	328	−14
(2)	1-Methyl	338	340	+2	338	−2	323	−15
(3)	3-Methyl	345	338	−7	324	−14	333	−12
		337sh						
(4)	1,3-Dimethyl	343	340	−3			329	−14
		334sh						
Class (*b*)								
(5)	7-Methyl	343	355	+12	330	−25	325	−18
(6)	1,7-Dimethyl	340	347	+7			323	−17
(7)	3,7-Dimethyl	347	325	−22			333	−14
(8)	1,3,7-Trimethyl [a]	344					327	−17
Class (*c*)								
(9)	9-Methyl	337	342	+5	322	−20	328	−9
(10)	1,9-Dimethyl	336	340	+4			326	−10
(11)	3,9-Dimethyl	342	328	−14			334	−8
(12)	1,3,9-Trimethyl [a]	338					328	−8

B Short-wavelength maxima

Compound	Substituents	Neutral form (*a*)	Monanion (*b*)	$\Delta\lambda_{\text{max.}}$ (*b*) − (*a*)	Dianion (*c*)	$\Delta\lambda_{\text{max.}}$ (*c*) − (*b*)	Cation (*d*)	$\Delta\lambda_{\text{max.}}$ (*d*) − (*a*)
Class (*a*)								
(1)		265	250	−15	224	−26	248	−17
					248sh	−2		
(2)	1-Methyl	271	248	−23	228	−20	246	−25
					254sh	+6	273	+2
(3)	3-Methyl	265	252	−13	277	+25	250	−15
(4)	1,3-Dimethyl	270	259	−11			247	−23
			234	−36			272sh	+2
Class (*b*)								
(5)	7-Methyl	257	251	−6	274	+23	253	−4
(6)	1,7-Dimethyl	266	258	−8			249	−17
(7)	3,7-Dimethyl	250	288	+38			252	+2
(8)	1,3,7-Trimethyl [a]	264					250	−14
Class (*c*)								
(9)	9-Methyl	258	254	−4	267	+13	250	−8
					250	−4		
(10)	1,9-Dimethyl	263	254	−9			253	−10
(11)	3,9-Dimethyl	253	284 [b]	+31			255	+2
(12)	1,3,9-Trimethyl [a]	264					257	−7

[a] Decomposes above pH 12. [b] Above pH 10, a further maximum appears at 240—245 nm.

TABLE 2

U.v. absorption spectra ($\lambda_{\text{max.}}$/nm) of 6-methylthio-2-oxopurines as neutral molecules

Compound	Substituents	Absorption maximum (nm) Higher	Lower
(1a)		316	268
(2a)	1-Methyl	335	246
(3a)	3-Methyl	317	268
(4a)	1,3-Dimethyl	336	258
(5a)	7-Methyl	317	270
(7a)	3,7-Dimethyl	319	272
(9a)	9-Methyl	332	252

Strong support for the above assumption is obtained by n.m.r. measurements. Both in class (*a*) and (*b*), the 8-H signals are found in the range δ 7·96—8·06 p.p.m., while in class (*c*) all values are shifted upfield by 0·3—0·4 p.p.m. (Table 3). Therefore, the thioxanthines in class (*a*) are represented predominantly by structure (I).

Anion Formation in 6-Thioxanthines.—Combination of the changes of both long and short-wavelength u.v. maxima allows definite conclusions about the sequence of anion formation in all members of the present series [see Figures 1 and 2 and Table 1 (A and B)].

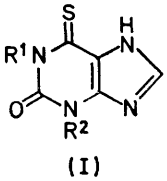
We consider first the dimethyl derivatives, in which

TABLE 3

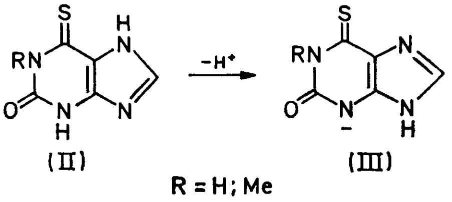
N.m.r. data for 8-H (δ/p.p.m.) in 6-thioxanthines

Compound	Substituents	Neutral form (*a*)	Monoanion (*b*)	Δδ (*a*) − (*b*)	Dianion (*c*)	Δδ (*b*) − (*c*)	Cation (*d*)	Δδ (*a*) − (*d*)
Class (*a*)								
(1)		7·98	7·62	+0·36	7·31	+0·31	8·02	−0·04
(2)	1-Methyl	7·96	7·52	+0·44	7·30	+0·22	8·01	−0·05
(3)	3-Methyl	8·03	7·34	+0·69	7·17	+0·17	8·04	−0·01
(4)	1,3-Dimethyl	8·06	7·33	+0·73			8·02	−0·04
Class (*b*)								
(5)	7-Methyl	7·96	7·81	+0·15	7·68	+0·13	7·97	−0·01
(6)	1,7-Dimethyl	7·97	7·87	+0·10			7·98	−0·01
(7)	3,7-Dimethyl	8·04	7·77	+0·27			8·04	0·00
(8)	1,3,7-Trimethyl	8·06					8·05	−0·01
Class (*c*)								
(9)	9-Methyl	7·67	7·53	+0·14	7·40	+0·13	8·80	−1·13
(10)	1,9-Dimethyl	7·65	7·56	+0·09			8·64	−0·99
(11)	3,9-Dimethyl	7·66	7·39	+0·27			8·60	−0·94
(12)	1,3,9-Trimethyl	7·65					8·72	−1·07

only a single NH-group is available for dissociation. In compounds (7) and (11), ionization of the 1-NH-group is accompanied by a marked hypsochromic shift of the long-wavelength absorption maximum (—22 and —14 nm, respectively), while the lower $\lambda_{max.}$ is shifted to longer wavelengths by 38 and 31 nm respectively. This combination is thus assumed to characterize dissociation at position 1.



(I)



(II) (III)

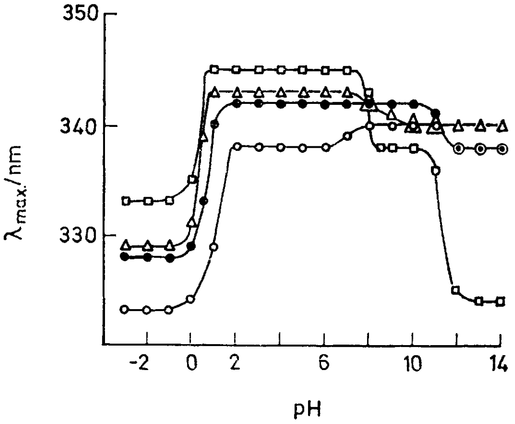


FIGURE 1 Long-wavelength maxima of 6-thioxanthines of class (*a*) as a function of pH: ● 6-thioxanthine (1); ○ 1-methyl-6-thioxanthine (2); □ 3-methyl-6-thioxanthine (3); △ 1,3-dimethyl-6-thioxanthine (4)

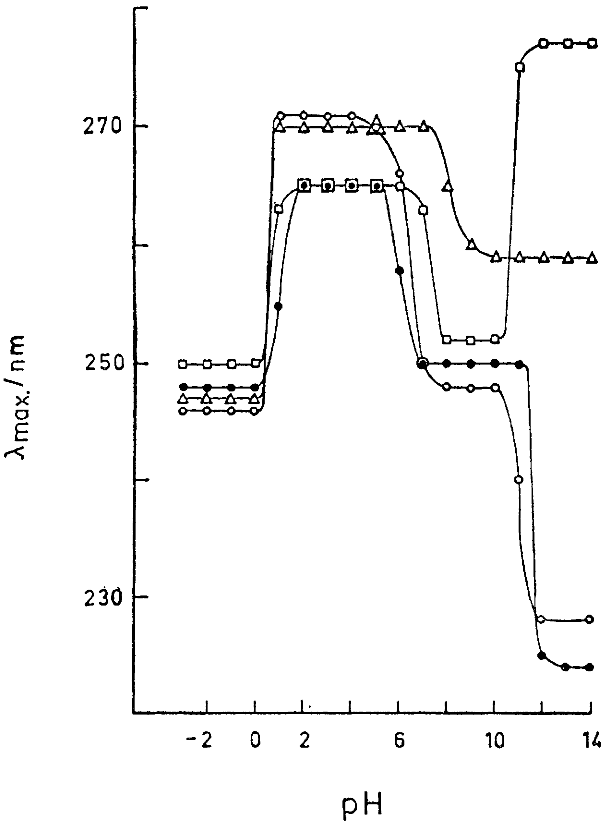


FIGURE 2 Short-wavelength maxima of 6-thioxanthines of class (*a*) as function of pH: symbols as in Figure 1

Ionization of the 3-NH-group in compounds (6) and (10) is associated with a bathochromic shift of 4—7 nm at the higher * and with a hypsochromic shift of 8—9 nm

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* It is remarkable that in contrast to ionization at N(1) or N(7), dissociation of the 3-NH-group causes a bathochromic shift of the long-wavelength $\lambda_{max.}$. This may perhaps indicate that here the negative charge is distributed less to the 6-thiocarbonyl group than in other cases.

at the lower maximum. This combination, which specifies dissociation at position 3, is thus the reverse of the changes characterizing dissociation of the 1-NH-group. Finally, ionization at position 7 in compound (4) is accompanied by hypsochromic shifts of both maxima (3 and 11 nm, respectively; see Figures 1 and 2).

These observations can be applied to the ionization of the monomethyl derivatives. In compound (5), formation of the monoanion is accompanied by a bathochromic shift of the higher and a hypsochromic shift of the lower maximum, while the reverse displacements characterize the second anionization step. This establishes the sequence 3 → 1. In the 9-methyl compound (9), the first anionization step shows the same changes as in the case of the 7-methyl compound (5). Thus, here again, the sequence is 3 → 1. However, formation of the bis-anion leads to a hypsochromic shift of the higher $\lambda_{max.}$, while the lower absorption maximum splits into two peaks (250 and 267 nm).

For 3-methyl-6-thioxanthine (3), we observed in the first step a hypsochromic shift of both maxima (of 7 and 13 nm, respectively); for the second step, the higher $\lambda_{max.}$ underwent a hypsochromic displacement of 14 nm and the lower one a bathochromic shift of 25 nm (see Figures 1 and 2). Thus the sequence 7 → 1 can be derived unequivocally.

Using the criteria established so far, we find that in both compounds (1) and (2), formation of the dianion is accompanied by hypsochromic shifts of either absorption maximum (see Figures 1 and 2), behaviour typical for dissociation of the 7-NH-group. For the 1-methyl derivative, this leads directly to the sequence 3 → 7. In this compound, the first dissociation step is characterized by a slight bathochromic shift (+2 nm) of the higher and a large hypsochromic displacement (—23 nm) of the lower $\lambda_{max.}$, in keeping with dissociation of the 3-NH-group. For the parent substance (1), the corresponding values are 0 and —15 nm, which certainly do not fulfill the criteria for dissociation at N(1). Thus here also the sequence is 3 → 7.*

Table 1A shows that the long-wavelength maxima of the monoanions of compounds (1) and (2) are identical with those of 9-methyl analogues (9) and (10), respectively, but differ markedly from those of the corresponding members of class (*b*), *viz.* the dimethyl compounds (5) and (6). It is thus probable that in the anions of (1) and (2), the tautomeric equilibrium has shifted in favour of the 9-NH-form [(II) → (III)], similar to findings regarding xanthine and its 1-methyl derivative.[3] This conclusion is also supported by n.m.r. data showing that the values for 8-H in the anions of (1), (2), (9), and (10) are close to each other but differ greatly from those of the anions of (5) and (6) (Table 3).

The foregoing results may explain several surprising observations. Bathochromic shifts of the long-wavelength maxima during monoanion formation are much smaller for compounds (1) and (2) than the changes accompanying dissociation at the same position 3 in compounds (5), (6), (9), and (10). This is due to combination of two opposing effects which nearly cancel each other: (*a*) a bathochromic shift of *ca.* 7 nm, following ionization of the 3-NH-group, and (*b*) a hypsochromic displacement of *ca.* 4 nm, caused by the shift of tautomeric equilibrium in favour of the 9-NH-form.

On the other hand, the hypsochromic shifts of the short-wavelength maxima are much larger for compounds (1) and (2) than for the derivatives (5), (6), (9), and (10). Here the two effects are synergistic, *viz.* (*a*) a hypsochromic displacement of $\lambda_{max.}$ of *ca.* 6 nm, due to ionization at N(3) and (*b*) the hypsochromic effect (*ca.* 8 nm) characteristic of the shift of tautomeric equilibrium in favour of the 9-NH-form.

Also the n.m.r. data are in agreement with the foregoing interpretations (Table 3). In compounds (5), (6), (9), and (10), ionization at position 3 causes an average upfield shift of the 8-H signal of *ca.* 0·12 p.p.m., while in (1) and (2) the analogous process shifts the 8-H band by *ca.* 0·4 p.p.m. to higher field. This large difference may again be ascribed to the accompanying transformation of the 7- into the 9-NH-form; the latter event is characterized by an upfield shift of *ca.* 0·35 p.p.m.

For ionization of the 1-NH-group in the dimethyl compounds (7) and (11) we find a p*K* of 8·8 (Table 4), *i.e.*

TABLE 4

Ionization constants of 6-thioxanthines [a]

		p*K* Values for			
		Anion formation at			Cation formation
Compound	Substituents	N(3)	N(7)(9)	N(1)	
Class (*a*)					
(1)		6·2	11·4		0·9
(2)	1-Methyl	6·7	11·0		1·1
(3)	3-Methyl		7·9	11·2	0·4
(4)	1,3-Dimethyl		8·2		0·4
Class (*b*)					
(5)	7-Methyl	6·8		12·1	0·3
(6)	1,7-Dimethyl	7·5			0·5
(7)	3,7-Dimethyl			8·8	0·3
(8)	1,3,7-Trimethyl				0·2
Class (*c*)					
(9)	9-Methyl	4·9		12·6	1·5
(10)	1,9-Dimethyl	5·3			1·4
(11)	3,9-Dimethyl			8·8	0·9
(12)	1,3,9-Trimethyl				1·4

[a] The values represented are the arithmetic mean of 3—5 determinations: higher u.v. absorption maximum; lower u.v. absorption maximum; higher and lower $\varepsilon_{max.}$; and chemical shift of 8-H signals.

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* One of the referees has pointed out that the difference between the p*K* values of compounds (2) and (3) or (6) and (7) indicates a tautomeric equilibrium (pK_T) between the 1- and 3-NH-forms in the monoanions of compounds (1) and (5). The value of pK_T of *ca.* 1·3 (see Table 4) would indicate that in a solution of the monoanions, *ca.* 5% are in the 3-NH-form, while 95% are present as 1-NH-tautomers. This would not alter materially the conclusions drawn in this paper. It should however be noted that the p*K* values of compounds (1) and (5) are lower than those of the 1-methyl derivatives (2) and (6) (Δp*K* 0·5 and 0·7 respectively). Therefore no exact evaluation of the pK_T values can be made for compounds (1) and (5). In class (*c*), the difference of p*K* values for dimethyl compounds (10) and (11) is 3·5, *i.e.* here the contribution of the 3-NH-form to the monoanion of (9) would be <0·1%.

[3] W. Pfleiderer and G. Nübel, *Annalen*, 1961, **647**, 155.

this value is independent of the tautomeric structure of the imidazole function. On the other hand, dissociation of the 3-NH group is characterized by different p*K* values in each class. Thus, for compounds (1) and (2) we find p*K* values of 6·2 and 6·7 respectively. This difference is probably due to the inductive, *i.e.* acidity-lowering, effect of the 1-methyl substituent. Similarly, a 7-methyl group raises the p*K* of the 3-NH group, as shown by the values for the 7-methyl (5) (p*K* 6·8) and 1,7-dimethyl compound (6) (p*K* 7·5). In contrast, introduction of a 9-methyl group lowers the p*K* value of the 3-NH group considerably [p*K* of compound (9) = 4·9 and of (10) = 5·3]. This effect may be ascribed to relief of steric strain between the 3- and 9-substituents by anion formation. Monoanion formation by dissociation of 7-NH in compounds (3) and (4) is characterized by p*K* values of 7·9 and 8·2, respectively.

Comparison of the dissociation constants of 6-thioxanthines with the corresponding data for xanthines (see Table 5 of ref. 1) shows that all p*K* values for monoanion formation are lower in the 6-thioxanthine series. The largest difference (2·2 units) is observed for dissociation of the 1-NH-group [compounds (7) and (11)] and clearly expresses the greater polarizability of the 6-thiocarbonyl group. For ionization at position 3, Δp*K* is 1·0—1·6 [compounds (5), (6), (9), and (10)], while for dissociation of the 7-NH-group the difference is considerably smaller [0·6 for compound (3) and 0·3 for compound (4)].

All the ionization steps of 6-thioxanthines are identical with the corresponding processes in the xanthine series, with the exception of compounds (1) and (2). In xanthine and its 1-methyl derivative, the experimental data led us to the assumption that anion formation involves both position 3 and the NH-group of the imidazole ring, *i.e.* the monoanions were represented as a mixture of tautomers.[1] For the corresponding members in the 6-thioxanthine series, however, the first dissociation step is clearly confined to position 3. This may be explained by the changed order of acidities, which in 6-thioxanthines is 3 > 7 > 1, while in xanthines it is 3 ~ 7 > 1.

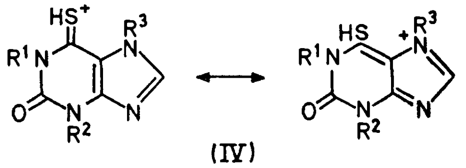
Cation Formation in 6-*Thioxanthines*.—Table 3 reveals that cation formation has a very slight effect on the 8-H signal in the n.m.r. spectra for class (*a*) and a negligible one in class (*b*). On the other hand, in class (*c*), large downfield shifts of *ca.* 1 p.p.m. are observed. The situation is thus qualitatively similar to that in the xanthine series. On the other hand, the long-wavelength maxima in the u.v. for the cations in Table 1 show much larger hypsochromic shifts than those of the xanthines.[1] It appears possible that cation formation involves mainly the thiocarbonyl group [as, *e.g.*, in (IV)] and that only in class (*c*) is the proton partially attached also to the free N(7) (Va and b). This would explain the large downfield shift of the 8-H signal and the smaller hypsochromic shift of the higher $\lambda_{max.}$ in class (*c*).

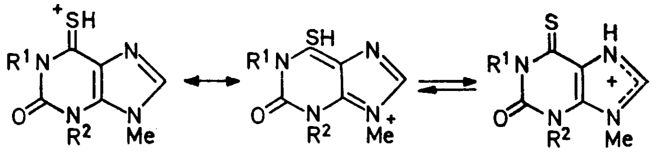
N.m.r. Signals of the N-*Methyl Groups*.—According to Table 5, the order of methyl signals (upfield ⟶ downfield) is 3 ⟶ 1 ⟶ 9 ⟶ 7. This sequence differs from that of the xanthines, in that the signal of the 1-methyl group is shifted downfield relative to that of the 3-methyl substituent. This is due to the proximity of the 6-thiocarbonyl group.[4]

TABLE 5

N.m.r. signals (δ/p.p.m.) of *N*-methyl groups in 6-thioxanthines

		1-Methyl				3-Methyl				7-Methyl				9-Methyl			
Compound	Substituents	Neutral	Mono-anion	Di-anion	Cation	Neutral	Mono-anion	Di-anion	Cation	Neutral	Mono-anion	Di-anion	Cation	Neutral	Mono-anion	Di-anion	Cation
Class (*a*)																	
(2)	1-Methyl	3·67	3·68	3·70	3·67												
(3)	3-Methyl					3·45	3·42	3·40	3·47								
(4)	1,3-Dimethyl	3·75	3·75		3·72	3·56	3·50		3·54								
Class (*b*)																	
(5)	7-Methyl									4·05	4·01	4·04	4·06				
(6)	1,7-Dimethyl	3·72	3·70		3·73					4·05	4·10		4·15				
(7)	3,7-Dimethyl					3·41	3·39		3·43	4·06	4·04		4·05				
(8)	1,3,7-Trimethyl	3·69			3·71	3·50			3·52	4·08			4·10				
Class (*c*)																	
(9)	9-Methyl													3·73	3·48	3·48	3·93
(10)	1,9-Dimethyl	3·62	3·65		3·70									3·73	3·51		3·85
(11)	3,9-Dimethyl					3·67	3·63		3·68					3·94	3·89		4·16
(12)	1,3,9-Trimethyl	3·74			3·78	3·74			3·78					3·92			4·16


(IV)


(Va) (Vb)

Usually, *N*-methyl signals are shifted only very little by the presence of other *N*-methyl groups. Strong interaction has been encountered only in 3,9-dimethyl deriva-

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[4] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc.* (*C*), 1971, 1939.

tives. The signal of the 3-methyl group is shifted downfield by 0·22 p.p.m., when passing from the 3-methyl (3) to 3,9-dimethyl (11) and by 0·18 p.p.m. from the 1,3-dimethyl (4) to 1,3,9-trimethyl (12) compound. Similarly the 9-methyl signal is displaced *ca.* 0·2 p.p.m. to lower field, from (9) to (11) or from (10) to (12). These changes are best explained by steric interference, similar to our previous observations on xanthines [1] and 8-phenyl-6-thiopurines.[5] Assignment of the individual methyl signals in compounds (9) and (10) is based on the nuclear Overhauser effect (see Experimental section).

TABLE 6

New 6-thioxanthines

Compound	Derivative of 6-thioxanthine	Yield (%)	R_F [a]	log $\varepsilon_{max.}$ [b]	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(6)	1,7-Dimethyl	60	0·72	4·31	42·7	4·1	28·6	16·3	$C_7H_8N_4OS$	42·7	4·3	28·6	16·0
(10)	1,9-Dimethyl	55	0·70	4·38	36·2	5·2	24·1	13·8	$C_7H_8N_4OS,2H_2O$	35·8	4·8	24·1	13·7

[a] In ethanol–dimethylformamide–water (3 : 1 : 1 v/v); violet fluorescence under a Mineralight lamp of λ *ca.* 255 nm. [b] Referring to the long-wavelength maximum of the neutral form.

TABLE 7

New 6-methylthio-2-oxopurines

Compound	Derivative of 6-methylthio-2-oxopurine	Reaction Conditions	Time (min)	Yield (%)	M.p. (°C)	R_F [a]	Fluorescence	log $\varepsilon_{max.}$	Crystal form	Solvent for crystallization	Calc. (%) C	H	N	S	Formula	Found (%) C	H	N	S
(2a)	1-Methyl [c]	MeI–N-NaOH	20	8	*c*	0·6	Green	4·09	Rhombic plates	H_2O	42·7	4·1	28·6	16·3	$C_7H_8N_4OS$	42·85	4·2	27·35	15·5
(5a)	7-Methyl	MeI–N-NaOH	20	55	280	0·4	Violet	4·20	Needles	H_2O	42·7	4·1	28·6	16·3	$C_7H_8N_4OS$	43·1	4·3	28·5	16·0
(9a)	9-Methyl	Me_2SO_4–0·1N-NaOH	50	51	284—287	0·55	Violet	4·02	Prisms	MeOH	42·7	4·1	28·6	16·3	$C_7H_8N_4OS$	43·0	4·2	28·7	16·0

[a] Solvent as in Table 6; spots were detected by their fluorescence under a Mineralight lamp. [b] Refers to the long-wavelength maximum of the neutral molecule.
[c] Compound (2a) is unstable and highly sensitive to alkali. This explains the low yield, the variabilty in m.p. (220—260°), and the unsatisfactory elemental analysis.

The position of the methyl signals is, in general, influenced only slightly by anion formation. The only exceptions are compounds (9) and (10), where the negative charge at N(3) displaces the 9-methyl signal by 0·25 and 0·22 p.p.m., respectively, to higher field, similar to previous observations with 9-methylxanthine.

Similarly, cation formation displaces the methyl signals only slightly, with the exception of the 9-methyl bands in class (*c*). This result supports the foregoing conclusions about the site of protonation in 6-thioxanthines.

EXPERIMENTAL

U.v. spectra were measured on a Cary model 14 spectrophotometer; n.m.r. spectra were obtained with Jeol C-60-H and MH-100 instruments at 70°, with sodium 2,2-dimethyl-2-silapentanesulphonate as internal standard in a mixture of [$^2H_6$]dimethyl sulphoxide and deuterium oxide (9 : 1, v/v). Alkaline solutions were produced by addition of sodium deuterioxide and acid media by addition of trifluoroacetic acid. Chemical shifts are in p.p.m. The nuclear Overhauser effect was measured for the cation of compound (11) by irradiation of the solution with the frequency of the 9-methyl signal (δ 4·16; see Table 5). This caused the area of the 8-H signal to increase by 45%, while under irradiation with the frequency of 3-methyl (δ 3·68) this signal grew only by 25%.

6-Thioxanthines.—The following were synthesized by known methods: 6-thioxanthine [6] and its 1-methyl,[7] 3-methyl-,[8] and 1,3-dimethyl- [9] derivatives; 7-methyl-,[10] 3,7-dimethyl-,[9] and 1,3,7-trimethyl-6-thioxanthine; [9] and the 9-methyl-, 3,9-dimethyl-, and 1,3,9-trimethyl-derivatives.[6]

The new purines, 1,7- (6) and 1,9-dimethyl-6-thioxanthine (10) were prepared by heating under reflux a solution of the corresponding xanthines [1, 11] with 3 equiv. of phosphorous pentasulphide in pyridine for 15 h. The solvent was removed *in vacuo*, the residual syrup was decomposed with warm water, and the insoluble part was recrystallized from water. Both compounds (6) and (10) crystallized in yellow needles, m.p. >300° (decomp.) (see Table 6).

6-Methylthio-2-oxopurines were obtained by methylation of the corresponding 6-thioxanthines in alkaline solution with methyl iodide or dimethyl sulphate followed by subsequent neutralization. Compounds (1a),[12] (3a),[13] (4a),[13] and (7a) [9] (see Table 2) have been synthesized previously. The new derivatives are described in Table 7.

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