Kinetics of Reactions in Heterocycles. Part XI.[1] Reactions of 2-, 6-, and 8-Chloro-7-methylpurines and 2-, 6-, and 8-Methylsulphonyl-7(and 9)-methylpurines with Hydroxide Ions

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Kinetics have been measured for the reactions of 6- and 8-chloro-7-methylpurine and 2-, 6-, and 8-methylsulphonyl-7(and 9)-methylpurine with hydroxide ions. Generally, at 20°, the 7-methylpurines were more reactive than their 9-methyl isomers, but 2-methylsulphonyl-9-methylpurine was 3·6 times more reactive than its 7-methyl isomer. Relative reactivities of the 2-, 6-, and 8-methylsulphonyl-7-methylpurines were 1 : 840 : 29,000, and for the 9-methyl series 1 : 110 : 830. Preparations of 2-, 6-, and 8-methylsulphonyl-7-methylpurine are described. Ionisation constants and u.v. and ^{1}H n.m.r. spectra are recorded and discussed.

KINETICS of the reactions of substituted 9-methylpurines with various nucleophiles have been studied extensively [2-6] but quantitative studies of the reactivity of 1-, 3-, or 7-methylpurines have not been described. In this paper we report the preparation of the three methylsulphonyl-7-methylpurines and the kinetics of the reactions of chloro- and methylsulphonyl-7-methylpurines, and of the methylsulphonyl-9-methylpurines for comparison, with hydroxide ions in water. This nucleophilic system was chosen so that the parent compounds did not react with the solvent alone, and to permit a comparison across a broad spectrum of reactivity.

The results of the kinetic studies are shown in Tables 1—3. Typical kinetic runs (Table 1) and times of 50% reaction (Table 2) revealed that the reaction of each purine with hydroxide ion follows regular second-order kinetics. Examination of the rate coefficients calculated at 20°, and Arrhenius parameters derived from the kinetic results (Table 3), revealed that at 20° 6-chloro-7-methylpurine was 1·95 times more reactive than its 9-methyl isomer [5] despite the higher energy of activation of the former (E_a 19·85 compared to 17·8 kcal mol^{-1}), which was compensated by a higher frequency factor (log A 10·95 compared to 9·2). 6-Chloro-7-methylpurine at 20° was 19·2 times less reactive than the 8-chloro-isomer owing mainly to its much higher energy of activation (19·85 compared to 17·35 kcal mol^{-1}). It was not possible to study the kinetics of hydrolysis of 2-chloro-7-methylpurine as a mixture of products was formed.[7]

Amongst the methylsulphonyl-*N*-methylpurines, 2-methylsulphonyl-9-methylpurine was 3·6 times more reactive than the 7-methyl isomer; but in contrast, the 7-methyl-6- and -8-methylsulphonylpurines were more reactive than their 9-methyl analogues. Reactivity was enhanced by *ca.* 2·15 for the 6-methylsulphonyl com-

TABLE 1

Reactions of hydroxide ions

6-Chloro-7-methylpurine at 40·7°; 0·05N-hydroxide; [purine] 0·0035M

Time (min)	19·1	42·4	62·4	104·6	145·1	178·7	248·9	362·9	421·2
Reaction (%)	7·6	15·5	21·9	34·5	43·9	51·4	62·2	76·6	80·6
10^3k/l mol^{-1} s^{-1}	1·37	1·33	1·33	1·37	1·35	1·38	1·34	1·38	1·34

Mean 10^3k = 1·35 ± 0·02; after correction for solvent expansion, 1·36

2-Methylsulphonyl-7-methylpurine at 40·5°; 0·05N-hydroxide; [purine] 0·003296M

Time (s)	192	500	863	1360	1945	2610	3369	5666
Reaction (%)	7·4	17·9	28·5	40·1	52·5	63·2	72·8	88·5
10^3k/l mol^{-1} s^{-1}	7·98	7·96	7·86	7·66	7·81	7·86	7·96	7·96

Mean 10^3k = 7·88 ± 0·11; after correction for solvent expansion, 7·93

8-Methylsulphonyl-7-methylpurine at 35·5°; 0·0006N-hydroxide; [purine] 0·0000648M

Time (s)	2·9	5·9	8·8	11·8	14·7	17·6	23·5	29·4	35·3	44·1	64·7
Reaction (%)	11·3	20·7	29·3	37·6	44·7	50·0	59·4	68·8	73·7	81·6	91·4
k/l mol^{-1} s^{-1}	68·2	66·4	66·7	68·3	69·1	67·5	66·3	69·1	66·3	67·7	67·7

Mean k = 67·6 ± 1·0; after correction for solvent expansion, 67·9

8-Methylsulphonyl-9-methylpurine at 29·7°; 0·005N-hydroxide; [purine] 0·0000466M

Time (s)	3·0	5·9	9·9	13·8	17·7	25·6	35·5	41·4	59·1	70·9
Reaction (%)	9·7	17·1	27·4	36·2	43·5	56·2	67·9	73·5	85·0	90·3
k/l mol^{-1} s^{-1}	6·47	6·33	6·49	6·52	6·46	6·46	6·43	6·45	6·45	6·61

Mean k = 6·47 ± 0·07; after correction for solvent expansion, 6·49

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TABLE 2

Kinetic results for the reactions of chloro- and methylsulphonyl-7- and -9-methylpurines with hydroxide ions

Temp. (°C) [a]	10^3[OH$^-$] (N)	10^4[Purine] (M)	10^3k [b]	$10^3k_{corr.}$ [c]	$t_{\frac{1}{2}}$ [d]	$t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [e]	Anal. λ (nm) [f]
			6-Chloro-7-methylpurine [g]				
40·7	50	35·1	1·35	1·36			257
50·8	50	3·43	3·77	3·79			257
60·2	50	3·30	8·63	8·77	1635		257
60·2	25	1·65	8·58	8·72	3291	2·0	257
			8-Chloro-7-methylpurine [g]				
20·1	50	2·67	2·81	2·81			268
30·6	50	2·66	7·68	7·70	1831		268
30·6	25	1·33	7·47	7·49	3770	2·06	268
36·1	50	2·66	1·28	1·29			268
			2-Methylsulphony-7-methylpurine [g]				
30·2	50	32·46	3·20	3·21			330
40·5	50	32·96	7·88	7·93	1792		330
40·5	25	16·48	7·78	7·84	3626	2·02	330
49·6	50	33·02	16·49	16·66			330
			6-Methylsulphonyl-7-methylpurine [h]				
36·2	0·6	0·769	2660	2670			285
45·2	0·6	0·769	4270	4310			285
52·8	0·6	0·769	6330	6390	189		285
52·8	0·3	0·3845	6280	6340	381	2·01	285
			8-Methylsulphonyl-7-methylpurine [h]				
24·5	0·6	0·648	43,580	43,600			285
35·5	0·6	0·648	67,600	67,900			285
45·4	0·6	0·606	101,200	10,200	11·75		285
45·4	0·3	0·303	103,300	104,200	23·02	1·97	285
			2-Methylsulphonyl-9-methylpurine [g]				
19·5	20	27·6	4·34	4·34			316
29·5	20	27·44	10·46	10·49	3444		316
29·5	10	13·71	10·49	10·52	6869	1·99	316
39·5	20	27·5	22·76	22·89			316
			6-Methylsulphonyl-9-methylpurine [h]				
20·1	15	9·75	486	486			290
30·3	15	9·75	1021	1024			290
41·1	15	9·75	2052	2065	22·6		290
41·1	7·5	4·875	2024	2038	45·7	2·03	290
			8-Methylsulphonyl-9-methylpurine [h]				
20·3	5	0·467	3803	3803			290
29·7	5	0·467	6470	6480			290
40·2	5	0·467	11,060	11,120	12·6		290
40·2	2·5	0·2335	10,850	10,920	25·6	2·04	290

[a] ±0·1°. [b] In l mol^{-1} s^{-1}; the standard deviation was generally <2%. [c] Corrected for solvent expansion. [d] Time for 50% reaction in s. [e] The ratio of $t_{\frac{1}{2}}$ for two experiments at the same temperature but with the reactant concentrations in one being 0·5 times that in the other. [f] Analytical wavelength for determination of percentage reaction. [g] pH 5 Buffer was used to stop the reactions, and for spectroscopic measurements. [h] A stopped flow technique (D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43) was used to study this reaction.

TABLE 3

Rate coefficients and Arrhenius parameters for reactions with hydroxide ions

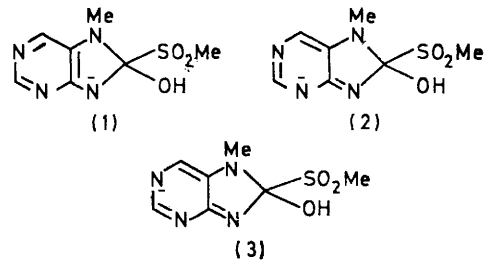
Compound	$10^3k_{20°}$ [a]	E_a [b]/kJ mol^{-1} (kcal mol^{-1})	log A [c]	$\Delta H^{\ddagger}$ [b]/kJ mol^{-1} (kcal mol^{-1})	$-\Delta S^{\ddagger}$ [d]/J mol^{-1} K^{-1} (cal mol^{-1} K^{-1})
6-Chloro-7-methylpurine	0·144	83·1 (19·85)	10·95	80·4 (19·2)	44·3 (10·6)
6-Chloro-9-methylpurine [e]	0·074	74·5 (17·8)	9·2		
8-Chloro-7-methylpurine	2·77	72·6 (17·35)	10·5	70·1 (16·7)	52·3 (12·5)
2-Methylsulphonyl-7-methylpurine	1·24	68·9 (16·5)	9·4	66·3 (15·85)	73·7 (17·6)
2-Methylsulphonyl-9-methylpurine	4·52 [f]	65·35 (15·6)	9·3	62·8 (15·0)	75·1 (17·95)
6-Methylsulphonyl-7-methylpurine	1040	43·8 (10·5)	7·82	41·1 (9·8)	104·2 (24·9)
6-Methylsulphonyl-9-methylpurine	484 [g]	52·8 (12·6)	9·10	50·2 (12·0)	79·1 (18·9)
8-Methylsulphonyl-7-methylpurine	35,800	31·9 (7·6)	7·24	29·4 (7·0)	115·1 (27·5)
8-Methylsulphonyl-9-methylpurine	3760 [h]	41·0 (9·80)	7·9	38·5 (9·2)	103·6 (24·4)

[a] In l mol^{-1} s^{-1}, calculated from the experimental results. [b] Accurate to ±2·1 kJ mol^{-1}. [c] Accurate to ±0·3 unit. [d] Accurate to ±1·2 J mol^{-1} K^{-1}. [e] Ref. 5. [f] Ref. 4. gives 8·43 l mol^{-1} s^{-1}. [g] Ref. 4. gives 980 l mol^{-1} s^{-1}. [h] Ref. 4 gives 6020 l mol^{-1} s^{-1}.

pounds and by *ca.* 9·5 for the 8-methylsulphonyl isomers. In these pairs of compounds, the reactivity differences were attributable mainly to the lower energy of activation of the more reactive isomers. The relative reactivities of the 2-, 6-, and 8-methylsulphonyl-*N*-methylpurines were for the 9-methyl series 1 : 110 : 830 and for the 7-methyl series 1 : 840 : 29,000, compared to 1 : 80 for 9-methylpurin-2- and -6-yltrimethylammonium chloride.[5] In each of these series the increase in reactivity was paralleled by a decrease in energy of activation, although the frequency factor also decreased.

Comparable contributions to the stabilisation of the

intermediate complexes can be proposed for 2-methylsulphonyl-7- and -9-methylpurine, and for 6-methylsulphonyl-7- and -9-methylpurine, and the relative rates



show small variations. However for 8-methylsulphonyl-7-methylpurine three significant contributors (1)—(3) can be proposed, whereas for the much less reactive 8-methylsulphonyl-9-methylpurine the only contributor is that analogous to form (1). The relative reactivity of the corresponding chloro and methylsulphonyl compounds varied from 6500 for the 6-substituted 9-methylpurines to 12,900 for the 8-substituted 7-methylpurines and is to be compared with a maximum of *ca.* 100-fold in monoazabicyclic systems,[8] and a difference of 1600-fold in the reactivity of 6-chloro-9-methylpurine and 9-methylpurin-6-yltrimethylammonium chloride.[5]

Ionisation Constants and Spectra.—Inspection of the ionisation constants (Table 4) reveals that 2- and 6-chloro-7-methylpurine are significantly weaker bases than 8-chloro-7-methylpurine (and 7-methylpurine). This is due to the proximity of the inductive electron-withdrawing chloro-substituent to the basic centres in the pyrimidine ring, a situation also shown by the chloro-9-methylpurines.[2] 8-Chloro-7-methylpurine is a weaker base than 8-chloro-9-methylpurine [2] by 0·45 units, and this may be due to an indirect facilitation of electron withdrawal (4) by the chloro-substituent from N-1 or N-3 in 8-chloro-7-methylpurine which is not possible in 8-chloro-9-methylpurine, or to a greater stabilisation of the cation of 8-chloro-9-methylpurine [(5) ⟷ (6)].

8-Mercapto-7-methylpurine is an appreciably stronger base than 2- or 6-mercapto-7-methylpurine, and as it has been claimed [9] that both 6-mercapto- and 6-hydroxy-7-methylpurine protonate in the imidazole ring, 8-mercap-

TABLE 4

pK_a Values and u.v. spectra

	Ionisation (water 20°)					Spectroscopy in water [e]		
Purine	Species [a]	pK_a	Spread (±)	Concn. (M)	Anal. λ (nm)	$\lambda_{max.}$ (nm)	log ε	pH [d]
2-Cl-7-Me [c]	+	0·54	0·04	0·0008	290	274	3·95	−1·5
6-Cl-7-Me [f]	0					271	3·91	5·0
	+	0·43	0·05	0·001	280	245, *261*, 266, *271*	3·68, *3,90*, 3·93 *3·85*	−1·5
8-Cl-7-Me [g]	0					271	3·89	5·0
	+	1·55	0·05	0·00006	290	272	4·01	−0·5
2-SH-7-Me	0					233, 264, *279*, 354	4·02, 4·25, *4·21*, 3·22	4·0
	+	1·17	0·03	0·00001	298	284, 385	4·34, 3·34	−1·0
	−	6·98	0·05	0·0001	290	248, *265*, 336	4·32, *4·17*, 3·54	9·0
6-SH-7-Me		*h*				*i*		
8-SH-7-Me	0					232, 312	4·09, 4·41	4·0
	+	1·80	0·03	0·00001	340	242, *280*, 334	4·17, *3·51*, 4·27	−0·5
	−	6·92	0·05	0·0001	335	230, 317	4·19, 4·41	9·0
2-SMe-7-Me	0					240, 313	4·34, 3·70	4·0
	+	1·88	0·02	0·00002	266	232, 253, 319	4·17, 4·16, 3·68	−0·2
6-SMe-7-Me [f]	0					255, 294, *300*	3·63, 4·21, *4·17*	5·0
	+	1·98	0·03	0·00004	320	306, *315*	4·15, *4·06*	−0·5
8-SMe-7-Me	0					294	4·35	5·0
	+	2·88	0·03	0·00007	320	232, 307	4·05, 4·35	0·0
2-SO_2Me-7-Me	0	<1 [j]				272	3·88	5·0
6-SO_2Me-7-Me	0	*k*				285	3·86	5·0
8-SO_2Me-7-Me	0	*k*				275	4·04	5·0
2-OH-7-Me	0					262, 331	3·73, 3·73	5·0
	+	2·50	0·03	0·0001	275	274, 326	3·84, 3·74	0·0
	−	8·73	0·04	0·0001	265	254, 316	3·66, 3·80	11·0
6-OH-7-Me [l]	0					257	4·00 [m]	5·0
8-OH-7-Me [n]	0					242, 280	3·64, 4·04 [m]	5·0
2-SMe-9-Me	+	2·11	0·03	0·0001	300	*236*, 248, *273*, 315	*3·97*, 4·08, *3·63*, 3·49	0·0
7-Me	+	2·29 [o]				*o*		
9-Me	+	2·48 [o]				*o*		

[a] 0, Neutral species; +, cation; −, anion. [b] Analytical wavelength for spectroscopic determinations of pK_a. [c] Shoulders and inflections in italics. [d] pH Values below 0 have been obtained in solutions of hydrochloric acid to which the Hammett acidity functions of M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1, have been assigned. [e] Ref. 24 records the spectra at pH 1 and 11. [f] Ref. 23 records the spectrum at pH 1. [g] The spectra recorded in ref. 24 may be for the hydroxy-compound. [h] The ionisation constants have been recorded in refs. 9 and 12. [i] The u.v. spectra are given in ref. 12. [j] The pK_a could not be determined because a constant spectrum for the monocation could not be obtained. [k] Instability of the cation did not permit the determination of the basic pK_a. [l] The ionisation constants and u.v. spectra have been recorded in ref. 12. [m] The intensity readings are slightly higher than those in published data. [n] The ionisation constants and u.v. spectra have been recorded in ref. 11. [o] A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073.

[8] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 736.
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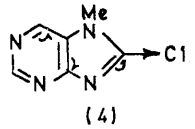
to-7-methylpurine probably protonates in the pyrimidine ring at N-1 like 8-hydroxypurine.[10] The mercapto-7-methylpurines were stronger acids by 1·08—1·75 units



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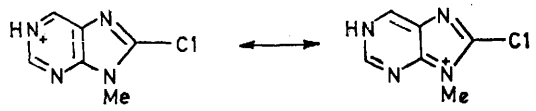

(5) (6)

and weaker bases by 0·82—1·33 units than their oxygen analogues. These differences are comparable with those for 6- and 8-hydroxy- and -mercapto-9-methylpurines[11,12] except that 6-mercapto-9-methylpurine is a weaker base than its oxygen analogue by only 0·41 units.

Both 2- and 8-methylthio-7-methylpurine were weaker bases than their 9-methyl isomers[11] by 0·23 and 0·10 units but 6-methylthio-7-methylpurine was a stronger base[13] by 0·58 units. In the methylsulphonyl-7-methylpurines, the general enhanced reactivity on formation of the cations[1] was sufficient to preclude the determination of the basic pK_a values because of the ease of the reaction of their cations with water.[1]

Amongst the ^1H n.m.r. spectra (Table 5) the chloro- and methylthio-compounds showed similar spectra while that for the methylsulphonyl compounds was at lower field, consistent with the strong electron-withdrawal by the methylsulphonyl group.[14] There appeared to be no correlation of the spectra of the hydroxy- and mercapto-compounds. As expected, the signal due to the methyl group attached to both N and S in the methylsulphonyl compounds was at lower field than in the corresponding methylthio-compounds.

Preparation of Compounds.—The 2- and 6-chloro-7-methylpurines were prepared by known procedures, and the former also by a catalytic reduction of 2,6-dichloro-7-methylpurine by a method similar to that used for its 9-methyl isomer.[15] 8-Chloro-7-methylpurine was prepared by direct chlorination of the 8-hydroxy-compound with phosphoryl chloride which gave also another product, assigned the structure 7,8-dihydro-7-methyl-9-(7-methylpurin-8-yl)purin-8-one. The 4-amino-5-methylaminopyrimidine required for this synthesis could not be prepared from 6-chloro-4,5-diaminopyrimidine using the general trifluoroacetylation and methylation procedure[16] because ring closure occurred to a 7-methyl-8-trifluoromethylpurine. It was readily prepared however from 7-methylpurine with alkali[17] or by catalytic reduction of 4-amino-6-chloro-5-methylaminopyrimidine.

All the methylsulphonyl compounds required in this work were best prepared by oxidation of the methylthio-compounds with potassium permanganate in dilute acetic acid solution. *m*-Chloroperbenzoic acid was less satisfactory. The intermediate 2-mercapto-7-methylpurine was readily prepared in good yield from 2-chloro-7-methylpurine and potassium hydrogen sulphide. Contrary to previous findings with 4-amino-5-methylaminopyrimidines,[18,19] we were able to prepare 8-mercapto-7-methylpurine from 4-amino-5-methylaminopyrimidine with carbon disulphide and triethylamine in refluxing pyridine.

TABLE 5

N.m.r. spectra

Chemical shifts (δ) of protons [a]

Purine	2	6	8	N-Me	S-Me
2-Cl-7-Me		9·15	8·65	4·05	
6-Cl-7-Me	8·82		8·78	4·11	
8-Cl-7-Me	8·86	9·06		3·77	
2-SH-7-Me [b]		8·46	8·10	3·80	
6-SH-7-Me [c,d]	8·50		8·22	4·28	
8-SH-7-Me	8·81	8·78		3·71	
2-SMe-7-Me		9·07	8·58	3·92	2·55
6-SMe-7-Me	8·82		8·58	4·12	2·72
8-SMe-7-Me	8·9	9·02		3·78	2·82
2-SO_2Me-7-Me		9·52	9·01	4·09	3·46
6-SO_2Me-7-Me	9·23		9·04	4·20	3·76
8-SO_2Me-7-Me	9·4	9·58		4·24	3·7
2-OH-7-Me		8·8	8·39	3·85	
6-OH-7-Me [d]	8·22		8·00	4·00	
8-OH-7-Me	8·60	8·41		3·36	
2,6-Cl_2-7-Me			8·7	4·07	
2-Cl-6-OH-7-Me [b]			7·95	3·99	
7-Me [e]	9·03	9·24	8·68	4·00	

[a] Spectra were determined in $(CD_3)_2SO$ solution unless otherwise stated, and at 33·5° with tetramethylsilane as internal standard. [b] Spectrum in N-NaOD. [c] For preparation see ref. 23. [d] Ref. 9 records the spectrum in D_2O. [e] For preparation see ref. 24.

EXPERIMENTAL

All compounds were examined for impurities by paper chromatography on Whatman No. 1 paper with (a) 3% aqueous ammonium chloride, and (b) butan-1-ol–5N-acetic acid (7 : 3) as solvent, and by t.l.c. and were recrystallised to constant m.p.

Analyses were performed by the Australian National University Analytical Services Unit. Solids for analysis were dried at 100° unless otherwise stated and each m.p. was taken in a Pyrex capillary. Ionisation constants were determined spectroscopically,[20] and in some cases the absorption of the cation was obtained by extrapolation. U.v. spectra were measured with a Unicam SP 800 spectrophotometer and ε values were checked on a Unicam SP 500 manual instrument. ^1H N.m.r. spectra were recorded at 60 MHz

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and 33·5° on a Perkin-Elmer R 10 spectrometer. Where required, portions of the spectra were expanded, and all signals were integrated.

2,6-*Dichloro-7-methylpurine*.—This compound was prepared in 41% yield essentially as described previously [21] from 1,2,3,6-tetrahydro-3,7-dimethylpurine-2,6-dione and phosphoryl chloride but with diethylaniline instead of dimethylaniline.

2-*Chloro-7-methylpurine*.—(a) 2,6-Dichloro-7-methylpurine was best reduced in aqueous solution with zinc as described by Fischer [22] to give 2-chloro-7-methylpurine, m.p. 199—201° (lit.,[22] 200—201°).

(b) A solution of sodium acetate trihydrate (3·0 g) in water (40 ml) was added to a mixture of 2,6-dichloro-7-methylpurine (2·03 g), palladium–charcoal (0·35 g; 10%), and ethanol (200 ml) and the mixture was hydrogenated at atmospheric pressure. Uptake of one mole of hydrogen was complete in 15 min. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was extracted with boiling benzene (2 × 150 ml) and concentration of the extracts gave 2-chloro-7-methylpurine (0·85 g, 51%) which after a further recrystallisation had m.p. 199—201° (lit.,[22] 200—201°). It was identical on paper chromatography with the product isolated in (a).

Reaction of 2-Chloro-7-methylpurine with N-*Sodium Hydroxide*.—2-Chloro-7-methylpurine and N-sodium hydroxide at 100° (instead of potassium hydroxide at 100° as described by Fischer [7]) gave 2-hydroxy-7-methylpurine, m.p. 325° (decomp.) (lit.,[7] 323°) (Found: C, 47·8; H, 4·35; N, 37·25. Calc. for $C_6H_6N_4O$: C, 48·0; H, 4·0; N, 37·3%) and a second product, m.p. 246° (lit.,[7] 251°), thought to be 4-amino-2-chloro-5-methylaminopyrimidine, δ [$(CD_3)_2SO$] 2·80 (d, MeN), 5·10br (5-HN), 7·0br (4-H_2N), and 7·35 (6-H).

6-*Hydroxy-7-methylpurine*.—A solution of 2-chloro-6-hydroxy-7-methylpurine [22] (1·6 g) in 0·5N-sodium hydroxide (30 ml) with palladium–charcoal (0·26 g; 10%) was hydrogenated at atmospheric pressure. Hydrogen uptake ceased after 4 h and the catalyst was filtered off, the filtrate adjusted to pH 5, and evaporated to dryness. The product was extracted with boiling ethanol (3 × 100 ml), and the solution concentrated to give 6-hydroxy-7-methylpurine (0·92 g, 71%), m.p. >320° (lit.,[22] 355°) (Found: C, 48·25; H, 4·5; N, 37·7%).

6-*Chloro-7-methylpurine*.—This compound was prepared from 6-hydroxy-7-methylpurine as described by Prasad and Robins.[23] It had m.p. 198—199° (lit.,[23] 199°) (Found: N, 32·9. Calc. for $C_6H_5ClN_4$: N, 33·2%).

4-*Amino-6-chloro-5-methylaminopyrimidine*.— 4,6-Dichloro-5-methylaminopyrimidine [16] (0·15 g) and ethanolic ammonia (5 ml) were heated in a sealed tube at 175° for 4 h. The mixture was evaporated to dryness, the residue extracted with hot benzene (3 × 15 ml), and the extracted product recrystallised from cyclohexane to give 4-*amino-6-chloro-5-methylaminopyrimidine* (0·11 g, 85%), m.p. 138—140° (Found: C, 38·1; H, 4·3; N, 35·2. $C_5H_7ClN_4$ requires C, 37·9; H, 4·45; N, 35·3%).

4-*Amino-5-methylaminopyrimidine*.—This compound was prepared for preparative purposes from 7-methylpurine [24] with aqueous sodium hydroxide as described by Bredereck *et al.*[17] However it was also prepared as described below.

4-Amino-6-chloro-5-methylaminopyrimidine (0·1 g) in 3% aqueous ammonia (10 ml) with palladium–charcoal (0·02 g; 10%) was hydrogenated at atmospheric temperature and pressure for 12 h. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was extracted with ethyl acetate (2 × 25 ml) and gave 4-amino-5-methylaminopyrimidine (0·05 g, 65%), m.p. 193—195° (from benzene), not depressed on admixture with an authentic specimen [25] (lit.,[17] 196—197°).

8-*Chloro-7-methylpurine*.— 8-Hydroxy-7-methylpurine [11] (0·5 g) and phosphoryl chloride (40 ml) were refluxed for 8 h, and the excess of phosphoryl chloride was removed under reduced pressure. Ice cold sodium hydrogen carbonate solution was then added to the residue and the resulting solution extracted immediately with chloroform (3 × 50 ml). The extract was dried (Na_2SO_4), the solvent evaporated, and the residue, which contained two compounds, was subjected to t.l.c. (alumina–chloroform). The product at higher R_F was recrystallised from benzene to give 8-chloro-7-methylpurine (0·35 g, 57%), m.p. 155—160° (decomp.) (lit.,[24] 150°) (Found: C, 43·0; H, 3·2; N, 32·7. Calc. for $C_6H_5ClN_4$: C, 42·7; H, 3·0; N, 33·2%).

The product at lower R_F was recrystallised from ethanol to give 7,8-*dihydro-7-methyl-9-(7-methylpurin-8-yl)purin-8-one* (0·065 g, 13%), decomposing slowly above 270° (Found: C. 51·5; H, 3·5; N, 39·7. $C_{12}H_{10}N_8O$ requires C, 51·1; H, 3·6; N, 39·7%). The n.m.r., i.r., and mass spectra were consistent with this structure, δ [$(CD_3)_2SO$] 3·52 [MeNC(O)], 3·98 (MeN), 8·76, 8·78, 9·18, and 9·42 (2- and 6-H), M^+ 282, $\nu_{max.}$ 1760 cm^{-1} (C=O), no NH.

2-*Mercapto-7-methylpurine*.— 2-Chloro-7-methylpurine and potassium hydrogen sulphide solution (60 ml; prepared by saturating N-potassium hydroxide with hydrogen sulphide) were heated on a steam bath for 5 h. The mixture was filtered, cooled, adjusted to pH 5, and the product filtered off. It was recrystallised from water to give 2-*mercapto-7-methylpurine* (2·5 g, 65%), m.p. 285° (decomp.) (Found: C, 43·4; H, 3·7; N, 33·8. $C_6H_6N_4S$ requires C, 43·4; H, 3·7; N, 33·8%). Fischer [7] reports decomposition at 295° for an unanalysed thione obtained from 2-iodo-7-methylpurine and potassium hydrogen sulphide.

7-*Methyl-2-methylthiopurine*.— 2-Mercapto-7-methylpurine (0·035 g) was dissolved in N-sodium hydroxide (1·0 ml), stirred with methyl iodide (0·05 ml) at 25° for 1·5 h and then evaporated to dryness. The residue was extracted with chloroform and the product extracted was recrystallised from benzene to give 7-*methyl-2-methylthiopurine* (0·025 g, 60%), m.p. 180—182° (Found: C, 46·7; H, 4·75; N, 31·3. $C_7H_8N_4S$ requires C, 46·6; H, 4·5; H, 31·1%).

7-*Methyl-2-methylsulphonylpurine*.—(a) 7-Methyl-2-methylthiopurine (0·05 g) was dissolved in 12N-acetic acid (1·5 ml) and a solution of potassium permanganate (0·07 g) in water (3·0 ml) was added dropwise with stirring at <10° over 45 min. This mixture was stirred for 15 min, and then decolourised by passing sulphur dioxide, adjusted to pH 7 with aqueous ammonia, and extracted with chloroform (2 × 15 ml) at <10° throughout. The extract was dried (Na_2SO_4), the solvent evaporated, and the product recrystallised from ethanol to give 7-*methyl-2-methylsulphonylpurine* (0·042 g, 72%), m.p. 219—221° (Found: C, 39·8; H, 4·1; N, 26·2. $C_7H_8N_4O_2S$ requires C, 39·6; H, 3·8; N, 26·4%).

(b) 7-Methyl-2-methylthiopurine (0·1 g) in chloroform

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(10·0 ml) was added dropwise to a stirred solution of *m*-chloroperbenzoic acid (0·3 g) in chloroform (10·0 ml) at 0° and the mixture stirred for 2 h. It was then allowed to warm to room temperature and after 5 h the precipitate was collected. The product in chloroform was washed with aqueous sodium hydrogen sulphite and sodium hydrogen carbonate and then recrystallised from ethanol to give 7-methyl-2-methylsulphonylpurine (0·065 g), identical with that prepared in (a).

7-Methyl-6-methylsulphonylpurine.—(a) 7-Methyl-6-methylthiopurine [26] (0·1 g) was oxidised with potassium permanganate in aqueous acetic acid as described above for the 2-methylsulphonyl isomer. The product was recrystallised from ethanol to give *7-methyl-6-methylsulphonylpurine* (0·075 g), m.p. 209—211° (Found: C, 39·9; H, 4·0; N, 26·7%).

(b) 7-Methyl-6-methylthiopurine (0·5 g) was also oxidised with *m*-chloroperbenzoic acid in chloroform and gave 7-methyl-6-methylsulphonylpurine (0·26 g 44%), m.p. 209—211°, identical with that prepared in (a).

8-Mercapto-7-methylpurine.— 4-Amino-5-methylaminopyrimidine [17] (0·25 g) was dissolved in a mixture of pyridine (7·5 ml), carbon disulphide (3·5 ml), and triethylamine (0·5 ml) and the mixture refluxed for 40 h. More carbon disulphide (2·0 ml) was added after 20 h. The mixture was evaporated to dryness and the product recrystallised from water to give *8-mercapto-7-methylpurine* (0·21 g, 63%), m.p. 255—258° (Found: C, 43·8; H, 3·7; N, 33·3%).

When anhydrous sodium carbonate was used in place of triethylamine, a 50% yield was obtained. Fusion of 4-amino-5-methylaminopyrimidine with thiourea gave the thiazolopyrimidine.[27]

7-Methyl-8-methylthiopurine.— 8-Mercapto-7-methylpurine (0·5 g) in N-sodium hydroxide (5·0 ml) was stirred with methyl iodide for 3·5 h, and the precipitate collected. It was recrystallised from water to give *7-methyl-8-methylthiopurine* (0·42 g, 78%), m.p. 178—180° (Found: C, 46·9; H, 4·9; N, 31·5%).

7-Methyl-8-methylsulphonylpurine.— 7-Methyl-8-methylthiopurine (0·3 g) was oxidised with potassium permanganate in aqueous acetic acid to give *7-methyl-8-methylsulphonylpurine* (0·15 g, 43%), m.p. 183—185° (decomp.) (from ethanol) (Found: C, 39·5; H, 4·0; N, 26·3%).

6-Chloro-7-methyl-8-trifluoromethylpurine.— 4,5-Diamino-6-chloropyrimidine [16] (0·2 g) and trifluoroacetic anhydride (3·0 ml) were stirred at 20° for 0·5 h, and the solution was then evaporated to dryness at 20° *in vacuo*. The residue (0·35 g) was dissolved in *NN*-dimethylformamide (3·0 ml) containing anhydrous potassium carbonate (0·2 g), methyl iodide (0·3 ml) added, and the mixture stirred at 20° for 12 h. The mixture was filtered, the filtrate diluted with water (10 ml), and extracted with ether (2 × 15 ml). The extract was evaporated to dryness at 20°, aqueous triethylamine (0·3 g in 10 ml) was added, and the mixture stirred for 2 h. The product was filtered off and recrystallised from water to give *6-chloro-7-methyl-8-trifluoromethylpurine* (0·19 g, 45%), m.p. 119—120° (Found: C, 35·8; H, 1·8; N, 23·3. $C_7H_4ClF_3N$ requires C, 35·5; H, 1·7; N, 23·7%).

9-Methyl-2-methylsulphonylpurine.—Oxidation of 9-methyl-2-methylthiopurine [4] (0·5 g) in aqueous acetic acid with potassium permanganate gave 9-methyl-2-methylsulphonylpurine (0·367 g, 61%), m.p. 165—167° (from methanol) (lit.,[4] 167—168°) (Found: C, 39·6; H, 4·1; N, 26·2%).

9-Methyl-6-methylsulphonylpurine.—This was prepared from 9-methyl-6-methylthiopurine [28] as described by Barlin and Young.[5] It had m.p. 211—213° (lit.,[4] 210—212°).

8-Mercapto-9-methylpurine.—A mixture of 5-amino-4-methylaminopyrimidine [25] (0·45 g), carbon disulphide (6 ml), pyridine (15 ml), and triethylamine (1 ml) was refluxed for 24 h and evaporated to dryness. The residue was dissolved in N-sodium hydroxide, filtered with charcoal, and the filtrate adjusted to pH 5 to give 8-mercapto-9-methylpurine (0·40 g, 67%) m.p. 310—314° (from water) (lit.,[11] 314°) (Found: C, 43·0; H, 3·9; N, 33·7%).

9-Methyl-8-methylsulphonylpurine.— 9-Methyl-8-methylthiopurine [11] (0·2 g) was oxidised with potassium permanganate in aqueous acetic acid to give 9-methyl-8-methylsulphonylpurine (0·15 g, 64%), m.p. 144—145° (from methanol) (lit.,[4] 133—135°) (Found: C, 40·0; H, 3·9; N, 26·7%).

Kinetic Procedure.—This was similar to that described in Part X,[1] and the rate coefficients were calculated from

$$k = \frac{2{\cdot}303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)} \qquad (1)$$

expression (1) where a is the initial concentration of hydroxide ion, b that of the chloro- or methylsulphonyl-*N*-methylpurine, x the concentration of hydroxy-*N*-methylpurine formed at time t, and k is the second-order rate coefficient in l mol^{-1} s^{-1}. The product of each reaction was confirmed by its u.v. spectrum (Table 4 and ref. 11).

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