136. *Purine Studies. Part III.* The Structure of the Monohydroxy- and Monomercapto-purines: Some Thiazolo*[5 : 4-d]*pyrimidines.*

By D. J. Brown and S. F. Mason.

Infrared and ultraviolet spectra, compared with those of the various *O*- and *N*-methyl derivatives, indicate that monohydroxypurines have a –CO·NH– structure, *e.g.*, (III; R = H). The structures of the momomercaptopurines are discussed. In the preparation of several 6-mercaptopurine derivatives, thiazolo[5 : 4-*d*]pyrimidines have been isolated. Under alkaline conditions the 7-amino-derivative is converted into 6-mercaptopurine.

For the monohydroxypurines a number of alternative tautomeric forms are possible. Each isomer may exist in one or more of four different hydroxy-forms, and there are five different amide forms for the 2-isomer, four for the 6-isomer, and three for the 8-isomer. The identification of the particular tautomer predominant in each case was attempted by the comparison of the infrared and ultraviolet spectra of a given monohydroxypurine with those of its methylated derivatives having fixed structures, or structures in which the possibility of tautomerism is reduced. The ultraviolet spectra of the purines are rather simple, consisting, in general, of one or two symmetrical bands in the region 220—350 mμ. For this reason ultraviolet provided less information than infrared spectroscopy concerning the tautomerism of the hydroxypurines, unlike the closely related cases of the hydroxy-pyrimidines [1] and -pteridines [2] where the infrared and the ultraviolet evidence proved to be complementary. 6-Hydroxy-, 6-methoxy-, and 1 : 6-dihydro-1 : 7-dimethyl-6-oxo-purine, for example, possess closely similar ultraviolet spectra (Table 1), even though the last two compounds have fixed, and different, conjugated structures (I; III; R = R′ = Me).

The infrared spectra indicate that the hydroxypurines exist largely in amide forms in the solid state. 2- and 6-Hydroxypurine both show a strong band near to 1670 cm.$^{-1}$, due to a C:O stretching vibration, and the 8-isomer has a similar band at 1740 cm.$^{-1}$. No OH band was observed, though the examination of solid specimens does not permit bands due to OH groups to be readily distinguished from those due to NH groups. By using solutions, such a distinction can be made, and it was found that the available 7- and 9-methyl derivatives of the hydroxypurines, which may all exist in the hydroxy-form, gave no OH band in chloroform. Thus it is probable that the hydroxypurines themselves do not exist to any appreciable extent in the hydroxy-form (*e.g.*, I; R = H). Several alternative amide forms are possible for each monohydroxypurine, and the particular form adopted may be identified in the cases of the 6- and the 8-isomer.

It has been found [3] that, in chloroform or carbon tetrachloride solution, cyclic conjugated amides with *ortho*-quinonoid structures show a band in the infrared due to the N–H stretching vibration in the range 3360—3415 cm.$^{-1}$, whilst for their *para*-quinonoid isomers and for their analogues with five-membered rings this band is in the range 3415—3470 cm.$^{-1}$. The position of the band due to the C:O stretching vibration in such compounds is sensitive to the structural type as well, though it is dependent also upon

* Part II, *J.*, 1954, 2071.

[1] Brown, Hoerger, and Mason, *J.*, 1955, 211.
[2] Brown and Mason, *J.*, 1956, 3443.
[3] Mason, unpublished results.

TABLE 1. *Ultraviolet spectra.* (*Italics denote shoulders or inflexions.*)

Purine derivative	Basic pK_a [b]	Acidic pK_a [b]	pH	Species charge	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
Unsubst.[a]	2·39 [c]	8·93 [c]	0·28	+	<220; 260	>4·09; 3·79
			5·70	0	<220; 263	>3·48; 3·90
			11·00	—	219; 271	3·92; 3·88
2-Hydroxy- [a]	1·69 [c]	8·43 [c]	−0·75 [e]	+	264; 322	3·67; 3·81
		11·90	6·05	0	238; 315	3·46; 3·69
			10·15	—	271; 313	3·68; 3·68
			13·00	Mainly =	219; 265; 312	4·29; 3·60; 3·83
2-Methoxy- [a]	2·44 [c]	9·2 [c]	0	+	284	3·83
			6·0	0	246; 283	3·41; 3·91
			11·4	—	283	3·88
2-Hydroxy-9-methyl	<1·5	9·19	−2·5 [e]	+ ?	246; 317	3·29; 3·61
		±0·01	6·5	0	218; 246; 259; 316	4·48; 3·41; 3·38; 3·68
			11·2	—	*240*; 308	*3·65*; 3·91
6-Hydroxy- [a]	1·98 [c]	8·94 [c]	−0·75 [e]	+	248	4·02
		12·10	5·18	0	249	4·02
			10·35	—	258	4·05
			13·0	Mainly =	262	4·04
6-Methoxy- [a]	2·21 [c]	9·16 [c]	0·2	+	254	4·01
			5·6	0	253	3·99
			11·3	—	261	3·99
6-Hydroxy-9-methyl	1·86	9·32	−0·25 [g]	+	250	3·99
	±0·02	±0·04	5·5	0	250	4·08
			12·0	—	254	4·11
1 : 6-Dihydro-1 : 7-dimethyl-6-oxo-	2·16	—	0·0	+	250	4·00
	±0·04		7·0	0	255	3·94
8-Hydroxy [a]	2·58 [c]	8·24 [c]	0	+	280	4·02
		>12	5·4	0	235; 277	3·51; 4·05
			10·1	—	285	4·11
8-Methoxy-	3·14	7·73	1·0	+	271	4·05
	±0·08	±0·04	5·4	0	271	4·03
			10·0	—	279	3·98
8-Hydroxy-7-methyl-	2·69	8·20	0·3	+	284	3·90
	±0·01	±0·02	5·5	0	240; 278	3·60; 3·97
			12·0	—	186	4·06
8-Hydroxy-9-methyl-	2·80	9·05	0·3	+	281	4·07
	±0·02	±0·03	5·5	0	*235*; 277	*3·45*; 4·01
			12·0	—	*257*; 289	*3·63*; 3·97
7 : 8-Dihydro-7 : 9-dimethyl-8-oxo-	2·8	—	0·3	+	285	4·03
	±0·1		7·0	0	241; 279	3·56; 4·01
2-Mercapto- [a]	0·50 [c]	7·15 [c]	−1·2 [h]	+	230; 287; 382	3·87; 4·27; 3·26
		10·40	4·98	0	241; 286; 346	4·10; 4·25; 3·18
			8·8	—	235; 263; 328	4·12; 4·19; 3·49
2-Methylthio- [a]	1·91 [c]	8·91 [c]	0·0	+	242; *250*; 314	4·13; *4·09*; 3·64
			5·9	0	232; *250*; 305	4·22; *3·93*; 3·78
			11·6	—	240; 301	4·28; 3·79
6-Mercapto- [a]	<2·5 [c]	7·77 [c]	5·09	0	225; 325	3·87; 4·27
		10·84	9·30	—	228; 312	3·98; 4·16
6-Methylthio- [a]	0·0 [a]	8·75 [a]	−3·5 [i]	+	222; 313	4·08; 4·41
			5·8	0	*255*; 290	*3·66*; 4·35
			11·1	—	222; 290	4·27; 4·31
8-Mercapto- [a]	<2·5 [c]	6·64 [c]	4·5	0	231; 310	4·01; 4·46
		11·16	8·9	—	228; 313	4·13; 4·37
			13·0	=	230; 315	4·18; 4·31
8-Methylthio- [a]	2·95 [c]	7·67 [c]	0	+	232; 305	4·04; 4·32
			5·07	0	246; 290	3·59; 4·30
			9·9	—	220; 296	4·23; 4·27
8-Mercapto-9-methyl-	<2·5	7·48 [d]	5·0	0	232; 309	4·09; 4·43
		±0·04	10·0	—	233; 311	4·18; 4·35
9-Methyl-8-methylthio-	2·98	—	0·3	+	238; 301	4·25; 4·23
	±0·02		7·0	0	211; *255*; 289	4·10; *3·57*; 4·24

[a] From Mason, *J.*, 1954, 2071. [b] Determined at M/100. [c] From Albert and Brown, *J.*, 1954, 2060. [d] Determined at M/500. [e–i] H_2SO_4: *e* 4N, *f* 10N, *g* 2N, *h* 5N, *i* 13·5N.

any substituents present. However, in general, for nuclei similarly substituted, the stretching vibration of the C:O group of a cyclic conjugated amide with a five-membered ring lies at a higher frequency than that of such a group in a six-membered ring with an *ortho*-quinonoid structure, and this in turn at a higher frequency than for the *para*-quinonoid isomer. With ring systems containing two nuclear nitrogen substituents, for example, this band lies at 1728 cm.$^{-1}$ for 2-hydroxybenziminazole (Table 2), 1675 cm.$^{-1}$ for 1 : 2-dihydro-1-methyl-2-oxopyrimidine, and 1653 cm.$^{-1}$ for 1 : 4-dihydro-1-methyl-4-oxopyrimidine.[1]

These correlations applied to the case of 6-hydroxypurine and its *N*-methyl derivatives suggest that the tautomeric hydrogen atom derived from the hydroxy-group is linked mainly to the 1-nitrogen atom. 6-Hydroxy-7- and -9-methylpurine in chloroform solution both show an NH band at 3390 cm.$^{-1}$, that is, in the range of cyclic conjugated amides with an *ortho*-quinonoid structure. 6-Hydroxy-1-, -7-, and -9-methylpurine, and 1 : 6-dihydro-1 : 7-dimethyl-6-oxopurine give rise to a C:O band between 1679 and 1711 cm.$^{-1}$, a little above that of 6-hydroxypurine itself (1670 cm.$^{-1}$), whilst 3 : 6-dihydro-3-methyl-

TABLE 2. *Infrared spectra in the* N–H *and* C:O *stretching vibration regions.*

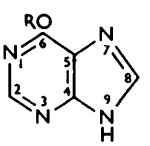
Purine	N–H stretching (cm.$^{-1}$) (in $CHCl_3$)	C:O stretching (cm.$^{-1}$) In $CHCl_3$	Solid
2-Butyl-	3444	*b*	*b*
2-Hydroxy-	*a*	*a*	1674
2-Hydroxy-9-methyl-	3411	1637	1647
6-Hydroxy-	*a*	*a*	1670
6-Methoxy-	3440	*b*	*b*
1 : 6-Dihydro-1-methyl-6-oxo-	3438	1698	1695
3 : 6-Dihydro-3-methyl-6-oxo-	3440	1638	1648
6-Hydroxy-7-methyl-	3390	1702	1697
6-Hydroxy-9-methyl-	3388	1711	1679
1 : 6-Dihydro-1 : 7-dimethyl-6-oxo-	*b*	1689	1683
8-Hydroxy-	*a*	*a*	1740
8-Hydroxy-7-methyl-	3444	1739	1742
8-Hydroxy-9-methyl-	3450	1744	1745
7 : 8-Dihydro-7 : 9-dimethyl-8-oxo-	*b*	1731	1733
8-Methoxy-	3442	*b*	*b*
2-Hydroxybenziminazole	3469	1722	1728

a, Insoluble. *b*, No band observed.

6-oxopurine shows a C:O band at 1638—1648 cm.$^{-1}$ (Table 2). As the enol forms do not occur (lack of an OH band and the presence of a C:O band), the pyrimidine ring in 1 : 6-dihydro-1-methyl-6-oxopurine must possess an *ortho*-quinonoid structure (III or IV; R′ = Me), whilst in 3 : 6-dihydro-3-methyl-6-oxopurine it must have a *para*-quinonoid structure (*e.g.*, II; R = Me). Thus the position of the C:O band suggests that an *ortho*-quinonoid structure is assumed in the cases where tautomerism is possible in the pyrimidine ring, namely, 6-hydroxypurine and its 7- and 9-methyl derivatives. Such a phenomenon is general. When a hydroxyl group is placed both α and γ to a ring-nitrogen atom in a *N*-heterocyclic nucleus, or in other conjugated positions in the polycyclic cases, the hydrogen atom is attached predominantly to the α-ring nitrogen atom.[1,2,4] The infrared evidence from both the N–H and C:O stretching vibration regions accordingly suggests that 6-hydroxypurine has the structure (III; R = R′ = H) or (IV; R = R′ = H). Structure (IV; R=R′ = H) is perhaps to be preferred, as the NH band of 1 : 6-dihydro-1-methyl-6-oxopurine lies at a slightly lower frequency than that of purine itself (Table 2). The lowering may be ascribed to intramolecular hydrogen bonding, which is likely to be much more effective between the oxygen and the 7-nitrogen atom in structure (IV; R′ = H, R = Me) than between the 3- and the 9-nitrogen atom in structure (III; R′ = H, R = Me). However, in the solid state or in aqueous solution it may be expected that

[4] Hearn, Morton, and Simpson, *J.*, 1951, 3318.

intermolecular hydrogen bonding would render the 7- and the 9-position, and thus the structures (III and IV; R = R′ = H), largely equivalent.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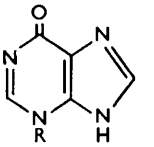
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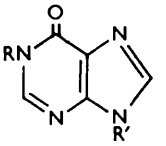
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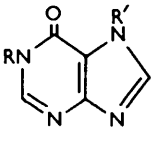
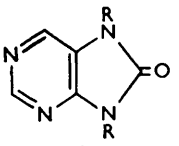

(IV)

8-Hydroxypurine shows a C:O band close to those of its 7- and 9-methyl and its 7 : 9-dimethyl derivatives (Table 2). 7 : 8-Dihydro-7 : 9-dimethyl-8-oxopurine has a fixed structure (V; R and R′ = Me), and it is probable therefore that the parent compound has the similar structure (V; R = R′ = H). In either of the alternative amide forms, *e.g.*, (VI), 8-hydroxypurine and its 7-methyl derivative would be expected to show a C:O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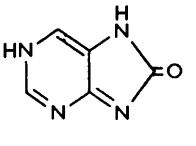
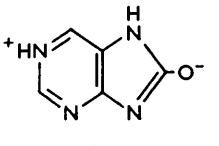
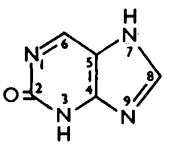
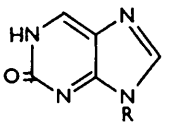

(VIa)


(VIb)

band at a lower frequency than the 9-methyl and the 7 : 9-dimethyl derivatives. (VIa) is an energetically " strained " structure in which part of the resonance energy of the pyrimidine has been lost, and thus the ionic form (VIb), retaining the pyrimidine ring resonance, would be expected to make a large contribution to the hybrid. Such a contribution would lower the double-bond character of the C:O link, resulting in a C:O bond absorption at a lower frequency.

The ultraviolet evidence supports the assignment of structure (V; R = R′ = H) to 8-hydroxypurine. In their neutral molecular forms, the ultraviolet spectra of 8-hydroxypurine and its 7- and 9-methyl and 7 : 9-dimethyl derivatives are very similar and different from that of 8-methoxypurine (Table 1), suggesting that the conjugated system of 8-hydroxypurine resembles that of its *N*-methyl derivatives but not that of its *O*-methyl derivative. Further, the absorption spectrum of the anion of 8-hydroxypurine resembles that of the anion of its 7-methyl derivative more closely than that of its 9-methyl derivative, indicating that the first acidic ionisation in the parent compound probably takes place from the 9- and not the 7-nitrogen atom (Table 1).


(VII)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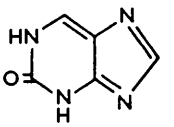

(IX)

Of the five possible amide forms of 2-hydroxypurine, structure (VII) and the isomer with a hydrogen atom attached to the 9- instead of the 7-nitrogen atom are the most probable, since they involve no modification of the aromatic resonance of the glyoxaline ring. 2-Hydroxypurine gives rise to an absorption band in the C:O stretching vibration region at 1674 cm.$^{-1}$, close to its position for 1 : 2-dihydro-1-methyl-2-oxopyrimidine (1675 cm.$^{-1}$),[1] suggesting that the pyrimidine ring in 2-hydroxypurine possesses an *ortho*-quinonoid pyrimidone structure, rather than a reduced pyrimidone structure as in (IX). 2-Hydroxy-9-methylpurine shows a C:O band at a lower frequency (1637—1647 cm.$^{-1}$), indicating that this compound may have an energetically " strained " structure in which the double-bond character of the C:O link is lowered by a substantial contribution from

an ionic resonance form. Such a structure might arise if the normal tautomeric form of 2-hydroxypurine were (VII), or the isomer with an NH group in the 9- instead of the 7-position, by virtue of steric hindrance between the 9-methyl group and the hydrogen atom on the 3-nitrogen atom. In these circumstances the mobile hydrogen atom in 2-hydroxy-9-methylpurine might be linked to the 1-nitrogen atom, forming the structure (VIII; R = Me), without full aromatic resonance in the glyoxaline ring. The ultraviolet evidence also indicates that 2-hydroxypurine and its 9-methyl derivative possess different conjugated systems, the absorption spectra of both the neutral molecule and the cation of 2-hydroxypurine differing from those of the corresponding ionic species of the 9-methyl derivative (Table 1). Thus in the case of 2-hydroxypurine it is probable that there is an *ortho*-quinonoid structure in the pyrimidine ring and full aromatic resonance in the glyoxaline ring, conditions which are satisfied by structure (VII) or the isomer with an NH group in the 9- instead of the 7-position.

The mercaptopurines in the solid state show infrared absorption bands near to 2600 cm.$^{-1}$ (Table 3), the region of the S–H stretching vibration. However, purine itself shows bands in this region, due to combination and overtone frequencies and the intermolecular hydrogen bonded N–H stretching vibration (Table 3). On deuteration the bands near to 2600 cm.$^{-1}$ in the case of the mercaptopurines shift to the 2100 cm.$^{-1}$ region, as might be expected for bands due to the S–H link. However, the band due to the intermolecular hydrogen bonded N–H stretching vibration in purine itself shows a similar shift on deuteration, so that the infrared evidence for the existence of the mercaptopurines in the thiol form in the solid state is equivocal.

TABLE 3. *Infrared spectra in the* N–H *and* S–H *stretching vibration regions.*

Purine	N–H stretching (cm.$^{-1}$) (in $CHCl_3$)	N–H and S–H stretching (cm.$^{-1}$) Solid
Unsubstituted	3441	2724 s
deuterated	—	2095 s
2-Mercapto-	—	2876 s, 2748 s, 2682 m, 2591 s
deuterated	—	2180 m, 2135 s, 2100 s, 2055 m
6-Mercapto-	—	3165 w, 2787 s, 2650 w
deuterated	—	2533 m, 2175 s, 2105 s, 1980 w
6-Mercapto-7-methyl-	3365	
8-Mercapto-	3422	2942 s, 2665 s, 2590 m
deuterated	—	2260 s, 2145 s, 2015 s, 1925 m
8-Mercapto-9-methyl-	3435	—

s = strong; m = medium; w = weak

In chloroform solution 8-mercapto-9-methylpurine and 6-mercapto-7-methylpurine both show well-marked bands due to the free N–H stretching vibration (Table 3), so that these compounds, and presumably the parent mercaptopurines, exist at least in part in the thione form. No band due to the S–H stretching vibration was detected, though absorption due to this vibration is intrinsically weak, and the solubility of 8-mercapto-9-methyl- and 6-mercapto-7-methyl-purine in chloroform is small. The ultraviolet spectra of the mercaptopurines differ markedly from those of the corresponding methylthiopurines (Table 1), but the spectra of 8-mercaptopurine and its 9-methyl derivatives are closely similar, supporting the view that the mercaptopurines exist partly, and perhaps predominantly, in the thione form.

Preparation.—As purine has little solubility in carbon tetrachloride and in *cyclo*hexane for fine spectral analysis, 2-*n*-butylpurine appeared a convenient substitute where the alkyl group was sterically remote from the NH group. It was made by formylation of 4 : 5-diamino-2-*n*-butylpyrimidine [5] followed by thermal ring closure.

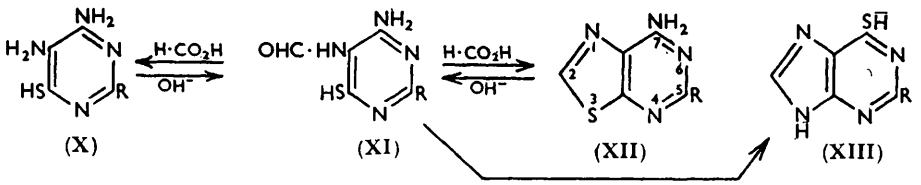
A selection of the required 8-hydroxy- and 8-mercapto-purine derivatives was made by fusion of urea or thiourea with appropriate pyrimidine diamines. Thus 8-hydroxy-7- and

[5] Brown, *J.*, 1956, 2312.

-9-methylpurine were made from 4-amino-5- [6] and 5-amino-4-methylaminopyrimidine [7] instead of by using known complicated routes.[8,9] 7 : 8-Dihydro-7 : 9-dimethyl-8-oxopurine [9] (V; R = R′ = Me) was made similarly from 4 : 5-bismethylaminopyrimidine [10] but the method is undesirable because of a persistent impurity in the product. 5-Amino-4-methylaminopyrimidine was also used to give 8-mercapto-9-methylpurine which on methylation furnished 9-methyl-8-methylthiopurine.

Despite previous difficulties,[11] 8-methoxypurine has now been conveniently obtained by oxidation of 8-methylthiopurine with chlorine to 8-methylsulphonylpurine which reacted smoothly with sodium methoxide. 6-Hydroxy-9-methylpurine was prepared directly from 5-amino-4-hydroxy-6-methylaminopyrimidine instead of *via* 9-methyladenine.[12] 9-Methyl-6-methylthiopurine was also made directly from 5-amino-4-methylamino-6-methylthiopyrimidine.[13]

An attempt to prepare 2-*n*-butyl-6-mercaptopurine (XIII; R = Bu^n) from 4 : 5-diamino-2-*n*-butyl-6-mercaptopyrimidine [5] (X; R = Bu^n) by formylation and ring closure, gave an isomeric compound which had no acidic function below pK_a 12 and basic pK_a 3·5 and was therefore 7-amino-5-*n*-butylthiazolo[5 : 4-*d*]pyrimidine (XII; R = Bu^n). Similarly were formed the 7-amino-5-methyl (XII; R = Me), 7-methylamino- and 7-amino- (XII; R = H) derivatives. The conditions governing ring closure of 4-amino-5-formamido-6-mercaptopyrimidine (XI; R = H) either to 7-aminothiazolo[5 : 4-*d*]-pyrimidine or to 6-mercaptopurine are now known.[14] It has not been realised however



that the thiazolopyrimidine (XII; R = H) is converted into the purine (XIII; R = H) under alkaline conditions. Thus treatment of the former with sodium hydroxide (as in a previous ring closure by Elion and Hitchings [15]), or even with boiling commercial formamide, gives the latter. That this isomerisation proceeds by ring opening to the formyl compound (XI) and subsequent ring closure of the *anion* to the purine, is suggested by a considerable by-product of 4 : 5-diamino-2-mercaptopyrimidine (X; R = H) formed when sodium hydroxide is used, and arising presumably by deacylation of the intermediate formyl derivative.

Experimental

Analyses were done by Mr. P. R. W. Baker, Wellcome Research Laboratories, Beckenham. The homogeneity of analysed compounds was checked by paper chromatography.

Ultraviolet Spectra.—These were measured with a Hilger Uvispek H700/305 Quartz Spectrophotometer, with buffer solutions with the pH values recorded in Table 1. The buffer solutions were 0·01M-glycine (for pH 1·5—3·5), 0·01M-acetate (for pH 3·8—5·7), 0·01M-phosphate (for pH 6·0—7·9 and 10·3—11·3), and 0·01M-borate (for pH 8·2—10·0), together with N- (pH 0) and 0·1N-hydrochloric acid (pH 1·0), and 0·1N- (pH 13) and 0·01N-potassium hydroxide (pH 12).

Infrared Spectra.—These were measured with a Perkin-Elmer model 12C spectrometer,

[6] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[7] Brown, *ibid.*, 1954, **4**, 72.
[8] Fischer, *Ber.*, 1895, **28**, 2480.
[9] Fischer, *Ber.*, 1884, **17**, 328.
[10] Albert, Brown, and Wood, *J.*, 1956, 2066.
[11] Albert and Brown, *J.*, 1954, 2060.
[12] Fischer, *Ber.*, 1898, **31**, 114.
[13] Brown, *J. Appl. Chem.*, 1957, **7**, in the press.
[14] Elion, Lange, and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 2858.
[15] Elion and Hitchings, *ibid.*, 1954, **76**, 4027.

with a prism of lithium fluoride for the O–H, N–H, and S–H stretching vibration region, and a prism of sodium chloride for the C:O stretching vibration region. The compounds were examined as solids included in pressed potassium bromide discs, or in chloroform solution.

8-*Hydroxy*-7- *and* -9-*methylpurine*.—5-Amino-4-methylaminopyrimidine [7] (2·5 g.) and urea (4·5 g.) were heated at 170° for 30 min. The residue in boiling water (~25 ml.) was treated with charcoal, adjusted to pH 5—6, and evaporated to dryness. Two recrystallisations from ethanol (50 ml.) gave needles of 8-hydroxy-9-methylpurine (1·5 g.), m. p. 233° (lit.,[9] 233°) (Found : N, 37·3. Calc. for $C_6H_6ON_4$: N, 37·3%).

Similarly 4-amino-5-methylaminopyrimidine [6] and urea at 200° for 40 min. gave, after recrystallisation from ethanol (250 ml.), 8-hydroxy-7-methylpurine, m. p. 256—257° [lit.,[8] 266—267° (corr.)] (Found : N, 37·35%).

8-*Methylsulphonylpurine*.—Chlorine was passed into a suspension of 8-methylthiopurine (3·4 g.) in water (20 ml.) at $<5°$ for 15 min. A thick precipitate was formed on scratching. It was filtered off and suspended in water (3 ml.) and 10N-sodium hydroxide was added to pH 4. The solid was recrystallised from ethanol (~130 ml.), giving 8-*methylsulphonylpurine* (1·2 g.). It shrinks and darkens about 140°, but has m. p. ~300° (Found : N, 27·95; S, 15·7. $C_6H_6O_2N_4S$ requires N, 28·25; S, 16·1%).

8-*Methoxypurine*.—The above sulphone (0·5 g.) was heated at 180° for 4 hr. with sodium methoxide solution (sodium, 0·15 g.; methanol, 25 ml.). The residue after evaporation in a vacuum was dissolved in water (3 ml.) and brought to pH 4. Recrystallisation from ethyl acetate (15 ml.) gave 8-*methoxypurine* (0·2 g.), m. p. 153—154° (Found : C, 48·3; H, 3·8; N, 37·15. $C_6H_6ON_4$ requires C, 48·0; H, 4·0; N, 37·3%).

8-*Mercapto*-9-*methylpurine*.—5-Amino-4-methylaminopyrimidine (1·2 g.) was heated at 190° with thiourea (1·8 g.) for 20 min. Water (5 ml.) was added and the pH adjusted to 4. Refrigeration overnight produced a grey solid which was extracted with boiling water (200 ml.) (carbon) to give colourless needles (0·5 g.) of 8-*mercapto*-9-*methylpurine*, m. p. 314° (Found : N, 33·7; S, 19·05. $C_6H_6N_4S$ requires N, 33·7; S, 19·25%).

9-*Methyl*-8-*methylthiopurine*.—8-Mercapto-9-methylpurine (0·4 g.) in N-sodium hydroxide (2·5 ml.) was shaken with methyl iodide (0·16 ml.) for 30 min. Extraction with chloroform, evaporation, and sublimation (100°/0·01 mm.) gave 9-*methyl*-8-*methylthiopurine* (0·32 g.), m. p. 147° (Found : N, 30·9; S, 17·85. $C_7H_8N_4S$ requires N, 31·1; S, 17·75%).

4-*Amino*-2-n-*butyl*-5-*formamidopyrimidine*.—4 : 5-Diamino-2-*n*-butylpyrimidine [5] (0·33 g.) was heated on the water-bath for 1 hr. with 98% formic acid (3 ml.). The residue after evaporation in a vacuum was dissolved in warm water (3 ml.) and brought to pH 9—10 with ammonia. Recrystallisation of the solid (0·34 g.) from water gave needles of *formyl derivative*, m. p. 143°, decomp. ~170° (Found : C, 55·45; H, 7·4; N, 28·75. $C_9H_{14}ON_4$ requires C, 55·65; H, 7·3; N, 28·85%).

2-n-*Butylpurine*.—The above formyl compound (0·3 g.) was heated at 195° for 5 min. Recrystallisation of the solid from benzene (12 ml.) gave 1-n-*butylpurine*, m. p. 144° strongly depressed by starting material (Found : C, 61·9; H, 6·6; N, 31·8. $C_9H_{12}N_4$ requires C, 61·4; H, 6·85; N, 31·8%).

5-*Formamido*-4-*methylamino*-6-*methylthiopyrimidine*.—5-Amino-4-methylamino-6-methylthiopyrimidine [13] (5 g.) was heated with 98% formic acid (40 ml.) at 65° for 1 hr. The formic acid was removed *in vacuo* at 60°, and the residue dissolved in boiling water (40 ml.) and adjusted to pH 5—6. Recrystallisation of the crude solid (41· g.) from water (220 ml.) gave the *formyl derivative*, m. p. 204—205° (decomp.) (Found : N, 28·2. $C_7H_{10}ON_4S$ requires N, 28·25%).

9-*Methyl*-6-*methylthiopurine*.—The above *formyl* compound (1·8 g.) was heated at 210° for 10 min. Recrystallisation from ethanol (15 ml.) gave the *purine* (1·25 g.), m. p. 165—167° (Found : C, 46·8; H, 4·4; N, 31·45. $C_7H_8N_4S$ requires C, 46·65; H, 4·5; N, 31·1%).

6-*Hydroxy*-9-*methylpurine*.—5-Amino-4-hydroxy-6-methylaminopyrimidine (1·5 g.) and 98% formic acid (6 ml.) were refluxed for 4 hr. The residue after evaporation was ground with water (5 ml.), and the pH adjusted to 5. The solid (1·4 g.) was recrystallised from water (40 parts), giving fine needles of 6-hydroxy-9-methylpurine, m. p. $<360°$ (Fischer [12] gives 390°) (Found : C, 48·35; H, 3·85; N, 37·5. Calc. for $C_6H_6ON_4$: C, 48·0; H, 4·0; N, 37·3%).

7-*Methylaminothiazolo*[5 : 4-d]*pyrimidine*.—5-Amino-4-mercapto-6-methylaminopyrimidine (2·0 g.) was refluxed for 2 hr. with 98% formic acid (15 ml.). The residue after evaporation was dissolved in hot water (15 ml.) and brought to pH 10 with ammonia. The solid (90%) was recrystallised from water (25 parts), giving colourless needles of the 7-*methylamino-derivative*.

m. p. 155° (Found : C, 43·2; H, 3·9; N, 33·95. $C_6H_6N_4S$ requires C, 43·4; H, 3·65; N, 33·75%), pK_a (basic) 2·84 ± 0·02 (M/100). The 7-amino-analogue [13] has pK_a 2·77 ± 0·02.

7-Amino-5-n-butyl- and 7-Amino-5-methyl-thiazolo[5 : 4-d]*pyrimidine.*—Made as above from 4 : 5-diamino-2-*n*-butyl-6-mercaptopyrimidine [5] and recrystallised from water (*ca.* 200 parts), the n-*butyl derivative* formed stout needles, m. p. 101—102° (Found : C, 51·9; H, 5·7; N, 27·1; S, 15·3. $C_9H_{14}ON_4S$ requires C, 51·9; H, 5·8; N, 26·9; S, 15·4%), pK_a (basic) 3·49 ± 0·01 (M/100). 4 : 5-Diamino-6-mercapto-2-methylpyrimidine similarly gave (from water, 30 parts) the *methyl derivative*, m. p. 208° (Found : N, 33·8; S, 19·55. $C_6H_6N_4S$ requires N, 33·75; S, 19·3%), pK_a (basic) 3·56 ± 0·01 (0·005M).

6-Mercaptopurine.—7-Aminothiazolo[5 : 4-*d*]pyrimidine [14] (0·2 g.) was heated at 190° in formamide (1 ml.) for 30 min. Water (1 ml.) was added, the solution adjusted to pH 4—5, and the solid recrystallised (carbon) from water (10 ml.). It was dissolved in cold 0·2N-sodium hydroxide (4 ml.), filtered from some thiazolopyrimidine, and the 6-mercaptopurine was reprecipitated (yield, 0·08 g.). It was identical with authentic material in paper chromatography and m. p. [305—310° (decomp.)]. 2-Hydroxy-9-methylpurine was made by Johns's method.[16]

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[16] Johns, *J. Biol. Chem.*, 1911, **9**, 166.