SIMPLE PYRIMIDINES

VIII.* THE FINE STRUCTURE OF ISOCYTOSINE, THIOCYTOSINE, AND SOME ISOMERS

By D. J. Brown† and T. Teitei†

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Summary

The fine structures of 4-amino-6-hydroxy-, 4-amino-6-mercapto-, 4-amino-2-mercapto-, 2-amino-4-hydroxy-, and 2-amino-4-mercapto-pyrimidine are revealed by comparing their ultraviolet spectra and ionization constants with those of their *N*- and *O*-, or *N*- and *S*-methyl derivatives. On the evidence here presented they appear to exist largely in aqueous solution as the tautomers containing an amino group, namely: 4-amino-1,6-dihydro-6-oxopyrimidine, 4-amino-1,6-dihydro-6-thiopyrimidine, 4-amino-1,2(and 2,3)-dihydro-2-thiopyrimidine, 2-amino-1,4(and 3,4)-dihydro-4-oxopyrimidine, and 2-amino-1,6-dihydro-6-thiopyrimidine, respectively. Syntheses of hitherto unknown methyl derivatives are recorded.

Introduction

It is now generally agreed that 2-, 4-, and 6-hydroxypyrimidines[1] and 2-, 4-, and 6-mercaptopyrimidines[2,3] exist as cyclic amides and thioamides respectively, while 2-, 4-, and 6-aminopyrimidines[4] exist as amino rather than imino derivatives. In addition, where either an amide form or a vinylogous amide form is possible, the former is generally preferred.[1,2] Less simple compounds such as 2,4-dihydroxypyrimidine,[5] 2,4-diaminopyrimidine,[6] and their derivatives also follow these rules. Moreover, it has been found that even 4,6-dihydroxypyrimidines[7] and 4-hydroxy-6-mercaptopyrimidines,[8] which are precluded by valency from having a normal cyclic diamide structure, still exist predominantly as dioxo- and oxothio-pyrimidines respectively with a methylene group in the 5-position, despite the energy barrier to be surmounted in so destroying the formal aromaticity of the pyrimidine system. Among pyrimidines bearing both amino and hydroxy or mercapto groups, cytosine has already been shown[9,10] by spectral and n.m.r. evidence to exist both in aqueous and dimethylsulphoxide solutions as 4-amino-1,2-dihydro-2-oxopyrimidine.

* Part VII, *Aust. J. Chem.*, 1964, **17**, 567.

† Department of Medical Chemistry, John Curtin School of Medical Research, Canberra.

[1] Brown, D. J., Hoerger, E., and Mason, S. F., *J. Chem. Soc.*, 1955, 211.

[2] Albert, A., and Barlin, G. B., *J. Chem. Soc.*, 1962, 3129.

[3] Spinner, E., *J. Chem. Soc.*, 1960, 1237.

[4] Brown, D. J., Hoerger, E., and Mason, S. F., *J. Chem. Soc.*, 1955, 4035.

[5] Shugar, D., and Fox, J. J., *Biochim. Biophys. Acta*, 1952, **9**, 199.

[6] Brown, D. J., and Teitei, T., *J. Chem. Soc.*, 1965, in press.

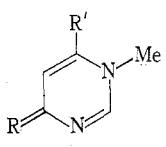
[7] Brown, D. J., and Teitei, T., *Aust. J. Chem.*, 1964, **17**, 567.

[8] Brown, D. J., and Teitei, T., *J. Chem. Soc.*, 1963, 4333; 1964, 3204.

[9] Brown, D. J., and Lyall, J. M., *Aust. J. Chem.*, 1962, **15**, 851.

[10] Katritzky, A. R., and Waring, A. J., *J. Chem. Soc.*, 1963, 3046.

The present paper extends the spectral study to thiocytosine, to isomers of cytosine and their thio analogues, and incidentally to their methylamino and dimethylamino homologues. In each case an amino-oxo or amino-thio structure is indicated, but it is not possible at present in every case to allot the tautomeric hydrogen predominantly to N 1 or N 3 on experimental evidence.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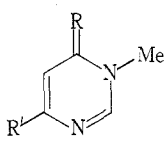
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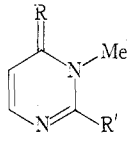
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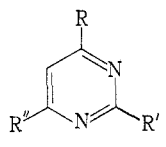
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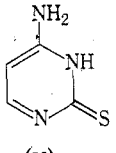
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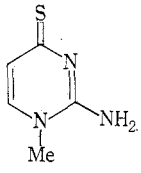
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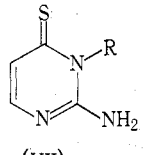
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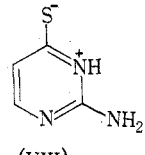
(VIII)

Preparation of Methylated Reference Compounds

For each of the compounds to be investigated (4-amino-6-hydroxy-, 4-amino-6-mercapto-, 4-amino-2-mercapto-, 2-amino-4-hydroxy-, and 2-amino-4-mercapto-pyrmidine) there were seven possible tautomeric structures (cf.[9]). However, no attempt was made to prepare fixed methylated derivatives representing the three imino forms of each. Not only did such forms seem unlikely on the accumulated general evidence, but in any case their presence would have been immediately obvious in an abnormally high basic strength[4] for any compound in which one or more occurred to any extent. In addition, the necessarily zwitterionic tautomer, in which the proton from O or S was attached to the extracyclic amino group, could be eliminated (see below) without recourse to models. Accordingly, syntheses of only three reference compounds were attempted in each case: one *O*- or *S*-methyl and two *N*-methyl derivatives. Those which were as yet unknown were prepared as follows (see Table 1 for references to the others).

Treatment of 4-chloro-3,6-dihydro-3-methyl-6-methyliminopyrimidine[11] (I; R = NMe, R′ = Cl) with sodium hydrogen sulphide gave 1,6-dihydro-1-methyl-4-methylamino-6-thiopyrimidine (II; R = S, R′ = NHMe), which was converted into its 4-dimethylamino homologue (II; R = S, R′ = NMe_2) by transamination with dimethylamine by the general procedure of Whitehead and Traverso.[12] The same compound was also obtained from its oxo analogue (II; R = O, R′ = NMe_2)

[11] Brown, D. J., and Teitei, T., *J. Chem. Soc.*, 1963, 3535; 1965, in press.
[12] Whitehead, C. W., and Traverso, J. J., *J. Amer. Chem. Soc.*, 1960, **82**, 3971.

by thiation with phosphorus pentasulphide, and by treating 4-chloro-6-dimethylamino-3-methylpyrimidinium iodide[13] with ethanolic sodium hydrogen sulphide. 4-Chloro-2-dimethylaminopyrimidine[14] similarly reacted with sodium hydrogen sulphide to give 2-dimethylamino-4-mercaptopyrimidine which was methylated to 2-dimethylamino-4-methylthiopyrimidine. The use of aqueous sodium hydrogen sulphide was found to be rather superior to a previous method[15] for converting 2-amino-4-chloropyrimidine into 2-amino-4-mercaptopyrimidine, an intermediate for 2-amino-4-methylthiopyrimidine.

Thiation of 2-amino-1,6-dihydro-1-methyl-6-oxopyrimidine[16,17] (III; R = O, R′ = NH_2) and its dimethylamino homologue[13] (III; R = O, R′ = NMe_2) with phosphorus pentasulphide gave the thio analogues (III; R = S, R′ = NH_2) and (III; R = S, R′ = NMe_2) respectively.

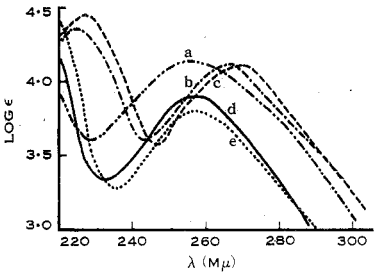

Fig. 1

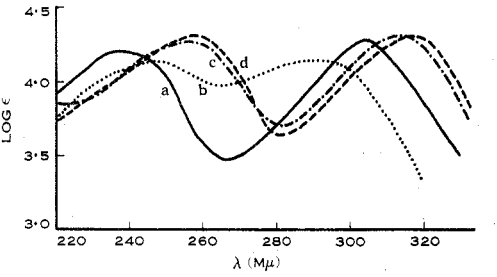

Fig. 2

Fig. 1.—Ultraviolet spectra in aqueous buffers of neutral molecules of (*a*) 4-dimethylamino-6-methoxypyrimidine; (*b*) 4-dimethylamino-6-hydroxypyrimidine; (*c*) 4-dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine; (*d*) 4-amino-6-hydroxypyrimidine; (*e*) 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine.

Fig. 2.—Ultraviolet spectra in aqueous buffers of neutral molecules of (*a*) 4-amino-6-mercaptopyrimidine; (*b*) 4-dimethylamino-6-methylthiopyrimidine; (*c*) 4-dimethylamino-6-mercaptopyrimidine; (*d*) 4-dimethylamino-1,6-dihydro-1-methyl-6-thiopyrimidine.

We were unable to prepare two reference compounds. Thus the preparation of 4-dimethylamino-3,6-dihydro-3-methyl-6-oxopyrimidine (I; R = O, R′ = NMe_2) was attempted by methylating 4-dimethylamino-6-methylaminopyrimidine, but the only product was the 1-methylated compound (II; R = NMe, R′ = NMe_2) as shown by hydrolysis to the known[13] 6-oxopyrimidine (II; R = O, R′ = NMe_2). As a result, the thio analogues (I; R = S, R′ = NH_2 or NMe_2) could not be made by thiation, and also remain unknown.

[13] Brown, D. J., and Teitei, T., *Aust. J. Chem.*, 1965, **18**, 199.

[14] Overberger, C. G., and Kogon, I. C., *J. Amer. Chem. Soc.*, 1954, **76**, 1065.

[15] Koppel, H. C., Springer, R. H., Robins, R. K., and Cheng, C. C., *J. Org. Chem.*, 1961, **26**, 792.

[16] Angier, R. B., and Curran, W. V., *J. Org. Chem.*, 1961, **26**, 1891.

[17] Brown, D. J., and Jacobsen, N. W., *J. Chem. Soc.*, 1962, 3172.

Results and Discussion

*4-Amino-6-hydroxypyrimidine** (*Table 1,† Nos. 1–10*)

The close similarity in shape and normal small bathochromic progression in the spectra of 4-amino-, 4-methylamino-, and 4-dimethylamino-6-hydroxypyrimidine (as neutral molecules) confirmed the amino rather than imino nature of the parent in aqueous solution. In addition, the spectra of these same neutral molecules all closely resembled (Fig. 1) those of their respective 1-methyl derivatives (II; R = O, R′ = NH_2, NHMe, or NMe_2), but differed from those of 4-amino-6-methoxypyrimidine and its homologues suggesting that 4-amino-6-hydroxypyrimidine existed as 4-amino-1,6-dihydro-6-oxopyrimidine.

This conclusion is valid providing the spectra of the N 1 methylated derivatives differed appreciably from those of their N 3 isomers and from that of the zwitterion (IV; R = O^-, R′ = H, R″ = $^+NH_3$). Although suitable methylated reference compounds were not available for such comparisons, the difference between N 1 and N 3 methylated derivatives might be assumed because such molecules would have quite different chromophoric systems and have indeed been shown to differ markedly in related pairs, such as 2-amino-1,6-dihydro-1-methyl-6-oxopyrimidine and 2-amino-1,4-dihydro-1-methyl-4-oxopyrimidine (Table 1, Nos. 28 and 29). In addition, a zwitterion (IV; R = O^-, R′ = H, R″ = $^+NH_3$) of net change nil would have a spectrum closely resembling that of the anion of 4-hydroxypyrimidine (see ref.[9] for a full explanation of this statement). However, the neutral molecule of 4-amino-6-hydroxypyrimidine bore no such similarity, so that it might be reasonably formulated as 4-amino-1,6-dihydro-6-oxopyrimidine in aqueous solution.

4-Amino-6-mercaptopyrimidine (*Table 1, Nos. 11–17; Fig. 2*)

By similar comparisons and reasoning, it appeared that the dominant tautomer of 4-amino-6-mercaptopyrimidine in aqueous solution was 4-amino-1,6-dihydro-6-thiopyrimidine.

4-Amino-2-mercaptopyrimidine; Thiocytosine (*Table 1, Nos. 18–23*)

The ultraviolet spectrum of the neutral molecule of thiocytosine differed from those of 4-amino-2-methylthiopyrimidine and its similar 4-dimethylamino homologue. An amino-mercapto structure was thus eliminated. However, its expected close similarity to 4-dimethylamino-2-mercaptopyrimidine and 4-dimethylamino-1,2-dihydro-1-methyl-2-thiopyrimidine was not experimentally convincing (see Fig. 3) in that the main peak of each dimethylamino derivative was hypsochromic to that

* Here and elsewhere the terms "hydroxy" and "mercapto" are used in a loose sense for the sake of simplicity.

† Table 1 summarizes the data on ionization constants and ultraviolet spectra; cf. also refs. 2, 9, 11, 13, and 15–21.

[18] Brown, D. J., and Harper, J. S., *J. Chem. Soc.*, 1961, 1298.

[19] Brown, D. J., and Short, L. N., *J. Chem. Soc.*, 1953, 331.

[20] Brown, D. J., *J. Appl. Chem.*, 1959, **9**, 203.

[21] Karlinskaya, R. S., and Khromov-Borisov, N. V., *J. Gen. Chem.*, 1957, **27**, 2170 (English translation).

of the amino compound. Moreover, the amino compound had a major second peak at 242 mμ which could scarcely be represented in the dimethylamino derivatives by the minor peaks at 222 mμ. A contribution from the thione (V) and/or the zwitterion (IV; R = $^+NH_3$, R′ = O^-, R″ = H) must therefore be invoked. However, the absorption of the anion of 2-mercaptopyrimidine precluded the zwitterion from contributing appreciably to the 242 mμ peak, so that the thione (V), for which no fixed methylated analogue could be made, was implicated by default. Thus thiocytosine might well consist of the equilibrium mixture, 4-amino-1,2(and 2,3)-dihydro-2-thiopyrimidine. On the other hand, 4-dimethylamino-2-mercaptopyrimidine clearly consists almost entirely of 4-dimethylamino-1,2-dihydro-2-thiopyrimidine as judged

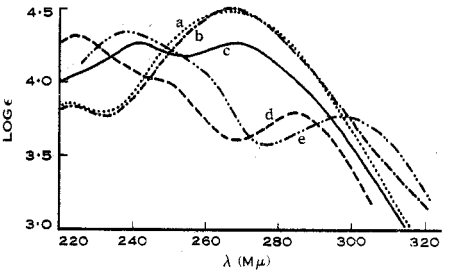

Fig. 3

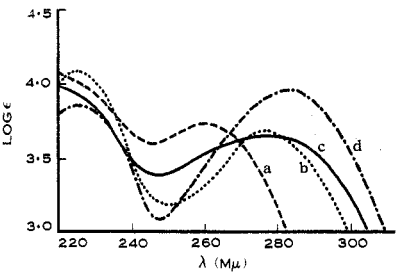

Fig. 4

Fig. 3.—Ultraviolet spectra in aqueous buffers of neutral molecules of (*a*) 4-dimethylamino-2-mercaptopyrimidine; (*b*) 4-dimethylamino-1,2-dihydro-1-methyl-2-thiopyrimidine; (*c*) 4-amino-2-mercaptopyrimidine; (*d*) 4-amino-2-methylthiopyrimidine; (*e*) 4-dimethylamino-2-methylthiopyrimidine.

Fig. 4.—Ultraviolet spectra in aqueous buffers of neutral molecules of (*a*) 2-amino-1,4-dihydro-1-methyl-4-oxopyrimidine; (*b*) 2-amino-4-methoxypyrimidine; (*c*) 2-amino-4-hydroxypyrimidine; (*d*) 2-amino-1,6-dihydro-1-methyl-6-oxopyrimidine.

on the very close spectral similarity of its neutral molecule to that of its 1-methyl derivative (see Fig. 3). This difference is unaccountable but the reason for it might perhaps be steric and related to that which causes 6-halocytosines to accommodate[22] their tautomeric hydrogen at N 3, instead of at N 1 as does cytosine.[9]

2-Amino-4-hydroxypyrimidine; Isocytosine (*Table 1, Nos. 24–30*)

The curve for the neutral molecule of isocytosine fell between those of its 1- and 3-methyl derivatives (Fig. 4), and it all but passed through their isosbestic point at 267 mμ. This suggested that isocytosine existed in aqueous solution as a mixture of 2-amino-1,4-dihydro-4-oxopyrimidine and 2-amino-1,6-dihydro-6-oxopyrimidine. The zwitterionic form could be precluded by considering the spectrum of the anion of 4-hydroxypyrimidine (Table 1, No. 10), but a contribution from the hydroxy form (IV; R = OH, R′ = NH_2, R″ = H) could not be totally eliminated in this case because the curves for 2-amino-4-methoxypyrimidine and its 2-dimethylamino homologue did bear at least a superficial resemblance to that of isocytosine. However, we felt that the resemblance was fortuitous for two reasons: (i) A major contribution from such an hydroxy form was unprecedented. (ii) The acidic pK_a value

[22] Wempen, I., and Fox, J. J., *J. Amer. Chem. Soc.*, 1964, **86**, 2474.

TABLE 1

IONIZATION CONSTANTS AND ULTRAVIOLET SPECTRA

No.	Pyrimidine Derivative	pK_a*	λ_{max}(log ϵ)†	pH
1	4-Amino-6-hydroxy- (cf.[18])		258(3·88), 212·5(4·42)	7·0
	cation	1·36	257(4·07), *217(4·02)*	−2·0‡
	anion	10·05	254(3·60), 213(4·54)	12·5
2	4-Hydroxy-6-methylamino- (cf.[18])	10·47 and 1·7	261(4·06), 219(4·40)	4·8
3	4-Dimethylamino-6-hydroxy- (cf.[18])		267(4·11), 224(4·37)	7·0
	cation	1·22	265(4·19)	−1·3‡
	anion	10·42	260(3·92), 223(4·47)	13·3
4	4-Amino-6-methoxy- (cf.[11])	4·02	235(3·88)	7·0
5	4-Methoxy-6-methylamino- (cf.[11])	4·23	243(4·05)	7·0
6	4-Dimethylamino-6-methoxy- (cf.[18])		257(4·14)	7·0
	cation	4·23	262(4·16)	0·2
7	4-Amino-1,6-dihydro-1-methyl-6-oxo- (cf.[18])	0·98	257(3·80), 216(4·54)	4·8
8	1,6-Dihydro-1-methyl-4-methylamino-6-oxo- (cf.[11])		260(3·93), 223(4·44)	7·0
	cation	0·82±0·06 (Sp)	262(4·01), 220(4·34)	−2·0‡
9	4-Dimethylamino-1,6-dihydro-1-methyl-6-oxo- (cf.[18])	<1	270(4·11), 228(4·45)	7·0
10	4-Hydroxy- (anion; cf.[19])	8·6	263(3·56), 227(4·05)	13·0
11	4-Amino-6-mercapto- (cf.[11])	9·25 and −0·24	304(4·29), 238(4·21)	2·5
12	4-Dimethylamino-6-mercapto- (ref.[13])		315(4·32), 258(4·28)	7·0
	cation	−0·27±0·06 (Sp)	*340(3·38)*, 280(4·12), 236(4·09)	−3·0‡
	anion	*c.* 9·5 (M/200)	300(4·02), 259(4·38)	12·0
13	4-Amino-6-methylthio- (cf.[11])	3·94	274(3·82), 235(4·39)	7·0
14	4-Dimethylamino-6-methylthio- (ref.[13])		289(4·17), 247(4·24)	7·0
	cation	4·57±0·05 (M/200)	289(4·19), 247(4·25)	0·0
15	1,6-Dihydro-1-methyl-4-methylamino-6-thio-		312(4·32), 257(4·31)	7·0
	cation	−0·48±0·05 (Sp)	328(3·94), 271(4·06), 234(4·16)	−3·0‡
16	4-Dimethylamino-1,6-dihydro-1-methyl-6-thio-		317(4·31), 259(4·31)	7·0
	cation	−0·80±0·06 (Sp)	*337(3·53)*, 281(4·16), 236(4·15)	−3·0‡
17	4-Mercapto- (anion; cf.[2])	6·9	292–294(4·04)	13·0
18	4-Amino-2-mercapto- (cf.[20])		269(4·26), 242(4·26)	7·0
	cation	3·33±0·03 (M/100)	*315(3·74)*, 277(4·30), 224(4·15)	0·2
	anion	10·58±0·06 (M/200)	*298(3·80)*, 264(4·13), 222(4·32)	13·3

19	4-Dimethylamino-2-mercapto- (ref.[19])		267(4·48), 222(3·86)	7·0
	cation	2·40±0·02 (M/100)	314(3·89), 278(4·32), 240(4·18)	0·2
	anion	11·18±0·07 (Sp)	306(3·83), 248(4·42)	13·3
20	4-Amino-2-methylthio- (ref.[17])		285(3·79), *250(4·00)*, 224(4·31)	7·8
	cation	4·91±0·06 (M/200)	241(4·45)	0·2
21	4-Dimethylamino-2-methylthio-§ (ref.[9])		297(3·76), 238(4·34)	9·6
	cation	5·73±0·04 (M/200)	251(4·41)	0·2
22	4-Dimethylamino-1,2-dihydro-1-methyl-2-thio- (ref.[13])		267(4·50), 222(3·84)	7·0
	cation	2·62±0·03 (M/100)	319(3·87), 274(4·29), 242(4·20)	0·2
23	2-Mercapto- (anion)‖	7·1	270(4·24), 231(3·69)	13·0
24	2-Amino-4-hydroxy- (cf.[17])	9·59 and 4·0	280(3·64)	7·0
25	2-Dimethylamino-4-hydroxy- (ref.[13])		297(3·51), 224(4·30)	7·0
	cation	3·68±0·05 (M/100)	265(3·80), 222(4·11)	0·2
	anion	9·89±0·01 (M/200)	285(3·73), 231(4·11)	13·3
26	2-Amino-4-methoxy- (ref.[21])		277(3·68), 225(4·10)	7·8
	cation	5·53±0·04 (M/200)	268(3·58)	0·2
27	2-Dimethylamino-4-methoxy- (ref.[13])		294(3·52), 241(4·19)	7·8
	cation	5·87±0·05 (M/200)	280(3·39), *233(4·21)*	0·2
28	2-Amino-1,6-dihydro-1-methyl-6-oxo- (cf.[16,17])	—	284(3·96), 225(3·86)	9·8 and 13·3
29	2-Amino-1,4-dihydro-1-methyl-4-oxo- (cf.[16,17])	—	260(3·74)	13·0
30	2-Dimethylamino-1,6-dihydro-1-methyl-6-oxo- (ref.[13])		297(4·04), 237(3·89)	9·8
	cation	3·49±0·02 (M/100)	268(3·86), 235(3·95)	0·2
31	2-Amino-4-mercapto- (ref.[15])		342(4·11), 258(3·65), 236(3·67)	5·4
	cation	2·86±0·05 (M/100)	325(4·13), 259(3·72)	−0·2‡
	anion	8·03±0·06 (M/200)	312(4·16), 262(3·77)	10·4
32	2-Dimethylamino-4-mercapto-		351(3·94), 315(3·93), 225(4·23)	5·4
	cation	2·20±0·04 (M/100)	330(4·13), 266(3·76), 222(4·24)	0·2
	anion	8·02±0·02 (M/200)	322(3·94), *276(3·90)*, 234(4·27)	13·3
33	2-Amino-4-methylthio-		300(4·02), *234(3·90)*	7·0
	cation	4·75±0·03 (M/200)	299(4·06), *275(4·01)*	0·2
34	2-Dimethylamino-4-methylthio-		317(3·72), 249(4·42)	9·8
	cation	5·04±0·06 (M/200)	282(4·16), 234(4·25)	0·2
35	2-Amino-1,6-dihydro-1-methyl-6-thio-		337(4·21), 258(3·68)	7·0
	cation	2·92±0·05 (M/100)	323(4·16), 262(3·67)	−0·2‡
36	2-Dimethylamino-1,6-dihydro-1-methyl-6-thio-		351(4·15), 271(3·87), 235(4·09)	7·0
	cation	2·00±0·03 (M/100)	330(4·09), 277(3·90), 237(4·08)	−0·2‡

* Measured at 20° potentiometrically (molarity given) or spectrometrically (Sp). † In aqueous buffer of given pH; inflexions in italics. ‡ H_0 values attained in aqueous sulphuric acid, cf.[7] § The *sulphate* had m.p. 252° (Found: C, 31·6; H, 4·9; N, 15·5. $C_7H_{13}N_3O_4S_2$ requires C, 31·5; H, 4·9; N, 15·7%). ‖ N.B. Major peak at 270 mμ instead of inflexion quoted[2] from earlier workers.

of isocytosine (9·6) was in line with those of its oxo-isomers, cytosine, and 4-amino-6-hydroxypyrimidine, and was quite consistent with that of 4-hydroxypyrimidine (8·6; of definite oxo form) as modified by an amino group. If isocytosine had a true hydroxy group, a higher acidity would be expected (cf. 5-hydroxypyrimidine, pK_a 6·8).

2-Amino-4-mercaptopyrimidine (Table 1, Nos. 31–36)

Although the 1-methyl derivative (VI) was unavailable, the very close resemblance of the ultraviolet spectrum of the neutral molecule of 2-amino-4-mercaptopyrimidine to that of its 3-methyl derivative (VII; R = Me) indicated (Fig. 5) that the dominant tautomer of the parent compound in aqueous solution was probably 2-amino-1,6-dihydro-6-thiopyrimidine (VII; R = H). The spectrum of 2-dimethylamino-4-mercaptopyrimidine was more complex towards lower wavelengths. The thiol form (IV; R = SH, R′ = NH_2, R″ = H) was definitely eliminated by the spectrum of its *S*-methyl derivative and the zwitterionic form by that of anionic 4-mercaptopyrimidine (No. 17).

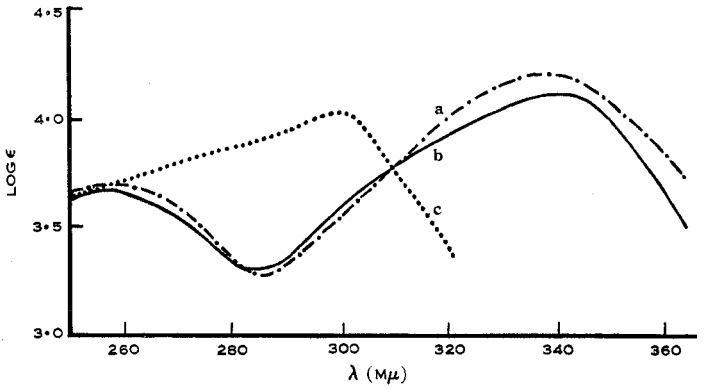

Fig. 5.—Ultraviolet spectra in aqueous buffers of neutral molecules of (*a*) 2-amino-1,6-dihydro-1-methyl-6-thiopyrimidine; (*b*) 2-amino-4-mercaptopyrimidine; (*c*) 2-amino-4-methylthiopyrimidine.

The possibility that any of the above preferred tautomers, e.g. (VII; R = H), existed largely in their zwitterionic canonical forms, e.g. (VIII), seemed highly unlikely because the basic pK_a value of each was numerically so close to that of its appropriate methylated derivative, e.g. (VII; R = Me) which could not be a zwitterion (Table 1: cf. Nos. 1 with 7; 3, 9; 12, 16; 19, 22; 25, 30; 31, 35; and 32, 36).

Experimental

Analyses were performed by Dr. J. E. Fildes and her staff. Spectra were recorded on a Perkin–Elmer Spectracord 4000A and peaks were checked on a manual Uvispek instrument. The methods of Albert and Serjeant[23] were used to measure pK_a values.

[23] Albert, A., and Serjeant, E. P., "Ionization Constants of Acids and Bases." (Methuen: London 1962.)

Methylation of 4-Dimethylamino-6-methylaminopyrimidine

The pyrimidine[18] (0·26 g), methyl iodide (0·5 ml), and ethanol (2 ml) were refluxed for 2 hr. The resulting solid was recrystallized from ethanol to give *4-dimethylamino-1,6-dihydro-1-methyl-6-methyliminopyrimidine hydriodide* (0·38 g), m.p. 268° (decomp.) (Found: C, 32·8; H, 5·2; N, 19·2. $C_8H_{15}IN_4$ requires C, 32·65; H, 5·1; N, 19·05%). Hydrolysis of this compound with 3N sodium hydroxide gave 4-dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine, identified with authentic material.[13]

1,6-Dihydro-1-methyl-4-methylamino-6-thiopyrimidine

4-Chloro-3,6-dihydro-3-methyl-6-methyliminopyrimidine hydriodide[11] (2·85 g) was slowly added to ethanolic sodium hydrogen sulphide (60 ml; sodium, 0·5 g). The mixture was refluxed for 3 hr, neutralized with hydrochloric acid, and evaporated to dryness. The residue was crystallized from water giving the *thiopyrimidine* (1·46 g), m.p. 167–168° (Found: C, 46·3; H, 5·8; N, 26·95. $C_6H_9N_3S$ requires C, 46·45; H, 5·8; N, 27·1%).

Transamination of 1,6-Dihydro-1-methyl-4-methylamino-6-oxopyrimidine

The pyrimidine[11] (0·7 g) and dimethylamine hydrochloride (0·45 g) were cooled in ethanol/carbon dioxide, free dimethylamine (*c.* 1 ml) was added, and the tube was sealed and heated at 150–160° for 5 hr. Extraction with light petroleum and concentration gave 4-dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine (0·43 g), identified[13] by mixed m.p. 156°.

4-Dimethylamino-1,6-dihydro-1-methyl-6-thiopyrimidine

(i) 4-Chloro-6-dimethylamino-3-methylpyrimidinium iodide[13] (1·67 g) was dissolved in ethanolic sodium hydrogen sulphide (30 ml; sodium, 0·23 g), refluxed for 1 hr, and neutralized with hydrochloric acid. The salt was filtered off and concentration of the filtrate gave the thio compound (0·64 g), which on recrystallization from water had m.p. 182–183° undepressed on admixture with authentic material.[13]

(ii) Transamination of 1,6-dihydro-1-methyl-4-methylamino-6-thiopyrimidine (0·8 g), as for its oxo analogue, gave the same dimethylamino derivative (0·28 g).

(iii) 4-Dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine[18] (3·6 g) and phosphorus pentasulphide (8·8 g) were refluxed for 3 hr in dry pyridine (50 ml). The solvent was distilled off *in vacuo* and the residue was refluxed in water (50 ml) for 1 hr. The filtered solution deposited the thio compound (2·5 g) on cooling.

4-Chloro-2-dimethylamino-6-methylthiopyrimidine

4,6-Dichloro-2-dimethylaminopyrimidine[24] (6·1 g) and ethanolic sodium hydrogen sulphide (30 ml; sodium, 0·72 g) were refluxed for 3·5 hr, neutralized, and evaporated. The residue was dissolved in alkali and the clarified solution was neutralized to give *4-chloro-2-dimethylamino-6-mercaptopyrimidine* (1·83 g from water), m.p. 304° (decomp.) (Found: N, 22·1. $C_6H_8ClN_3S$ requires N, 22·2%).

The above (0·65 g) in 0·5N sodium hydroxide (20 ml) was shaken with methyl iodide (1 ml) for 10 min. Extraction with ether, removal of the solvent, and recrystallization of the residue from light petroleum (b.p. 60–80°), gave the *methylthiopyrimidine* (0·69 g). After sublimation at 45°/0·6 mm it had m.p. 51–52° (Found: C, 41·3; H, 5·1; N, 20·5. $C_7H_{10}ClN_3S$ requires C, 41·3; H, 4·9; N, 20·6%).

2-Dimethylamino-4-methylthiopyrimidine

Thiation of 4-chloro-2-dimethylaminopyrimidine[14] (1·0 g) as for the dichloro compound above, gave *2-dimethylamino-4-mercaptopyrimidine* (0·5 g), m.p. 161–162° (from ethanol) (Found: C, 46·0; H, 5·9; N, 26·8. $C_6H_9N_3S$ requires C, 46·45; H, 5·8; N, 27·1%).

[24] Boon, W. R., *J. Chem. Soc.*, 1952, 1532.

Treatment of this compound (0·35 g) in alkali with methyl iodide (0·5 ml) as above, gave the *methylthiopyrimidine* (0·3 g). After sublimation at 28°/0·7 mm it had m.p. 29–30° (Found: C, 49·4; H, 6·4; N, 24·5. $C_7H_{11}N_3S$ requires C, 49·7; H, 6·5; N, 24·85%). The *picrate* had m.p. 184–185° (from ethanol) (Found: C, 39·1; H, 3·5. $C_{13}H_{14}N_6O_7S$ requires C, 39·2; H, 3·5%).

2-Amino-4-methylthiopyrimidine

2-Amino-4-chloropyrimidine[25] (2·47 g) and aqueous sodium hydrogen sulphide (50 ml; sodium hydroxide, 1·6 g) were refluxed for 3 hr. Neutralization with acetic acid and concentration of the solution gave 2-amino-4-mercaptopyrimidine (2·3 g), m.p. 230° (decomp.) (lit.[15] 231–233°). It was converted as above into the 4-methylthio derivative which had m.p. 152–154° (from water) (lit.[15] 150–153°).

2-Dimethylamino-1,6-dihydro-1-methyl-6-thiopyrimidine

2-Dimethylamino-1,6-dihydro-1-methyl-6-oxopyrimidine[13] (0·85 g), phosphorus pentasulphide (2·1 g), and anhydrous pyridine (12 ml) were refluxed for 3 hr. After removal of the solvent *in vacuo*, the residue was refluxed in water for 30 min, clarified with charcoal, and filtered. Extraction with ether and evaporation to dryness gave a residue which was recrystallized from light petroleum to give the *thiopyrimidine* (0·24 g), m.p. 75–76° (Found: C, 49·6; H, 6·5; N, 24·7. $C_7H_{11}N_3S$ requires C, 49·7; H, 6·5; N, 24·85%).

2-Amino-1,6-dihydro-1-methyl-6-thiopyrimidine

2-Amino-1,6-dihydro-1-methyl-6-oxopyrimidine[16,17] (1·0 g), phosphorus pentasulphide (4·0 g), and dry pyridine (25 ml) were refluxed for 3 hr. The clarified aqueous solution (see above) deposited the *thiopyrimidine* (0·4 g) on cooling. Recrystallized from water it had m.p. 233–234° (Found: C, 42·15; H, 5·1; N, 29·7. $C_5H_7N_3S$ requires C, 42·5; H, 4·95; N, 29·7%).

Reaction of 2-Chloro-4-methoxypyrimidine with Methyl Iodide

The pyrimidine[26] (7·2 g) and methyl iodide (5 ml) were refluxed for 12 hr. Methyl iodide was removed and the oily residue solidified when triturated with ethanol. Treatment of an aqueous solution with charcoal followed by filtration and concentration gave 1-methyluracil (4·3 g), m.p. and mixed[1] m.p. 233° (Found: C, 47·6; H, 5·0; N, 22·2. Calc. for $C_5H_6N_2O_2$: C, 47·6; H, 4·8; N, 22·2%). The mother liquor was evaporated to dryness and the residue, recrystallized from ethyl acetate, gave 1,3-dimethyluracil (0·58 g) m.p. and mixed[27] m.p. 122–123°.

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[25] Hilbert, G. E., and Johnson, T. B., *J. Amer. Chem. Soc.*, 1930, **52**, 1152.
[26] Kenner, G. W., Reese, C. B., and Todd, A. R., *J. Chem. Soc.*, 1955, 855.
[27] Davidson, D., and Baudisch, O., *J. Amer. Chem. Soc.*, 1926, **48**, 2379.