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1,3-Dimethyl-1,2-dihydro-2-imino-4(3*H*)pyrimidinone (1,3-dimethylisocytosine) was prepared by methylation of 2-amino-3-methyl-4(3*H*)pyrimidinone and was degraded in alkaline solution to a mixture of 3-methyl-2-methylamino-4(3*H*)pyrimidinone, 1,3-dimethyl-2,4-(1*H*,3*H*)pyrimidindione, 2-methylamino-1-methyl-4(1*H*)pyrimidinone, 1-methyl-2,4-(1*H*,3*H*)pyrimidindione and 3-methyl-2,4-(1*H*,3*H*)pyrimidindione. Thiation of the title compound gave both 1,2-dihydro-1,3-dimethyl-2-thio-4(3*H*)pyrimidinone and 1,3-dimethyl-2,4-(1*H*,3H)pyrimidinedithione. The title compound is a tautomerically fixed pyrimidine and its uv spectra were compared with related compounds, notably 3-methyl-2-dimethylamino-4(3*H*)pyrimidinone which is also tautomerically fixed.

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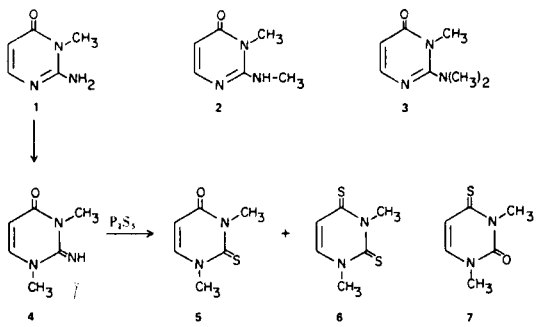
Whereas 1,3-dimethyl-3,4-dihydro-4-imino-2(1*H*)-pyrimidinone (1,3-dimethylcytosine) has been prepared by several routes (1), the isomeric 1,3-dimethyl-1,2-dihydro-2-imino-4(3*H*)pyrimidinone (1,3-dimethylisocytosine, **4**) has not been previously described.

Methylation of 2-amino-4-hydroxypyrimidine with dimethyl sulfate in dilute sodium hydroxide solution was reported to give 2-amino-1-methyl-4(1*H*)pyrimidinone (1-methylisocytosine) as major and 2-amino-3-methyl-4-(3*H*)pyrimidinone (3-methylisocytosine, **1**) as minor product, both characterized by hydrolysis in hot 1*N* sodium hydroxide to 1-methyl-2,4-(1*H*,3*H*)pyrimidindione (1-methyluracil, **10**) and 3-methyl-2,4-(1*H*,3*H*)pyrimidindione (3-methyluracil, **12**), respectively (2). Similarly, methylation of 2-amino-4-hydroxypyrimidine with iodomethane, only possible in the presence of an equivalent of sodium methoxide, afforded 1- and 3-methylisocytosines (3). 3-Methylisocytosine (**1**) was also prepared by aminolysis of 2-methylthio-3-methyl-4(3*H*)pyrimidinone (2), a type of reaction suitable for the preparation of **2** and **3**. Of the two latter compounds, **3** had been prepared previously by either methylation of 2-dimethylamino-4-hydroxypyrimidine after separation from the coproduced 2-dimethylamino-4methoxypyrimidine or thermal decomposition of 2-dimethylamino-1(or 3),4-dihydro-1,3-dimethyl-4-oxopyridinium iodide (4a).

Treatment of **1** with iodomethane gave **4** hydroiodide, readily converted to the free base by passage through a column of Dowex 1 (OH^- form). The structure of **4** was originally suggested by its dissimilarity to **2** and was confirmed by its spectroscopic properties, thiation products, pK_a value and hydrolytic behavior.

The two signals for methyl groups in the ^{1}Hnmr spectrum of **4** were compatible with nuclear *N*-methyl groups and **4** was converted to the known monothio- and dithio-1,3-dimethyluracils, **5** and **6**, respectively (Table 1, Figure 3). Under the conditions chosen, the thiation of **4** proceeded to **6** *via* **5**, apparently without the intermediacy of 1,3-dimethyl-1,2-dihydro-2-imino-4(3*H*)-pyrimidinethione (Scheme 1). The thiation of 1,3-dimethyluracil, by contrast, yields first the 4-thiopyrimidine **7**, and the dithio derivative **6** is then formed under more vigorous reaction conditions.

Scheme 1



Compounds **3** and **4** are tautomerically fixed 2-amino- and 2-imino-4-pyrimidinones, respectively. As shown in Figure 1, the uv spectra of the free bases (0.1 *N* potassium hydroxide) of **1**, **2** and **3** are of similar shape, the successive replacement of hydrogen by methyl groups at the N^2-position causing bathochromic shifts of the maxima. Similar bathochromic shifts are found upon successive *N*-methylations of aniline. The 2-imino tautomer **4**, by comparison, exhibits a characteristically less intense long wavelength maximum and an increased maximum at 220 nm. A still further hypsochromically and hypochromically displaced long wavelength maximum can be noted for yet another tautomer, **9**, whose low pK_a value suggests a preponderance of the 2-methylamino form.

Compound **3** is the weakest base (pK_a = 3.53) of the series, but the pK_a values of **2** (4.21) and **1** (4.40) are not much higher, precluding significant 2-imino character (4b). Similar decreases of basicities were noted upon methylation of the 4-amino group in the cytosine series, but successive methylation of the amino group in 2-aminopyrimidine is slightly base-strengthening (5). Nuclear methylation of **3** gives rise to the tautomerically fixed

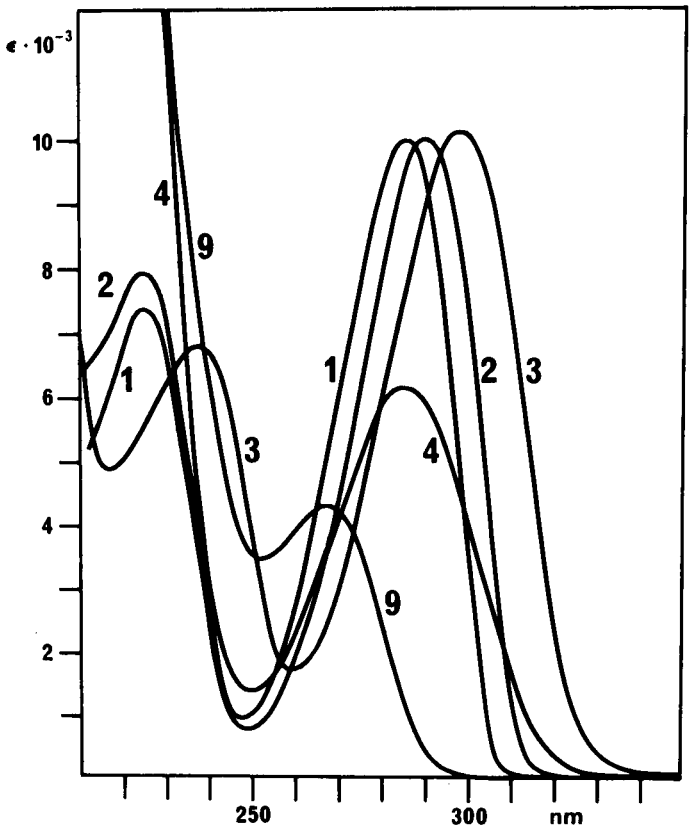


Figure 1. Uv Spectra of Various Uncharged Pyrimidines

2-imino-4-pyrimidinone (**4**) with a concomitant 7500 fold increase in base strength. Making allowance for the small spectral shifts due to *N*-methylations, the cationic species **1**, **2**, **3**, **4** and **9** exhibit similar spectra suggesting a common resonant cation shown in Figure 2 (6).

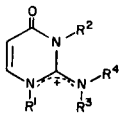
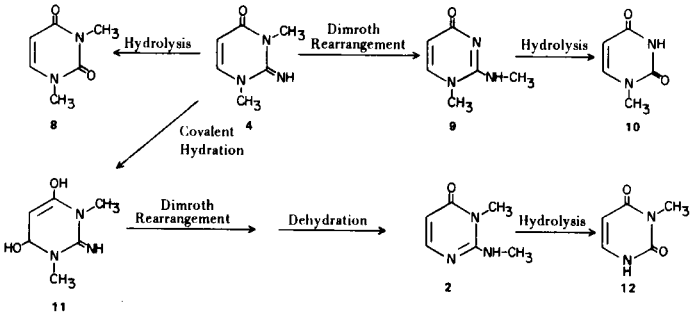


Figure 2

Scheme 2



Remarkably, short treatment of **4** with barium hydroxide gave five products (Scheme 2). They were identified as **2**, **8**, **9**, **10** and **12** by comparison of chromatographic data as well as uv, nmr and mass spectra of authentic specimens (Table 1, Figure 3). Reference compounds **2** and **9** were prepared by aminolysis of the corresponding *N*-methyl-2-methylthio-4-pyrimidinones. Hydrolysis of **4** accounts for the formation of 1,3-dimethyluracil (**8**). Dimroth rearrangement with cleavage between positions 3 and 4 and recyclization involving the incipient primary amino group gives rise to **9** which is amenable to hydrolysis to produce **10**. Alternatively, covalent hydration (12) of **4** forms the carbinolamine **11**, and a subsequent Dimroth rearrangement with cleavage between positions 5 and 6, recyclization with the primary amino group and dehydration gives **2** which is hydrolyzed to **12**.

Table 1

Chromatographic and physico-chemical data of various pyrimidines

Compound	R_f values in system 1	R_f values in system 2	pK_a	^{1}Hnmr Chemical Shifts (δ) Nuclear N-CH_3	N-CH_3	H-5	H-6	$J_{5,6}$ (Hz)	NH	Reference
1	0.46	0.73	4.40	3.26		5.59 (d)	7.52 (d)	6.5	7.10 (2)	2.3
2	0.47	0.78	4.21 ± 0.05	3.24	2.81 (d) J = 4.5 Hz	5.60 (d)	7.58 (d)	6.5	7.10	-
3	0.51	0.78	3.53 ± 0.05	3.35	2.84 (2)	5.90 (d)	7.68 (d)	6.5	-	4
4	0.17	0.69	7.40 ± 0.1	3.14, 3.25	-	5.25 (d)	7.95 (d)	8	6.28	-
5	0.70	0.79		3.57, 3.65	-	6.06 (d)	7.94 (d)	8	-	8
6	0.80	0.82		3.69, 4.14	-	6.87 (d)	7.79 (d)	7	-	1,10
7	0.69	0.78		3.36, 3.63	-	6.45 (d)	7.59 (d)	7.5	-	9
8	0.55	0.75		3.15, 3.29	-	5.63 (d)	7.66 (d)	8	-	11
9	0.25	0.50	3.70 ± 0.05	3.34	2.75	5.46 (d)	7.36 (d)	7.5	7.05	-
10	0.48	0.57		3.21	-	5.51 (d)	7.59 (d)	8	11.16	7,11
12	0.63	0.68		3.11	-	5.58 (d)	7.41 (d)	8	11.01	7,11

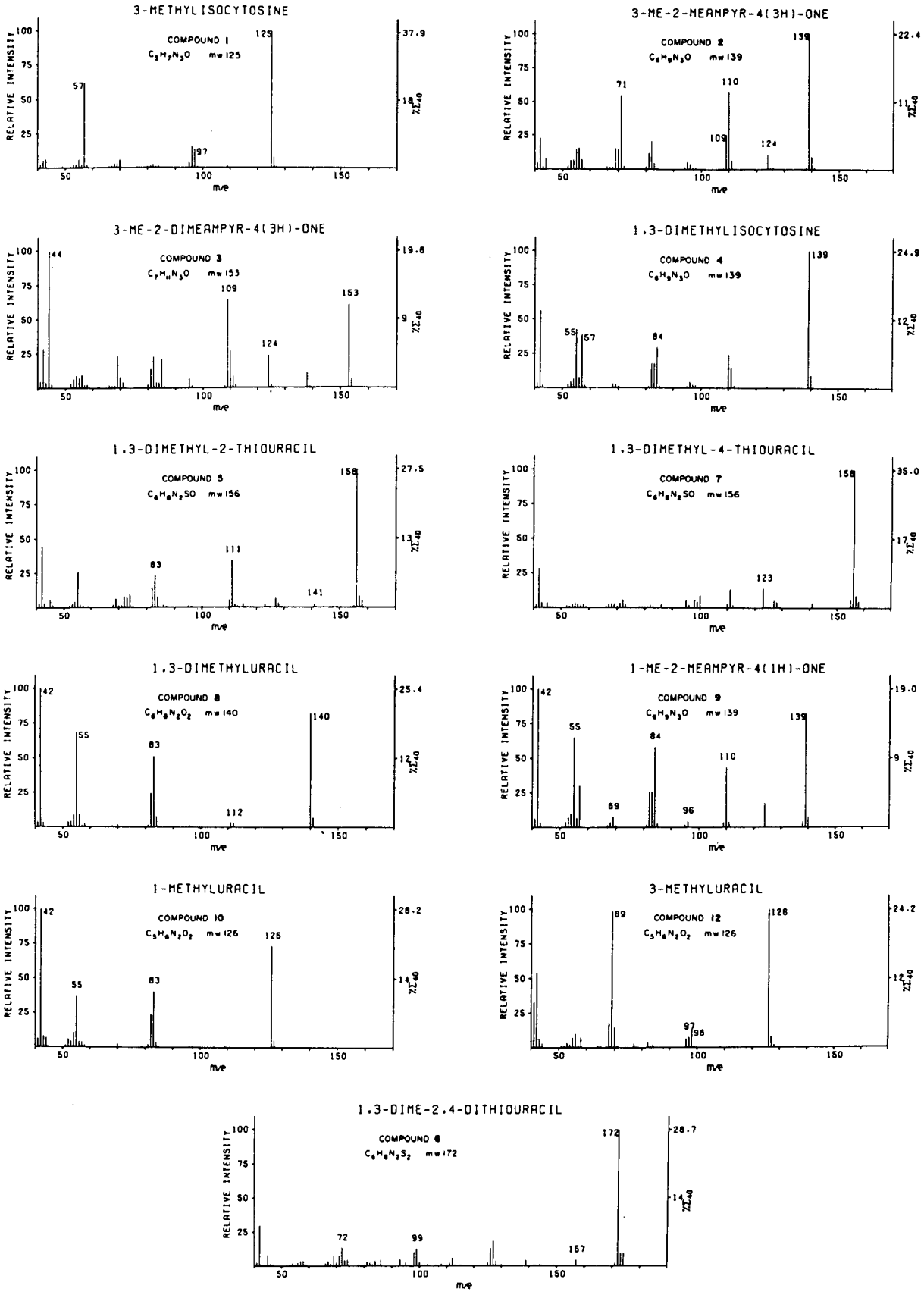


Figure 3. Mass Spectra of Various Pyrimidines

EXPERIMENTAL

Melting points were determined on a Reichert Thermopan hot stage and are uncorrected. Nmr spectra were recorded on a Varian HA-100 spectrometer using deuteriodimethylsulfoxide as solvent and tetramethylsilane as internal reference. Uv spectra were obtained on a Cary 14 spectrophotometer in aqueous solutions and apparent dissociation constants were computed from uv spectral data at different *p*H values at ionic strength of buffers of 0.01 (13). Mass spectra were recorded on a Varian MAT Model CH5 spectrometer operating at 70 eV with ion-source temperature of 250°. Tlc was carried out with silica gel G-F254 plates (E. Merck, Darmstadt) using solvent systems 1 (1-butanol-acetic acid-water, 4:1:1, v/v), 2 (2-propanol-concentrated ammonium hydroxide-water, 8:1:1, v/v) and 3 (chloroform-2-propanol, 9:1, v/v). For analysis, a layer thickness of 0.25 mm and for preparative runs a thickness of 2.5 mm was employed.

3-Methyl-2-methylamino-4(3*H*)pyrimidinone (**2**).

A solution of 3-methyl-2-methylthio-4(3*H*)pyrimidinone (7) (7.0 g., 44.8 mmoles) in *ca.* 25 ml. of methylamine was kept in a sealed glass tube for 4 days. The clear solution was allowed to evaporate to dryness, and the crystalline residue was dissolved in hot 2-propanol, filtered, concentrated to a thin oil, and diluted with an equal volume of benzene and *ca.* 80 ml. of ether to give colorless needles of **2** (6.2 g., 44.6 mmoles, 99%), m.p. 101-102°; λ max ($\epsilon \cdot 10^{-3}$): 215 (sh., 10.63) and 259 (6.48) in 0.1 *N* hydrochloric acid; 224 (7.15) and 288 (9.25) in *p*H 7.0 buffer; 224 (7.90) and 288 nm (10.0) in 0.1 *N* potassium hydroxide.

Anal. Calcd. for $C_6H_9N_3O$ (139.16): C, 51.79; H, 6.52; N, 30.20. Found: C, 52.00; H, 6.61; N, 30.45.

3-Methyl-2-dimethylamino-4(3*H*)pyrimidinone (**3**).

A suspension of 3-methyl-2-methylthio-4(3*H*)pyrimidinone (1.87 g., 12 mmoles) in dimethylamine (5 ml.) at 78° was diluted with methanol (2 ml.) and the mixture kept at 46° for 5 days. The solvents were evaporated, and the crystalline residue was redissolved in ethanol (5 ml.), the solution diluted with benzene (5 ml.) and concentrated to a volume of *ca.* 4 ml. Addition of ether resulted in crystallization of **3** as large plates (900 mg., 5.9 mmoles, 49%) which were recrystallized from ethyl acetate-ether-hexane, m.p. 95°; λ max ($\epsilon \cdot 10^{-3}$): 207 (15.12), 233 (9.75) and 268 (7.82) in 0.1 *N* hydrochloric acid; 201 (12.10), 237 (6.70) and 298 (10.05) in *p*H 7.0 buffer; 238 (6.62) and 298 nm (10.25) in 0.1 *N* potassium hydroxide. Additional **3** could be obtained from the original mother liquor by fractional crystallization.

Anal. Calcd. for $C_7H_{11}N_3O$ (153.19): C, 54.89; H, 7.24; N, 27.43. Found: C, 54.84; H, 7.40; N, 27.38.

1,3-Dimethyl-1,2-dihydro-2-imino-4(3*H*)pyrimidinone (**4**).

A solution of **1** (2) (1.5 g., 12 mmoles) in methanol (25 ml.) and iodomethane (50 ml.) was heated for 24 hours under reflux under exclusion of moisture. The crystalline **4** hydroiodide (2.2 g., 8.2 mmoles, 68%) was collected and washed with small amounts of methanol, 2-propanol and ether. Prolonged treatment of the filtrate with additional iodomethane and silver oxide failed to yield additional **4**. The hydroiodide was recrystallized from methanol-2-propanol to give colorless needles, m.p. 262-263° dec.; λ max ($\epsilon \cdot 10^{-3}$): 223 (20.70) and 260 (7.45) in 0.1 *N* hydrochloric acid; 223 (23.50) and 263 (6.20) in *p*H 7 buffer; 222 (29.75) and 284 nm (6.15) in 0.1 *N* potassium hydroxide.

Anal. Calcd. for $C_6H_9N_3O \cdot HI$ (267.07): C, 26.99; H, 3.77; N, 15.73. Found: C, 26.77; H, 3.90; N, 15.60.

An aqueous solution of **4** hydroiodide (2.2 g.) was passed through a column of Dowex 1-X4 (OH^-, 50 ml., 100-200 mesh), the basic effluent and water washes combined and concentrated to dryness, and the residue redissolved in hot ethyl acetate and diluted with ether and petroleum ether to give **4** as clusters of prisms (965 mg., 6.9 mmoles, 84%), m.p. 139-140°; λ max ($\epsilon \cdot 10^{-3}$): 217 (7.90) and 261 (7.25) in 0.1 *N* hydrochloric acid; 218 (12.10) and 265 (5.42) in *p*H 7 buffer; 220 (16.85) and 284 nm (6.00) in 0.1 *N* potassium hydroxide.

Anal. Calcd. for $C_6H_9N_3O$ (139.16): C, 51.79; H, 6.52; N, 30.20. Found: C, 51.67; H, 6.55; N, 30.34.

Degradation of 1,3-Dimethyl-1,2-dihydro-2-imino-4(3*H*)pyrimidinone (**4**).

A solution of **4** (400 mg.) in saturated barium hydroxide (20 ml.) was heated on the steam bath for 2 hours. The solution was neutralized with carbon dioxide, and the suspension diluted with methanol and filtered. The filtrate was concentrated to dryness to yield a crystalline mixture of **2**, **8**, **9**, **10** and **12**. Components **2** and **9** predominated and **8** was the minor component. All 5 components could be separated preparatively by tlc on silica gel G by a combination of systems 1 and 2 (Table 1); the bands were eluted with chloroform-methanol mixtures.

1,2-Dihydro-1,3-dimethyl-2-thio-4(3*H*)pyrimidinone (1,3-Dimethyl-2-thiouracil, **5**) and 1,3-Dimethyl-2,4-(1*H*,3*H*)pyrimidinedithione (1,3-Dimethyl-2,4-dithiouracil, **6**).

A mixture of **4** (80 mg.) and phosphorus pentasulfide (300 mg.) in pyridine (4 ml.) was heated on the steam bath under exclusion of moisture for 3 hours. The solution was diluted with toluene (5 ml.), filtered, and the residue extracted twice with hot toluene. The combined filtrate and extracts were concentrated to small volume and chromatographed on a preparative layer with system 3. The major band (R_f 0.6) was eluted with acetone; the resulting residue was crystallized from ethyl acetate-heptane to give 15 mg. of colorless needles of **5** (8) with m.p. 108-109°.

Anal. Calcd. for $C_6H_8N_2OS$ (156.20): C, 46.14; H, 5.16; N, 17.94. Found: C, 46.01; H, 5.18; N, 17.85.

The minor band (R_f 0.8) was eluted with chloroform, and the residue crystallized from aqueous methanol furnishing yellow needles of **6** (9,10) with m.p. 124° (5 mg.).

Anal. Calcd. for $C_6H_8N_2S_2$ (172.14): S, 37.25. Found: S, 37.01.

2-Methylamino-1-methyl-4(1*H*)pyrimidinone (**9**).

1-Methyl-2-methylthio-4(1*H*)pyrimidinone (1.0 g., 6.4 mmoles) (7) was suspended in methylamine (*ca.* 15 ml.) in a sealed glass tube and kept at *ca.* 65° for one week. The tube content was allowed to evaporate to dryness and the crystalline residue recrystallized from ethanol-2-propanol and 2-propanol-ethyl acetate (0.73 g., 5.2 mmoles, 82%), m.p. 200-201°; λ max ($\epsilon \cdot 10^{-3}$): 221 (11.30) and 267 (7.45) in 0.1 *N* hydrochloric acid; 208 (23.35) and 266 (4.35) in *p*H 7.0 buffer; 266 nm (4.75) in 0.1 *N* potassium hydroxide.

Anal. Calcd. for $C_6H_9N_3O$ (139.16): C, 51.79; H, 6.52; N, 30.20. Found: C, 51.81; H, 6.61; N, 30.31.

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REFERENCES AND NOTES

(1) Previous paper in this series: H. Maehr, M. Leach and V. Toome, *J. Heterocyclic Chem.*, **9**, 1389 (1972).

(2) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 1891 (1961).

(3) D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 3172 (1962). Note: D. J. Brown uses two different numbering systems for the pyrimidine nucleus.

(4a) D. J. Brown and T. Teitei, *Austr. J. Chem.*, **18**, 199 (1965); (b) **18**, 559 (1965).

(5) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solutions", Butterworths, London 1965; Supplement 1972, and references cited therein.

(6) R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970).

(7) D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, 211 (1955).

(8) R. N. Warrener and E. N. Cain, *Chem. Ind. (London)*, 1989 (1964).

(9) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **69**, 2138 (1947).

(10) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).

(11) D. Shugar and J. J. Fox, *Biochem. Biophys. Acta*, **9**, 199 (1952).

(12) D. D. Perrin and I. H. Pitman, *J. Chem. Soc. (C)*; 7071 (1965).

(13) A. Albert and E. P. Serjeant, "The Determination of Ionization Constants", Chapman and Hall Ltd., London, 1971.