829. *Simple Pyrimidines. Part V.*[1] *Tautomerism in 4-Hydroxy-6-mercaptopyrimidine.*

By D. J. Brown and T. Teitei.

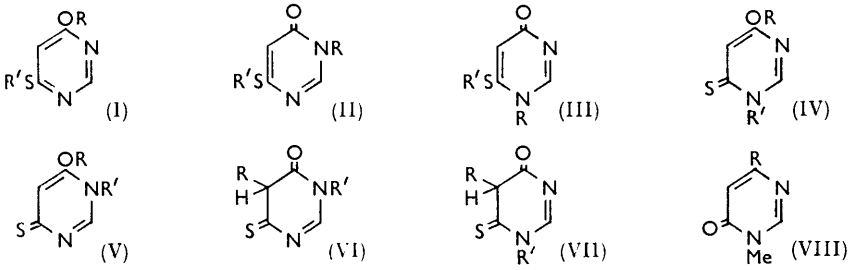
Fully *O*-, *S*-, and *N*-methylated derivatives of 4-hydroxy-6-mercaptopyrimidine have been synthesised. Comparison of their spectra with that of the parent compound strongly suggests that the latter exists in aqueous solution predominantly as 1,6-dihydro-4-hydroxy-6-thiopyrimidine. The possibility cannot yet be excluded that a form involving C-5 in tautomerism is preferred. Ionisation constants are recorded.

Whereas it is accepted [2,3] that 2-, 4-, and 6-hydroxy- and mercapto-pyrimidines normally exist as cyclic amides and thioamides, respectively, 4-hydroxy-6-mercaptopyrimidine is precluded by valency from having a cyclic diamide structure. Thus, a choice must be made from among the hydroxy-mercapto- (I; R = R′ = H), the oxo-mercapto- (II and III; R = R′ = H), the hydroxy-thio- (IV and V; R = R′ = H), and those forms (VI and VII; R = R′ = H) involving C-5 as a repository for one tautomeric hydrogen atom.

The infrared spectrum of 4-hydroxy-6-mercaptopyrimidine shows unmistakable strong bands for C=O (1680 cm.$^{-1}$) and C=S (1090 cm.$^{-1}$; cf. Spinner [4]), suggesting that the solid compound exists as a mixture of the oxo-mercapto- and hydroxy-thio-forms, or as the

[1] Part IV, Brown and Lyall, *Austral. J. Chem.*, 1962, **15**, 851.
[2] Mason, in Brown, " The Pyrimidines," Interscience Publ., Inc., New York, 1962, p. 482 *et seq.*
[3] Albert and Barlin, *J.*, 1962, 3129.
[4] Spinner, *J.*, 1960, 1237.

oxo-thio-form (VI/VII). In the present paper the first of these possibilities is explored in detail by comparing the ultraviolet spectra with those of methylated derivatives having fixed (non-tautomeric) or partly fixed structures. It is concluded that 1,6-dihydro-4-hydroxy-6-thiopyrimidine (IV; R = R′ = H) may well predominate in aqueous solution, a finding which would be in accord with the fact [3] that the ratio of hydroxy- to oxo-forms



in such cyclic amides is invariably much higher than the ratio of mercapto- to thio-forms in the thio-analogues. At this stage, the possibility of a preferred form (VI/VII), in which the 5-position is involved in tautomerism, is not excluded and is being investigated.

Preparations.—4-Chloro-6-methoxypyrimidine [5] and sodium hydrogen sulphide gave 4-mercapto-6-methoxypyrimidine which on gentle methylation yielded 4-methoxy-6-methylthiopyrimidine (I; R = R′ = Me). Similar processes applied to 4-chloro-1,6-dihydro-1-methyl-6-oxopyrimidine [6] (VIII; R = Cl) gave, in turn, 1,4-dihydro-6-hydroxy-1-methyl-4-thiopyrimidine (V; R = H, R′ = Me), tautomeric with (II; R = Me, R′ = H), and then 1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine (II; R = R′ = Me). Treatment of the same chloro-compound with sodium methoxide, or more simply, the action of diazomethane on 4,6-dihydroxypyrimidine, furnished 1,6-dihydro-4-methoxy-1-methyl-6-oxopyrimidine (VIII; R = OMe). Thiation of this with phosphorus pentasulphide gave 1,6-dihydro-4-methoxy-1-methyl-6-thiopyrimidine (IV; R = R′ = Me) which was hydrolysed by alkali to 1,6-dihydro-4-hydroxy-1-methyl-6-thiopyrimidine (IV; R = H, R′ = Me or III; R = Me, R′ = H), and then on methylation gave 1,4-dihydro-1-methyl-6-methylthio-4-oxopyrimidine (III; R = R′ = Me). Attempts to prepare the compound (V; R = R′ = Me) failed.

Spectra.—Comparison of the ultraviolet spectrum of the neutral molecule 4-hydroxy-6-mercaptopyrimidine with those of the fixed structures (I—IV; R = R′ = Me) reveals a reasonable similarity only to the fourth of these (see Table and Figures). This spectrum is also similar to that of 1,6-dihydro-4-methoxy-6-thiopyrimidine (IV; R = Me, R′ = H) which can be thus formulated because of the known [3] preference of 4-mercaptopyrimidine to exist as an α- rather than a γ-thioamide. In addition, the spectrum of 1,6-dihydro-4-hydroxy-1-methyl-6-thiopyrimidine is again similar to that of (IV; R = R′ = Me) but dissimilar to that of (III; R = R′ = Me), indicating that the cyclic thioamide structure (IV; R = H, R′ = Me) is preferred to the alternative cyclic amide structure (III; R = H, R′ = Me). This indicates that the isomeric 1,4-dihydro-6-hydroxy-1-methyl-4-thiopyrimidine would also exist as the cyclic thioamide (V; R = H, R′ = Me) rather than the cyclic amide (II; R = H, R′ = Me) and this is confirmed, albeit negatively, by the dissimilarity of its spectrum to that of the fixed structure (II; R = R′ = Me). It further follows that the fixed structure (V; R = R′ = Me), which could not be prepared, is reasonably represented for spectroscopic purposes by compound (V; R = H, R′ = Me), and a comparison of its spectrum with that of 4-hydroxy-6-mercaptopyrimidine excludes the possibility that the latter exists in the remaining form (V; R = R′ = H). It is curious that the above four compounds with generally similar spectra fall naturally into two pairs

[5] Isbecque, Promel, Quinaux, and Martin, *Helv. Chim. Acta*, 1959, **42**, 1317.
[6] Brown and Harper, *J.*, 1961, 1298.

Ionisation and ultraviolet spectra of pyrimidine derivatives.

Derivative	pK_a*	$\lambda_{max.}$ (log ε) †	pH
1,4-Dihydro-6-hydroxy-1-methyl-4-thio		*280* (*3·72*), 228 (4·36)	1·1
cation	−1·13 ± 0·03 (sp.)	*280* (*3·66*), 230 (4·26)	−2·9
anion	5·05 ± 0·1 (M/1000) ‡	*280* (*3·69*), *250* (*3·89*), 228 (4·24)	8·0
1,6-Dihydro-4-hydroxy-1-methyl-6-thio		304 (4·08), 252 (3·93)	0·6
cation §	−2·20 ± 0·07 (sp.)	316 (4·03), 266 (3·86), 236 (4·04)	—
anion	4·38 ± 0·1 (M/1000) ‡		
1,6-Dihydro-4-methoxy-1-methyl-6-oxo		259 (3·65)	4·5
cation	−0·44 ± 0·04 (sp.)	240 (3·95)	−2·5
1,6-Dihydro-4-methoxy-1-methyl-6-thio		299 (4·24), 225 (4·17)	0·4
cation §	−1·65 ± 0·03 (sp.)	314 (4·27), 234 (3·93), 225 (3·89)	—
1,4-Dihydro-1-methyl-6-methylthio-4-oxo		274 (4·05), 232 (4·33)	6·0
cation	1·77 ± 0·04 (sp.)	278 (3·97), 241 (4·17)	−0·5
1,6-Dihydro-1-methyl-4-methylthio-6-oxo		268 (3·94), 237 (4·24)	3·0
cation	0·13 ± 0·02 (sp.)	277 (3·96), 243 (4·24)	−1·8
4-Hydroxy-6-mercapto ¶		304 (4·09), 241 (3·93), 229 (3·96)	0·5
cation	−1·7 ± 0·04 (sp.)	264 (3·97), 231 (4·11)	−3·6
anion	4·33 **	294 (4·11), 222 (4·16)	7·0
dianion	10·52 **	— ††	
4-Hydroxy-6-methylthio ¶		278 (3·95), 236 (4·19)	1·8
cation	−0·11 ± 0·05 (sp.)	277 (4·01), 242 (4·14)	−2·2
anion	8·52 **	*270* (*3·75*), 229 (4·34)	11·0
4-Methoxy-6-methylthio		266 (4·02)	7·0
cation	1·62 ± 0·05 (sp.)	286 (4·08), 223 (4·19)	−0·8
4-Mercapto-6-methoxy		300 (4·22)	3·0
cation §	−1·98 ± 0·06 (sp.)	320 (4·29), 222 (4·05)	—
anion	7·51 ± 0·03 (M/200)	285 (4·28), 226 (4·16)	10·0

* Measured at 20° potentiometrically (concn. given) or spectrometrically (sp.); cf. Albert and Serjeant, "Ionization of Acids and Bases," Methuen, London, 1962. † Inflexions in italics; peaks below 220 mμ omitted. ‡ Partial decomposition during titration. § Values obtained by extrapolation. ¶ Cf. ref. 5 in which some spectra are of mixed species. ** From ref. 6. †† Unstable in alkali.

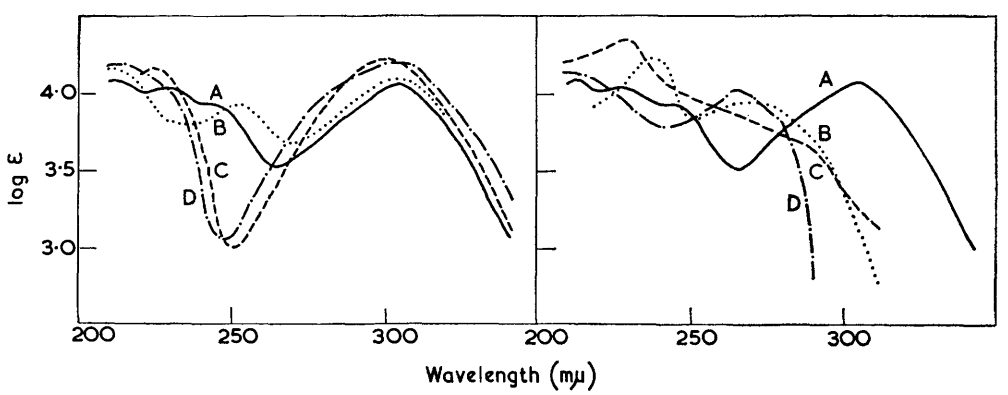


FIG. 1.

FIG. 2.

FIG. 1. Ultraviolet absorption of neutral molecules: A, 4-hydroxy-6-mercaptopyrimidine; B, 1,6-dihydro-4-hydroxy-1-methyl-6-thiopyrimidine; C, 1,6-dihydro-4-methoxy-1-methyl-6-thiopyrimidine; D, 4-mercapto-6-methoxypyrimidine.

FIG. 2. Ultraviolet absorption of neutral molecules: A, 4-hydroxy-6-mercaptopyrimidine; B, 1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine; C, 1,4-dihydro-6-hydroxy-1-methyl-4-thiopyrimidine; D, 4-methoxy-6-methylthiopyrimidine.

with similar curves (Fig. 1). It might be significant that the first two compounds (I; R = R′ = H and IV; R = H, R′ = Me) could each assume an oxo-thio-form by involving the 5-position in tautomerism while the other pair cannot. Of the same four compounds, three undergo an appreciable bathochromic shift in the long-wavelength band on protonation, while 4-hydroxy-6-mercaptopyrimidine alone shows a considerable hypsochromic shift. The monoanionic spectrum of the last-mentioned compound is unlike that of 4-amino-6-mercaptopyrimidine,[7] confirming the view that ionisation does not occur at the oxygen atom. On the other hand, R. N. Jones's rule [8] is obeyed by 4-hydroxy-6-methylthiopyrimidine, the anionic spectrum of which is similar to that of the neutral molecule of 4-amino-6-methylthiopyrimidine.[7]

Experimental

Analyses were done by Dr. J. E. Fildes and her staff. Infrared spectra were measured in a Unicam S.P. 200 spectrophotometer for hexachlorobutadiene mulls, and the chief C:O and C:S assignments are recorded in square brackets below.

4-Mercapto-6-methoxypyrimidine.—A solution of sodium hydroxide (10·0 g.) in alcohol (175 ml.) was saturated with hydrogen sulphide at 0—5°. 4-Chloro-6-methoxypyrimidine [5] (5·0 g.) was added, and the mixture gently refluxed with stirring for 2 hr., then adjusted to pH 4. After refrigeration, the solid was washed with water, and recrystallisation from ethanol gave the *mercaptopyrimidine* (2·3 g.), m. p. 193—194° (Found: C, 42·5; H, 4·3; N, 19·6. $C_5H_6N_2OS$ requires C, 42·25; H, 4·2; N, 19·7%) [—; 1105 cm.$^{-1}$].

4-Methoxy-6-methylthiopyrimidine.—4-Mercapto-6-methoxypyrimidine (1·7 g.) in 0·2N-sodium hydroxide (72 ml.) was shaken for 1·5 hr. at 20° with methyl iodide (1·9 g.). Extraction with ether and distillation gave the *methylthiopyrimidine* (1·3 g.), b. p. 60°/0·3 mm., n_D^{23} 1·5692 (Found: C, 46·4; H, 5·3; N, 17·9. $C_6H_8N_2OS$ requires C, 46·15; H, 5·1; N, 17·95%). The *picrate* had m. p. 117—118° (Found: C, 37·3; H, 2·7. $C_{12}H_{11}N_5O_8S$ requires C, 37·4; H, 2·9%).

1,4-Dihydro-6-hydroxy-1-methyl-4-thiopyrimidine (or Tautomer).—4-Chloro-1,6-dihydro-1-methyl-6-oxopyrimidine [6] (1·0 g.) was heated for 2 hr. on a steam-bath with alcoholic M-sodium hydrogen sulphide (50 ml.). A sample of the resulting precipitate recrystallised from alcohol to give a hygroscopic *sodium salt*, m. p. 281—283° (decomp.) (Found: N, 16·3. $C_5H_5N_2NaOS,0·5H_2O$ requires N, 16·2%). The bulk of the suspension was acidified with acetic acid (10 ml.), and the residue obtained on evaporation was extracted with ethanol (100 ml.). The solvent was removed from the extract, and the solid was dissolved in concentrated aqueous ammonia and reprecipitated with acetic acid. Recrystallised from ethanol, the *thio-compound* (0·35 g.) had m. p. 209—211° (decomp.) (Found: C, 42·5; H, 3·45; N, 19·7. $C_5H_6N_2OS$ requires C, 42·25, H, 4·2, N, 19·7%) [1665, 1070(?) cm.$^{-1}$].

1,6-Dihydro-1-methyl-4-methylthio-6-oxopyrimidine.—The above thio-compound (0·3 g.) in 0·2N-sodium hydroxide (13 ml.) was shaken for 1 hr. at 20° with methyl iodide (0·3 g.). The solid recrystallised from alcohol to give the thioether (0·22 g.), m. p. 174—175° (lit.,[6] 172—175°) [1680;—cm.$^{-1}$].

1,6-Dihydro-4-methoxy-1-methyl-6-oxopyrimidine.—(*a*) 4-Chloro-1,6-dihydro-1-methyl-6-oxopyrimidine [6] (2·4 g.) was refluxed for 1 hr. with methanolic sodium methoxide (from 0·9 g. of sodium). The solution was neutralised with acetic acid and evaporated to dryness. Extraction with ethyl acetate (200 ml.), evaporation, and recrystallisation of the residue from the same solvent gave the *methoxy-compound* (1·6 g.), m. p. 146—147° (Found: C, 51·5; H, 5·6; N, 19·8. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·7; N, 20·0%) [1680;—cm.$^{-1}$]. (*b*) 4,6-Dihydroxypyrimidine [9] (28 g.) was added slowly to ethereal diazomethane (from 90 g. of methylnitrosourea). After 2 days, the solution was filtered from unchanged material (18·4 g.). The residue obtained on evaporating the filtrate recrystallised from ethyl acetate, to give the methoxy-compound (60%), identified by mixed m. p.

1,6-Dihydro-4-methoxy-1-methyl-6-thiopyrimidine.—The preceding methoxypyrimidine (1·4 g.) and phosphorus pentasulphide (4·1 g.) were refluxed for 3 hr. in dry pyridine (40 ml.). The excess of pyridine was removed under reduced pressure, and the residue refluxed for 1 hr. with

[7] Brown and Teitei, *J.*, 1963, 3535.
[8] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[9] Hull, *J.*, 1951, 2214; Katritzky, Shepherd, and Waring, *Rec. Trav. chim.*, 1962, **81**, 443.

water (20 ml.). The remaining solid was extracted with ether. The residue obtained on evaporation of the extract recrystallised from ethyl acetate, to give the *thiopyrimidine* (0·55 g.), m. p. 138—139° (Found: C, 45·8; H, 4·9; N, 18·0. $C_6H_8N_2OS$ requires C, 46·15; H, 5·1; N, 17·95%) [—; 1100 cm.$^{-1}$].

1,6-*Dihydro*-4-*hydroxy*-1-*methyl*-6-*thiopyrimidine* (*or Tautomer*).—1,6-Dihydro-4-methoxy-1-methyl-6-thiopyrimidine (1·0 g.) and N-sodium hydroxide (8·0 ml.) were heated for 15 min. at 100°. The solution was neutralised with hydrochloric acid and refrigerated. The solid was washed and recrystallised from water, to give the *hydroxy-compound* (0·73 g.), m. p. 209—210° (decomp.) (Found: C, 42·2; H, 4·3; N, 19·7. $C_5H_6N_2OS$ requires C, 42·25; H, 4·2; N, 19·7%).

1,4-*Dihydro*-1-*methyl*-6-*methylthio*-4-*oxopyrimidine*.—The above thiopyrimidine (0·7 g.), 0·5N-sodium hydroxide (8·0 ml.), and methyl iodide (0·7 g.) were shaken for 3 hr. at 25°. The solution was adjusted to pH 6 and exhaustively extracted with chloroform. Evaporation of the solvent and recrystallisation of the residue from ethanol gave the *methylthio-compound* (0·39 g.), m. p. 196—197° (Found: C, 46·0; H, 5·0; N, 17·8. $C_6H_8N_2OS$ requires C, 46·15; H, 5·1; N, 17·95%). Its *picrate* had m. p. 190—191° (Found: C, 37·8; H, 3·1. $C_{12}H_{11}N_5O_8S$ requires C, 37·4; H, 2·9%) [1620(?);—cm.$^{-1}$].

We thank Professor Adrien Albert, Dr. R. F. Evans, Dr. E. Spinner, and Mr. J. Harper, for discussion, and acknowledge support of T. T. as a Scholar of this University.

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Canberra. [*Received, March 11th,* 1963.]