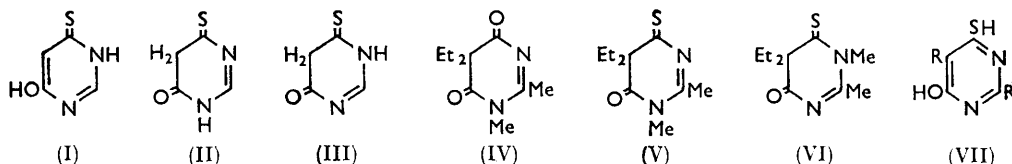


### 609. Simple Pyrimidines. Part VI.<sup>1</sup> The Dominant Tautomer in Aqueous 4-Hydroxy-6-mercaptopyrimidine.

By D. J. BROWN and T. TEITEI.

Syntheses of 5,5-diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-4-thiopyrimidine and its *N*-3-methyl-isomer are described. The former displays a normal spectrum in cyclohexane and in alcohol but not in water in which it exists probably as an hydrated molecule. The isomer could not be obtained anhydrous. Comparison of the ultraviolet spectra of these substances (and of other fixed reference compounds) with that of 4-hydroxy-6-mercaptopyrimidine indicates that the latter exists in aqueous or alcoholic solution mainly as a tetrahydro-4-oxo-6-thiopyrimidine, a form which involves C-5 in tautomerism as in barbituric acid. Insertion of a 5-*n*-alkyl-group does not alter this predominance, but the modified spectrum of the 5-isopropyl derivative suggests some steric interference.

In a previous Paper<sup>1</sup> the tautomerism of 4-hydroxy-6-mercaptopyrimidine was investigated by comparing its ultraviolet spectrum with those of *O*-, *S*-, and *N*-methylated derivatives. 5,5-Dialkylated models such as (V) to represent forms, characterised by having *sp*<sup>3</sup> hybridisation at position 5, were not then available, but have now been prepared. Comparison of their spectra with that of 4-hydroxy-6-mercaptopyrimidine showed that the latter consists of a tautomeric mixture in which the tetrahydro-4-oxo-6-thiopyrimidine (II), or possibly (III), predominates in aqueous solution. This finding corrects the earlier conclusion<sup>1</sup> that 1,6-dihydro-4-hydroxy-6-thiopyrimidine (I) is the predominant tautomer, although it is still possible that it makes an appreciable contribution. 5-*n*-Alkyl-4-hydroxy-6-mercaptopyrimidines were similarly shown to exist predominantly in the form with *sp*<sup>3</sup> hybridisation at position 5, and hence the 5-alkyl-group exerts little steric hindrance to the attachment of tautomeric hydrogen at position 5.



**Preparations.**—5,5-Diethyltetrahydro-4-oxo-6-thiopyrimidines were first approached from their 4,6-dioxo-analogues. Diethyl diethylmalonate with formamidine failed to yield a pyrimidine but with acetamidine (cf. Boon *et al.*<sup>2</sup>), it gave 5,5-diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-oxopyrimidine. As neither this, nor its methylated derivative (IV) reacted satisfactorily with phosphorus pentasulphide, the introduction of sulphur was tried at an earlier stage. Thus cyanoacetamide and *N*-methylcyanoacetamide were each diethylated on the  $\alpha$ -carbon atom. These derivatives, by appropriate hydrolysis, thiation, and addition of hydrogen sulphide, gave 3-carbamoyl-3-thiocarbamoylpentane ( $\text{H}_2\text{NOC}\cdot\text{C}(\text{Et})_2\cdot\text{CSNH}_2$ ), and the analogous compounds ( $\text{MeHNOC}\cdot\text{C}(\text{Et})_2\cdot\text{CSNH}_2$ ) and ( $\text{H}_2\text{NOC}\cdot\text{C}(\text{Et})_2\cdot\text{CSNHMe}$ ). Each underwent a modified Remfry–Hull synthesis with acetyl chloride to yield, respectively, 5,5-diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-thiopyrimidine and its *N*-methyl derivatives (V) and (VI).

The 5-alkyl-4-hydroxy-6-mercaptopyrimidines were made thus: diethyl alkylmalonate and formamidine<sup>3</sup> gave the 5-alkyl-4,6-dihydroxypyrimidine which was converted by phosphoryl chloride into 5-alkyl-4,6-dichloropyrimidine (cf. the methyl homologue<sup>4</sup>). As

<sup>1</sup> Part V, Brown and Teitei, *J.*, 1963, 4333.

<sup>2</sup> Boon, Carrington, Greenhalgh, and Vasey, *J.*, 1954, 3263.

<sup>3</sup> Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388.

<sup>4</sup> Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.

in analogous cases,<sup>5,6</sup> partial hydrolysis with aqueous alkali gave 5-alkyl-4-chloro-6-hydroxypyrimidine and treatment with sodium hydrogen sulphide completed the synthesis. 2-Butyl-4-hydroxy-6-mercaptopyrimidine was made similarly. The mercaptopyrimidines were then S-methylated in alkali with methyl iodide.

*Spectra.*—It was observed that the ultraviolet spectra of compounds (V), (VI), and 5,5-diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-thiopyrimidine were all similar as neutral molecules in water, but differed profoundly from that of 4-hydroxy-6-mercaptopyrimidine (Table 1 and Fig. 1). However, the spectrum of (V) in ethanol or cyclohexane showed a far greater bathochromic shift than could be due to a normal solvent effect, and corresponded closely to that of 4-hydroxy-6-mercaptopyrimidine in ethanol or water (Fig. 1).

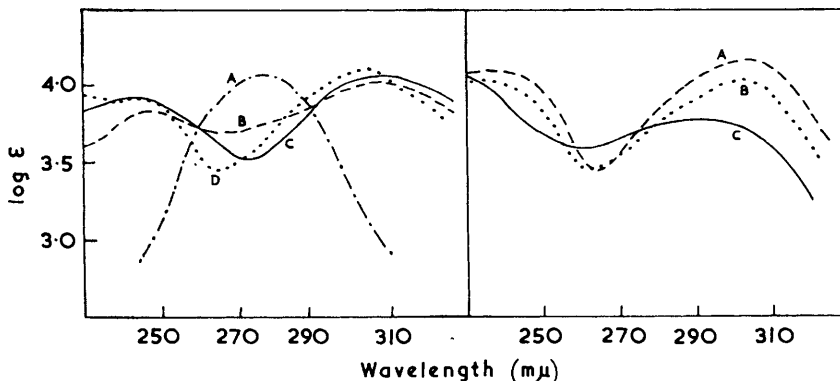


FIG. 1.

FIG. 2.

FIG. 1. Ultraviolet absorption of neutral molecules: 5,5-diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-4-thiopyrimidine in aqueous buffer (A); in ethanol (B); in cyclohexane (C); 4-hydroxy-6-mercaptopyrimidine in aqueous buffer (D).

FIG. 2. Ultraviolet absorption of 4-hydroxy-6-mercaptopyrimidine derivatives in ethanol: (A) 5-n-butyl; (B) 5-methyl; (C) 5-isopropyl.

This major shift could not be due to a change in tautomeric form because the structure (V) is fixed; indeed other fixed structures, such as 1,6-dihydro-4-methoxy-1-methyl-6-thio- and 1,6-dihydro-1-methyl-4-methylthio-6-oxo-pyrimidine, showed little change between spectra determined in water and cyclohexane. It therefore appeared that (V) was hydrated in water, whereas in ethanol or cyclohexane it was normal. This hypothesis was supported by a first-order change in spectrum (apparently  $H^+$ -catalysed) when an alcoholic solution of (V) was mixed with an equal volume of aqueous buffer; at pH 7 the change was very slow, but at pH 5 the time of half-change was 38 min. (Fig. 3). The final spectrum was almost the same as that of (V) in aqueous solution. The curve in cyclohexane passed as nearly through the two isosbestic points as permitted by the usual solvent effect. It is not impossible that this "hydration" is ring fission but the ease of "dehydration" (or re-cyclisation) by mere drying suggests otherwise. Hydration of the carbonyl or thiocarbonyl group could be involved as in diethyl oxomalonate or in ninhydrin. However, both these ketones are hydrated in an environment of electron-withdrawing groups, whereas, the present compounds are hydrated in the presence of electron-releasing groups. It therefore seems that (V), in water, is hydrated across  $C=N$  as suggested by Boon *et al.*<sup>2</sup> for analogous derivatives. Whatever the mechanism, the spectral argument is unaffected. This behaviour was not shared by the isomer (VI) which could be obtained only as a hydrate or alcoholate, so that no direct spectral comparison with the parent pyrimidine was possible.

<sup>5</sup> Brown and Harper, *J.*, 1961, 1298.

<sup>6</sup> Henze, Clegg, and Smart, *J. Org. Chem.*, 1952, 17, 1320.

TABLE I.  
 Ionisation and ultraviolet spectra of pyrimidine derivatives.

Pyrimidine	$pK_a^*$	$\lambda_{max.}$ (log $\epsilon$ ) †	pH
2-Butyl-4-chloro-6-hydroxy-cation	$-0.97 \pm 0.05$	274 (3.75), 227 (3.75)	4.0
anion	$8.25 \pm 0.04$	233 (3.92)	-3.6
5-Butyl-4-chloro-6-hydroxy-cation	$-1.10 \pm 0.05$	267 (3.62), 230 (3.96)	10.8
anion	$8.05 \pm 0.04$ (p.)	274 (3.76), 234 (3.73)	5.0
5-Butyl-4,6-dihydroxy-cation	$-0.54 \pm 0.03$	243 (3.96)	-3.6
anion	$6.24 \pm 0.03$ (p.)	269 (3.73), 237 (3.93)	11.1
2-Butyl-4-hydroxy-6-mercapto-cation	$-1.17 \pm 0.06$	261 (4.13)	3.5
anion	$5.25 \pm 0.04$	256 (4.00)	-2.7
dianion	$12.02 \pm 0.04$	259 (4.03)	8.6
5-Butyl-4-hydroxy-6-mercapto-cation	$-1.08 \pm 0.06$	306 (4.23), 242 (4.04)	2.0
anion	$5.09 \pm 0.06$	282 (3.75), 227 (4.24)	— ‡
dianion	$11.96 \pm 0.05$	304 (4.18), 251 (3.76), 218 (4.11)	— §
2-Butyl-4-hydroxy-6-methylthio-cation	$0.48 \pm 0.05$	262 (3.95), 230 (4.12)	-3.6
anion	$9.39 \pm 0.04$	294 (4.24), 235 (4.21), 222 (4.21)	8.0
5-Butyl-4-hydroxy-6-methylthio-cation	$-1.08 \pm 0.06$	283 (4.02), 240 (4.30)	14.8
anion	$5.09 \pm 0.06$	310 (4.22), 242 (4.00), 217 (4.05)	2.0
dianion	$11.96 \pm 0.05$	282 (3.75), 230 (4.26)	— ‡
2-Butyl-4-hydroxy-6-methylthio-cation	$0.48 \pm 0.05$	303 (4.17), 235 (4.12)	— §
anion	$9.39 \pm 0.04$	270 (3.99), 227 (4.01)	-3.6
5-Butyl-4-hydroxy-6-methylthio-cation	$0.40 \pm 0.04$	300 (4.21), 235 (4.22)	9.0
anion	$9.24 \pm 0.05$	288 (4.09), 240 (4.29), 233 (4.23)	14.0
4-Chloro-6-hydroxy-5-isopropyl-cation	$-0.91 \pm 0.06$	278 (3.99), 236 (4.20)	4.8
anion	$8.11 \pm 0.04$ (p.)	277 (4.03), 240 (4.14)	-2.0
4-Chloro-6-hydroxy-5-methyl-cation	$-1.11 \pm 0.04$	268 (3.78), 223 (4.33)	12.0
anion	$7.77 \pm 0.05$ (p.)	292 (3.94), 233 (4.14)	4.8
5,5-Diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-thio-¶	—	286 (3.99), 238 (3.94)	-2.0
cation	—	279 (3.82), 224 (4.29)	12.0
5,5-Diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-4-oxo-6-thio-cation	$ca. -4 \uparrow \uparrow$	274 (3.75), 234 (3.72)	5.0
5,5-Diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-4-thio-cation	$ca. -4 \uparrow \uparrow$	242 (3.95)	-3.6
1,6-Dihydro-4-methoxy-1-methyl-6-thio- ‡‡	—	270 (3.72), 237 (3.93)	11.1
1,6-Dihydro-1-methyl-4-methylthio-6-oxo- ‡‡	—	272 (3.72), 232 (3.74)	5.0
4,6-Dihydroxy-5-isopropyl-cation	$-0.59 \pm 0.03$	241 (3.96)	-3.6
anion	$6.40 \pm 0.02$ (p.)	267 (3.69), 235 (3.93)	11.1
4,6-Dihydroxy-5-methyl-cation	$-0.51 \pm 0.04$	277 (4.04)	<i>ca.</i> 2.0
anion	$6.01 \pm 0.04$ (p.)	345 (—)	— **
4-Hydroxy-6-mercapto- ‡‡	—	302 (4.04)	-4.6
4-Hydroxy-5-isopropyl-6-mercapto-cation	$-0.66 \pm 0.04$	267 (3.99)	5.8
anion	$5.12 \pm 0.06$	240 (3.85), 224 (3.68)	<i>ca.</i> -6
dianion	$12.30 \pm 0.04$	277 (4.08)	5.0
4-Hydroxy-6-mercapto-5-methyl-cation	$-1.16 \pm 0.05$	310 (4.05), 247 (3.85)	— §
anion	$4.92 \pm 0.05$	310 (4.08), 244 (3.95)	— ‡
dianion	$11.61 \pm 0.05$	312 (4.06), 226 (3.60)	-2.8
4-Hydroxy-5-isopropyl-6-mercapto-cation	$-0.66 \pm 0.04$	303 (4.26), 223 (4.05)	— ‡
anion	$5.12 \pm 0.06$	300 (3.48), 264 (3.79), 236 (4.22)	— ‡
dianion	$11.61 \pm 0.05$	261 (4.11)	3.5
4-Hydroxy-6-mercapto-5-methyl-cation	$-1.16 \pm 0.05$	250 (3.98)	-2.7
anion	$4.92 \pm 0.05$	259 (4.02)	8.6
dianion	$11.61 \pm 0.05$	260 (4.13)	3.5
4-Hydroxy-5-isopropyl-6-mercapto-cation	$-0.51 \pm 0.04$	249 (3.98)	-2.7
anion	$6.01 \pm 0.04$ (p.)	258 (4.03)	8.6
dianion	$11.61 \pm 0.05$	299 (4.20), 250 (3.87), 225 (4.08)	— §
4-Hydroxy-6-mercapto-5-methyl-cation	$-0.66 \pm 0.04$	307 (3.97), 236 (3.96)	2.0
anion	$5.12 \pm 0.06$	291 (3.78), 231 (4.07)	— §
dianion	$12.30 \pm 0.04$	268 (3.88), 229 (3.93)	-2.7
4-Hydroxy-5-isopropyl-6-mercapto-cation	$-0.66 \pm 0.04$	297 (3.97), 233 (4.09)	9.0
anion	$5.12 \pm 0.06$	286 (3.97), 240 (4.19)	15.3
dianion	$11.61 \pm 0.05$	308 (3.99), 235 (3.87), 218 (3.88)	2.0
4-Hydroxy-6-mercapto-5-methyl-cation	$-1.16 \pm 0.05$	302 (4.04), 235 (4.05)	— §
anion	$4.92 \pm 0.05$	266 (3.84), 227 (3.90)	-3.6
dianion	$11.61 \pm 0.05$	297 (3.98), 233 (4.11)	9.0
4-Hydroxy-5-isopropyl-6-mercapto-cation	$-0.66 \pm 0.04$	283 (3.90), 237 (4.14)	14.0

TABLE I.—(Continued.)

Pyrimidine	$pK_a^*$	$\lambda_{max.}$ (log $\epsilon$ ) †	pH
4-Hydroxy-5-methyl-6-methylthio-			
cation	$-0.03 \pm 0.03$	290 (3.97), 237 (4.16)	5.0
anion	$9.10 \pm 0.04$ (p.)	284 (3.98), 237 (3.88)	-2.8
4-Mercapto-6-methoxy-5-methyl-			
cation	$-1.59 \pm 0.06$	277 (3.90), 223 (4.29), 308 (4.10), 277 (3.89), 224 (4.20)	5.0
anion	$7.89 \pm 0.04$ (p.) §§	281 (4.13), 217 (4.29) 286 (4.20), 227 (4.14)	-3.6 11.1

\* Measured at 20° spectrometrically or potentiometrically (p.) at  $m/200$ ; cf. Albert and Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. † In cyclohexane. ‡ In aqueous solution where pH given; inflexions in italics. ‡ In cyclohexane. § In ethanol. ¶ Spectrum of neutral molecule necessarily in buffered 5% ethanolic water. Measured  $pK_a$  of ca. -1 clearly inaccurate. \*\* In dioxan; low solubility makes  $\epsilon$  value unreliable. †† Equilibrium  $pK_a$  (see text) not necessarily comparable with other values. ‡‡ For other spectra see ref. 1. §§ At  $m/400$ .

Moreover, its spectra and very weak basic properties suggested that the cation was at least partly hydrated even at pH -6.

Unlike its methyl derivatives (V) and (VI), 5,5-diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-thiopyrimidine (or tautomer), which has a partly fixed structure, was insufficiently soluble in cyclohexane for its spectrum to be determined. However, in dioxan it showed an even stronger bathochromic shift than did (V), thus suggesting hydration in water and/or a change of predominant tautomer in a different solvent.

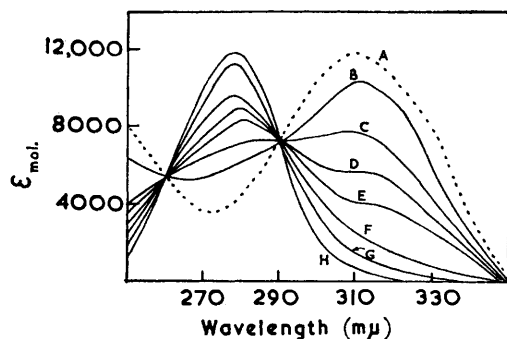


FIG. 3. Ultraviolet absorption of 5,5-diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-4-thiopyrimidine: in cyclohexane (A); in equal volumes of ethanol and aqueous buffer (pH 5.0), recorded after 1 min. (B); 10 min. (C); 30 min. (D); 50 min. (E); 80 min. (F); 110 min. (G); 150 min. (H).

Because 4-hydroxy-6-mercaptopyrimidine was too insoluble to furnish a spectrum in cyclohexane, its 2-butyl derivative (VII;  $R = H$ ,  $R' = Bu$ ) was examined. The alkyl group of this compound is sterically remote from position 5 and should affect the two nitrogen atoms equally. Moreover the spectra in water and alcohol were similar to those of the parent. In cyclohexane it showed a marked hypsochromic displacement suggesting a change in predominant tautomer rather than a change from hydrated to anhydrous molecule which might be reasonably expected (as above) to induce a bathochromic shift. There was, therefore, no reason to think that the parent compound was hydrated in aqueous solution. The spectra of 5-n-butyl-4-hydroxy-6-mercaptopyrimidine, its isomer (VII;  $R = H$ ,  $R' = Bu$ ), and its methyl homologue (VII;  $R = Me$ ,  $R' = H$ ) were quite similar in all solvents indicating that even a n-butyl group at position 5 caused no appreciable steric hindrance to involvement of the position in tautomerism. On the other hand, the spectrum of its 5-isopropyl homologue showed a small but definite abnormality especially in alcohol (Fig. 2), suggesting some interference by this bulkier group.

Thus, within the limitations of this method of spectral comparison in a complicated system, the predominance of structure (II) in an aqueous or alcoholic solution of 4-hydroxy-6-mercaptopyrimidine is indicated without excluding a contribution from (I) or (III). This conclusion is compatible with the strong carbonyl and thiocarbonyl bands found<sup>1</sup> in the infrared spectrum of the solid.

## EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff. Spectra were recorded on a Shimadzu spectrophotometer: peaks were checked on a manual Uvispek instrument.

*5,5-Diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-oxopyrimidine*.—Acetamidine acetate (40.5 g.), diethyl diethylmalonate (65.2 g.), and ethanolic sodium ethoxide (340 ml.; sodium, 15.7 g.), were heated in an autoclave at 110–120° for 20 hr. The cooled mixture was neutralised with hydrochloric acid and set aside at 0°. The solid crystallised from ethanol giving the *oxo-pyrimidine ethanolate* (34 g.), m. p. 132–135° (Found: C, 57.6; H, 8.65; N, 12.2.  $C_9H_{14}N_2O_2 \cdot C_2H_6O$  requires C, 57.9; H, 8.8; N, 12.3%). The ethanolate and ethereal hydrogen chloride gave the hydrochloride, m. p. 251° (decomp.) (lit.,<sup>7</sup> 253°). It was also obtained (in poor yield) by condensing diethylmalondiamide (6.9 g.), acetyl chloride (23 g.), and acetic acid (2.9 ml.).

*5,5-Diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-4,6-dioxypyrimidine*.—The above ethanolate (0.5 g.) and methyl iodide (5 ml.) were heated for 1 hr. at 100°. The solid was washed with ethyl acetate and recrystallised from acetic acid to give the *dioxypyrimidine hydriodide* (0.35 g.), m. p. 190–192° (decomp.) (Found: N, 8.5.  $C_{10}H_{17}IN_2O_2$  requires N, 8.65%). An aqueous solution of the hydriodide was adjusted to pH 7 and extracted with chloroform. Evaporation gave the base *hydrate*, m. p. 128–129° (from light petroleum) (Found: C, 56.1; H, 8.4; N, 12.8.  $C_{10}H_{18}N_2O_3$  requires C, 56.05; H, 8.5; N, 13.1%).

*Reaction of Diethyl Diethylmalonate with Formamidine*.—Diethyl diethylmalonate (45.4 g.) and formamidine hydrochloride (16.1 g.) were added to methanolic sodium methoxide (200 ml.; sodium, 9.2 g.) at 0°, stirred at 30–40° for 20 hr., and then refluxed for 2 hr. The cooled solution was acidified, and the residue from evaporation washed with water and crystallised from alcohol to give diethylmalonodiamide (17.5 g.), m. p. 225–226° (lit.,<sup>8</sup> 224°) (Found: C, 53.0; H, 9.0; N, 17.9. Calc. for  $C_9H_{14}N_2O_2$ : C, 53.1; H, 8.9; N, 17.7%).

*3-Carbamoyl-3-cyanopentane*.—This has been made<sup>9</sup> in 33% yield from cyanoacetamide by two successive monoethylations. Use of twice the ratio of reagents to starting material directly gave the product, m. p. 121° (lit.,<sup>9</sup> 121–122°) in 70% yield (Found: N, 19.7. Calc. for  $C_7H_{12}N_2O$ : N, 20.0%).

*3-Cyano-3-methylcarbamoylpentane*.—In the same way *N*-methylcyanoacetamide<sup>10</sup> gave 55% of the *methylcarbamoyl* compound, m. p. 99–100° (from water) (Found: C, 62.4; H, 9.3; N, 18.4.  $C_8H_{14}N_2O$  requires C, 62.3; H, 9.15; N, 18.2%).

*3-Methylcarbamoyl-3-thiocarbamoylpentane*.—Ethanolic sodium ethoxide (50 ml.; sodium, 1.2 g.) was saturated with hydrogen sulphide at –20°. *3-Cyano-3-methylcarbamoylpentane* (7.7 g.) was added, and the mixture heated at 140–150° for 20 hr. The neutralised solution was evaporated to dryness and the residue extracted with hot benzene. Removal of the solvent and recrystallisation from water gave the *thioamide* (5.3 g.), m. p. 145–146° (Found: C, 51.1; H, 8.8; N, 14.9.  $C_8H_{16}N_2OS$  requires C, 51.05; H, 8.6; N, 14.9%).

*3-Carbamoyl-3-N-methylthiocarbamoylpentane*.—*3-Cyano-3-methylcarbamoylpentane* (15.4 g.) and phosphorus pentasulphide (33.5 g.) in xylene (70 ml.) were refluxed for 1.5 hr. and evaporated to dryness. Extraction with hexane and concentration gave *3-cyano-3-N-methylthiocarbamoylpentane* (13.2 g.), m. p. 78–79° (from hexane) (Found: C, 56.4; H, 8.3; N, 16.4.  $C_8H_{14}N_2S$  requires C, 56.45; H, 8.3; N, 16.5%). This nitrile (12.8 g.) and sulphuric acid (50 ml.) were heated at 98° for 2.5 hr. and poured on ice. Ether extraction and evaporation gave *3-carbamoyl-3-N-methylthiocarbamoylpentane* (11.8 g.), m. p. 110–111° (from benzene) (Found: C, 51.2; H, 8.7; N, 15.05.  $C_8H_{16}N_2OS$  requires C, 51.05; H, 8.6; N, 14.9%).

Similar treatment of *3-cyano-3-methylcarbamoylpentane* gave *3-carbamoyl-3-methylcarbamoylpentane*, m. p. 170–171° (from benzene) (Found: C, 55.5; H, 9.45; N, 16.4.  $C_8H_{16}N_2O_2$  requires C, 55.8; H, 9.4; N, 16.3%).

*3-Carbamoyl-3-thiocarbamoylpentane*.—*3-Cyano-3-carbamoylpentane* (21.0 g.) phosphorus pentasulphide (50.0 g.), and toluene (300 ml.) were refluxed for 1.5 hr. Decantation and concentration of the solution gave *3-cyano-3-thiocarbamoylpentane* (15.4 g.), m. p. 131–132° (from water) (Found: C, 54.0; H, 7.8; N, 17.8.  $C_7H_{12}N_2S$  requires C, 53.8; H, 7.7; N, 17.9%).

This nitrile (4.1 g.) and concentrated sulphuric acid (20 ml.) were set aside at 25° for 1 day and then warmed to ca. 70° for 20 min. The cooled mixture was poured on ice and extracted

<sup>7</sup> Freund and Fleischer, *Annalen*, 1911, **379**, 27.

<sup>8</sup> Fischer and Diltney, *Ber.*, 1902, **35**, 844.

<sup>9</sup> Doerge and Wilson, *J. Amer. Pharm. Assoc. (Sci. Edn.)*, 1951, **40**, 407.

<sup>10</sup> Naik and Bhat, *Quart. J. Indian Chem. Soc.*, 1927, **4**, 547; *Chem. Zentr.*, 1928, I, 1759.

with ether ( $\times 5$ ). Removal of solvent gave 3-carbamoyl-3-thiocarbamoylpentane (3.4 g.), m. p. 136° (from ethanol) (Found: C, 48.3; H, 8.1; N, 15.9.  $C_7H_{14}N_2OS$  requires C, 48.3; H, 8.1; N, 16.1%). It was also made in poor yield by the action of alcoholic sodium hydrogen sulphide on 3-carbamoyl-3-cyanopentane.

5,5-Diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-4-oxo-6-thiopyrimidine.—3-Carbamoyl-3-N-methylthiocarbamoylpentane (2.8 g.), acetyl chloride (7.1 g.), and acetic acid (0.9 ml.) were heated at 100° for 1 hr. in a sealed tube. Addition of benzene to the oily residue from evaporation gave a crude hydrochloride. Its solution in water was neutralised and extracted with ether. Removal of ether and recrystallisation from alcohol, gave the pyrimidine hydrate, m. p. 142.5—143.5° (Found: C, 52.0; H, 8.0; N, 12.2.  $C_{10}H_{16}N_2OS \cdot H_2O$  requires C, 52.2; H, 7.9; N, 12.2%).

5,5-Diethyl-1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-4-thiopyrimidine.—Similar treatment of 3-methylcarbamoyl-3-thiocarbamoylpentane gave a hydrochloride, which on trituration with water gave the base, m. p. 151—152° (from ethanol) (Found: C, 56.4; H, 7.5; N, 12.9.  $C_{10}H_{16}N_2OS$  requires C, 56.6; H, 7.6; N, 13.2%).

5,5-Diethyl-4,5-dihydro-6-hydroxy-2-methyl-4-thiopyrimidine (or Tautomer).—3-Carbamoyl-3-thiocarbamoylpentane gave a hydrochloride as above. The base ethanolate (from ethanol) softened at 130° and decomposed at 188—192° (Found: C, 54.1; H, 8.2.  $C_{11}H_{20}N_2O_2S$  requires C, 54.3; H, 8.3%). When dried at 140—145° *in vacuo* it gave the base, m. p. 192—195° (decomp.) (Found: N, 14.1.  $C_9H_{14}N_2OS$  requires N, 14.1%).

5-Alkyl-4,6-dihydroxypyrimidines (Table 2).—Formamide hydrochloride (42 g.) and diethyl alkylmalonate (0.5 mol.) were added successively to ethanolic sodium ethoxide (370 ml.; sodium, 23 g.) at ca. 25°. After stirring for 16 hr., the mixture was refluxed for 1 hr., cooled, and filtered. The solid and the residue from evaporating the filtrate were dissolved in water and acidified to pH ca. 2. The precipitated pyrimidine was crystallised from ethanol.

2- or 5-Alkyl-4,6-dichloropyrimidines (Table 2).—The 2- or 5-alkyl-4,6-dihydroxypyrimidine (0.2 mol.) was refluxed with phosphoryl chloride (180 ml.) for 40 min. The excess of phosphoryl chloride was distilled off *in vacuo* and the residue was poured on crushed ice. Ether extraction and distillation gave the dichloropyrimidine.

TABLE 2.  
2- and 5-Alkylpyrimidines.

Pyrimidine	M. p. or B. p.	Yield (%)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
4,6-Dihydroxy-5-isopropyl-	> 310°	52	54.7	6.3	18.2	$C_7H_{10}N_2O_2$	54.5	6.5	18.2
5-Butyl-4,6-dihydroxy-	291—293	99	57.3	7.3	16.65	$C_8H_{12}N_2O_2$	57.1	7.1	16.7
4,6-Dichloro-5-isopropyl-	112/71 mm.	81	44.4	4.4	—	$C_7H_8Cl_2N_2$	44.0	4.2	—
5-Butyl-4,6-dichloro-	136/71 mm.	77	46.3	5.1	—	$C_8H_{10}Cl_2N_2$	46.8	4.9	13.7
2-Isomer	108/62 mm.	76	—	—	13.6				
4-Chloro-6-hydroxy- 5-methyl-	202—203	77	41.6	3.55	19.5	$C_5H_5ClN_2O$	41.6	3.5	19.4
5-Isopropyl homologue	174—175	90	48.55	5.2	16.2	$C_7H_9ClN_2O$	48.7	5.2	16.2
5-Butyl-4-chloro-6-hydroxy-	140	86	51.5	5.9	14.9	$C_8H_{11}ClN_2O$	51.5	5.95	15.0
2-Isomer	121—122	58	—	—	15.05				
4-Hydroxy-6-mercapto- 5-methyl	ca. 200	84	42.0	4.2	19.5	$C_5H_6N_2OS$	42.25	4.3	19.7
4-Hydroxy-5-isopropyl- 6-mercapto-	272—273	50	49.5	5.7	16.2	$C_7H_{10}N_2OS$	49.4	5.9	16.5
5-Butyl-4-hydroxy- 6-mercapto-	207—209	76	51.8	6.5	15.2	$C_8H_{12}N_2OS$	52.2	6.6	15.2
2-Isomer	238—240	67	52.1	6.6	—				
4-Hydroxy-5-methyl- 6-methylthio-	236—237	77	46.0	4.95	17.7	$C_6H_8N_2OS$	46.15	5.2	17.9
5-Butyl-4-hydroxy- 6-methylthio-	219—220	98	—	—	14.1	$C_9H_{14}N_2OS$	54.5	7.1	14.1
2-Isomer	126	93	54.55	7.1	14.0				

2- or 5-Alkyl-4-chloro-6-hydroxypyrimidines (Table 2).—The dichloropyrimidine (0.1 mole) and 1.25N-sodium hydroxide (500 ml.) were refluxed until homogenous (2—3 hr.). Acidification of the cooled solution gave the chlorohydroxypyrimidine, which recrystallised from water.

2- or 5-Alkyl-4-hydroxy-6-mercaptopyrimidines (Table 2).—The chlorohydroxypyrimidine (0.02 mol.) and sodium hydrogen sulphide (0.06 mol.) in ethanol (30 ml.) were heated for 5 hr.

at 140—150°. The cooled solution was acidified to pH 2—3, and the resulting mercaptopyrimidine recrystallised from ethanol or water.

2- or 5-Alkyl-4-hydroxy-6-methylthiopyrimidines (Table 2).—The mercaptopyrimidine (0.01 mol.), methyl iodide (1.5 g.), and sodium hydroxide (0.8 g.) in water (50 ml.) were shaken at 25° for 2 hr. The solution was acidified and the resulting sulphide recrystallised from water or ethanol.

4-Mercapto-6-methoxy-5-methylpyrimidine.<sup>11</sup>—4,6-Dichloro-5-methylpyrimidine<sup>11</sup> (10.0 g.) was refluxed with methanolic sodium methoxide (180 ml.; sodium, 1.4 g.). The residue from evaporation was dissolved in water and extracted with ether. Distillation (40°/0.1 mm.) gave crude 4-chloro-6-methoxy-5-methylpyrimidine (7.6 g.). This compound (6.0 g.) and potassium hydrogen sulphide from potassium hydroxide (7.1 g.) in ethanol (60 ml.) were heated for 2 hr. at 130—140°. The acidified solution yielded the *mercapto-compound* (3.5 g.), m. p. 220—222° (from ethanol) (Found: C, 45.9; H, 5.15; N, 17.9. C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>OS requires C, 46.15; H, 5.2; N, 17.9%).

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<sup>11</sup> Basford, Curd, Rose, Openshaw, Hull, and Todd, Brit. Pat. 590,706 (1947) (*Chem. Abs.*, 1948, **42**, 228).

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