## 251. *Pyrimidine Reactions. Part III.*[1] *The Methylation Product of 4-Amino-6-hydroxypyrimidine, and Related Compounds.*

By D. J. Brown and J. S. Harper.

Methylation of 4-amino-6-hydroxypyrimidine is rigorously proved to occur at $N_{(1)}$, and a substance recently described by others as the 3-methyl derivative is shown to have rearranged to 4-hydroxy-6-methylamino-pyrimidine during preparation. Derived purines and pteridines are described. 4-Hydroxy-6-methylthio- and 4-chloro-6-hydroxy-pyrimidine are shown to be methylated also on the ring-nitrogen atom that stands α to the hydroxy-group, although a little methoxy-derivative is also formed in the first case. A variety of the $N_{(4)}$- and *O*-methylated derivatives of 4-amino-6-hydroxypyrimidine, of related compounds, and of dithiouracil are recorded. The ionisation constants are discussed.

Although a great many methylated pyrimidines bearing two tautomeric groups in positions 2 and 4 are known, relatively few of the analogous 4,6-disubstituted derivatives have been made. This paper mainly describes methylation products theoretically derivable from 4-amino-6-hydroxypyrimidine (I; R = $NH_2$) and examples of their use in preparing purines and pteridines required in connexion with mammalian xanthine oxidase studies.[2]

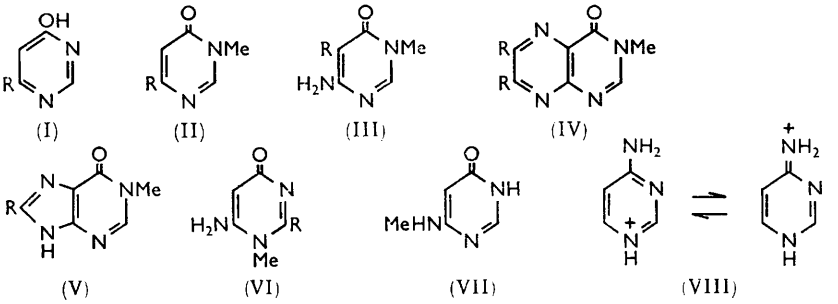
Treatment of 4-amino-6-hydroxypyrimidine with dimethyl sulphate and alkali gives a single methylated derivative formulated[3] as 4-amino-1,6-dihydro-1-methyl-6-oxo-pyrimidine (II; R = $NH_2$) because it can be also made by desulphurising its 2-methylthio-derivative. However, this evidence is inadmissible because the structure of the methyl-thio-derivative is in fact unproved.[4] Moreover, contrary to published data, the 3-methylated isomer of (II; R = $NH_2$) is still unknown (see below) and cannot therefore be invoked in a process of elimination. The structure of the methylation product as (II; R = $NH_2$) was therefore proved as follows: its 5-nitro-derivative (III; R = $NO_2$) was catalytically reduced to 4,5-diamino-1,6-dihydro-1-methyl-6-oxopyrimidine (III; R = $NH_2$), and condensation with glyoxal gave a pteridine identified by direct comparison as 3,4-dihydro-3-methyl-4-oxopteridine[5] (IV; R = H). The 3,6,7-trimethyl analogue (IV; R = Me) was similarly made, and fusion of the diamino-derivative (III; R = $NH_2$) with urea and thiourea then gave 1,6-dihydro-8-hydroxy-1-methyl-6-oxopurine (V; R = OH) and its 8-mercapto-analogue (V; R = SH) respectively. A related synthesis of 6,8-dihydroxy-9-methylpurine (previously made indirectly by Fischer and Ach[6]) is also described below.

6-Amino-1,4-dihydro-1-methyl-4-oxopyrimidine (VI; R = H), isomeric with the methylation product of 4-amino-6-hydroxypyrimidine, has been assumed[3] as the structure of the product obtained by desulphurising the 2-mercapto-derivative[7] (VI; R = SH) with Raney nickel. However, the close similarity in ultraviolet spectra[3] of the desulphurisation product and its isomer (II; R = $NH_2$) is puzzling if the former is really represented by (VI; R = H). On the other hand, if the possible rearrangement[8] to (VII) had occurred, the spectral coincidence would be reasonable. Accordingly, the desulphurisation product was prepared, and direct comparison with an authentic specimen[9] of (VII), showed them identical. Since the structure of the thiol (VI; R = SH) has been indirectly proved by Elion,[10] and moreover its *S*-methylated derivative (VI; R = SMe) shows no acidic properties, rearrangement must have taken place during desulphurisation.

[1] Part II, *J.*, 1959, 3647.
[2] Bergmann, Kwientny, Levin, and Brown, *J. Amer. Chem. Soc.*, 1960, **82**, 598.
[3] Pfleiderer and Liedek, *Annalen*, 1958, **612**, 163.
[4] Johns and Hendrix, *J. Biol. Chem.*, 1915, **20**, 153.
[5] Albert, Brown, and Wood, *J.*, 1956, 2066.
[6] Fischer and Ach, *Ber.*, 1899, **32**, 250.
[7] Traube and Winter, *Arch. Pharm.*, 1906, **244**, 11; through *Chem. Zentr.*, 1906, I, 1336.
[8] Brown, *Nature*, 1961, in the press, and bibliography therein.
[9] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[10] Elion, in the Ciba Symposium, "The Chemistry and Biology of Purines," Churchill Ltd., London, 1957, p. 39.

Attempted gentle desulphurisation of the sulphide (VI; R = SMe) in ethanol failed to yield the missing isomer (VI; R = H).

The syntheses of other methylated analogues of the pyrimidines (I) and (II) were approached through 4,6-dichloropyrimidine.[11] Partial hydrolysis in acid gave 4-chloro-6-hydroxypyrimidine (I; R = Cl) which has been previously made only indirectly. With diazomethane this gave two products. The minor one was identical with the recently described [12] 4-chloro-6-methoxypyrimidine. The major one was identified as 4-chloro-1,6-dihydro-1-methyl-6-oxopyrimidine (II; R = Cl) when it was converted by ammonia into the amine (II; R = $NH_2$). Mono- and di-methylamine likewise gave analogues (II; R = NHMe and $NMe_2$). Methylation of 4-hydroxy-6-methylthiopyrimidine [12] (I; R = SMe) gave a single *N*-methyl derivative shown to be 1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine (II; R = SMe) by conversion into the above base (II; R = $NMe_2$). Preparation by conventional routes of other methylated derivatives of the amine (I; R = $NH_2$) starting from 4,6-dichloropyrimidine or 4-chloro-6-hydroxypyrimidine (I; R = Cl), and of related and derived compounds, is described in the Experimental section. Several known compounds appear therein because an improved route to each has been used, and some new methylated derivatives of dithiouracil are also included. Among these is 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dithiopyrimidine, prepared by vigorous thiation of *NN'*-dimethyluracil. Although much gentler conditions have been claimed by Klingsberg and Papa [13] to yield this dithio-derivative, repetition revealed that their product had the analysis, m. p., and spectrum of the known [14] monothiated, 1,3-dimethyl-4-thiouracil.




The ionisation constants recorded in the Table provide some insight into factors affecting basic and acidic strength in pyrimidines. The basic nature of pyrimidine, whose p$K_a$ 1·3 is strikingly lower [15] than that of pyridine (5·2), is usually assumed to result from a depletion of π-electrons by the second nitrogen atom. If this is true, 3-nitropyridine which contains a similarly placed and strongly electron-attracting centre, should approximate to pyrimidine in p$K_a$. In fact, the value now determined (0·8) supports this hypothesis. Insertion of a 4-amino-group into pyrimidine might be expected to increase basic strength by only one unit of p$K_a$, as is seen in passing from aniline to the diaminobenzenes, but 4-aminopyrimidine is a much stronger base [15] (p$K_a$ 5·7) because it has a strongly resonance-stabilised cation (VIII). The base-weakening effect of an electron-withdrawing group on 4-aminopyrimidine is seen in 4-amino-6-chloropyrimidine (2·1) and its analogues, and in comparing 4,6-diaminopyrimidine (6·0) with its 5-bromo-derivative (4·2). The normal small base-strengthening effect of an electron-releasing group applies in 4,6-diaminopyrimidine and in its extranuclear methylated derivatives, but the introduction of an oxo- or " hydroxy "-group (always in the oxo-form,[16]) at once destroys the basis of 4-aminopyrimidine's basic strength by rearranging the double bonds to exclude a cation

[11] Hull, *J.*, 1951, 2214.
[12] Isbecque, Promel, Quinaux, and Martin, *Helv. Chim. Acta*, 1959, **42**, 1317.
[13] Klingsberg and Papa, U.S.P. 2,676,969/1954.
[14] Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2138.
[15] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[16] Brown, Hoerger, and Mason, *J.*, 1955, 211.

| Pyrimidine derivative | $pK_a$,[a] spread (in parentheses), and concn. ($10^{-3}$M) (in square brackets): acidic | basic |
|---|---|---|
| 4-Amino-6-hydroxy- | 10·05 (±0·03) [10] | 1·36 (±0·04) [50] |
| 4-Amino-6-methoxy- | — | 4·02 (±0·06) [5] |
| 4-Hydroxy-6-methylamino-[b] | 10·47 (±0·02) [5] | <1·7 |
| 4-Dimethylamino-6-hydroxy- | 10·42 (±0·03) [50] | 1·22 (±0·03) [50] |
| 4-Methoxy-6-methylamino- | — | 4·23 (±0·03) [5] |
| 4-Dimethylamino-6-methoxy- | — | 4·29 (±0·04) [5] |
| 4-Amino-1,6-dihydro-1-methyl-6-oxo-[c] | — | 0·98 (±0·03) [50] |
| 1,6-Dihydro-1-methyl-4-methylamino-6-oxo- | — | <1 |
| 1,6-Dihydro-4-dimethylamino-1-methyl-6-oxo- | — | <1 |
| 6-Amino-1-methyl-2-thiouracil | 9·84 (±0·05)[d] | 0·0 (±0·08)[d] |
| 4-Hydroxy-6-mercapto- | 4·33 (±0·03) [5] | — |
| | 10·52 (±0·06) [5] | |
| 4-Hydroxy-6-methylthio- | 8·52 (±0·01) [5] | — |
| Di(4-hydroxypyrimidin-6-yl) sulphide | 7·20 (±0·02) [2·5] | — |
| | 8·48 (±0·02) [2·5] | |
| 4-Amino-6-chloro- | — | 2·10 (±0·02) [5] |
| 4-Chloro-6-methylamino- | — | 2·24 (±0·03) [5] |
| 4-Chloro-6-dimethylamino- | — | 2·42 (±0·05) [5] |
| 4-Chloro-6-hydroxy- | 7·43 (±0·03) [2] | — |
| 4,6-Diamino- | — | 6·01 (±0·04) [2] |
| 4-Amino-6-methylamino- | — | 6·32[e] |
| 4,6-Bismethylamino- | — | 6·39 (±0·05) [50] |
| 4-Dimethylamino-6-methylamino- | — | 6·39 (±0·03) [5] |
| 4,6-Bisdimethylamino- | — | 6·36 (±0·02) [5] |
| 4,6-Diamino-5-bromo- | — | 4·22 (±0·02) [2·5] |
| 4,5-Diamino-1,6-dihydro-1-methyl-6-oxo- | — | 3·46 (±0·02) [20] |
| 2,4-Bismethylthio-[b] | — | — |
| 1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dithio-[b] | — | — |
| 1-Methyldithiouracil[b] | 7·47 (±0·05) [0·5] | — |
| 1,2,3,4-Tetrahydro-1,3-dimethyl-2-oxo-4-thio-[b] | — | — |
| *Other compounds* | | |
| 1,6-Dihydro-8-hydroxy-1-methyl-6-oxopurine[b] | 8·52 (±0·02) [2·5] | <2 |
| | 11·83 (±0·04) [2·5] | |
| 6,8-Dihydroxy-9-methylpurine[b] | 8·31 (±0·01) [5] | <1·5 |
| | 11·74 (±0·04) [5] | |
| 3,4-Dihydro-3,6,7-trimethyl-4-oxopteridine[b] | — | −0·05 (±0·05) |
| 3-Nitropyridine[f] | — | 0·77 (±0·04) [50] |

[a] Determined by potentiometric titration in water at 20° (cf. Albert and Phillips, *J.*, 1956, 1294). [b] Ultraviolet spectra in Experimental section. [c] Light absorption as neutral molecule at pH 4·8, $\lambda_{max.}$ 257, 216 (log ε 3·80, 4·54). [d] Spectrophotometric determination. [e] From Brown and Jacobsen, *J.*, 1960, 1978. [f] Prepared as by den Hertog and Overhoff, *Rec. Trav. chim.*, 1930, **49**, 552. Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4871, gives $pK_a$ 0·81 at 25°.

stabilised as is (VIII). Thus 4-amino-6-hydroxypyrimidine ($pK_a$ 1·4) and its 1-methyl derivative have basic strengths of the order of pyrimidine. Naturally, when the "hydroxy"-configuration is preserved by *O*-methylation, basic strength does not suffer in this way, so that 4-amino-6-methoxypyrimidine and its analogues have $pK_a$ values above 4.

The acidic strength of 4-hydroxypyrimidine ($pK_a$ 8·6) is increased as usual by the electron-withdrawing chloro-group (4-chloro-6-hydroxypyrimidine; $pK_a$ 7·4), and weakened by the electron-releasing amino- or dimethylamino-group (4-amino-6-hydroxypyrimidine; $pK_a$ 10·0). The acidic values for di-(4-hydroxypyrimidin-6-yl) sulphide (7·2 and 8·5) are interesting in that the equivalent ionising centres are neither far enough apart in space to give the same figure, nor yet close enough for the formation of the first anion to affect profoundly the second figure.

## Experimental

Analyses are by Dr. J. E. Fildes and her staff.

*4-Amino-1,6-dihydro-1-methyl-5-nitro-6-oxopyrimidine.*—Nitric acid (*d* 1·5; 27 ml.) was slowly added with stirring to 4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine[3] (18·2 g.) dissolved in concentrated sulphuric acid (55 ml.), kept at 35—40° during the addition and for a further 30 min. The mixture was poured on ice (400 g.), and the solid (20·8 g.) recrystallised

from water (90 parts), giving the *nitro-compound*, m. p. 184° (Found: C, 35·3; H, 3·4. $C_5H_6N_4O_3$ requires C, 35·3; H, 3·55%).

*4,5-Diamino-1,6-dihydro-1-methyl-6-oxopyrimidine.*—The above nitro-compound (18·3 g.), suspended in methanol (500 ml.), was hydrogenated over Raney nickel. The catalyst was filtered off and extracted with boiling water (50 ml.). The residue from evaporation of the combined filtrates was twice recrystallised (with concentration) from ethanol (25 parts), giving the *diamine* (7 g.), m. p. 193° (Found: N, 40·0. $C_5H_8N_4O$ requires N, 40·0%).

*3,4-Dihydro-3-methyl-4-oxopteridine.*—The pyrimidine-diamine (0·25 g.) was refluxed for 30 min. with polygloxal (0·25 g.) in methanol (5 ml.). After removal of solvent and successive recrystallisation from water and ethanol, the material was identical (mixed m. p. and chromatography) with the authentic [5] pteridine.

*3,4-Dihydro-3,6,7-trimethyl-4-oxopteridine.*—The diamine (0·5 g.), biacetyl (0·5 g.), and water (1 ml.) were heated at 95° for 30 min., then evaporated to dryness. Recrystallisation from ethanol (25 parts) gave the *oxopteridine*, m. p. 241° (Found: C, 56·8; H, 5·3; N, 29·4. $C_9H_{10}N_4O$ requires C, 56·8; H, 5·3; N, 29·45%), $\lambda_{max.}$ (at pH 7) 312, 282sh, 238 (log ε 3·89, 3·67, 4·13).

*1,6-Dihydro-8-hydroxy(and -mercapto)-1-methyl-6-oxopurine.*—A mixture of the diamine (0·5 g.) and urea (0·5 g.) was fused at 175° for 5 min. The residue was adjusted to pH 5—6 during recrystallisation from water (125 parts), to give the *hydroxypurine* (0·4 g.), m. p. *ca.* 415° (Found, for material dried at 170°: N, 33·55. $C_6H_6N_4O_2$ requires N, 33·7%). Light absorption as monoanion at pH 10·18, $\lambda_{max.}$ 274 (log ε 4·11); as neutral molecule at pH 4·7, $\lambda_{max.}$ 259 (log ε 4·10).

Made similarly with thiourea at 210°, and twice reprecipitated with acetic acid from warm dilute soda, the *mercapto-analogue* (0·48 g.) did not melt below 360° (Found: C, 39·8; H, 3·5; N, 30·6. $C_6H_6N_4OS$ requires C, 39·55; H, 3·3; N, 30·75%).

*6,8-Dihydroxy-9-methylpurine.*—5-Amino-4-hydroxy-6-methylaminopyrimidine [9] was fused with urea as for the above hydroxypurine. The product (80%), recrystallised from water, did not melt below 360° and corresponded to Fischer and Ach's product [6] in solubilities (Found: N, 33·5. Calc. for $C_6H_6N_4O_2$: N, 33·7%). Light absorption as monoanion at pH 9·94, $\lambda_{max.}$ 264 (log ε 4·12); as neutral molecule at pH 4·7, $\lambda_{max.}$ 259 (log ε 4·12).

*4-Hydroxy-6-methylaminopyrimidine.*—Desulphurisation [3] of 6-amino-1-methyl-2-thiouracil [7] gave the product of m. p. 251°, undepressed on admixture with 4-hydroxy-6-methylaminopyrimidine [9] (Found: C, 47·75; H, 5·8; N, 33·4. Calc. for $C_5H_7N_3O$: C, 48·0; H, 5·65; N, 33·55%). The specimens gave identical paper chromatograms in each of three solvents and agreed in ultraviolet spectrum as neutral molecules in water at pH 4·8 ($\lambda_{max.}$ 261, 219; log ε 4·06, 4·40).

*6-Amino-1,4-dihydro-1-methyl-2-methylthio-4-oxopyrimidine.*—6-Amino-1-methyl-2-thiouracil [7] (0·8 g.) in N-potassium hydroxide (5·5 ml.) was shaken with methyl iodide (0·4 ml.) for 20 min. The *methylthio-derivative* (0·6 g.), after recrystallisation from water (10 ml.), had m. p. 272° (decomp.) (Found: C, 42·2; H, 5·35; N, 24·5. $C_6H_9N_3OS$ requires C, 42·1; H, 5·3; N, 24·55%). It was insoluble in aqueous sodium hydroxide.

*4-Chloro-6-hydroxypyrimidine.*—4,6-Dichloropyrimidine [11] (38·5 g.) was stirred on the steam-bath for 1 hr. with 3N-hydrochloric acid (510 ml.). The mixture was adjusted to pH 9—10 with ammonia (*d* 0·91; *ca.* 170 ml.) and treated with carbon and kieselguhr. The filtrate was acidified to pH 2—3, to give the chlorohydroxypyrimidine (21 g.), which, recrystallised from ethanol (12 parts), had m. p. 192—193° (lit.,[12] 192—193°) (Found: C, 36·9; H, 2·4; N, 21·5. Calc. for $C_4H_3ClN_2O$: C, 36·8; H, 2·3; N, 21·5%).

*4-Chloro-1,6-dihydro-1-methyl-6-oxopyrimidine.*—4-Chloro-6-hydroxypyrimidine (27·2 g.) was added slowly to ethereal diazomethane (from 100 g. of nitrosomethylurea). Next morning, the residue from evaporation was twice recrystallised from light petroleum (b. p. 80—100°; 3 l. and 1·1 l.) giving the *1-methylpyrimidine* (28%), m. p. 87—88° (Found: N, 19·3. $C_5H_5ClN_2O$ requires N, 19·4%). Distillation of the mother-liquors from the first recrystallisation gave an oily residue which was dissolved in ether and treated with carbon; the ether was allowed to evaporate in air. After several days, the solid was removed and the oil fractionally distilled, to give 4-chloro-6-methoxypyrimidine (2·6%), b. p. 80° (18 mm.). The ultraviolet spectrum and m. p. (29°) agreed with published figures.[12]

The 1-methyl derivative (1 g.) and 7% ethanolic ammonia (6 ml.) were heated at 140° for 2 hr. Evaporation and removal of ammonium chloride by trituration with water (2 ml.) gave

4-amino-1,6-dihydro-1-methyl-6-oxopyrimidine (0·3 g.), identified by mixed m. p. and paper chromatography.

1,6-*Dihydro*-1-*methyl*-4-*methylamino*- *and* 4-*Dimethylamino*-1,6-*dihydro*-1-*methyl*-6-*oxopyrimidine*.—4-Chloro-1,6-dihydro-1-methyl-6-oxopyrimidine (1 g.) and 33% w/w ethanolic methylamine (4 ml.) were kept at 25° for 24 hr. The residue after evaporation was added to methanol (10 ml.) with which sodium (0·14 g.) had reacted. The solution was reduced to 10 ml. *in vacuo* to remove the excess of amine and adjusted to pH 3—4 with hydrochloric acid. The residue after evaporation was extracted with boiling isobutyl methyl ketone (2 × 15 ml.) and treated with carbon. The *methylamino-derivative* (0·3 g.), when recrystallised from the ketone, had m. p. 187—188° (Found: C, 51·9; H, 6·6; N, 30·1. $C_6H_9N_3O$ requires C, 51·8; H, 6·5; N, 30·2%). Made similarly, the crude *dimethylamino-analogue* (0·5 g.) was sublimed *in vacuo*, and recrystallised from ethyl acetate, and then had m. p. 156—157° (Found: C, 55·35; H, 7·3; N, 27·4. $C_7H_{11}N_3O$ requires C, 54·9; H, 7·25; N, 27·4%). It was also made in small yield by treating 1,6-dihydro-1-methyl-4-methylthio-6-oxopyrimidine with dimethylamine at 110°, and identified by mixed m. p. and chromatography.

1,6-*Dihydro*-1-*methyl*-4-*methylthio*-6-*oxopyrimidine*.—A shaken solution of 4-hydroxy-6-methylthiopyrimidine [12] (3·25 g.) in 2N-potassium hydroxide (13 ml.) at 20° was treated with dimethyl sulphate (5 × 0·5 ml.) at 10 min. intervals, then shaken for 90 min. longer. Refrigeration gave a solid (3·3 g.) which was twice recrystallised from 15 ml. of a 1 : 1 mixture of 0·1M-sodium carbonate and 0·1M-sodium hydrogen carbonate, to remove a little starting material. The *oxopyrimidine*, crystallised from ethanol (13 parts), had m. p. 172—175° (Found: C, 45·8; H, 4·95; N, 17·9. $C_6H_8N_2OS$ requires C, 46·15; H, 5·15; N, 17·95%).

4-*Amino*-6-*chloropyrimidine*.—4,6-Dichloropyrimidine (16 g.) and 8% ethanolic ammonia (72 ml.) were heated at 100° for 1 hr. Refrigeration, and recrystallisation of the resulting solid from water (500 ml.), gave 60% of aminochloropyrimidine, m. p. 204—205° (lit.,[17] 215°) (Found: C, 36·8; H, 3·05; N, 32·45. Calc. for C $H_4ClN_3$: C, 37·05; H, 3·1; N, 32·4%).

4-*Amino*-6-*methoxypyrimidine*.—A suspension of the preceding chloro-amine (2·6 g.) in methanolic sodium methoxide (0·7 g. of sodium) was stirred under reflux for 90 min. Carbon dioxide was then led in, and the whole evaporated to dryness. Sublimation (85°/0·05 mm.) gave the aminomethoxypyrimidine (96%), m. p. 150—151° (lit.,[3] 156—157°) (Found: C, 47·7; H, 5·6; N, 33·6. Calc. for $C_5H_7ON_3$: C, 48·0; H, 5·6; N, 33·6%).

4-*Chloro*-6-*dimethylaminopyrimidine*.—4,6-Dichloropyrimidine (10·45 g.) and 33% w/w ethanolic dimethylamine (36·5 ml.) were shaken for 2 hr. at 25°. The *pyrimidine* (6·85 g.), recrystallised from water (55 parts), or sublimed (70°/0·05 mm.), had m. p. 102—103° (Found: C, 45·5; H, 5·05; N, 26·75. $C_6H_8ClN_3$ requires C, 45·7; H, 5·1; N, 26·65%).

4-*Dimethylamino*-6-*methoxy*(*and* -*hydroxy*)*pyrimidine*.—The last-mentioned compound (10 g.) was stirred for 90 min. in refluxing methanolic sodium methoxide (50 ml.; sodium, 2·2 g.). After treatment with carbon dioxide and evaporation, the residual paste was extracted (Soxhlet) with light petroleum (b. p. 40—60°). Removal of solvent and distillation gave the *methoxy-derivative* (6·3 g.), b. p. 136° (20 mm.), $n_D^{20}$ 1·5418 (Found: C, 54·4; H, 7·25; N, 27·4. $C_7H_{11}N_3O$ requires C, 54·9; H, 7·25; N, 27·4%). This product (6 g.) was refluxed for 30 min. with 6N-hydrochloric acid. After evaporation to dryness, the residue was dissolved in hot water (6 ml.) and adjusted to pH 7. The resulting *hydroxy-derivative* (2·1 g.), recrystallised from water (*ca.* 20 parts), had m. p. 271—275° (decomp.) (Found, in sample dried at 140°: C, 51·5; H, 6·55; N, 30·25. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%).

4-*Dimethylamino*-6-*methylaminopyrimidine*.—4-Chloro-6-dimethylaminopyrimidine (1·58 g.) and 25% w/v aqueous methylamine (3·8 ml.) were heated at 170° for 4 hr. After evaporation, the residue was extracted with boiling ethyl acetate (3 × 25 ml.). The solvent was removed and sublimation (80°/0·05 mm.) gave the *diamine* (1·2 g.), which, recrystallised from ethyl acetate (12 parts), had m. p. 138—141° (Found: C, 55·0; H, 7·85; N, 36·8. $C_7H_{12}N_4$ requires C, 55·25; H, 7·95; N, 36·8%).

4,6-*Bisdimethylaminopyrimidine*.—The solution obtained by heating 4,6-dichloropyrimidine (3·0 g.) with aqueous 25% w/v dimethylamine (21·7 ml.) for 4 hr. at 170° was extracted with ether (7 × 30 ml.). The solid (3·3 g.) left on evaporation of the extract recrystallised (with concentration) from light petroleum (b. p. 80—100°; 80 ml.); on sublimation, the *bisdimethylaminopyrimidine* had m. p. 107·5° (Found: C, 57·8; H, 8·3; N, 33·55. $C_8H_{14}N_4$ requires C, 57·8; H, 8·5; N, 33·7%).

[17] Whitehead and Traverso, *J. Amer. Chem. Soc.*, 1958, **80**, 2185.

4,6-*Dimethoxypyrimidine*.—4,6-Dichloropyrimidine (3·0 g.) was refluxed for 90 min. with sodium methoxide (sodium, 1·4 g.) in methanol (35 ml.). The solution was treated with carbon dioxide and evaporated (without a vacuum) to an oil, which was extracted with light petroleum (b. p. 40—60°; 4 × 100 ml.). Removal of the solvent and distillation gave the *dimethoxypyrimidine* (0·75 g.), b. p. 85°/16 mm., and $n_D^{20}$ 1·4980 (Found: C, 51·85; H, 6·0; N, 20·1. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·75; N, 20·0%).

4,6-*Diamino-5-bromo- and* 4-*Amino-5-bromo-6-hydroxy-pyrimidine*.—Bromine (1·6 ml.) was added during 10 min. to a stirred suspension of 4,6-diaminopyrimidine [18] (3 g.) in water (30 ml.). After 30 min. the solution was adjusted to pH 9. The *bromo-diamine* (5·1 g.), recrystallised from water (80 parts), had m. p. 213° (Found: Br, 42·35; N, 29·5. $C_4H_5BrN_4$ requires Br, 42·3; N, 29·6%).

The *aminobromohydroxypyrimidine* was similarly made in 90% yield; recrystallised from water (*ca.* 30 parts) it had m. p. 268° (Found: C, 25·1; H, 2·3. $C_4H_4BrN_3O$ requires C, 25·1; H, 2·15%).

5-Bromocytosine was also made in 65% yield as above, except that about 12 hr. was needed for bromine-uptake. It had m. p. 240—242° (decomp.; lit.,[19] 235°) (Found: N, 22·0. Calc. for $C_4H_4BrN_3O$: N, 22·1%). Amination of this with 33% aqueous methylamine (10 parts) at 150° or 180° gave a small yield of 5-methylaminouracil, m. p. 290° (decomp.) (lit.,[20] 240° and 280°) (Found: N, 29·8. Calc. for $C_5H_7N_3O_2$: N, 29·8%).

*Di*-(4-*hydroxypyrimidin*-6-*yl*) *Sulphide*.—4-Chloro-6-hydroxypyrimidine (2·6 g.), thiourea (1·6 g.), hydrochloric acid (0·4 ml.), and water (100 ml.) were refluxed for 8 hr. After concentration to 30 ml. and refrigeration, the solid was recrystallised from water (*ca.* 100 ml.), giving the *sulphide* (0·2 g.), m. p. *ca.* 330° (decomp.) (Found: C, 43·35; H, 2·7; N, 24·9; S, 14·3. $C_8H_6N_4O_2S$ requires C, 43·25; H, 2·7; N, 25·2; S, 14·4%). The mother-liquors contained much of the starting material.

2,4-*Bismethylthiopyrimidine*.—2,4-Dimercaptopyrimidine (2·9 g.) in N-potassium hydroxide (37·5 ml.) was shaken for 1 hr. with methyl iodide (2·9 ml.). Chloroform-extraction (3 × 25 ml.) and distillation gave *bismethylthiopyrimidine*, b. p. 98°/0·25 mm., m. p. 9—10° (Found: C, 41·9; H, 4·9; N, 16·25. $C_6H_8N_2S_2$ requires C, 41·85; H, 4·7; N, 16·25%). Light absorption as neutral molecule at pH 7, $\lambda_{max.}$ 302, 252 (log ε 3·74, 4·27).

1,2,3,4-*Tetrahydro*-1,3-*dimethyl*-2,4-*dithiopyrimidine*.—1,3-Dimethyluracil (2 g.) and phosphorus pentasulphide (7·0 g.) in tetralin (45 ml.) were stirred at 180° for 4 hr. Volatile materials were removed at 130° *in vacuo*, and the pasty residue sublimed at 160°/0·05 mm. and recrystallised from water, to give the *dithiopyrimidine*, m. p. 121° (Found: C, 41·8; H, 4·6; N, 16·3. $C_6H_8N_2S_2$ requires C, 41·85; H, 4·7; N, 16·3%). Light absorption as neutral molecule at pH 5, $\lambda_{max.}$ 360 infl., 343, 286 (log ε 3·86, 3·98, 4·22).

Thiation in boiling pyridine gives 1,3-dimethyl-4-thiouracil in good yield, with m. p. 131—132° (depressed below 90° by admixture with the preceding compound) (Found: C, 46·3; H, 5·1; N, 17·8; S, 20·8. Calc. for $C_6H_8N_2OS$: C, 46·15; H, 5·15; N, 17·95; S, 20·5%). Light absorption as neutral molecule at pH 5, $\lambda_{max.}$ 328, 257 infl., 246 (log ε 4·30, 3·53, 3·56).

1-*Methyldithiouracil*.—1-Methyluracil was treated as above in tetralin. A solid separated when the reaction mixture cooled. This was extracted with hot 5N-ammonia (4 × 15 ml.), and the extract adjusted to pH 4·5. The precipitate was extracted with boiling water (5 × 250 ml.); refrigeration followed by sublimation at 150°/0·1 mm. gave 1-*methyldithiouracil* (0·6 g.), m. p. 255—260° (Found: C, 37·9; H, 3·9; N, 17·7. $C_5H_6N_2S_2$ requires C, 38·0; H, 3·8; N, 17·7%). Light absorption as neutral molecule at pH 5, $\lambda_{max.}$ 350, 276 (log ε 4·02, 4·34); as anion at pH 10, $\lambda_{max.}$ 313, 276, 219 (log ε 4·34, 4·26, 3·94).

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