612. *Pyrimidine Reactions. Part IV.*[1] *The Methylation of 2,4- and 4,5-Diaminopyrimidine and Related Compounds.*

By D. J. Brown and N. W. Jacobsen.

That the methylation of 2,4- and 4,5-diaminopyrimidine (and related compounds) occurs at $N_{(1)}$ is shown by unambiguous syntheses of the highly basic imino-products. 2,4,6-Triaminopyrimidine is also methylated at $N_{(1)}$ but 2,4-diamino-6-hydroxypyrimidine at $C_{(5)}$. Ionization constants and spectra of the products were measured and are discussed. 1,4-Dihydro-4-imino-1-methyl-2-methylaminopyrimidine is an extraordinarily strong base (pK_a 14).

4-Aminopyrimidine [2,3] (I; R = R′ = H) and its pteridine analogues [1,4] undergo methylation on the nuclear nitrogen atom in the γ-position to the amino-group rather than that in the α-position. As this contrasts with the behaviour of hydroxy-derivatives in these series, the present paper extends the observation to several simple unsymmetrical 4-aminopyrimidine derivatives, which are also shown to undergo γ- at the expense of α-methylation.

2,4-Diaminopyrimidine (I; R = NH_2, R′ = H) with methyl iodide gives a single

[1] Part III, *J.*, 1961, 1298.
[2] Curd and Richardson, *J.*, 1955, 1853.
[3] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[4] Brown and Jacobsen, *J.*, 1960, 1978.

product.[3] This is now shown to be 2-amino-1,4-dihydro-4-imino-1-methylpyrimidine * (II; R = NH_2, R′ = H) by its identity with the product of reductive desulphurization of 2-amino-1,4-dihydro-4-imino-1-methyl-6-methylthiopyrimidine (II; R = NH_2, R′ = SMe). The latter was prepared, together with the 3-methyl isomer (III; R = SMe), by methylation of 2,4-diamino-6-methylthiopyrimidine (I; R = NH_2, R′ = SMe). That these products were the two possible nuclear *N*-methyl derivatives was shown by their highly basic pK_a values (12·0 and 11·2, respectively). To distinguish between the isomers 2,4-diamino-3,6-dihydro-3-methyl-4-oxopyrimidine [7] was allowed to react, presumably in its enolic form (III; R = OH), with phosphoryl chloride. The resulting 2-amino-4-chloro-1,6-dihydro-6-imino-1-methylpyrimidine (III; R = Cl) with sodium methyl sulphide gave the 3-methyl isomer (III; R = SMe).

4-Amino-2-methylaminopyrimidine (I; R = NHMe, R′ = H) also furnished a single strongly basic monomethyl derivative. When allowance is made for the small bathochromic displacements induced by an additional methyl group, its ultraviolet spectra are similar to those of the 1-methyl derivative of 2,4-diaminopyrimidine (see Table). Substitution had therefore again occurred at $N_{(1)}$, giving 1,4-dihydro-4-imino-1-methyl-2-methylaminopyrimidine (II; R = NHMe, R′ = H).

4-Amino-2-methylthiopyrimidine (I; R = SMe, R′ = H) with methyl iodide gave 1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine (II; R = SMe, R′ = H), the structure of which was proved by acid hydrolysis to 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine,[8] the oxo-form of (II; R = OH, R′ = H).

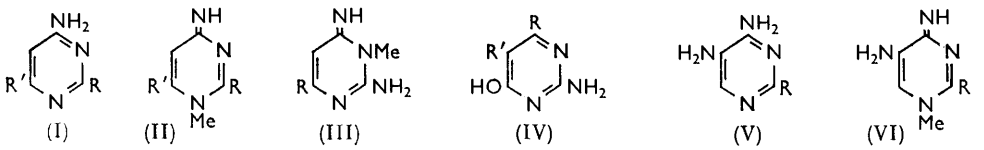
Methylation of isocytosine (2-amino-4-hydroxypyrimidine) with methyl iodide proved possible only with an equivalent of sodium methoxide present. Two isomeric monomethyl derivatives were obtained and these were identified as 1- and 3-methylisocytosine by the close similarity of their observed properties and spectra with those recently reported by Angier and Curran.[9] Paper chromatography of the mother-liquors revealed no spot representing 4-hydroxy-2-methylaminopyrimidine (unambiguously made *via* the methoxy-analogue), 2-amino-4-methoxypyrimidine,[10] or a *C*-methylisocytosine.

2,4-Diamino-6-hydroxypyrimidine (I; R = NH_2, R′ = OH) could not be methylated by methyl iodide alone, but addition of an equivalent of sodium methoxide led to a single monomethyl product. Of the six possibilities, four comprising the compounds (I; R = NHMe, R′ = OH),[7] (I; R = NH_2, R′ = OMe),[11] (III; R = OH),[7] and (IV; R = NHMe; R′ = H)[12] were known and could be eliminated by their physical properties. Although a fifth isomer, 2,4-diamino-1,6-dihydro-1-methyl-6-oxopyrimidine is also reported in the literature,[13] the compound described is in fact the 3-methyl derivative (III; R = OH).[7] A further attempt to prepare it by hydrolysis of 2-amino-1,4-dihydro-4-imino-1-methyl-6-methylthiopyrimidine (II; R = NH_2, R′ = SMe) failed, but the remaining possibility, 2,4-diamino-6-hydroxy-5-methylpyrimidine (IV; R = NH_2, R′ = Me), was prepared by condensing ethyl β-cyanopropionate with guanidine, and it proved identical with the methylation product. This *C*-methylation is all but unique in the pyrimidine series, the formation of 5,5-dimethylbarbituric acid being previously the only authenticated example.[14]

* This and related compounds have been named here as *para*-quinonoid rather than the tautomeric *ortho*-quinonoid structures only because, in general, the former are the more stable configurations.[5] However, in an analogous pteridine, experimental evidence suggests that the reverse pertains.[6]

[5] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[6] Brown and Jacobsen, *J.*, 1961, 4413.
[7] Roth, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2864; Boon and Bratt, *J.*, 1957, 2159.
[8] Flynn, Hinman, Caron, and Woolf, *J. Amer. Chem. Soc.*, 1953, **75**, 5867.
[9] Angier and Curran, *J. Org. Chem.*, 1961, **26**, 1891.
[10] Adams and Whitmore, *J. Amer. Chem. Soc.*, 1945, **67**, 735.
[11] Roth, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2869.
[12] Fidler and Wood, *J.*, 1957, 4157.
[13] Yamada, Chibata, and Kiguchi, *Tanabe Seiyaku Kenkyû Nempô*, 1957, **2**, 13; *Chem. Abs.*, 1958, **52**, 1177.
[14] Conrad and Guthzeit, *Ber.*, 1881, **14**, 1643.

Methylation of the closely related 2,4,6-triaminopyrimidine (I; R = R′ = NH_2) gave, not a *C*-methyl derivative, but 2,4-diamino-3,6-dihydro-6-imino-3-methylpyrimidine (II; R = R′ = NH_2), distinguished from all possible isomers by its strongly basic nature.



4,5-Diaminopyrimidine (V; R = H) was methylated at position 1, giving 5-amino-1,4-dihydro-4-imino-1-methylpyrimidine (VI; R = H) because this product was identical with material obtained by Raney nickel desulphurization of 5-amino-1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine (VI; R = SMe) obtained by methylating the diamine (V; R = SMe). The structure (VI; R = SMe) was established by acid hydrolysis to 4,5-diamino-1,2-dihydro-1-methyl-2-oxopyrimidine [15] the enolic form of which is (VI; R = OH), and which with glyoxal gave 2,3-dihydro-3-methyl-2-oxopteridine.[16]

Only five pK_a values for the highly basic iminopyrimidines appear in the literature.[3,4,17,18] The additional nine in the Table now permit several points to be made. As with 2- and 4-aminopyrimidines, the basic strength of iminopyrimidines is moderately increased by an electron-releasing amino-group, but profoundly decreased by the electron-withdrawing chloro-substituent. Thus the strength of 1,4-dihydro-4-imino-1-methylpyrimidine [3] (pK_a 12·2) rises in its 5-amino-derivative, to pK_a 12·5, in its 2-amino-derivative to pK_a 12·9, and in its 2-methylamino-derivative to pK_a 14·0 which is the highest recorded value for a pyrimidine base. Moreover, 1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine and the three related amino-imino-methylthiopyrimidines are all strong bases. On the other hand, 2-amino-4-chloro-1,6-dihydro-6-imino-1-methylpyrimidine is far weaker (pK_a 9·9). The base-weakening effect of the chloro-group is again illustrated in comparing 2- and 4-methylaminopyrimidine (respective pK_a values [3] 3·8 and 6·1) with 4-chloro-2-methylaminopyrimidine (2·6) and its reversed isomer (2·8), as well as by comparing 4-amino-2-methylaminopyrimidine (7·5) with its 6-chloro-derivative (3·8). The methylthio-group is seen to be mildly base-weakening in passing from 2-amino-1,4-dihydro-4-imino-1-methylpyrimidine (12·9) to its 6-methylthio-derivative (12·0), or from 2,4- and 4,5-diaminopyrimidines (7·3 and 6·0) to their 6-methylthio-derivatives (5·5 and 5·0), but other examples indicate little, or even the contrary, effect.

Attention is drawn, in footnotes to the Table, to the usual base-strengthening and acid-weakening effects of methyl groups other than the nuclear *N*-methylation. The acid-weakening effect of amino-groups is seen in the series 4-hydroxypyrimidine [19] (pK_a 8·6), its 2-methylamino-derivative (9·8), and 4-amino-6-hydroxy-2-methylaminopyrimidine (11·0).

Experimental

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

Methylation of 2,4-*Diaminopyrimidine.*—2,4-Diaminopyrimidine [20] (1·35 g.) was refluxed with methanol (7 ml.) and methyl iodide (7 ml.) for 1 hr. Recrystallization of the insoluble product by dissolution in boiling ethanol and addition of hot ethyl acetate gave 76% of 2(4)-*amino*-1,4(1,2)-*dihydro*-4(2)-*imino*-1-*methylpyrimidine hydriodide*, m. p. 273—274° (Found: C, 23·7; H, 3·55; I, 50·4; N, 22·1. $C_5H_9IN_4$ requires C, 23·8; H, 3·6;

[15] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[16] Albert, Brown, and Wood, *J.*, 1956, 2066.
[17] Kenner, Reese, and Todd, *J.*, 1955, 855.
[18] Whitehead and Traverso, *J. Amer. Chem. Soc.*, 1958, **80**, 2185.
[19] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[20] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

Properties of the pyrimidines.

Pyrimidine derivative	pK_a [a] and concn.	$\lambda_{max.}$ (mμ) [b]	pH	log ε
2-Amino-4-clhoro-1,6-dihydro-6-imino-1-methyl		297; 243	12·0	3·82; 3·98
cation	9·90 ± 0·04 (M/100)	296; 234	7·0	4·07; 3·88
4-Amino-6-chloro-2-methylamino		288; *230*; 210(?)		3·83; *4·09*; 4·35(?)
cation	3·81 ± 0·01 (M/200)	305; 226	1·0	3·94; 4·15
2-Amino-1,4-dihydro-4-imino-1-methyl		297	14·8 [d]	3·44
cation	12·9 [c] (M/15,000)	270; *235*	9·0	3·83; *4·02*
2-Amino-1,4-dihydro-4-imino-1-methyl-6-methylthio				
cation	12·0 [c] (M/10)	288; 226	9·0	4·18; 4·33
2-Amino-3,4-dihydro-4-imino-3-methyl-6-methylthio				
cation	11·2 [c] (M/50)	302; *254*; 242	9·0	4·25; *4·18*; 4·19
5-Amino-1,4-dihydro-4-imino-1-methyl				
cation	12·5 [c] (M/20)	292	9·0	3·98
5-Amino-1,4-dihydro-4-imino-1-methyl-2-methylthio				
cation	12·6 [c] (M/20)	300; 246	9·0	4·00; 4·39
4-Amino-6-hydroxy-2-methylamino		271; 215	7·0	4·16; 4·43
cation	3·22 ± 0·04 (M/200)	265	1·0	4·25
anion	11·03 ± 0·06 (M/100)	267; 216	13·0	3·97; 4·09
4-Amino-2-methylamino		270; 215	5·0	3·63; 4·41
cation	7·55 ± 0·01 (M/200)	288; *230*	10·0	3·78; *4·06*
2-Chloro-4-methylamino		281; 244	7·0	3·65; 4·16
cation	2·83 ± 0·03 (M/100)	257	0·0	4·20
4-Chloro-2-methylamino		309; 238	7·0	3·49; 4·17
cation	2·63 ± 0·01 (M/50)	315; *228*; 217	0·0	3·55; *4·23*; 4·33
2,4-Diamino-6-chloro		282; *228*	7·0	3·87; *3·98*
cation	3·57 ± 0·01 (M/200)	298; 227	1·0	3·92; 4·05
2,4-Diamino-3,6-dihydro-6-imino 3-methyl [g]				
cation	12·7 [e] (M/40)	273	7·0	4·23
2,4-Diamino-6-hydroxy		267; 211	7·0	4·19; 4·47
cation	3·33 ± 0·02 (M/100)	264	1·0	4·31
anion	10·78 ± 0·06 (M/100)	263; *240*	13·0	4·01; *3·61*
2,4-Diamino-6-hydroxy-5-methyl		276; 237	7·0	4·18; 3·63
cation	3·61 ± 0·02 (M/100) [h]	273	1·0	4·28
anion	11·07 ± 0·06 (M/100) [h]	270; 237	13·0	4·03; 3·69
4,5-Diamino-6-hydroxy-2-methylamino [j]				
cation	5·44 ± 0·02 (M/200) [k]	270; *230*; 214	2·0	4·11; *3·77*; 4·36
anion [j]	10·63 ± 0·05 (M/100) [k]			
4,5-Diamino-6-methylamino		279; 216	8·0	4·02; 4·47
cation	5·93 ± 0·01 (M/100) [l]	286; 222	4·0	4·04; 4·22
2,4-Diamino-6-methylthio		286; 228	8·0	4·05; 4·34
cation	5·46 ± 0·01 (M/200)	289; 225	2·0	4·15; 4·26
4,5-Diamino-2-methylthio		304; 261; 217	8·0	3·78; 4·02; 4·18
cation	5·05 ± 0·01 (M/200)	275; 246	2·0	3·99; 4·29
1,4-Dihydro-4-imino-1-methyl-2-methylamino		307	[m]	3·36
cation	14·0 [c] (M/30,000)	277; *225*; 213	10·0	3·77; *4·26*; 4·37
1,4-Dihydro-4-imino-1-methyl-2-methylthio				
cation	12·5 [e] (M/20)	242	7·0	4·45
4-Hydroxy-2-methylamino		291; 212	7·0	3·69; 4·23
cation	3·93 ± 0·03 (M/100) [n]	260; 215	1·0	3·85; 4·17
anion	9·82 ± 0·02 (M/200) [n]	279; *233*; *228*	12·0	3·78; *3·95*; *3·98*

[a] By potentiometric titration in water at 20° (cf. Albert and Phillips, *J.*, 1956, 1294). [b] Inflexions in italics. [c] Spectrometrically determined. [d] Spectrum unchanged after 1 hr. [e] Not below this figure. [f] Cf. 2,4-diaminopyrimidine, pK_a 7·3 (ref. 5). [g] Spectrum measured on hydriodide with balanced I^- concentration in reference cell. [h] Cf. preceding compound for effect of *C*-methylation. [j] Rapid change in spectrum (oxidation?) precluded measurement. [k] 4,5-Diamino-6-hydroxypyrimidine has pK_a 3·6 and 9·9 (Mason, *J.*, 1954, 2071). [l] Cf. 4,5,6-triaminopyrimidine (pK_a 5·8; ref. in *k*). [m] Figures for pure neutral species kindly extrapolated from curve at pH 14·8 by Dr. D. D. Perrin. [n] 2-Amino-4-hydroxypyrimidine (isocytosine) has pK_a 4·00 ± 0·04 and 9·59 ± 0·04 (spectrometrically determined at 20°); cf. Levene and Bass (*J. Biol. Chem.*, 1926, **70**, 229) who give 4·0 and 9·4 at 25°.

I, 50·35; N, 22·25%). An aqueous suspension of silver chloride, converted this into the *hydrochloride* which, recrystallized from methanol, had m. p. 275—276° (Found: C, 37·15; H, 5·65; Cl, 22·35; N, 34·6. $C_5H_9ClN_4$ requires C, 37·4; H, 5·65; Cl, 22·1; N, 34·9%). It was identical (mixed m. p.) with the product obtained by desulphurizing 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methyl-6-methylthiopyrimidine hydrochloride (see below).

2,4-*Diamino*-6-*methylthiopyrimidine*.—2,4-Diamino-6-chloropyrimidine [21] (12·0 g.) and N-potassium hydrogen sulphide (240 ml.) were heated at 135° for 12 hr. (optimum conditions determined chromatographically). The 2,4-diamino-6-mercaptopyrimidine (78%) crystallized rapidly on cooling (this is a marked improvement on recorded procedure [22]). Crystallized from water it had m. p. 300—301° (lit., 309—310°) (Found: C, 33·95; H, 4·4; N, 39·25. Calc. for $C_4H_6N_4S$: C, 33·8; H, 4·25; N, 39·4%). This product (7·5 g.) was shaken in 2·5N-sodium hydroxide (21·1 ml.) with methyl iodide (3·6 ml.) for 10 min. The *methylthio-compound* (86%), recrystallized from water, had m. p. 200—202° (Found: C, 38·3; H, 5·1; N, 35·85. $C_5H_8N_4S$ requires C, 38·45; H, 5·15; N, 35·9%).

Methylation of 2,4-*Diamino*-6-*methylthiopyrimidine*.—The last-mentioned pyrimidine (9·5 g.) was refluxed in methanol (135 ml.) and methyl iodide (75 ml.) for 24 hr. 2(4)-*Amino*-1,4(1,2)-*dihydro*-4(2)-*imino*-1-*methyl*-6-*methylthiopyrimidine hydriodide* (39%) was filtered off from the hot solution and, recrystallized from water, had m. p. 281—282° (Found: C, 24·1; H, 3·6; I, 42·4; N, 18·8. $C_6H_{11}IN_4S$ requires C, 24·15; H, 3·7; I, 42·55; N, 18·8%). Treatment with silver chloride gave the *hydrochloride* which on recrystallization from methanol or water had m. p. 287—288° (Found: C, 34·6; H, 5·4; Cl, 17·15; N, 27·0. $C_6H_{11}ClN_4S$ requires C, 34·85; H, 5·35; Cl, 17·15; N, 27·1%).

Evaporation of the initial filtrate, and recrystallization of the residue from water gave the isomeric 2(4)-*amino*-3,4(2,3)-*dihydro*-4(2)-*imino*-3-*methyl*-6-*methylthiopyrimidine hydriodide* (22%) with m. p. 248—250° (Found: C, 23·9; H, 3·65; I, 42·45; N, 18·5%). Silver chloride furnished from this the *hydrochloride* which, when recrystallized from methanol or water, had m. p. 281—282° depressed on admixture with the first isomer (Found: C, 34·9; H, 5·45; Cl, 17·3; N, 26·9%).

The second isomer was unambiguously synthesized: 2,4-Diamino-3,6-dihydro-3-methyl-6-oxopyrimidine [6,7] (5·0 g.) and phosphoryl chloride (60 ml.) were refluxed for 3 hr. After removal of phosphoryl chloride *in vacuo*, the residue was poured on ice, and the solution adjusted at 0° with 50% sodium hydroxide solution to pH 12. Continuous extraction with ether yielded 2(6)-*amino*-4-*chloro*-1,6(1,2)-*dihydro*-6(2)-*imino*-1-*methylpyrimidine* (17%), which, recrystallized from water, decomposed at *ca.* 192—193° (Found: C, 37·9; H, 4·45; Cl, 22·25. $C_5H_7ClN_4$ requires C, 37·85; H, 4·45; Cl, 22·35%).

This pyrimidine (0·5 g.) in 0·5N-ethanolic sodium methyl sulphide (8 ml.) was refluxed for 15 min. and the filtered solution evaporated to dryness *in vacuo*. Water (5 ml.) was added to the residue, and the 2(4)-*amino*-3,4(2,3)-*dihydro*-4(2)-*imino*-3-*methyl*-6-*methylthiopyrimidine* (83%) collected. Recrystallized from water, it had m. p. 191—192° (Found: C, 42·6; H, 5·9; N, 32·85. $C_6H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 32·95%). This base was converted into the hydrochloride, the m. p. of which was undepressed by admixture with the second isomer above.

To this hydrochloride (0·5 g.) and ammonium chloride (0·5 g.) in water (15 ml.) at 80° Raney nickel (*ca.* 5 g.) was added portionwise. The mixture was refluxed and stirred for 5 hr. Evaporation of the filtered solution and extraction of the residue with hot methanol (7 ml.), gave 2-amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (64%), identical with the methylation product of 2,4-diaminopyrimidine.

Desulphurization was also attempted with chlorine: the methylthio-pyrimidine hydrochloride (0·68 g.) was suspended in anhydrous methanol (20 ml.), and dry chlorine passed into the stirred mixture for 30 min. at such a rate that the temperature did not rise above 10° with external cooling. The mixture was then stirred at 10° for a further 30 min. and concentrated *in vacuo* to 10 ml. The solid (66%) was collected and recrystallized from 95% ethanol, to give 2(4)-*amino*-5,6-*dichloro*-1,4(1,2)-*dihydro*-4(2)-*imino*-1-*methylpyrimidine hydrochloride*, m. p. 269—270° [Found: C, 25·7; H, 3·1; Cl (ionic), 15·15. $C_5H_6Cl_2N_4$,HCl requires C, 26·15; H, 3·05; Cl (ionic), 15·45%]. The hydrochloride (0·2 g.), in water (4 ml.), was adjusted to pH 12. The free *base* had m. p. 173° (decomp.) (Found: C, 30·9; H, 3·2; Cl, 36·8;

[21] Pfleiderer and Lohrmann, *Chem. Ber.*, 1961, **94**, 12.
[22] Elion, Lange, and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 2858.

N, 28·6. $C_5H_6Cl_2N_4$ requires C, 31·1; H, 3·15; Cl, 36·75; N, 29·0%). It did not liberate iodine from potassium iodide solution, thus precluding an *N*-halogeno- or 5,5-dihalogeno-structure.

4-Amino-2-methylaminopyrimidine.—(*a*) 4-Amino-6-hydroxy-2-methylaminopyrimidine (5 g.) and phosphoryl chloride (30 ml.) were refluxed for 1 hr. After removal of the phosphoryl chloride *in vacuo*, the residue was poured on ice, neutralized to pH 7, and extracted with ether (5 × 100 ml.). The dried ($MgSO_4$) extracts on evaporation gave the *4-amino-6-chloro-2-methylaminopyrimidine* (35%). Recrystallized from 1 : 1 ethanol–light petroleum (b. p. 80—100°) it had m. p. 198—200° (Found: C, 37·95; H, 4·55; Cl, 22·25; N, 35·25. $C_5H_7ClN_4$ requires C, 37·85; H, 4·45; Cl, 22·35; N, 35·35%). This chloropyrimidine (0·4 g.) was hydrogenated in water (30 ml.) over 5% palladium–charcoal (0·3 g.) in the presence of magnesium oxide (0·3 g.). The mixture was heated to 100°, then filtered, and the filter-cake was extracted with acetone (2 × 10 ml.). 2·5N-Sodium carbonate (2 ml.) was added to the filtrate and washings, and these were then reduced to dryness. Extraction with hot isobutyl methyl ketone (75 ml.) gave *4-amino-2-methylaminopyrimidine* (80%), m. p. 123—126°, raised on sublimation (110°/0·04 mm.) to 131—133° (Found: C, 48·55; H, 6·35; N, 44·65. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%).

(*b*) 4-Amino-2-mercaptopyrimidine (30 g.) was shaken in 2·5N-sodium hydroxide (95 ml.) with methyl iodide (18 ml.) for 30 min. 4-Amino-2-methylthiopyrimidine (88%), washed with water and recrystallized from 13 : 3 light petroleum (b. p. 60—80°)–ethanol, had m. p. 123—125° (cf. m. p. 125—126° recorded [23] for material made by a less convenient route). This compound (14 g.) and 30% aqueous methylamine (50 ml.) were heated for 20 hr. at 155°. Evaporation and trituration of the residue with isobutyl methyl ketone (4 × 10 ml.) gave a solid (53%), which was recrystallized from ethyl acetate and sublimed. It was identical with the material prepared in (*a*).

Methylation of 4-Amino-2-methylaminopyrimidine.—4-Amino-2-methylaminopyrimidine (1·5 g.), methanol (2 ml.), and methyl iodide (3·75 ml.) were refluxed for 3 hr. The solution was chilled and *1,4-dihydro-4-imino-1-methyl-2-methylaminopyrimidine hydriodide* (81%) recrystallized from ethanol. It had m. p. 228—231° (Found: C, 26·8; H, 3·95; I, 47·5; N, 20·8. $C_6H_{11}IN_4$ requires C, 27·1; H, 4·15; I, 47·7; N, 21·05%). The *hydrochloride* made from it with silver chloride and recrystallized from ethanol had m. p. 288—289° (Found: C, 41·35; H, 6·35; Cl, 20·25; N, 32·25. $C_6H_{11}ClN_4$ requires C, 41·25; H, 6·35; Cl, 20·3; N, 32·1%).

Methylation of 4-Amino-2-methylthiopyrimidine.—4-Amino-2-methylthiopyrimidine (3 g.), methyl iodide (12 ml.), and methanol (15 ml.) were refluxed for 3 hr. The *1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine hydriodide* (91%), obtained by evaporation and recrystallized from water and then from ethanol, had m. p. 224—225° (Found: C, 25·6; H, 3·5; I, 44·85; N, 14·75. $C_6H_{10}IN_3S$ requires C, 25·45; H, 3·55; I, 44·8; N, 14·85%). By shaking with silver chloride it was converted into the *hydrochloride* which after recrystallization from 1 : 1 ethanol–ethyl acetate had m. p. 237—238° (Found: C, 37·65; H, 5·2; Cl, 18·35; N, 21·85. $C_6H_{10}ClN_3S$ requires C, 37·6; H, 5·25; Cl, 18·5; N, 21·9%).

The above hydriodide (2 g.) was refluxed in 6N-hydrochloric acid (16 ml.) for 1 hr. After evaporation *in vacuo*, the residue was dissolved in water (10 ml.) and adjusted to pH 9. The precipitate (0·8 g.) obtained on chilling and recrystallization from ethanol had m. p. 296—297°, undepressed on admixture with authentic [8] 4-amino-1,2-dihydro-1-methyl-2-oxopyrimidine (Found: C, 48·2; H, 5·5; N, 33·5. Calc. for $C_5H_7N_3O$: C, 48·0; H, 5·65; N, 33·6%).

Methylation of Isocytosine (2-Amino-4-hydroxypyrimidine).—Isocytosine (1·1 g.) was refluxed with methanolic sodium methoxide (12 ml.; from sodium, 0·23 g.) and methyl iodide (1·5 ml.) for 1·5 hr. After evaporation, the residue was dissolved in water (25 ml.) and shaken with silver carbonate (2·7 g.). The filtrate was adjusted to pH 7 with hydrochloric acid and again clarified. Extraction of the residue from evaporation with hot ethanol (2 × 100 ml.) and concentration of the extract to 20 ml. gave a solid (0·5 g.). Further concentration to 5 ml. gave a second crop (0·2 g.).

Repeated recrystallization of the first crop from ethanol gave 2-amino-3,4-dihydro-3-methyl-4-oxopyrimidine (3-methylisocytosine), m. p. 257—260°, R_F 0·60 in butanol–acetic acid [Angier and Curran [9] record m. p. 262—266° (corr.) and R_F 0·62] (Found: C, 47·8; H, 5·45;

[23] Wheeler and Bristol, *Amer. Chem. J.*, 1905, **33**, 437.

N, 33·15. Calc. for $C_5H_7N_3O$: C, 48·0; H, 5·65; N, 33·6%). Recrystallization of the second crop from ethanol gave 2-amino-1,4-dihydro-1-methyl-4-oxopyrimidine (1-methylisocytosine), m. p. 283—285°, R_F 0·35 (lit.,[9] m. p. 275—280°, R_F 0·38) (Found: C, 48·2; H, 5·55; N, 33·25%). Ultraviolet spectroscopy confirmed the identity of both isomers with those recently prepared.[9]

2-Chloro-4- and 4-Chloro-2-methylaminopyrimidine.—2,4-Dichloropyrimidine [24] (40 g.) was added to a 7·5% solution of methylamine in ethanol (300 ml.) cooled to 5°. The pressure bottle was stoppered and shaken during the initial exothermal reaction (35°). After a further 18 hr. at 20°, the mixture was evaporated to dryness; the residue was suspended in water (200 ml.) containing ammonia (*d* 0·90; 15 ml.) and rapidly steam-distilled. *4-Chloro-2-methylaminopyrimidine* (10%) obtained from the distillate recrystallized from ethanol and had m. p. 123—124° (Found: C, 41·9; H, 4·3; Cl, 24·8; N, 28·85. $C_5H_6ClN_3$ requires C, 41·8; H, 4·2; Cl, 24·7; N, 29·25%).

The aqueous residue, on chilling, gave *2-chloro-4-methylaminopyrimidine* (30%). Recrystallized from water it had m. p. 128—129° which was depressed on admixture with its isomer (Found: C, 41·65; H, 4·3; Cl, 24·55; N, 29·0%).

4-Hydroxy-2-methylaminopyrimidine.—4-Chloro-2-methylaminopyrimidine (1 g.) was refluxed in methanolic sodium methoxide (15 ml.; from sodium, 0·2 g.) for 2 hr. The residue obtained on evaporation was sublimed (70°/20 mm.), to give the *4-methoxy-2-methylaminopyrimidine* (93%), m. p. 55—57° (Found: C, 51·6; H, 6·4; N, 30·2. $C_6H_9N_3O$ requires C, 51·8; H, 6·5; N, 30·2%).

This pyrimidine (0·45 g.) was heated with concentrated hydrochloric acid (2·3 ml.) on a steam-bath for 1 hr. When adjusted to pH 6 with 10N-sodium hydroxide and refrigerated, the solution deposited the *4-hydroxy-2-methylaminopyrimidine* (62%), m. p. 214—215° (from ethanol) (Found: C, 48·0; H, 5·7; N, 33·3. $C_5H_7N_3O$ requires C, 48·0; H, 5·65; N, 33·6%). The above structures follow from the fact that 2-hydroxy-4-methylaminopyrimidine [15] has m. p. 275—278°.

Methylation of 2,4-Diamino-6-hydroxypyrimidine.—2,4-Diamino-6-hydroxypyrimidine [25] (5·0 g.), methanolic sodium methoxide (30 ml.; from sodium, 0·92 g.), and methyl iodide (5 ml.) were refluxed for 1 hr. The residue left on evaporation was triturated with cold water (20 ml.), to yield *2,4-diamino-6-hydroxy-5-methylpyrimidine* (22%) (Found: C, 42·7; H, 5·6; N, 39·9. $C_5H_8N_4O$ requires C, 42·85; H, 5·75; N, 40·0%). Recrystallized from water or ethanol, it had m. p. 308—310° (decomp.), undepressed on admixture with authentic material prepared as follows.

Ethyl cyanoacetate (22·6 g.) was dissolved in methanolic sodium methoxide (65 ml.; from sodium, 4·6 g.). Methyl iodide (12·5 ml.) was added, with cooling and stirring, during 10 min. and the mixture then refluxed for 30 min. Water (180 ml.) was added, and the product extracted with ether (3 × 80 ml.). The fraction of ethyl 2-cyanopropionate (57%) boiling at 68—74°/12 mm. was shown by gas chromatography to be free from ethyl cyanoacetate present in higher fractions. Redistilled it had b. p. 68°/12 mm. (cf. lit.,[26] b. p. 87—88°/15 mm.) (Found: C, 56·3; H, 7·0; N, 11·0. Calc. for $C_6H_9NO_2$: C, 56·7; H, 7·15; N, 11·0%).

This ester (9·5 g.) was added with stirring to a mixture of guanidine hydrochloride (7·2 g.) and ethanolic sodium ethoxide (45 ml.; from sodium 3·45 g.). After refluxing for 2 hr., the mixture was evaporated to dryness. The residue in water (30 ml.) was adjusted to pH 7 with acetic acid, to give 2,4-diamino-6-hydroxy-5-methylpyrimidine (56%). Recrystallized as above it had m. p. 308—310° (decomp.).

Methylation of 2,4,6-Triaminopyrimidine.—2,4,6-Triaminopyrimidine [27] (5 g.) was refluxed with methanol (60 ml.) and methyl iodide (12 ml.) for 6 hr. The solid (47%) recrystallized from water, to give *2,4-diamino-3,6-dihydro-6-imino-3-methylpyrimidine hydriodide* (or tautomer), m. p. 309—310° (Found: C, 22·5; H, 3·8; I, 47·45; N, 26·05. $C_5H_{10}IN_5$ requires C, 22·5; H, 3·75; I, 47·5; N, 26·2%).

Methylation of 4,5-Diaminopyrimidine.—4,5-Diaminopyrimidine [28] (5 g.), methanol (80 ml.), and methyl iodide (30 ml.) were refluxed for 3 hr. Concentration to 15 ml. and chilling gave *5-amino-1,4-dihydro-4-imino-1-methylpyrimidine hydriodide* (77%), with m. p. 175—177° after

[24] Whittaker, *J.*, 1951, 1565.
[25] Van Allan, *Org. Synth.*, 1952, **32**, 45.
[26] Gagnon and Boivin, *Canad. J. Res.*, 1948, **26**, *B*, 503.
[27] Traube, *Ber.*, 1904, **37**, 4544.
[28] Brown, *J. Appl. Chem.*, 1952, **2**, 239.

recrystallization from 90% ethanol or absolute ethanol (Found: C, 23·85; H, 3·55; I, 49·9; N, 22·15. $C_5H_9IN_4$ requires C, 23·8; H, 3·6; I, 50·35; N, 22·25%). It was converted with silver chloride into the *hydrochloride*, which after recrystallization from boiling ethanol by the addition of ethyl acetate had m. p. 213—214° (Found: C, 37·45; H, 5·6; N, 34·85. $C_5H_9ClN_4$ requires C, 37·4; H, 5·65; N, 34·9%). It was also prepared by desulphurizing 5-amino-1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine (see below).

Methylation of 4,5-Diamino-2-methylthiopyrimidine.—4,5-Diamino-2-methylthiopyrimidine [29] (5 g.), methanol (30 ml.), and methyl iodide (20 ml.) were refluxed for 1 hr. *5-Amino-1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine hydriodide* (31%) obtained from the chilled solution recrystallized from ethanol, after which it had m. p. 234—235° (Found: C, 24·25; H, 3·7; I, 42·7; N, 18·6. $C_6H_{11}IN_4S$ requires C, 24·15; H, 3·7; I, 42·55; N, 18·8%). Silver chloride converted it into the *hydrochloride* which recrystallized from methanol or water and had m. p. 276—277° (Found: C, 34·7; H, 5·45; N, 26·95. $C_6H_{11}ClN_4S$ requires C, 34·85; H, 5·35; N, 27·1%).

The hydriodide (1 g.) was refluxed in 6N-hydrochloric acid (50 ml.) for 5 hr., and the solution evaporated to dryness. The residue, in water (5 ml.), was treated with charcoal and adjusted to pH 9. Recrystallized from water, the 4,5-diamino-1,2-dihydro-1-methyl-2-oxopyrimidine (53%) decomposed at *ca.* 250° (lit.,[15] >220°). Its *picrate*, recrystallized from water, had m. p. 239° (decomp.) unaltered on admixture with the picrate made from authentic material [15] (Found: C, 35·45; H, 3·1; N, 25·45. $C_{11}H_{11}N_7O_8$ requires C, 35·75; H, 3·0; N, 25·55%). Further confirmation of structure was provided by condensation of the oxopyrimidine (0·25 g.) in water (8 ml.) with glyoxal monohydrate (0·15 g.), to give 2,3-dihydro-3-methyl-2-oxopteridine monohydrate (0·24 g.). Recrystallized from water it began to decompose above 212°, and melted at *ca.* 280°. This behaviour was unchanged on admixture with authentic material [15] (Found: C, 46·8; H, 4·55; N, 31·0. Calc. for $C_7H_8N_4O_2$: C, 46·65; H, 4·5; N, 31·1%).

5-Amino-1,4-dihydro-4-imino-1-methyl-2-methylthiopyrimidine hydrochloride (0·5 g.) was desulphurized by adding Raney nickel (*ca.* 5 g.) to its solution at 80° in water (15 ml.) containing ammonium chloride (0·5 g.). After refluxing for 4 hr. the filtered mixture was evaporated, and the residue extracted with boiling ethanol (15 ml.). Addition of light petroleum (b. p. 80—100°; 10 ml.) precipitated ammonium chloride; an additional 8 ml. furnished 5-amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (28%). Recrystallized as above, it had m. p. 213° unchanged on admixture with the methylation product of 4,5-diaminopyrimidine.

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[29] Albert and Brown, *J.*, 1954, 2060.