120. *Pyrimidine Reactions. Part VII.*[1] *Methylation of Substituted 2,4-Diaminopyrimidines.*

By D. J. Brown and T. Teitei.

2,4-Diaminopyrimidine, and most of its methylamino- and dimethylamino-analogues with or without a 5- or 6-halogeno-substituent undergo methylation only at N-1. Some of the dimethylamino-derivatives fail to react and one, 2-dimethylamino-4-methylaminopyrimidine, is methylated at N-3. The pK_a values and ultraviolet spectra confirm that the diamino-tautomer predominates in an aqueous solution of the parent pyrimidine, but the fine structure of 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine remains uncertain. A general procedure is described for preparing the 2,4-diamines by way of their 6-chloro-derivatives in uniformly good yield.

Treatment of 2,4-diaminopyrimidine with methyl iodide was found[2] to give a single product methylated at N-1. This observation has now been extended to methylamino- and dimethylamino-analogues with and without a 5-bromo- or 6-chloro-substituent. The object was twofold: to find where such aminopyrimidines methylated and, if possible, to determine the predominant tautomeric structure in the parent amino-imine (I; R = H) ⇌ (II; R = H).

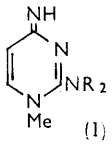
Most of the above diamines methylated uniformly at position 1. However, five of the 2-dimethylamino-derivatives were exceptional; four bearing a halogen substituent completely resisted methylation and 2-dimethylamino-4-methylaminopyrimidine afforded its 3-methyl derivative (III; R = Me, R′ = H).*

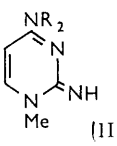
An ultraviolet-spectral comparison of the tautomeric amino-imine (I/II; R = H) with its derivatives (I; R = Me) and (II; R = Me) of fixed structure was now possible. However, it did not reveal a predominating tautomer because the spectra of the reference compounds differed far less than did that of the tautomeric substance from either. Similar comparisons of their 5-bromo- and 6-chloro-analogues were incomplete without appropriate 2-dimethylamino-derivatives (*v.s.*). Moreover, the reference compounds that could be made in the bromo-series were extremely unstable as free bases.

* Here and elsewhere in this Paper, the imino- rather than the methylimino-tautomers have been arbitrarily chosen for formulation and naming.

[1] Part VI, *Austral. J. Chem.*, 1964, **17**, 794.
[2] Brown and Jacobsen, *J.*, 1962, 3172.

Preparations.—Appropriate 2,4-diamino-6-chloropyrimidines were obtained from 2,4,6-trichloropyrimidine by two consecutive aminations. The procedure invariably gave yields well above those of published methods. Dehalogenation by catalytic hydrogenation [3] thence afforded the 2,4-diamines, which all gave 5-bromo-derivatives in good yield by treatment in acetic acid with bromine.[4]


(I)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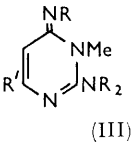
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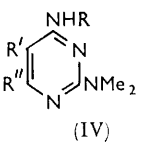
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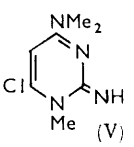
(V)

Like 2,4-diamino-,[2] 4-amino-2-methylamino-,[2] and 2-amino-4-dimethylamino-pyrimidine,[5] the analogous 2-amino-4-methylamino-, 4-amino-2-dimethylamino-, and 4-dimethylamino-2-methylamino-pyrimidine each gave with methyl iodide a single monomethyl derivative. These were clearly nuclear-*N*-methylated imines from their high basic strength (pK_a values >13), and the site of methylation was confirmed as N-1 by the progressive similarity in ultraviolet spectra of all six molecules (see Table). In contrast, 2-dimethylamino-4-methylaminopyrimidine (IV; R = R′ = R″ = H), under the same conditions, gave a less strongly basic methyl derivative with a rather different spectrum. Since it was not 2,4-bisdimethylaminopyrimidine, it was tentatively formulated as 2-dimethylamino-1,6-dihydro-1-methyl-6-methyliminopyrimidine (III; R = Me, R′ = H). Its pK_a (10·6) is consistent with this formulation (*v.i.*).

Methylation of the 5-bromodiamines was generally parallel in that the 2,4-diamino-5-bromopyrimidine and its 4-amino-2-methylamino-, 2-amino-4-methylamino-, 2-amino-4-dimethylamino-, and 4-dimethylamino-2-methylamino-homologues each afforded a strongly basic methylated derivative, whereas 4-amino-5-bromo-2-dimethylaminopyrimidine and its 4-methylamino-homologue (IV; R = Me, R′ = Br, R″ = H) resisted methylation under similar conditions. The site of methylation was identified as N-1 by catalytic hydrogenation of typical examples such as the methylated 2,4-diamino-5-bromopyrimidine to yield 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine (I/II; R = H). The similarity in the spectra of the other homologues confirmed their methylation at N-1.

The methylation of 2,4-diamino-6-chloropyrimidine [6] and its homologues followed a similar pattern although each took a longer time. The site of methylation of the products was again shown to be N-1 by pK_a values, by spectra, and by dechlorinating typical examples (see Experimental section). The 2-dimethylamino-derivatives (IV; R = H or Me, R′ = H, R″ = Cl) failed to methylate.

Ionisation and Spectra.—The basic strength (pK_a 7·3) of 2,4-diaminopyrimidine, already uniquely high among its isomers,[7] was increased progressively by extranuclear methylation (see Table) to pK_a 8·2 in 2,4-bisdimethylaminopyrimidine. The strength of the parent diamine was sharply decreased in its 6-chloro-derivative [2] (pK_a 3·6), but far less so in its 5-bromo-derivative (5·6). This marked difference was clearly more dependent on the proximity of the halogens to the basic centre (N-1) than to any intrinsic difference in their electron-withdrawing powers (cf. 2-amino-5-chloropyrimidine,[8] pK_a 1·73, with its bromo-analogue,[5] 1·95; also [9] 2- and 3-chloropyridine, 0·7 and 2·8, with 2- and 3-bromopyridine, 0·9 and 2·8). In either 2,4-diamino-5-bromo- or -6-chloro-pyrimidine progressive extranuclear methylation again produced a general increase in basic strength, but it was neither as marked nor as regular as in the parent diamines.

[3] Cf. Brown, *J. Appl. Chem.*, 1954, **4**, 72; Fidler and Wood, *J.*, 1957, 4157.
[4] Cf. English, Clark, Clapp, Seeger, and Ebel, *J. Amer. Chem. Soc.*, 1946, **68**, 453.
[5] Brown and Harper, *J.*, 1963, 1276.
[6] Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.
[7] Brown, " The Pyrimidines," Interscience, New York, 1962, p. 469.
[8] Brown and Paddon-Row, unpublished data.
[9] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959, p. 343.

Ionisation and ultraviolet spectra of substituted pyrimidines.

Derivative	pK_a *	$\lambda_{max.}$ (log ε) †	pH
2-Amino-5-bromo-1,4-dihydro-4-imino-1-methyl	‡	286(3·76), 210(4·44) ‡	7·0 15·0
2-Amino-5-bromo-4-dimethylamino	5·98 ± 0·04(p)	294(3·88), *257(3·95)*, 220(4·36) 307(3·91), 220(4·30)	1·0 9·4
4-Amino-5-bromo-2-dimethylamino	6·17 ± 0·06(p)	290(3·38), 235(4·45) 309(3·74), 240(4·28)	1·0 9·4
2-Amino-5-bromo-4-methylamino	6·23 ± 0·05(p)	280(3·76), *243(4·07)*, 214(4·47) 296(3·87), 238(4·03)	1·0 9·4
4-Amino-5-bromo-2-methylamino	5·74 ± 0·05(p)	289(3·53), 225(4·39), 216(4·39) 303(3·78), 231(4·19)	1·0 9·4
2-Amino-4-chloro-1,6-dihydro-6-imino-1-methyl §	9·90	296(4·07), 234(3·88) 297(3·82), 243(3·98)	7·0 12·0
2-Amino-4-chloro-3,6-dihydro-6-imino-3-methyl	11·88 ± 0·02	276(3·85), *237(3·98)* 303(3·63), 232(4·29)	7·0 14·0
2-Amino-4-chloro-6-dimethylamino	4·00 ± 0·06	*322(3·38)*, 280(3·96), 234(4·07) 292(3·97), 239(4·06)	1·0 7·7
4-Amino-6-chloro-2-dimethylamino	3·80 ± 0·03	310(3·95), 233(4·24) 294(3·76), 241(4·19)	1·0 7·7
2-Amino-4-chloro-6-methylamino	3·90 ± 0·05(p)	302(3·73), 275(3·82), *238(4·06)*, 212(4·26) 286(3·95), *241(3·97)*	1·0 6·4
2-Amino-1,4-dihydro-4-imino-1-methyl §	12·9	270(3·83), *235(4·02)* 297(3·44)	9·0 14·8
2-Amino-4-dimethylamino	7·96 ¶	274(3·96), 246(4·03) 291(3·95), 238(4·04)	1·0 10·4
4-Amino-2-dimethylamino	7·64 ± 0·04(p)	*279(3·43)*, 225(4·45) 294(3·72), 236(4·20)	1·0 10·4
2-Amino-4-methylamino	7·77 ± 0·04(p)	265(3·85), 235(4·07) 286(3·90), 234(3·99)	1·0 10·4
2,4-Bisdimethylamino	8·18 ± 0·06(p)	*262(4·06)*, 228(4·47) 300(3·89), 226(4·47)	1·0 10·4
5-Bromo-1,2-dihydro-2-imino-1-methyl-4-methylamino	‡	285(3·83), *246(4·02)*, 215(4·41) ‡	7·0 15·0
5-Bromo-1,4-dihydro-4-imino-1-methyl-2-methylamino	‡	293(3·66), 229(4·28), 214(4·35) ‡	7·0 15·0
5-Bromo-1,2-dihydro-1-methyl-2-methylimino	10·67	388(3·21), 252(4·15) **	12·8
5-Bromo-4-dimethylamino-1,2-dihydro-2-imino-1-methyl	‡	299(3·92), 255(3·94), 220(4·34) ††	7·0 14·6
5-Bromo-4-dimethylamino-1,2-dihydro-1-methyl-2-methylimino	‡	303(3·89), *261(3·98)*, 225(4·34) ‡‡	7·0 14·6
5-Bromo-2-dimethylamino-4-methylamino	6·49 ± 0·06(p)	*293(3·51)*, 229(4·50) 307(3·81), 242(4·26), 220(4·31)	1·0 9·4
5-Bromo-4-dimethylamino-2-methylamino	6·12 ± 0·04(p)	*304(3·79)*, 226(4·39) 313(3·86), 229(4·35)	1·0 9·4
4-Chloro-2,6-bisdimethylamino	3·69 ± 0·05	266(4·05), 232(4·42) 300(3·89), 229(4·42)	1·0 7·2
4-Chloro-2,6-bismethylamino	4·06 ± 0·04(p)	308(3·75), 280(3·72), 221(4·26) 291(3·90), *242(4·05)*, 216(4·44)	1·0 6·4
4-Chloro-2,3-dihydro-2-imino-3-methyl-6-methylamino	12·17 ± 0·06	278(3·94), *243(4·08)*, 214(4·37) *302(3·58)*, *239(4·29)*	7·0 15·0
4-Chloro-3,6-dihydro-6-imino-3-methyl-2-methylamino	12·88 ± 0·04	282(3·81), 216(4·33) 310(3·49), 239(4·32)	7·0 15·0
4-Chloro-6-dimethylamino-2,3-dihydro-2-imino-3-methyl	12·72 ± 0·03	284(4·04), 215(4·35) 274(3·98)	7·0 15·0
4-Chloro-6-dimethylamino-2,3-dihydro-3-methyl-2-methylimino	—	294(3·97), 221(4·43)	7·0
4-Chloro-2-dimethylamino-6-methylamino	4·00 ± 0·05(p)	315(3·64), 231(4·38) 296(3·86), *248(4·16)*, 222(4·38)	1·0 7·7
4-Chloro-6-dimethylamino-2-methylamino	4·03 ± 0·05	*326(3·34)*, 280(3·96), 222(4·32) 296(3·94), 222(4·40)	1·0 7·2

TABLE. (*Continued.*)

Derivative	pK_a *	$\lambda_{max.}$ (log ε) †	pH
2,4-Diamino	7·26 §§	266(3·73)	1·0
		282(3·84), 228(3·97)	10·4
2,4-Diamino-5-bromo		282(3·64)	1·0
	5·60 ± 0·03(p)	295(3·83), 230(4·06)	9·4
2,4-Diamino-6-chloro §		298(3·92), 227(4·05)	1·0
	3·57	282(3·87), *228(3·98)*	7·0
1,4-Dihydro-4-imino-1-methyl	12·22	260(4·23) ¶¶	14·8
1,2-Dihydro-2-imino-1-methyl-4-methylamino	13·14 ± 0·05	270(3·96), 239(4·13), 209(3·40)	7·0
		297(3·57), 234(4·35)	15·0
1,4-Dihydro-4-imino-1-methyl-2-methylamino	14·0 §	277(3·77), *225(4·26)*, 213(4·37)	10·0
		310(3·25), 236(4·36)	15·6
2-Dimethylamino-1,4-dihydro-4-imino-1-methyl	13·51 ± 0·02	279(3·94), *250(4·02)*, 211(4·34)	7·0
		268(3·92)	15·0
4-Dimethylamino-1,2-dihydro-2-imino-1-methyl	13·68 ¶	279(4·00), 247(4·01), 211(4·35)	7·0
		268(3·94)	15·6
2-Dimethylamino-1,6-dihydro-1-methyl-6-methylimino (?)	*c* 10·6	*280(3·70)*, 232(4·38)	7·0
		290(3·74), 239(4·31)	13·0
4-Dimethylamino-1,2-dihydro-1-methyl-2-methylimino	13·85 ± 0·02	281(3·99), *255(3·99)*, 217(4·35)	7·0
		267(4·02)	15·6
2-Dimethylamino-4-methylamino	8·10 ± 0·05(p)	*280(3·61)*, 226(4·50)	1·0
		296(3·82), *245(4·15)*, 219(4·36)	10·4

* Measured at 20° spectrometrically or potentiometrically (p) at M/200; cf. Albert and Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. † Inflexions in italics; peaks below 220 mμ considered quantitatively doubtful. ‡ Too unstable in alkali for measurement. § From ref. 2. ¶ From ref. 5. ** I. Pitman, personal communication; cf. ref. 5. †† Stabilised within 3 min. to 269(4·02), 228(4·22). ‡‡ Stabilised similarly to 270(4·00), 232(4·18). §§ From: Albert, Goldacre, and Phillips, *J.*, 1948, 2240. ¶¶ Cf. Brown, Hoerger, and Mason, *J.*, 1955, 4035.

When the last-mentioned bases were methylated at N-1, the usual 6 log unit increase in basic strength occurred to yield bases of pK_a 13—14. The only case of methylation at N-3 produced a more modest base (III; R = Me, R′ = H) of pK_a 10·6. This relationship was parallel to that of the chlorinated 3-methyl-derivative (III; R = H, R′ = Cl) and its 1-methyl-isomer (pK_a 9·9 and 11·9, respectively). The homologues of the latter were about one unit weaker as bases than were the parent molecules. The 5-bromo-derivatives were too unstable in alkali for accurate measurement of their constants even by the rapid reaction technique, but a similar relationship is suggested by the simple analogues previously discussed.[5]

Although the spectra and pK_a values provided no unequivocal answer to the tautomeric structure of 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine, they did confirm, for all practical purposes, the expected diamino-nature of 2,4-diaminopyrimidine and its 6-chloro-derivative. In these respects the parent amine closely resembled the fixed structure (IV; R = Me, R′ = H) but differed markedly from the 1-methylated bases (I; R = Me) and (II; R = Me) and the 3-methylated base (III; R = Me, R′ = H). Similarly, 2,4-diamino-6-chloropyrimidine [2] resembled the base (IV; R = Me, R′ = H, R″ = Cl) but differed from the 1-methyl-derivative (V) and the 3-methyl-derivative (III; R = H, R′ = Cl). Although 2,4-diamino-5-bromopyrimidine likewise spectrally resembled the fixed form (IV; R = Me, R′ = Br, R″ = H), meaningful comparison with other forms was impossible.

The spectra of the cations were generally hyposochromically displaced from those of the free bases, but in some dimethylamino-derivatives the band of longest wavelength was bathochromically displaced, unless an additional band had appeared in the cation. These exceptions are exemplified in the simple chloro-diamines (IV; R = H or Me, R′ = H, R″ = Cl) and in the nuclear-methylated derivatives (I; R = Me), (II; R = Me), and (V). Attempts to correlate this behaviour with any likely variation in the site of protonation were unconvincing.

Experimental

Analyses were done by Dr. J. E. Fildes and her staff. Compounds were checked for homogeneity by paper chromatography in butanol–acetic acid and in 3% ammonium chloride, followed by examination under light of 254 and 365 mμ. Spectra were measured with a Shimadzu RS27 spectrophotometer, and peaks checked on a manual instrument.

General Amination Procedure.—The chloropyrimidine (10·0 g.) and 33% ethanolic methylamine or dimethylamine (*c.* 50 ml.) were set aside at room temperature for 1—2 days. After removal of solvent, the residue was washed with a little water and recrystallised from ethanol, to give the aminated pyrimidine in >80% yield.

In this way 4-chloro-2,6-bisdimethylaminopyrimidine was formed directly from 2,4,6-trichloropyrimidine [11] (cf. poor yield by indirect route [12]); 2,4-dichloro-6-methylaminopyrimidine [13] gave 4-chloro-2,6-bismethylaminopyrimidine, m. p. 133° (lit.,[13] 133°), as well as 2-*chloro*-4,6-*bismethylaminopyrimidine* (0·7 g.), obtained as an ethanol-insoluble residue, m. p. 258—259° (from dimethylformamide) (Found: C, 42·25; H, 5·4; N, 32·2. $C_6H_9ClN_4$ requires C, 41·7; H, 5·2; N, 32·5%); 2-amino-4-chloro-6-methylaminopyrimidine (from 2-amino-4,6-dichloropyrimidine) had m. p. 164° (lit.,[12] 164°); 4-amino-6-chloro-2-methylaminopyrimidine (from 4-amino-2,6-dichloropyrimidine) had m. p. 202° (lit.,[2] 200°); 2-amino-4-chloro-6-dimethylaminopyrimidine (from 2-amino-4,6-dichloropyrimidine) had m. p. 165° (lit.,[12] 165°); 4-amino-6-chloro-2-dimethylaminopyrimidine (from 4-amino-2,6-dichloropyrimidine) had m. p. 152° (lit.,[14] 151°); 4-chloro-2-dimethylamino-6-methylaminopyrimidine (from 2,4-dichloro-6-methylaminopyrimidine or 4,6-dichloro-2-dimethylaminopyrimidine) had m. p. 78° (lit.,[12,14] 78°) [in the former case, 2-*chloro*-4-*dimethylamino*-6-*methylaminopyrimidine* (0·6 g.), m. p. 206—207° was also isolated by its relative insolubility in alcohol (Found: C, 44·8; H, 5·8; N, 30·1. $C_7H_{11}ClN_4$ requires C, 45·0; H, 5·9; N, 30·0%)]; and 4-*chloro*-6-*dimethylamino*-2-*methylaminopyrimidine* (from 2,4-dichloro-6-dimethylaminopyrimidine [15] or 4,6-dichloro-2-methylaminopyrimidine [12]) had m. p. 181—182° (Found: C, 45·2; H, 5·9; N, 30·1. $C_7H_{11}ClN_4$ requires C, 45·0; H, 5·9; N, 30·0%).

General Dechlorination Procedure.—The chloropyrimidine (5·0 g.) was hydrogenated at 25° in water over 5% palladium–chlorcoal (3·0 g.) and magnesium oxide (4·0 g.). The suspension was filtered hot and the solid was extracted with acetone. The filtrate and extracts were made alkaline with sodium carbonate and evaporated *in vacuo* to dryness. Extraction with ethyl acetate, followed by evaporation and recrystallisation gave the dechlorinated diaminopyrimidine. In this way, 2,4-diamino-6-chloropyrimidine gave 2,4-diaminopyrimidine (98%), m. p. 145° (from ethyl acetate) (lit.,[16] 145°); 4-amino-6-chloro-2-dimethylaminopyrimidine gave 4-*amino*-2-*dimethylaminopyrimidine* (84%), m. p. 151—152° (from benzene) (Found: C, 52·6; H, 7·4; N, 40·65. $C_6H_{10}N_4$ requires C, 52·15; H, 7·3; N, 40·55%); 4-chloro-2-dimethylamino-6-methylaminopyrimidine gave 2-*dimethylamino*-4-*methylaminopyrimidine* (84%), m. p. 77—78° (from light petroleum or by sublimation) (Found: C, 55·5; H, 8·1; N, 37·1. $C_7H_{12}N_4$ requires C, 55·2; H, 7·95; N, 36·8%); 4-chloro-6-dimethylamino-2-methylaminopyrimidine gave 4-dimethylamino-2-methylaminopyrimidine (50%), m. p. 98° (lit.,[5] 98°); and 4-chloro-2,6-bisdimethylaminopyrimidine gave 2,4-*bisdimethylaminopyrimidine* (58%), b. p. 98°/0·9 mm., m. p. 47—49° (Found: C, 57·6; H, 8·4; N, 33·6. $C_8H_{14}N_4$ requires C, 57·8; H, 8·5; N, 33·7%). Its *picrate* had m. p. 168—169° (Found: C, 43·0; H, 4·3. $C_{14}H_{17}N_7O_7$ requires C, 42·5; H, 4·3%).

General Bromination Procedure.—Bromine (1·6 g.) was added dropwise with shaking to the pyrimidine (0·01 mol.) in acetic acid (15 ml.). An aqueous solution of the resulting solid was adjusted to pH 7—8 and the bromopyrimidine recrystallised from water. A second crop from the filtrates and washings increased the yield to 80—90%.

The following pyrimidines were so obtained from their 5-debromo-analogues: 2-*amino*-5-*bromo*-4-*methylaminopyrimidine*, m. p. 145—146° (Found: C, 29·5; H, 3·35; N, 27·45. $C_5H_7BrN_4$ requires C, 29·6; H, 3·45; N, 25·6%); 4-*amino*-5-*bromo*-2-*methylaminopyrimidine*, m. p. 120—121° (Found: C, 29·7; H, 3·45; N, 27·6. $C_5H_7BrN_4$ requires C, 29·6; H, 3·45; N, 27·6%); 2-*amino*-5-*bromo*-4-*dimethylaminopyrimidine*, m. p. 114—115° (Found: C, 33·3;

[10] Katritzky and Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 412.
[11] Masuda, *Pharm. Bull.* (*Japan*), 1957, **5**, 28.
[12] Boon, *J.*, 1957, 2146.
[13] Winkelmann, *J. prakt. Chem.*, 1927, **115**, 292.
[14] Boon, *J.*, 1952, 1532.
[15] King and King, *J.*, 1947, 726.
[16] Büttner, *Ber.*, 1903, **36**, 2227.

H, 4·3; N, 25·7. $C_6H_9BrN_4$ requires C, 33·2; H, 4·15; N, 25·8%); *4-amino-5-bromo-2-dimethylaminopyrimidine*, m. p. 139—140° (Found: C, 33·2; H, 4·3; N, 25·9. $C_6H_9BrN_4$ requires C, 33·2; H, 4·15; N, 25·8%); *5-bromo-2-dimethylamino-4-methylaminopyrimidine*, m. p. 70—71° (Found: C, 36·8; H, 4·8; N, 24·0. $C_7H_{11}BrN_4$ requires C, 36·4; H, 4·8; N, 24·2%), and *5-bromo-4-dimethylamino-2-methylaminopyrimidine*, m. p. 121—122° (Found: C, 36·1; H, 4·8; N, 24·0. $C_7H_{11}BrN_4$ requires C, 36·4; H, 4·8; N, 24·2%).

General Methylation Procedure.—The diaminated pyrimidine (0·5 g.) was refluxed with ethanol (3 ml.) and methyl iodide (2 ml.) for 3 hr. (increased to 8 hr. for a bromo-, and 24 hr. for a chloro-derivative). After chilling, the solid was removed and recrystallised from ethanol, to give the hydriodide of the methylated pyrimidine. Silver chloride thence gave the hydrochloride.

This method gave: *1,2-dihydro-2-imino-1-methyl-4-methylaminopyrimidine hydriodide* (95%), m. p. 215—217° (decomp.) (Found: C, 27·1; H, 3·8; N, 20·8. $C_6H_{11}IN_4$ requires C, 27·1; H, 4·1; N, 21·05%), and the *hydrochloride*, m. p. 301° (decomp.) (from acetone–ethanol) (Found: N, 32·1. $C_6H_{11}ClN_4$ requires N, 32·1%); *2-dimethylamino-1,4-dihydro-4-imino-1-methylpyrimidine hydriodide* (35%), m. p. 280—281° (decomp.) (Found: C, 29·9; H, 4·6; N, 20·0. $C_7H_{13}IN_4$ requires C, 30·0; H, 4·6; N, 20·0%) and the *hydrochloride*, m. p. 287° (decomp.) (from acetone–ethanol) (Found: N, 30·0. $C_7H_{13}ClN_4$ requires N, 29·7%); *4-dimethylamino-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydriodide* (36%), m. p. 220—221° (Found: C, 32·6; H, 5·1; N, 19·0. $C_8H_{15}IN_4$ requires C, 32·65; H, 5·1; N, 19·05%), and the *hydrochloride*, m. p. 266—267° (decomp.) (from acetone–ethanol) (Found: N, 27·3. $C_8H_{15}ClN_4$ requires N, 27·65%); *2-dimethylamino-1,6-dihydro-1-methyl-6-methyliminopyrimidine*(?) *hydriodide* (75%, from 2-dimethylamino-4-methylaminopyrimidine), m. p. 146—148° (Found: C, 32·9; H, 5·15; N, 19·2. $C_8H_{15}IN_4$ requires C, 32·65; H, 5·1; N, 19·05%), the *hydrochloride*, m. p. 194—197° (decomp.) (from acetone) (Found: N, 28·0. $C_8H_{15}ClN_4$ requires N, 27·65%), and the *picrate*, m. p. 167—169° (depressed on admixture with 2,4-bisdimethylaminopyrimidine picrate, above) (Found: C, 43·1; H, 4·6. $C_{14}H_{17}N_7O_7$ requires C, 42·5; H, 4·3%); *2(4)-amino-5-bromo-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine hydriodide* (68%), m. p. 234—236° (decomp.) (from water) (Found: C, 17·9; H, 2·5; N, 16·7. $C_5H_8BrIN_4$ requires C, 18·1; H, 2·4; N, 16·9%) and the *hydrochloride*, m. p. 289° (decomp.) (from methanol) (Found: N, 23·2. $C_5H_8BrClN_4$ requires N, 23·4%); *5-bromo-1,4-dihydro-4-imino-1-methyl-2-methylaminopyrimidine hydriodide* (67%), m. p. 249—250° (decomp.) (Found: C, 21·1; H, 3·0; N, 16·1. $C_6H_{10}BrIN_4$ requires C, 20·9; H, 2·9; N, 16·2%) and the hydrated *hydrochloride*, m. p. 209—210° (from acetone–ethanol) (Found: C, 26·4; H, 4·4. $C_6H_{10}BrClN_4,H_2O$ requires C, 26·5; H, 4·4%); *5-bromo-1,2-dihydro-2-imino-1-methyl-4-methylaminopyrimidine hydriodide* (60%), m. p. 255° (decomp.) (Found: C, 20·9; H, 2·8; N, 15·9. $C_6H_{10}BrIN_4$ requires C, 20·9; H, 2·9; N, 16·2%) and the *hydrochloride*, m. p. 280—281° (decomp.) (Found: N, 22·2. $C_6H_{10}BrClN_4$ requires N, 22·1%); *5-bromo-4-dimethylamino-1,2-dihydro-2-imino-1-methylpyrimidine hydriodide* (84%), m. p. 248—250° (decomp.) (from methanol) (Found: C, 23·5; H, 3·35; N, 15·6. $C_7H_{12}BrIN_4$ requires C, 23·4; H, 3·3; N, 15·6%) and the *hydrochloride*, m. p. 227—230° (Found: N, 20·6. $C_7H_{12}BrClN_4$ requires N, 20·9%); *5-bromo-4-dimethylamino-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydriodide* (79%), m. p. 185—186° (Found: C, 25·9; H, 3·8; N, 14·9. $C_8H_{14}BrIN_4$ requires C, 25·7; H, 3·75; N, 15·0%) and the *hemi-hydrated hydrochloride*, m. p. 208—209° (from acetone–ethanol) (Found: C, 33·1; H, 5·4; N, 19·3. $C_8H_{14}BrClN_4,0·5H_2O$ requires C, 33·0; H, 5·2; N, 19·3%); *2(4)-amino-4(6)-chloro-3,6(1,2)-dihydro-6(2)-imino-3(1)-methylpyrimidine hydriodide* (56%), m. p. 268—270° (decomp.) (from water) (Found: C, 21·0; H, 2·9; N, 19·55. $C_5H_8ClIN_4$ requires C, 20·9; H, 2·8; N, 19·55%) and the *hydrochloride*, m. p. 272—273° (decomp.) (from methanol) (Found: C, 30·5; H, 4·5. $C_5H_8Cl_2N_4$ requires C, 30·8; H, 4·1%); *4-chloro-3,6-dihydro-6-imino-3-methyl-2-methylaminopyrimidine hydriodide* (52%), m. p. 245—247° (decomp.) (Found: C, 24·0; H, 3·6; N, 18·4. $C_6H_{10}ClIN_4$ requires C, 24·0; H, 3·3; N, 18·6%) and the *hydrochloride*, m. p. 272—273° (decomp.) (from methanol) (Found: C, 34·2; H, 5·0. $C_6H_{10}Cl_2N_4$ requires C, 34·45; H, 4·8%); *4-chloro-2,3-dihydro-2-imino-3-methyl-6-methylaminopyrimidine hydriodide* (52%), m. p. 222° (decomp.) (from acetone–ethanol) (Found: C, 24·4; H, 3·45; N, 18·4. $C_6H_{10}ClIN_4$ requires C, 24·0; H, 3·3; N, 18·6%) and the *hydrochloride*, m. p. 239° (decomp.) (Found: N, 26·7. $C_6H_{10}Cl_2N_4$ requires N, 26·8%); *4-chloro-2,3-dihydro-6-dimethylamino-2-imino-3-methylpyrimidine hydriodide* (58%), m. p. 203—204° (decomp.) (Found: C, 27·05; H, 4·0; N, 17·3. $C_7H_{12}ClIN_4$ requires C, 26·7; H, 3·8; N, 17·8%) and the *hydrochloride*, m. p. 232—233° (decomp.) (from acetone–ethanol) (Found: N, 24·95. $C_7H_{12}Cl_2N_4$

requires N, 25·1%); and *4-chloro-2,3-dihydro-6-dimethylamino-3-methyl-2-methyliminopyrimidine hydriodide* (62%), m. p. 195—197° (from acetone–ethanol) (Found: N, 16·9. $C_8H_{14}ClIN_4$ requires N, 17·05%) and the *hydrochloride*, m. p. 200—201° (decomp.) (Found: N, 23·8. $C_8H_{14}Cl_2N_4$ requires N, 23·6%).

Attempted methylation of 4-amino-6-chloro-2-dimethylaminopyrimidine as above, or with methyl iodide alone at 100° for 5 hr., gave only its *hydriodide*, m. p. 251° (decomp.) (from methanol) (Found: C, 24·1; H, 3·4; N, 18·4. $C_6H_{10}ClIN_4$ requires C, 24·0; H, 3·3; N, 18·6%), converted into the *hydrochloride*, m. p. 226—228° (Found: N, 27·0. $C_6H_{10}Cl_2N_4$ requires N, 26·8%). Similarly 4-chloro-2-dimethylamino-6-methylaminopyrimidine gave its *hydriodide*, m. p. 218° (decomp.) (Found: C, 26·3; H, 4·0; N, 17·8. $C_8H_{14}ClIN_4$ requires C, 26·7; H, 3·8; N, 17·8%) and the *hydrochloride*, m. p. 219—221° (from acetone) (Found: N, 24·7. $C_8H_{14}Cl_2N_4$ requires N, 25·1%).

Dehalogenation of Typical Methylated Derivatives.—2-Amino-4-chloro-3,6-dihydro-6-imino-3-methylpyrimidine hydrochloride (0·4 g.) was hydrogenated at 25° in water (20 ml.) over 5% palladium–charcoal (0·5 g.). The filtrate was evaporated *in vacuo* to dryness. Recrystallisation of the residue from methanol gave 2-amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (0·3 g.), m. p. 276° (decomp.) undepressed on admixture with authentic material.[2] Both samples of hydrochloride yielded the same *picrate*, m. p. 253—255° (decomp.) (from alcohol) (Found: C, 37·8; H, 3·1. $C_{11}H_{11}N_7O_7$ requires C, 37·5; H, 3·1%). When treated similarly, 4-chloro-6-dimethylamino-2,3-dihydro-3-methyl-2-methyliminopyrimidine hydrochloride gave 4-dimethylamino-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydrochloride, identified by mixed m. p.

Debromination of 2-amino-5-bromo-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (0·6 g.) in the same way gave a mixed hydrohalide (0·42 g.) of 2-amino-1,4-dihydro-4-imino-1-methylpyrimidine, identified as the picrate described above. Similarly, 5-bromo-4-dimethylamino-1,2-dihydro-2-imino-1-methylpyrimidine hydriodide gave its 5-debromo-analogue, identified as the *picrate* (Found: C, 41·3; H, 3·8. $C_{13}H_{15}N_7O_7$ requires C, 41·0; H, 4·0%). It had m. p. 186—187°, undepressed by picrate made from authentic hydriodide.[5]

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