239. *The Dimroth Rearrangement. Part I. Some Alkylated 2-Iminopyrimidines.*

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

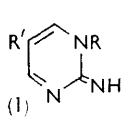
The rearrangement of 1-alkyl-1,2-dihydro-2-iminopyrimidines to the corresponding 2-alkylaminopyrimidines proceeds by a slow rate-determining ring fission and a relatively rapid recyclization. The change is conveniently followed spectrometrically and the rate obeys a first-order equation when it is determined at a wavelength where by-products do not interfere. The fission reaction is mildly hastened by increase in size of the *N*-alkyl group; it is profoundly hastened through electron-depletion of the ring by a bromo-substituent, and retarded by stabilizing the ring with an electron-releasing *C*-alkyl or dimethylamino-substituent. Ionization constants, spectra, and the rates of reaction expressed as times of half completion, are tabulated and discussed. Several wrongly assigned structures and constants in the literature of the imines are corrected.

The apparent migration[1] of an alkyl group from heterocyclic nitrogen to an α-amino- or -imino-group was first reported by Rathke in 1888. It became soundly based in 1909 when Dimroth described the rearrangement of 5-amino-1-phenyl- into 5-anilino-1,2,3-triazole. Studies with nitrogen-15 have shown[2] that his postulated mechanism of ring fission and recyclization is correct for the ready conversion[3,4] of 1,2-dihydro-2-imino-1-methylpyrimidine (I; R = Me, R′ = H) into 2-methylaminopyrimidine (II; R = Me, R′ = H), and to examples already noted[2] may be added others in the pteridine,[5] pyridine,[6] pyrimidine,[7–9] purine,[10] and quinazoline[11] series. Study of these and of several failures to rearrange[12–15] suggests that the ease of the reaction increases mildly with the size of alkyl group, or with electron depletion of the ring, and decreases with electron-enrichment. In this and the following[16] paper, the effects produced on the rearrangement of 1-alkyl-1,2-dihydro-2-iminopyrimidines (I) by electron-withdrawing and -releasing substituents and by variation of the alkyl group are examined.

Preparation of Compounds.—Variation of the *N*-alkyl group in (I; R′ = H) was confined to normal chains. 2-Aminopyrimidine gave, with appropriate alkyl iodides, 1,2-dihydro-2-imino-1-methylpyrimidine hydriodide,[4] and its ethyl, butyl, and heptyl homologues, further characterized as hydrochlorides and picrates. As noted in the Experimental section, Kogon[8] has assigned the wrong constitution and constants to several of these compounds. Each imine was allowed to rearrange in hot alkali to the corresponding 2-alkylaminopyrimidine (II; R′ = H) isolated also as the hydrochloride and picrate for comparison. These, and representative hydriodides, were made unambiguously by the action of alkylamines on 2-chloropyrimidine.

[1] Rathke, *Ber.*, 1888, **21**, 867; Dimroth, *Annalen*, 1909, **364**, 183.
[2] Brown, *Nature*, 1961, **189**, 828.
[3] Carrington, Curd, and Richardson, *J.*, 1955, 1858.
[4] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[5] Brown and Jacobsen, *Tetrahedron Letters*, 1960, No. 25, p. 17; Angier and Curran, *J. Amer. Chem. Soc.*, 1959, **81**, 5650.
[6] Gol'dfarb and Danyushevskii, *Doklady Akad. Nauk S.S.S.R.*, 1952, **87**, 223.
[7] Gluntz, *Diss. Abs.*, 1961, **21**, 2476.
[8] Kogon, *J. Org. Chem.*, 1956, **21**, 1027.
[9] Brown and Harper, *J.*, 1961, 1298.
[10] Elion, in " The Chemistry and Biology of Purines," Churchill Ltd., London, 1957, p. 44; *J. Org. Chem.*, 1962, **27**, 2478; Fischer, *Ber.*, 1898, **31**, 542; Leese and Timmis, Abs. 7th Internat. Cancer Congress, London, 1958, p. 144.
[11] Taylor and Ravinoranathan, *J. Org. Chem.*, 1962, **27**, 2622.
[12] Angier and Curran, *J. Org. Chem.*, 1961, **26**, 1891.
[13] Brookes and Lawley, *J.*, 1962, 1348.
[14] Jacobsen, Ph.D. Thesis, Canberra, 1961, p. 56.
[15] Curran and Angier, *J. Amer. Chem. Soc.*, 1958, **80**, 6095.
[16] Part II, Perrin, *J.*, following paper.

The effect of an electron-withdrawing group is exemplified in 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (I; R = Me; R′ = Br). Rearrangement of the imine occurred in a few seconds in warm ammonia to give 5-bromo-2-methylaminopyrimidine (II; R = Me, R′ = Br), also made unambiguously by brominating 2-methylaminopyrimidine. An attempt to use similarly the more powerfully withdrawing nitro-group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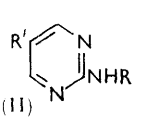
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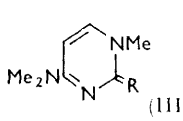
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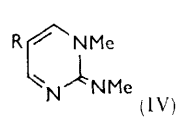
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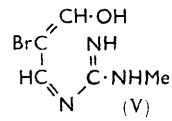
(V)

was unsuccessful because 2-amino-5-nitropyrimidine (pK_a 0·35) was too weakly basic to be methylated. Steric factors probably account for failure to methylate 2-amino-4,6-diphenylpyrimidine (pK_a 3·8).

The effect of mildly electron-releasing groups was exemplified in *C*-alkyl derivatives. Thus 2-amino-5-ethylpyrimidine (made by catalytic dehalogenation of its 4,6-dichloro-derivative) and 2-amino-4,6-dimethylpyrimidine were *N*-methylated and the imines subsequently rearranged to 5-ethyl- and 4,6-dimethyl-2-methylaminopyrimidine. These were made unambiguously by methylamination of 2-chloro-5-ethylpyrimidine (produced from the 2-amino-analogue by diazotization) and 2-chloro-4,6-dimethylpyrimidine respectively. A stronger degree of electron-release would ideally be found in the 5-amino-analogue (I; R = Me, R′ = NH_2), but methylation of 2,5-diaminopyrimidine was unsatisfactory. On the other hand, although 2,4-diaminopyrimidine is methylated well [17] the preferred tautomeric form of the resulting 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpyrimidine is unknown, making results from it difficult to interpret. This was obviated by using 2-amino-4-dimethylaminopyrimidine made by dehalogenation of its 6-chloro-derivative.[18] Methyl iodide gave a strongly basic methyl derivative shown to be 4-dimethylamino-1,2-dihydro-2-imino-1-methylpyrimidine (III; R = NH) by alkaline hydrolysis to the corresponding 2-oxo-derivative (III; R = O).[19] During this reaction, another substance was slowly formed. It was not isolated but corresponded chromatographically to the rearrangement product, 4-dimethylamino-2-methylaminopyrimidine, which was made unambiguously from 2-chloro-4-dimethylaminopyrimidine [20] by amination.

Several alkyliminopyrimidines such as (IV; R = H) and (IV; R = Br) were made from the appropriate secondary bases. These (the first examples in this series) closely resembled the corresponding imines in their ability to hydrolyze and even to ring-open, but were by their very nature unable to recyclize to an isomer.

The Rearrangements.—The Dimroth rearrangement consists [16] of two distinct reactions, presumably ring-opening and -reclosure. In the present paper the comparative susceptibility to rearrangement of various iminopyrimidines is expressed simply as the time for half the initial imine to disappear under standardized conditions ($t_{\frac{1}{2}}$). This was done by plotting, against time, the change in ultraviolet spectrum of the free base, most conveniently at a wavelength (*ca.* 350 mμ) where only the imine absorbed. Thus the spectrum of 1,2-dihydro-2-imino-1-methylpyrimidine changed progressively until after several hours it approximated to that of authentic 2-methylaminopyrimidine (Fig. 1) except for a minor flat peak at *ca.* 270 mμ. The plot (Fig. 2) of log (optical density) at 350 mμ against time is linear, indicating that the disappearance of imine is a reaction of first order with $t_{\frac{1}{2}}$ = 114 min. The formation of 2-methylaminopyrimidine, represented by the rise of the peak at 306 mμ, occurs at a similar rate ($t_{\frac{1}{2}}$ = 108 min.), thus precluding an appreciable build up of intermediate. This, coupled with the fact that the rapid reaction technique [16]

[17] Brown and Jacobsen, *J.*, 1962, 3172.
[18] Boon, *J.*, 1957, 2146.
[19] Kenner, Reese, and Todd, *J.*, 1955, 855.
[20] Westphal, U.S. Patent 2,219,858 (1940).

gave no indication of an initial fast reaction, shows that the rearrangement must here consist of a slow (rate-determining) ring fission followed by a relatively rapid reclosure. Similar results were obtained for rearrangement of the other imines bearing only alkyl substituents, although the formation of by-products in small and varying quantities caused the general picture to vary in detail. These by-products are thought to arise by hydrolysis, because related imines, which do not ring-open or rearrange (*e.g.*, 1,4-dihydro-4-imino-1-methylpyrimidine [4]), normally undergo slow alkaline hydrolysis to the corresponding oxo-derivative. In addition a minor peak at *ca.* 270 mμ slowly emerges during rearrangement of the imines, and gradually becomes more intense over a longer period; this behaviour is shared for example by 1,2-dihydro-1-methyl-2-oxopyrimidine in similar circumstances. In the rearrangement of 1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine, this

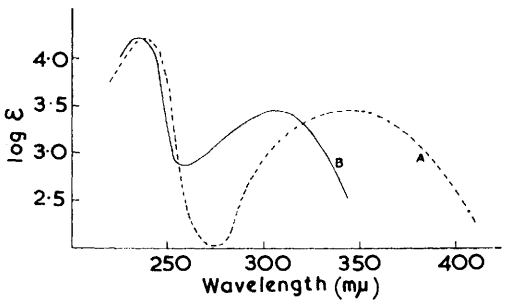

FIG. 1. Ultraviolet absorption of neutral molecules. A, 1,2-Dihydro-2-imino-1-methylpyrimidine; B, 2-methylaminopyrimidine.

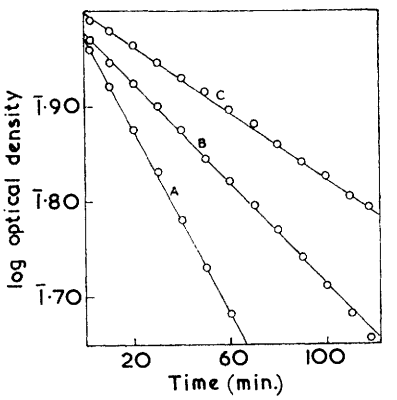

FIG. 2. Plot of log $(D - D_\infty)$ against time for 4×10^{-4}M-solutions at 25° and pH 14. A, 1-Ethyl-1,2-dihydro-2-iminopyrimidine at 347 mμ; B, 1,2-dihydro-2-imino-1-methylpyrimidine at 350 mμ; C, 1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine at 335 mμ.

extraneous peak is bathochromically displaced so that it overlaps the hypsochromically displaced 300 mμ peak of the major product. The resulting sharp composite peak ($\lambda_{max.}$ 297 mμ) eventually reaches almost twice the expected extinction, so that the rate of formation of 4,6-dimethyl-2-methylaminopyrimidine cannot be followed by measurements in this region. Two fortuitous isosbestic points (Fig. 3) are maintained throughout the whole sequence. Inspection of the curves suggests that 1,2-dihydro-2-imino-1-methylpyrimidine, for example, is hydrolyzed to the extent of about 10% at the expense of the rearrangement.

From 4-dimethylamino-1,2-dihydro-2-imino-1-methylpyrimidine (III; R = NH) the major product was the corresponding oxo-compound (III; R = O) with relatively little rearranged material. The slow formation of this minor product could not be followed spectrometrically, so that the reaction rate had to be studied qualitatively, by paper chromatography of samples taken periodically. On the other hand, the rearrangement of 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (I; R = Br) was so fast as to necessitate use of the rapid-reaction technique for measuring the spectra.[16] Moreover, in this case the fission reaction was much faster than subsequent ring closure (see below). The corresponding methylimine (V; R = Br) underwent ring fission rather less rapidly.

Discussion.—As suggested above, the $t_{\frac{1}{2}}$ values recorded in the Table represent the ease of opening of the ring of the free iminopyrimidines, in most cases the rate-determining step in rearrangement. It is therefore here that altered or additional groups will be seen to exert their effects.

Variation of the *N*-alkyl group can have little electronic effect on the molecule, as indicated in the close similarity of the pK_a values of the four related imines in the Table. The reason for the change in $t_{\frac{1}{2}}$ from methyl to heptyl derivatives must therefore be sought elsewhere. Steric hindrance to the appoach of a hydroxyl ion is not involved since absence of base catalysis [16] suggests that the initial step in ring-opening involves heterolytic fission. However it is possible that the increasing size of the alkyl group interferes sterically with the re-formation of the broken C–N bond, thus facilitating rearrangement.

Addition of electron-releasing *C*-alkyl groups, accompanied naturally by a rise in basic strength, leads to the slower rearrangement of 5-ethyl-1,2-dihydro-2-imino-1-methylpyrimidine and its 4,6-dimethyl-analogue. Addition of the powerfully-releasing dimethylamino-group (pK_a 13·7) so profoundly slows rearrangement that hydrolysis becomes the predominant reaction. In general terms, it is a matter of electron release restabilizing

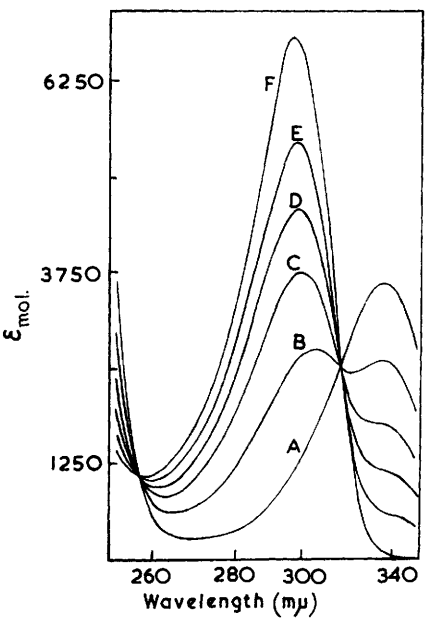

FIG. 3. Ultraviolet absorption of a solution at 25° and pH 14 initially containing 1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine, and recorded after 0 hr. (A), 2 hr. (B), 4 hr. (C), 6 hr. (D), 9 hr. (E), and 30 hr. (F).

the 1,6-bond of a semi-aromatic ring (I; R′ = H) previously depleted of π-electrons by its nitrogen atoms.

The results of adding an electron-withdrawing group are discussed in detail in Part II [16] for the case of 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (I; R = Me, R′ = Br) in which the rates of the two consecutive reactions have been measured. The ring-fission reaction is the one to be compared with other values in the Table and its rapidity is indicated by a $t_{\frac{1}{2}}$ value of 0·9 min. This results from electron depletion of the π-layer, experimentally evident in the marked lowering of pK_a. Reversal of the relative rates of fission and recyclization arises because a ring-open intermediate such as (V) would be stabilized by electron-withdrawal from the hydroxyl group which must be lost as OH^- on cyclization. The closure rate is therefore diminished ($t_{\frac{1}{2}}$ = 26 min.). In comparison with this bromo-imine, the bromo-methylimine (IV; R = Br) clearly reflected electron-release by the added methyl group, not only in a higher pK_a but also in a fourfold slowing ($t_{\frac{1}{2}}$ = *ca.* 4 min.) of ring fission.[16]

Ionization and Spectra.—The pK_a values in the Table and at the end of the Experimental provide interesting comparisons with 2-aminopyrimidine [21] (pK_a 3·54). Electron

[21] Brown and Short, *J.*, 1953, 331.

Ionisation and spectra of pyrimidine derivatives.

Compound	$t_{\frac{1}{2}}$ [a]	pK_a [b]	$\lambda_{max.}$ (log ε) [c]	pH
1,2-Dihydro-2-iminopyrimidine derivatives				
1-Methyl	114	10·75 [d]	347 (3·45), 237 (4·22)	13·0
			302 (3·64), 223 (4·09)	7·6
1-Ethyl	63	10·94 ± 0·02 (M/200)	350 (3·44), 240 (4·21)	13·0
			304 (3·63), 224 (4·07)	7·6
1-Butyl	58	10·93 ± 0·02 (M/200)	350 (3·46), 241 (4·21)	13·0
			304 (3·60), 225 (4·03)	7·6
1-Heptyl	57	10·86 ± 0·03 (M/200)	351 (3·44), 241 (4·18)	13·0
			304 (3·64), 224 (4·09)	7·6
5-Ethyl-1-methyl	196	11·45 ± 0·04 (sp.)	357 (3·47), 243 (4·25)	14·0
			311 (3·64), 225 (4·20)	7·0
1,4,6-Trimethyl	166 [e]	11·56 ± 0·02 (sp.)	335 (3·57), 240 (4·13)	14·0
			296 (3·80), 224 (3·99)	7·0
5-Bromo-1-methyl	0·9; 26 [f]	9·95 ± 0·05 (sp.) [g]	371 (3·30), 247 (4·21)	12·8 [g]
			328 (3·57), 237 (4·27)	7·0
5-Bromo-1,2-dimethyl [h]	3·8	10·67 ± 0·05 (M/200)	252 (4·15) [i]	12·8
			340 (3·53), 241 (4·34)	7·0
4-Dimethylamino-1-methyl	*ca.* 2000 [j]	13·68 ± 0·04 (sp.)	279 (4·00), 247 (4·01), 211 (4·35)	7·0
Pyrimidine derivatives				
2-Amino-5-bromo	—	1·95 ± 0·04 (sp.)	313 (3·37), 237 (4·20)	7·0
			326 (3·48), 236 (4·26)	0·0
5-Bromo-2-methylamino	—	2·09 ± 0·04 (sp.)	327 (3·35), 246 (4·32)	6·0
			338 (3·43), 242 (4·33)	−2·0
2-Butylamino	—	4·09 ± 0·03 (M/1000)	308 (3·35), 236 (4·16)	7·6
			315 (3·48), 230 (4·18)	1·0
4-Dimethylamino-2-methylamino	—	8·11 ± 0·01 (M/200)	296 (3·94), 247 [k] (3·95), 218 (4·42)	11·0
			251 (4·04), 219 (4·41)	5·0
4,6-Dimethyl-2-methylamino	—	5·25 ± 0·03 (M/200)	300 (3·59), 236 (4·15)	8·0
			308 (3·71), 229 (4·17)	2·0
2-Ethylamino	—	4·03 ± 0·04 (M/1000)	306 (3·47), 236 (4·24)	7·6
			315 (3·58), 229 (4·26)	1·0
5-Ethyl-2-methylamino	—	4·31 ± 0·01 (M/200)	315 (3·41), 237 (4·26)	7·6
			324 (3·53), 232 (4·29)	1·0
2-Heptylamino	—	4·09 ± 0·04 (M/1000)	309 (3·41), 237 (4·25)	7·6
			318 (3·56), 230 (4·27)	1·0

[a] Time in minutes for disappearance of half of imine at 25° and pH 14. Measured at peak *ca.* 350 mμ. [b] For notes and additional values see Experimental section. [c] Extinctions for unstable free imines have been extrapolated when necessary to zero time. [d] From ref. 4. [e] $t_{\frac{1}{2}}$ = 375 min. at 20°. [f] Calculated from Part II, ref. 16. First value for fission, second for reclosure. [g] Rapid reaction technique. [h] The 2-methylimino-compound; $t_{\frac{1}{2}}$ refers to ring opening, ref. 16. [i] Another peak at >330 mμ was not measured. [j] Estimated by paper chromatography; corrected for cation present. [k] Inflexion.

enrichment by *N*-alkylation on the amino-group is seen to raise the basic strength by about 0·5 unit, and this is further raised by each *C*-alkylation as in 5-ethyl-2-methylaminopyrimidine (4·3) and 4,6-dimethyl-2-methylaminopyrimidine (5·2). Electron-depletion on the other hand sharply lowers the basic strength in 2-amino-5-bromopyrimidine (1·9) and its nitro-analogue (I; R = H, R′ = NO_2; pK_a 0·35). The smallness of the change in basic strength from 2-aminopyrimidine to its 4,6-diphenyl derivative (pK_a 3·8) would seem to be the resultant of several opposing tendencies in view of the relation of pyridine (pK_a 5·2) with its 2-, 3-, and 4-phenyl derivatives [22] (respectively, 4·48, 4·80, and 5·55).

Nuclear *N*-alkylation of 2-aminopyrimidine produces a fundamental structural change to an imine accompanied by a large increase in basic strength. Such a product as 1,2-dihydro-2-imino-1-methylpyrimidine (I; R = Me, R′ = H; pK_a 10·75) is affected by further substitution in a way similar to its parent amine (see Table).

The ultraviolet spectra of 1-alkyl-1,2-dihydro-2-iminopyrimidines (I, R′ = H) are unaffected by the length of the alkyl group but show in all peaks a small bathochromic shift on 5-ethylation, and one of 10—20 mμ on 5-bromination. The 4,6-dimethyl derivative is unusual in its hypsochromic shift of the longer-wavelength peaks of both species.

[22] Katritzky and Simmons, *J.*, 1960, 1511.

In the rearrangement products of these imines, the above relationships are repeated, even to hypsochromic shifts in 4,6-dimethyl-2-methylaminopyrimidine as compared with 2-methylaminopyrimidine.[21]

Experimental

Analyses were done by Dr. J. E. Fildes and her staff. Spectra were recorded on a Shimadzu model RS27 recording spectrophotometer.

1,2-Dihydro-2-imino-1-methylpyrimidine.—An aqueous solution of the hydriodide [4] (1 part) was shaken for 1 hr. with silver chloride (from silver nitrate, 2 parts). The residue after evaporation of the filtrate gave the *hydrochloride*, m. p. *ca.* 265° (decomp.) (from ethanol) (Found: Cl, 24·6; N, 28·9. $C_5H_8ClN_3$ requires Cl, 24·35; N, 28·8%).

1-Ethyl-1,2-dihydro-2-iminopyrimidine.—2-Aminopyrimidine (15 g.), ethyl iodide (60 ml.), and ethanol (60 ml.) were refluxed for 28 hr. Refrigeration gave the *hydriodide* (32·7 g.) which, recrystallized from ethanol (3·5 parts), had m. p. 189° (Found: C, 28·7; H, 4·0; N, 16·6. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·8%); Kogon [8] recorded m. p. 154—155° for a similarly prepared compound and inferred that it was 2-methylaminopyrimidine hydriodide. Made as the methyl homologue above, the hydrochloride (65%) had m. p. 232—233° (Found: C, 45·3; H, 6·4; Cl, 22·1. $C_6H_{10}ClN_3$ requires C, 45·15; H, 6·3; Cl, 22·2%). The hydriodide (2 g.), with saturated aqueous picric acid (200 ml.), gave the *picrate*, m. p. 178—179° (from ethanol) (Found: C, 40·7; H, 3·3. $C_{12}H_{12}N_6O_7$ requires C, 40·9; H, 3·4%).

The imine was rearranged by heating the hydriodide (0·25 g.) in N-sodium hydroxide (10 ml.) on the steam-bath for 10 min. The solution, adjusted with acetic acid to pH 5, was added to saturated aqueous picric acid (25 ml.) and the solid (0·23 g.; 70%), recrystallized from water, had m. p. 167° undepressed on admixture with 2-ethylaminopyrimidine picrate (see below) but depressed by the imine picrate above.

2-Ethylaminopyrimidine.—2-Chloropyrimidine [23] (11·4 g.) and ethanolic ethylamine (33% w/w; 50 ml.) were refluxed for 4 hr. Sodium ethoxide (from sodium, 3 g.) was added and the residue after evaporation, extracted with ether (3 × 50 ml.). Distillation gave 2-ethylaminopyrimidine (9·9 g.), b. p. 102—103°/22 mm., m. p. 58—60° (cf. lit.[8] m. p. 50—51°) (Found: C, 58·7; H, 7·25; N, 34·0. Calc. for $C_6H_9N_3$: C, 58·5; H, 7·4; N, 34·1%). Its picrate had m. p. 167—168° (lit.[8] 160—161°) (Found: C, 40·5; H, 3·5. Calc. for $C_{12}H_{12}N_6O_7$: C, 40·9; H, 3·4%). The base (0·85 g.) in anhydrous ether (35 ml.) was treated with hydrogen iodide, generated by dropwise addition of water (3·4 ml.) to a mixture of phosphorus tri-iodide (78 g.; this large excess was needed to produce anhydrous hydrogen iodide), and red phosphorus (2 g.). The red oil gradually solidified. Recrystallized from ethyl acetate (15 ml.) and washed with a little acetone, the *hydriodide* (0·35 g.) had m. p. 119° (Found: C, 28·7; H, 3·9; N, 16·6. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·8%).

1-Butyl-1,2-dihydro-2-iminopyrimidine.—2-Aminopyrimidine (9·4 g.) and butyl iodide (37 g.) were mechanically stirred on the steam-bath for 10 hr. The solid was triturated in ether (20 ml.). The product (20 g.) was recrystallized by dissolution in boiling ethanol (27 ml.) and addition of boiling ethyl acetate (150 ml.). Yield 45%. Repetition gave the *imine hydriodide*, m. p. 153—154° (Found: C, 34·7; H, 5·0. $C_8H_{14}IN_3$ requires C, 34·4; H, 5·05%). Kogon [8] recorded m. p. 144—146° for material made similarly, but erroneously inferred that it was 2-butylaminopyrimidine hydriodide. The *picrate* (made as the ethyl homologue) had m. p. 166—167° (from water) (Found: C, 44·0; H, 4·15. $C_{14}H_{16}N_6O_7$ requires C, 44·2; H, 4·25%). The *hydrochloride*, made from the hydriodide and recrystallized from 1 : 3 propan-2-ol–ethyl acetate, had m. p. 151° after drying at 100°/0·1 mm. for 6 hr. (Found: C, 50·9; H, 7·4; N, 22·15. $C_8H_{14}ClN_3$ requires C, 51·2; H, 7·5; N, 22·4%).

Rearrangement of the imine as for its homologue gave 2-butylaminopyrimidine picrate, m. p. and mixed m. p. 129—131° (*cf.* lit.[8,24]).

1,2-Dihydro-1-heptyl-2-iminopyrimidine.—2-Aminopyrimidine (23·5 g.) and heptyl iodide (80 ml.) were heated for 16 hr. as above. The ether-washed crude product was extracted with boiling ethyl acetate (12 × 1000 ml. for 10 min. each time). Refrigeration gave the *hydriodide* (25 g.) which, recrystallized from ethyl acetate (450 parts), had m. p. 120° (Found: C, 40·8; H, 6·1; N, 13·0. $C_{11}H_{20}IN_3$ requires C, 41·1; H, 6·3; N, 13·1%). It was converted, as above, into the *picrate*, m. p. 131—132° (Found: C, 48·45; H, 5·4. $C_{17}H_{22}N_6O_7$ requires C,

[23] Howard, U.S. Patent 2,477,409 (1949).
[24] Behnisch and Mietzsch, Ger. Patent 889,445 (1953); *Chem. Zentr.*, 1954, **125**, 4950.

48·35; H, 5·25%), and the hygroscopic *hydrochloride*, m. p. 74—75° (from chloroform) (Found: C, 57·5; H, 8·7; N, 18·25. $C_{11}H_{20}ClN_3$ requires C, 57·5; H, 8·8; N, 18·3%).

The hydriodide was rearranged as described above. The new base was extracted with a little ether, added to aqueous picric acid, and the ether removed by passing air through the mixture. 2-*Heptylaminopyrimidine picrate* had m. p. 102—103° (from ethanol) undepressed by material made from the authentic base below (Found: C, 48·2; H, 5·2. $C_{17}H_{22}N_6O_7$ requires C, 48·3; H, 5·25%).

2-*Heptyl-*, 2-*Pentyl-*, and 2-*Propyl-aminopyrimidine.*—These were prepared as the ethylamino-homologue. The *heptylamine* (*ca.* 60%) had b. p. 166°/18 mm., m. p. 31° (Found: C, 68·2; H, 10·0; N, 21·45. $C_{11}H_{19}N_3$ requires C, 68·35; H, 9·9; N, 21·75%); picrate, see above. The *pentylamine* (75%) had b. p. 138—139°/19 mm., n_D^{20} 1·5260 (Found: C, 65·2; H, 9·1; N, 25·45. $C_9H_{15}N_3$ requires C, 65·4; H, 9·15; N, 25·4%); *picrate*, m. p. 116—117° (Found: C, 45·5; H, 4·5. $C_{15}H_{18}N_6O_7$ requires C, 45·7; H, 4·6%). The *propylamine* had b. p. 115°/20 mm., m. p. 19·5° (Found: C, 61·1; H, 8·1; N, 30·85. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%); *picrate*, m. p. 151—152° (Found: C, 42·6; H, 4·0. $C_{13}H_{14}N_6O_7$ requires C, 42·6; H, 3·85%).

1,2-*Dihydro*-2-*imino*-1,4,6-*trimethylpyrimidine.*—2-Amino-4,6-dimethylpyrimidine [25] (5 g.) and methyl iodide (5 ml.) gave, as above, the *hydriodide* (60%), m. p. 274—275° (from ethanol) (Found: C, 31·75; H, 4·45; N, 15·65. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·55; N, 15·85%). It was converted into the *hydrochloride*, m. p. 244° (from ethanol–acetone) (Found: Cl, 20·6. $C_7H_{12}ClN_3$ requires Cl, 20·4%), and the *picrate* (decomp. *ca.* 169°) (Found: C, 42·7; H, 3·9. $C_{13}H_{14}N_6O_7$ requires C, 42·6; H, 3·85%).

The hydriodide (0·8 g.) was heated for 5 min. with N-sodium hydroxide (30 ml.). Extraction with ether and evaporation gave needles, m. p. 98° undepressed on admixture with the 4,6-dimethyl-2-methylaminopyrimidine described below.

4,6-*Dimethyl*-2-*methylaminopyrimidine.*—2-Chloro-4,6-dimethylpyrimidine [26] (7·1 g.) was heated at 100° for 3 hr. with alcoholic methylamine (12% w/v; 30 ml.). Methanolic sodium methoxide (from sodium, 1·2 g.) was added, and the residue after evaporation of the filtrate was extracted with boiling light petroleum (b. p. 80—100°; 70 ml.). Refrigeration and concentration gave the amine (65%), m. p. 99—100° (lit.[27] 98°). The *picrate* had m. p. 200—201° (from ethanol) (Found: C, 42·65; H, 3·8. $C_{13}H_{14}N_6O_7$ requires C, 42·6; H, 3·85%).

5-*Ethyl*-1,2-*dihydro*-2-*imino*-1-*methylpyrimidine.*—The unsatisfactory zinc dechlorination of 2-amino-4,6-dichloro-5-ethylpyrimidine [28] (best prepared like the 5-methyl homologue [29]) was avoided. Catalytic dechlorination of 10·3 g. in water containing 2·5% palladium–charcoal (10 g.) and magnesium oxide (10 g.) took *ca.* 4 hr. The solid was filtered off and extracted with boiling ethyl acetate (3 × 150 ml.), and the extract evaporated. The residue, dissolved in water, was mixed with the initial filtrate and treated with 2N-sodium carbonate (100 ml.). After removal of water at 40° *in vacuo*, the residue was extracted with ethyl acetate (3 × 150 ml.). Evaporation gave 2-amino-5-ethylpyrimidine (>90%), m. p. 139—141° (lit.[28] 142—143°).

This amine (3 g.) was refluxed in methyl iodide (15 ml.) for 24 hr. The resulting *imine hydriodide* (90%) had m. p. 205—206° (from propan-2-ol) (Found: C, 31·9; H, 4·8; N, 15·9. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·85%). Its *hydrochloride* had m. p. 255° (from ethanol) (Found: N, 24·25. $C_7H_{12}ClN_3$ requires N, 24·2%), and its *picrate* had m. p. 147—148° (from water) (Found: C, 42·75; H, 3·7. $C_{13}H_{14}N_6O_7$ requires C, 42·6; H, 3·85%).

5-*Ethyl*-2-*methylaminopyrimidine.*—Rearrangement of the above hydriodide (as for its analogue) in alkali gave an oily base (50%) which, after recrystallization from a little light petroleum, had m. p. 51° (Found: N, 30·5. $C_7H_{11}N_3$ requires N, 30·6%). It was shown to be 5-*ethyl*-2-*methylaminopyrimidine* by conversion into its *picrate*, m. p. 168° (Found: C, 42·6; H, 3·9. $C_{13}H_{14}N_6O_7$ requires C, 42·6; H, 3·8%), which was also made unambiguously as follows: 2-Chloro-5-ethylpyrimidine was prepared in small yield from 2-amino-5-ethylpyrimidine by Howard's general method; [23] the crude product was methylaminated as for the 4,6-dimethyl analogue above, and the resulting amine isolated as its picrate, m. p. 168° (from ethanol) undepressed by admixture with the above compound.

[25] Combes and Combes, *Bull. Soc. chim. Fr.*, 1892, [3], **7**, 788.
[26] Angerstein, *Ber.*, 1901, **34**, 3956.
[27] Majima, *Ber.*, 1908, **41**, 176.
[28] Von Merkatz, *Ber.*, 1919, **52**, 869.
[29] Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.

Attempted Methylation of 2-Amino-4,6-diphenylpyrimidine.—Refluxing of the amine [30] in ethanolic methyl iodide for 24 hr. gave only the *hydriodide* of the starting material, m. p. *ca.* 212° (from propanol) (Found: C, 51·15; H, 3·75; N, 11·1. $C_{16}H_{14}IN_3$ requires C, 51·2; H, 3·75; N, 11·2%). Trituration with ammonia refurnished the base,[30] m. p. 134—135°.

1,2-Dihydro-1-methyl-2-methyliminopyrimidine.—2-Methylaminopyrimidine [21] (0·5 g.) and methyl iodide (1 ml.) were refluxed for 18 hr. The resulting *hydriodide* (90%), m. p. 216—218° (from propanol) (Found: C, 28·55; H, 3·95; N, 16·6. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·7%), was converted into the *picrate*, m. p. 147° (Found: C, 41·3; H, 3·2. $C_{12}H_{12}N_6O_7$ requires C, 40·9; H, 3·4%).

1-Ethyl-1,2-dihydro-2-methyliminopyrimidine.—Made as above but by using ethyl iodide, the resulting *hydriodide* had m. p. 156—157° (from propanol) (Found: C, 31·6; H, 4·4; N, 15·85. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·85%).

2-Ethylimino-1,2-dihydro-1-methylpyrimidine.—2-Ethylaminopyrimidine and methyl iodide gave a *hydriodide*, isomeric with the preceding one. It had m. p. 160—161° (from propan-2-ol) (Found: C, 31·65; H, 4·4; I, 48·0. $C_7H_{12}IN_3$ requires I, 47·9%).

5-Bromo-1,2-dihydro-2-imino-1-methylpyrimidine.—2-Amino-5-bromopyrimidine [31] (2·5 g.), methyl iodide (10 ml.), and methanol (25 ml.) were refluxed for 3 hr. Refrigeration gave the *imine hydriodide* (80%), m. p. *ca.* 250° (decomp.) (from methoxyethanol) [Found: C, 19·1; H, 2·25; I (ionic), 40·3; N, 13·2. $C_5H_7BrIN_3$ requires C, 19·0; H, 2·25; I, 40·2; N, 13·3%]. The *hydrochloride*, from a mixture of methanol and ethyl acetate, had m. p. 261° (Found: N, 18·5. $C_5H_7BrClN_3$ requires N, 18·7%), and the *picrate* had m. p. 184—185° (Found: C, 31·8; H, 2·2. $C_{11}H_9BrN_6O_7$ requires C, 31·7; H, 2·2%).

Addition of 15N-ammonia (0·5 ml.) to the hydriodide (0·3 g.) dissolved in hot water (3 ml.) caused a transitory yellow coloration followed by a white precipitate (95%), undepressed in m. p. by admixture with authentic 5-bromo-2-methylaminopyrimidine.

5-Bromo-2-methylaminopyrimidine.—2-Methylaminopyrimidine [21] and powdered calcium carbonate (2·5 g.) were stirred in water (40 ml.) at 55° while bromine (2·7 ml.) was added during 20 min. The *bromo-amine* (90%), recrystallized from water and sublimed (90°/0·1 mm.), had m. p. 121° (Found: C, 31·8; H, 3·2; N, 22·05. $C_5H_6BrN_3$ requires C, 31·95; H, 3·2; N, 22·35%). A solution of the base (0·4 g.) in concentrated hydrochloric acid (1·0 ml.) was diluted with acetone (15 ml.) and ether (5 ml.). Recrystallization of the precipitate from acetone gave the *hydrochloride*, m. p. 168° (Found: N, 18·5. $C_5H_7BrClN_3$ requires N, 18·7%). The *picrate* had m. p. 180—181° (from ethanol), depressed on admixture with the isomeric picrate above (Found: C, 31·5; H, 2·2%).

5-Bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine.—5-Bromo-2-methylaminopyrimidine (2·2 g.), methyl iodide (8 ml.), and methanol (20 ml.) were heated at 100° for 4 hr. Colour was removed from the crude product by warming with ethanol (20 ml.) and allowing to cool. The *hydriodide* had m. p. 238° (decomp.) (from methoxyethanol) (Found: C, 21·75; H, 2·75; N, 12·6. $C_6H_9BrIN_3$ requires C, 21·85; H, 2·75; N, 12·75%). Its *hydrochloride* had m. p. 253° (from ethanol) (Found: C, 30·0; H, 3·95. $C_6H_9BrClN_3$ requires C, 30·2; H, 3·8%), and the *picrate* had m. p. 210—212° (Found: C, 33·4; H, 2·6. $C_{12}H_{11}BrN_6O_7$ requires C, 33·4; H, 2·6%).

2-Amino-4-dimethylaminopyrimidine.—2-Amino-4-chloro-6-dimethylaminopyrimidine was best made according to Boon.[18] When the amination of 2-amino-4,6-dichloropyrimidine was attempted at 100°, a second compound was separated from the above by its sparing solubility in ether. It was *2-amino-4,6-bisdimethylaminopyrimidine*, m. p. 200° (from benzene) (Found: C, 53·2; H, 8·4; N, 38·6. $C_8H_{15}N_5$ requires C, 53·0; H, 8·35; N, 38·65%).

The chloro-derivative (3·4 g.) was hydrogenated in water with 5% palladium–charcoal (2 g.) and magnesium oxide (2·6 g.). The filtrate and washings were treated with 2N-sodium carbonate (20 ml.) and reduced to dryness. The residue was boiled with ethyl acetate (3 × 40 ml.). Concentration of the extracts and recrystallization from the same solvent gave *2-amino-4-dimethylaminopyrimidine* (80%), m. p. 155—156° (Found: N, 40·7. $C_6H_{10}N_4$ requires N, 40·55%).

2-Amino-4-dimethylamino-1,2-dihydro-1-methylpyrimidine.—The last diamine (2·5 g.) in methanol (5 ml.) was refluxed with methyl iodide (10 ml.) for 1 hr. Filtration and concentration of the filtrate gave the *imine hydriodide* (95%), m. p. 286° (from ethanol) (Found: C,

[30] Clark, English, Winnek, Marson, Cole, and Clapp, *J. Amer. Chem. Soc.*, 1946, **68**, 96.
[31] Ziegler, U.S. Patent 2,609,372 (1952); *Chem. Zentr.*, 1953, **124**, 5934.

30·0; H, 4·6; N, 20·15. $C_7H_{13}IN_4$ requires C, 30·0; H, 4·7; N, 20·0%). The *hydrochloride* had m. p. 298° (decomp.) (from propan-2-ol) (Found: C, 44·3; H, 6·9. $C_7H_{13}ClN_4$ requires C, 44·55; H, 6·9%).

This salt (0·25 g.) was heated on the steam-bath for 1 hr. in 2·5N-sodium hydroxide (2 ml.). The solution, adjusted to pH 10, was evaporated, and the residue boiled with ethyl acetate (20 ml.). Concentration of the extract gave 4-dimethylamino-1,2-dihydro-1-methyl-2-oxopyrimidine, m. p. 178° undepressed on admixture with authentic material.[19] The mother liquors showed a second chromatographic spot corresponding in three solvent systems to 4-dimethylamino-2-methylaminopyrimidine. It was not isolated.

4-Dimethylamino-2-methylaminopyrimidine.—2-Chloro-4-dimethylaminopyrimidine [20] (0·6 g.) and 15% alcoholic methylamine (10 ml.) were heated at 100° for 2 hr. The residue from careful evaporation was extracted with boiling light petroleum (b. p. 80—100°; 10 ml.). Concentration gave the *diamine* (0·15 g.), m. p. 98° (Found: C, 55·15; H, 7·9. $C_7H_{12}N_4$ requires C, 55·2; H, 7·95%).

Ionization Constants.—In addition to those in the Table, values were measured at 20° in water by potentiometric titration [32] (molarity given) or spectrometrically (sp.) for these pyrimidines: 2-amino-4-dimethylamino-, 7·96 ± 0·03 (M/200); 2-amino-4,6-diphenyl-, 3·78 ± 0·02 (sp.); 2-amino-5-nitro-, 0·35 ± 0·04 (sp.); 5-bromo-2-hydroxy-, 7·36 ± 0·03 (sp.); 2,5-diamino-, *ca.* 4·0 and 1·0 (sp.); 4,6-diamino-2-hydroxy-, 6·49 ± 0·02 (M/400; cation), 11·98 ± 0·06 (sp.; anion); 4-methoxy-2-methylamino-, 5·76 ± 0·02 (M/200); 2-methylamino-, 4·00 ± 0·04 (M/1000; cf. lit.[21] 3·82 at M/100 and 22°); 2-pentylamino-, 4·04 ± 0·03 (M/1000); 2-propylamino-, 4·10 ± 0·03 (M/1000).

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[32] Albert and Phillips, *J.*, 1956, 1294; Albert and Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.