65. *Simple Pyrimidines. Part I. Spectroscopic Studies.*

By D. J. Brown and L. N. Short.

The nature of the potentially tautomeric groups in hydroxy- and amino-pyrimidines has been studied by means of ultra-violet and infra-red spectroscopy. In aqueous solution 4-" hydroxypyrimidine " exists predominantly in the lactam (ketonic) form and the aminopyrimidines in the amino-form. The preparation of hitherto unknown monosubstituted pyrimidines is described.

Our knowledge of the structure of potentially tautomeric groups in the pyrimidine and related systems has been summarized by Marshall and Walker (*J.*, 1951, 1004). Although the structure of the hydroxy- and mercapto-groups in the simple pyrimidines seems fairly clear from their ultra-violet spectra, there is some uncertainty regarding the amino-pyrimidines.

In order to extend the spectroscopic data, we examined a series of pyrimidines having only one group attached to the nucleus, and that of the simplest type (OMe rather than OEt). The decision to exclude superfluous alkyl groups necessitated the synthesis of a number of new pyrimidines. Such of these as lacked a hydrogen-bonding group (*e.g.*, 2-dimethylaminopyrimidine) were characterized by high volatility, high solubility in the majority of solvents, and marked hygroscopicity.*

* Since this investigation was undertaken, Boarland and McOmie (*J.*, 1952, 3716) have reported the spectra of 2-methoxy-, and 2- and 4-amino-pyrimidine.

Preparations.—For simplicity, the potentially tautomeric compounds will be referred to as " amino- " or " hydroxy- " without prejudice to the final conclusions.

The commercially available 2-aminopyrimidine has been hydrolysed to 2-hydroxypyrimidine (Brown, *Nature*, 1950, **165**, 1010). It was also readily converted by diazotization, etc. (Howard, U.S.P. 2,477,409/1949) into 2-chloropyrimidine, and this yielded 2-methoxy-, 2-methylamino-, and 2-dimethylamino-pyrimidine.

Both 2- and 4-aminopyrimidine were readily acetylated in good yield (cf. Baddiley, Lythgoe, and Todd, *J.*, 1943, 561; Marshall and Walker, *loc. cit.*). Although this does not contribute evidence in favour of the amino-form for these amines, it at least disposes of the supposed difference in behaviour towards acetylating agents between the 2- and 4-isomers on the one hand and the unequivocally *amino*-5-isomer on the other.

Since 4-chloropyrimidine can be obtained only in small yield from 4-hydroxypyrimidine and is unstable (Boarland and McOmie, *J.*, 1951, 1218), it was used as an intermediate in only one case. The crude mixture derived from 4-hydroxypyrimidine and phosphoryl chloride gave with excess of sodium methoxide a poor yield of 4-methoxypyrimidine. It resembled the 2-methoxypyrimidine in general properties but was so readily hydrolysed in weakly acidic aqueous solution that complete potentiometric titration could not be satis-

FIG. 1. FIG. 2.

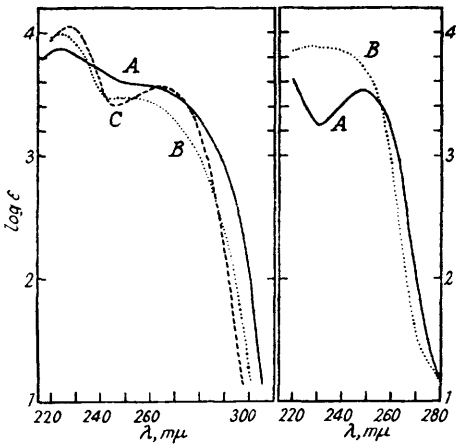


FIG. 1. *4-Hydroxypyrimidine:*
A, *neutral* (pH 6·16).
B, *cation* (pH *approx.* — 1; 5N-H_2SO_4).
C, *anion* (pH 13; N/10-KOH).

FIG. 2. *4-Methoxypyrimidine:*
A, *neutral* (pH 6·95).
B, *cation* (pH 0; N-HCl).

factorily performed nor could the ultra-violet spectrum of the cation be recorded with the usual accuracy. In the case of 4-methylaminopyrimidine, the unfavourable direct synthesis from 4-chloropyrimidine and the cumbersome method of Winkelmann (*J. pr. Chem.*, 1927, **115**, 292) were both replaced by a much simpler route. 2 : 4-Dimercaptopyrimidine was converted into 2-mercapto-4-methylaminopyrimidine according to Russell, Elion, Falco, and Hitchings (*J. Amer. Chem. Soc.*, 1949, **71**, 2279). Desulphurization with Raney nickel thence produced 4-methylaminopyrimidine. A related method gave 4-dimethylaminopyrimidine. Although 4-aminopyrimidine was available by a similar synthesis from thiocytosine (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353), it was decided to explore a new route from 4-amino-5-cyanopyrimidine, available in one step from formamidine and malononitrile (Baddiley, Lythgoe, and Todd, *J.*, 1943, 386). This nitrile was readily converted in good yield into the acid both directly and by way of the amide. Decarboxylation, however, gave only a 25% yield of 4-aminopyrimidine on a small scale, and even this could not be achieved with larger quantities.

Spectroscopy.—In considering the structure of compounds such as the hydroxypyrimidines it is important to note that in solution an equilibrium will exist between the possible tautomeric forms (*e.g.*, I). For the simpler case of 4-hydroxyquinoline Tucker and Irvin (*J. Amer. Chem. Soc.*, 1951, **73**, 1923) have found that the equilibrium constant for the tautomerism (K_T), defined as $K_T = C_K/C_E$ (where C_K and C_E are the concentrations of the ketonic and the enolic form respectively), has the value $1{\cdot}29 \times 10^4$ at 20°, showing that the ketonic (lactam) form predominates. The simple treatment used by the above authors

cannot be applied to the pyrimidines owing to the number of possible structures involving the two ring-nitrogen atoms. For example, use of the pK_a values given by Marshall and Walker (*loc. cit.*) and the method of Tucker and Irvin (*loc. cit.*) leads to a value of 9 for K_T of 4-hydroxy-6-methylpyrimidine, favouring the ketonic form : this seems unreasonably low; however, the ultra-violet spectra of aqueous solutions indicate the keto to be the predominant form.

The spectra obtained for 4-hydroxypyrimidine (anion, cation, and neutral molecule, Fig. 1) and 4-methoxypyrimidine (cation and neutral molecule, Fig. 2) closely resemble those reported by Marshall and Walker (*loc. cit.*) for 4-hydroxy- and 4-methoxy-6-methylpyrimidine respectively. The spectra of the two compounds, however, are so different that the proportion of 4-hydroxypyrimidine existing in the lactim form (I*a*) in aqueous solution must be very small. Boarland and McOmie (*loc. cit.*) compared the spectra of 2-hydroxy- and 2-methoxy-pyrimidine and concluded that the lactam form (II*b*) is strongly favoured in aqueous solution. The conclusions reached by Marshall and Walker (*loc. cit.*)

FIG. 3. FIG. 4.

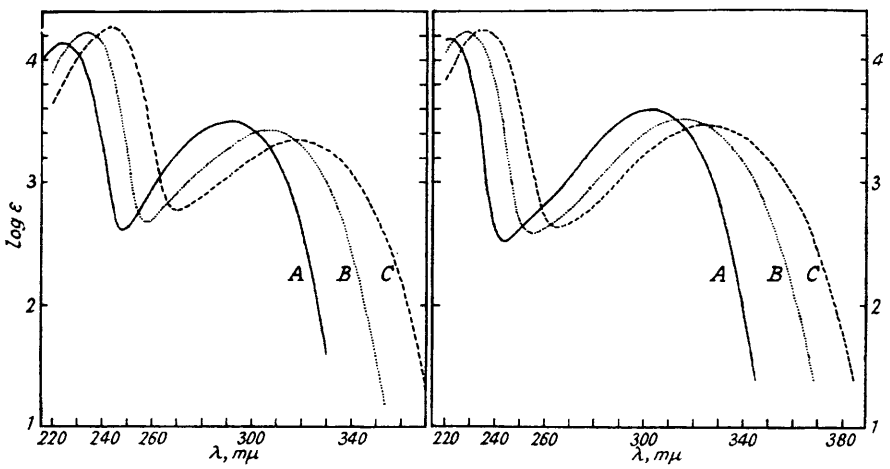
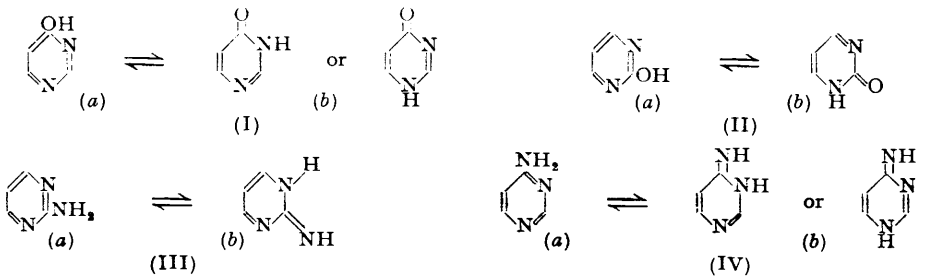


FIG. 3. *A*, 2-*Aminopyrimidine* (*neutral;* pH 7·0). *B*, 2-*Methylaminopyrimidine* (*neutral;* pH 7·0). *C*, 2-*Dimethylaminopyrimidine* (*neutral;* pH 7·0).

FIG. 4. *A*, 2-*Aminopyrimidine* (*cation;* pH 1; N/10-HCl). *B*, 2-*Methylaminopyrimidine* (*cation;* pH 1). *C*, 2-*Dimethylaminopyrimidine* (*cation;* pH 1).

from a study of the monomethylhydroxypyrimidines are thus confirmed, and their claim that the methyl group in such compounds as 2-hydroxy-4-methylpyrimidine makes little difference to the structure and spectral behaviour of the compounds is substantiated.



Considerable uncertainty has existed regarding the tautomerism of 2- and 4-amino-pyrimidine, which may exist in the corresponding iminodihydro-forms (III*b*, IV*b*). The spectra of these compounds and of the corresponding monomethylamino- and dimethyl-amino-pyrimidines are shown in Figs. 3—6. From the method of synthesis, the structures

of the dimethylamino-compounds are unambiguously known. The close similarity between the spectra of the amino-, monomethylamino-, and dimethylamino-compounds provides strong, if not conclusive, evidence that 2- and 4-aminopyrimidine exist chiefly

FIG. 5. FIG. 6.

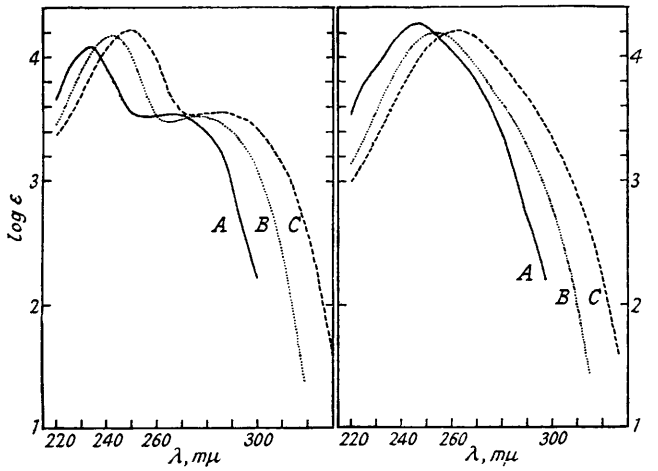


FIG. 5. *A*, 4-*Aminopyrimidine* (*neutral*; pH 13). *B*, 4-*Methylaminopyrimidine* (*neutral*; pH 9·05). *C*, 4-*Dimethylaminopyrimidine* (*neutral*; pH 9·28).

FIG. 6. *A*, 4-*Aminopyrimidine* (*cation*; pH 0). *B*, 4-*Methylaminopyrimidine* (*cation*; pH 2·07). *C*, 4-*Dimethylaminopyrimidine* (*cation*; pH 3·15).

in the amino- (III*a*; IV*a*) rather than the iminodihydro-form (III*b*; IV*b*) in aqueous solution. The substitution of a methyl group for a hydrogen atom of the amino-group produces a small bathochromic shift in the absorption maxima.

Pyrimidine	pK_a[1] (20°)	pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$ *
4-Hydroxy-	1·69 ± 0·04	13	227, 263	4·05, 3·56
	8·60 ± 0·02	6·2	223,[2] 260 †	3·87, 3·57
		−1	224, 251	3·99, 3·47
4-Methoxy-[3]	2·5 ± 0·2	6·95	247—248	3·53
		0	227—228, 238 †	3·89, 3·86
2-Amino	3·54 [4]	7·0	224, 292	4·13, 3·50
		1 [5]	221, 302—303	4·17, 3·60
2-Methylamino-	3·82 ± 0·03 ‡	7·0	234, 306—307	4·23, 4·33
		1	228, 315	4·23, 3·53
2-Dimethylamino-	3·96 ± 0·01	7·0	243, 318	4·26, 3·35
		1	235, 324—325	4·24, 3·47
4-Amino-[6]	5·71 [4]	13	233, 268—269	4·26, 3·72
		0	246	4·27·
4-Methylamino-	6·12 ± 0·04 §	9·0	242, 276—277	4·18, 3·54
		2·1	254	4·20
4-Dimethylamino-	6·35 ± 0·02	9·3	250, 286	4·22, 3·56
		3·15	262	4·21

* ε (molar extinction coefficient) = d/Cl, where d = optical density, C = molar concn., l = cell length. † Inflexion. ‡ 22°. § 23°.

[1] All the pK_a's are for M/100-solution except those of 2-aminopyrimidine (M/10) and 4-aminopyrimidine (M/200). [2] Boarland and McOmie gave $\lambda_{max.}$ 227·5 (log ε 3·97) and Albert, Brown, and Cheeseman (*J.*, 1951, 474) gave $\lambda_{max.}$ 225 (log ε 3·83). The latter result was obtained from measurements at 5-mμ intervals and the maximum was between 220 and 225 mμ. [3] Sensitive to acid. [4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [5] Stimson (*J. Amer. Chem. Soc.*, 1949, **71**, 1470) gave $\lambda_{max.}$ 220 (log ε 4·10) and 300 (3·58) at pH 3 when about 20% of the compound would have been present as the neutral molecule. [6] Values taken from Boarland and McOmie (*J.*, 1952, 3716).

Infra-red spectra of some of the compounds discussed above have also been measured. It has been shown (Short and Thompson, *J.*, 1951, 168) that the infra-red spectra of the hydroxypyrimidines in the solid state indicate their ketonic character. The spectra of 2- and 4-methoxypyrimidine have now been measured and are shown along with those of

2- and 4-hydroxypyrimidine in Fig. 7 for the range 1300—1800 cm.$^{-1}$. Each of the hydroxy-compounds has a very strong absorption band in the 1600—1700 cm.$^{-1}$ region which has no counterpart in the spectra of the methoxy-compounds and must be due to carbonyl bond stretching vibrations.

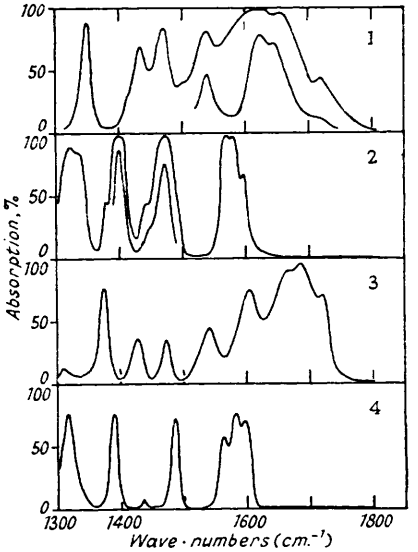


FIG. 7. *Infra-red spectra:*
1, 2-*Hydroxypyrimidine* (*solid*),
2, 2-*methoxypyrimidine* (*liquid*),
3, 4-*hydroxypyrimidine* (*solid*),
4, 4-*methoxypyrimidine* (*liquid*).

The infra-red spectra of 2- and 4-aminopyrimidine in dilute solution in carbon tetrachloride have been measured in the region of N–H bond stretching vibration frequencies. Each compound gives the two strong bands characteristic of the amino-group, proving that these compounds exist in the amino-form in this solvent. These spectra will be discussed in more detail in a later paper.

EXPERIMENTAL

Physical Measurements.—pK_a *Values.* These were determined by potentiometric titration of aqueous solutions of the compound with hydrochloric acid or potassium hydroxide solution. The values determined are shown in the Table.

Ultra-violet spectra. The ultra-violet spectra were measured with a Hilger "Uvispek" Spectrophotometer. The substances were dissolved in suitable buffers (phosphate, glycine) or acid or alkali solution (potassium hydroxide, hydrochloric acid, sulphuric acid) of pH such as to give the desired species (neutral, anion, or cation). The pH was chosen to be at least 2 units greater or less than the relevant pK_a value, thus ensuring at least 99% of the required species.

Infra-red spectra. These were measured with a Perkin–Elmer Model 12C recording spectrometer, a lithium fluoride prism being used for the 3000—3550 cm.$^{-1}$ region and a sodium chloride prism for the 1300—1800 cm.$^{-1}$ region.

Syntheses.—(Analyses were by Mr. P. R. W. Baker, Beckenham. M. p.s are uncorrected.)

2-*Methoxypyrimidine.* Crude 2-chloropyrimidine (2 g.) was added to sodium methoxide (from sodium, 0·5 g., and methanol, 25 ml.), and the solution refluxed for 30 min. After cooling, carbon dioxide was passed in to saturation, the solution was filtered, and the solvent removed in a vacuum. The residual mass was extracted with ether (40 ml.). After drying (K_2CO_3), the ether was removed, and distillation then gave 0·83 g. (43%) of colourless mobile 2-*methoxypyrimidine*, b. p. 70—71°/15 mm., n_D^{20} 1·5060 (Found: C, 54·15; H, 5·5; N, 25·15. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%).

2-*Dimethylaminopyrimidine.* Crude 2-chloropyrimidine (2·4 g.) and methanolic dimethylamine (15%; 20 ml.) were heated at 120° for 1 hour. Sodium methoxide (from sodium, 0·4 g., in methanol, 20 ml.) was added and the product worked up as above (but with omission of the refluxing); 2-*dimethylaminopyrimidine* (1·2 g., 46%) was obtained as a colourless hygroscopic liquid, b. p. 78—81°/17 mm., n_D^{22} 1·5438 (Found: C, 58·5; H, 7·35; N, 33·8. $C_6H_9N_3$ requires C, 58·45; H, 7·4; N, 34·1%).

2-*Methylaminopyrimidine.* Ethanolic methylamine and 2-chloropyrimidine similarly gave

a 49% yield of distillate, b. p. 91—92°/14 mm., which solidified. Recrystallization from light petroleum (b. p. 60—80°; 10 parts) gave colourless laths of 2-*methylaminopyrimidine* (non-hygroscopic), m. p. 59—61° (Found: C, 55·15; H, 6·45; N, 38·95. $C_5H_7N_3$ requires C, 55·05; H, 6·5; N, 38·5%). Concentration gave a second crop of slightly less pure material.

4-*Methoxypyrimidine*. Phosphoryl chloride (25 ml.) was heated with 4-hydroxypyrimidine (7 g.) under reflux at 125° (bath) for 25 min. The cooled mixture was shaken with light petroleum (b. p. 40—60°; 6 × 15 ml.) which removed most of the phosphoryl chloride. To the residue was added dry methanol (60 ml.). A vigorous reaction ensued, some liquid boiling over. The clear yellow solution was added in a thin stream to sodium methoxide solution (from sodium, 10 g., and methanol, 125 ml.) Salts were precipitated, and the suspension was refluxed on the steam-bath for 30 minutes. After treatment as for the 2-isomer, 4-*methoxypyrimidine* was obtained as a colourless, mobile liquid (2·2 g.), b. p. 69—70°/30 mm., n_D^{20} 1·4980 (Found: C, 54·45; H, 5·45; N, 25·0%). It was hygroscopic and miscible with all solvents.

4-*Dimethylaminopyrimidine*. 2 : 4-Dimercaptopyrimidine (10·2 g.) was heated in a sealed tube with aqueous (or aqueous-alcoholic) dimethylamine (25%; 60 ml.) for 3 hours at 130°. After evaporation, the residue was treated with cold hydrochloric acid (0·5N; 200 ml.) in which most of it dissolved, leaving dimercaptopyrimidine. The filtrate was brought to pH 3—4, thereby precipitating colourless crystalline 4-dimethylamino-2-mercaptopyrimidine (8·25 g.; m. p. 278°, decomp. from 265°). This material was dissolved in boiling water (370 ml.) and treated portionwise with Raney nickel (45 g. wet weight). The suspension was boiled under reflux for 30 minutes and filtered hot, the solid washed with hot water (100 ml.), and the combined green filtrates were treated again with fresh nickel (20 g.) as before. To the now colourless filtrate was added sodium chloride (160 g.), and the solution was continuously extracted with ether for 15 hours. The extract was dried (K_2CO_3), the solvent removed, and the residue distilled at 131—132°/50 mm., to give 3·1 g. (50%) of 4-*dimethylaminopyrimidine*, hygroscopic, m. p. *ca.* 40° (Found, for solid dried for 48 hours over P_2O_5: C, 57·9; H, 7·4; N, 34·2%), readily soluble in all common solvents.

4-*Methylaminopyrimidine*. 2-Mercapto-4-methylaminopyrimidine (12 g.; Russell *et al.*, *loc. cit.*) was treated in boiling water (300 ml.) with Raney nickel (60 + 40 g.) as above. The crude product was distilled from a flask with a very wide side arm in which the product solidified (5 g., 54%). It had b. p. 142—144°/16 mm. and m. p. 69—72° (Winkelmann, *loc. cit.*, gives 74—75°), forming very hygroscopic needles from light petroleum (Found: C, 54·95; H, 6·0; N, 38·2. Calc. for $C_5H_7N_3$: C, 55·05; H, 6·5; N, 38·5%).

2-*Acetamidopyrimidine*. 2-Aminopyrimidine (0·48 g.) and acetic anhydride (1·5 ml.) were heated at 120° (bath) for 1 hour. The red liquid was cooled and deposited a solid. Acetone (5 ml.) was added, the slurry chilled to 0° and filtered, and the cake washed with cold acetone (3 ml.) to give 0·45 g. (56%) of almost white solid, m. p. 145°. Two recrystallizations (the first with charcoal) from *iso*butyl methyl ketone (25 parts) gave large, colourless laths of 2-*acetamidopyrimidine*, m. p. 145—146·5° (Found: C, 52·5; H, 5·1; N, 30·7. $C_6H_7ON_3$ requires C, 52·6; H, 5·15; N, 30·65%). It was readily soluble in cold water, ethanol, or chloroform and in hot carbon tetrachloride, but rather less in hot light petroleum (b. p. 80—100°).

4-*Aminopyrimidine*-5-*carboxyamide*. Formamidine was condensed with malononitrile according to Baddiley *et al.* (*J.*, 1943, 386), and the resulting 4-amino-5-cyanopyrimidine recrystallized from water (40 parts); it had m. p. 248—251° (decomp.). The cyano-compound (7·4 g.) was added to a stirred mixture of N-potassium hydroxide (55 ml.) and hydrogen peroxide (3%; 225 ml.) in a bath at 50—55°. A crystalline deposit began to form after ½ hour, and after a further ½ hour the pH was adjusted to 7 and the suspension was cooled to 0° for 2 hours (yield, 5·6 g., 66%). Recrystallization from water (35 parts) with charcoal gave a 90% recovery of colourless laths of 4-*aminopyrimidine*-5-*carboxyamide*, m. p. 254—256° (Found: C, 43·4; H, 4·05; N, 40·45. $C_5H_6ON_4$ requires C, 43·5; H, 4·35; N, 40·55%), readily soluble in dilute acids but not in alkali. It is soluble in 28 parts of boiling water but not readily recrystallized therefrom.

4-*Aminopyrimdine*-5-*carboxylic acid*. (*a*) From the nitrile. The nitrile (1·9 g.) and sodium hydroxide solution (2·5N; 19 ml.) were heated on the steam-bath for 1 hour with occasional shaking at first. The solution was brought to pH 4 with concentrated hydrochloric acid. After refrigeration, the solid was washed with a little cold water and dried at 130° (2·0 g., 78%; m. p. 270—272°). Recrystallization from water (17 parts; charcoal) gave the acid (1·75 g.), m. p. 278—281° (Found, in material dried at 130°/0·1 mm.: C, 43·1; H, 3·7; N, 29·95. $C_5H_5O_2N_3$ requires C, 43·2; H, 3·6; N, 30·2%). It was readily soluble in dilute acids and alkali and showed only one fluorescent spot on a paper chromatogram.

(*b*) From the amide. 4-Aminopyrimidine-5-carboxyamide (4·25 g.) and 2·5N-sodium hydroxide (40 ml.) were heated on the steam-bath for 30 min.; the acid, worked up as above (3·8 g., 89%), had m. p. 270—274°, and was identical with that produced from the nitrile.

Decarboxylation of 4-aminopyrimidine-5-carboxylic acid. The carboxylic acid (0·5 g.) was added (2 min.) to benzophenone (5 g.) at 280°. Evolution of carbon dioxide ceased after a further 5 min. When the melt had cooled to 100°, light petroleum (b. p. 100—120°; 25 ml.) was added, and after being chilled the solid was filtered off. It was recrystallized from *iso*butyl methyl ketone (50 parts; carbon) to give 0·1 g. of 4-aminopyrimidine, m. p. 150° not depressed by an authentic sample of m. p. 151—152°. Decarboxylation by direct destructive distillation of the carboxylic acid, with collection of the product in the side arm of the flask, gave about the same yield of purified product. Neither method could be improved to give good yields.

4-*Acetamidopyrimidine.* 4-Aminopyrimidine was acetylated similarly to the 2-isomer (above) in 77% yield. Recrystallized from *iso*butyl methyl ketone (20 parts), 4-*acetamidopyrimidine* was obtained as colourless needles, m. p. 198—200° (Found: C, 52·55; H, 5·05; N, 30·65%). Its solubilities were slightly lower than those of the 2-isomer.

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