

85. A Novel Pyrimidine Synthesis. Part I. 4-Amino-5-phenylpyrimidine.

By W. H. DAVIES and H. A. PIGGOTT.

Phenylacetonitrile, heated at 180° with formamide in a stream of ammonia under distillation conditions, gives 4-amino-5-phenylpyrimidine and a trace of α -iminomethylphenylacetoneitrile. The structure of these compounds is proved by degradation, and the second compound also prepared by heating α -formylphenylacetoneitrile with ammonia. α -Formyl-, α -acetyl-, α -iminomethyl-, and α -phenyliminomethyl-phenylacetoneitriles with formamide give the same pyrimidine. Certain derivatives of 4-substituted 5-phenylpyrimidines are prepared.

Attempts to carry out similar reactions with other amides were unsuccessful.

In studying the mechanism of the reaction of β -benzoyl- α -phenylpropionitrile (Ph·CO·CH₂·CHPh·CN) with formamide to give a formylated 5-amino-2:4-diphenylpyrrole (Davies and Rogers, J., 1944, 126), it was necessary to investigate the reaction of formamide with nitriles. As a model experiment, therefore, formamide was refluxed with phenylacetonitrile. The reaction took a totally different course from that with the keto-nitrile and, apart from recovered material, phenylacetamide and two oxygen-free compounds, a base, C₁₀H₉N₃ (obtained in less than 10% yield), and a neutral product, C₉H₈N₂ (isolated in traces), were obtained. The present paper deals with the investigation of these two products.

It was noticed that the reaction mixture became acid during the heating and that the phenylacetamide arose from the reaction of the nitrile with water formed during the main condensation. The reaction conditions were therefore modified so that phenylacetonitrile and formamide were heated at 180° in a stream of ammonia gas under such conditions that any water formed could distil off. With this technique, phenylacetamide was not formed and the yield of the base (C₁₀H₉N₃), isolated by extraction with acid, was raised to 56% (66% after allowance for recovered nitrile), though the neutral product (C₉H₈N₂) was still obtained only in traces. Modification of the reaction conditions by varying the relative amounts of the reagents and the temperature did not improve the yields, and the use of sodium methoxide or hydrochloric acid as condensing agent at room temperature gave no trace of either of the products.

The compound C₁₀H₉N₃ was a weak base, soluble in dilute acetic acid but giving indefinite end-points to various indicators on titration with hydrochloric acid. It was stable to nitrous acid, concentrated alkalis, and dilute mineral acids; it decolorised both bromine and permanganate. It could be distilled at ordinary pressures, and its stability and low b. p. (332°) compared with its m. p. (153°) suggested a cyclic structure. It may be formed by the reaction CH₂Ph·CN + H·CO·NH₂ → C₁₀H₉N₃ + 2H₂O, and from the method of formation, the most likely structure was considered to be 4-amino-5-phenylpyrimidine (I). The isomeric 2-benzyl-1:3:5-triazine* was excluded when it was found that the base was not oxidised by selenium dioxide and that it formed a monomethiodide and a monoacetyl derivative. Prolonged treatment of the base with concentrated hydrochloric acid gave an amphoteric product, C₁₀H₈ON₂ (II), with the general properties of a hydroxypyrimidine. Treatment of (II) with phosphorus oxychloride (but not with thionyl chloride) gave a chloro-compound, C₁₀H₇N₂Cl (III), which with alcoholic ammonia regenerated the original base, C₁₀H₉N₃. It therefore follows that the main structure is not affected by heating with strong acid and that the following reactions are involved: C₁₀H₇N₂·NH₂ → C₁₀H₇N₂·OH → C₁₀H₇N₂Cl.

Attempts to reduce the chloro-compound with zinc in aqueous sodium phosphate (cf. Amer. Cyanamid Co., U.S.P. 2,242,079) were unsuccessful. Hydrogenation with 1-2% palladium on calcium carbonate as catalyst removed the chlorine and also caused further reduction. Although it is difficult to be certain of the hydrogen uptake because of the formation of carbon dioxide during the reduction, the product is believed to be a tetrahydro-derivative, C₁₀H₁₂N₂ (IV), though the possibility of the phenyl group being reduced to cyclohexyl cannot be excluded (cf. Folkers and Johnson, J. Amer. Chem. Soc., 1933, 55, 1140). The reduced product could not be purified, but gave a picrate C₁₀H₁₂N₂·C₆H₅O₇N₃ (?), m. p. 201–202°, identical with that obtained by a similar series of reactions from synthetic 2:4-dihydroxy-5-phenylpyrimidine (V), and thus substantiating the pyrimidine structure of the original base (I).

This proof was not entirely satisfactory because the structure of the reduced base (IV) was not known with certainty. An alternative degradation was based on Johnson's observation (J. Amer. Chem. Soc., 1916, 38, 1385, 1855) that some pyrimidines on treatment with sodium and alcohol are reduced to hexahydropyrimidines, which with water are hydrolysed to an aldehyde and an $\alpha\gamma$ -diaminopropane. Reduction of the parent base (C₁₀H₉N₃) in this way gave ammonia as the only identified product, but the corresponding hydroxy-derivative (C₁₀H₈ON₂) (II) gave a base (VII) from which a dipicrate and a dibenzoyl derivative were prepared. These appeared to be derivatives of $\alpha\gamma$ -diamino- β -phenylpropane previously prepared by Jackson and Kenner (J., 1928, 1657), though the picrate was a monohydrate of that reported by these workers. Unfortunately, no samples of the authentic derivatives were available for mixed m. p.'s.

It is therefore established that the base C₁₀H₉N₃ is an amino-derivative of 5-phenylpyrimidine. As the

* Since this work was completed, two papers by Novelli have appeared (Anal. Asoc. Quím. Argentina, 1943, 31, 23, 93). By heating phenylacetonitrile with formamide at 175–210° and working up the products by steam distillation, he obtained phenylacetamide and a monoacid base C₁₀H₉N₃, m. p. 155–156° [methiodide, C₁₀H₉N₃·CH₃I·H₂O, m. p. 172° (softening at 158°)]. As the base did not react with nitrous acid and he was unable to acetylate it, Novelli postulated that it was tertiary and thus, from its mode of preparation, 2-benzyl-1:3:5-triazine. The only degradation work reported was oxidation of the base with alkaline permanganate to give benzoic acid. There seems no doubt that the base reported by Novelli is identical with ours.

obtained which was sparingly soluble in water and gave a purple colour with ferric chloride. These properties resemble those of the sodio-derivative of (IX), and the addition compound is therefore considered to be the ammonium salt (XI) of the formyl derivative rather than the isomeric aldehyde-ammonia. When the ammonium salt was heated at its m. p. or in boiling toluene, it gave a trace of α -formylphenylacetonitrile (IX) and a good yield of α -iminomethylphenylacetonitrile (VIII), identical with the product $C_9H_8N_2$ obtained by the action of formamide on phenylacetonitrile.

The imine (VIII), when heated with formamide, gave the pyrimidine (I) in 52% yield, phenylacetonitrile (28%) and unchanged imine (6%) also being obtained. Although the yield of pyrimidine was no higher than from phenylacetonitrile itself, the reaction was very much more rapid, as might be expected if the imine was an intermediate in the reaction of phenylacetonitrile with formamide. Similarly, α -formylphenylacetonitrile (IX) and α -phenyliminomethylphenylacetonitrile (X) gave the pyrimidine (I) and phenylacetonitrile when heated with formamide. When α -acetylphenylacetonitrile was used in place of the α -formyl derivative, the product was not the expected 6-methyl derivative of (I) but (I) itself, the formation of which clearly involves the splitting of the α -acetyl derivative to phenylacetonitrile.

Attempts to form pyrimidines by condensing the imine (VIII) with hydrogen cyanide or benzamidine with alkaline catalysts were unsuccessful.

In the reaction with phenylacetonitrile, the use of amides other than formamide failed to give pyrimidines. With acetamide, no basic material was formed; thioacetamide decomposed into hydrogen sulphide and acetonitrile; with thioformamide, no reaction took place in the cold, and at higher temperatures, decomposition occurred. With acetamide and α -acetylphenylacetonitrile, however, a trace of basic material, possibly 4-amino-5-phenyl-2:6-dimethylpyrimidine, was obtained, but the yield was too poor for the reaction to warrant further investigation.

The mechanism of the reaction therefore appears to involve the direct condensation of formamide with phenylacetonitrile to give α -iminomethylphenylacetonitrile (VIII), which reacts further with formamide to give an open-chain compound, whereupon the terminal amino-group cyclises on to the nitrile group [cf. formation of 5-amino-2:4-diphenylpyrrole (Davies and Rogers, *loc. cit.*) and the condensation of ethyl α -cyanosuccinate with urea to give 4-amino-2:4-dihydroxy-5-carboxymethylpyrimidine (Johnson and Kohman, *Amer. Chem. J.*, 1913, **49**, 197)]. The slowness of the reaction is probably due to the fact that only part of the imine (VIII) is converted into pyrimidine, the rest being hydrolysed or ammonolysed back to phenylacetonitrile.

The stability of the imine (VIII) compared with that of the analogous "diacetonitrile" $[CH_3 \cdot C(:NH) \cdot CH_2 \cdot CN]$ is surprising. The former has been crystallised from hot water without serious decomposition, whereas the latter, because of its active methylene group, is converted by heating in water into 2-hydroxy-5-cyano-4:6-dimethylpyridine (Moir, J., 1902, **81**, 101). There has been no indication of the formation of pyridine derivatives in these formamide reactions.

Little work has so far been carried out on other derivatives of 5-phenylpyrimidine. The 4-amino-compound (I) was acylated to give an *acetyl* derivative and a *hydrochloride* of a diacetyl derivative, but attempts at formylation were unsuccessful. The 4-hydroxy-compound (II) gave a *monohydrochloride* which decomposed above its m. p. and was only slightly hydrolysed by water. The 4-chloro-derivative (III) was unstable and on storage was converted into a yellow, water-soluble complex, from which, by treatment with sodium hydroxide, approximately 50% by weight of 4-hydroxy-5-phenylpyrimidine (III) was obtained: a possible explanation of this curious behaviour is that the chloro-compound quaternises with itself [cf. the self-quaternisation of 4-halogenopyridines (Wibaut *et al.*, *Rec. Trav. chim.*, 1935, **54**, 807; 1939, **58**, 885)].

The three monomethyl derivatives of 4-hydroxy-5-phenylpyrimidine (II) have been prepared. The 4-methoxy-compound (XII), obtained by treating (III) with sodium methoxide, was not identified in the products of alkylation of the hydroxy-compound (II) with methyl sulphate and aqueous alkali (though this may have been due to the difficulties of isolating the isomer from the reaction mixture), the main products being the two isomeric 5-phenyl-N-methyl-4-pyrimidones, the higher-melting of which was also obtained by treating the methiodide of the aminopyrimidine (I) with alkali.

Throughout this paper, the amino- and hydroxy-pyrimidine structures have been used in preference to the tautomeric imino-dihydropyrimidines and pyrimidones. It should be emphasised that the choice has not been made on chemical grounds, and indeed the m. p.'s of the compounds and the conversion of the methiodide of the amino-compound into a methylated pyrimidone suggest that the dihydro-formulae are more probably correct.

It is proposed to examine the ultra-violet absorption spectra of these compounds and of (VIII) $[CHPh(CN) \cdot CH:NH \rightleftharpoons CPh(CN) \cdot CH:NH_2]$ in an attempt to define their precise structure.

These reactions and those described in Part II (following paper) are the subject of recent patent applications.

EXPERIMENTAL.

The m. p.'s are uncorrected and the micro-analyses were carried out by Mr. E. S. Morton.

1. 4-Amino-5-phenylpyrimidine (I).—Phenylacetonitrile (117 g.) was added to formamide (180 g.) heated at 180° in a stream of ammonia gas under distillation conditions. After 14 hrs.' heating with stirring, the distillate consisted of an aqueous layer (53 c.c.) and an oil (phenylacetonitrile, 21.5 c.c.). The reaction mixture was cooled, and the pyrimidine (94.8 g.) separated by filtration, m. p. 147–151°. An additional small amount was obtained by pouring the filtrate into water, extracting it with ether, washing the ethereal layer with 2N-sulphuric acid, and basifying the acid extract.

The pyrimidine was purified by heating in 8% hydrochloric acid (300 c.c.) (charcoal), and basifying the filtered solution. 4-Amino-5-phenylpyrimidine separated as a pale yellow powder (92.5 g., 54%), m. p. 151—153°, which crystallised from methyl alcohol or cyclohexane as white prisms, m. p. 152.5—153.5°, b. p. 332° [Found: C, 70.1; H, 5.2; N, 24.7; *M* (cryoscopic in dioxan), 180. $C_{10}H_8N_2$ requires C, 70.2; H, 5.3; N, 24.55%; *M*, 171].

The ethereal solution after acid extraction was dried, and the phenylacetoneitrile recovered by distillation (b. p. 108—110°/10 mm.). The high-boiling residue was washed with carbon tetrachloride and crystallised from water to give thin plates of α -iminomethylphenylacetoneitrile (VIII), m. p. 133—134° (Found: C, 75.1; H, 5.5; N, 19.2. $C_9H_8N_2$ requires C, 75.1; H, 5.5; N, 19.45%).

By carrying out the reaction under reflux without a stream of ammonia, the yield of pyrimidine by acid extraction was 8.5%, and a variable amount of phenylacetamide, m. p. 154—156° (relatively insoluble in ether and dilute acid), was formed. When the water was allowed to distil off, the yield was raised to 18.4%; by refluxing in a current of ammonia, the yield was 23.5%.

2. *Properties of 4-Amino-5-phenylpyrimidine (I)*.—Solubility in water, about 0.1—0.2% at 15° and 1.6% at 100°; readily soluble in dilute mineral or acetic acids and stable to prolonged heating with alkali or dilute acids. In chloroform solution, it took up 1 mol. of bromine per mol. of base to give a brick-red precipitate, m. p. 191—192°, which was very sparingly soluble in common solvents; this very unstable addition compound was not further investigated. The base was not readily oxidised by potassium permanganate, but prolonged treatment under acid conditions gave a small amount of benzoic acid (15%, m. p. and mixed m. p. 120—122°).

3. *Derivatives of 4-Amino-5-phenylpyrimidine (I)*.—(a) *Methiodide*. The pyrimidine (1.7 g.), methyl iodide (6.2 c.c.), and methyl alcohol (20 c.c.) were refluxed for 3 hours, and the solvent evaporated. The residual solid (3.3 g.) was crystallised from water to give the *monohydrate* of the monomethiodide, m. p. 170—172° (decomp.) (Found: C, 39.9; H, 4.2; N, 12.65; I, 39.1. $C_{11}H_{12}N_3I \cdot H_2O$ requires C, 39.9; H, 4.2; N, 12.7; I, 38.4%). The methiodide was heated above its decomposition point for 15 minutes but no definite products could be isolated.

(b) *Acyl derivatives*. (i) The pyrimidine (I) (2.5 g.), acetic acid (15 c.c.), and acetic anhydride (5 c.c.) were refluxed for 2 hours and poured into water. The resulting solution was cooled to 5° and exactly neutralised with sodium hydroxide. Unchanged pyrimidine (0.8 g., m. p. 146—154°) was collected, and the filtrate extracted with chloroform (6 times). After drying and removal of solvent, a solid was obtained (1.5 g., m. p. 131—135°) which after crystallising from benzene gave a *monoacetyl* derivative, m. p. 139—140° (Found: C, 67.5; H, 5.1; N, 19.3. $C_{11}H_{11}ON_2$ requires C, 67.6; H, 5.2; N, 19.7%). (ii) The pyrimidine (3.4 g.) was heated at 95° for 3 hours with acetyl chloride (3.0 c.c.) in acetic anhydride (20 c.c.), and the *hydrochloride* of a diacetyl derivative collected (2.8 g., m. p. 200—204° (decomp.) (Found: *M*, by titration with *n*-sodium hydroxide, 296. $C_{12}H_{13}N_2 \cdot HCl$ requires *M*, 291).

(c) *4-Hydroxy-5-phenylpyrimidine (II)*. The aminopyrimidine (I) (10.0 g.) in 36% hydrochloric acid (30 c.c.) was heated on a steam-bath in a current of hydrogen chloride until no more precipitate was formed (about 10 hours). The white crystals of the *hydrochloride* of 4-hydroxy-5-phenylpyrimidine (11.4 g., 94%) were separated, and crystallised from 36% hydrochloric acid; m. p. 272° (decomp.) (Found: C, 52.7; H, 4.4; N, 12.2; Cl, 16.2. $C_{10}H_8ON_2 \cdot HCl \cdot H_2O$ requires C, 53.0; H, 4.86; N, 12.4; Cl, 15.7%). Crude hydrochloride (16.0 g.) was ground with water (50 c.c.) and 35% sodium hydroxide (14 c.c.), and the resulting solution filtered and diluted with water (70 c.c.). 4-Hydroxy-5-phenylpyrimidine (11.1 g., 91%) was precipitated by saturation with carbon dioxide and crystallised from water; m. p. 173—174° (Found: C, 69.9; H, 4.8; N, 15.65. $C_{10}H_8ON_2$ requires C, 69.8; H, 4.65; N, 16.3%).

(d) *4-Chloro-5-phenylpyrimidine (III)*. The hydroxypyrimidine (II) (10 g.) in freshly distilled phosphorus oxychloride (20 c.c.) was refluxed for 1 hour, and excess of oxychloride removed under reduced pressure. The residual oil was treated with ice-water, and the crude chloro-compound (10.3 g., 93%), m. p. 69—71°, purified by distillation or crystallisation from light petroleum (b. p. 60—80°) to give 4-chloro-5-phenylpyrimidine (II), m. p. 71—72°, b. p. 156—158°/19 mm. (Found: C, 62.75; H, 3.1; Cl, 18.6. $C_{10}H_7N_2Cl$ requires C, 63.0; H, 3.68; Cl, 18.6%).

The chloro-compound (0.5 g.), when heated in a sealed tube with saturated alcoholic ammonia (5 c.c.) for 4 hours at 150—160° (but not at 100°), gave 4-amino-5-phenylpyrimidine (I) (0.23 g.) and ammonium chloride. After standing in glass for several months, or when heated at 40—60° for a few days, the chloropyrimidine was converted into a yellow, water-soluble product, presumably a quaternary salt.

4. *Methyl Derivatives of 4-Hydroxy-5-phenylpyrimidine*.—(a) *4-Methoxy-5-phenylpyrimidine (XII)*. Crude chloropyrimidine (10.3 g.) in methyl alcohol (30 c.c.) was refluxed for 1 hour with a solution of sodium methoxide (sodium, 1.25 g.; methyl alcohol, 20 c.c.), and the solvent evaporated. The residual oil was dissolved in ether, washed with alkali and then with water, dried, and the solvent removed, leaving an oil (9.5 g., 95%) which was very soluble in most solvents. Crystallisation from light petroleum (b. p. 40—60°) with good cooling gave 4-methoxy-5-phenylpyrimidine (7.9 g., 78%), m. p. 49—50° (Found: C, 71.0; H, 5.1; N, 15.2. $C_{11}H_{10}ON_2$ requires C, 71.0; H, 5.4; N, 15.05%).

(b) *5-Phenyl-N-methyl-4-pyrimidones*. The hydroxypyrimidine (II) (3.44 g.) in 2*n*-sodium hydroxide (10.5 c.c.) was treated with methyl sulphate (2.0 c.c.) at 10°±2°. After standing at room temperature for 20 hours, the solution was extracted with chloroform (18 times). Evaporation of the dried chloroform extract gave a sticky solid (3.3 g.), which crystallised from acetone to give 5-phenyl-1 (or 3)-methyl-4-pyrimidone (1.68 g., 45%), m. p. 171—172° (Found: C, 71.1; H, 5.35; N, 14.9. $C_{11}H_{10}ON_2$ requires C, 71.0; H, 5.4; N, 15.05%). The acetone mother-liquors were evaporated to dryness, and the residue crystallised from a small bulk of water to give 5-phenyl-3 (or 1)-methyl-4-pyrimidone (0.52 g., 14%), m. p. 111—112° (Found: C, 70.3; H, 5.0; N, 14.9%). This isomer was recovered unchanged after 3 hrs. heating at 250°.

4-Amino-5-phenylpyrimidine methiodide (3.31 g.) in *n*/2-sodium hydroxide (20 c.c.) was evaporated to small bulk, and the distillate shown to contain ammonia (identified as *p*-toluenesulphonamide) and no trace of methylamine (no colour with chloranil) (cf. Tsalapatani, *Chem. Zentr.*, 1908, 79, 1, 299). The residue from the distillation was filtered, saturated with sodium chloride, and extracted with chloroform (12 times). The extract was dried, the solvent removed, and the residual solid crystallised from acetone, giving 5-phenyl-1 (or 3)-methyl-4-pyrimidone, m. p. 171—172° [mixed m. p. with methiodide, 126—138°; mixed m. p. with 4-hydroxy-5-phenylpyrimidine, 116—133°; mixed m. p. with 5-phenyl-1 (or 3)-methyl-4-pyrimidone, prepared by alkali and methyl sulphate on the hydroxy-pyrimidine (II), 171—172°].

5. *Proof of Structure of 4-Amino-5-phenylpyrimidine (I)*.—(a) The chloro-compound (III) (3.8 g.) with methyl alcohol (40 c.c.) and 1.2% palladium on calcium carbonate (2.0 g.) was shaken in hydrogen until absorption was complete (absorption, 1040 c.c. at N.T.P. Calc. for replacement of Cl and reduction of two double bonds: 1120 c.c. after allowance for CO₂ evolved). The product was filtered off, and the filtrate evaporated to dryness, giving a solid (3.96 g.) very soluble in water and difficult to purify owing to the presence of calcium chloride. Part of the material (1 g.) in water was treated with picric acid (1.0 g.) to give a yellow picrate (1.48 g.), which separated from hot water in saw-edged prisms, m. p. 201—202°. This appears to be a *picrate* of 5-phenyltetrahydropyrimidine (Found: C, 49.4; H, 4.2; N, 18.1. $C_{10}H_{11}N_3 \cdot C_6H_3O_2$ requires C, 49.4; H, 3.9; N, 18.0%).

2:4-Dihydroxy-5-phenylpyrimidine (V) was prepared from ethyl α -formylphenylacetate and urea in the presence of aqueous sodium hydroxide; m. p. 360° (decomp.) (from acetic acid) (Found: C, 63.1; H, 4.4; N, 14.9. Calc. for $C_{10}H_8O_2N_2$: C, 63.8; H, 4.3; N, 14.9%). The dihydroxypyrimidine (3.4 g.) was heated for 9 hours with phosphorus

oxychloride (20 c.c.), and the product worked up as for the monochloro-derivative. The crude product (4.0 g., 98%) was purified to give 2: 4-dichloro-5-phenylpyrimidine, b. p. 181—182°/16 mm., m. p. 78—80° (from cyclohexane) (Found: Cl, 31.3. $C_{10}H_6N_2Cl_2$ requires Cl, 31.55%).

The dichloro-compound (1.0 g.) was reduced as in the case of the monochloro-derivative (absorption, 340 c.c. at N.T.P. Calc. for tetrahydrophenylpyrimidine: 324 c.c. after allowance for CO_2 formed). The product was filtered and the solvent removed, giving a sticky gum (1.2 g.) which could not be purified. This was converted into a picrate which, after crystallisation from water, had m. p. 199—200° and gave no depression with the picrate derived from the monochloro-derivative (III) (Found: N, 18.1%).

(b) The hydroxypyrimidine (II) (5.16 g.) in alcohol (300 c.c.) was treated with sodium (23 g.) during 1 hour, and the product steam-distilled until the distillate was no longer alkaline to brilliant-yellow (about 6 l.). The distillate was acidified with hydrochloric acid and evaporated to dryness; the residual solid was taken up in a small volume of water, the solution treated with carbon, filtered, and again evaporated to dryness to give a brown powder (mainly dihydrochloride of α -diamino- β -phenylpropane) (3.12 g.). A part of this in water was treated with aqueous sodium picrate, and the resulting picrate recrystallised from water; m. p. 244—246° (decomp.) (lit., m. p. 247°, decomp.). This appears to be a hydrate of the dipicrate of the base (Found: C, 40.6; H, 4.05; N, 18.0. $C_9H_{14}N_2 \cdot 2C_6H_3O_7N_3 \cdot H_2O$ requires C, 40.25; H, 3.5; N, 17.9%). By the Schotten-Baumann reaction the dihydrochloride gave a dibenzoyl derivative, m. p. 176—177° (lit., m. p. 179°) (Found: C, 76.95; H, 5.85; N, 7.95. Calc. for $C_{23}H_{22}O_2N_2$: C, 77.1; H, 6.1; N, 7.9%).

6. *Proof of Structure of α -Iminomethylphenylacetoneitrile (VIII).*—The neutral product ($C_9H_8N_2$) from the phenylacetoneitrile-formamide reaction (0.72 g.) was stirred with *n*-hydrochloric acid (4.0 c.c.) and heated to boiling. The mixture was acid to Congo-red until boiling had been continued for 1 minute. An additional 6 c.c. of *n*-hydrochloric acid were then added, and heating continued for 2 minutes, during which time the oil solidified. After cooling, the solid was collected, washed, and dried; m. p. 153—156° (0.59 g., 81%); recrystallised from toluene, it had m. p. 156—159° (0.47 g.), mixed m. p. with α -formylphenylacetoneitrile (IX), 156—160°. The ammonia in the aqueous filtrate was estimated and found to correspond to 94% of the theoretical amount.

7. *4-Hydroxy-2-furyl-5-phenylpyrimidine.*—Furamide hydrochloride hydrate (15.4 g.) (Pinner, *Ber.*, 1892, 25, 1415) was treated with 35% sodium hydroxide solution (9 c.c.). Ethyl α -formylphenylacetate (19.2 g.) (Wislicenus, *Ber.*, 1887, 20, 2931) was added during 10 minutes, the temperature being kept at $14^\circ \pm 2^\circ$ by ice-cooling. Alcohol (40 c.c.) was then added, and the mixture kept for several days. Water was added, followed by a few drops of acetic acid, and the white precipitate of 4-hydroxy-2-furyl-5-phenylpyrimidine was collected; it crystallised from methyl alcohol as fine white needles, m. p. 222—223° (6.2 g., 27%), soluble in dilute sodium hydroxide solution but only sparingly soluble in dilute hydrochloric acid (Found: C, 70.3; H, 3.8; N, 11.95. $C_{14}H_{10}O_2N_2$ requires C, 70.6; H, 4.2; N, 11.8%).

8. *Synthesis of α -Iminomethylphenylacetoneitrile (VIII).*— α -Formylphenylacetoneitrile (IX) (63 g.), dissolved in liquid ammonia (1 l.), was kept below -40° for 6 hours. The excess of ammonia was evaporated, leaving the ammonium salt of α -formylphenylacetoneitrile (XI) (70.5 g.), m. p. 137—138° (decomp.), which crystallised from alcohol, with some decomposition and loss, as compact white prisms, m. p. 137—138° (decomp.) (Found: N, 17.15. $C_9H_{10}ON_2$ requires N, 17.2%). In aqueous or alcoholic suspension, the salt gave a purple-red colour with aqueous ferric chloride.

A suspension of the ammonium salt (73 g.) in toluene (200 c.c.) was distilled in a stream of ammonia until no more water was evolved and all the solid was in solution (about 1½ hours). After removal of the residual solvent, the solid was washed with dilute aqueous sodium hydroxide to give α -iminomethylphenylacetoneitrile (55.8 g., 89%), m. p. 132—135°. Crystallisation from benzene gave plates, m. p. 134—135°, which did not depress the m. p. of the neutral product from the reaction of formamide with phenylacetoneitrile (see Section 1). Immediate acidification of the alkaline extract precipitated a small amount of crude α -formylphenylacetoneitrile, m. p. 138—145°.

A suspension of the formyl compound (IX) in benzene was distilled slowly in a current of ammonia for 7 hours, fresh benzene being added to replace the distillate; crude ammonium salt (XI), m. p. 115—125°, was obtained. Boiling toluene being used as a diluent in a similar experiment, the formyl compound passed into solution, and on cooling, the iminomethyl derivative (VIII) separated, m. p. 131—133°. With xylene in place of toluene, the product was again the iminomethyl compound (VIII), m. p. 128—130°, but contaminated with a yellow impurity presumed to be the bis-compound $[CPh(CN) \cdot CH]_2NH$ reported by Walther and Schickler (*loc. cit.*).

9. *Other Preparations of 4-Amino-5-phenylpyrimidine (I).*—(a) From α -iminomethylphenylacetoneitrile (VIII). The imino-compound (14.4 g.) was added to formamide (16 c.c.) at 180° and heated at that temperature for 1 hour in a stream of ammonia. After cooling, the solid was filtered off and washed with ether. The filtrate and ethereal washings were shaken with water and then extracted with ice-cold dilute sulphuric acid. The original precipitate was then combined with the acid extract in excess of sulphuric acid, clarified with carbon, and basified to precipitate the aminopyrimidine (I) (8.8 g., 52%), m. p. 152—154°. From the ethereal solution, phenylacetoneitrile (3.25 g., 28%), b. p. 103—107°/11 mm., and unchanged imine (VIII) (0.77 g., 5.3%), m. p. 132—134°, were obtained.

(b) From α -formylphenylacetoneitrile (IX). The α -formyl compound (14.5 g.) was treated as in (a) to give the aminopyrimidine (I) (7.72 g., 45%), m. p. 148—151°, phenylacetoneitrile (3.55 g., 30%), b. p. 101—104°/9 mm., and a trace of crude α -iminomethylphenylacetoneitrile (VIII), m. p. 122—126°.

(c) From α -phenyliminomethylphenylacetoneitrile (X). The imine (10 g.) was heated with formamide (20 c.c.) at 180° for 7 hours in a stream of ammonia, and the product worked up as in (a) to give crude aminopyrimidine (I) (3.0 g., 38.5%), m. p. 136—144°, and phenylacetoneitrile (1.1 g., 20.5%), b. p. 101—105°/9 mm., together with a high-boiling residue (1.9 g.) which was not the iminomethyl compound (VIII) and was not further investigated.

10. *Reaction of α -Acetylphenylacetoneitrile with Amides.*—(a) *With formamide.* Formamide (20 c.c.), saturated with ammonia, was heated with the acetyl compound (15.9 g.) at 180° for 6 hours. Water (1.4 c.c.) and a trace of acetamide distilled off. The product was worked up as in Section 1 to give phenylacetoneitrile, b. p. 100—103°/8 mm. (3.6 g., 31%), and crude 4-amino-5-phenylpyrimidine (I), m. p. 138—145°, mixed m. p. with authentic material, 143—148° (4.6 g., 27%). This product was difficult to purify, probably owing to the presence of a small amount of the 6-methyl derivative.

(b) *With acetamide.* α -Acetylphenylacetoneitrile (7.9 g.) was added to acetamide (11.8 g.) heated at 180° in a stream of ammonia, and the mixture heated at 200° for 5 hours. Water (1.6 c.c.) and an oil (1.3 c.c., probably phenylacetoneitrile) distilled over. A trace of basic material, m. p. 180—190°, was isolated after the usual working up; this was possibly 4-amino-5-phenyl-2:6-dimethylpyrimidine.

The authors are greatly indebted to Mr. C. Paine for his advice throughout this work.