

(iii) *o*-Methoxyphenylacetonitrile. (a) *o*-Methoxybenzaldehyde cyanohydrin. The bisulphite compound of *o*-methoxybenzaldehyde, prepared in the standard manner from the aldehyde (60 g.), was stirred with a concentrated solution of potassium cyanide (80 g.). The bisulphite compound dissolved immediately; the cyanohydrin, which separated as an oil, solidified on cooling, and was collected, washed, and dried in a vacuum (70 g., 97.3%). It is not necessary to purify it further for the preparation of the nitrile, but if desired it may be crystallised from a little benzene; m. p. 71°.

(b) *o*-Methoxyphenylacetonitrile (cf. Pschorr, Wolfes, and Buckow, *Ber.*, 1900, **33**, 166). A solution of the crude cyanohydrin (70 g.) in chloroform (60 c.c.) was cooled in ice and gradually treated, with stirring, with a solution of thionyl chloride (40 c.c.; approx. 15% excess) in chloroform (40 c.c.). When no more hydrogen chloride was evolved (30 mins.), the mixture was allowed to warm to room temperature and stirred for a further 15 mins.; the solvent was then removed under reduced pressure, the temperature being kept as low as possible. The crude chloro-compound in alcohol (150 c.c.) was treated with dilute acetic acid (90 c.c. in 120 c.c. of water), a little more alcohol being added if necessary in order to obtain a homogeneous solution. Zinc dust (60 g.) was added in small amounts during 20 mins., and the mixture refluxed for ½ hr. After hot filtration, the clear yellow solution was evaporated to one-third of its original bulk, poured into water, and extracted with ether (3 × 100 c.c.). The ethereal extract was washed free from acid, dried, and the solvent removed. Distillation of the residue gave *o*-methoxyphenylacetonitrile as a colourless oil, b. p. 141—143°/15 mm., which solidified on cooling. Crystallisation from light petroleum (b. p. 60—80°) gave colourless needles (42 g., 66.5%), m. p. 67—68°.

(iv) *p*-Chloro-*a*-iminomethylphenylacetonitrile. (a) Ammonium salt of *p*-chloro-*a*-formylphenylacetonitrile (V; R = *p*-ClC₆H₄). *p*-Chloro-*a*-formylphenylacetonitrile (2.0 g.) (Walther and Hirshberg, *J. pr. Chem.*, 1903, **67**, 393) was dissolved in liquid ammonia (100 c.c.) and kept below -40° for 7 hours. Evaporation of the ammonia left the ammonium salt of *p*-chloro-*a*-formylphenylacetonitrile (2.14 g.; 97.7%), m. p. 129—131° (decomp.) (Found: N, 14.25. C₉H₉ON₂Cl requires N, 14.3%).

(b) *p*-Chloro-*a*-iminomethylphenylacetonitrile (VI; R = *p*-ClC₆H₄). A suspension of the ammonium salt (2.0 g.) in toluene (60 c.c.) was evaporated to small bulk in a slow stream of ammonia. From the resulting clear solution, a yellow solid separated (1.25 g.), m. p. 110—122°. This was ground with water and sufficient sodium hydroxide to make this mixture just alkaline to Clayton-yellow. The insoluble solid was collected, m. p. 132—135° (0.5 g., 27.5%), and crystallised from toluene to give *p*-chloro-*a*-iminomethylphenylacetonitrile, m. p. 139—140° (Found: N, 15.5. C₉H₇N₂Cl requires N, 15.7%). *p*-Chloro-*a*-formylphenylacetonitrile was obtained from the alkaline extract on acidification (0.65 g.; 35%), m. p. 156—159°.

(v) *p*-Methoxy-*a*-iminomethylphenylacetonitrile. (a) Ammonium salt of *p*-methoxy-*a*-formylphenylacetonitrile (V; R = *p*-OMe·C₆H₄). This was prepared as described for the *p*-chloro-analogue from *p*-methoxy-*a*-formylphenylacetonitrile (Badhwar, Baker, Menon, and Venkataraman, *J.*, 1931, 1541) and liquid ammonia. Evaporation of the ammonia left the ammonium salt (97.1%), m. p. 130—132° (decomp.) (Found: N, 14.4. C₁₀H₁₂O₂N₂ requires N, 14.6%).

(b) *p*-Methoxy-*a*-iminomethylphenylacetonitrile (VI; R = *p*-OMe·C₆H₄). Prepared as for the *p*-chloro-derivative, the crude product after the alkaline extraction, m. p. 118—124° (75%), was contaminated with a yellow solid, presumably the secondary amine. Repeated crystallisation from benzene gave *p*-methoxy-*a*-iminomethylphenylacetonitrile as white plates, m. p. 138° (Found: N, 15.9. C₁₀H₁₀ON₂ requires N, 16.1%). From the alkaline extract, *p*-methoxy-*a*-formylphenylacetonitrile (11%) was obtained on acidification.

B. Reactions of Formamide with Nuclear-substituted Phenylacetonitriles.—The mixture of nitrile and formamide was heated with stirring at 180° in a stream of dry ammonia gas in a flask fitted with a short still-head.

(i) *With p*-methoxyphenylacetonitrile. The nitrile (18.4 g.) and formamide (25 g.) were heated for 7 hours; an aqueous fraction (5.5 c.c.) and unchanged nitrile (0.8 c.c.) distilled over. The mixture in the flask, after cooling, crystallised and was washed well with water, the residual solid being separated into a basic and a neutral fraction by thorough partition between 2*N*-hydrochloric acid (total 550 c.c.) and ether. From the ethereal solution, unchanged nitrile was recovered (b. p. 144—146°/11 mm., 5.85 g., 32%). The acid extract was cooled in ice, and 4-amino-5-*p*-methoxyphenylpyrimidine hydrochloride separated as plates (6.9 g., 23.2%), m. p. 246—250° raised to 268—270° by recrystallisation from *n*-hydrochloric acid. Titration showed this to be a monohydrochloride (Found: HCl, 15.1. C₁₁H₁₁ON₃·HCl requires HCl, 15.4%).

The hydrochloride, together with its acid mother-liquors, was made alkaline to Clayton-yellow with sodium hydroxide, and the precipitated base (II; R = *p*-OMe·C₆H₄) collected and washed (38.3% or 56.1% after allowance for recovered nitrile). The base crystallised from methyl alcohol (carbon) in colourless plates, m. p. 164—165° (Found: C, 65.5; H, 5.45; N, 20.7. C₁₁H₁₁ON₃ requires C, 65.8; H, 5.5; N, 20.9%).

(ii) *With p*-chlorophenylacetonitrile. The nitrile (19.4 g.) was heated with formamide (26 g.) for 7 hours; 3.0 c.c. of aqueous distillate and 1.0 c.c. of oil (unchanged nitrile) were collected. On cooling, the mixture crystallised completely to a pale yellow cake, which was thoroughly washed with water (3 × 50 c.c.). The solid was dissolved in 2*N*-hydrochloric acid (300 c.c.), the solution clarified by repeated treatment with carbon, and made alkaline to Clayton-yellow indicator with sodium hydroxide. The precipitated 4-amino-5-*p*-chlorophenylpyrimidine (II; R = *p*-ClC₆H₄) was separated, washed, and crystallised from methyl alcohol, forming colourless plates (13.4 g., 51.1%), m. p. 203—204° (Found: C, 57.95; H, 3.8; N, 20.0; Cl, 17.3. C₁₀H₈N₃Cl requires C, 58.3; H, 3.9; N, 20.5; Cl, 17.3%).

(iii) *With p*-hydroxyphenylacetonitrile. The nitrile (30.5 g.) was heated with formamide (40 g.) for 6 hours, 8.0 c.c. of an aqueous distillate containing hydrogen cyanide being obtained. On cooling overnight, the black residue which had partly crystallised was thoroughly washed with water (3 × 50 c.c.), and the residue dissolved in *n*-hydrochloric acid (200 c.c.). The boiling acid solution was clarified by repeated treatment with carbon, and on cooling in ice the crude hydrochloride of the base was precipitated. Crystallisation from *n*-hydrochloric acid together with further clarification by carbon gave 4-amino-5-*p*-hydroxyphenylpyrimidine hydrochloride (5.5 g.), as colourless prisms, m. p. 300—301° (Found: HCl, 16.75. C₁₀H₉ON₃·HCl requires HCl, 16.35%), soluble in cold water but only sparingly soluble in cold *n*-hydrochloric acid. The combined filtrates from the hydrochloride were made just alkaline to brilliant-yellow indicator; the precipitated crude base (II; R = *p*-OH·C₆H₄) (7.45 g.) was washed and dried. Crystallisation from methyl alcohol (carbon) yielded it as colourless plates (6.0 g.), m. p. 289—291° (Found: C, 63.75; H, 4.4; N, 22.15. C₁₀H₉ON₃ requires C, 64.2; H, 4.8; N, 22.5%). The overall yield (pure base + pure hydrochloride) was 24.7%.

(iv) *With o*-methoxyphenylacetonitrile. The nitrile (18.4 g.) was heated with formamide (25 g.) for 3½ hours and gave an aqueous distillate (12.2 c.c.) and an oil (4.8 c.c.) which readily solidified (unchanged nitrile). More formamide (25 g.) was then added, and the heating continued for 1 hour; an additional 7.1 c.c. of aqueous distillate and 1.0 g. of nitrile were collected. (The combined aqueous distillates gave a strong positive test for hydrogen cyanide.) After cooling, the reaction mixture was dissolved in ether (200 c.c.) and washed with 2*N*-hydrochloric acid (3 × 50 c.c.) and with aqueous sodium hydrogen carbonate. From the ethereal solution, unchanged nitrile was recovered (3.1 g., 17%; b. p. 138—142°/13 mm.). The acid extract was clarified (carbon) and addition of sodium hydroxide precipitated 4-amino-5-*o*-methoxyphenylpyrimidine (II; R = *o*-OMe·C₆H₄) (0.95 g., 3.8%; or, after allowance for recovered nitrile, 7.3%), which crystallised from methyl alcohol as colourless plates, m. p. 176—177° (Found: C, 66.05; H, 5.65; N, 20.45. C₁₁H₁₁ON₃ requires C, 65.8; H, 5.5; N, 20.9%).

(v) *With p-nitrophenylacetoneitrile.* The nitrile (10 g.) and formamide (20 c.c.) were heated for 10 hours, approximately 1 c.c. of distillate being obtained. After cooling, the residual thick oil was treated with water, and the sticky solid filtered off and ground with alcohol (20 c.c.); on drying at 40–60°, the dark brown powder melted to a black resin (6.0 g.). This was repeatedly extracted with 2*N*-hydrochloric acid, the acid solution clarified (carbon), and basified to give a yellow amorphous precipitate, m. p. 205–238° (0.5 g., 4.6%). Repeated crystallisation from benzene and from alcohol raised the m. p. of this 4-amino-5-*p*-nitrophenylpyrimidine (II; R = *p*-NO₂·C₆H₄) to 234–239° (sintering at 231°) and gave no depression with the material obtained by the diphenylformamidine route. Further purification was not possible with the small amount of material available.

C. *Reactions of Formamide with Nuclear-substituted α-Iminomethylphenylacetoneitriles.*—The mixture of the nitrile and formamide was heated with stirring at 180° in a stream of dry ammonia gas in a flask fitted with a short still-head.

(i) *With p-methoxy-α-iminomethylphenylacetoneitrile.* The nitrile (0.15 g.) and formamide (4 c.c.) were heated for 3 hours. The mixture, after cooling, was poured into water, and the precipitated solid (A) collected. The filtrate was separated into a basic and a neutral fraction by partition between 2*N*-sulphuric acid and ether. The precipitate (A) was dissolved in the acid fraction, the solution clarified (carbon) and made alkaline to Clayton-yellow with sodium hydroxide. The precipitated 4-amino-5-*p*-methoxyphenylpyrimidine crystallised from water (10 c.c.) as colourless plates (0.085 g.; 49%), m. p. (alone and mixed with the product obtained in Section B) 164–166°.

(ii) *With p-chloro-α-iminomethylphenylacetoneitrile.* The nitrile (0.065 g.) and formamide (4 c.c.) were heated for 3 hours, and the product treated as in the above experiment to yield 4-amino-5-*p*-chlorophenylpyrimidine (0.04 g.), m. p. (alone and mixed with the product obtained in Section B) 202–204°.

(iii) *With p-nitro-α-phenyliminomethylphenylacetoneitrile.* The nitrile (34 g.) (m. p. 274–276°; Grothaus and Dains, *loc. cit.*, do not record a m. p.) and formamide (45 c.c.) were heated for 7 hours, most of the distillate (4.2 c.c. and some white solid) coming over in the first 3 hours. The product was poured into water (about 100 c.c.), heated to boiling, and made strongly acid to Congo-red with 36% hydrochloric acid, sufficient being added to hydrolyse the excess of formamide. The hot solution was twice treated with kieselguhr to remove tar and then with carbon, and the hot orange-yellow filtrate made alkaline with sodium hydroxide. The crude pyrimidine was filtered off, and purified as its hydrochloride by repeated crystallisation (carbon) from 2*N*-hydrochloric acid (about 50 c.c.) to give the *hydrochloride* of 4-amino-5-*p*-nitrophenylpyrimidine (6.6 g., 20%), m. p. 302–304° (decomp.) (Found: HCl, 14.6. C₁₀H₈O₂N₄·HCl requires HCl, 14.5%). The hydrochloride, dissolved in hot water (100 c.c.), was treated with excess of *n*-sodium hydroxide (35 c.c.). The yellow precipitate was collected, washed, and crystallised successively from alcohol (about 400 c.c.) and dioxan to give 4-amino-5-*p*-nitrophenylpyrimidine (II; R = *p*-NO₂·C₆H₄) as fine deep yellow needles (4.6 g.), m. p. 241–243° (Found: C, 55.6; H, 4.05; N, 25.6. C₁₀H₈O₂N₄ requires C, 55.55; H, 3.7; N, 25.9%), which did not depress the m. p. of the crude product obtained as in Section B (v). This substance had the curious property that its solution in hot dioxan was practically colourless, but on cooling, the yellow colour reappeared and yellow crystals separated.

IMPERIAL CHEMICAL INDUSTRIES, LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

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