348. *Cinnolines. Part XIX. The Preparation and Reactions of Some* 8-*Nitro*-4-*hydroxy- and* 4-*Hydroxy*-Bz-*methyl-cinnolines.*

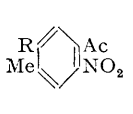
By J. R. KENEFORD, J. S. MORLEY, and J. C. E. SIMPSON.

A number of 4-substituted-8-nitro- and -7- and -8-methyl-cinnolines have been synthesised, starting from 2-nitro-5-amino-4-methylacetophenone and 2-nitro-*m*-toluic acid.

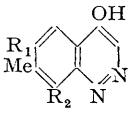
In the course of these preparations some further examples of unusual group interchange reactions have been encountered; 3-nitro-2-aminoacetophenone yields, according to conditions, either 8-nitro- or 8-chloro-4-hydroxycinnoline [cf. Parts X and XVIII of this series (*J.*, 1947, 232; this vol., p. 1170)], and 7-chloro-6-nitro-4-hydroxycinnoline gives 4 : 6 : 7-trichlorocinnoline when heated with a mixture of phosphoryl chloride and phosphorus pentachloride.

DEAMINATION of 2-nitro-5-amino-4-methylacetophenone (I; R = NH_2), previously prepared from *p*-methylacetophenone (Keneford and Simpson, *J.*, 1947, 227), leads smoothly to 2-nitro-4-methylacetophenone (I; R = H). Reduction of this nitro-ketone gave 2-*amino*-4-

methylacetophenone, which, under the conditions appropriate to this type of amine (Keneford and Simpson, *J.*, 1947,917; Schofield and Simpson, this vol., p. 1170), yielded 4-*hydroxy*-7-*methylcinnoline* (II; $R_1 = R_2 = H$), and thence, by routine methods, 4-*acetoxy*- and 4-*phenoxy*-7-*methylcinnoline*. Nitration of (II; $R_1 = R_2 = H$) yielded a single mono-nitro-derivative, which is regarded as 8-*nitro*-4-*hydroxy*-7-*methylcinnoline* (II; $R_1 = H$; $R_2 = NO_2$). No formal proof of the structure of this substance is available, but the 8-position is, clearly, the likely point of attack; furthermore, 8-nitro-4-hydroxycinnoline (III; R = OH) is a minor product of the nitration of 4-hydroxycinnoline (Simpson, *J.*, 1947, 237); and, finally, 8-nitro-4-hydroxycinnolines show certain properties, such as resistance to acetylation (these properties will be discussed in a future communication), which are exhibited by the nitro-hydroxy-methylcinnoline in question. By the usual procedures, 8-nitro-4-hydroxy-7-methylcinnoline was converted into 4-*chloro*-8-*nitro*-, 8-*nitro*-4-*amino*-, 8-*nitro*-4-*anilino*-, and 8-*nitro*-4-*phenoxy*-7-*methylcinnoline*.



(I.)



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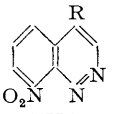

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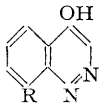

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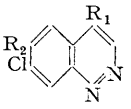

(VII.)

Nitration of 2-*acetamido*-4-*methylacetophenone* (IV; R = H) gave an almost quantitative yield of a *mononitro*-derivative, m. p. 136—137°, which by hydrolysis and cyclisation was converted into a nitro-hydroxycinnoline, m. p. 250—251°, which was not identical with 8-nitro-4-hydroxy-7-methylcinnoline. The substances, m. p. 250—251° and 136—137°, are therefore regarded as 6-*nitro*-4-*hydroxy*-7-*methylcinnoline* (II; $R_1 = NO_2$; $R_2 = H$) and 5-*nitro*-2-*acetamido*-4-*methylacetophenone* (IV; $R = NO_2$) respectively. The formation of the latter was accompanied by that of a small amount of a dinitro-derivative, evidently 3 : 5-*dinitro*-2-*acetamido*-4-*methylacetophenone*; this was hydrolysed to 3 : 5-*dinitro*-2-*amino*-4-*methylacetophenone*, which, however, did not give a cinnoline derivative under the usual conditions.

Condensation of the chloride of 2-nitro-*m*-toluic acid (Tomisek, Graham, Griffith, Pease, and Christensen, *J. Amer. Chem. Soc.*, 1946, **68**, 1587) with ethyl ethoxymagnesiomalonate (cf. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386) proceeded smoothly, and yielded, after hydrolysis, 2-*nitro*-3-*methylacetophenone* (V; $R = NO_2$). This was reduced to 2-*amino*-3-*methylacetophenone* (V; $R = NH_2$), from which 4-*hydroxy*-8-*methylcinnoline* (VI; R = Me) and thence, by the usual methods, 4-*phenoxy*-, 4-*amino*-, and 4-*anilino*-8-*methylcinnoline*, were prepared. Nitration of (VI; R = Me) gave in high yield a mono-nitro-derivative; this is probably 5- or 7-*nitro*-4-*hydroxy*-8-*methylcinnoline*. From the nitro-compound, 5- or 7-*nitro*-4-*phenoxy*-, -4-*amino*-, and -4-*anilino*-8-*methylcinnoline* were prepared by known methods.

Conversion of 8-nitro-4-hydroxycinnoline (III; R = OH) (Simpson, *loc. cit.*) into the 4-chloro-compound and treatment of the latter with phenol and ammonium carbonate gave both 8-*nitro*-4-*phenoxy*- (III; R = OPh) and 8-*nitro*-4-*amino*-*cinnoline* (III; $R = NH_2$). This is the first example in the cinnoline series in which this method of phenoxylation produces an appreciable amount of the corresponding amino-compound, although both reactions occur with 4-chloro-6- and -7-nitroquinazoline (Morley and Simpson, this vol., p. 360), and the amine is usually the sole product in the case of 5-chloroacridines (*e.g.*, Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169).

As an alternative route to (III; $R = NH_2$), the nitration of 4-chlorocinnoline was investigated, as it has been established that 4-chloro-8-nitroquinoline is a major product of the nitration of 4-chloroquinoline (cf., *e.g.*, Gouley, Moersch, and Mosher, *J. Amer. Chem. Soc.*, 1947, **69**, 303; Simpson and Wright, following paper). A crude nitration product, formed in poor yield, gave 8-nitro-4-phenoxycinnoline on phenoxylation, but the reaction was not of practical value, as 4-chlorocinnoline is considerably more resistant to nitration than 4-chloroquinoline, and side-reactions occur if the conditions are made sufficiently drastic to ensure that more than a small fraction of the chloro-compound is nitrated.

During this work it was observed that if 3-nitro-2-aminoacetophenone is diazotised and cyclised in concentrated hydrochloric acid, the product is not (III; R = OH) (obtained in sulphuric acid) but 8-chloro-4-hydroxycinnoline (VI; R = Cl) (Schofield and Simpson, *J.*, 1945, 520). The precise stage at which the exchange of groups occurs was not ascertained, but the reaction is probably a further example of the type of group-exchange, discussed in Parts X and XVIII (*J.*, 1947, 232; this vol., p. 1170), which is undergone by diazonium kations derived from certain *o*-aminoacetophenones before cyclisation. Group interchange can, however, also occur in a preformed cinnoline nucleus; thus, as examples involving a substituent in the *Bz*-ring, Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419) have found that 6-bromo-4-hydroxycinnoline yields what is undoubtedly 4 : 6-dichlorocinnoline (cf. Keneford and Simpson, *J.*, 1947, 917) when treated with a mixture of phosphorus pentachloride and oxychloride at 135—140°, and we have now found that 7-chloro-6-nitro-4-hydroxycinnoline (VII; R_1 = OH; R_2 = NO_2) (Atkinson and Simpson, *J.*, 1947, 232) similarly yields 4 : 6 : 7-trichlorocinnoline (VII; R_1 = R_2 = Cl) instead of the expected 4 : 7-dichloro-6-nitrocinnoline; and Dr. K. Schofield informs us (private communication) that group-exchange may also occur in the azine ring of the cinnoline nucleus, 3-bromo-4-hydroxycinnolines giving, under suitable conditions, the 3 : 4-dichloro-compounds.

Experimental.

M. p.s are uncorrected. Nitrations were performed with mechanical stirring. Unless otherwise stated, 4-chloro- and 4-phenoxy-cinnolines were prepared by the methods previously described (Keneford and Simpson, *J.*, 1947, 917) (phenoxy-compounds were better isolated by direct filtration than by ether-extraction). 4-Amino-compounds were prepared from the phenoxy-compounds and fused ammonium acetate by the method of Keneford, Schofield, and Simpson (this vol., p. 358); optimum conditions varied in different cases as detailed below.

2-*Amino*-4-*methylacetophenone*.—A hot solution of 2-nitro-5-amino-4-methylacetophenone (24 g.) in concentrated hydrochloric acid (760 c.c.) was rapidly cooled, and the resultant suspension diazotised at 0—5° with a solution of sodium nitrite (10 g.) in water (30 c.c.); cold hypophosphorous acid (30%, 280 c.c., 10 moles) was added with stirring during ½—1 hour, and the mixture left at 0° for 1 week. The product was collected with ether, the solution washed (aqueous sodium hydroxide and water), dried, solvent removed, and the crude 2-nitro-4-methylacetophenone (83% yield) distilled at 120—130°/1 mm. (yield of purified ketone, 75%). The use of 15 and 5 moles of hypophosphorous acid gave crude yields of 85% and 73% respectively. Reduction of the nitro-ketone (49·6 g.) with iron powder (100 g.), water (200 c.c.), and acetic acid (200 c.c.) by the method previously described (*J.*, 1945, 646) gave 2-*amino*-4-*methylacetophenone* (crude yield, 41·5 g., m. p. 50—52°), which crystallised from ligroin (b. p. 40—60°) in brittle amber blades, m. p. 55—56° (Found: C, 72·2; H, 7·45. $C_9H_{11}ON$ requires C, 72·45; H, 7·45%), and yielded (with acetic anhydride at 95°) 2-*acetamido*-4-*methylacetophenone* (95%) as long prismatic needles, m. p. 75—76°, from ligroin (b. p. 60—80°) (Found: C, 68·35; H, 6·85; N, 7·5. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85; N, 7·35%).

5-*Nitro*-2-*amino*-4-*methylacetophenone*.—2-Acetamido-4-methylacetophenone (5 g.) was added during 25 minutes to a mixture of nitric acid (*d* 1·483) and concentrated sulphuric acid (5 : 2 v/v, 30 c.c.) at − 8° to 0°. After a further 10 minutes, the solution was poured on ice; 5-*nitro*-2-*acetamido*-4-*methylacetophenone*, precipitated in almost quantitative yield, separated from alcohol in long, cream-coloured needles, m. p. 136—137° (Found: C, 56·05; H, 4·95; N, 11·65. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·15; N, 11·85%). Hydrolysis with 5N-hydrochloric acid (10 parts by vol., ½ hour's reflux) gave, quantitatively, 5-*nitro*-2-*amino*-4-*methylacetophenone*, which formed long greenish-yellow prismatic needles, m. p. 165·5—166·5°, from alcohol (Found: N, 14·25. $C_9H_{10}O_3N_2$ requires N, 14·45%).

3 : 5-*Dinitro*-2-*amino*-4-*methylacetophenone*.—The acid filtrate from the above acetamido-compound was basified (sodium carbonate) and extracted with ether, the extract dried and concentrated, and the solid residue (0·2 g.) recrystallised from benzene–ligroin (b. p. 60—80°), yielding 3 : 5-*dinitro*-2-*acetamido*-4-*methylacetophenone* as lemon-yellow elongated polyhedra, m. p. 183—183·5° (Found: C, 47·1; H, 4·05; N, 15·2. $C_{11}H_{11}O_6N_3$ requires C, 46·95; H, 3·95; N, 14·95%). Hydrolysis of this as above gave in good yield 3 : 5-*dinitro*-2-*amino*-4-*methylacetophenone*, deep yellow micro-prisms, m. p. 192—193°, from alcohol (Found: N, 17·7. $C_9H_9O_5N_3$ requires N, 17·55%), which gave no crystalline product when its solution in acetic acid–85% sulphuric acid was diazotised and heated.

2-*Nitro*-3-*methylacetophenone*.—2-Nitro-*m*-toluic acid (72·4 g.), phosphorus pentachloride (91·7 g.), and benzene (100 c.c.) were refluxed for ¾ hour, solvent removed, and the residue again evaporated with benzene under reduced pressure. A solution of the residue in ether–benzene (1 : 1, 400 c.c.) was added with stirring, during ½ hour at room temperature, to ethyl ethoxymagnesiomalonate [from magnesium (10·7 g.), alcohol (10 c.c.), carbon tetrachloride (1 c.c.), ether (150 c.c.), and a solution of ethyl malonate (70·4 g.) in alcohol (40 c.c.) and ether (50 c.c.)], and the suspension was refluxed for ½ hour and acidified with dilute sulphuric acid. The organic product was dried and freed from solvent, and the residue, which crystallised overnight, was refluxed for 5 hours with a mixture of acetic acid (120 c.c.), concentrated sulphuric acid (15 c.c.), and water (80 c.c.). Basification with 20% aqueous sodium hydroxide at 0° and extraction with ether gave 2-*nitro*-3-*methylacetophenone* (57·9 g., 81% based on 2-nitro-*m*-toluic acid), which formed colourless brittle rods, m. p. 85—86°, from ligroin (b. p. 60—80°) (Found: C, 60·45; H, 5·05; N, 7·9. $C_9H_9O_3N$ requires C, 60·3; H, 5·05; N, 7·8%).

2-*Amino*-3-*methylacetophenone*.—Reduction of the nitro-ketone (45 g.) with iron powder (90 g.), acetic acid (225 c.c.), and water (225 c.c.) at 95° gave 2-*amino*-3-*methylacetophenone* (36·7 g., 98%), which crystallised from ligroin (b. p. 60—80°) in pale amber, brittle plates, m. p. 55—56° (Found: C, 72·9; H, 7·7. $C_9H_{11}ON$ requires C, 72·4; H, 7·4%). 2-*Acetamido*-3-*methylacetophenone* (prepared with acetic

anhydride at 95°) formed colourless rhombohedra, m. p. 145—146°, from alcohol (Found: N, 7·45. $C_{11}H_{13}O_2N$ requires N, 7·3%).

4-*Hydroxy*-7-*methylcinnoline*.—A hot solution of 2-amino-4-methylacetophenone (33·6 g., m. p. 50—52°) in concentrated hydrochloric acid (850 c.c.) was quickly cooled, diazotised (16·7 g. of sodium nitrite in 24 c.c. of water), filtered, treated with concentrated hydrochloric acid (2550 c.c.), kept at 50—60° for 2 hours, and then concentrated under reduced pressure to a small volume. Addition of saturated aqueous sodium acetate precipitated 4-*hydroxy*-7-*methylcinnoline* (21 g., m. p. 235—237°); this was very soluble in alcohol, and crystallised from acetic acid in colourless silky needles, m. p. 243·5—244·5° (Found: C, 67·35; H, 4·95; N, 17·85. $C_9H_8ON_2$ requires C, 67·45; H, 5·05; N, 17·5%). 4-*Acetoxy*-7-*methylcinnoline*, prepared by refluxing the hydroxy-compound with acetic anhydride (6 parts) for ½ hour, separated from alcohol in tufts of jagged needles, m. p. 117—118° (Found: C, 65·2; H, 4·75; N, 14·0. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·85%).

4-*Phenoxy*-7-*methylcinnoline*.—The hydroxycinnoline (1 g.), phosphorus pentachloride (2·5 g.), and phosphorus oxychloride (3 c.c.) reacted spontaneously, and no further change seemed to occur on heating. The crude chloro-compound (bright yellow glittering scales, m. p. 115—117°) (0·85 g.) gave 4-*phenoxy*-7-*methylcinnoline* (0·9 g.), which formed colourless prismatic needles, m. p. 113—114°, from benzene–ligroin (b. p. 60—80°) (Found: C, 76·1; H, 5·3. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·15%).

8-*Nitro*-4-*hydroxy*-7-*methylcinnoline*.—4-Hydroxy-7-methylcinnoline (10 g.) was added during ½ hour to a mixture of nitric acid (*d* 1·53) and 65% oleum (5 : 2 v/v, 60 c.c.) at 0—5°. After a further ½ hour at 0°, the solution was poured on ice (500 g.) and the crude solid [11·85 g., m. p. 228—232° (decomp.)] collected. Digestion with hot alcohol and crystallisation from acetic acid gave lemon-yellow jagged blades, m. p. 243—244° (decomp.), of 8-*nitro*-4-*hydroxy*-7-*methylcinnoline* (Found: C, 52·7; H, 3·6; N, 20·4. $C_9H_7O_3N_3$ requires C, 52·65; H, 3·45; N, 20·45%), unchanged after being refluxed with acetic anhydride for 4 hours.

4-*Chloro*-8-*nitro*-7-*methylcinnoline*.—The crude chloro-compound [5·2 g., m. p. 195° (decomp.)] prepared from the above substance (5 g.), phosphorus pentachloride (12·5 g.), and phosphorus oxychloride (15 c.c.) was collected by filtration of the alkaline suspension; crystallisation from benzene gave pale green blades of 4-*chloro*-8-*nitro*-7-*methylcinnoline*, m. p. 210—211° (decomp.), sparingly soluble in ether (Found: C, 48·65; H, 3·0; Cl, 16·5. $C_9H_6O_2N_3Cl$ requires C, 48·3; H, 2·7; Cl, 15·9%). The optimum reaction time is 5—10 minutes; with 1 hour's heating, much dark, insoluble matter is formed, and only 25—30% of impure chloro-compound is isolable by extraction with a large volume of ether.

8-*Nitro*-4-*anilino*-7-*methylcinnoline*.—A mixture of aniline (0·1 g.), the foregoing chloro-compound (0·25 g.), 50% aqueous acetone (110 c.c.), and concentrated hydrochloric acid (6 drops) was refluxed for ½ hour. The solid (0·15 g.) obtained by basification with ammonia was recrystallised from alcohol, from which 8-*nitro*-4-*anilino*-7-*methylcinnoline* separated in greenish-yellow prismatic needles, m. p. 262—263° (decomp.) (Found: N, 19·7. $C_{15}H_{12}O_2N_4$ requires N, 20·0%). Dilution of the ammoniacal filtrate with water gave unchanged chloro-compound.

8-*Nitro*-4-*phenoxy*-7-*methylcinnoline*.—Reaction was incomplete at 95°, but at 150° (bath) 4-chloro-8-nitro-7-methylcinnoline gave 8-*nitro*-4-*phenoxy*-7-*methylcinnoline* in 84% yield as cream-coloured prismatic needles, m. p. 172—173°, from alcohol (Found: C, 64·05; H, 4·25. $C_{15}H_{11}O_3N_3$ requires C, 64·05; H, 3·95%).

8-*Nitro*-4-*amino*-7-*methylcinnoline*.—The reaction temperature, initially 160—170°, was raised to 200° and kept there for ½ hour (air-condenser). Dilution with water gave a solid [3·2 g., m. p. 255—260° (decomp.), from 4·1 g. of phenoxy-compound] which was extracted with 20% aqueous acetic acid; the insoluble fraction (1·1 g.) was unchanged phenoxy-compound, and the filtrate on basification (ammonia) yielded 8-*nitro*-4-*amino*-7-*methylcinnoline* (1·92 g.), which, after crystallisation from alcohol, formed sandy micro-prisms, m. p. 300° (decomp.) (Found: C, 53·35; H, 4·05; N, 27·8. $C_9H_8O_2N_4$ requires C, 52·9; H, 3·95; N, 27·45%).

6-*Nitro*-4-*hydroxy*-7-*methylcinnoline*.—A hot solution of 5-nitro-2-amino-4-methylacetophenone (1 g.) in concentrated hydrochloric acid (50 c.c.) was quickly cooled, diazotised [sodium nitrite (0·4 g.) in water (5 c.c.)], heated at 90° for ¼ hour, and poured into water. Crystallisation of the crude product (0·8 g., 76%, m. p. 244—246°) from acetic acid yielded 6-*nitro*-4-*hydroxy*-7-*methylcinnoline* as pale brown rhombohedra, m. p. 250—251° (200—210° when mixed with the 8-nitro-isomer) (Found: C, 52·9; H, 3·15. $C_9H_7O_3N_3$ requires C, 52·65; H, 3·45%).

8-*Chloro*-4-*hydroxycinnoline from* 3-*Nitro*-2-*aminoacetophenone*.—A filtered solution, prepared as in similar cases (above) from 3-nitro-2-aminoacetophenone (2 g.), concentrated hydrochloric acid (110 c.c.), and sodium nitrite (0·85 g.) in water (1·5 c.c.), was kept at 70—80° for ½ hour, concentrated (reduced pressure) to a small volume, and treated with sodium acetate. The solid so obtained (0·9 g., 45%, m. p. 192—194°) separated from alcohol in soft greenish-yellow needles, m. p. 195—196°, not depressed by admixture with authentic 8-chloro-4-hydroxycinnoline.

8-*Chloro*-4-*phenoxycinnoline*.—The crude chloro-compound from the above substance (0·65 g.), phosphorus pentachloride (1·3 g.), and phosphorus oxychloride (1·8 c.c.) formed yellow spikes, m. p. 146—147° (0·6 g.), from ether, and yielded 8-*chloro*-4-*phenoxycinnoline* (0·45 g. from 0·5 g.) as colourless prismatic needles, m. p. 158—159°, from benzene–ligroin (b. p. 60—80°) (Found: C, 64·8; H, 3·7. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·55%).

8-*Nitro*-4-*phenoxy- and* -4-*amino-cinnoline*.—(*a*) The method previously described (*J.*, 1947, 237) for the preparation of 8-nitro-4-hydroxycinnoline gave a somewhat improved yield on a larger scale, 7·5 g. (70%) resulting from 10·1 g. of 3-nitro-2-aminoacetophenone. 4-Chloro-8-nitrocinnoline (2·8 g. from 3 g. of hydroxy-compound) formed yellow needles, m. p. 180° (decomp.), from benzene. Treatment of this (1 part) with phenol (7·5 parts) and powdered ammonium carbonate (5 parts) at 90—95° for 1 hour gave, by basification and ether-extraction, a crude product which was digested with 20% aqueous acetic acid. The insoluble fraction (from 4·8 g. of chloro-compound), after recrystallisation from benzene, yielded 8-*nitro*-4-*phenoxycinnoline* (0·8 g., 13%) as pale green prismatic needles, m. p. 166—167° (Found: C, 63·05; H, 3·2; N, 15·6. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%). The acid-soluble material was 8-*nitro*-4-*aminocinnoline* (2·17 g., 50%); this base had a marked solubility lag in alcohol, from which

it separated in minute rust-red prismatic needles, m. p. 242—243° (decomp.) (Found : C, 47·1; H, 3·75; N, 28·2. $C_8H_6O_2N_4,\frac{3}{4}H_2O$ requires C, 47·15; H, 3·75; N, 27·5. $C_8H_6O_2N_4,\frac{2}{3}H_2O$ requires C, 47·5; H, 3·65; N, 27·7%).

(*b*) 4-Chlorocinnoline (5 g.) was added during ¼ hour to a mixture of nitric acid (*d* 1·53) and 65% oleum (5 : 2 v/v, 27 c.c.) kept at 40—45°. After a further hour at this temperature, the red solution was poured on ice; the mixture was made just alkaline (much alkali-soluble matter was present) and extracted with ether, the dried extract concentrated, and the solid material (1·45 g., m. p. 145—160°) added to phenol (7 g.) and ammonium carbonate (4 g.). After 1 hour on the steam-bath, the usual isolation procedure yielded 8-nitro-4-phenoxycinnoline (no 8-nitro-4-aminocinnoline was encountered) (0·25 g., 13·5%), m. p. 166—167° alone and mixed with the sample described in (*a*). The use of a shorter reaction time and/or lower temperatures in the nitration gave little or no nitration product, and much 4-chlorocinnoline was recovered.

4-*Hydroxy*-8-*methylcinnoline*.—The filtered solution, prepared as in similar cases from 2-amino-3-methylacetophenone (30 g.), concentrated hydrochloric acid (1 l.), sodium nitrite (16·5 g.), and water (25 c.c.), was treated with more concentrated hydrochloric acid (2 l.) and the whole left in the dark at room temperature for 7 days. The product which had separated was combined with that obtained by evaporating the filtrate under reduced pressure, dissolved in aqueous sodium hydroxide, filtered (charcoal), and acidified with acetic acid; 4-*hydroxy*-8-*methylcinnoline* (25·3 g., 78%) separated in fine colourless needles, m. p. 220—221° after crystallisation from aqueous alcohol or aqueous acetic acid (Found : C, 68·0; H, 4·9; N, 17·4. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%). Cyclisation at 50° reduced the yield to 65%. The compound was unchanged after being refluxed for 3 hours with acetic anhydride.

4-*Phenoxy*-8-*methylcinnoline*.—4-Chloro-8-methylcinnoline [from the hydroxy-compound (2 g.), phosphorus pentachloride (3 g.), and phosphorus oxychloride (4 c.c.)] (98% yield; glittering pale-green rods, m. p. 92—93°, from ligroin) had basic properties, could be crystallised unchanged from aqueous ethanol, and was unchanged after standing under aqueous ammonia (*d* 0·88, 5 days at room temperature). Interaction was incomplete when it (1·5 g.) was added with powdered ammonium carbonate (6 g.) to warm phenol (15 g.), the whole being kept at 95° for ¾ hour; the crude product gave 4-*phenoxy*-8-*methylcinnoline* (0·9 g.) as colourless prisms, m. p. 96·5—97°, when crystallised from ligroin (b. p. 40—60°) (Found : C, 76·0; H, 5·0. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1%), and the first ligroin filtrate gave material from which pure chloro-compound (0·32 g.) was isolated.

4-*Amino*-8-*methylcinnoline*.—The reaction temperature, initially 130°, was rapidly raised to 180—185° and kept there for 5 minutes. The cold melt was dissolved in water, made just alkaline with ammonia, and filtered (charcoal); the filtrate slowly deposited 4-*amino*-8-*methylcinnoline* (99%), which crystallised from water in almost colourless glittering blades, m. p. 142—147°, 145—152°, or intermediately according to the rate of heating, after softening at 120—130° (Found : C, 64·9; H, 5·9; N, 25·0. $C_9H_9N_3,\frac{1}{2}H_2O$ requires C, 64·3; H, 6·0; N, 25·0%).

4-*Anilino*-8-*methylcinnoline*.—4-Chloro-8-methylcinnoline (0·36 g.), aniline (0·22 g.), 50% aqueous acetone (20 c.c.), and concentrated hydrochloric acid (3 drops) were refluxed for ½ hour. Concentration and basification yielded 4-*anilino*-8-*methylcinnoline* (0·46 g.), which formed silky, lemon-yellow needles, m. p. 231—232°, from alcohol (Found : C, 76·2; H, 5·3; N, 18·3. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·55; N, 17·9%).

5- *or* 7-*Nitro*-4-*hydroxy*-8-*methylcinnoline*.—4-Hydroxy-8-methylcinnoline (10 g.) was added during ¼ hour at − 5° to 0° to a mixture of nitric acid (*d* 1·50) and concentrated sulphuric acid (5 : 2 v/v, 75 c.c.). After a further ¼ hour the solution was poured on ice (1 kg.), and the solid collected (11·2 g., 87%, m. p. 251—252°) and recrystallised from aqueous acetic acid, yielding 5- or 7-*nitro*-4-*hydroxy*-8-*methylcinnoline* as almost colourless needles, m. p. 255—256° after darkening at 245° (Found : C, 52·0; H, 3·1; N, 20·9. $C_9H_7O_3N_3$ requires C, 52·6; H, 3·5; N, 20·5%). The compound was unaffected by 1 hour's refluxing with acetic anhydride.

5- *or* 7-*Nitro*-4-*phenoxy*-8-*methylcinnoline*.—The hydroxy-compound (10 g.), phosphorus pentachloride (12 g.), and phosphorus oxychloride (40 c.c.) were well mixed and warmed on the water-bath for 3—5 minutes. The mixture was immediately cooled (prolonged heating seriously reduces the yield of product) and diluted with ligroin, and the solid collected, suspended in N/4-sodium hydroxide, and extracted with chloroform. The crude chloro-compound obtained by evaporation of the dried extract formed pale yellow-green prisms, m. p. 130—131° (10·03 g., 93%). It was recovered almost quantitatively after treatment with phenol and powdered ammonium carbonate at 95° for 1 hour. Addition of the chloro-compound (7·5 g.) to a solution of potassium hydroxide (1·9 g.) in phenol (20 g.), followed by heating at 150° (bath) for 1 hour, gave 5- or 7-*nitro*-4-*phenoxy*-8-*methylcinnoline* (7·66 g., 81%) as almost colourless, glittering rods, m. p. 160—161°, from benzene–ligroin (Found : C, 64·2; H, 4·0; N, 14·6. $C_{15}H_{11}O_3N_3$ requires C, 64·0; H, 3·95; N, 14·95%).

5- *or* 7-*Nitro*-4-*amino*-8-*methylcinnoline*.—The phenoxy-compound (1 g.) was added to ammonium acetate (10 g.) at 180° (bath), the temperature quickly raised to 195°, the melt immediately cooled and diluted with water, and the solid collected. Digestion with warm 20% acetic acid left a residue (0·42 g.) of almost pure phenoxy-compound, and addition of ammonia precipitated 5- or 7-*nitro*-4-*amino*-8-*methylcinnoline* (0·24 g.), which formed orange-red prismatic needles, m. p. 242—243° (decomp.), from alcohol (Found : C, 53·3; H, 3·95; N, 26·9. $C_9H_8O_2N_4$ requires C, 52·9; H, 4·0; N, 27·45%).

5- *or* 7-*Nitro*-4-*anilino*-8-*methylcinnoline*.—Prepared from 4-chloro-5- or 7-nitro-8-methylcinnoline (0·2 g.), aniline (0·1 g.), 50% aqueous acetone (10 c.c.), and concentrated hydrochloric acid (2 drops), 5- or 7-*nitro*-4-*anilino*-8-*methylcinnoline* (0·24 g.) crystallised from aqueous alcohol in soft, orange-red needles, m. p. 166—168° (Found : C, 63·9; H, 4·3; N, 20·3. $C_{15}H_{12}O_2N_4$ requires C, 64·2; H, 4·3; N, 20·0%).

4 : 6 : 7-*Trichlorocinnoline from* 7-*Chloro*-6-*nitro*-4-*hydroxycinnoline*.—Treatment of 7-chloro-6-nitro-4-hydroxycinnoline either as in the foregoing cases or with phosphorus oxychloride alone gave a chloro-derivative, m. p. 141—142° (Keneford and Simpson, *J.*, 1947, 227, give m. p. 141·5—142·5° for 4 : 6 : 7-trichlorocinnoline). Identification was established by conversion (with phenol and ammonium

carbonate at 95°) into 6 : 7-dichloro-4-phenoxycinnoline, m. p. 162—163° alone and when mixed with an authentic specimen (Keneford and Simpson, *loc. cit.*).

We are indebted to the Medical Research Council for Research Studentships (J. R. K. and J. S. M.).

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