53. *Cinnolines. Part IX. The Preparation of Some* 6 : 7- *and* 7 : 8-*Disubstituted*-4-*hydroxycinnolines.*

By J. R. Keneford and J. C. E. Simpson.

Syntheses are described, with proofs of structure, of 6-*chloro*-7-*methyl*-, 6-*bromo*-7-*methyl*-, 8-*chloro*-7-*methyl*-, 6 : 7-*dichloro*-, and 7 : 8-*dichloro*-4-*hydroxycinnoline*. *p*-Methyl-, *p*-chloro-, and 3 : 4-dichloro-acetophenone are used as starting materials, and the preparations are illustrative of the general method of 4-hydroxycinnoline synthesis from *o*-aminoacetophenones previously developed (*J.*, 1945, 520).

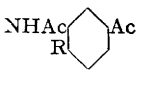
As part of an investigation of the uses of the cinnoline nucleus for the synthesis of antimalarial agents, we have prepared a variety of 6- and 8-substituted 7-chloro- and 7-methyl-4-hydroxycinnolines from appropriate *o*-aminoacetophenones by the method previously described (*J.*, 1945, 520). The present paper describes the preparation of these cinnolines and the intermediate amino-ketones starting from *p*-methyl-, *p*-chloro-, and 3 : 4-dichloro-acetophenone.

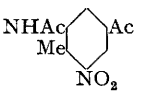
Nitration of *p*-methylacetophenone gives 3-nitro-4-methylacetophenone (Errera, *Gazzetta*, 1891, **21**, 92; Ganguly and Le Fèvre, *J.*, 1934, 852), the orientation of which was established, according to Ganguly and Le Fèvre (*loc. cit.*), by oxidation to 3-chloro-4-methylbenzoic acid *via* 3-chloro-4-methylacetophenone. In view of the fact that no experimental details of this oxidation are recorded (although details are given of oxidations which do not furnish proof of orientation), it may be pointed out that the transformations described below constitute proof of orientation independent of reference compounds.

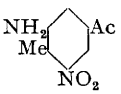
3-Nitro-4-methylacetophenone on reduction and acetylation gave 3-*acetamido*-4-*methylacetophenone* (I; R = Me), nitration of which gave all three possible mono-nitro compounds. Of these, 3-*nitro*-5-*acetamido*-4-*methylacetophenone* (II) was formed only in small amount (3·5%), and its formation could be suppressed completely under suitable conditions; it was, as expected, more basic than the *o*- and *p*-nitroacetamido-compounds. Its constitution was proved by hydrolysis to 3-*nitro*-5-*amino*-4-*methylacetophenone* (III) and deamination of the latter to 3-nitro-4-methylacetophenone. The remaining nitroacetamidomethylacetophenones, which formed the bulk of the nitration product (the *p*-nitroacetamido-compound predominating), could not usually be separated by crystallisation, although on one occasion an apparently pure specimen of 2-*nitro*-5-*acetamido*-4-*methylacetophenone* (IV; R = Me) was obtained by crystallisation from alcohol. Acid hydrolysis of the mixed products gave a mixture of 2-*nitro*-5-*amino*- (V; R = Me) and 2-*nitro*-3-*amino*-4-*methylacetophenone* (VI; R = Me), readily separated by use of the appropriate solvents. The orientation of the latter was proved by reduction and conversion into the *phenazine* (VII; R = Me). Additional proof of orientation, showing that the *C*-acetyl and nitro-groups occupy *o*-positions in (VI; R = Me), was obtained by conversion of this substance into 3-*chloro*-2-*nitro*-4-*methylacetophenone* (VIII; R = Cl), from which 8-*chloro*-4-*hydroxy*-7-*methylcinnoline* (IX; R_1 = H, R_2 = Cl) was prepared by reduction and diazotisation; 3-*bromo*-2-*nitro*-4-*methylacetophenone* (VIII; R = Br) was also prepared from (VI; R = Me). The orientation of (V; R = Me) follows from the establishment

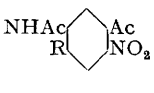
of the structures of (III) and (VI; R = Me); in agreement with this constitution, no phenazine could be obtained from the reduction product of (V; R = Me). The constitution of the substance as an *o*-nitroacetophenone was independently proved by its conversion into 6-*chloro*- and 6-*bromo*-4-*hydroxy*-7-*methylcinnoline* (IX; R_1 = Cl or Br, R_2 = H) *via* 5-*chloro*- and 5-*bromo*-2-*nitro*-4-*methylacetophenone* (X; R_2 = Me, R_1 = Cl or Br) by reduction and diazotisation. In contrast to that of the chloro-cinnoline, the formation of the bromo-cinnoline (IX; R_1 = Br, R_2 = H) did not proceed smoothly, and was accompanied by the production of much steam-volatile material. This consisted chiefly of 5-*bromo*-2-*hydroxy*-4-*methylacetophenone* (XI; R = OH), together with small amounts of a non-phenolic ketone which was not identified, but was apparently not 3-bromo-4-methylacetophenone (XI; R = H).

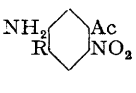
The fact that two isomeric chloro-4-hydroxy-7-methylcinnolines have been prepared from *p*-methylacetophenone by this series of reactions furnishes the confirmatory proof, referred to above, that nitration of this ketone gives 3-nitro-4-methylacetophenone; had nitration occurred in the 2-position, only one *o*-nitro-ketone, and hence only one cinnoline, could have been obtained from the resultant acetamido-methylacetophenone.

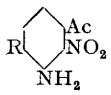

(I.)

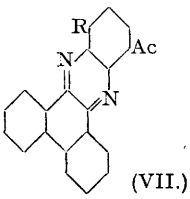

(II.)

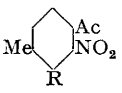

(III.)

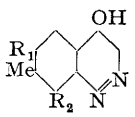

(IV.)

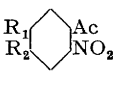

(V.)

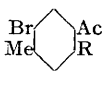

(VI.)

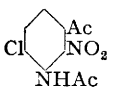

(VII.)

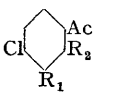

(VIII.)

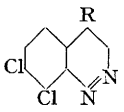

(IX.)

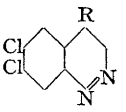

(X.)


(XI.)


(XII.)


(XIII.)


(XIV.)


(XV.)

The preparation of the cinnolines from *p*-chloroacetophenone followed similar general lines. The nitration of the ketone to 4-chloro-3-nitroacetophenone has been described by Mayer, Stark, and Schön (*Ber.*, 1932, **65**, 1333), who oriented the compound by oxidation to 4-chloro-3-nitrobenzoic acid. In agreement with this result, we observed that this chloronitroacetophenone gives a depression in m. p. when mixed with 4-chloro-2-nitroacetophenone of proved structure (following paper). Reduction and acetylation furnished 4-*chloro*-3-*acetamidoacetophenone* (I; R = Cl), nitration of which gave a mixture of 4-*chloro*-2-*nitro*-5- (IV; R = Cl) and -3-*acetamidoacetophenone* (XII). In contrast to the nitration of (I; R = Me), *m*-nitration of (I; R = Cl) (with reference to the *C*-acetyl group) did not occur to any appreciable extent; however, it is probable that this difference is due to experimental rather than to constitutional factors, because the formation of 3-nitro-5-acetamido-4-methylacetophenone is itself dependent on the conditions of nitration (see Experimental), and it has also been observed (this vol., p. 238), in the nitration of *o*-acetamidoacetophenone, that the size of the batch and the speed of admixture of reactants can influence the result considerably.

The structure of (XII) followed from its hydrolysis to the *nitro-amine* (VI; R = Cl), reduction of the latter, and conversion into the phenazine (VII; R = Cl), identical with the compound prepared (following paper) from 4-chloro-3-nitro-2-aminoacetophenone (XIII; R_1 = NO_2, R_2 = NH_2). Diazotisation of (VI; R = Cl) in hydrochloric acid followed by a Sandmeyer reaction gave only 2 : 3 : 4-*trichloroacetophenone* (XIII; R_1 = R_2 = Cl), but the use of sulphuric acid as diazotisation medium afforded 3 : 4-*dichloro*-2-*nitroacetophenone* (XIII; R_1 = Cl, R_2 = NO_2) in moderate yield, from which 7 : 8-*dichloro*-4-*hydroxycinnoline* (XIV; R = OH) was prepared by reduction, diazotisation, and ring-closure. By successive chlorination and phenoxylation, this substance was converted into 4 : 7 : 8-*trichlorocinnoline* (XIV; R = Cl) and 7 : 8-*dichloro*-4-*phenoxycinnoline* (XIV; R = OPh).

Hydrolysis of (IV; R = Cl) gave the free *amine* (V; R = Cl), and deamination yielded

4-chloro-2-nitroacetophenone (XIII; $R_1 = H$, $R_2 = NO_2$), thus (in view of the foregoing evidence) establishing its orientation. Diazotisation of (V; R = Cl), followed by the appropriate Sandmeyer reaction, furnished 4 : 5-dichloro-2-nitroacetophenone (X; $R_1 = R_2 = Cl$), identical with the compound obtained by nitrating 3 : 4-dichloroacetophenone (XIII; $R_1 = Cl$, $R_2 = H$). This nitration, originally* carried out by Roberts and Turner (*J.*, 1927, 1832), is stated by them to yield 3 : 4-dichloro-2-nitroacetophenone; this appears to be due to an error in nomenclature, as the work described by Roberts and Turner makes it clear that their compound is in reality 4 : 5-dichloro-2-nitroacetophenone; however, it seemed desirable to have independent proof of orientation (especially as 4 : 5-dichloro-2-nitroacetophenone is much more readily prepared from 3 : 4-dichloroacetophenone than from *p*-chloroacetophenone), and this has now been provided by the above identification. Reduction of this substance to 4 : 5-dichloro-2-aminoacetophenone, and diazotisation of the latter, gave 6 : 7-*dichloro*-4-*hydroxycinnoline* (XV; R = OH), which was converted by standard methods into 6 : 7-*dichloro*-4-*acetoxy*-, 4 : 6 : 7-*trichloro*-, and 6 : 7-*dichloro*-4-*phenoxy-cinnoline* (XV; R = OAc, Cl, and OPh).

Experimental.

Melting points are uncorrected. Nitrations were carried out with mechanical stirring. Nitro-amines were prepared from nitro-acetamido-compounds by refluxing for ½ hour with hydrochloric acid (6N, 5—7 parts by vol.) and isolated by basification with ammonia. Sandmeyer reactions were carried out by adding the diazonium to the cuprous solution in portions at room temperature, followed by heating for ½—1 hour at 70°; products were isolated by ether extraction, the extracts being washed successively with acid, sodium hydroxide, and water. 4-Hydroxycinnolines were prepared by heating the diazonium solutions at 70—90° until the coupling reaction with alkaline β-naphthol was negative or negligible (1—2 hours); they separated directly or were isolated by dilution with water. Unless otherwise specified in the text, the following statements apply: (i) Compounds were crystallised from alcohol. (ii) The ligroin used had b. p. 60—80°. (iii) Nitro-compounds were reduced to amines by heating (1 part) at 95° in acetic acid (7—8 vols.) with gradual addition of iron powder (1·5 parts) and water (7—8 vols.) (cf. *J.*, 1945, 646), and isolated by ether extraction.

3-*Nitro*-4-*methylacetophenone*.—This was prepared by the method of Ganguly and Le Fèvre (*loc. cit.*), using 110-g. batches of *p*-methylacetophenone, 740 c.c. of nitric acid (*d* 1·5), and a time of addition of 1—1¼ hours, the temperature being maintained below 0°. The clear solution was stirred for a further ¼ hour and then poured on crushed ice (*ca.* 2 kg.). The nitro-ketone had m. p. 60—62° after one crystallisation (average yield from 9 runs, 82%).

3-*Acetamido*-4-*methylacetophenone*.—The following modification of the method of Ganguly and Le Fèvre (*loc. cit.*) gave an improved yield. A solution of 3-nitro-4-methylacetophenone (100 g.) in alcohol (400 c.c.) was treated with iron powder (102 g.) and hydrochloric acid (28 c.c., 6N). The well-stirred suspension was refluxed for 1½ hours, more acid (28 c.c.) cautiously added, and heating continued for a further 1½ hours. A third 28 c.c. portion of acid was added, followed by 2 hours' heating. The suspension was then filtered, the sludge washed with hot alcohol (200 c.c.) containing concentrated hydrochloric acid (5 c.c.), and the filtrate and washings concentrated under reduced pressure to approximately 100 c.c. The residue was then basified with dilute ammonia and extracted with ether. Evaporation of the washed and dried extract yielded the crude amine as a dark brown oil which crystallised slowly on standing. Acetic anhydride (206 c.c.) was added, and the mixture heated on the steam-bath for 1 hour. 3-*Acetamido*-4-*methylacetophenone* separated from the reaction mixture in soft, cream-coloured needles, m. p. 143—144°, and more was obtained by decomposition of the filtrate (average yield from 10 runs, 73% based on nitro-compound); the m. p. was unchanged after crystallisation (Found: C, 69·05; H, 6·9. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9%).

Nitration of 3-*Acetamido*-4-*methylacetophenone*.—(*a*) The foregoing compound (40 g.) was added during 1 hour to a mixture of nitric acid (*d* 1·495) and concentrated sulphuric acid (220 c.c., 5 : 2 by volume) at − 15° to − 10°. After a further ½ hour the solution was poured on crushed ice, and the mixture of nitro-compounds (A) filtered off. Basification of the filtrate (ammonia) and extraction with ether gave a crystalline residue which yielded 3-*nitro*-5-*acetamido*-4-*methylacetophenone* in clusters of small, colourless needles, m. p. 200—200·5° (Found: C, 56·5; H, 5·4; N, 11·85. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%). 3-*Nitro*-5-*amino*-4-*methylacetophenone* formed long, feathery, reddish-brown needles, m. p. 158—159·5° (Found: C, 55·7; H, 5·3; N, 15·1. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2; N, 14·4%). Deamination of this substance was effected by addition of amyl nitrite (2 c.c.) to a solution of it (0·5 g.) in alcohol (100 c.c.) and concentrated sulphuric acid (8 c.c.); the solution was heated to boiling on the steam-bath during 5 minutes, boiled for a short time, made alkaline with solid sodium bicarbonate, and partly freed from alcohol (reduced pressure). The product was isolated by ether extraction, and yielded 3-nitro-4-methylacetophenone (0·3 g.), m. p. 60—61°, from ligroin, not depressed by admixture with authentic material.

No pure substance could be isolated from the mixture (A), which was therefore hydrolysed, although in one small-scale experiment (from 8 g. of 3-acetamido-4-methylacetophenone) direct crystallisation

* *Added in Proof*.—Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 405) state that they were unable to reproduce this result. In our experience, the experiment of Roberts and Turner is reproducible, and the nitration has been carried out many times under the more precise conditions which we describe in the Experimental. We would also point out that the compound, m. p. 176—177° (corr.), which Leonard and Boyd, on a conjectural basis, formulate as 4-chloro-2-nitro-5-acetamidoacetophenone, is clearly that which we have proved to be 4-chloro-2-nitro-3-acetamidoacetophenone.

afforded 2-*nitro*-5-*acetamido*-4-*methylacetophenone* as large, lemon-yellow rhombohedra, m. p. 164—165° (yield, 35%) (Found: C, 56·3; H, 4·95; N, 12·2. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%), identified by hydrolysis to the amine described below.

(*b*) On a larger scale, the acetamido-ketone (80 g.) was added during ¾ hour to a mixture of nitric acid (315 c.c., *d* 1·492) and concentrated sulphuric acid (126 c.c.) at 0—10°. After a further ¾ hour at the same temperature, the solution was poured on ice (2 kg.); the average yield of crude nitration product from eight runs was 54·6 g. (55%) (variations of these conditions in small-scale trials did not lead to substantially higher yields). The acid filtrates were basified and extracted with ether, but only a small quantity of oily product resulted. The mixed nitro-compounds (in 100-g. batches) were hydrolysed to the nitro-amines (428 g.). Crystallisation gave 2-*nitro*-5-*amino*-4-*methylacetophenone* as glistening bronze plates, m. p. 186—187° (230 g., 35%) (Found: C, 55·65; H, 5·45. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2%). Reduction of this substance gave a crystalline product, m. p. 175—180° (depressed by admixture with the nitro-amine), which gave no phenazine on attempted condensation with phenanthraquinone.

The alcoholic filtrates from the foregoing nitro-amine, freed as completely as possible from this substance, were concentrated further, and the residue crystallised from methyl ethyl ketone; 2-*nitro*-3-*amino*-4-*methylacetophenone* was thus obtained in gross, orange prisms, m. p. 102·5—103·5° (Found: C, 55·65; H, 5·35; N, 14·35. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2; N, 14·4%). A solution of the substance (0·3 g.) in acetic acid (6·5 c.c.) was reduced at 95° with iron filings (0·8 g.) and water (6·5 c.c.). The diamine, isolated in the known manner, had m. p. 75—85° (depressed by the starting material), and when it (0·15 g.) was refluxed with phenanthraquinone (0·21 g.) in alcohol (30 c.c.), the *phenazine* rapidly separated (small, soft, yellow needles, m. p. 289—290°, from acetic acid) (Found: C, 81·65; H, 5·0; N, 8·45. $C_{23}H_{16}ON_2$ requires C, 82·1; H, 4·8; N, 8·3%).

5-*Chloro*-2-*nitro*-4-*methylacetophenone*.—The finely-divided suspension obtained by rapid cooling of a hot solution of 2-nitro-5-amino-4-methylacetophenone (15 g.) in hydrochloric acid (300 c.c. of 9N) was diazotised with aqueous sodium nitrite (10%, 55 c.c.), and added to cuprous chloride (from 24 g. of copper sulphate crystals) in concentrated hydrochloric acid (38 c.c.). 5-*Chloro*-2-*nitro*-4-*methylacetophenone* (crude yield, 15·7 g.) formed long, almost colourless, brittle needles, m. p. 71—72° (Found: C, 50·8; H, 4·0. $C_9H_8O_3NCl$ requires C, 50·6; H, 3·8%).

5-*Chloro*-2-*amino*-4-*methylacetophenone*.—This *amine* (yield, 97%) formed irregular yellow blades, m. p. 109—109·5° (Found: C, 58·8; H, 5·45. $C_9H_{10}ONCl$ requires C, 58·8; H, 5·5%).

6-*Chloro*-4-*hydroxy*-7-*methylcinnoline*.—The suspension of the hydrochloride of the foregoing amine, obtained by cooling a hot solution of the crude base (13·1 g.) in hydrochloric acid (300 c.c., 6N), was diazotised with 10% sodium nitrite (54 c.c.). Crude 6-*chloro*-4-*hydroxy*-7-*methylcinnoline* (12·5 g., m. p. 260—266°) formed micro-prisms, m. p. 271—272°, after crystallisation (Found: C, 55·55; H, 3·85; N, 14·9. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·65; N, 14·4%).

5-*Bromo*-2-*nitro*-4-*methylacetophenone*.—Prepared similarly to the chloro-compound, but using hydrobromic acid (*d* 1·5) throughout (diluted with 3 vols. of water for the diazotisation), this *compound* (22 g. from 25 g. of 2-nitro-5-amino-4-methylacetophenone) separated from ligroin in large, jagged, pale yellow blades, m. p. 82—83° (Found: C, 42·2; H, 3·2; Br, 31·5. $C_9H_8O_3NBr$ requires C, 41·9; H, 3·1; Br, 31·0%).

5-*Bromo*-2-*amino*-4-*methylacetophenone*.—This *amine* (crude yield, 95%) formed long, lustrous, amber-coloured needles, m. p. 122·5—123·5° (Found: C, 47·6; H, 4·6; N, 6·5. $C_9H_{10}ONBr$ requires C, 47·4; H, 4·4; N, 6·1%).

6-*Bromo*-4-*hydroxy*-7-*methylcinnoline*.—A solution of the above amine (12·5 g.) in 2N-hydrochloric acid (200 c.c.) was diazotised with 10% sodium nitrite (40 c.c.); a condenser was used during the subsequent heating to retain volatile material. The crude product was digested with ether, and the insoluble residue (4·7 g.) gave 6-*bromo*-4-*hydroxy*-7-*methylcinnoline* as buff-coloured micro-prisms, m. p. 273—274° (Found: C, 45·15; H, 3·0; N, 12·0. $C_9H_7ON_2Br$ requires C, 45·2; H, 3·0; N, 11·7%).

5-*Bromo*-2-*hydroxy*-4-*methylacetophenone*.—The ethereal solution from the previous experiment was extracted with dilute sodium hydroxide; the alkaline solution was then acidified, and the product again taken into ether and isolated in the customary manner. The crude phenol (5·45 g.) was dissolved in hot ligroin, from which 5-*bromo*-2-*hydroxy*-4-*methylacetophenone* separated in long, pale yellow needles, m. p. 86—87° (Found: C, 47·7; H, 4·1. $C_9H_9O_2Br$ requires C, 47·2; H, 4·0%). The *benzoyl* derivative (Schotten–Baumann conditions) formed colourless, glistening rhombohedra, m. p. 95·5—96·5° (Found: C, 57·65; H, 4·2. $C_{16}H_{13}O_3Br$ requires C, 57·7; H, 3·9%).

The foregoing ethereal solution, after being freed from phenolic material, was washed with water, dried, and evaporated, yielding a red mobile oil (0·95 g.) which crystallised on standing. This material gave an oxime, m. p. 132—135°, and a semicarbazone, m. p. 290—300° (decomp.), under the usual conditions.

3-*Bromo*-4-*methylacetophenone*.—Acid hydrolysis of 3-acetamido-4-methylacetophenone gave the amine as a slowly crystallising oil. Diazotisation of this, followed by a Sandmeyer reaction (hydrobromic acid used at both stages), gave crude 3-bromo-4-methylacetophenone (8·4 g. from 10 g. acetamido-compound) as a low-melting solid. The oxime prepared from this had m. p. 94—95° (75—80° on admixture with the oxime described above), and the *semicarbazone* (small lustrous needles from pyridine) had m. p. 246—247° (230—235° when mixed with the foregoing semicarbazone) and was apparently slightly solvated after being dried in a vacuum (Found: C, 45·4; H, 4·6; N, 17·0. $C_{10}H_{12}ON_3Br$ requires C, 44·4; H, 4·5; N, 15·55%).

3-*Chloro*-2-*nitro*-4-*methylacetophenone*.—This *substance* (crude yield, 1 g.) was prepared from 2-nitro-3-amino-4-methylacetophenone (1 g.) using hydrochloric acid (25 c.c., 8N), sodium nitrite (8 c.c. of 5%), and cuprous chloride (from 1·6 g. of copper sulphate) in concentrated hydrochloric acid (2·5 c.c.). It formed almost colourless, fern-like blades, m. p. 128—129° (Found: C, 50·6; H, 3·5; Cl, 16·7. $C_9H_8O_3NCl$ requires C, 50·6; H, 3·8; Cl, 16·6%).

8-*Chloro*-4-*hydroxy*-7-*methylcinnoline*.—The foregoing nitro-ketone (0·6 g.), after reduction with acetic acid (5 c.c.), water (6 c.c.), and iron powder (1 g.), gave 0·45 g. of crude 3-chloro-2-amino-4-methyl-

acetophenone, m. p. 52—53°. This was dissolved in hydrochloric acid (10 c.c. of 2N and 3 c.c. of 12N) and diazotised (6 c.c. of 2% sodium nitrite), giving *8-chloro-4-hydroxy-7-methylcinnoline* (0·35 g.) as long, colourless, hair-like needles, m. p. 209—210° (Found: C, 55·1; H, 3·75; N, 14·2; Cl, 18·95. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·65; N, 14·4; Cl, 18·2%).

p-*Chloroacetophenone*.—By using acetyl chloride, this ketone was obtained in 80—90% yield by Straus and Ackerman (*Ber.*, 1909, **42**, 1804) and in 81% yield by Mayer, Stark, and Schön (*loc. cit.*). With acetic anhydride, Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1889) obtained an inferior yield (68%), but the following modification gave a yield of 93%. Acetic anhydride (2 mols., 186 c.c.) was slowly added (*ca.* 1 hour) to a well-stirred suspension of aluminium chloride (4·4 mols., 588 g.) in chlorobenzene (300 c.c.) at room temperature. The highly exothermic reaction proceeded smoothly and final heating on the water-bath for 1 hour brought about complete solution. The reaction mixture was poured on ice containing hydrochloric acid, and the product extracted with ether. The ethereal solution was washed with hydrochloric acid, sodium hydroxide solution, and water, dried, and concentrated. Distillation of the final residue yielded excess chlorobenzene followed by *p*-chloroacetophenone, b. p. 124—126°/*ca.* 30 mm.

4-*Chloro*-3-*nitroacetophenone*.—*p*-Chloroacetophenone (120 g.) was dissolved with vigorous stirring in concentrated sulphuric acid (278 c.c.) at − 12° to − 10° and treated with a mixture of nitric acid (*d* 1·5) and concentrated sulphuric acid (120 c.c., 1 : 2 v/v). Stirring was continued for a further 2 hours during which the nitration product began to separate. The suspension was poured on ice, and the moist solid recrystallised from methyl alcohol, giving short colourless blades, m. p. 102—103° (lit., 104°) (average yield 63%).

4-*Chloro*-3-*acetamidoacetophenone*.—4-Chloro-3-nitroacetophenone was reduced in 50-g. batches, and the amine (38·8 g., m. p. 106—108°) heated with acetic anhydride (80 c.c.) on the steam-bath for ½ hour; pure 4-*chloro*-3-*acetamidoacetophenone* separated on cooling, and a further crop was obtained by basification of the filtrate with ammonia (average yield, 72% based on nitro-compound). The compound formed large, colourless tetrahedra, m. p. 118·5—119·5° (Found: C, 56·95; H, 4·75. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·8%).

4-*Chloro*-2-*nitro*-5-*aminoacetophenone*.—4-Chloro-3-acetamidoacetophenone (20 g.) was added to nitric acid (110 c.c., *d* 1·5) at − 10° to − 5° during ½ hour. Stirring was continued for a further ¼ hour, after which the solution was poured on ice (600 g.). Recrystallisation of the solid product from 3 batches (58 g.) yielded long, soft, white needles (16·6 g.) of 4-*chloro*-2-*nitro*-5-*acetamidoacetophenone*, m. p. 142—143°, which turned red on exposure to light (Found: N, 11·4; Cl, 13·6. $C_{10}H_9O_4N_2Cl$ requires N, 10·9; Cl, 13·8%). 4-*Chloro*-2-*nitro*-5-*aminoacetophenone* (76%) formed brittle purple-red needles, m. p. 169—170° (Found: C, 45·15; H, 3·55. $C_8H_7O_3N_2Cl$ requires C, 44·75; H, 3·3%).

Deamination of the nitro-amine was effected by treatment of its alcoholic suspension (0·5 g. in 7·5 c.c.) with concentrated sulphuric acid (0·5 c.c.) and amyl nitrite (2·5 c.c.) at 10°. The solution was warmed to the b. p., boiled for 5 minutes, and then largely diluted with water. The neutral product, isolated by ether extraction, was crystallised from ligroin, yielding needles of 4-chloro-2-nitroacetophenone, m. p. 53—54° alone and when mixed with an authentic specimen (prepared from 4-chloro-2-nitrobenzoic acid; following paper); admixture with 4-chloro-3-nitroacetophenone (m. p. 102—103°) depressed the m. p. to 44—46°.

4-*Chloro*-2-*nitro*-3-*acetamidoacetophenone*.—On the small scale, this substance was obtained by spontaneous evaporation of the alcoholic mother-liquor of the 5-acetamido-compound, followed by manual separation of the residual red and colourless crystals and recrystallisation of the latter. The *substance* formed colourless needles, m. p. 174—175° (Found: N, 11·25. $C_{10}H_9O_4N_2Cl$ requires N, 10·9%).

4-*Chloro*-2-*nitro*-3-*aminoacetophenone*.—This *amine*, obtained from the foregoing compound (yield, 80%), crystallised in large, golden, brittle plates, m. p. 94—95° (Found: C, 44·75; H, 3·3; N, 13·5. $C_8H_7O_3N_2Cl$ requires C, 44·75; H, 3·3; N, 13·05%). It was more conveniently prepared from the crude mixture of acetamido-compounds (after removal of the bulk of the 5-acetamido-derivative), as it is appreciably less soluble than 4-chloro-2-nitro-5-aminoacetophenone in alcohol. Reduction of the substance (0·2 g.) in acetic acid (5 c.c.) with iron powder (0·6 g.) and water (5 c.c.) gave the diamine, m. p. 87—89°; this (0·1 g.) was refluxed with phenanthraquinone (0·12 g.) in alcohol (20 c.c.) and yielded a phenazine, m. p. 287—288° alone and when mixed with the sample prepared (following paper) from 4-chloro-3-nitro-2-aminoacetophenone.

2 : 3 : 4-*Trichloroacetophenone*.—The diazonium solution prepared from 4-chloro-2-nitro-3-aminoacetophenone (2 g.), concentrated hydrochloric acid (40 c.c.), and sodium nitrite (5%, 16 c.c.) was added to cuprous chloride (from 3·2 g. of copper sulphate) in concentrated hydrochloric acid (12 c.c.). 2 : 3 : 4-*Trichloroacetophenone* (crude yield, 1·5 g.) crystallised in long, colourless needles, m. p. 65·5—66° (Found: C, 42·9; H, 2·7; Cl, 47·4. $C_8H_5OCl_3$ requires C, 42·95; H, 2·2; Cl, 47·65%).

3 : 4-*Dichloro*-2-*nitroacetophenone*.—The suspension obtained by adding water (3·5 c.c.) to a solution of the above amine (2 g.) in sulphuric acid (18N, 26 c.c.) was treated with solid sodium nitrite (0·72 g.), and the resultant clear solution added to cuprous chloride (3·2 g. of copper sulphate) in concentrated hydrochloric acid (5 c.c.). Crude 3 : 4-*dichloro*-2-*nitroacetophenone* (1·6 g., m. p. 170—190°) formed small, orange-pink needles, m. p. 195—196°, after recrystallisation (Found: C, 41·55; H, 2·35; N, 6·0. $C_8H_5O_3NCl_2$ requires C, 41·0; H, 2·1; N, 6·0%).

7 : 8-*Dichloro*-4-*hydroxycinnoline and Derivatives*.—The above nitro-compound (0·9 g.) in acetic acid (12 c.c.) was reduced with iron powder (2 g.) and water (6 c.c.), and the resultant crude amine (0·8 g., m. p. 78—79°) suspended in a mixture of concentrated (5 c.c.) and 2N-hydrochloric acid (15 c.c.). Solid sodium nitrite (0·4 g.) was added, and the solution filtered from a little insoluble matter. The 7 : 8-*dichloro*-4-*hydroxycinnoline* which separated (0·5 g.) was virtually pure; the pure substance formed almost colourless needles, m. p. 253—254° (Found: C, 45·1; H, 2·2; N, 13·2; Cl, 33·1. $C_8H_4ON_2Cl_2$ requires C, 44·7; H, 1·85; N, 13·0; Cl, 33·0%). 4 : 7 : 8-*Trichlorocinnoline* was prepared by heating the hydroxy-compound (0·4 g.) with phosphorus pentachloride (0·7 g.) and phosphorus oxychloride (1 c.c.) on the steam-bath for 1 hour; the mixture was poured on ice and a slight excess of aqueous

sodium hydroxide added. The chloro-compound, isolated by ether extraction, had m. p. 221—222° (yield, 0·3 g.). The substance could also be isolated from the reaction mixture by removal of excess phosphorus oxychloride (reduced pressure) and extraction of the residual solid with boiling ligroin, from which it separated in soft needles with a slight greenish tinge (Found: C, 41·1; H, 1·5; N, 12·65; Cl, 45·5. $C_8H_3N_2Cl_3$ requires C, 41·1; H, 1·3; N, 12·0; Cl, 45·6%). The trichlorocinnoline (0·3 g.) was heated with solid potassium hydroxide (0·1 g.) dissolved in phenol (1 g.) for 1 hour at 95°; addition of excess of aqueous sodium hydroxide followed by extraction with ether gave 7 : 8-*dichloro*-4-*phenoxycinnoline* (0·24 g.), m. p. 213—214°, sparingly soluble in ether and alcohol, and unchanged by crystallisation from ethyl acetate, from which it formed small colourless blades (Found: C, 57·6; H, 2·75; Cl, 24·6. $C_{14}H_8ON_2Cl_2$ requires C, 57·7; H, 2·8; Cl, 24·4%).

4 : 5-*Dichloro*-2-*nitroacetophenone*.—(*a*) The suspension obtained by cooling a hot solution of 4-chloro-2-nitro-5-aminoacetophenone (1 g.) in concentrated hydrochloric acid (29 c.c.) and water (7 c.c.) was diazotised and added to cuprous chloride as in the preparation of 2 : 3 : 4-trichloroacetophenone. 4 : 5-Dichloro-2-nitroacetophenone crystallised in pale brown needles, m. p. 100—102° alone and when mixed with material prepared by method (*b*).

(*b*) From 3 : 4-dichloroacetophenone. This ketone was obtained by Roberts and Turner (*loc. cit.*) in 40% yield, and the yield of nitration product is not recorded. The following conditions gave 3 : 4-dichloroacetophenone in 75% yield (based on acetyl chloride), and 55—60% yields of 4 : 5-dichloro-2-nitroacetophenone. Acetyl chloride (108 c.c.) was added during *ca.* 1 hour to a well-stirred suspension of aluminium chloride (443 g.) in *o*-dichlorobenzene (300 c.c.). After the initial reaction had moderated, the mixture was heated (stirring throughout) on the steam-bath for 2 hours, after which it was poured on ice and hydrochloric acid, and the ketone and excess of dichlorobenzene collected with ether. Distillation gave recovery of dichlorobenzene and then yielded 211 g. of ketone, b. p. 130—132°/13 mm., m. p. 75·5—76° from benzene–ligroin (b. p. 40—60°) (lit., 76°). The ketone (40 g.) was added during 10 minutes to nitric acid (200 c.c., *d* 1·5) at 35—38°. After a further 15 minutes within the same temperature limits, the solution was poured on ice (1 kg.) and the nitro-ketone filtered off, digested with warm aqueous sodium carbonate, and recrystallised; yield, 140 g. from 200 g.; m. p. 100—102° (lit., 100—102°). Our experience with this nitration confirms the necessity for working within the temperature ranges stated.

6 : 7-*Dichloro*-4-*hydroxycinnoline*.—4 : 5-Dichloro-2-aminoacetophenone, m. p. 157—159° (lit., 154—156°), was obtained in 91% yield by reduction of 50-g. batches of the nitro-compound; the substance was prepared by Roberts and Turner (*loc. cit.*), but no details are recorded. A hot suspension of the amine (40 g.) in concentrated hydrochloric acid (500 c.c.) and water (200 c.c.) was cooled and diazotised with aqueous sodium nitrite (20%, 72 c.c.). 6 : 7-*Dichloro*-4-*hydroxycinnoline* (38 g., 91%) had m. p. 333—334°, and separated from acetic acid, in which it was sparingly soluble, in small, colourless needles (Found: C, 44·6; H, 2·1; N, 13·45. $C_8H_4ON_2Cl_2$ requires C, 44·7; H, 1·85; N, 13·0%).

6 : 7-*Dichloro*-4-*acetoxycinnoline* (with C. M. Atkinson).—Prepared by refluxing the hydroxy-compound (0·5 g.) with acetic anhydride (2·5 c.c.) for 1 hour, this *substance* formed irregular clusters of colourless needles, m. p. 148—149° (Found: N, 11·15; Cl, 27·5. $C_{10}H_6O_2N_2Cl_2$ requires N, 10·9; Cl, 27·6%).

4 : 6 : 7-*Trichlorocinnoline*.—This *compound* (yield, 85—90%) was prepared as for the 4 : 7 : 8-isomer from the hydroxycinnoline (24 g.), phosphorus pentachloride (42 g.), and phosphorus oxychloride (60 c.c.); the reaction was very rapid when the mixture was gently warmed on the water-bath, in notable contrast to the chlorination of nitro-4-hydroxycinnolines. The trichlorocinnoline, sparingly soluble in ether and ligroin, crystallised from the latter solvent in small pale yellow needles, m. p. 141·5—142·5° (Found: C, 41·5; H, 1·8; N, 12·65; Cl, 44·7. $C_8H_3N_2Cl_3$ requires C, 41·1; H, 1·3; N, 12·0; Cl, 45·6%); it is stable for a few days at least, but gradually undergoes hydrolysis in moist air; a sample which had been bottled for 3 months without special precautions had m. p. 317—319° alone and when mixed with the hydroxycinnoline.

6 : 7-*Dichloro*-4-*phenoxycinnoline*.—Prepared as for the 7 : 8-dichloro-isomer from the trichloro-compound (22·5 g.), potassium hydroxide (6 g.), and phenol (60 g.), this *cinnoline* (yield, 85%) crystallised in long, colourless needles, m. p. 162—163°, sparingly soluble in ether (Found: C, 57·6; H, 2·75; Cl, 24·7. $C_{14}H_8ON_2Cl_2$ requires C, 57·7; H, 2·8; Cl, 24·4%).

We are indebted to the Medical Research Council for a Research Studentship (J. R. K.), and to Imperial Chemical Industries Limited (Dyestuffs Division) for various facilities.

Warrington Yorke Department of Chemotherapy,
Liverpool School of Tropical Medicine. [*Received, June 17th,* 1946.]

---

54. *Cinnolines. Part X. The Preparation of 4-Chloro-2-aminoacetophenone and Related 4-Hydroxycinnolines.*

By C. M. Atkinson and J. C. E. Simpson.

A description is given of preparative routes to 4-*chloro*-2-*aminoacetophenone*, from which 7-*chloro*-4-*hydroxycinnoline* is prepared by diazotisation and ring closure.

Similar treatment of 4-*chloro*-5- and -3-*nitro*-2-*aminoacetophenone* in sulphuric acid solution yields, respectively, 7-*chloro*-6- and -8-*nitro*-4-*hydroxycinnoline*. Diazotisation of the chloro-