54. *Cinnolines. Part X. The Preparation of* 4-*Chloro*-2-*amino-acetophenone 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.

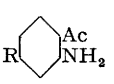
Similar treatment of 4-*chloro*-5- and -3-*nitro*-2-*aminoacetophenone* in sulphuric acid solution yields, respectively, 7-*chloro*-6- and -8-*nitro*-4-*hydroxycinnoline*. Diazotisation of the chloro-

nitro-amino-ketones in hydrochloric acid solution, however, produces, respectively, 6 : 7- and 7 : 8-dichloro-4-hydroxycinnoline.

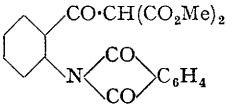
It is shown that the exchange of groups involved in the formation of the dichlorocinnolines occurs after diazotisation, but precedes the ring closure, and is thus an exchange reaction of the diazonium kations.

For various reasons we were interested in the preparation of cinnoline derivatives carrying a chlorine atom on C_7. The accessibility of such compounds clearly depended on the establishment of a relatively easy route to 4-*chloro*-2-*aminoacetophenone* (I; R = Cl). Several unsuccessful attempts to prepare this substance are mentioned by Roberts and Turner (*J.*, 1927, 1832), and it seemed unlikely that further investigation of the methods employed by them would prove successful.

In our own approach to the problem we were impressed by the statement of Gabriel and Löwenberg (*Ber.*, 1918, **51**, 1493) that methyl 2-phthalimidobenzoylmalonate (II) yields *o*-aminoacetophenone (I; R = H) on treatment with hydriodic acid. Phthaloylation of



(I.)



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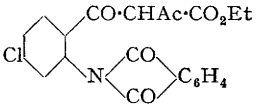


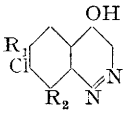
(III.)

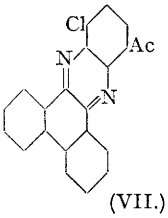
4-chloroanthranilic acid by fusion of the dry components (a method which is apparently satisfactory with anthranilic acid; Gabriel and Löwenberg, *loc. cit.*) was unreliable on the large scale, and the use of α-chloronaphthalene as solvent, although it induced a very rapid reaction, also gave erratic results. In glacial acetic acid solution, however (cf. *Chem. Abstr.*, 1944, **38**, 1221), a slow but smooth reaction occurred, furnishing 4-*chloro*-2-*phthalimidobenzoic acid* in about 70% yield, and, after much experimenting, the amino-ketone (I; R = Cl) was obtained as the N-*acetyl* derivative in a yield of about 45% (based on the acid) by condensation of 4-chloro-2-phthalimidobenzoyl chloride with malonic ester, hydrolysis with hydrobromic acid, and acetylation. An attempt was made to substitute acetoacetic for malonic ester, but here the results were not encouraging; some *ethyl* 4-*chloro*-2-*phthalimidobenzoylacetoacetate* (III) was readily isolated, but hydrolysis gave 4-chloroanthranilic acid as the only isolable product under the conditions used, and the route was not further explored.

We also examined the possibility of preparing (I; R = Cl) from 4-chloro-2-nitrobenzoic acid. Grohmann (*Ber.*, 1891, **24**, 3808) prepared this acid on the small scale, apparently in high yield, by bomb-tube oxidation of 4-chloro-2-nitrotoluene with dilute nitric acid, but we were unable to find a satisfactory large-scale method of achieving this oxidation. Preparation of the acid *via* the nitrile was more successful; hydrolysis of the latter proceeded smoothly (cf. Heller, *Ber.*, 1916, **49**, 523), but we could not substantiate the yield claimed either by Heller (*loc. cit.*) or by Hunn (*J. Amer. Chem. Soc.*, 1923, **45**, 1024) for the preparation of the nitrile from 4-chloro-2-nitroaniline, and a modification (giving 50% yield) of Hunn's method was therefore used. Condensation of 4-chloro-2-nitrobenzoyl chloride with ethyl acetoacetate proceeded smoothly, and hydrolysis of the product, following the method of Kermack and Smith (*J.*, 1929, 814), gave 4-*chloro*-2-*nitroacetophenone* in 74% yield (based on the acid). Reduction of the nitro-ketone to (I; R = Cl) was almost quantitative.

For reasons already advanced (Schofield and Simpson, *J.*, 1945, 520), we did not anticipate that a high yield of 7-*chloro*-4-*hydroxycinnoline* (IV; $R_1 = R_2 = H$) would result from diazotisation of 4-chloro-2-aminoacetophenone. The yield actually obtained (about 30%) is, as expected, intermediate between the yields of products obtained from *o*-aminoacetophenone on the one hand (*ca.* 10%) and from 5-nitro-, 5-cyano-, and 5-halogeno-2-aminoacetophenones (*ca.* 70—90%) on the other. It was further to be expected from earlier results (Schofield and Simpson, *loc. cit.*) that introduction of a nitro-group into the 5- or 3-position of the chloroaminoacetophenone would substantially favour cinnoline formation, and this also proved to be the case. Nitration of 4-chloro-2-acetamidoacetophenone gave, as main product, 4-*chloro*-5-*nitro*-2-*acetamidoacetophenone* (V; R = Ac), together with a small amount of the 3-*nitro*-isomer (VI; R = Ac). Diazotisation and cyclisation, in sulphuric acid solution, of the corresponding *amines* (V and VI; R = H) furnished 7-*chloro*-6-*nitro*- (IV; $R_1 = NO_2$; $R_2 = H$) and 7-*chloro*-8-*nitro*-4-*hydroxycinnoline* (IV; $R_1 = H$; $R_2 = NO_2$) as sole isolable products. The orientation of (VI; R = H) was proved by reduction and conversion into the *phenazine* (VII); by elimination, therefore, the constitution (V; R = H) could be confidently assigned

to the isomeric nitroamine, but formal proof of this orientation is provided by the work described below.

(IV.) 



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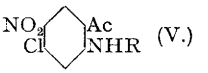

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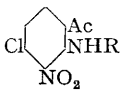
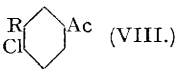
(VI.) 



(VIII.)

From our experience with various examples of cinnoline synthesis it would seem that the ring closures are independent, qualitatively, of the nature of the mineral acid used at the diazotisation stage, although it is customary to use hydrochloric acid for this purpose except in the case of very weak amines. It is therefore of interest that, when the diazotisations of (V; R = H) and (VI; R = H) were performed in hydrochloric acid, the sole isolable products were, respectively, 6 : 7-dichloro-4-hydroxycinnoline (IV; R_1 = Cl; R_2 = H) [thus proving the structure of (V; R = H)] and the 7 : 8-isomeride (IV; R_1 = H; R_2 = Cl). An exchange of groups is clearly involved in these reactions, and it became of interest to ascertain the precise stage at which this exchange occurs. This point was settled by deamination. Diazotisation of (V; R = H) in hydrochloric acid, followed by immediate addition to hypophosphorous acid, gave a mixture from which 4-chloro-3-nitroacetophenone (VIII; R = NO_2) was isolated, thus proving that the normal diazonium kation is an intermediate stage in the formation of 6 : 7-dichloro-4-hydroxycinnoline. When, however, the deamination was preceded by gentle warming of the diazotised solution until the first sign of dichlorocinnoline formation was evident, the sole deamination product was 3 : 4-dichloroacetophenone (VIII; R = Cl). Similar treatment of (VI; R = H) also gave the same ketone (no attempt was made in this case to achieve deamination without interchange of groups). Now it has already been stated that the dichlorohydroxycinnolines are the only isolable products when the respective reactions are carried through to completion, and it therefore follows, from these results and from the formation of 3 : 4-dichloroacetophenone, that the group exchange is effected principally by the attack of chloride ion on the (normal) diazonium kation before cyclistion (although the possibility cannot be entirely excluded that simultaneous ring closure and group interchange might also contribute in some measure to the final result).

That atypical transformations may occur in monocyclic aromatic diazonium salts was shown many years ago by Meldola and his co-workers (*J.*, 1900, **77**, 1172; 1901, **79**, 1076; 1902, **81**, 988) in the case of certain dinitroanisidines, which, so far as we are aware, are the only examples on record in the benzene series, although reactions of this type are more prone to occur with naphthalene compounds (*e.g.*, Morgan, *J.*, 1902, **81**, 1376; also references below). We have encountered other instances (unpublished) of reactions of substituted aminoacetophenones which appear to be essentially of the same type, and the formation of 2 : 3 : 4-trichloroacetophenone from 4-chloro-2-nitro-3-aminoacetophenone (Keneford and Simpson, preceding paper) is a further example of the same process, but until fuller knowledge of the governing factors is available it is not possible to define the scope of the reaction. The point we would stress, however, is that, in extension of Meldola's results (*locc. cit.*), our observations show that a substituted diazonium kation may become involved in an exchange of groups before removal of the diazonium residue, and that slight variations in experimental conditions, such as gentle warming, may suffice to determine whether or not such an interchange occurs. It is therefore possible to postulate, on grounds of analogy, a similar susceptibility for the diazonium kation derived from 1-nitro-2-aminonaphthalene, and thus to explain some apparently discordant results in the literature of this compound, in particular the production from it (after diazotisation in each case with hydrochloric acid and sodium nitrite) of 1-chloro-2-fluoro-, 1 : 2-dichloro-, and 2-chloro-1-bromo-naphthalene, according to conditions (Clemo, Cockburn, and Spence, *J.*, 1931, 1265; Willstaedt and Scheiber, *Ber.*, 1934, **67**, 466; Schiemann and Ley, *ibid.*, 1936, **69**, 960).

Experimental.

(Melting points are uncorrected.)

4-Chloro-2-phthalimidobenzoic Acid.—4-Chloroanthranilic acid (100 g.) and phthalic anhydride (100 g.) were ground together in a mortar, and the mixture refluxed in acetic acid (500 c.c.) for 7 hours. Small colourless prisms separated from the boiling solution, which was allowed to cool overnight,

whereupon the *phthalimido-acid* was filtered off (122 g.; 69%), m. p. 269—270° (Found: C, 59·65; H, 2·55. $C_{15}H_8O_4NCl$ requires C, 59·7; H, 2·65%). If the cooling of the reaction mixture were too prolonged, low-melting material sometimes separated along with the product, which in such cases could be purified by digestion with alcohol.

4-*Chloro*-2-*acetamidoacetophenone*.—Three successive experiments (carried out by Mr. J. R. Kenefford) gave yields of 25·6, 27·5, and 28 g. of acetamido-ketone (average, 45·8%). In two of our own earlier experiments the conditions were as described below except that the last traces of phosphorus oxychloride were removed by repeated evaporation with benzene under reduced pressure. This treatment is apparently disadvantageous, as the yields of acetamido-ketone were 21 and 24 g. The above acid (84 g.) and phosphorus pentachloride (64 g.) were refluxed in dry benzene (600 c.c.) for one hour. Solvent and phosphorus oxychloride were removed under reduced pressure and the resultant solid was immediately redissolved in dry, slightly warm benzene (900 c.c.). This clear solution was added dropwise during ½ hour to a well-stirred suspension of ethyl sodiomalonate prepared the previous day by addition, during 20 minutes, of ethyl malonate (108 c.c.) in benzene (300 c.c.) to a rapidly-stirred suspension of powdered sodium (12·8 g.) in benzene (500 c.c.), the suspension of ethyl sodiomalonate being then refluxed for 4 hours (cf. Wilds and Beck, *J. Amer. Chem. Soc.*, 1944, **66**, 1688). After the addition of the acid chloride, stirring was continued for 5 hours, and the turbid yellow reaction mixture allowed to stand overnight and then decomposed with 3N-hydrochloric acid (500 c.c.). The aqueous layer was extracted with ether and the extract combined with the original benzene layer, washed, dried, and concentrated. The oil so obtained was refluxed for 8 hours with hydrobromic acid (*d* 1·5, 600 c.c.), after which the mixture was cooled, basified with ammonia, and extracted with ether. Crude 4-chloro-2-aminoacetophenone was obtained by evaporation of this extract, after washing and drying, as a sweet-smelling, readily crystallising oil; acetylation with acetic anhydride (2 parts) gave fine white needles of pure 4-*chloro*-2-*acetamidoacetophenone*, m. p. 148—150°, directly from the reaction mixture (Found: C, 56·55; H, 4·8. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·7%).

4-*Chloro*-2-*aminoacetophenone*.—The above acetoamido-compound (1·5 g.) was refluxed for 15 minutes with hydrochloric acid (24 c.c., 5N); the mixture was then cooled and basified with ammonia. The *amino-ketone* separated from aqueous alcohol in small white needles, m. p. 91—93° (1·15 g.) (Found: C, 56·2; H, 4·65. C_8H_8ONCl requires C, 56·6; H, 4·7%).

Ethyl 4-*Chloro*-2-*phthalimidobenzoylacetoacetate*.—A mixture of ethyl acetoacetate (3 g.) and sodium ethoxide (1 g. of sodium; 18 c.c. of alcohol) was cooled to 5° and treated with a solution of 4-chloro-2-phthalimidobenzoyl chloride (prepared from 6 g. of the acid as above) in dry benzene (50 c.c.). The yellow solution was kept overnight at room temperature, and then decomposed with hydrochloric acid and extracted with ether. Concentration of the washed and dried extract gave the *ester* (3·6 g.), which crystallised from alcohol in white leaflets, m. p. 104° (Found: C, 60·6; H, 4·5; N, 4·0. $C_{21}H_{16}O_6NCl$ requires C, 60·9; H, 3·9; N, 3·4%).

For hydrolysis, the above compound (1·5 g.) was refluxed for ¾ hour with hydriodic acid (*d* 1·7; 4·5 c.c.), after which the solution was concentrated under reduced pressure on the steam-bath, and the residue basified with sodium carbonate and extracted with ether. The extract yielded a dark, crystallising oil (0·14 g.) which in no way resembled 4-chloro-2-aminoacetophenone; acidification of the alkaline mother-liquor yielded only 4-chloroanthranilic acid, m. p. and mixed m. p. 237° (decomp.) (Found: C, 48·85; H, 3·3; Cl, 20·5. Calc. for $C_7H_6O_2NCl$: C, 49·0; H, 3·5; Cl, 20·7%). In a second experiment, 1·5 g. were treated with a mixture of alcohol (7·5 g.) and sulphuric acid (1 g.) according to the method of Kermack and Smith (*loc. cit.*); the product was a pale yellow oil (1·2 g.) which could not be crystallised.

4-*Chloro*-2-*nitrobenzonitrile*.—(*a*) (Method of Hunn, *loc. cit.*). A solution of 4-chloro-2-nitroaniline (17·25 g.) in concentrated sulphuric acid (15 c.c.) was poured into water (170 c.c.) with vigorous stirring, and the finely divided suspension diazotised at 10° with sodium nitrite (7 g.) in water (70 c.c.), added during 2 hours. After a further hour's stirring, the filtered solution was added gradually to a solution of copper sulphate (43 g.) and sodium cyanide (34·5 g.) in water (215 c.c.). After 2 hours at room temperature, the mixture was heated at 70° for ½ hour, cooled, and filtered. The partly dried solid was steam-distilled from a flask immersed in an oil-bath at 180°, and the steam-volatile material isolated by ether extraction. Almost pure nitrile (m. p. 94—96°) was thus obtained [yield, 5 g., 27%; Hunn (*loc. cit.*) claims 75%].

(*b*) 4-Chloro-2-nitroaniline (34·5 g.) was diazotised exactly as described above, the solution filtered, treated with saturated aqueous sodium acetate until neutral to Congo-red, and added at 70° to a solution of copper sulphate (56 g.) and alkali cyanide ("double salt", 60 g.) in water (280 c.c.). The product was collected with ether, and the extract, after being washed with sodium hydroxide solution and water, was dried and evaporated. The yield of crude nitrile (31·5 g.) was not significantly altered when the reaction temperature was *ca.* 20°, or when the addition of sodium acetate was omitted (reaction temperature either 70° or 20°). Percolation through alumina (Merck), elution with benzene, and digestion of the solute with a little ether gave the pure nitrile (77·2 g. from 123 g.), m. p. 100—101°.

4-*Chloro*-2-*nitrobenzoic Acid*.—(*a*) Potassium permanganate (20 g.) was added during 24 hours to a refluxing suspension of 4-chloro-2-nitrotoluene (10 g.) in water (250 c.c.), the condenser being cleared of steam-volatile material from time to time. Filtration and acidification gave 4-chloro-2-nitrobenzoic acid (2·6 g.), m. p. 140—141° alone and when mixed with an authentic sample prepared from 2-nitro-4-aminobenzoic acid; unoxidised chloronitrotoluene (4·6 g.) was recovered from the manganese dioxide precipitate by ether extraction. This result could not be reproduced on a larger scale (with slight variations). The chloronitrotoluene was not attacked by a mixture (1 : 1) of concentrated nitric acid and water under reflux; bromination at 160—170° followed by oxidation (cf. Norris and Bearse, *J. Amer. Chem. Soc.*, 1940, **62**, 953) was ineffective, as the bromination was not confined to the side chain; and oxidation with permanganate in aqueous pyridine was unsuccessful.

(*b*) 4-Chloro-2-nitrobenzonitrile (10 g., m. p. 97—98°) was heated on the steam-bath with sulphuric acid (80 c.c. of 80%, v/v) for 1½ hours; the clear solution was then diluted with water (48 c.c.) and gently refluxed for 1½ hours. The oily suspension was cooled, water (130 c.c.) added, and the crystalline

acid filtered off and reprecipitated from sodium carbonate solution (charcoal); yield 8·8 g., m. p. 141—143°. In one or two experiments the yields were extremely poor, apparently owing to the fact that in these cases the concentration of the acid used was slightly greater than 80% (v/v).

4-Chloro-2-nitroacetophenone.—4-Chloro-2-nitrobenzoyl chloride was prepared (cf. Cohen and Armes, *J.*, 1906, **89**, 458) from 4-chloro-2-nitrobenzoic acid (24 g.) and phosphorus pentachloride (27 g., 1·1 mols.), the vigorous spontaneous reaction being completed by heating for 1½ hours on a steam-bath. Phosphorus oxychloride was removed under reduced pressure, and the resultant oil dissolved in dry benzene (50 c.c.). A solution of sodium ethoxide (from sodium, 6·15 g., and absolute alcohol, 100 c.c.), was divided into two equal parts. To one was added with stirring ethyl acetoacetate (17·85 g.), and this solution, cooled to 0°, was treated simultaneously with the acid chloride solution and the remainder of the sodium ethoxide by addition, at approximately equal rates (¾ hour), through two dropping funnels. After a further 3 hours (temperature below 5°; mechanical stirring throughout) the mixture was kept overnight at room temperature, and then decomposed with dilute hydrochloric acid and extracted with ether. The extract was washed with sodium bicarbonate solution and water, dried, and evaporated, yielding a red mobile oil (35 g.). This (17 g.) was hydrolysed with 10% (w/w) alcoholic sulphuric acid (255 g.) (manipulation according to Kermack and Smith, *loc. cit.*) and yielded *4-chloro-2-nitroacetophenone* as clusters of soft, white needles (8·8 g., m. p. 55—56°) from ether–ligroin (b. p. 60—80°) (Found: C, 48·25; H, 3·05. $C_8H_6O_3NCl$ requires C, 48·1; H, 3·0%). Reduction of the nitroketone (6·5 g.) with acetic acid (50 c.c.), iron powder (13 g.), and water (12 c.c.) in the known manner (*J.*, 1945, 646) gave 4-chloro-2-aminoacetophenone (4·7 g., 85%), m. p. [from ligroin (b. p. 60—80°)] 91—93° alone and when mixed with the material described earlier.

4-Chloro-5-nitro-2-aminoacetophenone.—4-Chloro-2-acetamidoacetophenone (10 g.) was added during 35 minutes to a mechanically stirred mixture of nitric acid (*d* 1·48) and concentrated sulphuric acid (5 : 2 v/v; 60 c.c.) at a temperature below − 10°. After a further 20 minutes the solution was poured on ice, and the product filtered off and washed. *4-Chloro-5-nitro-2-acetamidoacetophenone* separated from alcohol in slender yellow blades (9·4 g., 77%), m. p. 166—168° (Found: C, 46·5; H, 3·5. $C_{10}H_9O_4N_2Cl$ requires C, 46·8; H, 3·5%). This substance was hydrolysed by refluxing it (4 g.) with a mixture of alcohol (40 c.c.), water (40 c.c.), and concentrated hydrochloric acid (40 c.c.). More alcohol was added to dissolve the solid which rapidly separated, and after 10 minutes the solution was concentrated and basified; *4-chloro-5-nitro-2-aminoacetophenone* (3·2 g.) separated in fine yellow needles, m. p. 176—177°, unchanged by crystallisation from alcohol (Found: C, 45·2; H, 3·2; N, 13·05; Cl, 16·45. $C_8H_7O_3N_2Cl$ requires C, 44·8; H, 3·3; N, 13·05; Cl, 16·5%).

4-Chloro-3-nitro-2-aminoacetophenone.—The aqueous mother-liquor from the above nitration was basified with sodium carbonate and extracted with ether, and the extract was washed and dried. Concentration to a small volume yielded almost colourless needles of *4-chloro-3-nitro-2-acetamidoacetophenone* (0·5 g.), m. p. 142—143° (depressed by admixture with 4-chloro-2-acetamidoacetophenone and with the 5-nitro-isomer described above) (Found: C, 47·15; H, 3·45. $C_{10}H_9O_4N_2Cl$ requires C, 46·8; H, 3·5%). Hydrolysis of the compound (0·3 g.), carried out as for the 5-nitro-isomer, yielded the free *amine* as yellow plates (0·23 g., m. p. 148—150°), unchanged by crystallisation from alcohol (Found: C, 44·5; H, 3·2; Cl, 16·7. $C_8H_7O_3N_2Cl$ requires C, 44·8; H, 3·3; Cl, 16·5%). When the amine (0·2 g.) was reduced with iron (0·5 g.) and acetic acid (5 c.c.) and worked up as described above, the corresponding diamine (0·19 g.) was obtained as a readily crystallising oil. This was refluxed with phenanthraquinone (0·22 g.) in alcohol (30 c.c.) for 7 hours (condensation was incomplete after ½ hour). The fine brown needles of the *phenazine* (VII) were filtered off hot; m. p. 287° after crystallisation from acetic acid (Found: C, 74·2; H, 3·65. $C_{22}H_{13}ON_2Cl$ requires C, 74·0; H, 3·7%).

7-Chloro-4-hydroxycinnoline.—4-Chloro-2-aminoacetophenone (3 g.) was suspended in hydrochloric acid (6N, 60 c.c.), cooled to 5°, diazotised with sodium nitrite (1·3 g.) in water (10 c.c.), and the solution so formed heated on a steam-bath until the coupling reaction was negative. The resultant crude solid was dissolved in warm dilute aqueous sodium hydroxide, reprecipitated with hydrochloric acid, and washed with ether, which removed a fragrant-smelling oil, presumably 4-chloro-2-hydroxyacetophenone. Pure *7-chloro-4-hydroxycinnoline* (1·07 g., m. p. 276—277°) separated from alcohol in colourless needles (Found: C, 52·9; H, 2·75; N, 15·25. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

7-Chloro-6-nitro-4-hydroxycinnoline.—A solution of 4-chloro-5-nitro-2-aminoacetophenone (0·5 g.) in glacial acetic acid (7·5 c.c.), concentrated sulphuric acid (2 c.c.), and water (0·5 c.c.) was diazotised at 5° with solid sodium nitrite (0·18 g.). The slightly turbid solution was heated at 80—85° for 1 hour (coupling reaction then negative) and was then diluted with water (10 c.c.). The product which separated was dissolved in 0·25N-aqueous sodium hydroxide, precipitated by dilute acid (yield, 0·3 g.), and recrystallised from acetic acid, from which *7-chloro-6-nitro-4-hydroxycinnoline* separated in stout bronze needles, m. p. 252—254° (decomp.) (Found: C, 42·9; H, 2·0; N, 18·4; Cl, 15·4. $C_8H_4O_3N_3Cl$ requires C, 42·6; H, 1·8; N, 18·6; Cl, 15·7%), moderately soluble in aqueous sodium bicarbonate, easily soluble in dilute sodium hydroxide, but more difficultly soluble in 2N-sodium hydroxide owing to the tendency for the sodium salt to separate (minute yellow needles).

7-Chloro-8-nitro-4-hydroxycinnoline.—Diazotisation of 4-chloro-3-nitro-2-aminoacetophenone (0·5 g.) and purification of the crude product as described above gave material (0·3 g.), m. p. 254—255° (decomp.). Recrystallisation from alcohol furnished *7-chloro-8-nitro-4-hydroxycinnoline* as jagged yellow needles, m. p. 262—264° (decomp.) (Found: C, 42·8; H, 2·1; N, 18·1; Cl, 16·0. $C_8H_4O_3N_3Cl$ requires C, 42·6; H, 1·8; N, 18·6; Cl, 15·7%).

6 : 7-Dichloro-4-hydroxycinnoline.—A well-stirred suspension of 4-chloro-5-nitro-2-aminoacetophenone (5 g.) in hydrochloric acid (6N, 60 c.c.) was diazotised at 5—10° with 10% sodium nitrite solution. After being stirred for several hours at room temperature, the almost clear solution was set aside overnight and then heated on the steam-bath as above. The product, which separated from the hot solution, was purified by solution in dilute aqueous alkali, reprecipitation, and crystallisation from boiling acetic acid, yielding 6 : 7-dichloro-4-hydroxycinnoline (3 g.) as soft fawn leaflets, m. p. 333° (decomp.) alone and when mixed with a sample prepared as in the previous paper (Found: C, 44·8; H 2·4; N, 13·35; Cl, 32·5. Calc. for $C_8H_4ON_2Cl_2$: C, 44·7; H, 1·85; N, 13·0; Cl, 33·0%). For

further identification, the substance was converted into the 4-acetoxy-compound, m. p. 148—149°, and the 4-chloro-compound, m. p. 141·5—143°, and the latter was characterised as the 4-phenoxy-derivative, m. p. 162—163° (Found: C, 57·3; H, 2·7. Calc. for $C_{14}H_8ON_2Cl_2$: C, 57·7; H, 2·8%). These reactions were carried out as described in the previous paper, and each derivative was identified by mixed m. p. with an authentic sample.

7 : 8-*Dichloro*-4-*hydroxycinnoline*.—A suspension of 4-chloro-3-nitro-2-aminoacetophenone (0·67 g.) in hydrochloric acid (6N, 30 c.c.) was cooled in ice and diazotised with solid sodium nitrite (the reaction was slow and the suspension was finally left overnight at room temperature; an excess of nitrite had therefore to be used to compensate for loss of oxides of nitrogen). Cyclisation of the diazonium salt and purification of the crude product were carried out as described for the foregoing isomer, and yielded 0·5 g. of nearly pure 7 : 8-dichloro-4-hydroxycinnoline, which after one crystallisation from alcohol formed almost colourless needles, m. p. 253—254° alone and mixed with a specimen prepared from 3 : 4-dichloro-2-aminoacetophenone (previous paper). The derived 4 : 7 : 8-trichlorocinnoline, m. p. 217—218°, and 7 : 8-dichloro-4-phenoxycinnoline, m. p. 214·5°, gave no depressions in m. p. when mixed with authentic samples.

Deamination Experiments with 4-*Chloro*-5- *and* -3-*nitro*-2-*aminoacetophenones*.—(*a*) The 5-nitro-compound (0·5 g.) was diazotised in hydrochloric acid (6 c.c., 6N) as above, and the clear solution (after recovery of 0·2 g. of unreacted amine) was added at 0° during 10 minutes to 30% hypophosphorous acid (10 c.c.). After 4 hours at 0° the solid, which had gradually separated, was filtered off, washed, and dried; it had m. p. 84—87°, depressed to 62—66° on admixture with 3 : 4-dichloroacetophenone (m. p. 75—77°). After two crystallisations from alcohol the m. p. was 98—99° alone and when mixed with 4-chloro-3-nitroacetophenone (m. p. 99—101°).

(*b*) Diazotisation of the foregoing amine (3 g.) as above gave a 50% recovery of unchanged material. The filtrate was heated on the steam-bath until a slight turbidity occurred; it was then cooled rapidly in ice and added during a few minutes to 30% hypophosphorous acid (60 c.c.) with mechanical stirring. After standing for several days at 0°, the solid product was digested with warm dilute sodium hydroxide solution, filtered off, washed, and dried. The material (0·66 g., m. p. 71—73°) could not be further purified by crystallisation, but sublimed almost completely at 50—60°/0·05 mm., yielding pure 3 : 4-dichloroacetophenone, m. p. and mixed m. p. 76—77°.

(*c*) Diazotisation of 4-chloro-3-nitro-2-aminoacetophenone (1 g.) in hydrochloric acid (6N, 44 c.c.) at room temperature gave a 50% recovery of unchanged amine. Treatment of the filtrate as in (*b*) gave crude 3 : 4-dichloroacetophenone (0·25 g., m. p. 71—73°), which sublimed almost completely at 50—70°/0·05 mm. (m. p. and mixed m. p. 75—77°). The alkali-soluble material was identified as 7 : 8-dichloro-4-hydroxycinnoline by m. p. and mixed m. p.

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