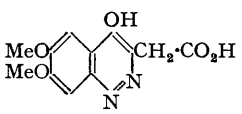
231. *Cinnolines. Part XVIII. The Preparation of 3-Halogeno-4-hydroxycinnolines, and Halogen Exchange Reactions of Diazotised ω-Halogeno-o-aminoacetophenones.*

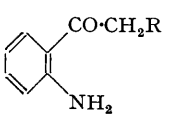
By K. Schofield and J. C. E. Simpson.

The synthesis of 3-halogeno-4-hydroxycinnolines by cyclisation of diazotised ω-halogeno-*o*-aminoacetophenones, and various concomitant halogen exchange reactions, are described. The bearing of this work and of other new data on the mechanism previously proposed for the formation of 4-hydroxycinnolines from diazotised *o*-aminoacetophenones (Part IV) is discussed, and acid-catalysed enolisation is postulated as an important step in the reaction.

In Part IV (*J.*, 1945, 520) we described the synthesis of the 4-hydroxycinnoline (I) containing a substituent at C_3, and a number of 4-hydroxy-3-methylcinnolines were subsequently described by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419) and by Keneford and Simpson (Part XVI, this vol., p. 324). These compounds were all prepared by the same method, *viz.*, diazotisation and cyclisation of appropriate ω-substituted *o*-aminoacetophenones (as II), and it therefore became of interest to see whether similar ring-closures could be effected with compounds of the type (II, R = Cl, Br).

Ruggli and Reichwein (*Helv. Chim. Acta*, 1937, **20**, 913) have described the preparation of ω-chloro- and ω-bromo-*o*-aminoacetophenones, obtained in 60% yields by reducing the corresponding nitro-compounds with copper and concentrated sulphuric acid. Repetition of

(I.) 



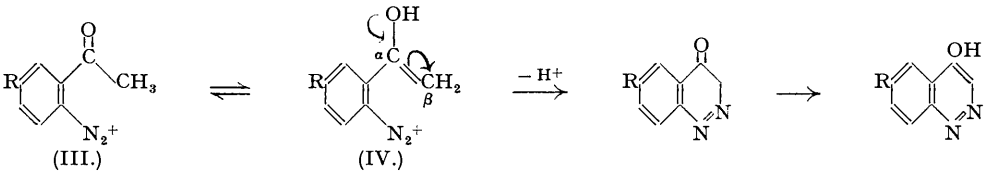
(II.)

this work has shown that the yields claimed are only obtained by rapid isolation of the amine, and has confirmed that the chloro-compound is much the more stable of the two. Two further examples of this reaction have now been examined; bromination of 5-chloro- and 5-bromo-2-nitroacetophenone gave *5-chloro-ω-bromo-* and *5 : ω-dibromo-2-nitroacetophenone*, and subsequent reduction under Ruggli's conditions converted these into the weakly basic *2-amino*-compounds, in 30% and 50% yield respectively. In view of the relationship between the basicity of *o*-aminoacetophenones and cinnoline formation (Part IV, *loc. cit.*), the low basicity and consequent high electrophilic activity of the derived diazonium compounds gave good grounds for expecting efficient ring-closure in these cases. In fact, by diazotising the ω-substituted amines in acetic acid–sulphuric acid, *3-chloro-*, *3-bromo-*, *6-chloro-3-bromo-*, and *3 : 6-dibromo-4-hydroxycinnoline* were obtained in 75—80% yields.

When ω-bromo-*o*-aminoacetophenone was diazotised in presence of hydrochloric acid, the product, again obtained in good yield, differed slightly in melting point from 3-bromo-4-hydroxycinnoline, and a similar difference was noticed between the two *acetyl* derivatives. Analysis revealed that halogen exchange had occurred, the product being *3-chloro-4-hydroxycinnoline*. *3 : 6-Dichloro-* and *3-chloro-6-bromo-4-hydroxycinnoline* were obtained similarly. Cyclisation of diazotised ω-chloro-*o*-aminoacetophenone in presence of hydrobromic acid, followed by acetylation, gave a product which melted between the values for pure 3-bromo-4-acetoxy- and 3-chloro-4-acetoxy-cinnoline, and, although the evidence is not conclusive, it would seem that here too some halogen exchange has taken place. We have not attempted to ascertain the precise stage at which these halogen exchanges occur, but it is likely that they are closely related to

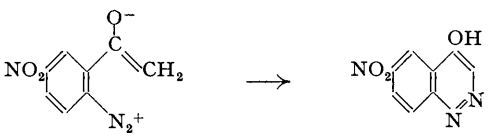
those reported in Part X (*J.*, 1947, 232), and that the diazonium kations are involved. [The halogen exchange observed by Leonard and Boyd (*loc. cit.*) during the chlorination of 6-bromo-4-hydroxycinnoline with a mixture of phosphorus pentachloride and phosphorus oxychloride, a reaction to which there is a parallel in certain 3-bromo-4-hydroxycinnolines (Schofield and Swain, unpublished), is not comparable with the present examples, as it involves a cinnoline nucleus already formed.]

In Part IV (*loc. cit.*) we suggested, on the basis of the data then available, that the synthesis of 4-hydroxycinnolines from *o*-amino-ketones proceeded by the following mechanism :



(III.) (IV.)

Leonard (*Chem. Reviews*, 1945, **37**, 269), on the other hand, suggested that " the reaction probably involves an intramolecular coupling of the diazonium kation with the enolate anion ", and has pointed out that " such a mechanism would be similar to the coupling of an aryldiazonium ion with a phenoxide ion to form an azo compound ". This could hardly be the case, however, under the conditions so far used; coupling of diazonium compounds with phenols, as with



enolic substances in general (*e.g.*, Japp–Klingemann reaction; cf. Linstead and Wang, *J.*, 1937, 807; Leonard, Boyd, and Herbrandson, *J. Org. Chem.*, 1947, **12**, 47), is carried out in alkaline media, and in any case it seems likely that the coupling reagent under such conditions is not the simple diazonium ion (Hodgson and Marsden, *J.*, 1945, 207).

The factors affecting the equilibrium between (III) and (IV), and the relative importance, in any given case, of the electrophilic and nucleophilic activity of the diazonium group and of C_β respectively—insofar as these may be separated at all in such a compact system as the molecule of a diazotised *o*-aminoacetophenone—were not discussed in Part IV because of lack of evidence. Information subsequently accumulated, however, and summarised in the Table,

Cinnoline.	Conditions.	Ref.	Yield, %.
4-Hydroxy-	75% (v/v) H_2SO_4 and AcOH; 10° ⟶ 90°	1	⩾10
	~3·5N-HCl; room temp.	2	43
	~Conc. HCl; 50—60°	3	70—75
7-Chloro-4-hydroxy-	~5N-HCl; 90°	4	30—35
	~3·5N-H_2SO_4; 28 days at room temp., then 70—80° for 1 hour	2	81
	~Conc. HCl; 50—60°	3	90—95
4-Hydroxy-7-acetyl-	~4N-HCl; 10 ⟶ 80°	5	55 of corresponding phenol
	~Conc. HCl; 3 days at room temp., then 75—80° for 2½ hours	5	65
4-Hydroxy-3-methyl-	~2N-HCl; room temp.	2	18
	~Conc. HCl; 50—60°	6	83
4-Hydroxy-7-methyl-	~Conc. HCl; 50—60°	7	60
4-Hydroxy-8-methyl-	~Conc. HCl; 50—60°	8	65
6-Chloro-4-hydroxy-7-methyl- ...	~5N-HCl; 70—80°	9	90—95
6-Bromo-4-hydroxy-7-methyl-	~2N-HCl; 70—80°	9	35—40 (with 45 of corresponding phenol)

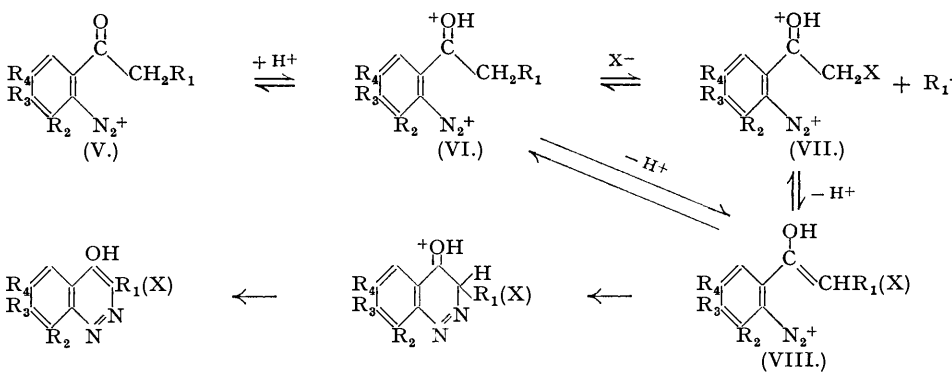
1. Part IV, *loc. cit.*,
2. Leonard and Boyd, *loc. cit.*
3. Keneford and Simpson, Part XIII, *J.*, 1947, 917.
4. Atkinson and Simpson, *J.*, 1947, 232.
5. Schofield and Theobald, unpublished.
6. Keneford and Simpson, Part XVI, *loc. cit.*
7. Keneford and Simpson, unpublished.
8. Morley and Simpson, unpublished.
9. Keneford and Simpson, *J.*, 1947, 227.

throws considerable light on these questions. It is clear from these data that ring-closure of diazotised *o*-aminoacetophenones in which the nucleus is so substituted as to reduce the

electrophilic activity of the diazonium ion occurs only to a small extent in dilute acid solution, but in concentrated acid the reaction is greatly facilitated. The employment of a low temperature also favours the reaction, as is illustrated by the yields for 4-hydroxycinnoline; this has been noted by Leonard and Boyd (*loc. cit.*), but appears to be of secondary importance in comparison with the effect of acid concentration (4-hydroxycinnoline, 4-hydroxy-3-methylcinnoline). The low yield of 6-bromo-4-hydroxy-7-methylcinnoline as compared with that of its 6-chloro-analogue may be partly due to the use of weaker acid in the first case, but it is undoubtedly also caused by the lower electron-attracting power of a bromine atom, as compared with a chlorine atom, in the *p*-position to the diazonium grouping.

These results afford strong evidence that the enolisation of the ketone grouping, suggested in Part IV as a working hypothesis, is an important stage in this method of cinnoline synthesis, and, further, that it is an acid-catalysed process. If suitably located electron-attracting substituents are not present, *i.e.*, if the electrophilic activity of the diazonium ion is relatively low, the reaction depends mainly on the acidity of the medium, which controls the rate of enolisation, and hence, by the development of a sufficiently high nucleophilic activity at C_β, the rate of cyclisation. If, on the other hand, the amino-ketone contains electron-attracting substituents so situated as to exert their maximum effect on the diazonium ion, the activity at that centre is sufficiently enhanced to become the controlling factor, and cyclisation can then be effected in good yield even in dilute acid when the rate of enolisation is low [cf. the high yields of 6-chloro- and 6-bromo-4-hydroxycinnoline obtained in ~ 2N-acid (Part IV); the yield of 4-hydroxy-6-cyanocinnoline (*loc. cit.*) was not given, but was 70% in both N- and 4N-acid].

On the basis of the accepted mechanism for acid-catalysed enolisation of a carbonyl group (*cf.* Watson, " Modern Theories of Organic Chemistry ", 2nd Edition, p. 169) the whole reaction may be represented by the scheme illustrated below, in which cinnoline ring-closure competes with phenol formation arising from one or more of the species (V)—(VIII), and in which group



interchange (shown only at R_1) may occur in presence of a hydrogen halide; this has been observed when R_1 = halogen (this paper), and when R_1 = H, R_3 = Cl, and R_2 or R_4 is a nitro-group (Part X), and presumably involves form (VI), in which C_β (or the particular carbon atom involved) would be rendered electrophilic by the presence of the activated carbonyl group and of the diazonium kation, and thus would be open to attack by neighbouring halide ions. Once a halide ion X^- had replaced R_1, etc., the cyclisation product formed subsequently would be expected to contain X rather than R_1, etc., because of the mere statistical preponderance of X^- in the reaction medium. The suggested cyclisation may be compared with the acid-catalysed halogenation of ketones, essentially the attack of an electrophilic reagent upon a potentially enolic grouping. Although the electron-attracting power of R_1 might increase the electrophilic activity of the diazonium ion and so facilitate cyclisation, its effect upon the rate of enolisation is not predictable, as pointed out by Hammett (" Physical Organic Chemistry ", McGraw-Hill, 1940, p. 241) for the bromination of acetone.

We have attempted to investigate one or two cases in which R_1 is a group other than methyl or halogen, but no clear-cut results have emerged. For example, we have previously pointed out (Part IV) that the compound obtained by de Diesbach and Klement (*Helv. Chim. Acta*, 1941, **24**, 158) from the diazotisation of *o*-amino-ω-anilinoacetophenone may have been 3-anilino-4-hydroxycinnoline. We were unable to obtain their compound, and the work of Julian (*J. Amer. Chem. Soc.*, 1945, **67**, 1203) casts some doubt on the general

utility of anilino-compounds in this connection, as apparently isomerisation of the type $NHPh{\cdot}CH(R'){\cdot}CO{\cdot}R \rightleftharpoons NHPh{\cdot}CH(R){\cdot}CO{\cdot}R'$ can occur. Having already examined (Part IV) the case of *o* : ω-diaminoacetophenone with negative results, it was natural to investigate the behaviour of *o*-amino-ω-phthalimidoacetophenone (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067); the product, obtained in *ca.* 40% yield, appears to be the normal phenolic compound. In an effort to modify the course of the reaction, ω-*phthalimido*-o-*acetamidoacetophenone* was nitrated, but attempts to hydrolyse the *mononitro*-derivative gave a high-melting compound of unknown constitution.

This work is being continued, and derivatives of the new cinnolines will be described later.

Experimental.

(Melting points are uncorrected.)

Diazotisations, unless otherwise stated, were effected at 0° with 5% aqueous sodium nitrite.

ω-*Bromo*-o-*nitroacetophenone*.—Pure *o*-nitroacetophenone was prepared by the acetoacetic ester method (Needham and Perkin, *J.*, 1904, **85**, 148; Kermack and Smith, *J.*, 1929, 814) and brominated according to Ruggli and Reichwein (*loc. cit.*); bromination under too powerful illumination (500-watt lamp) gave material which probably contained some of the dibromo-compound, as shown by its unsatisfactory behaviour on reduction.

Diazotisation of ω-*Bromo*-o-*aminoacetophenone*.—(*a*) A solution of the amine (2·6 g.) in acetic acid (25 c.c.) and concentrated sulphuric acid (13 c.c.) was diazotised and, after dilution with water (25 c.c.), heated at 70—75° during 30 minutes. The crude product [2 g. (73%), m. p. 275—276°] was recrystallised from ethanol, giving light fawn needles of 3-*bromo*-4-*hydroxycinnoline*, m. p. 276—276·5° (Found: C, 42·5; H, 2·45; N, 12·2; Br, 35·4. $C_8H_5ON_2Br$ requires C, 42·6; H, 2·2; N, 12·45; Br, 35·5%). When 10N-sulphuric acid was used in place of concentrated acid the yield was 56%. Treatment for 2 hours with boiling acetic anhydride, decomposition with water, and crystallisation from ethanol gave 3-*bromo*-4-*acetoxycinnoline*, m. p. 139—140°, as white needles or dense fawn prisms. Satisfactory analytical data could not be obtained for this and certain other compounds (Found: C, 45·8; H, 2·9; N, 10·9. $C_{10}H_7O_2N_2Br$ requires C, 44·9; H, 2·6; N, 10·95%).

(*b*) The suspension obtained from the amine (1 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (5 c.c.) was diazotised, kept for 1 hour at 70—75°, and the product collected (0·48 g., m. p. 275—276°). Recrystallisation from ethanol gave fawn needles of 3-*chloro*-4-*hydroxycinnoline*, m. p. 278—279° (Found: C, 52·05; H, 2·75; N, 15·9; Cl, 19·7. $C_8H_5ON_2Cl$ requires C, 53·19; H, 2·77; N, 15·52; Cl, 19·7%), identical with the compound described below. 3-*Chloro*-4-*acetoxycinnoline*, prepared as for the bromo-analogue, formed almost colourless needles from ethanol, m. p. 125—126° (Found: C, 53·25; H, 3·2; N, 12·4; Cl, 16·4. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·15; N, 12·58; Cl, 15·95%).

Diazotisation of ω-*Chloro*-o-*aminoacetophenone*.—(*a*) Diazotisation of the amine (0·83 g.) in acetic acid (5 c.c.) and concentrated hydrochloric acid (5 c.c.) gave a clear solution which, after being left at room temperature until it gave no further coupling with alkaline β-naphthol (2 days), yielded almost pure 3-chloro-4-hydroxycinnoline (84%); cyclisation at 70—75° gave a yield of 66% (Found: N, 15·4; Cl, 20·1%). The acetyl derivative had m. p. 124—125° (Found: N, 13·9; Cl, 16·9%).

(*b*) Replacement of the hydrochloric acid of (*a*) by an equal volume of *ca.* 10N-sulphuric acid in an otherwise similar experiment gave 85% of crude 3-chloro-4-hydroxycinnoline.

(*c*) The amine (0·6 g.) in acetic acid (7·2 c.c.) and *ca.* 10N-sulphuric acid (3·6 c.c.) was diazotised, and the solution poured into *ca.* 10N-hydrobromic acid (5 c.c.) and left at room temperature for 2 days, yielding 56% of a product, m. p. 275—276°; cyclisation at 70—75° (30 minutes) gave 37% of a similar product. Each specimen gave an acetyl derivative, m. p. 130—131°. An approximately 1 : 1 mixture of authentic 3-bromo- (m. p. 276—276·5°) and 3-chloro-4-hydroxycinnoline (m. p. 278—279°) melted at 275—276° after softening at 270°.

5-*Chloro*-ω-*bromo*-2-*nitroacetophenone*.—A solution of 5-chloro-2-nitroacetophenone (10 g.) (Simpson *et al.*, *J.*, 1945, 646) in chloroform (35 c.c.) was treated at 50° with a solution of bromine (8·05 g.) in chloroform (15 c.c.) during 30 minutes, under irradiation from a 200-watt lamp. Removal of solvent under reduced pressure and crystallisation of the crude product (13·8 g., m. p. 93—95°) from ether–ligroin gave soft white needles of 5-*chloro*-ω-*bromo*-2-*nitroacetophenone*, m. p. 99—99·5° (Found: C, 35·3; H, 2·0; N, 4·8; Cl + Br, 41·7. $C_8H_5O_3NClBr$ requires C, 34·5; H, 1·8; N, 5·0; Cl + Br, 41·5%).

5 : ω-*Dibromo*-2-*nitroacetophenone*.—5-Bromo-2-nitroacetophenone (10 g.) (Simpson *et al.*, *loc. cit.*) was brominated as described above. Crystallisation of the crude product (13·1 g., m. p. 104—105°) from ether–ligroin gave soft white needles of 5 : ω-*dibromo*-2-*nitroacetophenone*, m. p. 109—110° (Found: C, 30·3; H, 1·7; Br, 49·1. $C_8H_5O_3NBr_2$ requires C, 29·8; H, 1·6; Br, 49·5%).

5-*Chloro*-ω-*bromo*-2-*aminoacetophenone*.—A solution of the requisite nitro-compound (7 g.) in concentrated sulphuric acid (55 c.c.) was treated at 50° with copper powder (7 g.) during 30 minutes. The mixture was poured on ice, diluted to *ca.* 400 c.c., filtered from copper, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and concentrated; addition of ligroin gave the unstable amine as yellow needles, m. p. 105—107° (1·95 g.). The substance was not purified further, but was characterised as the *pyridinium* derivative, which (0·27 g.) separated when a solution of the base (0·37 g.) in ethanol (5 c.c.) and pyridine (5 c.c.) was boiled for several minutes; recrystallisation from ethanol gave yellow needles, m. p. 245—246° (decomp.) (Found: N, 9·4; Cl + Br, 34·95. $C_{13}H_{12}ON_2ClBr$ requires N, 8·5; Cl + Br, 35·2%).

5 : ω-*Dibromo*-2-*aminoacetophenone*.—The appropriate nitro-compound (8 g.) was reduced as above, and gave yellow needles of the amine (3·9 g.), m. p. 110—111°; as before it was not purified further, but was characterised as the *pyridinium* derivative [pale-green plates, m. p. 228—230° (decomp.)] (Found: Br, 40·7. $C_{13}H_{12}ON_2Br_2$ requires Br, 42·9%). Both in this and in the preceding preparation, extraction

of the copper residues with ether gave a second crop of impure amine from which some pure hydroxycinnoline (*q.v.*) could be obtained by diazotisation in sulphuric acid.

Diazotisation of 5-Chloro-ω-bromo-2-aminoacetophenone.—(*a*) A solution of the amine (0·93 g.) in acetic acid (9 c.c.) and concentrated sulphuric acid (4·5 c.c.) was diazotised, diluted with water (9 c.c.), and heated at 70—75° for 45 minutes, giving pure 6-*chloro*-3-*bromo*-4-*hydroxycinnoline* (0·79 g.), which separated from ethanol in very light fawn needles, m. p. 311—312° (Found: C, 37·9; H, 2·0; N, 11·1; Cl + Br, 44·8. $C_8H_4ON_2ClBr$ requires C, 37·0; H, 1·6; N, 10·8; Cl + Br, 44·5%). 6-*Chloro*-3-*bromo*-4-*acetoxycinnoline*, from the hydroxy-compound and acetic anhydride (2 hours under reflux), crystallised from ethanol in white prisms, m. p. 166—167° (Found: C, 40·1; H, 1·9; N, 9·05. $C_{10}H_6O_2N_2ClBr$ requires C, 39·8; H, 2·0; N, 9·2%).

(*b*) The solution obtained by diazotising the amine (0·31 g.) in acetic acid (3 c.c.) and concentrated hydrochloric acid (1·5 c.c.) was heated at 70—75° during 30 minutes. The crude 3 : 6-*dichloro*-4-*hydroxycinnoline* which separated (0·24 g., m. p. 298—300°) crystallised from ethanol in light fawn needles, m. p. 305—306° (Found: C, 44·02; H, 2·0; N, 11·9; Cl, 32·5. $C_8H_4ON_2Cl_2$ requires C, 44·70; H, 2·0; N, 13·0; Cl, 32·9%). 3 : 6-*Dichloro*-4-*acetoxycinnoline*, prepared with boiling acetic anhydride, formed white leaflets, m. p. 149—150°, from ethanol (Found: N, 10·5. $C_{10}H_6O_2N_2Cl_2$ requires N, 10·9%).

Diazotisation of 5 : ω-Dibromo-2-aminoacetophenone.—(*a*) The amine (1·41 g.) in acetic acid (12 c.c.) and sulphuric acid (7 c.c. of *ca.* 10N) was diazotised, water was added (12 c.c.), and the solution left for 84 hours and then heated at 70—75° for 45 minutes, giving pure 3 : 6-*dibromo*-4-*hydroxycinnoline* (1·1 g.) which crystallised from ethanol in soft, colourless needles, m. p. 315—316° (Found: C, 31·9; H, 2·1; N, 9·1. $C_8H_4ON_2Br_2$ requires C, 31·6; H, 1·3; N, 9·2%). Heating immediately after diazotisation reduced the yield to 0·94 g. 3 : 6-*Dibromo*-4-*acetoxycinnoline* separated from ethanol in colourless prisms, m. p. 176—177° (Found: C, 34·8; H, 2·1. $C_{10}H_6O_2N_2Br_2$ requires C, 34·7; H, 1·8%).

(*b*) Diazotisation of the amine (3·42 g.) in acetic acid (27·5 c.c.) and concentrated hydrochloric acid (17·1 c.c.), followed by heating at 70—75° for 45 minutes, gave pink needles (2·3 g., m. p. 305—307°) of 3-*chloro*-6-*bromo*-4-*hydroxycinnoline*, which had m. p. 310—311° after crystallisation from ethanol (Found: C, 36·4; H, 1·7; N, 10·2. $C_8H_4ON_2ClBr$ requires C, 37·0; H, 1·6; N, 10·8%). Cyclisation at room temperature during 84 hours gave an increased yield of crude product, m. p. 308—309° after recrystallisation, but analysis suggested that halogen-exchange was incomplete (Found: C, 35·6; H, 1·7; N, 11·1. $C_8H_4ON_2ClBr$ requires C, 37·0; H, 1·6; N, 10·8. $C_8H_4ON_2Br_2$ requires C, 31·6; H, 1·3; N, 9·2%). Acetylation of 3-chloro-6-bromo-4-hydroxycinnoline gave 3-*chloro*-6-*bromo*-4-*acetoxycinnoline*; colourless needles from ethanol, m. p. 169—170° (Found: C, 38·8; H, 2·0. $C_{10}H_6O_2N_2ClBr$ requires C, 39·8; H, 2·0%).

Diazotisation of ω-Phthalimido-o-aminoacetophenone.—The suspension obtained from the amine (6 g.) (Gabriel and Gerhard, *loc. cit.*) and concentrated hydrochloric acid (84 c.c.) was treated with water (12 c.c.) and diazotised at 0° with solid sodium nitrite (1·44 g.). Glacial acetic acid (72 c.c.) was added and the suspension kept at 80°. A clear solution was first formed, and after 1 hour the product which gradually separated was collected (2·4 g., m. p. 192—195°) and crystallised from ammoniacal alcohol, giving glistening red-brown prisms and fern-like clusters of, presumably, ω-*phthalimido*-o-*hydroxyacetophenone*, m. p. 196—198° [Found: C, 66·5; H, 3·6; N, 5·3; *M* (Rast), 288. $C_{16}H_{11}O_4N,\frac{1}{2}H_2O$ requires C, 66·2; H, 4·2; N, 4·8%; *M*, 290].

Nitration of ω-Phthalimido-o-acetamidoacetophenone.—ω-Phthalimido-*o*-aminoacetophenone (0·5 g.) and acetic anhydride (2 c.c.) at 95° rapidly yielded ω-*phthalimido*-o-*acetamidoacetophenone* (0·53 g.); colourless crystals, m. p. 225—226°, from acetic acid (Found: C, 66·0; H, 4·4; N, 8·8. $C_{18}H_{14}O_4N_2,\frac{1}{4}H_2O$ requires C, 66·15; H, 4·5; N, 8·6%). The acetyl compound (3·3 g.) was added during 20 minutes with stirring to a mixture of nitric acid (15 c.c., *d* 1·48) and concentrated sulphuric acid (6 c.c.) at − 5°. After a further 40 minutes (temperature ⩾ + 5°), the solution was poured on ice, and the solid collected (3·8 g., m. p. 255—260°). Four crystallisations from acetic acid gave almost colourless needles, m. p. 265—270° (decomp.), of x-*nitro*-ω-*phthalimido*-o-*acetamidoacetophenone* (Found: C, 58·5; H, 3·6. $C_{18}H_{13}O_6N_3$ requires C, 58·8; H, 3·5%). This compound (0·49 g.) was refluxed with acetic acid (5 c.c.) and concentrated hydrochloric acid (5 c.c.) for 30 minutes; more acetic acid (5 c.c.) was added, and refluxing continued for a further 6 hours, but dissolution did not occur. The *product* (0·37 g.) was collected and crystallised from acetic acid (220 c.c.), from which it formed glistening yellow needles (0·3 g.), darkening at 310° and decomposing at 325—328° (Found: C, 58·8; H, 3·6; N, 13·4. $C_{16}H_{11}O_5N_3$ requires C, 59·1; H, 3·7; N, 12·9%).

The initial stages of this work were carried out with the support of a grant from the Research Fund of the Durham Colleges, and of various facilities from Imperial Chemical Industries Ltd. (Dyestuffs Division). For the later work one of us (K. S.) wishes to thank the Chemical Society and the Council of University College, Exeter, for financial grants.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
UNIVERSITY COLLEGE OF THE SOUTH WEST, EXETER.
WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

[*Received, August 6th,* 1947.]