552. *A New Cinnoline Synthesis. Part I. Cyclisation of Mesoxalyl Chloride Phenylhydrazones to give Substituted 4-Hydroxycinnoline-3-carboxylic Acids.*

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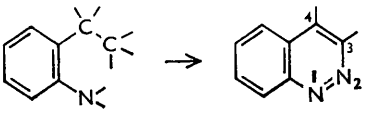
A new and convenient synthesis of the cinnoline ring system starting from the readily accessible diethyl mesoxalate phenylhydrazones (I) is described. The products are 4-hydroxycinnoline-3-carboxylic acids (V), which on decarboxylation gave the corresponding 4-hydroxycinnolines (VI). Except for a single case, attempts to extend the scope of the synthesis to a wide variety of phenylhydrazones of type (VII) were unsuccessful.

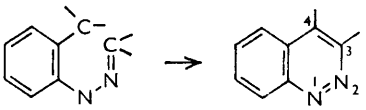
Most known syntheses of the cinnoline ring system [1] involve the formation of the hetero-ring from benzene derivatives carrying an amino-group *ortho* to a suitably activated two-carbon chain. The additional nitrogen atom is introduced by a diazo-reaction and cyclisation takes place between the nitrogen atom and the carbon atom representing positions 2 and 3 respectively in the newly formed ring (Scheme A). These syntheses

[1] Simpson, "The Chemistry of Heterocyclic Compounds," Interscience Publ. Ltd., London, 1953, pp. 3—62; Alford and Schofield, *J.*, 1952, 2102.

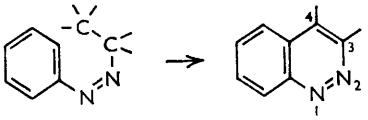
(A) 

depend on the availability of such starting materials as *o*-aminophenylpropiolic acids, *o*-aminoacetophenones, and *o*-aminophenylethylenes, very few of which are readily accessible.

A more recent synthesis [2] involves cyclisation between the carbon atoms which become positions 3 and 4 in the newly formed ring (Scheme B). Again the starting materials, *o*-acylphenylhydrazones, are relatively inaccessible.

(B) 

So far as we know no syntheses depending on cyclisation between the benzene ring and the carbon atom which becomes position 4 (Scheme C) have hitherto been described.

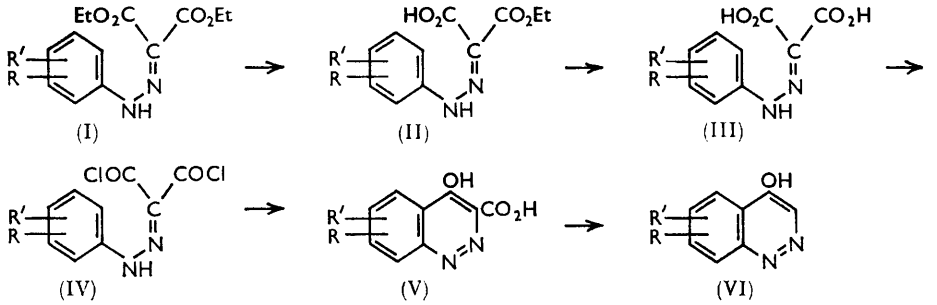
(C) 

The present series of papers describes the development of a novel synthesis of this type based on the Friedel–Crafts cyclisation of mesoxalyl chloride phenylhydrazones (IV) to derivatives of 4-hydroxycinnoline-3-carboxylic acids (V). An important feature of this route is the easy preparation, generally in excellent yield, of the starting materials—diethyl mesoxalate phenylhydrazones (I; see Table 1)—by coupling of diazotised aromatic amines with diethyl malonate in presence of sodium acetate.[3,4] Further, the yields at the subsequent stages often approach 90% and a very good overall yield is obtained. The reaction sequence is as in (I)—(V). We have adopted the phenylhydrazone rather than the tautomeric azo-structure for the products (I) in view of Bülow and Ganghöfer's chemical evidence,[5] Stevens and Ward's ultraviolet spectroscopic evidence,[6] and recent nuclear magnetic resonance studies.[7] In three cases the coupling reaction with diethyl malonate failed: 2,4-dinitrobenzenediazonium sulphate gave *m*-dinitrobenzene, *p*-dimethylaminobenzenediazonium chloride gave only an intractable tar, and from biphenyl-2-diazonium chloride the only product isolated was 2,2′-diazoaminobiphenyl. Most of the phenylhydrazones (I) separated in crystalline form after the coupling reaction; those which were liquid, with the exception of (I; R = *p*-OMe, R′ = H), distilled under a high vacuum and then crystallised.

The diesters (I) were best hydrolysed to the mesoxalic acid phenylhydrazones (III) in two steps. Treatment in boiling ethanol with sodium hydroxide (1 mol.) gave the relatively stable acid esters (II) rapidly and in high yield. Some of these intermediates (II) were isolated and characterised (Table 2). Usually, however, hydrolysis was completed *in situ* by reaction with further sodium hydroxide (2 mol.), normally at 50—80° but sometimes, to minimise decarboxylation and formation of by-products, at 18° (Table 3). Two diesters (I; R = *p*-OH, R′ = H; and R = *p*-O·CH_2Ph, R′ = H) underwent substantial decarboxylation during hydrolysis even at 25°, no diacid being obtained from the

[2] Baumgarten and de Brunner, *J. Amer. Chem. Soc.*, 1954, **76**, 3489; Baumgarten, Pedersen, and Hunt, *ibid.*, 1958, **80**, 1977; Baumgarten and Anderson, *ibid.*, p. 1981.
[3] Hantzsch and Thompson, *Ber.*, 1905, **38**, 2266.
[4] Meyer, *Ber.*, 1891, **24**, 1241.
[5] Bülow and Ganghöfer, *Ber.*, 1904, **37**, 4169.
[6] Stevens and Ward, *J.*, 1924, **125**, 1324.
[7] Anson, *Chem. and Ind.*, 1958, 1627.

former, and only a low yield of diacid from the latter. Three further diacids (III; R = *p*-OMe, R′ = H; R = *p*-NHAc, R′ = H; and R = *p*-NH·CO_2Et, R′ = H) showed similar instability on attempted recrystallisation. By contrast, the diacids (III; R = *o*- and *p*-NO_2, R′ = H) were particularly stable, being recovered after prolonged boiling with dilute hydrochloric acid.



Mesoxalyl chloride phenylhydrazones (IV) have not previously been described. They proved to be moderately stable, crystalline, and easily prepared by heating the corresponding diacids (III) with a slight excess of thionyl chloride in an inert solvent, chosen so that the product crystallised on cooling. When reaction with thionyl chloride was sluggish, phosphorus pentachloride was used. The reaction failed in two cases; the diacid (III; R = *p*-NHAc, R′ = H) was recovered, whilst (III; R = *p*-NH·CO_2Et, R′ = H) gave only unidentified products. Three other diacids (III; R = 3-Br, R′ = 4-Me; R = *p*-OMe, R′ = H; and R = *o*-O·SO_2·C_6H_4Me-*p*, R′ = H) gave chlorides which could not be characterised but nevertheless gave the expected cinnoline derivatives on cyclisation.

The optimum conditions for cyclisation to the acids (V) (see Table 5) consisted in heating the chlorides (IV) with titanium tetrachloride (1·1 mol.) in nitrobenzene at 100° and hydrolysing the products with dilute alkali, but the parent mesoxalyl chloride phenylhydrazone (IV; R = R′ = H) was best cyclised in ethylene dichloride.

The cinnoline structure of the product obtained from the chloride (IV; R = *p*-Cl, R′ = H) was established by its identity with authentic 6-chloro-4-hydroxycinnoline-3-carboxylic acid, prepared from 5-chloro-2-nitrobenzaldehyde by a five-stage Richter synthesis.[8] [In following Schofield and Swain's preparative details we were unable to isolate the intermediate 5-chloro-2-nitrophenylpropiolic acid on dehydrobromination of αβ-dibromo-β-(5-chloro-2-nitrophenyl)propionic acid with aqueous-ethanolic sodium hydroxide at 25°, the only product being 5-chloro-2-nitrocinnamic acid; when the ethanol was omitted, the desired dehydrobromination proceeded smoothly at 40—45° in 73% yield.]

Further evidence for the cinnoline structure of our cyclisation products was that three of them (from the chlorides IV; R = R′ = H; R = *p*-Br, R′ = H; and R = *p*-Cl, R′ = H) melted at temperatures substantially the same as those reported for the expected 4-hydroxycinnoline-3-carboxylic acids (V) synthesised [8,9] by the Richter method. Moreover, when the 4-hydroxycinnoline-3-carboxylic acids (V) were decarboxylated in benzophenone [9] or Dowtherm at 200—215° to give the corresponding 4-hydroxycinnolines (VI; Table 6), two of the latter (VI; R = R′ = H; R = 6-NO_2, R′ = H) were identical with authentic samples prepared by the Borsche–Herbert synthesis.[10,11]

Three of the mesoxalyl chloride phenylhydrazones (IV; R = *m*-Cl, R′ = H; R = 3-Cl, R′ = 4-Cl; and R = 3-Br, R′ = 4-Me) which on cyclisation could theoretically

[8] Schofield and Swain, *J.*, 1949, 2393.
[9] Schofield and Simpson, *J.*, 1945, 512.
[10] Borsche and Herbert, *Annalen*, 1941, **546**, 293.
[11] Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 419.

each give two isomers, gave in practice predominantly one isomer which was isolated pure in good yield. Structures were assigned (footnotes to Table 5) to two of these products; the orientation of the bromo-derivative was not determined.

The influence of reaction conditions on the cyclisation of mesoxalyl chloride phenylhydrazones (IV) was studied in some detail.

With the chloride (IV; R = *p*-Cl, R′ = H) in nitrobenzene at 95° very little cyclisation took place when 0·1 mol. of titanium tetrachloride was used as catalyst, and the yield and rate of reaction were not significantly improved by proportions of catalyst in excess of 1·1 mol. (behaviour typical of Friedel–Crafts acylation). Stannic chloride was as effective a catalyst as titanium tetrachloride for the cyclisation of both the chlorides (IV; R = R′ = H; and R = *p*-Cl, R′ = H), but often complete separation of the product from tin salts was very difficult. Moderate yields were obtained by using antimony pentachloride, anhydrous ferric chloride, or freshly sublimed aluminium chloride as catalyst for the cyclisation of the chloride (IV; R = *p*-Cl, R′ = H); these catalysts were unsuitable for the chloride (IV; R = R′ = H), intractable high-melting by-products being formed. Zinc chloride, silicon tetrachloride, phosphorus oxychloride, and the boron trifluoride–ether complex were ineffective as catalysts.

In the cyclisation of the chloride (IV; R = R′ = H) similar satisfactory yields were obtained by using ethylene dichloride, nitrobenzene, *sym*-tetrachloroethane, or chlorobenzene as solvent, but the first was preferred because the product separated as an insoluble crystalline complex. Isolation of a moderate yield when benzene was the solvent indicated that a polar solvent was not essential; on the other hand, no product was isolated on use of boiling toluene or tetralin at 95°. For other chlorides (IV) nitrobenzene was the preferred solvent.

In general, the optimum reaction temperature was 95—100°. For instance, although cyclisation of the chloride (IV; R = *p*-Cl, R′ = H) did not begin below 80°, a strongly exothermic reaction set in at 100°. Higher reaction temperatures were unsatisfactory; in fact, the starting material decomposed spontaneously in nitrobenzene above 130°.

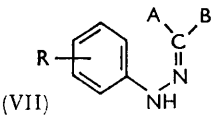
Normally, the optimum reaction time was 4—6 hr., but in some difficult cases, for example, the cyclisation of the chloride (IV; R = 2-Cl, R′ = 4-Cl), the yield was significantly improved by longer heating.

After this successful use of mesoxalyl chloride phenylhydrazones (IV), attempts were made to extend the synthesis to the cyclisation of the corresponding glyoxylyl chlorides (VII; A = COCl, B = CO_2Et, H, CN, or NO_2). Of the intermediate glyoxylic esters (VII; A = CO_2Et, B = H, CN, or NO_2, R = H, *p*-Cl, or *p*-OMe), those where B = H were prepared from the corresponding mesoxalic acid esters (II) by decarboxylation, and those where B = CN or NO_2 were prepared from the appropriately substituted acetic esters by methods similar to that described for the diesters (I) (see Table 7). Except for the nitroglyoxylic esters (VII; A = CO_2Et, B = NO_2, R = H or *p*-Cl) which decomposed, the foregoing glyoxylic esters gave the corresponding glyoxylic acids on alkaline hydrolysis. These acids, together with the mesoxalic acid esters (II; R = *p*-Me, R′ = H; and R = *p*-O·CH_2Ph, R′ = H) were converted into the acid chlorides by a method similar to that used for the mesoxalyl chlorides (IV).

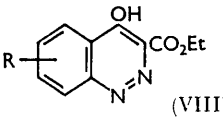
When the cyclisation of these acid chlorides was attempted under the previously determined optimum conditions, only the compound (VII; A = COCl, B = CO_2Et, R = *p*-Me) gave a cinnoline; instead of the expected ester (VIII; R = 6-Me), the product isolated was the corresponding acid (V; R = 6-Me, R′ = H) and owing to the presence of by-products the yield was low. This comparative lack of success may be due to the existence of these unsymmetrical phenylhydrazone monoacid chlorides in two stereoisomeric (*cis*- and *trans*-)forms, one of which has a configuration unfavourable to ring closure.

Further attempts to extend the reaction to a variety of phenylhydrazones of mesoxalic mono- and di-esters, acids, and nitriles, and to glyoxylic acids and esters, by using other established cyclisation methods were unsuccessful. Among the methods tried were

thermal cyclisation (cf. Leonard *et al.*[12]) of certain mesoxalic diesters (VII; A = B = CO_2Et and CO_2Me) and glyoxylic esters (VII; A = CO_2Et or CO_2Me, B = H), and treatment of mesoxalic and glyoxylic acids, esters, and nitriles (VII) with such reagents as concentrated sulphuric acid, concentrated sulphuric acid and acetic anhydride,[13] polyphosphoric acid, phosphorus oxychloride, anhydrous hydrofluoric acid, fluorosulphonic



(VII)



(VIII)

acid, and boron trifluoride–ether complex (Table 9). With sulphuric acid sulphonated starting material was sometimes obtained but, generally, either intractable by-products or unchanged material was isolated. In reactions of boron trifluoride–ether complex with the mesoxalic ester (I; R = *p*-Cl, R′ = H) crystalline boron-containing complexes were isolated that gave the corresponding mesoxalic acid ester (II; R = *p*-Cl, R′ = H) on treatment with acetic acid.

Experimental

o-*Benzyloxyaniline*.—*o*-Benzyloxynitrobenzene [14] (199 g.) in ethanol (2 l.) was hydrogenated in the presence of Adams catalyst (6 g.) at 40°/6 atm. Reduction required 4·5 hr. Evaporation and distillation gave *o*-benzyloxyaniline (162 g., 93·5%), b. p. 150—156°/0·1 mm., m. p. 37—39° (Sieglitz and Koch [15] give m. p. 39—40°).

o-*Aminophenyl Toluene*-p-*sulphonate*.—This was prepared similarly from the *o*-nitro-ester (384 g.) in ethanol (4 l.) over Adams catalyst (8 g.) at 6 atm. and a maximum temperature of 70°. Reduction was complete in 7·5 hr. After removal of the catalyst, the filtrate was concentrated; the amine (316 g., 93%) crystallised in buff plates, m. p. 97—98° (Bamberger and Rising [16] give m. p. 101°).

N-p-*Aminophenylurethane*.—*p*-Nitrophenylurethane (444 g.) in ethanol (2·5 l.) was similarly hydrogenated in the presence of Adams catalyst (4·4 g.) at room temperature and 20 atm. Reduction was complete in 40 min. After evaporation the residue was crystallised from benzene (500 ml.), giving *N*-*p*-aminophenylurethane (350 g., 92%) as a buff solid, m. p. 73—74° (Behrend [17] gives m. p. 73—74°).

Diethyl Mesoxalate Phenylhydrazones (I) (see Table 1).—In a typical preparation a slurry of *o*-chloroaniline hydrochloride made by adding molten *o*-chloroaniline (1·275 kg.) to concentrated hydrochloric acid (2·5 l.) was cooled to 0°, mixed with ice (5 kg.), and diazotised at 0—5° with sodium nitrite (705 g.) in water (1·67 l.). The filtered diazonium solution was added dropwise during 30 min. to a stirred mixture of diethyl malonate (1·6 l.), ethanol (20 l.), anhydrous sodium acetate (1·88 kg.), and water (3 l.) at 0°. Stirring was continued for 5 hr. while the temperature rose to 20°. The crystals were filtered off, washed with water (30 l.), and dried in air, giving a crude *product* (2·836 kg., 95%), m. p. 72—73°, suitable for use in the next stage.

Diethyl Mesoxalate p-*Hydroxyphenylhydrazone*.—Diethyl mesoxalate *p*-benzyloxyphenylhydrazone (52 g.) in ethanol (600 ml.) was hydrogenated in the presence of 10% palladised charcoal (10 g.) at 27° (max.)/5 atm. Reduction was complete in 7·5 hr. Evaporation and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave *diethyl mesoxalate* p-*hydroxyphenylhydrazone* (28·4 g.), m. p. 127—130°, which crystallised from ethylene dichloride in yellow prisms, m. p. 130—131° (Found: C, 55·7; H, 5·4; N, 10·3. $C_{13}H_{16}N_2O_5$ requires C, 55·7; H, 5·7; N, 10·0%).

Ethyl Hydrogen Mesoxalate Phenylhydrazones (II).—These esters are listed in Table 2. In a typical preparation 2N-sodium hydroxide (280 ml.) was added dropwise during 30 min. to a solution of ethyl mesoxalate *p*-tolylhydrazone (150 g.) in boiling ethanol (280 ml.), the mixture

[12] Leonard, Boyd, and Herbrandson, *J. Org. Chem.*, 1947, **12**, 47.
[13] Bangdiwala and Desai, *J. Indian Chem. Soc.*, 1953, **30**, 655.
[14] Kumpf, *Annalen*, 1884, **224**, 121.
[15] Sieglitz and Koch, *Ber.*, 1925, **58**, 78.
[16] Bamberger and Rising, *Ber.*, 1901, **34**, 241.
[17] Behrend, *Annalen*, 1886, **233**, 10.

being kept just alkaline to phenolphthalein. The clear red solution was heated under reflux for a further 10 min. and then acidified at room temperature with 0·5N-hydrochloric acid. The precipitated ethyl hydrogen mesoxalate *p*-tolylhydrazone crystallised from ethanol (600 ml.) in yellow needles (88 g., 65%), m. p. 141° (decomp.).

Mesoxalic Acid Phenylhydrazones (III).—These compounds are listed in Table 3. In a typical experiment, the reaction was carried out in two stages as described.

Stage (1). 2N-Sodium hydroxide (4·8 l.) was added with stirring during 15 min. to diethyl mesoxalate *m*-chlorophenylhydrazone (2·3 kg.) in boiling ethanol (4·8 l.).

Stage (2). To the solution thus obtained N-sodium hydroxide (19·2 l.) was added and after being refluxed gently with stirring for 20 min. the solution was filtered (charcoal) into a stirred mixture of concentrated hydrochloric acid (2·9 l.) and water (8·7 l.) kept at 35—40° by addition of ice (15—20 kg.) as required. The yellow precipitate was filtered off, washed by resuspension in water, and crystallised from ethyl acetate, to give *mesoxalic acid* m-*chlorophenylhydrazone* (1·594 kg., 85%), m. p. 162—164° (decomp.), suitable for use in the next stage. For large-scale preparations ethyl acetate was the most convenient solvent for the diacids.

Mesoxalyl Chloride Phenylhydrazones (IV).—These *hydrazones* are listed in Table 4. In a typical experiment phosphorus pentachloride (10·025 kg.) was added to a stirred suspension of mesoxalic acid *o*-chlorophenylhydrazone (4·98 kg.) in dry chloroform (16·25 l.) at room temperature. (Table 4 specifies the reagent and solvent used for each preparation.) After the initial vigorous reaction had subsided, the mixture was heated under reflux for 1·5 hr. The *product* (4·78 kg.), m. p. 126—128° (decomp.), which separated when the mixture was cooled in ice was washed with dry light petroleum (b. p. 60—80°). After being dried *in vacuo* over silica gel it was suitable for use in the cyclisation stage.

5-*Chloro*-2-*nitrophenylpropiolic acid* (cf. Schofield and Swain [8]).—Powdered αβ-dibromo-β-(5-chloro-2-nitrophenyl)propionic acid (10 g.) was added to stirred 10% aqueous sodium hydroxide (40 ml.), and the mixture warmed at 40—45° until a clear solution was obtained. After being kept at room temperature for 3 hr., the solution was poured into 2N-sulphuric acid (50 ml.). Crystallisation of the precipitate from 2N-acetic acid gave 5-chloro-2-nitrophenylpropiolic acid (5·0 g.), colourless needles, m. p. 135° (decomp.) [Schofield and Swain [8] give m. p. 138° (decomp.)].

4-*Hydroxycinnoline*-3-*carboxylic Acids* (V).—These are listed in Table 5. In a typical experiment titanium tetrachloride (1·975 l.) was added, with stirring, to mesoxalyl chloride *o*-chlorophenylhydrazone (4·78 kg.) suspended in dry nitrobenzene (27·5 l.) in a glass-lined vessel. After the initial exothermic reaction, during which the temperature was kept below 100° by external cooling, the vessel was heated at 95° for 6 hr. (until the evolution of hydrogen chloride ceased). Sodium hydroxide (5·5 kg.) in water (69 l.) was then added and the nitrobenzene removed by steam-distillation. The residual solution was filtered (Hyflo Supercel) and the solid extracted with hot water (2 × 40 l.). Acidification of the combined filtrates gave a crude product which was purified by dissolution in 2N-ammonia (45 l.), filtration (Hyflo; charcoal), and reprecipitation, giving 8-*chloro*-4-*hydroxycinnoline*-3-*carboxylic acid* (3·464 kg., 90%), m. p. 247—248° (decomp.). The *compounds* listed in Table 5, with the exception of those detailed below, were prepared in a similar way. In several cases the preparations were carried out in good yield on a 3—5 kg. scale. The yields of pure cinnoline were somewhat lower where separation of two possible isomers was involved, but the low yields in the case of 5,8- and 6,8-dichloro-4-hydroxycinnoline-3-carboxylic acid, even after long heating, were most surprising. The 6-methoxy-derivative was obtained in a satisfactory crude yield but was difficult to purify, whilst the 8-methoxy-isomer could be isolated pure only in low yield after repeated extraction with concentrated hydrochloric acid of an intractable high-melting acidic solid which was the major product (45%). Attempts to cyclise mesoxalyl chloride *o*-benzyloxyphenylhydrazone were unsuccessful, whilst the *o*-toluene-*p*′-sulphonyloxy-analogue gave only 6% of the corresponding cinnoline carboxylic acid.

As expected, substitution of the phenylhydrazone group by nitro exerted a deactivating effect, 6- and 8-nitro-4-hydroxycinnoline-3-carboxylic acid being obtained in only 20% and 12% yield, respectively.

4-*Hydroxycinnoline*-3-*carboxylic Acid*.—Titanium tetrachloride (420 ml.) was added during 20 min. to mesoxalyl chloride phenylhydrazone (858 g.) in dry ethylene dichloride (3·5 l.). When the initial vigorous reaction had subsided the solution was refluxed on the steam-bath for 7 hr. After removal of the solvent under reduced pressure, the solid residue was powdered

TABLE 1. *Diethyl mesoxalate phenylhydrazones* (I).

R	R′	Form	M. p.	Yield [g] (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
H	H	Plates [a]	33—34° [h]	95	$C_{13}H_{16}N_2O_4$	59·4	6·15	11·0	—	59·1	6·1	10·6	—
o-Me	H	Needles [a]	89—90	76	$C_{14}H_{18}N_2O_4$	60·8	6·6	10·3	—	60·4	6·5	10·1	—
p-Me	H	Needles [a]	32—33 [i]	62	$C_{14}H_{18}N_2O_4$	60·6	6·5	10·4	—	60·4	6·5	10·1	—
o-Cl	H	Plates [b]	76—77	96	$C_{13}H_{15}ClN_2O_4$	—	—	9·5	11·9	—	—	9·4	11·9
m-Cl	H	Prisms [b]	57—58 [j]	77	$C_{13}H_{15}ClN_2O_4$	52·0	5·1	9·5	11·9	52·3	5·0	9·4	11·9
p-Cl	H	Needles [b]	76	76	$C_{13}H_{15}ClN_2O_4$	—	—	9·6	12·0	—	—	9·4	11·9
2-Cl	3-Cl	Plates [c,q]	96—97	96	$C_{13}H_{14}Cl_2N_2O_4$	—	—	8·4	21·1	—	—	8·4	21·3
2-Cl	4-Cl	Plates [b,q]	92	63	$C_{13}H_{14}Cl_2N_2O_4$	46·9	4·4	8·7	—	46·9	4·2	8·4	—
2-Cl	5-Cl	Needles [c]	90—92	77	$C_{13}H_{14}Cl_2N_2O_4$	—	—	8·3	21·3	—	—	8·4	21·3
3-Cl	4-Cl	Needles [b]	80—81	74	$C_{13}H_{14}Cl_2N_2O_4$	—	—	8·5	21·5	—	—	8·4	21·3
p-Br	H	Needles [b]	73 [k]	62	$C_{13}H_{15}BrN_2O_4$	—	—	—	—	—	—	—	—
3-Br	4-Me	Prisms [b]	73	68	$C_{14}H_{17}BrN_2O_4$	47·1	4·6	8·2	—	47·1	4·8	7·8	—
o-OMe	H	Needles [c]	56—57	88	$C_{14}H_{18}N_2O_5$	56·9	6·2	9·7	—	57·2	6·1	9·5	—
p-OMe	H	Needles [a]	38 [l]	47 [m]	$C_{14}H_{18}N_2O_5$	56·8	6·2	9·3	—	57·2	6·1	9·5	—
o-O·CH_2Ph	H	Needles [c,r]	76—78	74	$C_{20}H_{22}N_2O_5$	65·2	6·0	7·8	—	64·9	5·9	7·6	—
p-O·CH_2Ph	H	Needles [b]	73—74	69	$C_{20}H_{22}N_2O_5$	65·5	6·0	8·0	—	64·9	5·9	7·6	—
o-OTos [p]	H	Prisms [b]	106	72	$C_{22}H_{22}N_2O_7S$	55·4	5·1	6·7	—	55·3	5·1	6·5	—
o-NO_2	H	Needles [b]	77—78 [n]	91 [m]	$C_{13}H_{15}N_3O_6$	50·6	5·0	13·6	—	50·5	4·9	13·6	—
p-NO_2	H	Plates [d,q]	79—82 [o]	82 [m]	$C_{13}H_{15}N_3O_6$	—	—	—	—	—	—	—	—
p-NHAc	H	Plates [e]	156—157	56	$C_{15}H_{19}N_3O_5$	55·6	5·9	13·0	—	56·1	5·9	13·1	—
p-NH·CO_2Et	H	Prisms [b]	186—187	75	$C_{16}H_{21}N_3O_6$	54·7	6·0	12·1	—	54·7	6·0	12·0	—

[a] From light petroleum (b. p. 40—60°). [b] From ethanol. [c] From light petroleum (b. p. 60—80°). [d] From ethyl acetate–light petroleum (b. p. 60—80°). [e] From benzene. [f] Crystalline form and m. p. of a pure sample; yellow unless otherwise stated. [g] Yield of product sufficiently pure for use at next stage; normally the total yield of solid from the coupling reaction or in the case of liquid products, the total yield after stripping off excess of diethyl malonate *in vacuo*. [h] B. p. 145—150°/0·2 mm.; isolated as an oil by Hantzsch and Thompson,[3] but not characterised. [i] B. p. 135—136°/0·05 mm.; Staudinger and Hammet (*Helv. Chim. Acta*, 1921, **4**, 217) give m. p. 77°. [j] Leonard, Boyd, and Herbrandson [12] give m. p. 56°. [k] Hantzsch and Thompson [3] give m. p. 76°. [l] B. p. 160—175°/0·1 mm. with steady decomposition of undistilled product. [m] Coupling reaction carried out in water instead of in aqueous alcohol. [n] Fries, Franke, and Bruns (*Annalen*, 1934, **511**, 241) give m. p. 74°. [o] Hünig and Boes (*ibid.*, 1953, **579**, 28) give m. p. 81°. [p] Tos = *p*-$C_6H_4Me{\cdot}SO_2$ here and in subsequent Tables. [q] Orange. [r] Brown.

TABLE 2. *Ethyl hydrogen mesoxalate phenylhydrazones* (II).

R	R′	Form [e]	M. p. [e] (decomp.)	Yield [f] (%)	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
H	H	Needles [b]	112—114° [g]	62	$C_{11}H_{12}N_2O_4$	—	—	—	—	—	—	—	—
p-Me	H	Needles [b]	141 [h]	65 [i]	$C_{12}H_{14}N_2O_4$	57·8	5·6	11·2	—	57·6	5·6	11·2	—
p-Cl	H	Needles [b]	167	47	$C_{11}H_{11}ClN_2O_4$	—	—	10·4	13·3	—	—	10·4	13·1
p-Br	H	Needles [d]	177—179	13 [j]	$C_{11}H_{11}BrN_2O_4$	—	—	9·1	25·0	—	—	8·9	25·4
p-OMe	H	Needles [b]	122—123	42	$C_{12}H_{14}N_2O_5$	54·1	5·2	10·8	—	54·1	5·3	10·5	—
p-O·CH_2Ph	H [k]	Needles [b]	122—123	97	$C_{18}H_{18}N_2O_5$	63·3	5·4	8·4	—	63·2	5·3	8·2	—
p-NO_2	H	Prisms [a,l]	201—202	66	$C_{11}H_{11}N_3O_6$	46·8	3·6	15·3	—	47·0	3·9	15·0	—
p-NHAc	H	Needles [b]	187	87	$C_{13}H_{15}N_3O_5$	53·0	4·8	14·3	—	53·2	5·1	14·3	—
p-NH·CO_2Et	H	Plates [b]	166—167	77	$C_{14}H_{17}N_3O_6$	51·7	5·1	13·4	—	52·0	5·3	13·0	—

[a] From 2-ethoxyethanol. [b] From ethanol. [c] From methanol. [d] From acetic acid. [e] Crystalline form and m. p. of a pure sample; yellow unless otherwise stated. [f] Yield of pure product. [g] Hantzsch and Thompson [3] give m. p. 115°. [h] von Pechmann (*Ber.*, 1894, **27**, 1679) gives m. p. 139·5°. [i] When hydrolysis was carried out in methanol instead of ethanol, transesterification occurred, the product being *methyl hydrogen mesoxalate p-tolylhydrazone* (50%), yellow prisms, m. p. 152—153° (decomp.) (from ethanol) (Found: C, 55·8; H, 5·1; N, 11·8; OMe, 13·0. $C_{11}H_{12}N_2O_4$ requires C, 55·9; H, 5·1; N, 11·9; OMe, 13·2%); mixed m. p. with authentic sample undepressed. [j] Isolated as a by-product, less soluble in ethanol than the corresponding mesoxalic acid phenylhydrazone (III; R = *p*-Br, R′ = H) in a preparation of the latter, in which the reaction time (10 min.) at 80° was too short. [k] Formed a very insoluble *sodium*, m. p. 168—170° (Found: N, 7·5; Na, 6·4. $C_{18}H_{17}N_2NaO_5$ requires N, 7·7; Na, 6·2%), and *potassium salt*, m. p. 239—240° (Found: K, 9·7; N, 6·9. $C_{18}H_{17}KN_2O_5$ requires K, 10·3; N, 7·4%). [l] Orange.

TABLE 3. *Mesoxalic acid phenylhydrazones* (III).

R	R′	Condns. for 2nd stage Temp.	Time (min.)	M. p.[g]	Yield[h] (%)	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
H	H	18°	150	162—163°[i]	97[a]	$C_9H_8N_2O_4$								
o-Me	H	70—80	15	181—182[j]	97[b]	$C_{10}H_{10}N_2O_4$	54·6	5·0	12·8	—	54·1	4·5	12·6	—
p-Me	H	50	15	169—170[k]	67[a]	$C_{10}H_{10}N_2O_4$	54·4	4·7	12·5	—	54·1	4·5	12·6	—
o-Cl	H	70—80	15	178—179[l]	90[c,ag]	$C_9H_7ClN_2O_4$	44·8	3·0	11·7	15·0	44·5	2·9	11·5	14·6
m-Cl	H[r]	70—80	15	170	85[c]	$C_9H_7ClN_2O_4$	—	—	11·6	14·7	—	—	11·5	14·6
p-Cl	H	70—80	15	186—187[m]	68[c]	$C_9H_7ClN_2O_4$	—	—	11·5	14·4	—	—	11·5	14·6
2-Cl	3-Cl	70—80	15	200—202	83[c]	$C_9H_6Cl_2N_2O_4$	—	—	10·2	26·0	—	—	10·1	25·7
2-Cl	4-Cl	70—80	15	177—178[n]	83[a,u]	$C_9H_6Cl_2N_2O_4$	—	—	—	—	—	—	—	—
2-Cl	5-Cl	70—80	15	210—211	86[c,v]	$C_9H_6Cl_2N_2O_4$	—	—	10·0	25·5	—	—	10·1	25·7
3-Cl	4-Cl	70—80	10—15	185—186	60[c]	$C_9H_6Cl_2N_2O_4$	—	—	10·2	25·8	—	—	10·1	25·7
p-Br	H[s]	70—80	10	191—193[o]	74[c]	$C_9H_7BrN_2O_4$	38·0	2·5	9·8	—	37·6	2·4	9·8	—
3-Br	4-Me	70—80	10	187—188	48[c,w]	$C_{10}H_9BrN_2O_4$	39·7	3·0	9·5	26·8	39·9	3·0	9·3	26·6
o-OMe	H	60—65	15	159	92[c]	$C_{10}H_{10}N_2O_5$	50·5	4·0	11·6	—	50·4	4·2	11·8	—
p-OMe	H	18	180	140—142[ab]	43[a,ac,y]	$C_{10}H_{10}N_2O_5$	50·7	4·1	12·0	—	50·4	4·2	11·8	—
o-O·CH_2Ph	H	60—65	15	154—155	88[c]	$C_{16}H_{14}N_2O_5$	61·2	3·9	9·1	—	61·1	4·5	8·9	—
p-O·CH_2Ph	H	60—65	30	153—154	45[c,z]	$C_{16}H_{14}N_2O_5$	60·9	4·5	9·1	—	61·1	4·5	8·9	—
o-OTos	H	70—80	10	175	66[a]	$C_{16}H_{14}N_2O_7S$	51·1	4·0	—	S 8·4	50·8	3·7	—	S 8·5
o-NO_2	H	70—80	10	195—197[p]	72[d,ad]	$C_9H_7N_3O_6$	42·4	2·4	16·4	—	42·7	2·8	16·6	—
p-NO_2	H[t]	70—80	10—15	199—200[q]	92[e,ae]	$C_9H_7N_3O_6$	42·8	3·3	16·9	—	42·7	2·8	16·6	—
p-NHAc	H	35	25	180—181	90[f,z]	$C_{11}H_{11}N_3O_5$	49·3	4·2	15·6	—	49·8	4·2	15·9	—
p-NH·CO_2Et	H	18	210	175—176	55[a,aa,af]	$C_{12}H_{13}N_3O_6$	49·0	4·5	14·0	—	48·8	4·4	14·2	—

[a] From ethanol. [b] From aqueous ethanol. [c] From acetic acid. [d] From ethyl acetate. [e] From 2-ethoxyethanol. [f] From water. [g] Chattaway and Harris (*J.*, 1922, **121**, 2703), who prepared the diacids from sodium mesoxalate and the substituted phenylhydrazines found that the m. p. varied with the rate of heating over a range of about 8°. The m. p.s recorded above were obtained by heating the sample to 5° below its m. p. in 5 min., then at 5°/min. [h] Yield of product sufficiently pure for use at the next stage, normally after one crystallisation from the solvent specified; yellow needles unless otherwise specified. [i] Meyer [4] gives m. p. 163—164°. [j–o] Chattaway and Harris (*loc. cit.*) give m. p. [j] 163·5—172°, [k] 170·5—178°, [l] 175—182°, [m] 186·5—193°, [n] 182·5—188°, [o] none. [p] Fries, Franke, and Bruns (*Annalen*, 1934, **511**, 241) give m. p. 192°. [q] Auwers and Müller (*ibid.*, 1923, **434**, 165) give m. p. 202°. [r] For diester see Leonard, Boyd, and Herbrandson.[12] [s] For diester see Hantzsch and Thompson.[3] [t] For diester see Hünig and Boes (*Annalen*, 1953, **579**, 28). [u] Precipitation with N-hydrochloric acid, even at 80°, gave the insoluble disodium salt, converted into the diacid only by stirring with 2N-hydrochloric acid at 85° for 2 hr. [v] Precipitated by addition of hot concentrated hydrochloric acid to hot reaction mixture. [w] No attempt made to obtain optimum yield. [x] Attempts to improve the yield by using more forcing conditions led to isolation of *glyoxylic acid* p-*benzyloxyphenylhydrazone*, m. p. 115—116° (decomp.) (from ethanol) (Found: C, 67·2; H, 5·4; N, 10·2. $C_{15}H_{14}N_2O_3$ requires C, 66·8; H, 5·2; N, 10·3%). [y] Low yield due to partial decarboxylation during crystn. [z] Crude yield; partial decarboxylation made crystallisation on more than 2-g. scale impracticable. [aa] Also 29% diester recovered; insolubility and instability of diacid make crystallisation on more than 2-g. scale impracticable. [ab] Decomp. [ac] Red. [ad] Orange prisms. [ae] Buff. [af] Orange rhombs. [ag] Prisms.

TABLE 4. *Mesoxalyl chloride phenylhydrazones* (IV).

R	R′	Solvent	Reagent	M. p.[a] (decomp.)	Yield [b] (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
H	H[i,j]	$CHCl_3$	$SOCl_2$	132—135° [e]	86	$C_9H_6Cl_2N_2O_2$	44·5	2·7	11·5	28·8	44·1	2·5	11·4	29·0
o-Me	H	$C_2H_4Cl_2$ [c]	PCl_5	145—147 [e]	86	$C_{10}H_8Cl_2N_2O_2$	—	—	10·8	27·3	—	—	10·6	27·4
p-Me	H	$CHCl_3$	PCl_5	143—144 [g]	71	$C_{10}H_8Cl_2N_2O_2$	46·7	3·4	10·7	26·2	46·3	3·1	10·6	27·4
o-Cl	H	$CHCl_3$	PCl_5	129—130 [e]	83	$C_9H_5Cl_3N_2O_2$	—	—	10·3	38·3	—	—	10·0	38·1
m-Cl	H	CCl_4	PCl_5	123—124 [g]	89	$C_9H_5Cl_3N_2O_2$	39·2	2·3	10·1	—	38·6	1·8	10·0	—
p-Cl	H [m]	$C_2H_4Cl_2$ [c]	PCl_5	156—157 [g]	89 [j]	$C_9H_5Cl_3N_2O_2$	—	—	10·3	38·0	—	—	10·0	38·1
2-Cl	3-Cl	CCl_4	PCl_5	103—104 [g]	83	$C_9H_4Cl_4N_2O_2$	—	—	9·0	45·2	—	—	8·9	45·2
2-Cl	4-Cl	$CHCl_3$	PCl_5	145—146 [h]	58	$C_9H_4Cl_4N_2O_2$	—	—	9·0	43·5	—	—	8·9	45·2
2-Cl	5-Cl	CCl_4	PCl_5	110—111 [e]	50	$C_9H_4Cl_4N_2O_2$	—	—	9·1	45·7	—	—	8·9	45·2
3-Cl	4-Cl	$CHCl_3$	$SOCl_2$	149—150 [g]	63	$C_9H_4Cl_4N_2O_2$	—	—	8·9	44·6	—	—	8·9	45·2
p-Br	H	$CHCl_3$	PCl_5	158—160 [g]	62	$C_9H_5BrCl_2N_2O_2$	—	—	9·0	47·0 [d]	—	—	8·6	46·6 [d]
o-OMe	H	C_6H_6	$SOCl_2$	172—173 [g]	83	$C_{10}H_8Cl_2N_2O_3$	—	—	10·4	24·9	—	—	10·2	25·8
o-O·CH_2Ph	H	$CHCl_3$	$SOCl_2$	142—143 [f,k]	98	$C_{16}H_{12}Cl_2N_2O_3$	53·7	3·7	7·9	22·6	54·7	3·4	8·0	20·2
p-O·CH_2Ph	H	$CHCl_3$	PCl_5	121—123 [g]	32	$C_{16}H_{12}Cl_2N_2O_3$	55·0	3·8	8·3	—	54·7	3·4	8·0	—
o-OTos	H	C_6H_6	PCl_5	121—123 [g,k]	90	$C_{16}H_{12}Cl_2N_2O_5S$	47·1	3·1	—	15·1	46·3	2·9	—	17·1
o-NO_2	H	$CHCl_3$	PCl_5	135—137 [g]	83	$C_9H_5Cl_2N_3O_4$	—	—	14·3	24·1	—	—	14·5	24·5
p-NO_2	H	C_6H_6	PCl_5	155—156 [e]	86	$C_9H_5Cl_2N_3O_4$	37·9	2·0	14·7	23·6	37·2	1·7	14·5	24·5

[a] M. p. of a pure sample, unless otherwise specified. [b] Yield of product sufficiently pure for use in the next stage. [c] Ethylene dichloride. [d] Total halogen as silver halide. [e] Yellow prisms. [f] Yellow prisms and plates. [g] Yellow needles. [h] Yellow plates. [i] Di-acid described by Meyer.[4] [j] Yield 83% in nitrobenzene. [k] A pure sample was not obtained. [l] Anilide, m. p. 174° (from ethanol) (Found: C, 70·5; H, 5·3; N, 15·7. Calc. for $C_{21}H_{18}N_4O_2$: C, 70·5; H, 5·0; N, 15·7%). Naik, Trivedi, and Mehta (*J. Indian Chem. Soc.*, 1943, **20**, 365) give m. p. 175°. [m] *Anilide*, m. p. 215° (from benzene) (Found: C, 64·3; H, 4·5; N, 14·55. $C_{21}H_{17}ClN_4O_2$ requires C, 64·2; H, 4·3; N, 14·3%).

TABLE 5. *4-Hydroxycinnoline-3-carboxylic acids* (V).

R	R′	Colour [o]	M. p.[a] (decomp.)	Yield (%)	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
H	H	Fawn [d]	267—268° [c]	77	$C_9H_6N_2O_3$	57·0	3·7	14·7	—	56·8	3·2	14·7	—
8-Me	H	Colourless [d]	263—264	92	$C_{10}H_8N_2O_3$	58·6	4·1	13·7	—	58·8	3·9	13·7	—
6-Me	H	Fawn [e]	269	87	$C_{10}H_8N_2O_3$	58·6	4·4	13·6	—	58·8	3·9	13·7	—
8-Cl	H	Fawn [d,p]	247—248	90	$C_9H_5ClN_2O_3$	48·2	2·5	12·4	—	48·1	2·2	12·5	—
5-Cl	H [b]	Silvery [e,p]	263—264	63	$C_9H_5ClN_2O_3$	48·3	2·5	12·2	15·8	48·1	2·2	12·5	15·8
6-Cl	H	Colourless [e]	267 [f]	96	$C_9H_5ClN_2O_3$	48·5	2·5	—	15·9	48·1	2·2	—	15·8
7-Cl	8-Cl	Colourless [e,q]	249—250	68 [k]	$C_9H_4Cl_2N_2O_3$	41·8	1·9	11·1	27·8	41·7	1·55	10·8	27·4
6-Cl	8-Cl	Fawn [d]	250—251	27 [g]	$C_9H_4Cl_2N_2O_3$	41·9	1·6	10·8	27·2	41·7	1·55	10·8	27·4
5-Cl	8-Cl	Fawn [d]	248—249	11	$C_9H_4Cl_2N_2O_3$	—	—	10·7	27·2	—	—	10·8	27·4
5-Cl	6-Cl [l]	Fawn [d]	268	46	$C_9H_4Cl_2N_2O_3$	42·1	2·2	10·5	—	41·7	1·55	10·8	—
6-Br	H	Yellow [e]	256—258 [h]	83	$C_9H_5BrN_2O_3$	—	—	—	—	—	—	—	—
5(or 7)-Br	6-Me [n]	Fawn [e]	262—263	40 [m]	$C_{10}H_7BrN_2O_3$	42·6	2·8	10·5	29·0	42·4	2·5	9·9	28·3
8-OMe	H	Pink [d]	274—275	16	$C_{10}H_8N_2O_4$	54·7	3·9	12·8	—	54·55	3·6	12·7	—
6-OMe	H	Fawn [d]	258—259 [j]	76	$C_{10}H_8N_2O_4$								
8-OTos	H	Colourless [d]	255	5	$C_{16}H_{12}N_2O_6S$	53·2	3·6	8·8	—	53·3	3·3	8·9	—
8-NO_2	H	Pale green [d,p]	253—254	12	$C_9H_5N_3O_5$	46·0	2·4	17·8	—	45·95	2·1	17·9	—
6-NO_2	H	Yellow [d]	275	20	$C_9H_5N_3O_5$	46·1	2·2	17·9	—	45·95	2·1	17·9	—

[a] M. p. of pure sample. [b] Obtained from cyclisation of (IV; R = *m*-Cl, R′ = H), after one crystallisation of the crude product from dimethyl formamide. Assigned structure based on the fact that the decarboxylated product and two derivatives, *5-chloro-4-phenoxycinnoline* and *4-amino-5-chlorocinnoline* had m. p.s different from those reported for the corresponding 7-chloro-isomers (see below and Table 6). [c] Schofield and Simpson [9] give m. p. 268—268·5° (decomp.). [d] From acetic acid. [e] From dimethylformamide. [f] This m. p. was undepressed in admixture with authentic sample (prepared as described by Schofield and Swain [8]), m. p. 267° (lit., 263—264°). [g] Reaction time 21 hr. [h] Schofield and Swain [8] give m. p. 264° (decomp.). [j] Not obtained completely pure; Schofield and Simpson [9] give m. p. 268° (decomp.). [k] 80% of the product isolated separated during the reaction as a nitrobenzene-insoluble titanium chloride complex which was filtered off and decomposed with boiling N-sodium hydroxide, to give a solution from which the required cinnoline was precipitated on acidification. The remainder of the product was recovered from the nitrobenzene solution in the usual way. [l] Obtained from cyclisation of (IV; R = 3-Cl, R′ = 4-Cl), after two crystallisations from acetic acid. Assigned structure based on the fact that the decarboxylated product and two derivatives, *4-acetoxy-5,6-dichloro-* and *5,6-dichloro-4-phenoxy-cinnoline* had m.p.s different from those reported for the corresponding 6,7-dichloro-isomers (see below and Table 6). [m] From crude acid chloride prepared *in situ* by treating (III; R = 3-Br, R′ = 4-Me) with thionyl chloride in benzene and subsequently evaporating the solvent *in vacuo*. [n] One crystallisation gave a single isomer the orientation of which has not been studied. [o] Needles unless otherwise stated. [p] Plates. [q] Prisms.

and extracted twice with hot 4N-sodium hydroxide (5·2 and 2·5 l.). Acidification of the combined filtrates with concentrated hydrochloric acid gave the crude acid (757 g.). A portion (400 g.) of this material was stirred with concentrated nitric acid (800 ml.) at 15° for 18 hr. The purified acid was precipitated when the solution was poured on ice. 4-Hydroxycinnoline-3-carboxylic acid (809 g.), m. p. 255—257° (decomp.), was thus obtained from the crude acid (3 × 400 g.).

4-Hydroxy-8-methoxycinnoline-3-carboxylic Acid.—Titanium tetrachloride (4·2 ml.) was added to mesoxalyl chloride *o*-methoxyphenylhydrazone (9·3 g.) dissolved in dry nitrobenzene (60 ml.). The solution was heated at 95° for 4 hr., during which it set to a black jelly. Boiling water (200 ml.) was added and the nitrobenzene was steam-distilled. The solid residue was extracted with 0·2N-sodium hydroxide (120 ml.), the extract filtered through " Hyflo Supercel," and the filtrate acidified. The purple precipitate was extracted with boiling concentrated hydrochloric acid (2 × 100 ml.), giving an insoluble black residue (4·2 g.), m. p. >360°. The combined extracts were diluted with water (800 ml.), and the precipitate (1·2 g.) was crystallised from acetic acid to give the carboxylic acid, pink needles, m. p. 274—275° (decomp.). The same yield was obtained when dry chlorobenzene was used as solvent under similar conditions.

4-Hydroxy-8-nitrocinnoline-3-carboxylic Acid.—A solution of mesoxalyl chloride *o*-nitrophenylhydrazone (67 g.) and titanium tetrachloride (32·5 ml.) in dry nitrobenzene (350 ml.) was heated at 95° for 8 hr. The solution was then poured into boiling water (4·5 l.), and the nitrobenzene removed by steam-distillation. The residual solution was filtered and cooled in ice. The yellow solid (32 g.), m. p. 180—190° (decomp.), which separated was dried and extracted with boiling ethyl acetate (400 ml.). The insoluble residue (6·9 g.) crystallised from acetic acid (300 ml.), giving the *nitro-acid* (5 g., 12%) as pale green plates, m. p. 253—254° (decomp.).

4-Hydroxy-6-nitrocinnoline-3-carboxylic Acid.—This *acid* was prepared by a method similar to that used for the 8-nitro-isomer.

5-Chloro-4-phenoxycinnoline.—5-Chloro-4-hydroxycinnoline (64 g.) was stirred with phosphorus pentachloride (84 g.) and phosphorus oxychloride (250 ml.) at 95° for 1 hr. After being cooled, the precipitate was collected and washed with successive portions of dry toluene and dry ether to give crude 4,5-dichlorocinnoline hydrochloride (71·3 g., 85%). This was added during 5 min. to an azeotropically dried suspension of potassium phenoxide [prepared from potassium hydroxide (44 g.) and phenol (300 g.)] in benzene (2 l.) at 70—80°. The solvent was evaporated *in vacuo* and the residue heated on the steam-bath for 1 hr. After being cooled, the product was extracted with chloroform (1 l.), and the extract was washed with 0·5N-sodium hydroxide (3 × 6 l.) and brine (3 × 250 ml.) and dried (Na_2SO_4). Evaporation of the solvent and crystallisation of the residue from light petroleum (b. p. 100—120°; 360 ml.) gave *5-chloro-4-phenoxycinnoline* (53·5 g., 69%) as brown prismatic needles, m. p. 115—117°; a further crystallisation raised the m. p. to 118—119° (Found: C, 65·7; H, 3·8; N, 10·8; Cl, 14·0. $C_{14}H_9ClN_2O$ requires C, 65·4; H, 3·5; N, 10·9; Cl, 13·8%). Keneford and Simpson [18] give m. p. 127—128° for 7-chloro-4-phenoxycinnoline.

4-Amino-5-chlorocinnoline.—This *base* was prepared from 5-chloro-4-phenoxycinnoline by the method of Keneford, Schofield, and Simpson [19] and obtained as fawn needles, m. p. 178—179° (Found: C, 52·7; H, 3·7; N, 23·2; Cl, 19·5. $C_8H_6ClN_3$ requires C, 53·3; H, 3·3; N, 23·4; Cl, 19·8%). Keneford *et al.*[19] give m. p. 209—210° for 4-amino-7-chlorocinnoline.

4-Acetoxy-5,6-dichlorocinnoline.—5,6-Dichloro-4-hydroxycinnoline (1·1 g.) and acetic anhydride (5·5 ml.) were heated under reflux for 1 hr. The mixture was poured on ice, and the product which separated recrystallised from light petroleum (b. p. 80—100°) to give *4-acetoxy-5,6-dichlorocinnoline* (1 g.) as colourless prisms, m. p. 178—179° (Found: C, 46·9; H, 2·4; N, 11·0; Cl, 27·1. $C_{10}H_6Cl_2N_2O_2$ requires C, 46·7; H, 2·3; N, 10·9; Cl, 27·6%). A mixed m. p. with 4-acetoxy-6,7-dichlorocinnoline,[20] m. p. 148—149°, was 125°.

5,6-Dichloro-4-phenoxycinnoline.—5,6-Dichloro-4-hydroxycinnoline (1·5 g.), phosphorus pentachloride (1·5 g.), and phosphorus oxychloride (4 ml.), were heated on a steam-bath for 1·5 hr. The 4,5,6-trichlorocinnoline hydrochloride (1·4 g.) was filtered off from the cooled mixture and washed with light petroleum (b. p. 60—80°). This material was heated with phenol (3 g.) and powdered potassium hydroxide (0·5 g.) at 95° for 1 hr. with occasional stirring.

[18] Keneford and Simpson, *J.*, 1947, 917.
[19] Keneford, Schofield, and Simpson, *J.*, 1948, 358.
[20] Keneford and Simpson, *J.*, 1947, 227.

TABLE 6. *4-Hydroxycinnolines* (VI).

R	R′	Method	Form [z]	M. p.[a]	Yield (%)	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
H	H	[b]	Colourless [c]	236—237° [d]	82 [t]	$C_8H_6N_2O$								
8-Me	H	A	Fawn [e]	219—221 [f]	56	$C_9H_8N_2O$								
6-Me	H	A	Fawn [g]	271	64	$C_9H_8N_2O$	67·9	5·2	17·7	—	67·5	5·0	17·5	—
8-Cl	H	B	Colourless [g]	198—199 [h]	74 [t]	$C_8H_5ClN_2O$	—	—	—	—	—	—	—	—
5-Cl	H	A	Fawn [j]	330—332 [k]	70 [l]	$C_8H_5ClN_2O$	53·2	3·2	15·8	19·4	53·2	2·8	15·5	19·7
6-Cl	H	B	Fawn [c]	296 [n]	85 [i]	$C_8H_5ClN_2O$	53·5	3·3	15·6	19·8	53·2	2·8	15·5	19·7
7-Cl	8-Cl	A	Colourless [g]	261—262 [o]	95 [i]	$C_8H_4Cl_2N_2O$	—	—	13·2	33·4	—	—	13·0	33·0
6-Cl	8-Cl	A	Grey [g]	221—223	90	$C_8H_4Cl_2N_2O$	44·5	2·0	12·8	33·0	44·7	1·9	13·0	33·0
5-Cl	8-Cl	A	Colourless [g]	222—224	70	$C_8H_4Cl_2N_2O$	—	—	13·1	32·8	—	—	13·0	33·0
5-Cl	6-Cl	A	Fawn [g]	336—337 [p]	65	$C_8H_4Cl_2N_2O$	44·9	3·3	13·2	32·8	44·7	1·9	13·0	33·0
6-Br	H	A	Fawn [c]	277—278 [q]	45	$C_8H_5BrN_2O$	—	—	—	—	—	—	—	—
5(or 7)-Br	6-Me	A	Colourless [s]	288—289 [r]	45	$C_9H_7BrN_2O$	—	—	11·8	33·0	—	—	11·7	33·5
8-OMe	H	A	Colourless [t]	162—163	96	$C_9H_8N_2O_2$	61·7	4·8	15·9	—	61·4	4·5	15·9	—
6-OMe	H	[v]	Grey [m,v]	254—255 [w]	31	$C_9H_8N_2O_2$	—	—	—	—	—	—	—	—
6-NO_2	H	A	Yellow [g,z]	336 [u]	70	$C_8H_5N_3O_3$	—	—	—	—	—	—	—	—

[a] M. p. of a pure sample. [b] Decarboxylation in Dowtherm. [c] From ethanol. [d] Schofield and Simpson [9] give m. p. 233—234°; Leonard and Boyd [11] give m. p. 236°. [e] The product crystallised when hydrochloric acid was added to a solution of the cinnoline in 20% aqueous sodium hydroxide. [f] Keneford, Morley, and Simpson (*J.*, 1948, 1702) give m. p. 220—221°. [g] From acetic acid. [h] Schofield and Simpson (*J.*, 1945, 520) give m. p. 198—199°. [i] Overall yield on stages I—VI greater than 35% on a kg. scale. [j] From dimethylformamide. [k] Atkinson and Simpson (*J.*, 1947, 232) give m. p. 276—277° for 7-chloro-4-hydroxycinnoline. [l] Overall yield on stages I—VI 28% on a kg. scale. [m] From methanol. [n] Schofield and Swain [8] give m. p. 294—295°. [o] Keneford and Simpson [20] give m. p. 253—254°. [p] Mixed m. p. 299—304° with 6,7-dichloro-4-hydroxycinnoline (m. p. 340—342°) prepared by the method of Keneford and Simpson [20] who give m. p. 333—334°. For comparison of the corresponding 4-acetoxy- and 4-phenoxy-derivatives see below. [q] Schofield and Swain [8] give m. p. 286—287°. [r] Orientation of bromo-substituent R not studied. [s] From 2-ethoxyethanol. [t] From water. [u] Borsche and Herbert [10] give m. p. 338—340°. [v] Precipitated from benzophenone with ether and repeatedly extracted with water. [w] Schofield and Simpson [9] give m. p. 255—256°. [z] Needles unless otherwise stated. [y] Plates. [z] Prisms.

TABLE 7. *Miscellaneous compounds of type* (VII).

R	A	B	Active methylene compound used	Yield (%)		M. p.	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
H	CO_2Et	CN	$CN{\cdot}CH_2{\cdot}CO_2Et$	93		124—125° [a,b]	$C_{11}H_{11}N_3O_2$								
p-Cl	CO_2Et	CN	,,	96	α-form	157—158 [c]	$C_{11}H_{10}ClN_3O_2$	52·55	4·0	16·6	14·0	52·6	4·0	16·7	14·2
					β-form	124—125 [d]		52·5	4·3	—	14·35	52·6	4·0	—	14·2
p-OMe	CO_2Et	CN	,,	98	α-form	120 [c,e]									
					β-form	81—82 [f]	$C_{12}H_{13}N_3O_3$	58·0	5·3	17·0	—	58·3	5·3	17·0	—
p-NHAc	CO_2Et	CN	,,	75		210 [g]	$C_{13}H_{14}N_4O_3$	56·8	5·1	20·0	—	56·9	5·1	20·4	—
p-Me	CO_2Me	CO_2Me	$CH_2(CO_2Me)_2$	78		84—85 [h]	$C_{12}H_{14}N_2O_4$	57·6	5·8	11·5	—	57·6	5·6	11·2	—
p-Cl	CN	CN	$CH_2(CN)_2$	66		187 [i,j]	$C_9H_5ClN_4$	53·1	2·6	—	17·3	52·8	2·4	—	17·4
H	CO_2Et	NO_2	$NO_2{\cdot}CH_2{\cdot}CO_2Et$ [k]	56		60—61 [l,m]	$C_{10}H_{11}N_3O_4$	—	—	—	—	—	—	—	—
p-Cl	CO_2Et	NO_2	,,	40		118—119 [i]	$C_{10}H_{10}ClN_3O_4$	44·7	3·7	14·8	12·9	44·3	3·7	15·4	13·05
p-Cl	COMe	COMe	CH_2Ac_2	96		132—133 [i]	$C_{11}H_{11}ClN_2O_2$	55·4	4·6	11·7	—	55·3	4·6	11·7	—
p-OMe	COMe	COMe	,,	96		100—101 [i]	$C_{12}H_{14}N_2O_3$	61·5	6·1	12·2	—	61·6	6·0	12·0	—

[a] From benzene. [b] Hantzsch and Thompson [3] give m. p. 125° for the α-form. [c] Precipitated from alkaline solution by 2N-HCl. [d] Precipitated from alkaline solution by CO_2. [e] Lax (*J. prakt. Chem.*, 1901, **63**, 1) gives m. p. 116—118° for this form. [f] From aqueous ethanol; Lax (*loc. cit.*) gave m. p. 85° for this form. [g] From pyridine–water (1 : 1). [h] From methanol; Bülow and Ganghöfer [5] give m. p. 88—89°. [i] From ethanol. [j] Lythgoe, Todd, and Topham (*J.*, 1944, 315) give m. p. 188—190°. [k] As the ammonium salt. [l] From light petroleum (b. p. 40—60°). [m] Meyer and Wertheimer (*Ber.*, 1914, **47**, 2374) give m. p. 60°.

The cooled melt was mixed with an excess of 2N-sodium hydroxide, and the product extracted with chloroform; the extract was washed with alkali and then with water and dried (Na_2SO_4). Evaporation gave crude 5,6-*dichloro*-4-*phenoxycinnoline* (1·45 g.) which crystallised from benzene–light petroleum (b. p. 80—100°) in colourless needles, m. p. 189° (Found: C, 58·0; H, 2·7; N, 9·6; Cl, 24·2. $C_{14}H_8Cl_2N_2O$ requires C, 57·8; H, 2·7; N, 9·6; Cl, 24·4%). 6,7-Dichloro-4-phenoxycinnoline is reported by Keneford and Simpson [20] to have m. p. 162—163°.

4-*Hydroxycinnolines* (VI).—Substituted 4-hydroxycinnoline-3-carboxylic acids were most conveniently decarboxylated by heating them in benzophenone (4 parts) at 180—210° (internal temperature) until the evolution of carbon dioxide ceased (30—60 min.[9]). The 4-hydroxycinnolines (see Table 6) were isolated in a highly pure form: (*A*) by extracting the benzophenone with ether or light petroleum (b. p. 80—100°), dissolving the residue in hot 5N-sodium hydroxide or ammonia, and reprecipitating the product with acid; or (*B*) by extracting the 4-hydroxycinnoline directly from the benzophenone into boiling N-sodium carbonate solution and reprecipitating the product with acid. The foregoing method was used to prepare 4-hydroxycinnoline [9] but on a kilogram scale higher yields were obtained when this decarboxylation was carried out in boiling Dowtherm from which the product crystallised on cooling.

Ethyl Mesoxalate 2,4-*Dinitrophenylhydrazone*.—This was prepared by heating a solution of diethyl mesoxalate (4·35 g.) and 2,4-dinitrophenylhydrazine (4·95 g.) in acetic acid (100 ml.) at 95° for 2 hr. After being cooled the mixture was poured with stirring into ice-water (800 ml.), and the bright yellow solid was filtered off and washed with water (7·4 g., 83%; m. p. 108—109°). This product (2 g.) was extracted with boiling light petroleum (b. p. 60—80°; 600 ml.), and the hot extract filtered from an unidentified by-product. The filtrate on cooling deposited the pure diester as bright yellow prisms (1·3 g., 55%), m. p. 116—117° (Found: C, 44·2; H, 3·95; N, 15·8. Calc. for $C_{13}H_{14}N_4O_8$: C, 44·1; H, 3·95; N, 15·8%). Allen [21] gave m. p. 128° (from ethanol).

Dimethyl Mesoxalate o-*Methoxyphenylhydrazone*.—This was prepared by addition of a diazonium solution, prepared in the usual way from *o*-anisidine (62·5 g.), to a stirred mixture of dimethyl malonate (66 g.), anhydrous sodium acetate (150 g.), methanol (1 l.), and water (400 ml.), at 20°. After working up as previously described for the diethyl mesoxalate phenylhydrazones and recrystallisation from methanol, the dimethyl ester was obtained as orange yellow plates (101 g., 76%). A sample recrystallised from methanol had m. p. 111—112° (Bülow and Ganghöfer [5] give m. p. 112—113°).

Other *derivatives* of type (VII) prepared similarly by coupling diazotised amines with the appropriate active methylene compound are shown in Table 7.

Methyl Hydrogen Mesoxalate p-*Tolylhydrazone*.—Dimethyl mesoxalate *p*-tolylhydrazone (50 g.) in boiling methanol (100 ml.) was treated with 2·46N-methanolic sodium hydroxide (81 ml.). After being refluxed for a short time the mixture solidified and after being cooled it was diluted with ether, and the yellow sodium salt was filtered off and washed with ether. The dry sodium salt was ground with an excess of 2N-hydrochloric acid, and the solid was filtered off, washed well with water, and recrystallised from methanol, to give the *hydrazone* 24 g., 49%), m. p. 153—154° (Found: C, 55·8; H, 5·35; N, 11·85. $C_{11}H_{12}N_2O_4$ requires C, 55·8; H, 5·1; N, 11·9%).

Methyl Glyoxylate p-*Tolylhydrazone*.—Methyl hydrogen mesoxalate *p*-tolylhydrazone (20 g.) was heated in an oil-bath at 165° (internal temperature) until evolution of carbon dioxide had ceased. The cold residue was triturated with excess of light petroleum (b. p. 40—60°), and the undissolved α-*form* of *methyl glyoxylate* p-*tolylhydrazone* (5·1 g., 31%) filtered off and washed with light petroleum. After crystallisation from methanol it had m. p. 174—175° (Found: C, 62·6; H, 6·4; N, 14·6. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·25; N, 14·6%). Evaporation of the light petroleum filtrate and washings gave a syrup which when triturated with methanol at −40° gave the β-*form* (9·5 g., 58%), m. p. 21—22°. A sample recrystallised from light petroleum (b. p. 40—60°) below 0° had m. p. 21—22° (Found: C, 62·7; H, 6·2; N, 14·8%).

Ethyl Glyoxylate p-*Chlorophenylhydrazone*.—Ethyl hydrogen mesoxalate *p*-chlorophenylhydrazone (20 g.) was heated in an oil-bath to 178° (internal temperature), kept at 175—180° until no more carbon dioxide was evolved, and then cooled. Light petroleum (b. p. 40—60°) was added and the crude *ethyl glyoxylate* p-*chlorophenylhydrazone* (14·7 g., 87%) was filtered off. Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the pure α-*form*,

[21] Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955.

TABLE 8. *Unsymmetrical acid chlorides* (VII; A = COCl).

B	R	Solvent	M. p	Yield (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
CO_2Et	*p*-Me	C_6H_6	76°	45	$C_{12}H_{13}ClN_2O_3$	54·0	4·9	10·7	13·2	53·6	4·8	10·4	13·2
CN	*p*-Cl [a]	,,	151—154	65	$C_9H_5Cl_2N_3O$	—	—	—	28·9	—	—	—	29·3
CN	*p*-OMe [b]	$CHCl_3$	138—140	68	$C_{10}H_8ClN_3O_2$	—	—	—	15·05	—	—	—	14·95
H	*p*-Cl	,,	127—128	49	$C_8H_6Cl_2N_2O$	—	—	—	32·75	—	—	—	32·8
CO_2Et	*p*-O·CH_2Ph	None [c]	105—107	85 [d]	$C_{18}H_{17}ClN_2O_4$	—	—	—	—	—	—	—	—

[a] *Anilide*, m. p. 218—219° (from ethanol) (Found: C, 60·45; H, 3·8; N, 18·6; Cl, 11·8. $C_{15}H_{11}ClN_4O$ requires C, 60·3; H, 3·7; N, 18·7; Cl, 11·9%). [b] *Anilide*, m. p. 167—169° (from ethanol) (Found: C, 65·5; H, 4·9; N, 19·0. $C_{16}H_{14}N_4O_2$ requires C, 65·3; H, 4·75; N, 19·0%). [c] Sodium salt of acid treated with thionyl chloride. [d] Crude yield; a pure sample was not obtained.

TABLE 9. *Attempted cyclisations of other compounds of type* (VII).

A	B	R	Conditions	Temperature	Result
CO_2Me	CO_2Me	*o*-OMe, *p*-Me	Thermal cyclisation in refluxing Dowtherm (250—260°) or benzophenone (297°)		Complete breakdown with evolution of MeOH or EtOH and HCN [a]
CO_2Et	CO_2Et	H, *p*-Cl, *p*-Me, *p*-NO_2, *p*-NHAc, *p*-NH·CO_2Et			
CO_2H	CO_2Et	*p*-Me	,,	,,	
CO_2Me	H	(α- and β-) *p*-Me	,,	,,	
CO_2Et	H	(α- and β-) *p*-Cl	,,	,,	
CO_2H	CO_2Et	*p*-Me, *p*-NHAc	Conc. H_2SO_4	Recovery of starting material or sulphonation at room temp.; sulphonation and/or decomp. at 60—95°	
CO_2H	CO_2H	*p*-Cl	,,	,, ,,	,,
Ac	Ac	*p*-Cl, *p*-OMe	,,	,, ,,	,,
CN	CO_2Et	H, *p*-NHAc	,,	Room temp.	Recovery of starting material or sulphonation [b]
CN	CN	*p*-Cl	,,	,,	Hydrolysis to *monoamide* [c]
CO_2Et	CO_2Et	*p*-Cl	Polyphosphoric acid	Recovery of starting materials at room temp. or 45—100°; decomp. at 100—165°	
CO_2H	CO_2Et	H, *p*-Cl, *p*-Me, *p*-NHAc	,, ,,	,, ,,	,, ,, ,,
CO_2H	CO_2H	H, *p*-Me, *o*-OMe, *p*-NO_2	,, ,,	,, ,,	,, ,,
CN	CN	*p*-Cl	,, ,,	,, ,,	,, ,,
Ac	Ac	*p*-Cl	,, ,,	,, ,,	,, ,,
CO_2Et	CO_2Et	*p*-Br	Conc. H_2SO_4–Ac_2O [d]	60—95°	Monosulphonated derivative [e] of diethyl mesoxalate *p*-bromophenylhydrazone isolated as Na salt in low yield
CO_2Et	CO_2Et	*p*-Cl	BF_3–Et_2O	110—120°	BF_3 complex, m. p. 193—194°, giving ethyl hydrogen mesoxalate *p*-chlorophenylhydrazone [f] with acetic acid
CO_2H	CO_2Et	*p*-NO_2, *p*-Me, *p*-NHAc	$POCl_3$	107°	Intractable by-product and some starting material recovered
CO_2H	CO_2H	H, *p*-Me			
CO_2H	CO_2H	*p*-Me, *p*-NHAc	Anhyd. HF	0—15°	Recovery of starting material
CO_2H	CO_2H	*m*-Cl	F·SO_3H	40°	Recovery of starting material

[a] In the case of (VII; A = B = CO_2Et, R = *p*-NH·CO_2Et), there was obtained a 46% yield of p-*ethoxycarbonylaminophenyl isocyanate*, m. p. 64—65° [from light petroleum (b. p. 40—60°)] (Found: C, 58·5; H, 4·8; N, 13·6; OEt, 22·3. $C_{10}H_{10}N_2O_3$ requires C, 58·4; H, 4·85; N, 13·7; OEt, 21·85%), giving on treatment with ethanol the corresponding diurethane, 1,4-diethoxycarbonylaminobenzene, m. p. 193—194° (from ethanol) (Schiff and Ostrogovitch, *Annalen*, 1896, **293**, 371, give m. p. 196—196·5°). [b] In the case R = H, the monosulphonated derivative was isolated as its *sodium salt* (from water), no m. p. <360° (Found: C, 41·3; H, 3·1; N, 13·2; S, 10·0. $C_{11}H_{10}N_3NaO_5S$ requires C, 41·3; H, 3·3; N, 13·2; S, 10·3%) (cf. Marquardt, *J. prakt. Chem.*, 1895, **52**, 175). [c] M. p. 266° (from acetic acid) (Found: C, 48·3; H, 3·1; Cl, 15·9. $C_9H_7ClN_4O$ requires C, 48·8; H, 3·4; Cl, 16·2%). [d] Cf. Bangdiwala and Desai.[13] [e] From water (Found: Br, 18·0; N, 6·4; Na, 4·5; S, 7·1. $C_{13}H_{14}BrN_2NaO_7S$ requires Br, 17·9; N, 6·3; Na, 5·2; S, 7·2%). In acetic acid or toluene. [f] M. p. and mixed m. p. 171°.

m. p. 151—152° (Found: C, 53·0; H, 5·0. $C_{10}H_{11}ClN_2O_2$ requires C, 53·0; H, 4·85%). Crystallisation from ethanol gave the β-*form*, m. p. 68—69°, identical with the product obtained (16%) after dry distillation of the crude material obtained by coupling of *p*-chlorobenzenediazonium chloride with potassium ethyl malonate (m. p. 69—70°; mixed m. p. 68—70°) (Found: C, 53·0; H, 5·0; Cl, 15·6. $C_{10}H_{11}ClN_2O_2$ requires C, 53·0; H, 4·85; Cl, 15·7%).

Cyanoglyoxylic Acid p-*Methoxyphenylhydrazone*.—The cyanoglyoxylic esters were surprisingly resistant to mild alkaline hydrolysis, being substantially unchanged after 1 hr. at 55° with an excess of 2N-aqueous-alcoholic potassium hydroxide. With 2N-aqueous sodium hydroxide at 95°, however, the cyano-group was attacked, and then decarboxylation of the diacid occurred. The best yield of the required cyano-acid was obtained by the following procedure. Ethyl cyanoglyoxylate *p*-methoxyphenylhydrazone (26·8 g.) was dissolved in 2N-sodium hydroxide (108 ml.) and after addition of further 2N-sodium hydroxide (324 ml.) the solution was heated at 65—70° for 80 min., cooled, and kept at room temperature overnight. Cautious acidification with 2N-hydrochloric acid gave the crude acid (24·7 g.), m. p. 146—148°. Extraction of this with boiling light petroleum (b. p. 60—80°; 500 ml.) gave a product sufficiently pure for further use (22·7 g., 95%; m. p. 150—152°). In some experiments the α-form of the starting ester was recovered from the petroleum extracts (m. p. and mixed m. p. 118—119°). A sample of the *acid*, crystallised (on a small scale only) from acetic acid, had m. p. 154—155° (Found: C, 55·1; H, 4·34; N, 18·8. $C_{10}H_9N_3O_3$ requires C, 54·9; H, 4·1; N, 19·1%). Crystallisation on a large scale gave much lower yields owing to partial decarboxylation. Attempted crystallisation from aqueous ethanol resulted in complete decarboxylation to give *glyoxylonitrile* p-*methoxyphenylhydrazone* (VII; A = CN, B = H, R = *p*-OMe), m. p. 127—128° (Found: C, 61·5; H, 5·38; N, 23·7. $C_9H_9N_3O$ requires C, 61·7; H, 5·15; N, 24·0%).

Cyanoglyoxylic acid p-*chlorophenylhydrazone*, m. p. 160—161° (from ethanol) (Found: C, 48·3; H, 2·6; N, 18·9; Cl, 15·7. $C_9H_6ClN_3O_2$ requires C, 48·3; H, 2·7; N, 18·8; Cl, 15·9%), was obtained similarly in 57% yield.

Glyoxylic Acid p-*Chlorophenylhydrazone*.—This was prepared only in low yield by hydrolysis of the ethyl ester with N-aqueous-alcoholic potassium hydroxide at 60°. Crystallisation from acetic acid gave the pure acid (9%), m. p. 143—144° (decomp.) [lit.,[22] 142° (decomp.)]. The acid decomposed when kept or on attempted large-scale recrystallisation and was best stored as the stable sodium salt, prepared as follows: Ethyl glyoxylate *p*-chlorophenylhydrazone (109·3 g.) in boiling dry ethanol (242 ml.) was treated with 2·4N-ethanolic sodium hydroxide (242 ml.), and the mixture was refluxed for 20 min. After being cooled to 0°, the solid, which had separated, was filtered off and washed with ice-cold dry ethanol. Crystallisation from ethanol (1·3 l.) (charcoal) gave the *sodium salt* as pale yellow needles (40 g., 30%), m. p. 259—263° (decomp.) (Found: N, 11·35; Cl, 14·4; H_2O, 10·55. $C_8H_6ClN_2NaO_2,1{\cdot}5H_2O$ requires N, 11·35; Cl, 14·4; H_2O, 10·5%). Acidification of this sodium salt with ice-cold 2N-hydrochloric acid gave the acid, m. p. 134—135°, sufficiently pure to be used for preparation of the acid chloride.

Preparation of Unsymmetrical Acid Chlorides.—The glyoxylic, cyanoglyoxylic, and ethoxycarbonylglyoxylic acid chlorides were prepared by using thionyl chloride in an inert solvent as described above for the mesoxalyl chlorides. Some were characterised as anilides (see Table 8).

Cyclisation of Unsymmetrical Acid Chlorides.—*Cyclisation of ethoxycarbonylglyoxylyl chloride* p-*tolylhydrazone*. The acid chloride was prepared *in situ* from ethyl hydrogen mesoxalate *p*-tolylhydrazone (25 g.), and thionyl chloride (13 g.) in dry benzene (700 ml.), benzene being then removed *in vacuo* at 50°; it was dissolved in dry nitrobenzene (200 ml.), and stannic chloride (27·4 g.) added as catalyst. The mixture was then heated at 95° for 2 hr. and divided into four equal portions. To one of these was added 1·95 N-sodium hydroxide (190 ml.), and the mixture was steam-distilled to remove nitrobenzene. After being filtered hot from tin salts, the filtrate was acidified while hot with concentrated hydrochloric acid (45 ml.) to give crude 4-hydroxy-6-methylcinnoline-3-carboxylic acid [2·7 g., 54%; m. p. 240—250° (decomp.)]. Crystallisation from acetic acid gave the pure acid, m. p. and mixed m. p. 265—266°. Alternative methods of working up the remaining portions by acid or neutral steam-distillation gave lower yields.

Unsuccessful attempted cyclisations of other unsymmetrical acid chlorides (VII; A = COCl)

[22] Busch and Meussdörffer, *J. prakt. Chem.*, 1907, **75**, 121.

at 95° gave only low-melting acid fractions (yield as stated) but no cinnoline: B = CO_2Et, R = *p*-O·CH_2Ph, 5% in 3·75 hr.; B = H, R = *p*-Cl, 18% in 6 hr.; B = CN, R = *p*-Cl, 17% in 5 hr.; B = CN, R = *p*-OMe, 2·5% in 6 hr.

Miscellaneous attempted cyclisations of mesoxalic and glyoxylic acid derivatives by other methods. A wide range of methods for cyclisation of acid derivatives, many of which have been successfully applied in the synthesis of 4-hydroxyquinolines, was applied to a variety of mesoxalic and glyoxylic acid derivatives (see Table 9) with uniform lack of success. In these experiments standard reaction conditions and methods of working-up which had been successful in other fields were used. In a few cases new derivatives formed by sulphonation or hydrolysis of the starting materials were isolated (see footnotes to Table 9).

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