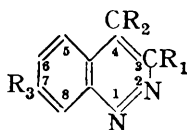


## 58. Cinnolines. Part I. Some New Examples.

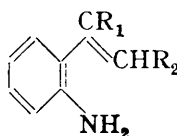
By JAMES C. E. SIMPSON and OLIVER STEPHENSON.

The syntheses are described of 6-bromo-4-phenyl-, 6-chloro-4-(4'-hydroxyphenyl)-, and 6-chloro-4-(2'-hydroxy-5'-methylphenyl)-cinnoline by the Stoermer reaction [cyclisation of diazotised  $\alpha$ -(2-amino-phenyl)- $\alpha$ -arylethylenes]. During the course of the work a number of new benzophenone derivatives have been prepared.

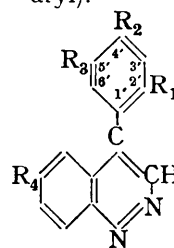
THE chemistry of cinnoline compounds has received scant attention since the discovery, nearly sixty years ago, of the first derivatives, 4-hydroxycinnoline-3-carboxylic acid (I;  $R_1 = \text{CO}_2\text{H}$ ,  $R_2 = \text{OH}$ ,  $R_3 = \text{H}$ ) (von Richter, *Ber.*, 1883, **16**, 677) and 4-methylcinnoline-7-carboxylic acid (I;  $R_1 = \text{H}$ ,  $R_2 = \text{Me}$ ,  $R_3 = \text{CO}_2\text{H}$ ) (Widman, *Ber.*, 1884, **17**, 722). Cinnoline itself (I;  $R_1 = R_2 = R_3 = \text{H}$ ) was prepared from the former acid some years later by Busch and Rast (*Ber.*, 1897, **30**, 521). A discouraging factor in this field has doubtless been the lack of a convenient method of preparation, in contrast to the isomeric phthalazines, which are readily accessible and have in consequence been widely studied. A somewhat easier route to the cinnoline ring system than the method of von Richter, which involved cyclisation of diazotised *o*-aminophenylpropionic acid, was explored by Stoermer and Fincke (*Ber.*, 1909, **42**, 3115). Employing the reaction originally discovered by Widman (*loc. cit.*), namely, the cyclisation of diazotised *o*-aminoarylethylenes, these authors showed that  $\alpha$ -(2-aminophenyl)- $\alpha$ -arylethylenes (II;  $R_1 = \text{aryl}$ ,  $R_2 = \text{H}$ ), on treatment with nitrous acid in presence of hydrochloric acid, passed smoothly and spontaneously into the corresponding 4-arylcinnolines (I;  $R_1 = R_3 = \text{H}$ ,  $R_2 = \text{aryl}$ ).



(I.)



(II.)



(III.)

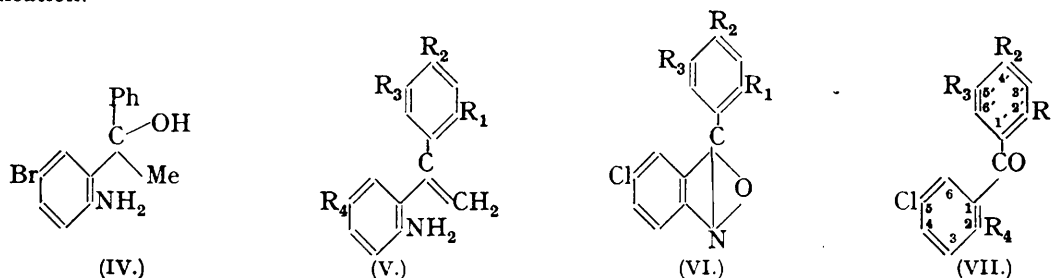
4-Phenyl-, 4-phenyl-3-methyl-, and 4-*p*-tolyl-cinnoline were synthesised by this means, the requisite diarylethylenes being obtained from the appropriate diaryl ketones and a Grignard reagent, followed by dehydration of the resulting carbinols. Later, Stoermer and Gaus (*Ber.*, 1912, **45**, 3104) prepared 4-*p*-anisyl- and 4-*p*-hydroxyphenyl-cinnoline, the latter by demethylation of the former. Stoermer and Fincke observed also that the substitution of bromine for hydrogen on the  $\beta$ -ethylenic carbon atom of (II) tended to inhibit the cyclisation of the diazonium salt, (II;  $R_1 = \text{Ph}$ ,  $R_2 = \text{Br}$ ) giving only 4-phenyl-cinnoline in poor yield; but (apart from Widman's acid) the influence on ring closure of strongly polar substituents in either of the two aryl nuclei has not been studied.

In this paper we describe the syntheses of 6-bromo-4-phenyl-4-cinnoline (III;  $R_1 = R_2 = R_3 = \text{H}$ ,  $R_4 = \text{Br}$ ), 6-chloro-4-(4'-hydroxyphenyl)cinnoline (III;  $R_1 = R_3 = \text{H}$ ,  $R_2 = \text{OH}$ ,  $R_4 = \text{Cl}$ ), and 6-chloro-4-(2'-hydroxy-5'-methylphenyl)cinnoline (III;  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{Me}$ ,  $R_4 = \text{Cl}$ ) by the Stoermer reaction. The yields, based on the diarylethylenes, were in all cases reasonably high, so the

scope of this method for the synthesis of cinnolines containing substituted aryl nuclei is in all probability fairly wide.

Condensation of 5-bromo-2-aminobenzophenone (Angel, J., 1912, **101**, 515) with methylmagnesium iodide gave *phenyl-(5-bromo-2-aminophenyl)methylcarbinol* (IV), which was smoothly dehydrated by sulphuric acid to the ethylene (V;  $R_1 = R_2 = R_3 = H$ ,  $R_4 = Br$ ). The latter was an oil, characterised by the formation of two crystalline, easily hydrolysable sulphates, each of which on basification and benzylation furnished the same *benzamido*-compound, m. p.  $114^\circ$ . A solution of the free amino-ethylene in dilute sulphuric acid was immediately converted into the cinnoline (III;  $R_1 = R_2 = R_3 = H$ ,  $R_4 = Br$ ), m. p.  $144^\circ$ , by addition of sodium nitrite.

For the synthesis of (III;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = Cl$ ), we utilised the observation of Zincke and Siebert (*Ber.*, 1906, **39**, 1930) that *o*-nitrobenzaldehyde and phenol condense in the presence of dry hydrogen chloride to the anthroxan (VI;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ), which on reduction yields 5-chloro-2-amino-4'-hydroxybenzophenone (VII;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = NH_2$ ). In our hands the conditions employed for this reduction by Zincke and Siebert (tin and hydrochloric acid) proved unsatisfactory, but the use of iron and acetic acid gave excellent yields of the ketone. The carbinol formed by treatment of the latter compound with methylmagnesium iodide underwent spontaneous dehydration to the *diarylethylene* (V;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = Cl$ ); this was isolated in high yield, and was characterised by the preparation of a *dibenzoyl* derivative. Addition of aqueous sodium nitrite to a solution of the amino-ethylene in hydrochloric acid gave a 70% yield of the cinnoline (III;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = Cl$ ), but in dilute sulphuric acid the yield was lower (50%) and accompanied by partial resinification.



Condensation of *o*-nitrobenzaldehyde, hydrogen chloride, and *p*-cresol yields the anthroxan (VI;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ) (Zincke and Siebert, *loc. cit.*), reduction of which to the corresponding amino-ketone proceeded smoothly, as in the former case, with iron and acetic acid, but was unsatisfactory when tin and hydrochloric acid were used. The product resulting from treatment of the amino-ketone with the methyl Grignard reagent was a resin which resisted all attempts at crystallisation. In an early effort to isolate the amino-ethylene (or amino-carbinol), it was found that benzylation of the resin furnished a crystalline *dibenzoyl* derivative, m. p.  $119^\circ$ , of the amino-ethylene (V;  $R_1 = OBz$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = Cl$ ,  $NHBz$  for  $NH_2$ ). This substance was accordingly hydrolysed in the expectation of obtaining the free amino-ethylene, since the parent amino-ketone had been found to be recoverable by a similar hydrolysis of its *dibenzoyl* compound. However, the product of hydrolysis of the compound, m. p.  $119^\circ$ , was a resin, which on rebenzylation gave a new *benzoyl* derivative, m. p.  $235^\circ$ ; this appeared from analysis to have the formula  $C_{36}H_{26}O_4NCl$ , and we therefore regard it as a tribenzoyl derivative (V;  $R_1 = OBz$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = Cl$ ,  $NBz_2$  for  $NH_2$ ). The compound was not investigated further, for the isolation of the pure *amino-ethylene* (V;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = Cl$ ) had in the meantime been achieved through the crystalline *hydrochloride*, which was converted into the cinnoline (III;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = Cl$ ) in the usual manner.

The orientations of the three new cinnolines are obviously dependent on those of the related ketones, and in the case of the two phenolic ketones [(VII;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = NH_2$ ), m. p.  $178^\circ$ , and (VII;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = NH_2$ ), m. p.  $114^\circ$ ] no rigid proof of structure appears to exist. By means of the procedure described below, we have been able to establish the correctness of the constitutions assigned to these ketones in so far as the positions of the chlorine atoms are concerned.

Zincke and Siebert (*loc. cit.*) describe the conversion of the ketone, m. p.  $178^\circ$ , into 3-chloro-4'-hydroxybenzophenone, a result which we have in part confirmed by oxidation of this substance to *m*-chlorobenzoic acid. 3-Chloro-4'-hydroxybenzophenone, however, could also arise from the ketone, m. p.  $178^\circ$ , if the latter were represented by an alternative structure with the chlorine atom on  $C_3$  instead of  $C_5$ . We have eliminated this possibility by conversion of the ketone into 2 : 5-dichloro-4'-hydroxybenzophenone, the orientation of the halogen-substituted ring being proved by oxidation to 2 : 5-dichlorobenzoic acid. The position of the chlorine atom in the second amino-ketone (m. p.  $114^\circ$ ) was similarly established by

transformation of the ketone into 2 : 5-dichloro-2'-hydroxy-5'-methylbenzophenone, followed by oxidation of the latter to 2 : 5-dichlorobenzoic acid. Incidentally, the preparation of these dichloro-ketones contradicts the experience of Zincke and Siebert, who were unable to prepare any derivatives of the diazotised amino-ketones except 3-chloro-4'-hydroxybenzophenone (the recorded m. p. of which is considerably lower than that found by us).

In an attempt to establish the position of the phenolic group in each of the amino-ketones, we prepared the methyl ethers of the two anthroxans [(VI;  $R_1 = R_3 = H$ ,  $R_2 = OMe$ ) and (VI;  $R_1 = OMe$ ,  $R_2 = H$ ,  $R_3 = Me$ )], and reduced these to the corresponding amino-ketones. On the assumption that the positions assigned to the phenolic groups in the anthroxans are correct it was anticipated that oxidation of the methoxy-amino-ketones would furnish anisic acid and 4-methoxyisophthalic acid respectively. However, the ketone from (VI;  $R_1 = OMe$ ,  $R_2 = H$ ,  $R_3 = Me$ ) was incompletely oxidised by alkaline permanganate, and no crystalline product could be obtained when the oxidation was continued in acid solution. In view of this result, the ketone from (VI;  $R_1 = R_3 = H$ ,  $R_2 = OMe$ ) was diazotised with a view to obtaining a phenol more amenable to oxidation, but, in spite of several trials, almost the whole of the product was an alkali-insoluble resin, and only a trace of crystalline phenol could be obtained.

It is our intention to develop this preliminary work when an opportunity occurs.

#### EXPERIMENTAL.

(Melting points are uncorrected.)

*Phenyl-(5-bromo-2-aminophenyl)methylcarbinol* (IV).—An ethereal solution of methylmagnesium iodide prepared from 2 g. of magnesium and 12 g. of methyl iodide was treated with a similar solution of 5-bromo-2-aminobenzophenone (5 g., m. p. 110°, prepared by the method of Angel, *loc. cit.*, who gives m. p. 111°), added slowly with cooling. The resultant deep red solution was refluxed for 1 hour, solid material separating. The product was decomposed with ice and dilute hydrochloric acid, and the ethereal solution dried over sodium sulphate and evaporated. The residue, which rapidly solidified, was recrystallised from ether-ligroin (b. p. 40–60°), yielding pale yellow, thick prisms of the *carbinol*, m. p. 100° (Found: C, 58.3, 58.5; H, 5.05, 5.1; N, 5.05.  $C_{14}H_{14}ONBr$  requires C, 57.5; H, 4.8; N, 4.8%). The high values for carbon are possibly attributable to the facility with which the carbinol undergoes dehydration, this explanation being supported by the facts that the *N*-acetyl and the *N*-benzoyl derivative give similar high values, whereas the *N*-benzoyl ethylene (*q.v.*) gives satisfactory analytical data.

The *N*-acetyl derivative of the carbinol was prepared by treatment of the latter in excess of pyridine with acetic anhydride at room temperature. After 4 days the solution was diluted with water, and the acetamido-compound recrystallised from aqueous methanol, forming cream-coloured, long, prismatic needles, m. p. 181–182° (Found: C, 58.4; H, 4.5.  $C_{16}H_{16}O_2NBr$  requires C, 57.5; H, 4.8%). The *N*-benzoyl derivative (from pyridine and benzoyl chloride) separated from aqueous alcohol in colourless prisms, m. p. 196° (Found: C, 64.4; H, 4.6.  $C_{21}H_{18}O_2NBr$  requires C, 63.6; H, 4.6%).

*Derivatives of  $\alpha$ -Phenyl- $\alpha$ -(5-bromo-2-aminophenyl)ethylene*.—(i) After the foregoing carbinol (0.5 g.) had been refluxed for 2½ hours with 4*N*-sulphuric acid (60 c.c.), white feathery crystals, m. p. 107°, separated on cooling (Found: C, 40.6; H, 5.2.  $C_{14}H_{12}NBr.H_2SO_4.2H_2O$  requires C, 41.2; H, 4.4%). This *sulphate* was extremely hygroscopic and somewhat unstable, being slowly decomposed in cold water, and rapidly in hot, to the free amino-ethylene.

(ii) Treatment of the carbinol with 2*N*-sulphuric acid under identical conditions yielded a second sulphate of the amino-ethylene; this salt crystallised from the acid solution in fine white needles, m. p. 154°. Although this compound appeared to be rather more stable than the sulphate, m. p. 107°, it likewise decomposed slowly in aqueous solution.

(iii) Each of the above sulphates was shaken with aqueous-alcoholic ammonia, and the base was isolated by extraction with ether. In each case the uncrystallisable oil obtained was identified as the same diaryl-ethylene by benzoylation (benzoyl chloride and pyridine),  $\alpha$ -phenyl- $\alpha$ -(5-bromo-2-benzamidophenyl)ethylene separating in each instance from aqueous methanol in colourless prismatic needles, m. p. and mixed m. p. 113.5–114° (Found: C, 67.0; H, 4.3.  $C_{21}H_{16}ONBr$  requires C, 66.65; H, 4.2%).

*6-Bromo-4-phenylcinnoline*.—A solution of the sulphate (0.4 g.), m. p. 150°, in warm dilute sulphuric acid was cooled to 10° and treated with solid sodium nitrite (0.1 g.). The crystalline *cinnoline*, which separated almost immediately in nearly quantitative yield, was recrystallised from aqueous alcohol containing ammonia and subsequently from ether-ligroin or slightly aqueous methanol. It formed yellow, light, silky needles, m. p. 143.5–144.5°. The same result was obtained when the addition of sodium nitrite was carried out at 40° (Found: C, 59.7, 59.9, 59.9; H, 3.1, 3.0, 3.5; N, 9.6; Br, 26.9.  $C_{14}H_9N_2Br$  requires C, 58.95; H, 3.2; N, 9.8; Br, 28.0%). No explanation can be advanced in respect of the high carbon values, which were obtained with three different samples. A solution of the cinnoline in concentrated hydrochloric acid gave an amorphous insoluble chloroplatinate, and benzene solutions of the base and picric acid gave a crystalline picrate, m. p. 270–275° (decomp.). The base showed no tendency to form a sulphate in aqueous solution.

*5-Chloro-2-amino-4'-hydroxybenzophenone* (VII;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = NH_2$ ).—The anthroxan prepared from *o*-nitrobenzaldehyde and phenol had m. p. 240–241° after crystallisation from alcohol (Zincke

and Siebert, *loc. cit.*, give m. p. 241°). The reduction was carried out by addition of iron filings (5 g.) to a suspension of the powdered anthroxan (10 g.) in glacial acetic acid (200 c.c.) heated on the water-bath. After the anthroxan had dissolved ( $\frac{1}{2}$  hour), the solution was diluted with water (50 c.c.), and a further quantity of iron filings (10 g.) added in five equal portions during 2 hours with frequent shaking. After a further  $\frac{1}{2}$  hour the solution was treated with water (50 c.c.), filtered from inorganic matter, and diluted with water until crystallisation occurred in the hot. After several crystallisations from aqueous methanol the amino-ketone formed yellow, flattened needles, m. p. 177—178° (lit., m. p. 174°); yield (pure), 70%. The *dibenzoyl* derivative, m. p. 143°, was comparatively sparingly soluble, and separated from rectified spirit in colourless needles (Found: C, 70.6; H, 3.8.  $C_{27}H_{18}O_4NCl$  requires C, 71.1; H, 4.0%).

**3-Chloro-4'-hydroxybenzophenone** (VII;  $R_1 = R_3 = R_4 = H$ ,  $R_2 = OH$ ).—The foregoing amino-ketone (1 g.) was dissolved in absolute alcohol (15 c.c.) and treated successively with concentrated sulphuric acid (1 c.c.) and amyl nitrite (5 c.c.), added at 10° with shaking. After 5 minutes the solution was warmed somewhat, and when the reaction had subsided the solution was refluxed for 5 minutes, diluted with water, and extracted with ether. The extract was washed with water and with 4% sodium hydroxide solution; the latter was then acidified with hydrochloric acid, and the free phenol extracted with ether. The crude product was crystallised several times from aqueous methanol (charcoal), from which the phenol separated in fluffy, somewhat discoloured needles, m. p. 169.5—171° (Zincke and Siebert, *loc. cit.*, describe the compound as colourless needles, m. p. 161°); yield, approx. 50% (Found: C, 67.2; H, 4.1. Calc. for  $C_{13}H_9O_2Cl$ : C, 67.1; H, 3.9%). The phenol dissolved easily in warm aqueous sodium carbonate.

Oxidation of the phenol in alkaline potassium permanganate solution gave *m*-chlorobenzoic acid, m. p. 153—155° after crystallisation from hot water.

**2:5-Dichloro-4'-hydroxybenzophenone** (VII;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = Cl$ ).—5-Chloro-2-amino-4'-hydroxybenzophenone (1 g.) was warmed with glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (1.5 c.c.), water (5 c.c.) being added to obtain complete solution. Diazotisation was effected at 5° with a solution of sodium nitrite (0.4 g.) in water (20 c.c.), starch-iodide paper being used as indicator. The clear solution was added during 10 minutes to a hot solution of cuprous chloride (2 g.) in concentrated hydrochloric acid (20 c.c.) and water (20 c.c.). The resultant suspension was boiled for 5 minutes, filtered cold, and the crude product recrystallised from aqueous methanol (charcoal), from which the *dichloro-phenol* separated in dense, brittle, yellow prisms, m. p. 171—172.5°; yield, 80%. The compound gave a deep brown solution with ferric chloride in alcohol, and dissolved in aqueous sodium carbonate (Found: C, 58.6; H, 2.9; Cl, 27.1.  $C_{13}H_8O_2Cl_2$  requires C, 58.4; H, 3.0; Cl, 26.6%).

In one of a number of preliminary attempts to prepare the above compound from the amino-benzophenone, the amount of sodium nitrite added was not rigidly controlled, but the other conditions were as described above. The major crystalline product in this case was a poor yield of a *substance* which crystallised from aqueous methanol in canary-yellow, hair-like needles, m. p. 224—226° (Found: N, 5.7; Cl, 15.8%).

**Oxidation of 2:5-Dichloro-4'-hydroxybenzophenone**.—A solution of the phenol (400 mg.) in 0.2N-sodium carbonate (20 c.c.) was mixed with 2% potassium permanganate solution (75 c.c.) and left over-night at 40—45°. The solution was filtered, concentrated, and acidified, and the precipitate collected. Some unchanged phenol (*ca.* 50 mg.) was removed by dissolving the crude product in ether and extracting the acid fraction with aqueous bicarbonate. The purified acid, after crystallisation from hot water, formed needles (150 mg.), m. p. 153—154° both alone and when mixed with authentic 2:5-dichlorobenzoic acid prepared by the method of Crauw (*Rec. Trav. chim.*, 1931, 50, 753). The identity of the acid was confirmed by the preparation of the *m*-nitroanilide (*via* the acid chloride in pyridine solution); this derivative separated from aqueous methanol in colourless needles, m. p. 151—152° both alone and when mixed with an authentic specimen (Found: N, 9.0; Cl, 22.4.  $C_{13}H_8O_3N_2Cl_2$  requires N, 9.0; Cl, 22.8%).

**5-Chloro-2-amino-4'-methoxybenzophenone** (VII;  $R_1 = R_3 = H$ ,  $R_2 = OMe$ ,  $R_4 = NH_2$ ).—5 G. of the anthroxan, m. p. 239—240°, were added to a solution of sodium (0.6 g.) in methanol (50 c.c.). The clear orange solution which soon formed was treated with a large excess (10 c.c.) of methyl iodide and heated under reflux. After  $\frac{1}{2}$  hour, crystalline material separated; this was redissolved by addition of benzene (25 c.c.), and refluxing continued for a further 3 hours. The solution was then concentrated, water added, and the whole extracted with ether. The extract was washed with dilute sodium hydroxide solution and water, dried, and evaporated. Crystallisation of the residue from acetone gave long, brittle, yellow needles (4.5 g.) of the *chloro-methoxyanthroxan*, m. p. 143—145° (Found: C, 65.35; H, 4.25.  $C_{14}H_{10}O_2NCl$  requires C, 64.7; H, 4.0%).

The above compound (4 g.) was dissolved in glacial acetic acid (40 c.c.) and reduced with iron filings (6 g.), as described for the methoxyanthroxan, m. p. 98° (*q.v.*), for 2½ hours. The product was isolated and crystallised first from aqueous methanol and then from a small volume of absolute methanol, from which the *amino-ketone* (3.5 g.) separated in dense yellow rhombs or prisms, m. p. 100—101° (Found: C, 64.1, 64.4; H, 4.9, 4.6.  $C_{14}H_{12}O_2NCl$  requires C, 64.2; H, 4.6%).

**$\alpha$ -(5-Chloro-2-aminophenyl)- $\alpha$ -(4'-hydroxyphenyl)ethylene** (V;  $R_1 = R_3 = H$ ,  $R_2 = OH$ ,  $R_4 = Cl$ ).—5-Chloro-2-amino-4'-hydroxybenzophenone was recovered unchanged after treatment with 3—4 equivalents of methylmagnesium iodide. Accordingly a solution of the ketone (10 g.) in ether (300 c.c.) was added to a Grignard solution prepared from magnesium (6.5 g.; 6.5 equivs.) and methyl iodide (40 g.) in ether (200 c.c.). A bright orange solid rapidly separated and methane was evolved. After 10 minutes, the solution was refluxed for 5 hours; it was then decomposed with ice and dilute hydrochloric acid, and the ethereal layer was washed,



dried, and evaporated. A solution of the residue in aqueous methanol deposited the *diaryl-ethylene* in faintly yellow cubes, which after several recrystallisations had m. p. 159°; yield, 6.7 g. (Found: C, 68.2; H, 4.8.  $C_{14}H_{12}ONCl$  requires C, 68.4; H, 4.9%). It was recovered unchanged after being refluxed with sulphuric acid of various concentrations up to 8N.

The *dibenzoyl* derivative, prepared with benzoyl chloride and pyridine, was somewhat sparingly soluble in methanol; it separated from this solvent in clusters of colourless prisms, and from aqueous acetone in very slender, prismatic needles, m. p. 130.5—132° in each case (Found: C, 73.9; H, 4.3.  $C_{28}H_{20}O_3NCl$  requires C, 74.0; H, 4.45%).

*6-Chloro-4-(4'-hydroxyphenyl)cinnoline*.—The suspension obtained by cooling a solution of the above aminoethylene (1 g.) in warm 2N-hydrochloric acid (60 c.c.) was treated at 5° with sodium nitrite (0.25 g. in 10 c.c. of water). After 1 hour, the precipitate was collected and dissolved in alcohol by the addition of ammonia, and the hot solution acidified with glacial acetic acid. The *cinnoline*, which separated on cooling, crystallised from slightly aqueous acetic acid in lustrous yellow plates with a red reflex, m. p. 257—259° (decomp.) (Found: C, 65.3; H, 3.5.  $C_{14}H_9ON_2Cl$  requires C, 65.5; H, 3.5%).

The *benzoate*, prepared by the usual method, crystallised from aqueous alcohol in small, pale yellow needles, m. p. 156° (Found: C, 69.8; H, 3.8; N, 7.8; Cl, 9.6.  $C_{21}H_{13}O_2N_2Cl$  requires C, 69.9; H, 3.6; N, 7.8; Cl, 9.85%).

*5-Chloro-2-amino-2'-hydroxy-5'-methylbenzophenone* (VII;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = NH_2$ ).—The anthroxan prepared from *p*-cresol and *o*-nitrobenzaldehyde melted at 208—209° (Zincke and Siebert, *loc. cit.*, give m. p. 210°). On reduction with iron and acetic acid under the conditions already described for the anthroxan, m. p. 240°, a 65% yield of the pure amino-ketone was obtained; this formed small dull yellow needles, m. p. 114—115°, from acetic acid (Zincke and Siebert give m. p. 115°). The sparingly soluble *dibenzoyl* derivative separated from benzene-alcohol in small stout needles, m. p. 156—157° (Found: C, 71.5; H, 4.4.  $C_{28}H_{20}O_4NCl$  requires C, 71.5; H, 4.3%). This derivative (380 mg.) was refluxed for 2 hours with 6 c.c. of 5% alcoholic potassium hydroxide, and the solution then concentrated, diluted with water, and made slightly acid with acetic acid; two crystallisations of the product from aqueous acetic acid gave the ketone, m. p. and mixed m. p. 114°.

*2:5-Dichloro-2'-hydroxy-5'-methylbenzophenone* (VII;  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = Cl$ ).—The foregoing amino-ketone (3 g.) was dissolved in warm glacial acetic acid (40 c.c.) and concentrated hydrochloric acid (5 c.c.) and cooled to 5—10°, and the suspension diazotised with sodium nitrite (1 g. in 50 c.c. of water). The solution, containing an appreciable flocculent precipitate, was added during 10 minutes to a hot solution of cuprous chloride (6 g.) in concentrated hydrochloric acid (60 c.c.) and water (50 c.c.); the suspension was then boiled for a few minutes and cooled. The product, crystallised twice from alcohol (charcoal), yielded the *dichloro-compound* in long yellow needles (2 g.), m. p. 149—150°, insoluble in aqueous sodium carbonate and only moderately soluble in hot alcohol (Found: C, 60.1; H, 3.6; Cl, 24.8.  $C_{14}H_{10}O_2Cl_2$  requires C, 59.75; H, 3.6; Cl, 25.25%).

A suspension of the dichloro-phenol in aqueous sodium carbonate was oxidised by essentially the same procedure as that described for the oxidation of 2:5-dichloro-4'-hydroxybenzophenone. The resultant 2:5-dichlorobenzoic acid (250 mg. from 1 g. of the phenol) had m. p. and mixed m. p. 153—154°, and the identification was confirmed by its conversion into the *m*-nitroanilide, m. p. and mixed m. p. 151—152°. (When freshly prepared, the *m*-nitroanilide frequently shows a double melting point, melting at 138—139° to a vitreous mass which on further heating becomes opaque and then melts sharply at 151—152°.)

*5-Chloro-2-amino-2'-methoxy-5'-methylbenzophenone* (VII;  $R_1 = OMe$ ,  $R_2 = H$ ,  $R_3 = Me$ ,  $R_4 = NH_2$ ).—The anthroxan (2 g.), m. p. 208—209°, was added to a solution of sodium (0.2 g.) in methanol (35 c.c.) and refluxed with methyl iodide (3 c.c.) for 1½ hours. After dilution with water the crystalline precipitate obtained on scratching was twice recrystallised from aqueous methanol, the *methoxy-anthroxan* forming elongated yellow laminae, m. p. 96—98°; more was obtained from the mother-liquors after removal of unmethylated anthroxan with dilute sodium hydroxide solution; total yield, 75% (Found: C, 65.6; H, 4.1; Cl, 12.7.  $C_{15}H_{13}O_2NCl$  requires C, 65.8; H, 4.4; Cl, 13.0%).

A solution of the methoxy-anthroxan (1.25 g.) in glacial acetic acid (12.5 c.c.) was heated on the water-bath with iron filings (2 g.), added during 1½ hours; water (4 c.c.) was added after the reduction had been in progress for 10 minutes. After 1½ hours the solution was largely diluted with water and extracted with ether. The filtered extract was washed with sodium carbonate solution and water, dried, and evaporated. A solution of the residue in aqueous methanol yielded the *amino-ketone* in small, dull yellow prisms, m. p. 100—101°, strongly depressed by the parent anthroxan (Found: C, 65.5; H, 5.1.  $C_{16}H_{14}O_2NCl$  requires C, 65.3; H, 5.1%).

The ketone did not form a semicarbazone under the ordinary conditions, but yielded an *N*-*acetyl* derivative, which separated from aqueous methyl alcohol in cream-coloured, brittle, prismatic needles, m. p. 136—137° (Found: C, 64.7; H, 5.2.  $C_{17}H_{16}O_2NCl$  requires C, 64.2; H, 5.1%).

*α-(5-Chloro-2-aminophenyl)-α-(2'-hydroxy-5'-methylphenyl)ethylene and Derivatives*.—A solution of 5-chloro-2-amino-2'-hydroxy-5'-methylbenzophenone (12 g.) in ether (400 c.c.) was refluxed with an ethereal solution of methylmagnesium iodide (from 7.2 g. of magnesium and 45 g. of methyl iodide) for 5 hours. The product was worked up in the usual way, yielding a brown viscous residue (13 g.). Portions of this material were treated as follows:

(i) When the resin was heated with its own weight of pyridine and of benzoyl chloride at 100° for 3 hours, it was converted into a crystalline *dibenzoyl* derivative, which separated from methanol in colourless prisms, m. p. 119° (Found : C, 74·4; H, 4·85.  $C_{29}H_{22}O_3NCl$  requires C, 74·4; H, 4·75%). The dibenzoyl derivative (9·5 g.) was refluxed for 2 hours with potassium hydroxide (5·5 g.) in water (20 c.c.) and alcohol (40 c.c.), the solution concentrated, and water added. A solution of the copious white precipitate (presumably potassium salt) produced in hot alcohol was neutralised with sulphuric acid, diluted with water, and extracted with ether, furnishing a clear brown resin. A part of this (1·28 g.) on treatment with pyridine (2 c.c.) and benzoyl chloride (1·3 c.c.) at 100° gave a *compound* which was not identical with the original dibenzoyl derivative; it was very sparingly soluble in ether and in methyl and ethyl alcohols, and separated from benzene-alcohol in fine colourless needles, m. p. 235° (Found : C, 75·45; H, 4·67; N, 2·4; Cl, 6·55.  $C_{36}H_{26}O_4NCl$  requires C, 75·6; H, 4·6; N, 2·45; Cl, 6·2%).

(ii) A solution of the crude resin in hot methanol was filtered (charcoal) and warmed with dilute hydrochloric acid. On cooling, pale yellow prismatic needles of the *hydrochloride* separated. This, dissolved in aqueous methanol and reprecipitated with concentrated hydrochloric acid, formed pale yellow prisms, m. p. 222—223° (decomp.) (Found : Cl, 23·5.  $C_{15}H_{14}ONCl$ , HCl requires Cl, 24·0%).

The base was obtained from the hydrochloride by addition of a slight excess of ammonia to its solution in aqueous methanol. After being warmed on the water-bath for 10 minutes, the solution was cooled and extracted with ether. Concentration of the dried extract to a small volume and addition of ligroin (b. p. 40—60°) precipitated some resin, followed by crystalline material. The latter was repeatedly crystallised from ether-ligroin, from which the *diarylethylene* separated in clusters of cream-coloured prismatic needles, m. p. 108° (yield, ca. 50%) (Found : C, 69·05; H, 5·4.  $C_{15}H_{14}ONCl$  requires C, 69·3; H, 5·4%).

6-Chloro-4-(2'-hydroxy-5'-methylphenyl)cinnoline.—A suspension of the above hydrochloride (2·5 g.) in dilute hydrochloric acid (150 c.c.) was cooled to 0°, and a solution of sodium nitrite (0·63 g.) in water (10 c.c.) added slowly with mechanical stirring. The precipitate was collected after 1 hour and purified exactly as described for 6-chloro-4-(4'-hydroxyphenyl)cinnoline. The pure *cinnoline* formed small, golden, prismatic needles (0·9 g.), m. p. 260—261° (decomp.) (Found : C, 66·7; H, 4·2; N, 10·2.  $C_{15}H_{11}ON_2Cl$  requires C, 66·5; H, 4·1; N, 10·35%). The compound was also obtained by the action of hydrochloric acid and sodium nitrite on the crude resinous diaryl-ethylene. Like the analogue already described, this hydroxy-cinnoline is very sparingly soluble in both cold and hot alcohol, benzene, and ethyl acetate.

Treatment of the cinnoline (0·4 g.) with benzoyl chloride (0·25 g.) and pyridine (1 c.c.) at 100° for 2 hours produced some decomposition and gave only a poor yield (30%) of the *benzoate*; this was very soluble in methyl alcohol, and formed yellow prisms, m. p. 140°, from ether-ligroin (Found : C, 69·9; H, 4·0.  $C_{22}H_{15}O_2N_2Cl$  requires C, 70·5; H, 4·0%).

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