

**802. Some Properties and Reactions of Quinoline-5 : 8-quinones.**

By R. LONG and K. SCHOFIELD.

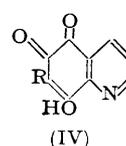
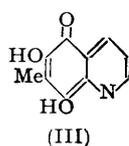
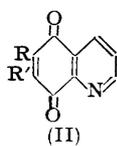
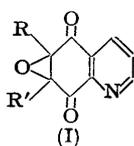
6- and 7-Alkylquinoline-5 : 8-quinones gave, with hydrogen peroxide, epoxides which were converted into 6-alkyl-7-hydroxy- and 7-alkyl-6-hydroxy-quinoline-5 : 8-quinones respectively.

6- and 7-Chloro- and 6 : 7-dichloro-5 : 8-dihydroxyquinoline have been prepared.

The dibromide formed from bromine and quinoline-5 : 8-quinone could not be obtained pure. The same quinone formed with aniline both of the possible anilinoquinones.

The ultra-violet light extinction curves of a number of quinoline-5 : 8-quinones have been obtained, and are discussed with regard to the postulated structure of the compounds.

WE have described the preparation of quinoline-5 : 8-quinone and a number of its alkyl derivatives (as II) (Long and Schofield, *J.*, 1953, 3161). In the present paper are described some experiments made with these compounds.



Since the presence of a hydroxyl group in position C<sub>6</sub> of certain 3-alkylnaphtha-1 : 4-quinones has been associated with antimalarial action (Fieser *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3151 *et seq.*) we examined the formation of similar derivatives from quinoline-5 : 8-quinones. In alcoholic solution a number of these quinones were readily converted by hydrogen peroxide in dilute sodium carbonate solution into 6 : 7-epoxy-6 : 7-dihydroquinoline-5 : 8-quinones (I) : these were appreciably soluble in water, and (I; R = H, R' = Me; and R = Bu, R' = H) were obtained as hydrates. With quinoline-5 : 8-quinone itself hydrogen peroxide produced a deep red colour, but an epoxide could not be isolated. [Cf. 2 : 3-epoxy-2 : 3-dihydronaphtha-1 : 4-quinone which is too alkalisensitive to be obtained by this method (Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165) ]

In contrast to the parent quinones (Long and Schofield, *loc. cit.*) the epoxides were all colourless, sharply melting compounds. Like 2 : 3-epoxy-2 : 3-dihydro-2-methylnaphtha-1 : 4-quinone (Madinaveitia, *Anal. Fis. Quim.*, 1933, **31**, 750) the heterocyclic compounds (I) possessed marked sternutatory and skin-irritant properties.

With aqueous ammonia the epoxy-compounds slowly formed dark-red solutions, and

from such a reaction with (I; R = H, R' = Me) a small yield of 6-hydroxy-7-methylquinoline-5 : 8-quinone (II; R = OH, R' = Me) was isolated. Such hydroxy-compounds were obtained in high yields by treatment of the epoxides with cold concentrated sulphuric acid. Physically they resembled the parent quinones rather than the epoxides, and like the hydroxynaphthaquinones (Ettlinger, *J. Amer. Chem. Soc.*, 1950, **72**, 3085), gave an immediate red colour with alkali.

In the presence of palladium-charcoal, a methanolic solution of 6 : 7-epoxy-6 : 7-dihydro-7-methylquinoline-5 : 8-quinone absorbed hydrogen very slowly and the originally colourless solution became green. When exposed to air the green solution became dark red, and 6-hydroxy-7-methylquinoline-5 : 8-quinone was isolated. This isomerisation was not effected by the catalyst without hydrogen. Prolonged hydrogenation gave a different product, probably 5 : 6 : 8-trihydroxy-7-methylquinoline. The colour changes probably indicate the intermediate formation of a semiquinone (III), stabilised by the presence of the heterocyclic nitrogen atom.

We next examined the action of hydrogen chloride on quinoline-5 : 8-quinone in carbon tetrachloride. The bright yellow product contained ionic chlorine, and from it was isolated (after exposure for some time to the atmosphere) 6 : 7-dichloro-5 : 8-dihydroxyquinoline. Treating the quinone with concentrated hydrochloric acid gave a mixture of chlorides from which was isolated 6(or 7)-chloro-5 : 8-dihydroxyquinoline, characterised as its diacetate, and in which the presence of the alternative 7(or 6)-isomer was demonstrated by the separation of a second diacetate. The difference thus observed between the action of hydrogen chloride and of (aqueous) hydrochloric acid is striking; since the formation in the former reaction of 6 : 7-dichloro-5 : 8-dihydroxyquinoline must proceed through the production and oxidation of 6(or 7)-chloro-5 : 8-dihydroxyquinoline the fact that the initial product was not examined until after some exposure to the atmosphere may be significant. Moness and Christiansen (*J. Amer. Pharm. Assoc.*, 1934, **23**, 228) obtained impure mono- and di-chloro-5 : 8-dihydroxyquinolines by chlorinating the dihydroxy-compound. Fischer and Renouf (*Ber.*, 1884, **17**, 1642) claimed to have isolated the hydrochloride of quinoline-5 : 8-quinone by treating the latter with 25% hydrochloric acid. Our experiments render doubtful the supposed character of their product. 7-Methylquinoline-5 : 8-quinone gave with hydrochloric acid the (hydrated) hydrochloride of 6-chloro-5 : 8-dihydroxy-7-methylquinoline, from which the base was isolated and characterised as its diacetate.

With bromine in acetic acid or carbon tetrachloride quinoline-5 : 8-quinone gave the impure dibromide. The composition of the product varied appreciably, depending on the solvent used in recrystallisation; thus, aqueous methanol evidently caused some dehydrobromination. Bromine in carbon tetrachloride converted 7-methylquinoline-5 : 8-quinone into its highly crystalline dibromide.

From the reaction between aniline and quinoline-5 : 8-quinone in ethanol Fischer and Renouf (*loc. cit.*) isolated 6(or 7)-anilinoquinoline-5 : 8-quinone. Re-investigation has disclosed that both possible products of this reaction, (II; R = Ph·NH, R' = H; and R = H, R' = Ph·NH), are actually formed, the earlier workers having overlooked the more soluble isomer. Under similar conditions (II; R = Ph·NH, R' = Me) and (II; R = Ph·NH, R' = Pr) were obtained from 7-methyl- and 7-propylquinoline-5 : 8-quinone.

The availability of a range of quinoline-5 : 8-quinones and related compounds made it of interest to examine the ultra-violet light absorption of these compounds. Such examination would provide useful confirmation of the *p*-quinone structure (Long and Schofield, *loc. cit.*). Other workers (Macbeth, Price, and Winsor, *J.*, 1935, 325; Braude, *J.*, 1945, 490) have established the presence in the ultra-violet light extinction curves of all simple *p*-benzo- and naphtha-1 : 4-quinones of a high-intensity peak at about 2400 Å (log  $\epsilon$  4.2). An inflexion discernible in this peak is accentuated by the introduction of alkyl groups. Naphtha-1 : 4-quinones possess a characteristic broad, medium-intensity band ( $\lambda$  3330 Å), not shown by *p*-benzoquinones.

The extinction curve of quinoline-5 : 8-quinone (Fig. 1) displays a high-intensity peak ( $\lambda$  2380 Å, log  $\epsilon$  4.28) which obviously corresponds to that mentioned above for

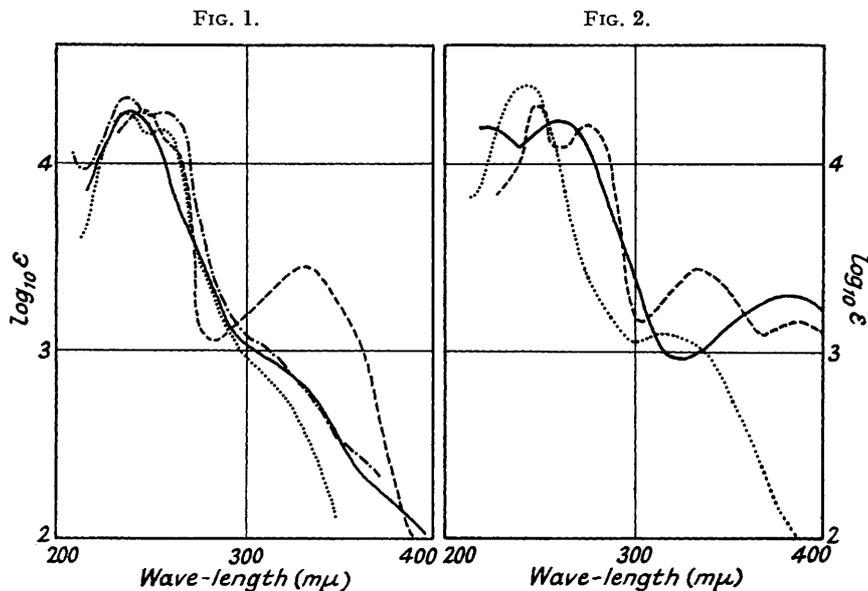


FIG. 1. ————— Quinoline-5 : 8-quinone.  
 - - - - - Naphtha-1 : 4-quinone (Macbeth *et al.*, *loc. cit.*).  
 . . . . . 6-Ethylquinoline-5 : 8-quinone.  
 - · - · - 7-Butylquinoline-5 : 8-quinone.

FIG. 2. ————— 6-Hydroxy-7-methylquinoline-5 : 8-quinone.  
 - - - - - Phthiocol (Crowe, *loc. cit.*).  
 . . . . . 2-Methylquinoline-5 : 8-quinone.

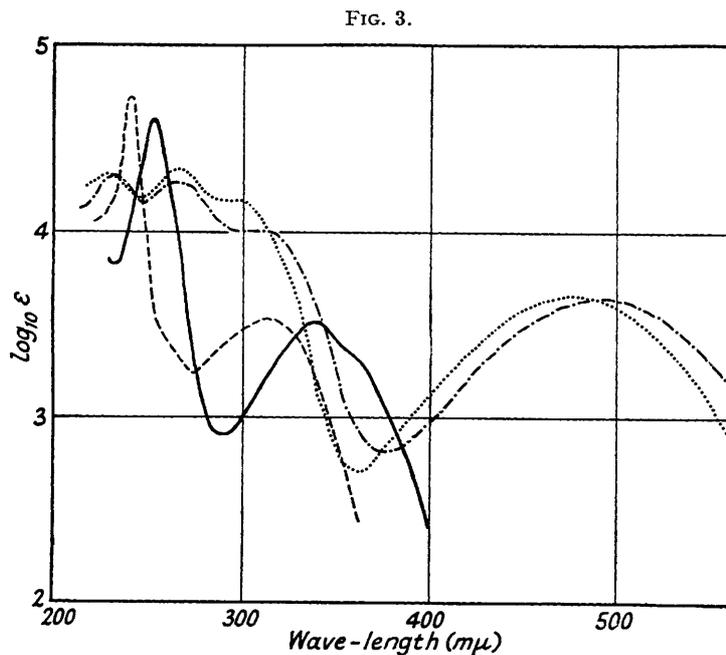


FIG. 3. ————— 6(or 7)-Chloro-5 : 8-dihydroxyquinoline.  
 - - - - - 8-Hydroxyquinoline.  
 . . . . . 6(or 7)-Anilinoquinoline-5 : 8-quinone.  
 - · - · - 6-Anilino-7-methylquinoline-5 : 8-quinone.

*p*-benzo- and naphtha-1 : 4-quinone, but which has suffered a small hypsochromic shift. There is also a faint suggestion of an inflexion at about 2475 Å, and a marked one at 2975 Å. Quinones with alkyl groups in the quinone ring have very similar extinction curves, but the first inflexion is now developed into a distinct maximum, behaviour paralleled to a less marked extent by *p*-benzo- and naphtha-1 : 4-quinones. An alkyl group in the heterocyclic ring (Fig. 2) produces a marked effect, removing the hypsochromic shift in the high-intensity peak and raising the latter's intensity, but most strikingly generating a broad, medium-intensity band (3150 Å, log  $\epsilon$  3.1) recalling that characteristic of naphtha-1 : 4-quinones. It is suggested that the alkyl groups in 2-methyl- and 2 : 4-dimethylquinoline-5 : 8-quinone compensate for the electronegativity of the nitrogen atom, and restore the system more nearly in spectroscopic character to that of naphtha-1 : 4-quinone. Thus, the second inflexion (2975 Å) observed with quinoline-5 : 8-quinone and its 6- and 7-alkyl derivatives may be identified as the broad, medium-intensity peak of 2-methyl- and 2 : 4-dimethylquinoline-5 : 8-quinone, removed to shorter wave-lengths and merged into the descending slope of the main peak by the electron-attracting power of the nitrogen atom.

Since no doubt attaches to the structure of 6- and 7-methyl- and 7-ethyl-quinoline-5 : 8-quinone (Long and Schofield, *loc. cit.*), the close similarity of all the extinction curves for our series of 6- and 7-alkyl homologues (up to butyl), and their rational relation to that for naphtha-1 : 4-quinone indicate that all these compounds are indeed quinoline-5 : 8-quinones, and further support the assumed orientation of the alkyl-nitroquinolines (Long and Schofield, *J.*, 1953, 3161) used in their synthesis.

The extinction curve for phthiocol (Crowe, *J. Biol. Chem.*, 1936, 115, 479) resembles the curves obtained for 7-alkyl-6-hydroxyquinoline-5 : 8-quinones, both possessing a broad maximum (*ca.* 3850 Å) (Fig. 2). This is possibly related to the ability of these compounds to assume the tautomeric *o*-quinonoid structure (IV); a band in this position occurs with *o*-benzoquinone and naphtha-1 : 2-quinone (Goldschmidt and Graef, *Ber.*, 1928, 61, 1858) and Macbeth *et al.* (*loc. cit.*) considered this to be a criterion of the 1 : 2-structure.

The extinction curves for the anilino-derivatives (Fig. 3) do not show any simple relation to those of the alkyl compounds, their predominant feature being the visible absorption responsible for the colour of these derivatives. The structures of the compounds obtained by the action of hydrochloric acid on quinoline-5 : 8-quinone are clearly indicated by the relation between their extinction curves and that of 8-hydroxyquinoline (Fig. 3).

The bacteriostatic properties of some of the compounds now described will be reported later.

#### EXPERIMENTAL

6 : 7-Epoxy-6 : 7-dihydroquinoline-5 : 8-quinones.—(i) To a suspension of 7-methylquinoline-5 : 8-quinone (1 g.) in alcohol (10 c.c.) a cooled solution of hydrogen peroxide (1 c.c.; 30%) and sodium carbonate (0.2 g. of anhydrous) in water (5 c.c.) was added. The initial brown colour was discharged. Pouring into iced water gave no precipitate, but ether removed from this solution the substantially pure product (0.85 g.).

(ii) When in a similar experiment the undiluted reaction mixture was cooled in ice the product (0.6 g.) separated. The *epoxide hemihydrate* separated from ether in star-shaped clusters of crystals. See section A of the Table, where these and other epoxides are described.

6- and 7-Hydroxyquinoline-5 : 8-quinones.—The epoxy-compound (0.5 g.) and concentrated sulphuric acid (10 c.c.) were set aside for 5 days. The deep red-brown solution was then diluted with water, and aqueous ammonia was added until the colour became faintly red. The product was extracted with chloroform. See section B of the Table.

*Reduction of 6 : 7-Epoxy-6 : 7-dihydroquinoline-5 : 8-quinone.*—The epoxide (0.25 g.) in methanol (25 c.c.) was shaken with palladium-charcoal (0.1 g.) and hydrogen for 30 hr. Very slow continuous absorption occurred, and the solution, originally colourless, became olive-green. Filtration and concentration gave dark red crystals. Crystallisation from benzene gave yellowish-brown crystals of 6-hydroxy-7-methylquinoline-5 : 8-quinone, m. p. 232—234° (decomp.) (Found : C, 63.3; H, 3.7%).

Repetition of the experiment with 0.65 g. of epoxide for 100 hr. gave a red solid (0.55 g.). Crystallisation from benzene-pyridine gave dark reddish crystals of 5 : 6 : 8-*trihydroxy-7-methylquinoline*, which when dried formed a light yellow powder, m. p. 240° (decomp.) (Found : C, 62.8; H, 3.8.  $C_{10}H_9O_3N$  requires C, 62.8; H, 4.7%).

6 : 7-*Dichloro-5 : 8-dihydroxyquinoline*.—The quinone (0.5 g.) in carbon tetrachloride (30 c.c.) was treated with hydrogen chloride for several minutes. After several days the precipitate (0.8 g.) was collected. Crystallisation from methanol-ether gave a yellow granular solid,

Substi- tuent	Yield (%)	Solvent <sup>6</sup>	Form	M. p.	Formula	Found, % C H	Reqd., % C H
(A) 6 : 7- <i>Epoxy-6 : 7-dihydroquinoline-5 : 8-quinones</i> .							
6-Methyl <sup>1</sup> ...	72	Et <sub>2</sub> O	Granular <sup>3</sup>	149—150°	C <sub>10</sub> H <sub>7</sub> O <sub>3</sub> N	63.4 3.85	63.5 3.75
7-Methyl <sup>1</sup> ...	80	"	Needles	123—124	"	63.3 4.0	60.6 4.1
" <sup>2</sup> ...	55	"	Prisms	118—120 <sup>4</sup>	C <sub>10</sub> H <sub>7</sub> O <sub>2</sub> N, $\frac{1}{2}$ H <sub>2</sub> O	59.8 4.1	60.6 4.1
7-Propyl <sup>2</sup> ...	83	"	Granular	87	C <sub>12</sub> H <sub>11</sub> O <sub>5</sub> N, $\frac{3}{4}$ H <sub>2</sub> O	62.0 4.9	62.5 5.5
6-Butyl <sup>1</sup> ...	95	Et <sub>2</sub> O-Pet	" <sup>3</sup>	64—65	C <sub>13</sub> H <sub>13</sub> O <sub>3</sub> N, $\frac{3}{4}$ H <sub>2</sub> O	63.8 5.5	63.8 5.7
(B) 6- or 7- <i>Hydroxyquinoline-5 : 8-quinones</i> .							
7-Methyl ...	65	Benzene	Yellow- brown plates	230—235 (decomp.)	C <sub>10</sub> H <sub>7</sub> O <sub>3</sub> N	64.1 3.8	63.5 3.7
7-Propyl ...	70	Et <sub>2</sub> O-Pet	Yellow needles	149—150	C <sub>12</sub> H <sub>11</sub> O <sub>3</sub> N	65.9 5.2	66.4 5.1
6-Butyl <sup>5</sup> ...	63	"	Yellow blades	116—117	C <sub>13</sub> H <sub>9</sub> O <sub>3</sub> N	67.1 5.8	67.5 5.7

<sup>1</sup> Method (i). <sup>2</sup> Method (ii). <sup>3</sup> Initially pale yellow oils, which were only induced to crystallise by being cooled in liquid air. <sup>4</sup> Mixed m. p. of hemihydrate and anhydrous form, 110—116°.

<sup>5</sup> Obtained as a dark oil which slowly deposited crystals. <sup>6</sup> Pet = light petroleum, b. p. 40—60°.

apparently a hydrated *salt* (Found : C, 39.3; H, 3.3; Cl, 30.1.  $C_9H_5O_2NCl_2 \cdot 0.5HCl \cdot 1.5H_2O$  requires C, 39.3; H, 3.1; Cl, 32.2%) which decomposed at about 200°. After being exposed to the air for several weeks a solution of this salt (0.5 g.) in water (500 c.c.) (the solution gave a positive test for ionic chlorine) was extracted with chloroform. Several recrystallisations of the product (0.25 g.) from ether-light petroleum (b. p. 40—60°) gave soft, light purple needles of 6 : 7-*dichloro-5 : 8-dihydroxyquinoline*, m. p. 157—158° (Found : C, 46.8; H, 2.1; Cl, 30.1.  $C_9H_5O_2NCl_2$  requires C, 47.0; H, 2.2; Cl, 30.8%).

*Reaction of Quinoline-5 : 8-quinone with Hydrochloric Acid*.—The quinone (2 g.) was boiled with concentrated hydrochloric acid (20 c.c.) for 5 min. The precipitate (2.5 g.) which separated on cooling formed yellow granules of mixed hydrated hydrochlorides (Found : C, 44.8; H, 3.7; N, 5.4; Cl, 27.5. Calc. for  $C_9H_{16}O_2NCl \cdot \frac{1}{2}H_2O$  : C, 44.8; H, 3.4; N, 5.8; Cl, 29.4%) when crystallised from methanol-ether. The chloroform extract of a solution of this salt (1.2 g.) in water (1.5 l.), when concentrated to 75 c.c., gave long needles (0.1 g.) of (6 or 7)-*chloro-5 : 8-dihydroxyquinoline*, m. p. 164° (Found : C, 55.0; H, 3.4.  $C_9H_6O_2NCl$  requires C, 55.3; H, 3.1%). Further concentration gave material (0.5 g.), m. p. 150—162°, and finally a residue (0.15 g.), m. p. 148—158°. When a portion of the second crop (0.15 g.) had been heated with acetic anhydride at 95° for  $\frac{1}{2}$  hr., dilution gave a solid (0.18 g.), which after crystallisation from ether-light petroleum (b. p. 40—60°) was separated manually into two types of crystals. One of these gave from ether-light petroleum spiky prisms of 5 : 8-*diacetoxy-6(or 7)-chloroquinoline*, m. p. 130—131° (Found : C, 55.5; H, 3.6; Cl, 12.5.  $C_{13}H_{10}O_4NCl$  requires C, 55.8; H, 3.6; Cl, 12.7%), identical with material obtained similarly from 6(or 7)-*chloro-5 : 8-dihydroxyquinoline*, m. p. 164°, and the other provided soft, feathery needles of 5 : 8-*diacetoxy-7(or 6)-chloroquinoline*, m. p. 159—161° (Found : C, 55.4; H, 3.6%), from the same solvent.

6-*Chloro-5 : 8-dihydroxy-7-methylquinoline*.—7-Methylquinoline-5 : 8-quinone (1.5 g.) was boiled with concentrated hydrochloric acid (15 c.c.) for 5 min. After several days the precipitate (1.6 g.) was collected. Crystallisation from methanol-ether gave bright yellow needles of the (probably hydrated) hydrochloride, m. p. 225° (decomp.) (Found : C, 46.1; H, 4.2; N, 5.5; Cl, 26.3. Calc. for  $C_{10}H_8O_2NCl \cdot HCl$  : C, 48.8; H, 3.7; N, 5.7; Cl, 28.8%). Concentration of the chloroform extract of a solution of the hydrochloride (1.25 g.) in water (800 c.c.) gave needles [0.7 g.; m. p. 165—166° (decomp.)], which appeared purple when collected. Less pure material remained in solution. 6-*Chloro-5 : 8-dihydroxy-7-methylquinoline* formed faintly purple needles, m. p. 167—168° (Found : C, 56.4; H, 4.0; Cl, 16.9.  $C_{10}H_8O_2NCl$  requires C, 57.3; H, 3.9; Cl, 16.9%), from ether-light petroleum (b. p. 40—60°). 5 : 8-*Di-*

*acetoxy-6-chloro-7-methylquinoline* formed needles, m. p. 209—210° (Found: C, 57.2; H, 4.0.  $C_{14}H_{12}O_4NCl$  requires C, 57.2; H, 4.1%), from the same solvent.

*Bromination of Quinoline-5:8-quinone.*—(For a full description see Long, Thesis, London, 1953. The following illustrates the type of behaviour encountered.) The quinone (0.5 g.) in carbon tetrachloride (25 c.c.) gave with bromine (0.2 c.c.) a deep red solution. With the separation of a yellow solid (0.95 g.) the colour disappeared, and recrystallisation of the product from aqueous methanol gave dull yellow crystals, m. p. *ca.* 240° (decomp.) (Found: C, 35.8; H, 1.0; Br, 50.1. Calc. for  $C_9H_5O_2NBr_2$ : C, 33.9; H, 1.6; Br, 50.1%). Crystallisation of the product from an identical experiment from methanol-light petroleum gave ochre granules, decomp. >300° (Found: C, 32.0; H, 1.7; Br, 51.7%), and this material formed from aqueous methanol a yellow-brown solid, m. p. *ca.* 220° (Found: C, 38.6; H, 1.5%).

When 7-methylquinoline-5:8-quinone was similarly brominated, removal of the precipitate and concentration of the filtrate provided pale yellow prisms which were recrystallised from ether-light petroleum, to give slightly impure 6:7-dibromo-6:7-dihydro-7-methylquinoline-5:8-quinone, m. p. 120° (Found: C, 38.4; H, 2.4; N, 5.2. Calc. for  $C_{10}H_7O_2NBr_2$ : C, 36.2; H, 2.1; N, 4.2%).

The addition of sodium acetate to the reaction solution during the bromination of quinoline-5:8-quinone gave a product intermediate in composition between a mono- and the di-bromo-compound.

*Anilinoquinoline-5:8-quinones.*—Quinoline-5:8-quinone (4 g.), aniline (4 g.), and ethanol (60 c.c.) gave a deep red solution which was boiled for  $\frac{1}{2}$  hr. After 24 hr. acetic acid (5 c.c.) was added and dilution with water gave a red solid (3.9 g.). Crystallised from ethanol this gave as the less soluble component 6(or 7)-anilinoquinoline-5:8-quinone (1.2 g.) [dark red needles (with a copper sheen), m. p. 212° (Found: C, 67.9; H, 4.4. Calc. for  $C_{15}H_{10}O_2N_2, H_2O$ : C, 67.2; H, 4.5%); Fischer and Renouf (*loc. cit.*) gave m. p. >190°], and as the more soluble isomer 7(or 6)-anilinoquinoline-5:8-quinone, which formed long red-black needles, m. p. 180—182° (Found: C, 70.5; H, 3.9.  $C_{15}H_{10}O_2N_2, \frac{1}{2}H_2O$  requires C, 70.8; H, 3.9%), from methanol-ether-light petroleum.

6-Anilino-7-methylquinoline-5:8-quinone.—7-Methylquinoline-5:8-quinone (1.7 g.), aniline (2.7 g.), and ethyl alcohol (30 c.c.), treated as above, gave by dilution after several days a red-black tar. This was set aside for some time, the aqueous layer was decanted, and the residue was crystallised from ether-light petroleum. 6-Anilino-7-methylquinoline-5:8-quinone formed crisp, dark-red needles (with a metallic sheen), m. p. 167—169° (Found: C, 72.7; H, 4.2.  $C_{16}H_{12}O_2N_2$  requires C, 72.7; H, 4.6%). The *hydrate* separated from ethanol-ether as dark red crystals, m. p. 180° (Found: C, 68.1; H, 4.1.  $C_{16}H_{12}O_2N_2, H_2O$  requires C, 68.1; H, 5.0%).

6-Anilino-7-propylquinoline-5:8-quinone.—Obtained as above, this *quinone* separated as dark red plates, m. p. 157—158° (Found: C, 72.6; H, 5.6.  $C_{18}H_{10}O_2N_2, \frac{1}{2}H_2O$  requires C, 72.5; H, 5.5%), from ether-light petroleum.

*Ultra-violet Light Absorption Data.*—Extinction curves obtained for 6- and 7-methyl-, 7-ethyl-, 6- and 7-propyl-, 6-butyl-, 2:4-dimethyl-, and 6-hydroxy-7-propyl-quinoline-5:8-quinone, and 6-chloro-5:8-dihydroxy-7-methylquinoline, closely resembled those of analogous compounds figured above. For details see Long, Thesis, London, 1953.

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