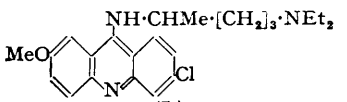
634. *Some* 4-(*Dialkylaminoalkylamino*)-3-*phenylquinolines.*

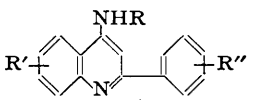
By (Mrs.) W. J. Adams and D. H. Hey.

A series of 4-hydroxy-3-phenylquinolines has been prepared by the reaction of an aromatic amine with ethyl formylphenylacetate and subsequent cyclisation of the resulting ethyl β-arylamino-α-phenylacrylate. The nature of the by-products formed in these reactions, and the experimental conditions necessary for optimum yields were investigated. The 4-hydroxy-3-phenylquinolines were converted into the 4-chloro-3-phenylquinolines and thence into 4-(dialkylaminoalkylamino)-3-phenylquinolines, which were isolated and characterised as dipicrates.

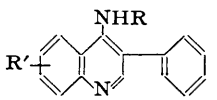
In numerous previous communications on synthetic antimalarial compounds considerable attention has been devoted to the preparation of *p*-chloroanilino-(dialkylaminoalkylamino)-quinolines. It appeared to be of interest to survey a series of compounds in which the *p*-substituted anilino-group was replaced by a phenyl or a substituted phenyl group, because such a study should throw light on the significance of the –NH– group interposed between the two nuclei, and in addition such compounds could be regarded as " open models " of the mepacrine molecule (I). Gilman and his co-workers (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1944, **66**, 621; Gilman, Christian, and Spatz, *ibid.*, 1946, **68**, 979; Gilman, Towle, and Spatz, *ibid.*, 1946, **68**, 2017; Gilman and Benkeser, *ibid.*, 1947, **69**, 123) have prepared a series of derivatives of 2-phenylquinoline. In such compounds one of the fused rings of the mepacrine molecule is replaced by a substituted phenyl group at the 2-position, as in (II).



(I.)



(II.)

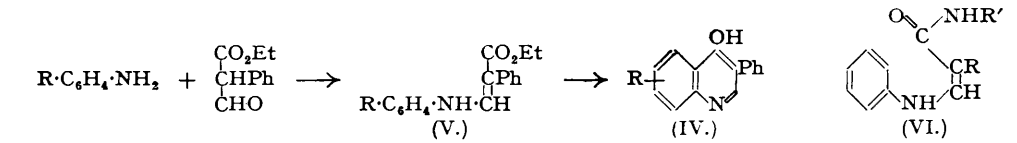


(III.)

The preparation of a series of compounds similarly derived by replacement of one of the fused rings by a phenyl group at the 3-position in the quinoline nucleus as in (III) is now described. Some compounds of this type have been prepared previously and have been shown to possess some antimalarial activity. Andersag, Breitner, and Jung (G.P. 683,692) prepared 7-chloro- and 5 : 7-dichloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline and 7-chloro-4-(2-diethylaminoethylamino)-3-phenylquinoline by treatment of the appropriate 4-amino-3-phenylquinoline with the dialkylaminoalkyl halide. Drake, Creech, Garman, Haywood, Peck, Van Hook, and Walton (*J. Amer. Chem. Soc.*, 1946, **68**, 1208) obtained 7-chloro-4-(4-diethyl-

amino-1-methylbutylamino)-3-phenylquinoline by the reaction of 4-diethylamino-1-methylbutylamine with 4 : 7-dichloro-3-phenylquinoline. The latter method was used in the present work, in view of the availability of 4-hydroxy-3-phenylquinolines and hence of 4-chloro-3-phenylquinolines.

A series of 4-hydroxy-3-phenylquinolines (IV) was prepared by the cyclisation in boiling phenyl ether of the ethyl β-arylamino-α-phenylacrylates (V) obtained from the condensation of the appropriately substituted amine with ethyl formylphenylacetate, as described by Elderfield and Wright (*J. Amer. Chem. Soc.*, 1946, **68**, 1276) for the reactions with aniline and



m-chloroaniline. This reaction has now been applied, in addition, to *o*- and *p*-nitroaniline, *o*- and *p*-chloroaniline, *p*-bromoaniline, and *p*-anisidine. The yields of these 4-hydroxy-3-phenylquinolines varied from 21% for *p*-anisidine to 55% for *p*-nitroaniline (see Table I). The successful use of the nitroanilines in this reaction is of some interest, because it has been reported that nitroanilines or substituted nitroanilines condense either with difficulty, or not at all, with β-ketonic esters (Coffey, Thomson, and Wilson, *J.*, 1936, 856; Misani and Bogert, *J. Org. Chem.*, 1945, **10**, 352; Kaslow and Stayner, *J. Amer. Chem. Soc.*, 1948, **70**, 3350; Halcrow and Kermack, *J.*, 1945, 415; Adams and Hey, *J.*, 1950, 2092).

In an attempt to establish the conditions necessary to give the maximum yield in these reactions, the effect of variations in experimental conditions was investigated. It was found that it was necessary to use pure ethyl formylphenylacetate free from phenylacetic acid, the presence of the latter showing itself in the formation of the phenylacetyl derivative of the amine used. In a set of experiments in which the ratio of aniline to ethyl formylphenylacetate was varied, it was found that when equimolecular quantities were used the yield of 4-hydroxy-3-phenylquinoline was >41%, and with slight excess of the ester 59% (calculated on the weight of aniline), and in these experiments no other product was isolated. When, however, twice the equivalent quantity of aniline was used the yield of 4-hydroxy-3-phenylquinoline dropped to 5%, and *s*-diphenylurea (>24%) and 4-anilino-3-phenylquinoline (22%) were also isolated. The effect of a change of concentration at the cyclisation stage was studied by cyclising ethyl β-anilino-α-phenylacrylate (0·02 mol.), formed in the presence of a slight excess of ester, in 20 c.c. and in 40 c.c. of phenyl ether. At the lower concentration 4-hydroxy-3-phenylquinoline was obtained in 81% yield. At the higher concentration the yield of 4-hydroxy-3-phenylquinoline was only 47%, and when the phenyl ether filtrate was heated for a further two hours with more aniline, *s*-diphenylurea was formed. Further, whereas the product obtained in the condensation of aniline with ethyl acetoacetate depends on the temperature at which the initial reaction takes place, ethyl β-anilinocrotonate being formed at room temperature (Conrad and Limpach, *Ber.*, 1887, **20**, 944) and acetoacetanilide at higher temperatures (Ewins and King, *J.*, 1913, **103**, 104), the reaction between aniline and ethyl formylphenylacetate follows the same course to give ethyl β-anilino-α-phenylacrylate (V; R = H) when the condensation is carried out at 0°, at room temperature, and at 100°, and the yields of 4-hydroxy-3-phenylquinoline are 48, 45, and 35%, respectively. The temperature at which the condensation is effected thus has little effect on the nature and yield of the product.

Elderfield and Wright (*loc. cit.*) do not report the occurrence of secondary products in their reactions between aniline or *m*-chloroaniline and ethyl formylphenylacetate, but Price, Leonard, and Reitsema (*J. Amer. Chem. Soc.*, 1946, **68**, 1256) found that the products from the cyclisation of the acrylate derived from *m*-chloroaniline and ethyl formylacetate depended on the concentration in the cyclising medium. At high concentration they obtained only *s*-bis-*m*-chlorophenylurea and an odour of acetaldehyde, but at low concentration 5- and 7-chloro-4-hydroxyquinolines were obtained together with 1 : 1-di-(7-chloro-4-hydroxy-3-quinolyl)ethane, a condensation product of acetaldehyde with 7-chloro-4-hydroxyquinoline. No corresponding product was obtained by using ethyl formylpropionate, which gave the corresponding 3-methylquinolines. The occurrence of diphenylureas as by-products in reactions between amines and various ketonic esters has been noted previously by many workers. The occurrence of 4-anilino-3-phenylquinoline in the products of the reaction between ethyl formylphenylacetate and an excess of aniline was unexpected. Curd, Raison, and Rose (*J.*, 1947, 899) have shown

that aniline does not react with 4-hydroxyquinolines except in the presence of its hydrochloride or some other acid, and it was confirmed that 4-anilino-3-phenylquinoline is not formed when 4-hydroxy-3-phenylquinoline is heated with aniline at 240°. 4-Anilino-3-phenylquinoline might have arisen from the ring closure, with loss of water, of β-anilino-α-phenylacrylanilide (VI; R = R′ = Ph). The ring closure of compounds of this type (*e.g.*, VI; R = CN or CO_2Et, R′ = Ph, substituted phenyl, or alkyl) has been described by Price and Boekelheide (*J. Amer. Chem. Soc.*, 1946, **68**, 1246), but the condensing agents used were phosphorus oxychloride in boiling benzene or phosphoric oxide in boiling toluene. Phenyl ether does not normally function as a cyclising agent by dehydration. The presence of β-anilino-α-phenylacrylanilide in the reaction mixture seemed not unlikely, because Wislicenus and Erbe (*Annalen*, 1920, **421**, 140) have shown that it can be obtained by the action of an excess of aniline on α-formylphenylacetanilide at 60°, or by heating α-formylphenylacetanilide to 180°, when the products were β-anilino-α-phenylacrylanilide, diphenylurea, and phenylacetaldehyde. It seemed possible that some α-formylphenylacetanilide might be formed in the reaction mixture from aniline and ethyl formylphenylacetate either directly or by a subsequent conversion. Reynolds and Hauser (*J. Amer. Chem. Soc.*, 1948, **70**, 2402) have shown that under certain conditions β-anilinocrotonates and acetoacetanilides are interconvertible. After the completion of this work Moszew and Famielcówna (*Roczn. Chem.*, 1948, **22**, 80; *Brit. Abstr.*, 1949, AII, 162) described the preparation of 4-anilino-3-phenylquinoline by heating diphenylthiourea with phenylacetaldehyde.

4-Chloro-3-phenylquinolines were obtained as described by Elderfield and Wright (*loc. cit.*) for 4-chloro-3-phenyl- and 4 : 7-dichloro-4-hydroxy-3-phenyl-quinoline, by heating the 4-hydroxy-3-phenylquinolines with a mixture of phosphorus pentachloride and phosphorus oxychloride. The preparation of 4 : 7-dichloro-3-phenylquinoline from a crude mixture of 5- and 7-chloro-4-hydroxy-3-phenylquinolines was confirmed, and 4 : 6-dichloro-, 4 : 8-dichloro-, 4-chloro-6-nitro- and 4-chloro-6-methoxy-3-phenylquinolines were also obtained in good yield (see Table II). Treatment of 4-hydroxy-3-phenylquinoline with phosphorus pentachloride or oxychloride alone, or with mixtures of the two in different proportions, sometimes gave evidence of the formation of products more highly chlorinated than the expected 4-chloro-3-phenylquinoline. A similar anomalous result was obtained with 4-hydroxy-6-methoxy-3-phenylquinoline, which gave a product shown by analysis to be a dichloro-6-methoxy-3-phenylquinoline. Koller (*Ber.*, 1927, **60**, 1110) has described a similar introduction of an additional chlorine atom in the treatment of 2 : 4-dihydroxyquinoline with phosphorus pentachloride.

4-(Dialkylaminoalkylamino)-3-phenylquinolines were prepared by a modification of the method of Drake *et al.* (*loc. cit.*) by heating the appropriate chloroquinoline with phenol and the (dialkylaminoalkyl)amine. The resulting bases, which were oils, were isolated by precipitation as the dipicrates (see Table III). Curd, Raison, and Rose's observation (*loc. cit.*) that (dialkylaminoalkyl)amines could be condensed directly with the 4-hydroxy-group of 2 : 4-dihydroxyquinoline led to an attempt to prepare 4-(2-diethylaminoethylamino)-3-phenylquinoline directly from 4-hydroxy-3-phenylquinoline, but the starting materials were recovered unchanged.

Experimental.

(M. p.s above 200° are uncorrected, those below 200° are corrected.)

4-Hydroxy-3-phenylquinolines (Table I).—The amine (1 mol.) was added to ethyl formylphenylacetate (Wislicenus, *Annalen*, 1896, **291**, 164) (1 mol.) at room temperature or, in the case of solid amines, with slight warming. After 24 hours at room temperature the product, dissolved in ether, was dried ($MgSO_4$). After filtration and removal of the ether, the residual oil was added to boiling phenyl ether, and heated for times varying with the substituent group in the amine used. The 4-hydroxy-3-phenylquinoline crystallised on cooling (except in the case of 8-substituted derivatives) and was filtered off, washed with light petroleum (b. p. 40—60° or b. p. 60—80°), dried, and recrystallised.

4-Chloro-3-phenylquinolines (Table II).—The 4-hydroxy-3-phenylquinoline (1 mol.) and phosphorus pentachloride (1 mol.) were heated in phosphorus oxychloride, as solvent. The mixture was poured on ice, and made alkaline with aqueous sodium hydroxide. The solid product was filtered off, washed thoroughly, dried, and recrystallised.

4-Anilino-3-phenylquinoline.—4-Chloro-3-phenylquinoline (0·5 g.) was heated with aniline (0·2 g.); reaction occurred at 130°, and this temperature was maintained for 5 minutes. The cooled product was extracted with 5% hydrochloric acid, and the solid residue was recrystallised from methyl alcohol. *4-Anilino-3-phenylquinoline hydrochloride* separated as bright yellow needles, m. p. 300° (Found: C, 75·2; H, 5·3. $C_{21}H_{16}N_2,HCl$ requires C, 75·8; H, 5·1%). *4-Anilino-3-phenylquinoline* was obtained by pouring a solution of the hydrochloride in glacial acetic acid into water and immediately neutralising the solution. It separated from methyl alcohol in cream rhombohedra, m. p. 179·5—180·5° (Found: C, 85·0; H, 5·2. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4%). Moszew and Famielcówna (*loc. cit.*) give m. p. 181°.

TABLE I.

4-Hydroxy-3-phenylquinolines.

3-Phenylquinoline	Quantities used. Amine (g.)	Phenyl ether (c.c.)	Time (hr.)	Yield (g.)	Solvent [a]	M. p.	Cryst. form	Formula	Analysis. Found, %, C	H	Calc., %, C	H
4-Hydroxy-	3·4	75	3	4	A	255—256° [b]	White plates	—	—	—	—	—
7-Chloro-4-hydroxy-	21·4	250	3½	3	B	354—356° [c] (decomp.)	White powder	—	—	—	—	—
6-*Chloro*-4-*hydroxy*-	12·9	150	1½	6	C	349—349·5 (decomp.)	Coarse white needles	$C_{15}H_{10}ONCl$	70·2	4·0	70·5	3·9
8-*Chloro*-4-*hydroxy*-	3·1	50	2	2·6 [d]	A	248—251	Cream needles	$C_{15}H_{10}ONCl$	70·3	4·2	70·5	3·9
6-*Bromo*-4-*hydroxy*-	1·7	15	½	1·4	C	365° (decomp.)	Cream crystals	$C_{15}H_{10}ONBr$	59·7	3·3	60·0	3·3
4-*Hydroxy*-6-*nitro*-	1·4	20	¼	1·5	C	349—350 (decomp.)	Yellow powder	$C_{15}H_{10}O_3N_2$	67·1	3·5	67·7	3·8
4-*Hydroxy*-8-*nitro*-	1·4	30	½	0·3 [e]	B	215—216	Bright orange needles	$C_{15}H_{10}O_3N_2$	68·2	4·1	67·7	3·8
4-*Hydroxy*-6-*methoxy*-	15·4	200	¾	6·5	C	337—338 (decomp.)	Transparent plates	$C_{16}H_{13}O_2N_2$	76·1	5·1	76·5	5·2

[a] A = methyl alcohol; B = ethyl alcohol; C = pyridine. [b] Elderfield and Wright (*loc. cit.*) give m. p. 259—260°. [c] Elderfield and Wright (*loc. cit.*) give m. p. 360·5—361·5°. [d] After concentration of phenyl ether solution. [e] After addition of light petroleum to phenyl ether solution.

TABLE II.

4-Chloro-3-phenylquinolines.

3-Phenylquinoline	Quantities used. Hydroxy compound (g.)	PCl_5 (g.)	$POCl_3$ (c.c.)	Time (hr.)	Solvent [a]	Yield (g.)	M. p.	Cryst. form	Formula	Analysis. Found, %, C	H	Calc., %, C	H
4-Chloro-	11·6	10·6	10	(25 min.)	A	6 [b]	73—75° [c]	White needles	—	—	—	—	—
4 : 7-Dichloro-	6·5 [d]	5·5	15	1½	B	5·5	119—120·3 [e]	White flakes	—	—	—	—	—
4 : 6-*Dichloro*-	5	4	30	1½	C	4·5	144·5	White needles	$C_{15}H_9NCl_2$	65·7	3·5	65·7	3·3
4 : 8-*Dichloro*-	1	0·8	7	1	A	1	112·5—113·5	White needles	$C_{15}H_9NCl_2$	65·9	3·0	65·7	3·3
4-*Chloro*-6-*nitro*-	0·7	0·5	3	1	C	0·9 [f]	170·5—172	Pale brown needles	$C_{15}H_9O_2N_2Cl$	62·7	3·0	63·3	3·2
4-*Chloro*-6-*methoxy*- [g]	3	3	10	1¼	C	2·3	138—138·5 [h]	Yellow needles	$C_{16}H_{12}ONCl$	70·9	4·6	71·2	4·5

[a] A = methyl alcohol; B = ethyl alcohol–methyl alcohol (1 : 2); C = ethyl alcohol. [b] Crystallisation of the crude product gave, besides 4-chloro-3-phenylquinoline (6 g.), a product, m. p. 85—95° (2·4 g.), and a product (0·8 g.), m.p. 124—158° raised to 144—157° on recrystallisation from benzene. These could not be obtained in a pure state. [c] Elderfield and Wright (*loc. cit.*) give m. p. 74—75°. [d] A crude mixture of 5- and 7-chloro-4-hydroxy-3-phenylquinolines was used without separation. [e] Elderfield and Wright (*loc. cit.*) give m. p. 121—122°. [f] Yield of crude product. [g] *Picrate*, fine yellow needles (from ethyl acetate), m. p. 206—207° (Found : C, 52·4; H, 3·1. $C_{16}H_{12}ONCl,C_6H_3O_7N_3$ requires C, 53·0; H, 3·0%). [h] In one case the product was 4 : x-*dichloro*-6-*methoxy*-3-*phenylquinoline*, m. p. 131—131·5° depressed on admixture with 4-chloro-6-methoxy-3-phenylquinoline (Found : C, 63·3; H, 3·7; Cl, 23·7. $C_{16}H_{11}ONCl_2$ requires C, 63·2; H, 3·6; Cl, 23·4%).

4-Anilino-6-methoxy-3-phenylquinoline.—Prepared in similar manner from 4-chloro-6-methoxy-3-phenylquinoline, *4-anilino-6-methoxy-3-phenylquinoline* separated from methyl alcohol as a cream powder, m. p. 172—173° (Found : C, 80·4; H, 5·4. $C_{22}H_{18}ON_2$ requires C, 81·0; H, 5·5%).

4-(Dialkylaminoalkylamino)-3-phenylquinolines (Table III).—The 4-chloro-3-phenylquinoline (1 mol.), phenol (1 mol.), and the (dialkylaminoalkyl)amine (2·5 mol.) were heated for 4 hours at 160—180° and then for 4 hours at 210°. Excess of amine was removed under reduced pressure and the residue was extracted with 66% aqueous acetic acid. The acid solution was made alkaline with 10% aqueous sodium hydroxide, and the liberated oil extracted with ether. Alcohol (5 c.c.) was added to this solution, and the base was precipitated as picrate by use of a saturated alcoholic solution of picric acid. The crude dried picrate was extracted twice with boiling ethyl alcohol (10 c.c.), in which the 4-(dialkylaminoalkylamino)-3-phenylquinoline picrates were practically insoluble, and the residue crystallised from acetone. The dipicrates separated as yellow crystalline solids, in some cases containing acetone of crystallisation, not removed by being dried at 80° at atmospheric pressure, but removed at 100° *in vacuo*.

TABLE III.

4-(Dialkylaminoalkylamino)-3-phenylquinolines.

3-Phenylquinoline dipicrate	Weight of chloro-compound (g.)	Yield (g.)	M. p.	Formula	Analysis. Found, % C	H	Calc., % C	H
4-(2-*Diethylamino-ethylamino*)-	1	2	201·5—202·5° (decomp.)	$C_{21}H_{25}N_3,2C_6H_3O_7N_3$	51·0	3·4	50·9	4·0
4-(4-*Diethylamino-1-methylbutyl-amino*)-	0·9	1·5	213—215 (decomp.)	$C_{24}H_{31}N_3,2C_6H_3O_7N_3$	53·0	4·7	52·7	4·5
6-*Chloro*-4-(2-*di-ethylaminoethyl-amino*)-	0·5	1	202·5—204·5 (decomp.)	$C_{21}H_{24}N_3Cl,2C_6H_3O_7N_3,C_3H_6O$	49·6	3·8	49·7	4·1
6-*Chloro*-4-(4-*di-ethylamino*-1-*methylbutylamino*)-	1	1·7 [a]	210—218 (decomp.)	$C_{24}H_{30}N_3Cl,2C_6H_3O_7N_3,C_3H_6O$	51·2	4·3	51·3	4·6
7-*Chloro*-4-(2-*di-ethylaminoethyl-amino*)-	1	1·7	205—206 (decomp.)	$C_{21}H_{24}N_3Cl,2C_6H_3O_7N_3,C_3H_6O$	49·8	4·1	49·7	4·1
4-(2-*Diethylamino-ethylamino*)-6-*methoxy*-	1	2·2	170—173 [b] (decomp.)	$C_{22}H_{27}ON_3,2C_6H_3O_7N_3,C_3H_6O$	51·7	3·5	51·3	3·6
			170—172 [c] (decomp.)	$C_{22}H_{27}ON_3,2C_6H_3O_7N_3$	50·9	4·0	50·6	4·1
4-(4-*Diethylamino*-1-*methylbutylamino*)-6-*methoxy*-	1	1·1	194—195 (decomp.)	$C_{25}H_{33}ON_3,2C_6H_3O_7N_3,C_3H_6O$	52·8	5·3	52·7	5·0

[a] 6-*Chloro-4-phenoxy-3-phenylquinoline*, insoluble in aqueous acetic acid, was also obtained. It had m. p. 152·5—153·5°, undepressed by a specimen prepared by heating 4 : 6-dichloro-3-phenylquinoline with phenol (Found : C, 75·6; H, 4·2. $C_{21}H_{14}ONCl$ requires C, 76·0; H, 4·2%). [b] Melting with preliminary softening at 110—118°. Dried at 80° at atmospheric pressure. [c] Dried at 100° for two hours over potassium hydroxide *in vacuo*.

Substituted Phenylacetanilides.—The following were prepared by heating phenylacetyl chloride (1 mol.) with the appropriate amine (1 mol.) : Phenylacetanilide, transparent plates, m. p. 115·5—116·5° (lit., m. p. 117—118°); p-(*phenylacet*)*anisidide*, $PhCH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}OMe$-*p*, white flattened octahedra, m. p. 122—123° (Found : C, 74·4; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%); *p*-chloro-(phenylacet)anilide, $PhCH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4Cl$-*p*, fine white needles, m. p. 164—165° (von Walther and Grossman, *J. prakt. Chem.*, 1908, **78**, 483, give m. p. 163—164°).

Reaction between Amines and Ethyl Formylphenylacetate.—(i) *Production of phenylacetanilides.* This occurred when impure ethyl formylphenylacetate was used. The phenyl ether solution, after removal of the hydroxyquinoline by filtration, was diluted with four times its volume of light petroleum (b. p. 40—60° and b. p. 60—80°). The precipitated solid was filtered off, washed with light petroleum, and recrystallised from methyl alcohol. The following were obtained from the appropriate amines and were identified by melting point and mixed melting point : phenylacetanilide, *p*-(phenylacet)anisidide, *p*-chloro(phenylacet)anilide.

(ii) *Influence of temperature on initial condensation.* (*a*) Aniline (1·9 g.) and ethyl formylphenylacetate (3·8 g.) were mixed at room temperature. After 24 hours at room temperature the resulting acrylate was dried and then cyclised by being heated in boiling phenyl ether (20 c.c.) for 2 hours. 4-Hydroxy-3-phenylquinoline (2·1 g., 48%) separated from the phenyl ether solution. Dilution of the filtrate with light petroleum (b. p. 40—60°) precipitated 4-anilino-3-phenylquinoline (0·7 g.), m. p. 179—180° both alone and on admixture with an authentic specimen prepared as described above. (*b*) Aniline (1·9 g.) was added to ethyl formylphenylacetate (3·8 g.) in a flask surrounded by an ice-bath. After 30 minutes at 0° the mixture was kept at room temperature for 24 hours, then treated as above. The products were 4-hydroxy-3-phenylquinoline (2 g., 45%) and 4-anilino-3-phenylquinoline (0·5 g.).

(*c*) Aniline (1·9 g.) was added to ethyl formylphenylacetate (3·8 g.) in a flask heated on a water-bath. After 30 minutes at 100° the mixture was kept at room temperature for 24 hours, and then treated as above. During the heating in phenyl ether, diphenylurea sublimed into the condenser. The products were 4-hydroxy-3-phenylquinoline (1·5 g., 34%) and 4-anilino-3-phenylquinoline (0·2 g.).

(iii) *Effect of excess of aniline.* (*a*) The acrylate formed from ethyl formylphenylacetate (3·8 g., 0·02 mol.) and aniline (1·8 g., 0·02 mol.) was cyclised in phenyl ether (20 g.). The product was 4-hydroxy-3-phenylquinoline (>1·8 g., 41%; slight loss). No solid was precipitated on dilution of the phenyl ether filtrate with light petroleum. (*b*) The acrylate, from the ester (3·8 g., 0·02 mol.) and aniline (1·6 g., 0·018 mol.), was cyclised in phenyl ether (20 g.). The product was 4-hydroxy-3-phenylquinoline (2·6 g., 59%), and no solid was precipitated on dilution of the phenyl ether. (*c*) The acrylate, from the ester (3·8 g., 0·02 mol.) and aniline (3·6 g., 0·04 mol.), was cyclised in phenyl ether (20 g.). Diphenylurea (0·8 g.) sublimed into the condenser during heating. The product which crystallised from the phenyl ether after 24 hours was 4-hydroxy-3-phenylquinoline (0·2 g., 5%). After 48 hours, 4-anilino-3-phenylquinoline (0·2 g.) crystallised from the phenyl ether filtrate, and addition of light petroleum to the phenyl ether distillates and residue gave more 4-anilino-3-phenylquinoline (1 g.).

(iv) *Effect of dilution.* The acrylate was prepared from ethyl formylphenylacetate (3·8 g.) and aniline (1·7 g.). (*a*) Cyclisation was carried out in phenyl ether (20 c.c.) for 2 hours and the yield of 4-hydroxy-3-phenylquinoline was 1·8 g. (47%). Half the phenyl ether filtrate was heated for a further 2 hours with more aniline (1 c.c.). Addition of light petroleum to the cooled solution gave diphenylurea (0·4 g.). Addition of light petroleum to the untreated diphenyl ether filtrate gave no solid product. (*b*) Cyclisation was carried out in phenyl ether (40 c.c.) for 2 hours and the yield of 4-hydroxy-3-phenylquinoline was 3·3 g. (81%). Half the phenyl ether filtrate was heated for 2 hours with more aniline (2 c.c.); no solid was precipitated either from this or from the untreated filtrate.

Part of the work described in this paper was carried out during the tenure by one of us (W. J. A.) of a University of London Postgraduate Studentship.

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