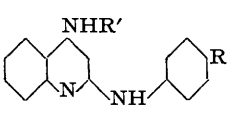
167. *Synthetic Antimalarials. Part XVII. Some Arylamino-aminoalkylaminoquinoline Derivatives.*

By F. H. S. Curd, C. G. Raison, and F. L. Rose.

The differential reactivities of the substituent groups in 2 : 4-dihydroxy- and 2 : 4-dichloro-quinoline have been investigated and have been utilised for the preparation of a series of 2-arylamino-4-aminoalkylaminoquinolines (I) and their isomers (II). The former show the higher degree of antimalarial activity against *P. gallinaceum* in chicks, and this is discussed in the light of recent hypotheses.

The purpose of this communication is to report work leading to the synthesis of quinoline derivatives of types (I and II; R′ = aminoalkyl) that have not hitherto been investigated in the search for antimalarials based on the quinoline nucleus. The new compounds have an



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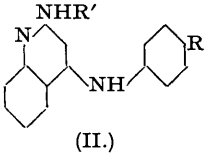

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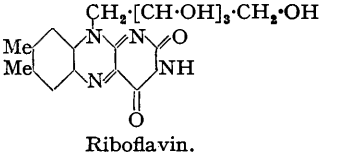
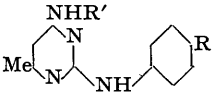


Riboflavin.



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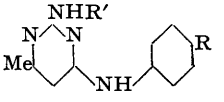

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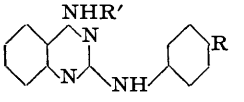

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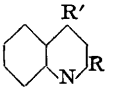
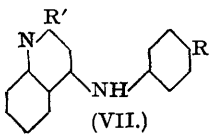


(VI.)

arylamino- and an aminoalkylamino-group attached to a heterocyclic ring system and in this respect are related to the pyrimidines of types (III) and (IV) described in Parts I, II, VI, and IX (*J.*, 1946, 343, 351, 370, 720) and the 2-arylamino-4-aminoalkylaminoquinazolines (V) (Part XIV, this vol., p. 775), all of which are actively plasmodicidal.

To achieve the synthesis of compounds of types (I) and (II) the possibility of a stepwise replacement of the groups R and R′ in a quinoline derivative of type (VI; R = R′ = OH or halogen) was first considered because the simplest of such compounds, namely 2 : 4-dihydroxyquinoline, was available as a dye intermediate. Further, literature methods were available for the preparation of a considerable number of nuclear substituted derivatives. Very little information was available, however, on the feasibility of carrying out the desired stepwise replacements. The reaction of 2 : 4-dihydroxyquinoline with a number of primary and secondary aliphatic amines at temperatures of 150—250° to give exclusively 4-amino- or 4-alkylamino-quinolines in high yields has been described (G.P. 681980). A similar reaction has now been found to occur with dialkylaminoalkylamines such as γ-diethylaminopropylamine giving 4-*γ-diethylaminopropylamino*-2-*hydroxyquinoline* (VI; R = OH, R′ = NH·$[CH_2]_3$·NEt_2). This compound reacted slowly with boiling phosphoryl chloride to give 2-*chloro*-4-*γ-diethylamino-propylaminoquinoline* (VI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2) which was then condensed with *p*-chloroaniline by heating the reactants at *ca.* 200° for several hours, the product being 2-p-*chloroanilino*-4-*γ-diethylaminopropylaminoquinoline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2). The condensation was also possible using an equimolecular proportion of *p*-chloroaniline in aqueous suspension in presence of hydrochloric acid (1·1 mols.), but a reaction time of 48 hours was needed to achieve a good yield. The orientation of these derivatives was demonstrated by the smooth reduction of the intermediate 2-chloro-4-γ-diethylaminopropylaminoquinoline with hydrogen and Raney nickel (cf. Whitmore and Revukas, *J. Amer. Chem. Soc.*, 1940, **62**, 1691; Krahler and Burger, *ibid.*, 1941, **63**, 2367) to give 4-*γ-diethylaminopropylaminoquinoline*, identical with a specimen prepared by the condensation of γ-diethylaminopropylamine with 4-chloroquinoline.

G.P. 681980 makes no mention of the condensation of 2 : 4-dihydroxyquinoline with arylamines, and we have found that the former is recovered completely unchanged after being heated with excess of aniline at 180—200° for 48 hours. In the presence of aniline hydrochloride, however, a smooth reaction occurred with the elimination of water and the formation (in 90% yield) of 4-anilino-2-hydroxyquinoline (VII; R = H, R′ = OH). Even so weak an acid as boric acid catalysed the condensation but less efficiently than hydrochloric acid. This compound has been described previously by v. Niementowski (*Ber.*, 1907, **40**, 4285) and by Dziewonski and Dymek (*Chem. Zentr.*, 1937, I, 1153). The former obtained it as one product of the reaction of benzoylacetic ester with anthranilic acid, noted its insolubility in alkali, and obtained 4-anilinoquinoline in poor yield from it on distillation with zinc dust. The latter authors heated 2 : 4-dianilinoquinoline with potassium hydroxide, obtained 4-anilino-2-hydroxyquinoline, and in addition the isomeric 2-anilino-4-hydroxyquinoline which is alkali soluble. They apparently used v. Niementowski's work as a basis for the orientation of the two isomers. We have found that 4-anilino-2-hydroxyquinoline reacts readily with phosphoryl chloride to yield 2-chloro-4-anilinoquinoline, and this compound, on reduction with hydrogen and Raney nickel, gave 4-anilinoquinoline, m. p. 196—198°, identical with an authentic specimen prepared from 4-chloroquinoline (cf. Ephraim, *Ber.*, 1893, **26**, 2229; Backeberg, *J.*, 1933, 618). The corresponding *p*-chloroanilino-compound (VII; R = R′ = Cl) was similarly obtained by first bringing 2 : 4-dihydroxyquinoline into reaction with *p*-chloroaniline in presence of its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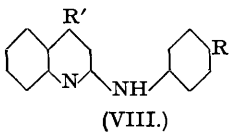
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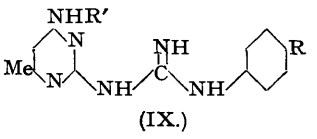
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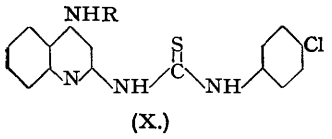
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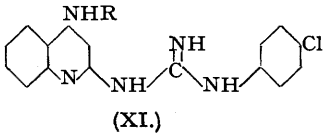
(XI.)

hydrochloride to give 4-p-*chloroanilino*-2-*hydroxyquinoline* (VII; R = Cl, R′ = OH) and then treating this with phosphoryl chloride. The 2-*chloro*-4-p-*chloroanilinoquinoline* thus obtained reacted readily with β-diethylaminoethylamine at 130—140° to give 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinoline and with γ-di-*n*-butylaminopropylamine to give 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylaminoquinoline which were most readily isolated as their *dihydriodides*.

The reactions described above sufficed for the preparation of the two isomeric types of quinoline derivatives (I) and (II) of undoubted orientation, but before they were fully worked out a number of compounds of type (I) had been prepared starting from 2 : 4-dichloroquinoline. As far as we are aware the relative reactivities of the halogen atoms in this compound have been investigated previously only by Buchmann and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1357) who heated it with potassium hydroxide in alcohol. Besides a small amount of 4-chlorocarbostyril they obtained approximately equal amounts of 4-chloro-2-ethoxy- and 2-chloro-4-ethoxy-quinoline. The reaction of (VI; R = R′ = Cl) with arylamines has now been investigated. When heated with an equimolecular amount of aniline, in alcohol or benzene in presence of anhydrous potassium carbonate, no reaction took place. This failure was understandable when it was found that the reaction of 2 : 4-dichloroquinoline and arylamines was catalysed by acid, so that in view of the formation of hydrochloric acid by the reaction the process was normally autocatalytic and indeed, in the absence of solvent, often violently exothermic. These general observations were later given confirmation by the work of Banks (*ibid.*, 1944, **66**, 1127). When equimolecular amounts of 2 : 4-dichloroquinoline and aniline, in acetic acid solution, were warmed together on the steam-bath, only a mildly exothermic reaction took place. The product was a mixture, but the only pure compound that could be isolated (in 53% yield) was 4-chloro-2-anilinoquinoline. This gave a considerable depression in melting point with 2-chloro-4-anilinoquinoline, whilst on reduction with hydrogen and Raney nickel it gave a substance, m. p. 102—103°, conforming to the description of 2-anilinoquinoline recorded in the literature (Friedländer and Weinberg, *Ber.*, 1885, **18**, 1532; Goldschmidt and Meissler, *ibid.*, 1890, **23**, 277). A number of other arylamines were then condensed with 2 : 4-dichloroquinoline to give products of type (VIII; R′ = Cl) which on heating with aminoalkylamines afforded compounds of type (I). Thus (VI; R = R′ = Cl) and *p*-chloroaniline led to 4-*chloro*-2-p-*chloroanilinoquinoline* which when condensed with γ-diethylaminopropylamine gave (I; R = Cl, R′ = $[CH_2]_3$·NEt_2) identical with that made from 2-chloro-4-γ-diethylaminopropylaminoquinoline and *p*-chloroaniline.

When tested against *P. gallinaceum* in chicks, 2-*p*-chloroanilino-4-β-diethylaminoethylamino- and 4-γ-diethylaminopropylamino-quinoline showed activity comparable with that of the analogous pyrimidines of type (III) but a certain lack of parallelism between the two series was observed when further variations in the arylamino- and aminoalkylamino-groups were investigated. An even greater divergence was noticeable between the quinoline derivatives of type (II) and the pyrimidine derivatives of type (IV), for the high activity of (IV; R = Cl, R′ = $[CH_2]_3$·NBu^{α}_2) (Part VI, *loc. cit.*) contrasted most markedly with the very low order of activity shown by (II; R = Cl, R′ = $[CH_2]_3$·NBu^{α}_2). This led us to examine the possibility that the activity of compounds of type (I) might be unconnected with their relationship to type (III), and this appeared to be a likely possibility since quinolines of types (I) and (II) do not allow conjugation between the pendant aryl and aminoalkyl groups *via* alternate carbon and nitrogen atoms as a result of either prototropy or resonance which, from our earlier work, we had come to believe might be a significant factor in the activity of our pyrimidine and diguanide types (Part XII, this vol., p. 154).

Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has reported that 4-δ-diethylamino-α-methylbutylamino-6-methoxyquinoline possesses antimalarial properties, and other work carried out in these laboratories (to be published) had shown that 4-dialkylaminoalkylaminoquinolines in general possessed such properties. It therefore seemed conceivable that the activity of quinolines of type (I) might be due to their being 4-dialkylaminoalkylaminoquinolines carrying a grouping in the 2-position which made no direct contribution to the antimalarial activity and at the same time was not markedly deactivating. This possibility was further illustrated by the antimalarial results obtained with some of the intermediates, containing a dialkylaminoalkylamino-group in the 4-position, used in the synthetic work described in this paper. Thus whereas 4-γ-diethylaminopropylamino-2-hydroxy- and 2-chloro-4-γ-diethylaminopropylamino-quinoline were without activity at high doses, 2-*amino*-4-β-*diethylaminoethylaminoquinoline* and the corresponding γ-*diethylaminopropylamino*-derivative (VI; R = NH_2, R′ = NH·$[CH_2]_3$·NEt_2) (see later) showed considerable antimalarial activity. In this connection the work of Gilman and Spatz (*Iowa State College J. Sci.*, 1942, **17**, 129; *J. Amer. Chem. Soc.*, 1944, **66**, 621), knowledge of which only reached us when our own work was largely completed, is perhaps relevant. They have reported activity in certain 4-dialkylaminoalkylamino-2-arylquinolines prepared as " open chain models " of mepacrine, but do not provide any substantial proof that the activity of the compounds is in fact due to their relationship to mepacrine. They can equally well be regarded simply as modified 4-dialkylaminoalkylaminoquinolines.

This point was examined further in respect of our own compounds by observing the effect on antimalarial activity of introducing substituents into type (I) with and without the presence of the 2-arylamino-group. Compounds of the latter type are described in G.P. 683692 and E.P. 481874, and we were ourselves at the time collecting information on such compounds. For this purpose we prepared 2-p-*chloroanilino*-4-*γ-diethylaminopropylamino*-7 : 8-*benzo*-, 7-*chloro*-2-p-*chloroanilino*-4-*γ-diethylaminopropylamino*-, and 2-p-*chloroanilino*-4-*γ-diethylaminopropylamino*-3-*methyl-quinoline*. 2 : 4-*Dichloro*-7 : 8-*benzoquinoline* did not react with *p*-chloroaniline in acetic acid solution on the steam-bath, but from the product obtained by heating the two reactants together in 2-ethoxyethanol at 160°, 4-*chloro*-2-p-*chloroanilino*-7 : 8-*benzoquinoline*, was obtained, in rather poor yield, and condensed with γ-diethylaminopropylamine. Methyl 4-chloroanthranilate was condensed with ethyl malonate in the presence of sodium methoxide and the product hydrolysed and decarboxylated to give 7-chloro-2 : 4-dihydroxyquinoline which was successively condensed with γ-diethylaminopropylamine and treated with phosphoryl chloride to yield 2 : 7-*dichloro*-4-*γ-diethylaminopropylaminoquinoline*; this reacted with *p*-chloroaniline to give 7-*chloro*-2-p-*chloroanilino*-4-*γ-diethylaminopropylaminoquinoline*. In attempting to prepare compounds of type (I) containing an additional 3-methyl or 3-ethyl substituent, difficulties were encountered which were probably due to steric hindrance. Both 2 : 4-dihydroxy-3-methyl- and -3-ethyl-quinoline condensed with γ-diethylaminopropylamine to give the expected 4-γ-diethylaminopropylamino-2-hydroxy-derivatives which when treated with phosphoryl chloride gave respectively 2-*chloro*-4-*γ-diethylaminopropylamino*-3-*methyl*- and -3-*ethyl-quinoline*; but whereas the former on heating with *p*-chloroaniline gave a product from which the desired 2-p-*chloroanilino*-4-*γ-diethylaminopropylamino*-3-*methylquinoline* could be isolated, the latter gave an intractable mixture. Further, both 2 : 4-dichloro-3-methyl- and -3-*ethyl-quinoline* condensed with *p*-chloroaniline in acetic acid solution at 100° to give respectively 4-*chloro*-2-p-*chloroanilino*-3-*methyl*- and -3-*ethyl-quinoline*, but, although the former condensed slowly with γ-diethylaminopropylamine at 190—200°, the latter hardly reacted with this amine or with β-diethylaminoethylamine at this temperature and at higher temperatures (up to 250° in sealed tubes) gave intractable products.

The antimalarial activities obtained with these compounds (see Table I) did not support the view that they functioned simply as modified 4-dialkylaminoalkylaminoquinolines, and the possibility, mentioned earlier, that they might then be related biologically to the pyrimidines of type (III) was re-examined.

In a previous paper in this series (Curd and Rose, *J.*, 1946, 362) it was shown that the antimalarial activity of compounds of type (III) was retained and in certain instances enhanced if the arylamino- was replaced by an arylguanidino-group to give type (IX). A similar modification was accordingly made in the quinolines of type (I) utilising a synthetic method originally worked out as an alternative procedure for the synthesis of compounds of type (IX) and related compounds, which we shall report in detail later. A 2-chloro-4-dialkylaminoalkylaminoquinoline was treated with ammonia in hot phenol to give the corresponding 2-amino-4-dialkylaminoalkylaminoquinoline (VI; R = NH_2, R′ = dialkylaminoalkylamino) which was then condensed with *p*-chlorophenyl *iso*thiocyanate. The 2-*p*-chlorophenylthioureido-compound (X) thus obtained was desulphurised in the presence of alcoholic ammonia by means of mercuric oxide to give the 2-*p*-chlorophenylguanidino-derivative (XI). 2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*- and -4-*γ-diethylaminopropylamino-quinoline* were prepared in this way, but both failed to show antimalarial activity at tolerated doses. The corresponding thioureido-compounds of type (X) were likewise without demonstrable activity.

Attempts to prepare compounds of type (XI) by condensation of the appropriate 2-chloro-4-dialkylaminoalkylaminoquinoline with *p*-chlorophenylguanidine were unsuccessful. The chloroquinoline was recovered unchanged from trial condensations at temperatures at which ammonia was copiously evolved by breakdown of the guanidine.

Reviewing the results obtained with these compounds it is not possible to draw any very definite conclusion concerning the chemotherapeutic relationship of the quinolines of types (I) and (II) with the pyrimidines of types (III) and (IV) respectively. So far, we have considered this relationship only from the point of view of the chemical hypotheses followed in developing the discovery of antimalarial activity in the pyrimidine of types (III) and (IV). In earlier papers, however, we have discussed the possibility that antiplasmodial activity of these latter types may be associated with a growth antagonism arising from their formal structural similarity to the riboflavin molecule. Examination of the formulæ of (I) and (II) on this basis shows the former to bear the closer structural resemblance to the growth factor. This holds whether the pyrimidine ring of (I) is considered to correspond to the pyrimidine ring or to the benzene ring of

TABLE I.

Antimalarial activities.

The activities are the results of tests against *P. gallinaceum* in chicks and are expressed in the same way as in Part I (*J.*, 1946, 343). The full biological results will be published elsewhere.

Ref. No.	Substance.	Dose (mg./kg.).	Activity.
3627	4-*p*-Chloroanilino-2-β-diethylaminoethylaminoquinoline dihydriodide	400	+
3628	2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinoline dihydriodide	120	++
		80	+ to ++
		40	+
4006	2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinoline dihydrochloride	60	+
		40	±
		20	−
4011	2-*p*-Chloroanilino-4-γ-diethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4321	2-*p*-Anisidino-4-β-diethylaminoethylaminoquinoline dihydriodide	120	+
		80	+
4322	2-*p*-Toluidino-4-β-diethylaminoethylaminoquinoline	100	++
		50	+
4323	2-β-Naphthylamino-4-β-diethylaminoethylaminoquinoline dihydriodide	160	+
		80	+
4324	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-7 : 8-benzoquinoline dihydrochloride	400	−
4342	2-*p*-Chloroanilino-4-γ-dimethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4385	2-*p*-Chloroanilino-4-γ-piperidinopropylaminoquinoline dihydrochloride	60	+ to ++
		40	−
4612	2-*p*-Nitroanilino-4-γ-diethylaminopropylaminoquinoline dihydrochloride	80	+ to ++
		40	−
4623	7-Chloro-2-*p*-chloroanilino-4-γ-diethylaminopropylaminoquinoline	160	+
		80	+
		40	+
4627	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylaminoquinoline dihydriodide	400	+
		200	±
4665	2-*p*-Chloroanilino-4-δ-diethylaminobutylaminoquinoline dihydrochloride	80	+ to ++
		60	+
		40	+
4921	2-(6′-Bromo-β-naphthylamino)-2-γ-diethylaminopropylaminoquinoline	120	+
5092	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-3-methylquinoline	160	+
		80	−
5129	2-*p*-Chloroanilino-4-δ-diethylamino-α-methylbutylaminoquinoline	80	+
		40	+
5226	2-*p*-Chlorophenylthioureido-4-γ-diethylaminopropylaminoquinoline	160	−
		80	−
5276	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline	80	−
		40	−
5463	2-*p*-Chlorophenylthioureido-4-β-diethylaminoethylaminoquinoline	160	−
		80	−
5477	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylaminoquinoline	160	−
		80	−
3738	4-γ-Diethylaminopropylamino-2-hydroxyquinoline	600	−
5099	2-Chloro-4-γ-diethylaminopropylaminoquinoline	160	−
5123	2-Amino-4-γ-diethylaminopropylaminoquinoline	80	++
		40	+
		20	−
5534	2-Amino-4-β-diethylaminoethylaminoquinoline	80	++
		40	++

riboflavin (in the latter case the fuzed benzene ring of the quinoline nucleus will correspond to the 6 : 7-dimethyl grouping in riboflavin, and examples of such a biological equivalence are provided among the polycyclic carcinogenic substances). This view affords some explanation of the variations in biological activity which occur on further substitution or modification of type (I). For instance, while type (IX) retains the property of being able to function as a riboflavin antagonist, the conversion of type (I) into type (XI) probably increases the total dimensions of the molecule to such an extent that a relationship with riboflavin is no longer discernible.

EXPERIMENTAL.

4-γ-Diethylaminopropylamino-2-hydroxyquinoline (VI; ·R = OH, R′ = NH·$[CH_2]_3$·NEt_2).—2 : 4-Dihydroxyquinoline (32·2 g., 1 mol.) and γ-diethylaminopropylamine (52 g., 2 mols.) were heated under reflux by means of an oil-bath at 170—180° for 18 hours. The cooled mixture was lixiviated

with water, and the product collected and washed with water. It was then extracted with dilute acetic acid and the filtered extract made alkaline with ammonia to reprecipitate the *compound* as an oil which rapidly solidified (yield, 68%). It formed colourless needles from aqueous alcohol, m. p. 174—175° (Found: C, 70·9; H, 8·6; N, 15·3. $C_{16}H_{23}ON_3$ requires C, 70·3; H, 8·4; N, 15·4%). It is insoluble in alkalis.

4-*β*-*Diethylaminoethylamino*-2-*hydroxyquinoline* (VI; R = OH, R′ = NH·$[CH_2]_2$·NEt_2).—2 : 4-Dihydroxyquinoline (80 g.) and *β*-diethylaminoethylamine (84 g., 1·45 mols.) were heated under reflux with stirring at 170—180° for 27 hours. After cooling, the mixture was extracted with dilute acetic acid and filtered from insoluble material (unchanged 2 : 4-dihydroxyquinoline, 32·6 g.). The acetic acid extract was made alkaline with ammonia which precipitated the product as an oil. This gradually solidified (yield, 56·8 g.), and subsequent purification by crystallisation from aqueous acetone gave 4-*β*-*diethylaminoethylamino*-2-*hydroxyquinoline*, m. p. 61—63° (Found: C, 61·1; H, 8·4; N, 13·8. $C_{15}H_{21}ON_3,2H_2O$ requires C, 61·0; H, 8·5; N, 14·2%).

2-*Chloro*-4-*γ*-*diethylaminopropylaminoquinoline* (VI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2).—4-*γ*-Diethylaminopropylamino-2-hydroxyquinoline (134 g.) and phosphoryl chloride (268 c.c.) were boiled under reflux for 20 hours and the solution cooled and poured on ice. The oil liberated on basification with 40% potassium hydroxide solution was extracted with ether and the ethereal extract filtered, dried (Na_2SO_4), and evaporated. The residual *chloro*-compound, purified by vacuum distillation, had b. p. 193—194°/0·2 mm., 180—182°/0·08 mm., and crystallised on standing (yield, 68%). It then separated from light petroleum (b. p. 40—80°) as colourless prisms, m. p. 51—52° (Found: C, 66·0; H, 7·4; N, 14·4; Cl, 12·1. $C_{16}H_{22}N_3Cl$ requires C, 65·9; H, 7·55; N, 14·4; Cl, 12·2%). The *dipicrate* crystallised from 2-ethoxyethanol in fine yellow needles, m. p. 193—194° (Found: N, 16·5; Cl, 4·8. $C_{16}H_{22}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·8; Cl, 4·75%).

4-*γ*-*Diethylaminopropylaminoquinoline* (VI; R = H, R′ = NH·$[CH_2]_3$·NEt_2).—(*a*) 2-Chloro-4-*γ*-diethylaminopropylaminoquinoline in alcohol solution was shaken with hydrogen, Raney nickel, and potassium hydroxide (1 mol.), absorption of hydrogen ceasing when 1 mol. of hydrogen had been taken up. After filtration and evaporation to dryness the residue was treated with water and sodium hydroxide, and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract left an oil, purified by vacuum distillation, b. p. 171—172°/0·15 mm. (yield, 65%) (Found: N, 15·8. $C_{16}H_{23}N_3$ requires N, 16·3%), which crystallised on adding water to form a *hydrate*, m. p. 57° not depressed by an authentic specimen prepared according to method (*b*) (Found: C, 69·5; H, 8·6. $C_{16}H_{23}N_3,H_2O$ requires C, 69·8; H, 9·1%).

(*b*) 4-Chloroquinoline (1·95 g.), *γ*-diethylaminopropylamine (3 c.c.), and potassium iodide (0·05 g.) were stirred and heated at 180° for 8 hours. The resulting mixture after being cooled was extracted with 10% acetic acid containing sodium acetate (0·5 g.), and the extract treated with decolorising carbon, filtered, and made alkaline with sodium hydroxide. The product, isolated with ether, had b. p. 173—174°/0·15 mm. and gave the hydrate, m. p. 56°. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as pale yellow needles, m. p. 180—182° (Found: C, 47·2; H, 4·1; N, 18·0. $C_{16}H_{23}N_3,2C_6H_3O_7N_3$ requires C, 47·0; H, 4·1; N, 17·6%).

2-*Chloro*-4-*β*-*diethylaminoethylaminoquinoline* (VI; R = Cl, R′ = NH·$[CH_2]_2$·NEt_2).—Prepared by careful addition of phosphoryl chloride to the dihydrate of the corresponding hydroxy-compound, followed by boiling for 18 hours and working up in the manner described for the corresponding *γ*-diethylaminopropylamino-derivative, this was obtained as a faintly yellow viscous oil, b. p. 183—184°/0·07 mm., which crystallised on addition of water to give the *hydrate* (yield, 36·6 g.) which crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 80—82° (Found: C, 60·9; H, 7·2; Cl, 11·6. $C_{15}H_{20}N_3Cl,H_2O$ requires C, 60·9; H, 7·45; Cl, 12·0%).

4-*Anilino*-2-*hydroxyquinoline* (VII; R = H, R′ = OH).—2 : 4-Dihydroxyquinoline (8·05 g.), aniline (23·3 g., 5 mols.), and aniline hydrochloride (6·5 g., 1 mol.) were stirred and heated at 180—190° for 12 hours. After removal of excess of aniline by steam distillation, the crystalline residue was collected and extracted with hot dilute sodium hydroxide and then washed, first with water, and then with hot methanol to remove a violet-coloured impurity. 4-Anilino-2-hydroxyquinoline remained as slightly bluish-grey prisms, m. p. 319—321° unchanged on crystallisation from 2-ethoxyethanol (v. Niementowski, *loc. cit.*, gives m. p. 318°; Dziewoński and Dymek, *loc. cit.*, give m. p. 316°) (Found: N, 12·1. Calc. for $C_{15}H_{12}ON_2$: N, 11·9%).

The same product was obtained in 87% yield by using boric acid in place of aniline hydrochloride and heating for 40 hours, but without an acid catalyst no product was formed.

4-p-*Chloroanilino*-2-*hydroxyquinoline* (VII; R = Cl, R′ = OH).—2 : 4-Dihydroxyquinoline (40·25 g.), *p*-chloroaniline (160 g.), and *p*-chloroaniline hydrochloride (41·0 g.) were heated with stirring for 4 hours at 180—190°. While still warm, the mixture was stirred with warm methanol (150 c.c.), and the residue filtered off and washed with methanol until free from blue colour, to leave a colourless crystalline product. This was ground with hot water and then with dilute sodium hydroxide, filtered, washed with water, and dried (yield, 89%). It formed colourless crystals from 2-ethoxyethanol, m. p. 296—298° (Found: N, 10·6; Cl, 13·8. $C_{15}H_{11}ON_2Cl$ requires N, 10·35; Cl, 13·1%).

2-*Chloro*-4-*anilinoquinoline* (VII; R = H, R′ = Cl).—4-Anilino-2-hydroxyquinoline (10·6 g.) and phosphoryl chloride (25 c.c.) were heated at 110—120° for 1½ hours and the solution was then evaporated under reduced pressure at 50—60°. The remaining greenish-yellow solid was ground under alcohol, and the mixture made alkaline with ammonia, diluted with water, filtered, washed, and dried. The chloro-compound (yield, 98%) had m. p. 162—164° unchanged after crystallisation from methanol from which it separated as thick colourless prisms (Found: N, 11·4; Cl, 13·9. Calc. for $C_{15}H_{11}N_2Cl$: N, 11·0; Cl, 13·9%). v. Niementowski (*loc. cit.*) gives m. p. 156°.

When the chloro-compound (1·28 g.) in alcohol (50 c.c.) was shaken with hydrogen in presence of Raney nickel and potassium hydroxide (0·3 g.), absorption of 1 mol. of hydrogen took place fairly rapidly. The mixture was then filtered and the solvent evaporated. Digestion of the solid residue with water gave a product which after crystallisation from methanol had m. p. 196—198° undepressed by an authentic specimen prepared from 4-chloroquinoline and aniline (Found: C, 81·5; H, 5·2; N, 12·8. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%).

2-*Chloro*-4-p-*chloroanilinoquinoline* (VII; R = R′ = Cl), prepared in theoretical yield from 4-*p*-chloroanilino-2-hydroxyquinoline (58 g.) and phosphoryl chloride (150 c.c.) followed by working up in the manner described above for (VII; R = H, R′ = Cl), had m. p. 174—175° unchanged by crystallisation from alcohol (Found: N, 9·4. $C_{15}H_{10}N_2Cl_2$ requires N, 9·7%).

4-p-*Chloroanilino*-2-*β*-*diethylaminoethylaminoquinoline* (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).—2-Chloro-4-*p*-chloroanilinoquinoline (14·5 g.) and *β*-diethylaminoethylamine (9·0 g.) were heated at 130—140° for 14 hours. The mixture was dissolved in warm dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The extract was shaken with 5% acetic acid, the acetic acid extract made alkaline, and the product again extracted with chloroform. After drying (K_2CO_3), evaporation of the solvent left the base as an uncrystallisable oil which gave a gelatinous hydrochloride but a crystalline *dihydriodide* by evaporation of an alcoholic hydriodic acid solution of the base. This salt crystallised from alcohol in stout colourless prisms, softening from 240° and decomposing at 248° (Found: C, 39·8; H, 3·9. $C_{21}H_{25}N_4Cl,2HI$ requires C, 40·3; H, 4·3%) (3627).

4-p-*Chloroanilino*-2-*γ*-*di*-n-*butylaminopropylaminoquinoline* (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2).—2-Chloro-4-*p*-chloroanilinoquinoline (9·35 g.), *γ*-*di*-*n*-butylaminopropylamine (10 g.), and powdered potassium iodide (0·1 g.) were heated and stirred at 150—160° for 6 hours. The resulting mixture was treated with warm sodium hydroxide, cooled, and extracted with chloroform. The residue left after evaporation of the chloroform was extracted with 5% acetic acid (200 c.c.), decanted from a little undissolved oil, and extracted with ether. The aqueous layer was made alkaline and extracted with chloroform. After removal of the chloroform from the dried extract, excess of amine was removed by heating to 200°/0·1 mm. and the residual base converted into its *dihydriodide* which was induced to crystallise by trituration with dilute alcohol and then recrystallised from methanol–ethyl acetate; m. p. 200—202° (Found: C, 45·1; H, 5·7; 1 mg. ≡ 0·76 mg. AgX. $C_{26}H_{35}N_4Cl,2HI$ requires C, 45·0; H, 5·3; 1 mg. ≡ 0·88 mg. AgX).

4-*Chloro*-2-*arylaminoquinolines* (VIII; R′ = Cl).—A mixture of 2 : 4-dichloroquinoline (0·1 g.-mol.), the appropriate arylamine (0·1 g.-mol.), and acetic acid (40 c.c.) was stirred and heated on the steam-bath for times varying from ¾ hour to 2 hours. In some experiments (procedure *a*) fused sodium acetate was then added to neutralise the liberated hydrochloric acid and the mixture poured into water. In others (procedure *b*) the mixture was diluted with water to precipitate the hydrochloride which was then collected and boiled with methanolic ammonia followed by dilution with water. In either case, the precipitated base was collected when solid, dried, and crystallised to constant m. p. Table II gives details of the compounds prepared.

TABLE II.

4-*Chloro*-2-*arylaminoquinolines* (VIII; R′ = Cl)

R.	Procedure.	Yield (%).	Formula.	M. p.	Solvent.	Analysis. Found (%). N.	Found (%). Cl.	Reqd. or calc. (%). N.	Reqd. or calc. (%). Cl.
H	*a*	53	$C_{15}H_{11}N_2Cl$	162—163° *	alcohol (rhombic prisms)	10·6	14·6	11·0	13·95
Cl	*b*	50	$C_{15}H_{10}N_2Cl_2$	135—136	methanol (needles)	9·7	24·5	9·7	24·5
MeO	*a*	43	$C_{16}H_{13}ON_2Cl$	140	alcohol (needles)	10·1	12·0	9·85	12·4
Me	*a*	40	$C_{16}H_{13}N_2Cl$	115·5—116·5	methanol (stout prisms)	10·8	13·5	10·4	13·2
NO_2	*b*	43	$C_{15}H_{10}O_2N_3Cl$	263—265	dioxan (prisms)	13·7	12·0	14·0	11·85
2-*β*-Naphthylamino-derivative	*b*	34	$C_{19}H_{13}N_2Cl$	108—110	aq. methanol (needles and prisms)	9·8	11·7	9·2	11·65
2-(6′-Bromo-*β*-naphthylamino)-derivative	*b*	50	$C_{19}H_{12}N_2ClBr$	152—154	*n*-propanol	7·8	1 mg. ≡ 0·853 mg. AgX	7·3	1 mg. ≡ 0·864 mg. AgX

* Dziewoński and Dymek, *Chem. Zentr.*, 1938, II, 1953, give m. p. 161°.

Reductive Dehalogenation of 4-*Chloro*-2-*anilinoquinoline*.—4-Chloro-2-anilinoquinoline (1·28 g.) and potassium hydroxide (0·3 g.) in alcohol (50 c.c.) were shaken with hydrogen and Raney nickel. Absorption of hydrogen was rapid and ceased after the theoretical uptake had occurred. The solution was filtered from catalyst and evaporated and water was added. The resulting oil soon solidified and was filtered off and dried. Crystallisation from dilute methanol and then from light petroleum (b. p. 60—80°) gave 2-anilinoquinoline as glistening colourless plates, m. p. 102—103° (Found: C, 81·4; H, 5·3; N, 13·0. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%).

2-p-*Chloroanilino*-4-*γ*-*diethylaminopropylaminoquinoline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2).—(*a*) 2-Chloro-4-*γ*-diethylaminopropylaminoquinoline (8·1 g.), *p*-chloroaniline (10·65 g.), and powdered potassium iodide (0·1 g.) were heated at 200° for 6 hours with stirring. The mixture was dissolved in hot dilute hydrochloric acid and the filtered solution cooled and made alkaline with sodium hydroxide. The precipitated product was isolated with chloroform and partitioned between 5% acetic acid (100 c.c.) and ether. The aqueous layer was made alkaline with sodium hydroxide and the product again extracted

with chloroform. After drying (K_2CO_3), removal of the chloroform left an oil which rapidly solidified and then crystallised from benzene–light petroleum and finally from benzene giving the *base* as colourless fine needles, m. p. 154—156° (Found : C, 69·2; H, 7·0; N, 14·9; Cl, 9·3. $C_{22}H_{27}N_4Cl$ requires C, 69·0; H, 7·05; N, 14·6; Cl, 9·35%). It was converted into the *dihydrochloride* by dissolving in alcohol, adding hydrochloric acid until the solution was acid to Congo-red, evaporating to dryness under reduced pressure at 50—60°, and then evaporating with benzene–alcohol to remove the last traces of hydrochloric acid. The solid residue then crystallised from alcohol–ethyl acetate in colourless fine needles, which were hydrated and decomposed above 110° (Found : C, 54·0; H, 6·7; N, 11·4; Cl′, 15·0. $C_{22}H_{27}N_4Cl,2HCl,2H_2O$ requires C, 53·7; H, 6·7; N, 11·4; Cl′, 14·5%). This salt is readily soluble in water.

(*b*) 2-Chloro-4-*γ*-diethylaminopropylaminoquinoline (5·15 g.), *p*-chloroaniline (2·25 g.), water (20 c.c.), ethanol (5 c.c.), and 10N-hydrochloric acid (1·7 c.c.) were refluxed together for 48 hours. After cooling and addition of sodium acetate, a little unreacted *p*-chloroaniline was removed by ether extraction. Basification of the aqueous layer precipitated a solid which was filtered off, dried, and crystallised from benzene giving the same product as in (*a*), m. p. and mixed m. p. 155—156° (yield, 4·3 g.).

(*c*) 4-Chloro-2-*p*-chloroanilinoquinoline (20 g.), *γ*-diethylaminopropylamine (18·0 g.), and powdered potassium iodide (0·3 g.) were heated with stirring in an oil-bath at 180—190° for 16 hours. A solution of the mixture in warm dilute hydrochloric acid was made alkaline with sodium hydroxide and extracted with chloroform. The solvent was removed, the residue digested with warm 50% acetic acid (250 c.c.), and the filtered solution basified and extracted with chloroform. After drying (K_2CO_3) and removal of the chloroform an oil was obtained which quickly solidified and was then crystallised from benzene (yield, 17·6 g.); it had m. p. 153—155°, and was identical with the compound made by methods (*a*) and (*b*) (Found : C, 68·6; H, 7·1%).

Using method (*c*) a number of other 2-arylamino-4-dialkylaminoalkylaminoquinolines were prepared. Details are given in Table III.

2 : 4-*Dichloro*-7 : 8-*benzoquinoline*.—2 : 4-Dihydroxy-7 : 8-benzoquinoline (78 g.) (prepared from α-naphthylamine and ethyl malonate, cf. E.P. 332911 and Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832) and phosphoryl chloride (200 c.c.) were heated at 90—100° for ½ hour during which time hydrogen chloride was copiously evolved. The temperature was then raised to 120—125° and maintained for 3½ hours. The resulting clear solution was cooled and added to crushed ice with stirring. The precipitated product was filtered off, washed free from acid, dried, and refluxed with acetone (1 l.). After filtration from insoluble matter, the acetone was distilled off and the residue crystallised from ethyl acetate (yield, 48·5 g.). 2 : 4-*Dichloro*-7 : 8-*benzoquinoline* formed long colourless needles from acetone, m. p. 134—135° (Found : C, 63·0; H, 3·5; Cl, 28·3. $C_{13}H_7NCl_2$ requires C, 62·9; H, 2·8; Cl, 28·6%).

4-*Chloro*-2-p-*chloroanilino*-7 : 8-*benzoquinoline*.—2 : 4-Dichloro-7 : 8-benzoquinoline (24·8 g.), *p*-chloroaniline (12·7 g.), *p*-chloroaniline hydrochloride (0·1 g.), and 2-ethoxyethanol (30 c.c.) were heated in an oil-bath at 160° for 3·5 hours. The mixture was then cooled and diluted with water, and the precipitated product filtered off and dissolved in boiling alcohol (350 c.c.) with the addition of sufficient ammonia to give an alkaline reaction. The resulting solution was treated with an equal volume of water. The product, when solid, was collected, dried, and crystallised first from benzene and then from butanol (yield, 40%) giving needles, m. p. 160—162° (Found : Cl, 20·4. $C_{19}H_{12}N_3Cl_3$ requires Cl, 20·4%).

2-p-*Chloroanilino*-4-*γ*-*diethylaminopropylamino*-7 : 8-*benzoquinoline*.—The preceding chloro-compound (17·6 g.), *γ*-diethylaminopropylamine (13·5 g.), and powdered potassium iodide (0·3 g.) were heated at 175—185° with stirring for 24 hours. Worked up in the usual way for this type of compound the base was obtained as a glass which could not be induced to crystallise. It was therefore dissolved in hot acetone (100 c.c.), and hydrochloric acid added until the solution showed acidity to Congo-red. On cooling, the *dihydrochloride* crystallised out as a hydrate and was recrystallised from acetone–water, m. p. 108—110° (Found : C, 55·3; H, 6·4; N, 10·0; Cl′, 13·6. $C_{26}H_{29}N_4Cl,2HCl,3H_2O$ requires C, 55·8; H, 6·3; N, 10·0; Cl′, 12·7%).

7-*Chloro*-2 : 4-*dihydroxyquinoline*.*—This was prepared by a modification of a method for 2 : 4-dihydroxyquinoline described by Koller (*Ber.*, 1927, **60**, 1108). Methyl 4-chloroanthranilate (100 g.) (Hunn, *J. Amer. Chem. Soc.*, 1923, **45**, 1028), ethyl malonate (86·2 g.), and sodium methoxide (29 g.) were mixed in a flask fitted with a condenser arranged for distillation. After the mixture had been stirred at 70° until homogeneous (*ca.* 1 hour), the temperature was raised slowly to 140—150° and then maintained for 6 hours. Alcohol distilled and the mixture thickened, eventually becoming quite solid. After cooling, the mixture was repeatedly extracted with cold dilute sodium hydroxide and the extracts were acidified to precipitate what was probably methyl 7-chloro-2 : 4-dihydroxyquinoline-3-carboxylate (89 g.). This ester (35 g.) was hydrolysed and decarboxylated by heating on the steam-bath overnight with sodium hydroxide (13 g. in 350 c.c. water); after being filtered from a little insoluble material the filtrate was acidified. The precipitate was collected, washed, and boiled with dilute sodium carbonate solution, and the solution cooled, filtered, and acidified. 7-Chloro-2 : 4-dihydroxyquinoline was precipitated as an almost colourless powder, m. p. 332—340° (decomp.) (Found : N, 6·7; Cl, 18·5. Calc. for $C_9H_6O_2NCl$: N, 7·2; Cl, 18·2%). This substance has been prepared very recently by another modification of Koller's method by Lutz *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1285).

7-*Chloro*-4-*γ*-*diethylaminopropylamino*-2-*hydroxyquinoline*.*—7-Chloro-2 : 4-dihydroxyquinoline (30 g.) and *γ*-diethylaminopropylamine (41·2 g.) were heated at 170—180° for 20 hours and then worked up as described for 4-*γ*-diethylaminopropylamino-2-hydroxyquinoline to give the *compound* as practically colourless needles, m. p. 228—229° (Found : C, 62·2; H, 6·9; N, 13·9; Cl, 12·0. $C_{16}H_{22}ON_3Cl$ requires C, 62·4; H, 7·1; N, 13·7; Cl, 11·55%).

2 : 7-*Dichloro*-4-*γ*-*diethylaminopropylaminoquinoline*.*—The above hydroxy-compound (12 g.) and phosphoryl chloride (24 c.c.) were heated by means of an oil-bath at 130—140° for 16 hours followed by working up in the usual way for this type of compound to give the product, m. p. 82—87°, characterised as

* Experiments by Mrs. J. M. Wilson.

TABLE III.

2-Arylamino-4-aminoalkylaminoquinolines.

Substituent at 2.	Substituent at 4.	Derivative.	M. p.	Solvent; crystalline form.	Formula.	Analysis. Found (%). C.	H.	N.	Cl′.	Required (%). C.	H.	N.	Cl′.
p-Chloroanilino	$NH\cdot[CH_2]_2\cdot NEt_2$	—	B.p. 258°/0·1 mm.	Very viscous oil	—	—	—	—	—	—	—	—	—
		Dihydrochloride	169—171° (decomp.)	Alcohol–ethyl acetate; needles	$C_{21}H_{25}N_4Cl,2HCl,H_2O$	55·3	6·3	—	15·6	54·9	6·3	—	15·45
		Dihydriodide	253—254 (decomp.)	Alcohol–ethyl acetate; prisms	$C_{21}H_{25}N_4Cl,2HI$	40·1	4·4	—	—	40·3	4·3	—	—
p-Chloroanilino	$NH\cdot[CH_2]_4\cdot NEt_2$	Dihydrochloride	201—203 (decomp.)	Alcohol–ethyl acetate; needles	$C_{23}H_{29}N_4Cl,2HCl,H_2O$	56·8	6·4	11·8	14·9	56·6	6·8	11·5	14·6
p-Chloroanilino	$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$ [1]	Dipicrate	230—232 (decomp.)	2-Ethoxyethanol-pyridine; yellow needles	$C_{24}H_{31}N_4Cl,2C_6H_3O_7N_3$	49·1	4·5	16·6	—	49·7	4·3	16·1	—
p-Chloroanilino *	$NH\cdot[CH_2]_3\cdot NMe_2$	Dihydrochloride	86—88 (decomp.)	Alcohol–ethyl acetate	$C_{20}H_{23}N_4Cl,2HCl,1{\cdot}5H_2O$	52·9	6·3	12·2	15·0	52·8	6·2	12·3	15·6
p-Chloroanilino *	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	Dihydrochloride	86—88	Dilute hydrochloric acid	$C_{23}H_{27}N_4Cl,2HCl,5H_2O$	49·6	6·8	10·6	13·1	49·5	7·0	10·05	12·8
p-Anisidino	$NH\cdot[CH_2]_2\cdot NEt_2$	Dihydriodide	146—148 (decomp.)	Aqueous alcohol; needles	$C_{22}H_{28}ON_4,2HI,H_2O$	41·7	5·1	—	—	41·4	5·0	—	—
p-Toluidino	$NH\cdot[CH_2]_2\cdot NEt_2$	—	109—111	*cyclo*Hexane; prisms	$C_{22}H_{28}N_4,0{\cdot}5H_2O$	74·4	7·8	16·0	—	74·0	8·1	15·7	—
p-Nitroanilino	$NH\cdot[CH_2]_3\cdot NEt_2$	Dihydrochloride	182—184 (softening at 172)	Alcohol–ethyl acetate	$C_{22}H_{27}O_2N_5,2HCl,4H_2O$	49·2	6·0	13·7	—	49·1	6·8	13·0	—
β-Naphthylamino	$NH\cdot[CH_2]_2\cdot NEt_2$	Dihydriodide	127—128	Methanol	$C_{25}H_{28}N_4,2HI,H_2O$	45·6	5·0	—	—	45·6	5·0	—	—
6-Bromo-β-naphthylamino	$NH\cdot[CH_2]_3\cdot NEt_3$	—	149—150	Benzene–light petroleum	$C_{26}H_{29}N_4Br$	65·9	5·8	11·8	—	65·4	6·1	11·7	—

[1] For biological test the picrate was dissolved in pyridine, the solution added to aqueous sodium hydroxide, and the base extracted with ether which was then thoroughly washed with sodium hydroxide and water, dried, and evaporated, giving the base as an oil. This was made soluble with lactic acid.

its *dipicrate* which crystallised from aqueous 2-ethoxyethanol and had m. p. 194—195° (Found: N, 15·8; Cl, 9·5. $C_{16}H_{21}N_3Cl_2,2C_6H_3O_7N_3$ requires N, 16·1; Cl, 9·1%).

*7-Chloro-2-p-chloroanilino-4-γ-diethylaminopropylaminoquinoline.**—2 : 7-Dichloro-4-γ-diethylaminopropylaminoquinoline (8·96 g.), *p*-chloroaniline (10·6 g.), and potassium iodide (0·1 g.) were heated for 8 hours at 200°. The mixture was treated with hot dilute hydrochloric acid, made alkaline with sodium hydroxide, and steam distilled to remove unchanged *p*-chloroaniline. The residual oil was separated and dissolved in 5% acetic acid, and the solution extracted with ether. Basification followed by isolation with chloroform then gave the *product* which crystallised from benzene–light petroleum as colourless laminæ, m. p. 144—145° (Found: C, 63·0; H, 6·1; N, 13·7; Cl, 17·1. $C_{22}H_{26}N_4Cl_2$ requires C, 63·3; H, 6·2; N, 13·4; Cl, 17·1%).

2 : 4-Dihydroxy-3-methylquinoline.—Aniline (46·5 g.) and ethyl methylmalonate (87 g.), contained in a flask fitted with a long condenser allowing only the liberated alcohol to escape, were heated at 230—240° for ½ hour, then at 290—300° for 1½ hours, and finally raised to 340° during ½ hour. The cooled mass was boiled with acetone (100 c.c.) for 10 hours and the insoluble material filtered off after cooling. It was then boiled with sodium carbonate solution (700 c.c. of 10%) for 10 minutes and cooled, and the solution was filtered and the product precipitated with hydrochloric acid (yield, 53%). Crystallised from 2-ethoxyethanol and then from butanol it formed almost colourless prisms, m. p. 265—268° (decomp.) (Found: C, 68·3; H, 4·9; N, 8·4. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·1; N, 8·0%) (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, give m. p. >270°).

2 : 4-Dichloro-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (25 g.) and phosphoryl chloride (75 c.c.) were heated at 100—110° for ½ hour and then at 120—125° for 5 hours. The mixture was then cooled and poured on ice. The precipitated product was filtered off, washed free from acid with water, dried (yield, 29·7 g.), and crystallised from 80% alcohol, m. p. 90—91° (Found: Cl, 33·1. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%) (Gabriel and Gerhard, *loc. cit.*, give m. p. 83—84°).

4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (20 g.) and γ-diethylaminopropylamine (30 g.) were heated at 180—190° for 22·5 hours and the mixture was cooled and poured into water. The *prodnct*, precipitated as an oil, soon solidified. It was collected, dissolved in 5% acetic acid, precipitated with ammonia, and dried at 60° (yield, 47·5%). It crystallised from aqueous alcohol as pale yellow stout prisms, m. p. 105—106° (Found: N, 14·7. $C_{17}H_{25}ON_3$ requires N, 14·6%).

4-γ-Diethylaminopropylamino-2-hydroxy-3-ethylquinoline, prepared in exactly the same manner from 2 : 4-dihydroxy-3-ethylquinoline (Baumgarten and Kärgel, *loc. cit.*) and γ-diethylaminopropylamine, crystallised from aqueous alcohol; m. p. 100—101° (Found: N, 14·2. $C_{18}H_{27}ON_3$ requires N, 14·0%).

2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline.—4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline (13·35 g.) and phosphoryl chloride (30 c.c.) were heated at 115—125° for 18 hours. Most of the excess of phosphoryl chloride was then removed under diminished pressure and the residue dissolved in water, made alkaline with potassium hydroxide, and extracted with ether. The dried ethereal extract was evaporated and the residual oil extracted with cold light petroleum (b. p. 40—60°) (100 c.c.), filtered, and evaporated. 2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline remained as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as fine yellow needles of indefinite melting point (*ca.* 160°) (Found: N, 16·6; Cl, 4·7. $C_{17}H_{24}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·5; Cl, 4·65%).

4-Chloro-2-p-chloroanilino-3-methylquinoline.—2 : 4-Dichloro-3-methylquinoline (21·2 g.) and *p*-chloroaniline (12·75 g.) in acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring. Crystalline material was deposited during the reaction. This was collected after dilution with water, washed, and stirred overnight with methanol containing excess of ammonia. Water was then added, and the product collected, washed, and dried. This crude material was ground and extracted with cold dioxan leaving undissolved 2 : 4-*di*-p-*chloroanilino-3-methylquinoline* (3·1 g.), m. p. 266—268° (Found: Cl, 18·0. $C_{22}H_{17}N_3Cl_2$ requires Cl, 18·0%). The dioxan filtrate from this di-condensation product was diluted with water and the precipitated material, initially an oil which gradually solidified, filtered off and crystallised from alcohol, giving *4-chloro-2-p-chloroanilino-3-methylquinoline* as colourless fine needles, m. p. 120—121° (Found: N, 9·3; Cl, 22·9. $C_{16}H_{12}N_2Cl_2$ requires N, 9·25; Cl, 23·4%) (yield, 15·85 g.).

2-p-Chloroanilino-4-γ-diethylaminopropylamino-3-methylquinoline.—(*a*) Crude 2-chloro-4-γ-diethylaminopropylamino-3-methylquinoline (9·65 g.), *p*-chloroaniline (12·1 g.), and potassium iodide (0·1 g.) were heated at 200° for 12 hours. The mass was dissolved in alcohol, and the solution made alkaline with sodium hydroxide and steam distilled. The residual oil was isolated with chloroform and shaken with 5% acetic acid (150 c.c.) and ether. The aqueous layer was separated and re-extracted with ether, and then made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract left the base as an oil which could not be induced to crystallise. The picrate and hydrochloride likewise failed to crystallise. A solution of the base in dilute hydrochloric acid on treatment with perchloric acid gave the *perchlorate* which crystallised from alcohol in rosettes of colourless needles, m. p. 216—218° (Found: C, 46·1; H, 4·9; N, 9·7. $C_{23}H_{29}N_4Cl,2HClO_4$ requires C, 46·2; H, 5·2; N, 9·4%).

(*b*) 4-Chloro-2-*p*-chloroanilino-3-methylquinoline (10 g.), γ-diethylaminopropylamine (8·6 g.), and potassium iodide (0·15 g.) were heated under reflux in an oil-bath at 190—200° for 22 hours. When cool, the semi-solid mass was treated with aqueous sodium hydroxide and extracted with chloroform. After evaporation of the solvent the residue was stirred with 5% acetic acid (150 c.c.), filtered and extracted with ether. The acetic solution was then basified and extracted with chloroform. Evaporation of the dried chloroform extract left an oily base contaminated with γ-diethylaminopropylamine. This was removed by heating overnight at 120—130°/15 mm. and the residue dissolved in dilute hydrochloric acid and treated with perchloric acid to give the same perchlorate as in (*a*), m. p. and mixed m. p. 215—217° (Found: C, 45·7; H, 5·2%).

For biological testing the perchlorates from (*a*) and (*b*) were combined and treated with aqueous sodium hydroxide, and the liberated base was isolated with chloroform.

2-Chloro-4-γ-diethylaminopropylamino-3-ethylquinoline.—4-γ-Diethylaminopropylamino-2-hydroxy-3-ethylquinoline (15 g.) and phosphoryl chloride (35 c.c.) were heated at 115—125° for 16 hours followed by working up as described for the corresponding 3-methyl compound to give the product as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as yellow plates, m. p. 144—146° (Found: N, 16·3; Cl, 4·6. $C_{18}H_{26}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·2; Cl, 4·6%).

2 : 4-*Dichloro-3-ethylquinoline.*—2 : 4-Dihydroxy-3-ethylquinoline (50 g.) and phosphoryl chloride (150 c.c.) were heated with stirring at 100—110° for ½ hour and then at 120—125° for 4 hours. The cooled mixture was poured on ice and after being stirred for several hours the product was extracted with ether. Evaporation of the washed and dried ethereal extract gave an oil which was purified by vacuum distillation, b. p. 182—184°/21 mm. (yield, 88%) (Found: Cl, 31·0. $C_{11}H_9NCl_2$ requires Cl, 31·4%).

4-*Chloro-2-p-chloroanilino-3-ethylquinoline.*—2 : 4-Dichloro-3-ethylquinoline (22·6 g.), *p*-chloroaniline (12·75 g.), and acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring and then refluxed for 10 minutes. When cold, the mixture was diluted with water and made strongly acid to Congo-red with hydrochloric acid. The practically colourless crystalline powder thereby obtained was filtered off, washed with water, and heated on the steam-bath for 10 minutes with methanol (100 c.c.) and sufficient ammonia to give an alkaline reaction. Dilution with water gave a product which was filtered off, dried, and crystallised from alcohol; it was obviously a mixture (18·4 g.). Crystallisation from dioxan (40 c.c.) gave fine needles of 2 : 4-*di*-p-*chloroanilino-3-ethylquinoline* (3·6 g.), m. p. 224—226° (Found: Cl, 17·3. $C_{23}H_{19}N_3Cl_2$ requires Cl, 17·4%), and dilution with water the required 4-*chloro*-2-p-*chloroanilino-3-ethylquinoline* which crystallised from alcohol in stout prisms, m. p. 132—133° (Found: N, 9·0; Cl, 22·4. $C_{17}H_{14}N_2Cl_2$ requires N, 8·8; Cl, 22·4%).

2-*Amino-4-γ-diethylaminopropylaminoquinoline* (VI; R = NH_2, R′ = NH·[CH_2]$_3$·NEt_2).—Ammonia was passed through a solution of 2-chloro-4-γ-diethylaminopropylaminoquinoline (5·2 g.) in phenol (20 g.) at 170—180° for 18 hours. The cooled mixture was treated with aqueous sodium hydroxide and ether, and the ether layer washed thoroughly with dilute sodium hydroxide and then with water and dried (Na_2SO_4). Removal of the solvent left a syrup which solidified on trituration with light petroleum (b. p. 60—80°). By crystallisation from benzene–light petroleum the *amino*-compound was obtained as colourless stout prisms, m. p. 125—126° (Found: N, 20·0. $C_{16}H_{24}N_4$ requires N, 20·6%).

2-p-*Chlorophenylthioureido-4-γ-diethylaminopropylaminoquinoline* (X; R = [CH_2]$_3$·NEt_2).—2-Amino-4-γ-diethylaminopropylaminoquinoline (13·5 g.), *p*-chlorophenyl *iso*thiocyanate (9·0 g.), and dry xylene (30 c.c.) were refluxed for 1 hour. On cooling, the clear solution deposited crystals which were filtered off, washed with benzene, and dried. Crystallisation from xylene gave pale yellow stout prisms (yield, 72%), m. p. 188—189° (Found: N, 15·4; S, 6·9. $C_{23}H_{28}N_5ClS$ requires N, 15·9; S, 7·25%).

2-p-*Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline* (XI; R = [CH_2]$_3$·NEt_2).—The above thioureido-compound (6·5 g.) was stirred with saturated alcoholic ammonia (100 c.c.) and mercuric oxide (7 g.) for 24 hours at 30—35° with the continuous passage of ammonia into the solution. After cooling, the mixture was filtered and the dried residue extracted with hot xylene from which the product separated on cooling (yield, 78%). It formed colourless needles from xylene, m. p. 208° (Found: C, 65·3; H, 6·5; N, 19·8. $C_{23}H_{29}N_6Cl$ requires C, 65·0; H, 6·8; N, 19·8%). 2-p-*Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline* is only very sparingly soluble in alcohol.

2-*Amino-4-β-diethylaminoethylaminoquinoline* (VI; R = NH_2, R′ = NH·[CH_2]$_2$·NEt_2.—Ammonia was passed for 22 hours into a solution of 2-chloro-4-β-diethylaminoethylaminoquinoline (21·9 g.) in phenol (50 g.) at 170—180°. The mixture was cooled, treated with sodium hydroxide solution, and shaken with ether. The ether solution after being washed with sodium hydroxide and then with water was extracted with 5% acetic acid. Addition of ammonia to this extract to render it alkaline to Brilliant-yellow precipitated 4-*β-diethylaminoethylamino-2-phenoxyquinoline* (VI; R = OPh, R′ = NH·[CH_2]$_2$·NEt_2) as an oil which rapidly solidified. After being collected and dried, it crystallised from *cyclo*hexane in large irregular prisms, m. p. 104—105° (Found: N, 12·9. $C_{21}H_{25}ON_3$ requires N, 12·5%). Addition of sodium hydroxide to the aqueous filtrate precipitated 2-*amino-4-β-diethylaminoethylaminoquinoline* as an oil which gradually solidified (yield, 13 g.). After drying, it crystallised from *cyclo*hexane with the addition of a little water as practically colourless laminæ, m. p. 114—115° (Found: C, 69·8; H, 8·7; N, 21·8. $C_{15}H_{22}N_4$ requires C, 69·75; H, 8·5; N, 21·75%). Under the above conditions of crystallisation it was sometimes obtained as a *hydrate*, m. p. 75—77° (Found: C, 63·2; H, 8·8; N, 18·9. $C_{15}H_{22}N_4,1·5H_2O$ requires C, 63·2; H, 8·8; N, 19·6%).

2-p-*Chlorophenylthioureido-4-β-diethylaminoethylaminoquinoline* (X· R = [CH_2]$_2$·NEt_2), prepared by heating the above amino-compound (10 g.) with *p*-chlorophenyl *iso*thiocyanate (6·6 g.) in boiling xylene (30 c.c.) for 1 hour, crystallised from benzene in colourless needles, m. p. 181—182° (Found: N, 16·3; S, 7·2. $C_{22}H_{26}N_5ClS$ requires N, 16·4; S, 7·5%).

2-p-*Chlorophenylguanidino-4-β-diethylaminoethylaminoquinoline* (XI; R = [CH_2]$_2$·NEt_2).—The preceding thiourea (6 g.) and mercuric oxide (6 g.) were added to saturated alcoholic ammonia (100 c.c.) at 0°. With stirring, the mixture was allowed to regain room temperature, then warmed to 30—35° and ammonia passed in for 2 hours. After being stirred at this temperature for 19 hours the mixture was filtered and the insoluble residue dried and extracted with benzene to give the *product* as colourless needles, m. p. 202—203° (Found: N, 20·2. $C_{22}H_{27}N_6Cl$ requires N, 20·5%).

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