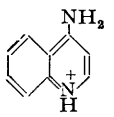
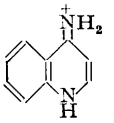
311. *Synthetic Antimalarials. Part XLI. Physicochemical Studies on Quinoline Derivatives.*

By J. C. Gage.

The absorption spectra and dissociation constants of a number of 4-aminoquinoline derivatives have been measured. The influence of substituents on these properties is correlated with their effect on antimalarial activity, and it is shown that the activity is closely connected with the distribution of cationic charge between the 4-amino- and heterocyclic-nitrogen atoms; a similar charge distribution can be identified in a number of chemical types which show a specific antimalarial activity.

The structure of the 4-aminoquinoline ion has been discussed by Albert and Goldacre (*Nature*, 1944, **153**, 467), Drake, Creech, Draper, Garman, Haywood, Peck, Walton, and Van Hook (*J. Amer. Chem. Soc.*, 1946, **68**, 1214), and by Irvin and Irvin (*J. Amer. Chem. Soc.*, 1947, **69**, 1091); it has been suggested that the proton is attached to the heterocyclic nitrogen atom and that the ion is stabilised by resonance of the type (I*a*, *b*), which involves a distribution of the charge between the two nitrogen atoms.

(I*a*.)   (I*b*.)

Quinoline derivatives carrying a dialkylaminoalkylamino-group or basic side-chain in the 4-position form a well-known group of drugs with a high specific antimalarial activity. The ultra-violet absorption spectra and pK values of certain members of this series were studied by Irvin and Irvin (*loc. cit.*). The present communication extends the investigation of these authors, and the findings are discussed with reference to Parts XXXIV and XXXVI of this series (Gage, this vol., pp. 221, 469).

The Calculation of Dissociation Constants.

In Part XXXVI (Gage, *loc. cit.*) equations (1) and (2) were derived for calculating the dissociation exponents (pK values) of an unsymmetrical diacid base by potentiometric titration, where K_1 and K_1' are the constants of the equilibria between the base B_1B_2 and protons to form the ions $H^+B_1B_2$ and $B_1B_2H^+$, respectively (B_1 being the more basic centre), and K_2 the constant of the equilibrium of $H^+B_1B_2$ and a proton; y and pH are quantities determined from the titration. The exponents of 4-aminoquinoline and the aliphatic diamines (Tables I and II), from which an approximation to K_1/K_1' can be obtained, indicate that in the dialkylamino-alkylaminoquinolines this term may not be negligible. It is not possible to derive K_1/K_1' from titration data, but, as indicated below, it may be determined from the spectrometric results.

$$pK_1 = pH - \log_{10}[(1 - y)/y] - \log_{10}(1 + K_1/K_1') \quad . \quad . \quad . \quad . \quad (1)$$

$$pK_2 = pH + \log_{10}[(2 - y)/(y - 1)] + \log_{10}(1 + K_1/K_1') \quad . \quad . \quad . \quad (2)$$

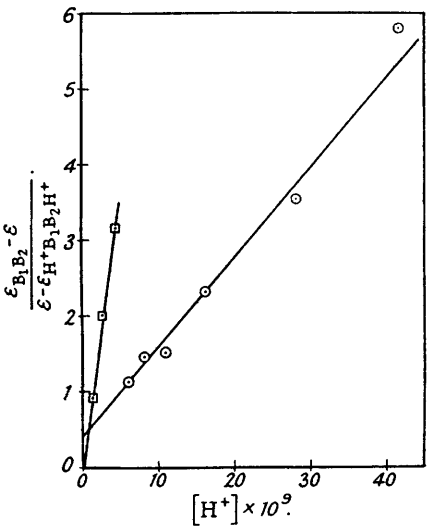
The difference between the first and second dissociation constants of the basic-side-chain pyrimidines examined in Part XXXVI (Gage, *loc. cit.*) permitted them to be regarded as monoacid bases for the purpose of deriving K_2 from spectrometric observations, but the probable value of K_1/K_1' in the quinolines containing a basic side-chain at position 4 suggests that this treatment may not justifiably be extended to this series. It can readily be shown that K_2 may be calculated by equation (3) from the molar extinction coefficient ε of a solution at hydrogen-ion concentration $[H^+]$, provided that the coefficients of the four components of the equilibrium of the base B_1B_2 in the presence of hydrogen ions ($\varepsilon_{B_1B_2}$, $\varepsilon_{H^+B_1B_2}$, $\varepsilon_{B_1B_2H^+}$, $\varepsilon_{H^+B_1B_2H^+}$) are known. If $[H^+]$ is selected so that $K_1'/[H^+]$ is negligible, and if it is assumed, as by Irvin and Irvin, that $\varepsilon_{B_1B_2}$ equals $\varepsilon_{H^+B_1B_2}$, and $\varepsilon_{B_1B_2H^+}$ equals $\varepsilon_{H^+B_1B_2H^+}$, then (3) reduces to (4).

$$[H^+]/K_2 = (\varepsilon_{H^+B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+}) + [(\varepsilon_{B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+})]K_1/[H^+] + [(\varepsilon_{B_1B_2H^+} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+})]K_1/K_1' \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$[H^+]/K_2 = (\varepsilon_{B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+}) - K_1/K_1' \quad . \quad . \quad . \quad . \quad . \quad (4)$$

A plot of $[H^+]$ against $(\varepsilon_{B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+})$ should yield a straight line, the slope of which gives K_2, and the intercept when $[H^+]$ equals zero will be K_1/K_1'. It is shown later that the

absorption spectrum of the ionised 4-aminoquinoline system is influenced by the electron affinity of the 4-amino-substituent, and the considerable electronegative inductive effect of the charged β-diethylaminoethyl group (Gage, Part XXXVI, *loc. cit.*) suggests that in 4-β-diethylaminoethylaminoquinoline the assumption that $\varepsilon_{B_1B_2H^+}$ equals $\varepsilon_{H^+B_1B_2H^+}$ may not be justifiable. The figure, however, shows that with this compound the plot of $[H^+]$ against $(\varepsilon_{B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{H^+B_1B_2H^+})$ is almost a straight line, which suggests that any deviations from the assumptions on which (4) is based are of no great significance.



⊙ 4-β-*Diethylaminoethylaminoquinoline.*
⊡ 4-γ-*Diethylaminopropylaminoquinoline.*

Discussion.

The results in Table I show that the dissociation exponent of the heterocyclic system (pK_2) of the 4-basic side chain quinolines (II) increases as the chain length increases; this may be attributed to the decrease in the electronegativity of the charged substituent on the 4-amino-group, and some measure of this inductive effect may be obtained from the difference between the pK_1 and pK_2 values (ΔpK) of the corresponding alkylenediamines (Table II).

In weakly acid solution the absorption spectra of 4-aminoquinoline derivatives show an absorption band with a double peak within the range 325 to 350 mμ. which is closely associated with the existence of the resonance forms (I*a*, *b*) (Drake *et al.*, *loc. cit.*; Irvin and Irvin, *loc. cit.*). Table I shows the effect of substituents on the 4-amino-group on the difference between the extinction coefficients of these two peaks (Δε). Since the basic side-chain is saturated its influence on the absorption spectrum must be attributed to its inductive effect; the alternative assumption, that there is an interaction between the terminal nitrogen atom of the chain and

TABLE I.

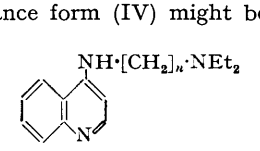
The antimalarial activities were communicated privately by Dr. D. G. Davey. The detailed results will be published later; the methods of assessing activity and reporting the results are referred to in Part I (Curd and Rose, *J.*, 1946, 343). Experimental details of the spectrometric and titrimetric determinations are given in Part XXXVI (*loc. cit.*).

Quinoline substituents.	$\varepsilon_{max.}$ at λλ given in parentheses.		Δε.	p*K*. Titrimetric, pK_1.	p*K*. Titrimetric, pK_2.	p*K*. Spectrometric, pK_2.	Antimalarial activity. Dose mg./kg.	Activity.
4-Amino	12,450(320)	10,900(335)	1550					
4-Methylamino	15,100(325)	15,050(338)	50					
4-Methylamino-6-methoxy	11,800(338)	12,200(350)	−400					
7-Chloro-4-methylamino	15,000(328)	15,500(340)	−500					
4-β-Diethylaminoethylamino-6-methoxy	10,650(338)	10,700(347)	− 50				80	++
							40	+ to ++
							20	+
7-Chloro-4-β-diethylaminoethylamino	15,150(325)	14,400(337)	750				10	++
							5	±
6-Chloro-4-γ-diethylaminopropylamino	14,400(334)	14,200(346)	200				40	++
							20	(?)
7-Chloro-4-γ-diethylaminopropylamino	16,150(328)	16,350(340)	−200				5	++
							2	±
4-β-Diethylaminoethylamino	16,300(325)	15,000(338)	1300	8·95	7·90	8·10	80	++
							40	+ to ++
							20	+
4-γ-Diethylaminopropylamino	16,500(326)	16,000(337)	500	10·00	8·55	8·75	10	++
							8	+
4-δ-Diethylaminobutylamino	15,700(327)	15,800(340)	−100	10·25	8·80	9·10	20	++
							10	+
4-δ-Diethylamino-α-methylbutylamino	17,100(328)	17,500(340)	−400	10·25	8·85	9·05	20	++
							10	+
							5	±
4-3′-Diethylaminopropylamino 3′-methiodide	16,650(326)	15,850(337)	800	—	8·55	8·65	—	—

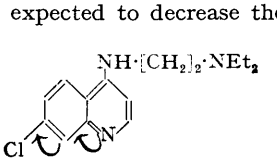
TABLE II.

Compound.	pK_1.	pK_2.	ΔpK ($= \log_{10} 1/E$).
$NEt_2 \cdot [CH_2]_2 \cdot NEt_2$	9·3	6·65	2·65
$NH_2 \cdot [CH_2]_3 \cdot NH_2$	9·8	8·8	1·0
$NEt_2 \cdot [CH_2]_3 \cdot NEt_2$	9·75	8·60	1·15
$NEt_2 \cdot [CH_2]_4 \cdot NH_2$	10·3	9·2	1·1
$NEt_2 \cdot [CH_2]_3 \cdot CHMe \cdot NH_2$	10·1	9·55	0·55

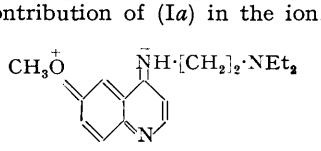
some part of the heterocyclic system, is improbable in the doubly charged cation, and, moreover, quaternisation of the terminal nitrogen does not significantly affect $\Delta\varepsilon$ or pK. A decrease in the electronegativity of the 4-amino-substituent is attended by a decrease in $\Delta\varepsilon$, and, since an electronegative group in this position will favour the resonance form (I*b*), it is a reasonable hypothesis that $\Delta\varepsilon$ is determined to some extent by the relative contributions of the two structures (I*a*, *b*). The influence, on $\Delta\varepsilon$, of substituents on the quinoline nucleus supports the hypothesis insofar as their effect on the electron-density distribution between the heterocyclic and 4-amino-nitrogen atoms can be predicted; chlorine in the 7-position might be expected to attract electrons preferentially from the heterocyclic nitrogen atom (III) to a greater extent than it does in the 6-position, and there are three examples of 7-chloro-compounds which show a marked decrease in $\Delta\varepsilon$, while one 6-chloro-derivative does not. A 6-methoxy-group decreases $\Delta\varepsilon$, and, if this is regarded as an electron-donating group in conformity with the σ value ascribed to it by Hammett (" Physical Organic Chemistry ", New York, 1940, p. 188), rather than, as stated by Irvin and Irvin (*loc. cit.*), as an electron-attracting group, then the possibility of the resonance form (IV) might be expected to decrease the contribution of (I*a*) in the ion.



(II.)



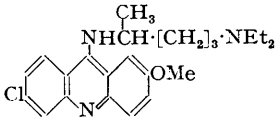
(III.)

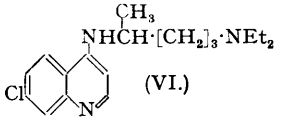


(IV.)

The antimalarial activities recorded in Table I indicate that 4-β-diethylaminoethylamino-quinoline (II; $n = 2$) has an appreciably lower biological activity than its higher homologues; this cannot be attributed entirely to the effect of the length of the basic side-chain on pK_2 since the activity reappears in the 7-chloro-derivative. The pK_2 of this latter compound has not been accurately determined, but a potentiometric-titration curve has shown that it is not higher than that of (II; $n = 2$). A 7-chloro-group also increases the biological activity of (II; $n = 3$), but there is evidence from the 6-chloro-derivative of this compound that chlorine in this position has a dystherapeutic effect, though the biological results available at present are not sufficiently conclusive for this to be definitely established. The above observations suggest that there is some parallel between the effect of substituents on $\Delta\varepsilon$ and their influence on antimalarial activity. According to this hypothesis, 4-β-*diethylaminoethylamino-6-methoxyquinoline* should possess a higher antimalarial activity than does (II; $n = 2$); this is not evident in the biological results. The active antimalarial mepacrine (V) does, however, contain a methoxy-group in an analogous position relative to the heterocyclic and amino-nitrogen atoms, in addition to a chlorine atom in a position analogous to that in which it occurs in the 7-chloroquinolines. Both (V) and the antimalarial " Chloroquine " (VI) contain the δ-diethylamino-α-methylbutyl group in the basic side-chain; this group produces the lowest ΔpK value of the diamines recorded in Table II, and it also gives the lowest value for $\Delta\varepsilon$ in the series (II).

The analogy between (V) and (VI) is very close; it can be extended to include a number of other chemical types which show a specific antimalarial activity, and the diagram (VII;

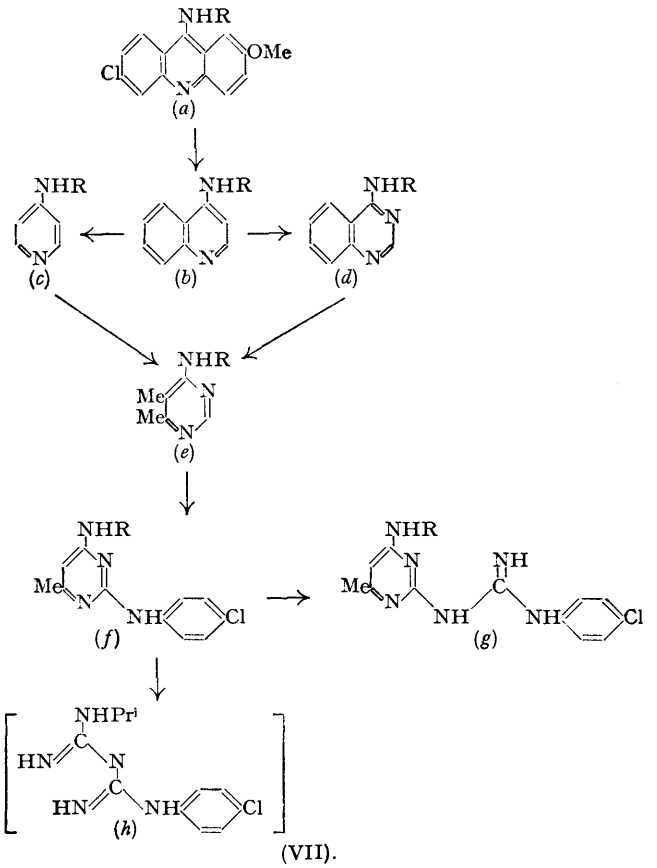
(V.)




(VI.)

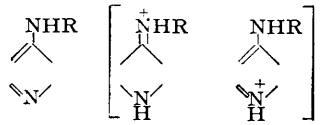
R = dialkylaminoalkyl) shows the family relationships which exist between the acridine, quinoline, quinazoline, pyridine, and pyrimidine antimalarials. It will be seen that the system consisting of a substituted amino-group *para* to a heterocyclic nitrogen atom (VIII) is common to each of these chemical types. The recorded dissociation exponents of mepacrine (Christophers, *Ann. Trop. Med. Parasitol.*, 1937, **31**, 43), 4-aminopyridine (Albert and Goldacre,

loc. cit.), the pyrimidine derivatives (Gage, Part XXXVI, *loc. cit.*), and the 4-aminoquinolines (Table I) indicate that in these compounds the heterocyclic system exists largely as the ion at the pH of biological fluids. pK_2 of the quinazoline derivative (VII*d*; R = $NEt_2{\cdot}[CH_2]_2$) has been found by potentiometric titration to be 7·6 and is therefore of the same order as that of the pyrimidines (VII*e* and *f*). It is possible, therefore, that the essential pharmaco-dynamic group of all these chemical types comprises an amino-nitrogen atom *para* to a protonised heterocyclic nitrogen atom, both of which share the cationic charge (IX); this may be regarded as an extension of Schönhöfer's suggestion that antimalarial activity is connected with the tautomeric possibilities of the group (VIII) (*Z. physiol. Chem.*, 1942, **274**, 1). If the hypothesis that $\Delta\varepsilon$ depends on the electron-distribution of (IX) be accepted, the parallelism between the effect of substituents on the biological activity of the quinolines containing a basic side-chain and their effect on $\Delta\varepsilon$ indicates that an important function of the remainder of the molecule may be suitably to regulate this electron distribution. It is necessary to exclude from this



(VII).

generalisation the peculiar property of the charged terminal nitrogen atom of the basic side-chain, which, as suggested by Delektorskaya and Lipowitsch (*Arch. Pharm.*, 1934, **272**, 24), is most probably conductophoric and which appears to be entirely divorced from the function of the group (IX); although, since both parts of the molecule are essential for specific antimalarial activity, some limit to their spatial relationship may be required.



(VIII.) (IX.)

The above hypothesis does not exclude the existence of structures other than (IX) with a high potential antimalarial activity; there are notable omissions from scheme (VII), for example, quinine, the quinoline carbinols, and pamaquin; the first two of these do not possess the amino-nitrogen of (IX), and in none is the heterocyclic system appreciably ionised at physiological pH values. The inclusion of the diguanide antimalarials (VII*h*) may be criticised as the structure of the ion has not been elucidated (Gage, Part XXXIV, *loc. cit.*); nevertheless, it is evident that a structure analogous to (IX) may also exist in this chemical type.

Experimental.

The molar extinction coefficients were determined as described in Part XXXVI (Gage, *loc. cit.*). The figure shows the variation of $(\varepsilon_{B_1B_2} - \varepsilon)/(\varepsilon - \varepsilon_{HB_1B_2H^+})$ with $[H^+]$ for 4-β-diethylaminoethylaminoquinoline and 4-γ-diethylaminopropylaminoquinoline; the value of K_2 and K_1/K_1' for the former may be calculated from the slope of the line and the intercept by equation (4); the intercept and, therefore, K_1/K_1' of the latter compound is negligible.

For potentiometric titration 4×10^{-4}M-solutions of the bases in a known excess of hydrochloric acid were prepared and titrated with 0·01N-sodium hydroxide. Equations (1) and (2) were used to calculate the dissociation exponents of the 4-diethylaminoalkylaminoquinolines; for the derivative with two carbon atoms in the alkyl chain K_1/K_1' was taken from the spectrometric results, whilst with three or more carbon atoms this term is negligible. The dissociation exponents of the symmetrical alkylenediamines with two or three carbon atoms in the chain were also determined by (1) and (2), but with four carbon atoms in the chain the conditions of these equations are not fulfilled, and Barton's equation (Barton, *Nature*, 1947, **160**, 752; Gage, Part XXXVI, *loc. cit.*) was used. For this calculation, K_1 was assumed to be equal to K_1'; the dissociation exponents of trimethylenediamine and its tetraethyl derivative (Table II) indicate that no serious error is thereby involved.

The experimental results do not permit a statistical determination of precision, but there is little doubt that the great majority of the dissociation exponents lie within the limits $\pm 0{\cdot}05$ unit, with the possible exception of the pK_1 values of the quinolines with basic side-chain for which the error may be somewhat greater.

4-*Methylaminoquinolines*.—4-Chloroquinoline (1·0 g.) was dissolved in ethanol (15 c.c.) and treated with 21·5% aqueous methylamine (3·0 c.c.) in a sealed tube at 155—165° for 12 hours. 4-*Methylaminoquinoline* was poured into water, and the precipitate collected; it was treated with charcoal in hot ethanol and crystallised twice from aqueous ethanol, m. p. 230—231° (Found: C, 75·5; H, 6·1; N, 17·35. $C_{10}H_{10}N_2$ requires C, 75·9; H, 6·35; N, 17·7%). 7-*Chloro*-4-*methylaminoquinoline* was similarly prepared from 4 : 7-dichloroquinoline (2·0 g.) and 21·5% methylamine solution (5·0 c.c.) and had m. p. 247—248° (Found: N, 14·6; Cl, 18·8. $C_{10}H_9N_2Cl$ requires N, 14·55; Cl, 18·85%). 4-*Methylamino*-6-*methoxyquinoline*, similarly prepared from 4-chloro-6-methoxyquinoline (19 g.) and 21·5% methylamine solution (46·5 c.c.), had m. p. 211—212° (Found: C, 69·8; H, 6·3; N, 15·3. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

4-β-*Diethylaminoethylamino*-6-*methoxyquinoline*.—4-Chloro-6-methoxyquinoline (2·0 g.), β-diethylaminoethylamine (3·5 c.c.), and potassium iodide (0·01 g.) were heated at 160—170° for 6 hours. The mixture was dissolved in 10% acetic acid (20 c.c.) and sodium acetate (1·0 g.), treated with charcoal, made alkaline, and extracted with benzene. After removal of the benzene from the dried extract, the *product* was distilled in a vacuum and crystallised from light petroleum, m. p. 99° (Found: C, 69·8; H, 8·35; N, 14·9. $C_{16}H_{23}ON_3$ requires C, 70·3; H, 8·45; N, 15·4%).

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