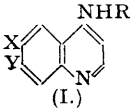
231. *Synthetic Antimalarials. Part XLVI. Some 4-Dialkylaminoalkylaminoquinoline Derivatives.*

By Justus K. Landquist.

The 4-3′-diethylaminopropylamino-derivatives of quinoline, 2- and 3-methylquinoline, and 2 : 3-dimethylquinoline, and the corresponding 6-methoxy- and 7-chloro-compounds have been made. Their absorption spectra and antimalarial activities are discussed. The orientation of the 7-chloro-compounds was established by synthesis. Preparation of miscellaneous 4-dialkylaminoalkylaminoquinoline derivatives from 4-chloroquinolines, 2 : 4-dihydroxyquinolines, and quinoline-4-sulphonic acids is described. Formation of acylanthranilic acids in the Camps 4-hydroxyquinoline synthesis, and of a 4-ethoxyquinoline derivative in the Conrad–Limpach reaction, is recorded.

Concurrently with the investigations described in other papers of this series, a limited study of certain 4-dialkylaminoalkylaminoquinolines was made. Conflicting reports about the antimalarial activity of compounds of this type had appeared in the literature. Thus, Holcomb and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1309) stated that 4-3′-diethylaminopropylamino-6-methoxyquinaldine is active in avian malaria although Kermack and Smith (*J.*, 1931, 3096) and Magidson and Rubtsov (*J. Gen. Chem., U.S.S.R.*, 1937, **7**, 1896) had reported that compounds of this type are inactive. Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) stated that 4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline is active and in B.P. Appl. 27,673/38 and its foreign equivalents (G.P. 683,692; U.S.P. 2,233,970, etc.) I.G. Farbenind. claimed high antimalarial activity for 4-aminoalkylaminoquinolines bearing at least a further substituent in the 7-position, but stated that the 2-position should be unsubstituted. It seemed likely that these discrepancies were due to differences in susceptibility to a given drug between different species of plasmodia either in the same or in different hosts (cf. Curd, *Ann. Trop. Med. Parasitol.*, 1943, **37**, 115). The importance of species susceptibility in relation to the search for new antimalarial drugs has been discussed by Davey (*ibid.*, 1946, **40**, 52) and the 4-dialkylaminoalkylaminoquinolines appeared to afford a suitable class of compounds with which to study this problem.

The synthesis of representative compounds of this class was undertaken to determine whether German work subsequent to the discovery of mepacrine had disclosed antimalarials of greater potency, to examine these drugs against the species of plasmodia used in these laboratories, and to provide a basis for comparison with our own novel types. When the work was projected in 1942 no proof had been offered of the structure of the 7-chloro-4-dialkylaminoalkylaminoquinolines, so unambiguous syntheses were devised. Since the completion of this work details of the preparation and clinical testing of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (" Chloroquine ") and its 3-methyl derivative (" Sontochin ") have been published (Wiselogle, " Survey of Antimalarial Drugs, 1941—1945," Edwards, Ann Arbor, 1946; C.I.O.S. Reports XXIII-12, XXV-54; Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1214, etc.).



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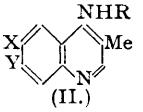

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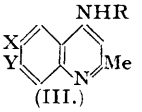

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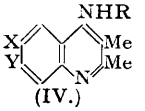
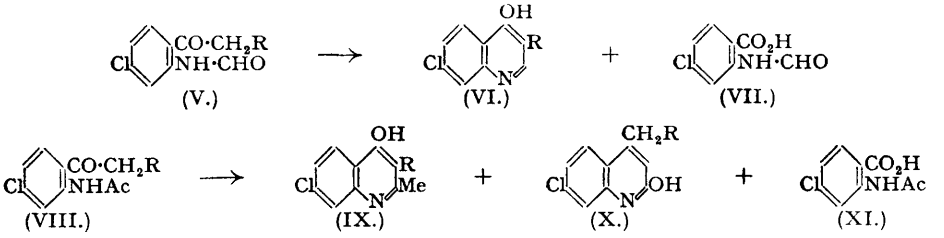


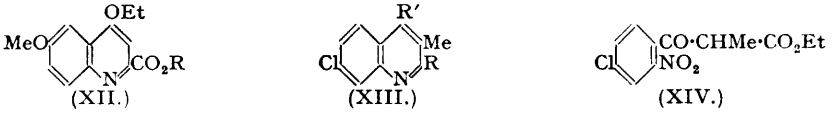
(IV.)

Apart from " Chloroquine " which was not then available from other sources, the substances synthesised fell into three series of four compounds (I—IV), where R = $Et_2N{\cdot}[CH_2]_3{\cdot}$ and (*a*) X = Y = H, (*b*) X = MeO, Y = H, and (*c*) X = H, Y = Cl, representing successive stages of simplification of the " Acrichin " molecule. The diethylaminopropyl side chain was chosen for convenience in synthesis; it gives high activity in known types of antimalarials, *e.g.*, " Plasmocide," " Acrichin," " Brachysan." A few further variations were examined. With the publication of the original German work (Andersag, *Ber.*, 1948, **81**, 499) and of numerous papers from American laboratories much of the preparative work has now been described, but a number of features of this investigation are novel.

4-Hydroxy-3-methylquinoline was made by heating 2-formamidopropiophenone with aqueous-alcoholic sodium hydroxide (cf. Camps, *Ber.*, 1899, **32**, 3228; 1901, **34**, 2703; Wohnlich, *Arch. Pharm.*, 1913, **251**, 526). Cyclisation of 4-chloro-2-formamido-acetophenone (V; R = H) and -propiophenone (V; R = Me) gave 7-chloro-4-hydroxyquinoline (VI; R = H) and its 3-methyl derivative, together with 4-chloro-*N*-formylanthranilic acid (VII). From 2-acetamido-4-chloroacetophenone (VIII; R = H) the Camps ring-closure gave 7-chloro-4-hydroxyquinaldine (IX; R = H), 7-chloro-2-hydroxylepidine (X; R = H), and *N*-acetyl-4-chloroanthranilic acid (XI), and similarly 2-acetamido-4-chloropropiophenone (VIII; R = Me) gave 7-chloro-4-hydroxy-2 : 3-dimethylquinoline (IX; R = Me), 7-chloro-4-ethyl-2-hydroxyquinoline (X; R = Me), and (XI). The formation of *N*-acylanthranilic acids in the Camps reaction has not hitherto been reported. The identity of the compounds (IX and X; R = H or Me) was established by comparison of their absorption spectra with those of known 2- and 4-hydroxyquinolines, and by syntheses by alternative routes. 7-Chloro-2-hydroxylepidine (X; R = H) is obtained by ring-closure of acetoaceto-*m*-chloroanilide with sulphuric acid (C.I.B.A., B.P. 351,605). Condensation of *m*-chloroaniline with acetoacetic ester and with α-methylacetoacetic ester by the Conrad–Limpach method gave mixtures of 5- and 7-chloroquinoline derivatives from which (IX; R = H and Me) were isolated (cf. Spivey and Curd, *J.*, 1949, 2656).



The yields of 4-hydroxyquinoline derivatives from the Camps reaction were poor, and larger quantities were made by condensation of arylamines with ethyl ethoxalylacetate, α-ethoxalylpropionate, or ethoxymethylenemalonate (Andersag, *loc. cit.*; Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890; Surrey and Hammer, *ibid.*, 1946, **68**, 113; Steck, Hallock, and Holland, *ibid.*, pp. 129, 380; Price and Roberts, *ibid.*, p. 1204, etc.). In the preparation of ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate from *p*-anisidine and ethyl ethoxalylacetate the formation of a small amount of ethyl 4-ethoxy-6-methoxyquinoline-2-carboxylate (XII; R = Et) was observed. This compound separated from the mother-liquors from the cyclisation on long storage. Possibly this side reaction, the elimination of water instead of ethanol, occurs in other cases but the 4-ethoxyquinoline derivatives escape detection because of their greater



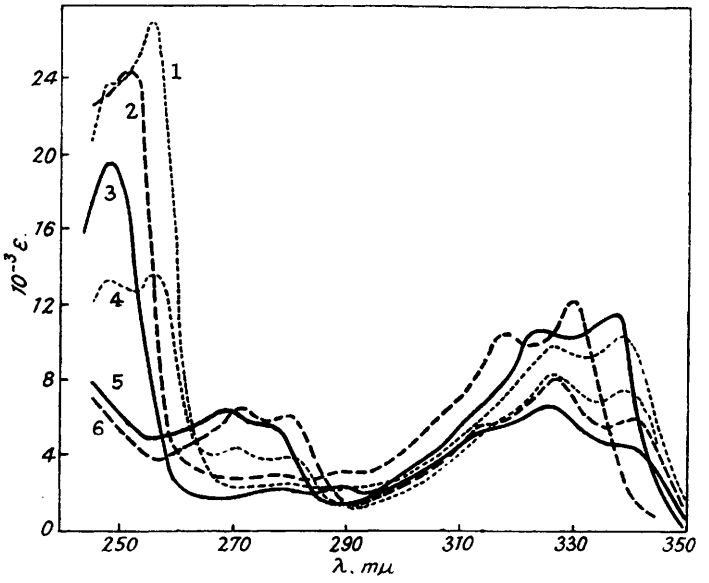
solubility in the reaction mixture. 4-Ethoxy-6-methoxyquinoline-2-carboxylic acid (XII; R = H) was decarboxylated above its m. p., giving 4-ethoxy-6-methoxyquinoline, but its hydrochloride under the same conditions was converted into 4-hydroxy-6-methoxyquinoline. As an alternative to ethyl ethoxalylacetate, ethyl acetylenedicarboxylate was condensed with *p*-anisidine to give ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate, but this route offered no advantage.

The preparation of 4-dialkylaminoalkylaminoquinolines from 2 : 4-dihydroxyquinolines by condensation with dialkylaminoalkylamines, conversion into 2-chloro-4-dialkylaminoalkylaminoquinolines, and dehalogenation by catalytic reduction (Part XVII, Curd, Raison, and Rose, *J.*, 1947, 899) was investigated further, and 4-3′-piperidinopropylaminoquinoline (I; X = Y = H, R = ·$[CH_2]_3$·N < $[CH_2]_5$), 4-3′-diethylaminopropylamino- and 4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline (II; X = Y = H, R = ·$[CH_2]_3$·NEt_2 and ·CHMe·$[CH_2]_3$·NEt_2 respectively), and 4-3′-diethylaminopropylamino-7 : 8-benzoquinoline were made by this method. Attempts to prepare the 7-chloro-derivatives by selective reduction of 2 : 7-dichloro-4-3′-diethylaminopropylaminoquinoline (Part XVII) and 2 : 7-dichloro-4-3′-diethylaminopropylamino-3-methylquinoline (XIII; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2) were

unsuccessful, the only identifiable products after absorption of the required amount of hydrogen being the halogen-free 4-3′-diethylaminopropylaminoquinoline (or its 3-methyl derivative) and unchanged dichloro-compound which were separated by crystallisation of their 3 : 5-dinitrobenzoates. 7-Chloro-2 : 4-dihydroxy-3-methylquinoline (XIII; R = R′ = OH) was obtained by condensing *m*-chloroaniline with ethyl methylmalonate (cf. Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832) and was characterised by conversion into 2 : 4 : 7-trichloro-3-methylquinoline (XIII; R = R′ = Cl). The orientation of these compounds was established by their preparation from ethyl α-(4-chloro-2-nitrobenzoyl)propionate (XIV) by reduction and ring closure. Gentle hydrolysis of 2 : 4 : 7-trichloro-3-methylquinoline (cf. Rowlett and Lutz, *J. Amer. Chem. Soc.*, 1946, **68**, 1288) gave 4 : 7-dichloro-2-hydroxy-3-methylquinoline (XIII R = OH, R′ = Cl).

FIG. 1.

Absorption spectra of quinoline derivatives in chloroform.



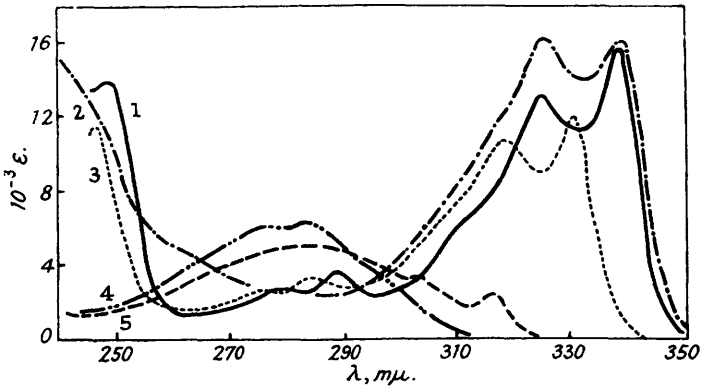
Substituent at position :

Curve no.	2.	3.	4.	7.
1	Me	Me	OH	Cl
2	Me	—	OH	Cl
3	Me	Me	OH	—
4	OH	—	Et	Cl
5	OH	—	Et	—
6	OH	—	Me	Cl

In general, the 4-dialkylaminoalkylaminoquinolines were prepared by heating the corresponding 4-chloroquinolines and dialkylaminoalkylamines at 180°. Condensation of quinoline-4-sulphonic acids with dialkylaminoalkylamines is a useful alternative (I.G Farbenind., B.P. 437,317; Swiss P. 212,594; Rubtsov *et al.*, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 215, 1873; Walker, *J.*, 1947, 1552). 7-Chloroquinoline-4-sulphonic acid, prepared from 4 : 7-dichloroquinoline and sodium hydrogen sulphite (Norton, Benson, Seibert, and Bergstrom, *J. Amer. Chem. Soc.*, 1946, **68**, 1330), reacted very cleanly with 3-diethylaminopropylamine or 4-diethylamino-1-methylbutylamine in aqueous solution at 140—150°, giving (I; X = H, Y = Cl, R = $[CH_2]_3$·NEt_2 or CHMe·$[CH_2]_3$·NEt_2). In B.P. 437,317 (I.G. Farbenind.) it was stated that quinoline-2 : 4-disulphonic acid is obtained from 2 : 4-dichloroquinoline and sodium sulphite, but under conditions comparable with the preparation of quinoline-4-sulphonic acid (Besthorn and Geisselbrecht, *Ber.*, 1920, **53**, 1017) the reaction was very sluggish and the product was 2-hydroxyquinoline-4-sulphonic acid. Reaction of this compound with aqueous 3-piperidinopropylamine at 140—150° gave 2-hydroxy-4-3′-piperidinopropylaminoquinoline which was also prepared from 2 : 4-dihydroxyquinoline and 3-piperidinopropylamine at 180°.

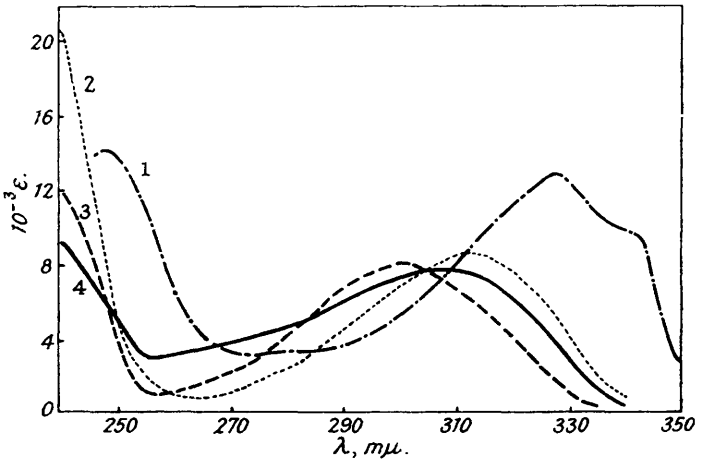
Reaction of (XIII; R = R′ = Cl) with sodium hydrogen sulphite was even more sluggish, the product being 7-chloro-2-hydroxy-3-methylquinoline-4-sulphonic acid (XIII; R = OH, R′ = SO_3H). In view of the instability of quinoline-2-sulphonic acid (Besthorn and Geisselbrecht, *loc. cit.*) the failure to obtain quinoline-2 : 4-disulphonic acids in these reactions is not surprising. Reaction of 2 : 4-dichloroquinoline with 4-diethylamino-1-methylbutylamine gave 2 : 4-bis-(4-diethylamino-1-methylbutylamino)quinoline.

FIG. 2.



1, 1-*Methyl*-4-*quinolone in* $CHCl_3$.
2, 4-3′-*Diethylaminopropylaminoquinoline in* 0·1N-HCl.
3, 4-*Hydroxyquinoline in* $CHCl_3$.
4, 4-*Methoxyquinoline in* $CHCl_3$.
5, 4-*Chloroquinoline in* $CHCl_3$.

FIG. 3.



1, 4-3′-*Diethylaminopropylaminoquinoline in* $CHCl_3$.
2, 4-*Hydroxyquinoline in* 0·1N-NaOH.
3, 4-*Methoxyquinoline in* 0·1N-HCl.
4. 1-*Methyl*-4-*quinolone in* 0·1N-HCl.

The ultra-violet absorption spectra of the 2- and 4-hydroxyquinolines produced by the Camps reaction were determined in order to identify the compounds. Both types have broadly similar spectra with three main regions of absorption at 230—250, 270—280, and 310—350 mμ., but the two series are sharply differentiated by the relative intensities of these bands. In the 2-hydroxyquinolines the middle bands are more intense than in the 4-hydroxy-compounds, and the long-wave-length band approximates to a triplet with the greatest absorption in the middle (Fig. 1). The spectrometric measurements were later extended to a number of 4-chloro-,

4-hydroxy-, and 4-3′-diethylaminopropylamino-quinolines in the hope of discovering some relation between molecular polarisation and antimalarial activity. Potentiometric and spectrometric studies of certain of these compounds have already been described by Gage (Part XLI, *J.*, 1949, 1458), and similar investigations have been made by Irvin and Irvin (*J. Amer. Chem. Soc.*, 1947, **69**, 1091), Steck and Ewing (*ibid.*, 1946, **68**, 2181; 1948, **70**, 3397), and Steck, Ewing, and Nachod (*ibid.*, 1948, **70**, 3410, 3954; 1949, **71**, 238, 2334). The last authors concluded that " little, if any, clear interrelation may be found between absorption spectra here determined and antimalarial activity," and the present studies have been no more

TABLE I.

Spectroscopic data.

Parent compound and substituent.	Solvent.	$\lambda_{max.}$, (mμ.); ε × 10^{-3} in parentheses.
1-Methyl-4-quinolone ...	$CHCl_3$	249 (13·9); 279 (2·76); 289 (3·88); 325 (13·2); 339 (15·8).
	0·1N-HCl	310 (7·61).
4-Methoxyquinoline ...	$CHCl_3$	277 (6·16); 283 (6·24).
	0·1N-HCl	~296 (7·60); 301 (8·02).
7-Chloro-2-hydroxy-4-methylquinoline	$CHCl_3$	271 (6·42); 279 (6·02); 327 (8·28); 341 (6·01).
4-Ethyl-2-hydroxyquinoline.		
Unsubstituted	$CHCl_3$	268 (6·35); 275·5 (5·61); 326 (6·68); ~340 (4·60).
7-Chloro	,,	248·5 (13·35); 256 (13·55); 270·5 (4·27); 279 (3·97); 326 (8·35); 339 (7·44).
4-Hydroxyquinoline.		
Unsubstituted	0·1N-NaOH	312 (8·60).
	$CHCl_3$	246 (11·6); 276 (2·71); 285 (3·43); 318 (10·75); 331 (12·1).
2-Methyl	,,	247 (13·75); 273 (1·96); 285 (2·70); 317 (10·7); 329 (11·5).
3-Methyl	,,	248 (17·15); 278 (2·52); 287 (3·20); 325 (10·95); 338 (12·6).
2 : 3-Dimethyl	,,	248 (19·65); 277 (2·13); 288 (2·22); 324 (10·7); 337 (11·7).
7-Chloro-4-hydroxyquinoline.		
Unsubstituted	$CHCl_3$	246 (19·2); 253 (21·35); 278 (2·02); 290 (2·34); 320 (10·3); 333 (12·0).
2-Methyl	,,	252 (24·25); 277 (2·84); ~290 (3·00); 318 (10·65); 330 (12·4).
3-Methyl	,,	248 (22·85); 255 (26·7); 280 (1·55); 327·5 (9·35); 340 (10·3).
2 : 3-Dimethyl	,,	249 (23·85); 256 (27·2); 281 (2·34); 326 (9·90); 339 (10·55).
4-Chloroquinoline.		
Unsubstituted	$CHCl_3$	284·5 (5·04); 303 (3·37); 316·5 (2·53).
2-Methyl	,,	245·5 (5·15); 282 (4·52); 307 (3·55); 320 (3·63).
3-Methyl	,,	282 (3·66); 306 (2·54); 320 (2·61).
2 : 3-Dimethyl	,,	282 (3·50); 306 (3·08); 320 (3·83).
4 : 7-Dichloroquinoline.		
Unsubstituted	$CHCl_3$	279 (4·73); 310 (2·86); 324 (3·30).
2-Methyl	,,	243 (4·07); 278 (4·76); 310 (3·68); 324 (4·68).
3-Methyl	,,	244 (3·29); 277 (5·25); 314 (3·32); 327 (3·84).
2 : 3-Dimethyl	,,	243 (4·30); 276 (4·70); 312 (3·63); 326 (4·74).
4-3′-Diethylaminopropylaminoquinoline.		
Unsubstituted	$CHCl_3$	248 (14·15); 328 (12·85); ~ *ca.* 340.
	0·1N-HCl	232 (19·3); 326 (16·1); 339 (16·0).
2-Methyl	$CHCl_3$	248 (17·5); 321 (11·45).
	0·1N-HCl	233 (21·3); 323 (15·0); 333 (14·2).
3-Methyl	$CHCl_3$	247·5 (19·4); 328 (8·55).
	0·1N-HCl	243 (26·1); 336 (15·35); 348 (15·3).
2 : 3-Dimethyl	$CHCl_3$	247 (20·2); 318 (7·47).
	0·1N-HCl	244 (30·3); 333·5 (14·5); 342 (14·3).
7-Chloro-4-3′-diethylaminopropylaminoquinoline.		
Unsubstituted	0·1N-HCl	~249 (16·4); 255 (17·0); 328 (18·0); 341 (18·7).
2-Methyl	$CHCl_3$	253·5 (18·7); 326 (12·3); ~ *ca.* 335.
	0·1N-HCl	246·5 (19·35); 324 (15·7); 335 (15·75).
3-Methyl	$CHCl_3$	257 (22·25); 335 (7·88).
	0·1N-HCl	253·5 (17·0); 337 (10·5); 350 (10·65).
2 : 3-Dimethyl	$CHCl_3$	253 (21·8); 323 (6·11).
	0·1N-HCl	255 (33·15); 335 (14·0); 346 (13·85).

successful. Gage (*loc. cit.*) suggested a possible relation between antimalarial activity of 4-aminoquinoline derivatives and the difference between the extinction coefficients of the two peaks in the range 325—350 mμ., but this has not been confirmed.

(XV.) (XVI.)

Because of its high basic strength the 4-aminoquinoline ion is regarded as a resonance hybrid (XV) (Albert and Goldacre, *Nature*, 1944, **153**, 467). The resemblance between the absorption spectra of 4-aminoquinoline derivatives in dilute acid and those of 1-methyl-4-quinolone (XVI) and " 4-hydroxyquinoline " (4-quinolone) (Fig. 2) in which similar resonance is possible supports this view. When such resonance is prevented, *e.g.*, by addition of a proton to 1-methyl-4-quinolone or removal of a proton from 4-hydroxyquinoline, the two characteristic maxima in the 310—350 mμ. region disappear and there is more diffuse absorption at 300—320 mμ. resembling that of 4-aminoquinoline derivatives as free bases (Fig. 3). 4-Chloroquinoline derivatives and quinoline itself (Steck and Ewing, *loc. cit.*) have two sharp maxima in the region 300—320 mμ. which may be indicative of similar resonance forms, but no such maxima are shown by 4-methoxyquinoline.

The spectroscopic data, which were determined with a Beckman quartz spectrophotometer, are given in Table I.

The results of tests carried out by Dr. D. G. Davey (*loc. cit.*) against the blood-invasive form of *P. gallinaceum* in chicks are indicated in Tables II and III. In all three series substitution in

TABLE II.

Antimalarial activity of 4-3′-diethylaminopropylaminoquinolines.

Ref. no.	Substituents.	Formula.	Approx. M.E.D., mg./kg.
5271	—	I; X = Y = H	20
5284	3-Me	II; X = Y = H	40
4628	2-Me	III; X = Y = H	80
5372	2 : 3-Me_2	IV; X = Y = H	>80
5293	6-MeO	I; X = OMe, Y = H	20
5120	6-MeO-3-Me	II; X = OMe, Y = H	80
4935	6-MeO-2-Me	III; X = OMe, Y = H	>40
5068	6-MeO-2 : 3-Me_2	IV; X = OMe, Y = H	>160
5371	7-Cl	I; X = H, Y = Cl	10
5578	7-Cl-3-Me	II; X = H, Y = Cl	10
5732	7-Cl-2-Me	III; X = H, Y = Cl	80
5735	7-Cl-2 : 3-Me_2	IV; X = H, Y = Cl	>80

TABLE III.

Antimalarial activity of miscellaneous 4-aminoalkylaminoquinolines.

Ref. no.	Quinoline derivative.	Approx. M.E.D., mg./kg.
5554	4-3′-Dimethylaminopropylamino-	20
5444	4-4′-Diethylaminobutylamino-	20
5384	4-(4-Diethylamino-1-methylbutylamino)-	20
5707	4-(3-Diethylamino-1-methylpropylamino)-	<40
5555	4-(1 : 3-Bisdiethylamino-2-propylamino)-	40
5695	4-3′-Piperidinopropylamino-	>40
5474	2 : 4-Bis-(4-diethylamino-1-methylbutylamino)-	160
5702	6-Chloro-4-3′-diethylaminopropylamino-	40
5553	7-Chloro-4-2′-diethylaminoethylamino-	20
5623	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-	5
5323	4-3′-Diethylaminopropylamino-7 : 8-benzo-	160
5464	4-3′ -Diethylaminopropylamino-5 : 6-benzo-	160

the heterocyclic ring had reduced the therapeutic effect, least in the 3-substituted and most in the 2 : 3-disubstituted compounds. In the same test mepacrine had a minimum effective does (M.E.D.) of 40 mg./kg. of body weight, so the extra nucleus in the acridine molecule had an adverse effect whether mepacrine is regarded as a derivative of 6-methoxy- or of 7-chloro-quinoline.

Experimental.

4-Chloro-2-nitropropiophenone.—To a stirred suspension of sodium methoxide (38 g.) in dry ether (550 c.c.), cooled in ice, ethyl α-methylacetoacetate (101 g.) was added, followed during 15—20 minutes by 4-chloro-2-nitrobenzoyl chloride (154 g.) in dry ether (150 c.c.), and the mixture was boiled under reflux. After 1 hour water was added to dissolve the precipitated sodium chloride and the ethereal layer was separated, dried (Na_2SO_4), and evaporated. The residual oil (160—170 g.) was refluxed with ethanol (1400 c.c.) and concentrated sulphuric acid (60 c.c.) for 7 hours and then kept overnight. Ethanol and ethyl acetate were removed by steam-distillation and the aqueous mixture was stirred and refluxed for 1—2 hours, cooled, and extracted with ether. The extract was washed with 10% sodium carbonate solution and with water, dried (Na_2SO_4), and distilled. *4-Chloro-2-nitropropiophenone* (40 g.) was obtained as an oil, b. p. 100—110°/0·25 mm., which was not further purified (Found : N, 6·7; Cl, 15·9. $C_9H_8O_3NCl$ requires N, 6·6; Cl, 16·6%), and *ethyl α-4-chloro-2-nitrobenzoylpropionate* (19 g.) as a waxy solid, b. p. 160—162°/0·25 mm., giving white tabular crystals, m. p. 71°, from methanol (Found : C, 51·0; H, 4·4; N, 5·1; Cl, 12·0. $C_{12}H_{12}O_5NCl$ requires C, 50·45; H, 4·2; N, 4·9; Cl, 12·45%).

2-Amino-4-chloropropiophenone.—4-Chloro-2-nitropropiophenone (31 g.) and 50% acetic acid (400 c.c.) were stirred and heated on the steam-bath, and iron (pin dust, 65 g.) was added cautiously during 30 minutes, water being added to make up loss by evaporation. The mixture was stirred for ½ hour longer at 100°, cooled, and extracted with ether. The extract was washed successively with sodium carbonate solution, 5% sodium hydroxide solution, and water, dried (Na_2SO_4), and evaporated. The *amine* (15 g.) crystallised from light petroleum (b. p. 60—80°) in colourless prisms with a strong sweet odour, m. p. 72—73° (Found : C, 58·55; H, 5·5; N, 7·8. $C_9H_{10}ONCl$ requires C, 58·75; H, 5·45; N, 7·6%).

4-Chloro-2-formamidopropiophenone.—2-Amino-4-chloropropiophenone (6 g.) and anhydrous formic acid (7 c.c.) were refluxed for 10 minutes. On cooling, the *formyl* derivative crystallised in fine needles which were filtered off and crystallised from ethanol as colourless prisms or needles, m. p. 86—87° (Found : N, 6·8. $C_{10}H_{10}O_2NCl$ requires N, 6·6%).

2-Acetamido-4-chloropropiophenone.—2-Amino-4-chloropropiophenone (4 g.), acetic acid (10 c.c.), and acetic anhydride (10 c.c.) were heated on the steam-bath for 2 hours and poured into water (150 c.c.), and the *amide* was collected and crystallised from ethanol; from light petroleum (b. p. 100—120°), it formed needles, m. p. 123° (Found : N, 6·1. $C_{11}H_{12}O_2NCl$ requires N, 6·2%).

4-Chloro-2-formamidoacetophenone.—2-Amino-4-chloroacetophenone (10 g.) and anhydrous formic acid (10 c.c.) were refluxed for 10 minutes. The *formyl* derivative crystallised on cooling, and gave needles (from ethanol), m. p. 123° (Found : Cl, 17·6. $C_9H_8O_2NCl$ requires Cl, 17·95%).

4-Hydroxy-3-methylquinoline.—*o*-Formamidopropiophenone (5·9 g.), ethanol (40 c.c.), water (120 c.c.), and 40% aqueous sodium hydroxide (5·2 c.c.) were refluxed for 2 hours, filtered, and acidified with acetic acid. The product (2 g.) separated slowly from the cold solution, a further crop being obtained by evaporation of the mother-liquors. It crystallised from ethanol in stout colourless prisms, m. p. 228—229° (Found : C, 75·3; H, 5·7; N, 9·1. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·65; N, 8·8%).

Cyclisation of 4-chloro-2-formamidoacetophenone.—The formyl derivative (4·3 g.), ethanol (75 c.c.), water (300 c.c.), and 40% sodium hydroxide solution (2 c.c.) were refluxed for 5 hours, the ethanol was distilled off, and the boiling solution filtered. On cooling, 2-amino-4-chloroacetophenone crystallised (1·5 g.; m. p. 88°) and was filtered off. The filtrate, acidified with acetic acid, gave a crystalline precipitate of 7-chloro-4-hydroxyquinoline (0·55 g.), m. p. 274° (Found : N, 7·7. Calc. for C_9H_6ONCl : N, 7·8%), identical with material prepared by other methods. The product was characterised by conversion into 4 : 7-dichloroquinoline, m. p. 84° (Found : Cl, 35·1. Calc. for $C_9H_5NCl_2$: Cl, 35·8%).

Cyclisation of 2-Acetamido-4-chloroacetophenone.—2-Acetamido-4-chloroacetophenone (Atkinson and Simpson, *J.*, 1947, 232) (12 g.), ethanol (240 c.c.), water (900 c.c.), and 40% aqueous sodium hydroxide (6·5 c.c.) were refluxed for 3 hours and allowed to cool overnight. The crystalline precipitate *A* (8 g.) was filtered off and the filtrate was acidified with acetic acid, giving a precipitate of 7-chloro-4-hydroxyquinaldine (0·4 g.), needles, m. p. 313—316°, from ethanol, characterised by conversion into 4 : 7-dichloroquinaldine, m. p. 101° (Found : Cl, 32·9. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%). Precipitate *A*, extracted with boiling benzene, gave a residue of 7-chloro-2-hydroxylepidine (3·8 g.), m. p. 280°, and 2-amino-4-chloroacetophenone was recovered from the benzene. In another experiment, the material precipitated by acetic acid consisted mainly of *N*-acetyl-5-chloroanthranilic acid, white needles (from ethanol), m. p. 211°, not depressed by an authentic specimen

Cyclisation of 4-Chloro-2-formamidopropiophenone.—4-Chloro-2-formamidopropiophenone (6·3 g.), ethanol (30 c.c.), water (100 c.c.), and 40% aqueous sodium hydroxide (3·3 c.c.) were refluxed for 2 hours and the ethanol was distilled off, and the solution diluted with hot water (50 c.c.) and filtered. Acidification of the filtrate with acetic acid precipitated 7-chloro-4-hydroxy-3-methylquinoline (4·6 g.) which crystallised from ethanol in white needles, m. p. 320—325° (depending on rate of heating) (Found : C, 61·95; H, 4·4; N, 8·0. Calc. for $C_{10}H_8ONCl$: C, 61·95; H, 4·15; N, 7·25%). In other experiments appreciable amounts of *5-chloro-N-formylanthranilic acid* were also formed [white needles (from ethanol), m. p. 205—207°, not depressed by admixture with a specimen prepared from 5-chloroanthranilic acid and formic acid] (Found : C, 48·4; H, 3·7; N, 7·2; Cl, 16·9. $C_8H_6O_3NCl$ requires C, 48·1; H, 3·0; N, 7·0; Cl, 17·8%).

Cyclisation of 2-Acetamido-4-chloropropiophenone.—2-Acetamido-4-chloropropiophenone (3·3 g.), ethanol (50 c.c.), water (150 c.c.), and 40% aqueous sodium hydroxide (1·5 c.c.) were refluxed for 3 hours, the ethanol removed by distillation, and the hot solution filtered from *7-chloro-4-hydroxy-2 : 3-dimethylquinoline* (0·1 g.) (laminæ, m. p. 340°, from ethanol, see below). The filtrate, on cooling, deposited

7-*chloro*-2-*hydroxy*-4-*ethylquinoline* (0·6 g.) which formed white needles, m. p. 261—262°, from ethanol (Found: C, 61·9 ± 1·5; H, 5·1. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8%. Owing to a mishap there was insufficient material for accurate analysis). Acidification of the aqueous mother-liquor precipitated *N*-acetyl-5-chloroanthranilic acid (1·8 g.), needles (from ethanol or benzene), m. p. 211° not depressed by admixture with an authentic specimen.

7-*Chloro*-2-*hydroxylepidine*.—Acetoaceto-*m*-chloroanilide (55 g.) and concentrated sulphuric acid (30 c.c.) were mixed at 0° and warmed on the steam-bath. An exothermic reaction started at 85—90°, the temperature being kept below 100° by cooling. After 2 hours at 95° the mixture was poured into water (500 c.c.) and the product collected, washed until acid-free, and crystallised from acetic acid and then from ethanol, giving colourless laminæ, m. p. 280° (C.I.B.A., *loc. cit.*, give m. p. 272°) (Found: Cl, 18·2. Calc. for $C_{10}H_8ONCl$: Cl, 18·35%).

7-*Chloro*-4-*hydroxy*-2 : 3-*dimethylquinoline*.—*m*-Chloroaniline (25·5 g.) and ethyl α-methylacetoacetate (28·8 g.) were boiled with chloroform until water ceased to separate from the condensate (24 hours). The chloroform was removed on the water-bath under reduced pressure and the residual oil was added to medicinal paraffin (300 c.c.) at 280°, stirred at 260° for 2—3 minutes, and cooled. After dilution with light petroleum (b. p. 100—120°) (300 c.c.), the crystalline product was filtered off and washed with light petroleum. The crude product (23 g.), m. p. 305—310°, was extracted with boiling ethanol (800 c.c.) leaving the sparingly soluble 5-*chloro*-4-*hydroxy*-2 : 3-*dimethylquinoline* which crystallised from a large volume of ethanol in irregular prisms, m. p. 365—370° (Found: Cl, 16·8. $C_{11}H_{10}ONCl$ requires Cl, 17·1%). Repeated crystallisation of the more soluble fraction from ethanol gave white laminæ of 7-chloro-4-hydroxy-2 : 3-dimethylquinoline, m. p. 340—345°, not depressed by material prepared from 2-acetamido-4-chloropropiophenone (Found: N, 7·1. $C_{11}H_{10}ONCl$ requires N, 6·75%).

Condensation of p-*Anisidine with Ethyl Ethoxalylacetate*.—Commercial ethyl ethoxalylacetate (sodium salt) (70 g.), suspended in ethanol (200 c.c.), was treated at <20° with *p*-anisidine hydrochloride (54 g.) in warm ethanol (120 c.c.), kept at room temperature overnight, and poured into 30% brine (2 l.). The oil was extracted with ether (2 × 500 c.c.) and the extract washed with water (3 × 500 c.c.), dried (Na_2SO_4), and evaporated. The residual oil (57 g.) was added during 5 minutes to medicinal paraffin (400 c.c.) pre-heated to 300° and the mixture was stirred for 5 minutes at 240—245°, cooled, and diluted with light petroleum (400 c.c.; b. p. 80—100°). When cold the crystals of ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate (10 g.) were collected, washed with light petroleum, and crystallised from ethanol, forming pale yellow needles, m. p. 216° (Found: C, 63·4; H, 5·35; N, 5·9. Calc. for $C_{13}H_{13}O_4N$: C, 63·1; H, 5·26; N, 5·66%). The petroleum–paraffin mother-liquor slowly deposited *ethyl* 4-*ethoxy*-6-*methoxyquinoline*-2-*carboxylate* (4·5 g.) which formed fine white needles, m. p. 125°, from ethanol (Found: C, 65·1; H, 5·5; N, 5·3. $C_{15}H_{17}O_4N$ requires C, 65·4; H, 6·18; N, 5·08%). Repetition of this experiment frequently gave as a sparingly soluble by-product p-*anisidino*-N-p-*methoxyphenylmaleinimide*, yellow needles (from acetic acid), m. p. 225—226° (Found: C, 66·2; H, 5·2; N, 8·8. $C_{18}H_{16}O_4N_2$ requires C, 66·6; H, 4·95; N, 8·65%). Formation of this compound was avoided by removing free *p*-anisidine from the *p*-methoxyphenyliminosuccinic ester by washing with dilute acid before cyclisation.

In a similar manner ethyl α-ethoxalylpropionate and *p*-anisidine gave ethyl 4-hydroxy-6-methoxy-3-methylquinoline-2-carboxylate, pale yellow microscopic needles, m. p. 185—186°, from ethanol (Found: C, 59·8; H, 5·7; N, 5·4; H_2O, 6·1. Calc. for $C_{14}H_{15}O_4N,H_2O$: C, 60·2; H, 6·3; N, 5·0; H_2O, 6·45%), and 1-p-*anisidino*-2-*methyl*-N-p-*methoxyphenylmaleinimide*, flat yellow needles (from ethanol), m. p. 163—164° (Found: C, 67·2; H, 5·2; N, 8·7. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·3; N, 8·3%). Unlike the compounds from *m*-chloroaniline (Surrey and Cutler, *J. Amer. Chem. Soc.*, 1946, **68**, 514) these maleinimides from *p*-anisidine were readily separated from the quinoline derivatives.

p-Anisidine (6·15 g.) and ethyl acetylenedicarboxylate (8·9 g.) in ether (70 c.c.) reacted exothermically. After refluxing for 1 hour, the ether was removed and the residual oil cyclised by being heated for 3—4 minutes in medicinal paraffin (120 c.c.) at 250°. The crystalline product was separated by crystallisation from ethanol into *p*-anisidino-*N*-*p*-methoxyphenylmaleinimide (2 g.) and ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate (5 g.).

4-*Ethoxy*-6-*methoxyquinoline*-2-*carboxylic Acid*.—The ester (4 g.) was refluxed for 3 hours with 10% sodium hydroxide solution (75 c.c.) and then cooled, and the sparingly soluble sodium salt was collected, dissolved in hot water (100 c.c.), and acidified. The *acid*, m. p. 212—213° (decomp.), was crystallised from water (Found: C, 60·5; H, 4·8; N, 5·5. $C_{13}H_{13}O_4N,0{\cdot}5H_2O$ requires C, 60·8; H, 5·45; N, 5·45%); the *hydrochloride* formed cream-coloured needles (from 2N-hydrochloric acid), m. p. 276° (decomp.) (Found: Cl′, 10·7. $C_{13}H_{13}O_4N,HCl,2{\cdot}5H_2O$ requires Cl′, 10·8%). The hydrochloride, when heated above its m. p., gave 6-methoxy-4-hydroxyquinoline, m. p. 237°.

4-*Ethoxy*-6-*methoxyquinoline*.—4-Ethoxy-6-methoxyquinoline-2-carboxylic acid was heated above its m. p. until evolution of carbon dioxide ceased, and the *product* was crystallised from light petroleum (b. p. 40—60°), giving colourless prisms, m. p. 39—40° (Found: N, 6·4. $C_{12}H_{13}O_2N$ requires N, 6·9%).

7-*Chloro*-2 : 4-*dihydroxy*-3-*methylquinoline*.—(*a*) *m*-Chloroaniline (63·7 g.) and ethyl methylmalonate (87 g.) were heated under a long air-condenser allowing ethanol formed in the reaction to distil off. The temperature was held at 230—240° for ½ hour, then at 290—300° for 1½—2 hours, and finally raised to 340° during ½ hour. After cooling, the glassy product was refluxed with acetone (100 c.c.) until broken down to a crystalline solid, cooled, filtered off, and washed with acetone until free from colour. The crude *product* (58·5 g.) was purified by dissolution in hot 10% sodium carbonate solution (600 c.c.), filtration, and re-precipitation with hydrochloric acid (recovery 54 g., m. p. >280°). It crystallised from butanol in faintly cream-coloured prisms sintering at 280°, m. p. 290—295° (Found: C, 57·2; H, 3·9; N, 6·9. $C_{10}H_8O_2NCl$ requires C, 57·3; H, 3·8; N, 6·7%).

(*b*) Ethyl α-(4-chloro-2-nitrobenzoyl)propionate (3 g.) was hydrogenated over Raney nickel in ethanol (H_2 uptake 700 c.c.; reduction of the nitro-group requires 770 c.c. at 25°/760 mm.), and the

filtered solution was evaporated to dryness. The gummy residue was digested with 10% aqueous sodium hydroxide (30 c.c.) at 80—90° and the solution was filtered and acidified with acetic acid to precipitate the crude product (0·6 g.), m. p. >300°, which was characterised by conversion into 2 : 4 : 7-trichloro-3-methylquinoline.

2 : 4 : 7-*Trichloro*-3-*methylquinoline*.—7-Chloro-2 : 4-dihydroxy-3-methylquinoline (3 g.) and phosphoryl chloride (12 c.c.) were heated under reflux for 3 hours, cooled, poured on ice and, when the phosphoryl chloride had decomposed, the *product* was filtered off, washed until acid-free, and dried at 60° (3·45 g.; m. p. 102—104°). It crystallised from light petroleum (b. p. 60—80°) in long colourless needles, m. p. 105—106° (Found : N, 5·6. $C_{10}H_6NCl_3$ requires N, 5·7%).

The following were prepared similarly, but were isolated by making the reaction mixture alkaline and extracting it with ether :

4 : 7-*Dichloro*-2 : 3-*dimethylquinoline*, white needles [from light petroleum (b. p. 60—80°)], m. p. 89° (Found : N, 6·35. $C_{11}H_9NCl_2$ requires N, 6·2%).

4 : 5-*Dichloro*-2 : 3-*dimethylquinoline*, needles [from light petroleum (b. p. 80—100°)], m. p. 90—91° (Found : N, 6·5.

2 : 7-Dichlorolepidine, needles [from light petroleum (b. p. 80—100°)], m. p. 97° (Found : Cl, 32·7. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%).

4 : 7-*Dichloro*-2-*hydroxy*-3-*methylquinoline*.—2 : 4 : 7-Trichloro-3-methylquinoline (3 g.), 20% hydrochloric acid (30 c.c.), and dioxan (15 c.c.) were refluxed for 6 hours, diluted with water (250 c.c.), and left overnight. The *product* (2·7 g.) was filtered off and crystallised from 2-ethoxyethanol in white needles, m. p. 276° (Found : N, 6·3. $C_{10}H_7ONCl_2$ requires N, 6·13%).

Condensation of 2 : 4-*Dihydroxyquinolines with Dialkylaminoalkylamines*.—The following 4-dialkylaminoalkylamino-2-hydroxyquinolines were prepared by the method described in Part XVII, ***i.e.***, reaction of the components at 180—190° for 24—48 hours and separation of the products by dissolution in dilute acetic acid and precipitation with ammonia. They were converted into the corresponding 2-chloro-compounds by prolonged (24 hours') heating with phosphoryl chloride.

2-*Hydroxy*-4-3′-*piperidinopropylaminoquinoline*, white plates (from ethanol), m. p. 253° (Found : C, 71·3; H, 8·0; N, 14·6. $C_{17}H_{23}ON_3$ requires C, 71·5; H, 8·05; N, 14·75%).

7-*Chloro*-4-3′-*diethylaminopropylamino*-2-*hydroxy*-3-*methylquinoline*, pale yellow prisms (from ethanol), m. p. 125—126° (Found : N, 13·05, 13·2. $C_{17}H_{24}ON_3Cl$ requires N, 13·1%).

4-2′-*Diethylaminoethylamino*-2-*hydroxy*-7 : 8-*benzoquinoline*, yellow platelets (from ethanol), m. p. 228° (Found : C, 73·9; H, 7·45; N, 13·8. $C_{19}H_{23}ON_3$ requires C, 73·7; H, 7·45; N, 13·6%).

4-3′-*Diethylaminopropylamino*-2-*hydroxy*-7 : 8-*benzoquinoline*, colourless prisms (from ethanol), m. p. 242° (Found : C, 74·3; H, 7·85; N, 13·4. $C_{20}H_{25}ON_3$ requires C, 74·25; H, 7·75; N, 13·0%).

2-*Chloro*-4-3′-*piperidinopropylaminoquinoline*, white foliated plates (from aqueous ethanol), m. p. 142—143° (Found : Cl, 11·8. $C_{17}H_{22}N_3Cl$ requires Cl, 11·7%).

2-*Chloro*-4-(4-*diethylamino*-1-*methylbutylamino*)-3-*methylquinoline*, yellow oil, b. p. 184—186°/0·2 mm. (Found : N, 12·5. $C_{19}H_{18}N_3Cl$ requires N, 12·6%). The hydroxy-compound was a viscous oil which was not characterised.

2 : 7-*Dichloro*-4-3′-*diethylaminopropylamino*-3-*methylquinoline*, pale yellow solid, m. p. 52—54°, b. p. 205°/0·2 mm. (Found : Cl, 20·9. $C_{17}H_{23}N_3Cl_2$ requires Cl, 20·9%).

2-*Chloro*-4-2′-*diethylaminoethylamino*-7 : 8-*benzoquinoline*, white needles (from *cyclo*hexane), m. p. 118—119° (Found : N, 12·75. $C_{19}H_{22}N_3Cl$ requires N, 12·83%).

2-*Chloro*-4-3′-*diethylaminopropylamino*-7 : 8-*benzoquinoline*, white rhombic prisms (from *cyclo*hexane), m. p. 112° (Found : N, 12·4; Cl, 9·8. $C_{20}H_{24}N_3Cl$ requires N, 12·3; Cl, 10·4%).

7-*Chloroquinoline*-4-*sulphonic Acid*.—4 : 7-Dichloroquinoline (5 g.) was added to a solution of sodium sulphite heptahydrate (15 g.) in water (50 c.c.), made neutral to litmus with hydrochloric acid, and refluxed until no more oil was present (1½ hours), a few drops of *n*-butanol being added to prevent the volatile chloro-compound collecting in the condenser. On cooling, *sodium* 7-*chloroquinoline*-4-*sulphonate* crystallised in white needles (Found : Cl, 12·5; S, 11·8. $C_9H_5O_3NSClNa,H_2O$ requires Cl, 12·54; S, 11·3%).

The following compounds were obtained by the same procedure : 7-Iodoquinoline-4-sulphonic acid, from 4-chloro-7-iodoquinoline (Surrey and Hammer, *loc. cit.*), as yellow prisms, m. p. 318—320°. *Sodium* salt, white needles (Found : N, 3·2; I, 32·35; S, 8·5. $C_9H_5O_3NISNa,2H_2O$ requires N, 3·55; I, 32·3; S, 8·15%).

7 : 8-Benzoquinoline-4-sulphonic acid, from 4-chloro-7 : 8-benzoquinoline (reaction time 14 hours) as pale yellow microcrystalline solid, m. p. 390° (decomp.); *sodium* salt, yellow platelets (Found : S, 11·7. $C_{13}H_8O_3NSNa$ requires S, 11·4%).

2-*Hydroxyquinoline*-4-*sulphonic acid*, from 2 : 4-dichloroquinoline (reaction time 16 hours), as colourless needles, m. p. 356—358° (decomp.) (Found : N, 6·15. $C_9H_7O_4NS$ requires N, 6·2%); *sodium* salt, white needles (Found : S, 10·7. $C_9H_6O_4NSNa,3H_2O$ requires S, 10·65%).

7-Chloro-2-hydroxy-3-methylquinoline-4-sulphonic acid, from 2 : 4 : 7-trichloro-3-methylquinoline (reaction incomplete after 64 hours); *sodium* salt, long white needles (Found : N, 4·7; Cl, 11·3; S, 10·5; H_2O, 6·2. $C_{10}H_9O_4NSClNa,H_2O$ requires N, 4·5; Cl, 11·3; S, 10·2; H_2O, 5·7%).

2-*Hydroxy*-4-3′-*piperidinopropylaminoquinoline from* 2-*Hydroxyquinoline*-4-*sulphonic Acid*.—2-Hydroxyquinoline-4-sulphonic acid (3 g.), 3-piperidinopropylamine (3 c.c.), and water (10 c.c.) were heated at

Table IV.

4-Dialkylaminoalkylaminoquinolines.

Ref. no.	4-Substituent.	Other substituents.	Method.	Formula.	B. p. (°/mm.).	M. p.	Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
5554	$Me_2N\cdot[CH_2]_3\cdot NH$	—	*a*	$C_{14}H_{19}N_3$	168/0·2	—	—	—	—	—	—	—	—	—
				$C_{14}H_{19}N_3,H_2O$	—	73°	67·7	8·3	16·5	—	67·9	8·5	17·0	—
5553	$Et_2N\cdot[CH_2]_2\cdot NH$	7-Cl	*a*	$C_{15}H_{20}N_3Cl$	164/0·05	—	—	—	—	—	—	—	—	—
				$C_{15}H_{20}N_3Cl,2HCl,H_2O$	—	258—259	48·7	6·6	11·4	—	48·8	6·5	11·4	—
5271	$Et_2N\cdot[CH_2]_3\cdot NH$	—	*a*, *b*	(see Part XVII)										
4628	,,	2-Me	*a*	$C_{17}H_{25}N_3,2HCl,0·5H_2O$	—	210—212	57·7	8·5	12·4	20·2	57·8	7·9	11·9	20·1
5284	,,	3-Me	*a*, *b*	$C_{17}H_{25}N_3$	163/0·15	—	—	—	—	—	—	—	—	—
				$C_{17}H_{25}N_3,2HCl,0·5H_2O$	—	242—243	58·3	7·6	11·8	20·5	57·8	7·9	11·9	20·1
5372	,,	2 : 3-Me_2	*a*	$C_{18}H_{27}N_3$	162/0·18	—	—	—	—	—	—	—	—	—
				$C_{18}H_{27}N_3,2H_2SO_4,H_2O$	—	109	43·3	6·6	8·7	12·3*	43·3	6·6	8·4	12·8*
5702	,,	6-Cl	*a*	$C_{16}H_{22}N_3Cl$	168/0·05	—	—	—	—	—	—	—	—	—
				$C_{16}H_{22}N_3Cl,H_2O$	—	60	62·1	7·7	14·3	—	62·0	7·75	13·6	—
5371	,,	7-Cl	*a*, *c*	$C_{16}H_{22}N_3Cl$	192/0·1	54—58	65·4	7·4	14·25	—	65·85	7·55	14·4	—
				$C_{16}H_{22}N_3Cl,H_2O$	—	40—45	—	—	13·5	11·4†	—	—	13·6	11·5†
5732	,,	7-Cl 2-Me	*a*	$C_{17}H_{24}N_3Cl$	187/0·12	—	—	—	—	—	—	—	—	—
				$C_{17}H_{24}N_3Cl,2HCl,3H_2O$	—	253—254	47·4	7·5	10·5	—	47·15	7·4	9·7	—
5578	,,	7-Cl 3-Me	*a*	$C_{17}H_{24}N_3Cl$	163/0·03	—	—	—	—	—	—	—	—	—
				$C_{17}H_{24}N_3Cl,2HCl,H_2O$	—	217—218	51·2	6·8	10·4	18·7	51·4	7·05	10·6	18·0
5735	,,	7-Cl 2 : 3-Me_2	*a*	$C_{18}H_{26}N_3Cl$	190/0·3	—	—	—	—	—	—	—	—	—
				$C_{18}H_{26}N_3Cl,2HCl,2H_2O$	—	233—234	50·7	7·6	9·8	17·3	50·4	7·45	9·8	16·6
5293	,,	6-MeO	*a*	$C_{17}H_{25}ON_3$	172/0·05	76—77	—	—	14·45	—	—	—	14·65	—
				$C_{17}H_{25}ON_3,H_2O$	—	60	67·3	8·6	14·0	—	66·8	8·8	13·8	—
4935	,,	6-MeO 2-Me	*a*	$C_{18}H_{27}ON_3$	193/0·2	114—115	71·3	8·6	13·95	—	71·6	8·95	13·95	—
5120	,,	6-MeO 3-Me	*a*	$C_{18}H_{27}ON_3$	184/0·13	45	—	—	—	—	—	—	—	—
				$C_{18}H_{27}ON_3,2HCl,0·5H_2O$	—	260	57·0	7·5	10·9	—	56·4	7·3	11·0	—
5068	,,	6-MeO 2 : 3-Me_2	*a*	$C_{19}H_{29}ON_3$	192/0·35	—	—	—	—	—	—	—	—	—
				$C_{19}H_{29}ON_3,2HCl,0·5H_2O$	—	245—246	57·8	7·6	10·7	18·2	57·4	8·05	10·6	17·9
5464	,,	5 : 6-benzo	*a*	$C_{20}H_{25}N_3$	180/0·005	51—54	77·8	8·05	13·7	—	78·1	8·15	13·7	—
5323	,,	7 : 8-benzo	*a*, *b*	$C_{20}H_{25}N_3$	200/0·08	—	—	—	—	—	—	—	—	—
				$C_{20}H_{25}N_3,H_2O$	—	75—78	73·1	7·6	13·2	—	73·7	8·3	12·9	—
5695	$CH_2<[CH_2]_4>N\cdot[CH_2]_3\cdot NH$	—	*b*	$C_{17}H_{23}N_3$	176/0·03	—	—	—	—	—	—	—	—	—
				$C_{17}H_{23}N_3,H_2O$	—	105—106	69·7	8·3	14·5	—	71·0	8·7	14·65	—
6027	,,	8-MeO	*a*	$C_{18}H_{25}ON_3$	210/0·1	165—166	—	—	14·6	—	—	—	14·05	—
5444	$Et_2N\cdot[CH_2]_4\cdot NH$	—	*a*	$C_{17}H_{25}N_3$	166/0·05	—	—	—	15·4	—	—	—	15·5	—
				$C_{17}H_{25}N_3,H_2O$	—	65—67	70·7	9·3	14·45	—	70·5	9·3	14·5	—
5707	$Et_2N\cdot[CH_2]_2\cdot CHMe\cdot NH$	—	*a*	$C_{17}H_{25}N_3$	150/0·03	—	74·1	8·0	15·2	—	75·1	9·2	15·5	—
5384	$Et_2N\cdot[CH_2]_3\cdot CHMe\cdot NH$	—	*a*	$C_{18}H_{27}N_3$	155/0·05	72—74	75·3	9·2	15·4	—	75·7	9·45	14·75	—
5469	,,	3-Me	*b*	$C_{19}H_{29}N_3,H_2O$	168/0·2	—	71·8	9·5	12·9	—	71·9	9·75	13·25	—
5623	,,	7-Cl	*a*, *c*	$C_{18}H_{26}N_3Cl$	187/0·09	87	67·8	7·9	13·3	—	67·55	8·15	13·45	—
5474	,,	2-$Et_2N\cdot[CH_2]_3\cdot CHMe\cdot NH$	*a*	$C_{27}H_{47}N_5$	208/0·06	—	71·4	9·4	15·0	—	73·4	10·7	15·9	—
5555	$(Et_2N\cdot CH_2)_2CH\cdot NH$	—	*a*	$C_{20}H_{32}N_2$	192/0·2	—	—	—	—	—	—	—	—	—
				$C_{20}H_{32}N_4,3HCl,4H_2O$	—	267	47·8	8·45	11·2	20·4	47·2	8·45	11·0	20·9

* Analysis for S. † Analysis for Cl.

140—150° for 8 hours. The crystalline product was filtered off when cold and crystallised from ethanol in colourless plates, m. p. 253°, not depressed on admixture with a specimen prepared from 2 : 4-dihydroxyquinoline.

Preparation of 4-Dialkylaminoalkylaminoquinolines.—The following three preparative methods were employed. (*a*) The requisite 4-chloroquinoline (0·02 mol.), dialkylaminoalkylamine (0·04 mol.), and potassium iodide (0·1 g.) were stirred and heated at 180° for 8 hours and the product when cold was dissolved in 10% acetic acid containing 5% of sodium acetate. The solution was treated with carbon, filtered, and made strongly alkaline with sodium hydroxide, and the bases were extracted with ether. After drying (Na_2SO_4), the ether was removed, the excess of dialkylaminoalkylamine distilled off at 10—15 mm., and the residue distilled at 0·05—0·25 mm. The products were viscous oils which crystallised in some cases, or were converted into crystalline hydrates, hydrochlorides, or sulphates. (*b*) 2-Chloro-4-dialkylaminoalkylaminoquinolines, dissolved in methanol, were hydrogenated at ordinary temperature and pressure over Raney nickel. After filtration, removal of the solvent, and treatment with sodium hydroxide, the products were distilled at 0·05—0·25 mm. (*c*) 7-Chloroquinoline-4-sulphonic acid (4·7 g.), 4-diethylamino-1-methylbutylamine (6 c.c.), and water (15 c.c.) were heated at 140—150° for 8 hours in a sealed tube. When cold the mixture was made alkaline with sodium hydroxide, and the bases were extracted with ether, dried (Na_2SO_4), and distilled.

Of the 4-dialkylaminoalkylaminoquinolines listed in Table IV, numbers 4935, 5271, 5293, 5323, 5371, 5384, 5465, 5469, 5553, 5578, and 5623 have previously been described.

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