Diaminoquinoline Antimalarials[1]

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A series of 4,8-diaminoquinolines, some including chloro substitution on the benzenoid ring, has been synthesized and evaluated against *Plasmodium berghei* in the mouse and *Plasmodium gallinaceum* in the mosquito and chick. Antimalarial activity has been observed in those members bearing a 3-diethylaminomethyl-4-hydroxyanilino attachment at C-4.

Two of the most active classes of antimalarial agents which were developed by the research program of the Office of Scientific Research and Development during World War II were the 8-amino- and 4-aminoquinolines. Even in recent years, until the onslaught of malignant *falciparum* malaria, no drug fully equivalent to chloroquine or hydroxychloroquine had been discovered.[2] Research on the current refractory strain of *Plasmodium* sponsored under the reactivated Army Antimalarial Program has capitalized on many clues from the structure–activity relationships developed in the 1940's.

There is some evidence that the additivity principle in candidate drug design may be of merit in malaria chemotherapy. The 2-methoxy-6-chloro-9-aminoacridines, *e.g.*, mepacrine, can be envisioned as the molecular combination of the 7-chloroquinoline moiety (as for example in chloroquine) with the 6-methoxy (as characterized by quinine and pamaquine). Similar logic stimulated the development of 4,8-diaminoquinolines in the hope that the favorable suppressive activity and low toxicity of the 4-aminoquinoline family and the prophylactic activity of the 8-aminoquinolines might be combined in the same molecule.[3,4]

Considerable synthetic difficulty was experienced by previous workers in their efforts to obtain substituted members of the 4,8-diaminoquinoline family. Only two of this class were evaluated and tabulated in the Wiselogle index:[5] 8-amino-7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (I) and 8-amino-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (II). Modest activity was observed for these two compounds; quinine equivalents of 0.3 for the A-1 test on I and of 1.0 for the B-4 test on II were tabulated. Recently, 8-amino-7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (**12**) has been reported to display "suppressive antimalarial activity."[6]

We have prepared a series of eight 4,8-diaminoquinolines and related model compounds to evaluate their efficacy in the current screening program.[7] We have utilized 4(1H)-quinolones as the crucial synthetic intermediates for introduction of the 4-amino function. These quinolones, with the exception of 8-chloro-4(1H)-quinolone (**2b**), have been reported previously. For our purposes they have been prepared by a modified Conrad–Limpach cyclization of aniline–acetylene dicarboxylate adducts[8] with subsequent saponification–decarboxylation of the 2-carboxylates. Yields and physical properties of the 4(1H)-quinolones prepared by this technique are reported in Table I.

The 4(1H)-quinolones were converted by $POCl_3$ treatment (Table I) into 4-chloroquinolines. The various 4-chloro-8-aminoquinolines required for preparation of the candidate drugs, by displacement of the 4-chloro function with an appropriate amine, were obtained from the haloquinolines (**3a–d**) listed in Table I. Thus, reduction of 4-chloro-8-nitroquinoline (**3a**) by the Fe–HOAc method of Elderfield, *et al.*,[9] yielded 4-chloro-8-aminoquinoline (**3e**). The nitration–reduction of 4,7-dichloroquinoline (**3c**) gave 4,7-dichloro-8-aminoquinoline[4] (**3f**) while a similar operation on 4,5,7-trichloroquinoline (**3d**) gave 4,5,7-trichloro-8-aminoquinoline (**3g**). Nmr studies have now firmly established the site of nitration in **3c** to be at C-8,[10] while proof of C-8 nitration in 4,5,7-trichloroquinoline rests on the identity of its nitro reduction product with the compound obtained by chlorination of authentic 4,7-dichloro-8-aminoquinoline.

Amination of the 4-chloroquinolines was performed in excess dialkylaminoalkylamine as solvent. In reactions involving 3-diethylamino-2-hydroxypropylamine it was necessary to avoid reflux temperatures to minimize the dehydration–elimination reactions occurring in the side-chain portion. For the incorporation of the 3-diethylaminomethyl-4-hydroxyanilino residue, the presence of DMF was found to facilitate reaction by providing a homogeneous medium. Again, reaction temperatures under 100° must be employed since at

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(2) Chemotherapy of Malaria, World Health Organization Technical Report No. 375, Geneva, 1967, p 25.

(3) R. W. Gouley, G. W. Moersch, and H. W. Mosher, *J. Am. Chem. Soc.*, **69**, 303 (1947).

(4) C. C. Price, E. W. Maynert, and V. Boekelheide, *J. Org. Chem.*, **14**, 484 (1949).

(5) F. Y. Wiselogle, "A Survey of Antimalarial Drugs," J. W. Edwards, Publishers, Ann Arbor, Mich., 1946.

(6) K. R. Chandran, A. K. Sen, and V. P. Basu, *J. Sci. Ind. Res.* (India), **10b**, 290 (1951).

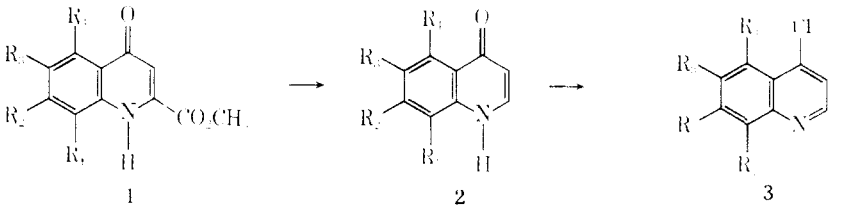
(7) Mouse and chick testing was carried out at the University of Miami under the sponsorship of the U. S. Army Medical Research and Development Command. Mouse screening was performed according to the standard profile described by T. S. Osdene, P. D. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Chick screening techniques were developed by L. Rane and experimental details will appear in a forthcoming publication. The mosquito screening procedure has been described by E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(8) (a) N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocyclic Chem.*, **3**, 222 (1966); (b) N. D. Heindel, I. S. Bechara, P. D. Kennewell, J. Molnar, C. J. Ohnmacht, S. M. Lemke, and T. F. Lemke, *J. Med. Chem.*, **11**, 1218 (1968).

(9) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1524 (1946).

(10) N. D. Heindel, C. J. Ohnmacht, J. Molnar, and P. D. Kennewell, *J. Chem. Soc., C*, in press.

TABLE I



1 2 3

					2		3	
Series	R_1	R_2	R_3	R_4	Mp, °C	Yield, %	Mp, °C	Yield, %
a	NO_2	H	H	H	202–205[a]	61	125–126[c]	90
b	Cl	H	H	H	212–213[b]	49	155[f]	95
c	H	Cl	H	H	276–278[c]	78	85–86[g]	86
d	H	Cl	H	Cl	344–345[d]	83	105–106[h]	94

[a] R. H. Baker, G. R. Lappin, C. J. Albisetti, Jr., and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1267 (1946), reported mp 199–200°. [b] *Anal.* (C_9H_6ClNO) C, H, N. [c] A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 113 (1946), reported mp 277–279°. [d] A. R. Surrey and H. F. Hammer, *ibid.*, **68**, 1244 (1946), reported mp 345–346°. [e] B. Riegel, *et al.*, *ibid.*, **68**, 1264 (1946), reported mp 126–127°. [f] *Anal.* ($C_9H_5Cl_2N$) C, H, N. [g] Lit.[c] mp 83.5–84.5°. [h] Lit.[d] mp 105–106°.

higher temperatures DMF has been shown to aminate haloquinolines with the dimethylamino group.[11]

Although two of the 4,8-diaminoquinolines prepared for inclusion in this study, **11** and **12**, are apparently known materials, only **12**[6] appears in the primary literature. 8-Amino-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (I) appears only in Wiselogle.[5] Our syntheses of these materials by amination in a homogeneous DMF–H_2O phase is described in the Experimental Section.

Considerable experimental effort was expended in attempting to alkylate the free primary 8-amino group in **4**, **6**, 8, and **12**. Price and Guthrie have already commented upon some negative attempts to alkylate an 8-amino-7-chloroquinoline system.[12] In summary, no reaction could be effected under mild conditions, and, if forcing conditions were employed, intractable tars representing multicomponent mixtures were observed by tlc.

The following specific techniques were investigated. Equimolar quantities of **12**, 4-bromo-1-phthalimidopentane, and $NaHCO_3$ were heated at 100° in 50 ml of DMF for 24 hr. The initial quinoline was recovered unchanged. A similar procedure in which 8 and 4-bromo-1-phthalimidopentane were heated for 6 hr at 130° in a solvent-free medium containing excess K_2CO_3 resulted in an intractable resin. Further, if the same reaction was carried out in refluxing xylene, the starting quinoline was recovered unreacted. It was apparent that on prolonged thermal treatment the bromophthalimidopentane side chain underwent elimination. The refluxing (70 hr) of 0.08 mole of 4,7-dichloro-8-aminoquinoline (**3f**) and 0.04 mole of 4-bromo-1-phthalimidopentane in EtOH (400 ml) precipitated the HBr salt of the initial quinoline upon ether dilution of the product mixture.

Utilization of a 2 *M* excess of PhMgCl in THF to increase the reactivity of the 8-amino moiety in **6** for alkylation by 4-bromo-1-phthalimidopentane was likewise unsuccessful. Attempted condensation under N_2 of **6** and 3-dimethylaminopropyl chloride for 24 hr in DMF produced an intractable black gum which tlc revealed to be mainly unreacted **6**.

The reductive alkylation technique of Schellenberg[13] in which an anil of 4,7-dichloro-8-aminoquinoline (**3f**) and butanone is ostensibly generated *in situ* and reduced by $NaBH_4$ likewise returned unreacted **3f**. Similar attempts to produce anils of 2-pyridinecarboxaldehyde and **6** for subsequent reduction were unsuccessful as was the attempted NaH-catalyzed Michael addition of **6** to 4-vinylpyridine. Although a sulfonamide of **6** could be prepared, its Na salt was too insoluble for alkylation in any appropriate solvent.

The application of any of the four methods for 8-amino alkylation outlined by Elderfield[9] would, if applied to a 4-chloro-8-aminoquinoline, result in extensive hydrolysis of the 4-halo group. Attempts to alkylate the substituted 4,8-diaminoquinolines bearing a side-chain amine function at C-4 are complicated by the low basicity ($pK_a = 3.93$)[14] of the primary 8-amino and the base-strengthening effect of the 4-amino on the quinoline nitrogen. Alkylation attempts on 2- or 4-aminoquinoline are often directed onto the ring N.[15] In all of our alkylation attempts, ir spectra of the crude reaction products displayed the unchanged 8-amino absorptions.

The Michael addition to methyl propiolate has been shown to occur with many arylamines of low basicity,[16] and, although condensation with **6** did produce a 1:1 adduct, nmr and ir evidence clearly demonstrated that the primary 8-amino had not reacted.

Biological Activity.[7]—The 4,8-diaminoquinolines and the model compounds were screened for antimalarial activity against *Plasmodium berghei* in mice. Additional screening was performed on a standard strain of *Aedes aegypti* mosquito infected with *Plasmodium gallinaceum*. Compound evaluation was based on the ability of the chemical to suppress the development of malarial oocysts in the midgut or to suppress the number of sporozoites in the salivary gland of the mosquito.

In the case of **4**, **6**, **10**, and **11**, evaluation against a blood-induced *P. gallinaceum* infection in white Leghorn cockerel chicks was also carried out by Dr. Leo Rane at the University of Miami. In the chick and

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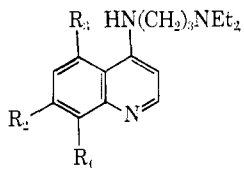
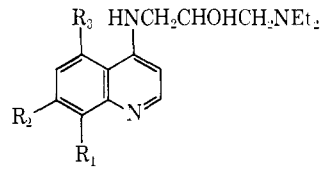
(12) C. C. Price and D. H. Guthrie, *J. Am. Chem. Soc.*, **68**, 1592 (1946).
(13) K. Schellenberg, *J. Org. Chem.* **28**, 3259 (1963).
(14) R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 169.
(15) (a) J. C. E. Simpson and P. H. Wright, *J. Chem. Soc.*, 1707 (1948); (b) W. Schneider and B. Müller, *Chem. Ber.*, **93**, 1579 (1960).
(16) (a) N. D. Heindel, P. D. Kennewell, and C. J. Ohnmacht, *J. Org. Chem.*, **34**, 1168 (1969); (b) N. D. Heindel, P. D. Kennewell, and V. B. Fish, *J. Heterocyclic Chem.*, **6**, 77 (1969).

TABLE II

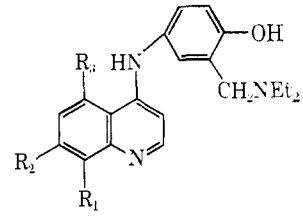
ANTIMALARIAL ACTIVITIES OF AMINOQUINOLINES



A



B



C

Compd	R_2	R_3	R_8	4 side chain	Test system[a]	Activity[b]
4	NH_2	H	H	A	M, Mo, and C	Inactive
5	Cl	H	H	A	M	Toxic
					Mo	Inactive
6	NH_2	Cl	H	A	M, Mo, and C	Inactive
7 (SN 8137)	H	Cl	H	B	M	Sl at low doses, toxic at 640 mg/kg
8	NH_2	Cl	Cl	B	M	Inactive
9	NH_2	Cl	H	B	M	Inactive
10	NH_2	H	H	B	C	Inactive
11 (SN 13,797)	NH_2	H	H	C	M	msti 4.5 (160 mg/kg)
						msti 7.0 (320 mg/kg)
						msti 9.7 (640 mg/kg)
					C	msti 9.3 (120 mg/kg)
12	NH_2	Cl	H	C	M	msti 3.2 (320 mg/kg)
						msti 6.4 (640 mg/kg)
13	NH_2	Cl	Cl	C	Mo	Inactive

[a] M = mice, Mo = mosquito, C = chick. [b] msti = mean survival time increase of treated animal minus control in days; see text for discussion.

mouse screen, data are reported in terms of mean survival time increase of the infected chemically treated host compared to an infected untreated host. Ability of a candidate drug to sustain the animal to a 100% increase in normal survival time (7.0 ± 0.5 days in the mouse and 3.5 ± 0.5 days in the chick) permits classification as an "active" material. Testing data for all the compounds are tabulated in Table II.

No significant antimalarial activity was observed in those 4,8-diaminoquinolines bearing the 2-hydroxy-3-diethylaminopropyl side chain on the 4-amino, *i.e.*, in **8–10**. The Cl-containing members of this family, 8 and **9**, when evaluated in the mouse screen, displayed no increase in mean survival time. A maximum dose level of 320 mg/kg was utilized in **9** and a level of 160 mg/kg was employed for 8. It is of interest to note that the 7-chloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline (III) which lacks the NH_2 moiety at C-8 appears to be somewhat more active and displays a mean survival time increase of 3.8 days in the mouse.[17] It could not be tested at higher concentrations because toxic effects on the host became evident. Five toxic deaths in five test animals occurred at the 640-mg/kg dose level.[18] The nonchloro analog, 8-amino-4-(2-hydroxy-3-diethylaminopropylamino)quinoline (**10**), was tested only in the chick, but it too gave little evidence of activity up to 480 mg/kg (mean survival time increase 1.7 days). It appears that in this side-chain series the pendant 8-amino group imparts no activity and in fact may be deleterious in effect compared to the nonamino compound **7**.

The compounds bearing the diethylaminopropyl group at C-4 were similarly nonactive. In both mouse and chick screens, **4** and **6** were inactive. Against the *P. gallinaceum* infected mosquito they displayed no suppression of sporozoites. The compound selected for model comparison, 8-chloro-4-(3-diethylaminopropylamino)quinoline (**5**), was too toxic for evaluation in the mouse (two toxic deaths at 160 mg/kg and five deaths at 640 mg/kg) but it gave no evidence of suppression in the mosquito profile.

Three 4,8-diaminoquinolines bearing a 4-hydroxy-3-diethylaminomethylanilino attachment at C-4 were prepared and evaluated. Two of these compounds, **11** and **12**, were tested against *P. berghei* in the mouse and were found to be active. The 8-amino-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (**11**) showed an increase in mean survival time of 9.7 days at 640 mg/kg and of 7.0 days at 320 mg/kg. No activity outside of the limits of experimental error was observed below 160 mg/kg. 7-Chloro-8-amino-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (**12**) was somewhat less active and displayed survival time increases of 6.4 days at 640 mg/kg and 3.2 days at 320 mg/kg. The 5,7-dichloro analog, *i.e.*, 8-amino-5,7-dichloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (**13**), was evaluated in the mosquito screen and was found to be ineffective. Thus, the activities in this series seem to diminish with increasing Cl substitution.

A comparison with amodiaquine, 7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline, reveals that none of our 4,8-diaminoquinolines was equal in activity to the parent system lacking the 8-amino.[19] Amodiaquine showed a mean survival time increase of 7.7 ± 0.5 days at 40 mg/kg and cured five mice out of five at 640 mg/kg.

(17) III was resynthesized for screening in the current antimalarial profile exactly as described by N. L. Drake, H. J. Creech, J. A. Garman, S. T. Haywood, R. M. Peck, J. Van Hook, and E. Walton, *J. Am. Chem. Soc.*, **68**, 1208 (1946). It is listed in Table II as **7**.

(18) Toxic deaths in the mouse screen are recorded for treated animals which survived less than the normal 7.0 ± 0.5 days observed for untreated test animals.

(19) Testing data in the Rane mouse screen for amodiaquine was provided by Dr. Bing T. Poon of the Walter Reed Army Institute of Research.

Experimental Section[20]

Preparation of 4(1H)-Quinolones.—These intermediates were synthesized by the saponification-decarboxylation of the previously reported 2-carbomethoxy-4(1H)-quinolones prepared by Michael addition and cyclization of anilines and dimethyl acetylenedicarboxylate.[8,21] Several of these quinolones have been reported in the literature but with the exception of **2c** none was prepared from the 2-carboxylates. See Table I for yields.

4-Chloroquinolines.—Chlorination by the standard $POCl_3$ method converted the 4(1H)-quinolones into 4-chloroquinolines. Yields, properties, and literature citations are reported in Table I.

4-Chloro-8-aminoquinolines.—Literature methods were employed to prepare 4-chloro-8-aminoquinoline[9] and 4,7-dichloro-8-aminoquinoline[4] from their respective precursors **3a** and **3c**.

4,5,7-Trichloro-8-nitroquinoline.—4,5,7-Trichloroquinoline (**3d**)[22] (40 g, 0.17 mole) was added to 200 g of a mixture of one part by weight of fuming HNO_3 and two parts of concentrated H_2SO_4 at 0°. In our experience it is important to maintain the temperature at 0° throughout the addition process. After the addition was completed the mixture was allowed to stand at room temperature for 2 hr after which it was added to 800 g of crushed ice. The light yellow precipitate that was formed was isolated by filtration and recrystallized from MeOH to yield 40 g (84%) of product, mp 114°. *Anal.* ($C_9H_3Cl_3N_2O_2$) N.

4,5,7-Trichloro-8-aminoquinoline (3g).—A mixture of 100 ml of 50% AcOH and 5.5 g (0.02 mole) of 4,5,7-trichloro-8-nitroquinoline was warmed on the steam bath, and 3.36 g (0.06 mole) of powdered Fe was added in small portions so that gentle boiling resulted. After all the Fe had been introduced the mixture was heated for 1 hr, cooled to room temperature, and diluted with 200 ml of H_2O to precipitate the product. The amine was recrystallized (Et_2O) to yield 4.5 g (90%) of product, mp 109–110°. *Anal.* ($C_9H_3Cl_3N_2$) C, H, N.

Chlorination of 4,7-Dichloro-8-aminoquinoline (3f).—A solution of Cl_2 (0.5 g) in dioxane was added to 4,7-dichloro-8-aminoquinoline (1.0 g) dissolved in 20 ml of dioxane. An immediate formation of a yellow precipitate ensued; the precipitate was removed by filtration, washed with Et_2O, dissolved in H_2O, and basified with NaOH. The aqueous phase was extracted with Et_2O and the extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield 4,5,7-trichloro-8-aminoquinoline (**3g**) (0.40 g, 35%), mp 107–108°. The material, spectrally identical with that obtained by nitration–reduction of 4,5,7-trichloroquinoline, establishes the site of nitration in that compound as C-8.

8-Amino-4-(3-diethylaminopropylamino)quinoline (4).—A stirred solution of 4.25 g (0.024 mole) of 4-chloro-8-aminoquinoline (**3e**) and 60 g (0.46 mole) of 3-diethylaminopropylamine was refluxed for 20 hr, then the cooled mixture was poured onto 1.5 l. of H_2O, and extracted with three 100-ml portions of Et_2O. The Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated to dryness. The residual oil on trituration with petroleum ether (30–60°) readily solidified to a tan solid. The yield of dry crude solid was 5.11 g (79%), mp 80–82°. Two recrystallizations from petroleum ether afforded 3.72 g of analytically pure pale orange crystals, mp 82–84°. *Anal.* ($C_{16}H_{24}N_4$) C, H, N.

8-Chloro-4-(3-diethylaminopropylamino)quinoline (5).—A solution of 0.50 g (2.5 mmoles) of 4,8-dichloroquinoline (**3b**), 1.0 g of phenol, and a crystal of KI was heated at 125° for 5 min. To this was added 3.0 g of 3-diethylaminopropylamine, and the mixture heated at reflux for 10 hr. The brown solution was poured into 50 ml of 35% aqueous NaOH and extracted with 100 ml of CH_2Cl_2, and the dried extract was concentrated to dryness under reduced pressure. The semisolid residue was taken up in a minimum of 1:1 Et_2O–petroleum ether (60–80°) and Et_2O was removed by slow evaporation on a steam bath. The resulting crystals (78%) were purified by a second recrystallization from 30–60° petroleum ether, analytical mp 109–110°. *Anal.* ($C_{16}H_{22}ClN_3$) C, H, N.

8-Amino-7-chloro-4-(3-diethylaminopropylamino)quinoline (6).—A solution of 0.092 mole of 4,7-dichloro-8-aminoquinoline (**3f**) in 0.46 mole of 3-diethylaminopropylamine was refluxed with stirring for 36 hr. Salt precipitation began to appear after 15 hr. The reaction was poured into 1 l. of cold H_2O, made basic (NaOH), and extracted (Et_2O). The dried (K_2CO_3) Et_2O layer was evaporated and the resulting oil crystallized by trituration with petroleum ether. The pure product (22.6 g, 80%) was obtained by recrystallization from petroleum ether (sparingly soluble); mp 70.5–71.5°. *Anal.* ($C_{16}H_{23}ClN_4$) C, H, N.

8-Amino-5,7-dichloro-4-(2-hydroxy-3-diethylaminopropylamino)quinoline (8).—4,5,7-Trichloro-8-aminoquinoline (**3g**) (5 g, 0.02 mole) was mixed with a large excess (50 ml) of 2-hydroxy-3-diethylaminopropylamine. The mixture was heated overnight at 70°, after which the temperature was increased by 10° every 2 hr for a period of 6 hr. To complete the alkylation the mixture was held at 175–180° for 3 hr. The dark reaction material was cooled and poured into 1 l. of ice-cold H_2O. The product accumulated as a dark gum which was separated by decantation of the H_2O. The residual gum was dissolved in Et_2O and dried ($MgSO_4$). Et_2O was evaporated, the oil was triturated with petroleum ether, and crystallization into a white solid was induced. The product was recrystallized from petroleum ether (bp 30–60°) to yield 4.25 g (60%) of a creamy white solid, mp 96–97°. *Anal.* ($C_{16}H_{22}Cl_3N_4O$) C, H, N.

8-Amino-7-chloro-4-(2-hydroxy-3-diethylaminopropylamino)quinoline (9).—A 4.26-g (0.02 mole) sample of 4,7-dichloro-8-aminoquinoline (**3f**) in 11 g of 2-hydroxy-3-diethylaminopropylamine was heated with stirring at 90–120° for 2 hr and then at 150–160° for 1 hr. An exothermic reaction occurred at the higher temperature as evidenced by a vigorous reflux. The reaction mixture was cooled, poured into 100 ml of 35% NaOH, and extracted (Et_2O). After drying and evaporation of the extracts, excess side-chain amine was distilled off *in vacuo*. The residue was then distilled under reduced pressure yielding 51% of the pure alkylated quinoline **10**: bp 230–232° (0.07 torr). *Anal.* ($C_{16}H_{23}ClN_4O$) C, H, N.

8-Amino-4-(2-hydroxy-3-diethylaminopropylamino)quinoline (10).—A solution of 15.5 mmoles of 4-chloro-8-aminoquinoline (**3e**) and 45 ml of 2-hydroxy-3-diethylaminopropylamine was stirred at 140° for 48 hr. Dilution with H_2O (1.5 l.) and extraction of the product into Et_2O gave, upon evaporation, a viscous oil which crystallized when triturated with xylene. Tan crystals were filtered off and purified by two recrystallizations from petroleum ether (bp 90–100°); yield 2.62 g (58%), mp 102–104°. *Anal.* ($C_{16}H_{24}N_4O$) C, H, N.

8-Amino-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (11).—3-Diethylaminomethyl-4-hydroxyacetanilide (0.022 mole) was deacetylated by refluxing in 15 ml of 20% HCl for 1 hr. A solution of 0.024 mole 4-chloro-8-aminoquinoline (**3e**) in 25 ml of DMF was added and the mixture was stirred at 90° for 16 hr, cooled, and diluted with 1 l. of H_2O. After filtration to remove a trace of suspended matter, the solution was basified and the precipitated product was taken up in $CHCl_3$, washed with 5% Na_2CO_3, dried ($MgSO_4$), and evaporated *in vacuo*. The crystalline **11** was purified by recrystallization from C_6H_6, then 1:1 C_6H_6–hexane, then EtOH, to yield 3.37 g (45%) of product, mp 141.5–143°. *Anal.* ($C_{20}H_{24}N_4O$) C, H, N.

8-Amino-7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (12).—The preparation was carried out as described[5] with DMF added to ensure a homogeneous medium: yield 38%, mp 157–159°, lit.[5] mp 160–161°.

8-Amino-5,7-dichloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (13).—After deacetylation of 1.5 g of the acetanilide as described above, the pH was adjusted to 9 with aqueous NaOH and 1.5 g of 4,5,7-trichloro-8-aminoquinoline (**3g**) in 20 ml of DMF was added. The solution was heated on steam cone for 24 hr and made slightly basic, and the precipitated product was collected and recrystallized (Et_2O), 0.40 g, 16%, mp 125–126°. *Anal.* ($C_{20}H_{22}Cl_3N_4O$) C, H.

Propiolation of 8-Amino-7-chloro-4-(3-diethylaminopropylamino)quinoline (6).—Equimolar amounts (0.01 mole) of **6** and methyl propiolate in 25 ml of MeOH reacted exothermically and the solution was allowed to stand at room temperature for 24 hr. Evaporation of the solvent gave a yellow oil which solidified to 2.73 g (71%) of a yellow material, mp 91–93°, from petroleum ether. Analysis indicated a 1:1 adduct. *Anal.* ($C_{20}H_{27}ClN_4O_2$) C, H, N. Although the site of propiolation could not be determined with complete certainty, both the presence of the unreacted 8-amino (δ 6.20 ppm in nmr and 3300 and 3430 cm^{-1})

(20) Nmr analyses were carried out on a Varian A60 nmr spectrometer and are reported in δ (ppm) calibrated against TMS. We acknowledge the financial assistance of the National Science Foundation in the purchase of this instrument. Combustion analyses were performed by the late Dr. Velmer B. Fish of these laboratories. Melting points were obtained on a Fisher-Johns block and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements are within ±0.4% of theoretical values.

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and the analogy with other known cases of attack at the quinoline $N^{15,16}$ support the assignment of propiolate addition to the tautomeric quinoline ring N–H. Two *trans*-vinyl proton resonances from the propiolate portion (J = 14 Hz) could be observed at 4.79 and 7.72 ppm in the nmr. These not only rule out the possibility that the compound is a stable charge-transfer entity but also support the conclusion that NH to triple bond addition had occurred.

Antimalarials. 4-"Proximal" Hydrazino Derivatives of 7-Chloroquinoline

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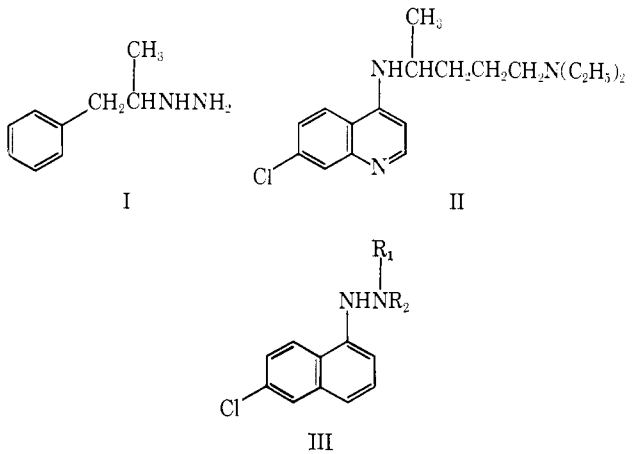
Sixteen "proximal" hydrazino derivatives of 7-chloroquinoline of the general structure III have been prepared and tested as antimalarials. Three of these have shown curative activity without toxic deaths up to doses of 640 mg/kg sc.

In our earlier work[1,2] with drugs bearing a hydrazine moiety, as in α-methylphenethylhydrazine (I), it was found that, in contrast to the parent amines, drug resistance did not develop to the corresponding hydrazines, thereby affording a long duration of action without decrease in efficacy on repeated administration. On this basis, it was considered worthwhile to incorporate a hydrazine moiety in the chloroquine (II) side chain in the hope of obtaining antimalarial drugs which would be effective in chloroquine-resistant malarial strains of *Plasmodium falciparum*. Accordingly, we prepared the "proximal" hydrazino derivatives of chloroquine represented by the generic structure III where R_1 is H, CH_3, and C_2H_5; R_2 is dialkylaminoalkyl; and R_1 and R_2 being the same part of a hydrazone derivative as in compounds **2**, **3**, **5**, **7**, **9**, and **10** (Table I).



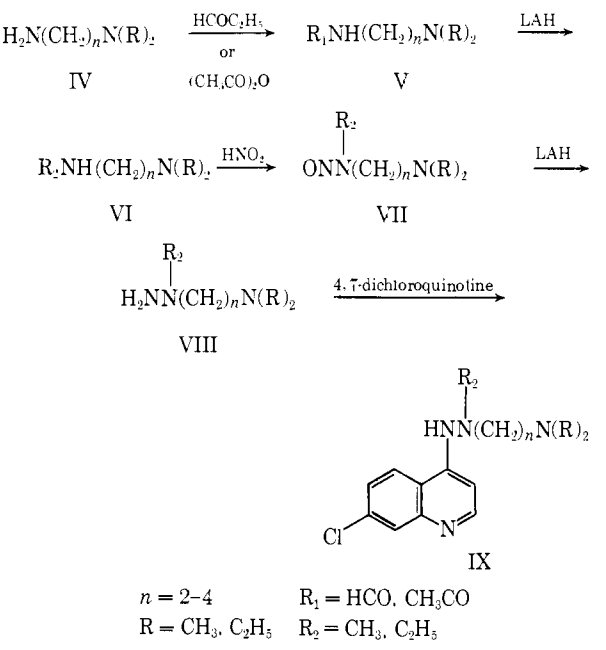
I II

III

The key intermediate for the preparation of **2–10** was 7-chloro-4-hydrazinoquinoline (**1**) which was obtained according to the procedure of Surrey and Cutler.[3] The hydrazones were prepared by the reaction of 4-hydrazinoquinoline with appropriate aldehyde or the diethyl acetal of the aldehyde in the conventional manner. The hydrazines **4**, **6**, and **8** were obtained by catalytic (Pt) hydrogenation of the corresponding hydrazones in EtOH at room temperature and atmospheric pressure. Because of the premature poisoning of the catalyst, it had to be changed once or twice to complete the hydrogenation.

For the preparation of **11–16**, the hydrazino-side-chain amines were first prepared and then put on 4,7-dichloroquinoline according to the sequence of reactions outlined in Scheme I.

Scheme I



IV V VI VII VIII IX

n = 2–4; R = CH_3, C_2H_5; R_1 = HCO, CH_3CO; R_2 = CH_3, C_2H_5

For **13**, the side chain could also be prepared by the alkylation of methylhydrazine with dimethylaminopropyl chloride according to the procedure of Elslager, *et al.*[4]

Biological Activity.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla. The screening procedure is described by T. S. Osdene, *et al.*[5] Compound **1** was toxic. It killed one animal at 40 mg/kg and all five at 160 mg. Compounds **6–10** were inactive. Compounds **2–5** were slightly active, showing an increase in mean survival time of about 7.4 days.

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(5) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).