Research Laboratories, Parke, Davis and Company

# Amodiaquine N-Oxides and other 7-Chloro-4-aminoquinoline N-Oxides

Edward F. Elslager, Eva H. Gold, Frank H. Tendick,
Leslie M. Werbel, and Donald F. Worth

Oxidation of amodiaquine with perbenzoic acid gave amodiaquine N-α-oxide, whereas $N^4$-methylamodiaquine and amodiaquine 1-oxide afforded $N^4$-methylamodiaquine N-α,1-dioxide and amodiaquine N-α,1-dioxide, respectively. Amodiaquine 1-oxide, *O*-methylamodiaquine 1-oxide, oxychloroquine 1-oxide, and a variety of other 4-(7-chloro-4-quinolylamino)-α-dialkylamino-*o*-cresol 1-oxides and 7-chloro-4-[(mono- and dialkylamino)-alkylamino]quinoline 1-oxides were prepared by the condensation of 4,7-dichloroquinoline 1-oxide with a 4-amino-α-(dialkylamino)-*o*-cresol, N-α,N-α-diethyl-6-methoxytoluene-α,-3-diamine, or a mono- or dialkylaminoalkylamine in phenol or aqueous ethanol. $N^4$-Methylamodiaquine was synthesized from *p*-[(7-chloro-4-quinolyl)methylamino]phenol, diethylamine, and paraformaldehyde. Many of the N-oxides are highly active against the plasmodia of malaria.

The 4-aminoquinoline antimalarials exhibit outstanding activity against asexual erythrocytic parasites of all species of plasmodia causing human malaria. Amodiaquine (Ia) (1) and chloroquine (IIa) are among the most widely used drugs both for the treatment of acute malaria and for suppression (2,3). Amopyroquin (Ib) is relatively nontoxic and is particularly useful intramuscularly (2,4,5), while hydroxychloroquine (IIb) is less toxic than chloroquine and has similar antimalarial activity, orally or parenterally (2,6). Oxychloroquine (III) is reputed to be less toxic than chloroquine but in small-scale field trials has not shown any advantages over chloroquine (2). Various 4-aminoquinolines have also been employed in the treatment of rheumatoid arthritis, lupus erythematosus, and photoallergic reactions (7,8). In view of the broad utility of the 4-aminoquinolines in the treatment of disease, it was of interest to synthesize various 7-chloro-4-aminoquinoline N-oxides for biological evaluation. Details of the synthetic work are described in the present communication (Chart I).

Literature reports (9-14) indicate that the direct oxidation of quinolines to quinoline 1-oxides with peracids is a general reaction with few exceptions. However, the product we obtained by the oxidation of amodiaquine (Ia) with two moles of perbenzoic acid in chloroform absorbed in the ultraviolet at the same wave lengths as amodiaquine (Table I), suggesting that it was not amodiaquine 1-oxide (V) or amodiaquine N-α,-1-dioxide (VI). However, the infrared spectra of the two materials were different and the melting point of a mixture of the oxidation product (m.p. 191°) with amodiaquine base (m.p. 205-208°) was depressed. Microanalytical values (Table I) were in good agreement with a mono N-oxide and the product was thus assigned the N-α-oxide structure IV. In contrast, the ultraviolet spectrum of the oxidation product of $N^4$-methylamodiaquine (XI) showed a pronounced bathochromic shift (Table I), indicating formation of the 1-oxide. Microanalytical results, including Karl Fischer water titrations (Table I), supported assignment of the hydrated $N^4$-methyl amodiaquine N-α,1-dioxide structure XII. These results, together with previous observations that quinacrine N-ω-oxide and 3,6-dichloro-9-(4-diethylamino-1-methylbutylamino)acridine N-ω-oxide are formed by direct peracid oxidation of quinacrine and 3,6-dichloro-9-(4-diethylamino-1-methylbutylamino)acridine, respectively (15), suggest that oxidation does not occur on the heterocyclic nitrogen atom if the aminoheterocyclic systems can exist in tautomeric quinoid forms.

The synthesis of amodiaquine 1-oxide (V) and amodiaquine N-α,1-dioxide (VI) was accomplished according to the following scheme. Oxidation of 4,7-dichloroquinoline with perbenzoic acid in chloroform gave 4,7-dichloroquinoline 1-oxide (VIII) (16). The ultraviolet absorption spectrum of VIII showed a bathochromic shift indicative of the presence of the 1-oxide. Condensation of VIII with 4-amino-α-diethylamino-*o*-cresol dihydrochloride (1) in phenol gave amodiaquine 1-oxide (V). This compound absorbed at 400 mμ (Table I), indicating that the 1-oxide function was retained during the reaction. Oxidation of amodiaquine 1-oxide (V) with one equivalent of perbenzoic acid in chloroform at 0-5° gave the desired amodiaquine N-α,1-dioxide (VI); the ultraviolet spectrum of this compound showed the expected absorption at 400 mμ (Table I).

A variety of other 4-(7-chloro-4-quinolylamino)-α-dialkylamino-*o*-cresol 1-oxides (Table II) were prepared from VIII and the appropriate 4-amino-α-dialkylamino-*o*-cresol hydrochlorides (1,17) in phenol (Method I) or aqueous ethanol (Method II). In general, yields were low and deoxygenated by-products were frequently isolated from the reaction mixtures. 7-Chloro-4-[α-(diethylamino)-4-methoxy-*m*-toluidino]quinoline 1-oxide (O-methylamodiaquine 1-oxide) (VII) and *p*-(7-chloro-4-quinolylamino)phenol 1-oxide were prepared in a similar manner from VIII and N-α,N-α-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (1) and *p*-aminophenol hydrochloride, respectively. The characteristic bathochromic shift was observed in the ultraviolet spectrum of both compounds (Table I).

Initially the synthesis of $N^4$-methylamodiaquine (XI) was planned *via* the condensation of α-(diethylamino)-4-(methylamino)-*o*-cresol with 4,7-dichloroquinoline. However, unexpected difficulties were encountered during attempts to prepare the intermediate α-(diethylamino)-4-(methylamino)-*o*-cresol. Efforts to condense

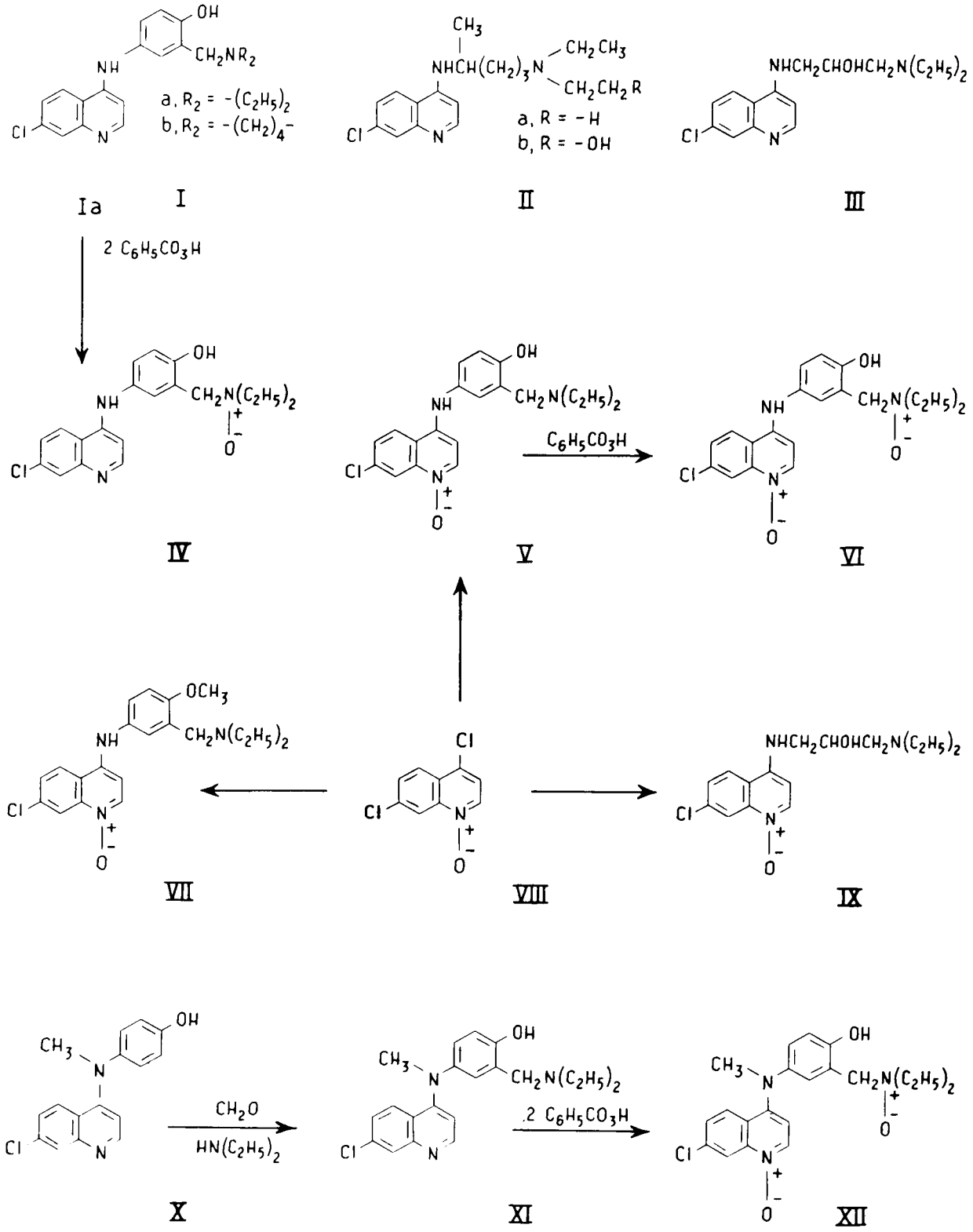

OH
CH2NR2
NH
a, R2 = -(C2H5)2
b, R2 = -(CH2)4-
Cl
N
Ia
I
CH3
NHCH(CH2)3N
CH2CH3
CH2CH2R
a, R = -H
b, R = -OH
II
NHCH2CHOHCH2N(C2H5)2
III
2 C6H5CO3H
CH2N(C2H5)2
O
IV
C6H5CO3H
V
VI
OCH3
VII
VIII
IX
CH3
CH2O
HN(C2H5)2
X
2 C6H5CO3H
XI
XII

Table I

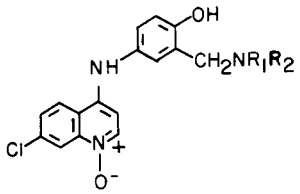
Properties of Representative 4-Aminoquinolines and 4-Aminoquinoline N-Oxides

| Compound | M.p., °C. | Formula | Ultraviolet Absorption (a) Ethanol λ | Ethanol ε | 0.1N HCl λ | 0.1N HCl ε | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found | Water, % (b) Calcd. | Water, % (b) Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amodiaquine (Ia) | 205-208 | $C_{20}H_{22}ClN_3O$ | 339 | 12,800 | 342 | 17,300 | 67.50 | | 6.23 | | 11.81 | | 0.00 | |
| Amodiaquine N-α-oxide (IV) | 191 dec. | $C_{20}H_{22}ClN_3O_2$ | 338 | 12,600 | 341 | 17,000 | 64.59 | 64.75 | 5.96 | 6.12 | 11.30 | 11.32 | 0.00 | 0.00 |
| Amodiaquine 1-oxide (V) | 226 dec. | $C_{20}H_{22}ClN_3O_2$ | 400 | 13,900 | 356 | 17,500 | 64.59 | 64.69 | 5.96 | 5.88 | 11.30 | 11.30 | 0.00 | 0.00 |
| Amodiaquine N-α,1-dioxide (VI) | 189-190 dec. | $C_{20}H_{22}ClN_3O_3 \cdot 0.25\,H_2O$ | 400 | 14,000 | 357 | 17,200 | 61.22 | 61.02 | 5.78 | 5.83 | 10.71 | 10.51 | 1.15 | 1.35 |
| O-Methylamodiaquine | 202-204 | $C_{21}H_{24}ClN_3O$ | 340 | 12,300 | 342 | 16,500 | 68.19 | | 6.54 | | 11.36 | | 0.00 | |
| O-Methylamodiaquine 1-oxide (VII) | 208-211 | $C_{21}H_{24}ClN_3O_2 \cdot 0.5H_2O$ | 400 | 14,500 | 355 | 18,000 | 63.87 | 63.73 | 6.38 | 6.46 | 10.64 | 10.64 | 2.28 | 2.51 |
| $N^4$-Methylamodiaquine (XI) | 78-81 | $C_{21}H_{24}ClN_3O$ | 348 | 8,500 | 355 | 12,900 | 68.19 | 68.11 | 6.54 | 6.40 | 11.36 | 11.31 | 0.00 | 0.00 |
| $N^4$-Methylamodiaquine N-α,1-dioxide (XII) | 162-165 dec. | $C_{21}H_{24}ClN_3O_3 \cdot 0.5H_2O$ | 404 | 11,700 | 374 | 13,300 | 61.38 | 61.44 | 6.13 | 5.91 | 10.23 | 10.20 | 2.19 | 1.95 |
| Oxychloroquine (IIb) | 120-122 | $C_{18}H_{20}ClN_3O$ | 328 | 11,800 | 340<br>328 | 17,900<br>17,300 | 62.43 | | 7.21 | | 13.65 | | 0.00 | |
| Oxychloroquine 1-oxide (IX) | 205 | $C_{18}H_{20}ClN_3O_2$ | 390 | 12,600 | 353<br>343 | 16,900<br>17,400 | 59.34 | 59.11 | 6.85 | 6.78 | 12.98 | 12.83 | 0.00 | 0.00 |
| *p*-(7-Chloro-4-quinolylamino)-phenol | 254-256 | $C_{15}H_{11}ClN_2O$ | 339 | 12,600 | 342 | 15,300 | 66.54 | | 4.10 | | 10.35 | | 0.00 | |
| *p*-[(7-Chloro-4-quinolylmethyl-amino]phenol (X) | 248-258 | $C_{16}H_{13}ClN_2O$ | 345 | 8,800 | 352 | 13,600 | 67.49 | 67.35 | 4.60 | 4.62 | 9.84 | 10.07 | 0.00 | 0.00 |

(a) Spectra were taken with a Cary-11 spectrophotometer. (b) Water determinations by the Karl Fischer method.

Table II

4-(7-Chloro-4-quinolylamino)-α-dialkylamino-*o*-cresol 1-Oxides (a)

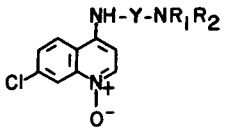



| Compd. No. | $NR_1R_2$ | M.p., °C. (b) | Yield purified, % | Procedure | Purification Solvent (c) | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $N(CH_3)_4$ | 238 | 18 | II | A | $C_{20}H_{20}ClN_3O_2$ | 64.94 | 64.75 | 5.45 | 5.35 | 11.36 | 11.47 |
| 2 | $N[(CH_2)_2]_2O$ | 235-236 | 20 | I | B | $C_{20}H_{20}ClN_3O_3 \cdot 0.33H_2O$ (d) | 61.30 | 61.33 | 5.31 | 5.34 | 10.72 | 10.44 |
| 3 | $N(C_4H_9)_2$ | 226 | 33 | I | C | $C_{20}H_{22}ClN_3O_2$ | 64.59 | 64.69 | 5.96 | 5.88 | 11.30 | 11.30 |
| 4 | $NC_2H_5CH_2CH_2OH$ | 224-225 | 26 | I | F | $C_{20}H_{22}ClN_3O_3$ | 61.93 | 61.68 | 5.72 | 5.66 | 10.83 | 10.94 |
| 5 | $N[(CH_2)_2]_2CHOH$ | 251 | 17 | I | B | $C_{21}H_{22}ClN_3O_3$ | 63.07 | 63.04 | 5.55 | 5.55 | 10.51 | 10.35 |
| 6 | $N(CH_2)_5$ | 217-218 | 33 | II | E | $C_{21}H_{22}ClN_3O_2$ | 65.70 | 65.68 | 5.77 | 5.87 | 10.94 | 10.89 |
| 7 | $N[(CH_2)_2]_2NCH_3$ | 244-245 | 27 | I | D | $C_{21}H_{23}ClN_4O_2 \cdot 0.25H_2O$ (e) | 62.52 | 62.70 | 5.86 | 5.57 | 13.89 | 13.72 |
| 8 | $NCH_3(CH_2)_3CH_3$ | 215-216 | 34 | I | B | $C_{27}H_{36}ClN_3O_2$ | 68.98 | 68.98 | 7.72 | 7.91 | 8.94 | 8.97 |

(a) Compounds are yellow crystalline solids. (b) Compounds melt with decomposition. (c) A, ethanol-chloroform-carbon tetrachloride. B, methanol. C, chloroform. D, methanol-ethyl acetate. E, methanol-carbon tetrachloride. F, ethanol. Water determination (Karl Fischer); (d) Calcd.: 1.53; Found: 1.98. (e) Calcd.: 1.11; Found: 0.82.

Table III

7-Chloro-4-[(mono- and dialkylamino)alkylamino]quinoline 1-Oxides (a)




| Compd. No. | Y | $NR_1R_2$ | M.p., °C. | Yield purified (b), % | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | $-(CH_2)_3-$ | $NHCH(CH_3)_2$ | 176-179 | 57 | $C_{15}H_{20}ClN_3O$ | 61.32 | 61.36 | 6.86 | 6.75 | 14.31 | 14.19 |
| 10 | $-(CH_2)_2-$ | $N(C_2H_5)_2$ | 185-187 | 33 | $C_{15}H_{20}ClN_3O$ | 61.32 | 61.24 | 6.86 | 6.71 | 14.31 | 14.11 |
| 11 | $-(CH_2)_2-$ | $NC_2H_5(CH_2)_2OH$ | 148-150 | 2 | $C_{15}H_{20}ClN_3O_2$ | 58.12 | 57.79 | 6.50 | 6.47 | 13.55 | 13.50 |
| 12 | $-(CH_2)_2-$ | $N(CH_2)_5$ | 196-198 | 37 | $C_{16}H_{20}ClN_3O$ | 62.84 | 62.68 | 6.59 | 6.45 | 13.74 | 13.84 |
| 13 | $-(CH_2)_3-$ | $N(CH_2)_4$ | 185-187 | 46 | $C_{16}H_{20}ClN_3O$ | 62.84 | 62.65 | 6.59 | 6.35 | 13.74 | 13.71 |
| 14 | $-(CH_2)_3-$ | $N(C_2H_5)_2$ | 150-152 | 60 | $C_{16}H_{22}ClN_3O$ | 62.43 | 62.35 | 7.20 | 7.04 | 13.66 | 13.70 |
| 15 | $-CH_2CHOHCH_2-$ | $N(C_2H_5)_2$ | 190-191 | 30 | $C_{16}H_{22}ClN_3O_2$ (d, e, f) | 59.34 | 59.11 | 6.85 | 6.78 | 12.98 | 12.83 |
| 16 | $-(CH_2)_3-$ | $N(CH_2)_5$ | 185-187 | 57 | $C_{17}H_{22}ClN_3O$ | 63.84 | 63.66 | 6.94 | 6.84 | 13.14 | 13.35 |
| 17 | $-(CH_2)_3-$ |  | 205-210 | 25 | $C_{17}H_{22}ClN_3O_2$ | 60.80 | 61.07 | 6.60 | 6.75 | 12.51 | 12.67 |
| 18 | $-(CH_2)_5-$ | $N(CH_2)_5$ | 174-176 | 31 | $C_{19}H_{26}ClN_3O \cdot 0.5H_2O$ (c) | 63.95 | 64.00 | 7.63 | 7.49 | 11.71 | 11.61 |
| 19 | $-(CH_2)_3-$ | $NH(CH_2)_7CH_3$ | 107-108 | 51 | $C_{20}H_{30}ClN_3O$ | 66.01 | 65.85 | 8.31 | 8.20 | 11.54 | 11.61 |

(a) Compounds are yellow crystalline solids. (b) Compounds were recrystallized from dimethylformamide. (c) Calcd. water determination (Karl Fischer): 2.52; Found: 2.23. (d) Dihydrochloride salt from ethanol-ether, m.p. 218-221°; *Anal.* Calcd. for $C_{16}H_{22}ClN_3O_2 \cdot 2HCl$: C, 48.43; H, 5.96; N, 10.59. Found: C, 48.17; H, 6.00; N, 10.25. (e) Salt with 4,4'-methylenebis (3-hydroxy-2-naphthoic acid), m.p. 192-197°; *Anal.* Calcd. for $C_{16}H_{22}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot H_2O$: C, 64.15; H, 5.52; N, 5.75. Found: C, 64.13; H, 5.69; N, 5.73. (f) Salt with 1,5-naphthalenedisulfonic acid, m.p. 298-308°; *Anal.* Calcd. for $C_{16}H_{22}ClN_3O_2 \cdot C_{10}H_8O_6S_2$: C, 51.00; H, 4.94; N, 6.83. Found: C, 50.94; H, 5.13; N, 6.75.

either 4'-hydroxy-N-methylacetanilide or *p*-(methylamino)phenol with formaldehyde and diethylamine under a variety of experimental conditions (1,17) were unsuccessful. Alternatively, *p*-(methylamino)phenol was allowed to react with 4,7-dichloroquinoline to give *p*-[(7-chloro-4-quinolyl)methylamino]phenol (X), which condensed readily with diethylamine and paraformaldehyde in 2-methoxyethanol to afford the desired $N^4$-methylamodiaquine (XI) (18). A comparison of the ultraviolet spectra of *p*-[(7-chloro-4-quinolyl)amino]-phenol (18), *p*-[(7-chloro-4-quinolyl)methylamino]phenol (X), amodiaquine (Ia), and $N^4$-methylamodiaquine (XI) revealed that methylation of the secondary amine caused a displacement of the absorption maxima toward the visible in both ethanol and 0.1N hydrochloric acid (Table I). In a recent study (19) with 2-(7-chloro-4-quinolylamino)ethanol and its $N^4$-methyl derivative, a similar shift was observed in 0.01N hydrochloric acid which was ascribed to steric hindrance.

While exploring synthetic routes to chloroquine, Yoshida (16) observed that the condensation of 4,7-dichloroquinoline 1-oxide (VIII) with $N^1$,$N^1$-diethyl-1,4-pentanediamine at 180° proceeded with deoxygenation to give chloroquine in 67% yield. Further, Ochiai (10) reported the isolation of 4-piperidinoquinoline in 67% yield after 4-chloroquinoline 1-oxide was heated with excess piperidine in a sealed tube for 5 hr. at 135-145°. It therefore appeared unlikely that 7-chloro-4-[(mono- and dialkylamino)alkylamino]quinoline 1-oxides could be prepared by the condensation of VIII with the appropriate mono- or dialkylaminoalkylamine. Nevertheless, the successful preparation of amodiaquine 1-oxide (V) stimulated us to reinvestigate the problem.

$N^1$,$N^1$-Diethyl-1,4-pentanediamine was allowed to react with VIII under a variety of experimental conditions, but in no instance were materials isolated which exhibited a bathochromic shift from 328 mμ. Variations studied included heating VIII with an excess of the diamine: 1) at 120-130° for 4 hr.; 2) in aqueous ethanol at 125° and 50 p.s.i.g. for 24 hr.; 3) in 2-propanol or pentanol on a steam bath for 2-3 hr.; 4) in aqueous ethanol containing a trace of hydrochloric acid under reflux for 24 hr. (20). When the reagents were heated at 160° for 2 hr., some 4,7-dichloroquinoline could be isolated. Heating the mixture in phenol for 1 hr. at 100-110° yielded 7-chloro-4-phenoxyquinoline 1-oxide; prolonged heating in phenol led to deoxygenated products.

In an additional study, VIII was heated at 120° in an excess of $N^1$,$N^1$-diethyl-1,4-pentanediamine and samples were removed at intervals for ultraviolet analysis. After 50 minutes no absorption at 390 mμ was present and broad absorption at 320-50 mμ was noted. After 80 minutes a plateau developed at 390 mμ and peaks were present at 331 and 323 mμ. No change in peak position occurred upon further heating and the intensity of the 390 mμ absorption remained nearly constant. However, the ratio of intensities of the 331 to 390 mμ absorption gradually increased and finally leveled off after 4 hr. Assuming that the absorption at 390 mμ is due to the aminoquinoline-1-oxide product, one may interpret the data as favoring deoxygenation of VIII followed by formation of the 4-amino-7-chloroquinoline rather than deoxygenation of the aminoquinoline 1-oxide.

The hypothesis that the condensation might proceed more readily with unhindered diamines prompted a study of the reaction of 4,7-dichloroquinoline 1-oxide with 1-amino-3-diethylamino-2-propanol. Initially, VIII was heated at 110-120° for 4 hr. with an excess of the diamine containing a trace of hydrochloric acid. The reaction mixture was poured into aqueous sodium hydroxide and the yellow solid that precipitated was triturated with boiling acetone and the residue crystallized from dimethylformamide. The compound, m.p. 205°, absorbed strongly at 390 mμ (Table I), indicating retention of the 1-oxide function. Microanalytical results were in excellent agreement with the oxychloroquine 1-oxide structure IX (Table I). Optimum yields (30%) were obtained when the reagents were refluxed for 24 hr. in aqueous ethanol containing a few drops of hydrochloric acid (20). Yields were lower (10%) without hydrochloric acid or when VIII was heated with a molar excess of diamine in phenol on a steam bath for 5 hr. The yield increased to 18% when the heating period in phenol was extended to 18 hr. No product was isolated when a 1:2 mole ratio of VIII to diamine was heated in dimethylformamide containing 2 drops of hydrochloric acid at 130-140° for 5 hrs., or when the reagents were heated under reflux for extended periods in acetone or toluene. Use of pyridine as a solvent allowed isolation only of 4,7-dichloroquinoline.

Subsequently, 4,7-dichloroquinoline 1-oxide (VIII) was allowed to react with a variety of aliphatic amines in ethanol containing a trace of hydrochloric acid. With sterically-hindered amines such as 2-[(4-aminopentyl)-ethylamino]ethanol, N,N-dimethyl-1,4-cyclohexanediamine, 3-aminoheptane, and N,N-diethyl-$N^1$-methylethylenediamine, no 4-aminoquinoline 1-oxides could be isolated. Unhindered mono- and dialkylaminoalkylamines (15), however, afforded the corresponding 7-chloro-4-[(mono- and dialkylamino)alkylamino]quinoline 1-oxides (Table III) in yields ranging from 2 to 60% (21). The 4-aminoquinoline 1-oxide free bases exhibited unexpectedly high melting points that averaged approximately 85° higher than the corresponding des N-oxide bases.

During the synthesis work it was noted that the 7-chloro-4-[(mono- and dialkylamino)alkylamino]quinoline 1-oxides exhibited a strong yellow-green fluorescence under ultraviolet light. Subsequently, the activation and fluorescence spectra of these N-oxides (Table III) were compared with the spectra of several of the corresponding des N-oxides in 0.01 N hydrochloric acid on a Aminco-Bowman spectrophotofluorimeter. Activation and fluorescence peaks of the N-oxides occurred at 350 and 510 mμ respectively. The des N-oxides exhibited a weaker bluish fluorescence at 340 and 390 mμ respectively. As a group the N-oxides were approximately twenty-three times more fluorescent than the corresponding des N-oxides and are detectable in concentrations of less than 0.1 μg./ml.

The 7-chloro-4-aminoquinoline N-oxides were tested against a variety of parasites, bacteria, and viruses including *Plasmodium berghei*, *P. lophurae*, *Entamoeba histolytica*, *Trichomonas vaginalis*, *Trypanosoma cruzi*, *Schistosoma mansoni*, *Syphacia obvelata*, *Aspiculuris tetraptera*, *Nematospiroides dubius*, *Hymenolepis nana*, *Strongyloides ratti*, *Nippostrongylus muris*, *Strepto-*

*coccus pyogenes* (C 203), *Staphylococcus aureus* (UC-76), *Klebsiella pneumoniae* (AD), *Proteus vulgaris* (MGH-1), *Pseudomonas aeruginosa* (No. 28), *Salmonella typhimurium* (V-31), *Mycobacterium tuberculosis* (H37Rv), herpes simplex, polio, measles, and adenovirus (22-24). Highlights of these tests are summarized below.

Among various 4-(7-chloro-4-quinolylamino)-α-dialkylamino-*o*-cresol 1-oxides (Table II), the antimalarial activity of amodiaquine 1-oxide (V) was outstanding (22). When administered subcutaneously to mice infected with *P. berghei* (25) twice daily for 4 days starting one day after infection, amodiaquine 1-oxide was 3.4 times as potent as amodiaquine base. Amodiaquine 1-oxide also exhibits radioprotectant activity in mice (26). Compounds 5 and 7 were active against *A. tetraptera* and *S. obvelata* when administered to mice at drug-diet levels of 0.0625 to 0.25% for six days (27). 4-(7-Chloro-4-quinolylamino)-α-morpholino-*o*-cresol 1-oxide (No. 2) and 4-(7-chloro-4-quinolylamino)-α-(4-methyl-1-piperazinyl)-*o*-cresol 1-oxide (No. 7) showed reproducible activity against measles virus in tissue culture at levels ranging from 30 to 300 μg./ml. whereas the corresponding des N-oxides were inactive (24,28).

Several of the 7-chloro-4-[(mono- and dialkylamino)-alkylamino]quinoline 1-oxides (Table III) exhibited good antimalarial activity against *P. berghei* in the mouse (25); compounds 9 and 13 through 19 were approximately five times as active as amodiaquine base when administered subcutaneously twice daily for 4 days.

Schönhöfer (29) has postulated that the antimalarial activity of certain basically substituted 4-, 6-, and 8-aminoquinolines is dependant on their capacity to allow tautomerism and form quinoid linkages. It was therefore surprising that $N^4$-methylamodiaquine (XI), which presumably is incapable of existing in quinoid form, was approximately six times as active as quinine (0.2-amodiaquine) against *P. lophurae* in the chick when administered orally in the diet for five days. These results suggest either that $N^4$-methylamodiaquine is an exception to the Schönhöfer theory or that it undergoes metabolic activation in the chick, possibly leading to amodiaquine *via* demethylation.

## EXPERIMENTAL (30)

Amodiaquine N α-Oxide (IV).

A solution of 16.5 g. (0.12 mole) of perbenzoic acid (31) in 360 ml. of chloroform was added with stirring to a solution of 35.6 g. (0.10 mole) of amodiaquine base in 1 l. of chloroform. The reaction was slightly exothermic and the temperature rose from 29 to 35°. A deep color developed and no active oxygen could be detected with starch-iodide paper immediately after the addition was complete. The mixture was stirred for 1 hr. at room temperature and an additional 13.8 g. (0.10 mole) of perbenzoic acid in 300 ml. of chloroform was added. Once again the addition was exothermic but unexpectedly no active oxygen could be detected upon completion of the addition. The mixture was allowed to stand at room temperature for 18 hr., a small amount of precipitate was removed by filtration, and the chloroform solution was washed successively with two 500 ml. portions of 10% aqueous sodium carbonate solution and water. The chloroform layer was filtered, concentrated to a volume of 500 ml. and cooled. The yellow solid was collected, washed with ether and dried *in vacuo* at 45°; weight 17.0 g., m.p. 189° dec. A second crop obtained by concentration of the filtrate weighed 7.0 g., m.p. 187-192° dec. For analysis, the compound was crystallized twice from ethanol and dried *in vacuo* at 75°; m.p. 191° dec.

Preparation of 4-(7-Chloro-4-quinolylamino)-α-dialkylamino-*o*-cresol 1-Oxides (Table II). Method I.

A mixture of 133.6 g. (0.5 mole) of 4-amino-α-diethylamino-*o*-cresol dihydrochloride (I) and 300 g. of phenol was heated *in vacuo* on a steam bath for 40 min. 4,7-Dichloroquinoline 1-oxide (107 g., 0.5 mole) and 42 g. (0.5 mole) of sodium bicarbonate were added and the mixture was stirred and heated on a steam bath for 2 hr. The reaction mixture was made acid by the dropwise addition of concentrated hydrochloric acid and heating was continued for 0.5 hr. The mixture was allowed to cool and was poured into an ether-acetone mixture with vigorous stirring. The supernatant was decanted, the sticky precipitate was dissolved in dilute hydrochloric acid, and the mixture was filtered. The filtrate was made alkaline with 10% aqueous sodium hydroxide and the dark-colored precipitate that separated was collected and dried. The solid was triturated with boiling ethyl acetate, washed with anhydrous ether, and crystallized twice from a chloroform-methanol mixture (decolorizing charcoal). Amodiaquine 1-oxide was obtained as yellow leaflets, m.p. 226° dec.

Method II.

To a solution of 27.9 g. (0.1 mole) of 2-N-piperidylmethyl-4-aminophenol dihydrochloride (I) in 400 ml. of water was added 21.4 g. (0.1 mole) of 4,7-dichloroquinoline 1-oxide, 25 ml. of ethanol, and a few drops of concentrated hydrochloric acid. The mixture was stirred and heated on a steam bath for 2 hr., cooled and filtered. The filtrate was neutralized with dilute ammonium hydroxide and the mixture was extracted with chloroform. The combined chloroform extracts were washed with water, the chloroform was removed on a steam bath, and the residue was crystallized successively from ethanol and a methanol-carbon tetrachloride mixture (decolorizing charcoal). The 4-(7-chloro-4-quinolylamino)-α-piperidino-*o*-cresol 1-oxide was obtained as bright yellow crystals, m.p. 217-218° dec.

Amodiaquine N-α,1-Dioxide (VI).

A solution of 3.72 g. (0.0269 mole) of perbenzoic acid (31) in 80 ml. of chloroform was added dropwise with stirring over a period of 40 min. to a slurry of 10.0 g. (0.0269 mole) of amodiaquine 1-oxide in 1 l. of chloroform while maintaining the temperature at 0-5°. Stirring was continued at 0-5° for 1.5 hr. and the solution was treated with hydrogen chloride and diluted with anhydrous ether. The yellow precipitate that separated was collected, washed with anhydrous ether and air-dried; weight, 15.0 g. An aqueous slurry of the crude hydrochloride salt was made alkaline with ammonium hydroxide and the base was collected, washed with water and dried *in vacuo* at 60°. The base was triturated successively with hot ethyl acetate and acetone and dried *in vacuo* at 60°; it weighed 7.0 g., m.p. 180° dec. For analysis, the compound was crystallized three times from ethanol-ether giving gold-colored crystals, m.p. 189-190° dec.

7-Chloro-4-[α-(diethylamino)-4-methoxy-*m*-toluidino]quinoline 1-Oxide (O-Methylamodiaquine 1-Oxide) (VII).

Utilizing the procedure described under method II, 9.14 g. (0.0427 mole) of 4,7-dichloroquinoline 1-oxide and 12.0 g. (0.0427 mole) of N-α,N-α-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (I) were condensed to give 6.3 g. of a crude dark-colored product. Successive crystallizations from methanol-water, chloroform-ether, and acetonitrile-water gave 2.9 g. (17%) of shiny olive-green platelets, m.p. 208-211°.

4,7-Dichloroquinoline 1-Oxide (VIII).

A solution of 138 g. (1 mole) of perbenzoic acid (31) in 2 l. of chloroform was added to a solution of 198 g. (1 mole) of 4,7-dichloroquinoline in 600 ml. of chloroform and the mixture was allowed to stand at room temperature for 18 hr. The reddish-brown solution was extracted twice with 1 l. portions of 10% aqueous sodium carbonate, then washed with water. The chloroform solution was dried over anhydrous potassium carbonate, the drying agent was collected and the chloroform was removed *in vacuo* in the presence of platinum foil. The residue was crystallized twice from ethanol (decolorizing charcoal) to give 90 g. (42%) of colorless crystals, m.p. 165-166°.

*Anal.* Calcd. for $C_9H_5Cl_2NO$: C, 50.49; H, 2.35; N, 6.54. Found: C, 50.40; H, 2.30; N, 6.65.

Preparation of 7-Chloro-4-[(mono- and dialkylamino)alkylamino]quinoline 1-Oxides (Table III).

A mixture of 10.7 g. (0.05 mole) of 4,7-dichloroquinoline 1-oxide and 12.8 g. (0.1 mole) of 3-(1-pyrrolidinyl)propylamine in 200 ml. of ethanol and 30 ml. of water containing 3 drops of concentrated hydrochloric acid was heated under reflux for 24 hr. Volatile materials were removed *in vacuo* and the residue was triturated with dilute aqueous sodium hydroxide. The oil which formed solidified upon standing at room temperature for 48 hr. with intermittent stirring. The yellow solid was collected, stirred with hot acetone to remove unreacted 4,7-dichloroquinoline 1-oxide, and crystallized from dimethylformamide. 7-Chloro-4-{[3-(1-pyrrolidinyl)propyl]amino}quinoline 1-oxide was obtained as yellow crystals, m.p. 185-187°.

*p*-[(7-Chloro-4-quinolyl)methylamino]phenol (X).

A mixture of 99 g. (0.5 mole) of 4,7-dichloroquinoline, 86 g. (0.5 mole) of *p*-(methylamino)phenol hemisulfate, and 200 g. of phenol was stirred and heated on a steam bath for 4 hr. The mixture was transferred to a beaker, the flask was rinsed with ethanol, and the mixture was diluted with anhydrous ether. The oily residue was separated, redissolved in ethanol, and once again precipitated with anhydrous ether. The supernatant was decanted and the oily residue was stirred into 4 l. of hot water containing an excess of sodium hydroxide. The tan solid that separated was collected by filtration, washed with water, and dried *in vacuo* at 55° for 18 hr. The crude product was crystallized twice from dimethylacetamide-water to give 68 g. (48%) of yellow crystals, m.p. 248-258°.

4-[(7-Chloro-4-quinolyl)methylamino]-α-diethylamino-*o*-cresol ($N^4$-Methylamodiaquine) (XI).

A mixture of diethylamine (33 g., 0.456 mole), paraformaldehyde (10 g., 0.342 mole) and ethanol (250 ml.) was stirred and heated on a steam bath for 15 min. The hot solution was added to a hot solution of *p*-[(7-chloro-4-quinolyl)methylamino]phenol (65 g., 0.228 mole) in 1.5 l. of 2-methoxyethanol with stirring, and heating was continued for 6 hr. A second identical portion of the paraformaldehyde-amine reagent was then added and heating was continued on the steam bath for an additional 6 hr. Volatile materials were removed *in vacuo* on a steam bath and the oily residue was dissolved in anhydrous ether and filtered. Excess hydrogen chloride was bubbled into

the ether solution and the orange-yellow precipitate that separated was collected and dried. The crude product was dissolved in dilute hydrochloric acid, the solution was filtered, and the filtrate was made alkaline with aqueous sodium hydroxide. The mixture was extracted with ether and the combined ether extracts were dried over anhydrous potassium carbonate. The drying agent was collected by filtration and the ether filtrate was treated with excess hydrogen chloride. The precipitate was collected and dried *in vacuo*; weight, 93 g. (92%), m.p. 105° with foaming. The material was crystallized twice from ethanol-ether and dried *in vacuo* at 75° for 18 hr. to give 60 g. of $N^4$-methylamodiaquine dihydrochloride ethanolate as yellow-orange crystals, m.p. 223-224° dec. The presence of ethanol was confirmed by vapor phase chromatography.

*Anal.* Calcd. for $C_{21}H_{24}ClN_3O \cdot 2HCl \cdot C_2H_5OH$: C, 56.50; H, 6.61; N, 8.59; Cl, 21.80. Found: C, 56.51; H, 6.30; N, 8.61; Cl, 21.92.

An aqueous solution of the dihydrochloride salt (35 g., 0.0716 mole) was poured into a mixture of ether and excess aqueous sodium hydroxide. The ether layer was separated and the aqueous layer was washed with several portions of ether. The combined ether extracts were washed with water and dried over anhydrous potassium carbonate; the drying agent was collected and the ether filtrate was concentrated to a viscous oil. The oily residue was crystallized twice from methanol-water to give 19 g. (72% recovery) of the base as yellow crystals, m.p. 78-81°.

4-[(7-Chloro-4-quinolyl)methylamino]-α-diethylamino-*o*-cresol N-α,1-Dioxide ($N^4$-Methylamodiaquine N-α,1 Dioxide) (XII).

4-[(7-Chloro-4-quinolyl)methylamino]-α-diethylamino-*o*-cresol (10.0 g., 0.0270 mole) and perbenzoic acid (7.8 g., 0.0567 mole) were allowed to react in chloroform and the mixture was worked up according to the procedure used for the preparation of amodiaquine N-α-oxide. The chloroform concentrate was diluted with anhydrous ether and the yellow solid that separated (5.5 g.) was crystallized from acetone-ether (decolorizing charcoal) to give 2.15 g. (19%) of golden orange crystals, m.p. 162-165° dec.

*p*-(7-Chloro-4-quinolylamino)phenol 1-Oxide.

A filtered solution of 14.5 g. (0.1 mole) of 4-aminophenol hydrochloride in 500 ml. of water was added to 21.4 g. (0.1 mole) of 4,7-dichloroquinoline 1-oxide which had been moistened with ethanol. The mixture was stirred and heated on a steam bath for 2.5 hr., cooled, and the solid that separated was collected and washed successively with water and acetone. The hydrochloride was suspended in water, excess ammonium hydroxide was added, and the mixture was stirred for 1 hr. The base was collected, washed with water, dried, and crystallized twice from ethanol. The yellow crystals weighed 14 g. (49%), m.p. 285° dec.

*Anal.* Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.86; N, 9.77. Found: C, 62.48; H, 3.99; N, 9.77.

7-Chloro-4-phenoxyquinoline 1-Oxide.

A mixture of 2.1 g. (0.01 mole) of 4,7-dichloroquinoline 1-oxide, 3.2 g. (0.02 mole) of $N^1$,$N^2$-diethyl-1,4-pentanediamine and 5 g. of phenol was heated at 100-110° for 1 hr. The reaction mixture was cooled and poured into ice containing an excess of 2 N aqueous sodium hydroxide. The precipitate was collected, washed with water, and dried. Two crystallizations from petroleum ether (b.p. 60-80°) (decolorizing charcoal) gave 1.9 g. (70%) of pale yellow, fluffy needles, m.p. 126-127°.

*Anal.* Calcd. for $C_{15}H_{10}ClNO_2$: C, 66.3; H, 3.7; N, 5.2. Found: C, 66.5; H, 3.5; N, 5.2.

Acknowledgement.

The authors take this opportunity to thank Dr. Loren M. Long for encouragement in this investigation and Dr. Paul E. Thompson, Miss Anita Bayles, Mrs. Sheila Herbst, Dr. D. A. McCarthy, Miss Priscilla McClay, Dr. Haig Najarian, Miss Bronislawa Olszewski, Dr. M. W. Fisher, Dr. A. L. Erlandson, Dr. G. J. Dixon and Dr. F. Schabel for the biological evaluation of these compounds. The authors also are indebted to Mr. Charles E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and associates for the determination of the infrared and ultraviolet absorption spectra, and Dr. J. R. McLean for the fluorescence spectra studies.

REFERENCES

(1) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, 70, 1363 (1948).
(2) *Wld. Hlth. Org. techn. Rep. Ser.*, 1961, 226.
(3) For a historical review of the development of the 4-aminoquinolines, see P. B. Russell in "Medicinal Chemistry", A. Burger, ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 832-835.
(4) P. E. Thompson, K. Weston, A. J. Glazko, R. A. Fisken, T. F. Reutner, A. Bayles, and J. K. Weston, *Antibiot. Chemotherapy*, 8, 450 (1958).
(5) M. T. Hoekenga, *Am. J. Trop. Med. Hyg.*, 11, 1 (1962).
(6) M. T. Hoekenga, *ibid.*, 4, 221 (1955).
(7) R. B. Conn, "Current Therapy", W. B. Saunders Co., Philadelphia, Pa., 1962.
(8) L. E. Bartholomew and I. F. Duff, *Arthritis and Rheumat.*, 5, 282 (1962).
(9) C. C. J. Culvenor, *Rev. Pure Appl. Chem.*, 3, 83 (1953).
(10) E. Ochiai, *J. Org. Chem.*, 18, 534 (1953).
(11) D. E. Ames, C. S. Franklin, and T. F. Grey, *J. Chem. Soc.*, 3079 (1956).
(12) H. Tanida, *J. Pharm. Soc. Japan*, 78, 613 (1958).
(13) E. Profft, G. Buchmann, and N. Wackrow, *Wiss. Z. Tech. Hochsch. Chem. Leuna-Merseburg*, 2, 93 (1959-1960); *Chem. Abstr.*, 55, 1615c (1961).
(14) D. V. Ioffe and L. S. Efros, *Russian Chem. Rev.*, 30, 569 (1961).
(15) E. F. Elslager, R. E. Bowman, F. H. Tendick, D. J. Tivey, and D. F. Worth, *J. Med. Pharm. Chem.*, 5, 1159 (1962).
(16) Prepared previously from 7-chloro-4-nitroquinoline 1-oxide by S. Yoshida, *J. Pharm. Soc. Japan*, 66, 60 (1946).
(17) E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, 5, 1153 (1962).
(18) Amodiaquine has been synthesized by an analogous procedure, *cf.* J. H. Burckhalter, H. A. DeWald, and F. H. Tendick, *J. Am. Chem. Soc.*, 72, 1024 (1950).
(19) R. M. Peck, *J. Org. Chem.*, 28, 1998 (1963).
(20) The beneficial effect of acid catalysis on the reaction rate of activated heterocyclic halogen compounds with amines in aqueous media has been demonstrated, *cf.* C. K. Banks, *J. Am. Chem. Soc.*, 66, 1127 (1944).
(21) T. Okamoto, H. Hayatsu, and Y. Baba, *Chem. and Pharm. Bull.*, 8, 892 (1960), reported that piperidine reacts more than ten times faster with 4-haloquinoline 1-oxides than with 4-haloquinolines, 4-piperidinoquinoline 1-oxide being the sole product.
(22) P. E. Thompson, A. Bayles, D. A. McCarthy, J. E. Meisenhelder, and B. J. Olszewski, unpublished results, Parke, Davis and Co., Ann Arbor, Michigan.
(23) M. W. Fisher and A. L. Erlandson, unpublished results, Parke, Davis, and Co., Detroit, Michigan.
(24) G. J. Dixon and F. Schabel, unpublished results, Southern Research Institute, Birmingham, Alabama.
(25) For a description of test methods, see P. E. Thompson, B. J. Olszewski, E. F. Elslager, and D. F. Worth, *Am. J. Trop. Med. Hyg.*, 12, 481 (1963).
(26) T. J. Haley, A. M. Flesher, and L. Mavis, *Arch. Intern. Pharmacodynamie*, 138, 133 (1962).
(27) For a description of test methods, see H. G. Sheffield, J. E. Meisenhelder, and P. E. Thompson, *J. Parasitol.*, 45, 653 (1959).
(28) For a description of test methods, see W. A. Rightsel, J. R. Dice, and R. Pittillo, *University of Michigan Medical Bulletin*, 24, 222 (1958).
(29) F. Schönhöfer. *Z. physiol. Chem.*, 274, 1 (1942).
(30) Melting points (corrected) were taken on a Thomas Hoover capillary melting point apparatus.
(31) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, 1946, p. 431.

Received October 18, 1963 Ann Arbor, Michigan