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Antifilarial Agents. I. Effects of 4-[(7-Chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresols and Related Compounds against *Litomosoides carinii* in Gerbils

EDWARD F. ELSLAGER, S. C. PERRICONE, AND F. H. TENDICK

Department of Chemistry, Medical and Scientific Affairs Division, Parke, Davis & Company, Ann Arbor, Michigan 48106

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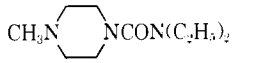
Various 4-[(7-chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresol derivatives (X) related to amodiaquine were prepared by treating 4′-hydroxyacetanilide with formaldehyde and the appropriate amine, followed by hydrolysis of the intermediate α-(mono- or dialkylamino)-4′-hydroxy-*m*-acetotoluidide and condensation of the resulting 4-amino-α-(mono- or dialkylamino)-*o*-cresol with 4,7-dichloroquinoline in aqueous EtOH or phenol. Other amodiaquine congeners were also prepared. Among them, ten compounds exhibited antifilarial activity and killed adult *Litomosoides carinii* in gerbils when administered in daily gavage doses of 25–100 mg/kg for 5 days. The most active compounds, 4-[(7-chloro-4-quinolyl)amino]-α-(4-methyl- and 4-ethyl-1-piperazinyl)-*o*-cresol trihydrochlorides (XVIa and b), were equipotent with amodiaquine.

Filariasis comprises a group of diseases produced by the invasion of the lymphatic system or connective tissues by the nematodes *Filarioidea*.[1] The most formidable pathogens of man include *Wuchereria bancrofti*, *Brugia* (*Wuchereria*) *malayi*, *Loa loa*, and *Onchocerca volvulus*. Other relatively common filaria species parasitic to man include *Acanthocheilonema perstans*, *Acanthocheilonema streptocerca*, and *Mansonella ozzardi*. It is estimated that 189–250 million people in the world harbor these dread infections.[2]

American interest in filarial infections peaked toward the end of World War II. Several hundred thousand soldiers were exposed to filariae, especially in the South Pacific, and approximately 15,000 troops were known to have circulating microfilariae.[1b] Elaborate plans were contrived to cope with the anticipated hordes developing scrotal and pedal elephantiasis, but such complications were almost never seen. The main problem was a psychological one of reassuring the frightened soldiers that their sexual life was not impaired.[1b]

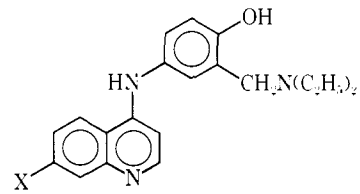
Because of the dynamics of the transmission of filariasis and the long life span of the adult worm, control of the infection hinges greatly on chemotherapy.[3] Diethylcarbamazine (I)[4] is the drug of choice for the treatment of filariasis and is effective orally against



I

W. bancrofti, *B. malayi*, and *L. loa*. The drug removes almost all of the microfilariae from the blood and has an incapacitating, if not lethal, effect on the adult worms. In patients with *Onchocerca*, treatment is effective in temporarily removing microfilariae from the skin, but adult worms are not killed and the microfilariae usually return after some weeks. Although opinions conflict on the value of diethylcarbamazine for mass treatment, it is doubtful whether this drug alone will ultimately achieve cessation of transmission, and better antifilarial drugs are needed.[3] Therefore, new types of antifilarial agents are being sought in these laboratories utilizing *Litomosoides carinii* in gerbils as the primary test system.

In a recent communication Thompson, *et al.*, reported[5a] that amodiaquine[6,7] (IIa) exhibits strong



IIa, X = Cl
b, X = Br
c, X = I

therapeutic effects against adult forms of *L. carinii* in Mongolian gerbils, but is not directly active against circulating microfilariae. Gavage doses of 100, 50, or 25 mg/kg daily for 5 days had significant activity, and female worms were more susceptible to the drug than

(1) (a) For recent reviews, see F. Hawking in "Experimental Chemotherapy," Vol. I, R. J. Schnitzer and F. Hawking, Ed., Academic Press, New York, N. Y., 1963, p 893 ff; (b) K. M. Cahill, *N. Y. State J. Med.*, **63**, 1379, 1551 (1953).

(2) N. R. Stoll, *J. Parasitol.*, **33**, 1 (1947).

(3) *World Health Organ., Tech. Rept. Ser.*, **No. 359**, 1 (1967).

(4) R. I. Hewitt, S. Kushner, H. W. Stewart, E. White, W. S. Wallace, and Y. Subbarow, *J. Lab. Clin. Med.*, **32**, 1314 (1947).

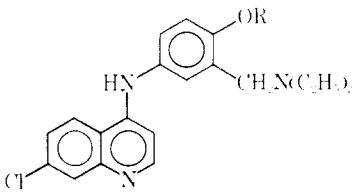
(5) (a) P. E. Thompson, L. Boche, and L. S. Blair, *J. Parasitol.*, **54**, 834 (1968); (b) E. F. Elslager, D. B. Capps, P. E. Thompson, and L. Boche, unpublished results.

(6) Camoquin®.

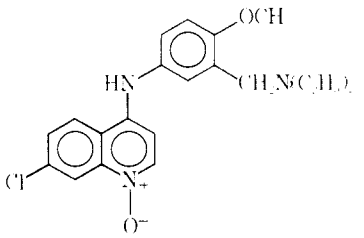
(7) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **70**, 1363 (1948).

males.[5a] In contrast, amodiaquine had only feeble activity againt the same strain of *L. carinii* in cotton rats when administered in daily gavage doses of 100 mg/kg for 5 days.

In subsequent studies in these laboratories, many known congeners[7-12] of amodiaquine and chloroquine were evaluated against *L. carinii* in gerbils.[5b] Among them, 4-[(7-bromo-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol (IIb),[12] α-(diethylamino)-4-[(7-iodo-4-quinolyl)amino]-*o*-cresol (IIc),[12] O-methylamodiaquine (IIIa),[8] O-ethylamodiaquine (IIIb),[7] O-methylamodiaquine 1-oxide (IV),[10] and 4-[(7-chloro-4-quinolyl)-



IIIa, R = CH_3
b, R = C_2H_5



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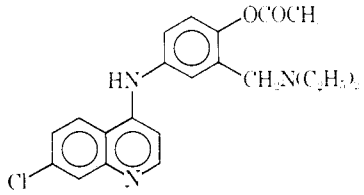
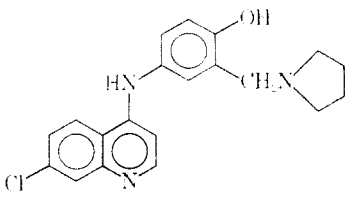
amino]-α-(diethylamino)-*o*-cresol acetate ester (V)[11] also killed many adult *L. carinii* in gerbils at daily gavage doses of 50–100 mg/kg for 5 days, but none was

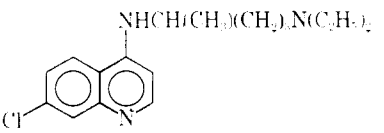


V

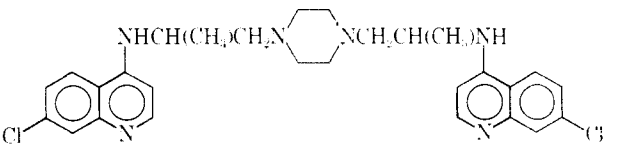
more promising than amodiaquine.[5b] Surprisingly, many other basically substituted 4-aminoquinoline derivatives, including amopyroquin (VI),[9,13] chloroquine (VII),[12] 4,4′-[1,4-piperazinediylbis(1-methylethyleneimino)]bis(7-chloroquinoline) (VIII),[14,15] and 4,4′-(1,4-piperazinediyldiimino)bis(7-chloroquinoline) (IX),[16] lacked appreciable antifilarial activity in the gerbil when administered orally in doses ranging from 50 to 200 mg/kg daily for 5 days.[5b]



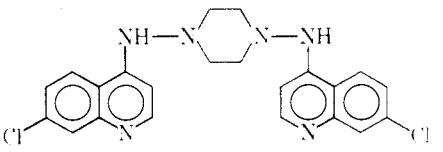
VI



VII



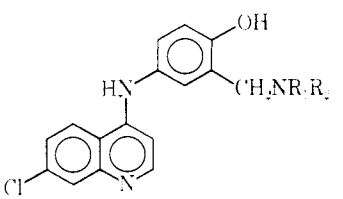
VIII



IX

The present communication describes the synthesis of a variety of novel 4-[(7-chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresol derivatives as potential antifilarial and antimalarial agents. Several of these compounds exhibited strong antifilarial properties in gerbils, but none was more potent than amodiaquine.

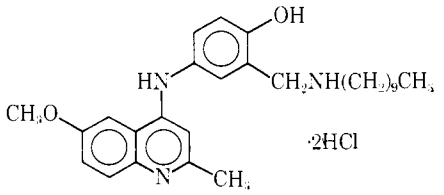
The 4-[(7-chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresols (X) (**1–25**, Table I) were prepared by the condensation of 4,7-dichloroquinoline with a purified 4-amino-α-(mono- or dialkylamino)-*o*-cresol dihydrochloride precursor in phenol (procedure I),[7,10]



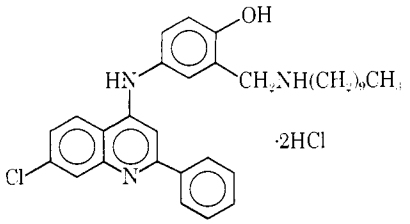
X

or by a sequence involving the reaction of 4′-hydroxyacetanilide with the requisite amine and formaldehyde followed by hydrolysis of the intermediate α-(mono- or dialkylamino)-4′-hydroxy-*m*-acetotoluidide and condensation of the resulting crude diamine with 4,7-dichloroquinoline in aqueous EtOH (procedures II and III) in which the intermediates were not purified.[7,9-11] The yields ranged from 23 to 69%. α-(Decylamino)-4-[(6-methoxy-2-methyl-4-quinolyl)amino]-*o*-cresol dihydrochloride (XI) (31%) and 4-[(7-chloro-2-phenyl-4-quinolyl)amino]-α-(decylamino)-*o*-cresol dihydrochloride (XII) (40%) were prepared similarly from 4′-hydroxyacetanilide, decylamine, formaldehyde, and 4-chloro-6-methoxyquinaldine and 4,7-dichloro-2-phenylquinoline,[17] respectively (procedure III). Alternatively, 4-[(7-chloro-4-quinolyl)methylamino]-α-(decylamino)-

(8) J. H. Burckhalter, *J. Am. Pharm. Assoc. Sci. Ed.*, **38**, 658 (1949).
(9) W. L. Nobles, R. F. Tietz, Y. S. Koh, and J. H. Burckhalter, *J. Pharm. Sci.*, **52**, 600 (1963).
(10) E. F. Elslager, E. H. Gold, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Heterocyclic Chem.*, **1**, 6 (1964).
(11) E. F. Elslager, F. H. Tendick, and L. M. Werbel, *J. Med. Chem.*, **12**, 600 (1969).
(12) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. II, Part 2, J. W. Edwards, Ann Arbor, Mich., 1946.
(13) Propoquin®.
(14) J. Schneider, M. Bouvry, and J. LeQuellec, *Ann. Soc. Belge Med. Trop.*, **45**, 435 (1965).
(15) F. Benazet, *ibid.*, **45**, 459 (1965).
(16) E. F. Elslager, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **12**, 970 (1969).
(17) H. Gilman and R. A. Benkeser, *J. Am. Chem. Soc.*, **69**, 123 (1947).

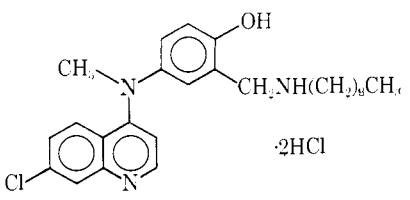


XI

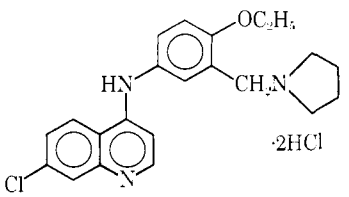


XII

o-cresol dihydrochloride (XIII) was obtained in 32% yield by boiling *p*-[(7-chloro-4-quinolyl)methylamino]-phenol[10] with decylamine and paraformaldehyde in EtOH. Treatment of 4,7-dichloroquinoline with 1-(5-amino-2-ethoxybenzyl)pyrrolidine dihydrochloride[18] in boiling EtOH afforded 7-chloro-4-(4-ethoxy-α-1-pyrrolidinyl-*m*-toluidino)quinoline dihydrochloride (O-ethylamopyroquin) (XIV) (63%).

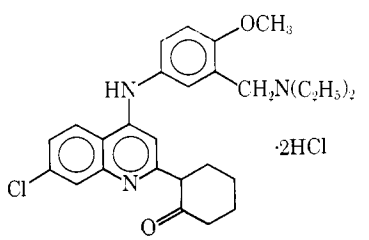


XIII



XIV

In 1967 Hamana and Noda[19] reported the preparation of 2-(4-chloro-2-quinolyl)cyclohexanone in 78% yield from 4-chloroquinoline 1-oxide and N-(1-cyclohexen-1-yl)morpholine in the presence of benzoyl chloride. Extension of this reaction to 4,7-dichloroquinoline 1-oxide[10] afforded 2-(4,7-dichloro-2-quinolyl)cyclohexanone in 70% yield. Condensation of the latter compound with N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride[7,18] in refluxing EtOH gave 2-(7-chloro-4-{3-[(diethylamino)methyl]-*p*-anisidino}-2-quinolyl)cyclohexanone (XV) (58%).



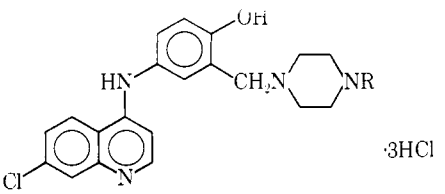
XV

(18) E. F. Elslager and N. F. Haley, *J. Heterocyclic Chem.*, **6**, 105 (1969).

(19) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 474 (1967).

Representative 4-[(7-chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresols and related compounds described in the present communication were supplied to Dr. P. E. Thompson and coworkers of these laboratories for evaluation as potential antifilarial agents against *Litomosoides carinii* in gerbils. As in previous work,[5] drugs were administered by gavage as solutions or suspensions in aqueous 1% (hydroxyethyl)cellulose and 0.1% Tween 80 (volumes of 5 ml/kg). Doses are expressed in terms of the free base equivalent. Examinations for microfilariae were made in Giemsa-stained thick films of blood drawn from the retroocular sinus. These parasite counts were started early in patency and were continued at 1–4-day intervals until the animals were examined for adult worms.[5] Surviving animals were sacrificed and examined for adult worms on day 15 after the first drug dose by searching the pleural and peritoneal cavities. The numbers of live and dead worms at autopsy were scored relative to untreated infections in control gerbils.[5]

Among the 4-[(7-chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresols (X) (**1–25**, Table I) and congeners XI–XV, ten compounds (**3–5**, 7, **9**, **16**, **17**, **19**, XIV, and XV) killed adult *L. carinii* in gerbils when administered in daily oral 25–100-mg/kg doses for 5 days. The most active compounds, 4-[(7-chloro-4-quinolyl)amino]-α-(4-methyl-1-piperazinyl)-*o*-cresol trihydrochloride (**3**, XVIa)[9] and 4-[(7-chloro-4-quinolyl)-amino]-α-(4-ethyl-1-piperazinyl)-*o*-cresol trihydrochloride (**5**, XVIb), were equipotent with amodiaquine.



XVIa, R = CH_3
b, R = C_2H_5

None of the compounds showed direct action against the circulating microfilariae.

Experimental Section[20,21]

4-[(7-Chloro-4-quinolyl)amino]-α-(mono- and dialkylamino)-*o*-cresols (1–25, Table I). Procedure I.—4,7-Dichloroquinoline (9.9 g, 0.05 mole), 4-amino-α-(decylmethylamino)-*o*-cresol dihydrochloride (18.3 g, 0.05 mole), and 50 g of phenol was stirred and heated on a steam bath for 4 hr. The product was cooled and poured into a stirred mixture containing 1 l. of $CHCl_3$, 500 ml of 10% aqueous NaOH, and 100 g of ice. The layers were separated and the aqueous layer was discarded. The $CHCl_3$ layer was then washed with three 300-ml portions of dilute aqueous NaOH and three 1-l. portions of H_2O. The $CHCl_3$ solution was dried (K_2CO_3) and the $CHCl_3$ was removed *in vacuo*. The viscous residue was dissolved in 500 ml of MeOH, treated with decolorizing charcoal, and concentrated to 200 ml. Me_2CO (600 ml) and excess ethanolic HCl were added and the product was collected by filtration. Crystallization from MeOH–Me_2CO gave 15.5 g (59%) of 4-[(7-chloro-4-quinolyl)amino]-α-(decylmethylamino)-*o*-cresol dihydrochloride (**21**) as yellow crystals, mp 204–206°.

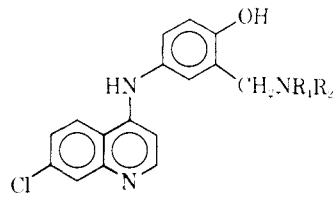
Procedure II.—4′-Hydroxyacetanilide (15.1 g, 0.1 mole) and

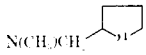
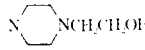
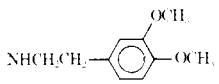
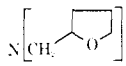
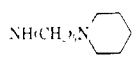
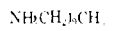
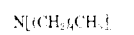
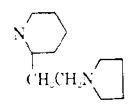
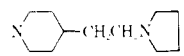
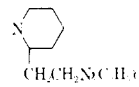
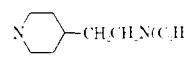
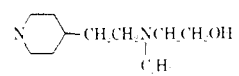
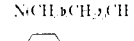
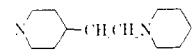
(20) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

(21) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Water determinations were by the Karl Fischer method.

TABLE I

4-[(7-CHLORO-4-QUINOLYL)AMINO]-α-(MONO- AND DIALKYLAMINO)-o-CRESOLS



No.	NR_1R_2	Mp, °C	Yield purified, %	Procedure	Purified solvent	Formula	Analyses[a]
1	$N(C_2H_5)(CH_2)_2OH$	230 dec	37	III	*i*-PrOH–Me_2CO	$C_{20}H_{22}ClN_3O_2 \cdot 2HCl \cdot 0.25H_2O$	C, H, N, H_2O
2		255 dec	36	III	MeOH–Me_2CO	$C_{20}H_{22}ClN_3O_2 \cdot 2HCl \cdot 0.75H_2O$	C, H, N; H_2O[c]
3		259–260 dec[d]	28	I	EtOH–Me_2CO	$C_{21}H_{25}ClN_4O \cdot 3HCl \cdot 0.75H_2O$	C, N, H_2O; H[b]
4		171–173	49	II	EtOAc	$C_{22}H_{24}ClN_3O_2$	C, H, N
5		240 dec	68	III	EtOH–Me_2CO	$C_{23}H_{25}ClN_4O \cdot 3HCl \cdot 2.5H_2O$	C, H, N, H_2O
6		222–225 dec	38	III	EtOH–Me_2CO	$C_{22}H_{25}ClN_4O_2 \cdot 3HCl \cdot 2.25H_2O$	C, H, N, H_2O
7	$N(CH_2CH_2OCH_3)_2$	220–225 dec	54	I	EtOH–Me_2CO	$C_{22}H_{26}ClN_3O_3 \cdot 2HCl \cdot 1.5H_2O$	C, H, N; H_2O[c]
8	$NHCH_2CH_2C_6H_5$	247–249	55	III	MeOH–Me_2CO	$C_{18}H_{22}ClN_3O \cdot 2HCl$	C, H, N
9	$N(C_2H_5)CH_2CH_2N(C_2H_5)_2$	148	43	I	MeOH–petr Et_2O	$C_{18}H_{31}ClN_4O$	C, H, N
10		208–210	31	II	EtOAc	$C_{20}H_{28}ClN_3O$	C, H, N
11		242–245 dec	63	III	EtOH–Me_2CO	$C_{26}H_{26}ClN_3O_3 \cdot 2HCl \cdot 0.5H_2O$	C, H, N
12		203–205	36	III	MeOH–Me_2CO	$C_{23}H_{26}ClN_3O_3 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, H_2O
13		125 dec	23	III	MeOH–Et_2O	$C_{26}H_{33}ClN_4O \cdot 3HCl \cdot 0.5H_2O$	C, H, N
14		275–278	33	I	MeOH	$C_{26}H_{34}ClN_3O \cdot 2HCl$	C, H, N
15		120	69	II	$CHCl_3$–petr Et_2O	$C_{26}H_{34}ClN_3O$	C, H, N
16		140–141	27	II	C_6H_6–petr Et_2O	$C_{27}H_{36}ClN_4O$	C, H, N
17		204–205	33	II	MeOH	$C_{27}H_{36}ClN_4O$	C, H, N
18		120 dec	51	I	*i*-PrOH–Me_2CO	$C_{25}H_{36}ClN_4O \cdot 3HCl \cdot 2H_2O$	C, H, N; H_2O[e]
19		174–175	41	II	EtOAc	$C_{27}H_{36}ClN_4O$	C, H, N
20		145	31	II	Me_2CO	$C_{27}H_{36}ClN_4O_2$	C, H, N
21		204–206	59	I	MeOH–Me_2CO	$C_{27}H_{36}ClN_3O \cdot 2HCl$	C, H, N
22		160–161	45	II	EtOH–H_2O	$C_{28}H_{35}ClN_4O$	C, H, N
23	$NH(CH_2)_6CH_3$	277–279	52	III	MeOH–Me_2CO	$C_{28}H_{38}ClN_3O \cdot 2HCl$	C, H, N
24	$N[CH_2CH_2N(C_2H_5)_2]_2$	150 dec	39	III	EtOH–Me_2CO	$C_{28}H_{46}ClN_5O \cdot 4HCl$	C, H, N
25	$NH(CH_2)_{10}CH_3$	280	41	III	EtOH–Me_2CO	$C_{36}H_{42}ClN_3O \cdot 2HCl$	C, H, N

[a] H_2O: calcd, 2.87; found, 2.44. [b] H: calcd, 5.48; found, 6.09. [c] H_2O: calcd, 5.24; found, 5.80. [d] H_2O: calcd, 5.88; found, 5.30. [e] Lit.[9] mp 240–300° dec.

N-methylfurfurylamine (11.5 g, 0.1 mole) were stirred in 100 ml of *i*-PrOH while 7.5 ml (0.1 mole) of 40% formaldehyde in 20 ml of *i*-PrOH was added dropwise over 30 min. The mixture was stirred for 1 hr at room temperature, then refluxed for 3 hr. Volatile materials were removed *in vacuo*, 70 ml of 1:1 HCl–H_2O was added, and the mixture was heated on a steam bath for 3.5 hr. The mixture was diluted with H_2O, neutralized with NaOH, and made just acid to congo red. 4,7-Dichloroquinoline (19.8 g, 0.1 mole) and 25 ml of EtOH were added and the mixture was stirred and heated on a steam bath for 3 hr. The product was filtered and the filtrate was made alkaline with NH_4OH and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with dilute NaOH and H_2O and dried (K_2CO_3). The drying agent was collected by filtration and

volatile materials were removed *in vacuo*. The residue was dissolved in EtOAc, treated with decolorizing charcoal, and concentrated until crystallization began. 4-[(7-Chloro-4-quinolyl)amino]-α-[(furfuryl)methylamino]-*o*-cresol (**4**) was obtained as yellow crystals, mp 171–173°, yield 19.5 g (49%).

Procedure III.—4′-Hydroxyacetanilide (45.3 g, 0.3 mole), 39.0 g (0.3 mole) of 1-piperazineethanol, and 9.0 g (0.3 mole) of CH_2O were allowed to react according to procedure II, and the intermediate 4-amino-α-amino-*o*-cresol was heated with 59.4 g (0.3 mole) of 4,7-dichloroquinoline. The crude base was crystallized from EtOH (decolorizing charcoal) to give 49.5 g of 4-{5-[(7-chloro-4-quinolyl)amino]salicyl}-1-piperiazineethanol, mp 207–209°. This material was suspended in warm EtOH and treated with excess concentrated HCl. A yellow precipitate separated and the mixture was diluted with Me_2CO. The trihydrochloride **6** was collected by filtration and dried *in vacuo* at 60° for 18 hr; yield 65 g (38%), mp 222–225°.

α-(Decylamino)-4-[(6-methoxy-2-methyl-4-quinolyl)amino]-*o*-cresol Dihydrochloride (XI).—4-Chloro-6-methoxyquinaldine (31.0 g, 0.15 mole), 4′-hydroxyacetanilide (22.6 g, 0.15 mole), decylamine (25.9 g, 0.16 mole), and paraformaldehyde (4.5 g, 0.15 mole) were allowed to react according to procedure III. The product was obtained as an off-white solid, mp 125–130°, yield 25.7 g (31%). *Anal.* ($C_{28}H_{39}N_3O_2 \cdot 2HCl \cdot 1.5H_2O$) C, H, N.

4-[(7-Chloro-2-phenyl-4-quinolyl)amino]-α-(decylamino)-*o*-cresol Dihydrochloride (XII).—The reaction of 25.0 g (0.091 mole) of 4,7-dichloro-2-phenylquinoline,[17] 13.7 g (0.091 mole) of 4′-hydroxyacetanilide, 15.7 g (0.1 mole) of decylamine, and 2.7 g (0.091 mole) of paraformaldehyde according to procedure III afforded 21.7 g (40%) of the title compound as yellow crystals, mp 277–278° dec. *Anal.* ($C_{32}H_{38}ClN_3O \cdot 2HCl$) C, H, N.

4-[(7-Chloro-4-quinolyl)methylamino]-α-(decylamino)-*o*-cresol Dihydrochloride (XIII).—Decylamine (15.7 g, 0.1 mole) and paraformaldehyde (3.0 g, 0.1 mole) were boiled under reflux in 50 ml of EtOH for 30 min. This reagent was then added to 14.2 g (0.05 mole) of *p*-[(7-chloro-4-quinolyl)methylamino]phenol[10] in 350 ml of EtOH and the mixture was stirred and boiled under reflux for 6 hr. The mixture was concentrated to dryness *in vacuo*, 100 ml of DMF was added, and the mixture was stirred and heated at 135–140° for 3 hr. The product was poured into 500 ml of H_2O and the viscous oil that separated was extracted with Et_2O. The combined Et_2O extracts were washed successively with dilute NaOH and H_2O and dried over anhydrous K_2CO_3. The Et_2O was removed and the oily residue was treated with excess ethanolic HCl and diluted with Me_2CO. The crude product (16.3 g) was crystallized from EtOH–Me_2CO to give 8.5 g (32%) of the product as orange-yellow crystals, mp 150–160°.

7-Chloro-4-(4-Ethoxy-α-1-pyrrolidinyl-*m*-toluidino)quinoline Dihydrochloride (XIV).—A mixture of 10.0 g (0.05 mole) of 4,7-dichloroquinoline and 15.0 g (0.05 mole) of 1-(5-amino-2-ethoxybenzyl)pyrrolidine dihydrochloride[18] was refluxed in EtOH for 1 hr. The mixture was cooled and the product was collected by filtration, washed with EtOH, and dried. Crystallization from *i*-PrOH containing a few drops of *i*-PrOH–HCl afforded 17.3 g (63%) of brilliant yellow crystals, mp 285°. *Anal.* ($C_{22}H_{24}ClN_3O \cdot 2HCl \cdot H_2O$) C, H, N, H_2O

2-(7-Chloro-4-{3-[(diethylamino)methyl]-*p*-anisidino}-2-quinolyl)cyclohexanone Dihydrochloride (XV).—A mixture of 2.3 g (0.0078 mole) of 2-(4,7-dichloro-2-quinolyl)cyclohexanone and 2.3 g (0.0078 mole) of N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride[7,18] in EtOH was refluxed for 2 hr and cooled. Volatile materials were removed *in vacuo*, and the residue was triturated with boiling Me_2CO, cooled, and filtered. The yellow product weighed 2.5 g (58%), mp 187–190° dec. *Anal.* ($C_{27}H_{32}ClN_3O_2 \cdot 2HCl \cdot 0.75H_2O$) C, H, N, H_2O.

2-(4,7-Dichloro-2-quinolyl)cyclohexanone.—A mixture of 50.0 g (0.23 mole) of 4,7-dichloroquinoline 1-oxide[10] and 80.0 g (0.48 mole) of N-(1-cyclohexen-1-yl)morpholine (Aldrich) in 300 ml of $CHCl_3$ was cooled to 5–10° and 35 g (0.25 mole) of benzoyl chloride was added dropwise with stirring. The solution turned from yellow to deep red. The mixture was allowed to stand for 2 days at room temperature and the $CHCl_3$ was removed *in vacuo*. The residue was boiled with 2 l. of MeOH to give 34.5 g of crystals, mp 133–135°. Concentration of the MeOH filtrate afforded 13.0 g of a second crop, mp 132–135°, total yield 47.5 g (70%). *Anal.* ($C_{15}H_{13}Cl_2NO$) C, H, N, Cl.

4-Amino-α-(decylmethylamino)-*o*-cresol Dihydrochloride.—A suspension of 71.0 g (0.41 mole) of N-methyldecylamine and 12.3 g (0.41 mole) of paraformaldehyde in 100 ml of EtOH was heated on a steam bath for 0.5 hr. The resulting clear, colorless solution was then added slowly over a period of 35 min to a refluxing solution of 62.0 g (0.41 mole) of 4′-hydroxyacetanilide in 1 l. of EtOH. The resulting solution was stirred and heated under reflux for 3 hr and cooled, and volatile materials were removed *in vacuo*. The intermediate α-(decylmethylamino)-4′-hydroxy-*m*-acetotoluidide was thus obtained (137 g) as a viscous, yellow oil which was not purified further but was refluxed for 1 hr with 250 ml of 1:1 H_2O–concentrated HCl. Volatile materials were removed *in vacuo* and the product was crystallized twice from *i*-PrOH–Et_2O (decolorizing charcoal). The product weighed 97 g (65% over-all), mp 105–110°. *Anal.* ($C_{18}H_{32}N_2O \cdot 2HCl$) C, H, N.

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