Repository Drugs. VIII. Ester and Amide Congeners of Amodiaquine, Hydroxychloroquine, Oxychloroquine, Primaquine, Quinacrine, and Related Substances as Potential Long-Acting Antimalarial Agents[1]

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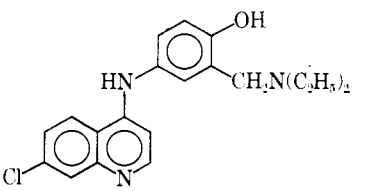
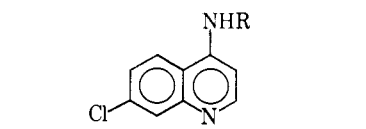
An array of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol esters (Va–d, VI), ({5-[(7-chloro-4-quinolyl)amino]salicyl}alkylamino)alkanol esters (VIIa and b, VIIIa and b), 2-({4-[(7-chloro-4-quinolyl)amino]-pentyl}ethylamino)ethanol esters (Xa–c), 1-[(7-chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol esters (XIa–c), ({[(6-chloro-9-acridinyl)amino]alkyl}amino)alkanol esters (XVIIa–e, XVIII), and amide derivatives (IXa and b, XII–XV, XIX, and XX) of representative basically substituted aminoquinoline and aminoacridine antimalarials was prepared as potential repository drugs. Eight compounds exhibited noteworthy activity and protected mice against challenge with *Plasmodium berghei* for 2–4 weeks following a single 400-mg/kg sc dose. Structure–activity relationships are discussed.

Previous investigations in these laboratories concerning repository drugs led successively to the development of cycloguanil pamoate,[2-4] acedapsone,[5-10] and a cycloguanil pamoate–acedapsone combination.[5-7,10-13] Additional studies on repository sulfones afforded various 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisanilides,[14] 4′-[N-(benzylidene- and -salicylidene)sulfanilyl]anilides,[15] and polymers of 4,4′-sulfonyldianiline (DDS)[1] that also exhibited noteworthy repository properties.

We have now probed the feasibility of utilizing esters or amides of selected 4-aminoquinolines, 8-aminoquinolines, and 9-aminoacridines as parenteral repository antimalarial agents. The present communication describes the synthesis and repository antimalarial effects of an array of ester and amide congeners of amodiaquine (I), hydroxychloroquine (IIa), oxychloroquine (IIb), primaquine (III), quinacrine (IV), and related substances.[16] Several of these new derivatives exhibited noteworthy repository activity against *Plasmodium berghei* in the mouse.

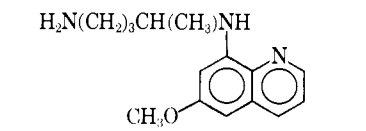


I

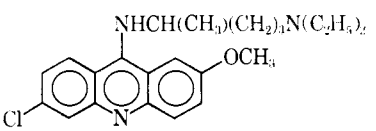


IIa, R = $CH(CH_3)(CH_2)_3N(C_2H_5)CH_2CH_2OH$

b, R = $CH_2CHOHCH_2N(C_2H_5)_2$

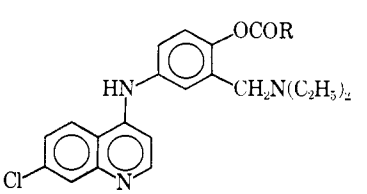


III



IV

Acylation of amodiaquine base (I)[17a] with the appropriate acid halide in $CHCl_3$ or pyridine afforded the corresponding 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol esters (Va–d) in 44–61% yield



Va, R = CH_3
b, R = C_6H_5
c, R = $(CH_2)_5CH_3$
d, R = $(CH_2)_{14}CH_3$

(1) Previous paper: E. F. Elslager, D. B. Capps, and D. F. Worth, *J. Med. Chem.*, **12**, 597 (1969).

(2) E. F. Elslager and P. E. Thompson, Abstracts, 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 1964, p 6A.

(3) P. E. Thompson, B. J. Olszewski, E. F. Elslager, and D. F. Worth, *Am. J. Trop. Med. Hyg.*, **12**, 481 (1963).

(4) Camolar®.

(5) E. F. Elslager, Z. B. Gavrilis, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 357 (1969).

(6) E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965). Acedapsone is Hansolar®; Dapolar® is the acedapsone–cycloguanil pamoate combination.

(7) P. E. Thompson, B. Olszewski, and J. A. Waitz, *Am. J. Trop. Med. Hyg.*, **14**, 343 (1965).

(8) C. C. Shepard, *Proc. Soc. Exp. Biol. Med.*, **124**, 430 (1967).

(9) C. C. Shepard, J. G. Tolentino, and D. H. McRae, *Am. J. Trop. Med. Hyg.*, **17**, 192 (1968).

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(11) (a) R. H. Black, W. B. Hennessy, B. McMillan, B. B. Dew, and J. C. Biggs, *Med. J. Australia*, **2**, 801 (1966); (b) A. B. G. Laing, G. Pringle, and F. C. T. Lane, *Am. J. Trop. Med. Hyg.*, **15**, 838 (1966); (c) K. H. Rieckmann, *Trans. Roy. Soc. Trop. Med. Hyg.*, **61**, 189 (1967); (d) W. Chin, G. R. Coatney, and H. K. King, *Am. J. Trop. Med. Hyg.*, **16**, 13 (1967); (e) W. Chin, P. G. Contacos, G. R. Coatney, M. H. Jeter, and E. Alpert, *ibid.*, **16**, 580 (1967).

(12) D. F. Clyde, Abstracts, 8th International Congresses on Tropical Medicine and Malaria, Teheran, Iran, Sept 7–15, 1968, p 1380.

(13) For recent reviews, see (a) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p 136; (b) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, New York, N. Y., 1967, p 131.

(14) E. F. Elslager, A. A. Phillips, and D. F. Worth, *J. Med. Chem.*, **12**, 363 (1969).

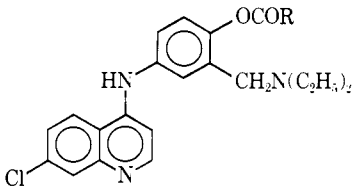
(15) D. F. Worth, E. F. Elslager, and A. A. Phillips, *ibid.*, **12**, 591 (1969).

(16) For a historical review, see P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 814.

(17) (a) 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); (b) E. F. Elslager, S. C. Perricone, and F. H. Tendick, *J. Med. Chem.*, in press.

TABLE I

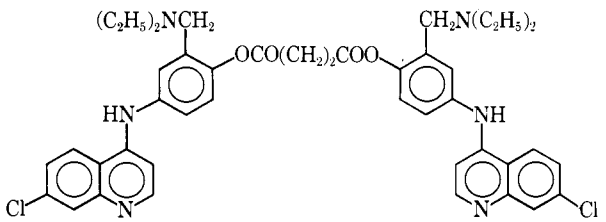
4-[(7-CHLORO-4-QUINOLYL)AMINO]-α-(DIETHYLAMINO)-*o*-CRESOL (AMODIAQUINE) ESTERS



No.	R	Mp, °C	Yield purifd, %	Purifien solvent	Formula	Analyses[26]	Repository act., PMW[a]
1	CH_3	206.5–211.5 dec	48	*i*-PrOH	$C_{22}H_{24}ClN_3O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O	N
2	CH_3	289–291	74	*b*	$C_{22}H_{24}ClN_3O_2 \cdot C_{10}H_8O_6S_2 \cdot xH_2O$[c]	C, H, N, H_2O[d]	2.5
3	CH_3	245 dec	72	DMF	$C_{22}H_{24}ClN_3O_2 \cdot C_{12}H_{10}O_6S_2 \cdot 2H_2O$[e]	C, H, N; H_2O[f]	3
4	C_6H_5	144–145.5	49	*i*-Pr_2O	$C_{27}H_{26}ClN_3O_2$	C, H, N	<1
5	$(CH_2)_5CH_3$	168–175	44	*i*-PrOH	$C_{27}H_{34}ClN_3O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O	N
6	$(CH_2)_5CH_3$	221–222	52	MeOH-DMF	$C_{27}H_{34}ClN_3O_2 \cdot C_{12}H_{10}O_6S_2 \cdot 1.5H_2O$[e]	C, H, N, H_2O	<1
7	$(CH_2)_5CH_3$	158–170 dec	66	*b*	$C_{27}H_{34}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot xH_2O$[g]	C, H, N, H_2O[h]	2
8	$(CH_2)_{14}CH_3$	179–184	61	*i*-PrOH	$C_{36}H_{52}ClN_3O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O	3[i]
9	$(CH_2)_{14}CH_3$	198–200	68	C_6H_6–DMF–petr ether	$C_{36}H_{52}ClN_3O_2 \cdot C_{10}H_8O_6S_2 \cdot 0.67H_2O$[e]	C, H, N, H_2O	2.5[j]
10	$(CH_2)_{14}CH_3$	197–201	50	MeOH	$C_{36}H_{52}ClN_3O_2 \cdot C_{12}H_{10}O_6S_2 \cdot 1.5H_2O$[e]	C, H, N; H_2O[i]	4[j]
11	$(CH_2)_{14}CH_3$	138–148 dec	38	*b*	$C_{36}H_{52}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot H_2O$[g]	C, H, N, H_2O	3.5[j]

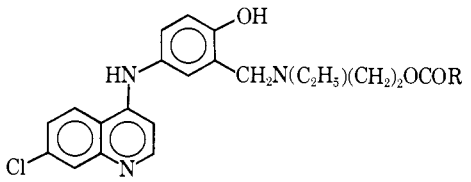
[a] Unless otherwise indicated, drugs were suspended in 5 ml/kg of benzyl benzoate–castor oil (40:60) and administered subcutaneously to groups of 15–25 female albino mice in a single 400-mg/kg dose.[1-3] Subgroups of five mice were challenged by the intraperitoneal injection of 15 million *Plasmodium berghei* at various intervals, usually at 1, 3, 5, 7, and 9 weeks, for susceptibility to malaria.[1-3] Activity is based on the number of weeks 50% of the mice were protected (PMW). N signifies not tested. [b] Not recrystallized. [c] $C_{10}H_8O_6S_2$ represents 1,5-naphthalenedisulfonic acid. [d] Found values are corrected for 0.70% H_2O. [e] $C_{12}H_{10}O_6S_2$ represents 4,4′-biphenyldisulfonic acid. [f] H_2O: calcd, 4.81; found, 4.27. [g] $C_{23}H_{16}O_6$ represents 4,4′-methylenebis(3-hydroxy-2-naphthoic acid). [h] Found values are corrected for 3.16% H_2O. [i] H_2O: calcd, 2.89; found, 2.35. [j] Drug was given as a suspension in 1.5% pectin–0.1% Tween 60 in H_2O.

(procedures I, II). The esters were isolated as salts with hydrochloric, 1,5-naphthalenedisulfonic, 4,4′-biphenyldisulfonic, and 4,4′-methylenebis(3-hydroxy-2-naphthoic acids) (**1–11**, Table I). The succinic acid diester VI with amodiaquine was obtained from succinoyl chloride and amodiaquine base in $CHCl_3$.



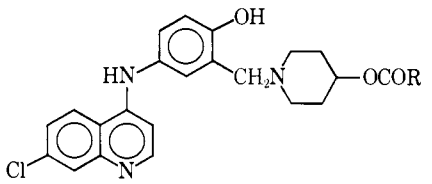
VI

Representative side-chain esters of amodiaquine were prepared similarly (**12–15**, Table II). The condensation of 2-({5-[(7-chloro-4-quinolyl)amino]salicyl}ethylamino)ethanol[17b] with Ac_2O or *n*-heptanoyl chloride in pyridine afforded 2-({5-[(7-chloro-4-quinolyl)amino]-salicyl}ethylamino)ethanol 1-acetate ester (VIIa) (63%) (procedure III) and 2-({5-[(7-chloro-4-quinolyl)-



VIIa, R = CH_3
b, R = $(CH_2)_5CH_3$

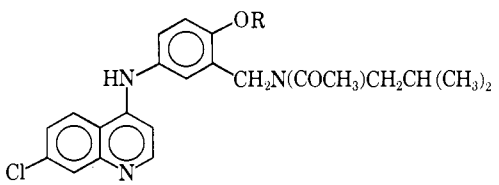
amino]salicyl}ethylamino)ethanol 1-heptanoate ester (VIIb) (21%) (procedure IV). 1-{5-[(7-Chloro-4-quinolyl)amino]salicyl}-4-piperidinol 4-acetate ester (VIIIa) (23%) and 1-{5-[(7-chloro-4-quinolyl)amino]-salicyl}-4-piperidinol 4-benzoate ester (VIIIb) (33%)



VIIIa, R = CH_3
b, R = C_6H_5

were obtained from 1-{5-[(7-chloro-4-quinolyl)amino]-salicyl}-4-piperidinol, AcCl, and benzoic anhydride (procedures V, VI). The ir spectra of the side-chain esters clearly demonstrate that acylation was effected on the aliphatic alcohol rather than on the phenol. The spectra of VIIa and b and VIIIa exhibited carbonyl absorption (KBr) at 1743, 1738, and 1740 cm^{-1}, respectively. By contrast, the *o*-cresol esters Va, c, and d have carbonyl absorption at 1772, 1766, and 1765 cm^{-1}.

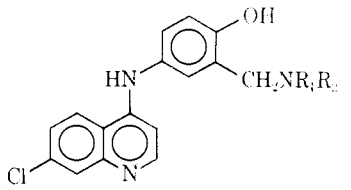
Two amide relatives of amodiaquine were also synthesized. Reaction of 4-[(7-chloro-4-quinolyl)amino]-α-(isobutylamino)-*o*-cresol[17a] with AcCl in $CHCl_3$ gave N-{5-[(7-chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide (IXa) (22%), which upon treatment with

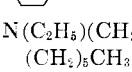
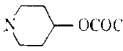


IXa, R = H
b, R = $COCH_3$

Table II

({5-[(7-Chloro-4-quinolyl)amino]salicyl}alkylamino)alkanol Esters

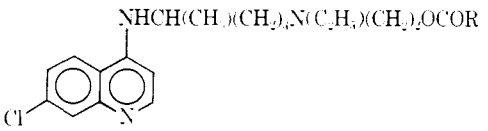


No.	NR_1R_2	Mp, °C	Yield purifd, %	Purifcn solvent	Formula	Analyses[25]	Repository act., PMW[a]
12	$N(C_2H_5)(CH_2)_2OCOCH_3$	156	63	EtOH	$C_{23}H_{24}ClN_3O_3$	C, H, N	<3
13		158–160	23	C_6H_6–CCl_4	$C_{23}H_{24}ClN_3O_3 \cdot 0.5H_2O$	C, H, N, H_2O	<1
14	$N(C_2H_5)(CH_2)_2OCO(CH_2)_5CH_3$	135–137	21	EtOAc	$C_{27}H_{34}ClN_3O_3$	H, N; C[b]	<1
15		184–185	33	C_6H_6	$C_{28}H_{26}ClN_3O_3 \cdot H_2O$	C, H, N; H_2O[c]	<1

[a] See footnote *a*, Table I. [b] C: calcd, 66.99; found, 66.56. [c] H_2O: calcd, 3.56; found, 4.00.

Table III

2-({4-[(7-Chloro-4-quinolyl)amino]pentyl}ethylamino)ethanol (Hydroxychloroquine) Esters

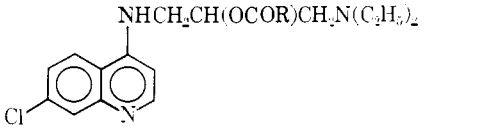


No.	R	Mp, °C	Yield purifd, %	Purifcn solvent	Formula	Analyses[25]	Repository acc., PMW[a]
16	CH_3	196–199	65	DMF–H_2O	$C_{20}H_{28}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot 0.67H_2O$[b]	C, H, N, H_2O	<1
17	$(CH_2)_5CH_3$	163–164	20	EtOH	$C_{45}H_{58}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot 1.5H_2O$[b]	C, H, N, H_2O	1
18	$(CH_2)_{14}CH_3$	55	23	Et_2O–petr ether	$C_{34}H_{56}ClN_3O_2 \cdot 2HCl \cdot 2H_2O$	C, H, N; H_2O[c]	N
19	$(CH_2)_{24}CH_3$	138–140	25	Cellosolve–H_2O	$C_{34}H_{56}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot H_2O$[b]	C, H, N, H_2O	<1

[a] See footnote *a*, Table I. [b] $C_{23}H_{16}O_6$ represents 4,4′-methylenebis(3-hydroxy-2-naphthoic acid). [c] H_2O: calcd, 5.27; found, 5.75.

Table IV

1-[(7-Chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol (Oxychloroquine) Esters

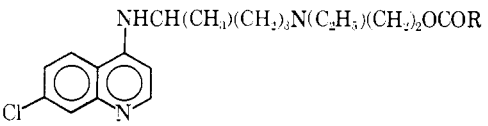


No.	R	Mp, °C	Yield purifd, %	Purifcn solvent	Formula	Analyses[25]	Repository act., PMW[a]
20	CH_3	245–246 dec	43	DMA–H_2O	$C_{18}H_{24}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot 0.5H_2O$[b]	C, H, N, H_2O	3.5
21	$(CH_2)_5CH_3$	62–63	15	MeCN	$C_{23}H_{34}ClN_3O_2$	C, H, N	<2
22		242–244 dec	53	DMF–H_2O	$C_{24}H_{24}ClN_3O_2 \cdot C_{23}H_{16}O_6$[b]	C, H, N	<1

[a] See footnote *a*, Table I. [b] $C_{23}H_{16}O_6$ represents 4,4′-methylenebis(3-hydroxy-2-naphthoic acid).

boiling Ac_2O in HOAc afforded N-{5-[(7-chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide acetate ester (IXb) (63%).

2-({4-[(7-Chloro-4-quinolyl)amino]pentyl}ethylamino)ethanol (hydroxychloroquine) esters of structure Xa–c (**16–19**, Table III) were prepared by stirring



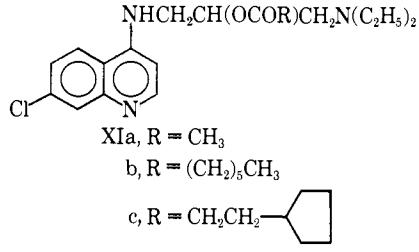
Xa, R = CH_3
b, R = $(CH_2)_5CH_3$
c, R = $(CH_2)_{14}CH_3$

hydroxychloroquine[18] (IIa) for 18 hr with excess AcCl, heptanoyl chloride, or palmitoyl chloride in refluxing $CHCl_3$ saturated with HCl. 2-({4-[(7-Chloro-4-quinolyl)amino]pentyl}ethylamino)ethanol acetate ester (Xa), heptanoate ester (Xb), and palmitate ester (Xc) were conveniently isolated and purified as insoluble salts with 1 formula wt 4,4′-methylenebis(3-hydroxy-2-naphthoic acid) (pamoic acid) (20–60% yield, procedure VII).

Various ester (**20–22**, Table IV) and amide derivatives of oxychloroquine[16] were obtained as follows. Treatment of 1-[(7-chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol with *n*-heptanoic anhydride

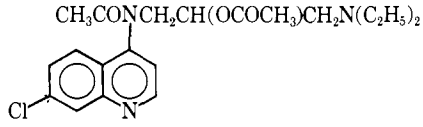
(18) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **72**, 1814 (1950).

in refluxing DMF yielded 1-[(7-chloro-4-quinolyl)-amino]-3-(diethylamino)-2-propanol heptanoate ester (XIb) (15%) (procedure VIII). 1-[(7-Chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol acetate ester (XIa) (43%) and cyclopentylpropionate ester (XIc)



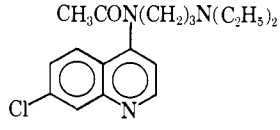
XIa, R = CH_3
b, R = $(CH_2)_5CH_3$
c, R = CH_2CH_2-cyclopentyl

(53%) were prepared by heating oxychloroquine with AcCl or cyclopentylpropionyl chloride in $CHCl_3$ utilizing procedure VII. The products were isolated and purified as the pamoic acid salts. When oxychloroquine base was heated under reflux with excess Ac_2O for 7 hr, N-(7-chloro-4-quinolyl)-N-[3-(diethylamino)-2-hydroxypropyl]acetamide acetate ester (XII) was obtained in 58% yield.

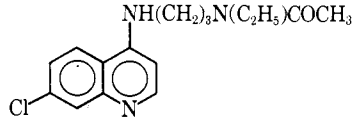


XII

In addition to the amide ester XII, several other basically substituted 4-aminoquinoline amides were also prepared. When 7-chloro-4-{[3-(diethylamino)propyl]amino}quinoline[16] was heated under reflux for 48 hr with excess AcCl in $CHCl_3$, N-(7-chloro-4-quinolyl)-N-[3-(diethylamino)propyl]acetamide (XIIIa) was isolated in 33% yield. The base was converted to the



XIIIa, base
b, pamoate



XIV

pamoate salt (XIIIb) for repository testing. Condensation of N-(3-aminopropyl)-N-ethylacetamide with 4,7-dichloroquinoline at 150–185° yielded N-{3-[(7-chloro-4-quinolyl)amino]propyl}-N-ethylacetamide (XIV) (13%). The intermediate N-(3-aminopropyl)-N-ethylacetamide was obtained by the following scheme. Acylation of 3-(ethylamino)propionitrile[19] with Ac_2O in HOAc afforded N-(2-cyanoethyl)-N-ethylacetamide (83%). Catalytic hydrogenation of this intermediate in toluene over Raney cobalt in the presence of Et_3N gave the desired N-(3-aminopropyl)-N-ethylacetamide (15%), together with a product presumed to be the rearranged terminal amide N-[3-(ethylamino)propyl]acetamide (27%).

(19) D. S. Tarbell, N. Shakespeare, C. J. Claus, and J. F. Bunnett, *J. Am. Chem. Soc.*, **68**, 1217 (1946).

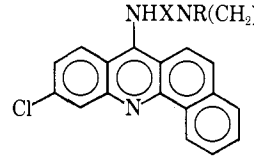
A repository 8-aminoquinoline derivative that would destroy the exoerythrocytic forms of *Plasmodium vivax* and *Plasmodium malariae* in a single dose would be useful either alone or in combination with other repository preparations. In anticipation that insoluble N-{4-[(6-methoxy-8-quinolyl)amino]alkyl}amides might undergo metabolic activation *in vivo* following parenteral administration, several representative compounds (XVa–c) (**23–25**, Table V) were prepared. The synthesis of 2,2-dichloro-N-{4-[(6-methoxy-8-quinolyl)-amino]pentyl}acetamide (XVa) (18%) and N-{4-[(6-methoxy-8-quinolyl)amino]pentyl}hexadecanamide (XVc) (66%) was accomplished by treating primaquine base with methyl dichloroacetate or palmitoyl chloride in $CHCl_3$ (procedures IX, XI). N-(6-Methoxy-8-quinolyl)-N-(3-phthalimidopropyl)acetamide (XVb) was obtained in 36% yield from N-{3-[(6-methoxy-8-quinolyl)amino]propyl}phthalimide[20] and Ac_2O in HOAc (procedure X).

XVa, NRYNR$_1$R$_2$ = $NHCH(CH_3)(CH_2)_3NHCOCHCl_2$

b, NRYNR$_1$R$_2$ = $N(COCH_3)(CH_2)_3$-phthalimido

c, NRYNR$_1$R$_2$ = $NHCH(CH_3)(CH_2)_3NHCO(CH_2)_{14}CH_3$

In an earlier communication[21] we described the preparation of various {[(benz[*c*]acridin-7-yl)amino]-alkylamino}alkanol esters (XVI) that exhibit potent



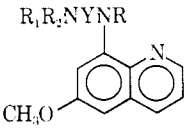
XVI

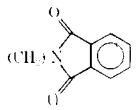
antiamebic activity against *Entamoeba histolytica in vitro* and in experimental animals. Since 7-aminobenz[*c*]acridine derivatives are known to possess only weak antimalarial activity,[22] esters of structure XVI were not evaluated for repository antimalarial effects. However, it was of interest to investigate 9-aminoacridine esters and amides related to quinacrine (IV). A variety of ({[(6-chloro-9-acridinyl)amino]alkyl}amino)-alkanol esters (**26–33**, Table VI) were prepared. Acylation of 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl}amino)ethanol dihydrochloride[23,24] or 2,2′-({3-[(3,6-dichloro-9-acridinyl)amino]propyl}imino)diethanol dihydrochloride[23] with AcCl, hexanoyl chloride, nonanoyl chloride, lauroyl chloride, or palmitoyl chloride gave the corresponding 2-({2-[(6-chloro-2-

(20) L. W. Kissinger, I. Von, and M. Carmack, *ibid.*, **68**, 1563 (1946).
(21) E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *ibid.*, **80**, 451 (1958).
(22) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *ibid.*, **79**, 4699 (1957).
(23) N. B. Ackerman, D. K. Haldorsen, F. H. Tendick, and E. F. Elslager, *J. Med. Chem.*, **11**, 315 (1968).
(24) A. R. Surrey, C. M. Suter, and J. S. Buck, *J. Am. Chem. Soc.*, **74**, 4102 (1952).

TABLE V

N-{4-[(6-METHOXY-8-QUINOLYL)AMINO]ALKYL}AMIDES

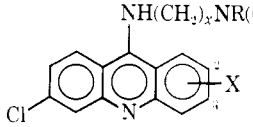


No.	R	YNR$_1$R$_2$	Mp, °C	Yield purifd, %	Purifen solvent	Formula	Analyses[a]	Reposiory acr., PMW[a]
23	H	$CH(CH_3)(CH_2)_3NHCOCHCl_2$	101–102.5	18	*n*-Heptane	$C_{17}H_{24}Cl_2N_3O_2$	C, H, N	<1
24	$COCH_3$		150–151	36	*i*-PrOH	$C_{28}H_{21}N_3O_4$	C, H, N	<1
25	H	$CH(CH_3)(CH_2)_3NHCO(CH_2)_{14}CH_3$	79–86	66	*n*-Heptane	$C_{31}H_{51}N_3O_2$	C, H, N	<1

[a] See footnote *a*, Table I.

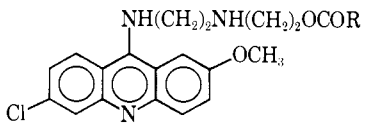
TABLE VI

({[(6-CHLORO-9-ACRIDINYL)AMINO]ALKYL}AMINO)ALKANOL ESTERS



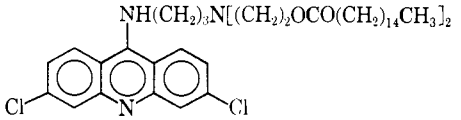
No.	*x*	R	R′	X	Mp, °C	Yield purifd, %	Purifen solvent	Procedure	Formula	Analyses[a]
26	2	H	CH_3	2-OCH_3	150–155	48	EtOH–*i*-PrOH–petr ether	XII	$C_{26}H_{32}ClN_3O_4 \cdot 2HCl \cdot 1.25H_2O$	C, H, N, Cl, Cl^-, H_2O
27	2	$COCH_3$	CH_3	2-OCH_3	180–182	83	MeOH–*i*-PrOH	XIV	$C_{22}H_{24}ClN_3O_4 \cdot HCl$	C, H, N, Cl, Cl^-
28	2	H	$(CH_2)_4CH_3$	2-OCH_3	150 dec	39	MeOH	XIII	$C_{24}H_{30}ClN_3O_3 \cdot HCl \cdot 0.75H_2O$	C, H, Cl^-, H_2O; N[a]
29	2	H	$(CH_2)_7CH_3$	2-OCH_3	170–172	77	EtOH	XIII	$C_{27}H_{36}ClN_3O_3 \cdot 2HCl \cdot 2H_2O$	C, H, Cl^-; N[b]
30	2	H	$(CH_2)_{10}CH_3$	2-OCH_3	158–160	58	EtOH	XIII	$C_{30}H_{42}ClN_3O_3 \cdot HCl \cdot 0.25H_2O$	C, H, Cl^-, H_2O; Cl,[c] N[d]
31	2	H	$(CH_2)_{14}CH_3$	2-OCH_3	185–190	73	EtOH	XIII	$C_{34}H_{50}ClN_3O_3 \cdot 2HCl \cdot H_2O$	C, H, N
32	2	$CO(CH_2)_{14}CH_3$	$(CH_2)_{14}CH_3$	2-OCH_3	155	60	MeOH	XV	$C_{50}H_{86}ClN_3O_4 \cdot HCl \cdot 0.25H_2O$	C, H, H_2O; N[e]
33	3	$(CH_2)_2OCO(CH_2)_{14}CH_3$	$(CH_2)_{14}CH_3$	3-Cl	217–218	90	EtOH–MeOH	XIII	$C_{52}H_{93}Cl_2N_3O_4 \cdot 2HCl$	C, H, N

[a] N: calcd, 8.51; found, 7.83. [b] N: calcd, 7.06; found, 7.50. [c] Cl: calcd, 12.46; found, 13.10. [d] N: calcd, 7.38; found 6.75. [e] N: calcd, 4.87; found, 5.31.



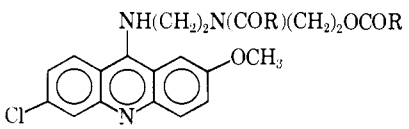
XVIIa, R = CH_3
b, R = $(CH_2)_4CH_3$
c, R = $(CH_2)_7CH_3$
d, R = $(CH_2)_{10}CH_3$
e, R = $(CH_2)_{14}CH_3$

methoxy-9-acridinyl)amino]ethyl}amino)ethanol esters (XVIIa–e) (procedures XII, XIII) and 2,2′-({3-[(3,6-dichloro-9-acridinyl)amino]propyl}imino)diethanol dipalmitate ester (XVIII) (procedure XIII).



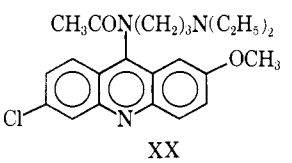
XVIII

When 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl}amino)ethanol dihydrochloride[23,24] was heated at 125–130° for 2 hr with Ac_2O (procedure XIV) or refluxed with palmitoyl chloride in toluene for 7 hr (procedure XV), the corresponding N-{2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}-N-(2-hydroxyethyl)amide esters XIXa and b were formed. The



XIXa, R = CH_3
b, R = $(CH_2)_{14}CH_3$

N^9-acetyl derivative N-(6-chloro-2-methoxy-9-acridinyl)-N-[3-(diethylamino)propyl]acetamide (XX) was obtained in 27% yield from 6-chloro-9-{[3-(diethyl-



XX

amino)propyl]amino}-2-methoxyacridine dihydrochloride upon treatment with excess AcCl in boiling $CHCl_3$.

The ester and amide congeners of amodiaquine, hydroxychloroquine, oxychloroquine, primaquine, quinacrine, and related substances were supplied to Dr. P. E. Thompson and coworkers of these laboratories for evaluation as potential repository antimalarial agents against *Plasmodium berghei* in the mouse. As in previous work,[1–3,5–7,14,15] drugs were suspended in 5 ml/kg of benzyl benzoate–castor oil (BBCO, 40:60) or 1.5% pectin–0.1% Tween 60 in H_2O and given to groups of

15–25 albino mice in a single subcutaneous 400-mg base equivalent/kg dose. Subgroups of treated mice were subsequently challenged with *P. berghei* trophozoites at weekly or biweekly intervals. Assessment of repository action was based on the period of protection against patent infections afforded by a single dose of the drug. Activity is expressed as the number of weeks 50% of the mice were protected.

Among the ester derivatives Va–d, VI, VIIa and b, VIIIa and b, Xa and b, XIa–c, XVIIa–e, and XVIII, eight compounds conferred slight to moderate protection against challenge with *P. berghei* ranging from 2 to 4 weeks. These substances comprised the 1,5-naphthalenedisulfonic and 4,4′-biphenyldisulfonic acid salts of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol acetate ester (**2**, **3**, Table I), the pamoate salt of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol heptanoate ester (**7**, Table I), the hydrochloride, pamoate, 1,5-naphthalenedisulfonate, and 4,4′-biphenyldisulfonate salts of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol palmitate ester (**8**–**11**, Table I), and the pamoate salt of 1-[(7-chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol acetate ester (**20**, Table IV). However, none of these was as promising as the repository cycloguanil, pyrimethamine, and DDS derivatives described previously.[1–3,5–7,14,15] Further, in the face of increasing reports of resistance by *P. falciparum* to the 4-aminoquinoline and 9-aminoacridine drugs,[13] the impetus to develop repository agents of this type has diminished. None of the amide derivatives (IXa and b, XII, XIIIa and b, XIV, XVa–c, XIXa and b, and XX) displayed significant repository effects.

Experimental Section[25,26]

4-[(7-Chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol (Amodiaquine) Esters (Va–d) (1–11, Table I). Procedure I.—To 5.0 g (0.014 mole) of amodiaquine base (I)[17a] suspended in $CHCl_3$ was added 2 ml (2 equiv) of AcCl. An exothermic reaction occurred and a solution resulted. The mixture was heated under reflux for 2.5 hr and concentrated to dryness. The residue was recrystallized twice from *i*-PrOH to give 3.3 g of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol acetate ester dihydrochloride monohydrate (**1**) as a yellow solid, mp 206.5–211.5° dec. The ir spectrum of the product showed a strong peak at 1772 cm^{-1} indicative of ester carbonyl.

A H_2O solution of 3.6 g (0.01 mole) of 4,4′-biphenyldisulfonic acid disodium salt was added to a H_2O solution of 4.9 g (0.01 mole) of the above ester hydrochloride. A viscous oil formed which gradually solidified to give 6.3 g of a yellow solid, mp 263–270°. The crude product was dissolved in warm DMF, but after a short time reprecipitated from the hot solution. Further addition of DMF and heating did not effect solution. The solid was collected, washed with H_2O, and dried to give 5.1 g of the 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol acetate ester salt with 1 formula wt of 4,4′-biphenyldisulfonic acid dihydrate (**3**), mp 245° dec. The salt (**2**) with 1,5-naphthalenedisulfonic acid, mp 289–291°, was prepared similarly.

Compounds **5**–**11** (Table I) were prepared utilizing the above procedures.

Procedure II.—A solution of 7.1 g (0.02 mole) of amodiaquine base (I)[17a] in pyridine was treated with 2.8 g (0.02 mole) of benzoyl chloride. A precipitate soon formed. After standing for 1 hr, the reaction mixture was poured into iced H_2O. The precipitate was collected by filtration, washed with H_2O, dried in air, and crystallized twice from *i*-Pr_2O to give 4.5 g of 4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol benzoate ester (**4**) as yellow crystals, mp 144–145.5°.

({5-[(7-Chloro-4-quinolyl)amino]salicyl}alkylamino)alkanol Esters (VIIa and b, VIIIa and b) (12–15, Table II). Procedure III.—A mixture of 13.5 g (0.03 mole) of 2-({5-[(7-chloro-4-quinolyl)amino]salicyl}ethylamino)ethanol dihydrochloride quarterhydrate,[17b] 100 ml of dry pyridine, and 50 ml of Ac_2O was heated on a steam bath for 1 hr. The mixture was diluted with H_2O, made alkaline with NH_4OH, and extracted with Et_2O. The combined extracts were washed with H_2O, dried (K_2CO_3), and evaporated to dryness. The residue was dissolved in EtOH and diluted with 3 vol of hot H_2O to give 11.0 g of crude product, mp 154°. Two crystallizations from EtOH gave 7.8 g of 2-({5-[(7-chloro-4-quinolyl)amino]salicyl}ethylamino)ethanol 1-acetate ester (VIIa) as yellow crystals, mp 156°.

Procedure IV.—2-({5-[(7-Chloro-4-quinolyl)amino]salicyl}-ethylamino)ethanol dihydrochloride quarterhydrate[17b] (13.5 g) was dissolved in H_2O and converted to the base with NH_4OH. The base (10.0 g, 0.027 mole) in 50 ml of pyridine was treated with 11.9 g (3 equiv) of *n*-heptanoyl chloride and stirred for 1 hr. The mixture was poured into dilute HCl, made alkaline with aqueous NaOH, and extracted with Et_2O. The combined extracts were washed with dilute NaOH and H_2O, dried, and concentrated. Excess *i*-PrOH saturated with HCl was added to the oily residue and the mixture was concentrated to a small volume and triturated with Et_2O. The rubberlike mass was reprecipitated from EtOH with Et_2O. The resulting tan solid was suspended in a mixture of H_2O and Et_2O and the mixture was made basic with NH_4OH. The Et_2O layer was dried and concentrated to a viscous oil which, upon standing in EtOAc, gave 2.7 g of 2-({5-[(7-chloro-4-quinolyl)amino]salicyl}ethylamino)ethanol 1-heptanoate ester (VIIb) as a pale yellow solid, mp 135–137°.

Procedure V.—1-{5-[(7-Chloro-4-quinolyl)amino]salicyl}-4-piperidinol dihydrochloride quarterhydrate (27.6 g, 0.06 mole) was heated *in vacuo* on a steam bath for 1 hr. The solid was suspended in 100 ml of DMF and 40 ml of pyridine, and 30 ml of AcCl was added dropwise. The mixture was stirred at room temperature for 1 hr, warmed on a steam bath for 1 hr, poured into 2 l. of H_2O, and made basic with NH_4OH. The semisolid mass that separated was dissolved in EtOH and diluted with Et_2O, and the mixture was washed repeatedly with H_2O. The organic layer was separated and filtered, and the filtrate was diluted with CCl_4 and concentrated to the cloud point. Cooling yielded a solid which was redissolved in a little MeOH and reprecipitated with CCl_4. The yellow crystals (8.5 g), mp 145–150°, were dissolved in C_6H_6 and the C_6H_6 solution was treated with decolorizing charcoal, concentrated to a small volume, and diluted with an equal volume of CCl_4. Recrystallization from C_6H_6–CCl_4 gave 6.0 g of 1-{5-[(7-chloro-4-quinolyl)amino]salicyl}-4-piperidinol 4-acetate ester hemihydrate (VIIIa) as pale yellow crystals, mp 158–160°.

The hydrochloride salt of VIIIa was prepared in EtOH by addition of *i*-PrOH saturated with HCl. Addition of Me_2CO precipitated the salt which was collected, dried *in vacuo*, and equilibrated in the air for 18 hr. The dihydrochloride salt hemihydrate was thus obtained as a yellow solid, mp 254–255° dec. *Anal.* ($C_{23}H_{24}ClN_3O_3 \cdot 2HCl \cdot 0.5H_2O$) C, H, N, H_2O.

Procedure VI.—A solution of 7.9 g (0.02 mole) of 1-{5-[(7-chloro-4-quinolyl)amino]salicyl}-4-piperidinol dihydrochloride quarterhydrate in 225 ml of DMF was treated with 4.5 g (0.02 mole) of benzoic anhydride and the mixture was warmed on a steam bath for 1 hr. The product was poured into iced H_2O and the mixture was made alkaline with aqueous NaOH. The solid thus obtained was crystallized from C_6H_6 to give 3.3 g of 1-{5-[(7-chloro-4-quinolyl)amino]salicyl}-4-piperidinol 4-benzoate ester monohydrate (VIIIb) as yellow crystals, mp 184–185°.

2-({4-[(7-Chloro-4-quinolyl)amino]pentyl}ethylamino)ethanol (Hydroxychloroquine) Esters (Xa–c) (16–19, Table III). Procedure VII.—Hydroxychloroquine sulfate[18] (10.0 g, 0.023 mole) was converted to the base with NH_4OH and extracted into $CHCl_3$. The dried $CHCl_3$ solution was saturated with HCl, 10 ml of AcCl was added, and the mixture was stirred and heated under reflux for 18 hr. Removal of the solvent *in vacuo* and trituration of the residue with Et_2O gave a gummy solid which could not be induced to crystallize. The hydrochloride was converted to the 4,4′-methylenebis(3-hydroxy-2-naphthoate) salt according to procedure I. Recrystallization of the crude salt twice from DMF–H_2O gave 11.7 g of 2-({4-[(7-chloro-4-

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

(26) 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.

quinolyl)amino]pentyl}ethylamino)ethanol acetate ester salt with 1 formula wt of 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) (**16**), as a pale yellow solid, mp 196–199°.

Compounds **17–19** were prepared by a similar procedure.

1-[(7-Chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol (Oxychloroquine) Esters (XIa–c) (20–22, Table IV). Procedure VIII.—A solution of 5.0 g (0.0162 mole) of oxychloroquine base[16] and 3.9 g (0.0162 mole) of *n*-heptanoic anhydride in DMF was heated under reflux for 5 hr. The mixture was cooled, poured into iced H_2O, and made alkaline with NaOH. The resulting gum was dissolved in Et_2O, and the Et_2O extracts were dried and concentrated to dryness. The white powder was crystallized from MeCN to give 1.0 g (15%) of 1-[(7-chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol heptanoate ester (XIb), mp 62–63°.

Compounds **20** and **22** were prepared from AcCl and cyclopentylpropionyl chloride *via* procedure VII and were converted to the 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) salts utilizing procedure I.

N-{4-[(6-Methoxy-8-quinolyl)amino]alkyl}amides (XVa–c) (23–25, Table V). Procedure IX.—A solution of 5.2 g (0.02 mole) of primaquine base (III) in $CHCl_3$ was treated with 2.9 g of methyl dichloroacetate and the mixture was heated under reflux for 3 hr. The solvent was removed *in vacuo* to give a brown oil. Crystallization from *i*-PrOH–H_2O gave on long standing 3.0 g of brown solid. Two recrystallizations from *n*-heptane gave 1.3 g (18%) of 2,2-dichloro-N-{4-[(6-methoxy-8-quinolyl)amino]pentyl}acetamide (XVa) as a white solid, mp 101–102.5°. The ir spectrum showed a carbonyl absorption at 1673 cm^{-1}.

Procedure X.—N-{3-[(6-Methoxy-8-quinolyl)amino]propyl}-phthalimide[20] (5.4 g, 0.015 mole) was heated on a steam bath for 0.5 hr with 400 ml of HOAc and 15 ml of Ac_2O. The cooled solution was poured into a mixture of ice and dilute aqueous NaOH and allowed to stand overnight. The viscous oil that formed gradually solidified. Crystallization from *i*-PrOH gave 2.2 g (36%) of N-(6-methoxy-8-quinolyl)-N-(3-phthalimidopropyl)acetamide (XVb) as a tan powder, mp 150–151°.

Procedure XI.—A solution of 5.2 g (0.02 mole) of primaquine base (III) in $CHCl_3$ was heated under reflux with 11.0 g (0.04 mole) of palmitoyl chloride. Volatile materials were removed *in vacuo* and the residue was treated with aqueous NaOH. The solid was crystallized from heptane to give 13.2 g (66%) of N-{4-[(6-methoxy-8-quinolyl)amino]pentyl}hexadecanamide (XVc) as a tan solid, mp 79–86° (indistinct). The ir spectrum showed carbonyl absorption at 1647 cm^{-1}.

({[(6-Chloro-9-acridinyl)amino]alkyl}amino)alkanol Esters (XVIIa–e, XVIII, and XIXa and b) (26–33, Table VI). Procedure XII.—2-({2-[(6-Chloro-2-methoxy-9-acridinyl)amino]-ethyl}amino)ethanol dihydrochloride[23,24] (21.6 g, 0.052 mole) was stirred and heated under reflux with 140 ml of AcCl for 4 hr. The suspension was allowed to stand at room temperature overnight and 100 ml of Ac_2O was added to facilitate stirring. After warming for 30 min, the mixture was diluted with Et_2O and filtered. The solid was crystallized from EtOH–MeOH to give 12.0 g (48%) of 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl}amino)ethanol acetate ester dihydrochloride $1.25H_2O$ (XVIIa) as bright yellow crystals, mp 150–155°.

Procedure XIII.—A mixture of 5.0 g (0.012 mole) of 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}amino)ethanol dihydrochloride[23,24] and 50 ml of palmitoyl chloride was stirred and heated on a steam bath for 18 hr, cooled, and diluted with Et_2O. The precipitate was collected and crystallized from EtOH to give 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}amino)-ethanol palmitate ester dihydrochloride monohydrate (XVIIe) (5.5 g, 73%), mp 185–190°.

Compounds XVIIb–d and XVIII were prepared in a similar manner utilizing procedure XIII.

Procedure XIV.—Ac_2O (100 ml) and 21.6 g (0.052 mole) of 2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}amino)ethanol dihydrochloride[23,24] was heated in a metal bath for 2 hr at 125–130°. The solution was cooled, an equal volume of Et_2O was added, and the product was collected by filtration. Crystallization from MeOH–*i*-PrOH gave 20.0 g (83%) of N-{2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}-N-(2-hydroxyethyl)acetamide acetate ester monohydrochloride (XIXa) as yellow crystals, mp 180–182°.

Procedure XV.—2-({2-[(6-Chloro-2-methoxy-9-acridinyl)-amino]ethyl}amino)ethanol dihydrochloride[23,24] (21.6 g, 0.052 mole) and 70 ml of palmitoyl chloride was heated under reflux in 500 ml of PhMe for 7 hr. Upon cooling, a gel formed. A small amount of EtOH was added and the mixture was warmed to effect solution. Addition of Me_2CO produced a yellow precipitate which was collected by filtration and crystallized from MeOH. The N-{2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl}-N-(2-hydroxyethyl)hexadecanamide palmitate ester (XIXb) was obtained as bright yellow crystals, mp 155°, yield 27.0 g (60%).

Succinic Acid Diester with 4-[(7-Chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol Tetrahydrochloride Tetrahydrate (VI).—To a suspension of 17.8 g (0.05 mole) of amodiaquine base (I)[6a] in 200 ml of $CHCl_3$ was added 15.5 g (0.1 mole) of succinoyl chloride. Heat was evolved and a gummy solid separated from solution. The mixture was boiled under reflux for 2 hr, the solvent was decanted, and the residue gradually solidified. Crystallization (twice from EtOH yielded 2.4 g (10%) of product, mp 195–199°. *Anal.* ($C_{44}H_{46}Cl_2N_6O_4 \cdot 4HCl \cdot 4H_2O$) C, H, Cl, Cl$^-$, N; H_2O: calcd, 7.12; found, 6.61.

N-{5-[(7-Chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide Monohydrochloride (IXa).—A mixture of 4.5 g (0.0127 mole) of 4-[(7-chloro-4-quinolyl)amino]-α-(isobutylamino)-*o*-cresol[17a] and 2.0 g (0.0254 mole) of AcCl in $CHCl_3$ was heated under reflux for 3 hr. Filtration gave 4.6 g of a yellow solid, mp 265–270° dec. Crystallization from MeOH afforded on prolonged standing 1.2 g (22%) of product as yellow plates, mp 292–293° dec. *Anal.* ($C_{22}H_{24}ClN_3O_2 \cdot HCl$) C, H, Cl, N.

N-{5-[(7-Chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide Acetate Ester (IXb).—A mixture of 5.0 g (0.0141 mole) of N-{5-[(7-chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide monohydrochloride (IXa), 30 ml of AcOH, and 10 ml of Ac_2O was heated under reflux for 4 hr. The cooled mixture was poured into cold H_2O, made alkaline with NH_4OH, and the solid that precipitated was washed with H_2O. Crystallization (twice from MeCN gave 3.9 g (63%) of the desired product, mp 179.5–181°. *Anal.* ($C_{24}H_{26}ClN_3O_3$) C, H, N. This compound displayed a sharp ester band at 1766 cm^{-1}, but neither this nor the amide IXa showed an obvious peak due to the amide carbonyl which was apparently hidden under the broad aromatic absorption between 1620 and 1640 cm^{-1}.

N-(7-Chloro-4-quinolyl)-N-[3-(diethylamino)-2-hydroxypropyl]acetamide Acetate Ester (XII).—A mixture of 5.0 g (0.0163 mole) of oxychloroquine base[16] and 50 ml of Ac_2O was heated under reflux for 7 hr. The solvent was removed *in vacuo* and the residue was stirred with H_2O. The insoluble material was collected by filtration and crystallized from *i*-Pr_2O to give 1.0 g of the desired product, mp 124–127°. The aqueous filtrate was made alkaline with NaOH to give an oil which solidified on standing. Recrystallization from *i*-Pr_2O gave an additional 2.7 g of product, mp 124–126°, total yield 58%. The ir spectrum showed carbonyl peaks at 1664 and 1729 cm^{-1}. *Anal.* ($C_{20}H_{26}ClN_3O_3$) C, H, N.

N-(7-Chloro-4-quinolyl)-N-[3-(diethylamino)propyl]acetamide (XIIIa) and Pamoate Salt (XIIIb).—A solution of 32.5 g (0.11 mole) of 7-chloro-4-{[3-(diethylamino)propyl]amino}quinoline[18] and 50 ml of AcCl in $CHCl_3$ was heated under reflux for 48 hr. The solvent was removed *in vacuo* and the residue was dissolved in H_2O, treated with aqueous NaOH, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried, the solvent was removed, and the residue was subjected to vacuum distillation to give 12.3 g (33%) of product, bp 182–183° (0.2 mm). The material had a carbonyl band at 1675 cm^{-1} in the ir spectrum. *Anal.* ($C_{18}H_{24}ClN_3O$) C, H, N.

The salt with 1 formula wt of 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) was prepared by adding an aqueous solution of 1 equiv of the disodium salt of 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) to an aqueous solution containing 1 equiv of the quinoline base and 2 equiv of HCl. The gummy solid was crystallized from DMF to give the product, mp 261–263° dec. *Anal.* ($C_{18}H_{24}ClN_3O \cdot C_{23}H_{16}O_6$) C, H; N: calcd, 5.82; found, 6.35.

N-{3-[(7-Chloro-4-quinolyl)amino]propyl}-N-ethylacetamide (XIV).—A mixture of 28.9 g (0.146 mole) of 4,7-dichloroquinoline and 42.0 g (0.292 mole) of N-(3-aminopropyl)-N-ethylacetamide was heated in an oil bath to 185°, and then maintained at 150–160° for 6 hr. The resulting gum was dissolved in Me_2CO, diluted with H_2O, and treated with aqueous NaOH. Two layers formed. The mixture was refrigerated for 3 days and the aqueous layer was separated. The residual oil was dissolved in $CHCl_3$, and the combined $CHCl_3$ extracts were dried over K_2CO_3 and concentrated. Distillation of the residue afforded 6.0 g (13%) of product, bp 215–225° (0.2 mm), together with a

large mass of polymeric pot residue. *Anal.* ($C_{16}H_{20}ClN_3O$) C, H, N.

N-(6-Chloro-2-methoxy-9-acridinyl)-N-[3-(diethylamino)propyl]acetamide (XX).—A solution of 46.3 g (0.1 mole) of 6-chloro-9-{[3-(diethylamino)propyl]amino}-2-methoxyacridine dihydrochloride hydrate[16] in warm H_2O was made basic with NH_4OH and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$) and treated with 25 ml of AcCl. The mixture was boiled under reflux for 48 hr, filtered hot, and cooled to give 11.9 g of yellow solid, mp 266–274°. This material was presumed to be starting material from its lack of C=O absorption in the ir. The filtrate was concentrated to dryness to give a yellow semisolid. Crystallization from 95% EtOH gave 6.0 g of a solid of indeterminate melting point which was discarded. The EtOH filtrate was concentrated to dryness, and the residue was dissolved in H_2O, filtered, and made basic with NaOH. The gummy material which formed solidified on standing and was crystallized twice from heptane. The bright yellow crystals thus obtained, mp 113–114.5°, weighed 11.2 g (27%) and showed strong C=O absorption in the ir at 1665 cm^{-1}. *Anal.* ($C_{23}H_{28}ClN_3O_2$) C, H, N.

1-{5-[(7-Chloro-4-quinolyl)amino]salicyl}-4-piperidinol Dihydrochloride.—To a mixture of 4′-hydroxyacetanilide (45.3 g, 0.3 mole) and 30.4 g (0.3 mole) of 4-piperidinol in 200 ml of *i*-PrOH was added dropwise during 1 hr 22.5 ml of 40% CH_2O. The mixture was heated under reflux for 5 hr, the solvent was removed *in vacuo*, and 100 ml of H_2O was added. The mixture was heated on a steam bath for 3 hr, cooled, and neutralized until just acid to congo red. 4,7-Dichloroquinoline (59.4 g, 0.3 mole) and 50 ml of EtOH were added and the resulting mixture was heated on a steam bath for 3 hr. The pasty mass was stirred with 2 l. of H_2O and filtered. The filtrate was diluted to 4 l. and made alkaline with NH_4OH. The solid was collected by filtration, digested with a mixture of boiling MeOH–EtOH, and filtered. The residue was suspended in hot EtOH and treated with concentrated HCl. The suspension of the hydrochloric acid salt was diluted with Me_2CO and filtered to yield 97.0 g (70%) of product, mp 298–300° dec. *Anal.* ($C_{21}H_{22}ClN_3O_2 \cdot 2HCl \cdot 0.25H_2O$) C, H, N, H_2O.

N-(2-Cyanoethyl)-N-ethylacetamide.—To a mixture of 147 g of HOAc and 225 g of Ac_2O was added dropwise 236 g (2.4 moles) of 3-(ethylamino)propionitrile.[19] Heat was evolved and the temperature was maintained at 50–60° by controlling the rate of addition. The solvent was removed *in vacuo* and the residue was distilled to give 278 g (83%) of product, bp 95° (0.3 mm), $n^{25}D$ 1.4640. *Anal.* ($C_7H_{12}N_2O$) C, H, N. The ir spectrum contained a carbonyl band at 1647 cm^{-1}.

N-(3-Aminopropyl)-N-ethylacetamide.—N-(2-Cyanoethyl)-N-ethylacetamide (272 g, 1.94 moles) was hydrogenated in 500 ml of toluene over 60 g of Raney cobalt in the presence of 60 ml of Et_3N at 100° and an initial hydrogen pressure of 140.6 kg/cm^2. The solvent was removed *in vacuo* and the residue was distilled to give 170 g of product, bp 90–99° (0.2 mm). The ir spectrum showed a strong carbonyl peak at 1635 and a shoulder at 1670 cm^{-1}; in CCl_4 a split peak at 1678, 1652 cm^{-1} was present. The material was redistilled through a 30-cm Vigreux column and yielded 42 g (15%) of fraction A, bp 73° (0.2 mm), $n^{25}D$ 1.4725, and 77 g (27%) of fraction B, bp 83° (0.2 mm), $n^{25}D$ 1.4668. The ir spectrum of fraction A showed C=O at 1640 and a split primary amine band at 3300, 3370 cm^{-1} and was presumed to be the desired N-(3-aminopropyl)-N-ethylacetamide. *Anal.* ($C_7H_{16}N_2O$) C, H, N.

Fraction B exhibited a C=O peak at 1650, a strong NH absorption at 3300, and an amide II band at 1560 cm^{-1} and was presumed to be the rearranged terminal amide N-[3-(ethylamino)-propyl]acetamide. *Anal.* ($C_7H_{16}N_2O$) C, H, N.

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Comparison of Schistosomicidal Activity of Xanthenones and 4-Methyl-3-chloroanilines and Their Hydroxymethyl Analogs in Swiss Mice and Syrian Hamsters Infected with *Schistosoma mansoni*

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The schistosomicidal activity of a number of xanthenones, 4-methyl-3-chloroanilines, and their hydroxylated derivatives were tested against *Schistosoma mansoni*. It was demonstrated that hydroxylation enhanced schistosomicidal activity one- to sixfold in the mouse and two- to 33-fold in the hamster.

A series of xanthenones initially synthesized in the thirties by Mauss[1] and designated as "miracils" were demonstrated by Kikuth and Gönnert[2] to be orally effective against *Schistosoma mansoni* infection in white mice and monkeys. Of the several xanthenones, lucanthone (Miracil D) was found to be effective not only in experimental animal infections but also in natural infections of humans. Although highly efficacious in the monkey, lucanthone was less effective in humans and mice. Of the hundreds of xanthenones synthesized during the past quarter of a century a few were more active than lucanthone in experimental infections in animals but less effective when field tested against schistosome infections of man. The erratic and unpredictable activity in different hosts was found to be related to the ability of the host to hydroxylate the 4-methyl group *para* to the alkylamino side chain. Hycanthone, the hydroxymethyl analog of lucanthone, was the most active of the several metabolites produced by each host species. It was also demonstrated that the variety and the proportion of lucanthone metabolites whether urinary excretion products or products obtained after incubation with liver microsomes were different for each host species.[3-6]

Swiss mice and Syrian hamsters infected experimentally with *S. mansoni* were treated with xanthenones, 4-

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