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

Edward F. Elslager, Frank H. Tendick, and Leslie M. Werbel

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

Received March 14, 1969

An array of 4-[(7-chloro-4-quinolyl)amino]-a-(diethylamino)-o-cresol esters (Va-d, VI), ({5-[(7-chloro-4quinolyl)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(methylidyne-imino-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

(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).

(10) P. E. Thompson, Intern. J. Leprosy, 35, 605 (1967).

(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.



exhibited noteworthy repository activity against *Plas*modium berghei in the mouse.

Acylation of amodiaquine base (I)^{17a} with the appropriate acid halide in CHCl₃ or pyridine afforded the corresponding $4 - [(7 - \text{chloro} - 4 - \text{quinolyl}) \text{amino}] - \alpha - (\text{di-}$ ethylamino)-o-cresol esters (Va-d) in 44-61% yield



^{(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.

11

 $(CH_2)_{14}CH_3$



^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 C₁₉-H₃O₆S₂ represents 1,5-naphthalenedisulfonic acid. ^d Found values are corrected for 0.70% H₂O. ^e C₁₂H₁₀O₆S₂ represents 4,4'-biphenyl-disulfonic acid. ^f H₂O: calcd, 4.81; found, 4.27. ^g C₂₃H₁₆O₆ represents 4,4'-methylenebis(3-hydroxy-2-naphthoic acid). ^h Found values are corrected for 3.16% H₂O. ⁱ H₂O: calcd, 2.89; found, 2.35. ^j Drug was given as a suspension in 1.5% pectin-0.1% Tween 60 in H₂O.

 $C_{36}H_{52}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot H_2O^g$

(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 CHCl₃.

138-148 dec

38

b



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 Ac₂O 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-($\{5-[(7-chloro-4-quinolyl)-$



amino]salicyl}ethylamino)ethanol 1-heptanoate ester (VIIb) (21%) (procedure IV). 1-{5-[(7-Chloro-4quinolyl)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%)

C, H, N, H₂O



were obtained from 1- $\{5-[(7-\text{chloro-4-quinoly})]$ 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 CHCl₃ gave N-{5-[(7-chloro-4-quinolyl)amino]salicyl}-N-isobutylacetamide (IXa) (22%), which upon treatment with



 3.5^{i}

Repository



0H CH₃NR₁R

			Yield				Repository act.,
No.	NR_1R_2	Mp, °C	purifd, %	Purificn solvent	Formula	Analyses ²⁶	PMW^{a}
12	$N(C_2H_5)(CH_2)_2OCOCH_3$	156	63	EtOH	$\mathrm{C}_{12}\mathrm{H}_{24}\mathrm{ClN}_3\mathrm{O}_3$	С, Н, N	<3
13	N OCOCH ²	158 - 160	23	C_6H_6 - CCl_4	$C_{23}H_{24}ClN_{3}O_{3}\cdot0.5H_{2}O$	C, H, N, H ₂ O	<1
14	$\begin{array}{c} N(C_2H_{\delta})(CH_2)_2OCO-\\ (CH_2)_5CH_3 \end{array}$	135–137	21	EtOAc	$\mathrm{C}_{27}\mathrm{H}_{34}\mathrm{ClN}_3\mathrm{O}_3$	II, N; С ^ь	<1
15	N OCOC ₆ H ₅	184 - 185	33	C_6H_6	$\mathrm{C}_{28}\mathrm{H}_{26}\mathrm{ClN}_{3}\mathrm{O}_{3}\cdot\mathrm{H}_{2}\mathrm{O}$	C, H, N; H ₂ O ^e	<1

^a See footnote a, Table I. ^b C: calcd, 66.99; found, 66.56. ^c H₂O: calcd, 3.56; found, 4.00.

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

NHCH(CH₂)(CH₂)₃N(C₂H₅)(CH₂)₂OCOR



			Yield				act.,
No.	\mathbf{R}	Mp, °C	purifd, $\%$	Purificn solvent	Formula	Analyses ²⁶	PMW^{a}
16	CH_3	196 - 199	65	DMF-H _i O	$C_{20}H_{28}ClN_3O_2\cdot C_{23}H_{16}O_6\cdot 0.67H_2O^b$	C, H, N, H ₂ O	<1
17	$(CH_2)_5CH_3$	163 - 164	20	EtOH	${ m C_{25}H_{38}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot 1.5H_2O^b}$	C, H, N, H ₂ O	1
18	$(CH_z)_{14}CH_3$	55	23	Et ₂ O- petr ether	$\mathrm{C}_{34}\mathrm{H}_{56}\mathrm{ClN}_{3}\mathrm{O}_{2}\cdot 2\mathrm{H}\mathrm{Cl}\cdot 2\mathrm{H}_{2}\mathrm{O}$	C, H, N; H_2O^c	N
19	$(CH_{\Sigma})_{14}CH_{3}$	138-140	25	Cellosolve-H ₂ O	$C_{34}H_{56}ClN_3O_2 \cdot C_{23}H_{16}O_6 \cdot H_2O^b$	C, H, N, H_2O	<1

^a See footnote a, Table I. ^b C₂₃H₁₆O₆ represents 4,4'-methylenebis(3-hydroxy-2-naphthoic acid). ^c H₂O; calcd, 5.27; found, 5.75.

TABLE IV

1-[(7-Chloro-4-quinolyl)amino]-3-(diethylamino)-2-propanol (Oxychloroquine) Esters NHCHCH(OCOR)CHN(C.H.)

					(000h)0h2h(C3h5/3		
				<u>Ó</u> C			
			Yield purifd,				Repository act.,
No.	R	Mp, °C	%	Purificn solvent	Formula	$Analyses^{26}$	PMW^{a}
20	CH_3	245–246 dec	43	DMA-H ₂ O	$\mathrm{C_{18}H_{24}ClN_{3}O_{2}}\cdot\mathrm{C_{23}H_{16}O_{6}}\cdot0.5H_{2}O^{\hbar}$	C, H, N, H_2O	3.5
21	$(CH_2)_5CH_3$	62 - 63	15	MeCN	$\mathrm{C}_{23}\mathrm{H}_{34}\mathrm{ClN}_{3}\mathrm{O}_{2}$	С, Н, N	$<\!\!2$
22	CH2CH2	242–244 dec	53	DMF-H ₂ O	$\mathrm{C}_{24}\mathrm{H}_{34}\mathrm{ClN}_{3}\mathrm{O}_{\downarrow}\cdot\mathrm{C}_{23}\mathrm{H}_{16}\mathrm{O}_{6}{}^{b}$	С, Н, N	<1
a S00	footnote a Table I	hCHO warman	asta A A	methylopobie (2	hydroxy 2 nanhthoig said)		

See footnote a, Table I. b C₂₃H₁₆O₆ represents 4,4'-methylenebis(3-hydroxy-2-naphthoic acid).

boiling Ac₂O in HOAc afforded N-{5-[(7-chloro-4quinolyl)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



 $Xa, R = CH_3$ $\mathbf{b}, \mathbf{R} = (\mathbf{CH}_2)_5 \mathbf{CH}_3$ $c, R = (CH_2)_{14}CH_3$ hydroxychloroquine¹⁸ (IIa) for 18 hr with excess AcCl, heptanoyl chloride, or palmitoyl chloride in refluxing CHCl₃ 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 oxychloroquine¹⁶ 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)



(53%) were prepared by heating oxychloroquine with AcCl or cyclopentylpropionyl chloride in CHCl₃ utilizing procedure VII. The products were isolated and purified as the pamoic acid salts. When oxychloroquine base was heated under reflux with excess Ac₂O for 7 hr, N-(7-chloro-4-quinolyl)-N-[3-(diethylamino)-2-hydroxypropyl]acetamide acetate ester (XII) was obtained in 58% yield.



In addition to the amide ester XII, several other basically substituted 4-aminoquinoline amides were also prepared. When 7-chloro-4- $\{[3-(diethylamino)pro$ $pyl]amino\}$ quinoline¹⁶ was heated under reflux for 48 hr with excess AcCl in CHCl₃, N-(7-chloro-4-quinolyl)-N-[3-(diethylamino)propyl]acetamide (XIIIa) was isolated in 33% yield. The base was converted to the



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)propionitrile¹⁹ with Ac₂O in HOAc afforded N-(2-cyanoethyl)-Nethylacetamide (83%). Catalytic hydrogenation of this intermediate in toluene over Raney cobalt in the presence of Et₃N 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 excerpthrocytic 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-[(6methoxy-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 syn-



thesis of 2,2-dichloro-N- $\{4-[(6-methoxy-8-quinoly])-amino]pentyl\}$ 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 CHCl₃ (procedures IX, XI). N-(6-Methoxy-8-quinolyl)-N-(3-phthalimidopropyl)acetamide (XVb) was obtained in 36% yield from N- $\{3-[(6-methoxy-8-quinolyl)amino]propyl\}$ phthalimide²⁰ and Ac₂O in HOAc (procedure X).

In an earlier communication²¹ we described the preparation of various $\{[(benz[c]acridin-7-yl)amino]-alkylamino\}alkanol esters (XVI) that exhibit potent$



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 dihydrochloride²³ 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).



713		1 / T
1	ABLE	V I -

 \sim

(† [(6-Chloro-9-acridinyl)amino]alkyl{amino)alkanol Esters

NH(CH₂)_xNR(CH₂)₂OCOR'

				Cl	Q	\bigcup_{N}	J x			
No.	x	R	R'	Х	Mp. °C	Yield purifd, %	Purifien solvent	Pro- cedure	Formula	Analyses ²⁶
26	2	11	CH ₃	2-0CH3	150155	48	EtOH- <i>i</i> -PrOH- petr ether	XII	$C_{20}H_{22}CIN_{3}O_{3}\cdot 2HCl\cdot 1\cdot 25H_{2}O$	C, H, N, Cl, Cl [−] , H ₂ O
27	2	COCH ₈	CH_3	$2-OCH_3$	180-182	83	MeOH- i-PrOH	XIV	$\mathrm{C}_{22}\mathrm{H}_{24}\mathrm{CIN}_{3}\mathrm{O}_{4}\cdot\mathrm{H}\mathrm{Cl}$	C. H, N, CI, CI
28	2	11	$(CH_2)_4CH_3$	$2-OCH_3$	150 dec	39	MeOH	ХШ	$C_{24}H_{30}ClN_3O_3 \cdot HCl \cdot 0.75H_2O$	C, H, Cl ⁻ , H ₂ O; \mathbf{N}^{u}
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	$C_{30}H_{42}C_1N_3O_3 \cdot HC_1 \cdot 0$. 25 H_2O	C, H, Cl ⁻ , H ₂ O; Cl, ^c N ⁶
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	$C_{50}H_{80}ClN_{3}O_{4} \cdot HCl \cdot 0.25H_{2}O$	C, H, H ₂ O; N ^e
33	3	(CH2) OCO(CH2) CH2	(CH ₂) ₂ CH ₂	3-C1	217-218	90	EtOH-MeOH	VIII	Colling Clange 2HCl	CHN

^a N: caled, 8.51; found, 7.83. ^b N: caled, 7.06; found, 7.50. ^c Cl: caled, 12.46; found, 13.10. ^d N: caled, 7.38; found 6.75. ^r N: caled, 4.87; found, 5.31.



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).



When $2-({2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl}amino)ethanol dihydrochloride^{23,24} was heated at 125–130° for 2 hr with Ac₂O (procedure XIV) or refluxed with palmitoyl chloride in toluene for 7 hr (procedure XV), the corresponding N-{2-[(6-chloro-2-methoxy-9-acridinyl)amino]ethyl}-N-(2-hydroxy-ethyl)amide esters XIXa and b were formed. The$



 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-



amino)propyl]amino]-2-methoxyacridine dihydrochloride upon treatment with excess AcCl in boiling CHCl₃.

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 H₂O 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)-ocresol acetate ester (2, 3, Table I), the pamoate salt of 4-[(7-chloro-4-quinolyl)amino]- α -(diethylamino)-ocresol 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-4quinolyl)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-quinoly1)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 CHCl₃ 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-quinoly1)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 H₂O solution of 3.6 g (0.01 mole) of 4,4'-biphenyldisulfonic acid disodium salt was added to a H₂O 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. Further solid was collected, washed with H₂O, and dried to give 5.1 g of the 4-[(7-chloro-4-quinolyl)amino]- α -(diethylamino)- σ -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 H₂O. The precipitate was collected by filtration, washed with H₂O, dried in air, and crystallized twice from i-Pr₂O 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-quinoly1)amino]salicy1}alky1amino)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-quinoly1)amino]salicy1}ethy1amino)ethanol dihydrochloride quarterhydrate,^{17b} 100 ml of dry pyridine, and 50 ml of Ac₂O was heated on a steam bath for 1 hr. The mixture was diluted with H₂O, made alkaline with NH₄OH, and extracted with Et₂O. The combined extracts were washed with H₂O, dried (K₂CO₃), and evaporated to dryness. The residue was dissolved in EtOH and diluted with 3 vol of hot H₂O to give 11.0 g of crude product, mp 154°. Two crystallizations from EtOH gave 7.8 g of 2-({5-[(7-chloro-4-quinoly1)amino]salicy1}ethy1amino)ethanol 1acetate 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 H₂O and converted to the base with NH₄OH. 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_{*}O. The combined extracts were washed with dilute NaOH and H₂O, 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 Et₂O. The rubberlike mass was reprecipitated from EtOH with Et₂O. The resulting tan solid was suspended in a mixture of H_2O and Et_2O and the mixture was made basic with NH₄OH. 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}-4piperidinol 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 H₂O, and made basic with NH₄OH. 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, and concentrated to the cloud point. Cooling yielded a solid which was redissolved in a little MeOH and reprecipitated with CCl.. 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 CCl₄. Recrystallization from C₆H₆-CCl₄ 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 Me₂CO 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. (C₂₃H₂₄ClN₃O₃·2HCl·0.5H₂O) C, H, N, H₂O.

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 H₂O and the mixture was made alkaline with aqueous NaOH. The solid thus obtained was crystallized from C₆H₆ 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-quinoly])amino]penty]}ethylamino)ethanol (Hydroxychloroquine) Esters (Xa-c) (16-19, Table III). Procedure VII.—Hydroxychloroquine sulfate¹⁸ (10.0 g, 0.023 mole) was converted to the base with NH₄OH and extracted into CHCl₈. The dried CHCl₈ 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 Et₂O 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-H₂O 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 $\pm 0.4\%$ of the theoretical values. Water determinations were by the Karl Fischer method.

quinolyl)amino]pentylethylamino)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-quinoly1)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 base¹⁶ and 3.9 g (0.0162 mole) of *n*-beptanoic anhydride in DMF was heated under reflux for 5 hr. The mixture was cooled, poured into iced H₂O, and made alkaline with NaOH. The resulting gum was dissolved in Et₂O, and the Et₂O extracts were dried and concentrated to dryness. The white powder was crystallized from MeCN to give 1.0 g (15%) of 1-[(7-chloro-4quinoly1)amino]-3-(diethylamino)-2-propanol heptanoate ester (X1b), 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 CHCl₂ 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-H₂O 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}phthalimide²⁰ (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 Ac₂O. 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 CHCl₃ 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 (NVc) as a tan solid, mp 79–86° (indistinct). The ir spectrum showed carbonyl absorption at 1647 cm⁻¹.

($\{[(6-Chloro-9-acridinyl)amino]alkyl\}amino)alkanol Esters (XVIIa-e, XVIII, and XIXa and b) (26-33, Table VI). Procedure XII.—2-(<math>\{2-[(6-Chloro-2-methoxy-9-acridinyl)amino]-ethyl\}amino)ethanol dihydrochloride^{23,24} (21.6 g, 0.052 mole) was stirred and heated under reflux with 140 ml of Accl for 4 hr. The suspension was allowed to stand at room temperature over night and 100 ml of Ac₂O was added to facilitate stirring. After warming for 30 min, the mixture was diluted with Et₂O and filtered. The solid was crystallized from EtOH-MeOH to give 12.0 g (48%) of 2-(<math>\{2-[(6-chloro-2-methoxy-9-acridinyl)amino]-ethyl\}amino)ethanol acetate ester dihydrochloride 1.25H₂O (XVIIa) as bright yellow crystals, mp 150–155°.$

Procedure XIII.—A mixture of 5.0 g (0.012 mole) of 2-($\{2-|(6-chloro-2-methoxy-9-acridiny|)amino\}ethyl | amino)ethanol dihydrochloride^{28,24} and 50 ml of palmitoyl chloride was stirred and heated on a steam bath for 18 hr, cooled, and diluted with Et₂0. The precipitate was collected and crystallized from EtOH to give 2-(<math>\{2-|(6-chloro-2-methoxy-9-acridiny|)amino]ethyl | amino)ethanol palmitate ester dihydrochloride monohydrate (XVIIe) (5.5 g, 73%), mp 185–190°.$

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

Procedure XIV.—Ac₂O (100 ml) and 21.6 g (0.052 mole) of 2-([2-](6-chloro-2-methoxy-9-acridinyl)amino]ethyl}amino)ethanol dibydrochloride^{23,24} was heated in a metal bath for 2 hr at 125-130°. The solution 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)acetanide acetate ester monohydrochloride (XIXa) as yellow crystals, mp 180–182°.

Procedure XV.—2-($\{2-|(6-Chloro-2-methoxy-9-acridiny|)-amino]ethyl<math>\{amino\}$ 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 Me₂CO 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-quinoly])amino]- α -(diethylamino)-o-cresol Tetrahydrochloride Tetrahydrate (VI).-To a suspension of 17.8 g (0.05 mole) of amodiaquine base (1)^{17a} in 200 ml of CHCl₃ was added 15.5 g (0.1 mole) of succinoyd 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. (C₄H₄₆Cl₂N₄O₄·4HCl·4H₂O) C. H, Cl, Cl⁻, N: H₂O: calcd, 7.12; found, 6.61.

N- $[5-[(7-\text{Chloro-4-quinolyl})amino]\text{salicyl}]-N-\text{isobutylaceta$ mide Monohydrochloride (IXa).—A mixture of 4.5 g (0.0127 $mole) of 4-<math>[(7-\text{chloro-4-quinolyl})amino]-a-(\text{isobutylamino})-a-\text{cres$ sol^{17a} and 2.0 g (0.0254 mole) of AcCl in CHCl₂ was heatedunder reflux for 3 hr. Filtration gave 4.6 g of a yellow solid,mp 265-270° dec. Crystallization from MeOH afforded onprolonged standing 1.2 g (22%) of product as yellow plates, mp292-293° dec. Anal. (C₂₂H₂₄ClN₃O₂·HCl) C, H, Cl, N.

N-{5-[(7-Chloro-4-quinoly1)amino]salicy1}-N-isobutylacetamide Acetate Ester (IXb).--A mixture of 5.0 g (0.0141 mole) of N-{5-[(7-chloro-4-quinoly1)amino]salicy1}-N-isobutylacetamide monohydrochloride (IXa), 30 ml of AcOH, and 10 ml of Ac₂O was heated under reflux for 4 hr. The cooled mixture was poured into cold H₂O, made alkaline with NH₄OH, and the solid that precipitated was washed with H₂O. Crystallization twice from MeCN gave 3.9 g (63%) of the desired product, mp 179.5-181°. Anal. (C₂₄H₂₆ClN₂O₃) 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-quinoly1)-N-[3-(diethylamino)-2-hydroxypropyl]acetamide Acetate Ester (XII).—A mixture of 5.0 g (0.0163 mole) of oxychloroquine base¹⁶ and 50 ml of Ac₂O was heated under reflux for 7 hr. The solvent was removed *in vacuo* and the residue was stirred with H₂O. The insoluble material was collected by filtration and crystallized from *i*-Pr₂O 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*-Pr₂O 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. (C₂₀H₂₈-ClN₃O₃) 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}quinolme¹⁶ and 50 ml of AcCl in CHCl₃ was heated under reflux for 48 hr. The solvent was removed *in vacuo* and the residue was dissolved in H₂O, treated with aqueous NaOH, and extracted with CHCl₃. The combined CHCl₃ 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.* (C₁₈H₂₄ClN₃O) 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. ($C_{18}H_{24}ClN_3O\cdot C_{23}H_{18}O_6$) C, H: N: calcd, 5.82; found, 6.35.

N- $\{3^{-1}|(7\text{-Chloro-4-quinolyl)amino|propyl|-N-ethylacetamide (XIV).--A mixture of 28.9 g (0.146 mole) of 4,7-dichloro$ quinoline and 42.0 g (0.292 mole) of N-(3-aminopropyl)-N-ethylacetamide was heated in an oil bath to 185°, and then maintainedat 150-160° for 6 hr. The resulting gum was dissolved in Me₂CO,diluted with H₂O, and treated with aqueous NaOH. Twolayers formed. The mixture was refrigerated for 3 days and theaqueous layer was separated. The residual oil was dissolvedin CHCl₃, and the combined CHCl₄ extracts were dried overK₂CO₅ and concentrated. Distillation of the residue afforded6.0 g (13C₄) 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 6chloro-9-{[3-(diethylamino)propyl]amino}-2-methoxyacridine dihydrochloride hydrate¹⁶ in warm H_2O was made basic with NH₄OH and extracted with CHCl₃. The combined CHCl₃ extracts were dried (MgSO₄) and treated with 25 ml of AcCl. The mixture was boiled under reflux for 48 hr, filtered hot, Thisand cooled to give 11.9 g of yellow solid, mp 266-274°. 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 H₂O, 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. (C₂₃H₂₈ClN₃O₂) 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% CH₂O. The mixture was heated under reflux for 5 hr, the solvent was removed in vacuo, and 100 ml of H₂O 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 H₂O and filtered. The filtrate was diluted to 4 l. and made alkaline with NH4OH. 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 Me₂CO and filtered to yield 97.0 g (70%) of product, mp 298-300° dec. Anal. (C21H22Cl-N₃O₂·2HCl·0.25H₂O) C, H, N, H₂O.

N-(2-Cyanoethyl)-N-ethylacetamide.—To a mixture of 147 g of HOAc and 225 g of Ac₂O 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. (C₇H₁₂N₂O) 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 Et₃N at 100° and an initial hydrogen pressure of 140.6 kg/cm². 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 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.* (C₇H₁₆N₃O) 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. (C₇H₁₆N₂O) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Paul E. Thompson and coworkers for the antimalarial studies, Mrs. Eva Gold and Miss Maria Limson for assistance in the chemical work, Mr. William Pearlman for carrying out the hydrogenations, Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the ir and uv absorption spectra.

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

D. A. BERBERIAN, E. W. DENNIS, H. FREELE, D. ROSI, T. R. LEWIS, R. LORENZ, AND S. ARCHER

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

Received March 26, 1969

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 Mauss¹ and designated as "miracils" were demonstrated by Kikuth and Gönnert² 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-

⁽¹⁾ H. Mauss, Chem. Ber., 81, 19 (1948).

⁽²⁾ W. Kikuth and R. Gönnert, Z. Tropenmed. Parasitol., 1, 234 (1949).

⁽³⁾ D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, Nature, 208, 1005 (1965).

⁽⁴⁾ D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, J. Med. Chem., 10, 867 (1967).

⁽⁵⁾ D. Rosi, T. R. Lewis, R. Lorenz, H. Freele, D. A. Berberian, and S. Archer, *ibid.*, **10**, 877 (1967).

⁽⁶⁾ D. Rosi, A. J. Merola, and S. Archer, Life Sci., 6, 1433 (1967).