Antimalarial and Antischistosomal Effects of Proximal Hydrazine and Hydroxylamine Analogs of Chloroquine and Quinacrine[1,2]

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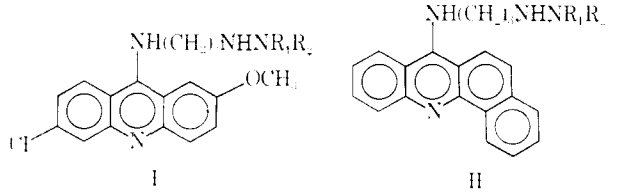
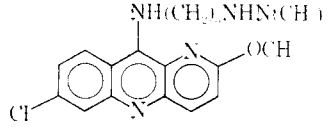
Representative 4-(2,2-dialkylhydrazino)quinolines (IV–VII), 6-chloro-9-(2,2-dialkylhydrazino)-2-methoxyacridines (VIII, IX), 12-(2,2-dialkylhydrazino)benz[*b*]acridines (X), 2,2′-(benz[*c*]acridin-7-ylhydrazono)diethanol (XI), 7-chloro-4-{[2-(dialkylamino)ethoxy]amino}quinolines (XII), and 6-chloro-9-{[2-(dimethylamino)ethoxy]amino}-2-methoxyacridine (XIII) were synthesized to enable an assessment of the antiparasitic effects conferred by substituting a hydrazine or hydroxylamine moiety for the proximal amine function of chloroquine, quinacrine, and 7-{[3-(octylamino)propyl]amino}benz[*c*]acridine relatives. The compounds were isolated in 3–92% yield by the condensation of 4,7-dichloroquinoline, 4-chloro-6-methoxyquinoline, 4-chloro-6-methoxyquinaldine, 6,9-dichloro-2-methoxyacridine, 12-chlorobenz[*b*]acridine, or 7-chlorobenz[*c*]acridine with the appropriate 1,1-dialkylhydrazine or 2-(dialkylamino)ethoxyamine in phenol or EtOH. Among them, 6-methoxy-4-(morpholinoamino)quinaldine (IV) exhibited modest activity against *Schistosoma mansoni* in mice and effected a 28–51% reduction of live worms at drug-diet doses of 224–303 mg/kg daily for 14 days. Six compounds were active against a normal strain of *Plasmodium berghei* in mice at doses ranging from 2.7–219 mg/kg/day for 6 days. 7-Chloro-4-(4-methyl-1-piperazinylamino)quinoline (Vb) and 4,4′-(1,4-piperazinediyldiimino)bis(7-chloroquinoline) (VII) were approximately 28 and 27 times as potent as quinine, respectively, against *P. berghei*, but VII was highly cross-resistant with chloroquine. Structure–activity relationships are discussed.

To enable an assessment of the effects of a distal hydrazine moiety on the antiprotozoal, anthelmintic, and antibacterial properties of quinacrine,[3] 7-{[3-(octylamino)propyl]amino}benz[*c*]acridine,[4] and azacrine[5] analogs, various {[3-(2,2-dialkylhydrazino)propyl]amino}acridines (I), benz[*c*]acridines (II), and benzo[*b*][1,5]naphthyridines (III) were recently synthesized for biological evaluation.[1] From the results of these studies it was concluded that the substitution of a hydrazine moiety for an amine function at the distal position of such compounds had a deleterious effect on antimalarial activity, but that potent antiamebic, anthelmintic, and antibacterial properties were maintained.[1] Moreover, Schraufstätter[6] recently reported that 7-chloro-4-[2-(2-diethylaminoethyl)hydrazino]-quinoline and several related compounds possessed only slight antimalarial activity in mice and canaries. Other studies in these laboratories revealed that 6-methoxy-4-(morpholinoamino)quinaldine (IV), which

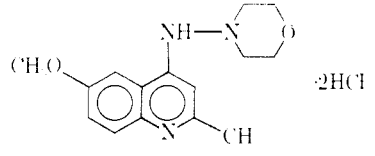


I

II



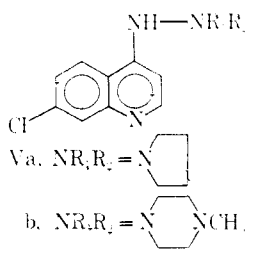
III



IV

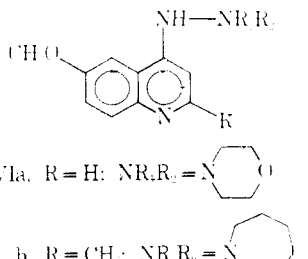
was originally synthesized by Gilman as a potential antimalarial drug during World War II,[7] exhibited modest antischistosome activity in mice.[8] When administered orally by drug-diet to mice infected with a Puerto Rican strain of *Schistosoma mansoni* at doses of 224–303 mg/kg/day for 14 days, IV effected a 28–51% reduction of live schistosomes. The present communication describes a further extension of the aforementioned studies, namely, the synthesis of proximal hydrazine and hydroxylamine analogs of chloroquine and quinacrine.

The condensation of 4,7-dichloroquinoline with excess 1-aminopyrrolidine or 1-amino-4-methylpiperazine in phenol gave 7-chloro-4-(1-pyrrolidinylamino)-quinoline (Va) and 7-chloro-4-[(4-methyl-1-piperazinyl)amino]quinoline (Vb) in poor yield (3–8%) (Table I, procedure I). 6-Methoxy-4-(morpholinoamino)-



Va, NR_1R_2 =

b, NR_1R_2 =



VIa, R = H; NR_1R_2 =

b, R = CH_3; NR_1R_2 =

(1) This is paper XVIII of a series on antimalarial substances; for the previous paper, see E. F. Elslager and D. F. Worth, *J. Med. Chem.*, **12**, 955 (1969).

(2) This is communication XIII of a series relating to synthetic schistosomicides. For paper XII, see E. F. Elslager and A. A. Phillips, *ibid.*, **12**, 519 (1969).

(3) A. Albert, "The Acridines," 2nd ed, Edward Arnold, London, 1966.

(4) F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 223 (1958).

(5) D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 2448 (1954).

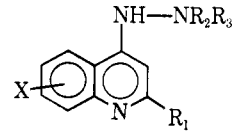
(6) E. Schraufstätter, *Arch. Pharm.*, **298**, 655 (1965).

(7) (a) The original sample of this compound was kindly supplied by Dr. Henry Gilman, Iowa State University; (b) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. II, Part 2, J. W. Edwards, Ann Arbor, Mich., 1946, p 1259.

(8) For a description of the antischistosomal test methods, see F. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).

TABLE I

4-(2,2-DIALKYLHYDRAZINO)QUINOLINES

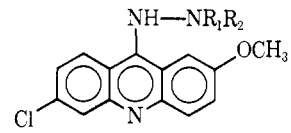


No.	R	X	NR_2R_3	Procedure	Purifcn solvent	Yield purified, %	Mp, °C	Formula	Analyses[23]
Va	H	7-Cl		I	C_6H_6	8	205 dec	$C_{13}H_{14}ClN_3$	C, H, N
Vb	H	7-Cl		I	EtOAc	3	222	$C_{14}H_{17}ClN_4$	C, H, N
VIa	H	6-OCH_3		II	EtOH–H_2O	33	254–256	$C_{14}H_{17}N_3O_2$	C, H, N
IV	CH_3	6-OCH_3		II	EtOH	57	255–257	$C_{15}H_{19}N_3O_2$	C, H; N[a]
VIb	CH_3	6-OCH_3		II	MeCN	26	195–196	$C_{17}H_{23}N_3O$	C, H; N[b]

[a] N: calcd, 15.37; found, 15.82. [b] N: calcd, 14.73; found, 15.26.

TABLE II

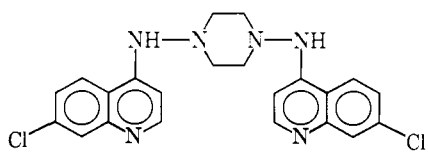
6-CHLORO-9-(2,2-DIALKYLHYDRAZINO)-2-METHOXYACRIDINES[a]



No.	NR_1R_2	Procedure	Purifcn solvent	Yield purified, %	Mp, °C	Formula	Analyses[23]
VIIIa		I	EtOH–Me_2CO	12	>305	$C_{18}H_{18}ClN_3O \cdot HCl \cdot 1.1H_2O$	C, H, N, H_2O
VIIIb		III	Et_2O	85	205	$C_{18}H_{18}ClN_3O_2$	C, H, N
VIIIc	$N(C_2H_5)_2$	I	EtOH–Me_2CO	92	230 dec	$C_{18}H_{20}ClN_3O \cdot HCl \cdot 0.1H_2O$	C, H, N, H_2O
VIIId	$N(C_2H_5)(CH_2)_2OH$	I	EtOH–Et_2O	84	233 dec	$C_{18}H_{20}ClN_3O_2 \cdot HCl$	C, H, N
VIIIe	$N[(CH_2)_2OH]_2$	I	EtOH–Me_2CO	30	210–212	$C_{18}H_{20}ClN_3O_3 \cdot HCl \cdot H_2O$	C, H, N, H_2O
VIIIf		IV	*i*-PrOH	24	204–206 dec	$C_{19}H_{20}ClN_3O \cdot HCl \cdot 0.6H_2O$	C, H, N, Cl
VIIIg		I	EtOH–Me_2CO	93	293 dec	$C_{19}H_{21}ClN_4O \cdot 2HCl \cdot 2.1H_2O$	C, H, N, H_2O

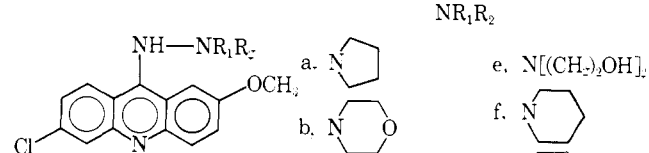
[a] Compounds varied from yellow to orange.

quinaldine (IV) (57%), 6-methoxy-4-(morpholinoamino)quinoline (VIa) (33%), and 4-[(hexahydro-1H-azepin-1-yl)amino]-6-methoxyquinaldine (VIb) (26%) were obtained in a similar manner from 4-chloro-6-methoxyquinoline, 4-chloro-6-methoxyquinaldine, and 4-aminomorpholine or 1-aminohexamethyleneimine (Table I, procedure II). Treatment of 2 equiv of 4,7-dichloroquinoline with 1 equiv of 1,4-diaminopiperazine[9] afforded 4,4′-(1,4-piperazinediyldiimino)bis(7-chloroquinoline) (VII) (11%).

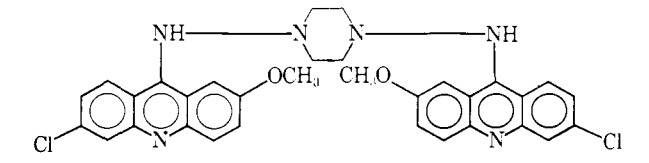


VII

A group of 6-chloro-9-(2,2-dialkylhydrazino)-2-methoxyacridine analogs (VIIIa–g, Table II) of quinacrine was prepared by the condensation of 6,9-dichloro-2-methoxyacridine with 1-aminopyrrolidine, 4-aminomorpholine, 1,1-diethylhydrazine, 2-(1-ethylhydrazino)-ethanol, 2,2′-hydrazonodiethanol, 1-aminopiperidine, and 1-amino-4-methylpiperazine, respectively, in phenol (procedures I–IV) (12–93% yield). 9,9′-(1,4-Piperazinediyldiimino)bis(6-chloro-2-methoxyacridine) (IX)



VIII



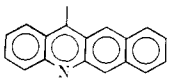
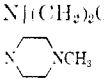
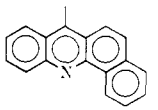
IX

(9) E. F. Elslager, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **7**, 493 (1964); M. Rink and M. Mehta, *Naturwissenschaften*, **48**, 51 (1961).

TABLE III

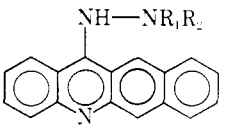
(2,2-DIALKYLHYDRAZINO)BENZ[*b*]ACRIDINES AND BENZ[*c*]ACRIDINES[a,b]

HET-NH-NR_1R_2

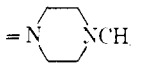
No.	HET	NR_1R_2	Purifen solvent	Yield purified, %	M.p., °C[c]	Formula	Analyses[d]
Xa		$N[(CH_2)_2OH]_2$	EtOH–Me_2CO	16	217 dec	$C_{21}H_{21}N_3O_2 \cdot HCl$	C, H, N, Cl
Xb			EtOH–Me_2CO	72	233 dec	$C_{22}H_{22}N_4 \cdot 2HCl \cdot 2H_2O$	C, H, N, H_2O
XI		$N[(CH_2)_2OH]_2$	EtOH–Et_2O	74	159 dec	$C_{21}H_{21}N_3O_2 \cdot HCl \cdot 0.6H_2O$	C, H, N; H_2O[e]

[a] Compounds range from yellow to red. [b] Prepared by procedure I. [c] Compounds melt with decomposition. [d] H_2O: calcd, 2.73; found, 3.49.

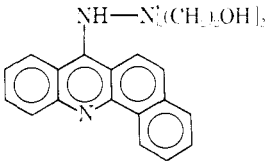
was isolated in 55% yield from the reaction of 2 equiv of 6,9-dichloro-2-methoxyacridine and 1 equiv of 1,4-diaminopiperazine.[9] Treatment of 2,2′-hydrazonodiethanol or 1-amino-4-methylpiperazine with 12-chlorobenz[*b*]acridine[10] or 7-chlorobenz[*c*]acridine[11] afforded 2,2′-(benz[*b*]acridin-12-ylhydrazono)diethanol (Xa) (16%), 12-[(4-methyl-1-piperazinyl)amino]benz-



Xa. $NR_1R_2 = N[(CH_2)_2OH]_2$

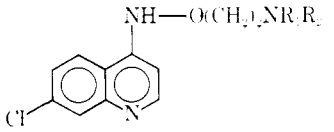
b. NR_1R_2 = 

[*b*]acridine (Xb) (72%), and 2,2′-(benz[*c*]acridin-7-ylhydrazono)diethanol (XI) (74%) (Table III, procedure I).



XI

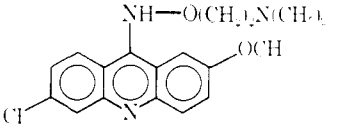
Several proximal hydroxylamine analogs of chloroquine and quinacrine were also prepared. 7-Chloro-4-{[2-(dimethylamino)ethoxy]amino}quinoline (XIIa)



XIIa. $NR_1R_2 = N(CH_3)_2$

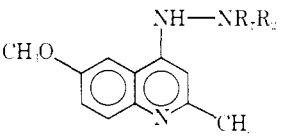
b. $NR_1R_2 = N(C_2H_5)_2$

(33%) and 7-chloro-4-{[2-(diethylamino)ethoxy]-amino}quinoline (XIIb) (17%) were obtained from 4,7-dichloroquinoline, 2-(dimethylamino)ethoxyamine dihydrochloride,[12] and 2-(diethylamino)ethoxyamine[13] in phenol and EtOH, respectively. The condensation of 2-(dimethylamino)ethoxyamine dihydrochloride[12] with 6,9-dichloro-2-methoxyacridine in phenol gave 6-chloro-9-{[2-(dimethylamino)ethoxy]amino}-2-methoxyacridine (XIII) (11%).

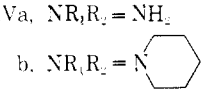


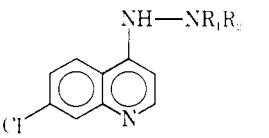
XIII

The proximal hydrazine and hydroxylamine derivatives Va, VIa and b, VIIIa–g, IX, Xa and b, XI, and XIIa and b described in the present communication were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for evaluation against a Puerto Rican strain of *Schistosoma mansoni* in mice.[8] Drugs were administered in a powdered diet for 14 days, and drug amounts are expressed as free base. None of these substances displayed significant activity against *S. mansoni* when administered to infected mice at near-toxic drug–diet doses ranging from 71 to 495 mg/kg/day for 14 days. Moreover, other 4-hydrazino-6-methoxyquinaldine (XIVa and b) and 7-chloro-4-hydrazinoquinoline (XVa–d) derivatives, which were kindly



XIVa, $NR_1R_2 = NH_2$

b, NR_1R_2 = 



XVa, $NR_1R_2 = NH_2$

b, $NR_1R_2 = NH(CH_2)_2OH$

c, NR_1R_2 = 

d, NR_1R_2 = 

supplied by Dr. Henry Gilman, also lacked appreciable antischistosome effects when given in 90–350-mg/kg doses daily for 14 days.

Compounds IV, Vb, VIb, VII, VIIIg, IX, XIIa and b, XIII, and XVd were also tested for antimalarial activity by Dr. Paul E. Thompson and associates of these laboratories utilizing *Plasmodium berghei* in mice.[14] In the initial screening, drugs were administered continuously in the diet for 6 days to mice infected with a normal drug-sensitive strain of *P. berghei*. Results are expressed both in terms of the SD_{90} (daily dose required

(10) G. B. Bachman and F. M. Cowen, *J. Org. Chem.*, **13**, 89 (1948).

(11) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **79**, 4699 (1957).

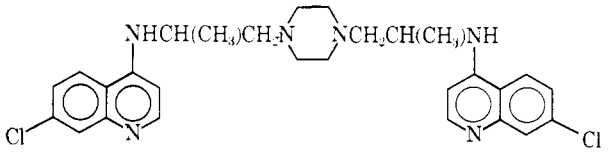
(12) F. Winternitz and R. Lachazette, *Bull. Soc. Chim. France*, 661 (1958).

(13) Ciba Ltd., U. S. Patent 3,060,177 (1962).

(14) For a description of the antimalarial test methods, see P. E. Thompson, A. Bayles, B. Olszewski, and L. Boehe, *Am. J. Trop. Med. Hyg.*, in press.

for 90% suppression of the parasitemia) and the quinine equivalent Q (the ratio of the SD_{90} of quinine to the SD_{90} of the test substance under comparable experimental conditions). Six compounds (IV, Vb, VII, VIIIg, XIIb, and XVd) exhibited antimalarial activity against *P. berghei* in the mouse. 6-Methoxy-4-(morpholinoamino)quinaldine dihydrochloride (IV) (SD_{90} = >219 mg/kg/day, Q = <0.34), 6-chloro-2-methoxy-9-(4-methyl-1-piperazinylamino)acridine dihydrochloride (VIIIg) (SD_{90} = >39 mg/kg/day, Q = <1.9), 7-chloro-4-{[2-(diethylamino)ethoxy]amino}quinoline (XIIb) (SD_{90} = 115 mg/kg/day, Q = 0.65), and 7-chloro-4-(morpholinoamino)quinoline (XVd) (SD_{90} = 53 mg/kg/day, Q = 1.4) exhibited modest activity but were considerably less potent than chloroquine or quinacrine. However, 7-chloro-4-[(4-methyl-1-piperazinyl)amino]quinoline (Vb) (SD_{90} = 2.7 mg/kg/day, Q = 28) and 4,4′-(1,4-piperazinediyldiimino)bis(7-chloroquinoline) (VII) (SD_{90} = 2.8 mg/kg/day, Q = 27) were much more potent, and displayed antimalarial activity of the same magnitude as chloroquine diphosphate (SD_{90} = 6.9 mg/kg/day, Q = 11) and amodiaquine dihydrochloride (SD_{90} = 2.7 mg/kg/day, Q = 28).

In 1965 Benazet[15] reported that 4,4′-[1,4-piperazinediylbis(1-methylethyleneimino)]bis(7-chloroquinoline) (XVI) was active against a chloroquine-resistant strain of *P. berghei* in mice. This report is startling since all



XVI

other chloroquine-resistant strains studied to date have proved to be uniformly cross-resistant to an array of 4-aminoquinoline and 9-aminoacridine derivatives, including amodiaquine,[16] amopyroquin,[16] quinacrine,[16] 3-chloro-9-{[4-(diethylamino)-1-methylbutyl]amino}-acridine 10-oxide dihydrochloride,[16,17] 7-chloro-10-{3-[(diethylamino)methyl]-*p*-anisidino}-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride,[18] and miscellaneous 4-aminoquinolines.[19-21] However, more recent studies by Warhurst[20] utilizing a different chloroquine-resistant strain of *P. berghei* showed a high degree of cross-resistance between XVI and chloroquine, while independent studies in these laboratories with another chloroquine-resistant line of *P. berghei* demonstrated at least a 16-fold cross-resistance.[14] Faint hopes that the proximal hydrazine analogs of chloroquine might possess significantly broader action against chloroquine-resistant lines were not realized. Thus a high degree of cross-resistance (>12-fold) was observed between 4,4′-(1,4-piperazinediyldiimino)bis(7-chloroquinoline) (VII) and chloroquine; the daily SD_{90} of VII against a line of *P. berghei* made highly resistant (77-fold)[14] to chloroquine was >32 mg/kg.

The over-all results of the present study suggest that the substitution of a hydrazine or hydroxylamine moiety for an amine function at the proximal position of quinacrine analogs has a deleterious effect on antimalarial activity in mice. In the chloroquine series, replacement of the proximal amine group by a hydroxylamine moiety also diminishes antimalarial potency. In contradistinction, potent antimalarial effects are retained when a suitable proximal hydrazine function is introduced into the chloroquine molecule, but such derivatives are highly cross-resistant with chloroquine. It is also concluded that the antischistosome effects of 6-methoxy-4-(morpholinoamino)quinaldine (IV) are remarkably structure specific.

Experimental Section[22,23]

4-(2,2-Dialkylhydrazino)quinolines (IV, Va and b, VIa and b, Table I), 6-Chloro-9-(2,2-dialkylhydrazino)-2-methoxyacridines (VIIIa–g, Table II), and (2,2-Dialkylhydrazino)benz[*b*]acridines and Benz[*c*]acridines (Xa and b, XI, Table III). Procedure I.—A mixture of 10.6 g (0.12 mole) of 1,1-diethylhydrazine and 27.8 g (0.10 mole) of 6,9-dichloro-2-methoxyacridine in 40 g of phenol was heated and stirred for 3 hr on a steam bath. Treatment of the warm solution with excess HCl in EtOH followed by dilution with Me_2CO–Et_2O gave a yellow precipitate which was collected by filtration. This was dissolved in H_2O, the solution was filtered, and the filtrate was made alkaline with concentrated NH_4OH. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ extracts were combined and washed successively with dilute NaOH and H_2O. After drying (K_2CO_3), the $CHCl_3$ solution was concentrated on a rotary evaporator. The residue was dissolved in EtOH, acidified with excess HCl in EtOH, and diluted with Me_2CO. The yellow solid was collected by filtration, washed with Et_2O, and dried at 60° *in vacuo*. The 6-chloro-9-(2,2-diethylhydrazino)-2-methoxyacridine monohydrochloride (VIIIc) (34.0 g, 92%) thus obtained, mp 230° dec, was slightly hygroscopic and was allowed to equilibrate in the atmosphere prior to analysis.

Procedure II.—A mixture of 17.0 g (0.167 mole) of 4-aminomorpholine, 16.6 g (0.080 mole) of 4-chloro-6-methoxyquinaldine, and 10 g of phenol was heated to 150° where a mildly exothermic reaction occurred. Heating was continued at 145–155° for an additional 2 hr. After cooling, the mixture was treated with excess dilute NaOH, and the resulting precipitate was collected by filtration. Recrystallization from EtOH gave 13.0 g (57%) of 6-methoxy-4-(morpholinoamino)quinaldine (IV) as colorless crystals, mp 255–257° dec.

Procedure III.—A mixture of 15.3 g (0.15 mole) of 4-aminomorpholine, 27.8 g (0.10 mole) of 6,9-dichloro-2-methoxyacridine, and 60 g of phenol was stirred and heated on a steam bath for 2.5 hr. After cooling, the reaction mixture was stirred into 1 l. of Me_2CO containing excess concentrated HCl, and the resulting brown precipitate was collected by filtration. This was stirred into H_2O and the mixture was made alkaline with excess NaOH. The mixture was extracted repeatedly with Et_2O, and the combined extracts were washed successively with dilute NaOH and H_2O. Upon standing, crystals began to form in the Et_2O solution. Concentration to approximately 200 ml followed by dilution with petroleum ether (bp 30–60°) and cooling gave 29.0 g (85%) of 6-chloro-2-methoxy-9-(morpholinoamino)acridine (VIIIb) as orange crystals, mp 205°.

Procedure IV.—A mixture of 2.50 g (0.025 mole) of 1-aminopiperidine, 6.95 g (0.025 mole) of 6,9-dichloro-2-methoxyacridine,

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(23) 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.

and 25 g of phenol was heated and stirred on a steam bath for 4 hr. After cooling, the mixture was treated with 100 ml of Me_2CO containing 10 ml of concentrated HCl, and the resulting precipitate was collected by filtration. Two recrystallizations from *i*-PrOH gave 2.3 g (24%) of 6-chloro-2-methoxy-9-(piperidinoamino)acridine monohydrochloride (VIIIf) as a bright yellow powder, mp 204–206° dec.

4,4′-(1,4-Piperazinediyldiimino)bis(7-chloroquinoline) (VII).—A mixture of 19.8 g (0.10 mole) of 4,7-dichloroquinoline and 5.8 g (0.050 mole) of 1,4-diaminopiperazine[9] was heated in 50 g of phenol for 4 hr on a steam bath. Excess concentrated HCl was added, and the mixture was poured into 3 l. of Me_2CO. Trituration with fresh Me_2CO, then with Et_2O, gave 9.2 g of yellow solid, mp >300°. This was dissolved in H_2O, and the solution was made alkaline with NaOH. The resulting precipitate was collected by filtration, washed well with H_2O, and dried at 65° *in vacuo* to give 2.5 g (11%) of a pale yellow solid, mp >310°. *Anal.* ($C_{22}H_{20}Cl_2N_6$) C, H, N.

9,9′-(1,4-Piperazinediyldiimino)bis(6-chloro-2-methoxyacridine) (IX).—A mixture of 9.3 g (0.080 mole) of 1,4-diaminopiperazine,[9] 49.0 g (0.18 mole) of 6,9-dichloro-2-methoxyacridine, and 220 g of phenol was heated on a steam bath for 4 hr. Excess concentrated HCl was added, and the mixture was diluted with 1.5 l. of Me_2CO. The resulting precipitate was collected by filtration and washed with Me_2CO. The crude hydrochloride was suspended in H_2O, excess NaOH was added, and the resulting base was extracted into warm EtOAc. Upon standing, crystals were deposited. These were collected by filtration, washed successively with hot 75% EtOH and Me_2CO, and dried at 60° *in vacuo* to give 26.5 g (55%) of yellow-orange crystals, mp 251°. *Anal.* ($C_{32}H_{28}Cl_2N_6O_2$) H, N; C: calcd, 64.10; found, 63.68.

7-Chloro-4-{[2-(dimethylamino)ethoxy]amino}quinoline Dihydrochloride (XIIa).—A mixture of 9.9 g (0.05 mole) of 4,7-dichloroquinoline, 8.9 g (0.05 mole) of 2-(dimethylamino)-ethoxyamine dihydrochloride,[12] and 25 g of phenol was stirred and heated on a steam bath for 4 hr. The resulting brown solution was cooled and poured into Me_2CO. The gummy product which formed solidified on standing and was dried *in vacuo*. Crystallization from *i*-PrOH afforded 5.9 g (33%) of product, mp 213–216° dec. *Anal.* ($C_{13}H_{16}ClN_3O \cdot 2HCl \cdot 0.75H_2O$) C, H, N, H_2O.

7-Chloro-4-{[2-(diethylamino)ethoxy]amino}quinoline (XIIb).—A solution of 50.0 g (0.25 mole) of 4,7-dichloroquinoline and 57.0 g (0.28 mole) of 2-(diethylamino)ethoxyamine[13] in 500 ml of EtOH containing 65 ml (3 equiv) of concentrated HCl was heated under reflux for 8 hr. Volatile materials were removed *in vacuo*, and the residue was dissolved in H_2O, overlaid with $CHCl_3$, and made basic with aqueous NaOH. The $CHCl_3$ layer was separated, dried (K_2CO_3), and concentrated to dryness *in vacuo*. The residue was dissolved in EtOH and diluted with 2 l. of H_2O. The solid which formed was collected and crystallized from hexane to give 17.0 g, mp 69–76°. This material was recrystallized twice from a mixture of *i*-Pr_2O-heptane. The solid was then dissolved in dilute HCl and the pH was adjusted to 6.0 with NaOH. A small amount of solid which formed was removed and discarded. The filtrate was brought to pH 8.0, and the yellow solid was collected by filtration. Recrystallization from hexane gave 13.0 g (17%) of the product, mp 76–82°. *Anal.* ($C_{15}H_{20}ClN_3O \cdot H_2O$) C, H, N, H_2O; Cl: calcd, 11.57; found, 11.84.

6-Chloro-9-{[2-(dimethylamino)ethoxy]amino}-2-methoxyacridine (XIII).—A mixture of 13.9 g (0.05 mole) of 6,9-dichloro-2-methoxyacridine and 8.9 g of 2-(dimethylamino)ethoxyamine dihydrochloride[12] in 50 g of phenol was heated on a steam bath for 5 hr. The cooled solution was poured into Me_2CO to give a brownish solid which was collected by filtration and dried. The crude material was crystallized twice from MeOH. This procedure did not provide a completely pure material. The solid was then dissolved in H_2O, filtered to remove a small amount of insoluble material, and made basic with NH_4OH. The resulting yellow solid was collected and recrystallized from MeCN to give 1.9 g (11%) of the product, mp 155–157°. *Anal.* ($C_{18}H_{20}ClN_3O_2$) C, H, N.

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Lincomycin. IX. 7-Thiol and Thioamido Analogs of Lincomycin[1]

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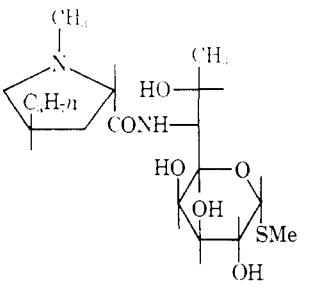
7-Deoxy-7(*R*)- and -7(*S*)-thiolincomycin (**10** and **15**) were prepared from methyl thiolincosaminide, a degradation product of lincomycin. Thioamido analogs (**18** and **20**) were prepared from lincomycin (**1**) and clindamycin (**16**), respectively. The 7-thiol analogs possessed slight antibacterial activity, while the thioamido analogs were about one-fourth as active as the antibiotic from which they were derived.

Potentiation of antibacterial activity of lincomycin (**1**) was achieved by a variety of chemical modifications.[2] Introduction of halogen at C-7, preferably in the 7(*S*) configuration, enhanced the *in vitro* and *in vivo* antibacterial activity in several series of analogs.[3] This substituent is also primarily responsible for the antimalarial activity encountered in 1′-demethylclindamycins.[3b,4] Introduction of other substituents at C-7 was therefore undertaken. The preparation and antibacterial activity of 7-thiol analogs of lincomycin are now described. In addition to the introduction of sulfur into the critical 7 position of lincomycin, replacement of the oxygen of the amide carbonyl by sulfur was also accomplished in both the lincomycin and clindamycin series.



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