Synthetic Amebicides. VIII. 7,7′-[Iminobis(alkyleneimino)]bis[benz[c]acridines] and Congeneric 9-Aminoacridines, 12-Aminobenz[*a*]acridines, 12-Aminobenz[*b*]acridines, and 4-Aminoquinolines (1)

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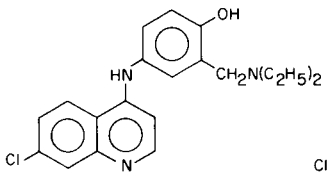
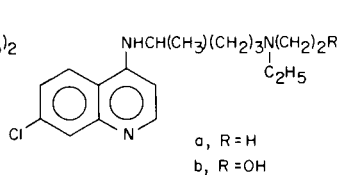
Thirty-five 7,7′-(iminodialkylenediimino)bis[benz[c]acridines] (VII), 7,7′-(alkylene- and phenylenediimino)bis[benz[c]acridines] (VIII and IXa-c), [iminobis(alkyleneimino)]bis[acridines, benz[*a*]acridines, benz[*b*]acridines, and quinolines] (X, XIa-c, XII, XIII, and XIVa-c), and [alkylenebis(iminoalkyleneimino)]bis[acridines, benz[c]acridines, and quinolines] (XVI, XVII, XVIIIa and b, and XIXa-c) were synthesized by the condensation of one equivalent of the appropriate alkylenediamine with two equivalents of the requisite chloroheterocycle in phenol. Many of the bis(aminoheterocyclic) compounds are highly active against *Entamoeba histolytica in vitro* and in experimental animals.

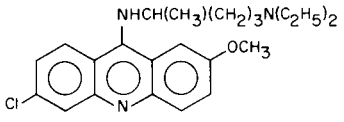
In addition to their potent antimalarial properties, amodiaquine (I), chloroquine (IIa), hydroxychloroquine (IIb), and quinacrine (III) are effective against amebic hepatitis in hamsters and in man (2). Unfortunately these drugs lack promising activity against intestinal amebic infections, presumably because they are readily absorbed and do not reach the lower intestine in effective concentration. By contrast, various 7-[[(mono- and



I

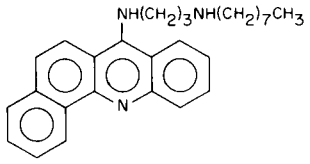


II



III

dialkylamino)alkyl]amino][benz[c]acridines exhibit broad antiamebic effects and are highly active against *Entamoeba histolytica in vitro*, intestinal amebiasis in rats and dogs, and amebic hepatitis in hamsters (3-6). Among them, 7-[[3-(octylamino)propyl]amino][benz[c]acridine (IV) (4) has been studied most extensively. *In vitro*, IV is amebicidal at concentrations of 2.5 to 20 μg./ml. against several strains of *E. histolytica*, a potency range comparable with emetine under similar test conditions (6). The drug acts rapidly, and its effects are not appreciably reduced by protein; concomitant studies on the supporting microorganisms indicate that it is a direct-acting



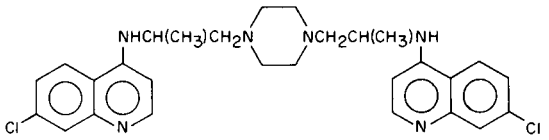
IV

amebicide (6). On a weight basis, IV is approximately eight times as active as chloroquine against amebic hepatitis in hamsters, and it is more active than acetarsone, carbarsone, chiniofon, diiodohydroxyquinoline, or bialamicol against intestinal amebiasis in rats and dogs (6). Few types of amebicides have shown this versatility of action either in experimental animals or in man, the best known exceptions being emetine, 2-dehydroemetine, bialamicol, metronidazole, and niridazole. Preliminary clinical studies indicate that IV is effective against both intestinal amebiasis and amebic liver abscess in man and is tolerated well (7).

A variety of other basically-substituted heteropolycyclic compounds has been evaluated as potential antiamebic agents, including 12-aminobenz[*b*]acridines (8), dibenz[*f,ij*]isoquinoline-2,7(3*H*)diones (9), benzo[*e*]perimidines

(10,11), benzo[*b*][1,8]phenanthrolines (12), benzo[*b*]-[1,10]phenanthrolines (12), dibenzo[*b*,*h*][1,6]naphthyridines (12), benzo[*h*]quino[4,3-*b*]quinolines (12), benzo-[*lmn*][3,8]phenanthrolines (13), and anthradipyrazoles (14). Although many of these compounds possess significant antiamebic properties, none has been studied in man.

Various bis(4-aminoquinoline) derivatives possess remarkable therapeutic and repository antimalarial properties (15-18). The most interesting of these, 4,4′-[1,4-piperazinediylbis(1-methylethyleneimino)]bis[7-chloroquinoline](V), has an oral CD_{50} of 10 mg./kg. against *Plasmodium berghei* in mice and protects mice against intervening challenge with *P. berghei* for 8 weeks following a single oral dose of 500 mg./kg. (15-17). Prior to these

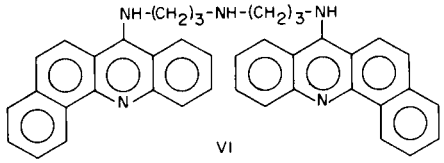


V

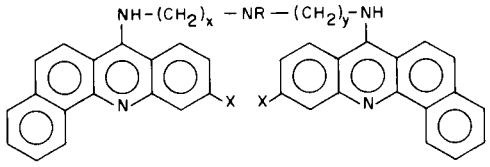
recent reports, we had independently initiated work on the synthesis of various bis(aminoheterocyclic) compounds for antiparasitic evaluation, and these studies are the subject of the present communication.

In the initial stages of this investigation, it was observed that 7,7′-[iminobis(trimethyleneimino)]bis[benz[c]-acridine] [VI] exhibited good antiamebic effects *in vitro* and in experimental animals. The drug killed *E. histolytica in vitro* at a concentration of 13 μg./ml., and cured intestinal amebic infections in rats and dogs at doses of 140 mg./kg. and 40 mg./kg., respectively. These interesting and somewhat surprising results stimulated the synthesis of other 7,7′-[iminobis(alkyleneimino)]bis[benz-[*c*]acridines], simple 7,7′-(alkylene- and phenylenediimino)-bis[benz[*c*]acridines], [iminobis(alkyleneimino)]bis[acridines, benz[*a*]acridines, benz[*b*]acridines, and quinolines], and [alkylenebis(iminoalkyleneimino)]bis [acridines, benz[*c*]acridines, and quinolines].

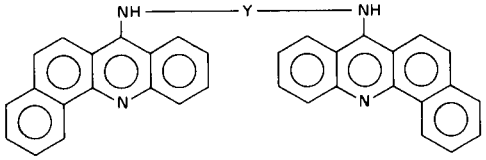
The condensation of two equivalents of 7-chlorobenz-[*c*]acridine (3) or 7,10-dichlorobenz[*c*]acridine (4) with one equivalent of the requisite iminodialkylenediamine in phenol afforded 7,7′-[iminobis(alkyleneimino)]bis[benz-[*c*]acridines] (XII) (compounds **1-9**, Table I) in yields ranging from 46-94% (procedures I and II). In general structure VII, X is H or Cl; R is H, CH_3, C_2H_5, or $(CH_2)_2N(C_2H_5)_2$; and x and y represent integers from 2 to 6. In a similar manner, various 7,7′-(alkylene- and phenylenediimino)bis[benz[*c*]acridines] (VIII and IXa-c) (compounds **10-19**, Table II) lacking a distal nitrogen atom were prepared from 7-chlorobenz[*c*]acridine (3) and the appropriate alkylenediamine or dianiline derivative (21-97% yield, procedure I). In formula VIII, Y represents $-(CH_2)_x-$ (x = 3, 5, 6, 8, 10), $-CH_2CH[(CH_2)_2]_2CHCH_2-$, and $-(CH_2)_3O(CH_2)_2O(CH_2)_3-$.



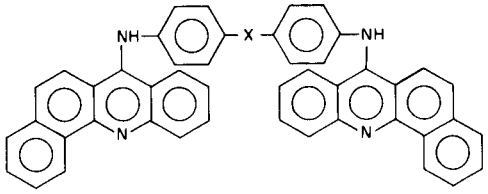
VI



VII

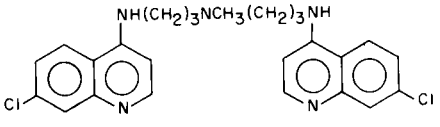


VIII

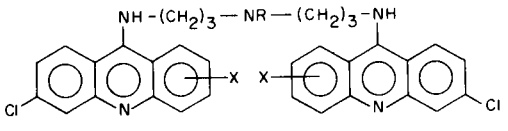


a, X = —; b, X = SO_2; c, X = CH_2

IX

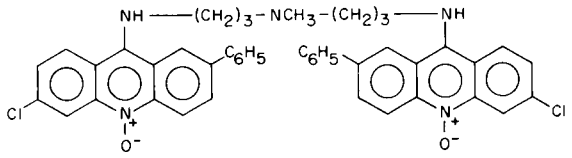


X

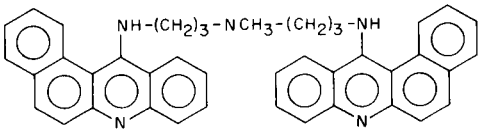


a, X = H; R = CH_3; b, X = 6-Cl; R = C_2H_5;
c, X = 7-C_6H_5; R = CH_3

XI



XII

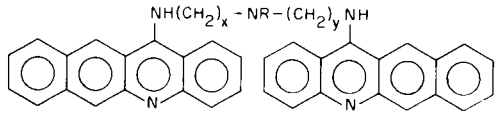


XIII

To enable an appraisal of the effect of the heterocyclic moiety on antiamebic properties, a group of [iminobis(alkyleneimino)]bis[acridines, benz[*a*]acridines, benz[*b*]acridines, and quinolines] (X, XIa-c, XII, XIII, XIVa-c) (compounds **20-28**, Table III) was prepared. The reaction of an iminodialkylenediamine with two equivalents of 4,7-dichloroquinoline, 3,9-dichloroacridine (19), 3,6,9-trichloroacridine (20), 6,9-dichloro-2-phenylacridine (19), 6,9-dichloro-2-phenylacridine 1-oxide (19), 12-chlorobenz[*a*]acridine (21), and 12-chlorobenz[*b*]acridine (8, 22) gave 4,4′-[methyliminobis(trimethyleneimino)]bis[7-chloroquinoline] (X), 9,9′-[alkyliminobis(trimethyleneimino)]bis[3-chloroacridines] (XIa-c), 9,9′-[methyliminobis(trimethyleneimino)]bis[6-chloro-2-phenylacridine 10-oxide](XII), 12,12′-[methyliminobis(trimethyleneimino)]bis[benz[*a*]acridine] (XIII), and 12,12′-[iminobis(alkyleneimino)]bis[benz[*b*]acridines] (XIVa-c), respectively, in 29-93% yield.

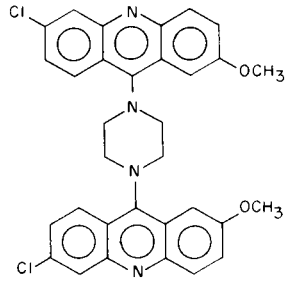
In connection with a related problem an attempt was made to synthesize a quinacrine relative containing a piperazine ring at position 9 by the amination of 6,9-dichloro-2-methoxyacridine with 4 equivalents of anhydrous piperazine in phenol. The only product isolated in pure form was 9,9′-(1,4-piperazinediyl)bis[6-chloro-2-methoxyacridine] (XV).

Representative [alkylenebis(iminoalkyleneimino)]bis[acridines, benz[*c*]acridines, and quinolines] (XVI, XVII, XVIIIa and b, and XIXa-c) (compounds **29-35**, Table IV) were also prepared to discern the effect of tetraza and pentaza side-chains on amebicidal activity. The condensation of triethylenetetramine with two equivalents of 4,7-dichloroquinoline, 3,6,9-trichloroacridine (20), 6,9-dichloro-2-methoxyacridine, and 7-chlorobenz[*c*]acridine (3) in phenol gave 4,4′-[ethylenebis(iminoethyleneimino)]bis[7-chloroquinoline] (XVI) (25%), 9,9′-[ethylenebis(iminoethyleneimino)]bis[3-chloroacridines] (XVIIIa and

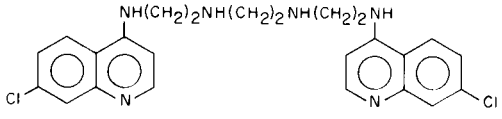


a, R = H; x = 3, y = 4; b, R = CH_3; x, y = 3; c, R = C_2H_5; x, y = 3

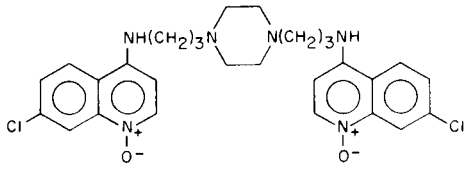
XIV



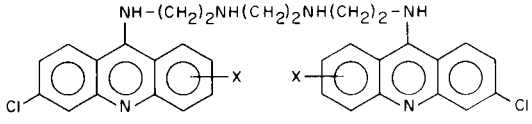
XV



XVI

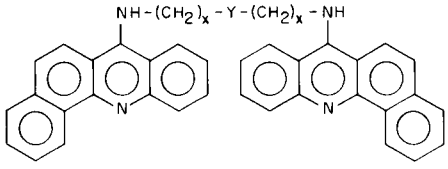


XVII



a, X = 6-Cl; b, X = 7-OCH_3

XVIII

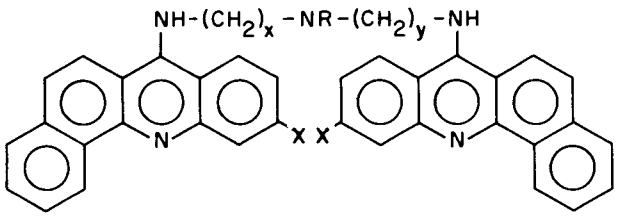


a, Y = $NH(CH_2)_2NH$; x = 2;
b, Y = $NH(CH_2)_2NH(CH_2)_2NH$; x = 2;
c, Y = $N[(CH_2)_2]_2N$; x = 3

XIX

TABLE I

7,7'-[Iminobis(alkyleneimino)]bis[benz[*c*]acridines] (a)

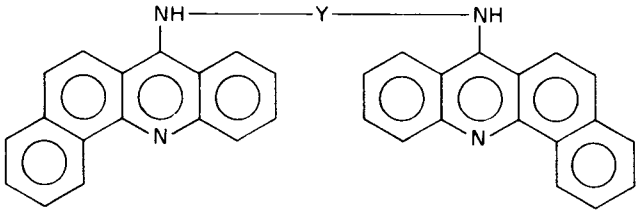


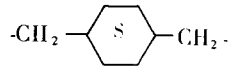
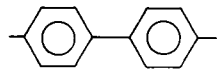
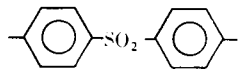
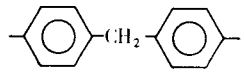
Compd. No.	x	y	X	R	M.P. °C dec.	Yield purified, %	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Amebicidal Concentration *in vitro* (μg./ml.) (h)
1	2	2	H	H	260	64	MeOH	I	$C_{38}H_{31}N_5 \cdot 3HCl \cdot 4.25H_2O$	61.37	61.33	5.76	5.69	9.42	9.36	167 (1)
2	2	3	H	H	240	82	EtOH-HCl	I	$C_{39}H_{33}N_5 \cdot 3HCl \cdot 3.1H_2O$ (b)	63.65	63.25	5.77	5.56	9.50	9.53	<200 (4)
3(VI)	3	3	H	H	220	73	EtOH	I	$C_{40}H_{35}N_5 \cdot 3HCl \cdot 4.25H_2O$	62.25	62.16	6.07	6.32	9.08	9.21	13 (1)
4	3	4	Cl	H	275	92	*i*-PrOH	I	$C_{41}H_{35}Cl_2N_5 \cdot 3HCl \cdot 4H_2O$ (c)	57.92	58.22	5.45	5.69	8.24	8.18	<200 (4)
5	3	4	H	H	250	87	EtOH-HCl	I	$C_{41}H_{37}N_5 \cdot 3HCl \cdot 4H_2O$ (d,e)	63.03	62.83	6.19	6.13	8.97	8.90	<200 (4)
6	3	3	H	CH_3	200	76	*i*-PrOH-H_2O	I	$C_{41}H_{37}N_5 \cdot 3HCl \cdot 3.5H_2O$	63.77	63.53	6.14	6.40	9.07	9.07	2 (3)
7	3	3	H	C_2H_5	240	46	MeOH	II	$C_{42}H_{39}N_5 \cdot 3HCl \cdot 2.5H_2O$ (f,g)	65.66	65.51	6.17	6.13	9.12	9.22	<200 (4)
8	3	6	H	H	105	94	EtOAc-Me_2CO	I	$C_{43}H_{41}N_5 \cdot 3HCl \cdot 3H_2O$	65.27	65.50	6.37	6.65	8.85	8.38	<200 (4)
9	3	3	H	$(CH_2)_2N(C_2H_5)_2$	185-187	66	MeOH-Me_2CO	I	$C_{46}H_{48}N_6 \cdot 4HCL \cdot 4.5H_2O$	60.59	60.58	6.74	6.98	9.22	9.20	<200 (4)

(a) Compounds are yellow or chartreuse. (b) Calcd. for H_2O: 7.58. Found: 7.42. (c) Calcd. for Cl^-: 12.51. Found: 12.70. (d) Calcd. for Cl^-: 13.62. Found: 13.62. (e) Calcd. for H_2O: 9.22. Found: 8.90. (f) Base from benzene-petroleum ether, m.p. 60° dec. *Anal.* Calcd. for $C_{42}H_{39}N_5$: C, 82.18; H, 6.40; N, 11.41. Found: C, 82.18; H, 6.41; N, 11.55. (g) Calcd. for Cl^-: 13.85. Found: 13.95 (h) Definition of test codes against *Entamoeba histolytica in vitro:* (1) University of Chicago (UC) strain of *E. histolytica* with mixed bacterial associates cultured in an essentially protein-free infusion of egg yolk containing 0.5% liver extract, activity measured after 24 hours and titrated to an approximate endpoint using 2-fold dilutions; (2) test corresponds to test 1, except that the overlay from diphasic whole egg medium is used instead of the infusion of egg yolk; (3) U. C. strain of *E. histolytica* with mixed bacterial associates grown in diphasic whole egg-Locke's solution medium utilizing a smaller amebic inoculum and a 48 hour test period; (4) same as test 3 except that endpoints below 200 μg./ml. were not determined; (5) same as test 3 except that endpoints below 20 μg./ml. were not determined; (6) the 200T strain of *E. histolytica* was used in a liver-serum medium, activity was measured after 48 hours.

TABLE II

7,7′-(Alkylene- and Phenylenediimino)bis[benz[c]acridines] (a,b)



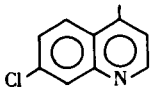
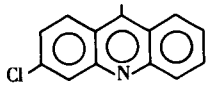
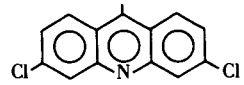
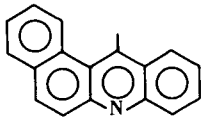
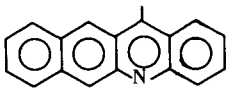
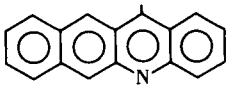
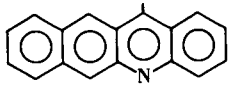
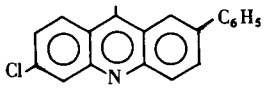
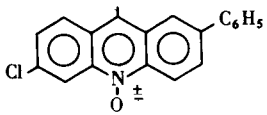
Compd. No.	-Y-	M.P. °C	Yield purified, %	Purification solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Amebicidal concentration *in vitro* (μg./ml.) (e)
10	$-(CH_2)_3-$	>300	68	MeOH	$C_{37}H_{28}N_4 \cdot 2HCl \cdot 1.7H_2O$	70.29	70.30	5.32	5.17	8.86	8.86	10 (2)
11	$-(CH_2)_5-$	210	78	MeOH	$C_{39}H_{32}N_4 \cdot 2HCl \cdot 2.5H_2O$	69.43	69.43	5.83	5.94	8.31	8.35	17 (2)
12	$-(CH_2)_6-$	219	46	MeOH	$C_{40}H_{34}N_4 \cdot 2HCl \cdot 1.1H_2O$	72.41	72.30	5.80	6.33	8.45	8.70	17 (2)
13		>300	21	MeOH-Me_2CO	$C_{42}H_{36}N_4 \cdot 2HCl \cdot 0.5H_2O$ (c)	74.32	74.15	5.79	5.95	8.26	8.39	< 200 (4)
14	$-(CH_2)_8-$	277-280	62	MeOH	$C_{42}H_{38}N_4 \cdot 2HCl \cdot 0.9H_2O$	73.33	73.30	6.12	6.24	8.15	8.20	40 (2)
15	$-(CH_2)_3O(CH_2)_2O(CH_2)_3-$	235-240	73	DMAc	$C_{42}H_{38}N_4O_2 \cdot 2HCl \cdot H_2O$ (d)	69.89	69.50	5.87	5.92	7.76	8.12	1 (3)
16	$-(CH_2)_{10}-$	260-265	68	EtOH	$C_{44}H_{42}N_4 \cdot 2HCl \cdot 1.6H_2O$	72.53	72.51	6.53	6.82	7.69	7.66	40 (2)
17 (IXa)		>300	77	MeOH	$C_{46}H_{30}N_4 \cdot 2HCl \cdot 2.1H_2O$	73.71	73.74	4.87	5.10	7.48	7.54	> 2000 (2)
18 (IXb)		270-273	97	MeOH	$C_{46}H_{30}N_4O_2S \cdot 2HCl \cdot 1.1H_2O$	69.45	69.43	4.33	4.17	7.04	7.14	> 2000 (2)
19 (IXc)		250	76	MeOH	$C_{47}H_{32}N_4 \cdot 2HCl \cdot 2.9H_2O$	72.56	72.51	5.16	5.67	7.20	7.42	> 2000 (2)

(a) The compounds are yellow. (b) Prepared by procedure I. (c) Calcd. for H_2O: 1.33. Found: 1.41. (d) Calcd. for Cl^-: 9.82. Found: 9.89. (e) See footnote h, Table I.

TABLE III

[Iminobis(alkyleneimino)]bis[acridines, Benz[*a*]acridines, Benz[*b*]acridines, and Quinolines]

$$\text{Het-NH(CH}_2\text{)}_x\text{NR(CH}_2\text{)}_y\text{NH-Het}$$

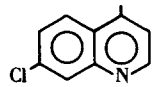
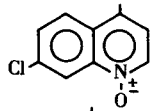
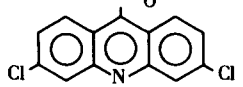
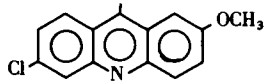
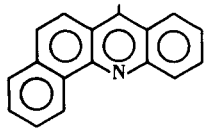
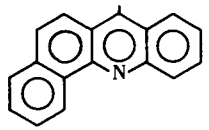
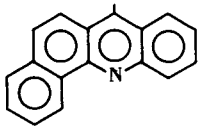
Compd. No.	x	y	R	Het	M.P. °C	Color	Yield purified, %	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Amebicidal concentration *in vitro* (μg./ml.) (e)
20 (X)	3	3	CH_3		130	White	29	MeOH-EtOAc	II	$C_{25}H_{27}Cl_2N_5$	64.10	63.81	5.81	6.00	14.95	14.70	< 200 (4)
21 (XIa)	3	3	CH_3		215 dec.	Yellow	90	EtOH-Me_2CO	II	$C_{33}H_{31}Cl_2N_5 \cdot 3HCl \cdot 4.5H_2O$ (a)	52.22	52.04	5.71	5.67	9.23	9.25	33 (5)
22 (XIb)	3	3	C_2H_5		294 dec.	Yellow	41	MeOH-Me_2CO	II	$C_{34}H_{31}Cl_4N_5 \cdot 3HCl$	53.67	53.77	4.50	4.78	9.21	9.38	<200 (4)
23 (XIII)	3	3	CH_3		110 dec.	Yellow	68	HCl	II	$C_{41}H_{37}N_5 \cdot 3HCl \cdot 6.5H_2O$ (b)	59.60	59.71	6.47	6.81	8.48	8.53	> 40 (5)
24 (XIVa)	3	4	H		199 dec.	Red	50	H_2O	I	$C_{41}H_{37}N_5 \cdot 3HCl \cdot 1.5H_2O$	66.89	77.00	5.89	6.18	9.51	9.69	33 (5)
25 (XIb)	3	3	CH_3		246 dec.	Red	68	EtOH	I	$C_{41}H_{37}N_5 \cdot 3HCl \cdot 3.5H_2O$	63.77	64.06	6.14	6.18	9.07	9.22	33 (5)
26 (XIVc)	3	3	C_2H_5		200 dec.	Red	85	EtOAc	I	$C_{42}H_{39}N_5 \cdot 3HCl \cdot 3H_2O$	64.90	64.92	6.22	6.27	9.01	9.22	< 20 (5)
27 (XIc)	3	3	CH_3		300 dec.	Yellow	93	EtOH	II	$C_{45}H_{39}Cl_2N_5 \cdot 3HCl \cdot 1.5H_2O$ (c)	63.05	63.32	5.29	5.40	8.17	8.18	< 20 (5)
28 (XII)	3	3	CH_3		220 dec.	Orange	41	EtOH-Me_2CO	II	$C_{45}H_{39}Cl_2N_5O_2 \cdot 3HCl \cdot 4H_2O$ (d)	57.85	57.60	5.40	5.87	7.50	7.77	> 20 (5)

(a) Calcd. for H_2O: 10.68. Found: 10.26. (b) Calcd. for H_2O: 14.17. Found: 13.77. (c) Calcd. for H_2O: 3.15. Found: 3.07. (d) Calcd.for H_2O: 7.71. Found: 7.27. (e) See footnote h, Table I.

TABLE IV

[Alkylenebis(iminoalkyleneimino)]bis[acridines, Benz[*c*]acridines, and Quinolines]

$$\text{Het-NH(CH}_2\text{)}_x\text{NRYNR(CH}_2\text{)}_x\text{NH-Het}$$

Compd. No.	x	NRYNR	Het	M.P. °C	Color	Yield, % purified,	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Amebicidal concentration *in vitro* (μg./ml.) (a)
29 (XVI)	2	-NH(CH$_2$)$_2$NH-		178-180	Colorless	25	EtOH	II	$C_{24}H_{26}Cl_2N_6 \cdot 1.25H_2O$	58.59	58.56	5.84	5.91	17.09	17.14	36 (2)
30 (XVII)	3			225 dec.	Yellow	7	*i*-PrOH	II	$C_{28}H_{32}Cl_2N_6O_2 \cdot 2H_2O$	56.85	56.60	6.13	6.11	14.21	14.24	>40 (6)
31 (XVIIIa)	2	-NH(CH$_2$)$_2$NH-		309 dec.	Yellow	18	EtOH	II	$C_{32}H_{28}Cl_4N_6 \cdot 4HCl$	49.00	49.12	4.11	4.23	10.72	10.60	27 (3)
32 (XVIIIb)	2	-NH(CH$_2$)$_2$NH-		250 dec.	Yellow	94	H$_2$O-*i*-PrOH	I	$C_{34}H_{34}Cl_2N_6O_2 \cdot 4HCl \cdot 2H_2O$	50.32	50.60	5.22	5.38	10.36	10.30	<200 (4)
33 (XIXa)	2	-NH(CH$_2$)$_2$NH-		240 dec.	Yellow	90	H$_2$O-*i*-PrOH	I	$C_{40}H_{36}N_6 \cdot 4HCl \cdot 4.25H_2O$	58.36	58.48	5.94	5.86	10.21	10.39	83 (1)
34 (XIXb)	2	-NH(CH$_2$)$_2$NH(CH$_2$)$_2$NH-		230 dec.	Yellow	86	H$_2$O-*i*-PrOH	I	$C_{42}H_{41}N_7 \cdot 5HCl \cdot 5H_2O$	55.06	54.89	6.16	6.08	10.70	10.39	67 (1)
35 (XIXc)	3			200 dec.	Chartreuse	66	H$_2$O-*i*-PrOH	I	$C_{44}H_{42}N_6 \cdot 4HCl \cdot 4.5H_2O$	59.93	59.81	6.29	6.28	9.53	9.32	2 (3)

(a) See footnote h, Table I.

b) (18, 94%), and 7,7′-[ethylenebis(iminoethyleneimino)]-bis[benz[c]acridine] (XIXa) (90%). Similarly, 4,4′-[1,4-piperazinediylbis(trimethyleneimino)]bis[7-chloroquinoline] 1,1′-dioxide (XVII) and 7,7′-[1,4-piperazinediylbis(ethyleneimino)]bis[benz[c]acridine] (XIXc) were obtained from 1,4-bis(3-aminopropyl)piperazine, 4,7-dichloroquinoline 1-oxide (23), and 7-chlorobenz[c]acridine (3) in 7 and 66% yield, respectively. The reaction of 7-chlorobenz[c]acridine and tetraethylenepentamine yielded the pentaza system 7,7′-[iminobis(ethyleneiminoethyleneimino)]bis[benz[c]acridine] (XIXb) (86%).

A majority of the polyamines utilized in this investigation are available commercially. The others, namely *N*-(2-aminoethyl)-1,3-propanediamine (24), *N*-(3-aminopropyl)-1,4-butanediamine (24), *N*-(3-aminopropyl)-1,6-hexanediamine (24), and 3,3′-diamino-*N*-[2-(diethylamino)ethyl]-dipropylamine, were obtained by cyanoethylation of the appropriate diamine followed by catalytic hydrogenation of the aminopropionitrile precursors utilizing Raney cobalt.

The bis(aminoheterocyclic) compounds described in the present communication were tested against *Entamoeba histolytica in vitro* (6) and against symptomatic intestinal amebiasis in rats (6) by Dr. Paul R. Thompson and co-workers of these laboratories; when indicated, expanded studies with selected compounds were carried out against amebic colitis in dogs and amebic hepatitis in hamsters (6). Antiamebic activity *in vitro* (Tables I-IV) and in rats is widespread among the bis(aminoheterocyclic) compounds of structure VI-VIII and X-XIX, although the 7,7′-(phenylenediimino)bis[benz[c]acridines] (IXa-c) and 9,9′-(1,4-piperazinediyl)bis[6-chloro-2-methoxyacridine] (XV) were inactive.

In vitro amebicidal endpoints for several compounds were not determined because they showed sufficient promise in preliminary *in vitro* tests to merit trial in rats. However, nine compounds (**6**, **10-12**, **15**, VI, XIc, XIVc, and XIXc) were amebicidal at concentrations of 1-20 μg./ml., and seven (**14**, **16**, XIa and b, XIVa, XVI, and XVIIIa) were cidal at 20-40 μg./ml.

Twenty two compounds (**1-9**, **11**, **12**, **14**, X, XIa-c, XIVa and c, XVI, and XIXa-c) were active against intestinal amebiasis in rats (6), and caused > 50% suppression of the average degree of infection and cured > 50% of infected rats when administered in the diet for 7 days at doses ranging from 12 to 1094 mg./kg./day. Four compounds (**5**, **6**, **7**, **9**) were effective in rats at doses ranging from 12 to 42 mg./kg. daily, and thus showed activity comparable with or superior to 7-[[[3-(octylamino)propyl]amino]benz-[c]acridine (IV) (4,6). Against amebic dysentery in dogs (6), compounds **6** and **7** cured or strongly suppressed infections at oral doses of 10-20 mg./kg. daily for 10 days, while compounds **5**, VI, and XIXa were effective at 40 mg./kg. 7,7′-[Ethyliminobis(trimethyleneimino)bis[benz-[c]acridine] (7) was approximately eight times as active as chloroquine against hepatic amebiasis in hamsters (6).

EXPERIMENTAL (25)

7,7′-[Iminobis(alkyleneimino)]bis[benz[c]acridines] (VI, VII) (Table I), 7,7′-(Alkylene- and phenylenediimino)bis[benz[c]-acridines] (VIII and IXa-c) (Table II), [Iminobis(alkyleneimino)]-bis[acridines, benz[*a*]acridines, benz[*b*]acridines, and quinolines] (X, XIa-c, XII, XIII, XIVa-c) (Table III), and [alkylenebis(imino-alkyleneimino)]bis[acridines, benz[*c*]acridines, and quinolines] (XVI, XVII, XVIIIa and b, and XIXa-c) (Table IV). Procedure I.

A mixture of 20.0 g. (0.076 mole) of 7-chlorobenz[c]acridine (3), 5.5 g. (0.038 mole) of 3,3′-diamino-*N*-methyldipropylamine, and 80 g. of phenol was stirred and heated on a steam bath for 2 hours. Upon cooling, the mixture was poured slowly with vigorous stirring into a solution of 15 ml. of concentrated hydrochloric acid in 500 ml. of acetone. The mixture was refrigerated for 2 hours, and the yellow solid was collected by filtration and washed thoroughly with acetone. The precipitate was ground up under acetone, collected, washed again with acetone, and dried *in vacuo*. The crude product (30.2 g.) was then suspended in 500 ml. of hot 2-propanol, hot water (500-600 ml.) was added until solution occurred, the solution was filtered, and the filtrate was treated with additional hot 2-propanol until the product began to crystallize. The mixture was cooled, and the bright yellow product (6) was collected, washed with 2-propanol, and dried *in vacuo* at 78° for 6 hours, yield, 22.2 g. (76%), m.p. 200° dec.

Procedure II.

7-Chlorobenz[c]acridine (3) (185.0 g., 0.7 mole), 3,3′-diamino-*N*-ethyldipropylamine (55.7 g., 0.35 mole), and 250 g. of phenol were stirred and heated on a steam bath for 3 hours, and the reaction mixture was poured into a beaker and made strongly acidic with concentrated hydrochloric acid. The mixture was diluted with acetone, and the crude yellow product was collected by filtration, washed with acetone, and dried. The crude hydrochloride (273 g.) was stirred with 1 l. of boiling ethanol, the mixture was cooled, and the product was collected, washed with acetone, and dried. The salt was dissolved in boiling water, the solution was filtered, and the filtrate was made strongly alkaline with ammonium hydroxide. The base was extracted with chloroform, and the combined chloroform extracts were washed successively with aqueous sodium hydroxide and two portions of water. The chloroform was removed *in vacuo*, an excess of ethanolic hydrogen chloride was added, and the mixture was diluted with acetone. The product was digested with hot methanol containing concentrated hydrochloric acid, collected, washed with acetone, and dried *in vacuo* at room temperature for 24 hours. Compound **7** was thus obtained as a bright yellow solid (124 g., 46%), m.p. 240° dec.

9,9′-(1,4-Piperazinediyl)bis[6-chloro-2-methoxyacridine] (XV).

6,9-Dichloro-2-methoxyacridine (80 g., 0.288 mole) and anhydrous piperazine (100 g., 1.16 moles) were allowed to react in phenol (160 g.) and the reaction mixture was processed according to procedure II. The only product isolated in pure form was 9,9′-(1,4-piperazinediyl)bis[6-chloro-2-methoxyacridine], yellow crystals from ethanol, m.p. 290° dec.; 7.2 g. (9%).

Anal. Calcd. for $C_{32}H_{26}Cl_2N_4O_2$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.20; H, 4.76; N, 9.90.

3,3′-[[2-(Diethylamino)ethyl]imino]dipropionitrile.

Acrylonitrile (425 g., 8 moles) was added slowly with stirring to 349 g. (3 moles) of *N,N*-diethylethylenediamine. The temperature rose to 40° during the addition. The reaction mixture was heated on a steam bath for 96 hours and concentrated *in vacuo* using a water aspirator. The residue was distilled under high vacuum to give 213 g. (32%) of the dinitrile, b.p. 162-165° (0.8 mm.); n_D^{23} 1.4648.

Anal. Calcd. for $C_{12}H_{22}N_4$: C, 64.82; H, 9.98; N, 25.20. Found: C, 64.71; H, 10.42; N, 25.48.

3,3′-Diamino-N-[2-(diethylamino)ethyl]dipropylamine.

3,3′-[[2-(Diethylamino)ethyl]imino]dipropionitrile (213 g., 0.96 mole) was hydrogenated at 100° and 1700 p.s.i.g. in a mixture of cyclohexane and triethylamine utilizing Raney cobalt as catalyst. The catalyst was removed by filtration and low boiling materials were removed *in vacuo* on a water aspirator. The residue was distilled under high vacuum to give 145 g. (66%) of the tetramine, b.p. 93-94° (0.08 mm); n_D^{25} 1.4760.

Anal. Calcd. for $C_{12}H_{30}N_4$: C, 62.55; H, 13.13; N, 24.32. Found: C, 62.56; H, 13.26; N, 24.45.

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