with Tween 80 and administered at either 50, 30, 10, or 3 mg/kg po, unless otherwise indicated. Animals were dosed every day. Four animals were used in the preliminary screen, while four to eight animals per dose were used in the dose–response screen.

Renal hypertension was produced by a modification of the method of Grollman.[15,16] Briefly, male Sprague–Dawley rats were anesthetized with pentobarbital sodium (50 mg/kg ip), and the right kidney was removed through a right subcostal incision. The left kidney was exposed through an incision in the left flank. Silk sutures (size 00) were passed around both poles of the kidney and tightened to produce a visible constriction of the renal parenchyma. Animals were returned to their cages and given food and water ad libitum. After 3 weeks of stabilization, systolic blood pressures were determined as above, and rats with blood pressures >150 mmHg were selected for use in evaluating drugs.

Standard Cardiovascular Challenges in Anesthetized Dogs. Beagle dogs of either sex were anesthetized with barbital sodium (200 mg/kg iv), thiopental sodium (15 mg/kg iv), and pentobarbital sodium (60 mg iv). The trachea was intubated, and the animals were artificially respired with a Harvard apparatus respirator. A femoral artery and vein were cannulated with PE tubing for measurement of blood pressure and intravenous administration of drugs, respectively. Bilateral vagotomies were performed, and blood pressure and heart rate were continuously displayed on a Beckman R 511 recorder. The effects of various challenge drugs on the blood pressure and heart rate were determined; test drug was administered, and responses to the challenge drugs were again obtained. Each challenge drug was intravenously administered twice predrug to obtain matched responses and once postdrug. Challenge drugs and doses were as follows: epinephrine and norepinephrine, 0.5 to 1.0 μg/kg; isoproterenol and carbachol, 0.25 μg/kg; tyramine, 100 μg/kg. Adjustments were made in test doses to compensate for animal to animal variation. The effect of the test drug on the responses to the challenge drugs was noted, and results were expressed as change from predrug control responses.

Hypotensive Activity in the Sinoaortic-Deafferented Dogs. Adult dogs of either sex were anesthetized with barbital sodium (200 mg/kg iv), thiopental sodium (15 mg/kg iv), and pentobarbital sodium (60 mg iv). A femoral vein and artery were cannulated with PE tubing for intravenous administration of drugs and to record blood pressure and heart rate, respectively. Left ventricular pressure was recorded from a catheter inserted into the left ventricle via the left common carotid artery (postdeafferentation), and the first derivative, dP/dt, was derived from it. Cardiac output was determined by thermodilution technique using ice-cold 5% dextrose in water injected into a Swan–Ganz catheter inserted into the right side of the heart with the tip placed in the pulmonary artery.

Deafferentation was accomplished by clearing both of the carotid arteries up to the internal and external carotid artery bifurcation. The carotid sinus nerves were isolated, ligated, and sectioned, and a bilateral vagotomy was performed to produce neurogenic hypertension (mean arterial pressure >150 mmHg). Dogs were allowed to stabilize for approximately 30 min, and then a bolus intravenous injection of the test compound was administered. Heart rate, arterial pressure, left ventricular pressure, dP/dt, and cardiac output were monitored for 90 min postdose.

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Registry No. 1, 63880-21-7; **2**, 79227-66-0; **3**·HCl, 79227-46-6; *cis*-**4**, 82830-95-3; *cis*-**4** oxalate, 82830-96-4; *trans*-**4**, 82831-05-8; *trans*-**4** oxalate, 82831-06-9; **5**, 79227-49-9; **5**·HCl, 79227-48-8; *cis*-**6**, 82831-04-7; *trans*-**6**, 82831-03-6; **7**, 79227-53-5; *cis*-**8**, 86632-59-9; *cis*-**8** maleate, 86632-60-2; *trans*-**8**, 86632-61-3; *trans*-**8** maleate, 86632-62-4; **9**, 79227-51-3; **9** oxalate, 79227-52-4; **10**, 82830-99-7; **11**, 82830-97-5; **11** oxalate, 82830-98-6; **12a**, 79227-71-7; **12a** oxalate, 79227-72-8; **12a** ($R^1 = COCH_3$), 79227-73-9; **12b**, 79227-75-1; **12b** ($R^1 = CH_2CO_2Et$), 79227-76-2; **12c**, 79227-63-7; **12c** oxalate, 79227-64-8; **12c** ($R^1 = COCH_2CH_3$), 79227-65-9; **12d**, 79227-58-0; **12d** 2-oxalate, 79227-59-1; **12e**, 79227-61-5; **12e** oxalate, 79227-62-6; **12e** ($R^1 = COCH_2C_6H_5$), 79227-60-4; **12f**, 79227-56-8; **12f** oxalate, 79227-57-9; **13**, 79227-55-7; **13** (R^1 = CN), 79227-54-6; 2-fluorobenzylamine, 89-99-6; 2,5-dimethoxytetrahydrofuran, 696-59-3; 1-methyl-4-piperidone, 1445-73-4; 1-benzyl-3-pyrrolidinone, 775-16-6; ethyl chloroformate, 541-41-3; 2-(diethylamino)ethyl chloride, 100-35-6; ethyl bromoacetate, 105-36-2; cyanogen bromide, 506-68-3; hydroxylamine, 7803-49-8.

9-Acridinyl and 2-Methoxy-6-chloro-9-acridinyl Derivatives of Aliphatic Di-, Tri-, and Tetraamines. Chemistry, Cytostatic Activity, and Schistosomicidal Activity

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9-acridinyl derivatives of 1,6-hexanediamine, 1,8-octanediamine, bis(3-aminopropyl)amine, *N,N'*-bis(3-aminopropyl)piperazine, and *N*-ethyl-1,6-hexanediamine in the form of their hydrochlorides were prepared in high yields and converted into potential hetero bis DNA intercalating diacridines. The corresponding potential homo bis DNA intercalating reagents were prepared by heating the above amines with 9-chloroacridines. The chemical stability of the acridines was examined. Their cytostatic activity against Cloudman melanoma cells, in vitro, has been determined. The strongest cytostatic activity was observed for the acridine derivatives of the tri- and tetraamines. The schistosomicidal activity of selected acridine and diacridine derivatives against *Schistosoma mansoni* in mice was found to be insignificant. The *S. mansoni* egg development was apparently suppressed by this treatment.

In the design of biomolecular tools and drugs, it is important to obtain high target specificity. The target could either be an entire organ, a type of tissue, or it could be molecular. Thus, compounds that could be directed not only toward DNA but even toward particular nucleotide sequences in DNA might exhibit high specific biological activity. Such compounds would be potential drugs against tumors,[1] virus,[1,2] bacteria,[3] and parasites.[4]

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§ Danish Bilharziasis Laboratory.

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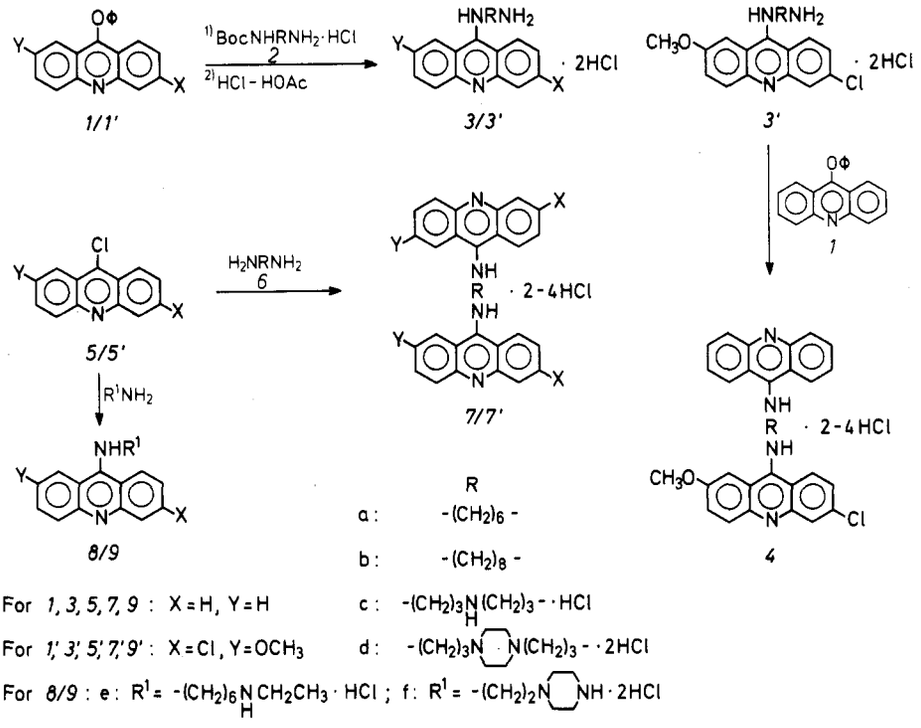
Scheme I



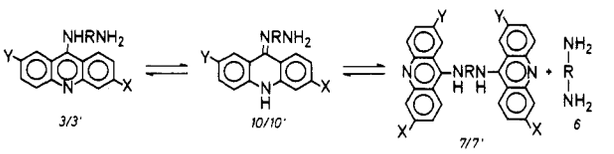
The biological activity of 9-aminoacridine derivatives has been widely demonstrated, and such compounds have a long history in the treatment of, for example, malaria[1] and bacterial infections,[3] and their potentials as antitumor drugs have been examined.[4-6]

It is generally assumed that most of the biological activity of these compounds is connected with their well-established DNA intercalation.[1-6] Their binding to DNA is dependent on a number of structural factors, particularly the substituent pattern in the acridine nucleus and the substituents on the 9-amino group.[7-9] The presence of aliphatic amino groups, which are protonated under physiological conditions, is believed to enhance the binding to DNA by electrostatic attraction to the phosphates of the DNA backbone.[7-9]

The presence of two 9-aminoacridine groups in a molecule may lead to bis intercalation, resulting in a considerable increase in the binding to DNA.[10,11] The mode of bis intercalation was shown to be dependent on the length of the linker between the intercalators and on their structures.

It was found that unsubstituted diacridines, linked via simple α,ω-alkanediamines or polyamine derivatives, bis intercalate when the length of linker corresponds to six or more methylene groups,[12,13] whereas similar bis(2-methoxy-6-chloro-9-aminoacridine)s[13,14] and unsubstituted diacridines joined via more rigid linkers[15] require longer distances between the ligands for bis intercalation.

Scheme II



The mono intercalating compounds exhibit some degree of base-pair specificity in their DNA binding,[16] and a pronounced specificity for selected sites on the DNA was found for at least one bis intercalating agent.[17] If reagents with two or more different intercalators are employed and the linkers between these are varied, it may be possible to obtain very high site specific DNA binding.

Previously, certain acridine and diacridine derivatives of α,ω-alkanediamines, bis(3-aminopropyl)amine (norspermidine), *N*-(3-aminopropyl)-1,4-butanediamine (spermidine), and *N,N'*-bis(3-aminopropyl)-1,4-butanediamine (spermine), were prepared by treatment of the amines with 9-chloro- or 9-phenoxyacridine.[13,15,18-20] The yields of the diacridines as a rule were good, whereas the

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yields of acridine derivatives of the polyamines were low (<10%).[18-20] Furthermore, it was inferred that the acridine derivatives were rather unstable.[20]

We are now able to synthesize such acridine derivatives in high yields[21] and show that they are sufficiently stable for biological testing and as synthons. Furthermore, we describe the transformation of these acridinamines to hetero diacridine derivatives of polyamines. The cytostatic properties of both acridines and diacridines toward Cloudman melanoma cells, in vitro, are presented, as well as an examination of the schistosomicidal properties of selected acridines and diacridines toward *S. mansoni*.[22,23]

Results

Chemistry. The symmetrical diacridines (**7** and **7′**) were prepared as described previously from the amines (**6**) and the 9-chloroacridines (**5** and **5′**) in phenol (Scheme I).[6,18-20] It was confirmed that the diacridines were formed almost exclusively under the experimental conditions even with a large excess of amine.[18-20] Thus, another approach was needed in order to obtain the elusive acridine derivatives (**3** and **3′**). This consisted of treating the Boc-protected amines (**2**)[24] with the appropriate 9-phenoxyacridine (**1** or **1′**) to give the Boc-protected derivatives of **3** and **3′**, which as a rule were not purified but directly deprotected to give the stable hydrochlorides of **3** and **3′** in good yields. Alternatively, 9-chloroacridines were reacted with the Boc-protected amines in Me_2SO.

It was previously found that nonprotonated acridines of type **3/3′** were unstable, i.e., underwent "dismutation" (Scheme II) to the corresponding diacridines (**7/7′**), presumably via intermediates like (**10/10′**, which can react with **3/3′** in a nucleophilic addition–elimination to form compounds **7/7′** and the amines **6**. It was presumed that such a process took place during the workup procedure.[19]

We can confirm that the free acridines (**3/3′**) are unstable in solution under basic conditions, but we did not observe any dismutation during their use as synthons. On the contrary, the acridines, in the form of their hydrochlorides, are stable in the solid form. In methanol solution and in neutral aqueous solution (Tris buffer, pH 7), they were stable at room temperature for more than 20 h. Their rate of dismutation is appreciably dependent upon structure. Thus, compound **3a** in methanol/triethylamine (9:1), at room temperature, gave substantial amounts of the corresponding diacridine, **7a**, within 2 h, at which time the equilibrium appeared to have been reached. Compound **3′a** reached its equilibrium somewhat slower, whereas **3d** showed very little dismutation under similar conditions within 48 h. The dismutation of **3a** and **3′a** in Me_2SO-d_6, in the presence of triethylamine, was examined by ^1H NMR spectroscopy. The aromatic protons of the diacridines, as compared to those of the acridines, are shifted toward higher field, presumably due to intramolecular stacking of the acridine moieties in the former.[25] Based on this, the relative concentrations of the acridines and the corresponding diacridines can be determined. As seen from Figures 1 and 2, the dismutation of **3a** was faster ($\tau_{1/2} \approx 1$ h) than that of **3′a** ($\tau_{1/2} \approx 14$ h), and the equilibrium was shifted more toward the diacridine for **3a** ⇄ **7a** than for **3a′** ⇄ **7′a**. It was also observed (Figure 2) that the addition of benzene-d_6 increased both the dismutation rate and the equilibrium constant for the reaction **3a** ⇄ **7a**.

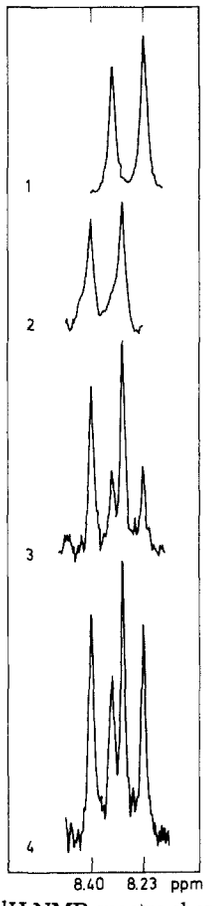

Figure 1. Details of ^1H NMR spectra showing the acridine H(1) protons[18] of (1) **7′a**.2HCl dissolved in Me_2SO-d_6 containing ~4 equiv of Et_3N, (2) **3′a**.2HCl dissolved in Me_2SO-d_6 containing ~4 equiv of Et_3N at 0 h, (3) at 25 h, and (4) at 120 h after mixing. The concentration of the compounds was ca. 1.5×10^{-2} M (**7′a**) and 3×10^{-2} M (**3′a**).

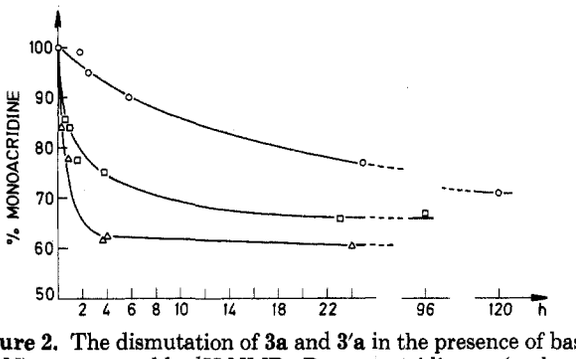

Figure 2. The dismutation of **3a** and **3′a** in the presence of base (Et_3N) as measured by ^1H NMR. Percent acridine, = (moles of acridine)/(moles of acridine + moles of diacridine), was calculated from the ^1H NMR signals of the acridine H_1 and H_8 protons of **3a** and the acridine H_8 protons of **3′a**: (○) **3′a** in Me_2SO-d_6; (□) **3a** in Me_2SO-d_6; (△) **3a** in Me_2SO-d_6/benzene-d_6 (2:1, v/v).

From these preliminary results, it is inferred that both the rate and the equilibrium constant reflect the tendency of the diacridines to undergo intramolecular stacking, which is expected to be higher for nonsubstituted acridines, where it is easier to obtain the correct orientation for dismutation, as well as for stacking. Similarly, compound **3d** with its less flexible side chain would be expected to

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Table I. Physical and Cytostatic Data for the Prepared Acridines and Diacridines

compd	yield, %	mp,[a] °C	formula[b]	growth[c] at the following concn's 0.1 μM	0.5 μM	1.0 μM
3a	64	>260 dec	$C_{19}H_{22}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	nd		95
3d	78	226-230 dec	$C_{23}H_{31}N_5 \cdot 4HCl \cdot 3H_2O$	39		3
3'a	96	>230 dec	$C_{20}H_{24}N_3OCl \cdot 2HCl \cdot {}^1/_2H_2O$	105		105
3'b	81	243-246 dec	$C_{22}H_{28}N_3OCl \cdot 2HCl \cdot 1{}^1/_2H_2O$	nd		86
3'c	74	>160 dec	$C_{20}H_{25}N_4OCl \cdot 3HCl \cdot 1{}^1/_2H_2O$	nd		28
3'd	94	>235 dec	$C_{24}H_{32}N_5O_2Cl \cdot 4HCl \cdot 3H_2O$	nd		78
4a	95	230-237 dec	$C_{33}H_{31}N_4OCl \cdot 2HCl \cdot 1{}^1/_4H_2O$	nd		49
4b	90	>204 dec	$C_{35}H_{35}N_4OCl \cdot 2HCl \cdot H_2O$	nd		44
4c	92	>250 dec	$C_{33}H_{32}N_5OCl \cdot 3HCl \cdot H_2O$	66		3
4d	93	>205 dec	$C_{37}H_{39}N_6OCl \cdot 4HCl \cdot 4{}^1/_4H_2O$	50		20
7a	82	165-170 dec	$C_{32}H_{30}N_4 \cdot 2HCl \cdot 2H_2O$	nd		39
7c	55	>230 dec	$C_{32}H_{31}N_5 \cdot 3HCl \cdot 2{}^1/_2H_2O$	103		31
7d	98	>285 dec	$C_{36}H_{38}N_6 \cdot 4HCl \cdot 2H_2O$	24		2
7'a	89	>260 dec	$C_{34}H_{32}N_4O_2Cl_2 \cdot 2HCl \cdot H_2O$	nd		83
7'c	70	>208 dec	$C_{34}H_{33}N_5O_2Cl_2 \cdot 3HCl \cdot 4H_2O$	85	16	0
7'd	65	208-225 dec	$C_{38}H_{40}N_6O_2Cl_2 \cdot 4HCl \cdot 3H_2O$	nd		43
9e	60	214-215 dec	$C_{21}H_{27}N_3 \cdot 2HCl \cdot {}^1/_3H_2O$	102		7
9f	92	>260 dec	$C_{19}H_{22}N_4 \cdot 2HCl \cdot 1{}^1/_2H_2O$	nd		30

[a] Melting points of the hydrochlorides. [b] The elementary analyses for C, H, N, and Cl were within ±0.4% of the calculated values for the formula provided, except in the following cases. For 3a, Cl calcd, 19.84; found, 19.35. For 3'b, Cl calcd, 21.89; found, 22.60. For 4b, Cl calcd, 16.27; found, 15.85. For 4c, Cl calcd, 20.93; found, 21.90. For 4d, Cl calcd, 21.06; found, 21.70. For 9e, Cl calcd, 17.80; found, 17.02. [c] The concentration of drug in the medium was 0.1, 0.5, or 1.0 μM. Values are number of cells as percentage of control; nd = not determined.

undergo such a bimolecular reaction with a slower rate than those with a flexible linker, due to steric constraints. This was further substantiated by UV spectroscopic measurements, which showed that the hypochromism (percent H) of **7a** was 19%, whereas that of **7'a** was 6%. Compound **7d** showed no hypochromism.

The dismutation of compounds **3** to **7** was reversible. This was shown by treating methanol solutions of compounds **7** with a twofold excess of the appropriate amines, at room temperature, which caused appreciable formation of the corresponding compounds **3**. Compound **7d** turned out to be the least stable under these conditions, which is in good correspondance with the dismutation experiments. As a control experiment, we treated a methanol/triethylamine solution (9:1) of **3a** with a tenfold excess of 1,6-hexanediamine. This led to no detectable dismutation within 24 h.

Biology. The inhibition of the Cloudman melanoma cells, in vitro, is shown in Table I. From this it is seen that all the acridine derivatives of 1,6-hexanediamine and 1,8-hexanediamines are inactive or even increased the cell growth slightly, whereas the closely related acridine derivative of *N*-ethyl-1,6-hexanediamine (**9e**) showed an appreciable growth inhibition. The acridine derivatives of norspermidine (**6c**) and *N,N'*-bis(3-aminopropyl)-piperazine (**6d**) showed a moderate activity (the apparently rather good activity of compounds **3d** may be due to contamination with very small amounts of **7d**). The diacridine derivatives of 1,6-hexanediamine and 1,8-hexanediamine showed a moderate activity, while those of the tri- and tetraamine showed moderate to strong activity. In the triamine derivatives (**4c**, **7c**, and **7'c**), there appears to be a dependency in the activity on the substitution pattern in the acridines. However, the results as a whole do not allow any general conclusions about the influence of the substitution pattern in the acridine nucleus.

The schistosomicidal activity of selected compounds against *S. mansoni* in mice was tested with doses of 75, 150, and 3 × 100 mg/kg. None of the tested compounds showed a reduction in the number of schistosomes. However, in several cases the egg development of the schistosomes was severely impaired, and the presently described compounds, as well as various other derivatives, are under further scrutiny as antischistosomal drugs.

All of the new compounds are being subjected to a detailed biophysical examination. So far we have found that all of the examined acridines are strongly bound to DNA, and viscosimetric measurements with linear DNA indicate that they are intercalating. Several of the diacridines appear to be bis intercalating.[26]

Experimental Section

In Vitro Cytotoxicity. An established line of Cloudman melanoma S91 was provided by the EG&G Mason Research Institute, DCT Tumor Bank, MA. The doubling time for S91 control cultures was 36 h during the experimental period.

In order to test the compounds for cytostatic activity, 4-mL volumes of media containing 0.1 × 10^6 Cloudman melanoma cells were seeded into T25 culture flasks (Nunc), incubated for 72 h at 37 °C in Hams medium F 10, containing 15% horse serum and 2.5% fetal bovine serum, and supplemented with glutamine (8 mM), penicillin (25 IU/mL), and streptomycin (25 μg/mL). Control cultures were harvested by trypsinization (0.25% trypsin in phosphate-buffered saline without magnesium and calcium, pH 7.8) for 1 min and counted visually. The medium was discarded and replaced with medium containing the compounds to be tested at final concentrations of 1 and 0.1 μM. Dimethyl sulfoxide at a final concentration of 0.1% was present in the media of the test, as well as of the control, culture. After 72 h of further cultivation, cells were harvested by trypsinization and counted. The control culture and the test culture were in triplicate.

Schistosomicidal Activity. *Schistosoma mansoni* from Puerto Rico were maintained under laboratory conditions as described by Frandsen.[27] Cercariae, 120, were exposed to each mouse, and 6 weeks later, the mice were treated with the chosen substance. The compounds were dissolved or suspended in water, at a concentration of about 5 or 9 mg/mL, given orally with a stomach tube. Five to eight mice were used in each experimental group. One week later, the effect of the substance was evaluated by counting the number of living schistosomes, isolated from the mice via normal perfusion.[27] Schistosome-infected, but untreated, mice functioned as a control group. Alternatively, treatment was repeated for 3 days, resulting in a total dose of approximately 3 × 100 mg/kg. One week after the first treatment, the living schistosomes were isolated and counted as described above.

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(27) F. Frandsen, *Acta Pharmacol. Toxicol.*, **49** (Suppl. V), 118 (1981).

Chemistry. Elemental analyses were performed by Preben Hansen, The H. C. Ørsted Institute, Copenhagen. All the compounds reported in Table I had analytical data of C, H, N, and Cl within ±0.4% of the calculated values, unless otherwise specified. Melting points, which are uncorrected, were obtained with a Büchi melting point apparatus. Thin-layer chromatography (TLC) was performed on premade plates (Merck) with a mixture of ethanol/acetone/triethylamine (1:1:0.05) as eluent. NMR spectra were recorded on a JEOL FX90Q spectrometer. Chemical shifts are given in δ units (parts per million) with Me_4Si as internal standard. The NMR spectra of the compounds reported in Table I were all in agreement with the assigned structures.

The absorption spectra of compounds **3a**, **3'a**, **7a**, and **7'a** in water at ambient temperature were recorded on a UNICAM SP800A spectrophotometer. Percent hypochromism (% H) was calculated from the following equation: % H = $[\epsilon_3/(0.5\epsilon_7) - 1]100$.[15] The extinction coefficients were as follows: **3a**, ϵ_{410} = 11 400; **3'a**, ϵ_{420} = 8600; **3d**, ϵ_{410} = 11 300; **7a**, ϵ_{410} = 19 100; **7'a**, ϵ_{420} = 16 200; **7d**, ϵ_{410} = 22 400.

2-Methoxy-6,9-dichloroacridine (**5'**) and all the amines, except *N*-ethylhexane-1,6-diamine (**8e**), were purchased from EGA Chemie. 9-Chloroacridine (**5**),[28] 9-phenoxyacridine (**1**),[28] 2-methoxy-6-chloro-9-phenoxyacridine (**1'**),[28] *N*-ethyl-1,6-hexanediamine (**8e**),[29] and the Boc-protected polyamines (**2a–c**), were synthesized as reported previously.[24] The diacridines **7** and **7'** and acridines **9** were prepared from the corresponding amines and 9-chloroacridine (**5**) or 2-methoxy-6,9-dichloroacridine (**5'**) in phenol, by a slightly modified procedure of that of Canellakis.[20]

For each type of compound, a representative synthetic procedure is described below.

Boc Protection. *N,N'*-Bis(3-aminopropyl)piperazine (60 g, 0.3 mol) was dissolved in Me_2SO (125 mL), and Boc-N_3 (55.5 mL of a ~3.6 M solution of Boc-N_3 in ether, 0.2 mol) was added as described previously.[24] The mixture was stirred at room temperature for 2 (**2a**·HCl; Addition of water (250 mL, pH 8–9) resulted in precipitation of crude *N,N'*-bis[3-[(*tert*-butyloxycarbonyl)amino]propyl]piperazine (17.7 g, 0.044 mol). The aqueous phase was adjusted to pH ~12–13 with NaOH and extracted continuously with ether. From the ether phase was isolated *N*-[3-[(*tert*-butyloxycarbonyl)amino]propyl]-*N'*-(3-aminopropyl)piperazine trihydrochloride (**2d**·3HCl; 44.8 g, 54.5% yield), mp 190 °C.

2-Methoxy-6-chloro-9-[(6-aminohexyl)amino]acridine Dihydrochloride (3'a·2HCl). Method A. 2-Methoxy-6,9-dichloroacridine (**5'**; 600 mg, 2.16 mmol) and 1-[(*tert*-butyloxycarbonyl)amino]-6-hexanamine hydrochloride (**2a**·HCl; 600 mg, 2.52 mmol) were stirred at room temperature for 7 days in a mixture of anhydrous potassium carbonate (1.1 g) and anhydrous magnesium sulfate (250 mg) in dimethyl sulfoxide (10 mL). The mixture was taken up in a mixture of ether (25 mL) and H_2O (50 mL). The aqueous phase was extracted with ether (3 × 50 mL). The combined ether phases were dried ($MgSO_4$) and concentrated in vacuo, and to the resulting yellow oil was added 1 M HCl in glacial acetic acid (25 mL). The mixture was stirred at room temperature for 30 min and concentrated in vacuo. Trituration with ether gave yellow crystals, which were washed with ethanol and ether to give 775 mg of **3'a**·H_2O (~80%).

Method B. 2-Methoxy-6-chloro-9-phenoxyacridine (**1'**; 600 mg, 2.16 mmol) and 1-[(*tert*-butyloxycarbonyl)amino]-6-hexanamine (**2a**·HCl; 2.16 mmol) were stirred in phenol (3 g) at 100–120 °C for 1.5 h. The mixture was cooled to room temperature, and 2-methoxy-6-chloro-9-[[6-[(*tert*-butyloxycarbonyl)amino]hexyl]-amino]acridine was precipitated by addition of ether (75 mL), giving 1.25 g (~100%).

Deprotection was achieved by treatment with 1 M HCl in AcOH, and the product was recrystallized from ethanol/ether to give **3'a**·2HCl (1.0 g, ~96% yield).

1-(9-Acridinylamino)-6-[(2-methoxy-6-chloro-9-acridinyl)amino]hexane Dihydrochloride (4a·2HCl). Compound **3'a**·2HCl (225 mg, 0.5 mmol) and 9-phenoxyacridine (165 mg, 0.61 mmol) were stirred in phenol (1.5 g) at 80–100 °C for 2.5 h, upon which the mixture was allowed to cool to room temperature, and ether (75 mL) was added to precipitate the product. This was isolated and recrystallized from ethanol and minute amounts of ether to give **4a**·2HCl (290 mg, 95%), mp 230–237 °C dec.

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Registry No. **1'**, 7478-26-4; **2a**·HCl, 65915-94-8; **2b**·HCl, 82408-99-9; **2c**·2HCl, 82409-05-0; **2d**·3HCl, 86689-01-2; **3a**·2HCl, 86689-02-3; **3'a**·2HCl, 86689-03-4; **3'b**·2HCl, 86689-04-5; **3'c**·3HCl, 86689-05-6; **3d**·4HCl, 86689-06-7; **3'd**·4HCl, 86689-07-8; **4a**·2HCl, 86536-88-1; **4b**·2HCl, 86536-89-2; **4c**·3HCl, 86536-90-5; **4d**·4HCl, 86536-91-6; **5**, 1207-69-8; **5'**, 86-38-4; **6a**, 124-09-4; **6b**, 373-44-4; **6c**, 56-18-8; **6d**, 7209-38-3; **7a**·2HCl, 35555-85-2; **7'a**·2HCl, 75340-78-2; **7c**·3HCl, 75340-74-8; **7'c**·3HCl, 86689-08-9; **7d**·4HCl, 86689-09-0; **7'd**·4HCl, 86689-10-3; **8e**, 40043-26-3; **8f**, 140-31-8; **9e**·HCl, 86689-11-4; **9f**·2HCl, 86689-12-5; *N,N'*-bis[3-[(*tert*-butyloxycarbonyl)amino]propyl]piperazine, 86689-13-6; 2-methoxy-6-chloro-9-[[6-[(*tert*-butyloxycarbonyl)amino]hexyl]amino]-acridine, 86689-14-7; 9-phenoxyacridine, 2148-14-3.

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Optical Resolution, Absolute Configuration, and Activity of the Enantiomers of Proxyphylline

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The enantiomers of proxyphylline have been separated via their corresponding camphanates. Synthesis of (+)-proxyphylline from theophylline and (*S*)-propylene oxide derived from (*S*)-lactic acid established the absolute configuration of the (+) and (−) isomer as *S* and *R*, respectively. The activity of the enantiomers as cyclic nucleotide phosphodiesterase inhibitors was tested in human lung tissue homogenate. No differences were found either between the two enantiomers or between the enantiomers and racemic proxyphylline.

The bronchodilator proxyphylline [(±)-3,7-dihydro-7-(2-hydroxypropyl)-1,3-dimethyl-1*H*-purine-2,6-dione] was patented in 1955 as a water-soluble, stable, and neutral theophylline derivative suitable for oral and parenteral administration.[1] The potency and/or efficacy of proxyphylline, which is being used in the racemic form, is reported to vary from one-eighth to one-half of that of theophylline.[2-5] The metabolism and pharmacokinetics

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