their appreciation to Dr. Paul E. Thompson, Mr. R. E. Voigtman, and Dr. M. W. Fisher of these laboratories for the antischistosome and antibacterial testing. We also thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for the physical chemistry data.

Synthetic Schistosomicides. XVIII. N-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)amides, N-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}amides, and Related Amide and Urea Derivatives[1]

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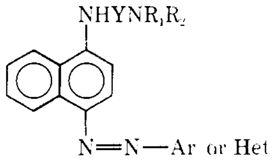
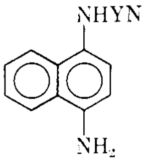
An array of *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)alkyl- and aralkylamides [VIIIa and b (**1–35**), XIa and b], *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)arylamides [VIIIc (**36–47**), Xa and b, XV], and *N*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}amides (XXIVa–e) was prepared by treating *N*-(4-amino-1-naphthyl)-*N*-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide (VI) or *N*-(4-amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-*N*-(3-piperidinopropyl)acetamide (XXIII) with the appropriate acid chloride or anhydride in pyridine, benzene, or acetic acid. Several *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)ureas, thioureas, and sulfonamides (XII, XVI–XVIII) were also prepared. Schistosomicidal activity is widespread among the amides of structure VIIIa–c, Xa and b, and XXIVe, and 15 compounds cured *Schistosoma mansoni* infections in mice at diet or gavage doses ranging from 45 to 326 mg/kg per day for 3 to 14 days. Four amides also displayed significant activity against *S. mansoni* in Rhesus monkeys. Structure–activity relationships are discussed.

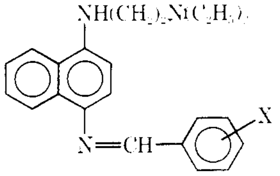
Schistosomicidal activity is rife among the *N*,*N*-dialkyl-*N*′-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (I),[2–7] *N*-[(dialkylamino)alkyl]-1,4-naphthalenediamines (II),[8] and *N*-(benzylidene and cinnamylidene)-*N*′-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (III and IV).[1] Moreover, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (Va and b) are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *M. lepraemurium in vitro* and in mice.[9,10] Unfortunately, these substances usually produce gastrointestinal side effects in experimental animals at doses only severalfold higher than therapeutically effective doses.



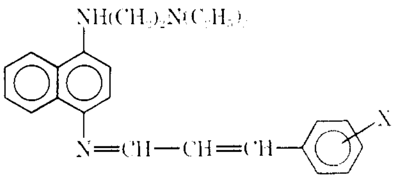
I



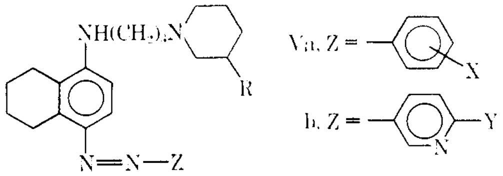
II



III



IV



In a further expatiation of previous work, various *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)alkyl- and aralkylamides, *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)benzamides, *N*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}amides, and related substances have been synthesized for antischistosomal and antimycobacterial evaluation. It was hypothesized that such compounds, like the sulfanilylanilide antimalarials,[11] might undergo slow enzymatic scission upon contact with body tissues and fluids, and thus display more favorable tolerance, ab-

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(1) For paper XVII, see E. F. Elslager, J. Battaglia, A. A. Phillips, and L. M. Werbel, *J. Med. Chem.*, **13**, 587 (1970).

(2) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *ibid.*, **6**, 217 (1963).

(3) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(4) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *ibid.*, **9**, 378 (1966).

(5) S. T. Ch'en, I. F. Ch'en, P. C. Kun, Y. C. Hu, J. H. Yao, and T. H. Chou, *Yao Hsueh Hsueh Pao*, **13**, 30 (1966).

(6) E. F. Elslager, D. B. Capps, D. H. Kurtz, and D. F. Worth, *J. Med. Chem.*, **11**, 1201 (1968).

(7) E. F. Elslager and A. A. Phillips, *ibid.*, **12**, 519 (1969).

(8) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *ibid.*, **7**, 487 (1964).

(9) L. M. Werbel, E. F. Elslager, M. W. Fisher, Z. B. Gavrilis, and A. A. Phillips, *ibid.*, **11**, 411 (1968).

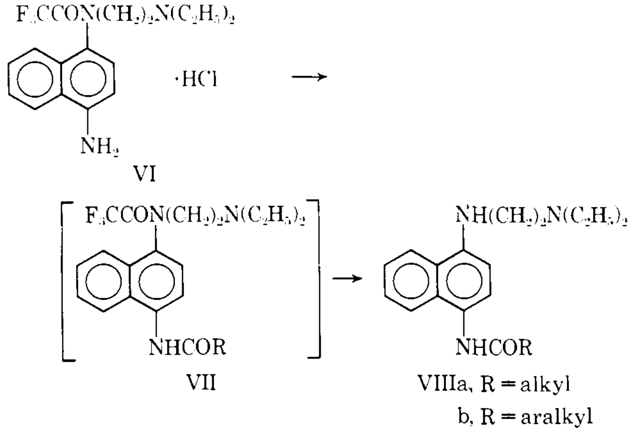
(10) Y. T. Chang, *Antimicrob. Ag. Chemother.*, 465 (1966).

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

sorption, and excretion patterns than the corresponding diamines.[8,9]

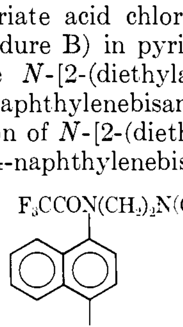
Previous work in these laboratories[1–4,6–8] showed that the diethylaminoethyl side chain among types I–IV usually conferred optimum schistosomicidal potency; therefore, initial efforts were directed toward the preparation of various *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)alkyl- and aralkylamides (**1–35**, Table I) (VIIIa and b) and *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)benzamides (**36–47**, Table II) (VIIIc). Early attempts to acylate *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine (XIV)[8] revealed that attack on both of the aromatic amine functions proceeded indiscriminately. Therefore, the direct acylation route was, for the most part, abandoned in favor of the scheme outlined in Scheme I.

SCHEME I



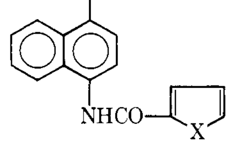
VIIIa, R = alkyl
b, R = aralkyl
c, R = aryl

Acylation of *N*-(4-amino-1-naphthyl)-*N*-[2-(diethylamino)ethyl]-2,2,2-trifluoroacetamide monohydrochloride (VI)[4,6] with the appropriate acid chloride (procedure A) or anhydride (procedure B) in pyridine or benzene gave the intermediate *N*-[2-(diethylamino)ethyl]-2,2,2-trifluoro-*N*,*N*′-1,4-naphthylenebisamides (VII) which, with the exception of *N*-[2-(diethylamino)ethyl]-2,2,2-trifluoro-*N*,*N*′-1,4-naphthylenebisacetamide (IX), were not purified but were hydrolyzed directly to give the desired *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)amides (**1–3, 6–47,** Tables I and II) in 11–74% overall yield.



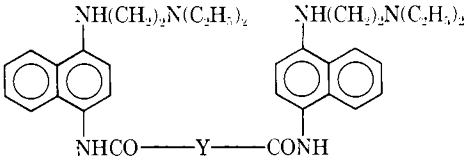
IX

The facile, selective removal of the F_3CCO protecting group was accomplished utilizing NaOH in aq EtOH.



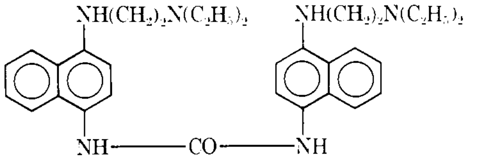
Xa, X = O
b, X = S

N-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)-2-furamide (Xa) (37%) and *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)-2-thiophenecarboxamide (Xb) (53%) were obtained in a similar manner from VI, 2-furoyl chloride, and 2-thenoyl chloride, while the condensation of 2 equiv of VI with 1 equiv of oxalyl chloride and sebacyl chloride afforded *N*,*N*′-bis(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)oxamide (XIa) (21%) and *N*,*N*′-bis(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)decanediamide (XIb) (34%) (procedure A).



XIa, Y = —
b, Y = $(CH_2)_8$

Surprisingly, attempts to prepare a diethylcarbamoyl derivative from VI and diethylcarbamoyl chloride led instead to the formation of 1,3-bis(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)urea (XII) (35%).

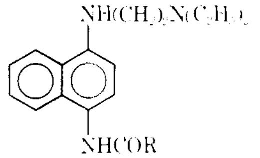


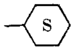
XII

Other *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)amide and urea derivatives (**4, 5,** XIII, XV–XVIII) were prepared directly from *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine (XIV)[8] (Scheme II). Treatment of XIV with benzoyl chloride in the presence of CaH_2 gave *N*-(4-amino-1-naphthyl)-*N*-[2-(diethylamino)ethyl]benzamide (XIII), a position isomer of **41,** in low yield (12%). *N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)phthalimide (XV) was obtained in 26% yield by the condensation of XIV with phthalic anhydride in HOAc, while the reaction of XIV with maleic and succinic anhydride afforded *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)maleamic acid (**4**) (76%) and *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)succinamic acid (**5**) (36%), respectively (procedure D). *N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)benzenesulfonamide monohydrochloride (XVI) (8%), 1-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)-3-phenylurea dihydrochloride (XVII) (54%), and 1-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)-3-heptyl-2-thiourea dihydrochloride (XVIII) (38%) were produced when XIV was allowed to react with benzenesulfonyl chloride, phenyl isocyanate, and heptyl isothiocyanate.

Although potent antischistosome activity is not widespread among the antimycobacterial 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines Va and b, recent studies in these laboratories showed that several compounds in the series exhibited strong activity against *S. mansoni* in mice. Among them, 5-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthylazo}resorcinol (XIX),[9]

TABLE I
N-(4-{[2-(DIETHYLAMINO)ETHYL]AMINO}-1-NAPHTHYL)ALKYL- AND ARALKYLAMIDES



No.	R	Mp, °C	Yield purified, %	Procedure	Purifn solvent	Formula[a]
1	CH_3	96–98	64	C	EtOAc	$C_{18}H_{25}N_3O$
2	CH_2CH_3	96.5–99	55	B	C_6H_6–petr ether	$C_{19}H_{27}N_3O$
3	CH_2OCH_3	84.5–85.5	32	A	Heptane	$C_{19}H_{27}N_3O_2$
4	$CH{=}CHCO_2H$	179–180 dec	76	D	C_6H_6	$C_{20}H_{25}N_3O_3 \cdot 0.5H_2O$[b]
5	$(CH_2)_2CO_2H$	181–183 dec	36	D	MeOH–Et_2O	$C_{20}H_{27}N_3O_3$
6	$(CH_2)_2CH_3$	104–105	64	A	EtOH–H_2O	$C_{20}H_{29}N_3O$
7	$CH(CH_3)_2$	110–112.5	74	B	Heptane	$C_{20}H_{29}N_3O$[c]
8	$(CH_2)_3CH_3$	100–103	69	B	Heptane	$C_{21}H_{31}N_3O$
9	$CH(CH_3)CH_2CH_3$	106–108	41	A	i-Pr_2O	$C_{21}H_{31}N_3O$
10	$C(CH_3)_3$	113.5–115.5	34	A	Heptane	$C_{21}H_{31}N_3O$
11	$(CH_2)_4CH_3$	101–103.5	71	B	Heptane	$C_{22}H_{33}N_3O$
12	$(CH_2)_2CH(CH_3)_2$	100–101	14	A	Heptane	$C_{22}H_{33}N_3O$
13		119–120.5	56	B	MeCN	$C_{23}H_{33}N_3O$
14	$(CH_2)_5CH_3$	95–98	43	B	Heptane	$C_{23}H_{35}N_3O$
15	$C(CH_3)_2CH_2CH_2CH_3$	88–89	30	A	i-Pr_2O	$C_{23}H_{35}N_3O$
16	$CH_2OC_6H_5$	111–113	11	A	EtOH–H_2O	$C_{24}H_{29}N_3O_2$
17	$(CH_2)_6CH_3$	98–100	33	A	EtOH–H_2O	$C_{24}H_{37}N_3O$
18	$CH(C_2H_5)(CH_2)_3CH_3$	109.5–113	53	A	Heptane	$C_{24}H_{37}N_3O$
19	$CH{=}CHC_6H_5$	149.5–151.5	22	A	EtOAc	$C_{25}H_{29}N_3O$
20	$(CH_2)_2C_6H_5$	87–90	31	A	i-Pr_2O	$C_{25}H_{31}N_3O$
21	$(CH_2)_7CH_3$	59–62	39	A	Heptane	$C_{25}H_{39}N_3O$
22	$CH_2CH(CH_3)CH_2C(CH_3)_3$	115–116	39	A	i-Pr_2O	$C_{25}H_{39}N_3O$[d]
23	$CH(C_6H_5)CH_2CH_3$	113–114	21	A	i-Pr_2O	$C_{26}H_{33}N_3O$
24	$(CH_2)_8CH_3$	57–61	58	B	Heptane	$C_{26}H_{41}N_3O$
25	$(CH_2)_8CH{=}CH_2$	48–51	44	A	i-Pr_2O	$C_{27}H_{41}N_3O$
26	$(CH_2)_9CH_3$	52–54	38	A	Heptane	$C_{27}H_{43}N_3O$
27	$(CH_2)_{10}CH_3$	52–54	38	B	Heptane	$C_{28}H_{45}N_3O$
28	$(CH_2)_{11}CH_3$	68–69	11	A	EtOH–H_2O	$C_{29}H_{47}N_3O$
29	$CH(C_6H_5)_2$	120–122	13	A	Heptane	$C_{30}H_{33}N_3O$
30	$(CH_2)_{12}CH_3$	55–57.5	64	A	Heptane	$C_{30}H_{49}N_3O$
31	$(CH_2)_{13}CH_3$	74–77	35	A	Heptane	$C_{31}H_{51}N_3O$
32	$(CH_2)_{14}CH_3$	70–72	49	B	Heptane	$C_{32}H_{53}N_3O$[e]
33	$(CH_2)_{15}CH_3$	80–81	46	A	Heptane	$C_{33}H_{55}N_3O$
34	$(CH_2)_{16}CH_3$	77.5–79.5	17	B	Heptane	$C_{34}H_{57}N_3O$
35	$(CH_2)_{17}CH_3$	84–85	47	A	Heptane	$C_{35}H_{59}N_3O$

[a] All compounds were analyzed for C, H, N. [b] H_2O: calcd, 2.47; found, 2.73. [c] C: calcd, 73.36; found, 72.91. [d] C: calcd, 75.52; found, 75.02. [e] C: calcd, 77.52; found, 77.09.

SCHEME II

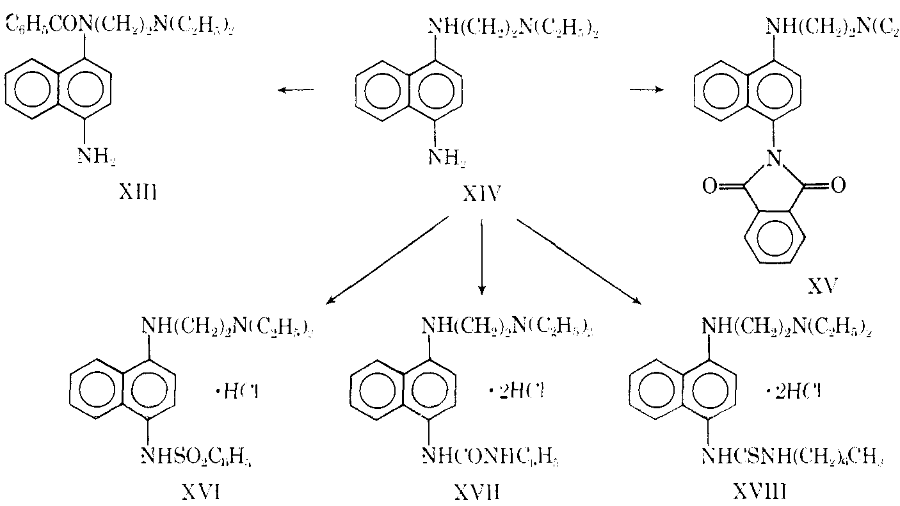
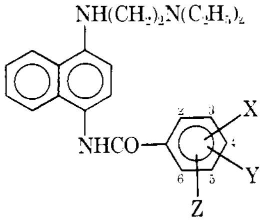


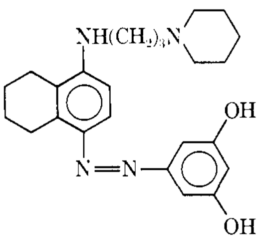
Table II

N-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)benzamides[a]

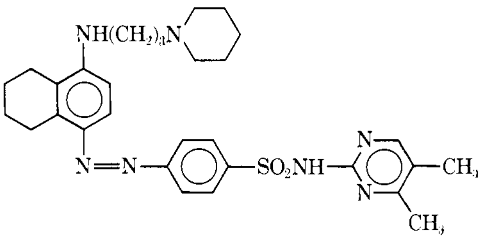


No.	X,Y,Z	Mp, °C	Yield purified, %	Purifn solvent	Formula[b]
36	3,4-Cl_2	154.5–156.5	29	$EtOH-H_2O$	$C_{23}H_{25}Cl_2N_3O$
37	3-Br	128–130	24	Heptane	$C_{23}H_{26}BrN_3O$
38	4-Br	192–194	27	MeCN	$C_{23}H_{26}BrN_3O$
39	4-Cl	177–180	30	MeCN	$C_{23}H_{26}ClN_3O$
40	4-NO_2	227–229	52	C_6H_6	$C_{23}H_{26}N_4O_3$
41	H	134–135.5	58	$EtOH-H_2O$	$C_{23}N_{27}N_3O$
42	2-CH_3	116–119	48	Heptane	$C_{24}H_{29}N_3O$
43	4-CH_3	143–145	46	C_6H_6	$C_{24}H_{29}N_3O \cdot 0.33C_6H_6$
44	4-OCH_3	160–162	65	EtOH	$C_{24}H_{29}N_3O_2$
45	3,4,5-$(OCH_3)_3$	163–164	63	i-$PrOH-H_2O$	$C_{26}H_{33}N_3O_4$
46	4-$O(CH_2)_4CH_3$	171–172.5	39	MeCN	$C_{28}H_{37}N_3O_2$
47	4-C_6H_4-p-N=NC_6H_5	155–157	13	C_6H_6	$C_{29}H_{31}N_5O$

[a] Compounds were prepared by procedure A. [b] All compounds were analyzed for C, H, N.

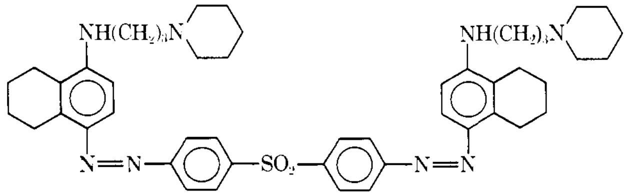


XIX



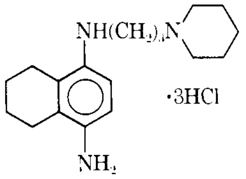
XX

N-(4,5-dimethyl-2-pyrimidinyl)-*p*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthylazo}-benzenesulfonamide (XX),[9] and 1,1′-{sulfonylbis-[*p*-phenyleneazo(5,6,7,8-tetrahydro-1,4-naphthylene)im-inotrimethylene}dipiperidine (XXI)[7] were especially noteworthy and effected a 76–100% reduction of live schistosomes when administered in the diet to mice for 14 days at daily doses of 256–364 mg/kg.[12,13]



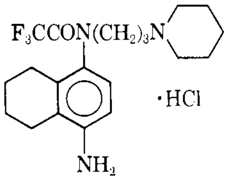
XXI

Moreover, 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine trihydrochloride (XXII),[9] a likely metabolite of the antimycobacterial and antischistosomal 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (Va and b, XIX–XXI), was considerably more potent and reduced the live worm burden 90 and 98% at daily diet doses of 88 and 159 mg/kg, respectively.[12,13]

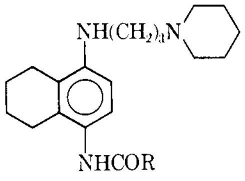


XXII

It was therefore of interest to synthesize representative *N*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}amides (XXIVa–e) for antischistosomal and antimycobacterial evaluation.



XXIII



XXIV

a, R = CH_3
b, R = CH_2CH_3
c, R = $(CH_2)_5CH_3$
d, R = $(CH_2)_{14}CH_3$
e, R = C_6H_5

Compounds XXIVa–d were prepared in 37–83% yield by treating *N*-(4-amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-*N*-(3-piperidinopropyl)acetamide hydrochloride (XXIII)[9] with the requisite acid anhydride in HOAc,

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(12) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Amer. J. Trop. Med. Hyg.*, **11**, 31 (1962).

(13) P. E. Thompson and R. E. Voigtman, unpublished results, Parke, Davis and Company, Ann Arbor, Mich.

propionic acid, or pyridine followed by removal of the F_3CCO protecting group with aq EtOH–NaOH. *N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}benzamide (XXIVe) (33%) was obtained directly from 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine trihydrochloride (XXII)[9] and benzoic anhydride in benzene.

The *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)alkyl- and aralkylamides (VIIIa and b) (**1–35**, Table I), *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)benzamides (VIIIc) (**36–47**, **Table II**), *N*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl]amino]-1-naphthyl}amides (XXIVa–e), and related amide and urea derivatives (IX–XIII and XV–XVIII) 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 *S. mansoni* in mice.[12] As in previous work, drugs were administered in a powdered diet for 7 or 14 days or by gavage in 10 ml/kg of aq 1% hydroxyethyl- or carboxymethylcellulose for 3 to 10 days. Drug amounts are expressed as free base. Schistosomicidal activity is widespread among the *N*-(4-{[2-(diethylamino)ethyl]-amino}-1-naphthyl)alkyl- and aralkylamides (VIIIa and b). *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)benzamides (VIIIc), and the related amides Xa and b and XXIVe. The most potent substances (**2, 7, 8, 14, 16, 19, 24,** Xa) completely eliminated live schistosomes from infected mice at drug–diet doses ranging from 45 to 90 mg/kg per day for 7 or 14 days and gavage doses of 50 or 100 mg/kg daily for 3 or 5 days.[13] Compounds **17, 28, 31, 32, 40,** Xb, and XXIVe also cured all of the mice at somewhat higher dose levels ranging from 130 to 326 mg/kg daily for 14 days by drug–diet or 200 mg/kg daily by gavage for 3 to 10 days.[13] The above compounds, therefore, possessed distinctly more promising antischistosomal activity in mice than lucanthone hydrochloride,[12,14] hycanthone,[15] the tris-(*p*-aminophenyl)carbonium salts,[12,16] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[17,18] *N*-[5-(*p*-aminophenoxy)pentyl]phthalimide,[19] or 3-[4-(3-chloro-*p*-tolyl)-1-piperazinylcarbonyl]acrylic acid[20] when tested under comparable experimental conditions.[12,13] Moreover, 18 other amides (**1, 3, 9, 11–13, 20, 21, 25–27, 34, 37–41, 43**) effected a marked reduction (74–99%) in live schistosomes at daily diet doses of 49–365 mg/kg for 7 or 14 days or gavage doses of 50–200 mg/kg per day for 3 or 5 days.[13] The amide and urea derivatives **4, 5, 15, 18, 22, 23, 29, 45–47,** IX, XI–XIII, XV–XVIII, and XXIVc and d lacked significant antischistosome effects in mice at diet doses ranging from 109 to 668 mg/kg per day for 7 or 14 days or gavage doses of 50–200 mg/kg daily for 5 or 10 days.[13]

Ten compounds (**2, 8, 9, 13, 14, 17, 19, 27, 32, 34**) were selected for trial against the Puerto Rican strain of *S. mansoni* in Rhesus monkeys,[2,12] and 4 of them (**2, 8, 14, 17**) showed significant antischistosomal activity in this host.[13] Drugs were given orally by gavage twice daily 5 days a week for 1 or 2 weeks. *N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)octanamide (**17**, Table I) was the most active compound tested and cured monkeys or strongly suppressed egg production at a well-tolerated dose of 50 mg/kg per day for 10 days. However, the drug exhibited a poor therapeutic index in monkeys. Doses of 100 mg/kg per day for 5 days produced intolerance variably reflected by death, diarrhea, and inappetence. Moreover, the drug caused CNS effects in dogs at a dose of 50 mg/kg daily for 2 to 5 days. *N*-(4-{[2-(Diethylamino)ethyl]-amino}-1-naphthyl)propionamide (**2**), *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)valeramide (**8**), and *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)heptanamide (**14**) produced a moderate to strong suppression of egg production at doses of 25–100 mg/kg per day for 5 or 10 days but were not curative. Therefore, hopes that the *N*-(4-{[2-(diethylamino)-ethyl]amino}-1-naphthyl)amides might exhibit enhanced antischistosome activity coupled with more favorable host tolerance were not realized.

It is noteworthy that *N*-(4-{[2-(diethylamino)ethyl]-amino}-1-naphthyl)heptanamide (**14**) was highly active against *S. mansoni in vitro* and killed all adult worms within 24 hr at a concentration of 50 μg/ml and within 120 hr at a concentration of 12.5 μg/ml. Thus **14** was approximately twice as active *in vitro* as the parent *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine (XIV)[8] when tested in parallel. These observations demonstrate that the amides are active against schistosomes *per se*, and suggest that the antischistosome properties of these substances may not necessarily depend upon enzymatic scission to XIV in the host.

The *N*-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)-amino]-1-naphthyl}amides XXIVa–e were also tested against representative bacteria *in vitro*, including *Streptococcus pyogenes* (C203), *Staphylococcus aureus* (UC-76), *Proteus mirabilis* (MGH-1), *Pseudomonas aeruginosa* (28), *Salmonella typhimurium* (V-31), and *Mycobacterium tuberculosis* ($H_{37}Rv$).[9] Compound XXIVe completely inhibited *M. tuberculosis* $H_{37}Rv$ *in vitro* at a concentration of 10 μg/ml, but the amides XXIVa–d were inactive even at 20 μg/ml. Each of the amides (XXIVa–e) was ineffective against *M. tuberculosis* $H_{37}Rv$ infections in mice when the drugs were administered at 0.1–0.2% (87–206 mg/kg daily) in the diet for 7 days.[9]

Experimental Section[21,22]

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)alkyl- and aralkylamides (VIIIa and b) (Table I). Procedure A.**—To a suspension of 10.0 g (0.026 mol) of *N*-(4-amino-1-naphthyl)-*N*-[2-(diethylamino)ethyl]-2,2,2-trifluoroacetamide·HCl (VI)[4] in 75 ml of pyridine was added 4.2 g (0.026 mol) of octanoyl chloride. Heat was evolved and the solid dissolved. The mixture was heated under reflux for 3 hr, and volatile materials were removed *in vacuo*. The residue was dissolved in

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(15) D. A. Berberian, E. W. Dennis, H. Freele, D. Rosi, T. R. Lewis, R. Lorenz, and S. Archer, *J. Med. Chem.*, **12**, 607 (1969), and ref cited therein.

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(17) C. G. Raison and O. D. Standen, *Brit. J. Pharmacol.*, **10**, 191 (1955).

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(20) G. Lämmler, *Z. Tropenmed. Parasitol.*, **9**, 294 (1958).

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

(22) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values.

EtOH, several ml of 50% aq NaOH in a small volume of H_2O were added, and the mixture was heated under reflux for 3 hr and cooled. The solid which formed was collected by filtration and crystallized from EtOH–H_2O to give 3.3 g *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)octanamide (**17**) as an off-white solid, mp 98–100°. A second crop was obtained by concentrating the filtrate to dryness, triturating the residue with H_2O, and crystallizing the insoluble material from EtOH–H_2O.

Procedure B.—To a suspension of 20.0 g (0.051 mol) of VI[4] in 150 ml of pyridine was added 13.0 g (0.054 mol) of heptanoic anhydride. The mixture was heated under reflux for 3 hr and volatile materials were removed *in vacuo*. The residue was dissolved in EtOH, made basic with aq NaOH, and heated under reflux for 10 hr. The solvent was removed *in vacuo*, and the residue was triturated with H_2O, filtered, dried, and crystallized from heptane to give 8.7 g (43%) of *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)heptanamide (**14**) as offwhite crystals, mp 95–98°.

Procedure C.—A solution of 10.0 g (0.026 mol) of VI[4] in 50 ml of HOAc and 10 ml of Ac_2O was heated under reflux for 2 hr and volatile materials were removed on a rotary evaporator. The residue was dissolved in EtOH, aq NaOH was added, and the mixture was heated under reflux for 2 hr. The solvent was removed *in vacuo* and the residue was triturated with H_2O, dried, and crystallized from EtOAc to give 5.0 g (64%) of *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)acetamide (**1**) as off-white crystals, mp 96–98°.

Procedure D.—*N*-[2-(Diethylamino)ethyl]-1,4-naphthalenediamine·2HCl·0.25 hydrate (XIV)[8] (10.0 g, 0.03 mol) was dissolved in H_2O and the solution was chilled, made basic with NH_4OH, and extracted with C_6H_6. To the dried C_6H_6 extracts was added 2.9 g (0.03 mol) of maleic anhydride and the mixture was heated under reflux for 2 hr and allowed to cool to room temperature. The C_6H_6 was decanted and the residual gum was heated with EtOH to give a solid. The product was triturated with several portions of C_6H_6, filtered, and dried to give 8.5 g (76%) of *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)maleamic acid hemihydrate (**4**), mp 179–180° dec.

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)benzamides (VIIIc) (Table II).**—*N*-[2-(Diethylamino)ethyl]-1,4-naphthalenediamine·2HCl·0.25 hydrate (XIV)[8] (20.0 g, 0.06 mol) was converted into the base as in procedure D and a solution of the base in C_6H_6 was heated under reflux for 2 hr with 13.5 g (0.06 mol) of Bz_2O. The mixture was filtered hot and the solid that formed in the filtrate upon cooling was crystallized from 500 ml of EtOH to give 16.8 g (58%) of *N*-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)benzamide benzoic acid salt, mp 176.5–177.5°. *Anal.* ($C_{23}H_{27}N_3O \cdot C_7H_6O_2$) C,H,N.

A portion (6.5 g, 0.0135 mol) of the benzoic acid salt was suspended in aq NaOH and warmed on a steam bath for 1 hr. The solid was collected by filtration and crystallized from EtOH–H_2O to give 3.4 g (70%) of the base (**41**), mp 134–135.5°.

Alternatively, the reaction of VI[4] with BzCl in pyridine according to procedure A gave material that was identical with the base described above. Procedure A was utilized for the preparation of all of the compounds listed in Table II.

***N*-[2-(Diethylamino)ethyl]-2,2,2-trifluoro-*N*,*N*′-1,4-naphthylenebisacetamide (IX).**—A solution of 10.0 g (0.026 mol) of VI[4] in 50 ml of HOAc and 10 ml of Ac_2O was heated under reflux for 2 hr. The mixture was cooled and poured into a large vol of Et_2O. The gummy solid that formed was removed by filtration, added to dil NaOH, and warmed on a steam bath for 1 hr. The solid which formed was collected by filtration, crystallized twice from MeCN, and triturated with hot EtOAc to give 1.7 g (17%) of the product, mp 173–174°. *Anal.* ($C_{20}H_{24}F_3N_3O_2$) C,H.

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)-2-furamide (Xa).**—The monohydrochloride VI[4] (10.0 g, 0.026 mol) and 2-furoyl chloride (3.4 g, 0.026 mol) were allowed to react and the reaction mixture was processed according to procedure A. The product (3.3 g, 37%) was obtained as off-white crystals from *i*-Pr_2O, mp 115–117.5°. *Anal.* ($C_{21}H_{25}N_3O_2$) C,H,N.

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)-2-thiophenecarboxamide (Xb).**—From 10.0 g (0.026 mol) of VI[4] and 3.8 g (0.026 mol) of 2-thenoyl chloride utilizing procedure A was obtained 5.0 g (53%) of product as beige crystals from *i*-PrOH, mp 162–164.5°. *Anal.* ($C_{21}H_{25}N_3OS$) C,H,N.

***N*,*N*′-Bis(4-[2-(diethylamino)ethyl]amino}-1-naphthyl)oxamide (XIa).**—A mixture of 10.0 g (0.026 mol) of VI[4] and 1.7 g (0.013 mol) of oxalyl chloride in 75 ml of pyridine was heated under reflux for 3 hr. The solvent was removed *in vacuo*, and the residue was dissolved in EtOH, diluted with an equal vol of 20% aq NaOH, and heated under reflux for 1 hr. Filtration afforded a gummy solid which was crystallized from C_6H_6–petr ether to give 1.5 g (21%) of yellow crystals, mp 162–163°. *Anal.* ($C_{34}H_{44}N_6O_2$) C,H,N.

***N*,*N*′-Bis(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)decanediamide (XIb).**—Utilizing the procedure described for XIa, VI[4] (10.0 g, 0.026 mol), and sebacyl chloride (3.1 g, 0.013 mol) afforded 3.0 g (34%) of product as off-white crystals from C_6H_6, mp 144–146°. *Anal.* ($C_{42}H_{60}N_6O_2$) C,H,N.

1,3-Bis(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)urea (XII).—A solution of 10.0 g (0.026 mol) of VI[4] and 4.0 g (0.026 mol) of diethylcarbamoyl chloride in 30 ml of pyridine was heated under reflux for 1.5 hr. The mixture was cooled, poured into iced aq NaOH, and filtered. The solid was dissolved in EtOH, and the mixture was made basic with NaOH, heated under reflux for 2 hr, cooled, and filtered. The solid obtained was crystallized from EtOH to give 2.4 g (35%) of the product as colorless crystals, mp 198–200°. *Anal.* ($C_{33}H_{44}N_6O$) C,H,N.

***N*-(4-Amino-1-naphthyl)-*N*-[2-(diethylamino)ethyl]benzamide (XIII).**—*N*′-[2-(Diethylamino)ethyl]-1,4-naphthalenediamine·2HCl·0.25 hydrate (XIV)[8] (20.0 g, 0.06 mol) was dissolved in H_2O and the solution was chilled, made basic with NH_4OH, and extracted with C_6H_6. To the dried C_6H_6 extracts was added 1.26 g (0.03 mol) of CaH_2 (fine 4–40 mesh). The solution was stirred vigorously and to it was added dropwise a solution of 8.2 g (0.06 mol) of BzCl in C_6H_6. The mixture was stirred at room temperature for 2 hr, diluted with H_2O, and filtered. The solid thus obtained was crystallized from EtOH–H_2O to give 2.5 g (12%) of tan needles, mp 166–167°. *Anal.* ($C_{23}H_{27}N_3O$) C,H,N.

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)phthalimide (XV).**—A mixture of 10.0 g (0.03 mol) of *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine·2HCl·0.25 hydrate (XIV),[8] 2.45 g of NaOAc, and 4.42 g (0.03 mol) of phthalic anhydride in 30 ml of HOAc was heated under reflux for 1 hr. The reaction mixture was poured into H_2O, made basic with aq NaOH, and the gummy semisolid that separated was crystallized twice from EtOH–H_2O to give 3.0 g (26%) of tan plates, mp 135–137°. *Anal.* ($C_{24}H_{25}N_3O_2$) C,H,N.

***N*-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)benzenesulfonamide Monohydrochloride (XVI).**—Compound XIV[8] (20.0 g, 0.06 mol) was converted into the base and dissolved in xylene. $PhSO_2Cl$ (10.6 g, 0.06 mol) and Et_3N (6.0 g, 0.06 mol) were added to the dried xylene extracts and the mixture was heated under reflux for 3 hr and cooled. The gummy solid which separated was dissolved in dil HCl and the solution was allowed to stand at room temperature for 48 hr. The solid that separated was collected by filtration and crystallized from MeOH–H_2O to give 2.0 g (8%) of the product as beige crystals, mp 204–205°. *Anal.* ($C_{22}H_{27}N_3O_2S \cdot HCl$) C,H,N.

The same product was obtained from VI[4] and $PhSO_2Cl$ in pyridine utilizing procedure A.

1-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)-3-phenylurea Dihydrochloride (XVII).—Compound XIV[8] (14.0 g, 0.042 mol) was converted into the base and dissolved in C_6H_6. Phenyl isocyanate (4.6 g, 0.038 mol) was added to the dried C_6H_6 extracts and the mixture was heated under reflux for 0.5 hr and concentrated to 50 ml *in vacuo*. This was poured into 2 l. of Et_2O and the small amount of precipitate that formed was removed by filtration and discarded. A solution of HCl in *i*-PrOH was added to the filtrate and the solid that separated was collected and dried. The crude product was crystallized from *i*-PrOH-Et_2O. This material was dissolved in H_2O, the H_2O solution was made basic with NaOH, and the base was extracted with Et_2O. An excess of HCl in *i*-PrOH was added to the Et_2O extracts, and the salt was collected and dried to give 10.0 g (54%) of off-white crystals, melting point indefinite from 150°. *Anal.* ($C_{23}H_{28}N_4O \cdot 2HCl \cdot 2H_2O$) C,H,Cl,N;$H_2O$: calcd, 7.42; found, 6.64.

1-(4-{[2-(Diethylamino)ethyl]amino}-1-naphthyl)-3-heptyl-2-thiourea Dihydrochloride (XVIII).—Utilizing the procedure for XVII *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine·2HCl·0.25 hydrate (XIV)[8] (17.4 g, 0.05 mol) was allowed to react with 7.9 g (0.05 mol) of heptyl isothiocyanate to give 9.2 g (38%) of pale lavender crystals from MeCN, mp 183–186°. *Anal.* ($C_{24}H_{38}N_4S \cdot 2HCl$) C,H,N.

***N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}acetamide (XXIVa).**—A solution of 8.4 g (0.02 mol) of *N*-(4-amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-*N*-(3-piperidinopropyl)acetamide·HCl (XXIII)[9] and 2.0 g (0.02 mol) of Ac_2O in 75 ml of HOAc was heated under reflux for 2.5 hr.

Volatile materials were removed *in vacuo* and the residue was dissolved in EtOH containing several ml of 50% aq NaOH and a small vol of H_2O. The mixture was heated under reflux for 2 hr and the solvent was removed *in vacuo*. The residue was triturated with H_2O, collected by filtration, and crystallized from *i*-PrOH-H_2O to give 5.5 g (83%) of pale yellow platelets, mp 148–150°. *Anal.* ($C_{20}H_{31}N_3O$) C,H,N.

N-**{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}propionamide (XXIVb).**—The hydrochloride XXIII[9] (8.4 g, 0.02 mol) and $(EtCO)_2O$ (2.6 g, 0.02 mol) were allowed to react in 70 ml of $EtCO_2H$ and the reaction mixture was processed according to XXIVa. The product (4.5 g, 66%) was obtained as beige crystals from heptane, mp 124–125°. *Anal.* ($C_{21}H_{33}N_3O$) C,H,N.

N-**{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}heptanamide (XXIVc).**—From 8.4 g (0.02 mol) of XXIII[9] and 4.8 g (0.02 mol) of heptanoic anhydride in 75 ml of pyridine utilizing procedure B was obtained 3.0 g (37%) of product as off-white crystals from heptane, mp 91–92°. *Anal.* ($C_{25}H_{41}N_3O$) C,H,N.

N-**{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}hexadecanamide (XXIVd).** From 8.4 g (0.02 mol) of XXIII[9] and 9.9 g (0.02 mol) of palmitic anhydride in 100 ml of pyridine utilizing procedure B was obtained 7.5 g (71%) of product as tan crystals from *i*-PrOH–H_2O, mp 85° dec. *Anal.* ($C_{34}H_{59}N_3O$) C,H,N.

N-**{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}benzamide (XXIVe).** An aq solution of 10.0 g (0.024 mol) of 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine·3HCl (XXII)[9] was made basic with NH_4OH and extracted with C_6H_6. The dried C_6H_6 extracts were treated with 5.5 g (0.024 mol) of Bz_2O and the mixture was heated under reflux for 2 hr and cooled. The crude product was collected by filtration, dried, and crystallized twice from *i*-PrOH–EtOH to give 4.1 g (33%) of off-white crystals of the benzoic acid salt, mp 184–186°. *Anal.* ($C_{25}H_{33}N_3O \cdot C_7H_6O_2$) C,H,N.

The alcohol filtrate from the final recrystallization was heated with concentrated NaOH for 1.5 hr. The alcohol layer was decanted, evaporated to dryness, and the residue crystallized from EtOH–H_2O to give 0.62 g of the free base, mp 152–153.5°. *Anal.* ($C_{25}H_{33}N_3O$) C,H,N.

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Synthesis and Schistosomicidal Activity of 6-Chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinemethanol[1]

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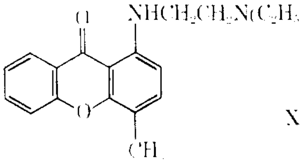
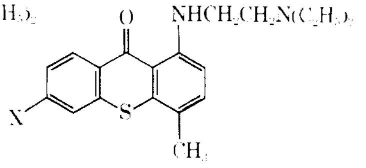
The title compound (XVIII) has been synthesized chemically in a seven-step sequence and also by microbiological oxidation of 6-chloro-5-{[2-(diethylamino)ethyl]amino}-8-methylquinoline,[2] IX, by *Aspergillus sclerotiorum*. The Skraup reaction on 4-chloro-*o*-toluidine produced 6-chloro-8-methylquinoline which was nitrated and then oxidized to 6-chloro-5-nitro-8-quinolinecarboxylic acid. Catalytic reduction of the Me ester followed by NaH-induced alkylation with diethylaminoethyl chloride produced methyl 6-chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinecarboxylate. Reduction of the latter compound with LAH at low temperatures gave XVIII. A comparison of the oral and parenteral activities of IX and XVIII against *Schistosoma mansoni* and *S. japonicum* infections has been carried out in mice and hamsters.

Since the discovery by Kikuth and Gönnert[3] that compounds I–III, synthesized earlier by Mauss,[4] had oral schistosomicidal activity in mice, chemical investigations in various laboratories have produced a number of related compounds (*e.g.*, IV–IX)[2,5] of which IX[2] is most relevant to the present work.

Compelling evidence[3,4,6,7] has been accumulated that the structural feature necessary for biological activity against schistosomes in mice in this broad class of compounds is a dialkylaminoalkylamino group *para* to Me



I



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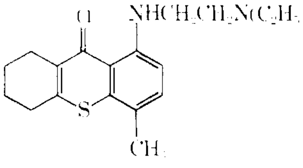
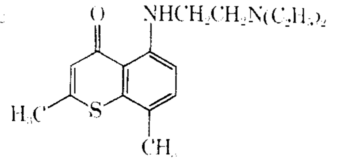
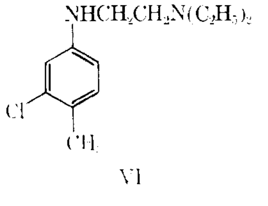
III, X = Cl



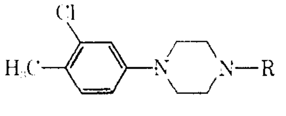
IV



V



VI



VII, R = H
VIII, R = p-$(CH_2)_6OC_6H_4C(CH_3)_2C_2H_5$

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[1] Presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

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