Journal of Medicinal Chemistry

VOLUME 13, No. 4 JULY 1970

Synthetic Schistosomicides. XVII. *N*-(Benzylidene and Cinnamylidene)-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines and Related Schiff Bases[1]

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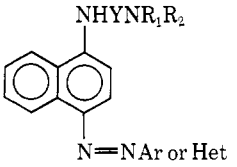
Received February 6, 1970

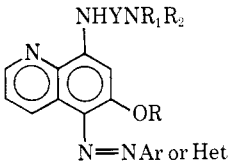
Representative *N*-(benzylidene, cinnamylidene, and naphthylidene)-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (VIII–X, XIII), 1-[3-({4-[(benzylidene, cinnamylidene, and naphthylidene)amino]-5,6,7,8-tetrahydro-1-naphthyl}amino)propyl]piperidines (XI, XII, XIV), and 5,5'-[*p*-phenylenebis(methylidyneimino)]bis(8-{[2-(diethylamino)ethyl]amino}quinoline) (XV) were synthesized by the condensation of *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine, 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine (VII), or 5-amino-8-{[2-(diethylamino)ethyl]amino}quinoline with the appropriate aldehyde in xylene. Several *N*-(benzylidene and cinnamylidene)-1-naphthylamines (XVI–XVIII) substituted with other basic distal moieties were also prepared. Schistosomicidal activity among Schiff bases of structure VIII–XV is widespread, and ten compounds cured *Schistosoma mansoni* infections in mice at doses ranging from 66 to 271 mg/kg per day for 14 days. Three compounds were evaluated against *S. mansoni* in Rhesus monkeys and each showed significant antischistosomal activity in this host. Structure–activity relationships are discussed.

Schistosomicidal activity is widespread among various *N,N*-dialkyl-*N'*-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (I)[2–5] and simple 4-arylazo-

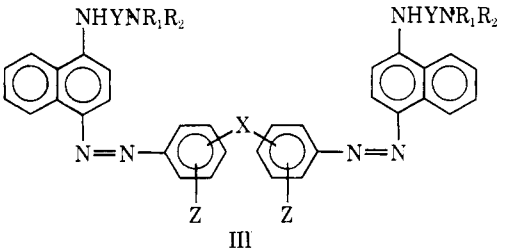


I

and 4-heterocyclic azo-1-naphthylamines,[6–9] 5-azo-6-alkoxy-8-{[(dialkylamino)alkyl]amino}quinolines

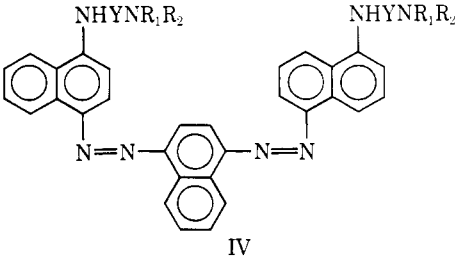


II



III

(II),[10] *N,N*-[bis(phenyleneazo-1,4-naphthylene)]bis-(*N',N'*-dialkylalkylenediamines) (III),[11,12] and *N,N''*-



IV

[1,4-naphthylenebis(azo-1,4-naphthylene)]bis(*N',N'*-dialkylalkylenediamines) (IV).[11] Moreover, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (Va and

(1) For paper XVI, see E. F. Elslager, M. P. Hutt, and L. M. Werbel *J. Med. Chem.*, **13**, 370 (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).
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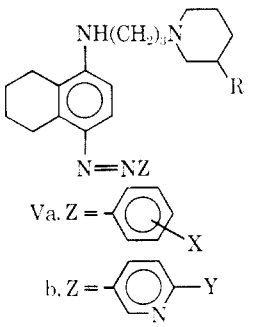
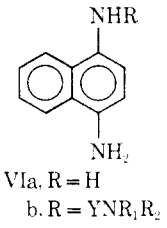
(8) A. Korolkovas, *ibid.*, **6**, 147 (1968).
(9) A. Korolkovas, *ibid.*, **6**, 153 (1968).
(10) E. F. Elslager and D. B. Capps, *J. Med. Chem.*, **7**, 663 (1964).
(11) E. F. Elslager, D. B. Capps, D. H. Kurtz, and D. F. Worth, *ibid.*, **11**, 1201 (1968).
(12) E. F. Elslager and A. A. Phillips, *ibid.*, **12**, 519 (1969).



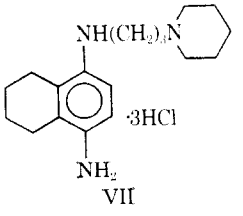
b) are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *Mycobacterium lepraemurium in vitro* and in mice.[13,14]

While investigating potential metabolites of the simple 4-azo-1-naphthylamines,[6] it was observed that the reduction product 1,4-naphthalenediamine (VIa) killed adult *S. mansoni in vitro* at drug concentrations



VIa, R = H
b, R = YNR_1R_2

as low as 25 μg/ml.[6] Results in mice were disappointing; the diamine was ineffective when administered orally at the maximum tolerated dose. Anticipating that factors such as metabolic alteration, excretion rate, absorption, and tissue localization might be favorably influenced by the introduction of a basic side chain, a study of potential metabolites of the *N,N*-dialkyl-*N'*-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (I, III, IV) was initiated.[15-17] This work led to the discovery that various *N*-[(dialkylamino)alkyl]-1,4-naphthalenediamines (VIb) were highly active against *S. mansoni in vitro* and in experimental animals.[15] In contradistinction, 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine trihydrochloride (VII), a likely metabolite of the antimycobacterial 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (Va and b), was inactive against *M. tuberculosis* $H_{37}Rv$ *in vitro* and in mice.[13] Nevertheless, these

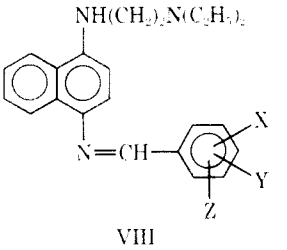


VII

observations do not preclude the possibility that such metabolites may be formed intracellularly.

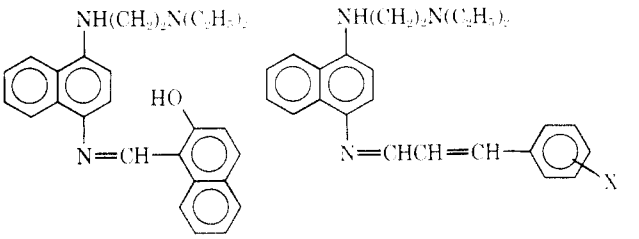
In a further extension of the above work, an array of Schiff bases derived from 1,4-naphthalenediamine (VIa), *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine,[15] 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine (VII),[13] and 5-amino-8-{[2-(diethylamino)ethyl]amino}quinoline[18] has been prepared for antischistosomal and antimycobacterial evaluation. It was hypothesized that such compounds, like the *N*-(benzylidene)-4,4'-sulfonyldianiline antimalarials,[19-21] might undergo nonenzymatic hydrolytic scission upon contact with body tissues and fluids, and concurrently display more favorable tolerance, absorption, and excretion patterns than the corresponding diamines.[13,15]

In previous studies[2-5,11,12,15] the diethylaminoethyl derivatives among types I, III, IV, and VIb exhibited optimum potency; therefore we undertook initially the preparation of a group of *N*-benzylidene-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (**1–20**, Table I) (VIII). An aqueous solution of *N*-[2-(diethylamino)-ethyl]-1,4-naphthalenediamine dihydrochloride[15] was



VIII

made alkaline with NH_4OH and the free base was extracted with xylene. The diamine solution was dried and treated promptly with the appropriate aldehyde to minimize air oxidation. H_2O was removed from the mixture as the reaction progressed. This procedure afforded the *N*-benzylidene-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines **1–20** (Table I) in 6–95% yield. Similarly, 1-({4-[(2-diethylaminoethyl)amino]-1-naphthylimino}methyl)-2-naphthol (IX) (56%), *N*-(2-diethylaminoethyl)-*N'*-(*p*-dimethylaminocinnamyli-



IX

Xa, X = 4-$N(CH_3)_2$
b, X = 2-NO_2

dene)-1,4-naphthalenediamine (Xa) (61%), and *N*-[2-(diethylamino)ethyl]-*N'*-(*o*-nitrocinnamylidene)-1,4-naphthalenediamine (Xb) (60%) were prepared from *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine and 2-hydroxy-1-naphthaldehyde, *p*-dimethylaminocinnamaldehyde, and *o*-nitrocinnamaldehyde, while the treatment of 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine (VII)[13] with 2-hydroxy-1-naphthaldehyde or *p*-dimethylaminocinnamaldehyde afforded 1-({5,6,7,8-tetrahydro-4-[(3-pi-

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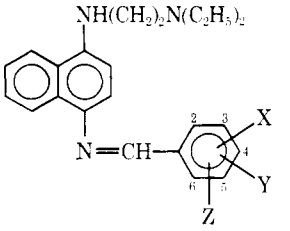
TABLE I

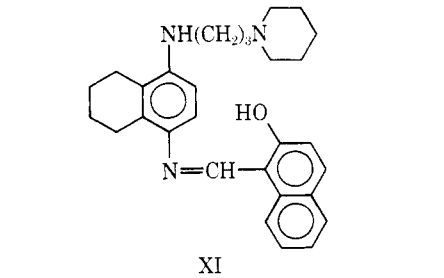
N-BENZYLIDENE-*N'*-[2-(DIETHYLAMINO)ETHYL]-1,4-NAPHTHALENEDIAMINES[a]



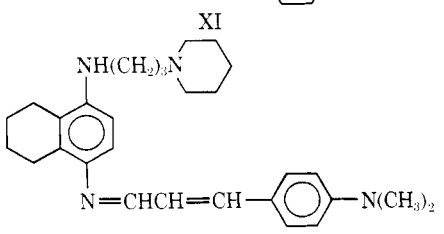
No.	X, Y, Z	Mp, °C	Yield purified, %	Purifn solvent	Formula[d]	Stability (half-life, hr) in 50% MeOH–50% pH 7 PB
1	2,4,5-Cl_3	110–112	39	MeCN	$C_{23}H_{24}Cl_3N_3$	
2	4-Cl, 3-NO_2	92–95	80	EtOH–Et_2O	$C_{23}H_{25}ClN_4O_2$[b]	47
3	5-Cl, 2-NO_2	111–115	57	EtOH–Et_2O	$C_{23}H_{25}ClN_4O_2$	200
4	2,4-Cl_2	60–65	44	Petr ether	$C_{23}H_{25}Cl_2N_3$	31
5	2,6-Cl_2	63–67	78	Petr ether	$C_{23}H_{25}Cl_2N_3$	60
6	2-OH, 3,5-Cl_2	93–96	33	2,2,4-Trimethylpentane	$C_{23}H_{23}Cl_2N_3O$	1
7	4-Br	76–78	38	Petr ether	$C_{23}H_{26}BrN_3$	14
8	2-OH, 5-Cl	119–120	32	Petr ether	$C_{23}H_{26}ClN_3O$	5
9	2-F	75–77	44	Petr ether	$C_{23}F_{26}FN_3$	17
10	4-F	70–72	38	Petr ether	$C_{23}H_{26}FN_3$	19
11	2-NO_2	82–83	51	2-PrOH–petr ether	$C_{23}H_{26}N_4O_2$	90
12	4-NO_2	119–121	95	Petr ether	$C_{23}H_{26}N_4O_2$	31
13	2-OH	83–85	6	2,2,4-Trimethylpentane	$C_{23}H_{27}N_3O$	
14	4-OH	73 dec	17	Xylene	$C_{23}H_{27}N_3O$	4
15	2,4-$(OH)_2$	93 dec	32	Xylene	$C_{23}H_{27}N_3O_2$	30
16	4-CN	86–90	91	Petr ether	$C_{24}H_{26}N_4$	28
17	3-OCH_3, 4-OH	134–137	46	Petr ether	$C_{24}H_{29}N_3O_2$	5
18	4-$NHCOCH_3$	137–140	56	C_6H_6–petr ether	$C_{25}H_{30}N_4O$[c]	12
19	2-NO_2, 4,5-$(OCH_3)_2$	114–116	54	EtOH–H_2O	$C_{25}H_{30}N_4O_4$	90
20	2,4,6-$(CH_3)_2$	65–70	93	Et_2O	$C_{26}H_{33}N_3$	40

[a] Compounds ranged from orange to black in color. [b] C: calcd, 65.01; found, 64.59. [c] C: calcd, 74.59; found, 73.92. [d] All compounds were analyzed for C, H, N.

peridinopropyl)amino]-1-naphthylimino}methyl)-2-naphthol (XI) (76%) and 1-[3-({4-[(*p*-dimethylamino-

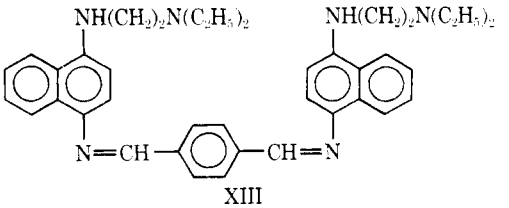


XI



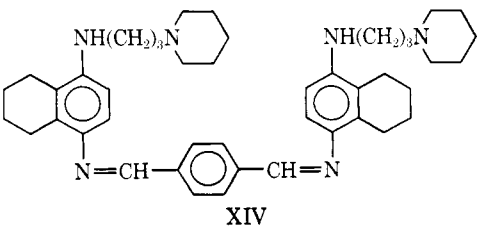
XII

cinnamylidene)amino]-5,6,7,8-tetrahydro-1-naphthyl}amino)propyl]piperidine (XII) (53%). The condensation of 1 equiv of terephthalaldehyde with 2 equiv of *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine, 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine (VII),[13] or 5-amino-8-{[2-diethylamino)ethyl]amino}quinoline[13] gave *N*,*N''*-(*p*-phenylenedimethylidyne)bis[*N'*-(2-diethylaminoethyl)-1,4-naphthalenediamine] (XIII) (52%), 1,1'-{*p*-phenylenebis[methylidyneimino(5,6,7,8-tetrahydro-1,4-naphthy-



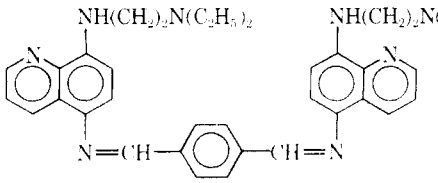
XIII

lene)iminotrimethylene]}dipiperidine (XIV) (56%),



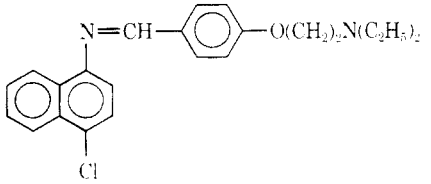
XIV

and 5,5'-[*p*-phenylenebis(methylidyneimino)]bis(8-{[2-(diethylamino)ethyl]amino}quinoline) (XV) (60%), respectively.



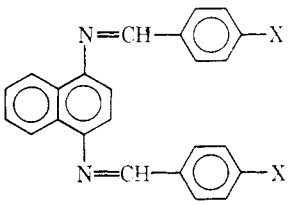
XV

Representative *N*-(benzylidene and cinnamylidene)-1-naphthylamines substituted with other basic distal moieties were also prepared. Thus, the reaction of 4-chloro-1-naphthylamine with *p*-[2-(diethylamino)-ethoxy]benzaldehyde in the presence of *p*-toluenesulfonic acid afforded 4-chloro-*N*-{*p*-[2-(diethylamino)-ethoxy]benzylidene}-1-naphthylamine (XVI) (28%),



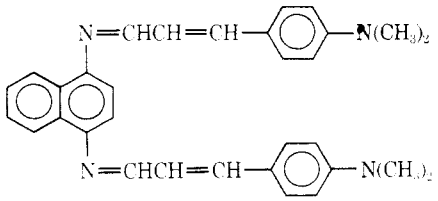
XVI

while the condensation of 1 equiv of 1,4-naphthalenediamine with 2 equiv of *p*-[2-(diethylamino)ethoxy]benzaldehyde, *p*-(dimethylamino)benzaldehyde, or *p*-(dimethylamino)cinnamaldehyde gave *N*,*N*′-bis{*p*-(2-(diethylamino)ethoxy]benzylidene}-1,4-naphthalenediamine (XVIIa) (44%), *N*,*N*′-bis[*p*-(dimethylamino)-



XVIIa, X = $O(CH_2)_2N(C_2H_5)_2$
b, X = $N(CH_3)_2$

benzylidene]-1,4-naphthalenediamine (XVIIb) (27%), and *N*,*N*′-bis[*p*-(dimethylamino)cinnamylidene]-1,4-naphthalenediamine (XVIII) (45%).



XVIII

The *N*-(benzylidene and cinnamylidene)-*N*′-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (**1–20**, Xa and b) and related Schiff bases (IX, XI–XVIII) described in the present communication were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for screening against a Puerto Rican strain of *S. mansoni* in mice.[22] As in previous work, drugs were administered in a powdered diet for 14 days or by gavage in 10 ml/kg of aqueous 1% hydroxyethyl or carboxymethyl cellulose for 5 days. Drug amounts are expressed as free base. Schistosomicidal activity was widespread among the *N*-(benzylidene, cinnamylidene, and naphthylidene)-*N*′-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (VIII–X), 1-[3-({4-[(cinnamylidene and naphthylidene)amino]-5,6,7,8-tetrahydro-1-naphthyl}amino)propyl]piperidines (XI, XII), and *p*-phenylenebis(methylidyneimino)bis(1,4-naphthalenediamines and 8-aminoquinolines) (XIII–XV). The most promising compounds (**4, 6, 7, 14, 17, 18,** IX, XII, XIII, and XV) completely eliminated live schistosomes from infected mice at doses ranging from 66 to 271 mg kg per day when administered orally in the diet for 14 days.[23] These compounds, therefore, possessed distinctly more promising antischistosome activity in mice than lucanthone hydrochloride,[22,24] hycanthone,[25] the tris(*p*-aminophenyl)carbonium salts,[22,26] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[27,28] *N*-[5-(*p*-aminophenoxy)pentyl]phthalimide,[29] or 3-[4-(3-chloro-*p*-tolyl)-1-piperazinylcarbonyl]acrylic acid[30] when tested under comparable experimental conditions.[22,23] Moreover, 16 other Schiff bases (**1–3, 5, 9–12, 15, 16, 19, 20,** Xa and b, XI and XIV) effected a marked reduction (32–97%) in live worms at daily diet doses of 79–287 mg/kg for 14 days.[23] The *N*-(benzylidene and cinnamylidene)-1-naphthylamine derivatives XVI–XVIII lacked appreciable antischistosome effects at doses of 271–316 mg/kg. There appears to be no significant correlation between the degree of antischistosome potency and the relative stability of the Schiff bases in MeOH–pH 7 phosphate buffer (Table I).

Three compounds (**4,** XIII, and XV) were selected for trial against the Puerto Rican strain of *S. mansoni* in Rhesus monkeys,[2,22] and each substance tested showed significant antischistosomal activity in this host.[23] Drugs were given orally by gavage or in gelatin capsules twice daily 5 days a week for 1 or 2 weeks. *N*-(2,4-Dichlorobenzylidene)-*N*′-[2-(diethylamino)ethyl]-1,4-naphthalenediamine (**4**) was the most active compound and cured monkeys or strongly suppressed egg production at doses of 50 mg/kg per day for 5 or 10 days or 100 mg/kg per day for 5 days. However, the compound exhibited a poor therapeutic index. Doses of 100 mg/kg per day for 5 to 7.5 days produced intolerance variably reflected by death, diarrhea, and a transient fall in the hematocrit. *N*,*N*″-(*p*-Phenylenedimethylidyne)bis[*N*′-(2-diethylaminoethyl)-1,4-naphthalenediamine] (XIII) and 5,5′-[*p*-phenylenebis(methylidyneimino)]bis(8-{[2-(diethylamino)ethyl]amino}quinoline) (XV) caused a slight to strong suppression of egg production at doses of 25–100 mg/kg per day for 5 or 10 days but were not curative.

The 1-[3-({4-[(benzylidene, cinnamylidene, and naphthylidene)amino]-5,6,7,8-tetrahydro-1-naphthyl}-

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

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amino)propyl]piperidine derivatives XI, XII, and XIV 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* ($H_{37}Rv$).[13] Compound XI was active *in vitro* against *M. tuberculosis* ($H_{37}Rv$) at a concentration of 10 μg/ml, but XI, XII, and XIV were all inactive against *M. tuberculosis* $H_{37}Rv$ in mice when administered at 0.1% (67–80 mg/kg) in the diet for 7 days.[13]

Experimental Section[31,32]

Stability Studies on Schiff Bases.—The Schiff bases hydrolyzed almost instantaneously in acidic solutions. To obtain a comparison of their relative stability, hydrolysis rates were examined in 50% methanol–pH 7 phosphate buffer. The sample was dissolved in methanol and diluted into pH 7 phosphate buffer to obtain a 50% solution. The high uv wavelength band was observed and used as a measure of the per cent compound remaining which was plotted against time on semilog paper. The time at which 50% of the compound remained was read from the plot and designated the half-life. The precision of this determination is estimated to be ±10%.

***N*-Benzylidene-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (VIII) (1–20, Table I).**—A solution of 8.4 g (0.024 mol) of *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine·2HCl[15] in ice water was made strongly basic with NH_4OH and the mixture was extracted with 600 ml of xylene. The xylene extract was heated under reflux for 0.5 hr under a water separator to remove any H_2O present. To this warm solution was added a warm solution of 5.0 g (0.024 mol) of 2,4,5-trichlorobenzaldehyde in 150 ml of xylene and the mixture was heated at reflux for 3 hr utilizing a water separator. The cooled reaction mixture was diluted with petroleum ether (bp 40–60°) and the dark brown crystals that formed were collected by filtration and recrystallized from MeCN. The product, *N*-[2-(diethylamino)ethyl]-*N'*-(2,4,5-trichlorobenzylidene)-1,4-naphthalenediamine (**1**) weighed 4.2 g (39%), mp 110–112°.

1-({4-[(2-Diethylaminoethyl)amino]-1-naphthylimino}methyl)-2-naphthol (IX).—*N*-(2-(Diethylamino)ethyl]-1,4-naphthalenediamine·2HCl (16.5 g, 0.05 mol) was converted into the base and condensed with 8.6 g (0.05 mol) of 2-hydroxy-1-naphthaldehyde according to the procedure for *N*-[2-(diethylamino)ethyl]-*N'*-(2,4,5-trichlorobenzylidene)-1,4-naphthalenediamine (**1**). The product was obtained as purple–red crystals from xylene–petr ether, mp 112–114°, yield 11.5 g (56%). *Anal.* ($C_{27}H_{29}N_3O$) C, H, N.

***N*-(2-Diethylaminoethyl)-*N'*-(*p*-dimethylaminocinnamylidene)-1,4-naphthalenediamine (Xa).**—*p*-(Dimethylamino)cinnamaldehyde (8.8 g, 0.05 mol) was allowed to react with *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine·2HCl[15] (16.5 g, 0.05 mol) utilizing the procedure for **1**. The product (12.7 g, 61%) was isolated as rust-colored crystals from xylene–petr ether, mp 146–148°. *Anal.* ($C_{27}H_{34}N_4$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-*N'*-(*o*-nitrocinnamylidene)-1,4-naphthalenediamine (Xb).**—The reaction of *N*-[2-(diethylamino)-ethyl]-1,4-naphthalenediamine·2HCl (5.5 g, 0.016 mol) with *o*-nitrocinnamaldehyde (2.8 g, 0.016 mol) in xylene according to the procedure for **1** afforded 4.0 g (60%) of maroon crystals from xylene, mp 99–102°. *Anal.* ($C_{25}H_{28}N_4O_2$) C, H, N.

1-({5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthylimino}methyl)-2-naphthol (XI).—1-[3-(4-Amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine·3HCl (VII)[13] (17.0 g, 0.043 mol) was converted into the base and condensed with 7.4 g (0.043 mol) of 2-hydroxy-1-naphthaldehyde according to the procedure for *N*-[2-(diethylamino)ethyl]-*N'*-(2,4,5-trichlorobenzylidene)-1,4-naphthalenediamine (**1**). The product was obtained as red needles from xylene–petr ether, mp 178–180°, yield 14.2 g (76%). *Anal.* ($C_{29}H_{35}N_3O$) C, H, N.

1-[3-({4-[(*p*-Dimethylaminocinnamylidene)amino]-5,6,7,8-tetrahydro-1-naphthyl}amino)propyl]piperidine (XII).—*p*-(Dimethylamino)cinnamaldehyde (7.5 g, 0.043 mol) was allowed to react with 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)-propyl]piperidine·3HCl (VII)[13] (17.0 g, 0.043 mol) utilizing the procedure for **1**. The product (10.0 g, 53%) was isolated as orange–brown crystals from xylene–petr ether, mp 148–149°. *Anal.* ($C_{29}H_{40}N_4$) C, H, N.

***N,N''*-(*p*-Phenylenedimethylidyne)bis[*N'*-(2-diethylaminoethyl)-1,4-naphthalenediamine] (XIII).**—A solution of 16.5 g (0.05 mol) of *N*-[2-(diethylamino)ethyl]-1,4-naphthalenediamine·2HCl[15] in 200 ml of H_2O was made alkaline with NH_4OH and extracted with xylene. The combined xylene extracts were washed with H_2O and dried (K_2CO_3) briefly. A solution of 3.35 g (0.025 mol) of terephthalaldehyde in xylene was added and the mixture was heated under reflux until H_2O was no longer collecting in the water separator (about 3 hr). The reaction mixture was allowed to cool, and the orange-red crystals that separated were collected by filtration, washed with 2,2,4-trimethylpentane, and dried *in vacuo* at 60° for 18 hr. The product weighed 8.0 g (52%), mp 175–177°. *Anal.* ($C_{40}H_{48}N_6$) C, H, N.

1,1'-{*p*-Phenylenebis[methylidyneimino(5,6,7,8)-tetrahydro-1,4-naphthylene)iminotrimethylene]}dipiperidine (XIV).—Terephthalaldehyde (2.86 g, 0.0213 mol) was allowed to react with 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl] piperidine·3HCl (VII)[13] (17.0 g, 0.043 mol) utilizing the procedure for **1**. The product (8.0 g, 56%) was isolated as orange crystals from xylene–petr ether, mp 216–218°. *Anal.* ($C_{44}H_{60}N_6$) C, H, N.

5,5'-[*p*-Phenylenebis(methylidyneimino)]bis(8-{[2-(diethylamino)ethyl]amino}quinoline) (XV).—A solution of 7.0 g (0.019 mol) of 5-amino-8-{[2-(diethylamino)ethyl]amino}quinoline·3HCl[18] in 30 ml of ice–water was made basic with NH_4OH and extracted with xylene. The xylene extracts were combined, washed with H_2O, and dried (K_2CO_3). A solution of 1.3 g (0.0095 mol) of terephthalaldehyde in xylene was added and the mixture was heated under reflux for 3 hr under a water separator. The xylene mixture was concentrated to 100 ml and cooled. The red crystals that formed were collected by filtration and dried *in vacuo* at 60° for 18 hr. The product, mp 196–198°, weighed 3.5 g (60%). *Anal.* ($C_{38}H_{46}N_8$) C, H, N.

4-Chloro-*N*-{*p*-[2-(diethylamino)ethoxy]benzylidene}-1-naphthylamine (XVI).—4-Chloro-1-naphthylamine (35.6 g, 0.2 mol) and *p*-[2-(diethylamino)ethoxy]benzaldehyde (44.2 g, 0.2 mol) were dissolved in 250 ml of xylene and the mixture was heated under reflux for 16 hr. *p*-Toluenesulfonic acid was added periodically to catalyze the reaction, and the water formed was collected in a water separator. The mixture was concentrated to 100 ml on a rotary evaporator and filtered and the filtrate refrigerated. The product that separated was collected by filtration and crystallized three times from *i*-PrOH to give 20.7 g (28%) of yellow crystals, mp 49–50°. *Anal.* ($C_{28}H_{25}ClN_2O$) C, H, N.

***N,N'*-Bis{*p*-[2-(diethylamino)ethoxy]benzylidene}-1,4-naphthalenediamine (XVIIa).**—A solution of 15.8 g (0.1 mol) of 1,4-naphthalenediamine in 360 ml of EtOH was added to a solution of 44.3 g (0.2 mol) of *p*-[2-(diethylamino)ethoxy]benzaldehyde in 200 ml of EtOH and the mixture was heated under reflux for 7 hr. Volatile materials were removed on a rotary evaporator and the residue was dissolved in $CHCl_3$ and reprecipitated with petr ether (bp 40–60°). The product was collected by filtration and crystallized twice from $CHCl_3$–*i*-PrOH to give 25.0 g (44%) of yellow crystals, mp 68–69°. *Anal.* ($C_{36}H_{44}N_4O_2$) C, H, N.

***N,N'*-Bis[*p*-(dimethylamino)benzylidene]-1,4-naphthalenediamine (XVIIb).**—A solution of 15.8 g (0.1 mol) of 1,4-naphthalenediamine and 29.8 g (0.1 mol) of *p*-(dimethylamino)benzaldehyde in 560 ml of EtOH was heated under reflux for 5 hr and cooled. The orange–yellow precipitate that separated was collected by filtration and dried *in vacuo* at 60° for 18 hr. Crystallization from $CHCl_3$ afforded 11.6 g (27%) of orange crystals, mp 280–282° dec. *Anal.* ($C_{28}H_{28}N_4$) C, H, N.

***N,N'*-Bis[*p*-(dimethylamino)cinnamylidene]-1,4-naphthalenediamine (XVIII).**—*p*-(Dimethylamino)cinnamaldehyde (35.0 g, 0.2 mol) and 1,4-naphthalenediamine (15.8 g, 0.1 mol) were allowed to react in 560 ml of EtOH according to the procedure for XVIIb. The product (21.3 g, 45%) was isolated as reddish brown crystals from $CHCl_3$, then EtOH, mp 253–256°. *Anal.* ($C_{32}H_{32}N_4$) C, H, N.

Acknowledgments.—The authors wish to express

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

(32) 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.

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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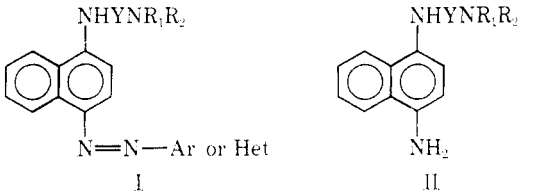
Received February 18, 1970

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



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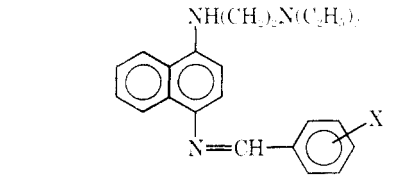
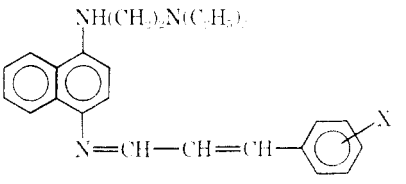
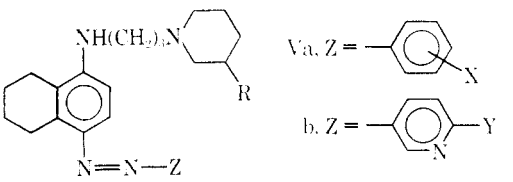
and cinnamylidene)-*N'*-[2-(diethylamino)ethyl]-1,4-naphthalenediamines (III and IV).[1] Moreover, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (Va and b) are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *M. lepraemurium in 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.



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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