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Novel Antituberculosis and Antileprotic Agents. 1-(3-{[5,6,7,8-Tetrahydro-4-(phenylazo- and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines and Related Compounds

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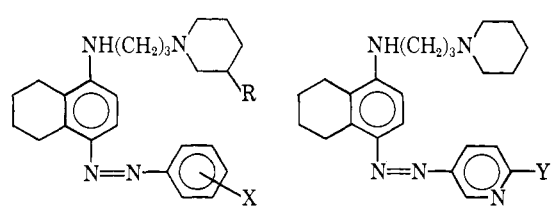
A variety of N-mono- and N,N-dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines were synthesized by (1) coupling a diazotized aromatic or heterocyclic amine with the requisite N,N-dialkyl-N′-(5,6,7,8-tetrahydro-1-naphthyl- or -2,3-xylyl)alkylenediamine, (2) condensation of N-(3-bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine with the appropriate amine, and (3) alkaline hydrolysis of the corresponding N-(aminoalkyl)-2,2,2-trifluoro-N-(5,6,7,8-tetrahydro-4-azo-1-naphthyl)acetamides. Potent *in vitro* antituberculosis activity among the N-mono- and N,N-dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines is widespread, and 28 compounds exhibited a similar order of potency as isoniazid. However, activity against *Mycobacterium tuberculosis* $H_{37}Rv$ in mice is relatively specific, and strong effects were observed only among the 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo)-1-naphthyl]amino}propyl)piperidines (I) and 1-(3-{[5,6,7,8-tetrahydro-4-(3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (II). Four representative compounds among the latter types also showed definite suppressive antileprotic activity against *M. lepraemurium* in mice. Structure–activity relationships are discussed.

Among acid-fast bacilli, the tubercle bacillus *Mycobacterium tuberculosis* and *M. leprae*, the bacillus of human leprosy, have major medical significance. Tuberculosis is now generally regarded to be one of the most important specific communicable diseases in the world, and there are millions of new cases each year.[1,2] Some eleven million people are afflicted with leprosy. In addition, more than two billion people live in areas with leprosy prevalence rates of 0.5/1000 or higher; in these areas nearly one million new cases of leprosy can be expected within the next 5 years.[3,4] The long duration of the disease, the disabilities it causes, and the human and social consequences to the patients and their families give to leprosy a special position among diseases. Therefore, the search for more effective chemotherapeutic agents continues.[5]

The synthesis of various 4-amino-1-naphthylazo schistosomicides was reported in previous communications from these laboratories.[6-9] Several representative N,N-dialkyl-N′-(5,6,7,8-tetrahydro-4-azo-1-naphthyl)alkylenediamines were also prepared. While none of these possessed significant antischistosome properties, several compounds unexpectedly exhibited remarkable activity against *Mycobacterium tuberculosis*, strain $H_{37}Rv$. Subsequently, extensive chemical and microbiological studies were initiated to explore this new lead. These studies led to the discovery of two novel classes of antituberculosis and antileprotic agents, namely 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo)-1-naphthyl]amino}propyl)piperidines (I) and 1-(3-{[5,6,7,8-tetrahydro-4-(3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (II). These compounds exhibit potent antituberculosis activity against *M. tuberculosis* $H_{37}Rv$ *in vitro* and in mice, and show definite suppressive antileprotic activity against *M. lepraemurium* in mice.[5] In structure I, R is hydrogen or methyl and X represents a hydrogen or halogen atom; a lower alkyl, hydroxyalkyl, or alkoxyalkyl radical containing from one to three carbon atoms inclusive; or an acetyl, trifluoromethyl, or nitro group. In formula II, Y represents a hydrogen atom or a methoxy group. The present paper describes the synthesis and microbiological properties of these and related compounds in detail.

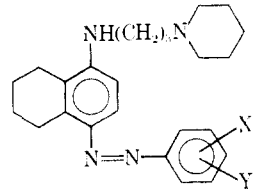


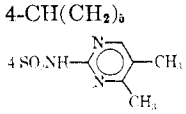
I II

Chemistry.—Among the N-mono- and N,N-dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-

(1) *World Health Organ. Tech. Rept. Ser.*, 195 (1960).
(2) *Ibid.*, 290 (1964).
(3) L. M. Bechelli and V. M. Dominguez, *Bull. World Health Organ.*, **34**, 811 (1966).
(4) *World Health Organ. Tech. Rept. Ser.*, 319 (1966).
(5) Y. T. Chang, *Antimicrobial Agents Chemotherapy 1965*, 465 (1966).
(6) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *J. Med. Chem.*, **6**, 217 (1963).
(7) E. F. Elslager and D. F. Worth, *ibid.*, **6**, 444 (1963).
(8) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).
(9) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *ibid.*, **9**, 378 (1966).

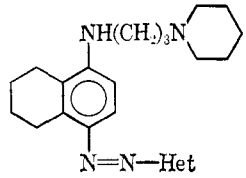
TABLE I: 1-{3-[(5,6,7,8-TETRAHYDRO-4-PHENYLAZO-1-NAPHTHYL)AMINO]PROPYL}PIPERIDINES[a]



No.	X, Y	Mp, °C	Yield purified, %	Purification[b] solvent	Formula[c]	MIC[g] *vs. M. tuberculosis* $H_{37}Rv$
1	2,3-Cl_2	154–156	28	E	$C_{24}H_{30}Cl_2N_4$	++
2	3,5-Cl_2	160–161	37	H	$C_{24}H_{30}Cl_2N_4$	+
3	4-Br	173–175	84	J	$C_{24}H_{31}BrN_4$	+++
4	2-Cl	137–139	55	H	$C_{24}H_{31}ClN_4$	++
5	3-Cl	111–113	69	H	$C_{24}H_{31}ClN_4$	+++
6	4-Cl	156–158	86	I	$C_{24}H_{31}ClN_4$	+++
7	2-F	128–129	71	D	$C_{24}H_{31}FN_4$	+++
8	3-F	104–106	64	G	$C_{24}H_{31}FN_4$	++
9	4-F	114–115	36	A	$C_{24}H_{31}FN_4$	+++
10	3-I	101–103	60	E	$C_{24}H_{31}IN_4$	++
11	4-I	188–190	49	O	$C_{24}H_{31}IN_4$	+
12	3-NO_2	161–162.5	71	H	$C_{24}H_{31}N_5O_2$[h]	+++
13	4-NO_2	208–209.5	68	O	$C_{24}H_{31}N_5O_2$	+
14	H	115–116	83	H	$C_{24}H_{32}N_4$	+++++
15	3-OH	233 dec	15	K	$C_{24}H_{32}N_4O \cdot HCl$[e]	+++
16	3,5-$(OH)_2$	141 dec	21	N	$C_{24}H_{32}N_4O_2 \cdot 0.1H_2O$[d,i]	--
17	4-SO_3H	277 dec	82	X	$C_{24}H_{32}N_4O_3S \cdot 0.33H_2O$[f,j]	--
18	3-CF_3	107–108	65	E	$C_{25}H_{31}F_3N_4$	+++
19	4-CF_3	189–190	34	A	$C_{25}H_{31}F_3N_4$	+
20	2-CH_3, 3-Cl	139–141	52	S	$C_{25}H_{33}ClN_4$	++
21	4-CH_3	146–148	28	A	$C_{25}H_{34}N_4$	+++
22	2-OCH_3	125–127	49	E	$C_{25}H_{34}N_4O$	++
23	3-OCH_3	125–126	68	E	$C_{25}H_{34}N_4O$	+++
24	4-OCH_3	128.5–130.5	77	B	$C_{25}H_{34}N_4O$	+++
25	3-SCH_3	109.5–113	73	E	$C_{25}H_{34}N_4S$[k]	+++
26	4-SCH_3	169–171	55	L	$C_{25}H_{34}N_4S$	+++
27	3-$COCH_3$	140–141	77	A	$C_{26}H_{34}N_4O$	+++
28	4-$COCH_3$	193–194	78	L	$C_{26}H_{34}N_4O$	++
29	4-C_2H_5	158–160	60	C	$C_{26}H_{36}N_4$	+++
30	3,4-$(CH_3)_2$	141–142	80	B	$C_{26}H_{36}N_4$	+++
31	3,5-$(CH_3)_2$	137–143	20	D	$C_{26}H_{36}N_4$[l]	--
32	4-OC_2H_5	129–131	33	E	$C_{26}H_{38}N_4O$[m]	++
33	3-$CHOHCH_3$	96–101	71	E	$C_{26}H_{36}N_4O \cdot C_3H_7OH$	++
34	2,5-$(OCH_3)_2$	116–118	50	E	$C_{26}H_{36}N_4O_2$	+
35	4-CH=CHCOOH	256 dec	67	L	$C_{27}H_{34}N_4O_2$	–
36	4-$COOC_2H_5$	144–146	80	E	$C_{27}H_{36}N_4O_2$	++
37	4-$CH(CH_3)_2$	139–141	20	E	$C_{27}H_{38}N_4$	++
38	3,4,5-$(OCH_3)_3$	125–126	73	W	$C_{27}H_{38}N_4O_3$	++
39	2,3-$(CH_2)_4$	165–167	8	E	$C_{28}H_{38}N_4$	+
40	2-$C(CH_3)_3$	147–149	58	A	$C_{28}H_{40}N_4$	+
41	4-$C(CH_3)_3$	138–141	9	D	$C_{28}H_{40}N_4$[n]	++
42	4-$OCH_2CH(CH_3)_2$	136–137	28	E	$C_{28}H_{40}N_4O$	+
43	4-$SO_2N(C_2H_5)_2$	145–146	57	A	$C_{28}H_{41}N_5O_2S$	+
44	4-(2-Pyridyl)	176–179	83	I	$C_{29}H_{35}N_5$	+
45	3-$CH_2N(CH_2)_4$, 4-OH	193 dec	31	M	$C_{29}H_{41}N_5O \cdot 3HCl \cdot 2H_2O$[e]	+
46	4-OC_6H_4-*p*-Cl	133–134	44	A	$C_{30}H_{35}ClN_4O$	–
47	4-$CH(CH_2)_5$	165–167	43	F	$C_{30}H_{42}N_4$	--
48		224–225	82	R	$C_{30}H_{39}N_7O_2S$[o]	--
49	4-$O(CH_2)_2N(C_2H_5)_2$	96–99	68	N	$C_{30}H_{45}N_5O$	+

[a] Compounds prepared by coupling the appropriate benzenediazonium salt[9] with 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}-piperidine (**101**, Table VI) (procedures I and II.) [b] A, ethanol; B, 2-propanol–water; C, 2-propanol–chloroform; D, ethanol–water; E, 2-propanol; F, ethyl acetate; G, acetonitrile–water; H, acetone; I, acetonitrile–Methyl Cellosolve; J, chloroform–petroleum ether (bp 30–60°); K, methanol–ether; L, dimethylformamide; M, ethanol–ether; N, methanol; O, chloroform; P, 2-propanol–Methyl Cellosolve–water; Q, acetonitrile; R, dimethylformamide–water; S, 2-propanol–ethyl acetate; T, 2-propanol–ether; U, ethanol–2-propanol; V, methanol–2-propanol; W, 2,2,4-trimethylpentane; X, reprecipitated from aqueous sodium hydroxide with acetic acid. [c] Cl: calcd 8.27; found, 8.31. [d] H_2O: calcd, 0.49; found, 0.47. [e] H_2O: calcd, 5.80; found, 5.78. [f] H_2O: calcd, 1.30; found, 1.47. [g] *In vitro* activity against *Mycobacterium tuberculosis* $H_{37}Rv$ was evaluated in a defined medium[17] containing 10% (v/v) bovine serum.[16] Activity is based on the minimum drug concentration (μg/ml) causing total inhibition, and potency ratings are assigned within the following concentration ranges (μg/ml): ++++, <0.01; +++, 0.01–0.1; ++, 0.1–1.0; +, 1.0–10.0; –, >10.0. The reference drug, isoniazid, gives complete inhibition at 0.02 μg/ml, a rating of +++. [h] H: calcd, 7.41; found, 6.98. [i] C: calcd, 70.04; found, 69.48. [j] C: calcd, 62.31; found, 62.89. [k] C: calcd, 71.05; found, 71.65. [l] C: calcd, 77.18; found, 77.60. [m] C: calcd, 74.25; found, 73.83. [n] N: calcd, 12.95; found, 12.39. [o] N: calcd, 17.46; found, 16.98. [p] All compounds were analyzed for C, H, N.

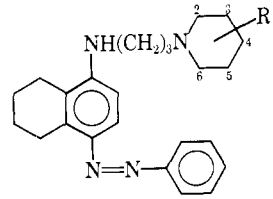
TABLE II
1-{3-[(5,6,7,8-TETRAHYDRO-4-HETEROCYCLIC AZO-1-NAPHTHYL)AMINO]PROPYL}PIPERIDINES[a]



No.	Heterocycle	Mp, °C	Yield purified, %	Purification[b] solvent	Formula[c]	MIC vs.[b] *M. tuberculosis* H37Rv
50	2-Thiazolyl	144–146	31	D	$C_{21}H_{29}N_5S$	++
51	2,4-Dihydroxy-5-pyrimidinyl	185 dec	35	R	$C_{22}H_{30}N_6O_2 \cdot 0.5H_2O$[d]	–
52	3-Pyridyl	117–119	58	B	$C_{23}H_{31}N_5$	+++
53	6-Methoxy-3-pyridyl	129–131	64	E	$C_{24}H_{33}N_5O$	+++
54	2,1,3-Benzothiadiazol-4-yl	158–159	12	Q	$C_{24}H_{30}N_6S$[e]	+
55	3-Quinolyl	185–188	75	P	$C_{27}H_{33}N_5$	+
56	6-Butoxy-3-pyridyl	123–124	45	E	$C_{27}H_{39}N_5O$	+

[a] Compounds prepared by coupling a diazotized[g] heterocyclic amine with 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**, Table VI) (procedures I and II). [b] See footnotes *b* and *g*, Table I. [c] H_2O: calcd, 2.15; found, 2.55. [d] H: calcd, 6.96; found, 6.48. [e] See Table I, footnote *p*.

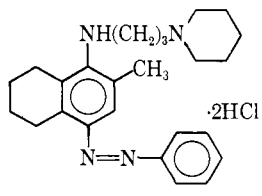
TABLE III
SUBSTITUTED 1-{3-[(5,6,7,8-TETRAHYDRO-4-PHENYLAZO-1-NAPHTHYL)AMINO]PROPYL}PIPERIDINES[a]



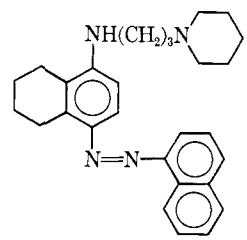
No	R	Mp, °C	Yield purified, %	Purification[b] solvent	Formula[g]	MIC vs.[b] *M. tuberculosis* H37Rv
57	3-OH	195.5–196.5 dec	20	U	$C_{21}H_{32}N_4O \cdot 2HCl$[e]	++
58	3-CH_3	101–102	44	E	$C_{25}H_{34}N_4$	+++
59	4-CH_3	114–118	56	E	$C_{25}H_{34}N_4$	+++
60	4,4-$O(CH_2)_2O$	136–138	84	E	$C_{26}H_{34}N_4O$	–
61	2-C_2H_5	70.5–72.5	49	E	$C_{26}H_{36}N_4$	+++
62	2-CH_2CH_2OH	149 dec	61	A	$C_{26}H_{36}N_4O \cdot 2HCl \cdot 1.5H_2O$[c]	++
63	4-CH_2CH_2OH	152 dec	65	M	$C_{26}H_{36}N_4O \cdot 2HCl$	+
64	3-$CHOHCH_3$	171 dec	32	V	$C_{26}H_{36}N_4O \cdot 2HCl \cdot H_2O$[d]	+
65	4-$CHOHCH_3$	128.5–131	69	E	$C_{26}H_{36}N_4O$	+
66	2-CH_3, 5-C_2H_5	198–199.5	22	E	$C_{27}H_{38}N_4 \cdot HBr$	++
67	4,4-$(CH_2)_5$	158–160	24	C	$C_{29}H_{40}N_4$	+
68	4-$N(CH_2)_5$	130–132	55	C	$C_{29}H_{41}N_5$	+
69	4-$(CH_2)_2N(CH_2)_5$	136.5–138	34	E	$C_{31}H_{45}N_5$[f]	+
70	4-$(CH_2)_3CH_3$	79–81	69	E	$C_{33}H_{50}N_4$	–

[a] Compounds prepared by amination of N-(3-bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine (VII) with the appropriate piperidine derivative (procedure IV). [b] See footnotes *b* and *g*, Table I. [c] H_2O: calcd, 5.19; found, 4.90. [d] H_2O: calcd, 3.52; found, 3.53. [e] C: calcd, 61.93; found, 61.41. [f] H: calcd, 9.30; found, 8.86. [g] See Table I, footnote *p*.

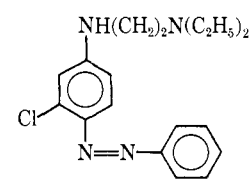
xylyl)]alkylenediamines described in Tables I–V, the 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)-amino]propyl}piperidines (Table I), 1-{3-[(5,6,7,8-tetrahydro-4-heterocyclic azo-1-naphthyl)amino]-propyl}piperidines (Table II), N,N-dialkyl-N′-(4-azo-2,3-xylyl)alkylenediamines (Table V), and various other N-mono- and N,N-dialkyl-N′-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)alkylenediamines (Table IV)



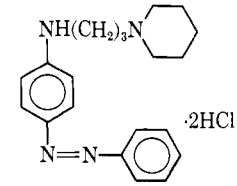
III



IV



V

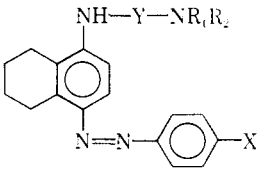


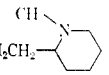
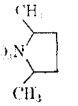
VI

were prepared by coupling a diazotized aromatic or heterocyclic amine with the appropriate N,N-dialkyl-N′-(5,6,7,8-tetrahydro-1-naphthyl- or -2,3-xylyl)alkylenediamine (Table VI) in an acidic media (procedures I–III).[7–9] Similarly, 1-{3-[(5,6,7,8-tetrahydro-2-methyl-4-phenylazo-1-naphthyl)amino]propyl}piperidine dihydrochloride (III), 1-(3-{[5,6,7,8-tetrahydro-4-(1-naphthylazo)-1-naphthyl]amino}propyl)piperidine (IV), and N′-[3-chloro-4-(phenylazo)phenyl]-N,N-diethylethylenediamine (V) were prepared by coupling

TABLE IV

OTHER N-MONO- AND N,N-DIALKYL-N'-(5,6,7,8-TETRAHYDRO-4-PHENYLAZO-1-NAPHTHYL)ALKYLENEDIAMINES

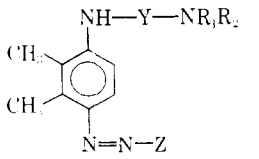


No.	X	—Y—NR1R2	Mp, °C	Yield purified, %	Procedure	Purification[a] solvent	Formula[j]	MIC vs.[c] *M. tuberculosis* H37Rv
71	H	$CH[(CH_2)_2]_2NCH_3$	138.5–140	74	I	A	$C_{22}H_{23}N_4$	+
72	H	$(CH_2)_2N(C_2H_5)_2$	99–101	22	I	A	$C_{22}H_{30}N_4$	+++
73	H		101.5–102.5	71	IV	E	$C_{23}H_{28}N_4$	++
74	H	$(CH_2)_3N(CH_2)_4$	106–107	46	IV	E	$C_{23}H_{30}N_4$	++
75	H	$(CH_2)_2N(CH_2)_5$	111.5–113.5	69	I	E	$C_{23}H_{30}N_4$	++
76	H	$(CH_2)_3N[(CH_2)_2]_2O$	120–121.5	77	IV	E	$C_{23}H_{30}N_4O$	++
77	H	$(CH_2)_3NHCHC_2H_5CH_2OH$	119–120.5	74	IV	E	$C_{23}H_{32}N_4O$	++
78	H		174–175 dec	21	I	M	$C_{24}H_{32}N_4 \cdot 2HCl \cdot H_2O$[b]	+++
79	H	$(CH_2)_3N[(CH_2)_2]_2NCH_3$	141–142	54	IV	E	$C_{24}H_{33}N_5$	+
80	H		178.5 dec	46	IV	T	$C_{25}H_{34}N_4 \cdot 2HCl$	++
81	H	$(CH_2)_3N(CH_2)_6$	185.5–187	56	IV	V	$C_{25}H_{34}N_4 \cdot 2HCl \cdot 0.5(CH_3)_2CHOH$[e]	+++
82	Cl	$ClCH_3(CH_2)_3N(C_2H_5)_2$	118 dec	42	I	T	$C_{25}H_{35}ClN_4 \cdot C_2H_2O_4$[d]	+
83	H		163.5 dec	64	IV	M	$C_{25}H_{33}N_5 \cdot 3HCl \cdot 2H_2O$[c,f]	+
84	H	$CH_3C(CH_3)_2CH_2N(CH_3)_2$	127–128.5	72	I	A	$C_{26}H_{36}N_4$	–
85	H		93.5–95	50	IV	F	$C_{25}H_{36}N_4$	+
86	H	$(CH_3)_2NCH_2CH(CH_3)_5$	176–177	23	IV	E	$C_{27}H_{38}N_4 \cdot 2HCl \cdot 0.75H_2O$[g,h]	++
87	H		121–123	52	IV	F	$C_{28}H_{38}N_4$	++
88	H		117.5–119	61	IV	E	$C_{28}H_{38}N_4$	+++

[a] See footnotes *b* and *g*, Table I. [b] H_2O: calcd, 3.85; found, 3.74. [c] Cl: calcd, 14.37; found, 14.14. [d] Monooxalate salt. [e] H_2O: calcd, 6.54; found, 6.21. [f] Cl: calcd, 19.31; found, 18.96. [g] H_2O: calcd, 2.69; found, 2.66. [h] Cl: calcd, 14.10; found, 13.96. [i] H: calcd, 7.91; found, 8.35. [j] See Table I, footnote *p*.

TABLE V

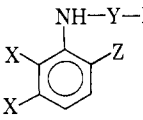
N,N-DIALKYL-N'-(4-AZO-2,3-XYLYL)ALKYLENEDIAMINES[a]

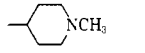
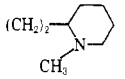


No.	—Y—NR1R2	Z	Mp, °C	Yield purified, %	Purification[b] solvent	Formula[b]	MIC vs.[b] *M. tuberculosis* H37Rv
89	$(CH_2)_2N(C_2H_5)_2$	Phenyl	184–186	71	E	$C_{20}H_{28}N_4 \cdot HCl$[c]	+
90	$(CH_2)_3N(CH_2)_5$	3-Pyridyl	202–203	36	H	$C_{21}H_{29}N_5 \cdot HCl$[d]	–
91	$(CH_2)_3N(CH_2)_5$	*p*-Chlorophenyl	218.5–219.5	50	H	$C_{22}H_{29}ClN_4 \cdot HCl$[e]	+++
92	$(CH_2)_3N(CH_2)_5$	Phenyl	95–97	39	H	$C_{22}H_{30}N_4$	+++
93	$(CH_2)_3N(CH_2)_5$	*p*-Methoxyphenyl	123–124	53	H	$C_{23}H_{32}N_4O$	++
94	$(CH_2)_3N(CH_2)_5$	3,4-Xylyl	165.5–166.6	48	C	$C_{24}H_{34}N_4$	++
95	$(CH_2)_3N(CH_2)_5$	*m*-(1-Hydroxyethyl)phenyl	219–220	71	A	$C_{24}H_{34}N_4O \cdot HCl$[f,g]	+

[a] Compounds prepared by coupling a diazotized[8,9] aromatic or heterocyclic amine with the appropriate N,N-dialkyl-N'-(2,3-xylyl)-alkylenediamine (Table VI) (procedures I, III). [b] See footnotes *b* and *g*, Table I. [c] Cl: calcd, 9.82; found, 9.72. [d] Cl: calcd, 9.14; found, 9.29. [e] Cl^-: calcd, 8.41; found, 8.70. [f] Cl: calcd, 8.23; found, 8.39. [g] N: calcd, 13.00; found, 12.57. [h] See Table I, footnote *p*.

TABLE VI
N,N-DIALKYL-N'-(5,6,7,8-TETRAHYDRO-1-NAPHTHYL- AND -2,3-XYLYL)ALKYLENEDIAMINES[a]

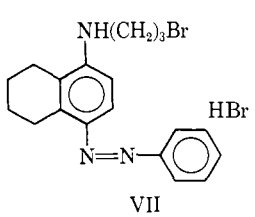


No.	X, X'	Z	—Y—NR$_1$R$_2$	Bp, °C (mm)	Yield purified, %	Procedure[a]	Formula[d]
96	$(CH_3)_2$	H	$(CH_2)_2N(C_2H_5)_2$	170–171 (20)	74	II	$C_{14}H_{24}N_2$
97	$(CH_2)_4$	H		137–138 (0.25)	43	III	$C_{16}H_{24}N_2$
98	$(CH_3)_2$	H	$(CH_2)_3N(CH_2)_5$	123–124 (0.07)	50	II	$C_{16}H_{26}N_2$
99	$(CH_2)_4$	H	$(CH_2)_2N(C_2H_5)_2$	118–119 (0.3)	35	I	$C_{16}H_{26}N_2$
100	$(CH_2)_4$	H	$(CH_2)_2N(CH_2)_5$	142–145 (0.2)	15	I	$C_{17}H_{26}N_2$
101	$(CH_2)_4$	H	$(CH_2)_3N(CH_2)_5$	147–148 (0.1)[b]	66	II	$C_{18}H_{28}N_2$
102	$(CH_2)_4$	H		158–160 (0.17)	61	II	$C_{18}H_{28}N_2$
103	$(CH_2)_4$	CH_3	$(CH_2)_3N(CH_2)_5$	139–140 (0.6)	79	II	$C_{19}H_{30}N_2 \cdot 2HCl$[c]
104	$(CH_2)_4$	H	$CHCH_3(CH_2)_3N(C_2H_5)_2$	148–151 (0.1)	57	III	$C_{13}H_{32}N_2$
105	$(CH_2)_4$	H	$CH_2C(CH_3)_2CH_2N(CH_2)_5$	165–166 (0.4)	52	III	$C_{20}H_{32}N_2$

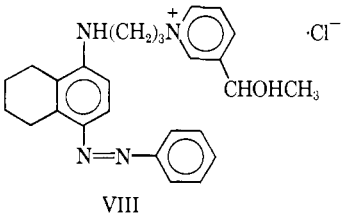
[a] Procedures employed were similar to those described previously[10] [L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **6**, 637 (1963)]; cited methods I–III correspond to those described on p 644 of this reference. [b] Mp 55.5–56.5°. [c] Dihydrochloride crystallized from *i*-PrOH, mp 228.5–231.5°. [d] See Table I, footnote *p*.

diazotized aniline or 1-naphthylamine with 1-{3-[(5,6,7,8-tetrahydro-2-methyl-1-naphthyl)amino]-propyl}piperidine (**103**), 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**), and N,N-diethyl-N'-(3-chlorophenyl)ethylenediamine, respectively. 1-[3-(*p*-Phenylazoanilino)propyl]piperidine dihydrochloride (VI) was prepared by alkylation of the sodium salt of *p*-phenylazoaniline with 1-(3-chloropropyl)piperidine in toluene. The intermediate N,N-dialkyl-N'-(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)alkylenediamines (Table VI) were prepared by alkylation of 5,6,7,8-tetrahydro-1-naphthylamine or 2,3-xylylamine with a dialkylaminoalkyl halide (methods I and II, Table VI), or by reductive alkylation of 5,6,7,8-tetrahydro-1-naphthylamine with an aminoaldehyde or ketone (method III, Table VI).[10]

Alternatively, the condensation of N-(3-bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine hydrobromide (VII) with an excess of the appropriate amine afforded a facile route to 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]-propyl}piperidine compounds substituted in the piperi-



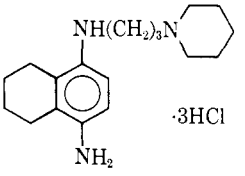
VII



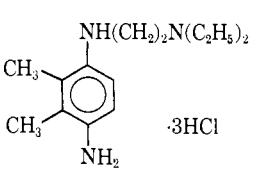
VIII

dine ring (Table III)[11] and to certain N-mono- and N,N-dialkyl-N'-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)-1,3-propanediamines (Table IV) in which the piperidine ring is replaced with other amine substituents (procedure IV). In like manner, 3-(1-hydroxyethyl)-1-[3-(5,6,7,8-tetrahydro-4-phenyl-azo-1-naphthylamino)propyl]pyridinium chloride (VIII) was prepared from VII and 3-(1-hydroxyethyl)-pyridine. The starting material VII was prepared from 3-(5,6,7,8-tetrahydro-1-naphthylamino)propanol[12] by treatment with 48% hydrobromic acid followed by coupling of the intermediate N-(3-bromopropyl)-5,6,7,8-tetrahydro-1-naphthylamine hydrobromide with diazotized aniline in dilute hydrobromic acid.

In anticipation that the N,N-dialkyl-N'-[4-azo-(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines, like 4'-sulfamyl-2,4-diaminoazobenzene[13] and the 4-(aminoalkylamino)-1-naphthylazo schistosomicides,[7-9,14] might undergo reductive scission *in vivo* to give active metabolites,[14] the reduction products 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)-propyl]piperidine (IX) and N-(2-diethylaminoethyl)-2,3-dimethyl-*p*-phenylenediamine (X) were prepared. The synthesis of these diamines was readily accom-



IX



X

plished by catalytic hydrogenation of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}-piperidine (**14**) and N,N-diethyl-N'-(4-phenylazo-2,3-xylyl)ethylenediamine (**89**), respectively, over Raney nickel in methanol or ethanol.[14] The preparation of 1,1'-[azobis(5,6,7,8-tetrahydro-1,4-naphthyleneimino-trimethylene)]dipiperidine (XIVa) and 1-[3-(4-{5,6,7,8-tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl-

(10) L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **6**, 637 (1963).

(11) The authors are indebted to Dr. F. E. Cislak of the Reilly Tar and Chemical Corp., Indianapolis, Ind., for his generosity in supplying samples of many of the piperidine derivatives employed in this investigation.

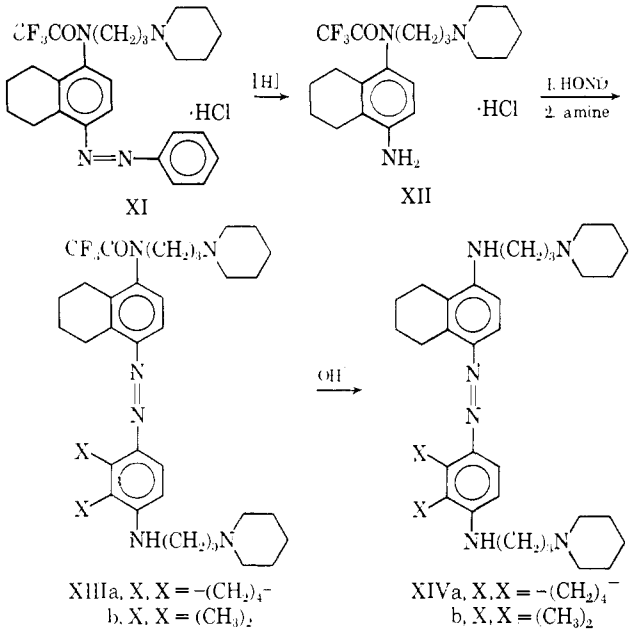
(12) Purchased from Kaplop Laboratories, Detroit, Mich.

(13) Prontosil®. For an historical summary, see A. Borger, "Medicinal Chemistry," 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, pp 800–801.

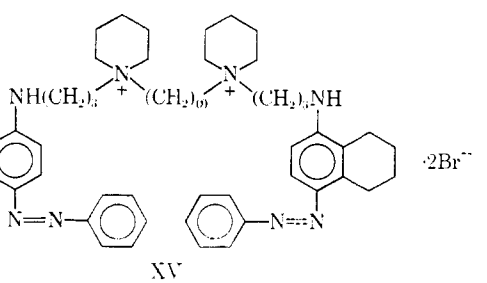
(14) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *J. Med. Chem.*, **7**, 487 (1964).

azo}-2,3-xylidino)propyl]piperidine (XIVb) was also initiated, since reductive scission would yield IX and related diamines exclusively. Compounds XIVa and b were prepared according to the scheme outlined in Chart I. Acylation of **14** with trifluoroacetic anhydride in dimethylformamide gave 2,2,2-trifluoro-N-(3-piperidinopropyl)-N-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)acetamide hydrochloride (XI) in 98% yield. Hydrogenation of XI utilizing Raney nickel in methanol gave N-(4-amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-N-(3-piperidinopropyl)acetamide hydrochloride (XII) (52%), which was diazotized and coupled with 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**) or 1-[3-(2,3-xylidino)propyl]piperidine (**98**) to give the intermediate 2,2,2-trifluoroacetanilides XIIIa and b. The latter compounds were hydrolyzed directly to XIVa and b without purification.

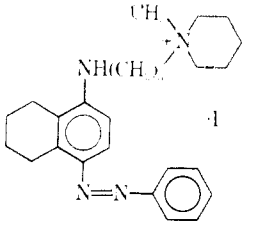
CHART I



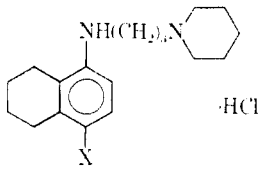
In order to study the influence of quaternization on antituberculosis activity, two representative quaternary salts of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) were prepared, namely 1,1'-decamethylenebis{1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]-piperidinium bromide} (XV) and 1-methyl-1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]-piperidinium iodide (XVI). 1-{3-[(4-Chloro- and 4-methoxy-5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}-piperidine hydrochlorides (XVIIa and b) were prepared by alkylation of 4-chloro- and 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine with 1-(3-chloropropyl)-piperidine.[15]



XV



XVI



XVIIa, X = Cl; b, X = OCH3

Biological Section

Antituberculosis Studies.—The N-mono- and N,N-dialkyl-N'-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines (Tables I–V) and compounds III–XVIIa,b were tested against the human virulent $H_{37}Rv$ strain of *M. tuberculosis in vitro* and in mice. Inasmuch as details of these test procedures have been described elsewhere,[16,17] only the main features will be reviewed here.

In vitro studies against *M. tuberculosis* $H_{37}Rv$ were conducted in a defined medium[17] containing 10% (v/v) bovine serum. Minimum total inhibition concentrations were estimated by visual inspection after incubation for 7 days at 37°. Activity was based on the minimum inhibitory concentration (MIC) of drug that caused total inhibition, and potency ratings (Tables I–V, VII) were assigned to indicate the approximate level of growth inhibition within the following concentration ranges (μg/ml): ++++, <0.01; +++, 0.01-0.1; ++, 0.1-1.0; +, 1.0-10.0; −, >10.0. The reference drug, isoniazid, causes complete inhibition at approximately 0.02 μg/ml and is therefore assigned a rating of +++.

TABLE VII
ACTIVITY OF MISCELLANEOUS COMPOUNDS AGAINST *Mycobacterium tuberculosis* $H_{37}Rv$ *in Vitro*

No.	MIC[a]
III	+
IV	+
V	−
VI	+
VII	−
VIII	+
IX	−
X	+
XI	+
XII	−
XIVa	−
XIVb	−
XV	++
XVI	+
XVIIa	+
XVIIb	−

[a] See footnote *g*, Table I.

(15) E. F. Elslager, D. B. Capps, and L. M. Werbel, *J. Med. Chem.*, **7**, 658 (1964).

(16) M. W. Fisher, M. C. Manning, L. A. Gagliardi, M. R. Gaetz, and A. L. Erlandson, *Antibiot. Ann. 1959–1960*, 293 (1960).

(17) M. W. Fisher, *Proc. Soc. Exp. Biol. Med.*, **85**, 538 (1954).

Evaluation of the drugs *in vivo* was carried out in CF-1 male mice initially weighing 12–14 g. The mice were challenged intravenously with approximately 0.1 mg wet weight of *M. tuberculosis* $H_{37}Rv$, subdivided randomly into treatment and control groups of ten animals, and placed on drug–diet the same day. Drugs were administered in a powdered diet for 7 or 14 days, and drug ingestion was determined by weighing unused and spilled food. Death and survival data was computed following observation periods ranging up to 120 days. Groups of untreated mice, and mice given *p*-aminosalicylic acid (PAS) at a diet level of 0.5% for 7 days or 0.75% for 14 days, were included in each experiment as controls. Assessment of *in vivo* activity was based on the magnitude of the difference (ΔST_{50}) between the median survival time (ST) of treated and untreated groups of mice.

Antituberculosis activity *in vitro* is widespread among the N-mono- and N,N-dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines (Tables I–V), and 28 compounds exhibited a similar order of potency as isoniazid. However, activity in mice is relatively specific, and strong effects were observed only among the 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo)-1-naphthyl]amino}propyl)piperidines (I) and 1-(3-{[5,6,7,8-tetrahydro-4-(3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (II). Five of the more promising compounds (**3**, **6**, **14**, **24**, **53**) were selected for expanded *in vivo* studies. A comparison of the relative effectiveness of these compounds, *p*-aminosalicylic acid (PAS), and isoniazid (INH) against *M. tuberculosis* $H_{37}Rv$ in mice is set forth in Table VIII.

Antileprosy Studies.—In view of the interesting activity of **3**, **6**, **14**, **24**, and **53** against *M. tuberculosis* in mice (Table VIII), the drugs were supplied to Dr. Y. T. Chang of the National Institutes of Health for evaluation against murine leprosy.[5,18] Female Swiss albino mice weighing 16–20 g were used in groups of 20, and the groups were caged separately. Each mouse was inoculated intraperitoneally with 0.5 ml of a 1:30 suspension in normal saline of the omenta and pelvic fatty pads from mice which had been infected 4–5 months previously with the Hawaiian strain of *Mycobacterium lepraemurium*. The drugs were administered continuously by drug–diet, and treatment commenced on the day after inoculation. In most experiments, mice were killed at the end of 3 months. In a single long-term experiment, designed to observe the survival time, the animals were continuously treated with drugs until the time of death.

Autopsy was performed on all animals killed at the end of 3 months and on those which died during the observation period of the long-term experiments. The average weight of the omenta and pelvic fatty pads and a "leprosy index," which is an average evaluation of the gross lesions in various sites and organs, served as the basis for evaluating chemotherapeutic activity.[18] It was concluded that compounds **6**, **14**, **24**, and **53** showed definite suppressive activity in murine leprosy when administered in dose levels ranging from 0.00625 to 0.025% in the diet.[5]

Toxicological Studies.—Results of preliminary toxicological studies[19] with 1-{3-[4-(*p*-chlorophenylazo)-5,6,7,8-tetrahydro-1-naphthylamino]propyl}piperidine (**6**) indicate that the acute oral toxicity of the compound is relatively low; acute single dose LD_{50} values in rats and mice are 1122 ± 83 and 302 ± 31 mg/kg, respectively. However, chronic administration of the drug to rats in daily doses as low as 5 mg/kg for 28 days induces clinical and pathological findings, including cutaneous discoloration, food intake and weight gain depression, and pulmonary lesions, which are not readily reversed after an equal period of drug withdrawal. The relative toxicological properties of other active members of the series have not yet been assessed.

TABLE VIII

EFFECTS OF 1-(3-{[5,6,7,8-TETRAHYDRO-4-(PHENYLAZO- AND -3-PYRIDYLAZO)-1-NAPHTHYL]AMINO}PROPYL)PIPERIDINES AGAINST *Mycobacterium tuberculosis* $H_{37}Rv$ IN MICE

No.	Compound	Drug: % in diet	Drug: mg/kg daily, 14 days	Mice median survival time, days: ST_{50}	Mice median survival time, days: ΔST_{50}[a]
3	I, R = H; X = 4-Br	0.01	11	38	27
		0.005	5	19	8
		0.0025	3	11	0
6	I, R = H; X = 4-Cl	0.02	16	78	67
		0.01	9	42	31
		0.005	5	33	22
		0.0025	2	11	0
14	I, R = H; X = H	0.04	41	50	39
		0.02	25	37	26
		0.01	11	13	2
24	I, R = H; X = 4-OCH_3	0.04	42	50	39
		0.02	24	26	15
		0.01	8	13	2
		0.005	4	11	0
53	II, Y = OCH_3	0.02	24	46	35
		0.01	12	31	20
		0.005	5	13	2
		0.0025	3	10	0
	p-Aminosalicylic acid (PAS)	0.75	850	25	12
	Isoniazid (INH)	0.004	6	52	39
		0.0026	4	26	13
		0.0013	2	17	4

[a] Median survival time for untreated control animals ranged from 11 to 13 days. ΔST_{50} represents the difference between the median survival time of treated and untreated mice.

Experimental Section[20]

N-Mono- and N,N-Dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl- and -2,3-xylyl)]alkylenediamines (Tables I–V). Procedure I.—A solution of 107 g (1.55 moles) of $NaNO_2$ in 1.5 l. of H_2O was added at 0° with stirring to a solution of 144 g (1.55 moles) of aniline in a mixture of 450 ml of concentrated HCl and 1.5 l. of H_2O. When diazotization was complete, the diazonium salt solution was added at 0° with stirring to a solution of 422 g (1.55 moles) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]-propyl}piperidine (**101**) in a mixture of 750 ml of concentrated HCl and 8 l. of 50% aqueous EtOH. The deep reddish brown mixture was stirred for 3 hr at 0–5° and then allowed to warm to room temperature overnight. Excess aqueous NaOH was added and the orange-red precipitate that separated was collected by filtration, washed with H_2O, and dried. Crystallization from Me_2CO gave 487 g (83%) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) as orange-red crystals, mp 115–116°.

(18) Y. T. Chang *Intern. J. Leprosy*, **21**, 47 (1953).

(19) D. H. Kaump, R. W. Bucklin, R. A. Fisken, J. E. Fitzgerald, J. A. Lucas, T. F. Reutner, J. L. Schardein, and O. J. Sorenson, Jr., unpublished data in the files of Parke, Davis and Co., Ann Arbor, Mich.

(20) Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover melting point apparatus. Water determinations were made by the Karl Fischer method. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Procedure II.—A solution of 5.0 g (0.05 mole) of 2-aminothiazole in 250 ml of 50% (v/v) H_2SO_4 was diazotized at 0 to $-10°$ by the slow addition of $NOHSO_4$ (prepared from 3.5 g of $NaNO_2$ and 35 ml of concentrated H_2SO_4). The mixture was stirred for 30 min at $-5°$ and added to a solution of 13.6 g (0.05 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}-piperidine (**101**) in 250 ml of 50% H_2SO_4 at 0 to $-10°$. After 15 min, 1.5 l. of H_2O was added dropwise at 0 to $-5°$ and the mixture was allowed to warm to room temperature overnight. During this time the mixture became a deep red-purple. An additional 1 l. of H_2O was then added, and the cooled solution was made alkaline with concentrated aqueous NaOH and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were concentrated to dryness leaving a viscous mass which solidified on standing overnight. This material was dissolved in $CHCl_3$ and filtered. The filtrate was washed with H_2O and dried (K_2CO_3). The solvent was removed *in vacuo* and the residue crystallized from aqueous EtOH to give 6.0 g (31%) of 1-(3-{[5,6,7,8-tetrahydro-4-(2-thiazolylazo)-1-naphthyl]amino}propyl)piperidine (**50**) as dark red-green iridescent crystals, mp 144–146°.

Procedure III.—Aniline (4.6 g, 0.05 mole) was diazotized and added at 0–5° to a solution of 12.3 g (0.05 mole) of 1-[3-(2,3-xylidino)propyl]piperidine (**98**) in 300 ml of H_2O and 25 ml of glacial AcOH. The mixture was stirred for 2 hr and neutralized with NaOAc. The orange gum which formed solidified on standing. The solid was collected by filtration and resuspended in H_2O, and the mixture was treated with NH_4OH. The gum which formed was again suspended in H_2O and the mixture was heated on a steam bath to induce crystallization. The crude product was collected by filtration, washed with H_2O, and dried. Crystallization from Me_2CO gave 7.0 g (39%) of the desired 1-[3-(4-phenylazo-2,3-xylidino)propyl]piperidine (**92**) as orange crystals, mp 95–97°.

Procedure IV.—A mixture of 7.4 g (0.0164 mole) of N-(3-bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine (VII) and 100 ml of 4-methylpiperidine was heated on a steam bath for 2 hr and poured into H_2O, and the mixture was extracted with $CHCl_3$. The organic layer was washed thoroughly with H_2O, dried (K_2CO_3), and concentrated to dryness *in vacuo*. The residue was crystallized from *i*-PrOH to give 3.6 g (56%) of 4-methyl-1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)-amino]propyl}piperidine (**59**) as orange needles, mp 114–118°.

When supplies of the amine component were scarce, the reaction was carried out in DMF (10 ml/0.02 mole run) utilizing 3 equiv of amine. In those cases where the bases could not be induced to crystallize, salts were prepared either by triturating the base with a *i*-PrOH–HCl mixture or by bubbling anhydrous HCl into a solution of the base in anhydrous Et_2O.

1-{3-[(5,6,7,8-Tetrahydro-2-methyl-4-phenylazo-1-naphthyl)-amino]propyl}piperidine Dihydrochloride (III).—Aniline (9.3 g, 0.1 mole) was diazotized and coupled with 23.0 g (0.1 mole) of 1-{3-[(5,6,7,8-tetrahydro-2-methyl-1-naphthyl)amino]propyl}-piperidine (**103**) according to procedure I. The crude dye was purified as the dihydrochloride salt and was obtained as orange crystals from EtOH: mp 171–173°, yield 20.3 g (42%). *Anal.* ($C_{28}H_{34}N_4 \cdot 2HCl \cdot H_2O$) C, H, N, Cl, H_2O.

1-{3-[5,6,7,8-Tetrahydro-4-(1-naphthylazo)-1-naphthyl]amino}propyl)piperidine (IV).—1-Naphthylamine (7.2 g, 0.05 mole) was diazotized and coupled with 13.6 g (0.05 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**) according to procedure I. The product crystallized from MeCN–Methyl Cellosolve as maroon needles, 17.7 g (83%), mp 169–170°. *Anal.* ($C_{28}H_{34}N_4$) C, H, N.

N'-[3-Chloro-4-(phenylazo)phenyl]-N,N-diethylethylenediamine Salt with 0.5 Formula Weight of 1,5-Naphthalenedisulfonic Acid (V).—Aniline (9.3 g, 0.1 mole) was diazotized and coupled with 22.6 g (0.1 mole) of N,N-diethyl-N'-(3-chlorophenyl)ethylenediamine according to procedure I. A small sample of the crude dye (16.7 g, 51%) was purified as the 1,5-naphthalenedisulfonic acid salt and was obtained as reddish brown crystals from DMF–Et_2O; mp 208–210°. *Anal.* ($C_{16}H_{20}ClN_4 \cdot 0.5C_{10}H_8O_6S_2$) C, H, N.

1-[3-(*p*-Phenylazoanilino)propyl]piperidine Dihydrochloride (VI). To a slurry of 9.6 g (0.2 mole) of a 50% NaH dispersion in oil in toluene was added a solution of 39.4 g (0.2 mole) of 4-phenylazoaniline in toluene (total volume 650 ml). The mixture was heated under reflux for 1 hr, cooled, and to it was added a solution of 32.3 g (0.2 mole) of 1-(3-chloropropyl)piperidine in 150 ml of dry toluene. The mixture was heated under reflux for 22 hr and cooled. Water was cautiously added and the organic layer was separated, dried (K_2CO_3), and concentrated to dryness *in vacuo*. The oily residue was treated with an excess of a *i*-PrOH–HCl mixture and the crude red dye was filtered off and dried (72 g). Crystallization from EtOH gave 41.0 g (48%) of a red-purple solid, mp 142–147°. *Anal.* ($C_{28}H_{26}N_4 \cdot 2HCl \cdot 1.67H_2O$) C, H, N, Cl, H_2O.

N-(3-Bromopropyl)-5,6,7,8-tetrahydro-1-naphthylamine Hydrobromide.—A solution of 67 g (0.33 mole) of 3-(5,6,7,8-tetrahydro-1-naphthylamino)propanol[12] in 530 g (3.3 moles) of 48% HBr was heated under reflux for 5 hr and cooled. The solid was collected by filtration, washed with *i*-PrOH, and dried *in vacuo* at 50°. Purification from *i*-PrOH gave 78 g (69%) of product, mp 194–198°. *Anal.* ($C_{13}H_{18}BrN \cdot HBr$) C, H, N, Br^-.

N-(3-Bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine Hydrobromide (VII).—N-(3-Bromopropyl)-5,6,7,8-tetrahydro-1-naphthylamine hydrobromide (105 g, 0.3 mole) was dissolved in 1.4 l. of boiling EtOH and the solution was cooled rapidly to 0° with vigorous stirring to produce a fine suspension. To it was added with stirring at 0–5° a solution of phenyldiazonium bromide prepared from 27.9 g (0.3 mole) of aniline, 1.2 l. of H_2O, 77 ml (0.7 mole) of 48% HBr, and 20.7 g (0.3 mole) of $NaNO_2$. The mixture was stirred for 3 hr at 4°, then refrigerated overnight. The precipitate thus obtained was collected by filtration, washed with cold H_2O, and dried in the air for 2 days and at 50° *in vacuo* for 24 hr. The product weighed 126.8 g (93%), mp 197–200.5°. For analysis, a small sample was crystallized from MeOH containing HBr. *Anal.* ($C_{19}H_{22}BrN_3 \cdot HBr$) C, H, N; Br: calcd, 35.27; found, 34.83.

3-(1-Hydroxyethyl)-1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]pyridinium Chloride (VIII).—A mixture of 9.1 g (0.02 mole) of N-(3-bromopropyl)-5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamine hydrobromide (VII) and 50 ml of 3-(1-hydroxyethyl)pyridine was heated on a steam bath for 2 hr. The orange-red solution was poured onto 500 g of ice and H_2O. The red solution was saturated with NaCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was concentrated to small volume and Et_2O was added to the cloud point. Cooling and scratching induced precipitation of a yellow solid which was collected and recrystallized from *i*-PrOH giving 7.0 g (78%) of yellow needles, mp 192.5–194°. *Anal.* ($C_{26}H_{30}ClN_4O$) C, H, N, Cl.

1-{3-[4-Amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl}-piperidine Trihydrochloride (IX).—A solution of 33.6 g (0.089 mole) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) in 300 ml of EtOH was hydrogenated over 3 g of Raney nickel at an initial H_2 pressure of 3.5 kg/cm². When the theoretical amount of H_2 had been absorbed, the catalyst was removed by filtration and the filtrate was treated immediately with an excess of a 30% HCl–*i*-PrOH solution to arrest air oxidation. The mixture was concentrated to 200 ml and the off-white solid was collected by filtration, washed with *i*-PrOH, and dried *in vacuo* at 40° for 24 hr. The product weighed 34.7 g (94%), mp 198.5–201.5°. *Anal.* ($C_{19}H_{29}N_3 \cdot 3HCl \cdot H_2O$) C, H, N, Cl.

N-(2-Diethylaminoethyl)-2,3-dimethyl-*p*-phenylenediamine Trihydrochloride (X).—N,N-Diethyl-N'-(4-phenylazo-2,3-xylyl)-ethylenediamine hydrochloride (**89**) (14.0 g, 0.039 mole) was hydrogenated in MeOH over Raney nickel and the reaction mixture was processed according to the procedure described for IX. Crystallization from MeOH–*i*-PrOH gave 11.3 g (83%) of colorless crystals, mp 221–225°. *Anal.* ($C_{14}H_{25}N_3 \cdot 3HCl$) C, H, N, Cl.

2,2,2-Trifluoro-N-(3-piperidinopropyl)-N-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)acetamide Hydrochloride (XI).—To a solution of 412 g (1.1 moles) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) in 2 l. of DMF was added during 45 min a solution of 277 g of trifluoroacetic anhydride in 500 ml of DMF. The reaction was slightly exothermic and the temperature rose to 40°. After stirring for 4 hr the mixture was poured into 12 l. of iced H_2O containing 750 ml of concentrated HCl. The precipitate was collected by filtration, washed thoroughly with H_2O, and dried to give 571 g (98%) of orange crystals, mp 186–187°. *Anal.* ($C_{28}H_{30}F_3N_5O \cdot HCl \cdot H_2O$) C, H, N, Cl, H_2O.

N-(4-Amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-N-(3-piperidinopropyl)acetamide Hydrochloride (XII).—A solution of 53.9 g (0.1 mole) of XI was reduced in MeOH over Raney nickel at room temperature and an initial pressure of 3.5 kg/cm². The solvent was removed and the residue recrystallized succes-

sively from 450 ml of *i*-PrOH and 300 ml of MeOH. The pale yellow solid weighed 22.0 g (52%), mp 255–257°. *Anal.* ($C_{20}H_{28}F_3N_3O \cdot HCl$) C, H, N, Cl.

1,1'-[Azobis(5,6,7,8-tetrahydro-1,4-naphthyleneiminotrimethylene)]dipiperidine (XIVa).—A solution of 11.0 g (0.026 mole) of XII in 300 ml of H_2O containing 8 ml of concentrated HCl was diazotized at 0° with 26 ml of 1 *N* $NaNO_2$. The diazonium solution was added at 0–5° to a cold solution of 7.1 g (0.026 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**) in 100 ml of EtOH, 200 ml of H_2O, and 12.5 ml of concentrated HCl. The purple solution was stirred overnight and made alkaline with NH_4OH, and the sticky product was washed with H_2O. The crude amide XIIIa was dissolved in 500 ml of Me_2CO–MeOH, 20 ml of 2 *N* methanolic NaOH was added, and the mixture was stirred overnight. The solid was collected by filtration, dried, and crystallized from $CHCl_3$ to give 7.5 g (51% over-all) of red needles, mp 235–237°. *Anal.* ($C_{36}H_{54}N_6$) C, H, N.

1-[3-(4-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthylazo}-2,3-xylidino)propyl]piperidine (XIVb).—N-(4-Amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-N-(3-piperidinopropyl)acetamide hydrochloride (XII) (28.1 g, 0.067 mole) was coupled with 1-[3-(2,3-xylidino)propyl]piperidine (**98**) (16.5 g, 0.067 mole) using the procedure described for XIVa. The crude amide (XIIIb) was hydrolyzed without purification and the product was crystallized from $CHCl_3$–petroleum ether (bp 30–60°) to give orange crystals, mp 199.5–201°, yield 18.0 g (49% over-all). *Anal.* ($C_{34}H_{52}N_6$) C, H, N.

1,1'-Decamethylenebis{1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]piperidinium Bromide} (XV).—A solution of 10.0 g (0.027 mole) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) and 3.9 g (0.013 mole) of 1,10-dibromodecane in 150 ml of MeCN was heated under reflux for 74 hr. Some solid had formed. Me_2CO was added to induce further precipitation and the solid was removed by filtration. The crude quaternary salt was triturated with boiling Me_2CO, filtered, and dried to give 7.5 g (53%) of an orange-red solid, mp 209–213° *Anal.* ($C_{58}H_{84}Br_2N_8$) H, N, Br; C: calcd, 66.14; found, 65.67.

1-Methyl-1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]piperidinium Iodide (XVI).—A mixture of 10.0 g (0.027 mole) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) and 50 ml of MeI was stirred briefly. Solution began followed by an exothermic reaction and precipitation of an orange solid. The reaction mixture was warmed on a steam bath for 15 min, and the product was collected by filtration and recrystallized from 1.2 l. of EtOH. The orange needles thus obtained weighed 11.3 g (82%), mp 210–212°. *Anal.* ($C_{25}H_{35}N_4I$) C, H, N.

1-{3-[(4-Chloro-5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}-piperidine Hydrochloride (XVIIa).—To a solution of 41.6 g (0.229 mole) of 4-chloro-5,6,7,8-tetrahydro-1-naphthylamine in 1 l. of dry toluene was added 50.0 g (0.25 mole) of 1-(3-chloropropyl)piperidine hydrochloride and 64 g of anhydrous K_2CO_3, and the mixture was heated under reflux with stirring for 24 hr. Excess aqueous NaOH was added and the mixture was stirred for 2 hr. The toluene layer was separated and dried (K_2CO_3), and volatile materials were removed *in vacuo*. The product was purified as the HCl salt, off-white crysals from *i*-PrOH, mp 204–207°, yield 18.5 g (24%). *Anal.* ($C_{18}H_{27}ClN_2 \cdot HCl$) C, H, N.

1-{3-[(5,6,7,8-Tetrahydro-4-methoxy-1-naphthyl)amino]propyl}piperidine Hydrochloride (XVIIb).—Alkylation of 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine (50.0 g, 0.283 mole) with 1-(3-chloropropyl)piperidine hydrochloride (56.0 g, 0.283 mole) according to the procedure described for the preparation of XVIIa gave 45.8 g (48%) of the desired product as off-white crystals from EtOH, mp 208–211°. *Anal.* ($C_{19}H_{30}N_2O \cdot HCl$) C, H, N.

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Antiprotozoal Quinones. I. Synthesis of 2-Hydroxy-3-alkyl-1,4-naphthoquinones as Potential Coccidiostats[1]

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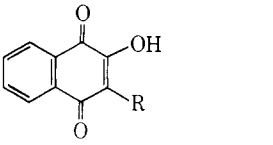
A series of 2-hydroxy-3-alkyl-1,4-naphthoquinones has been synthesized; the compounds have been screened as potential coccidiostats. Six of the new quinones have activity against *Eimeria brunetti* infections in chickens with 0.0125% of compound in the feed. The alkyl groups imparting greatest activity are 3-(4-cyclopentylphenyl)propyl, 3-(4-cycloheptylphenyl)propyl, 3-[4-(3-pentyloxy)phenyl]propyl, and 3-[4-(4-heptyloxy)phenyl]-propyl. In a series of quinones having 3-(4-alkoxyphenyl)propyl side chains, the activity increases with increasing lipophilicity of the alkoxy group. This parallels the effect first observed by Fieser, *et al.*, for the antimalarial activity of 2-hydroxy-3-alkyl-1,4-naphthoquinones.

The 2-hydroxy-3-alkyl-1,4-naphthoquinones have been extensively studied by Fieser and his coworkers[3,4] as potential antimalarials. In 1960 a number of hydroxyquinones selected from Fieser's extensive collection (Table I) were screened by Merck Sharp and Dohme as potential coccidiostats.[5] Several of the



1a, R = $(CH_2)_9$–S

b, R = $(CH_2)_4$–O–

c, R = $(CH_2)_3$–S

compounds, especially **1a–c**, showed a significant level of coccidiostat activity in chickens infected with

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(2) Arthur D. Little, Inc., Acorn Park, Cambridge, Mass. 02140.

(3) L. F. Fieser, *et al.*, *J. Am. Chem. Soc.*, **70**, 3151–3244 (1948).

(4) (a) L. F. Fieser, J. P. Shirmer, S. Archer, R. L. Lorenz, and P. J. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967); (b) L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berbarian, and R. G. Slighter, *ibid.*, **10**, 517 (1967).

(5) The selection of most of the compounds in Table I was made by E. F. Rogers, Merck Sharp and Dohme.