2-methoxyethanol. After 19 hr at room temperature, the solution was diluted to about 300 ml with water and acidified to pH 2.9 by gradual addition of 1 *N* HCl. After cooling, the solid was collected and washed with water, to yield 1.26 g (76%) of XX, mp 232–236° dec. A sample was recrystallized from ethanol to give pale yellow flakelets, mp 228–229° dec.

Anal. Calcd for $C_{15}H_{17}ClN_6O_3S$: C, 43.64; H, 4.15; Cl, 8.59; N, 20.36. Found: C, 43.57; H, 4.44; Cl, 8.66; N, 20.47.

Acknowledgments.—The authors wish to express their appreciation to Dr. Arnold Brossi for helpful suggestions and continued interest. We wish to thank Dr. V. Toome for the determination of the ultraviolet spectra and the pK_a values, Dr. Al Steyermark for the microanalyses, and Dr. L. O. Randall and his staff for the pharmacology.

Synthetic Schistosomicides. VIII. N-Mono- and N,N-Dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines and Related Compounds[1]

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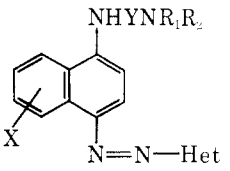
Several hundred N-mono- and N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines (III) were synthesized by (1) coupling a diazotized arylamine with the appropriate 1-(aminoalkyl)naphthylamine, (2) amination of a N-(ω-haloalkyl)-4-(arylazo)-1-naphthylamine, and (3) hydrolysis of N-(aminoalkyl)-N-[4-(arylazo)-1-naphthyl]-2,2,2-trifluoroacetamides or formamides. Schistosomicidal activity among the N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines is widespread, and twenty-nine compounds cured *Schistosoma mansoni* infections in mice at doses ranging from 78 to 734 mg/kg per day for 14 days. Six compounds were evaluated against *S. mansoni* infections in rhesus monkeys and each showed significant antischistosomal activity in this host. Structure–activity relationships are discussed.

During the course of continuing efforts in these laboratories to develop novel schistosomicidal agents, it was discovered that various [4-(dialkylaminoalkylamino)-1-naphthylazo]heterocyclic compounds (I) possess strong therapeutic activity against *Schistosoma*

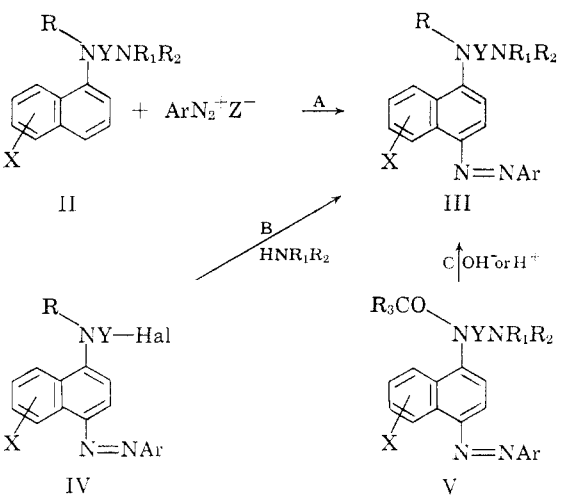


I

mansoni in experimental animals.[2,3] We have been actively engaged in extending this work to other series[1,4–8] and now wish to report the synthesis of a group of N-mono- and N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines (III, where R, R_1, and R_2 represent a hydrogen atom or an alkyl group, Y an alkylene radical, X a hydrogen or halogen atom or a hydroxy or alkoxy group, and Ar a phenyl or naphthyl radical), many of which exhibit remarkable schistosomicidal activity in mice. After the completion of this work, the synthesis of several azo derivatives of 1-diethylamino-3-(1-naphthylamino)-2-propanol was reported.[9]

Three major routes (Chart I) were utilized in the preparation of the N-mono- and N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines (III) (Tables

CHART I



I–V): (1) coupling a diazotized arylamine with the appropriate 1-(aminoalkyl)naphthylamine (II)[10] (route A) (procedures I–IV); (2) amination of a N-(ω-haloalkyl)-4-(arylazo)-1-naphthylamine (IV) with the appropriate amine (route B) (procedure VI); and (3) hydrolysis of an N-(aminoalkyl)-N-[4-(arylazo)-1-naph-

(1) Previous paper: E. F. Elslager and D. B. Capps, *J. Med. Chem.*, **7**, 663 (1964).

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

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(8) E. F. Elslager, D. B. Capps, and L. M. Werbel, *ibid.*, in preparation.

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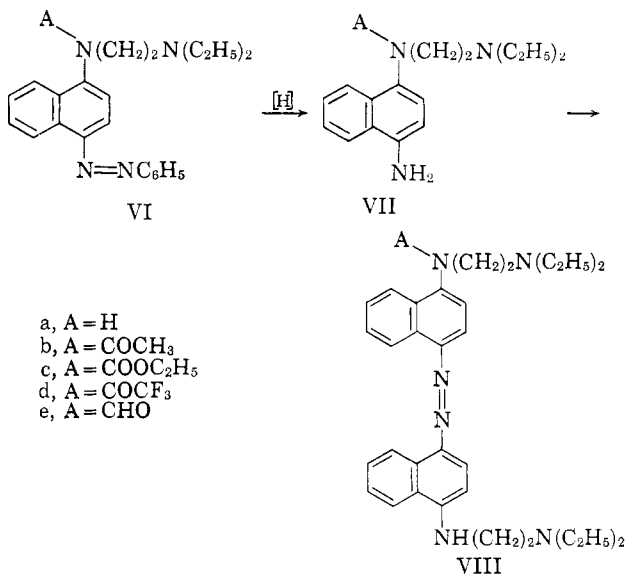
thyl]-2,2,2-trifluoroacetamide or formamide (V) (route C) (procedures V, VII, and VIII). Among them, route A proved to be the most useful because of the ready availability of a variety of diazo components and 1-(aminoalkyl)naphthylamines (II).[10] Route B was especially applicable for the preparation of groups of 4-arylazo-1-naphthylalkylenediamines in which only the aliphatic amine portion was varied.

The action of nitrous acid on various aromatic diamines and hydroxyamines leads to the formation of undesirable by-products,[11] thereby limiting the usefulness of route A for the preparation of certain 4-arylazo-1-naphthylalkylenediamines with amino or hydroxy substituents in the aryl function. Efforts were made, therefore, to develop a more versatile synthetic route to such compounds utilizing N-(dialkylaminoalkyl)-1,4-naphthalenediamine derivatives as diazo components (route C).

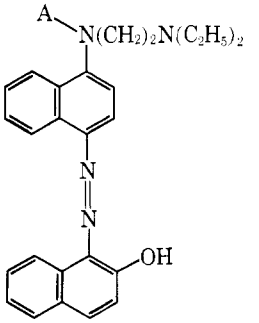
As anticipated,[11] attempts to use N-(2-diethylaminoethyl)-1,4-naphthalenediamine (VIIa)[4] in diazotization–coupling procedures with aromatic amines and phenols under a variety of experimental conditions were unsuccessful, presumably because compounds of type VIIa undergo rapid oxidative decomposition both in basic and acidic media.[4] However, N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)acetamide



(VIIb), 4-amino-N-(2-diethylaminoethyl)-1-naphthalenecarbamic acid ethyl ester (VIIc), N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide (VIId), and N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)formamide (VIIe) diazotized normally and coupled readily with 1-(2-diethylaminoethylamino)naphthalene[10] in acidic media to give the azo compounds VIIIb–e (procedures V, VII, and VIII). Compounds VIIIb–e were prepared by acylation of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa, **17**) with acetic anhydride, ethyl chloroformate, trifluoroacetic anhydride, and formic–acetic anhydride, respectively, followed by reductive scission of the intermediate N′-acyl-N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamines (VIb–e) with hydrogen over Raney nickel.

(11) For a brief review, see K. H. Saunders, "The Aromatic Diazo-compounds and Their Technical Applications," Edward Arnold and Co., London, 1949, pp 21, 30.

Surprisingly, attempts to hydrolyze VIIIb and c to N,N′′-(azodi-1,4-naphthylene)bis(N′,N′-diethylethylenediamine) (VIIIa, **209**) under a variety of experimental conditions failed. However, N-(2-diethylaminoethyl)-N-{4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1-naphthyl}-2,2,2-trifluoroacetamide (VIIId) hydrolyzed readily when treated with 2 *N* methanolic sodium hydroxide at room temperature to give VIIIa in 52% over-all yield from VIId (procedure V). Compounds **27**, **61**, **84**, and IXb (**203**) were prepared by alkaline hydrolysis of the corresponding trifluoroacetamides in a similar manner (procedures V and VII). On the other hand formamide derivatives such as N-(2-diethylaminoethyl)-N-{4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1-naphthyl}formamide (VIIIe) and N-(2-diethylaminoethyl)-N-[4-(2-hydroxy-1-naphthylazo)-1-naphthyl]formamide (IXa) were especially susceptible to acid hydrolysis yielding VIIIa and 1-[4-(2-diethylaminoethylamino)-1-naphthylazo]-2-naphthol (IXb), respectively (procedure VIII).



IXa, A = CHO
b, A = H

The hypothetical mode of action of several of the N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines is worthy of special comment. Assuming that the azo function of N,N′′-(azodi-1,4-naphthylene)bis(N′,N′-diethylethylenediamine) (VIIIa, **209**) undergoes reductive scission *in vivo*,[4] 2 moles of N-(2-diethylaminoethyl)-1,4-naphthalenediamine (VIIa) would be formed. The diamine VIIa has been postulated[4] to be a metabolite of 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]uracil and related azo compounds[2,3] and has been shown to have potent antischistosome activity *in vitro* and in mice.[4] By analogy, the cleavage of bis(*p*-aminophenyl){*p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]phenyl}methanol (X, **93**) or N-(5-{*p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]phenoxy}pentyl)phthalimide (XI, **94**) would simultaneously release two different active moieties, namely VIIa and tris(*p*-aminophenyl)methanol[12] or N-[5-(*p*-aminophenoxy)pentyl]phthalimide,[13] respectively. An alternate approach to hybrids that might possess a dual mode of action[5] involved the linkage of two active moieties through the side chain. Thus, certain structural features of both the (4-arylazo-1-naphthyl)alkylenediamines and the *p*-tolylpiperazines[14–16] were incorporated in 1-(3-chloro-*p*-tolyl-

(12) E. F. Elslager, F. W. Short, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *Nature*, **190**, 628 (1961).

(13) R. F. Collins, M. David, N. D. Edge, J. Hill, H. W. Reading, and E. R. Turnbull, *Brit. J. Pharmacol.*, **14**, 467 (1959).

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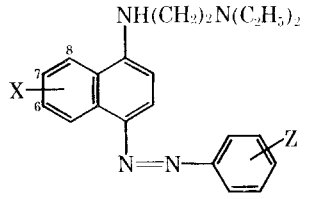
TABLE I

N′-[4-(PHENYLAZO)-1-NAPHTHYL]-N,N-DIETHYLETHYLENEDIAMINES[a]



No.	X	Z	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1	H	2-Cl, 4-Br	89–91	45	I	A	$C_{22}H_{24}BrClN_4$	57.46	57.37	5.26	5.34	12.19	12.36
2	H	3,5-Br_2	110–112	48	I	A	$C_{22}H_{24}Br_2N_4$[c]	52.40	52.62	4.80	4.93	11.11	11.00
3	H	3,5-Cl_2	107–108	69	I	A	$C_{22}H_{24}Cl_2N_4$[d]	63.61	63.38	5.82	5.85	13.49	13.50
4	H	3-Br	171–172	54	II	D	$C_{22}H_{25}BrN_4 \cdot 2HCl \cdot 1.5H_2O$[e]	50.30	50.04	5.76	6.00	10.67	10.80
5	H	4-Br	85–86	34	I	F	$C_{22}H_{25}BrN_4$	62.12	61.82	5.92	5.78	13.17	13.05
6	7-Cl	H	168–170 dec	50	II	F	$C_{22}H_{25}ClN_4 \cdot 2HCl \cdot 0.5H_2O$[f]	57.09	56.77	6.10	6.22	12.11	12.18
7	8-Cl	H	163–165	40	II	B	$C_{22}H_{26}ClN_4 \cdot 2HCl \cdot 2H_2O$[g,h]	53.94	53.45	6.38	6.33	11.44	11.48
8	H	2-Cl	99–100	76	I	B	$C_{22}H_{25}ClN_4$	69.37	69.41	6.62	6.76	14.71	14.56
9	H	3-Cl	63–64	62	I	C	$C_{22}H_{25}ClN_4$	69.37	69.03	6.62	6.57	14.71	14.57
10	H	4-Cl	94–95	70	I	A	$C_{22}H_{25}ClN_4$[i]	69.37	68.78	6.62	6.70	14.71	14.88
11	H	2-F	94–96	15	II	A	$C_{22}H_{25}FN_4 \cdot HCl$[j]	65.90	66.65	6.54	6.63	13.98	13.92
12	H	3-F	66–68	38	I	A	$C_{22}H_{25}FN_4$	72.50	72.38	6.91	7.16	15.37	15.30
13	H	4-F	70–72	47	I	A	$C_{22}H_{25}FN_4$	72.50	72.12	6.91	7.08	15.37	15.19
14	H	2-NO_2	92–93	36	III	B	$C_{22}H_{25}N_5O_2$	67.49	67.38	6.44	6.43	17.89	18.16
15	H	3-NO_2	117–118	56	III	B	$C_{22}H_{25}N_5O_2$	67.49	67.30	6.44	6.49	17.89	17.95
16	H	4-NO_2	137–138	77	III	B	$C_{22}H_{25}N_5O_2$	67.49	67.50	6.44	6.51	17.89	18.07
17	H	H	57–59	87	I	F	$C_{22}H_{26}N_4$	76.26	76.20	7.57	7.70	16.17	16.25
18	H	3-OH	179–180	65	II	E	$C_{22}H_{26}N_4O \cdot 2HCl \cdot 0.5H_2O$[k,l]	59.46	59.72	6.58	6.95	12.61	12.53
19	H	4-OH	215–216	55	II	A	$C_{22}H_{26}N_4O \cdot HCl$[m,n]	66.23	66.25	6.82	6.69	14.05	13.84
20	H	3,5-OH	194–195 dec	35	II	G	$C_{22}H_{26}N_4O_2 \cdot 2HCl \cdot 0.5H_2O$[o,p]	57.39	57.39	6.35	6.60	12.17	12.30
21	H	2-SO_3H	185 dec	86	IV	H	$C_{22}H_{26}N_4O_3S \cdot 0.75H_2O$[q]	60.05	60.11	6.30	6.41	12.73	12.71
22	H	3-SO_3H	197–198 dec	93	IV	H	$C_{22}H_{26}N_4O_3S \cdot 1.5H_2O$[r]	58.26	58.60	6.44	6.52	12.35	12.26
23	H	4-SO_3H	213–214	92	IV	H	$C_{22}H_{26}N_4O_3S$	61.95	61.79	6.15	6.35	13.14	12.93
24	7-OH	4-SO_3H	205 dec	76	IV	H	$C_{22}H_{26}N_4O_4S \cdot 2H_2O$[s]	55.21	55.27	6.32	6.14	11.71	11.76
25	H	4-AsO_3H_2	158 dec	80	IV	H	$C_{22}H_{27}AsN_4O_3 \cdot 1.5H_2O$[t]	53.12	53.43	6.08	6.24	11.26	11.26
26	H	4-$PO(OH)_2$	225–226 dec	58	IV	H	$C_{22}H_{27}N_4O_3P$	61.96	61.29	6.38	6.56	13.14	13.08
27	H	4-NH_2	200 dec	62	V	I	$C_{22}H_{27}N_5 \cdot 2.6HCl \cdot 1.2H_2O$[u,v]	55.29	55.31	6.75	6.83	14.66	14.41
28	H	4-SO_2NH_2	170–172	87	I	A	$C_{22}H_{27}N_5O_2S$	62.09	62.16	6.40	6.39	16.46	16.63
29	H	2-Br, 5-CF_3	150–152	23	II	I	$C_{23}H_{24}BrF_3N_4 \cdot 2HCl$	48.78	48.91	4.63	4.92	9.89	9.91
30	H	3-CF_3	152–154 dec	34	II	G	$C_{23}H_{25}F_3N_4 \cdot 2HCl \cdot H_2O$[w,x]	54.65	54.49	5.78	5.72	11.09	10.97
31	H	4-CN	111–112	62	I	A	$C_{23}H_{25}N_5$	74.36	74.19	6.78	6.82	18.85	18.99
32	H	2-COOH	162	31	IV	A	$C_{23}H_{26}N_4O_2 \cdot 2HCl \cdot 1.25H_2O$[y]	56.85	56.68	6.33	6.27	11.53	11.12
33	H	3-COOH	202–203 dec	64	IV	J	$C_{23}H_{26}N_4O_2$	70.74	70.99	6.71	6.91	14.35	14.21
34	H	4-COOH	146–149	81	IV	J	$C_{23}H_{26}N_4O_2 \cdot H_2O$[z]	67.62	68.01	6.91	6.75	13.72	13.93
35	H	3-OH, 4-COOH	220 dec	64	IV	J	$C_{23}H_{26}N_4O_3$	67.96	67.88	6.45	6.58	13.78	13.74
36	H	2-CH_3	92–93	75	I	F	$C_{23}H_{28}N_4$	76.63	76.95	7.83	7.73	15.54	15.67
37	H	3-CH_3	102–107	76	II	K	$C_{23}H_{28}N_4 \cdot C_6H_8O_7$[aa]	63.03	62.80	6.57	6.69	10.14	10.09
38	H	4-CH_3	78–79	44	I	A	$C_{23}H_{28}N_4$	76.63	76.87	7.83	8.12	15.54	15.69
39	6-OCH_3	H	145–148 dec	87	II	K	$C_{23}H_{28}N_4O \cdot C_6H_8O_7$[aa]	61.25	61.23	6.38	6.52	9.85	9.98
40	7-OCH_3	H	164–165	82	II	E	$C_{23}H_{28}N_4O \cdot 2HCl \cdot 2.5H_2O$[bb,cc]	55.87	55.76	7.14	7.36	11.33	10.88
41	H	4-OCH_3	100–102	92	II	E	$C_{23}H_{28}N_4O \cdot 2HCl \cdot 0.75H_2O$[dd,ee]	59.67	59.55	6.86	7.03	12.10	12.14
42	6-OCH_3	4-SO_3H	210–211	92	IV	H	$C_{23}H_{28}N_4O_4S \cdot 0.75H_2O$[f,ff]	58.77	58.80	6.32	6.55	11.92	11.65
43	7-OCH_3	4-SO_3H	210 dec	90	IV	H	$C_{23}H_{28}N_4O_4S \cdot 1.5H_2O$[gg]	57.12	56.63	6.46	6.42	11.59	11.57

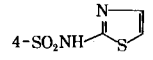
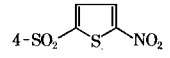
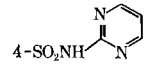
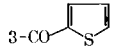
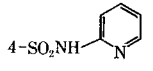
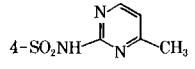
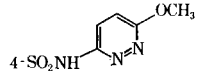
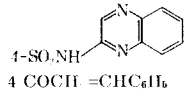
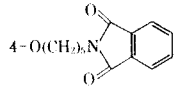
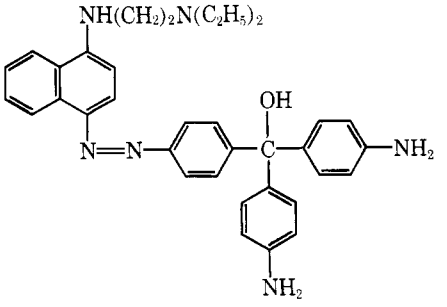
No.	X	Z	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
44	H	2-SCH_3	203–205	52	II	L	$C_{23}H_{28}N_4S \cdot HCl$	64.39	64.57	6.81	6.89	13.06	12.88
45	H	4-SCH_3	76–78	40	I	B	$C_{23}H_{28}N_4S$	70.37	69.88	7.19	7.40	14.27	14.34
46	H	4-$SO_2NHC{=}NHNH_2$	224–226	60	I	A	$C_{23}H_{29}N_7O_2S$	59.08	59.29	6.25	6.49	20.97	20.96
47	H	3,5-CF_3	89–90	20	I	A	$C_{24}H_{24}F_6N_4$	59.74	60.10	5.01	5.18	11.61	11.75
48	H	3,4-COOH	190 dec	10	IV	J	$C_{24}H_{26}N_4O_4$	66.34	66.16	6.03	6.30	12.90	12.80
49	H	3-$COCH_3$	96–97	70	I	A	$C_{24}H_{28}N_4O$	74.19	74.11	7.26	7.25	14.42	14.32
50	H	4-$COCH_3$	102–103	53	I	A	$C_{24}H_{28}N_4O$	74.19	74.16	7.26	7.15	14.42	14.65
51	H	4-CH_2COOH	187–189	64	I	M	$C_{24}H_{28}N_4O_2$	71.26	71.21	6.98	7.16	13.85	13.63
52	H	4-SCH_2COOH	159–160	23	I	J	$C_{24}H_{28}N_4O_2S$	66.03	65.75	6.46	6.46	12.83	12.64
53	H	3-$NHCOCH_3$	168–169	66	I	A	$C_{24}H_{29}N_5O$	71.43	71.45	7.24	7.39	17.36	17.62
54	H	4-$NHCOCH_3$	174–182	87	I	H	$C_{24}H_{29}N_5O \cdot 1.5H_2O$	66.95	66.80	7.49	7.54	16.27	16.33
55	H	3,4-CH_3	180–182	33	I	A	$C_{24}H_{30}N_4 \cdot HCl$[hh]	70.13	70.17	7.60	7.61	13.63	13.72
56	H	4-CH_2CH_2OH	178–179	63	II	I	$C_{24}H_{30}N_4O \cdot 2HCl \cdot 1.5H_2O$[ii,jj]	58.77	58.79	7.19	7.12	11.66	11.61
57	H	3-$CHOHCH_3$	90–92	70	I	N	$C_{24}H_{30}N_4O$[kk]	73.81	73.78	7.74	7.58	14.35	14.59
58	H	4-OC_2H_5	170–172	41	II	O	$C_{24}H_{30}N_4O \cdot 2HCl$	62.20	62.36	6.96	6.89	12.09	11.94
59	H	3,4-OCH_3	87–89	39	I	P	$C_{24}H_{30}N_4O_2$	70.91	71.02	7.41	7.21	13.78	13.93
60	H	4-OCH_2CH_2OH	99–101	52	I	P	$C_{24}H_{30}N_4O_2$	70.91	71.28	7.44	7.55	13.78	13.85
61	H	4-$N(CH_3)_2$	150–153	22	V	L	$C_{24}H_{31}N_5 \cdot 3HCl$	57.77	57.40	6.87	7.05	14.04	13.75
62	H	4-$C(CF_3)_2OH$	125–127	90	I	FF	$C_{25}H_{26}F_6N_4O$	58.59	58.61	5.11	5.03	10.93	10.79
63	H		220–222	72	I	M	$C_{25}H_{28}N_6O_2S_2$	59.03	59.00	5.55	5.57	16.52	16.15
64	H	4-COC_2H_5	113–114	83	I	A	$C_{25}H_{30}N_4O$	74.59	74.30	7.51	7.64	13.92	14.20
65	H		173–175	11	I	A	$C_{26}H_{27}N_5O_4S_2$	58.08	58.06	5.06	4.84	13.03	12.71
66	H		215–217	81	I	Q	$C_{26}H_{29}N_7O_2S$	62.00	62.21	5.80	5.77	19.47	19.51
67	H	2,3-$(CH_2)_4$—	108–110	48	I	A	$C_{26}H_{32}N_4$	77.96	77.65	8.05	7.73	13.99	14.03
68	H	4-$CO(CH_2)_2CH_3$	89–91	67	I	B	$C_{26}H_{32}N_4O$	74.96	74.75	7.74	7.99	13.45	13.43
69	H	2-$C(CH_3)_3$	149 dec	82	II	H	$C_{26}H_{34}N_4 \cdot 2HCl \cdot 2.5H_2O$[ll,mm]	59.99	59.88	7.91	7.87	10.76	10.85
70	H	4-$OCH_2CH(CH_3)_2$	110–112	31	I	A	$C_{26}H_{34}N_4O$	74.60	74.82	8.19	8.32	13.39	13.67
71	H	4-$OCHCH_2C_2H_5$	147–149	40	II	K	$C_{26}H_{34}N_4O \cdot 2HCl \cdot 1.67H_2O$[nn]	59.87	59.58	7.60	7.85	10.74	10.67
72	H		171–172	30	II	G	$C_{27}H_{28}N_4OS \cdot 2HCl \cdot 0.5H_2O$[oo,pp]	60.22	60.85	5.80	5.94	10.40	10.22
73	H		94–96	45	I	A	$C_{27}H_{29}N_5$	76.56	76.51	6.90	6.82	16.54	16.50
4	H		164–165	84	I	J	$C_{27}H_{30}N_6O_2S$	64.52	64.60	6.02	5.99	16.72	16.87
75	H		192–194	81	I	J	$C_{27}H_{31}N_7O_2S$	62.64	62.53	6.04	6.30	18.94	18.91
76	H		202–204	77	I	J	$C_{27}H_{31}N_7O_3S$	60.76	60.72	5.85	5.72	18.37	18.30
77	H	4-$CO(CH_2)_3CH_3$	93–94	66	I	B	$C_{27}H_{34}N_4O$	75.31	75.45	7.96	7.95	13.01	12.97
78	H	4-$CHOHCH(NHCOCH_3)CH_2OH$]	173–174	20	I	A	$C_{27}H_{35}N_5O_3$	67.90	67.79	7.39	7.46	14.67	14.55
79	H	3-$CH_2N(C_2H_5)_2$, 4-OH	181–184 dec	32	II	O	$C_{27}H_{37}N_5O \cdot 3HCl \cdot 2H_2O$[qq,rr]	54.68	54.60	7.48	7.55	11.81	11.76
80	H	2-SC_6H_5	129–130	97	I	R	$C_{28}H_{30}N_4S$	73.97	73.67	6.65	6.70	12.32	12.54
81	H	4-$N{=}NC_6H_5$	120–122	19	I	A	$C_{28}H_{30}N_6$	74.63	74.54	6.71	6.56	18.65	18.73
82	6-$O(CH_2)_2N(C_2H_5)_2$	H	170–172	68	II	H	$C_{28}H_{39}N_5O \cdot 3HCl \cdot 1.5H_2O$[ss,tt]	56.23	56.47	7.58	7.88	11.71	11.92

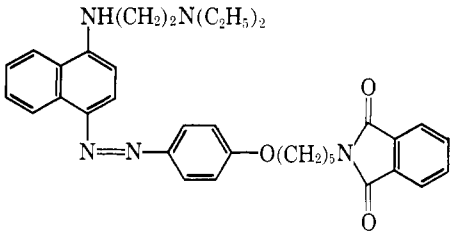
TABLE I (*Continued*)

No.	X	Z	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
83	H	4-$O(CH_2)_2N(C_2H_5)_2$	170–173	56	H	I	$C_{28}H_{39}N_5O\cdot3HCl\cdot2.5H_2O$[uu]	54.19	53.85	7.72	7.79	11.29	10.94
84	H	4-$NH(CH_2)_2N(C_2H_5)_2$	160–163	58	V	P	$C_{28}H_{40}N_6\cdot3HCl\cdot2H_2O$[vv]	55.48	55.71	7.82	8.11	13.87	13.43
85	H	4-COC_6H_5	160 dec	55	H	L	$C_{29}H_{30}N_4O\cdot2HCl$[ww]	66.53	66.30	6.16	6.17	10.70	10.58
86	H	4-$OCH_2C_6H_5$	104–106	30	I	A	$C_{29}H_{32}N_4O$	76.96	77.21	7.13	7.09	12.38	12.26
87	H	4-$CO(CH_2)_5CH_3$	82–84	58	I	B	$C_{29}H_{38}N_4O$	75.94	75.64	8.35	8.39	12.22	12.17
88	H	3-OH, 4-$COO(CH_2)_2N(C_2H_5)_2$	87–89	50	I	B	$C_{29}H_{39}N_5O_3$	68.88	69.14	7.77	7.75	13.85	14.01
89	H		181–183	83	H	H	$C_{30}H_{31}N_7O_2S\cdot2HCl\cdot H_2O$[xx,yy]	55.89	56.40	5.47	5.15	15.21	15.70
90	H	4 $COCH{=}CHC_6H_5$	116–117	28	I	P	$C_{31}H_{32}N_4O$	78.11	77.95	6.77	6.71	11.76	11.82
91	H	3-$SO_2NC_2H_5C_6H_5$, 4-CH_3	175–178	15	H	III	$C_{31}H_{37}N_5O_2S\cdot2HCl$	60.38	60.35	6.37	6.41	11.36	11.08
92	H	4-$CO(CH_2)_7CH_3$	79–80	60	I	B	$C_{31}H_{42}N_4O$	76.50	76.68	8.70	8.71	11.51	11.77
93	H	4-$COH(p\text{-}NH_2C_6H_4)_2$	142–146	26	I	F	$C_{35}H_{28}N_6O$	75.24	75.40	6.86	7.00	15.04	15.37
94	H		94–98	34	I	B	$C_{36}H_{39}N_5O_3$	72.76	72.82	6.80	6.67	12.12	12.10

[a] The free bases range from orange to purple in color; the acid addition salts range from orange to black in color. [b] A, ethanol; B, 2-propanol; C, methanol–water; D, 2-propanol–water; E, dilute HCl; F, ethanol–water; G, ethanol–ethanolic HCl; H, not crystallized; I, 2-propanol–ethanolic HCl; J, dimethylacetamide–water; K, ethanol–ether; L, methanol–2-propanol; M, dimethylacetamide–2-propanol; N, ether; O, ethanol–acetone; P, methanol; Q, dimethylacetamide; R, ethanol–2-propanol; S, methanol–ethyl acetate; T, chloroform–petroleum ether (bp 30–60°); U, chloroform; V, ethanol–ether–HCl; W, acetone; X, chloroform–2-propanol; Y, dimethylformamide–ethyl acetate; Z, dimethylformamide–water; AA, methanol–2-propanol–hydrogen chloride; BB, dimethylformamide–ethyl acetate–water; CC, 2-propanol–ethyl acetate; DD, acetonitrile; EE, cyclohexane; FF, *n*-heptane; GG, ethyl acetate; HH, 2-propanol–HCl; II, acetone–*n*-heptane. [c] *Anal.* Calcd: Br, 31.70. Found: Br, 31.69. [d] *Anal.* Calcd: Cl, 17.07. Found: Cl, 17.04. [e] *Anal.* Calcd: Cl, 13.50. Found: Cl, 13.88. [f] *Anal.* Calcd: H_2O, 1.95. Found: H_2O, 2.25. [g] *Anal.* Calcd: H_2O, 7.35. Found: H_2O, 6.97. [h] *Anal.* Calcd: organic Cl, 7.24. Found: organic Cl, 7.54. [i] *Anal.* Calcd: Cl, 9.31. Found: Cl, 8.99. [j] *Anal.* Calcd: Cl^-, 8.84. Found: Cl^-, 8.86. [k] *Anal.* Calcd: Cl^-, 15.96. Found: Cl^-, 15.68. [l] *Anal.* Calcd: H_2O, 2.03. Found: H_2O, 2.19. [m] *Anal.* Calcd: Cl, 8.89. Found: Cl, 8.70. [n] Base, mp 86–94°. [o] *Anal.* Calcd: Cl, 15.40. Found: Cl, 15.01. [p] *Anal.* Calcd: H_2O, 1.96. Found: H_2O, 1.83. [q] *Anal.* Calcd: volatile loss at 100°, 3.07. Found: 2.83. [r] *Anal.*, Calcd: volatile loss at 100°, 5.96. Found: 4.58. [s] *Anal.* Calcd: H_2O, 7.53. Found: H_2O, 6.19. [t] *Anal.* Calcd: H_2O, 5.43. Found: H_2O, 5.82. [u] *Anal.* Calcd: Cl^-, 19.29. Found: Cl^- 19.14. [v] *Anal.* Calcd: H_2O, 4.52. Found: H_2O, 4.71. [w] *Anal.* Calcd: Cl^-, 14.03. Found: Cl^-, 13.91. [x] *Anal.* Calcd: H_2O, 3.56. Found: H_2O, 3.88. [y] *Anal.* Calcd: H_2O, 4.63. Found: H_2O, 4.47. [z] *Anal.* Calcd: H_2O, 4.41. Found: H_2O, 4.49. [aa] Monocitrate salt. [bb] *Anal.* Calcd: Cl, 14.34. Found: Cl, 14.45. [cc] *Anal.* Calcd: H_2O, 9.10. Found: H_2O, 8.74. [dd] *Anal.* Calcd: Cl, 15.32. Found: Cl, 15.33. [ee] *Anal.* Calcd: H_2O, 2.92. Found: H_2O, 3.03. [ff] *Anal.* Calcd: H_2O, 2.87. Found: H_2O, 2.26. [gg] *Anal.* Calcd: volatile loss at 100°, 5.59. Found: 5.66. [hh] *Anal.* Calcd: Cl, 8.63. Found: Cl, 8.71. [ii] *Anal.* Calcd: Cl, 14.46. Found: Cl, 14.25. [jj] *Anal.* Calcd: H_2O, 5.51. Found: H_2O, 4.80. [kk] Dihydrochloride salt, monohydrate, mp 150–152°; monohydrochloride salt, mp 167–168°. [ll] *Anal.* Calcd: Cl, 13.62. Found: Cl, 14.00. [mm] *Anal.* Calcd: H_2O, 8.65. Found: H_2O, 7.47. [nn] *Anal.* Calcd: H_2O, 5.77. Found: H_2O, 5.50. [oo] *Anal.* Calcd: Cl, 13.17. Found: Cl, 13.23. [pp] *Anal.* Calcd. H_2O, 1.67. Found: H_2O, 1.77. [qq] *Anal.* Calcd: Cl, 17.94. Found: Cl, 17.51. [rr] *Anal.* Calcd: H_2O, 6.07. Found: H_2O, 6.18. [ss] *Anal.* Calcd: Cl, 17.79. Found: Cl, 17.13. [tt] *Anal.* Calcd: H_2O, 4.52. Found: H_2O, 4.23. [uu] *Anal.* Calcd: H_2O, 7.98. Found: H_2O, 7.06. [vv] *Anal.* Calcd: Cl, 17.55. Found: Cl, 17.63. [ww] *Anal.* Calcd: Cl, 13.55. Found: Cl, 13.76. [xx] *Anal.* Calcd: Cl, 11.00. Found: Cl, 10.79. [yy] *Anal.* Calcd: H_2O, 2.79. Found: H_2O, 2.60.

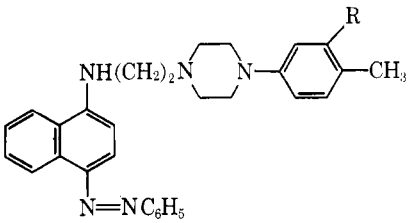


X



XI

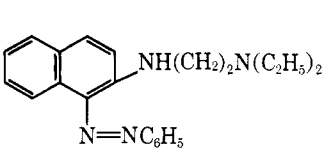
and 3,4-xylyl)-4-{2-[(4-phenylazo-1-naphthyl)amino]-ethyl}piperazine (XIIa, **154**, and XIIb, **156**). How-



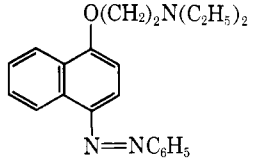
XIIa, R = Cl
b, R = CH_3

ever, no evidence has been obtained (*infra*) that would suggest any superiority of compounds VIIIa, X, and XI over other highly active members of the series (III), and compounds XIIa and b proved to be ineffective against *S. mansoni* in mice.

Among related compounds, N,N-diethyl-N′-(1-phenylazo-2-naphthyl)ethylenediamine (XIII) was prepared by coupling diazotized aniline with 2-(2-diethylaminoethylamino)naphthalene[10] and 2-(4-phenylazo-1-naphthyloxy)triethylamine (XIV) was obtained by alkylation of the sodium salt of 4-phenylazo-1-naphthol with 2-chlorotriethylamine. Oxidation of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine



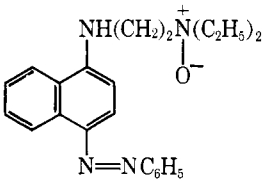
XIII



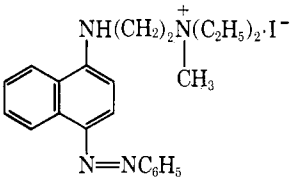
XIV

(VIa, **17**) with perbenzoic acid in chloroform gave the corresponding N-oxide (XV), while treatment of VIa with methyl iodide afforded diethylmethyl[2-(4-phenylazo-1-naphthylamino)ethyl]ammonium iodide (XVI).

The N-mono- and N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines and related compounds described in the present communication were tested in mice against a Puerto Rican strain of *Schistosoma mansoni*[2,17] by Dr. Paul E. Thompson and co-workers of these laboratories. Drugs were given in a powdered diet for 14 days or by gavage in 10 ml/kg of aqueous 1% hydroxyethyl- or carboxymethylcellulose for 10 days. Drug amounts are expressed as free base. Schistosomicidal activity among the N,N-dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines of structure III is widespread. Compounds **2**, **8**, **13**, **22**, **23**, **29**, **30**, **34**, **41–43**, **48**, **50**, **55**, **57**, **69**, **83**, **92–94**, **99**, **103**, **104**, **114**, **177**, **188**, **196**, **201**, and **206** (Tables I–III and V), which are representative of the more promising members of the series, completely eliminated live schistosomes from infected mice at doses ranging from 78 to 734 mg/kg per day when administered orally in the diet for 14 days.[18] These compounds were, therefore, distinctly more promising in mice than lucanthone hydrochloride,[17,19] the tris(*p*-aminophenyl)carbonium salts,[12,17] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[20,21] N-[5-(*p*-aminophenoxy)pentyl]phthalimide,[13] or 3-[4-(3-chloro-*p*-tolyl)-1-piperazinylcarbonyl]-acrylic acid[14] when tested under comparable experimental conditions.



XV



XVI

Several representative naphthylazo compounds were selected for trial against the Puerto Rican strain of *S. mansoni* in rhesus monkeys[2,17] and each substance tested showed significant antischistosomal activity in this host.[18] Drugs were given orally by gavage twice daily 5 days a week for 1–4 weeks. Among various [4-(dialkylaminoalkylamino)-1-naphthylazo]benzenesulfonic acid derivatives tested, *p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]benzenesulfonic acid monohydrochloride (**23**) at tolerated doses of 25–100 mg/kg/day for 10 days caused a moderate to strong suppression of egg production but was not curative. Doses of 100 mg/kg/day for 15 or 20 days usually effected a cure and were tolerated well except for transient weight loss and some mucoid diarrhea. No improvement in activity was observed with the 7-methoxy derivative (**43**) and it was more toxic for monkeys. The most potent sulfonic acid derivative in monkeys was *p*-{4-[2-(isopropylmethylamino)ethylamino]-1-naphthylazo}benzenesulfonic acid monohydrochloride (**114**). Doses of 25 mg/kg per day for 10 days usually effected a cure and were tolerated well. However, doses in the range of 50–100 mg/kg per day for either 5 or 10 days produced gastrointestinal side effects such as emesis, weight loss, inappetence, and mucoid diarrhea. The unusually high therapeutic index noted with *p*-

(16) Abbott Laboratories, South African Patent 63/593 (March 7, 1963).

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

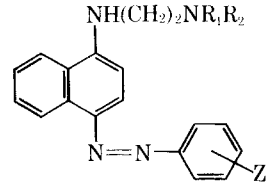
(18) P. E. Thompson, J. E. Meisenhelder, and H. Najarian, unpublished results, Parke, Davis and Company, Ann Arbor, Mich.

(19) W. Kikuth and R. Gönnert, *Ann. Trop. Med. Parasitol.*, **42**, 256 (1948).

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

(21) R. F. Collins, M. Davis, N. D. Edge, and J. Hill, *ibid.*, **13**, 238 (1958).

TABLE II: N-MONO- AND N,N-DIALKYL-N′-(4-PHENYLAZO-1-NAPHTHYL)ETHYLENEDIAMINES[a]



No.	Z	NR_1R_2	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
95	4-NO_2	$N(CH_3)_2$	164–166	44	III	W	$C_{20}H_{21}N_5O_2$	66.10	66.22	5.83	5.86	19.27	19.34
96	H	NHC_2H_5	156–157	81	II	E	$C_{20}H_{22}N_4 \cdot 2HCl \cdot 3.25H_2O^c$	53.39	53.06	6.83	7.17	12.45	12.32
97	H	$NH(CH_2)_2OH$	175–177	83	II	H	$C_{20}H_{22}N_4O \cdot 2HCl \cdot 2.25H_2O^{d,e}$	53.63	53.80	6.41	6.37	12.51	12.48
98	4-SO_3H	NHC_2H_5	211–213	95	IV	H	$C_{20}H_{22}N_4O_3S$	60.28	59.93	5.57	5.65	14.06	14.05
99	4-SO_3H	$N(CH_3)_2$	198 dec	92	IV	H	$C_{20}H_{22}N_4O_3S \cdot HCl \cdot 2.33H_2O^f$	50.36	50.71	5.85	5.93	11.75	11.78
100	4-SO_3H	$NH(CH_2)_2OH$	199–200	69	IV	E	$C_{20}H_{22}N_4O_4S \cdot HCl$	53.27	53.34	5.11	5.44	12.43	12.38
101	H	$NCH_3C_2H_5$	150 dec	93	II	E	$C_{21}H_{24}N_4 \cdot 2HCl \cdot 0.25H_2O^{g,h}$	61.54	61.62	6.52	6.73	13.67	13.76
102	H	$NCH_3(CH_2)_2OH$	190–192	84	II	S	$C_{21}H_{24}N_4O \cdot 2HCl \cdot 0.5H_2O^{i,j}$	58.60	58.35	6.32	6.45	13.02	13.15
103	4-SO_3H	$NCH_3C_2H_5$	189–205	97	IV	H	$C_{21}H_{24}N_4O_3S \cdot HCl \cdot 3.5H_2O^k$	49.26	49.31	6.30	6.22	10.94	11.02
104	4-C(=NH)NH_2	$N(CH_3)_2$	210	90	II	C	$C_{21}H_{24}N_6 \cdot 3HCl \cdot 2H_2O^l$	49.86	49.52	6.18	6.10		
105	H		93–95	54	VI	B	$C_{22}H_{22}N_4$	77.16	77.12	6.48	6.70	16.36	16.44
106	H	$N(CH_3)_4$	82–83	71	I	T	$C_{22}H_{24}N_4$	76.71	76.81	7.02	7.14	16.27	16.23
107	H	$N[(CH_2)_2]_2O$	173–174	99	I	T	$C_{22}H_{24}N_4O$	73.30	73.39	6.71	6.53	15.54	15.61
108	4-SO_3H	$N(CH_2)_4$	207–210	91	IV	E	$C_{22}H_{24}N_4O_3S \cdot HCl \cdot 2.5H_2O^m$	52.2	52.21	5.98	5.88	11.07	11.06
109	H	$N[(CH_2)_4]_2NH$	218–220	65	II	G	$C_{22}H_{28}N_6 \cdot HCl^n$	66.73	66.94	6.62	6.34	17.69	17.75
110	H	$NCH_2CH(CH_3)_2$	77–80	57	I	A	$C_{22}H_{26}N_4$	76.26	76.33	7.57	7.54	16.17	16.37
111	4-OH	$NCH_2CH(CH_3)_2$	204–206 dec	58	II	G	$C_{22}H_{26}N_4O \cdot HCl^o$	66.23	66.30	6.82	6.86	14.05	14.29
112	H	$NC_2H_5(CH_2)_2OH$	178–180	71	II	S	$C_{22}H_{26}N_4O \cdot 2HCl \cdot 0.67H_2O^{p,q}$	59.05	58.79	6.61	6.65	12.52	12.82
113	H	$N[(CH_2)_2OH]_2$	155–156	60	II	D	$C_{22}H_{26}N_4O_2 \cdot 2HCl \cdot 0.25H_2O^{r,s}$	57.96	57.90	6.30	6.33	12.29	12.21
114	4-SO_3H	$NCH_2CH(CH_3)_2$	200 dec	95	IV	H	$C_{22}H_{26}N_4O_3S \cdot HCl \cdot 1.75H_2O^t$	53.43	53.32	6.22	6.19	11.33	11.02
115	4-SO_3H	$N[(CH_2)_2OH]_2$	186–188	85	IV	E	$C_{22}H_{26}N_4O_5S \cdot HCl \cdot 0.5H_2O^u$	52.43	52.10	5.60	5.83	11.12	11.27
116	H	$NC_2H_5CH_2CH{=}CH_2$	62–63	48	I	P	$C_{23}H_{26}N_4$	77.06	77.20	7.31	7.38	15.63	15.74
117	H	$N(CH_2)_5$	180 dec	89	II	E	$C_{23}H_{26}N_4 \cdot 2HCl \cdot 4H_2O^v$	54.87	55.36	7.21	7.58	11.13	11.16
118	H		143–144	52	I	A	$C_{23}H_{26}N_4O$	73.77	73.52	7.00	7.09	14.96	15.08
119	H	$N[(CH_2)_2]_2CHOH$	166–167	70	I	A	$C_{23}H_{26}N_4O$	73.77	73.81	7.00	6.88	14.96	15.08
120	4-SO_3H	$N(CH_2)_5$	198 dec	86	IV	H	$C_{23}H_{26}N_4O_3 \cdot HCl \cdot 4H_2O^w$	50.49	50.16	6.45	6.61	10.24	10.42
121	H	$N[(CH_2)_2]_2NCH_3$	153–155	85	II	E	$C_{23}H_{27}N_5 \cdot 3HCl \cdot 1.5H_2O^{x,y}$	54.17	54.12	6.52	6.75	13.71	13.70
122	H	$NCH_2(CH_2)_3CH_3$	67–69	83	I	A	$C_{23}H_{28}N_4$	76.63	76.20	7.83	7.98	15.54	15.62
123	4-Cl	$N[(CH_2)_2]_2N(CH_2)_2OH$	165–167	99	I	B	$C_{24}H_{28}ClN_5O$	65.81	66.04	6.44	6.39	15.99	15.80
124	H	$NHCH(CH_2)_5$	183–185	73	II	A	$C_{24}H_{28}N_4 \cdot C_2H_4O_2^z$	72.19	72.02	7.46	7.32	12.95	13.30
125	H	$N[(CH_2)_2]_2CHCH_3$	104–105	81	I	A	$C_{24}H_{28}N_4$	77.38	77.15	7.58	7.68	15.04	15.10
126	H	$N(CH_2)_6$	200 dec	87	II	E	$C_{24}H_{28}N_4 \cdot 2HCl \cdot 3.75H_2O^{aa,bb}$	56.19	56.07	7.37	7.62	10.92	10.86
127	H	$N(CH_2CH(CH_3)_2O$	167–168	61	I	P	$C_{24}H_{28}N_4O$	74.19	74.48	7.26	7.33	14.42	14.35
128	4-SO_3H	$N(CH_2)_6$	185–190	96	IV	H	$C_{24}H_{28}N_4O_3S \cdot HCl \cdot 2.5H_2O^{cc}$	53.97	53.89	6.42	6.41	10.49	10.51
129	3-CHOHCH$_3$	$NCH_2CH(CH_3)_2$	99–101	61	I	B	$C_{24}H_{30}N_4O$	73.81	73.90	7.74	7.69	14.35	14.45
130	4-SO_3H	$N[CH(CH_3)_2]_2$	201–203	87	IV	H	$C_{24}H_{30}N_4O_3S \cdot HCl \cdot 1.5H_2O^{dd}$	55.64	55.77	6.62	6.86	10.82	11.05
131	H	$NH(CH_2)_2N(C_2H_5)_2$	165–167	64	II	V	$C_{24}H_{31}N_5 \cdot 3HCl \cdot 2H_2O^{ee,ff}$	53.88	53.27	7.16	7.46	13.09	12.80
132	H	$N[(CH_2)_2]_2NCOOC_2H_5$	87–90	65	VI	B	$C_{25}H_{29}N_5O_2$	69.58	69.47	6.77	6.90	16.23	15.99
133	H	$NCH_3CH(CH_2)_5$	208–209	69	II	W	$C_{25}H_{30}N_4 \cdot HCl^{gg}$	70.98	71.04	7.39	7.25	13.25	13.27
134	H	$N(CHCH_3CH_2)_2CH_2$	222–223	68	II	Q	$C_{25}H_{30}N_4 \cdot HCl^{hh}$	70.98	71.16	7.39	7.43	13.25	13.25
135	3-CHOHCH$_3$	$NCH_3(CH_2)_3CH_2$	94–95	72	I	F	$C_{25}H_{32}N_4O$	74.22	74.47	7.97	7.86	13.85	13.96

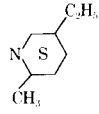
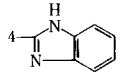
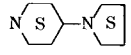
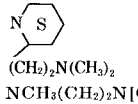
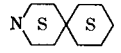
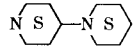
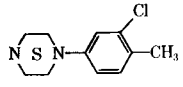
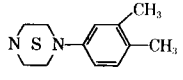
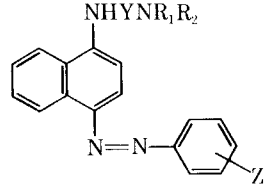
136	H		164–166	78	VI	X	$C_{26}H_{30}N_4$	78.35	78.03	7.59	7.43	14.06	14.07
137	H	$NHCH(CH_2)_7$	175–177	60	II	A	$C_{26}H_{32}N_4 \cdot C_2H_4O_2$[z]	73.01	73.03	7.88	7.86	12.16	12.34
138	4-OH		215–216	36	II	Y	$C_{26}H_{32}N_4O \cdot HCl$	68.93	69.07	7.34	7.13	12.37	12.44
139	H	$N[CH_2CH(CH_3)_2]_2$	157–159	68	II	E	$C_{26}H_{34}N_4 \cdot 2HCl \cdot 0.75H_2O$[ii]	63.86	64.24	7.73	7.64	11.46	11.46
140	3-$CHOHCH_3$	$N[CH(CH_3)_2]_2$	108–110	36	II	W	$C_{26}H_{34}N_4O \cdot C_3H_6O \cdot HCl$[jj,kk]	67.88	68.03	8.05	8.04	10.92	11.28
141	4-SO_3H	$N[(CH_2)_3CH_3]_2$	200–205	93	IV	H	$C_{26}H_{34}N_4O_3S \cdot HCl \cdot 2H_2O$[ll,mm]	56.25	56.23	7.08	7.23	10.09	10.45
142	H	$NC_2H_5(CH_2)_2N(C_2H_5)_2$	82–85	80	II	H	$C_{26}H_{36}N_5 \cdot 2.5HCl \cdot 1.5H_2O$[nn,oo]	58.28	58.40	7.62	7.63	13.07	13.24
143		$N(CH_3)_2$	212–215	31	I	A	$C_{27}H_{26}N_6$	74.69	74.67	6.03	6.35	19.34	19.23
144	3-C_6H_5	$NCH_3C_2H_5$	192–194	17	II	B	$C_{27}H_{28}N_4 \cdot HCl$[pp]	72.87	73.13	6.57	6.54	12.59	13.11
145	H	$NCH_2CH{=}CH_2CH(CH_2)_5$	215–216	42	II	K	$C_{27}H_{32}N_4 \cdot HCl \cdot 0.5H_2O$	70.80	70.83	7.48	7.66	12.23	12.19
146	H		105–107	67	VI	B	$C_{27}H_{32}N_4$	78.60	78.64	7.82	7.75	13.58	13.73
147	H		70 dec	75	I	P	$C_{27}H_{32}N_4 \cdot 0.25H_2O$[qq]	77.75	77.64	7.85	7.93	13.43	13.46
148	H		162–164	33	VI	Z	$C_{27}H_{33}N_5$	75.84	75.85	7.78	7.71	16.38	16.34
149	4-SO_3H		213–215	50	IV	J	$C_{27}H_{35}N_5O_3S \cdot 0.5H_2O$[rr]	62.52	62.75	7.00	7.08	13.50	13.22
150	H	$NCH_3(CH_2)_2N[CH(CH_3)_2]_2$	169–171	10	II	AA	$C_{27}H_{37}N_5 \cdot 3HCl \cdot 1.5H_2O$[ss,tt]	57.09	56.72	7.63	7.83	12.33	12.00
151	H		204 dec	62	VI	AA	$C_{28}H_{34}N_4 \cdot 2HCl$	67.32	67.15	7.27	7.33	11.22	11.20
152	H		136–138	48	VI	BB	$C_{28}H_{36}N_5$	76.15	76.63	7.99	7.79	15.86	16.10
153	3-$CHOHCH_3$	$N(CH_2CH_2OC_2H_5)_2$	144–146	68	II	CC	$C_{28}H_{38}N_4O_3 \cdot 2HCl \cdot 0.33H_2O$[uu,vv]	60.31	60.21	7.35	7.26	10.05	10.22
154	H		142–144	84	I	DD	$C_{29}H_{30}ClN_5$	71.96	72.02	6.25	6.28	14.47	14.47
155	3-$CHOHCH_3$	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_3)_2$	168 dec	77	II	H	$C_{29}H_{39}N_5O \cdot 3HCl \cdot H_2O$[ww]	57.95	58.40	7.38	7.65	11.65	11.40
156	H		144–145	37	VI	DD	$C_{30}H_{33}N_5$	77.72	77.84	7.17	6.90	15.11	15.32
157	4-$O(CH_2)_2N(C_2H_5)_2$	$N[CH(CH_3)_2]_2$	120 dec	78	II	H	$C_{30}H_{43}N_5O \cdot 3HCl \cdot 1.5H_2O$[xx]	57.55	57.64	7.89	7.85	11.19	11.19
158	3-$CHOHCH_3$	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_2)_4$	120–123	35	I	EE	$C_{31}H_{41}N_5O$	74.51	74.95	8.27	8.16	14.02	14.10
159	3-$CHOHCH_3$	$N[(CH_2)_2]_2CH(CH_2)_2N[(CH_2)_2]_2O$	143–145	78	I	B	$C_{31}H_{41}N_5O_2$	72.27	72.50	8.01	7.65	13.58	13.72
160	3-$CHOHCH_3$	$N[(CH_2)_2]_2CH(CH_2)_2N(C_2H_5)_2$	95 dec	68	II	H	$C_{31}H_{43}N_5O \cdot 3HCl \cdot 2.5H_2O$[yy,zz]	56.74	56.74	7.84	7.37	10.67	10.74
161	3-$CHOHCH_3$	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_2)_5$	125–127	88	I	DD	$C_{32}H_{43}N_5O$	74.81	75.30	8.44	8.33	13.63	13.52
162	3-$NHCOCH_3$	$N[(CH_2)_2N(C_2H_5)_2]_2$	89 dec	29	II	V	$C_{32}H_{47}N_7O \cdot 4HCl \cdot 2.5H_2O$[aaa]	52.17	52.33	7.66	7.71	13.31	13.32
163	3-$CHOHCH_3$	$NCH_3(CH_2)_{11}CH_3$	157–158	54	II	II	$C_{33}H_{48}N_4O \cdot 0.5C_2H_2O_4$[bbb]	72.69	72.65	8.79	8.66	9.97	10.06
164	H	$N[(CH_2)_7CH_3]_2$	164–166	70	II	F	$C_{34}H_{50}N_4 \cdot 2HBr$	60.35	60.00	7.75	7.65	8.28	8.12

TABLE II (*Continued*)

[a] The free bases range from orange to green in color; the acid addition salts range from orange to black in color. [b] See footnote *b*, Table I. [c] *Anal.* Calcd: H_2O, 13.01. Found: H_2O, 12.96. [d] *Anal.* Calcd: Cl, 15.83. Found: Cl, 15.78. [e] *Anal.* Calcd: H_2O, 9.05. Found: H_2O, 9.13. [f] *Anal.* Calcd: H_2O, 8.80. Found: H_2O, 9.06. [g] *Anal.* Calcd: Cl, 17.30. Found: Cl, 17.20. [h] *Anal.* Calcd: H_2O, 1.10. Found: H_2O, 0.94. [i] *Anal.* Calcd: Cl, 16.48. Found: Cl, 16.47. [j] *Anal.* Calcd: H_2O, 2.09. Found: H_2O, 1.75. [k] *Anal.* Calcd: H_2O, 12.30. Found: H_2O, 12.28. [l] *Anal.* Calcd: H_2O, 7.12. Found: H_2O, 7.31. [m] *Anal.* Calcd: H_2O, 8.89. Found: H_2O, 8.82. [n] *Anal.* Calcd: Cl, 8.96. Found: Cl, 8.74. [o] *Anal.* Calcd: Cl, 8.88. Found: Cl, 9.04. [p] *Anal.* Calcd: Cl, 15.85. Found: Cl, 16.01. [q] *Anal.* Calcd: H_2O, 2.68. Found: H_2O, 2.05. [r] *Anal.* Calcd: Cl, 15.55. Found: Cl, 15.41. [s] *Anal.* Calcd: H_2O, 0.99. Found: H_2O, 0.98. [t] *Anal.* Calcd: H_2O, 6.37. Found: H_2O, 6.65. [u] *Anal.* Calcd: H_2O, 1.79. Found: H_2O, 1.88. [v] *Anal.* Calcd: H_2O, 14.30. Found: H_2O, 14.03. [w] *Anal.* Calcd: H_2O, 13.16. Found: H_2O, 13.07. [x] *Anal.* Calcd: H_2O, 5.29. Found: H_2O, 5.20. [y] *Anal.* Calcd: Cl, 20.86. Found: Cl, 20.97. [z] Monoacetate salt. [aa] *Anal.* Calcd: H_2O, 13.16. Found: H_2O, 13.14. [bb] *Anal.* Calcd: Cl, 13.82. Found: Cl, 14.00. [cc] *Anal.* Calcd: H_2O, 8.43. Found: H_2O, 8.39. [dd] *Anal.* Calcd: Cl, 6.84. Found: Cl, 7.15. [ee] *Anal.* Calcd: Cl, 19.88. Found: Cl, 19.85. [ff] *Anal.* Calcd: H_2O, 6.73. Found: H_2O, 6.74. [gg] *Anal.* Calcd: Cl, 8.38 Found: Cl, 8.15. [hh] *Anal.* Calcd: Cl, 8.38. Found: Cl, 8.16. [ii] *Anal.* Calcd: H_2O, 2.76. Found: H_2O, 3.11. [jj] Acetone of crystallization. [kk] *Anal.* Calcd: Cl, 6.91. Found: Cl, 6.96. [ll] *Anal.* Calcd: Cl, 6.39. Found: Cl, 6.13. [mm] *Anal.* Calcd: H_2O, 6.49. Found: H_2O, 7.00. [nn] *Anal.* Calcd: Cl, 16.54. Found: Cl, 16.49. [oo] *Anal.* Calcd: H_2O, 5.04. Found: H_2O, 4.30. [pp] *Anal.* Calcd: Cl, 7.97. Found: Cl, 8.18. [qq] *Anal.* Calcd: H_2O, 1.08. Found: H_2O, 0.93. [rr] *Anal.* Calcd: H_2O, 1.74. Found: H_2O, 1.93. [ss] *Anal.* Calcd: Cl, 18.73. Found: Cl, 18.84. [tt] *Anal.* Calcd: H_2O, 4.75. Found: H_2O, 4.67. [uu] *Anal.* Calcd: Cl, 12.72. Found: Cl, 12.68. [vv] *Anal.* Calcd: H_2O, 1.08. Found: H_2O, 1.42. [ww] *Anal.* Calcd: H_2O, 2.99. Found: H_2O, 2.96. [xx] *Anal.* Calcd: Cl, 16.99. Found: Cl, 16.92. [yy] *Anal.* Calcd: Cl, 16.21. Found: Cl, 16.01. [zz] *Anal.* Calcd: H_2O, 6.86. Found: H_2O, 7.00. [aaa] *Anal.* Calcd: H_2O, 6.11. Found: H_2O, 6.02. [bbb] Hemioxalate salt.

TABLE III: N-MONO- AND N,N-DIALKYL-N′-(4-PHENYLAZO-1-NAPHTHYL)ALKYLENEDIAMINES[a]



No.	Z	YNR$_1$R$_2$	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
165	H	$(CH_2)_3N(CH_3)_2$	108–110	83	II	H	$C_{21}H_{24}N_4\cdot 2HCl\cdot 2H_2O$[c,d]	57.14	57.51	6.85	6.98	12.69	12.79
166	H	$CHCH_3CH_2N(CH_3)_2$	196–199	75	II	T	$C_{21}H_{24}N_4\cdot HCl$[e]	68.37	68.49	6.83	6.86	15.19	15.19
167	4-SO_3H	$(CH_2)_3N(CH_3)_2$	220–222	91	IV	H	$C_{21}H_{24}N_4O_3S\cdot HCl\cdot 2H_2O$[f]	52.00	52.50	6.03	6.40	11.55	12.05
168	H	$CH_2CHCH_3CH_2N(CH_3)_2$	127–129	63	I	FF	$C_{22}H_{26}N_4$	76.26	75.95	7.57	7.49	16.17	16.34
169	4-SO_3H	$(CH_2)_3NHCH(CH_3)_2$	215–217	77	IV	E	$C_{22}H_{26}N_4O_3S\cdot HCl\cdot H_2O$[g]	54.93	55.18	6.08	6.15	11.65	11.72
170	4-C=NHNH_2	$(CH_2)_3N(CH_3)_2$	212	48	II	C	$C_{22}H_{26}N_6\cdot 3HCl\cdot H_2O$[h]	52.65	52.76	6.23	6.07		
171	2,4,5-Cl_3	$ClH_2C(CH_3)_2CH_2N(CH_3)_2$	165–166	49	I	GG	$C_{23}H_{25}Cl_2N_4$	59.55	59.56	5.43	5.50	12.08	12.13
172	H	$(CH_2)_3N(CH_2)_4$	104–105	97	I	A	$C_{23}H_{26}N_4$	77.06	77.09	7.31	7.27	15.63	15.98
173	H	$(CH_2)_3N[(CH_2)_2]_2O$	154–156	82	I	A	$C_{23}H_{26}N_4O$	73.77	74.11	7.00	6.89	14.96	15.00
174	4-SCH_3	$CH[(CH_2)_2]_2NCH_3$	131–134	47	I	B	$C_{23}H_{26}N_4S$	70.73	70.37	6.71	6.69	14.35	14.27
175	H	$(CH_2)_3N(C_2H_5)_2$	90–92	87	I	A	$C_{23}H_{28}N_4$	76.63	76.46	7.83	7.91	15.54	15.79
176	H	$(CH_2)_3N(CH_2)_5$	186 dec	40	II	E	$C_{24}H_{28}N_4\cdot 2HCl\cdot 2H_2O$[i]	59.87	60.04	7.12	7.30	11.64	11.52
177	H	$ClH_2CHOHCH_2N(CH_2)_5$	112 dec	83	VI	F	$C_{24}H_{28}N_4O\cdot H_2O$[j]	70.91	71.09	7.44	7.33	13.78	13.79
178	4-CO_2H	$CH[CH_2N(CH_3)_2]_2$	195–197	42	IV	D	$C_{24}H_{29}N_5O_2\cdot 2HCl\cdot 0.33H_2O$[k,l]	57.83	57.63	6.40	6.92	14.05	13.37
179	4-SO_2NH_2	$(CH_2)_3N(CH_2)_5$	211–213	64	I	J	$C_{24}H_{29}N_5O_2S$	63.83	63.50	6.47	6.48	15.51	15.45
180	H	$(CH_2)_2O(CH_2)_2N(C_2H_5)_2$	100 dec	23	II	H	$C_{24}H_{30}N_4O\cdot 1.67HCl\cdot 0.5H_2O$[m,n]	62.60	62.95	7.15	7.65	12.17	11.54
181	4-SO_3H	$(CH_2)_2O(CH_2)_2N(C_2H_5)_2$	195–198	61	IV	E	$C_{24}H_{30}N_4O_4S\cdot 1.25HCl\cdot 0.5H_2O$[o,p]	54.89	54.67	6.19	6.31	10.67	10.32
182	H	$(CH_2)_2S(CH_2)_2N(C_2H_5)_2$	115–118	53	II	B	$C_{24}H_{30}N_4S\cdot HCl$[q]	65.06	65.25	7.05	7.22	12.65	12.36
183	3-OH, 4-COOH	$(CH_2)_3N(CH_2)_5$	218–219 dec	57	IV	Z	$C_{25}H_{31}N_4O_3\cdot 0.5H_2O$[r]	68.01	68.08	6.62	6.89	12.69	12.61
184	H	$(CH_2)_5N(C_2H_5)_2$	180–182	54	II	H	$C_{25}H_{32}N_4\cdot 2HCl\cdot 0.25H_2O$[s,t]	64.44	64.51	7.46	7.43	12.02	11.97
185	H	$CHCH_3(CH_2)_3N(C_2H_5)_2$	120–125 dec	62	II	AA	$C_{25}H_{32}N_4\cdot 1.67HCl\cdot H_2O$[u,v]	64.23	64.56	7.69	7.73	11.99	11.95
186	4-OC_2H_5	$(CH_2)_3N(C_2H_5)_2$	100–102	20	I	P	$C_{25}H_{32}N_4O$	74.22	74.20	7.97	8.06	13.85	14.10
187	4-SO_3H	$(CH_2)_5N(C_2H_5)_2$	229 dec	86	IV	H	$C_{25}H_{32}N_4O_3S$	64.07	63.90	6.88	6.77	11.96	11.71

188	4-SO_3H	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	200 dec	94	IV	H	$C_{25}H_{42}N_4O_3S\cdot1.5HCl\cdot2.5H_2O^{w,x}$	52.83	52.85	6.83	7.02	9.86	9.74
189	3-CH_2OH	$CH_2C(CH_3)_2CH_2N(CH_2)_4$	101–103	65	I	B	$C_{26}H_{32}N_4O$	74.96	75.23	7.74	7.80	13.45	13.52
190	3-CF_3	$CH_2C(CH_3)_2CH_2N(CH_2)_5$	132–134	75	I	B	$C_{27}H_{31}F_3N_4$	69.21	69.42	6.67	6.74	11.96	11.89
191	H	$(CH_2)_3NH(CH_2)_7CH_3$	78–79	70	I	B	$C_{27}H_{36}N_4$	77.84	77.95	8.71	8.94	13.45	13.39
192	3-$CHOHCH_3$	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	125 dec	19	II	V	$C_{21}H_{36}N_4O\cdot2HCl\cdot0.5H_2O^{y,z}$	63.02	63.31	7.64	7.89	10.89	10.78
193	4-$CONHC_6H_5$	$CHCH_3CH_2N(CH_3)_2$	156–160	25	I	B	$C_{28}H_{29}N_5O$	74.47	74.96	6.47	6.68	15.51	15.76
194		$(CH_2)_3N[(CH_2)_2]_2O$	240–241	61	I	Y	$C_{28}H_{30}N_6O_3S$	63.37	63.46	5.70	5.71	15.84	15.84
195		$(CH_2)_3N(CH_2)_5$	190–192	83	I	Q	$C_{29}H_{32}N_6O_2S$	65.88	65.70	6.18	6.05	15.90	15.92
196	3-$CHOHCH_3$		163 dec	85	II	AA	$C_{30}H_{40}N_4O\cdot2HCl\cdot0.5H_2O^{aa,bb}$	64.97	65.33	7.81	7.62	10.10	9.85

[a] The free bases ranged from orange to reddish brown in color; the acid addition salts ranged from orange to blue-black in color. [b] See footnote *b*, Table I. [c] *Anal.* Calcd: H_2O, 8.16. Found: H_2O, 8.03. [d] *Anal.* Calcd: Cl, 16.07. Found: Cl, 16.41. [e] *Anal.* Calcd: Cl, 9.61. Found: Cl, 9.32. [f] *Anal.* Calcd: Cl, 7.31. Found: Cl, 7.80. [g] *Anal.* Calcd: H_2O, 3.74. Found: H_2O, 3.35. [h] *Anal.* Calcd: H_2O, 3.59. Found: H_2O, 3.31. [i] *Anal.* Calcd: H_2O, 7.48. Found: H_2O, 7.32. [j] *Anal.* Calcd: H_2O, 4.43. Found: H_2O, 4.54. [k] *Anal.* Calcd: Cl, 14.23. Found: Cl, 13.61. [l] *Anal.* Calcd: H_2O, 1.20. Found: H_2O, 1.00. [m] *Anal.* Calcd: Cl, 12.86. Found: Cl, 12.95. [n] *Anal.* Calcd: H_2O, 1.95. Found: H_2O, 1.93. [o] *Anal.* Calcd: Cl, 8.44. Found: Cl, 8.09. [p] *Anal.* Calcd: H_2O, 1.71. Found: H_2O, 1.84. [q] *Anal.* Calcd: Cl, 8.00. Found: Cl, 7.80. [r] *Anal.* Calcd: H_2O, 2.04. Found: H_2O, 1.47. [s] *Anal.* Calcd: Cl, 15.22. Found: Cl, 15.54. [t] *Anal.* Calcd: H_2O, 0.97. Found: H_2O, 0.69. [u] *Anal.* Calcd: Cl, 12.67. Found: Cl, 12.71. [v] *Anal.* Calcd: H_2O, 3.85. Found: H_2O, 3.70. [w] *Anal.* Calcd: Cl, 9.36. Found: Cl, 9.68. [x] *Anal.* Calcd: H_2O, 7.92. Found: H_2O, 7.24. [y] *Anal.* Calcd: Cl, 13.78. Found: Cl, 13.18. [z] *Anal.* Calcd: H_2O, 1.75. Found: H_2O, 1.49. [aa] *Anal.* Calcd: Cl^-, 12.79. Found: Cl^-, 12.81. [bb] *Anal.* Calcd: H_2O, 1.62. Found: H_2O, 1.65.

[4-(3-diethylamino-2,2-dimethylpropylamino)-1-naphthylazo]benzenesulfonic acid hydrochloride (**188**) in mice was not duplicated in the monkey. N′-{4-[*p*-(2-Diethylaminoethoxy)phenylazo]-1-naphthyl}-N,N-diethylethylenediamine trihydrochloride (**83**) caused strong permanent suppression of eggs or was curvative in monkeys at a dose of 100 mg/kg per day for 5 days or 50 mg/kg per day for 10 days, but was essentially ineffective in doses of 12.5 or 25 mg/kg daily for 10 days. The effects of *m*-[4-(2-diethylaminoethylamino)-1-naphthylazo]-α-methylbenzyl alcohol dihydrochloride (**57**) were particularly noteworthy because the compound cured or strongly suppressed *S. mansoni* infections in the monkey following a single dose of 400 mg/kg or single doses of 200 mg/kg per day on two successive days.

The antischistosome properties of compounds of structure III are abolished or drastically reduced when alkyl substituents at R_1 and/or R_2 are replaced by hydrogen (compounds **96–98**, **100**, **124**, **137**, **169**, and **191**) or when R is methyl or ethyl (**197–199**). Among compounds having a structural relationship to N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa), the position isomer N,N-diethyl-N′-(1-phenylazo-2-naphthyl)ethylenediamine (XIII), the oxygen isostere 2-(4-phenylazo-1-naphthyloxy)triethylamine (XIV), and the quaternary salt diethylmethyl[2-(4-phenylazo-1-naphthylamino)ethyl]ammonium iodide (XVI) lacked appreciable effect. Activity was also diminished by conversion to the N-oxide XV, an interesting and unexpected result in view of the beneficial effects of N-oxidation on the antimalarial properties of the 4-aminoquinolines and 9-aminoacridines.[22–24] A variety of N,N-dialkyl-N′-(4-azophenyl)alkylenediamines[6,7,25] and N-mono- and N,N-dialkyl-N′-[4-azo(5,6,7,8-tetrahydro-1-naphthyl)]alkylenediamines were also prepared[6,7] but none of these showed promising antischistosome activity.

Experimental Section[26]

Preparation of N-Mono- and N,N-Dialkyl-N′-(4-arylazo-1-naphthyl)alkylenediamines (III) (Tables I–V). Procedure I.—To a solution of 12.7 g (0.1 mole) of *o*-chloroaniline in 25 ml of concentrated HCl, 100 ml of water, and 100 g of crushed ice, there was added at 0–5° a solution of 6.9 g (0.1 mole) of $NaNO_2$ in 100 ml of cold water. After diazotization was complete, the diazonium salt solution was added with stirring at 0–5° to a cold solution of 24.2 g (0.1 mole) of 1-(2-diethylaminoethylamino)-naphthalene[10] in 17 ml of concentrated HCl and 250 ml of water. The mixture was stirred for 3 hr at 0–5° and allowed to warm to room temperature. The addition of excess aqueous NaOH precipitated the crude dye which was collected by filtration, washed throughly with water, and dried *in vacuo* at 50°. Crystallization from 2-propanol gave 28.9 g (76%) of N′-[4-(*o*-chlorophenylazo)-1-naphthyl]-N,N-diethylethylenediamine (**8**) as deep maroon crystals, mp 99–100°.

Procedure II.—*p*-(2-Diethylaminoethoxy)aniline (13.5 g, 0.065 mole) was diazotized and coupled with 15.8 g (0.065 mole) of 1-(2-diethylaminoethylamino)naphthalene[10] according to procedure I. The purple reaction mixture was made alkaline (NH_4OH)

(22) E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, **5**, 1153 (1962).

(23) E. F. Elslager, R. E. Bowman, F. H. Tendick, D. J. Tivey, and D. F. Worth, *ibid.*, **5**, 1159 (1962).

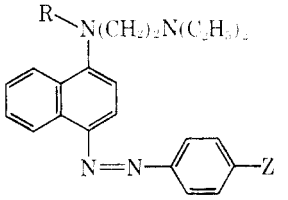
(24) E. F. Elslager, E. H. Gold, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Heterocyclic Chem.*, **1**, 6 (1964).

(25) F. Mietzsch and J. Klarer, U. S. Patent 2,022,921 (Dec. 3, 1935).

(26) Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus. Water determinations were made by the Karl Fischer method.

TABLE IV

N,N-DIETHYL-N′-ALKYL-N′-(4-PHENYLAZO-1-NAPHTHYL)ETHYLENEDIAMINES[a]



No.	R	Z	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
197	CH_3	H	110–120	65	II	K	$C_{28}H_{28}N_4 \cdot C_6H_5O_7 \cdot C_2H_6O$[c,d]	62.19	62.53	7.07	6.84	9.36	9.30
198	CH_3	SO_3H	240 dec	97	IV	H	$C_{28}H_{28}N_4O_3S \cdot 0.5H_2O$[e,f]	61.44	61.38	6.50	6.49	12.46	12.29
199	C_2H_5	SO_3H	226–229 dec	87	IV	H	$C_{34}H_{39}N_4O_3S \cdot 0.25H_2O$[g]	62.79	62.72	6.70	6.79	12.21	11.87

[a] Compounds range from orange to brown in color. [b] See footnote *b*, Table I. [c] Monocitrate salt. [d] Ethanol of crystallization. [e] *Anal.* Calcd: S, 7.13. Found: S, 7.24. [f] *Anal.* Calcd: volatile loss at 100°, 2.00. Found: 1.64. [g] *Anal.* Calcd: volatile loss at 100°, 0.98. Found: 0.88.

and the sticky precipitate that formed was extracted with chloroform. The combined chloroform extracts were dried (K_2CO_3), the drying agent was collected by filtration, and the chloroform was removed *in vacuo*. The residue was dissolved in hot 2-propanol and the solution was treated with excess HCl–2-propanol. Upon cooling, deep blue crystals separated. The product was collected by filtration and recrystallized from 2-propanol–HCl. N′-{4-[*p*-(2-Diethylaminoethoxy)phenylazo]-1-naphthyl}-N,N-diethylethylenediamine (**83**) was obtained as a hydrated trihydrochloride salt, mp 170–173°, yield 22.5 g (56%). The salt was allowed to equilibrate in the air prior to analysis.

Procedure III.—A mixture of 13.8 g (0.1 mole) of *p*-nitroaniline, 30 ml of water, and 30 ml of concentrated HCl was heated until solution occurred. The solution was cooled rapidly to room temperature with vigorous stirring. Ice (80 g) was then added followed by 6.9 g (0.1 mole) of $NaNO_2$ in one portion. After most of the precipitate had dissolved, the diazonium salt solution was added with stirring at 0–5° to a solution of 24.2 g (0.1 mole) of 1-(2-diethylaminoethylamino)naphthalene[10] in 250 ml of water, 250 ml of 95% ethanol, and 25 ml of concentrated HCl. The purple reaction mixture was stirred for 2 hr at 0–5°, then for 2 hr at room temperature. The mixture was made alkaline with NaOH and the precipitate was collected by filtration, washed with water, and dried *in vacuo*. Crystallization of the crude dye from 2-propanol gave 30.1 g (77%) of N,N-diethyl-N′-[4-(*p*-nitrophenylazo)-1-naphthyl]ethylenediamine (**16**) as purple-black crystals, mp 137–138°.

Procedure IV.—A solution, prepared by combining 34.7 g (0.20 mole) of sulfanilic acid, 34 ml (0.20 mole) of 6 *N* NaOH solution, 250 ml of water, and 200 ml (0.20 mole) of 1 *M* $NaNO_2$ solution, was cooled to 0° and added with stirring to a mixture of 50 ml (0.60 mole) of concentrated HCl and 500 g of an ice–water mixture. After stirring for 5 min, the suspension of the diazonium salt was added to a mixture of 48.6 g (0.20 mole) of 1-(2-diethylaminoethylamino)naphthalene,[10] 100 ml (1.20 moles) of concentrated HCl, and 2 kg of ice–water. The deep purple suspension was stirred for 18 hr during which time it was allowed to warm to room temperature. The precipitate was collected by filtration, washed with 0.5 *N* HCl, and dried *in vacuo* at 78° for 18 hr. After exposure to the atmosphere for 24 hr, *p*-[4-(2-diethylaminoethylamino)-1-naphthylazo]benzenesulfonic acid monohydrochloride dihydrate was obtained as a purple-green solid, mp 200° dec.

The free base was prepared as follows. The acid hydrochloride salt was suspended in water and neutralized with aqueous sodium acetate or $(NH_4)_2CO_3$ solution. The orange precipitate that separated was collected by filtration, washed successively with water and methanol, and dried *in vacuo* at 100° for 16 hr. The base (**23**) weighed 78.5 g (92%), mp 243–244°.

Procedure V.—A solution of 5.3 g (0.0136 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VIId) in 50 ml of ice and water containing 2.5 ml (0.03 mole) of concentrated HCl was treated with 13.6 ml (0.0136 mole) of a 1 *M* aqueous solution of $NaNO_2$ over a period of 5 min. The red diazonium salt solution was stirred for 5 min at 0–5° and poured into a stirred solution of 3.3 g (0.0136 mole) of 1-(2-diethylaminoethylamino)naphthalene[10] in 150 ml of water and 7.5 g (0.09 mole) of concentrated HCl while maintaining the temperature below 5°. The resulting purple mixture was stirred and allowed to warm to room temperature during 1 hr, whereupon it was treated with 170 ml of 1 *M* aqueous $NaHCO_3$. The mixture was extracted with ether and the combined extracts were washed successively with water and saturated aqueous NaCl solution and dried ($MgSO_4$). The drying agent was collected by filtration, and the ether was evaporated to give 7.2 g of the intermediate N-(2-diethylaminoethyl)-N-{4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1-naphthyl}-2,2,2-trifluoroacetamide (VIIId) as a deep red solid with green iridescence. In another run, a sample of the dihydrochloride salt was prepared by adding a 2-propanol–HCl solution to a solution of the crude base in 2-propanol. Crystallization from methanol–2-propanol–ethyl acetate gave dark red crystals, mp 203–205° dec.

Anal. Calcd for $C_{34}H_{41}F_3N_6O \cdot 2HCl$: C, 60.08; H, 6.38; Cl, 10.43; N, 12.37. Found: C, 60.00; H, 6.38; Cl, 10.66; N, 12.85.

The crude iridescent base (7.2 g) was dissolved in 75 ml of warm methanol, 25 ml (0.05 mole) of 2 *N* methanolic NaOH was added, and the mixture was stirred at room temperature for 1 hr. The dye was collected by filtration, washed with cold methanol, and recrystallized twice from an ethanol–acetone mixture to give 3.7 g (52% over-all) of N,N′′-(azodi-1,4-naphthylene)bis(N′,N′-diethylethylenediamine) (VIIIa, **209**) as iridescent brown needles, mp 163–165°.

Procedure VI.—A mixture of 7.1 g (0.02 mole) of N-(2-bromoethyl)-4-phenylazo-1-naphthylamine, 5.0 g (0.04 mole) of 3-azabicyclo[3.2.2]nonane, and 12 ml of dimethylformamide was heated on a steam bath for 2 hr. The mixture was poured into a mixture of 300 ml of water and 400 g of ice and allowed to stand overnight. The orange precipitate that separated was collected by filtration, washed with water, and dried *in vacuo* at 55°. Crystallization from chloroform–2-propanol gave 6.2 g (78%) of 3-{2-[(4-phenylazo-1-naphthyl)amino]ethyl}-3-azabicyclo[3.2.2]-nonane (**136**) as lustrous orange-red plates, mp 164–166°.

Procedure VII.—N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VIId) (9.8 g, 0.025 mole) was diazotized according to procedure V. The diazonium salt solution was added in one portion to a solution of 3.6 g (0.025 mole) of 2-naphthol and 4.2 g of $NaHCO_3$ in 200 ml of water, 200 ml of ethanol, and 200 g of ice containing a trace of Carbowax stearate. The temperature was maintained at 5° for 3 hr, the mixture was allowed to warm to room temperature overnight, and the red precipitate that separated was collected by filtration, dried, and crystallized from 2-propanol. The intermediate N-(2-diethylaminoethyl)-2,2,2-trifluoro-N-[4-(2-hydroxy-1-naphthylazo)-1-naphthyl]acetamide weighed 9.2 g, mp 158–162°. It was suspended in a mixture of 100 ml of methanol and 50 ml of methanol containing 0.1 mole of NaOH and warmed to 60° when solution occurred. The mixture was stirred at room temperature for 48 hr, excess solid CO_2 was added, and the iridescent dark green crystals that separated were collected by filtration, washed with water, and dried *in vacuo*. The 1-[4-(2-diethylaminoethylamino)-1-naphthylazo]-2-naphthol (IXb, **203**) thus obtained weighed 6.4 g (62% over-all), mp 146–150°.

Procedure VIII.—A cooled solution of 0.77 g (0.011 mole) of $NaNO_2$ in 50 ml of water was added to a solution of 4.0 g (0.011 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)formamide dihydrochloride (VIIe) in dilute HCl. After 5 min, the

TABLE V: N,N-DIALKYL-N′-(4-NAPHTHYLAZO-1-NAPHTHYL)ALKYLENEDIAMINES[a]

No.	YNR1R2	Naphthalene ring attachment	Z	Mp, °C	Yield purified, %	Procedure	Purification[b] solvent	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
200	$(CH_3)_2N(CH_2)_2$	1	4-SO_3H	228–230	82	IV	H	$C_{25}H_{28}N_4O_3S\cdot HCl\cdot 1.5H_2O$[c,d]	57.08	56.87	5.75	5.92	10.65	10.60
201	$(CH_2)_2N(C_2H_5)_2$	1	4-Cl	123–124	64	I	A	$C_{26}H_{27}ClN_4$	72.46	72.43	6.32	6.26	13.00	12.84
202	$(CH_2)_2N(C_2H_5)_2$	1	4-NO_2	170–171	36	III	A	$C_{26}H_{27}N_5O_2$	70.72	71.03	6.17	6.20	15.86	15.78
203	$(CH_2)_2N(C_2H_5)_2$	1	2-OH	146–150	62	VII	H	$C_{26}H_{28}N_4O$	75.70	75.78	6.84	6.91	13.58	13.82
204	$(CH_2)_2N(C_2H_5)_2$	1	5-OH	150–155 dec	83	II	H	$C_{26}H_{28}N_4O\cdot 2HCl\cdot 1.75H_2O$[e,f]	60.40	60.39	6.53	6.58	10.84	10.23
205	$(CH_2)_2N(C_2H_5)_2$	1	4-SO_3H	229–230	87	IV	II	$C_{26}H_{28}N_4O_3S\cdot 0.25H_2O$[g]	64.91	64.91	5.97	5.76	11.65	11.27
206	$(CH_2)_2N(C_2H_5)_2$	2	3-COOH	176–178	73	II	H	$C_{27}H_{28}N_4O_2\cdot 2HCl\cdot 1.25H_2O$[h,i]	60.50	60.51	6.11	6.14	10.45	10.36
207	$(CH_2)_2N(C_2H_5)_2$	1	4-$NHCOCH_3$	112–114	40	I	P	$C_{28}H_{31}N_5O$	74.14	73.91	6.89	6.82	15.44	15.64
208	$(CH_2)_2N[(CH_2)_2CH_3]_2$	1	4-SO_3H	205–210	99	IV	H	$C_{30}H_{36}N_4O_3S\cdot HCl\cdot H_2O$[j,k]	61.36	61.87	6.69	6.88	9.54	9.20
209	$(CH_2)_2N(C_2H_5)_2$	1	4-$NH(CH_2)_2N(C_2H_5)_2$	163–165	52	V	O	$C_{32}H_{42}N_6$	75.25	75.32	8.29	8.22	16.46	16.46
210	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	1	4-$COO(CH_2)_2N(C_2H_5)_2$	90 dec	95	II	H	$C_{44}H_{48}N_6O_2\cdot 3HCl\cdot 2.5H_2O$[l]	57.66	57.19	7.26	7.57	9.89	9.93
211	$(CH_2)_2N[(CH_2)_2OC_2H_5]_2$	1	4-SCH_3	100–102	66	II	H	$C_{36}H_{40}N_4O_2S\cdot 1.5HCl\cdot 0.5H_2O$[m]	65.86	66.00	6.53	6.85	8.53	8.55

[a] Compounds range from red to black in color. [b] See footnote *b*, Table I. [c] *Anal.* Calcd: Cl, 6.74. Found: Cl, 6.57. [d] *Anal.* Calcd: H_2O, 5.13. Found: H_2O, 4.14. [e] *Anal.* Calcd: Cl, 13.72. Found: Cl, 13.65. [f] *Anal.* Calcd: H_2O, 6.09. Found: H_2O, 5.75. [g] *Anal.* Calcd: H_2O, 0.94. Found: H_2O, 1.28. [h] *Anal.* Calcd: Cl, 13.23. Found: Cl, 13.09. [i] *Anal.* Calcd: H_2O, 4.20. Found: H_2O, 4.22. [j] *Anal.* Calcd: Cl, 6.04. Found: Cl, 5.75. [k] *Anal.* Calcd: H_2O, 3.07. Found: H_2O, 3.14. [l] *Anal.* Calcd: Cl, 15.02. Found: Cl, 15.25. [m] *Anal.* Calcd: Cl, 8.10. Found: Cl, 8.66.

diazonium salt solution was added at 0–5° with stirring to a solution of 1.6 g (0.011 mole) of 2-naphthol and 1.9 g (0.022 mole) of $NaHCO_3$ in 80 ml of water and 100 ml of ethanol. The reaction mixture was allowed to warm to room temperature and stand overnight. The red precipitate was collected by filtration, dried, and crystallized from ethanol. The intermediate N-(2-diethylaminoethyl)-N-[4-(2-hydroxy-1-naphthylazo)-1-naphthyl]formamide (IXa) weighed 1.7 g (35%), mp 170–172°.

Anal. Calcd for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.54; H, 6.66; N, 12.52.

Hydrolysis to 1-[4-(2-diethylaminoethylamino)-1-naphthylazo]-2-naphthol (IXb, **203**) was accomplished by allowing a solution of IXa in 2-propanol containing an excess of HCl to stand at room temperature overnight.

N-(2-Diethylaminoethyl)-N-(4-phenylazo-1-naphthyl)acetamide (VIb).—A mixture of 5.0 g (0.014 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa, **17**) and 25 ml of acetic anhydride was boiled under reflux for 1 hr, cooled, and poured into an ice–water mixture. The mixture was made basic with NH_4OH and the oily precipitate that separated was extracted with ether. The combined ether extracts were dried (K_2CO_3), the drying agent was collected by filtration, and the filtrate was evaporated to dryness. The residual oil was dissolved in petroleum ether (bp 30–60°) and an orange-red solid was deposited as the petroleum ether was allowed to evaporate slowly in the air. After drying *in vacuo* for 3 days, the product weighed 3.7 g (66%), mp 69–72°.

Anal. Calcd for $C_{24}H_{25}N_4O$: C, 74.19; H, 7.26; N, 14.42. Found: C, 74.56; H, 7.28; N, 14.60.

N-(2-Diethylaminoethyl)-N-(4-phenylazo-1-naphthalenecarbamic Acid) Ethyl Ester (VIc).—The addition of ethyl chloroformate (113 g, 1.04 moles) to 17.3 g (0.05 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa, **17**) was accompanied by an exothermic reaction and the temperature rose to 50°. The mixture was heated on a steam bath for 2 hr and cooled, and the residue dissolved in 250 ml of water. The mixture was made basic with NH_4OH and the orange precipitate that separated was extracted with ether. The combined ether extracts were washed successively with water and saturated aqueous NaCl and dried ($MgSO_4$). The drying agent was separated and the ether solution was concentrated to dryness *in vacuo*. The red, viscous residue (20.0 g, 95%) could not be induced to crystallize and was used directly in the reduction step.

Anal. Calcd for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.23; N, 13.39. Found: C, 72.01; H, 7.23; N, 13.39.

N-(2-Diethylaminoethyl)-2,2,2-trifluoro-N-(4-phenylazo-1-naphthyl)acetamide Monohydrochloride (VId).—Trifluoroacetic anhydride (77 g, 0.367 mole) was added slowly with stirring and external cooling to 50 ml of dimethylformamide and the mixture was added over a period of 40 min with stirring to a solution of 106 g (0.306 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)-ethylenediamine (VIa, **17**) in a mixture of 200 ml of benzene and 425 ml of dimethylformamide contained in a 1-l. flask fitted with a dropping funnel, thermometer, mechanical stirrer, and drying tube. An exothermic reaction ensued and the temperature rose to 45°. The dark red homogeneous reaction mixture was allowed to cool to room temperature and stand overnight. It was then poured into a briskly stirred mixture of 1 kg of ice and water and 425 ml of benzene. A cold solution of 28.7 ml (0.430 mole) of concentrated NH_4OH and 100 ml of water was then added to the stirred mixture and the aqueous layer was removed in a separatory funnel and extracted with 50 ml of benzene. The benzene extract was combined with the original benzene layer and the benzene solution was washed successively with 200 ml of water, 100 ml of water, and 50 ml of saturated aqueous NaCl. The benzene solution was dried ($MgSO_4$) and the drying agent was collected by filtration. The filtrate volume was 720 ml. A portion (625 ml) of the benzene filtrate was treated with 45 ml of a 5.8 *N* 2-propanol–HCl mixture and concentrated to a volume of approximately 400 ml. The mixture was allowed to cool slowly to room temperature and the orange crystalline precipitate that separated was collected by filtration, washed with benzene and ether, and dried *in vacuo* at 50°; 105.9 g (83.5%), mp 206.5–208.5°.

Anal. Calcd for $C_{24}H_{25}F_3N_4O\cdot HCl$: C, 60.18; H, 5.47; Cl, 7.40; N, 11.70. Found: C, 59.98; H, 5.54; Cl, 7.58; N, 11.69.

N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)acetamide (VIIb).—N-(2-Diethylaminoethyl)-N-(4-phenylazo-1-naphthyl)-acetamide (VIb) (91.0 g, 0.234 mole) was dissolved in methanol

and hydrogenated over 3 g of Raney nickel at an initial hydrogen pressure of 3.5 kg/cm². The catalyst was collected by filtration and the methanol solution was poured into 180 ml (0.12 mole) of 4 *N* ethanolic HCl. Volatile materials were removed *in vacuo* and the residue was crystallized successively from 2-propanol and methanol to give 60.0 g (76%) of the hydrochloride salt as off-white crystals, mp 230° dec. For analysis, a small sample was converted to the free base, mp 68–71°.

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.03. Found: C, 71.94; H, 8.43; N, 14.04.

4-Amino-N-(2-diethylaminoethyl)-1-naphthalenecarbamic Acid Ethyl Ester Dihydrochloride (VIIa).—N-(2-Diethylaminoethyl)-N-(4-phenylazo-1-naphthalenecarbamic acid) ethyl ester (VIc) (20.0 g, 0.048 mole) was dissolved in 250 ml of absolute ethanol and hydrogenolyzed over 3 g of Raney nickel at an initial hydrogen pressure of 3.5 kg/cm². The catalyst was removed by filtration and volatile materials were removed *in vacuo*. The dark residue was dissolved in 200 ml of 2-propanol and the solution was treated with 35 ml of 4 *N* ethanolic HCl. The hydrochloride salt was precipitated by the addition of anhydrous ether and the dull pink solid was collected and dried; 16.0 g (83%), mp 212–213°.

Anal. Calcd for $C_{19}H_{27}N_3O_2 \cdot 2HCl$: C, 56.71; H, 7.26; Cl, 17.62; N, 10.44. Found: C, 56.57; H, 7.54; Cl, 17.41; N, 10.54.

N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide Monohydrochloride (VIId).—N-(2-Diethylaminoethyl)-2,2,2-trifluoro-N-(4-phenylazo-1-naphthyl)acetamide monohydrochloride (VId) (88 g, 0.184 mole) was dissolved in 600 ml of methanol and hydrogenolyzed at 23–35° at an initial hydrogen pressure of 3.5 kg/cm² in the presence of 5 g of Raney nickel. The solvent was removed on a rotatory evaporator while maintaining the temperature below 45° and the residue was triturated with anhydrous ether. The precipitate was collected by filtration, washed with ether, and dried *in vacuo* at 50°. Crystallization from ethanol gave 65.9 g (92%) of colorless crystals, mp 215–218°.

Anal. Calcd for $C_{18}H_{22}F_3N_3O \cdot HCl$: C, 55.45; H, 5.95; N, 10.78 Found: C, 55.42; H, 5.82; N, 10.80.

N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)formamide Dihydrochloride (VIIe).—A mixture of 25 ml of formic acid, 60 ml of acetic anhydride, and 200 ml of tetrahydrofuran was stirred and heated on a steam bath for 2 hr, and to it was added 50.0 g (0.45 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)-ethylenediamine (VIa, **17**). The mixture was heated under reflux with stirring for 24 hr and volatile materials were removed *in vacuo*. The residue was suspended in aqueous NaOH solution and the mixture was extracted with ether. The combined ether extracts were dried (K_2CO_3), the drying agent was collected by filtration, and the ether filtrate was evaporated to dryness *in vacuo*. The viscous red oil thus obtained (47.0 g, 86%) could not be induced to crystallize and the crude N-(2-diethylaminoethyl)-N-(4-phenylazo-1-naphthyl)formamide (VIe) was used directly in the hydrogenation step.

A solution of 47.0 g (0.126 mole) of the crude formamide (VIe) in 300 ml of methanol was hydrogenated over 1 g of Raney nickel at an initial hydrogen pressure of 3.5 kg/cm². When the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in 2-propanol and the hydrochloride salt was precipitated by the addition of an excess of a HCl–2-propanol mixture. The product was collected by filtration and dried *in vacuo* at 40°; 43.4 g (95%), mp 150° dec.

Anal. Calcd for $C_{17}H_{23}N_3O \cdot 2HCl \cdot 0.33\ H_2O$: C, 56.20; H, 7.12; N, 11.52; H_2O, 1.63. Found: C, 56.59; H, 7.83; N, 11.13; H_2O, 2.13.

N,N-Diethyl-N′-(1-phenylazo-2-naphthyl)ethylenediamine (XIII).—Aniline (7.9 g, 0.085 mole) was diazotized and coupled with 20.7 g (0.085 mole) of 2-(2-diethylaminoethylamino)naphthalene[10,27] according to procedure I. The product (XIII) was obtained as red crystals from 2-propanol; mp 78–79°, yield 21.5 g (73%).

Anal. Calcd for $C_{22}H_{26}N_4$: C, 76.26; H, 7.57; N, 16.17. Found: C, 76.27; H, 7.70; N, 16.21.

2-(4-Phenylazo-1-naphthyloxy)triethylamine Monocitrate (XIV).—A mixture of 24.8 g (0.1 mole) of 4-phenylazo-1-naphthol, 17.2 g (0.1 mole) of 2-chlorotriethylamine hydrochloride, 10.8 g (0.2 mole) of sodium methoxide, and 200 ml of ethanol was boiled under reflux for 24 hr. The ethanol was removed *in vacuo*, and the residue was treated with an excess of aqueous NaOH and extracted with ether. The combined ether extracts were dried (Na_2SO_4), the drying agent was collected by filtration, and the ether was removed *in vacuo*. The residue was dissolved in warm ethanol and treated with an excess of citric acid in ethanol. Upon cooling, the crude product separated, mp 140–143° dec. Crystallization from ethanol–ether gave 14.6 g (27%) of orange crystals, mp 143–145° dec.

Anal. Calcd for $C_{22}H_{25}N_3O \cdot C_6H_8O_7$: C, 62.32; H, 6.16; N, 7.79. Found: C, 62.41; H, 6.30; N, 7.99.

N,N-Diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine N-Oxide Dihydrochloride (XV).—To a solution of 17.3 g (0.05 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa, **17**) in 500 ml of dry $CHCl_3$ was added slowly with stirring a solution of 6.9 g (0.05 mole) of perbenzoic acid[28] in 100 ml of $CHCl_3$. The reaction was mildly exothermic and the temperature rose to 30°. After 3 hr, the chloroform was removed *in vacuo* in the presence of platinum foil, and the residue was dissolved in 2-propanol and treated with 5 ml (0.047 mole) of a 34% 2-propanol–HCl mixture. Upon cooling, the dark red precipitate that separated was collected by filtration and dried *in vacuo* at 40° for 72 hr. The product weighed 6.9 g (31%), mp 155–157°.

Anal. Calcd for $C_{22}H_{26}N_4O \cdot 2HCl$: C, 60.69; H, 6.48; N, 12.87; H_2O, 0.0. Found: C, 60.69; H, 6.36; N 12.69; H_2O, 0.0.

Diethylmethyl[2-(4-phenylazo-1-naphthylamino)ethyl]ammonium Iodide (XVI).—A mixture of 5.0 g (0.0145 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine (VIa, **17**) and 5.0 g (0.0352 mole) of methyl iodide was heated on a steam bath for 15 min, then dissolved in 500 ml of hot ethanol. Upon cooling, a deep red solid separated weighing 3.8 g (54%), mp 191–193°.

Anal. Calcd for $C_{23}H_{39}IN_4$: C, 56.56; H, 5.98; N, 11.47. Found: C, 56.60; H, 5.66; N, 11.34.

N-(2-Bromoethyl)-4-phenylazo-1-naphthylamine.—N-(2-Bromoethyl)-1-naphthylamine hydrobromide[10] (33.1 g, 0.1 mole) was dissolved in a mixture of 420 ml of methanol and 100 ml of ethanol on a steam bath and the solution was cooled to −2°. Aniline (9.3 g, 0.1 mole) was dissolved in a mixture of 200 ml of water and 26 ml (38.4 g., 0.23 mole) of 48% HBr, and 100 ml of ethanol was added. The aniline hydrobromide solution was then cooled to −1° and was slowly treated with a cold solution of 6.9 g (0.1 mole) of $NaNO_2$ in 60 ml of water with stirring so that the temperature was maintained below 2°. After 10 min, a test for nitrous acid (KI–starch paper) was essentially negative and the diazonium salt solution was added to the stirred solution of the naphthylamine salt at such a rate as to maintain the temperature below 5°. The purple reaction mixture was stirred at 0–5° for 3 hr, 250 ml of cold water was added, and the mixture was allowed to stand overnight. The green precipitate was collected by filtration, washed thoroughly with water, and suspended in a mixture of 600 ml of $CHCl_3$ and 500 ml of 5% aqueous NaOH. The mixture was stirred for 1 hr and the red chloroform layer was separated and dried ($MgSO_4$). The drying agent was collected by filtration and the chloroform solution was concentrated to 150 ml and diluted with 150 ml of ethanol. The resulting solution was concentrated to approximately 100 ml and petroleum ether (bp 30–50°) was added to the cloud point. Upon scratching, the product crystallized as golden brown needles. The precipitate was collected by filtration and dried *in vacuo* at 55°; 21.6 g, mp 93–95°. A second crop was obtained by concentration of the filtrate, 7.1 g, mp 93–95°; total yield 28.7 g (81%).

Anal. Calcd for $C_{18}H_{16}BrN_3$: C, 61.02; H, 4.55; N, 11.86. Found: C, 61.31; H, 4.69; N, 12.05.

1-Chloro-3-(4-phenylazo-1-naphthylamino)-2-propanol.—Aniline (4.64 g, 0.05 mole) was diazotized and coupled with 13.6 g (0.05 mole) of 1-chloro-3-(1-naphthylamino)-2-propanol[29] utilizing the conditions described under procedure I. The crude dye was extracted with $CHCl_3$, the combined chloroform extracts were dried (K_2CO_3), the drying agent was collected by filtration, and the $CHCl_3$ filtrate was evaporated to dryness. The residue

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was crystallized from ethanol to give 12.2 g (72%) of a reddish brown solid, mp 140–141°.

Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.34; Cl, 10.44; N, 12.37. Found: C, 67.45; H, 5.55; Cl, 10.58; N, 12.26.

1-Chloro-2-methyl-3-(4-phenylazo-1-naphthylamino)-2-propanol.—Utilizing the procedure described above for the preparation of 1-chloro-3-(4-phenylazo-1-naphthylamino)-2-propanol, aniline (3.25 g, 0.035 mole) and 1-chloro-2-methyl-3-(1-naphthylamino)-2-propanol[29] (10.0 g, 0.035 mole) gave 7.8 g (63%) of maroon crystals, mp 130–131°.

Anal. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.88; H, 5.70; N, 11.88. Found: C, 67.98; H, 5.67; N, 12.05.

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Reactions of Mercaptoamines. III. Synthesis of N-Monosubstituted 2-Mercaptoethylamines[1,2]

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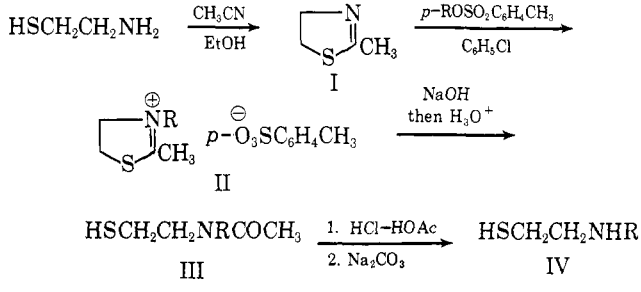
As part of a program on the synthesis of antiradiation drugs, a four-step novel synthesis of N-monosubstituted 2-mercaptoethylamines has been developed. The synthesis involves (1) conversion of 2-mercaptoethylamine by reaction with nitriles to 2-substituted 2-thiazolines (I), (2) quaternization of the thiazolines by tosylate esters to thiazolinium salts (II), (3) alkaline hydrolysis of the salts to an N-(2-mercaptoethyl)acetamide derivative (III), and (4) hydrolysis of the amides in concentrated HCl and glacial acetic acid to N-monosubstituted 2-mercaptoethylamines (IV).

Because of the potential use of 2-mercaptoethylamines as antiradiation drugs,[5–8] it has become imperative that additional synthetic routes to compounds of this class be devised.

Previous studies of the reactions of mercaptoamines have shown that many compounds capable of reacting with the amine function also react with the mercaptan function.[9,10] In the work reported here, a method was devised for protecting the mercaptan function in 2-mercaptoethylamine, allowing the amine function to react, and then regenerating the free mercaptan. N-Monosubstituted 2-mercaptoethylamines were thereby obtained.



Two recent investigations have independently shown that 2-mercaptoethylamine reacts with nitriles to give 2-substituted 2-thiazolines.[11,12] It had been shown earlier that 2-thiazolines are quaternized with alkyl iodides or *p*-toluenesulfonates.[13] It was found that low molecular weight alkyl iodides indeed gave good yields of solid quaternary thiazolinium iodides when heated with 2-methyl-2-thiazoline (I) in refluxing absolute ethanol. However, when more complex halides were used, the reaction appeared to be sluggish. Benzyl chloride and 2-bromoethylamine hydrobromide both gave ill-defined syrups with 2-methyl-2-thiazoline, and chloroacetone gave a tarry product. It became apparent that only active alkylating agents would serve to quaternize the thiazoline. Since esters of *p*-toluenesulfonic acid ("tosylates") are known to be more effective in displacement reactions than alkyl halides (*i.e.*, the tosylate anion is a better "leaving group" than any of the halide anions), they seemed a likely choice for the thiazoline quaternization. In the first experiments, refluxing absolute ethanol was used as solvent and ethyl and *n*-heptyl tosylates were the alkylating agents. The same solid product was obtained in both reactions, and it proved to be the simple tosylate salt of 2-methyl-2-thiazoline. From the reaction with heptyl tosylate, a liquid product was isolated and identified as ethyl *n*-heptyl ether. The isolation of this compound provided a basis for explaining what had happened in these reactions. The tosylate ester had alkylated the solvent in preference to the thiazoline, and the latter had acted merely as an acid acceptor. When refluxing dry acetonitrile

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