ring and cooling until just basic. The solid was filtered and washed with benzene and water.

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N-Mono- and N,N-Dialkyl-N'-1-naphthylalkylenediamines

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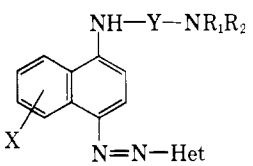
A series of N-mono- and N,N-dialkyl-N'-1-naphthylalkylenediamines were prepared by: (1) alkylation of 1-naphthylamine with an alkylaminoalkyl halide; (2) reductive alkylation of 1-naphthylamine with an amino aldehyde or ketone; (3) treatment of a N-(ω-haloalkyl)-1-naphthylamine with an amine; (4) reaction of 1-naphthol with an alkylenediamine; (5) the action of ethylene oxide, aldehydes, or alkyl halides on a N-(1-naphthyl)ethylenediamine. The use of sodium hydrosulfite in the Bucherer reaction with 1-naphthol is described. 1-(1-Naphthyl)aziridine was prepared by the action of strong base on N-(2-bromoethyl)-1-naphthylamine.

During the course of continuing efforts in these Laboratories to develop new schistosomicidal agents, it was discovered that various 4-(aminoalkylamino)-1-naphthylazo heterocyclic compounds of structure I exhibit strong therapeutic activity against *Schistosoma mansoni* infections in experimental animals.[1,2] The synthesis of many of these azo compounds required the preparation of the corresponding N-mono- and N,N-di-

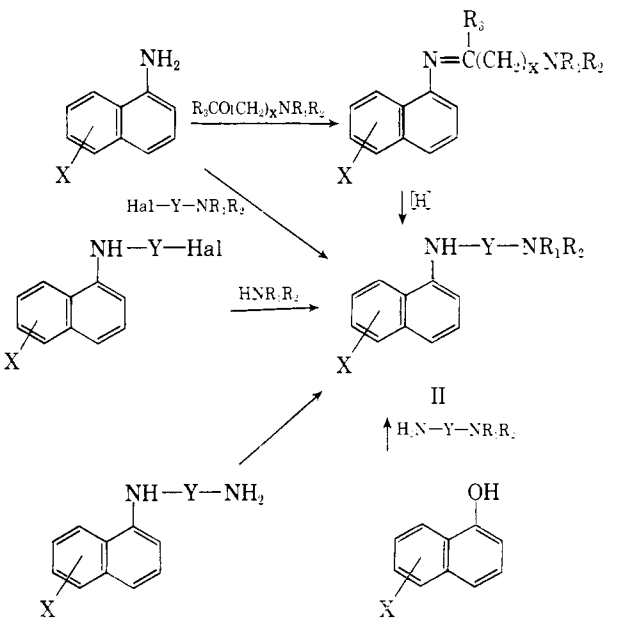


I

alkyl-N'-1-naphthylalkylenediamines (II), where R_1 and R_2 represent hydrogen, alkyl, or aralkyl groups, Y an alkylene radical, and X a hydrogen or halogen atom or alkoxy group. This paper describes in detail the methods used for the synthesis of these intermediates.

Chart A outlines the major synthetic routes used in the present work. The classic technique for the attachment of an alkylaminoalkyl side chain to an aromatic amine involves alkylation of the amine with an alkylaminoalkyl halide in ethanol[3] or in a hydrocarbon solvent in the presence of an acid acceptor such as potassium carbonate.[4] Where the alkylaminoalkyl halides are readily available,[5] the latter method affords a convenient route since the salts can be used directly (method I, Tables I and II). When the carbonate procedure gave poor yields or where it was necessary to prepare the intermediate aminoalkyl halides[6-14] from the corresponding amino alcohols, it was often advantageous to pre-form the more reactive anion of the aromatic amine, utilizing sodium hydride (method II, Tables I and II) or sodamide. Although no extensive comparisons of these methods were made, the sensitivity of the reaction to temperature and base is illustrated by the condensation of 1-naphthylamine with

Chart A



(1) 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).

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(3) D. A. Peak and T. I. Watkins, *J. Chem. Soc.*, 445 (1950).

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(5) The hydrochloride salts of N,N-dimethyl-2-chloroethylamine, 2-chlorotriethylamine, N-(2-chloroethyl)diisopropylamine, N,N-diethyl-3-chloropropylamine, N,N-dimethyl-2-chloropropylamine, and 3-chloro-N,N,2-trimethylpropylamine were purchased from the Michigan Chemical Co., St. Louis, Mich.; 2-bromotriethylamine hydrobromide from Columbia Organic Chemical Co., Columbia, So. Carolina; N-2-chloroethylpyrrolidine hydrochloride from the Aldrich Chemical Co., Milwaukee, Wis.

(6) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 2120 (1961).

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(8) F. Blicke, U. S. Patent 2,922,795 (1960).

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(11) S. Gabriel and J. Colman, *Ber.*, **39**, 2879 (1906).

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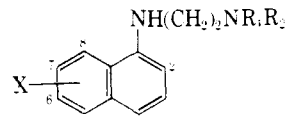
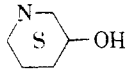
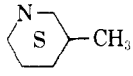
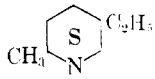
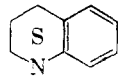
TABLE I

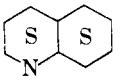
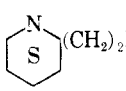
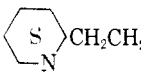
N-MONO- AND N,N-DIALKYL-N'-(1-NAPHTHYL)ETHYLENEDIAMINES[a]



Compd. no.	NR_1R_2	X	B.p., °C. (mm.) or (m.p., °C.)	$n^{25}D$	Yield purified, %	Method
1	NHC_2H_5	H	(207–207.5)		45	V
2	$N(CH_3)_2$	H	161–162 (2.5)	1.6118	40	I
3	$NH(CH_2)_2OH$	H	(173–174)		63	V
4	$NCH_3C_2H_5$	H	143–146 (0.3–0.4)	1.5990	43	I
5	$NCH_3(CH_2)_2OH$	H	183 (0.5)	1.6220	24	VIII
6	$NHCH_2CCH_3{=}CH_2$	H	135 (0.04)	1.6113	62	VIII
7	$N(CH_2)_4$	H	142–143 (0.1)	1.6183	33	I
8	$N[(CH_2)_2]_2O$	H	(185–190)		27	I
9	$N(C_2H_5)_2$	7-Cl	(171–172)		33	I
10	$N(C_2H_5)_2$	8-Cl	(177–181 dec.)		9	II
11	$N[(CH_2)_2]_2NH$	H	170–173 (0.25)	1.7023	27	IV
12	$N(C_2H_5)_2$	H	170–172 (1.5)	1.5903	76	I
13	$NCH_3CH(CH_3)_2$	H	131–135 (0.09)	1.5909	70	I
14	$NC_2H_5(CH_2)_2OH$	H	170–172 (0.2)	1.6109	38	VIII
15	$NH(CH_2)_2OC_2H_5$	H	152–153 (0.07)	1.5936	65	VIII
16	$N[(CH_2)_2OH]_2$	H	(155–157)		45	IX
17	$NC_2H_5CH_2CH{=}CH_2$	H	147 (0.07)	1.5941	65	VIII
18	$NHCH(CH_2)_3$	H	150 (0.05)	1.6132	39	VIII
19	$N(CH_2)_5$	H	168–173 (0.4–0.6)	1.6088	75	VIII
20	$N[(CH_2)_2]_2CHOH$	H	(104–106)		92	VIII
21		H	(105–108)		76	VIII
22	$N[(CH_2)_2]_2NCH_3$	H	163–165 (0.2)		87	VIII
23	$NCH_3(CH_2)_5CH_3$	H	146–151 (0.08–0.2	1.5802	79	I
24	$N(C_2H_5)_2$	6-OCH_3	195–196 (2)	1.5904	73	I
25	$N(C_2H_5)_2$	7-OCH_3	169–173 (0.7)	1.5875	51	I
26	$NH(CH_2)_3O(CH_2)_2OH$	H	210–213 (0.1)	1.6049	40	VIII
27	$N(CH_2CH{=}CH_2)_2$	H	169–172 (0.7)	1.5965	78	VIII
28	$NHCH(CH_2)_5$	H	169 (0.2)	1.6067	88	VIII
29	$N[(CH_2)_2]_2CHCH_3$	H	163 (0.4)	1.5943	71	VIII
30		H	162 (0.5)	1.5980	68	VIII
31	$N(CH_2)_6$	H	164–166 (0.1)	1.6062	84	I
32	$N[(CH_2CHCH_3)_2]_2O$	H	160–161 (0.1)	1.5953	69	VIII
33	$N[(CH_2)_2]_2N(CH_2)_2OH$	H	(207–211)		37	VIII
34	$N[CH(CH_3)_2]_2$	H	178–179 (0.9)	1.5782	50	I
35	$N(C_2H_5)_2$	2-OC_2H_5	144–146 (0.2)	1.6198	20	I
36	$N(CH_2CH_2OCH_3)_2$	H	171–180 (0.2)	1.5826	7	VIII
37	$NH(CH_2)_2N(C_2H_5)_2$	H	155–156 (0.2)	1.5820	33	VII
38	$NHCH_2C_6H_5$	H	(200–202)		65	III[c]
39	$N(CHCH_3CH_2)_2CH_2$	H	162 (0.4)	1.5990	38	VIII
40	$NCH_3CH(CH_2)_3$	H	167 (0.2)	1.5985	75	VIII
41	$NCH_3CH_2C_6H_5$	H	(200–202)		18	XI
42	$N(CH_2CCH_3{=}CH_2)_2$	H	112–114 (0.05)	1.5852	47	VIII
43	$NHCH(CH_2)_7$	H	(250–252)		20	VIII
44	$N(CHCH_3CH_2)_2CHCH_3$	H	(230–234)		5	VIII
45		H	158–159 (0.05)	1.5841	70	VIII
46	$N[(CH_2)_3CH_3]_2$	H	183–185 (0.7)	1.5616	83	I
47	$N[CH_2CH(CH_3)_2]_2$	H	191–192 (1.5)	1.5608	29	I
48	$N[(CH_2)_2OC_2H_5]_2$	H	158 (0.07)	1.5600	70	VIII
49	$NC_2H_5(CH_2)_2N(C_2H_5)_2$	H	147–148 (0.1)	1.5715	40	VIII
50		H	201 (0.1)		39	VIII

Purification solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
A	$C_{14}H_{18}N_2 \cdot C_6H_3N_3O_7$[c,d]	54.17	54.30	4.77	4.81	15.80	15.98
	$C_{14}H_{18}N_2$	78.46	78.28	8.46	8.64	13.07	13.16
A	$C_{14}H_{18}N_2O \cdot C_6H_3N_3O_7$[d,e]	52.28	52.38	4.61	4.63	15.25	14.97
	$C_{15}H_{20}N_2$	78.90	78.70	8.83	8.80	12.27	12.36
	$C_{15}H_{20}N_2O$	73.73	73.23	8.25	8.19	11.47	11.55
	$C_{16}H_{20}N_2$[g]	79.95	80.26	8.39	8.69	11.66	11.76
	$C_{16}H_{20}N_2$	79.95	79.54	8.39	8.41	11.66	11.75
	$C_{16}H_{20}N_2O \cdot 2HCl$[f]	58.36	58.50	6.74	7.04	8.51	8.50
B	$C_{16}H_{21}ClN_2 \cdot HCl$	61.34	61.64	7.08	7.26	8.94	8.84
C	$C_{16}H_{21}ClN_2 \cdot 1.75HCl$[h]	56.42	56.03	6.73	6.74	8.23	8.21
	$C_{16}H_{21}N_3$	75.25	75.19	8.29	8.22	16.46	16.52
	$C_{16}H_{22}N_2$[f]	79.29	79.20	9.15	8.88	11.56	10.80
	$C_{16}H_{22}N_2$	79.29	79.04	9.15	9.44	11.56	11.49
	$C_{16}H_{22}N_2O$	74.37	74.05	8.58	8.46	10.85	11.07
I	$C_{16}H_{22}N_2O$	74.38	74.60	8.58	8.65	10.85	11.05
D	$C_{16}H_{22}N_2O_2 \cdot HCl$	61.82	61.69	7.46	7.40	9.01	9.18
	$C_{17}H_{22}N_2$	80.26	79.99	8.72	8.68	11.02	11.25
	$C_{17}H_{22}N_2$	80.26	80.08	8.72	8.89	11.02	10.88
	$C_{17}H_{22}N_2$	80.26	80.12	8.72	8.83	11.02	11.27
E	$C_{17}H_{22}N_2O$	75.52	75.55	8.20	8.30	10.36	10.52
E	$C_{17}H_{22}N_2O$	75.52	75.64	8.20	8.40	10.36	10.56
	$C_{17}H_{23}N_3$[i]	75.80	75.88	8.61	8.66	15.60	15.81
	$C_{17}H_{24}N_2$[i]	79.64	79.40	9.44	9.49	10.93	11.07
	$C_{17}H_{24}N_2O$	74.96	74.61	8.88	8.89	10.29	10.42
	$C_{17}H_{24}N_2O$	74.96	75.09	8.88	8.62	10.29	10.15
	$C_{17}H_{24}N_2O_2$	70.80	70.47	8.39	8.37	9.72	9.69
	$C_{18}H_{22}N_2$	81.15	81.14	8.33	8.29	10.52	10.68
	$C_{18}H_{24}N_2$	80.55	80.40	9.01	9.07	10.44	10.55
	$C_{18}H_{24}N_2$	80.55	80.48	9.01	9.05	10.44	10.58
	$C_{18}H_{24}N_2$	80.55	80.43	9.01	9.15	10.44	10.45
	$C_{18}H_{24}N_2$	80.55	80.87	9.01	8.96	10.44	10.52
	$C_{18}H_{24}N_2O$	76.02	76.07	8.51	8.55	9.85	9.93
F	$C_{18}H_{25}N_3O \cdot 3HCl$[k]	52.88	52.56	6.90	6.95	10.28	10.34
	$C_{18}H_{26}N_2$	79.95	79.88	9.69	9.93	10.36	10.53
	$C_{18}H_{26}N_2O$[g]	75.48	75.45	9.15	9.07	9.78	9.80
	$C_{18}H_{26}N_2O_2$	71.49	71.54	8.67	8.63	9.27	9.75
	$C_{18}H_{27}N_3$	75.74	75.31	9.54	9.47	14.72	14.80
D	$C_{19}H_{20}N_2 \cdot HCl$	72.94	73.11	6.77	6.68	8.96	8.94
	$C_{19}H_{26}N_2$	80.80	80.61	9.28	9.35	9.92	10.13
	$C_{19}H_{26}N_2$	80.80	81.11	9.28	9.53	9.92	10.10
F	$C_{20}H_{22}N_2 \cdot HCl$[k]	73.49	72.91	7.09	6.95	8.57	8.68
	$C_{20}H_{26}N_2$	81.58	81.31	8.90	8.75	9.52	9.71
G	$C_{20}H_{28}N_2 \cdot HBr$[o]	63.65	63.78	7.75	7.91	7.43	7.82
B	$C_{20}H_{28}N_2 \cdot HCl$[p]	72.15	71.54	8.78	8.79	8.42	8.45
	$C_{20}H_{28}N_2$	81.03	81.11	9.52	9.49	9.45	9.56
	$C_{20}H_{30}N_2$	80.48	80.87	10.13	10.16	9.39	9.36
	$C_{20}H_{30}N_2$	80.48	80.07	10.13	10.35	9.39	9.44
	$C_{20}H_{30}N_2O_2$	72.69	72.45	9.15	9.25	8.48	8.70
	$C_{20}H_{31}N_3$	76.63	76.29	9.97	9.90	13.40	13.55
	$C_{21}H_{22}N_2$	83.40	83.62	7.33	7.48	9.27	9.28

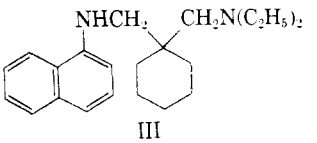
TABLE I (*Continued*)

Compd no.	NR_1R_2	X	B.p., °C. (mm.) or (m.p., °C.)	$n^{25}D$	Yield purified, %	Method
51		H	(252–254)		48	VIII
52	$NCH_2CH{=}CH_2CH(CH_2)_5$	H	180 (0.4)	1.5033	26	VIII
53		H	170 (0.07)	1.5877	13	VIII
54	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_3)_2$	H	205 (0.3)	1.5013	62	VIII
55	$NCH_3(CH_2)_2N[CH(CH_3)_2]_2$	H	151 (0.2)	1.5613	56	VIII
56	$N[CH(CH_2)_4]_2$	H	(180–183)		8	VIII
57	$N(C_2H_5)_2$	7-O$(CH_2)_2N(C_2H_5)_2$	196–198 (0.2)	1.5615	22	II
58	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_2)_4$	H	(258–262)		9	VIII
59	$N[(CH_2)_2]_2CH(CH_2)_2N[(CH_2)_2]_2O$	H	(261–265 dec.)		76	VIII
60	$N[(CH_2)_2]_2CH(CH_2)_2N(CH_2)_5$	H	(221–224)		38	VIII
61		H	(185–188)		5	VIII
62	$N[(CH_2)_2N(C_2H_5)_2]_2$	H	177 (0.1)	1.5563	22	VIII
63	$N[(CH_2)_3N(C_2H_5)_2]_2$	H	207–208 (0.1)	1.5467	49	VIII
64	$NCH_2C_6H_5(CH_2)_2OC_6H_5$	H	(95–97)		10	XII

[a] Where analytical values for salts are given, yields are for materials isolated directly from the reaction mixtures unless indicated otherwise in the footnotes. Liquids are colorless or pale yellow in color and often exhibit a purple fluorescence. Solids are colorless or off-white. [b] A, ethanol–methanol; B, 2-propanol; C, dimethylformamide–ethyl acetate; D, ethanol; E, benzene; F, methanol; G, dimethylformamide; H, methanol–2-propanol; I, ethanol–ether. [c] Base, b.p. 134.5–136° (0.3 mm.). [d] $C_6H_3N_3O_7$ represents picric acid; analyzed as the picrate, yields indicated are for the distilled free bases. [e] Base, b.p. 188–193° (0.3–0.4 mm.); *Anal.* Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.65; H, 7.97; N, 12.09. [f] Reported previously by M. A. Stalmann and A. C. Cope, *J. Am. Chem. Soc.*, 68, 2494 (1946). [g] Picrate from ethanol–methanol, m.p. 158–160°. [h] Cl, Calcd.: 28.63. Found: 28.95. [i] Solidifies, m.p. 58–60°. [j] Monohydrochloride, m.p. 138–140°. [k] Cl, Calcd.: 26.02. Found: 26.41; base b.p. 192° (0.07

3-chloro-N,N,2-trimethylpropylamine.[5] The carbonate procedure in toluene gave only 13% of the desired N,N,2-trimethyl-N'-1-naphthyl-1,3-propanediamine. The substitution of xylene as the solvent raised the yield to 66%, while the use of sodium hydride in xylene increased the yield to 93%. Sodamide in xylene[15,16] gave 75% of the product, although a shorter reflux period was used. Similarly, alkylation of N-methyl-1-naphthylamine with 1-(3-chloropropyl)piperidine using the xylene sodium hydride technique gave the desired alkylated naphthylamine in 42% yield, whereas attempts to alkylate the amine with 2-chlorotriethylamine hydrochloride utilizing the benzene–potassium carbonate method failed. When 2-bromotriethylamine hydrobromide was substituted for 2-chlorotriethylamine in the latter procedure, the desired N,N-diethyl-N'-methyl-N'-1-naphthylethylenediamine was obtained in 46% yield. These results suggest that alkylaminoalkyl bromides could be used to advantage in certain instances where low yields are obtained with the alkylaminoalkyl chloride–sodium hydride method.

The availability of certain amino aldehydes and ketones[17,18] prompted us to investigate their usefulness in the preparation of naphthylalkylenediamines. In 1942, Bergman[19] described the preparation of N^1,N^1-diethyl-N^4-1-naphthyl-1,4-pentanediamine by the reductive alkylation of 1-naphthylamine with 5-diethylamino-2-pentanone utilizing a 5% palladium–barium sulfate catalyst in the presence of diethylaniline hydrochloride. This procedure proved unsatisfactory in our Laboratory. Alternatively, pre-forming the Schiff base by heating 1-naphthylamine and the appropriate amino aldehyde or ketone with a small amount of *p*-toluenesulfonic acid in an aromatic solvent, followed by hydrogenation in methanol over palladium on charcoal (method III, Tables I and II) provided the desired products in satisfactory yields. With 1-diethylamino-



III

methyl-3-cyclohexene-1-carboxaldehyde and 1-naphthylamine, reductive alkylation gave, as expected, N,N-diethyl-N'-1-naphthyl-1,1-cyclohexanebis(methylamine) (III) rather than the cyclohexene derivative. The structure III was assigned on the basis of hydrogen uptake, microanalytical values, and the n.m.r. spectrum (CCl_4, 60 Mc.), which showed no ethylenic proton peak at 4.4 τ. This peak was present in curves of 3-cyclohexene-1-carboxaldehyde and 1-diethylaminomethyl-3-cyclohexene-1-carboxaldehyde.

The ring-substituted 1-naphthylamine precursors used in the foregoing reactions are available com-

(15) N. B. Chapman, J. W. James, and J. F. A. Williams, *J. Chem. Soc.*, 4024 (1952).

(16) G. F. Grail, L. E. Tenenbaum, A. V. Tolstoouhov, C. J. Duca, J. F. Reinhard, F. E. Anderson, and J. V. Scudi, *J. Am. Chem. Soc.*, **74**, 1313 (1952).

(17) 1-Methyl-4-piperidone and 5-diethylamino-2-pentanone were purchased from the Aldrich Chemical Co., Milwaukee, Wis., and 3-diethylamino-2,2-dimethylpropionaldehyde from Distillation Products Industries, Rochester, N. Y.

(18) α,α-Dimethylpyrrolidinopropionaldehyde and α,α-dimethylpiperidinopropionaldehyde were made available through the courtesy of Dr. J. M. Straley, Tennessee Eastman Co., Kingsport, Tenn.

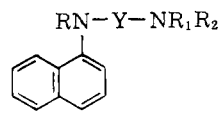
(19) E. Bergman, British Patent 547,301 (August 21, 1942).

Purification solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	$C_{21}H_{28}N_2 \cdot HCl$[q]	73.12	73.20	8.47	8.51	8.12	8.22
	$C_{21}H_{28}N_2$	81.77	82.07	9.15	9.22	9.08	9.17
	$C_{21}H_{31}N_3$	77.49	77.57	9.60	9.80	12.91	13.12
	$C_{21}H_{31}N_3 \cdot 2HCl \cdot 0.33H_2O$[r,s]	62.37	62.14	8.39	8.24	10.39	10.29
	$C_{21}H_{33}N_3$	77.01	76.74	10.16	10.06	12.83	12.92
F	$C_{22}H_{30}N_2 \cdot HCl$[t]	73.61	73.65	8.71	8.42	7.81	7.59
	$C_{22}H_{35}N_3O$	73.90	73.52	9.87	9.72	11.75	11.52
F	$C_{23}H_{33}N_3 \cdot 2HCl$[u]	65.08	64.87	8.31	8.27	9.90	9.74
A	$C_{23}H_{33}N_3O \cdot 2HCl \cdot 0.25H_2O$[v,w]	62.08	62.26	8.04	7.94	9.44	9.09
A	$C_{24}H_{35}N_3 \cdot 2HCl$[x]	65.74	65.96	8.51	8.34	9.58	9.70
F	$C_{24}H_{35}N_3 \cdot 2HCl$[y]	65.74	65.43	8.51	8.64	9.58	9.50
	$C_{24}H_{40}N_4$	74.95	75.18	10.48	10.28	14.57	14.66
	$C_{26}H_{44}N_4$	75.67	75.37	10.75	10.52	13.58	13.75
	$C_{27}H_{28}N_2O$	81.78	81.56	7.12	7.05	7.07	7.19

mm.). [l] Yield expressed as base, b.p. 174-6° (0.3 mm.). [m] From N-1-naphthylethylenediamine. [n] Cl, Calcd.: 10.85. Found: 10.77. [o] Br, Calcd.: 21.18. Found: 21.21. [p] Cl, Calcd.: 10.65. Found: 10.77, from the base, b.p. 187-191° (0.5 mm.). [q] Cl, Calcd.: 10.28. Found: 10.49. [r] Yield expressed as base, analyzed as the hydrochloride; Cl, Calcd.: 17.53. Found: 17.78. [s] Water (Karl Fischer), Calcd.: 1.49. Found: 1.51. [t] Cl, Calcd.: 9.88. Found: 9.53. [u] Cl, Calcd.: 16.71. Found: 16.20. [v] Cl, Calcd.: 15.94. Found: 15.87. [w] Water (Karl Fischer), Calcd.: 1.01. Found: 0.97. [x] Cl, Calcd.: 16.17. Found: 16.02. [y] Cl, Calcd.: 16.17. Found: 15.99. [z] Reported previously by M. Yokoyama, K. Iwata, and S. Toyoshima, *Yakugaku Zasshi*, **78**, 428 (1958); *Chem. Abstr.*, **52**, 14573*d* (1958).

TABLE II

OTHER N-MONO- AND N,N-DIALKYL-N'-1-NAPHTHYLALKYLENEDIAMINES[a]



Compd. no.	R	—Y—NR1R2	B.p., °C. (mm.) or (m.p., °C.)	$n^{25}D$	Yield purified, %	Method	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
65	H	—CH(CH3)CH2N(CH3)2	120(0.2)	1.6050	32	I	$C_{16}H_{20}N_2$	78.90	79.23	8.83	8.87	12.27	12.40
66	H	—(CH2)3N(CH3)2	146–151 (0.8)	1.6040	79	IV	$C_{16}H_{20}N_2$	78.90	78.79	8.83	9.09	12.27	11.93
67	H	—CH[(CH2)2]2NCH3	144–145 (0.2)[b]		66	III	$C_{16}H_{20}N_2$	79.95	79.70	8.39	8.59	11.66	11.72
68	H	—CH2CH(CH3)CH2N(CH3)2	117–118 (0.15)[j]		93	II	$C_{16}H_{22}N_2$	79.29	79.20	9.15	8.98	11.56	11.55
69	H	—(CH2)3NHCH(CH3)2	150–155 (0.25)	1.6130	65	V	$C_{16}H_{22}N_2$	79.29	79.27	9.15	8.99	11.56	11.00
70	H	—(CH2)3N(CH2)4	153–155 (0.1)[c]		71	I	$C_{17}H_{22}N_2$	80.26	80.32	8.72	8.69	11.02	11.32
71	H	—(CH2)3N[(CH2)2]2O	(82–84)		72	V	$C_{17}H_{22}N_2O$	75.52	75.45	8.20	8.29	10.36	10.45
72	CH3	—(CH2)2(C2H5)2	129–132 (0.5)	1.5713	43	I[d]	$C_{17}H_{24}N_2$[e]	79.63	79.69	9.44	9.82	10.93	10.89
73	H	—CH2C(CH3)2CH2N(CH3)2	141–143 (0.75)	1.5850	72	III	$C_{17}H_{24}N_2$	79.63	79.60	9.44	9.41	10.93	11.08
74	H	—(CH2)3N(C2H5)2	150–154 (0.12)	1.5866	71	I	$C_{17}H_{24}N_2$[i]	79.63	79.24	9.44	9.48	10.93	11.15
75	H	—CH2CHOHCH2N(C2H5)2	176 (0.5)		31	V	$C_{17}H_{24}N_2O$[f]	74.96	74.46	8.88	8.47	10.29	10.48
76	H	—CH[CH2N(CH3)2]2	136 (0.3)	1.5836	11	IV	$C_{17}H_{26}N_2$	75.23	75.02	9.29	9.04	15.48	15.67
77	H	—(CH2)3N(CH2)5	165 (0.2)[g]		75	I	$C_{18}H_{24}N_2$	80.55	80.47	9.01	9.11	10.44	10.56
78	H	—(CH2)2S(CH2)2N(C2H5)2	164 (0.1)	1.6015	36	X	$C_{18}H_{26}N_2S$	71.47	71.02	8.67	8.65	9.26	9.22
79	CH3	—(CH2)3N(CH2)5	128 (0.07)	1.5725	42	II	$C_{19}H_{28}N_2$	80.80	81.30	9.28	9.57	9.92	9.68
80	H	—CH2C(CH3)2CH2N(CH2)4	(57–58)		55	III	$C_{19}H_{26}N_2$	80.80	80.93	9.28	9.14	9.92	9.82
81	H	—CH2C(CH3)2CH2N(C2H5)2	158 (0.8)	1.5803	47	III	$C_{19}H_{28}N_2$	80.23	80.55	9.92	9.92	9.85	9.85
82	H	—CHCH3(CH2)3N(C2H5)2	147–151 (0.15)	1.5730	73	III	$C_{19}H_{28}N_2$[h]	80.23	80.20	9.92	9.93	9.85	9.88
83	H	—(CH2)3N(C2H5)2	198–199 (1.7)	1.5740	47	I	$C_{19}H_{28}N_2$	80.23	80.38	9.92	9.90	9.85	9.68
84	H	—CH2C(CH3)2CH2N(CH2)5	(74–76)		85	III	$C_{20}H_{28}N_2$	81.03	80.90	9.52	9.35	9.45	9.22
85	H	—(CH2)3NH(CH2)7CH3	182 (0.2)	1.5630	27	IV	$C_{21}H_{32}N_2$	80.71	80.41	10.32	9.91	8.97	9.12
86	H	—CH2C(CH2)5CH2N(C2H5)2	161 (0.07)		26	III	$C_{22}H_{32}N_2$	81.43	81.46	9.94	9.48	8.63	8.71

[a] Liquids are colorless or pale yellow in color and often exhibit a purple fluorescence. Solids are colorless or off-white in color. [b] Solidifies on standing, m.p. 81–83°. [c] Solidifies on standing, m.p. 62-63°. [d] 2-Diethylaminoethyl bromide used. [e] Dihydrochloride from 2-propanol, m.p. 168° dec. *Anal.* Calcd. for $C_{17}H_{24}N_2 \cdot 2HCl$: Cl, 21.53; N, 8.51. Found: Cl, 21.64; N, 8.82. [f] Picrate, orange crystals from ethanol-petroleum ether, m.p. 155-156°. *Anal.* Calcd. for $C_{17}H_{24}N_2O \cdot C_6H_3N_3O_7$: C, 55.08; H, 5.43; N, 13.97. Found: C, 54.99; H, 5.34; N, 14.10. [g] Solidifies on standing, m.p. 71-73°. [h] Previously reported by E. Bergman, British Patent 547,301 (August 21, 1942). [i] Previously reported by A. M. Simonov, *Zh. Obshch. Khim.*, **16**, 621 (1946); *Chem. Abstr.*, **41**, 1220*b* (1947). [j] Solidifies on standing, m.p. 51–53°.

TABLE III

N,N-DIMETHYL-N'-1-NAPHTHYL-1,3-PROPANEDIAMINE *VIA* THE BUCHERER REACTION

Experiment	Reactants (moles) 1-Naphthol	N,N-Dimethyl-1,3-propanediamine	Sulfur reagent	Conditions[a] temp. °C., time (hr.)	Yield[b] purified, %	Recovered 1-naphthol, %
1	0.60	0.60	None	200/16[d]	8	70
2	.10	.25	SO_2 (0.25)	100/18	32	19
3	.20	.20	SO_2 (0.63)	150/8	0	56
4	.25	.50	$NaHSO_3$ (0.50)	Reflux/21	0	53
5	.60	.66	$NaHSO_3$ (0.90)	150/8	44	
6	.60	.60	$NaHSO_3$ (1.8)	150/8	17	[c]
7	.20	.40	$NaHSO_3$ (0.30)	150/8	68	10
8	.60	1.2	$NaHSO_3$ (0.90)	150/8[e]	28	[c]
9	.60	0.64	$NaHSO_3$ (0.90)	200/8	[g]	[c]
10	.60	.64	$Na_2S_2O_5$ (0.60)	150/8	61	20
11	.61	.64	$Na_2S_2O_4$ (0.60)	150/12	63	20
12	.60	.64	$Na_2S_2O_4$ (0.60)	200/8	[g]	[c]
13	.60	.99	$Na_2S_2O_4$ (0.60)	150/8	11	[c]
14	.60	.64	$Na_2S_2O_4$ (0.60) + NaOH (0.63)	150/8	16	10
15	.60	.64	$Na_2S_2O_4$ (0.60) + SO_2 (1.3)	150/8	[g]	[c]

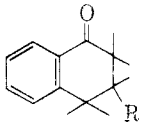
[a] Except when indicated in footnotes, reactions were run in an aqueous mixture in a bomb. [b] Yield not adjusted for recovered 1-naphthol. [c] No attempt made to recover 1-naphthol. [d] Solvent, benzene. [e] Bomb not used. [f] Solvent, 50% methanol–50% water. [g] Extensive decomposition occurred and no product could be isolated.

mercially or were prepared by known methods.[20-25] 6-(2-Diethylaminoethoxy)-1-naphthylamine was obtained by alkylation of the sodium salt of N-(6-hydroxy-1-naphthyl)acetamide with 2-chlorotriethylamine followed by acid hydrolysis of the intermediate N-[6-(2-diethylaminoethoxy)-1-naphthyl]acetamide.

A third scheme used for the preparation of the naphthylalkylenediamines involved the Bucherer reaction with 1-naphthol and aliphatic diamines. Once again, the ready availability of a variety of starting materials made this synthetic route particularly attractive. The reaction between 1-naphthol and N,N-dimethyl-1,3-propanediamine was selected as a prototype for determining optimum experimental conditions (Table III). Unexpectedly, some of the desired N,N-dimethyl-N'-1-naphthyl-1,3-propanediamine was isolated (8%) when equimolar quantities of 1-naphthol and the amine in benzene were heated in a bomb for 16 hr. at 200° in the absence of any sulfur reagent. When 1-naphthol, excess amine, and aqueous sulfur dioxide[26] were heated in a bomb at 100° for 18 hr., the yield was increased to 32% (method VI). With sodium bisulfite (method V), optimum yields (68%) were obtained when 1-naphthol was allowed to react for 8 hr. with excess diamine and bisulfite in water at 150° in a sealed vessel. Surprisingly, it was found that sodium hydrosulfite ($Na_2S_2O_4$) (method IV) could be substituted effectively for sodium bisulfite in the Bucherer reaction. The former reagent was particularly advantageous because the use of excess diamine could be avoided.

The Bucherer reaction with 1-naphthol and alkylenediamines proved to be a versatile method and was used successfully for the preparation of a variety of naphthylalkylenediamines (Tables I and II). In general, the yields obtained with sodium bisulfite or hydrosulfite under optimum conditions are comparable to yields obtained by other methods. In the case of N,N-dimethyl- and N-isopropyl-N'-1-naphthyl-1,3-propanediamine and 2-[2-(1-naphthylamino)ethylamino]ethanol, the Bucherer reaction afforded significantly higher yields than the alkylation procedures. Results of the present study, together with results of unpublished work with analogous systems, suggest that the sodium hydrosulfite procedure often gives higher yields than the sodium bisulfite procedure. In several instances, the structures of the products of the Bucherer reaction were verified by comparison with authentic samples of naphthylalkylenediamines synthesized by the other methods described herein.

Although no attempt was made in the present study to elucidate the mechanism of the Bucherer reaction with 1-naphthol and sodium hydrosulfite, certain observations are pertinent. The key intermediate postulated recently for the Bucherer reaction with 1-naphthol and sodium bisulfite is shown in formula IVa.[27,28] It is possible that IVa may also be present



a, R = SO_3Na
b, R = SO_2Na

IV

when hydrosulfite is used, since the dithionite anion $S_2O_4^{-2}$ is known to decompose in aqueous solution to bisulfite (HSO_3^-) and thiosulfate ($S_2O_3^{-2}$). Alternatively, an intermediate of structure IVb would not be unreasonable. In a similar reaction, the product from sodium hydrosulfite and formaldehyde has been formulated as an equimolar mixture of sodium hydroxymethylsulfite and sodium hydroxymethylsulfoxylate.[29]

Results from several experiments (Table III) are suggestive of a ketonic intermediate for the reaction of 1-naphthol with an aliphatic diamine. In experiment

(20) H. E. Fierz-David, L. Blangey, and W. von Kraunichfeldt, *Helv. Chim. Acta*, **30**, 831 (1947).

(21) A. Buttenandt and G. Schramm, *Ber.*, **68**, 2087 (1935).

(22) C. C. Steele and R. Adams, *J. Am. Chem. Soc.*, **52**, 4528 (1930).

(23) H. E. Armstrong and W. P. Wynne, *Proc. Chem. Soc.*, **5**, 71 (1889).

(24) W. F. Bruce and N. Legg, *J. Chem. Soc.*, 1889 (1949).

(25) 2-Ethoxy-1-naphthylamine was obtained through the courtesy of Dr. W. A. Fisher, National Aniline Division, Allied Chemical Corp., Buffalo, N. Y.

(26) E. B. Hartshorn and S. L. Baird, Jr., *J. Am. Chem. Soc.*, **68**, 1562 (1946).

(27) S. V. Bogdanov and N. N. Karandasheva, *Zh. Obshch. Khim.*, **26**, 3365 (1956).

(28) A. Rieche and H. Seeboth, *Ann. Chem.*, **638**, 66 (1960).

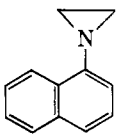
(29) R. Scholder and G. Denk, *Z. anorg. allgem. Chem.*, **222**, 17 (1935).

14, the yield of N,N-dimethyl-N′-1-naphthyl-1,3-propanediamine was drastically reduced by the addition of 1 equivalent of sodium hydroxide to the hydrosulfite mixture. Such conditions would be expected to suppress ketone formation. In experiment 1, a low yield of product was obtained when equivalent amounts of 1-naphthol and the diamine were allowed to react in benzene in the absence of any sulfur reagent. Since this may have involved a simple displacement reaction, the experiment was repeated with the tosylate of 1-naphthol which would be expected to undergo a more facile replacement by amine. No reaction occurred, although admittedly the use of a polar solvent would have afforded more rigorous evidence. Further, no product was obtained when 1-naphthol was treated with equivalent amounts of N,N-diethylethylenediamine and sodium carbonate under similar conditions.

The preparative methods described afforded naphthylalkylenediamines of diverse structure. However, when variations of the terminal amine were the primary objective, the most convenient method involved the condensation of a N-(ω-haloalkyl)-1-naphthylamine with an amine. The reactions of N-(2-bromoethyl)-1-naphthylamine with amines were studied most extensively. The preferred procedure involved 1 equivalent of N-(2-bromoethyl)-1-naphthylamine, 2 equivalents of the amine, and a high boiling hydrocarbon solvent such as xylene (methods VIIIA–C). Alkylation, using a suspension of N-(2-bromoethyl)-1-naphthylamine hydrobromide either in dimethylformamide or xylene with potassium carbonate (method VII), or in xylene in the presence of excess amine, was less satisfactory. As anticipated, primary aliphatic amines and secondary saturated heterocyclic amines lacking bulky substituents adjacent to the amine function afforded optimum yields. Yields were poor with amines such as N,N-dicyclopentylamine, 2,6-dimethylpiperidine, 2,4,6-trimethylpiperidine, and 2-(2-dimethylaminoethyl)piperidine, where molecular models clearly reveal the existence of a bulk factor which might inhibit formation of the Sn2 transition state. Respective yields of 5% and 71% with 2,4,6-trimethylpiperidine and 4-pipecoline, though extreme, are illustrative. In other cases, poor yields undoubtedly resulted from isolation inefficiencies. The reaction was also extended to the preparation of N-(3-piperidinopropyl)-1-naphthylamine from N-(3-bromopropyl)-1-naphthylamine and piperidine. The yield was comparable to that obtained by alkylation of 1-naphthylamine with 1-(3-chloropropyl)piperidine.

N-(2-Bromoethyl)- and N-(3-bromopropyl)-1-naphthylamine were obtained by the action of hydrobromic acid on 2-(N-1-naphthylamino)ethanol[30] and 3-(N-1-naphthylamino)-1-propanol,[31] respectively. The aliphatic amines are commercially available[32] or were prepared by methods described previously.[33,34]

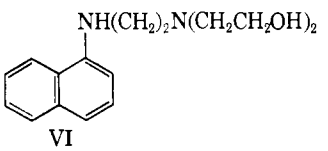
N-[2-(2-Diethylaminoethylthio)ethyl]-1-naphthylamine was prepared by the condensation of N-(2-bromoethyl)-1-naphthylamine with the sodium salt of 2-



V

diethylaminoethanethiol. However, attempts to prepare the corresponding oxygen analog utilizing the sodium salt of N,N-diethylaminoethanol (sodium hydride in toluene) resulted in the isolation of a low boiling liquid which on the basis of microanalyses and the lack of absorption in the NH region of its infrared spectrum was presumed to be 1-(1-naphthyl)aziridine (V). The formation of the aziridine may be explained by the greater base strength of alkoxide *vs.* thiolate anion, which facilitates removal of the proton on the aromatic amine, followed immediately by displacement of bromide. Subsequent work demonstrated that the amino alcohol did not represent a special case. Indeed, as might be expected from a consideration of the relative ionic base strengths, $R_2N^- > RO^- > RS^-$, the aziridine was formed readily by the action of sodium methoxide, sodium hydroxide, sodium hydride, or the sodium salt of N-ethylacetamide on N-(2-bromoethyl)-1-naphthylamine.

When equimolar quantities of N-1-naphthylethylenediamine and ethylene oxide were allowed to react, a mixture of mono- and bis-(hydroxyethyl) derivatives was obtained. The mixture was easily separable by vacuum distillation. A comparison of the picrate salts of the mono-(hydroxyethyl) derivative and a sample of 2-[(1-naphthylamino)ethylamino]ethanol prepared from 1-naphthol and N-2-aminoethylaminoethanol *via* the Bucherer reaction showed them to be identical. Although the structure of the bis-(hydroxyethyl) derivative was not confirmed by synthesis, a comparison of the ultraviolet spectrum of this material[35] (λ



VI

330, ε 6900; λ 247, ε 17,300) with those of N,N-diethyl-N′-1-naphthylethylenediamine (λ 330, ε 7100; λ 247,

(30) Yu. K. Yurev, K. Yu. Novitskii, and L. G. Liberov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 317 (1951); *Chem. Abstr.*, **46**, 932c (1952).

(31) Purchased from Kaplop Laboratories, Detroit, Michigan.

(32) N-Ethylethylenediamine, N-ethylallylamine, N,N-diethylethylenediamine, 2-(2-dimethylaminoethyl)piperidine, 4-(2-dimethylaminoethyl)-piperidine, 4-[2-(1-pyrrolidinyl)ethyl]piperidine, 4-[2-(4-piperidyl)ethyl]-morpholine, 4-(2-piperidinoethyl)piperidine, 2-(2-piperidinoethyl)piperidine, and N-isopropyl-1,3-propanediamine were purchased from the Sapon Laboratories, Valley Stream, N. Y.; 2-[(2-aminoethyl)amino]ethanol, 2-methylaminoethanol, 1-(2-aminoethyl)piperazine, 2-ethylaminoethanol, 1-methylpiperazine, 3,5-dimethylmorpholine, 1-piperazinoethanol, 5-ethyl-2-pipecoline, N,N-dimethyl-1,3-propanediamine, 4-(3-aminopropyl)morpholine, and 2-(3-aminopropoxy)ethanol from Union Carbide Chemical Co., South Charleston 3, W. Va.; 2-methylallylamine and 4-pipecoline from Chemical Research and Intermediates Corp., Cuyahoga Falls, Ohio; 2-ethoxyethylamine from Wyandotte Chemicals Corp., Wyandotte, Mich.; 3-pipecoline from K and K Laboratories, Jamaica, N. Y.; 2,6-dimethylpiperidine from Reilly Tar and Chemical Corp., Indianapolis, Ind.; N-methylcyclohexylamine from E. I. du Pont de Nemours and Co., Wilmington, Del.; 2,2′-dimethyldiallylamine from Shell Chemical Corp., Emeryville, Calif.; N,N,N′-triethylethylenedianine from Ames Laboratories, So. Norwalk, Conn., N^1,N^1,N^3,N^3-tetramethyl-1,2,3-propanetriamine from Commercial Solvents Corp., New York, N. Y.; 3-piperidinol, 4-piperidinol, cyclopentylamine, cyclooctylamine, 2,4,6-trimethylpiperidine, decahydroquinoline, N-allylcyclohexylamine, dicyclopentylamine, and N,N-diethyl-1,3-diamino-2-propanol from Aldrich Chemical Co., Milwaukee, Wis.

(33) E. F. Elslager, J. F. Cavalla, W. D. Closson, and D. F. Worth, *J. Org. Chem.*, **26**, 2837 (1961).

(34) E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, **5**, 646 (1962).

(35) Spectra were taken with a Cary Model 11 spectrophotometer. Bases were run in methanol; hydrochlorides were run in methanolic sodium hydroxide.

ϵ 17,900), *N*,*N*-diethyl-*N*′-methyl-*N*′-1-naphthylethylenediamine (λ 302, ϵ 4800; λ 238, ϵ 11,600), and 1-[3-(methyl-1-naphthylamino)propyl]piperidine (λ 303, ϵ 4500; λ 237, ϵ 10,800) clearly indicated that structure VI was correct. The higher wave length absorption and higher ϵ values of the secondary aromatic amines were consistent within the entire series examined and provided a useful tool for the structure elucidation of several of the compounds. The ultraviolet spectra also revealed a striking difference in basicity between the secondary and tertiary aromatic amines. In 0.1 *N* hydrochloric acid the secondary amines exhibited a band at about 320 mμ, while the tertiary amines absorbed at 280 mμ. The use of stronger acid shifted the peak of the secondary amine to 280 mμ, indicating that the aromatic nitrogen was now protonated.

N-Benzyl-*N*-methyl-*N*′-1-naphthylethylenediamine was prepared by reductive methylation of *N*-benzyl-*N*′-1-naphthylethylenediamine with formalin in the presence of platinum oxide. The assignment of structure was based on the ultraviolet spectrum[35] (λ 332, ϵ 6900; λ 248, ϵ 17,300) which indicated the presence of a secondary naphthylamine. Similarly, alkylation of *N*-benzyl-*N*′-1-naphthylethylenediamine with β-bromophenetole gave *N*-benzyl-*N*-(2-phenoxyethyl)-*N*′-1-naphthylethylenediamine (λ 330, ϵ 6900; λ 248, ϵ 17,600).

Although the *N*-mono- and *N*,*N*-dialkyl-*N*′-1-naphthylalkylenediamines (II) were synthesized primarily for use as intermediates, many of them were tested against a variety of parasites, bacteria, and fungi. Compounds 9, 18, 40, 44, 45, 50, 51, and 56 were amebicidal *in vitro* when incubated for 48 hr. with the UC or 200 F strain of *Entamoeba histolytica* at drug concentrations ranging from 40 to 80 μg./ml.[36,37] By comparison, paromomycin is active in the range of 2 to 10 μg./ml.[36] Against *Trichomonas vaginalis in vitro*,[36] compounds 5, 21, 28, 29, 30, 32, 37, 40, 43, and 55 killed more than 90% of the parasites at drug concentrations of 6.25–25 μg./ml.[37] Eleven compounds (no. 17, 23, 24, 28, 29, 41, 43, 44, 45, 51, and 82) were lethal to *Mycobacterium tuberculosis* (H37Rv) *in vitro* at concentrations of 0.31 to 20 μg./ml.,[38] while five (no. 38, 54, 59, 60, and 84) exhibited activity against *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Nocardia asteroides*, *Trichophyton interdigitale*, and *Blastomyces dermatitidis in vitro* at concentrations varying from 6.25 to 200 μg./ml.[39] None of the compounds exhibited promising activity in experimental animals.

Experimental[40]

Preparation of N-Mono- and N,N-Dialkyl-N¹-1-naphthylalkylenediamines (II) (Tables I and II). Method I.—A suspension of 196 g. (1.0 mole) of 1-(3-chloropropyl)piperidine hydrochloride,[11] 143 g. (1.0 mole) of 1-naphthylamine, and 276 g. (2.0 mole) of anhydrous potassium carbonate in 1 l. of toluene was stirred and heated under reflux for 17 hr. A solution of 50 g. of sodium hydroxide in 1 l. of water was added to the cooled mixture. After stirring for 2 hr., the toluene layer was separated and washed with water. The solid which formed was collected, dissolved in chloroform, and the chloroform solution dried over anhydrous sodium sulfate. The chloroform was removed *in vacuo* and the residue distilled through a 25-cm. Vigreux column. After recovery of 25 g. of 1-naphthylamine [b.p. 103–108° (0.4 mm.)], 164 g. of 1-[3-(1-naphthylamino)propyl]piperidine was obtained, b.p. 165° (0.2 mm.). The yield was 75%, based on recovered 1-naphthylamine.

In most cases no solid formed and the toluene layer was separated, dried, and distilled to give the product.

Method II.—To a suspension of 36 g. of 50% sodium hydride dispersion in oil (0.75 mole)[41] in 200 ml. of xylene was added a solution of 72 g. (0.50 mole) of 1-naphthylamine in 300 ml. of xylene and the mixture was heated under reflux for 1.5 hr. Stirring became difficult at this point because of the separation of the sodium salt as a thick green mass. 3-Chloro-*N*,*N*,2-trimethylpropylamine hydrochloride[5] (100 g., 0.58 mole) was suspended in 200 ml. of concentrated ammonium hydroxide. The resultant oil was extracted with three 100-ml. portions of xylene and the combined extracts were dried over anhydrous sodium sulfate. The xylene solution was then added dropwise to the sodium salt of 1-naphthylamine and the mixture was heated under reflux for 20 hr. To the cooled reaction mixture was added dropwise 200 ml. of water. The organic layer was separated, washed with two 200-ml. portions of water, and dried over anhydrous potassium carbonate. After removal of the solvent, the residue was distilled through a 25-cm. Vigreux column to give 112 g. (36%) of *N*,*N*,2-trimethyl-*N*′-1-naphthyl-1,3-propanediamine, b.p. 117–118° (0.15 mm.).

Method III. A solution of 143 g. (1.0 mole) of 1-naphthylamine, 140 g. (1.08 moles) of 3-dimethylamino-2,2-dimethylpropionaldehyde,[7] and 1 g. of *p*-toluenesulfonic acid in 500 ml. benzene was heated under reflux for 4 hr. while the theoretical amount of water was collected in a trap. The benzene was removed *in vacuo* and the residue was taken up in 300 ml. of methanol and hydrogenated over 5 g. of 20% Pd/C under an initial hydrogen pressure of 3.78 kg./cm.² After the theoretical quantity of hydrogen had been absorbed, the mixture was filtered and the solvent removed *in vacuo*. The residue was treated with 250 ml. of 10% sodium hydroxide and the mixture was extracted with ether. The ether extracts were dried over anhydrous potassium carbonate; the ether was removed and the residue distilled through a 30-cm. Vigreux column to give 185 g. (72%) of *N*,*N*,2,2-tetramethyl-*N*′-1-naphthyl-1,3-propanediamine, b.p. 141–143° (0.75 mm.).

In several instances the product solidified and was isolated directly from the reaction mixture. Thus with 2,6-dimethylpiperidinopropionaldehyde a solid precipitated in the hydrogenation bottle. The mass was dissolved in 90 ml. of concentrated hydrochloric acid and filtered to remove the catalyst. The solvent was removed *in vacuo* and the residue cooled and made basic with aqueous sodium hydroxide. The resultant oil solidified on short standing and was crystallized from aqueous ethanol to give 1-[2,2-dimethyl-3-(1-naphthylamino)propyl]piperidine, m.p. 71–76°, in 85% yield.

Method IV.—A mixture of 86 g. (0.60 mole) of 1-naphthol, 65 g. (0.64 mole) of *N*,*N*-dimethyl-1,3-propanediamine,[32] and 104 g. (0.60 mole) of sodium hydrosulfite ($Na_2S_2O_4$) in 600 ml. of water was heated in a bomb for 12 hr. at 150°. The cooled mixture was removed from the bomb with chloroform and the solvent was distilled *in vacuo*. The residue was made strongly basic with aqueous sodium hydroxide and extracted with ether. The extracts were dried over anhydrous sodium sulfate and distilled through a 25-cm. Vigreux column to give 86 g. of *N*,*N*-dimethyl-*N*′-1-naphthyl-1,3-propanediamine, b.p. 146–151° (0.8 mm.). The aqueous layer yielded 17 g. of 1-naphthol upon acidification. The yield was 79% based on recovered 1-naphthol.

Method V.—A mixture of 28.2 g. (0.2 mole) of 1-naphthol, 46.4 g. (0.4 mole) of *N*-isopropyl-1,3-propanediamine,[32] and 31.2 g. (0.3 mole) of sodium bisulfite in 250 ml. of water was heated in a bomb at 150° for 8 hr. The mixture was made strongly basic with aqueous potassium hydroxide and extracted with ether. The ether solution was processed according to method IV above to give 31 g. (65%) of *N*-isopropyl-*N*′-1-naphthyl-1,3-propanediamine, b.p. 150–155° (0.25 mm.).

(36) For a description of test methods, see P. E. Thompson, A. Bayles, S. F. Herbst, B. Olszewski, and J. E. Meisenhelder, *Antibiot. Chemotherapy*, **9**, 618 (1959).

(37) P. E. Thompson, A. Bayles, and P. McClay, unpublished results, Parke, Davis and Co.

(38) M. W. Fisher and A. L. Erlandson, unpublished results, Parke, Davis and Co.

(39) A. B. Billegas, unpublished results, Parke, Davis and Co.

(40) Melting points and boiling points are uncorrected. U. S. Bureau of Standards thermometers were used. Melting points were taken on a Thomas Hoover capillary melting point apparatus.

(41) Purchased from Metal Hydrides Inc., Beverly, Mass.

Method VI.—To a solution of 16 g. (0.25 mole) of sulfur dioxide in 200 ml. of water was added 14.4 g. (0.10 mole) of 1-naphthol and 25.5 g. (0.25 mole) of N,N-dimethyl-1,3-propanediamine.[32] The mixture was heated and shaken in a bomb at 100° for 18 hr. The contents of the bomb were made strongly basic with sodium hydroxide and extracted with ether. The extracts were dried over anhydrous sodium sulfate and distilled to give 32% of N,N-dimethyl-N′-1-naphthyl-1,3-propanediamine, identical with the material described under method IV above.

Method VII.—A suspension of 166 g. (0.5 mole) of N-(2-bromoethyl)-1-naphthylamine hydrobromide, 138 g. (0.5 mole) of potassium carbonate, and 232 g. (2.0 mole) of N,N-diethylethylenediamine was heated under reflux for 30 hr. The cooled mixture was treated with 1 l. of 10% aqueous sodium hydroxide and stirred for 2 hr. The aqueous layer was extracted with 200 ml. of benzene and the extract was combined with the original organic phase, dried over anhydrous potassium carbonate, and concentrated *in vacuo*. Upon standing, a water-soluble solid precipitated. The entire residue was taken up in 500 ml. of ether, the solid was collected and discarded, and the filtrate was concentrated on a steam bath. Distillation of the residue through a 25-cm. Vigreux column gave 64 g. (33%) of 1,1-diethyl-7-(1-naphthyl)diethylenetriamine, b.p. 155–156° (0.2 mm.).

Method VIIIA.—N-(2-Bromoethyl)-1-naphthylamine hydrobromide (166 g., 0.5 mole) was suspended in aqueous ammonium hydroxide and extracted with several portions of xylene (total volume 1.5 l.). The xylene was dried over anhydrous magnesium sulfate, 127 g. (1.0 mole) of 5-ethyl-2-pipecoline was added, and the mixture was heated under reflux with stirring for 24 hr. The cooled mixture was treated with 500 ml. of 10% aqueous sodium hydroxide and stirred for about 1 hr. or until two clear layers had formed. The organic layer was separated, washed with two 100-ml. portions of 10% sodium hydroxide, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, the solvent removed *in vacuo*, and the residue distilled through a 15-cm. Vigreux column to give 104 g. (70%) of 5-ethyl-1-[2-(1-naphthylamino)ethyl]-2-pipecoline, b.p. 158–159° (0.05 mm.).

VIIIB.—Xylene solutions of 200 g. (1.1 moles) of 4-[2-(1-pyrrolidinyl)ethyl]piperidine and N-(2-bromoethyl)-1-naphthylamine, prepared from 200 g. (0.6 mole) of the hydrobromide salt as described above, were combined and heated under reflux for 20 hr. The reaction mixture was cooled, 1 l. of 10% sodium hydroxide was added, and the mixture was stirred for 1 hr. The organic layer was separated, washed with aqueous sodium hydroxide, and dried over anhydrous sodium sulfate. Volatile materials were removed *in vacuo* on a steam bath and the residue was distilled. At head temperatures exceeding 90° and a pressure of 0.1 mm., extensive gassing occurred and the distillation was discontinued. The residue was dissolved in 3 l. of boiling heptane and the solution was treated with decolorizing charcoal and filtered. Upon cooling, a small amount of solid separated which was collected and discarded. The heptane was removed *in vacuo* and the residue was treated with an excess of 2-propanol saturated with hydrogen chloride. The resulting solution was poured into anhydrous ether and the beige solid was collected and crystallized from ethanol. The 1-[2-(1-naphthylamino)-ethyl]-4-[2-(1-pyrrolidinyl)ethyl]piperidine dihydrochloride thus obtained weighed 22.9 g., m.p. 258–262°.

VIIIC.—A solution of 254 g. (2.0 moles) of cyclooctylamine and 1.0 mole of N-(2-bromoethyl)-1-naphthylamine base in 1.5 l. of xylene was heated under reflux for 20 hr. The solid which separated upon cooling was collected and suspended in 500 ml. of 30% aqueous sodium hydroxide. The solid was collected, crystallized from dimethylformamide, washed with acetone, and dried *in vacuo*. The N-cyclooctyl-N′-1-naphthylethylenediamine hydrobromide thus obtained weighed 76.2 g., m.p. 250–252°.

Method IX.—N-1-Naphthylethylenediamine dihydrochloride (575 g., 2.22 moles) was dissolved in 1 l. of hot water. The solution was treated with decolorizing charcoal, filtered, made strongly alkaline with aqueous sodium hydroxide, and the oily base was extracted with ether. The ether extracts were dried over anhydrous potassium carbonate, and the ether was removed on the steam bath to give 378 g. (2.03 moles) of base. To a solution of the diamine in 250 ml. of 95% ethanol was added a cold solution of 90 g. (2.03 moles) of ethylene oxide in 200 ml. of 95% ethanol at an initial temperature of 20°. The temperature was maintained below 50° until the reaction was no longer exothermic. After standing at room temperature overnight, the mixture was heated on the steam bath for 2.5 hr. The alcohol was removed and the residue distilled *in vacuo* through a 20-cm. Vigreux column. Several low-boiling fractions were obtained and discarded. The fractions boiling at 193–210° (0.15 mm.) were combined (151 g., 32%) and induced to solidify by trituration with anhydrous ether. Microanalyses and ultraviolet absorption data indicated that the compound was 2-[(1-naphthylamino)-ethylamino]ethanol. Its picrate salt was identical with the picrate of an authentic sample prepared from 1-naphthol and N-2-aminoethylaminoethanol *via* the Bucherer reaction. The distillation residue was dissolved in 500 ml. of hot ethanol. The solution was treated with decolorizing charcoal, filtered, and diluted to about 4 l. with ether. Treatment with anhydrous hydrogen chloride gave 143 g. of solid, m.p. ≅ 145°. Two recrystallizations from 95% ethanol gave 96 g. (45%) of 2,2′-{[2-(1-naphthylamino)ethyl]imino}diethanol monohydrochloride, m.p. 155–157°.

Method X.—A suspension of 33.9 g. (0.20 mole) of 2-diethylaminoethanethiol hydrochloride[42] in aqueous ammonia was extracted with toluene. The solution of the base was dried over anhydrous magnesium sulfate, and to it was added a solution of 12 g. (0.22 mole) of sodium methoxide in 40 ml. of methanol. After stirring for 2 hr., a toluene solution of N-(2-bromoethyl)-1-naphthylamine, prepared from 66.2 g. (0.20 mole) of the hydrobromide salt as in method VIII, was added. The mixture was heated under reflux for 18 hr., cooled, and filtered. The filtrate was washed twice with water, dried over anhydrous sodium sulfate, and distilled to give 21.5 g. of N-[2-(2-diethylaminoethylthio)ethyl]-1-naphthylamine, b.p. 164° (0.1 mm.).

Method XI.—N-Benzyl-N′-1-naphthylethylenediamine hydrochloride (38) (11.0 g., 0.035 mole) was suspended in 150 ml. of water and 10 ml. of 6 *N* sodium hydroxide and 200 ml. of benzene were added. The mixture was stirred until the solid had dissolved and the benzene layer was separated, washed with water, and dried. The solvent was removed *in vacuo* and the residue subjected to reductive methylation in 100 ml. of ethanol using 2.9 g. of 36% formalin, 0.5 g. of platinum oxide catalyst, and an initial hydrogen pressure of 3.5 kg./cm.^{2}. The product was dissolved in ether and the ether solution was washed successively with water, dilute aqueous sodium bicarbonate, and water and dried over anhydrous magnesium sulfate. The ether was removed and the residual oil suspended in petroleum ether (b.p. 30–60°) was treated with 25 ml. of 4 *N* ethanolic hydrogen chloride. The solvents were decanted from the sticky solid that resulted and the residue was crystallized from 200 ml. of methanol. The desired N-benzyl-N-methyl-N′-1-naphthylethylenediamine hydrochloride weighed 2.0 g. (18%), m.p. 200–202°. The melting point of a mixture of the starting material and product was depressed to 178–186°.

Method XII.—A mixture of 62.4 g. (0.2 mole) of N-benzyl-N′-1-naphthylethylenediamine hydrochloride (38), 40.2 g. (0.2 mole) of β-bromophenetole, and 138 g. (1.0 mole) of potassium carbonate in 500 ml. of benzene was heated under reflux for 48 hr. To the cooled mixture was added 300 ml. of water and stirring was continued until all the solid had dissolved. The benzene layer was separated, the solvent removed *in vacuo*, and the residue treated with aqueous sodium hydroxide. The oil was extracted with ether, dried over anhydrous magnesium sulfate, and evaporated to dryness to give 8 g. of N-benzyl-N-2-phenoxyethyl-N′-1-naphthylethylenediamine, m.p. 95–97°.

2-(1-Naphthylamino)ethanol.—A solution of 1.1 kg. (25 moles) of ethylene oxide in 10 l. of 95% ethanol maintained at 0° was added in a slow stream over 3 hr. to a stirred solution of 3.25 kg. (22.7 moles) of 1-naphthylamine in 15 l. of 95% ethanol at 40°. The reaction was not exothermic. After the addition was complete, the reaction mixture was allowed to stand overnight at room temperature and was then heated under reflux for 3 hr. Volatile materials were removed *in vacuo*, and the residue was distilled through a 25-cm. Vigreux column to give 3.14 kg. (73%) of 2-(1-naphthylamino)ethanol as a colorless, sirupy liquid, b.p. 157–161° (0.25 mm.), which solidified in the receiver. The hydrochloride salt, prepared by adding an excess of a 2-propanol-hydrogen chloride mixture to a solution of the base in ether, melted at 192–195°.

Anal. Calcd. for $C_{12}H_{13}NO\cdot HCl$: C, 64.42; H, 6.31; N, 6.26. Found: C, 64.59; H, 6.49; N, 6.35.

N-(2-Bromoethyl)-1-naphthylamine Hydrobromide.—A mixture of 1 kg. (5.35 moles) of 2-(1-naphthylamino)ethanol and 9

(42) Purchased from Evans Chemetics, Waterloo, N. Y.

l. of reagent hydrobromic acid (48%) was boiled with stirring for 24 hr. in a flask equipped with a condenser fitted for distillation. The temperature was adjusted so that approximately 500 ml. of the hydrobromic acid–water distillate was collected during this period. Upon cooling, the hydrobromide salt precipitated and was collected and stirred with 3 l. of boiling 2-propanol. The off-white crystals were collected by filtration, washed with fresh 2-propanol, and dried *in vacuo* at 50° for 48 hr. The desired N-(2-bromoethyl)-1-naphthylamine hydrobromide weighed 1.58 kg. (89%), m.p. 208–211° with prior softening at 200°.

Anal. Calcd. for $C_{12}H_{12}BrN \cdot HBr$: C, 43.53; H, 3.96; N, 4.23; Br, 48.28. Found: C, 43.73; H, 4.22; N, 4.42; Br, 48.69.

N-(3-Bromopropyl)-1-naphthylamine Hydrobromide.—A solution of 201 g. (1.0 mole) of 3-(1-naphthylamino)-1-propanol[3] in 1.5 kg. of 48% reagent hydrobromic acid was heated under reflux for 22 hr. A greenish brown oil separated. The mixture was cooled in ice and the supernatant liquid decanted. The residue was taken up in 500 ml. of warm methanol and cooled to give 189 g. of the hydrobromide salt, m.p. 149–151°. A second crop weighing 55 g., m.p. 142–146°, was obtained by concentration of the filtrate. The total crude yield was 71%. For analysis, a sample was recrystallized twice from methanol giving off-white crystals, m.p. 152–154°.

Anal. Calcd. for $C_{13}H_{14}BrN \cdot HBr$: C, 45.24; H, 4.38; Br, 46.32. Found: C, 45.09; H, 4.64; Br, 45.30.

6-(2-Diethylaminoethoxy)-1-naphthylamine.—A mixture of 100 g. (0.5 mole) of N-(6-hydroxy-1-naphthyl)acetamide, 54 g. (1.0 mole) of sodium methoxide, and 86 g. (0.5 mole) of 2-chlorotriethylamine hydrochloride in 300 ml. of ethanol was heated under reflux for 22 hr. The mixture was cooled, 130 ml. of concentrated hydrochloric acid was added, and the mixture was heated under reflux for an additional 17 hr. The solvent was removed from the reaction mixture, and the residue was treated with aqueous sodium hydroxide and extracted with ether. The ether extracts were dried and distilled to give 49 g. (38%) of 6-(2-diethylaminoethoxy)-1-naphthylamine, b.p. 160° (0.15 mm.).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.85. Found: C, 74.40; H, 8.55; N, 10.68.

The hydrochloride salt prepared in ethanol with 2-propanol saturated with hydrogen chloride gave off-white needles, m.p. 248–253° from ethanol–ether.

Anal. Calcd. for $C_{16}H_{22}N_2O \cdot 2HCl$: C, 58.01; H, 7.30; N, 8.46; Cl, 21.40. Found: C, 58.10; H, 7.10; N, 8.53; Cl, 21.26.

1-Diethylaminomethyl-3-cyclohexene-1-carboxaldehyde.—A mixture of 226 g. (2.05 moles) of 3-cyclohexene-1-carboxaldehyde, 185 g. (1.69 moles) of diethylamine hydrochloride, and 78 g. (2.6 moles) of paraformaldehyde in 125 g. of ethanol was heated on the steam bath for 2 hr. An additional 78 g. of paraformaldehyde was added and heating was continued for 6 hr. The mixture was poured into 2 l. of water and extracted with ether, and the ether extracts were discarded. The aqueous layer was made basic with sodium hydroxide and the oil which separated was extracted with ether. The extracts were dried over anhydrous sodium sulfate, the ether was removed, and the residue distilled to give 200 g. (61%) of 1-diethylaminomethyl-3-cyclohexene-1-carboxaldehyde, b.p. 59–61° (0.1–0.2 mm.), $n^{25}D$ 1.4780.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.57; H, 10.91; N, 7.29.

1-(1-Naphthyl)aziridine.—To a stirred solution of 27.8 g. (0.69 mole) of sodium hydroxide in 80 ml. of water and 300 ml. of ethanol was added a solution of 100 g. (0.30 mole) of N-(2-bromoethyl)-1-naphthylamine hydrobromide in 1 l. of ethanol. The mixture was heated under reflux for 4 hr. and allowed to stand at room temperature overnight. The mixture was filtered to remove a small amount of solid, and the solvent was removed from the filtrate *in vacuo*. The residue was poured into water and extracted with ether. The extracts were dried over anhydrous sodium sulfate, the solvent was removed, and the residue distilled to give 38 g. (75%) of 1-(1-naphthyl)aziridine, b.p. 81–83° (0.2 mm.), $n^{25}D$ 1.6462.

Anal. Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 84.94; H, 6.55; N, 8.45.

A solution of the aziridine base in ethanol was treated with 2-propanol saturated with hydrogen chloride. The N-(2-chloroethyl)-1-naphthylamine hydrochloride obtained was crystallized from ethanol–ether to give off-white crystals, m.p. 181–183° dec.

Anal. Calcd. for $C_{12}H_{12}ClN \cdot HCl$: C, 59.52; H, 5.41; N, 5.79; Cl, 29.28. Found: C, 59.63; H, 5.57; N, 5.83; Cl, 28.97.

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Synthetic Schistosomicides. IV. 5-[4-(2-Diethylaminoethylamino)-1-naphthylazo]uracil and Related [4-(Aminoalkylamino)-1-naphthylazo]heterocyclic Compounds[1]

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A variety of [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds have been synthesized by (1) coupling a diazotized heterocyclic amine with the appropriate 1-(aminoalkyl)naphthylamine; (2) allowing a N-(ω-haloalkyl)-4-(heterocyclicazo)-1-naphthylamine to react with the appropriate amine; (3) alkaline hydrolysis of the corresponding N-(aminoalkyl)-2,2,2-trifluoro-N-[4-(heterocyclicazo)-1-naphthyl]acetamides. Many of the [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds are highly active against experimental *Schistosoma mansoni* infections.

In previous communications from these Laboratories,[1-3] it was reported that 5-(4-amino-1-naphthylazo)uracil (I) and various [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds (II) exhibit strong therapeutic activity against *Schistosoma mansoni* infections in experimental animals. This paper de-

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

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