cohol, 1.0 g. (0.010 mole) of succinic anhydride, and 15 drops of triethylamine in 50 ml. of methylene chloride was refluxed for 30 min. and then evaporated *in vacuo*. The residue was dissolved in 75 ml. of MIBK and extracted twice with 30-ml. portions of 5% sodium bicarbonate solution. The combined extracts were washed with ether (30 ml.), acidified to pH 2 with 20% sulfuric acid, and extracted twice with 35-ml. portions of ether. The combined ethereal extracts were washed twice with 10-ml. portions of water, dried over sodium sulfate, filtered, and treated with 3.5 ml. (0.01 mole) of a 50% solution of sodium 2-ethylhexanoate in 1-butanol. The product crystallized on standing at 8° for 17 hr. It was collected and dried *in vacuo* over phosphorus pentoxide; weight, 1.5 g. (28%); m.p. 195.5–197.5° dec. The infrared spectrum indicated the presence of NH at 3350 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; ester, 1730 cm.$^{-1}$; amide, 1670 cm.$^{-1}$; carboxylate, 1590 cm.$^{-1}$; primary ester, 1160 cm.$^{-1}$; and aromatic, 1570 and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{24}N_3O_7SNa \cdot 0.5H_2O$: C, 53.27; H, 4.86; N, 8.10. Found: C, 53.50; H, 4.72; N, 8.16.

6-(DL-α-Phenoxypropionamido)penicillanyl N-Phenylcarbamate (XX).—A solution of 3.0 g. (8.5 mmoles) of 6-(DL-α-phenoxypropionamido)penicillanyl alcohol in 25 ml. of dry benzene was treated with 1.1 ml. (0.01 mole) of phenyl isocyanate. After 7 days at room temperature the solution was concentrated and the residual amber gum was dissolved in ether, from which it crystallized on scratching. The product was recrystallized from benzene and Skellysolve B to yield 1.05 g. (26%) of white solid, m.p. 164.5–167.5°. The infrared spectrum was consistent with the expected structure, having NH at 3345 cm.$^{-1}$; β-lactam, 1787 cm.$^{-1}$; carbamate, 1739 cm.$^{-1}$; amide, 1680 cm.$^{-1}$; phenyl ether, 1225 cm.$^{-1}$; and aromatic bands at 1600, 760, and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{27}N_3O_5S$: C, 61.38; H, 5.80; N, 8.95. Found: C, 61.00; H, 5.63; N, 8.90.

6-(5-Methyl-3-phenylisoxazole-4-carboxamido)penicillanyl N-Phenylcarbamate (XXI).—A solution of 870 mg. (2.2 mmoles) of 6-(5-methyl-3-phenylisoxazole-4-carboxamido)penicillanyl alcohol and 330 mg. (3.0 mmoles) of phenyl isocyanate in 20 ml. of dimethylformamide was allowed to stand at 25° for 10 days. It was diluted with 80 ml. of water and cooled. The crystalline solid was collected, dissolved in 75 ml. of ethyl acetate, and concentrated to dryness *in vacuo*. The residue was redissolved in ethyl acetate, concentrated to a small volume, and filtered to remove a small amount of crystalline product which was identified as carbanilide by melting point and infrared spectrum. Dilution of the ethyl acetate solution with Skellysolve B gave a crystalline solid. It was dissolved in methylene chloride, filtered to remove a trace of insoluble material, concentrated to dryness *in vacuo*, and recrystallized in turn from ethyl acetate and benzene–Skellysolve B. After drying *in vacuo* over phosphorus pentoxide the product weighed 300 mg. (33%) and had m.p. 150.5–151°. An infrared spectrum showed absorptions for NH at 3280 cm.$^{-1}$, β-lactam, 1785 cm.$^{-1}$; carbamate, 1738 cm.$^{-1}$; amide, 1670 cm.$^{-1}$; and aromatic at 765 and 700 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{26}N_4O_5S$: C, 61.50; H, 5.16; N, 11.10. Found: C, 61.10; H, 4.98; N, 11.05.

Synthetic Schistosomicides. V. N-(Mono- and dialkylaminoalkyl)-1,4-naphthalenediamines and Related Naphthylamines[1]

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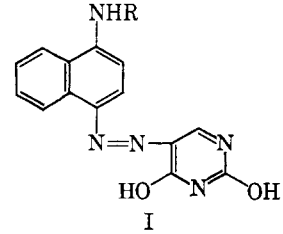
A group of N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines (IV) (Tables I and II), which represent potential metabolites of various 1-(mono- and dialkylaminoalkylamino)-4-naphthylazo schistosomicides (III), has been prepared by hydrogenolysis of the appropriate N-mono- and N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)-alkylenediamines. N²-(2-Diethylaminoethyl)-1,2-naphthalenediamine (V), 1,4-bis[2-(4-amino-1-naphthylamino)ethyl]piperazine (VIa), and N,N′′-[methyliminobis(trimethylene)]di-1,4-naphthalenediamine (VIb) were prepared in a similar manner. Alternatively, N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb), N-(2-diethylaminoethyl)-N-methyl-1,4-naphthalenediamine (VII), and 4-(2-diethylaminoethylthio)-1-naphthylamine (X) were obtained from the corresponding nitronaphthalenes by catalytic hydrogenation. Condensation of IIb with diethyl (ethoxymethylene)malonate, ethyl 2-cyano-3-ethoxyacrylate, 4,7-dichloroquinoline, 6,9-dichloro-2-methoxyacridine, and 2-chlorotriethylamine afforded diethyl {{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}-amino}methylene}malonate (XI), ethyl 2-cyano-3-{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}amino}acrylate (XII), 7-chloro-4-[4-(2-diethylaminoethylamino)-1-naphthylamino]quinoline (XIII), 6-chloro-9-[4-(2-diethylaminoethylamino)-1-naphthylamino]-2-methoxyacridine (XIV), and N,N′-bis(2-diethylaminoethyl)-1,4-naphthalenediamine (XV), respectively. Many of the N-(dialkylaminoalkyl)-1,4-naphthalenediamines are highly active against experimental *Schistosoma mansoni* infections in mice. Structure–activity relationships and biochemical studies are summarized.

In a previous communication[2] it was reported that 5-(4-amino-1-naphthylazo)uracil (ANU) (Ia) exhibits good activity against *Schistosoma mansoni* in experimental animals. Additional studies in these laboratories[3] revealed that the antischistosome activity of ANU was markedly enhanced when a diethylaminoethyl side chain was atttached to the aromatic amine (Ib). Potent antischistosome activity was also observed among a variety of related 1-(mono- and dialkylaminoalkylamino)-4-naphthylazo compounds (III).[1,3–5]



I

a, R=H
b, R=$(CH_2)_2N(C_2H_5)_2$

(1) Presented before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 5–10, 1964. Previous paper: E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **6**, 646 (1963).

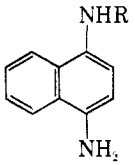
(2) E. F. Elslager and D. F. Worth, *ibid.*, **6**, 444 (1963).

(3) 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).

(4) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, in preparation.

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

While investigating potential metabolites of ANU, it was discovered that the reduction product [1,4-naphthalenediamine (IIa)] kills adult *S. mansoni in vitro* at drug concentrations as low as 25 γ/ml.[2] Results in mice were disappointing; the diamine was

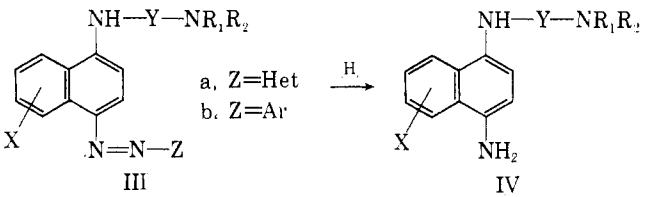


a, R=H
b, R=$(CH_2)_2N(C_2H_5)_2$

II

ineffective when administered orally at the maximum tolerated dose. Anticipating that factors such as metabolic alteration, excretion rate, absorption, and tissue localization might be favorably influenced by the introduction of the basic side chain, a study of the potential metabolites of 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]uracil (Ib) and related compounds was initiated.

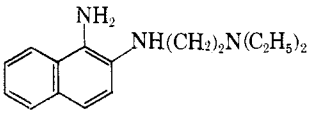
Early efforts were directed toward the preparation of N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb), a likely metabolite of Ib. The synthesis was readily accomplished by catalytic hydrogenation of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)ethylenediamine[4] over Raney nickel in ethanol. *In vitro* tests revealed that IIb kills adult *S. mansoni* at drug concentrations of 12.5 γ/ml. Subsequently, it was found that this base-substituted diamine possesses curative activity against experimental *S. mansoni* infections in mice. These encouraging results stimulated the synthesis of a variety of N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines (IV) which represent potential metabolites of many of the 1-(mono- and dialkylaminoalkylamino)-4-naphthylazo dyes (III) reported previously.[1,3,4]



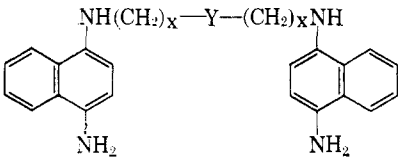
a, Z=Het
b, Z=Ar

III IV

The base-substituted 1,4-naphthalenediamines (IV) listed in Tables I and II were conveniently prepared by reductive cleavage of the corresponding azo compounds (III), which were readily available.[1,3,4] Although reduction was accomplished with a variety of substituted aryl- and heterocyclicazo compounds utilizing several chemical and catalytic methods, isolation and purification problems were minimized when the corresponding N-mono- and N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)alkylenediamines were hydrogenolyzed in methanol or ethanol over palladium-on-charcoal or Raney nickel catalysts. Prompt treatment with excess hydrogen chloride minimized air oxidation and allowed facile separation of the alcohol-soluble aniline hydrochloride from the less soluble naphthalenediamine hydrochloride salts. Similarly, N^2-(2-diethylaminoethyl)-1,2-naphthalenediamine (V), 1,4-bis[2-(4-amino-1-naphthylamino)ethyl]piperazine (VIa), and N,N′-[methyliminobis(trimethylene)]-di-1,4-naphthalenediamine (VIb) were prepared by hydrogenation of



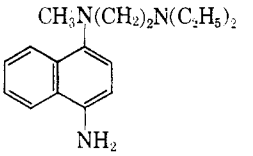
V



VIa, x = 2; Y = $N[(CH_2)_2]_2N$
b, x = 3; Y = NCH_3

the corresponding phenylazo derivatives.[4]

Alternatively, N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb) and N-(2-diethylaminoethyl)-N-methyl-1,4-naphthalenediamine (VII) were prepared by catalytic hydrogenation of N,N-diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine (VIII)[6] and the corresponding N′-methyl derivative,[6] respectively. 4-(2-Diethylaminoethylthio)-1-naphthylamine (X), a sulfur isostere of IIb, was synthesized in a similar manner from 2-[(4-nitro-1-naphthyl)thio]triethylamine (IX), which was obtained by the condensation of 1-chloro-4-nitronaphthalene with 2-[2-(diethylamino)ethyl]-2-thiopseudourea.



VII

Condensation of IIb with diethyl (ethoxymethylene)-malonate and ethyl 2-cyano-3-ethoxyacrylate in benzene gave diethyl {{[4-[(2-diethylaminoethyl)amino]-1-naphthyl}amino}methylene}malonate (XI) and ethyl 2-cyano-3-{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}amino}acrylate (XII), respectively. When the hydrochloride salt of IIb was allowed to react with 4,7-dichloroquinoline and 6,9-dichloro-2-methoxyacridine, respectively, in phenol, 7-chloro-4-[4-(2-diethylaminoethylamino)-1-naphthylamino]quinoline (XIII) and 6-chloro-9-[4-(2-diethylaminoethylamino)-1-naphthylamino]-2-methoxyacridine (XIV) were isolated in low yield. Alkylation of the sodium salt of IIb with 2-chlorotriethylamine in boiling xylene[7] afforded N,N′-bis(2-diethylaminoethyl)-1,4-naphthalenediamine (XV).

The naphthalenediamines described in the present communication were tested[8] in albino mice infected with a Puerto Rican strain of *Schistosoma mansoni*. As a group, the N-(dialkylaminoalkyl)-1,4-naphthalenediamines (IV) (Tables I and II) were more active against schistosomes and less toxic for mice than the corresponding N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)alkylenediamines from which they were derived. Compounds **3**, **5**, **8–10**, **12–17**, **20**, **30**, **32**, **35**, and **36** (Tables I and II), which are representative of the more promising members of the series, effected a 98–100%

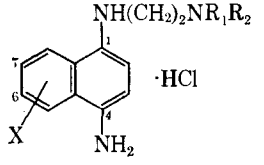
(6) E. F. Elslager, D. B. Capps, and L. M. Werbel, *J. Med. Chem.*, in press.

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

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

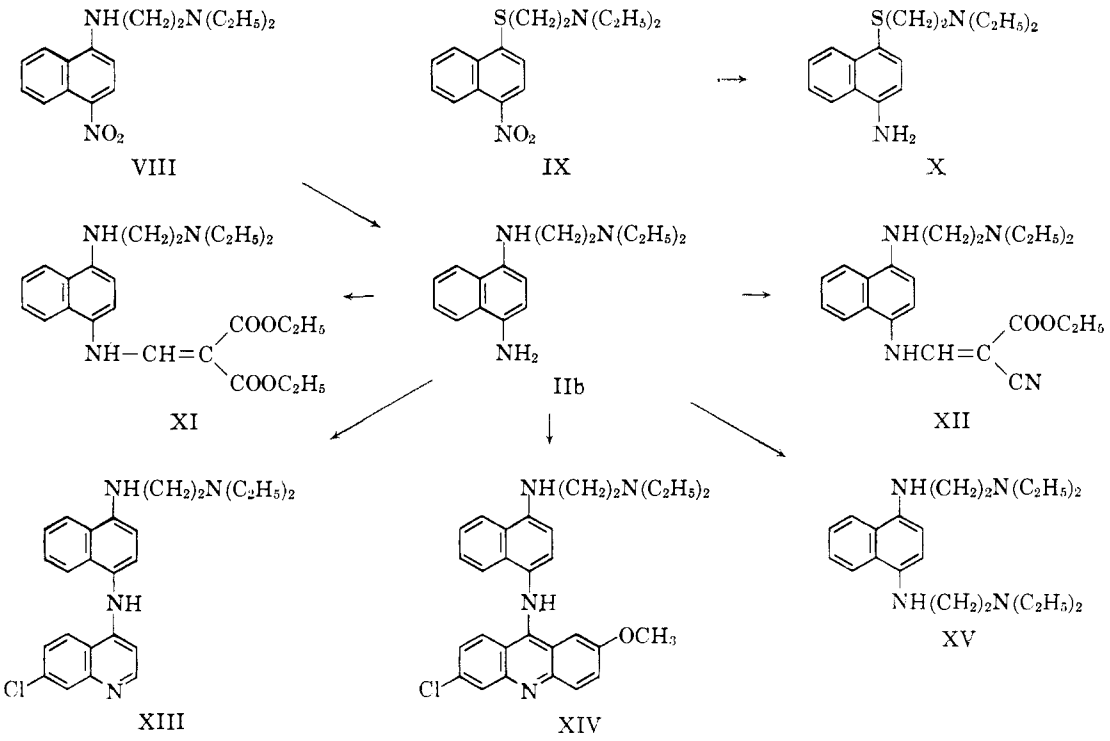
TABLE I

N-(MONO- AND DIALKYLAMINOETHYL)-1,4-NAPHTHALENEDIAMINE HYDROCHLORIDES[a]



Compd. no.	X	NR_1R_2	M.p., °C.[b]	Yield purified, %	Purification[c] solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	H	NHC_2H_5	245	96	A	$C_{14}H_{19}N_3 \cdot 3HCl$	49.64	49.83	6.55	6.72	12.40	12.50	31.40	31.09
2	H	$NH(CH_2)_2OH$	245–248	65	B	$C_{14}H_{19}N_3O \cdot 2.6HCl \cdot 0.67H_2O$[e]	47.75	47.84	6.55	6.36	11.93	12.29	26.18	26.27
3	H	$NCH_3C_2H_5$	245–255	35	B	$C_{15}H_{21}N_3 \cdot 2HCl$	56.96	56.95	7.33	7.29	13.29	12.93	22.42	22.42
4	H	$NCH_3(CH_2)_2OH$	213–215	89	B	$C_{15}H_{21}N_3O \cdot 3HCl$	48.86	48.46	6.56	6.73	11.40	11.01	28.85	28.58
5	H	$N(CH_2)_4$	303	79	A	$C_{16}H_{21}N_3 \cdot 2HCl$	58.54	58.60	7.06	7.19	12.80	12.67	21.60	21.27
6	H	$N[(CH_2)_2]_2O$	195–200	55	F	$C_{16}H_{21}N_3O \cdot 2HCl \cdot H_2O$[e]	53.04	53.25	6.96	7.05	11.60	11.56	19.57	20.14
7	H	$N[(CH_2)_2]_2NH$	283–285	74	C	$C_{16}H_{22}N_4 \cdot 3HCl \cdot 0.5H_2O$[e]	49.43	49.50	6.74	6.65	14.41	14.38	27.36	27.34
8	H	$N(C_2H_5)_2$	215–220	68	K	$C_{16}H_{23}N_3 \cdot 2HCl \cdot 0.5H_2O$[e]	56.63	56.44	7.72	7.98	12.38	12.25	20.90	20.72
9	H	$NCH_3CH(CH_3)_2$	235–250	33	I	$C_{16}H_{23}N_3 \cdot 2HCl$	58.18	58.10	7.63	7.59	12.72	12.92	21.47	21.40
10	H	$NC_2H_5(CH_2)_2OH$	213–216	75	B	$C_{16}H_{23}N_3O \cdot 2HCl$	55.49	55.02	7.28	7.47	12.13	12.21	20.48	20.54
11	H	$NC_2H_5CH_2CH{=}CH_2$	216–218	36	D	$C_{17}H_{23}N_3 \cdot 2.6HCl$	56.06	55.97	7.08	6.76	11.54	11.35	25.31	25.43
12	H	$N(CH_2)_5$	280	73	I	$C_{17}H_{23}N_3 \cdot 2HCl$	59.65	59.99	7.36	7.32	12.28	12.08	20.72	20.52
13	H	$N[(CH_2)_2]_2CHOH$	227–230	81	E	$C_{17}H_{23}N_3O \cdot 3HCl$	51.72	51.59	6.64	6.82	10.64	10.88	26.94	26.69
14	H	$N[(CH_2)_2]_2NCH_3$	237–239	74	B	$C_{17}H_{24}N_4 \cdot 3HCl \cdot 0.33H_2O$[e]	51.07	51.01	6.98	7.06	14.02	13.97	26.61	27.10
15	H	$NCH_3(CH_2)_3CH_3$	230	61	E	$C_{17}H_{26}N_3 \cdot 2HCl \cdot 0.25H_2O$[e]	58.53	58.51	7.95	8.05	12.05	12.00	20.33	20.71
16	6-OCH_3	$N(C_2H_5)_2$	202–205	55	F	$C_{17}H_{25}N_3O \cdot 3HCl$	51.46	51.58	7.11	7.16	10.59	10.37	26.81	26.73
17	7-OCH_3	$N(C_2H_5)_2$	240	54	G	$C_{17}H_{25}N_3O \cdot 3HCl$	51.46	51.56	7.11	7.18	10.59	10.57	26.81	26.52
18	H	$NHCH(CH_2)_5$	279–280	47	J	$C_{18}H_{25}N_3 \cdot 2HCl$	60.67	60.78	7.64	7.63	11.79	11.93	19.90	19.81
19	H	$N[(CH_2)_2]_2CHCH_3$	289–291	94	B	$C_{18}H_{25}N_3 \cdot 2HCl \cdot 0.25H_2O$[e]	59.91	59.90	7.68	7.86	11.65	11.67	19.65	19.57
20	H	$N(CH_2)_6$	255–280	66	I	$C_{18}H_{25}N_3 \cdot 2HCl$	60.67	60.51	7.64	7.66	11.79	11.49	19.90	20.09
21	H	$NCH_3CH(CH_2)_5$	250–255	95	B	$C_{19}H_{27}N_3 \cdot 3HCl \cdot 1.33H_2O$[e]	52.97	52.91	7.64	7.86	9.75	9.71	24.69	24.97
22	H	$NHCH(CH_2)_7$	262–268	88	B	$C_{20}H_{29}N_3 \cdot 2HCl \cdot 0.75H_2O$[e]	60.37	60.34	8.23	8.39	10.56	10.29	17.82	17.65
23	H	$N[CH_2CH(CH_3)_2]_2$	240–242	68	H	$C_{20}H_{31}N_3 \cdot 2HCl$	62.17	62.22	8.61	8.63	10.88	10.81	18.35	18.25
24	H	$NC_2H_5(CH_2)_2N(C_2H_5)_2$	174–178	59	E	$C_{20}H_{32}N_4 \cdot 3HCl \cdot 0.6H_2O$[e]	53.53	53.53	8.13	8.09	12.49	12.38	23.71	23.70
25	6-$O(CH_2)_2N(C_2H_5)_2$	$N(C_2H_5)_2$	125–136	41	D	$C_{22}H_{36}N_4O \cdot 3HCl \cdot 1.25H_2O$[e]	52.38	52.26	8.29	8.43	11.11	11.17	21.09	21.81
26	H	$N[(CH_2)_2]_2NC_8H_9$[d]	230–234	84	F	$C_{24}H_{30}N_4 \cdot 2.5HCl \cdot 2H_2O$[e]	57.45	57.66	7.33	7.47	11.17	10.91	17.67	17.27

[a] Compounds are colorless or off-white solids. [b] Compounds melt with decomposition. [c] A, methanol–ether; B, methanol–2-propanol containing ethanolic hydrogen chloride; C, ethanol–concentrated hydrochloric acid; D, 2-propanol; E, ethanol–2-propanol; F, ethanol; G, methanol–concentrated hydrochloric acid; H, methanol–ether; I, methanol–2-propanol; J, methanol; K, water. [d] C_8H_9 represents the 3,4-xylyl radical. [e] Compounds interfere with Karl Fischer water determinations.



reduction of live worms at doses ranging from 33 to 334 mg./kg./day when administered orally in the diet for 14 days or by gavage for 5–10 days. Many of these were distinctly more promising in mice than lucanthone hydrochloride,[8,9] the tris(*p*-aminophenyl)-carbonium salts,[8,10] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[11,12] 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. The base-substituted 1,4-naphthalenediamines (IV), like the 1-(dialkylaminoalkylamino)-4-naphthylazo compounds (III), consistently cured a higher percentage of infected mice than the reference drugs cited. N-(2-Diethylaminoethyl)-1,4-naphthalenediamine (IIb) was also tested by the drug–diet method against a Liberian strain of *S. mansoni* in mice; the effects observed were comparable to the effects noted against the Puerto Rican strain.

N-(2-Diethylaminoethyl)-1,4-naphthalenediamine dihydrochloride (IIb) and 1-[2-(4-amino-1-naphthylamino)ethyl]pyrrolidine dihydrochloride (**5**) were selected for trial in rhesus monkeys infected with the Puerto Rican strain of *S. mansoni*. When administered in gavage doses of 25 or 50 mg./kg. daily for 10 days, both salts suppressed egg production but were rarely curative. Effective doses produced a high incidence of side effects: emesis, inappetence, and weight loss. A variety of salts of N-(2-diethylaminoethyl)-1,4-naphthalenediamine with organic acids was prepared in anticipation that some of these might exhibit a greater spread between the schistosomicidal dose and the toxic dose. A salt with one formula weight of 4,4′-methylenebis[3-hydroxy-2-naphthoic acid] (pamoic acid) proved to be less toxic for dogs than the dihydrochloride, but exhibited very erratic activity and toxicity in rhesus monkeys at gavage doses ranging from 25 to 200 mg./kg. daily for 5–10 days.

Among the N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines of structure IV and VI, activity in mice is abolished or substantially reduced when R_1 and/or R_2 represent hydrogen (compounds **1**, **2**, **18**, **22**, and **37**) or when the secondary amine at position 1 is alkylated (VII). Similarly, N^2-(2-diethylaminoethyl)-1,2-naphthalenediamine (V), 4-(2-diethylaminoethylthio)-1-naphthylamine (X), and N-(2-diethylaminoethyl)-*p*-phenylenediamine[15] were devoid of activity. The condensation products (XI–XV) of IIb with diethyl (ethoxymethylene)malonate, ethyl 2-cyano-3-ethoxyacrylate, 4,7-dichloroquinoline, 6,9-dichloro-2-methoxyacridine, and 2-chlorotriethylamine were also inactive.

Inasmuch as 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]uracil (Ib)[1,3] and N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb) are both potent schistosomicides, it was of interest to study the possible enzymatic conversion of Ib to IIb.[16] The diamine exhibits a strong fluorescence in benzene when extracted from strongly alkaline solutions, while the naphthylazouracil compound shows no fluorescence under these conditions. However, assay results were complicated by the instability of the diamine. Solutions of IIb in dilute hydrochloric acid turned yellow in several hours; in dilute sodium bicarbonate solution, a red-brown color appeared in 1 hr. at 38°. Paper chromatography and countercurrent extraction studies indicated that three or four different compounds were present in these

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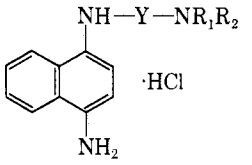
TABLE II

N-(MONO- AND DIALKYLAMINOALKYL)-1,4-NAPHTHALENEDIAMINE HYDROCHLORIDES[a]



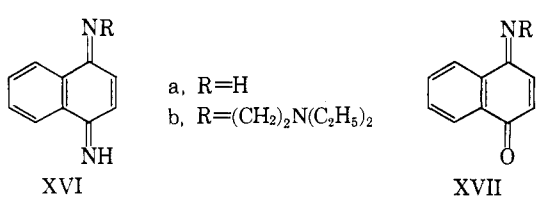
Compd. no.	—Y—NR₁R₂	M.p., °C.[b]	Yield purified, %	Purification solvent[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
27	$CHCH_3CH_2N(CH_3)_2$	181–183	35	A	$C_{16}H_{21}N_3 \cdot 3HCl$	51.07	51.24	6.86	7.05	11.91	11.73		
28	$(CH_2)_3N(CH_3)_2$	260	66	B	$C_{15}H_{21}N_3 \cdot 3HCl$	51.07	51.03	6.86	6.79	11.91	12.02	30.16	30.19
29	$CH_2CHCH_3CH_2N(CH_3)_2$	260	52	C	$C_{16}H_{23}N_3 \cdot 3HCl \cdot H_2O$[d]	49.94	50.44	7.33	7.48	10.92	10.46	27.65	27.71
30	$(CH_2)_3N(CH_2)_4$	194	72	A	$C_{17}H_{23}N_3 \cdot 2HCl \cdot H_2O$[d]	56.66	56.50	7.55	7.59	11.66	11.64	19.68	19.37
31	$(CH_2)_3N[(CH_2)_2]_2O$	206–208	47	F	$C_{17}H_{23}N_3O \cdot 2HCl \cdot H_2O$[d]	54.25	54.40	7.23	7.12	11.17	11.33	18.84	19.37
32	$(CH_2)_3N(C_2H_5)_2$	200–210	82	D	$C_{17}H_{25}N_3 \cdot 2HCl$	59.30	59.19	7.91	8.08	12.20	12.10	20.59	20.52
33	$(CH_2)_3N(CH_2)_5$	248–253	84	G	$C_{18}H_{25}N_3 \cdot 3HCl \cdot 0.67H_2O$[d]	53.41	53.43	7.30	7.37	10.38	10.33	26.28	26.21
34	$(CH_2)_5N(C_2H_5)_2$	169–171	46	C	$C_{19}H_{29}N_3 \cdot 3HCl \cdot H_2O$[d]	53.46	53.20	8.03	8.19	9.84	9.47	24.92	24.52
35	$CHCH_3(CH_2)_3N(C_2H_5)_2$	162–183	29	D	$C_{19}H_{29}N_3 \cdot 2.5HCl \cdot 0.75H_2O$[d]	56.47	56.76	8.23	8.40	10.40	10.38	21.93	22.30
36	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	192–194	24	E	$C_{19}H_{29}N_3 \cdot 3HCl \cdot 0.5H_2O$[d]	54.61	54.90	7.96	7.88	10.06	9.86	25.46	25.24
37	$(CH_2)_3NH(CH_2)_7CH_3$	268–271	99	D	$C_{21}H_{33}N_3 \cdot 3HCl$	57.73	58.20	8.31	8.24	9.62	9.88	24.35	24.31

[a] Compounds are colorless or off-white solids. [b] Compounds melt with decomposition. [c] A, 2-propanol–hydrogen chloride; B, methanol–2-propanol–water; C, ethanol–2-propanol–hydrogen chloride; D, methanol–2-propanol; E, ethanol–ether; F, ethanol–5% hydrochloric acid; G, ethanol. [d] Compounds interfere with Karl Fischer water determinations.

solutions. Further, paper chromatography of highly purified diamine indicated that some decomposition occurred even during the course of development of the chromatogram.

Subsequently, Ib and IIb were added to minced rat liver suspensions (Tyrode's) in equimolar amounts, and incubated at 38° for 1 hr.[16] The suspensions were then made strongly alkaline and were extracted with benzene. The benzene extract from the liver suspension containing the azo compound showed fluorescence (Farrand spectrofluorometer) equivalent to 5% diamine; but the extract from the suspension containing the diamine showed approximately the same amount of fluorescence. Extracts taken from similar preparations immediately after the addition of the drugs showed less than 1% diamine in the azo sample and more than 70% in the diamine sample. Excitation and fluorescence spectra of all four samples were similar to the spectrum obtained earlier with IIb. These results indicate that the diamine is rapidly converted to nonfluorescent products under these conditions.

Although the decomposition products of IIb have not been isolated and characterized, a logical metabolic pathway involves oxidation to N′-(1,4-dihydro-4-imino-1-naphthylidene)-N,N-diethylethylenediamine (XVIb), followed by hydrolysis to 1,4-naphthoquinone *via* 1,4-naphthoquinone imine (XVIIa) or N-[2-(diethylamino)ethyl]-1,4-naphthoquinone imine (XVIIb). Likewise, oxidation of 1,4-naphthalenediamine (IIa)[2] to 1,4-naphthoquinone diimine (XVIa) followed by hydrolysis would give 1,4-naphthoquinone imine (XVIIa) and 1,4-naphthoquinone. Inasmuch as various naphthoquinones are known to inhibit the glycolysis of adult *S. mansoni in vitro* at low concentrations,[17,18] a similar mode of action can be postulated for 1,4-naphthalenediamine (IIa) and the N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines (IV).



XVI XVII

Alternatively, complex colors related to Aniline Black[19] or the quinone imine dyes[19] may be formed. Either hypothesis would explain the therapeutic failure of N-(2-diethylaminoethyl)-N-methyl-1,4-naphthalenediamine (VII) and 4-(2-diethylaminoethylthio)-1-naphthylamine (X), which presumably cannot be oxidized to quinone imines of structure XVI. Similarly, Schönhöfer[20] has postulated that the antimalarial activity of certain base-substituted 4-, 6-, and 8-aminoquinolines is conditional upon their capacity to allow tautomerism and form quinoid linkages. However, the schistosomicidal action of various thiaxanthenones,[21] *p*-toluidine derivatives,[22] and phenylpiperazines[14] is apparently not dependent on this capability.

Experimental[23]

Preparation of N-(Mono- and dialkylaminoalkyl)-1,4-naphthalenediamines (IV) (Tables I, II). N-(2-Diethylaminoethyl)-1,4-naphthalenediamine Dihydrochloride (IIb).—A solution of 100 g. (0.29 mole) of N,N-diethyl-N′-(4-phenylazo-1-naphthyl)-ethylenedianine[4] in 600 ml. of ethanol was hydrogenated over 10 g. of Raney nickel at an initial hydrogen pressure of 3.5 kg./cm.². When the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was treated immediately with an excess of a 30% hydrogen chloride–2-propanol solution to arrest air oxidation. The mixture was cooled and the crude product collected by filtration. The filter cake was washed with 2-propanol and the off-white solid was dried *in vacuo* at 45° for 18 hr.; weight, 88 g. (92%). Two crystallizations from water containing a few drops of hydro-

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chloric acid (decolorizing charcoal) gave off-white crystals, m.p. 215–220° dec.

A solution of 107 g. (0.24 mole) of disodium 4,4′-methylenebis-[3-hydroxy-2-naphthoic acid] monohydrate in 900 ml. of water was added dropwise with stirring to a solution of 80 g. (0.24 mole) of N-(2-diethylaminoethyl)-1,4-naphthalenediamine dihydrochloride in 1 l. of water. The mixture was stirred for 1 hr. and the salt that had separated was collected by filtration, triturated with several portions of water, and dried *in vacuo* at 50° for 48 hr. The off-white solid weighed 138 g. (87%), m.p. 205° dec.

Anal. Calcd. for $C_{16}H_{24}N_3 \cdot C_{23}H_{16}O_6 \cdot H_2O$: C, 70.57; H, 6.23; N, 6.33; H_2O, 2.72. Found: C, 70.43; H, 6.02; N, 6.39; H_2O (Karl Fischer), 2.87.

N^2-(2-Diethylaminoethyl)-1,2-naphthalenediamine Dihydrochloride (V).—N,N-Diethyl-N′-(1-phenylazo-2-naphthyl)ethylenediamine[4] (14.4 g., 0.042 mole) was hydrogenated in methanol over Raney nickel and the reaction mixture was processed according to the procedure described for the preparation of IIb. Crystallization from a methanol–2-propanol mixture containing ethanolic hydrogen chloride gave 13.0 g. (95%) of pink crystals, m.p. 190–192°.

Anal. Calcd. for $C_{16}H_{23}N_3 \cdot 2HCl$: C, 58.18; H, 7.63; N, 12.72; Cl, 21.47. Found: C, 58.21; H, 7.88; N, 12.07; Cl, 21.39.

1,4-Bis[2-(4-amino-1-naphthylamino)ethyl]piperazine Hydrochloride (VIa).—1,4-Bis[2-(4-phenylazo-1-naphthylamino)ethyl]-piperazine[4] (12.0 g., 0.019 mole) was hydrogenated in 600 ml. of dimethylacetamide over 2 g. of Raney nickel, the catalyst was removed by filtration, and the filtrate was treated with excess ethanolic hydrogen chloride and concentrated *in vacuo* to 200 ml. The residue was diluted with 2-propanol and chilled. The precipitate that separated was collected by filtration, crystallized from dilute hydrochloric acid, triturated with boiling ethanol, and dried *in vacuo* at 40° for 40 hr. The off-white solid thus obtained weighed 9.3 g. (74%), m.p. 270–273°.

Anal. Calcd. for $C_{28}H_{34}N_6 \cdot 5HCl \cdot 1.5H_2O$: C, 50.65; H, 6.38; N, 12.66; Cl, 26.70. Found: C, 50.76; H, 6.53; N, 12.59; Cl, 26.74.

N,N′′-[Methyliminobis(trimethylene)]di-1,4-naphthalenediamine Hydrochloride (VIb).—N,N′′-[Methyliminobis(trimethylene)]bis[4-phenylazo-1-naphthylamine][4] (14.7 g., 0.024 mole) was hydrogenated according to the procedure described for the preparation of VIa. The product (12.2 g., 85%) was obtained as an off-white solid, m.p. 225° dec.

Anal. Calcd. for $C_{27}H_{33}N_5 \cdot 4HCl \cdot 1.5H_2O$: C, 54.00; H, 6.71; N, 11.66; Cl, 23.62. Found: C, 53.94; H, 7.06; N, 11.58; Cl, 24.20.

N-(2-Diethylaminoethyl)-N-methyl-1,4-naphthalenediamine Dihydrochloride (VII).—N,N-Diethyl-N′-methyl-N′-(4-nitro-1-naphthyl)ethylenediamine[5] (17.5 g., 0.058 mole) was hydrogenated in ethanol over Raney nickel and the reaction was worked up according to the procedure employed for the preparation of IIb. Crystallization of the crude hydrochloride salt from 2-propanol containing excess ethanolic hydrogen chloride gave 18.2 g. (89%) of beige crystals, m.p. 100° dec.

Anal. Calcd. for $C_{17}H_{25}N_3 \cdot 2HCl \cdot 0.5H_2O$: C, 57.79; H, 7.99; N, 11.89. Found: C, 57.66; H, 8.40; N, 11.86.

4-(2-Diethylaminoethylthio)-1-naphthylamine Dihydrochloride (X).—To a stirred mixture of 10.4 g. (0.05 mole) of 1-chloro-4-nitronaphthalene[24] and 12.4 g. (0.05 mole) of 2-[2-(diethylamino)ethyl]-2-thiopseudourea dihydrochloride in 125 ml. of ethanol was slowly added a solution of 4.5 g. (0.11 mole) of sodium hydroxide in 50 ml. of water. The mixture was heated under reflux for 18 hr. and the solvent was removed *in vacuo*. The residue was acidified and extracted with ether. The combined ether extracts were discarded. The aqueous layer was made alkaline and extracted thoroughly with ether. The ether was removed *in vacuo* and the crude oily 2-[(4-nitro-1-naphthyl)-thio]triethylamine (IX) was taken up in 200 ml. of ethanol and hydrogenated over 2 g. of Raney nickel under an initial hydrogen pressure of 51 p.s.i.g. (3.59 kg./cm.^{2}). After the theoretical quantity of hydrogen had been absorbed, the mixture was filtered, an excess of a 2-propanol–hydrogen chloride mixture was added, and the solution was concentrated to a small volume *in vacuo* on a steam bath. The solid that separated was collected by filtration, washed with anhydrous ether, and dried. Crystallization from ethanol–ether gave 9.7 g. (56% over-all) of off-white crystals, m.p. 195–197° dec.

Anal. Calcd. for $C_{16}H_{22}N_2S \cdot 2HCl$: C, 55.32; H, 6.96; N, 8.07. Found: C, 55.29; H, 6.91; N, 8.01.

Diethyl {{4-[(2-Diethylaminoethyl)amino]-1-naphthyl}amino}-methylene}malonate Dihydrochloride (XI).—To a benzene solution of N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb) prepared from 33.5 g. (0.1 mole) of the dihydrochloride salt was added 21.6 g. (0.1 mole) of diethyl (ethoxymethylene)malonate and the resulting mixture was heated on a steam bath for 4 hr. Volatile materials were removed *in vacuo* and the residue was dissolved in hot 2-propanol containing an excess of a 2-propanol-hydrogen chloride mixture. The mixture was cooled and the crude hydrochloride that separated was collected and dried. Two crystallizations from 2-propanol gave 22.6 g. (44%) of chartreuse crystals, m.p. 160–164° dec.

Anal. Calcd. for $C_{24}H_{33}N_3O_4 \cdot 2HCl$: C, 57.60; H, 7.05; N, 8.40. Found: C, 57.30; H, 7.01; N, 8.40.

Ethyl 2-Cyano-3-{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}amino}acrylate (XII).—Ethyl 2-cyano-3-ethoxyacrylate (16.9 g., 0.1 mole) was added to a benzene solution of N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb) prepared from 33.5 g. (0.1 mole) of the hydrochloride salt and the mixture was heated on a steam bath for 4 hr. Volatile materials were removed *in vacuo* and the residue was crystallized from 2-propanol to give 18.0 g. (47%) of chartreuse crystals, m.p. 133–136°.

Anal. Calcd. for $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.25; H, 7.22; N, 14.78.

7-Chloro-4-[4-(2-diethylaminoethylamino)-1-naphthylamino]-quinoline (XIII).—A mixture of 9.9 g. (0.05 mole) of 4,7-dichloroquinoline, 16.6 g. (0.05 mole) of N-(2-diethylaminoethyl)-1,4-naphthalenediamine dihydrochloride (IIb), and 35 g. of phenol was stirred and heated on a steam bath for 3 hr. Upon cooling, the reaction mixture was diluted with acetone and the supernatant liquid was separated from the sticky solid that separated. The residue was extracted with a mixture of excess ammonium hydroxide and ether and the ether extracts were combined and dried over anhydrous potassium carbonate. Anhydrous hydrogen chloride was bubbled into the ether solution and the hydrochloride salt that separated was collected and dried. The hydrochloride salt was again converted to the free base and the ether extracts were concentrated to dryness. The residue was crystallized from ethyl acetate (decolorizing charcoal) to give 4.0 g. (19%) of chartreuse crystals, m.p. 197–198°.

Anal. Calcd. for $C_{25}H_{27}ClN_4$: C, 71.67; H, 6.50; N, 13.37. Found: C, 71.94; H, 6.62; N, 13.41.

6-Chloro-9-[4-(2-diethylaminoethylamino)-1-naphthylamino]-2-methoxyacridine Dihydrochloride (XIV).—6,9-Dichloro-2-methoxyacridine (13.9 g., 0.05 mole) and N-(2-diethylaminoethyl)-1,4-naphthalenediamine dihydrochloride (IIb) (16.6 g., 0.05 mole) were allowed to react in phenol utilizing the procedure described for the preparation of XIII. The base, which was obtained as a sticky solid, was triturated with petroleum ether (b.p. 30–60°) and dissolved in hot carbon tetrachloride (decolorizing charcoal). The solution was evaporated to dryness, the residue was treated with an excess of ethanolic hydrogen chloride, and the dark reddish brown hydrochloride was precipitated with acetone. The salt was dried *in vacuo* at 60° for 18 hr.; yield, 10.0 g. (34%), m.p. 230–235° dec.

Anal. Calcd. for $C_{30}H_{31}ClN_4O \cdot 2HCl \cdot 1.25H_2O$: C, 60.61; H, 6.02; N, 9.42; H_2O, 3.79. Found: C, 60.75; H, 6.20; N, 9.33; H_2O (Karl Fischer), 3.57.

N,N′-Bis(2-diethylaminoethyl)-1,4-naphthalenediamine (XV).—To a suspension of 24.0 g. of 50% sodium hydride dispersion in mineral oil (0.5 mole)[25] in 200 ml. of xylene was added a xylene solution of N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb) prepared from 167 g. (0.5 mole) of the dihydrochloride salt. The mixture was stirred and heated under reflux for 2 hr. and to it was cautiously added a xylene solution of 2-chlorotriethylamine prepared from 68 g. (0.5 mole) of the hydrochloride salt. The mixture was stirred and heated under reflux for 24 hr., cooled, and cautiously treated with water. The organic layer was separated and dried over anhydrous potassium carbonate. After removal of volatile materials on a water aspirator, the residue was distilled under high vacuum through a 25-cm. Vigreux column to give 23.5 g. (18%) of a viscous yellow liquid, b.p. 194–197° (0.3 mm.), $n^{25}D$ 1.5866.

Anal. Calcd. for $C_{22}H_{36}N_4$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.18; H, 9.85; N, 15.22.

(24) Purchased from Kay-Fries Chemicals, Inc., New York, N. Y.

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

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Synthesis and Biological Properties of Aminoalkylhydrazines. A Unique Nitrogen–Nitrogen Scission of 1-(2-Diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine

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Several 2-(3-aminopropyl)-1,1-dialkylhydrazines (IIIa–d, Table I) were prepared by reduction of the appropriate 3-(2,2-dialkylhydrazino)propionitriles (IIa–d) with lithium aluminum hydride. Treatment of various dialkylaminoalkyl chlorides with excess hydrazine gave the corresponding (dialkylaminoalkyl)hydrazines (IV, Table II) as the preponderant products; small amounts of the 1,1-bis(dialkylaminoalkyl)hydrazines (V, Table III) were isolated from high boiling fractions of the larger-scale runs. Condensation of IV, V, and 1,4-diaminopiperazine with various aldehydes and ketones gave the corresponding dialkylaminoalkylhydrazones (VI, VII, Tables IV, V), which were reduced with lithium aluminum hydride to the appropriate 1-(dialkylaminoalkyl)-2-(1-phenyl-2-propyl)hydrazines (VII, Table VI), 1-substituted-2-(2-diethylaminoethyl)hydrazines (Table VII), and 1,4-bis(phenylalkylamino)piperazines (IX, Table VIII). Upon acid treatment, 1-(2-diethylaminoethyl)-2-(1-phenyl-2-propyl)hydrazine (X) undergoes a unique scission of the nitrogen–nitrogen bond to give amphetamine (XII) in good yield. Details of this novel reaction are discussed. A summary of the biological properties of the aminoalkylhydrazines is presented.

Interest in the synthesis of aminoalkylhydrazines was evidenced as early as 1925 when Sommer and coworkers[1] reported the synthesis of 1-hydrazino-2-aminoethane from ethylenediamine and hydroxylamine-O-sulfonic acid. In recent years research on related compounds has skyrocketed,[2–20] sparked in part by reports of the usefulness of isoniazid, nitrofurantoin, iproniazid, phenelzine, (1-phenyl-2-propyl)-hydrazine, and analogous materials in medicine. During the past decade we have prepared a variety of novel aminoalkylhydrazines for biological evaluation and for use as synthetic intermediates, many of which are the subject of this report.

The addition of acrylonitrile to 1,1-dimethylhydrazine (Ia) utilizing the procedure of Hinman and Rosene[21] gave 3-(2,2-dimethylhydrazino)propionitrile (IIa) as a colorless liquid, b.p. 54–55° (0.6 mm.), $n^{25}D$ 1.4387 (lit.[21] b.p. 80–90° (3 mm.), $n^{25}D$ 1.441), in yields from 53 to 56% in three runs. The addition of acrylonitrile to 1,1-diethylhydrazine (Ib), 1-amino-

$$\underset{\text{I}}{R_1R_2NNH_2} + CH_2{=}CHCN \longrightarrow \underset{\text{II}}{R_1R_2NNHCH_2CH_2CN} \xrightarrow{LiAlH_4} \underset{\text{III}}{R_1R_2NNH(CH_2)_3NH_2}$$

R_1R_2N = (a) $N(CH_3)_2$ (b) $N(C_2H_5)_2$ (c) $N(CH_2)_5$ (d) $N[(CH_2)_2]_2NCH_3$

piperidine (Ic), and 1-amino-4-methylpiperazine (Id) afforded 3-(2,2-diethylhydrazino)propionitrile (IIb), 3-(1-piperidinoamino)propionitrile (IIc), and 3-(4-methyl-1-piperazinylamino)propionitrile (IId), respectively. The hygroscopic nitriles were difficult to analyze and in most instances were not completely characterized, but following distillation were reduced to the corresponding amines III (**1–4**, Table I) with lithium aluminum hydride in anhydrous ether. Compound IId was characterized by formation of 3-(*p*-butoxyphenyl)-1-(2-cyanoethyl)-1-(4-methyl-1-piperazinyl)-2-thiourea upon heating with *p*-butoxyphenylisothiocyanate.

The condensation of hydrazine with alkyl halides usually gives a mixture of monoalkyl and asymmetric dialkylhydrazines.[22] With long chain alkyl chlorides,

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