condensed with chloromercuri-6-benzamidopurine.[8] After removal of the blocking groups with methanolic sodium methoxide and neutralization with glacial acetic acid the product crystallized. Additional product was obtained by concentration of the mother liquor to a sirup which was triturated with water. The combined material was recrystallized three times from water to give 820 mg. (20% from β-D-allose pentaacetate) of product. This material decomposed between 273–315°, $[\alpha]^{25}D$ −8.0° (*c* 3.25, 1 *N* HCl). Paper chromatography with solvent 1 gave an R_{fad} 1.66 and 0.13 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 258 mμ (ε 14,700); λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.05, 6.25, 6.3, 6.7 (NH and purine ring), 9.0, 9.15, 9.35, 9.55 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5 \cdot 0.5H_2O$: C, 43.13; H, 5.23; N, 22.87; H_2O, 2.94. Found: C, 43.14; H, 5.12; N, 22.70; H_2O, 2.86.

D-Altropyranose Pentaacetate.—D-Altrose (7.67 g., 42.6 mmoles) was acetylated as described.[3,22] A thick sirup (16.0 g.) was obtained which crystallized easily but the product was not isolated.

9-α-D-Altropyranosyladenine.—Tetraacetylaltropyranosyl chloride was prepared from the pentaacetate[7b,d] and condensed with chloromercuri-6-benzamidopurine.[8] Following removal of the blocking groups with methanolic sodium methoxide, the picrate was prepared.[11] After recrystallization from water 7 g. (42%) of the picrate was obtained as tiny needles which decomposed between 182–270°, $[\alpha]^{25}D$ +9° (*c* 3.40, dimethylformamide).

Anal. Calcd. for $C_{17}H_{18}N_8O_{12}$: C, 38.79; H, 3.45; N, 21.29. Found: C, 37.94; H, 3.48; N, 23.21.

9-α-D-Altropyranosyladenine was regenerated from the picrate[11] and crystallization occurred on concentration of the aqueous solution. After recrystallizing twice from water 1.38 g. (15%) of product was obtained, m.p. 156–158°, $[\alpha]^{25}D$ +22.0° (*c* 3.50, 1 *N* HCl); R_{fad} 1.65 in solvent 1 and 0.14 in solvent 2; ultraviolet and infrared spectra: $\lambda_{max}^{H_2O}$ 259 mμ (ε 16,000); λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.1, 6.3, 6.7 (NH and purine ring), and 9.0–9.55 (C–O–C, C–O–H).

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.25; H, 5.12; N, 23.52.

Polarimetric Studies.—A solution of 16–20 mg. of each nucleoside in 1 ml. of hot water was prepared, cooled to room temperature, and 0.65 ml. of 0.25 *M* sodium metaperiodate was added. The volume was adjusted to 2 ml. and the solution was permitted to stand in the dark for 40–48 hr. until a constant optical rotation was reached. The solution was treated with 80 mg. of sodium borohydride and, after 0.5 hr., 1 ml. of 10% acetic acid solution was very carefully added. After the bubbling had ceased and the solution had reached room temperature, the specific rotation was again determined. The results of these determinations are shown in Table I in which 9-β-D-mannopyranosyladenine was used as the reference compound.

Polarimetric studies of the periodate oxidation product derived from 9-β-D-mannopyranosyladenine have been reported (lit.[8] $[\alpha]^{25}D$ −20.8°) as have the oxidation and reduction products of adenosine (lit.[12] $[\alpha]^{20}D$ +66°) and 9-α-D-ribofuranosyladenine (lit.[12] $[\alpha]^{20}D$ −66°).

Synthetic Schistosomicides. VI. 4-Substituted 1-(Dialkylaminoalkylamino)naphthalenes[1]

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Various 4-substituted 1-(dialkylaminoalkylamino)naphthalene compounds have been prepared as potential antischistosome agents. 4-[(2-Diethylaminoethyl)amino]-1-naphthol (XIV) was synthesized according to the following scheme. Treatment of 2,2,2-trifluoro-N-(4-hydroxy-1-naphthyl)acetamide (X) with dihydropyran gave 2,2,2-trifluoro-N-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}acetamide (XI), which upon alkaline hydrolysis afforded 4-[(tetrahydropyran-2-yl)oxy]-1-naphthylamine (XII). Alkylation of XII with 2-chlorotriethylamine gave N,N-diethyl-N′-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}ethylenediamine (XIII), which was converted into XIV with acid. Two N-(dialkylaminoalkyl)napthionic acids (XVa and b) were prepared from 1-naphthol-4-sulfonic acid and the appropriate dialkylaminoalkylamine. N,N-Diethyl-N′-(4-chloro, 4-methoxy-, 4-methylthio-, and 4-phenylthio-1-naphthyl)ethylenediamine (XVIa–d) were synthesized by alkylation of the appropriate 4-substituted 1-naphthylamine with 2-chlorotriethylamine. Various N,N-dialkyl-N′-(4-nitro-1-naphthyl)alkylenediamines (XVIIa–d) were obtained by the condensation of 1-chloro-4-nitronaphthalene with the requisite dialkylaminoalkylamine. Treatment of N,N-diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine (XVIIa) with methyl iodide and benzyl chloride gave the corresponding quaternary salts XVIIIa and b.

1,4-Naphthoquinones inhibit the glycolysis of adult *Schistosoma mansoni in vitro* at low concentrations.[2,3] A similar mode of action has been postulated for the 1-amino-4-naphthylazo schistosomicides (Ia and b),[1,4–7] which can exist in quinoid form (IVa and b), and for various potential metabolites thereof (Chart I).[1]

The initial step of one likely metabolic pathway involves reduction to the corresponding 1,4-naphthalenediamines (IIa and b).[1] Indeed, certain N-(dialkylaminoalkyl)-1,4-naphthalenediamines (IIb) are more active against schistosomes and less toxic for mice than the N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)alkylenediamines from which they are derived.[1] However, the 1,4-naphthalenediamines are very susceptible to oxidation and are unstable both in acidic and in basic media. Although the decomposition products of the naphthalenediamines have not yet been isolated and characterized, it is likely that oxidation products such as the N′-(1,4-dihydro-4-imino-1-naphthylidene)-N,N-dialkylalkylenediamines (IIIb) are formed initially. Subsequent hydrolysis would lead to N-[(dialkylamino)alkyl]-1,4-naphthoquinone imines (VIb) or 1,4-naphthoquinone imine (VIa), and ultimately to 1,4-naphthoquinone (IX). Similarly, oxidation of 1,4-naphthalenediamine (IIa)[2] would afford

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

(2) E. Bueding, L. Peters, and J. F. Waite, *Proc. Soc. Exptl. Biol. Med.*, **64**, 111 (1947).

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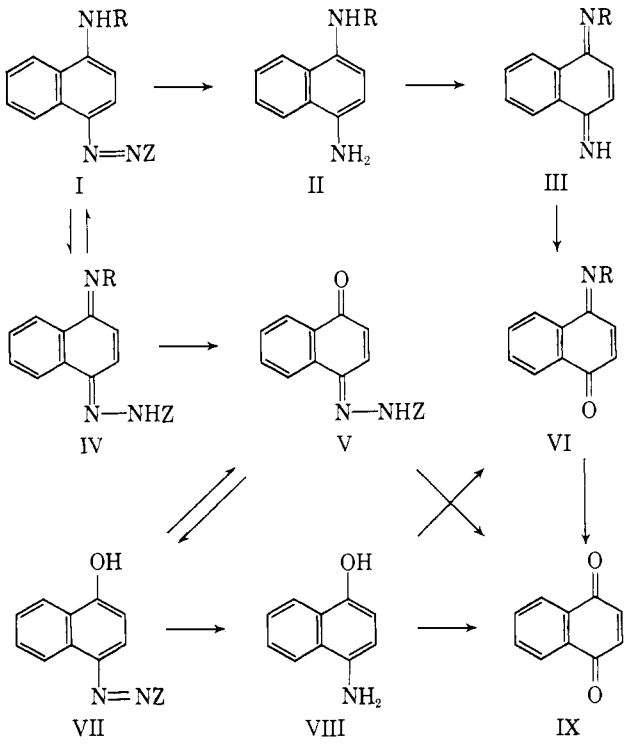
(7) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, in preparation.

CHART I



Z = aryl or heterocyclic
a, R = -H
b, R = -YNR$_1$R$_2$

1,4-naphthoquinone diimine (IIIa), which upon hydrolysis would give 1,4-naphthoquinone imine (VIa) and 1,4-naphthoquinone (IX). It should be noted that N,N-dialkyl-N′-(4-azo-1-naphthyl)-N′-alkylalkylenediamines,[5-7] which cannot exist in quinoid form, and N-(dialkylaminoalkyl)-N-alkyl-1,4-naphthalenediamines,[1] which presumably cannot be oxidized to quinone imines, are devoid of antischistosome activity.

Further, the 1-amino-4-naphthylazo compounds (Ia and b) may undergo metabolic alteration *via* hydrolysis of their tautomeric hydrazone forms (IVa and b). Although relatively stable in basic media, many of these azo compounds hydrolyze at an appreciable rate in an acid environment.[8-10] Presumably 4-azo-1-naphthols (VII), which can also exist in quinoid form (V), are the initial products formed, but under certain conditions naphthoquinones have also been isolated from the reaction mixtures.[9,11-14] Alternatively, reductive scission of the 4-azo-1-naphthols can occur with the formation of 4-amino-1-naphthol (VIII), which following oxidation and hydrolysis could also lead to 1,4-naphthoquinone (IX) *via* 1,4-naphthoquinone imine (VIa).

In contrast, 2-amino-1-naphthylazo compounds decompose in acid media to give 2-naphthylamine and phenol.[9] This phenomenon may explain the therapeutic failure of the 2-(dialkylaminoalkylamino)-1-naphthylazo compounds in experimental schistosomiasis.[5-7]

The theoretical implication of 4-amino-1-naphthol and the 4-azo-1-naphthols in the metabolic sequence stimulated an investigation of the antischistosome properties of these compounds. Several representative 4-azo-1-naphthols exhibited detectable activity against *S. mansoni* in the mouse but were much less active than the 4-azo-1-naphthylamines. Thus, 4-phenylazo-1-naphthol and *p*-(4-hydroxy-1-naphthylazo)benzenesulfonic acid monosodium salt (orange I), which were the most promising compounds tested, effected only a 23–36% reduction of live worms when administered in the diet for 14 days at doses ranging from 487–661 mg./kg./day.[15] 4-Amino-1-naphthol hydrochloride (VIII) killed adult *S. mansoni in vitro* at drug concentrations of 12.5 and 50 γ/ml., but was ineffective in mice when given orally at the maximum tolerated dose.[15]

The thesis that potent antischistosome activity is associated with the capacity of naphthylamines to exist in quinoid form prompted the synthesis of various 4-substituted 1-(dialkylaminoalkylamino)naphthalene derivatives in which the substituent at position 4 might be expected either to facilitate or block quinone formation. The preparation of 4-[(2-diethylaminoethyl)amino]-1-naphthol (XIV) was of particular interest because it represented a likely precursor of quinone imines of structure VIb.

Several routes to 4-[(2-diethylaminoethyl)amino]-1-naphthol (XIV) were investigated, including the alkylation of 4-amino-1-naphthol (VIII) with 2-chlorotriethylamine,[16] the hydrobromic acid scission of N,N-diethyl-N′-(4-methoxy-1-naphthyl)ethylenediamine (XVIb), and the reaction of 1,4-naphthalenediol with N,N-diethylethylenediamine.[17] None was satisfactory. However, XIV was prepared successfully according to the scheme outlined in Chart II. Acylation of 4-amino-1-naphthol (VIII) with trifluoroacetic anhydride in dimethylformamide gave 2,2,2-trifluoro-N-(4-hydroxy-1-naphthyl)acetamide (X), which upon treatment with dihydropyran gave 2,2,2-trifluoro-N-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}acetamide (XI). Hydrolysis of XI with sodium methoxide in methanol afforded 4-[(tetrahydropyran-2-yl)oxy]-1-naphthylamine (XII). Alkylation of XII with 2-chlorotriethylamine in ethyl acetate gave N,N-diethyl-N′-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}ethylenediamine (XIII), which was converted into XIV by acid hydrolysis in aqueous methanol. Ultraviolet absorbence maxima of XIV, in methanol, occur at 339 and 252 mμ. Addition of alkali to the methanolic solution causes an immediate and drastic alteration of the spectrum, followed by progressive changes indicative of decomposition.

1-(Dialkylaminoalkylamino)naphthalenes substituted at position 4 with chloro, methoxy, methylthio, phenylthio, nitro, or sulfonic acid groups (Table I) were synthesized by three routes. The N-(dialkylaminoalkyl)-naphthionic acids (XVa and b) were prepared from 1-

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(13) H. T. Bucherer and M. Hayashi, *ibid.*, **132**, 302 (1931).
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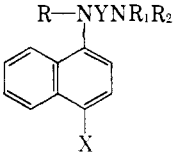
(15) P. E. Thompson, unpublished results, Parke, Davis and Company, Ann Arbor, Mich.
(16) Farbenfabriken Bayer Aktiengesellschaft, British Patent 868,884 (May 25, 1961).
(17) L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **6**, 637 (1963).

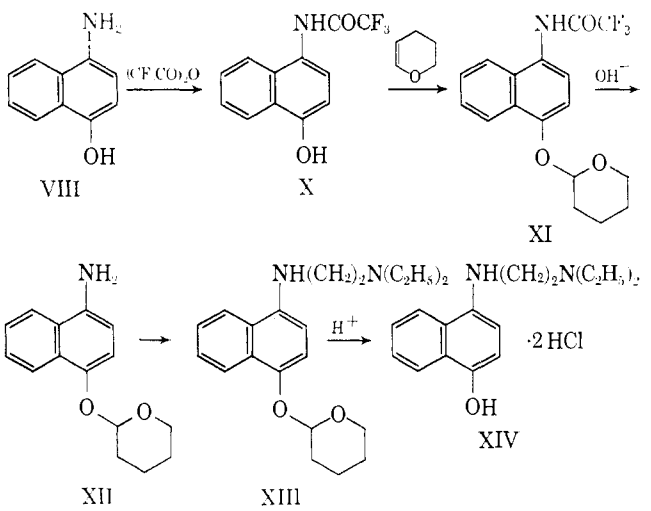
TABLE I
4-SUBSTITUTED 1-(DIALKYLAMINOALKYLAMINO)NAPHTHALENES



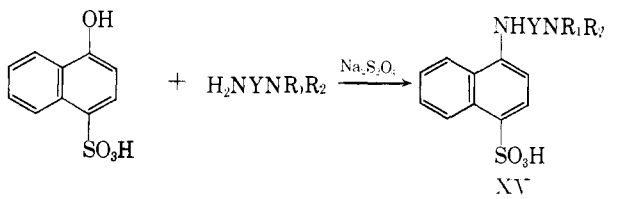
Compd. no.	R	Y	R_1R_2	X	B.p. (mm.) or m.p., °C.	Yield purified, %
XVa	H	$(CH_2)_3$	$(CH_3)_2$	SO_3H	290–293	23
XVIa	H	$(CH_2)_2$	$(C_2H_5)_2$	Cl	177–181	29
XVIIa	H	$(CH_2)_2$	$(C_2H_5)_2$	NO_2	80–83	80
XVb	H	$(CH_2)_2$	$(C_2H_5)_2$	SO_3H	275–278	22
XVIIb	CH_3	$(CH_2)_2$	$(C_2H_5)_2$	NO_2	188–190 (40)	63
XVIIc	H	$(CH_2)_3$	$(C_2H_5)_2$	NO_2	82–84	37
XVIb	H	$(CH_2)_2$	$(C_2H_5)_2$	OCH_3	177–180	44[d]
XVIc	H	$(CH_2)_2$	$(C_2H_5)_2$	SCH_3	162–164 (0.2)[e]	22
XVIId	H	$CH[(CH_2)_2]_2CH$	$(CH_3)_2$	NO_2	145–148	11
XVId	H	$(CH_2)_2$	$(C_2H_5)_2$	SC_6H_5	145–149	6

[a] A, dimethylformamide–water; B, ethanol; C, ethanol–ether; D, not crystallized; E, 2-propanol. [b] Cl: Calcd., 30.41; Found, 30.25. [c] Cl: Calcd., 20.54; Found, 20.39. [d] Base, b.p. 147–149° (0.3 mm.), $n^{25}D$ 1.5837. *Anal.* Calcd. for $C_{17}H_{24}N_2O$: C, 74.94; H,

CHART II

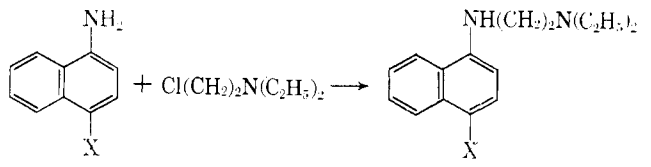


naphthol-4-sulfonic acid and the appropriate dialkylaminoalkylamine utilizing sodium hydrosulfite.[17] N,N-



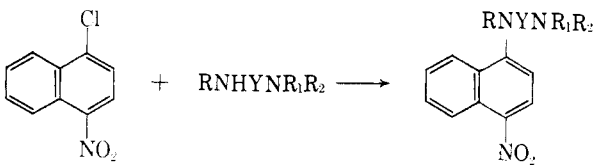
a, Y = $(CH_2)_4$; R_1R_2 = $(CH_3)_2$
b, Y = $(CH_2)_2$; R_1R_2 = $(C_2H_5)_2$

Diethyl-N′-(4-chloro-, 4-methoxy-, 4-methylthio-, and 4-phenylthio-1-naphthyl)ethylenediamine (XVIa–d) were prepared by alkylation of the appropriate 4-



XVIa, X = Cl
b, X = OCH_3
c, X = SCH_3
d, X = SC_6H_5

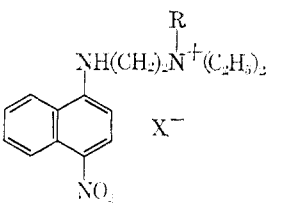
substituted 1-naphthylamine with 2-chlorotriethylamine.[17] Various N,N-dialkyl-N′-(4-nitro-1-naphthyl)-alkylenediamines (XVIIa–d) were obtained by the condensation of 1-chloro-4-nitronaphthalene with the requisite dialkylaminoalkylamine. Quaternization of N,N-



XVII

XVIIa, R = H; Y = $(CH_2)_2$; R_1R_2 = $(C_2H_5)_2$
b, R = CH_3; Y = $(CH_2)_2$; R_1R_2 = $(C_2H_5)_2$
c, R = H; Y = $(CH_2)_3$; R_1R_2 = $(C_2H_5)_2$
d, R = H; Y = $CH[(CH_2)_2]_2CH$; R_1R_2 = $(CH_3)_2$

diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine (XVIIa) with methyl iodide and benzyl chloride gave diethylmethyl[2-(4-nitro-1-naphthylamino)ethyl]ammonium iodide (XVIIIa) and benzyl diethyl[2-(4-nitro-1-naphthylamino)ethyl]ammonium chloride (XVIIIb), respectively.



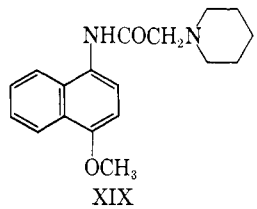
XVIIIa, R = CH_3; X = I
b, R = $CH_2C_6H_5$; X = Cl

N-(4-Methoxy-1-naphthyl)-1-piperidineacetamide (XIX), a relative of XVIb in which a carbonyl group is substituted for the methylene group adjacent to the naphthylamine, was prepared from 4-methoxy-1-naphthylamine by treatment with chloroacetic anhydride followed by amination of the intermediate 2-chloro-N-(4-methoxy-1-naphthyl)acetamide with piperidine.

The 4-substituted 1-(dialkylaminoalkylamino)naphthalene compounds were tested in mice against a Puerto

Procedure	Purification solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	A	$C_{15}H_{20}N_2O_3S$	58.42	58.41	6.54	6.65	9.09	9.04
II	B	$C_{16}H_{21}ClN_2 \cdot 2HCl$[b]	54.95	54.95	6.63	6.68	8.01	8.05
III	E	$C_{16}H_{21}N_3O_2$	66.87	66.80	7.37	7.34	14.62	14.53
I	A	$C_{16}H_{22}N_2O_3S$	59.60	59.53	6.88	6.79	8.69	8.57
III	D	$C_{17}H_{23}N_3O_2$	67.75	67.83	7.69	7.77	13.94	14.05
III	E	$C_{17}H_{23}N_3O_2$	67.75	67.88	7.69	7.69	13.94	13.89
II	C	$C_{17}H_{24}N_2O \cdot 2HCl$[c]	59.13	59.22	7.59	7.68	8.11	8.05
II[f]	D	$C_{17}H_{24}N_2S$	70.78	71.49	8.38	8.55	9.71	9.34
III	E	$C_{18}H_{23}N_3O_2$	68.98	69.15	7.40	7.32	13.41	13.60
II[f]	E	$C_{22}H_{26}N_2S \cdot HCl$	68.28	68.53	7.03	7.05	7.24	6.68

8.88; N, 10.28. Found: C, 74.96; H, 8.91; N, 10.27. [e] $n^{25}D$ 1.6130. [f] The sodium salt of the starting naphthylamine was formed in xylene using a 50% sodium hydride dispersion in oil.



XIX

Rican strain of *S. mansoni*[15,18] by Dr. Paul E. Thompson and co-workers of these laboratories. None of these exhibited significant antischistosome activity following drug-diet administration to mice in doses ranging from 136–564 mg./kg./day for 14 days. No satisfactory explanation is evident for the surprising therapeutic failure of 4-[(2-diethylaminoethyl)amino]-1-naphthol (XIV).

The compounds described in the present communication were also tested against several other parasites and against representative fungi and bacteria. Compounds XIV, XVIa and d, and XVIIc were amebicidal *in vitro* when incubated for 48 hr. with the UC or 200F strain of *Entamoeba histolytica* at drug concentrations ranging from 20–40 γ/ml.[19] By comparison, paromomycin is active in the range of 2–10 γ/ml.[19] *In vitro*, nine compounds (XIII, XIV, XVIa and b, XVIIa, c, and d, and XVIIIa and b) were lethal to *Streptococcus pyogenes* (C 203) at concentrations of 5–20 γ/ml., two compounds (XIV and XVIIIb) were lethal against *Staphylococcus aureus* (UC-76) at concentrations of 10–20 γ/ml., and six compounds (XVIa–c, XVIIa and c, and XVIIIb) were lethal to *Mycobacterium tuberculosis* (H37Rv) at concentrations of 0.63–20 γ/ml. None exhibited promising activity in experimental animals.

Experimental[20]

2,2,2-Trifluoro-N-(4-hydroxy-1-naphthyl)acetamide (X).—A solution of 300 g. (1.43 moles) of trifluoroacetic anhydride in 150 ml. of dimethylformamide was added with stirring to a mixture of 264 g. (1.35 moles) of 1-amino-4-naphthol hydrochloride, 189 ml. (1.35 moles) of triethylamine, and 300 ml. of dimethylformamide. The temperature of the reaction mixture rose to 65° during the addition. Stirring was continued while the mixture was heated to 80°, then cooled. The reaction mixture was stirred into 7 l. of an ice–water mixture and the precipitate that separated was collected and washed thoroughly with water. The crude product was crystallized twice from ethanol–water (decolorizing charcoal) to give 112 g. (33%) of off-white needles, m.p. 202–205°.

Anal. Calcd. for $C_{12}H_8F_3NO_2$: C, 56.48; H, 3.16. Found: C, 56.55; H, 3.28.

2,2,2-Trifluoro-N-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}acetamide (XI).—To a mixture of 112 g. (0.44 mole) of 2,2,2-trifluoro-N-(4-hydroxy-1-naphthyl)acetamide (X) and 375 ml. of dihydropyran was added 4 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was warmed for 10 min., cooled, and filtered. The crude product was crystallized twice from benzene giving 102.5 g. (72%) of colorless crystals, m.p. 171–174°.

Anal. Calcd. for $C_{17}H_{16}F_3NO_3$: C, 60.17; H, 4.75. Found: C, 60.30; H, 4.86.

4-[(Tetrahydropyran-2-yl)oxy]-1-naphthylamine (XII).—2,2,2-Trifluoro-N-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}-acetamide (XI) (71 g., 0.21 mole) was dissolved in a mixture of 125 ml. of 2 *N* sodium methoxide in methanol and 10 ml. of water. The mixture was allowed to stand at room temperature for 10 days. Methanol (125 ml.) and water (200 ml.) were added and the mixture was flushed with nitrogen and refrigerated. The solid that separated was collected, washed with methanol–water, and dried *in vacuo* at 30°, 27.7 g., m.p. 92–>120°. A second crop weighing 9.7 g., m.p. 91–>120°, was obtained by dilution of the filtrate with water. The crude materials were crystallized twice from cyclohexane (decolorizing charcoal) to give 25.2 g. (49%) of pale lavender crystals, m.p. 94–96°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.75. Found: C, 74.49; H, 7.07; N, 5.82.

N,N-Diethyl-N'-{4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl}ethylenediamine Monohydrochloride (XIII).—To a solution of 22 g. (0.09 mole) of 4-[(tetrahydropyran-2-yl)oxy]-1-naphthylamine (XII) in 250 ml. of boiling ethyl acetate was added dropwise with stirring 13 g. (0.096 mole) of 2-chlorotriethylamine and the mixture was boiled under reflux for 24 hr. The mixture was cooled and the off-white solid that separated was collected by filtration, dried *in vacuo*, and crystallized from methanol–ether; yield, 7.4 g.; m.p. 133–136° dec. The residue obtained by concentration of the ethyl acetate solution was triturated with anhydrous ether and crystallized twice from methanol–ether to give 13.7 g. of a second crop, m.p. 130–134° dec; total yield, 21.1 g. (62%).

(18) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1963).

(19) 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).

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

Anal. Calcd. for $C_{21}H_{30}N_2O_2 \cdot HCl$: C, 66.56; H, 8.24; N, 7.39. Found: C, 66.53; H, 8.36; N, 7.41.

4-[(2-Diethylaminoethyl)amino]-1-naphthol Dihydrochloride (XIV).—N,N-Diethyl-N′-[4-[(tetrahydropyran-2-yl)oxy]-1-naphthyl]ethylenediamine monohydrochloride (XIII) (12.0 g., 0.0317 mole) was dissolved in 125 ml. of warm methanol and to it was added a solution of 25 ml. (0.05 mole) of 2 *N* HCl in 25 ml. of methanol. After 30 min., 200 ml. of 2-propanol was added and the mixture was refrigerated for 4 hr. The colorless crystalline solid thus obtained was collected by filtration, washed successively with cold 2-propanol and anhydrous ether, and dried *in vacuo* at 60° for 18 hr., 8.6 g. (82%), m.p. 208–212° dec.

Anal. Calcd. for $C_{16}H_{22}N_2O \cdot 2HCl$: C, 58.00; H, 7.30; Cl, 21.40; N, 8.45. Found: C, 58.09; H, 7.41; Cl, 21.48; N, 8.67.

Preparation of 4-Substituted 1-(Dialkylaminoalkylamino)-naphthalenes (XVa and b, XVIa–d, XVIIa–d, Table I). Method I.—A mixture of 100 g. (0.41 mole) of sodium 1-naphthol-4-sulfonate, 51 g. (0.44 mole) of 2-diethylaminoethylamine, 71 g. (0.41 mole) of sodium hydrosulfite, and 500 ml. of water was heated at 150° in a bomb for 8 hr. Upon cooling, the contents of the bomb were removed and the solid that had separated was collected by filtration and dried. Crystallization from a dimethylformamide–water mixture afforded N-(2-diethylaminoethyl)naphthionic acid as off-white needles, m.p. 275–278°.

Method II.—A mixture of 120 g. (0.7 mole) of 4-methoxy-1-naphthylamine, 120 g. (0.7 mole) of 2-chlorotriethylamine hydrochloride, 193 g. (1.4 moles) of anhydrous potassium carbonate, and 1 l. of toluene was stirred and boiled under reflux for 18 hr. and cooled. A solution of 100 g. of sodium hydroxide in 1 l. of water was added and the toluene layer was separated. The aqueous layer was extracted with toluene and the combined toluene solutions were dried over anhydrous potassium carbonate. Volatile materials were removed *in vacuo* and the residue was distilled in high vacuum through a 25-cm. Vigreux column. The product (83 g., 44%) was obtained as a viscous liquid, b.p. 147–149° (0.3 mm.), $n^{25}D$ 1.5837.

The hydrochloride salt was prepared by bubbling hydrogen chloride into an ether solution of the base. The oily precipitate that separated solidified after standing for 18 hr. and was collected and crystallized from ethanol–ether.

Method III.—A mixture of 45.8 g. (0.22 mole) of 1-chloro-4-nitronaphthalene and 77 g. (0.66 mole) of 2-diethylaminoethylamine was heated on a steam bath for 15 min. at which time an exothermic reaction occurred and the temperature rose to 140°. Heat was removed for 15 min. and the mixture was subsequently heated on a steam bath for 1 hr. Volatile materials were removed *in vacuo* on a steam bath and the residue was warmed with 750 ml. of water containing an excess of ammonium hydroxide. Upon cooling, the oily precipitate solidified and was collected and crystallized twice from 2-propanol. N,N-Diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine was obtained as yellow platelets, m.p. 80–83°.

In the case of N,N-diethyl-N′-methyl-N′-(4-nitro-1-naphthyl)-ethylenediamine, the crude base failed to crystallize and the product was distilled *in vacuo* through a 15-cm. Vigreux column.

Diethylmethyl[2-(4-nitro-1-naphthylamino)ethyl]ammonium Iodide (XVIIIa).—A mixture of 10 g. (0.035 mole) of N,N-diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine and 100 g. (0.705 mole) of methyl iodide was boiled under reflux for 2 hr. and cooled. The mixture was diluted with anhydrous ether and the solid was collected by filtration and dried. Two crystallizations from methanol gave 9.8 g. (66%) of orange needles, m.p. 173–175°.

Anal. Calcd. for $C_{17}H_{24}IN_3O_2$: C, 47.56; H, 5.63; N, 9.79. Found: C, 47.63; H, 5.97; N, 9.65.

Benzyldiethyl[2-(4-nitro-1-naphthylamino)ethyl]ammonium Chloride (XVIIIb).—To a solution of 7.2 g. (0.025 mole) of N,N-diethyl-N′-(4-nitro-1-naphthyl)ethylenediamine in 100 ml. of acetonitrile–ether was added a solution of 9.6 g. (0.076 mole) of benzyl chloride in 50 ml. of acetonitrile, and the mixture was boiled under reflux for 17 hr. and cooled. The mixture was concentrated to a small volume and the residue was triturated with anhydrous ether. A solid separated which was collected, dried, and crystallized twice from ethanol–ethyl acetate. The yellow needles thus obtained weighed 5.2 g. (50%), m.p. 191–194° dec.

Anal. Calcd. for $C_{23}H_{28}ClN_3O_2$: C, 66.73; H, 6.82; N, 10.15. Found: C, 66.92; H, 6.95; N, 10.09.

4-(Phenylthio)-1-naphthylamine.—4-Nitro-1-naphthyl phenyl sulfide[23] (17.4 g., 0.062 mole) was hydrogenated in methanol (250 ml.) over 2 g. of Raney nickel at an initial hydrogen pressure of 3.87 kg./cm.^{2}. The catalyst was removed by filtration and the filtrate was concentrated to dryness on a steam bath. The resulting brown oil solidified upon standing at room temperature for 3 days, 14.5 g. (82%). Crystallization of a small sample from ethanol–ether gave lavender crystals, m.p. 218–220°.

Anal. Calcd. for $C_{16}H_{13}ClNS$: C, 66.77; H, 4.90; N, 4.87. Found: C, 66.71; H, 4.85; N, 4.83.

2-Chloro-N-(4-methoxy-1-naphthyl)acetamide.—To a solution of 17.3 g. (0.1 mole) of 4-methoxy-1-naphthylamine in 250 ml. of benzene was added with stirring a solution of 17.1 g. (0.1 mole) of chloroacetic anhydride in 50 ml. of benzene. A thick purple solid separated immediately. The mixture was stirred and heated on a steam bath for 2 hr. and cooled. The solid was collected and dried, 21.0 g., m.p. 162–165°. The crude product was crystallized twice from ethanol (decolorizing charcoal) to give 13.2 g. (53%) of pale blue needles, m.p. 191–192°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.85; N, 5.61. Found: C, 62.47; H, 4.83; N, 5.61.

N-(4-Methoxy-1-naphthyl)-1-piperidineacetamide (XIX).—A mixture of 5.0 g. (0.002 mole) of 2-chloro-N-(4-methoxy-1-naphthyl)acetamide and 150 ml. of piperidine was stirred and boiled under reflux for 20 hr., filtered hot, and the filtrate was concentrated *in vacuo* to 70 ml. The residue was poured into a mixture of water and ice and allowed to stand for 2 hr. The solid was collected, washed with ether, and dried. Crystallization from aqueous ethanol gave 5.0 g. (84%) of pale lavender needles, m.p. 83–84°.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.30; H, 7.52; N, 9.58.

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(23) H. H. Hodgson and E. Leigh, *J. Chem. Soc.*, 1094 (1939).