Reduction of 119 g (0.5 mole) of ethyl 2-(*p*-methoxyphenoxy)-butyrate with 10.6 g (0.28 mole) of $LiAlH_4$ was effected in 1 l. of Et_2O to give 94 g (95%) of crude 2-(*p*-methoxyphenoxy)-1-butanol; glpc, 99%; nmr (CCl_4), δ 0.90 ppm (t, 3, J = 7 Hz, CH_3CH_2CH).

A mixture of 52 g (0.26 mole) of 2-(*p*-methoxyphenoxy)-1-butanol, 7.8 ml of pyridine, and 27 g (0.1 mole) of PBr_3 was heated at 95–110° for 2 hr and then stirred at room temperature for 16 hr giving 39 g (52%) of 1-[1-(bromomethyl)propoxy]-4-methoxybenzene: bp 106–113° (0.6 mm); glpc, 97%. *Anal.* ($C_{11}H_{15}BrO_2$) C, H, Br.

1-(4-Bromobutoxy)-4-propoxybenzene.—Alkylation of 100 g (0.66 mole) of *p*-propoxyphenol with 1,4-dibromobutane (339 g, 1.57 moles) was effected in Me_2CO in the presence of K_2CO_3.[36] Distillation of the crude product gave 25 g of forerun and 95.6 g (50%) of material: bp 143–155° (0.5–1 mm); glpc, 98%; the nmr peaks were as expected. *Anal.* ($C_{13}H_{19}BrO_2$) C, H, Br.

4-Bromobutyl Cyclohexyl Ether.—Alkylation of 50 g (0.5 mole) of cyclohexanol as the Na salt (NaH) with 162 g (0.75 mole) of 1,4-dibromobutane was effected in a benzene–toluene mixture. Distillation gave 44 g (38%) of product, bp 56–67° (0.1 mm); the nmr peaks were as expected. *Anal.* ($C_{10}H_{19}BrO$) C, H, Br.

5-Bromopentyl Phenyl Sulfide.—Thiophenol (55 g, 0.5 mole) was alkylated with 1,5-dibromopentane (345 g, 1.5 moles) in absolute EtOH containing 27 g (0.5 mole) of $NaOCH_3$.[36] Distillation of crude product gave 37 g (28%) of material: bp 120–140° (0.3 mm); glpc, 95%; uv, λ_{max}^{MeOH} 254 mμ (ε 8700); the nmr peaks were as expected. *Anal.* ($C_{11}H_{15}BrS$) Br.

In addition, 34 g of 1,5-di(phenylthio)pentane was obtained: bp 177–192° (0.3 mm); uv, λ_{max}^{MeOH} 254 mμ (ε 15,000).

(36) Reference 23, pp 226–228.

Acknowledgment.—We wish to express appreciation to Mr. William M. Pearlman for performing the catalytic hydrogenations; to Mrs. Elizabeth C. Y. Huang for some experimental work; to Mr. C. E. Childs and his associates for the microanalytical data; to Dr. J. M. Vandenbelt, Mr. R. B. Scott, Mr. E. J. Schoeb, and Mrs. Carola Spurlock for nmr, ir, and uv analyses; and to the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for the antiradiation test data.

Synthetic Schistosomicides. X. Bis(4-arylazo-1-naphthylamines)

EDWARD F. ELSLAGER, DAVID B. CAPPS, DIANNE H. KURTZ, AND DONALD F. WORTH

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106

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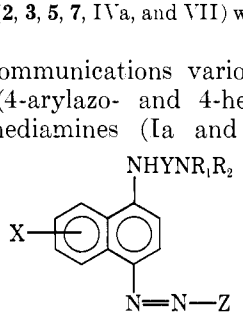
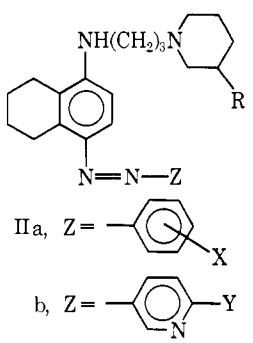
Fifteen bis(4-arylazo-1-naphthylamines) were synthesized for evaluation as potential antischistosomal and antimycobacterial agents. Various N,N-[bis(phenyleneazo-1,4-naphthylene)]bis(N′,N′-dialkylalkylenediamines) (III) were prepared by coupling a tetrazotized dianiline derivative with the appropriate N,N-dialkyl-N′-1-naphthylalkylenediamine. Likewise, several bis[(4-phenylazo-1-naphthylamino)alkyl]amines (IVa–c) were obtained from benzenediazonium chloride and the corresponding bis[(1-naphthylamino)alkyl]amines. Condensation of diazotized N-[4-(4-amino-1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide (VII) with an N,N-dialkyl-N′-1-naphthylalkylenediamine followed by alkaline hydrolysis of the intermediate trifluoroacetamides afforded a series of N′,N′-diethyl-N‴,N‴-dialkyl-N,N″-[1,4-naphthylenebis(azo-1,4-naphthylene)]bis(alkylenediamines) (IXa–c). Five compounds (1, **2**, and IXa–c) effected a 94–100% reduction of live *Schistosoma mansoni* in mice at drug-diet doses ranging from 110–692 mg/kg daily for 14 days. Six compounds (**2**, **3**, **5**, **7**, IVa, and VII) were active against *Mycobacterium tuberculosis* $H_{37}Rv$ *in vitro*.

In previous communications various N-mono- and N,N-dialkyl-N′-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (Ia and b) and related



Ia, Z = Ar
b, Z = Het



IIa, Z =

b, Z =

substances were reported to have strong therapeutic effects against *Schistosoma mansoni*[1–7] and *Schistosoma japonicum*[8] in experimental animals. Further, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo- and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (IIa and b) are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *Mycobacterium lepraemurium in vitro* and in mice.[9,10] In a further extension of this work, representative bis(4-arylazo-1-naphthylamines) were synthesized for antischistosomal and antimycobacterial evaluation. Several of the bis(4-arylazo-1-naphthylamines) showed good activity against *S. mansoni* in mice.

A group of N,N-[bis(phenyleneazo-1,4-naphthylene)]-bis(N′,N′-dialkylalkylenediamines) (III) (Table I) was prepared by coupling a tetrazotized dianiline derivative with the appropriate N,N-dialkyl-N′-1-naph-

(1) Previous paper: L. M. Werbel, E. F. Elslager, and D. F. Worth, *J. Med. Chem.*, **11**, 950 (1968).

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

(3) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

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

(5) E. F. Elslager, D. B. Capps, and L. M. Werbel, *ibid.*, **7**, 658 (1964).

(6) E. F. Elslager and D. B. Capps, *ibid.*, **7**, 663 (1964).

(7) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *ibid.*, **9**, 378 (1966).

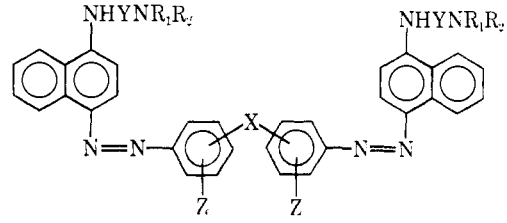
(8) S. T. Ch'en, I. F. Ch'en, P. C. Kun, Y. C. Hu, J. H. Yao, and T. H. Chou, *Yao Hsueh Hsueh Pao*, **13**, 30 (1966).

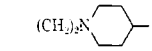
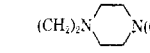
(9) Y. T. Chang, *Antimicrobial Agents Chemotherapy 1965*, 465 (1966).

(10) L. M. Werbel, E. F. Elslager, M. W. Fisher, Z. B. Gavrilis, and A. A. Phillips, *J. Med. Chem.*, **11**, 411 (1968).

TABLE I

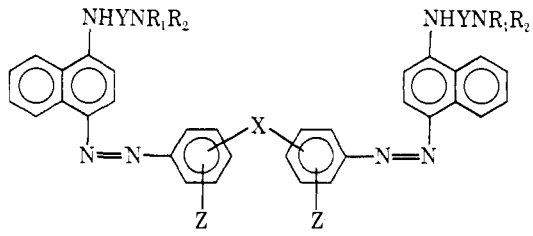
N,N-[BIS(PHENYLENEAZO-1,4-NAPHTHYLENE)]BIS(N',N'-DIALKYLALKYLENEDIAMINES)[a]



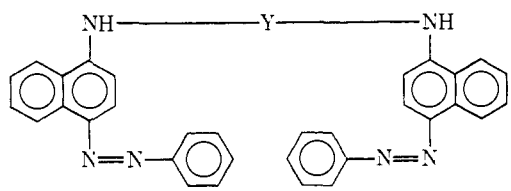
No.	YNR$_1$R$_2$	Position, bridge attachment	X	Z	Mp, °C[b]	Yield purified, %	Purifn solvent	Formula	Analyses[c]
1	$CHCH_3CH_2N(CH_3)_2$	4	SS_+	H	112 dec	86	DMF–H_2O	$C_{42}H_{46}N_8S_2$	C, H, N
2	$(CH_2)_3N(CH_3)_2$	3	$^-ON{=}N-$	H	188–192	28	$CHCl_3$–Et_2O	$C_{42}H_{46}N_{10}O\cdot HCl$	C, H, Cl, N
3		4	O	H	134 dec	60	DMF–H_2O	$C_{46}H_{50}N_8O_4\cdot 0.5H_2O$	C, H, N, H_2O
4	$(CH_2)_2N(CH_3)_3$	4	CH=CH	H	275–277	97	DMSO	$C_{48}H_{52}N_8\cdot 0.5H_2O$	C, H, N, H_2O
5		4		3-OCH_3	218–221	18	$CHCl_3$–*i*-PrOH	$C_{50}H_{60}N_{10}O_4\cdot 0.5H_2O$	C, H, N, H_2O
6	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	4	S	H	98 dec	69	DMF–H_2O	$C_{50}H_{62}N_8S$	C, H, N
7	$CHCH_3(CH_2)_3N(C_2H_5)_2$	4	CH_2	H	76 dec	80	DMF–H_2O	$C_{51}H_{64}N_8$	C, H, N
8	$(CH_2)_2N[CH(CH_3)_2]_2$	4	$O(CH_2)_2O$	H	154–156	78	Me_2CO	$C_{55}H_{72}N_8O_2$	C, H, N

[a] The compounds ranged from orange-red to dark green in color.

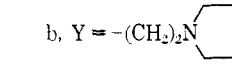
thylalkylenediamine[11] in aqueous ethanol. Likewise, N,N'-[methyliminobis(trimethylene)]bis(4-phenylazo-1-naphthylamine) (IVa), 1,4-bis[2-(4-phenylazo-1-naphthylamino)ethyl]piperazine (IVb), and 1,4-bis[2,2-dimethyl-3-(4-phenylazo-1-naphthylamino)propyl]-piperazine (IVc) were obtained by the condensation of diazotized aniline with N,N'-[methyliminobis(trimethylene)]bis(1-naphthylamine), 1,4-bis[2-(1-naphthylamino)ethyl]piperazine, and 1,4-bis[2,2-dimethyl-3-(1-naphthylamino)propyl]piperazine, respectively. The intermediate N,N'-[methyliminobis(trimethylene)]bis(1-naphthylamine) was prepared from 3,3'-diamino-N-methyldipropylamine, 1-naphthol, and $Na_2S_2O_4$ under Bucherer conditions,[11] while 1,4-bis[2-(1-naphthylamino)ethyl]piperazine was obtained by alkylation of piperazine with N-(2-bromoethyl)-1-naphthylamine.[11] Reductive alkylation of 2 moles of 1-naphthylamine with $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,4-piperazinedipropionaldehyde afforded 1,4-bis[2,2-dimethyl-3-(1-naphthylamino)propyl]piperazine.

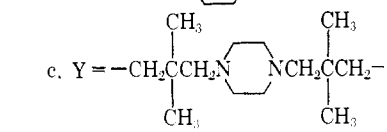


III

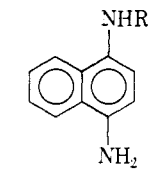


IVa, Y = $-(CH_2)_3NCH_3(CH_2)_3-$

b, Y = 

c, Y = 

The synthesis of N,N''-[1,4-naphthylenebis(azo-1,4-naphthylene)]bis(N',N'-dialkylalkylenediamines) of structure IX was of particular interest. Assuming that the azo functions in IX undergo reductive scission *in vivo*,[4] 2 moles of an N-(dialkylaminoalkyl)-1,4-naphthalenediamine (Va) and 1 mole of 1,4-naphthalenediamine (Vb) would be formed. The diamines Va have



Va, R = YNR$_1$R$_2$
b, R = H

been postulated[4] to be metabolites of the N,N-dialkyl-N'-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines[2,3,7] and exhibit potent antischistosome activity *in vitro* and in mice,[4] while 1,4-naphthalenediamine (Vb) kills adult *S. mansoni in vitro* at concentrations as low as 25 μg/ml.[12]

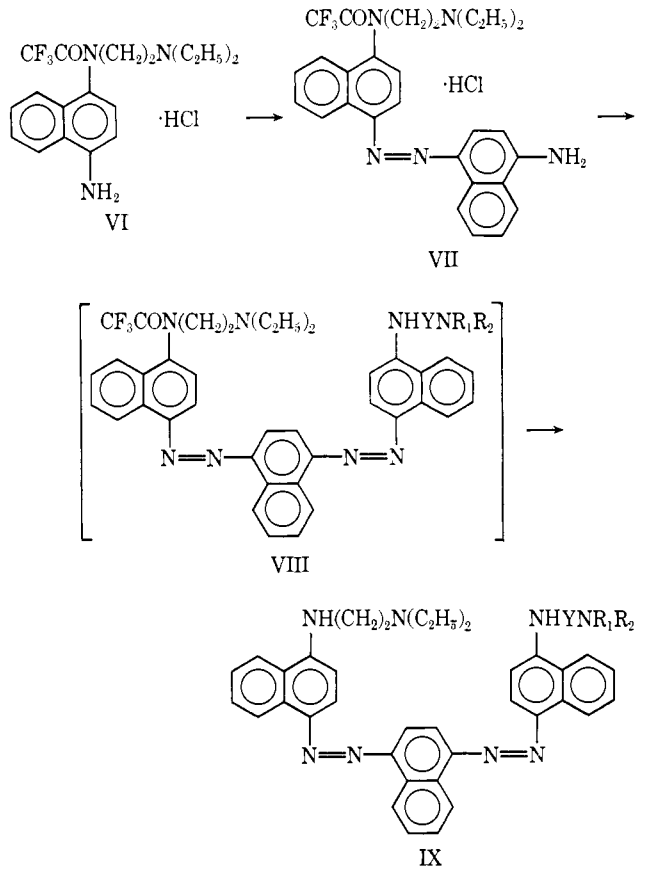
Since the action of nitrous acid on various aromatic diamines leads to the formation of undesirable by-products,[13] the preparation of compounds of structure IX was approached according to the scheme outlined in Chart I. N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VI)[7] was diazotized and coupled with 1-naphthylamine to give N-[4-(4-amino-1-naphthylazo)-1-naphthyl]-N-(2-

(11) 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).

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

(13) For a brief summary, see K. H. Saunders, "The Aromatic Diazocompounds and Their Technical Applications," Edward Arnold and Co., London, 1949, pp 21, 30.

CHART I



a, YNR_1R_2 = $(CH_2)_2N(C_2H_5)_2$; b, YNR_1R_2 = $(CH_2)_2N[CH(CH_3)_2]_2$; c, YNR_1R_2 = $CH_2C(CH_3)_2CH_2N(C_2H_5)_2$

diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VII). Compound VII was then diazotized and condensed with N,N-diethyl-N′-1-naphthylethylenediamine,[11] N,N-diisopropyl-N′-1-naphthylethylenediamine,[11] and N,N-diethyl-N′-1-naphthyl-2,2-dimethyl-1,3-propanediamine[11] to give the intermediate N-(2-diethylaminoethyl)-2,2,2-trifluoro-N-[4-(naphthylazo)-1-naphthyl]acetamides (VIIIa–c). The intermediate trifluoroacetamides VIIIa–c were not purified but were hydrolyzed directly with methanolic NaOH to give N,N′′-[1,4-naphthylenebis(azo-1,4-naphthylene)]-bis(N′,N′-diethylethylenediamine) (IXa), N′,N′-diethyl-N′′′,N′′′-diisopropyl-N,N′′-[1,4-naphthylenebis-(azo-1,4-naphthylene)]bis(ethylenediamine) (IXb), and N,N-diethyl-N′-(4-{4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1-naphthylazo}-1-naphthyl)-2,2-dimethyl-1,3-propanediamine, respectively.

The bis(4-arylazo-1-naphthylamines) described in the present communication were tested in mice against a Puerto Rican strain of *Schistosoma mansoni*[2,14] by Dr. Paul E. Thompson and co-workers of these laboratories. Drugs were given in a powdered diet for 14 days and drug amounts are expressed as free base. The most promising bis(4-arylazo-1-naphthylamines) (**1**, **2**, and IXa–c) effected a 94–100% reduction of live schistosomes in mice at doses ranging from 110 to 692 mg/kg/day when administered in the diet for 14 days.[15] Compounds **5**–**7** produced a 47–83% reduction in live worms at doses of 244–534 mg/kg. It is noteworthy that **1**, **2**, and IXa–c completely eliminated worms from a markedly higher percentage of the infected mice than lucanthone hydrochloride,[14,16] the tris(*p*-aminophenyl)-carbonium salts,[14,17] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[18,19] N-[5-(*p*-aminophenoxy)pentyl]phthalimide,[20] or 3-[4-(3-chloro-*p*-tolyl)-1-piperazinylcarbonyl]acrylic acid[2,21] under comparable experimental conditions. Surprisingly N,N′′-[heptamethylenebis(oxy-*p*-phenyleneazo-1,4-naphthylene)]bis(N′,N′′′-diisopropylethylenediamine) (**8**), which might be expected to cleave *in vivo* and simultaneously release the two active moieties N-(2-diethylaminoethyl)-1,4-naphthalenediamine[4] and 4,4′-(heptamethylenedioxy)-dianiline,[18,19] was devoid of antischistosome activity even at high doses. Compounds VIa–c and VII were similarly inactive.

The azo compounds were also tested against representative bacteria *in vitro*, including *Streptococcus pyogenes* (C203), *Staphylococcus aureus* (UC-76), *Proteus mirabilis* (MGH-1), *Pseudomonas aeruginosa* (28), *Salmonella typhimurium* (V-31), and *M. tuberculosis* (H_{37}Rv).[10] Compounds **2**, **3**, **5**, **7**, IVa, and VII were active against *M. tuberculosis* (H_{37}Rv) at a concentration of 20 μg/ml, while **2**, **3**, **5**, and VII were active against *S. pyogenes* (C203) at the same concentration. N,N′-[Methyliminobis(trimethylene)]bis(4-phenylazo-1-naphthylamine) (IVa) was inactive against *M. tuberculosis* H_{37}Rv in mice when administered at 0.125% (116 mg/kg) in the diet for 7 days.

Experimental Section[22,23]

N,N-[Bis(phenyleneazo-1,4-naphthylene)]bis(N′,N′-dialkylalkylenediamines) (III) (**Table I**).—A solution of 4.5 g (0.011 mole) of 4,4′-(heptamethylenedioxy)dianiline dihydrochloride monohydrate[19] in 400 ml of H_2O and 4 ml of concentrated HCl was cooled to 0° and the amine was tetrazotized by the slow, portionwise addition of 1.5 g (0.022 mole) of $NaNO_2$ in 25 ml of H_2O. The mixture was stirred at 0° for 15 min and then added at 0–5° to a solution of 5.9 g (0.022 mole) of N,N-diisopropyl-N′-1-naphthylethylenediamine[11] in 800 ml of EtOH. After 10 min, the mixture was acidified with HCl and allowed to stir at room temperature for 18 hr. The royal purple mixture was made strongly alkaline with NaOH and the solid was collected by filtration and dried at 65° *in vacuo*. Crystallization of the crude product (9.0 g, 100%) from 800 ml of Me_2CO afforded 7.5 g (78%) of N,N′′-[heptamethylenebis(oxy-*p*-phenyleneazo-1,4-naphthylene)]bis(N,N′′′-diisopropylethylenediamine) (**8**) as orange crystals, mp 154–156°.

N,N′-[Methyliminobis(trimethylene)]bis(4-phenylazo-1-naphthylamine) (**IVa**).—Aniline (12.4 g, 0.128 mole) was dissolved in a mixture of 29 ml of concentrated HCl and 50 ml of ice and H_2O and diazotized at 0° by the addition of 9.3 g of $NaNO_2$. The diazonium salt solution was then added at 0–5° to a solution of 25.4 g (0.064 mole) of N,N′-[methyliminobis(trimethylene)]bis-(1-naphthylamine) in 600 ml of AcOH. A deep purple precipitate

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

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

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

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

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

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

(20) R. F. Collins, M. Davis, N. D. Edge, J. Hill, H. W. Reading, and E. R. Turnbull, *ibid.*, **14**, 467 (1959).

(21) G. Lämmler, *Z. Tropenmed. Parasitol.*, **9**, 294 (1958).

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

(23) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Water determinations by the Karl Fischer method.

formed. The mixture was stirred for 5 hr and made alkaline (cooling) with concentrated NH_4OH. The crude product was collected by filtration, washed with H_2O, and dried. It was dissolved in $CHCl_3$, and the $CHCl_3$ solution was washed (H_2O, saturated NaCl) and dried ($MgSO_4$). The $CHCl_3$ was removed *in vacuo* and the residue crystallized from DMF–*i*-PrOH. Recrystallization from DMF–*i*-PrOH gave 22.2 g (58%) of iridescent red crystals, mp 140–142°. *Anal.* ($C_{39}H_{32}N_7$) C, H, N.

1,4-Bis[2-(4-phenylazo-1-naphthylamino)ethyl]piperazine (IVb).—Aniline (3.4 g, 0.037 mole) was diazotized and coupled with 7.8 g (0.018 mole) of 1,4-bis[2-(1-naphthylamino)ethyl]-piperazine according to the procedure for IVa. The product (IVb) was obtained as tomato red crystals from DMA–*i*-PrOH, mp 259–260°, yield 8.8 g (76%). *Anal.* ($C_{40}H_{36}N_8$) H, N; C: calcd, 75.92; found, 75.46.

1,4-Bis[2,2-dimethyl-3-(4-phenylazo-1-naphthylamino)propyl]-piperazine (IVc).—Aniline (9.3 g, 0.1 mole) was diazotized and coupled with 25.4 g (0.05 mole) of 1,4-bis[2,2-dimethyl-3-(1-naphthylamino)propyl]piperazine according to the procedure for IVa. The product (IVc) was obtained as red crystals from DMF, mp 245–246°, yield 28.5 g (79%). *Anal.* ($C_{46}H_{52}N_8$) C, H, N.

N-[4-(4-Amino-1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide Monohydrochloride (VII).—A solution of 58.5 g (0.15 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VI)[7] in 750 ml of ice and H_2O containing 25.5 ml of concentrated HCl was treated with 150 ml (0.15 mole) of 1 *M* aqueous $NaNO_2$ at 0°. The red diazonium salt solution was then added to a stirred solution of 21.6 g (0.15 mole) of 1-naphthylamine in 600 ml of H_2O, 37.5 ml of concentrated HCl, and 300 ml of EtOH while maintaining the temperature below 5°. The resulting purple mixture was stirred for 2 hr at 0–5° and then made alkaline with 45 ml of concentrated NH_4OH. The dark red solid that separated was collected by filtration, washed with H_2O, dried, and crystallized from 375 ml of DMA and 2 l. of *i*-PrOH to give 45.0 g (51%) of VII as maroon crystals, mp 228–230°. *Anal.* ($C_{28}H_{28}F_3N_5O \cdot HCl$) C, H, Cl, N.

N,N′′-[1,4-Naphthylenebis(azo-1,4-naphthylene)]bis(N′,N′-diethylethylenediamine) (IXa).—The reactions were carried out in a 1.5-l. beaker cooled with an ice bath and stirred throughout. N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride[7] (VI) (19.5 g, 0.05 mole) was dissolved in a mixture containing 200 ml of ice and H_2O and 8.4 ml of concentrated HCl, and diazotized at 0–2° by the addition of 50 ml of 1 *M* aqueous $NaNO_2$. The resulting deep red solution was stirred for 5 min; 4.1 ml of concentrated HCl was then added in one portion, followed by the dropwise addition of a solution of 7.2 g (0.05 mole) of 1-naphthylamine in 50 ml of EtOH over 10 min. Ice was added followed by 50 ml (0.05 mole) of 1 *M* $NaNO_2$ over 5 min. To the resulting orange-brown mixture was subsequently added a solution of 12.2 g (0.05 mole) of N,N-diethyl-N′-1-naphthylethylenediamine[11] in 8.4 ml of concentrated HCl and 300 ml of H_2O. The deep blue suspension was stirred at 2–5° for 2 hr and then made alkaline with 20 ml (0.3 mole) of concentrated NH_4OH. The blue-black precipitate of the intermediate trifluoroacetamide VIIIa was collected by filtration, washed with 2 l. of H_2O, and dried. A sample, mp 85–100°, was submitted for microanalysis. *Anal.* ($C_{31}H_{27}F_3N_8O$) C, H, N.

The trifluoroacetamide VIIIa was dissolved in 800 ml of Me_2CO, 120 ml (0.24 mole) of 2 *N* NaOH in MeOH was added, and the mixture was stirred at room temperature for 50 hr. The iridescent green crystals that separated were collected by filtration, washed with *i*-PrOH, and suspended in H_2O containing a small amount of Dreft. The product was collected, washed (H_2O), and air dried. Crystallization from 180 ml of DMAc and 800 ml of *i*-PrOH gave 23.0 g (69% over-all) of iridescent green crystals, mp 193–195°. *Anal.* ($C_{42}H_{48}N_8$) C, H, N.

N′,N′-Diethyl-N‴,N‴-diisopropyl-N,N′′-[1,4-naphthylenebis(azo-1,4-naphthylene)]bis(ethylenediamine) (IXb).—A solution of 15.0 g (0.028 mole) of N-[4-(4-amino-1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VII) in 500 ml of EtOH, 500 ml of ice and H_2O, and 42 ml of concentrated HCl was cooled to −5° and treated with 27.6 ml (0.028 mole) of 1 *M* aqueous $NaNO_2$. To the resulting solution of the diazonium salt was added dropwise a solution of 7.2 g (0.028 mole) of N,N-diisopropyl-N′-1-naphthylethylenediamine[11] in 50 ml of EtOH. The reaction mixture was stirred at room temperature for 18 hr and the blue-black precipitate of the intermediate trifluoroacetamide VIIIb was collected by filtration, washed thoroughly with H_2O, and air dried. The trifluoroacetamide was then dissolved in a mixture of 500 ml of Me_2CO and 120 ml of 2 *N* methanolic NaOH and allowed to stir at room temperature for 48 hr. The solvent was concentrated to one-third volume and the dark blue-green crystals that separated were collected by filtration. Crystallization from 300 ml of DMF and 1 l. of *i*-PrOH gave 10.0 g (52% over-all) of iridescent green crystals, mp 194–195°. *Anal.* ($C_{43}H_{52}N_8$) C, H, N.

N,N-Diethyl-N′-(4-[4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1-naphthylazo}-1-naphthyl)-2,2-dimethyl-1,3-propanediamine (IXc).—N-[4-(4-Amino-1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (VII) (15.0 g, 0.028 mole) was diazotized and coupled with 7.9 g (0.028 mole) of N,N-diethyl-N′-1-naphthyl-2,2-dimethyl-1,3-propanediamine[11] according to the procedure for IXb. Hydrolysis of the intermediate trifluoroacetamide VIIIc with NaOH in MeOH–Me_2CO afforded 15.5 g (78% over-all) of IXc as dark green crystals from DMF–*i*-PrOH, mp 158–160°. *Anal.* ($C_{56}H_{72}N_8$) C, H, N.

N,N′-[Methyliminobis(trimethylene)]bis(1-naphthylamine).—3,3′-Diamino-N-methyldipropylamine (87.0 g, 0.6 mole), 1-naphthol (172.8 g, 1.2 moles), $Na_2S_2O_4$ (209.0 g, 1.2 moles), and 800 ml of H_2O was heated in a bomb for 8 hr at 150°, and the reaction mixture was worked up according to the procedure described in method V, ref 11. The product was obtained as pale pink plates from EtOH; mp 97–99°, yield 37.3 g (16%). *Anal.* ($C_{27}H_{29}N_3$) C, H, N.

1,4-Bis[2-(1-naphthylamino)ethyl]piperazine.—N-(2-Bromoethyl)-1-naphthylamine hydrobromide[11] (200.0 g, 0.605 mole) and anhydrous piperazine (520.0 g, 6.05 moles) were heated at 150° for 20 hr. The mixture was cooled and shaken with $CHCl_3$ and 10% aqueous NaOH. The combined $CHCl_3$ extracts were washed with H_2O and dried (K_2CO_3). The drying agent was removed by filtration, the filtrate was evaporated to dryness *in vacuo*, and the residue was slurried with Et_2O to give 71.0 g (55%) of crude product, mp 159–173°. Crystallization from Me_2CO gave 53.0 g (41%) of colorless crystals, mp 173–175°. *Anal.* ($C_{28}H_{32}N_4$) C, H, N.

1,4-Bis[2,2-dimethyl-3-(1-naphthylamino)propyl]piperazine.—A solution of α,α,α′,α′-tetramethyl-1,4-piperazinedipropionaldehyde (100.0 g, 0.39 mole), 1-naphthylamine (113.0 g, 0.79 mole), 2.0 g of *p*-toluenesulfonic acid, and 1 l. of $C_6H_5CH_3$ was heated under reflux for 2 hr while the theoretical amount of water was collected in a trap.[10] The solvent was removed *in vacuo* and the residue was taken up in EtOH and hydrogenated over 4 g of PtO_2 catalyst under an initial hydrogen pressure of 54 psig. The catalyst was removed by filtration and the filtrate was concentrated to a small volume. The residue was crystallized from dioxane to give 53.0 g (17%) of the desired product, mp 150–151°. *Anal.* ($C_{34}H_{44}N_4$) C, H, N.

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