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

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

N-(3-Bromopropyl)-1-naphthylamine Hydrobromide.—A solution of 201 g. (1.0 mole) of 3-(1-naphthylamino)-1-propanol[31] in 1.5 kg. of 48% reagent hydrobromic acid was heated under reflux for 22 hr. A greenish brown oil separated. The mixture was cooled in ice and the supernatant liquid decanted. The residue was taken up in 500 ml. of warm methanol and cooled to give 189 g. of the hydrobromide salt, m.p. 149–151°. A second crop weighing 55 g., m.p. 142–146°, was obtained by concentration of the filtrate. The total crude yield was 71%. For analysis, a sample was recrystallized twice from methanol giving off-white crystals, m.p. 152–154°.

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

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

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

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

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

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

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

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

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

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

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

Acknowledgment.—The authors wish to express their appreciation to Dr. Loren M. Long for his interest during the tenure of this work. Further, we take this opportunity to thank Dr. Paul E. Thompson, Miss Anita Bayles, Miss P. McClay, Dr. M. W. Fisher, Dr. A. L. Erlandson, and Dr. A. B. Hillegas for the biological testing; Mr. Charles E. Childs and associates for the microanalytical data; Dr. John M. Vandenbelt and associates for the spectral data; Dr. W. D. Closson and Mrs. Dianne Kurtz for the preparation of several of the compounds described herein; and Miss Carolyn Eady for assistance with the chemical nomenclature used. We also wish to acknowledge the helpful discussions with Professor Harry Mosher regarding the hydrosulfite Bucherer reaction.

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

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

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

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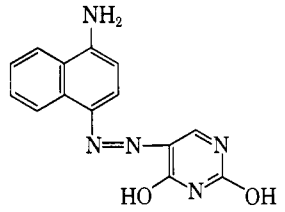
A variety of [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds have been synthesized by (1) coupling a diazotized heterocyclic amine with the appropriate 1-(aminoalkyl)naphthylamine; (2) allowing a N-(ω-haloalkyl)-4-(heterocyclicazo)-1-naphthylamine to react with the appropriate amine; (3) alkaline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

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

(1) Presented before the Division of Medicinal Chemistry, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1, 1963. Abstracts of papers, p. 15L.

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

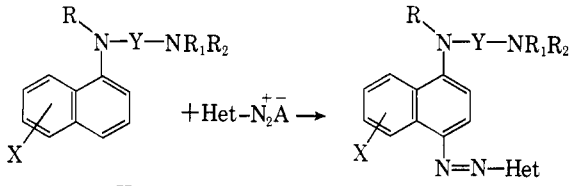
(3) E. F. Elslager and D. F. Worth, *ibid.*, **6**, 444 (1963).



I

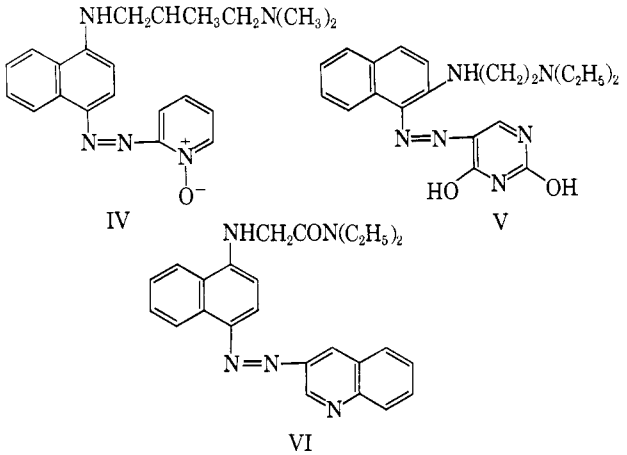
scribes the synthesis of selected members of the latter class of compounds in detail.

A majority of the [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds (III, where R, R_1, and R_2 represent a hydrogen atom or an alkyl group, Y an alkylene radical, X a hydrogen or halogen atom or alkoxy group, and Het a heterocyclic radical) were prepared by coupling a diazotized heterocyclic amine with



II III

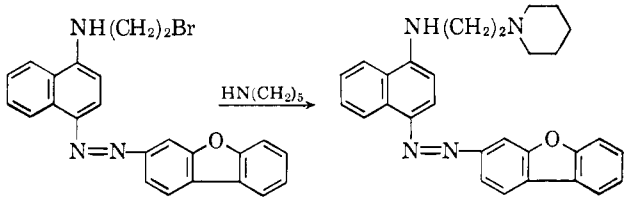
the appropriate 1-(aminoalkyl)naphthylamine[4] (II) (methods I–III). These azo compounds are summarized in Tables I–IV. In addition, the coupling of diazotized 2-aminopyridine 1-oxide with N,N,2-trimethyl-N′-1-naphthyl-1,3-propanediamine[4] and diazotized 5-aminouracil with 2-(2-diethylaminoethylamino)-naphthalene afforded 2-{4-[(3-dimethylamino-2-methylpropyl)amino]-1-naphthylazo pyridine 1-oxide (IV) and 5-[2-(2-diethylaminoethylamino)-1-naphthylazo]-uracil (V), respectively. Diazotized 3-aminoquinoline was coupled with N,N-diethyl-2-(1-naphthylamino)acetamide to give N,N-diethyl-2-[4-(3-quinolylazo)-1-naphthylamino]acetamide (VI).



IV V

VI

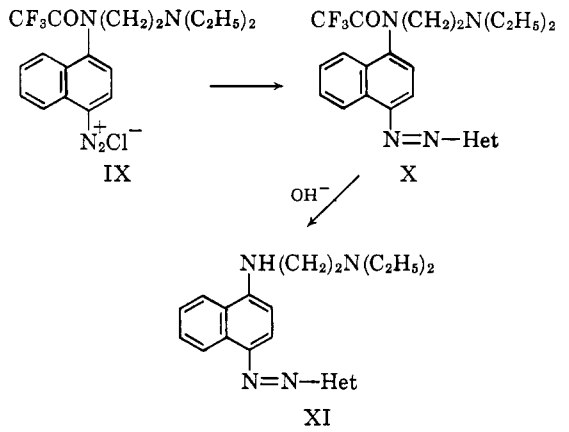
Several alternate routes for the preparation of the heterocyclic azo compounds (III) were examined, including the condensation of a N-(ω-haloalkyl)-4-(heterocyclicazo)-1-naphthylamine with an amine. Thus, condensation of N-(2-bromoethyl)-4-(3-dibenzofuranylazo)-1-naphthylamine (VII) with excess piperidine gave 1-{2-[4-(3-dibenzofuranylazo)-1-naphthylamino]ethyl}piperidine (VIII) in 82% yield (Table IV, method IV). The intermediate VII was prepared



VII VIII

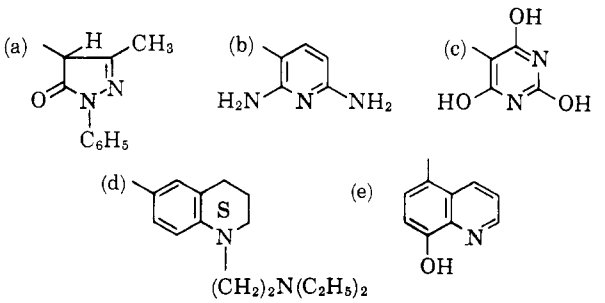
by allowing diazotized 3-aminodibenzofuran to react with 1-(2-bromoethyl)aminonaphthalene hydrobromide[4] in dilute hydrobromic acid. When the coupling reaction was carried out in hydrochloric acid, N-(2-chloroethyl)-4-(3-dibenzofuranylazo)-1-naphthylamine was obtained.

A third route employed in the synthesis of the [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds involved the coupling of diazotized N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride (IX)[5] with a heterocyclic coupling component to give the intermediate N-(2-diethylaminoethyl)-2,2,2-trifluoro-N-[4-(heterocyclicazo)-1-naphthyl]acetamides (Xa–e). Alkaline hydrolysis of Xa–e (methods V and VI) gave 4-[4-(2-diethylaminoethylamino)-1-naphthylazo]-3-methyl-1-phenyl-2-pyrazolin-5-one (XIa), 2,6-diamino-3-[4-(2-diethylaminoethylamino)-1-naphthylazo]pyridine (XIb), 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]barbituric acid (XIc), 1-(2-diethylaminoethyl)-6-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1,2,3,4-tetrahydroquinoline (XId), and 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]-8-quinolinol (XIe), respectively (Tables I–IV).



IX X XI

where Het represents



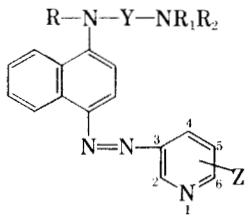
An insoluble 3-[4-(2-diethylaminoethylamino)-1-naphthylazo]pyridine salt with one-half formula weight

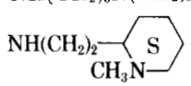
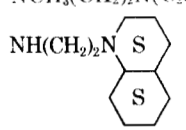
(4) L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.* **6**, 637 (1963).,

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

TABLE I

3-[4-(AMINOALKYLAMINO)-1-NAPHTHYLAZO]PYRIDINES[a]

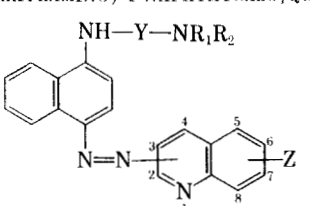


Compd. no.	—NR—Y—NR₁R₂	—Z—	M.p., °C.	Yield purified, %	Procedure	Purification[b] solvent	Formula	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found	—Nitrogen, %— Calcd.	Found	—Water, %[c]— Calcd.	Found
1	$NH(CH_2)_2NH(CH_2)_2OH$	6-Cl	165–168	81	I	A	$C_{19}H_{21}ClN_5O$	61.70	61.63	5.45	5.59	18.94	19.16		
2	$NHCH[(CH_2)_2]_2NCH_3$	H	171–172	61	I	A	$C_{21}H_{24}N_5$	73.01	72.90	6.71	6.59	20.28	20.16		
3	$NH(CH_2)_2N(C_2H_5)_2$	H	139–141	85	II	E	$C_{21}H_{25}N_5 \cdot 3HCl \cdot 3.25H_2O$[d]	48.94	48.84	6.75	6.79	13.59	13.33	11.35	10.33
4	$NH(CH_2)_2N(C_2H_5)_2$	2,6-NH_2	234 dec.	28[i]	V	F	$C_{21}H_{27}N_7 \cdot HCl \cdot 0.33H_2O$[e]	59.96	59.92	6.87	7.00	23.31	23.28	1.43	1.13
5	$NHCH_2CHOHCH_2N(C_2H_5)_2$	H	154–157	16	II	D	$C_{23}H_{27}N_5O \cdot 3HCl \cdot 0.5H_2O$	53.28	52.92	6.30	6.66	14.12	13.84	1.82	1.98
6	$NH(CH_2)_3N(CH_3)_2$	H	130–132	64	I	A	$C_{23}H_{27}N_5$	73.96	73.78	7.29	7.15	18.75	18.77		
7		H	166 dec.	18	II	C	$C_{23}H_{27}N_5 \cdot 3HCl \cdot 2.25H_2O$[f]	52.78	53.19	6.64	6.58	13.38	13.31	7.74	7.68
8	$NH(CH_2)_2N(C_2H_5)_2$	6-$O(CH_2)_3CH_3$	92–94	69	I	B	$C_{25}H_{33}N_5O \cdot 0.5H_2O$	70.06	70.14	8.00	7.87	16.34	16.41		
9	$NCH_3(CH_2)_2N(C_2H_5)_2$	6-$O(CH_2)_3CH_3$	90–95	48	II	A	$C_{26}H_{36}N_5O \cdot 2HCl \cdot H_2O$[g]	59.42	59.34	7.67	7.45	13.33	13.45		
10		6-OCH_3	214–216 dec.	29	I	A	$C_{27}H_{33}N_5O \cdot HCl \cdot 0.4H_2O$[h]	66.55	66.38	7.20	7.32	14.37	13.81	1.48	1.51

[a] The free bases range from deep orange to maroon in color; the hydrochloride salts range from orange to black in color. [b] A, 2-propanol; B, ethanol; C, methanol–2-propanol; D, ethanol–ether; E, not recrystallized; F, dimethylformamide 2-propanol. [c] Water determination by Karl Fischer method. [d] Calcd. for Cl: 20.63. Found: 20.85. [e] Calcd. for Cl: 8.43. Found: 8.30. [f] Calcd. for Cl: 20.32. Found: 20.52. [g] Calcd. for Cl: 13.49. Found: 13.95. [h] Calcd. for Cl: 7.28. Found: 7.68. [i] Yield over-all.

TABLE II

[4-(AMINOALKYLAMINO)-1-NAPHTHYLAZO]QUINOLINES[a]



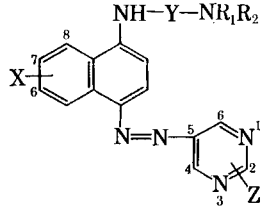
Compd. no.	—Y—NR₁R₂	Quinoline ring attachment	Z	M.p., °C.	Yield purified, %	Procedure	Purification[b] solvent	—Formula—	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found	—Nitrogen, %— Calcd.	Found	—Water, %[c]— Calcd.	Found
11	$(C_2H)_2N[(CH_2)_2]_2NH$	8	H	210 dec.	30	II	A	$C_{25}H_{26}N_6 \cdot 3HCl \cdot 2.5H_2O$	53.15	52.77	6.07	5.97	14.88	14.49	7.97	7.24
12	$(C_2H)_2N(C_2H_5)_2$	3	H	124–125	63	I	A	$C_{25}H_{27}N_5$	75.53	75.70	6.85	6.94	17.62	17.51		

13	$(CH_2)_2N(C_2H_5)_2$	6	H	186–188	22	II	B	$C_{25}H_{27}N_5 \cdot 2.5HCl \cdot 1.3H_2O$[d]	58.63	58.57	6.32	6.34	13.68	13.66	4.69	4.74
14	$(CH_2)_2N(C_2H_5)_2$	8	H	156–158	43	II	A	$C_{25}H_{27}N_5 \cdot 2HCl \cdot 3.3H_2O$[e]	56.66	56.47	6.77	6.81	13.22	13.01	11.21	10.80
15	$(CH_2)_2N(C_2H_5)_2$	5	8-OH	158–162	24[g]	VI	A	$C_{25}H_{27}N_5O$	72.61	72.87	6.58	6.54	16.94	17.05		
16	$(CH_2)_2NC_2H_5(CH_2)_4OH$	5	8-OH	190–192	73	II	C	$C_{25}H_{27}N_5O_2 \cdot 2HCl \cdot 1.25H_2O$	57.20	57.62	6.05	5.80	13.34	13.52	4.29	4.56
17	$(CH_2)_2N[(CH_2)_2]_2CHOH$	8	H	169 dec.	35	I	D	$C_{26}H_{27}N_5O$	73.38	73.04	6.40	6.47	16.46	16.36		
18	$(CH_2)_2N(C_2H_5)_2$	5	8-CH_3	119–121	70	I	C	$C_{26}H_{29}N_5$	75.88	76.08	7.10	7.14	17.02	17.23		
19	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	8	5,6-OCH_3	166–170	23	II	A	$C_{30}H_{37}N_5O_2 \cdot 3HCl \cdot 1.25H_2O$	57.14	57.25	6.63	7.11	11.10	10.54	3.57	3.75
20	$(CH_2)_2N[(CH_2)_2]_2CH(CH_2)_2N(C_2H_5)_2$	5	8-CH_3	145–147	52	II	B	$C_{33}H_{42}N_6 \cdot 3HCl \cdot 0.5H_2O$	61.82	61.76	7.23	6.91	13.11	13.33	1.40	1.10
21	$(CH_2)_2N[(CH_2)_2N(C_2H_5)_2]_2$	3	H	133–139	29	II	B	$C_{33}H_{45}N_7 \cdot 4.6HCl \cdot 4H_2O$[f]	50.84	51.55	7.45	7.12	12.58	12.37	9.24	9.20

[a] The free bases range from red to deep maroon in color; the hydrochloride salts range from brown to deep purple in color. [b] A, 2-propanol; B, methanol–2-propanol; C, ethanol; D, acetonitrile. [c] Water determination by Karl Fischer method. [d] Calcd. for Cl: 17.31. Found: 17.23. [e] Calcd. for Cl: 13.38. Found: 13.38. [f] Calcd. for Cl: 20.92. Found: 21.10. [g] Yield over-all.

TABLE III

5-[4-(AMINOALKYLAMINO)-1-NAPHTHYLAZO]PYRIMIDINES[a]

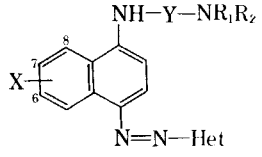


Compd. no.	X	—Y—NR_1R_2	Z	M.p., °C.	Yield purified, %	Procedure	Purification[b] solvent	Formula	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found	—Nitrogen, %— Calcd.	Found
22	H	$(CH_2)_2NH_2$	2,4-OH	204	34	I	A	$C_{16}H_{16}N_6O_2 \cdot 3.25H_2O$	50.19	49.94	5.92	5.24	21.95	21.65
23	H	$(CH_2)_2N(CH_3)_2$	2,4-OH	230–231 dec.	85	I	B	$C_{18}H_{20}N_6O_2 \cdot 1.25H_2O$ [c]	57.66	57.79	6.05	6.09	22.42	22.51
24	H	$(CH_2)_3N(CH_3)_2$	2,4-OH	215–216 dec.	56	I	C	$C_{19}H_{22}N_6O_2$	62.28	61.94	6.05	6.36	22.94	22.88
25	H	$CHCH_3CH_2N(CH_3)_2$	2,4-OH	212–213 dec.	74	I	B	$C_{19}H_{22}N_6O_2 \cdot 0.25H_2O$[d]	61.52	61.56	6.11	6.30	22.66	22.80
26	7-Cl	$(CH_2)_2N(C_2H_5)_2$	2,4-OH	211–212 dec.	70	I	H	$C_{20}H_{23}ClN_6O_2 \cdot H_2O$[i]	55.48	55.18	5.82	5.96	19.42	19.41
27	H	$(CH_2)_3NHCH(CH_3)_2$	2,4-OH	219–220	50	I	E	$C_{20}H_{24}N_6O_2$	63.14	62.98	6.36	6.38	22.09	22.25
28	H	$(CH_2)_2N(C_2H_5)_2$	2,4-OH	210–211	62	I	F	$C_{20}H_{24}N_6O_2 \cdot 0.5H_2O$[e]	61.68	61.70	6.47	6.95	21.58	21.59
29	H	$(CH_2)_2N(C_2H_5)_2$	2,4,6-OH	209–213 dec.	43[h]	VI	G	$C_{20}H_{24}N_6O_3$	60.59	60.46	6.10	6.36	21.20	21.46
30	H	$(CH_2)_2N[CH(CH_3)_2]_2$	2,4-OH	219–221	61	I	H	$C_{22}H_{28}N_6O_2$	64.68	64.40	6.91	7.21	20.58	20.71
31	H	$(CH_2)_5N(C_2H_5)_2$	2,4-OH	170 dec.	82	I	E	$C_{23}H_{30}N_6O_2$	65.37	65.19	7.16	7.37	19.89	19.82
32	H	$(CH_2)_2N[(CH_2)_3CH_3]_2$	2,4-OH	194–196 dec.	60	I	D	$C_{24}H_{32}N_6O_2$	66.02	65.85	7.39	7.07	19.25	19.04
33	H	$(CH_2)_2N[CH_2CH(CH_3)_2]_2$	2,4-OH	227–228 dec.	78	I	F	$C_{24}H_{32}N_6O_2 \cdot 0.25H_2O$	65.35	65.05	7.43	7.51	19.06	19.04
34	H	$(CH_2)_2N[CH(CH_3)_2]_2$	2,4-OCH_3	157–158	45	I	I	$C_{24}H_{32}N_6O_2$	66.02	66.27	7.39	7.12	19.25	19.27
35	H	$(CH_2)_2NC_2H_5(CH_2)_2N(C_2H_5)_2$	2,4-OH	164–167 dec.	22	II	J	$C_{24}H_{33}N_7O_2 \cdot 2.5HCl \cdot H_2O$[f,g]	49.80	49.75	6.88	6.94	16.94	16.45
36	H	$CH_2C(CH_2)_5CH_2N(C_2H_5)_2$	2,4-OH	202 dec.	49	I	F	$C_{26}H_{34}N_6O_2$	67.50	67.51	7.41	7.39	18.17	18.45
37	6-$O(CH_2)_2N(C_2H_5)_2$	$(CH_2)_2N(C_2H_5)_2$	2,4-OH	203–205	59	I	J	$C_{26}H_{37}N_7O_3$	63.00	63.32	7.52	7.67	19.79	19.57

[a] The free bases range from red to black in color. [b] A, acetone–water; B, not recrystallized; C, dimethylformamide; D, dimethylformamide–water; E, dimethylacetamide–water; F, ethanol–water; G, ethanol–dimethylformamide; H, ethanol; I, acetone; J, methanol. [c] Water determination (Karl Fischer). Calcd. for H_2O: 6.00. Found: 5.98. [d] Calcd. for H_2O: 1.21. Found: 1.08. [e] Calcd. for H_2O: 2.31. Found: 2.35. [f] Calcd. for H_2O: 6.22. Found: 6.22. [g] Calcd. for Cl: 15.31. Found: 15.01. [h] Over-all yield. [i] Calcd. for H_2O: 4.16. Found: 4.45.

TABLE IV

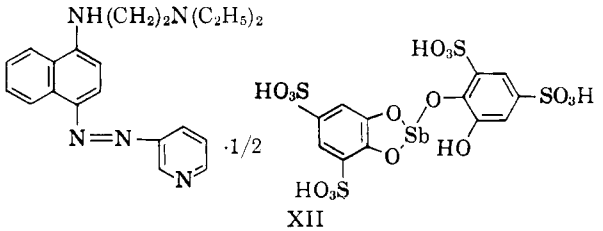
MISCELLANEOUS [4-(AMINOALKYLAMINO)-1-NAPHTHYLAZO]HETEROCYCLIC COMPOUNDS[a]



Compd. no.	X	—Y—NR1R2	Het	M.p., °C.	Yield purified, %	Procedure	Purification[b] solvent	Formula	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found	—Nitrogen, %— Calcd.	Found
38	H	$(CH_2)_2N(C_2H_5)_2$	2-Thiazolyl	135–137	38	III	A	$C_{20}H_{23}N_5S$	65.72	65.55	6.34	6.29	19.16	18.98
39		$CHCH_3CH_2N(CH_3)_2$	5-Benzotriazolyl	197–199	63	I	B	$C_{21}H_{23}N_7$	67.54	67.50	6.21	6.33	26.26	26.48
40	H	$(CH_2)_2N(C_2H_5)_2$	2,1,3-Benzothiadiazol-5-yl	126–128	37	I	C	$C_{22}H_{24}N_6S$	65.32	64.90	5.98	6.00	20.78	20.17
41	H	$(CH_2)_2N(CH_2)_4$	1,2-Benzisothiazol-5-yl	161–165	58	I	C	$C_{23}H_{23}N_5S$	68.80	68.75	5.77	5.70	17.44	17.50
42	H	$(CH_2)_3N(CH_3)_2$	5-Isoquinolyl	158–160	66	I	C	$C_{24}H_{25}N_5$	75.16	75.23	6.57	6.49	18.26	18.46
43	H	$(CH_2)_3N[(CH_2)_2]_2O$	5-Benzimidazolyl	220–223	18	I	D	$C_{24}H_{26}N_6O$	69.54	69.61	6.32	6.26	20.28	20.34
44	H	$(CH_2)_2N(C_2H_5)_2$	1,2,3,4-Tetrahydro-1,4-dioxo-5-phthalazinyl	211–213	27	I	E	$C_{24}H_{26}N_6O_2$	66.95	66.71	6.09	6.10	19.52	19.32
45	H	$(CH_2)_2N(C_2H_5)_2$	3,4-Dihydro-3-oxo-2H-1,4-benzothiazin-6-yl	213–214	45	I	C	$C_{24}H_{27}N_5OS$	66.48	66.59	6.28	6.06	16.15	16.25
46	H	$(CH_2)_2N(CH_2CH{=}CH)_2$	1H-Indazol-6-yl	73–74	27	I	C	$C_{25}H_{26}N_6 \cdot 0.33H_2O$	72.09	72.27	6.45	6.96	20.18	20.07
47	H	$(CH_2)_2N(C_2H_5)_2$	5-Isoquinolyl	132–133	74	I	C	$C_{25}H_{27}N_5$	75.53	75.80	6.85	6.87	17.62	17.43
48	H	$(CH_2)_2N(CH_2)_6$	2-Benzothiazolyl	150–153	9	III	F	$C_{25}H_{27}N_5S$	69.90	70.19	6.34	6.31	16.30	16.50
49	H	$(CH_2)_2N(C_2H_5)_2$	3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl	154–155	15[h,i]	VI	A	$C_{26}H_{30}N_6O$	70.56	70.30	6.83	7.10	18.99	18.91
50	H	$(CH_2)_2NCH_3C_2H_5$	Benzo[f]quinolin-7-yl	182–184	65	I	A	$C_{28}H_{27}N_5$	77.57	77.95	6.28	6.38	16.16	16.43
51	H	$(CH_2)_2N(C_2H_5)_2$	3-Dibenzofuranyl	160–162	58	II	B	$C_{28}H_{28}N_4O \cdot 2HCl \cdot 0.5H_2O$[c]	64.86	64.55	6.03	6.40	10.81	10.83
52	6-OCH_3	$(CH_2)_2N(C_2H_5)_2$	4-Antipyrinyl	200–202	74	II	G	$C_{28}H_{34}N_6O_2 \cdot 2HCl \cdot H_2O$[d,e]	58.23	58.33	6.63	6.52	14.55	14.44
53	H	$(CH_2)_2NCH_3(CH_2)_2N[CH(CH_3)_2]_2$	2H-Indazol-5-yl	107–109	15	I	H	$C_{28}H_{37}N_7$	71.30	71.44	7.91	7.61	20.79	21.42
54	H	$(CH_2)_2N(CH_2)_5$	3-Dibenzofuranyl	164–165	82	IV	I	$C_{29}H_{28}N_4O$	77.65	77.62	6.29	6.63	12.49	12.40
55	H	$(CH_2)_2NC_2H_5CH_2CH{=}CH_2$	Dibenzothiophene-2-yl-(5,5-dioxide)	220–223	60	I	E	$C_{29}H_{28}N_4O_2S$	70.13	70.56	5.68	5.34	11.28	11.47
56	H	$(CH_2)_2NCH_3(CH_2)_3CH_3$	Dibenzothiophene-2-yl	120–121	67	I	A	$C_{29}H_{30}N_4S$	74.64	74.93	6.48	6.34	12.01	11.96
57	H	$(CH_2)_2N[(CH_2)_2]_2N(CH_2)_2OH$	4-Antipyrinyl	181–182	60	I	A	$C_{29}H_{35}N_7O_2$	67.81	67.74	6.87	6.70	19.09	19.29
58	H	$(CH_2)_2NH(CH_2)_2N(C_2H_5)_2$	4-Antipyrinyl	206–208	69	II	G	$C_{29}H_{37}N_7O \cdot 3HCl \cdot 0.33H_2O$[f,g]	56.63	56.57	6.66	6.57	15.94	15.84
59	H	$CH[CH_2N(CH_3)_2]_2$	10-Ethylphenothiazin-3-yl (5,5-dioxide)	195–197	49	II	I	$C_{31}H_{36}N_6O_2S \cdot 3HCl$	55.89	56.30	5.90	5.59	12.62	12.51
60	H	$CH_2C(CH_3)_2CH_2N(CH_2)_5$	1-Thianthrenyl	80 dec.	93	I	E	$C_{32}H_{34}N_4S_2$	71.34	71.30	6.36	6.79	10.40	10.41

[a] The free bases range from orange to brown-black in color; the hydrochloride salts range from green to purple in color. [b] A, ethanol–water; B, ethanol; C, 2-propanol; D, chloroform–acetone; E, dimethylacetamide–2-propanol; F, acetonitrile–water; G, ethanol–2-propanol; H, cyclohexane; I, acetone; [c] Calcd. for Cl: 13.68. Found: 13.50. [d] Calcd. for Cl: 12.28. Found: 12.38. [e] Calcd. for Cl: 17.29. Found: 17.29. [f] Water (Karl Fischer). Calcd. for H_2O: 3.12. Found: 2.96. [g] Calcd. for H_2O: 0.97. Found: 0.87. [h] Intermediate N-(2-diethylaminoethyl)-2,2,2-trifluoro-N-[4-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-ylazo)-1-naphthyl]acetamide, m.p. 154–155° from acetone: *Anal.* Calcd. for $C_{28}H_{29}F_3N_6O_2$: C, 62.44; H, 5.43; N, 15.97. Found: C, 62.38; H, 5.58; N, 16.46. [i] Yield over-all.

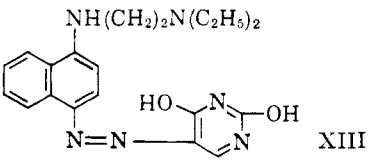
of 2-(4,6-disulfo-1,3,2-benzodioxastibiol-2-yloxy)-1-phenol-3,5-disulfonic acid (XII) was prepared by combining aqueous solutions of 3-[4-(2-diethylaminoethylamino)-1-naphthylazo]pyridine trihydrochloride and stibophen.



XII

Many of the intermediate heterocyclic compounds are available commercially.[6] Others were synthesized by known methods: 5-aminobenzimidazole,[7] 5-amino-1,2-benzisothiazole,[8] 7-aminobenzo[f]quinoline,[9] 5-amino-2,1,3-benzothiadiazole,[10] 6-amino-2H-1,4-benzothiazin-3(4H)one,[11] 5-aminobenzotriazole,[12] 3-aminodibenzofuran,[13,14] 2-aminodibenzothiophene,[14,15] 2-aminodibenzothiophene 5,5-dioxide,[14,16] 5-amino-2,4-dimethoxypyrimidine,[17] 8-amino-5,6-dimethoxyquinoline,[18] 3-amino-10-ethylphenothiazine 5,5-dioxide,[14,19] 5-aminoisoquinoline,[20] 5-amino-8-methylquinoline,[21] 2-aminopyridine 1-oxide,[22] and 1-thianthrenamine.[14,23] N-(2-Diethylaminoethyl)-1,2,3,4-tetrahydroquinoline was prepared by the alkylation of 1,2,3,4-tetrahydroquinoline with 2-diethylaminoethyl chloride according to a modification of the procedure described by Thyagarajan, et al.[24]

The [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds described in the present communication were tested in mice against a Puerto Rican strain of *Schistosoma mansoni*[2,25] by Dr. Paul E. Thompson and co-workers of these Laboratories; when indicated, expanded studies were carried out against *S. mansoni* infections in the monkey.[2,25] Among the simple (4-amino-1-naphthylazo)heterocyclic compounds described previously,[3] significant antischistosome activity was observed only with 5-(4-amino-1-naphthylazo)uracil (I). In contrast, schistosomicidal activity is widespread among the [4-(aminoalkylamino)-1-naphthylazo]heterocyclic compounds of structure III.[2] Compounds IV, VIII, XIc, XIe, and XIII and compounds 5, 8, 12, 14, 15, 28, 29, 38–41, 45, 52, and 54 (Tables I–IV), which are representative of the more promising members of the series, effected a 97–100% reduction of live schistosomes in mice at doses ranging from 85 to 750 mg./kg./day when administered in the diet for 14 days or by gavage for 10 days. It is noteworthy that worms were completely eliminated from a markedly higher percentage of the infected mice following administration of the naphthylazo compounds than after treatment with lucanthone hydrochloride,[25,26] the tris(*p*-aminophenyl)carbonium salts,[25,27] 4,4′-(heptamethylenedioxy)dianiline dihydrochloride,[28,29] N-[5-(*p*-aminophenoxy)pentyl]phthalimide,[30] or 3-[4-(3-chloro-*p*-tolyl)-1-piperazinylcarbonyl]acrylic acid[2,31] under comparable experimental conditions. 5-[4-(2-Diethylaminoethylamino)-1-naphthylazo]uracil (XIII) was selected for expanded laboratory studies and for trial



XIII

against schistosomiasis in man. Details of these studies have been reported previously.[2]

Among compounds of structure III, activity is abolished or drastically reduced when R_1 and/or R_2 represent hydrogen (compounds 1, 22, 27), when the secondary amine at position 1 is alkylated (9), or when a carbonyl group is substituted for the methylene group adjacent to the terminal aliphatic amine (VI). 5-[2-(2-Diethylaminoethylamino)-1-naphthylazo]uracil (V) was devoid of activity, as were representative 4-azo-1-(dialkylaminoalkyl)aniline derivatives.[32]

Experimental[33]

Preparation of [4-(Aminoalkylamino)-1-naphthylazo]heterocyclic Compounds (III) (Tables I–IV). Method I.—A solution of 41.2 g. (0.325 mole) of 5-aminouracil[6] in 1 l. of 50% ethanol and 85 ml. (1 mole) of concentrated hydrochloric acid was cooled to 0° and the amine diazotized by the slow, portionwise addition of 22.4 g. (0.325 mole) of sodium nitrite in 200 ml. of water. The mixture was stirred at 0° for 15 min. and then added at 0–5° to a solution of 78.7 g. (0.325 mole) of 1-(2-diethylaminoethylamino)naphthalene[4] in 1 l. of 95% ethanol containing sufficient concentrated hydrochloric acid to make the solution acidic to Congo red. The deep purple solution initially formed changed slowly to a green suspension as the hydrochloride salt gradually precipitated. The suspension was stirred for 1 hr. at 0°, the pH was adjusted to 8 by the addition of sodium hydroxide solution, and the red dye that precipitated was collected by filtration, washed thoroughly with water, and dried. Crystallization of the

(6) 4-Aminoantipyrine, 2-aminobenzothiazole, 5-amino-2,3-dihydro-1,4-phthalazinedione, 3-aminoquinoline, 8-aminoquinoline, 5-aminouracil, 2-aminothiazole, barbituric acid, 3-methyl-1-phenyl-2-pyrazolin-5-one, 8-quinolinol, and 1,2,3,4-tetrahydroquinoline were purchased from Distillation Products Industries, Rochester 3, N. Y.; 5-amino-2-butoxypyridine, 5-amino-2-methoxypyridine, 3-aminopyridine, 6-aminoquinoline, and 2,6-diaminopyridine from the Aldrich Chemical Co., Milwaukee, Wis.; 5-aminoindazole and 6-aminoindazole from the Gallard–Schlesinger Chemical Co., Garden City, N. Y.; and 5-amino-2-chloropyridine from Reilly Coal Tar Chemicals, Indianapolis, Ind.

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crude product from ethanol–water afforded 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]uracil as bright red crystals, m.p. 210–211°.

Method II.—A solution of 6.9 g. (0.1 mole) of sodium nitrite in 200 ml. of water was added slowly at 0° with stirring to a solution of 9.3 g. (0.1 mole) of 3-aminopyridine[6] in 250 ml. of water and 35 ml. of concentrated hydrochloric acid. Upon completion of the diazotization, the diazonium salt solution was added at 0–3° to a solution of 27.2 g. (0.1 mole) of 1-diethylamino-3-(1-naphthylamino)-2-propanol[4] in 1 l. of water containing 17 ml. of concentrated hydrochloric acid and 300 ml. of 95% ethanol. A deep red color formed immediately. After 3 hr., the reaction mixture was made strongly alkaline with aqueous sodium hydroxide and the organic layer that separated was extracted with chloroform. The combined chloroform extracts were washed thoroughly with water and dried over anhydrous sodium sulfate. The drying agent was collected by filtration, the chloroform was removed *in vacuo*, and the residue was dissolved in ether and treated with anhydrous hydrogen chloride. The purple hydrochloride salt that separated was collected by filtration and crystallized from an ethanol–ether mixture. After drying *in vacuo* for 48 hr. at 40°, the sample was allowed to equilibrate in the air. The reddish brown 1-diethylamino-3-[4-(3-pyridylazo)-1-naphthylamino]-2-propanol trihydrochloride hemihydrate thus obtained melts at 154–157°.

Method III.—A solution of 5.0 g. (0.05 mole) of 2-aminothiazole[6] in 250 ml. of 50% sulfuric acid was cooled to −10° and nitrosyl sulfuric acid (3.5 g. of sodium nitrite in 35 ml. of concentrated sulfuric acid) was slowly added, keeping the temperature between −10 and −5°. The resulting light brown solution was stirred for 30 min., then added to a solution of 12.7 g. (0.05 mole) of 1-[2-(1-naphthylamino)ethyl]piperidine[4] in 250 ml. of 10% sulfuric acid. The solution became dark red. After stirring for 2 hr. at 0° to −10°, 1 l. of water was added, giving a purple solution. Stirring was continued for 1 hr. and the mixture was made alkaline with aqueous sodium hydroxide with cooling. The mixture was stirred for 24 hr. and the crude dye was collected by filtration and washed with copious amounts of water to remove inorganic salts. The product was dissolved in chloroform; the chloroform solution was washed well with water, dried over anhydrous potassium carbonate, and the solvent removed *in vacuo*. The viscous residue was dissolved in acetone and precipitated by pouring the acetone solution into water. Upon heating the suspension, a crystalline solid separated which was collected by filtration and dried *in vacuo* at 45°. Crystallization from an ethanol–water mixture gave 1-{2-[4-(2-thiazolylazo)-1-naphthylamino]ethyl}piperidine as shimmering emerald green crystals, m.p. 135–137°.

Method IV.—A mixture of 4.4 g. (0.01 mole) of N-(2-bromoethyl)-4-(3-dibenzofuranylazo)-1-naphthylamine (VII) and 50 ml. of piperidine was heated on the steam bath for 1 hr. The red solution was poured into 1 l. of water and the product which precipitated was collected by filtration, washed thoroughly with water, and dried *in vacuo* at 55° for 18 hr. Crystallization from acetone gave the desired 1-{2-[4-(3-dibenzofuranylazo)-1-naphthylamino]ethyl}piperidine as glistening red crystals, m.p. 164–165°.

Method V.—To a stirred solution of 9.75 g. (0.025 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride[5] in 90 g. of water and ice containing 4.5 ml. of concentrated hydrochloric acid was added 25 ml. of *M* sodium nitrite over a period of 5 min. The mixture was stirred at 0° for 5 min. and was added immediately to a solution of 2.8 g. (0.025 mole) of 2,6-diaminopyridine[6] in 5.5 ml. of concentrated hydrochloric acid and 275 g. of ice and water. After stirring for 1 hr. at 1–12° and 1 hr. at 12–18°, a solution of 8 ml. of concentrated ammonium hydroxide diluted to 100 ml. with water was added and the orange solid which separated was collected, washed with 200 ml. of water containing a few drops of concentrated ammonium hydroxide, and dried *in vacuo*. The crude N-[4-(2,6-diamino-3-pyridylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide (12.0 g., 0.025 mole) was dissolved in 250 ml. of 2-propanol, filtered, and the filtrate was treated with 25 ml. (0.050 mole) of 2 *N* sodium hydroxide solution in methanol containing 5 ml. of water. Stirring was continued for 25 hr., after which time excess Dry Ice was added and the mixture was diluted with ice water to a volume of 1 l. The precipitate was collected and the filtrate concentrated to a volume of approximately 400 ml., during which process a precipitate appeared. It was collected by filtration and combined with the previous crop. The combined solids were dissolved in 300 ml. of 2-propanol, filtered, and the filtrate was concentrated to 250 ml. and treated with 12 ml. of a 2 *N* 2-propanol hydrogen chloride mixture. The precipitate was collected and crystallized from a dimethylformamide–2-propanol mixture to give 2,6-diamino-3-[4-(2-diethylaminoethylamino)-1-naphthylazo]pyridine monohydrochloride as black crystals, m.p. 231° dec.

Method VI.—N-(4-Amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride[5] (9.75 g., 0.025 mole) was diazotized according to the procedure described under method V. To this cold diazonium salt solution was then added 400 g. of ice, followed by the slow addition of a warm solution of 3.2 g. (0.025 mole) of barbituric acid[6] in 4.2 ml. (0.025 mole) of 6 *N* aqueous sodium hydroxide, 2.1 g. (0.025 mole) of sodium bicarbonate and 200 ml. of water. The resulting golden orange suspension was stirred for 1 hr. at 0°, a mixture of 25 ml. (0.025 mole) of *M* sodium bicarbonate and 4.2 ml. (0.025 mole) of 6 *N* aqueous sodium hydroxide was added, and the mixture was allowed to warm slowly to room temperature. Stirring was continued for 48 hr. and the brown gelatinous precipitate was collected by filtration. It was resuspended in water, stirred for 18 hr., and treated with an excess of Dry Ice. The suspended solid was collected, washed with water, and dried. Crystallization from an ethanol–dimethylformamide mixture afforded the desired 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]barbituric acid as reddish black crystals, m.p. 209–213°.

2-{4-[3-Dimethylamino-2-methylpropyl)amino]-1-naphthylazo}pyridine 1-Oxide (IV).—To a solution of 7.33 g. (0.05 mole) of 2-aminopyridine 1-oxide monohydrochloride[22] in 300 ml. of water containing 13 ml. (0.15 mole) of concentrated hydrochloric acid was added at 0° a solution of 3.5 g. (0.05 mole) of sodium nitrite in 50 ml. of water. The mixture was stirred at 0° for 0.5 hr. and added portionwise to a solution of 12.1 g. (0.05 mole) of N,N-diethyl-2-methyl-N′-1-naphthyl-1,3-propanediamine[4] in 200 ml. of 95% ethanol while maintaining the temperature between −5 and 5° by external cooling. After 0.5 hr., the reaction mixture was diluted with water to a volume of 3 l., made strongly alkaline with concentrated sodium hydroxide, and the oily precipitate that separated was extracted with several portions of chloroform. The combined chloroform extracts were washed with water, dried over anhydrous potassium carbonate, and evaporated to dryness *in vacuo* on the steam bath. The residue was crystallized from a methanol–acetonitrile mixture to give 4.6 g. (25%) of green-black irridescent crystals, m.p. 185–186° dec.

Anal. Calcd. for $C_{21}H_{29}N_5O$: C, 69.40; H, 6.93; N, 19.27. Found: C, 69.71; H, 6.91; N, 19.21.

5-[2-(2-Diethylaminoethylamino)-1-naphthylazo]uracil (V).—5-Aminouracil[6] (9.6 g., 0.0752 mole) was diazotized and coupled with 18.2 g. (0.0752 mole) of 2-(2-diethylaminoethylamino)naphthalene[34] according to the procedure described under method I. The product (V) was obtained as red crystals from dimethylformamide–water, m.p. 227–228°; yield, 15.0 g. (53%).

Anal. Calcd. for $C_{20}H_{23}N_6O_2$: C, 63.14; H, 6.36; N, 22.09. Found: C, 63.26; H, 6.23; N, 22.03.

N,N-Diethyl-2-[4-(3-quinolylazo)-1-naphthylamino]acetamide (VI).—3-Aminoquinoline (2.42 g., 0.0168 mole)[6] was diazotized and coupled with 4.30 g. (0.0168 mole) of N,N-diethyl-2-(1-naphthylamino)acetamide according to method I. The product crystallized from ethanol as red needles, 4.6 g. (67%), m.p. 167–169°.

Anal. Calcd. for $C_{25}H_{29}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 72.86; H, 6.10; N, 17.01.

N-(2-Bromoethyl)-4-(3-dibenzofuranylazo)-1-naphthylamine (VII).—A suspension of 18.3 g. (0.1 mole) of 3-aminodibenzofuran[18] in 1 l. of water containing 35 ml. (0.3 mole) of 48% aqueous hydrogen bromide was cooled to 0° and to it was added slowly a solution of 6.9 g. (0.1 mole) of sodium nitrite in 50 ml. of water while maintaining the temperature at 0–5°. The resulting yellow suspension was stirred at 0° for 0.5 hr. and was poured with vigorous stirring into a solution of 33.1 g. (0.1 mole) of N-(2-bromoethyl)-1-naphthylamine hydrobromide[4] in 300 ml. of water. The thick purple suspension thus obtained was stirred for 2 hr. at room temperature and the solid was collected and dried *in vacuo* at 55° for 18 hr. The hydrobromide salt was converted to the base by grinding in a mortar with a mixture of concentrated sodium hydroxide solution and acetone, the base was extracted with chloroform, and the red chloroform solution was dried over

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anhydrous potassium carbonate. The drying agent was removed by filtration, the chloroform filtrate was evaporated to dryness *in vacuo*, and the residue was crystallized from chloroform. The material (VII) thus obtained weighed 21.0 g. (48%), m.p. 157–158°.

Anal. Calcd. for $C_{24}H_{18}BrN_3O$: C, 64.87; H, 4.08; Br, 17.99. Found: C, 64.86; H, 4.13; Br, 17.74.

N-(2-Chloroethyl)-4-(3-dibenzofuranylazo)-1-naphthylamine.—A suspension of 18.3 g. (0.1 mole) of 3-aminodibenzofuran[13] in a mixture of 200 ml. of water and 25 ml. of concentrated hydrochloric acid was cooled to 0° and diazotized by the addition of a solution of 6.9 g. (0.1 mole) of sodium nitrite in 50 ml. of water while maintaining the temperature at 0–5°. The yellow solution thus obtained was added slowly at 5–10° to a solution of 33.1 g. (0.1 mole) of 1-(2-bromoethyl)aminonaphthalene hydrobromide[4] in 1 l. of 95% ethanol containing 20 ml. of concentrated hydrochloric acid. The thick, purple reaction mixture was diluted with water to a volume of 3 l. and stirred for 3 hr. at 0–15°. The precipitate was collected, washed thoroughly with hot dilute hydrochloric acid, and dried *in vacuo* at 65° for 48 hr.; yield, 41 g. The crude salt was suspended in dilute sodium hydroxide solution, the base was extracted with chloroform, and the chloroform extracts were dried over anhydrous potassium carbonate. The drying agent was collected, the chloroform was removed *in vacuo*, and the residue was crystallized three times from chloroform. The product was obtained as orange-red needles, m.p. 170–171°.

Anal. Calcd. for $C_{24}H_{18}ClN_3O$: C, 72.09; H, 4.54; Cl, 8.87. Found: C, 71.89; H, 4.74; Cl, 8.95.

1-(2-Diethylaminoethyl)-6-[4-(2-diethylaminoethylamino)-1-naphthylazo]-1,2,3,4-tetrahydroquinoline Dihydrochloride (XI d).—Utilizing method V, 11.7 g. (0.03 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide monohydrochloride[5] was diazotized and coupled with 7.0 g. (0.03 mole) of N-(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoline. Hydrolysis of the crude trifluoroacetamide gave 4.0 g. (23% over-all) of product as maroon crystals, m.p. 195–198.5°.

Anal. Calcd. for $C_{31}H_{44}N_6 \cdot 2HCl$: C, 64.90; H, 8.08; N 14.65; Cl, 12.36. Found: C, 64.42; H, 8.20; N, 14.53; Cl, 12.27.

N-(2-Diethylaminoethyl)-1,2,3,4-tetrahydroquinoline.—A mixture of 111.0 g. (0.834 mole) of 1,2,3,4-tetrahydroquinoline,[6] 143.5 g. (0.834 mole) of 2-diethylaminoethyl chloride hydrochloride, 230 g. (1.67 mole) of anhydrous potassium carbonate, and 800 ml. of toluene was boiled under reflux for 17 hr. Upon cooling, the reaction mixture was stirred with 10% aqueous sodium hydroxide solution, the organic layer was separated, and the aqueous layer was extracted with ether. The hydrocarbon and ether solutions were combined, washed with water, and dried over anhydrous potassium carbonate. Volatile materials were removed on a steam bath and the residue was distilled *in vacuo* through a 30-cm. Vigreux column. The product was obtained as a pale yellow oil, b.p. 98–103° (0.2 mm.), $n^{25}D$ 1.5411; yield, 56 g. (29%).

Anal. Calcd. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.61; H, 10.47; N, 12.24.

N,N-Diethyl-2-(1-naphthylamino)acetamide.—To a suspension of 16.1 g. (0.33 mole) of 50% sodium hydride dispersion in oil in 200 ml. of toluene was added a solution of 47.8 g. (0.33 mole) of 1-naphthylamine in 200 ml. of toluene. The mixture was heated under reflux for 2 hr., during which time a solid separated. The mixture was cooled to room temperature and to it was added a solution of 50 g. (0.33 mole) of N,N-diethylchloroacetamide in 200 ml. of toluene. The mixture was heated under reflux for 21 hr. and cooled. Water was added cautiously, and the organic layer was separated and dried over sodium sulfate. Volatile materials were removed *in vacuo* on a steam bath and the residue was distilled under high vacuum through a 15-cm. Vigreux column. A majority of the distillate was low boiling and appeared to be unreacted 1-naphthylamine. A high boiling fraction weighing 7.5 g., b.p. 188–190° (0.3 mm.), was obtained which solidified in the receiver. Crystallization from ethanol gave 4.3 g. (5%) of colorless plates, m.p. 92–98°.

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.17; H, 7.79; N, 11.04.

3-[4-(2-Diethylaminoethylamino)-1-naphthylazo]pyridine Salt with 1/2 F. Wt. 2-(4,6-Disulfo-1,3,2-benzodioxastibiol-2-yloxy)-1-phenol-3,5-disulfonic Acid (XII).—A solution of 2.57 g. (0.005 mole) of 3-[4-(2-diethylaminoethylamino)-1-naphthylazo]pyridine trihydrochloride·3.25 hydrate in 20 ml. of water was added with stirring to a solution of 2.71 g. (0.003 mole) of stibophen in 30 ml. of water. A dark-colored oil separated. The supernatant liquid was decanted and the residue was triturated with methanol, whereupon the salt solidified. The salt was collected, washed with methanol, and dried *in vacuo* at 60° for 18 hr.; weight, 2.85 g. (83%), m.p. > 200°.

Anal. Calcd. for $C_{21}H_{25}N_5 \cdot 0.5\ C_{12}H_9O_{16}S_4Sb$: N, 10.32; S, 9.45. Found: N, 10.10; S, 9.01.

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Preparation and Antibiotic Properties of Some Phosphinylaminopenicillanic Acids and Phosphinothioylaminopenicillanic Acids[1]

B. K. KOE, T. A. SETO, A. R. ENGLISH, AND T. J. MCBRIDE

Medical Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Conn.

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A novel class of N-substituted 6-aminopenicillanic acid derivatives exhibiting noteworthy inhibitory action against antibiotic-resistant strains of *Staphylococcus aureus* and a high degree of inertness toward penicillinase has been synthesized by the reaction of 6-aminopenicillanic acid with organophosphorus chlorides. This class consists of phosphinylaminopenicillanic acids (I, X = O) and phosphinothioylaminopenicillanic acids (I, X = S). In general, I with aryloxy groups attached to phosphorus are slightly more active *in vitro* against sensitive and resistant staphylococci than those with alkoxy groups on phosphorus, while the latter type of compounds are more effective *in vivo* in protecting mice against resistant staphylococcal infections.

An objective in the screening program of semisynthetic N-substituted 6-aminopenicillanic acids is the discovery of compounds which are effective against antibiotic-resistant strains of *Staphylococcus aureus*. The reaction of 6-aminopenicillanic acid (6-APA) with organophosphorus chlorides affords a novel series of

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