Synthesis and Antimalarial Effects of 5,6-Dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole and Related Benzimidazoles and 1*H*-Imidazo[4,5-*b*]pyridines (1,2)

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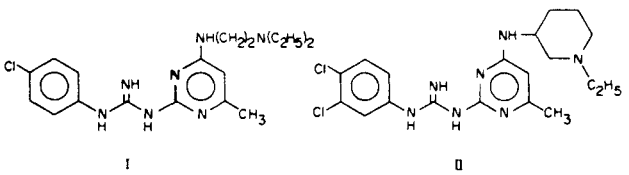
A group of fifty-five 2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]-benzimidazoles (VII) was synthesized in 3-88% yield by the condensation of the requisite 2-[(2-benzimidazolyl)amino]-4-chloro-6-methylpyrimidine (VI) with the appropriate polyamine in ethanol-hydrochloric acid or neat with excess amine containing potassium iodide. The 2-[(2-benzimidazolyl)amino]-6-methyl-4-pyrimidinol precursors (V), obtained in 11-51% yield by cyclization of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine with a suitably substituted *o*-phenylenediamine, were chlorinated with phosphorus oxychloride to give the intermediate 2-[(2-benzimidazolyl)amino]-4-chloro-6-methylpyrimidines (VI) (27-99%). Oxidation of 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**29**) with *m*-chloroperbenzoic acid gave the distal N^4'-oxide (**31**) (19%). Fusion of 2,3-diaminopyridine with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine provided 2-[(4-hydroxy-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]pyrimidine (VIII) (30%), which upon chlorination with phosphorus oxychloride (63%) followed by amination with *N*,*N*-diethylethylenediamine afforded 2-(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)-1*H*-imidazo[4,5-*b*]pyridine (X) (8%). Thirty-eight of the novel 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]-benzimidazoles possessed "curative" activity against *Plasmodium berghei* at single subcutaneous doses ranging from 20-640 mg./kg. Orally, thirty-one compounds exhibited suppressive activity against *P. berghei* comparable with or superior to the reference drugs 1-(*p*-chlorophenyl)-3-(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)guanidine (I) and quinine hydrochloride, while twelve of them were 5 to 28 times as potent as I and quinine hydrochloride. Eight compounds also displayed strong suppressive activity against *P. gallinaceum* in chicks. 5,6-Dichloro-2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]benzimidazole (**18**) showed marked activity against a cycloguanil-resistant line of *P. berghei*, and the most promising member of the series, namely 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**29**) (Q = 28), was designated for preclinical toxicological studies and clinical trial. Structure-activity relationships are discussed.

Recent confirmation that there is no apparent cross-resistance between the antimalarial drug 1-(*p*-chlorophenyl)-3-(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)guanidine (I) (3,4) and folate antagonists (5) such as chlorguanide, cycloguanil, and pyrimethamine against *P. berghei* in mice (6) sparked a rebirth of interest in the guanidinopyrimidines, and led to the discovery of an array of new congeners that were considerable more active and less toxic than I (6). Among them, 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (II) was designated for preclinical toxicological studies and clinical trial (6-8).



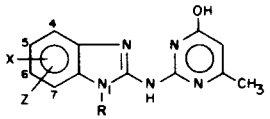
I

II

The overall promise of II and related guanidinopyrimidines spurred an investigation of hypothetical metabolites that might result from *in vivo* dehydrogenation involving the unsubstituted nitrogen of the guanidine moiety and the *ortho* position of the pyrimidine or phenyl rings. Cyclization on the pyrimidine ring would afford [[(dialkylamino)alkyl]amino]-*s*-triazolo[1,5-*a*]pyrimidines exemplified by III and IV. Such compounds have been

TABLE I

2-[(2-Benzimidazolyl)amino]-6-methyl-4-pyrimidinols

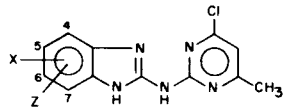


No.	X, Z	R	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	5(or 6)-Cl	H	340-345 dec.	36	DMSO	$C_{12}H_{10}ClN_5O$	52.27	52.12	3.66	3.52	25.40	24.88
2	5,6-Cl_2	H	>375	23-42	DMSO	$C_{12}H_9Cl_2N_5O$ (a)	46.47	46.43	2.92	3.11	22.58	22.74
3	5,6-Cl_2	CH_3	330-333	11	EtOH-C_6H_6	$C_{13}H_{11}Cl_2N_5O$	48.17	47.97	3.42	3.44	21.60	21.46
4	4,5,6,7-Cl_4	H	>390	24	EtOH	$C_{12}H_7Cl_4N_5O$	38.03	38.46	1.86	1.98	18.48	18.36
5	6-Cl, 4-NO_2	H	>390	42	MeOH	$C_{12}H_9ClN_6O_3$	44.94	45.01	2.83	2.97	26.20	26.34
6	4-NO_2	H	>390	51	EtOH	$C_{12}H_{10}N_6O_3$	50.35	50.19	3.52	3.47	29.37	29.26
7	5(or 6)-$(CH_2)_3CH_3$	H	251-253	37	EtOH	$C_{16}H_{19}N_5O$	64.63	64.51	6.44	6.55	23.55	23.40
8	5(or 6)-C_6H_5	H	>390	35	EtOH	$C_{18}H_{15}N_5O$	68.13	68.34	4.76	4.71	22.07	22.10

(a) *Anal.* Calcd. for Cl: 22.86. Found: 23.05.

TABLE II

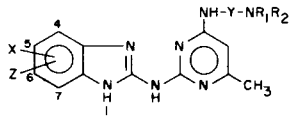
2-[(2-Benzimidazolyl)amino]-4-chloro-6-methylpyrimidines



No.	X, Z	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
9	5(or 6)-Cl	330-333 dec.	74	MeOH-H_2O	$C_{12}H_9Cl_2N_5$	49.00	48.79	3.08	3.20	23.81	23.65
10	5,6-Cl_2	343-347	78-100	MeOH	$C_{12}H_8Cl_3N_5$	43.86	43.84	2.45	2.42	21.31	21.41
11	4,5,6,7-Cl_4	316-318	75	MeOH	$C_{12}H_6Cl_5N_5$	36.26	36.27	1.53	1.72	17.62	17.82
12	5(or 6)-C_6H_5	>300	27	EtOH-H_2O	$C_{18}H_{14}ClN_5$	64.38	64.08	4.20	4.32	20.85	20.33

TABLE III

Substituted 2-[(4-[[(Dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles



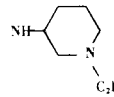
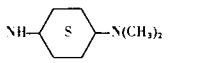
NH-Y-NR$_1$R$_2$	Procedure	X, Z	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
NH(CH$_2$)$_2$N(CH$_2$)$_4$	B	5(or 6)-Cl	213-215	40	MeCN	$C_{18}H_{22}ClN_7$	58.13	58.00	5.96	5.87	26.37	26.56
	B	5(or 6)-Cl	191-193	16	MeCN-*i*-PrOH	$C_{19}H_{24}ClN_7$	59.13	59.19	6.27	6.36	25.41	25.36
NH(CH$_2$)$_2$N(CH$_3$)(CH$_2$)$_3$CH$_3$	B	5(or 6)-Cl	167-170	68	MeCN	$C_{19}H_{26}ClN_7$	58.82	58.94	6.76	6.68	25.28	25.23
NH(CH$_2$)$_2$N(CH$_2$CH=CH$_2$)$_2$	B	5(or 6)-Cl	177-179	53	MeCN	$C_{20}H_{24}ClN_7$	60.37	60.67	6.08	6.36	24.64	24.70
NH(CH$_2$)$_2$N[CH(CH$_3$)$_2$]$_2$	B	5(or 6)-Cl	220-221	61	MeCN	$C_{20}H_{28}ClN_7$	59.76	59.90	7.02	6.92	24.39	24.15
NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	245-246	33	MeOH	$C_{18}H_{23}Cl_2N_7$	52.94	52.77	5.68	5.56	24.01	23.74
NH(CH$_2$)$_2$N(CH$_3$)(CH$_2$)$_3$CH$_3$	B	5,6-Cl$_2$	179-180	38	EtOH-H$_2$O	$C_{19}H_{25}Cl_2N_7$	54.02	53.84	5.97	5.71	23.22	23.29
NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	224-227	35	CHCl$_3$	$C_{19}H_{25}Cl_2N_7$	54.02	54.23	5.97	6.13	23.22	23.17
NH(CH$_2$)$_2$N(CH$_2$CH=CH$_2$)$_2$	B	5,6-Cl$_2$	206-209	9	EtOCH$_2$CH$_2$OH-H$_2$O	$C_{20}H_{23}Cl_2N_7$	55.56	55.07	5.36	5.39	22.68	22.63
NH(CH$_2$)$_2$N[CH(CH$_3$)$_2$]$_2$	B	5,6-Cl$_2$	285-287	46	CH$_3$CN	$C_{20}H_{27}Cl_2N_7$	55.04	54.76	6.24	6.16	22.47	22.44
NHCH(CH$_3$)CH$_2$N(CH$_3$)$_2$	B	5,6-Cl$_2$	195-200	21	ClCH$_2$CH$_2$Cl	$C_{17}H_{21}Cl_2N_7$	51.78	51.48	5.37	5.27	24.87	25.06
NHCH$_2$CH(CH$_3$)N(CH$_3$)$_2$	B	5,6-Cl$_2$	257-260	14	ClCH$_2$CH$_2$Cl	$C_{17}H_{21}Cl_2N_7$	51.78	51.91	5.37	5.65	24.87	24.50
NHCH(CH$_3$)CH$_2$N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	145-148	15	CH$_3$CN	$C_{19}H_{25}Cl_2N_7$	54.02	53.80	5.97	5.92	23.22	23.19
NHCH$_2$CH(CH$_3$)N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	252-253.5	37	MeOH	$C_{19}H_{25}Cl_2N_7$	54.02	53.78	5.97	5.79	23.22	22.95
	B	5,6-Cl$_2$	263-267	27	DMF	$C_{20}H_{25}Cl_2N_7$	55.30	55.32	5.80	5.74	22.57	22.59
NHCH(CH$_3$)(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	150-155	8	*n*-heptane	$C_{20}H_{27}Cl_2N_7$	55.04	55.05	6.24	6.09	22.47	22.21
NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	B	5,6-Cl$_2$	124-130	56	*i*-PrOH-H$_2$O	$C_{21}H_{29}Cl_2N_7 \cdot 0.85$ H$_2$O (a)	54.16	53.92	6.64	6.53	21.05	20.78
NHCH(CH$_3$)CH$_2$N(CH$_2$CH$_2$CH$_3$)$_2$	B	5,6-Cl$_2$	152-155	7	*n*-heptane	$C_{21}H_{29}Cl_2N_7$	56.00	55.88	6.49	6.43	21.77	21.60
NHCH(CH$_3$)(CH$_2$)$_3$$\overset{+}{\underset{\underset{O^-}{\vert}}{N}}$(C$_2H_5$)$_2$		5,6-Cl$_2$	175-177 dec.	19		$C_{21}H_{29}Cl_2N_7O$	54.08	53.90	6.27	6.17	21.02	21.26

TABLE III (continued)

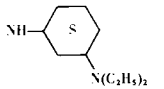
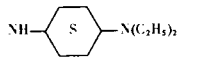
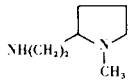
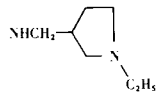
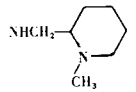
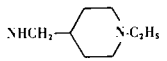
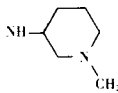
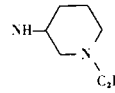
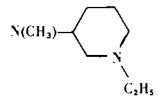
No.	NH-Y-NR_1R_2	Procedure	X, Z	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
32		B	5,6-Cl_2	140-150 indef.	17	$ClCH_2CH_2Cl$	$C_{22}H_{29}Cl_2N_7$	57.14	56.95	6.32	6.29	21.20	21.40
33		B	5,6-Cl_2	282-284	13	DMF	$C_{22}H_{29}Cl_2N_7 \cdot H_2O$ (b)	55.00	55.20	6.50	6.34	20.41	20.31
34	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$, 1-$CH_3$	B	5,6-Cl_2	200-205	42		$C_{22}H_{31}Cl_2N_7 \cdot 2HCl \cdot 0.6H_2O$ (c)	48.20	47.87	6.29	6.32	17.88	17.80
35	$NH(CH_2)_2N(CH_2)_4$	B	5,6-Cl_2	253-254	37	$ClCH_2CH_2Cl$	$C_{18}H_{21}Cl_2N_7$	53.21	53.01	5.21	5.31	24.13	24.15
36	$NH(CH_2)_3N(CH_2)_4$	B	5,6-Cl_2	216-220	32	$EtOCH_2CH_2OH$-H_2O	$C_{19}H_{23}Cl_2N_7$	54.29	54.25	5.51	5.28	23.33	23.53
37	$NH(CH_2)_2N(CH_2)_5$	B	5,6-Cl_2	265	11	$ClCH_2CH_2Cl$	$C_{19}H_{23}Cl_2N_7$	54.29	54.07	5.51	5.23	23.33	22.97
38	$NH(CH_2)_3N(CH_2)_5$	B	5,6-Cl_2	225-226	13	$ClCH_2CH_2Cl$	$C_{20}H_{25}Cl_2N_7$	55.30	55.04	5.80	5.76	22.57	22.60
39	$NH(CH_2)_2N(CH_2)_6$	B	5,6-Cl_2	249-251	41	$EtOCH_2CH_2OH$-H_2O	$C_{20}H_{25}Cl_2N_7$	55.30	55.42	5.80	5.79	22.57	22.78
40		B	5,6-Cl_2	260-261	13	$ClCH_2CH_2Cl$	$C_{19}H_{23}Cl_2N_7 \cdot 0.2$ H_2O (d)	53.83	53.79	5.56	5.35	23.13	23.17
41		B	5,6-Cl_2	256-259	32	$ClCH_2CH_2Cl$	$C_{19}H_{23}Cl_2N_7$	54.29	54.32	5.51	5.43	23.33	23.54
42		B	5,6-Cl_2	274-277	26	DMF	$C_{19}H_{23}Cl_2N_7$	54.29	54.29	5.51	5.55	23.33	23.48
43		B	5,6-Cl_2	277-279	56	DMF	$C_{20}H_{25}Cl_2N_7$	55.30	55.22	5.80	5.77	22.57	22.55
44		B	5,6-Cl_2	267-270	20	$EtOCH_2CH_2OH$-H_2O	$C_{18}H_{21}Cl_2N_7 \cdot 0.7$ H_2O (e)	51.60	51.70	5.39	5.27	23.41	23.26
45		B	5,6-Cl_2	149-151 dec.	40	EtOH	$C_{19}H_{23}Cl_2N_7$	54.29	54.11	5.51	5.44	23.33	22.99
46		B	5,6-Cl_2	252-254	15	C_6H_6	$C_{20}H_{25}Cl_2N_7$	55.30	55.42	5.80	5.83	22.57	22.37

TABLE III (continued)

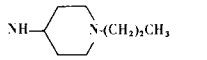
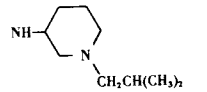
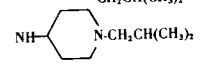
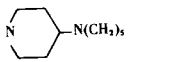
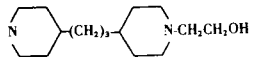
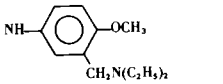
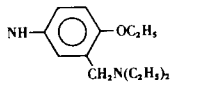
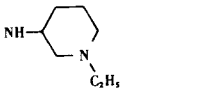
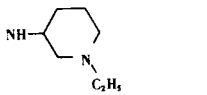
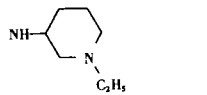
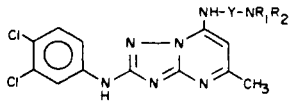
No.	NH-Y-NR_1R_2	Procedure	X, Z	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
47		B	5,6-Cl_2	246-249	3	Me_2CO	$C_{20}H_{25}Cl_2N_7$	55.30	55.37	5.80	5.90	22.57	22.48
48		B	5,6-Cl_2	257-259	22	$ClCH_2CH_2Cl$	$C_{21}H_{27}Cl_2N_7$	56.25	56.48	6.07	5.94	21.87	21.76
49		B	5,6-Cl_2	285-288 dec.	19	$ClCH_2CH_2Cl$	$C_{21}H_{27}Cl_2N_7$	56.25	55.95	6.07	6.20	21.87	21.66
50		B	5,6-Cl_2	311-314	33	DMF-H_2O	$C_{22}H_{27}Cl_2N_7$	57.39	57.16	5.91	5.84	21.30	21.61
51		B	5,6-Cl_2	254-256	59	$CHCl_3$-Et_2O	$C_{27}H_{37}Cl_2N_7O$	59.33	59.11	6.82	6.66	17.94	18.02
52		A	5,6-Cl_2	270-272	18	$CHCl_3$	$C_{24}H_{27}Cl_2N_7O$	57.60	57.33	5.44	5.27	19.59	19.66
53		A	5,6-Cl_2	275-277	48		$C_{25}H_{29}Cl_2N_7O$	58.36	58.12	5.68	5.58	19.06	19.23
54	$NH(CH_2)_2N(C_2H_5)_2$	B	4,5,6,7-Cl_4	254-256	88	MeOH	$C_{18}H_{21}Cl_4N_7$	45.30	45.69	4.44	4.31	20.55	20.61
55	$NH(CH_2)_2N(C_2H_5)_2$	B	6-Cl, 4-NO_2	274-277 dec.	52	MeOH	$C_{18}H_{23}ClN_8O_2$	51.61	51.34	5.53	5.55	26.75	26.38
56	$NH(CH_2)_2N(C_2H_5)_2$	B	4-NO_2	221-222	20	$ClCH_2CH_2Cl$	$C_{18}H_{24}N_8O_2$	56.23	56.41	6.29	6.18	29.15	29.05
57	$NH(CH_2)_2N(C_2H_5)_2$		6-Cl, 4-NH_2	225-230 dec.	34		$C_{18}H_{25}ClN_8 \cdot 2.6$ HCl·2.4H_2O (f)	41.03	40.61	6.20	5.95	21.27	20.86
58	$NH(CH_2)_2N(C_2H_5)_2$	A	H	198-199 (g)	26	C_6H_6	$C_{18}H_{25}N_7$	63.69	63.98	7.42	7.10	28.88	28.87
59		B	6-Cl, 4-NO_2	197-199	16	MeOH	$C_{19}H_{23}ClN_8O_2$	52.96	52.69	5.38	5.46	26.00	26.11
60	$NH(CH_2)_2N(C_2H_5)_2$	B	5(or 6)-CF_3	225	24	C_6H_6	$C_{19}H_{24}F_3N_7$	56.00	55.78	5.94	5.77	24.06	24.07
61		A	H	148-153	5		$C_{19}H_{25}N_7$	64.93	64.57	7.17	6.83	27.90	27.91
62		B	5(or 6)-CF_3	240-250	10	EtOH-H_2O	$C_{20}H_{24}F_3N_7 \cdot 2HCl$	48.79	48.45	5.32	5.72	19.91	19.98

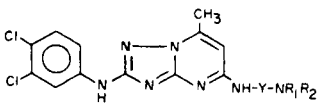
TABLE III (continued)

No.	NH-Y-NR$_1$R$_2$	Procedure	X, Z	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
63	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	B	5,6-(CH$_3$)$_2$	252-254	42	EtOH	$C_{20}H_{29}N_7$	65.37	65.35	7.95	7.66	26.68	26.87
64		B	5,6-(CH$_3$)$_2$	212-215 dec.	47	Cl$_3$CN	$C_{21}H_{29}N_7$	66.46	66.23	7.70	7.45	25.84	25.90
65	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	B	5(or 6)-(CH$_2$)$_3$CH$_3$	156-159	21	EtOAc	$C_{22}H_{33}N_7$	66.80	67.22	8.41	8.22	24.79	25.03
66	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	B	5(or 6)-C$_6$H$_5$	245-247	50	ClCH$_2$CH$_2$Cl	$C_{24}H_{29}N_7$	69.37	69.06	7.03	6.76	23.60	23.74
67		B	5(or 6)-C$_6$H$_5$	225	5	C$_6$H$_{16}$-isooctane	$C_{25}H_{29}N_7$	70.23	69.92	6.84	6.78	22.93	22.75

(a) *Anal.* Calcd. for H_2O: 3.29. Found, 2.88. (b) *Anal.* Calcd. for H_2O: 3.75. Found, 3.59. (c) *Anal.* Calcd. for H_2O: 1.97. Found, 1.68. *Anal.* Calcd. for Cl: 12.94. Found, 12.94. (d) *Anal.* Calcd. for H_2O: 0.85. Found, 0.67. (e) *Anal.* Calcd. for H_2O: 2.88. Found, 2.89. (f) *Anal.* Calcd. for H_2O: 8.21. Found, 7.63. *Anal.* Calcd. for Cl: 17.49. Found, 17.26. (g) Literature (10) reports m.p. 198-200°.



III

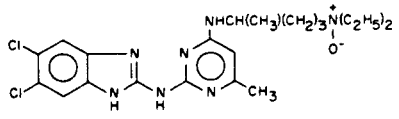


IV

described in contemporary studies in these laboratories (9). Ring closure on phenyl would give 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles (VII) which are the subject of the present communication. A cursory patent report published several decades ago (10) indeed claimed that such benzimidazoles possessed antimalarial activity. However, no details were disclosed and this lead was not pursued further with the advent of chlorguanide and its active metabolite, cycloguanil (5,6).

Chemistry.

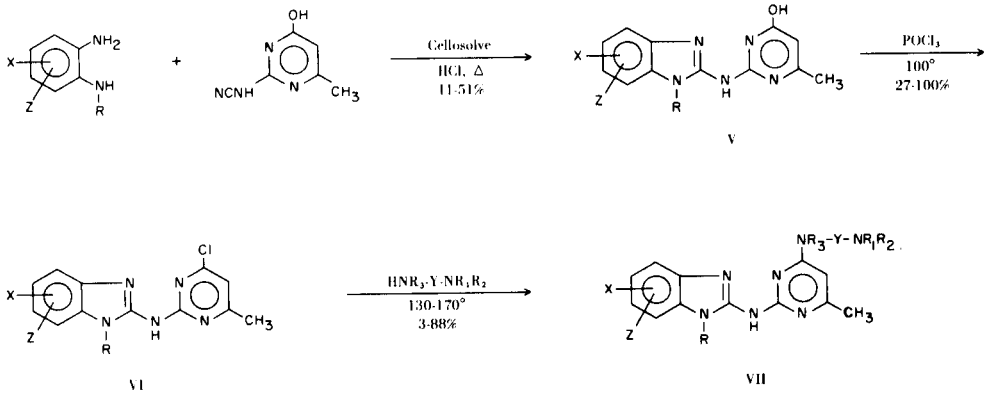
The 2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles (VII) (**13-30**, **32-56**, **58-67**, Table III) were prepared according to the general synthetic route depicted in Scheme I utilizing modifications of the procedures described previously (10). Thus, the requisite 2-[(2-benzimidazolyl)amino]-6-methyl-4-pyrimidinols (V) (**1-8**, Table I), obtained in 11-51% yield by the condensation of a suitably substituted *o*-phenylenediamine with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine, were chlorinated with phosphorus oxychloride to give the intermediate 2-[(2-benzimidazolyl)amino]-4-chloro-6-methylpyrimidines (VI) (**9-12**, Table II) (27-100%). In the latter stages of the work, it was determined that it was unnecessary to use analytically pure chloropyrimidines for subsequent reactions, and the crude products were employed directly. Treatment of the appropriate chloropyrimidines (VI) with a polyamine side chain in refluxing ethanol-hydrochloric acid (Procedure A) or neat with excess amine at 130-185° for 0.75-4 hours in the presence of a catalytic amount of potassium iodide (Procedure B) afforded the desired 2-[(4-amino-6-methyl-2-pyrimidinyl)-amino]benzimidazoles (VII) in 3-88% yield.



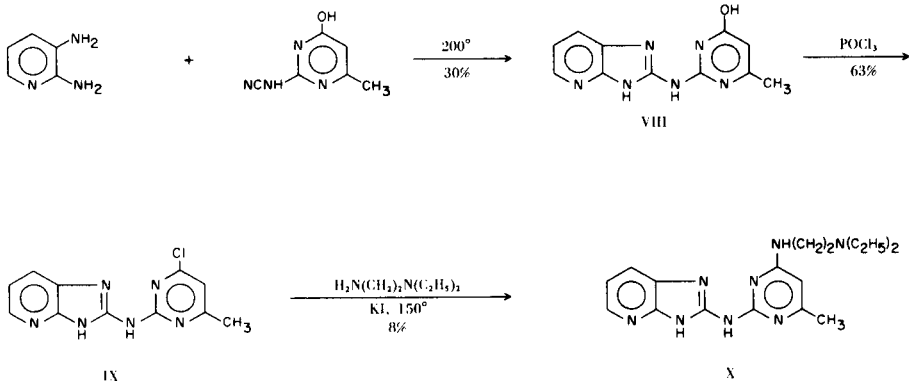
31

Oxidation of 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**29**) with *m*-chloroperbenzoic acid in chloroform gave the distal $N^{4'}$-oxide **31** in 19% yield. The nmr spectrum of **31** exhibited a downfield shift of the side chain protons, thus confirming that oxidation had occurred on the tertiary side chain nitrogen. 4-Amino-6-chloro-2-

SCHEME I



SCHEME II



[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**57**) was obtained in 34% yield by the hydrogenation of 6-chloro-2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]-4-nitrobenzimidazole (**55**) in methanol-dimethylformamide over Raney nickel at 26°.

2-(4-[[2-(Diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)-1*H*-imidazo[4,5-*b*]pyridine (X), the 4-aza isostere of 2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**58**), was prepared according to Scheme II. Fusion of 2,3-diaminopyridine with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine gave 2-[(4-hydroxy-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]pyrimidine (VIII) (30%). Chlorination with phosphorus oxychloride yielded 2-[(4-chloro-6-methyl-2-pyrimidinyl)-amino]-1*H*-imidazo[4,5-*b*]pyridine (IX) (63%), which upon heating at 150° with excess *N*,*N*-diethylethylenediamine and a trace of potassium iodide afforded X in 8% yield. Spectral data (ir, uv, nmr) were in agreement with the structures depicted for the 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles (VII), 2-(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)-1*H*-imidazo[4,5-*b*]pyridine (X), and their precursors V, VI, VIII, and IX.

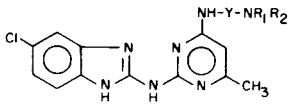
Suppressive Antimalarial Screening in Mice.

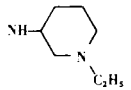
The 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles **13-60** and **62-66** (Table III) and 2-(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)-1*H*-imidazo[4,5-*b*]pyridine (X) described in the present communication were tested initially against a normal drug-sensitive strain of *P. berghei* in mice by the parenteral route (11,12). The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hours post infection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity (12). Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of treated mice. Animals that survive to 60 days are considered "cured". The mean survival time of infected control mice in the present study ranged from 6.1 to 6.5 days. Results are summarized in Tables IV-XI.

The vast majority of these pyrimidinylaminobenzimidazoles were also evaluated orally against another normal drug-sensitive strain of *P. berghei* in mice (13,14). The drugs were given continously in the diet of mice for 6 consecutive days, and all drug doses were calculated

TABLE IV

Effects of 5(or 6)-Chloro-2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

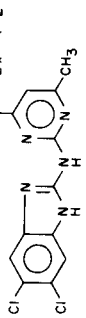


No.	NH-Y-NR$_1$R$_2$	Diet, 6 days: No. of mice	Diet, 6 days: SD_{90} (a), mg./kg./day	Diet, 6 days: Q (b)	*P. berghei* — Single s.c. dose — ΔMST; T or C (c) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* — Single s.c. dose — mg./kg.	ΔMST T or C (d)
13	$NH(CH_2)_2N(CH_2)_4$	14	75	1.0	C5 C5	19.5; C4	12.5; C3 18.6; C2	4.5	3.1 3.0	0.5	120 60	7.2; C1 4.6
14		14	23	3.2	19.1; C3 17.6; C3	10.4	7.6 6.8	4.6	2.0 1.8	1.8		
15	$NH(CH_2)_2N(CH_3)(CH_2)_3CH_3$	14	92	0.8	C5 C5	15.0; C1	9.1 9.2	6.5	5.7 5.4	5.1	120	0.2
16	$NH(CH_2)_2N(CH_2CH{=}CH_2)_2$	14	82	0.9	13.5 12.8	7.9	4.1 3.8	3.5	0.7 0.6	0.7	120	0.7
17	$NH(CH_2)_2N[CH(CH_3)_2]_2$	14	90	0.8	C5 C5	C5	10.5 10.8	6.1	2.5 2.4	0.7	120	0.4
I		21	68	1.1	T5		T5 7.9; T3	7.9; T2	6.3 6.9	2.7	100	12.3; C4
II		40	7	11	C5 C5 C3, T2 C4, T1	C5 C5	C5 C5 C5 C5	16.3; C3 16.9; C3	9.3; C1 11.7; C1 13.4; C3 12.4; C3	6.6 4.5	100 120	6.2 12.0; C1
	Quinine (e)	224	74.5	1.0	5.4	3.2	2.0	1.4	1.0	0.2		
	Cycloguanil hydrochloride	40	2.1	35	T5 C2, T3		C4 C4		5.3 6.7			

(a) SD_{90} represents the daily dose (mg./kg.) required for 90% suppression of the parasitemia in treated mice relative to control mice. The SD_{90} was estimated graphically using semi-log paper. (b) The quinine equivalent Q is the ratio of the SD_{90} of quinine·HCl (74.5 mg. base/kg./day) to the SD_{90} of the test substance under comparable experimental conditions. (c) ΔMST is the mean survival time (days) of treated mice (MSTT) minus the mean survival time (days) of control mice (MSTC). In the present study the MSTC ranged from 6.1 to 6.5 days. T signifies the number of toxic deaths occurring on days 2-5 after infection which are attributed to drug action. C indicates the number of mice surviving at 60 days post infection and termed "cured"; data to establish parasitological cure based on sub-inoculation are unavailable. (d) ΔMST is the mean survival time (days) of treated chicks (MSTT) minus the mean survival time (days) of control chicks (MSTC). In the present study the MSTC ranged from 3.0 to 4.0 days. C designates the number of chicks surviving to 30 days post infection and termed "cured"; data to establish parasitological cure based on sub-inoculation are unavailable. T indicates the number of deaths occurring within 48 hours after infection which are attributed to drug action and are counted as toxic deaths. Control birds do not die before 48 hours. Each entry at each dose level represents results with a 5 animal group. (e) Tested parenterally as the sulfate salt and orally as the hydrochloride salt.

TABLE V

Effects of 5,6-Dichloro-2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



No.	X	NR_1R_2	*P. berghei* Diet, 6 days — No. of mice	SD_{90} (a), mg./kg./day	Q (a)	*P. berghei* Single s.c. dose — ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* Single s.c. dose — ΔMST; T or C (a) mg./kg.
18	2	$N(C_2H_5)_2$	30	14.3	5.2	C5	C5	24.6; C3	12.2	2.2	1.6	480
						C5		20.7; C4		2.1		0.1
19	2	$N(CH_3)(CH_2)_3CH_3$	21	20	3.7			5.1	2.3	0.9	0.5	480
20	3	$N(C_2H_5)_2$	21	14	5.3	C5	C5	10.1	4.1	2.3	0.5	100
						C5		10.6		2.4		0.2
21	2	$N(CH_2CH{=}CH_2)_2$										240
22	2	$N[CH(CH_3)_2]_2$	21	18	4.1	26.8; C4	22.8; C3	17.0	1.6	0.2	0.2	0.3
						21.8; C4		16.6		0.2		

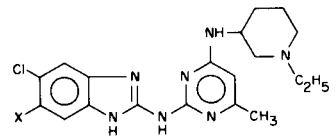
(a) See footnotes a-d, Table IV.

as free base equivalent. Results (Tables IV-XI) are expressed both in terms of the SD_{90} (daily dose required for 90% suppression of the parasitemia in treated mice relative to control mice) and the quinine equivalent Q (the ratio of the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance under comparable experimental conditions).

Both oral and parenteral baseline data for the reference drugs 1-(*p*-chlorophenyl)-3-(4-[[2-(diethylamino)ethyl]-amino]-6-methyl-2-pyrimidinyl)guanidine (I), 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (II), quinine hydrochloride or sulfate, and cycloguanil hydrochloride are included for comparative purposes (Table IV).

Overall Results and Structure-Activity Relationships in Mice.

Early work in this series was directed toward the preparation of representative 5(or 6)-chloro-2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]-benzimidazoles (**13-17**, Table IV). Widespread antimalarial activity, albeit modest, was encountered throughout this group, and by analogy with the corresponding guanidinopyrimidines (6), optimal oral activity was encountered in the 1-ethyl-3-piperidyl compound **14** (SD_{90} = 23 mg./kg./day, Q = 3.2). Moreover, it was discovered concurrently



14, X = H
45, X = Cl

that the introduction of a second chlorine atom into the benzimidazole ring led to a further enhancement in potency, reminiscent of the 3,4-dichlorophenylguanidinopyrimidines (II) (6). Thus, 5,6-dichloro-2-([4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]amino)benzimidazole (**45**) was 8.3 times as potent as quinine hydrochloride orally and exhibited "curative" action subcutaneously through 160 mg./kg.

In view of this promising turn of events, an intensive synthesis program was launched to enable a more definitive delineation of structure-activity relationships in the series and to determine whether or not more potent analogs of **45** could be developed. This effect culminated in the discovery of the remarkable antimalarial drug 5,6-

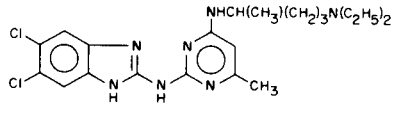


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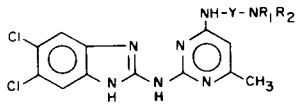
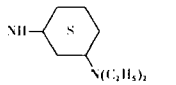
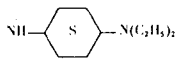
TABLE VI

Effects of Side Chain Branched
5,6-Dichloro-2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles
Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



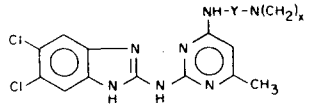
No.	NH-Y-NR$_1$R$_2$	*P. berghei* — Diet, 6 days — No. of mice	SD$_{90}$ (a), mg./kg./day	Q (a)	*P. berghei* — Single s.c. dose — ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* — Single s. c. dose — mg./kg.	ΔMST T or C (a)
23	NHCH(CH$_3$)CH$_2$N(CH$_3$)$_2$	28	4.8	15.5		C5 C5	C5	22.9; C3 14.9; C4	10.4; C1	3.3 3.5	320 160 80	6.7 6.3 5.3
24	NHCH$_2$CH(CH$_3$)N(CH$_3$)$_2$				C3, T2	C5	25.9; C4 22.8; C4	13.9; C1	7.2; C1 5.3; C1	1.3	320	0.4
25	NHCH(CH$_3$)CH$_2$N(C$_2$H$_5$)$_2$	14	5.9	12.6	C5	C5 C5	C5 C5	22.8; C4 25.8; C4	9.3; C1 8.8; C2	7.4 (c) 7.4	120	3.1
26	NHCH$_2$CH(CH$_3$)N(C$_2$H$_5$)$_2$	21	13	5.7	30.9; C4 C5	25.9; C4	25.4; C3 27.1; C2	16.2; C2	16.2; C1 9.8; C2	1.7	320	0.5
27		14	45	1.7	31.8; C4 C5	11.8	8.0 7.8	3.6	0.2 0.2	0.2	120	0.5
28	NHCH(CH$_3$)(CH$_2$)$_2$N(C$_2$H$_5$)$_2$				C5	C5 C5	C5 C5	C5 C5	24.8; C4 27.8; C4	9.5; C2 (d) 10.8; C2		
29	NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	21	2.7	28			C5 21.9; C4	17.9; C2	12.2; C2 10.6; C2	4.7	480 240	4.5 1.9
29a	NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$ (b)	14	7.9	9.4	C5	C5 C5	C5 C5	C5 C5	C5 C5	9.7; C1 (e) 10.3; C1		
30	NHCH(CH$_3$)CH$_2$N(CH$_2$CH$_2$CH$_3$)$_2$				C5	21.8; C4 25.9; C4	19.8; C1 17.6; C2	10.2 10.5	2.8 3.1	1.2 1.5	120	0.6
31	NHCH(CH$_3$)(CH$_2$)$_3$$\overset{+}{\underset{O^-}{N}}$(C$_2H_5$)$_2$					15.2; C3	7.1 7.4	2.7 2.6	0.5 0.4	0.1 0.4		

32		21	15.5	4.8	C5 C5	C5	C5 C5	15.8; C3	11.8; C1 12.3; C1	0.6	100	0.0
33					17.9; C4 21.9; C4	21.6; C2	8.7; C1 9.2; C1	3.3	0.9 0.9	0.9	120	0.6
34	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$, 1-$CH_3$	21	140	0.5	C2, T3	C2, T3 C3, T2	15.3 14.8; T1	9.8 10.0	8.0 7.8	2.6 2.6		

(a) See footnotes a-d, Table IV. (b) Tested as the sulfamate salt. (c) ΔMST at 10 mg./kg., 3.4 days. (d) ΔMST at 10 mg./kg., 3.8 days. (e) ΔMST at 10 mg./kg., 3.4 days.

TABLE VII

Effects of 5,6-Dichloro-2-[(4-[[(heterocyclic)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

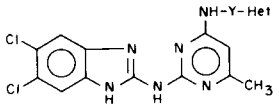


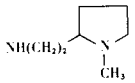
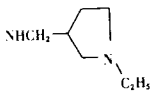
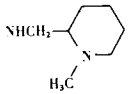
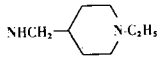
		P. berghei									*P. gallinaceum*	
		Diet, 6 days			Single s.c. dose						Single s.c. dose	
					ΔMST; T or C (a) after mg./kg.:							
No.	NH-Y-$N(CH_2)x$	No. of mice	SD_{90} (a), mg./kg./day	Q (a)	640	320	160	80	40	20	mg./kg.	ΔMST; T or C (a)
35	$NH(CH_2)_2N(CH_2)_4$	21	18.5	4.0	C4, T1 C4, T1	27.9; C3	21.4; C3 19.3; C3	9.1	1.1 1.0	0.3	320	0.5
36	$NH(CH_2)_3N(CH_2)_4$	21	22	3.4		12.9 12.7	2.7	0.5 0.7	0.3	0.1 0.3	320	0.4
37	$NH(CH_2)_2N(CH_2)_5$					C5		5.1 5.3	4.7	0.3 0.5	320	0.3
38	$NH(CH_2)_3N(CH_2)_5$				11.9 11.7	5.9	0.7 0.5	0.7	0.3 0.3	0.3		
39	$NH(CH_2)_2N(CH_2)_6$	21	20	3.7	14.9; C3 6.4; C3	4.7; C1	0.7 0.3	0.3	0.3 0.3	0.1	120	0.1

(a) See footnotes a-d, Table IV.

TABLE VIII

Effects of Branched 5,6-Dichloro-2-[(4-[[(heterocyclic)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

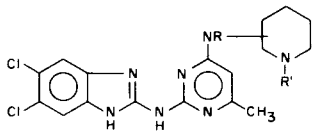


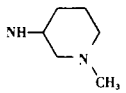
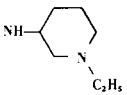
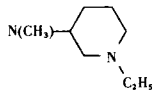
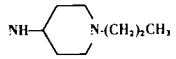
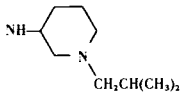
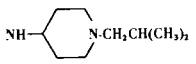
No.	NH-Y-Het	*P. berghei* — Diet, 6 days — No. of mice	SD90 (a), mg./kg./day	Q (a)	*P. berghei* — Single s.c. dose — ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* — Single s.c. dose — mg./kg.	ΔMST; T or C (a)
40					19.9; C3 18.2; C2	6.9	4.3 4.3	1.1	0.7 0.3	0.3		
41		21	19	3.9	29.8; C4	16.6; C2	8.9 8.2	4.3	0.5 0.2	0.3	320	0.4
42		21	10.5	7.1	C5 C5	C5	C5 C5	13.4; C3	0.9 0.9	0.3	120	0.6
43		14	37	2.0	23.9; C3 21.9; C3	11.9; C2	5.3 5.1	2.3	0.5 0.3	0.5	120	0.5

(a) Footnotes a-d, Table IV.

TABLE IX

Effects of 5,6-Dichloro-2-([[4-[(1-alkyl-3- or -4-piperidyl)amino]-6-methyl-2-pyrimidinyl]]amino)benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

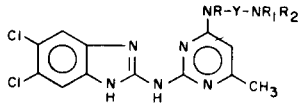


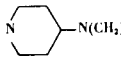
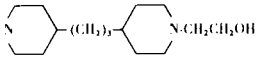
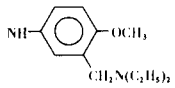
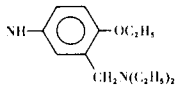
No.		Diet, 6 days — No. of mice	Diet, 6 days — SD_{90} (a), mg./kg./day	Diet, 6 days — Q (a)	*P. berghei* — Single s.c. dose — ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* — Single s.c. dose — mg./kg.	ΔMST; T or C (a)
44		14	13.5	5.5	C5	18.3; C3 19.8; C3	15.8; C3 16.3; C3	9.8 10.0	6.8 7.0	1.0 1.0	120	0.0
45		21	9	8.3	27.5; C3 27.6; C4		19.5; C1 16.6; C2		6.7 6.2		100	0.2
46					C5	16.9; C1 16.9; C1	7.1 7.1	2.1 2.3	1.9 2.1	1.1 1.1		
47						C5	20.7; C3 21.8; C3	3.7 4.0	2.5 2.8	0.3 0.4		
48		14	>19	<3.9	13.2; C2	9.5 9.3	2.3 2,5	0.5 0.5 0.3	0.3 0.5 0.3	0.3 0.3		
49		14	6.8	11.0	C5	15.6; C2 15.2; C2	10.2; C1 10.7; C1	3.7 3.7	0.7 0.9	0.3 0.3		

(a) See footnotes a-d, Table IV.

TABLE X

Effects of Miscellaneous 5,6-Dichloro-2-[(4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)-amino]benzimidazoles Against *Plasmodium berghei* in Mice



No.	NR-Y-NR$_1$R$_2$	Diet, 6 days: No. of mice	Diet, 6 days: SD_{90} (a), mg./kg./day	Diet, 6 days: Q (a)	*P. berghei*: Single s.c. dose: ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20
50		14	28.5	2.6	9.7; C3	8.2; C1 8.1; C1	0.7 0.6	0.5 0.6	0.1 0.4	0.1 0.2
51		14	>167	<0.4	0.3	0.3	0.1	0.1	0.1	0.1
52		7	>105	<0.7	0.2		0.2		0.0	
53		7	>83	<0.9	0.5		0.3		0.3	

(a) See footnotes a-d, Table IV.

dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**29**). The free base **29** was active orally against *P. berghei* in mice at a dose of 2.7 mg./kg./day, and was thus approximately 28 times as potent as quinine hydrochloride (Table VI). The drug was also superior to the guanidinopyrimidines I and II orally, and was nearly as potent as cycloguanil hydrochloride (Table IV). Parenterally, **29** cured mice at single subcutaneous doses ranging from 40-160 mg./kg. and was thus comparable with the guanidinopyrimidine II and superior to I, quinine sulfate, and cycloguanil hydrochloride. The water soluble sulfamate salt **29a** was somewhat less active than the base orally (SD_{90} = 7.9 mg./kg./day, Q = 9.4), but was more active parenterally (Table VI). Curative effects were observed over the entire dose range 20-640 mg./kg., and no toxicity was encountered at any dose level. Moreover, unlike the pyrimidinylaminobenzimidazoles as a class, **29** displayed significant suppressive activity against *P. gallinaceum* in chicks (*vide infra*). In view of the overall promise of this drug, the sulfamate salt **29a** was selected for preclinical toxicological studies and clinical trial.

Overall, thirty-eight of the novel 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles VII (**13-15**, **17**, **18**, **20**, **22-35**, **37**, **39-50**, **60**, **62**, **63**, and **66**) (Tables IV-XI) possessed curative antimalarial effects against *P. berghei* when administered to mice in a single subcutaneous dose ranging from 20-640 mg./kg., and nearly all of them were tolerated well by mice. Among forty-two compounds tested by the oral route, thirty-one exhibited antimalarial activity comparable with or superior to the reference drugs I and quinine hydrochloride, and twelve (**18**, **20**, **23**, **25**, **26**, **29**, **29a**, **32**, **42**, **44**, **45**, **49**) were 5 to 28 times more potent than I or quinine hydrochloride (Tables IV-XI). In general, there was an excellent correlation between subcutaneous and oral test results in mice.

An analysis of these results enables the following generalizations concerning structure-activity relationships against *P. berghei* in mice:

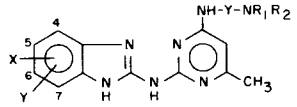
(1) Optimal activity predominates in the 5,6-dichlorobenzimidazole series (Tables V-IX *vs.* Table IV; **13-15**, **17** *vs.* **19**, **22**, **35**, **45**).

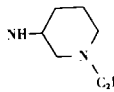
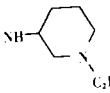
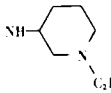
(2) Within the 5,6-dichlorobenzimidazole series, potent activity is encountered among the simple [(dialkylamino)-alkyl]derivatives (Tables V, VI) and saturated heterocyclic analogs (Tables VII-X).

(3) Side chain branching is usually favorable (Table VI).

TABLE XI

Effects of Other Substituted 2-[(4-[[(Dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



No.	NH-Y-NR_1R_2	X, Y	Diet, 6 days: No. of mice	Diet, 6 days: SD_{90} (a), mg./kg./day	Diet, 6 days: Q (a)	*P. berghei* Single s.c. dose: ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* Single s.c. dose: mg./kg.	*P. gallinaceum* Single s.c. dose: ΔMST T or C (a)
54	$NH(CH_2)_2N(C_2H_5)_2$	4,5,6,7-Cl_4	7	>85	<0.9	0.9		0.7		0.3		320	0.8
55	$NH(CH_2)_2N(C_2H_5)_2$	6-Cl,4-NO_2	7	>61	<1.2	1.8		0.2		0.2		100	0.0
56	$NH(CH_2)_2N(C_2H_5)_2$	4-NO_2	7	>151	<0.5	2.5 2.5	0.5	0.5 0.5	0.3	0.1 0.3	0.1	320	0.5
57	$NH(CH_2)_2N(C_2H_5)_2$	6-Cl,4-NH_2	7	>95	<0.8	6.1 6.1	2.7	0.5 0.3	0.5	0.3 0.3	0.1	120	0.5
58	$NH(CH_2)_2N(C_2H_5)_2$	H	21	38	2.0	7.9 7.2	6.5	4.7 4.4	2.9	0.9 1.6	0.5	100	4.9
59		6-Cl,4-NO_2						0.5	0.3	0.3	0.3		
60	$NH(CH_2)_2N(C_2H_5)_2$	5(or 6)-CF_3	14	79	0.9	C5 C5	19.9; C3	5.1 4.9	1.7	0.5 0.3	0.3	120	0.5
62		5(or 6)-CF_3	7	>18	<4.1	14.4; C3 13.4; C3	9.9; C1	3.9 3.7	0.9	0.3 0.3	0.3	320 160 80	3.9 3.1 2.7
63	$NH(CH_2)_2N(C_2H_5)_2$	5,6-$(CH_3)_2$	14	54	1.4	15.4; C1 10.9; C2	8.9	4.7 4.9	0.7	0.3 0.5	0.3	320 160 80	8.5 5.5 5.1
64		5,6-$(CH_3)_2$	14	69	1.1	14.5 14.8	4.5	3.1 2.8	2.9	2.1 1.2	0.5	120	3.4
65	$NH(CH_2)_2N(C_2H_5)_2$	5(or 6)-$(CH_2)_3CH_3$	14	96	0.8			0.8		0.6			
66	$NH(CH_2)_2N(C_2H_5)_2$	5(or 6)-C_6H_5	14	120	0.6	19.2; C2 19.6; C2	3.3	2.3 2.5	0.5	0.3 0.5	0.3	120	0.6

(a) See footnotes a-d, Table IV.

(4) The length of the biospacer between the proximal and distal nitrogen atoms of the side chain can be varied between two and four carbon atoms with retention of strong activity (Tables V-IX).

(5) Activity is reduced when the proximal nitrogen atom is tertiary (**46**, **50**, **51** *vs.* **45**, Tables IX, X).

(6) *N*-oxidation of the distal amine function diminishes antimalarial potency (**31** *vs.* **29**, **29a**, Table VI).

(7) Introduction of amodiaquine-type side chains (5) results, surprisingly, in a drastic loss of potency (**52**, **53**, Table X).

(8) *N*-methylation at position 1 of the benzimidazole nucleus is dystherapeutic (**34** *vs.* **29**, **29a**, Table VI).

(9) The introduction of chloro, nitro, or amino substituents at position 4 on the benzimidazole nucleus results in a diminution or loss of antimalarial activity (**54-57**, **59**, Table XI).

(10) Substitution of hydrogen by one or more methyl, butyl, trifluoromethyl, or phenyl groups at positions 5 or 6 of the benzimidazole nucleus is unfavorable (**58**, **60**, **62**, **63-66**, Table XI).

(11) The 4-aza isostere is inactive (X *vs.* **58**).

Suppressive Antimalarial Effects in Chicks.

The guanidinopyrimidines I and II and thirty-six of the 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles were also tested for suppressive antimalarial effects against *P. gallinaceum* infections in white Leghorn cockerels (Tables IV-IX, XI) (11,12). The drugs were administered to infected chicks in a single subcutaneous dose in peanut oil. In this test, as in the parenteral mouse assay, the antimalarial activity of candidate compounds was assessed by comparing the mean survival times of treated malaria-infected chicks with the survival times of untreated malaria-infected chicks. A compound was arbitrarily considered to be active against malaria if it produced survival times of treated chicks that were at least 100% greater than the survival times of untreated control animals.

In contrast with the guanidinopyrimidines (3,4,6), the pyrimidinylaminobenzimidazoles as a group lacked widespread suppressive activity against *P. gallinaceum*. Among thirty-six compounds that were tested, only eight were active. Compounds **13**, **23**, **29**, **58**, **62-64**, and **66** increased the mean survival time of chicks > 100% at single subcutaneous doses ranging from 60 to 320 mg./kg., but only one (**13**) was curative (Tables IV-IX, XI). It is also noteworthy that the benzimidazoles that were most active against *P. gallinaceum* did not correspond to those substances that showed outstanding effects against *P. berghei*. It must be concluded that the correlation of the predictive value of the two test systems in assessing the antimalarial potential of the pyrimidinylaminobenzimidazoles is poor, but the relative predictive value for man is as yet unknown.

Evaluation of Prophylactic Action in Chicks.

Four of the 2-[(4-amino-6-methyl-2-pyrimidinyl)amino]benzimidazoles (**20**, **29a**, **48**, and **53**) were evaluated for prophylactic action in chicks (11,15). White Leghorn cockerels were parasitized by the intrajugular injection of *P. gallinaceum* sporozoites. All control chicks died between 6 and 11 days post-infection. In the present study, the mean survival time of control animals ranged from 7.4 to 9.5 days. A drug is considered active if the mean survival time of treated chicks is at least twice as long as that of untreated control chicks, or if any of the chicks survive to 30 days.

The above drugs were suspended in peanut oil and were administered subcutaneously in a single dose on the day of infection. Each compound was tested in groups of 5 chicks at one to six dose levels ranging from 10 to 480 mg./kg. None of the pyrimidinylbenzimidazoles tested possessed prophylactic activity based on the above criteria.

Drug Resistance Studies in Mice.

To determine whether the pyrimidinylaminobenzimidazoles, like the guanidinopyrimidines, represented a unique chemical class with regard to apparent mode of action relative to chlorguanide and cycloguanil (*vide supra*) (6), one of the more promising members of the series, namely, 5,6-dichloro-2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**18**), was evaluated against representative drug-resistant lines of *P. berghei* (13,14). The drug was administered continuously in the diet at levels of 0.0313, 0.008, and 0.004% for six days to groups of ten mice infected with the parent (P) drug-susceptible strain of *P. berghei*, line T which was completely (> 300-fold) resistant to cycloguanil hydrochloride, and line C which was 77-fold resistant to chloroquine. The SD_{90} was estimated to be 14.3 mg./kg./day (Q = 5.2) for the susceptible line P, 18 mg./kg./day (Q = 4.1) for the cycloguanil-resistant line T, and > 49 mg./kg./day (Q = < 1.5) for the chloroquine-resistant line C. These results indicate that there is no appreciable cross-resistance between **18** and folate antagonists such as chlorguanide, cycloguanil, and pyrimethamine. Moreover, antimetabolite studies conducted in these laboratories showed that **18** lacked appreciable antifolate activity. Thus 50% inhibition of *Streptococcus faecalis* R (*Strep. faecium* var. *durans*, ATCC 8043) (16) by the pyrimidinylaminobenzimidazole **18** required 15,000 ng./ml., while cycloguanil hydrochloride and pyrimethamine produced 50% inhibition at concentrations of 8 ng./ml. and 4 ng./ml., respectively (16). However, compound **18**, like the guanidinopyrimidine II, showed definite cross-resistance with chloroquine. It thus seems likely that the mode of action of both the guanidinopyrimidines (3,4,6) and the pyrimidinylaminobenzimidazoles is more closely

allied with that of chloroquine (5) than with that of the folate antagonists.

EXPERIMENTAL (17)

2-(2-Benzimidazolylamino)-6-methyl-4-pyrimidinols (V) (**1-8**, Table I).

A mixture of 17.7 g. (0.1 mole) of 4,5-dichloro-*o*-phenylenediamine and 15.0 g. (0.1 mole) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine in 100 ml. of cellosolve, 8.6 ml. of concentrated hydrochloric acid, and 25.4 ml. of water was heated under reflux for 24 hours. The solid which formed on heating was removed by filtration, and washed first with ethanol and then with dimethylformamide. Recrystallization from dimethylsulfoxide followed by a wash with hot methanol gave 7.2 g. (23%) of 2-[(5,6-dichloro-2-benzimidazolyl)amino]-6-methyl-4-pyrimidinol (**2**), m.p. $>375°$.

This procedure was repeated on a 1.0 mole scale. The reflux period was extended to 40 hours, and the solid was slurried in ethanol, recrystallized from about 8 l. of dimethylsulfoxide, and slurried in ethanol to give 131 g. (42%) of the product.

In later 1.0 mole runs the recrystallization was omitted. The crude product was boiled with 1.5 l. of ethanol, filtered hot, dried, and used directly in the chlorination step.

6-Methyl-2-[[5(or 6)-(trifluoromethyl)-2-benzimidazolyl]amino]-4-pyrimidinol, m.p. $>390°$, was obtained in 34% crude yield after slurrying in ethanol and was used directly in the chlorination. 2-[(2-Benzimidazolyl)amino]-6-methyl-4-pyrimidinol and 2-[(5,6-dimethyl-2-benzimidazolyl)amino]-6-methyl-4-pyrimidinol were purchased from the Alfred Bader Division, Aldrich Chemical Co., Milwaukee, Wisconsin.

2-[(2-Benzimidazolyl)amino]-4-chloro-6-methylpyrimidines (VI) (**9-12**, Table II).

A suspension of 5.0 g. (0.016 mole) of 2-[(5,6-dichloro-2-benzimidazolyl)amino]-6-methyl-4-pyrimidinol (**2**) and 20 ml. (33 g., 0.2 mole) of phosphorus oxychloride was heated on a steam bath for 45 minutes. The heavy paste which resulted was dropped into 750 ml. of iced-water. The solid was removed by filtration and washed with hot methanol to give 4.1 g. (78%) of 5,6-dichloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]benzimidazole (**10**), m.p. 343-347°.

This procedure was repeated using 62 g. (0.2 mole) of the pyrimidinol and 800 g. of phosphorus oxychloride. The reaction mixture was added to 3.5 l. of iced water, filtered, and slurried with 2 l. of boiling methanol to give a quantitative yield of the product.

The following chloropyrimidines were prepared by the above procedure, but were not analyzed and were used crude following trituration with ethanol, methanol, or water: 2-(2-benzimidazolylamino)-4-chloro-6-methylpyrimidine, m.p. 286-300° (29%); 5(or 6)-butyl-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]benzimidazole, m.p. 220-225° (94%); 6-chloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]-4-nitrobenzimidazole, m.p. $>320°$ (93%); 2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]-5,6-dimethylbenzimidazole, m.p. $>300°$ (52%); 4-nitro-2-[(4-chloro-6-methyl-2-pyrimidinyl)-amino]benzimidazole (99%); 5(or 6)-(trifluoromethyl)-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]benzimidazole (95%); 5,6-dichloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]-1-methylbenzimidazole, m.p. 238-240° dec. (99%).

2-[(4-[[(Dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazoles (VII) (**13-30**, **32-56**, **58-67**, Table III).

5,6-Dichloro-2-[(4-[[3-[(diethylamino)methyl]-*p*-phenetidinol]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**53**).

Procedure A.

A mixture of 9.9 g. (0.03 mole) of 5,6-dichloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]benzimidazole (**10**) and 8.5 g. (0.03 mole) of N^{α},N^{α}-diethyl-6-ethoxy-α,3-toluenediamine dihydrochloride (18) in 600 ml. of ethanol was heated under reflux for 105 hours. The hot solution was treated with charcoal and the solvent was removed *in vacuo*. The semi-solid was dissolved in water, filtered, and treated with 2 *N* sodium hydroxide. The solid which formed was triturated with water, ethyl acetate, and ethanol to give 7.4 g. (48%) of the product, m.p. 275-277°.

5,6-Dichloro-2-([4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]amino)benzimidazole (**45**).

Procedure B.

A mixture of 10.0 g. (0.03 mole) of 5,6-dichloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]benzimidazole (**10**) and 11.3 g. (0.09 mole) of 3-amino-1-ethylpiperidine containing a catalytic amount of potassium iodide was heated in an oil bath at 170° (external) for 45 minutes. The cooled mixture was dissolved in 1 l. of dilute hydrochloric acid, treated with charcoal, and filtered. The filtrate was made basic with 50% aqueous sodium hydroxide solution, and the solid obtained was recrystallized from ethanol to give 5.0 g. (40%) of the product, m.p. 149-151° dec.

5,6-Dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole $N^{4'}$-Oxide (**31**).

To a solution of 2.6 g. (0.0056 mole) of 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)-amino]benzimidazole 0.85 hydrate (**29**) in 90 ml. of chloroform was added a slurry of 1.3 g. (0.0062 mole) of 80% *m*-chloroperbenzoic acid in 10 ml. of chloroform. The mixture was stirred at room temperature for 50 hours and concentrated to dryness *in vacuo*. The residue was triturated with acetonitrile and the insoluble material was triturated with ethyl acetate to afford 0.5 g. (19%) of the product, m.p. 175-177° dec.

The nmr spectrum exhibited a downfield shift of the side chain protons confirming that oxidation had occurred on the side chain tertiary nitrogen.

5,6-Dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]-1-methylbenzimidazole (**34**).

A mixture of 4.5 g. (0.013 mole) of 5,6-dichloro-2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]-1-methylbenzimidazole and 6.2 g. (0.039 mole) of 4-(diethylamino)-1-methylbutylamine containing a catalytic amount of potassium iodide was heated in an oil bath at 140-150° for 1.5 hours. After slight cooling, the reaction mixture, a deep red mush, was taken up in 5 *N* hydrochloric acid, filtered, and poured into excess iced dilute sodium hydroxide to precipitate a blue solid. This was collected, washed with water, dried in air, and taken up in ether. An insoluble gum was discarded. The red ether solution was treated with 2-propanol saturated with gaseous hydrogen chloride to give a bright blue solid which was collected and dried *in vacuo* at 100° to give 3.0 g. (42%) of the product, m.p. 200-205° with preliminary softening. The material was hygroscopic.

4-Amino-6-chloro-2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole Hydrochloride Hydrate (**57**).

A mixture of 12.9 g. (0.031 mole) of 6-chloro-2-[(4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)amino]-4-nitrobenzimidazole (**55**) in 50 ml. of methanol and 200 ml. of dimethyl-

formamide was hydrogenated over 1.0 g. of Raney nickel at 26° and an initial pressure of 3.5 kg./cm^2. The catalyst was removed by filtration, and the filtrate was poured into 1 l. of water. The solid which formed was collected, dried, and dissolved in ethanol. The solution was acidified with 2-propanol saturated with hydrogen chloride and poured into a large excess of ether. The solid was collected, dried *in vacuo*, and equilibrated in air to give 5.6 g. (34%) of the product, m.p. 225-230° dec.

5,6-Dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole Monosulfamate Monohydrate (**29a**).

To an acetone solution of crude 5,6-dichloro-2-[(4-[[4-(diethylamino)-1-methylbutyl]amino]-6-methyl-2-pyrimidinyl)amino]benzimidazole (**29**) obtained from a 0.054 mole run as in procedure B was added a saturated solution of sulfamic acid in acetone. The salt which precipitated was collected, dried, and recrystallized three times from ethanol to provide 3.2 g. (11%) of the product, m.p. softens at 158-160°, decomposes at 220-222°.

Anal. Calcd. for $C_{21}H_{29}Cl_2N_7 \cdot H_2NSO_3H \cdot H_2O$: C, 44.60; H, 6.06; N, 19.81; S, 5.67; H_2O, 3.19. Found: C, 44.76; H, 5.80; N, 19.48; S, 6.12; H_2O, 3.00.

2-[(4-Hydroxy-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]-pyridine (VIII).

A mixture of 5.4 g. (0.05 mole) of 2,3-diaminopyridine and 7.5 g. (0.05 mole) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine was stirred in an oil bath at 200° for 45 minutes. Trituration of the cooled mixture with methanol, acetone, β-ethoxyethanol, and isopropyl ether failed to produce an analytically pure sample. The yield was 3.6 g. (30%) of the crude intermediate, m.p. 389-391°.

2-[(4-Chloro-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]-pyridine (IX).

A solution of 3.6 g. (0.015 mole) of 2-[(4-hydroxy-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]pyridine (VIII) in 50 ml. of phosphorus oxychloride was stirred under reflux for three hours and then poured cautiously with brisk stirring into 1.2 l. of ice water containing sufficient sodium hydroxide to maintain a strongly basic medium. A dark green solid formed which was collected, washed with water, and dried to give 2.5 g. (63%) of the crude chloro compound which was used without further purification.

2-(4-[[2-(Diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl)-1*H*-imidazo[4,5-*b*]pyridine (X).

A mixture of 2.5 g. (0.0096 mole) of 2-[(4-chloro-6-methyl-2-pyrimidinyl)amino]-1*H*-imidazo[4,5-*b*]pyridine (IX) and 3.5 g. (0.03 mole) of *N,N*-diethylethylenediamine containing a catalytic amount of potassium iodide was stirred in an oil bath at 150° for 2 hours. The reaction mixture was then taken up in 5 *N* hydrochloric acid and filtered into excess aqueous sodium hydroxide. The brown oily precipitate that formed was extracted with chloroform. The organic layer was treated with decolorizing charcoal, dried over magnesium sulfate, and evaporated to a brown oil. Trituration of this with acetonitrile gave a beige solid which was recrystallized twice from acetonitrile to give 0.26 g. (8%) of the desired product, m.p. 177-179°.

Anal. Calcd. for $C_{17}H_{24}N_8$: C, 59.98; H, 7.11; N, 32.92. Found: C, 59.95; H, 6.89; N, 32.68.

Aliphatic and Heterocyclic Diamines.

The majority of these intermediates were procured from commercial sources. The following compounds were synthesized according to the cited literature: N^1,N^1-diethyl-1,3-butanediamine (19); 1-ethyl-3-(2-aminoethyl)pyrrolidine (20); N^α,N^α-diethyl-6-methoxy-α,3-toluenediamine (21); and N^α,N^α-diethyl-6-ethoxy-α,3-toluenediamine (18). Representative experimental procedures for the preparation of several miscellaneous diamines are given below.

N,N-Dimethyl-1,4-cyclohexanediamine.

To a solution of 413 g. (4.05 moles) of acetic anhydride in 500 ml. of acetic acid was added gradually 500 g. (3.67 moles) of *N,N*-dimethyl-*p*-phenylenediamine at such a rate that the temperature did not exceed 70°. The mixture was then heated under reflux for 2 hours and allowed to remain at room temperature overnight. It was poured into 5 l. of iced water and treated with 50% aqueous sodium hydroxide. The solid was collected, washed thoroughly with water, and dried to provide 488 g. (75%) of 4′-(dimethylamino)acetanilide, m.p. 126-128°. A solution of 226 g. (1.27 moles) of this material in 1.2 l. of methanol was hydrogenated over 10 g. of 10% rhodium on carbon at 3.5 kg./cm^2. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was dissolved in 500 ml. of 6 *N* hydrochloric acid and extracted with ether. The ether extract was discarded and the aqueous layer was heated under reflux for 22 hours and cooled. The mixture was made strongly alkaline and extracted with ether. The extracts were dried, the solvent was removed, and the residue was distilled to provide 126 g. (71%) of the product, b.p. 90-94°/14 mm., n_D^{25} = 1.4772, which was homogeneous by vapor phase chromatography.

N,N-Diethyl-1,3-cyclohexanediamine.

A solution of 100 g. (0.515 mole) of *N,N*-diethyl-*m*-nitroaniline in 500 ml. of acetic acid and 160 ml. of acetic anhydride was hydrogenated over 0.5 g. of 20% palladium on carbon at 23.5° and an initial pressure of 3.5 kg./cm^2 for 4.2 hours. The catalyst was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in 500 ml. of ethanol and made basic with 800 ml. of 22% ammonium hydroxide. The mixture was diluted to 3 l. with water and cooled. The solid was collected and recrystallized from aqueous ethanol to give 68.7 g. (65%) of 3′-(diethylamino)acetanilide, m.p. 70-72°.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.68; H, 8.75; N, 13.78.

A mixture of 216 g. of this material (1.05 moles) and 1 l. of methanol was hydrogenated over 10 g. of 10% rhodium on carbon at 22.5° and an initial pressure of 3.55 kg./cm^2 for 22.1 hours. The catalyst was removed by filtration, and the solvent was removed *in vacuo*. The resulting oil in 700 ml. of 6 *N* hydrochloric acid was heated under reflux for 29 hours. The mixture was concentrated *in vacuo*, and the residue was dissolved in 250 ml. of water and made alkaline with 150 ml. of 50% sodium hydroxide. The mixture was extracted with 1 l. of ether, the extracts were dried, and the solvent was removed *in vacuo*. Distillation gave 122 g. (68%) of the product, b.p. 115-116°/36-38 mm. Vapor phase chromatography indicated this material to be homogeneous.

Anal. Calcd. for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.19; H, 12.66; N, 15.85.

N,N-Diethyl-1,4-cyclohexanediamine.

This amine (22) was prepared by a procedure similar to that used for the above analogs by hydrogenation of 4′-(diethylamino)-acetanilide in methanol over rhodium on carbon in 69% yield, b.p. 108-111°/20 mm.

4-(Aminomethyl)-1-ethylpiperidine.

Isonipecotamide was dehydrated with phosphorus oxychloride

to 4-cyanopiperidine (23). To 340 ml. of acetic anhydride maintained at 25-30° was added dropwise 102 g. (0.925 mole) of 4-cyanopiperidine. The mixture was stirred at room temperature for 1.3 hours, the solvents were removed *in vacuo*, and the residue was taken up in chloroform. The chloroform was washed with 250 ml. of 10% sodium hydroxide, dried, and concentrated *in vacuo*. The residue was dissolved in 300 ml. of tetrahydrofuran and added dropwise over 3.5 hours to a slurry of 70.2 g. (1.85 moles) of lithium aluminum hydride in 1.5 l. tetrahydrofuran. The mixture was heated under reflux for 8 hours, diluted with 800 ml. of ether, and 74 ml. of water was added slowly followed by 55 ml. of 20% sodium hydroxide and 259 ml. of water. The salts were collected, the solvents were removed *in vacuo*, and the residue was distilled to give 83.1 g. (63%) of the product (24), b.p. 84-86°/10 mm., n_D^{25} = 1.4720-4.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.69. Found: C, 67.58; H, 12.42; N, 19.76.

3-Amino-1-methylpiperidine.

Bromomethane (100 g., 1.05 moles) chilled to 0° was added to 3-aminopyridine (60 g., 0.635 mole) dissolved in 500 ml. of cold (0-5°) methanol. The mixture was stirred at 0-5° for 3 hours, allowed to warm to room temperature, and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol to give 93 g. (77%) of 3-amino-1-methylpyridinium bromide, m.p. 179-182°.

Anal. Calcd. for $C_6H_9BrN_2$: C, 38.12; H, 4.80; N, 14.82. Found: C, 38.46; H, 4.80; N, 14.57.

A solution of 73 g. (0.386 mole) of this material in 500 ml. of acetic acid was hydrogenated over 5 g. of 10% rhodium on carbon at 3.6 kg./cm^2. The catalyst was removed and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water, made basic with 50% aqueous sodium hydroxide, and extracted with ether. The extract was dried and distilled to give 26.5 g. (62%) of the product, b.p. 89-93°/72-73 mm., which was homogeneous by vapor phase chromatography.

4-Amino-1-propylpiperidine.

This intermediate was prepared similarly *via* 4-amino-1-propylpyridinium bromide, m.p. 176-179° from ethanol-ethyl acetate.

Anal. Calcd. for $C_8H_{13}BrN_2$: C, 44.26; H, 6.03; N, 12.90. Found: C, 44.48; H, 5.92; N, 12.79.

Hydrogenation of the above compound over rhodium on carbon gave the product (53%), b.p. 70-75°/33 mm.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.69. Found: C, 67.43; H, 12.52; N, 19.33.

4-Amino-1-isobutylpiperidine.

This intermediate was prepared similarly. 4-Amino-1-isobutylpyridinium bromide was obtained by heating 4-aminopyridine and 1-bromo-2-methylpropane at 140° for 4 hours, yield 87% from acetonitrile, m.p. 151-154°.

Anal. Calcd. for $C_9H_{15}BrN_2$: C, 46.77; H, 6.54; N, 12.12. Found: C, 46.64; H, 6.50; N, 12.37.

Hydrogenation of the above compound in methanol over rhodium on carbon afforded the product (26%), b.p. 98-100°/10 mm.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.18; H, 12.90; N, 17.92. Found: C, 69.48; H, 12.76; N, 18.26.

3-Amino-1-isobutylpiperidine.

3-Amino-1-isobutylpyridinium bromide was prepared as above (58%), m.p. 113-117° from acetonitrile-acetone.

Anal. Calcd. for $C_9H_{15}BrN_2$: C, 46.77; H, 6.54; N, 12.12. Found: C, 46.55; H, 6.48; N, 11.86.

Hydrogenation of 3-amino-1-isobutylpyridinium bromide over rhodium on carbon in methanol gave the product in 31% yield, b.p. 85-91°/10 mm.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.90; N, 17.92. Found: C, 69.39; H, 12.73; N, 18.29.

1-Ethyl-3-(methylamino)piperidine.

A solution of 51 g. (0.4 mole) of 3-amino-1-ethylpiperidine in 200 ml. of methanol was treated with 43 g. (0.4 mole) of benzaldehyde to form the Schiff base. Reduction over 2 g. of 10% platinum on carbon at an initial pressure of 3.6 kg./cm^2 was slightly exothermic, the temperature rising to 41°. Hydrogen uptake was complete after 1.6 hours. The 3-(benzylamino)-1-ethylpiperidine thus obtained was treated *in situ* with 31 g. (0.38 mole) of 37% formalin and hydrogenated in the presence of an additional 2 g. of 10% platinum on carbon to give 3-(benzylmethylamino)-1-ethylpiperidine. Debenzylation was effected during 23 hours over 4 g. of 20% palladium on carbon. The reaction mixture was filtered and the solvent was removed *in vacuo*. Distillation of the residue provided 37.6 g., b.p. 79-81°/≅40 mm. This material was shown to be a mixture containing approximately 65% of the desired product by vapor phase chromatography and was used without further purification.

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